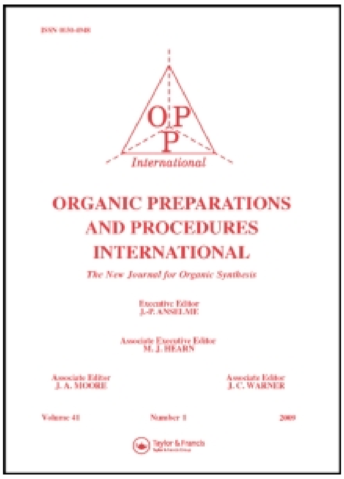

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RECENT ADVANCES IN THE SYNTHESIS OF INDAN SYSTEMS. A REVIEW

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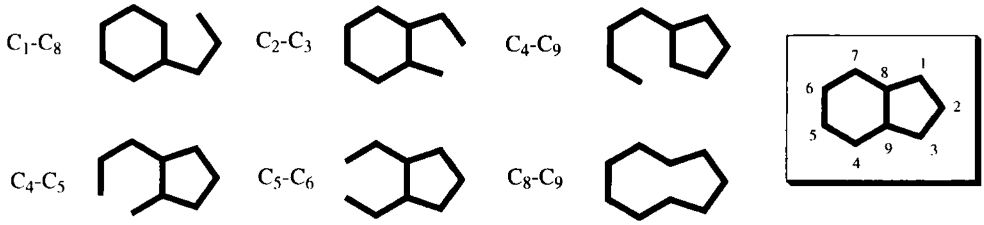
INTRODUCTION

Organic synthetic chemists are enjoying an era in which many new molecular skeletons may now be deemed accessible. Construction of carbocyclic systems, such as steroids and indans, has occupied a special chapter in the repertoire of modern synthetic methods. The fused [5,6] indan ring system is present in many naturally occurring polycarbocyclic compounds.[1] It has also served as a useful building block for the synthesis of a wide variety of natural and purely synthetic molecules, including vitamin D. Due to their interesting biological activities and natural abundance, indans have thus been a favorite topic of research for organic chemists. Much of the effort in the area of indan synthesis has been dedicated to the development of novel carbon-carbon bond forming methods.

The present article highlights recent synthetic approaches to indan systems. This review is classified into three main sections, namely: one-bond, two-bond and multiple bond disconnection approaches. The literature reviewed covers the period from 1988 to 1997. Some work prior to 1988 was also covered due to its novelty.

I. ONE-BOND DISCONNECTION APPROACHES

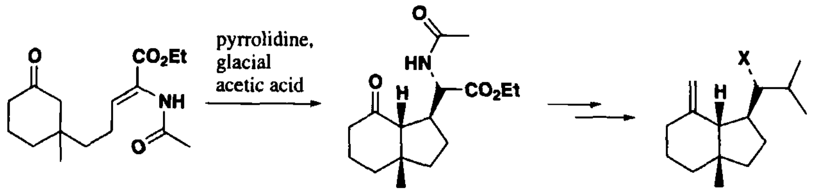
Various one-bond disconnection approaches to indan system are summarized in the following scheme.



A. C_1-C_8 Bond Formation Methods

1. Anion Alkylations

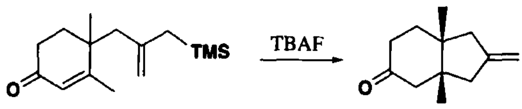
Anion cyclizations are the most common synthetic procedures in C_1-C_8 bond formation methods. The majority of these approaches are enolate condensations. Pyrrolidine-acetic acid mediated intramolecular conjugate additions of ketoesters provide perhydroindans with high levels of diastereoselectivity. The methodology was applied to the total synthesis of axane sesquiterpenoids: (±)-axamide and (±)-axisonitrile.[2]



1 2

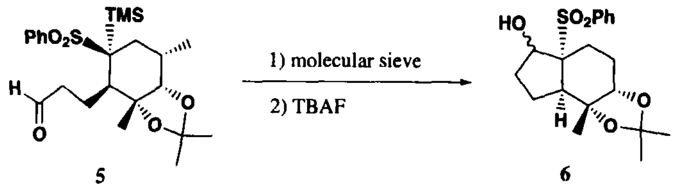
axisonitrile: X= N=C
axamide: X = NHCHO

Tetrabutylamoniumfluoride (TBAF) catalyzed intramolecular addition of allylsilanes to various Michael acceptors has lead to cyclopentane annulations.[3]



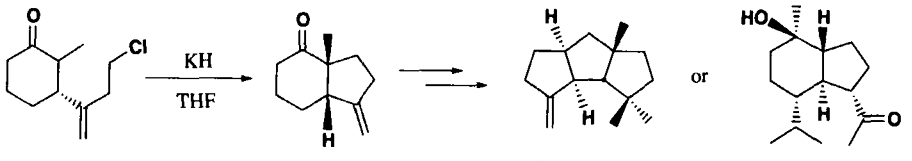
3 4

Alternatively, TBAF also promotes the intramolecular 1,2-addition of α-silyl sulfones to aldehydes.[4]



5 6

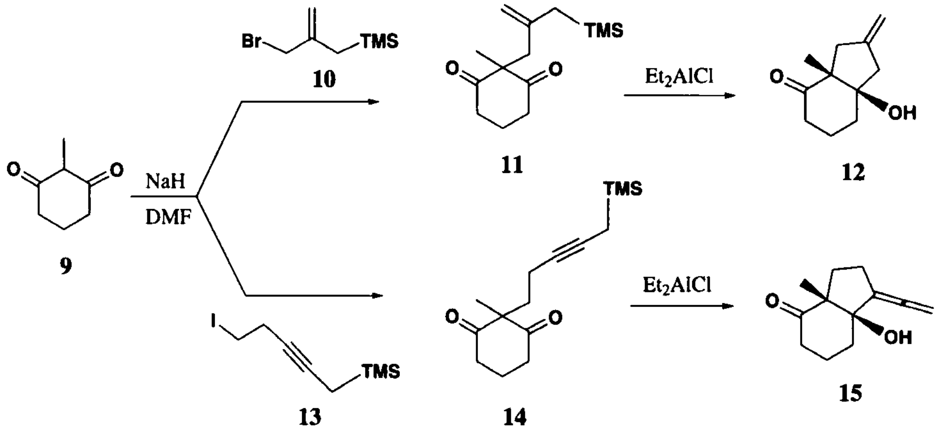
Intramolecular enolate addition to an alkyl halide is a traditional C-C bond formation method. Piers *et. al.* have applied this method to the synthesis of the indan skeleton. As shown in the following scheme, this novel annulation method played a key role in the total synthesis of the sesquiterpenoid (±)-$\Delta^{9(12)}$-capnellene and (±)-oplopanone.[5]



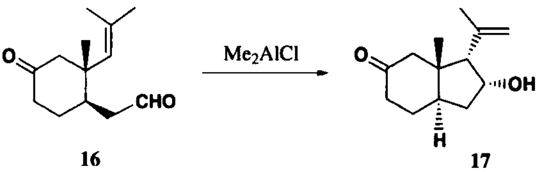
7 8 (±)-$^{9(12)}$-capnellene (±)-oplopanone

2. Lewis Acids Cyclization Methods

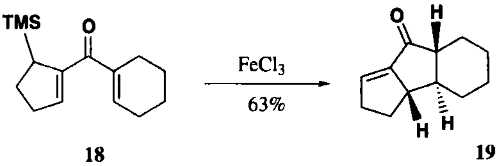
In a synthetic study of hopane type triterpenoids, Schinzer *et. al.* used Et_2AlCl to promote the intramolecular cyclization of allyl and propargylsilanes with 1,3-diketones to form hydroindanones.[6] A similar cyclization catalyzed by Amberlyst 15 was also reported.[7]



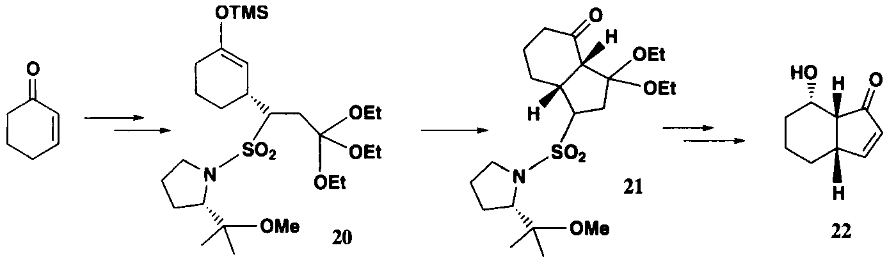
In a total synthesis of (±)-cortisone, Me_2AlCl has been used for the intramolecular cyclization of alkene **16** to aldehyde **17**.[8]



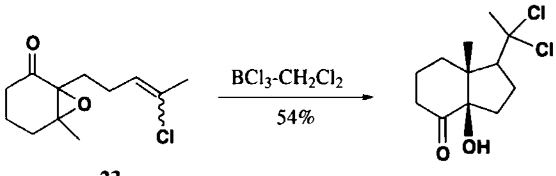
$FeCl_3$ was used as Lewis acid to facilitate a silicon directed Nazarov cyclization which involves the cyclization of divinyl ketones incorporating an allylsilane as the control unit.[9]



Stereocontrolled synthesis of five-membered carbocycles is an important subject in organic synthesis. Recently, Huart *et. al.* reported an asymmetric $TMSOT_f$ catalyzed cyclopentannulation of cyclic enones with a chiral 1,3-dipole equivalent.[10] The method is conceptually similar to the Robinson annulation and allows the conversion of a prochiral cyclic enone into a bicyclic cyclopentenone of high enantiomeric purity.

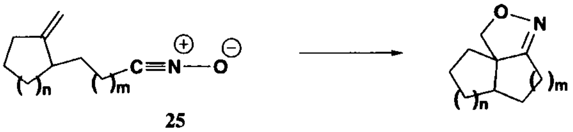


Sutherland and coworkers have utilized BCl_3 in the cyclization of 2-substituted 3-methylcyclohex-2-enone epoxides to a variety of hydrindanone derivatives.[11]



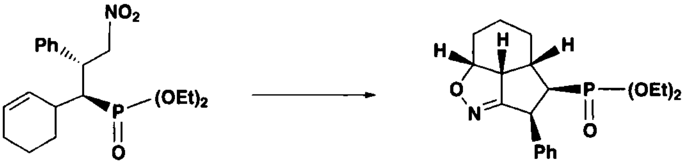
3. 1,3-Dipolar Cycloadditions

Intramolecular nitrile oxide-olefin cycloadditions (INOCs) have been employed in the construction of cyclic compounds with well defined stereochemistry. Padwa *et. al* reported an application of the INOC reaction in the formation of fused ring systems possessing a functionalized angular methyl group.[12]

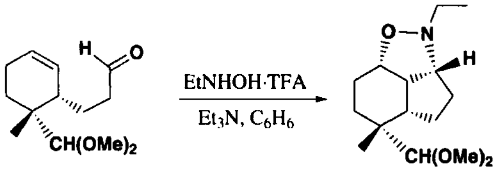


n = 1, 2
m = 1, 2, 3

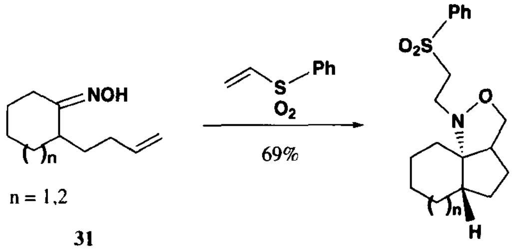
The intramolecular nitrile oxide-olefin cycloaddition of a nitro alkenylphosphonate provides another stereoselective route to indan systems.[13]



In a synthetic study toward the norditerpenoid alkaloid methylcaconitine, a potent inhibitor of neurotransmission, an intramolecular nitrile oxide-olefin cycloaddition was employed in the construction of the tricyclic indan.[14]



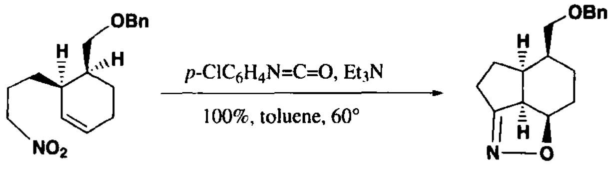
C-3,-4,-5 and -6 alkenyl oximes reacted with electronegative olefins at the nitrogen atom *via* Michael-type addition process to generate the corresponding C-alkenyl nitrones which undergo an intramolecular cycloaddition leading to indans.[15]



31

32

The INOC reaction provides a potential synthon for the E ring segment of (-)-reserpine.[16] The isoxazoline indan **34** was obtained in quantitative yield when the nitro olefin precursor **33** reacted with excess *p*-chlorophenyl isocyanate in the presence of Et_3N.

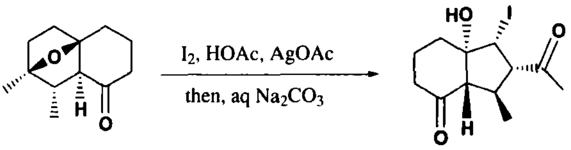


33

34

4. Ring Contraction.

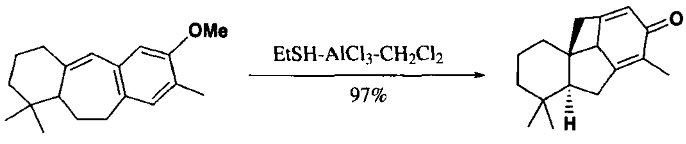
Ring contraction strategies are usually employed to adjust ring sizes in accordance with final structural requirements. Indans have been prepared in this manner starting from 11-oxotricyclo[6.2.1.0] undec-9-enes. The latter undergo a Wagner-Meerwein rearrangement when treated with either iodine/silver acetate/acetic acid or iodine/iodic acid/methanol.[17]



35

36

In synthetic studies toward (±)-faveline and (±)-isopisiferin, Ghatak *et. al.* utilized $AlCl_3$-EtSH for the demethylation step in construction of the indan segment.[18]

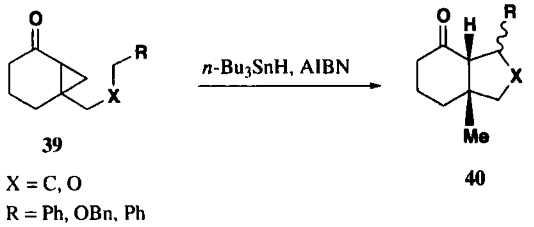


37

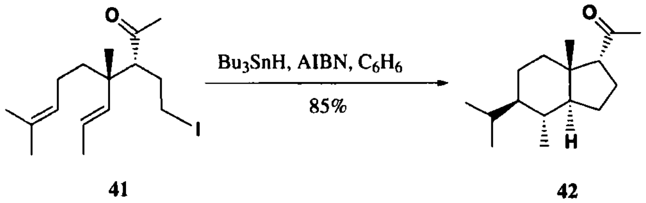
38

5. Radical Reactions

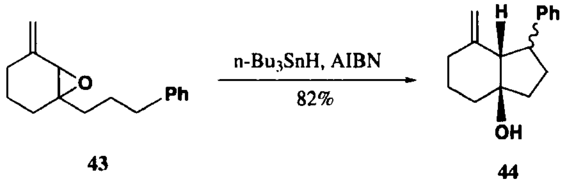
Intramolecular hydrogen abstraction by an alkyl radical has been exploited in a synthetically useful tandem fragmentation-H-translocation-cyclization sequence that gives *cis*-fused bicyclic systems with bridgehead methyl groups. The studies demonstrate that 1,5-hydrogen abstraction by an aliphatic radical can be successfully incorporated into a reaction design, provided a good hydrogen donor site is available.[19]



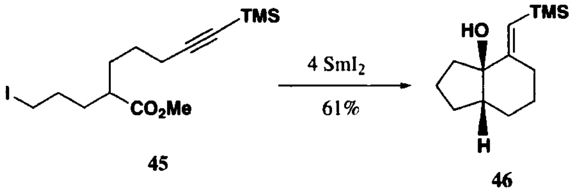
An efficient synthesis of the steroid CD-ring was accomplished by using tandem radical cyclization. The major "*trans*-8-methyl hydrindan" including the *trans-anti-trans* relative stereochemistry in ring C of the major product was in good agreement with MM2 transition state model calculation results.[20]



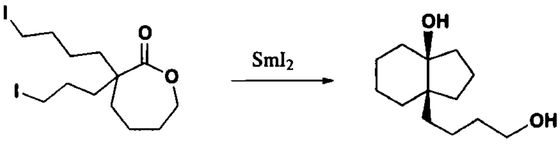
Radical translocation reactions of vinyl epoxides involving a 1,5-n-Bu$_3$Sn or a 1,5-hydrogen shift provide access to allylic or other carbon centered radicals.[21] A tandem process of radical-mediated epoxide fragmention, radical translocation, and cyclization has also been reported.[22]



The SmI$_2$-promoted intramolecular nucleophilic acyl substitution/ketyl-olefin cyclization sequence has been utilized to convert a variety of suitable substrates to bicyclic, tricyclic, and spirocyclic ring systems with high diastereoselectivity. The versatile reaction sequence allows entry to several different naturally occurring tricyclic systems containing the angular and linear triguinane framework.[23]

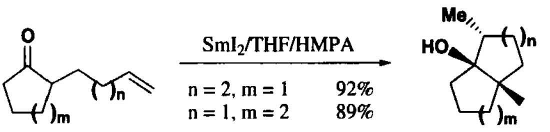


Samarium(II) iodide has also been employed by Molander *et. al.* to promote a tandem intramolecular nucleophilic acyl substitution/intramolecular Barbier cyclization sequence, generating bicyclic and tricyclic ring systems in high diastereoselectivity.[24] Cyclization of diiodide **47** with SmI_2 afforded the tricyclic indan **48**.[25]



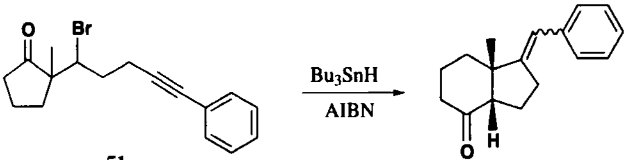
47 **48**

Samarium(II) iodide in the presence of HMPA effectively promotes the intramolecular coupling of unactivated olefinic ketones by a reductive ketyl-olefin radical-cyclization process. The reaction provides a facile synthesis of indans.[26]



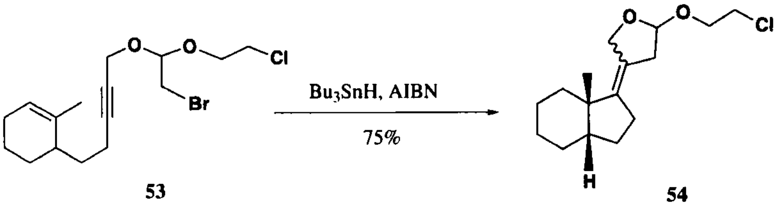
49 **50**

Boger has described a study of phenylselenoesters as precursors to acyl radicals and their subsequent participation in intermolecular and intramolecular alkene addition reaction.[27] Intramolecular cyclizations of difluoromethyl radicals with olefins, silylacetylenes and enol acetates to afford a variety of difluorocyclopentanes have also been reported.[28]



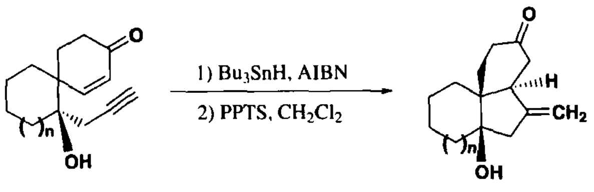
51 **52**

Dicyclization *via* selective formation of unsaturated vinyl radicals by intramolecular addition to triple bonds has been applied to the synthesis of the naturally occurring β-substituted furan perillene.[29] Stereochemical control of hex-5-enyl radical cyclization in the synthesis of indans has also been described.[30]



53 **54**

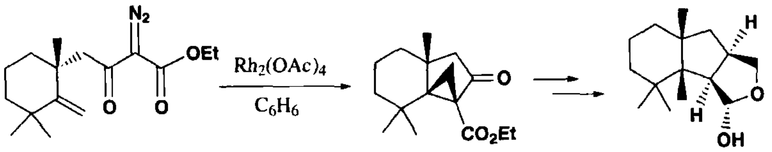
An efficient strategy for the synthesis of angularly fused tricyclic carbocycles with indan segments was achieved by means of regioselective addition of $(n\text{-}Bu)_3Sn$. followed by sequential radical cyclization.[31]



55 **56**

6. Carbenoid Reactions

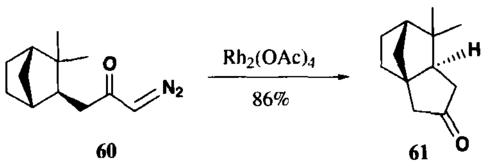
Carbenoids are employed most often in synthesis for their facile addition to double bonds to form cyclopropanes. Rhodium acetate-catalyzed intramolecular cyclopropanation of α-diazo keto ester **57** furnished cyclopropyl indanone **58** which was converted to a natural thapsane **59** in only a few steps.[32]



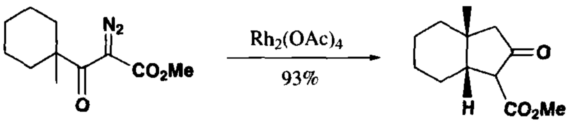
57 **58** **59**

a natural
thapsane

Treatment of α-diazoketones with catalytic amounts of $Rh_2(OAc)_4$ led to selective carbene insertion into C-H bonds resulting in cyclopentane-annulated products in high yields. Steric and electronic effects of cyclopentane construction (including indans) by $Rh_2(OAc)_4$-mediated intramolecular C-H insertion has also been studied.[33]

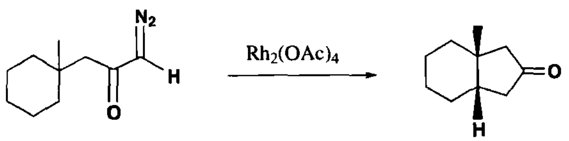


60 **61**



62 **63**

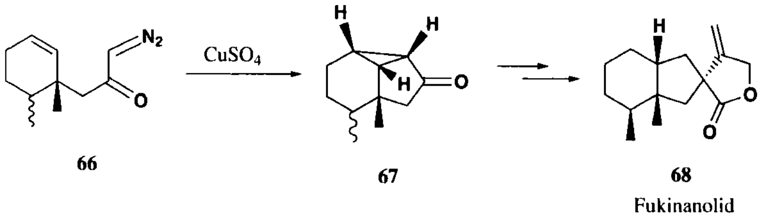
The decomposition of diazoketone **64** in the presence of $Rh_2(OAc)_4$ catalyst leads to a 92:8 cis/trans mixture of indan **65**.[34]



64 **65**

cis / trans
92 : 8

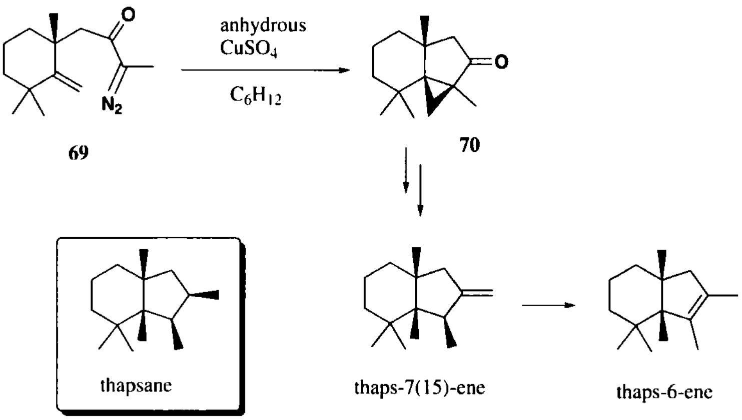
A highly stereoselective synthesis of bakkenolide A, fukinanolide, was reported. The key step employed the intramolecular insertion of the keto-carbenoid **66** into the olefin to generate the indanone **67**.[35]



