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The Synthesis of Carbocyclic Eight-Membered Rings

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Contents

1. Introduction

The unique symmetry of eight-membered rings and their intriguing conformational properties have attracted much theoretical interest over the years. The synthesis of compounds containing this ring size has been a long standing problem because of difficulties stemming from the high degree of ring strain and transannular interactions. In recent years, however, we have witnessed great progress in the synthesis of eight-membered rings. Much of this work was prompted by the discovery of an increasing number of natural products possessing this ring system in their structures.

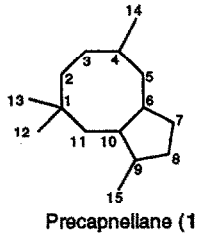
Herein we outline the chemistry of carbocyclic eight-membered rings, excluding pertinent work on the various heterocyclic systems. The review begins with an overview of the cyclooctanoid natural products and continues with a brief discussion of structural and conformational aspects. Subsequently, the review provides a systematic presentation of the different synthetic approaches to eight-membered rings, classified by the type of key reactions or strategies used.

1.1 Naturally occurring eight-membered ring carbocycles

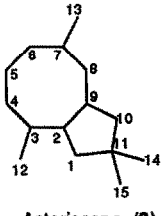
Although eight-membered rings are not as abundant as some of the smaller ring sizes, they occur widely in nature particularly in higher plants and marine organisms.[1] Many cyclooctanoid natural products, especially terpenoids and lignans, exhibit interesting biological activities and have served as target molecules for numerous synthetic studies.[2]

1.1.1 Terpenoid ring systems

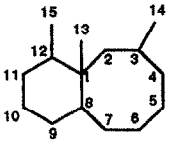
There are over one hundred known terpenoid natural products containing an eight-membered ring carbocycle in their structures. Compounds of this type have been isolated from a variety of sources including terrestrial plants, marine organisms and fungi. Typically, the eight-membered ring is fused or bridged to other smaller rings and contains double bonds and other functionalities. The most typical ring systems and their numbering sequences are shown below.



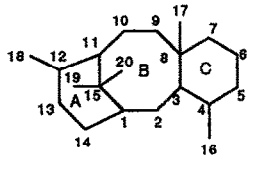
Precapnellane (1)



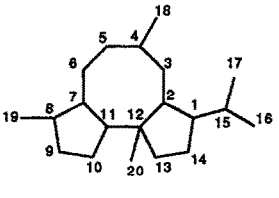
Asteriscane (2)



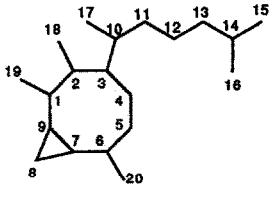
Neolemnane (3)



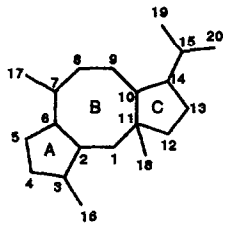
Taxane (4)



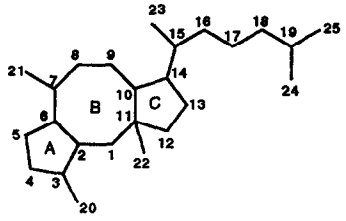
Basmane (5)



Crenulane (6)



Fusicoccane (7)

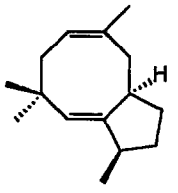


Ophiobolane (8)

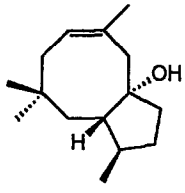
The few sesquiterpenoids known are represented by precapnellane (**1**), asteriscane (**2**) and neolemnane (**3**). More widespread are the diterpenoids of the taxane family (**4**), while some rare types such as basmane (**5**) and crenulane (**6**) have also been identified. A characteristic 5-8-5 tricyclic skeleton is found in the widely occurring diterpenoids of the fusicoccane family (**7**) and the ophiobolane sesteterpenoids (**8**). Specific examples of natural products containing these ring systems are represented in the following discussion.

1.1.2 Sesquiterpenoids

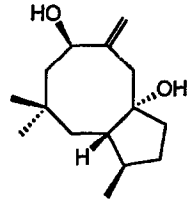
A number of sesquiterpenes characterized by an eight-membered ring fused to a five-membered ring have been isolated from marine sources, including precapnelladiene[3,4] (**9**), dactylol[5,6] (**10**), poitediol[7,8] (**11**), and asteriscanolide[9,10] (**12**). Less common are the 8-6 fused systems found in neolemnalyl acetate[11,12] (**13**), and parvifoline[13,14] (**14**).



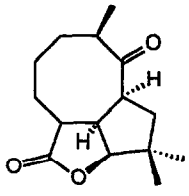
Precapnelladiene (**9**)



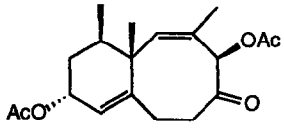
Dactylol (**10**)



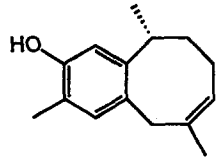
Poitediol (**11**)



Asteriscanolide (**12**)



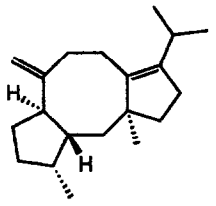
Neolemnalyl acetate (**13**)



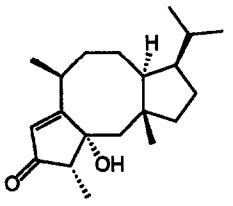
Parvifoline (**14**)

1.1.3 Diterpenoids

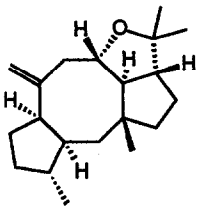
The most diverse group of eight-membered ring natural products are the diterpenoids. Many of these belong to the fusicoccane family, characterized by a fused 5-8-5 tricyclic ring system.



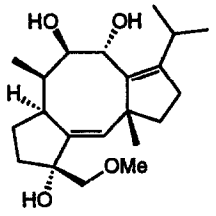
Cycloaraneosene (15)



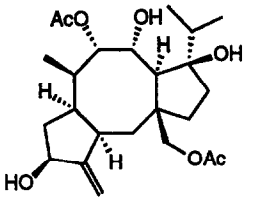
Anadensin (16)



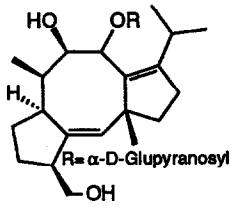
Epoxydictymene (17)



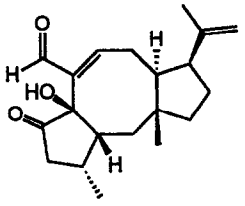
Cotylenol (18)



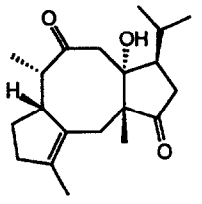
Fusicoplagin A (19)



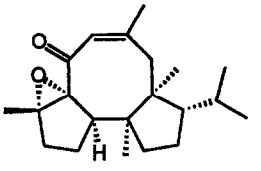
Fusicoccin H (20)



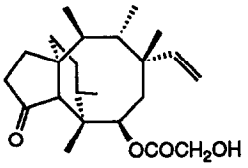
Traversianal (21)



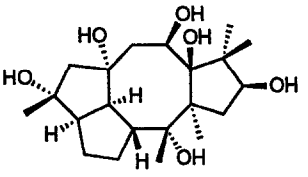
Roseadione (22)



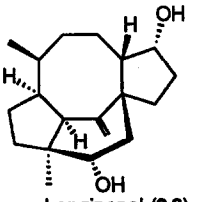
7,8-Epoxy-4-basmen-6-one (23)



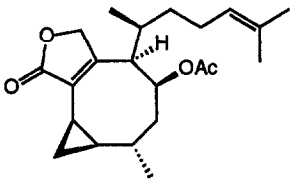
Pleuromutilin (24)



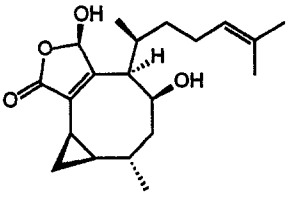
Kalmanol (25)



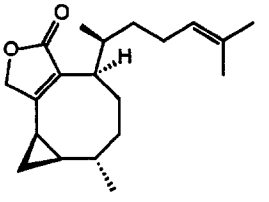
Longipenol (26)



Acetoxycrenulide (27)



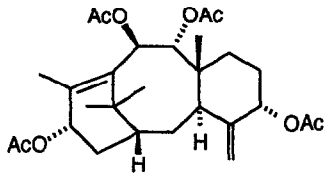
Dihydroxycrenulide (28)



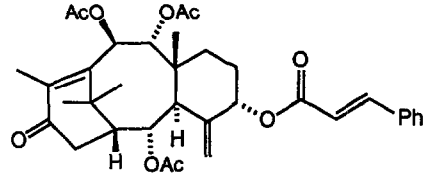
Pachylactone (29)

Some examples include: cycloaraneosene[15,16] (**15**), anadensin[17] (**16**), epoxydictymene[18,19] (**17**), cotylenol[20] (**18**), fusicoplangin A[21] (**19**), fusicoccin H[22,23] (**20**), traversianal[24,25] (**21**) and roseadione[26] (**22**). The fusicoccins, isolated from several higher plants, exhibit interesting phytohormone activities.[27] A different type of 5-8-5 ring system occurs in the tobacco-derived 7,8-epoxy-4-basmen-6-one[28,29] (**23**), while a unique 5-8-6 skeleton exists in the antibiotic pleuromutilin[30,31] (**24**). Additional rings are found in the cardiotoxic substance kalmanol[32] (**25**) and in longipenol[33,34] (**26**). Another group of marine diterpenoids are the crenulides, which contain a butenolide-fused 8-3 ring system, as in acetoxycrenulide[35,36] (**27**), dihydroxycrenulide[37] (**28**) and pachylactone[38] (**29**).

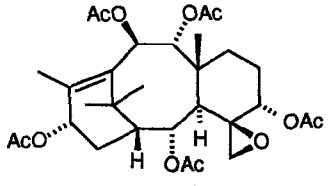
One of the most biologically interesting families of cyclooctanoid diterpenoids are the taxanes.[39] These uniquely bridged tricyclic ring skeletons are found in several species of the yew tree. The most common substitution patterns of the taxanes are exemplified by taxusin[40,41] (**30**), taxinine[42] (**31**), baccatin I[43] (**32**), taxagifine[44] (**33**), taxol[45,46] (**34**) and the related ring system shown in taxin A[47] (**35**). Taxol (**34**), the most important member of this class, has been the focus of much attention recently because of its unique antimitotic properties and its effectiveness for the treatment of ovarian and other types of cancer.[48] The novel structures and bioactivities of the taxanes have prompted extensive synthetic work in this area.[49,50,51]



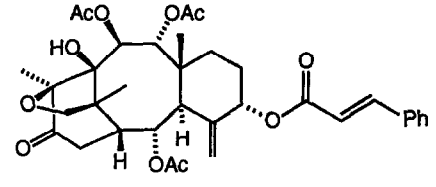
Taxusin (**30**)



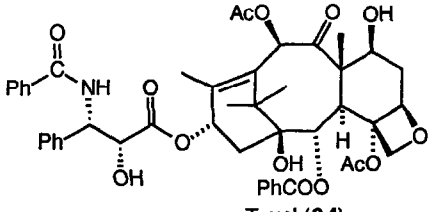
Taxinine (**31**)



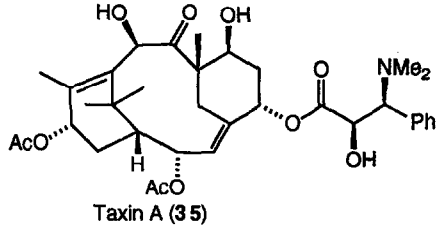
Baccatin I (**32**)



Taxagifine (**33**)



Taxol (**34**)



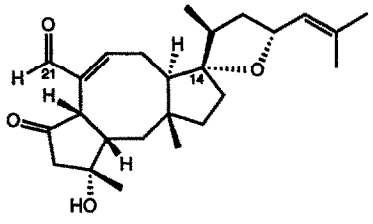
Taxin A (**35**)

1.1.4 Sesteterpenoids

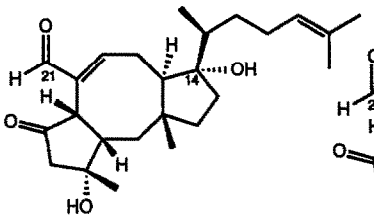
Several phytotoxic sesteterpenoids of the ophiobolin/ceroplastol family have structures characterized by a functionalized 5-8-5 ring system. The ophiobolins[52,53] are distinguished by their oxygenation pattern at C-14 and C-21 and include ophiobolin A[54] (**36**), B[55] (**37**), C[56] (**38**), D[57] (**39**), F[58] (**40**) and J[59] (**41**).

Members of the ceroplastol family, such as ceroplastol I[60] (**42**), ceroplasteric acid[61] (**43**), ceroplastol II[62] (**44**) and albolic acid[63] (**45**) differ from the ophiobolins in the stereochemistry at the ring junctions and have different oxidation states at C-25.

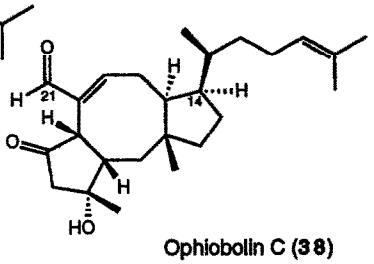
A novel tetracyclic sesteterpenoid with antihypertensive properties was recently identified and termed variecolin[64] (**46**).



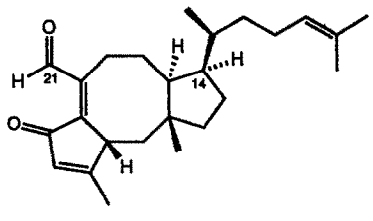
Ophiobolin A (**36**)



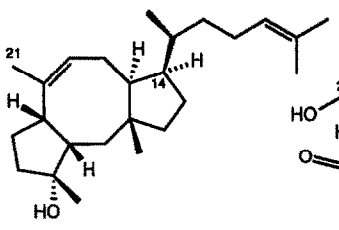
Ophiobolin B (**37**)



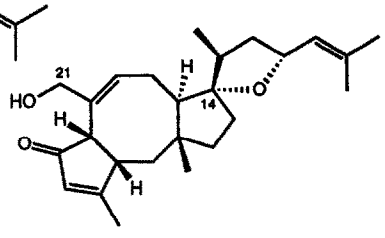
Ophiobolin C (**38**)



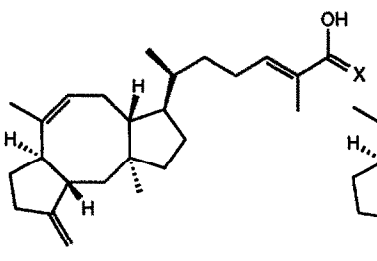
Ophiobolin D (**39**)



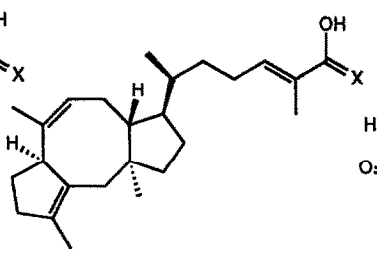
Ophiobolin F (**40**)



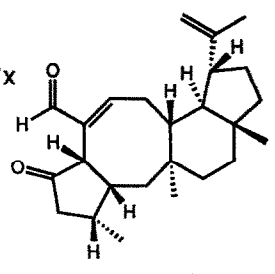
Ophiobolin J (**41**)



Ceroplastol I (**42**) X=H,H
Ceroplasteric Acid (**43**) X=O



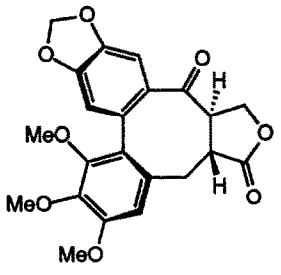
Ceroplastol II (**44**) X=H,H
Albolic Acid (**45**) X=O



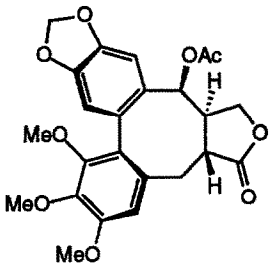
Variecolin (**46**)

1.1.5 Lignans and pigments

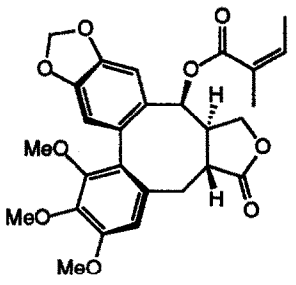
Several dibenzocyclooctadiene lignans[65] possessing significant antileukemic activity have been reported. These include the members of the steganone family[66] such as: steganone[67] (**47**), steganacin[68] (**48**), steganangin (**49**), schizadrin[69,70] (**50**), isoschizadrin[71,72] (**51**) and the gomisins, such as gomisin-S[73] (**52**).



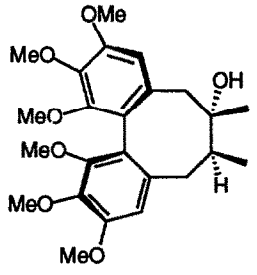
Steganone (**47**)



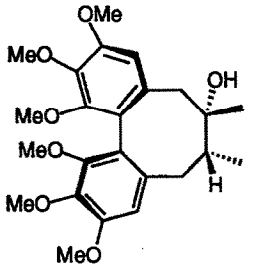
Steganacin (**48**)



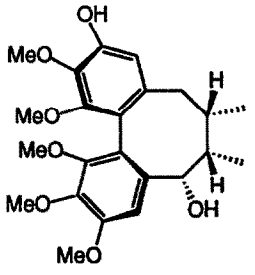
Steganangin (**49**)



Schizadrin (**50**)

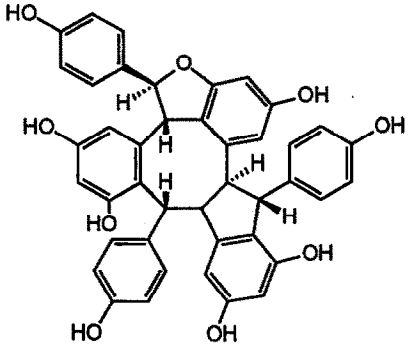


Isoschizadrin (**51**)

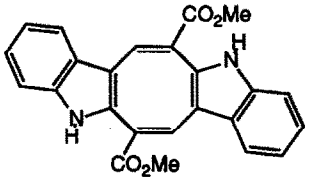


Gomisin-S (**52**)

Distichol[74] (**53**) an antibacterial polyphenol lignan has recently been isolated. A unique cyclooctadiene indole pigment, caulerpin[75] (**54**) was recently characterized and shown to be a plant growth regulator.



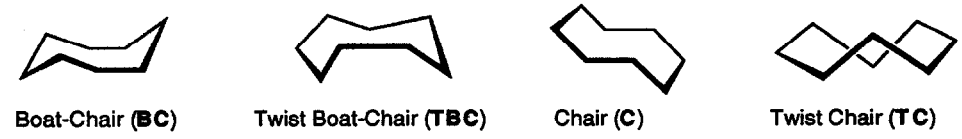
Distichol (**53**)



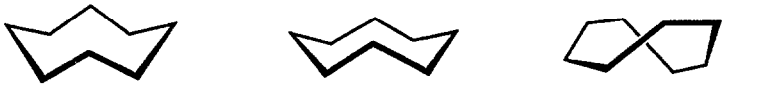
Caulerpin (**54**)

1.2 Conformations of eight-membered rings

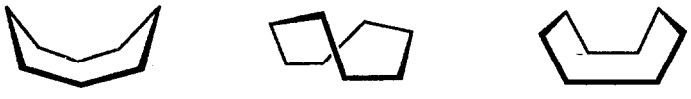
The conformational properties of molecules containing eight-membered rings have been studied extensively.[76] Spectroscopic methods (NMR, IR), X-ray crystallography and molecular mechanics calculations[77] have revealed that there are three major conformational families: the boat-chair (**BC**), crown (**CR**) and boat-boat (**BB**). The most common conformations that have been identified are shown below. Depending on the substitution pattern, significant energy barriers may affect the interconversion of these forms.



