Tandem Diels–Alder Cycloadditions in Organic Synthesis

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Contents

I.	Reactions of Bicyclic Bis-Dienes	168
II.	Acetylenic Bis-Dienophiles	169
III.	Exocyclic Bis-Dienes	169
IV.	Equivalents of 3-Methylene-1,4-pentadiene and Related Species as Bis-Dienes	170
V.	Masked Bis-Dienes	171
VI.	Masked Bis-*o*-Quinodimethanes as Bis-Dienes	172
VII.	Nonacetylenic Bis-Dienophiles	173
VIII.	Tandem Cycloaddition Using Acyclic Bis-Dienes	173
IX.	Conclusion	176

Jeffrey D. Winkler was born in 1956 in Chicago, IL. As an undergraduate at Harvard College, where he graduated *cum laude* in Chemistry in 1977, he participated actively in the chemical research programs of Professor James Wuest, Dr. Larry Blaszczak, and Professor E. J. Corey. At Columbia University, he worked with Professor Gilbert Stork on the stereochemistry of the intramolecular Michael addition and the application of this methodology to the synthesis of adrenosterone. Upon receiving his Ph.D. degree in 1981, he joined the laboratories of Professor Ronald C. D. Breslow as an American Cancer Society Postdoctoral Fellow, where he pursued projects involving the synthesis of transamination mimics and organic ferromagnets. In 1983, he joined the Chemistry Department at the University of Chicago as an Assistant Professor. He moved to the University of Pennsylvania in 1990, where he is currently Associate Professor of Chemistry and a Member of the University of Pennsylvania Cancer Center. In his independent career first at Chicago and now at Penn, he has established an active research laboratory engaged in both synthetic organic and bioorganic chemistry. A theme common to most of the synthetic program in Professor Winkler's laboratory, which forms the subject of this review, is the application of the [2+2]photocycloaddition of dioxenone and vinylogous amide chromophores to the stereoselective construction of structurally complex carbon skeleta. He is the coauthor of over 40 publications in refereed journals and has delivered over 70 invited lectures at academic and industrial research laboratories. His honors and awards include the first American Cyanamid Young Faculty Award (1989–1992), the H. Martin Friedmann Lectureship at Rutgers University (1993), the National Institutes of Health Career Development Award (1988–1993), and a Merck Foundation Award for Faculty Development (1985). He was also a Fellow of the Alfred P. Sloan Foundation (1987–89) and he currently serves as Chairman of the Philadelphia Organic Chemists' Club. Professor Winkler lives in suburban Philadelphia with his wife, Beverly D. Eskreis, M.D., a dermatologist, and their three children, Sarah, 11, Lauren, 9, and Jonathan, 6.

The construction of multiple carbon−carbon bonds in a single chemical step represents a particularly efficient approach to the synthesis of complex molecular structures.[1] Dramatic examples of the utility of this strategy include (1) the polyene cyclization approach to steroid synthesis as pioneered by Johnson,[2] in which three rings and six contiguous stereogenic centers are established in a single chemical step; (2) the biomimetic synthesis of the Delphimium alkaloids by Heathcock;[3] and (3) the intramolecular arene−olefin cyclization, which has been applied by Wender to the exceedingly direct syntheses of a series of polycyclic compounds which are otherwise available only by considerably less efficient pathways.[4]

The focus of this review will be the use of tandem Diels−Alder reactions in organic synthesis.[5] Webster's International Dictionary defines tandem as "a two-seated carriage drawn by horses harnessed one before the other." This definition was subsequently expanded to include "a group of two or more arranged in conjunction...". In the context of multiple chemical reactions, "tandem" can therefore be taken to indicate two reactions which follow one another.

From a chemical point of view, the nature by which the reactions "follow one another" can be distinguished in the following ways. These cycloaddition reactions may or may not include intervening steps which lead to the unmasking of diene and dienophilic partners for the second cycloaddition reaction. An example of the first process could involve the extrusion of carbon dioxide from a pyrone Diels−Alder adduct **2** to generate a second diene moiety, i.e., 1,3-cyclohexadiene, **3**, as outlined in Scheme 1, which can undergo a second cycloaddition reaction to give **4**. Both interrupted and uninterrupted cycloaddition reactions will be considered tandem processes for the purpose of this review.

The uninterrupted cascades can be further categorized into (a) reaction sequences in which both diene−dienophile pairs are present in the starting compounds and (b) a necessarily "sequential" pathway in which the first cycloaddition unleashes a new diene or dienophilic alkene which can then undergo a second cycloaddition reaction. The reaction of a bis-diene **5** and divinyl ketone **6** to give tricyclic product **7** illustrates pathway a, in which "simultaneous reaction" is possible, even if the reaction sequence

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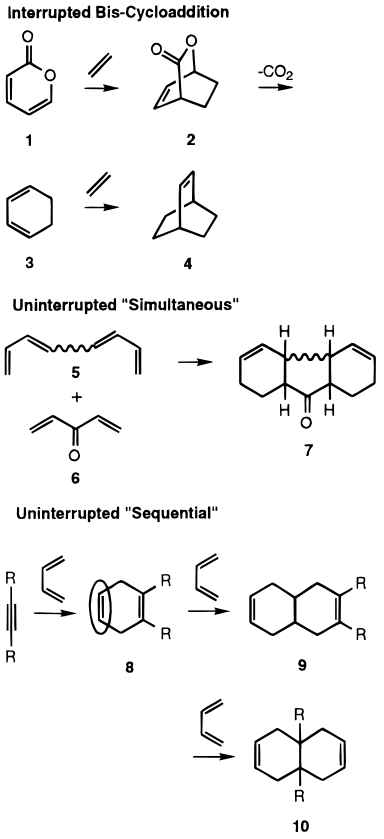
Scheme 1

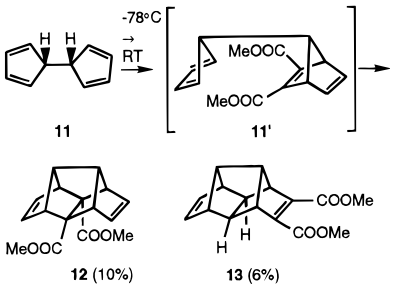


proceeds in a nonsynchronous manner. The "domino" Diels–Alder reaction provides an excellent example of this group of reactions. As illustrated in Scheme 1, the first Diels–Alder reaction of the acetylenic dienophile and a diene generates a second dienophilic alkene, as indicated in **8**, which reacts with another equivalent of diene to give the "domino" bicyclic product, **9**. It is noteworthy here that cyclohexadiene **8** is an ambident dienophile and that cycloaddition of the second diene equivalent with the tetrasubstituted alkene would lead to the formation of an "uninterrupted simultaneous" pincer product, **10**, which is discussed in greater detail in Section II of this review (Acetylenic Bis-Dienophiles). Each of the pathways outlined in Scheme 1 will be regarded as a tandem Diels–Alder reaction, since each involves two [4+2]-cycloaddition reactions. As outlined in the table of contents, this review will be organized by the nature of the bis-diene and bis-dienophilic partners employed in each of the tandem reaction sequences.

