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Total Synthesis

Strained Alkenes in Natural Product Synthesis

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distortion · natural products · strain release · strained alkenes · total synthesis

Strained molecules continue to challenge the ingenuity of chemists as their high-energy bonds serve as fuel for the promotion of complex synthetic transformations. Developments in this area have resulted in the recent emergence of strained alkenes as intermediates in natural product synthesis. This Minireview highlights these recent advances along with current developments toward understanding the unique reactivity of strained alkenes.

1. Introduction

The enhanced reactivity of highly strained molecules has captivated the scientific community for over a century. Immense interest in these unique molecules arose after Adolf von Baeyer correctly assumed in 1885 that the perceived deficiency, at the time, of three- and four-membered rings in nature could be attributed to deformed ∡CCC bond angles and instability.[1] After von Baeyer's pronouncement, many chemists yearned to understand the relationship between strain, stability, and reactivity.[2] The early 1900s brought considerable interest in understanding this special relationship within strained alkenes. In 1922, Dem'yanov and Doyarenko reported the first synthesis of cyclopropene, the simplest strained olefin, by thermal decomposition (300 °C) of trimethylcyclopropylammonium hydroxide.[3] They found that, like other distorted alkenes, cyclopropene possesses a short lifetime at low temperature and requires trapping for further structural characterization. As methods employing "milder" reaction conditions developed swiftly, chemists began synthesizing numerous strained alkenes with diverse architectures.[4] Many of these strained alkenes exhibit increased reactivity in comparison to their "strain-free" counterparts. For example, Danishefsky and co-workers recently reported that an unsubstituted cyclobutenone participates in a facile Diels–Alder cycloaddition with cyclopentadiene at room temperature, whereas the reaction with cyclopentenone affords only a minimal amount of product after heating at 150 °C for 36 hours.[5]

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Multiple factors influence this increased reactivity, including angle compression and twisting/pyramidalization of the alkene π-bond. Angle strain results from incorporating one or more trigonal centers within a molecule, which cause bond-angle deviations from the ideal 120°. Conversely, twisting and pyramidalization affects the π-orbital framework by distorting the overlapping p-orbitals out of co-planarity (Figure 1). Electron diffraction shows an example of this

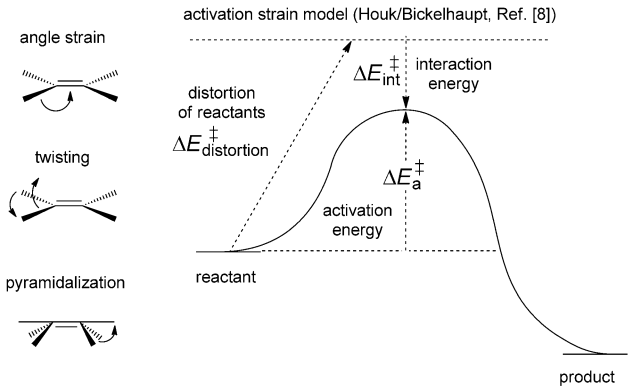
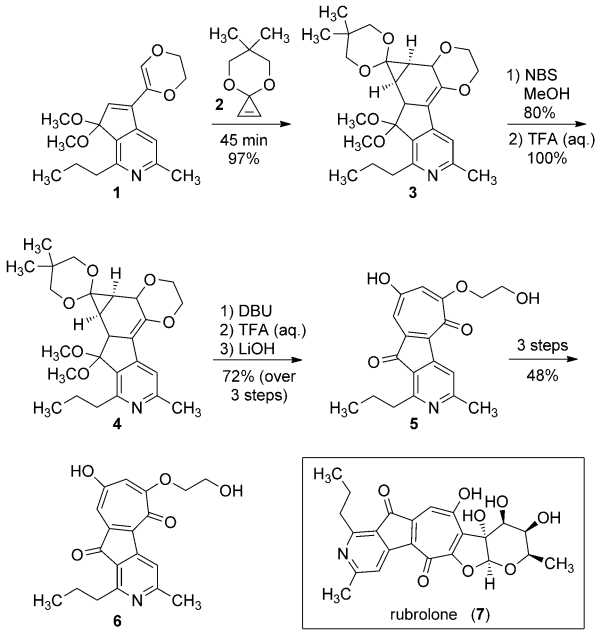


Figure 1. Distortion of alkene π-bond causes increased reactivity.

out-of-plane distortion in the highly strained *trans*-cyclooctene as the π-bond is twisted 44° from planarity.[6] The weaker alkene bond consequently raises the HOMO energy of the molecule, thus minimizing its HOMO–LUMO gap and activation energy. In conjunction with increasing HOMO energy, previous schools of thought have also argued that the favorable $sp^2 \rightarrow sp^3$ rehybridization, formally called "strain release", in the transition state accounts for the major rate enhancements observed with torsionally distorted alkenes.[7] However, recent evidence provided by the groups of Houk and Bickelhaupt[8] suggests that the lower activation energy

correlates most accurately with distortion/interaction energy (Figure 1). The distortion energy represents the deformation of the reactants required for an optimal transition-state geometry, whereas the interaction energy encompasses stabilizing electrostatic, charge-transfer, and repulsion interactions between approaching reactants. Therefore, the groups of Houk and Bickelhaupt contend that strained alkenes already resemble the optimal pyramidal transition state, thus allowing less distortion energy for the reaction.[8]

Strained alkenes represent privileged structures in multiple areas of science, including chemical biology[9],theoretical chemistry,[10] and organic chemistry.[11] Recent developments with strained alkenes showcase their unique ability to control chemoselectivity, regioselectivity, and asymmetry, while also promoting otherwise difficult complexity-building transformations. In addition, newer synthetic methods have allowed the construction of strained alkenes in natural product settings.[12] Herein, we highlight these recent advances, focusing on the ability of these molecules to drive otherwise unfavorable reactions and generate complexity in an atom-economical fashion.



Scheme 1. Diels–Alder reaction with cyclopropenone ketal en route to rubrolone, described by Boger et al. in 2000.[15] DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid.