Boat-Chair (**BC**) Twist Boat-Chair (**TBC**) Chair (**C**) Twist Chair (**TC**)

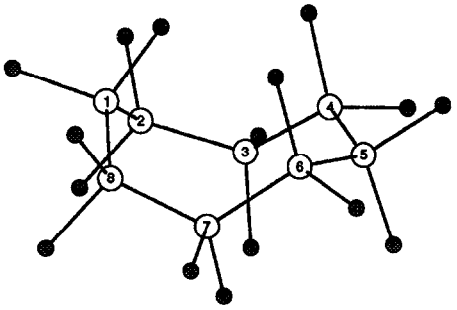


Crown (**CR**) Chair-Chair (**CC**) Twist Chair-Chair (**TCC**)

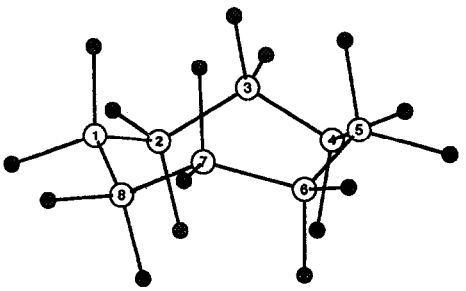


Boat-Boat (**BB**) Twist Boat-Boat (**TBB**) Boat (**B**)

The most stable conformation is usually the boat-chair (**BC**), which minimizes transannular interactions and has a lower torsional strain. Several conformations are populated at room temperature due to relatively small barriers of pseudorotation and ring inversion. Cyclooctane exists predominantly (>94%) in one of the boat-chair conformations and the remainder in the crown family.



Boat Chair (**BC**)

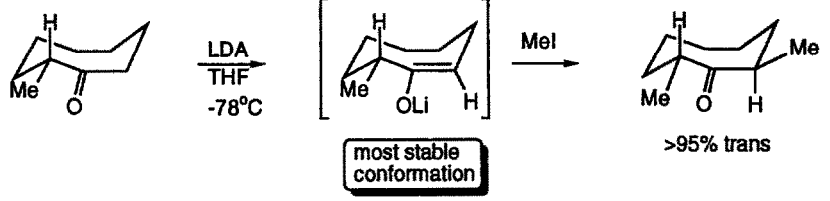


Crown (**CR**)

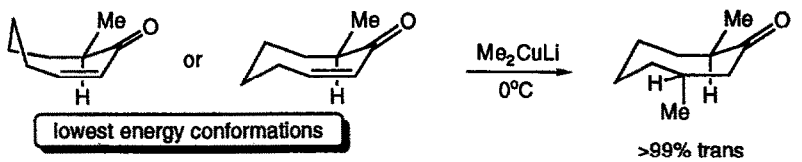
The presence of heteroatoms (e.g., O, N, S) or sp^2-carbons (e.g., C=O, C=C) in the ring can have a dramatic effect on the conformational strain by limiting the severe steric repulsions, particularly the transannular ones. In these systems the heteroatom or sp^2-carbon prefers to occupy "internal" positions (e.g., 3 or 7 for the **BC** conformation). The conformations of heterocycles of this type, particularly oxocanes, were studied extensively,[78] since these systems are found in many marine natural products.[79] The fully conjugated cyclooctatetraene ring system exists in the boat (or tub) conformation. This molecule has attracted much synthetic and theoretical attention[80] because of its non-aromatic character.

1.3 Structural modifications of eight-membered rings

The conformational rigidity of substituted eight-membered rings can lead to dramatic stereocontrol of reactions taking place on the ring. This effect was nicely demonstrated by Still[81] in his study of the alkylation of cyclooctanone enolates (1.3.1) and the addition of organocuprates to substituted cyclooctenones (1.3.2).

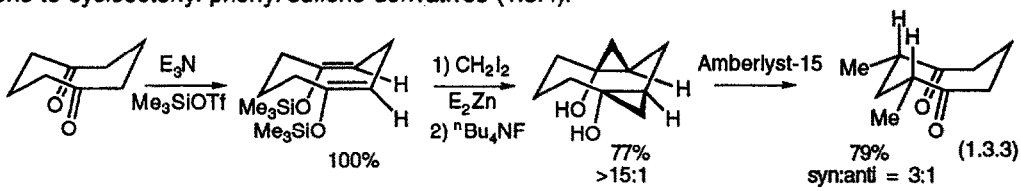


(1.3.1)

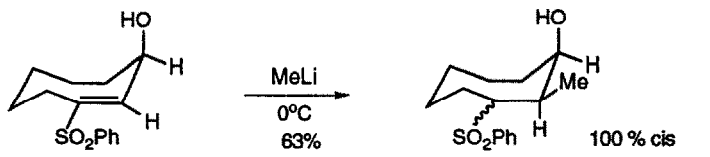


(1.3.2)

A regio- and stereo- selective functionalization of 1,5-cyclooctanedione was reported by Schreiber.[82] Conversion of the diketone to the corresponding bis(silyl)enol ether, followed by periferal cyclopropanation, desilylation and ring opening, led to the syn-2,4-dimethyl derivative (1.3.3). Significant degree of stereocontrol was also observed by Fuchs[83] during conjugate additions to cyclooctenyl phenyl sulfone derivatives (1.3.4).

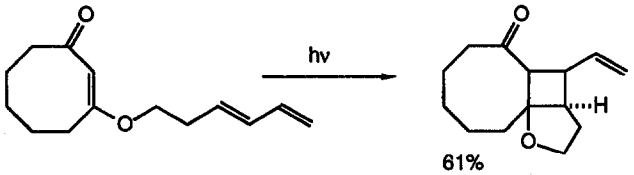


(1.3.3)

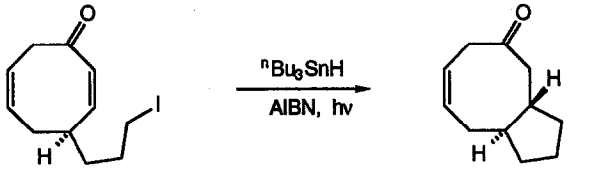


(1.3.4)

The annulation of four- five- or six-membered rings onto eight-membered ring carbocycles as an approach to pertinent bicyclic or tricyclic products has been explored by several groups. Pirrung[84] studied the intramolecular photocycloaddition of cyclooctenone derivatives (1.3.5). Winkler[85] reported a stereoselective radical cyclization for appending a five-membered ring onto a cyclooctadiene derivative (1.3.6). Mehta[86] utilized an aldol condensation-alkylation sequence for the preparation of a tricyclic 8-7-5 ring system (1.3.7).



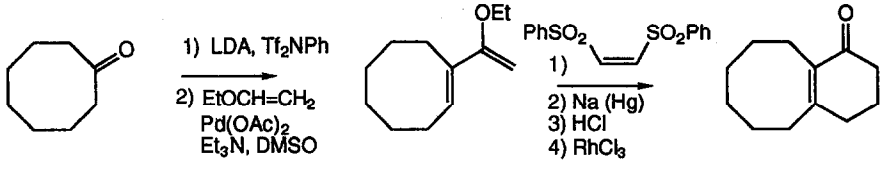
(1.3.5)



(1.3.6)

(1.3.7)

Several multistep sequences leading to this type of annulation were also recently developed. Paquette[87] reported a six-step sequence for appending a cyclohexenone ring (1.3.8), while Mehta[88] developed a four-step cyclopentenone annulation (1.3.9). Also, Helquist[89] reported an iron carbene mediated annulation of 2,2-dimethyl cyclopentane onto a cyclooctenone precursor.



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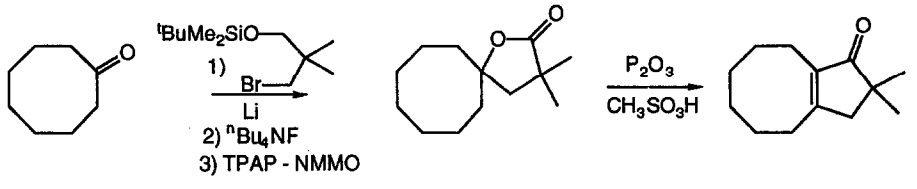


(1.3.9)

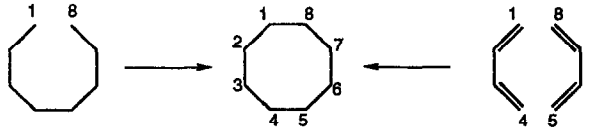
1.4 Strategies for the synthesis of eight-membered rings

As a result of the unique structural characteristics of eight-membered rings, their synthesis is often not possible using methods that are effective for the synthesis of smaller (3-7) or larger (10-16) ring systems. For this reason, many new synthetic methods and strategies aimed specifically at eight-membered rings were recently developed, some of which were employed in the synthesis of natural products and other target molecules.

While some of the approaches to eight-membered ring carbocycles are also suitable for the construction of other ring systems, many methods are only applicable to eight-membered rings. The various strategies are classified according to the chemical transformation in which this ring size is formed as follows:

1.4.1 Intramolecular C-C bond formation

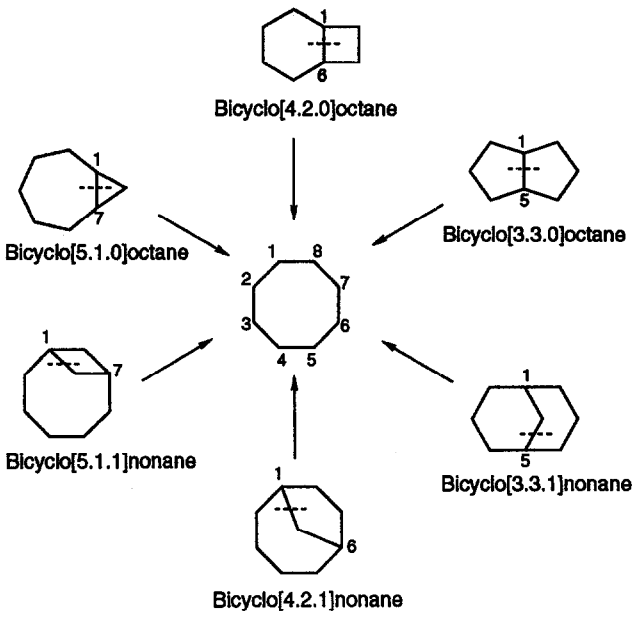
Direct cyclization to eight-membered rings can be accomplished by several types of ring closures at C_1-C_8. These include electrophilic cyclizations, aldol reactions, additions to carbonyls, conjugate additions, carbonyl coupling, radical cyclizations, phenolic coupling, [2+2]-cyloadditions and Diels-Alder reactions. A special case of ring closure involves the ring contraction of larger rings. The intramolecular C-C bond formation in these cases may be facilitated by favorable entropic and conformational characteristics. The simultaneous formation of two C-C bonds has been accomplished with several types of [4+4] cycloadditions, which take place under thermal or photochemical conditions, or in the presence of transition metals particularly nickel.



1.4.2 Fragmentation

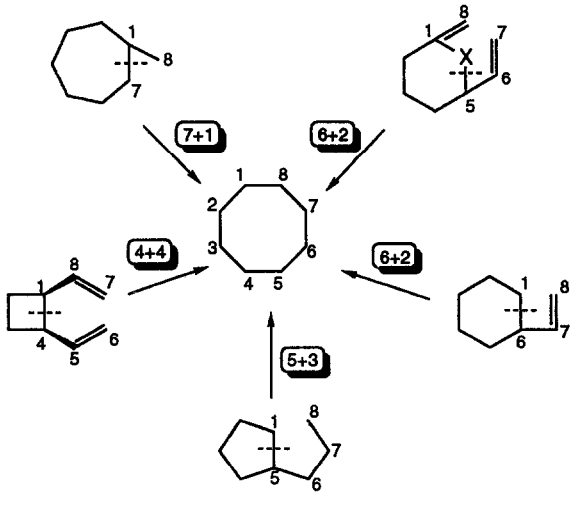
In a bicyclic system, the cleavage of a bond bridging two atoms of an eight-membered ring is a very effective method for the synthesis of cyclooctanoids. There are three general modes of this type of process, involving fragmentation at C_1-C_7, C_1-C_6 and C_1-C_5. If these atoms are joined directly by a C-C bond the corresponding precursors are the bicyclooctanes, i.e., bicyclo[5.1.0]octane, bicyclo[4.2.0]octane and bicyclo[3.3.0]octane. Similarly the presence of a one-atom bridge between these atoms, results in the corresponding bicyclononane precursors.

All of these bicyclic precursors have been utilized in a variety of ways for the synthesis of eight-membered rings, with the exception of the bicyclo[5.1.1]nonane system. Since the rings present in these molecules are smaller, they are much easier to construct. The conditions for the key fragmentation step vary from oxidative to reductive cleavage to the many variants of the Wharton fragmentation process.

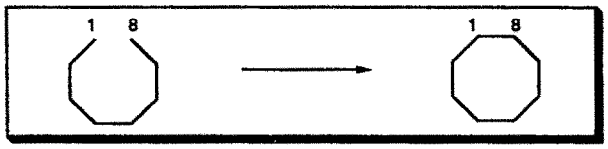


1.4.3 Ring expansion

Several methods for eight-membered ring synthesis involve the direct ring expansion of smaller rings. In these cases, there is a transition state or a reactive intermediate being formed that has similar framework with the bicyclic skeletons shown above. Variations of the [3,3] and [1,3]-sigmatropic rearangements, resulting in overall two- or four-atom ring expansions, are among the most prominent strategies. These processes can take place thermally or under Lewis acid catalysis.



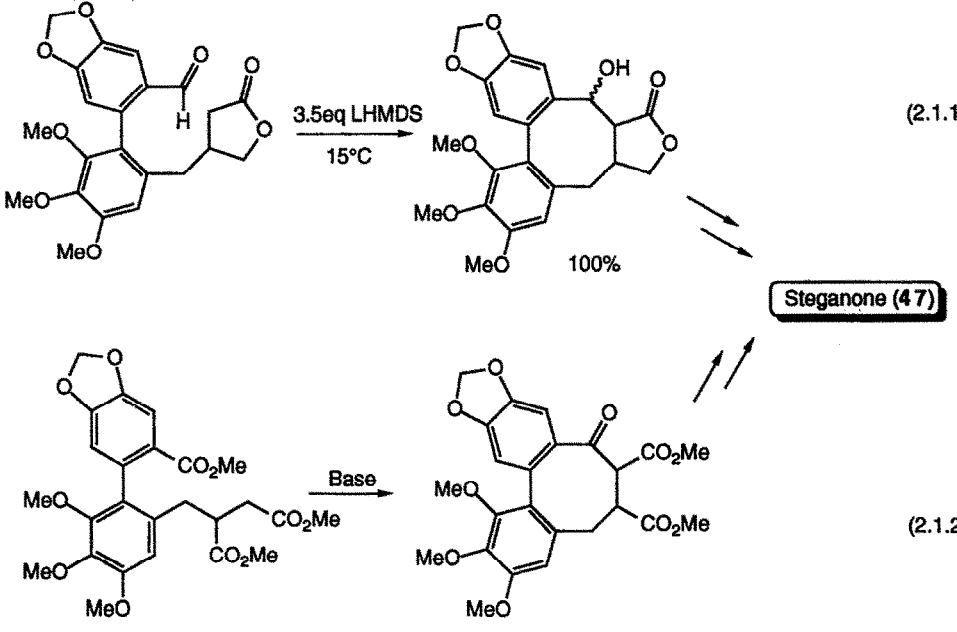
2. Intramolecular C-C bond formation



Of all ring sizes, the formation of eight-membered ring carbocycles by intramolecular ring closure reactions is often the most difficult.[90] Due to the intrinsic conformational and entropic problems, the usual C-C bond forming processes either give very low yields or do not work at all. However, a number of reactions were shown to be suitable for certain eight-membered rings and are discussed in this section. These cyclizations, often involving highly reactive intermediates, are classified by the type of ring forming reaction utilized. In general, the syn orientation of the reacting atoms, provided by a cis olefinic bond or ring, facilitates the cyclization.

2.1 Aldol reactions and other additions to carbonyl derivatives

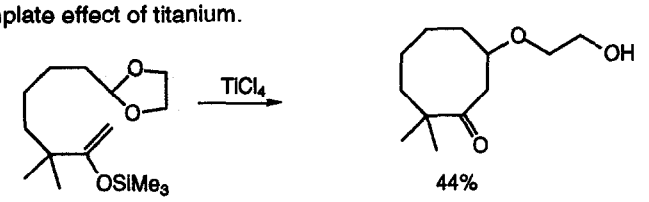
Variations of the aldol reaction have been used successfully for the synthesis of eight-membered rings. The intramolecular addition of a lactone enolate to an aryl aldehyde was employed in the synthesis[91] of steganone (**47**) (2.1.1). The same researchers also reported the basic enolization of a similar 1,3 diester which cyclized via an intramolecular Claisen condensation[92] (2.1.2).



(2.1.1)

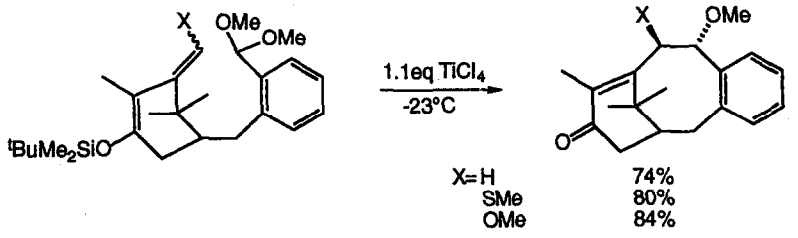
(2.1.2)

Several examples[93] of the intramolecular aldol reaction among silyl enol ethers and acetals catalyzed by $TiCl_4$ have been reported (2.1.3). This type of intramolecular variant of the Mukaiyama aldol reaction provided medium rings in yields ranging from 30-88% and was rationalized in terms of the known template effect of titanium.



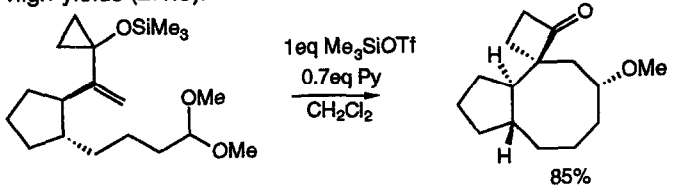
(2.1.3)

A similar reaction was used by Kuwajima[94] for the synthesis of the taxane carbon framework in very good yields, depending on the nature of the enol ether (2.1.4).



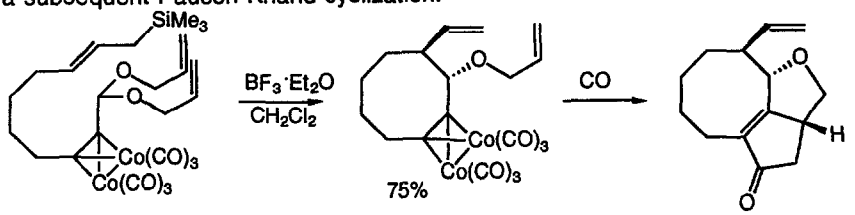
(2.1.4)

Trost[95] has reported the use of silylated vinylcyclopropanols, which serve as homoenolate equivalents, in a novel intramolecular addition to an acetal leading to eight-membered ring carbocycles in high yields (2.1.5).



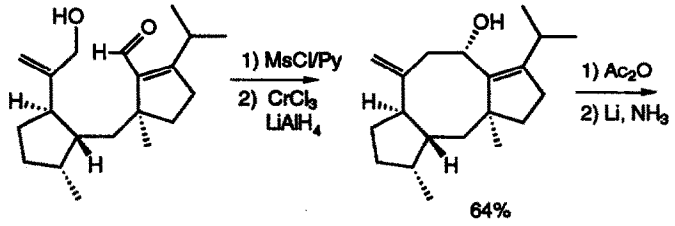
(2.1.5)

Schreiber[96] has devised an intramolecular Nicholas-type reaction involving addition of an allylsilane moiety to a cobalt-masked propargylic ether or acetal, activated by a Lewis acid (2.1.6). This process provided functionalized eight-membered rings in good yields and has been explored for the synthesis of cyclooctanoid natural products. For this purpose, the cobalt moiety was removed via a subsequent Pauson-Khand cyclization.



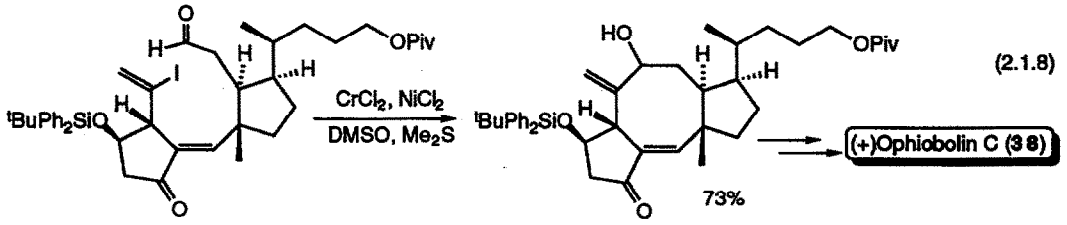
(2.1.6)

Kato and Takeshita[97] in their synthesis of cycloaraneosene (**15**) reported the intramolecular addition of an in situ generated allylic chromium species to an aldehyde (2.1.7).