66 **67** **68**

Fukinanolid

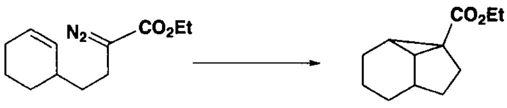
The same methodology was also applied in the stereospecific synthesis of thaps-7(15)-ene and thaps-6-ene, possible biogenetic precursors of thapsanes.[36] Alternatively, Srikrishna *et. al.* have applied the same cyclopropanation methodology in the total synthesis of (±)-norbakkenolide-A.[37]



69 **70**

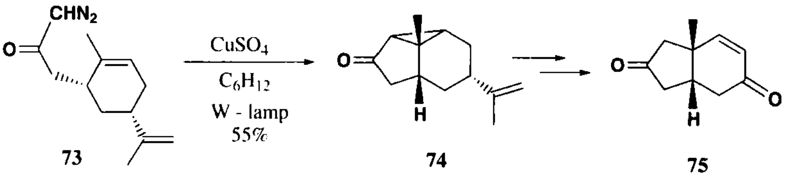
thapsane thaps-7(15)-ene thaps-6-ene

Other applications of $Rh_2(OAc)_4$ catalyzed cyclopropanation in the synthesis of indans were also reported.[38]



71 **72**

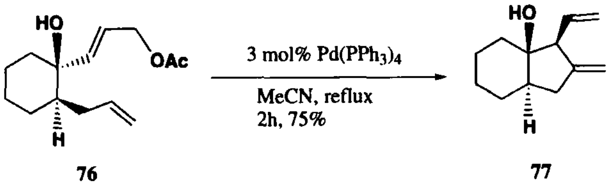
Enantioselective synthesis of (+)- and (-)-derivatives of bicyclo[4.3.0]nonane-8-one and -3,8-diones as potential chiral precursors in terpenoid synthesis has been described.[39]



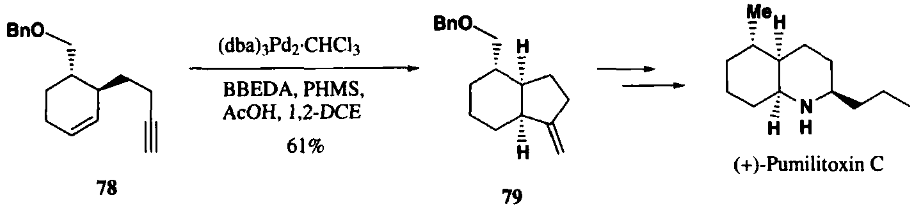
73 **74** **75**

7. Transition Metal Mediated Cyclization

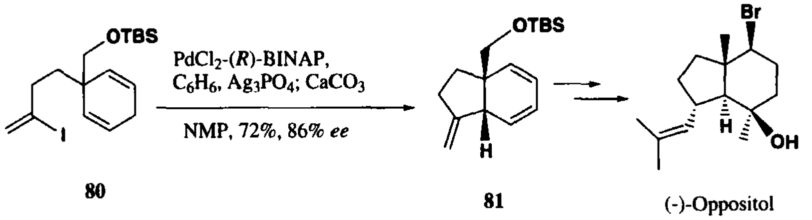
Pd-catalyzed cyclic allylmetallation-dehydrometallation cyclization of 4-hydroxy-2,7-octadienyl acetate derivatives in refluxing MeCN afforded the indan derivatives.[40]



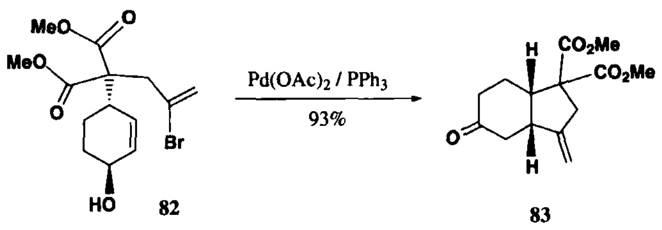
An enantioelective formal total synthesis of (+)-pumilitoxin C has been achieved *via* stereoselective transformation of enantiopure cyclohexenol **78** into *cis*-hydrindan **79**.[41]



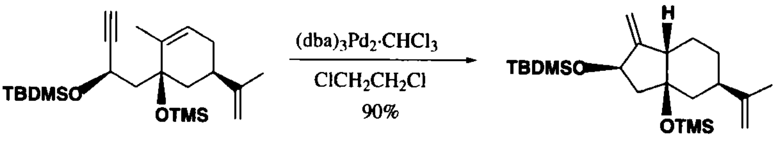
Furthermore, the synthesis of a *cis*-hydrindan was accomplished employing an intramolecular Heck reaction. The product of this reaction allowed for the formal asymmetric synthesis of oppositol and prepinnaterpene.[42]



The intramolecular Heck reaction, the palladium-catalyzed coupling of vinyl halides with allylic alcohols, afforded a wide variety of functionalized 5- or 6- membered carbo- or heterocycles, including indanones.[43]

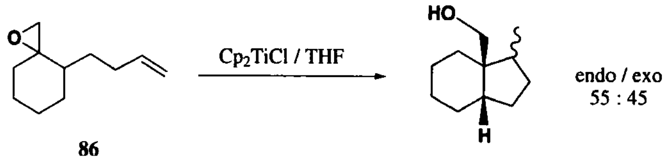


Intramolecular carbametalation reaction of enynes and diynes *via* the palladium-based method to indan systems have been explored.[44] The method was also diastereoselective and efficient.



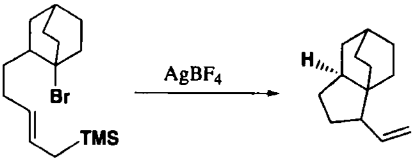
84 **85**

bis(Cyclopentadienyl)titanium (III) chloride reacts with epoxides by initial C-O bond homolysis. These radicals undergo intramolecular hex-5-enyl cyclization to afford the indan products.[45]



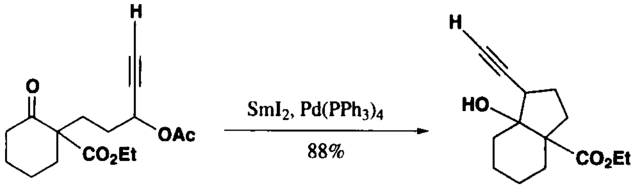
86 **87**

The intramolecular reactions of bridgehead carbocations derived from 1-bromobicyclo-[2.2.2]octanes and silver triflate established the feasibility of employing these intermediates in the synthesis of indan compounds.[46]



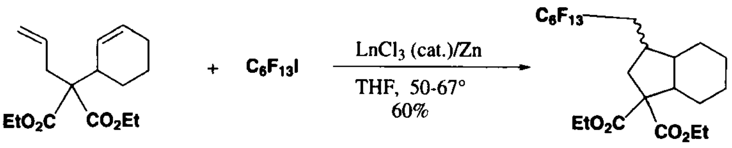
88 **89**

Treatment of alkynyl keto esters **90** with $SmI_2/Pd°$ results in intramolecular cyclization to afford acetylenyl indanol **91**. The methodology features the use of the stable and convenient propargyl ester functionality as a propagyl anion synthetic equivalent in carbocycle ring-forming reactions.[47]



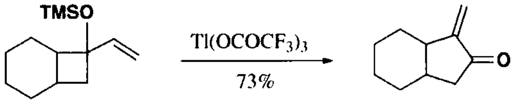
90 **91**

A free-radical addition-cyclization of diallylmalonic acid esters with per(poly)fluoroalkyl iodides initiated by $LnCl_3$ (cat.)/Zn yields indans.[48]



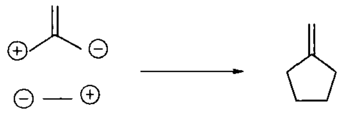
92 **93**

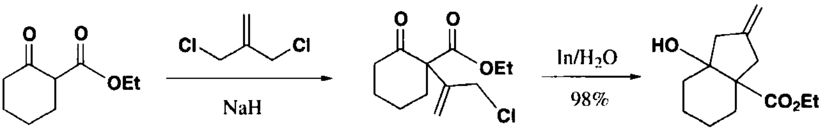
Thallium ion mediated ring expansion of 1-trimethylsilyloxy-1-alkenylcycloalkanes **94** in acetonitrile affords indanone **95** in 73% yield.[49]



94 **95**

Sequential nucleophilic and electrophilic alkylations of 1,3-dicarbonyl compounds with a trimethylenemethane zwitterion equivalent led to a novel [3+2] annulation and afforded indans. The carbonyl alkylation was carried out *via* an indium mediated allylation reaction in water.[50]

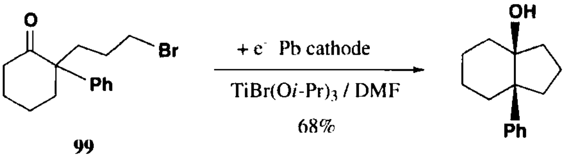




96 **97** **98**

8. Miscellaneous Reactions

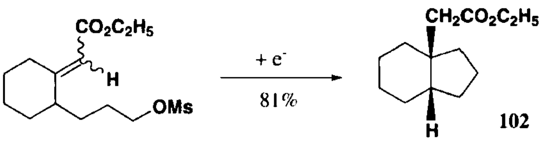
Intramolecular coupling occurs when keto bromide **99** is electrochemically reduced in the presence of promoters and affords the corresponding cyclized products.[51]



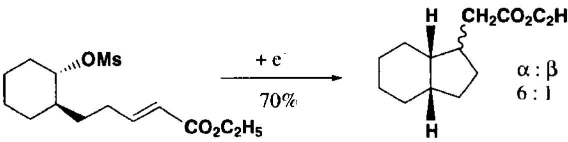
99

100

Reductive cyclization reactions of α,β-unsaturated esters with tethered mesylate leaving groups give the indan compounds.[52]

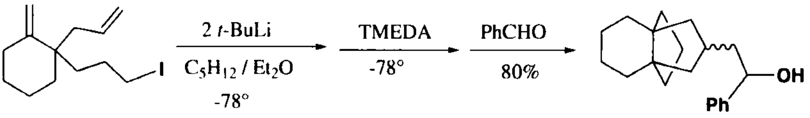


101 **102**



103 **104**

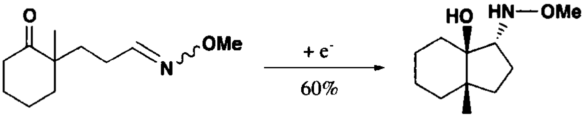
Anion-initiated polyolefinic cyclization of iodide **105** results in the formation of two new C-C bonds. Trapping of the intermediate with benzaldehyde gives product **106** bearing an indan moiety.[53]



105

106

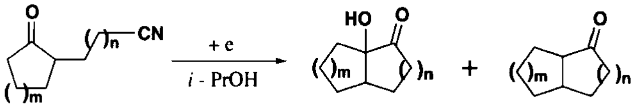
The intramolecular electroreductive coupling of ketones with O-methyl oximes takes place to give indans when the substrate tethering both components is electrochemically reduced in *i*-PrOH with a tin cathode.



107

108

Guaiazulene, (-)-valeranone, polyquinanes, dihydrojasmone, methyl dihydrojasmonate, and rosaprostol have been synthesized by utilizing the electroreductive intramolecular coupling of γ- and δ-cyano ketones in *i*-PrOH with a Sn cathode as one of the key steps.[54]

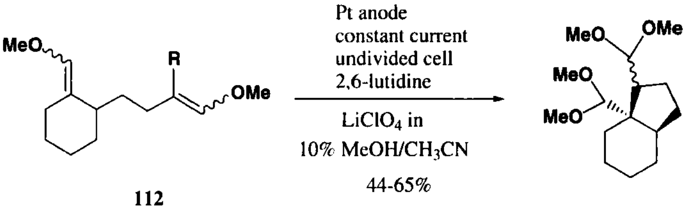


109

110

111

Intramolecular anodic olefin coupling reactions involving the use of either an allylsilane as one of the olefin participants or a vinylsilane as part of a temporary silicon tether have been applied to the synthesis of indans.[55]



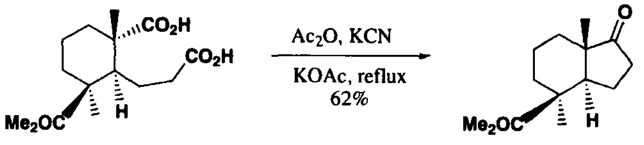
112

113

B. C_2-C_3 Bond Formation Methods

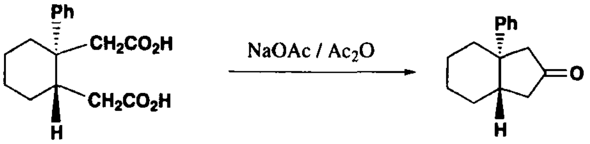
1. Anion Alkylations.

Ring closure of the dicarboxylic acid **114** in refluxing acetic anhydride containing potassium cyanide and potassium acetate gave the indanone **115** in 62%. The compound was used as a CD-ring synthon in the preparation of vitamin D analogs and steroids.[56]



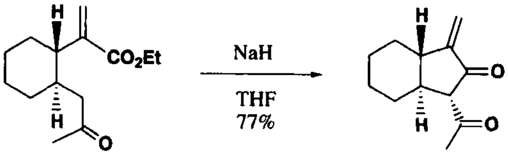
114 115

In an approach to the synthesis of morphinans and 4α-aryldecahydroisoquinolines, cyclization of diacid **116** with sodium acetate and acetic anhydride was achieved to provide indanone **117** in 74% yield.[57]



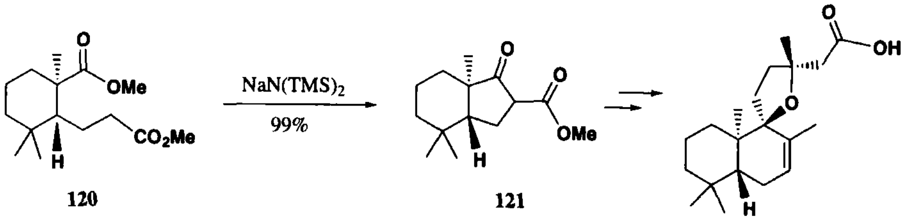
116 117

Bicyclo[4.3.0]nonane ring systems with exo-methylene groups were synthesized by intramolecular cyclization between β-(alkoxycarbonyl)allylsilanes and α,β-unsaturated ketones.[58]



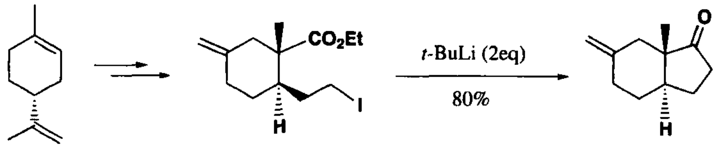
118 119

In an enantioselective total synthesis of (+)-grindelic acid, Paquette has achieved the cyclization by sodium hexamethyldisilazide-promoted Dieckmann reaction.[59]



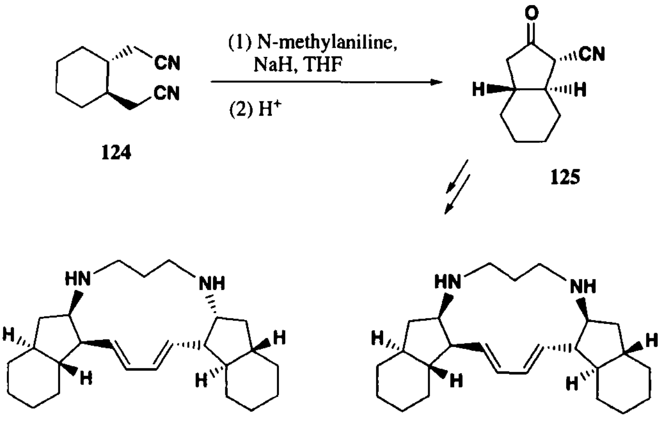
120 121 (+)-grindelic acid

The *trans*-hydrindanone **123** was synthesized from (R)-limonene in a highly stereoselective manner by intramolecular enolate alkylation and metal-halogen exchange-initiated anionic cyclization.[60]



(R)-limonene 122 123

In the total synthesis of the pentacyclic marine alkaloids, (-)-papuamine and (-)-haliclonadiamine, Heathcock *et. al.* have applied the Thorpe-Ziegler cyclization of **124** using sodium N-methylaniline as a base, followed by acid hydrolysis of the intermediate imine to go to keto nitrile **125** in excellent yield as a 13:1 mixture of epimers at the newly formed stereocenter.[61]



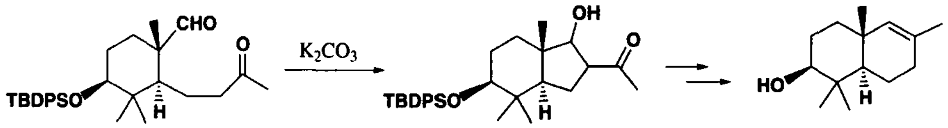
124

125

(-)-papuamine

(-)-haliclonadiamine

In a convenient multi-gram synthesis of octalins, Falck and coworkers have applied the intramolecular aldol condensation of ketoaldehydes to construct the indan skeleton.[62]

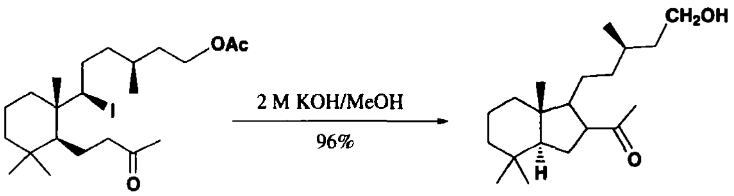


126

127

octalin

In a study of the chemistry of labdanediol, treatment of the iodoketone **128** with KOH/MeOH afforded the indan **129** *via* intramolecular enolate alkylation.[63]

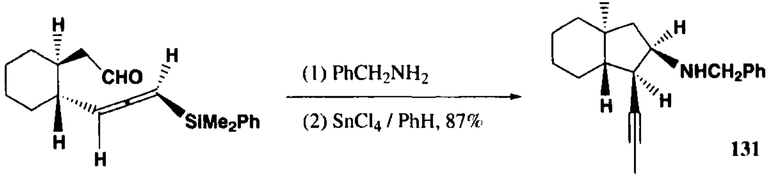


128

129

2. Lewis Acids Cyclizations

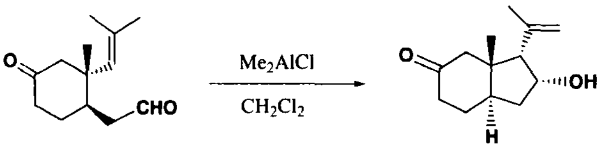
In a concise enantioselective total synthesis of the antibacterial and antifungal marine alkaloid (-)-papuamine, Weinreb and coworkers investigated the pivotal intramolecular Danheiser-type cyclization of allenyl silane aldehyde **130** with benzylamine in the presence of 4Å molecular sieves. The substrate was further exposed to stannic chloride to produce the silyl acetylene **131** in 87% yield.[64]



130

131

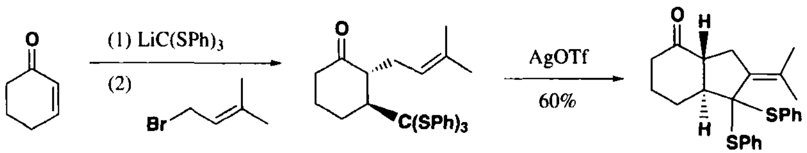
In a total synthesis of (±)-cortisone, Kuwajima and coworkers utilized the Me_2AlCl mediated cyclization of olefinic aldehyde **132** to afford the hydrindanone **133** in 85% yield.[65]



132

133

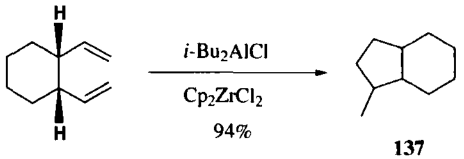
[1+2+2]-Pentannulation was accomplished by Posner and coworkers *via* 2-dimethallylated cyclohexanone and a pentanolide intermediate. Lewis acid promoted cyclization led effectively and simply to construction of regiospecifically polyfunctionalized indanones in 48% overall yield.[66]



134

135

Regioselective hydroalumination of unsaturated hydrocarbons by alkylalanes catalyzed by zirconium complexes was reported to synthesize indans.[67]

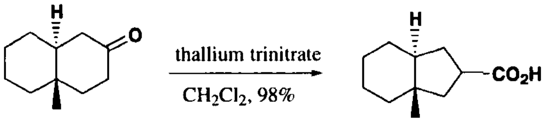


136

137

3. Ring Contraction

Thallium trinitrate (TTN) mediated ring contraction of cyclohexanone **138** lead to indan **139** in 98% yield and high degree of stereoselectivity.[68]

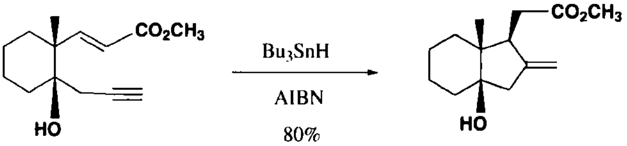


138

139

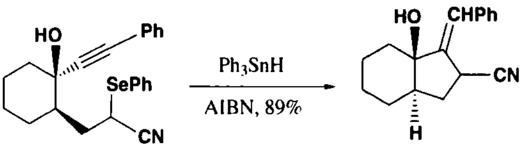
4. Radical Reactions

The stereocontrolled synthesis of functionalized indans involving tin-mediated vinyl radical cyclization was studied.[69] For example, the α,β-unsaturated ester **140** underwent 5-*exo-trig* cyclization to furnish indan **141** in 80% yield.



