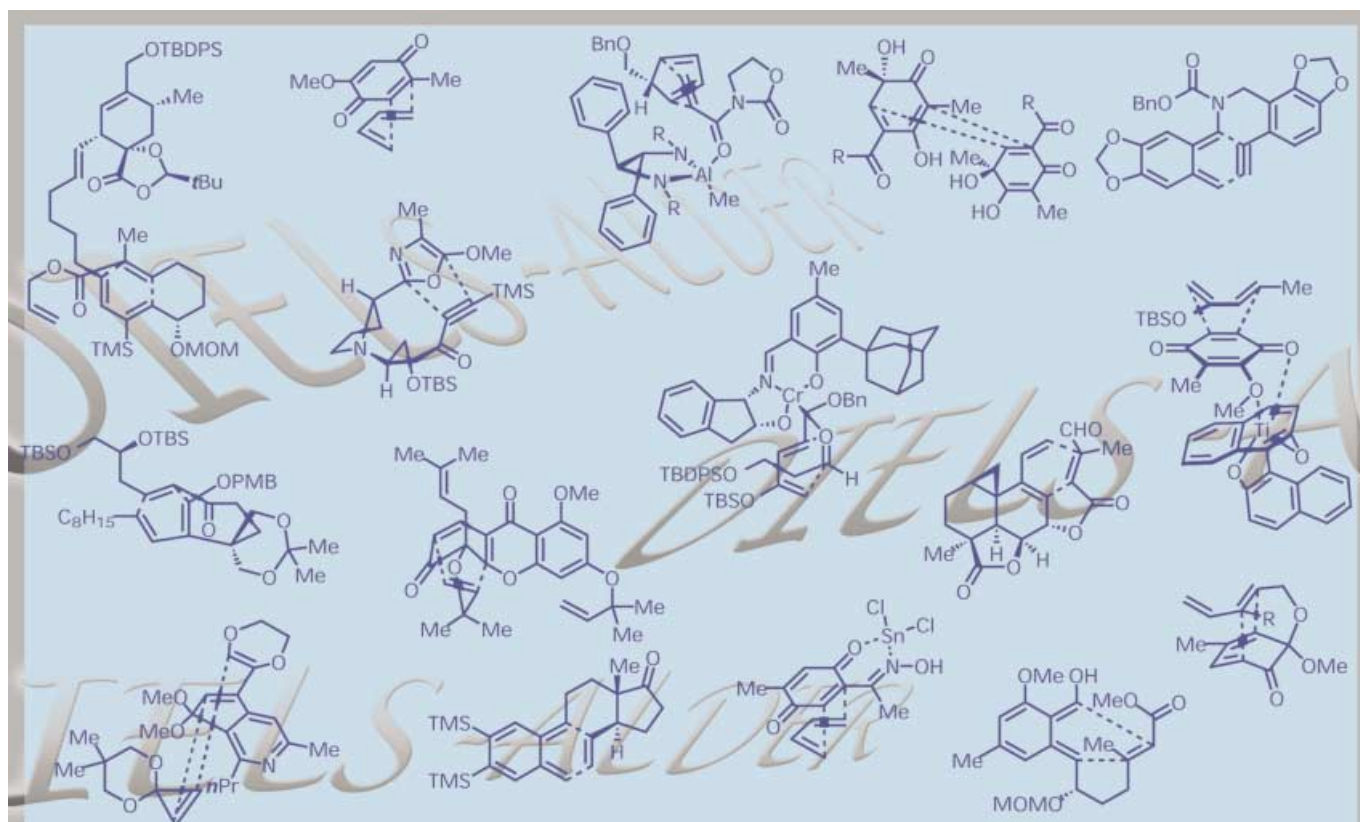
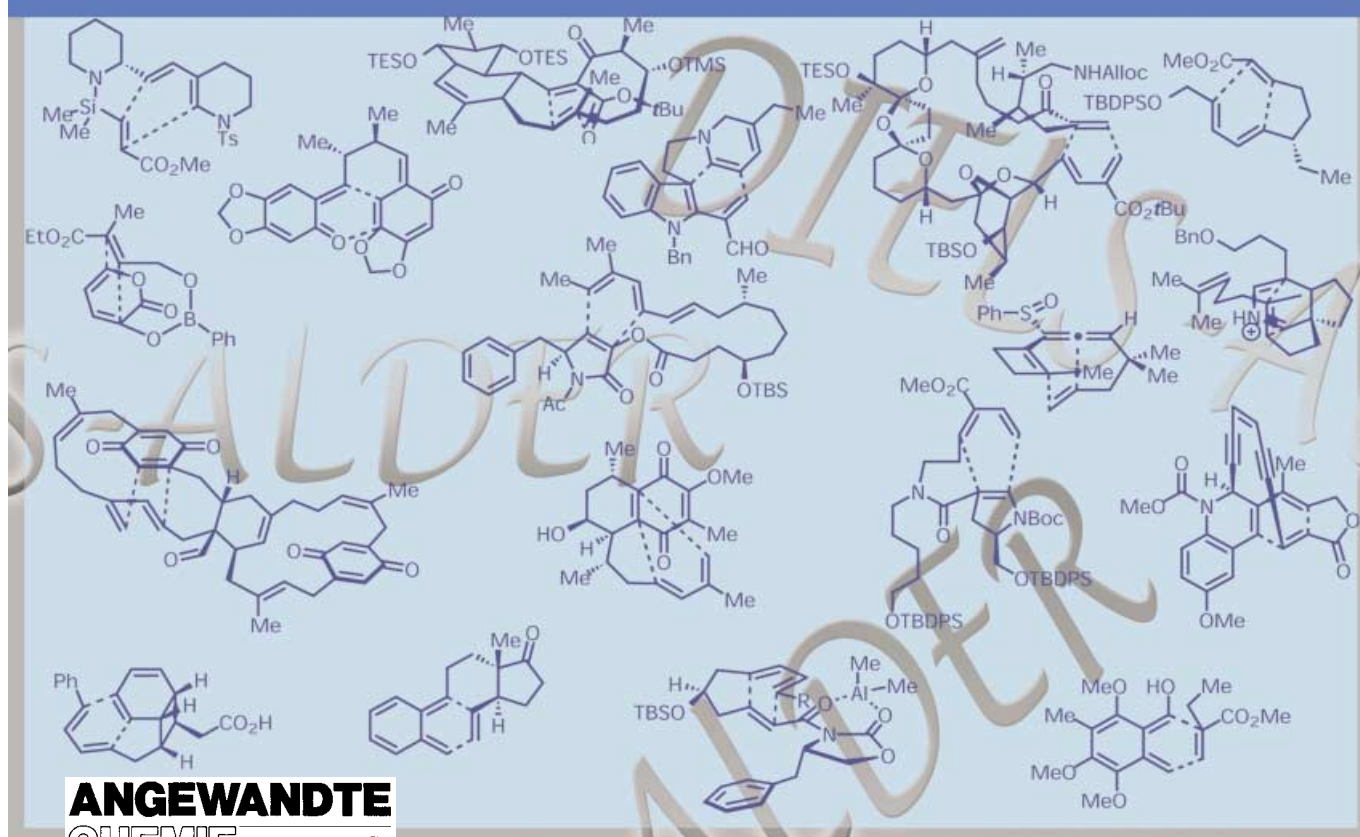




The *Diels-Alder* Reaction in Action



The Diels–Alder Reaction in Total Synthesis

K. C. Nicolaou,* Scott A. Snyder, Tamsyn Montagnon, and Georgios Vassilikogiannakis

The Diels–Alder reaction has both enabled and shaped the art and science of total synthesis over the last few decades to an extent which, arguably, has yet to be eclipsed by any other transformation in the current synthetic repertoire. With myriad applications of this magnificent pericyclic reaction, often as a crucial element in elegant and programmed cascade sequences

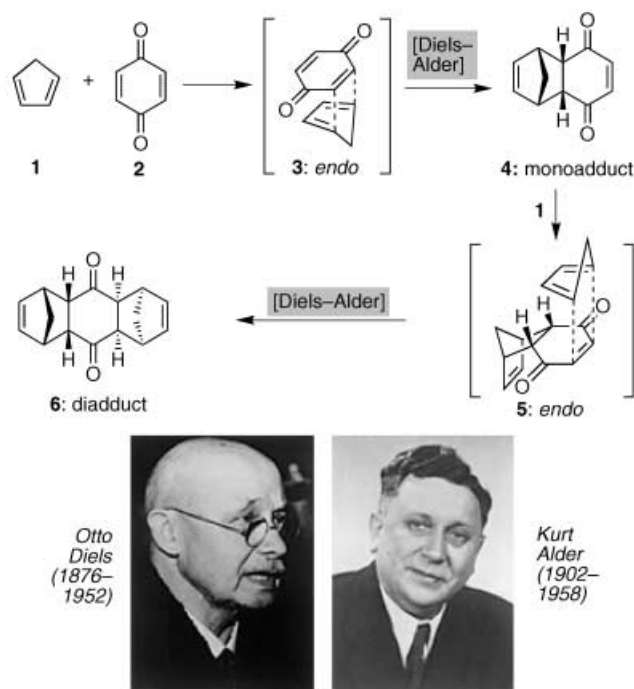
facilitating complex molecule construction, the Diels–Alder cycloaddition has afforded numerous and unparalleled solutions to a diverse range of synthetic puzzles provided by nature in the form of natural products. In celebration of the 100th anniversary of Alder's birth, selected examples of the awesome power of the reaction he helped to discover are discussed in this

review in the context of total synthesis to illustrate its overall versatility and underscore its vast potential which has yet to be fully realized.

Keywords: biomimetic synthesis • cycloaddition • Diels–Alder reaction • molecular diversity • total synthesis

1. Introduction

After numerous near-discoveries of the [4+2] cycloaddition reaction by several luminaries in the field of organic chemistry during the early part of the 20th century,^[1, 2] the keen insight of Professor Otto Diels^[3] and his student, Kurt Alder,^[4] in properly identifying the products (**4** and **6**, Scheme 1) arising from the reaction of cyclopentadiene (**1**) with quinone (**2**) denotes a historic event in the field of chemistry for which these two individuals were rewarded with a reaction that would henceforth bear their names.^[5] With prophetic foresight, Diels and Alder clearly anticipated the importance of this discovery in their landmark 1928 paper, particularly as applied to natural product synthesis, through the following remark: “Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps even alkaloids, has been moved to the near prospect.” However, in an intriguing moment of scientific territoriality, which might appear slightly off-color or even amusing to a contem-



Scheme 1. The discovery of the Diels–Alder reaction in 1928, a reaction for which the namesakes would receive the Nobel Prize in Chemistry in 1950: Diels the professor, Alder the student.^[5]

porary audience, the authors issued the following ominous warning to those researchers interested in applying their discovery to total synthesis: “We explicitly reserve for ourselves the application of the reaction developed by us to the solution of such problems.”^[2]

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Up to the time of their receipt of the Nobel Prize in 1950 it seems that, for the most part, the synthetic community heeded the demand of Diels and Alder, as their cycloaddition reaction did not feature prominently in any total synthesis prior to the stereocontrolled generation of cantharidin^[6] by Stork et al. in 1951, or the first synthesis of morphine^[7] reported a few months later in which Gates and Tschudi employed the pericyclic process. The apparent delay in applying the Diels–Alder reaction, or “diene synthesis” as it was known at the time, to total synthesis was likely the consequence of a variety of factors. First, with few exceptions, total synthesis during

that period played a role inclined more towards structure verification than as its own unique vehicle to advance the field of organic synthesis, as it is practiced today. As such, in a discipline defined by converting known materials by existing methods into other compounds, practitioners would not likely have regarded being the “first” to employ a particular transformation in a synthesis as an important contribution, and the number of compounds in which the Diels–Alder reaction had been demonstrated was limiting in terms of potential synthetic targets. Moreover, the founders of the reaction, while they certainly made significant forays in the



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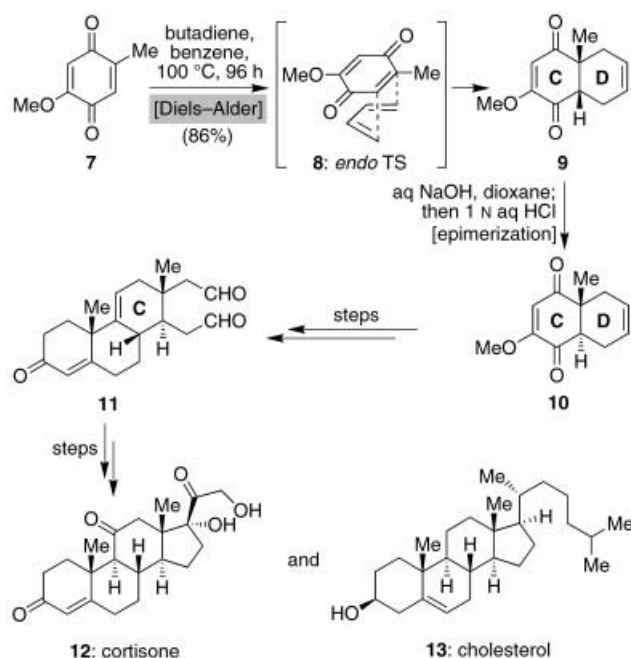
Scott A. Snyder, born in Palo Alto, California in 1976, spent his formative years in the suburbs of Buffalo, New York. He received his B.A. in Chemistry (summa cum laude) from Williams College, Williamstown, Massachusetts, in 1999, where he explored the hetero-Diels–Alder reaction with Prof. J. Hodge Markgraf. He then began graduate studies with Prof. K. C. Nicolaou, where he has devoted his attention to the chemistry and biology of the marine-derived antitumor agent diazonamide A. He is the recipient of a Barry M. Goldwater Fellowship in Science and Engineering, a National Science Foundation Predoctoral Fellowship, and a Graduate Fellowship from Pfizer, Inc. His research interests include complex natural product synthesis, reaction mechanism and design, and application of these fields to chemical biology.

Tamsyn Montagnon was born in Hong Kong in 1975. She received her B.Sc. in Chemistry with Medicinal Chemistry from the University of Leeds, UK, which was followed by a move to the University of Sussex where she obtained a D.Phil in 2000 for research conducted under the supervision of Professor P. J. Parsons, towards the synthesis of complex natural products, including the squalostatins and triptotoquinone C. She was awarded a GlaxoWellcome post-doctoral fellowship and joined Professor K. C. Nicolaou's group in January 2001. Her research interests include natural product synthesis, medicinal chemistry, and reaction methods and mechanisms.

Georgios E. Vassilikogiannakis was born in Iraklion, Crete, Greece in 1970. He received his B.Sc. in Chemistry in 1993 and his Ph.D. in 1998 from the University of Crete under the guidance of Professor Michael Orfanopoulos exploring the mechanisms of the electrophilic additions of singlet oxygen, tetracyanoethylene, triazolinediones, and fullerenes to alkenes and dienes. He joined Professor K. C. Nicolaou's group in 1999, and was involved in the total syntheses of bisorbicillinol, bisorbibutenolide, trichodimerol, and colombiasin A. He was recently appointed Assistant Professor of chemistry at the University of Crete, Greece. His primary research interests involve the synthesis of natural products as an enabling endeavor for the discovery of new chemical knowledge and its application to chemical biology.

area of terpene synthesis,^[8] became diverted by other research concerns of greater interest to them, particularly in regard to understanding the mechanistic underpinnings of the reaction they had discovered.^[9] Significantly, these efforts ultimately resulted in such important advances as the Alder *endo* rule that governs the stereochemical outcome of the typical Diels–Alder reaction.^[10] The most dominant reason for the delay in the incorporation of the Diels–Alder cycloaddition into total synthesis, however, might be attributed to World War II and its aftermath, a period for which no analysis can properly estimate the challenges to conducting research in organic synthesis, particularly in Germany.

As such, the truly visionary application of the Diels–Alder reaction to total synthesis would have to await the imagination of chemical artists such as R. B. Woodward, who would apply new levels of creativity to the reaction at hand through some highly elegant and instructive syntheses. In 1952, Woodward et al. disclosed their historic routes to the steroids cortisone and cholesterol (**12** and **13**, respectively, Scheme 2)

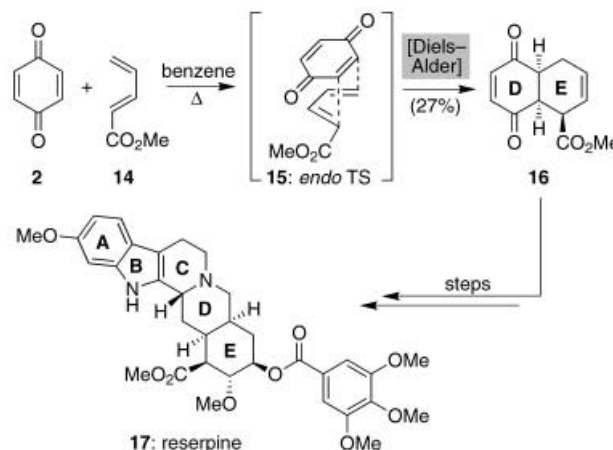


Scheme 2. The pioneering adoption of a quinone-based Diels–Alder reaction by Woodward et al. in 1952 as the key step in the total synthesis of the steroid hormones cortisone (**12**) and cholesterol (**13**).^[11]

where, in the initial step, reaction of quinone **7** with butadiene in benzene at 100 °C for 96 hours effected a smooth Diels–Alder cycloaddition to form bicyclic adduct **9** via the intermediacy of *endo* transition state **8**.^[11] Several features of this particular [4+2] cycloaddition reaction are of note. First, Woodward recognized that by using a differentiated quinone nucleus it would be possible to effect regioselective control of the intermolecular Diels–Alder union, as the more electron-rich methoxy-substituted olefin would be less dienophilic than its methyl-substituted counterpart. An equally insightful design element was the anticipation that even though a *cis*-fused adduct would arise from the Diels–Alder reaction, conversion into the requisite thermodynamically

more stable *trans*-fused system present in the targeted natural products would be relatively simple to achieve. Thus, in the next synthetic operation, base-induced epimerization readily provided the coveted *trans*-fused ring system (**10**), thus setting the stage for an eventual ring-contraction process that would allow completion of this region of the steroid nucleus.^[12]

Similar levels of synthetic ingenuity are reflected in the total synthesis of reserpine (**17**, Scheme 3) by Woodward et al. in 1956,^[13] where again an opening Diels–Alder reaction forged the critical bicyclic system (**16**) that would serve as the



Scheme 3. Application of the Diels–Alder reaction in the total synthesis of reserpine (**17**) by Woodward et al. in 1956.^[13]

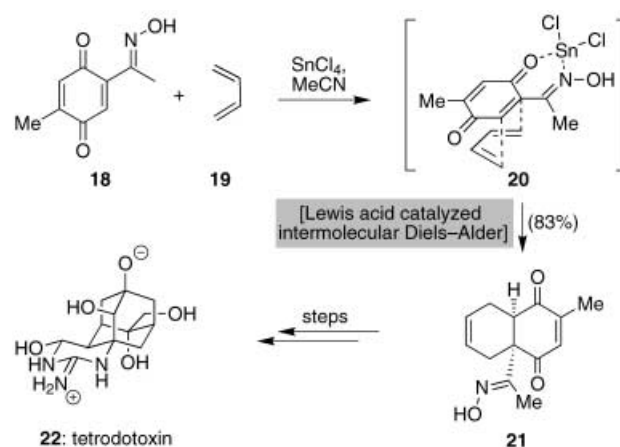
scaffold for the ensuing synthetic sequence.^[14] This use of a Diels–Alder strategy to form an initial array of rings and stereocenters, elements which pave the way for subsequent stereocontrolled elaboration to the final target molecule, represents a distinctive hallmark of Woodward's synthetic acumen. Moreover, these two examples from Woodward's research group are illustrative of a new school of thought that emerged in the 1950s which involved approaching the synthesis of complex molecules by rational synthetic strategies, and they admirably demonstrated the inherent strength of the Diels–Alder reaction to solve challenging synthetic puzzles which might otherwise have remained hopelessly complex.

