The Application of Cyclobutane Derivatives in Organic Synthesis

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Contents

I. Introduction

The predictable, rapid, and efficient synthesis of highly complex molecules requires the development of new regio- and stereoselective synthetic transformations. Among these, the introduction of small-ring systems, especially cyclobutane derivatives, as molecular building blocks has gained increasing importance, mainly due to two reasons. Cyclobutane derivatives are easily accessible by a number of reliable preparative methods that are known to give high yields.[1] Primarily due to the inherent ring strain, the selective cleavage of a cyclobutane bond is facile. Cleavage point and rate are dependent on the reaction mechanism, the ring substituents, the nature of the reagents, and the reaction conditions. Additionally, the whole field of organic synthesis benefits from the development of novel organometallic reagents and procedures that have proved inevitable in the generation of many strained small-ring hydrocarbons.

Cyclobutane derivatives can be used as starting materials for the synthesis of both acyclic and cyclic systems, including carbo- and heterobicyclic and oligocylic compounds. Apparently, this broad synthetic range of applications is one important reason that the chemistry of cyclobutane derivatives has experienced such a strong development during the last two decades. A quick literature search reveals more than 10,000 patents and papers published in this area during this time period, containing almost 3,000 papers dealing with synthetic aspects of cyclobutane chemistry. Therefore, the reader of this review should not expect a complete compendium but a careful selection of the most important reaction types and representative synthetic examples. Since 1985, several areas of cyclobutane chemistry have attracted research activity. A number of specialized reviews, some comprehensive, have already appeared during that time period dealing with the following topics: cyclobutenes as dienophiles,[2] cyclobutadienes,[3] methylenecyclobutanes,[4] cyclobutanones and cyclobutenones in nature and in synthesis,[5−9] cascade rearrangements with squarate esters,[10] radical-mediated ring expansions,[11] photochemistry,[12,13] metathesis,[14] and polymerizations.[15]

II. Scope of This Review

The purpose of the present review is to summarize the papers that have appeared in the literature following publication of an overview on cyclobutane chemistry by Wong et al. in 1986,[16] which had been focused mainly on ring-opening reactions. Whatever appeared in the literature on cyclobutane chemistry since 1985, and especially from 1995 to present, has been carefully skimmed for synthetically valuable transformations of racemic cyclobutanes, excluding heterocyclobutanes and benzoannelated derivatives. Synthetic examples from quite different fields of application are presented. Since the most important aspect is the synthesis of natural products, section IV is focused on this area, and not only on the basic frameworks of the products as does section III. Due to the large number of publications in most of the cases only one representative example was selected and graphically depicted. Whenever no yields or no experimental section is provided in the particular reference, it is not mentioned. In graphical schemes, essential precursors for the relevant cyclobutane derivatives are placed in parentheses, whereas nonisolated intermediates are marked with square brackets.

This review is organized according to the following classes of key steps: ring opening, ring contraction, and ring expansion. A more detailed classification is

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Dieter E. Kaufmann was born in Cuxhaven, Germany, in 1948. He received his diploma in Chemistry in 1971 from the University of Göttingen and obtained his Ph.D. under the guidance of A. de Meijere in 1975 working in the field of small-ring hydrocarbons. After a postdoctorate at the IBM Research Lab in San Jose, CA, USA with R. D. Miller, he received his habilitation in Hamburg in 1986 on asymmetric syntheses with organoboranes. Starting 1988, he became head of the homogeneous catalysis group at the central research lab of Bayer AG, Leverkusen. In 1993, he accepted a call to a Chair of Organic Chemistry at the Technical University of Clausthal and since 1997 he has been the Director of the Institute of Organic Chemistry. His research interests include the development of selective and efficient synthetic methods such as transition metal-catalyzed reactions, ligand design for asymmetric syntheses, development of new synthetic pathways to bioactive compounds, and synthesis and application of new *B*,*N*-chromophoric systems.

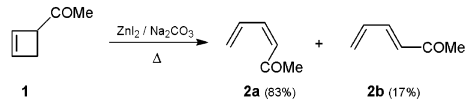
made based on the particular reaction mechanisms involved: cycloaddition, carbene insertion, sigmatropic rearrangement, cationic or anionic rearrangement, ring-opening/closure reaction via radical intermediates, and ring enlargement by oxidative reaction. As the synthetic application is emphasized, the reader is referred to the original literature for detailed mechanistic considerations. A number of transition metal-catalyzed reactions and bioconversions are also included. All synthetic steps in which a four-membered ring system is retained, all enantioselective conversions, all metathetic reactions via a metallacyclobutane as the key compound,[17] and all polymerizations of cyclobutane derivatives are excluded. Literature coverage is through the middle of 2002.

III. Transformations of Cyclobutane Derivatives in Organic Syntheses

A. Ring-Opening Reactions

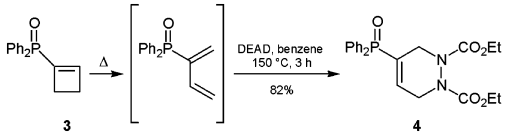
The benefits of strategies based on the stereoselective electrocyclic ring opening of cyclobutene and cyclobutenone derivatives have been largely demonstrated in the last 15 years. Among them, in 1987 Houk et al. have confirmed initial computational predictions[18a] on thermal activation processes with experimental studies.[18b] Later, they published the reversal from outward rotation in these electrocyclizations to the inward mode favored upon addition of the soft Lewis acid zinc iodide during the thermal opening of 3-acetylcyclobutene (**1**). In comparison to $Sn(OTf)_2$ which only gave *E* dienes, using ZnI_2 a mixture of *Z* and *E* dienes **2a** and **2b** was obtained from **1**, clearly favoring the *Z* diene **2a** (83:17).[18c] 6-Substituted hexa-2,4-dienals have also been prepared stereoselectively from a cyclobutene derivative by electrocyclic ring opening.[18d]

Scheme 1



Minami et al. applied this methodology to the thermal ring opening of oxyphosphanyl-substituted cyclobutenes, e.g., **3**.[19] The subsequent Diels−Alder reaction of the intermediate diene led to the expected cyclohexene derivatives (in most cases regioisomeric mixtures). With diethyl azodicarboxylate as the dienophile the corresponding tetrahydropyridazine **4** was obtained in 82% yield.

Scheme 2

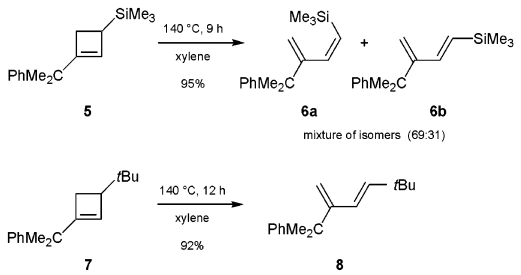


A thermal ring opening of 3-trialkylsilylcyclobutenes was investigated by Murakami et al. The stereoselective outcome was electronically driven by the silyl substituent in **5** to the (*Z*)-diene **6a** with minor amounts of **6b** (7:3). In comparison, the 3-*tert*-butylcyclobutene (**7**) gave the *E* product **8**, exclusively.[20]

This thermal ring opening has also been applied to trialkylsilyl-substituted cyclobutanols (prepared from the appropriate cyclobutenones), mainly leading to the correspondingly substituted (*Z*)-1,3-dienes.[21]

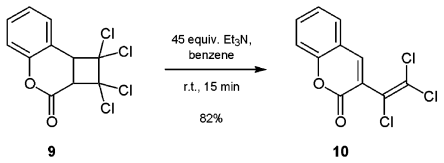
Hasegawa et al. investigated the reaction of the photoadduct of tetrachloroethene and 2-chromenone with different nucleophiles to yield bisannelated cyclic ethers via lactone ring opening followed by dehydrochlorination and subsequent ring closure. In

Scheme 3



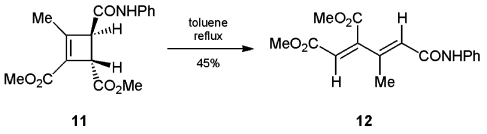
the case of the tetrachloro-substituted photoadduct **9**, the ring-opening product 3-(trichloroethenyl)coumarin (**10**) was isolated in 82% yield after dehydrochlorination to an intermediate cyclobutene.[22]

Scheme 4



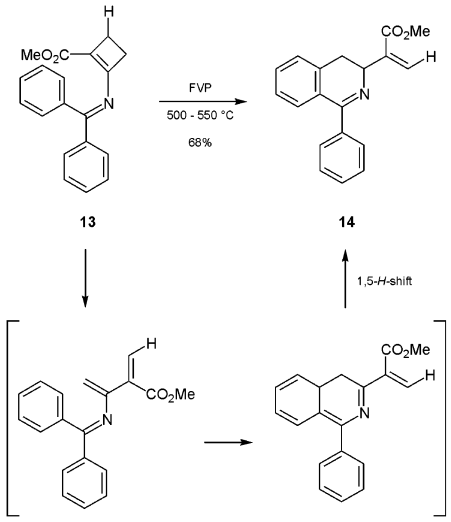
In 1999, Yavari and Asghari reported the ring opening of a highly substituted cyclobutene derivative to give 1,3-dienes in 40−45% yield. For example, in refluxing toluene, the methylcyclobutene tricarboxylic acid dimethyl ester monocarboxanilide **11** provided the electron-deficient (*Z*,*E*)-1,3-diene **12**.[23]

Scheme 5



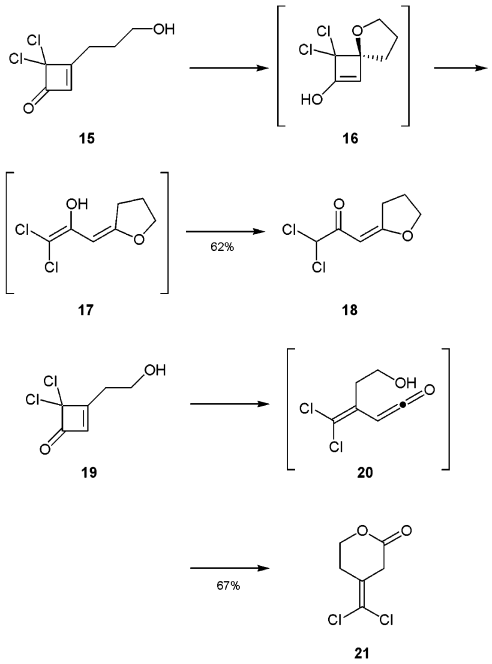
Applying such a cyclobutene ring opening under FVP conditions de Meijere et al. prepared dihydroisoquinolines in good yields.[24] The reaction proceeds via an intermediate azahexatriene followed by a 6π-electrocyclization to a dearomatized dihydroisoquinoline, which, by a 1,5-*H* shift, gave the 1,3-disubstituted dihydroisoquinoline, e.g., **14** was generated from **13** in 68% yield.

Scheme 6



It is interesting to note that the opening of cyclobutene derivatives can be extended to cyclobutenones. Dillon et al. applied this principle to 2,2-dichloro-3-ω-hydroxyalkylcyclobutenones as precursors to ketenes undergoing further intramolecular transformations. Depending on the chain length of the hydroxyalkyl substituent at position 3 either a dichloromethylene δ-lactone **21** or 1,1-dichloro-3-(dihydrofuran-2-ylidene)-propan-2-one (**18**) was formed, the latter from the hydroxypropyl derivative **15**, which apparently initially undergoes an intramolecular Michael addition to give **16**. Subsequent ring opening leads to the enol **17**, which tautomerizes to **18** (62% yield). However, the hydroxyethyl analogue **19** does not undergo the less favored 4-*exo*-*trig* cyclization by intermolecular Michael addition, but cycloreversion to the ketene **20**, which cyclizes to give the lactone **21** in 67% yield.[25]

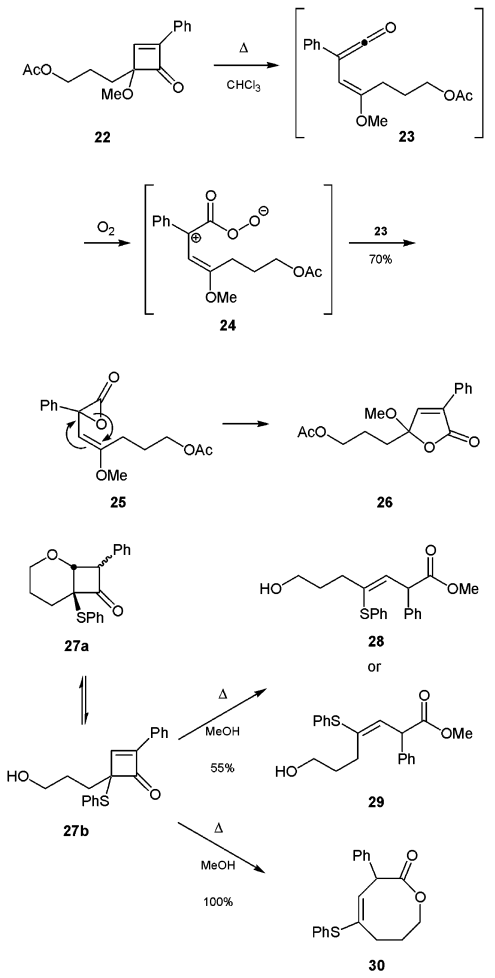
Scheme 7



Similar vinylketenes, e.g., **23** generated by electrocyclic ring opening of cyclobutenone **22**, are in situ attacked by molecular oxygen. The resulting zwitterionic intermediate **24** acts as a Prileschajew reagent for a second molecule of ketene **23** eventually yielding two molecules of an α-lactone **25** which finally rearranges to the γ-lactone **26** (70% yield). A similarly substituted cyclobutenone with a phenylthio donor substituent on C-4 and an unprotected hydroxyalkyl side chain **27a**,**b** upon ring opening and external trapping of the ketene with methanol provided the (*Z*)- or (*E*)-configurated β,γ-unsaturated ester **28** or **29** (55%) along with a minor amount of the eight-membered ring lactone **30** (35%). Without an external nucleophile, lactone **30** was formed exclusively. Trapping of the same vinylketene from **27b** with Danishefsky's diene afforded an undecatrienone in 46% yield.[26,27]

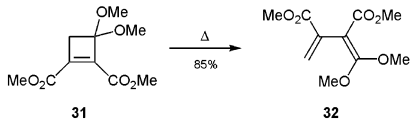
Graziano et al. reported the thermal ring opening of highly functionalized 3,3-dimethoxy-cyclobutenes providing 1,1-dimethoxyalka-1,3-dienes as interest-

Scheme 8



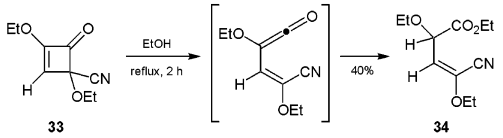
ing substrates for further transformations, e.g., by Diels−Alder reactions. Thus, dimethyl 3,3-dimethoxycyclobut-1-ene-1,2-dicarboxylate (**31**) afforded the butadiene **32** in 85% yield upon heating to 90 °C for 15 h without a solvent.[28]

Scheme 9



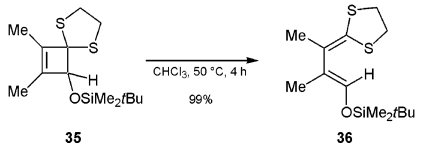
The cyanodiethoxy-substituted cyclobutenone **33** underwent thermal ring opening upon heating in refluxing ethanol and the vinylketene intermediate was trapped by ethanol to give the ester **34** in 40% yield.[29]

Scheme 10



Moore et al. reported the thermal electrocyclic ring-opening reactions of cyclobutenone ethylenedithioacetals such as **35** (Scheme 11) to give the 1,3-diene **36** in an almost quantitative yield at 50 °C. This

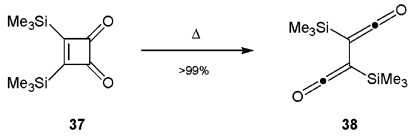
Scheme 11



diene, however, undergoes [4+2] cycloadditions only with highly reactive dienophiles.[30]

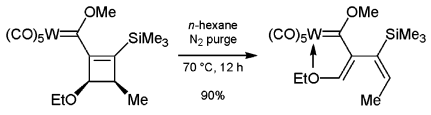
The ring-opening reaction can even be extended to cyclobutenediones. Thus, Dejmek and Selke thermolyzed the bissilylated derivative **37** to obtain the bisketene **38** in nearly quantitative yield.[31] Similarly, the cleavage of the corresponding bisphenylcyclobutenedione derivative succeeds quantitatively upon irradiation (350 nm).

Scheme 12



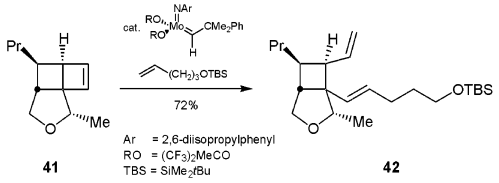
Transition metal and cyclobutene chemistry also are compatible with each other. The electrocyclic ring opening of cyclobutenylcarbene complexes led to the corresponding butadienylcarbenes, which afforded the dienyl esters upon oxidation with ceric ammonium nitrate (CAN) as reported by Wulff et al. The cycloreversion proceeds stereoselectively placing the 1-alkoxy group *syn* to the carbene moiety, i.e., the alkoxy substituent rotates outward. For example, the conrotatory ring opening of the tungsten complex **39** gave the chelated (dien-2-yl)methoxycarbenetungsten complex **40** in 90% yield.[32]

Scheme 13



Snapper et al. applied a ring-opening cross metathesis using the classical Grubbs catalyst to annelated cyclobutene derivatives to prepare functionalized divinylcycloalkanes.[33] For example, the cross-metathesis reaction of the oxatricyclononene **41** with the 5-silyloxypent-1-ene (Scheme 14) gave the 1,7-

Scheme 14

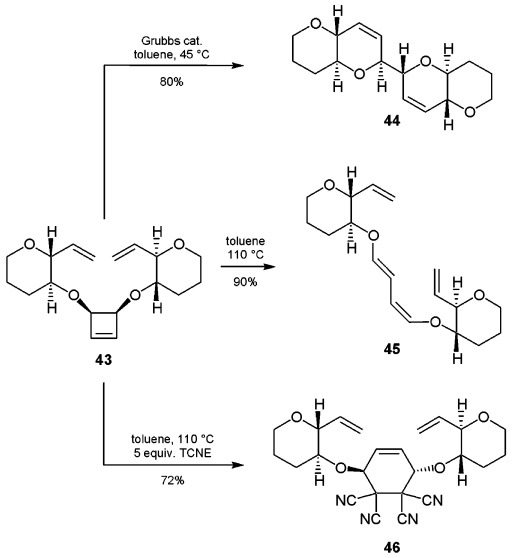


dialkenyl-3-oxabicyclo[3.2.0]heptane **42** with the ω-silyloxyalkyl functionality in 72% yield completely stereoselectively as an 8:1 mixture of two regioisomers. Interestingly, the rutheniumalkylidene in-

termediates with striking chemical proton shifts at around 20 ppm were detected by ^{1}H NMR spectroscopy.

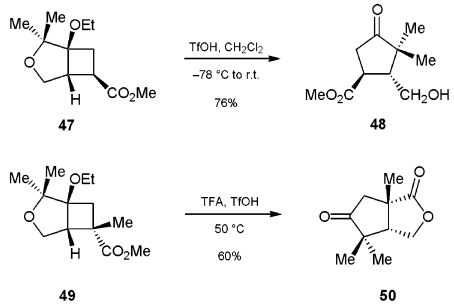
Concentrating upon a stereoselective access to polyether systems Nicolaou et al. applied *cis*-3,4-dichlorocyclobutene as a versatile building block. Two types of reactions are noteworthy in this context. On one hand, there is the cascade ring-opening/ring-closure metathesis of the *cis*-3,4-dialkoxycyclobutene derivative **43** leading to the 1,5-diene **44** in 80% yield by means of a third generation Grubbs catalyst. Furthermore, the substituted (*Z*,*E*)-1,3-diene **45** was the only product (90%) of the thermal conrotatory ring-opening reaction, and the Diels−Alder adduct **46** was formed in 72% yield upon heating **43** in the presence of tetracyanoethylene (TCNE).[34]

Scheme 15



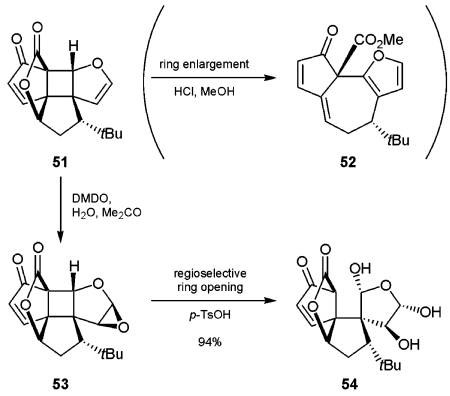
Toward a capnellene synthesis, tetrahydrofuran-annelated cyclobutyl ethers were transformed in a protolytic ring-opening reaction either to cyclopentanones or γ-lactone-annelated cyclopentanones by Patra and Ghosh. For example, under relatively mild conditions (TfOH at −78 °C) the ring opened monocyclic ketone **48** was obtained from **47** in 76% yield, whereas **49**, bearing an additional methyl group upon treatment with TfOH/TFA at 50 °C, gave the bicyclic cyclopentanone **50**.[35]

Scheme 16



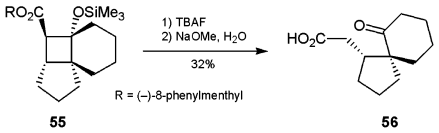
Along a recent synthetic route to ginkgolide B, Crimmins et al. prepared the intramolecular photocycloaddition product **51** providing the core of the ginkgolide skeleton.[36] The requisite regioselective cyclobutane fragmentation is a key step in this natural product synthesis and was eventually achieved by an acid-catalyzed rearrangement. Initial attempts using HCl in methanol failed to manage this cleavage selectively. Unfortunately, fragmentation of an undesired cyclobutane bond gave the ring-enlargement product **52**. Therefore, the dihydrofuran double bond in **51** was first epoxidized, and the oxirane **53** was treated with *p*-toluenesulfonic acid leading to regioselective cleavage and the desired framework **54** in excellent yield.

Scheme 17



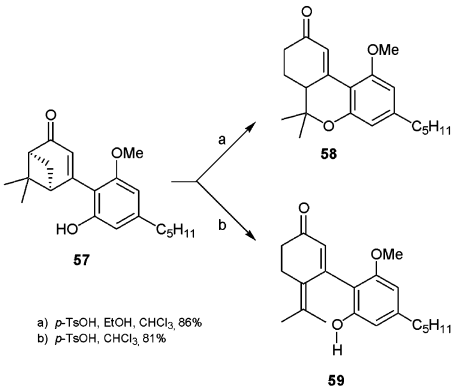
Concerning fused oligocyclic cyclobutanes as key intermediates for biologically and medicinally interesting target molecules, Ihara et al. published the ring opening of the cyclobutane moiety of **55** (Scheme 18). Upon desilylation of **55** by means of tetrabutylammonium fluoride, the (6-oxospiro[4.5]dec-1′-yl)-acetic acid ester was obtained, which upon subsequent saponification gave the corresponding free acid **56** in 32% overall yield.[37]

Scheme 18



Huffman et al. reported the *p*-toluenesulfonic acid-catalyzed, regioselective cyclobutane ring opening of an *o*-hydroxyarylated *apo*-verbenone **57**. In the absence of an external nucleophile, the intermediate

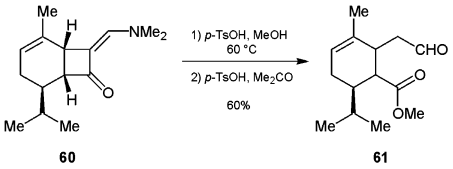
Scheme 19



cation undergoes deprotonation forming the isopropylidene derivative **59**, whereas in the presence of ethanol, the cation is attacked by the phenolic hydroxy group. The resulting tricyclic cannabinoid **58**, a principal human metabolite of THC, was isolated in 86% yield.[38]

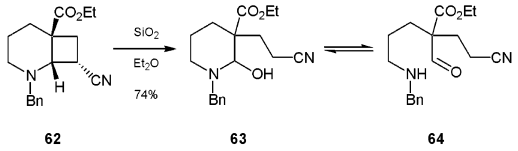
Along the synthetic route to marine eleuthesides, Danishefsky et al. used the ring-opening reaction of a 2-enamino-substituted ring-annelated cyclobutanone. With *p*-toluenesulfonic acid as the catalyst, the ring cleavage of **60** gave the ester-functionalized aldehyde **61** in 60% yield (two steps). This aldehyde was used to introduce the oxacyclic subunit of eleutherobin and similar structurally intereresting eleuthesides.[39]

Scheme 20



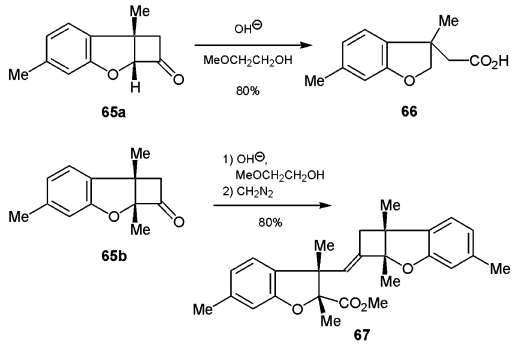
Ponticelli et al. used milder conditions for the ring opening of an annelated cyclobutane derivative prepared by photochemical [2+2] cycloaddition of acrylonitrile to a tetrahydropyridine. The hydrolytic cleavage of the cyclobutane-annelated piperidine derivative **62** by means of wet silica gel in diethyl ether furnished the highly substituted 2-hydroxypiperidine **63**, which easily forms the open-chain aminoaldehyde **64**.[40]

Scheme 21



The base-induced Haller−Bauer-type cleavage of nonenolizable ketones has found useful application in organic synthesis.[41] In 1998, Venkateswaran et al. reported this cleavage of cyclobutabenzofuranones.[42] The regioselectivity is influenced by the substitution pattern of the cyclobutanone: In the presence of the furanyl oxygen in *β*-position to the carbonyl group, the ring opening upon treatment of the cyclobutanone **65a** with sodium hydroxide in 2-methoxyethanol led to the oxabicyclic carboxylic acid **66**. When the acidic

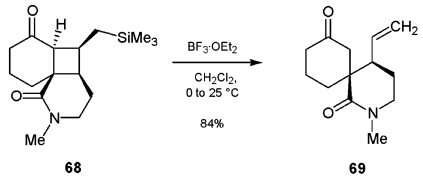
Scheme 22



α-position is blocked by a methyl group, the opposite C−C bond adjacent to the carbonyl group is cleaved regioselectively, e.g., in **65b**. Subsequently, coupling with a second cyclobutabenzofuranone molecule takes place to give, after methylation, **67** in 80% overall yield.

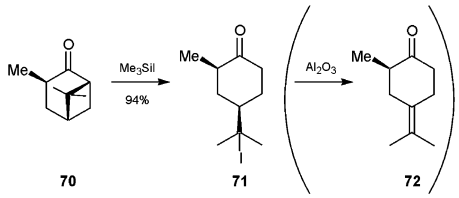
Lewis acids are also capable of cleaving cyclobutane derivatives. Recently, Piva et al. reported the boron trifluoride-etherate-catalyzed ring opening of tricyclic trimethylsilylmethylcyclobutane-annelated six- or seven-membered lactones and lactams. Under these conditions, the *syn*-isomers such as **68** gave the vinyl-substituted spiroannelated lactone or lactam, respectively, whereas the corresponding *anti*-isomers were recovered due to their lower reactivity. For example, lactam **69** was obtained from **68** in 84% yield.[43]

Scheme 23



Yoshikoshi et al. published an electrophile-initiated ring scission of a cyclobutane ring in *cis*-3-methylnopinone (**70**). Heating this ketone in tetrachloromethane with trimethylsilyl iodide afforded the cyclohexanone **71** in 94% yield. Subsequent elimination of HI by means of neutral alumina in diethyl ether afforded the isopropylidene derivative **72** in almost quantitative yield.[44] In a similar way, Razdan et al.[45] transformed a phenylselenyl-substituted norpinan-2-one to an acetoxy-phenylselenylcyclohexene (69%) using $BF_3{\cdot}OEt_2/Zn(OAc)_2$ in Ac_2O (conditions that were also previously used by Yoshikoshi). Subsequent transformation into the corresponding α-selenylcyclohexanone derivative followed by elimination of the selenyl group gave the THC-metabolite 4-(1-acetoxy-1-methylethyl)cyclohex-2-enone. In 1993, Kato et al. applied this type of reaction to a bicyclo[4.4.0]decane skeleton.[46]

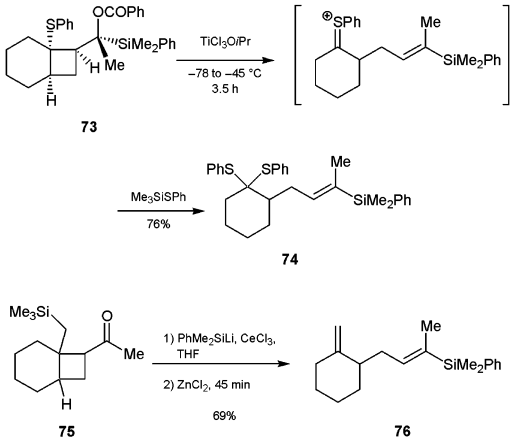
Scheme 24



The synthesis of alkenylsilanes and, in a similar fashion germanes, by Lewis acid-catalyzed ring opening of *O*-protected adducts of triorganosilyllithium to an appropriate cyclobutyl ketone was developed by Takeda et al.[47] For example, the phenylthio-substituted benzoate **73** gave the open-chain thioacetal **74** in 76% yield upon treatment with trichloroisopropoxytitanium(IV). The corresponding *γ*,*δ*-unsaturated ketone was accessible by means of mercury(II) chloride in aqueous acetonitrile via a thionium ion intermediate. A similar thioacetal with the double bond functionalized as an allylic alcohol was reported

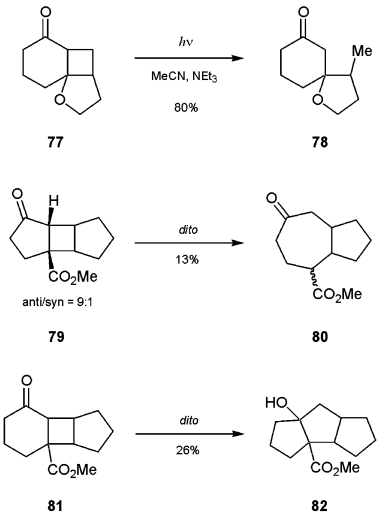
by Takeda and Fujiwara as a useful precursor for the naturally occurring hexadecatetraenol plaunotol based on the synthetic utility of 2-phenylthiocyclobutyl ketones.[48] In comparison, the transformation of α-metalated unprotected alcohols bearing a trimethylsilylmethyl substituent instead of the phenylthio group at the bridgehead of the cyclobutane moiety upon treatment with zinc choride as the catalyst gave exclusively (*E*)-1,5-disubstituted hexa-1,5-dienylsilanes or -germanes, depending on the metalated precursor.[47]

Scheme 25



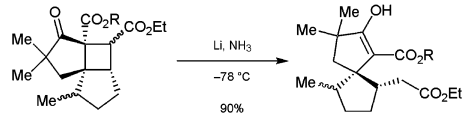
Different photoinduced electron-transfer reactions of tricyclic cyclobutane derivatives, e.g., the reductive ring opening of bridged bicyclo[4.2.0]octanones led to spiroannelated cyclohexanones. For example, upon irradiation in acetonitrile in the presence of triethylamine, the bisannelated cyclobutane derivative **77** was converted by Mattay et al. to 4-methyl-1-oxaspiro[4.5]decan-7-one (**78**) in 80% yield. Applying the same method to linearly fused tricyclic ketones such as **79** and **81**, depending on the ring size, either the ring enlarged bicyclic ketone **80** or the rearranged tricyclic alcohol **82** were formed, albeit in low yields.[49]

Scheme 26



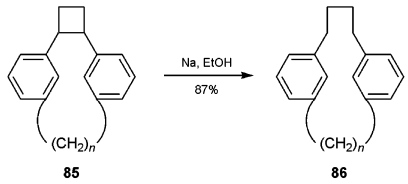
Crimmins and DeLoach reported the reductive cleavage of the 2-fold activated cyclobutane ring in an isomeric mixture of the tricyclic ketodiester photoadducts **83**, leading to the enolized spirocyclic β-ketoester **84** in 90% yield.[50]

Scheme 27



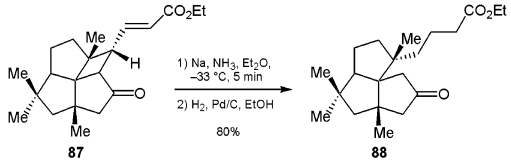
In the field of cyclophane chemistry, Nishimura et al. reported a fragmentation of a cyclobutane backbone. The ring scission of a *cis*-1,2-bisarylated cyclobutyl radical anion obtained by a Birch-type reduction of an intramolecular bisstyrene [2+2] photoadduct after protic workup provided either the chain-extended cyclophane or the corresponding open-chain compound. For example, with dissolving sodium in ethanol the cyclobutane-annelated cyclophane **85** afforded the ring-enlarged hydrocarbon **86** in 87% yield.[51]

Scheme 28



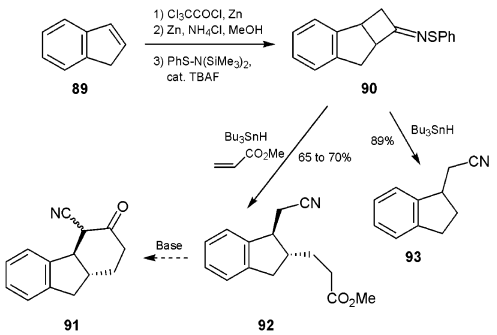
A reductive cleavage of a cyclobutane moiety in a fenestrane-type skeleton was reported by Crimmins and Gould in 1987. Treatment of the tetracyclic ketoester **87** with sodium metal in liquid ammonia and subsequent catalytic hydrogenation of the unsaturated side chain with palladium on charcoal furnished the tricyclic ketoester **88** in 80% yield providing a key precursor of the diterpene laurenene.[52]

Scheme 29



Zard published the radical-triggered ring opening of a cyclobutanone sulfenimide **90**, readily available in three steps from 1*H*-indene (**89**). Generating an iminyl radical upon treatment with tributyltin hy-

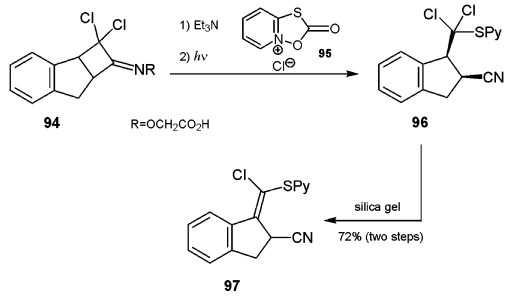
Scheme 30



dride without any further reagent furnished the ring-opened product **93**, whereas in the presence of methyl acrylate β-addition takes place affording the cyanoester **92**, and subsequently under basic conditions the tricyclic α-cyanoketone **91**.[53,54]

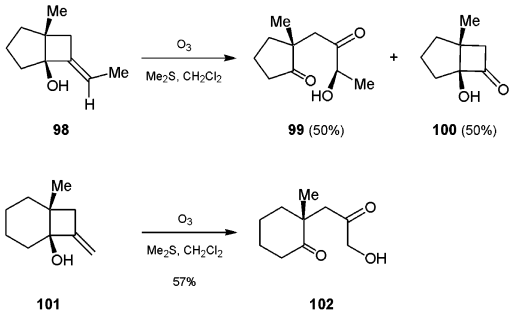
The same group had observed earlier that the annelated dichlorocyclobutane derivative **94** undergoes ring opening with the other possible regioselectivity, as it proceeds via the more stable trisubstituted carbon radical.[55] The appropriate iminyl radical which was formed photochemically by means of 1-oxa-2-oxo-3-thiaindolizinium chloride (**95**) led to the substituted nitrile **96**. Upon subsequent treatment with silica gel, the elimination product **97** was obtained in 72% yield.

