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Natural Product Synthesis

Cascade Reactions in Total Synthesis

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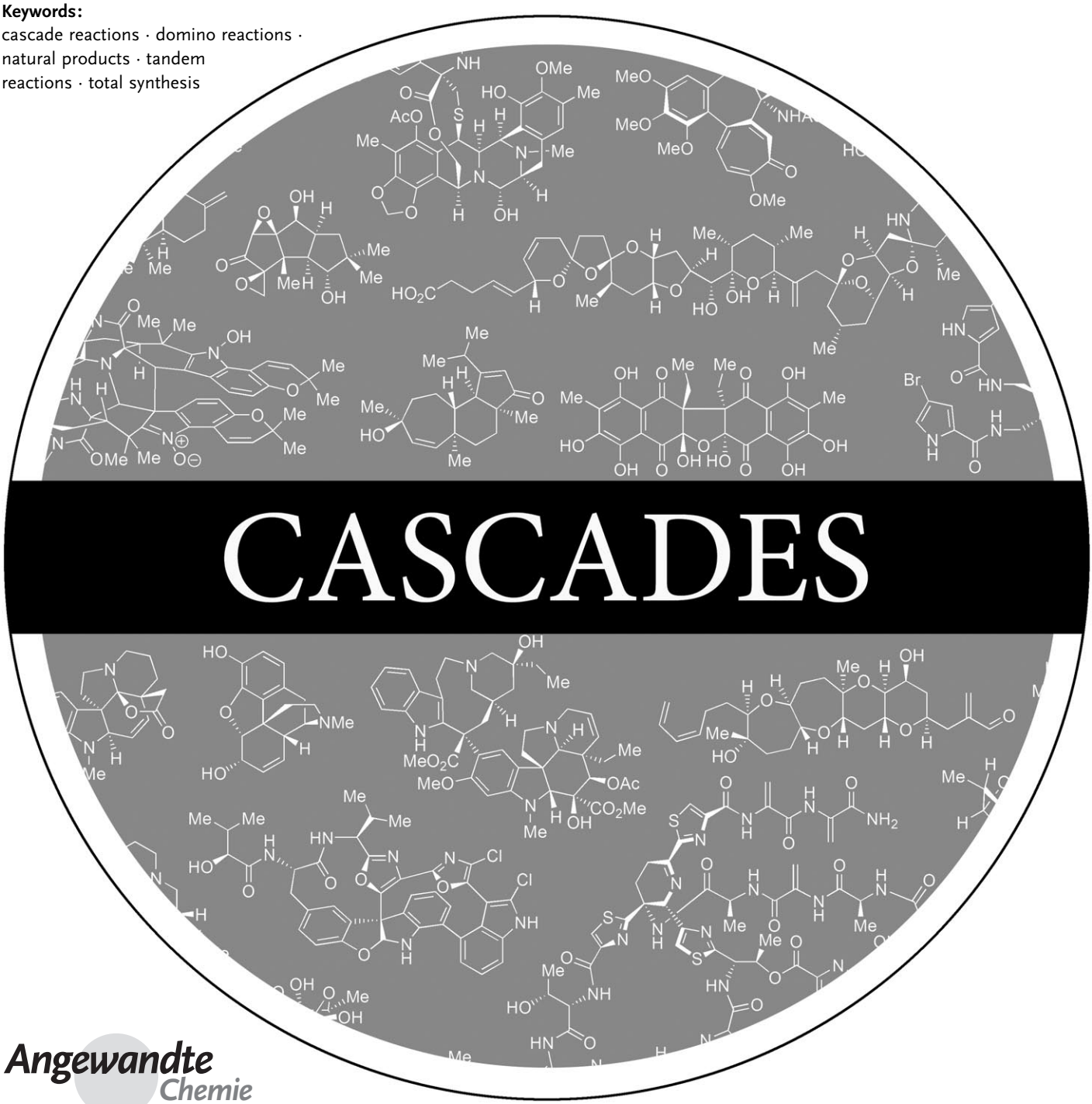