In this review, we hope to highlight didactic exemplars of the Diels–Alder reaction in the context of natural product total synthesis representing work which has decisively advanced both the power and scope of this pericyclic process beyond the pioneering applications of Woodward. In selecting our case studies, we accepted the fact that any review of such a widely used reaction with nearly three-quarters of a century of history could not possibly be comprehensive. Our aspiration is that the delineated examples will sufficiently cover the various areas in which Diels–Alder methodology represents an indispensable tool for the art of total synthesis, and will reflect key paradigm shifts in the field through novel and inventive approaches to this classic reaction. We hope that these discussions will inspire you not only to further explore the literature in terms of syntheses not expounded upon here, but also to create even more fantastic applications of the Diels–Alder reaction in your own research.

2. Regiocontrol and Beyond: Achieving Stereoselection

The early total syntheses by Woodward described above amply illustrate the ability of the Diels–Alder reaction to create molecular complexity. Not only is a cyclohexene ring generated through the formation of two new σ bonds, but up to four contiguous stereocenters are also concomitantly fashioned in the process. Fortunately, as a result of the regio- and stereospecific nature of the Diels–Alder reaction (always a *cis* addition) and the diastereoselectivity of the union based on the Alder *endo* rule^[10] (where a more sterically crowded and seemingly less thermodynamically stable transition state results when the dienophile possesses a suitable conjugating substituent), the formation of these chiral elements is often predictable in a relative sense. However, new principles and approaches to the Diels–Alder reaction would be needed beyond those delineated in the syntheses of reserpine and cholesterol if absolute control of stereochemistry is required. In addition, although Woodward's Diels–Alder reactions elegantly achieved regioselectivity, results which can be rationalized successfully on the basis of frontier molecular orbital theory,^[15] these examples do not reflect the challenges faced in attempting to achieve such control in certain contexts where particular unsymmetrical diene and/or dienophile units having specific steric and electronic properties are employed. As such, general solutions would be required to address the problem of selectively incorporating useful sets of diverse functionality in Diels–Alder cycloaddition products. In this section, we highlight some answers to the issues of regio- and stereoselectivity which have been developed by leading synthetic chemists to provide a qualitative measure of the current state of the art in Diels–Alder technology.

A classical method to enhance regioselectivity is based on the use of Lewis acid catalysts. Upon complexation of such species to the dienophile, the normal demand Diels–Alder reaction is promoted since the energy gap between the lowest unoccupied molecular orbital (LUMO) of the dienophile and the highest occupied molecular orbital (HOMO) of the diene is reduced, thus decreasing the activation energy required to achieve the cycloaddition. Moreover, as this stabilization is greater for the *endo* transition state, as a result of beneficial enhancement of secondary orbital overlap that is unobtainable in an *exo* mode of reaction, the use of Lewis acids favors an increased ratio of *endo:exo* products. More valuable synthetically, however, is the fact that Lewis acids can often reverse the regiochemical course of a Diels–Alder addition and generate products that would not otherwise be observed in a simple, thermally induced reaction.^[16] An early and elegant example of this concept is provided by the total synthesis of tetrodotoxin (**22**, Scheme 4) by Kishi et al.^[17] As in the Woodward paradigm, an initial Diels–Alder union between quinone **18** and butadiene (**19**) was employed to generate a preliminary set of rings and stereocenters for subsequent elaboration. However, the intriguing feature of this example is that the use of SnCl_4 in the Diels–Alder reaction proved critical for the chemoselective engagement of butadiene with the oxime-bound dienophile to form **20**; in the absence of the Lewis acid, the other olefinic bond of quinone

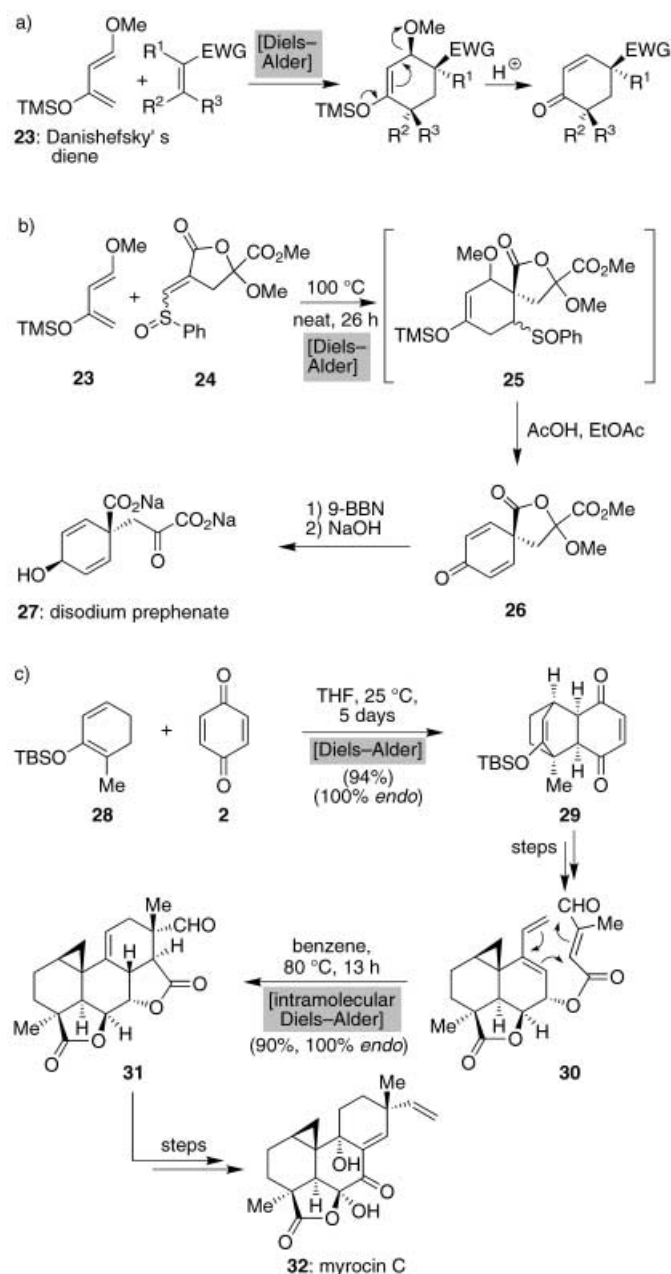


Scheme 4. Use of Lewis acid catalysis by Kishi et al. (1972) to achieve chemoselective control in the formation of key intermediate **21** leading to tetrodotoxin (**22**).^[17]

18 reacted exclusively. Although oximes normally behave mesomerically as electron-donating substituents, thus deactivating the neighboring olefin for Diels–Alder reaction, coordination of the Lewis acid reverses this behavior by drawing electron density away from this group, which leads to an adjacent highly competent electron-deficient dienophile.^[18] Thus, Lewis acid activation nicely effected regiochemical control in the employed [4+2] cycloaddition that could not have been achieved otherwise.

Among other methods introduced to achieve excellent regioselectivity, as well as to incorporate useful functional groups, Danishefsky's widely applicable diene system (**23**, Scheme 5a) represents one of the most important advances in this regard within the past quarter century.^[19] Initially developed as part of a method to selectively generate pyran rings upon reaction with aldehyde dienophiles,^[20] the power of the prototype diene **23** rests in the synergistic effects of the two incorporated oxygen groups, which provide mutually reinforcing electronic contributions to the diene system such that regiospecific formation of a lone *endo* adduct results upon reaction with most dienophiles. In addition, upon treatment with mild acid after the Diels–Alder reaction, cleavage of the silyl protecting group residing within the product and the strategic location of the methoxy leaving group enables an ensuing cascade sequence that results in the formation of an α,β -unsaturated system. An early demonstration of this strategy in total synthesis can be found in the route used by Danishefsky et al. to form disodium prephenate (**27**, Scheme 5b),^[21] where, although the target may not seem to possess great molecular complexity, application of this designed diene technology provided a highly elegant and concise solution to the synthetic problem at hand. As illustrated, after regioselective formation of Diels–Alder product **25**, in situ treatment of this compound with acetic acid formed the desired α,β -unsaturated system which concurrently eliminated phenyl sulfoxide to provide **26**, a product which was easily elaborated to the target structure.

The versatility of this particular technology is underscored by the wide variety of such dienes that can be employed.^[22] For example, use of a Danishefsky-type diene (**28**, Scheme 5c)

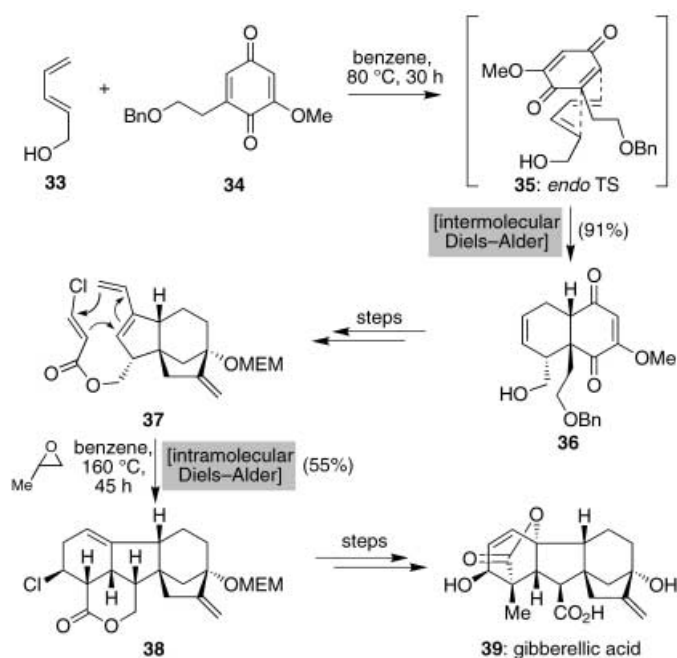


Scheme 5. Danishefsky's diene (**23**) and its use in organic synthesis: a) generalized stereochemical outcome of Diels–Alder reactions in this paradigm; b) use of **23** as part of the total synthesis of disodium prephenate (**27**; 1979);^[21] c) employment of a Danishefsky-type diene (**28**) in the total synthesis of myrocin C (**32**) featuring two Diels–Alder reactions (1994).^[23]

provided an impressive entry into the total synthesis of myrocin C (**32**),^[23] even though in this particular case achieving regioselective addition to quinone **2** was clearly not a critical feature of the designed route. The second Diels–Alder reaction in Danishefsky and co-workers elegant sequence to myrocin C (**30**→**31**) is also significant as it reflects an additional means of controlling relative stereochemistry of the process, pertinent only in intramolecular cases, on the basis of substrate control. As illustrated in this example, the stereocenter proximal to the dienophile governed the addition of this unit to only one diastereotopic face

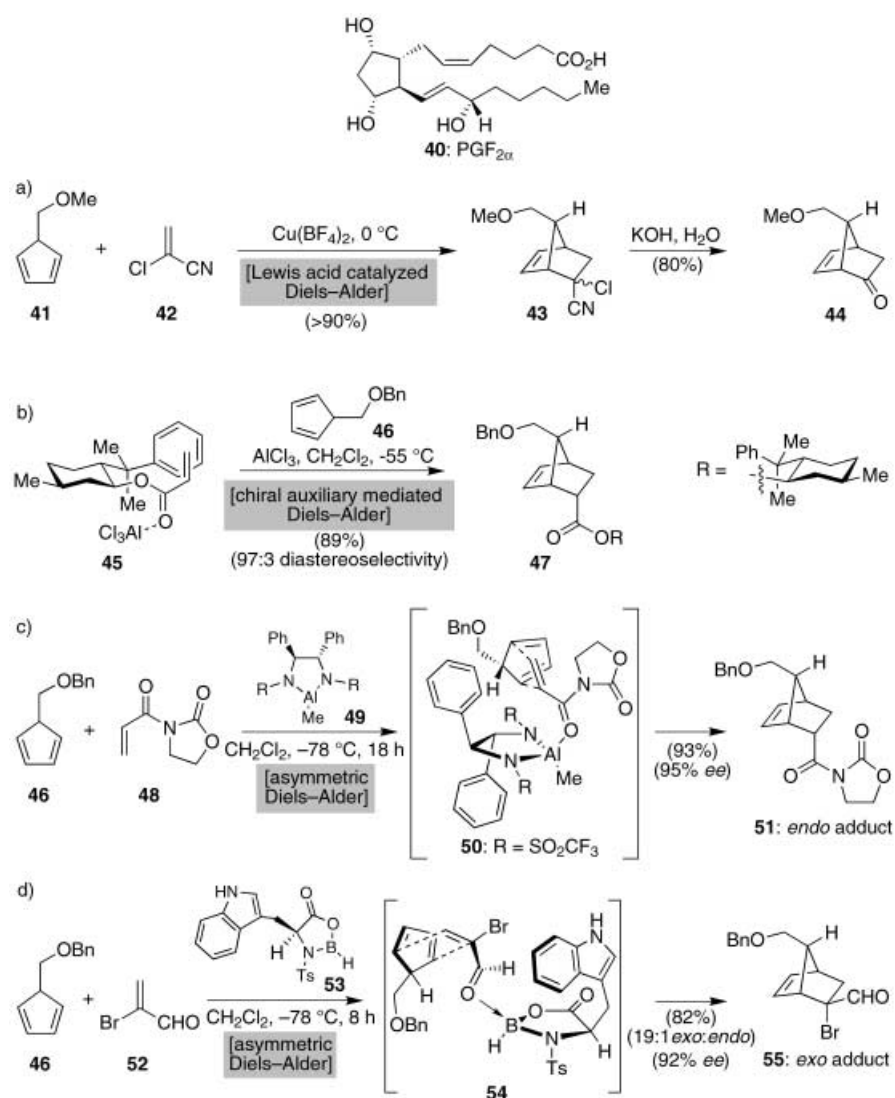
of the 1,3-diene system, thus setting the resultant stereochemistry of the product (**31**) in a relative sense.

The power of such strategies to exert stereochemical control is similarly reflected in the brilliant total synthesis of gibberellic acid (**39**, Scheme 6) by Corey et al.,^[24] where an initial chemo- and regioselective Diels–Alder union between diene **33** and quinone **34** forged the relative stereochemistry in **36**, and subsequent elaboration to **37** enabled a substrate-controlled intramolecular Diels–Alder reaction which proceeded with selective formation of the expected product (**38**).^[25] Overall, one should note that the outcome of the Diels–Alder reaction in these intramolecular instances is generally predictable based on the stereochemical requirements of the resident set of functionalities.



Scheme 6. Use of both inter- and intramolecular Diels–Alder reactions in the stereocontrolled synthesis of gibberellic acid (**39**) by Corey et al. (1978).^[24]

Despite these remarkable early advances in developing methods to achieve relative stereochemistry, the issue of controlling the absolute stereochemistry of the Diels–Alder reaction was not successfully addressed until more recent times. An instructive entry into the several elegantly conceived solutions to this problem is afforded by following the progression of the numerous total syntheses of prostaglandin $F_{2\alpha}$ (PGF_{2 α} , **40**, Scheme 7) and its relatives by Corey et al.^[26] The overall challenge of governing the absolute stereochemistry of Diels–Alder products in contexts pertinent to the synthesis of these secondary metabolites is demonstrated in the initial total synthesis of PGF_{2 α} , first disclosed in 1969 by Corey et al.^[26c] In this approach (Scheme 7a), a Lewis acid catalyzed Diels–Alder union between diene **41** and 2-chloroacrylonitrile (**42**) afforded a racemic mixture of Diels–Alder adducts (**43**), as would be expected since the enantiotopic faces of **41** are not differentiated. The random stereochemistry at the carbon center



Scheme 7. Creative and didactic applications of the Diels–Alder reaction by Corey et al. to the total synthesis of prostaglandin $\text{F}_{2\alpha}$ (**40**): a) original approach using a ketene equivalent (1969);^[26c] b) application of a chiral auxiliary to orchestrate the enantioselectivity of the Diels–Alder union (1975);^[26f] c) asymmetric catalysis of the Diels–Alder reaction to afford the *endo* adduct in high enantiomeric excess (1989);^[26g] d) reversal of selectivity to near-complete *exo* topicity by using chelation with a chiral oxazaborolidinone catalyst (1992).^[26h]

bearing the chloro and cyano substituents was of no consequence since it was destroyed in a subsequent hydrolysis event to reveal ketone **44**. As such, an asymmetric synthesis of prostaglandin $\text{F}_{2\alpha}$ (**40**) would demand a controlled facial interaction between the diene and dienophile units in the initial Diels–Alder reaction transition state. Ingenious designs and years of research would be required before Corey and his research group would reach the desired goal, despite the simply stated nature of the problem.^[26, 27]

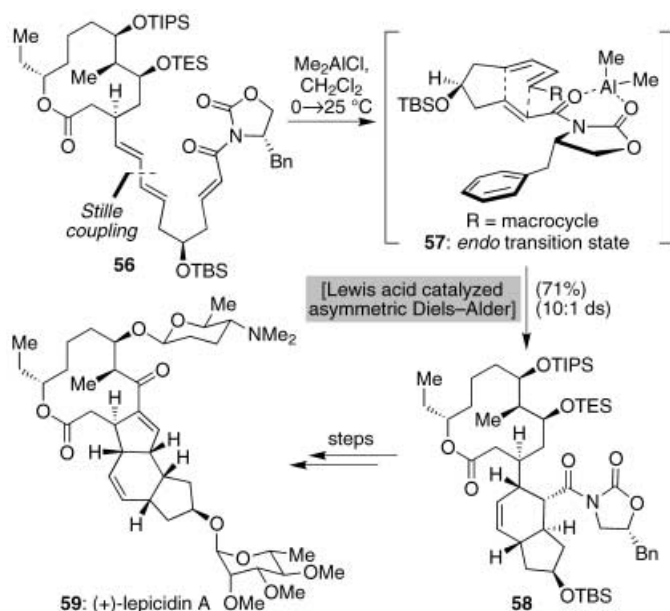
The first successfully identified solution involved attachment of the dienophile to a homochiral cyclohexane ring system, that of menthol, to effect the near-exclusive enantioselective formation of *endo* adduct **47** in 98% ee (Scheme 7b).^[26f] Presumably, this product was the result of closely controlled presentation of the dienophile, achieved through minimization of steric repulsion between the AlCl_3 -chelated carbonyl group and the menthol-derived phenyl ring

and aided by π stacking, with approach of the diene occurring from the more exposed side of the dienophile. Overall, this Diels–Alder strategy represents one of the earliest examples of this mode of asymmetric synthesis, and reflects the value of the induction of asymmetry by a chiral auxiliary^[28]—a process in which a temporarily implanted element of stereochemistry in the reacting molecule dictates the stereochemical outcome of the reaction. Although certainly useful, the general strategy is not without drawbacks. Not only must the auxiliary eventually be excised, but the chiral element also has to be placed in proximity to the reacting center (pertinent only to the dienophile component, as such directing groups on the diene portion would likely be too distal to achieve any control). Perhaps the more significant concern, however, is that the chiral auxiliary often needs to be retailored to achieve the opposite stereoselection.

As such, the Corey research group did not remain content with this single solution, but instead sought, through rational design, suitable systems in which they could control the induction of asymmetry through catalysis. The first successful reagent developed in this regard was the C_2 -symmetric aluminum catalyst **49** (Scheme 7c), which accomplished the asymmetric union of diene **46** and dienophile **48** to provide *endo* adduct **51** in 95% ee.^[26g, 27a,b] The observed induction of asymmetry can be rationalized readily through the presumed transition state **50**, in which the aluminum center acts as a Lewis acid that activates **48** for facile reaction

under mild conditions, thereby enhancing the opportunity to achieve high levels of enantiomeric excess. Significantly, the chiral ligand could be recovered from the reaction mixture and subsequently converted back to the initial catalyst system. In an additional demonstration of asymmetric catalysis, the use of the chiral oxazaborolidinone system **53** (Scheme 7d) induced formation of the *exo* product **55** in equally impressive levels of enantiomeric excess.^[26h, 27c] Indeed, these latter catalytic approaches persist today as preeminent solutions to asymmetrically controlling topicity in Diels–Alder reactions. Moreover, subtle alteration of these catalysts has enabled their widespread application^[29] in numerous other types of reactions where they admirably regulate asymmetric induction. In the ensuing schemes of this section, a number of other elegant and unique expressions of the same general principles in the asymmetric total synthesis of complex natural products are delineated.

