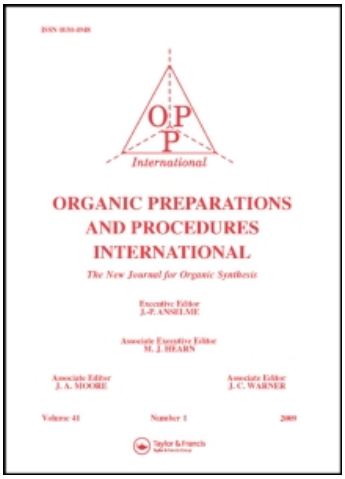

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CYCLOADDITIONS OF *ortho*-QUINODIMETHANES DERIVED FROM BENZOCYCLOBUTENES IN ORGANIC SYNTHESIS. A REVIEW

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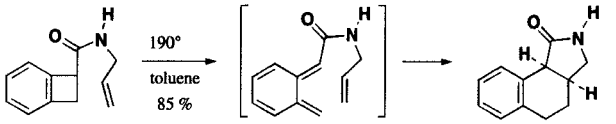
INTRODUCTION

A number of natural products like steroids, alkaloids and some antibiotics exhibit complicated polycyclic structures. Their synthesis require stereoselective cyclization procedures, such as intramolecular cycloaddition of *o*-xylylenes and substituted double bonds. This strategy was first investigated by Oppolzer in 1971 who pointed out that heating of a benzocyclobutene bearing a double bond provided a tricyclic compound arising from an intramolecular Diels-Alder reaction (*Eq.* 1).[1,2] If the reaction can form a five- or six-membered-ring, the yield is generally excellent as for the two following examples (*Eqs.* 2 and 3).

(1)



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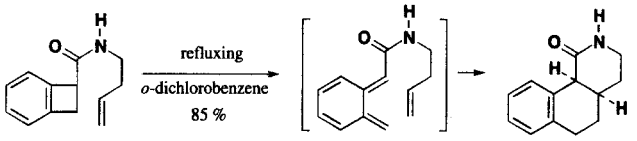
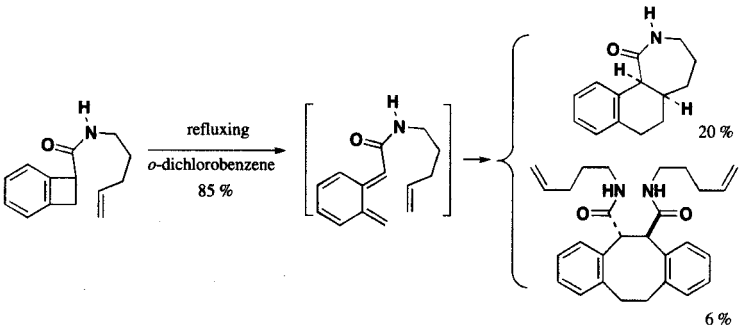


(3)

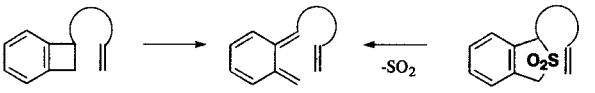
The probability of the intramolecular process depends strongly on the distance between the reaction partners. In some cases, the reaction becomes under entropic control and a competing bimolecular cycloaddition takes place.



(4)

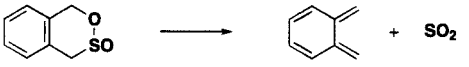
o-Xylylenes can be generated in several ways. The most frequent routes are summarized below.[3–12]

a) Thermal ring opening of benzocyclobutenes is the most frequent way of generating *o*-quinodimethanes (*Eq.* 5).



(5)

b) Thermal extrusion of sulfur dioxide from sulfones or sultines provides *o*-xylylenes (*Eq.* 6).



(6)

c) 1,4-Elimination process involving thermal elimination, base-catalyzed elimination, reductive elimination or fluoride ion catalyzed elimination, also affords *o*-quinodimethanes (*Eq.* 7).

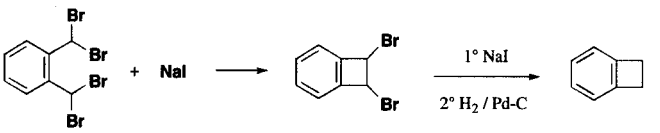
(7)

Indeed, the most frequently used method for the preparation of *o*-quinodimethanes is the thermolysis of benzocyclobutenes. This process is also of a great theoretical interest.

This review concerns organic synthesis involving benzocyclobutene derivatives almost exclusively.

I. SYNTHESIS OF BENZOCYCLOBUTENES

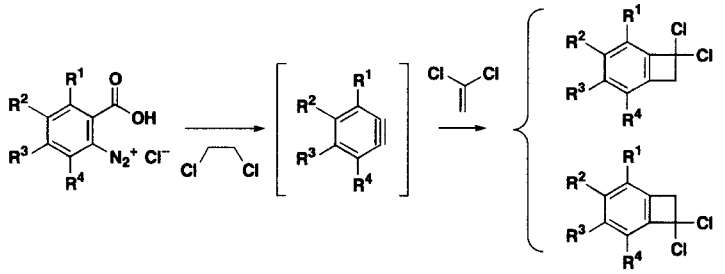
In 1956, Cava first suggested[13] the participation of an *o*-quinodimethane as a reaction intermediate in the conversion of α,α,α',α'-tetrabromo-*o*-xylene to *trans*-α,α'-dibromo-benzocyclobutene, a reaction reported earlier by Finkelstein (*Eq.* 8).[14]



(8)

a. [2+2] Cycloaddition of Benzynes

The most serious drawback to the use of benzocyclobutenes is the difficulty in their synthesis and especially if they are α-substituted. The most convenient non-pyrolytic route to 1-substituted benzocyclobutenes is the [2+2] cycloaddition of benzynes to electron-rich alkenes. Anthranilic acids are readily diazotized by alkyl nitrites to give benzenediazonium-2-carboxylates which undergo fragmentation to benzynes,[15–18] and in presence of 1,1-dichloroethene, the *gem*-dichlorobenzocyclobutenes are obtained directly (*Eq.* 9). This technique avoids the isolation and handling of the hazardous benzenediazonium-2-carboxylate and moreover the yield of the sequence is good.[19] The dichlorobenzocyclobutenes are then hydrolyzed into benzocyclobutenones which are of a high synthetic interest as they represent suitable building blocks for the preparation of other derivatives such as benzocyclobutenediones (*Eq.* 10).[20]



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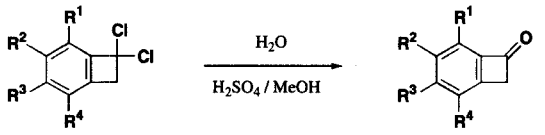
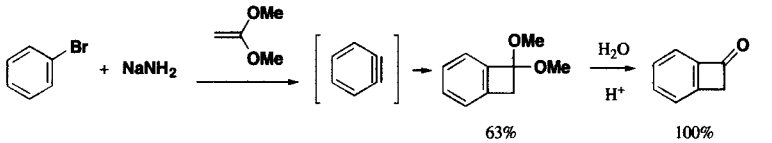


(10)

Treatment of a bromoarene by sodium amide generates the corresponding benzyne which can react with 1,1-dimethoxyethylene to yield the dimethylbenzocyclobutenone ketal.[21,22] Hydrolysis of this ketal to the benzocyclobutenone proceeded in quantitative yield at room temperature (*Eq.* 11). The intermediate formation of benzyne was confirmed by the exclusive obtention of one ketal, starting from either *ortho* or *meta*-methoxybromobenzene. The regiospecificity of the cycloaddition is noteworthy (*Eq.* 12). The reaction may be extended to other bromoarenes, such as dimethoxybromobenzenes (*Eq.* 13).



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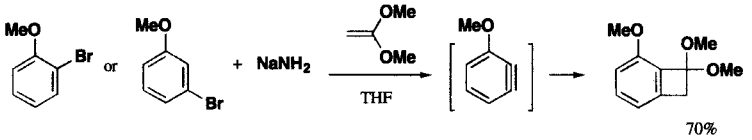

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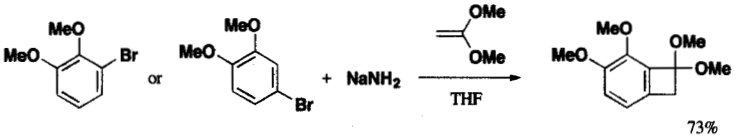
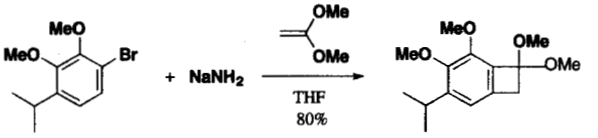


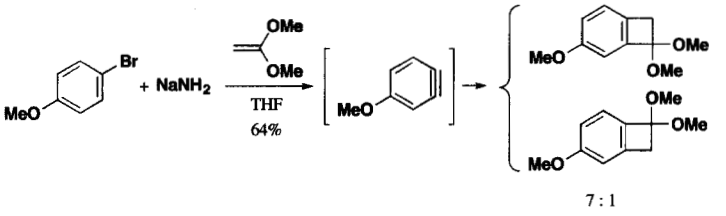
(13)

Taxodione, which is a diterpene, has been prepared from the ketal obtained in *Eq.* 14.[23]



(14)

The regioselectivity of the reaction decreased in the case of *para*-methoxybromoarene (*Eq.* 15). Benzynes may also be generated by halogen-lithium exchange reaction of *ortho*-halo-aryl triflates (*Eq.* 16).[24,25]



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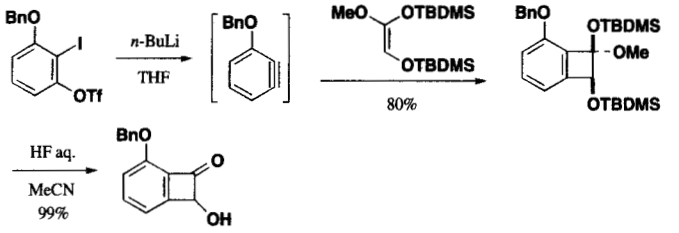
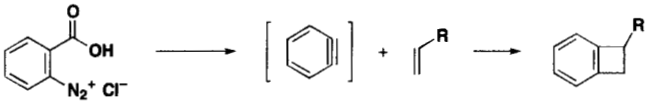


(16)

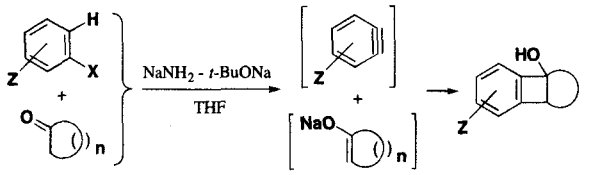
Cycloaddition reactions of benzynes with vinyl ethers and esters afford benzocyclobutene derivatives (*Eq.* 17).[26] If the olefin bears a withdrawing group, the yield of the reaction decreases dramatically.



(17)

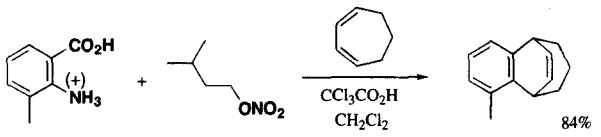
R = OMe, 40%; R = OCOMe, 45%; R = CN, 20%; R = CO_2Et, 7%

Benzynes react more rapidly with electron-rich alkenes than electron-deficient alkenes. This result is due to the abnormally low energy LUMO of benzyne[27] and is illustrated by the arynic condensation of ketone enolates (*Eq.* 18). The two reactive species are prepared *in situ* in presence of a complex base mixture.[28,29]



(18)

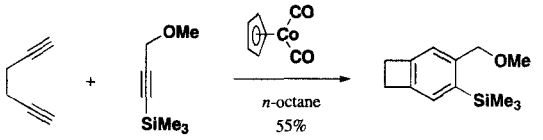
Unlike previous examples, the reaction of cycloheptadiene and toluyne is a [4+2] cycloaddition process (*Eq.* 19).[30]



(19)

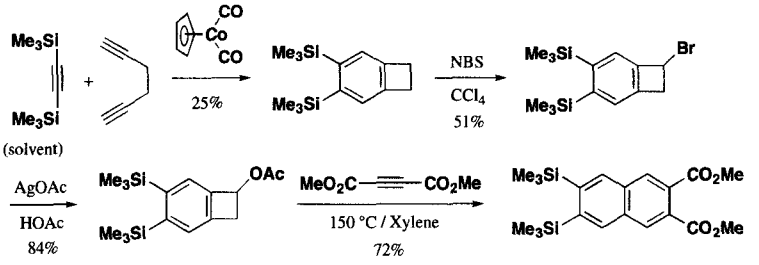
b. [2+2+2] Cycloaddition of Three Acetylenic Bonds

Vollhardt showed that the [2+2+2] cycloaddition of three appropriately substituted acetylenic bonds is a potential route to benzocyclobutenes. The reaction is usually catalyzed by η-5-cyclopentadienyl-dicarbonylcobalt (*Eq.* 20).[31]



(20)

In order to prepare lin-naphthopurine derivatives, Leonard has studied the cycloaddition of substituted benzocyclobutenes arising from such a [2+2+2] process (*Eq.* 21).[32]

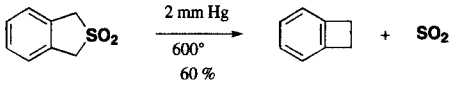


(21)

c. Extrusion Reactions

A benzocyclobutene can be generated by the extrusion of a small stable species from a molecule. Cava first described the extrusion of SO_2 from a sulfone.[33–35] The decomposition requires low pressure and high temperature (*Eq.* 22). In contrast, decomposition of sulfone in diethyl phtalate leads only to the unexpected 1,2,5,6-dibenzocyclooctadiene, arising from dimerisation of intermediate *ortho*-xylylene (*Eq.* 23). The stereochemistry of the cycloaddition of *o*-xylylenes arising from sulfones decomposition has been studied by Charlton. Substituent effects of the sulfone on the thermolysis temperature are notable. The presence of electron-rich substituents allows the extrusion of

SO_2 to be performed at lower temperature. This elimination occurs *via* a disrotatory process, hence, *cis* sulfone leads to (E,E)-*o*-xylylene (*Eq.* 24).[36]



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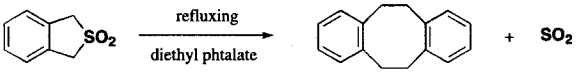

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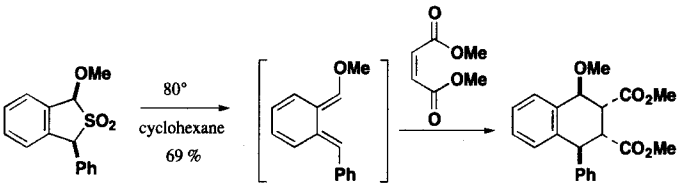
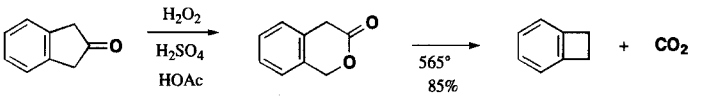


(24)

The extrusion of CO_2 also requires a high reaction temperature (*Eq.* 25).[37,38] In the same way, an indanone can lead to a benzocyclobutene by CO-elimination. The drawback of this procedure is the necessity of a very high temperature (800°) for the gas-phase pyrolysis.[39] Extrusion of nitrogen from the *N*-nitrene also constitutes a new route to benzocyclobutenes (*Eq.* 26).[40,41]



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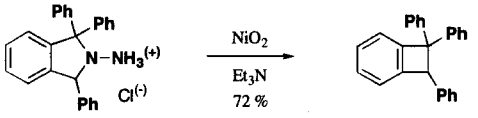
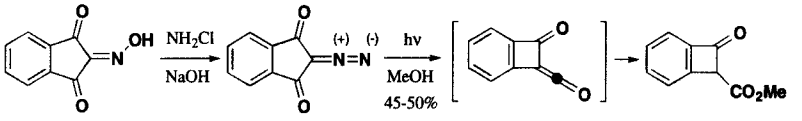


(26)

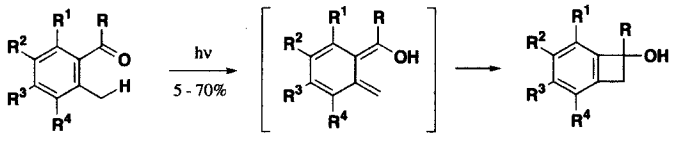
Substituted benzocyclobutenones can be elaborated by a Wolff rearrangement of α-diazoketones obtained *via* the Forster reaction (*Eq.* 27).[42–44]



(27)

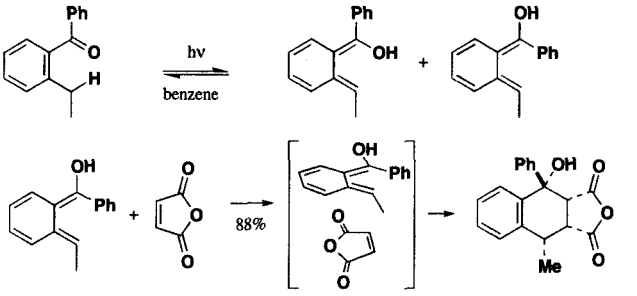
d. Photochemical Cycloadditions

Irradiation of *o*-alkylbenzophenones brings about intramolecular hydrogen-transfer yielding hydroxy-*o*-xylylenes, which leads to benzocyclobutenols.[45–47] Photoenolization is a very general and efficient process for the synthesis of benzocyclobutene derivatives (*Eq.* 28).[48] When the reaction is carried out in the presence of a dienophile, the Diels-Alder adduct is usually obtained in high yields.[49–51]



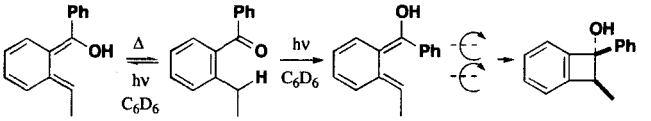
(28)

The hydrogen-transfer can lead to the (E,E)-dienol or the (Z,E)-dienol. Stereochemical determinations of the adduct have shown that the Diels-Alder addition proceeds from the (E,E)-dienol by an *endo* approach. The (Z,E)-dienol can also be formed during the photochemical step, but is unreactive towards maleic anhydride (*Eq.* 29).[52,53]



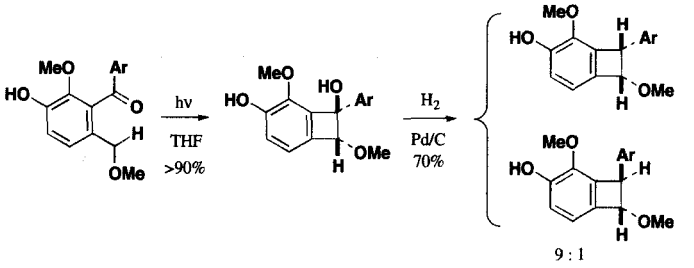
(29)

Complementary works reported that, even if the two dienols (Z,E and E,E) are photochemically generated, only the latter cyclizes through a conrotatory process to the cyclobutenol. The (Z,E)-dienol undergoes a rapid 1,5-sigmatropic H shift to regenerate the ketone (*Eq.* 30).[54]



(30)

Various substituted benzocyclobutenes can be obtained by photocyclization of congested benzophenones.[55] *cis*-2-Arylbenzocyclobutenols provided from hydrogenolysis (*Eq.* 31), cycloadd to methyl fumarate to give potential precursors of lignans (*Eq.* 32). According to AM1 semi-empirical calculations, the *o*-xylylene is more stable than the corresponding benzocyclobutene.