Scheme 31



Upon attempted ozonolysis of the strained double bond in α-hydroxymethylenecyclobutane derivatives, Jung and Davidov observed an unexpected type of ring-opening product.[56] For example, the cyclopentane-annelated (*E*)-ethylidenecyclobutanol **98** gave the α-hydroxy ketone **99** (50%) upon treatment with ozone by *exo*-face attack of ozone and subsequent Grob-type fragmentation of the primary ozonide, along with the regular ozonolysis product **100** in 50% yield. The cyclohexane-annelated 2-methylenecyclobutanol **101** afforded only the unusual ring-opening product **102**.

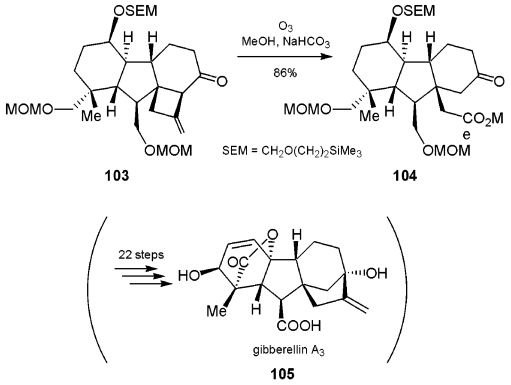
Scheme 32



In the course of the total synthesis of gibberillic acid, a member of C_{19}-gibberellin phytohormones, Yamada et al. treated the tetracyclic compound **103** with ozone in methanol in the presence of sodium bicarbonate. Ozonolysis of the *exo*-methylene group and subsequent nucleophilic opening of the cyclobutane ring led stereoselectively to the tricyclic keto ester **104** in 86% yield, an early precursor of gibberellin A_3 (**105**).[57]

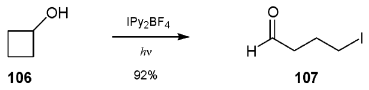
Barluenga et al. developed a mild and efficient general method for the synthesis of ω-iodocarbonyl

Scheme 33



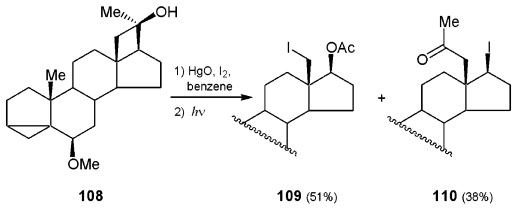
compounds from cycloalkanols by means of bis(pyridine)iodonium(I) tetrafluoroborate under visible light irradiation. This type of oxidative ring cleavage converted cyclobutanol (**106**) to γ-iodobutanal (**107**) in 92% yield.[58]

Scheme 34



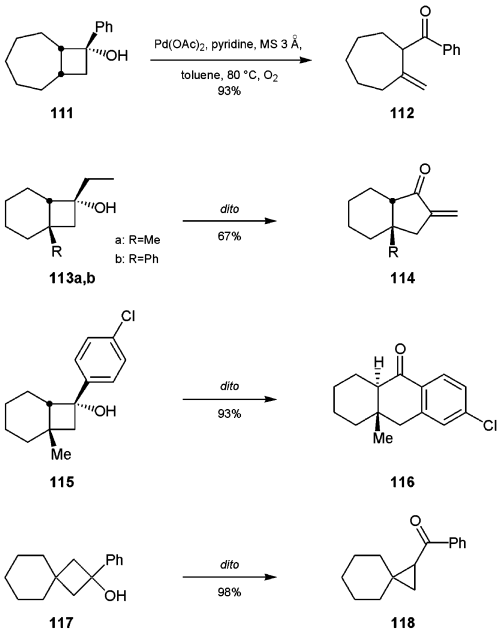
The synthesis of bifunctionalized androstanes reported by Suginome et al. involves a photoinduced cyclobutane ring opening. Starting from pregnan-20-one an androstane-related cyclobutanol **108** is easily available photochemically. Subsequent photolytic β-scission of the cyclobutoxy radical in the presence of either HgO/I_2 or NOCl-pyridine gave a 5:4 ratio of the corresponding ring-opening products **109** and **110** in 89% yield (see Scheme 35).[59]

Scheme 35



A variety of palladium(II)-catalyzed oxidative transformations have also been successfully applied to tertiary cyclobutanols.[60,61] Among these, the ring opening by β-carbon elimination was reported by Uemura et al. starting from mono-, bi-, or tricyclic tertiary cyclobutanol derivatives, preferentially with a phenyl group as the unsaturated substituent in the 1-position giving better results than a vinyl group. For example, the 2-methylene-cycloheptylphenyl ketone **112** was obtained by ring cleavage of the annelated cyclobutanol **111** in 93% yield. A second type of metal-catalyzed transformations were ring enlargements of vinyl-substituted bicyclic cyclobutanols as in the case of **113a**,**b**, bearing an angular substituent to block β-hydride elimination from the σ-alkylpalladium intermediate. The resulting ring-annelated 2-methylenecyclopentanones **114** were isolated in up to 67% yield. A similar ring expansion affording ring-annelated cyclohexanone **116** from the 1-aryl-substituted cyclobutanol **115** is also achieved

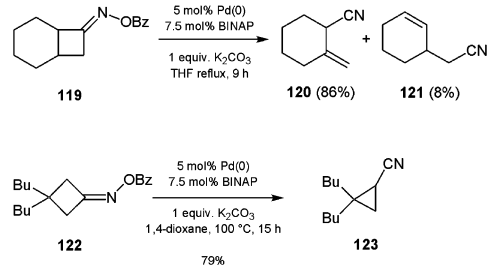
Scheme 36



by Pd(II)-catalyzed oxidation (Scheme 36). It is noteworthy that in some cases higher yields were obtained upon addition of ethyl acrylate. Subjecting 1,3,3-trisubstituted cyclobutanols to these oxidative conditions led to an unexpected ring contraction instead of an expansion, giving cyclopropane derivatives in good to excellent yields. For example, the spirocyclic cyclopropyl ketone **118** was obtained from **117**.[60]

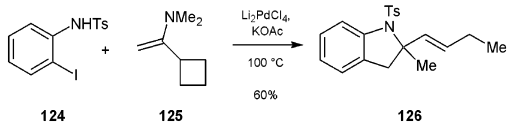
Besides studying palladium(0)-catalyzed ring-opening reactions of cyclobutanone oximes, e.g., **119** leading to the nitriles **120** and **121** via β-carbon elimination, Nishimura and Uemura investigated the ring contraction of similar 3,3-disubstituted cyclobutanone derivatives to give the corresponding cyclopropyl cyanides.[62] This reaction, which occurred under more vigorous conditions, was assumed to proceed via formation of a palladacyclobutane and subsequent reductive elimination of Pd(0) in the presence of the base. For example, the substituted cyclopropyl cyanide **123** was obtained in refluxing 1,4-dioxane in 79% yield from **122**.

Scheme 37



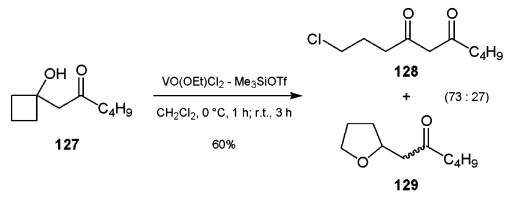
A range of palladium-catalyzed hetero- and carboannelation reactions involving cyclobutanes has been reported by Larock.[63,64] For example, in the course of the heteroannelation of isopropenylcyclobutane (**125**) to *N*-(2-iodophenyl)toluenesulfonamide (**124**) a 2-butenyl-substituted dihydro-1-tosylindole **126** was formed in 60% yield within 4 days at 100 °C.[64]

Scheme 38



With oxovanadium(V) derivatives as a one-electron oxidant, 6-chloro-1,3-diketones as well as 2-tetrahydrofuranylmethyl ketones are formed from 1-(1-hydroxycyclobutyl)hexan-2-one (**127**) or other 1-(2'-oxoalkyl)cyclobutanols.[65] This oxidative ring-opening reaction can also be carried out as a sequential reaction with nucleophilic addition of the silyl enol ether as the first step, providing the β-hydroxyketone, and subsequent oxidative ring transformation. Moderate to good yields are obtained, but the ring-opening product is the preferred one. The product ratios range from 95:5 to 56:44. The cyclobutanol **127** was transformed with 60% yield to the diketone **128** and the tetrahydrofuran derivative **129** (73:27).

Scheme 39

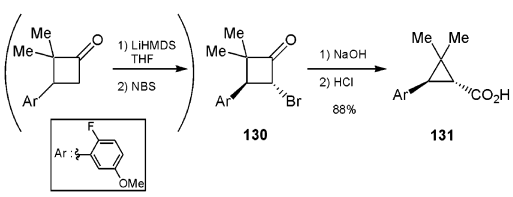


B. Ring-Contraction Reactions

Among the transformations of cyclobutane derivatives applicable in organic synthesis, ring contractions play a minor role, since frequently it is easier to build up a cyclopropane ring from an acyclic precursor than to contract a larger ring. Yet, there is a representative collection of mechanistically different examples that deserve synthetic interest.

In 2001, Chen and Ahmad published a facile method for the stereoselective synthesis of 2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids by base-induced ring contraction of an in situ formed 2-bromocyclobutanone. For example, the rearrangement reaction of **130** is initiated by addition of aqueous sodium hydroxide and provides the *trans*-2-arylcyclopropane-carboxylic acid **131** in 88% yield after protic workup.[66]

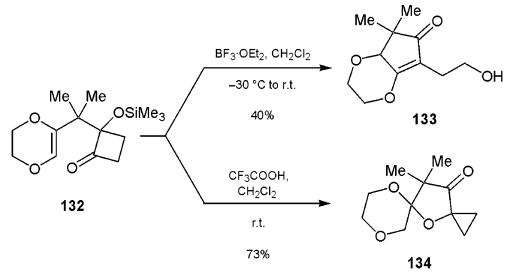
Scheme 40



An acid-catalyzed transformation of a 2-silyloxycyclobutanone derivative was reported by Hanna and Ricard, leading either to a ring opening with subsequent ring closure to a cyclopentenone or a ring

contraction depending on the reaction conditions.[67] The reactant **132** was prepared under Lewis-acidic conditions with boron trifluoride-etherate at −30 °C from a dioxene-derived allylic alcohol and 1,2-bis-(trimethylsilyloxy)cyclobutene in 90−95% yield. Exposure to an excess of the same Lewis acid at room temperature in methylene chloride led to the 1,4-dioxane-annelated cyclopentenone **133**, whereas the ring-contracted tricyclic spiroacetal **134** was formed by a pinacol-type rearrangement using trifluoroacetic acid (73% yield).

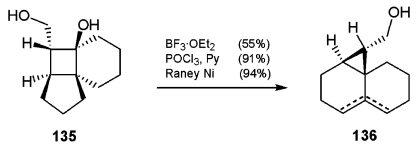
Scheme 41



In 1994, Fukumoto et al. developed a novel ring-contraction reaction using three different sets of conditions. Starting from the tricyclic cyclobutanol derivative **135**, treatment with $POCl_3$ led to the tricyclic product **136** (isomers) in 91% yield, whereas boron trifluoride-etherate gave this ring-contraction product in only 55% yield. In comparison, heating of **135** with an excess of Raney nickel (W-2) in refluxing toluene afforded **136** with 94% yield. However, starting from similar substrates the product yield dropped using Raney nickel.[68]

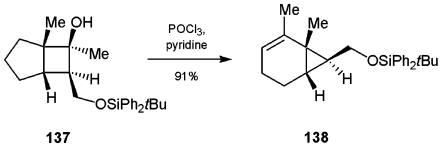
A cationic rearrangement of a ring-annelated cyclobutanol leading to a cyclopropane derivative has also been reported. Among different reaction conditions tested (same reagents as in Scheme 42), the use

Scheme 42



of phosphoryl chloride in the presence of pyridine gave the best results. The norcarene derivative **138** was obtained from the cyclopentacyclobutanol **137** in 91% yield as a single stereoisomer.[69]

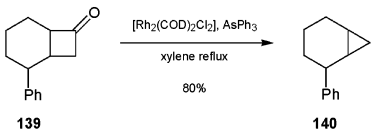
Scheme 43



In the course of palladium(II)-catalyzed oxidative transformations of 1-aryl- and 1-vinylcyclobutanols[60,61] ring-contraction products were obtained from 1,3,3-trisubstituted cyclobutanols in good to excellent yields (see Scheme 36). Nishimura and Uemura showed the Pd(0)-catalyzed ring contraction of 3,3-disubstituted cyclobutanone oxime ethers leading to the corresponding cyclopropyl cyanides (see Scheme 37).

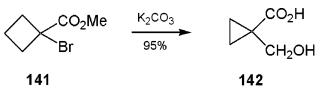
In 1996, Murakami et al. reported the transition metal-catalyzed decarbonylation of cyclobutanones with Wilkinson's catalyst leading to the corresponding cyclopropanes. The reverse carbonylative ring enlargement of a cyclopropane is also known. The previously only with stoichiometric amounts of Rh(I) complexes achievable decarbonylation of 3-alkylated cyclobutanones can be carried out with only 5 mol % of dirhodium biscyclooctadiene dichloride with two molecules of triphenylarsine as stabilizing ligand. Thus, 2-phenylnorcarane (**140**) was obtained from the annelated cyclobutanone **139** by catalytic decarbonylation in 80% yield, whereas the stoichiometric variant gave a quantitative yield (Scheme 44).[70]

Scheme 44



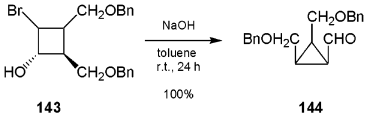
During the investigation of a regioselective synthesis of α,α-dialkylcyclopentanones Salaün et al. additionally found that 1-hydroxymethylcyclopropanecarboxylic acid (**142**) is formed in 95% yield upon treatment of methyl 1-bromocyclobutanecarboxylate (**141**) with aqueous potassium carbonate. The ring contraction is initiated by α-deprotonation and subsequent S_N2' attack at the quaternary carbon.[71]

Scheme 45



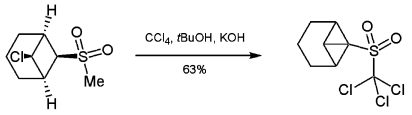
In search of a synthetic access to novel three-membered carbocyclic nucleoside analogues, Mévellec and Huet developed a stereoselective ring contraction of the bromohydrin **143** to give, upon treatment with a suspension of sodium hydroxide in toluene at room temperature, the trisubstituted cyclopropanecarbaldehyde **144** in quantitative yield.[72]

Scheme 46



Vasin et al. obtained according to Meyer's modification of the Ramberg-Baecklund reaction, i.e., the dehydrohalogenation−desulfonation of α-halodialkyl sulfones, 1-substituted tricyclo[4.1.0.$0^{2,7}$]heptanes as formal ring-contraction products from methylsulfonylbicyclo[3.1.1]heptanes as the cyclobutyl-ring bearing unit. The modified reaction protocol involves treatment of these dialkyl sulfones with potassium hydroxide in *tert*-BuOH/CCl_4 and provided the carbocyclic products typically in yields of up to 80%. For example, the tricyclo[4.1.0.$0^{2,7}$]heptane **146** was obtained from **145** in 63% yield within 3 h.[73]

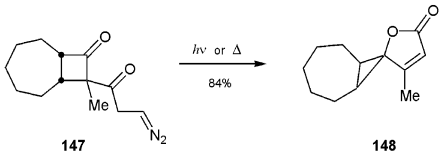
Scheme 47



145 146

Photolysis or thermolysis of 2-diazoacetylcyclobutanone derivatives leads to a completely regioselective ring contraction of the intermediate α-ketenylcyclobutanones to spirocyclopropane-$\Delta^{\alpha,\beta}$-butenolides. Miller et al. described, e.g., the thermolysis of the bicyclic diazodiketone **147** in refluxing toluene (and alternatively photolysis) to afford the tricyclic spiroannelated butenolide **148** as a mixture of isomers (2.2:1) in 84% yield.[74]

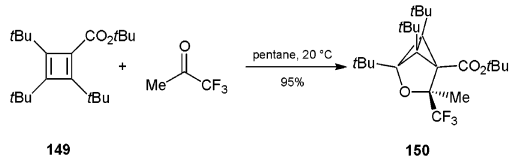
Scheme 48



147 148 (mixture of isomers)

Besides other cyclobutane derivatives resulting from reactions that are beyond the scope of this article, Fink and Regitz obtained oxatricyclohexanes as formal ring-contraction products in 31−95% yield from the reaction of 2,3,4-tri-*tert*-butyl-cyclobuta-1,3-dienecarboxylic acid *tert*-butyl ester with CF_3-, CO-, or CN-activated ketones. For example, the unusual [2+2+2] cycloaddition of the stabilized cyclobutadiene **149** to methyltrifluoromethyl ketone in pentane at 20 °C gave the corresponding tricyclic ether **150** in 95% yield.[75]

Scheme 49



149 150

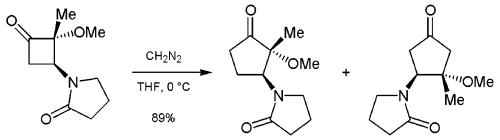
C. Ring-Expansion Reactions

Ring-expansion reactions of four-membered ring systems, which cover 60% of the cited references, frequently offer efficient stereocontrolled access to functionalized monocyclic or ring-annelated carbo- and heterocycles, starting from easily available cyclobutanes, cyclobutenes, or cyclobutenones. This reaction type is especially important for the formation of five- and six-membered ring systems, but seven-, eight-, and nine-membered ring systems can be also synthesized by intra- or intermolecular sequential reaction modes. From a mechanistic point of view this chemistry is multifacetted.

1. Five-Membered Rings

Ring-enlargement reactions of cyclic ketones based on the Wolff rearrangement have been known for a long time. Hegedus et al. applied the regioselective ring expansion of β-substituted α-methyl-α-methoxycyclobutanones with diazomethane to obtain valuable starting materials for butenolides.[76] Recently, they focused on aminocyclopentitols as the final products.[77] For example, the homologation of the functionalized cyclobutanone **151** led to a 97:3 mixture of regioisomeric cyclopentanones **152** and **153** in 89% yield.[76]

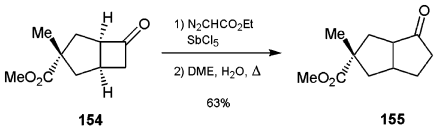
Scheme 50



151 152 153

On a synthetic route to hirsutic acid C, Greene et al. developed a regioselective ring enlargement of the cyclopentane-annelated cyclobutanone **154** to the bicyclo[3.3.0]octanone **155**.[78] With antimony pentachloride as an activator, this ring enlargement with diazomethane as well as ethyl diazoacetate was selective, whereas with boron trifluoride-etherate or oxonium salt it was not. This way, the homologation of **154** afforded the ring expanded product **155** in 63% yield.

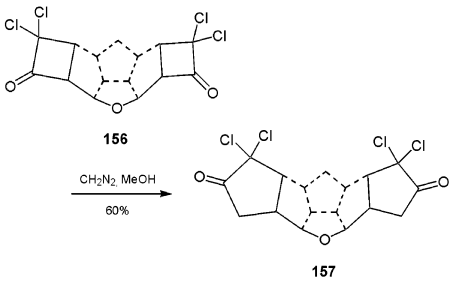
Scheme 51



154 155

The same type of transformation was used by Mehta and Nair for the ring enlargement of the bis(dichloroketene) adduct **156** with diazomethane in methanol. The structurally interesting half-cage polyquinane derivative **157** was obtained in 60% yield.[79]

Scheme 52

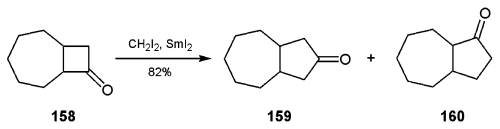


156 157

To avoid the toxic and dangerous diazomethane, one may use other methods such as the Tiffeneau-Demjanov rearrangement of amino alcohols, yet Fukuzawa and Tsuchimoto developed a new iodomethylation/rearrangement sequence. Upon treatment with CH_2I_2/SmI_2 at room temperature, the ring enlargement of cyclobutanones to cyclopentanones takes place in good yields, for example, the octahydroazulenones **159** and **160** (ratio 97:3) were obtained from the annelated cyclobutanone **158** in 82% yield.[80]

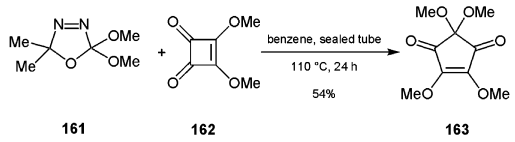
Venneri and Warkentin reported the reaction of the relatively long-lived, singlet ground state dimethoxycarbene (thermally generated from dimethoxydimethyldihydro[1,3,4]oxadiazole **161**) with strained cyclic carbonyl compounds. Starting from cyclobutanones,

Scheme 53



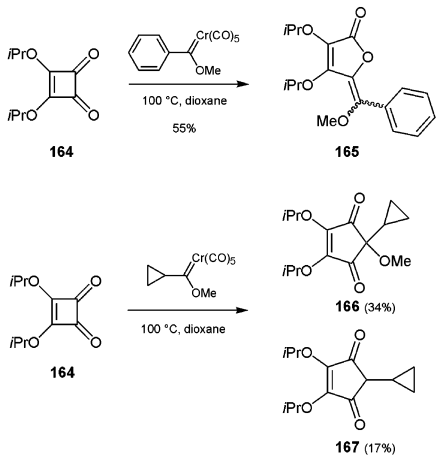
cyclopentanones were synthesized by formal insertion of the carbene into the C−C bond adjacent to the carbonyl group. However, applying the dimethyl squarate (**162**) as the cyclic carbonyl species, 2,2,4,5-tetramethoxycyclopent-4-ene-1,3-dione (**163**) was isolated in 54% yield.[81]

Scheme 54



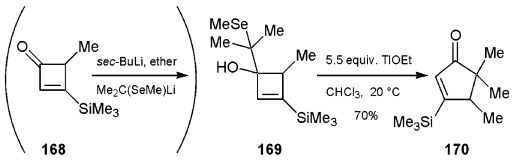
An interesting one-step procedure for the synthesis of cyclopentenediones and/or 5-alkylidenefuranones was published in 1999 by Herndon et al.[82] Although usually mixtures of the carbo- and oxacyclic products were obtained from squaric acid esters and carbene complexes, which limited the synthetic applicability, arylalkoxycarbene complexes afforded 5-alkylidenefuranones selectively. For example, the methoxy(phenyl)methylidene butenolide **165** was obtained exclusively in 55% yield from diisopropyl squarate (**164**). In contrast, cyclopentenediones with and without the methoxy group were obtained (**166** and **167**, respectively) starting from **164** and a carbene complex with a cyclopropyl instead of the phenyl substituent. The reported yield of the resulting 2:1 mixture was 51%.

Scheme 55



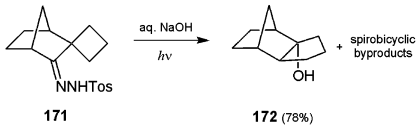
Unsaturated β-hydroxyselenides, obtained from a cyclobutenone and an (α-selenylalkyl)lithium, underwent a ring enlargement closely related to the pinacolic rearrangement, to give the corresponding cyclopentenone using thallium(I) ethoxide in trichloromethane. In contrast to the general trend, Krief et al. found the migratory tendency of an alkyl group to be higher than that of a vinyl substituent, but also to depend on ring size and substitution pattern. Prediction of the regioisomeric ratio remains difficult. As an example, the silylated cyclobutenone **168** reacts via the cyclobutenol **169** to the cyclopentenone **170** in 70% yield.[83]

Scheme 56



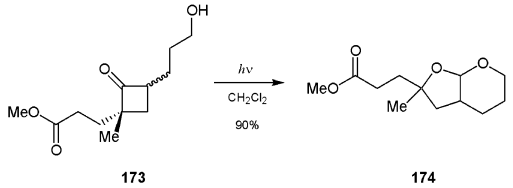
In 1998, Kirmse et al. investigated the cationic rearrangements of α-spirocyclobutane-annelated 2-norbornane derivatives.[84] Under irradiation in aqueous sodium hydroxide the tosylhydrazone **171** gave 1-hydroxytricyclo[5.2.1.$0^{2,6}$]decane (**172**) in 78% yield besides bicyclic alcohols (9%) with an unchanged spirocyclobutyl moiety which was separated by HPLC from the main product.

Scheme 57



A photochemical ring expansion of cyclobutanones was developed by Pirrung et al.[85,86] Intermediate oxacarbenes were trapped with different alcohols or amines or with a thiol to give the 2-substituted tetrahydrofurans. Primary and secondary alcohols, most secondary amines, and also benzylmercaptan afforded the carbene-inserted nucleophiles usually in good yields of up to 71%.[86] This concept was extended to prepare oxabicyclo[*n*.3.0]alkanes in excellent yields using cyclobutanone derivatives bearing an appropriate ω-hydroxyalkyl side chain.[87] Applying this insertion-ring closure sequence, e.g., to the propanol-substituted cyclobutanone **173**, gave the ω-methoxycarbonyl-functionalized dioxabicyclo[4.3.0]nonane **174** in 90% yield.

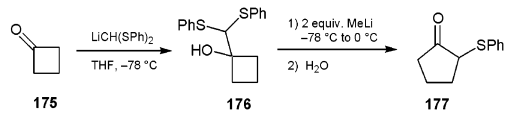
Scheme 58



A novel ring enlargement of cyclobutanones via a sulfur-substituted carbenoid under mild conditions was described by Cohen et al.[88] Two equivalents of methyllithium were added to the adduct **176** of bis(phenylthio)methyllithium and cyclobutanone (**175**). Upon 2-fold deprotonation **176** yields a carbenoid that can undergo α-elimination, and the resulting carbene then rearranges to the ring expanded enolate, which, after protonation furnishes the 2-phenylthiocyclopentanone (**177**) in 70% yield.

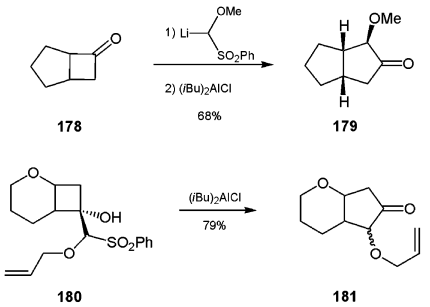
In 1987, Trost and Mikhail developed a simple one-pot procedure for a ring-expansion of cyclic ketones with concomitant introduction of an α-methoxy group. After adding lithiated methoxymethylphenyl sulfone

Scheme 59



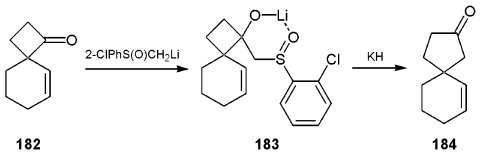
to the appropriate ketone, the cationic rearrangement was initiated by an excess of diisobutylaluminum chloride. For example, bicyclo[3.2.0]heptan-6-one (**178**) afforded the ring-enlarged 2-methoxybicyclo[3.3.0]-octane-3-one (**179**) in 68% yield; the substituted 2-oxabicyclo[4.2.0]octane **180** furnished the oxabicyclic ketone **181** (79%).[89]

Scheme 60



A generally applicable ring expansion of cyclobutanones to cyclopentanones via α-lithioalkyl aryl sulfoxides and related selenoxides was reported by Gadwood et al. The adducts from the reaction of α-lithioalkyl 2-chlorophenyl sulfoxides or phenyl selenoxides with 2-substituted cyclobutanones underwent ring enlargement to cyclopentanones upon treatment with potassium hydride. The substitution pattern of the inserted carbon atom is variable. Depending on the number and the nature of the substituents on C-2, the reaction may be restricted to selenoxides rather than sulfoxides. Best results were obtained with a lithiated sulfoxide and an alkylalkenyl-substituted cyclobutanone, e.g., spiro-[3.5]non-5-en-2-one (**182**), which gave the ring-enlarged spiro[4.5]dec-6-en-2-one (**184**) via the chelated lithium alkoxide **183** in 94% yield.[90]

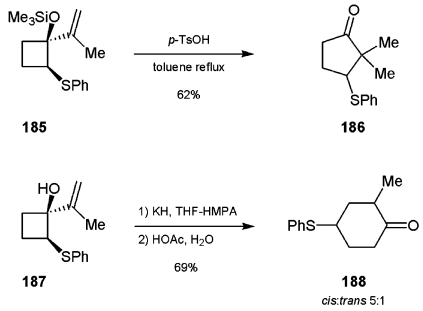
Scheme 61



In 1985, Cohen et al. pointed out that a phenylthio group as a carbanion-stabilizing sulfur substituent at the 2-position of 1-vinylcyclobutanol led to different ring expanded products. Reacting the silylated 1-isopropenyl-2-phenylthiocyclobutanol **185** with *p*-TsOH gave the 2,2-dimethyl-3-phenylthiocyclopentanone (**186**) in 62% yield, whereas the unprotected cyclobutanol **187** upon treatment with potassium hydride gave 2-methyl-4-phenylthiocyclohexanone (**188**) as a mixture of *cis*- and *trans*-isomers (ratio 5:1) in 69% yield.[91]

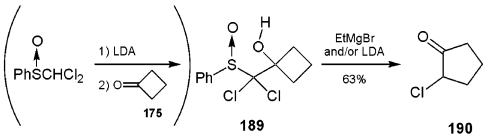
A procedure for a one-carbon homologation of ketones was published by Yamakawa et al. Addition

Scheme 62



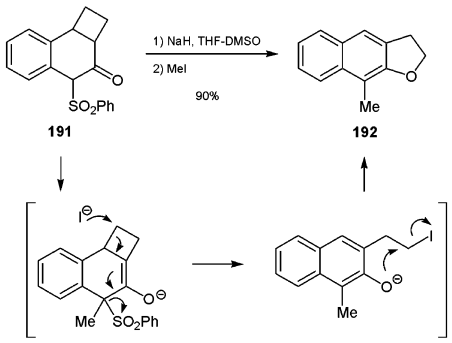
of the lithium carbenoid from dichloromethylphenyl sulfoxide to a carbonyl compound, e.g., cyclobutanone (**175**), provided the tertiary alcohol **189** which, upon treatment with lithium diisopropylamide or ethylmagnesium bromide, yielded α-chlorocyclopentanone (**190**) (63%).[92]

Scheme 63



Ghera and Maurya reported the ring expansion of sulfonylated cyclobuta-2-tetralones to naphthofuran derivatives. After initial α-methylation with NaH/MeI, reenolization takes place followed by iodide-mediated cyclobutane-ring fission and concomitant desulfinylation. Subsequent recyclization furnishes naphthodihydrofuran derivatives. For example, the sulfonylated tricyclic ketone **191** afforded the methyl-substituted naphthodihydrofuran **192** in 90% yield.[93]

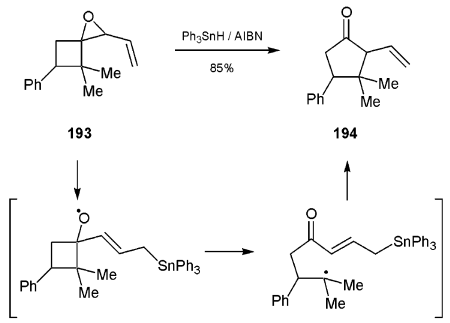
Scheme 64



In 1991, a ring enlargement of substituted vinyloxiranes was shown by Kim and Lee, based on a free radical mechanism. Best results were obtained starting from PhSSPh and/or Ph_3SnH as the radical source. For example, the spirocyclobutane-annelated vinyloxirane **193** gave the ring-expanded vinylcyclopentanone **194** in 85% yield along with small amounts of a regioisomer (<2%) and a tin-bearing cyclohexanone (5%). The reaction proceeds via initial opening of the epoxide by addition of the tin radical, regioselective *β*-cleavage of the resulting alkoxy radical, and subsequent ring closure with concomitant elimination of the tin radical.[94]

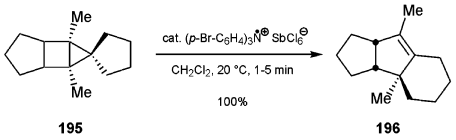
Sahin et al. reported the tris(*p*-bromophenyl)-aminium hexachloroantimonate mediated diastereo-

Scheme 65



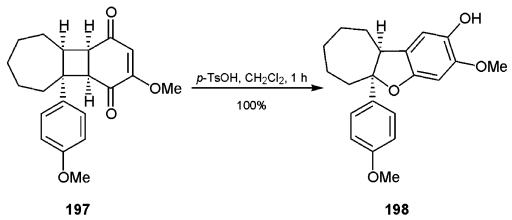
and regioselective formation of di- and triquinanes.[95] This stereocontrolled oxidative ring expansion proceeded within one to five minutes at ambient temperature by chemical electron transfer (CET) to (spirocyclic) C-3-substituted tricyclo[3.3.0.0^{2,4}]octanes (easily available from 1,3-propanediones). For example, the spirocyclic hydrocarbon **195** gave the diquinane **196** in quantitative yield.

