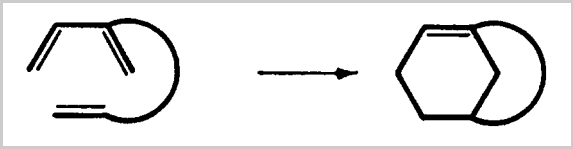
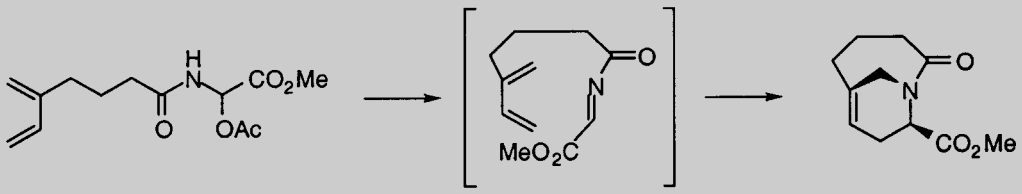
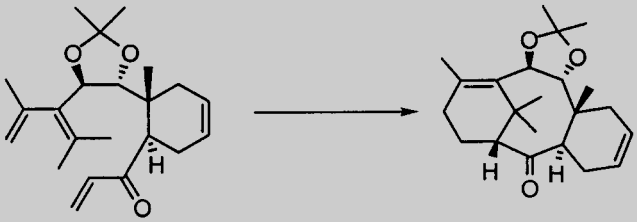
# The Type 2 Intramolecular Diels–Alder Reaction

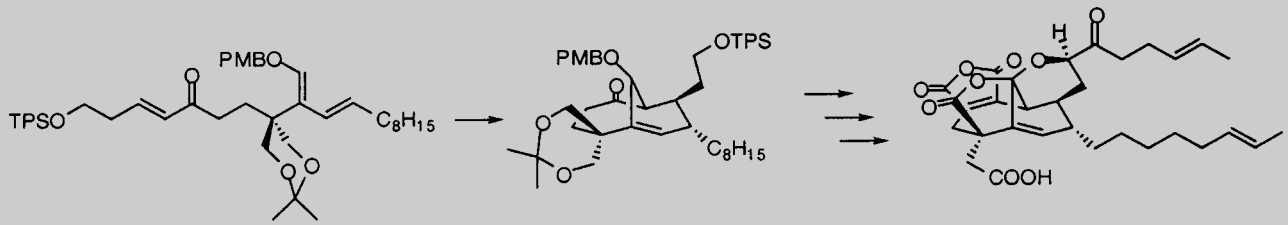


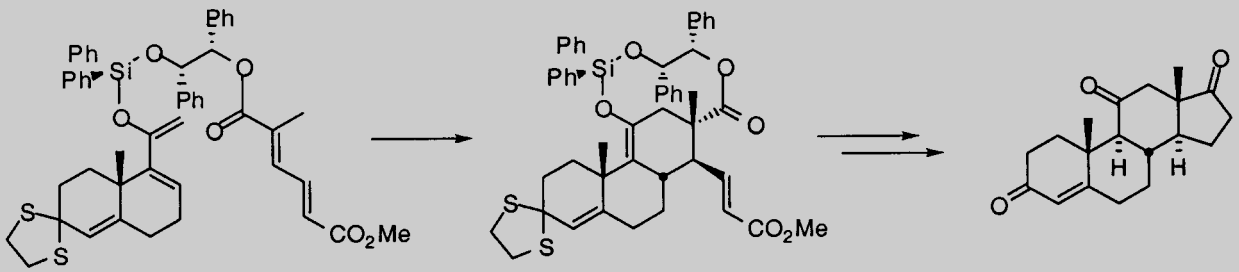
## a Versatile Synthetic Tool

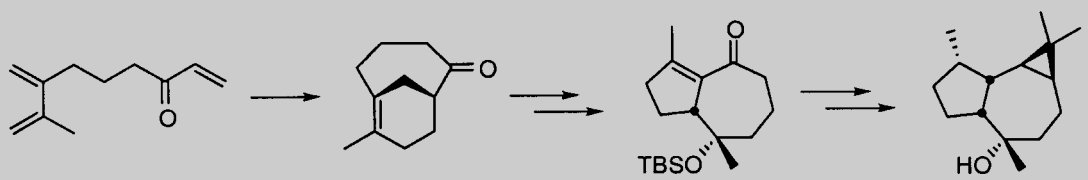




# The Type 2 Intramolecular Diels–Alder Reaction: Synthesis and Chemistry of Bridgehead Alkenes

**Brian R. Bear, Steven M. Sparks, and Kenneth J. Shea***

Anti-Bredt alkenes, bicyclic molecules that contain a bridgehead double bond, were for many years regarded as chemical curiosities. The type 2 intramolecular Diels–Alder (IMDA) reaction provides a one-step entry into this fascinating class of molecules. The reaction has made available numerous anti-Bredt alkenes for structural and chemical studies. X-ray crystallography has revealed the magnitude of the deformations associated with the bridgehead double bond, and rate studies of reactions of bridgehead alkenes have allowed quantification of the kinetic consequences of the torsional distortions. More recently, the type 2 intramolecular Diels–Alder reaction and the resulting anti-Bredt alkenes have found application in organic synthesis. The constraints resulting from the connectivity in the Diels–Alder precursor creates a strong regio- and stereochemical bias in the cycloaddition step. The end result of this bias is the stereoselective synthesis of highly substituted six-membered rings. The reaction also achieves a facile synthesis of seven- and eight-membered rings in a single step from acyclic precursors. The utility of this reaction has been verified in recent applications of the type 2 IMDA reaction as a key step in the total synthesis of complex natural products.

**Keywords:** bridgehead alkenes · natural products · strained molecules · synthetic methods

## 1. Introduction

There are two types of connectivity available to the intramolecular variant of the Diels–Alder reaction. When diene and dienophile are joined at position 1 of the diene (type 1), cycloaddition usually gives rise to a fused bicyclic adduct [Eq. (1)]. This reaction has assumed considerable

(1)

importance in contemporary organic synthesis.[1] A second variant involves union of diene and dienophile at position 2 of the diene (type 2). Cycloaddition in this case results in formation of a bridged bicyclic ring system [Eq. (2)]. The reaction has substantial synthetic potential since there are few methods that yield a bridged bicyclic structure in a single step

(2)

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from an acyclic precursor. The product of the type 2 intramolecular Diels–Alder (type 2 IMDA) cycloaddition contains a bridgehead double bond, it is an anti-Bredt alkene. Thus, the reaction provides a direct entry into this interesting class of molecules.[2]

We describe herein events leading to the discovery of the type 2 IMDA cycloaddition, as well as a summary of the scope of the reaction and an evaluation of its synthetic utility. The reaction has been used for synthesis of both strained and unstrained bridgehead alkenes. The availability of bridgehead alkenes has provided opportunities to study both their structure and reactivity. As the extent of the reaction unfolded, type 2 intramolecularity has found increasing importance in synthetic methodology as a general strategy for controlling both stereochemistry and regiochemistry of the Diels–Alder reaction. More recently, there has been a growing number of applications of this reaction in the synthesis of natural products. A survey of these applications is included in the final section of the review.

## 2. Background

The first report of a type 2 IMDA cycloaddition appeared in 1978.[3] The reaction was discovered serendipitously during a mechanistic study of the Cope rearrangement.[4, 5] The [3,3]

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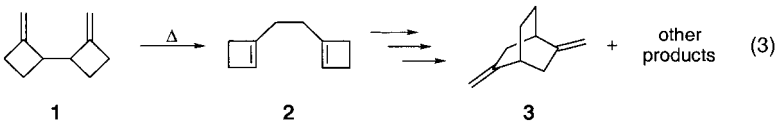
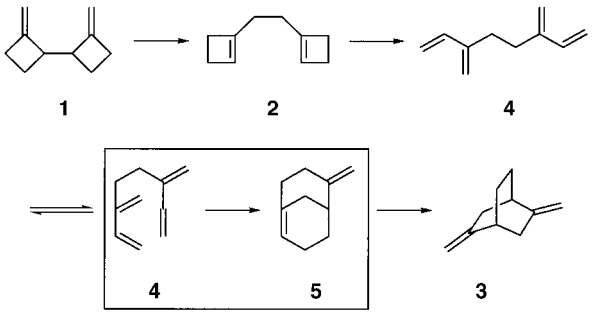
sigmatropic rearrangement of the *d,l*- and *meso*-bismethylene cycloalkanes was investigated as a method to independently probe the chair and boat transition states of the Cope rearrangement. As part of the study, the thermolysis of bis(methylenecyclobutane) **1** was undertaken [Eq. (3)]. The




reaction was unexpectedly complex, ultimately leading to no less than seven isomeric products. The anticipated Cope product **2** was not detected from the thermolysis of **1** at high temperatures (flow pyrolysis, $T \geq 300\,^{\circ}C$, 10 s). From this complex reaction mixture, one of the more interesting compounds was 2,5-bismethylenebicyclo[2.2.2]octane (**3**).

The connectivity of **3** presented the investigators with a mechanistic conundrum. Following its independent synthesis to verify the proposed structure, a tentative explanation was forwarded. The proposal involved the cascade of reactions outlined in Scheme 1. Bis(methylenecyclobutane) (**1**) was thought to undergo an initial [3.3] sigmatropic rearrangement to produce **2**. At high temperatures ($\geq 300\,^{\circ}C$) sequential electrocyclic ring opening of both cyclobutenes followed to afford intermediate tetraene **4**.[6] At this point, the connectivity in the final product **3** strongly implied a two-step sequence initiated by an intramolecular Diels–Alder reaction (type 2!) which would give rise to the highly strained anti-Bredt alkene **5**. A *formal* [3,3] sigmatropic rearrangement remained to complete the transformation to **3**, a local thermodynamic sink. What was troubling at the time was the seemingly improbable and unprecedented Diels–Alder step in this cascade of reactions. Notwithstanding, careful reexamination of the thermolysis reaction mixture provided support for the proposal. Guided initially by olfactory clues,[7] small quantities of bridgehead alkene **5** were isolated from reaction mixtures by preparative GC. Despite limited quantities of this reactive molecule, it was possible to acquire adequate spectroscopic data for characterization. It was also established that when the reactive bridgehead alkene **5** was subjected to the gas-phase




Scheme 1. Proposed reaction cascade leading to **3**.

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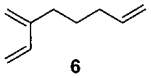
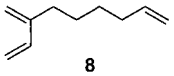
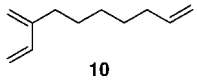
*Steven M. Sparks was born in 1972 and grew up in Stockbridge, Massachusetts. He received his BS degree from Rensselaer Polytechnic Institute in 1995, during which he completed a research internship at Burroughs Wellcome in the division of Organic Chemistry. Following a year as a research technician at Albany Molecular Research, he began graduate studies at the University of California, Irvine under the direction of Professor Kenneth J. Shea. His research interests include development of hetero type 2 Diels–Alder methodology and natural product synthesis.*

*Kenneth J. Shea was born in Queens, New York. He received his B.S. and M.S. degrees in Chemistry from the University of Toledo. He did his graduate studies in physical organic chemistry at Pennsylvania State University. Following postdoctoral studies at the California Institute of Technology, he joined the faculty of the University of California at Irvine in 1974. His research interests are in synthetic and mechanistic organic chemistry and polymer and materials chemistry.*

thermolysis conditions it underwent rearrangement to **3**. The isolation and characterization of strained bridgehead alkene **5** provided the first evidence that type 2 connectivity was compatible with the Diels–Alder cycloaddition despite the fact that the product of the reaction was a strained anti-Bredt alkene. These findings not only resolved a mechanistic puzzle, but presented an opportunity to consider the generality of the reaction.

The first step in this evaluation involved an investigation of the thermal behavior of a series of acyclic trienes (Table 1).[3] These homologous trienes were found to undergo type 2 IMDA reaction under conditions similar to those used for the thermolysis of **1** (400–500 °C, gas phase, atmospheric pressure, ca. 10–15 s contact time). The products of the reaction, the corresponding carbocyclic bridgehead alkenes, were produced as single regioisomers. Of special note was the formation of the prototypical anti-Bredt alkene, bicyclo[3.3.1]nonene (**7**), a molecule first prepared in 1967 by Marshall and Faubl[8] as well as Wiseman[9] by elimination of the corresponding bridgehead-substituted bicyclic precursor. Interestingly, under the high temperatures of the thermolysis conditions, triene **6** and bicyclo[3.3.1]nonene (**7**) exist in equilibrium (30:70 at 350 °C). The cycloadducts in Table 1 include products that contain seven- and eight-membered rings, a feature of this reaction that was later found to have considerable synthetic importance.

Table 1. Type 2 IMDA cycloadditions of acyclic trienes.

| Starting material | Conditions | Product | Conversion [%] |
|---|---|---|---|
|  **6** | 420 °C, 23 s |  **7** | 32 |
|  **8** | 455 °C, 5 s |  **9** | 55 |
|  **10** | 510 °C, 8 s |  **11** | 29 |

In the examples in Table 1, high temperatures were necessary to achieve cycloaddition. The high activation energy arises in part from the unactivated dienophiles in the Diels–Alder precursors and the strain in the bridgehead alkene product.[10] Despite these high temperatures, atmospheric pressure flow thermolysis is amenable to large-scale preparation of simple bridgehead alkenes. The products can be separated by distillation to afford pure cycloadduct. These initial findings established that type 2 connectivity can be used for the synthesis of bridgehead alkenes.

Bridgehead alkenes incorporate a *trans*-cycloalkene substructure. The cycloadducts from the type 2 IMDA reaction possess the bicyclo[*n*.3.1] skeleton. The strain associated with the bridgehead double bond is related to the size of the variable (*n*) bridge. For $n = 3$, that is bicyclo[3.3.1] nonene (**7**), the molecule contains a *trans*-cyclooctene ring and is the smallest, isolatable bridgehead alkene.[2] The bridgehead double bond has been found to be $10^6$ times more reactive towards electrophiles than a simple unstrained trisubstituted double bond. The strain and reactivity fall off rapidly as *n* increases to 4 (*trans*-cyclononene) or 5 (*trans*-cyclodecene). Bridgehead alkenes incorporating the *trans*-cyclononene have been found to be $10^3$ times more reactive towards electrophiles than unstrained alkenes, while bicyclo[5.3.1]undecene derivatives are unstrained and exhibit similar reactivity to their nonbridged counterparts.

## 3. Development of the Scope of the Reaction

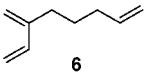
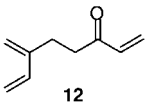
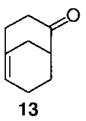
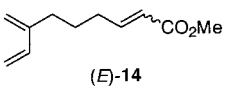
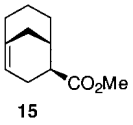
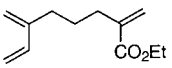
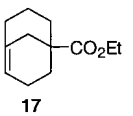
### 3.1. Synthesis of Substituted Derivatives of Bridgehead Alkenes

#### *3.1.1. Activated Dienophiles*

The introduction of activating substituents on the dienophile was found to moderate the conditions necessary for cycloaddition and importantly, provide synthetic entries into substituted derivatives of bridgehead alkenes.[4, 11]

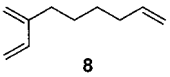
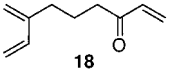
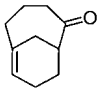
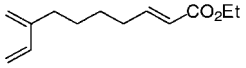
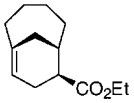
The cycloaddition of three- and four-atom bridged trienes (see Tables 2 and 3, respectively) reveal the influence of substituents on the reaction rate. In all cases, the reaction conditions were milder than those for the unactivated precursors. Enhanced activity was noted for activating groups both endocyclic and exocyclic to the tether joining diene and

Table 2. Gas-phase thermolysis of three-atom-bridged triene esters and ketones.

| Starting material | Conditions[a] | Product | Yield [%][b] |
|---|---|---|---|
|  **6** | 420 °C, 23 s |  **7** | 32 |
|  **12** | 395 °C, 18 s |  **13** | 72 |
|  (*E*)-**14** | 318 °C, 18 s |  **15** | 76 |
| (*Z*)-**14** | 365 °C, 12 s | **15**[c] | |
|  **16** | 390 °C, 12 s |  **17** | 30 |

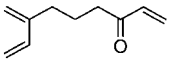
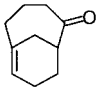
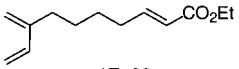
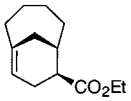
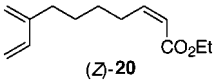
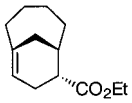
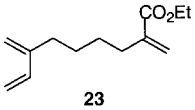
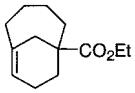
[a] Atmospheric pressure, $N_2$ carrier gas; thermolysis temperature and contact time are given. [b] Determined by GC, percentages based upon starting material remaining after thermolysis. [c] The *Z* isomer underwent isomerization to the *E* isomer under the thermolysis conditions. The cycloaddition product was identical with that obtained from (*E*)-**14**.

Table 3. Gas-phase thermolysis of four-atom-bridged triene esters and ketones.

| Starting material | Conditions[a] | Product | Conversion [%][b] |
|---|---|---|---|
|  **8** | 455 °C, 8 s |  **9** | 55 |
|  **18** | 398 °C, 8 s |  **19** | 85 |
|  (*E*)-**20** | 420 °C, 8 s |  **21** | 80 |

[a, b] See Table 2.

Table 4. Solution-phase thermolysis of triene esters and ketones.

| Starting material | Conditions[a] | Product | Yield [%][b] |
|---|---|---|---|
|  **18** | 201 °C, 15 min |  **19** | 57 |
|  (*E*)-**20** | 206 °C, 2 h |  **21** | 80[c] (91) |
|  (*Z*)-**20** | 232 °C, 4 h |  **22** | 65 |
|  **23** | 232 °C, 4 h |  **24** | 63 |

[a] Reactions were run in dilute (0.04 – 0.09 M) xylene solution. [b] Yields are calculated by GC referenced to an internal standard. [c] Yield of isolated product.

dienophile. This later point is interesting since inspection of models of the transition state of the reaction of **12** reveals that it is not possible to achieve coplanarity of the carbonyl and alkene fragments of the dienophile.

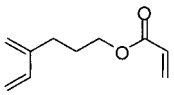
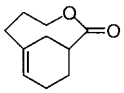
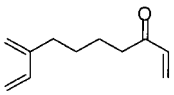
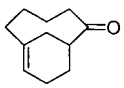
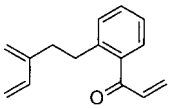
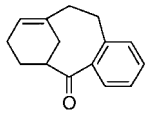
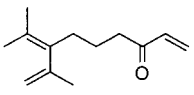
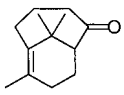
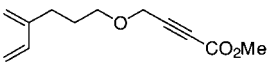
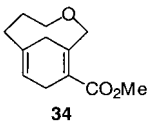
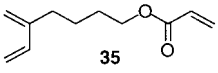
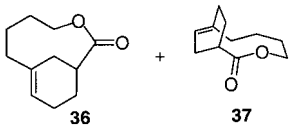
Subsequent investigations revealed that many of the cycloadditions could also be run in solution. Table 4 summarizes some of the first examples of these reactions. Cycloadditions are typically run in aromatic solvents in sealed tubes. Reaction temperatures ranged from 170 to 250 °C.

The preceding cycloadditions provide a one-step route to functionalized bridgehead alkenes from an acyclic precursor. In most cases the configuration of the dienophile is retained. The stereospecific formation of *endo*- and *exo*-bicyclic derivatives from the corresponding *cis*- and *trans*-alkenes, respectively, is consistent with a *concerted* cycloaddition (Table 4).