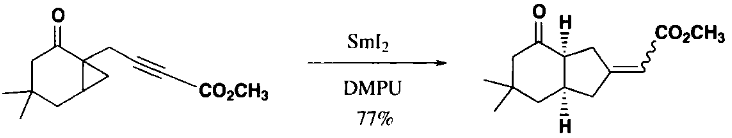
140 **141**

The hydroxy acetylene **142** undergoes radical cyclization when treated with triphenyltin hydride and AIBN to form indan **143**.[70]



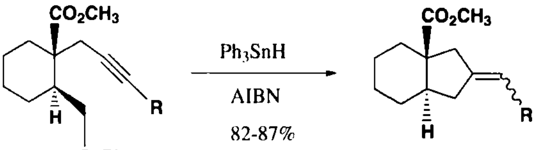
142 **143**

Radical ring opening reactions of cyclopropyl ketones mediated by samarium (II) iodide-induced single electron transfer have permitted the elaboration of the tandem rearrangement cyclization strategy to result in indans.[71]



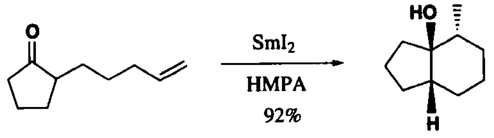
144 **145**

Radical cyclization of selenides **146** to bicyclic indans **147** was performed thermally by addition of benzene solution of triphenyltin hydride and AIBN to a refluxing benzene.[72]



146 **147**

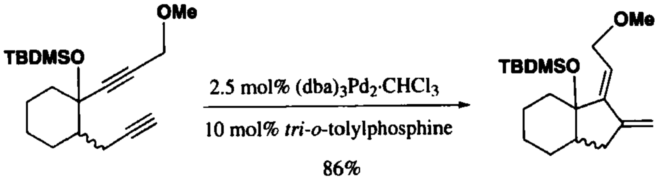
Samarium (II) iodide in the presence of HMPA promotes the intramolecular coupling of olefinic ketones by a reductive ketyl-olefin radical-cyclization to give the indan derivatives in good yield.[73]



148 **149**

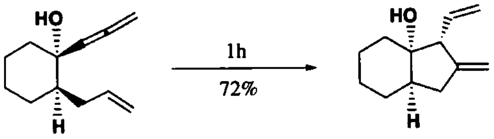
5. Transition Metal Mediated Cyclizations

Intramolecular carbametalation is a useful strategy for ring construction. A catalytic reductive cyclization of 1,6-diynes was reported by Trost and coworkers. The methodology provides an expeditious synthesis of indans.[74]



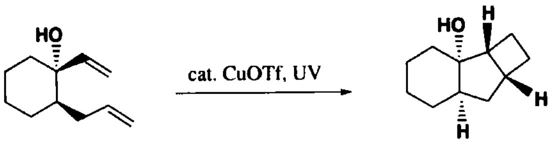
150 **151**

A novel nickel-chromium bimetallic catalyst was used for cyclization of enallene **152** to give indan **153**.[75]



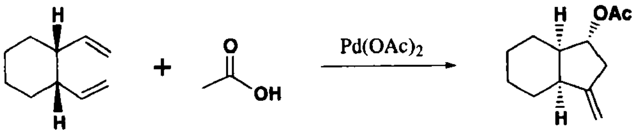
152 **153**

A single stereoisomeric bicyclo[3.2.0]heptanol **155** was synthesized from hydroxy diene **154** upon ultraviolet irradiation in the presence of copper (I) trifluoromethanesulfonate as catalyst.[76]



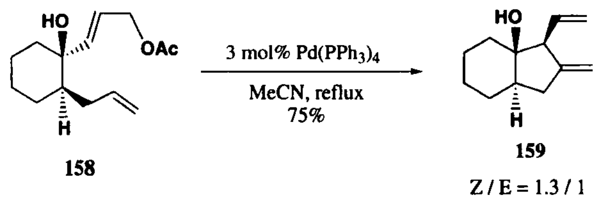
154 **155**

Oxidation of *cis* 1,2-divinylcyclohexane **156** with palladium acetate using hydrogen peroxide and benzoquinone resulted in 60% yield of the indan **157**.[77]



156 **157**

Synthesis of indanol derivative **159** *via* palladium-catalyzed cyclic allylmetallation-dehydrometallation was reported. Treatment of 4-hydroxy-2,7-octadienyl acetate **158** with 3 mol% $Pd(PPh_3)_4$ in refluxing MeCN provides in 75% yield the corresponding indanol **159**.[78]

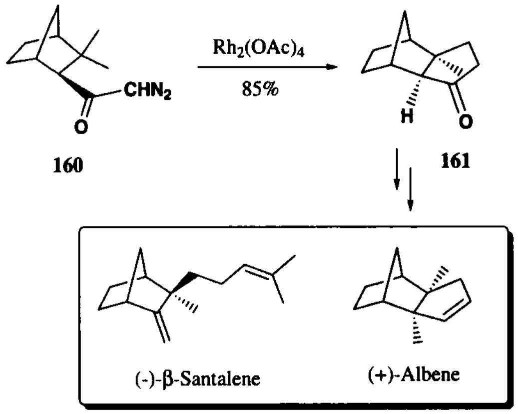


158

159

Z / E = 1.3 / 1

Application of carbenoids mediated by $Rh_2(OAc)_4$ to insert into a C-H linkage to form cyclic products has been achieved in the synthesis of (+)-albene and (-)-β-santalene.[79]



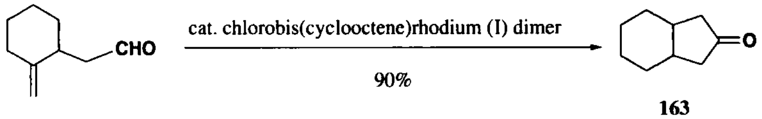
160

161

(-)-β-Santalene

(+)-Albene

The rhodium(I)-catalyzed intramolecular hydroacylation of unsaturated aldehydes to indans has been investigated. The catalysts are prepared by the addition of 2 equivalents of tri-*p*-tolylphosphine, tri-*p*-anisylphosphine, or tris(*p*-dimethylaminophenyl)phosphine to chloro-*bis*(cyclooctene)rhodium (I) in ethylene-saturated methylene chloride.[80]

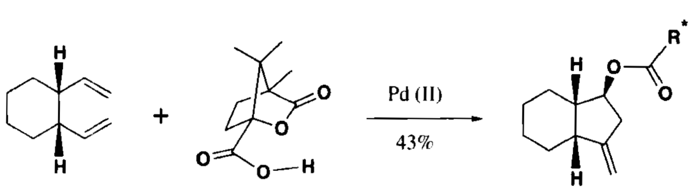


162

163

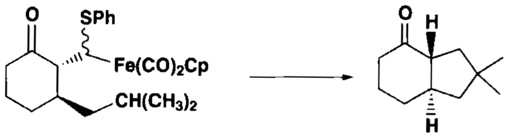
cis / trans
64 / 36

Molecular sieves have been shown to improve greatly the stereoselectivity in the palladium(II)-catalyzed reaction of cis-1,2-divinylhexane with chiral acid. Reactions run with molecular sieves and derivatives of (*R*)-lactic acids as nucleophiles always gave the indans with *S* configuration at the newly formed chiral center in contrast to the reactions without molecular sieve that gave products with either *S* or *R* configuration.[81]



164 **165** **166**

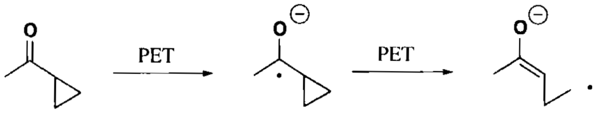
Intramolecular C-H insertion reactions of iron carbene complexes was used for the synthesis of indanones.[82]

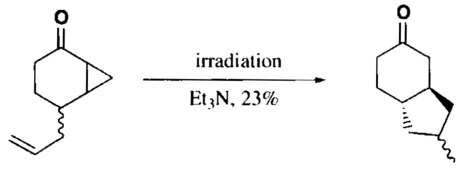


167 **168**

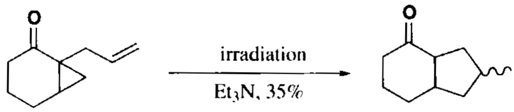
6. Miscellaneous Reactions

Reductive photoinduced electron transfer (PET) reactions have been studied on various bicyclic α-cyclopropyl-substituted ketones and tertiary amines. The tandem fragmentation-cyclization reaction resulted in regioselective cleavage of one cyclopropyl bond under formation of an exocyclic radical with an endocyclic enolate.[83]



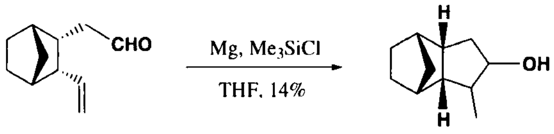


169 **170**

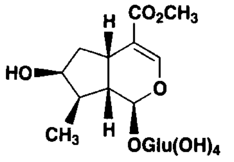


171 **172**

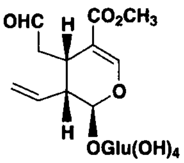
In the study of the mechanism of the biological conversion of the iridoid loganin to the secoiridoid secologanin, Hutchinson and coworkers have found a reductive, radical induced cyclization of 5-hexenals as a biomimetic model of the chemistry of secologanin formation and have applied this to the synthesis of indans.[84]



173 **174**

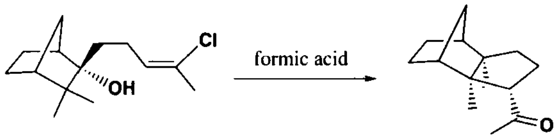


loganin



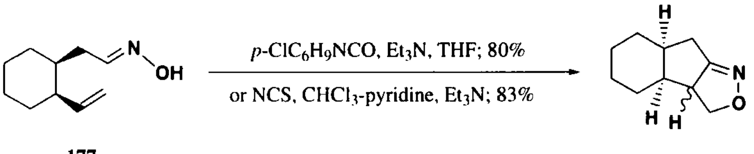
secologanin

In the first total synthesis of (-)-albene, cationic cyclization of the chloroolefin yielded the tricyclic indans.[85]



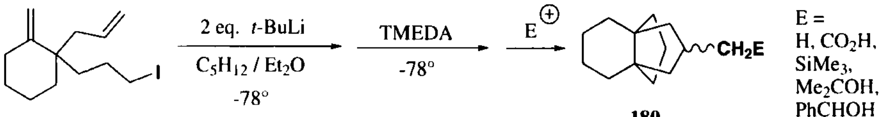
175 **176**

Hydrindans have been efficiently constructed by intramolecular nitrile oxide-olefin cycloaddition of 1-methyl-2-nitroalkylcyclohexanes.[86]



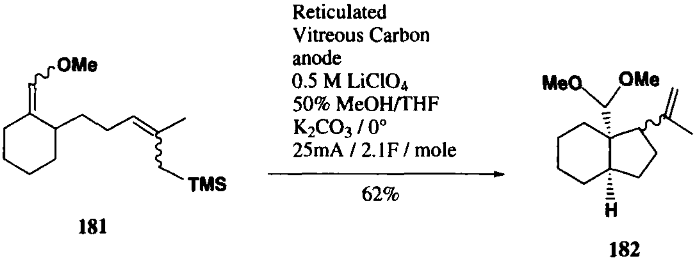
177 **178**

Bailey and coworkers have reported a facile cyclization of an olefinic alkyllithium to the preparation of a variety of cyclic indans.[87]



179 **180**

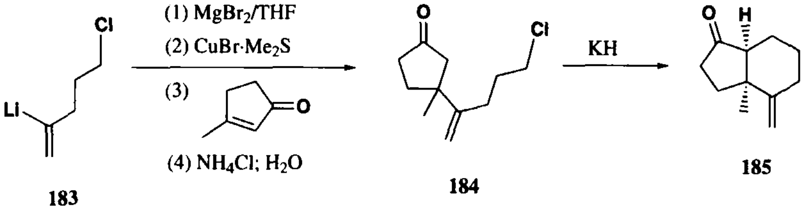
A number of intramolecular anodic olefin coupling reactions have been examined in order to determine the feasibility of using a sequential electrochemical oxidation-aldol condensation approach for constructing polycyclic compounds.[88]



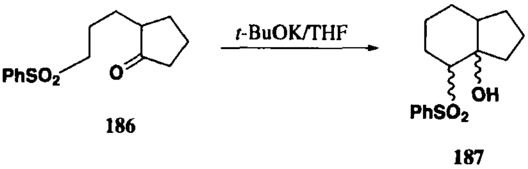
C. C_4-C_9 Bond Formation Methods

1. Anion Alkylations

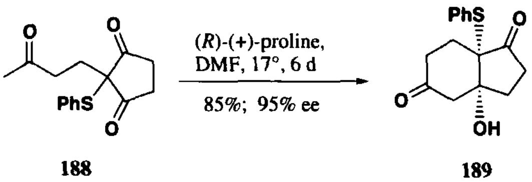
5-Chloro-2-lithio-1-pentene was converted into the corresponding Grignard and organocopper reagents. Conjugate addition of these reagents to the enones, followed by ring closure of the resultant adducts, provided the indan annulation products.[89]



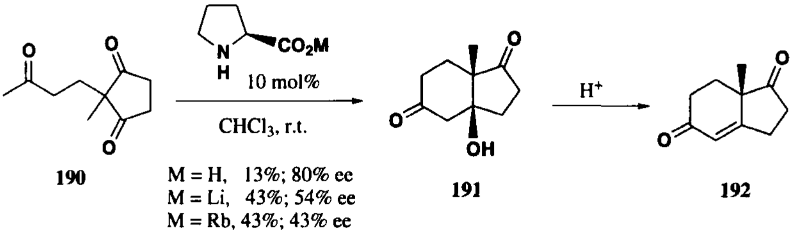
Synthesis of indanol **187** *via* trapping of sulfonate anion with ketone was achieved by treatment of the ketosulfonate **186** with *t*-BuOK in THF at room temperature, in 75%, yield.[90]



Application of the Hajos-Parrish asymmetrically biased aldol condensation to 2-(3-oxobutyl)-2-phenylthio-1,3-cyclopentanedione using (*R*)-(+)-proline provided indandione **189** in greater than 95% enantioselective excess.[91]

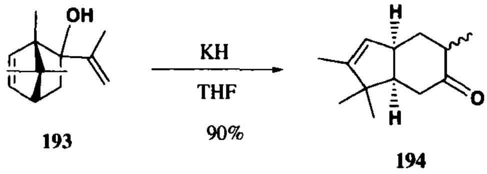


L-proline or its alkali metal salts promoted the asymmetric aldol reaction of trione **190** to give the indandione **192**.[92]



190 **191** **192**

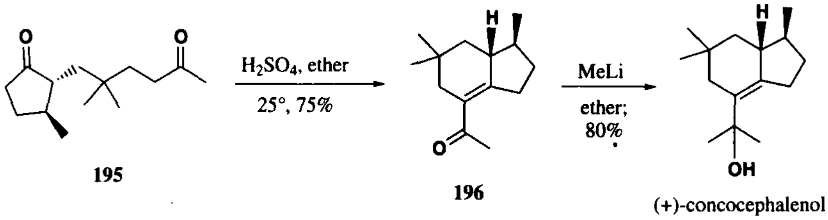
Treatment of 2-vinyl-5,6-dehydroisoborneol **193** with KH/THF at room temperature for 15 min led to the formation of *cis*-indanone **194** *via* Cope rearrangement.[93]



193 **194**

2. Lewis Acids Cyclizations

The synthesis of (+)-conocephalenol, a brasilane sesquiterpenoid alcohol, was achieved in 7 steps from (R)-pulegone. The key step for the construction of the indan skeleton involved an aldol cyclization under acidic conditions.[94]



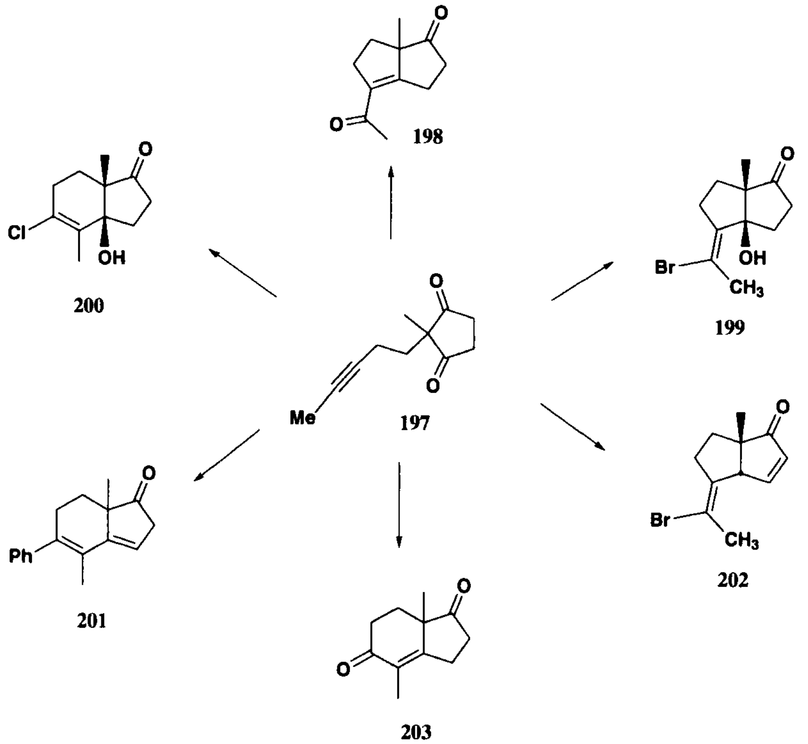
195 **196** (+)-concocephalenol

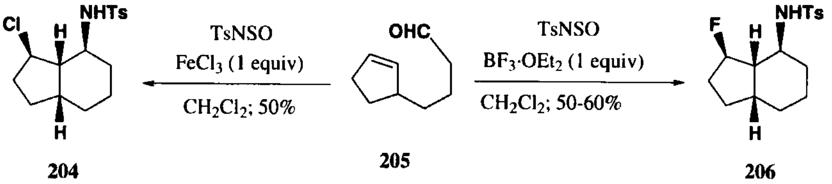
Cationic π-cyclization of alkenylcyclopentane-1,3-dione **197**, promoted by $BF_3 \bullet Et_2O$ was reported for producing bicyclic ring systems of varying functionality.[95]

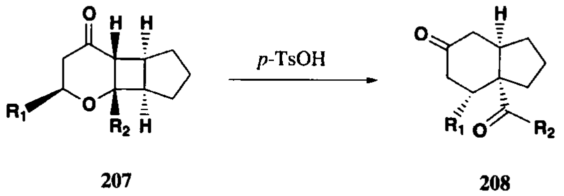
Boron trifluoride diethyl etherate promotes formation of N-tosyliminium complexes from olefinic enolizable aldehydes and N-sulfinyl-p-toluenesulfonamide, and subsequent intramolecular cationic cyclization gives indans.[96]

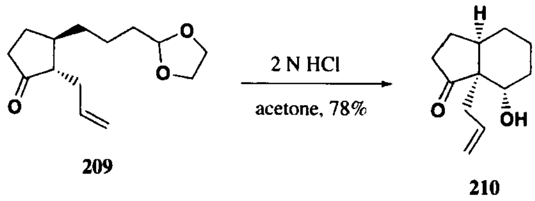
A de Mayo reaction of photo[2+2]cycloadduct **207** was applied to the synthesis of indans. Refluxing a solution of pyran **207** and *p*-toluenesulphonic acid in benzene results in a retro-Michael and retro-aldol eaction of the pyran ring, followed by intramolecular Michael reaction of the unsaturated 1,5-diketone intermediate to furnish the *cis*-fused hydrindan **208**.[97]

In the synthesis of the subunit of Manzamin A, Yamamura and coworkers treat the ketoacetal **209** with HCl to induce sequential acetal hydrolysis and intramolecular aldol reaction to give indan **210**.[98]

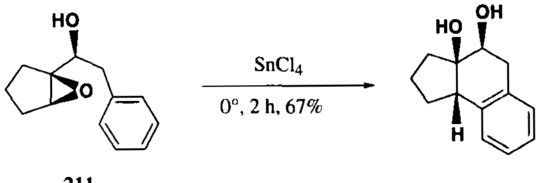

198
199
200
197
Me
201
202
203
O
OH
Cl
Ph
Br
CH3


TsNSO
FeCl3 (1 equiv)
CH2Cl2; 50%
TsNSO
BF3·OEt2 (1 equiv)
CH2Cl2; 50-60%
OHC
NHTs
Cl
F
H
204
205
206


p-TsOH
O
H
R1
R2
207
208


2 N HCl
acetone, 78%
O
H
OH
209
210

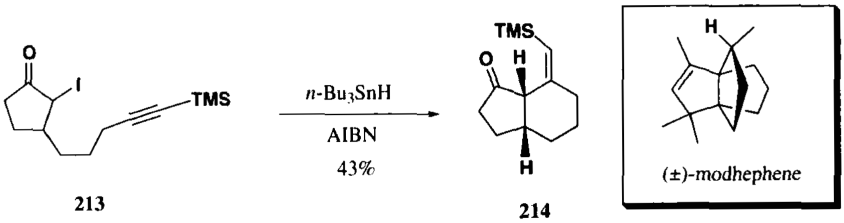
2,3-Epoxyalcohol **211** undergoes cyclization in the presence of $SnCl_4$ to give indan **212**.[99]



211 **212**

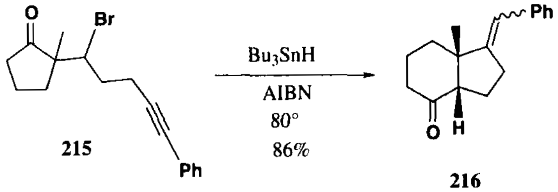
3. Radical Reactions

In a total synthesis of (±)-modhephene, silylacetylenic or olefinic α-iodoketones were treated with Bu_3SnH and AIBN to give indanones by intramolecular α-carbonyl radical cyclization reaction.[100]



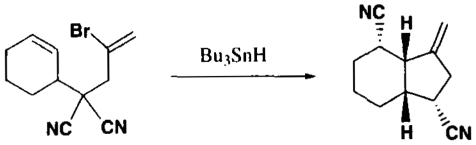
213 **214**

The effective preparation of hydrindan-1,4-diones *via* implementation of tandem free-radical ring expansion and 5-*exo-dig* 5-hexynyl radical cyclization was reported.[101]

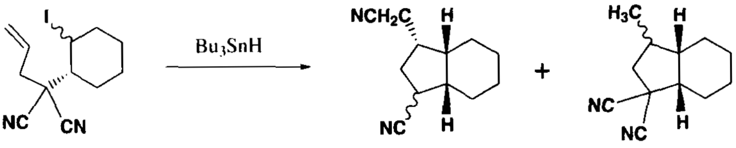


215 **216**

Radical annulation reactions of allyl iodomalononitriles by Bu_3SnH gives indans.[102]



217 **218**

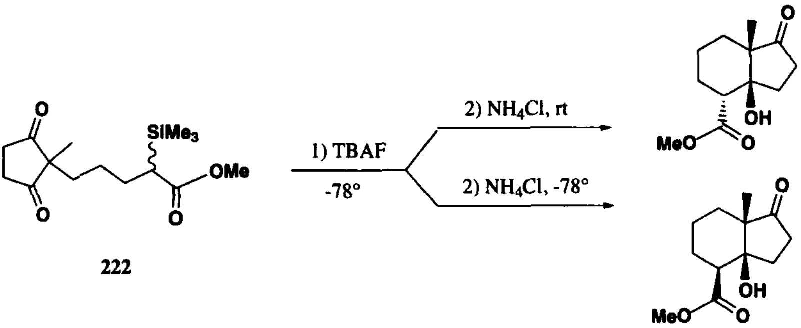


219 **220** **221**

55% 13%

4. Miscellaneous Reactions

Alicyclic tricarbonyl compound **222**, in which ester enolate was selectively formed, reacted to yield functionalized hydrindanone **223** or **224** *via* intramolecular aldol reactions, as reported recently.[103]

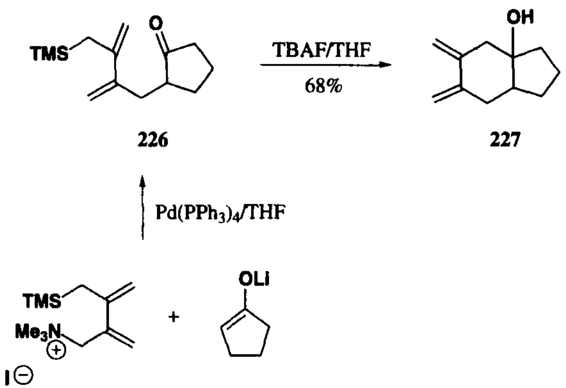


222

223

224

2-Dimethylaminomethyl-3-trimethylsilylmethylbuta-1,3-diene was treated with methyl iodide to give the corresponding ammonium salt **225** and the salt was treated with lithium enolate in the presence of a catalytic amount of $Pd(PPh_3)_4$ to afford the corresponding substitution product **226**. The allylation product was annulated by a cat. amount of TBAF to give indan **227**.[104]

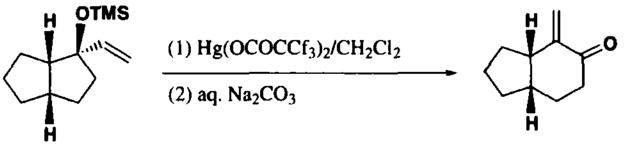


226

227

225

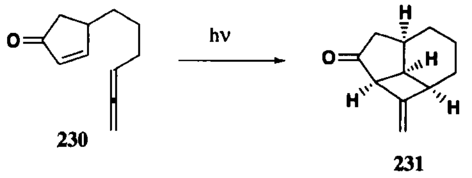
1-Alkenyl-1-cycloalkanol TMS ether **228** rearranged to the ring expanded β-mercuriocycloalkanones *via* mercurinium ion mediated ring expansion and was then converted into α-methylene indanone **229**.[105]