Scheme 66



In the course of asymmetric reactions of 2-methoxy-1,4-benzoquinones, Engler et al. used the acid-catalyzed rearrangement of comparable cyclobutabenzoquinone derivatives to give, by ring enlargement, the skeleton of the biologically interesting pterocarpans. For example, the bisannelated cyclobutane **197** quantitatively forms the corresponding annelated 2,3-dihydrobenzofuran **198** upon treatment with *p*-toluenesulfonic acid in dichloromethane at ambient temperature.[96]

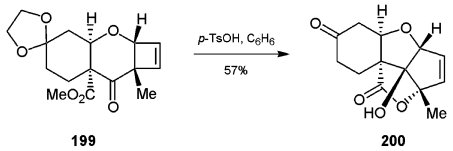
Scheme 67



In 1998, White et al. reported the application of an interrupted Cargill-type rearrangement of the cyclobutene moiety within the cyclohexane-annelated oxabicyclo[4.2.0]octene **199**.[97] The proper choice of both the acid and the solvent is important, e.g., with *p*-toluenesulfonic acid in benzene at ambient temperature the acid-catalyzed ring expansion of **199** led to the tetracyclic γ-lactone **200** in 57% yield. The reaction pathway involves formation of an allylic carbocation which is internally trapped by the methoxycarbonyl group. This product serves as a precursor for the trichothecenoids consisting of an oxabicyclo-[3.2.1]octene skeleton.

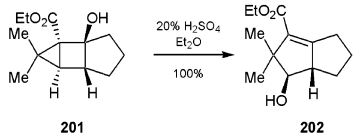
The acid-catalyzed rearrangement of cyclopropane-annelated cyclobutanes (bicyclo[2.1.0]pentanes) to yield cyclopentene derivatives was investigated by

Scheme 68



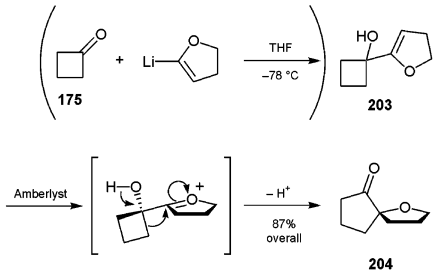
Franck-Neumann et al.[98] Thus, the tricyclic hydroxycyclobutanecarboxylate **201** was treated with diluted sulfuric acid in diethyl ether to give the diquinane **202** stereoselectively in quantitative yield.

Scheme 69



As part of the synthesis of enantiomerically pure spirocyclic α,β-butenolides, Paquette et al. used the acid-catalyzed ring enlargement of 1-vinylcyclobutanols to cyclopentanones. The addition of 2-lithiodihydrofuran to cyclobutanone (**175**) gave the highly acid-sensitive carbinol **203**. Among different acidic reagents, Amberlyst-15 showed the best result: The spirocyclic ketone **204** was formed in 87% yield.[99] This method was also applied to the synthesis of spirocyclic bis-*C*,*C*-glycosides by ring expansion of glycal-derived carbinols.[100] Numerous examples are given, but mixtures of diastereoisomers were always formed.

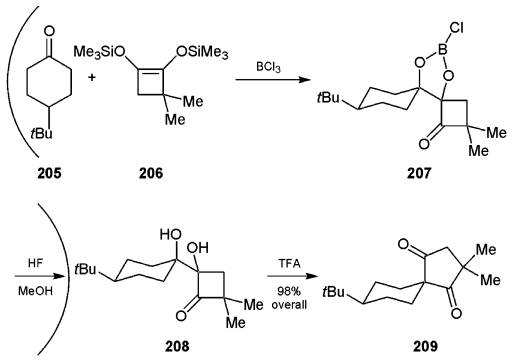
Scheme 70



In an acid-induced acyl migration reaction, Crane and Burnell prepared 1,3-cyclopentanediones from 2-hydroxy-2-alkylcyclobutanones which were generated from open-chain or cyclic ketones by boron halide-mediated aldol reactions.[101] In the case of boron trifluoride, yields are moderate, whereas with boron trichloride almost quantitative yields were obtained. The latter Lewis acid not only induces the initial aldol reaction, but is incorporated into a cyclic borate **207** that inhibits the subsequent equilibration of the aldol intermediate. For example, reacting 4-*tert*-butylcyclohexanone (**205**) with the bissilylated cyclobutenediol **206** and boron trichloride initially gave the diol **208** after treatment with hydrofluoric acid. The spirocyclohexane-annelated 4,4-dimethyl-1,3-cyclopentanedione **209** was obtained applying TFA (Scheme 71). The yield was 98% in contrast to 40% using $BF_3 \cdot OEt_2$.

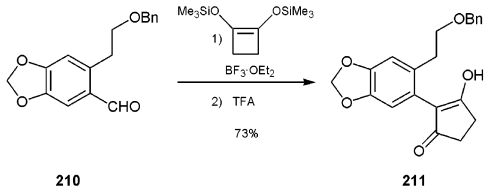
Kavash and Mariano demonstrated an excellent example of Kuwajima's cyclobutene to cyclopentanedione ring expansion protocol.[102] The E-ring of harringtonine alkaloids such as cephalotaxine was

Scheme 71



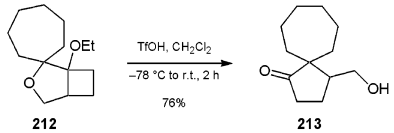
prepared by boron trifluoride-catalyzed addition of an appropriate aromatic aldehyde to 1,2-bistrimethylsilyloxycyclobutene followed by pinacol rearrangement. The resulting enolized arylcyclopentanedione **211** was obtained from the aldehyde **210** in 73% overall yield.[103]

Scheme 72



The synthesis of spirocyclopentanones which involved a cyclobutane rearrangement of a 3-oxabicyclo-[3.2.0]heptane was reported in 1995 by Ghosh and Patra (Scheme 73).[104]

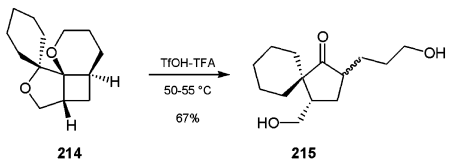
Scheme 73



In the key step after acid-induced opening of the tetrahydrofuran ring in **212**, the resulting cyclobutyl carbinyl cation undergoes ring enlargement to the cyclopentanone **213** in 76% yield. This four-step sequence was used to form α-cedrene as a representative for the naturally occurring spiro[4.*n*]systems, such as ginkgolide B.

In a subsequent paper, highly acidic conditions have been applied to **214** using a mixture of TFA and TfOH at 50 °C and above. For example, the spiro-[4.5]decanone **215** was obtained in 67% yield.[105] This mixture of strong acids was also applied in the synthesis of highly substituted cyclopentanones such as **50** (see Scheme 16).[35]

Scheme 74

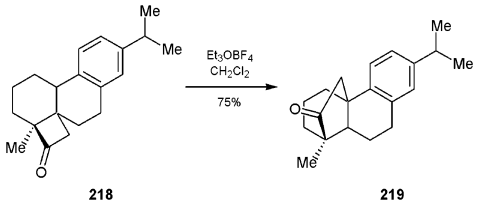


In 1989, Rao et al. published an improved version of Kuwajima's protocol[102] to prepare 2-alkyl-1,3-cyclopentanediones from appropriate 2-silyloxycyclobutanone derivatives. By using TFA/Nafion-H instead of neat trifluoroacetic acid, e.g., the 2-silyloxycyclobutanone **216** was converted to 2-ethyl-1,3-cyclopentanedione (**217**) in 70% yield, whereas the original protocol never furnished the desired product.[106]

Scheme 75

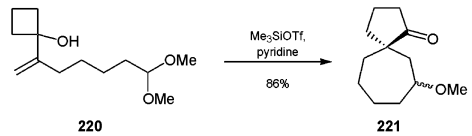
Banik and Ghatak published the synthesis of a cyclopentanone-bridged tricyclic system involving a Meerwein salt-initiated cationic rearrangement of the ring-annelated cyclobutanone **218**. Using triethyloxonium tetrafluoroborate in dichloromethane afforded this cycloabietaoxotriene **219** in 75% yield.[107]

Scheme 76



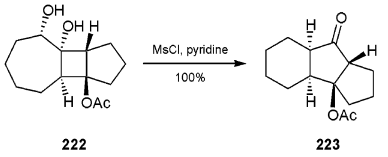
The scope of the Brønsted and Lewis acid-promoted spirocyclization of 1-vinylcyclobutanols with an acetal moiety acting as terminator in the cyclization reaction was demonstrated in 1996 by Trost and Chen. The spiroannelated products are cyclopentanones derived from ring expansion of the cyclobutanol unit and the second ring is formed by attack of the terminator on the initiator moiety. Among numerous reactions of this type, one illustrative example is the vinylcyclobutanol **220** yielding the 7-methoxyspiro-[4.6]undecan-1-one (**221**) (Scheme 77). It is noteworthy that by attaching the cyclization termini to an appropriate previously existing ring unit, even spiro[4.7]dodecane in addition to spiro[4.5]decane and spiro[4.6]undecane ring systems became accessible.[108]

Scheme 77



Tricyclic methylenecyclobutanols with the four-membered ring located in the middle of the framework are useful precursors for bisannelated cyclopentanones. After the bishydroxylation reaction, Caubere et al. subjected the monomesylated diol to a ring-enlargement reaction of the intermediate cation generated by means of an amine in refluxing dichloromethane. Usually, the resulting ketones were obtained in good to excellent yields. For example, the tricyclo[6.4.0.0^{2,6}]dodecanone **223** was obtained quantitatively from **222**.[109]

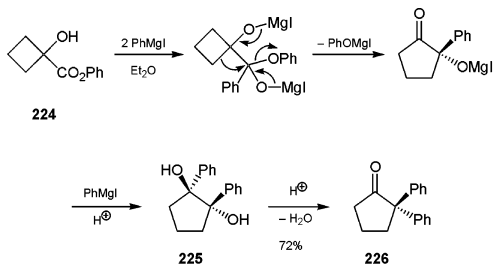
Scheme 78



222 223

Salaün et al. reported the synthesis of dialkyl- or diarylcyclopentanones from 1-hydroxycyclobutanecarboxylic acids or from *O*-protected cyclobutanone cyanohydrins.[71] For example, starting from cyclobutanol **224**, 2,2-diphenylcyclopentanone (**226**) was obtained in 72% yield. The reaction proceeds via addition of two equivalents of phenylmagnesium bromide to **224**, followed by ring expansion. The second addition of the same Grignard reagent afforded the *trans*-diol **225**. Finally, protic workup furnished the 2,2-diphenylcyclopentanone (**226**). In the case of cyclobutanone cyanohydrins, 2-alkylated or arylated 2-hydroxy- (or 2-amino-) cyclopentanones were obtained in quantitative yield via metalated imines using Grignard or lithium reagents.

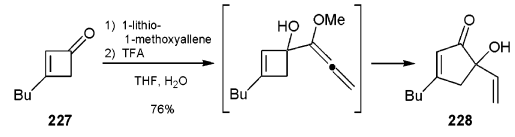
Scheme 79



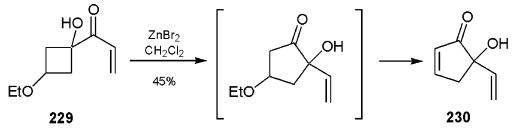
224 225 226

A stereoselective synthesis of 5-hydroxy-5-vinylcyclopentenones starting from cyclobutenones was developed by Stone and Liebeskind. A 1-(1′-methoxyallenyl)cyclobutenol, prepared by adding 1-lithio-1-methoxyallene to a cyclobutenone, gave the ring expanded product upon treatment with trifluoroacetic acid. For example, the substituted 5-hydroxy-5-vinylcyclopentenone **228** was obtained in 76% yield from 3-butylcyclobutenone (**227**). Analogously, the ethoxy-substituted cyclobutanol derivative **229**, under the action of zinc bromide underwent ring enlargement and subsequent elimination to the corresponding cyclopentenone **230** in 45% yield. These products were used as starting materials for allyl esters which, upon palladium-catalyzed substitution gave 5-alkylidene-2-cyclopentenones as substructures of naturally occurring bioactive compounds.[110]

Scheme 80



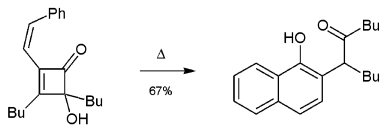
227 228



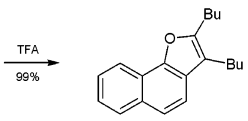
229 230

Moore and Liebeskind et al. discovered independently that 4-alkenyl/aryl-cyclobutenones can be ring expanded to aromatic systems. Moore et al. used 2-dienyl-4-oxycyclobutenones as starting materials for the synthesis of annelated furans and monocyclic lactones.[111,112] Thermal rearrangement of corresponding (2*Z*)-alkenylcyclobutenones gave exclusively the ring-annelated products after subsequent treatment with trifluoroacetic acid. For example, the naphthofuran **233** was obtained from hydroxycyclobutenone **231** via the α-naphthol derivative **232**.[111] On the other hand, *o*-styryl-substituted cyclobutenediones such as **234**, gave naphthofuranones of type **235** by intramolecular addition of an intermediate *β*-naphthol to the *ortho*-attached ketene unit (Scheme 81).[112]

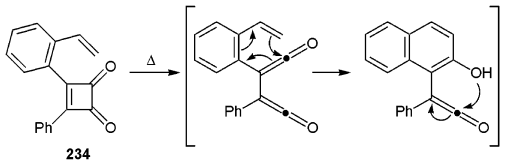
Scheme 81



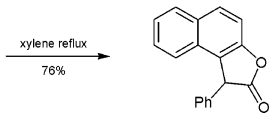
231 232



233



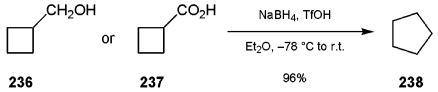
234



235

In a formal reductive ring enlargement, Olah et al. transformed hydroxymethyl- or carboxyl-substituted cyclic or oligocyclic hydrocarbons to the next higher homologues by treatment with a mixture of sodium borohydride and triflic acid in diethyl ether.[113] In the original paper, the authors focused mainly on adamantane derivatives, but also described the ring enlargement of hydroxymethylcyclobutane (**236**) and cyclobutanecarboxylic acid (**237**) to cyclopentane (**238**), which with 96% yield was highly efficient.

Scheme 82

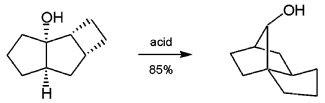


236 237 238

Avasthi and Salomon published as early as 1986 the acid-catalyzed rearrangement of tertiary bi- or tricyclic cyclobutacyclopentane-2-ols via carbenium ions to 7-hydroxynorbornane derivatives. The structurally interesting products were obtained in yields of 43−85%, e.g., the *exo*,*syn*-tricyclo[5.2.1.$0^{1,5}$]decan-10-ol (**240**) was formed from **239** (85% yield) diaste-

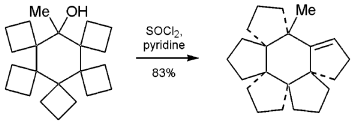
reoselectively with a maximum of 1.5% of the *endo*-isomer.[114]

Scheme 83



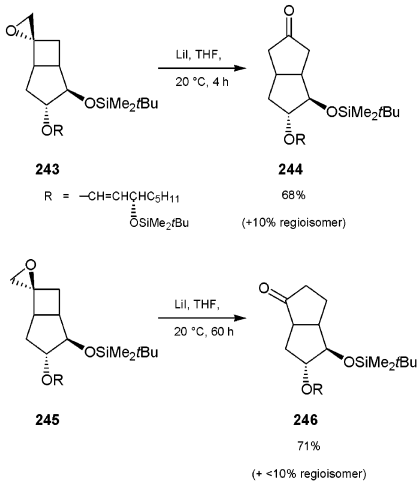
A striking example of a cationic cascade reaction is the 5-fold cyclobutylmethyl−cyclopentyl rearrangement of the pentaspirohenicosanol **241** to the all-*cis*-annelated precursor **242** of [6.5]coronane (83% yield) reported by Fitjer et al.[115] This reaction was speculated to proceed with conformational control starting from an initially formed chlorosulfite. Fitjer and Quabeck had previously reported the formation of [4.5]coronane in 40% yield by means of a comparable cationic cascade rearrangement followed by a photolytic decarbonylation.[116]

Scheme 84



A ring enlargement of a cyclobutanone or an appropriate derivative annelated to a cyclopentane leads to the bicyclo[3.3.0]octane skeleton which is found in natural sesquiterpenes as well as in prostacyclins. As shown by Hart and Comte,[117] the α-epoxide **243** rearranges to the ring-enlarged bicyclo-[3.3.0]octan-3-one **244** with acceptable regioselectivity (68%: 10%) within 4 h upon treatment with lithium iodide in THF at ambient temperature (Scheme 85). However, the epimeric *β*-epoxide **245**

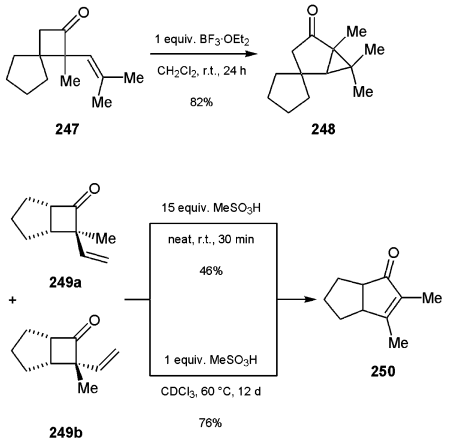
Scheme 85



slowly (60 h) gives the regioisomeric bicyclo[3.3.0]-octan-2-one **246** (71%:10%).

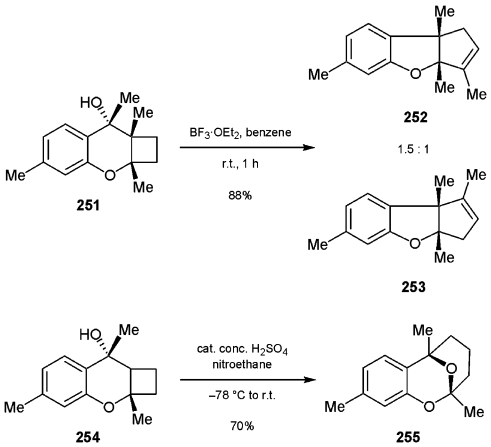
In 1985, Dreiding et al. reported an acid or Lewis-acid catalyzed rearrangement of α-vinylcyclobutanones either leading to ring-annelated cyclopentenones or bicyclo[3.1.0]hexanones such as **248** along with linear dienones as ring-opening products. The mechanistic details of the ring enlargement have been speculated to depend on the substitution pattern and on the reaction conditions. Illustrative examples showing the scope of these reactions are that of the spirocyclopentane-annelated cyclobutanone **247** leading to **248** in 82% yield, and that of an isomeric mixture of vinylcyclobutanones **249a** and **249b** furnishing the cyclopenta-cyclopentenone **250** (Scheme 86).[118]

Scheme 86



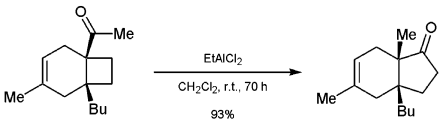
Venkateswaran et al. developed the acid- or Lewis acid-catalyzed rearrangement reactions of the methylcyclobutane unit attached to chromanol to three different types of five-membered ring systems, i.e., cyclopentanones, cyclopentenes, or cyclopentanes, each with an annelated dioxolane moiety.[119] According to the substitution pattern as well as to the solvent and the acid, the authors found the outcome of the reaction to be predictable. In the case of a secondary alcohol and *p*-toluenesulfonic acid in DMSO, the intermediate cyclobutylmethyl cation underwent ring enlargement to the corresponding cyclopentanone.[120] However, upon treatment with $BF_3{\cdot}OEt_2$ in benzene, **251** furnished a mixture of the two isomeric cyclopentenes **252** and **253** (1.5:1) in 88% yield.[119] These cyclopentenes were used as precursors to the marine sesquiterpene debromoaplysin. Alternatively, when treated with concentrated sulfuric acid in nitroethane at −78 °C, the ring-annelated cyclobutane **254** afforded the tricyclic 1,3-dioxane **255** in 70% yield.[121]

Scheme 87



Cyclohexene-annelated acetylcyclobutanes upon treatment with an appropriate Lewis acid afford hydrindanone derivatives, as reported by Takeda et al.[122,48] With ethylaluminum dichloride, the ring enlargement of (substituted) annelated cyclobutyl ketones provided *cis*-hydrindanones with high stereoselectivity. For example, the acetylcyclobutane **256** gave the annelated cyclopentanone **257** in 93% yield with complete *cis*-selectivity. With analogous isopropyl- and *tert*-butyl instead of the methyl ketones, a reduced stereoselectivity or even a reversal was observed, according to the steric demand of these substituents.

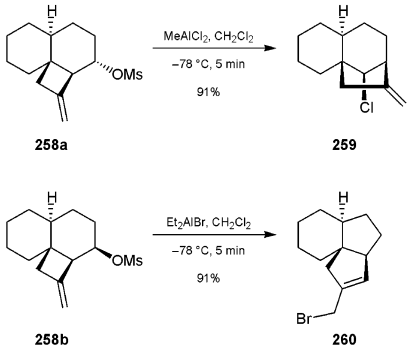
Scheme 88



256 **257**

Toward the construction of the bicyclo[3.2.1]octane skeleton found in kaurenoids and gibberellins, Corey and Liu rearranged the (methylenecyclobutane)-annelated mesyloxydecalin **258a** applying methylaluminum dichloride/$AlCl_3$. This Lewis acid-catalyzed ring-expansion reaction proceeded with 91% yield within 5 min affording the annelated bicyclo[3.2.1]-octane **259**. Interestingly, the epimer **258b** furnished the allyl bromide **260** in 91% yield.[123]

Scheme 89

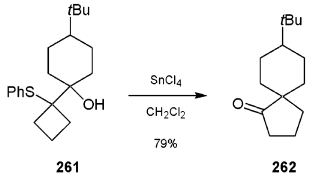


258a **259**

258b **260**

Fitjer et al. reported the formation of spiroannelated cyclopentanones[124] starting from an appropriate 1-(1′-phenylthiocyclobutyl)cycloalkanol by means of tin tetrachloride in dichloromethane within 20 min. For example, the cyclohexanol **261** afforded the spiro-[4.5]decan-2-one **262** in 79% yield.

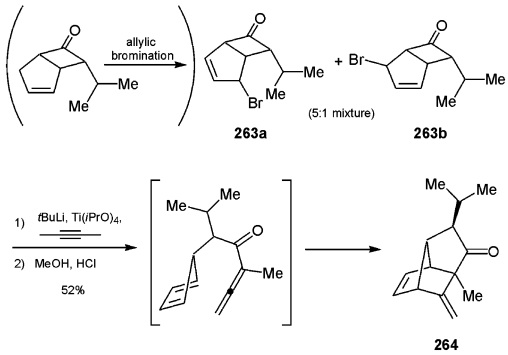
Scheme 90



261 **262**

The mixture of two isomeric bromobicyclo[3.2.0]-heptenones **263a** and **263b** yielded the ring enlarged ketone **264** upon treatment with the buta-1,2-dienyltitanium complex generated from 2-butyne, *tert*-butyllithium, and Ti(O*i*Pr)$_4$ in hexane at −80 °C, and subsequent hydrolysis. This multistep ring expansion involves an intramolecular Diels−Alder cycloaddition of an intermediate allene moiety and a cyclopentadiene leading to the tricyclic cyclopentanone **264** in 52% yield.[125]

Scheme 91

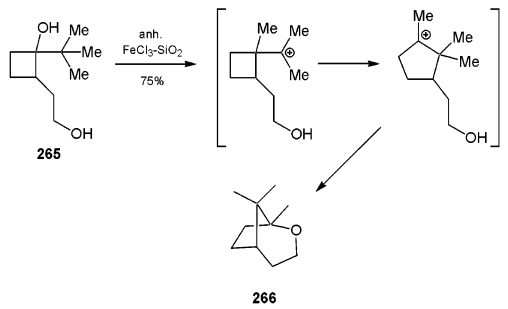


263a **263b**

264

Fadel and Salaün reported a combination of a dehydration, 1,2-methyl migration, and subsequent C-4 to C-5 ring enlargement starting from cyclobutanols with a bulky substituent at C-1 by means of anhydrous ferric trichloride on silica gel. Usually, this process leads to substituted cyclopentene derivatives; for example, the simple 1,5,5-trimethylcyclopentene (isolaurolene) was prepared from 1-*tert*-butylcyclobutanol in quantitative yield without solvent at room temperature. However, if a hydroxyethyl (or tetrahydropyranylethyl) group is present as in the case of **265**, the rearranged cyclopentyl cation is trapped to form the 2-oxabicyclo[3.2.1]octane derivative **266**.[126]

Scheme 92



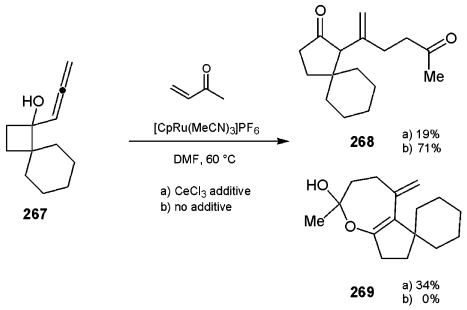
265

266

A novel ruthenium-catalyzed ring-expansion reaction of 1-allenylcyclobutanols with α,β-unsaturated carbonyl compounds to give cyclopentanone derivatives was developed by Ihara et al.[127] Under conditions such as those of Trost et al. for cycloetherifications,[128] but without added cerium trichloride, the allenylcyclobutanol **267** was exclusively transformed to the desired cyclopentanone **268**. With added $CeCl_3$, mixtures of **268** and the cyclohemiacetalization product **269** were isolated. In addition, product distributions depend on the solvent and the structure of the starting materials.

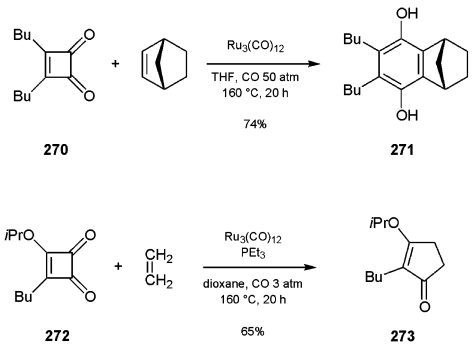
A novel method for the transition metal-catalyzed preparation of cyclopentenones was published by Mitsudo et al.[129] 3,4-Disubstituted cyclobutenediones under the action of dodecacarbonylruthenium react with alkenes to yield Pauson-Khand type products,

Scheme 93



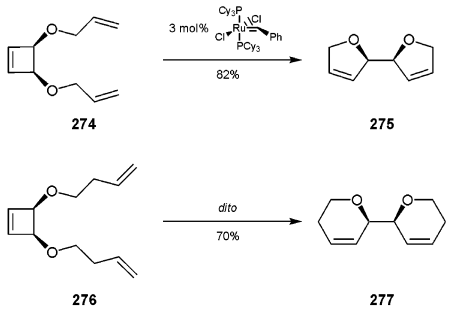
e.g., **273** from **272** and ethylene. Under 50 bar pressure of CO, the 1,2-dialkyl derivatives such as **270** led to hydroquinones of type **271** (74% yield). The difference is that **272** is a 1-alkoxy-2-alkylcyclobutenedione and was treated under a lower pressure of carbon monoxide in the presence of triethylphosphine with $Ru_3(CO)_{12}$ (5 mol %) and ethylene to provide the cyclopentenone **273** in 65% yield. 3,4-Dialkoxycyclobutenediones react the same way.

Scheme 94



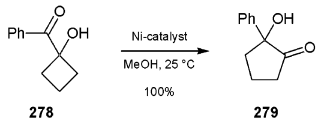
In 1996, Grubbs et al. demonstrated the sequence of ring-opening and ring-closing metathesis to convert 3,4-bisallyloxy- (**274**) and the corresponding bis(homoallyloxy)cyclobutene (**276**) to prepare 2,2′-bis(2,5-dihydrofuranyl) (**275**) in 82% yield and 2,2′-bis(2,5-dihydropyranyl) (**277**) in 70% yield, respectively. The reaction is catalyzed by a Ru-alkylidene complex.[130]

Scheme 95



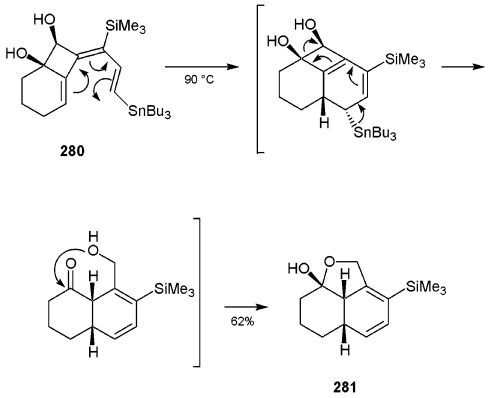
Recently, Brunner and Kagan et al. published an α-ketol rearrangement of 1-benzoylcyclobutanol (**278**). Treatment with catalytic amounts (2 mol %) of nickel chloride/TMEDA in methanol at room temperature led to ring-enlarged 2-phenyl-2-hydroxycyclopentanone (**279**) in quantitative yield.[131]

Scheme 96



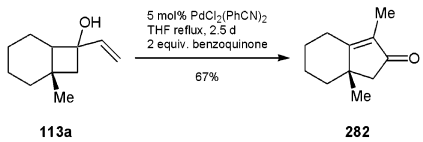
An elegant one-pot cascade reaction using the side-chain bismetalated 1,8-dihydroxy-7-dienylidenebicyclo-[4.2.0]oct-5-ene **280** was performed by Suffert et al.[132] This highly functionalized *cis*-diol (obtained from a propargylic *anti*-diol and 1,2-bis(tributylstannyl)-ethene in a domino carbopalladation/Stille cross-coupling reaction) was subjected to a thermal disrotatory ring opening of the cyclobutane moiety and subsequent hemiacetal formation leading to a complex tricyclic lactol **281** with a *cis*-fused decalin skeleton (62% yield). Interesting mechanistic details are discussed in the original paper.

Scheme 97



With only 5 mol % of bis(benzonitrile)palladium as catalyst, 1-vinyl-1-cyclobutanol derivatives (accessible from the corresponding cyclobutanone and vinylmagnesium bromide) are ring enlarged to 2-methyl-2-cyclopenten-1-ones in refluxing tetrahydrofuran within 2.5 days as reported by Clark and Thiensathit.[133] For example, the annelated cyclopentenone **282** was accessed from the vinyl-substituted cyclobutanol **113a** in 67% yield. Two equivalents of added benzoquinone take care of regenerating the active catalyst. The corresponding ring-enlargement product of a 3-ethoxy derivative of such a vinylcyclobutanol provides a potential building block for the synthesis of prostaglandins.