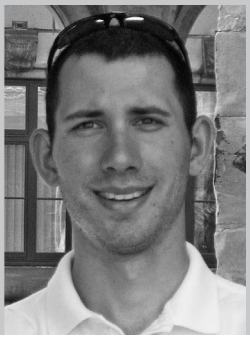
2. Strained Alkenes

2.1. Strained Alkenes in [4+2] Cycloadditions

2.1.1. Intermolecular Diels–Alder Cycloaddition with Cyclopropenone Ketal

Torsionally distorted alkenes participate in Diels–Alder cycloadditions as extraordinarily reactive dienophiles. In 1960, Wiberg and co-workers documented an early example of this behavior with cyclopropene and cyclopentadiene.[13] Approximately two decades later, Boger and Brotherton similarly discovered that strained cyclopropenone ketals undergo rapid cycloaddition with electron-poor, electron-rich, and neutral dienes at room temperature.[14] A beautiful application of this facile reaction by Boger and co-workers has permitted the efficient formation of the tropone ring system present within the complex alkaloid rubrolone (**7**; Scheme 1).[15]

The synthesis commenced with the treatment of electron-rich diene **1** with unsubstituted cyclopropenone acetal **2** at ambient temperature, resulting in nearly quantitative yield of cycloadduct **3** as a single *exo* diastereomer. As an example of an ideal reaction, the process was run in the absence of solvent, required short reaction times, and minimal purification. The high *exo* selectivity arises from an unfavorable steric interaction between the geminal dimethyl group of the acetal and the alkyl substituents of the pyridine ring in the *endo* transition state. Boger and co-workers attribute the rate enhancement to the ring strain that is released (25 kcal mol^{-1}) upon alkene rehybridization. Qualitatively, ring strain raises the ground-state energy and decreases the HOMO–LUMO gap, thereby accelerating the rate of the cycloaddition.[16] However, computational analysis shows a small difference in HOMO–LUMO energies ($\approx$0.6 eV) between ethylene and cyclopropene.[17] Therefore, rate enhancement most likely arises from the ease of out-of-plane distortion in cyclopropene.[5] Subsequent functional-group manipulation of the cyclopropane acetal **3** gave a reactive norcaradiene intermediate, which spontaneously underwent electrocyclic ring opening to form the tropone moiety **6** in high yield.

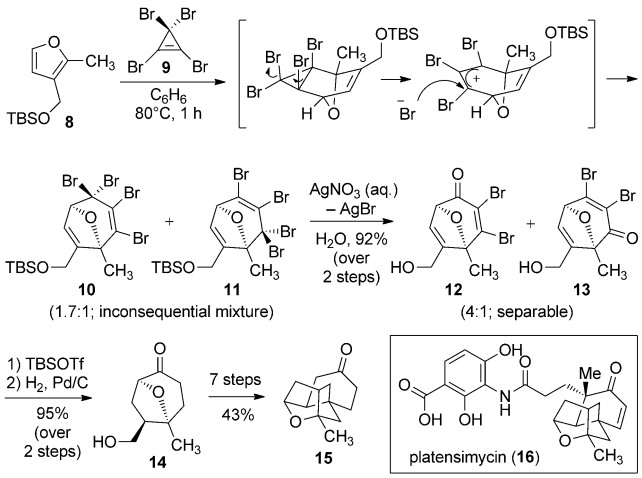


Matthew Wilson was born in Goose Creek, South Carolina, USA in 1986. He received his B.S. in chemistry from Winthrop University where he did undergraduate research with Prof. Christian Grattan. He currently is a fourth-year graduate student in the laboratory of Prof. Richard Taylor at the University of Notre Dame where his studies focus on the synthesis, conformational analysis, and characterization of the microtubule-binding site of (−)-zampanolide.

Richard Taylor received his B.S. degree from SUNY Oswego (1987) and his Ph.D. degree from Rensselaer (1992). He did postdoctoral work at Stanford with Professor Paul Wender. He joined the faculty of the University of Notre Dame (1995) and rose to his current rank of Professor (2004). His interests encompass natural product synthesis, medicinal chemistry, and polyketide biosynthesis.

2.1.2. Intermolecular Diels–Alder Cycloaddition with Tetrabromocyclopropene

Oblak and Wright exploited a distorted tetrabromocyclopropene in their formal synthesis of platensimycin (**16**), which is a potent antibiotic isolated from South African soil and contains an architecturally complex bicyclic skeleton. Because of its intricate structure and the increasing resistance to current antibiotics, numerous synthetic chemists[18] have developed creative strategies to access the octabicyclo-[3.2.1]-octane hydrophobic cage of **16**. Oblak and Wright envisioned the utilization of a unique intermolecular Diels–Alder cycloaddition of two readily accessible precursors, tetrabromocyclopropene **9** and furan **8**, to quickly assemble the carbon framework **14** of platensimycin (Scheme 2).[19]



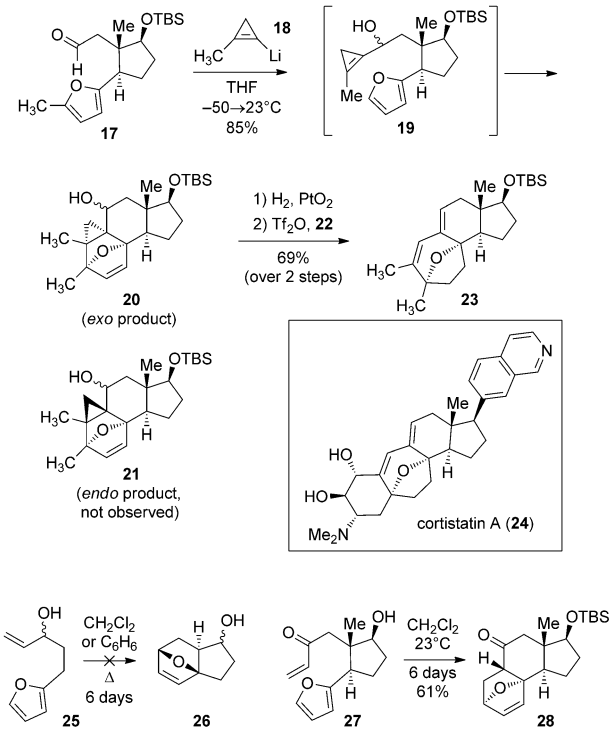
Scheme 2. Formal synthesis of platensimycin described by Oblak and Wright in 2011.[19] TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