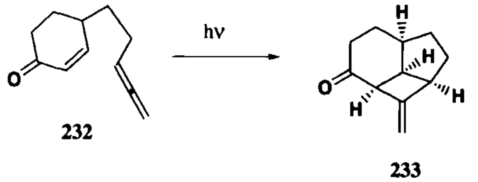
228

229

The intramolecular [2+2] photocycloaddition of 4-(allenic-substituted)-2-cycloalken-1-ones has been applied to the synthesis of indans.[106]

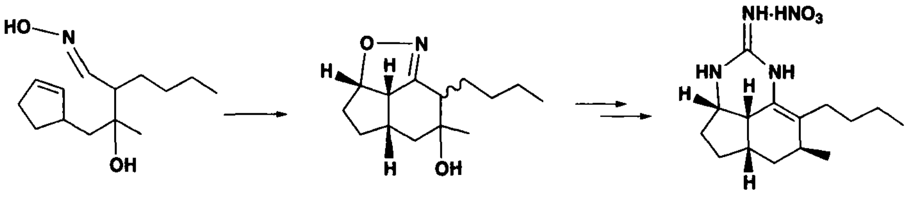


230 231



232 233

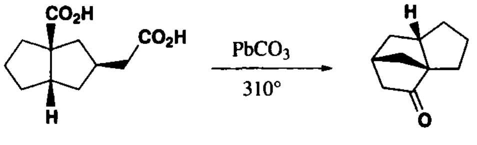
In a total synthesis of (±)-ptilocaulin, Hassner and coworkers utilized intramolecular INOC reactions.[107]



234 235 (±)-ptilocaulin

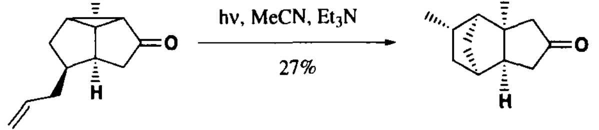
D. C_4-C_5 Bond Formation Methods

Reaction of carboxylic acid **236** with $PbCO_3$ at high temperature led to the formation of tricyclic indanone **237**.[108]



236 237

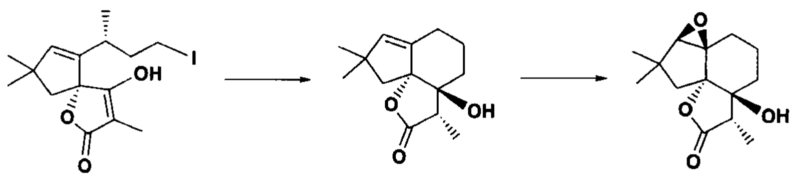
Reductive photoinduced electron transfer reactions have been performed with various bicyclic α-cyclopropyl substituted ketones and tertiary amines to give indans.[109]



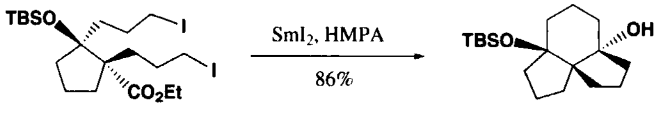
238 239

Intramolecular conjugate addition of a radical species to β-hydroxybutenolide is the pivotal step in an approach to alliacolide.[110]

Samarium(II) iodide has been employed on iodide **243** to promote a tandem intramolecular nucleophilic acyl substitution/intramolecular Barbier cyclization sequence, generating bicyclic and tricyclic ring system **244** which contain the indan skeleton in excellent yield and high diastereoselectivity.[111]

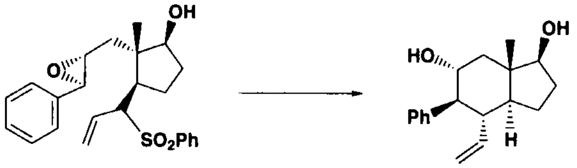


240 **241** **242**



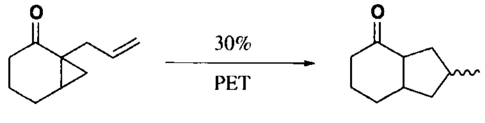
243 **244**

In a synthesis of an aromatic steroid, the key step was a highly stereoselective acid-catalyzed cyclization of an epoxystannane to give the indan skeleton.[112]

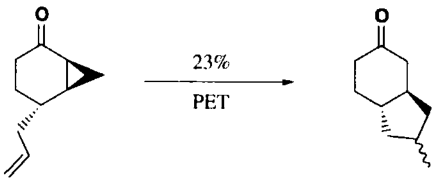


245 **246**

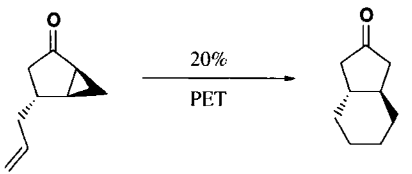
Irradiation of unsaturated bicyclo[3.1.0]hexanones under reductive photoinduced electron transfer conditions leads to regioselective cleavage of the cyclopropane moiety followed by cyclization to give indanone.[113]



247 **248**

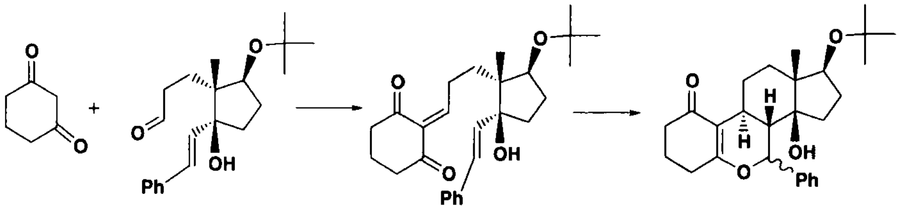


249 **250**



251 **252**

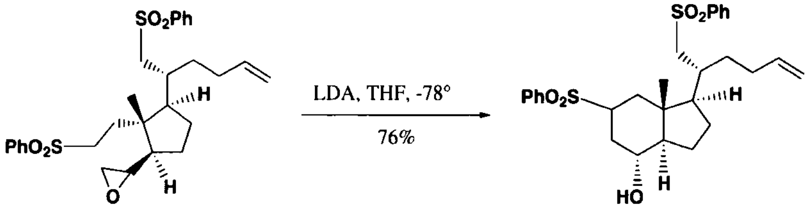
The synthesis of enantiomerically pure heterosteroid **255** possessing the indan skeleton has been achieved based on the tandem Knoevenagel-hetero-Diels-Alder reaction in the presence of a catalytic amount of ethylenediammonium diacetate (EDDA).[114]



253 **254** **255**

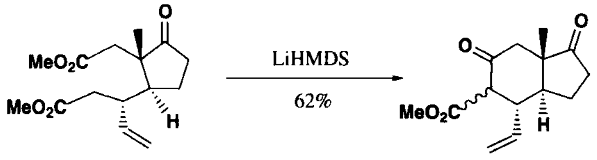
E. C_5-C_6 Bond Formation Methods

A highly diastereoselective total synthesis of indan **257** was achieved *via* a regiocontrolled C-C bond formation by an intramolecular epoxide ring opening reaction of the bissulfonyl epoxide **256** as a key step.[115]



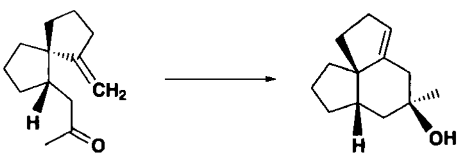
256 **257**

An optically active indanone **259** was synthesized *via* Dieckmann condensation of the corresponding dimethyl ester **258**.[116]



258 **259**

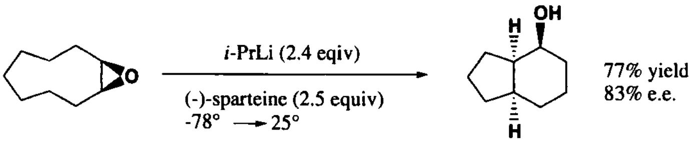
In a study of Mn(III) based oxidative fragmentation-cyclization reactions, Snider have reported enone **260** to undergo an intramolecular ene reaction on standing in $CDCl_3$ for 2 days to give indanone **261**.[117]



260 **261**

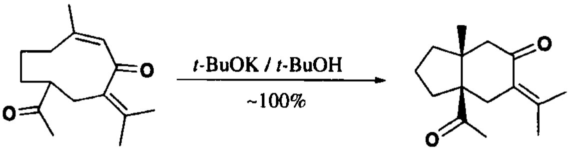
F. C_8-C_9 Bond Formation Methods

Enantioselective α-deprotonation-rearrangement of 9-membered cycloalkene-derived meso-epoxide **262** using organolithium in the presence of (-)-sparteine to give indan **263** in good yield and *ee* was reported.[118]



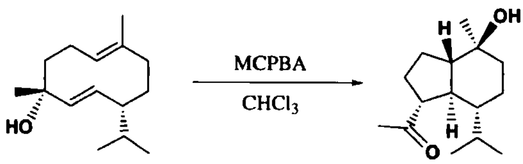
262 **263**

The presence of the enone system in the sesquiterpenoid **264** and the acyl group located in a suitable position for intramolecular Michael addition afforded the indan product **265** quantitatively, with base catalysis.[119]



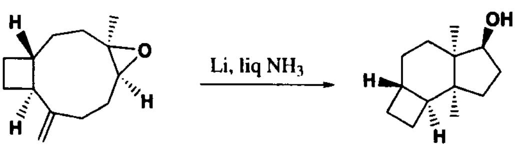
264 **265**

In a study of new cytotoxic hydroperoxygermacrane sesquiterpenes, Kitagawa and coworkers have synthesized the *ent*-oplopanone **267** by the oxidation of alcohol **266** with MCPBA in $CHCl_3$.[120]



266 **267**

The reduction of the 4,5-epoxy derivatives of the caryophyllene series with lithium in liquid ammonia gives the products from C-C cyclization with participation of the 8,13-double bond in addition to the normal reduction products, *i.e.*, the 4-hydroxy- and 5-hydroxycaryophyllene compounds.[121]



268 **269**

II. TWO-BOND DISCONNECTION APPROACHES

Various two-bond disconnection approaches to indan system are summarized in the following Scheme. References of these approaches are also summarized in the following Table.

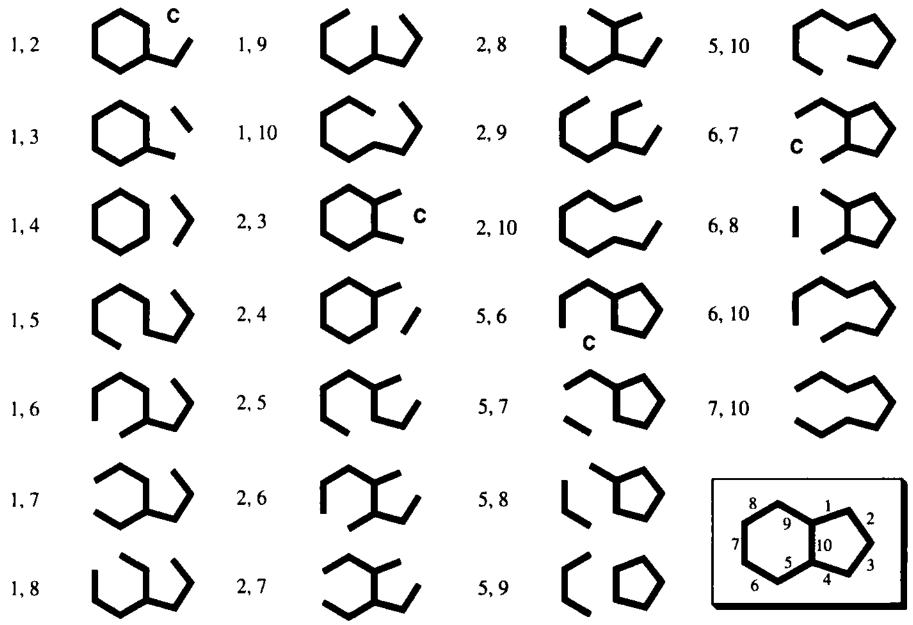
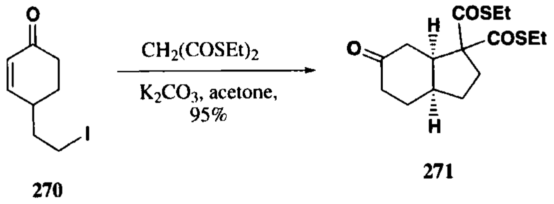


TABLE 1. References for the Two-Bond Disconnection Approaches to Indans

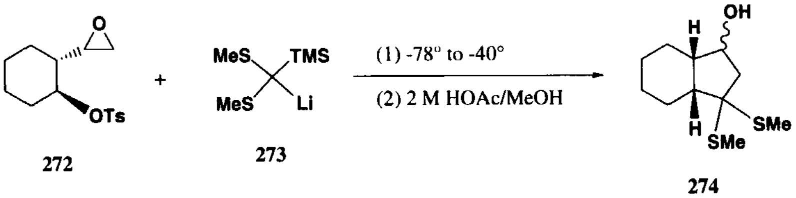
Bond Formation	Anion Alkylations	Lewis Acids	Cycloadditions	Transition Metal	Miscellaneous
1,2	122-124	125-128		129	
1,3	130-133	134-140		141, 142	143-147
1,4	148, 149	150-163		164, 165	166-169
1,5		170	171-173	174-175	176
1,8	177				178
1,9		179		180	
1,10					181, 182
2,3	183-198	199			200
2,4	201, 202	203-210		211-217	218-222
2,10	223, 224			225-228	229, 230
5,6	231				
5,7	232, 233		234-242		
5,8	243, 244			245	246
5,9	247, 248		249-254	255, 256	
5,10					257
6,7	258-260	261			
6,8	267-269		262-266		
6,10			270-278		

A. *Bond 1 and Bond 2 Formation Methods*

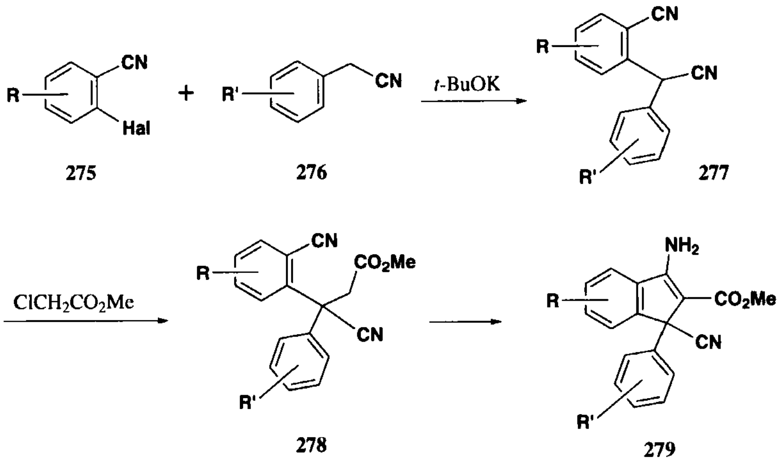
S, S'-Dimethyldithiomalonate undergoes concomitant alkylation reaction and Michael reaction with ω-iodo-α,β-unsaturated ketones **270** to give indanone **271**.[122]



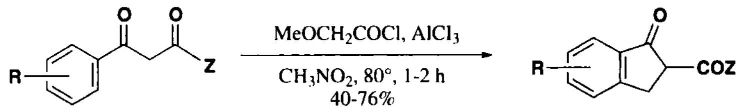
Synthesis of indans by a silicon-induced cascade reaction has been reported. The annelated indan product **274** from the substituted epoxy para-toluenesulfonate **272** provide an example of [4+1] cycloaddition reactions.[123]



A sequence of one-pot alkylation and cyclization for the synthesis of indans has been reported. 2-(cyanoaryl)arylacetonitriles **277**, obtained from O-halocyanoaromatics **275** and aryl acetonitriles **276** were alkylated with methyl chloroacetate under basic conditions. Subsequent Dieckman reaction gave the annulated 3-arylindans **279**.[124]



1-Oxo-2-acetylindans were synthesized by methylenation of aromatic β-dicarbonyl compounds with $MeOCH_2COCl \cdot AlCl_3$.[125]

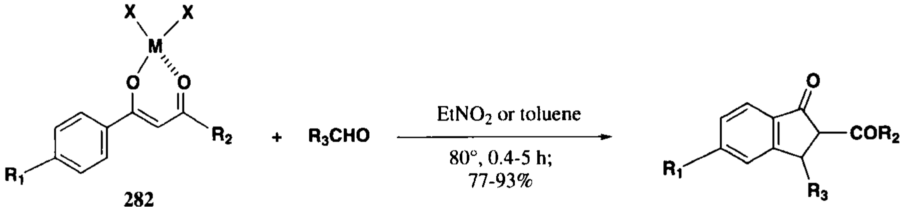


280

Z = OEt, Me
R = H, Me, OMe

281

Similarly, 1-oxoindans were synthesized by *bis*-alkylation of aromatic β-dicarbonyl compounds with enolizable aldehydes.[126]

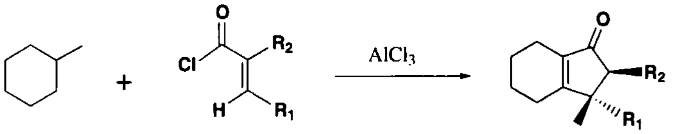


282

283

R$_1$ = H, Me, OMe; R$_2$ = OEt, Me; R$_3$ = H, Ar, CH=CH-Ar; M = MgBr(OEt$_2$), AlCl$_2$

Acylation of alkenes generated *in situ* by hydride transfer from isoalkanes has been applied to the synthesis of hydrindenones. The acylation, in the presence of AlCl$_3$ and a hydride acceptor, of methyl cyclohexane by ethylenic acyl chloride, in CH$_2$Cl$_2$ solution, gives the indenones. The yields are better than those two-step process involving acylation of alkenoyl chlorides and subsequent Nazarov cyclization of the resulting divinylketones.[127]



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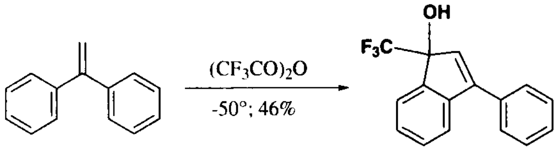
285

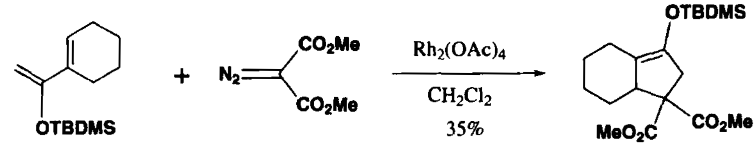
Reaction of 1,1-diphenylethylene **286** with trifluoroacetic anhydride activated by BF$_3$·SMe$_2$ complex leads to trifluoromethyl indenol **287**.[128]



286

287

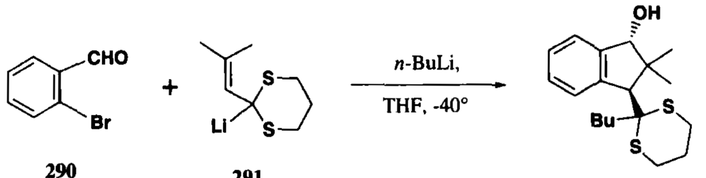
[4+1] Cycloadditions of the rhodium di(methoxycarbonyl) carbenoid to 2-siloxy-1,3-diene has been applied to the synthesis of indans. The possible mechanism was also discussed.[129]



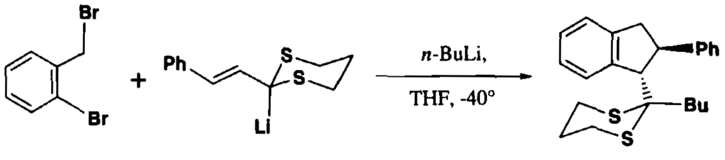
288 **289**

B. Bond 1 and Bond 3 Formation Methods

A cyclopentannulation sequence leading to indans was achieved by the addition of organolithiums to ketenethioacetals. The cyclization protocol is effected *via* the initial addition of 2-lithio-2-vinyl-1,3-dithiane to an aryl bromide leading to a ketenethioacetal. Transmetallation to the corresponding aryllithium, followed by an intramolecular 5-oxo-trig cyclization onto the ketenethioacetal moiety and subsequent alkylation afforded indans.[130, 131]

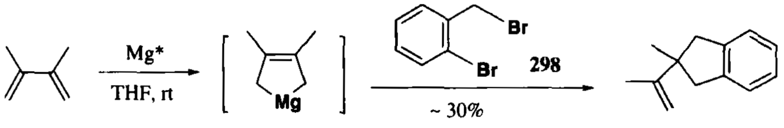


290 **291** **292**



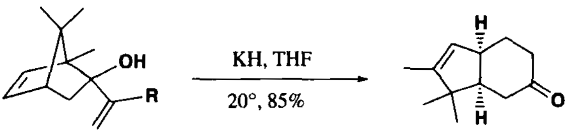
293 **294** **295**

Reaction of (2,3-dimethyl-2-butene-1,4-diyl)magnesium with arylbromide yields the indans.[132]



296 **297** **299**

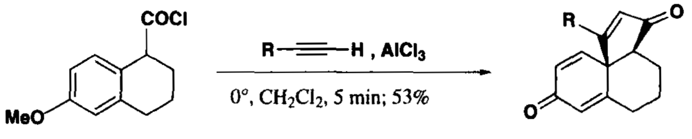
Anionic oxy-Cope rearrangements of alkoxides derived from camphor derivative **300** afford indanone **301** which are potential intermediates for the enantioselective synthesis of terpenoids.[133]



300
R = H, Me

301

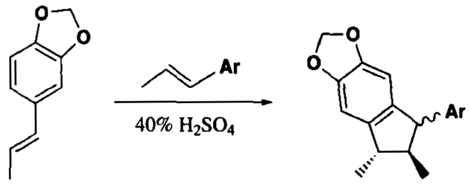
In a synthesis of potential aromatase P-450 inhibitors, Whiting and coworkers have reported a method for generating the indan moiety in the spirotricyclic compound from tetralins.[134]



302
R = Ph, *n*-propyl

303

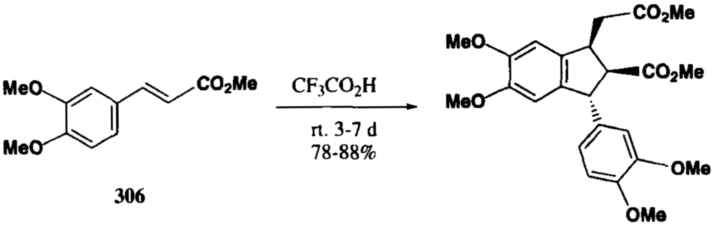
The reaction of benzylic cations with styrene affords dihydro(1H)indenes *via* a formal [3+2] cycloaddition.[135]



304

305

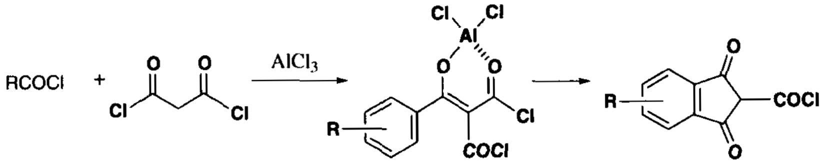
3,4-Disubstituted cinnamic acids and esters undergo cyclodimerization on treatment with CF_3CO_2H to yield the indan derivatives.[136]



306

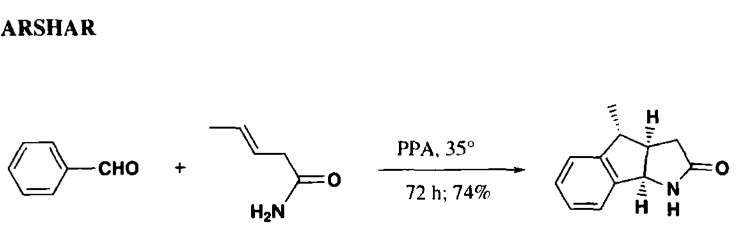
307

Various indan-1,3-diones have been prepared *via* a template Friedel-Crafts process, by sequential crosscondensation-cycloacylation of aromatic acyl chlorides and acetyl chloride or malonyl dichloride.[137]