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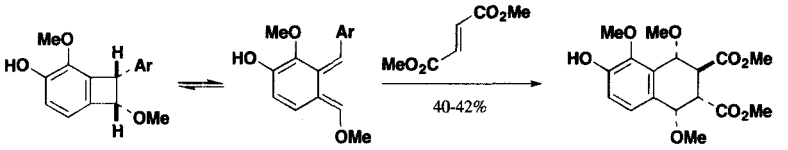
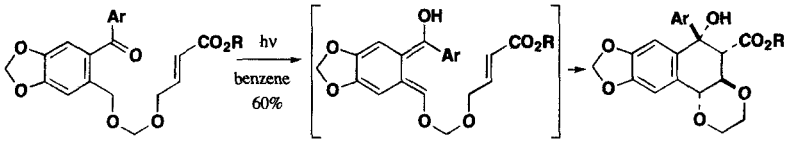


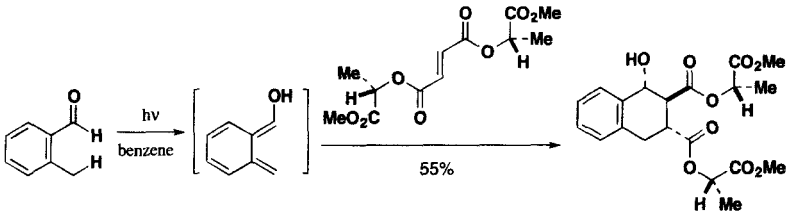
(32)

A similar structure has been synthesized by a tandem photoenolization/Diels-Alder sequence, thus by-passing the benzocyclobutene (*Eq.* 33).[56]



(33)

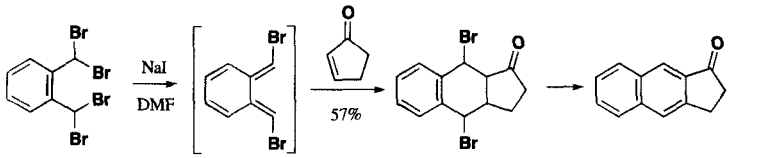
The cycloaddition of the α-hydroxy-*ortho*-quinodimethane generated from 2-methylbenzaldehyde with the fumarate of methyl lactate yields a single diastereoisomer of a tetralin derivative (*Eq.* 34).[57]



(34)

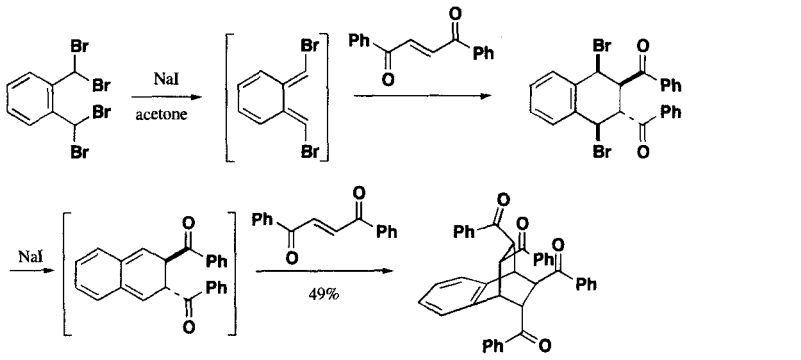
e. γ-Elimination Reactions

α,α'-Dibromo-*ortho*-xylenes undergo 1,4-dehalogenation by means of reducting agents or metals. Indeed, this procedure constitutes an efficient route to *o*-xylylenes. Finkelstein reported in 1910 the use of sodium iodide, which has been employed by Cava to elaborate the *(d,l)*-4-demethoxydaunomycinone.[58] A more recent example of the use of sodium iodide is the general preparation of 2,3-disubstituted naphtalenes *via* a tandem Diels-Alder/aromatization reaction (*Eq.* 35).[59]



(35)

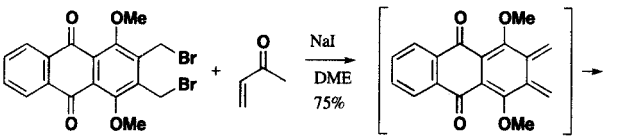
In the case where the dienophile is *trans*-1,4-diphenyl-2-butene-1,4-dione, a tetrabenzoylbenzobicyclo[2.2.2]octane is the sole product of the reaction. This product arises from a process involving the tandem generation of two *o*-quinodimethane intermediates (*Eq.* 36).[60]

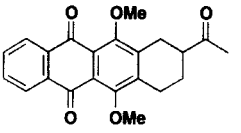


(36)

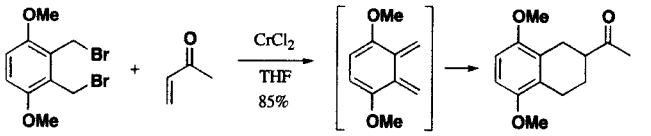
Other reducing agents such as zinc[61,62] (used for the synthesis of *(d,l)*-4-demethoxydaunomycinone (*Eq.* 37),[63]), copper-isonitrile complex,[64] iron powder in water suspension,[65] stannous chloride in presence of palladium,[66] chromous chloride in THF (*Eq.* 38),[67] metallic nickel[68] (prepared by

the lithium metal reduction of nickel iodide in presence of naphtalene (*Eq.* 39)) have also been employed.

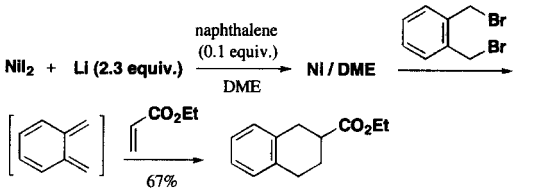




(37)

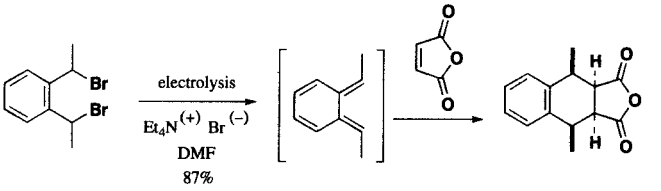


(38)



(39)

The cathodic reduction of α,α'-dibromo-*ortho*-xylenes gives Diels-Alder adducts of transient *o*-xylylenes (*Eq.* 40).[69] The stannyl anion generated from $Me_3SiSnBu_3$ and fluoride anion is also an efficient reductive agent (*Eq.* 41).[70]



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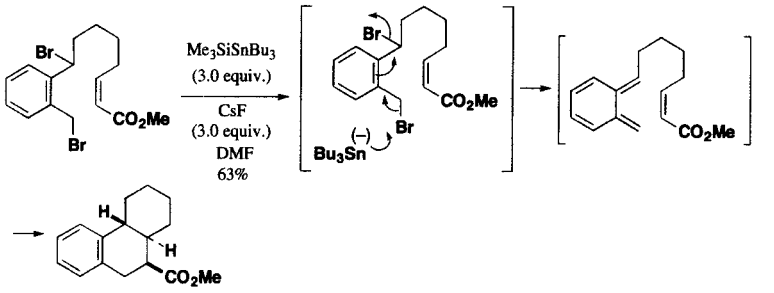
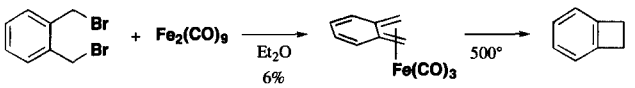


(41)

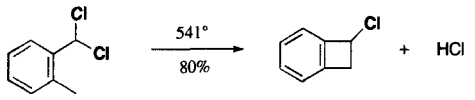
In the case where Fe_2CO_9 is used, the expected *o*-xylylene tricarbonyl iron is obtained in only a low yield (this complex can be the precursor of the benzocyclobutene by heating or *via* oxidation)(*Eq.* 42).[71] In contrast, the use of platinium induces the formation of a benzoplatinacyclopentene

complex[72] (for other complexes, see ref. 73–75).



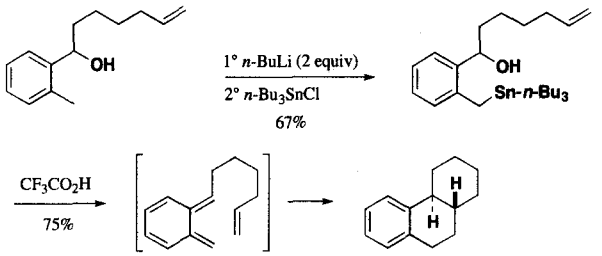
(42)

Substituted benzocyclobutenes are economically obtained from α,α-dichloro-*o*-xylenes through a reaction sequence involving a pyrolytic 1,4-elimination of HCl (*Eq.* 43),[76,77] while pyrolysis of *o*-substituted benzylidene chlorides has been shown to be a useful route to benzocyclobutene derivatives.[78–83]



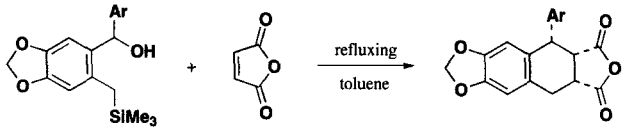
(43)

Proton-induced 1,4-elimination of *o*-(1-hydroxyalkyl)benzyltributylstannanes is a convenient method for the generation of *o*-quinodimethanes, which can be involved in intramolecular cycloaddition reactions (*Eq.* 44).[84]



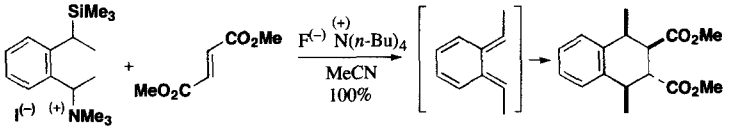
(44)

Thermolysis of *o*-hydroxymethylbenzylsilanes with maleic anhydride affords the corresponding tricyclic anhydrides directly. The *o*-xylylene intermediate is generated by the benzo-Peterson reaction (*Eq.* 45).[85,86]



(45)

Saegusa has shown that treatment by CsF of [α-[*o*-[α-(trimethylsilyl)alkyl]-phenyl]alkyl]trimethylammonium halides provides α,α'-dialkyl-*o*-quinodimethanes (*Eq.* 46).[87,88] This procedure has been applied to a trimethylsilyl derivative bearing a chiral ammonium cation at the γ-position suitable for the asymmetric synthesis of an α-alkoxy *o*-xylylene (*Eq.* 47).[89]



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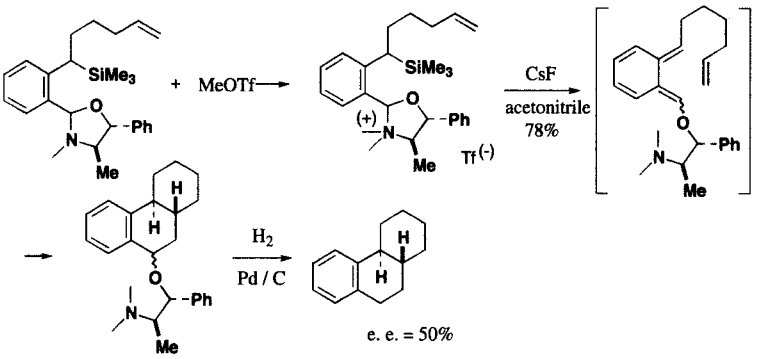
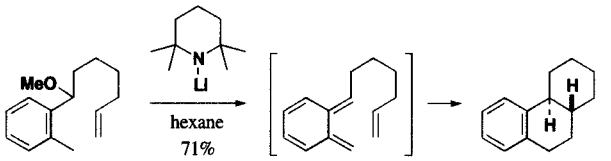


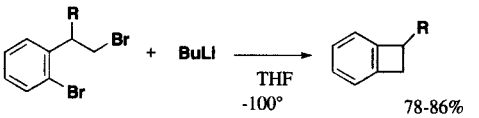
(47)

Strong bases such as lithium dialkylamide induce 1,4-elimination of methyl-*o*-methylbenzyl ethers giving *o*-xylylenes (*Eq.* 48).[90]



(48)

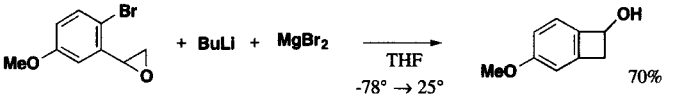
Another route to 1-substituted benzocyclobutenes is by the Parham cycloaddition of conveniently substituted dibromides (*Eq.* 49).[91,92]



R = $-CH_2-Ph$; $-C_4H_9$; $-CH_2-CH_2-CH=CH_2$

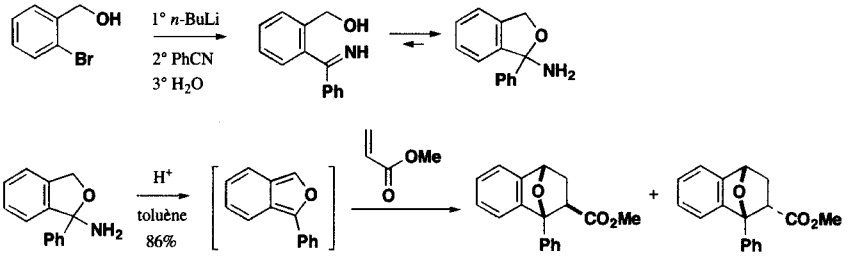
(49)

Benzocyclobutenols can be elaborated by cyclization of *o*-halostyrene oxides (*Eq.* 50).[93]



(50)

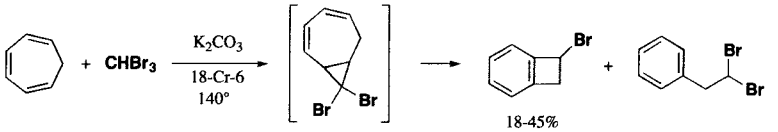
1,4-Elimination is also applied to the synthesis of isobenzofurans. These compounds are highly reactive dienes, which can be involved with a variety of dienophiles.[94] The isobenzofuran is generated in presence of a dienophile as for the example mentioned in *Eq.* 51.[95]



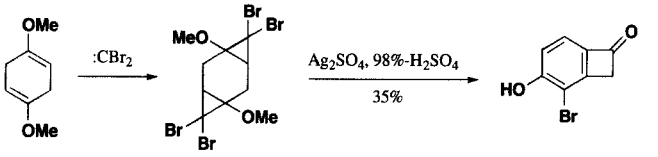
(51)

f. Rearrangement of gem-Dibromocyclopropanes

The thermal rearrangement of dibromocarbenes coming from cycloheptatrienes leads in part to bromobenzocyclobutenes (*Eq.* 52).[96] An interesting benzocyclobutenone is similarly prepared. Reaction of dibromocarbene with *p*-dimethoxydihydrobenzene leads to a tricyclic compound which is rearranged into the expected ketone (*Eq.* 53).[97]



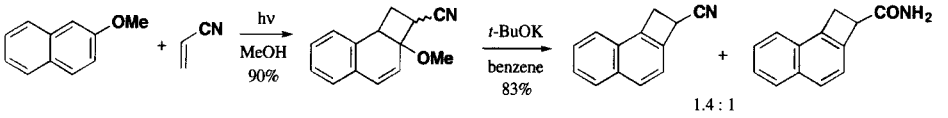
(52)



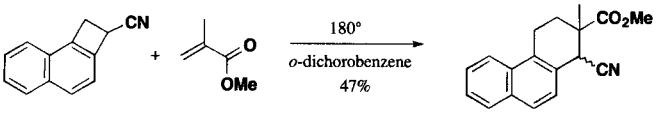
(53)

g. Photochemical Cycloadditions

Bicyclo[4.2.0]octadienes can be elaborated through [2+2] photochemical cycloaddition of aromatic compounds.[98,99] This unusual strategy has been applied to β-methoxynaphtalene and acrylonitrile.[100] The product undergoes an elimination giving the expected naphthocyclobutene (*Eq.* 54).[101] Thermolysis of this latter compound is a route to equileine (*Eq.* 55).

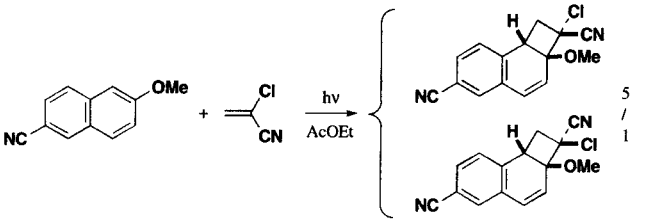


(54)



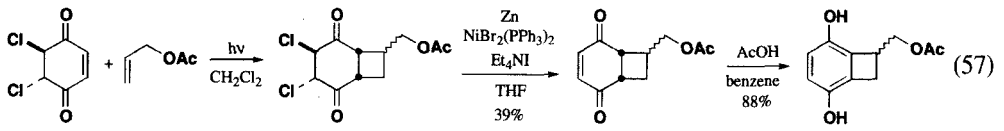
(55)

Recently, Jalal has showed that 6-methoxy-2-naphthonitrile undergoes photocycloaddition to 2-chloroacrylonitrile affording [2+2] cyclobutane adducts (*Eq.* 56).[102,103]



(56)

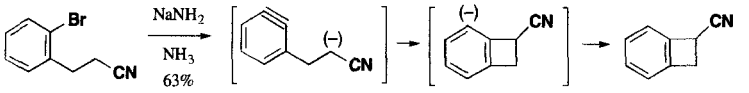
Photochemical cycloaddition of quinone derivatives is an efficient way to substituted benzocyclobutenes (*Eq.* 57).[104]



(57)

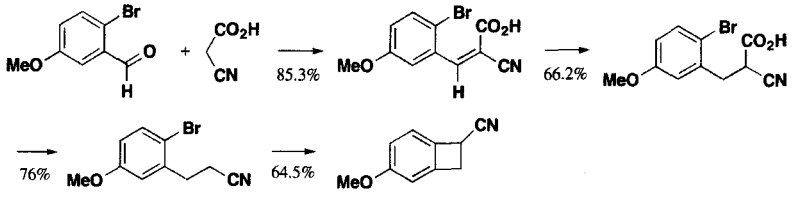
h. Intramolecular Addition of Carbanions to Benzynes

Strong nucleophiles add readily to arynes. If the nucleophile is situated on a side-chain of the aryne, intramolecular addition forms a new ring fused to the original aromatic nucleus. This principle of ring closure constitutes an efficient way to substituted benzocyclobutenes. Thus, treatment of 4-(*o*-bromophenyl)butanonitrile with sodium amide in liquid ammonia affords 1-cyanobenzocyclobutene. The presumed key step is the intramolecular addition of the carbanion with the aryne generated by elimination (*Eq.* 58).[105–107] The same procedure has been employed to prepare benzocyclobutyl phenyl sulfones which are precursors of several 7-substituted benzocyclobutenes.[108] The mechanism involves cyclization of an *o*-chlorophenylethylsulfone.

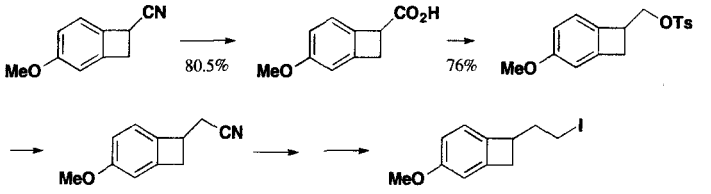


(58)

Kametani has developed a strategy providing methoxycyanobenzocyclobutene which represents, after alkylation, an important building block for the synthesis of natural products (*Eq.* 59).[109] Futhermore, an interesting iodide can be easily elaborated from methoxycyanobenzocyclobutene (*Eq.* 60).