### 3.1.2. Lewis Acid Catalysis

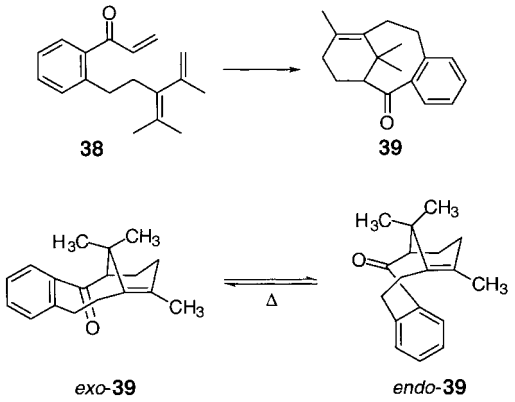
Despite the high yields of the reactions given in Section 3.1.1, high temperatures were necessary to achieve cycloaddition. A later report described that many of the type 2 IMDA cycloadditions are amenable to Lewis acid catalysis. As with many reactions, the choice of catalyst is, in part at least, empirical. Table 5 summarizes the results of a study that uses diethylaluminum chloride for inducing the cycloaddition. These mild conditions (low temperatures) and short reaction times are compatible with construction of more highly functionalized bridged bicyclic structures, further extending the synthetic utility of the reaction.[12]

Table 5. Lewis acid catalyzed type 2 IMDA reactions.

| Starting triene | Conditions[a] | Product | Yield [%] |
|---|---|---|---|
|  **25** | 4 h, 21 °C |  **26** | 50 |
|  **27** | 2 h, 21 °C |  **28** | 75 |
|  **29** | 1 h, 21 °C |  **30** | 71 |
|  **31** | < 5 min, 21 °C |  **32** | 70 |
|  **33** | 12 h, 21 °C |  **34** | 85 |
|  **35** | 1 h, 21 °C |  **36** + **37** | 90 (**36**:**37** = 4:1) |

[a] In $CH_2Cl_2$ with $Et_2AlCl$ as Lewis acid; thermolysis temperature and reaction time are given.

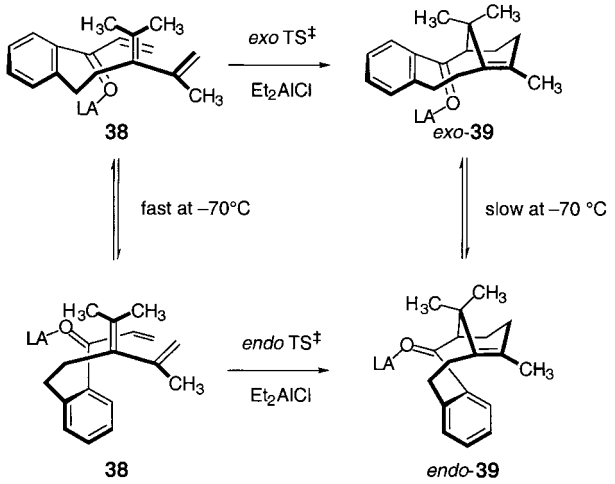
Lewis acid catalysis provided a unique opportunity to quantify the relative energies of two transition state conformers of the type 2 IMDA reaction of triene **38** (Scheme 2).[13] Cycloadduct **39** exists as two conformers, *exo*-




Scheme 2. Cycloaddition of triene **38**.

**39** and *endo*-**39**. The two conformational isomers are separated by an activation energy barrier of 16.5 kcal mol$^{-1}$. Under conditions of the thermal cycloaddition (155 °C, 93 h), the two conformers are rapidly equilibrated. At 25 °C, *endo*-**39** is the dominant conformational isomer (*endo*-**39**/*exo*-**39** = 89/11, $\Delta\Delta G^\circ = 1.24 \pm 0.15$ kcal mol$^{-1}$).

Alternatively, the reaction can be catalyzed by $Et_2AlCl$. At −70 °C, interconversion of the *endo* and *exo* conformational isomers of **38** is fast (Scheme 3). Interconversion of conforma-




Scheme 3. Competing reactions in the Lewis acid catalyzed cycloaddition of **38**.

tional isomers of **39**, however, is slow. Under Lewis acid catalysis the ratio *endo*-**39**/*exo*-**39** represents the kinetically controlled rate of product formation, $k_{endo}/k_{exo} = 70$ (−70 °C), from which the difference in free energy of activation for the two competing reactions was calculated ($\Delta\Delta G^{\pm}_{-70\,^\circ C} = 1.70 \pm 0.02$ kcal mol$^{-1}$). The energy difference between the two transition states was very similar to, but slightly larger than, the ground state energy difference between the two conformations of the product. The authors conclude that the relative stability of the conformational isomers of the product are amplified slightly in the transition state leading to them.

Since these initial investigations, Lewis acid catalyzed type 2 IMDA reactions have proven to be extremely valuable for inducing the reaction of complex Diels–Alder precursors.

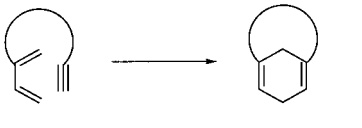
### *3.1.3. Acetylenic and Allenic Dienophiles—Synthesis of Bridgehead Dienes*

Alkyne and allene dienophiles provide a greater thermodynamic driving force for the Diels–Alder cycloaddition (Table 6). In the type 2 intramolecular variant, this consid-

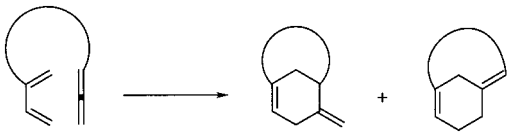
Table 6. Thermodynamic values for bimolecular Diels–Alder cycloadditions.[15]

| Reaction Components | Cycloadduct | $\Delta H^\circ$ [kcal mol$^{-1}$] | $\Delta S^\circ$ [cal K mol$^{-1}$] |
|---|---|---|---|
|  |  | −40.5 | −44.8 |
|  |  | −52.4 | −42.6 |
|  |  | −50.0 | −42.0 |

eration must be balanced by the greater strain energy in the cycloadduct. Cycloaddition in either case results in formation of bridgehead dienes, molecules that contain two nonconjugated bridgehead double bonds that are held in close proximity [Eq. (4) and (5)].[14]



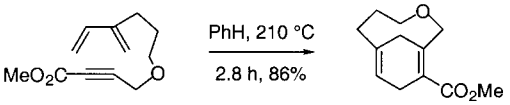
(4)



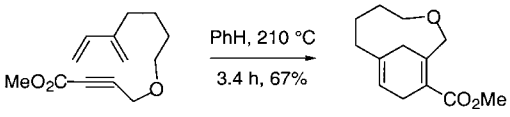
(5)

#### *3.1.3.1. Acetylenic Dienophiles*

The first examples employing acetylenic dienophiles are shown in Equations (6) and (7). The cycloaddition of dienyne esters **33** and **40** affords high yields of bridgehead diene



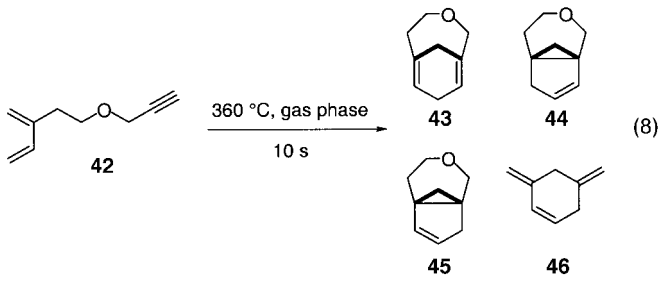

(6)




(7)

cycloadducts **34** and **41**.[16] The reactions proceed in good yield to produce stable bridgehead diene esters. Solid derivatives, suitable for X-ray structure analysis, provided structural data for the two bridgehead double bonds.[17]

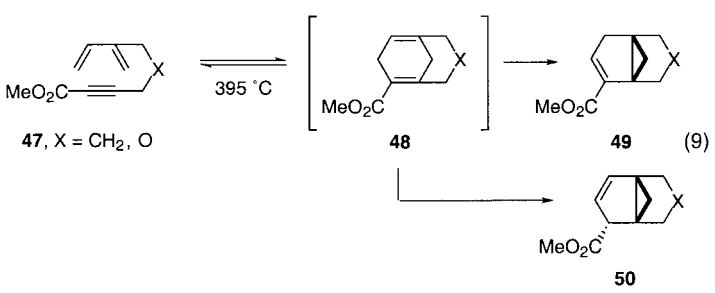
The enthalpy change for a Diels–Alder cycloaddition of butadiene and acetylene is approximately $\Delta H \approx -52$ kcal mol$^{-1}$ (see Table 6). This exothermicity can provide the thermodynamic driving force for the formation of very highly strained organic molecules. The current limit of an isolable molecule of this type is cycloadduct **43**, a highly reactive bridgehead diene formed by cycloaddition of dienyne **42** [Eq. (8)].[18] Diene **43** has a half-life of several hours at 0 °C



(8)

in dilute benzene solution. It is a derivative of *trans, trans*-1,4-cyclononadiene and contains two highly distorted bridgehead double bonds. The smaller, more highly strained bridgehead dienes will, at elevated temperatures, undergo reactions that alleviate the source of strain. For example, bridgehead diene **43** was found to undergo a homodienyl 1,5-hydrogen shift under the reaction conditions resulting in formation of propellanes **44** and **45**. Interestingly, the usual homo-1,5-hydrogen shift is in the direction of cyclopropane ring cleavage. In the above example, hydrogen transfer results in formation of a cyclopropane ring with concomitant loss of both bridgehead double bonds. Triene **46** was found to arise from both a 10-electron pericyclic reaction from bridgehead diene **43** and also a cleavage reaction of the cyclopropyl bond and extrusion of formaldehyde from the propellanes **44** and **45**.

Another striking illustration is found in Equation (9). Cycloaddition of dienyne **47** results in formation of bridgehead diene **48**, a molecule containing a *trans,trans*-1,4-cyclo-

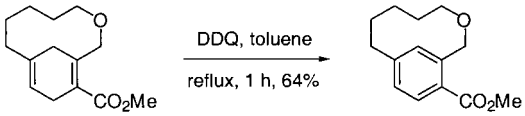


(9)

octadiene ring.[19] The cycloadduct does not accumulate under the reaction conditions, rather it undergoes a homo-1,5-hydrogen shift to produce an isomeric pair of [3.3.1]propellanes, **49** and **50**. A single isomeric ester **50** (*endo*) is consistent with exclusive migration of the C-3 *exo* hydrogen atom. Estimates of the strain energy in **48** range from 35–45 kcal mol$^{-1}$,[20, 21] thus, the bulk of the reaction exothermicity has been stored as strain energy in the cycloadduct. Although pericyclic reactions are not usually employed for the synthesis of strained molecules, the preceding examples reveal that the strong exothermicity can provide new strategies for the synthesis of strained anti-Bredt alkenes.

2,4-Bridged-1,4-cyclohexadienes that are spanned by larger rings exhibit thermal chemistry more characteristic of 1,4-cyclohexadienes. For example, extrusion of hydrogen to produce metacyclophanes [Eq. (10) and (11)] are representative examples.[22]

(10)

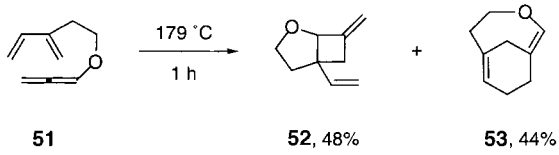


(11)

*3.1.3.2. Allene Dienophiles*

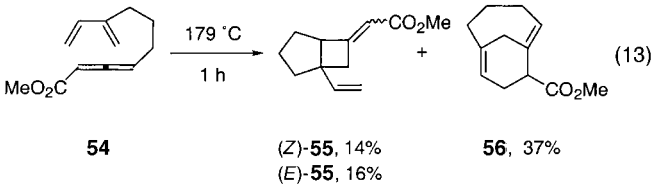
The reaction of butadiene with allene is calculated to be strongly exothermic, only slightly less exothermic than that with acetylene (Table 6). Type 2 IMDA reactions with allene dienophiles can undergo two modes of cycloaddition. In the first mode, reaction with the distal double bond gives rise to a bridged bicyclic skeleton containing two nonconjugated bridgehead double bonds constrained in a criss-cross arrangement [see Eq. (5)]. In the second mode, reaction of the proximal double bond gives rise to a bridgehead alkene containing an exocyclic double bond. A further complication arises from the fact that allenes can also react as 2π-electron donors in [2+2] cycloadditions.[23] Experimentally, all three reaction modes have been observed in allene–diene cycloadditions. Selected examples are shown in the equations below.

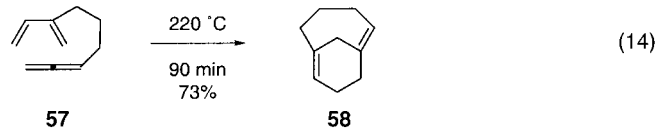
Thermolysis of 1,2-propadienyl-3-methylene-4-pentenyl ether (**51**) gives two major products, **52** and **53** in a combined yield of 92% [Eq. (12)].[24] The major product, an oxabicyc-



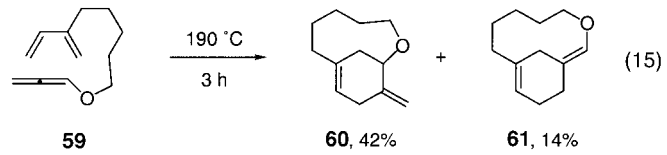
(12)

lo[3.2.0]heptane, arises from a formal [2+2] cycloaddition of the diene and allene moieties of **51**. The minor cycloadduct, 3-oxabicyclo[4.3.1]deca-1,6-diene **53**, contains a *trans,trans*-cyclononadiene embedded in the bicyclic ring structure. This product arises from a [4+2] cycloaddition of the diene with the distal double bond of the allene. An activated allene in the carbocyclic series results in a somewhat faster rate of reaction but with similar distribution of [4+2] and [2+2] cycloadducts [Eq. (13)]. In contrast, the "parent" hydrocarbon 7-methylene-1,2,8-nonatriene (**57**) gave exclusively [4+2] cycloadduct **58** [Eq. (14)].

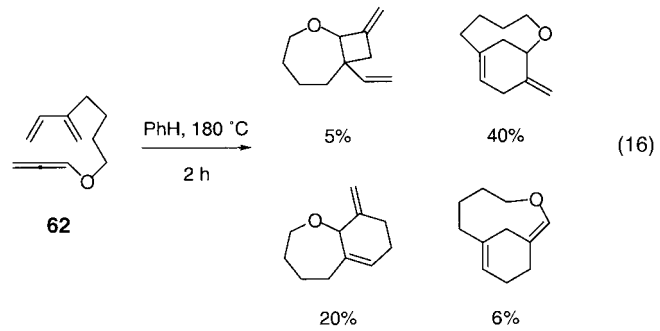


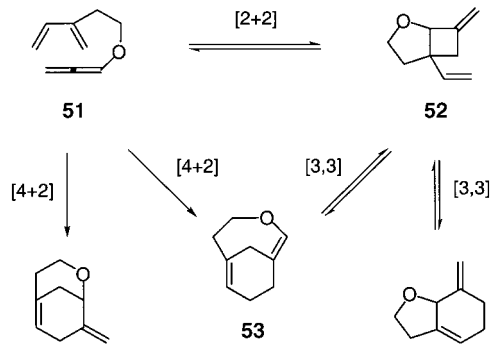

The introduction of additional atoms in the tether joining diene to allene results in the formation of new product mixtures. For example, the six-atom-bridged ether **59** gave [4+2] cycloadducts arising from cycloaddition to both proximal and distal double bonds (**60** and **61**) [Eq. (15)]. The five




-atom-bridged ether **62**, on the other hand, gives no less than four cycloaddition products, two each from the [4+2] and [2+2] cycloaddition modes [Eq. (16)].



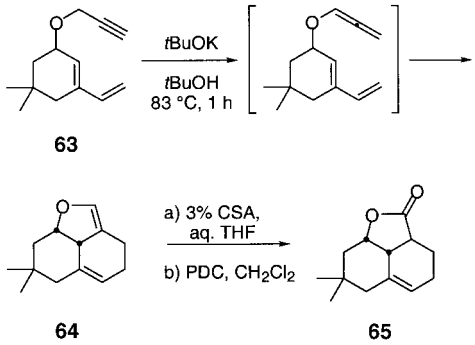

Several kinetic studies have established the dynamics between the reactants and products. Scheme 4 shows one such interrelationship between starting material **51** and the




Scheme 4. Interconversion of reactant **51** and products **52** and **53**.

two major products **52** and **53**. At 190 °C, there was a rapid build up of the [2+2] cycloaddition product followed by a slower accumulation of the [4+2] product. Thermolysis of an enriched sample of **53** (210 °C, 89 min, toluene) resulted in an equilibrium mixture of cycloadducts **52** and **53** (32:68). The two products were interconverted under the reaction conditions. Kinetic studies of the rate of disappearance of **51** and interconversion of **52** and **53** suggest the direct interconversion pathway is viable but may not be exclusive. There are at least two pathways interconnecting the two products **52** and **53**, one involves an equilibrium between the starting material and [2+2] cycloadduct (retro [2+2]), and the second a formal [3,3] sigmatropic rearrangement between **52** and **53**.

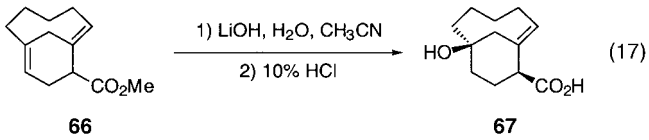
The synthesis of tricyclic lactones via intramolecular allene cycloaddition was reported by Kanematsu et al.[25] Treatment of propargyl ether **63** with base at elevated temperatures resulted in the formation of cycloadduct **64** (Scheme 5). The



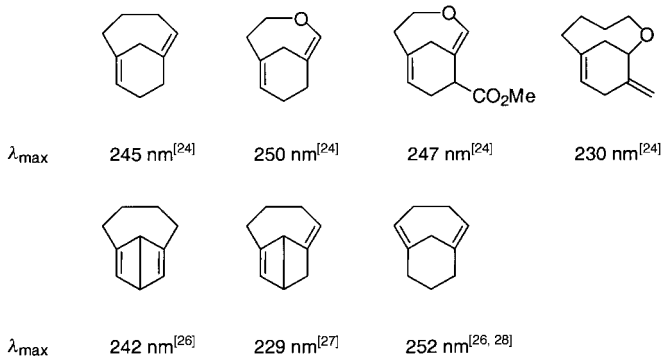

Scheme 5. Kanematsu's approach to tricyclic compounds using an allene dienophile. CSA = camphorsulfonic acid, PDC = pyridinium dichromate.

product arises from in situ isomerization to the allene intermediate followed by cycloaddition. Tricycle **64** was then hydrated and oxidized to produce the corresponding tricyclic lactone **65**.

The bridgehead dienes formed in the preceding examples have exceptional chemical and spectroscopic properties. For example, during efforts to saponify carboxylate ester **66** the more reactive bridgehead double bond underwent hydration [Eq. (17)].[24] An X-ray crystal structure of product **67**




confirmed the chemo- and regiochemistry of the addition. Bridgehead dienes were found to have UV spectra that indicate transannular interactions between the two formally nonconjugated double bonds. Although simple trisubstituted nonconjugated double bonds rarely have UV absorption maxima above 200 nm, bridgehead dienes can have significant absorption maxima extending to greater than 250 nm. Several examples are included in Scheme 6.

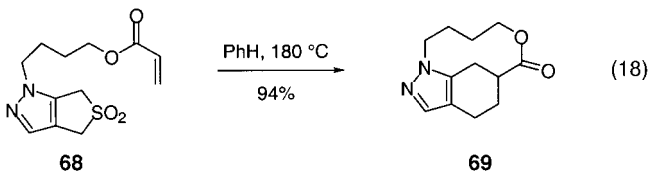



Scheme 6. UV absorption of several non-conjugated bridgehead dienes.

### 3.2. Masked Dienes and Dienophiles

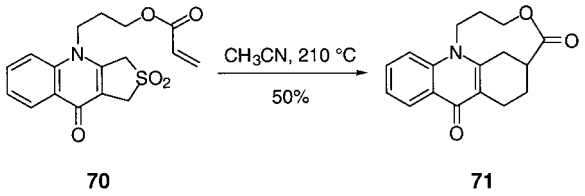
A consequence of the reactivity of 2-substituted dienes is that they may have limited compatibility with some synthetic transformations. In these cases, a strategy to overcome this would be to append this fragment last or to utilize a masked diene that is liberated before or during the intramolecular Diels–Alder step.