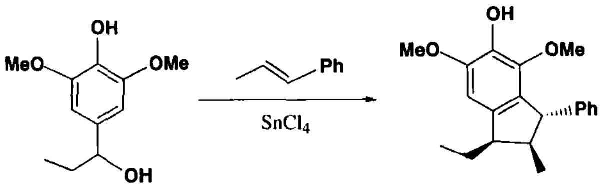
308

Condensation of 3-alkenamides with benzaldehyde in polyphosphoric acid, afford indans with a γ-lactam ring.[138]



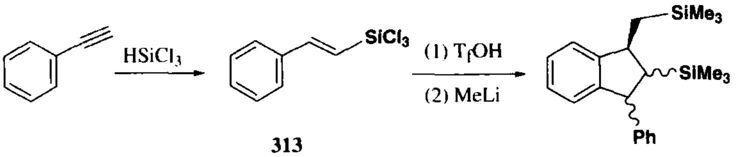
309 310

The Lewis acid-promoted intramolecular [3+2] cycloaddition of alkenes with benzylic cations derived from benzylic alcohols and quinone methides affords indans in good yield and stereoselectivity.[139]



311 312

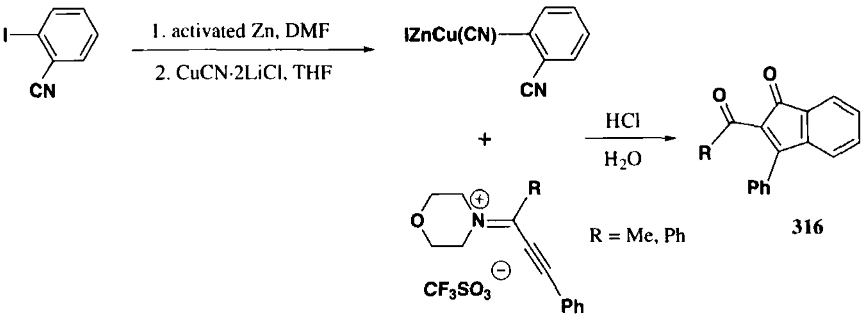
(E)-β-(Trichlorosilyl)styrene **313** dimerized when reacted with triflic acid to give indan derivative **314**.[140]



313

314

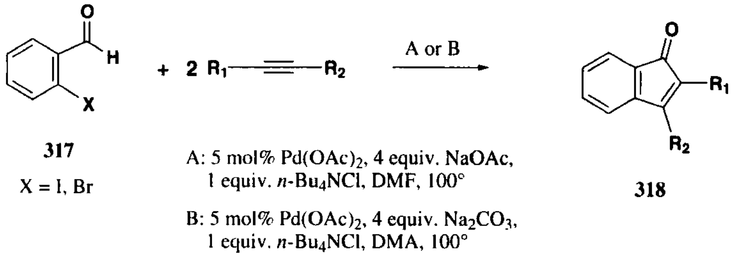
2-Acylindenones **316** are prepared *via* conjugated addition of functionalized organozinc and copper reagents to (2-propynylidene)morpholinium triflates **315**.[141]

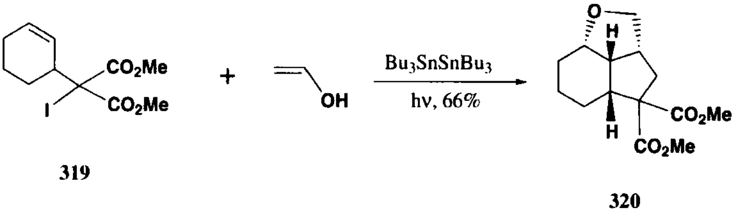


315

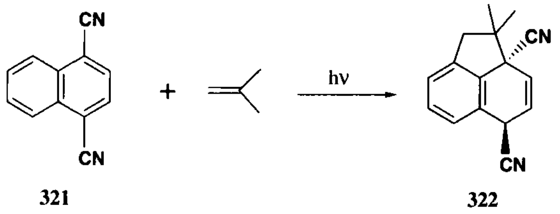
A number of 2,3-disubstituted 1-indenones have been synthesized *via* palladium-catalyzed annulation of internal alkynes and *o*-iodo- or *o*-bromobenzaldehyde.[142]

Atom transfer addition and annulation reaction of iodomalonate **319** with alkene affording indan derivatives **320** has been reported by Curran and co-workers[143]

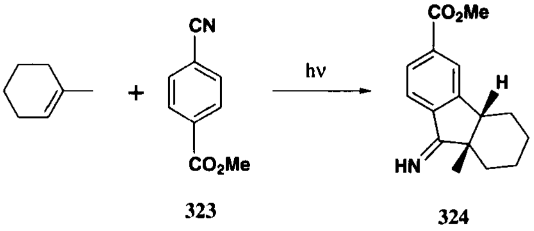




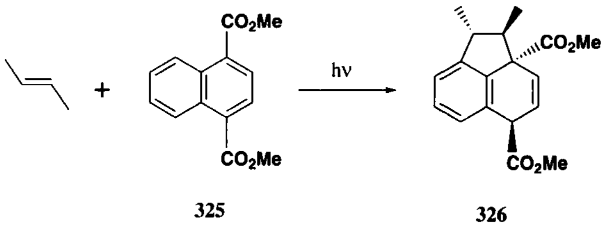
A 1,8-photoaddition of 1,4-naphthalene dicarbonitrile with alkenes to yield indenes was reported.[144]



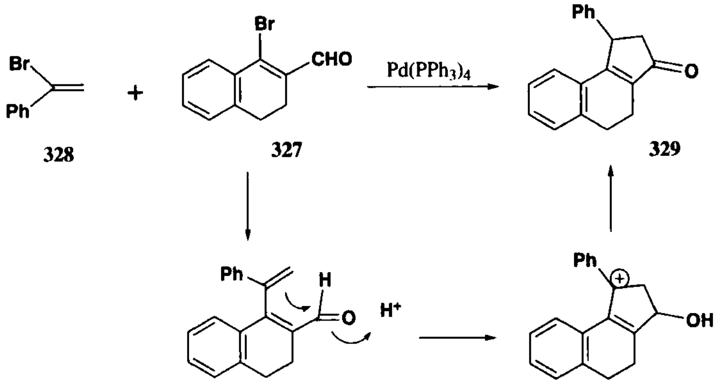
The photochemical reaction of alkenes and methyl cyanobenzoate was reported to afford indan products.[145]



Irradiation of dimethyl 1,4-naphthalenedicarboxylate **325** with various alkenes was found to give 1,8-photoaddition adducts bearing the indan skeleton.[146]



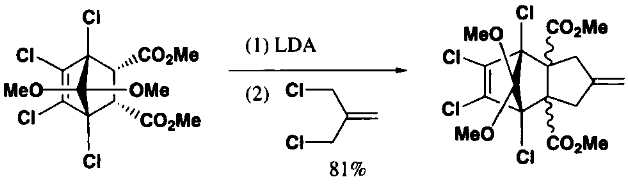
1-Bromo-3,4-dihydronaphthalene-2-carboxaldehyde **327** has been coupled with vinyl bromides, followed by cyclization, to give indanone **329**.[147]



328 **327** **329**

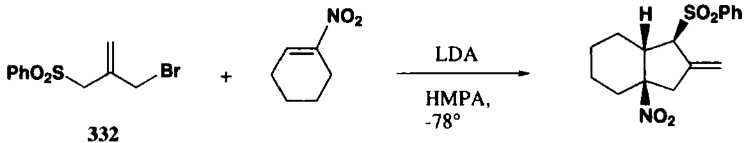
C. Bond 1 and Bond 4 Formation Methods

Treatment of the tetrachloro dimethylester **330** with LDA in THF followed by treatment of the resulting solution with 1 equivalent of 1,3-dichloroisobutylene gave the annelated indan product **331**.[148]

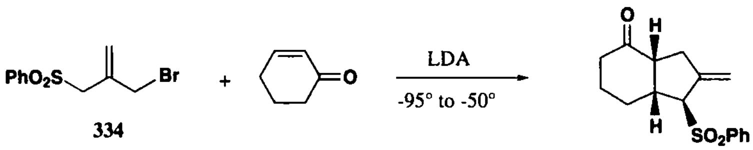


330 **331**

Synthesis of nitrohydrindan derivatives have been achieved *via* a tandem [3+2]-annulation by the reaction of 1-(phenylsulfonyl)-2-methylene-3-bromopropane with 1-nitrocyclohexene.[149]

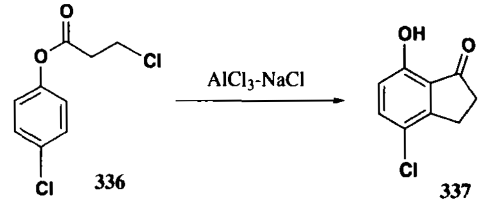


332 **333**

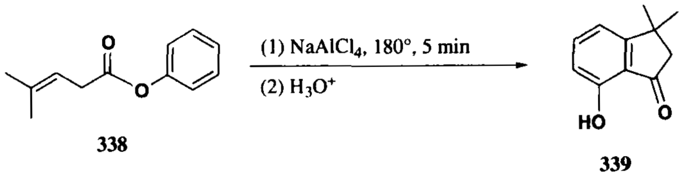


334 **335**

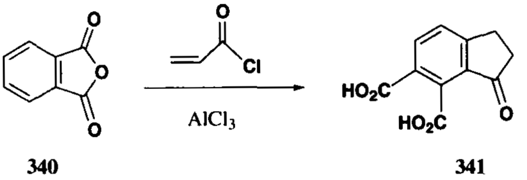
A Fries rearrangement, after an internal Friedel-Crafts reaction, was reported to afford indanones.[150]



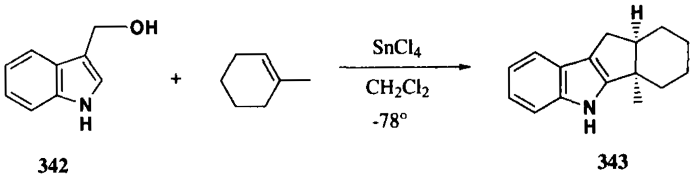
The key step in a total synthesis of (±)-isolongifolene was acomplished *via* Fries rearrangement and concomitant intramolecular cyclization of the phenolic ester to furnish the hydroxyindanone.[151]



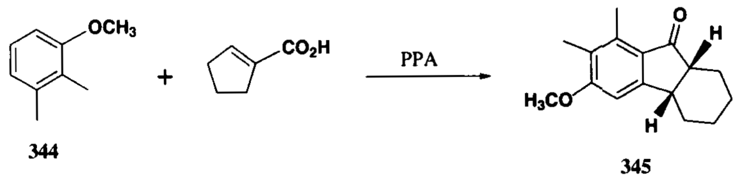
In a study of reactive annulenones, Gaviña and coworkers treated phthalic anhydride with acryloyl chloride to give the indanones.[152]



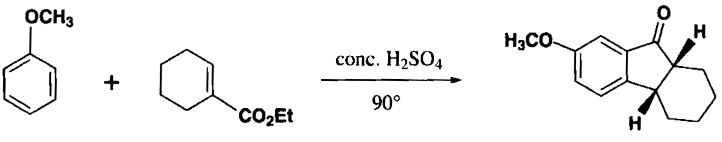
Treatment of indol-3-methanol **342** with $SnCl_4$ as Lewis acid in the presence of methylcyclohexene gives formal [3+2] addition of indolylmethyl cation to the alkene and furnishes the indan product.[153]



The reaction of substituted phenol ether **344** with 1-cyclopentene-1-carboxylic acid in the presence of polyphosphoric acid affords cyclopent[a]-inden-8(1H)-one **345**.[154]

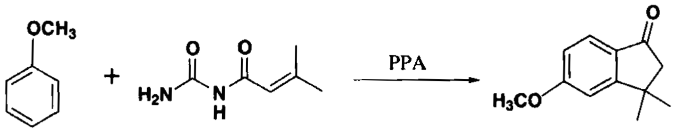


Ethyl cyclohexene-1-carboxylate undergoes reaction with aromatic substrates in the presence of concentrated sulfuric acid to give indanones.[155]



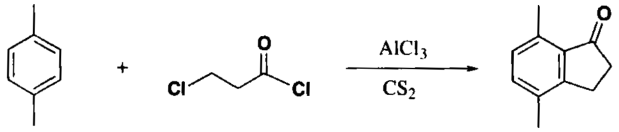
347 346 348

α,β-Unsaturated N-acylureas **349** react with aryl alkyl ether **350** in the presence of polyphosphoric acid to afford 5-methoxy-3,3-dimethyl-indan-1-one **351**.[156]



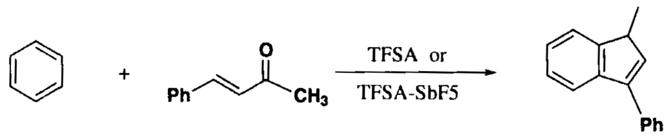
350 349 351

In a study of cyclophane chemistry, 1,4-dimethylindan-1-one **353** was prepared by treating *p*-xylene and β-chloropropanoyl chloride with $AlCl_3$.[157]



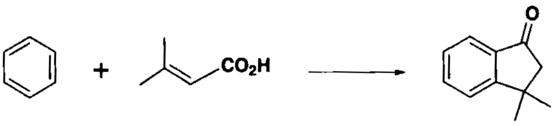
352 353

Acid-catalyzed reaction of cinnamaldehyde, 4-phenyl-3-butene-2-one, and related compounds with benzene in trifluoromethanesulfonic acid (TFSA) gives the corresponding phenylated indans.[158]



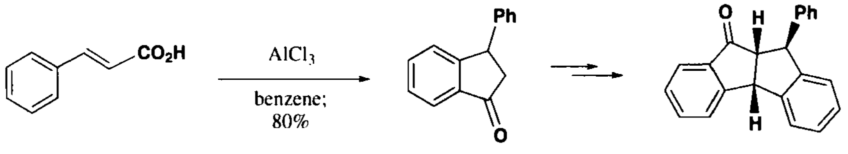
354 355

Reaction of 3-methyl-but-2-enoic acid with benzene has been reported to give 3-methyl-indan-1-one in 70% yield.[159]



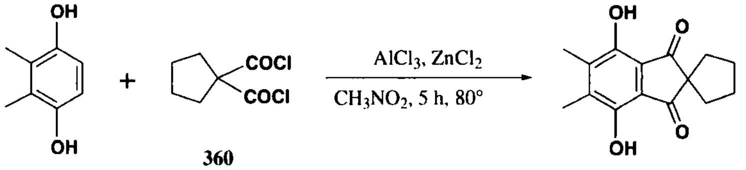
356

In the study of phenyl substituted C_s-diindans, Kuck and coworkers have prepared 3-phenyl-1-indanone by reaction of cinnamic acid with $AlCl_3$ in benzene.[160]



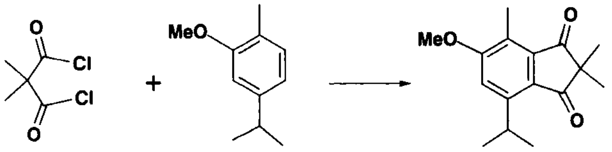
357 358

Reactions of various aromatic substrates and dicarboxylic acyl chlorides by using a 1:1 mixture of dry $AlCl_3$ and $ZnCl_2$ as Lewis acid promoter in nitromethane afford indandiones.[161]



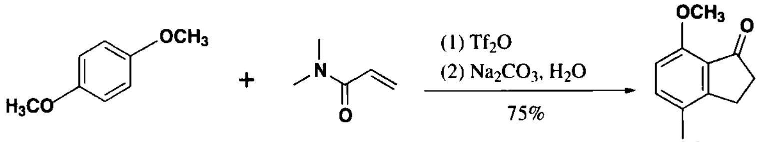
359 360 361

In a total synthesis of marine sesquiterpenoids containing a primnatriene skeleton, Meijere and coworkers have prepared the indandione **364** by Friedel-Crafts acylation of dimethylmalonyl chloride **362** and methyl phenyl ether **363**.[162]



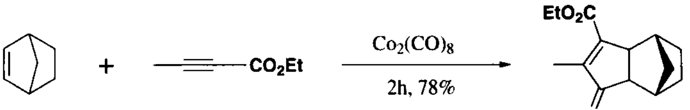
362 363 364

The reaction of N,N-dimethylacrylamide/trifluoromethanesulfonic anhydride complex with alkoxybenzenes followed by hydrolysis leads to the formation of indan-1-ones.[163]



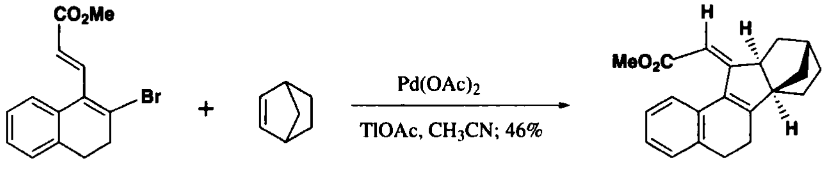
365 366 367

Pauson-Khand reaction with electron-deficient internal alkynes has been applied to the synthesis of indans.[164]



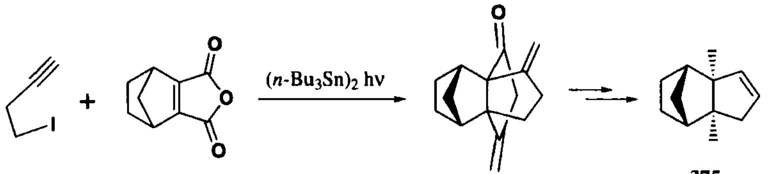
368 369 370

The vinyl bromide **371** reacted with norbornene to give the indan product **372** *via* palladium catalyzed [3+2] cycloaddition.[165]



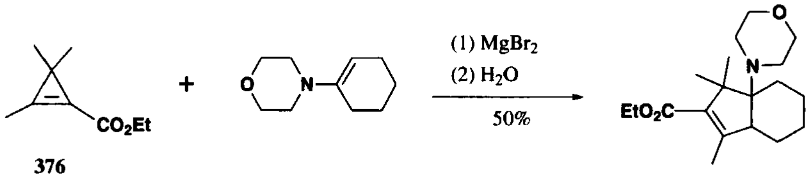
371 **372**

Radical annulation of propargyliodomalononitrile with cyclohexene was used for the preparation of indans.[166] Methylenecyclopentannulation initiated by radical addition of 3-butyn-1-yl to conjugated systems is a valuable method in organic synthesis. Its complementarity to the [2+3] cycloaddition is best illustrated in a concise synthesis of albene.[167]



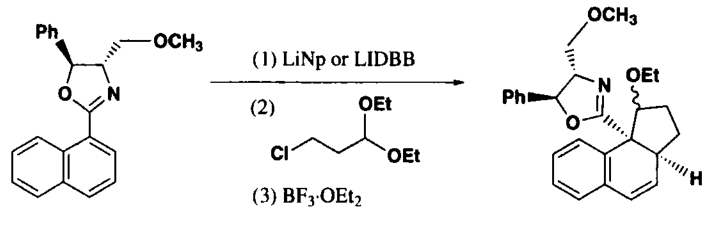
373 **374** **375**

Electrophilic cyclopropene esters reacted with 1-morpholinocyclohexene to give indans.[168]



376 **377**

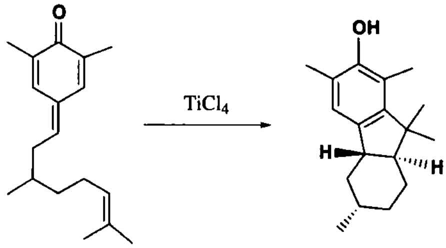
Reaction of lithium 4,4-di-*tert*-butylbiphenyl (LiDBB, Freeman's reagent) or lithium naphthalide (LiNp) with 3-chloropropanal diethylacetal, followed by addition of BF_3•OEt_2, gives indan derivatives.[169]



378 **379**

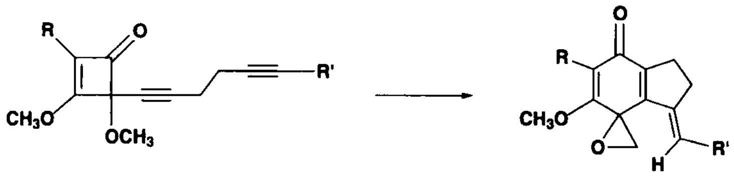
D. Bond 1 and Bond 5 Formation Methods

In a study of intramolecular formal [3+2] cycloaddition of alkenes and benzylic cations. Angel *et. al.* have reported a synthesis of indans *via* a bond 1 and bond 4 formation method. Treatment of quinone methide **380** with $TiCl_4$ at -78° afforded indan **381** in 88% as a single diastereomer.[170]



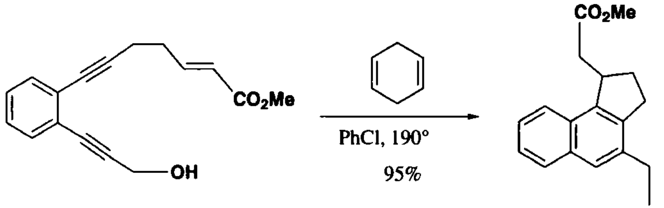
380 **381**

4-(1,5-Dialkynyl)-4-methoxycyclobutenone **382** was shown to undergo a unique rearrangement to afford the spiroepoxide indan **383**.[171]



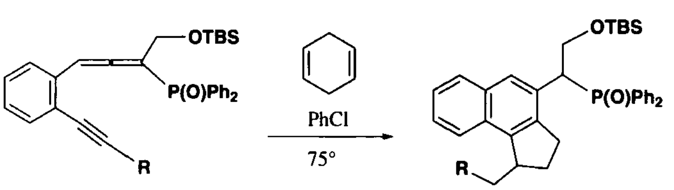
382 **383**

Enediynes possessing a tethered olefin radical acceptor can undergo a tandem enediyne-radical cyclization to yield dihydrobenzindene derivatives in good yield.[172]



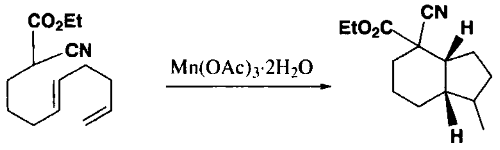
384 **385**

Tandem eneyne allene-radical cyclization *via* [2,3] sigmatropic shifts afford the indan derivatives.[173]



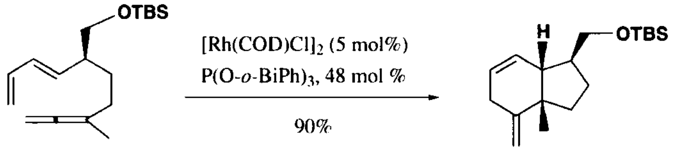
386 **387**

Oxidative free-radical cyclization of cyano acetate ester **388** in the presence of $Mn(OAc)_3$ afforded hydrindan **389**.[174]



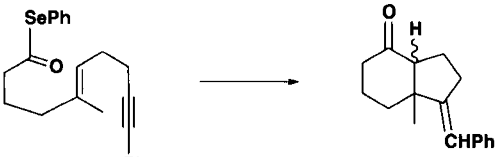
388 389

Transition metal-catalyzed intramolecular [4+2] diene-allene cyclization was reported as a convenient synthesis of angularly substituted indan systems.[175]



390 391

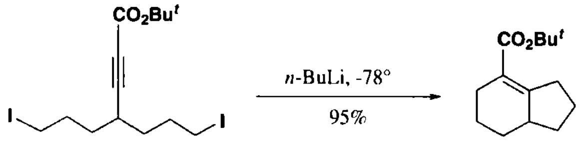
Selenide **392** was converted to indanone **393** *via* free-radical 5-*exo-dig* 5-hexynyl radical cyclization.[176]