I. Reactions of Bicyclic Bis-Dienes

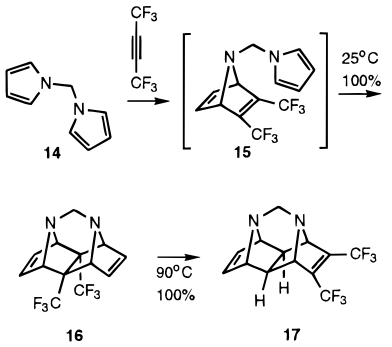
One of the most historically important and practically significant applications of this methodology involves the Diels–Alder reaction of bicyclic bis-dienes, which can lead to a variety of bridged polycyclic ring systems. Intermolecular reaction of the bicyclic bis-diene **11** with dimethyl acetylenedicarboxylate presumably leads to the formation of a bimolecular adduct, **11′** (not isolated), which can then undergo intramolecular cycloaddition to give the bridged tetracyclic products **12** and **13**, albeit in modest yield.[6] This reaction, which has been described as a "domino" Diels–Alder reaction, serves as the cornerstone of the synthesis of dodecahedrane by Paquette[7] (Scheme 2).

Scheme 2



Similar reactivity is observed with *N*,*N*′-dipyrrolylmethane (**14**) (Scheme 3). It is interesting to note

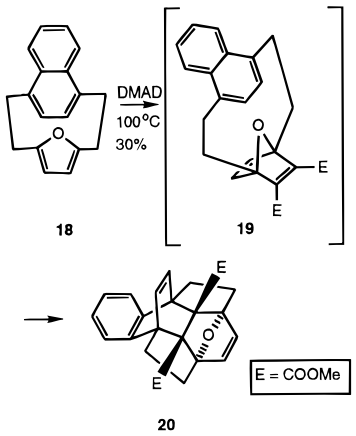
Scheme 3



that the kinetic product formed in the intramolecular Diels–Alder reaction of **15** is **16** (quantitative), via reaction of the pyrrole diene with the more reactive doubly activated alkene. However, on prolonged heating, the thermodynamic product is obtained, i.e., the "domino" adduct, in which the two trifluoromethyl groups are attached to the carbon–carbon double bond as shown in **17** (quantitative yield), indicating that the intramolecular Diels–Alder reaction is reversible under these reaction conditions.[8]

The analogous reaction of furan dienophiles to give complex cage structures has been reported independently by Wasserman[9] and Wynberg.[10] An illustrative example is shown in Scheme 4. Reaction of furan

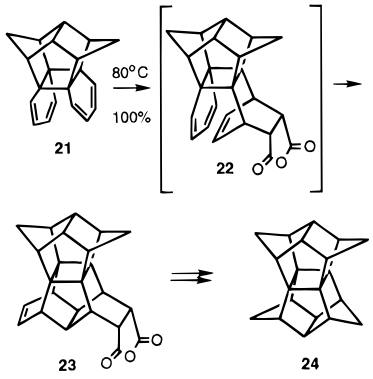
Scheme 4



18 with dimethyl acetylenedicarboxylate leads to the formation of **20**, the product of intramolecular Diels–Alder cycloaddition of intermediate **19**.

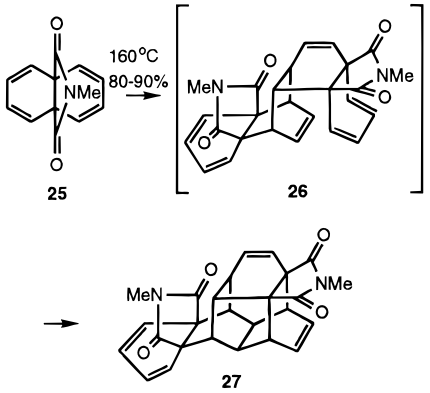
Another important example of the utility of this methodology for the synthesis of complex polycyclic ring systems involves reaction of **21**[11] with maleic anhydride, which results in the formation of **23** (quantitative yield), a useful precursor for the synthesis of pagodanes.[12] Neither the putative intermediate **22** nor any of the corresponding bis-adduct (via reaction of **21** with 2 equiv of maleic anhydride) was observed under any reaction conditions, indicating that the intramolecular cycloaddition of **22** is much faster than bimolecular reaction of either **21** or **22** with maleic anhydride (Scheme 5).

Scheme 5



The dimerization of bis-diene **25**, which serves as both diene and dienophile, is also noteworthy (Scheme 6). The stereoselective formation of the complex cage

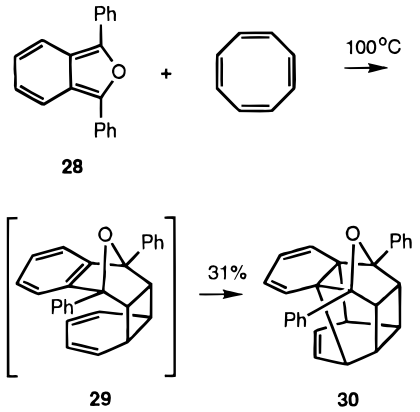
Scheme 6



structure **27** in 80–90% yield, containing nine rings and 12 stereogenic centers, underscores the utility of the tandem Diels–Alder reaction for the highly efficient formation of complex polycyclic structures.[13]

Finally, Gassman and co-workers have reported that cyclooctatetraene can react as both diene and dienophile in reaction with **28** to give complex cage structures.[14] Cycloaddition of **28** with the bicyclo[4.2.0]octatriene isomer of cyclooctatetraene leads to the formation of **29**, which then undergoes intramolecular cycloaddition to give **30** in 31% overall yield (Scheme 7).