(2.1.7)

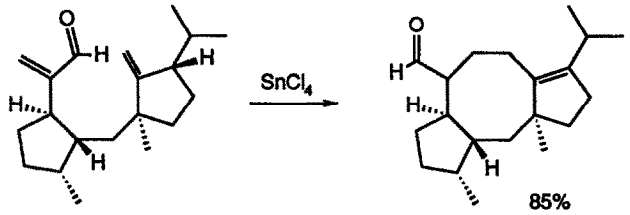
Kishi[98] reported a $CrCl_2$-$NiCl_2$ catalyzed intramolecular addition of a vinyl iodide to an aldehyde during his synthetic studies towards the ophiobolins. This strategy[99] has led to the total synthesis of (+)-ophiobolin C (**38**) (2.1.8).



(2.1.8)

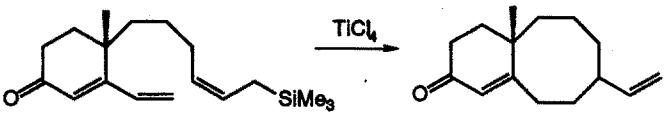
2.2 Conjugate additions

An efficient intramolecular ene-type conjugate addition to an α,β-unsaturated aldehyde mediated by $SnCl_4$, was reported by Kato and Takeshita[100] (2.2.1). However, in another example this type of electrophilic cyclization failed to produce the more strained taxane ring system.[101]



(2.2.1)

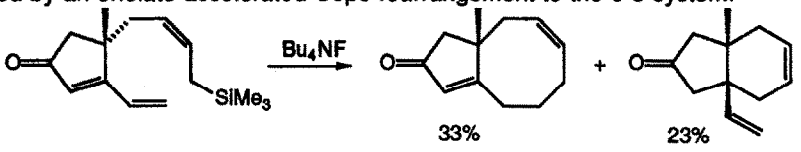
The use of intramolecular conjugate addition reactions of allylic and propargylic silanes for the synthesis of fused eight-membered ring systems has been studied in detail by Majetich[102] and Schinzer.[103] It was found that this cyclization is quite sensitive to the substitution pattern of the substrate and the conditions used. While the yields vary due to several other competing reactions, it was found that in some cases this intramolecular 1,6-conjugate addition can be catalyzed by Lewis acids such as $EtAlCl_2$ and $TiCl_4$ (2.2.2).[104]



(2.2.2)

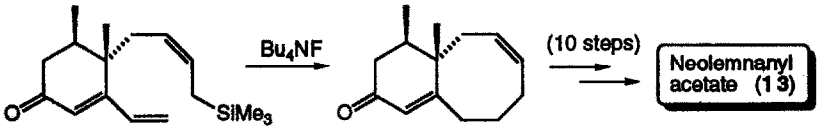
35%

The reaction also takes place under fluoride anion catalysis (2.2.3).[105] Majetich[106,107] used this strategy in a 15-step total synthesis of neolemnanyl acetate (**13**) (2.2.4). It was postulated that cyclooctene formation proceeded via an initial Michael addition of the allylsilane to form a 6-4 system followed by an enolate accelerated Cope rearrangement to the 6-8 system.



(2.2.3)

33% 23%

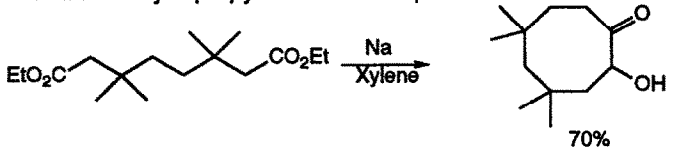


(2.2.4)

56%

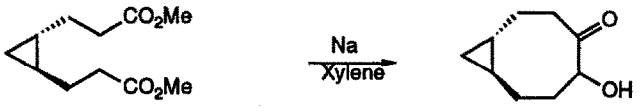
2.3 Carbonyl coupling

A wide variety of carbonyl coupling reactions have been fruitful for the synthesis of eight-membered ring carbocycles. An early example reported by Krebs[108] en route to a cyclooctyne derivative was an acyloin reaction mediated by sodium metal (2.3.1). Gassman[109] reported a similar reaction with a trans cyclopropyl diester which produced the fused 3-8 ring system (2.3.2).



(2.3.1)

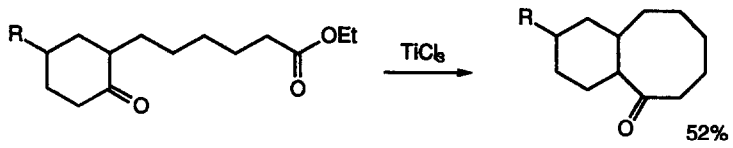
70%



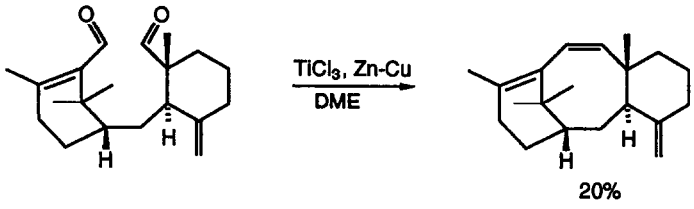
(2.3.2)

76%

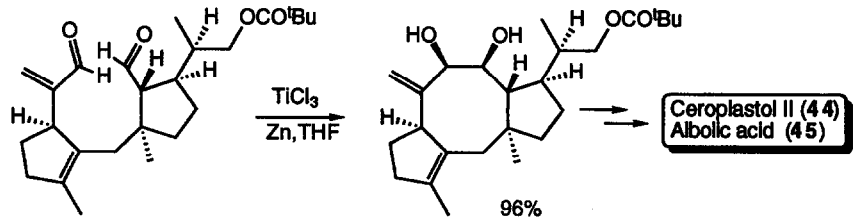
The well-known McMurry[110] coupling reaction was introduced as a new method for cycloalkanone synthesis by the titanium(III) induced cyclization of keto esters (2.3.3). Kende[111] utilized this type of reaction on a dialdehyde precursor in the first direct cyclization of the taxane B-ring, although only with limited success (2.3.4). Kato and Takeshita[112] used a similar titanium coupling reaction during their syntheses of albolic acid and ceroplastol II (2.3.5).



(2.3.3)



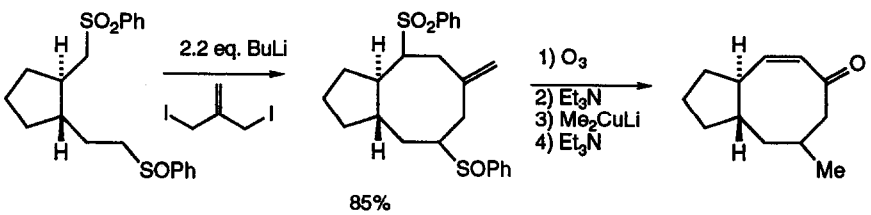
(2.3.4)



(2.3.5)

2.4 Intramolecular alkylations

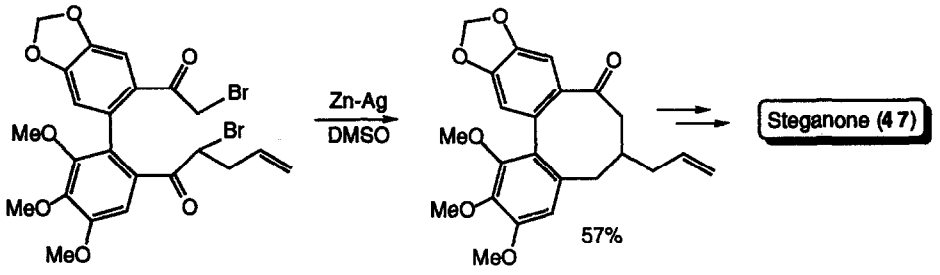
Reactions involving the intramolecular displacement of a leaving group by a carbanionic nucleophile to form an unconstrained eight-membered ring, typically proceed in low yields. This type of cyclization, however, may be favored when the substrate can easily adopt the required gauche relationship between the two ends of the chain. The presence of fused rings, cis olefinic bonds and bulky substituents can have a dramatic effect on the yields of these cyclizations. An illustrative example recently provided by Lansbury[113] involves the bis-alkylation of a suitable dicarbanion (2.4.1). Interestingly, the presence of a cyano group instead of the phenylsulfinyl moiety resulted in yields of only 20-25% of the cyclized product. This difference was attributed to the inability of the cyano group to promote the required conformation for cyclization.



(2.4.1)

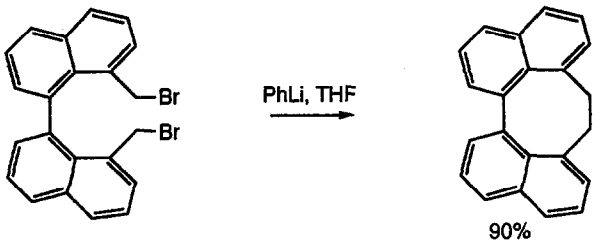
2.5 Miscellaneous cyclizations

Ghera[114] explored a zinc-silver induced intramolecular coupling of a dibromide which was employed in a synthesis of steganone (47) (2.5.1).



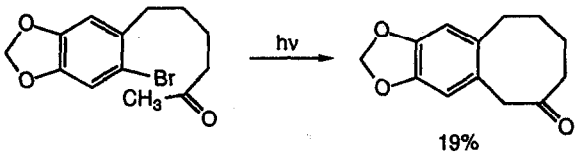
(2.5.1)

Schriver[115] reported a facile Wurtz-type coupling during a synthesis of a binaphthyl-fused eight-membered ring (2.5.2).



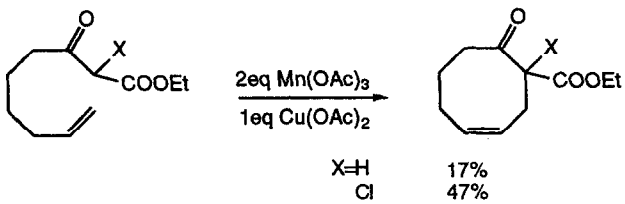
(2.5.2)

Semmelhack[116] has illustrated an intramolecular alkylation via a photochemical $S_{RN}1$ reaction of a keto aryl halide (2.5.3). However, the resulting cyclooctanone was obtained only in a low yield and was accompanied by several other products.



(2.5.3)

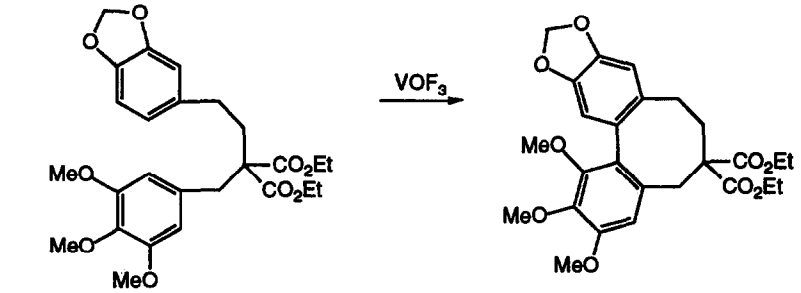
Snider[117] has shown that eight-membered ring derivatives can be formed in moderate yields via oxidative radical cyclization of olefinic chloro-β-ketoesters mediated by $Mn(OAc)_3$ and $Cu(OAc)_2$ (2.5.4).



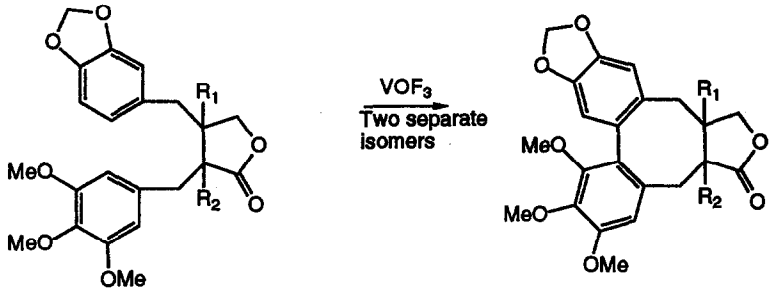
(2.5.4)

2.6 Oxidative phenolic coupling

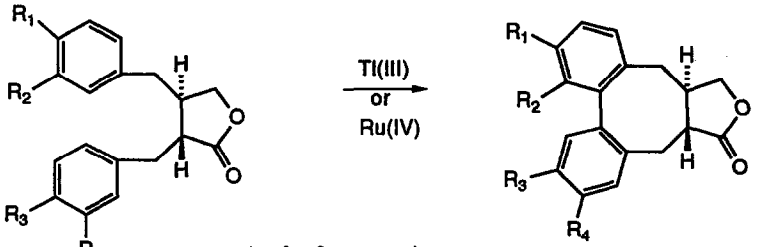
Oxidative coupling of phenolic derivatives under a variety of conditions has been widely used for the synthesis of dibenzocyclooctane lignans.[65] The most common reagents used for this purpose are the vanadium oxy-halides, particularly VOF_3, which was employed in the synthesis of Kende's[118] synthesis of steganone (**47**) (2.6.1) and in Koga's[119] asymmetric synthesis of (-) natural and (+) unnatural steganacin (**48**) (2.6.2). Recently, new conditions for oxidative phenolic coupling involving Ru(IV)dioxide were reported by Robin[120] (2.6.3). The use of ultrasound or BF_3 resulted in faster reactions under these conditions. Another modification involving Tl_2O_3 as the co-catalyst was attempted but only provided about 50% yield of cyclized product.



(2.6.1)



(2.6.2)



$R^1=R^2=R^3=OMe$; $R^4=OH$

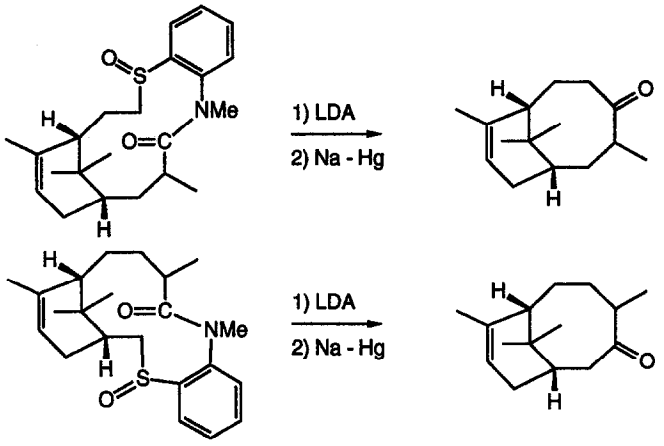
Ru	15h	80%
Ru/ultrasound	6h	82%
Ru/BF_3	3h	80%
Tl/BF_3	2h	45%

(2.6.3)

2.7 Ring contractions of larger rings

The transannular bridging of larger rings can be very effective for eight-membered ring synthesis. The preorientation of the two ends (C_1 - C_8) towards cyclization removes some of the unfavorable entropic factors and facilitates ring formation.

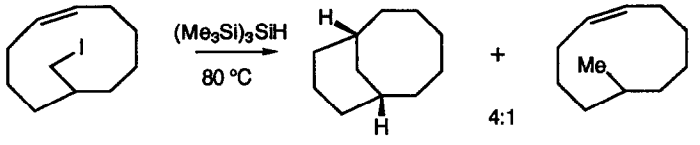
Ohtsuka and Oishi[121] developed a method for the synthesis of medium ring ketones involving ring contraction via the transannular addition of a sulfoxide (or sulfone)-stabilized carbanion to a lactone or lactam carbonyl, followed by desulfurization. Two alternative applications of this chemistry to the taxane AB ring system were investigated,[122] involving isomeric twelve membered ring lactam sulfoxides (2.7.1), (2.7.2).



(2.7.1)

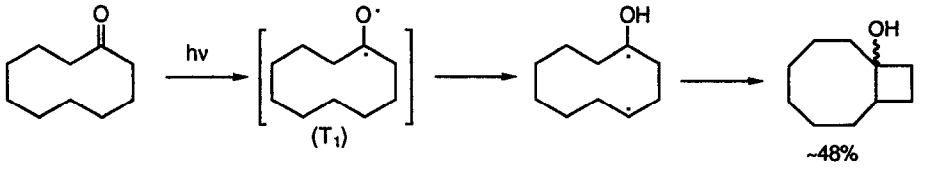
(2.7.2)

Winkler[123] explored the radical cyclization of cyclodecene derivatives towards the synthesis of the bicyclo[5.3.1]nonane taxane system (2.7.3). The yields of the bridged eight-membered ring products were higher with the cis cyclodecene precursor than with its trans isomer.



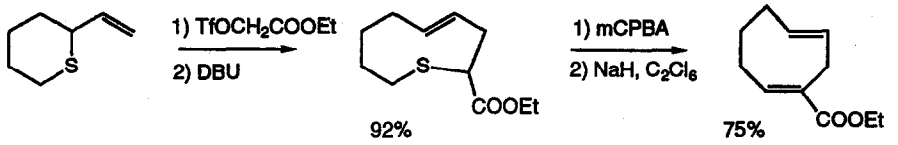
(2.7.3)

Sauers[124] has reported a unique photochemical Norrish Type II reaction of cyclodecanone resulting in radical coupling and formation of bicyclo[6.2.0]decan-2-ol (2.7.4).



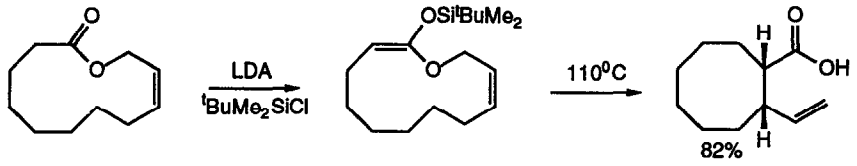
(2.7.4)

During his studies[125] on sulfur-mediated ring expansions, Vedejs[126] reported a Ramberg-Backlund sulfur extrusion of a cyclic sulfide to form a strained cyclooctadiene derivative (2.7.5).

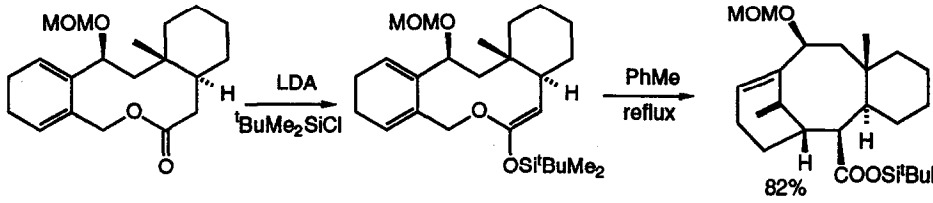


(2.7.5)

Funk[127] has devised a four-atom ring contraction strategy based on the Ireland-Claisen rearrangement, which is applicable to the synthesis of a variety of carbocycles, including eight-membered rings (2.7.6). The method was later adapted[128] for the taxane ring system (2.7.7).

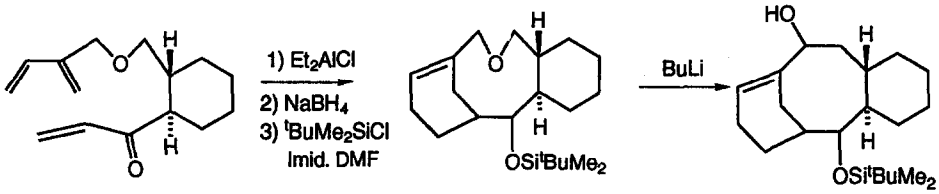


(2.7.6)



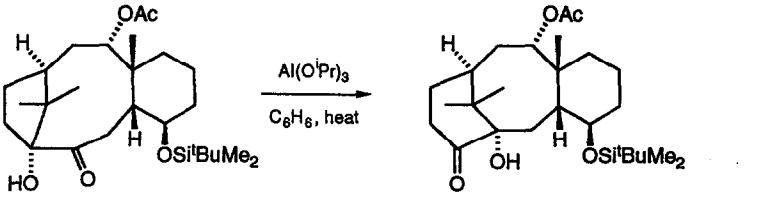
(2.7.7)

Yadav[129] has recently described an expedient approach to the taxane skeleton involving the Wittig rearrangement mediated ring contraction of nine-memberd ring oxygen heterocycle, which was formed via an intramolecular Diels-Alder reaction (2.7.8).



(2.7.8)

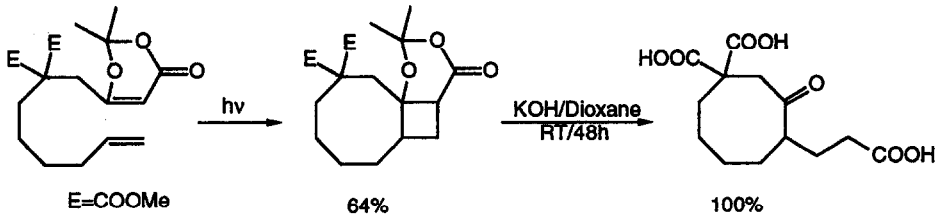
Paquette[130] has recently utilized an aluminum-mediated pinacol-type rearrangement for the formation of the tricyclic taxane ring system (2.7.9). This process, which involved a nine to eight ring contraction, afforded the taxol framework properly oxygenated at the bridgehead C-1 position.