Toward this end, gently heating tetrabromocyclopropene **9** with furan **8** initiated a near instantaneous *exo*-selective [4+2] cycloaddition, followed by in situ rearrangement to afford an inconsequential mixture of tetrabromides **10** and **11**. The *endo*/*exo* selectivity obtained in these perhalocyclopropene cycloadditions has remained unclear since they were first reported by Tobey and Law in 1968.[20] However, Wright and co-workers independently confirmed the *exo* selectivity through formation of a triazole adduct and subsequent X-ray crystallography.[21] The increased stability of **9** compared to cyclopropene stems from its extensive bromo substitution. The geminal bromo substituents invoke substantial stability to the cyclopropene ring, whereas the bromo substituents at the alkene tame its significant dienophilicity for ease of handling.[22]

The cyclopropyl–allyl rearrangement initially occurs through bromide ionization and electrocyclic ring opening, followed by bromide addition to the resulting allyl cation (Scheme 2). Subsequent silver-promoted hydrolysis of the resulting tetrabromides **10** and **11** provided a separable mixture of dibromoenones **12** and **13** in a ratio of 4:1 in 92% yield over two steps. Silyl ether protection of enone **12** and exhaustive hydrogenolysis gave ketone **14** in excellent yield as one diastereomer. Finally, transformation of **14** to the known bicyclic core **15** proceeded efficiently in seven steps and 43% overall yield, thus completing a formal synthesis of platensimycin (**16**).

2.1.3. Intramolecular [4+2] Cycloaddition with Cyclopropene

In 2009, Magnus and Littich also demonstrated the utility of cyclopropene cycloadditions in their swift assembly of the polycyclic ring system embedded within cortistatin A (**24**; Scheme 3), a marine steroid that possesses anti-angiogenic



Scheme 3. Synthesis of **23** en route to cortistatin A, described by Magnus and Littich in 2009.[23] **22** = DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

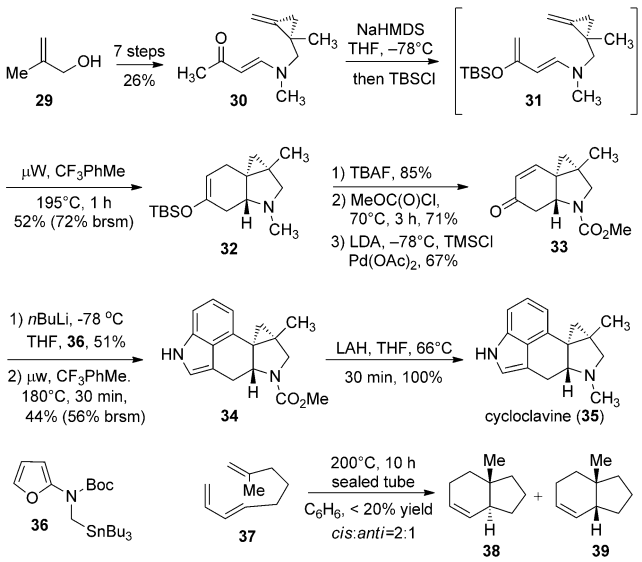
activity.[23] They envisaged the formation of the oxabicyclic core and steroid ring system through a tandem nucleophilic addition/intramolecular cyclopropene Diels–Alder reaction. Consequently, the lithiated cyclopropene **18** was added to aldehyde **17**, which was prepared in six steps from commercially available methyl furan, at low temperature, resulting in the in situ formation of alcohol intermediate **19**. Remarkably, slowly warming the reaction mixture initiated the desired *exo*-selective Diels–Alder reaction, giving oxabicycle **20** in 85% yield. The exclusive *exo* selectivity in this cycloaddition differs from the normally observed selectivity obtained with cyclopropene. Trost and co-workers reported that trapping cyclopropene gas with excess furan results in a 1:1 mixture of the corresponding *endo* and *exo* cycloadducts.[24] Magnus and Littich suggest that the combination of exothermic ring strain

release along with the highly strained nature of the *endo* cycloadduct **21** accounts for the high *exo* selectivity.

It is also noteworthy that similar strategies with Diels–Alder reactions of a substituted furan and an unstrained dienophile lacked efficiency and sometimes failed completely. For instance, studies by De Clercq and co-workers showed that heating alkene **25** to reflux in toluene for six days results in only recovered starting material.[25] Moreover, the reactive enone **27** underwent the desired Diels–Alder cycloaddition very slowly, affording cycloadduct **28** in only a modest yield.[26] The cortistatin ring system was ultimately completed by alkene hydrogenolysis and Lewis acid mediated cyclopropylcarbinol rearrangement of cyclopropane **20**, providing the cortistatin core **23** in 69% yield over two steps.

2.1.4. Intramolecular Diels–Alder Cycloaddition with Methylenecyclopropane

Petronijevic and Wipf employed a novel intramolecular methylenecyclopropane cycloaddition en route to the ergot alkaloid cycloclavine (**35**; Scheme 4).[27] The complex alkaloid, until then synthesized only once by Szanty and co-workers,[28] contains three contiguous stereocenters, a fused disubstituted indole ring, and a densely functionalized cyclopropane. It was proposed that simultaneous installation of the quaternary cyclopropane stereocenter and the *trans*-hydroindole ring system could be efficiently controlled by the intramolecular Diels–Alder reaction of methylenecyclopropane **31**. The cycloaddition precursor **30** was easily prepared in seven steps from commercially available methallyl alcohol **29**.



Scheme 4. Synthesis of cycloclavine described by Petronijevic and Wipf in 2011.[27] Boc = *tert*-butoxycarbonyl, HMDS = hexamethyldisilazane, LAH = lithium aluminum hydride, LDA = lithium diisopropylamide, TMS = trimethylsilyl.