Although homochiral auxiliaries often lack broad generality, as mentioned earlier, one glaring exception to this trend resides in the chiral oxazolidinone systems of Evans et al. which have found extensive applications in numerous reactions of prominence in organic synthesis.^[30] Within the Diels–Alder paradigm, a wonderful illustration of the power of this class of chiral auxiliary is found in the asymmetric synthesis of (+)-lepicidin A (**59**, Scheme 8), achieved in 1993 by Black and



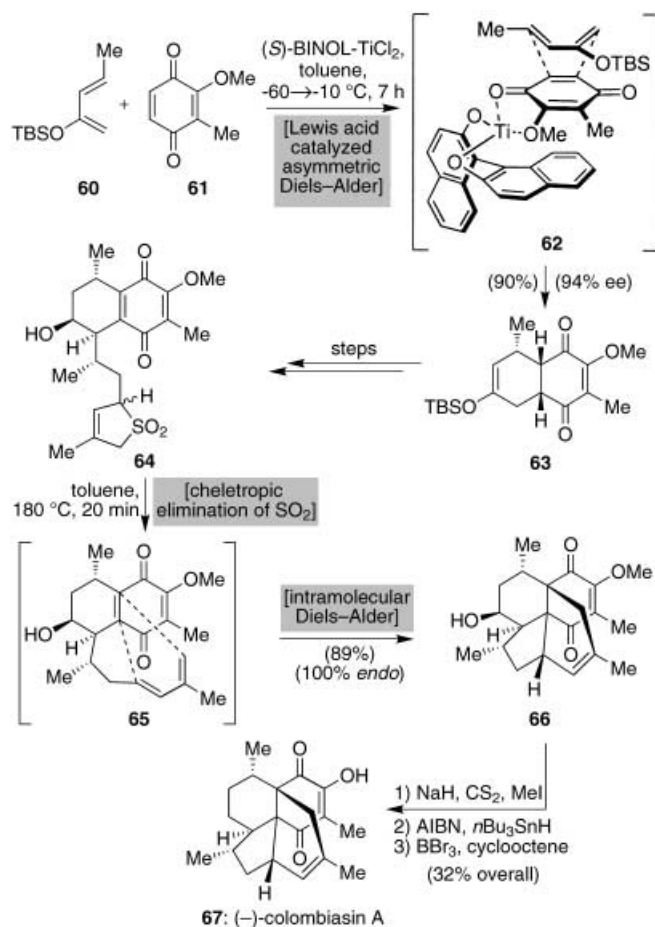
Scheme 8. Use of Evans' chiral auxiliary in a Lewis acid mediated Diels–Alder reaction as part of a stereocontrolled route to (+)-lepicidin A (**59**; Evans and Black, 1993).^[31]

Evans.^[31] After formation of **56**, in which a Stille coupling reaction was employed to prepare the diene system, exposure of this compound to catalytic amounts of Me_2AlCl effected the stereocontrolled generation of *endo* adduct **58** by an intramolecular [4+2] cycloaddition. In the event, concurrent coordination of the aluminum center to the two carbonyl groups on the dienophile segment framed a rigid six-membered ring system (**57**) in which the lowest energy conformation strategically positioned the benzyl group, thus ensuring approach of the diene moiety exclusively from the opposite face of the activated dienophile to furnish the desired *endo* adduct **58** in high diastereoselectivity (about 10:1). When an achiral imide auxiliary was used in the same reaction, however, the Diels–Alder reaction led to a 6:1 mixture of *endo:exo* isomers, except that in the conversion of **57** into **58** the opposite sense of induction resulted than was observed in the case shown! Clearly, the power of the chiral oxazolidinone auxiliary to overcome the latent internal bias of the Diels–Alder cycloaddition represents a remarkable strength of the approach. As an additional beneficial feature, the chiral auxiliary was smoothly recovered from the product, and, although not illustrated in this particular synthesis, can be cleaved in several different ways to leave unique functionality for subsequent elaboration. In terms of advancing this technique beyond substrate control, the Evans research group

has recently introduced several exogenous catalytic variants using a copper(II) center,^[32] catalysts which have already demonstrated their usefulness in several total syntheses, including selective asymmetric routes to *ent*-shikimic acid and isopul'upone.^[33]

Despite the aforementioned advances, however, a universally applicable catalyst system for all types of Diels–Alder reactions remains elusive. Until recently, for example, no disclosed catalyst proved adequate to induce asymmetry in synthetically useful levels of enantiomeric excess for the [4+2] cycloaddition reaction of quinones, arguably one of the most important dienophiles for total synthesis purposes from both a historical perspective as well as a practical standpoint. Despite long-standing failures in this endeavor, an initial proof-of-principle in the context of total synthesis was achieved in 2000 by White and Choi in their disclosed route to (–)-ibogamine,^[34] in which Mikami's catalyst system (formed in situ through reaction of either (*S*)- or (*R*)-BINOL with $[(i\text{PrO})_2\text{TiCl}_2]$) provided excellent enantioselectivity in a quinone-based Diels–Alder event.^[35]

More recently, the Nicolaou group extended the versatility of this catalyst in their total synthesis of the unique terpenoid (–)-colombiasin A (**67**, Scheme 9).^[36] In an early step, the Danishefsky-type diene **60** and quinone **61** were successfully combined in a selective asymmetric Diels–Alder reaction by

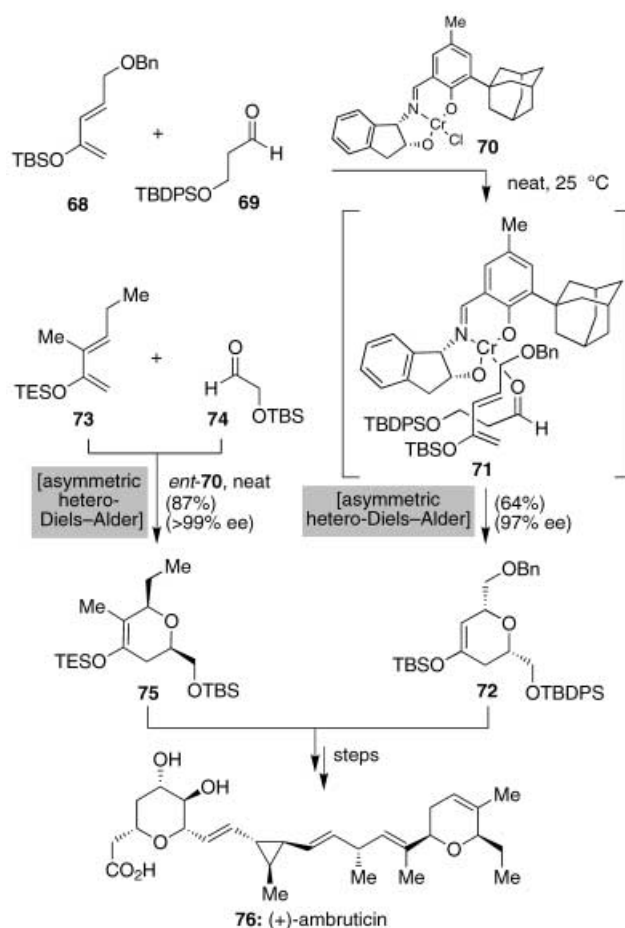


Scheme 9. Reiterative quinone-based Diels–Alder reactions incorporating the use of a sulfone-masked diene in the asymmetric total synthesis of (–)-colombiasin A (**67**; Nicolaou et al., 2001).^[36]

using the Mikami catalyst (30 mol %) to orchestrate the event. Although a 5:1 mixture of **63** and its corresponding regioisomer were isolated, significantly **63** was generated in greater than 94 % *ee*. As shown in transition state **62**, this high level of asymmetric induction was anticipated as the inherent chirality of the coordinated (*S*)-BINOL molecule, effectively presented through the formation of π – π interactions between **61** and one of the naphthol rings of the catalyst, blocked the lower face of the quinone and guided the approach of diene **60** preferentially from the top face onto the reactive olefin of dienophile **61**. Although the catalyst system achieved a stable bidentate mode of chelation in this transition state, the observed mixture of regioisomers was likely the product of partial coordination of the catalyst to the other carbonyl group of **61**, an event which results in less-favored monodentate chelation. Such complexation is conceivable, however, as a consequence of the much higher Lewis basicity of this oxygen atom resulting from it being part of a vinylogous ester. Finally, one should note that the use of a relatively high level of catalyst loading proved critical in achieving sufficient asymmetric induction, as the uncatalyzed background Diels–Alder union proceeded readily, thus eroding enantioselectivity in the presence of less catalyst. After elaboration of adduct **63** to precursor **64** (an entity with a sulfone-masked diene system), thermal extrusion of SO₂ followed by a second, this time intramolecular, Diels–Alder reaction with the regenerated quinone system completed the architectural skeleton of the target molecule. This latter *endo*-stereospecific Diels–Alder event, which remarkably installed two adjacent quaternary centers and formed two new rings using exactly the same carbon atoms for the dienophile component as in the initial Diels–Alder reaction, will be revisited in greater detail in Section 4.

A recent elegant application of a novel asymmetric catalyst to solve a long-standing synthetic problem is found in the synthesis of (+)-ambruticin (**76**, Scheme 10) by Liu and Jacobsen,^[37a] in which use of the salen-type catalyst **70**^[37b] and its enantiomer smoothly directed the asymmetric syntheses of pyran ring systems **72** and **75** in exceptional yield and exceedingly high enantiomeric excess. This catalyst system reflects the first-known method capable of controlling the induction of asymmetry in Diels–Alder reactions between unactivated carbonyl compounds and dienes that are less-activated than the Danishefsky-type possessing two oxygen substituents.^[38] Although the mechanistic rationale for the selectivity observed in these unions has not been explicitly defined, it is reasonable to assume that Lewis acid activation of the aldehyde, with the orientation of the alkyl side chain directed by the bulky adamantyl group and eventual approach of the dienophile dictated by the stereochemistry of the indanone skeleton, is the controlling pathway to the observed enantiospecificity. It is worth noting that the erosion in enantioselectivity obtained in related systems with aldehydes possessing less steric bulk than either **69** or **74** is in agreement with this hypothesis.^[37b]

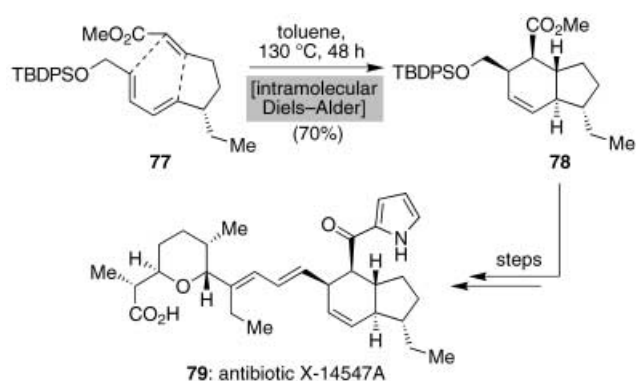
In the absence of homochiral catalysts or auxiliaries, however, the only viable method for achieving absolute stereocontrol in Diels–Alder fusions relies on the presence of homochirality in the starting substrate which then governs the



Scheme 10. Use of a novel chromium-catalyzed hetero-Diels–Alder reaction by Jacobsen and co-workers to fashion the two terminal pyran systems in an asymmetric total synthesis of (+)-ambruticin (**76**; 2001).^[37]

resultant stereochemistry of the [4+2] cycloaddition product. This substrate-controlled approach is the direct extension of the concepts discussed earlier in the intramolecular Diels–Alder reactions of myrocin C^[23] and gibberellic acid,^[24] except that nonracemic starting material is employed in the pericyclic reaction. Within the large group of total syntheses that demonstrate such substrate-controlled diastereoselectivity, an early example includes the conversion of triene **77** into bicyclic system **78** as part of the asymmetric synthesis of the antibiotic X-14547A (**79**, Scheme 11) by Nicolaou et al.^[39] Although the outcome of this Diels–Alder process was anticipated, the achieved attachment of a *trans*-fused five-membered ring onto a cyclohexene template is rather remarkable, as this molecular motif would be challenging to construct by means other than a Diels–Alder reaction.^[40]

As a further example illustrative of such Diels–Alder reactions in the context of generating polycyclic systems, we turn to the CP molecules (**84** and **85**, Scheme 12), natural products that combine fascinating and complex molecular architectures with interesting biological properties. In successful approaches to these naturally occurring substances, the research groups of both Nicolaou^[41] and Fukuyama^[42] employed an intramolecular Diels–Alder reaction to fashion the carbogenic core possessing the *anti*-Bredt bridgehead ole-

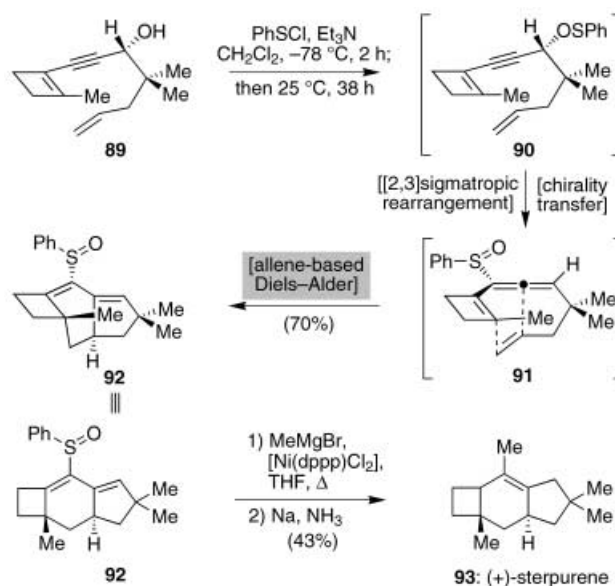


Scheme 11. Asymmetric total synthesis of antibiotic X-14547A (**79**) featuring an intramolecular Diels–Alder reaction to fashion the bicyclic core (Nicolaou et al., 1985).^[39]

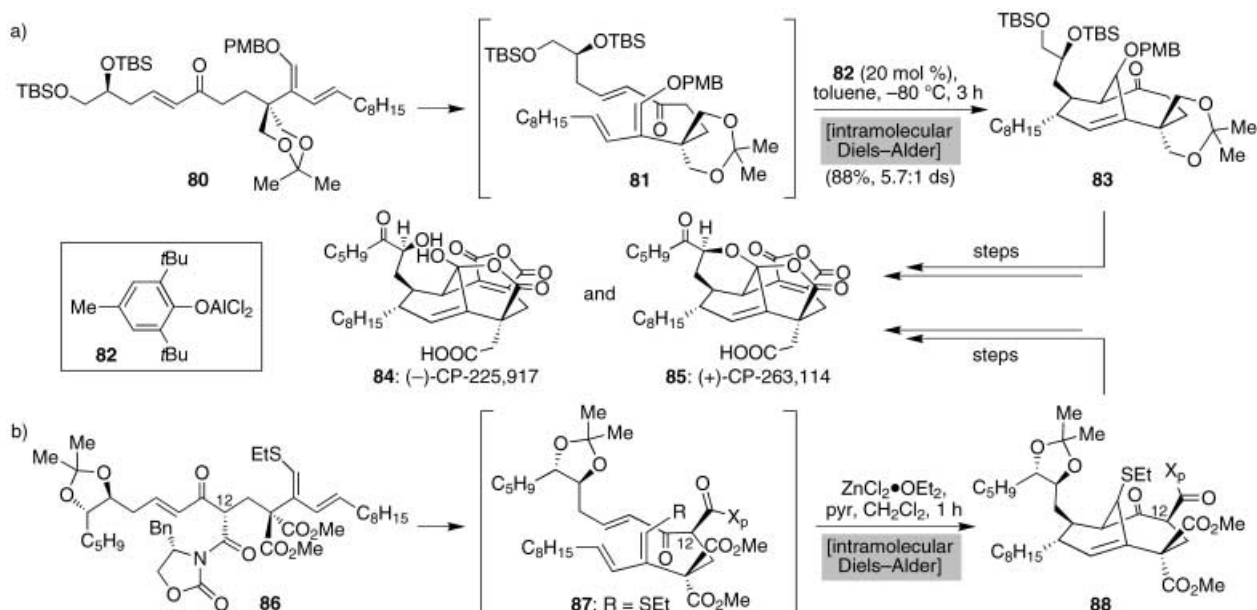
fin.^[43] Besides demonstrating the power of the Diels–Alder cycloaddition as an expedient avenue to fashion such congested and strained structures, each of these syntheses utilized unique substrate-controlled methods to induce diastereoselectivity within the same Diels–Alder-based retrosynthetic blueprint. In the synthesis by Nicolaou et al., the use of a homochiral starting material incorporating a lone, distal stereocenter on the alkyl chain (**80**) in conjunction with the bulky Lewis acid catalyst **82** created a sufficiently controlled chiral environment (**81**) to effect a diastereoselective intramolecular Diels–Alder reaction to provide **83** along with a small amount of its diastereomer (5.7:1). Significantly, attempts to achieve superior induction in this reaction with a number of other chiral Lewis acids failed. In the paradigm of Fukuyama and co-workers, attachment of an Evans' chiral auxiliary on the carbon atom α to the central enone in **86** led to stereoselective formation of *endo* adduct **88** upon activation with ZnCl_2 . Interestingly, in this scenario the auxiliary did not mediate the selectivity in the same fashion as in the earlier

example by Evans and Black (Scheme 8). Instead, the oxazolidinone served solely as a bulky group capable of sufficiently inducing formation of the desired diastereomer, since the C_{12} center had already been installed in a stereochemically pure form.

Along related lines, a striking example of an intramolecular Diels–Alder reaction accompanied by chirality transfer was provided by Okamura and co-workers in 1988.^[44] In this elegant synthesis of (+)-sterpurene (**93**, Scheme 13), the controlled generation of a single allene isomer directed the orientation of the diene and dienophile units in such a way as



Scheme 13. Asymmetric total synthesis of (+)-sterpurene (**93**) by Okamura and co-workers based on a [2,3] sigmatropic rearrangement accompanied by chirality transfer to an allene and subsequent intramolecular Diels–Alder reaction (1988).^[44]



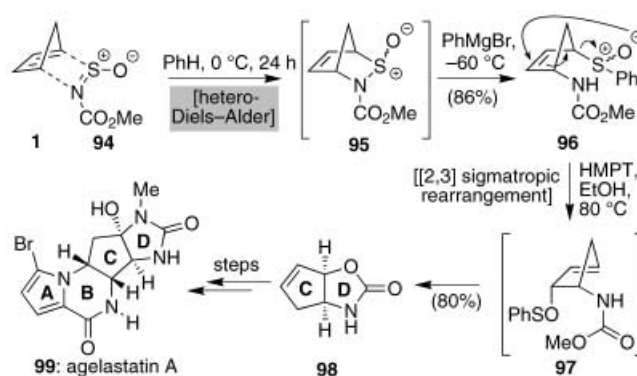
Scheme 12. Applications of the Diels–Alder reaction to form the bicyclic system of the CP molecules, a novel, naturally occurring architecture violating Bredt's rule: a) the approach used by Nicolaou et al. that utilizes a substrate-controlled Lewis acid catalyzed Diels–Alder reaction (1999);^[41] b) employment of an Evans' chiral auxiliary by Fukuyama et al. to achieve a diastereoselective union (2000).^[42]

to allow entrance into only one of the two possible Diels–Alder pathways, thereby leading to a single product. In the event, attachment of a thiophenyl group to the homochiral alcohol in **89** provided intermediate **90**, a species poised for a [2,3] sigmatropic rearrangement. With the preexisting chiral center in **90** transferred as an axial chiral element in **91**, the smooth formation of **92** was achieved as a single enantiomer in 70 % yield. As such, this synthesis reflects a highly creative approach to the stereocontrolled construction of **93**.^[45] Finally, we should note that a particularly interesting advance in methodology involving the use of allenes in intramolecular Diels–Alder reactions was recently described by the Wender research group: application of rhodium and nickel catalyst systems engendered the selective reaction of either of the allene olefinic units as the 2π -electron component.^[46]

3. Hetero-Diels–Alder Reactions

With the lone exception of the total synthesis of (+)-ambruticin (Scheme 10) by Liu and Jacobsen,^[37a] all of the examples discussed thus far involve the formation of solely carbogenic products arising from Diels–Alder cycloaddition reactions. However, the ability to incorporate various heteroatoms at any of the six possible positions in the diene and dienophile components of the reaction constitutes a challenge which has occupied the hearts and minds of synthetic chemists since the discovery of the Diels–Alder reaction.^[47] In fact, one of the first examples of a hetero-Diels–Alder reaction was disclosed by Alder himself in 1943 when he discovered, purely by serendipity, that an imine tautomer could engage appropriate dienes in a productive [4+2] cycloaddition.^[48] Limited by the confines of space, what we hope to accomplish in this section is to appropriately whet the appetite of the reader with a few, select examples from the vast smorgasbord of total syntheses in which this type of process is employed. In the schemes that follow we illustrate the broad themes that have guided synthetic approaches along these lines, with particular emphasis on cascade-based syntheses and non-obvious retrosynthetic disconnections.