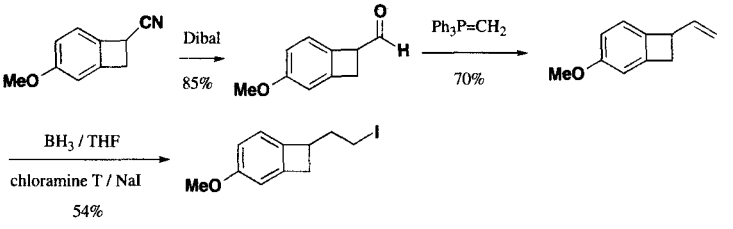


(59)



(60)

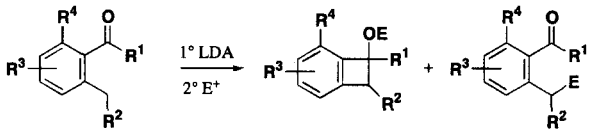
Taber has prepared the same iodide more directly (*Eq.* 61).[110]



(61)

i. Intramolecular Cyclization of o-Acylbenzyllithiums

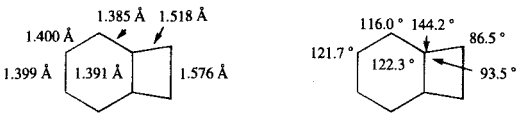
Kobayashi has recently described a novel and convenient route to functionalized benzocyclobuten-1-ols and especially, those bearing a trimethylsilyl group at the 2-position which are difficult to obtain by conventional methods. The key step is the intramolecular cyclization of *o*-acylbenzyllithiums (*Eq.* 62).[111]



(62)

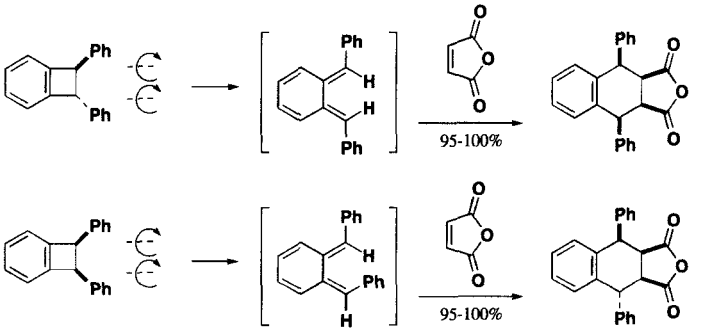
II. REACTIVITY OF BENZOCYCLOBUTENES

An X-ray crystallographic analysis of benzocyclobutene at -170° shows a special structure. The bonds in the benzene ring adjacent to the annelated bond are shortened (*Eq.* 63)[112,113] (crystal structures of benzocyclobutene-1,2-dione, *cis*-benzocyclobutene-1,2-diol dinitrate and dihalobenzocyclobutenes are studied in references[114–116]). Although electrophilic substitution in benzocyclobutenes occurs primarily at the 4-position,[117] metalation occurs primarily at the 3, or *ortho*-position.[118]



(63)

A conrotatory electrocyclic process is implied for thermal opening of benzocyclobutene into the corresponding *o*-xylylene according to Woodward-Hoffmann rule.[119] This is confirmed with the reaction of *cis* and *trans* 1,2-diphenylbenzocyclobutenes respectively with maleic anhydride.[120]. At 50°, the *trans* isomer is seventy times more reactive than the *cis* isomer (*Eq.* 64).[121]

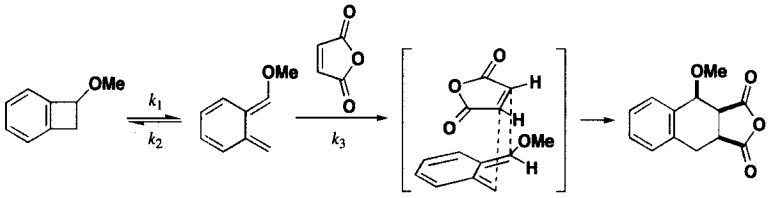


(64)

The activation parameters have been determined for the equilibrated opening of benzocyclobutene into *o*-xylylene (ΔH = 37.4 kcal.mol^{-1}, ΔS = 1.06 cal.K^{-1}.mol^{-1}) and for its later cyclization (ΔH = 26.3 kcal.mol^{-1}, ΔS = -6.1 cal.K^{-1}.mol^{-1}). Consequently, benzocyclobutene exhibits a greater stability (11.1 kcal.mol^{-1}) than the corresponding *o*-quinodimethane.[122–124]

The ring opening of homochiral methoxybenzocyclobutene in the presence of maleic anhydride has been studied by Sammes who concluded that cycloaddition is a much faster process than

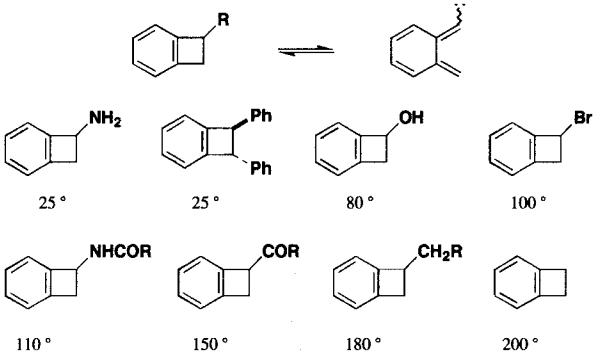
electrocyclic opening of the benzocyclobutene ring ($k_3 > k_2 > k_1$). The rate of electrocyclic process is increased by the presence of heteroatom substituents (*Eq.* 65).[125]



(65)

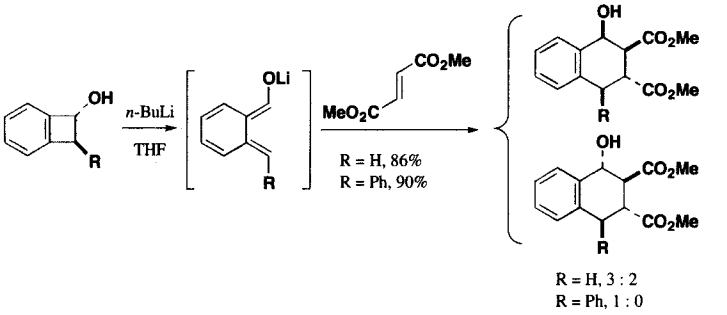
The ring opening of benzocyclobutene can occur with outward or inward rotation of the substituent. Recent *ab initio* calculations on the transition states indicate that the tendency for outward rotation of substituents leading to (E)-xylylenes, increases with the donor character of the substituent.[126] Clearly, the presence of electron-rich substituents makes the opening benzocyclobutene easier (the required temperature varies from 25° to 200°)(*Eq.* 66).[127]

A relationship between reactivity and ^{13}C chemical shifts of benzocyclobutenes has been revealed by Kametani in order to predict their reactivity.[128]



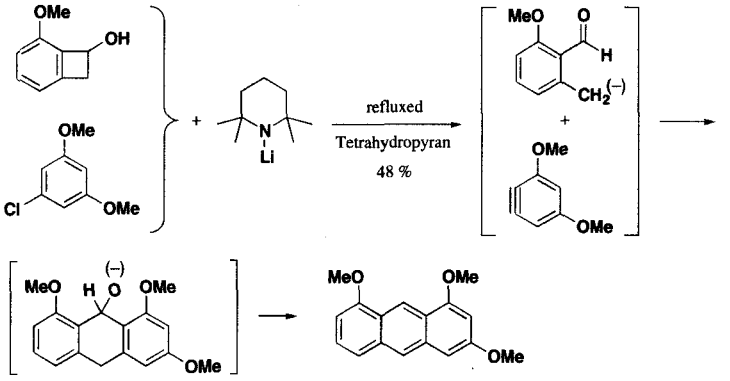
(66)

Intermolecular cycloadditions carried out at low temperature constitute applications of this phenomenon. Thus, the alkoxide ion of benzocyclobutenol tautomerizes at -78° to the corresponding enolate ion of *o*-methylbenzaldehyde which in the presence of a dienophile undergoes a Diels-Alder reaction, generating tetralol derivatives (*Eq.* 67).[129] The same process can be achieved with the tricarbonylchromium complexe of the 1-hydroxybenzocyclobutene.[130,131]



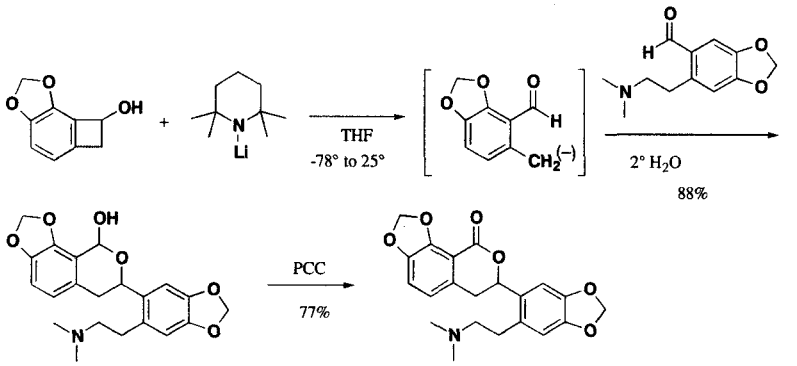
(67)

The simultaneous treatment of an aryl halide and a benzocyclobutenol with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF affords anthracenes after dehydration. The success of the reaction depends on the fact that LTMP is an extremely poor trap for benzynes (*Eq.* 68).[132]



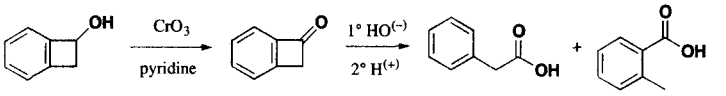
(68)

Deprotonation of benzocyclobutenols in the presence of aldehydes affords benzopyranols. This reaction has been extended to the synthesis of natural products such as pashawarine (*Eq.* 69).[133]



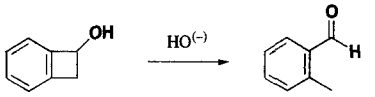
(69)

Some benzocyclobutenes are not quite stable to bases. For instance, benzocyclobutenone is slowly destroyed by aqueous sodium hydroxide addition to give both the corresponding *o*-toluic acid and phenylacetic acid (*Eq.* 70).[134,135] In contrast, benzocyclobutenone is quite stable to dilute mineral acids.



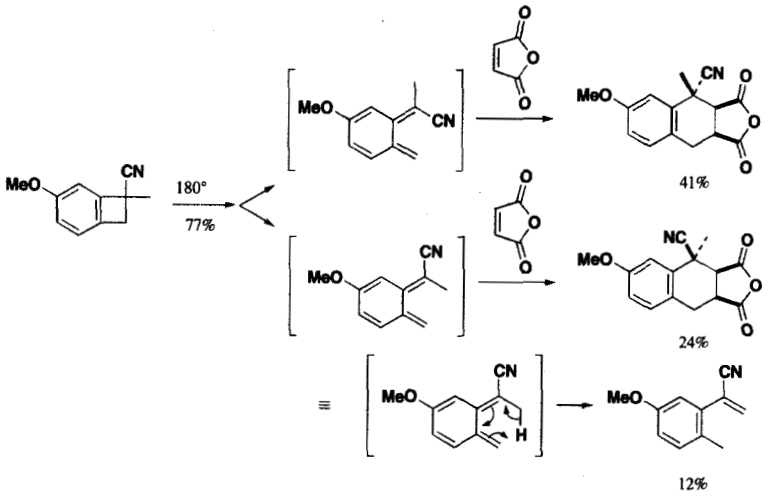
(70)

Similarly, the base treatment of benzocyclobutenol provides tolualdehyde (*Eq.* 71). Thus, the reaction between Grignard reagents and benzocyclobutenones leads to tertiary alcohols which can be rearranged into *o*-methylphenylketones by treatment with sodium methyloxide.[136]



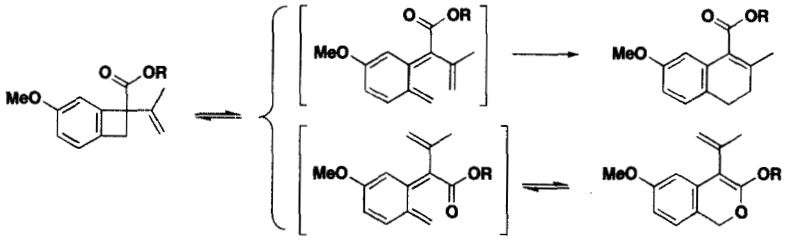
(71)

Substituted benzocyclobutenes can lead to two *o*-quinodimethanes according to the direction of ring opening. In some cases, a competitive [1,5]-sigmatropic reaction generates substituted styrenes (*Eq.* 72).[137]



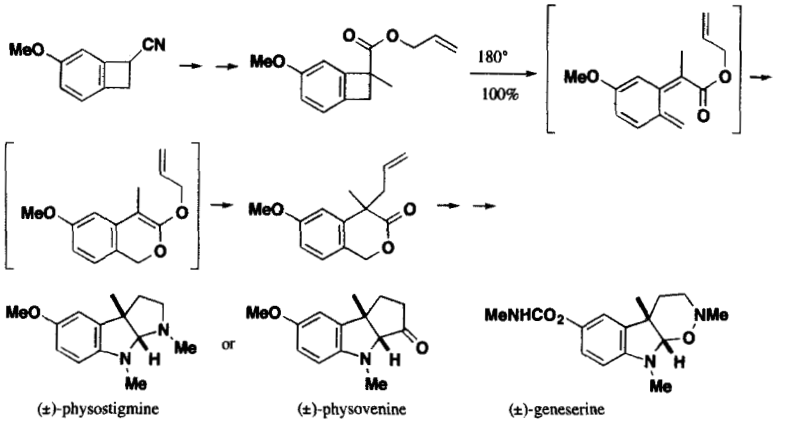
(72)

Thermolysis of 1-acyl-1-alkylbenzocyclobutenes provides an efficient route to substituted isochromenes through an electrocyclic reaction (*Eq.* 73).[138]



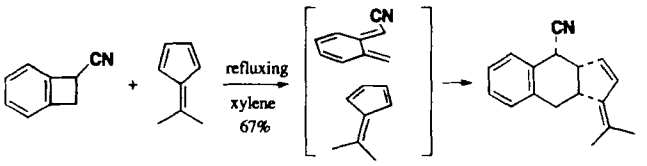
(73)

The presence of an allyl ester functionality at the C(1) position of the benzocyclobutene affords an isochromanone derivative *via* a tandem electrocyclic sigmatropic process. Subsequently, this compound is converted into natural products such as physovenine, physostigmine or geneserine (*Eq.* 74).[139–143]

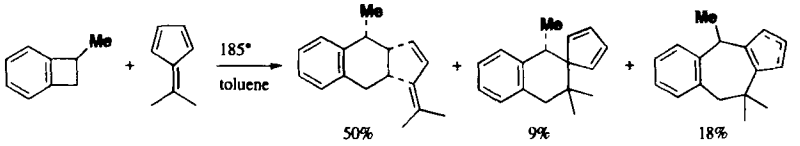


(74)

Cycloaddition of cyanobenzocyclobutene and 6,6-dimethylfulvene occurs in a [4+2] fashion and involves the most electron-rich double bond (*Eq.* 75). The same reaction performed with methyl-*o*-xylylene is less regioselective (*Eq.* 76).[144]

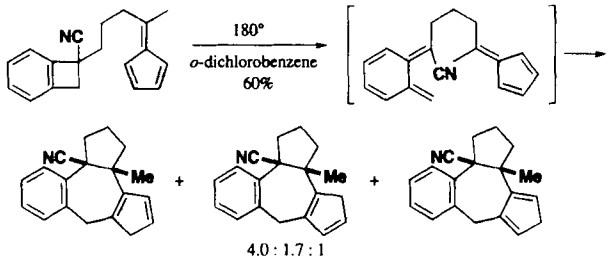


(75)



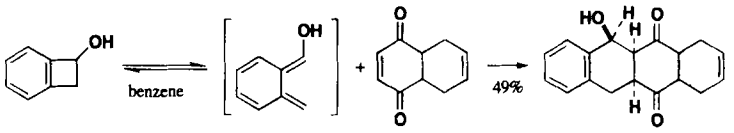
(76)

In contrast, intramolecular reaction between *o*-xylylene and fulvene gives the [6+4] cycloadduct (*Eq.* 77).[145]



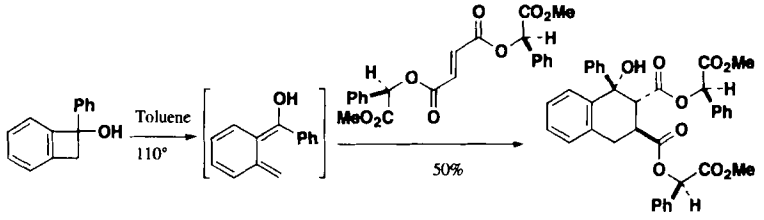
(77)

A number of compounds have been elaborated through intermolecular cycloaddition of dienophiles and *o*-xylylenes, generated thermally from functionalized benzocyclobutenes (*Eq.* 78).[146,147]



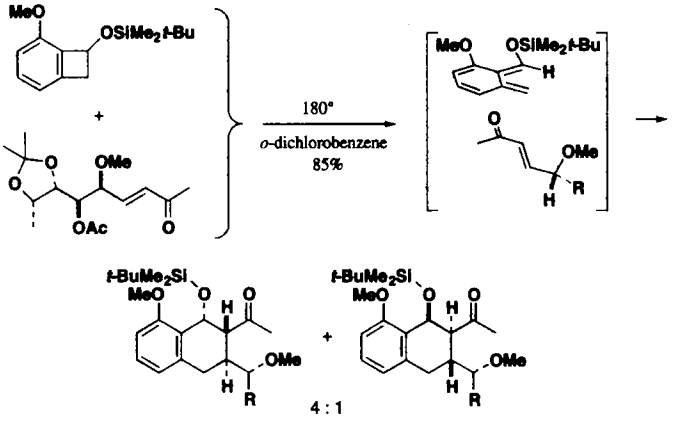
(78)

In order to prepare aryltetralin lignans, Charlton has investigated the cycloaddition of α-hydroxy-*o*-xylylenes to the fumarate of methyl mandelate. He established the absolute stereochemistry of the reaction, since a single diastereoisomer is formed exclusively (*Eq.* 79).[148]



(79)

The reaction of *o*-xylylenes and enones bearing γ-chiral substituents is controlled by orbital effects.[149] The Houk theory predicts that the LUMO-HOMO interaction of the *syn* methoxy is more unfavorable than the *syn* alkyl interaction (*Eq.* 80).[150]

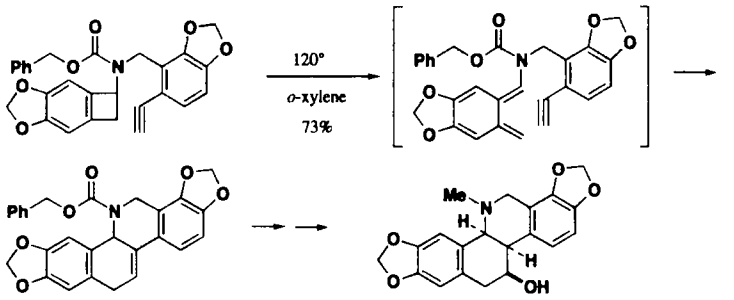


(80)

Birch reduction of cyanobenzocyclobutenes yields natural products such as *(d,l)*-gradisol or *(d,l)*-lineatin.[151]

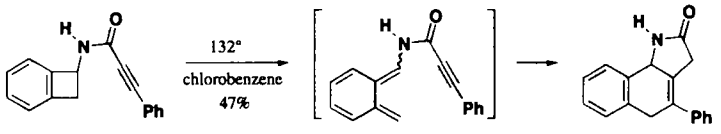
III. SYNTHESIS OF TRICYCLIC HETEROCYCLIC COMPOUNDS

In 1971, Oppolzer reported a synthesis of *(d,l)*-chelidonine, revealing the great importance of intramolecular *o*-quinodimethane cycloadditions (*Eq.* 81).[152]



(81)

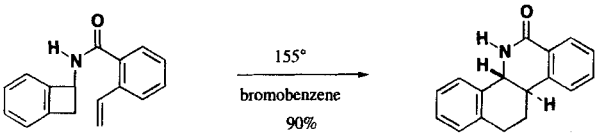
Application of this strategy to propargylic amides is a convenient route to benzo[g]indolin-2-ones (*Eq.* 82).[153]



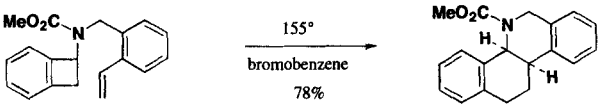
(82)

When the dienophile is an alkyne, there is no ambiguity for the stereochemistry of the newly formed bonds. In the case of styrene derivatives, Oppolzer has shown that the stereochemistry of the ring junction depends on the nature of the bridge between the dipole and the dipolarophile. For

instance, thermolysis of benzamides affords *trans* cycloadducts (*Eq.* 83). However, if the bridge between the two partners exhibits a flexible function such as an amine, the created ring junction will be *cis* (*Eq.* 84).

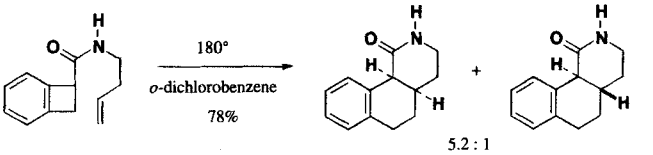


(83)

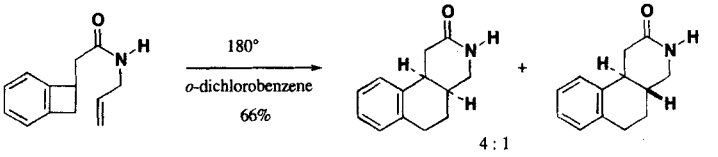


(84)

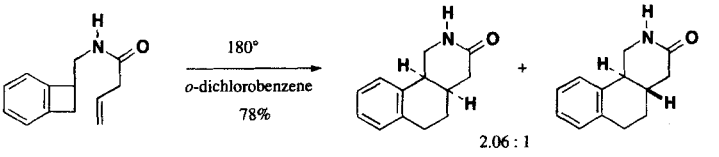
Similarly, the stereochemical outcome of intramolecular cycloadditions involving a nonconjugated dienophile is related to the nature of the bridge.[154] For example, pyrolysis of amides leads preferentially to the *cis*-fused cycloadducts (*Eq.* 85–87).