Chou and Chen successfully used heterocycle-fused 3-sulfolenes as masked dienes in the type 2 IMDA cycloaddition. Thermolysis of **68** at 180 °C for 4 h produced the intermediate diene by extrusion of $SO_2$ which underwent a type 2 IMDA reaction to give pyrazole **69** [Eq. (18)].[29] Chou and Chen also




(18)

synthesized a 2-substituted diene in a similar manner to effect the first type 2 IMDA cycloaddition of an *o*-quinodimethane. Thermolysis of **70** at 210 °C led to the formation of tetracycle **71** [Eqs. (19)].[30]

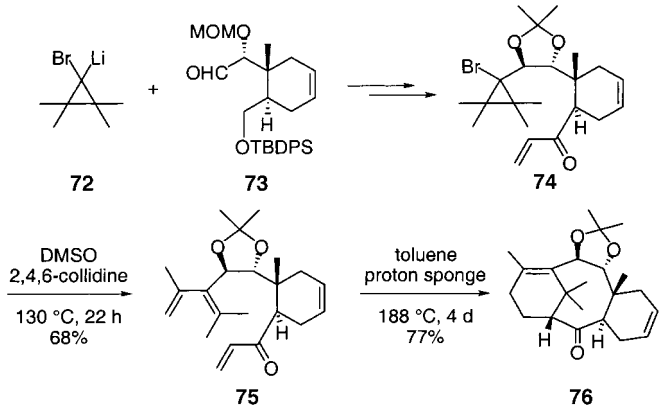



(19)

2-Metallo 1,3-butadienes are common precursors to 2-substituted dienes. Unfortunately, their reactions with electrophiles suffer from competing reaction of the metalloallenes, which are in equilibrium with the diene [Eq. (20)].[31] To

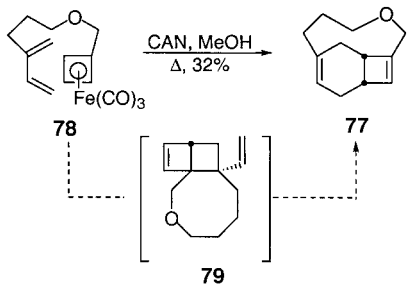

(20)

circumvent this problem, a 1-bromo-1-lithiocyclopropane was utilized as a masked diene for the synthesis of an advanced taxusin intermediate. Bromolithiotetramethylcyclopropane (**72**) was added to aldehyde **73** and subsequently converted to enone **74** (Scheme 7).[32] Liberation of highly methylated diene **75** and thermolysis of the product at 188 °C provided taxusin intermediate **76** in 77 % yield.




Scheme 7. Synthesis of advanced taxusin intermediate **76**.[32]

In addition to employing masked dienes in the type 2 IMDA reaction, reactive dienophiles can also be sequestered until needed. This approach was used by Snapper and Limanto to carry a tricarbonylcyclobutadieneiron in the synthesis of bridged bicyclic product **77** (Scheme 8).[33] Slow




Scheme 8. Synthesis of tricyclic adduct **77**.[33] CAN cerium(IV) ammonium nitrate

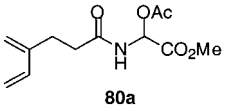
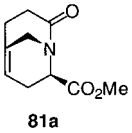
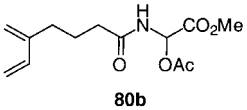
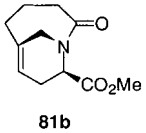
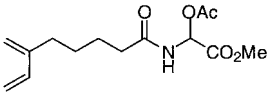
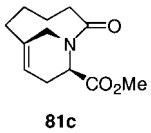
addition of **78** to a refluxing methanolic solution of a large excess of CAN (55 equiv) resulted in a 32 % yield of **77**. (It should be noted, however, that compound **77** could have arisen from a [2+2] cycloaddition producing **79**, followed by a Cope rearrangement.)

## 4. Hetero Diels–Alder Reactions

The heteroatom variant of the type 2 IMDA reaction can result in formation of bridged heterocycles in a single step from an acyclic precursor. This strategy was first recognized for the synthesis of bridgehead lactams.

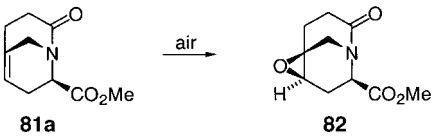
The type 2 intramolecular acyl imino Diels–Alder reaction was utilized as an entry to a class of compounds that possess both a bridgehead alkene and bridgehead lactam unit. Thermolysis of acetoxyamides **80a–c** produced intermediate *N*-acylimines which underwent subsequent cycloaddition to yield cycloadducts **81a–c** (Table 7).[34, 35] Compound **81a** is

Table 7. Intramolecular acyl iminium Diels–Alder cycloadditions.

| Starting material | Conditions[a] | Products | Yields [%][b] |
|---|---|---|---|
|  **80a** | 250 °C, 2 min |  **81a** | 29 |
|  **80b** | 200 °C, 2 h |  **81b** | 82 |
|  **80c** | 215 °C, 2 h |  **81c** | 76 |

[a] Reactions were performed in xylenes at 0.01M. [b] Yields refer to isolated products after chromatography.

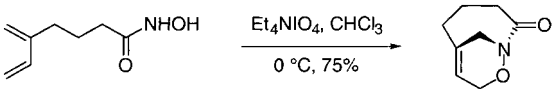
one of the most highly strained isolable bridgehead alkenes prepared to date. The high reactivity of this compound is demonstrated by its spontaneous air oxidation to form epoxide **82** [Eq. (21)]. The crystalline nature of the bridge-



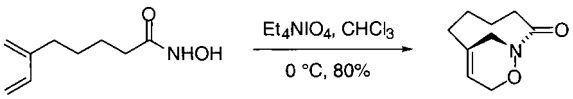

**81a** **82** (21)

head lactams have provided structural data for both torsionally distorted bridgehead double bonds and bridgehead lactams (see Section 6).

Type 2 hetero Diels–Alder reactions have also been examined using *N*-acyl nitroso dienophiles. The *N*-acylnitroso dienophile is generated in situ by the oxidation of the corresponding hydroxamic acids. Cycloaddition occurs under mild conditions due to the high reactivity of the *N*-acylnitroso dienophile. The reaction is demonstrated by the cycloadditions of Diels–Alder precursors **83a** and **83b**.[36] In situ generation of the acylnitroso functionality by periodate oxidation provide bridged oxazinolactams **84a** and **84b** [Eqs. (22) and (23)].




**83a** **84a** (22)



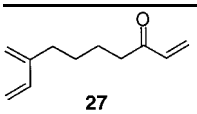
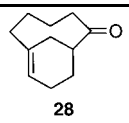
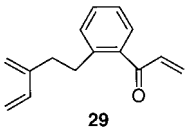
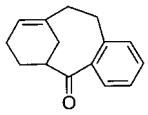
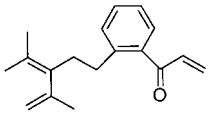
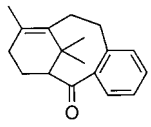

**83b** **84b** (23)

## 5. Kinetic Studies

Relatively few kinetic studies of the intramolecular Diels–Alder reactions have been reported.[37] The little information available suggests that in addition to the expected kinetic advantages of intramolecularity that can arise from entropic factors, the nature of the intervening tether can exert a significant influence on the intramolecular reaction. This may be advantageous or deleterious to the overall rate depending on the nature of the connector.

One example is illustrated in the cycloaddition of triene ketone **25**.[38] A comparison of the half-lives of cycloaddition for the series shown in Table 8 reveals that the introduction of

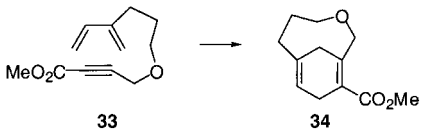
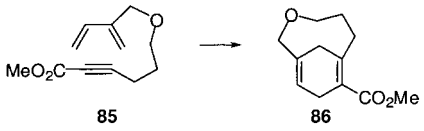
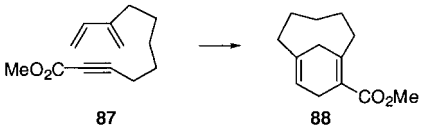
Table 8. Comparison of the half-lives of trienes **27**, **29**, and **38**.

| Starting material | Product | $\tau_{1/2}$ h ($T$ [°C]) |
|---|---|---|
|  **27** |  **28** | 15 (155) |
|  **29** |  **30** | 1 (65) |
|  **38** |  **39** | 18 (155) |

two $sp^2$ centers in the tether can result in a rate enhancement of $10^6$. There are several factors that contribute to this rate enhancement. The most important may be the reduced conformational freedom on transtion from **27** to **29** resulting from the introduction of three methyl groups including a *cis*-alkene linkage in the tether joining diene and dienophile in **29**. It was also noted, however, that aryl vinyl ketones are approximately 70 times more reactive than methyl vinyl ketone. This factor also contributes to the $10^6$ fold increase in the reaction rate. In contrast to enhanced reactivity resulting from conformational restrictions, the reactivity of the system is dramatically reduced upon introduction of a *cis*-methyl substituent on the diene.[39] This can produce up to a $10^6$ fold *decrease* in the rate of cycloaddition (cf. the reaction of **38** in Table 8).

In our group we have reported a systematic investigation of the effect of tether length and the location of heteroatoms on the rate and activation energy parameters for the intramolecular cycloaddition of alkynyldienyl ethers **33**, **85**, and **87** (Table 9).[40] At 210 °C, dieneyne ether **33** is approximately 60 times more reactive than isomer **85** and the hydrocarbon analogue **87**. The activation energies for the cycloadditions are summarized in Table 9. The entropies of activation are, within experimental error, identical for all three reactions. Thus the rate differences between **33** and **85** and **87** are enthalpic in

Table 9. Influence of tether length and heteroatom location on the activation energy and enthalpy of dienyne cycloaddition reactions.

| Reaction | $k_{rel}$ (210 °C) | $E_a^{\neq}$ [kcal mol$^{-1}$] | $\Delta S^{\neq}$ [cal K mol$^{-1}$] |
|---|---|---|---|
|  **33** **34** | 62 | 23.6 | −28 |
|  **85** **86** | 1 | 27.0 | −29 |
|  **87** **88** | 1 | 27.1 | −29 |

origin. An analysis of models of the transition state revealed the homopropargylic position in the tether and the diene hydrogen atoms of the exocyclic methylene group are in close proximity (Figure 1). In diene ether **33**, the homopropyargylic

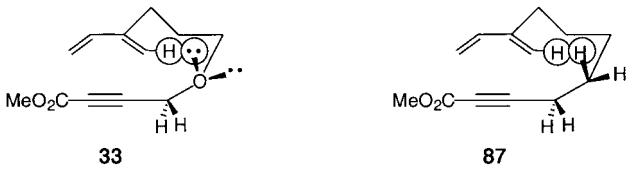

**33** **87**

Figure 1. Proposed transition states for the cycloaddition of **33** and **87**.

position of the tether is occupied by an oxygen atom but in **85** and **87** the position is occupied by a methylene group. The well-documented difference in steric demands between an oxygen lone pair and a C–H bond was attributed in part to raising the activation energy for **85** and **87** over that of **33**.

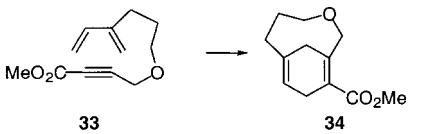
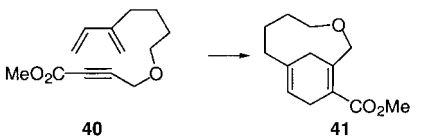
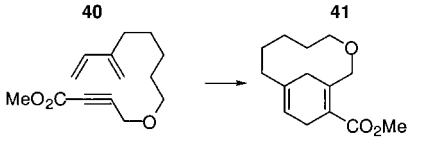
The effect of tether length on the rate of cycloaddition was examined for the alkynyldienyl ethers **33**, **40**, and **89** (Table 10). At 210 °C, the rates of cycloaddition of **33** and **40** are approximately equal, while the rate of the seven-atom homologue **89** falls off to approximately one fifth of the reference compound **33**. Analysis of $E_a^{\neq}$ and $\Delta S^{\neq}$ revealed no simple trends. As the tether length increases through the series, the activation *entropy* ($\Delta S^{\neq}$) levels off after an initial increase in tether atom number from five to six. It was proposed that in a series of this type with a progression of tether lengths, perhaps only three or four bonds need to be "frozen" in the transition state. The residual bonds can remain floppy and not extract an entropic price in the transition state entropy. Similar leveling off effects in entropy have been noted in macrocyclization reactions.[41] The activation energy $E_a^{\neq}$ on the other hand follows no pattern. This is not surprising since competing contributions are at work. For example, product steric energy decreases with increasing tether size. This can result in a change in the transition state from late to early modulating the contribution of nonbonding interactions in the transition state. The absence of a monotonic trend in both enthalpy and entropy of activation emphasizes the diversity of contributions to these terms that can complicate the ability to predict kinetic trends even within a closely related series of reactants.

The study also included an evaluation of the effective molarity (EM) of the cycloaddition **40** → **41** [see Eq. (7)]. A comparison of rate constants with the bimolecular counterpart gave an EM of ≈0.4–0.5 M, a relatively modest kinetic advantage compared with other intramolecular reactions.[42]

## 6. Structural Studies of Bridgehead Alkenes

Type 2 IMDA reactions provide a general route to substituted bridgehead alkenes and dienes and has made available a number of crystalline derivatives for X-ray structure analysis. The distinguishing substructural feature of a bridgehead alkene is the *trans*-cycloalkene (**91**, Figure 2) that is embedded in the bridged bicyclic structure. The double bond is subjected to a torsional distortion that twists the π bond out of coplanarity resulting in loss of overlap of the 2p orbitals. In response to this torsional distortion, the $sp^2$ carbon atoms also undergo rehybridization by incorporating s character into the p orbitals of the π bond. This results in pyramidalization of each of the $sp^2$ carbon atoms.

Table 10. Relative rates and activation energy parameters for the intramolecular Diels–Alder cycloaddition of alkynyldienyl ethers.

| Reaction | $k_{rel}$ (210 °C) | $E_a^{\neq}$ [kcal mol$^{-1}$] | $\Delta S^{\neq}$ [cal mol$^{-1}$] |
|---|---|---|---|
|  **33** **34** | 5.4 | 23.6 | −28 |
|  **40** **41** | 5.5 | 20.6 | −35 |
|  **89** **90** | 1 | 22.6 | −34 |

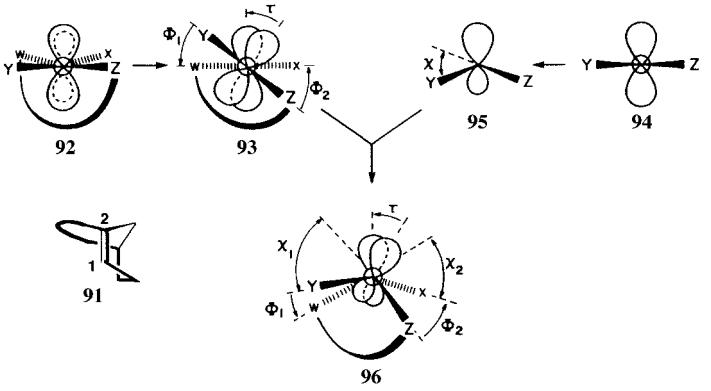


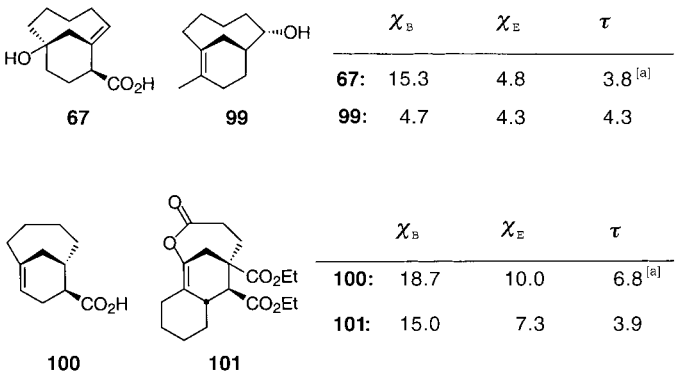

Figure 2. Analysis of the distortional parameters $\chi$ and $\tau$, for a torsionally distorted double bond.

The extent of these distortions can be quantified by the torsion angle $\tau$ between the p orbitals of the double bond and the pyramidalization angle $\chi$ of the constituent atoms of the $\pi$ system (see Figure 2).[43] The view along the C1–C2 axis of $\pi$-system **91** is represented by **92**. Rotation of C1 relative to C2 produces a misalignment of the p orbitals of the $\pi$ bond (**93**). The torsional deformation is quantified by the angle $\tau$ between the axes of the two p orbitals. The torsional angle $\tau$ is not directly measurable by X-ray crystallography but may be determined by measuring either of the four atom torsional angles $YC_1C_2W$ ($\Phi_1$) or $ZC_1C_2X$ ($\Phi_2$).

The two atoms of the $\pi$ system rehybridize independently. Incorporation of s character into the $\pi$ bond p orbital (rehybridization) produces a pyramidalized atom **95**. The degree of the pyramidalization of each atom is quantified by the pyramidalization angle $\chi$ (see **95**). For an $sp^{2.00}$ atom, $\chi$ is 0.0°, while for an $sp^{3.00}$ atom $\chi$ is 60.0°. In the composite structure **96**, $\Phi_1$ and $\Phi_2$ are no longer equivalent so the torsional distortion $\tau$ is defined as the average by the equation $\tau = (\phi_1 + \phi_2)/2$. Structural data for a number of bridgehead alkenes have been summarized in a review.[44] Selected examples, chosen to illustrate the degrees of distortion found in various bridgehead alkenes, are given below.

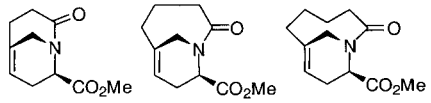
The magnitude of both pyrimidalization ($\chi$) and torsional distortion ($\tau$), are modest for bridgehead alkenes with five or more atoms in the tether. In these ring systems the *trans*-cycloalkene is in a ten-membered ring or greater.[44] Two bicyclo[5.3.1]undecenes, **67** and **99**, illustrate this point (Scheme 9). The bridgehead double bonds in **67** and **99** each have $\tau$ values of approximately 4°, and only the bridgehead carbon atom in **67** experiences more than negligible pyramidalization. As a consequence of these slight distortions, the reactivity of the bridgehead double bond is unexceptional.

Both pyramidalization and torsional distortion increase in the bicyclo[4.3.1] ring system (see data for structures **100** and **101** in Scheme 9).[44] The pyramidalization at both $sp^2$ carbon atoms is real and the $\tau$ values are 3.9 and 6.8°, respectively. Some of the most serious distortions are found in the bicyclo[3.3.1] ring system. The trends in the distortion are best observed in the homologous series of bridgehead alkene/lactams, **81a–c** (Scheme 9 and Figure 3).[35] Successive removal of a methylene group produces a corresponding increase in the value of $\chi$ at both carbon atoms and an increase in $\tau$. The distortions in **81a** are some of the largest reported.




| | $\chi_B$ | $\chi_E$ | $\tau$ |
|---|---|---|---|
| **67:** | 15.3 | 4.8 | 3.8 [a] |
| **99:** | 4.7 | 4.3 | 4.3 |

| | $\chi_B$ | $\chi_E$ | $\tau$ |
|---|---|---|---|
| **100:** | 18.7 | 10.0 | 6.8 [a] |
| **101:** | 15.0 | 7.3 | 3.9 |




| | $\chi_B$ | $\chi_E$ | $\tau$ |
|---|---|---|---|
| **81a:** | 39.1 | 18.7 | 10.4 |
| **81b:** | 22.7 | 8.2 | 6.5 |
| **81c:** | 8.4 | 0.0 | 0.4 |

Scheme 9. Geometric distortions of bicyclo[5.3.1]undecenes **67** and **99**, bicyclo[4.3.1]decenes **100** and **101**, and the homologous alkenes **81a–c**. $\chi_B$ corresponds to the pyramidalization of the bridgehead carbon, $\chi_E$ corresponds to the pyramidalization of the exocyclic carbon. [a] Average derived from calculated hydrogen atom position in the X-ray crystal structure.

The series of molecules also has a bridgehead lactam, a quasi double bond that responds similarly to the progressive distortions (Figure 4, Table 11). Due to the softer bending potential of nitrogen, the bridgehead nitrogen atom experiences complete pyramidalization. Interestingly unlike the C–C double bond which shows no variation in length upon increased torsional distortion, the C–N bond in **81a** is several hundredths of an angstrom longer than in **81b** and **81c**.