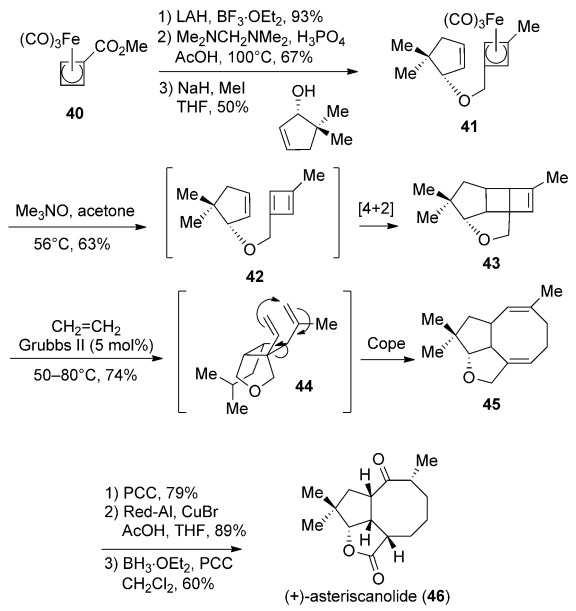
The synthesis commenced with treatment of ketone **30** with NaHMDS and TBSCl, quantitatively affording the corresponding silyl enol ether **31**. Brief microwave irradiation of crude compound **31** provided the desired cycloadduct **32** in 72% yield (brsm) as a single *trans* diastereomer. The *trans* hydroindole **32** was then converted to cycloclavine (**35**) in only six steps (Scheme 4). To our knowledge, the remarkable key cycloaddition is the only reported example that employs an intramolecular Diels–Alder reaction with a methylenecyclopropane in a complex molecular setting.[29] The observed rate acceleration, which results from methylenecyclopropane ring strain (40 kcal mol^{-1}), stands in stark contrast to other similar Diels–Alder reactions that utilize an unstrained dienophile. For instance, Parker and Iqbal reported that heating nonatriene **37** at 200 °C for ten hours gave cycloadducts **38** and **39** in less than 20% yield and with poor *cis*/*trans* selectivity.[30]

2.1.5. Intramolecular [4+2] Cycloaddition with Cyclobutadiene

The longstanding mystery behind the exceptional reactivity[31] and chemical structure of cyclobutadiene has captured the attention of numerous theoretical and structural chemists. In the past, this highly strained and antiaromatic molecule has proven difficult to employ in synthesis as it rapidly undergoes intermolecular dimerization and oligomerization in the absence of an alkene reaction partner. Fortunately, in 1965, it was shown by Pettit and co-workers[32] that it is possible to modulate the reactivity of cyclobutadiene by preparing a metalloaromatic complex with iron pentacarbonyl. Capitalizing on this important finding, Snapper and co-workers demonstrated that tethered alkenes undergo an efficient intramolecular cycloaddition with free cyclobutadiene, providing complex polycyclic cyclobutene ring systems.[33] The asymmetric preparation of (+)-asteriscanolide (**46**; Scheme 5) reported by Snapper and co-workers illustrates the use of this effective synthetic strategy in natural product synthesis.[34]

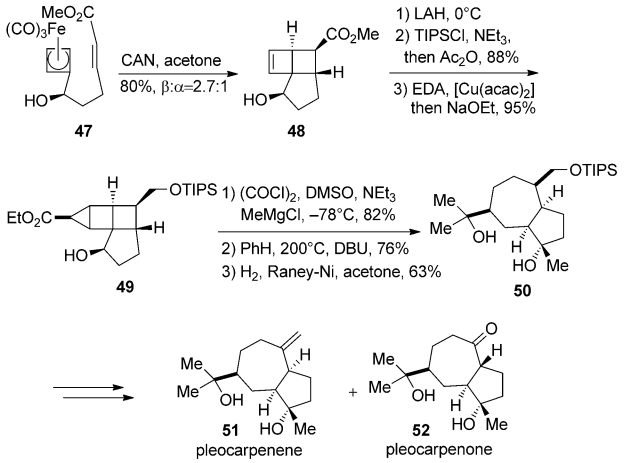
The synthesis began with the reduction, electrophilic aminomethylation, and etherification of cyclobutadiene/iron carbonyl complex **40**, which was prepared in one step from commercially available α-pyrone, to provide cycloaddition precursor **41** in good overall yield. Oxidative decomplexation of **41** with trimethylamine-*N*-oxide (TMAO) released cyclobutadiene intermediate **42**, which initiated a [4+2] cycloaddition to give cyclobutene **43** in 63% yield as a single diastereomer. Cross-metathesis of **43** with ethylene using Grubbs' second-generation catalyst gave the reactive cyclobutane **44**, which underwent in situ Cope rearrangement to give cyclooctadiene **45** in 74% yield. The synthesis was completed following the route previously described by Wender et al.[35] involving an allylic oxidation with PCC, conjugate reduction, and a tandem hydroboration/oxidation sequence.

Another recent application of the intramolecular cyclobutadiene cycloaddition is the enantioselective synthesis of pleocarpenene (**51**) and pleocarpenone (**52**) described by Snapper and co-workers.[36] In this example, the unveiled cyclobutadiene undergoes an intramolecular cycloaddition with an activated alkene. Assembly of the tethered alkene **47** required only six steps from the previously mentioned iron



Scheme 5. Synthesis of asteriscanolide described by Limanto and Snapper in 2000.[34] PCC = pyridinium chlorochromate, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.

cyclobutadiene methyl ester complex **40**. Oxidative liberation of **47** promoted a near instantaneous cycloaddition, providing cyclobutene **48** in 80% yield as a 3:1 mixture of diastereomers (Scheme 6). The increased cycloaddition efficiency with the electronically activated alkene results from lowering of the alkene LUMO.[33] A subsequent reduction/protection protocol and highly diastereoselective cyclopropanation gave the strained intermediate **49** in excellent yield. Tandem oxidation/Grignard addition of **49** followed by thermal fragmentation[37] and hydrogenolysis resulted in the desired 5,7-bicyclic compound **50** in 76% yield. Completion of the synthesis required only four additional steps and gave rise to both guanine