392 393

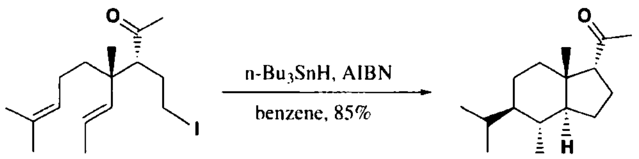
E. Bond 1 and Bond 8 Formation Methods

The lithium-iodine exchange-initiated intramolecular conjugate addition of γ-iodo-α,β-acetylenic esters affords indan derivatives in good yield.[177]



394 395

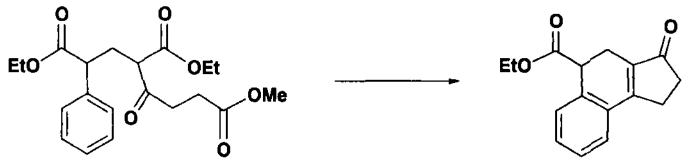
An efficient synthesis of the steroid CD-ring was accomplished by using tandem radical cyclization.[178]



396 397

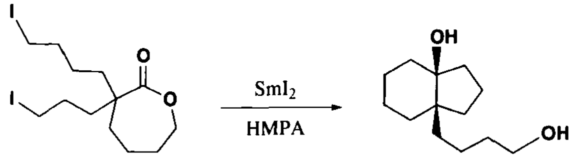
F. Bond 1 and Bond 9 Formation Methods

Reaction of the triester **398** with polyphosphoric acid gives cyclized indanone **399** in 66% yield.[179]

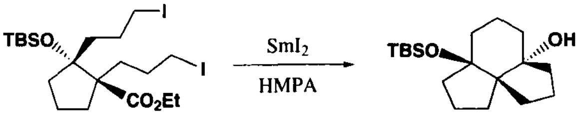


398 **399**

Samarium(II) iodide has been employed to promote a tandem intramolecular nucleophilic acyl substitution/intramolecular Barbier cyclization sequence to give indans.[180]



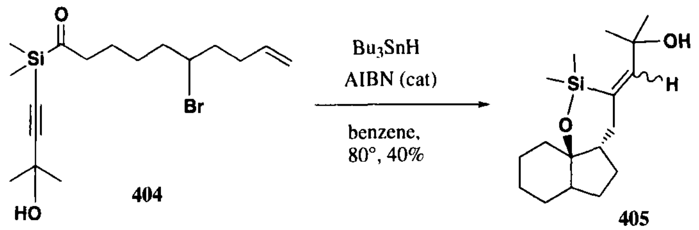
400 **401**



402 **403**

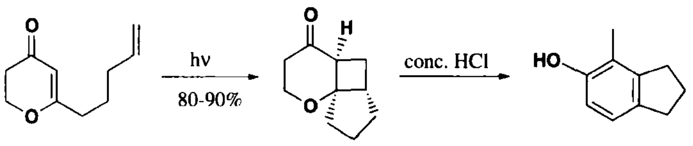
G. Bond 1 and Bond 10 Formation Methods

Tandem radical cyclizations of acylsilanes with alkene or alkyne functionalities attached to silicon afforded indans in reasonable yield.[181]



404 **405**

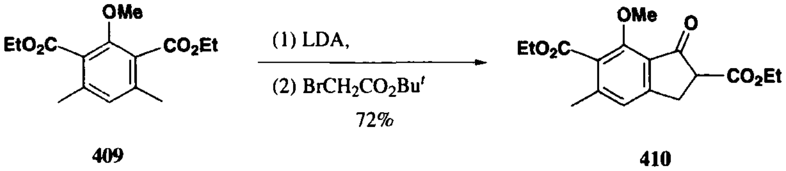
Intramolecular photocycloaddition of dihydro-4-pyrones to alkenes, followed by fragmentation and aromatic annulation provides indan derivatives.[182]



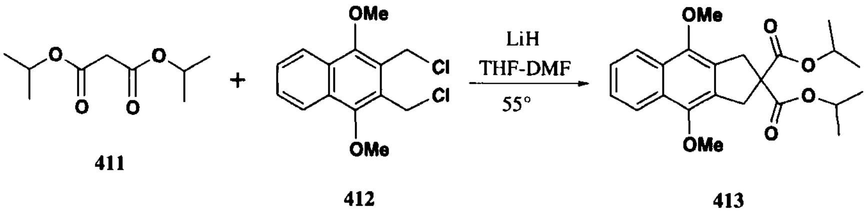
406 **407** **408**

H. Bond 2 and Bond 3 Formation Methods

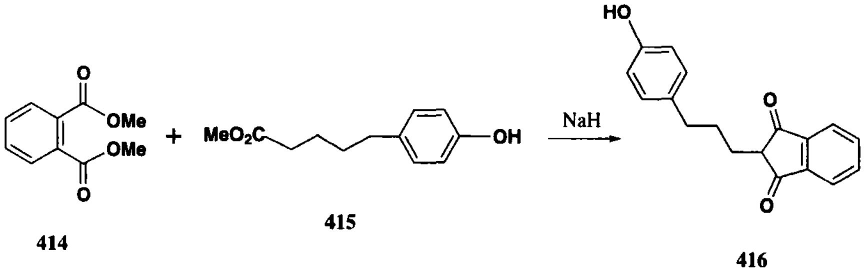
In the total synthesis of (±)-fredericamycin A, Julia and coworkers reported a metallation of a methyl group of aromatic compound to allow closure of the cyclopentanone ring by substitution with *tert*-butyl bromoacetate.[183]



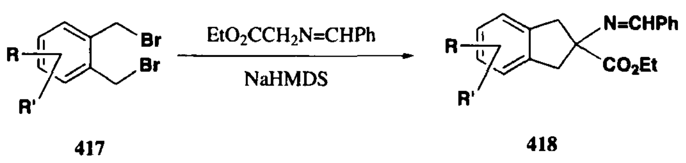
In an investigation of the lowest electronic states of osmium (I) tetratolylporphyrins, an indan derivative was prepared by tandem alkylations.[184]



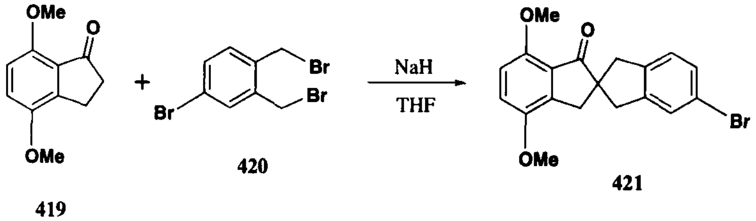
An indan derivative was synthesized by Kende *et. al. via* tandem alkylations.[185]



The benzylidene derivative of glycine ethyl esters **417** was alkylated with various dibromides to synthesize indans **418**.[186]

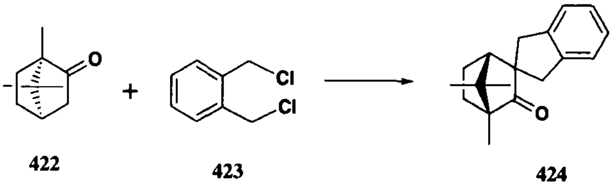


In the synthesis of porphyrin-quinone compounds, Sakata has employed the coupling reaction of ketones **419** and bromides **420** to afford the spiroketoindans **421**.[187]



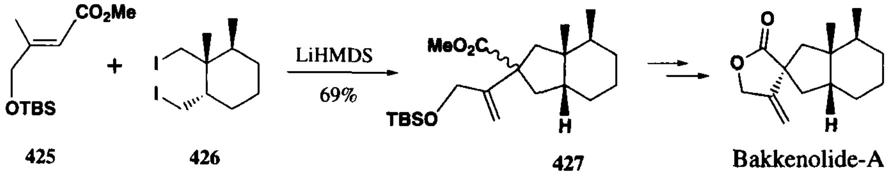
419 **420** **421**

Preparation of camphor indan derivative **424** was reported from the reaction of camphor and dihalide **423** with sodium amide.[188]



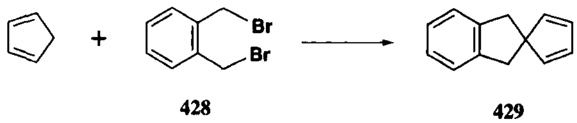
422 **423** **424**

In a total synthesis of (+)-bakkenolide A, Greene reported a lithium *bis*(trimethylsilyl)-amide-mediated cycloaddition of the lactone synthon with diiodide in DME-HMPA at -60° to give hydrindans.[189]



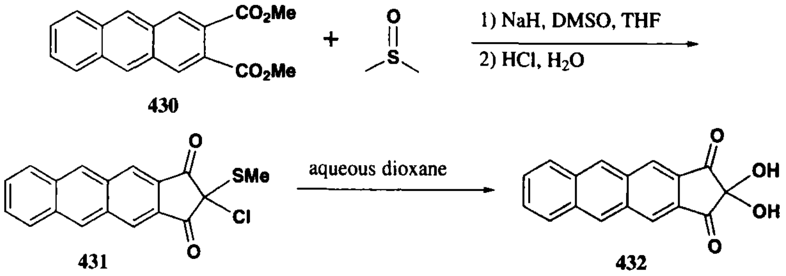
425 **426** **427** Bakkenolide-A

An indene derivative was prepared by the reaction of cyclopentadiene and α,α'-dibromo-*ortho*-xylene with NaH.[190]



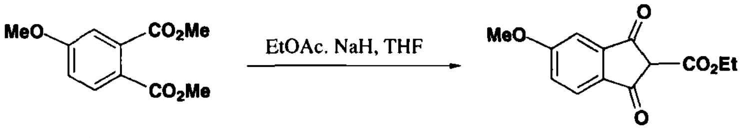
428 **429**

Condensation of diester **430** with dimsyl anion, NaH, followed by acidification with HCl provided naphtho[*f*]ninhydrin **432**.[191]



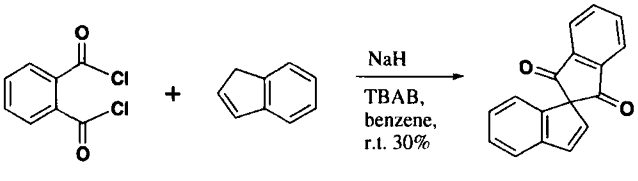
430 **431** **432**

In the same vein, Claisen condensation of diester **433** and ethyl acetate with NaH afforded 1,3-indandione **434** which was then used for the further synthesis of ninhydrins.[192]



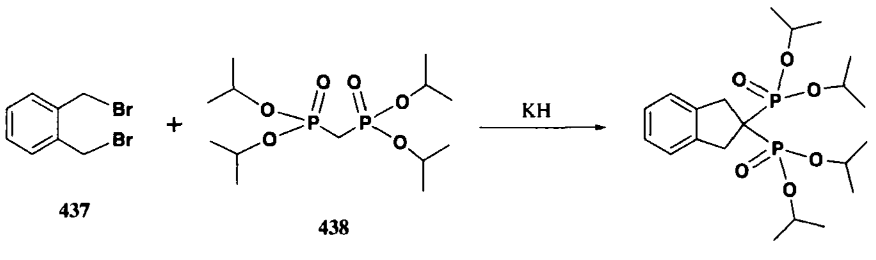
433 **434**

The indenyl dianion, generated by two equivelants of NaH and indene was spiro-acylated by quenching with phthaloyl chloride in the presence of phase transfer catalyst, to give spiro[4,4]ene-dione system.[193]



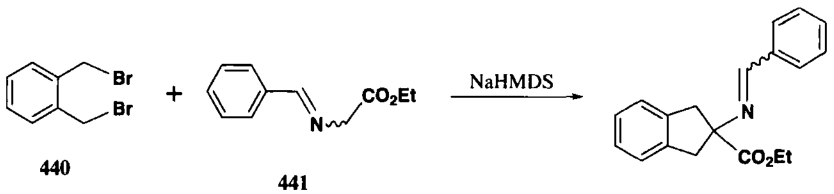
435 **436**

The dianion alkylation of phosphonoalkylphosphirate **438** to the dibromide **437** was used in the preparation of a series of bone antiresorptive phosphonates.[194]



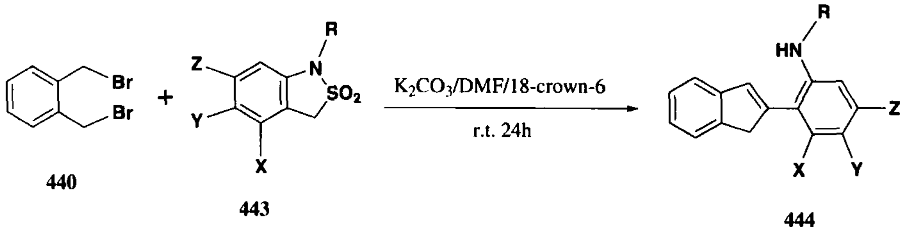
437 **438** **439**

The benzylidene derivative of glycine ethyl ester was alkylated with various electrophiles to synthesize cyclic α-amino acids bearing the indan skeleton.[195]



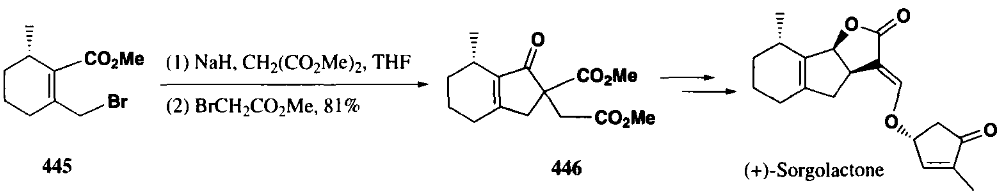
440 **441** **442**

2-Phenylindene derivatives were generated *via* alkylation of dibromide **440** and 1,3-dihydro-2,1-benzisothiazole-2,2-dioxides, followed by extrusion of SO_2 and 1,5-H shift.[196]

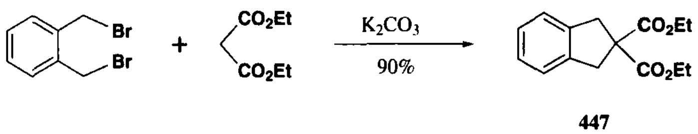


X = NO_2, H
Y = H, CH_3, F, OCH_3
Z = H, NO_2
R = CH_3, CH_2Ph

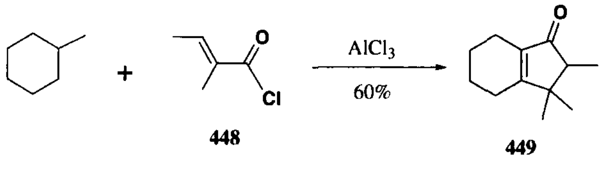
In a synthesis of (+)-sorgolactone, isolated from Sorghum bicolor as the germination stimulant for parasitic weeds, Mori and coworkers constructed the indan skeleton *via* malonate alkylation and Dieckmann condensation.[197]



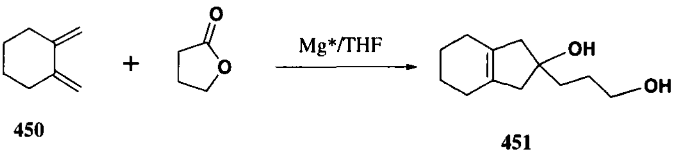
bis(Bromomethyl)benzene was condensed with diethyl malonate under basic conditions to give the indan derivative. Similar alkylation procedure for both the dibromide and dichloride with different alkylating agents were also reported.[198]



Acylation of methylcyclohexane in the presence of $AlCl_3$ and a hydride acceptor by ethylenic acyl chloride gave indan derivatives. The hydride acceptor could be either acetyl chloride or the alkenoyl chloride itself.[199]

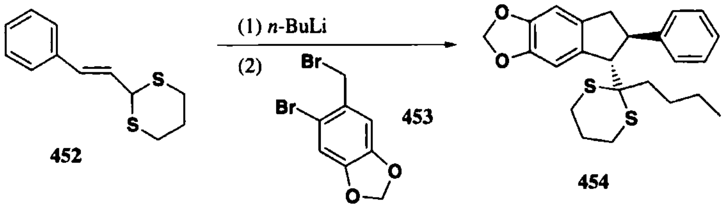


Reaction of the magnesium complexes of substituted 1,3-diene with either carboxylic esters or lactones led to formation of various derivatives.[200]

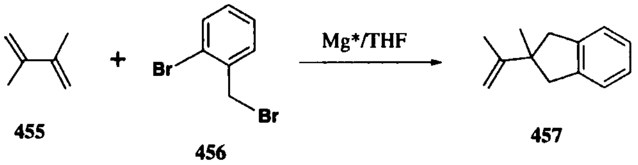


l. Bond 2 and Bond 4 Formation Methods

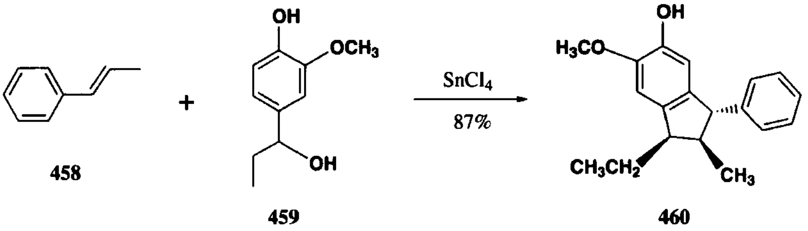
A facile cyclopentannulation sequence leading to the rapid preparation of highly substituted indans is reported. The novel cyclization protocol was proposed *via* the initial union of an aryl bromide with a 2-lithio-2-vinyl-1,3-dithiane leading to a ketenethioacetal. Transmetallation to the corresponding aryllithium, by addition of an alkyllithium reagent, next effects an intramolecular 5-*exo-trig* cyclization onto the ketenethioacetal moiety, leading to an indan intermediate. Subsequent in situ alkylation of this intermediate with the alkyl bromide generated as a consequence of transmetallation then completes the sequence.[201]



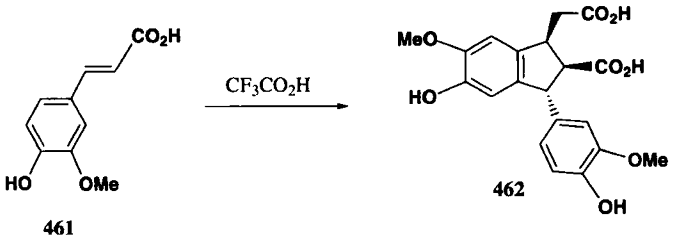
Highly reactive magnesium reacts with a variety of substituted 1,3-dienes, followed by treatment of α,ω-alkylene dihalides to form indans.[202]



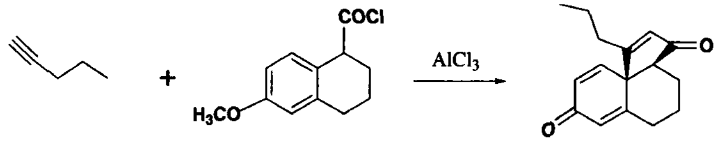
Reaction of benzylic cations generated from quinone methides and benzylic alcohols with styrenes affords dihydro(1H)indans *via* formal [3+2] cycloaddition.[203]



A dimerization of 3,4-disubstituted cinnamic acid and esters led to the formation of highly substituted indans.[204]

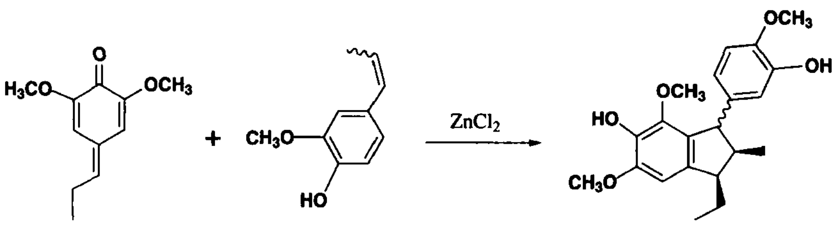


In a study of the synthesis of aromatase inhibitors, Whiting synthesized the tricyclospirodienes *via* an addition-cyclization reaction with alkynes and acid chloride, catalyzed by $AlCl_3$.[205]



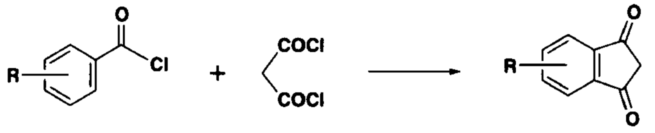
463 464

Synthesis of dihydro-1*H*-indenes *via* the formal [3+2] cycloaddition of electron-rich alkenes and *p*-quinone methide was reported.[206]



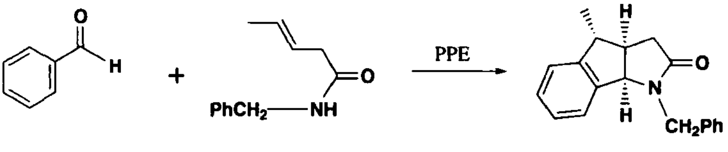
465 466 467

Various indan-1,3-diones have been prepared by sequential cross-condensation-cycloacylation of aromatic acyl chlorides and malonylchloride.[207]



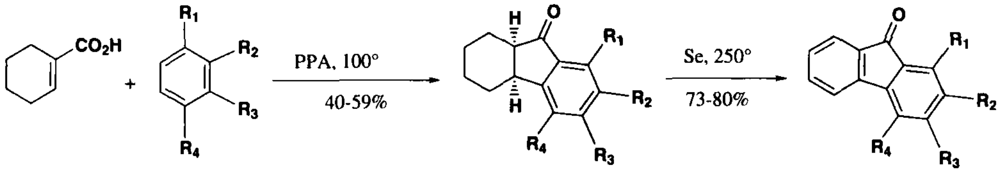
468 469

Condensation of 3-alkenamides **470** with benzaldehyde in polyphosphate ester leads to a γ-lactam ring **471** with the indan skeletone.[208]



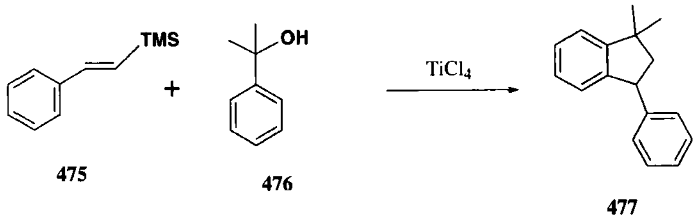
470 471

Cyclohexene-1-carboxylic acid reacted with various aromatic compounds in the presence of polyphosphoric acid at 100° to give indan derivatives, followed by dehydrogenation to give the fluoren-9-ones.[209]

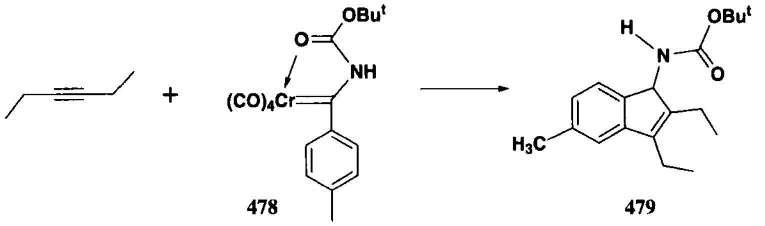


472 473 474

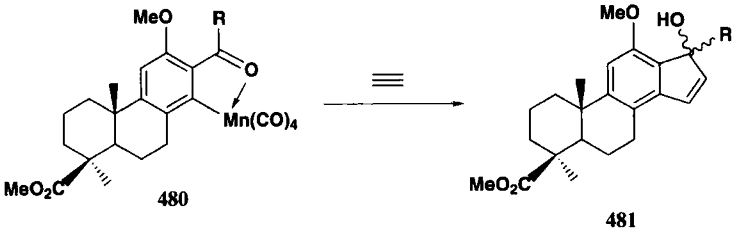
(E)-β-(Trimethylsilyl)styrene **475** reacts with $PhMe_2C^+$ generated from $TiCl_4$ and $PhCMe_2OH$ to give the indan derivative **477**.[210]