As a first example of the powerful hetero-Diels–Alder reaction we highlight a case where two heteroatoms are present in the dienophilic unit. Despite a report in the 1950s that describes the ability of *N*-sulfinylaniline to undergo reaction with 1,3-dienes in Diels–Alder fashion,^[49] this particular variant of the Diels–Alder cycloaddition remained, for the most part, an obscure entry in the literature until extensive studies much later honed this mode of reaction into a sharp synthetic tool. The overall power of this hetero-Diels–Alder-based methodology is beautifully illustrated in the total synthesis of agelastatin A (**99**, Scheme 14) by Weinreb and co-workers,^[50] the climax of extensive mechanistic studies and several creative syntheses achieved in this arena by this research group.^[51] In the initial step of this synthesis, *N*-sulfinylmethylcarbamate (**94**) smoothly engaged in a hetero-Diels–Alder union with cyclopentadiene (**1**) at 0 °C to provide adduct **95**. One should note that, in general, the addition process with this class of hetero dienophile is particularly reversible, and, as such, the observed products

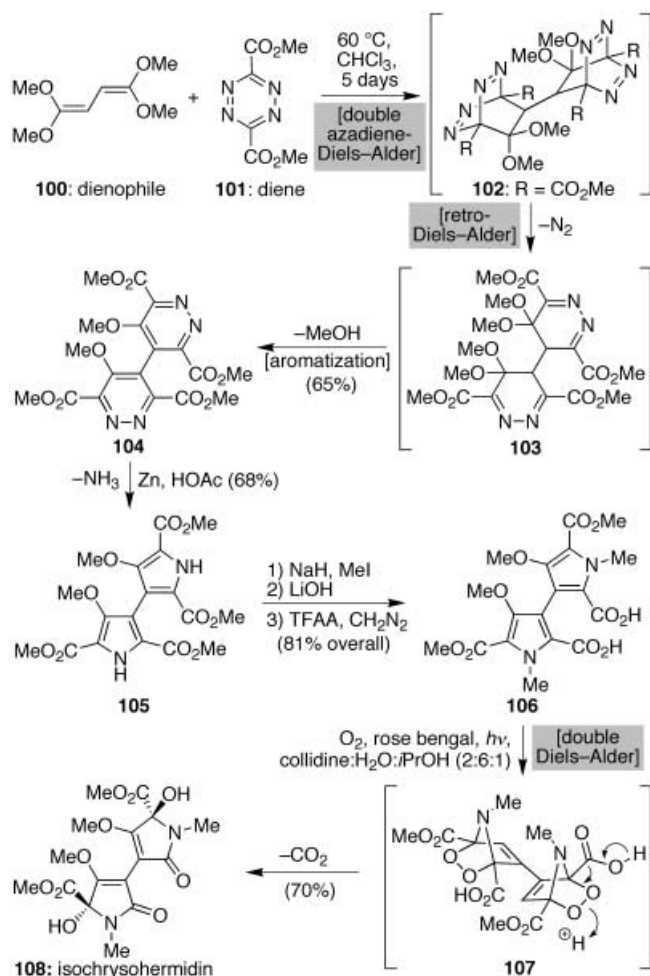


Scheme 14. Total synthesis of agelastatin A (**99**) by Weinreb and co-workers in which an *N*-methylcarbamate was employed as a dienophile in a hetero-Diels–Alder reaction (1999).^[50]

often do not reflect the kinetics of the initial addition. Additionally, the resultant sulfoxide stereochemistry in the Diels–Alder products is often difficult to predict or control. In this instance, however, the latter issue was of no consequence, as a subsequent rearrangement destroyed this element of chirality. Since **95** was prone to retro-Diels–Alder reaction at ambient temperature, the compound was treated immediately upon formation with phenylmagnesium bromide and furnished **96** as a result of nucleophilic attack on the sulfur atom and concurrent lysis of the S–N bond. Heating a solution of this compound in HMPT and Et₃N induced the anticipated conversion into sulfenate ester **97** by a [2,3] sigmatropic rearrangement (an event which is the reverse of the conversion discussed in Scheme 13). Subsequent attack by the resulting nucleophilic oxygen atom on the pendant ester then led to carbamate formation and afforded **98**. As such, the net transformation accomplished by this programmed hetero-Diels–Alder/rearrangement sequence was the regioselective *syn* addition of an oxygen and a nitrogen atom across one of the double bonds of cyclopentadiene to provide a 1,2-amino-alcohol, a motif which is found in numerous natural products besides agelastatin A (**99**).^[52] Finally, we should mention that among the relatively limited class of dienophiles possessing two heteroatoms, nitroso compounds (RN=O) are equally valuable participants in hetero-Diels–Alder reactions directed towards natural product total synthesis.^[53]

The recognition that the reversal of the electronic properties of the typical Diels–Alder diene/dienophile partners could still enable [4+2] cycloaddition reactions through LUMO_{diene}/HOMO_{dienophile}-controlled processes represents a significant advance in the field of organic synthesis.^[54] While such reactions are highly challenging to achieve in an all-carbon context, extensive studies in this area by several researchers have established the particular fertility of the approach in the hetero-Diels–Alder landscape.^[55] Thus, the development of complementary heteroatom-based diene/dienophile partners in such an inverse electron demand Diels–Alder paradigm has encouraged the application of these reactions to total synthesis endeavours with spectacular results.^[56] As one highly illustrative example of this approach, we include here the use of heteroaromatic azadienes as the 4π -electron component in [4+2] cycloaddition reactions, a

concept particularly championed and mastered by Boger and his group. Their synthesis of isochrysohermidin (**108**, Scheme 15), an effective DNA cross-linking agent, represents a beautiful and instructive case study.^[57] Commencing with a

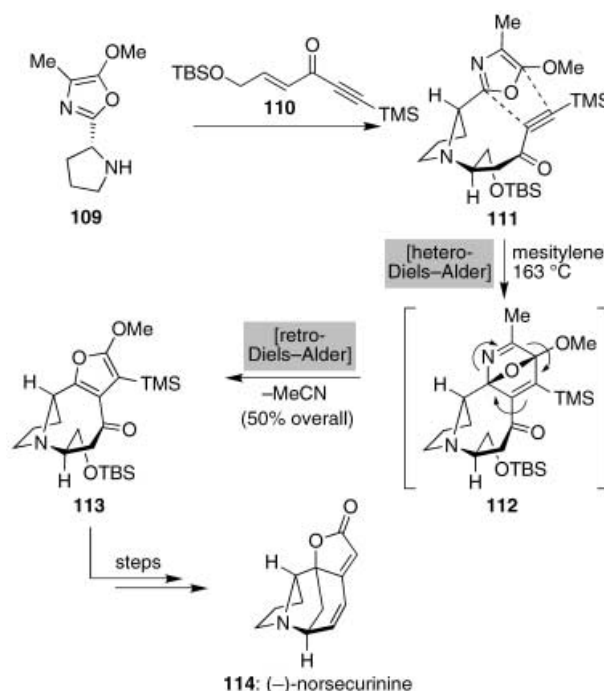


Scheme 15. The elegant total synthesis of isochrysohermidin (**108**) by Boger and co-workers involving a double azadiene inverse electron demand Diels–Alder reaction/nitrogen extrusion cascade and a singlet oxygen [4+2] cycloaddition/decarboxylation sequence (1993).^[57]

tandem azadiene Diels–Alder reaction between the electron-rich dienophile **100** and electron-deficient diene **101**, initial formation of the desired cycloadduct **102** was followed by a double retro-Diels–Alder extrusion of nitrogen to give intermediate **103**. The latter species eventually aromatized through loss of methanol, a transformation made possible by the strategic incorporation of methoxy groups flanking the central C–C bond. Use of molecular sieves to remove this alcohol by-product was critical for the success of the one-pot cascade that led to **104** in 65% yield, as the final aromatization otherwise proved sluggish. With admirable synthetic insight, subsequent exposure of **104** to zinc in hot acetic acid readily effected a double reductive ring contraction to bis-pyrrole derivative **105** through loss of two molecules of ammonia. N-methylation and selective deprotection of two of the four methyl esters achieved over three synthetic operations, then set the stage for the final hetero-Diels–Alder

reaction with singlet oxygen (generated from molecular oxygen with rose bengal and light). This successful pericyclic union led to intermediate **107**, which immediately collapsed in tandem fashion by the indicated endoperoxide decarboxylation/fragmentation pathway to the targeted natural product **108** in approximately 70% yield (40% *dl*-**108**, 30% *meso*-**108**) from **106**. As such, this sequence encompassing eight synthetic operations, including two different double hetero-Diels–Alder reactions, amounts to a beautiful total synthesis of extraordinary symmetry and appeal. Moreover, it exemplifies the power of this hetero-Diels–Alder approach to prepare highly substituted pyrrole and diazine ring systems, particularly in biaryl contexts.^[58]

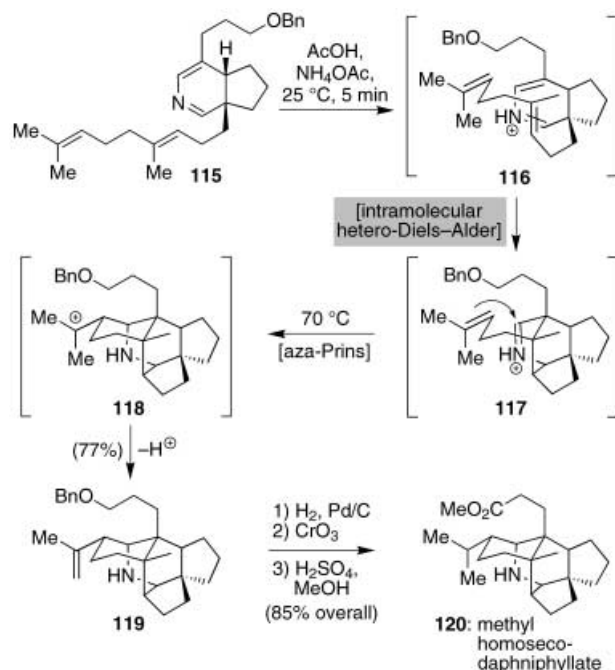
As illustrated above, the programming of hetero-Diels–Alder reactions in tandem with retro-Diels–Alder processes affords a highly effective strategy for the generation of novel heterocycles and molecular motifs which would otherwise be difficult to reach. A further notable example of this concept is the use of methyl-substituted oxazoles in a hetero [4+2] cycloaddition reaction with subsequent thermal extrusion of acetonitrile by a retro-Diels–Alder process to give substituted furan derivatives.^[59] In a highly elegant synthesis of norsecurinine (**114**, Scheme 16), Jacobi and co-workers both developed and utilized this strategem.^[60] Initial Michael addition of **109** to α,β -unsaturated system **110** afforded acetylenic ketone **111**, which upon heating in refluxing mesitylene provided furan adduct **112** in 50% overall yield through the intermediacy of Diels–Alder adduct **113**. The programmed incorporation of the methoxy group on the furan system in this particular example enabled the facile conversion of this moiety into the desired butenolide of the natural product upon subsequent deprotection and hydrolysis.^[61]



Scheme 16. The elegant use of a hetero-Diels–Alder/retro-Diels–Alder cascade sequence by Jacobi and co-workers to fashion the molecular framework of (–)-norsecurinine (**114**; 1989).^[60]

Parenthetically, the construction of such highly substituted furans and butenolides is otherwise quite challenging and, significantly, this method has been extended to thiazole systems, thus enabling the formation of thiophenes through Diels–Alder-based technology.^[62]

To achieve hetero-Diels–Alder reactions with some azadienes, however, protonation of the nitrogen atom is often required to sufficiently activate the species for facile reaction. A striking example of this process is illustrated in the highly concise and insightful synthesis of methyl homosecodaphniphyllate (**120**, Scheme 17) by Heathcock and co-workers.^[63]

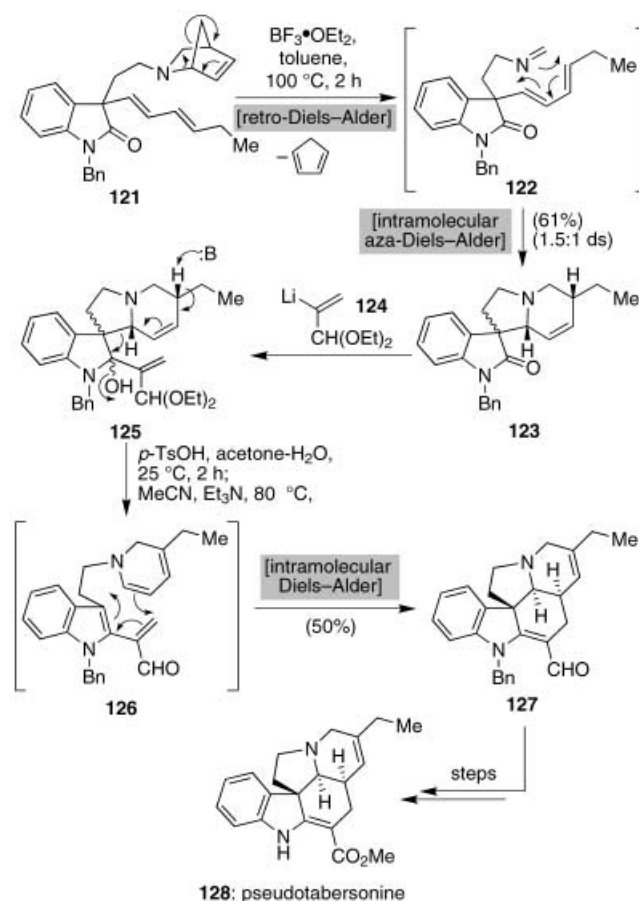


Scheme 17. The elegant Diels–Alder/aza–Prins cyclization cascade by Heathcock and co-workers leading to the core molecular architecture of the tetracyclic natural product methyl homosecodaphniphyllate (**120**; 1988).^[63]

Protonation of the azadiene system of **115** by exposure to ammonium acetate in acetic acid at ambient temperature was followed by rapid intramolecular Diels–Alder cycloaddition to **117**, a relatively stable intermediate which upon heating at 70 °C participated in an intramolecular aza-Prins cyclization reaction to afford **119** in 77% yield from **115** through the intermediacy of the stabilized cation **118**. In contrast, under neutral conditions the initial cycloaddition required several hours in refluxing toluene to achieve 50% conversion and the second, cationic process was precluded. With the entire molecular framework of methyl homosecodaphniphyllate assembled through this elegant, although putative, biomimetic cascade approach, the remaining sequence to complete the synthesis of this intriguing natural product comprised only three relatively routine steps.^[63] We should note, however, that in addition to protonation serving to activate dienes or dienophiles, similar enhancements can also be achieved using neighboring heteroatom-stabilized cations (such as oxallyl cations). These achievements represent a critical advance in Diels–Alder methodology within the

general class of ionic and radical cation-based pericyclic processes.^[64]

Attempts to switch the location of the nitrogen atom to the 2 π -electron component in the form of an imine, although certainly possible in hetero-Diels–Alder reactions, as mentioned in the opening of this section, can often pose challenges in practice.^[54a] For example, electron-deficient imines and iminium salts are typically unstable (since they can readily be hydrolyzed in the presence of the merest trace of water) and, as such, require in situ generation prior to trapping in Diels–Alder reactions. Moreover, imines can undergo a variety of other reactions with alkenes; acyl imines can, in fact, participate as dienes in Diels–Alder reactions. As such, synthetic strategies unveiling the requisite imino dienophile in the vicinity of a 1,3-diene system, particularly in an intramolecular setting, should serve to coax the reaction along the desired Diels–Alder pathway. A didactic example of this approach to create molecular complexity is found in the total synthesis of pseudotabersonine (**128**, Scheme 18) by Carroll and Grieco.^[65] After preparation of intermediate **121**, application of methodology originally developed by the Grieco research group enabled the formation of imino dienophile **122** through a BF₃·OEt₂-induced retro-Diels–Alder reaction that effected expulsion of cyclopentadiene.^[66] With a diene system appended from the same carbon atom of the indole skeleton



Scheme 18. Use of a cloaked imino dienophile, unveiled by a retro-Diels–Alder reaction, followed by an aza-Diels–Alder union and a subsequent intramolecular Diels–Alder reaction as part of an elegant total synthesis of pseudotabersonine (**128**) by Carroll and Grieco (1993).^[65]

in proximity, a facile intramolecular aza-Diels–Alder reaction ensued to form **123** as a 1.5:1 mixture of diastereomers. The anticipated poor diastereoselectivity in this process was of no consequence, however, as all of the newly formed stereocenters were later destroyed, thus enabling each of the obtained Diels–Alder adducts to eventually be converted into the target molecule through the designed sequence. After addition of 2-lithio-1,1-diethoxyprop-2-ene (**124**) to form oxindole derivative **125**, the stage was set to trigger a second Diels–Alder reaction through initial acid-induced deprotection of the ketal, followed by a base-catalyzed rearrangement to the fleeting **126** upon heating at 80 °C. This cascade generated the complete pentacyclic framework of the natural product as expressed in **127** which served as a convenient staging area from which to reach **128**. The elegant strategy used by Carroll and Grieco to generate pseudotabersonine (**128**) not only illustrates an inventive solution to the generation of imino dienophiles, but also provides a plausible strategy (possibly biomimetic) for the construction of several members of the *Aspidosperma* family of alkaloid natural products. We should note at this juncture that imino-based Diels–Alder reactions are prolific in the literature, and in particular we acknowledge the numerous elegant applications of imino-type hetero-Diels–Alder unions in various total syntheses developed by the Weinreb research group.^[54a]

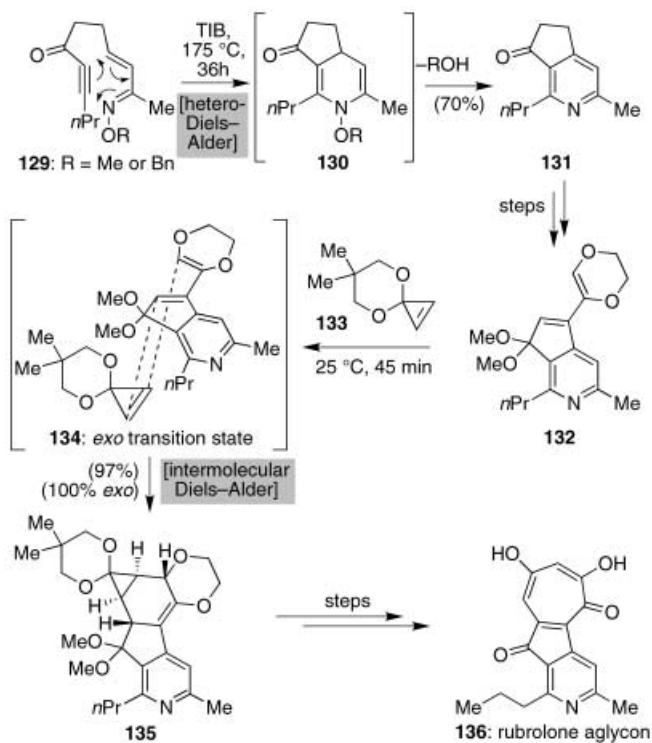
As a final entry to this section we present the total synthesis of rubrolone aglycon (**136**, Scheme 19) by Boger et al.^[67] which employed an oxime ether as a competent 4 π -electron component in an aza-Diels–Alder reaction to access a heavily

substituted pyridine.^[68] Unlike the inverse electron demand approaches discussed earlier in an aza-Diels–Alder context (Scheme 15),^[57] attachment of an oxime ether onto the nitrogen atom was expected to inject sufficient electron density into the diene portion such that it could enter into Diels–Alder reactions with typical electron-deficient dienophiles under appropriate thermal and/or Lewis acid conditions. Thus, in an early transformation in the synthesis, prolonged heating of either the benzyl or methyl ether (**129**) in 1,3,5-triisopropylbenzene at 175 °C afforded the intermediate aza-Diels–Alder adduct **130** which aromatized in situ to the desired pyridine system **131** through loss of either methanol or benzyl alcohol. After elaboration of the latter intermediate to **132**, a second Diels–Alder reaction with cyclopropenone ketal **133**^[69] was smoothly achieved at ambient temperature and provided the single *exo* adduct **135** in 97% yield. Presumably, the facile combination of these two partners into **135** is most likely a result of the mutually reinforcing facets of the electron-rich diene system bearing two adjacent oxygen atoms, and the relief of ring strain resulting in the conversion of the cyclopropene into a cyclopropane unit upon cycloaddition. Interestingly, despite the normal preference for the *endo* cycloadduct, this process proceeded exclusively through an *exo* pathway; presumably, the absence of any conjugating orbitals on the dienophile enabled the sterically less-congested *exo* transition state to dominate completely.