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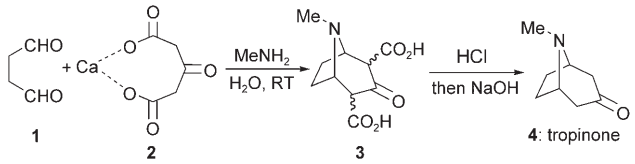
The design and implementation of cascade reactions is a challenging facet of organic chemistry, yet one that can impart striking novelty, elegance, and efficiency to synthetic strategies. The application of cascade reactions to natural products synthesis represents a particularly demanding task, but the results can be both stunning and instructive. This Review highlights selected examples of cascade reactions in total synthesis, with particular emphasis on recent applications therein. The examples discussed herein illustrate the power of these processes in the construction of complex molecules and underscore their future potential in chemical synthesis.

From the Contents

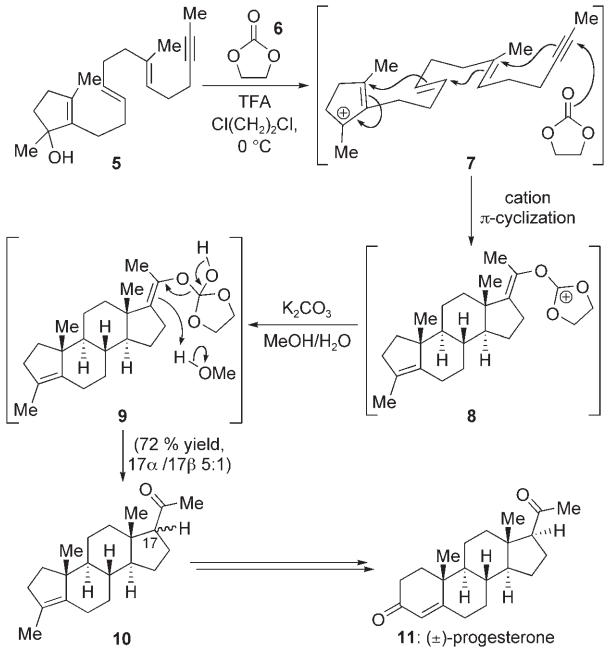
1. Introduction

Cascade reactions constitute a fascinating branch of organic chemistry, and one which has been the subject of intense research in recent years, as witnessed by the number of reviews that have appeared covering various aspects of these processes.[1] The undeniable benefits of cascade reactions are well established, having been recounted on numerous occasions, and include atom economy,[2] as well as economies of time, labor, resource management, and waste generation. As such, cascade reactions can be considered to fall under the banner of "green chemistry",[3] as the savings involved when one carries out several transformations in one synthetic operation can be considerable. For example, only a single reaction solvent, workup procedure, and purification step may be required to provide a product that would otherwise have to be made over the course of several individual steps. Such considerations will become increasingly important in years to come, as both chemists and society in general strive for evermore effective and responsible methods for the management of Earth's precious resources.

Target-oriented synthesis provides the ultimate test of reaction design and applicability. The design of cascades to provide specific targeted molecules of considerable structural and stereochemical complexity poses a significant intellectual challenge and can be one of the most impressive activities in natural product synthesis. Cascade reactions therefore contribute immeasurably to both the science and art of total synthesis, bringing not only improved practical efficiency but also enhanced aesthetic appeal to synthetic planning. The recognition of these dual benefits is, of course, by no means an exclusively modern phenomenon. Indeed, cascade reactions (either as designed sequences or serendipitous discoveries) have attracted the attention of organic chemists since the formative years of total synthesis, with Robinson's one-pot synthesis of tropinone (**4**, Scheme 1) in 1917 standing as the seminal work in this field.[4] Subsequent classic examples include the cationic polyolefin cyclization approach to progesterone (**11**, Scheme 2) developed by Johnson and co-



Scheme 1. Robinson's seminal total synthesis of tropinone (**4**).[4]



Scheme 2. The total synthesis of (±)-progesterone (**11**) involving a polyolefin cyclization (Johnson et al., 1971).[5]

