Progress in the Construction of Cyclooctanoid Systems: New Approaches and Applications to Natural Product Syntheses

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I. Introduction

During the evolution of alicyclic chemistry, medium rings, particularly cyclooctanes, aroused considerable interest and attention in the context of studies related to strain, conformations, and transannular interactions. Seminal investigations by Prelog, Cope, and others[1] and more recent access to incisive structural tools such as dynamic NMR have contributed much to our understanding of the reactivity and stereoselectivity exhibited by eight-membered rings.[2] However, interest and activity in the synthesis of eight-membered-ring compounds remained in a low key until the past two decades, perhaps due to the fact that unfavorable entropic and enthalpic factors precluded the adaptation of traditional methods of ring formation and annulation for their construction and the possibility of transannular reactions was always lurking as a complicating factor. In addition, the powerful stimulus in the form of complex and challenging natural product targets, with promising biological activities, that usually spearhead new developments and directions in synthetic methodology was also lacking. However, this scenario began to change with the onset of the 1980s.

The eight-membered ring is the latest entrant into the variegated assemblage of carbocyclic rings present in natural products, primarily among terpenoids. In the past few years, the number of carbocyclic skeletons in which a cyclooctane forms a part of the condensed or bridged polycyclic system have proliferated rapidly. The cyclooctane bearing carbon skeletons have now been located among lignans C_{15}-sesqui-, C_{20}-di-, C_{25}-sester-, and C_{30}-triterpenes. Presently, well over 100 natural products constitute

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Vishwakarma Singh was born in Bijaikaf, U.P., India, and received his Ph.D. degree from the University of Gorakhpur, under the supervision of Prof. S. Giri. He continued his scientific education as senior research fellow (CSIR, New Delhi) under the direction of Prof. Goverdhan Mehta at the Indian Institute of Technology, Kanpur, and the University of Hyderabad. He was awarded a Monbusho fellowship from the Ministry of Education, Government of Japan, to work with Prof. E. Osawa at Hokkaido University, Sapporo, Japan (1979–1980). He then moved to the United States and worked as a Research Associate with Prof. A. R. Martin, University of Arizona, and Prof. J. B. Hedrickson, Brandeis University. Dr. Singh returned to India, and after working at the Malti-Chem Research Center, Nandesari, Baroda, and M. S. University of Baroda, he joined the Indian Institute of Technology, Bombay, in October 1989, and currently he is Professor. His research interests are in the area of organic synthesis and photochemistry.

the structurally diverse and interesting family of cyclooctanoids. Selected examples of various skeletal types among them are spartidienedione **1**,[3] salsolene ketone **2**,[4] asteriscanolide **3**,[5] dumortenol **4**,[6] roseadione **5**,[7] paclitaxel **6**,[8] kalmanol **7**,[9] longipenol **8**,[10] acetoxycrenulide **9**,[11] varieocolin **10**,[12] plagiospirolide A **11**,[13] and distichol **12**,[14] Scheme 1. These natural products are fairly widely distributed in Nature and have been isolated from terrestrial plants, marine organisms, pathogenic fungi, and insects. Many of them exhibit exceptional and broad-ranging biological activity with dibenzocyclooctadiene lignans, in earlier years, and diterpene paclitaxel at present, being the most notable examples. Indeed, the current spurt in synthetic activity aimed at cyclooctanoid systems, to a large extent, can be attributed to the emergence of diterpene paclitaxel as a clinically used anticancer drug.

The isolation and characterization in recent years of many complex natural products containing cyclooctane ring and the quest by organic chemists to synthesize them in a regio-, stereo-, and enantioselective manner have also given much needed fillip to this arena, and significant progress both in methodology as well as total synthesis has been achieved in the 1990s. The time is therefore opportune to provide an update on the recent developments, particularly as the last review[15] on this subject appeared nearly seven years ago (covering the literature up to 1991). Although in the intervening period several reports have surfaced that cover some facet or the other of the cyclooctanoid ring construction, the present review attempts at a comprehensive coverage of the developments since 1991 and is organized under two main themes. First, the emphasis is on methodological advances and conceptual level innovations, with those having general applicability, preparative utility, and good regio- and stereocontrol receiving particular attention. All of the reported methods for the generation of an eight-membered ring either as a monocyclic entity or as a part of multicyclic condensed or bridged system have been included. Model studies directed toward taxoids, wherein the formation of the eight-membered B-ring is involved, form an important part of this report. The second section deals with applications to natural product synthesis with focus on specific targets, but only those key steps have been highlighted in which an eight-membered ring is created. The literature coverage is up to the middle of 1998.

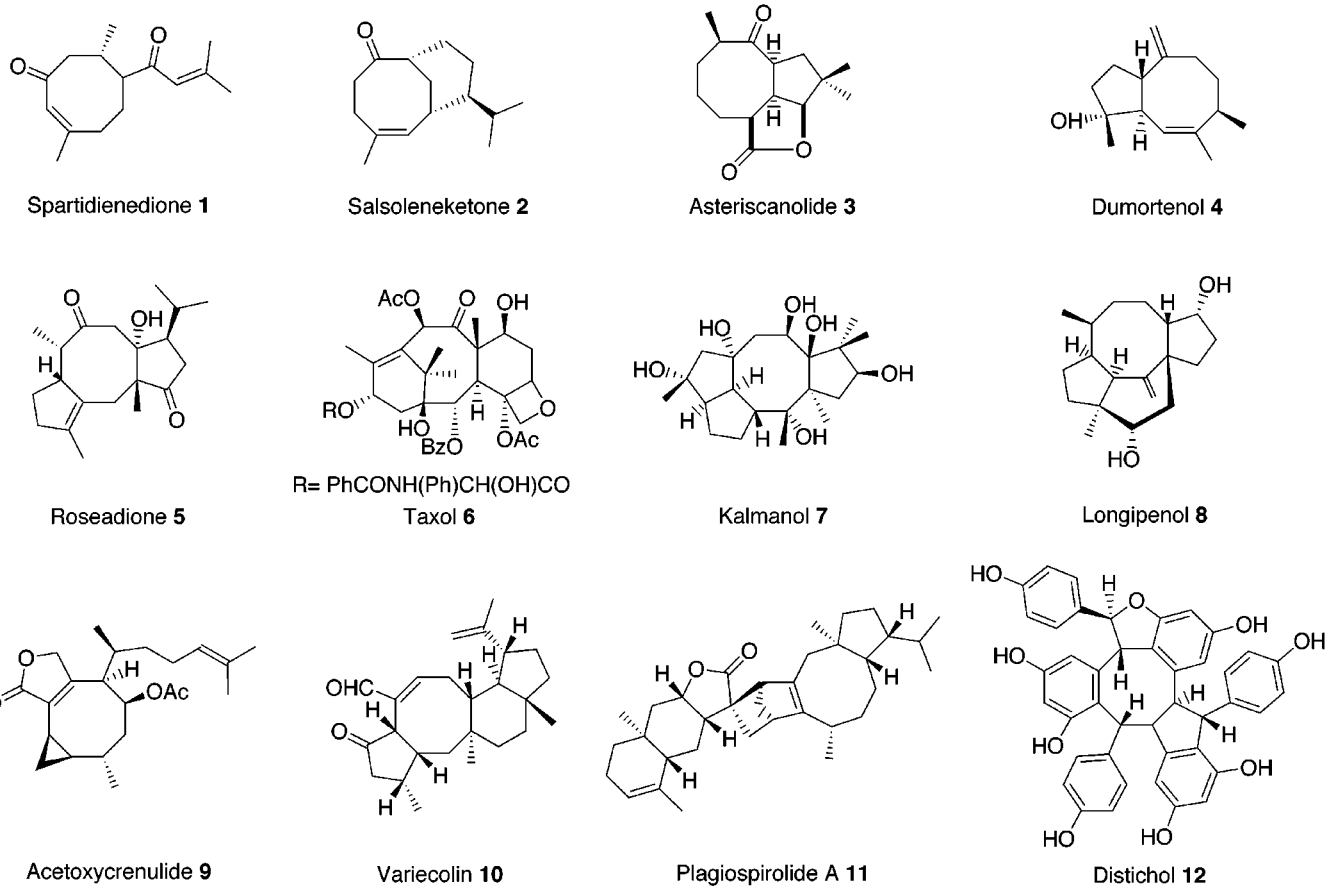
II. Methods Leading Directly to the Formation of Cyclooctanoids

This section deals with the protocols involving diverse cycloadditions, cyclizations, and coupling reactions in which an eight-membered ring is formed directly from the appropriate precursor(s) in a single step. Such direct methods exhibit preparative viability and sound regio- and stereocontrol. Illustrative examples from various methodologies leading directly to the generation of eight-membered rings are considered here.

A. Cycloaddition Approaches

Cycloadditions constitute one of the most powerful and versatile methods for the synthesis of carbocyclic systems.[16,17] Cycloadditions, especially higher order cycloadditions, have proved to be very important strategic tools for the rapid and efficient synthesis of cyclooctanoids.[18,19] In this section, various cycload-

Scheme 1



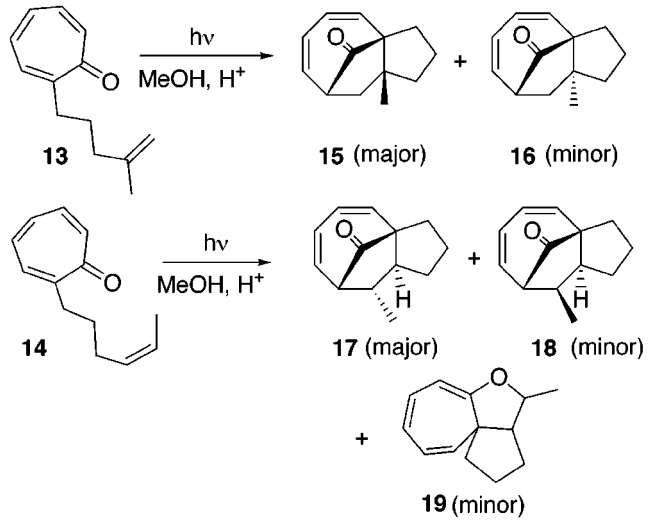
dition-based approaches to eight-membered rings are discussed.

1. [6π + 2π]-Cycloaddition

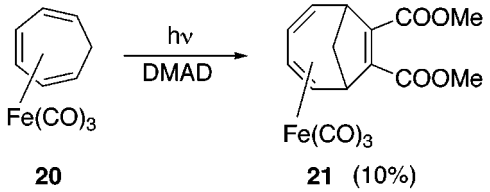
In principle, the connection between the termini of a six-carbon chain and a two-carbon unit should constitute a straightforward entry into an eight-membered ring. Since thermal [6π + 2π]-suprafacial cycloadditions are not symmetry allowed,[20] different strategies, particularly in photochemical mode, have been devised for this type of cycloaddition. Feldman and co-workers[21] have examined the viability and synthetic potential of photochemical intramolecular [6π + 2π]-cycloaddition of tropone derivatives in acidic medium as a route to cyclooctanoids. Thus, tropone derivatives of types **13** and **14** were reported to undergo photocycloaddition to furnish the tricyclic compounds **15**, **16** and **17**, **18**, respectively, Scheme 2.[21b] In some cases, [8 + 2]-adducts such as **19** are also concurrently formed. These [6π + 2π]-cycloadditions proceed through the intermediacy of tropylium ion, and while the yields are reasonable, stereoselectivity is only moderate. The ratio of the various products formed during the photocycloaddition was found to be susceptible to the substitution pattern on the tropone and/or the nature of the side chain. This method has been extended successfully to a synthesis of the cyclooctanoid marine natural product dactylol.[21c]

Photochemically induced intermolecular cycloadditions of metal-complexed cycloheptatriene (CHT) **20** with dienophiles were first reported by Pettit,[22] who

Scheme 2



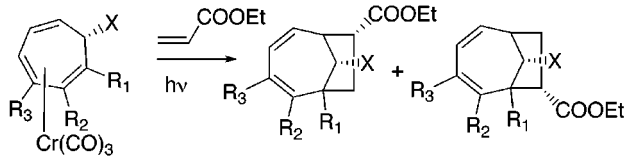
Scheme 3



isolated the [6 + 2]-adduct **21** with acetylenic ester (DMAD), although in poor yield, Scheme 3. Subsequently, Kreiter and co-workers[23] investigated the reactivity of (CHT)Cr(CO)$_3$ complexes with various

dienes under photochemical conditions and observed that both [6 + 2]- and [6 + 4]-cycloadditions can occur depending on the structure of the diene. Recently, Rigby and co-workers examined in detail the cycloaddition of (CHT)$Cr(CO)_3$ complexes with various types of alkenes with regard to selectivity and synthetic potential.[18,24,25] These cycloadditions (**22** → **23** and **24**) proceed in good yield, and the regioselectivity shows a marked dependence on the nature and position of the substituent on the CHT complex (Scheme 4). The adducts **23** and **24** result from an

Scheme 4



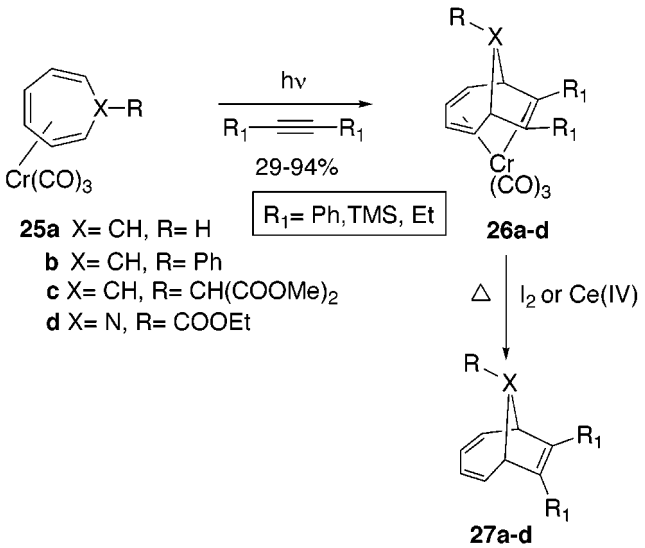
22 **23** **24**

R_1	R_2	R_3	X	Ratio	yield
OMe	H	H	H	0 : 1	81%
H	OMe	H	H	1 : 1	64%
H	H	OMe	H	1 : 4	82%
H	H	H	H	0 : 1	92%
H	H	H	OMe	0 : 1	68%

exclusive endo approach of the 2π partner and are isolated in metal-free state directly from the reaction mixture. An interesting example of potential synthetic use is the highly stereoselective reaction of 7-methoxy-substituted (CHT)$Cr(CO)_3$ complex with ethylacrylate in very good yield (last entry, Scheme 4).

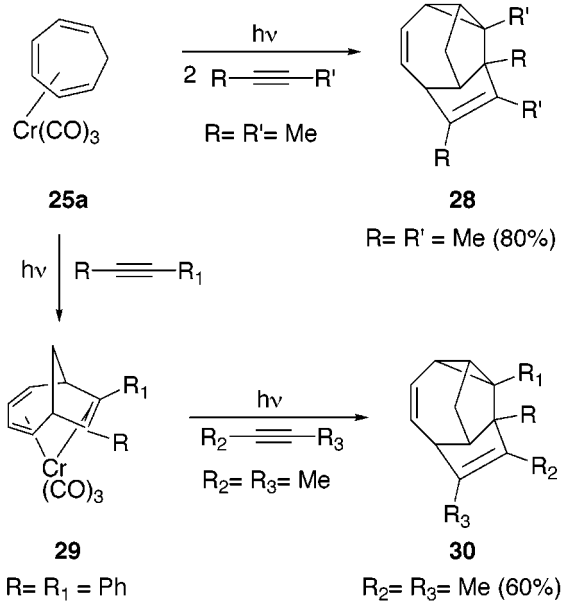
Sheridan has studied[26a] photochemical cycloaddition between electron-poor alkynes and chromium complexes of cycloheptatrienes **25a**−**c** and azepine **25d** to furnish chromium complexes of the adducts **26a**−**d**. Deligation in these adducts was effected on oxidation with either I_2 or Ce(IV) to furnish **27a**−**d**, Scheme 5. Novel, tandem [6 + 2]- and homo [6 +

Scheme 5



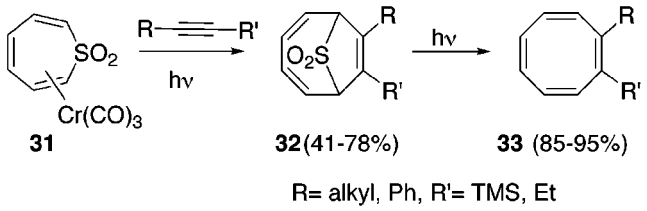
2]-photocycloadditions of cycloheptatriene−chromium complex **25a** with alkynes to give the adducts of type **28** in major amounts along with minor substituted benzene derivatives have also been reported by the same group.[26b] It is quite remarkable that the tandem addition of two different alkynes is possible. Thus, the reaction of (CHT)$Cr(CO)_3$ complex **25a** with diphenylacetylene led to the bicyclo[4.2.1]nonatriene complex **29**, which upon further reaction with another alkyne such as 2-butyne furnished a single regioisomer of the mixed double adduct **30**, Scheme 6.[26b] More recently, thiepin dioxide complex **31** was

Scheme 6



also shown to undergo [6 + 2]-photoaddition with alkynes, and the derived adducts **32** underwent photochemical extrusion to give substituted cyclooctatetraenes **33**, Scheme 7.[27] Several cyclooctatet-

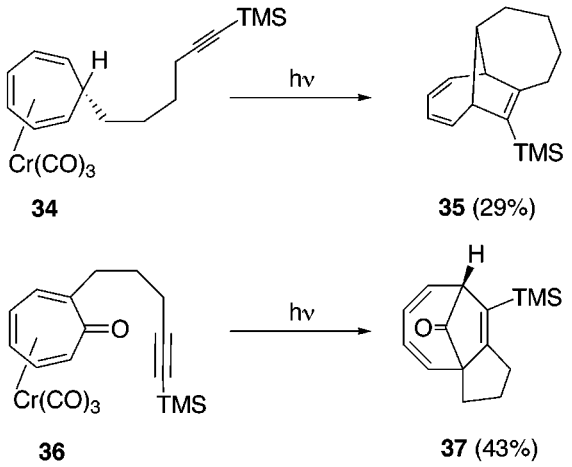
Scheme 7



raenes have been prepared in this manner, and this is an excellent route to substituted cyclooctatetraenes.

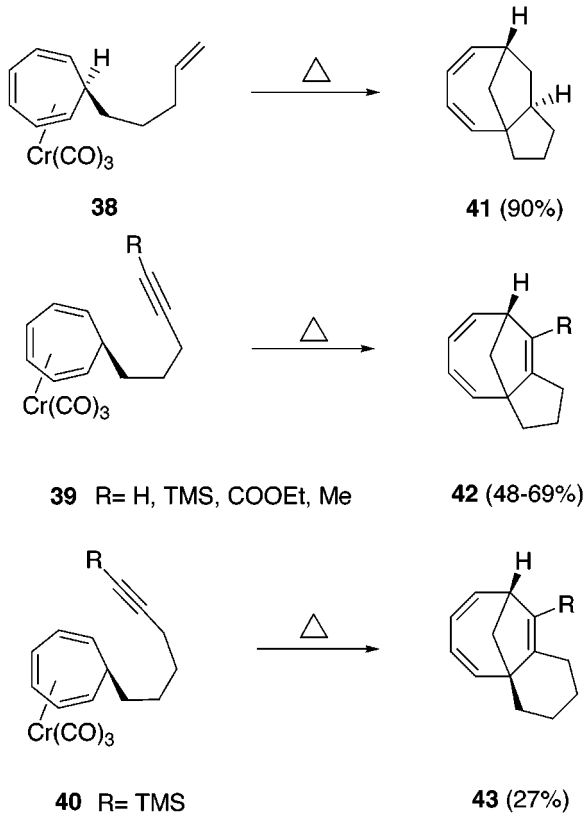
An intramolecular variant of the photochemical (CHT)$Cr(CO)_3$−alkyne [6 + 2]-cycloaddition has also been reported and constitutes a useful method for rapidly generating carbocyclic complexity. Thus, **34** furnished the tricyclic system **35**.[28a] In a similar manner, the tropone-derived complex **36** led to **37**, Scheme 8.[28a] Interestingly, intramolecular [6 + 2]-cycloadditions in alkene and alkyne-tethered (CHT)-$Cr(CO)_3$ complexes can be effected under thermal activation as well. However, in the thermal case, the

Scheme 8



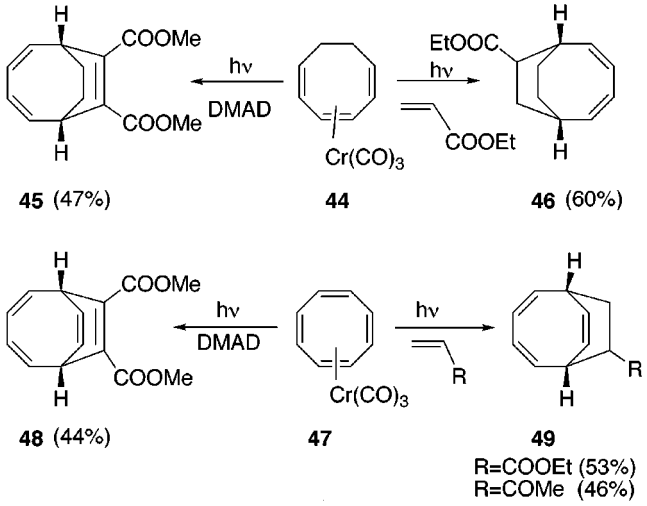
cycloaddition is preceded by isomerization to 1-substituted isomer through sigmatropic shift. Consequently, **38**−**40** furnished the bridged tricyclic compounds **41**−**43**, respectively, in preparatively useful yields, Scheme 9.[28a]

Scheme 9



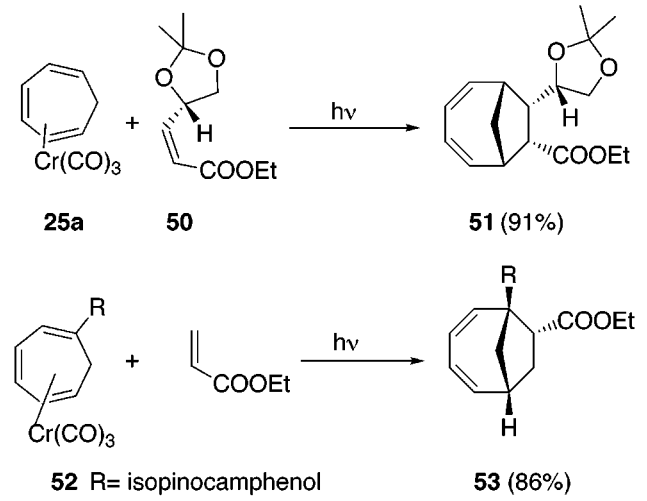
Recently, the photochemical [6 + 2]-cycloaddition strategy employing metal-complexed cyclic polyenes has also been extended to cyclooctatriene and cyclooctatetraene complexes, Scheme 10.[28b] Cyclooctatriene−chromium complex **44** and cyclooctatetraene−chromium complex **47** have been shown to engage dienophilic alkenes and alkynes in [6 + 2]-cycloaddition to give endo adducts **45**, **46** and **48**, **49**, respectively, Scheme 10.[28b]

Scheme 10



The [6 + 2]-photocycloaddition strategy is also amenable to enantioselective synthesis.[18] Reaction of γ-substituted chiral acrylate **50** with (CHT)Cr(CO)$_3$ complex **25a** furnished the adduct **51** in 91% de, Scheme 11. Rigby and co-workers have also shown

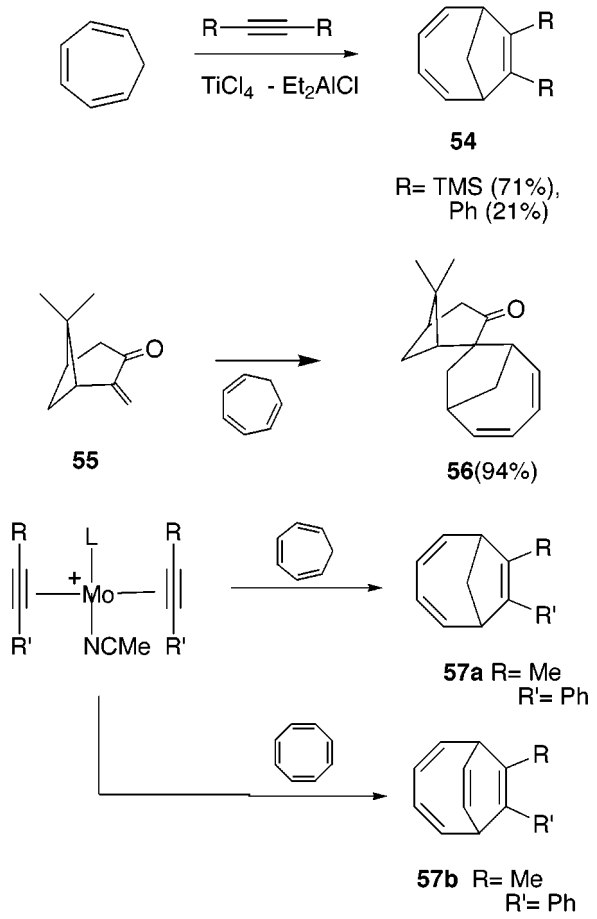
Scheme 11



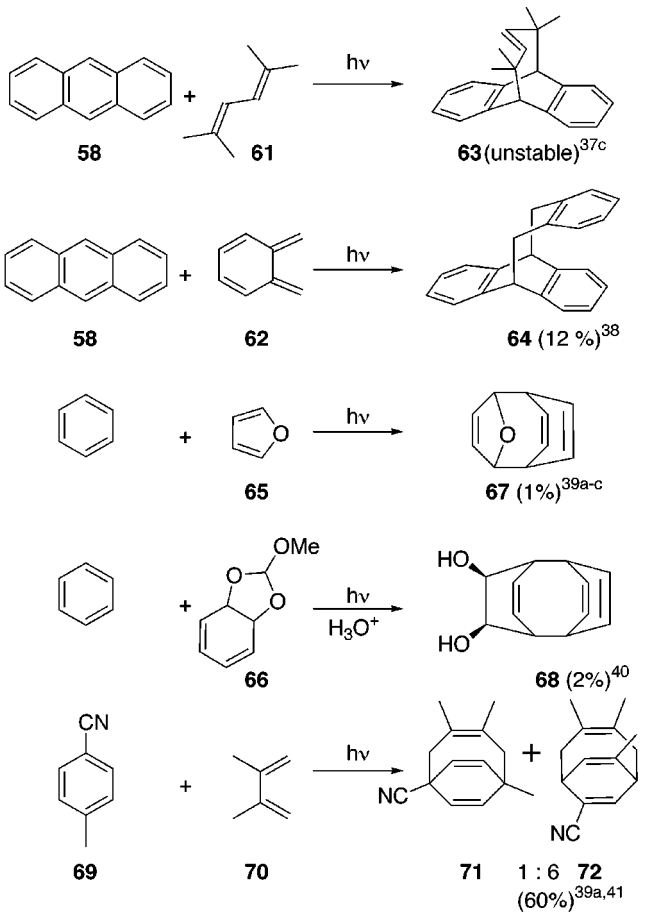
that tricarbonyl(cycloheptatriene)−chromium complexes bearing a chiral auxiliary, e.g., **52**,[25c] on cycloaddition with acrylate furnished the adduct **53** with high de (98%), Scheme 11.[25c]

In addition to photochemical and thermal additions, catalyzed [6 + 2]-cycloadditions have also been successful in accessing eight-membered rings. Reaction between CHT and bis(trimethylsilyl)acetylene, in the presence of titanium catalyst, led to the adduct **54** bearing an eight-membered ring within its bicyclo[4.2.1]nonane framework, Scheme 12.[29] Schmidt has reported[30] a molybdenum oxadiene complex catalyzed [6 + 2]-addition between (1R)-(+)-pinocarvone **55** and cycloheptatriene to give the adduct **56** in excellent yield, Scheme 12. Green also reported[31] [6 + 2]-addition of CHT and COT with disubstituted acetylenes to give corresponding adducts such as **57**.

Scheme 12



Scheme 14

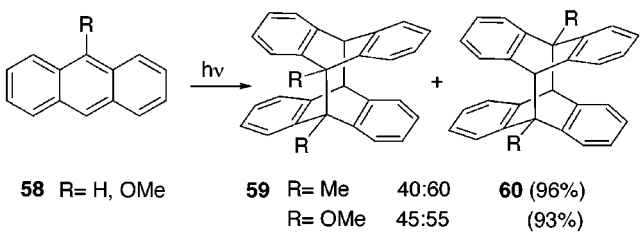


2. [4 + 4]-Cycloadditions

Conceptually, the formation of two σ bonds between the termini of two four carbon units should lead to the synthesis of eight-membered rings. However, in practice, such [4 + 4]-cycloadditions have presented considerable difficulties because of conformational uncertainties and intervention of alternate reaction pathways. But in recent years, some of these problems have been overcome, and [4 + 4]-cycloadditions have emerged as preparatively viable routes to cyclooctanoids. Different types of [4 + 4]-cycloadditions are briefly presented in the following subsections.

a. Photocycloadditions of Aromatic Compounds. Intermolecular photochemical dimerization of polycyclic aromatic compounds constitutes one of the earliest examples of [4 + 4]-cycloaddition leading to bridged, benzoannulated cyclooctanoids.[32,33] Anthracene and its derivatives[34−36] **58** have been studied extensively and are known to give head-to-head **59** and head-to-tail **60** dimers upon irradiation, Scheme 13. Anthracene also enters into [4 + 4]-photoaddition with other dienes such as **61** and **62** to furnish bridged systems **63** and **64**, respectively, Scheme 14.[37c,38]

Scheme 13

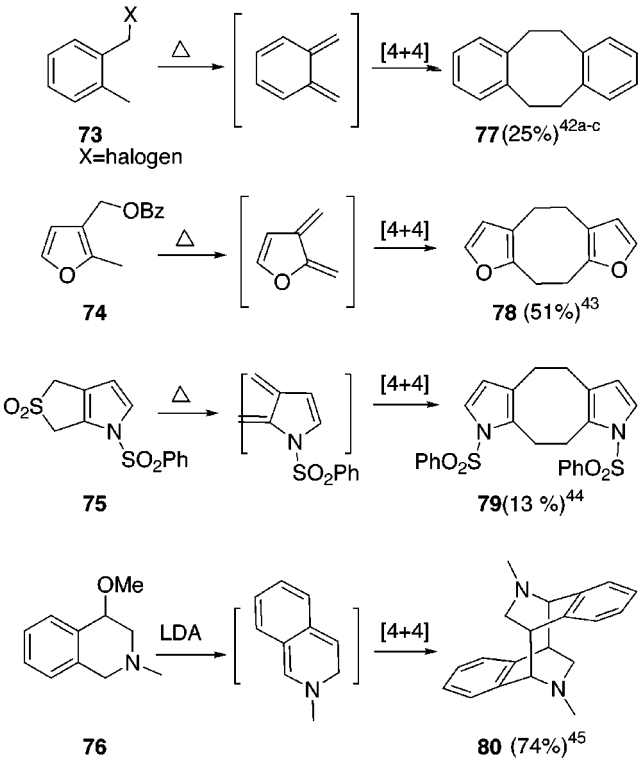


Simple aromatics such as benzene and naphthalene do not undergo photochemical [4 + 4]-dimerization; however, they do yield cycloadducts **67** and **68** with diene partners such as furan **65** and dihydroxylated benzene derivative **66**, although in very poor yields, Scheme 14.[39,40] Gilbert and co-workers have reported efficient [4 + 4]-photocycloaddition between several benzene derivatives such as **69** and acyclic 1,3-dienes (e.g., 2,3-dimethylbutadiene **70)** as an excellent route to bridged cyclooctadienes **71** and **72**, Scheme 14.[41] They also discuss the mechanism of these additions and the factors which affect the mode of cycloaddition and selectivity.

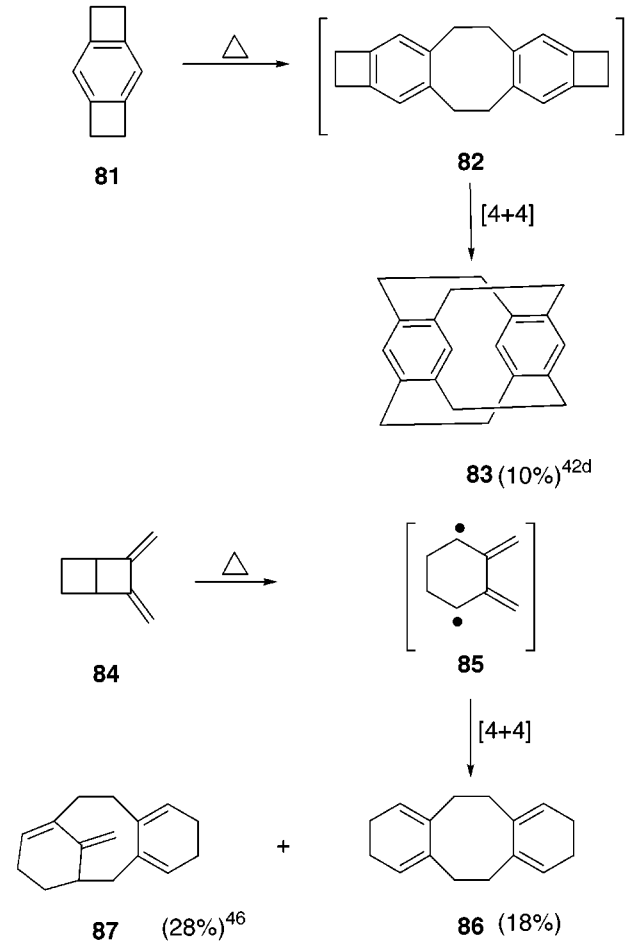
b. Cycloadditions of Orthoquinodimethanes. Being reactive intermediates, orthoquinodimethanes are known to readily undergo [4 + 4]-cycloaddition.[42−45] Such cycloadditions have proved particularly useful for the synthesis of aryl annulated cyclooctanes, cyclophanes, and other related compounds. Thus, orthoquinodimethane intermediates generated through thermolysis of appropriate precursors **73**−**76** furnish bisannulated cyclooctanoids **77**−**80**, respectively, in moderate yields, Scheme 15.

An extremely pleasing case of multiple cyclooctane ring formation, in a single operation involving two consecutive [4 + 4]-cycloadditions, is the transformation of dicyclobutabenzene **81** to [2.2.2.2]-cyclophane derivative **83**,[42d] via the intermediacy of **82**, Scheme

Scheme 15



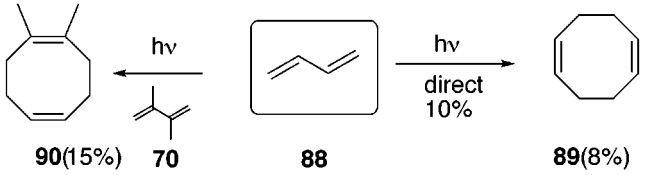
Scheme 16



16. An example related to the orthoquinodimethanes is the formation of both fused **86** and bridged **87** cyclooctanoids during the thermolysis of 2,3-bismethylene-bicyclo[2.2.0]hexane **84** through the intermediacy of the bis-allylic radical **85**, Scheme 16.[46]

c. Photocycloadditions of 1,3-Dienes. Photochemical [4 + 4]-cycloaddition among two 1,3-diene moieties constitutes the most direct approach toward eight-membered rings. However, irradiation of simple acyclic 1,3-dienes gives a complex mixture of products containing only a minor amount of cycloocta-1,5-dienes,[47−50] even though [4π + 4π]-suprafacial process is photochemically allowed. For example, direct irradiation of 1,3-butadiene **88** proceeds with a low conversion (10%) and leads to a complex mixture of products in which cycloocta-1,5-diene **89** (8% of the product mixture) is only a minor product.[47] Similarly, 1,2-dimethyl-1,5-cyclooctadiene **90** is also formed in meager yields along with other products from 2,3-dimethylbutadiene **70**.[48] In these photoreactions, 1,2-divinylcyclobutanes derived through [2 + 2]-cycloaddition are the more abundantly formed products, Scheme 17.