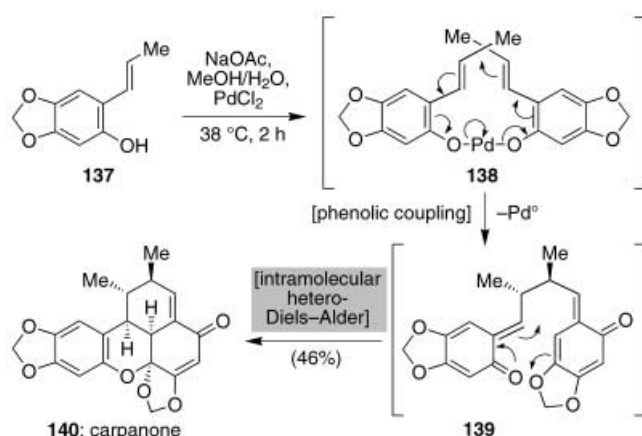
4. Diels–Alder Reactions in Disguise: Cloaked Dienes and Dienophiles

In the majority of applications of the Diels–Alder reaction in total synthesis the diene and dienophile moieties represent inherent parts of the molecular scaffold, readily visible to the naked eye throughout the synthetic sequence. An often more intriguing strategy, however, is the masking of such units until the key juncture in the synthesis, at which time they are uncloaked for the desired Diels–Alder reaction. Significantly, such approaches often constitute the only feasible method for realizing the desired Diels–Alder union when one or both components are fleeting intermediates or highly reactive species. Such was the case in the generation of an in situ imino dienophile (Scheme 18) by Carroll and Grieco discussed above.^[65] The same concept resides in the total synthesis of colombiasin A (Scheme 9) by Nicolaou et al.,^[36] where the exposed diene portion intended for the second Diels–Alder reaction caused significant synthetic challenges in the step preceding the key Diels–Alder cycloaddition unless it was masked as a sulfone prior to its unraveling and eventual pericyclic reaction.

The group of cascade-based total syntheses in which the generation of a highly reactive Diels–Alder component sets the stage for a subsequent immediate [4+2] cycloaddition reaction includes the classic biomimetic synthesis of carpanone (**140**, Scheme 20) in 1971 by Chapman et al.^[70] In this example, exposure of monomeric phenol **137** to PdCl₂ in basic media effected a phenolic dimerization to **139** via reactive intermediate **138**. This product (**139**), however, proved short-



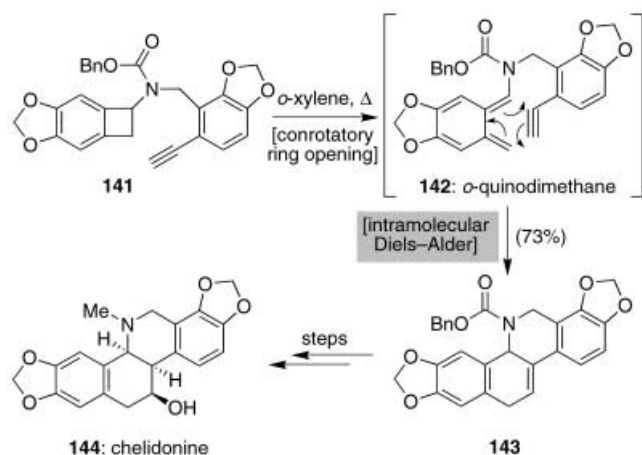
Scheme 19. The beautiful total synthesis by Boger et al. of rubrolone aglycon (**136**) featuring an intramolecular hetero-Diels–Alder reaction of an oxime-containing diene and an intermolecular Diels–Alder cycloaddition involving a highly strained cyclopropene as a dienophile (2000).^[67]



Scheme 20. The classic biomimetic synthesis by Chapman et al. of carpanone (**140**) featuring a sequential Pd-mediated phenolic coupling and an intramolecular Diels–Alder cycloaddition involving an *o*-oxoquinodimethane (1971).^[70]

lived as the highly reactive *o*-oxoquinodimethane which had been unveiled entered spontaneously into an intramolecular hetero Diels–Alder reaction with the resident dienophile in proximity to provide the targeted natural product (**140**) stereoselectively in 46% overall yield in a single operation from **137**. Of perhaps greater significance than the inherent beauty and concise nature of this total synthesis is the confidence it inspired in using related *o*-quinodimethanes in the context of complex molecule total synthesis.^[71]

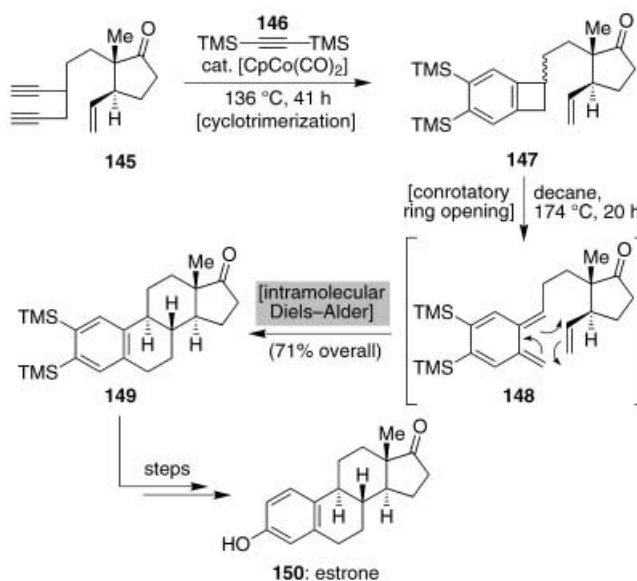
An equally inspirational and instructive approach incorporating *o*-quinodimethanes in a Diels–Alder context was pioneered through the landmark 1971 total synthesis of chelidoniumine (**144**, Scheme 21) by Oppolzer et al.,^[72] where it was anticipated that the desired reactive intermediate could be obtained through electrocyclic ring opening of a strained cyclobutene system. Upon heating **141** in refluxing *o*-xylene, reversible conrotatory ring opening indeed furnished a highly reactive *o*-quinodimethane (**142**) that immediately engaged the pendent alkyne moiety in a productive Diels–Alder union to afford polycyclic system **143** in 73% overall yield which served as the progenitor of the targeted natural



Scheme 21. The pioneering use of *o*-quinodimethanes generated through electrocyclic ring opening of a benzocyclobutene in the total synthesis of chelidoniumine (**144**) by Oppolzer and co-workers (1971).^[72]

product. Significantly, Oppolzer and Robbani optimized this cyclobutene-opening methodology^[72b] to achieve greatly enhanced yields of **143**. They also further extended this insightful Diels–Alder approach to heterocyclic systems by using tethered imines as substrates, thus paving the way for a plethora of subsequent applications.^[73]

A related and equally spectacular application of the intramolecular Diels–Alder reaction of benzocyclobutene-generated *o*-quinodimethanes is demonstrated in the total synthesis of estrone (**150**, Scheme 22)^[74] during the conversion of **147** into the steroidal skeleton **149** by Vollhardt and co-workers.^[75] Apart from this particular transformation, however, this elegant synthesis includes an additional tantalizing

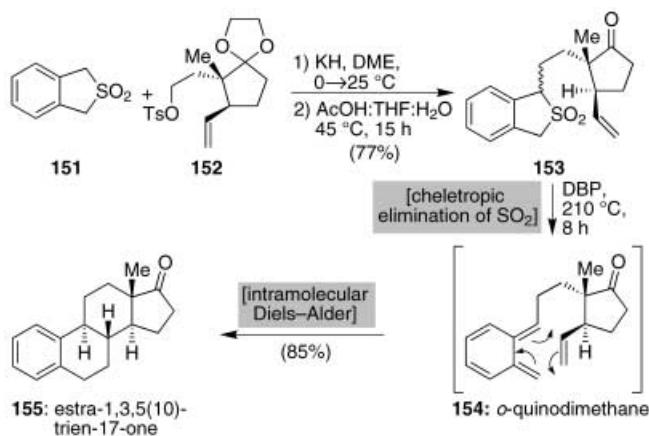


Scheme 22. The brilliant total synthesis of estrone (**150**) by a tandem ring opening/Diels–Alder sequence based on cobalt cyclotrimerization of acetylenic substrates by Vollhardt and co-workers (1979).^[74]

feature in its initial stages, namely the reaction of bis-(trimethylsilylacetylene) (**146**) with bisacetylene **145**, orchestrated by catalytic amounts of [CpCo(CO)₂]. In this [2+2+2] cycloaddition, as in the Diels–Alder reaction, the ultimate product reflects the direct summation of all the reacting pieces, thus providing an additional set of conversions with atom economy equal to the venerable reaction of Diels and Alder. We should note in passing that the benzocyclobutene technology adopted both in this and the preceding example was also championed and greatly extended by Kametani et al. in numerous complex molecular contexts, including steroids.^[76]

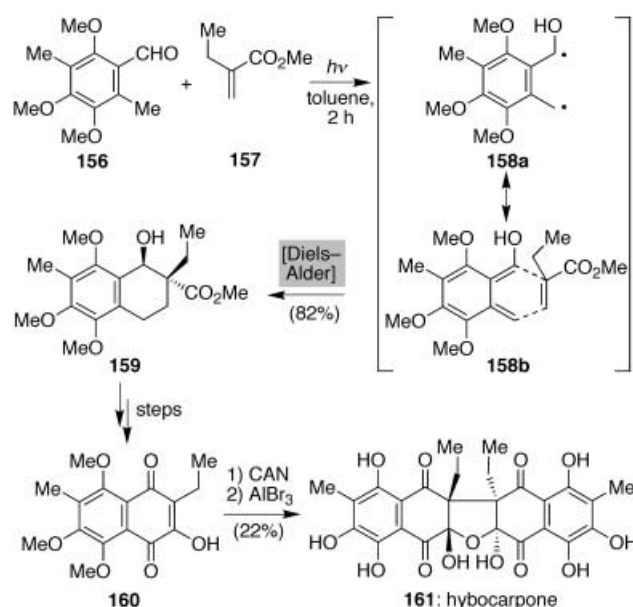
Complementary to the benzocyclobutene approach for *o*-quinodimethane generation is a method which relies on the use of a cyclic sulfone, a chemical entity encountered in the colombiasin A synthesis presented in Section 2 (Scheme 9).^[36] Since the pioneering work of Staudinger in the early part of the last century,^[77] it has been amply documented that sulfur dioxide can add cleanly to a diene system to provide an adduct that can be reverted back to the original starting material through a thermally induced retro-Diels–Alder reaction in

which SO_2 is extruded.^[78] Although sulfones were utilized in Diels–Alder reactions prior to 1950, the methodology was greatly extended through the pioneering work of Cava et al. which established that highly reactive *o*-quinodimethanes could be thermally generated from sulfones appended to aromatic systems.^[79] The first application of this strategy in total synthesis, which also represents the first instance in which it was employed in an intramolecular context, was in the synthesis of the steroid *estra-1,3,5(10)-trien-17-one* (**155**, Scheme 23) by Nicolaou and Barnette.^[80] Cheletropic elimination of SO_2 from sulfone **153** was readily effected under thermal conditions and led to the unveiling and trapping of *o*-quinodimethane **154** to form the targeted compound **155**. Both this example and the total synthesis of colombiasin A (Scheme 9) demonstrate the versatility of the sulfone group in facilitating synthetic operations while concurrently remaining inert to a diverse set of reaction conditions. As such, this moiety reflects one of the few effective protecting devices for dienes.



Scheme 23. Tandem cheletropic elimination of SO_2 and intramolecular Diels–Alder reaction in an expedient total synthesis of *estra-1,3,5(10)-trien-17-one* (**155**; Nicolaou and Barnette, 1979).^[80]

As a final set of entries demonstrating the power of *o*-quinodimethanes in total synthesis, we have chosen to highlight a recent series of achievements in a methods-based approach to total synthesis derived from the photochemical generation and trapping of these fleeting intermediates (Scheme 24).^[81] Although scant reports of this process have been reported in the chemical literature on simple precursors, the sequence has been virtually ignored in total synthesis endeavors. Enticed by the structurally unique and cytotoxic natural product hybocarpone (**161**, Scheme 24) possessing an aesthetically pleasing C_2 -symmetric molecular architecture, Nicolaou and Gray envisioned a plausible biosynthetic origin of this compound to be a dimerization of a precursor naphtharazin, initiated by a single-electron transfer (SET) process, followed by a hydration event.^[82] Although this biogenetic hypothesis had no empirical foundation, it nevertheless served as inspiration for the synthetic design. To prepare the dimerization precursor **160**, it was anticipated, and realized, that a photochemically generated hydroxy-*o*-quinodimethane from aromatic aldehyde **156** could engage



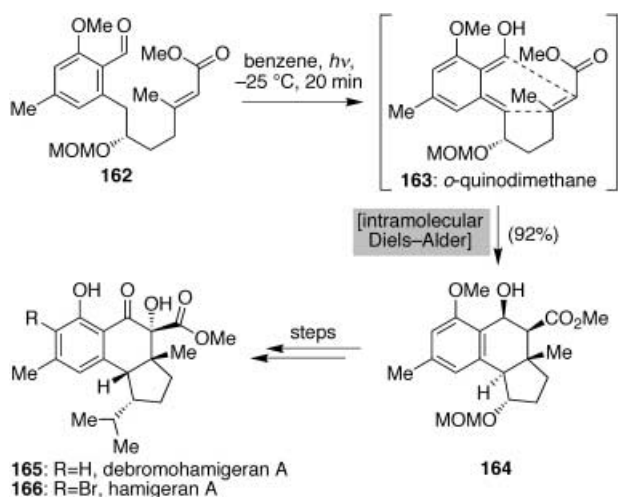
Scheme 24. Total synthesis of hybocarpone (**161**) featuring an intramolecular Diels–Alder trapping of a photolytically generated hydroxy-*o*-quinodimethane (Nicolaou and Gray, 2001).^[82]

methyl 2-ethylacrylate (**157**) in a Diels–Alder reaction to regioselectively form the desired bicyclic system **159**. One should note that in the event, initial excitation of the carbonyl group followed by 1,5-hydride abstraction provided diradical **158a**, whose canonical form is hydroxy-*o*-quinodimethane **158b**. The Diels–Alder reaction proceeded with admirable success in this initial testing ground, and as such, the reaction conditions were further optimized for both intra- and intermolecular cycloadditions in even more complex contexts with a variety of aromatic aldehydes and dienophiles.^[83a] Significantly, the developed intramolecular technology engendered facile construction of complex polycyclic scaffolds present in a myriad of natural products. As an initial demonstration of the utility of the approach, the Nicolaou group efficiently synthesized two members of the hamigeran family of natural products (**165** and **166**, Scheme 25).^[83b]

Before ending this section, one should note that the masking devices highlighted in the above schemes do not, by any means, represent the entire range of possibilities for unleashing reactive species for Diels–Alder interception. Other approaches are indeed viable,^[84, 85] and some will be encountered in the next section.

5. Diels–Alder Reactions as Part of Cascade Sequences

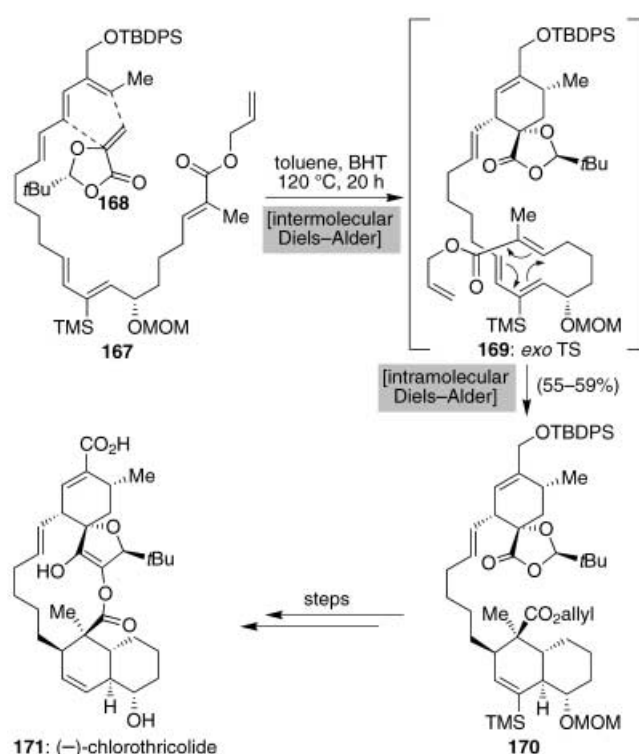
Among possible synthetic routes, cascade sequences offer an unparalleled ability to efficiently construct molecular complexity. Indeed, as most students of organic chemistry will recognize, the principle of cascade reactions in organic synthesis has a long and enviable history whose roots can be traced forward to the present day from such landmark achievements as Robinson's elegant biomimetic preparation



Scheme 25. Total synthesis of the hamigerans featuring an intramolecular Diels–Alder trapping of a photochemically generated hydroxy-*o*-quinodimethane (Nicolaou et al., 2001).^[83b]

of tropinone in 1917,^[86] and the total synthesis of progesterone by Johnson et al. in 1971 that was based on a series of cation- π cyclizations.^[87] With mounting pressure to rapidly construct molecular complexity through efficient and atom-economical^[88] processes with high degrees of selectivity, programmed cascade sequences will inevitably become increasingly utilized in total synthesis. In this section, we outline several examples of cascade processes incorporating the Diels–Alder reaction which have been employed in the total synthesis of naturally occurring substances as a sampling of the types of wondrous reaction sequences we might expect in the future.^[89]