(85)

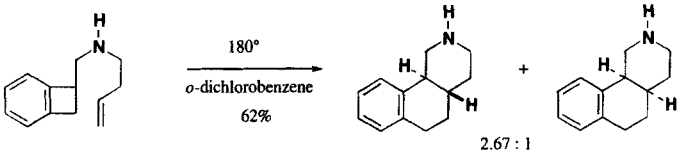


(86)

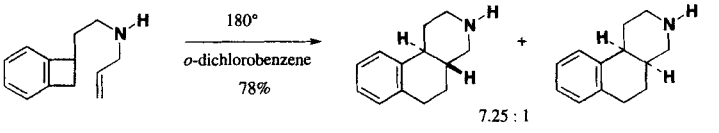


(87)

In contrast, amines afford mostly the corresponding *trans* isomers (*Eqs.* 88 and 89).

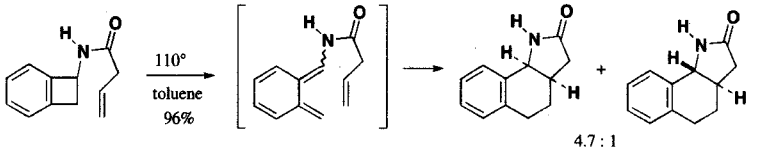


(88)



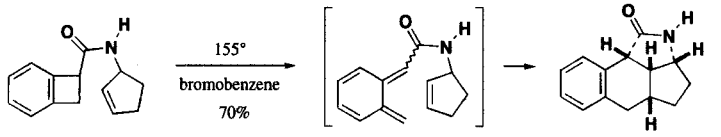
(89)

Benzocyclobutenylamide derived from vinylacetic acid gives principally the *cis*-fused cycloadduct.[155]

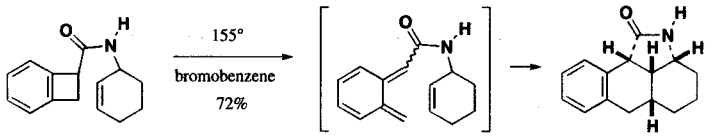


(90)

It is noteworthy that cycloaddition of amides bearing a cyclic olefin leads with high yields to tetracyclic adducts with stereochemical control of three stereogenic centers (*Eqs.* 91 and 92).

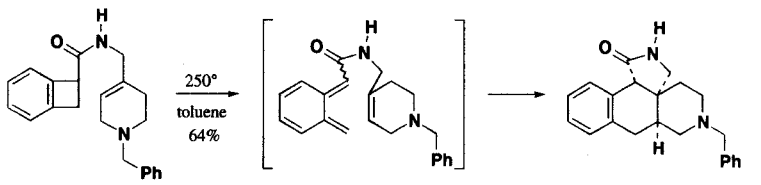


(91)



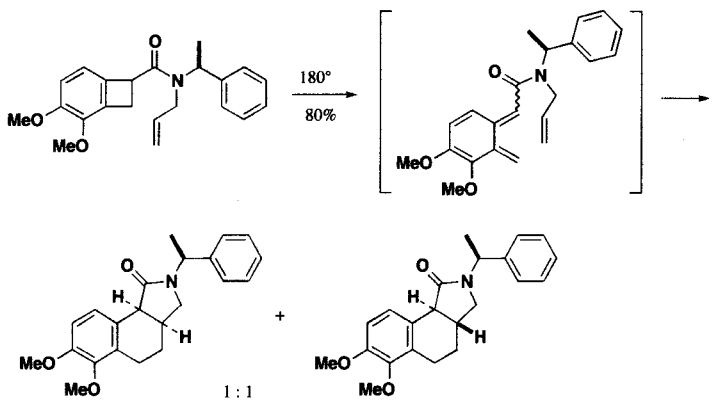
(92)

Similar control is still operative in the case of trisubstituted olefinic bonds (*Eq.* 93).



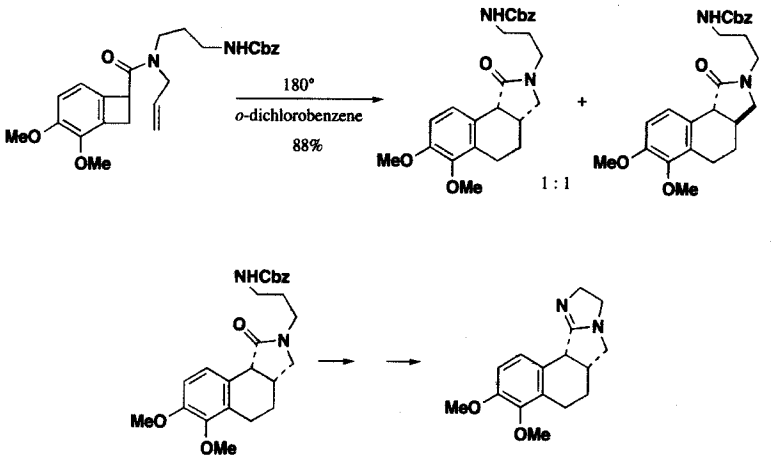
(93)

In order to induce *exo/endo* diastereoselectivity, the use of chiral auxiliaries have been investigated. Unfortunately, thermolysis of the following chiral amide gave a 1:1 mixture of *cis* and *trans* adducts (*Eq.* 94).[156]



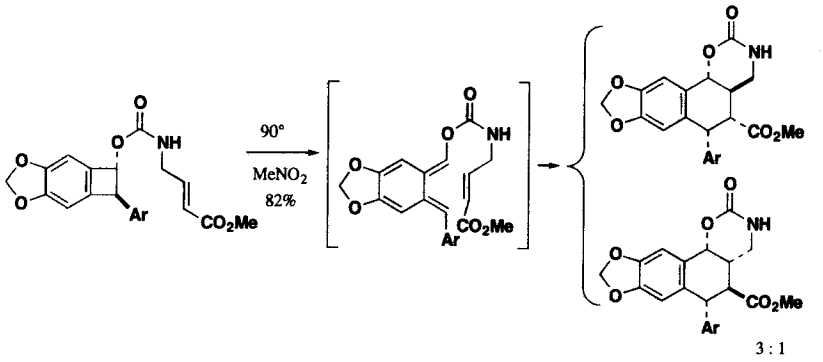
(94)

A potential α-adrenergic agent has been prepared *via* intramolecular Diels-Alder reaction of the following amide (*Eq.* 95).[157]

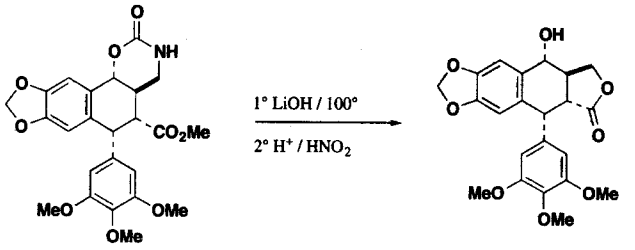


(95)

Strategies involving *o*-xylylenes cycloaddition have been described in order to generate lignane derivatives. Thus, several synthesis of *(d,l)*-podophillotoxin have been reported in the past decade.[158] For instance, Jung has developed a route to this important precursor of anticancer drugs such as etoposide (*Eqs*. 96 and 97).[159]

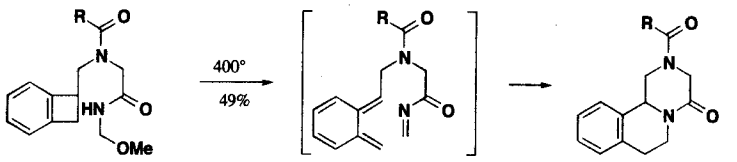


(96)



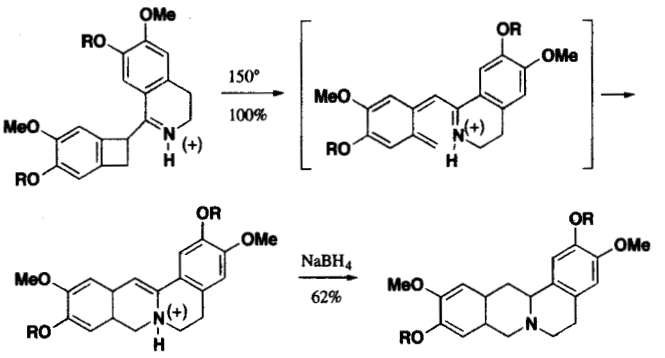
(97)

An efficient way to praziquantel, a well-known drug for the treatment of schistosomiasis, is constituted by an internal imino Diels-Alder (*Eq*. 98).[160]



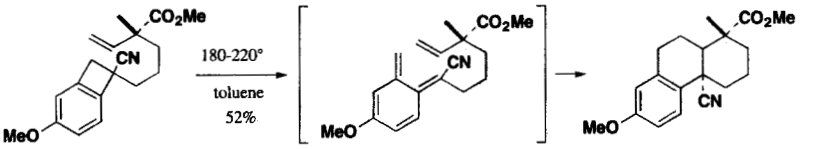
(98)

A benzocyclobutenic acid is readily converted into the corresponding 3,4-dihydroisoquinoline hydrochloride, whose thermolysis followed by sodium borohydride reduction furnishes *(d,l)*-tetrahydropalmatine.[161] In utilizing this strategy, other alkaloids such as *(d,l)*-coreximine can be obtained (*Eq.* 99).[162]



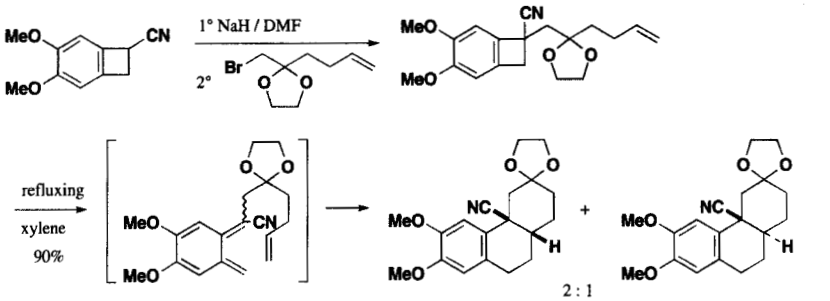
(99)

Kametani has described the preparation of a key intermediate in the total synthesis of atisine, veatchine, garryine or gibbereline A (*Eq.* 100).[163]

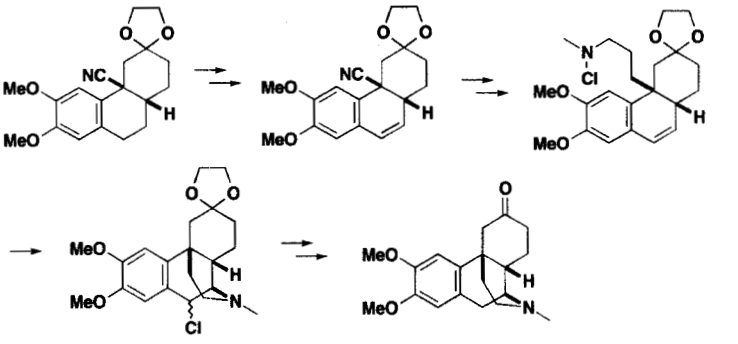


(100)

A stereoselective synthesis of a morphinan ring system has also been achieved by the same author (*Eq.* 101).[164] After manipulation of the cyano group of the tricyclic compound exhibiting a *cis* ring junction, morphinan derivatives can be afforded (*Eq.* 102).



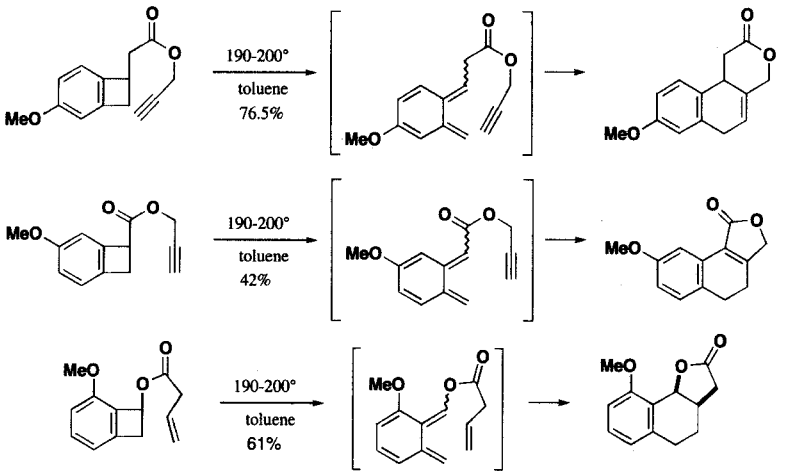
(101)



(102)

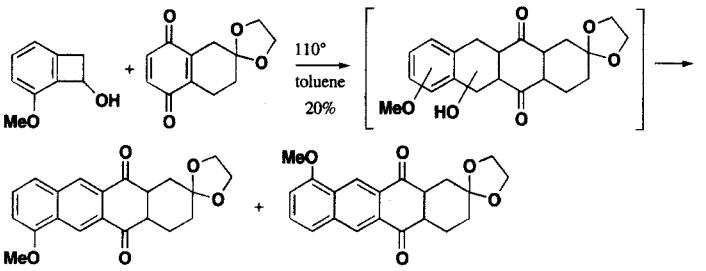
IV. SYNTHESIS OF POLYCYCLIC NATURAL COMPOUNDS

Basic skeletons of naturally occuring terpenoidal lactones can be synthesized *via* thermolysis of benzocyclobutenes (*Eq.*103).[165,166]

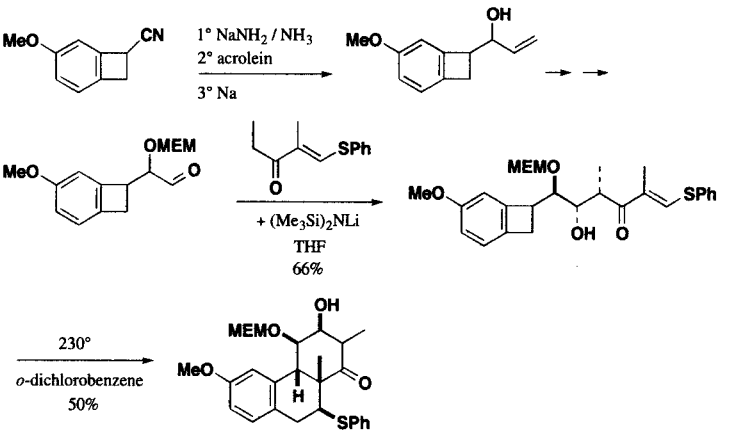


(103)

Benzocyclobutenes have also been involved in a useful synthesis aimed at tetracycline antibiotics. Unfortunately, no regioselectivity was observed (*Eq.* 104).[167] However, high diastereoselectivity is usually achieved as for the example of the *Eq.* 105.[168]

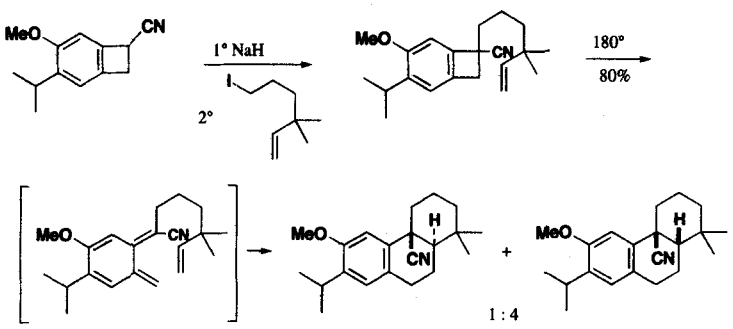


(104)



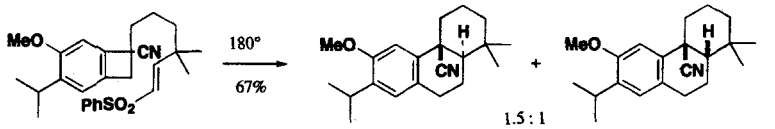
(105)

Jones has recently reported a revisited synthesis of pisiferol based on the use of benzocyclobutenes. When the dienophile is a simple vinyl group, the required product with *trans*-BC ring junction is unfortunately the minor product (*Eq.* 106).[169]



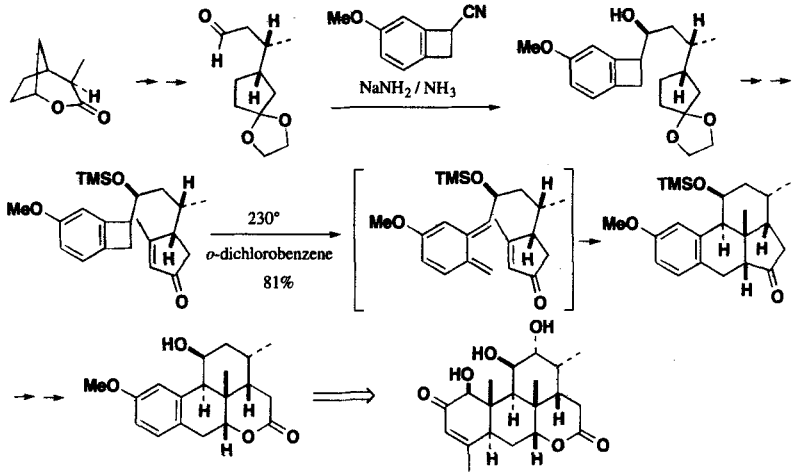
(106)

The stereochemical problem was corrected by the use of a dienophile possessing a sulfone group, leading to a much improved *trans*:*cis* ratio of 1.5:1 (*Eq.*107).



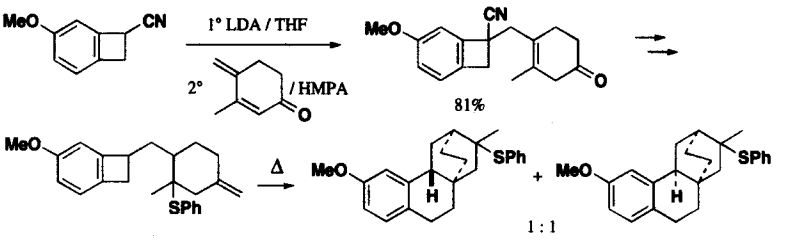
(107)

A stereoselective construction of the klaineanone ring system represents a new synthetic approach to quassinoids *via* the intramolecular Diels-Alder reaction of benzocyclobutenes (*Eq.* 108).[170]



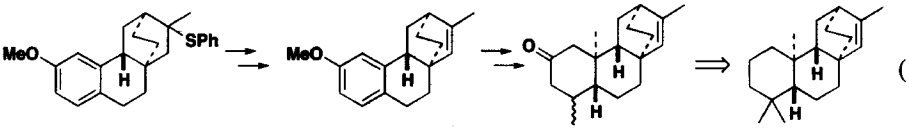
(108)

The opening of suitably substituted benzocyclobutenes affords polycyclic molecules such as bicyclo[2.2.2]octanes or bicyclo[3.2.1]octanes. This procedure was used by Fukumoto in a synthetic approach to isoatisirene. Thermolysis of dihydrocyclobutabenzene leads to the tetracyclic compounds as an inseparable mixture (*Eq.* 109).