Scheme 17



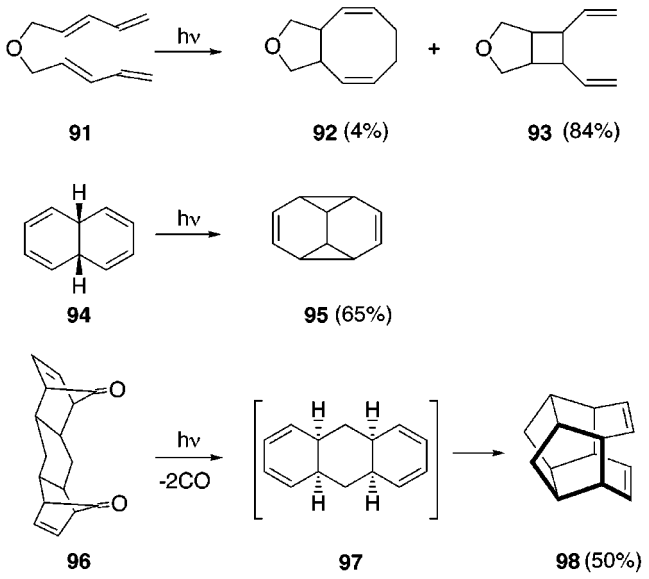
Low yield of [4 + 4]-addition products in the photochemical reactions of 1,3-dienes is presumably due to unfavorable conformational and other features that are detrimental to the attainment of a highly ordered transition state for the desired cycloaddition. One way to alleviate this difficulty could be through either an intramolecular variant or through the use of rigid frameworks. Wender et al.[51] have investigated the photocycloaddition in **91**, having both the diene moieties tied together through an ether tether. However, in this case, the [4 + 4]-addition product **92** was obtained in low yield along with the [2 + 2]-addition product **93** as the major product. The product **93**, however, could be converted into cyclooctadiene **92** via a Cope rearrangement.

Conformationally rigid polycyclic dienes undergo [4 + 4]-cycloaddition with some facility. For example, the tetraene **94** on irradiation gave the [4 + 4]-adduct **95** in decent yield.[52] Similarly, photolysis of **96** has been reported to give **98** via decarbonylation to the tetraene **97** followed by intramolecular [4 + 4]-cycloaddition, Scheme 18.[53]

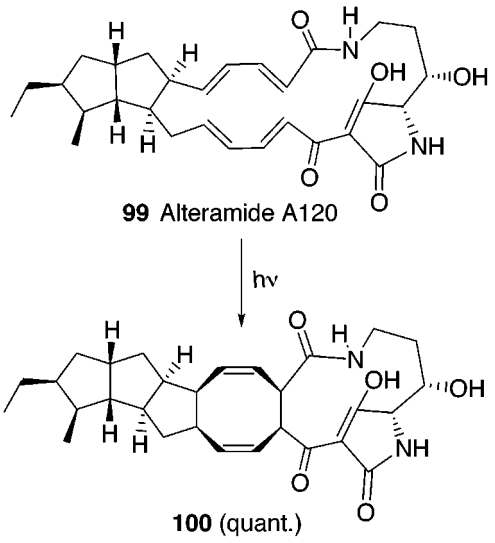
An interesting intramolecular [4 + 4]-cycloaddition[54] has been observed in the case of the natural product alteramide A 120 **99**, which on irradiation gave the cycloadduct **100** in quantitative yield, Scheme 19.

d. Transition Metal Mediated Cycloadditions of 1,3-Dienes. Transition metal catalysis has proved quite efficacious in overcoming the barriers that impede photochemical [4 + 4]-cycloaddition of acyclic 1,3-dienes. Many studies on transition metal catalyzed [4 + 4]-additions have been reported in recent years, some of them with

Scheme 18

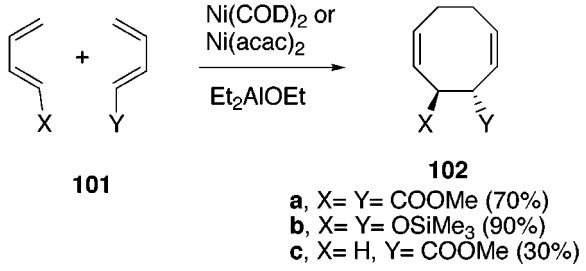


Scheme 19



potential industrial applications. Among the better known examples is the efficient dimerization[55] of butadiene to give cycloocta-1,5-diene using Ni catalyst in the presence of phosphine ligands. Regio- and stereoselectivity of the dimerization process employing substituted butadienes and nickel complexes as catalysts have been investigated by Waegell and coworkers.[56] The dimerization of 1-substituted butadienes **101** having carbomethoxy or siloxy groups has been found to be highly regio- and stereoselective and leads to the adducts **102a**,**b** in good yields. However, cross [4 + 4]-addition, such as the reaction between butadiene and methyl butadienoate, was found to be less successful, and the desired adduct **102c** was realized in low yield along with the [4 + 2]-adduct, Scheme 20. The nature and the position of the functional groups on the diene moiety is crucial to the [4 + 4]-addition process. For example, 1-acetoxybutadiene, 2-siloxybutadiene, and methyl sorbate failed to undergo cycloaddition, while dienes without polar functional groups gave mixtures of regioisomers.

Scheme 20



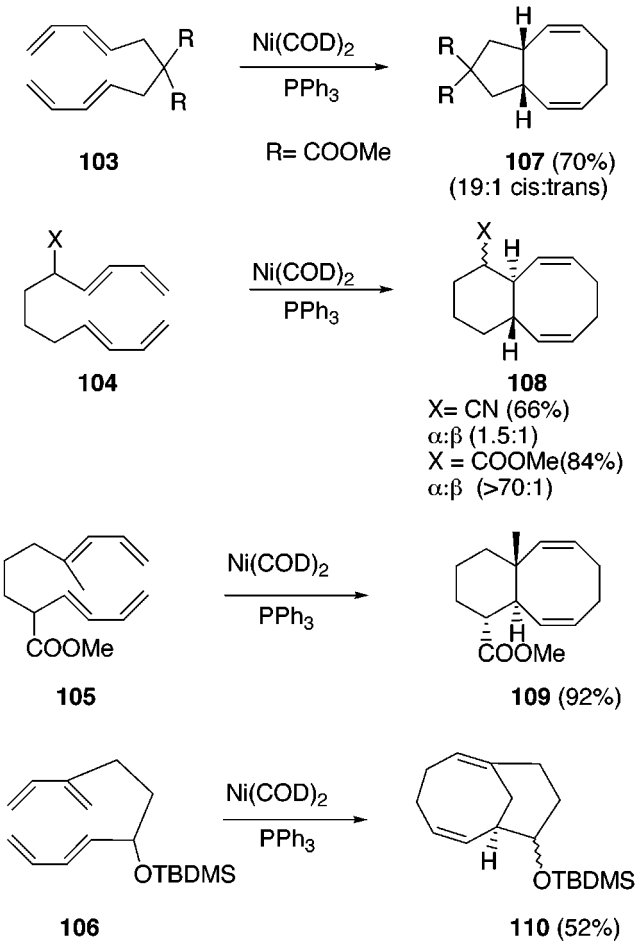
Recent efforts have also been directed toward developing an enantioseletive version of the Ni(0)-catalyzed [4 + 4]-additions employing chiral phosphine ligands. In this context, cycloaddition of methyl penta-2,4-dienoate and methyl sorbate to butadiene and homodimerization of methyl penta-2,4-dienoate have been explored.[57] Products resulting from [4 + 4] and [4 + 2] modes of addition were observed but with low ee's.[57a]

Effective use of nickel-catalyzed intramolecular [4 + 4]-cycloadditions of 1,3-dienes for preparative purposes and for application to complex synthesis has been detailed by Wender's group.[58] Exposure of **103**, having two 1,3-diene units joined through a three-carbon tether, to $Ni(COD)_2$ and triphenylphosphine furnished the adduct **107** stereoselectively (19:1 mixture of cis and trans isomers) and in good yield, along with minor amounts of other products. Other examples of cycloadditions include the transformation of **104**−**106** to **108**−**110**, respectively, Scheme 21. It is worth noting that dienes with four-atom tethers like **104** and **105** give preferentially trans-fused products (cf. **103**) via exo-cycloaddition mode. Manipulation of the position of the tether on the diene moieties can also be exploited to switch from fused to bridged cyclooctanoids. Thus, **106** leads to the bridged bicyclic compound **110** having the bicyclo-[5.3.1]undecane framework of taxoids. Total synthesis of a sesquiterpenoid natural product asteriscanolide **3** has been achieved employing this methodology (vide infra).

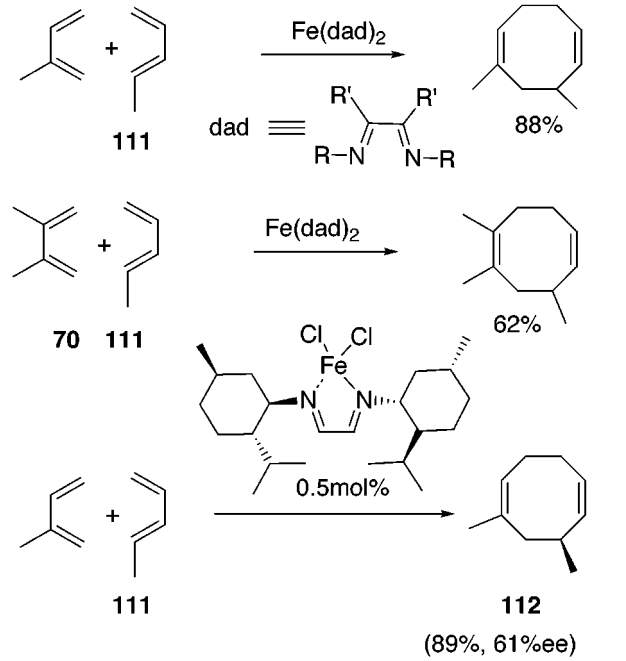
Iron diazadiene (dad) complex has also been found to efficiently induce [4 + 4]-cycloaddition in dienes.[57b] The substituents on the ligand have been found to exert significant control on regioselectivity and also induce preference for [4 + 4]-cycloaddition vs [4 + 2]-addition.[57b,c] Some examples of $Fe(dad)_2$-catalyzed cycloadditions are gathered in Scheme 22. Recently, enantioselective cross-cycloaddition between isoprene and *trans*-piperylene **111** in the presence of chiral Fe−dad catalyst leading to the formation of 1,7-dimethylcycloocta-1,5-diene **112** has been reported.[57e] Enantioselectivities in Ni- as well as Fe-catalyzed [4 + 4]-additions need further improvement to make them synthetically useful.

e. Cycloadditions of 2-Pyridones. Intermolecular photodimerization of 2-pyridones **113** to give stereoisomeric dimers of type **114** and **115** via head-to-head and head-to-tail [4 + 4]-cycloadditions, respectively, is known for quite some time[59,60] and constitutes a useful route to cyclooctanoids, Scheme 23. This theme has been further elaborated by several groups, and many structural variations

Scheme 21

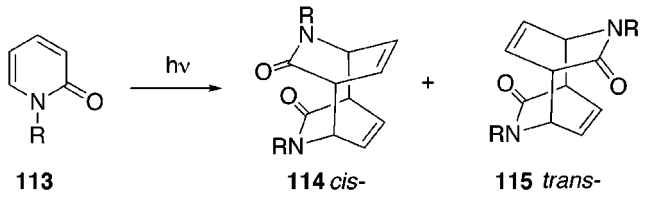


Scheme 22

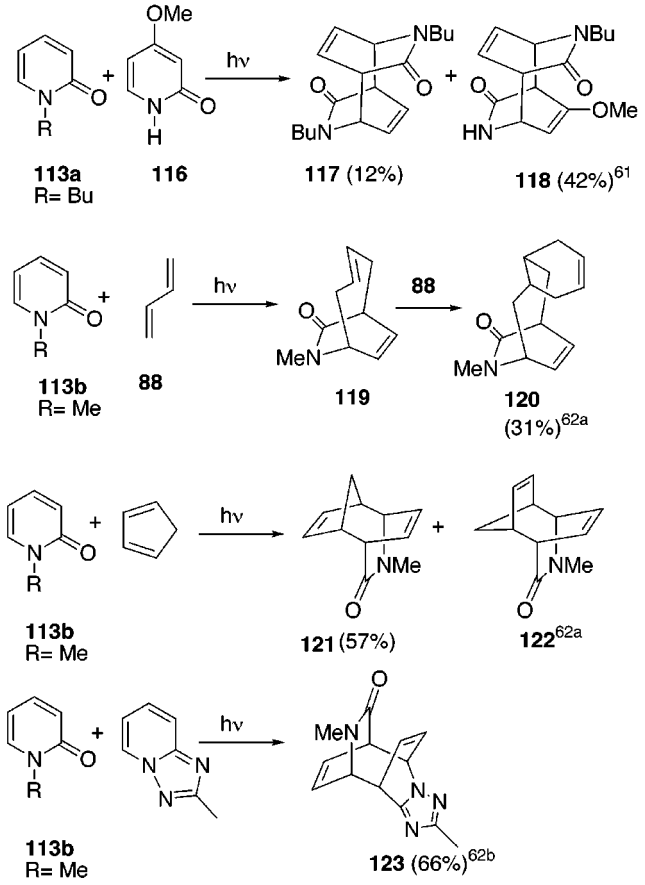


have been explored. Diverse 2-pyridones have been shown to undergo cross [4 + 4]-photocycloadditions with same or different 2-pyridones, e.g., **116**, as well as with a range of other 4π partners to furnish bridged cyclooctanoid compounds **117**−**123**, Scheme 24.

Scheme 23



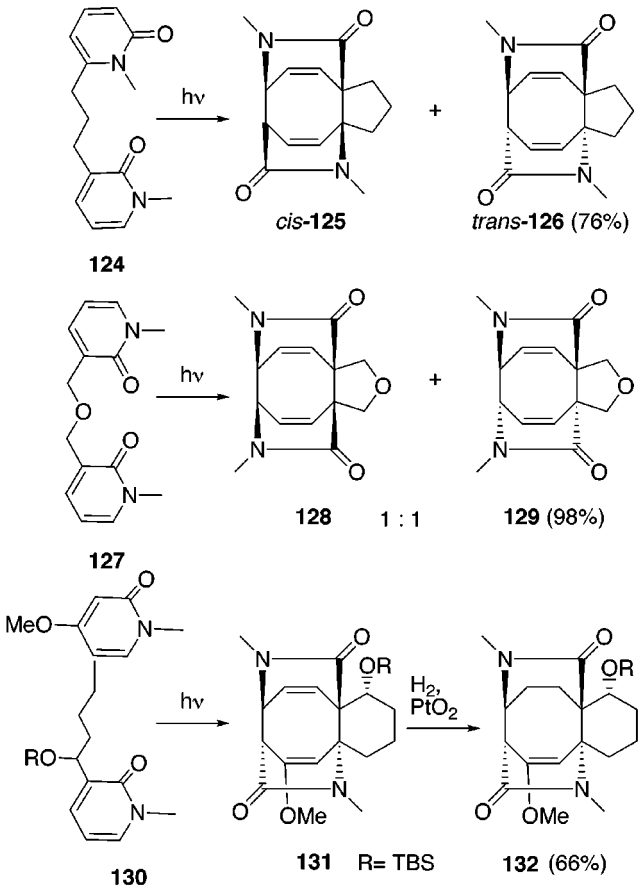
Scheme 24



The scope of intramolecular [4 + 4]-photocycloaddition of 2-pyridones toward the synthesis of cyclooctanoids has been subjected to detailed scrutiny by Sieburth and co-workers.[63,64] It was observed that the tethered 2-pyridone **124** undergoes efficient photoaddition to give a mixture of *cis*-**125** and *trans*-**126** isomers in which the latter predominates. Interestingly, the *cis*-adduct **125** could be converted into the trans adduct via Cope rearrangement followed by a photo cleavage/recombination pathway, eventuating in enhanced yield of the *trans*-adduct **126**, Scheme 25.[63d] It has been observed that when the tether contains an oxygen atom (see **127**), the relative ratio of *cis*-**128** and *trans*-**129** isomers is substantially affected and both are formed in equal amounts.

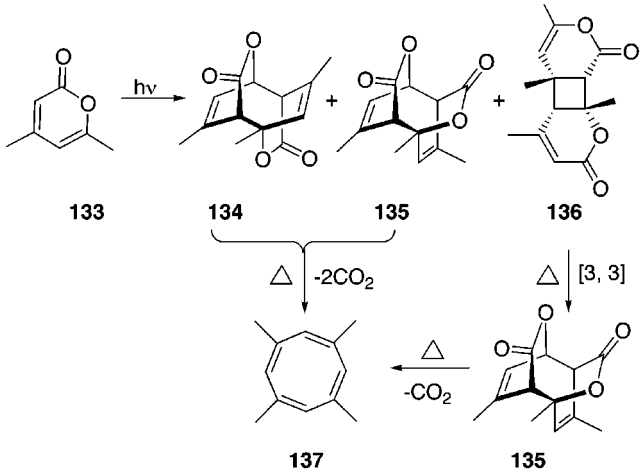
Recently, the same approach has been extended to construct BC rings of paclitaxel employing an intramolecular [4 + 4]-photocycloaddition in tethered **130** with two different 2-pyridone moieties to furnish *trans*-cycloadduct **131** selectively, through head-to-tail addition, Scheme 25. The two double bonds in the eight-membered ring of **131** could be differentiated, and it was readily transformed to **132** for further elaboration.[64a]

Scheme 25



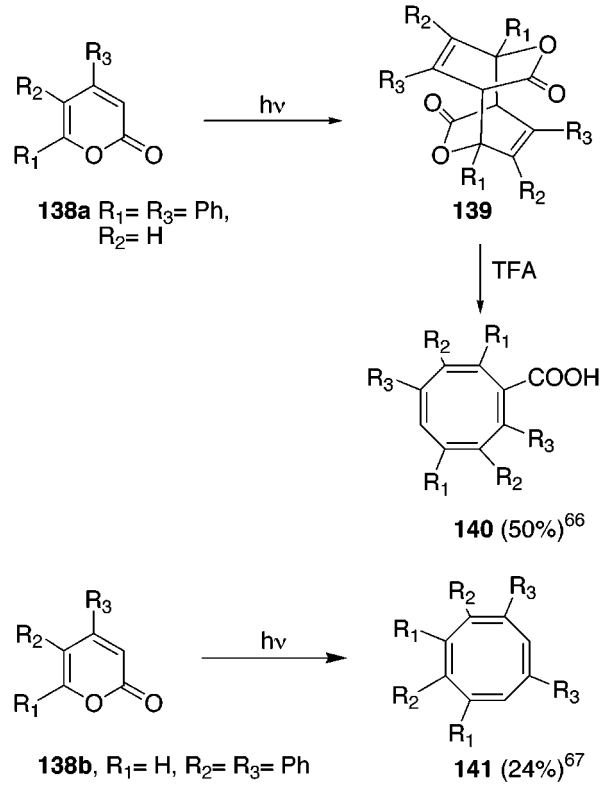
f. Cycloadditions of 2-Pyrones. 2-Pyrones are also known to exhibit propensity toward intermolecular photocycloadditions both in [4 + 4] and [2 + 2] fashion and, therefore, offer a potential route to cyclooctanoids. Previously, de Mayo had shown[65] that irradiation of 4,6-dimethyl-2-pyrone **133** gave two diastereomeric [4 + 4]-cycloadducts **134** and **135** along with a [2 + 2]-adduct **136**, all of which on thermal activation could be converted to tetramethylcyclooctatetraene **137**, Scheme 26.[65] Following this

Scheme 26



lead, several other pyrones, such as **138**, with different substitution patterns have been transformed into cyclooctatetraene derivatives **140** through the intermediacy of **139**, Scheme 27.[66] However, irradiation

Scheme 27



of **138b** adopts a more circuitous route to furnish the cyclooctatetraene derivative **141** after a series of cycloaddition, cycloreversion, and carbon dioxide extrusion.[67]

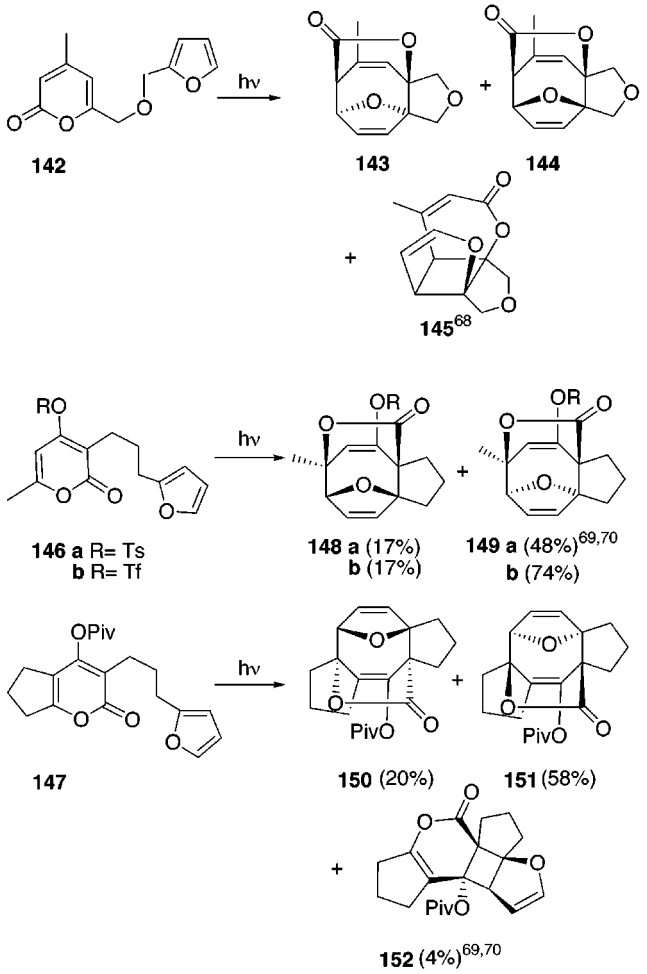
Wuest and his associates have studied cross [4 + 4] intramolecular photocycloaddition of 2-pyrones tethered at the 6-position with other dienes and examined their potential toward the construction of cyclooctanoids.[68−71] For example, photoreaction of furan-tethered pyrone **142** furnished three products, **143**, **144**, and **145**, as a result of exo [4 + 4]-, endo [4 + 4]-, and [2 + 2]-cycloadditions, Scheme 28.[68] The ratio of the products was found to be solvent dependent, and higher yields of [4 + 4] endo-adduct **144** could be obtained upon irradiation in an organized medium generated in aqueous LiCl. A number of other derivatives of **142** were also studied and gave similar results.[68]

Recently, more embellished pyrone derivatives **146** and **147** tethered to furan have been prepared and, on irradiation in aqueous methanol, led to products **148**, **149** and **150**, **152**, respectively, Scheme 28.[69,70] The [4 + 4]-adducts **150** and **151**, having 5-8-5 ring system, were suggested to be holding considerable synthetic potential for the construction of the fusicoccane and ophiobolin groups of natural products.

3. [4 + 3]-Cycloaddition of Oxyallyl Zwitterions

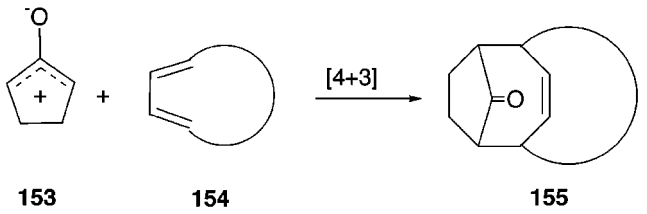
Addition of a 4π component **154** to a five-membered ring oxyallyl zwitterionic species, e.g., **153**, consti-

Scheme 28



tutes a potentially effective [4 + 3]-cycloaddition route to eight-membered rings, e.g., **155**, Scheme 29.

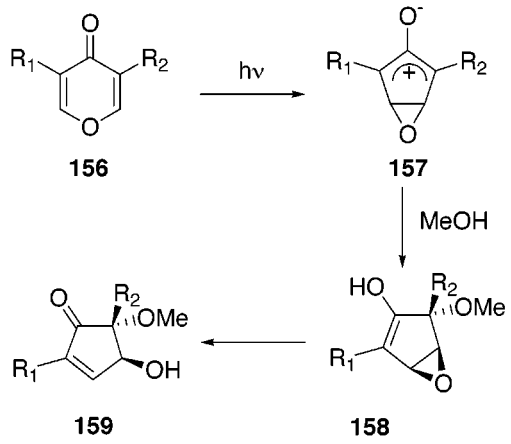
Scheme 29



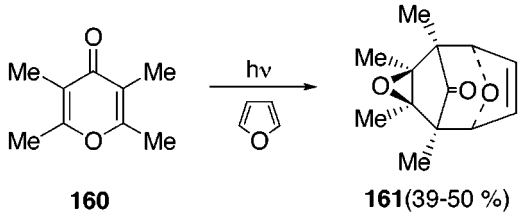
The main concern in the execution of this strategy is the generation of the species **153** for which both photochemical and chemical methods have been explored. 4-Pyrones **156** have been shown[72−75] to rearrange on irradiation to oxyallyl zwitterions of type **157**, which unfolds a variety of ground-state reactions to furnish products such as **158** and **159** through solvent trapping and rearrangement, depending upon experimental conditions, Scheme 30.[75] West and co-workers have reported that photochemical reaction of tetramethyl-4-pyrone **160** in the presence of furan furnished the [4 + 3]-adduct **161** in a reasonably good yield, Scheme 31.[76] However, in view of the limited success of this intermolecular cycloaddition, attention was turned toward the intramolecular version of this process.

In this context, pyrones of the type **162** and **163** in which a furan was tethered at 3-position of the

Scheme 30

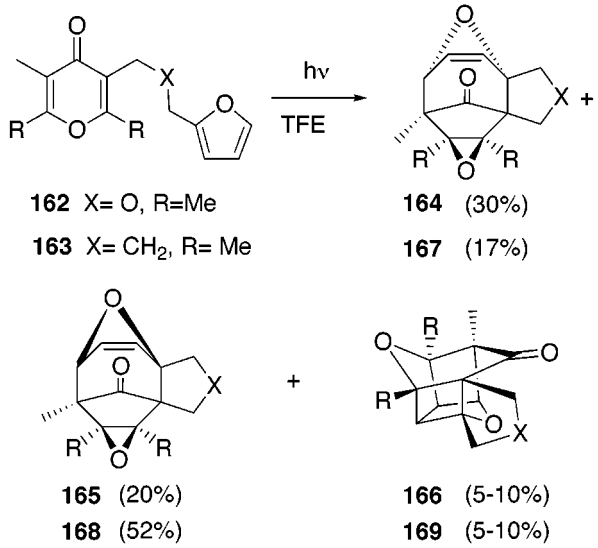


Scheme 31



4-pyrone were prepared, and their irradiation gave diastereomeric [4 + 3]-cycloadducts **164**, **167** and **165**, **168**, respectively, along with small amounts of caged products **166** and **169**, Scheme 32.[76] Several

Scheme 32

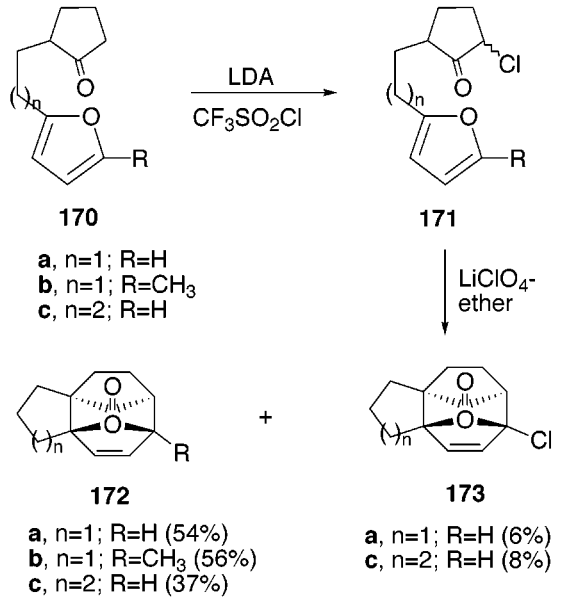


examples have been investigated, and while the yields are acceptable, many more studies are required to delineate the stereo- and regiochemical controls before this strategy can be extended toward cyclooctanoid natural products.

Harmata and co-workers[77,78] developed intramolecular [4 + 3]-cycloaddition of chemically generated oxyallyl zwitterions[79] as a new route to cyclooctanoids. Thus, treatment of the furan tethered ketones **170a**−**c** with LDA/CF_3SO_2Cl gave the corresponding chloroketones **171a**−**c**, which on exposure

to ethereal $LiClO_4$ gave the adducts **172a**−**c** along with minor amounts of **173a**−**c**, Scheme 33. This

Scheme 33



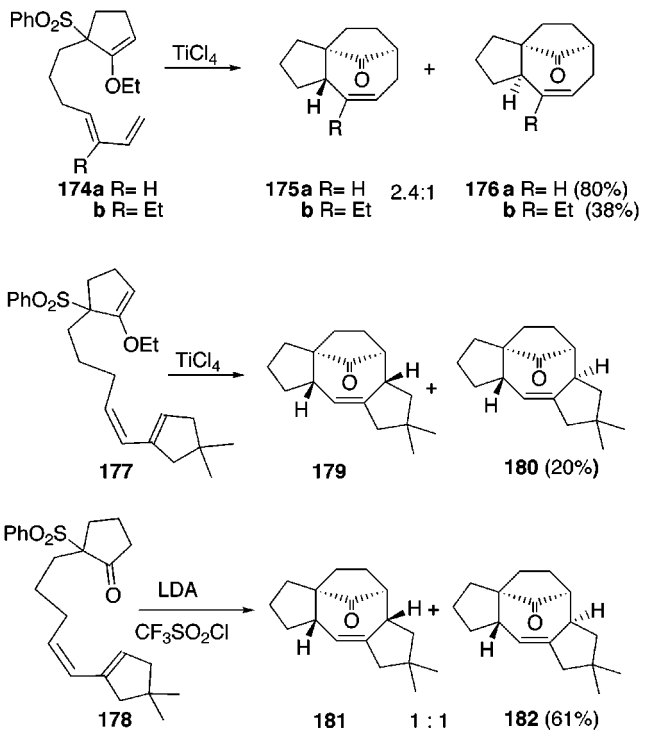
method is quite general for generating oxyallyl zwitterions and has found applications in the synthesis of many other carbocyclic systems.[78]

The oxyallyl zwitterion mediated intramolecular cycloadditions have been found to be highly selective and occur through endo addition as in the case of the intermolecular version.[78] However, when the method was applied to a substrate containing a butadiene moiety in place of furan, the reaction failed to give any adduct. Thus, a modification of the strategy was devised that enabled the success of such additions. Reaction of **174a**, an enol ether bearing a sulfone moiety as well, with $TiCl_4$ furnished the cycloadducts **175a** and **176a** in good yield, Scheme 34. However, the presence of alkyl substituents on the diene moiety was found to be detrimental and resulted in low yield of the adducts as shown in the case of **174b**. Several additional examples of intramolecular [4 + 3]-cycloadditions via oxyallyl zwitterions derived from **177** and **178** have been reported to furnish **179**, **180** and **181**, **182**, respectively, Scheme 34. Formation of 5-8-5-fused tricyclics **179**−**182** with four well-defined stereogenic centers and adequate functionalization is a notable feature of this approach.

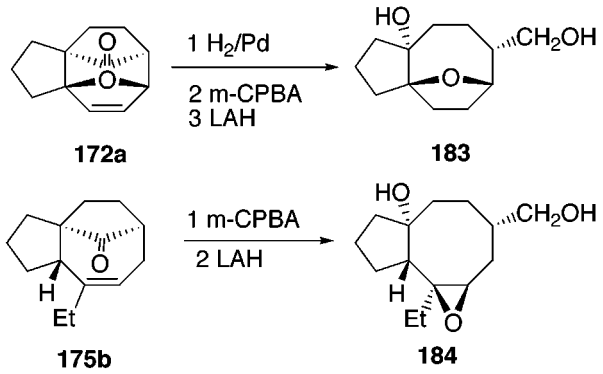
Harmata has also explored the synthetic utility of some of the adducts obtained from these [4 + 3]-cycloadditions by extracting the bicyclo[6.3.0]octane unit through routine transformations.[77c] Thus, the adduct **172a** was transformed into **183** and **175b** to **184** as possible building blocks for natural product synthesis, Scheme 35.

Pursuing a similar [4 + 3] theme, Cha et al.[80a,b] have reported analogous cycloadditions employing cyclic aza-allyl zwitterions to construct a bridged cyclooctanoid system. Reaction between **185a**,**b** and **186** in the presence of silver ions furnished **187a**,**b** having the elements of taxoid framework, Scheme 36. Further extension of this theme has been reported.[80c]

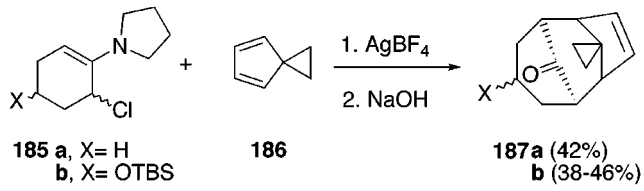
Scheme 34



Scheme 35



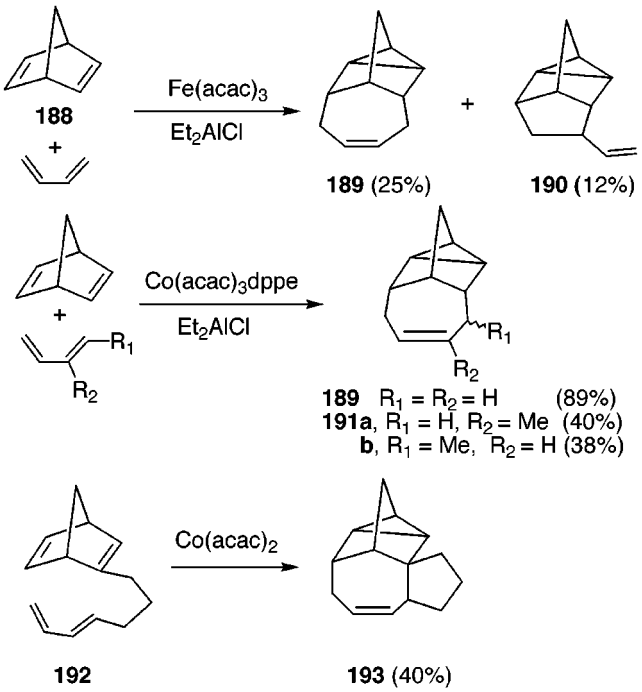
Scheme 36



4. [4π + 2π + 2π]-Cycloadditions

Greco and co-workers were the first to report metal-catalyzed [4 + 2 + 2]-cycloaddition between norbornadiene **188** and 1,3-butadiene **88** employing an iron catalyst,[81a] which furnished both [4 + 2 + 2]-adduct **189** and [2 + 2 + 2]-adduct **190** along with norbornadiene dimers, Scheme 37. This type of cycloaddition, reminiscent of the well-known homo-Diels−Alder reaction of norbornadiene, is fairly general, and improved yields of [4 + 2 + 2]-adducts, with the exclusion of the [2 + 2]-adducts, could be obtained when a cobalt catalyst system ($CoCl_2$/dppe/Et_2AlCl) was used.[81b] Lyons has also reported[81c] Co-

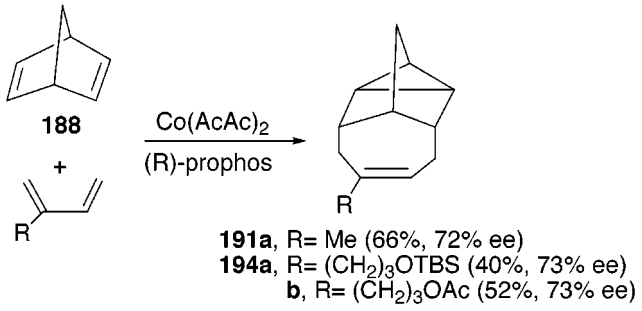
Scheme 37



$(acac)_3$-promoted coupling between norbornadiene and various butadienes to give [4 + 2 + 2]-adducts **189**, **191** in good yields. The intramolecular version of the [4 + 2 + 2]-cycloaddition has also been explored.[81e] Thus, 2-substituted norbornadiene **192** furnished the pentacyclic compound **193** in the presence of cobalt catalyst, Scheme 37.