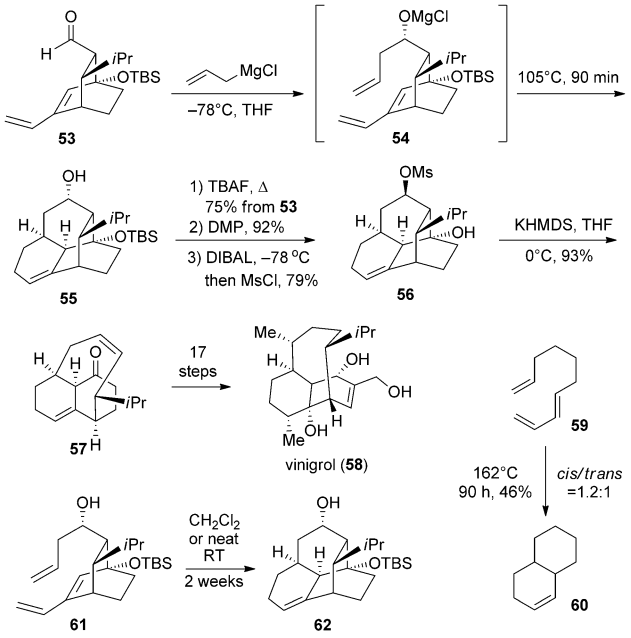


Scheme 6. Syntheses of pleocarpenone and pleocarpenene described by Snapper and co-workers in 2007.[36] acac = acetylacetonate, CAN = ceric ammonium nitrate, DMSO = dimethyl sulfoxide, EDA = ethyl diazoacetate, TIPS = triisopropylsilyl.

natural products (pleocarpenene and pleocarpenone) in good overall yield.

2.1.6. Intramolecular Diels–Alder Cycloaddition with Bicyclo-[2.2.2]octene

In 2008, Baran and co-workers described a concise approach to the diterpene natural product vinigrol (**58**) using a remarkable "proximity-induced" Diels–Alder cycloaddition.[38] The highly complex diterpene has challenged many research groups over the past 25 years, resulting in numerous failed attempts of its synthesis.[39] The difficulty with accessing the densely functionalized ring system results mainly from its structurally complex 1,5-butanonaphthalene core. Contrary to previous synthetic approaches, the Baran group anticipated relying on an intramolecular Diels–Alder reaction/Grob fragmentation for rapid assembly of the vinigrol skeleton **57** (Scheme 7). Gratifyingly, the allylation of aldehyde **53**,



Scheme 7. Synthesis of vinigrol described by Baran and co-workers in 2009.[38] DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, Ms = methanesulfonyl, TBAF = tetra-*n*-butylammonium fluoride.

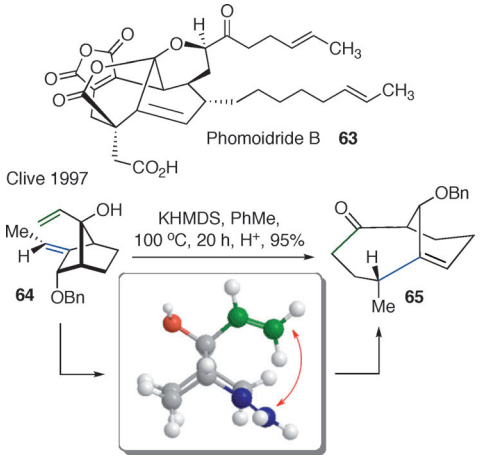
prepared in five steps from (*E*)-methyl 4-methyl-2-pentenoate, gave magnesium alkoxide **54**, which upon heating to 105 °C resulted in a [4+2] cycloaddition that furnished alcohol **55** in excellent yield and diastereoselectivity after only 90 minutes. Allowing the protonated intermediate **61** to stand at room temperature also provided **62** quantitatively after just two weeks. Alternatively, the Diels–Alder cycloaddition with acyclic alkadiene **59** results in only 46% of decalin **60** after 90 hours at 162 °C.[40]

The groups of Houk and Baran ascribe this difference in reactivity to decreased distortion energy, strain release, and hydrogen bonding.[41] Similar to other unsaturated bicyclic ring systems,[42] the constrained diene **54** requires less energy

to adopt the optimal pyramidalized transition-state geometry, thereby lowering the activation energy of the reaction. Density-functional calculations on an analogous bicyclic model system shows that **54** requires 1.6 kcal mol^{-1} less energy than its unstrained counterpart. The remaining acceleration results from relieving the steric strain imparted by the bridgehead substituents, and from the stabilizing hydrogen bond in the transition state. With a reasonable amount of tricycle **55** in hand, the synthesis of ketone **57** was completed by a three-step oxidation state adjustment and mild Grob fragmentation. The resulting ketone **57** was converted to vinigrol **58** in only 17 steps, thus accomplishing a significant milestone in diterpene chemistry.

2.2. Sigmatropic Strain-Driven Siloxy-Cope Rearrangement

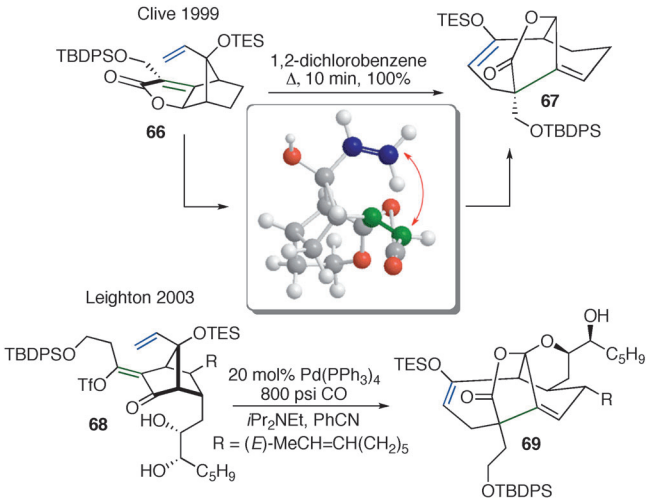
Sigmatropic rearrangements that employ highly strained alkenes represent an underdeveloped strategy in the synthesis of complex molecules. However, ring-strain release in sigmatropic reactions is often utilized by organic chemists.[43] Multiple natural products, such as deoxyharringtonine,[44] vibsanin E,[45] and gelsemoxonine[46] have all been prepared utilizing a strain-driven [3,3] Cope rearrangement with a divinylcyclopropane. Similar in this regard, the groups of Clive and Leighton showcased the powerful driving force of torsional strain in sigmatropic rearrangements with their synthetic efforts toward the Ras farnesyl transferase inhibitor phomoidride B (**63**; Scheme 8).