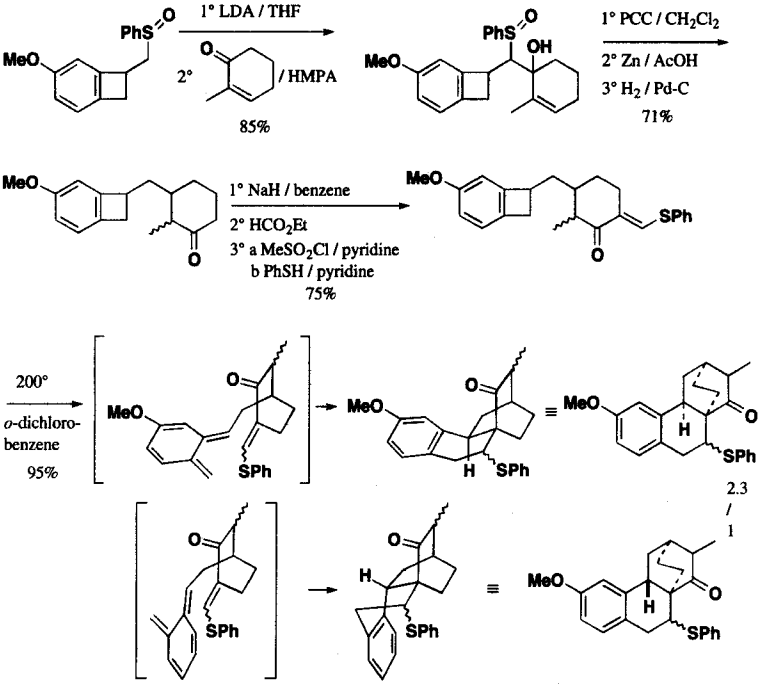
(109)

Conversion of the two diastereoisomers into the corresponding sulfoxides, followed by elimination and then chromatographic separation, afforded a useful precursor of isoatisirene (*Eq.* 110).[171]



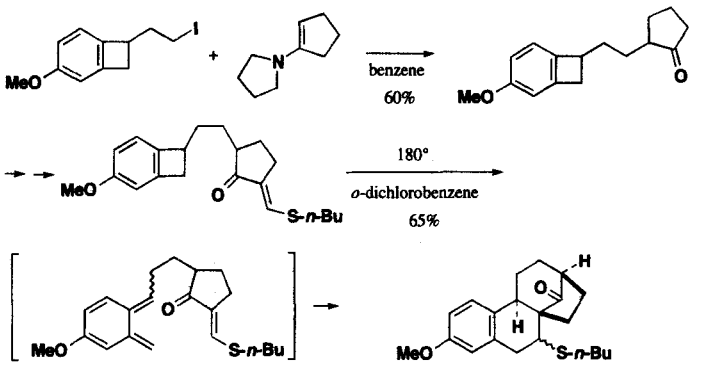
(110)

The absence of a bulky substituent at C(2) position on the cyclohexane ring of the dihydrocyclobutabenzene might be expected to increase the stereoselectivity of the cycloaddition. Unfortunately, the unwanted isomer with the *cis*-ring junction is favored through an *endo* approach (*Eq.* 111).



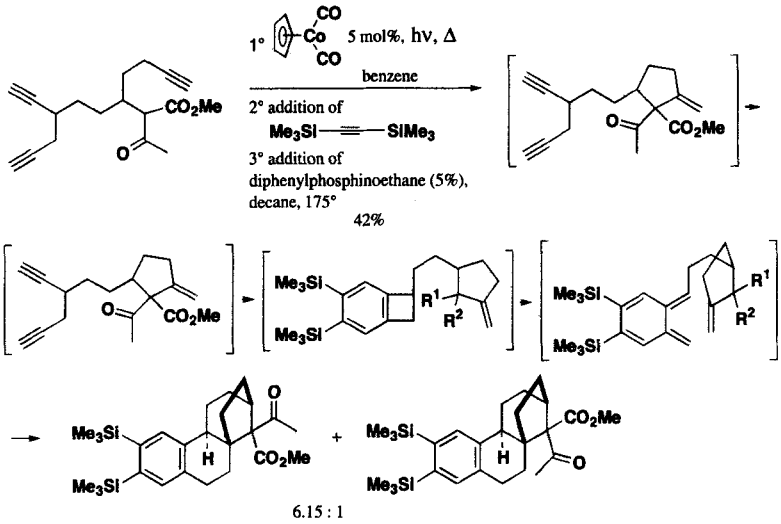
(111)

A large class of diterpenoids contains a bicyclo[3.2.1]octane skeleton. In a quest for preparing these compounds, Fukumoto has proposed a simple and efficient procedure involving benzocyclobutene derivatives (*Eq.* 112).[172–175]



(112)

Recently, an unprecedented entry to the basic framework of the tetracyclic diterpenes of the phyllocladane type has been reported by Malacria. The strategy is based on a sequence of three consecutive cycloaddition reactions: an ene type reaction, a [2+2+2] cobalt-catalyzed cyclization and an intramolecular [4+2] cycloaddition (*Eq.* 113).[176]

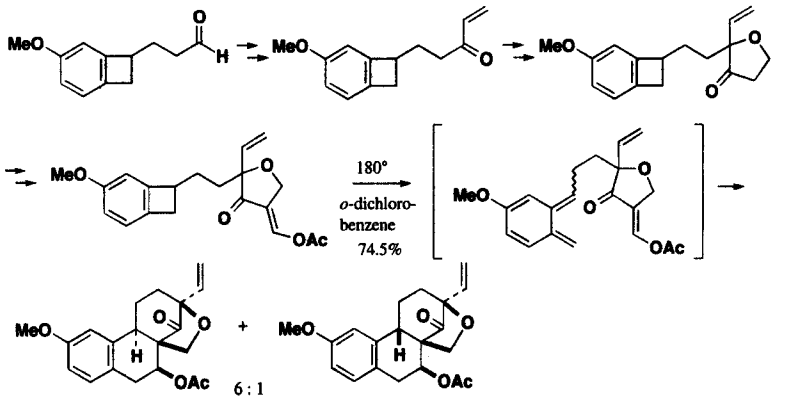


(113)

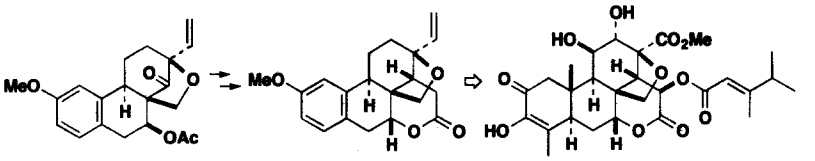
In 1983, Fukumoto successfully performed the intramolecular cycloaddition of an acetoxymethylene furanone in order to propose a novel approach to pentacyclic precursors of *(d,l)*-bruceantin (*Eq.* 114).[177,178]

The major compound is converted into a pentacyclic system which possesses the basic framework of bruceantin (*Eq.* 115).

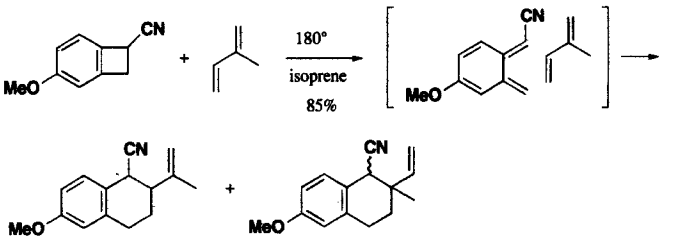
A convenient synthesis of key intermediates for the synthesis of alnusenone and friedelin has been described by Kametani. The methodology involves two successive *o*-xylylenes cycloadditions.[179] The first is a non-regioselective intermolecular cycloaddition of 1-cyano-4-methoxy benzocyclobutene with isoprene (*Eq.* 116).



(114)

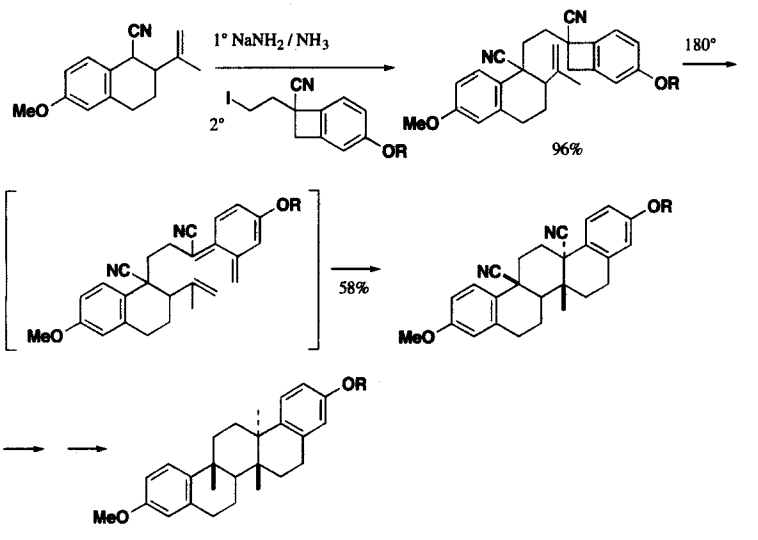


(115)



(116)

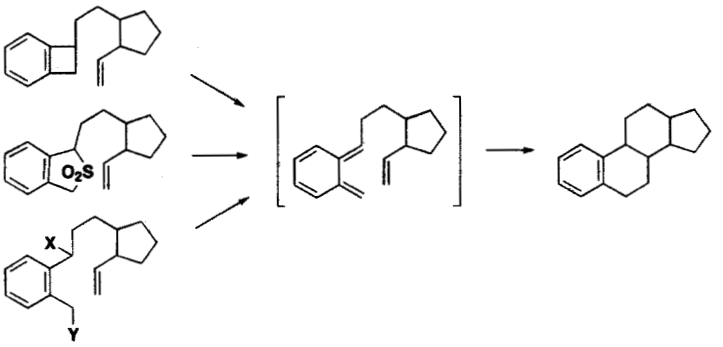
One of the two tetralin derivatives is then alkylated by a benzocyclobutene residue to give, after thermolysis, interesting pentacyclic compounds (*Eq.* 117).



(117)

V. SYNTHESIS OF STEROIDS

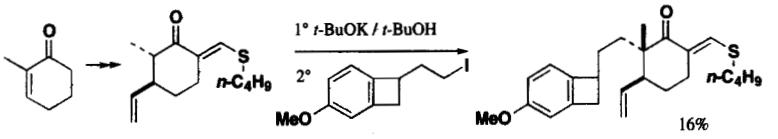
Intramolecular cycloaddition of an *o*-quinodimethane and a double bond attached to a cyclopentane ring, constitutes an efficient synthetic route to steroids. The most common way of producing *o*-xylylenes is by thermolysis of benzocyclobutenes.[180] But, other methods such as thermal extrusion of sulfur dioxide from sulfones, photoenolization of *o*-alkyl-benzaldehydes or 1,4-elimination are also applied to generate *o*-xylylenes (*Eq.* 118).



(118)

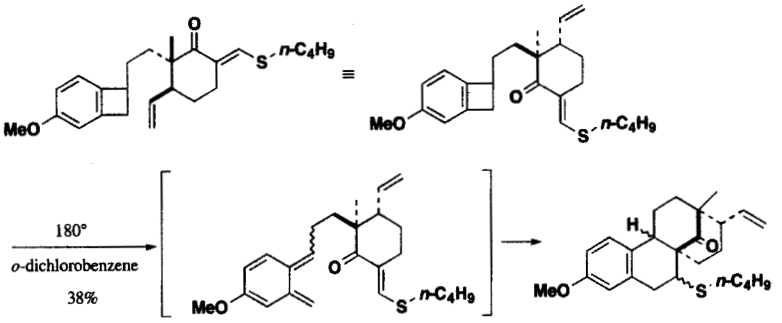
a. Synthesis of Estrone Derivatives

The synthesis of estrone has held a special fascination for organic chemists, and many types of approaches have been reported towards this natural sex hormone. The first total synthesis of D-estrone *via* the intramolecular cycloaddition reaction of benzocyclobutenes was reported by Kametani.[181] The preparation of methyl-D-homoestrone is straightforward, but the overall yield is low. The key intermediate is prepared from methylcyclohexenone (*Eq.* 119).



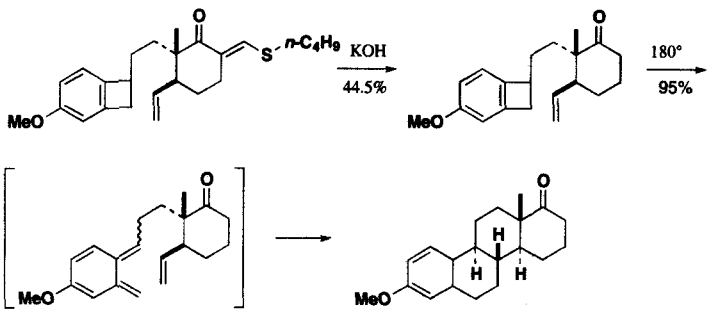
(119)

Actually, the cycloaddition involves the conjugated double bond (*Eq.* 120).



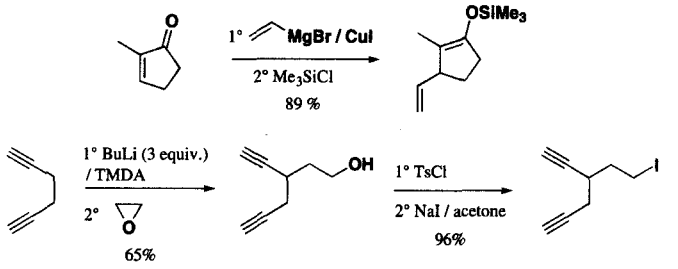
(120)

Removal of the protecting group in the benzocyclobutene followed by thermolysis affords methyl D-homoestrone having the correct stereochemistry (*Eq.* 121).[182]



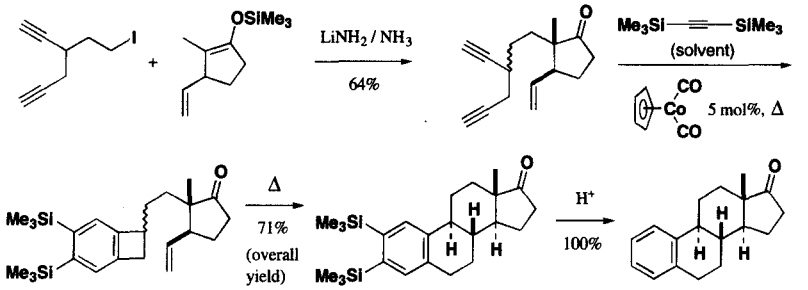
(121)

The strategy has been markedly improved by Vollhardt, who prepared the intermediate benzocyclobutene *in situ* from an ene diyne derivative.[183] This latter arises from methylcyclopentenone and 1,5-hexadiyne (*Eq.* 122).[184]



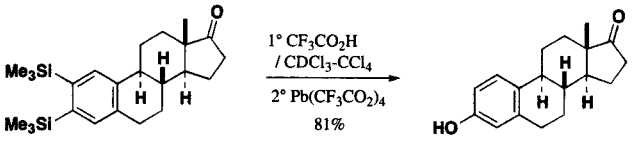
(122)

After alkylation, the cobalt-mediated [2+2+2] cycloaddition leads to the benzocyclobutene which is directly transformed into an estrone derivative (*Eq.* 123).



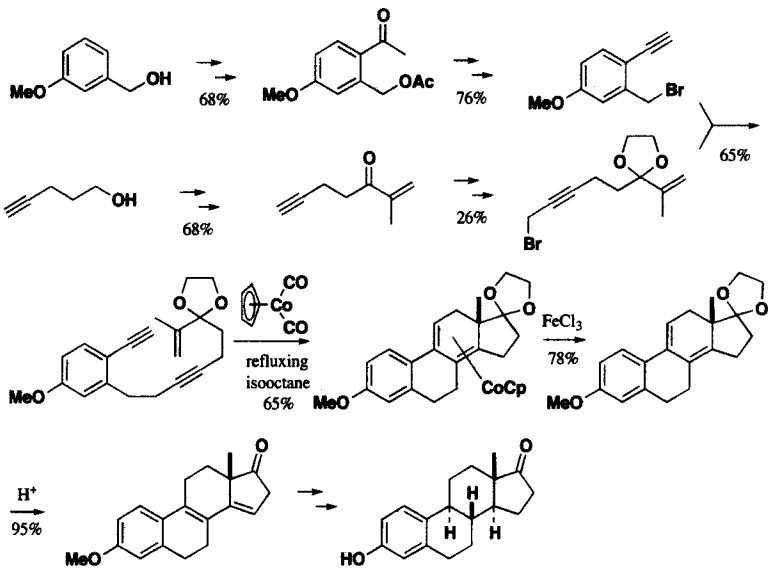
(123)

A further protodesilylation finally gives estratrienone (*Eq.* 124).[185] The most important drawback of this sequence is the necessity to use one equivalent of catalyst.[186]



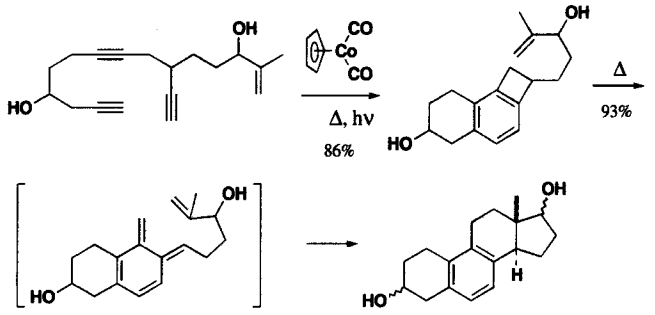
(124)

Vollhardt has proposed another methodology which provides in one-step the B,C,D framework of steroids from an A ring precursor. After a serie of reactions, the Torgov intermediate was isolated and easily converted into estrone (*Eq.* 125).[187]



(125)

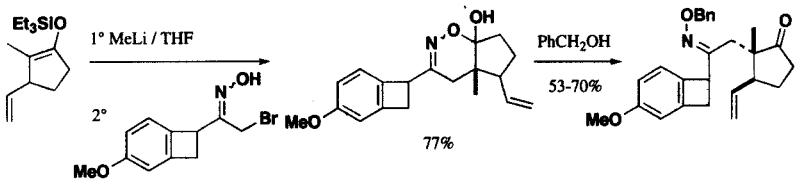
A total synthesis of equileine derivatives has been achieved in this fashion (*Eq.* 126).[188]



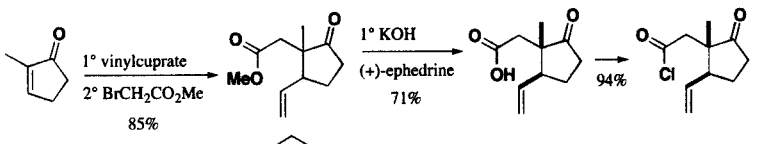
(126)

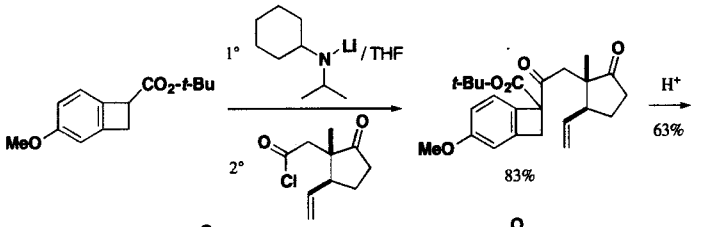
In 1977, Oppolzer reported a highly stereoselective synthesis of C(11)-functionalized aromatic steroids by intramolecular cycloaddition.[189] A selective *endo*-reaction of an *o*-xylylene leads exclusively to the *cis-anti-trans* steroid (*Eq.* 127). He later reported an enantioselective route to 11-oxoestrone involving a racemic resolution of the vinylcyclopentanone. The racemic benzocyclobutenecarboxylic ester was treated with lithium cyclohexylisopropylamide and then acylated to give the key intermediate, whose thermolysis leads to the optically pure steroid with natural *trans-anti-trans* configuration (*Eq.* 128).[190]

Fukumoto has described the synthesis of the following cyclobutanone with the aim of preparing aldosterone antagonists (*Eq.* 129).[191]

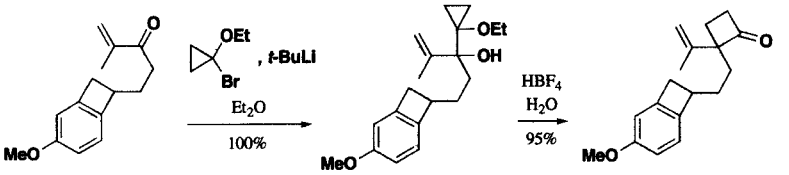


(127)



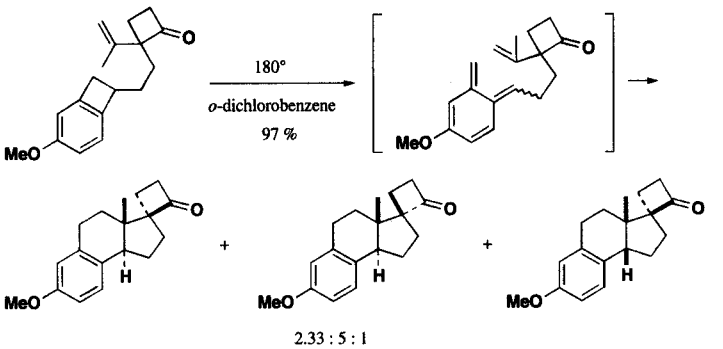


(128)



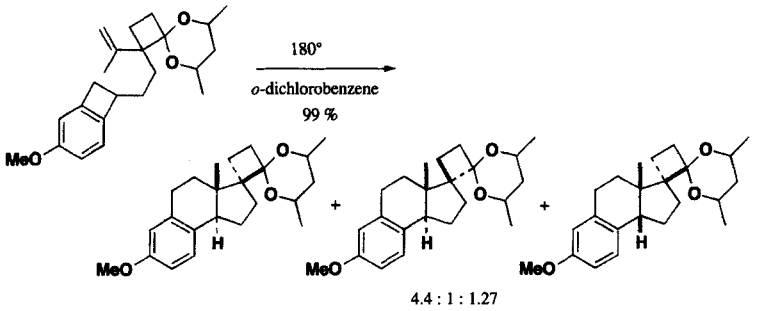
(129)

Thermolysis of this cyclobutanone provides a mixture of three tricyclic compounds (*Eq.* 130).