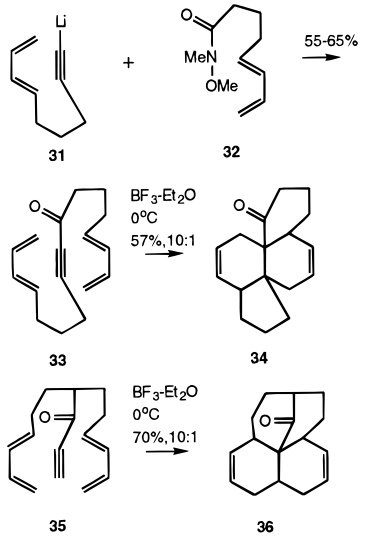
Scheme 7



II. Acetylenic Bis-Dienophiles

The reaction of two diene equivalents with acetylenic bis-dienophiles can follow either of the two sequences outlined in Scheme 1. In the "domino" pathway, which is common to each of the examples in section I of this review, the first cycloaddition leads to the formation of a new dienophilic alkene, which reacts with a second diene equivalent to give the bicyclic adduct **9**. Alternatively, the acetylenic dienophile can react as a bis-dienophile to give the "pincer" adduct **10**. The intramolecular variant of the "pincer" process leads to the direct formation of a tetracyclic ring system from an acyclic precursor, as recently described by Giguere. Exposure of **33** to $BF_3 \cdot Et_2O$ led to the formation of **34** as a 10:1 mixture of diastereomers (stereochemistry not determined) in 57% isolated yield.[15] The requisite cyclization substrate **33** could be prepared in good yield by reaction of the Weinreb amide **32**[16] with acetylide **31**. The same authors reported the analogous transformation of the branched substrate **35** to tetracyclic ketone **36**, as a 1:1 mixture of diastereomers in 66–70% yield under the same reaction conditions (Scheme 8).[17]

Scheme 8

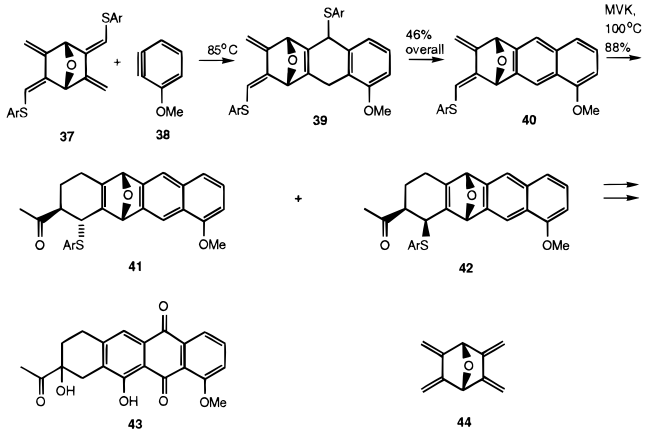


III. Exocyclic Bis-Dienes

The rich chemistry of tetramethylideneoxanorbornane bis-dienes, i.e., **37**, has been thoroughly studied by Vogel, who has reported the application of sequential Diels–Alder cycloaddition to the control of the

regiochemistry between the A and D rings in a synthesis of 11-deoxydaunomycinone (**43**). A critical feature of the reactivity of **37** and **44** is that the first Diels−Alder reaction is much faster than the second reaction, so that excellent selectivities in sequential Diels−Alder reaction with two different dienophiles is observed. In contrast to the less discriminating reactivity of the unsubstituted parent system, **44**, the cycloaddition of **37** is highly regioselective.[18] As outlined in Scheme 9, reaction of **37** with the highly

Scheme 9

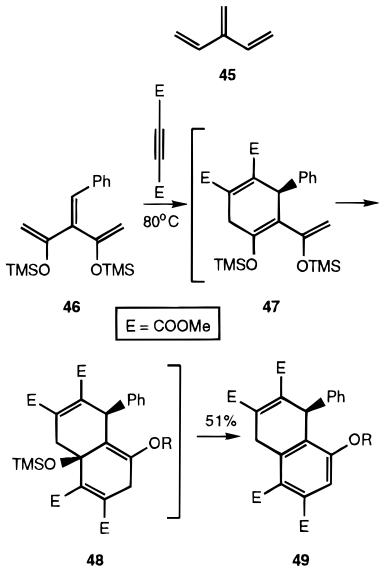


reactive dienophile **38** leads, after elimination of thiophenol from the initially formed product **39**, to the regioselective formation of **40** in 46% yield. A second Diels−Alder reaction with methyl vinyl ketone provides a 9:1 mixture of stereoisomeric products **41** and **42**, respectively, in 88% yield. The authors attribute the formation of endo-**41** and exo-**42** to the competition between a steric factor favoring exo-face attack and the stereoelectronic factor favoring the formation of the endo product.[19]

IV. Equivalents of 3-Methylene-1,4-pentadiene and Related Species as Bis-Dienes

The tandem Diels−Alder cycloaddition of bis-dienes related to 3-methylene-1,4-pentadiene **45** (Scheme 10) provides another important example of sequential

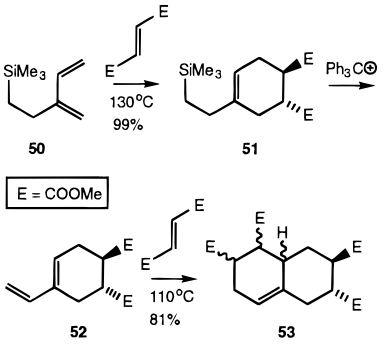
Scheme 10



cycloaddition, as the diene moieties in **45** can react only sequentially and not simultaneously. Reaction of **46** with dimethyl acetylenedicarboxylate leads to the formation of **47**, which then reacts with a second equivalent of dienophile to give **49** (after loss of trimethylsilanol) in 51% overall yield. The stereoselectivity of the second reaction is noteworthy and results from addition of the dienophile anti to the phenyl substituent in **47** via an endo transition state.[20]