Lautens and co-workers have reported on the asymmetric induction during cycloaddition of norbornadiene and several 2-substituted butadienes employing cobalt catalysts in the presence of chiral phosphines. Of the various chiral phosphines examined (*R*)-prophos gave the highest ee's. A few examples leading to the formation of **191a** and **194a**,**b** are shown, Scheme 38.[81d,e]

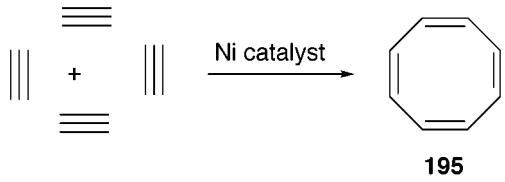
Scheme 38



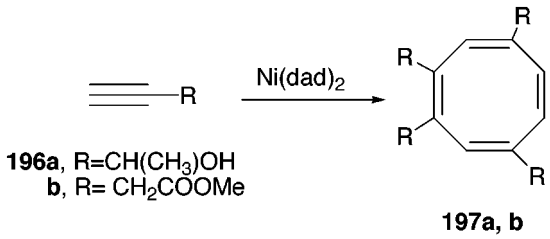
5. [2π + 2π + 2π + 2π]-Cycloadditions

Cycloaddition between four 2π partners was first discovered by Reppe[82] during his seminal preparation of cyclooctatetraene via telomerization of acetylene in the presence of $NiBr_2/CaC_2$. This reaction is also catalyzed by other nickel catalysts such as $Ni(acac)_2$ and $Ni(COD)_2$ and constitutes an industrial process for the production of cyclooctatetraene **195**, Scheme 39.[82,83] Extension of this methodology for the telomerization of substituted alkynes would naturally bring in problems of regioselectivity and may lead to a number of adducts with a variety of substitution patterns. In an effort to induce regioselective cycloaddition between substituted alkynes, sterically hindered 1,2-diazadiene (dad) nickel complexes have been employed as catalysts.[84] Thus, monosubstituted alkynes **196a,b** furnish **197a,b** in a regioselective manner, Scheme 40. [84]

Scheme 39



Scheme 40

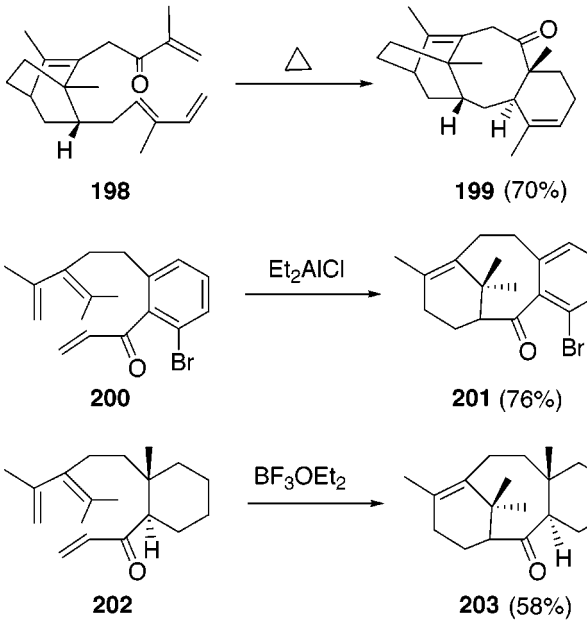


6. [4 + 2]-Cycloadditions

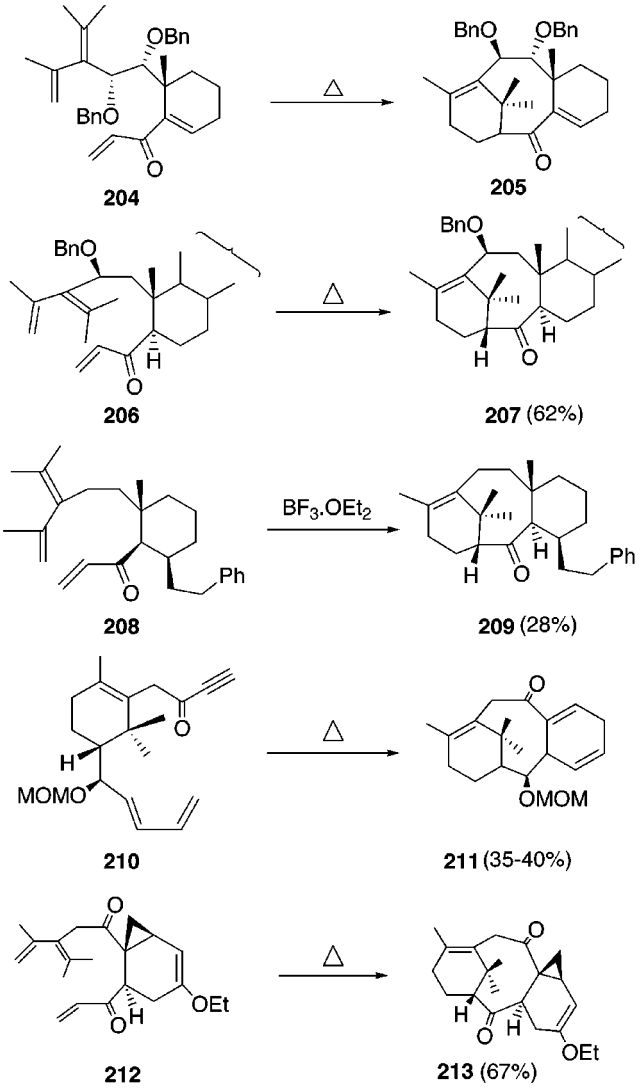
It is quite natural that [4 + 2]-cycloadditions (Diels−Alder reactions), which have proved to be so invaluable in carbocyclic construction, should also find applications in the synthesis of eight-membered rings. Obviously, [4 + 2] approaches to eight-membered rings have to be in intramolecular mode, and many elegant strategies have evolved with the taxane framework as the objective.[85−87] In this context, the [4 + 2]-cycloaddition is primarily setup to construct either ring A or C of the taxoids, but the diene and dienophilic moieties are so spaced that during the process of six-membered ring formation, an eight-membered ring is concurrently generated. The earlier approaches to the taxane system involving intramolecular [4 + 2]-cycloaddition, pursued by Sakan (**198** → **199**),[85a] continue to be refined by Shea (**200** → **201**)[86a,b] and Jenkins (**202** → **203**),[87a] employing more embellished precursors, Scheme 41. Thus, Shea has recently reported[88] the elaboration of highly functionalized **204** to **205** via intramolecular [4 + 2]-cycloaddition, Scheme 42. Danishefsky and associates[89a] have also utilized intramolecular Diels−Alder reaction for the synthesis of steroid−taxoid hybrids. Thus, **206** underwent facile [4 + 2]-cycloaddition to furnish **207**, Scheme 42.

Williams[90] and Fallis [91] have also explored the variants of the intramolecular [4 + 2]-cycloaddition approach to the ABC ring system of taxanes **208** → **209** and **210** → **211**, respectively. Recently, Winkler has reported[92a] an interesting example in which the precursor **212**, having a cyclopropane ring, underwent a Diels−Alder reaction to furnish tetracyclic compound **213**, Scheme 42.

Scheme 41

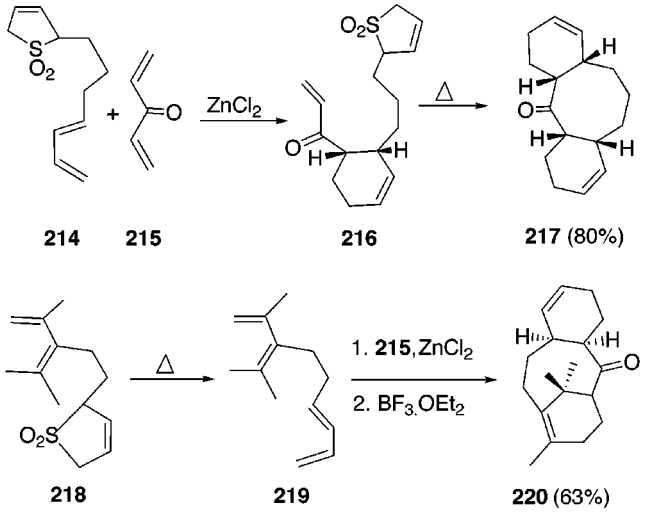


Scheme 42



Winkler has also devised[92] synthetic routes to fused and bridged cyclooctanoid systems through a double Diels–Alder approach involving inter- and intramolecular [4 + 2]-cycloadditions in tandem. In this approach, the sulfone moiety in **214** served as a masked 1,3-butadiene equivalent to sequentially generate two dienic moieties. Thus, [4 + 2]-cycloaddition of **214** with divinyl ketone **215** furnished the sulfone **216**, which upon unmasking of the second diene unit and [4 + 2]-cycloaddition evantuated in the tricyclic compound **217**, Scheme 43. This method

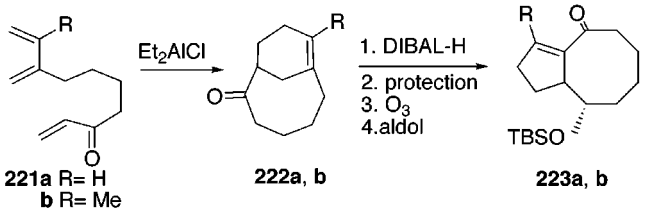
Scheme 43



has been further extended to access ABC ring systems of taxanes through unmasking of the 1,3-diene moiety in sulfone **218** to furnish **219**. Double Diels–Alder reactions, catalyzed by Lewis acids, between **219** and bis-dienophile **215** led to **220**, Scheme 43.[92c, d]

Very recently, Shea has coupled the intramolecular Diels–Alder strategy to bridged cyclooctane ring systems with an interesting ring restructuring process to prepare fused eight-membered rings. In this "bridged to fused ring exchange", the adducts **222**, readily obtained through intramolecular Diels–Alder reaction in **221**, were transformed to **223** through oxidative cleavage and aldol cyclization, Scheme 44.[93]

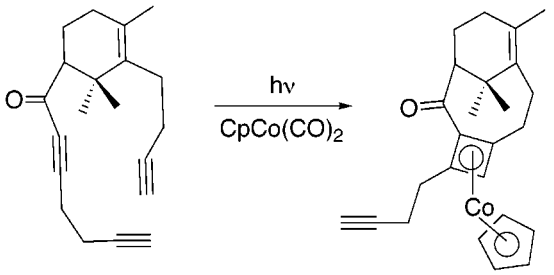
Scheme 44



7. [2 + 2]-Cycloadditions

So far only one example of intramolecular [2 + 2]-cycloaddition leading directly to the formation of eight-membered rings has been reported. Malacria et al. have reported[94] a cobalt-mediated cycloaddition in ene–triyne **224** leading to the formation of a novel Co-complexed polycyclic cyclobutadiene **225** incorporating the AB rings of taxanes, Scheme 45.

Scheme 45

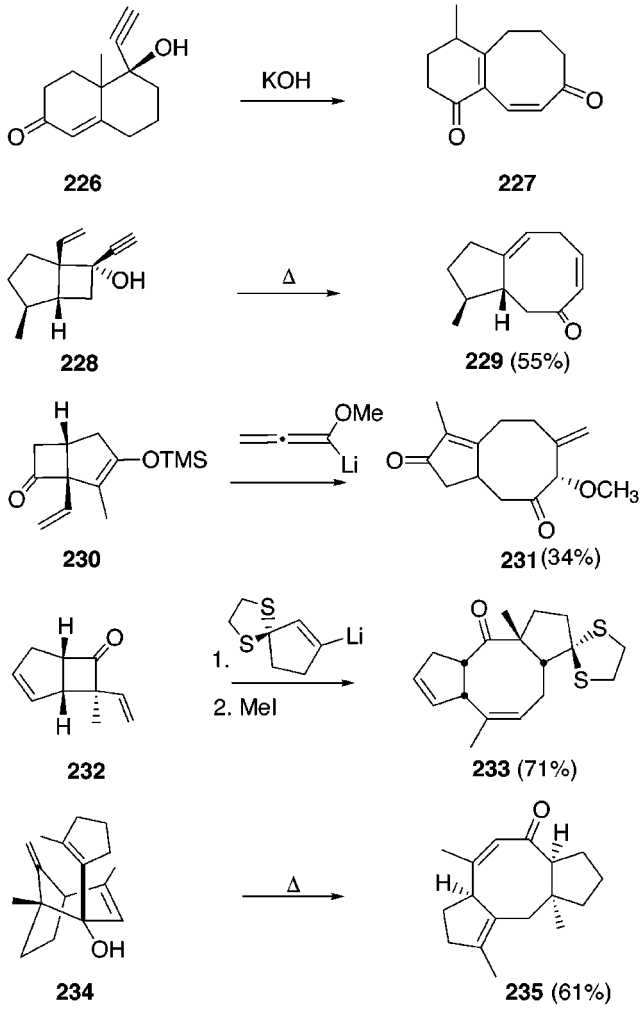


224 **225** (32%)

B. [3,3]-Sigmatropic Rearrangements

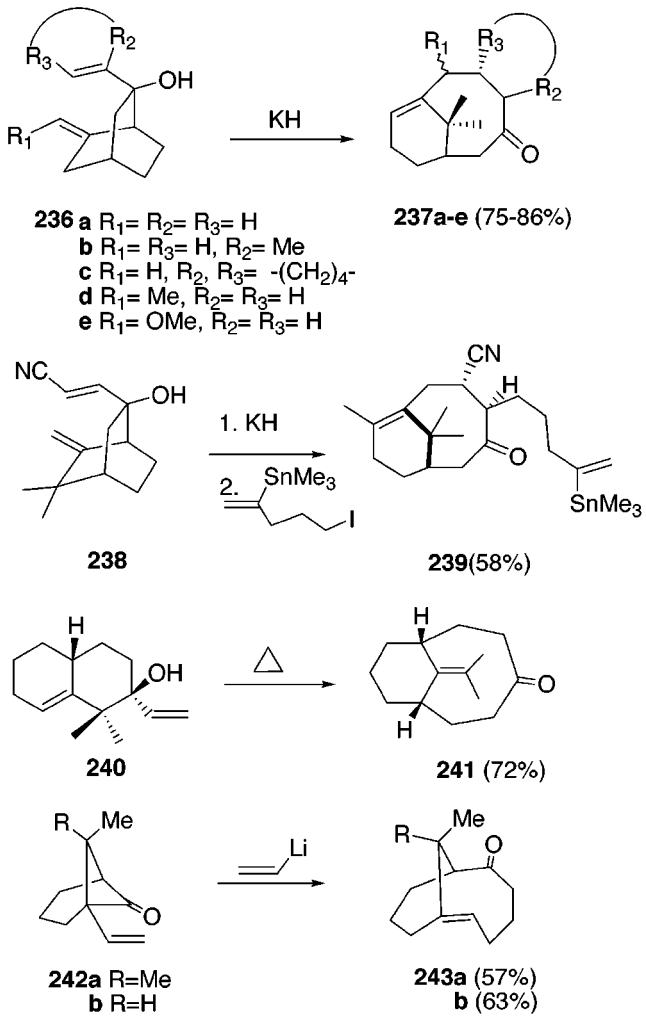
Electronic reorganizations through [3,3]-sigmatropic processes have emerged as a powerful strategy for the rapid construction of a variety of polycyclic frames, and eight-membered ring systems are no exception.[95] In particular, Cope and Claisen rearrangements and several of their variations (e.g., oxy-, anionoxy-, and dianionic-Cope) have proved efficacious in cyclooctanoid construction, both for fused and for bridged ring systems. The main advantage of approaches based on [3,3]-sigmatropic shifts is that the stereochemical outcome is mostly predictable, and often the complex carbocyclic framework can be generated in just one step.

Scheme 46



Early examples of the synthesis of fused cyclooctanoid systems through the oxy-Cope processes (**226** → **227**) and (**228** → **229**) were reported by Swaminathan et al.[96] and by Gadwood et al.,[97] respectively. The latter workers have further elaborated the bicyclo[6.3.0]undecadienone **229** to the sesquiterpenoids poitediol and dactylol.[97] Another example (**230** → **231**) of bicyclo[6.3.0]nonane construction, resembling the earlier work of Gadwood, has been recently described by the group of Moore.[98] Paquette and coworkers[99] have imaginatively exploited the oxy-Cope strategy to construct the 5-8-5-fused tricyclic system in a stereoselective fashion (**232** → **233**) and (**234** → **235**), Scheme 46. This approach has been further applied to the synthesis of natural products (vide infra).

Scheme 47

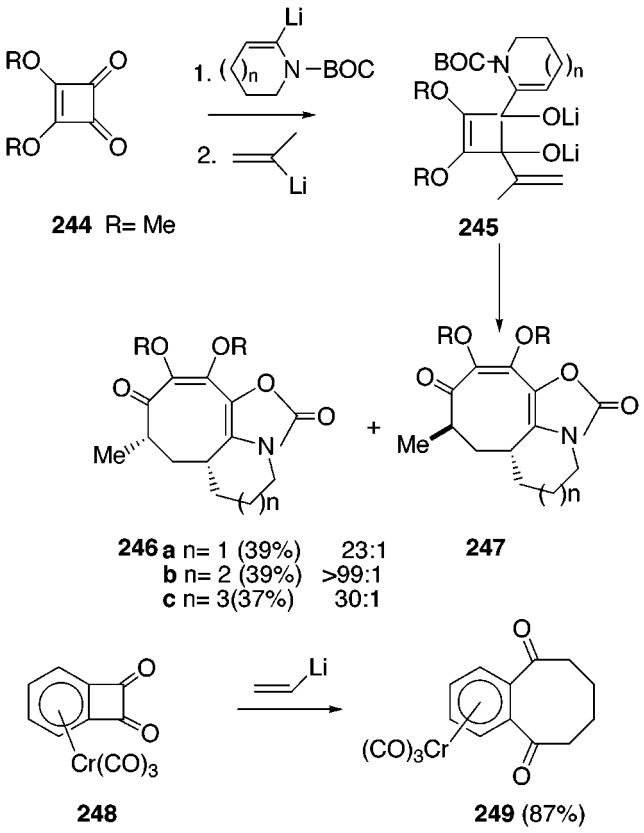


The oxy-Cope theme has been equally effective in the construction of the bridged cyclooctanoid systems. Some of the examples reported recently are considered here. Formation of the bicyclo[5.3.1]undecane ring system through this process is particularly noteworthy as it provides entry into the taxoid framework. In this context, Martin's[100] general synthesis of functionally embellished bicyclo[5.3.1]-undecanes such as **237** and **239** from the bicyclo-[2.2.2]octane precursors **236** and **238**, respectively, are particularly pleasing examples, and **239** has been further elaborated to the ABC ring system of taxanes, Scheme 47.[100] Other interesting examples of bicyclo-

[5.3.1]undecane formation are the oxy-Cope rearrangements in the readily available decalin derivative (**240** → **241**)[101] and the bridgehead-substituted bicyclo[3.1.1]heptane derivative (**242** → **243**).[102]

Dianionoxy-Cope rearrangements have also found application in the construction of cyclooctanoids as shown by the efforts of Paquette[103] and Butenchson.[104] Squaric acid derivative **244**, on sequential addition of two alkenyl lithium reagents, furnished the divinyl intermediate **245**, which further rearranged to diastereomeric polycyclic products **246** and **247**.[103] In a similar manner, chromium−tricarbonyl complex of benzocyclobutenedione **248**, on addition of 2 equiv of alkenyl lithium reagents, gave an intermediate dianionoxy-Cope system which rearranged to the benzocyclooctanedione **249**, Scheme 48. [104]

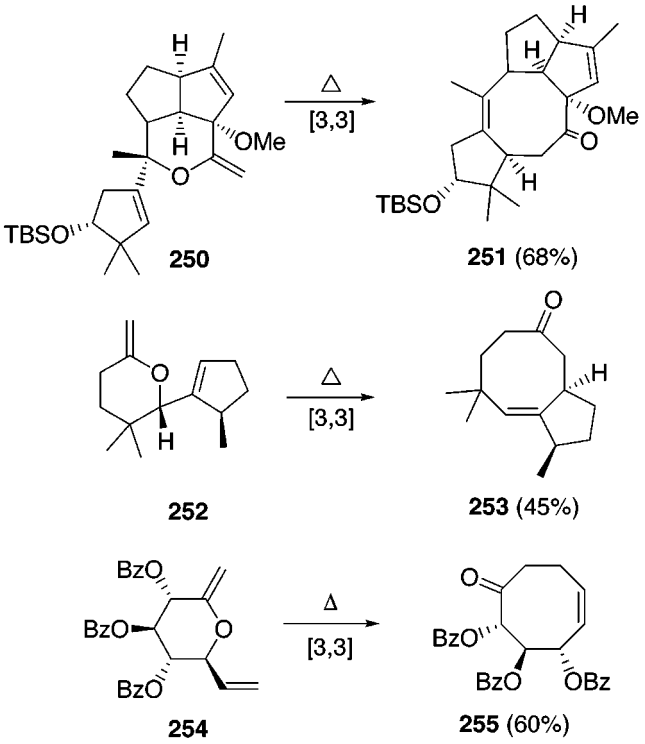
Scheme 48



Claisen rearrangements also constitute a versatile methodology for the synthesis of various cyclooctanoids especially after the emergence of Tebbe's reagent[105] which provides an easy access to exocyclic vinyl ethers via the olefination of lactone carbonyls. Interesting examples of the Tebbe−Claisen sequence have emanated from Paquette et al. (**250** → **251**), Scheme 49.[106] Petasis and co-workers[107] have exploited the Claisen rearrangement in vinyl ether **252** to furnish **253**, a precursor to the marine natural product precapnelladiene, Scheme 49. Recently, synthesis of optically pure cyclooctenone derivative **255** from the precursor **254**, which in turn is easily derived from D-glucose, has been reported.[108]

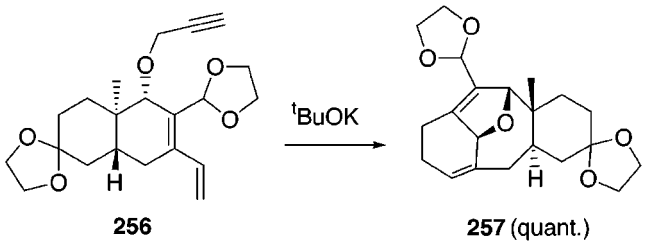
Kanematsu has reported[109] a novel route to a taxane carbon framework employing a bicyclic alkyne in which isomerization and a [2 + 2]-cycloaddition

Scheme 49



precede the key 3,3-shift step. Thus, treatment of enantiopure enyne **256** with base, in situ, generated an allene intermediate, which underwent tandem intramolecular [2 + 2]-addition and 3,3-shift to give a tetracyclic product **257** in stereo- and enantioselective manner, Scheme 50.

Scheme 50



C. Cyclizations

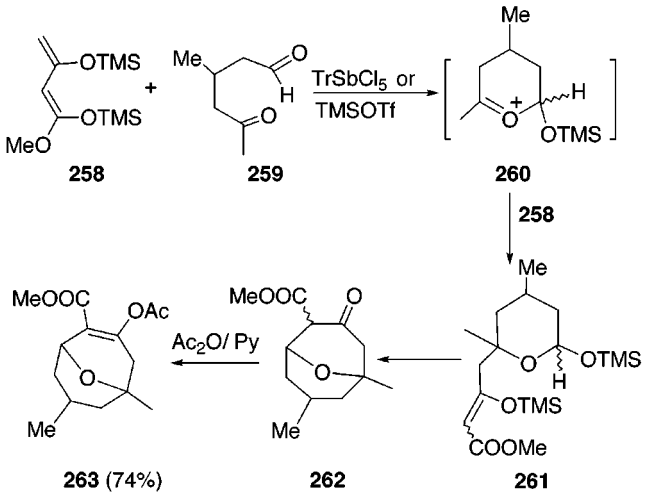
Cyclization reactions in appropriately functionalized precursors, catalyzed and promoted by various reagents and involving a range of intermediates (carbonium ions, radicals, organometallics, etc.), constitute a direct entry into cyclooctanoids. Consequently, these approaches have been extensively explored with a wide range of substrates and reagents and are discussed at some length here.

1. Cationic/Lewis Acid Catalyzed Cyclizations

Molander and his associates[110,111] have developed a new approach to cyclooctanoid synthesis involving a Lewis acid catalyzed reaction between bis(trimethylsilyl)enol ethers of β-keto ester **258** as 1,3-donor and 1,5-diones such as **259** as acceptors to furnish the keto ether **262**, which was conveniently isolated as enolacetate **263**. The cyclization proceeds through

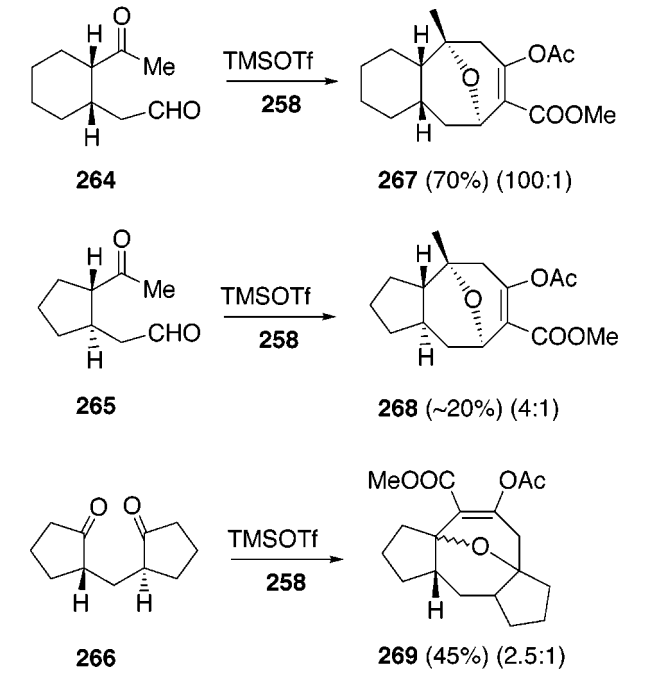
regioselective generation of oxocarbenium ion **260** and subsequent attack of the more nucleophilic terminal carbon of **258** on the second carbonyl group to give the intermediate **261**. Formation of a second cyclic oxocarbenium ion from **261**, followed by ring closure, delivers the bicyclic keto ether **262** in a regio- and stereoselective fashion, Scheme 51. The method

Scheme 51



is quite general, and a variety of cyclooctanoids have been prepared.[110] Thus, the reaction of keto aldehydes **264**−**266** with **258** followed by acetylation furnished the enolacetates **267**−**269**, respectively, Scheme 52.

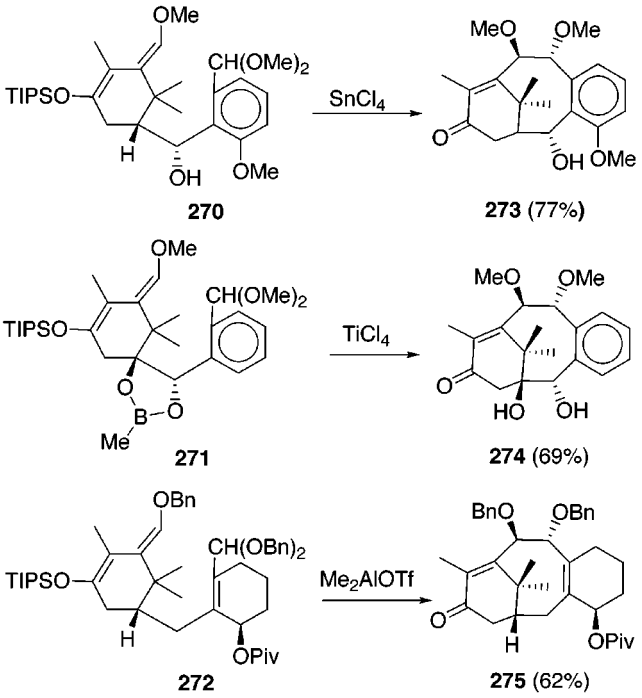
Scheme 52



Synthesis of marine natural product (+)-dactylol has been achieved following this methodology.

Kuwajima and co-workers have developed a novel intramolecular Lewis acid mediated cyclization involving enol ethers of 1,3-dione and dimethyl acetal of an aldehyde to construct bridged eight-membered rings.[112−116] Several examples (**270**−**272** → **273**−**275**) of such cyclizations in the context of synthesis of taxoids have been reported, Scheme 53. The inter-

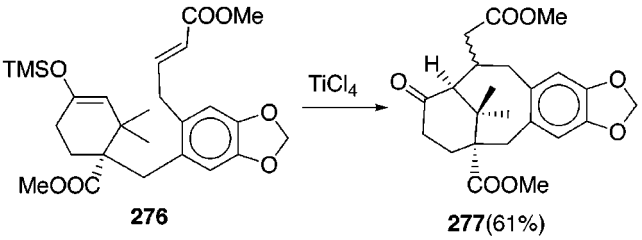
Scheme 53



mediate **275**, in particular, has been employed for a successful synthesis of the diterpene natural product taxusin.[116]

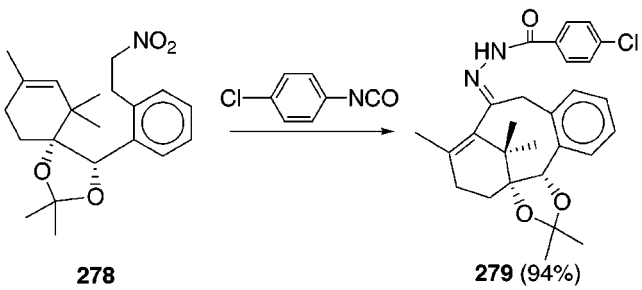
Recently, d'Angelo has demonstrated[117] the efficacy of a titanium(IV)-mediated Michael-type intramolecular ring closure in silyl enol ether **276** to a tricyclic ring C aromatic taxoid **277**, Scheme 54.

Scheme 54



An interesting intramolecular cyclization has recently been reported by Hirai et al.[118] in which the substrate **278**, having a nitroethyl chain on the aromatic ring, was transformed into **279** with exceptional efficiency, Scheme 55.