(2.7.9)

2.8 [2+2] Cycloadditions

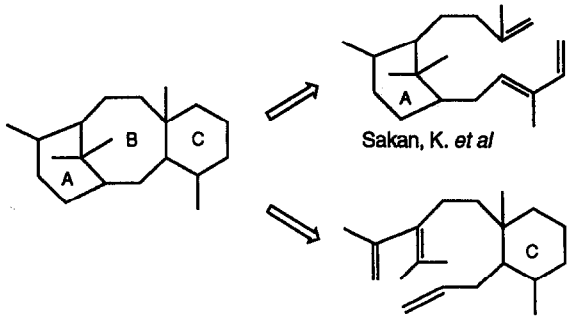
The use of photochemical [2+2] cycloadditions followed by fragmentation (de Mayo reaction) has found many applications in the synthesis of eight-membered rings and will be discussed in section **3.2.** The direct cyclization to the cyclooctane ring via this process is less common. Winkler[131] has reported some examples of this type, involving photocycloaddition of dioxinones to olefins in yields ranging from 55-64% (2.8.1).



E=COOMe 64% 100% (2.8.1)

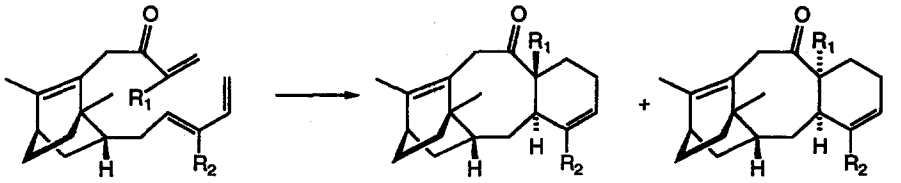
2.9 [4+2] Cycloadditions

Several approaches to the tricyclic taxane ring system have utilized intramolecular Diels-Alder reactions under thermolysis or Lewis acid catalysis (2.9.1). While these [4+2] cycloaddition reactions seem suitable for the construction of either rings B/C or A/B of the taxanes, these cyclizations are very sensitive to the substitution pattern and the conditions used.



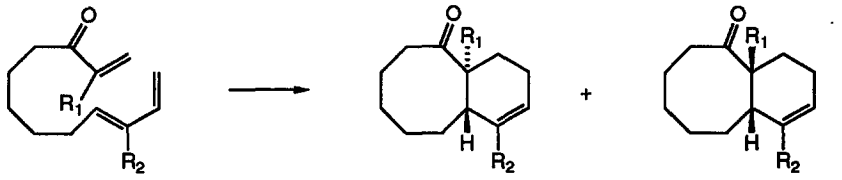
(2.9.1)

In one of the earliest model studies of taxane synthesis, Sakan[132] investigated the thermal and Lewis acid catalyzed formation of rings B/C (2.9.2). Variable amounts of the desired trans ring fusion were obtained only under thermal conditions, while Lewis acid catalysis gave only the cis fused product. Similar results were observed with a simpler model system (2.9.3). In both cases the presence of a methyl group at the diene or dienophile component had a significant steric effect on the stereochemical outcome of the thermal process.



(2.9.2)

$R_1, R_2 = H, Me$ 17-70% with 140-160°C 80-97% with Me_2AlCl, 25°C



(2.9.3)

$R_1=R_2=H$	Me_2AlCl, 25°C	69%	0 : 100
R_1=Me, R_2=H	Me_2AlCl, 25°C	62%	11 : 89
R_1=H, R_2=Me	Me_2AlCl, 55°C	74%	17 : 83
$R_1=R_2$=Me	Me_2AlCl, 50°C	69%	26 : 74

A systematic study of the alternative intramolecular Diels-Alder reaction which led to the formation of rings A/B of the taxanes was performed by Shea.[133] This type of strategy involves the formation of a strained bridgehead olefin and requires more drastic thermal conditions (2.9.4). A similar $ZnCl_2$ catalyzed cycloaddition resulted in a rare example of an atropselective reaction.[134]

(2.9.4)

$R_1=R_2=H$	185°C, 1h	70%
R_1=Me, R_2=H	155°C, 93h	70%
R_1=Me, R_2=OMe	$ZnCl_2$, 25°C, 2h	80%

In another approach directed towards the synthesis of the taxol skeleton having an unsaturated C-ring, Shea[135] found that the key intramolecular Diels-Alder reaction proceeded in only low yield both thermally and under Lewis acid conditions (2.9.5).

(2.9.5)

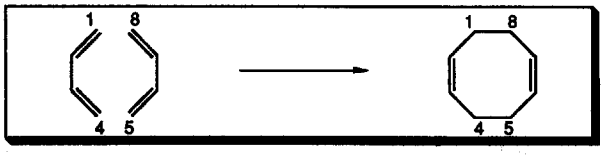
185°C, 86h 12%
Et_2AlCl, CH_2Cl_2, 25°C 30%

The synthesis of the taxane skeleton via the Lewis acid catalyzed intramolecular [4+2] cycloaddition was also studied by Jenkins.[136] The unsubstituted tricyclo[9.3.1.0]pentadecane ring system present in taxanes was formed in a good yield via an aluminum promoted reaction (2.9.6). Similar conditions led to the substituted variant, although in a lower yield, due to steric interference of the gem-dimethyl groups.

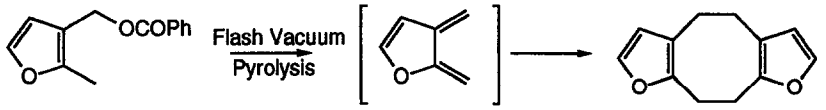
(2.9.6)

R=H Et_2AlCl, 25°C 72%
R=Me $BF_3 \cdot Et_2O$, -40°C 56%

2.10 [4+4] Cycloadditions

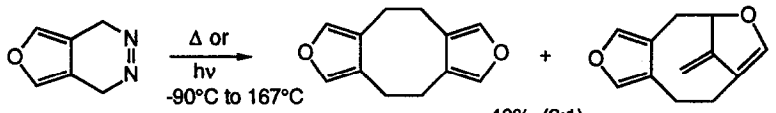


A variety of conditions for intramolecular [4+4] cycloadditions have been developed, including thermolysis, photolysis and transition metal catalysis. An early procedure for the thermal dimerization of 2-chloro-1,3-butadiene was reported by Cope,[137] but it proceeded only in low yield. More recently, Trahanovsky[138] has reported the flash vacuum pyrolysis of (2-methyl-3-furyl) methyl benzoate providing the air sensitive 3,3-dimethylene-2,3-dihydrofuran intermediate which readily underwent head-head dimerization providing the cyclooctanoid compound (2.10.1). Berson[139] has recently reported the thermal and photochemical biradical dimerization of diazene derivatives (2.10.2). Radical formation followed by dimerization produced two cyclooctanoids in ratio of 3:1.



51%

(2.10.1)

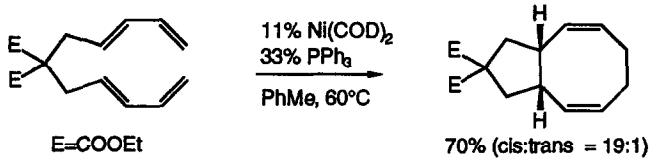


40% (3:1)

(2.10.2)

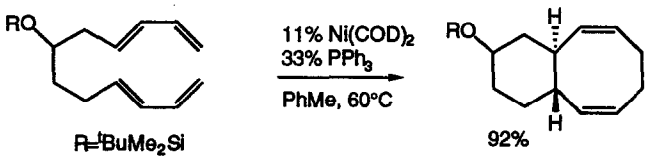
The Ni-catalyzed dimerization of 1,3-dienes is a reaction of mechanistic and commercial significance.[140] Intermolecular cyclizations of this type are often limited to dimerizations.[141] The intramolecular variant of this [4+4] cycloaddition was developed by Wender.[142] This unique cycloaddition takes advantage of two important properties of Ni(0): (a) its known oligomerization of

1,3-dienes as a C-C bond forming reaction and (b) its coordination chemistry of 1,5-octadienes. Among the first examples of this process was the reaction of a tetraene with $Ni(COD)_2$, PPh_3 in toluene at 60°C, affording the cyclooctanoid product with 19:1 diastereoselectivity (2.10.3). Fused five-eight and six-eight ring systems with varied substrates were also examined (2.10.4).



E=COOEt

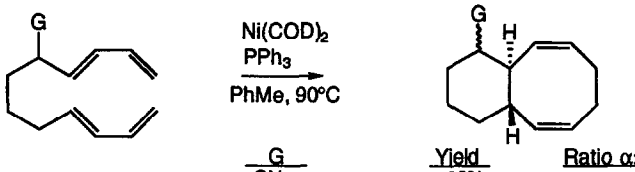
70% (cis:trans = 19:1) (2.10.3)



R=^{t}BuMe$_2$Si

92% (2.10.4)

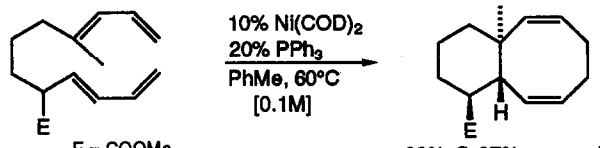
Wender[143] later reported a more detailed mechanistic investigation where the allylic groups in one position were varied to assess their influence on the stereochemistry of the products (2.10.5). The use of a nitrile group indicated its small size could exert only minimal stereoinductive effects (1.3:1). Substitution of a methyl group demonstrated a pronounced steric non-complexing selectivity (20:1). The relatively equivalent sized CH_2OAc produced similar results (21:1) to the methyl case despite the possibility of complexation, suggesting the selectivity was the result of steric factors. The CO_2CH_3 analogue invoked the greatest stereoselection (>70:1) which was attributed primarily to the increased sterics. These observations were rationalized by MM2 calculations of the various conformations available for the cyclization.



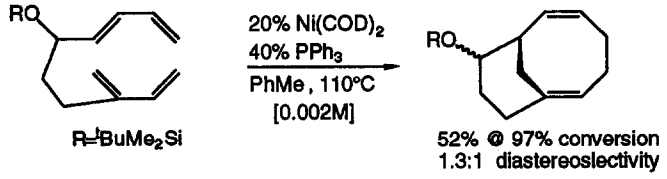
(2.10.5)

G	Yield	Ratio α:β
-CN	66%	1.5:1
-Me	88%	20:1
-CH_2OAc	92%	21:1
-COOEt	84%	>70:1

The same type of reaction was used by Wender[144] in studies directed towards the synthesis of taxane natural products. The fused six-eight carbon framework was synthesized in 92% yield with >97% diastereoselectivity (2.10.6), while the bridged six-eight system was obtained in 52% yield but with only minimal diastereoselectivity (2.10.7).

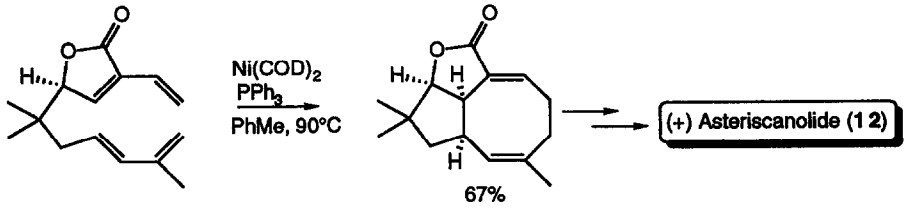


(2.10.6)



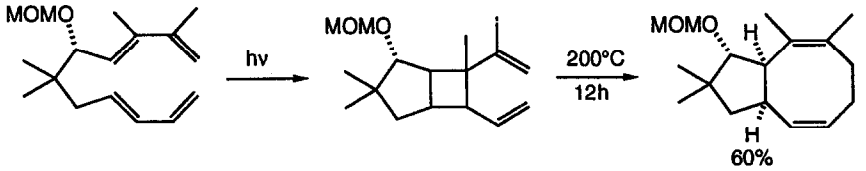
(2.10.7)

This [4+4] strategy was employed by Wender[145] for the enantioselective total synthesis of (+)asteriscanolide (2.10.8). The key eight-membered ring forming transformation was accomplished in 67% yield.



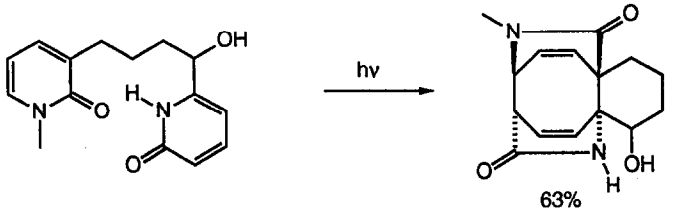
(2.10.8)

Wender[146] has also used similar precursors for an overall [4+4] intramolecular annulation, where the transformation entails an initial photochemical [2+2] cycloaddition followed by a thermal Cope rearrangement resulting in the cyclooctanoid product in good yields (2.10.9).



(2.10.9)

A photochemical [4+4] cycloaddition method for the synthesis of functionalized eight-membered rings involving pyridone derivatives (2.10.10) was recently reported by Sieburth.[147]



(2.10.10)

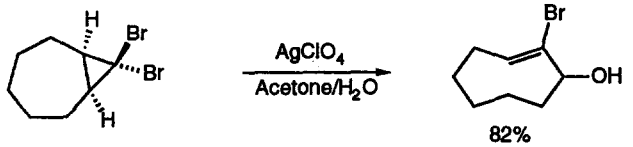
3. Fragmentations

Several types of bicyclic systems can be transformed into eight-membered rings upon cleavage of the appropriate bond. This section outlines methods involving the formation of such fused or bridged systems, followed by their fragmentation to the corresponding cyclooctanoid product.

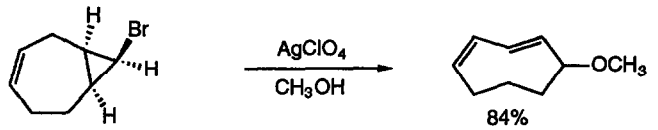
3.1 Fragmentation of bicyclo[5.1.0]octane systems

The facile cleavage of the strained cyclopropane ring on the bicyclo[5.1.0]octane ring systems makes them suitable precursors for the synthesis of cyclooctanoids.

Reese[148] has reported a silver perchlorate promoted ring expansion of halocarbene adducts of cyclic olefins to give cis or trans cyclooctene derivatives (3.1.1) or cis,trans cyclooctan-1,4-diene products (3.1.2).[149]

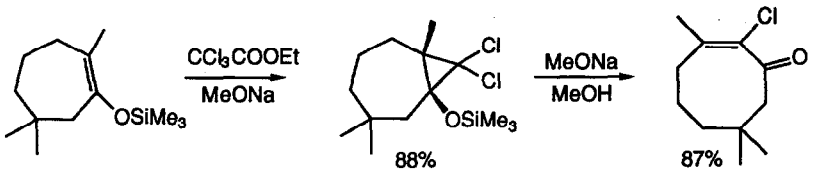


(3.1.1)



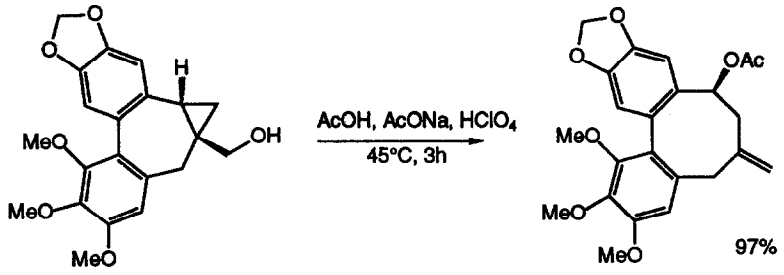
(3.1.2)

Wenkert[150] has reported a similar fragmentation of halocyclopropanes obtained from cyclopropanation of 2,6,6-trimethyl-1-(trimethylsilyloxy)cycloheptene under solvolysis conditions providing cyclooctenones in high yield (3.1.3).



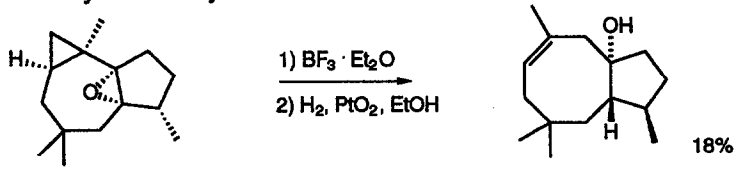
(3.1.3)

Magnus[151] has used a strategy for the synthesis of steganone natural products based on the ring expansion of fused biaryl cyclopropylmethanol cycloheptane derivatives in the presence of acetic acid, sodium acetate and perchloric acid (3.1.4). Presumably, in this case the cyclopropane ring opening is promoted by the protonation of the hydroxyl group.



(3.1.4)

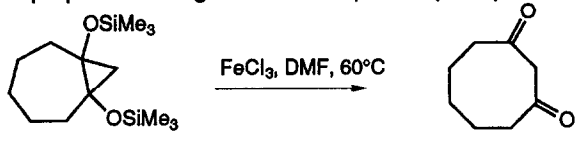
A Lewis acid catalyzed opening of an epoxy-substituted cyclopropane ring system was utilized by Paquette[152] in his total synthesis of dactylol (**10**) (3.1.5). This biogenetic-like transformation was previously outlined by Matsumoto.[153]



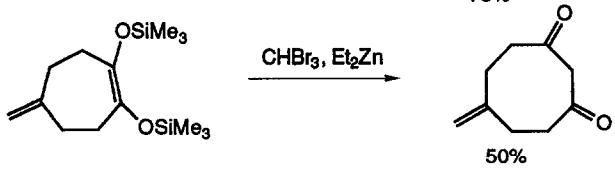
(3.1.5)

Dactylol (**10**)

Pirrung[154] has reported a synthesis of 1,3-cyclooctadione via oxidative cleavage of 1,7-bis(trimethylsiloxy)bicyclo[5.1.0]octane in the presence of $FeCl_3$ (3.1.6). Reingold[155] has recently reported a similar in situ cyclopropanation-fragmentation sequence (3.1.7).



(3.1.6)



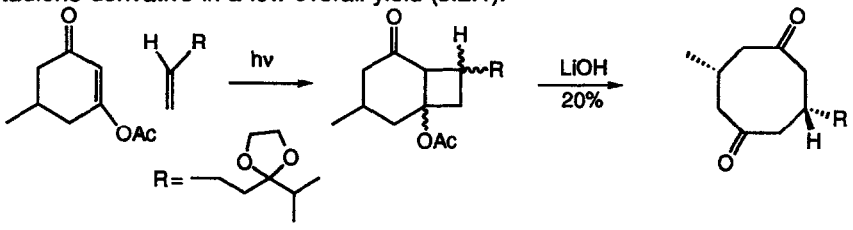
(3.1.7)

3.2 Fragmentation of bicyclo[4.2.0]octane systems

The photochemical [2+2] cycloaddition between an olefin and the enol form of 1,3-dicarbonyl derivatives, followed by fragmentation of the resulting cyclobutane ring, has been used in synthesis extensively.[156] This process, known as the deMayo reaction,[157] has been adapted for eight-membered ring synthesis by utilizing derivatives of cyclohexane-1,3-dione. Many variations

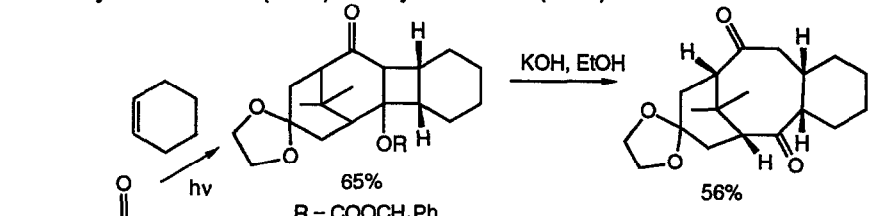
involving inter- and intra-molecular photochemical [2+2] cycloadditions towards a bicyclo[4.2.0] octane system, followed by a retroaldol process or other types of fragmentation have been reported.

In an approach to the fusicoccin H aglycone, Grayson[158] employed an intermolecular [2+2] photocycloaddition followed by lithium hydroxide initiated retroaldol reaction providing a 1,5-cyclooctadione derivative in a low overall yield (3.2.1).