Hosomi and co-workers have reported 2-trimethylsilylethyl-1,3-butadiene (**50**) (Scheme 11) as a

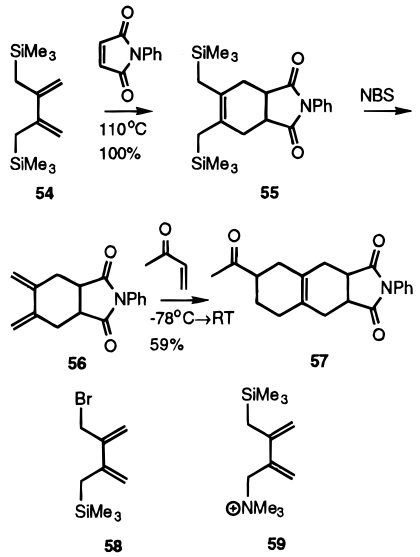
Scheme 11



synthetic equivalent of 3-methylene-1,4-pentadiene (**45**) (Scheme 10). The 1,3-diene **50** reacts smoothly with dimethyl fumarate to afford the corresponding cycloadduct **51** in 99% yield. Exposure of **51** to triphenylmethyl tetrafluoroborate liberates the second diene equivalent, **52**, via hydride abstraction at the β-position of the TMS group of cycloadduct **51**. Reaction of **52** with a second equivalent of dimethyl fumarate then gives **53** in 81% yield, which is formed as a ca. 2:1 mixture of diastereomers, although the full stereochemical determination of the two isomers was not reported.[21]

The substitution pattern of the bicyclo[4.4.0]decane ring products obtained in the sequence outlined in Scheme 11 differs substantially from that of the products derived from the 2,2′-bisallyl diradical synthon, **54**, the chemistry of which was originally reported by Trost[22] and has been subsequently extended by Hosomi (Scheme 12).[23] Reaction of **54** with N-phenylmaleimide leads to the formation of the bis-

Scheme 12

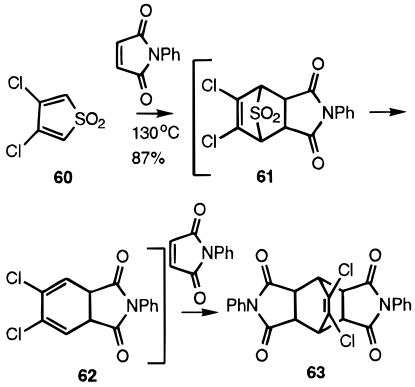


trimethylsilylmethylalkene cycloadduct **55** in quantitative yield. Oxidative bis-desilylation of **55** with Br_2 gives a new diene, **56**, which undergoes Diels–Alder cycloaddition in situ with methyl vinyl ketone to give the tricyclic adduct **57**, which is formed in 59% yield as a 5:1 mixture of diastereomers (the relative stereochemistry of the adducts was not determined). The same authors demonstrated that this methodology could be applied to the stereoselective synthesis of tetracene derivatives, with potential application to the synthesis of tetracyclines. This methodology has been extended by both Trost[24] and Hosomi,[25] who have separately reported the utility of **58** and **59** as differentiated bifunctional reagents that are useful in heterolytic annulation reactions as well as tandem Diels–Alder cycloadditions.

V. Masked Bis-Dienes

Much work has been done in the area of masked or latent bis-dienes in which a Diels–Alder cycloaddition reaction is followed by extrusion of a small molecule (SO_2, CO, or CO_2) or an elimination reaction, unleashing or triggering the formation of a second diene moiety which undergoes a second Diels–Alder cycloaddition. This approach was first described by Bluestone and co-workers, who observed that reaction of 3,4-dichlorothiophene 1,1-dioxide (**60**) with dienophiles such as N-phenylmaleimide leads to the formation of tandem Diels–Alder adducts such as **63** in 87% yield (Scheme 13).[26]

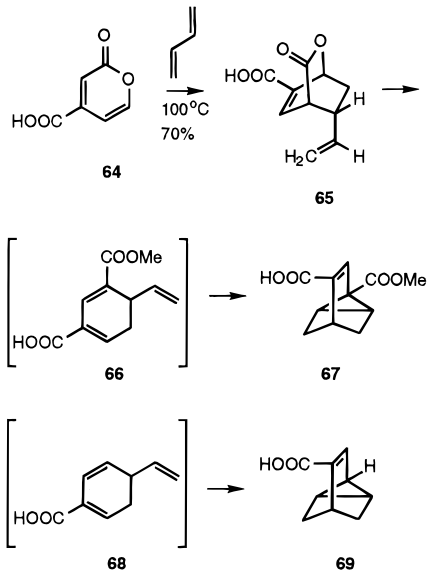
Scheme 13



Imagawa and co-workers have reported a simple synthesis of the tricyclo[3.2.1.$0^{2,7}$]oct-3-ene ring system **67**/**69** via a double Diels–Alder reaction starting from α-pyrone (Scheme 14). Heating a methanolic solution of **64** in the presence of an excess of butadiene at 100 °C leads to the formation of **67** in 70% yield. The lactone intermediate **65** can be isolated if the reaction is performed at lower temperature in aprotic solvent (benzene reflux). Exposure of **65** to the original reaction conditions (methanol, 100 °C) leads to the formation of a mixture of **67** and **69** (1:3 ratio), which are obtained from dienes **66** (obtained from **65** by β-elimination) and **68** (obtained from **65** by loss of CO_2).[27,28]

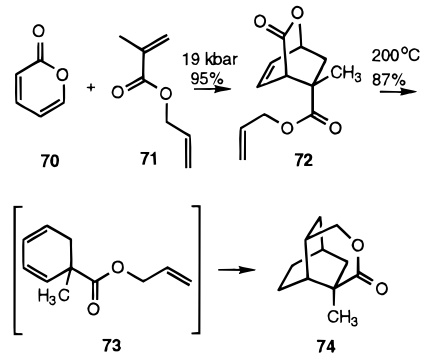
A closely related study was subsequently described by Marko and co-workers, who reported the cycloaddition of α-pyrone with substituted acrylates as well as unactivated α,ω-dienes at high pressure (19 Kbar). Reaction of **70** and **71** leads to the exclusive formation