The geometric distortions noted in the bicyclo[4.2.1] and [3.3.1] ring systems are paralleled by an increase in chemical reactivity. Bicyclo[3.3.1]nonenes are more than $>10^6$ times more reactive than the less highly strained bridged alkenes in electrophilic additions to the double bond.[45, 46]

## 7. Application of the Type 2 IMDA Reaction in Syntheses

The synthetic utility of any reaction is determined by the ability to control or limit the formation of isomeric products. Despite the enormous importance of the Diels–Alder reaction, isomer control remains as a serious limitation to its effective employment in solving synthetic problems. The type 2 IMDA reaction provides strategies for the solution of these problems.

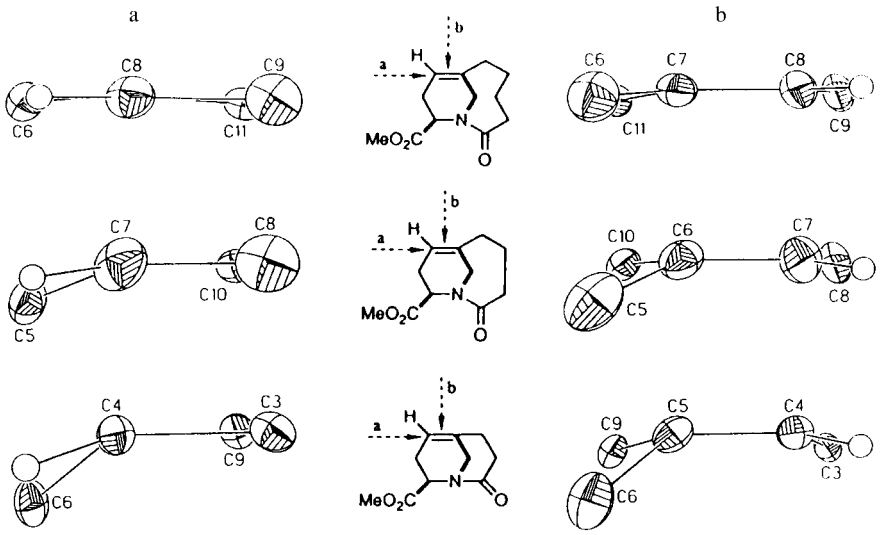



Figure 3. ORTEP plots (at 20% probability level for clarity) of the bridgehead alkene bonds and their substituents for **81a–c** with all other atoms omitted. a) Alkenes viewed along the axis of the C=C double bond with the exocyclic alkene carbon atom in front (indicated by dashed arrows a in the formulas). b) Side views (indicated by dashed arrows b in the formulas).

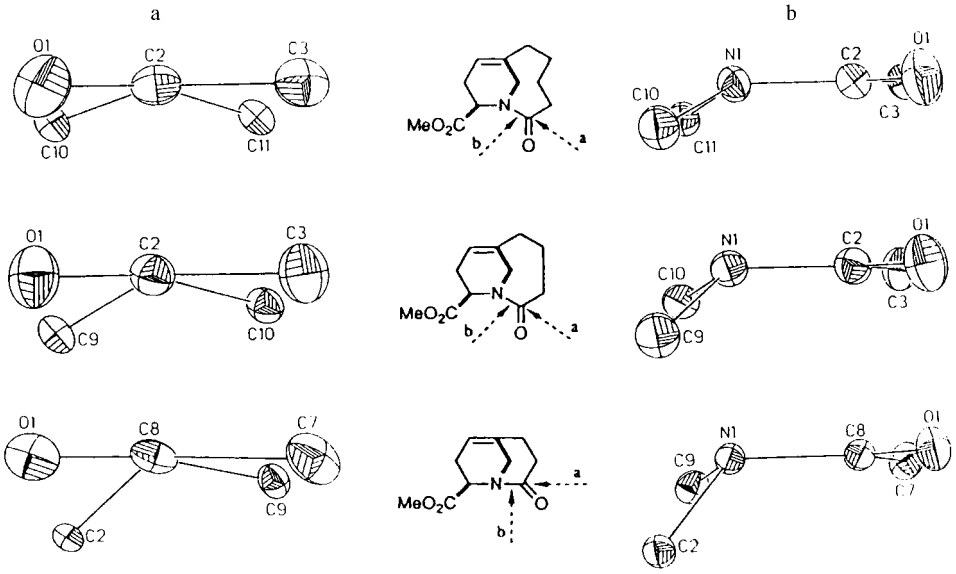



Figure 4. ORTEP plots (at 20% probability level for clarity) of the bridgehead lactam bonds and substituents for **81a–c** with all other atoms omitted. a) Lactams viewed along the axis of the C–N bond with the carbonyl carbon atom in front (indicated by dashed arrows a in the formulas). b) Side views (indicated by dashed arrows b in the formulas).

Table 11. Geometric distortions of homologous lactams **81a–c**.

| Compound | $\chi_N$[a] | $\chi_C$[a] | $\tau$ | $d$(C–N) [Å] |
|---|---|---|---|---|
| **81a** | 54.9 | 1.6 | 16.7 | 1.399 |
| **81b** | 46.5 | 1.1 | 7.5 | 1.374 |
| **81c** | 38.1 | 0.1 | 0.9 | 1.377 |

[a] $\chi_N$ corresponds to the pyramidalization of the bridgehead nitrogen atom, $\chi_C$ corresponds to the pyramidalization of the carbonyl carbon atom.

The type 2 IMDA reaction affords a general method for controlling the regio- and stereochemistry of the cycloaddition. In addition, by incorporation of a stereocenter in the triene precursor, the reaction allows discrimination between the diastereotopic faces of the reacting diene and dienophile. Finally, the conformational rigidity of the resulting bridged cycloadducts allows their stereoselective elaboration. Analysis of these control elements is detailed in the sections that follow.

### 7.1. Regiochemical Control

Regioselectivity in bimolecular Diels–Alder reactions is understood in terms of FMO analysis. The dominant perturbation between a diene with a donor substituted in the 2-position and a dienophile containing an electron-withdrawing group results in a 1,4-substituted cycloadduct. Selectivities >95:5 are observed for a 2-oxy-substituted diene and methyl acrylate.[47] This intrinsic regiochemical bias must be considered in anticipating the regiochemical outcome of any Diels–Alder reaction of this substitution pattern.

In contrast to the bimolecular reaction, the type 2 intramolecular Diels–Alder reaction exhibits a preference for formation of the *meta* cycloadduct. In small ring systems, this preference probably arises in part from the greater stability of the *meta* cycloadduct compared to the *para* cycloadduct since the *meta* regioisomer contains the *trans*-cycloalkene in the larger (less strained) ring (Figure 5). The *meta*–*para* energy difference diminishes as the ring size increases.[48] Therefore, as the tether size is increased, the cycloaddition reactions are influenced by the usual steric, conformational, and electronic factors.

Analysis of a considerable body of experimental data provides the basis for several generalizations. For tethers containing three, four, and five atoms, cycloaddition results in the *meta* regioisomer as the *exclusive* product regardless of the dieneophile's activation pattern.[49] The cycloaddition of trienes **102** and **104** illustrate this point [Eqs. (24) and (25)].[50] Lewis acid catalyzed cycloaddition of internal-

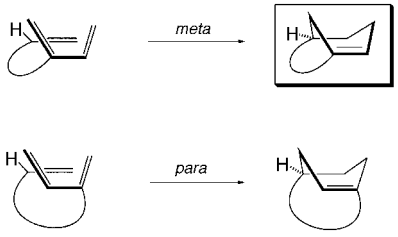
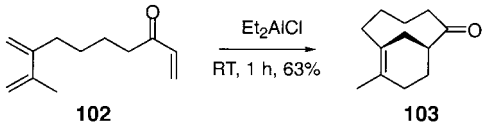
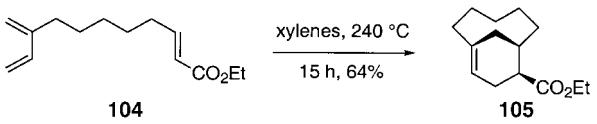



Figure 5. Regioadducts in the type 2 IMDA reaction.




(24)

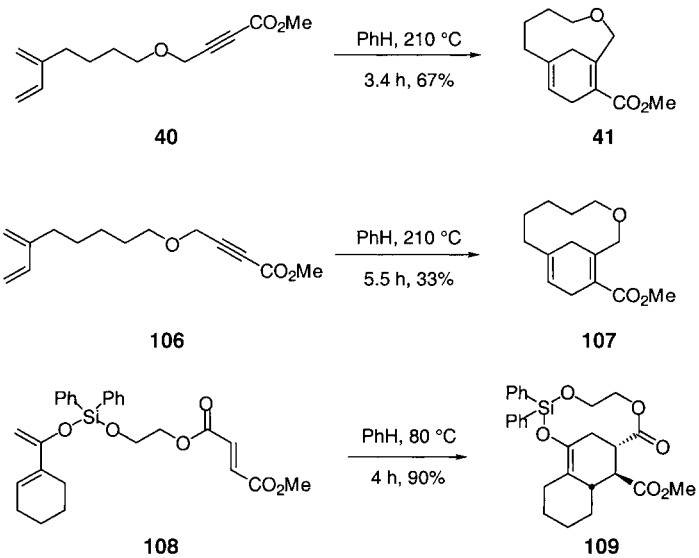



(25)

ly[51] activated triene **102** yields **103** as a single regioisomer. The thermal cycloaddition of externally[51] activated ester **104** furnishes cycloadduct **105**, also as a single product.

A balance of electronic considerations (FMO analysis) and steric or conformational factors govern the regioselectivity of tethers with six or more atoms. Externally activated trienes furnish the 1,3-regioisomer exclusively. Six- and seven-atom dienynes **40** and **106** illustrate this point, both dienyes afford 1,3-substituted bridgehead dienes as the sole products (Scheme 10).[18] Additionally, 1,2-diactivated dienophiles also furnish 1,3-regioisomers as the sole product. For example, seven-atom-tethered fumarate **108** undergoes cycloaddition to produce **109** as a single product.[52]

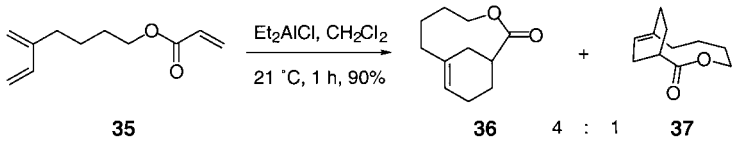
Internally activated dienophiles with six or more atoms in the tether can produce mixtures of regioisomers, whose ratio is determined by both the intrinsic biases of the reacting partners and conformational factors. For example, six-atom-tethered acrylate **35** undergoes Lewis acid catalyzed cycloaddition to afford the 1,3- and 1,4-regioisomers **36** and **37** in a 4:1 ratio [Eq. (26)].[12] The Diels–Alder cycloaddition of 2-siloxy-substituted methacrylate **110** proceeds to furnish 1,3- and 1,4-substituted regioisomers **111** and **112** in a 3:7 ratio in favor of the 1,4-substituted regioisomer [Eq. (27)].[53]




Scheme 10. Type 2 IMDA reactions of compounds in which the diene is tethered to the dienophile over six or seven atoms.

These concepts can be used to reverse the intrinsic regiochemical preferences of the intermolecular Diels–Alder reaction. This strategy, termed *pericyclic umpolung*, when coupled with disposable tether methodology, allows synthesis of cyclohexene derivatives with substitution patterns that are *reversed* from those from the bimolecular Diels–Alder reaction.[53]

The synthesis of substituted cyclohexanones is used to illustrate this concept. Bimolecular cycloaddition of 2-oxo-substituted dienes with methyl acrylate results in predominant

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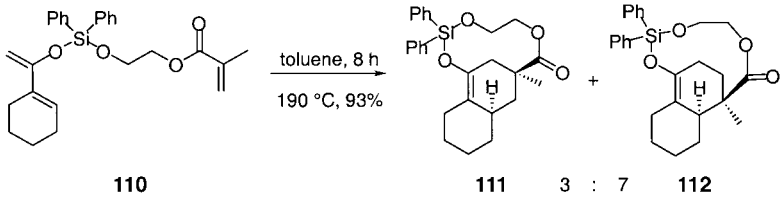
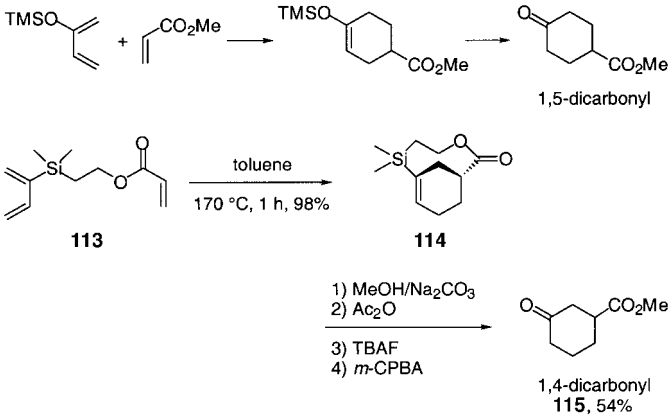



(27)

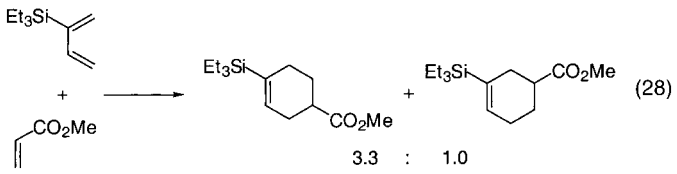
formation of the 1,4-cycloadduct (Scheme 11 top),[47] whose hydrolysis affords a cyclohexanone product with a 1,5-dicarbonyl orientation. Temporary union of the two reactants




Scheme 11. Pericyclic umpolung applied to the synthesis of methyl 3-oxocyclohexanecarboxylate (**115**). The course of the normal Diels–Alder reaction is shown above. TBAF = tetrabutylammonium fluoride, *m*-CPBA = *meta*-chloroperoxybenzoic acid.

and cyclization provides complete regiochemical control to deliver the 1,3-regioisomer. This is demonstrated by the cycloaddition of vinyl silane **113** which affords cycloadduct **114** as the sole product. Oxidative tether cleavage produces methyl 3-oxocyclohexanecarboxylate **115**, with a 1,4-dicarbonyl orientation.

In the preceding example silicon was used as an oxygen surrogate. The choice of silicon provides a broader range of coupling strategies for the Diels–Alder precursor in addition to relaxing the intrinsic (1,4) regiochemical bias. The corresponding bimolecular reaction of 2-triethylsilyl-1,3-butadiene with methyl acrylate provides a 3.3:1.0 mixture of 1,4- and 1,3-regioisomers [Eq. (28)].[54]




The patterns that emerge from these studies allow one to predict the regiochemical outcome of a type 2 IMDA reaction based upon tether length and the arrangement of activating groups on the reacting diene and dienophile. In addition to regioisomer control, the concept of pericyclic umpolung permits a completely revised analysis of synthetic strategies that employ Diels–Alder reactions for the synthesis of six-membered rings. These strategies have been reduced to practice in the context of natural product synthesis (see Section 8).

### 7.2. Stereochemical Control

The origins of stereoselectivity in the Diels–Alder reaction are attributed to secondary orbital interactions between the diene and dienophile. The magnitude of these interactions is typically less than several kcal mol$^{-1}$.[55] Understandably, control of stereochemistry presents special challenges. Unlike type 1 intramolecular Diels–Alder counterparts [Eq. (1)], type 2 intramolecular Diels–Alder reactions show *complete stereoselectivity*. Cycloaddition takes place from a conformation where the tether occupies the endo position affording an "out"-bridged bicyclic adduct (Figure 6). The origin of this

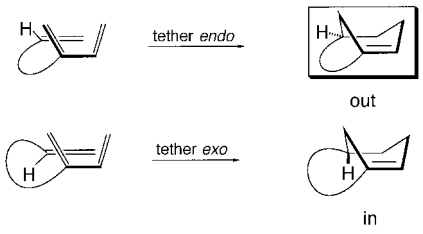
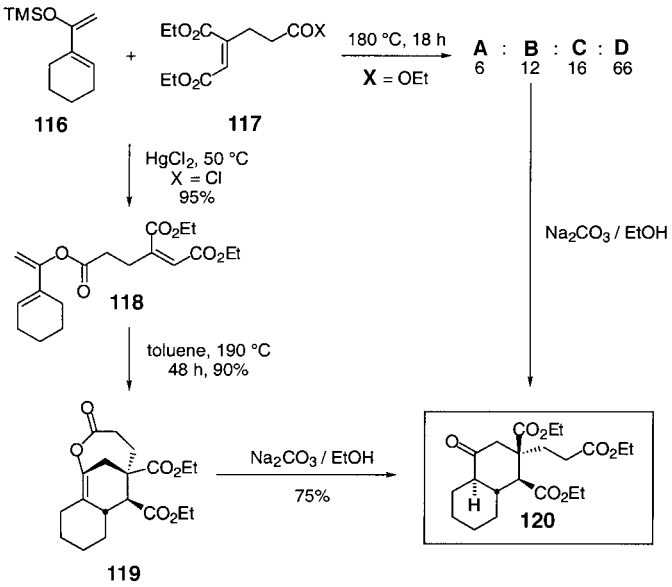



Figure 6. Stereoselectivity of the type 2 IMDA reaction.

preference is readily understood from consideration of the two possible stereoisomeric products. The tether *exo* stereochemistry results in formation of an in-bridged bicyclic adduct. In small- and medium-sized tethers ($n = 3-7$), this stereoisomer is considerably higher in energy than the corresponding cycloadduct resulting from the tether *endo* arrangement. The transition states leading to these two stereoisomeric products reflect the relative differences of strain in the cycloadducts. This energy difference is considerable and overrides the contributions that arise from what are the usual determinants in stereochemical control, namely secondary orbital interactions. As a result, the type 2 cycloaddition gives products that arise exclusively from *endo* tether stereochemistry.

The utility of the stereochemical control inherent to the type 2 IMDA reaction is illustrated by the example in Scheme 12.[56] The *bimolecular* cycloaddition of the dien-2-ol



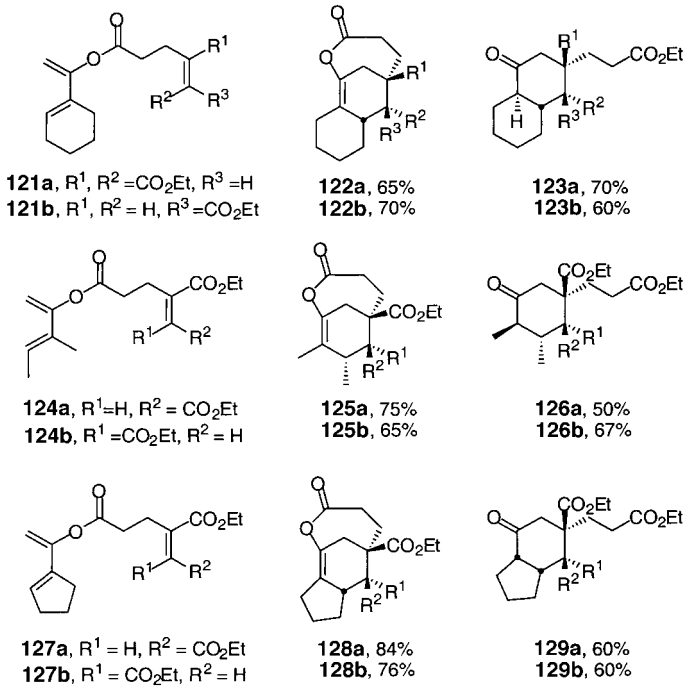

Scheme 12. Stereoselectivity of the type 2 IMDA reaction.

**116** and the trisubstituted dienophile **117** results in formation of all four regio- and stereoisomers, **A**, **B**, **C**, and **D** (excluding enantiomers) in a ratio of 6:12:16:66. Synthetically, this reaction is useless. However, union of **116** and **117** in a type 2 manner affords Diels–Alder precursor **118**. Cycloaddition (190 °C, 48 h, toluene) results in formation of *a single cycloadduct*, **119**, a bridgehead enol lactone, in 90% yield. The configuration of the three contiguous asymmetric centers was established unambiguously by X-ray crystallography. The reaction proceeds with *meta* regioselectivity and tether-*endo* stereochemistry to account for the relative configuration of the three contiguous asymmetric centers. Cleavage of the bridgehead enol lactone ($Na_2CO_3$, MeOH) produces the 1-decalone ring system **120**, which under the equilibrating conditions of the cleavage, gives rise to the thermodynamically controlled stereochemistry at the ring junction (*trans*-decalone).[57] A minor product (<12%) in the bimolecular cycloaddition, stereoisomer **B**, corresponds to the sole product of the type 2 IMDA reaction.