Scheme 8. Phomoidride model system described by Sgarbi and Clive in 1997.[47] Bn = benzyl.

In 1997, Sgarbi and Clive envisioned utilizing an anionic oxy-Cope rearrangement to form the phomoidride bicyclo [4.1.3] core.[47] However, a simple model system showed that harsh conditions were required to promote this transformation. Treatment of alcohol **64** with KHMDS followed by heating at 100 °C for 20 hours resulted in ketone **65**; however, increased substitution on the alkene was not tolerated. In order to render this transformation feasible, Sgarbi and Clive suggested that constraining the exocyclic norbornyl alkene within a pseudoester ring system might result in increased strain and closer proximity of the reacting termini, thus leading to a faster reaction.

Two years later,[48] Clive et al. confirmed the success of this approach by observing that the strained lactone **66** led to the silyl enol ether **67** in quantitative yield after only 10 minutes in refluxing 1,2-dichlorobenzene (Scheme 9). Similarly,



Scheme 9. Approaches to the phomoidrides (CP-molecules) described by Clive et al. (1999)[48] and Bio and Leighton (1999, 2003).[49] TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl.

Leighton developed a highly efficient one-pot Pd-catalyzed carbonylation/siloxy-Cope rearrangement[49] with enol triflate **68**, leading to nearly the complete phomoidride skeleton **69**. The remarkable difference in the model and strained pseudoester ring systems sheds light on the importance of torsional strain in organic synthesis. The rate enhancement may also be viewed in terms of distortion/interaction or strain-activation theory.

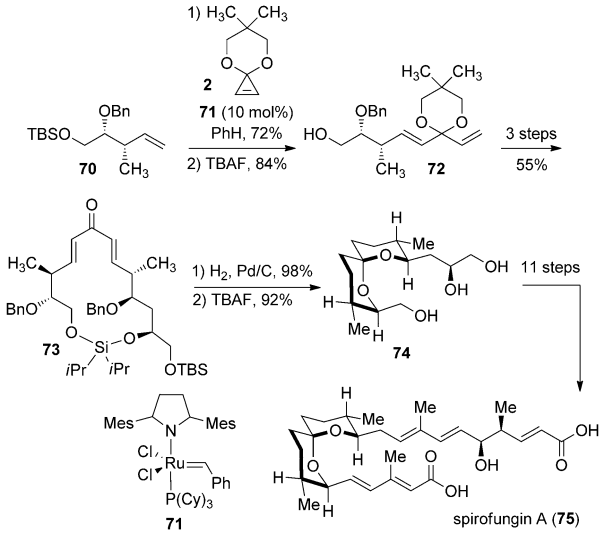
In the model system **64**, the alkene requires significant twisting of the bicyclic core to achieve optimum orbital overlap. This destabilizing distortion energy may account for the high activation barrier and the harsh conditions needed to promote the anionic oxy-Cope rearrangement. On the other hand, the strained lactone **66** requires less distortion and results in an approximately 10^7–10^{10} rate enhancement.

2.3. Metal-Catalyzed Reactions

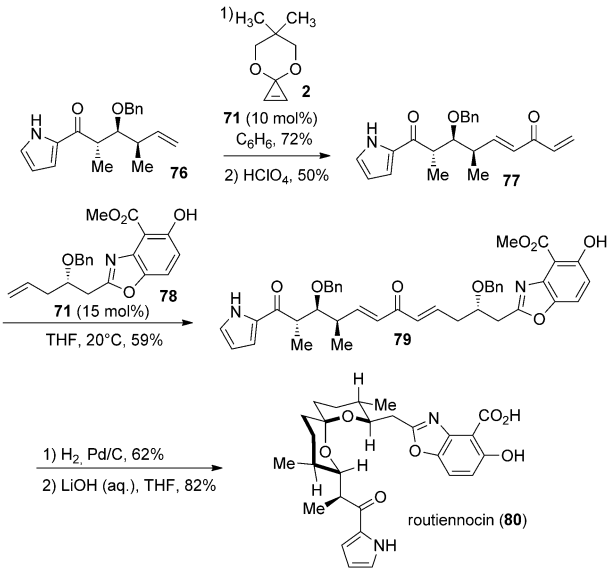
2.3.1. Cyclopropenone Ketal Cross-Metathesis

Strained alkenes bind transition metals unusually strong as a result of their high-lying HOMO and low-lying LUMO.[50] While transition-metal-based chemistry with distorted alkenes has been investigated significantly over the past two decades,[51] many of these reactions have not yet resulted in an application to natural product synthesis. However, in pioneering efforts Kozmin and co-workers have demonstrated the strained cyclopropenone acetal **2** as an effective linchpin for the convergent formation of several biologically active

polyketides; including bistramide A,[52] spirofungin A,[53] and routiennocin.[54] As representive examples of this chemistry, we highlight only the most recent applications, the enantioselective syntheses of spirofungin A (**75**) and routiennocin (**80**; Scheme 10).



Scheme 10. Synthesis of spirofungin A described by Marjanovic and Kozmin in 2007.[53] Cy = cyclohexyl, 2,4,6-trimethylphenyl.