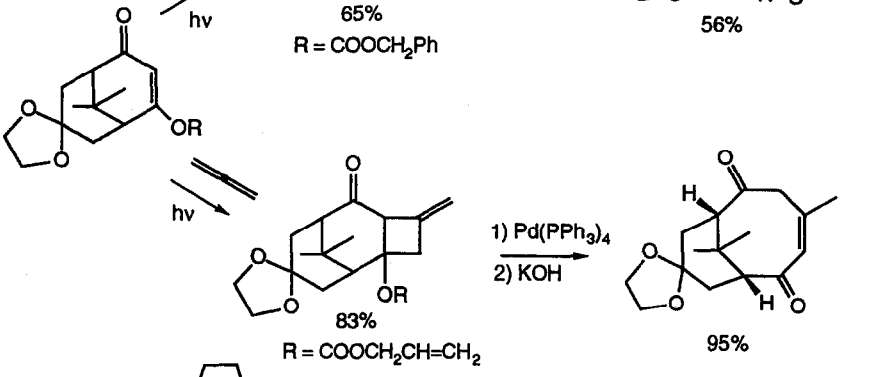


(3.2.1)

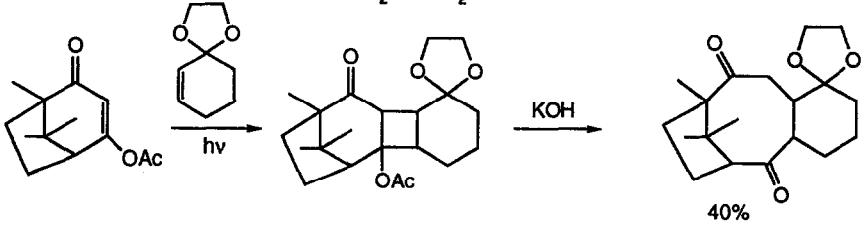
A variety of de Mayo type strategies were developed for the synthesis of the taxane skeleton. Blechert has explored an intermolecular photocycloaddition approach of carbonate derivatives of cyclohexane 1,3-dione. The use of cyclohexene in this process led to the tricyclic ABC taxane ring system (3.2.2),[159] while allene afforded a bicyclic dione (AB rings) amenable to subsequent annulation of ring C (3.2.3).[160] Additional examples of this type of chemistry was reported by Blechert,[161,162] by Berkowitz[163] (3.2.4) and by Fetizon[164] (3.2.5).



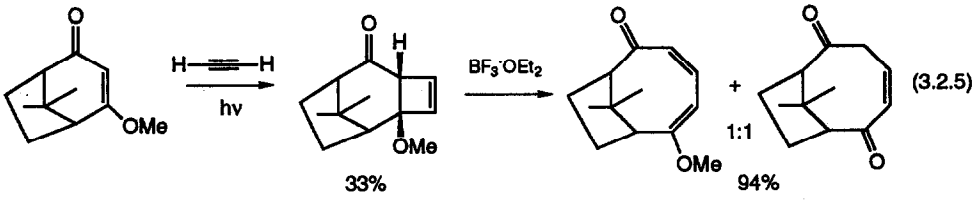
(3.2.2)



(3.2.3)

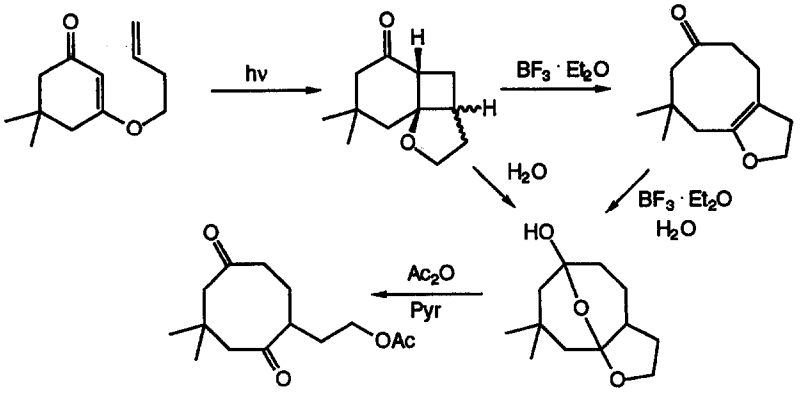


(3.2.4)



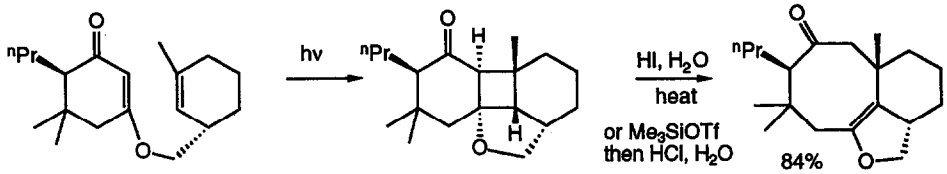
(3.2.5)

Intramolecular deMayo reactions have proven quite effective for the synthesis of eight-membered rings. The olefinic group can be attached at various positions of the 1,3-dicarbonyl system, leading to different products. An early report by Tamura[165] involved tethering the olefin onto the enolic oxygen. Intramolecular photocycloaddition formed a tricyclic system, which underwent a Lewis acid promoted fragmentation to cyclooctanoid products (3.2.6).

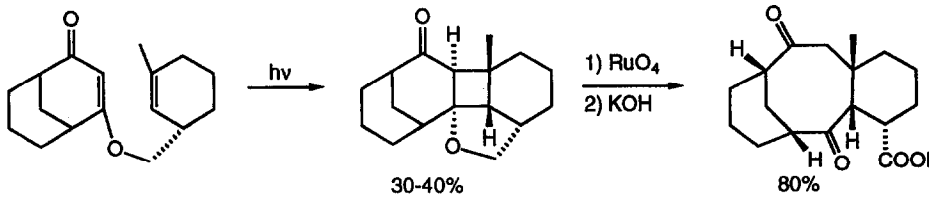


(3.2.6)

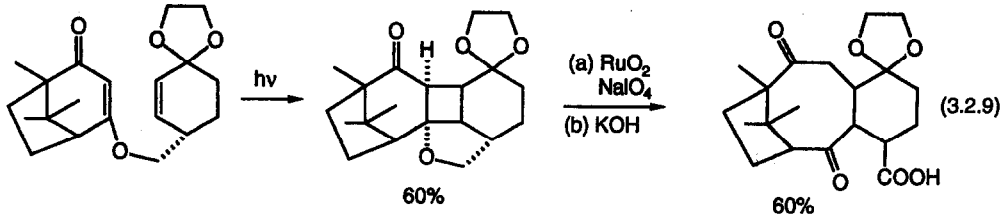
Adaptation of this transformation to taxane synthesis was studied by several groups. Kakisawa[166] has reported the use of other Lewis acids (TMSOTf, HI) for cleaving the cyclobutane ring (3.2.7). An oxidation-lactone hydrolysis sequence was utilized by the same group[167] (3.2.8), as well as by Berkowitz[168] (3.2.9).



(3.2.7)

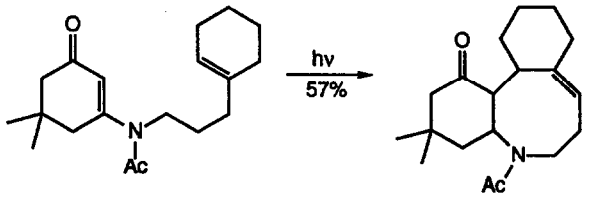


(3.2.8)

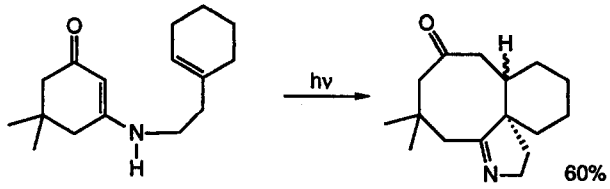


(3.2.9)

The aza-deMayo reaction was investigated by Schell. At first it was found[169] that the photolysis of vinylogous imides having olefinic substituents proceeds via an ene reaction (3.2.10). It was later reported[170] that a shorter olefinic tether gives a deMayo like intermediate, which can be hydrolyzed to the cyclooctanedione product. Similarly, eight-membered rings were obtained via the photocycloaddition of non-acylated vinylogous amide derivatives (3.2.11).[171] Some additional examples of this aza-deMayo reaction were recently reported by Schell.[172]

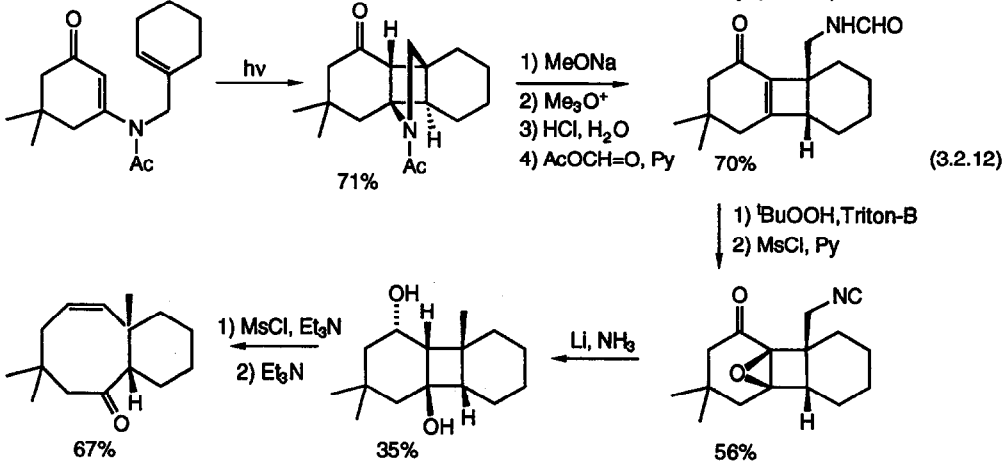


(3.2.10)



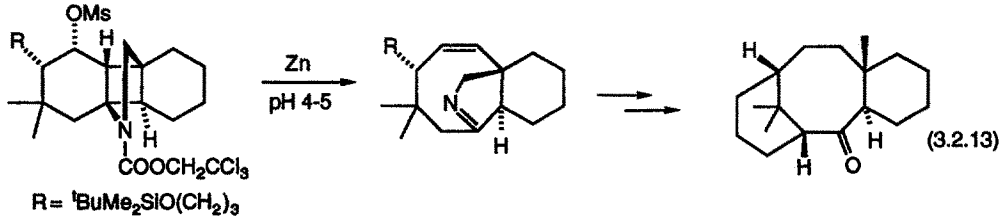
(3.2.11)

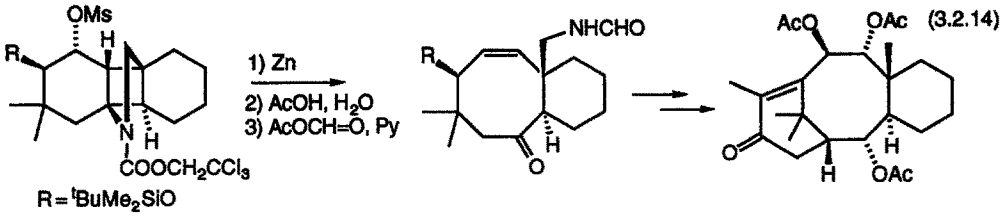
The application of this chemistry to taxane synthesis was undertaken by Swindell. Initially,[173] this approach led to the taxane BC ring system with incorrect stereochemistry (3.2.12).



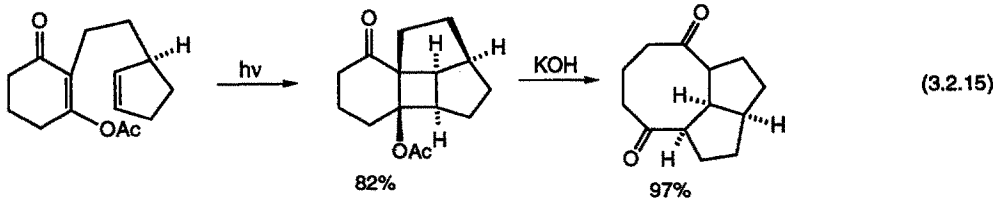
(3.2.12)

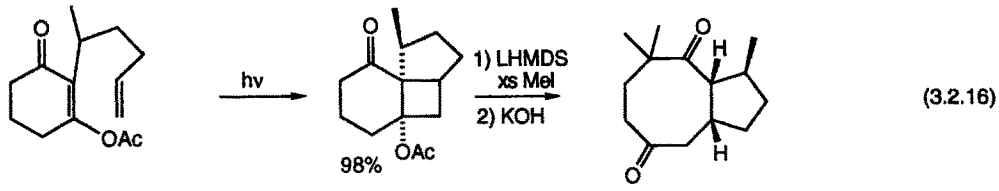
Subsequent modifications of this strategy resulted in the synthesis of the taxane ABC ring system[174] (3.2.13), while more recent work provided a taxinine substructure[175] (3.2.14).

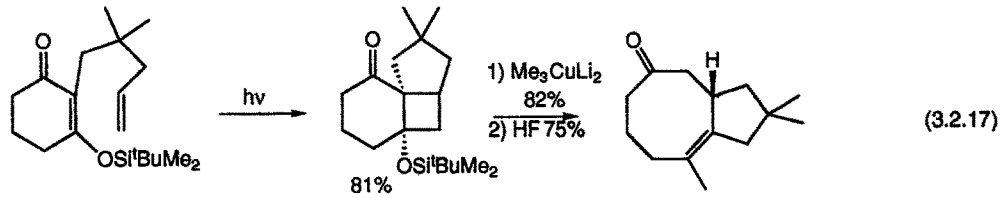




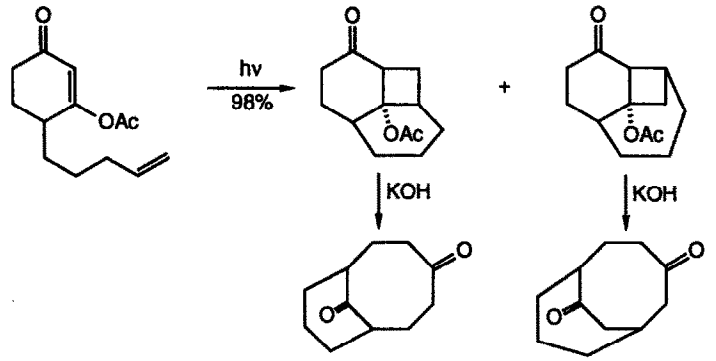
Attachment of the alkenyl substituent at the 2-position of the 1,3-dicarbonyl system, leads via the deMayo reaction, to fused bicyclic ring systems. Examples of this type were reported by Oppolzer[176] (3.2.15) and Pattenden[177] (3.2.16), who used this strategy for the total synthesis of epi-precapnelladiene[178] (3.2.17) and in an approach to (+)pentalenene.[179]





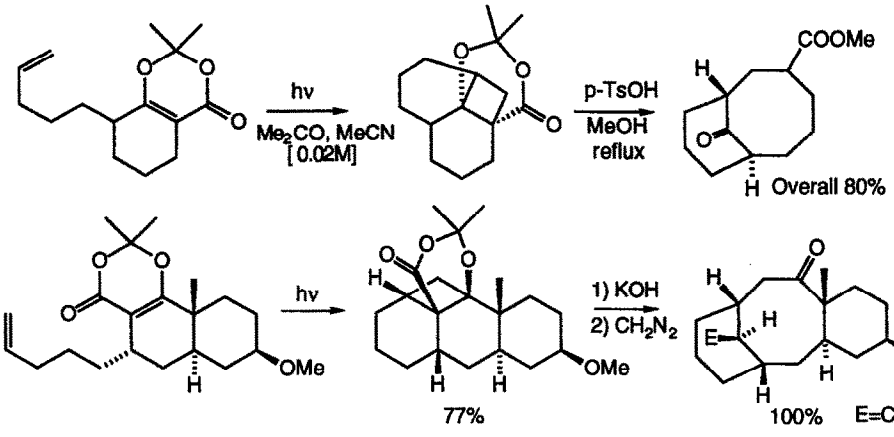


As an extension of this work Pattenden,[180] has reported additional examples where the tether for the photochemical [2+2] was located at the 4-position, providing bridged eight-membered ring products after saponification and retroaldol (3.2.18).



(3.2.18)

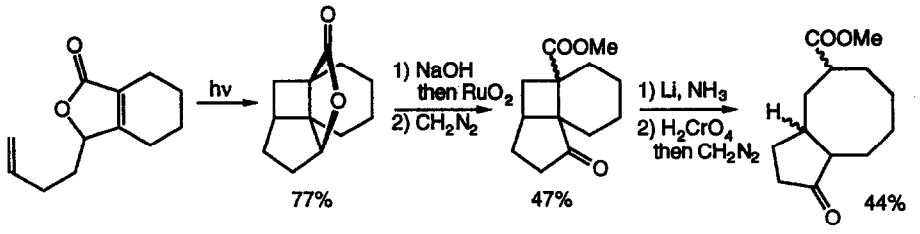
Winkler[181] has studied a modified deMayo process involving the intramolecular photocycloaddition of dioxenones to alkenes. In an initial approach to taxane synthesis[182] the alkene group was tethered at the γ-position of the dioxenone moiety and upon acidic hydrolysis resulted in the formation of an inside-outside bicyclic system (3.2.19). Subsequent work led to a similar tricyclic system.[183] More recently,[184] the correct stereochemistry for the taxane skeleton was achieved by attaching the olefinic tether at the β'-position of the dioxenone followed by basic hydrolysis (3.2.20).



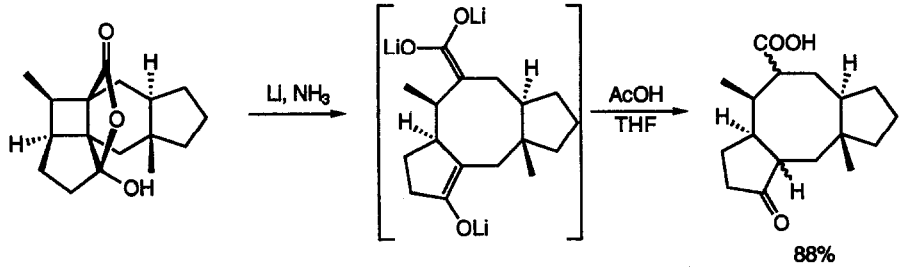
(3.2.19)

(3.2.20)

A different mode of fragmentation of the bicyclo[4.2.0]octane system was reported by Coates.[185] Instead of relying on 1,3-dicarbonyl derivatives, this approach was based on the intramolecular photocycloaddition of alkenes or allenes to $\Delta^{\alpha,\beta}$-butenolides. Reductive cleavage with lithium in liquid ammonia of the resulting adducts led to cyclooctanoid products in good yields (3.2.21). This strategy was employed by Coates[186] in an approach to the ophiobolins and ceroplastins (3.2.22).

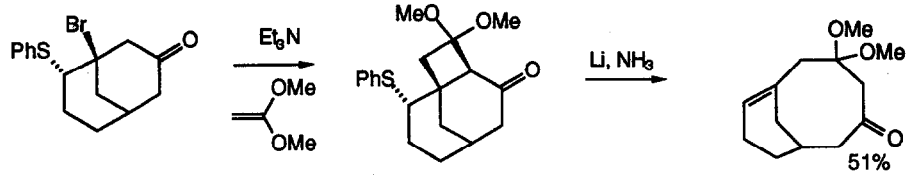


(3.2.21)



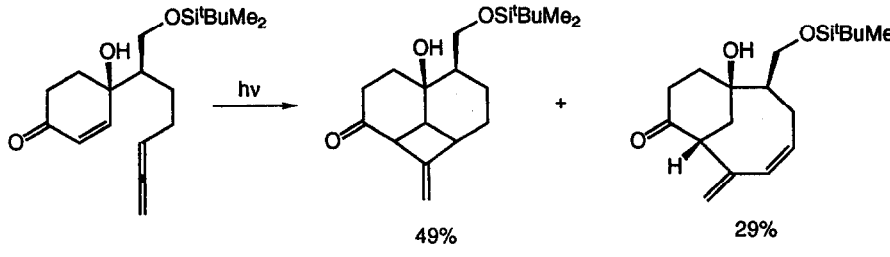
(3.2.22)

Kraus[187] has reported the facile cycloaddition of an insitu formed bridgehead enone to 1,1-dimethoxyethylene followed by a reductive fragmentation to give a taxane-like system (3.2.23).



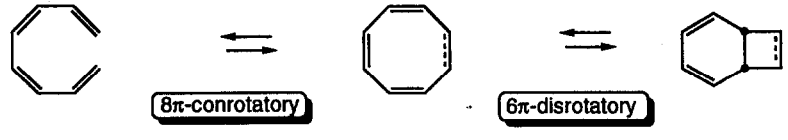
(3.2.23)

Dauben[188] has observed the formation of a bridged six-eight ring system (3.2.24) during an investigation of substitutent effects on the intramolecular photocycloadditions of enones and allenes.