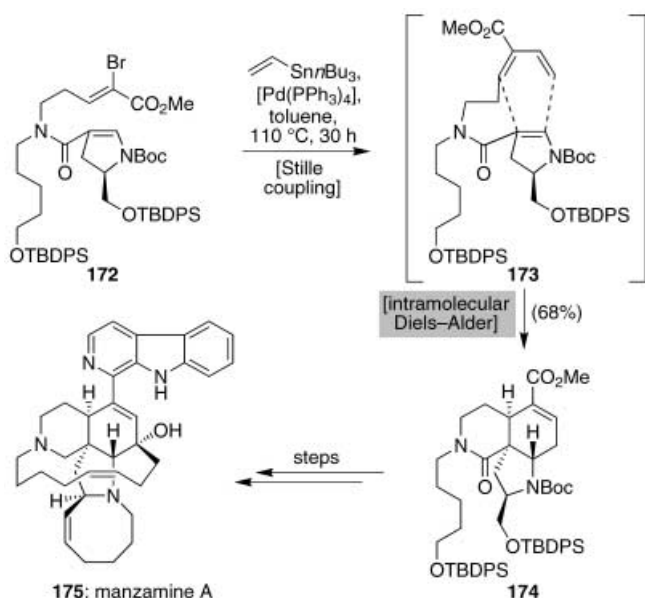
The highly concise and elegant enantioselective total synthesis of the antibiotic (–)-chlorothricolide (**171**, Scheme 26) by Roush and Sciotti certainly serves as an outstanding starting point.^[90] The key feature of this synthesis resides in a tandem inter-/intramolecular Diels–Alder sequence to simultaneously construct a pentasubstituted cyclohexene ring as well as a *trans*-fused decalin system, events which resulted in the formation of seven new asymmetric centers in a single operation. Critical to the success of the designed cascade, which was brought about through prolonged heating in toluene at 120 °C in the presence of BHT, was the high level of diastereofacial and regiospecific control achieved in the intermolecular *exo* Diels–Alder reaction between the more reactive diene system of **167** and dienophile **168**, a feature which had been soundly established by Roush and co-workers in several model studies.^[91] Similarly, the strategically placed trimethylsilyl group on the remaining diene segment enabled the other, intramolecular Diels–Alder reaction to proceed with high selectivity and led to the predominant formation of the anticipated product (**170**) at the expense of other potential Diels–Alder adducts possessing alternative stereochemistries. Indeed, there are 96 distinct Diels–Alder products that could have been formed from all of the possible *endo*, *exo*, diastereofacial, and regiochemical outcomes. The experimental execution of this amazing cascade process elicits further admiration in that the final yield (55–59%) of **170** reflects not only carefully optimized conditions, but also a recycling of the by-product that formed



Scheme 26. Beautiful enantioselective total synthesis by Roush and Sciotti of (–)-chlorothricolide (**171**) featuring a tandem inter-/intramolecular Diels–Alder cascade. Note that these processes could certainly occur in the reverse order from that shown here (1994).^[90]

in a deviation from the desired route. This latter compound was the result of successful intramolecular Diels–Alder reaction in the lower half of the molecule, but where reaction of the upper diene with **168** failed because of isomerization of the triene portion to an *E,E,E* system. After extensive studies, a method to convert this material into the desired adduct was found through additional treatment with **168**, this time in trichloroethylene.^[92]

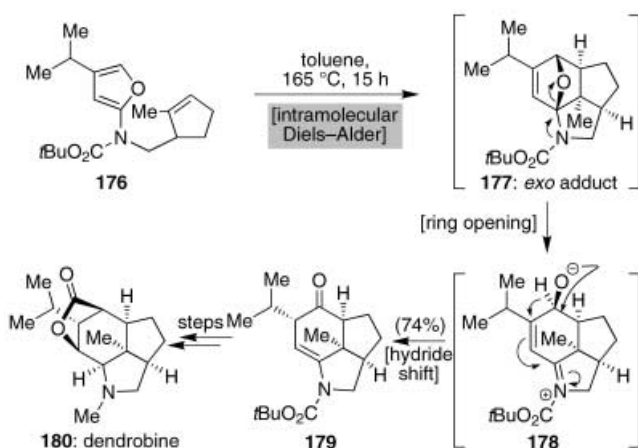
The recent total synthesis of manzamine A (**175**, Scheme 27) by Martin et al. represents another brilliant set of tandem reactions that provides a highly elegant solution to a challenging synthetic problem.^[93] Following a synthetic strategy which projected olefin metathesis reactions to forge both the 8- and 13-membered rings of the target molecule, an efficient synthesis of the tricyclic core was defined as the initial prerequisite. Thus, having reached intermediate **172**, exposure of this vinyl bromide to tri-*n*-butylvinylstannane in the presence of catalytic amounts of $[\text{Pd}(\text{PPh}_3)_4]$ in refluxing toluene initiated a tandem Stille coupling/Diels–Alder cascade sequence that led to **174** in 68% yield. Although the concept of combining these two reactions in domino fashion was not without precedent,^[94] the complexity of the obtained polycyclic system is particularly stunning. Other particularly remarkable features of the Diels–Alder step are the exclusive *endo* topicity (with respect to the five-membered ring) arising from the *E* olefin in the diene and the diastereofacial selectivity arising from the influence the lone distal stereocenter present in **172** which lead to the controlled installation of three new chiral centers, including a quaternary carbon



Scheme 27. Elegant use of a domino Stille coupling/Diels–Alder sequence by Martin et al. to construct stereospecifically three adjacent chiral centers and three of the five rings in a total synthesis of manzamine A (**175**; 1999).^[93]

atom. Indeed, such diene geometries are relatively rare participants in Diels–Alder reactions, particularly in intramolecular contexts, because of the overall strain of the system necessary to achieve proper orbital alignment for successful [4+2] cycloaddition.

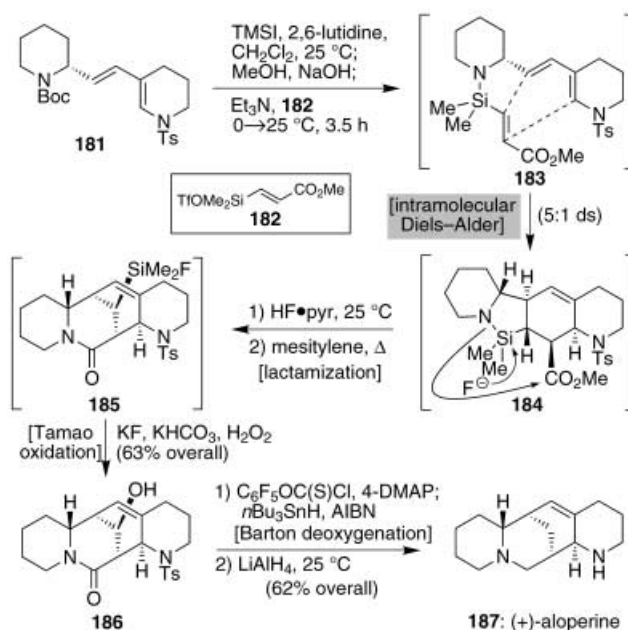
An additional recent example of a highly insightful cascade strategy based on strategic incorporation of functionality is featured in the total synthesis of dendrobine (**180**, Scheme 28) by Padwa et al.^[95] First, an initial *exo*-selective Diels–Alder reaction between the unactivated dienophile moiety with the tethered electron-rich furan system, both residing within **176**, provided **177**. The *exo* selectivity in this transformation arose from the fact that there is no conjugating π system on the dienophile to provide a secondary orbital interaction, thereby disfavoring an *endo* transition state. With this intermediate in hand, the placement of a nitrogen atom α to the bridged



Scheme 28. Elegant use of a tethered furan-based Diels–Alder reaction by Padwa et al. to fashion a precursor en route to the total synthesis of dendrobine (**180**; 2001).^[95]

system in **177** induced a spontaneous ring-opening reaction, with a subsequent hydride shift providing the functionalized tricyclic core of the natural product (**179**) in 74% overall yield. Among the numerous total syntheses of this substance based on Diels–Alder routes,^[96] this sequence certainly represents one of the most concise and beautiful solutions to the challenges posed by its molecular architecture, thus demonstrating, once again, a highly inventive use of the Diels–Alder reaction within a tandem reaction sequence.

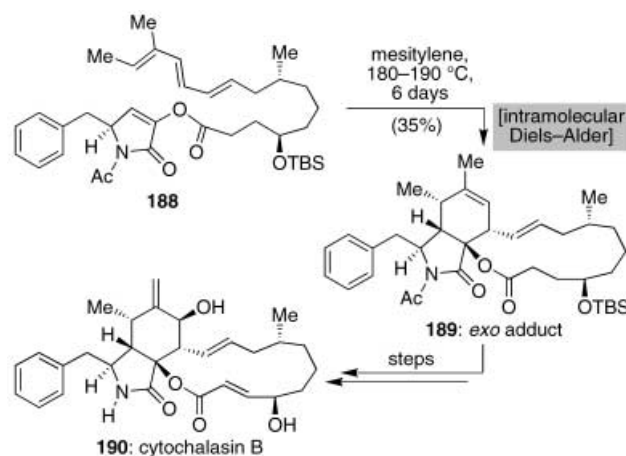
It is perhaps appropriate to close this section with the recently achieved total synthesis of (+)-aloperine (**187**, Scheme 29) by Overman and co-workers which featured a



Scheme 29. The elegant total synthesis of (+)-aloperine (**187**) by Overman and co-workers featuring a cascade sequence involving a silicon-tethered Diels–Alder reaction and a Tamao oxidation (1999).^[97]

temporarily tethered dienophile.^[97] Although aloperine is a relatively small molecule compared to some of the other targets reached by Diels–Alder technology, it took profound insight and skill to both design and execute the Diels–Alder-based cascade strategy which opened an entry to its skeleton. The approach is based on developing a temporary tether of the dienophile to the diene in the form of an *N*-silyl system (**183**), a concept which had not been previously demonstrated in a Diels–Alder context. However, success in controlling diastereoselectivity through such a strategy was anticipated on the basis of successful intramolecular Diels–Alder reactions in related systems by Gschwend,^[98] with the selection of an *N*-silyl-linked tether inspired by the pioneering studies of the research groups of Nishiyama and Stork who had employed *O*-silyl linkages to effect several intramolecular transformations.^[99] Starting with **181**, a series of protecting-group manipulations were performed in a one-pot operation that culminated in the attachment of fragment **182** and the transient generation of **183**, a species which rapidly converted into the desired product **184** at ambient temperature by an intramolecular Diels–Alder reaction in 67% de Since this

Diels–Alder product proved labile upon aqueous work-up, it was instead directly exposed to anhydrous HF·pyr and heated in mesitylene, conditions which impressively effected both cleavage of the N–Si bond and an ensuing lactamization to afford **185**. Finally, a subsequent Tamao-type oxidation smoothly completed the conversion of **181** into **186** in 63% overall yield, thus extruding the remnants of the original silicon tether and establishing a beachhead for the completion of the total synthesis of the coveted natural product **187**. This particular set of transformations, in which no intervening purifications were performed, certainly sets a high standard for future approaches to this class of natural products and confirms the status of *N*-silyl tethers as temporary devices to control stereoselectivity through intramolecular Diels–Alder reactions.^[100] We shall encounter an additional example of a temporary tether as a means to facilitate an intramolecular Diels–Alder reaction in the upcoming section.



Scheme 30. Use of a bold intramolecular Diels–Alder reaction by Stork and Nakamura in the total synthesis of cytochalasin B (**190**; 1983).^[102]

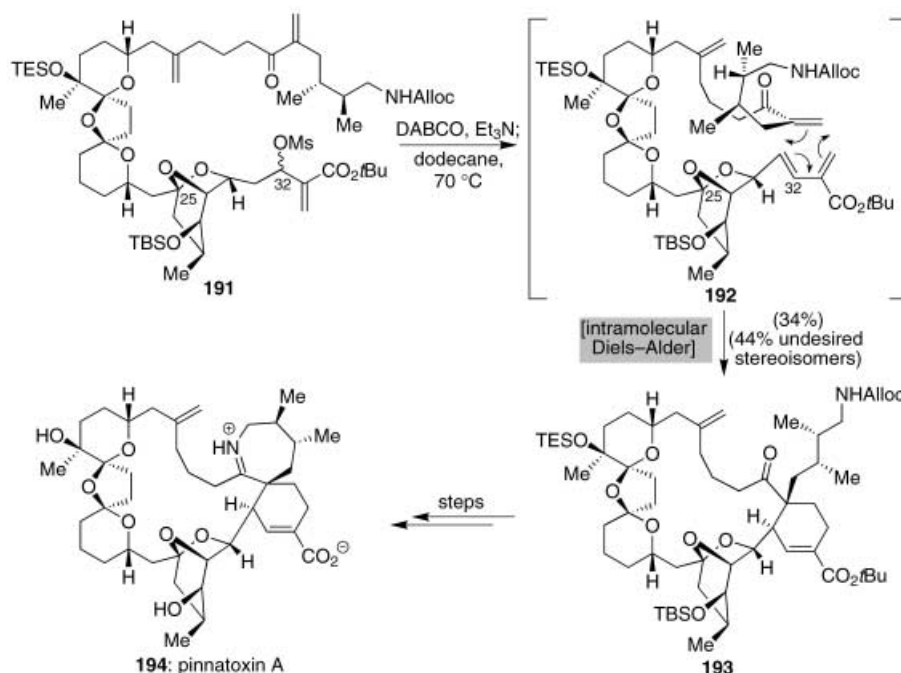
6. Daring Applications of the Diels–Alder Reaction in Total Synthesis

The chemical literature is adorned with many striking examples of the use of the Diels–Alder reaction in total syntheses which are derived from special and unique strategies. This situation renders these particular cases hard to classify under any of the other sections in this review. As such, a few of these instructive archetypes are discussed under this heading. To be sure, however, the elegant nature of all of the exemplars cited in this article certainly could have easily qualified for inclusion in this “daring” category.

Although the power of intramolecular Diels–Alder reactions to forge a five- or six-membered ring in either a fused or bridged fashion across the characteristic cyclohexene product has been amply demonstrated with the above examples, the utilization of this process to concurrently form medium-sized or macrocyclic rings remains to be discussed. First demonstrated as a viable option by Corey and Petrzilka in 1975,^[101] one of the earliest and most striking applications of this macrocyclization strategy in total synthesis was achieved by Stork and Nakamura in their 1982 synthesis of cytochalasins F and B (**190**, Scheme 30).^[102] In the key step, after achieving a homochiral synthesis of **188**, collapse of this polyunsaturated precursor to the desired tetracyclic system **189** was accomplished in 35% yield as a 4:1 mixture of *endo*:*exo* products upon heating in mesitylene at 180–190 °C for nearly a week. This process is remarkable not only because of the concomitant formation of the isoindolone and the highly strained 14-membered macrocyclic ring system, but also because of the fact

that the diene system was coaxed to undergo a Diels–Alder reaction with a dienophile that is not particularly electron deficient. Since Stork and Nakamura’s landmark synthesis of **190**, numerous other syntheses of members of the cytochalasin family of natural products through Diels–Alder reactions have appeared in the literature.^[103]

An equally impressive paragon of macrocyclization through an intramolecular Diels–Alder reaction resides in the bold total synthesis by Kishi and co-workers of pinnatoxin (**194**, Scheme 31), a marine-derived calcium-channel activator with a novel molecular architecture.^[104] After generation of advanced key intermediate **191**, subsequent displacement of the allylic mesylate with DABCO followed by Et₃N-induced elimination furnished the requisite diene system necessary for Diels–Alder reaction with the remote dienophile. Since this



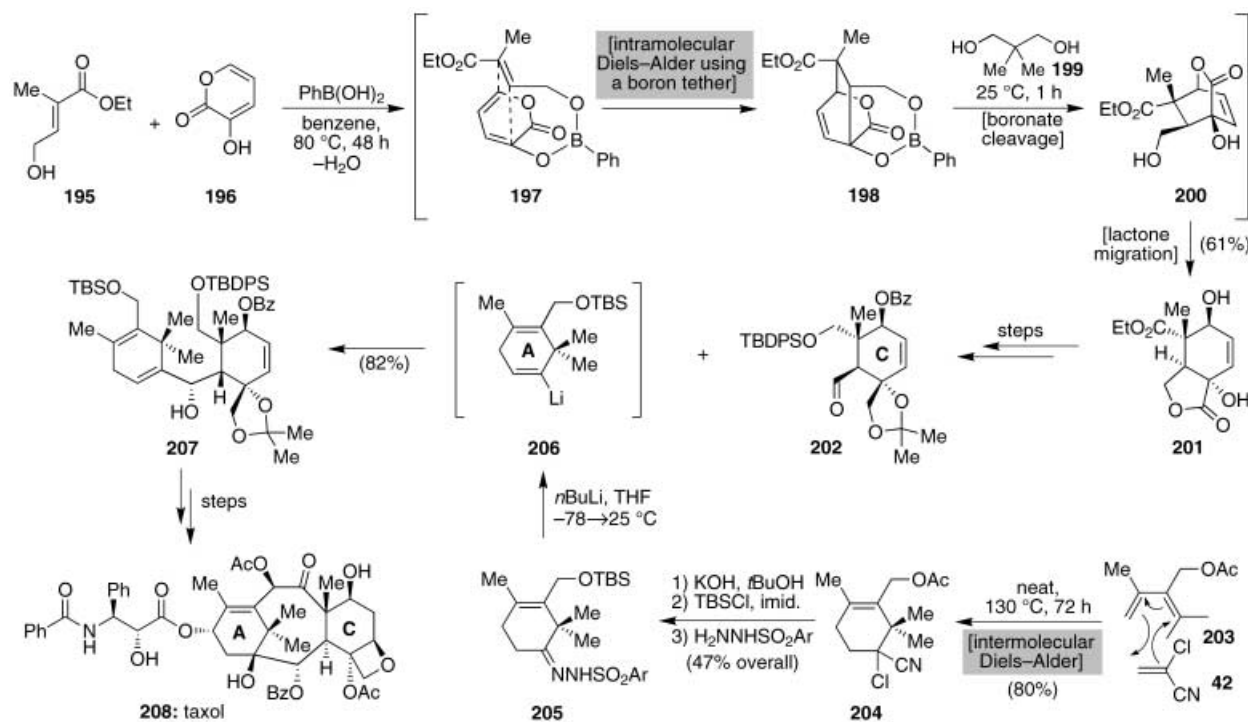
Scheme 31. The impressive adoption of an *exo*-selective Diels–Alder reaction by Kishi and co-workers to effect macrocyclization in the total synthesis of pinnatoxin A (**194**; 1998).^[104]

diene underwent intermolecular [4+2] dimerization upon attempted concentration, it was instead directly heated at 70 °C after formation in dodecane. The expected [4+2] fusion was effected to produce the desired *exo* adduct **193** in 34 % yield, along with another *exo* product and a minor *endo* congener (in the ratio 1.0:0.9:0.4), all possessing the desired regiochemistry. This result, in which the product corresponding to the target molecule is favored, is remarkable if one considers that a total of eight intramolecular Diels–Alder adducts are possible in this reaction. Although it would be challenging to predict the success of this approach in stereochemical terms on the basis of first principles, experimentation with other intermediates established that the facial selectivity of this Diels–Alder collapse depended critically upon the arrangement of functional groups along the C25–C32 chain. Interestingly, alteration of either the solvent or the temperature had profound effects on the ratios of the three products formed.