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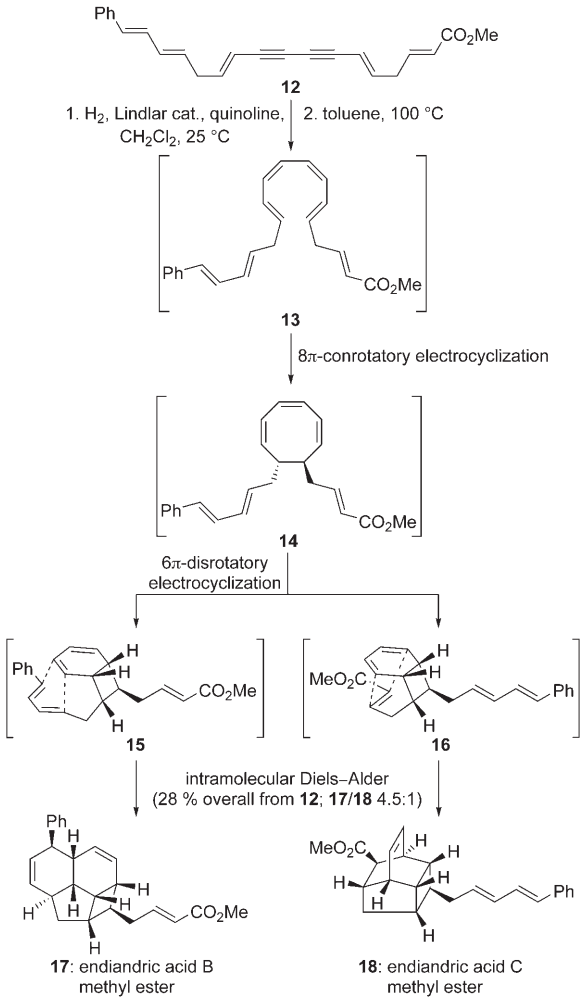
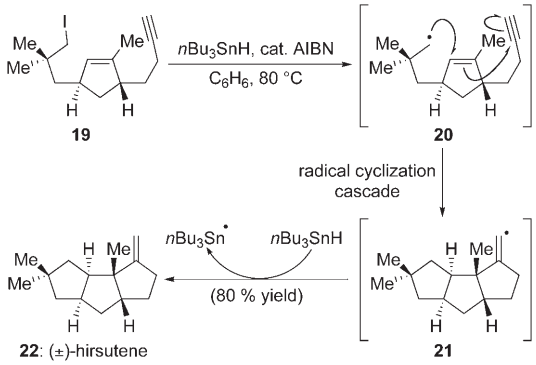
workers[5] on the basis of the Stork–Eschenmoser hypothesis,[6] the "endiandric acid cascade" (Scheme 3) proposed by Black and co-workers[7] and reduced to practice by the Nicolaou group,[8] and the radical-based synthesis of hirsutene (**22**, Scheme 4) and other triquinane natural products by Curran and co-workers.[9,10]

As masterful as each of the syntheses illustrated in Schemes 1–4 is, they should by now be familiar to most students of organic chemistry. Therefore, rather than dwell further on the triumphs of the past, this Review will highlight and discuss a selection of more recent examples of cascade reactions employed in the total synthesis of natural products, offering fresh evidence for the utility of these types of processes in chemical synthesis. We do not aim to present a comprehensive survey of the literature, but rather to highlight a broad variety of strategies developed for the construction of complex molecules using cascade reactions. Where possible, we have tried to avoid duplicating the content of previous reviews, although some examples are covered again in cases where they serve to illustrate a particular reaction class or strategy. Of course, in selecting only representative examples from the extensive literature in the field, and then further restricting the candidate pool to applications in the total synthesis of natural products, we will inevitably be omitting discussion of a wealth of impressive cascade processes, such as the landmark rational chemical synthesis of C_{60} (**24**, Scheme 5) by L. T. Scott et al.[11] Apologies are therefore due in advance to those whose work has been omitted.