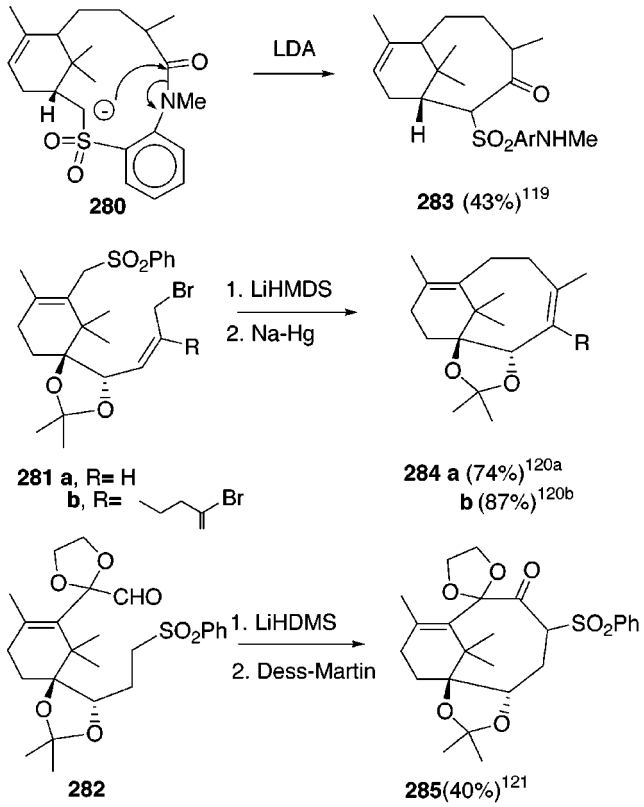
Scheme 55



2. Anionic Cyclizations

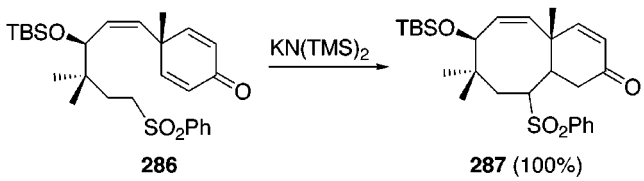
Carbanion-mediated cyclizations involving aldol condensations, intramolecular displacements, and Michael additions, among others, have proved very effective in the construction of bridged eight-membered rings. Intramolecular alkylations employing sulfonyl-stabilized carbanions have been exploited by several groups to construct the ring B of the taxane system. Thus, functionally embellished A ring bearing substrates **280**−**282** smoothly cyclized to AB ring products **283**−**285**, respectively, Scheme 56.[119−121] An

Scheme 56



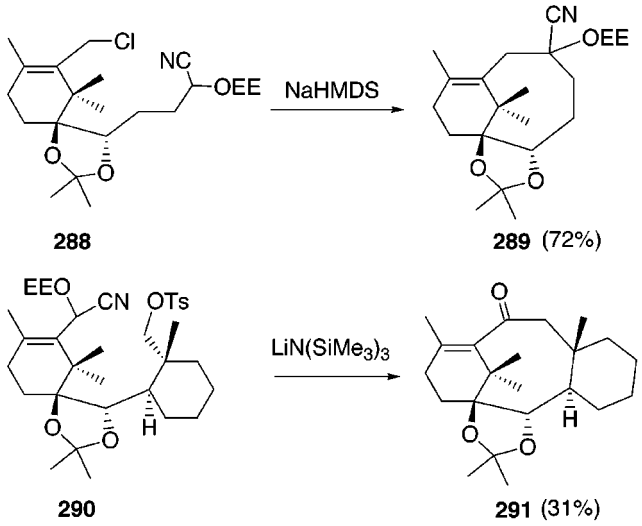
extension of the theme involving sulfonyl stabilized carbanions is the intramolecular Michael addition in **286** to deliver BC ring precursor **287** of the taxanes in quantitative yield, Scheme 57.[122]

Scheme 57



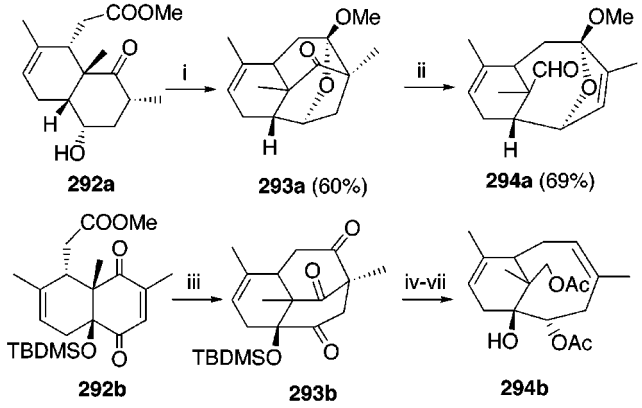
Stork and his group[123] have constructed the B ring of taxanes employing the protected cyanohydrin as the masked carbonyl anion equivalent.[124] Thus, treatment of **288** with base yielded the cyclized product **289** in good yield, representing the AB ring of taxoids, Scheme 58.[123a] An extension of this approach for the successful synthesis of the ABC rings of taxanes has been reported recently by the same authors.[123b] A conceptually similar cyclization of **290** to **291** has

Scheme 58



been described by Takahashi and co-workers.[125] Carbanion-mediated cyclization is also the key element of the approach to the AB ring of taxoids by Fetizon and co-workers.[126] Intramolecular acylation in the *cis*-decalin derivative **292a** followed by intramolecular hemiacetalization furnished **293a**. A photochemical Norrish-type cleavage in **293a** proceeded poorly (12% conversion) to the tricyclic hemiacetal **294a** having a bridged eight-membered ring, Scheme 59.[126] Inter-

Scheme 59[a]

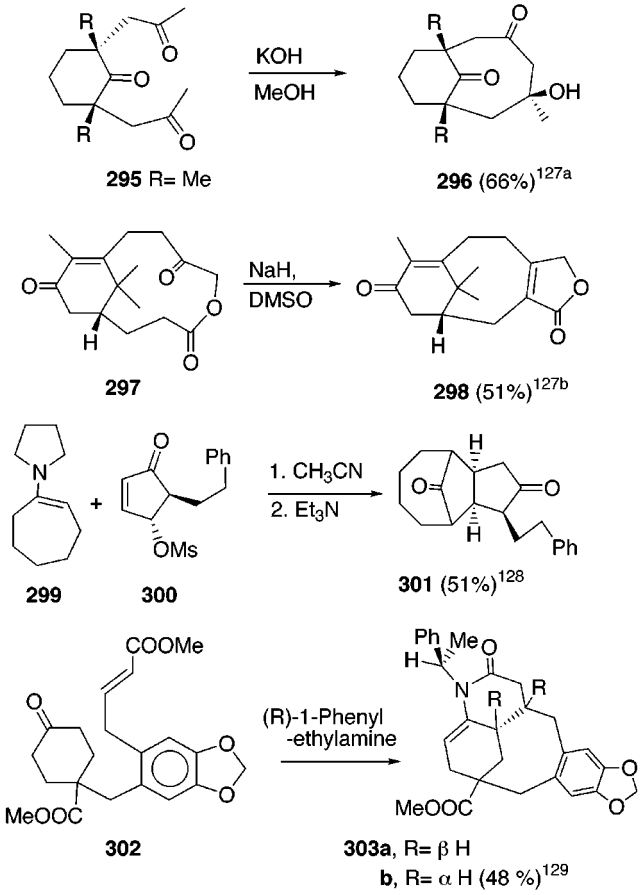


[a] Reagents: i (a) NaHDMS, (b) $HC(OCH_3)_3$; ii *hv*; iii Zn, AcOH, 67%; iv $NaBH_4$−$CeCl_3$, 90%; v $NaBH_4$, 100%; vi Ms_2O−pyridine; vii LAH, 60%.

estingly, treatment of the compound **292b** with zinc furnished the trione **293b** which was readily elaborated to **294b** having AB rings of taxoids via Grob fragmentation, Scheme 59. [126b]

Romero and co-workers[127a] were also able to construct the AB ring of taxoids via the classical aldol condensation in the triketone **295** to furnish the aldol product **296** in reasonable yield. It may be noted that methyl groups at α, α′ positions of the cyclohexanone **295** are necessary to provide conformational control for this cyclization to occur. It is significant in this context that the base treatment of the unsubstituted precursor (**295**, R = H) gave only intractable product mixture, Scheme 60.[127a] A similar intramolecular aldol condensation in the keto lactone **297** has also been reported to give **298** in good yields. [127b]

Scheme 60

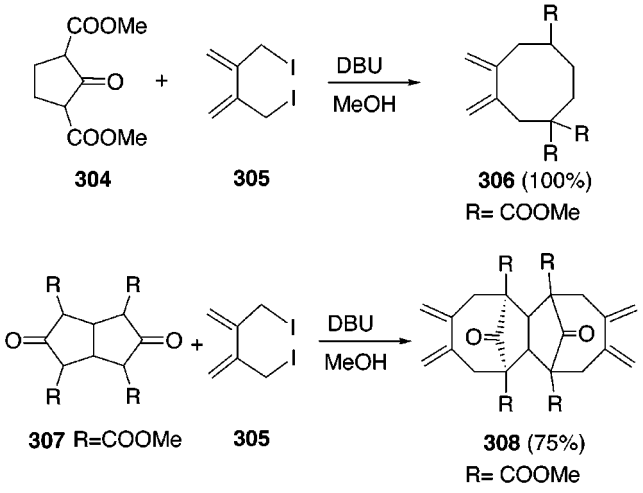


A tandem intramolecular enamine−Michael addition and intramolecular enamine alkylation was employed by West and co-workers to create an eight-membered ring, Scheme 60.[128] Thus, cycloheptanone enamine **299**, on reaction with the preformed synthon **300** underwent a series of reactions to furnish the tricyclic dione **301**. Similarly, d'Angelo has reported enamine mediated Michael addition and cyclization in **302**, in the presence of (*R*)-1-phenylethylamine, to give the tricyclic compound **303a, b** having the ring C aromatic ABC framework of taxanes, Scheme 60.[129]

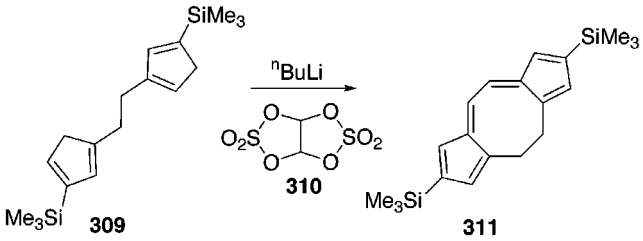
Rodriguez and co-workers[130] have developed a new and efficient method for cyclooctanoid synthesis via double displacement of allylic/benzylic 1,4-dihalides with cyclopentanone dicarboxylate **304** and diquinane tetracarboxylate **307**, Scheme 61. Reaction of **304** with dihalide **305** in the presence of DBU gave the cyclized products **306** in excellent yield. Interestingly, the initially formed intermediate bridged ketones cleaved in the reaction medium to unravel the cyclooctane ring. Similarly, the reaction of tetraester **307** with **305** led to the interesting building block **308**, Scheme 61.

Hafner and co-workers[131] have reported an interesting preparation of tricyclic array **311** incorporating a 5-8-5-fused ring system with a central eight-membered ring from 1,2-bis(trimethylsilylcyclopentadienyl)ethane **309** through base catalyzed double condensation with glyoxal sulfate **310**, Scheme 62.

Scheme 61



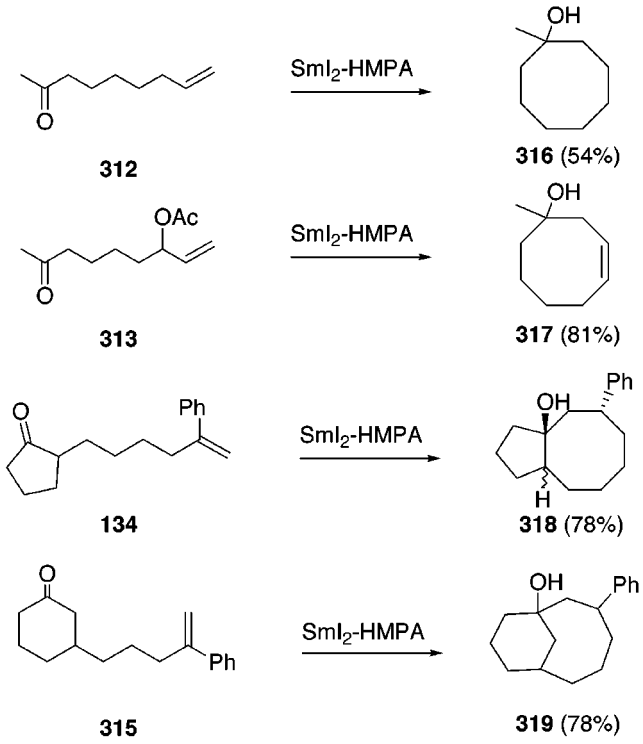
Scheme 62



3. Samarium Iodide Mediated Cyclizations

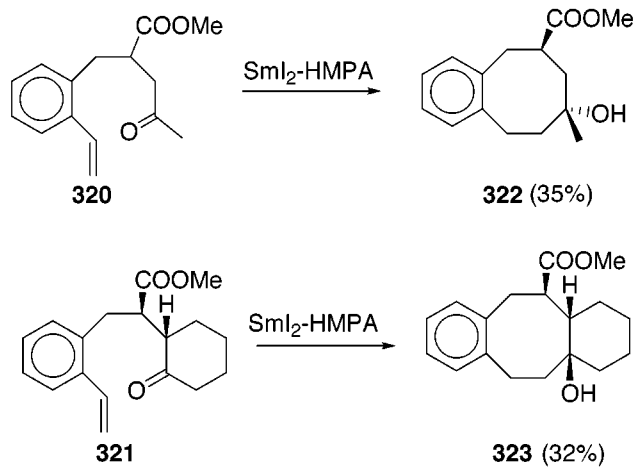
Samarium iodide mediated reductive cyclizations have found considerable application in carbocyclic ring construction.[132] Molander and co-workers have shown that simple α,ω-substituted unsaturated ketones such as 1-nonen-8-one **312** cyclize to cyclooctanol **316** via 8-endo-cyclization in the SmI_2−HMPA milieu, Scheme 63.[132b]

Scheme 63



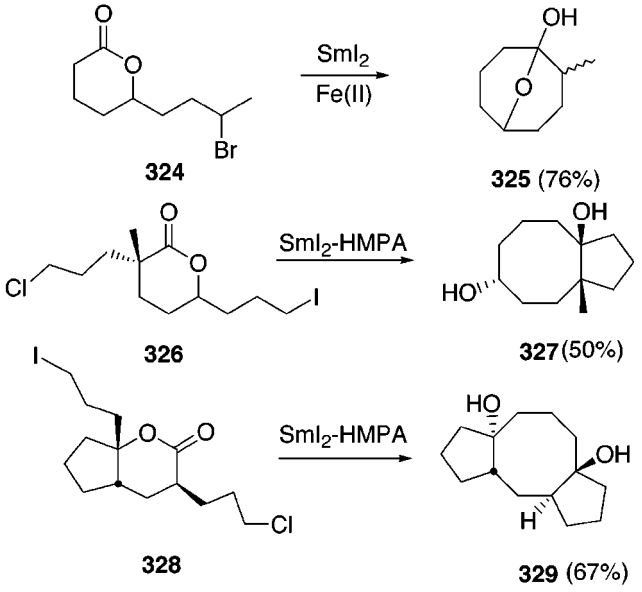
Likewise, a number of olefinic ketones **313**−**315** have been shown to undergo similar cyclizations to give cyclooctanols **317**−**319**, respectively, Scheme 63. These cyclizations are quite general and proceed in good yield. It is to be noted that these cyclizations can be effected to furnish both the fused and the bridged systems. Detailed analyses of the mechanism and factors controlling the stereochemical outcome have been discussed.[132] Recently, Reissig et al.[133] have extended this strategy to prepare benzocyclooctanes **322** and **323** from **320** and **321**, respectively, Scheme 64.

Scheme 64



Molander et al. have also reported reductive cyclization of halolactones such as **324** to cyclooctanoid **325**, Scheme 65.[134] This cyclization can also be

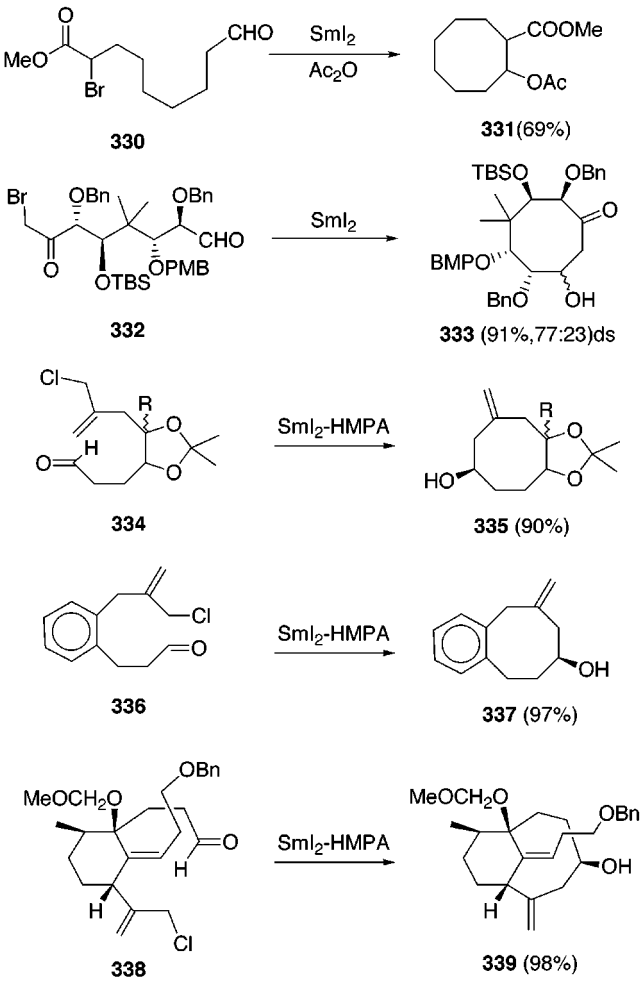
Scheme 65



effected in a sequential manner for the synthesis of annulated 5-8-fused (**326** → **327**) and 5-8-5-fused (**328** → **329**) cyclooctanoid systems.

Samarium iodide mediated Barbier/Grignard-type reactions have also been developed for the synthesis of eight-membered rings.[135,136] Inanaga et al.[135] have reported the cyclization of bromoaldehyde **330** → **331**. Shina et al.[136] have converted the highly functionalized bromoaldehyde **332** → **333** representing the highly embellished ring B of taxanes, Scheme 66.

Scheme 66

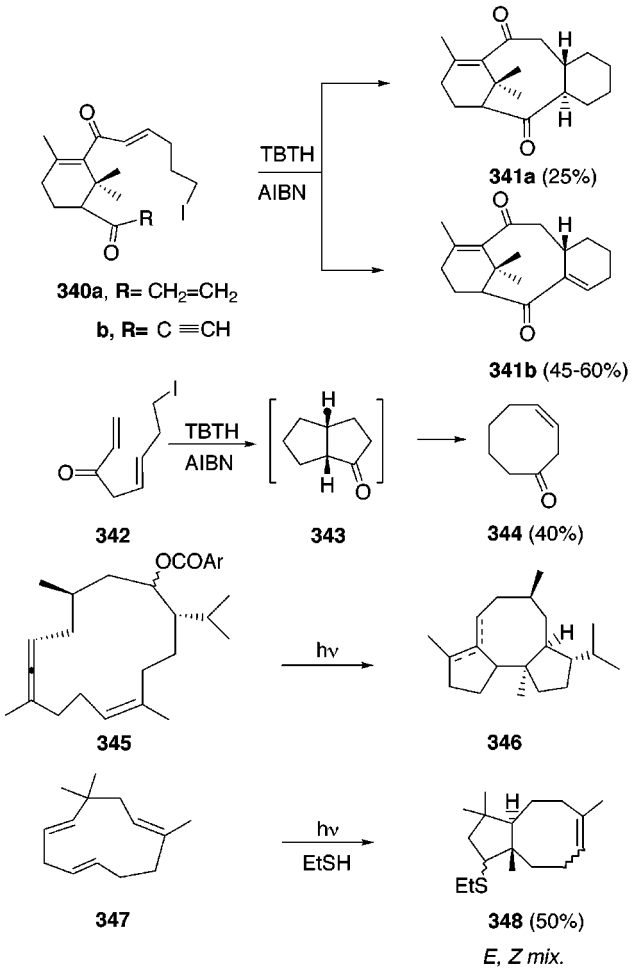


Other interesting examples include cyclization of **334** → **335** and **336** → **337**.[137] Recently, Matsuda has reported[138] intramolecular Barbier coupling in **338** which led to bicyclic compound **339** having a framework of biologically active diterpene vinigrol.

4. Radical Cyclizations

Radical-induced cyclizations have proliferated rapidly and constitute one of the most important methodological developments in recent years.[139,140] However, examples of radical cyclizations leading directly to eight-membered rings are relatively few. An early example of the formation of an eight-membered ring has been reported by Pattenden and co-workers.[141a] Thus, reaction of the iodo bis-enone **340a** with TBTH−AIBN led to the formation of the BC ring of taxanes **341a** through tandem radical cyclizations in a single operation, Scheme 67. In an analogous manner, the eneyne **340b** gave **341b** as a result of 12-*endo*-dig macrocyclization followed by transannulation.[141b] Pattenden and co-workers have also recently described tandem radical cyclization of iodo enone **342** to cyclooctenone **344**. The reaction appar-

Scheme 67



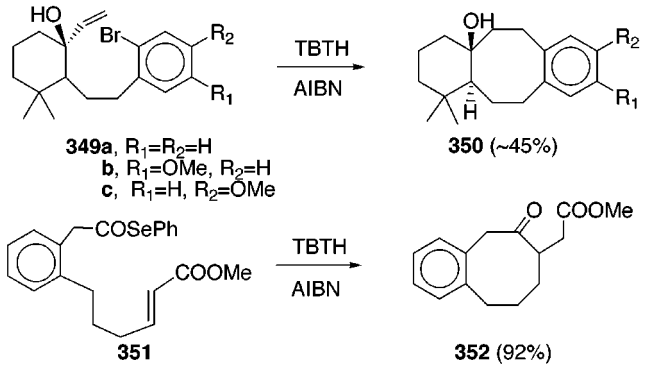
ently proceeds through the intermediacy of diquinane radical **343** which undergoes fragmentation to generate **344**.[142]

Another novel transannulation in a macrocyclic allene **345** leading to **346** involving the formation of an eight-membered ring has been reported by Myers and Condroski.[143] The reaction sequence involves tandem 5-*exo*-trig and 5-*exo*-dig radical cyclizations. This methodology has led to a synthesis of the tricyclic diterpene basmenone.

In an interesting observation, Pattenden and co-workers have described[144] a facile transannular cyclization of humulene **347**, upon exposure to ethanethiyl radical in the presence of light, to give a novel cyclooctanoid **348** in a stereoselective fashion, Scheme 67.

Formation of annulated benzocyclooctanes **350** upon radical-induced cyclization of bromoalkenes **349** has been reported by Ghatak et al.[145] This reaction is quite general and efficient, though small amounts of reduced uncyclized products are also obtained. Boger et al. have observed[146] an efficient formation of benzocyclooctanone **352** through intramolecular Michael-type radical cyclization of seleno ester **351** via acyl radical intermediate, Scheme 68. The observations of Ghatak and Boger on the ready formation of eight-membered rings through radical cyclizations offer many opportunities in complex synthesis and need to be explored further.

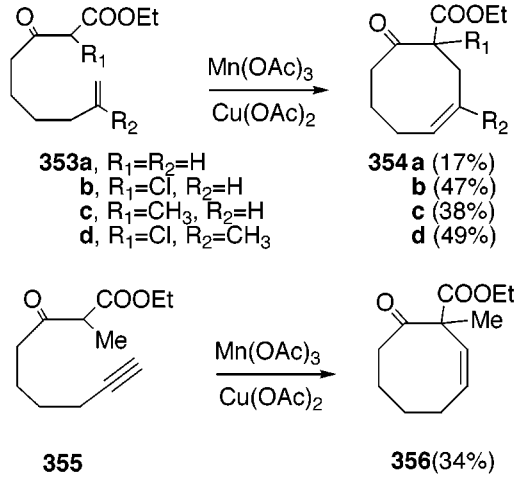
Scheme 68



5. Mn(III)-Promoted Oxidative Radical Cyclizations

Mn(III)-promoted oxidative free radical cyclizations have evolved into a useful synthetic methodology[147−149] for carbocyclic ring construction and have found applications in cyclooctanoid synthesis. Snider and his associates have reported[150] the cyclization of acyclic keto esters of type **353** to cyclooctenones **354** in the presence of $Mn(OAc)_3-Cu(OAc)_2$, Scheme 69.

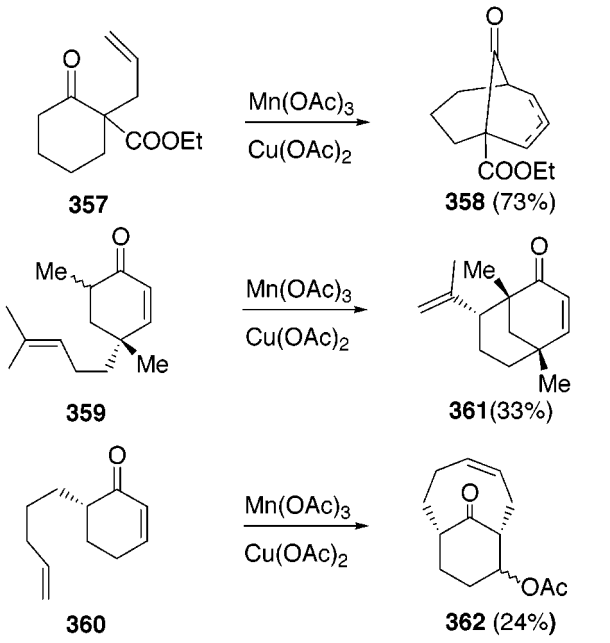
Scheme 69



It has been observed that substitution on active methylene carbon of the acyclic precursor facilitates cyclization and that a halogen substituent does so to a even greater extent. The method is also applicable to alkynyl keto esters **355** which gave the corresponding cyclooctenone **356** in moderate yield, Scheme 69.

Snider and co-workers have investigated oxidative free radical cyclization of cyclic β-keto esters having an olefinic side chain at α-position and developed it into a versatile method for carbocyclic construction that is also amenable to cyclooctanone synthesis. Thus, the cyclohexanone derivative **357** gave bicyclo[3.3.1]nonane derivatives **358** in good yield, Scheme 70.[151] Similarly, cyclohexenones **359** and **360** furnish bicyclo[3.3.1]nonane **361** and bicyclo[5.3.1]undecane **362**, respectively. The formation of these bicylic products established that unsaturated α'-keto radicals are formed during the above reaction and that 6-*exo*-cyclization of the resulting radical is much faster than its oxidation to an α'-acetoxy-enone.[152] Cyclization of cyclohexenone **360** → **362** is a conse-

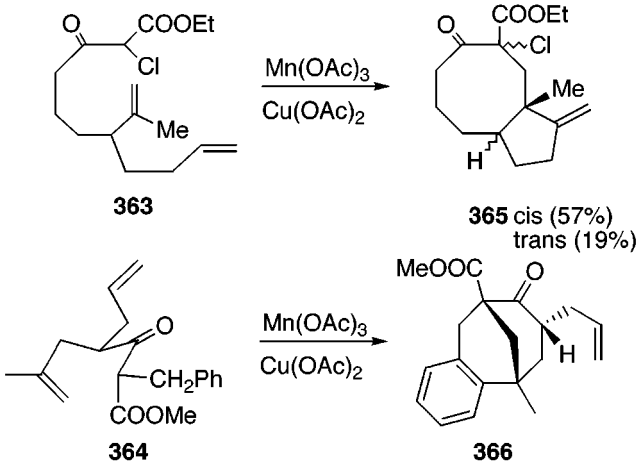
Scheme 70



quence of 8-*endo*-cyclization, albeit in low yield, Scheme 70.[152]

Snider et al. have also reported[150] tandem cyclization of the substrates **363** and **364** to furnish the bridged and fused bicyclic systems **365** and **366**, respectively, incorporating an eight-membered ring, Scheme 71.

Scheme 71

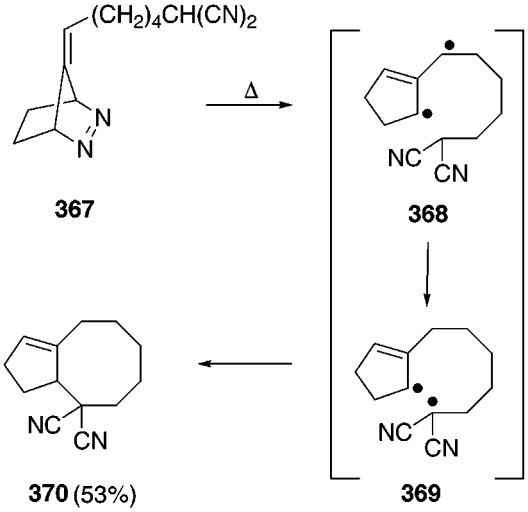


Paquette and Snider have employed Mn(III)-based methodology for the synthesis of terpenoid natural products upial and epi-upial bearing the bicyclo[3.3.1]-nonane skeleton, and these will be discussed later (vide infra).

6. Diyl Atom Transfer Cyclizations

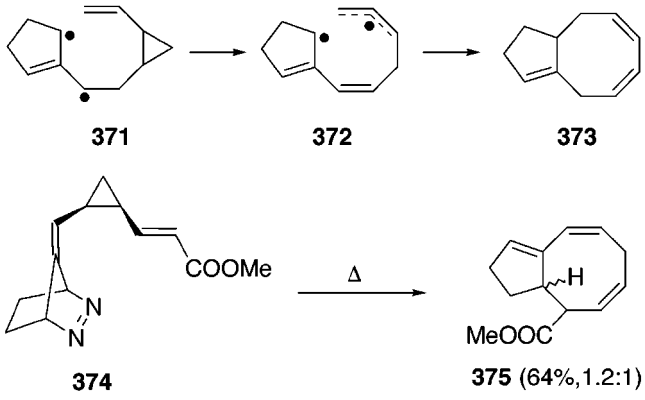
Diyls analogous to trimethylenemethane (TMM)[153,154] have proved to be versatile reactive intermediates, and their trapping with diylophiles has evolved into a general synthetic methodology for the assembly of diverse carbocyclic systems.[155] Little and co-workers have extended their work on diyl chemistry to develop methods for the synthesis of eight-membered rings.[155b] One of the strategies toward this objective involves atom transfer in the initially formed diyl **368** leading to **369** via translocation.[156] Subsequent cyclization in **369** furnished 5-8-fused cyclooctanoid **370**, Scheme 72.[157]

Scheme 72



Another method involving diyl-induced vinylcyclopropane fragmentation and recombination for the synthesis of cyclooctane rings has been recently reported from Little's laboratory.[158] It was envisaged that diyls of type **371** would furnish the distonic diyl **372** through cyclopropane ring opening, which may undergo further cyclization to give cyclooctanoid **373**. To test the idea, a few substrates of the type **374** were prepared and pyrolyzed to give the bicyclo[6.3.0]-undecane derivative **375** as the major product, Scheme 73.

Scheme 73

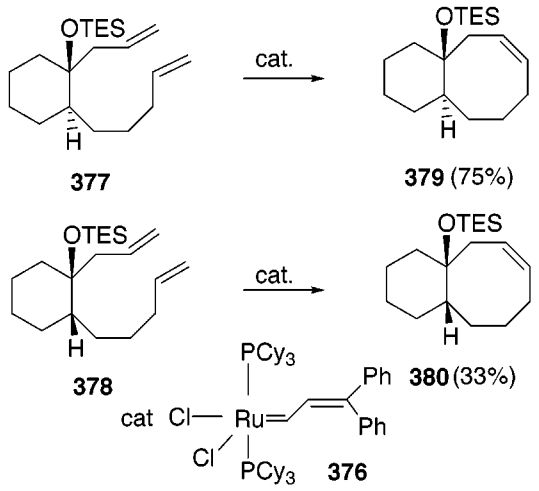


7. Ring Closure and Ring Opening Metathesis

Ring closing metathesis (RCM) has emerged as a versatile new methodology for the synthesis of a variety of five-, six-, and seven-membered carbo- and heterocyclic rings[159] as well as other large rings.[160] Synthesis of eight-membered carbocyclic rings using this method has been realized only recently by Grubbs and co-workers[161] using ruthenium carbene catalyst **376**. Thus, diolefinic precursors **377** and **378**

furnished the bicyclo[6.4.0]dodecanes **379** and **380**, respectively, Scheme 74.

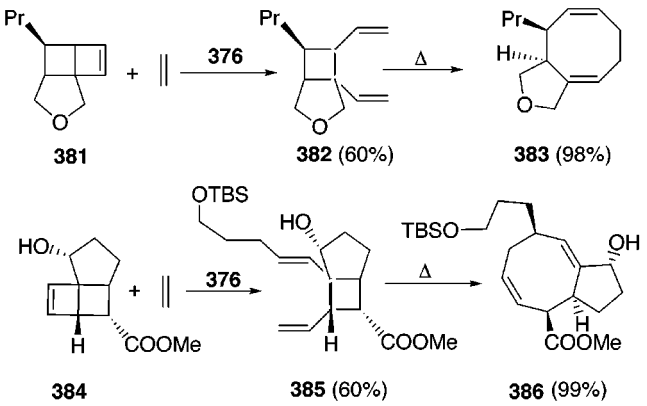
Scheme 74



Furstner and co-workers have developed an efficient synthesis of sesquiterpene dactylol, bearing a bicyclo[5.3.0]decane skeleton, through a ring closing metathesis strategy employing a molybdenum carbene catalyst, and this will be presented in a later section.

Synthesis of several annulated cycloocta-1,5-dienes via a sequential ring opening olefin metathesis−Cope rearrangement has been reported recently.[162] The metathesis of cyclobutenes **381** with ethylene gave the divinyl cyclobutane derivatives **382** which underwent Cope rearrangement to cyclooctadienes **383**, Scheme 75. Similarly, the cyclobutene **384** also

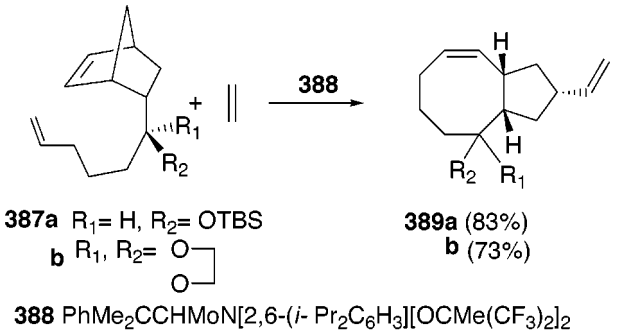
Scheme 75



furnished the cyclopentannulated cyclooctadiene **386** through the intermediacy of **385**. Stereochemistry of the substituents on cyclobutane **381** and **384** was found to play an important role in the metathetic opening of the cyclobutene ring. Following this sequence, a range of cyclooctadienes were prepared.

Recently, an eventful sequence involving ring-opening, ring-closing and cross-metathesis steps in a single pot operation has been reported. Thus, norbornene derivatives **387a**,**b** and ethylene, in the presence of molybdenum catalyst **388**, were transformed to fused cyclooctanoids **389a**,**b** in good yield, Scheme 76.[163]

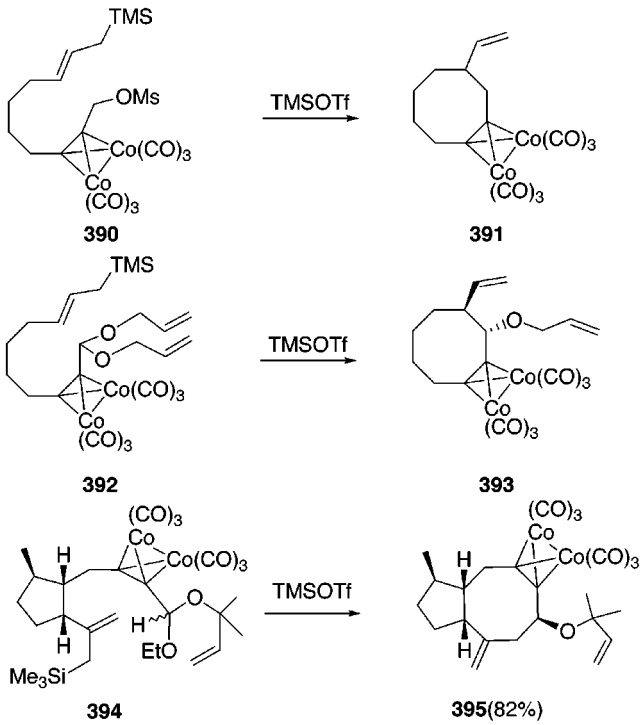
Scheme 76



8. Cobalt-Mediated (Nicholas) Cyclization

Schreiber and co-workers[164] have applied the Nicholas reaction[165] for the construction of cyclooctanoids systems. Thus, the cobalt cluster **390** underwent Lewis acid catalyzed cyclization to give the cyclooctanoid−cobalt complex **391**, Scheme 77. Similarly,

Scheme 77



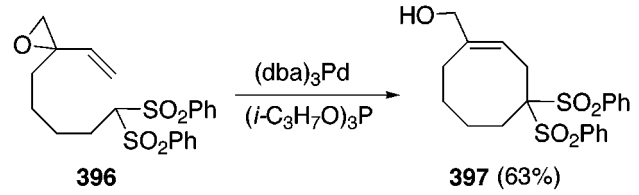
the substrate **392** was also transformed into cyclooctanoid **393**, and a more complex cyclooctanoid **395** was prepared from **394**.[166] The cyclooctanoid-based cobalt carbonyl complexes **391**, **393**, and **395** have been shown to undergo further Pauson−Khand reaction[167] to furnish the corresponding cyclopentanone-annulated cyclooctanoids, and **395** in particular has been elaborated through the Pauson−Khand sequence[167] to achieve a total synthesis of the diterpenoid natural product (+)-epoxydictymene having a 5-8-5-fused carbocyclic system.

9. Palladium-Mediated Cyclizations

Palladium-mediated reactions have proved to be extremely advantageous and useful in the synthesis of carbocyclic ring systems.[168] However, there are

only a few examples of the use of palladium-based reagents for the synthesis of eight-membered rings. Trost and co-workers[169] have observed the formation of an eight-membered ring during the palladium-catalyzed cyclization of an epoxy sulfone (**396** → **397**), Scheme 78.

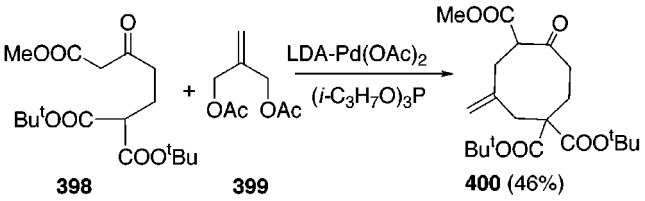
Scheme 78



396 **397** (63%)

Malacria et al.[170] have recently reported the addition−cyclization of keto ester **398** with TMM equivalent **399** to furnish the functionalized cyclooctane derivative **400**, Scheme 79.

Scheme 79

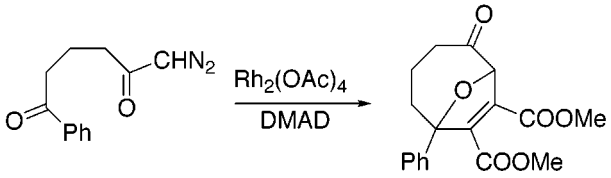


398 **399** **400** (46%)

10. Miscellaneous Cyclizations

Padwa and co-workers have reported a carbonyl ylide mediated cyclization leading to cyclooctane ring formation. Thus, the rhodium acetate catalyzed reaction of diazoketone **401** with dimethylacetylene dicarboxylate (DMAD) furnished bridged cyclooctenone **402** along with some cycloheptatriene derivative, Scheme 80.[171]

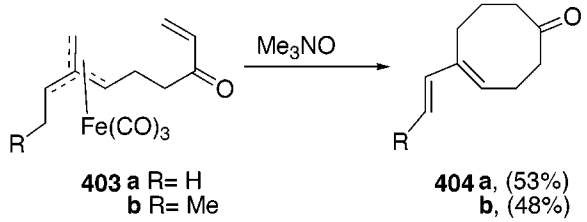
Scheme 80



401 **402** (45%)

Franck-Neumann and co-workers have recently described[172] an intramolecular cyclization of TMM−iron tricarbonyl complexes **403a**,**b**, which on deligation with trimethylamine oxide gave cyclooctenones **404a**,**b**, Scheme 81.