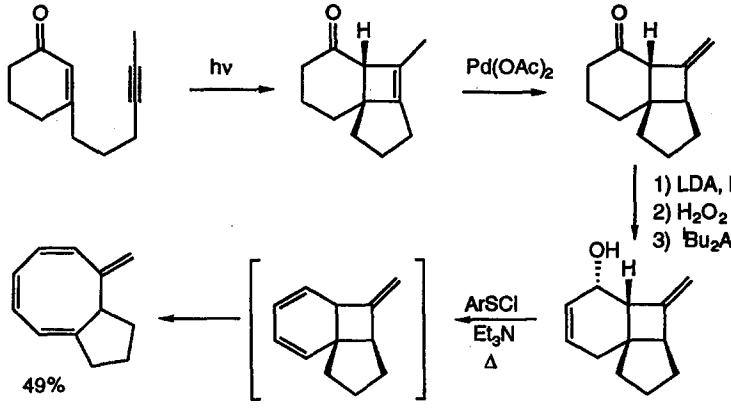
(3.2.24)

The well known[189] equilibrium among octatetraene, cyclooctatriene and bicyclo[4.2.0]octadiene (3.2.25) provides another method for the synthesis of polyunsaturated eight-membered rings.



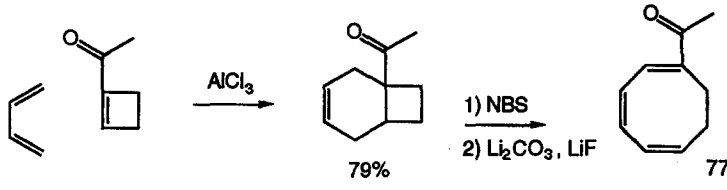
(3.2.25)

Paquette[190] has relied on this equilibrium for the synthesis of a methylene cyclooctatriene beginning with an intramolecular enone-alkyne photocycloaddition (3.2.26).



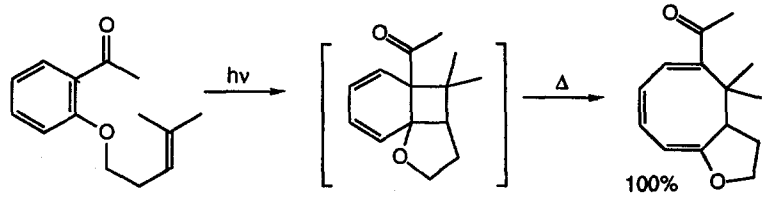
(3.2.26)

A stepwise formation of the bicyclic diene intermediate leading to the same type of cyclooctatriene product was recently reported by Takeda[191] (3.2.27).



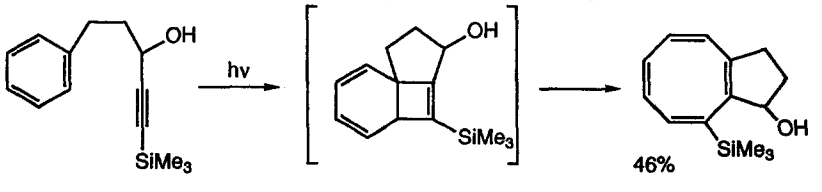
(3.2.27)

Wagner[192] has reported an analogous transformation, beginning with the intramolecular [2+2] photocycloaddition of an alkene to benzene forming a tricyclic product, which upon heating gave the cyclooctatriene (3.2.28).



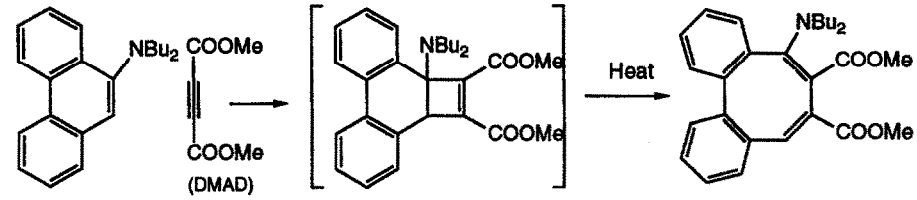
(3.2.28)

The photocycloaddition of alkyne derivatives to the benzene ring followed by electrocyclic ring opening according to (3.2.25) is a general method for the synthesis of cyclooctatetraenes. The intramolecular variant of this process was recently studied by Pirrung[193] (3.2.29).

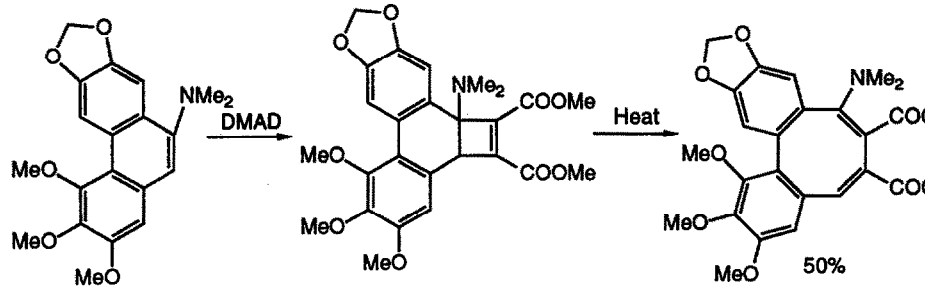


(3.2.29)

The photocycloaddition of electron poor alkynes to electron rich alkenes was also investigated. In this case, the intermediate is a fused cyclobutene, capable of electrocyclic ring opening to a cyclooctadiene. Raphael[194] has studied this transformation for the synthesis of biaryl lignans. Thus, photochemical [2+2] cycloaddition between an enamine and dimethylacetylene dicarboxylate(DMAD) provided a cyclobutene which upon heating underwent ring expansion to the eight-membered ring. Acid hydrolysis followed by decarboxylation supplied the unsaturated keto-ester which was further elaborated to become a steganone analogue (3.2.30). The same strategy was later used in the total synthesis of steganone by both Raphael[195] and Krow[196] (3.2.31).

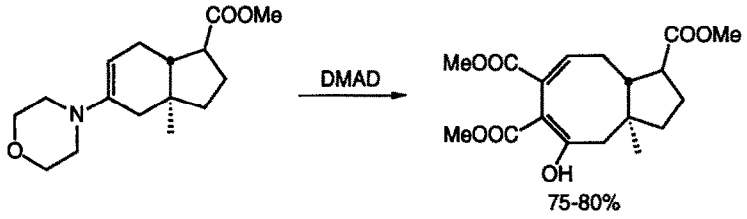


(3.2.30)



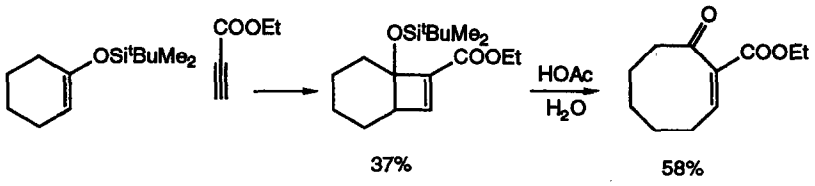
(3.2.31)

Dauben[197] has applied a similar strategy on an advanced fused bicyclic enamine towards the ophiobolin nucleus (3.2.32).



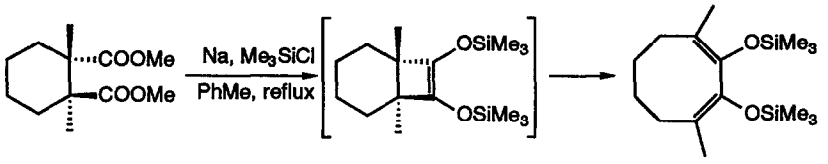
(3.2.32)

Similarly, Untch[198] studied the addition of silyl enol ethers to mono- and di- carboxy-acetylenes which provided the corresponding bicyclo[4.2.0]octane ring systems. Upon treatment with acetic acid, the cyclooctenones were formed in good yields (3.2.33).



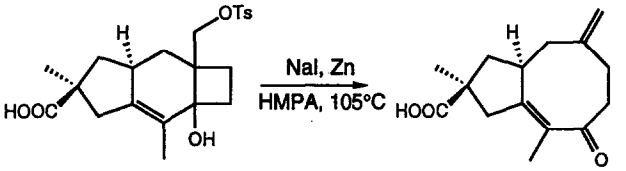
(3.2.33)

The use of the acyloin condensation for the formation of an analogous fused cyclobutene was reported by Gassman[199] (3.2.34). Under the reaction conditions, the strained intermediate underwent a spontaneous electrocyclic ring opening to the cyclooctadiene product.

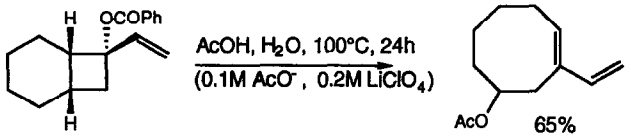


(3.2.34)

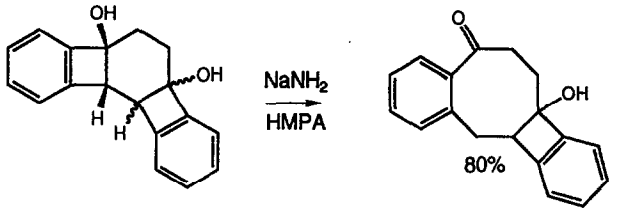
Some examples of other types of cleavage of the bicyclo[4.2.0]octane ring system were also reported. These include a Wharton fragmentation[200] (3.2.35), a solvolysis of an allylic benzoate[201] (3.2.36), a base induced fragmentation[202] (3.2.37) and a free radical cleavage[203] (3.2.38).



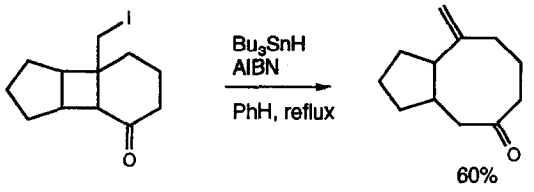
(3.2.35)



(3.2.36)

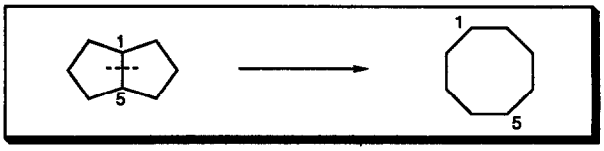


(3.2.37)

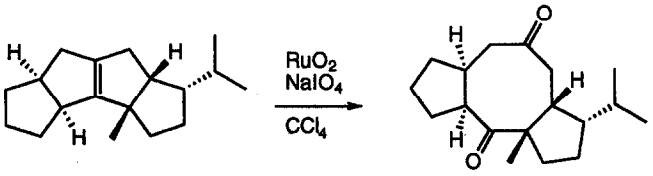


(3.2.38)

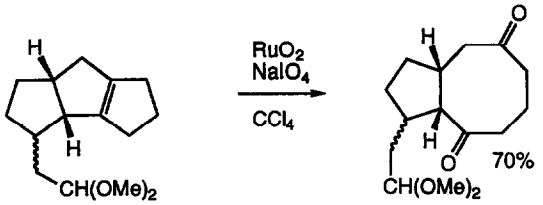
3.3 Fragmentation of bicyclo[3.3.0]octane systems



The cleavage of the C_1-C_5 bridging bond of fused 5-5 ring systems, available from a variety of precursors, provides another general method for the construction of eight-membered rings. Mehta[204] has explored the oxidative cleavage of a bridging olefinic bond providing 1,5-cyclooctadiones suitable for the construction of the 5-8-5 carbocyclic nucleus of fusicoccins and ophiobolins. Several types of linear di- and tri-quinane systems have been prepared and converted to functionalized cyclooctane products in good yields (3.3.1), (3.3.2).

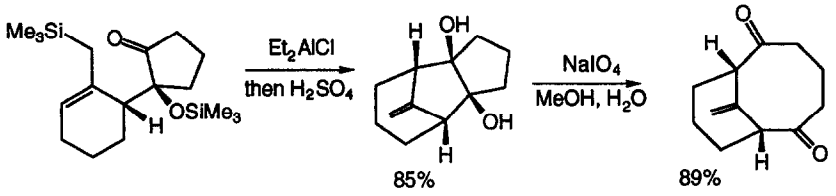


(3.3.1)



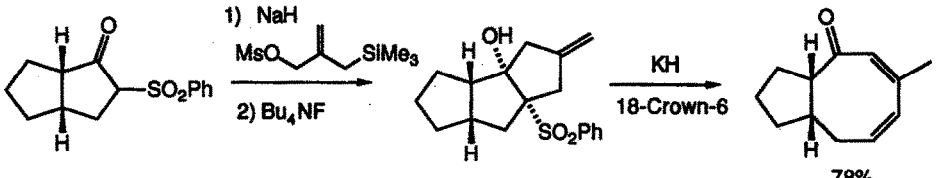
(3.3.2)

The direct formation of a vicinal diol at the bridge of a fused 5-5 system, followed by oxidative cleavage was reported by Trost[205] in a new approach to the taxane ring system (3.3.3).

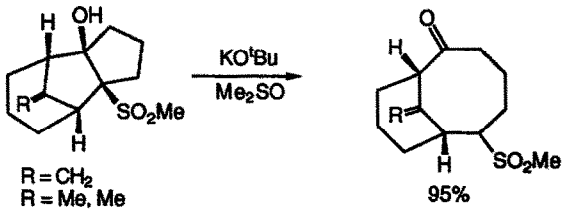


(3.3.3)

An alternative strategy developed by Trost[206] involved a three carbon expansion of a β-keto-sulfone via a base-mediated fragmentation of a fused 5-5 ring system (3.3.4). Also, a similar intermediate, constructed in a different manner, was subjected to an analogous basic cleavage to give the taxinine ring system in high yield[207] (3.3.5).

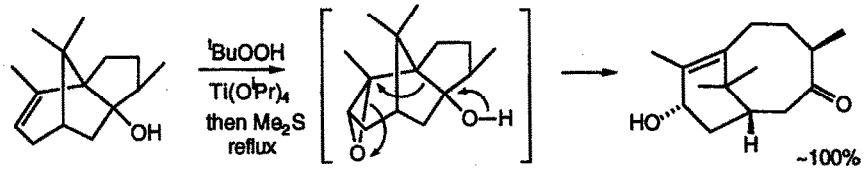


(3.3.4)

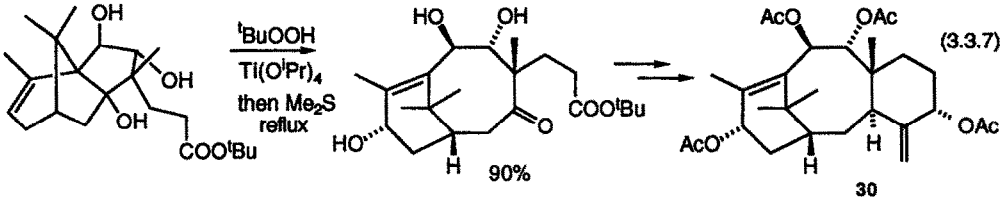


(3.3.5)

A rearrangement process involving a variant of the Wharton fragmentation, suitable for taxane synthesis, was developed by Holton.[208] In a model study it was shown that a hydroxy epoxide intermediate could undergo a fragmentation providing the taxane AB ring system (3.3.6). This approach was further extended[209] to a more substituted precursor which was utilized in the first total synthesis of taxusin (**30**), although in the opposite enantiomeric form (3.3.7).

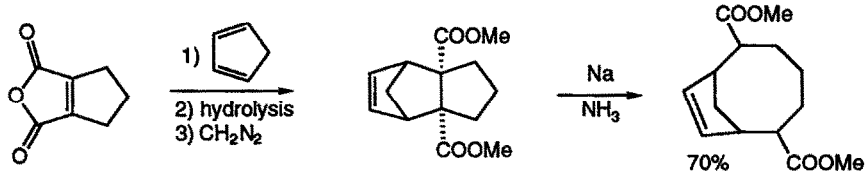


(3.3.6)



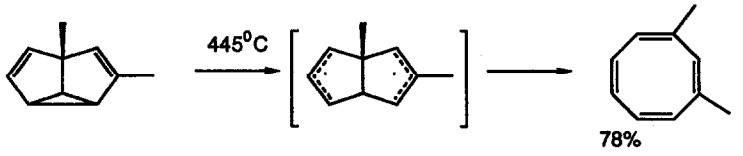
(3.3.7)

A reductive cleavage of a 5-5 fused system formed by a Diels-Alder reaction, was recently reported by Ghosh[210] (3.3.8).



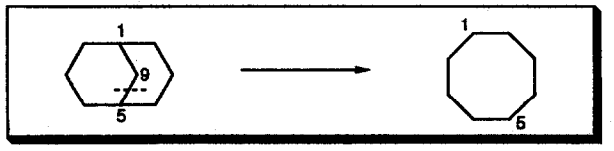
(3.3.8)

The formation and cleavage of a diradical bicyclo[3.3.0]octane intermediate takes place during the thermal isomerization of semibullvalenes to cyclooctatetraenes, a process studied in detail by Paquette[211] (3.3.9). This rearrangement was recently utilized in a synthesis of [2$_2$](1,5)cyclooctatetraenophane.[212]

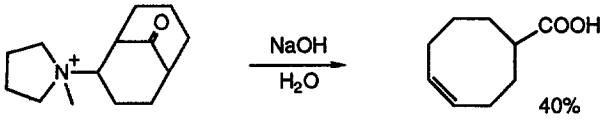


(3.3.9)

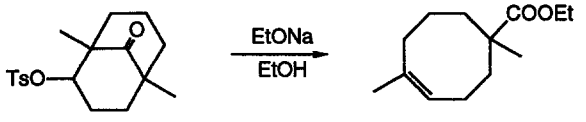
3.4 Fragmentation of bicyclo[3.3.1]nonane systems



Bicyclo[3.3.1]nonane systems bearing an alkoxy group at C_9 and a leaving group β– to this bridge position, undergo facile cleavage of the C_9-C_1 or C_9-C_5 bond to generate an eight-membered ring. This process, known as the Wharton fragmentation, a variant of the Grob fragmentation, has found numerous applications for the synthesis of polycyclic systems.[213] The required alkoxide can be formed either by treating an alcohol with base or by adding a variety of nucleophiles to carbonyls. Some early examples were reported by Stork[214] (3.4.1), Raphael[215] (3.4.2), Kraus[216] (3.4.3) and Marschall[217] (3.4.4).

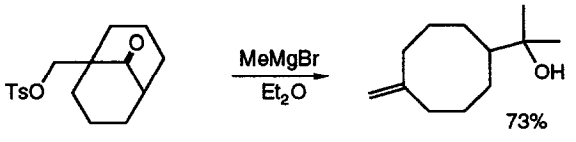


(3.4.1)



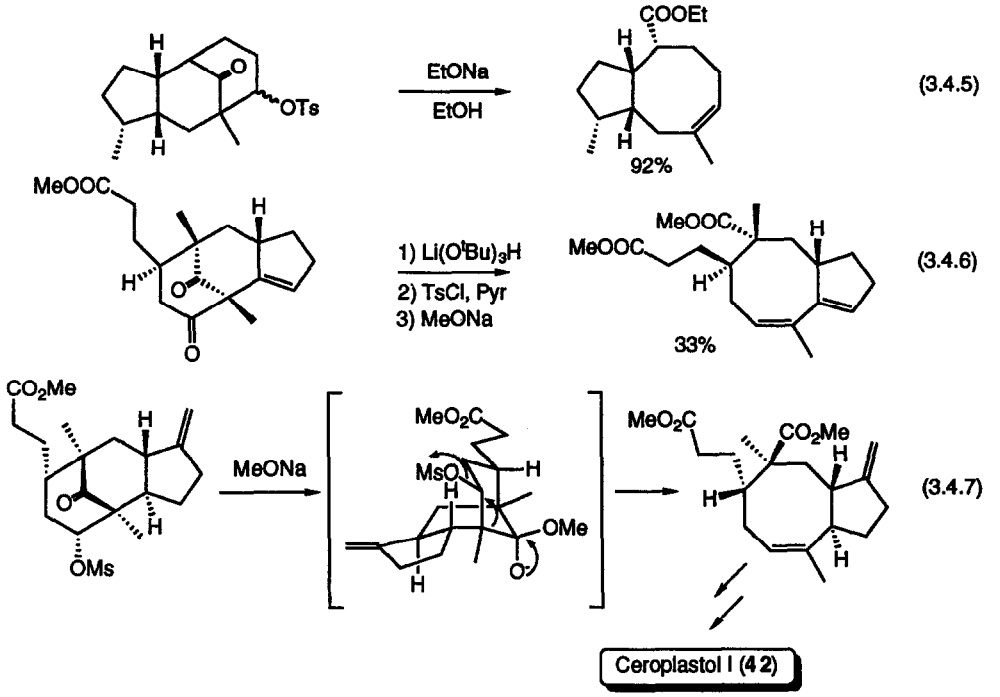
(3.4.2)

(3.4.3)

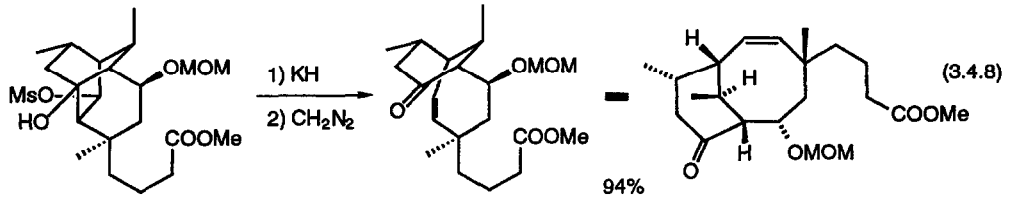


(3.4.4)

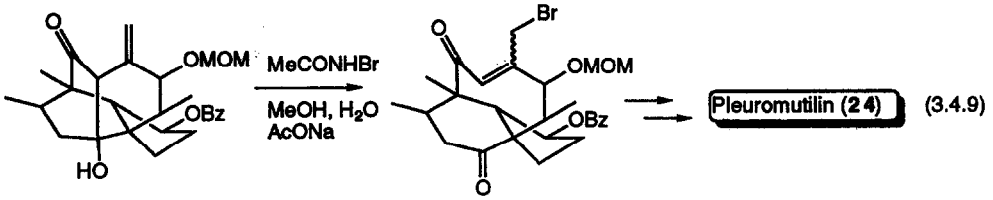
Dutta[218] has explored this type of Wharton fragmentation in synthetic studies directed towards the synthesis of ophiobolins (3.4.5). Boeckman[219] has also utilized the Wharton protocol for the stereospecific construction of the ceroplastol and ophiobolin ring systems (3.4.6), which he later employed in the total synthesis of ceroplastol I (**42**)[220] (3.4.7).