Scheme 14



of the CO_2 Diels–Alder cycloadduct **72** in 95% yield (no CO_2 loss is observed under these reaction conditions),[29] which is thermally stable at temperatures up to 150 °C (Scheme 15). Extrusion of CO_2 at 200–

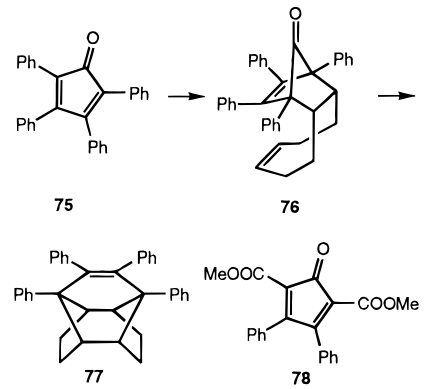
Scheme 15



220 °C then leads to the generation of a second diene moiety in **73**, which undergoes intramolecular cycloaddition to give **74** in 87% yield.[30]

The extrusion of carbon monoxide to generate the second diene equivalent in a Diels–Alder cascade has also been reported (Scheme 16). Cycloaddition of

Scheme 16

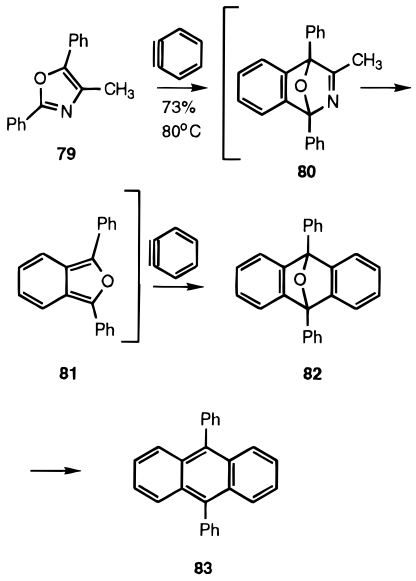


tetraphenylcyclopentadienone **75** and cyclooctadiene leads to the formation of **76**, which on decarbonylation and intramolecular cycloaddition gives the in-

teresting cage structure **77**, in good yield.[31] Analogous products have been obtained on reaction of cyclooctadiene with either 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone **78** (extrusion of CO) or 5-methoxycarbonyl-2-pyrone (extrusion of CO_2).

The synthesis of anthracenes via Diels−Alder cycloaddition of oxazole **79** with benzyne was subsequently reported by Bhatt (Scheme 17). Loss of

Scheme 17



acetonitrile from the initially formed cycloadduct **80** gave **81**, which reacted with a second equivalent of benzyne to give **82**. Treatment of the ether product **82** with zinc in acetic acid gave the anthracene **83**.[32]

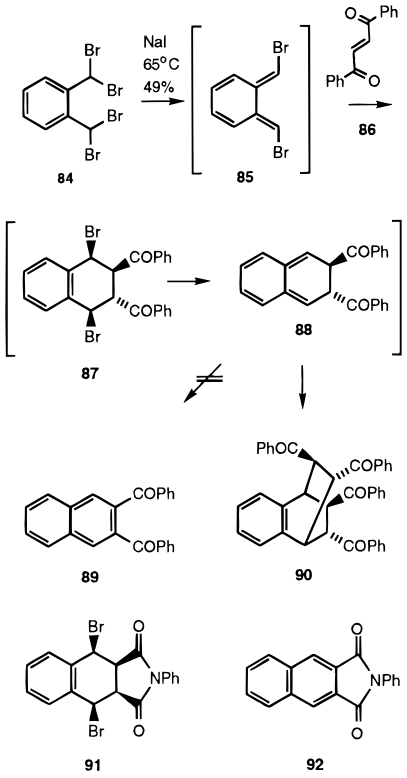
VI. Masked Bis-o-Quinodimethanes as Bis-Dienes

The use of bis-*o*-quinodimethanes can lead to the formation of both linear and bridged polycyclic ring systems, as recently described by Cava (Scheme 18).[33] Reaction of **84** and excess *trans*-1,4-diphenyl-2-butene-1,4-dione (**86**), in the presence of excess sodium iodide, led to the formation of the tricyclic tetraketone **90** in 49% yield. The stereoselective formation of **90** can be attributed to the minimization of steric interactions between the carbonyl substituents in the approach of the dienophile **86** to the *o*-quinodimethane **88**. The authors have applied **90** as an intermediate for the preparation of heterocyclic analogs of trypticene.

The same authors had previously reported that reaction of N-phenylmaleimide with **84** in the presence of sodium iodide led to the formation of **92**, the product of a single cycloaddition followed by aromatization.[34] However, none of the expected naphthalene product, **89**, was observed in the reaction of **84** with **86**, indicating that the generation of the second quinodimethane **88** from adduct **87** is considerably faster than its aromatization to **89**. The authors attribute this difference in product outcome to stereochemical differences in adducts of **85** with a transoid dienophile, i.e., **86**, as compared to adducts of **85** with a cis dienophile, i.e., maleimide.

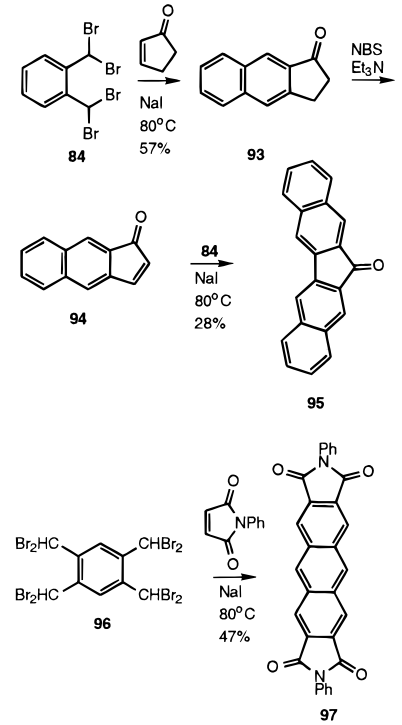
McLaughlin has recently reported the application of this approach to the synthesis of linear aromatic