Scheme 81

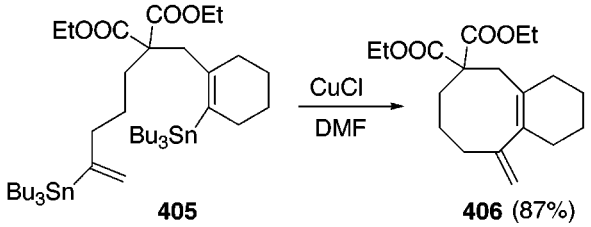


403 a R= H
b R= Me

404 a, (53%)
b, (48%)

An oxidative cyclization of a bis-vinyl stannane (**405** → **406**) in the presence of Cu(I) catalyst to furnish a fused bicyclo[6.4.0]dodecane system has been reported by Piers et al.,[173] Scheme 82.

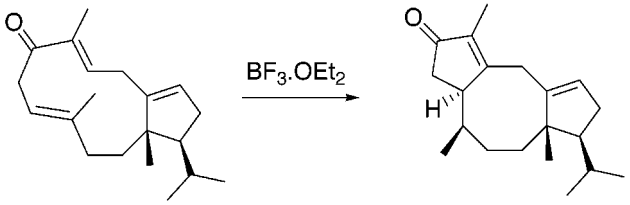
Scheme 82



405 **406** (87%)

Last, a diterpene **407** of rearranged dolabellane-type of marine origin, on Lewis acid catalysis undergoes transannular cyclization to furnish the compound **408** having a 5-8-5-fused fusicoccane frame work, Scheme 83.[174]

Scheme 83



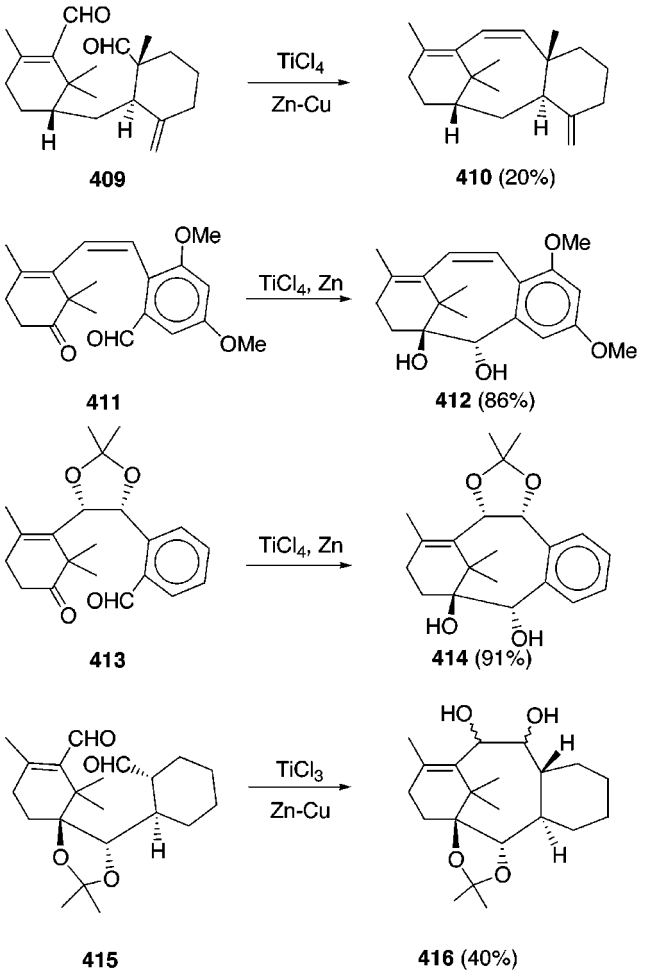
407 **408** (30%)

D. Coupling Reactions

A variety of coupling reactions, including the well-known McMurry coupling, Heck reaction, and Kishi reaction, have found useful applications in cyclooctanoid synthesis. The coupling of two electrophilic centers especially carbonyl/aldehyde groups in the presence of a suitable metal is one of the established methods for C−C bond formation.[175] McMurry[176] during his seminal work on low valent titanium mediated coupling of carbonyl compounds observed the formation of cyclooctane-1,2-diol from 1,6-hexanedialdehyde. Since then, the titanium based coupling approach has been often used for the construction of eight-membered rings, particularly in the context of generation of the B ring of taxoids. Depending on the reaction conditions, either olefins or diols have been obtained. Kende et al. constructed the B ring of taxanes via the coupling of the dialdehyde **409** in the presence of a Zn−Cu/$TiCl_4$ milieu to obtain the olefin **410** having ABC ring system of taxoids, Scheme 84.[177]

Swindell and co-workers have investigated in detail the titanium mediated coupling reactions in the context of taxoids employing precursors having rings A and C to construct the central eight-membered ring and identified suitable reagents/conditions for the process. It has been observed that the keto aldehyde **411** is smoothly converted into **412** upon treatment with TiCl/Zn/Py in excellent yield and with high stereoselectivity, placing both of the hydroxyl groups in correct relative stereochemistry, Scheme 84.[178] Another interesting example of this type of coupling is the conversion of the keto aldehyde **413** → **414**.[179]

Scheme 84

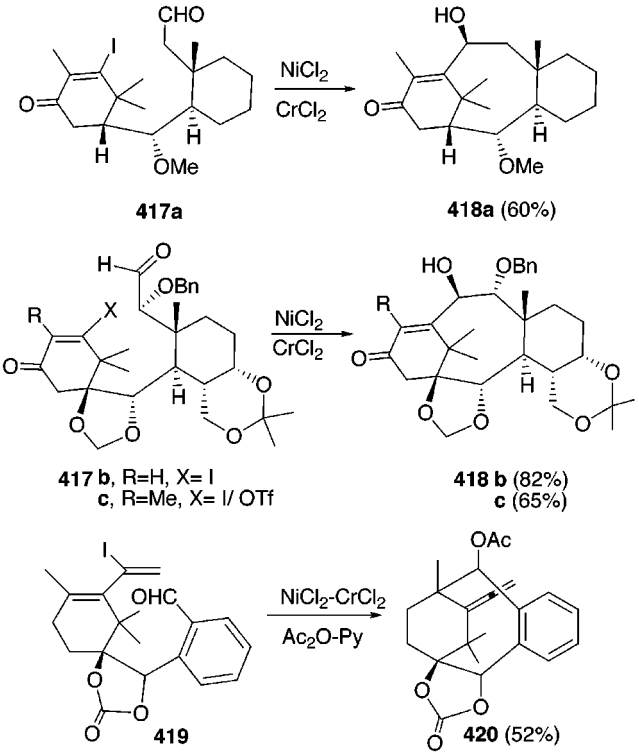


Nicolaou and his associates have also employed[180] the McMurry coupling to construct the B ring of taxanes. Thus, the reaction of the dialdehyde **415** with Ti(0) under high-dilution conditions led to the desired diol **416** as a mixture of two diastereomers, and this approach has been extended to achieve a total synthesis of paclitaxel, Scheme 84.

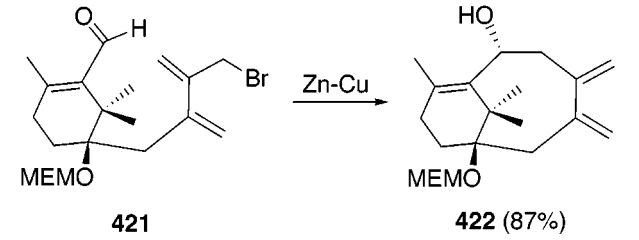
Kishi and his group have devised a methodology based on the coupling of vinyl halide/triflates with carbonyl groups in the presence of an $NiCl_2/CrCl_2$ reagent. They have effected the cyclization of iodoketone **417a** to tricyclic compound **418a** in good yield.[181a,b] In an improved version of this method, it has been noted that 4-*tert*-butylpyridine as an additive has a beneficial effect on this coupling process. It was observed that while the iodoaldehyde **417b** reacted with $NiCl_2-CrCl_2$ to give **418b** in excellent yield, the analogous iodoaldehyde **417c** did not undergo such cyclization. However, coupling of **417c** → **418c** could be effected on the addition of 4-*tert*-butylpyridine along with the catalyst in good yield, Scheme 85.[181c] However, an unusual coupling has been observed during the reaction of **419** with $NiCl_2-CrCl_2$ to evantuate in bicyclo[4.2.2]decane derivative **420**.[182]

Another interesting example of the coupling reaction leading to the cyclooctanoid formation is the Zn−Cu-mediated coupling of bromoaldehyde **421** → **422** to furnish the B ring of taxoids, Scheme 86.[183]

Scheme 85



Scheme 86

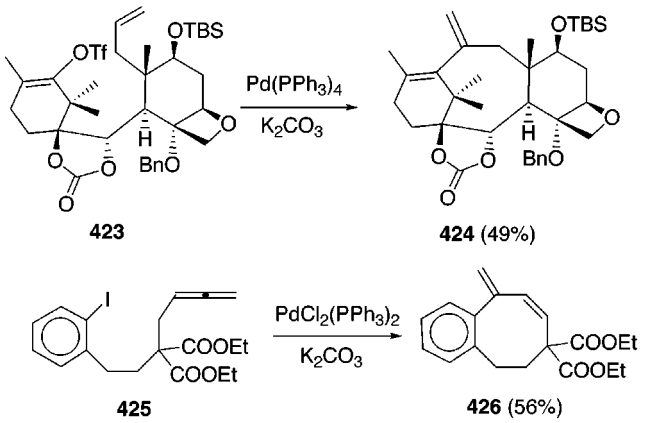


The well-known Heck reaction[184] too has found application in the construction of eight-membered rings. Danishefsky and co-workers[185] employed palladium-mediated coupling of vinyl triflate **423** to tetracyclic compound **424**, and this was a pivotal step in their paclitaxel synthesis. Negishi and co-workers[186] have observed the palladium-mediated intramolecular coupling in aryl iodide **425**, having an allenyl chain, to give benzocyclooctene **426**, Scheme 87. However, it may be noted that generally eight-membered rings are not formed during Heck reactions[184] involving alkenes.

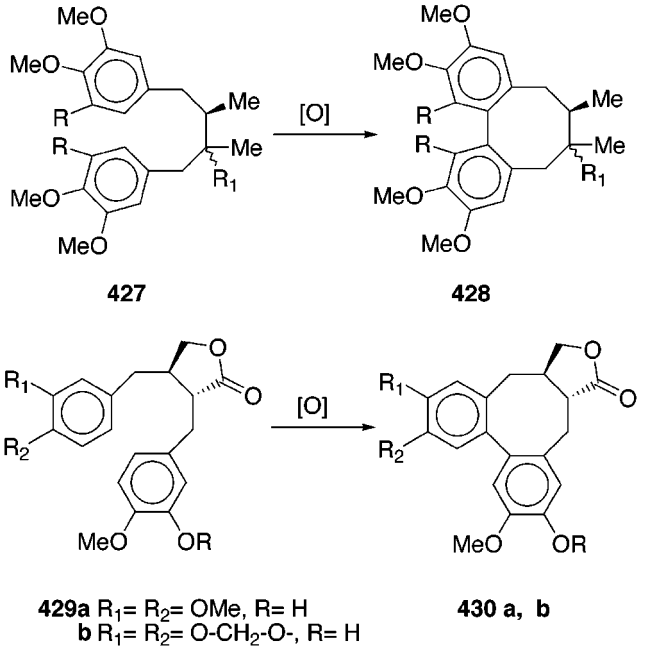
It has already been mentioned that dibenzocyclooctadiene lignans constitute an important class of natural products. In the synthesis of this class of compounds, Ar−Ar coupling in suitable diarylbutanes is a pivotal step to generate the eight-membered ring. Several reagents and methods to effect this Ar−Ar coupling are available and new ones are being introduced periodically. Studies on ruthenium oxide mediated coupling of diarylbutanes leading to bis-benzocyclooctadienes have been recently reported by Robin and co-workers.[187] Following their reaction conditions, diarylbutane **427** gave bis-benzocyclooctane **428**, Scheme 88.

Planchenault and Dhal have examined the reaction of dibenzylbutanolides **429a**,**b** under various oxida-

Scheme 87

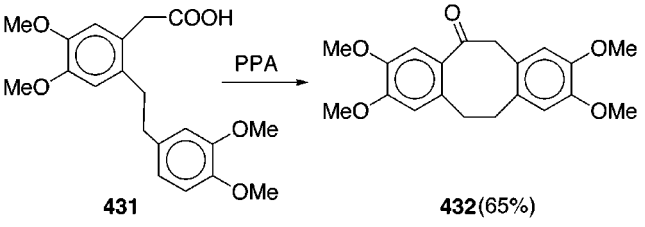


Scheme 88



tive conditions/reagents to give the corresponding bisbenzocyclooctanoids **430a**,**b**.[188] For example, in the case of **429a**, oxidation with V_2O_5 or $Cu(OAc)_2$ or RuO_2 gave good results, but best yields (96%) were obtained with Re_2O_7. In the case of **429b**, the best result was obtained with Tl_2O_3, Scheme 88.[188] Recently, the classical PPA cyclization approach has also been successfully applied for the elaboration of **431** to dibenzocyclooctanoid **432**, Scheme 89.[189]

Scheme 89



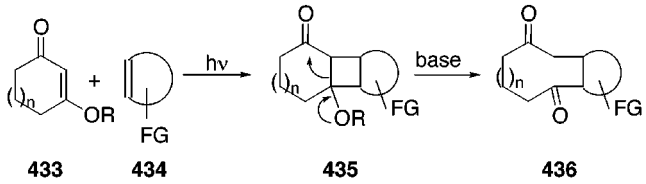
III. Cyclooctanoids through Indirect Methods

In this section, those methods are discussed in which the eight-membered rings are generated indirectly, through fragmentation−recombination, retroaldol−aldol condensation, ring expansions, ring contractions, rearrangements, etc.

A. Photochemical [2 + 2]-Cycloaddition–Fragmentation

de Mayo reaction,[190] consisting of [2 + 2]-photocycloaddition between enol acetates (ethers) **433** of 1,3-diketone and olefins **434** followed by fragmentation of the photoadduct **435** involving cyclobutane opening to **436**, provides a unique opportunity to construct various types of carbocyclic ring systems, Scheme 90.

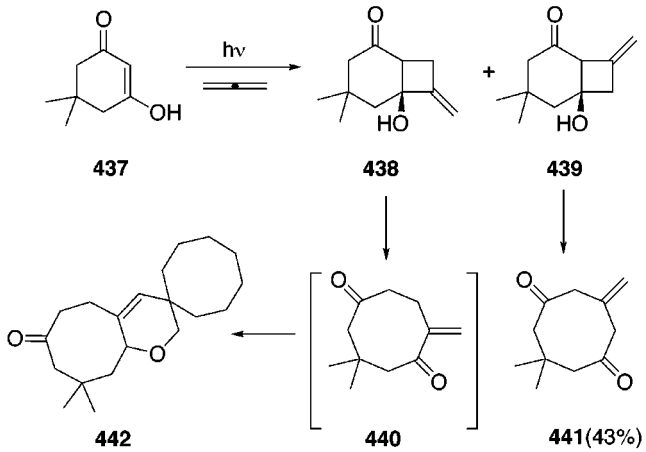
Scheme 90



The reaction is highly versatile with respect to both of the reacting partners, and variants of the original de Mayo reaction, both in inter- and intramolecular, have been effectively utilized for cyclooctanoid ring construction.[191,192] Several examples have recently surfaced in the literature that demonstrate the efficacy of this [2 + 2]-photocycloaddition−fragmentation sequence.

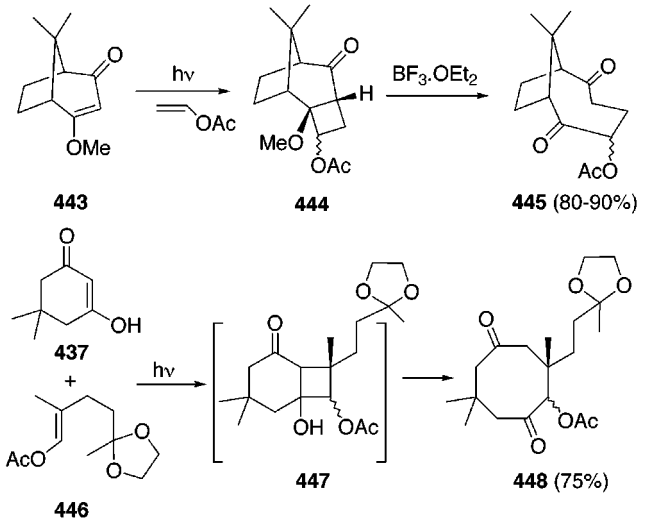
Petrzilka and Bajgrowicz[193] have reported a simple example of de Mayo reaction between dimedone **437** and allene to furnish regioisomeric adducts **438** and **439**, which underwent retroaldol reaction to give the cyclooctadienones **440** and **441**, respectively, but the former was isolated only as its [4 + 2]-dimer **442**, Scheme 91.

Scheme 91



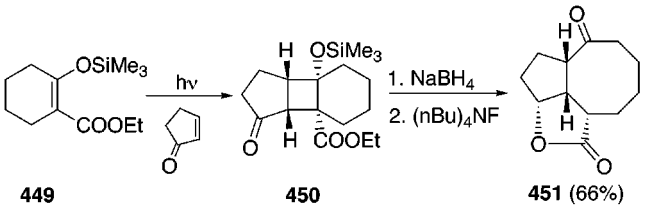
In the context of synthetic endeavors directed toward taxanes, Fetizon has reported [2 + 2]-photoaddition between the bicyclic compound **443** and vinyl acetate to furnish the diastereomeric adducts **444**, which upon retroaldol reaction led to the bridged cyclooctanedione **445**.[194] They also reported a synthesis of the eight-membered B ring of taxanes via photoreaction of dimedone **437** with **446**. The resulting adduct **447** underwent spontaneous retroaldol fragmentation to give **448**, Scheme 92.[195]

Scheme 92



Lange and Organ[196] have reported an approach toward a bicyclo[6.3.0]undecane system, employing photocycloaddition between cyclic β-keto ester derivative **449** and cyclopentenonone to give **450**. Reduction of the carbonyl group led to the lactonization, and further desilylation led to the formation of **451**, Scheme 93.

Scheme 93

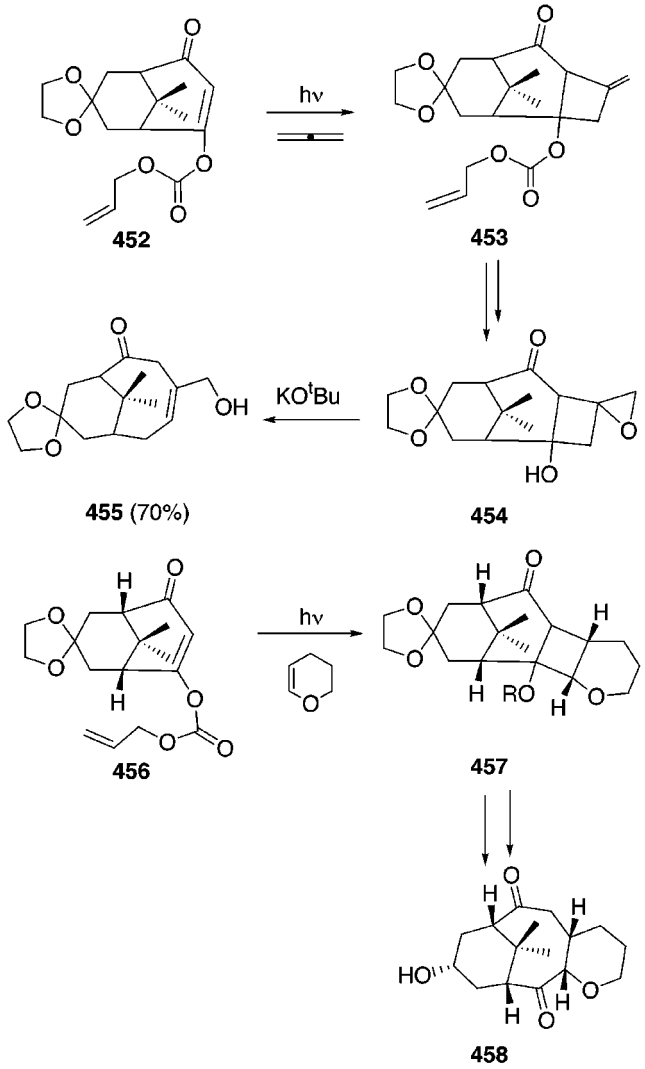


In an approach toward the AB ring system of taxanes, Blechert and co-workers[197,198] have studied the [2 + 2]-photocycloaddition between the enol carbonate **452** and allene to furnish the adduct **453** which was elaborated to the epoxide **454**. Base-catalyzed retroaldol fragmentation and epoxide opening led to the bicyclo[5.3.1]undecane system **455**.[198] A similar sequence employing enol carbonate **456** and dihydropyran as the photoaddends led to **457**. Carbonate deprotection, functional group alterations, and base-mediated fragmentation in **457** led to taxane ABC system **458** in which ring C is heterocyclic, Scheme 94.[199]

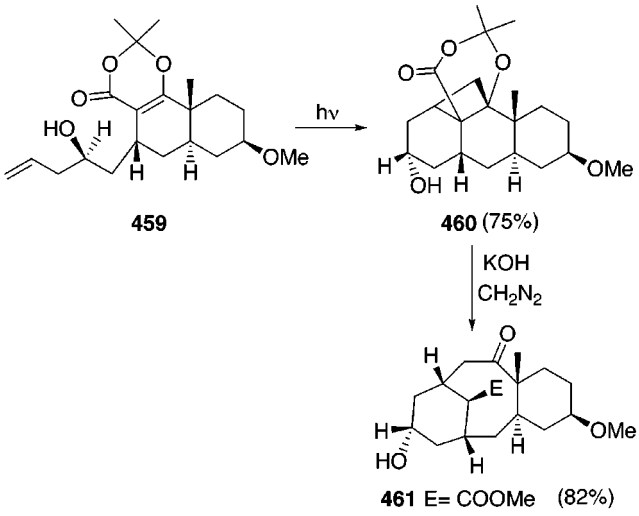
Intramolecular [2 + 2]-photoaddition and fragmentation has also proved very useful in the construction of cyclooctanoids. Winkler and Subramanyam[200] have employed intramolecular photoreaction in protected enolester **459** to create the B ring of taxanes, Scheme 95. The photoadduct **460** underwent fragmentation efficiently to give **461** as a single diastereomer, Scheme 95.

Kraus utilized the adduct **463**, which is readily available via intramolecular photoreaction in **462**, for the synthesis of the B ring of taxanes.[201] However, instead of retroaldol fragmentation on the photoadduct **463**, the authors elaborated it into **464** and induced cyclobutane fragmentation via a bridgehead carbocation intermediate to give **465** with a bridgehead double bond, Scheme 96.[202]

Scheme 94

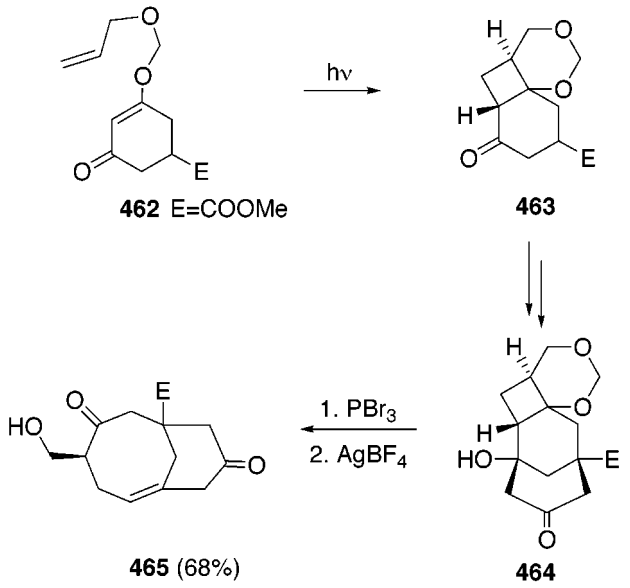


Scheme 95



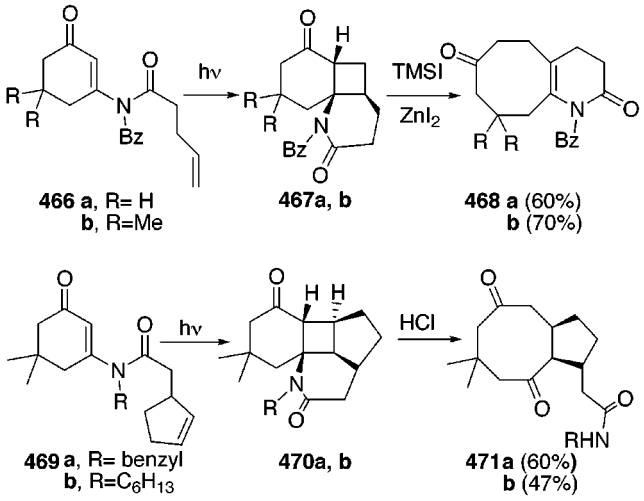
Pete and co-workers[203] have demonstrated the generality of intramolecular photocycloaddition in *N*-alkenoyl-β-enaminones, and the resulting adducts have been easily transformed into cyclooctanoids.

Scheme 96



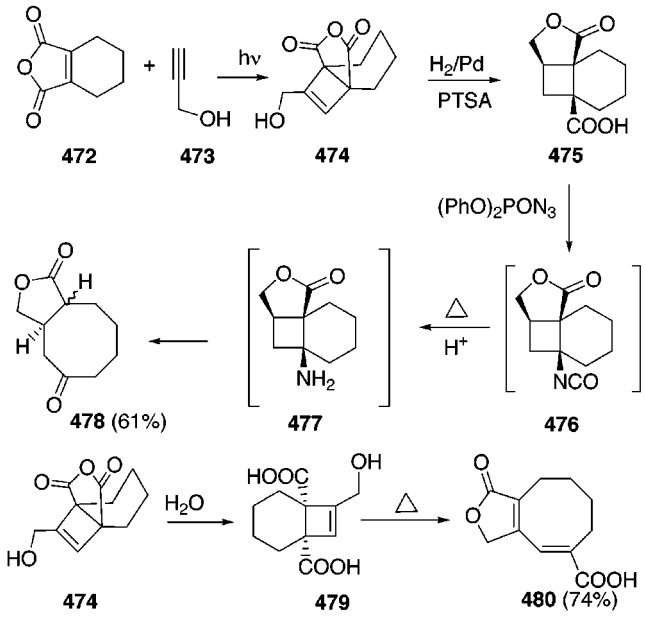
Irradiation of N-substituted enamino ketones **466a**,**b** gave the corresponding adducts **467a**,**b** and were readily transformed into cyclooctanoids **468a**,**b**. Similarly, irradiation of enaminones **469a**,**b** also furnished the adducts **470a**,**b** in decent yields which were readily converted into fused cyclooctanoids **471a**,**b**, Scheme 97.

Scheme 97



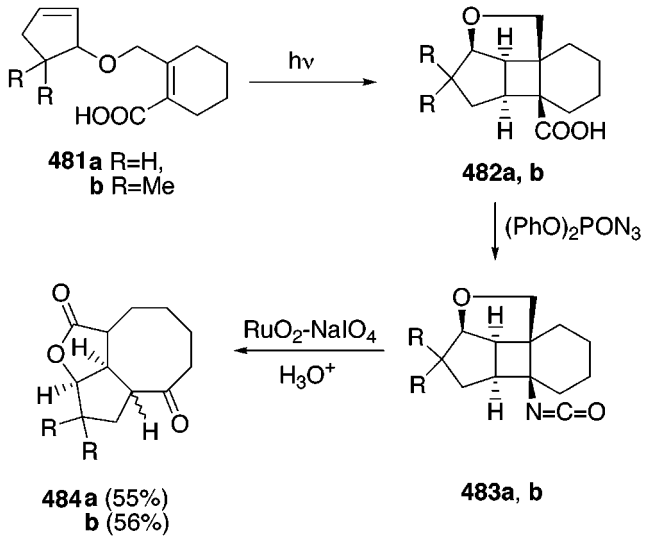
Booker-Milburn and co-workers have reported a novel variant, the aza-de Mayo reaction, for cyclooctanoids in the context of their studies on the synthesis of sesquiterpene asteriscanolide.[204−207] The key idea in their attempt was the deployment of a carboxylic acid group as an amine equivalent. The amino group in turn acts both as a nucleofugal group in the fragmentation reaction as well as a carbonyl equivalent, Scheme 98. Thus, the photoaddition of the anhydride **472** with propargyl alcohol **473** gave the adduct **474** in excellent yield, which was transformed into the lactone carboxylic acid **475**. Treatment of **475** with diphenylphosphoryl azide gave the isocyanate **476** (via Curtius rearrangement) which was hydrolyzed to generate amine **477** (in situ), and subsequent fragmentation of the cyclobutane ring in it furnished

Scheme 98



the cyclooctanoid lactone **478** as a diastereomeric mixture, Scheme 98.[204] The adduct **474** was also elaborated to **480**,[205] an intermediate for the synthesis of natural product pachylactone, via cycloreversion in the cyclobutene derivative **479** and lactonization, Scheme 98. A similar protocol was also employed for the synthesis of the more complex cyclooctanoid **484a** and extended to a synthesis of 7-desmethylasteriscanolide **484b**, Scheme 99. Thus,

Scheme 99

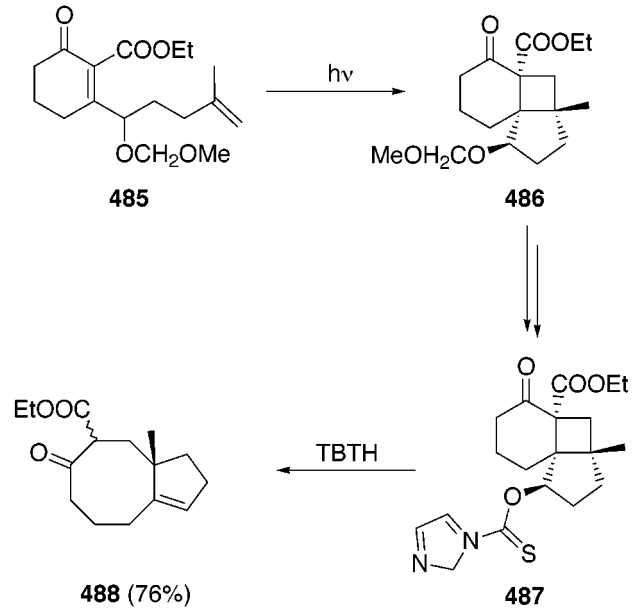


intramolecular photochemical [2 + 2]-cycloaddition in **481a**,**b** furnished the tetracyclic adducts **482a**,**b** in good yield and were converted into isocyanates **483a**,**b** following standard protocols. Oxidation of the tetrahydrofuran moiety to the corresponding lactone and hydrolysis of the isocyanate functionality to an amine led to concomitant fragmentation of the cyclobutane ring and furnished the bicyclo[6.3.0]-undecane-based lactones **484a**,**b** as a mixture of stereoisomers, Scheme 99.[206,207]

Crimmins et al. have reported[208] an approach to medium ring fused carbocycles employing [2 + 2]-cy-

cloaddition and radical fragmentation as the key steps. The enone **485** having an alkenyl chain was irradiated to give the photoadduct **486** as a single diastereomer, which was transformed into imidazole derivative **487**. Generation of the radical intermediate in **487** led to the cyclooctanone ester **488** in an efficient manner, Scheme 100. The viability of the

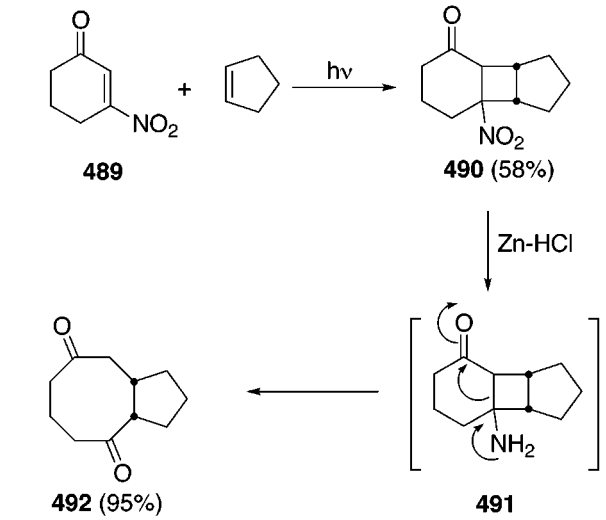
Scheme 100



method has been demonstrated through many examples.

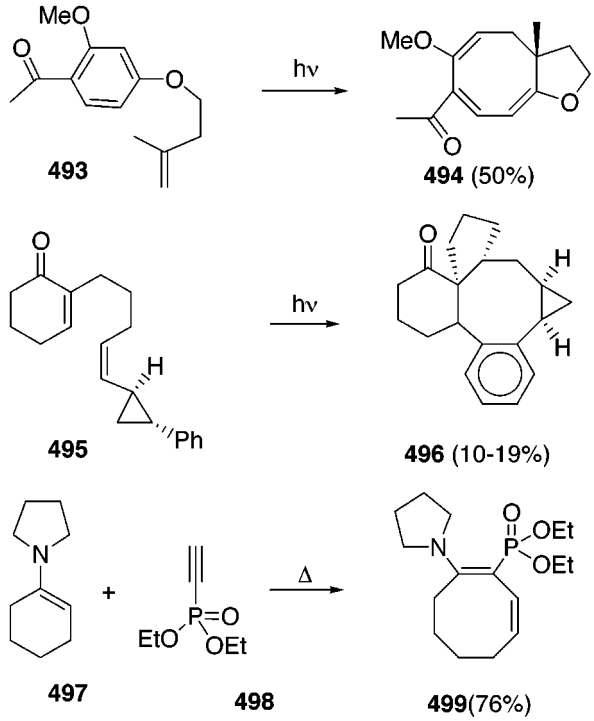
Recently, Weedon and Quevillon have disclosed[209] their preliminary results on the photocycloaddition of 3-nitro-2-cyclohexenone with cyclopentene and transformation of the resulting adduct to cyclooctandione. Irradiation of nitroenone **489** with cyclopentene furnished the tricyclic nitro ketone **490** as a major product. Reduction of the nitro group in **490** resulted in the direct formation of the known cyclooctanedione **492**, presumably through the formation of the aminoketone intermediate **491** and concomitant fragmentation of the cyclobutane ring, Scheme 101.

Scheme 101



Wagner has reported[210,211] the formation of cyclooctatrienes of type **494** during the irradiation of aromatic ketones such as **493**. The formation of **494** proceeds through intramolecular [2 + 2]-cycloaddition and valence isomerization in the intermediate bicyclo[4.2.0]octadiene intermediate, Scheme 102.