Scheme 11. Synthesis of routiennocin described by Mazumoto and Kozmin in 2008.[54]

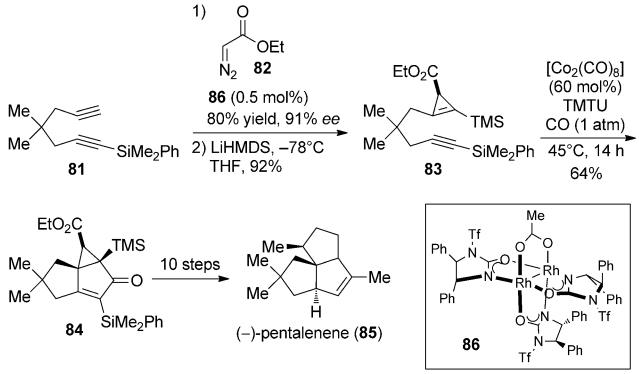
Isolated from *Streptomyces violaceusniger*, spirofungin A (**75**) displays antifungal and potent antiproliferative activity, and selectively inhibits isoleucyl-tRNA synthetase in mammalian cells. As a concise solution to the difficult spiroacetalization described by Shimizu et al.,[55] the Kozmin group opted for a metathesis strategy utilizing three readily available protected homoallylic fragments (Scheme 10).[53] The key metathesis reaction involved treatment of benzyl-protected homoallylic alcohol **70** with a slight excess of cyclopropenone acetal **2** in the presence of Grubbs' second-generation catalyst (**71**) to furnish the corresponding acetal in 72% yield. Subsequent functional-group manipulation led to cyclized macrolide **73**, which upon exhaustive-hydrogenolysis-initiated alkene reduction, debenzylation, and spiroacetalization in one pot afforded the spirofungin aglycon **74** in nearly quantitative yield. The success of the key metathesis reaction is due to irreversible metallocarbene formation and increased initiation rates as a result of strain release upon reaction with the Grubbs catalyst.[56] The increase in reactivity allows greater selectivity and the possibility of conducting metathesis reactions at low temperature.[57]

Shortly after, Kozmin and co-workers employed the same synthetic approach for the synthesis of the antibiotic routiennocin (**80**; Scheme 11).[54] The highly convergent synthesis relied on two nearly sequential cross-metathesis reactions to efficiently form the key enone intermediate **79**. To this end, the strained cyclopropenone acetal **2** was reacted with alkene **76** in the presence of Grubbs' catalyst **71** to give enone **77** in good yield after acetal hydrolysis. Remarkably, this ring-opening-metathesis reaction proceeds at room temperature and requires only 1.5 hours for completion. The synthesis was completed by hydrogenolysis-promoted spiroketal formation and ester hydrolysis, giving **80** in only eight overall steps.

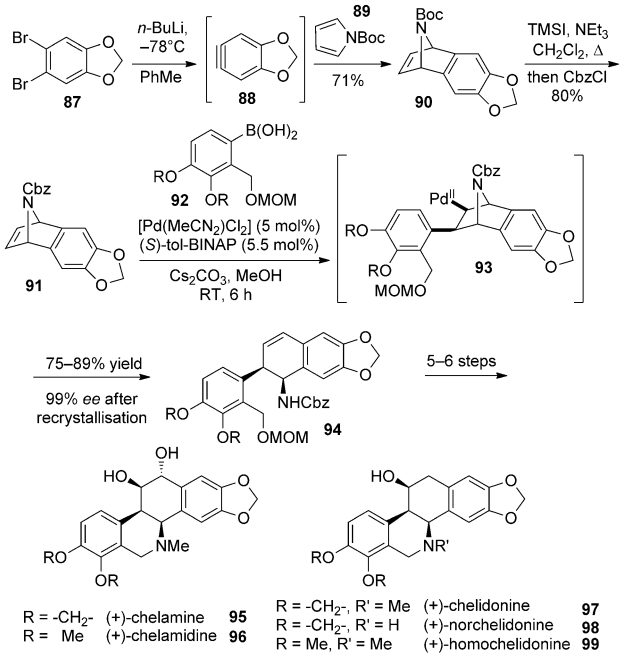
2.3.2. Intramolecular Pauson–Khand Reaction

The Pauson–Khand reaction, a multicomponent formal [2+2+1] cycloaddition, represents an atom-economical synthetic strategy for the formation of cyclopentenone ring systems.[58] The recent use of amine-based additives to increase reaction yields along with more multifaceted alkene and alkyne coupling partners has rendered the Pauson–Khand reaction a useful tool for natural product synthesis.[59] However, limitations such as the unreactive nature of tri- and tetrasubstituted alkenes represent obstacles for accessing higher complexity. In order to solve this problem, Pallerla and Fox[60] along with others[61] demonstrated that ring-strain energy serves as an efficient driving force for sluggish Pauson–Khand reactions. An elegant example of this strategy is showcased in the enantioselective synthesis of (−)-pentalenene (**85**; Scheme 12),[62] an angularly fused triquinane from *Streptomyces griseochromogenes*.

In the approach described by Pallerla and Fox, the quaternary stereogenic center embedded within the tricyclic core was assembled by an intramolecular Pauson–Khand reaction with the tetrasubstituted cyclopropene **83**. This enantiopure cyclopropene was prepared in only two steps from diyne **81** in 74% yield, using an enantioselective cyclopropenation reaction and an anion-promoted silylation. Subjecting the resulting cyclopropene **83** to catalytic dicobalt octacarbonyl complex in the presence of a thiourea promoter and atmospheric carbon monoxide furnished cyclopentenone **84** in 64% yield as the only stereoisomer. This result differs from the typical lack of reactivity observed with tetrasubstituted alkenes in the Pauson–Khand reaction.[63] Computational analysis by the groups of Gimbert and Pericàs suggests



Scheme 12. Synthesis of pentalenene described by Pallerla and Fox in 2007.[61] TMTU = 1,1,3,3-tetramethyl-2-thiourea.