Scheme 98

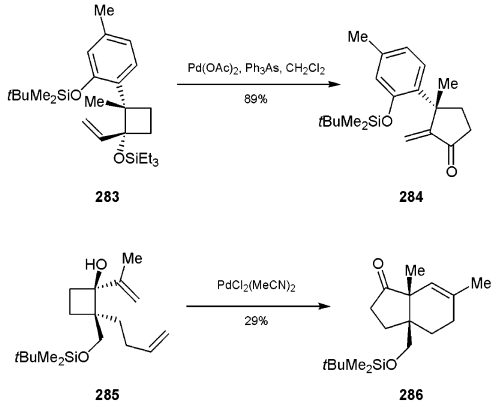


Among other palladium(II)-catalyzed oxidative transformations of tertiary cyclobutanols,[60,61] Uemura et al. reported the ring enlargement of bicyclic vinyl-substituted cyclobutanols to methylenecyclopentanones with up to 67% yield (see Scheme 36).

In 1994, Fukumoto et al. developed a palladium-mediated ring expansion of 2-aryl-1-vinylcyclobutanols (or the corresponding silyl ethers) providing

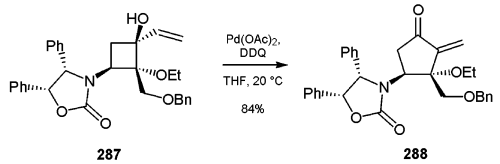
(protected) 3-aryl-2-methylenecyclopentanols.[134] With palladium acetate in the presence of triphenylarsine high yields were obtained; for example, the 1-vinylcyclobutanol **283** was converted to the 2-methylenecyclopentanone **284** in 89% yield. In the same year, the authors published an interesting extension of this reaction in that bis(acetonitrile)palladium dichloride at 85 °C mediated a consecutive ring expansion and intramolecular alkene insertion of the 1,2-dialkenylcyclobutanol **285** leading to the hydrindanol **286** in 29% yield.[135] In the cases of benzo- as well as naphthoannelated analogues, better yields were obtained under slightly modified conditions.[136] In 2000, the same group applied the palladium-mediated ring expansion to a 2-cyclohexyl-2-methyl-substituted 1-vinylcyclobutanol using 1.5 equivalents of palladium(II) acetate to provide a 2-methylenecyclopentanone derivative which served as a precursor for the tricyclic sesquiterpene 4-deoxyverrucarol.[137]

Scheme 99



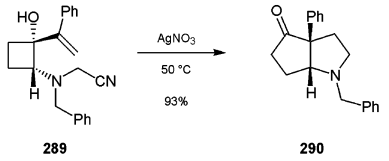
In addition to Clark's studies on the palladium-catalyzed oxidative ring enlargement of vinylcyclobutanols,[133] Hegedus and Ranslow reported a similar ring expansion of α-alkoxy-1-vinylcyclobutanols to cyclopentanones.[138] For example, the highly functionalized cyclobutanol **287** gave the corresponding cyclopentanone **288** in 84% yield. With DDQ as a reoxidizing agent and tetrahydrofuran as the solvent only 10 mol % of the palladium(II) catalyst was required.

Scheme 100



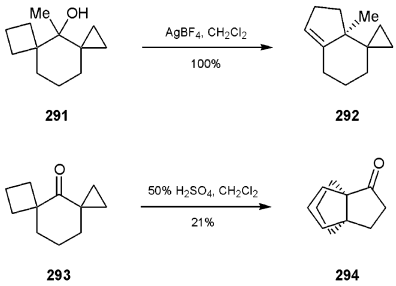
Overman et al. performed the silver nitrate-mediated cascade aza-Cope rearrangement-Mannich cyclization of 1-alkenylcyclobutanol derivative to substituted cyclopentanone-annelated pyrrolidines. In most of the cases, the [3,3] sigmatropic rearrangement of the intermediate iminium ion with subsequent Mannich cyclization led to a single isomer in good to very good yields. For example, the bicyclic ketone **290** was prepared from the cyclobutanol **289** in 93% yield.[139]

Scheme 101



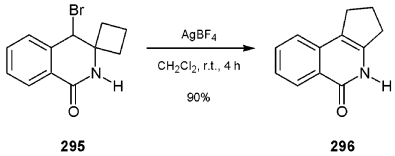
Cationic ring-enlarging rearrangements of cyclobutane derivatives to five-membered rings were also investigated by Fitjer et al. Fascinating reaction cascades were developed by this group, e.g., the dispiro[2.3.3.1]undecan-11-one (**293**) was converted to the [3.3.3]propellane **294**, albeit in only 21% yield, while the tertiary alcohol **291**, under acidic conditions, gave the spirocyclopropanated bicyclo[4.3.0]-nonene **292** in quantitative yield.[140]

Scheme 102



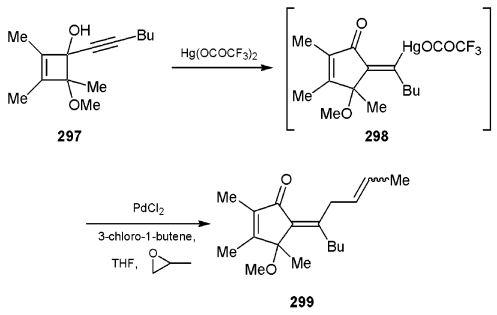
The formation of a cyclopentane-annelated isoquinolone from a spirocyclobutane dihydroisoquinolone was reported by Fisher et al. The bromomethylcyclobutane derivative **295**, prepared by bromination with NBS in the benzylic position, underwent ring enlargement upon treatment with silver tetrafluoroborate in anhydrous dichloromethane to give **296** in 90% yield (Scheme 103).[141]

Scheme 103



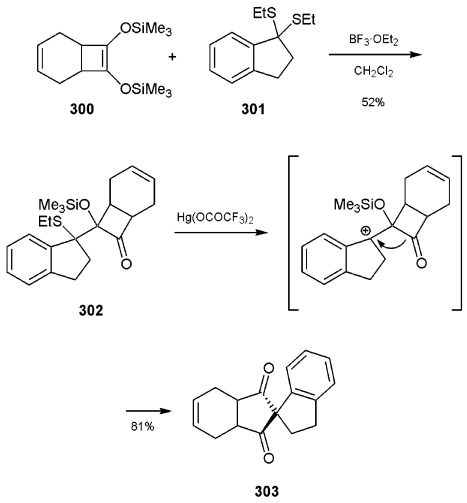
An interesting transition metal-catalyzed four- to five-membered ring expansion was published by Liebeskind and Bombrun in 1994. Under the action of a highly electrophilic mercury salt, e.g., $Hg(OCOCF_3)_2$ and a palladium catalyst, sequential ring expansion and cross-coupling of 1-alkynylcyclobutenols gave 4-methoxy-4-methyl-5-alkylidenecyclopentenones or 5-alkylidene-2-cyclopentene-1,4-diones stereoselectively in 70−92% yield. The first formed intermediates are alkenylmercury derivatives, such as **298**, which are then allylated under palladium catalysis providing 1,4-dienes (Scheme 104). For example, from the 1-alkynylcyclobutenol **297** and 3-chloro-1-butene in THF/propylene oxide the alkylidenecyclopentenone **299** was prepared in 92% yield.[142] Starting from analogous diethyl squarate derivatives and an electrophilic iodine reagent (HgO/I_2, NIS, $PhI(OAc)_2/I_2$), Ohno and Eguchi et al. obtained alkylidenecyclopentenediones via a hypoiodite intermediate.[143,144]

Scheme 104



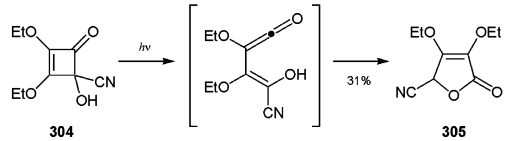
Bach and Klix reported a mercury-mediated acyl migration in a pinacol-type rearrangement in the course of the synthesis of fredericamycin A.[145] A substituted bicyclo[4.2.0]oct-3-ene-8-one **302** (generated from a bissilylated cyclobutenediol **300** and 1-indanonedithioacetal **301**) was desulfurated/desilylated in a single step and rearranged via acyl migration to the spiro compound **303** under the action of mercuric bistrifluoroacetate. This methodology was applied to the key step in a total synthesis of fredericamycin A.[146]

Scheme 105



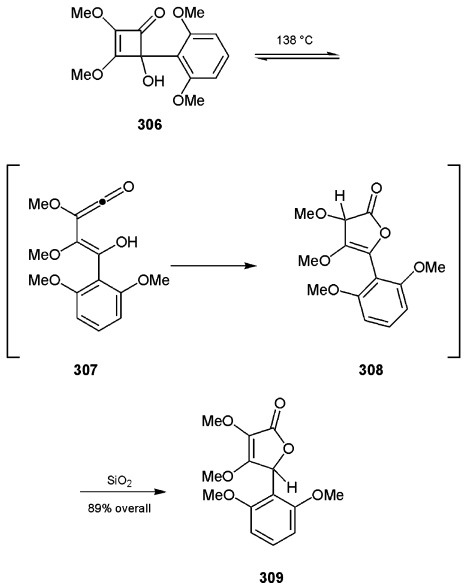
An interesting photochemically initiated ring enlargement of the monocyanohydrine of diethyl squarate leading to a γ-cyanobutenolide was also reported by Eguchi et al. Upon irradiation, 4-cyano-4-hydroxycyclobutenone **304** undergoes ring opening to a ketene, which subsequently rearranges to give the highly functionalized dihydrofuranone **305** in 31% yield.[147]

Scheme 106



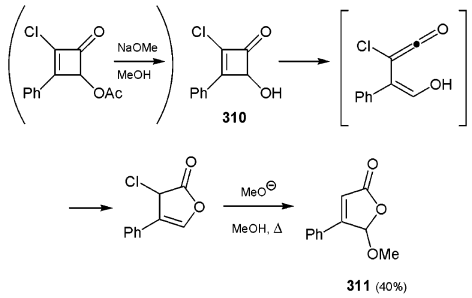
Concerning the ring-opening reactions of cyclobutenones, Moore and Perri reported an unusual inward conrotatory ring opening due to the substitution pattern on the aromatic ring attached to C-4. In boiling xylene, the hydroxyvinylketene **307** (generated by thermal ring opening of **306**) underwent ring closure to give a mixture of butenolides **308** and **309** (ratio 2:1) in 89% yield. Upon treatment with silica gel complete isomerization of **308** to the α,β unsaturated isomer **309** took place.[148]

Scheme 107



Instead of a squarate, Dillon and Gao used a 4-hydroxy-substituted 2-chloro-3-phenylcyclobutenone (**310**) to obtain the completely conjugated butenolide **311** in 40% yield after chromatography.[149]

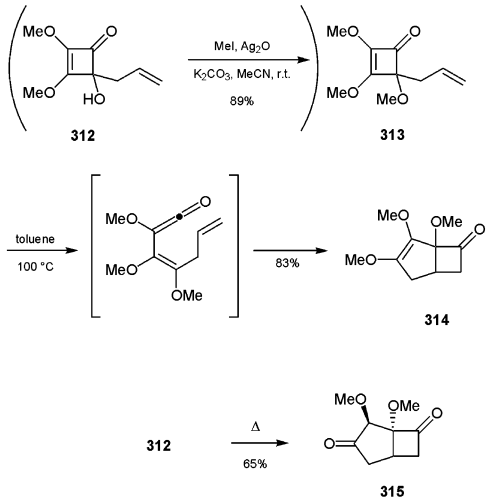
Scheme 108



The conversion of selected 4-allyl-4-oxycyclobutenones to bicyclo[3.2.0]heptenones via the corresponding nonconjugated vinylketenes was reported by Moore et al.[150,151] After thermal conrotatory ring opening of the 2-allyl-2,3,4-trimethoxycyclobutenone **313**, the vinylketene underwent an intramolecular [2+2] cycloaddition incorporating the allylic double bond to afford the cyclopentene-annelated cyclobutanone **314**. Cyclobutenones with different *O*- and *C*-substituents at C-2 were also investigated. With a hydroxy group at C-2 as in **312**, which is derived from dimethyl squarate, 1,2-dimethoxybicyclo[3.2.0]heptane-3,7-dione (**315**) was formed in 65% yield.

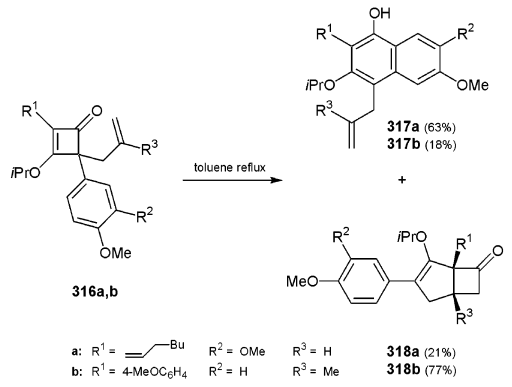
Moore et al. also investigated the thermal rearrangement of 4-allyl-4-arylcyclobutenones. Due to its 2-fold substitution at C-4, cyclobutenone **316** equilibrates with two different vinylketenes. Mixtures of products were obtained in up to 87% yield, stemming from an intramolecular [2+2] cycloaddition to give bicyclo[3.2.0]heptenones competing with an electro-

Scheme 109



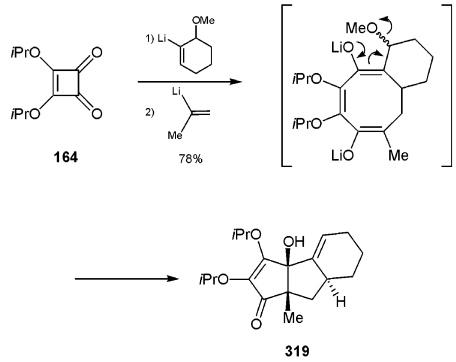
cyclic ring closure to form allylated naphthols. In general, naphthol formation increases with higher electrophilicity of the intermediate ketene and with the nucleophilicity of the aryl substituent. However, both product types can be favored by proper choice of the substituents. For example, thermolysis of **316a** with an electron-rich aryl group at C-4 and a 2-alkenyl group led to a mixture of α-naphthol **317a** and bicycloheptenone **318a** with a ratio of 3:1, while **316b** with a 2-aryl substituent gave mainly the bicycloheptenone **318b** and only minor amounts of the naphthol **317b** (Scheme 110).[152]

Scheme 110



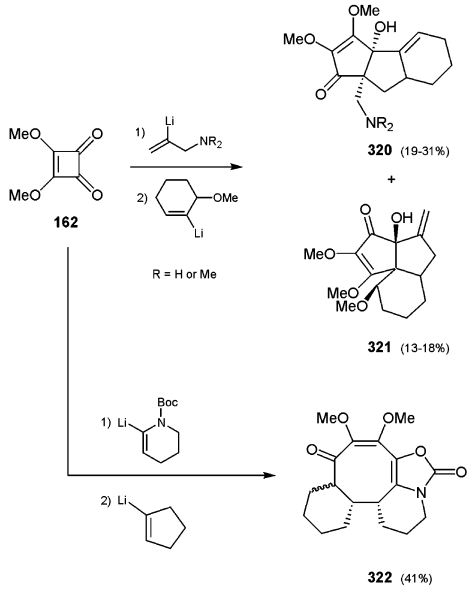
Paquette et al. developed an interesting cascade transformation of dialkyl squarates to oligoquinanes involving an eight-membered carbocyclic ring intermediate.[10,153] The sequence starts with the addition of two alkenyllithium reagents—if necessary, two different ones—and proceeds by conrotatory ring opening of the intermediate 3,4-dialkenylcyclobutene-3,4-diolate with subsequent reclosure to a cyclooctatriene. By kinetically controlled β-elimination of an appropriate leaving group in the cyclic or acyclic lithiated precursors the reaction can be controlled regioselectively to give either the linearly or angularly fused products.[154] Influenced by the bulk of the alkenyllithium used as the second reagent, yields up to 78% were obtained. For example, the addition of 6-methoxycyclohexenyllithium and then 2-propenyllithium to diisopropyl squarate **164** gave the ring expanded tricyclic product **319** (78%). Later, this protocol was extended to lithiated alkynes leading to the corresponding oligoquinanes.[155]

Scheme 111



Evaluating the scope of this squarate cascade, Paquette et al. in 1997 started to apply vinyllithium reagents containing nitrogen substituents, i.e., (alkyl)amino or carbamoyl groups.[156,157] The influence of such a group in 2-lithioallyl derivatives as attacking nucleophile with respect to the regio- and stereoselectivity in the formation of the di-, tri-, and tetracyclic ring systems was discussed. More than a dozen oligocyclic (hetero)quinanes and higher homologues were synthesized. For example, starting from dimethyl squarate (**162**) and a 2-lithioallylamine the tricyclic ring systems **320** and **321** were obtained, whereas the cyclooctadienone derivative **322** with three annelated rings resulted from the adduct of lithiated *N*-Boc-tetrahydropyridine and cyclopentenyllithium.

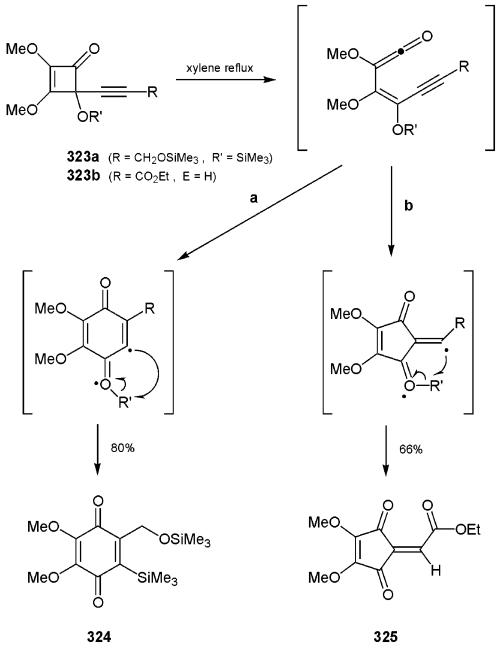
Scheme 112



Moore et al. observed the thermal rearrangement of 4-alkynyl-4-oxycyclobutenones prepared from dimethyl squarate leading either to 1,4-benzoquinones or 2-alkylidene-1,3-cyclopentenediones under mild conditions.[158] The selectivity is significantly influenced by the terminal substituent on the alkynyl moiety: With radical-stabilizing groups at this posi-

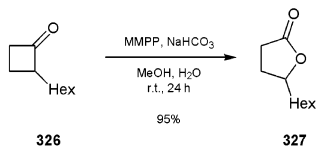
tion, the formation of cyclopentenediones is favored. The five-membered ring ethyl ester **325** is formed in 66% yield from **323a**, whereas **323b** provided the substituted quinone **324** in 80% yield. Both of the ring enlargements involve an intramolecular migration of the atom or group (i.e., hydrogen or trimethylsilyl) from the 4-oxygen substituent to the carbon radical center of the diradical species which is formed from the initially produced ketene (see Scheme 113).

Scheme 113



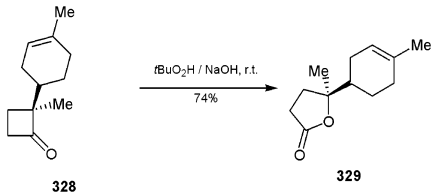
As demonstrated by Yamashita et al., Baeyer−Villiger oxidations of cyclobutanone derivatives occur regioselectively; thus, 2-hexylcyclobutanone (**326**) led to 4-hexyl-γ-butyrolactone (**327**) in 95% yield upon treatment with magnesium monoperphthalate hexahydrate (MMPP) as a nonshock sensitive and inexpensive oxidant.[159]

Scheme 114



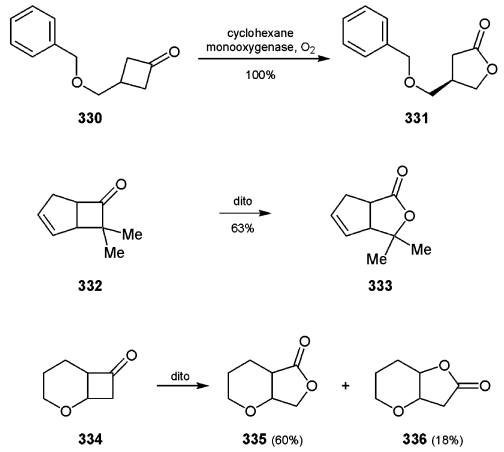
In 1993, Fukumoto et al. published the synthesis of the sesquiterpene (−)-α-bisabolol, a widespread naturally occurring fragrance. As a key step, they performed a Baeyer−Villiger-type oxidation with *tert*-butyl hydroperoxide and sodium hydroxide to prepare the butyrolactone **329** in 74% yield from the correspondingly substituted cyclobutanone **328**.[160]

Scheme 115



In a comprehensive review on the applications of cyclohexanone monooxygenase for Baeyer−Villiger oxidations,[161] it was pointed out that this enzyme can be expressed in baker's yeast so that whole yeast cells can be handled with usual laboratory equipment and without special biochemical expertise. Numerous examples for the application of this convenient method toward the oxidation of cyclobutanones are known. In most cases, high regio- and stereoselectivity combined with good to very good yields were found. For example, the benzyloxymethylcyclobutanone **330** gave the γ-lactone **331** in 89% yield (Scheme 116). While in the case of the cyclopentene-

Scheme 116



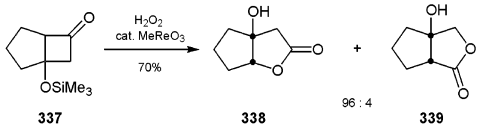
annelated 2,2-dimethylcyclobutanone **332**, the reaction proceeded regioselectively to give lactone **333** (63% yield), other reactions, e.g., the oxidation of 2-oxabicyclo[4.2.0]octan-7-one (**334**) resulted in mixtures of regioisomers (60% **335** with 18% **336**).

In this growing area of biocatalyzed synthetic transformations, Furstoss et al. published the first example of a Baeyer−Villiger oxidation of cyclic ketones to lactones using a flavin entity as a catalyst with hydrogen peroxide as the oxidant.[162] The oxidation of 3-benzyloxymethyl-substituted cyclobutanone (**330**) to lactone **331** proceeded with 93% yield (compared to <5% without the flavin catalyst). Annelated cyclobutanones were also converted with good to very good yields.

Although a methyltrioxorhenium-catalyzed variant of the Baeyer−Villiger oxidation with hydrogen peroxide was reported in 1994 by Herrmann et al.,[163] the applicability of this method was not explored much, until Phillips and Romao in 1999 published the rhenium-catalyzed oxidation of (fused) cyclobutanones by H_2O_2.[164] For example, 1-trimethylsilyloxybicyclo[3.2.0]heptan-6-one (**337**) was converted directly to the desilylated 3-hydroxy-γ-butyrolactones **338** and **339** within 1 h at room temperature with high regioselectivity (96:4). In other cases, neither double-bond epoxidation, nor aromatic oxidation took place, but extended reaction times were required for the oxidation of α,α-dichlorocyclobutanones.

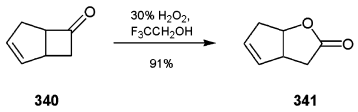
Matsumoto and Kobayashi published the oxidation of cyclobutanones to γ-butyrolactones using hydrogen peroxide in 2,2,2-trifluoroethanol. Specifically, the prostaglandin precursor **341** (Corey's lactone) was

Scheme 117



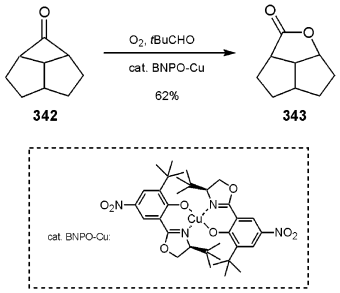
prepared regioselectively in 91% from bicyclo[3.2.0]-hept-2-ene-6-one (**340**) by means of this unique Baeyer−Villiger reagent system.[165]

Scheme 118



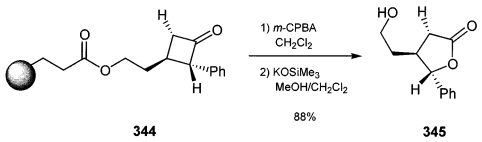
A complex formed by two molecules of (*S*)-2-*tert*-butyl-6-(4-*tert*-butyl-4,5-dihydro-2-oxazolyl)-4-nitrophenol and a copper center catalyzes the aerobic oxidation of Kelly's tricyclic ketone **342** to the corresponding Baeyer−Villiger product, i.e., 2-oxatricyclo-[5.2.1.$0^{4,10}$]decan-3-one (**343**), in 62% yield. Bolm et al. performed the oxidation of various 3-monosubstituted cyclobutanones with dioxygen in the presence of 0.5 to 3 equivalents of pivaldehyde as well as the depicted copper complex with increased chemical yields in the range from 77 to 92% (Scheme 119).[166]

Scheme 119



Brown et al. reported solid-phase Baeyer−Villiger oxidations as well as Beckmann rearrangement reactions of appropriate cyclobutanone derivatives.[167] Commercially available alkenols were ester-linked to a carboxylated Merrifield resin. After [2+2] cycloaddition of a ketene, the resulting cyclobutanone derivatives were oxidized with classical reagents (*m*-CPBA, *O*-mesitylenesulfonylhydroxylamine) to give the immobilized γ-butyrolactones regioselectively in 74−88% yield. For example, the 3-(hydroxyethyl)-4-phenyl-γ-butyrolactone (**345**) was obtained from the polymer-bound cyclobutanone **344** in 88% yield.

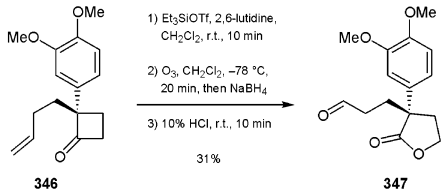
Scheme 120



An unusual lactone formation involving the oxidation of a ketene intermediate with molecular oxygen was already mentioned in Scheme 8.[26]

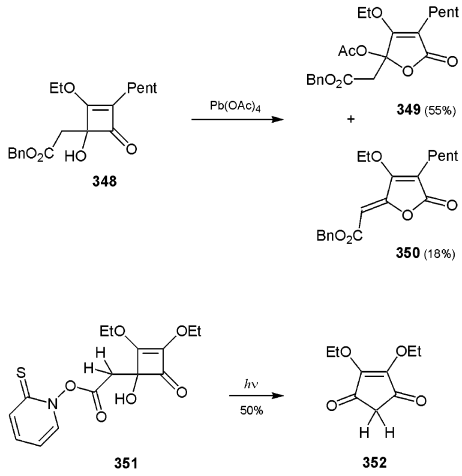
Succesive treatment of cyclobutanone **346** with triethylsilyl triflate in the presence of 2,6-lutidine and ozone followed by sodium borohydride led to the 2-(3′-oxopropyl)-substituted Baeyer−Villiger product **347** as reported by Fukumoto et al.[168] Although the yield was only moderate (31%), the molecule provides a key intermediate toward mesembrine analogues.

Scheme 121



Eguchi et al. developed ring-enlargement reaction of both oxocyclobutenyloxy- and oxocyclobutenylmethyl radicals. For example, lead tetraacetate (LTA) initiated oxidative rearrangements of 4-hydroxycyclobutenones prepared from diethyl squarate and organolithium compounds to the ring-enlarged 5-acetoxy-2(5*H*)-furanones and 5-(methoxycarbonylmethylene)-2(5*H*)-furanones in good yields. Thus, the cyclobutenone **348** was converted to a 3:1 mixture of acetoxytetronate **349** and γ-lactone **350**. The former could be transformed to the (*Z*)-multicolanate **350** by means of DBU in THF. Cyclopentenediones such as **352** could be obtained via radicals generated by photolysis of Barton esters such as **351**, which were prepared from *N*-hydroxythiopyridone and an appropriate squarate derived acetic acid.[169]

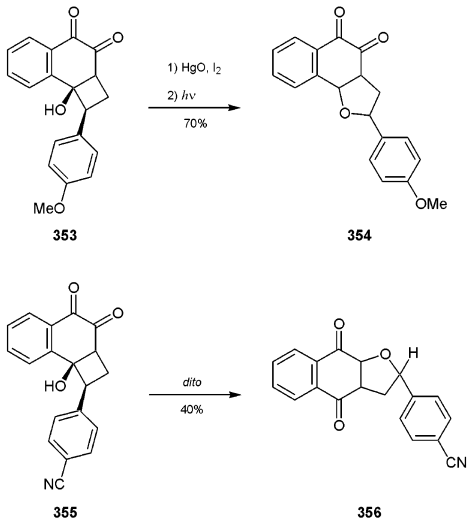
Scheme 122



A photolytic ring cleavage of oligocyclic tertiary cyclobutanols leading either to tetrahydrofuran derivatives or bifunctional open-chain products (see Scheme 35[59]) was developed by Suginome et al., e.g., a ring enlargement of the tricyclic 1-hydroxy-1,2-(2′-arylcyclobutadihydronaphthalene)-3,4-diones **353** and **355** led to the 2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione **354** and 2,3-dihydronaphtho[2,3-*b*]furan-4,9-dione **356**, respectively, by β-scission of the intermediate cyclobutyloxy radicals. The regiochemistry is controlled by the *para*-substituent on the aryl group. Exclusive 4,5-dione formation was obtained for *p*-methoxyphenyl (70% yield), whereas a *p*-cyanophenyl-substituted system gave the 4,9-dione (40%). On

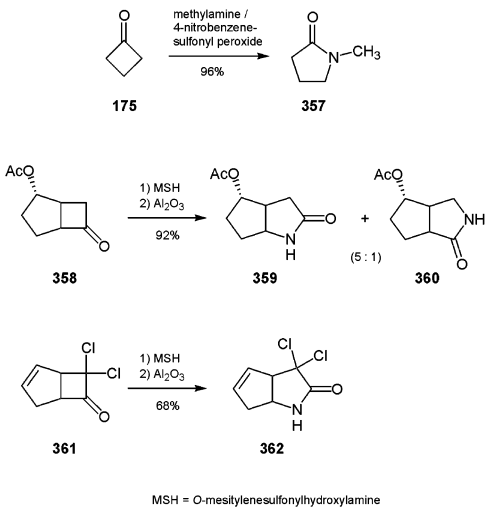
the other hand, the 4,9-dione **356** underwent isomerization to the 4,5-dione **354** on silica gel.[170]

Scheme 123



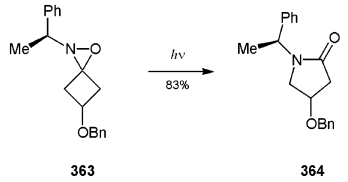
The ring expansion of cyclobutanones to γ-lactams in an addition−rearrangement sequence with *N*-alkyl-*N*-arylsulfonoxylamines in situ generated from amines and 4-nitrobenzenesulfonyl peroxide was reported by Hoffman and Salvador.[171] Starting from cyclobutanones and different primary amines, this novel method afforded the corresponding *N*-substituted pyrrolidinones in 62−100% yield, whereas secondary amines gave poor yields. The parent cyclobutanone (**175**) was expanded to 1-methylpyrrolidin-2-one (**357**) in 96% yield. Tertiary amines are not applicable. Luh et al. had already reported the regioselective nitrogen insertion into cyclobutanones by means of *O*-mesitylenesulfonylhydroxylamine (MSH) in 1995.[172] In this case, the γ-lactams usually were obtained as isomeric mixtures, e.g., **359** and **360** (5:1, 92%) from **358**. However, in the case of the α,α-dichlorocyclobutanone **361**, the single γ-lactam **362** was isolated in 68% yield.

Scheme 124



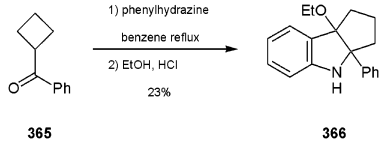
Aubé et al. reported the photochemical rearrangement of spirocyclobutane-annelated oxaziridines derived from cyclobutanones.[173] Thus, the γ-lactam **364** was obtained as a separable mixture of diastereomers upon photolysis of **363** at 254 nm in 83% yield. Subsequent catalytic hydrogenolysis followed by acidic hydrolysis provides a general route to the bioactive 4-amino-3-hydroxybutanoic acid and related compounds such as GABOB and carnitine.