Scheme 102



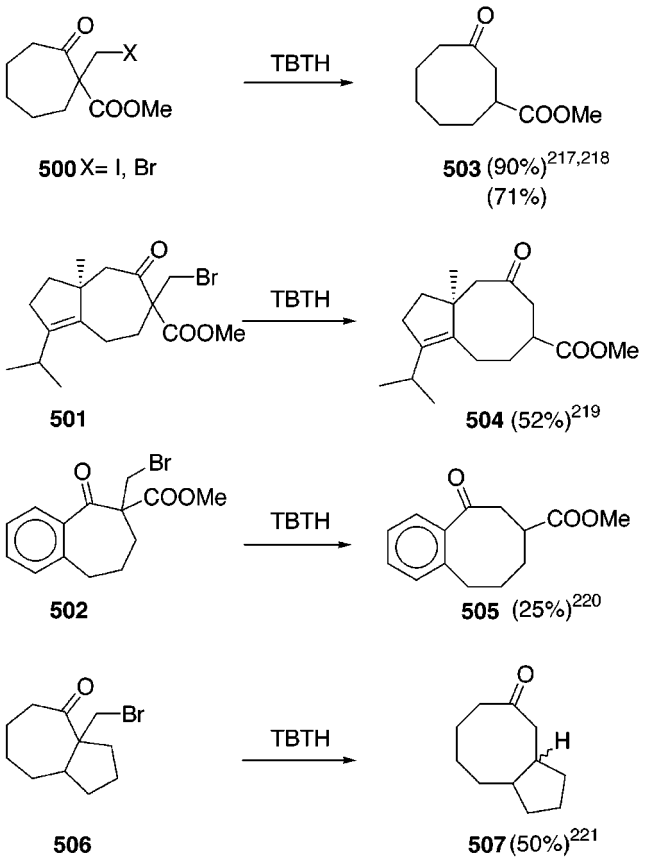
Haddad and co-workers have observed the formation of a complex multicyclic cyclooctanoid **496** during the irradiation of **495**.[212] However, further exploration is necessary to ascertain the synthetic potential of these reactions. Ruder and co-workers have observed [2 + 2]-cycloaddition−fragmentation during the reaction of enamine **497** with alkyne phosphonate **498** to furnish the cyclooctane derivative **499**, Scheme 102. [213, 214]

B. Radical-Mediated Ring Expansions

Ring expansions are routinely employed to make higher ring systems,[215] but their efficacy in the construction of eight-membered rings was quite limited until recently. Advances in radical chemistry, particularly extensive observation of new fragmentation/ring expansion pathways, have made it possible to access cyclooctanoid rings in a variety of ways.[216] Following this radical-based protocol, one to four carbon ring expansions have been accomplished; thus, making this approach attractive and flexible for obtaining cyclooctanoids.

One carbon expansion of cycloheptanones bearing α-carboalkoxy and α-halomethyl groups to the corresponding cyclooctanones in the presence of tributyltin hydride (TBTH) has been reported by several groups. Some of the synthetically useful examples are the formation of **503**−**505** from **500**−**502**, respectively, Scheme 103.[217−221] These ring expansions

Scheme 103



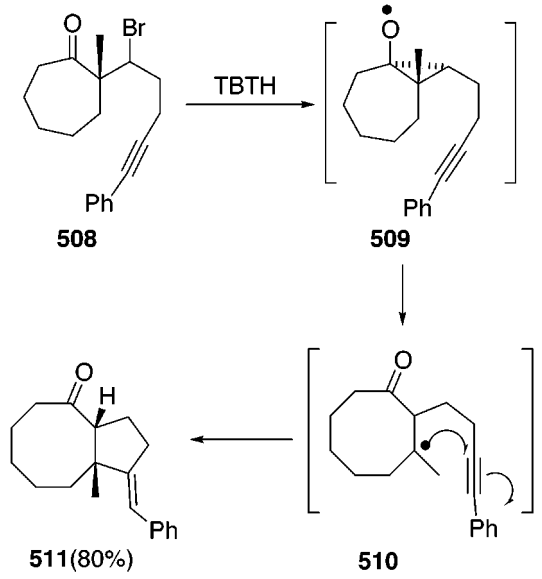
proceed through the addition of the initially formed carbon-centered radical to the carbonyl group to furnish an intermediate oxycyclopropyl radical, which fragments in a regiospecific manner to the ring-expanded product. The sequence is preparatively attractive as α-halomethyl ketones are readily prepared from the corresponding α-keto esters and dihaloalkanes. Ring expansion of α-halomethyl cycloheptanones, in certain cases (**506** → **507**), proceeds even in the absence of the α-carboalkoxy group, Scheme 103.

An elegant radical-induced fragmentation cyclization sequence in **508** to deliver an annulated eight-membered ring through the intermediacy of an oxycyclopropyl radical **509**, ring expansion to **510**, and interception of this radical by pendant alkynyl chain to give the annulated cyclooctanone **511** has been reported by Boger and Mathvink, Scheme 104.[222]

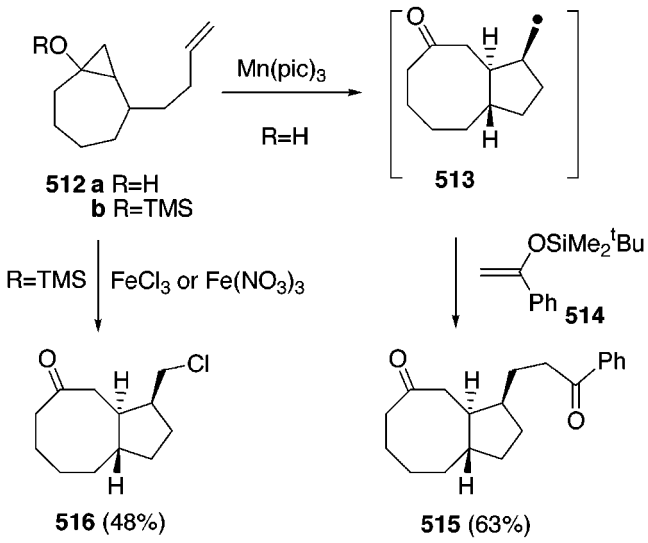
One carbon expansion route to annulated cyclooctanoids via cyclopropyl systems has also been explored by Iwasawa et al.[223a] Mn(III)-induced radical cyclization of cyclopropyl alcohol **512a** to **515** via the radical intermediate **513** and its intermolecular interception with **514** has been reported by them, Scheme 105.[223a] Booker-Milburn has also reported a similar cyclization of the TMS derivative **512b** to **516** mediated by Fe(III)-based reagents, Scheme 105.[223b,c]

Suginome et al. have observed fragmentation in tetracyclic alcohol **517** upon irradiation in the presence of I_2O-I_2 to give two carbon ring expanded

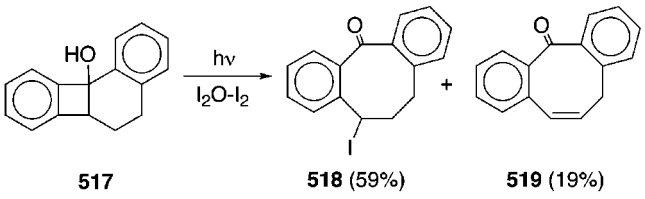
Scheme 104



Scheme 105



Scheme 106

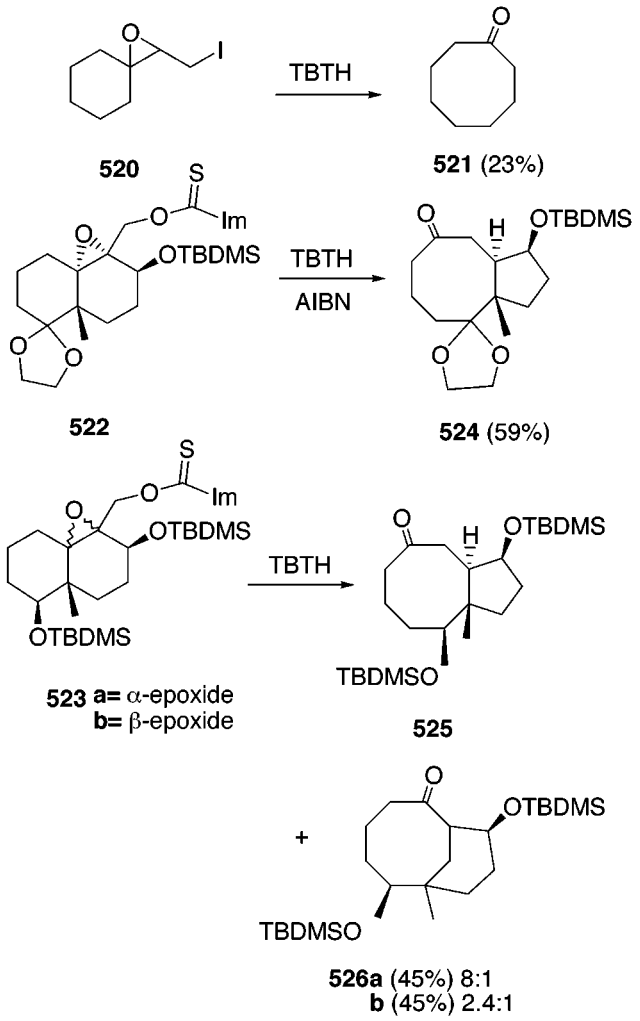


dibenzocyclooctanes **518** and **519** in preparatively useful yields, Scheme 106.[224]

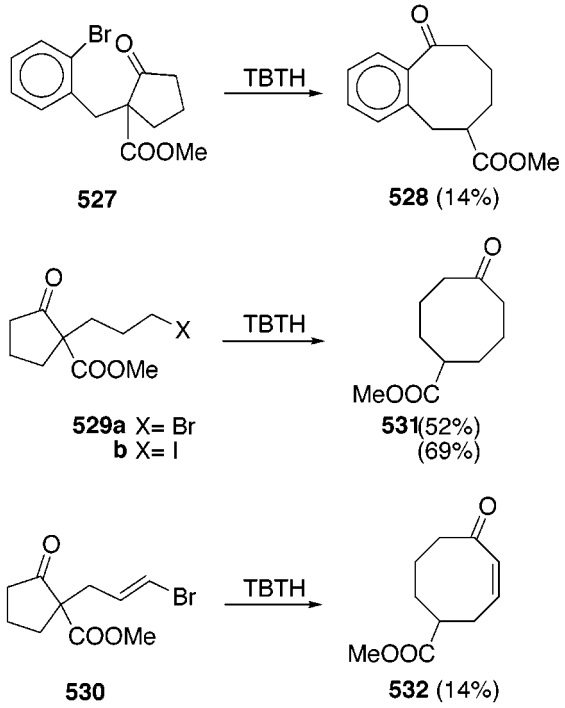
Galatsis et al. have observed[225] a two carbon ring expansion in epoxy iodide **520** to furnish cyclooctanone **521**, Scheme 107.[225] Several related examples involving the epoxy decalins **522** and **523** and leading to fused **524**, **525** and bridged cyclooctanes **526** have been reported, Scheme 107.[226] It is significant that these ring expansions proceed in a stereoselective manner to furnish only trans-fused products.

Several approaches to cyclooctanoids involving radical mediated three carbon ring expansion have also appeared recently. Beckwith has reported[217] the

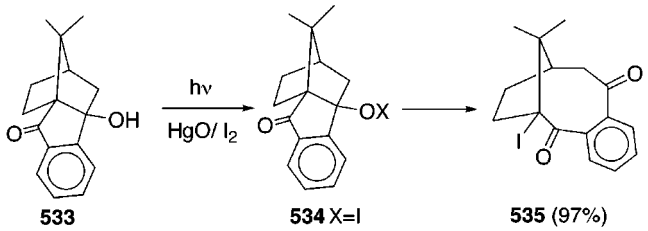
Scheme 107



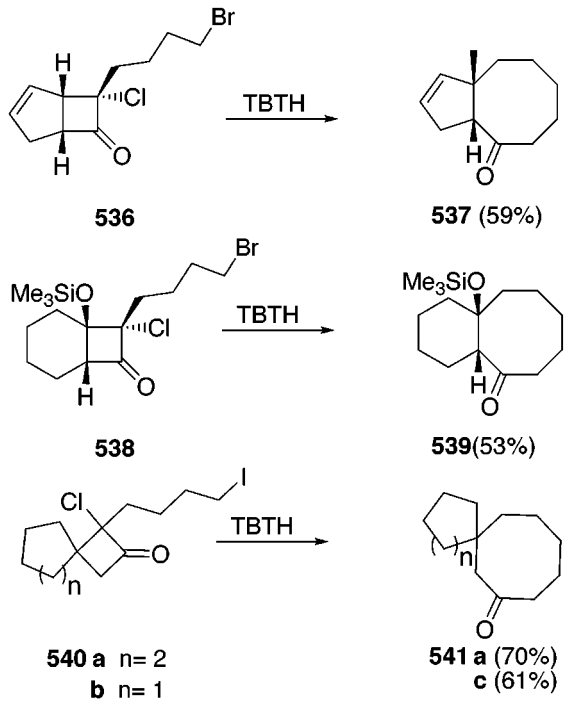
Scheme 108



Scheme 109



Scheme 110



formation of benzocyclooctanone ester **528** from the bromoketone **527** with TBTH in low yield, Scheme 108. Dowd et al. have reported[218] the synthesis of cyclooctanones **531** and cyclooctenone **532** from cyclopentanones **529** and **530**, respectively. The sequence proceeds through the addition of the initially formed radical intermediate to the carbonyl group, followed by fragmentation, Scheme 108. It may be noted that a similar sequence failed to effect two carbon expansion.[218]

Recently, keto alcohol **533** has been reported to give **535** via the light-induced fragmentation of the intermediate hypoiodide **534**, Scheme 109.[227] The radical-mediated **533** to **535** transformation is formally a three carbon ring expansion.

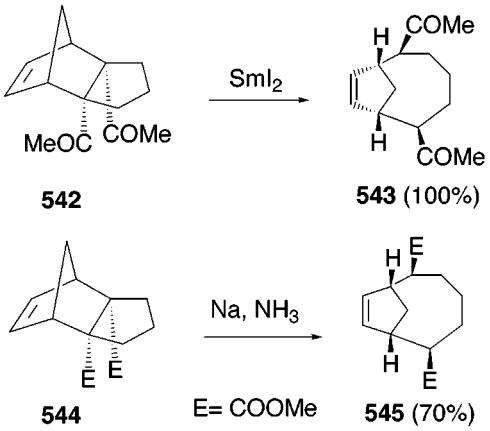
An elegant and simple four-carbon ring expansion on fused cyclobutanomes and spirocyclobutanones to furnish cyclooctanoids has been reported by Dowd and Zhang.[228−231] The annulated cyclobutanone **536**, which is easily available through dichloroketene addition, readily undergoes ring expansion upon treatment with TBTH to give fused cyclooctanone **537** in moderate yield, Scheme 110.[228,229] Other examples include ring expansion of **538** to **539**[230] and of the spirocyclobutanones **540** to **541**, Scheme 110.[231] It is to be noted that in the case of fused cyclobutanones such as **536** and **538** exo orientation of the haloalkyl

chain is essential for the radical cyclization−fragmentation to proceed.

C. Reductive and Oxidative Processes

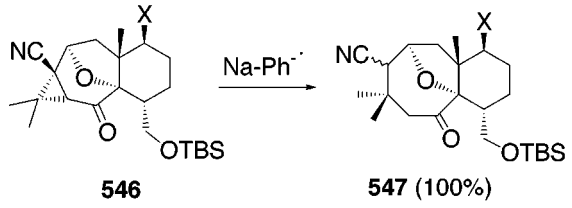
Reductive or oxidative cleavage of C−C and C=C bonds in carefully chosen polycyclic substrates can be employed to untangle the complexity of the carbocyclic frame and in the process unravel the latent cyclooctanoid moiety present in them. The propensity of succinic esters to undergo reductive C−C bond cleavage has been nicely exploited by Ghosh and co-workers[232] to access the bicyclio[5.3.1]undecane system. Thus, reaction of the tricyclo[5.2.1.0^{2,6}]decane derivative **542** with SmI_2 led smoothly to reductive C_2-C_6 bond cleavage to furnish **543** quantitatively and in a stereoselective manner.[232] The protocol appears to be fairly general and even liquid ammonia reductions can be gainfully employed as shown by the conversion of **544** to **545**, Scheme 111.[233]

Scheme 111



Magnus and co-workers have created the B ring of taxane via reduction of the internal cyclopropyl bond in the keto ether **546** with sodium naphthalenide to furnish **547** in a highly selective manner and in quantitative yield, Scheme 112.[234]

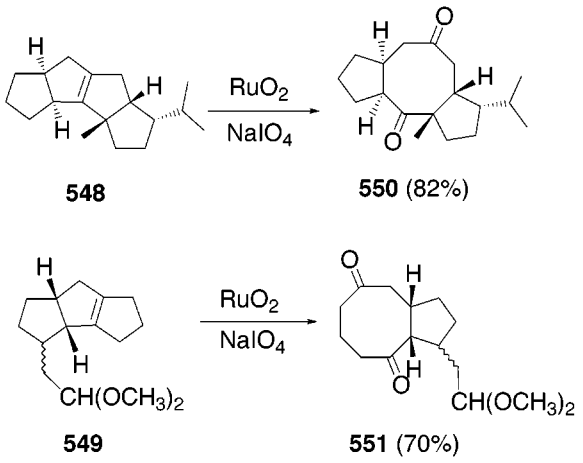
Scheme 112



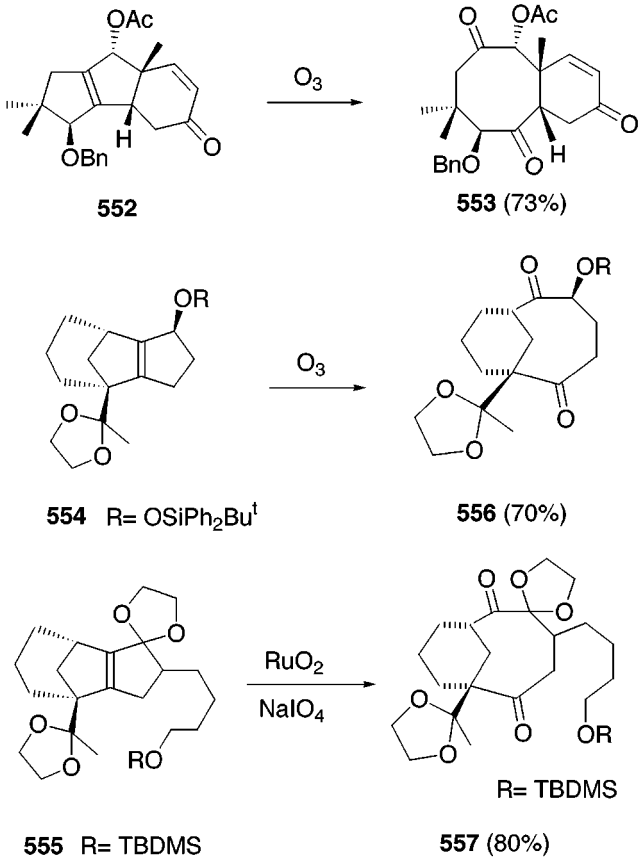
Earliest examples of cyclooctanoid ring construction through oxidative cleavage of bicyclo[3.3.0]oct-1(5)-ene moiety was reported by Mehta et al.[235,236] Thus, polyquinanes **548** and **549** were cleaved with RuO_2-NaIO_4 to 1,5-cyclooctadiones **550** and **551**, respectively, Scheme 113.

Arseniyadis reported the synthesis of ring BC of taxanes via regioselective ozonolytic cleavage of

Scheme 113

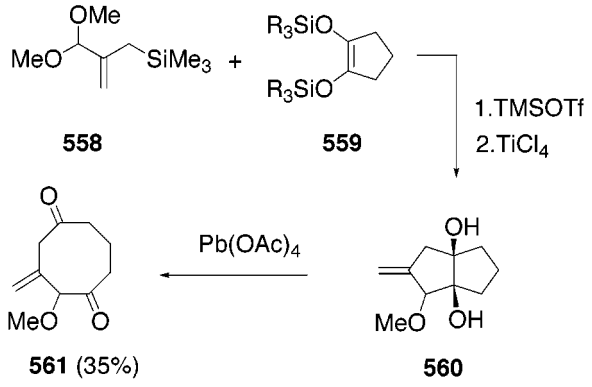


Scheme 114



tricyclic compound **552** to give a highly functionalized BC ring precursor **553** in excellent yield, Scheme 114.[237] Recently, Little and co-workers have also reported an approach toward taxanes which employed the oxidative cleavage in tricyclic systems to generate ring B. The tricyclic systems **554** and **555** prepared through the diyl methodology on oxidation led to **556** and **557**, respectively, in good yield, Scheme 114.[238] The bicyclic compound **557** having four carbon side chain on ring B was further elaborated to generate ring C of taxanes. Lee and co-workers[239] have reported an annulation−oxidative cleavage strategy to make cyclooctanones. The reaction of allyl silane **558** with bis-silylenolether **559**

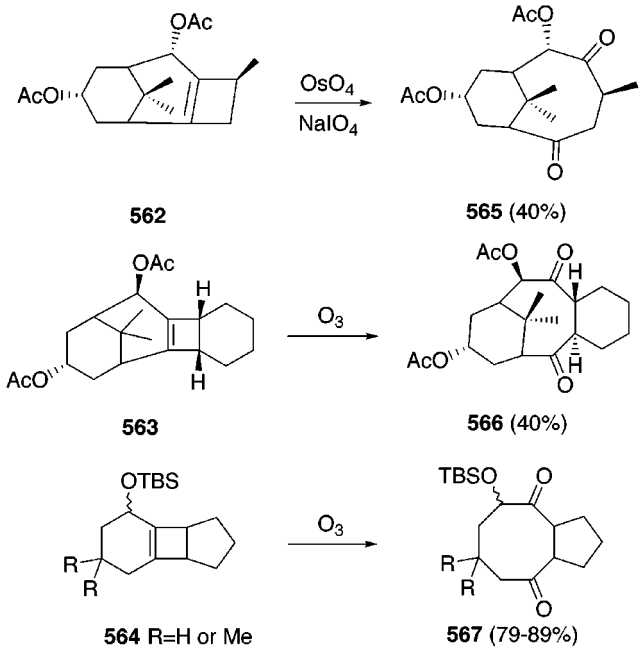
Scheme 115



gave the tricyclic diol **560**, which upon further treatment with lead tetraacetate furnished the cyclooctadione **561**, Scheme 115.[239]

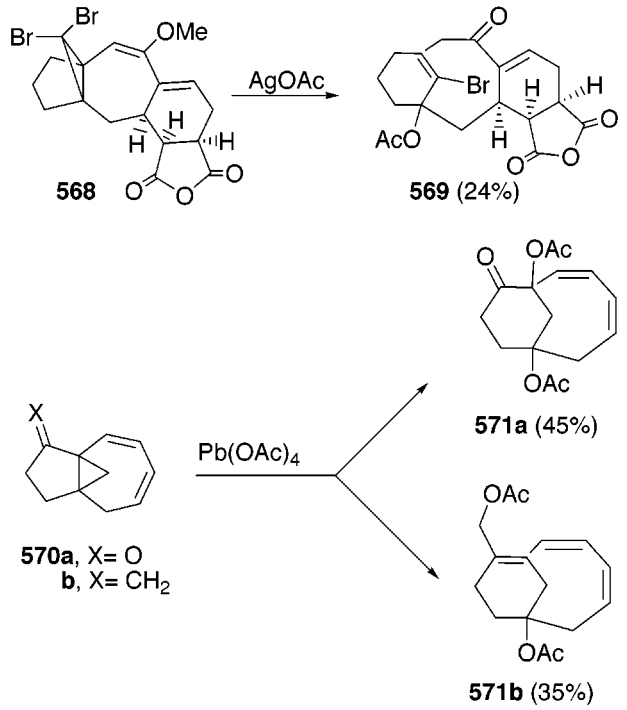
In analogy with the bicyclo[3.3.0]oct-1(5)-ene system, the bicyclo[4.2.0]oct-1(6)-ene derivatives also undergo smooth ozonolysis to furnish 1,4-cyclooctanediones. Thus, **562**−**564**, readily available through [2 + 2]-photocycloaddition protocols, on oxidative cleavage with ozone furnished **565**,[198] **566**,[240a] and **567**,[240b] respectively, representing various domains of the taxoid framework, Scheme 116.

Scheme 116



Banwell and co-workers have generated the ABC ring framework of taxoids in which the silver ion mediated rearrangement of the [5.3.1]-propellane derivative **568** to the bicyclo[5.3.1]undecane ring system **569** was the key step, Scheme 117.[241a] Kumar et al.[241b] have described the formation of the bicyclo[5.3.1]undecane system through the lead tetraacetate mediated oxidative cleavage in tricyclic propellanes **570a**,**b** to give bridgehead-functionalized bicyclo[5.3.1]undecanes **571a**,**b**, respectively, Scheme 117.

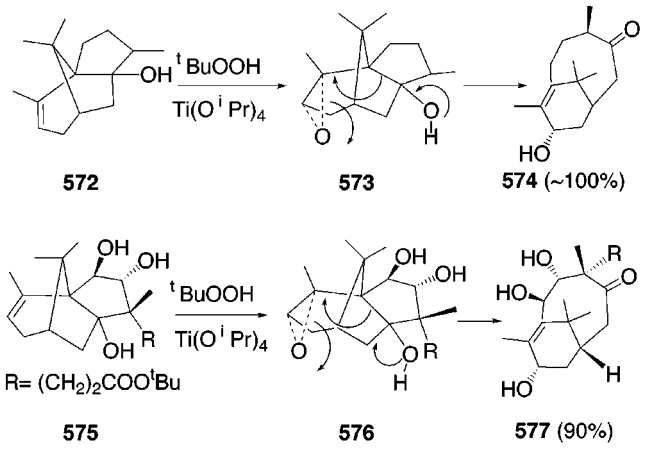
Scheme 117



D. Fragmentations and Rearrangements

Holton and co-workers have developed[242] an ingenious base-induced fragmentation protocol in the context of their synthetic assault on paclitaxel. The epoxide **573**, derived from tricyclic alcohol **572**, was shown to fragment to bridged cyclooctanone **574**, thus providing the taxoid AB ring system, Scheme 118.[242a]

Scheme 118

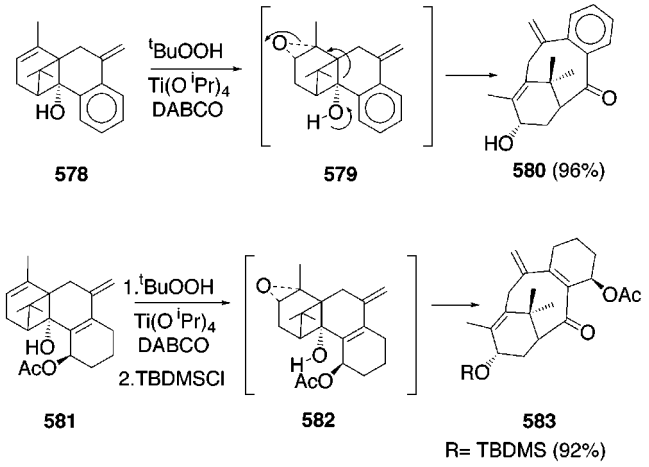


This approach was further extended to a more substituted precursor **575** which led to the functionalized AB ring system **577** with a side chain via the fragmentation of the epoxyalcohol **576**, Scheme 118.[242b] The side chain in **577** was used to annulate ring C. The first total synthesis of paclitaxel was achieved employing this fragmentation sequence as the pivotal step (vide infra).

Base-mediated epoxide fragmentation was also the key step in the generation of ring B of taxanes

by Wender's group.[243] Thus, the precursor **578** furnishedthe tricyclic framework **580** of taxanes in excellent yield through the intermediacy of epoxide **579**, Scheme 119. Similarly, the substrate **581**

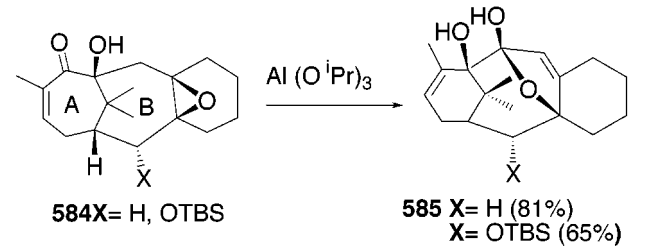
Scheme 119



was also transformed into **583** through the intermediacy of **582**.[244] Synthesis of paclitaxel by Wender's group will be presented later in the sequel (vide infra).

Rigby et al.[245] have deployed an interesting multievent rearrangement process in α-ketol **584** to furnish **585** in the presence of aluminum isopropoxide, Scheme 120. The α-ketol rearrangement

Scheme 120

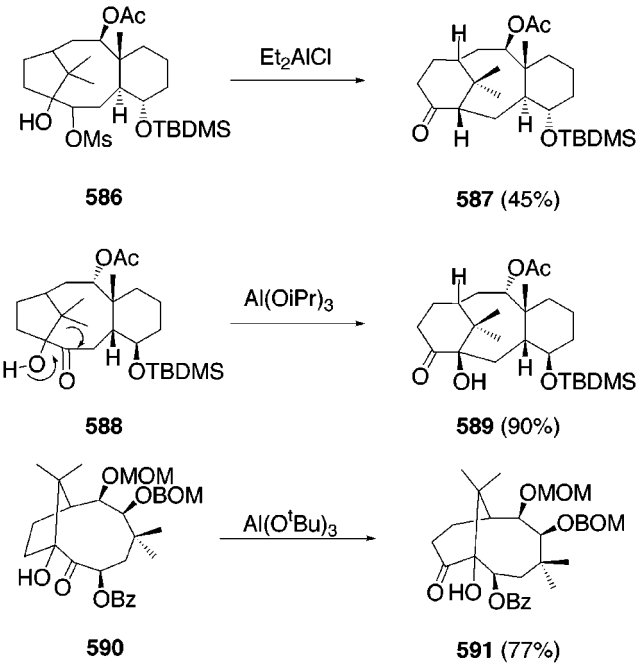


involving ring A contraction and ring B enlargement is followed by epoxide opening and intramolecular hemiacetal formation.

Paquette and co-workers have also generated eight-membered ring systems of taxane via the rearrangement of α-ketols.[246] In their earlier studies, the hydroxy mesylate **586** was rearranged to **587** on treatment with diethylaluminum chloride in which the nine-membered middle ring was contracted to furnish the ABC ring system of taxanes, Scheme 121. Similar rearrangement in keto alcohol **588** led to ring contraction to tricyclic keto alcohol **589** in excellent yield.[247a,b] Most recently, the same group has described the synthesis of a highly functionalized AB ring system of taxanes via rearrangement of bicyclo-[6.2.1]undecane system **590** to the bicyclo[5.3.1]-undecane system **591**, Scheme 121.[247c] Paquette has successfully accomplished a synthesis of (+)-taxusin, a diterpene related to paclitaxel, following an adaptation of these methodologies. [248]

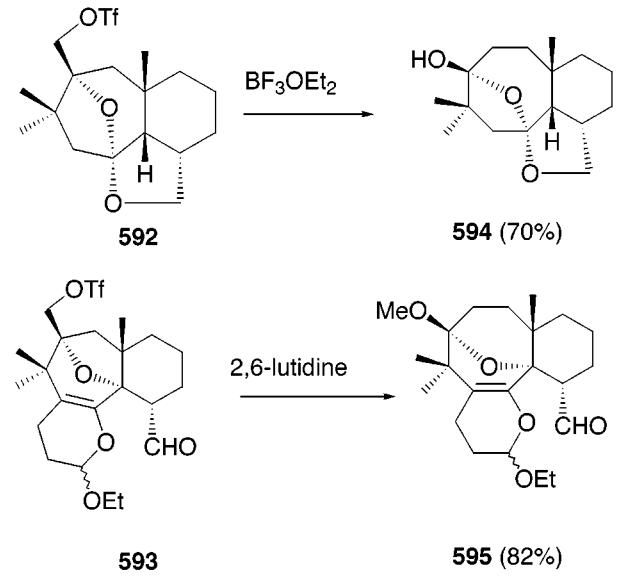
Regioselective ring expansion via semi-pinacol-type rearrangement in multifunctional substrates has

Scheme 121



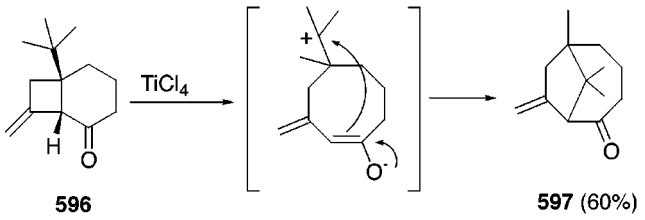
been employed by the Magnus group[249] for the construction of the eight-membered ring B of taxanes. Thus, the triflates **592** and **593** furnished **594** and **595**, respectively.[249] It is interesting that, despite the presence of many functionalities, these multievent processes led to decent yield of the products, Scheme 122.[249]

Scheme 122



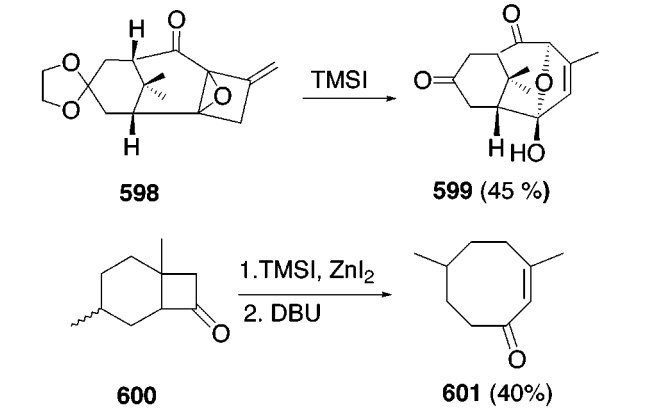
Kakiuchi et al. have reported a cationic rearrangement in bicyclo[4.2.0]octanone framework via cyclobutane fragmentation and methyl migration. When **596** was exposed to $TiCl_4$, bridged cyclooctanone **597** was formed in decent yield, Scheme 123.[250] This method is of general applicability and has been employed as a key step in a total synthesis of diterpenoid tetramethylmediterraniol B (vide infra).[250]

Scheme 123



Blechert has reported a fragmentation−ring enlargement methodology to prepare the AB ring system of taxanes. Treatment of the keto epoxide **598** with trimethylsilyl iodide gave the ring-expanded keto ether **599**, Scheme 124.[251] A simple example of

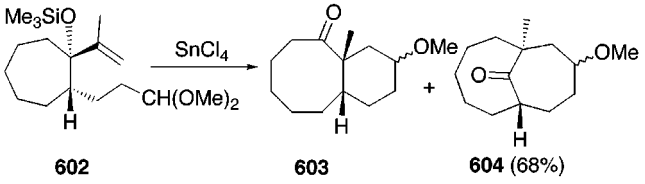
Scheme 124



similar rearrangement is the formation of dimethylcyclooctenone **601** from bicyclo[4.2.0]octanone **600** via two carbon ring expansion, Scheme 124.[252]

In continuation of his work on ring enlarging annulations,[253a] Overman has recently reported the construction of eight-membered rings.[253b] Thus, the functionalized cycloheptane derivative **602**, on exposure to $SnCl_4$, furnished fused cyclooctanone **603** and bridged cyclooctanone **604** in a combined yield of 68%, Scheme 125.

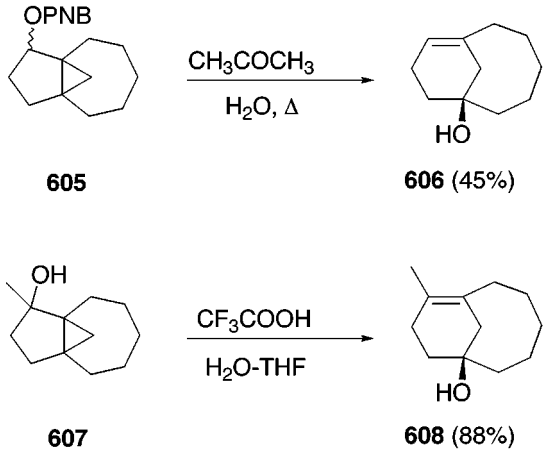
Scheme 125



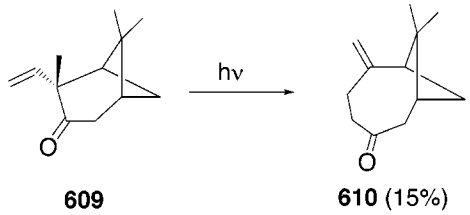
Cyclopropylcarbinyl−homoallylic rearrangement has also been exploited for the synthesis of AB rings of taxanes by Schafer and co-workers.[254] Thus, tricyclic [5.3.1]propellane based *p*-nitrobenzoate **605**, upon hydrolysis, gave the rearranged homoallylic alcohol **606** as the major product. Similarly, the tertiary carbinol **607** gave the bicyclic bridgehead alkene **608** on exposure to trifluoroacetic acid, Scheme 126.