The combination of type 2 IMDA reaction followed by lactone cleavage and epimerization allows one to set, in a predictable manner, the relative configuration of four contiguous asymmetric centers and, in effect, select a single regio- and stereoisomeric product from an otherwise unproductive reaction. Selected ring systems and substitution patterns that have been synthesized by this approach are provided in Scheme 13.

### 7.3. Disposable Tethers between Diene and Dienophile: General Solutions for Controlling Regio- and Stereochemistry

The application of disposable tether methodology in the type 2 IMDA reaction provides a method for temporarily staging the Diels–Alder reaction to control the regioselectivity and stereoselectivity.[58–60] This strategy capitalizes on

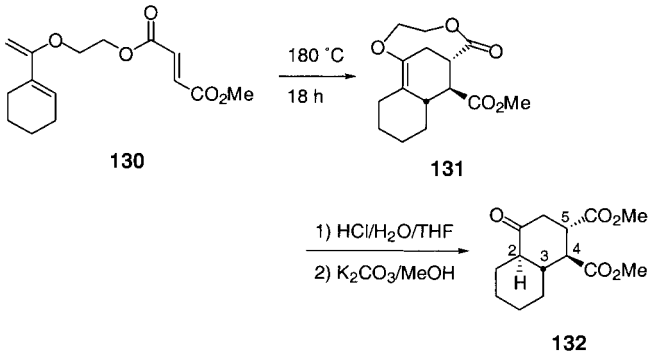



Scheme 13. Products of cycloadditions of enol lactones (left) before (center) and after (right) cleavage of the tether.

the inherent 1,3-regioselectivity of the type 2 IMDA reaction to provide, after removal of the tether, cyclohexene products that often correspond to the minor component formed in the corresponding bimolecular Diels–Alder reaction. The following sections review the types of tethers that have been used and present examples exploiting disposable tether methodology for controlling the regio-, stereo-, and enantioselectivity of the type 2 IMDA reaction.

### *7.3.1. Vinyl Ethers and Silyl Acetals*

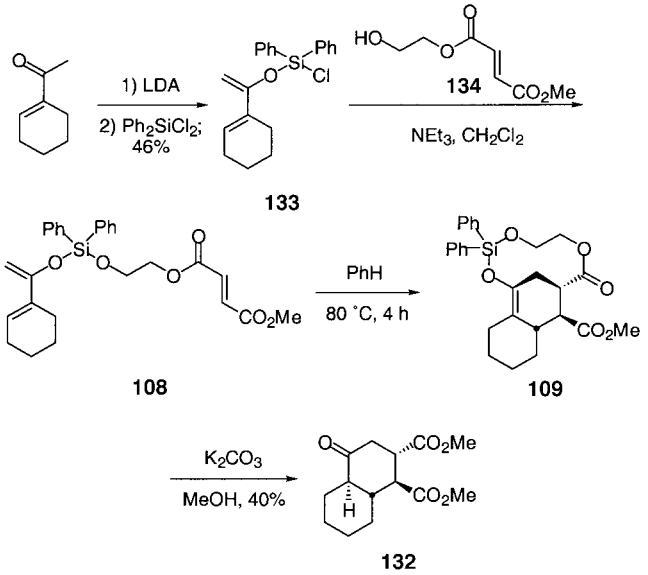
There are relatively few examples of vinyl ethers in the type 2 IMDA reaction (Scheme 14).[52] Heating a solution of vinyl ether **130** furnished cycloadduct **131**. The cycloaddition




Scheme 14. A disposable vinyl ether linker in the type 2 IMDA reaction.

establishes the relative configuration of centers 3, 4, and 5. Subsequent hydrolysis followed by esterification sets the relative configuration at C2 to provide *trans*-decalin **132**.

A more common strategy for uniting the diene and dienophile is to use silicon-containing tethers. The first example of this utilized a silyl acetal linkage (Scheme 15).[52] The reaction of dichlorodiphenylsilane with the enolate of 1-acetylcyclohexene gave the chlorosilyl enol ether **133**, followed by treatment with alcohol **134** yielded the Diels–Alder precursor **108**. The success of this strategy relies on the differential reactivity of the two chlorines in dichlorodiphenylsilane enabling the synthesis of mixed silyl acetals.[61] Triene **108** was cyclized in benzene at 80 °C to give cycloadduct **109**, whose structure was confirmed by single-crystal

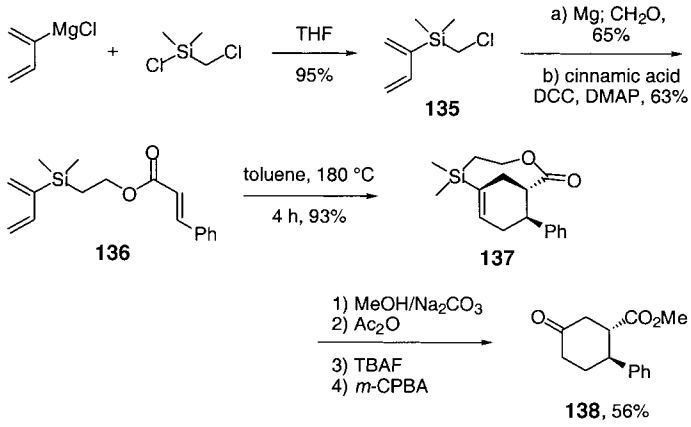



Scheme 15. The use of the silyl acetal linker in the type 2 IMDA reaction. Compound **109** was obtained in 53% yield starting from **133**.

X-ray structure analysis. Methanolic cleavage of silyl acetal **109** leads to decalone **132**. The corresponding bimolecular cycloaddition gives an inseparable mixture of stereoisomers.

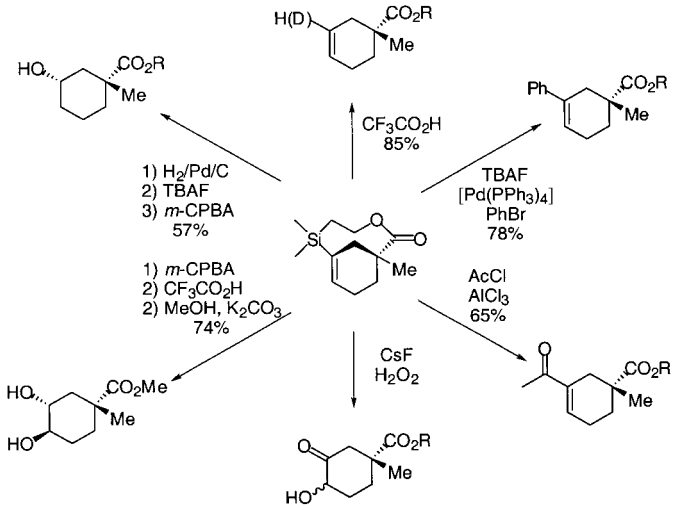
### *7.3.2. Vinyl Silanes*

Vinyl silane tethers have also been utilized to temporarily join the diene and dienophile.[53] The linker in Scheme 16 was synthesized from the chloroprene Grignard reagent and




Scheme 16. Synthesis of a cyclohexanone by using a vinyl silane tether. DCC = dicyclohexylcarbodiimide, DMAP = dimethylaminopyridine.

chloro(chloromethyl)dimethylsilane. The resulting diene product **135** is homologated by treatment with magnesium and formaldehyde. Acylation provided Diels–Alder precursor **136**. Cycloaddition of triene **136** in toluene at 180 °C for 4 h gave a 93% yield of cycloadduct **137**. Oxidative tether cleavage of the carbon–silicon bond provides cyclohexanone **138** as a single regioisomer. The resulting bridgehead vinyl silane cycloadducts are cleaved under a variety of conditions to give substituted cyclohexane derivatives (Scheme 17).[62, 63]




Scheme 17. Elaboration of bridgehead vinyl silanes.

### 7.3.3. Allyl Silanes

Allyl silane tethers have also been used to stage the type 2 IMDA reaction.[64] The Diels–Alder precursors **140a–h** were synthesized from (chloromethyl)(hydroxymethyl)dimethylsilane (**139**) [Eq. (29); Table 12]. Using this chemodifferentiated linker, chloroprene and various dienophiles were joined in a multistep one-pot procedure. This sequence of reactions

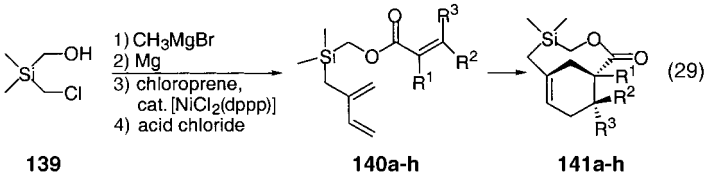


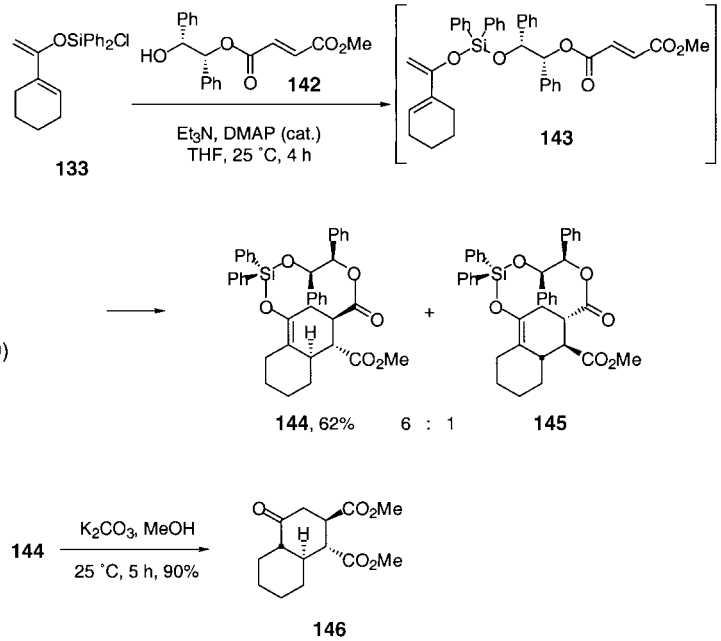

Table 12. Synthesis of allyl silane Diels–Alder precursors and their cycloaddition.

| Compound | $R^1$ | $R^2$ | $R^3$ | Yield of **140** [%] | Yield of **141** [%] |
|---|---|---|---|---|---|
| **a** | H | H | H | 92 | 80 |
| **b** | $CH_3$ | H | H | 82 | 90 |
| **c** | H | $CH_3$ | H | 95 | 94 |
| **d** | $CH_3$ | $CH_3$ | H | 90 | 77 |
| **e** | H | Ph | H | 89 | 96 |
| **f** | $CH_3$ | Br | H | 85 | 74 |
| **g** | H | $CO_2Me$ | H | 71 | 75 |
| **h** | CN | Ph | H | 72 | 89 |

involved the formation of a Normandt–Grignard reagent from **139**, followed by a nickel(0)-catalyzed coupling with chloroprene and finally addition of an $\alpha,\beta$-unsaturated acid chloride to form the desired trienes **140a–h**. The type 2 IMDA reactions of trienes **140a–h** were performed in heated sealed tubes in toluene with additives (proton sponge and 2,6-di-*tert*-butyl-4-methylphenol (BHT)). The cycloadditions occurred with complete regio- and stereochemical control (Table 12).

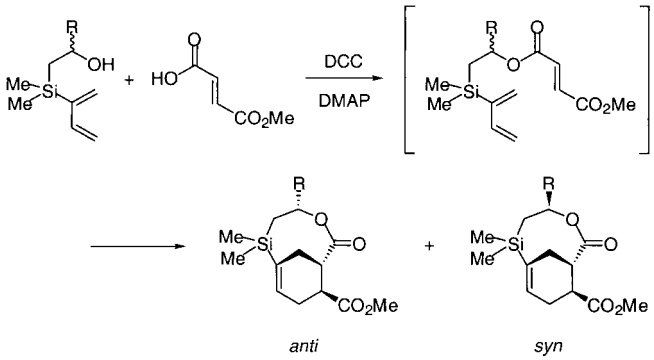
## 7.4. π-Facial Selectivity in the Type 2 IMDA

The disposable tether concept allows modularity of the linker joining the diene and dienophile. Introduction of an asymmetric segment on the tether provides an opportunity to influence the π-facial selectivity of the cycloaddition. An enantioselective decalone synthesis utilizing a chiral disposable tether illustrates this approach (Scheme 18).[65] The diene and dienophile were joined by using the (+)-hydrobenzoin auxiliary **142** and the silyl enol ether **133**. Cycloaddition of **143** led to a pair of diastereomers, **144** and **145**, in a 6:1 ratio. Pure **144** was isolated by chromatography in 62% yield. The absolute and relative configuration was determined by single-crystal X-ray structure analysis. Tether removal afforded *trans*-decalone **146** in 90% yield and >99.5% *ee*. Since both enantiomers of hydrobenzoin are readily available, this strategy allows the synthesis of the enantiomeric decalone **146**.




Scheme 18. Enantioselective synthesis of a decalone by the type 2 IMDA reaction.

The diastereoselectivity of the cycloaddition of vinyl silanes has also been studied (Scheme 19).[62] Coupling of substituted vinyl silanes and methyl fumarate led to Diels–Alder precursors whose cycloaddition resulted in formation of




| R | Conditions | Yields [%] | *anti/syn* |
|---|---|---|---|
| H | 60 °C, 18 h | 89 | – – |
| Me | 65 °C, 13 h | 77 | 3.1 : 1 |
| Ph | 65 °C, 16 h | 54 | 4.2 : 1 |
| *i*Pr | 60 °C, 14 h | 75 | 4.8 : 1 |
| *t*Bu | 25 °C, 18 h | 75 | 9.4 : 1 |

Scheme 19. Diastereoselective synthesis of vinyl silane cycloadducts.

*anti*/*syn* diastereomers. Increased steric bulk of the substituent on the tether led to a higher level of diastereoselectivity.

## 7.5. Stereoselective Elaboration of Bicyclo[*n*.3.1] Ring Systems

The restricted conformational mobility of bridged bicyclic compounds permits their stereoselective elaboration. The following sections illustrate this concept with examples of functionalization of the bridgehead alkene and the medium-sized rings embedded in bridgehead bicyclo[*n*.3.1]alkenes.

### *7.5.1. Additions to the Bridgehead Double Bond*

The torsional distortions associated with bridgehead double bonds can result in dramatic increases in chemical reactivity.[45, 46] More importantly for the present discussion, additions to these bridgehead double bonds occur in a *syn* manner (Figure 7).[2] Addition occurs exclusively from the *exo* face to

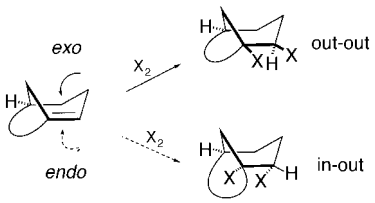
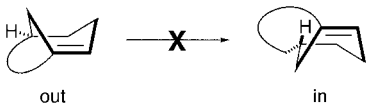


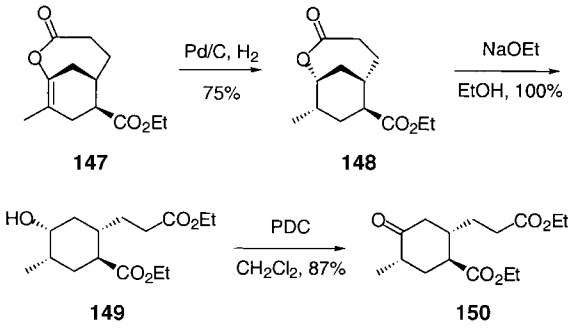

Figure 7. Stereochemistry of the addition to bridgehead double bonds.

give the out-out-bridged product rather than from the *endo* face to give the less stable in-out-bridged bicyclic product. The interconversion of the out-cycloadduct to the in-conformational isomer for short tether lengths is not energetically accessible; this process, referred to as homeomorphic isomerism, would involve movement of the one carbon bridge through the medium ring [Eq. (30)].[66] The conformational integrity of the out-cycloadduct exposes only the *exo* face of the alkene to reagents.



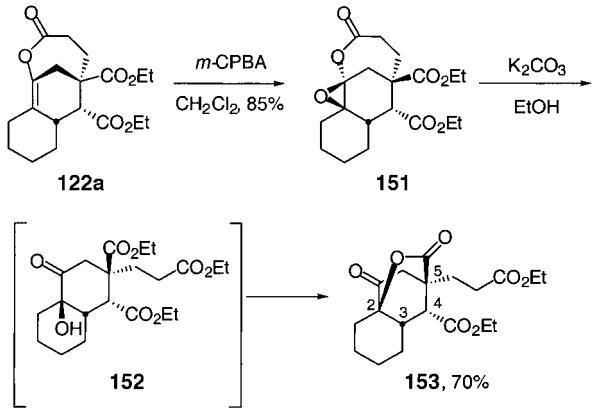

(30)

As a result of these restrictions, reactions of the bridgehead double bond provide a stereocontrolled entry into functionalized six-membered rings. Two examples are shown in reactions (31) and (32). Hydrogenation of bridgehead enol




(31)

lactone **147** affords, after lactone cleavage, isomerically pure cyclohexane **149**.[67] Subsequent oxidation provides cyclohexanone **150**. By comparison, the direct cleavage of **147** (NaOEt, EtOH) gives a mixture of **150** and its C-2 epimer in a 15:85 ratio.

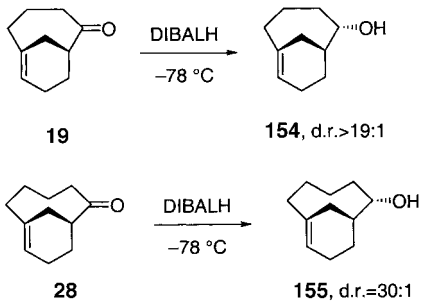



(32)

In reaction (32) the bridgehead alkene **122a** reacts with *m*CPBA to give the epoxy bridgehead lactone **151**.[56] Lactone cleavage triggers rupture of the C–O epoxide bond to give the *cis*-hydroxydecalone derivative **152**, which under the reaction conditions lactonizes to tricyclic ketone **153**. The configuration at C-3, -4, and -5 is established during the cycloaddition step, while that at C-2 is established during the epoxidation of the bridgehead double bond.

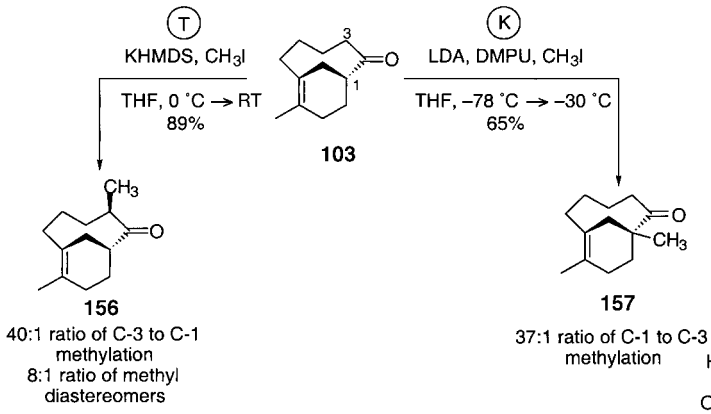
### *7.5.2. Functionalization of the Bicyclo[n.3.1] Ring System*

Bridged bicyclic rings often have a well-defined conformational minima. As a result, the medium ring embedded in the [*n*.3.1] bridged bicycle can be stereoselectively elaborated. In general, stereocontrolled additions to the medium ring of the bridged bicycle occur from the *exo* face. This level of stereochemical control is often difficult to achieve with the monocyclic medium ring.[68] The hydride reductions of ketones **19** and **28** demonstrate this principle (Scheme 20):[50] The reduction with DIBALH at low temperature provides alcohols **154** and **155**, respectively, with high levels of diastereoselectivity.




Scheme 20. Stereoselective reduction of bicyclo[*n*.3.1] ketones to give alcohols. DIBALH = diisobutylaluminum hydride.