Yamada[221] has applied the Wharton fragmentation as the key step in the synthesis of the AB ring system of the taxanes (3.4.8).

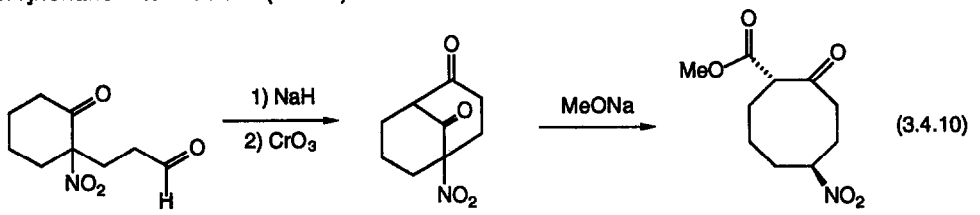


An interesting Wharton type process was used by Gibbons[222] in the total synthesis of pleuromutilin (**24**), where fragmentation was accomplished by deprotonation of a hydroxy group in the presence of a brominating agent (3.4.9).



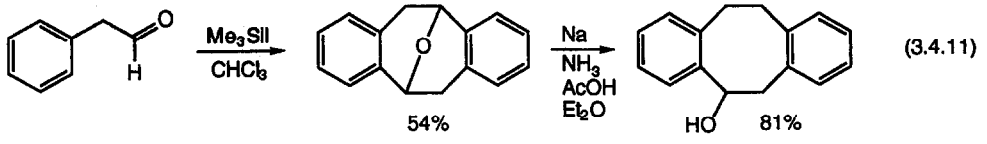
(3.4.9)

In his studies of "zip" ring enlarging reactions Hesse[223] studied the two-atom ring expansion of α-nitro cyclohexanone to the corresponding cyclooctanone via the fragmentation of a bicyclo[3.3.1]nonane intermediate (3.4.10).

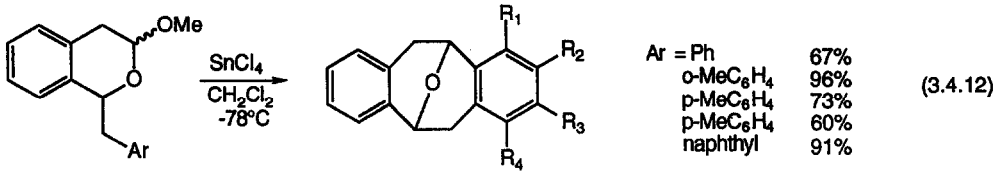


(3.4.10)

The preparation and fragmentation of oxygen-bridged bicyclo[3.3.1]nonanes is another route to cyclooctanoids. An early report by Jung[224] demonstrated the use of a Friedel-Crafts dimerization of an aryl aldehyde with trimethylsilyliodide. After several days a 54% yield of the crude oxygen-bridged product was formed which was then converted to the dibenzocyclooctane ring system (3.4.11). More recently a stepwise variant of this process was used by Harmata[225] for the synthesis of derivatives of Kagan's ether in yields ranging from 60-96% (3.4.12).



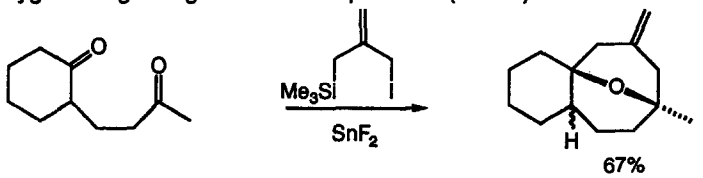
(3.4.11)



(3.4.12)

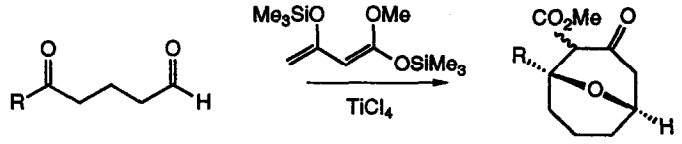
Molander has recently introduced two formal [3+5] annulation processes utilizing three carbon chain synthons that serve as 1,3 dianion equivalents which were added to 1,5 dicarbonyl compounds. While these methods produce oxygen-bridged eight-membered rings, they avoid the difficult direct cyclization by utilizing acetal or ketal templates as intermediates. The first of these[226] utilized an iodo-trimethylsilylpropene derivative, which was treated with stannous fluoride to

generate in situ the corresponding allylstannane. Upon addition of the reactive allylstannane moiety to one of the carbonyls followed by addition of the resulting tin alkoxide to the remaining carbonyl and subsequent displacement of the newly formed ketal by the allylsilane group resulted in the formation of oxygen bridged eight-membered products (3.4.13).



67% (3.4.13)

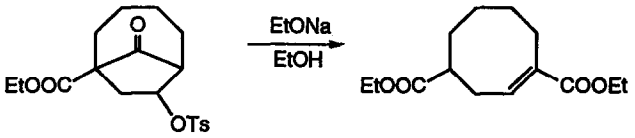
The second annulation process developed by Molander[227] involved bis(trimethylsilyl) enol ethers as 1,3-dianion equivalents. They were treated with 10% $TiCl_4$ followed by 1,5-dicarbonyl (ketones or mixed keto-aldehydes) which resulted in the formation of the bridged eight-membered ring products in yields ranging from 63-77% (3.4.14).



R= Me 77% (3.4.14)
tBu 71%
Ph 63%

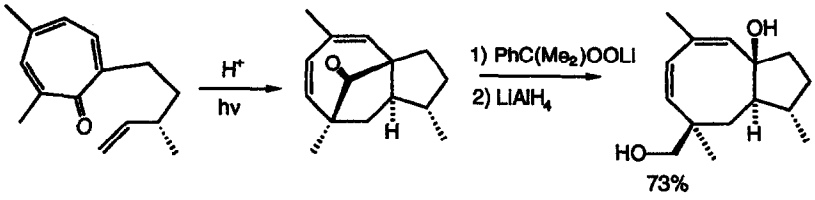
3.5 Fragmentation of bicyclo[4.2.1]nonane systems

Bicyclo[4.2.1]nonane systems have seldomly been utilized for eight-membered ring synthesis. An example involving the basic cleavage of a ketoester was reported by Carruthers[228] (3.5.1).



(3.5.1)

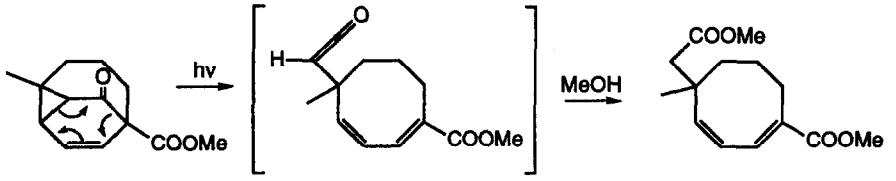
Feldman[229] has studied the intramolecular [6+2] photocycloaddition for the synthesis of cyclooctanoids. Alkenyltropones were photolyzed in the presence of acid forming the corresponding tropylium ions which were subsequently trapped. The resulting bridged system was then fragmented affording the 8-5 fused product. Further studies examining the mechanism and diastereoselectivity of the reaction were also carried out.[230] More recently,[231] this method was employed in an elegant synthesis of dactylol (**10**) (3.5.2).



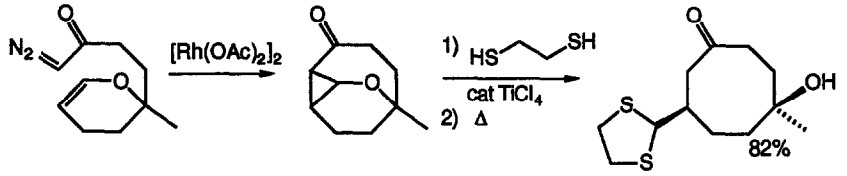
(3.5.2)

3.6 Fragmentation of tricyclic systems

The simultaneous cleavage of two bridging bonds of a tricyclic system can result directly in a single cyclooctane ring. Schultz[232] has reported a photochemically-induced fragmentation of this type (3.6.1). In another example, Adams[233] has reported the intramolecular cyclopropanation of diazo enol ethers followed by a $TiCl_4$-mediated thioacetalization and fragmentation (3.6.2).



(3.6.1)

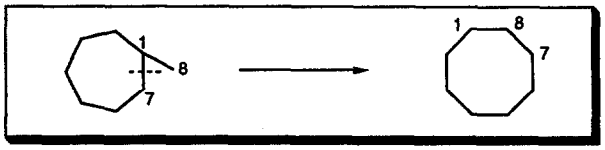


(3.6.2)

4. Ring expansions

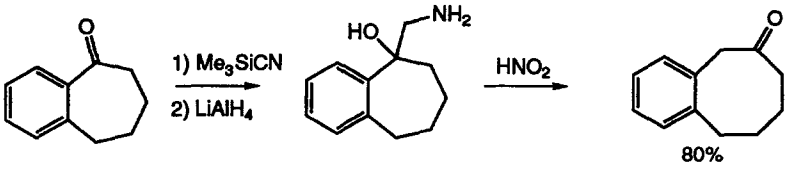
The ring expansion of cyclic compounds to larger rings has long been an effective strategy for the synthesis of specific ring sizes.[234] This section will address one-step processes leading directly to eight-membered ring carbocycles from smaller rings. One-, two-, three- or four-atom ring expansions of this type can take place via the intermediacy of unstable bicyclic systems similar to those discussed in the previous section. Instead of being stable neutral molecules, these systems are cationic, anionic, or free radical intermediates or transition states formed during pericyclic reactions. While many more possibilities exist, only those shown below have been developed.

4.1 One-atom ring expansion of seven-membered rings



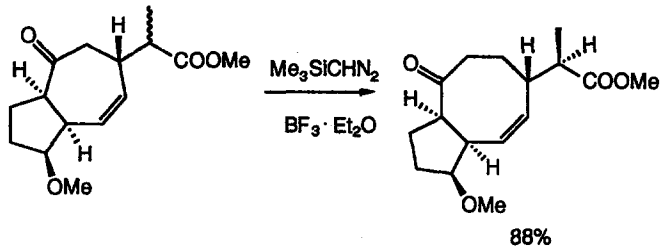
One of the earliest methods for the direct one-atom ring expansion of cyclic ketones, involves the reduction of the corresponding cyanohydrins, followed by a pinacol-like rearrangement of the

resulting hydroxy-amine upon treatment with nitrous acid. This process, called the Tiffeneu-Demyanov ring expansion, is suitable for eight-membered ring synthesis[235] and has been used by Thies[236] for the preparation of benzene-fused cyclooctanones (4.1.1).



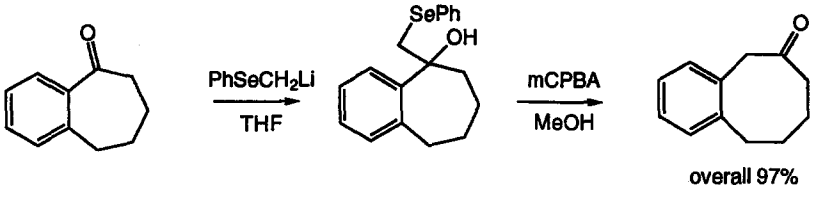
(4.1.1)

The addition of diazoalkanes to cyclic ketones followed by reaction with Lewis acids, is another general method for a one atom ring expansion. Rigby[237] has recently reported a reaction of this type during studies towards the ophiobolin ring system (4.1.2).

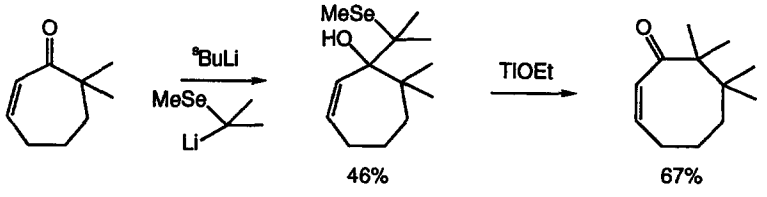


(4.1.2)

A one carbon homologation based on the addition of phenylselenomethyl-lithium, followed by oxidation and rearrangement was recently reported by Uemura[238] (4.1.3). A similar method was developed by Krief[239] for the ring expansion of cyclic enones. In this case a TlOEt - promoted alkyl migration proceeded with preferential migration of the alkyl group (4.1.4).

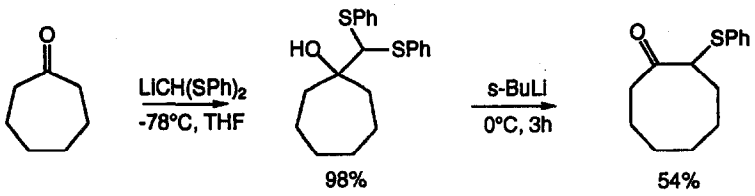


(4.1.3)



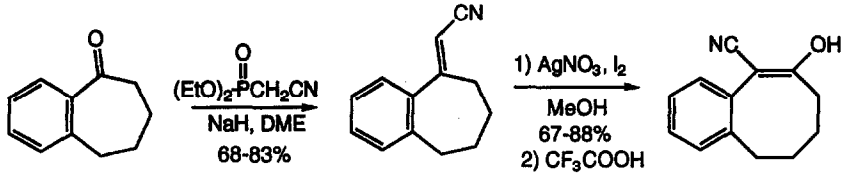
(4.1.4)

An organosulfur-based method was reported by Cohen,[240] involving the addition of the lithio derivative of bis(phenylthio)acetals followed by reaction with an alkyl lithium (4.1.5).



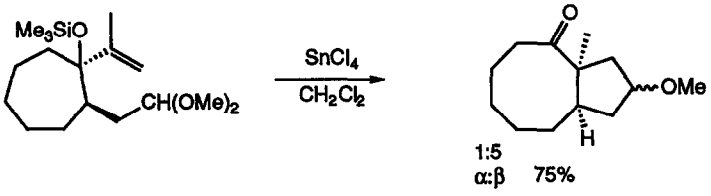
(4.1.5)

An olefination-ring expansion sequence has been developed by Hesse[241] for benzene-fused cycloheptanones (4.1.6).



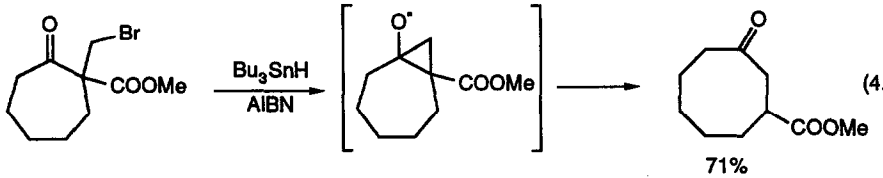
(4.1.6)

A novel ring-enlarging cyclopentane annulation has been developed by Overman.[242] This process involved a sequential ene type cationic cyclization of an acetal followed by pinacol rearrangement (4.1.7). A similar cyclopentene annulation was also reported.[243]

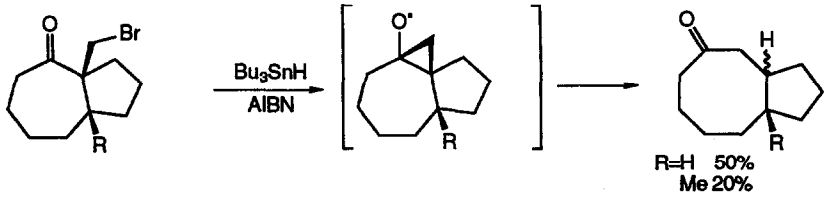


(4.1.7)

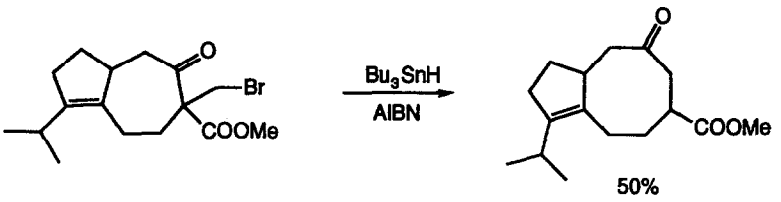
A fragmentation of an in situ formed bicyclo[5.1.0]octane ring system initiated by a free radical was reported by Dowd[244] (4.1.8). In this overall one atom ring expansion, the carbon radical added to the carbonyl and the resulting alkoxy radical underwent fragmentation towards the cyclooctanone products. Similar reactions were recently utilized by Pattenden[245] (4.1.9) and Mehta[246] (4.1.10) in separate approaches to the bicyclo[6.3.0]undecanone derivatives.



(4.1.8)

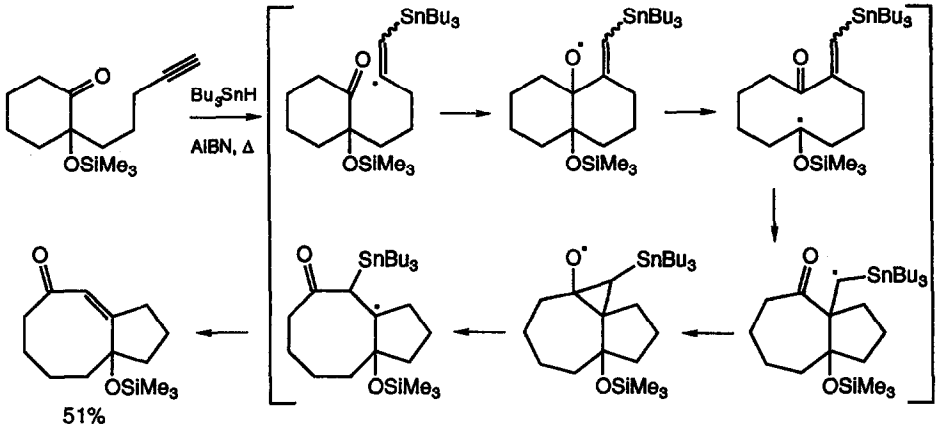


(4.1.9)



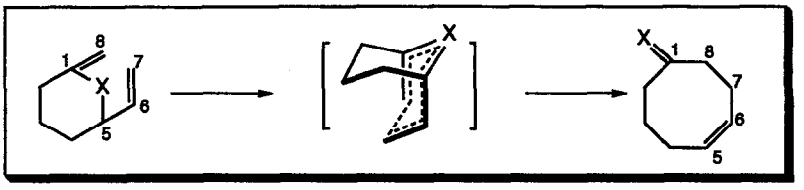
(4.1.10)

Nishida[247] has reported a multistep sequence to the same type of bicyclo[5.1.0]octane alkoxy radical, initiated from alkynyl cyclohexanone derivatives. Upon exposure to tributyl tin radical, formed thermally or photochemically, these compounds underwent a series of radical bond forming and bond breaking processes to form cyclooctenone products in moderate yields (4.1.11).