The annulation of Fischer type aminocarbene complexes **478** with alkynes led to indenes **479** in good yield.[211]

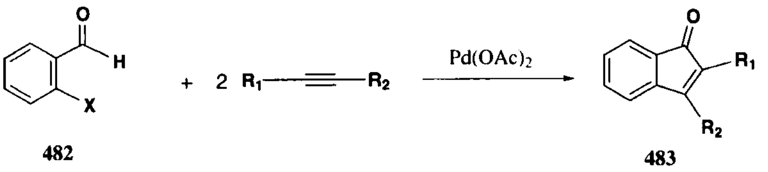


Reaction of the tetracarbonylmanganese complex **480** derived from a diterpenoid aryl aldehyde (or ketone) with acetylene (or ethylene) leads to cyclopentaannulation to give indenols **481**.[212]



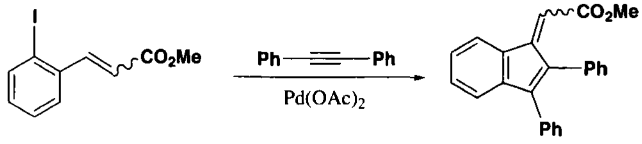
R = H, Me

A number of 2,3-disubstituted 1-indenones **483** have been prepared by treating *o*-iodo- or *o*-bromobenzaldehyde **482** with various internal alkynes in the presence of a palladium catalyst.[213]



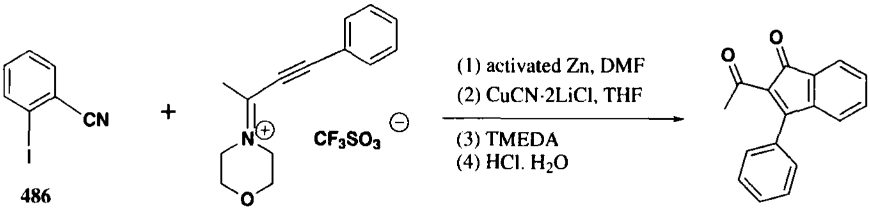
X = I, Br

The aryl halide **484** reacts with diphenylacetylene in the presence of $Pd(OAc)_2$ to give indan **485** *via* the [3+2] processes.[214]



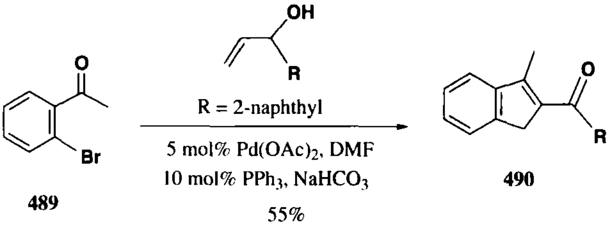
484 **485**

A zinc-copper reagent, prepared *in situ* from aryliodides, undergoes conjugate addition to the (2-propynylidene)morpholinium triflate to give 2-acylindenones, which result from cyclization of the initially formed morpholinoalleneS.[215]



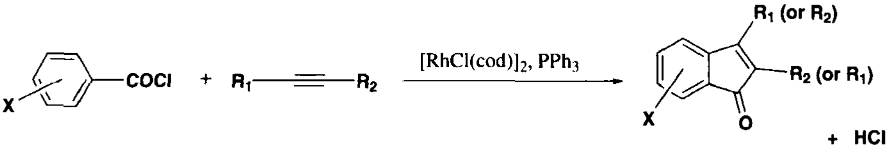
486 **487** **488**

o-Bromoacetophenone **489** reacted with allylic alcohols to give the substituted 1*H*-indene **490**.[216]



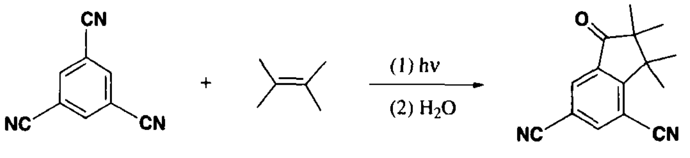
489 **490**

Aroyl chlorides **491** react with terminal alkynes accompanied by decarboxylation in the presence of a catalytic amount of $[RhCl(cod)]_2$ and PPh_3 to give the corresponding indan derivatives **492**.[217]



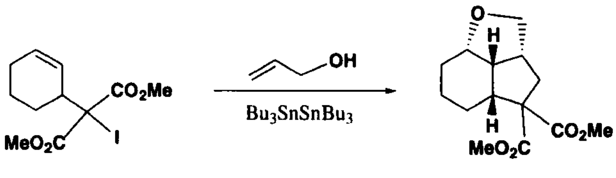
491 **492**

Photoinduced electron-transfer of 1,3,5-tricyanobenzene **493** with 2,3-dimethylbut-2-ene leads to a novel annulation to give an indan derivative **494**.[218]



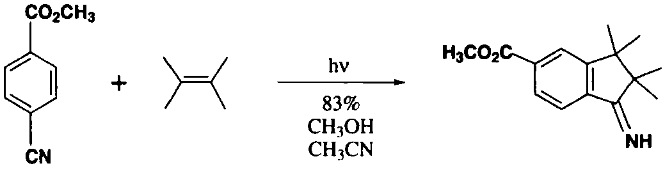
493 **494**

Atom transfer addition and annulation reactions of iodomalonate **495** with alkene give indan derivative **496**.[219]



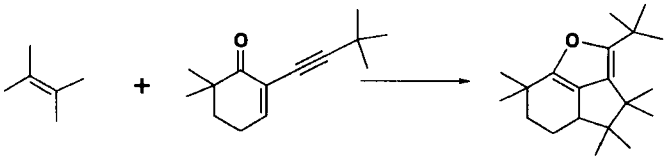
495 **496**

Irradiation of an acetonitrile-methanol (3:1) solution of methyl 4-cyanobenzoate and 2,3-dimethyl-2-butene gives the iminoindan **498** as the only significant product.[220]



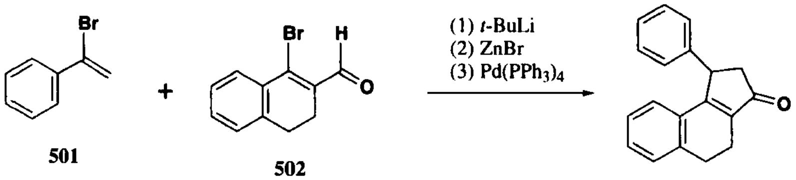
497 **498**

[3+2] Photocycloaddition of 2-alkynyl-substituted cyclohexenone **499** with alkenes leads to tricyclic furan indan **500**.[221]



499 **500**

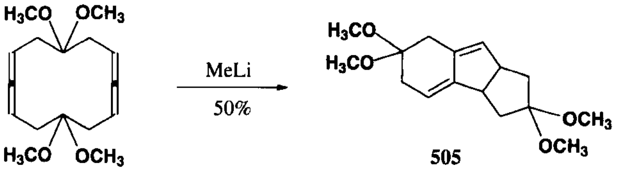
Reaction of 1-(phenylethenyl)zinc bromide, generated by the reaction of α-bromostyrene **501** with *t*-BuLi, followed by addition of ZnBr, with bromoaldehyde **502** in the presence of Pd(PPh_3)$_4$ gives the indan derivative. The expect product of simple coupling may have formed, but then underwent a cyclization reaction.[222]



501 **502** **503**

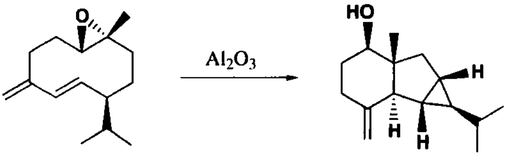
J. Bond 2 and Bond 10 Formation Methods

Treatment of the monocyclic diallene **504** with methyllithium in refluxing ether led to the formation of tricyclic compound **505**.[223]



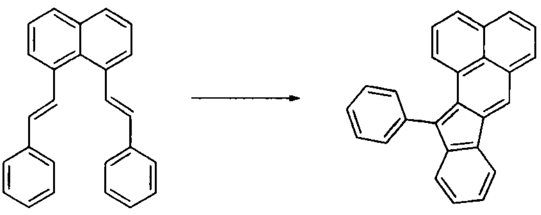
504 505

Epoxygermacrene-D **506** was treated with basic alumina to afford a new type of sesquiterpene **507** in quantitative yield which could be converted into oppositol- and axisonitrile- type sesquiterpenes.[224]



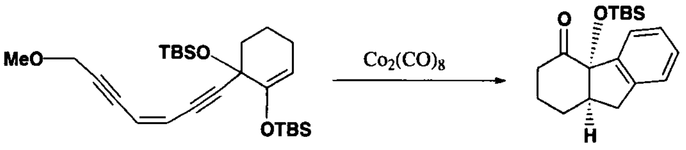
506 507

Reaction of 1,8-*bis*(arylethynyl)naphthalene **508** with mercuric acetate led to the formation of indeno[2.1-*a*]phenalene **509**.[225]



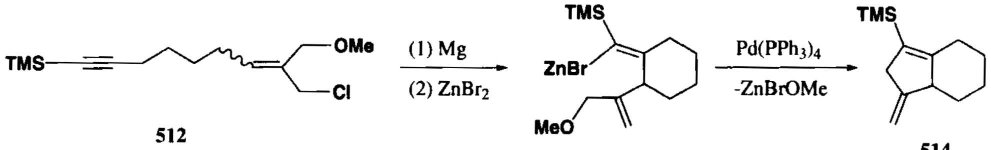
508 509

In a synthetic study of antibiotics esperamicin A_1 and calicheamicin γ_1, Magnus *et. al.* have synthesized the indans *via* dicobalt hexacarbonyl alkyne complexes.[226]



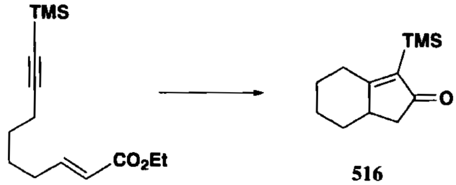
510 511

Intramolecular zinc-ene 3-(alkynyl)-2-(methoxymethyl)-2-propenylzinc bromide gave the carbometallation product, which on Pd (0)-catalyzed cyclization was converted to 1,5 annulated 4-methylenecyclopentenes.[227]



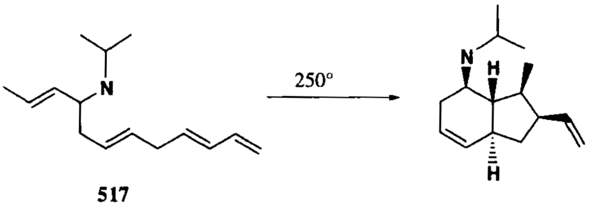
512 **513** **514**

A facile construction of indans was achieved by tandem cyclization of *bis*-unsaturated esters mediated by (η^2-propene)TiX_2 (X=Cl or O-*i*-Pr), generated *in situ* from Ti(O-*i*-Pr)$_3$Cl (1.2 eq) and *i*-PrMgCl.[228]



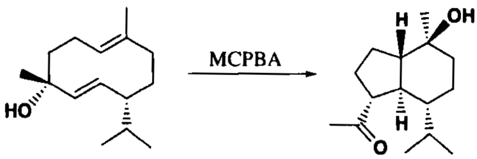
515 **516**

Cope reaction and intramolecular Diels-Alder cyclization of polyenes **517** lead to regio- and stereoselective synthesis of dehydroindans **518**.[229]



517 **518**

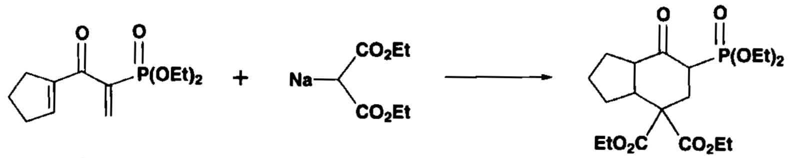
Oxidation of nephthenol **519**, a germacrane sesquiterpene marine natural product, with MCPBA in $CHCl_3$ provide *ent*-oplopanone **520**.[230]



519 **520**

K. Bond 5 and Bond 6 Formation Methods

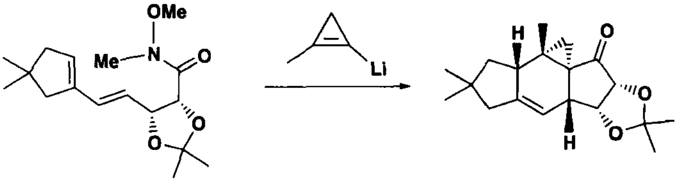
The indan ring skeleton was constructed by utilizing 1-(cyclopent-1-enylcarbonyl)vinyl phosphonates as a annulating reagents.[231]



521 **522** **523**

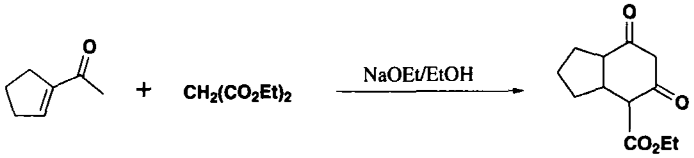
L. Bond 5 and Bond 7 Formation Methods

The reaction of N-methoxy-N-methylamide **524** with methylcyclopropenyllithium in ether, followed by a spotaneous intramolecular Diels-Alder reaction, gave the pentacyclic ketone **525** in 65% yield. The indanone was then used in the total synthesis of (±)-isovelleral.[232]



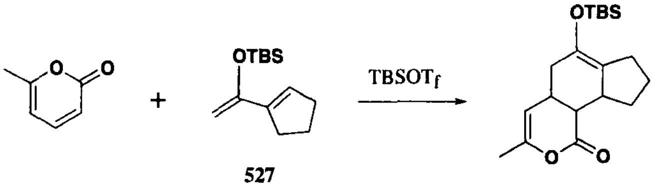
524 **525**

Reaction of diethyl malonate and 1-cyclopent-1-enyl-ethanone with sodium in refluxing ethanol led to the formation of indandione **526**.[233]



526

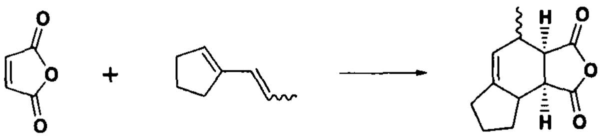
[4+2] Cycloaddition reaction of 6-methyl-2*H*-pyran-2-one with 2-(trialkylsilyl)oxy dienes in the presence of tert-butyldimethylsilyl triflate gave indan derivatives.[234]



527

528

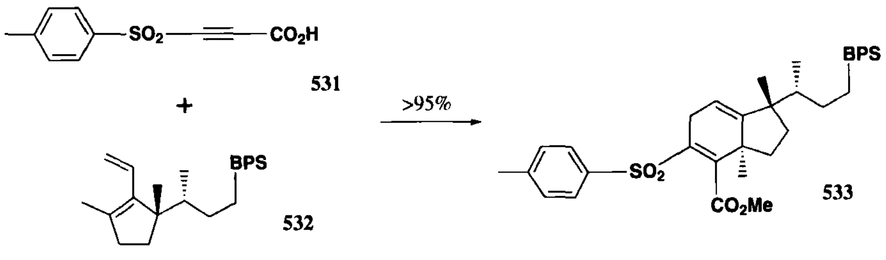
Diels-Alder reactions of maleic anhydride with 1-vinylcyclohexene in $CHCl_3$ afforded the indan adduct **530**.[235]



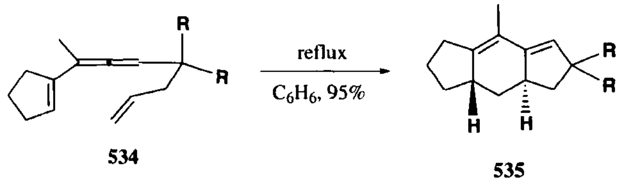
529

530

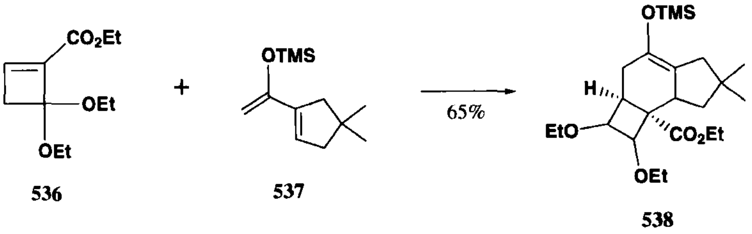
In a total synthesis of glycinoeclepin A, Corey reported a Diels-Alder reaction of diene **532** with 3-(*p*-toluene-sulfonyl)propiolic acid **531** proceed with position specificity to give the indan adduct **533** in excellent yield.[236]



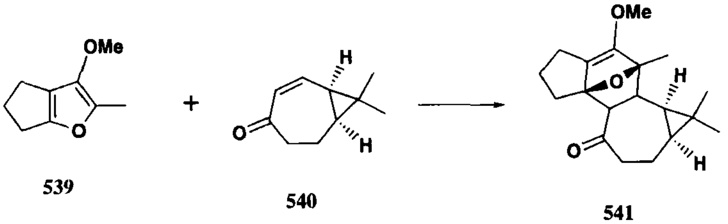
In a concise synthesis of (+)-sterpurene, Okamurta reported a cyclization of vinylallene **534** to afford the indan compound **535** in excellent yield.[237]



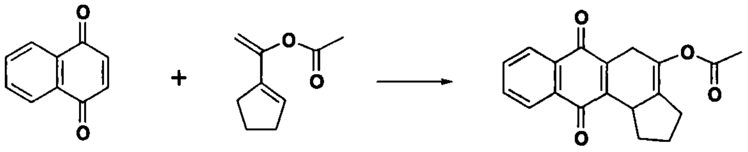
In a synthesis of formannosin and illudol, Semmelhack *et. al.* reported a Diels-Alder reaction of siloxy diene **537** and cyclobutene **536** to construct the indan skeleton.[238]



In a total synthesis of (+)-jatropholones A and B, Smith and coworkers reported a high-pressure (5 kbar) Diels-Alder reaction of furan **539** and enone **540** to construct the indan framework.[239]

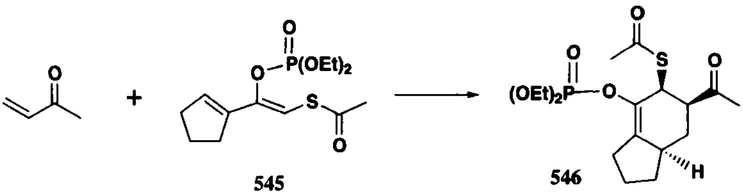


In a synthesis of cyclopentanthraquinones, analogs of mitomycin C, Su *et. al.* reported a Diels-Alder reaction of naphthoquinone **542** and diene **543** to afford the indan derivatives **544**.[240]



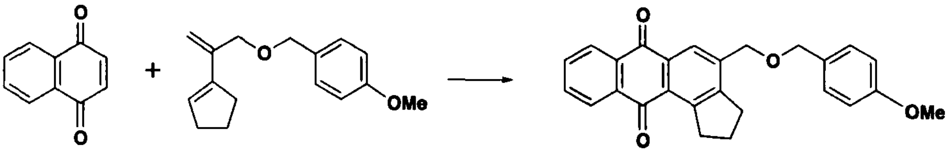
542 543 544

Thermal and Lewis acid catalyzed Diels-Alder reaction of (Z)-1,2-diheterosubstituted-1,3-dienes and dienophiles proceed with regio- and stereoselectivity and provide a route to the indan derivatives.[241]



545 546

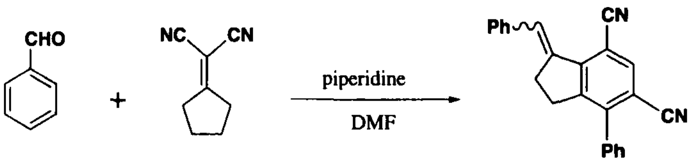
A series of mitomycin C analogs were synthesized *via* Diels-Alder cyclization of naphthoquinone with 1-vinylcyclopent-1-enes.[242]



547 548 549

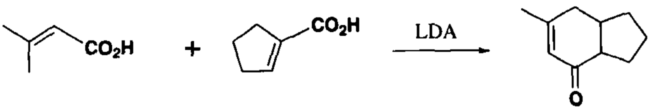
M. Bond 5 and Bond 8 Formation Methods

It was reported that instead of the Knoevenagel condensation of cyclopentylidene-malononitrile with aromatic aldehydes, a complex reaction takes place, leading to 5,7-dicyano-1-arylidene-4-arylindans. The same compounds were formed in the reaction of the cyclopentylidenemalononitrile dimer with aldehydes.[243]



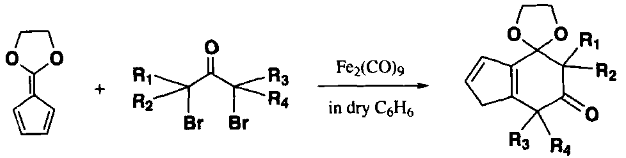
550 551

Indenone was prepared by tandem Michael-Dieckmann addition of lithium dienediolates of acyclic and alicyclic unsaturated carboxylic acids to the lithium salts of other unsaturated carboxylic acids.[244]



552

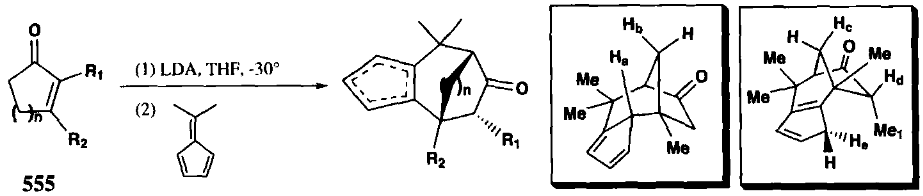
A novel [6+3] cycloaddition of 2-oxyallyl cation and fulveneketene acetal is described which provides a conceptually novel methodology for the synthesis of indan ring systems.[245]



553 **554**

R_1, R_2, R_3, R_4 = H or CH_3 or C_2H_5 or i-C_3H_7 or C_6H_5

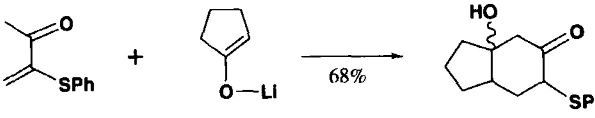
A highly efficient and stereoselective approach to the tricyclo-[5.3.0.n^{2,5}]alkan-4-one system has been achieved *via* the intermolecular double Michael reaction of lithium dienolates to fulvene.[246]



555 **556**

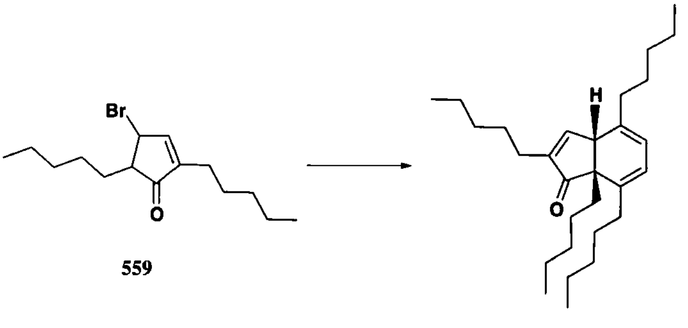
N. Bond 5 and Bond 9 Formation Methods

The annulation reaction of 2-phenylthiobut-1-en-3-one **557** with 1 equiv. of lithium cyclopent-1-enolate gave indan derivative **558** in good yield.[247]



557 **558**

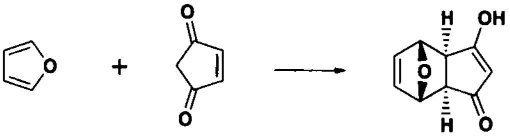
3a,7a-Dihydro-2,4,7,7a-tetrapentyl-1H-inden-1-one **560** was prepared from 4-bromo-2,5-dipentylcyclopent-2-en-1-one **559** with DBN in THF at ambient temperature.[248]