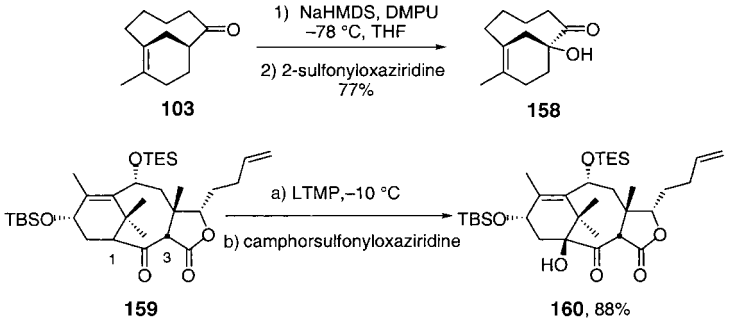
An interesting example of the control offered by a bridgehead alkene was in the alkylation of ketone **103** (Scheme 21).[69] In contrast to aliphatic ketones, deprotonation of bicyclo[5.3.1]undecenone **103** gives the more highly




Scheme 21. Kinetic Ⓚ versus thermodynamic control Ⓣ in the alkylation of ketone **103**. KHMDS = potassium salt of hexamethyldisilazane, DMPU = 1,3-dimethylhexahydro-2-pyrimidinone.

substituted bridgehead enolate under conditions of kinetic control, while the less substituted enolate is formed under conditions of thermodynamic control. The origin of this unusual selectivity is understood by consideration of both strain and stereoelectronic factors. The C-1 carbon–hydrogen bond is aligned with the carbonyl π system, while the C-3 protons bisect the carbonyl π system. Thus, under *kinetic* control, deprotonation occurs more rapidly at C-1, resulting in preferential alkylation at the bridgehead carbon (>37:1). In contrast, under conditions of thermodynamic control, the enolate with lower strain energy (C-2,C-3 double bond) is favored. As a consequence, methylation of ketone **103** under thermodynamic conditions gave exclusive (>40:1) C-3 alkylation consisting of an 8:1 ratio of diastereomers. The major diastereomer arises from *exo* addition of the methyl group.

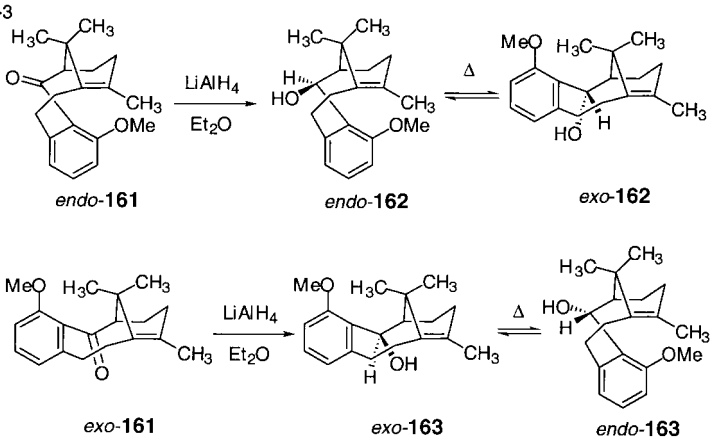
The bicyclo[5.3.1]undecene ring system is a key substructural feature of the taxane natural products. Bridgehead enolization/hydroxylation has been demonstrated on the parent bicyclo[5.3.1] ketone (**103** → **158**; Scheme 22).[69] A




Scheme 22. Bridgehead hydroxylations of the bicyclo[5.3.1]undecenone ring system. TES = triethylsilyl, TBS = tributylsilyl, LTMP = lithium tetramethylpiperidide.

related example of bridgehead functionalization (**159** → **160**) in the bicyclo[5.3.1] ring system was reported by Holton et al. in his Taxol synthesis.[70] Deprotonation of **159** occurs at the bridgehead position even though the C-3 proton is expected to be more acidic. Others have also used this transformation for installation of the C-1 hydroxy group of taxane intermediates.[71–73]

Other examples of stereoselective elaboration of medium-sized rings of bridged bicycles are found in the chemistry of a family of atropisomeric C-aromatic taxane derivatives. The type 2 IMDA reaction provided separable diastereomeric atropisomers of the tricyclo[9.3.1.0$^{3,8}$]pentadecane ring system.[74, 75] The conformationally locked derivatives allowed a study of the effect of conformation on reaction stereochemistry (Scheme 23). Compounds *endo*-**161** and *exo*-**161** were

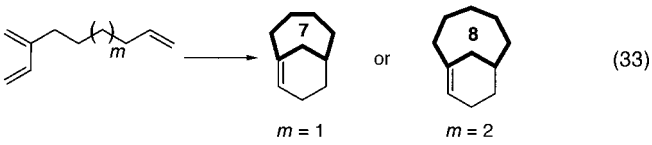



Scheme 23. Selective hydride reductions of atropisomers *endo*-**161** and *exo*-**161**.

selectively reduced with lithium aluminum hydride to afford the corresponding alcohols, *endo*-**162** and *exo*-**163**, respectively. The kinetic reduction products could be thermally equilibrated, *endo*-**162** and *exo*-**163**, with their corresponding atropisomeric counterparts, *exo*-**162** and *endo*-**163**.

### 7.6. Syntheis of Medium-Sized Rings

The most successful type 2 IMDA reactions contain four or five atoms in the tether [Eq. (33)]. These cycloadditions give rise to cycloadducts with seven- or eight-membered rings embedded in the bridged bicyclic skeleton. The medium-sized rings can be prepared in a single step from acyclic precursors. The constrained rings can then be stereoselectively elaborated. Finally, oxidative cleavage of the bridgehead alkene releases the medium-sized ring for further modification.

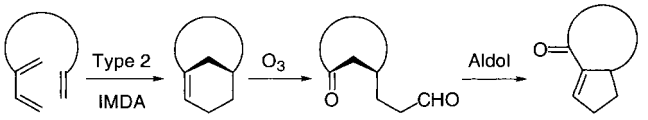



(33)

An alternative strategy for the synthesis of medium-sized rings relies on addition to the bridgehead double bond followed by ring expansion. Examples of both strategies are described in the following sections.

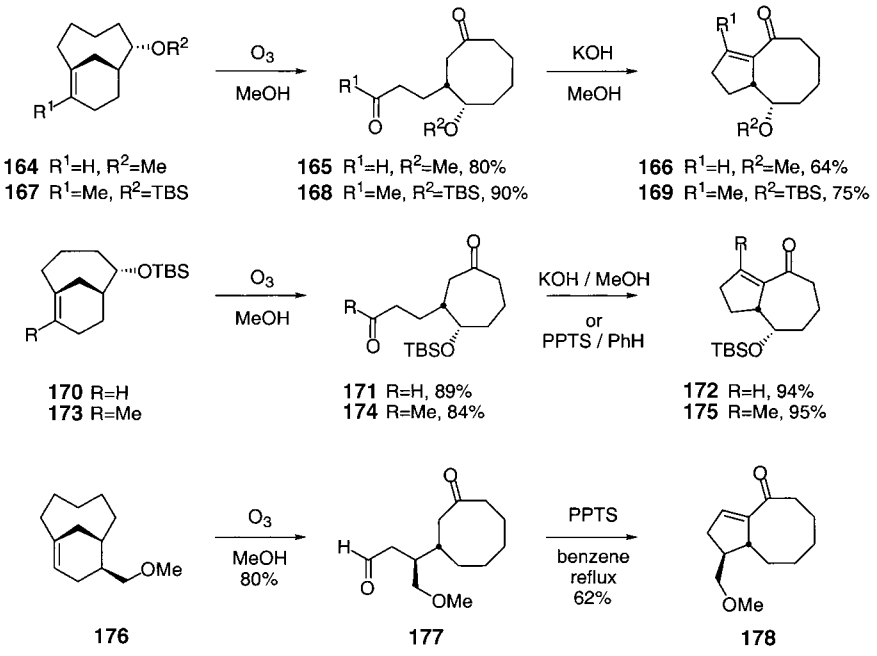
#### 7.6.1. Bridged to Fused Ring Interchange

Oxidative cleavage of the bridgehead alkene liberates the medium-sized (seven- or eight-membered) ring. The resulting 1,6-dicarbonyl compound can subsequently be converted into a fused ring sytem with five and seven or five and eight ring atoms via an aldol cyclization [Eq. (34)]. The overall process has been referred to as bridged to fused ring interchange.




(34)

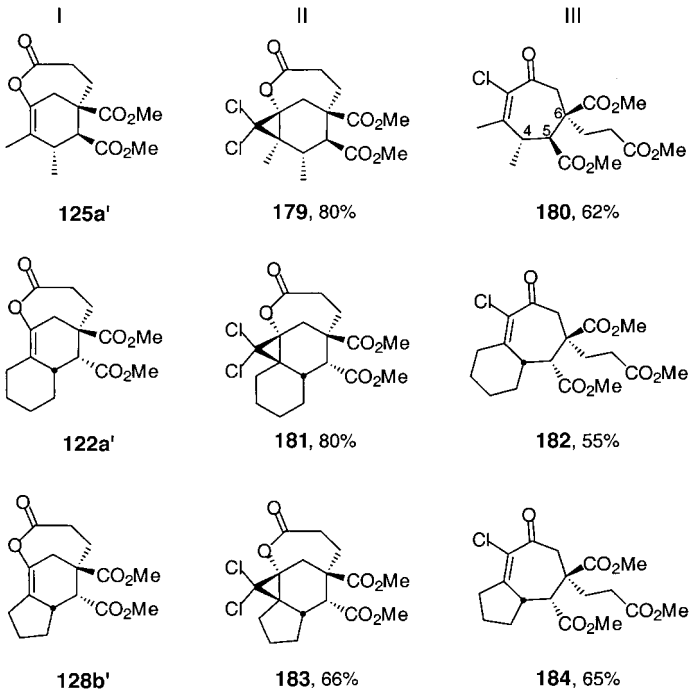
The reactions in Scheme 24 illustrate this concept.[50, 76, 77] Following cycloaddition, ozonolysis of the bridgehead double bonds proceeds in high yield to liberate medium-sized ring dicarbonyl compounds which are condensed (under basic or acidic conditions) to form fused cycloheptane and cyclooctane ring systems. This methodology has been exploited in several natural product syntheses (see Section 8).




Scheme 24. Examples for bridged to fused ring interchange. PPTS = pyridinium *para*-toluenesulfonate.

#### 7.6.2. Ring Expansion of Bridgehead Alkenes

An alternative strategy for the synthesis of medium-sized rings by an addition–ring expansion strategy was developed for the stereospecific synthesis of substituted seven-membered rings (Scheme 25).[78] The *exo* addition of dichlorocarbene ($PhHgCBrCl_2$, PhH, reflux) to bridgehead enol lactones **125a′**, **122a′**, and **128b′** produces bridgehead dichlorocyclopropanes **179**, **181**, and **183**, respectively. Under basic conditions (MeOH, $Na_2CO_3$) the lactone is cleaved. The inter-




Scheme 25. Ring expansion in bridgehead enol lactones (I) to cycloheptenones (III) via cyclopropane intermediates (II).

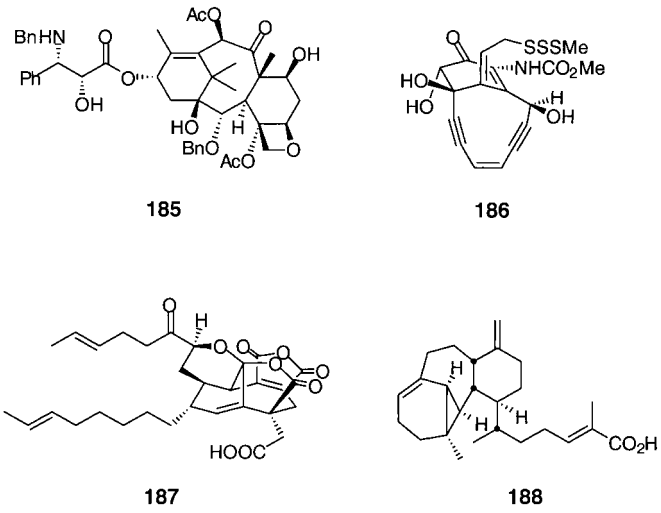
mediate dichlorocyclopropanol undergoes internal C–C bond cleavage with concomitant expulsion of chloride ion resulting in the formation of cycloheptenones **180**, **182**, and **184**, respectively. The cleavage of the internal C–C bond provides a stereoselective route to seven-membered chloroenones. The relative configuration of stereocenters 4, 5, and 6 are established in the cycloaddition step.

## 8. Applications in Natural Product Synthesis

The assembly of a bridged bicyclic skeleton in a single step from an acyclic precursor is a powerful synthetic tool. The direct application of this reaction as a key step in the synthesis of naturally occurring bridged bicyclic compounds is a confirmation of its practical utility. In addition to direct methods for the construction of naturally occurring bridged bicyclic rings, the regio- and stereocontrol of the type 2 IMDA has also been exploited in the synthesis of a number of natural products (i.e. adrenosterone, a *Plocamium* monoterpene, and ledol). Examples of both applications are given in the sections below.

### 8.1. Direct Applications

A number of biologically important natural products contain bridged bicyclic rings. Representative examples are the Taxol (**185**),[79] esperamicin $A_1$ aglycone (**186**),[80] CP-263,114 (**187**),[81] and cerorubenic acid (**188**)[82] families of natural products (Scheme 26). The synthesis of advanced



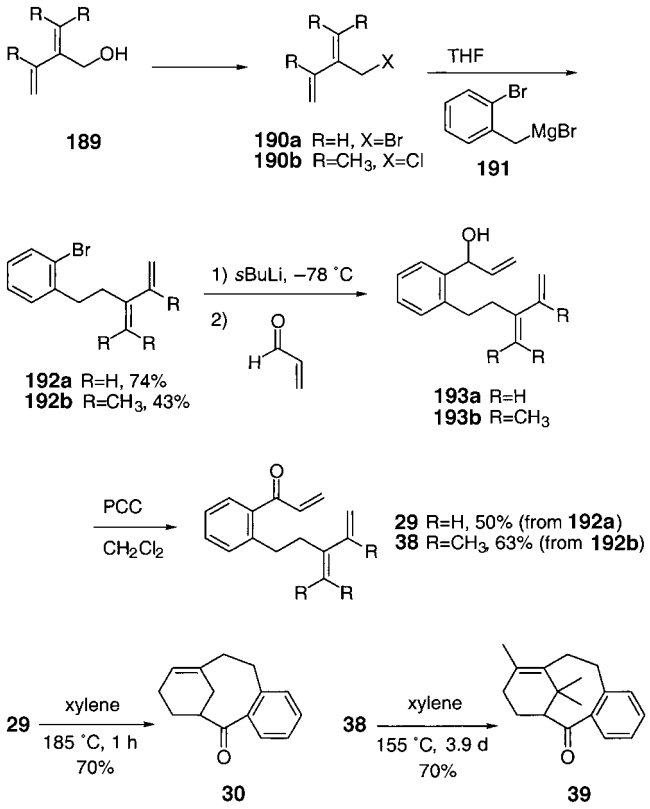

Scheme 26. Representative examples of complex natural products with bridgehead double bonds.

analogues of **185** and **186**[83] and the total synthesis of **187**[84] have used the type 2 IMDA reaction as the key step in the construction of the bridged bicyclic skeleton.

#### *8.1.1. Taxanes*

Taxol, the most celebrated member of the taxane family of natural products, was approved for the treatment of ovarian cancer in 1992.[79, 85] Prior to solving the problem of limited availability, there was an enormous synthetic effort toward the total synthesis of Taxol.[79] Embedded in its complex structural core is a bridged tricyclo[9.3.1.$0^{3,8}$]pentadecene ring system with 11 stereocenters and a variety of differentially protected oxygen substituents.

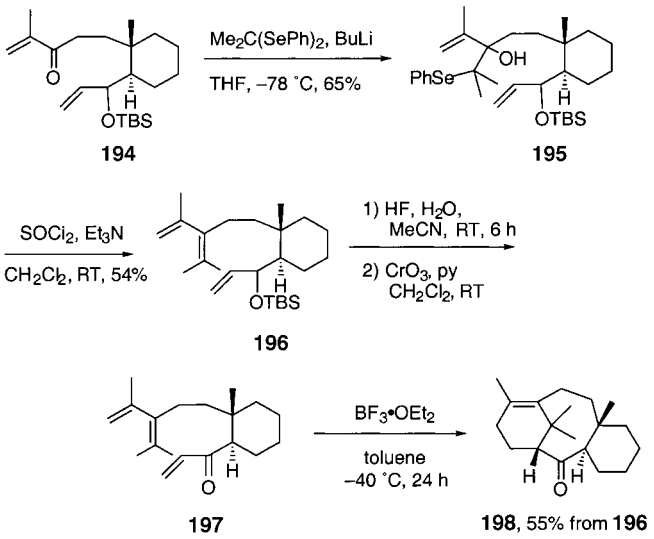
The type 2 IMDA reaction was employed in one of the first entries into this natural product, a C-aromatic taxane skeleton.[38] Cycloaddition precursors **29** and **38** were synthesized by reaction of Grignard reagent **191**, prepared directly from the dibromide, with butadiene derivatives **190a** and **190b**, respectively (Scheme 27). The dienophile moiety of **29**




Scheme 27. Our synthesis of the C-aromatic taxane cores **30** and **39**.

and **38** was introduced in two steps from **192a, b**. Metalation followed by addition of acrolein afforded alcohols **193a, b**, which upon oxidation yielded trienones **29** and **38**. Diels–Alder precursor **29** underwent thermally induced type 2 intramolecular Diels–Alder reaction to produce tricycle **30**. A particular concern in the application of this methodology to the taxane ring system was the use of a methylated diene. These concerns were assuaged with the successful cycloaddition of **38** in xylenes at 155 °C to produce the fully methylated A ring of taxane derivative **39**.

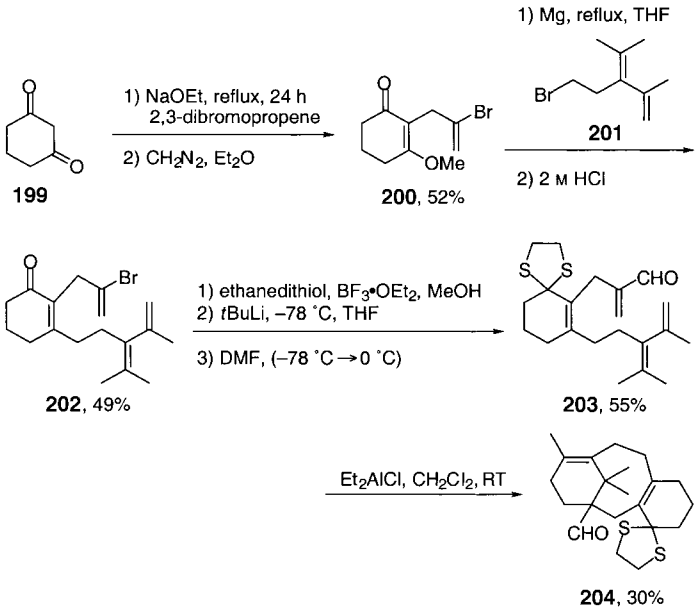
Jenkins and Bonnert were able to assemble the taxane core with the C-19 methyl substituent and the natural stereochemistry at C-1 and C-8 in a bridged-fused taxane tricycle containing a saturated C-ring (Scheme 28).[86] The synthesis of triene **197** used an alternative route to the 2-substituted diene. A selenide reagent was used to introduce the geminal methyl groups at C-17 and C-18 (taxane numbering) of the diene




Scheme 28. Synthesis of taxane core **198** according to Jenkins and Bonnert.

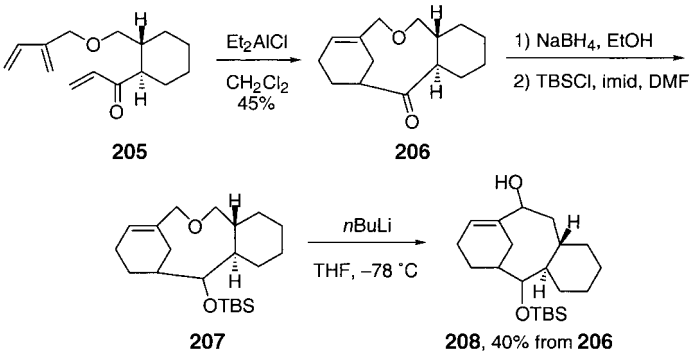
moiety. The synthesis involved the addition of $LiCMe_2SePh$ to enone **194** to produced hydroxy selenide **195**. Thionyl chloride assisted elimination of hydroxy selenide **195** gave desired triene **196**, which was deprotected and oxidized to give enone **197**. Treatment of **197** with a Lewis acid catalyst brought about the intramolecular Diels – Alder reaction to yield the taxane derivative **198**.