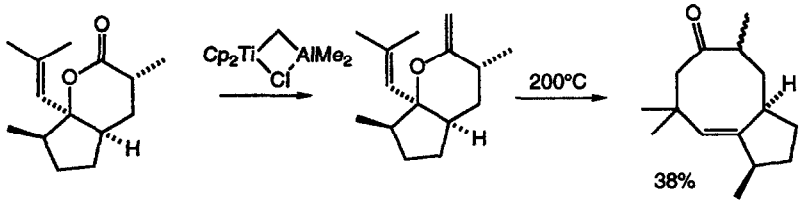
(4.1.11)

4.2 Two-atom ring expansion of six-membered rings



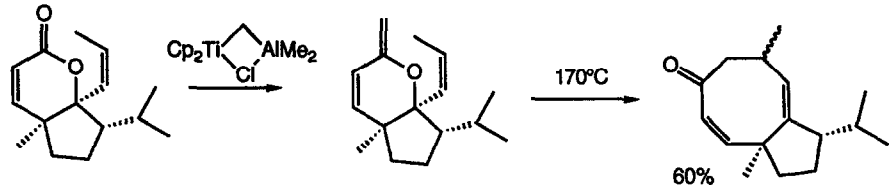
The direct ring expansion of a six- to an eight-membered ring is possible via the intermediacy of a bicyclo[3.3.1]nonane transition state, formed via a [3,3]-sigmatropic rearrangement. Most successful among the variations of this process have been the Claisen rearrangement (X = O) and several modes of the anionic oxy-Cope rearrangement.

The first example of cyclooctanone synthesis via the Claisen rearrangement was reported by Paquette,[248] in a synthetic approach to precapnelladiene (**9**). The required cyclic enol ether was prepared by methylenation with the Tebbe reagent of the corresponding bicyclic lactone which was synthesized from cyclopentanone (4.2.1).



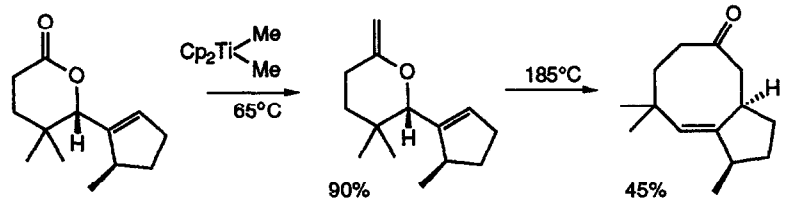
(4.2.1)

More recently Paquette[249] has utilized a similar approach to the total synthesis of (+)-7,8-epoxy-2-basmen-6-one (4.2.2), while a variation on this theme produced oxocene derivatives.[250]



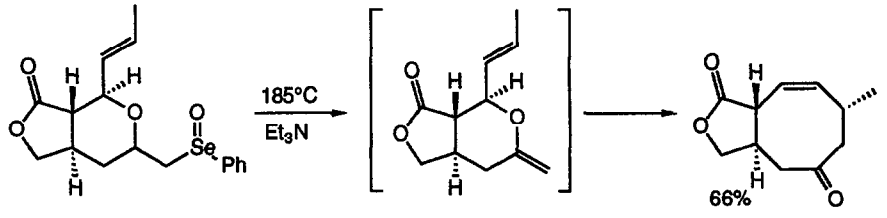
(4.2.2)

Petasis[251] has devised a strategy for the synthesis of cyclooctanones via a three-atom ring expansion of cyclopentanones. After aldol, Baeyer-Villiger and elimination reactions, the resulting vinyl-substituted lactone was olefinated with the newly developed dimethyl titanocene procedure (4.2.3). Upon heating of the enol ether at 185°C the cyclooctanone was formed via the thermal Claisen rearrangement. This approach was employed in a concise eight-step total synthesis of precapnelladiene (**9**).



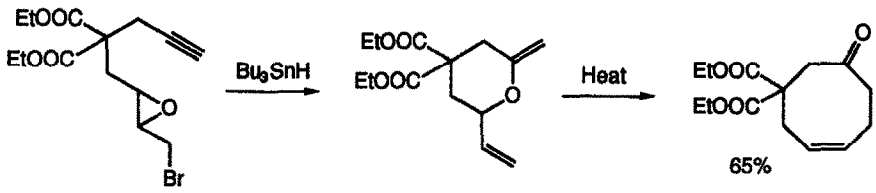
(4.2.3)

An alternative preparation of the six-membered ring enol ether was used by Paquette[252] in synthetic studies directed towards acetoxycrenulide (**27**) (4.2.4). The precursor was an exocyclic selenoxide which upon heating underwent syn-elimination and subsequent Claisen rearrangement forming the cyclooctanone in good yield.



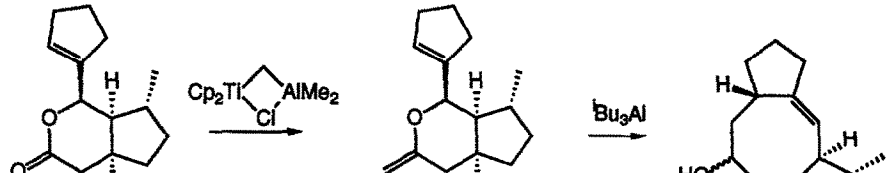
(4.2.4)

A radical cyclization approach to the same type of Claisen rearrangement substrate was reported by Murphy[253] (4.2.5).

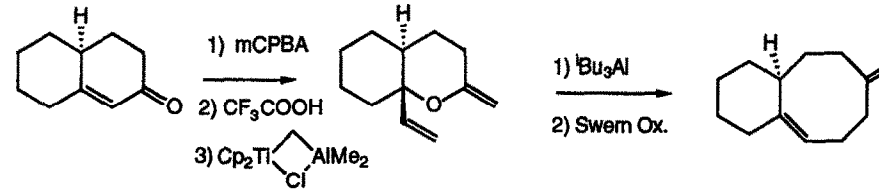


(4.2.5)

The aluminum-catalyzed Claisen rearrangement of similar enol ether precursors was studied by Paquette[254] during an approach to epoxydictymene (**17**). This process gave cyclooctanol derivatives in excellent yields under milder conditions than the corresponding thermal reactions (4.2.6). Paquette[255] has also recently reported a novel two-atom ring expansion of cyclohexenones employing this aluminum-catalyzed Claisen rearrangement (4.2.7).

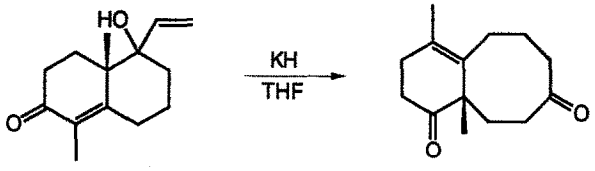


(4.2.6)



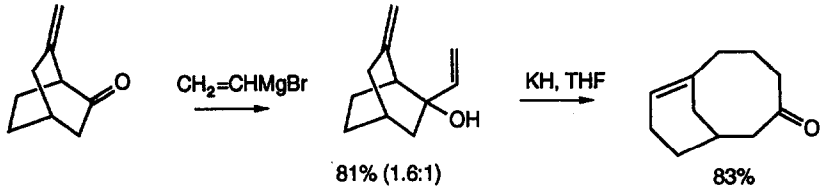
(4.2.7)

The first example of an anionic oxy-Cope process for the formation of cyclooctanones was reported by Swaminathan.[256] Later reports from the same laboratory[257] demonstrated that the mechanism of this process was a [3,3]-sigmatropic rearrangement with KH-THF, and a fragmentation-recombination sequence in the presence of KOH-MeOH (4.2.8).



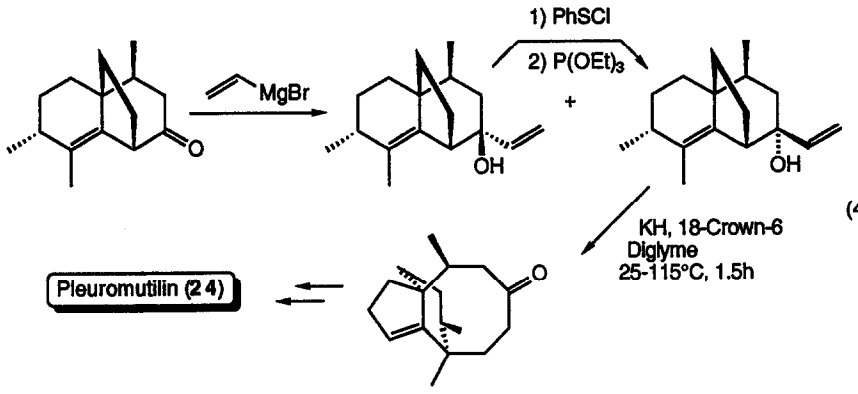
(4.2.8)

Martin[258] has examined the suitability of this anionic oxy-Cope for the synthesis of the bridged taxane skeleton (4.2.9).



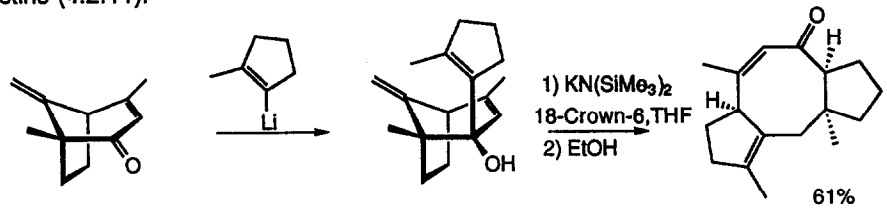
(4.2.9)

Another synthetic application of this process was employed by Boeckman[259] in the total synthesis of pleuromutilin (**24**). In this case the ring expansion process proceeded in almost quantitative yield furnishing the tricyclic skeleton of the natural product (4.2.10).



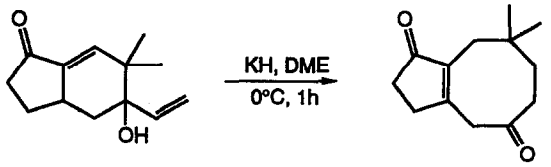
(4.2.10)

In a series of papers Paquette[260] has demonstrated the effectiveness and remarkable diastereoselectivity of the anionic oxy-Cope process for the synthesis of a diverse array of polycyclic molecules, including eight-membered rings. In a recent report[261] a completely stereocontrolled anionic oxy-Cope rearrangement provided a synthesis of the 5-8-5 tricyclic nucleus of the ceroplastins (4.2.11).



(4.2.11)

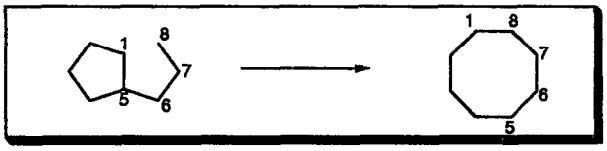
A metal hydride promoted [1,3]-sigmatropic rearrangement of substituted bicyclic vinylcyclohexanols resulting in two carbon homologation to cyclooctanones was reported by Rajagopalan[262] (4.2.12).



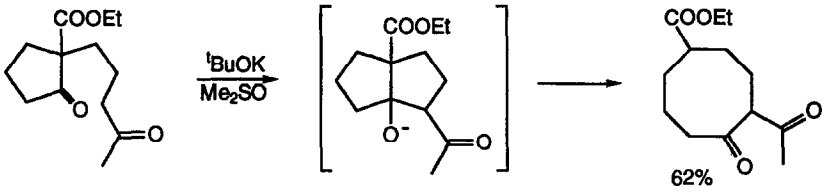
45%

(4.2.12)

4.3 Three-atom ring expansion of five-membered rings

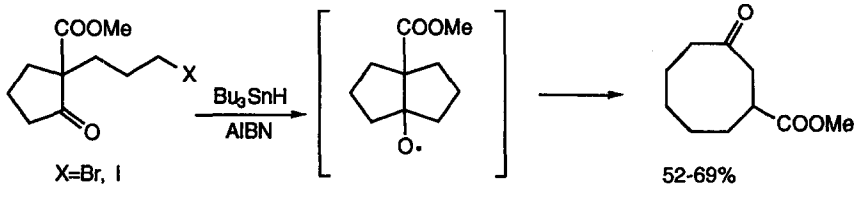


The in situ formation of the bicyclo[3.3.0]octane ring system, followed by a retroaldol-type cleavage was reported by Sakai[263] in a one pot three-carbon ring expansion strategy of carbocyclic β-keto esters (4.3.1). An analogous free radical transformation was developed by Dowd[264] (4.3.2).



62%

(4.3.1)



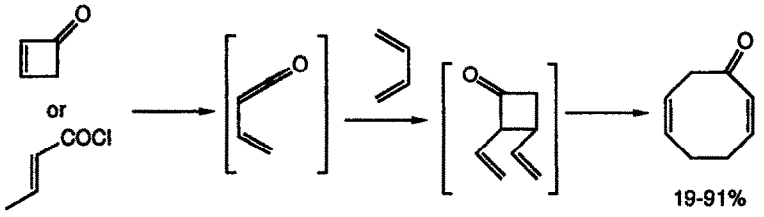
52-69%

(4.3.2)

4.4 Four-atom ring expansion of four-membered rings

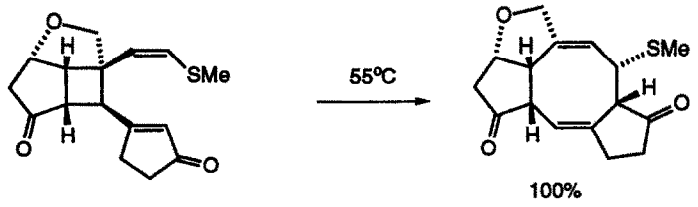
The ring-expansion of divinyl cyclobutanes to cyclooctadienes via a [3,3]-sigmatropic rearrangement is an efficient process and has been utilized in several configurations.

Danheiser[265] reported an intermolecular sequence involving a [2+2] cycloaddition of a ketene and an olefin forming a divinylcyclobutane which underwent an in situ Cope rearrangement resulting in the formation of cyclooctadienones (4.4.1).



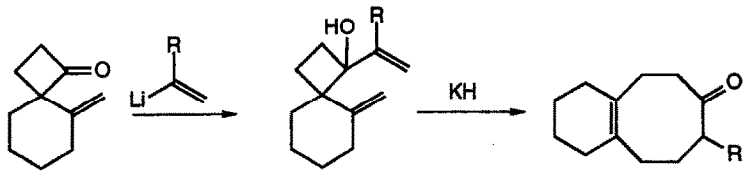
(4.4.1)

A Cope rearrangement of a highly functionalized divinylcyclobutane derivative taking place under mild conditions was recently reported by Jommi[266] (4.4.2).

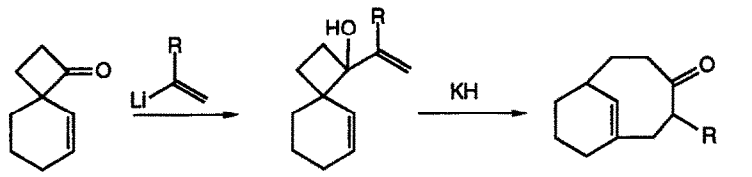


(4.4.2)

The four-atom ring expansion via an anionic oxy-Cope rearrangement has been explored by Kahn[267] and Levine[268] and was studied extensively by Gadwood. Initially Gadwood[269] reported that the addition of vinyl lithium reagents to unsaturated spirocyclobutanones provided isomeric mixtures of alcohols which upon treatment with KH underwent anionic oxy-Cope rearrangement giving fused- (4.4.3) or bridged-cyclooctenones (4.4.4).

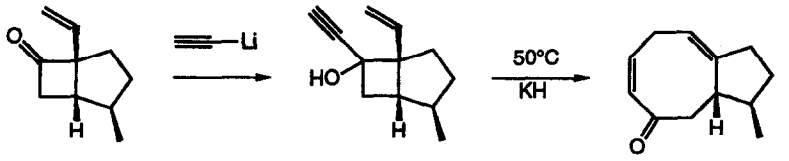


(4.4.3)



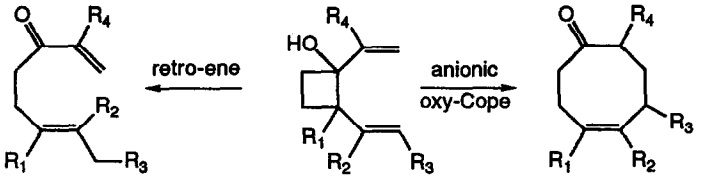
(4.4.4)

Gadwood[270] has also published a comprehensive study of substituent effects in this ring expansion process, where the rate dependency on steric effects of the rearrangement were evaluated by ^{1}H NMR. It was shown[271] that the addition of acetylide anions to vinylcyclobutanones produced adducts that underwent anionic oxy-Cope rearrangement forming cyclooctadienone products. This chemistry was employed in the total synthesis of poitediol (**11**) (4.4.5).



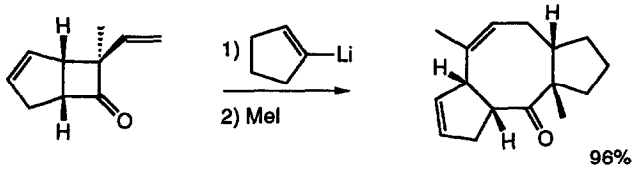
(4.4.5)

Barnier and coworkers[272] have investigated the influence of the stereochemistry on the rearrangement of 1,2-divinylcyclobutanols. It was determined that the trans isomers underwent a retro-ene process while the cis isomers exhibited oxy-Cope rearrangement to cyclooctenones in good yields (4.4.6).



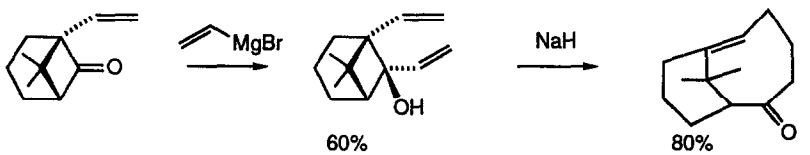
(4.4.6)

Paquette[273] has utilized this approach for the synthesis of ophiobolins. Addition of cyclopentenyl lithium to α–vinylcyclobutanone followed by anionic oxy-Cope rearrangement and in situ quenching with methyl iodide provided an alkylated tricyclic cyclooctenone (4.4.7). Detailed studies on this chemistry revealed very high diastereoselectivity.[274]



(4.4.7)

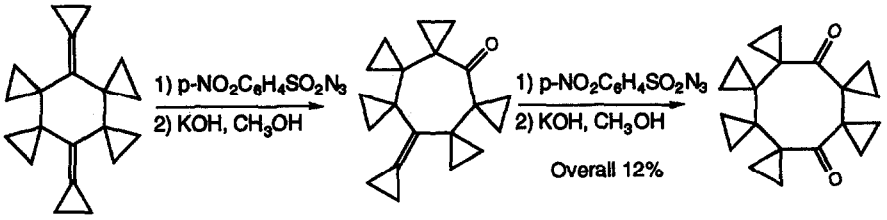
Zucker[275] and Snider[276] independently explored the use of this type of anionic oxy-Cope process to the synthesis of the taxane AB ring system (4.4.8). In both studies, the required bridged cyclobutanone was obtained via an intramolecular [2+2] ketene-olefin cycloaddition. Simultaneous incorporation of ring C via the use of cyclohexenyl lithium in this approach proved unsuccessful due to the reluctance of the corresponding intermediate to adopt the necessary conformation.



(4.4.8)

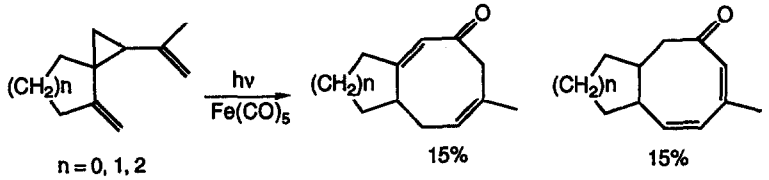
4.5 Miscellaneous ring expansions

Fitjer[277] has published an interesting stepwise ring enlargement of a functionalized six-membered ring polyspirane to the eight-membered ring polyspiradione in low yield (4.5.1).



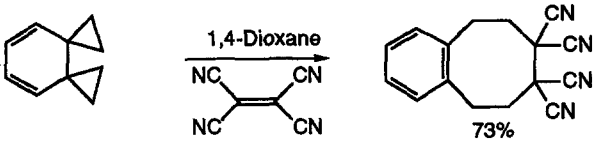
(4.5.1)

Sarel[278] has reported the synthesis of cyclooctadienones in modest yields from the photolysis of vinylcyclopropanes induced by iron pentacarbonyl (4.5.2).



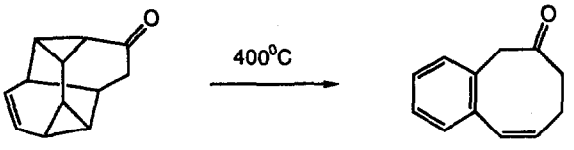
(4.5.2)

de Meijere[279] has reported the thermal ring expansion of dispiro[2.0.2.4]deca-7,9-diene in the presence of tetracyanoethylene resulting in benzocyclooctene tetranitrile (4.5.3).



(4.5.3)

Mukai[280] has reported a remarkable thermal rearrangement of a polycyclic ketone to benzocyclooctenone involving a series of homo-Cope, retro Diels-Alder and 1,5-hydrogen shifts (4.5.4).



(4.5.4)

Acknowledgements

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