Scheme 13. Synthesis of the B/C hexahydrobenzo[*c*]phenanthridine alkaloids **95**–**99** described by Lautens and co-workers in 2008.[65] BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl Cbz = benzyloxycarbonyl, MOM = methoxymethyl.

that the higher reactivity of strained alkenes in Pauson–Khand reactions results from greater back donation to the lower-lying LUMO of a strained alkene.[61b,c] This back donation allows a lower energy barrier for the formation of a cobaltacycle, thus leading to increased reaction rates and minimized side reactions. Therefore, the strain within cyclopropene **83** likely compensates for the unfavorable steric interactions encountered in the transition state, ultimately allowing a favorable reaction. With a preparative amount of cyclopropane **84** in hand, the synthesis was completed in ten steps, giving (−)-pentalenene **85** in 9% overall yield.

2.3.3. Addition to Strained Azabicyclic Alkenes

The favorable interaction of strained alkenes with transition metals also accelerates nucleophilic addition, even under mild reaction conditions.[51] For example, in numerous reports, Lautens and co-workers described the efficient metal-catalyzed asymmetric addition/ring-opening of strained oxa- and azabicyclic alkenes with several carbon atom and heteroatom nucleophiles.[64] In 2008, Lautens and co-workers applied this methodology to the enantioselective synthesis of a number of isoquinoline alkaloids **95**–**99** (Scheme 13).[65]

Lautens anticipated that two of the three contiguous stereocenters with *syn* configuration present within this class of natural products along with the entire carbon framework could arise in one step from the asymmetric ring-opening of *meso*-azabicyclic alkene **91**. Alkene **91** was readily accessible on a multigram scale from the [4+2] cycloaddition of benzyne intermediate **88**, generated in situ from dibromobenzene **87**, with pyrrole **89** followed by protecting-group exchange (**90** to **91**). In the key transformation, boronic acid **92** underwent facile Pd^{II}-catalyzed asymmetric addition, producing *syn*-azabicycle **93**, which upon β-heteroatom elimination gave dihydronaphthalene **94** in excellent yield and high enantiomeric excess. Notably, this reaction could also be conducted on a large scale and gave near full conversion after only two hours at room temperature. The structural distortion within alkene **91** facilitates the migratory insertion and directs the facial selectivity. From dihydronaphthalene **94**, completion of the synthesis required only five to six steps, thereby representing the first enantioselective synthesis of the hexahydrobenzo[*c*]phenanthridine alkaloids **95**–**99**.

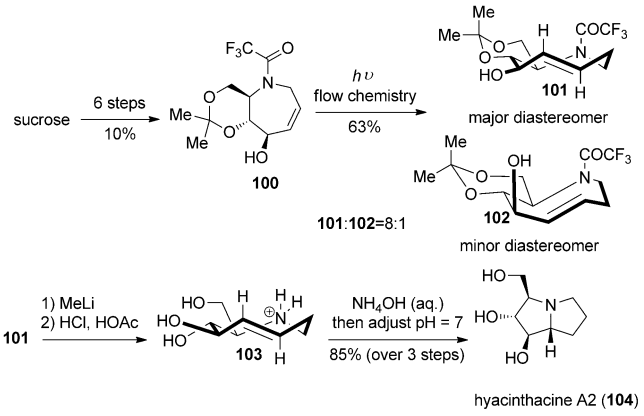
2.4. Nucleophilic Addition

2.4.1. Intramolecular trans*-Cyclooctene Hydroamination*

Several years later, Fox and co-workers employed an impressive strain-driven transannular hydroamination in their succinct, enantioselective synthesis of the pyrrolizidine alkaloid hyacinthacine A2 (**104**).[66] Central to their synthetic approach was the hydroamination of the highly reactive and functionalized *trans*-cyclooctene derivative **101**. Because *trans*-cyclooctene derivatives are difficult to access in pure form, Fox and co-workers recently established a practical and preparative photochemical method for the synthesis of *trans*-cyclooctenes from *cis*-cyclooctenes through selective metal complexation with $AgNO_3$.[12c] The application of this newly developed method toward hyacinthacine A2 commenced with the preparation of *cis*-cyclooctene **100**, which required only six steps from readily available and inexpensive sucrose. The resulting *cis*-cyclooctene was photoirradiated at 254 nm in a flow reactor, affording an 8:1 mixture of diastereomers **101** and **102** in 63% yield. The diastereocontrol results from the inability of the minor diastereomer **102** to adopt a favorable crown conformation because of a destabilizing *trans*-diaxial ring fusion. As a result, **102** must occupy a higher-energy chair conformation. Completion of the synthesis entailed removal of the trifluoroacetyl group with MeLi followed by acetal hydrolysis to give the unstable ammonium salt **103** (Scheme 14). Subjection of crude com-

pound **103** to aqueous NH_4OH initiated a rapid intramolecular hydroamination reaction, which provided hyacinthacine A2 as a single isomer in 85% overall yield after only five minutes at room temperature.

The increased reactivity with the strained *trans*-cyclooctene **101** likely results from significant twisting of the alkene π-system, leading to an unsymmetrical orbital framework.[67] Consequently, the HOMO of the alkene becomes significantly higher in energy, allowing the destabilizing NH lone pair to encounter the electron-rich olefin π-system. Again, the example showcased herein illustrates the ability of strain release to intrinsically override the destabilizing electronic features of a reaction.



Scheme 14. Synthesis of hyacinthacine A2 described by Fox and coworkers in 2011.[66]

3. Conclusion and Outlook

In summary, the strategic use of ring strain can promote complex transformations in an atom-economical fashion, including reactions that typically require significant activation. Since the early 1900s, the unusual reactivity of distorted alkenes has garnered tremendous attention from the synthetic community. Herein, recent applications of these distorted alkenes in natural product synthesis were highlighted, showcasing their exceptional applicability to various reaction types, including cycloadditions, rearrangements, metal-catalyzed reactions, and nucleophilic additions. The exciting progression in the development of synthetic methods has facilitated access to highly strained alkenes, such as cyclopropene, cyclobutadiene, and *trans*-cyclooctene derivatives, for use in synthesis. Moreover, detailed computational analysis has been conducted by the groups of Houk and Bickelhaupt to further probe the connection between distorted alkenes and reactivity, providing deeper insight into this exciting class of strained molecules. With newer tendencies in reactivity and easier synthetic access now available, it is certain that strained alkenes will continue to drive innovations in the synthesis of complex molecules.

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