Another well-celebrated application of the Diels–Alder reaction in the context of natural products synthesis is found in the first published total synthesis of taxol (**208**, Scheme 32), in which Nicolaou et al. employed two different [4+2] cycloadditions to construct each of the two six-membered rings of the target molecule.^[105] Initial efforts to effect a fusion between the Diels–Alder partners **195** and **196** failed, both in terms of yield and regioselectivity. Fortunately, however, joining the two components through a boron tether according to the procedure developed by Narasaka et al.^[106] provided an excellent solution to this regiochemical problem with concurrent enhancement of yield. In the event, treatment of a mixture of **195** and **196** with phenyl boronic acid led to intermediate **197**, by the loss of two molecules of water, thus affording a template in which the diene and dienophile reactants were brought together in a rigorously controlled

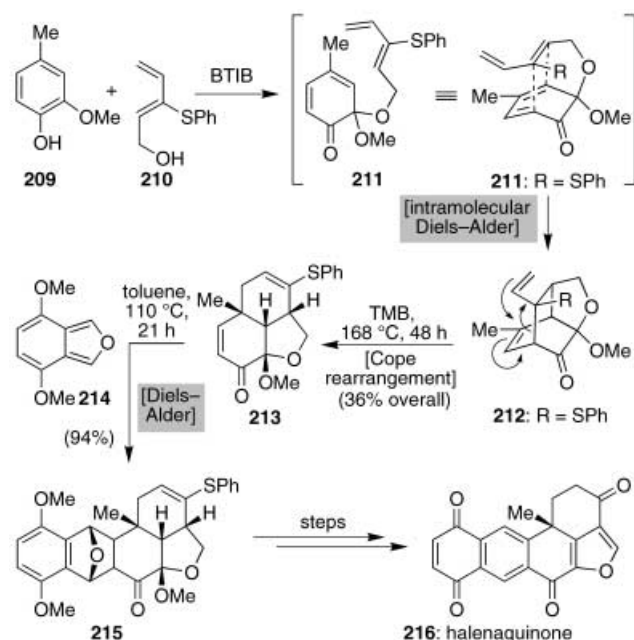
manner, and hence enabling complete regioselective fidelity in the enforced Diels–Alder transition state leading to *endo* adduct **198**. The boron tether was cleaved upon work-up with diol **199** to liberate bicyclic system **200** which rapidly rearranged through lactone migration to the isolated product **201** in 61 % yield.^[107] Impressively, two polyfunctional rings and four contiguous stereocenters were arrayed successfully in a relative sense during this cascade sequence. Construction of the other six-membered ring of taxol commenced with a Diels–Alder union of diene **203** with 2-chloroacrylonitrile (**42**) and led exclusively to adduct **204** in 80 % yield. Although the regiochemistry of the cycloaddition product was anticipated on the basis of the substitution pattern in the diene system, there was concern that potentially destabilizing steric congestion in the requisite transition state could thwart its formation.^[108] Nonetheless, the conversion proved regiospecific, and upon subsequent elaboration this fragment was smoothly joined with **202** in a Shapiro coupling reaction with eventual conversion into the final target molecule **208**. An additional feature of the latter Diels–Alder reaction worth noting is that 2-chloroacrylonitrile (**42**) represents the synthetic equivalent of ketene, as after cycloaddition had been achieved, hydrolysis with base afforded a ketone product (a concept first demonstrated in the total synthesis of the prostaglandins (Scheme 7a) by Corey et al.). Since ketenes cannot be employed directly in Diels–Alder reactions because of preferential [2+2] cycloaddition with one of the olefins of the 1,3-diene system, the development of ketene replacements such as **42** constitutes a highly established field and an objective of continuing interest.^[109]

In addition to ketenes, however, as a general precept, Diels–Alder reactions of simple *o*-benzoquinones are similarly highly challenging to achieve, not only because these highly reactive substances undergo facile polymerization



Scheme 32. The synthesis of taxol (**208**) by Nicolaou et al. featuring two Diels–Alder reactions to fashion the molecule's six-membered rings (1994).^[105]

through Diels–Alder processes, but also because the pericyclic process is typified by a lack of regiochemical control when successful. An elegant strategy which addresses these issues is found in an intramolecular version of the reaction, beautifully formulated in the elegant total synthesis of halenaquinone (**216**, Scheme 33) by Rodrigo and co-workers.^[110a] Thus, oxidative ketalization of 2-methoxy-4-methylphenol (**209**) with diene alcohol **210** in the presence of BTIB



Scheme 33. The elegant approach used by Rodrigo et al. to synthesize halenaquinone (**216**) using a tandem annulation strategy based on oxidative ketalization, a Diels–Alder reaction, and a Cope rearrangement to construct a substrate serving as a dienophile for a second Diels–Alder cycloaddition (2001).^[110]

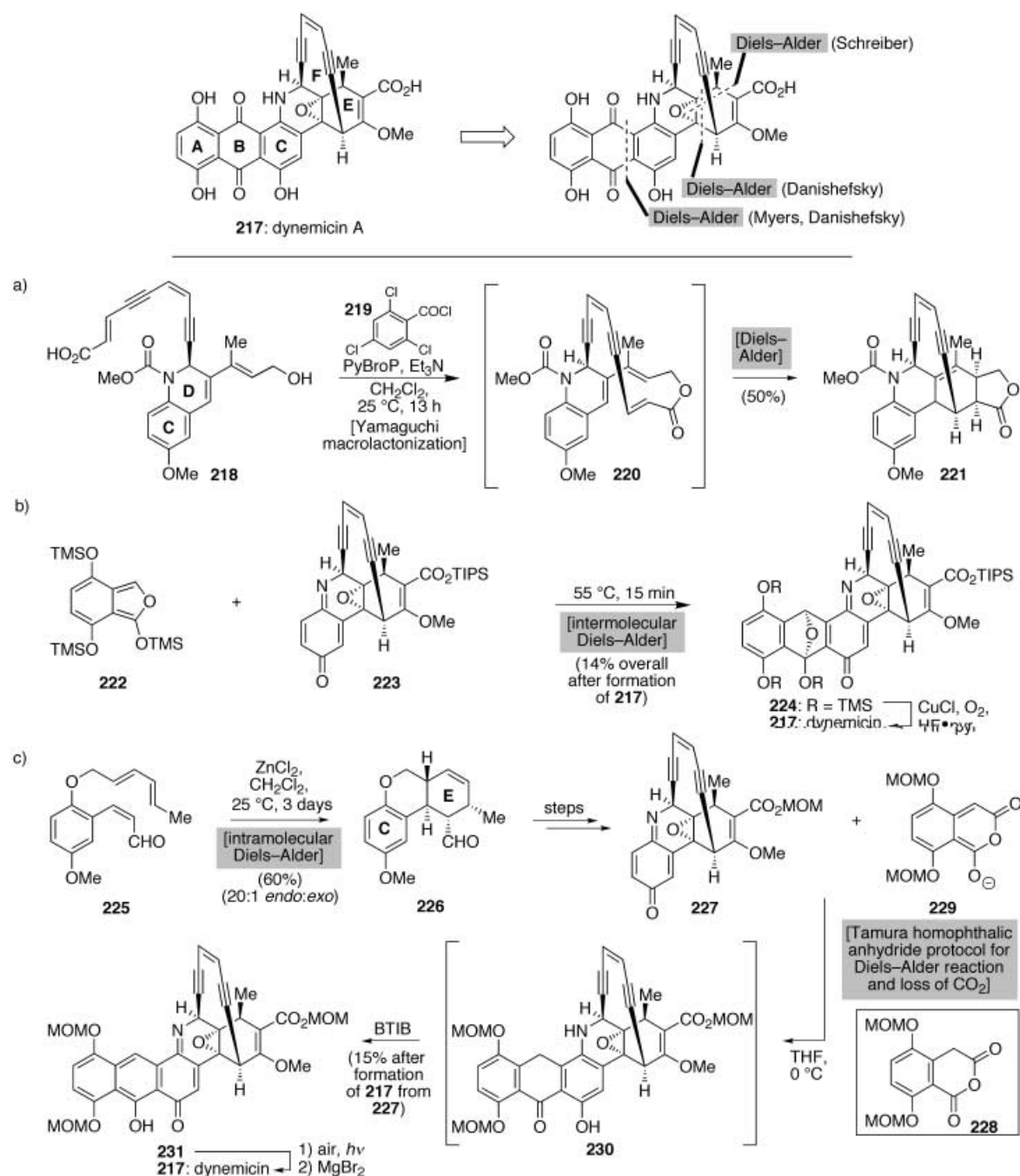
led to the formation of an *o*-quinone monoketal **211**,^[110b] an intermediate which smoothly underwent an intramolecular Diels–Alder reaction to provide both adduct **212** and tricyclic system **213** (the product of a Cope rearrangement of **212**). Rather than purify the melange at this juncture, the mixture of **212** and **213** was heated in 1,2,4-trimethylbenzene which resulted in complete conversion into **213**, a product which was isolated in a final yield of 36% from **209**. One should note that the thiophenyl moiety was incorporated as part of this sequence not so much to enhance the electron-richness of the diene, as might be expected, but rather to provide a functional handle for use later on in the sequence. In the next operation, a second Diels–Alder reaction with naphthofuranone **214** was realized in refluxing toluene and produced the expected bridged product **215** in a remarkable 94% yield.^[111] Parenthetically, naphthofuranones are particularly competent dienes in Diels–Alder reactions, as the resultant products restore aromaticity to the benzene-type ring. Conversely, although simple furans are excellent diene partners in [4+2] cycloadditions, as first demonstrated by Alder himself,^[112] the loss of aromaticity often leads to retro-Diels–Alder processes, which typically result in the ultimate formation of the thermodynamically favored *exo* product.

On the other hand, thiophene and pyrrole, furan's close cousins, are rarely employed with success as dienes in Diels–Alder reactions.^[113]

As a final example in this section, we turn to the rigorous testing ground for Diels–Alder chemistry provided by the challenging structure of dynemicin A (**217**, Scheme 34), a potent enediyne antitumor antibiotic bearing a complex heterocyclic skeleton and a network of sensitive functional groups. Three different research groups successfully applied [4+2] cycloadditions in their elegant and divergent strategies to reach the target molecule. In the first disclosed synthesis of tri-*O*-methyl dynemicin A methyl ester,^[114] Schreiber and co-workers accessed key elements of this striking molecular architecture (namely **221**) through use of a tandem Yamaguchi macrolactonization/Diels–Alder sequence (Scheme 34a). In the event, initial formation of **220** upon reaction of **218** with acid chloride **219** set the stage for a programmed transannular Diels–Alder reaction, which was achieved at ambient temperature to provide **221** in 50% yield. The remarkable facility with which this key Diels–Alder step was realized is likely the result of the inferred excellent proximity and alignment of the diene in relation to the macrocyclic dienophile, enforced by the unique structural characteristics of the enediyne motif, thereby allowing the Diels–Alder reaction to proceed with a relatively low activation energy. Significantly, attempted Diels–Alder cycloadditions with acyclic **218** failed under various scenarios examined, with decomposition observed upon heating at temperatures in excess of 180°C. As such, transannular activation, as achieved by initial macrocycle formation, clearly represented a crucial element to the success of this conversion.^[115]

The use of a late-stage Diels–Alder cycloaddition between two highly functionalized segments in the wholly unique approach to this target (Scheme 34b) by Myers et al. was designed not only from the standpoint of convergency, but also as a vehicle to explore structure–activity relationships, since facile entry into structural variations of dynemicin A would be expected through such a route.^[116] In the penultimate step, diene **222**, generated in situ from a protected phthalan derivative precursor, successfully added in Diels–Alder fashion to dienophile **223** to afford the complete hexacyclic framework of the goal structure **224**. This intermediate adduct was then directly converted into the natural product **217** upon application of an oxidation/deprotection protocol using CuCl and O₂ in the presence of HF·pyr.

The instructive synthesis of dynemicin A (Scheme 34c) by Danishefsky and co-workers relied on a similar late-stage Diels–Alder retrosynthetic disconnection as that discussed in the above route, but employed a different protocol to achieve the reaction in the actual forward synthesis.^[117] Before reaching this stage, however, Danishefsky and co-workers applied an initial ZnCl₂-induced Diels–Alder cycloaddition to form adduct **226** from precursor **225**, a process which proceeded with near-exclusive *endo* stereoselectivity. Adduct **226** was then advanced to intermediate **227**, in anticipation of the second and crucial intermolecular Diels–Alder union with **229**. One of the most versatile and general methods to deliver such naphthoquinone ring systems for Diels–Alder reactions derives from methodology developed by Tamura



Scheme 34. The Diels–Alder reaction in the total synthesis of dynemicin A (217): a) use of a tandem Yamaguchi macrolactonization/Diels–Alder sequence by Schreiber and co-workers (1993);^[114] b) the Diels–Alder approach used by Myers et al. to form the B ring (1995);^[116] c) the strategy used by Danishefsky and co-workers featuring two Diels–Alder cycloadditions (1996).^[117]

et al. using compounds of type **228**.^[118] When treated with base, these homophthalic anhydrides are deprotonated at the reactive methylene site, which leads to the formation of diene systems such as **229**. In this example, the action of LiHMDS on **228** at 0 °C, followed by the addition of **227**, effected a smooth intermolecular Diels–Alder reaction with concomitant loss of carbon dioxide to afford polycycle **230**, a highly reactive intermediate which was immediately oxidized with BTIB to furnish anthracenol **231**. Taken cohesively, these three separate but similarly effective approaches to the dynemicin A architecture clearly demonstrate the broad

scope of the Diels–Alder reaction when incorporated in ingenious schemes toward challenging molecular structures.

7. The Diels–Alder Reaction in Nature(?)

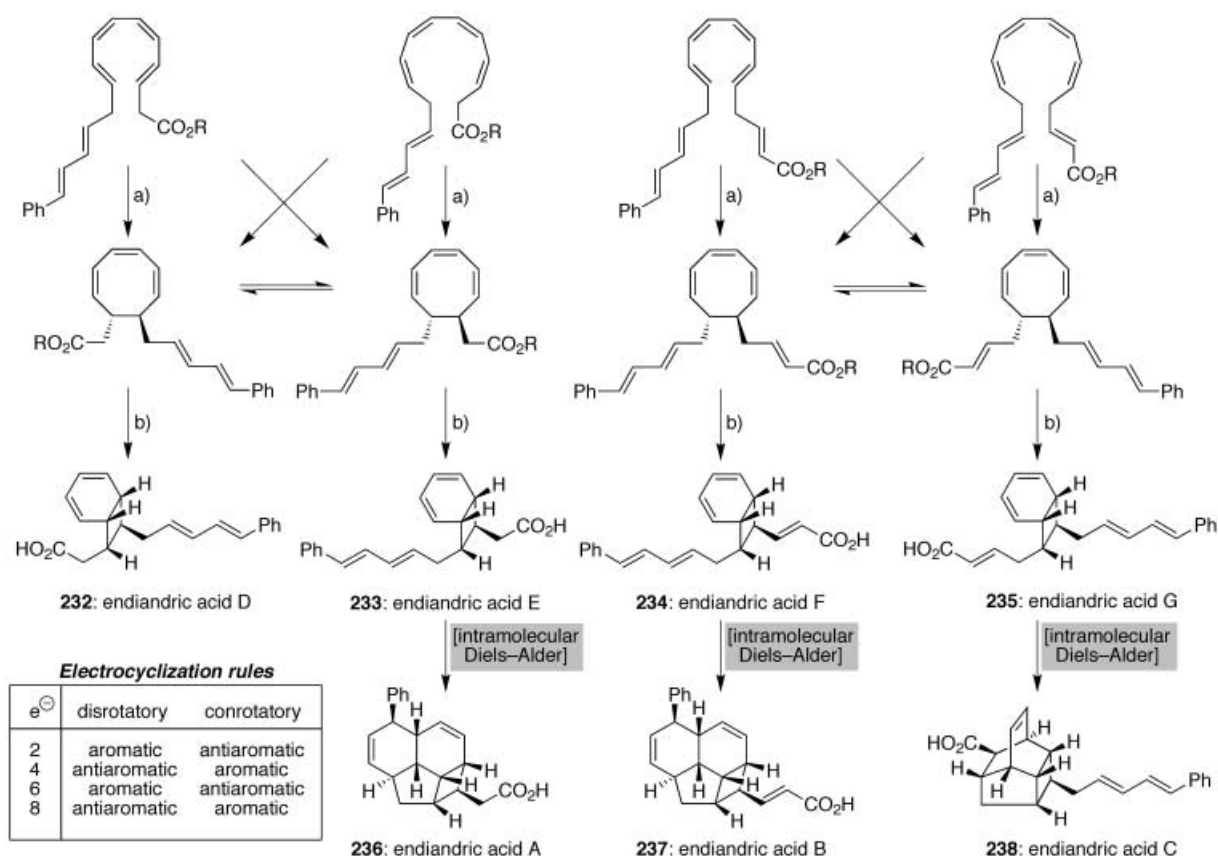
The numerous total syntheses delineated above appropriately define the awesome power of the Diels–Alder reaction to construct daunting molecular architectures. An issue not yet addressed is whether or not nature deploys [4+2] cyclo-

additions as a weapon in her arsenal to fashion molecular complexity. It is perhaps fair to state at the outset that despite the fact that the Diels–Alder reaction has proven to be a popular tool in the hands of synthetic chemists, its role in the biosynthesis of natural products, although often assumed, remains in question.^[119]

At present, several investigators have conclusively established that biological macromolecules such as catalytic antibodies^[120] and metal-binding RNA fragments^[121] are indeed competent catalysts for the Diels–Alder reaction. Each of these elegant and insightful cases, however, is the product of chemical manipulation as synthetic haptens are required for antibody production and the active RNA molecules are artificial. In an effort to address the question at hand from an absolutely pure biological perspective, considerable effort has been expended in searching for enzymes capable of effecting a Diels–Alder reaction. Although little evidence currently exists for authentic “Diels–Alderase” (entities whose sole and specific purpose is to engender a Diels–Alder reaction),^[122] mounting data indicate that enzymes which perform other functions, such as oxidations, are capable of activating bound substrates for in situ intramolecular Diels–Alder reactions in certain circumstances.^[119, 123] Such cycloadditions are likely driven by the relative proximity of the diene and dienophile partners enforced within the enzyme’s tertiary structure once the primary enzymatic function has been accomplished. As such, it would seem reasonable, despite the absence of confirmed Diels–Alderase, to assume that nature

does indeed employ the Diels–Alder reaction as a key C–C bond forming reaction, even if such reactions proceed only by virtue of activating encapsulation. In this section, we will highlight several instructive total syntheses guided by biosynthetic hypotheses that invoke the Diels–Alder reaction as a critical process with or without the aid of enzymes. Each example was selected on the basis of a context where the participation of the pericyclic reaction seems inevitable for the formation of the observed natural product; the sheer elegance of the chemistry involved was another selection criterion.