Scheme 125



A Fischer indolization of cyclobutylphenyl ketone with phenylhydrazine was published by Robinson et al. In principle, this reaction offers a synthetic route to tricyclic indoles, but the yields still need to be improved. The hexahydrophenylcyclopent[*b*]indole **366** was obtained from cyclobutylphenyl ketone (**365**) and phenylhydrazine in 23% yield.[174]

Scheme 126

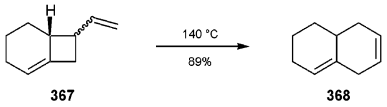


Subjecting 1-(1-hydroxycyclobutyl)hexan-2-one (**127**) to a one-electron oxidation by means of oxovanadium(V) compounds in minor amounts, the 2-tetrahydrofurylidene ketone **129** was formed besides a ring-opening product (see Scheme 39).[65]

2. Six-Membered Rings

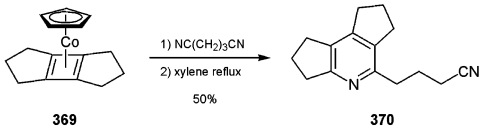
In 1987, Christl and Schreck reported the ring enlargement of cyclohexene-annelated vinylcyclobutane derivatives. Thermal rearrangement of isomeric mixtures of these 7-vinylbicyclo[4.2.0]oct-1-enes, e.g., **367**, which were prepared as [2+2] cycloadducts at 140−170 °C gave hexahydronaphthalenes, e.g., the unsubstituted **368** in 89% yield.[175]

Scheme 127



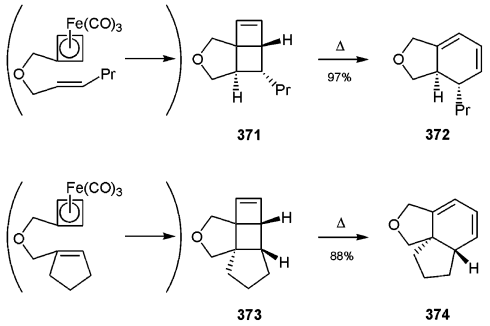
The reaction of the biscyclopentane-annelated cyclobutadienecobalt complex **369** with 1,3-dicyanopropane was published by Gleiter and Kratz. Decomplexation followed by [4+2] cycloaddition and cycloreversion let to the biscyclopentane-annelated 4-(2′-pyridyl)butyronitrile **370** in 50% yield.[176]

Scheme 128



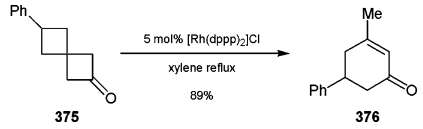
Snapper et al. developed a thermal ring-enlargement reaction of annelated bicyclo[2.2.0]hexenes, e.g., **371** and **373** generated by an intramolecular [4+2] cycloaddition of an in situ generated cyclobutadiene to the tethered alkene unit to yield ring-fused cyclohexadienes such as **372** and **374** which were obtained in 97 and 88% yield, respectively.[177]

Scheme 129



An interesting rhodium(I)-catalyzed ring-enlarging rearrangement of spirocyclobutanones was reported by Ito et al. The first ring cleavage occurs upon oxidative addition to the metal, and the second ring is opened by β-carbon elimination. For example, 6-phenylspiro[3.3]heptan-2-one (**375**) was converted to the substituted cyclohexenone **376** in 89% yield after isomerization of the first formed intermediate 3-methylenecyclohexanone.[178]

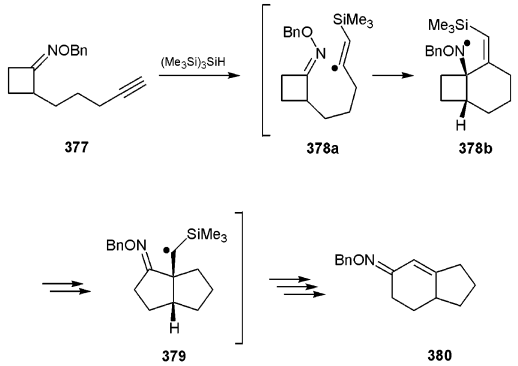
Scheme 130



As discussed above (see Scheme 95) Grubbs et al. prepared bisdihydropyranyl (**277**) and analogues by Ru-catalyzed metathesis of 3,4-bishomoallyloxycyclobutene **276**.[130]

A free radical-based ring enlargement involving a cyclobutanone oxime was reported by Pattenden and Schulz. Addition of tris(trimethylsilyl)silane to the alkynyl-substituted cyclobutanone oxime benzyl ether **377** led to the β-silyl-substituted vinyl radical **378a** which, in an 6-*exo*-*trig* ring closure, yielded a bicyclo[4.2.0]octylaminyl radical **378b**. A subsequent cascade radical rearrangement leads to an intermediate bicyclo[3.3.0]octyl ring system **379** and eventually

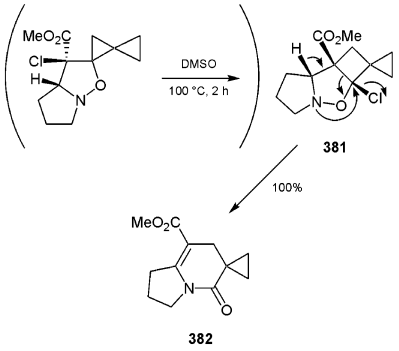
Scheme 131



gives the cyclopentane-annelated cyclohexenone oxime benzyl ether **380** after another ring enlargement and final elimination of the silyl radical (70% yield).[179]

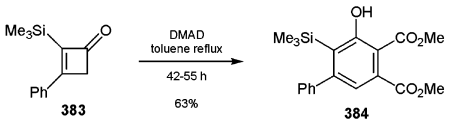
In a unique thermal ring enlargement, Brandi and de Meijere et al. obtained indolizin-5-ones from a tricyclic cyclobutane-annelated isoxazolidine, which was formed upon thermolysis of the 1,3-dipolar cycloaddition product of a nitrone to methyl 2-chloro-2-cyclopropylidene acetate. For example, the spirocyclopropanated cyclobutane derivative **381** quantitatively rearranged to the tetrahydro-1*H*-indolizin-5-one **382**.[180]

Scheme 132



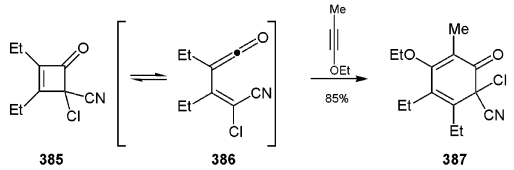
In 1998, Danheiser et al. used the 4π-electrocyclic ring opening of a 2-silyl-3-phenylcyclobutenone such as **383** to an isolable (37% yield) and remarkably robust ketene. Yet, when generated in the presence of a reactive dienophile such as dimethyl acetylenedicarboxylate (DMAD), this ketene underwent a Diels−Alder reaction to furnish an oligofunctionalized phenol **384** regioselectively in 63% yield.[181]

Scheme 133



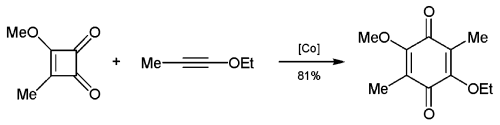
Comprehensive studies concerning the reactions of ketenes generated by thermal ring opening of substituted cyclobutenones were performed by Moore et al. within the last two decades: e.g., they used 4-chloro-4-cyanocyclobutenones as precursors to cyanovinylketenes, which reacted with a variety of alkynes to give highly substituted cyclohexadienones in moderate to good yields.[182] These are formal ring-enlargement products, e.g., the tetrasubstituted cyclobutenone **385** (in equilibrium with the vinylic ketene **386**) upon cycloaddition to 1-ethoxypropyne gave 6-chloro-6-cyano-4,5-diethyl-3-ethoxy-2-methyl-2,4-cyclohexadienone (**387**) in 85% yield. Subsequent reduction and dehydrochlorination offers a route to the corresponding hexasubstituted phenol derivative.

Scheme 134



In 1985, Liebeskind et al. published a mild and general synthesis of (benzo)quinones with high functional group tolerance.[183] Starting from either 2,3-dialkyl- or 2,3-alkylalkoxy-substituted cyclobutenediones, an appppropriate alkyne, and a cobalt complex, the quinones were isolated in up to 89% yield. The bisalkoxy-substituted benzoquinone **389** was obtained from 2-methoxy-3-methylcyclobutenedione (**388**) and 1-ethoxypropyne in 81% yield (regioisomeric ratio 13.5:1).

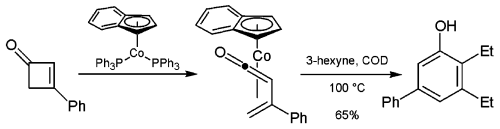
Scheme 135



388 **389**

Huffman and Liebeskind developed the ring opening of cyclobutenones such as **390**, mediated by (η^5-indenyl)cobalt(I) with subsequent [4+2] cycloaddition of the isolable η^4-cobalt vinylketene complex **391** to various alkynes to synthesize substituted phenols. Mixtures of regioisomers were obtained starting from unsymmetrical alkynes, whereas disubstituted vinylketenes led to the phenolic product only with the electron-deficient dimethyl acetylenedicarboxylate. The 3-phenylcyclobutenone (**390**) with 3-hexyne thus gave the biphenyl derivative **392** in 65% yield.[184]

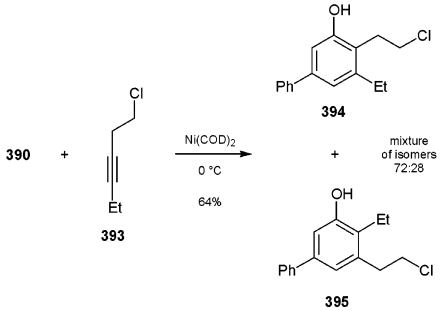
Scheme 136



390 **391** **392**

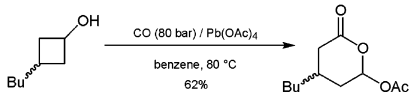
Later, a $Ni(COD)_2$-catalyzed variant was developed. Again, phenols were generated from cyclobutenones and more complex bissubstituted alkynes. Initially, a nickelacyclopentenone is formed into which the alkyne is inserted providing, after reductive elimination and enolization, the phenols in 43−81% yield, but usually with low regioselectivity. A second conceivable mechanistic pathway involves the cycloaddition of the alkyne to an intermediate Ni-complexed vinylketene. The cyclobutenone **390** and the halogenated alkyne **393** afforded the ring-enlarged isomeric phenols **394** and **395** in 64% yield (ratio 72:28).[185]

Scheme 137



In 1994, Sonoda et al. reported the high-pressure carbonylation (80 bar) of unsubstituted cyclobutanol upon oxidative ring cleavage with lead tetraacetate yielding substituted δ-lactones.[186] An acyl cation that was generated in two one-electron oxidation steps, underwent an intramolecular cyclization by attack on its terminal aldehyde group. Finally, the formed cation was attacked by an acetate anion or another cyclobutanol molecule. From cyclobutanol itself, 6-acetoxytetrahydropyran-2-one was formed in 50% yield accompanied by 5% of the corresponding 6-cyclobutyloxy derivative. In a similar manner, the 3-butylcyclobutanol **396** (or analogous 3-aryl derivatives) gave the acetoxy-δ-lactone **397** (62% yield). In the case of 1-substituted cyclobutanols, no cyclic product was found, but open chain 5-oxoacid derivatives were isolated in over 50% yield.

Scheme 138

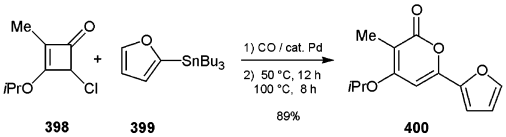


396 **397**

cis/*trans* 9:1 *cis*/*trans* 2:8

The sequence of Pd-catalyzed carbonylation and cross-coupling with unsaturated stannanes (vinyl, propenyl, aryl, or heteroaryl) and subsequent thermal ring opening and ring closure of cyclobutenones was found to be an efficient method to prepare 3,4,6-trisubstituted 2-pyrones.[187] This formal ring-enlargement reaction, developed by Liebeskind et al., proceeds in a regioselective manner via an intermediate vinylcyclobutenone. Good yields ranging from 60 to 89% were obtained. For example, coupling of the stannylated furan **399** to 4-chloro-3-isopropyloxy-2-methylcyclobutenone (**398**) in the presence of carbon monoxide under palladium catalysis afforded the furanylpyranone **400**.[188]

Scheme 139

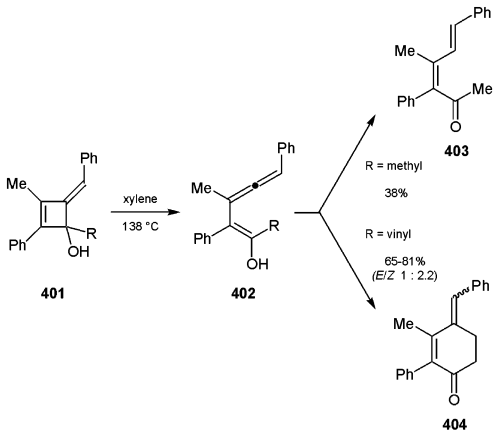


398 **399** **400**

Starting from squaric acid esters, 4-alkynyl-, 4-alkenyl-, and 4-alkyl-4-hydroxy-3-benzylidenecyclobutenes are available as reported by Moore et al. These cyclobutenols, e.g., **401**, undergo electrocyclic ring opening to conjugated allenes, such as **402**. Depending on the substituent on C-4 either an acyclic, fully conjugated dienyl ketone, e.g., **403** (in the case of alkyl), or a substituted *p*-dihydroquinonemethide, e.g., **404** (alkynyl or vinyl), is formed.[189]

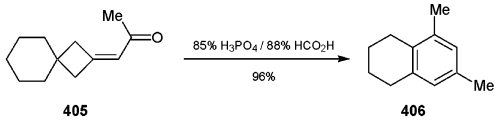
Gruhn and Reusch published a Nazarov-type reaction with an intervening acid-catalyzed rearrangement of, in this case, cyclobutylideneketones to a tetraline derivative using a mixture of 85% phosphoric acid and 88% formic acid. In a cascade cationic rearrangement, the aromatic ring is formed from the cyclobutane unit. For example, the reaction of the spirocyclic cyclobutylidenemethyl ketone **405** afforded

Scheme 140



regioselectively 5,7-dimethyltetraline (**406**) in excellent yield (96%).[190]

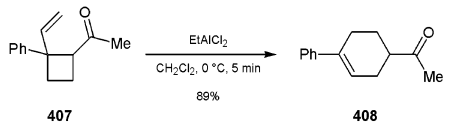
Scheme 141



Different Brønsted or Lewis acid-catalyzed rearrangements were reported by Venkateswaran et al. (see Scheme 87). Reacting the benzoannelated 2-oxabicyclo[4.2.0]octan-5-ol **254** with concentrated sulfuric acid in nitroethane at −78 °C, the pyran moiety within the tricyclic 1,3-dioxane **255** is generated (70% yield).[121]

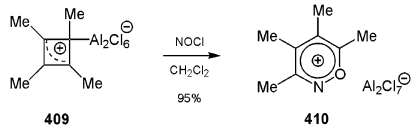
In 1990, Fujiwara and Takeda published the cationic ring expansion of appropriate adducts from alkenylmetals and cyclobutenyl ketones.[48,191] For example, the (2-vinylcyclobutyl)methyl ketone **407** gave the cyclohexenyl ketone **408** in 89% yield upon treatment with ethylaluminum dichloride (or phenoxyaluminum dichloride). In certain cases, this regioselective transformation can serve as a better access to cyclohexene derivatives than the Diels−Alder reaction. Interestingly, this particular reaction required very short reaction times (5 min) using two equivalents of the Lewis acid.

Scheme 142



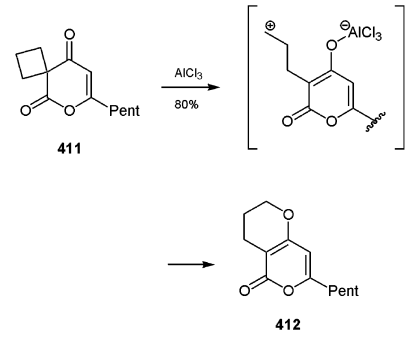
The dimerization of substituted alkynes and subsequent stabilization of the intermediate cyclobutadienes using aluminum trihalide leads to σ-aluminum halide cyclobutadiene complexes. In extension of the well-known cycloaddition of cyclobutadiene radical cations to alkynes as well as nitriles giving benzenes and pyridines, respectively, Hogeveen et al. developed the synthesis of 2-azapyrylium salts using nitrosyl chloride, thus broadening the scope of this methodology. The tetramethylazapyrylium salt **410** was obtained in 95% yield from the corresponding cyclobutyl cation **409**.[192]

Scheme 143



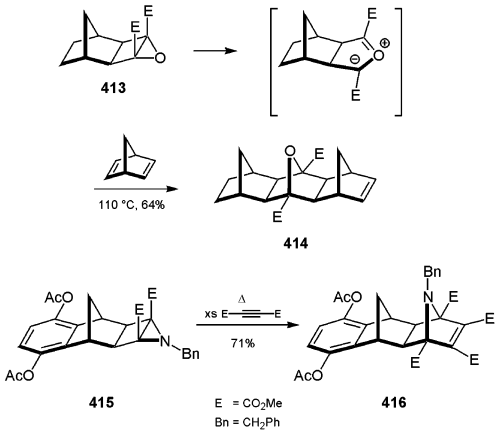
Saalfrank et al. reported a convenient access to 3,4-dihydro-2,4-dioxo-2*H*-pyrans and 2-pyrones providing synthetic equivalents of 1,3-dianions. In an interesting reaction without solvent, a mixture of the spirocyclic **411** and aluminum trichloride was heated at 130−140 °C to give the tetrahydropyran-annelated α-pyrone **412** in 80% yield.[193]

Scheme 144



In his long-standing interest in molecular architecture, Warrener in 2000 reported the stereocontrolled synthesis of heterobridged *syn*-facially fused norbornadienes by thermal ring expansion of norbornane-fused cyclobutene epoxides and related heteroanalogues.[194] The reactions of the epoxide **413** as well as of the aziridine **415** may serve as illustrative examples. The fused 7-oxanorbornane **414** which was obtained by a 1,3-dipolar cycloaddition, and also the related 7-aza derivative **416** were prepared in 64 and 71% yield, respectively. These oligo- or polynorbornanes represent LEGO[7]-type building blocks of curved molecular scaffolds which offer a great potential not only for (bio)organic chemistry, but possibly also for nanotechnology and related applications.

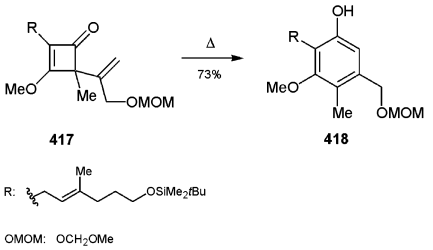
Scheme 145



As a key step in the synthesis of mycophenolic acid, Danheiser et al. published a cascade electrocyclic reaction involving the addition of a substituted alkyne to a ketene which was prepared from a highly

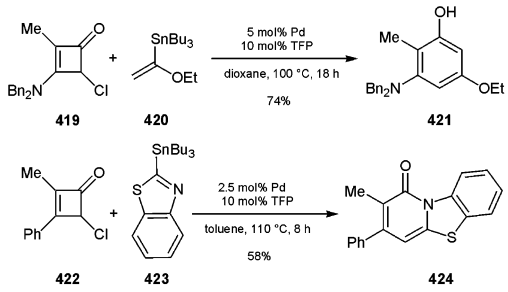
functionalized 3-methoxycyclobutenone. For example, the thermal cleavage of **417** to a butadienylketene followed by 6π-electrocyclic ring closure generated the highly substituted phenol derivative **418** in 73% yield.[195]

Scheme 146



In 1992, Liebeskind et al. reported a Pd-catalyzed cross-coupling thermolysis sequence of cyclobutenones bearing a vinylic or aromatic substituent at the 4-position. These unsaturated starting materials were generated from cyclobutenediones by cross-coupling with vinyl- and arylstannanes, respectively, or vinylzirconium compounds, and underwent rearrangement to phenols upon heating. Using high ligand concentrations (e.g., 40 mol % triphenylphosphine instead of only 20 mol % in the regular case) a regioisomeric mixture of phenols is obtained. Furthermore, depending on the nature of the substituents at the 2-(alkyl or phenyl) and 3-positions (alkyl, phenyl, isopropyloxy, or dibenzylamino) as well as the unsaturated group (ethenyl, substituted ethenyl, or phenyl) on the stannane, the yields range from 50 to 77%.[188] For example, the dibenzylaminochlorocyclobutenone **419** and stannane **420** provided the alkoxy-substituted aminophenol **421** in 74% yield. In the case of heteroarylstannanes, five- and six-membered ring-annelated α-pyridones are accessible in yields of up to 65%.[196] The tricyclic benzothiazol **424** was obtained from the cyclobutenone **422** and the tributylstannylbenzothiazole **423** in 58% yield.

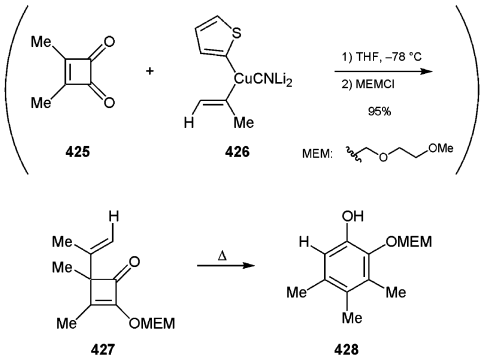
Scheme 147



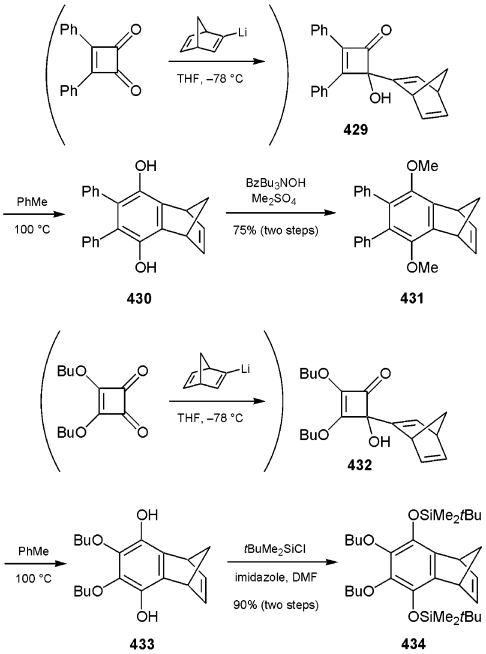
Liebeskind and Gurski applied the thermal ring-enlargement of protected 4-alkenyl-2-hydroxycyclobutenones to the synthesis of catechols. These substrates were prepared by 1,4-addition of an appropriate cuprate, e.g., **426**, to symmetrically substituted cyclobutenediones such as **425**. Thermolysis of the Michael adducts afforded the catechols in high yields. Thus, the (2-methoxyethoxy)methyl-protected 2-hydroxycyclobutenone **427** gave **428** (95%).[197]

Furthermore, a general route to highly functionalized benzonorbornadienes starting from 3,4-disubstituted cyclobutenediones was introduced by Petasis and Fu.[198] Addition of 2-norbornadienyllithium to these cyclobutenediones led to 4-alkenyl-4-hydroxycyclobutenones such as **429**. The subsequent thermal rearrangement in refluxing toluene furnished the expected hydroquinone derivative **430** which was methylated to give **431** with up to 80% overall yield for the last two steps. Starting from dibutyl squarate to obtain **432**, the protection of the rearrangement product **433** with *tert*-butyldimethylsilyl chloride eventually furnished the corresponding benzonorbornadiene derivative **434** (90% yield over two steps).

Scheme 148



Scheme 149

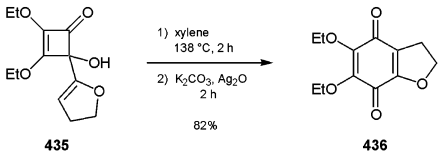


Similar reactions involving ketene intermediates with a focus on the regioselective synthesis of the highly substituted hydroquinone moiety and corresponding quinones were developed by Moore et al. Different 4-hydroxycyclobutenones bearing an unsaturated substituent, e.g., alkenyl, aryl, or heteroaryl, alkynyl, or an acyl group at C-4, proved to be useful starting materials. The scope is very broad as these compounds are readily available from squaric acid derivatives. Their ring expansions are facile due to the strain release associated with the electrocyclic ring opening of the cyclobutenones to the

corresponding vinylketene intermediates. The synthetic targets range from monocyclic *p*-quinone derivatives to oligocyclic heteroaromatic ring systems depending on the nature of the C-4 substituent.[6]

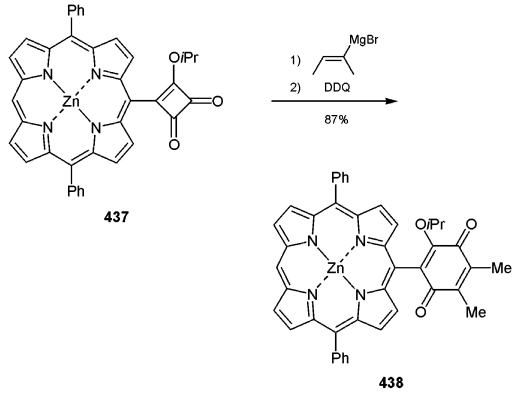
In 1990, Perri and Moore published the synthesis of (annelated) quinones by ring opening of an appropriate 4-alkenyl-4-hydroxycyclobutenone.[199] Recyclization of the intermediate ketene and subsequent oxidation afforded the quinone in 55−87% yield. The dihydrofuran-annelated diethoxyquinone **436** was obtained from **435** in 82% yield.

Scheme 150



Applying this ring-expansion methodology, Liebeskind et al. prepared (hydro)quinone- and naphthoquinone-substituted *meso*-linked porphyrins starting from the appropriate porphyrin-substituted cyclobutenediones. Due to the steric congestion, the formed atropisomers did not interconvert easily and could be separated. For example, the quinone **438** was obtained in 87% overall yield by reaction of **437** with 1-methyl-1-propenylmagnesium bromide and final oxidation with DDQ.[200]

Scheme 151

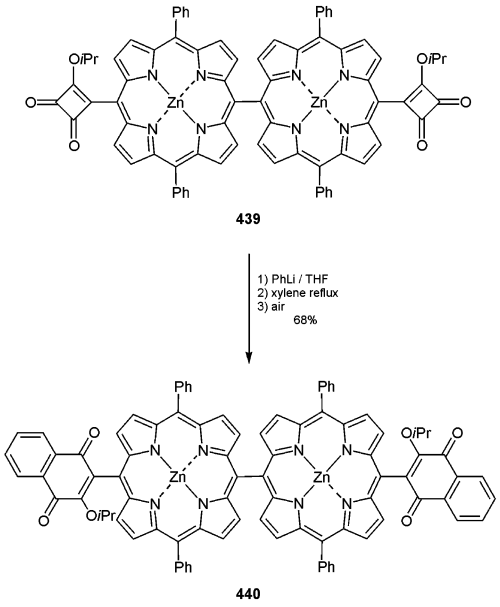


In a subsequent paper, quinone−porphyrin−porphyrin−quinone tetrads and related compounds as multichlorophyll structures with great potential as molecular electronic devices or nonlinear optics materials were reported. For instance, the dimeric porphyrinylcyclobutenedione **439** gave the doubled acceptor−donor pair **440** in 68% yield.[201]

The analogous transformation of 4-chloro-4-aryl- (or alkenyl)cyclobutenones led to *p*-chlorophenols.[202,203]

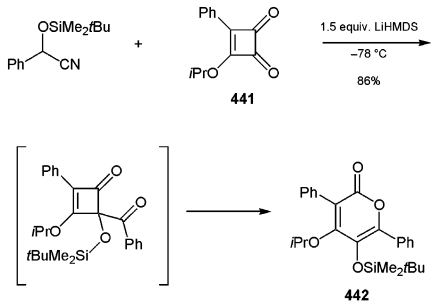
Liebeskind et al. also developed a synthetic route to highly substituted α-pyrones from cyclobutenediones.[204] The addition of lithiated *O*-silylated cyanohydrins to cyclobutenediones afforded 4-acylcyclobutenediones, which have been found to undergo a facile rearrangement leading to 5-silyloxy-2-pyrones. For example, the silylated cyanohydrin of benzaldehyde reacted with the squaric acid derivative

Scheme 152



441 gave the tetrasubstituted α-pyrone **442** in 86% yield.

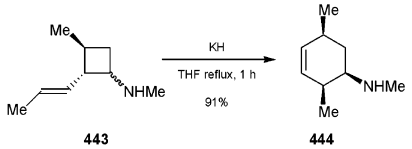
Scheme 153



As reported by Cohen et al., cyclohexanones can be prepared under basic conditions from the potassium salt of an appropriate isopropenyl cyclobutanol (see Scheme 62).[91]

In 1988, Bauld et al. reported a synthetic sequence to overcome the low cycloaddition reactivity of electron-rich alkenes such as enamides. Formal Diels−Alder products were obtained starting from a secondary cyclobutylamine, which, after deprotonation with potassium hydride, rearranges to the cyclohexene derivative. This thermal aminyl anion-assisted vinylcyclobutane rearrangement afforded the monocyclic or annelated products in acceptable to very good yields. For example, the diastereomeric mixture of cyclobutylamine **443**, generated from the appropriate enamide, gave the methylaminocyclohexene **444** stereoselectively in 91% yield.[205] Such reactions including those leading to tricyclic systems were reviewed by Bauld in 1989.[206] Furthermore, carbonyl-substi-

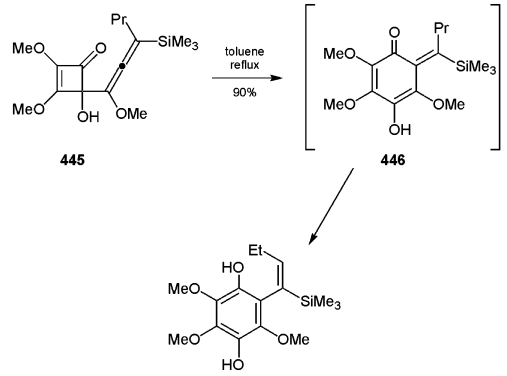
Scheme 154



tuted cyclohexenes were prepared in high yields by similar vinylcyclobutane rearrangements.[207]

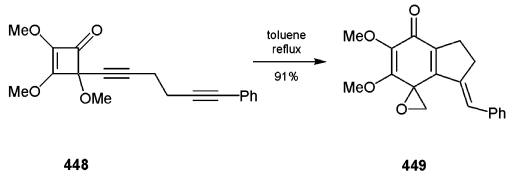
Taing and Moore in 1996 reported the ring expansion of 2,3-disubstituted 4-allenyl-4-hydroxycyclobutenones to the corresponding *ortho*-quinone methides upon thermolysis in refluxing toluene. These reactive intermediates rearrange regioselectively to highly functionalized 2-alkenylphenols and benzofurans. For example, the allenyl derivative **445** afforded the 2-alkenylhydroquinone **447** via **446** in 90% yield. In addition, the rearrangement of a geminal bis(trimethylsilyl)-substituted allenylcyclobutenone gave 1,2-benzoxasilols involving a methyl migration from silicon to carbon.[208]

Scheme 155



The same group also developed the thermal rearrangement of 4-alkynyl-4-silyloxycyclobutenones involving a migration of the silyl group from oxygen to carbon to yield tetrafunctionalized 1,4-benzoquinones. It is noteworthy that the product selectivity is controlled by the terminal substituent on the alkyne group (see Scheme 113).[158] According to this reaction principle, 4-(1,5-diynyl)-4-methoxycyclobutenones, upon heating in refluxing toluene, underwent a unique ring-enlarging rearrangement to annelated spiroepoxides.[209] For example, **449** was obtained in 91% yield from the dimethyl squarate derivative **448**. Mechanistic details are discussed in the original paper. A second type of rearrangement was found when starting from similar 4,4-disubstituted cyclobutenones. Depending on the substrate concentration, either annelated quinones were obtained with up to 80% yield (high dilution conditions) or quinones containing a side chain with a residual triple bond (up to 66%).

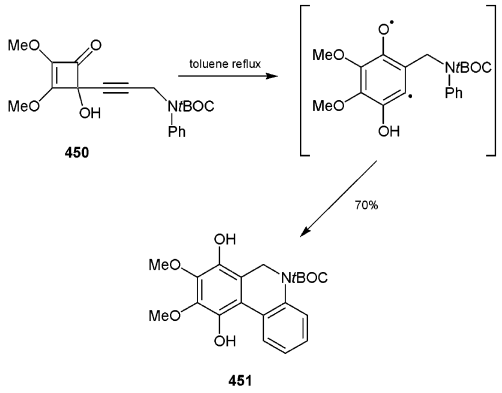
Scheme 156



Furthermore, Moore et al. extended the cyclobutenone ring-expansion technique to the regioselective formation of quinones with a variety of substitution patterns starting from the correspondingly substituted 4-(alkenyl or alkynyl)-4-hydroxycyclobutenones which were prepared from dimethyl squarate by sequential addition of an organometal reagent, formation of an intermediate acetal, and treatment with a second organometal compound. This mild and rapid conversion leads to 2,3,5-trisubstituted benzoquinones from appropriate 4-alkynyl derivatives, whereas 4-alkenyl analogues provide related 2,3-di-, 2,3,5-tri-, or 2,3,5,6-tetrasubstituted quinones. Similarly, 4-aryl derivatives lead to annelated quinones. In contrast, quinone derivatives with fewer substituents were obtained from 2,2,3-trimethoxy-2-cyclobuten-1-one.[210]

The thermal ring expansion of 4-alkynyl-4-hydroxycyclobutenones was applied to the synthesis of a variety of *N*-heterocycle-annelated quinones and hydroquinones using appropriate nitrogen substituents within the alkynyl side chain.[211] Thus, piperidinoquinones were obtained, e.g., **450** gave **451** in 70% yield (Scheme 157). In addition, benzophenanthridines, indolophenanthridines, isoindoloindoles, and pyrrolophenanthridines were synthesized. In a similar fashion, 4-hydroxy-4-(4-oxo-1,6-dialkynyl)-cyclobutenones were suitable for the synthesis of comparable *O*-heterocyclic derivatives, i.e., pyranoquinones which were prepared with up to 75% yield.[212] A further report using this rearrangement which focused on the synthesis of benzophenanthridines as a skeleton for naturally occurring alkaloids, appeared in 1999.[213]

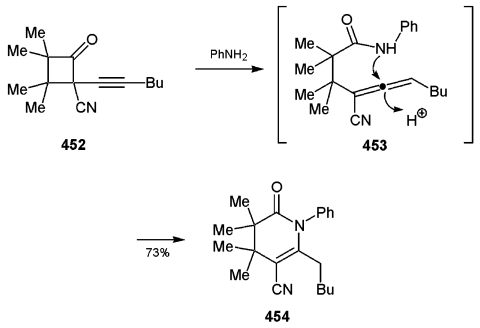
Scheme 157



Alkynylcyanoketenes were reported as the first examples of alkynylketenes by Moore et al. in 1987, available by thermolysis of 2,5-dialkynyl-3,6-diazido-1,4-benzoquinones.[214] Subsequent [2+2] cycloaddition of tetramethylethylene provided a tetramethylcyanocyclobutanone, e.g., **452**. The cyano group facilitates the nucleophilic ring opening upon reaction with aniline. In a Michael addition of the resulting amide nitrogen to the cyanoallene unit in **453**, the substituted lactam **454** is formed in 73% yield. Similarly, other lactams or lactones (by reaction with hydroxide) are accessible. Alternatively, methanolate-induced ring opening produced an acyclic ester in 95% yield.