Recently, elaboration of (−)-α-pinene to bicyclo-[5.1.1]nonane framework has been reported.[255] The main feature of this approach is the photorearrangement of **609**, obtained from α-pinene, to **610**, Scheme 127.

Scheme 126



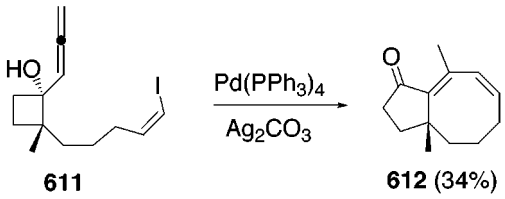
Scheme 127



E. Miscellaneous Methods

Nemoto et al. reported[256] formation of cyclooctadienones **612** during carbopalladation of cyclobutanol derivative **611** having allene and alkenyl side chains, Scheme 128. The stereochemical orientation of the

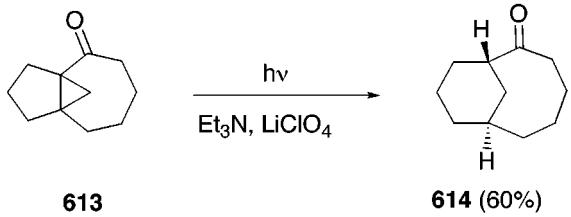
Scheme 128



hydroxyl group and the experimental conditions govern the formation of products.[256]

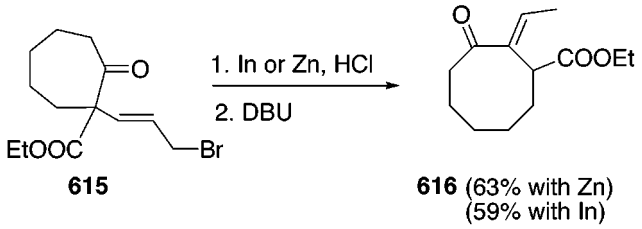
Cossy and Bouzbruz[257] have observed a photochemical ring expansion through a cyclopropyl ketone moiety within a [5.3.1]-propellane ketone **613**, under SET photochemical regime to give bridged cyclooctanone **614**, Scheme 129.

Scheme 129



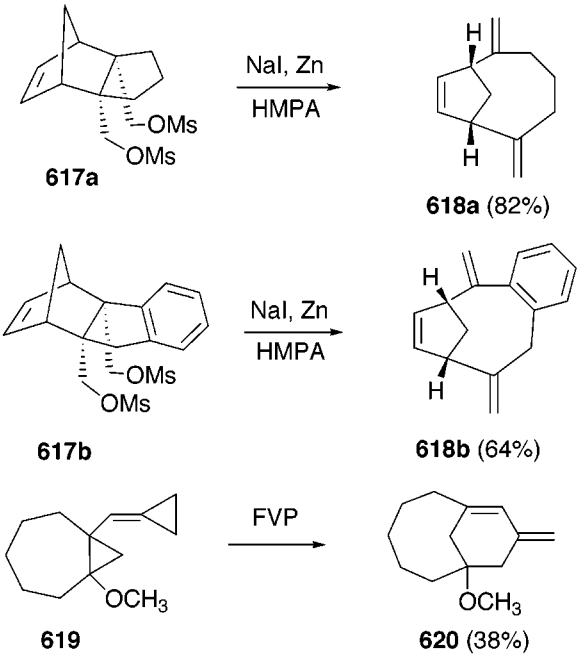
Recently, a one carbon ring expansion of the readily available cycloheptanone derivative **615** having a bromoallyl side chain to cyclooctanone ester **616** on reaction with zinc and/or indium has been reported, Scheme 130.[258]

Scheme 130



Ghosh et al.[259a−c] have reported a three carbon ring expansion in tricyclic systems **617a** and **617b** leading to **618a** and **618b**, respectively, having a bicyclo-[5.2.1]undecane framework via fragmentation involving 1,4-elimination, Scheme 131. Recently, Cohen has

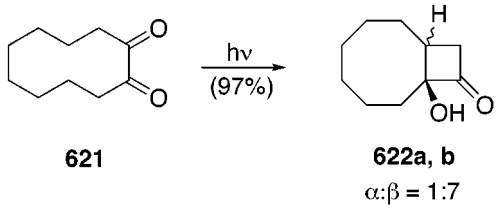
Scheme 131



observed efficient formation of bicyclo[5.3.1]undecane derivative **620** during the pyrolysis of the cyclopropyl compound **619**. The reaction proceeds through thermal double ring expansion involving the cyclopropylalkylidenecyclopropane intermediate. [259d]

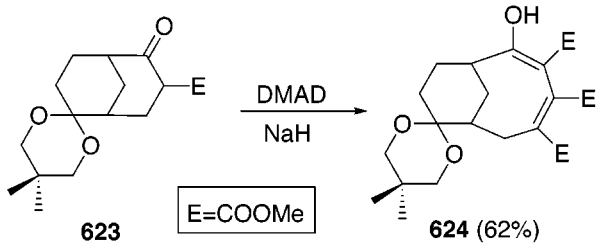
A photochemical ring contraction of 1,2-cyclodecanedione **621** has been observed by Scheffer and co-workers[260] and constitutes a useful method for the synthesis of cyclooctanoids. Irradiation of **621** gave fused cyclooctanes **622a**,**b** in a stereoselective manner and in excellent yield, Scheme 132.

Scheme 132



Franck-Neumann reported a two carbon expansion on bicyclo[3.3.1]nonanone system **623** on reaction with DMAD in the presence of base to give **624**, Scheme 133.[261]

Scheme 133



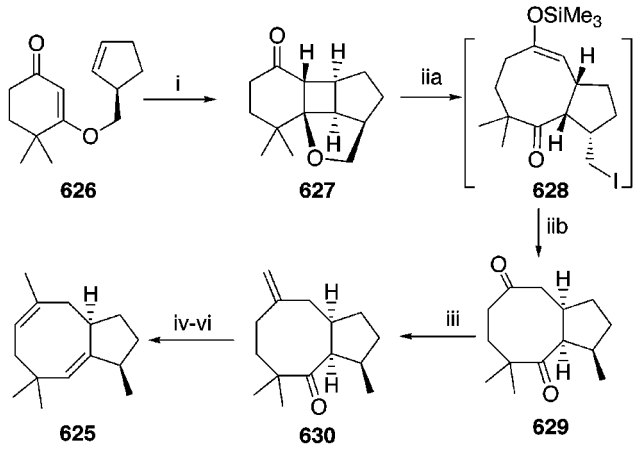
IV. Total Syntheses of Natural Products

Syntheses of many cyclooctanoid natural products have been achieved in recent years. In many cases, they represent the culmination of the methodological developments described above. The attainments of the past six years are summarized below.

A. Precapnelladiene

Several syntheses of precapnelladiene **625**, a sesquiterpene of marine origin isolated from *Capnella imbricata*[262a] and incorporating a bicyclo[6.3.0]-undecane framework, have been reported.[262b−g] Recently, syntheses, of (±)- and (−)-precapnelladiene have appeared[263,264] which are briefly presented here. The key step in both of these efforts is a photochemical [2 + 2]-cycloaddition and cyclobutane cleavage in the resulting adduct. Enantiopure keto enol ether **626** on intramolecular [2 + 2]-photoaddition furnished **627**. TMSI-mediated cleavage of the cyclobutane ring and TBTH reduction gave the dione **629** via **628** with correct relative stereochemistry at the three stereogenic centers. Functional group manipulation in **629** via **630** led to the natural product (−)-**625**, Scheme 134.[263]

Scheme 134[a]

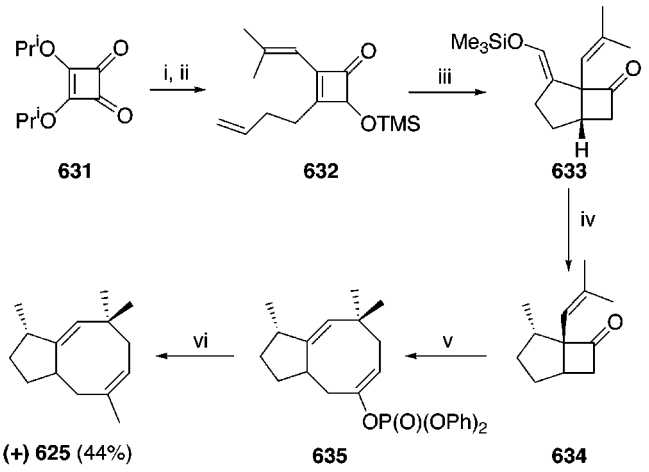


[a] Reagents; i *hν*, 70%; ii (a) TMSI, (b) Bu_3SnH, 98%; iii CH_2=PPh_3, 87%; iv $RhCl_3$, 86%; v (a) $LiAlH_4$, (b) $SOCl_2$, DBU, 70%.

Moore and co-workers [264] achieved a synthesis of (±)-precapnelladiene by exploiting the chemistry of squarate esters **631**. Thus, cyclobutenone **634** was prepared from squarate derivative **632** and was further transformed to **633** via thermal rearrangement. Addition of vinyl anion to cyclobutanone **634**

triggered the Cope rearrangement, and subsequent interception of the resulting enolate gave the compound **635**, having the requisite framework in a single step. Pd-mediated introduction of a methyl group in **635** furnished the natural product (±)-**625**, Scheme 135.

Scheme 135[a]

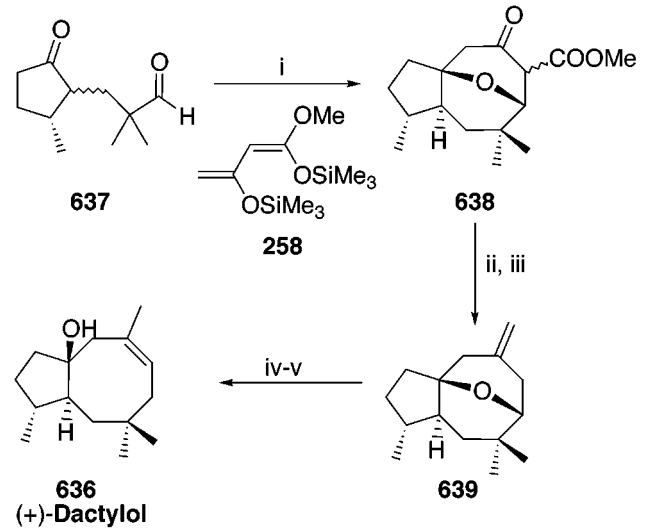


[a] Reagents: i (a) LiCH=CMe$_2$, (b) TFAA, (c) LiAlH(OtBu)$_3$, 81%; ii (a) BrMg(CH$_2$)$_2$CH=CH$_2$, (b) HCl, (c) TMSCl, NEt$_3$, 49%; iii Δ, 95%; iv (a) HCl, (b) HS(CH$_2$)$_3$SH, (c) Ni, 42% (from **632**); v LiCH=CH$_2$, ClPO(OPh)$_2$, 59%; vi Pd[P(Ph)$_3$]$_4$, AlMe$_3$, 44%.

B. Dactylol

Bicyclo[6.3.0]undecane based sesquiterpenoid dactylol **636** isolated from *Aplysia dactylomela*[265a] and *Laurencia poitei*[265b] with a bridgehead hydroxy group has also been a popular synthetic target, and many syntheses have appeared earlier.[21c,97b,265c−i] Recently, Molander and Eastwood[266] have reported a neat synthesis of (+)-dactylol from the chiral 1,5-dione **637**. Reaction of dione **637** with bis-silyl ether **258** generated the eight-membered ring and furnished keto ester **638** as a result of regioselective annulation. The keto ester **638** was readily elaborated to ether **639**. Isomerization of the double bond in **639** and reductive cleavage of the ether bridge gave (+)-dactylol **636**, Scheme 136.

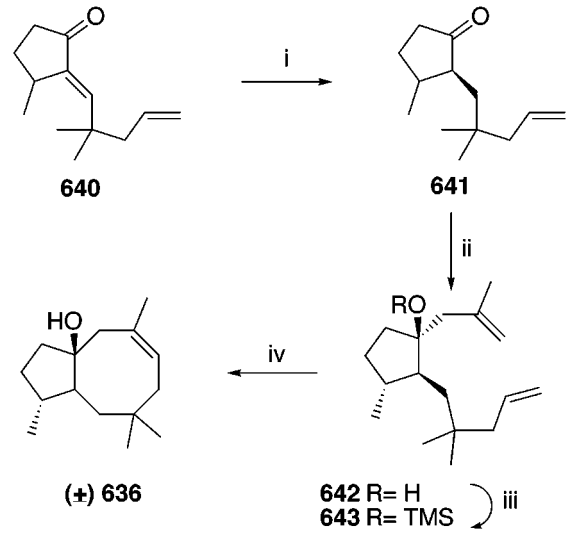
Scheme 136[a]



[a] Reagents: i TrSbCl$_6$, 77%; ii NaCl, DMSO, 85%; iii Cp$_2$TiClCH$_2$-AlMe$_2$, 92%; iv RhCl$_3$, 96%; v Li, H$_2$N (CH$_2$)$_2$NH$_2$, 25%.

Furstner and Langemann have also reported[267] a short synthesis of (±)-dactylol **636** employing RCM as the key step for generating the fused cyclooctane framework endowed with all of the functionalities correctly disposed, in a single step. The key precursor for the intramolecular metathesis was prepared from the ketone **641**, readily available from cyclopentenone derivative **640**. Addition of an organocerium reagent derived from methallyl bromide to **641** gave two diastereomeric products from which **642** was separated. Transformation to the corresponding silyl ether **643** and subsequent cyclization using Schrock's carbene catalyst gave (±)-dactylol **636** as shown in Scheme 137.

Scheme 137[a]



[a] Reagents: i Bu$_3$SnH, ZnCl$_2$, Pd(PPh$_3$)$_4$, 83%; ii (a) Mg−graphite, CH$_2$=C(CH$_3$)CH$_2$Br, (b) CeCl$_3$, 80%; iii (Me$_3$Si)$_2$NH, AcCl 93%; iv (a) PhMe$_2$CCH=Mo=N[2,6-(iso-Pr$_2$C$_6$H$_3$][OCMe(CF$_3$)$_2$]$_2$; (b) aq TBAF, 92%.

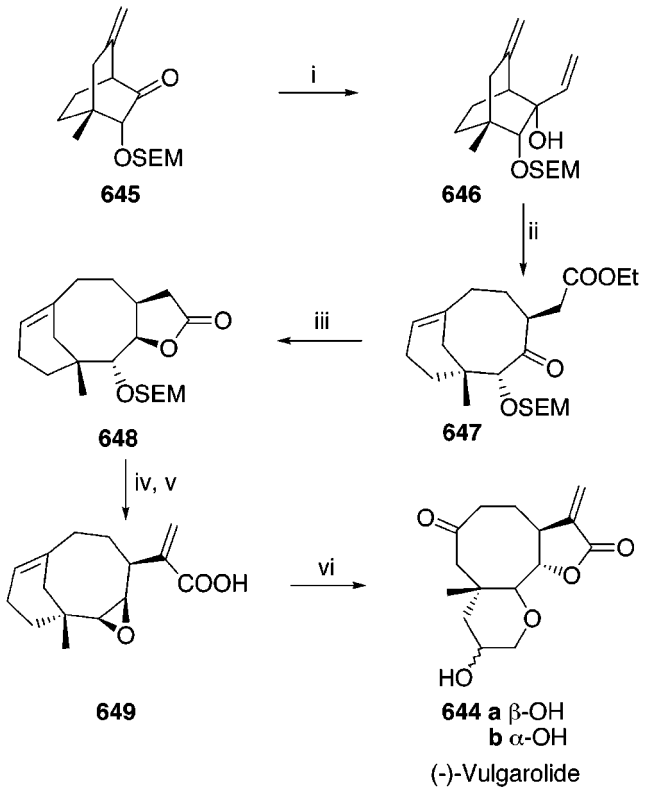
C. Vulgarolide

Total synthesis of (−)-vulgarolide **644a** isolated from *Tanacetum vulgare*[268] has been achieved by Paquette and co-workers.[269] Oxy-Cope rearrangement in the bicyclo[2.2.2]octane framework is the key step for the eight-membered ring construction. Optically active bicyclic enone **645** obtained via the Johnson sulfoximine methodology,[270] on addition of vinyl Grignard reagent, gave the key precursor **646** in a stereoselective manner. Anionic oxy-Cope rearrangement in **646** followed by alkylation of the resulting enolate gave bridged cyclooctanoid **647**, and it was further transformed into lactone **648**. Subsequent functional group alterations and transformation to epoxide **649** and ozonolysis gave (−)-vulgarolide **644a** along with its epimer **644b**, Scheme 138.

D. Upial

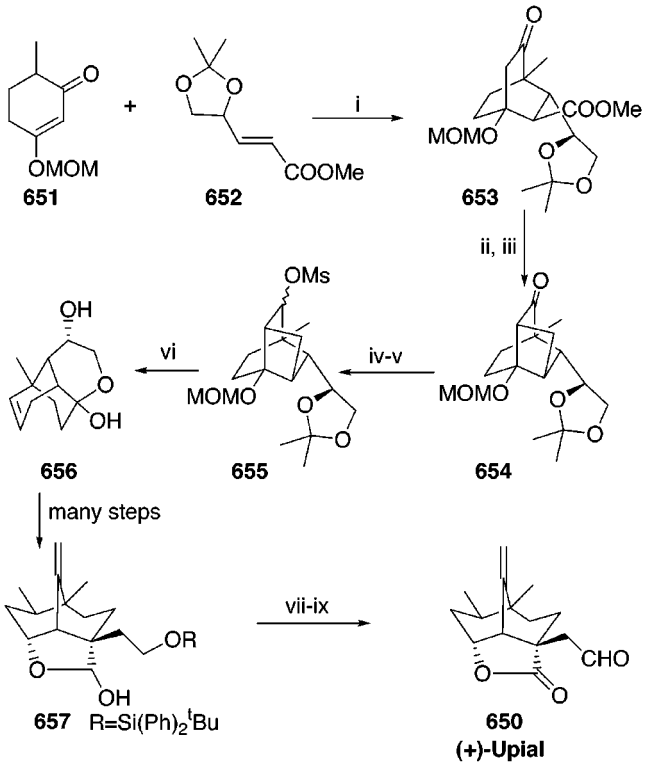
(+)-Upial **650** is a marine sesquiterpene isolated from *Dysidea fragilis*[271]and having a rare bicyclo-[3.3.1]nonane framework. Syntheses of (−)-upial and (±)-14-epi-upial were earlier accomplished by the research groups of Taschner[272] and Paquette,[273] respectively. Recently, two new syntheses of upial have been reported. Synthesis by Nagaoka emanates

Scheme 138[a]



[a] Reagents: i CH_2=$CHMgBr$, 94%; ii (a) $KN(SiMe_3)_2$, Δ, (b) ICH_2COOEt, 78%; iii (a) LAH, (b) TPAP, 76%; iv (a) LDA, CH_2O, (b) MsCl, Et_3N, DMAP, (c) DBU, (d) HF, 81%; v (a) MsCl, DMAP, (b) LiOH, CH_3OH, 31%; vi O_3, 70%.

Scheme 139[a]

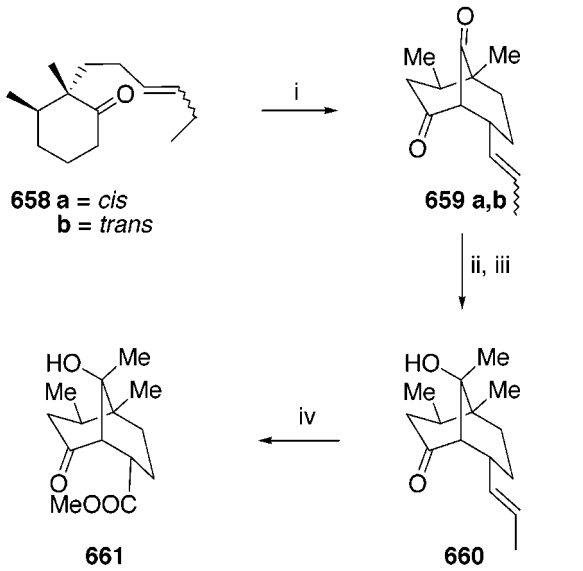


[a] Reagents: i LDA, 85%; ii (a) LAH, 94%, (b) TsCl, Py, 80%, (c) PDC, 90%; iii ^tBuOK, 93%; iv LAH, 97%; v MsCl, DMAP, 97%; vi HCl, 91%; vii PDC, 77%; viii Bu_4NF, 94%; ix PDC, 87%.

from the optically active tricyclo[2.2.2]octanone derivative **653** that was prepared from 6-methyl-3-methoxymethyloxy-2-cyclohexenone **651** and the ester **652** derived from D-mannitol. The bicyclo[2.2.2]-octane derivative **653** was converted to the tricyclic precursor **654** after several steps including an intramolecular displacement to form the four-membered ring. The tricyclic ketone **654** was elaborated to mesylate **655** to setup a fragmentation reaction that led to the unmasking of the bicyclo[3.3.1]nonane skeleton. Acid hydrolysis in **655** gave hemiacetal **656** having a framework of upial in good yield. The hemiacetal **656** was transformed into a lactol **657** en route to (+)-upial **650**, Scheme 139.[274]

Snider's formal synthesis[275] of upial employed Mn-(III) based oxidative cyclization for generating the bicyclo[3.3.1]nonane framework. Oxidative, radical mediated intramolecular cyclization of cyclohexan-1,3-dione derivative **658** gave the desired bicyclo-[3.3.1]nonanone **659a**,**b** along with another diastereomer. The isomer **659a** was converted to the keto alcohol **660** and further transformed into the known ester **661**, which had previously been taken to upial, Scheme 140.[272]

Scheme 140[a]

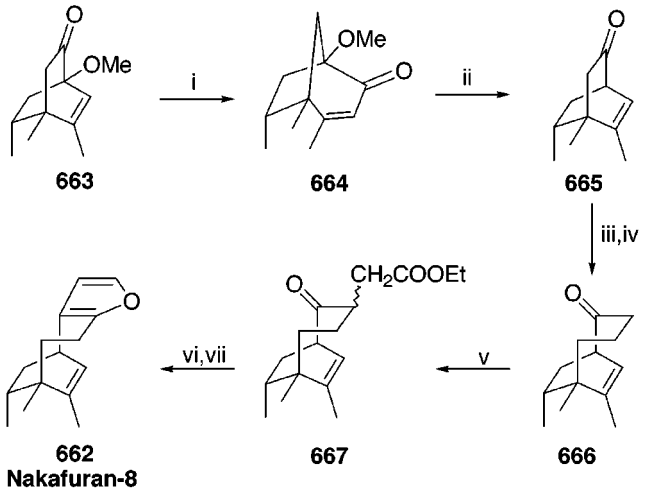


[a] Reagents: i $Mn(OAc)_3$, $Cu(OAc)_2$, 85%; ii TBDMSOTf, Et_3N; iii (a) MeLi, (b) TBAF, 83% (for ii and iii); iv (a) OsO_4, NMO, (b) KlO_4, (c) $NaClO_2$, (d) CH_2N_2, 83%.

E. Nakafuran-8

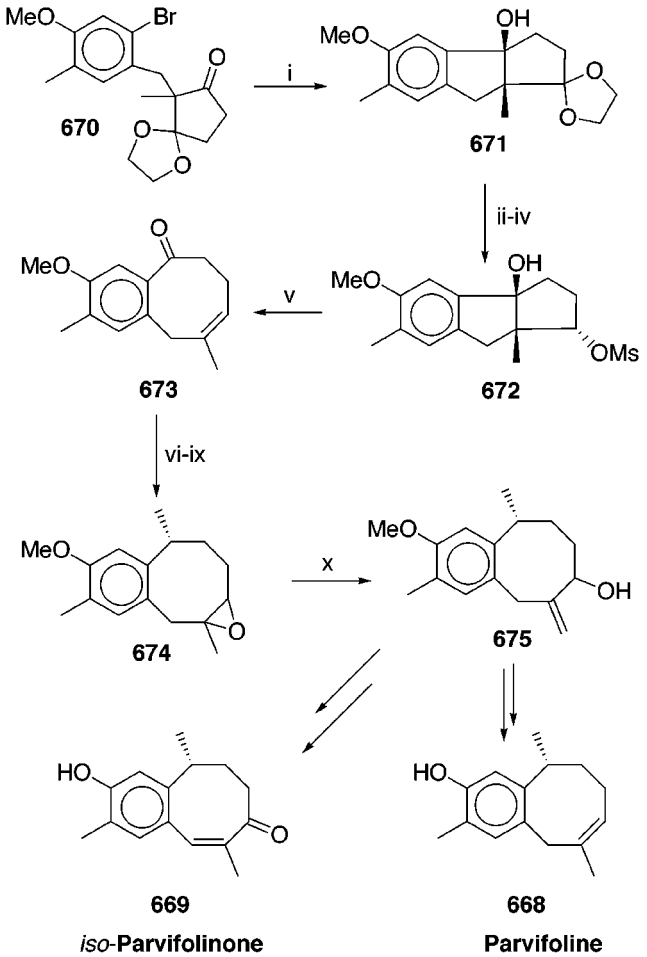
Nakafuran-8 **662**, a novel sesquiterpene containing a bicyclo[4.2.2]decadiene, was isolated from *D. fragilis*[276] and is known to act as a repellent against reef fish. Its synthesis has been accomplished by Uyehara and co-workers.[277] In their approach, the eight-membered ring was generated through sequential ring expansion of a bicyclo[2.2.2]octane skeleton. The key bicyclo[2.2.2]octenone **665** was readily prepared from **663** via bicyclo[3.2.1]octenone **664**. Sequential double ring expansion in **665** preferentially gave **666** having the requisite framework. Furan annulation was effected through alkylation of the ketone **666** to **667** which was further cyclized to nakafuran-8 **662**, Scheme 141.

Scheme 141[a]



[a] Reagents: i BF_3−MeOH; ii (a) DIBALH (b) *p*-TSA, 74% (for i and ii); iii (a) $(CH_3)_3SiCHN_2$, $BF_3{\cdot}OEt_2$, 70% or (b) $(CH_3)_3SiCN$, ZnI_2, then LAH and $NaNO_2$, AcOH, 61% both isomers; iv $(CH_3)_3SiCHN_2$, $BF_3{\cdot}OEt_2$, 79%; v LDA, ICH_2COOEt, quant; vi (a) K_2CO_3, (b) TsOH; vii DIBALH, 37% (from **666**).

Scheme 142[a]

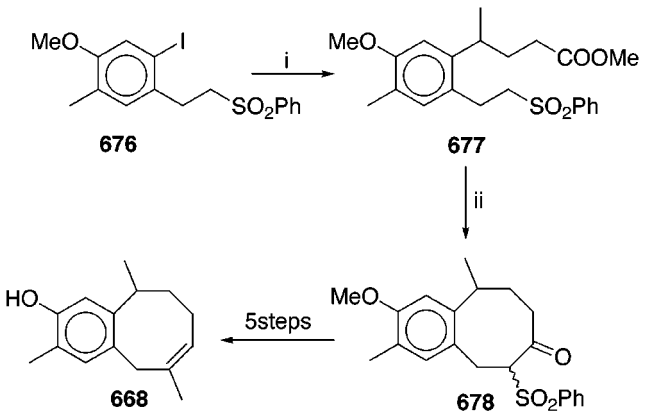


[a] Reagents: i Li, 43%; ii H_2SO_4, MeOH, 94%; iii $NaBH_4$, MeOH, 98%; iv MsCl, Py, ⁻4 °C, 68%; v NaOMe, MeOH, 80%; vi MeLi, 75%; vii MsCl, Py, 80%; viii mCPBA, 77%; ix PdC,H_2, 95%; x, *p*-TsOH, 78%.

F. Parvifoline and Isoparvifolinone

Parvifoline **668** and isoparvifolinone **669** are sesquiterpenoids isolated from the genera *Coreopsis* and *Perezia*[278] possessing a trimethylbenzocyclooctane skeleton and have yielded to synthesis earlier.[279a] Joseph-Nathan and co-workers[279b] have synthesized (±)-parvifoline employing a Grob-like fragmentation to generate the cyclooctane ring. The key precursor **672** was obtained from **670** via hydroxy ketal **671**. Fragmentation of the hydroxy mesylate **672** gave benzocyclooctanone **673** in good yield and transformed into alcohol **675** via epoxide **674**. The intermediate **675** was taken to both (±)-parvifoline **668** and (±)-isoparvifolinone **669**, Scheme 142. Grimm et al.[280] have also synthesized parvifoline in which the cyclooctane ring is constructed through intramolecular alkylation. The sulfone ester **677** was obtained from iodosulfone **676** in three routine steps. Treatment of the ester **677** with base gave benzocyclooctanone **678** in good yield, which was elaborated to parvifoline **668**, Scheme 143.[280]

Scheme 143[a]



[a] Reagents: i (a) $CH_3CH{=}CHCH_2CH_2OH$, $Pd(OAc)_2$, (b) H_2CrO_4, (c) CH_2N_2, 44%; ii LiHMDS, 67%.

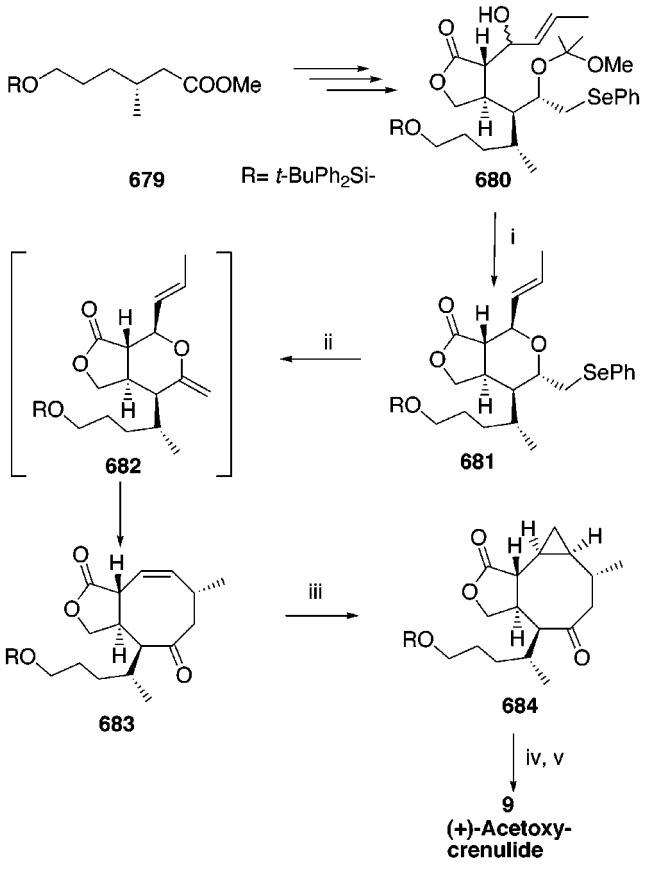
G. Acetoxycrenulide

Acetoxycrenulide **9**, a diterpenoid isolated from *Dictyotaceae*,[11] possesses an unusual bicyclo[6.1.0]-nonane framework having α,*β*-unsaturated lactone and acetoxy groups. Paquette and co-workers[281a,b] have reported the first synthesis of (+)-acetoxycrenulide employing a [3,3]-sigmatropic shift as a key step to generating the cyclooctanoid ring. The intermediate **680** was prepared in chiral form from the ester **679**, which itself is available from (*R*)-citronellol. Acid-catalyzed cyclization of **680** gave the key precursor **681**. Oxidation of **681**, selenoxide elimination to **682**, and [3,3]-shift gave the cyclooctenone **683** endowed with all of the structural and functional elements of acetoxycrenulide in correct stereochemical orientation. Simmon-Smith cyclopropanation followed by introduction of double bond gave the intermediate **684**, which was taken to the natural product (+)-**9**, Scheme 144.

H. Ceroplastol I

Ceroplastol I **685** belongs to a family of 5-8-5-fused sesterterpenes isolated from a pathogenic fungi and scale insect *Cereoplastes albolineatus*.[282] Some time ago, Boeckmann and co-workers reported its first synthesis.[283] Recently, Paquette and co-workers[284] have developed a synthesis of (+)-ceroplastol I **685**

Scheme 144[a]



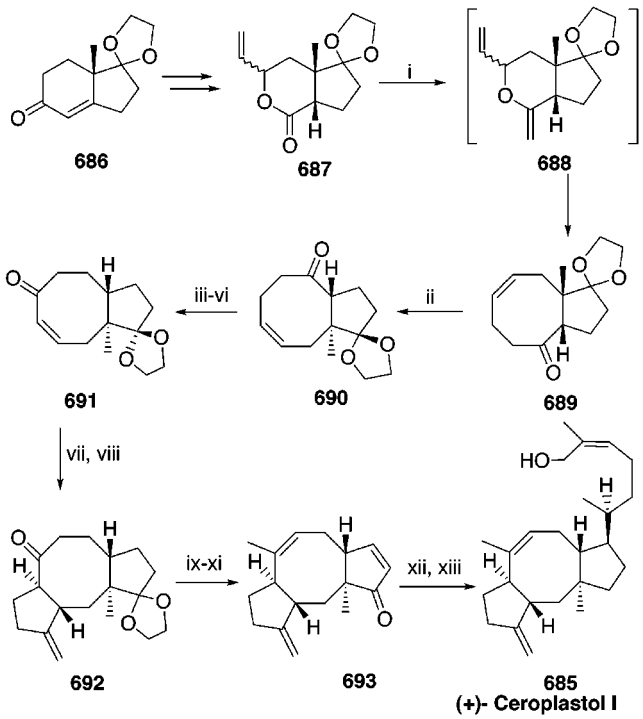
[a] Reagents: i *p*-TsOH, 49%; ii $NaIO_4$, (b) $CH_2{=}CH(OEt)$, Et_3N, Me_2NCOCH_3, 220 °C; iii CH_2I_2, Et_2Zn, 96%; iv (a) $(^iBu)_2AlH$, (b) Ag_2CO_3, Celite, (c) $KN(TMS)_2$, PhSeCl, $NaIO_4$, 65%; v (a) Ac_2O, DMAP, (b) Py−HF, (c) PDC, (d) $Ph_3P{=}C(CH_3)_2$, 54%.

in which the eight-membered ring was constructed through a two carbon intercalation employing a [3,3]-sigmatropic process. The key precursor **687** was synthesized from optically pure keto ketal **686**. Tebbe olefination in **686** followed by Claisen rearrangement (3,3-shift) in **688** gave fused cyclooctenone **689** in a reasonably good yield. The *cis*-ketone **689** was epimerized to *trans*-**690** and elaborated to tricyclic compound **692** via cyclopentene annulation of **691**. Subsequent functional group manipulation of **692** led to trienone **693**, and the introduction of the alkyl side chain furnished (+)-ceroplastol I **685**, Scheme 145.