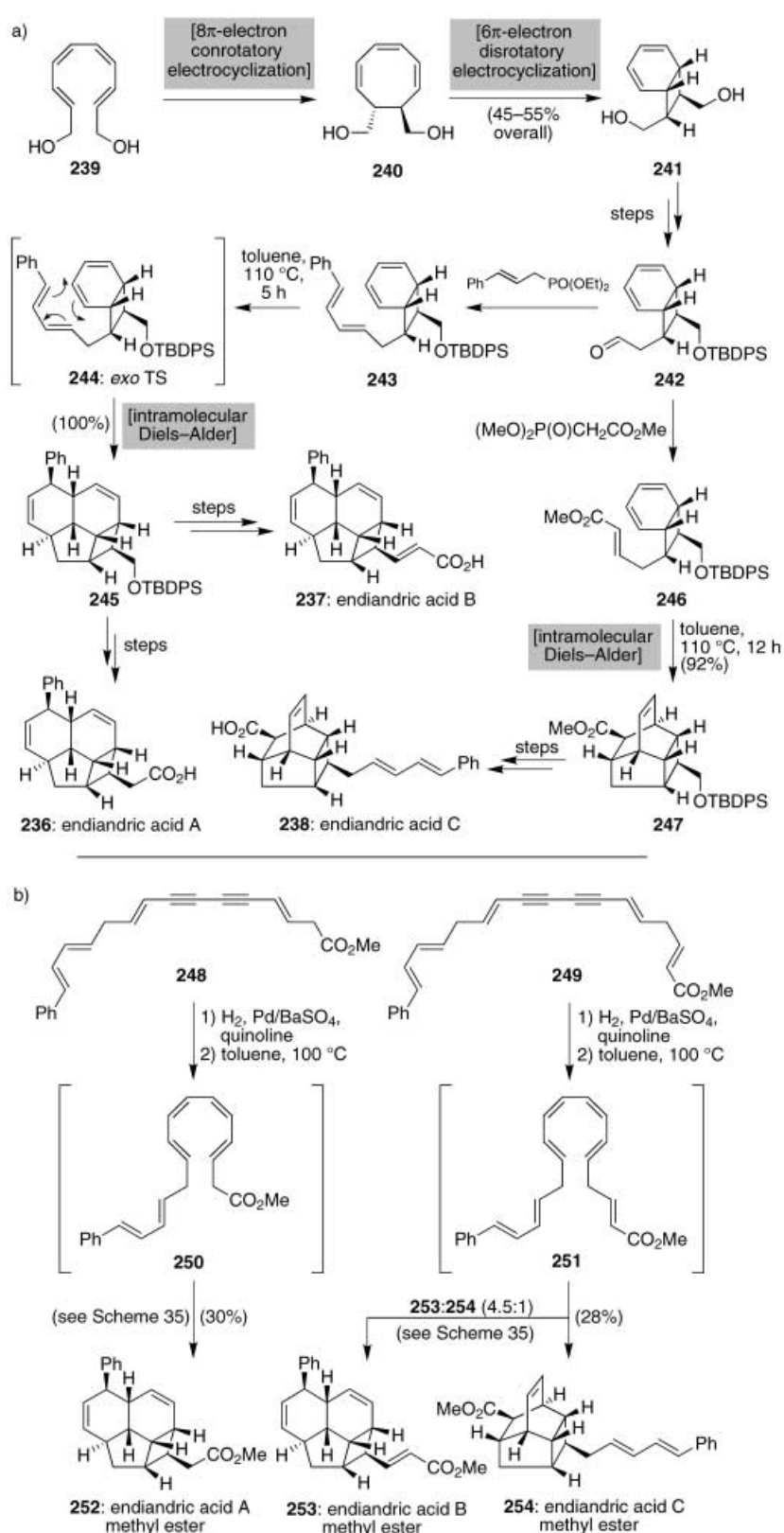
As an initial foray into this fascinating area, we offer the endiandric acids (**232–238**, Scheme 35) for closer analysis. This family of natural products, first isolated in 1980 from the Australian plant *Endiandra introrsa* by Black and co-workers, displays striking molecular architectures and unique structural interrelationships.^[124] Despite possessing eight chiral centers, the endiandric acids exist in nature as racemates, a highly unusual phenomenon for natural products bearing stereochemical elements, which suggests that these compounds are assembled in nature from prochiral precursors through non-enzymatic reactions. On the basis of this curious observation, Black advanced an intriguing biosynthetic hypothesis in which a series of electrocyclizations from achiral polyenes were postulated to form endiandric acids D–G (**232–235**), with a terminating Diels–Alder cycloaddition completing the sequence to endiandric acids A–C (**236–238**).^[124] As such, although the starting materials lack stereo-



Scheme 35. The biosynthetic endiandric acid cascade proposed by Black and co-workers (R = Me, H): a) conrotatory 8 π electrocyclization; b) disrotatory 6 π electrocyclization (1980).^[124]

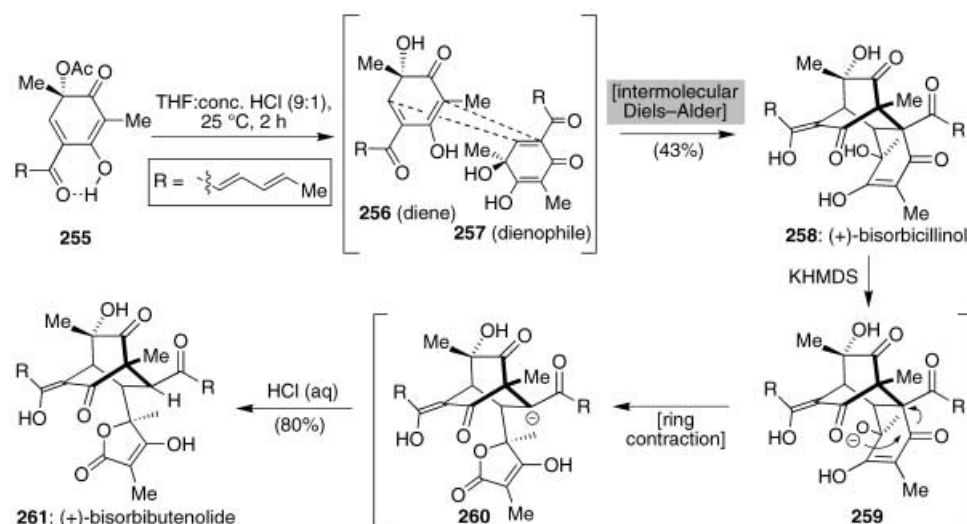
genic centers, the remarkable stereospecificity of the events in the proposed cascade sequence is subtly encoded within the geometry of the olefinic bonds in the postulated precursors. Inspired by this highly intriguing proposal, in 1982 Nicolaou et al. developed both stepwise and biomimetic synthetic routes to all of the endiandric acids (Scheme 36).^[125] Significantly, not only did these successful efforts define the first use of 8π and 6π electrocyclizations in natural product total synthesis, they also provided support for the veracity of the non-enzymatic hypothesis proposed by Black and co-workers for the origin of the endiandric acids. Indeed, the one-pot construction of **252**–**254** is particularly remarkable, as no less than eight stereocenters and four rings within each and every natural product were formed concomitantly. Significantly, one should note that endiandric acid methyl esters D–F (Scheme 35) were also observed as products of the biomimetic cascade sequence directly after hydrogenation, prior to heating. However, upon exposure to elevated temperatures, these compounds underwent reversible isomerization processes, eventually being funnelled into the pathways leading to endiandric acids A–C.

A more recent example of a Diels–Alder reaction as a critical component of a presumed biosynthetic pathway includes the dodecaketide (+)-bisorbicillinol (**258**, Scheme 37), a member of the bisorbicillinoid family of natural products possessing potent inhibitory activity against lipopolysaccharide-induced production of tumor necrosis factor α . Careful examination of this group of natural products has led to several biosynthetic hypotheses being advanced by the research groups of both Abe^[126] and Nicolaou^[127] which uniformly implicate a highly reactive quinol intermediate (tautomers **256** and **257**, masked as an acetate in **255**) as the key building block leading to the biosynthesis of all members of this family of compounds. In 1999, the Nicolaou group was the first to achieve experimental verification of this hypothesis when exposure of homochiral acetate **255** to a solution of base, or even better, concentrated HCl in THF, led to the Diels–Alder adduct **258** ((+)-bisorbicillinol) in 43% yield with complete regio- and diastereocontrol.^[127] The observed selectivity was rationalized on the basis of the anticipated *endo* selectivity (with respect to the six-membered ring) of the postulated transition state in the Diels–Alder union. NMR spectroscopic analysis confirmed the course of the reaction as deacetylation followed by formation of a quinolate system containing the rapidly equilibrating mixture of diene (**256**) and dienophile (**257**) units; these monomers then united in Diels–Alder fashion to form tricyclic skeleton **258** with concurrent installation of four chiral centers, two of which are quaternary.



Scheme 36. The total synthesis of endiandric acids A–C (**236**–**238**) by stepwise (a) and biomimetic (b) routes featuring intramolecular Diels–Alder reactions (Nicolaou et al., 1982).^[125]

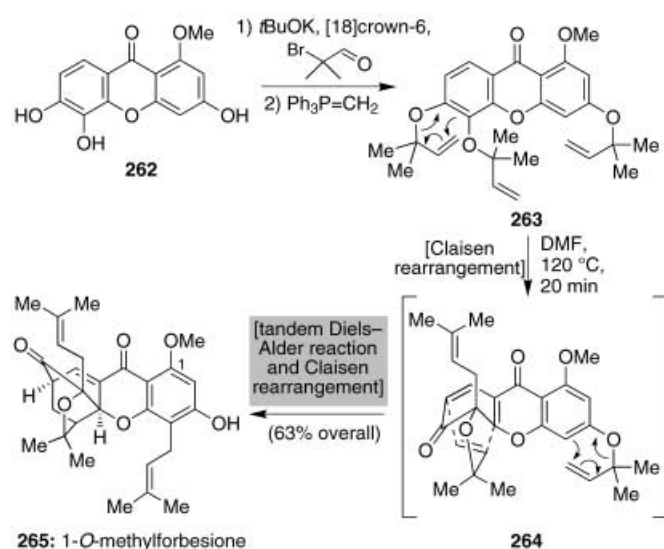
With **258** in hand, subsequent exposure to KHMDS in THF at ambient temperature followed by acidic work-up smoothly led to the formation of (+)-bisorbibutenolide (**261**) in 80%



Scheme 37. Biomimetic total synthesis of (+)-bisorbicillinol (**258**) and (+)-bisorbibutenolide (**261**) featuring a [4+2] dimerization of a quinol intermediate (Nicolaou et al., 1999).^[127]

yield, presumably through the delineated ring-contraction mechanism. Significantly, after the completion of these synthetic efforts, Abe et al. confirmed this biosynthetic hypothesis through careful isolation of the quinol monomer from natural sources.^[128]

Along related lines, Nicolaou and Li also recently confirmed^[129] a biosynthetic hypothesis first advanced over thirty years ago by Quillinan and Scheinmann^[130] in which a series of Claisen rearrangements followed by an intramolecular Diels–Alder reaction was postulated for the formation of the 4-oxatricyclo[4.3.1.0]decan-2-one ring system of numerous secondary metabolites, particularly those isolated from the *guttiferae* family of plants. As a test subject for the proposed cascade sequence the natural product forbesione (the C-1 phenol analogue of **265**, Scheme 38) was targeted: an expedient synthesis of triprenylated derivative **263** was

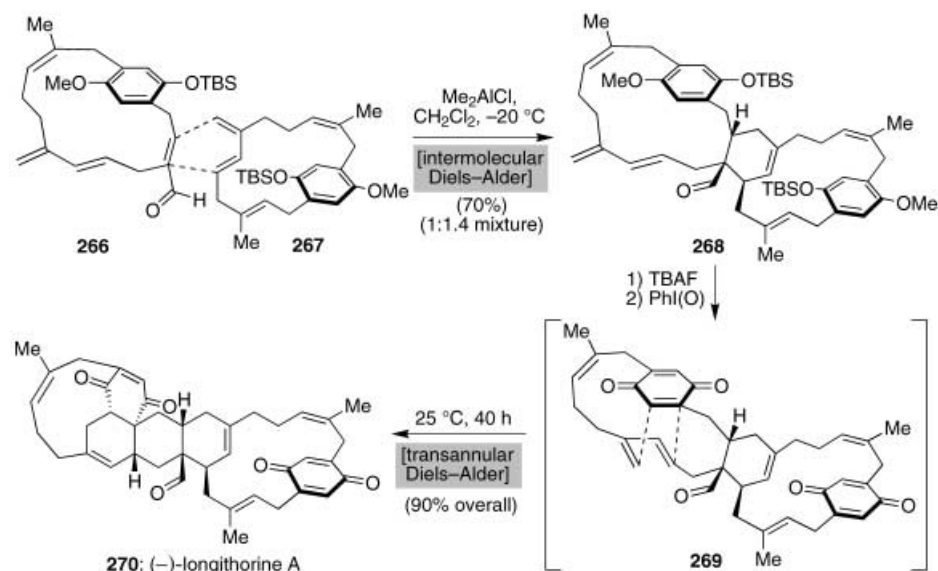


Scheme 38. Putative biomimetic total synthesis of 1-O-methylforbesione (**265**) by a cascade sequence featuring tandem Claisen rearrangements and an intramolecular Diels–Alder reaction (Nicolaou and Li, 2001).^[129]

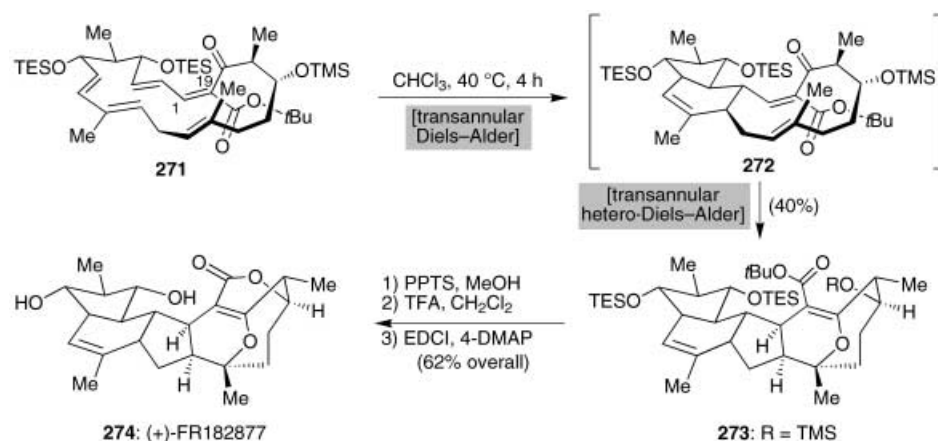
followed by heating the latter compound in DMF at 120 °C for 20 minutes to furnish 1-O-methylforbesione (**265**) in 63% yield. Presumably, the final adduct was the result of the anticipated biosynthetic route involving a double Claisen rearrangement/Diels–Alder sequence, via intermediate **264**. The successful development of this technology bodes well for the future construction of the entire functionalized skeleton of other members of this constantly expanding class of important natural products.

Recently, an admirable and highly elegant total synthesis of the marine-derived natural product (–)-longithorone A (**270**, Scheme 39) was achieved by Shair and co-workers^[131] based on a biosynthetic hypothesis first proposed by Schmitz and co-workers^[132] in which an intermolecular Diels–Alder union of two [12]cyclophanes of type **266** and **267**, followed by an intramolecular transannular Diels–Alder cycloaddition is proposed to concurrently fashion three new rings and completed the target molecule. Thus, in the synthesis by Shair and co-workers, following construction of compounds **266** and **267** by routes which each employed ene-yne metathesis for the macrocyclization step, the merger of these fragments in a Diels–Alder reaction was achieved regioselectively upon exposure to Me_2AlCl to afford a 1:1.4 mixture of diastereomers favoring the undesired adduct. Since careful scrutiny of **266** and **267** reveals no extenuating features which would lead one to expect a diastereoselective [4+2] union, the observed existence of a lone diastereomer of longithorone A in nature may imply an enzyme-mediated fusion of these two pieces, if the proposed biosynthetic pathway is accurate. With **268** in hand, deprotection and quinone formation using iodosylbenzene provided an intermediate (**269**) suitable for the anticipated transannular Diels–Alder reaction, an impressive cycloaddition which was ultimately realized in a remarkable 90% yield upon prolonged reaction at ambient temperature.

As a final entry for discussion in this review, we have selected the very recently achieved biomimetic total synthesis of (+)-FR182877 (**274**, Scheme 40) by Sorensen and co-workers.^[133] This example perhaps represents one of the ultimate expressions of the transannular Diels–Alder reaction.^[115] The synthesis of key precursor **271** was completed after a 16-step sequence starting with readily available building blocks, in which macrocyclization was brought about through a palladium-mediated Tsuji–Trost reaction. Warming **271** in chloroform at 40 °C then induced an unprecedented domino sequence of transannular Diels–Alder reactions and forged **273** stereoselectively as a lone diastereomer in the absence of any external asymmetric catalyst, with the overall process generating a pentacycle displaying a contiguous array



Scheme 39. The elegant dual Diels–Alder strategy of Shair and co-workers for the biomimetic total synthesis of (–)-longithorone A (270; 2002).^[131]



Scheme 40. The beautiful total synthesis of (+)-FR182877 (274) by Sorensen and co-workers featuring a novel double transannular Diels–Alder cascade to fashion the molecule's polycyclic scaffold (2002).^[133]

of seven stereocenters in 40% yield. One should note that this overall yield reflects the fact that 271 was taken into the reaction as a 1:1 mixture of *E* and *Z* isomers at the C1–C19 olefin, with approximately 80% of the *E* isomer successfully converting into the desired product. Importantly, the diastereoselectivity of the process, in combination with the observation that the tandem Diels–Alder reactions also proceeded smoothly at ambient temperature (albeit more slowly), are features suggestive of the plausibility of the cascade similarly occurring in nature. As such, this example provides a novel biosynthetic approach to the complete carbogenic framework of (+)-FR182877 (274) and, more significantly, represents the first realization of a double transannular Diels–Alder process in organic synthesis, an event conceivable only from a macrocyclic precursor composed of a minimum of 18 atoms. As such, this synthesis highlights the utility of transannular Diels–Alder reactions both in terms of the atom economy as well as the versatility of the process. Clearly, entropic and enthalpic activation in the macrocyclic environment, with the

overall geometry governed by transannular steric repulsion and electronic interactions, dictated the facility of the achieved cascade sequence.^[115]

Before closing this section, we should note that several of the total syntheses highlighted in the preceding segments of this review similarly employed Diels–Alder unions based on biosynthetic hypotheses, but were mentioned earlier for other overriding reasons. Furthermore, in no way should the present set of examples serve as a complete expression of the power of biomimetic approaches to total synthesis by the Diels–Alder reaction. As such, we refer the reader to several additional and enriching examples in the chemical literature.^[134]

8. Conclusions and Future Perspectives

The discussion of the Diels–Alder reaction in the preceding pages speaks volumes of the power of this reaction in total synthesis. As much as one should in general avoid speculation about the future, its application in the assembly of complex molecules is likely to be secured for a long time to come on the grounds of its efficiency, versatility, and scope.^[135] With little doubt, both nature and man are the guarantors

of its continuing prosperity in the art of total synthesis. Thus, the constantly expanding collection of constructs isolated from nature's library of molecular diversity is bound to contain myriad structures amenable to retrosynthetic analysis based on Diels–Alder transforms. Equally eager to contribute to the reaction's longevity, if not immortality, will be the sustained desire of synthetic chemists to adopt it in their total synthesis endeavors.

Of course, the employment of the Diels–Alder reaction in the total synthesis of naturally occurring substances, although telling, does not reveal the entire story of its widespread utility and enormous potential. Applications in the fabrication of designed molecules, which reflect structures of theoretical interest or chemical entities desired for biological investigations and for material science purposes, may prove even more important in future investigations than natural products. The vast literature pertaining to such examples is testimony to the faith synthetic chemists have placed in the Diels–Alder reaction as an assembly process for tailor-made compounds.

To be sure, this trend will only expand in the future as the demand for new compound libraries increases. Particularly attractive is the concept of incorporating the Diels–Alder reaction within powerful cascade sequences as a means of rapidly assembling molecular complexity and diversity. Such domino reactions are clearly highly desirable and also have the potential to contribute to our efforts for green chemistry.

Finally, we offer the conjecture that Diels and Alder would be enormously pleased to know of the many important and elegant applications of their reaction in total synthesis as seen from 2002. Indeed, they might even derive a considerable measure of satisfaction from the knowledge that their warning against the use of their reaction in total synthesis, a right they reserved for themselves alone, was not heeded by subsequent generations of chemists. What we dare not project, however, are the beautiful examples of Diels–Alder-based molecular constructions which might be included in a review on the subject on the bicentennial anniversary of Alder's birthday.

Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Alloc	allyloxycarbonyl
BBN	borabicyclo[3.3.1]nonane
BHT	<i>tert</i> -butylhydroxytoluene
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BTIB	[bis(trifluoroacetoxy)iodo]benzene
Bz	benzoyl
CAN	ceric ammonium nitrate
Cp	cyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBP	di- <i>n</i> -butyl phthalate
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	<i>N,N</i> -dimethylformamide
dppp	1,3-bis(diphenylphosphanyl)propane
EDC	3-(3-dimethylaminopropyl)-1-ethylcarbodiimide
EWG	electron withdrawing group
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPT	hexamethylphosphorous triamide
imid.	imidazole
MEM	(2-methoxyethoxy)methyl
MOM	methoxymethyl
PGF	prostaglandin F
PMB	<i>p</i> -methoxybenzyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
PyBroP	bromo-tris(pyrrolidino)phosphonium hexafluorophosphate
pyr	pyridine
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TIB	1,3,5-triisopropylbenzene
TIPS	triisopropylsilyl
TMB	1,2,4-trimethylbenzene
TMS	trimethylsilyl
TS	transition state
Ts	<i>p</i> -toluenesulfonyl
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
X _p	Evans' chiral auxiliary

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