Scheme 18



systems (Scheme 19). Reaction of **84** with cyclopentenone leads to the formation of **93** in 57% yield, which upon oxidation to enone **94** undergoes a second cycloaddition with the *o*-quinodimethane derived from **84** to give the pentacyclic ketone **95** in 28% overall yield. The same authors reported the utility of tetrakis(dibromomethyl)benzene **96** as a bis-*o*-quinodimethane, which undergoes cycloaddition with two equiv of maleimide to generate anthracene **97** in 47% yield.[35]

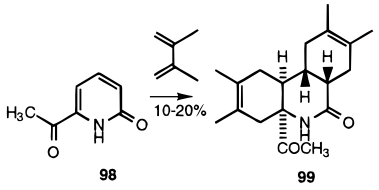
Scheme 19



VII. Nonacetylenic Bis-Dienophiles

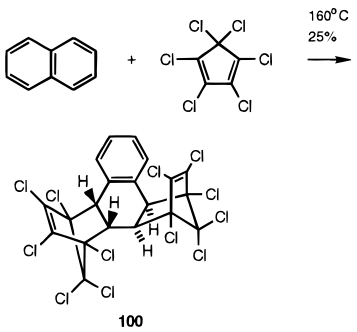
The utility of both masked and unmasked nonacetylenic bis-dienophiles has been the subject of extensive study. Hongo has reported that, in addition to their known reactivity as dienes, suitably substituted 2(1*H*)-pyridones **98** can react with 2,3-dimethylbutadiene to give tricyclic products such as **99**, albeit in modest (10−20%) yields (Scheme 20).[36]

Scheme 20



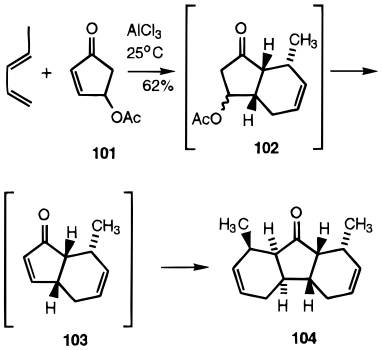
Chanon and co-workers have reported that naphthalene can react as a bis-dienophile under forcing reaction conditions (Scheme 21).[37] Exposure of naphthalene to hexachlorocyclopentadiene (160 °C, 120 h) led to the formation of the bis-Diels−Alder adduct **100**, albeit in modest (25%) yield. The stereochemistry of the product was determined unambiguously by single crystal X-ray analysis.

Scheme 21



A one-pot synthesis of hydrofluorenones has been described by Tatacchi, using 4-acetoxycyclopentenone as a synthetic equivalent of cyclopentadienone, which is itself thermally unstable.[38] Reaction of **101** with piperylene and aluminum chloride led to the formation of **102**, which upon elimination of an equivalent of acetic acid liberated the second dienophile, **103**, which reacted with additional piperylene and aluminum chloride to give a mixture of four diastereomeric tricyclic ketones (21:7:4:1) in 62% yield, of which **104** is the major product of the reaction (Scheme 22).[39]

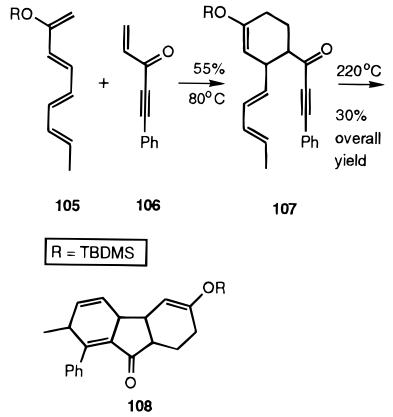
Scheme 22



VIII. Tandem Cycloaddition Using Acyclic Bis-Dienes

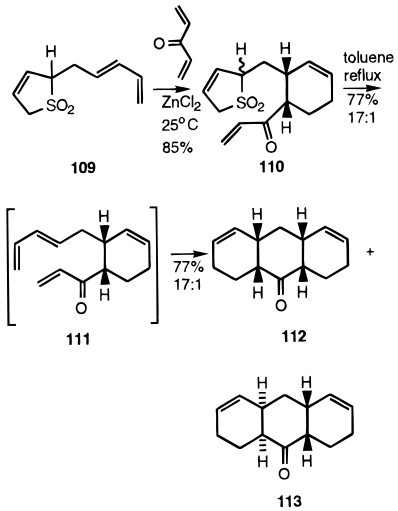
An alternative tandem approach to the synthesis of the fluorenone nucleus has been described by Kraus and Taschner, who have reported a "timed" Diels−Alder reaction with nona-1,3,6,8-tetraene **105** and divinyl or alkynyl vinyl ketones (Scheme 23) for the construction of the fluorenone ring system.[40] Reaction of **105** with **106** in refluxing carbon tetrachloride leads to the formation of **107** in good yield, which on heating in a sealed tube at elevated temperature (>200 °C) leads to modest yields (ca. 20−30%) of the fluorenone **108**. The authors reported that direct heating of **105** and **106** at 240 °C resulted in reduced yields of the desired tricyclic structures, presumably due to polymer formation.

Scheme 23



Recent results from our laboratory have demonstrated that the preparation of tricyclic ring systems using this strategy can be achieved in excellent overall yield by (1) changing the size of the central ring, i.e., extending the tether between the two dienes to greater than a single methylene, and (2) protecting one of the two dienes as a sulfolene ring,[41] which facilitates the controlled formation of the first ring by intermolecular Diels−Alder cyclization, with the caveat that the reaction temperature for the first cycloaddition must be lower than that required for the extrusion of SO_2 from **109** (Scheme 24).