559

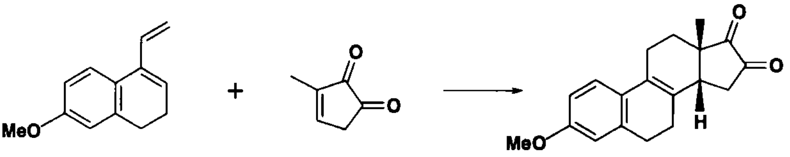
560

Diels-Alder reaction of furan and cyclopenten-1,4-dione or alkenes affords the indan derivative **561**.[249]



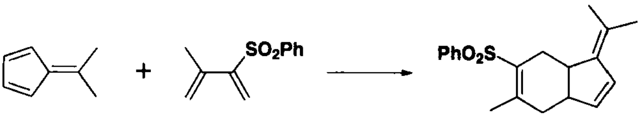
561

Diels-Alder reaction of the Dane diene and dienophiles afforded the adduct possesing the indan subunit.[250]



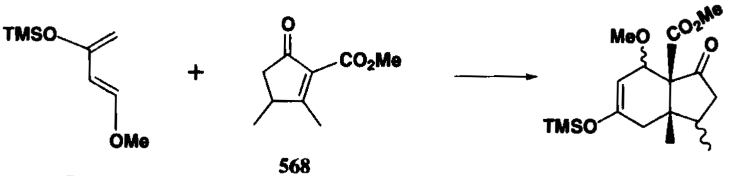
562 **563** **564**

Selective cross Diels-Alder reactions of 2-(phenylsulfonyl)-1,3-diene and fulvene to give the indan have been reported.[251]



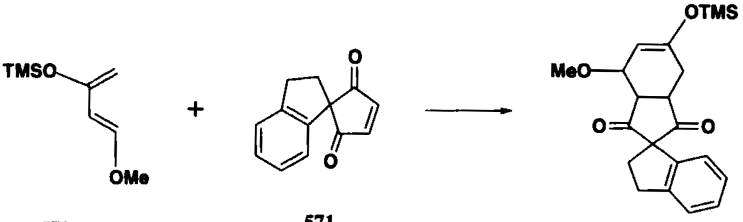
565 **566**

In a synthesis of 4-*epi*-pinguisone, Baber *et. al.* reported a Diels-Alder reaction of Danishefsky's diene with cyclopent-2-en-1-one to afford the indan derivatives.[252]



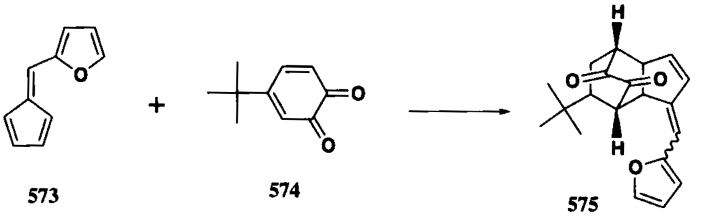
567 568 569

Bach *et. al.* also applied a similar reaction to the synthesis of compounds related to Fredericamycin A.[253]



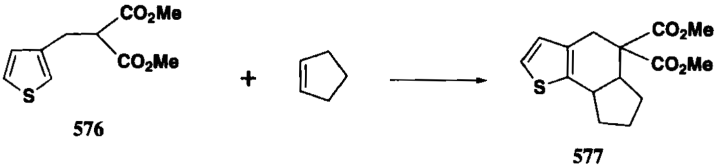
570 571 572

Diels-Alder reaction of 4-*t*-butyl-*o*-benzoquinone with fulvene furnished the tricyclic indan derivatives.[254]



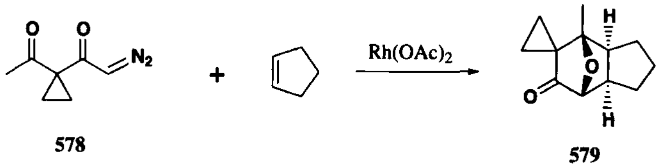
573 574 575

Manganese (III) acetate initiated oxidative free radical reactions of electron rich 3-heteroaryl substituted malonates with alkenes to synthesize the indan derivatives have been reported.[255]



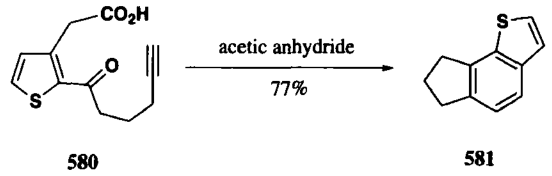
576 577

The Rh(II)-catalyzed reaction of 1-acetyl-1-(diazoacetyl)cyclopropane with alkenes afforded indan derivatives in good yield. The reaction involves the formation of a rhodium carbenoid and subsequent transannular cyclization of the electrophilic carbon onto the adjacent keto group. The methodology was also applied to synthetic efforts aimed at the illudin family of toxic sesquiterpenes.[256]



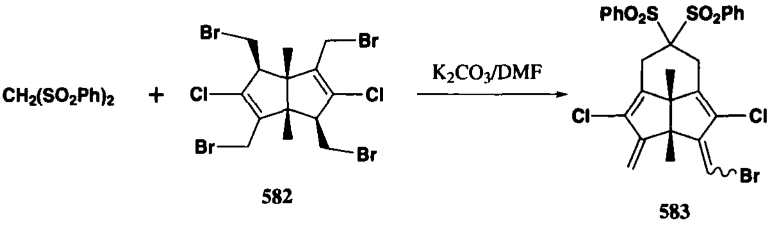
O. Bond 5 and Bond 10 Formation Methods

7,8-Dihydro-6H-1-thia-as-indacene **581** was prepared from 2-hex-5-ynoyl-3-thienylacetic acid **580** with acetic anhydride under refluxing conditions.[257]

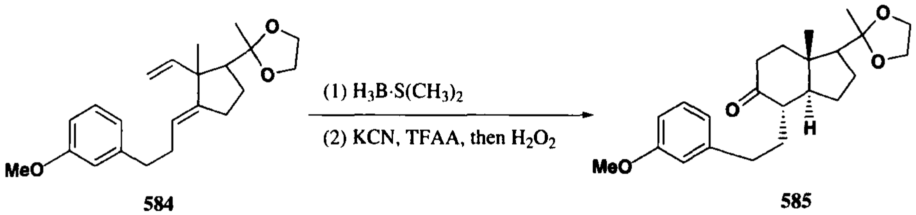


P. Bond 6 and Bond 7 Formation Methods

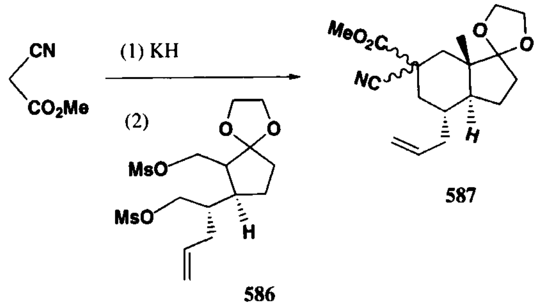
Treatment of the halide **582** with the potassium salt of *bis*(phenylsulfonyl)methane in DMF led to the formation of indan derivative **583**.[258]



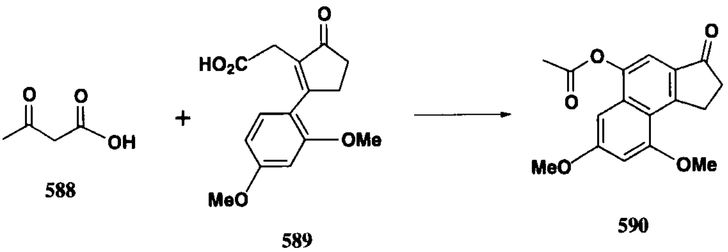
In a total synthesis of (±)-estrone methyl ester, Bryson have reported a hydroboration of the diene **584** followed by carbenylation (KCN, TFAA, then H_2O_2) to give hydrindanone **585** in 60% yield.[259]



Reaction of **586** with 2.5 equivalents of the potassium salt of methyl cyanoacetate in the presence of a catalytic amount of anhydrous sodium iodide in DMSO lead to the indan derivative **587**.[260]

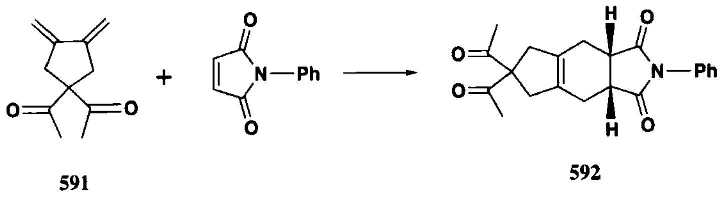


The reaction of the acids **588** and **589** in boiling acetic anhydride formed the indene derivative **590**.[261]

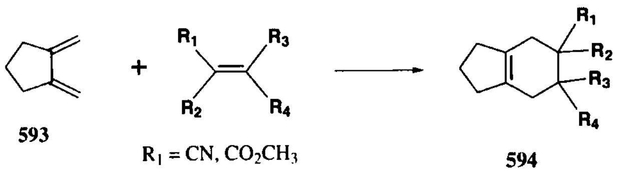


Q. Bond 6 and Bond 8 Formation Methods

Diels-Alder cycloaddition of diene **591** with N-phenylmaleimide gave a single indan cycloadduct **592**.[262]

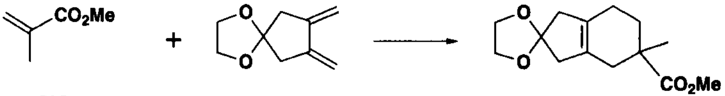


Diels-Alder cycloadditions of 1,2-dimethylenecyclopentanes **593** with α,β-unsaturated carboxylic esters and nitriles were studied and gave indan derivatives **594** in good yield.[263]



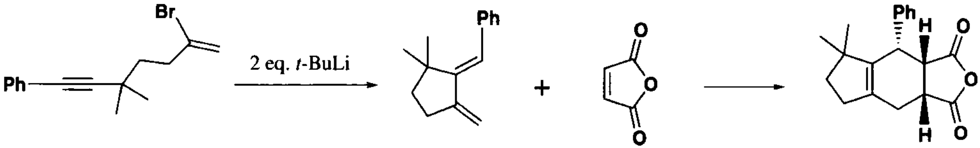
R_1 = CN, CO_2CH_3
R_2 = H, CN
R_3 = H, CN, CO_2CH_3
R_4 = H, CN, CO_2CH_3

[4+2] Cycloadditions of 3,4-bismethylenecyclopentanone ethylene ketal **596** and alkene **595** were designed to produce functionalized [6,5] ring systems **597** and applied to a formal synthesis of gibberellic acid. Similar reactions of dienes in the preparation of indans were also reported.[264]



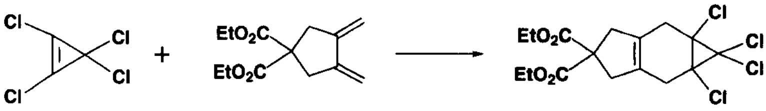
595 **596** **597**

The highly reactive *bis* exocyclic 1,3-diene **599**, generated by addition of 1 equiv. of *t*-BuLi to the acetylenic vinyl bromide, was reacted with various dienophiles to give the indan derivatives. The consecutive exchange-cyclization-cycloaddition methodology can be conducted in one pot without isolation of intermediate.[265]



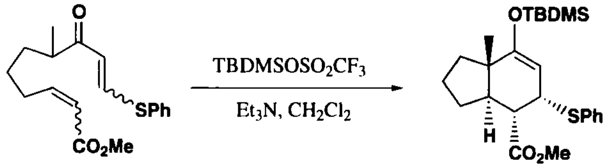
598 **599** **600**

The cycloprop[*f*]indene **603** was synthesized *via* cycloaddition of diene **602** to the cyclopropene **601**.[266]



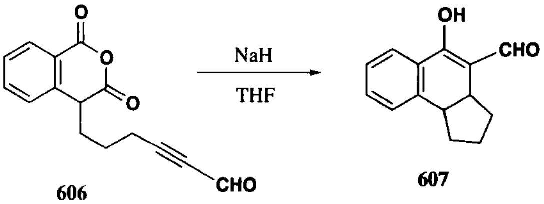
601 **602** **603**

A construction of polyfunctionalized *trans*-hydroindans **605** *via* sulfur-mediated intramolecular double Michael type reaction was achieved by treatment of the enone **604** with *tert*-butyldimethylsilyl trifluoromethanesulfonate.[267]



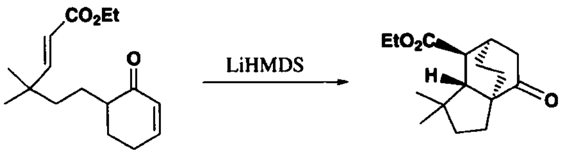
604 **605**

An efficient synthesis of aromatic indan **607** was reported by a strong-base-induced intramolecular cycloaddition of homophthalic anhydride **606**.[268]



606 **607**

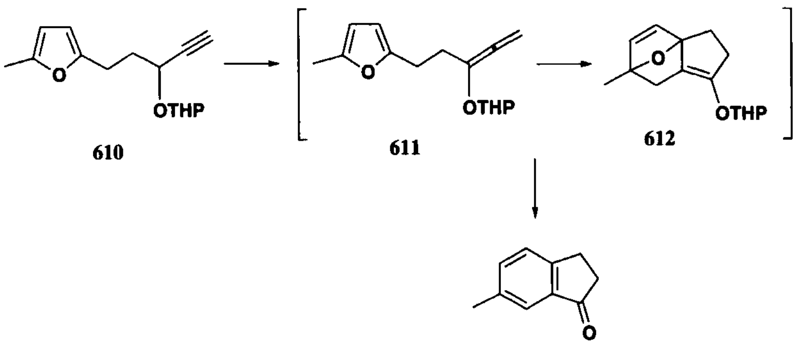
Intramolecular double Michael reaction of the α,β-unsaturated enone ester **608** using lithium hexamethyl disilazide produced the tricyclic indan derivative **609**, further converted to the CDF part of *Aconitum* alkaloids.[269]



608 **609**

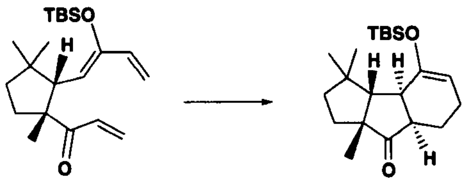
R. Bond 6 and Bond 10 Formation Methods

Diels-Alder cycloaddition took place across the terminal allene bond of **610** to provide the intermediate cycloadduct **612**, which underwent subsequent fragmentation to form indanone **613**.[270,271]



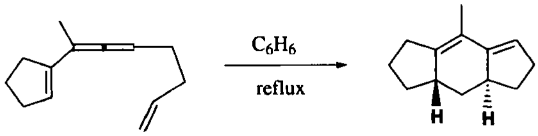
610 **611** **612** **613**

An intramolecular Diels-Alder reaction was reported for the construction of indan **615** that was applied in a stereoselective total synthesis of (±)-$\Delta^{9(12)}$-capnellene.[272]



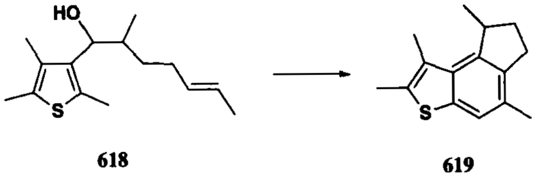
614 **615**

In a total synthesis of (+)-sterpurene, Okamura *et. al.* reported a intramolecular Diels-Alder reaction of vinylallene **616** to give tricyclic indan system **617**.[273]

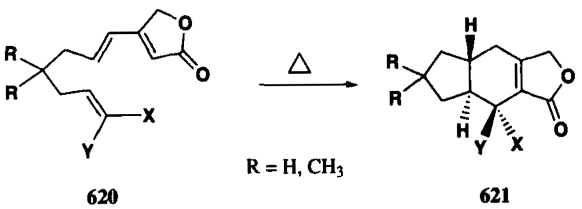


616 **617**

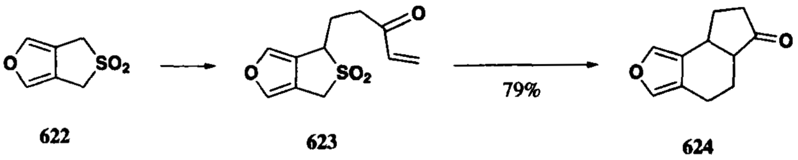
rac-Thiamarmelerin **619** was prepared by an intramolecular Diels-Alder reaction of a thieno[2,3-*c*]furan **618**.[274]



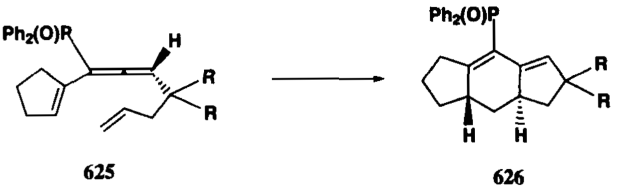
The [4+2] cycloadditions of a series of triene lactones **620** activated by electron-withdrawing groups at the terminus of the chain have been investigated and gave indan derivatives **621**.[275]



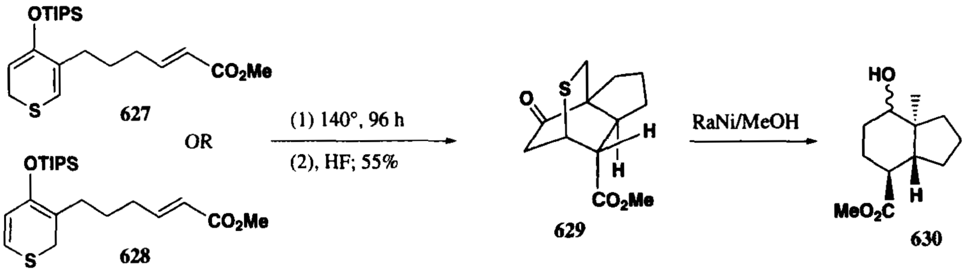
Alkylation of 4*H*, 6*H*-thieno[3,4-*c*]furan 5,5-dioxide **622**, followed by an intramolecular Diels-Alder reaction of furan enones **623**, afforded the indan adduct **624** in good yield.[276]



Synthetic and kinetic studies of the intramolecular Diels-Alder reactions of cycloalkenylallenylphosphine oxide **625** to indan **626** were reported.[277]

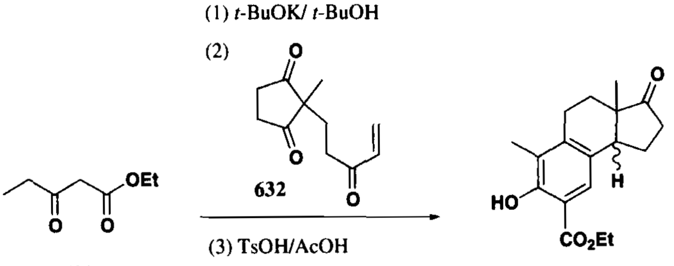


A C_6D_6 solution of 2*H*-thiopyran dienes was heated at 140° for 96 h to give the [4+2] adduct which was then desulfurized to give the *trans*-fused angularly methylated hydrindans.[278]



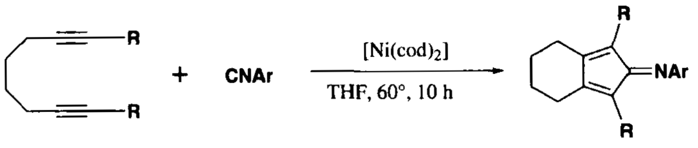
III. MULTIPLE-BOND DISCONNECTION APPROACHES

Condensation of ethyl propionyl acetate with enetrione **632** under basic conditions gave the tricyclic indanones *via* sequential alkylations.[279]



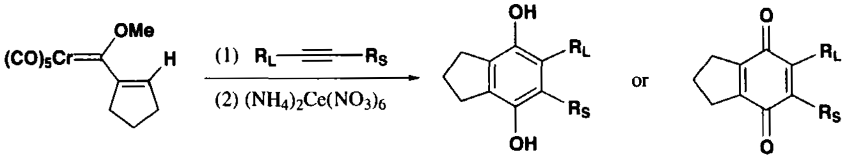
631 **633**

Nickel(0)-promoted cyclization of 1,7-diynes **634** with isocyanide takes place to form indan iminocyclopentadienes **635**.[280]



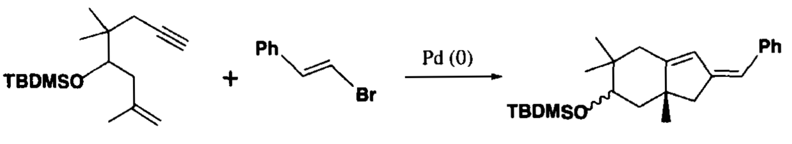
634 **635**

The benzannulation reaction of acetylene with α,β-unsaturated chromium carbene (Fischer carbene) complexes **636** allows for the construction of various indans.[281]



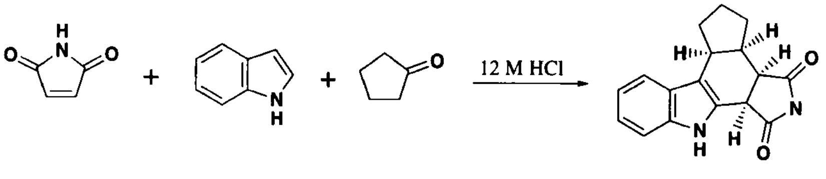
636 **637** **638**

Reaction of 1,7-enynes **639** and bromoalkenes in the presence of Pd(0), to undergo exo-type addition and intramolecular carbametalation, gives indan derivatives **640**.[282]



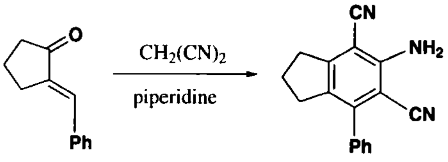
639 **640**

Tetrahydrocarbazole was prepared in a one-pot synthesis from indols, ketones or aldehydes, and maleimides, with acid catalysis. The reactions involve a condensation of the indole with the ketone or aldehyde, followed by *in situ* trapping of the vinylindole in a Diels-Alder reaction with maleimide.[283]



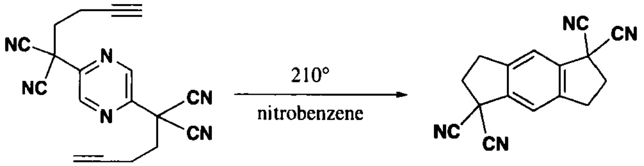
641

Reaction of 2-benzylidenecyclopentanone **642** with malononitrile in piperidine led to the formation of aminocyanoarylindan **643**.[284]



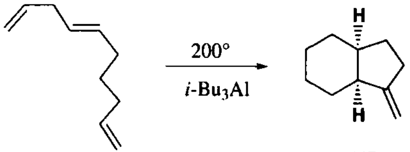
642 **643**

Plas *et. al.* reported a novel ring transformation of 2,5-*bis*(1,1-dicyano-4-pentynyl)pyrazine **644** to give 1,1,5,5-tetracyano-1,2,3,5,6,7-hexahydro-*s*-indacene **645** by intramolecular Diels-Alder reaction.[285]



644 **645**

Reaction of deca-1,4,9-triene **646** with i-Bu_3Al at 200° afforded 1-methylene-octahydro-indene **647**.[286]



646 **647**

IV. CONCLUSION

This review has attempted to provide a thorough and up to date synopsis of recent synthetic methodologies of indan systems. As the readers can judge by the size of the article, omissions are inevitable and we wish to apologize for any oversight which may have occurred. The discussion was classified first by bond disconnection and subsequently by reaction type. Many of the retrosynthetic approaches described involve traditional synthetic methods. As is usually the case, the increasing demand for more economical syntheses of biologically active scaffolds will fuel further research in this field. The rapid advent of novel electrochemical pathways, organometallic and transition metal reagents will almost certainly impact future synthetic approaches to indan systems.

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