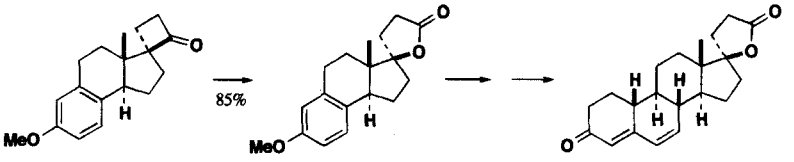
(130)

If the cyclobutanone is previously acetalized with 2,3-pentanediol, the distribution of the cycloadducts is different (*Eq.* 131).



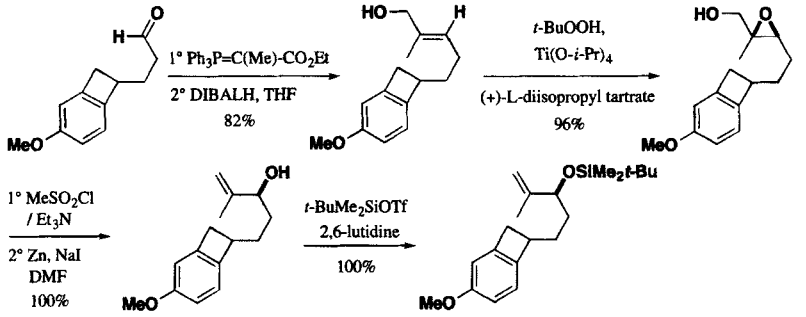
(131)

The major product afforded by cycloaddition of the free cyclobutanone has been efficiently converted into 19-norcanrenone (*Eq.* 132).



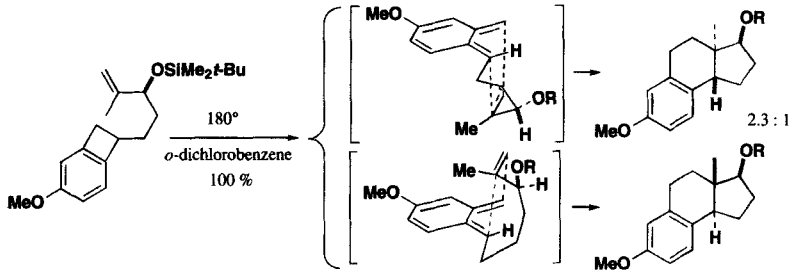
(132)

Fukumoto has achieved the synthesis of optically active alkenic benzocyclobutenes. Asymetric epoxidation of an allylic alcohol followed by reductive epoxide ring opening affords the intermediate isopropenyl alcohol whose cyclization gives two isomers in a ratio of 2.3:1 (*Eq.* 133).[192,193]



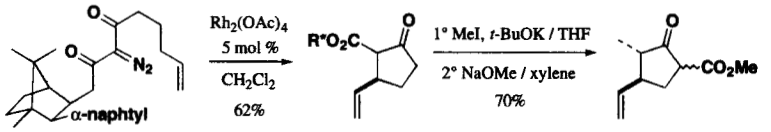
(133)

Both the two *trans*-fused steroids result from the reaction of the *o*-xylylene, exhibiting the (E)-configuration (*Eq.* 134). A stereoselective synthesis of des-AB-aromatic azasteroids has been achieved by thermolysis of 2-methylpropenamide.[194]



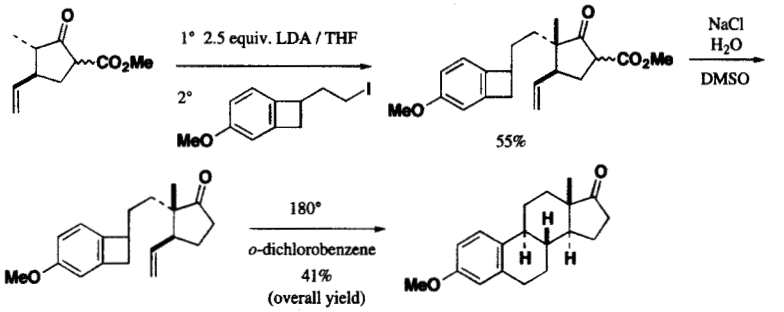
(134)

In 1987, Taber reported the first enantioselective synthesis of (+)-estrone, starting from a chiral vinylcyclopentanone, prepared from a chiral diazoester (*Eq.*135).[195]



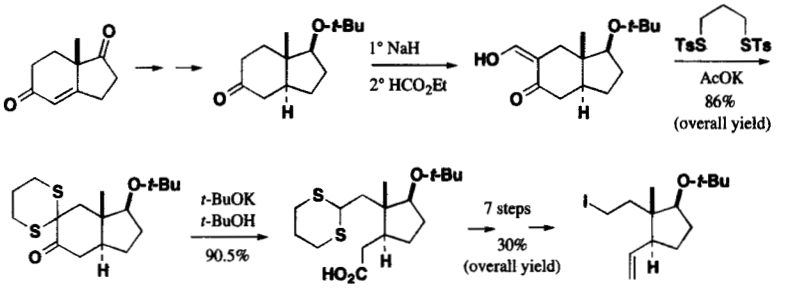
(135)

After geminal alkylation of the cyclic β-ketoester with the requisite iodide followed by decarbomethoxylation, final thermolysis leads to the expected (+)-estrone methyl ether (*Eq.* 136).



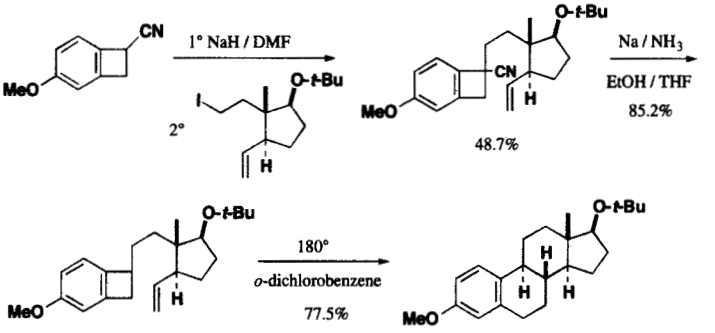
(136)

A chiral hydrindenone, readily available by Robinson annelation,[196] is the starting material of an asymmetric synthesis of estradiol.[197] A fragmentation reaction is involved to generate the intermediate vinylcyclopentanol (*Eq.* 137).



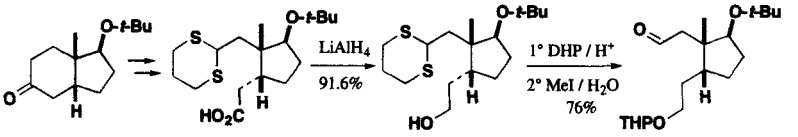
(137)

The estradiol precursor results from alkylation of a cyanobenzocyclobutene, followed by decyanation and cyclization (*Eq.* 138).



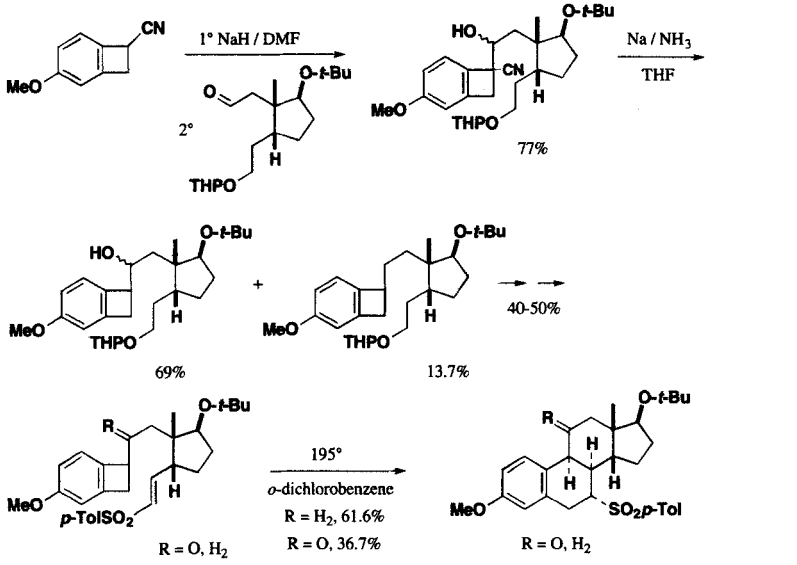
(138)

The same strategy has been applied to a *cis*-indanone, providing a chiral aldehyde bearing a masked vinyl group (*Eq.* 139).



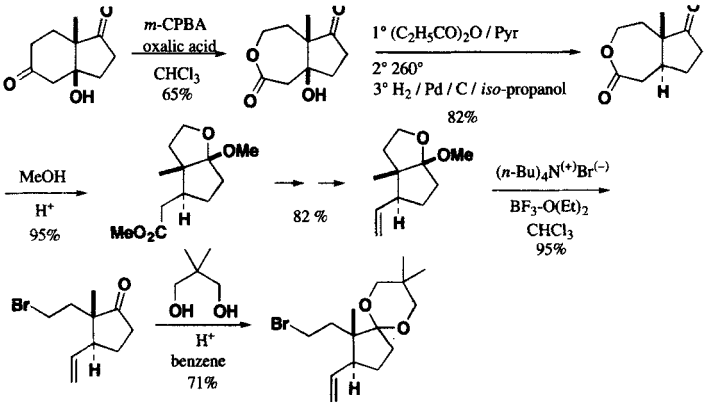
(139)

Condensation of this aldehyde with a cyanobenzocyclobutene promoted by sodium amide affords an hydroxy cyano compound, which is further partially reduced under Birch conditions. The double bond is then generated *via* phenylselenylation procedure. The final thermolysis is stereoselective, since the *cis-anti-cis* fused estrane is formed exclusively.[198] Moreover, this methodology is an efficient route to 11-substituted steroids (*Eq.* 140).



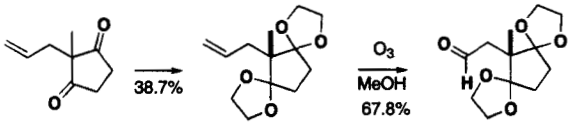
(140)

A hydroxydione, which is easily accessible in chiral form by proline-catalyzed Robinson annelation, can be converted into a chiral synthon for the total synthesis of estrone.[199] This compound is the future D ring component of the steroid (*Eq.* 141).



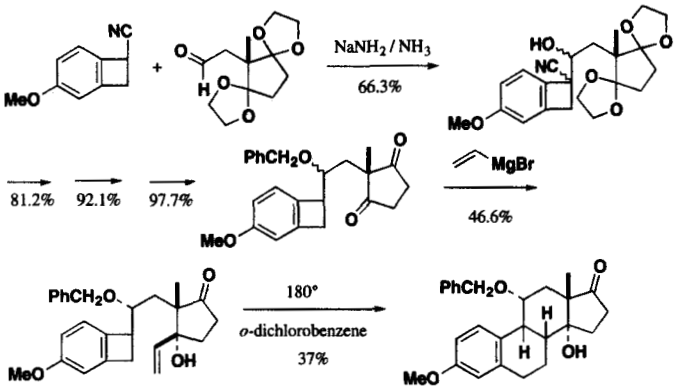
(141)

Kametani has developed a stereoselective synthesis of 11-functionalized 14α-hydroxyestrone methyl ether, by using methylcyclopentanedione as starting material (*Eq.* 142).



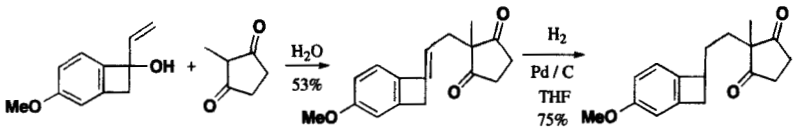
(142)

As described earlier, a cyanobenzocyclobutene is condensed with an aldehyde in the presence of a base to give an alcohol as a diastereoisomeric mixture. A three step-sequence provides the functionalized cyclopentadione, which is treated with vinylmagnesium bromide (or submitted to ethynylation followed by hydrogenation) to give the required olefinic benzocyclobutene (*Eq.* 143).[200-202]



(143)

Blazejewski has used a Torgov reaction to prepare a similar cyclopentanedione derivative, involved in a total synthesis of *(d,l)*-14α-hydroxyestrone (*Eq.* 144).[203]

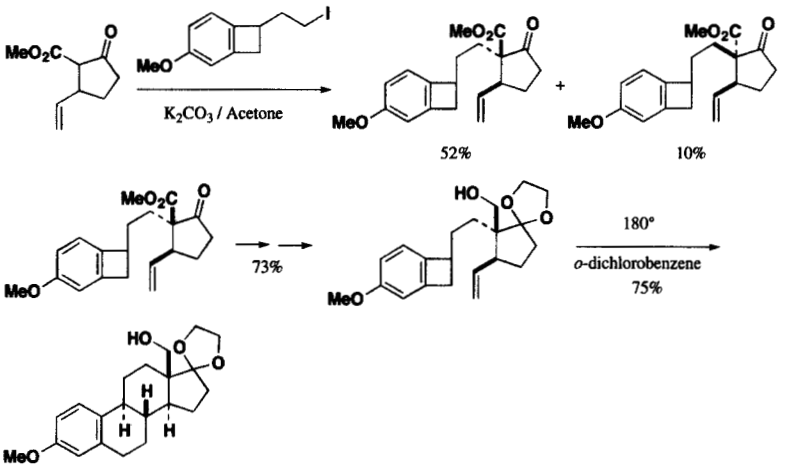


(144)

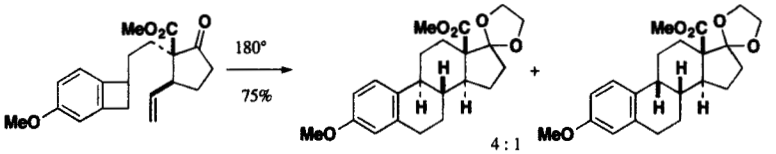
2-Methoxycarbonyl-3-vinyl-cyclopentanone,[204] easily prepared through a palladium-catalyzed cyclization reaction, has been used by Tsuji, as a precursor for a simple total synthesis of 18-hydroxyestrone methyl ether (*Eq.* 145).[205] In the case of the methyl ester, the stereoselectivity of the thermolysis is lower (*Eq.* 146).

Recently, Takahashi has proposed a very short synthesis of estrone (four steps). The first step is a Dieckmann condensation of diallyl adipate followed by alkylation of the resulting β-ketoester with the usual iodide. After formation of the cyclopentenone, conjugate addition of a vinylic cuprate and methylation, the expected precursor is obtained (*Eq.* 147).

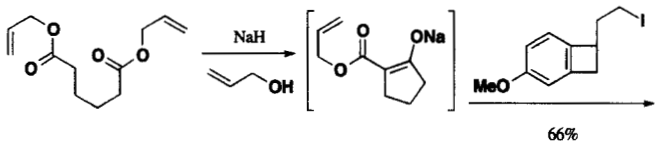
Heating the major isolated isomer gives a 90:10 mixture of *(d,l)*-estrone methyl ether and its C(9)-epimer (*Eq.* 148).[206] The corresponding enantioselective synthesis is based on the enantioselective conjugate addition of an alkenylcopper-phosphine complex to the enone previously mentioned. Fortunately, the major compound of the reaction exhibits the expected stereochemistry (*Eq.* 149).

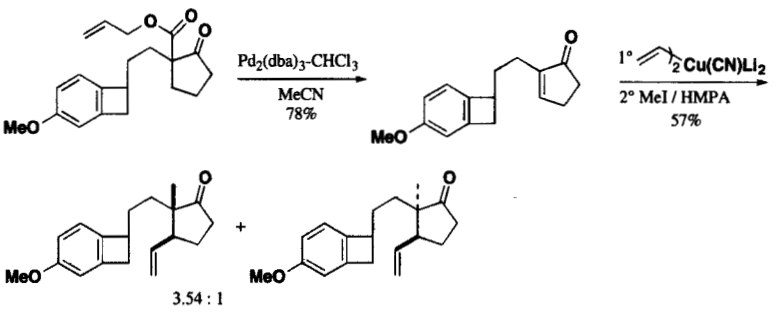


(145)

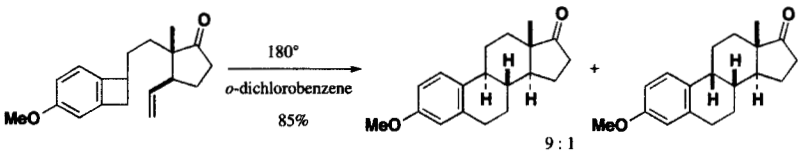


(146)

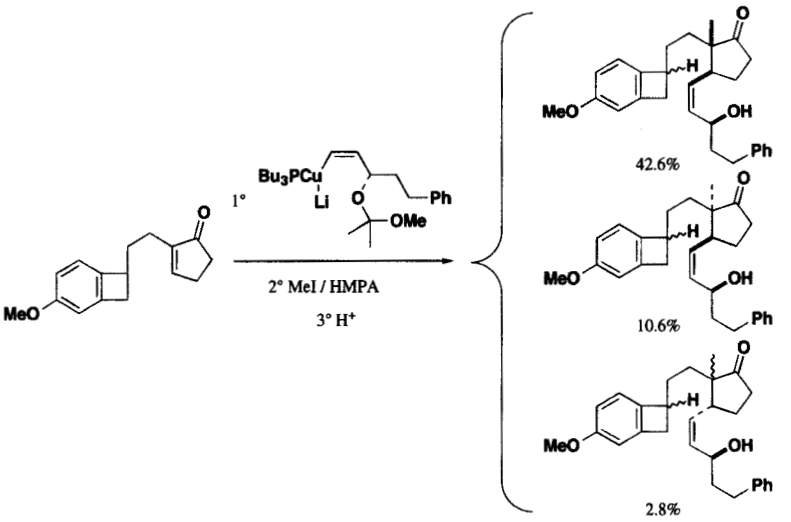




(147)

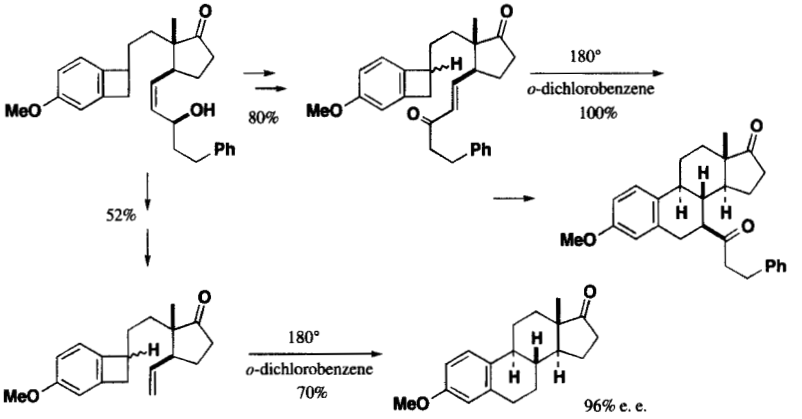


(148)



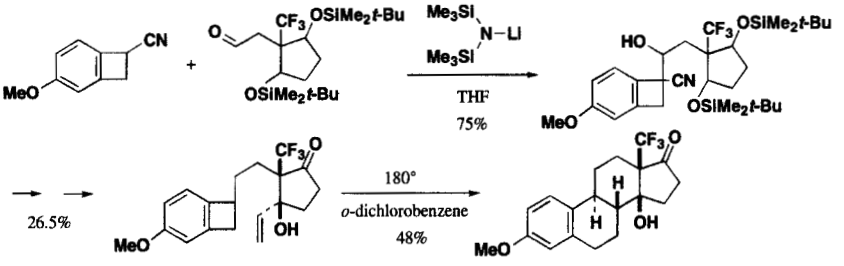
(149)

Since attempts to cyclize the allylic alcohol were unsuccessfull, the latter was first converted into the corresponding enone whose cycloaddition provided estrone derivatives. On the other hand, oxidative cleavage of the allylic alcohol followed by Wittig reaction of the resulting aldehyde affords (+)-estrone methyl ether (*Eq.* 150).[207]



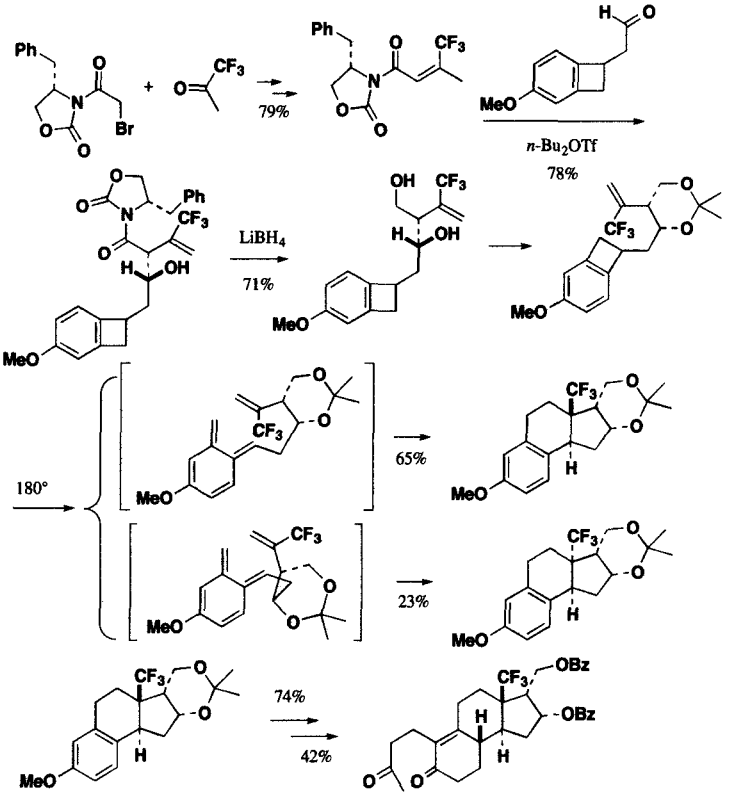
(150)

Synthesis of steroids bearing an angular trifluoromethyl group are of growing interest, because of biological activities of these molecules. For this purpose, Blazejewski has described an efficient preparation of 18-trifluoro-14-hydroxyestrone from trifluorocyclopentanedione (*Eq.* 151).[208]



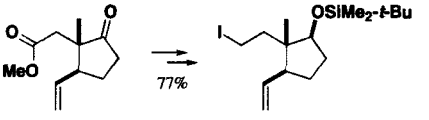
(151)

More recently, Fukumoto has achieved the first enantioselective synthesis of 18-trifluoro-steroids. In a first time, a chiral trifluorobenzocyclobutene is prepared in a straightforward manner from trifluoroacetone.[209] The second part of the synthesis consists in incorporating the A ring into the thermolysed tricyclic compound through a five-step sequence (*Eq.* 152).