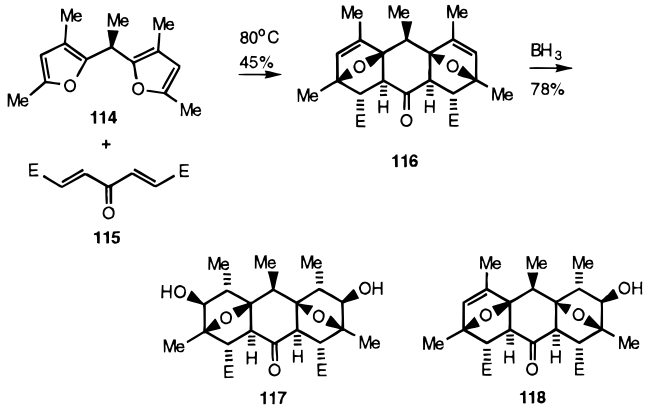
Scheme 24



Reaction of **109** with divinyl ketone in the presence of $ZnCl_2$ at 25 °C led to the formation of a 1:1.1 ratio of the diastereomeric mono-Diels−Alder adducts **110** in 85% yield. Heating **110** in refluxing toluene led, via extrusion of SO_2, to the diene intermediate **111**. Under these reaction conditions, intramolecular Diels−Alder cyclization occurred, leading to the formation of the second and third rings in this cascade and the isolation of two tricyclic ketodienes, **112** and **113**, in a 17:1 ratio in 77% yield. Both of the tricyclic products result from intramolecular Diels−Alder reaction via an endo transition state, i.e., only cis-fused products are obtained; however, the relative stereochemistry between the two ring fusions is different in **112** and **113**. The selective formation of the cis-syn-cis adduct **112** is consistent with results obtained by energy minimization of the diastereomeric transition state structures for the formation of **112** and **113** using the force field method described by Houk and co-workers for internally activated Diels−Alder reactions.[42] These calculations predict a product distribution of **112** and **113** in a ratio of 22:1, respectively (E_{rel} = 2.4 kcal/mol at 384 K), which is in excellent agreement with the experimentally observed product ratio (17:1).

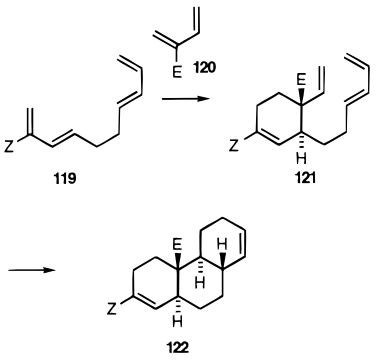
Vogel and Marchionni have independently applied this strategy in the context of synthesizing polypropionate fragments (Scheme 25).[43] The tandem cycloaddition reaction of **114** and **115** gives **116** in 45% yield. Bishydroboration (BH_3·DMS, $NaBO_3$·$4H_2O$) then gives the symmetrical diol **117** in 78% yield. These authors have also examined the desymmetrization of the Diels−Alder adduct by asymmetric hydroboration, which affords monoalcohol **118** with 80% ee, although the absolute stereochemistry of the product has not been established. The stereoselective synthesis of **117** in two steps from simple precursors underscores the utility of this double-Diels−Alder cycloaddition strategy for the rapid construction of stereochemically rich polycyclic ring systems.

Scheme 25



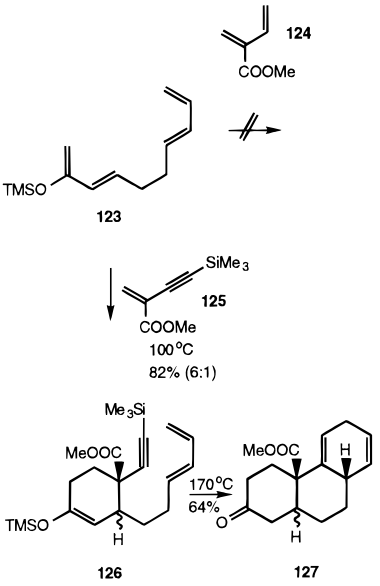
A synthesis of the perhydrophenanthrene skeleton, which is common to steroids and triterpenoids, using the tandem Diels−Alder reaction has recently been described by Spino and co-workers.[44,45] These authors proposed that the regiochemistry of the cycloaddition of tetraene **119** with diene **120** could be controlled by judicious addition of electron-donating (Z) and electron-withdrawing groups (E) to give the bimolecular adduct **121**, which could then undergo intramolecular addition to give **122** (Scheme 26).

Scheme 26



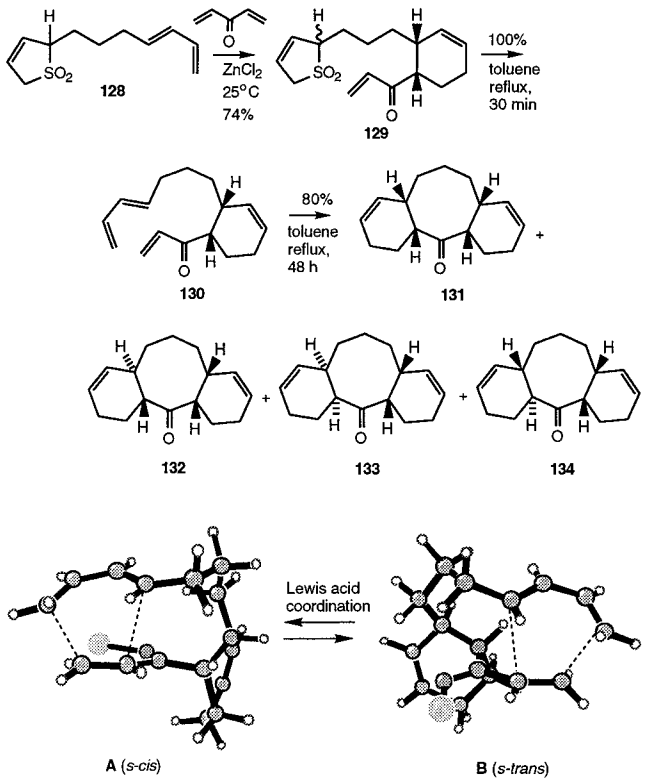
In the event, reaction of tetraene **123** with 2-carboxymethylbutadiene **124** gave none of the desired Diels−Alder adduct because of competing dimerization of **124**. Substitution of **125** for **124** led to the formation of the desired product, **126**, as a 6:1 mixture of diastereomers in 82% yield, which on enol ether hydrolysis, desilylation, and heating underwent intramolecular Diels−Alder cycloaddition in 64% yield to give a 5:1 mixture of the desired tricyclic ring system, **127** (Scheme 27).