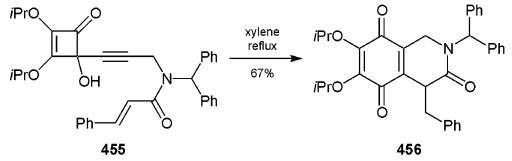
Wipf and Hopkins extended the well-known ring expansion of squaric acid derivatives to the synthesis of dihydroisoquinoline-3,5,8-triones.[215] While previously reported synthetic routes often involved low-yielding multistep sequences, this cyclobutenone ring enlargement with subsequent annelation proceeded in yields of up to 67%. The appropriate squaric ester

Scheme 158



was generated by addition of an unsaturated *N*-propargylic acid amide (Scheme 159). The double

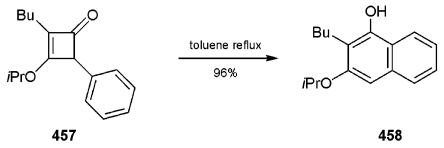
Scheme 159



bond in the side-chain enables the intermediate to close the second ring, presumably along a radical pathway. The thermal ring enlargement of the 4-alkynyl-4-hydroxycyclobutenone **455** afforded the dihydroisoquinoline-3,5,8-trione **456** (67%).

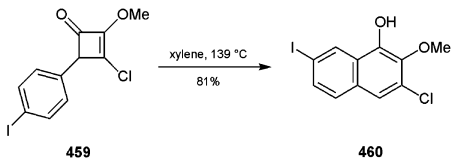
The thermal rearrangement of 4-allyl-4-arylcyclobutenones to annelated cyclopentenols as well as naphthols, especially in cases of electron-rich aryl groups, was already mentioned above (see Scheme 110).[152] In addition, the thermal reaction of 2-alkyl- and 2-aryl-3-alkoxy-4-arylcyclobutenones as well as of a 3-amino-2,4-diarylcyclobutenone also led to substituted naphthols as shown by Turnbull and Moore. For example, 2-*n*-butyl-3-isopropoxy-4-phenyl-2-cyclobutenone (**457**) was ring expanded regioselectively to the naphthol derivative **458** in 96% yield.[216]

Scheme 160



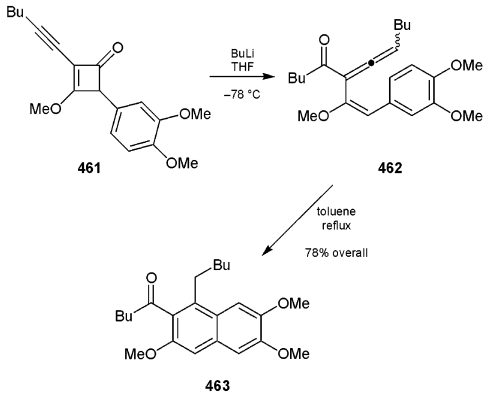
Schmidt et al. published the ring expansion of 4-aryl-3-chloro-2-(hydroxy or methoxy)cyclobutenones in boiling xylene to give 3-chloro-1,2-dihydroxynaphthalenes. Various examples were tested with yields ranging from 56 to 82%. Thus, the iodonaphthalene **460** was obtained from **459** in 81% yield.[217]

Scheme 161



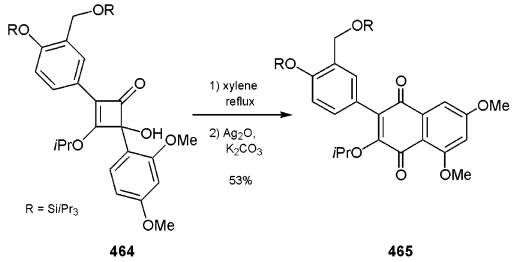
A stereocontrolled synthesis of substituted naphthols by electrocyclization of intermediate conjugated allenes with a terminal aryl substituent was also reported by Turnbull and Moore.[218] Initially, the addition of an organolithium reagent to 2-alkynyl-4-arylcyclobutenones such as **461** led to a lithium cyclobutenolate that underwent conrotatory electrocyclic ring opening. The resulting enolate afforded 3-acyl-4-alkoxy-5-aryl-1,2,4-(*E*)-pentatriene **462** in good yields upon protonation. Subsequent electrocyclization furnished the functionalized naphthalene upon heating. For example, the trimethoxy-substituted naphthyl ketone **463** was obtained from **461** in 78% overall yield.

Scheme 162



A naphthoquinone which was prepared from an appropriate 3-alkoxy-2,4-diaryl-4-hydroxycyclobutenone, served as a suitable precursor for a pyran-annelated naphthoquinone due to the second aryl substituent at C-2. For example, the substituted naphthoquinone **465** was obtained from **464** upon heating in boiling xylene, followed by oxidation with silver oxide. Additionally, subsequent photoannelation provided the skeleton of naphthgeranine E, a bioactive naphthoquinone from *Streptococcus violaceous*.[219]

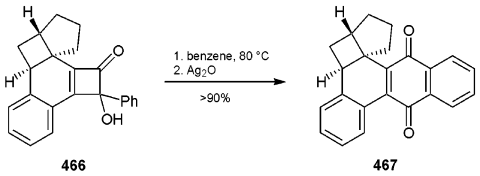
Scheme 163



Analogously, 4-aryl-4-acetoxy-2-acyl-3-aminocyclobutenones gave the hydroquinones as expected. However, with an electron-donating 4-dimethylaminophenyl substituent at C-4, a furan derivative is formed.[220] The hexacyclic quinone **467** was accessible in more than 90% overall yield upon final oxidation with Ag_2O of the thermal ring-expansion product of the pentacyclic 4-hydroxy-4-phenylcyclobutenone **466**. Strikingly, the remaining cyclobutane moiety in **467** can be photofragmented with visible light to give the basic framework of angucycline antibiotics, i.e., the benzo[*a*]anthracene-7,12-dione unit.[221]

As mentioned in section 2.1, the palladium(II)-catalyzed ring-expansion reactions involve a similar

Scheme 164

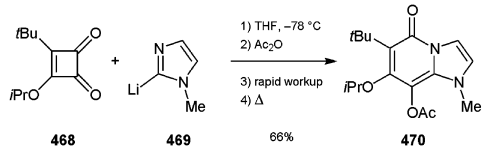


466 467

four- to six-membered ring enlargement leading to cyclohexanones from appropriate cyclobutanols in good yields (see Scheme 36).[60]

To extend the scope of cyclobutenedione-based ring expansions to six-membered carbo- and heterorings, Liebeskind and Liu started from monosubstituted cyclobutenediones bearing a stabilizing *tert*-butyl- or trimethylsilyl substituent which exhibit high regioselectivity. After highly regioselective alkenylation or (het)arylation, rapid workup, and thermal rearrangement, the ring expanded benzannelation products were formed in moderate to very good yields up to 97%. Thus, the annelated pyridone **470** was prepared in 66% yield starting from 4-*tert*-butyl-3-methylcyclobutenedione **468** and 2-lithio-1-methylimidazole **469**.[222] Subsequently, even the nonfused parent (dihydro)pyridinones were synthesized in good yields (using lithiated *N*-Boc-dimethylamine).[223]

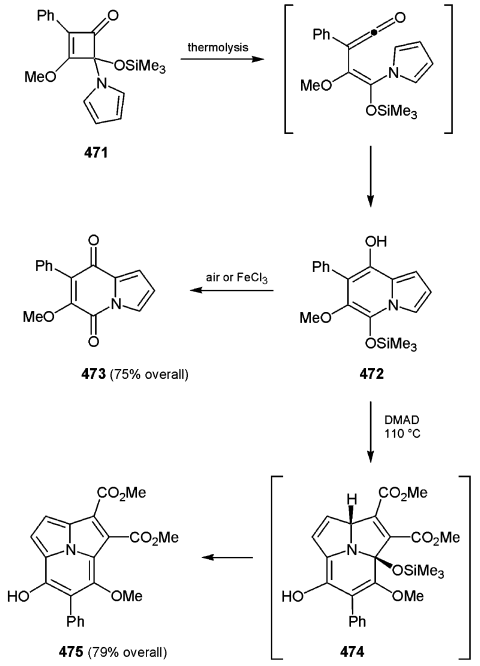
Scheme 165



468 469 66% 470

An interesting variant of the thermal ring enlargement of 4-alkenyl- or 4-(het)aryl-4-hydroxycyclobutenones was reported by Yerxa and Moore in 1992. Starting from appropriate silyl-protected 4-hydroxy-4-(1-pyrryl)cyclobutenone derivatives such as **471**, 5-hydroxy-8-trimethylsilyloxyindolizine **472** was obtained upon heating. Further oxidation produced the unique indolizine-5,8-dione **473** (75% overall yield). Alternatively, **472** can be trapped by dimethyl acetylene dicarboxylate (DMAD) to give a cyclo[3.2.2]azine **474** in an [8+2] cycloaddition. Subsequent elimination of trimethylsilanol led to cyclazine **475** in 79% overall yield.[224]

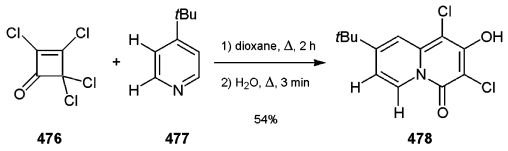
Scheme 166



471 473 (75% overall) 472 475 (79% overall) 474

Schmidt and Duemmler reported the synthesis of 4-quinolizinones from a 4-substituted pyridine and tetrachlorocyclobutenone (**476**). Thermal ring opening, *N*-attack, recyclization, and subsequent partial hydrolysis afforded the structurally interesting ring-enlarged products. For example, **476** and 4-*tert*-butylpyridine (**477**) gave the 8-*tert*-butyl-1,2,3-trichloroquinolizin-4-one (**478**) in 54% yield.[225]

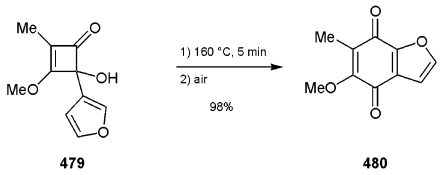
Scheme 167



476 477 478

A variety of (hydro)quinones (naphtho-, pyrrolo-, furo-, or pyridinoquinone) was synthesized by Liebeskind et al. starting from appropriate 4-(het)aryl-4-hydroxycyclobutenones, which were also obtained from the corresponding cyclobutenedione by addition of the (het)aryllithium reagent.[226–228] The resulting hydroquinones were subjected to oxidation, usually with air. The synthetically promising furoquinone **480** was obtained in 98% yield (Scheme 168).[226] At

Scheme 168



479 480

the same time, Moore et al. published the synthesis of benzoquinones[229] and annelated derivatives.[230] Analogously, the thermal ring enlargement of 4-(het)-aryl-4-hydroxycyclobutenones provided benzo- and naphthoquinones (up to 87% yield), furoquinones (94%), or a thiophenoquinone (84%).

Starting from azabicyclic cyclobutenones, Liebeskind and Zhang opened a synthetic access to the corresponding quinolinoquinones and 1,2,3,4-tetrahydroquinolinoquinones (71–91% yield).[231]

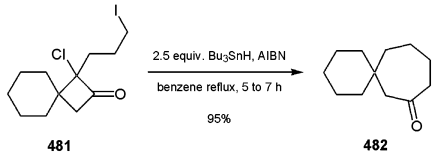
In extension, this synthetic methodology has also been used in combinatorial syntheses. Tempest and Armstrong generated 4-aryl-3-isopropoxycyclobutenediones on solid support through lithium–halogen exchange or Stille coupling of a resin-bound halobenzene. After regioselective 4-addition of aryllithium reagents, the well-known ring enlargement was initiated refluxing in toluene.[232]

3. Seven-Membered Rings

Zhang and Dowd reported a free-radical ring-enlargement reaction starting from spiroannelated 2-chloro-2-[ω-iodoalkyl]cyclobutanones to provide a variety of ring expanded, seven- and eight-membered

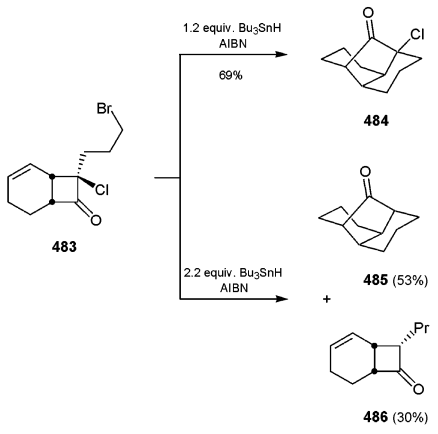
systems. Initial deiodination with tributyltin hydride and subsequent radical attack at the carbonyl group provided the ring enlarged, chlorinated or, alternatively dechlorinated ketone, depending on the employed amount of the tin hydride. For example, the 2-chloro-2-iodopropyl cyclobutanone **481** afforded the spiro[5.6]dodecan-8-one (**482**) in 95% yield.[233]

Scheme 169



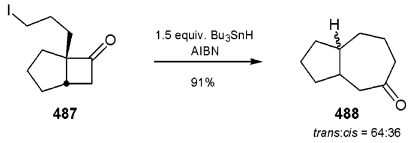
Dowd's free-radical rearrangement methodology shows broad applicability.[11] For example, a structurally interesting tricyclic ketone was obtainable from an *endo*-bromopropylbicyclo[4.2.0]oct-2-ene-7-one. Using a slight excess of tributyltin hydride (1.2 equivalents) together with AIBN as the radical source, the bicyclic ketone **483** gave the chlorinated carbonyl compound **484** in 69% yield. Further dehalogenation of this tricyclic ketone was observed upon treatment with 2.2 equivalents of Bu_3SnH to give **485** in 53% and, additionally, the reduced starting material 8-propylbicyclo[4.2.0]oct-2-en-7-one (**486**).[234] The radical ring enlargement of structurally similar bicyclic compounds with an additional bridgehead silyloxy group afforded the corresponding silyloxybicyclo[6.4.0], [5.4.0], and [5.5.0] ketones with up to 56% yield. The latter are useful precursors for unsaturated cyclic ketones, i.e., undecenones and dodecenones.[235] Additionally, starting from annelated methylenecyclobutanes (prepared by Nysted-methylenation of the corresponding annelated cyclobutanone) with an adjacent bromopropyl side chain, the free radical ring expansion provided *cis*-fused methylenecycloheptanes in up to 92% yield.[236]

Scheme 170



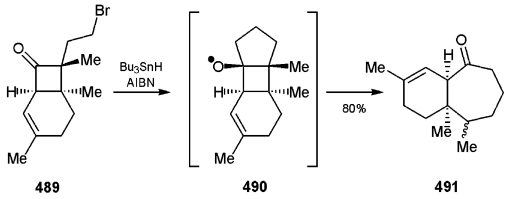
As an extension of this free radical reaction, similar annelated cyclobutanone derivatives with an ω-haloalkyl side chain at a bridgehead carbon led to mixtures of *cis*- and *trans*-fused seven- and eight-membered ring cycloalkanones. For example, the bicyclo[3.2.0]heptanone **487** gave the octahydroazulen-3-one (**488**) in 91% yield as a mixture of isomers.[237]

Scheme 171



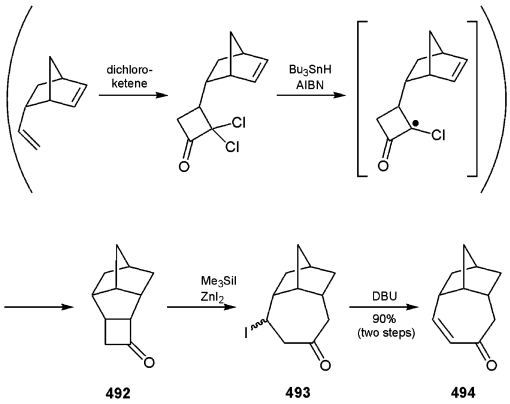
In addition to the synthesis of the sesquiterpene FS-2, Ziegler et al. reported the ring cleavage of the cyclobutoxy radical **490** affording a cyclohexene-annelated cycloheptanone **491**. This bicyclic ketone was obtained in 80% yield as the ring enlarged product starting from the appropriate bromoalkyl-substituted bicyclo[4.2.0]oct-2-en-8-one **489** upon treatment with tributyltin hydride/AIBN.[238]

Scheme 172



Dowd et al. reported the trimethylsilyl iodide-promoted ring opening of annelated cyclobutanones such as **492** to ring enlarged and bridged cyclic ketones.[239,240] The structurally interesting tetracyclic **492** was prepared from 5-vinylnorbornene and dichloroketene with subsequent radical ring closure (Scheme 173). Upon treatment with Me_3SiI/ZnI_2, the tricyclic

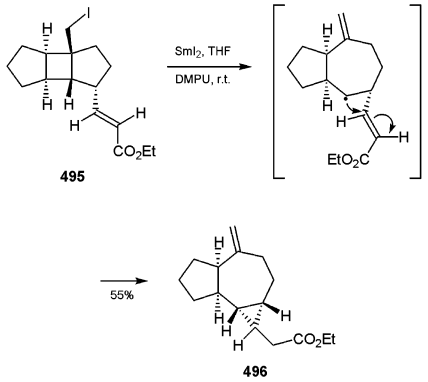
Scheme 173



3-iodocycloheptanone **493** was formed which eventually gave the conjugated cycloheptenone **494** upon elimination of HI by means of DBU. As an alternative, reductive removal of the iodide furnished the saturated cyclic ketone.

A radical fragmentation/cyclization sequence of a bisannelated iodomethylcyclobutane was published by Lange and Merica for the synthesis of the aromadendrane carbon skeleton.[241,242] Upon treatment with samarium diiodide, the depicted epimer of **495** (Scheme 174) underwent ring enlargement to a cyclopentane-annelated cycloheptyl radical which subsequently formed the fused cyclopropane moiety by 3-*exo*-*trig*-cyclization to give **496** in 55% yield. Starting from another epimer, a mixture of three products (51% in summa) with the corresponding

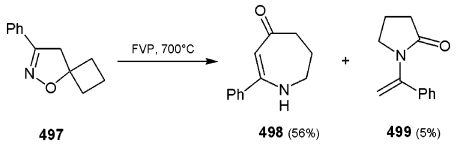
Scheme 174



annelated cyclopropadecahydroazulene as the main compound (25%) was formed.

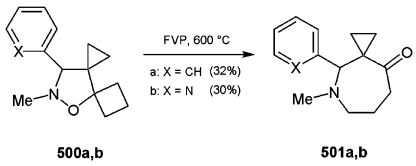
Goti et al. investigated the thermal rearrangement of 4,5-dihydro and tetrahydroisoxazole-5-spirocyclobutanes, which proceeds via initial N−O bond cleavage, subsequent opening of the cyclobutane ring, and final ring closure of the C,N-diradical. For example, 7-phenyl-5-oxa-6-aza-spiro[3.4]oct-6-ene (**497**) gave 2-phenyl-1,5,6,7-tetrahydro(4*H*)azepin-4-one (**498**) in 56% (as well as 5% 1-(1-phenylvinyl)pyrrolidin-2-one (**499**) as a byproduct) upon heating under FVP conditions (700 °C).[243]

Scheme 175



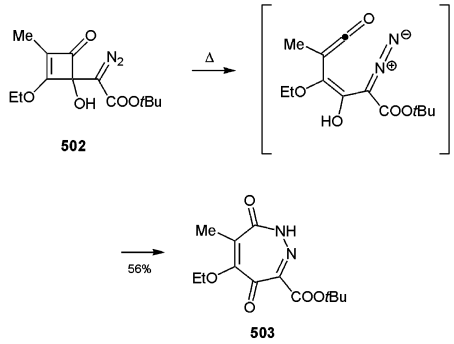
In 2001, de Meijere and Brandi et al. reported the thermal ring enlargement of aryl-substituted dispiro-[2.0.3.3]oxazadecanes, e.g., **500a**,**b**.[244] Under flash vacuum thermolysis conditions (600 °C), the rearrangement of the cyclobutyl ring led exclusively to the azepan-4-ones **501a**,**b** (see Scheme 176).

Scheme 176



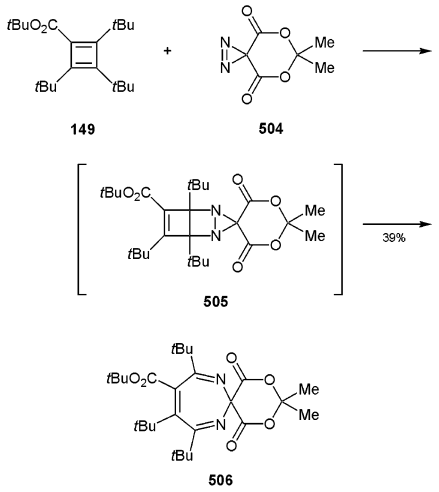
A novel method for the ring enlargement of 4-hydroxy-2-cyclobutenones with a diazo group attached to the C-4 side chain was developed by Ohno and Eguchi.[245] Whereas the acid or rhodium(II)-catalyzed (or photolytical) reaction of such substrates led to five-membered ring systems, i.e., 4-cyclopentene-1,3-diones and/or 5-methylene-(5*H*)-2-furanones, this thermal rearrangement provided a seven-membered ring. For example, the highly functionalized 4-hydroxy-2-cyclobutenone **502** exclusively gave the diazepinedione **503** in 56% yield upon heating in refluxing xylene. This ring-expansion reaction proceeds via sequential 4π- and 8π-electrocyclic ring opening and closure.

Scheme 177



In extension to previous work leading to dihydrodiazepines, Regitz et al. published the [4+2] cycloaddition of diazirines to a kinetically stabilized cyclobutadiene affording 5*H*-1,3-diazepines after rearrangement of the initially formed diazatricyclic system. For example, the highly substituted cyclobutadiene **149** reacts with the spirocyclic diazirine **504** to give the dioxospiro-diazepinedioxane **506** in 39% yield via the spirotricyclic intermediate **505**.[246]

Scheme 178

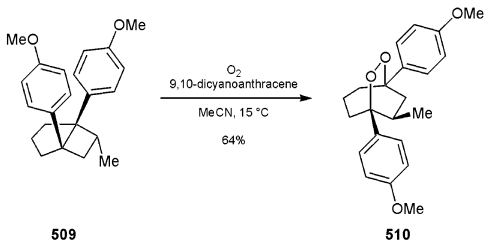


Martin et al. reported the synthesis of dihydrodiazepines by thermal rearrangement of the cycloadduct of ethyl diazoacetate and a bissulfonyl-activated cyclobutene.[247] For example, the 2,3-diazabicyclo-[3.2.0]heptene **507** provided ethyl-4,4-dihydro-3,6-bis-(phenylsulfonyl)-1-*H*-1,2-diazepine-7-carboxylate (**508**) in 82% yield.

Scheme 179

In a photooxygenation reaction sensitized by 9,10-dicyanoanthracene, 1,5-bis-(4-methoxyphenyl)-6-*endo*-methylbicyclo[3.2.0]heptane (**509**) underwent ring enlargement by insertion into the zero-bridge (Scheme 180). The substituted 6,7-dioxabicyclo[3.2.2]nonane **510** was obtained in 64% yield, selectively with *syn*-stereochemistry.[248]

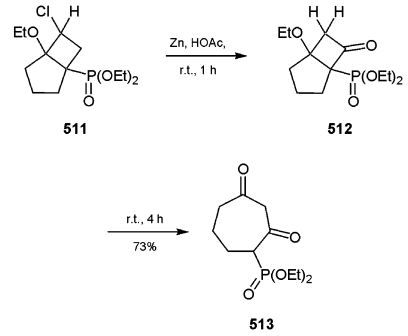
Scheme 180



509 510

During the investigation of [2+2] cycloadditions of cyclic β-alkoxyvinyl phosphonates to activated ketenes, Ruder and Ding reported the fragmentation of the resulting phosphonated 7-oxobicyclo[3.2.0]heptane derivatives, such as **511**, to ring-enlarged diketones.[249] For example, the (2,4-dioxocycloheptyl)-phosphonic acid diethyl ester (**513**) was generated from the chlorinated bicyclo[3.2.0]hept-1-ylphosphonic acid diethyl ester **511** in a cascade reaction initiated by zinc in acetic acid. In this one-pot procedure at ambient temperature, dechlorination to give **512** as well as ether cleavage occurred, leading to the ring enlarged diketone **513**.

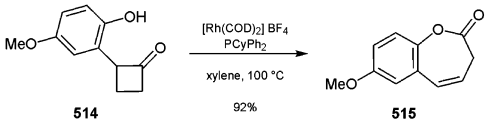
Scheme 181



511 512 513

Cyclobutanones, formed by [2+2] cycloaddition of *ortho*-methoxystyrenes to dichloroketene and subsequent dechlorination with zinc in acetic acid, was reported by Murakami et al. to be appropriate starting materials for a rhodium-catalyzed formation of benzoannelated lactones.[250] In addition to five- and six-membered ring lactones obtained in boiling xylene, cyclobutanones with an aryl unit at C-2, e.g., **514**, react in the presence of $[Rh(COD)_2]BF_4$, a phosphine ligand, and under CO atmosphere to give the unsaturated seven-membered lactone ring **515** in 92% yield.

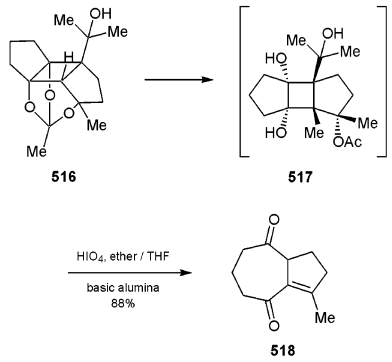
Scheme 182



514 515

Lange and Merica reported in 1998 a formal synthesis of compressanolide employing the ring enlargement of an annelated cyclobutane derivative.[251] The cyclobutanediol derivative **516**, along with elimination of the acetate substituent in **517**, was cleaved with periodic acid/basic alumina to give the A/B ring systems of abeotaxanes, and the skeleton of compressanolide, respectively. The yield of the bicyclic cycloheptane-1,4-dione **518** was 88%.

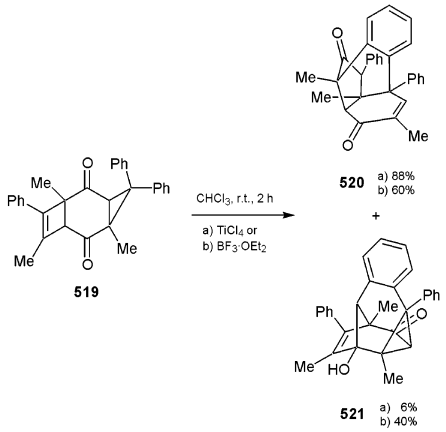
Scheme 183



516 517 518

The tricyclic enedione **519**, a cyclobutene-fused homoquinone, underwent a novel Lewis acid-mediated skeletal rearrangement to provide bi- to pentacyclic cage-like diketones or keto alcohols depending on the Lewis acid used (see Scheme 184). The

Scheme 184

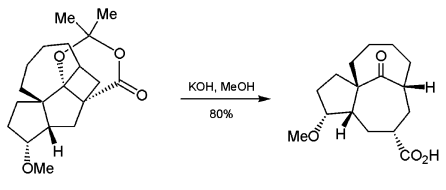


519

diketone **520** is formed from cleavage of the cyclopropyl ring and cyclization, whereas in the case of the pentacyclic keto alcohol **521** the multistep reaction involves vinyl migration and electrophilic attack of an intermediate carbocation. Mechanistic details are given in the literature.[252]

Toward the synthesis of C-3 oxygenated ingenane congeners, Winkler et al. prepared the pentacyclic precursor **522** which on treatment with aqueous potassium hydroxide gave exclusively the substituted tricyclo[7.4.1.$0^{1,5}$]tetradecane-7-carboxylic acid **523** in 80% yield.[253]

Scheme 185

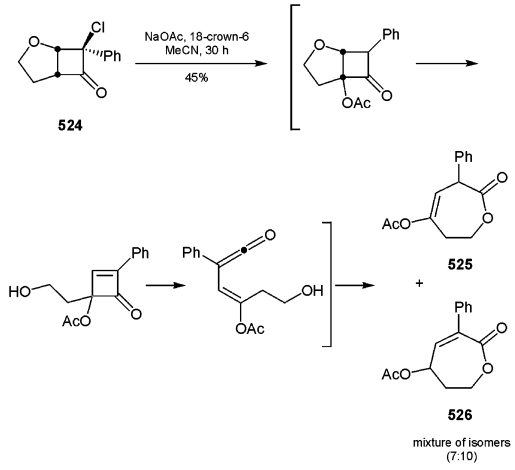


522 523

Hassner and Naidorf-Meir reported a nucleophile-initiated cascade reaction leading to unsaturated lactones instead of an expected *cine* substitution

product. The latter is formed only in the case of cyclohexane-annelated cyclobutanones. For example, upon addition of sodium acetate as the nucleophile, the tetrahydrofuran-annelated 2-chloro-2-phenylcyclobutanone **524** gave an isomeric mixture of the unsaturated seven-membered ring lactones **525** and **526** via a vinylketene intermediate and subsequent intramolecular ring closure. Further treatment of this mixture with triethylamine in refluxing acetonitrile led to complete isomerization to the enone **526**.[27,254]

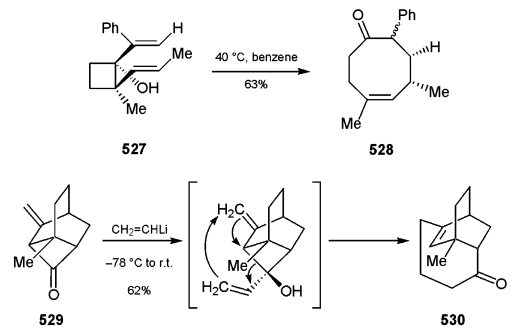
Scheme 186



4. Eight-Membered Rings

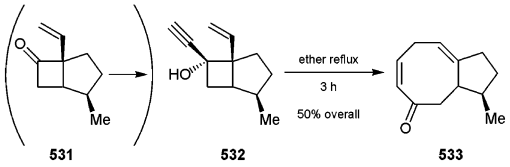
Miller and Gadwood offered a facile route to substituted cyclooctenones by reacting a 2-methyl-2-alkenylcyclobutanone with various alkenyllithium and metalated alkynyl reagents to give the corresponding 1,2-dialkenyl- or alkenylalkynylcyclobutanols. The in situ oxy-Cope rearrangement of **527** led to 4,6-dimethyl-2-phenylcyclooct-5-enone (**528**) in 63% yield. Substituent effects on the rate of this rearrangement were monitored. In comparison to the alkenylalkynyl compounds, the dialkenylcyclobutanols rearrange faster.[255] In an attempted synthesis of seychellene starting from cyclobutanone **529**, Snider and Beal embedded the 1,2-dialkenylcyclobutanol into a tricyclic system which gave rise to 1-methyltricyclo[6.4.0.0^{3,10}]dodec-2-en-7-one (**530**) in 62% yield.[256]

Scheme 187



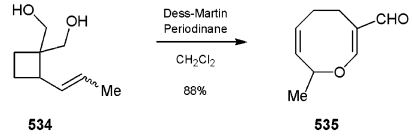
The oxy-Cope rearrangement of an intermediate cyclopentane-annelated 1-ethynyl-2-ethenylcyclobutanol derivative was published by Gadwood et al. as the key step in the synthesis of the cyclooctanoid sesquiterpene skeleton of marine origin. The bicyclic enyne **532** (isolated from the reaction of 2-methyl-5-ethenylbicyclo[3.2.0]heptan-6-one (**531**) with ethynyllithium) without purification led to the cyclopentacyclooctadienone **533**, the carbon framework of poitediol, dactylol, and precapnelladiene.[257]