A related approach for the synthesis of an unsaturated C-ring analogue involved an internally activated dienophile (Scheme 29). Cycloaddition precursor **203** was prepared from 1,3-cyclohexadione (**199**).[87] Alkylation with 2,3-dibromopropene followed by conversion to the vinylogous ester provided compound **200**. Treatment of **200** with the Grignard reagent of diene **201** followed by hydrolysis provided vinyl bromide **202**. Protection of the ketone and formylation of the vinyl bromide gave cycloaddition precursor **203**. Lewis acid catalyzed cyclization of **203** produced the taxane dithiane derivative **204**. The latent $\alpha,\beta$-unsaturation in the C-ring was designed to serve as a handle for incorporation of the C-18 methyl group.



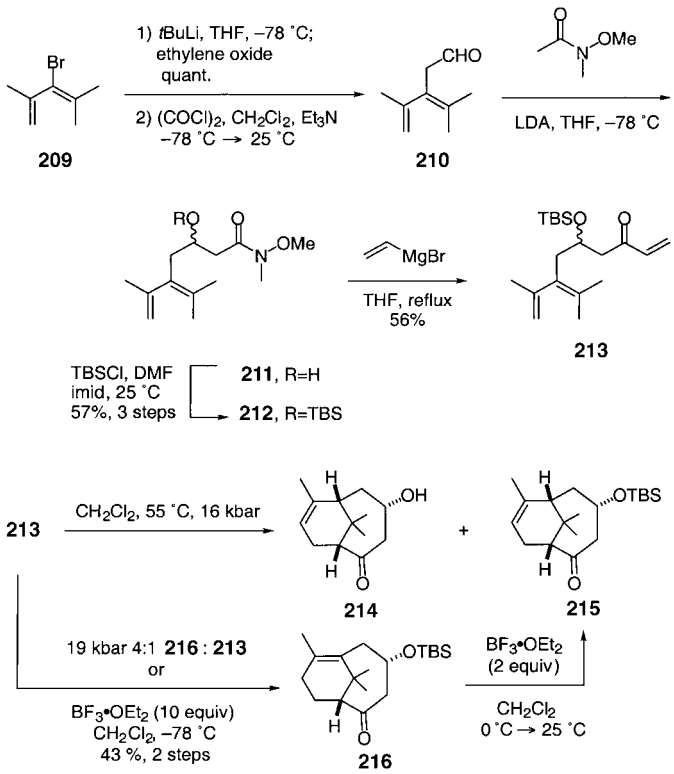

Scheme 29. Our synthesis of saturated C-ring taxane core **204**.

Yadav and Ravishankar used a combination of the type 2 IMDA reaction and a Wittig rearrangement to construct the taxane core (Scheme 30).[88] Lewis acid catalyzed cycloaddition of enone **205** gave tricyclic adduct **206**. Reduction of the carbonyl group of **206** and protection of the resultant alcohol provided silyl ether **207**. Wittig rearrangement of ether **207** produced taxane core **208**.




Scheme 30. Synthesis of taxane core **208** according to Yadav and Ravishankar. imid. = imidazole.

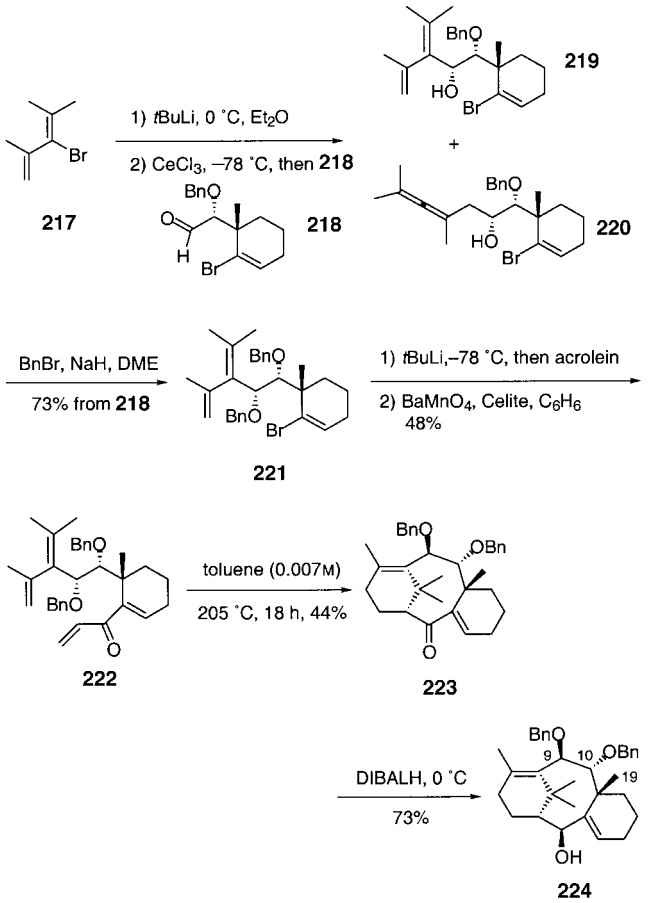
During the development of an intramolecular Diels – Alder ring-expansion approach to taxinine, Phillips and Abell were able to construct a bicyclo[4.2.1] ring system under conditions of high pressure (Scheme 31). Synthesis of cycloaddition




Scheme 31. Phillips and Abell's s high-pressure type 2 IMDA reactions.

precursor **213** was initiated with the conversion of bromide **209** to the vinyllithium species.[89] Addition of ethylene oxide gave the alcohol, which was oxidized to aldehyde **210** under Swern conditions. Introduction of the Weinreb amide moiety by aldol addition gave alcohol **211**. Protection of alcohol **211** followed by Grignard addition produced enone **213**. Subjecting **213** to high pressure (16 kbar) resulted in the formation of cycloadducts **214** and **215**, products arising from cycloaddition followed by double bond isomerization. Higher pressure (19 kbar) provided a 4:1 ratio of bridgehead alkene **216** to enone **213**. Alternatively, treatment of enone **213** with excess $BF_3 \cdot OEt_2$ also gave type 2 IMDA product **216**, which could also be reacted further to give **215**

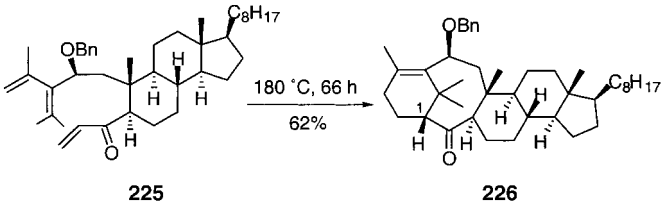
Efforts to incorporate functionality at C-9 and C-10 and the pivotal C-19 angular methyl group have been addressed by several groups. One example was a thermally induced type 2 intramolecular Diels–Alder reaction of dienone **222** (Scheme 32).[90] The synthesis of **222** started from aldehyde




Scheme 32. Our synthesis of the functionalized taxane core **224**. DME = dimethoxyethane, Bn = benzyl.

**218** which was treated with the cerium reagent derived from bromodiene **217** to produce a 4:1 mixture of diene alcohol **219** and allenyl alcohol **220**. Benzylation of the alcohols allowed isolation of bisbenzyl ether **221**. Metal–halogen exchange of bromide **221** followed by treatment with acrolein afforded a mixture of secondary alcohols, which were subsequently oxidized to enone **222**. Intermediate **222** underwent thermally induced cyclization to produce tricyclic cycloadduct **223**, which was reduced to alcohol **224**. The structure of **224**, which was established by X-ray crystallography, revealed the cycloaddition of triene **222** afforded the C-1 *epi*-taxinine cycloadduct **223**. The reversal in π-facial selectivity was attributed to the unsaturation at C-3 and C-4 in Diels–Alder precursor **222**. Although the cycloaddition gave the incorrect relative stereochemistry at C-1, the reaction achieved the taxusin pattern of oxygenation at C-9 and C-10.

In efforts to explore the effects of substituents at C-9 and C-10 on the π-facial selectivity of the Diels–Alder reaction, Park et al. used a steroid-platform on which to perform the type 2 IMDA cycloaddition.[91] This work resulted in a successful intramolecular Diels–Alder reaction leading to a Baccatin III-steroid hybrid [Eq. (35)]. Thermally induced

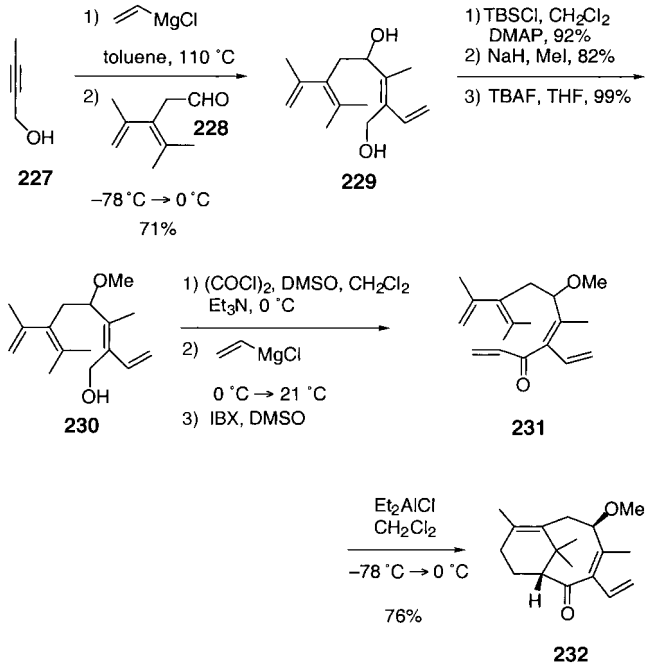



(35)

cyclization of **225** provided ketone **226**, which has the natural (C-1-$\beta$) configuration. Under the reaction conditions, elimination of the allylic alcohol at C-10 was found to compete with the cycloaddition.

Recently advanced taxusin intermediate **76** was synthesized by the type 2 IMDA reaction (see Scheme 7).[32] In addition to the fully methylated taxane core, cycloadduct **76** contains the natural relative configurations about C-1, C-3, C-8, C-9, and C-10.

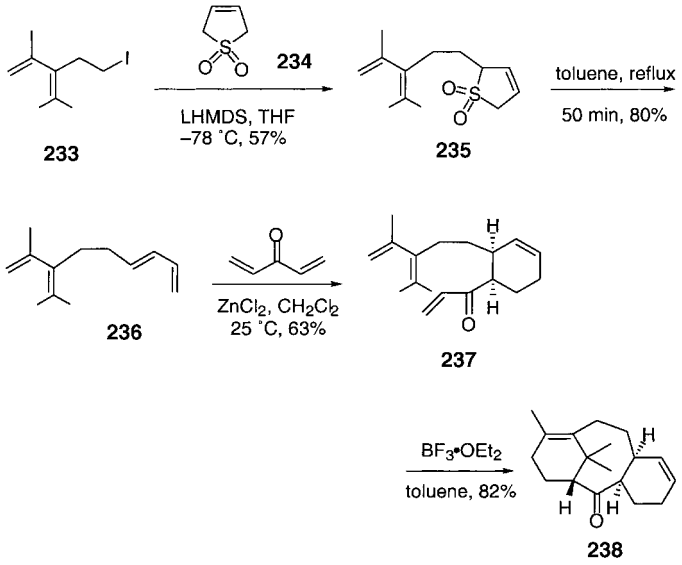
Fallis et al. were able to construct the AB rings of the taxane system using the type 2 IMDA reaction as the key step (Scheme 33).[92] This synthesis began with the addition of




Scheme 33. Synthesis of taxane bicycle **232** according to Fallis et al. IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide (or *o*-iodoxybenzoic acid).

vinylmagnesium chloride to 2-butynol (**227**). The resultant magnesium complex was treated with aldehyde **228** to afford the tetraenediol **229**. The secondary alcohol was protected selectively as its methyl ether in three steps to give allylic ether **230**. Swern oxidation followed by vinyl Grignard addition and oxidation provided Diels–Alder precursor **231**. Subsequent Lewis acid catalyzed type 2 IMDA cycloaddition yielded the taxane core **232** as a single diastereomer. The origin of the diastereoselectivity arises from chelation of the Lewis acid to the methyl ether and carbonyl oxgen atoms during cycloaddition.

Winkler and co-workers have developed a tandem Diels–Alder approach to the taxane core (Scheme 34).[93, 94] Reaction of the monoanion of the sulfone **234** with iodide **233**

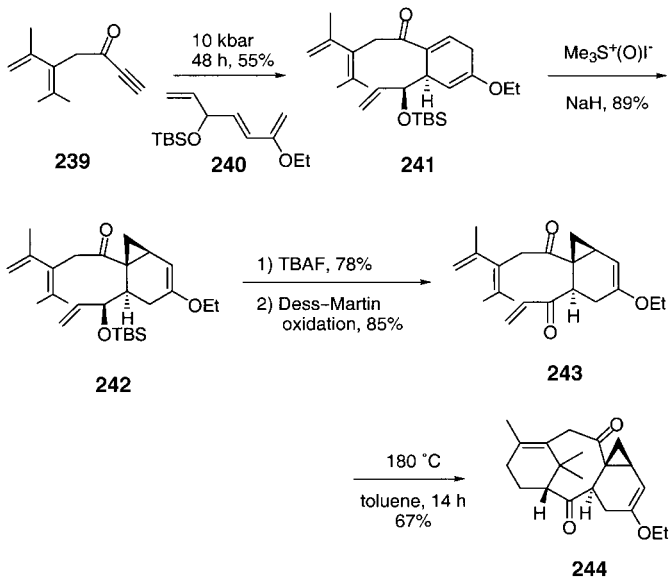



Scheme 34. Synthesis of taxane core **238** according to Winkler et al.

produced sulfone **235**. Extrusion of $SO_2$ from **235** (see Section 3.2.1) resulted in the formation of tetraene **236**. The choice of Lewis acid was important to stage the sequential Diels–Alder reactions (**236** → **238**). The C-ring was formed in a $ZnCl_2$-catalyzed intermolecular Diels–Alder reaction. This was followed by formation of the A-ring using $BF_3 \cdot OEt_2$. Although the core has limited substitution, this strategy provided a rapid entry into the tricyclic taxane framework. The synthesis plays upon the inherent reactivity of the two sets of dienes in tetraene **236**, where the difference in reactivity of the dienes allows the stepwise cycloadditions. Interestingly, neither Lewis acid was capable of catalyzing both Diels–Alder reactions in a one-pot transformation.

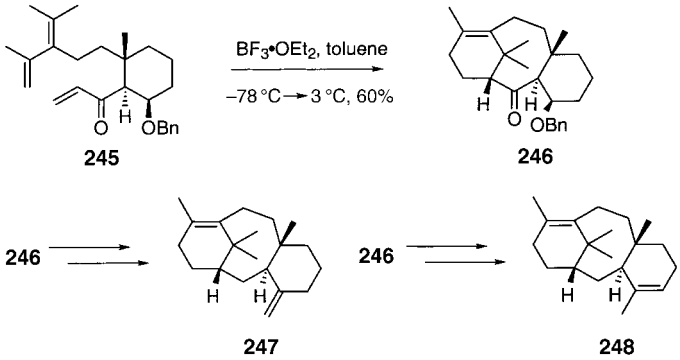
Winkler et al. were able to use a variation of the tandem Diels–Alder methodology to synthesize cyclopropyl taxane derivative **244** (Scheme 35).[95] Cycloaddition of alkyne **239** and triene **240** led to the formation of 1,4-cyclohexadiene **241**. Cyclopropanation of enone **241** with concomitant $\Delta^{4,5}$ alkene migration provided bicycle **242**. Desilylation and oxidation provided intramolecular Diels–Alder substrate **243**, which upon heating gave tetracycle **244**.

The type 2 IMDA methodology has also been employed for the construction of related compounds in the taxoid family.




Scheme 35. Synthesis of cyclopropyl taxane derivative **244** according to Winkler et al.

Williams and Rubenstein reported the synthesis of putative biosynthetic Taxol intermediates taxa-4(20), 11-diene **247** and taxa-4, 11-diene **248** (Scheme 36).[96] Lewis acid catalyzed type 2 IMDA cyclization provided tricyclic compound **246**, which was elaborated to both **247** and **248**.

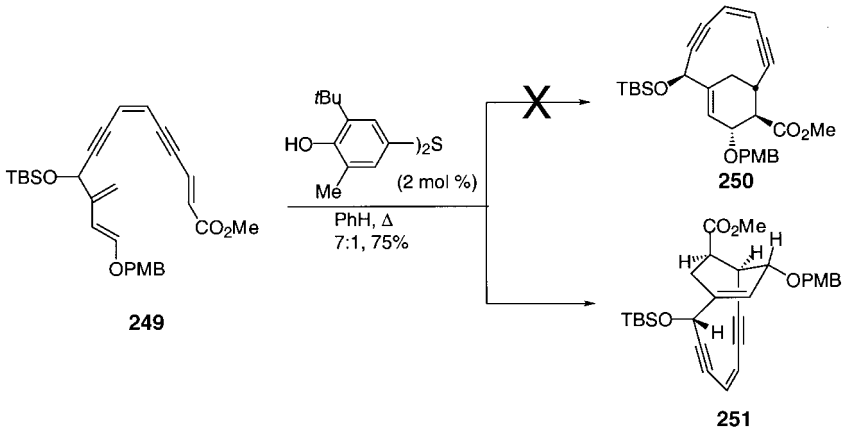



Scheme 36. Synthesis of Taxol biosynthetic intermediates **247** and **248** according to Williams and Rubenstein.

### *8.1.2. Esperamicin*

The esperamicin/calicheamicin core contains a bicyclo-[7.3.1]tridecanone bridged core (**186** in Scheme 26). Common to the esperamicin/calicheamicin natural products is the enediyne structural unit that imparts the unique biological activity of this class of antitumor agents. The enediyne unit is incorporated across the cyclohexene ring in a 1,3-disposition. This was recognized as a structural feature that could be synthesized by a type 2 IMDA reaction.

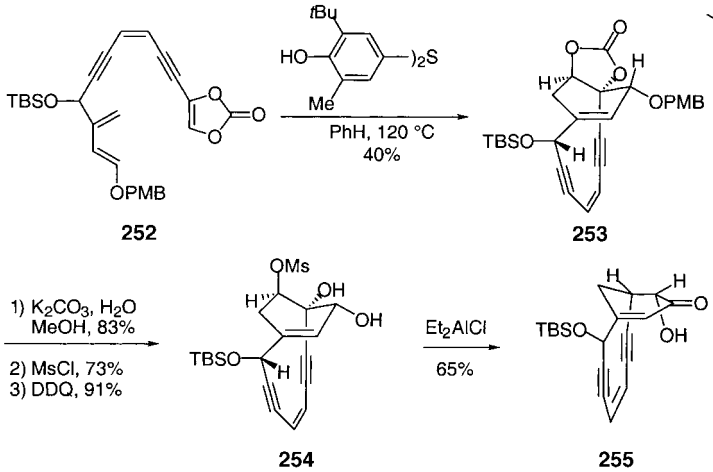
Entry into the esperamicin/calichemicin core was first attempted by the type 2 IMDA reaction of enediyne **249** (Scheme 37).[83] Inherent in the cycloaddition of compound **249** was the issue of the regiochemistry of the cycloaddition. The initial report concluded the cycloaddition of **249** afforded **250**. Interestingly, a reinvestigation of this reaction and the




Scheme 37. Type 2 IMDA cycloaddition of polyenyne **249**. PMB = *para*-methylbenzoyl.

products resulting from subsequent transformations of the putative cycloadduct revealed the original regiochemical assignment (*meta*) was incorrect, the product was reassigned to the para regioisomer **251**.[83c]

With a somewhat revised synthetic plan, Schreiber et al. developed a strategy to isomerize the initially formed 1,4-regioisomer to the required 1,3-regioisomer of the esperamicin/calichemicin natural products (Scheme 38).[83a] Diels–Alder precursor **252** was heated in the presence of a radical inhibitor to induce the intramolecular cycloaddition that afforded 1,4-regioisomer **253**. Saponification of the carbonate followed by mesylation of the secondary alcohol and debenzylation afforded the pinacol substrate **254**. The isomeric skeleton obtained from the cycloaddition was shown to undergo a Tsuchihashi–pinacol rearrangement with concomitant and diastereoselective acyloin shift to provide the natural ring system. Treatment of **254** with six equivalents of diethylaluminum chloride delivered the Tsuchihashi–pinacol adduct **255** in 65% yield. Confirmation of the structure was obtained by X-ray crystallographic analysis of a derivative of **255**.