Scheme 27



The formation of tricyclic systems in which the central ring is an eight-membered ring provides an important test for the generality of this double-Diels−Alder process, since the second, intramolecular cycloaddition reaction might not be expected to compete efficiently with intermolecular cycloaddition. We have recently demonstrated that eight-membered rings can be formed efficiently using this approach with interesting stereochemical consequences (Scheme 28). Reaction of **128**, prepared from butadiene sulfone and heptadienyl bromide, with divinyl ketone

Scheme 28



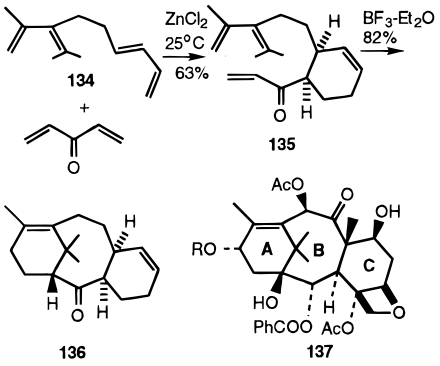
in the presence of 2 equiv of $ZnCl_2$ at 25 °C led to the formation of a ca. 1:1 ratio of two inseparable endo Diels–Alder adducts **129** in 74% yield. Thermolysis of this mixture in refluxing toluene gave a single diene, **130**, in quantitative yield, which on prolonged heating (5 mM in toluene, 36 h) led to the selective formation of two of the four possible diastereomeric tricyclic products, **131** and **132**, in a 1.1:1 ratio in 80% yield.[41] It is interesting to note that only one of the two possible endo intramolecular Diels–Alder adducts (**131** and not **133**) and only one of the two possible exo Diels–Alder adducts (**132** and not **134**) are formed under the thermal reaction conditions.

Intramolecular Diels–Alder cycloaddition of **130** in the presence of $EtAlCl_2$ led to the predominant formation of the cis-anti-cis product **133**, along with **131**, **132**, and the trans-syn-cis isomer **134** (55% yield in a 8.5:2.2:1.0:1.8 ratio). While the endo/exo selectivity (**131**+**133**/**132**+**134**) is increased relative to the thermal process (4:1 vs 1:1), it is striking that the Lewis acid does not promote the formation of **131** (the major product of the thermal reaction) but instead leads to the selective formation of **133**, the formation of which was not observed under the thermal (non-Lewis acid) reaction conditions.

Both the thermal and Lewis acid-catalyzed results are consistent with the transition state structures shown in Scheme 28, in which the light gray sphere in B represents a Lewis acid. The s-cis formation of the dienophile[42] as shown in A leads to the selective formation of products in which the angular hydrogens (α to the carbonyl group) have a cis stereochemical relationship on the eight-membered ring (the same relative stereochemistry observed in the formation of **112** from **111** in Scheme 24). However, Houk has previously demonstrated that Lewis acid complexation changes the preferred dienophile conformation from s-cis to s-trans.[42] Cyclization via the Lewis acid-complexed s-trans conformer B leads to the predominant formation of **133**, in which the two angular hydrogens α to the carbonyl have a trans stereochemical relationship on the eight-membered ring. While numerous examples exist for the enhancement of endo/exo selectivities in the Diels–Alder reaction by Lewis acid catalysis,[46] this is the first example of asymmetric induction in the Diels–Alder reaction via control of the dienophile conformation (s-cis vs s-trans) by Lewis acid complexation.

The synthetic utility of this tandem Diels–Alder cycloaddition strategy is underscored by the highly efficient two-step approach to the synthesis of taxanes that we have recently described.[47] The sequence outlined in Scheme 29, in which both the A and C

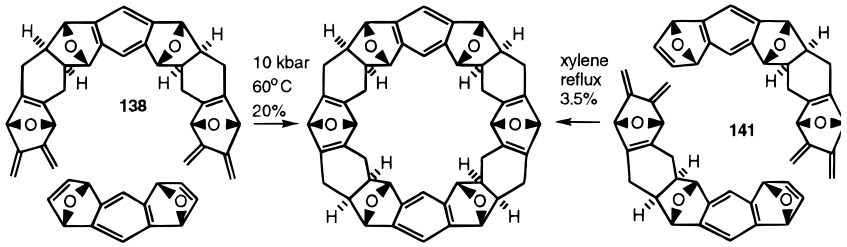
Scheme 29



rings of taxol are prepared via Diels–Alder cycloaddition,[48] proceeds in 50% overall yield. The intermolecular Diels–Alder reaction of **134** with divinyl ketone proceeded *via* $ZnCl_2$ catalysis to give cyclohexene **135** in 63% yield. In contrast to our preliminary study of the tandem Diels–Alder reaction (Schemes 24 and 28),[41] we find here that the difference in reactivity of the mono- and tetra-substituted diene units in **134** is sufficiently great that protection of the second diene moiety is not necessary for highly regioselective bimolecular cycloaddition to occur. The second, *intra*molecular, Diels–Alder cycloaddition occurs via $BF_3 \cdot Et_2O$ catalysis to give the tricyclic ketone **136** as a single diastereomer in 82% yield. It is interesting to note that neither Lewis acid is capable of catalyzing both Diels–Alder reactions.

Two complementary tandem Diels–Alder approaches to the synthesis of molecular belts have recently been described by Stoddart (Scheme 30).[49] The preparation of the target structure **140** can be achieved in 20% yield by subjecting bisdiene **138** and bisdienophile **139** to high pressure (10 kbars) in dichloromethane at 60 °C. In contrast to this "homo" Diels–Alder reaction, in which a bis-diene combines with a bis-dienophile, the same product, **140**, can be obtained, albeit in 3.5% yield in a "hetero" tandem-Diels–Alder construction in which two diene–dienophile hybrids **141** are dimerized.

Scheme 30



IX. Conclusion

The tandem Diels−Alder reaction leads to unique approaches to the synthesis of polycyclic ring systems. As noted in this review, important advances have been recorded in the application of this methodology to the construction of diverse classes of compounds. The syntheses of complex cage systems, anthracyclines, linearly fused aromatics, and molecular belts all underscore the utility of this methodology in organic synthesis. Work from laboratories around the world has amply demonstrated the importance of this reaction sequence for the highly stereoselective preparation of tricyclic ring systems, and these studies have led to a novel approach to the synthesis of taxanes from two simple acyclic precursors in our own laboratory. These studies suggest that this cycloaddition cascade will continue to play an important role in the highly efficient construction of complex organic structures.

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