I. 7,8-Epoxy-4-basmen-6-one

A novel synthesis of (±)-7,8-epoxy-4-basmen-6-one, a diterpenoid isolated from tobacco,[285] was accomplished by Myers and Condroski.[286] One of the most remarkable features of this synthesis is the generation of the tricyclic 5-8-5 ring system **346** in a single step, via tandem radical cyclization of a macrocycle as described earlier. To transform the tricyclic precursor **346** into epoxybasmenone **694**, it was necessary to correct the configuration at C-11. Therefore, the cyclopentene ring in **346** was opened and converted to the bicyclic compound **695**. Isomerization in **695** led to **696**, which was recyclized to tricyclic intermediate **697** having correct stereochemistry at C-11. The diene **697** was then converted to epoxy

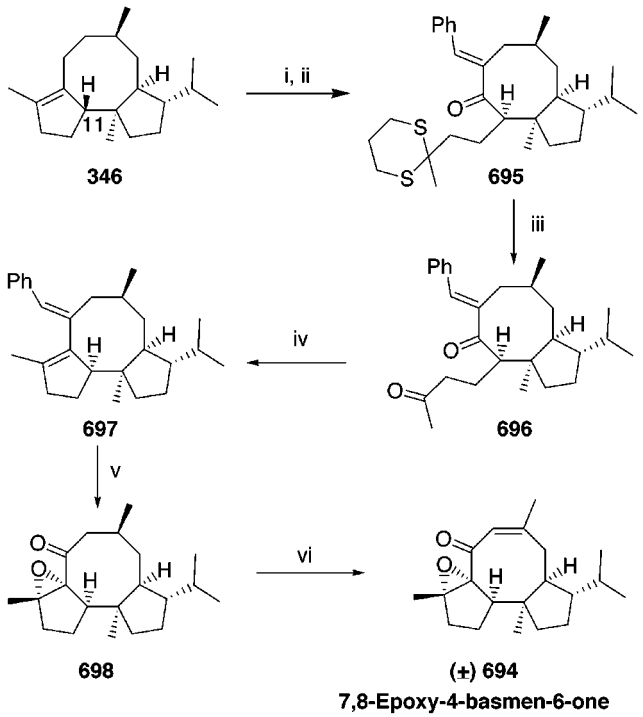
Scheme 145[a]



[a] Reagents: i $CpTi(Cl)(CH_2AlMe_2)$, Δ ~50−60%; ii K_2CO_3, 93%; iii $LiAlH_4$, 83%, *n*-BuLi, $ClP(O)(NMe_2)_2$, 73%; iv Li, $C_2H_5NH_2$; v SeO_2, 61%; vi PDC, 80%; vii $(ClCH_2CH_2C{=}CH_2)_2CuLi$, 78%; viii KH, 90%; ix $KN(TMS)_2$, Tf_2NPh, $(CH_3)_2CuLi$, 68%; x TsOH, 84%; xi $LiN(TMS)_2$, TMSCl, $Pd(OAc)_2$, 40%; xii $TBSOCH_2(CH_3)C{=}CHCH_2CH_2CH(Cl)CH_3$, Mg, CuBr−$Me_2S$, HMPA, TMSCl, 78%; xiii $TsNHNH_2$, $NaBH_3CN$, $ZnCl_2$, 55%.

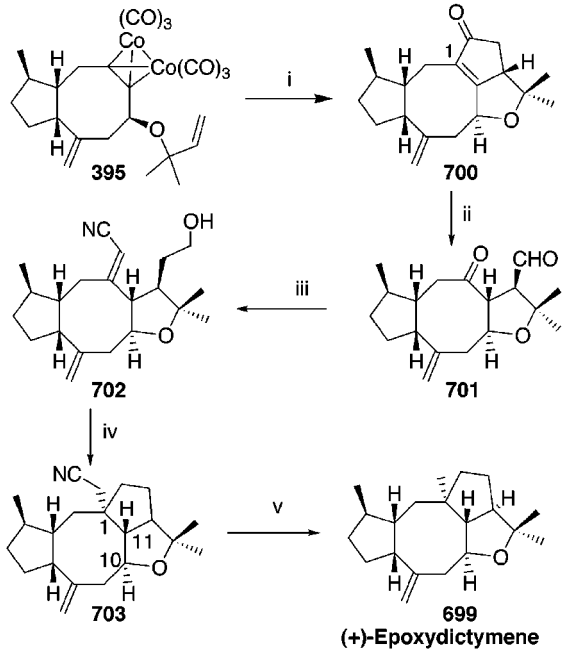
ketone **698**, which finally led to the natural product **694**, Scheme 146.

Scheme 146[a]



[a] Reagents: i (a) RuO_4, (b) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, (c) PhCHO, NaOH, 60%; ii (a) TMSI, Et_3N, (b) MeOH, HCl, 95%; iii MeI, aq CH_3CN, 96%; iv $TiCl_3$−DME, Zn−Cu, Δ; v mCPBA, RuO_4, 65% for both steps; vi LDA, PhSeCl, H_2O_2, 75%.

Scheme 147[a]



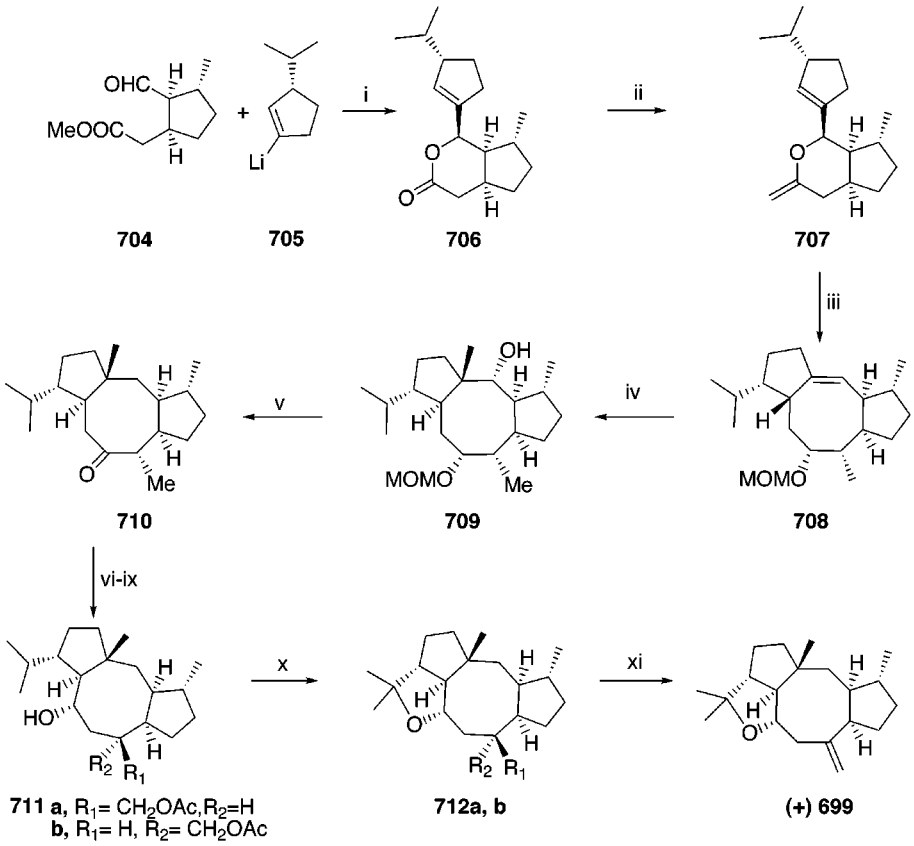
[a] Reagents: i CH_3CN, Δ, 85%; ii (a) Li, NH_3, NH_4Cl, (b) KHMDS, *N*-phenylsulfonylphenyloxaziridine, (c) $NaHB(OAc)_3$, (d) $Pb(OAc)_4$, (e) DBU, 31%; iii (a) $Ph_3P{=}CHOMe$, (b) NaH, $(EtO)_2P(O)CH_2CN$, 71% (for a, b), (c) HCl, (d) $NaBH_4$, 91% (for c, d); iv (a) Ph_3P, imidazole, I_2, 81%, (b) *t*-BuLi, 74%; v K, 18C6, 82%.

J. Epoxydictymene

Schreiber and his associates have accomplished[287] a total synthesis of (+)-epoxydictymene **699**, another 5-8-5-fused diterpene, isolated from *Dictyota dichotoma*.[288] Heating a solution of the readily available chiral cobalt cluster **395** (vide supra) furnished the tetracyclic intermediate **700** having a framework of epoxydictymene **699**. Unfortunately, introduction of the angular methyl at C-1 proved to be difficult. Hence, the cyclopentene ring was opened and manipulated to keto aldehyde **701**, which was transformed to cyano alcohol **702**. Subsequent ring closure in **702** gave the intermediate **703** having appropriate stereochemistry at C-1, C-10, and C-11. Removal of the nitrile group finally gave the (+)-epoxy dictymene **699**, Scheme 147.

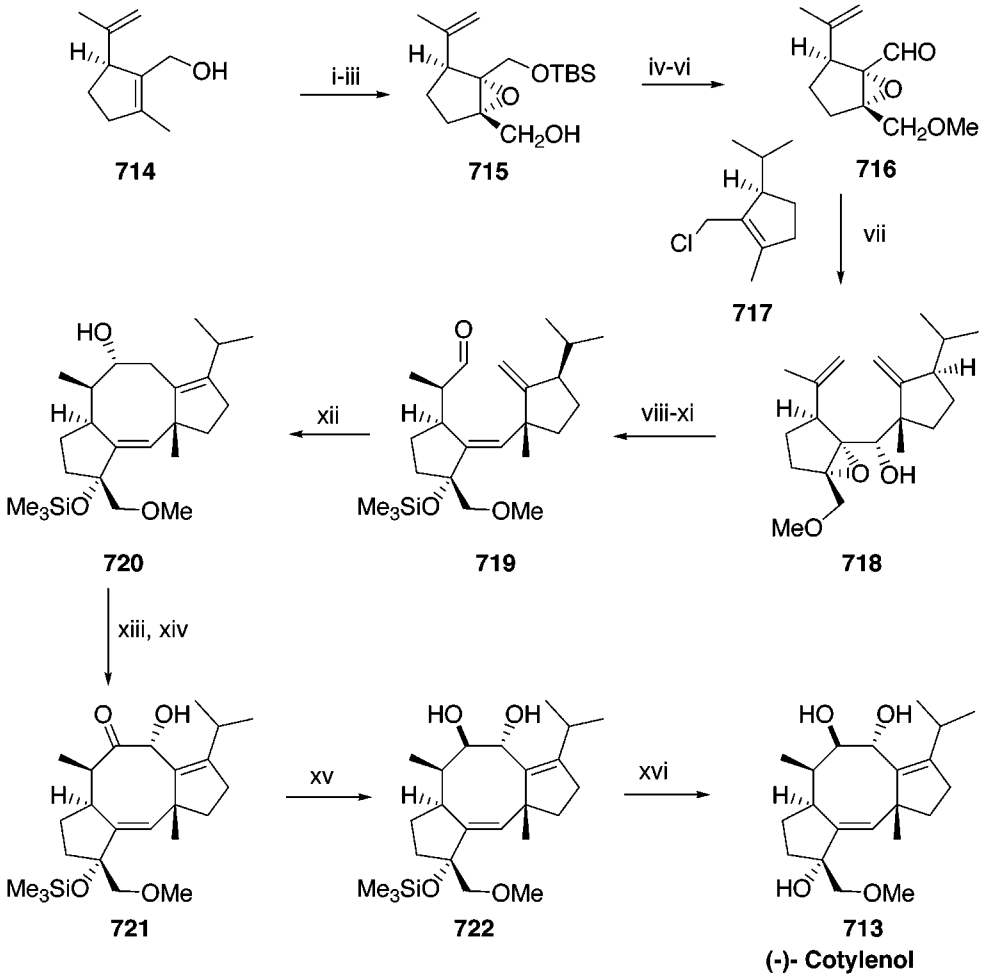
Recently, Paquette and co-workers have also achieved the synthesis of (+)-epoxydictymene **699** from the chiral aldehyde ester **704**.[289] The key precursor **706**, endowed with various structural/functional elements of the target, was readily obtained from **704** by reaction with **705** and subsequent lactonization. Tebbe's olefination of **706** to **707** and triisobutylaluminum catalyzed [3,3]-shift (with ensuing carbonyl reduction) and protection gave the tricyclic compound **708** efficiently and stereoselectively. Introduction of the angular methyl group and functional group manipulations led to alcohol **709**,

Scheme 148[a]



[a] Reagents: i (a) THF, (b) KOH, MeOH, HCl, 71%; ii Tebbe's reagent, Δ; iii (a) $(^iBu)_2AlH$, (b) MOMCl, $(^iPr)_2NEt$; iv (a) $BH_3{-}THF$, $LiBH_4$, H_2O_2, NaOH, (b) PCC, 49% for both steps, (c) LDA, MeI, 98%, (d) $LiAlH_4$, 100%; (v) (a) $COCl_2$, Py, (b) PhSeH, Py, (c) $(TMS)_3SiH$, AIBN, (d) HCl, MeOH, (e) PCC, 87% for five steps, (f) LDA, TMSCl, (g) DDQ, 90%, (h) Li, NH_3, (i) PCC, 90% for both steps; vi (a) LDA, TMSCl, (b) mCPBA, $NaHCO_3$, (c) K_2CO_3, MeOH, 72% for three steps; vii (a) MOMCl, $(^iPr)_2NEt$, (b) $LiAlH_4$, (c) Dess−Martin, 87% for three steps; viii (a) mCPBA, 85%, (b) $LiAlH_4$, 80%, (c) Dess−Martin, 86%; ix (a) $BH_3{-}THF$, H_2O_2, NaOH, 60%, (b) HCl, Ac_2O, Py, 89%; x $PhI(OAc)_2$, I_2, *hν*, (93% for a, 95% for b); xi HCl, MeOH, (*o*-NO_2)ArSeCN, Bu_3P, H_2O_2, (on b), 80%.

Scheme 149[a]



[a] Reagents: i (a) ^{t}BuOOH, VO(acac)$_2$, (b) Ac_2O, Py, (c) $LiAlH_4$, 86%; ii (a) (^{i}PrO)$_3$Al, (b) TBSCl/imidazole, 91%; iii (a) PCC, Celite, (b) $NaBH_4$, 8%; iv (a) NaH then MeI, (b) Bu_4NF, 86%; v (−)-diethyl tartrate, (^{i}PrO)$_4$Ti, ^{t}BuOOH, 88%; vi PDC, 75%; vii $CrCl_3$−$LiAlH_4$, 56%; viii (a) TMSCl, Py (b) 9-BBN, H_2O_2−NaOH, 78%; ix (a) Bu_4NF, TBSCl/imidazole, (c) MsCl/Py, 45%; x Ca, $FeCl_3$/liq. NH_3, 72%; xi (a) Bu_4NF, (b) TMSCl/Py, (c) PPTS, (d) PDC, 71%; xii Na_2CO_3, Δ, 90%; xiii PDC, 71%; xiv LiHMDS, MoOPH, 44%; xv $NaBH(OAc)_3$, 70%; xvi Bu_4NF, 100%.

which was then converted to ketone **710** after many steps. The ketone **710** was further transformed into hydroxy acetate **711** which was readily converted to tetracyclic ether **712**. Hydrolysis of the acetate and introduction of exocyclic double bond completed the synthesis, Scheme 148.

K. Cotylenol

Okamoto et al. reported the first total synthesis[290] of (−)-cotylenol **713**, a fungal metabolite[291] exhibiting a leaf growth activity. The synthetic route involves the carbonyl-ene reaction as the key step for the generation of the eight-membered ring. The precursor **719** was obtained from **718**, which itself was derived from the chiral olefinic alcohol **714** via **715** and **716**, Scheme 149. Thermal activation of **719** gave the tricyclic compound **720** stereoselectively. Oxidation of **720** followed by introduction of the hydroxyl group furnished the keto alcohol **721**. Subsequent reduction of **721** gave the *trans*-diol **722**, which was readily elaborated to (−)-cotylenol **713**, Scheme 149.

L. Tetramethyl Mediterraneol B

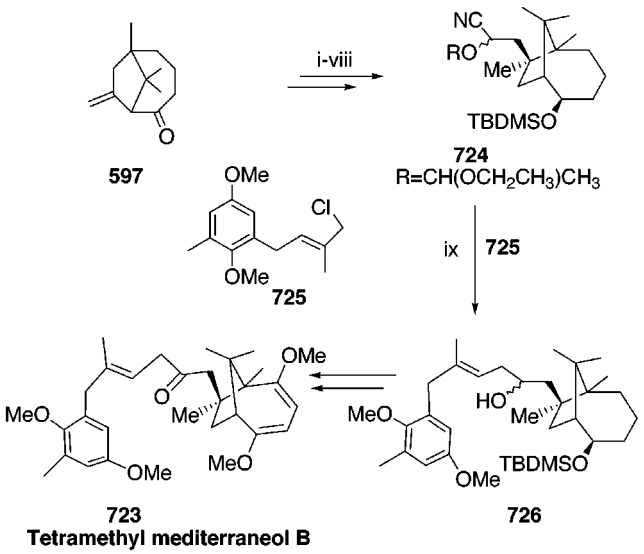
Synthesis of tetramethyl mediterraneol B **723**, a derivative of mediterraneol B isolated from the brown alga *Cystoseira mediterranea*,[292] was accomplished by Kakiuchi and co-workers.[250] The readily available enone **597** was transformed into **724** in many steps, which was further coupled with aromatic fragment **725** to furnish the intermediate **726**. The intermediate **726** was then taken to tetramethylmediterraneol **723**, Scheme 150.

M. Paclitaxel

The emergence of paclitaxel and related compounds as anticancer drugs is presumably one of the major factors that enhanced the interest in the chemistry of eight-membered rings. While enormous effort has been expended to this area,[293] only a few have reached the pinnacle. Syntheses of paclitaxel achieved so far are inevitably long and arduous besides being imaginative and ambitious, and each of the players has reported their travails in their own style. However, here we will be presenting these efforts in an abridged form with emphasis on the cyclooctane-forming step.

The first synthesis of paclitaxel **6** due to Holton et al.[294] employs fragmentation in a bicyclic epoxy alcohol to generate the ring B as a key transformation, and this step constitutes the cornerstone of his

Scheme 150[a]



[a] Reagents: i $LiAlH_4$, 86%; ii TBDMSCl, 99%; iii O_3, PPh_3, 65%; iv (a) LDA, HMPA, MeI, 63%, (b) LDA, HMPA, CH_2=CH−CH_2I, 20%; v (a) DIBALH, (b) NaI, CS_2, MeI, (c) TBTH, 72%; vi OsO_4, NMO, 90%; vii $NaIO_4$; viii (a) TMSCN, (b) NH_4F, (c) CH_2=$CHOCH_2CH_3$, PPTS, 88% (for vii and viii); ix (a) LDA, HMPA and **725**, (b) HCl, (c) NaOH, (d) $NaBH_4$, 86%.

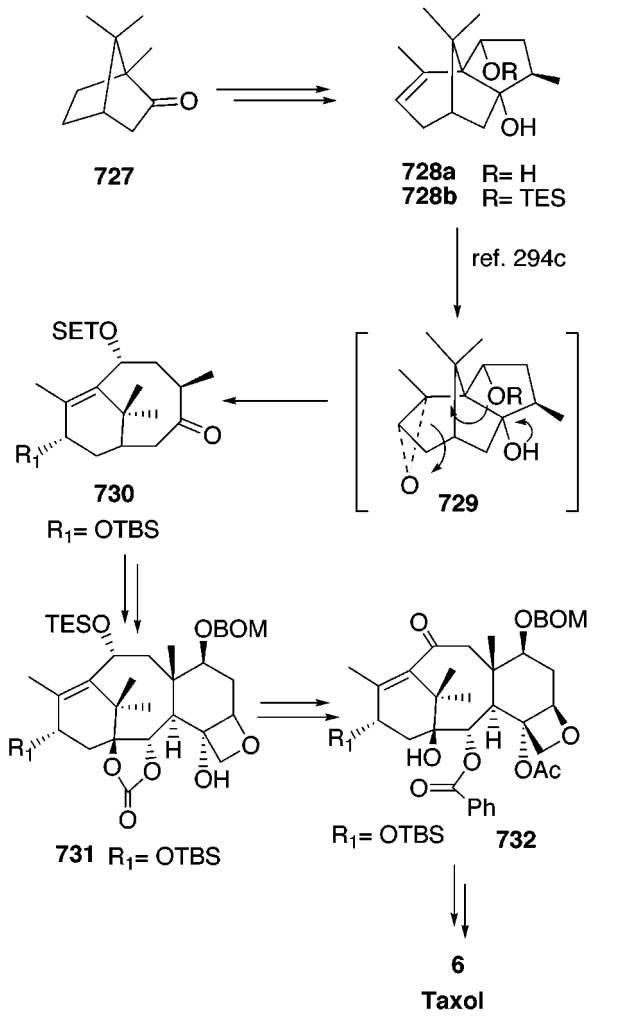
synthesis. The intermediate tricyclic diol **728a**, which is available from camphor **727** in both of the enantiomeric forms, was silylated to **728b** and, on epoxidation of the double bond, led to **729**. Subsequent fragmentation furnished the ketone **730** having AB rings, which was elaborated to paclitaxel in a sequence involving **731** and **732** as highly evolved intermediates, Scheme 151.

Nicolaou's synthesis[295] of paclitaxel employed an AC ring precursor and the B ring was formed through McMurry coupling. In a highly convergent approach, the key precursor **735** was obtained through the addition of vinyl anion generated from **733** to the highly substituted aldehyde **734**. Most of the desired functional and stereochemical attributes were predetermined in the building blocks **733** and **734**. The precursor **735** was elaborated to dialdehyde **736** to set up the McMurry coupling. Exposure of **736** to a low valent titanium reagent gave the tricyclic compound **737** having the ABC rings and was further taken to the natural product paclitaxel, Scheme 152.

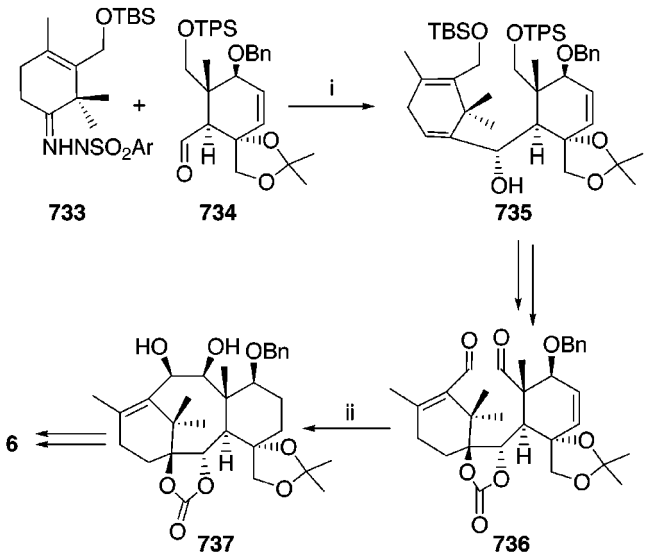
Danishefsky's route[185] to paclitaxel employed Heck-type coupling to generate the B ring. Thus, the highly advanced precursor **423**, upon treatment with Pd-$(PPh_3)_4$, furnished the intermediate **424** (vide supra), which was elaborated to paclitaxel, Scheme 153. The precursor **423** was obtained by the reaction of iododiene **738** with ketoacetal **739** having rings CD of paclitaxel. The synthesis is convergent and notable for stereocontrol.

Wender's elegant α-pinene based pathway[296] to paclitaxel relied mainly on a novel epoxide mediated fragmentation to create the B ring. Thus, the tricyclic precursor **742** was synthesized from verbenone **741** and transformed into epoxy alcohol **743**, which underwent fragmentation upon exposure to DABCO to furnish the AB ring segment **744**. Annulation of

Scheme 151



Scheme 152[a]

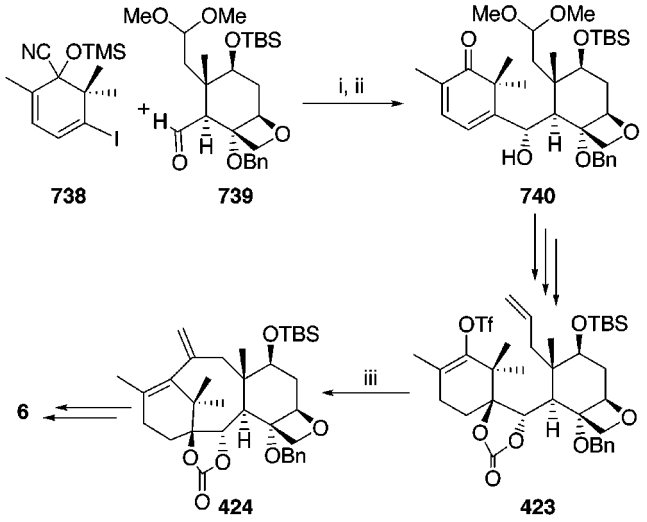


[a] Reagents: i BuLi, 82%; ii $TiCl_3$−DME, Zn−Cu, DME, 23%.

the C and D rings on **744** furnished the tetracyclic precursor **745** which was elaborated to paclitaxel, Scheme 154.

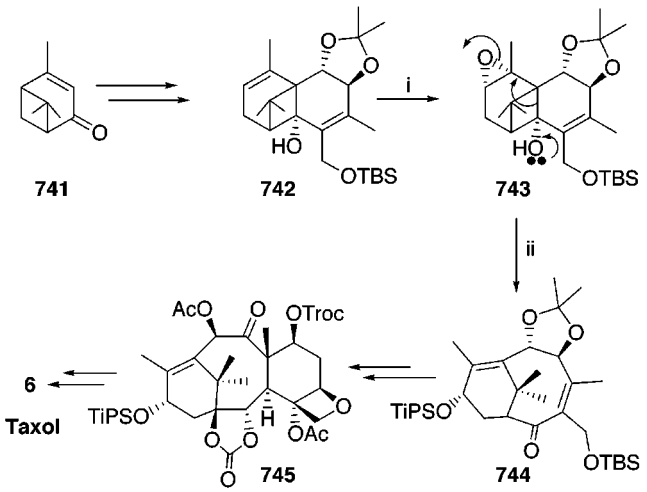
Recently, Mukaiyama and co-workers have also achieved a total synthesis of paclitaxel in which samarium iodide mediated coupling in the acyclic

Scheme 153[a]



[a] Reagents: i ^{t}BuLi; ii TBAF, 80% for both steps; iii $Pd(PPh_3)_4$, K_2CO_3, 49%.

Scheme 154[a]



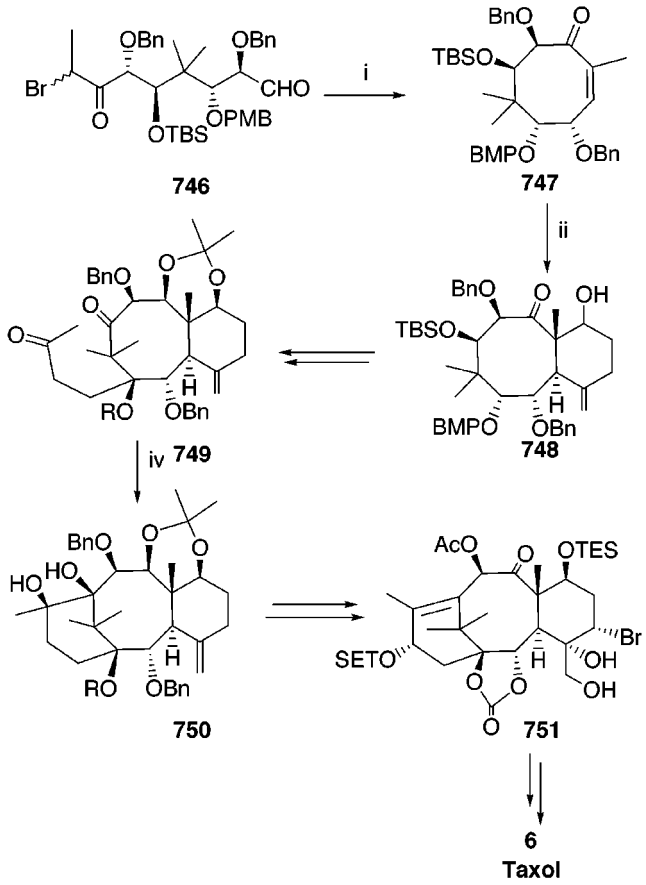
[a] Reagents: i mCPBA, Na_2CO_3; ii (a) DABCO, (b) TIPSOTf, lutidine, 85%.

precursor **746** generated the functionally embellished B ring intermediate **747**. Rings C (**747** → **748**) and A (**748** → **749** → **750**) were than added sequentially following a judicious mix of Michael addition−aldol cyclization and alkylation−reductive coupling steps. Further functional group manipulation led to **751**, which was well set for the generation of ring D following the previously developed protocols, Scheme 155. [297]

N. Dibenzocyclooctane Lignans

From the beginning, dibenzocyclooctadiene lignans had aroused interest on account of their interesting biological activity.[298] Synthesis of many members such as schizandrin[299,300a] and isoschizandrin,[300a] deoxyschizandrin and wuweizsu[301c] has been reported earlier. Meyers and co-workers[300a] have achieved the synthesis of (−)-schizandrin (unnatural isomer) **752** and (−)-isoschizandrin **753** and have revised the structure of the latter. (+)-schizandrin **752** and (−)-isoschizandrin **753** were isolated from the fruits of *Schizandra chinesis* Baill.[298b−d] Their approach em-

Scheme 155[a]



[a] Reagents: i (a) SmI_2, 70%, (b) Ac_2O, DMAP−Py, 85%, (c) DBU, 91%; ii (a) CH_2=C(Br)$CH_2CH_2CH_2$OTES, ^{t}BuLi, CuCN, 92%, (b) TPAP, NMO, 92%, (c) NaOMe, 90%; iii $TiCl_2$−LAH, 43−71%.

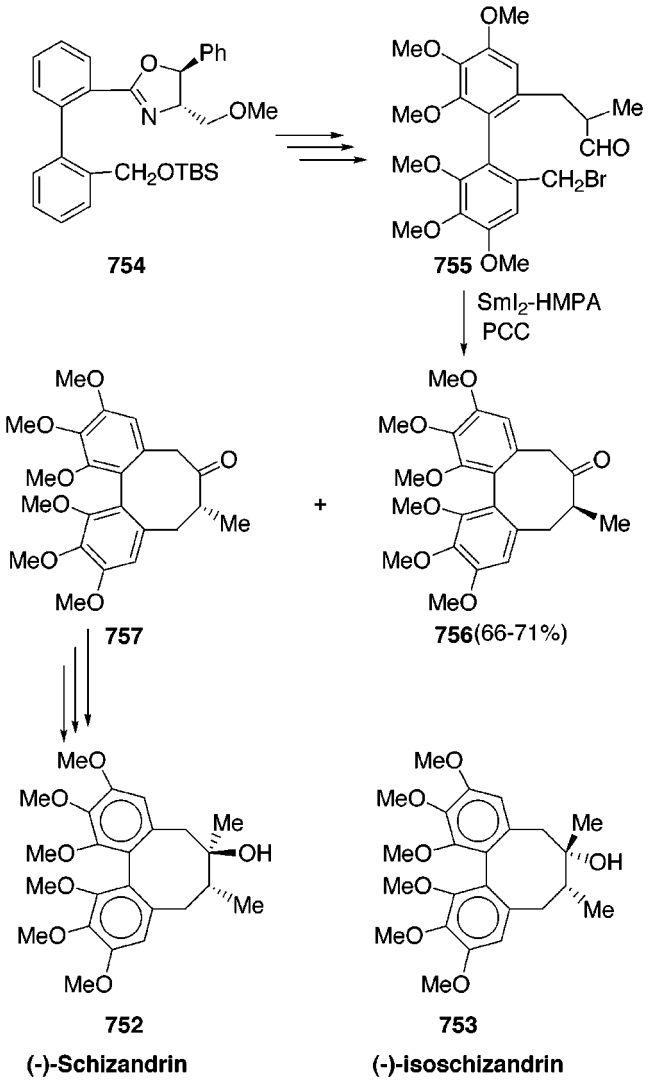
ployed the chiral biphenyl derivative **755**, available from chiral oxazoline **754** through their own chiral oxazoline methodology,[300c] and used samarium iodide mediated intramolecular coupling for the synthesis of cyclooctane ring, unlike other methods which generally use oxidative coupling of phenols. Thus, the treatment of **755** with SmI_2 followed by oxidation gave two stereoisomers of dibenzocyclooctanone **756** and **757** which were separated. The isomer **757** was elaborated to (−)-schizandrin **752** and (−)-isoschizandrin **753**, Scheme 156.[300a]

Wakamatsu et al. reported[302] the synthesis of (+)-schizandrin **752** and (+)-gomisin A **758** from chiral half ester **759**. Transformation of **759** to lactone **760** and the oxidative coupling of the latter furnished cyclooctanoidal lactone **761**. The lactone **761** was then elaborated to both (+)-schizandrin and (+)-gomisin A, Scheme 157. Recently, the same group has reported synthesis of many other related lignans.[303]

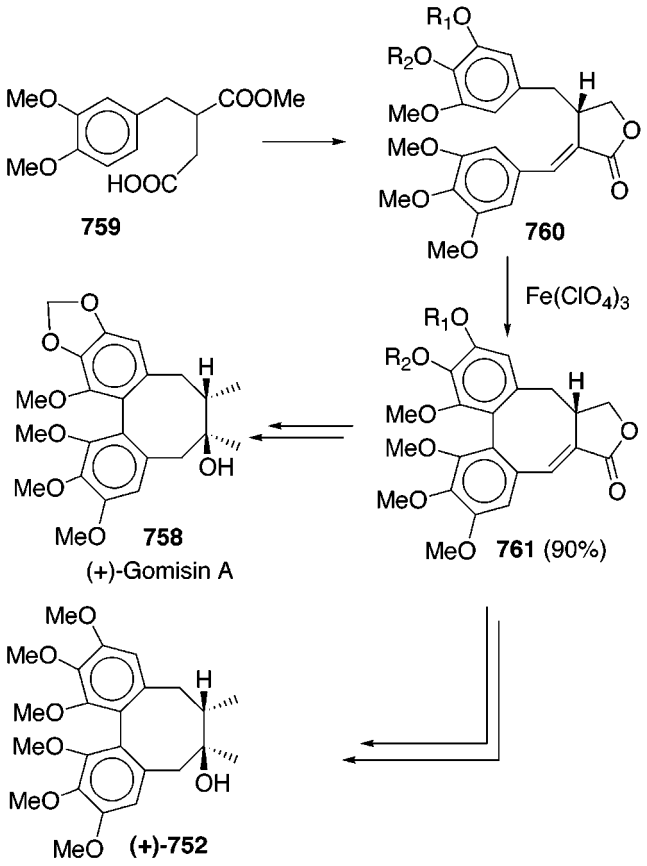
V. Concluding Remarks

The accomplishments enumerated above clearly demonstrate that there has been a renaissance in the synthetic developments directed toward cyclooctanoid systems, and remarkable progress has been registered, particularly since the onset of the 1990s. The notion that cyclooctane rings are recalcitrant and elusive, difficult to construct through classical chemi-

Scheme 156



Scheme 157



cal reactions, and not readily amenable to management of functionality and stereochemical controls, has now become untenable as an array of new synthetic strategies have come to fore that specifically address the problems of cyclooctanoid- and other medium-ring construction. Indeed, recent emergence of synthetic methodologies, such as, ring closure metathesis (RCM), radical cyclizations, higher order inter- and intramolecular cyclizations, intramolecular Pauson−Khand reaction, various fragmentation processes, and [3,3]-sigmatropic rearrangements, to name a few, and the discovery of new reagents, e.g., SmI_2, $Mn(OAc)_3$, and Ti(0), have enabled ready and efficacious applications in the synthesis of cyclooctanoids. Many total syntheses of complex cyclooctanoid natural products, including paclitaxel, have been achieved as a culmination of these methodological developments. There is no gainsaying the fact that, in the resurgence of interest in cyclooctanoid syntheses, diterpene paclitaxel had a major influence.

The surfacing of new, complicated, and architecturally enchanting cyclooctane-bearing frameworks from Nature, particularly from microbial and other exotic sources, and with the biologically powerful anticancer drug paclitaxel continuing to occupy center stage as a prized target, interest in the cyclooctanoid synthesis remains unabated. Many of the strategies toward cyclooctanoids have been developed in the context of a specific target, but their generality, operational simplicity, and regio- and stereocontrol elements still remain to be fully delineated. This aspect will continue to be a sustained challenge to practicing synthetic chemists.

VI. Acknowledgments

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