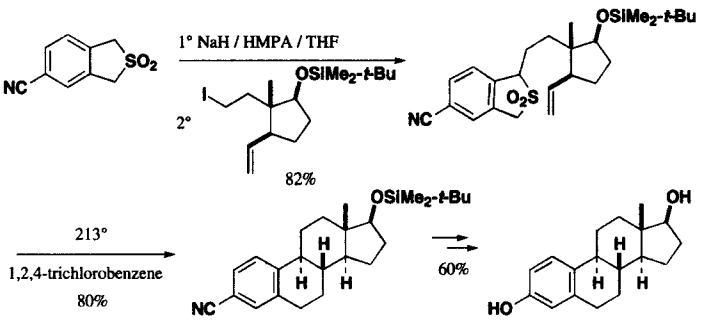


(152)

(+)-Estradiol has been synthesized by Oppolzer from a benzo-2,2-dioxothiophene by successive thermal SO_2-extrusion and cycloaddition. The second partner of the reaction is the chiral iodide obtained in *Eq.* 153. Treatment of this iodide with the sulfone in the presence of sodium hydride gives a precursor whose thermolysis extrudes SO_2. The pure isolated *trans-anti-trans* steroid is further converted into (+)-estradiol (*Eq.* 154).[210]

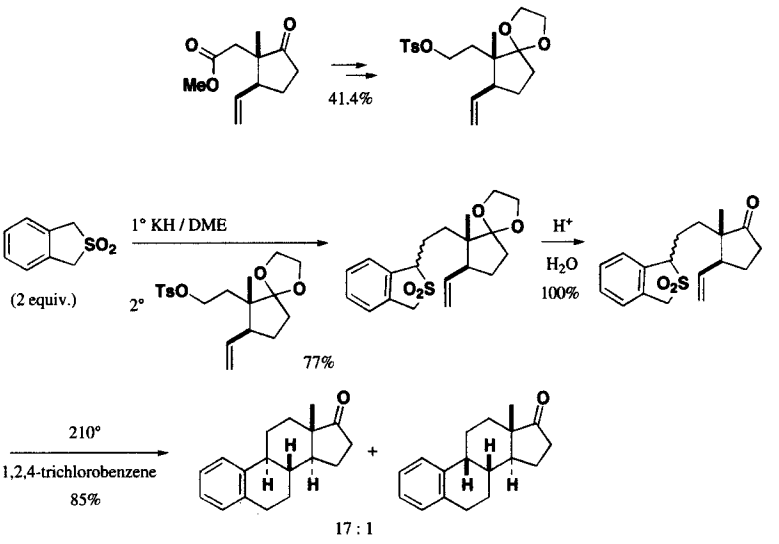


(153)



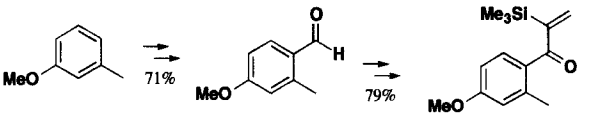
(154)

A similar methodology has been employed by Nicolaou to prepare several estrone derivatives (*Eq.* 155).[211]



(155)

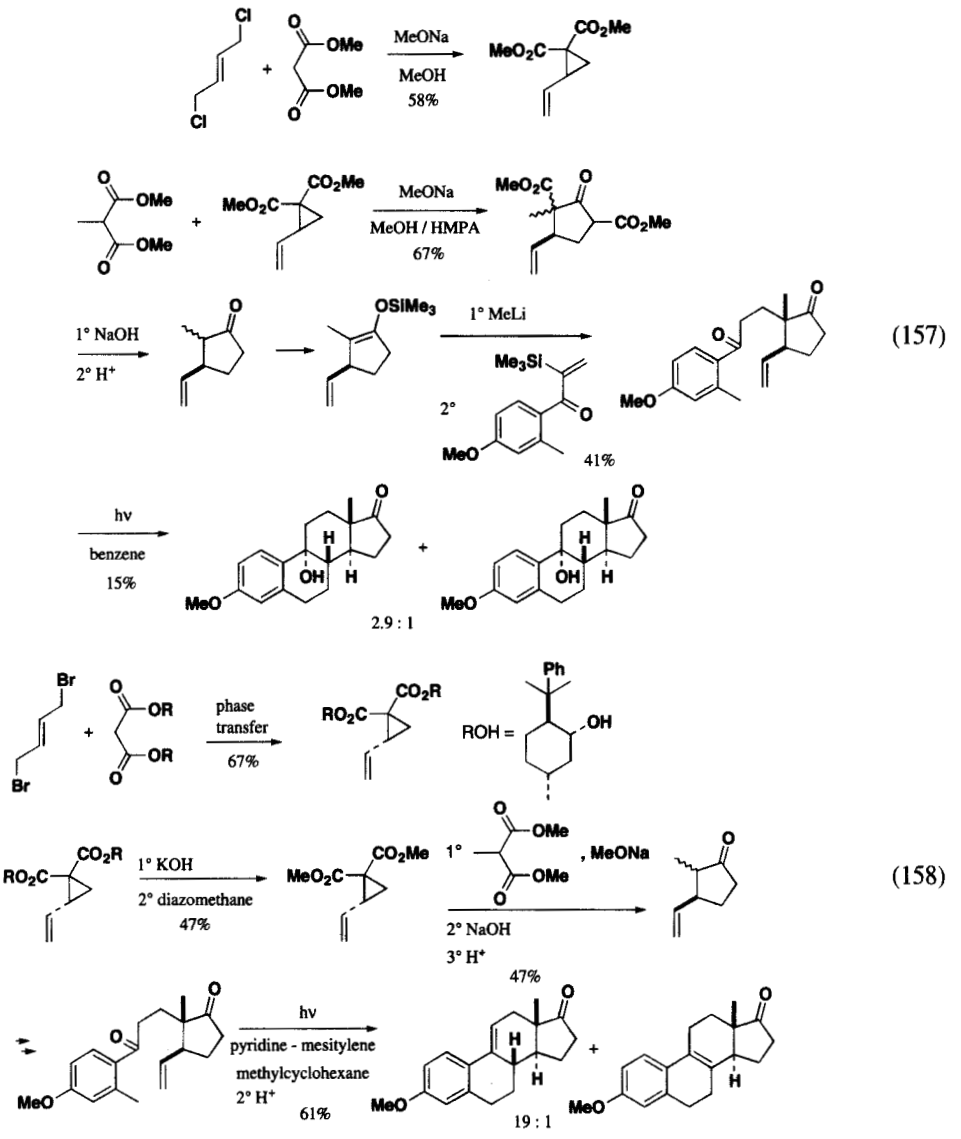
In his total synthesis of 19-nor-steroids, Quinkert generates *o*-xylylenes by photoenolization.[212] The starting material is an aromatic *o*-methyl ketone formed by Michael addition of vinylcyclopentanone enolate and a vinylketone, easily available from *m*-cresyl methyl ether (*Eq.* 156).



(156)

The precursor is obtained with a moderate yield by an original alkylation with malonic esters (*Eq.* 157).[213]

The involvement of a chiral synthetic building block such as 8-phenylmenthyl malonate allows the synthesis of enantiomerically pure target compounds.[214] The yield of the cyclization has been markedly enhanced by changing the photoenolization conditions (*Eq.* 158).

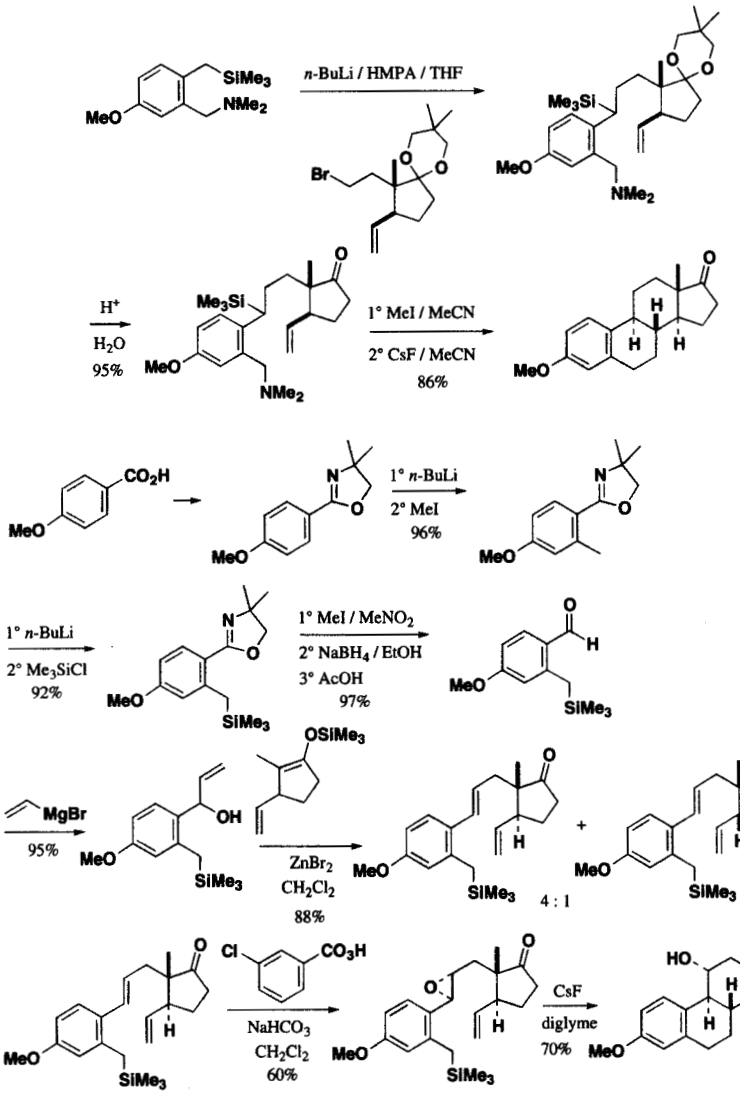


(157)

(158)

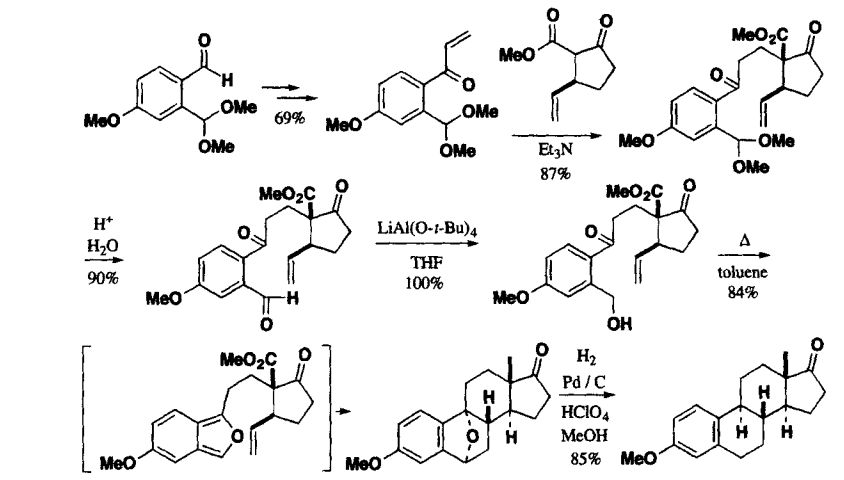
An efficient generation of *o*-xylylenes by fluoride anion induced 1,4-elimination of *o*-(α-trimethylsilylalkyl) benzyltrimethylammonium iodides, has been achieved by Saegusa in order to prepare estrone derivatives.[215] A simple alkylation of an α-silyl benzylic carbanion is performed to prepare the requisite precursor (*Eq.* 159).[216]

Magnus has employed a similar strategy in his exceptionally short synthesis of 11-hydroxy-estrone derivatives.[217] He used an epoxide group instead of an ammonium halide as the leaving group (*Eq.* 160).

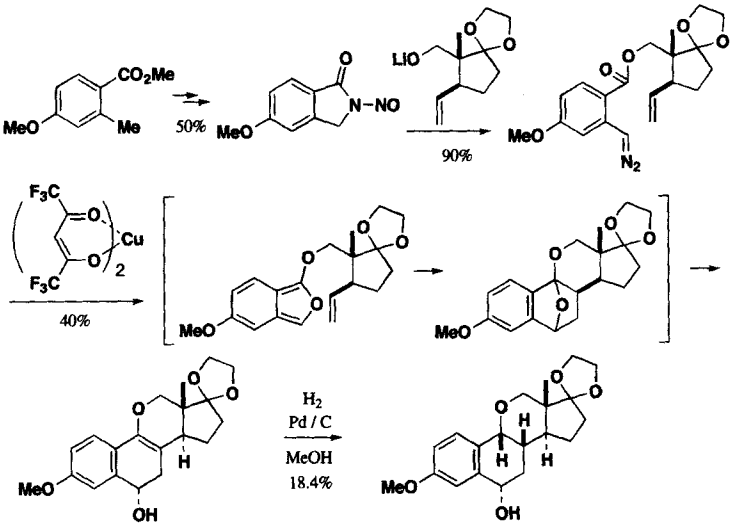


Friedrichsen has showed that the synthesis of 18-hydroxyestrone methyl ether can be performed by using an isobenzofuran generated *in situ* from a lactol dehydration. A further hydrogenolysis allows the removal of the oxygen bridge (*Eq.* 161).[218]

Several methods are available for the generation of isobenzofurans. For instance, diazo esters prepared *via* an Oppe reaction, may act as convenient precursors.[219] 11-Oxasteroid derivatives have been prepared by intramolecular cycloaddition of isobenzofurans prepared as shown in *Eq.* 162.

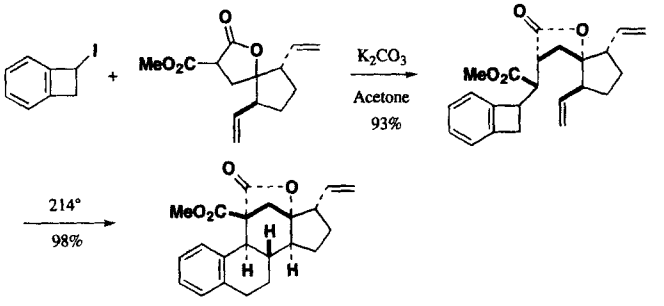


(161)



(162)

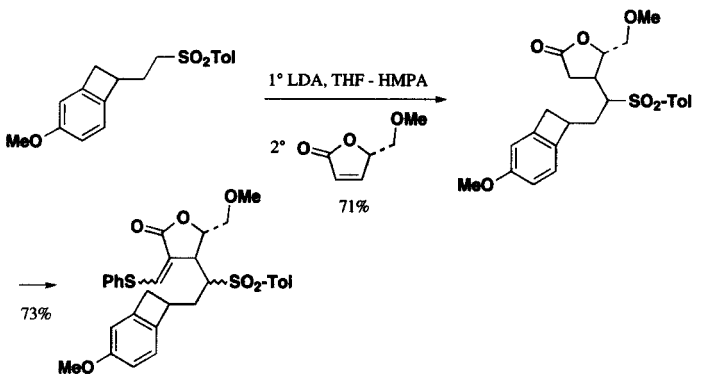
A stereoselective five-step synthesis of *(d,l)*-estrane derivatives from 1,3-butadiene has been recently elaborated (*Eq.* 163).[220]



(163)

b. Synthesis of Aldosterone

Much attention has been paid to the synthesis of aldosterone, because of its physiological importance as a mineral corticoid. Fukumoto has reported a synthetic approach of (+)-aldosterone starting from an homochiral butenolide conveniently prepared from D-(+)-ribonolactone (*Eq.* 164). Thermolysis of the resulting sulfoxide,[221] (R = SO_2Tol) or its corresponding reduced compound (R = H), yields a mixture of tricyclic products.[222] The stereoselectivity of the reaction is related to the nature of the substituent (*Eq.* 165).



(164)

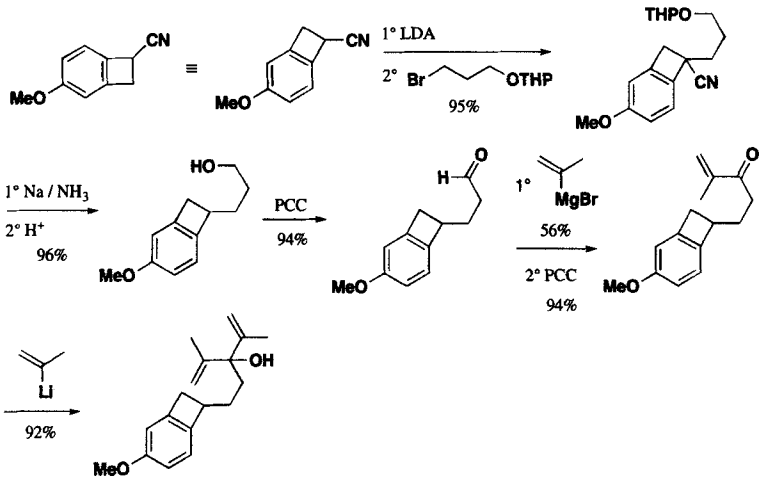
(165)

c. Synthesis of Adrenosterone and Cortisone

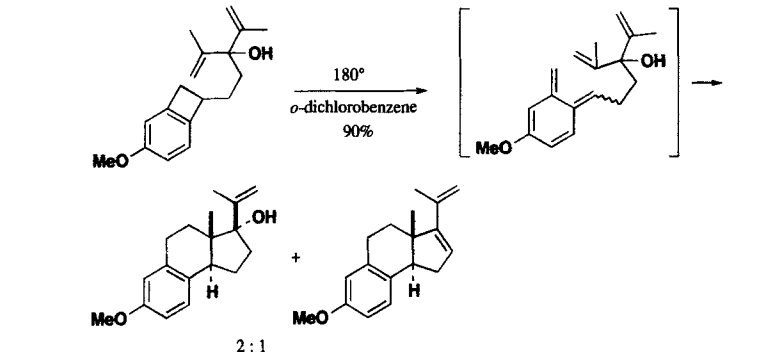
Because of their biological importance, corticosteroids have been intensively studied. In the quest for their synthesis, Kametani has prepared some precursors derived from cyanomethoxybenzocyclobutene.[223] An aldehyde, a ketone and a dienic alcohol are depicted in the *Eq.* 166. Next, the diisopropenylated alcohol is thermolysed to afford a tricyclic compound which constitutes a potent building block for the synthesis of corticosteroids (*Eq.* 167).