Scheme 188



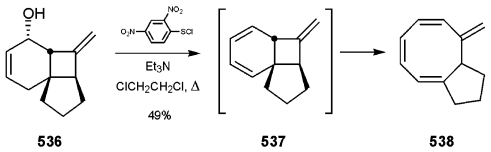
Boeckman et al. reported in 1993 the *retro*-Claisen rearrangement of formylated and alkenyl-substituted strained cycloalkane derivatives. The oxidation of 1,1-bishydroxymethyl-2-propenylcyclobutane (**534**) with Dess−Martin periodinane as oxidizing agent to the corresponding bisaldehyde allows the subsequent ring-enlargement reaction to 8-methyl-5,8-dihydro-4*H*-oxocine-3-carbaldehyde (**535**) in 88% yield.[258]

Scheme 189



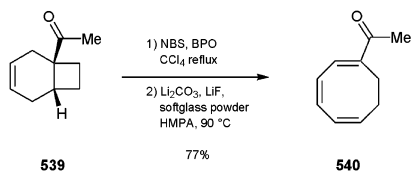
An unusual product of Paquette's squarate ester cascade methodology was already shown in Scheme 112, i.e., a cyclooctaoxazoledione **322**, obtained by sequential addition of two different vinyl anions to dimethyl squarate (**162**).[157] Wang and Paquette reported the thermal ring enlargement of the intermediate tricyclic triene **537** (generated from the alcohol **536**), which exclusively led to 7-methylenebicyclo[6.3.0]undeca-1,3,5-triene (**538**) in 49% yield.[259]

Scheme 190



In 1996, Takeda and Fujiwara published the ring-enlargement reaction of cyclohexene-annelated cyclobutyl ketones providing cyclooctatrienyl ketones. For example, using an allylic bromination/dehydrobromination sequence, **539** was converted to 1-cycloocta-1,3,5-trienylmethyl ketone (**540**) in 77% yield.[48]

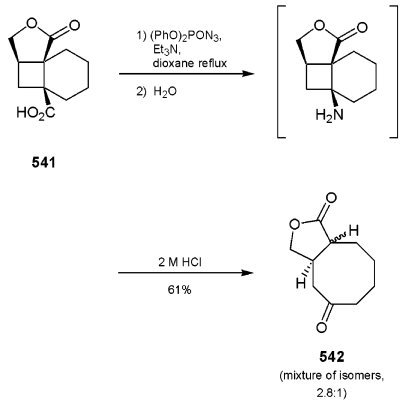
Scheme 191



Booker-Milburn et al. developed a Curtius-type rearrangement of a lactone-annelated tricyclic cyclobutane carboxylic acid **541** using diphenylphos-

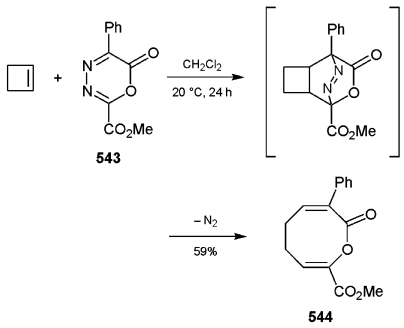
phoryl azide in refluxing dioxane. Subsequently, in the presence of water the intermediate bisannelated cyclobutylamine undergoes an aza de Mayo-type fragmentation to give the ring expanded bicyclic cyclooctanone **542** as a mixture of isomers in 61% yield (*cis:trans* 2.8:1).[260]

Scheme 192



Oxadiazinone derivatives bearing nitrogen and carbon dioxide as potential leaving units can serve as reactive heterodienes in Diels−Alder reactions with activated cycloalkenes. Under selective extrusion of nitrogen, these compounds represent interesting building blocks in lactone syntheses. Reacting oxadiazinone **543** with cyclobutene, Christl et al. obtained the desired cycloaddition product 5,8-dihydro-8-oxo-7-phenyl-4*H*-oxocine-2-carboxylic acid methyl ester (**544**) in 59% yield.[261]

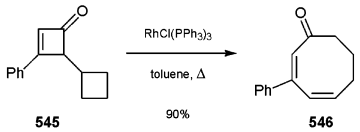
Scheme 193



A similar eight-membered ring lactone, i.e., **30**, was prepared from the phenylthio-substituted cyclobutenone **27b** in 100% yield as reported by Hassner et al. (see Scheme 8).[26]

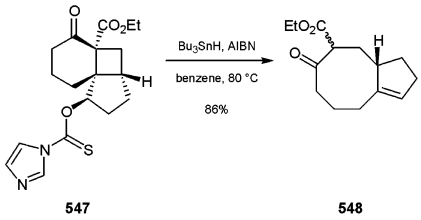
Huffman and Liebeskind reported the rhodium(I)-catalyzed ring fusion of a 4-cycloalkylcyclobutenone to give cyclohepta- or cyclooctadienones. In the case of a cyclobutylcyclobutenone, the initial ring opening required triphenylphosphine as the donor ligand. The phenyl derivative **545** gave regioselectively the conjugated 3-phenylcycloocta-2,4-dienone (**546**) in 90% yield.[262]

Scheme 194



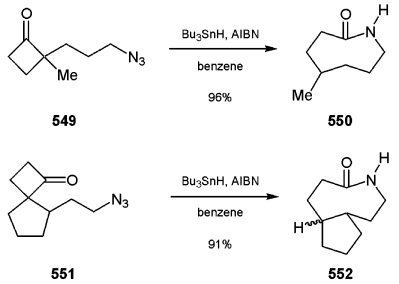
Crimmins et al. reported the rearrangement of cyclobutylcarbinyl radicals from a thiocarbamate precursor leading either to bicyclic or spirocyclic ketones depending on the ring size of the appropriate cycloalkanone and the position of the thiocarbamate. The reaction pathway involves a sequential alkoxy-radical fragmentation/enlargement. For example, the cyclopentene-fused octanone **548** was obtained in 86% yield starting from the tricyclic cyclohexanone **547**.[263] A similar transformation was reported with the thiocarbamate of a substituted octahydrocyclobuta-[1,2:1,4]dicyclopenten-3-one which led to an 8-oxospiro-[4.5]dec-1-ene in 92% yield.[264]

Scheme 195



A radical ring expansion leading to lactams developed by Kim et al. involves an aminyl radical cyclization. The formal ring enlargement of the substituted cyclobutanone **549** led to the eight-membered lactam **550** in excellent yield (96%) using tributyltin hydride as the initiating radical source. Employing the spirocyclobutanone **551** as starting material, the structurally interesting fused lactam **552** was obtained in 91% yield.[265]

Scheme 196

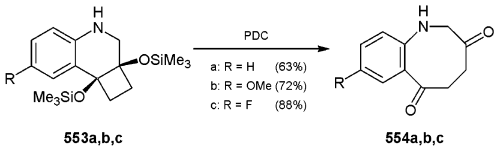


The free-radical promoted ring-enlargement reaction starting from spiroannelated (2-chlorinated) 2-[ω-iodoalkyl]cyclobutanones with an appropriate side-chain length can also provide eight-membered rings (see Scheme 169).[233,237]

In the course of their studies toward the cycloaddition of *N*-methyleneanilines as azadienes to 1,2-bis(trimethylsilyloxy)cyclobutene, Ha et al. also developed oxidative ring expansion of the cycloadducts, i.e., substituted hexahydrocyclobuta[*c*]quinoline derivatives **553**.[266] Using PDC as the oxidant, these intermediate tricyclic species were enlarged to the corresponding 1,2,4,5-tetrahydro-1-benzazocine-3,6-diones **554** in 69−88% yield depending on the substituent attached to the aryl unit. This reaction opens up an efficient way to 1-benzazocines, some of which are biologically active.

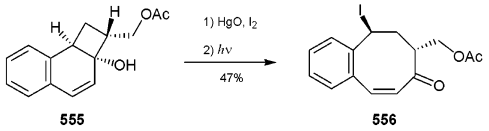
In comparison to the photolytic ring cleavage of tertiary cyclobutanols fused to an *ortho*-naphthoquinone, which led to tetrahydrofurans,[170] the pho-

Scheme 197



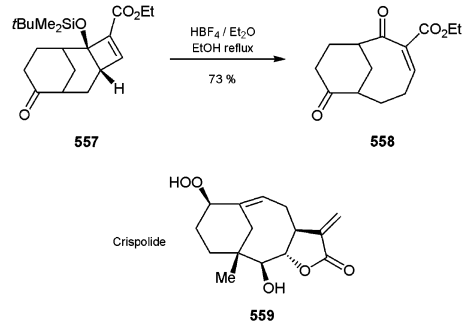
toadducts of enolized tetralones with either methyl acrylate or acrylonitrile gave benzoannelated eight-membered ring derivatives.[267] The cyclobutanol **555** gave the bifunctional benzocyclooctadienone **556** in 47% yield upon treatment with HgO/I_2 under irradiation conditions. In addition, starting from an α-tetralone, the cyclooctadienone serves as an intermediate that undergoes ring contraction to a benzohomotropone. This ring-expansion methodology was extended to the synthesis of benzoannelated cycloheptadienones and cyclononadienones, starting from *β*-indanone and *β*-suberone.[268]

Scheme 198



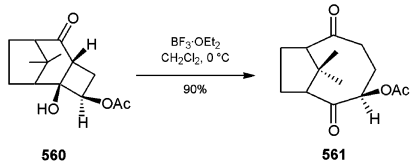
Mislin and Miesch applied a ring expansion to an eight-membered ring system using HBF_4/diethyl ether in refluxing ethanol.[269] The annelated cyclobutene carboxylic ester **557** undergoes fragmentation to the cyclooctenone **558** in 73% yield, forming the bicyclo[5.3.1]undecane subunit of naturally occurring products such as taxanes or crispolide (**559**).

Scheme 199



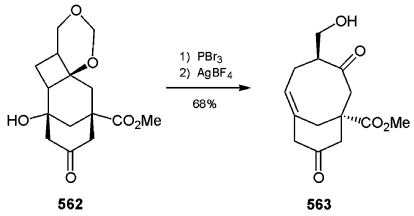
During the synthesis of the A and B rings of the taxane skeleton, Fetizon et al. used the cycloaddition step of a de Mayo reaction to build up an annelated cyclobutanol derivative. The subsequent *retro*-aldol like cyclobutane ring cleavage of the monoacylated tricyclic cyclobutanediol **560**, with boron trifluoride as the Lewis acid, led to the taxane fragment **561** in 90% yield.[270]

Scheme 200



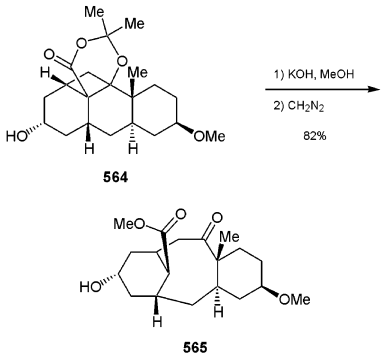
Kraus and Zheng constructed the [5.3.1]bicyclic subunit in **563** (68% yield) by fragmentation of a cyclobutane ring, which is annelated to the appropriate bicyclo[3.3.1]nonanone in **562**. The necessary bridgehead carbocation is generated by means of silver tetrafluoroborate after bromination of the ketol **562**.[271]

Scheme 201



The eight-membered ring of the taxol system was synthesized by Winkler and Subrahmanyam upon cleavage of the hexasubstituted bond in an embedded *δ*-lactone. The depicted epimer (with respect to the hydroxy group, see Scheme 202) of the taxane pre-

Scheme 202

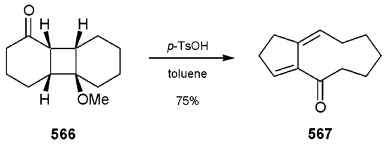


cursor **564** yielded exclusively the ring enlarged product **565** as a single diastereomer (82%) upon treatment with 2 N KOH in MeOH at 25 °C and subsequent reaction with diazomethane after acidic workup. However, the other epimer gave a 1:1 mixture of the expected diastereomers as well as a lactone which was formed with the hydroxy group.[272]

5. Nine-Membered Rings

Caubere et al. published in 1991 the formation of bicyclo[7.3.0]dodeca-8,12-diene-2-one (**567**) by acid-catalyzed rearrangement of the tricyclic bisannelated cyclobutanol derivative **566**. The use of *p*-toluenesulfonic acid in toluene furnished the bicyclic ketone **567** in 75% yield.[273]

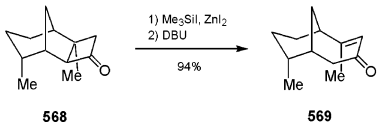
Scheme 203



A bicyclic decenone was prepared by application of the previously mentioned trimethylsilyl iodide promoted ring opening of annelated cyclobutanones to fused and bridged ring enlarged cyclic ketones as reported by Dowd et al.[239,240] (see Scheme 173):

Subjecting 5,9-dimethyltricyclo[4.3.1.0^{2,5}]decan-3-one (**568**) to this ring-expansion reaction the 5,9-dimethylbicyclo[4.3.1]dec-4-en-3-one (**569**) was obtained in 94% yield.

Scheme 204

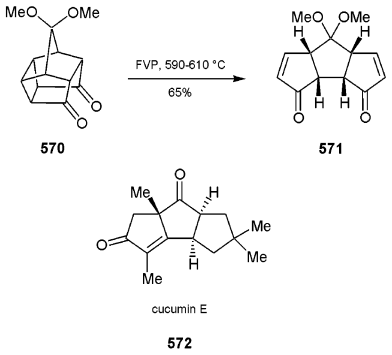


IV. Transformations of Cyclobutane Derivatives in Natural Product Syntheses

A. Ring-Opening Reactions

In 2001, Mehta et al. published the synthesis of the natural triquinane cucumin E (**572**).[274] A thermal cycloreversion of **570**, induced by flash vacuum pyrolysis (590−610 °C, 0.01 Torr) as the key step, furnished the highly functionalized carbon skeleton **571** in 65% yield. This strategy was also applied to the synthesis of similar triquinanes with up to quantitative yields, especially in the case of a hirsutene precursor.[275]

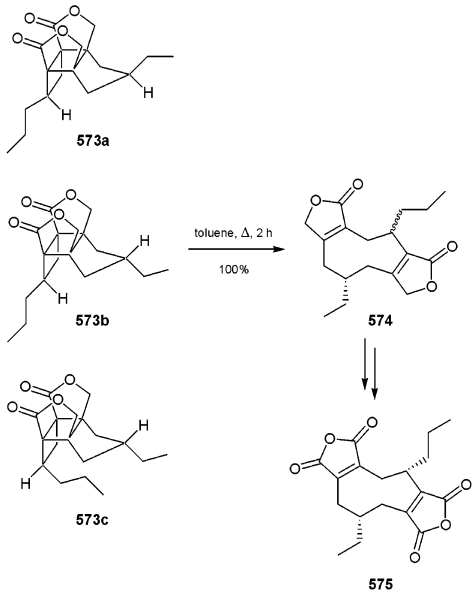
Scheme 205



White et al. also used a thermal cycloreversion in the synthesis of nonadrides such as **575**, which are naturally occurring cyclononadienes fused to two maleic anhydride units.[276] Exposure of a mixture of photoadducts **573a**−**c** to refluxing toluene furnished the cycloreversion product **574** quantitatively via opening of the cyclobutane ring in the orthogonal direction to the photoaddition. Subsequent hydrolysis of the two lactone rings, followed by permanganate oxidation of the carboxylates, provided **575**.

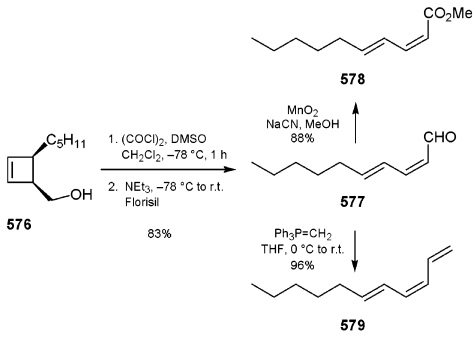
The thermal electrocyclic ring opening of a *cis*-4-alkyl-2-cyclobutene-1-carbaldehyde, generated in situ by Swern oxidation of a *cis*-4-alkyl-1-hydroxymethylcyclobutene at low temperature, gives (2*Z*,4*E*)-alka-2,4-dienals, such as **577**, exclusively. This method was applied by Wallace et al. either to the synthesis of various isomeric, naturally occurring 1,3,5-alkatrienes via Wittig olefination, or to the formation of decadienoates by means of manganese(IV) oxide and sodium cyanide. Thus, from *cis*-1-hydroxymethyl-4-pentylcyclobutene (**576**), the olefinated industrial fragrance **579** is obtainable in 96% yield as well as methyl decadienoate **578** in 88% yield, a pheromone

Scheme 206



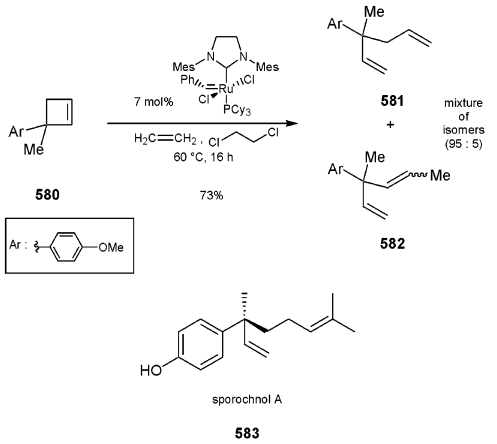
occurring in the forest pest *Pityogenes chalcographus* and in the seeds of the Chinese tallow tree.[277]

Scheme 207



Harrity et al. reported the employment of a cyclobutene ring-opening metathesis (ROM) as a key step in a formal synthesis of (±)-sporochnol A (**583**).[278] The ruthenium-catalyzed ROM of the 3,3-disubstituted cyclobutene **580** with ethylene afforded the natural product precursors **581** and **582** in 73% yield with high regioselectivity (95:5).

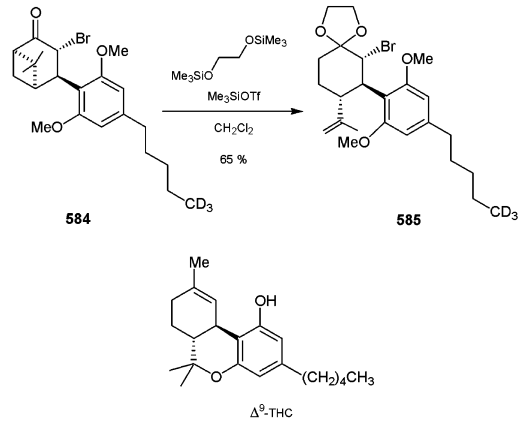
Scheme 208



The regioselective cleavage of the cyclobutane moiety in 4-aryl-3-bromonopinone **584** to give the

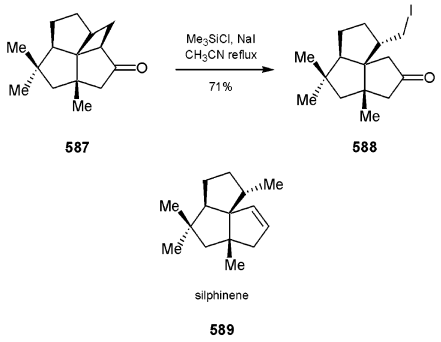
protected arylisopropenylcyclohexanone **585** was published by Tius and Kannangara. The reaction starts with initial *O*-attack of trimethylsilyl triflate at the carbonyl group, followed by cationic ring opening and subsequent generation of the alkene. An excess of bis-(trimethylsilyloxy)ethane provides the ring-opened, acetal-protected product, a direct precursor to derivatives of tetrahydrocannabinol, THC (**586**).[279]

Scheme 209



Crimmins and Mascarella used an intramolecular photocycloaddition/cyclobutane fragmentation pathway for the total synthesis of (±)-silphinene (**589**). The cyclobutyl moiety in a fenestranone **587** was smoothly cleaved by means of trimethylsilyl iodide, prepared in situ from sodium iodide and trimethylsilyl chloride, to provide the iodoketone **588** in 71% yield.[280]

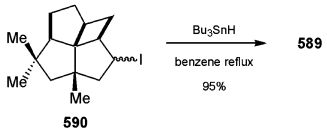
Scheme 210



The direct synthesis of **589** using a similar fenestrane-like iodomethylcyclobutane **590** involves two competitive reaction pathways: The efforts to force back the undesired reduction of the intermediate cyclobutylcarbinyl radical led to a protocol using extremely low concentrations of tributyltin hydride (addition by means of a syringe pump). With this method, silphinene (**589**) was formed in 95% yield from the appropriate iodide **590** in refluxing benzene.[281]

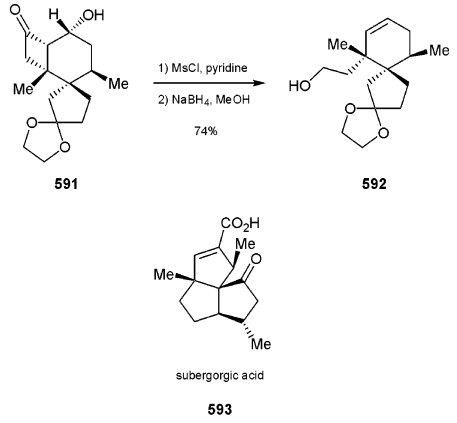
Iwata et al. published the reductive ring opening of a bicyclic cyclobutanol which was generated in situ from cyclobutanone **591** using sodium borohydride after initial mesylation of a β-hydroxy group.[282] The reduction step, associated with the preparation of the cyclobutanol, triggers the ring scission which is

Scheme 211



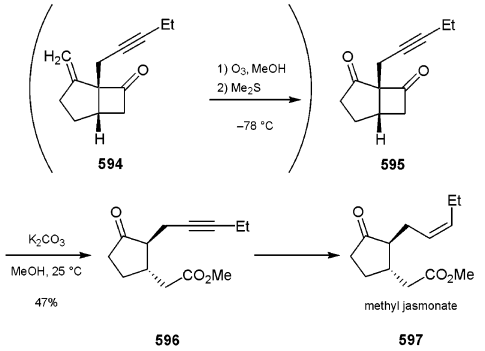
followed by formation of the cyclohexene double bond. Additionally, the sodium borohydride also reduces the intermediate aldehyde to give the product alcohol **592** in 74% overall yield. This spiro compound **592** provides an easy access to subergorgic acid (**593**), a bioactive angular triquinane sesquiterpene isolated from a pacific gorgonian coral.

Scheme 212



Snider et al. subjected the unpurified bicyclic 1,3-diketone **595**, prepared by ozonolysis of the appropriate *exo*-methylene precursor **594**, to a *retro*-Dieckmann condensation using methanolic potassium carbonate. The ring-opening product **596** which was obtained in 47% yield was directly transformed to methyl jasmonate (**597**) upon *cis*-hydrogenation of the triple bond.[283]

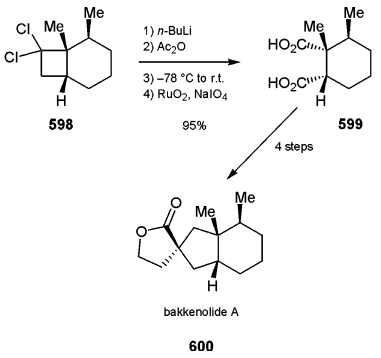
Scheme 213



On an efficient synthetic route to bakkenolide A (identical to fukinanolide) (**600**), a selective cytotoxic sesquiterpene which is known since 1968, Greene et al. used the bicyclic α,α-dichloroketone **598** as an appropriate precursor for the tricyclic terpene.[284] Generating the α-chloroenolate with *n*-butyllithium afforded the corresponding enol acetate upon treatment with acetic anhydride. Completing this novel dicarboxylation procedure[285] the intermediate acetate was subsequently cleaved with ruthenium dioxide-

sodium periodate to give the dicarboxylated cyclohexane **599** in 95% yield.[284]

Scheme 214

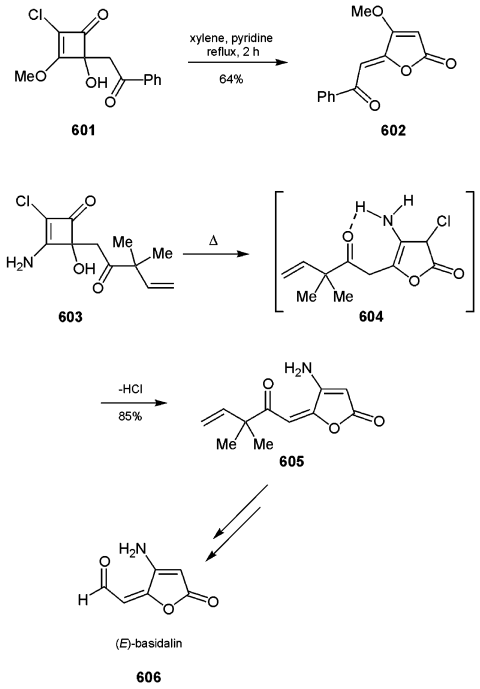


B. Ring-Expansion Reactions

1. Five-Membered Rings

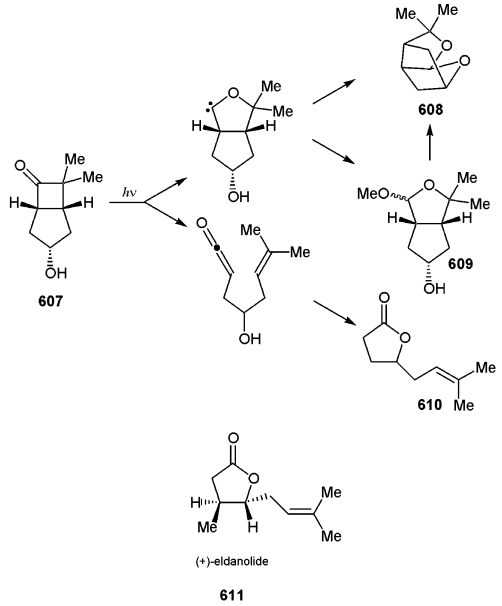
Eguchi et al. reported in 1994 the formal ring enlargement of 3-methoxy- or 3-amino-substituted 4-hydroxy-4-acylmethyl-2-chlorocyclobutenones to tetronates.[286] For example, the highly substituted hydroxycyclobutenone **601** gave the γ-acylmethylenetetronate **602** in 64% yield upon heating in xylene. A similar precursor with an amino group at C-3 as well as a comparable acylmethyl group at C-4 such as in **603** provided a stabilized intermediate **604** leading to the precursor **605** of basidalin (**606**) in 85% yield (two steps away from the natural product).

Scheme 215



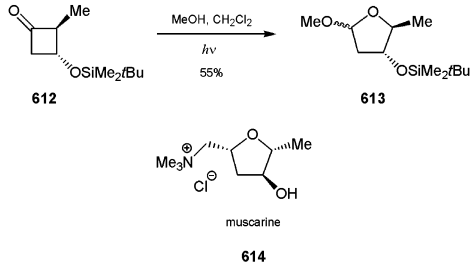
The photochemical ring-opening reaction of the *cis*-fused cyclobutanone **607** was published by Butt and Winders et al. as a key step in the synthesis of eldanolide (**611**). Depending on the solvent, either the tricyclic acetal **608** was obtained via an intermediate oxacarbene or the lactone **610**, providing the eldanolide skeleton. The latter occurred through the intermediacy of a ketene, which is subsequently trapped by an adjacent hydroxy group. When acetonitrile was used as the solvent, **608** was formed in 43% yield with an additional 37% of the γ-lactone **610**. However, in methanol **610** is the main product (41%) accompanied by 5% of **608**. Additionally, a bicyclic acetal **609** initially formed in 30% yield quantitatively rearranged to **608** with time.[287]

Scheme 216



On their synthetic route to muscarine (**614**), Pirrung and DeAmicis presented a ring enlargement of cyclobutanone derivatives.[288] The photochemical ring expansion of 3-(*tert*-butyldimethylsilyloxy)-2-methylcyclobutanone (**612**) with an excess of methanol in dichloromethane at −78 °C provides tetrahydrofuran derivative **613** in 55% yield as a 2:1 mixture of isomers (with respect to the methoxy group at C-5).

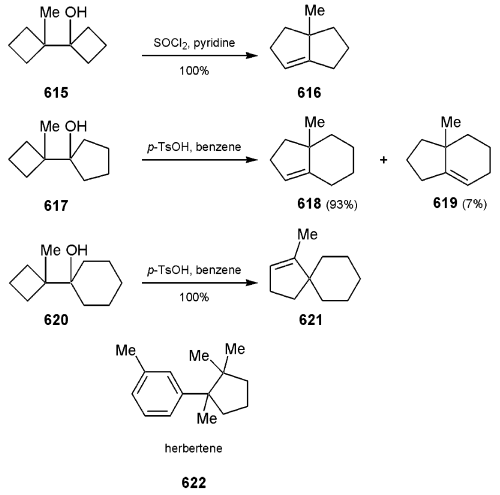
Scheme 217



In 1998, Fitjer and Mandelt reported an acid-catalyzed cascade rearrangement starting from 1-methylcyclobutylmethanols **615**, **617**, or **620** to obtain bi- and spirocyclic cyclopentenes **616**, **618**, and **619**, or **621**, respectively.[289] As an application of the cyclobutylmethyl to cyclopentyl rearrangement, this ring-expansion reaction afforded the depicted cyclopentenes as well as a tolyl derivative similar to herbertene (**622**). Usually, the pure hydrocarbons were obtained, but in one single case (enlargement

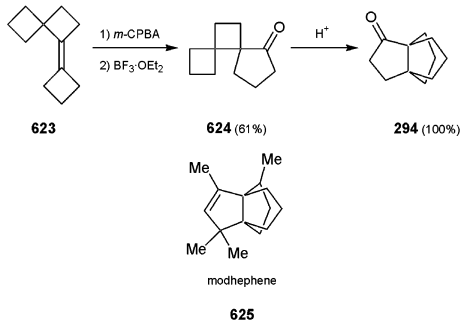
of **615**) the use of thionyl chloride was necessary to circumvent the formation of an alcohol.

Scheme 218



Among other cascade cationic reactions also reported by Fitjers's group, 1-cyclobutylidenespiro[3.3]-heptane (**623**) was epoxidized and subsequently rearranged in situ with boron trifluoride-etherate to give dispiro[3.0.4.2]undecan-6-one (**624**) in 61% yield. Further acid-catalyzed rearrangement by means of Nafion-H in benzene at 70 °C yielded exclusively the [3.3.3]propellane **294**.[290]

Scheme 219

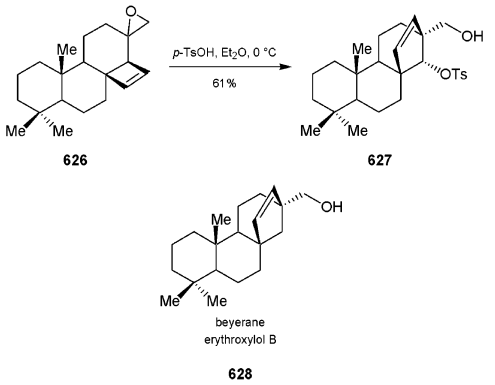


In a similar rearrangement, the natural product modhephene (**625**) was obtained in 62% yield from an appropriate dispiro[3.0.4.2]undecanol.[291] Following this report, such cationic rearrangements were extended to a variety of tricyclopentanoid sesquiterpenes.[292]

In the course of synthetic attempts to C-17 functionalized beyeranes, Abad et al. reported the rearrangement of the depicted 13-epimeric epoxides of this diterpene skeleton. Triggered by attack of *p*-toluenesulfonic acid on the oxirane ring of **626** a cyclobutenyl−cyclopentenyl Wagner-Meerwein rearrangement afforded the monotosylated diol **627** in 61% yield, a closely related precursor to beyeranes such as erythroxylol B (**628**).[293]

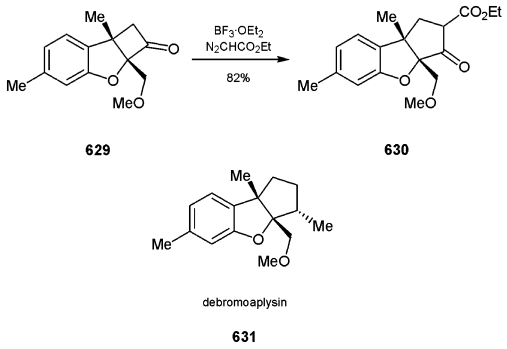
On the synthetic route to the marine sesquiterpene aplysin and related compounds, Venkateswaran et al. used the Lewis acid-promoted homologization of a cyclobutanone to the corresponding cyclopentanone by means of ethyl diazoacetate. The regioselective ring enlargement of **629** in the presence of boron

Scheme 220



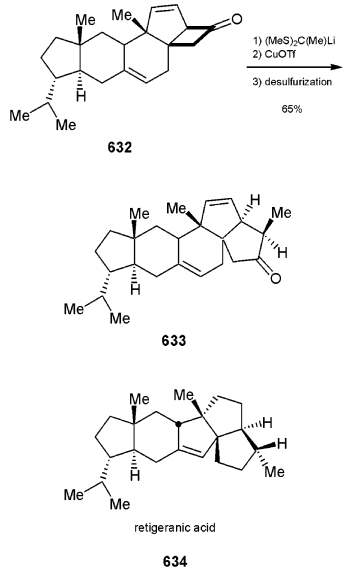
trifluoride-etherate afforded the precursor **630** to debromoaplysin (**631**) in 82% yield.[294]

Scheme 221



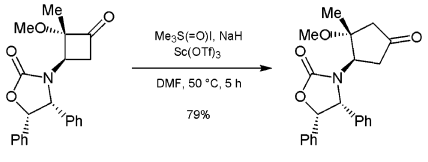
In the course of the synthesis of retigeranic acid (**634**), Corey et al. published the expansion of cyclobutanone **632** (ring E within this natural product skeleton) to the pentacyclic cyclopentanone **633**.[295] After addition of lithiated acetaldehyde dimethyl thioacetal to the carbonyl function of this E ring, the following rearrangement was initiated by cuprous triflate in the presence of triethylamine. After subsequent desulfurization, **633** was obtained in 65% overall yield.