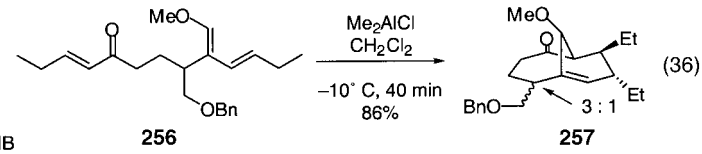



Scheme 38. Synthesis of esperamicin core **255** according to Schreiber et al. Ms = methanesulfonyl, DDQ = dichlorodicyanobenzoquinone.

This sequence of reactions demonstrates the range of sensitive functionality that can be successfully carried through the cycloaddition reaction.

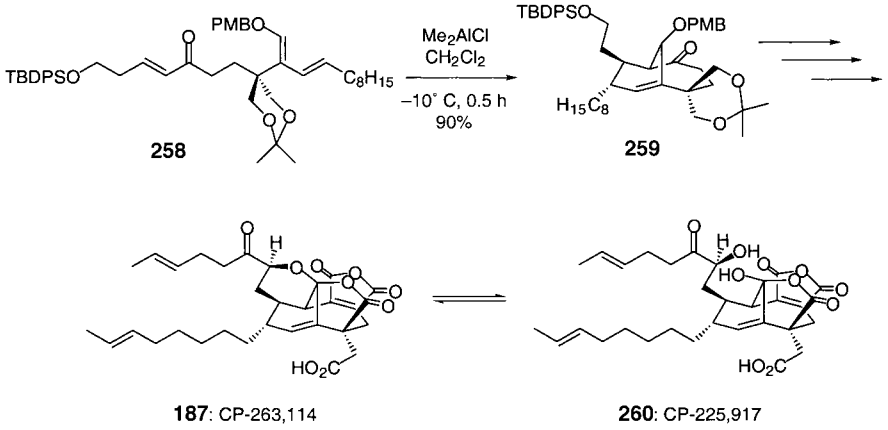
### *8.1.3. CP-263,114 and CP-225,917*

The CP family of natural products has received considerable attention based on their biological activity as leads for cholesterol-lowering and anticancer agents. The core of the CP molecules consists of a bicyclo[4.3.1]decene ring system. A number of syntheses of this ring system employing the type 2 IMDA reaction had been reported earlier,[4, 50] providing a strong precedent for its use in the CP series. Nicolaou et al. reported a synthesis of the bicyclic CP core starting from a type 2 IMDA reaction of triene **256** [Eq. (36)].[97] Lewis acid induced cyclization of IMDA precursor **256** afforded ketone **257** as a mixture of diastereomers. The configuration of the major diastereomer was not determined.



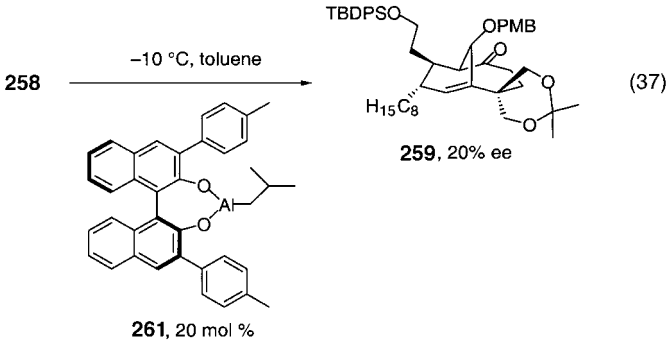

(36)

Nicolaou and co-workers employed a more highly elaborated Diels–Alder precursor (**258**) in the total syntheses of racemic CP-225,917 (**260**) and CP-263,114 (**187**) (Scheme 39).[84a,b] Lewis acid catalyzed intramolecular Diels–Alder cycloaddition of **258** provided bridged bicycle **259**. Following a series of functional group manipulations of the cycloadduct, bicycle **259** was converted to **187** and **260**. The Nicolaou group utilized this strategy for the development of an enantioselective synthesis of both CP compounds.[98] A variety of chiral



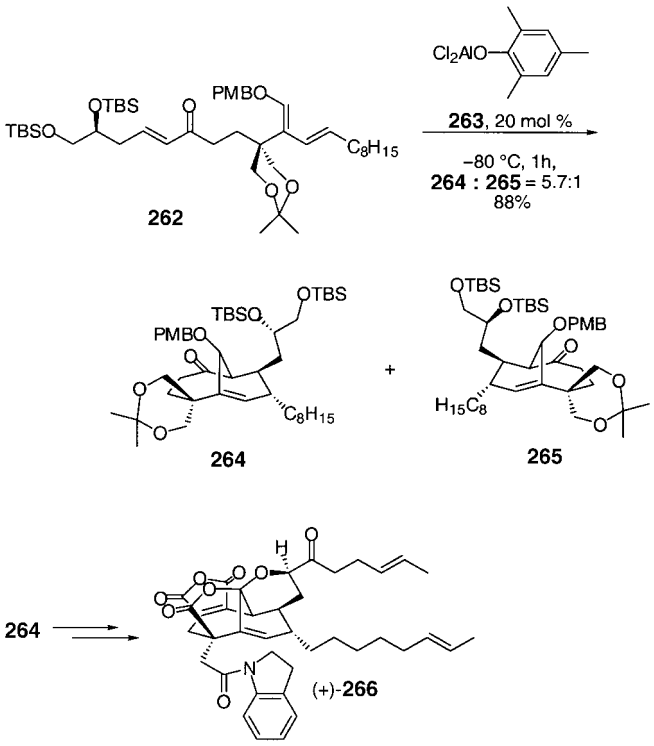

Scheme 39. Synthesis of CP molecules **187** and **260** according to Nicolaou et al.

Lewis acids were employed for the cycloaddition of prochiral ketone **258**. Catalyst screening identified the binol aluminum derivative **261** as the optimal inducer of asymmetry, although the best enantiomeric excess was a disappointing 20% [Eq. (37)].



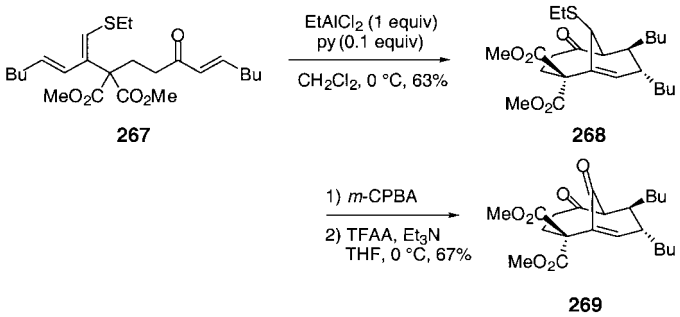

(37)

In efforts to determine the absolute configuration of the natural product, chiral precursor **262** was prepared from (*R*)-glycidol.[98] Treatment of **262** with 20 mol% of catalyst **263** at −80 °C in toluene led to a 5.7:1 mixture (70% *de*) of diastereomeric cycloadducts **264** and **265** in 88% yield (Scheme 40). Subsequent transformation of major diastereomer **264** to (+)-**266** allowed direct comparison with (−)-**266**, prepared from a natural sample of (−)-CP-263,114. This sequence established the absolute configuration of (−)-CP-263,114 and (+)-CP-225,917. The synthetic product (+)-**266** was processed to give *ent*-**187** and ent-**260**, thus establishing an asymmetric route to the CP molecules.

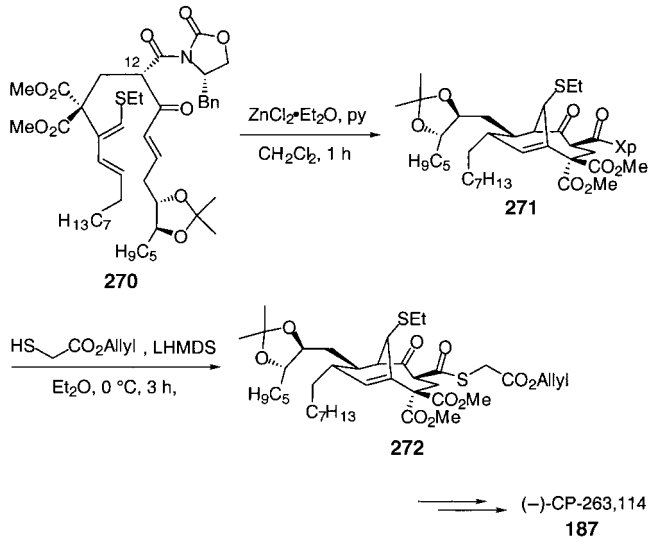



Scheme 40. Diastereoselective cycloaddition and determination of the absolute configuration of CP-263,114.

Fukuyama et al. also reported the synthesis of the CP core by a type 2 IMDA reaction. In the initial report the synthesis of bicyclic ketone **269**, a molecule that possesses many of the functional groups and stereogenic centers required for the construction of CP-225,917 and CP-263,114, was described (Scheme 41).[99] The core was synthesized by treatment of ketone **267** with $EtAlCl_2$ to give bridgehead alkene **268** in 63% yield. The structure of cycloadduct **268** was confirmed by X-ray crystallography. Elaboration of **268** to bicyclic diketone **269** was accomplished by sulfur oxidation followed by a Pummerer rearrangement. Fukuyama et al. subsequently reported the asymmetric total synthesis of (−)-CP-263,114 (**187**) in which they utilized a type 2 IMDA reaction to construct the bicyclo[4.3.1]decene ring system (Scheme 42).[84c] Diastereoselective cycloaddition of IMDA precursor **270** afforded cycloadduct **271** which was treated with lithium thiolate to produce thio ester **272** in 53% for the two steps . The diastereoselectivity of the cycloaddition is controlled by the C12 substituent.




Scheme 41. Synthesis of CP core **269** according to Fukuyama et al.




Scheme 42. Synthesis of (−)-CP-263,114 (**187**) according to Fukuyama et al.

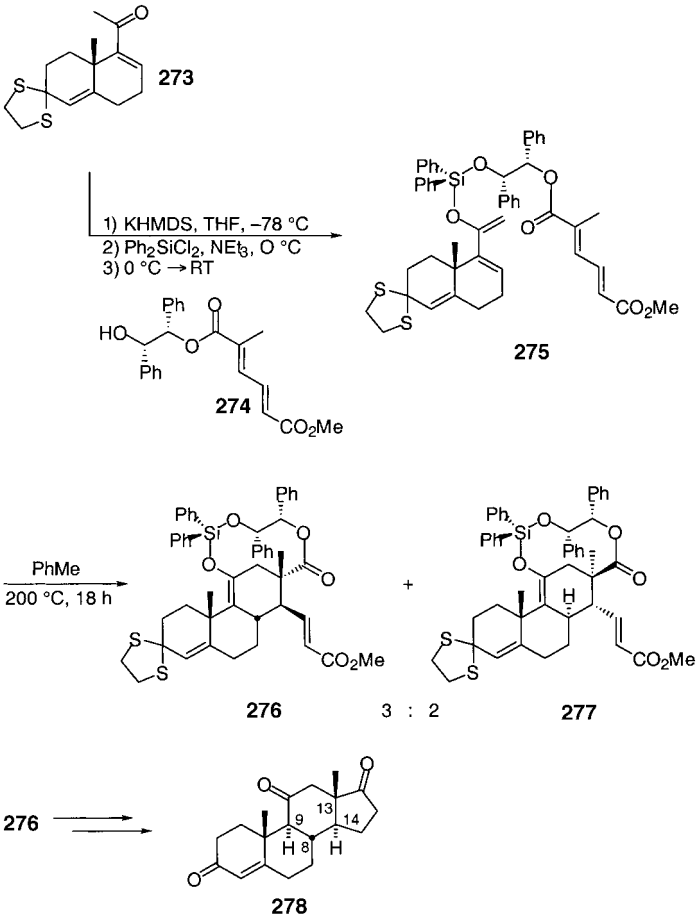
The total syntheses of CP-263,114 and CP-225,917 were important synthetic achievements. The structural complexity contained within a small, compact natural product reveals the utility of type 2 IMDA methodology in natural product synthesis.

### 8.2. Indirect Applications of the Type 2 IMDA Reaction in Natural Product Synthesis: Utilization of the Stereochemical and Regiochemical Control Elements

The direct application of the type 2 IMDA reaction to construct the bicyclic cores of naturally occurring substances will continue to expand the importance of this reaction. Perhaps as important however, is the ability of this reaction to control the stereo- and regiochemistry of the Diels–Alder cycloaddition. The use of this strategy provides new paradigms for the analysis of synthetic problems and enhances the opportunity to draw upon the Diels–Alder reaction for the synthesis of complex natural product targets.

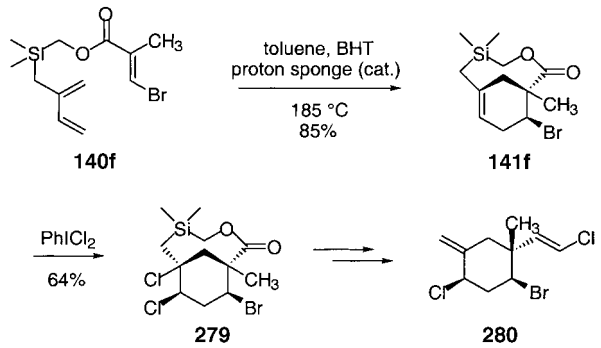
#### *8.2.1. Disposable Tethers*

The enantiospecific synthesis of the adrenalcorticosteroid (+)-adrenosterone was accomplished by using disposable tether methodology.[100] Building upon the Wieland–Miescher ketone, it was envisioned that a type 2 IMDA reaction could be used to construct the C-ring and establish the four stereocenters in the BCD ring junctures (C-8, C-9, C-13, and C-14) of the steroid. This step required reversal of the "normal" regiochemical outcome of the bimolecular cycloaddition. This requirement was realized by using a type 2 IMDA reaction that employed a chiral disposable silaacetal tether uniting the diene and dienophile. Enone **273** was kinetically deprotonated, trapped as the (chlorodiphenyl)silyl dienyl ether, and quenched with (−)-hydrobenzoin ester **274** to give silaacetal **275** (Scheme 43). Silaacetal **275** was heated to 200 °C in toluene for 18 h, which provided a 3:2 mixture of **276**:**277** in 90% yield (based on **273**, 45% conversion). The major cycloadduct **276** arose from $\alpha$-approach of the dienophile to provide the correct stereochemical relationship between the C-10 methyl and the stereocenters at the BCD ring junctures. Cycloadduct **276** was carried on to complete the synthesis of (+)-adrenosterone (**278**).




Scheme 43. Our enantioselective synthesis of (+)-adrenosterone (**278**).

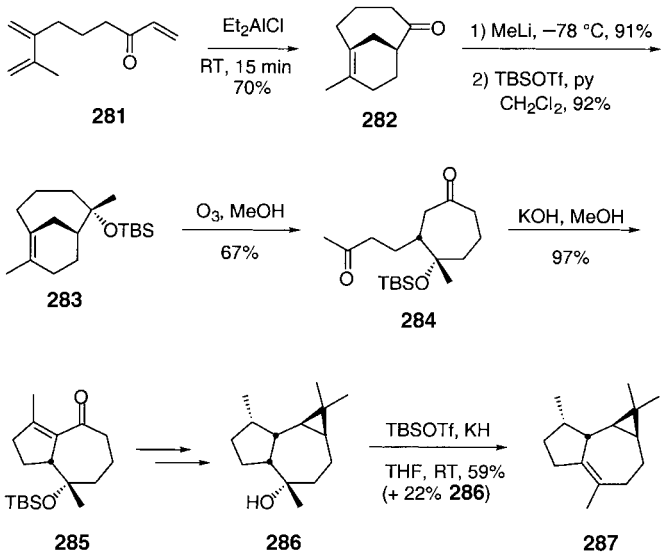
A variety of polyhalogenated monoterpene natural products have been isolated from the red marine algae *Placamium* sp.[101] The quaternary center and complex halogenation pattern of these compounds represent a significant synthetic challenge. Disposable tether methodology was employed in the total synthesis of *Placamium* monoterpene natural product **280** (Scheme 44).[102] The type 2 IMDA cycloaddition of **140 f** provides complete regiochemical control to deliver cycloadduct **141 f**. Bridgehead allylsilane **141 f** was then *exo*-chlorinated with (dichloroiodo)benzene to give the polyhalogenated cyclohexane **279**. This intermediate was subsequently elaborated in three steps to the polyhalogenated *Placamium* monoterpene natural product **280**.




Scheme 44. Our synthesis of *Placamium* monoterpene **280**.

#### *8.2.2. An Application of Bridged to Fused Ring Interchange*

The aromadendranes are a class of sesquiterpene natural products which are characterized by a dimethylcyclopropane unit fused to a hydroazulene core.[103] Ledol is a representative of this class and shows antifungal activity against *Coriolus renatus*.[104] The type 2 IMDA reaction has been shown to be an efficient method for the synthesis of medium rings. Setting stereochemistry in medium rings can be difficult due to their conformational flexibility.[68] An attractive feature of the type 2 IMDA methodology presented below is the stereochemistry of the medium ring can be set while taking advantage of the rigidity of the bicyclic intermediate. Capitalizing on this feature, we reported total syntheses of ledol and ledene.[50, 77] The seven-membered ring in ledol was formed from the type 2 IMDA cycloaddition. The Lewis acid catalyzed type 2 IMDA cycloaddition of triene **281** proceeded to give bridged bicycle **282** in 70% yield (Scheme 45). Stereoselective functional group manipulation of the bicyclo[*n*.3.1] ring system followed to establish the relative stereochemistry. Treatment of ketone **282** with MeLi afforded




Scheme 45. Our synthesis of ledol (**286**) and ledene (**287**).

the corresponding alcohol with complete stereoselection in 91% yield. After protection of the alcohol, the resulting bridgehead alkene **283** was subjected to bridged to fused ring interchange. This is accomplished first by ozonolysis to afford dicarbonyl **284** and then aldol cyclization to produce the fused ring system **285** required for the synthesis of ledol (**286**). Subsequently, ledol was successfully dehydrated to ledene (**287**).

## 9. Summary and Outlook

In a relatively short time, anti-Bredt alkenes have evolved from a class of chemical oddities to species that play a key role in the synthesis of complex natural products. The type 2 IMDA reaction, a simple intramolecular variant of the venerable Diels–Alder cycloaddition, provides a direct route to this family of compounds in a single step from an acyclic precursor. The scope of the type 2 IMDA reaction is impressive. Products range from some of the most highly strained isolable anti-Bredt alkenes to the core of Taxol. The regiochemical and stereochemical bias of the intramolecular cycloaddition have produced strategies for selecting a single isomeric product from the Diels–Alder reaction. The utility of this innovation was broadened by the development of disposable tethers, temporary connectors of the diene and dienophile that capitalized on the reactions selectivity. In some cases, the regiochemistry of the type 2 IMDA cycloadduct is *reversed* from the bimolecular counterpart. This *pericyclic umpolung* creates new strategies for planning organic syntheses. In more recent developments, the type 2 IMDA reaction has served a key step in the construction of complex polycyclic rings that make up the core of a number of important natural products. It is certain that the utilization of the type 2 IMDA reaction in organic synthesis will continue to grow. One important area for future development is the heteroatom variant of the reaction to afford direct synthetic entries into medium ring heterocycles. The regiochemical and stereochemical control of the type 2 IMDA reaction is a particularly attractive feature of this approach.

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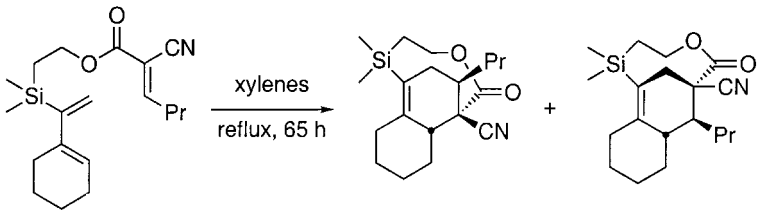


A′ B′, 25% C′, 6%


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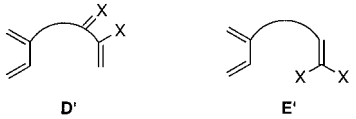
[51] The term internally activated refers to dienophile activation on the tether side of the dienophile (**D′**). In contrast, externally activated refers dienophile activation exocyclic to the tether (**E′**).


D′ E′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