The aldehyde has recently been involved in a practical approach to chiral Des-AB-trienic corticosteroids.[224,225] For this purpose, it had been previously converted into an allylic alcohol which was then submitted to a Sharpless procedure. Subsequently, the chiral epoxy alcohol was opened by

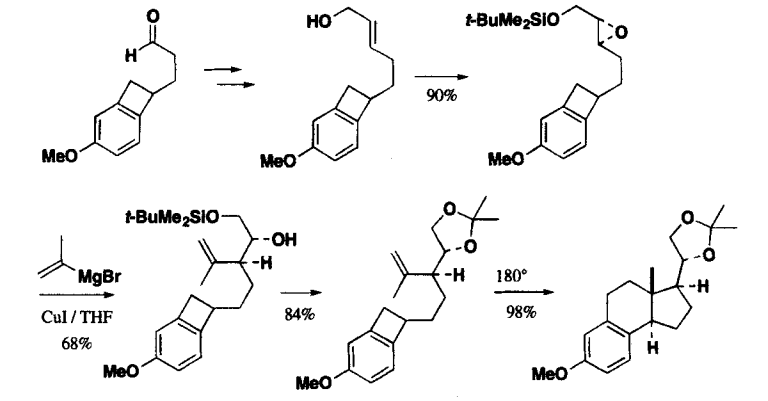
nucleophilic addition of an isopropenyl group and a final thermolysis affords the chiral tricyclic compound (*Eq.* 168).



(166)

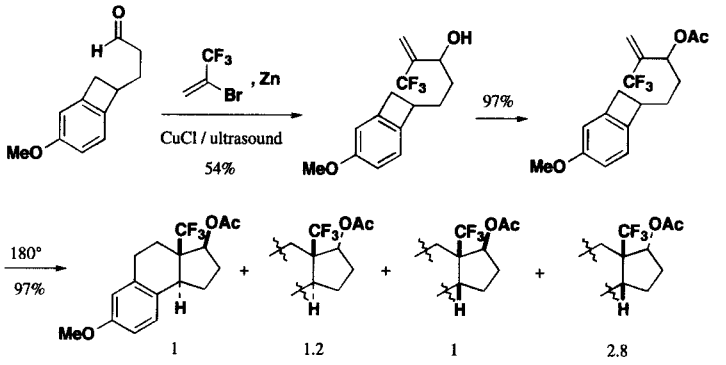


(167)



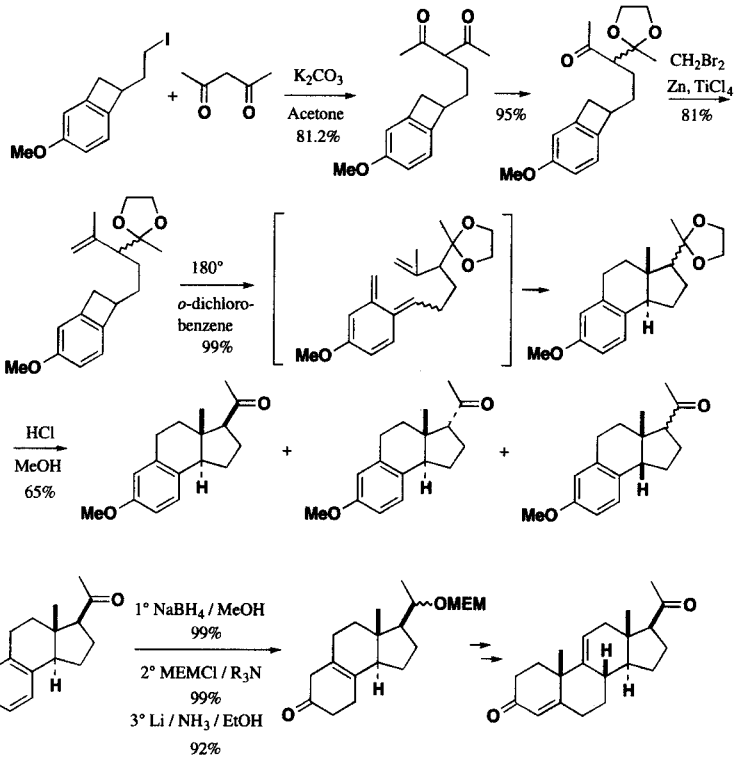
(168)

The same aldehyde has also been employed by Fukumoto as a suitable building block for the synthesis of 18-trifluoroestrans.[226,227] The approach consists in treating this adduct with trifluoroisopropenylbromide in the presence of zinc and CuI under irradiation of ultrasound. Thermolysis of the isolated allylic alcohol furnishes the expected estrans precursor (*Eq.* 169).



(169)

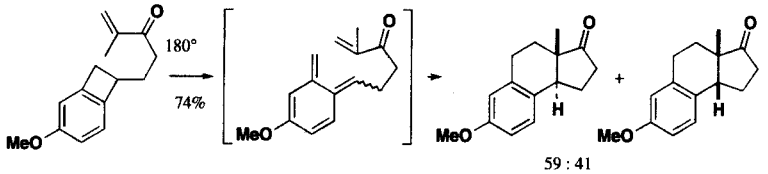
At the same time, Fukumoto described a very efficient preparation of an other tricyclic precursor bearing an acetyl group (*Eq.* 170).[228–230] The major ketone exhibiting the expected stereochemistry is then converted into cortisone *via* a potential intermediate (*Eq.* 171).



(170)

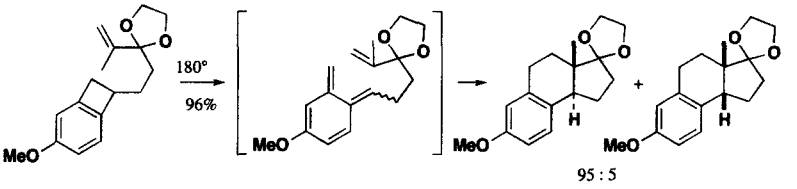
(171)

A few years later, Fukumoto performed the synthesis of *(d,l)*-adrenosterone, starting from another tricyclic derivative. However, the cyclization of the enone is not stereoselective (*Eq.* 172).

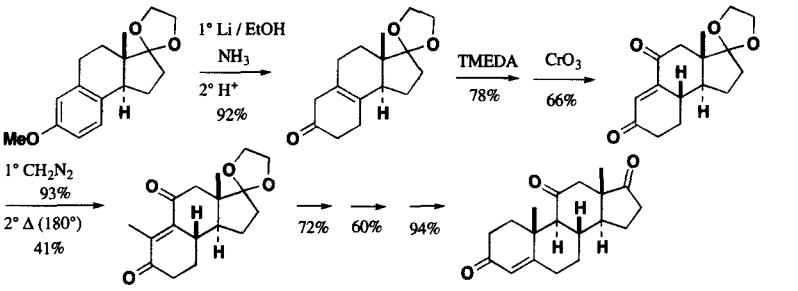


(172)

In order to increase the amount of isomer bearing the *trans* CD ring junction, Fukumoto investigated the thermolysis of the corresponding ethylene ketal, which allows the obtention of the expected compound in near quantitative yield. The conversion of the Diels-Alder adduct into adrenosterone is carried out as follows (*Eq.* 173). The ketal is subjected to Birch reduction, followed by methylation and then Robinson annelation (*Eq.* 174).[231,232]

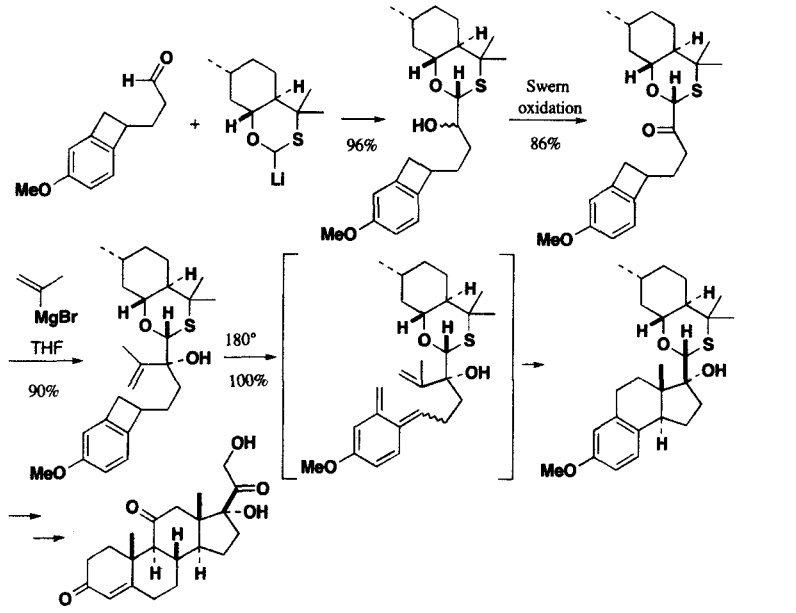


(173)



(174)

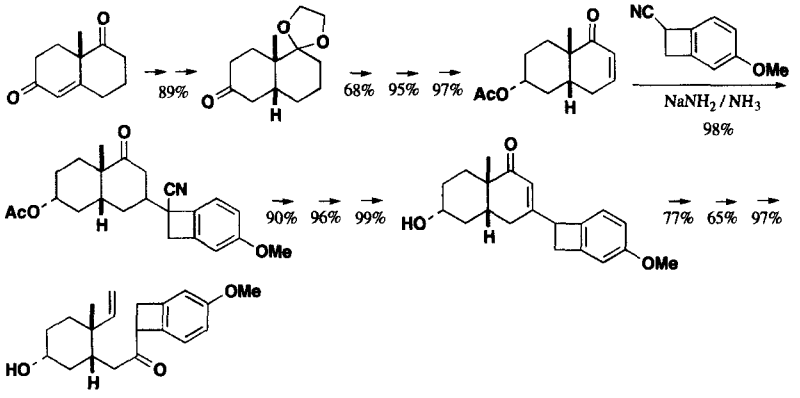
The application of this reaction to a chiral acetal affords the chiral steroids precursor, with an enantiomeric excess up to 36%.[233] This strategy has also been employed by Fukumoto for the first enantioselective synthesis of (+)-cortisone.[234] An optically active oxathiane, previously prepared from (+)-pulegone by Eliel,[235] is the stereodirecting group. The isolated tricyclic intermediate is treated by the same way as before (*Eq.* 175).



(175)

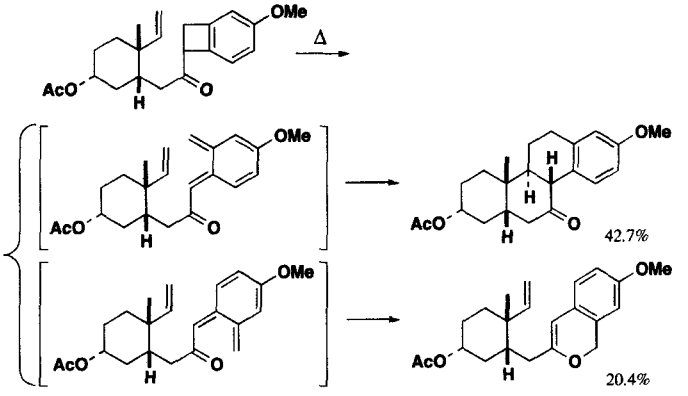
d. Synthesis of (+)-Chenodeoxycholic Acid

Chenodeoxycholic acid is one of the two primary bile acids in man and has clinical importance in the treatment of gallstone. In 1981, Kametani reported the preparation of a chiral *cis-anti-trans* fused tetracyclic intermediate, from the Wieland-Miescher ketone.[236,237] The first steps of the synthesis, afford an acylbenzocyclobutene (*Eq.* 176).



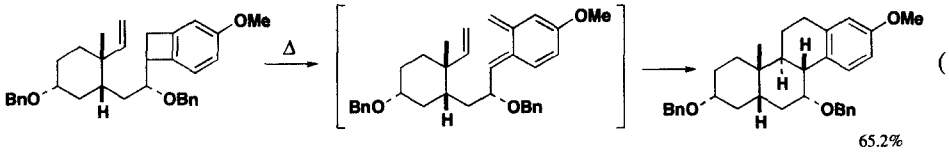
(176)

After thermolysis, the expected *cis-anti-trans* fused steroid is isolated, along with a benzopyrane, resulting from an electrocyclization of the (Z)-*o*-quinodimethane (*Eq.* 177).

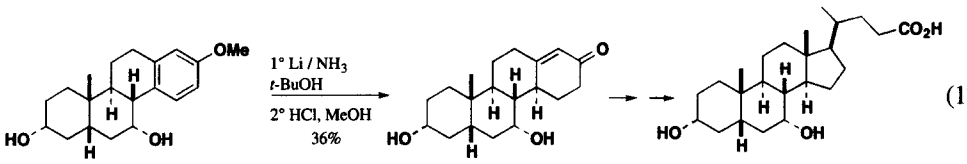


(177)

In order to avoid the competing side-reaction, Kametani transformed the acyl group of the benzocyclobutene into a benzyl ether. Thus, the tetracyclic compound, possessing six stereogenic centers, is obtained with a 65% yield (*Eq.* 178). This intermediate has been further converted into (+)-chenodeoxycholic acid *via* a multiple-step sequence (*Eq.* 179).



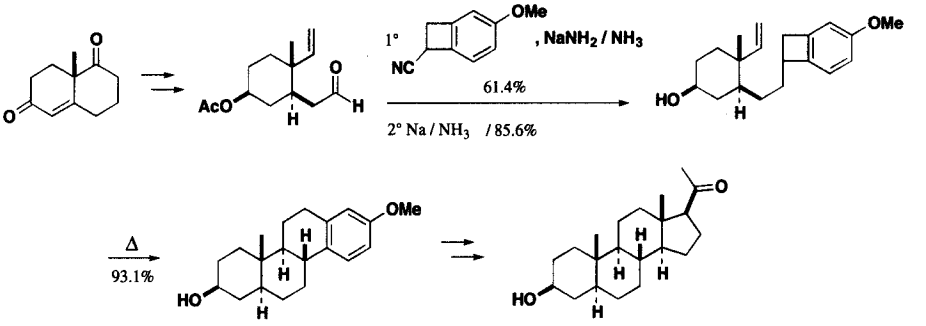
(178)



(179)

e. Synthesis of (+)-5-α-Dihydropregnenolone

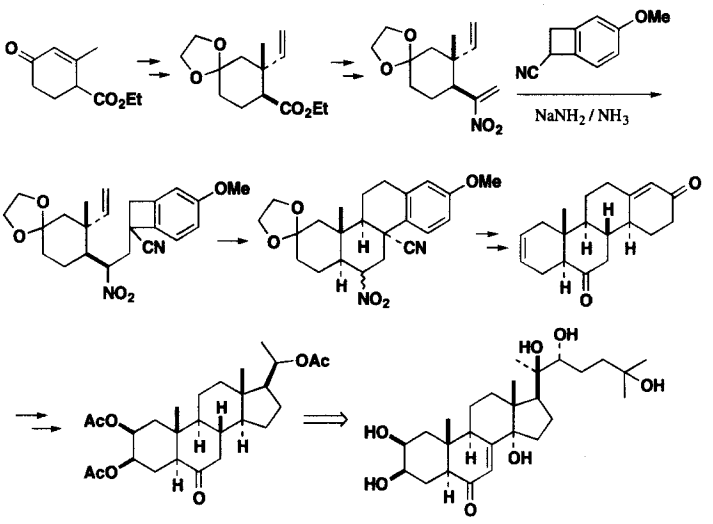
The Wieland-Miescher ketone,[238] has also been used by Kametani as a versatile building block,[239-241] for the synthesis of (+)-5α-dihydropregnenolone.[242] A tetracyclic intermediate is first prepared by a four-step sequence. Afterwards, the D cycle of the steroid is generated by a series of laborious reactions (*Eq.* 180).



(180)

f. Synthesis of 20-Hydroxyecdysone

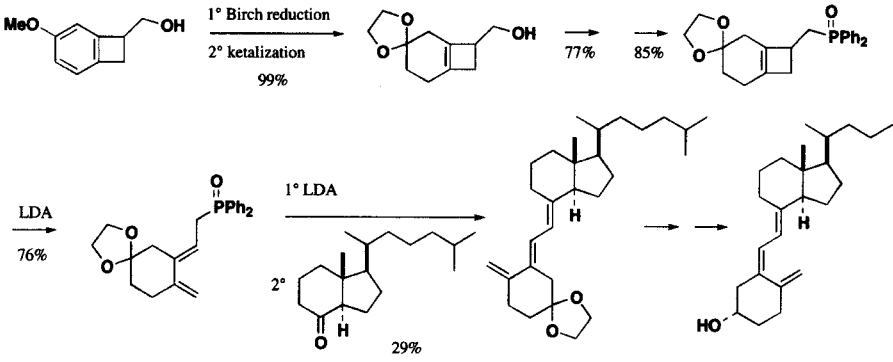
20-Hydroxyecdysone is an interesting crustacean molting hormone possessing biological activities. Kametani has reported a synthesis of this compound *via* a D ring aromatic steroid. This latter results from the transformation of the Hagemann's ester into a benzocyclobutene derivative, through a five-step procedure. After thermolysis, a tetracyclic intermediate is obtained and finally converted into a triacetate, which is a known building block for the synthesis of 20-hydroxyecdysone (*Eq.* 181).[243,244]



(181)

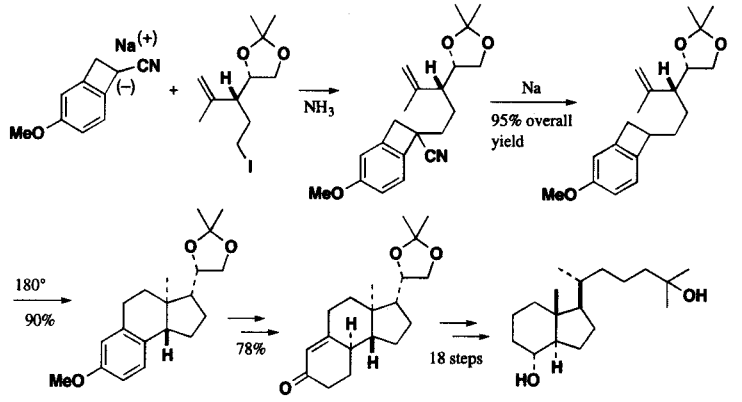
g. Synthesis of Vitamin D3

Because of the important therapeutic value of vitamin D in treating disorders of calcium and phosphorus metabolism, considerable attention has been directed towards its chemistry. A dienic phosphine oxide is essential to generate the trienic system of vitamin D. It is prepared by ring-opening of the corresponding benzocyclobutene carbanion. This reaction is accelerated compared to a neutral precursor.[245] Condensation of a stabilized benzocyclobutene carbanion on the Windaus-Grundmann ketone affords the trienic system (*Eq.* 182).[246]



(182)

Moreover, Fukumoto has recently prepared the enantiomeric 25-hydroxy Windaus-Grundmann ketone, by a complicated sequence involving condensation of methoxycyanobenzocyclobutene with a chiral iodide, arising from D-Mannitol (*Eq.* 183).[247]



(183)

VI. CONCLUSION

This review shows that the use of *o*-xylylenes as key intermediates for total synthesis, has been widely applied since the first reports of Oppolzer. Many elaborated bi-, tri- or tetracyclic molecules, have become accessible by using this methodology. In particular, compounds incorporating an aromatic cycle such as steroids (estrone), alkaloids or antibiotics may be obtained. Various efficient ways of generating *o*-xylylenes have been developed, but the most frequent route is by thermolysis of benzocyclobutenes. Unfortunately, approaches to substituted benzocyclobutenes *via* aromatic elec-

trophilic substitution often suffer from complications. These compounds cannot be obtained efficiently by the Friedel-Crafts reaction. Actually, 1,4-elimination of disubstituted *o*-xylenes, performed under very mild conditions or cycloaddition of benzynes with vinylic compounds, constitute the most efficient procedures to generate benzocyclobutenes.

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