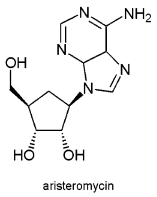
Scheme 222



Brown and Hegedus developed a novel Lewis acid-promoted one-pot ring-enlargement reaction of substituted cyclobutanones to the corresponding cyclopentanones.[296] An ylide generated from trimethyloxo-λ^4-sulfanium iodide ($Me_3S(O)I$) and sodium hydride works as the C_1-equivalent. Using 0.25 equivalents of scandium triflate as the catalyst, the 3-oxocyclobutyl-oxazolidinone **635** was ring expanded to **636** with 79% yield, a close precursor to aristeromycin (**637**). It should be pointed out that no dehydroalkoxylation within the enlarged cycloalkanone was observed, which is the favored reaction pathway applying triethylaluminum as the Lewis acid.

Scheme 223

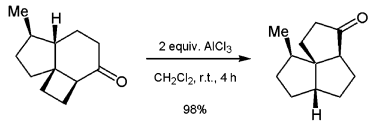


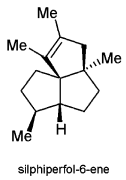


637

Developing a synthetic access to angularly fused triquinane natural products such as silphiperfol-6-ene (**640**), Kakiuchi et al. reported a novel Lewis acid-catalyzed rearrangement of bi- and tricyclic cyclobutyl ketones having a bicyclo[4.2.0]octan-2-one unit. The authors checked the scope and limitations of this ring-enlargement reaction with a focus on the competitive Cargill rearrangement. Starting from ketone **638**, this novel type of reaction afforded the triquinane derivative **639** in 98% yield involving a homoallylcarbinyl cation.[297]

Scheme 224

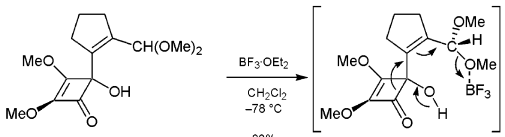


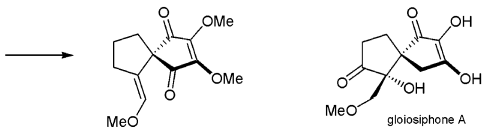


640

Extending the squarate methodology, Paquette et al. reported the boron trifluoride-catalyzed ring expansion of the addition product **641** of a cyclic alkenyllithium species to dimethyl squarate (**162**).[298] The reaction cascade involves the primary attack of the Lewis acid on the acetal oxygen resulting in the formation of the spirocyclic compound **642**. This cyclopentenedione was obtained from **641** in 80% yield providing a precursor of gloiosiphone A (**643**), a naturally occurring antimicrobial [4.4]spirononenedione from marine red algae.[299]

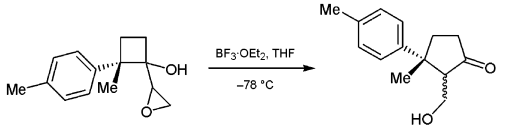
Scheme 225

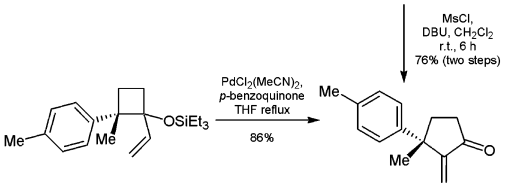


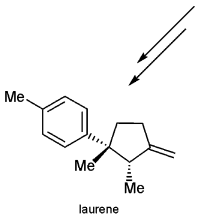


In the area of laurene (**648**), a sesquiterpene from Laurencia species as well as from a marine red algae, Fukumoto et al. published both a ring enlargement applying Lewis acid conditions and additionally, a palladium-mediated reaction. Using a tertiary cyclobutanol with an epoxide at the α-position of **644**, the ring expanded hydroxymethylcyclopentanone **645** was obtained in a classical way by means of boron trifluoride-etherate. However, starting from the corresponding triethylsilyl-protected cyclobutanol **646** bearing an α-vinyl group, the methylene-substituted laurene precursor **647** was prepared very efficiently using bis(acetonitrile)palladium(II)-chloride/*p*-benzoquinone (86%).[300,301]

Scheme 226



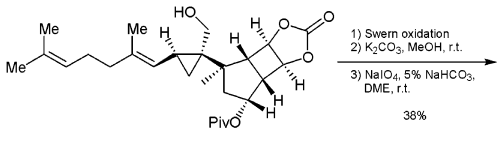




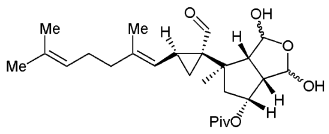
648

Yamada et al. applied an oxidative ring enlargement of a carbonate-protected, cyclopentane-annelated 1,2-cyclobutanediol to obtain the tetrahydrofuran moiety of the unique marine diterpene (+)-halimedatrial (**651**). Using sodium periodate as the oxidant in the presence of sodium bicarbonate the hemiacetal **650** was prepared from **649** in 38% overall yield.[302]

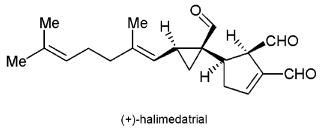
Scheme 227



649



650

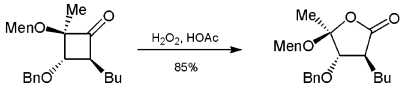


(+)-halimedatrial

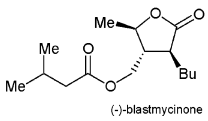
651

Concerning a synthesis of blastmycinone, Fráter et al. subjected the highly functionalized cyclobutanone **652** to a Baeyer−Villiger reaction using hydrogen peroxide in acetic acid as the oxidant. The obtained yield of this precursor **653** (four steps away from the natural product **654**) was 85%.[303]

Scheme 228



652 653

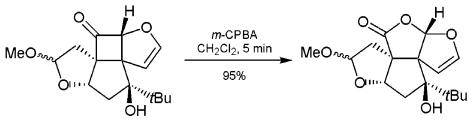


(-)-blastmycinone

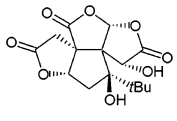
654

Crimmins et al. reported in 1992 the Baeyer−Villiger oxidation of the cyclobutane moiety within the tetracyclic ketone **655** to give **656**, a precursor of the tetracyclic trilactone bilobalide (**657**). The second γ-lactone unit was introduced in a regioselective manner using *m*-CPBA in dichloromethane to give **656** in 98% yield.[304]

Scheme 229



655 656

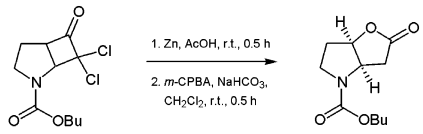


bilobalide

657

Correia et al. published a short and efficient synthesis of 2-oxa-6-azabicyclo[3.3.0]octan-3-one, the Geissman-Waiss lactone (**659**), a key precursor for pyrrolizidine alkaloids such as retronecine. The *cis*-fused bicyclic lactone was obtained regioselectively in 90% yield by Baeyer−Villiger oxidation of the dehalogenated [2+2] cycloadduct **658**.[305]

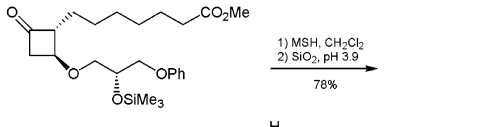
Scheme 230



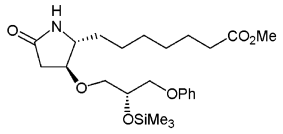
658 659

Starting from a cyclobutanone backbone and applying different ring-expansion methods, Taylor et al. developed unique prostaglandin analogues. These prostanoids, for example, useful as antiulcer compounds, exhibit pharmacological specificity and high metabolic stability. The *trans*-substituted cyclobutanone **660** served as a key precursor that could be converted either to a pentanone derivative (Me_3SiCHN_2, $BF_3{\cdot}OEt_2$, 52%), to a lactone (*m*-CPBA, 94%), or to the five-membered lactam **661**. The latter was obtained by means of *O*-mesitylenesulfonylhydroxylamine (MSH) in 78% yield.[306]

Scheme 231



660



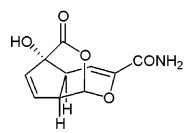
661

2. Six-Membered Rings

A precursor to echinosporin (**664**), a natural product from *Streptomyces echinosporus* MK-213 with antibiotic and antitumor activity, was prepared by Smith et al. The fused cyclobutanol **662** was subjected to oxidative conditions using sulfur trioxide/pyridine. The resulting de Mayo-type cyclobutanol fragmentation with subsequent recyclization gave the ring enlarged dihydropyran derivative **663** in 46% yield as a mixture of anomers (20:1).[307]

Scheme 232

662 663

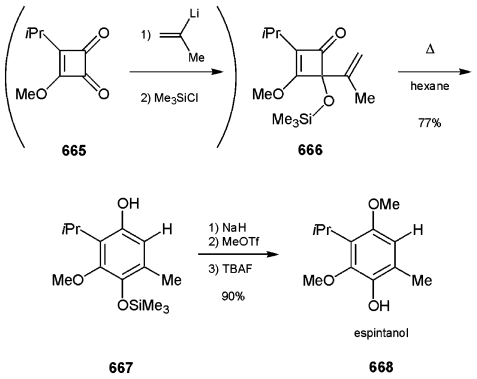


(-)-echinosporin

664

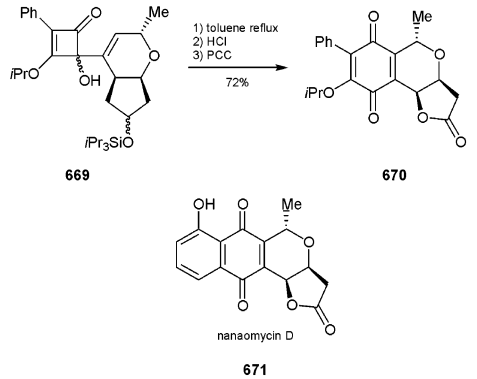
In 1996, Moore et al. reported the synthesis of the antiparasitic monoterpene espintanol (**668**). The required 4-oxycyclobutenone (**666**) with a vinylic substituent at the 4-position was obtained from **665**. Upon heating of the sample in hexane, ring enlargement to the monosilylated 3,6-dialkyl-2-methoxyhydroquinone **667** occurred (77% yield). Subsequent monomethylation and desilylation provided espintanol **668** in 90% yield.[308]

Scheme 233



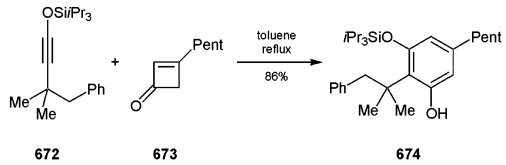
On the basis of the ring-enlargement reaction of 4-alkenyl-4-hydroxycyclobutenones, also a synthetic route to isochromanquinones was developed, especially to the biologically active natural product nanaomycin D (**671**) and some nonnatural analogues. The appropriate cyclobutenones, which were subjected to thermolysis, were obtained upon attachment of a fused dihydropyran to appropriate squaric acid derivatives. The starting cyclobutenone **669** gave **670** in 72% overall yield (including subsequent deprotection of a silyl ether and PCC oxidation).[309]

Scheme 234



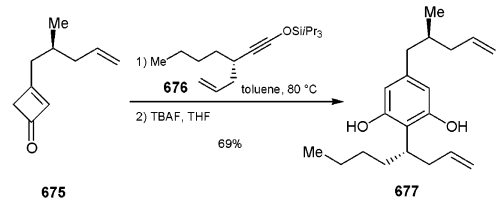
Kowalski et al. reported the cycloaddition reaction of silyloxyacetylenes, such as **672**, with ketenes generated from 3-alkylcyclobutenones such as **673** or related 4,4-dichlorocyclobutenones. Similar to Danheiser's protocol using alkoxyacetylenes,[195] highly substituted resorcinols were obtained, but acetylenes with a secondary, tertiary, or aromatic substituent at the triple bond could also be applied. For example, **672** furnished the resorcinol derivative **674** in 86% yield.[310]

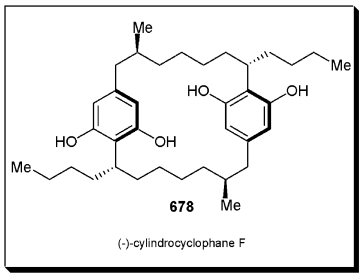
Scheme 235



In a ring-enlargement reaction, first published by Danheiser in 1984,[195] Smith et al. obtained 1,3-dihydroxy-2,5-dialkylbenzene derivatives by reacting the double bond of a 3-substituted cyclobutenone with a 2-functionalized 1-silyloxyalkyne.[311] The reaction proceeds via a cascade of electrocyclic reactions. For example, the metathesis reaction of cyclobutenone **675** with the enyne **676** followed by desilylation with TBAF gave the substituted 1,3-dihydroxybenzene **677** in 69% overall yield. Interestingly, this product provides a natural product precursor to cylindrocyclophanes, such as **678**.

Scheme 236

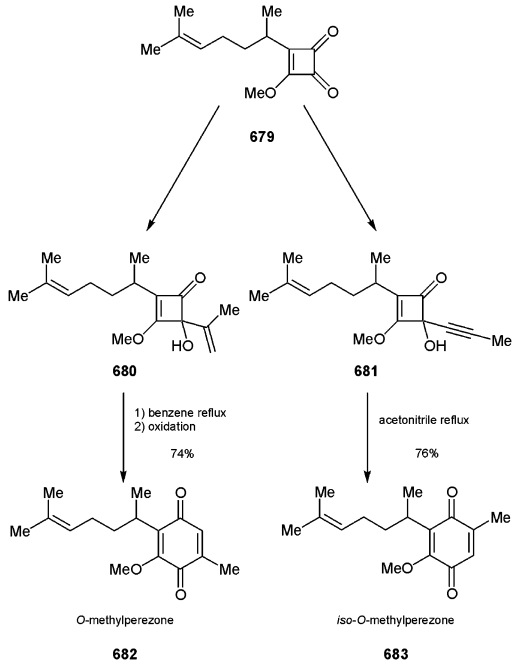




Controlling the regiochemistry in the synthesis of highly substituted quinones Moore et al. started from appropriate cyclobutenediones, e.g., **679** by adding either an alkenyl or an alkynyl group to one carbonyl center.[312] In the former case, the 4-alkenyl-4-hydroxycyclobutenone **680** gave the natural occurring *O*-methylperezone (**682**) upon thermolysis and subsequent oxidation in 74% yield, whereas in the case of the propyne derivative **681**, thermal treatment provided the regioisomeric *iso*-*O*-methylperezone (**683**) in 76% yield. Similar natural products (i.e., perezone, isoperezone, and terreic acid) bearing a hydroxy group instead of the methoxy substituent were prepared starting from the corresponding *tert*-butoxy derivatives of squaric acid. After the ring expansion step, the desired hydroxy group was generated by means of trifluoroacetic acid at low temperature.[313]

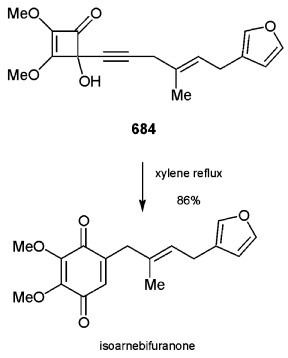
Using the thermal ring enlargement of the 4-alkynyl-4-hydroxycyclobutenone **684**, Moore et al. prepared the pharmacologically interesting isoarnebi-

Scheme 237



furanone (**685**), a prostaglandin synthesis inhibitor, in 86% yield.[158,314]

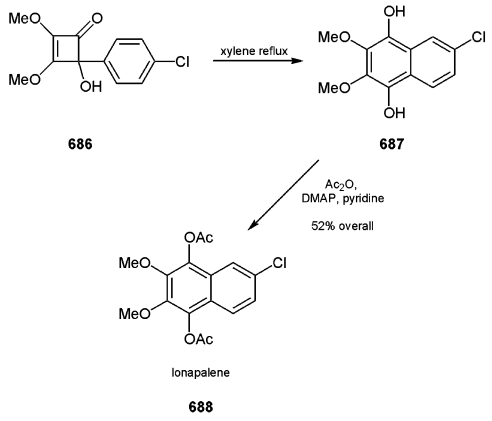
Scheme 238



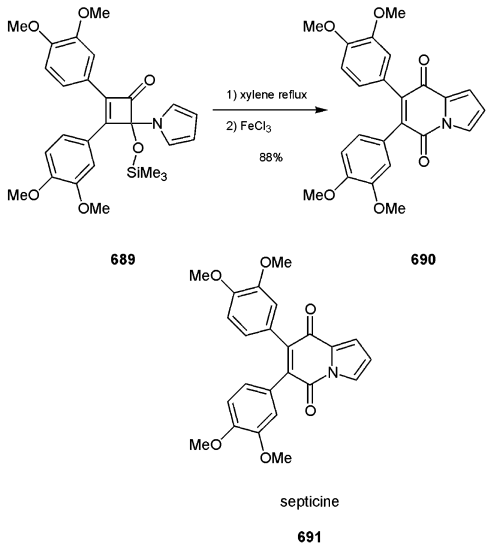
Perri and Moore published in 1987 the thermal ring expansion of a dimethyl squarate derived 4-(4-chlorophenyl)-4-hydroxycyclobutenone (**686**) to 6-chloro-1,4-dihydroxy-2,3-dimethoxynaphthalene (**687**) which served as a direct precursor to lonapalene (**688**), a selective lipoxygenase inhibitor. **688** was obtained from **686** in 52% overall yield.[315] The same methodology was used in 2002 to prepare a fused naphthoquinone as a precursor of a naturally occurring anthraquinone, a member of the angucycline antibiotics.[316]

Applying the cyclobutenone-based ring-expansion methodology to the 1-pyrroloylcyclobutenone **689**, the same group in 1994 obtained the indolizine ring system. Upon oxidation with ferric chloride, the corresponding indolizine-5,8-dione **690** was prepared in 88% overall yield, which serves as a direct precursor (four steps) to septicine (**691**), an alkaloid with, for example, antibiotic and anticancer activity.[317]

Scheme 239



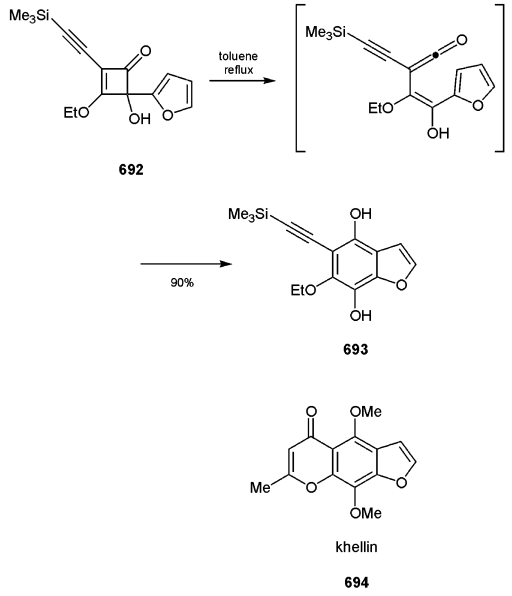
Scheme 240



In the area of furochromone and furocoumarin natural products such as the antiatherosclerotic agent khellin (**694**), the thermal rearrangement of 4-heteroaryl-4-hydroxycyclobutenones led to corresponding heteroannelated hydroquinones. For example, upon heating in refluxing toluene, the 2-alkynyl-3-ethoxy-4-furyl-4-hydroxycyclobutenone **692** furnished the highly substituted benzofuran **693** in 90% yield via a conjugated ketene intermediate.[318] Some years later, a similar 4-furyl-4-hydroxycyclobutenone was used to prepare the hydroquinone analogue of another naturally occurring sesquiterpene furanoquinone using a different strategy to obtain the functionalized cyclobutenone precursor.[319]

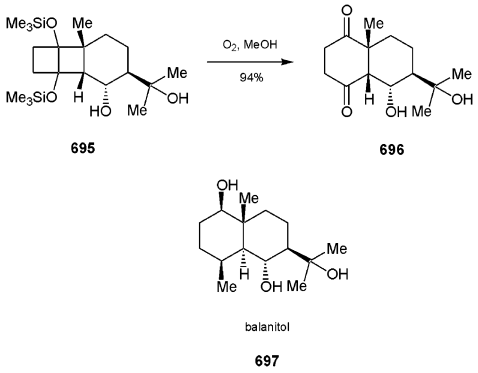
During the course of the synthesis of balanitol (**697**), a naturally occurring sesquiterpene alcohol, Anglea and Pinder reported the oxidative ring-enlargement reaction of tricyclic cyclobutane **695** affording methylbicyclo[4.4.0]decan-1,4-dione **696** in 94% yield. To obtain the stereochemistry of the natural product, quantitative isomerization to the

Scheme 241



trans-fused decalin system was achieved by means of silica gel.[320]

Scheme 242

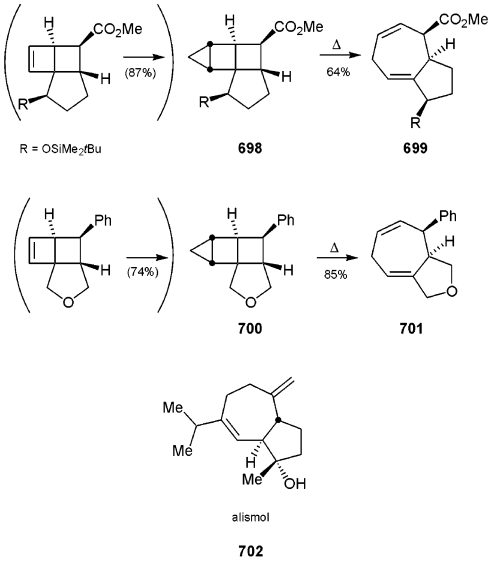


3. Seven-Membered Rings

As described by Snapper et al., bicyclo[5.3.0]ring systems, such as **699** and **701**, were obtained from annelated [2.2.0] bicyclic compounds via cyclopropanation and subsequent selective thermal fragmentation of the tetracyclic cyclobutane derivatives, e.g., **698** and **700**. Depending on the C-1 substituent, the necessary temperatures range from 130 to 240 °C.[321] Low fragmentation temperatures were found with substituents that stabilize electron-deficient intermediates. These products which were obtained in 64−85% yield provide the skeletal framework of interesting naturally occurring products such as alismol (**702**), parryin, or grayanotoxin.

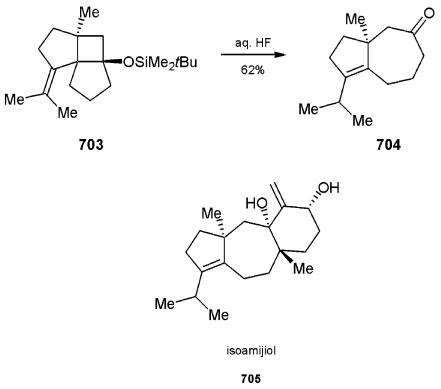
In the field of dolastane diterpenes such as isoamijiol (**705**), Pattenden et al. reported a Grob-type fragmentation of the unsaturated bisannelated silyloxycyclobutane **703**. A push−pull system with a C=C double bond and a silyloxy substituent at the terminal positions was used for the first time in such a reaction. The azulenone **704** was obtained in 62%

Scheme 243



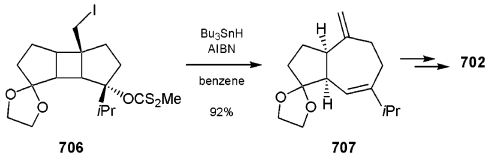
yield upon treatment with aqueous hydrofluoric acid.[322]

Scheme 244



In 1994, Lange and Gottardo reported a novel radical ring expansion of a tricyclic iodoxanthate **706**, which was ring enlarged by deiodination using tributyltin hydride/AIBN. The resulting cyclobutylcarbinyl radical undergoes a tandem fragmentation/elimination sequence with xanthate as a leaving group to yield the fused *exo*-methylenebicyclo[5.3.0]decene **707**. It is noteworthy that subsequent deprotection of the ketal, followed by treatment with methylmagnesium bromide in the presence of cerium trichloride to prevent enolization, furnished the naturally occurring alismol (**702**).[323]

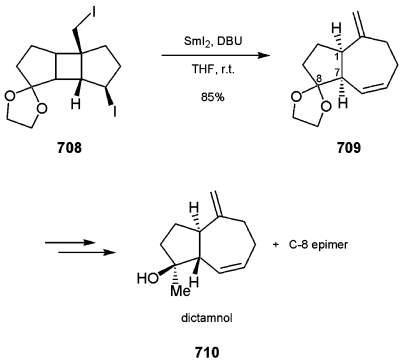
Scheme 245



An alternative synthesis of the same framework was published in 1997. The *cis*-fused bicyclic precursor **707** of the trinor-guaiane sesquiterpenoid dictam-

nol (**710**) was obtained in 85% yield by a samarium diiodide-mediated tandem fragmentation/elimination sequence from an diiodinated tricyclic ring system **708**. Subsequent deprotection of the ketal moiety accompanied by epimerization at C-7 to the *trans*-fused skeleton as well as employing a methyl Grignard afforded **710** and its C-8 epimer.[324]

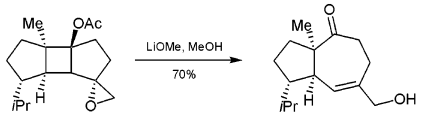
Scheme 246



708 **709** **710**

Wickberg applied an alkaline hydrolysis to the bisannelated cyclobutane derivative **711**, leading to the hydroazulene sesquiterpene aphanamol I (**712**). Treatment of the acetate **711** with LiOMe in methanol yielded the alkoxide which initiated the C−C bond cleavage of the adjacent zero bridge and subsequent opening of the epoxide. The resulting ring enlarged hydroxymethyl-substituted cycloheptenone **712** was obtained in 70% yield.[325]

Scheme 247



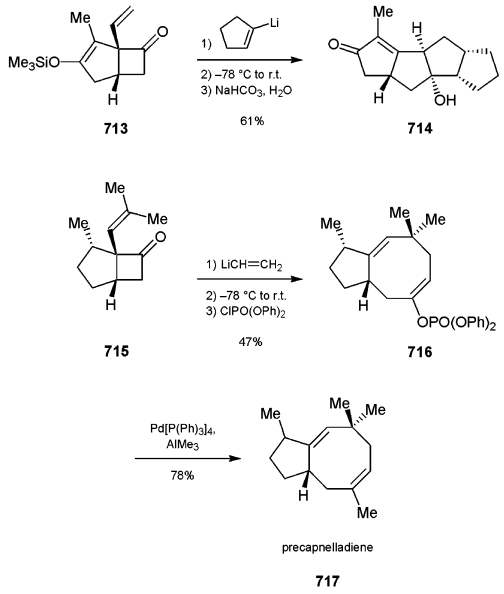
711 **712**

4. Eight-Membered Rings

Moore et al. attached a vinyl substituent at the α-position to the bridgehead carbon of bicyclo[3.2.0]-heptan-7-ones, such as in **713** and **715**. This represented the first step in a novel reaction sequence leading to linearly-fused oligoquinanes such as **714** or to bicyclo[6.3.0]undecadienes such as **716**.[326] Following this protocol, the regioselective synthesis of the [6.3.0]bicyclic sesquiterpene precapnelladiene (**717**) was achieved.

Recently, Limanto and Snapper published the application of a dialkenylcyclobutane ring-enlargement strategy via ring-opening metathesis of an appropriate cyclobutacyclobutene and subsequent Cope rearrangement.[327] Starting from the tetracyclic ether **718**, the bicyclo[6.3.0] skeleton of asteriscanolide (**720**) embedded in **719** (three steps away from

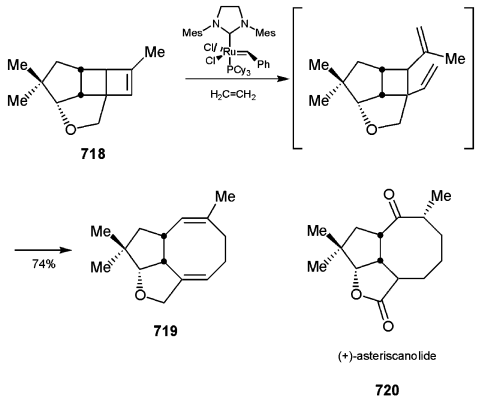
Scheme 248



713 **714** **715** **716** **717**

the naturally occurring compound) was obtained in 74% yield.

Scheme 249

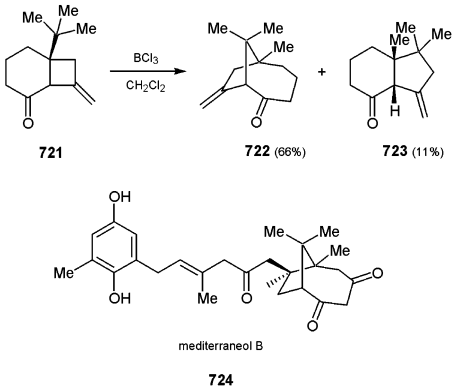


718 **719** **720**

The Lewis acid-catalyzed rearrangement of the *exo*-methylene ketone **721** is the key step in the total synthesis of the tetramethyl derivative of mediterraneol B (**724**) reported by Kakiuchi et al.[328] The reaction is performed by treatment of **721** with a boron trichloride solution and yields the 8-methylene-6,9,9-trimethylbicyclo[4.2.1]nonan-2-one (**722**) in up to 66% yield. The bicyclo[4.2.1] system is separated from the bicyclo[4.3.0] byproduct **723** (11%) by flash chromatography.

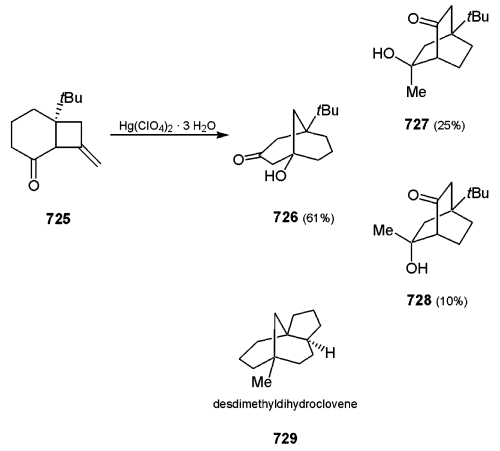
In the same year, the skeletal rearrangement of the similarly substituted 8-methylenebicyclo[4.2.0]-octan-2-one with mercury(II) perchlorate was published.[329] A remarkable substituent effect was recognized: While reactions of such ketones having methyl and ethyl groups on C-6 gave the bicyclo-[2.2.2]octanones along with a small amount of the bicyclo[3.3.1]nonanones, the yield of the bicyclo[3.3.1]-ketone increased with the bulkiness of this substituent. Thus, the *tert*-butyl derivative **725** afforded bicyclo[3.3.1]nonanone **726** as a major product (61% yield) together with a mixture of the bicyclo[2.2.2]-

Scheme 250



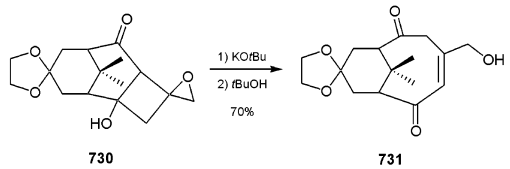
octanones **727** and **728** (25% *exo*-hydroxy and 10% *endo*-hydroxy, respectively). The naturally occurring (±)-desdimethyldihydroclovene (**729**) was easily synthesized via radical deoxygenation followed by transformation of the tertiary hydroxyl group to the methyl group.

Scheme 251



Blechert et al. published three types of ring-enlargement reactions to transform a cyclobutane unit into the eight-membered ring of the taxane system. Applying oxidative conditions to open a cyclobutene moiety, i.e., ozonolysis followed by reductive workup or use of osmium tetroxide/sodium periodate, the taxane skeletal framework was obtained in 40% yield. Alternatively, the spiroepoxide **730** gave the eight-membered ring diketone **731** in 70% yield via a potassium *tert*-butoxide mediated *retro*-aldol process.[330]

Scheme 252



V. Conclusion

This review has summarized the literature application of cyclobutane derivatives as versatile molecular building blocks in organic synthesis from 1985 to 2002. The future of organic synthesis lies in both the development of reliable, efficient, and highly selective methodologies and the discovery of new processes for building up complex chemical architecture. The use of cyclobutane transformations—including transition-metal catalysis and bioconversions—greatly extends the possibilities in synthetic organic chemistry, and has led to the discovery of a number of new and valuable types of (cascade) reactions. Many of these have already demonstrated their potential in the successful synthesis of bioactive, naturally occurring products.

VI. Acknowledgments

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