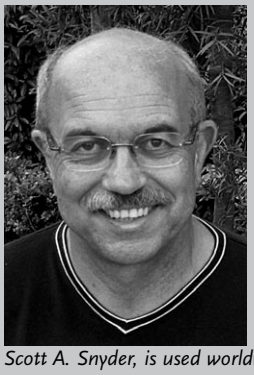
The very nature of cascade reactions, which often involve many distinct steps, can at times make them rather hard to classify. For convenience, we have grouped the examples that follow into five sections: nucleophilic, electrophilic, radical-mediated, pericyclic, and transition-metal-catalyzed processes. This classification scheme is rather arbitrary, particularly in the case of examples that feature more than one class of reaction, but we have tried to place each cascade according to



Scheme 3. The endiandric acid cascade (Nicolaou et al., 1982).[8]



Scheme 4. A radical cyclization cascade in the total synthesis of (±)-hirsutene (**22**; Curran and Chen, 1985).[10]



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David J. Edmonds was born in Glasgow (UK) in 1980. He received his MSci in Chemistry with Medicinal Chemistry from the University of Glasgow in 2001. He was awarded a University Scholarship for postgraduate research, and carried out his PhD work at Glasgow under the supervision of Dr. D. J. Procter on the application of samarium(II)-mediated reactions to total synthesis. In early 2005, he joined Professor K. C. Nicolaou's group, supported by a European Merck Postdoctoral Fellowship, where he has continued to pursue his research interests in the total synthesis of natural products..

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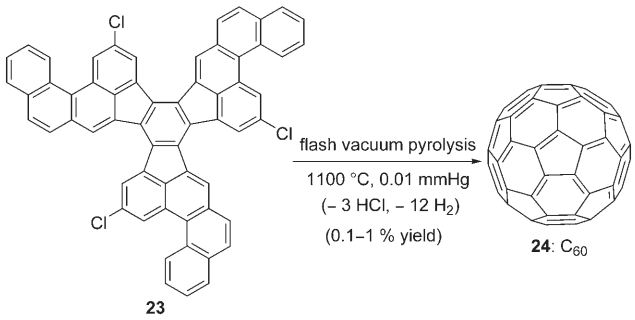
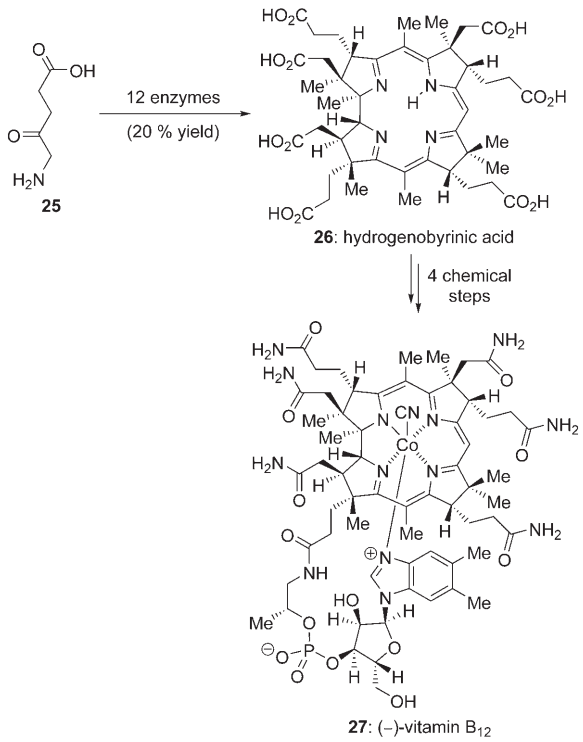


Scheme 5. The total synthesis of C_{60} (**24**; Scott et al., 2002).[11]

what can be argued as being the major theme of the sequence. Within each section, we have ordered the examples so as to provide a continuous discussion, rather than in chronological fashion. On the basis of space considerations, we shall not discuss the important class of enzyme-catalyzed cascade reactions,[12] except to highlight the current "gold standard" in this field by the group of A. I. Scott; namely the conversion of 5-aminolevulinic acid (**25**) into hydrogenobyrinic acid (**26**, Scheme 6) by treatment with a genetically engineered 12-enzyme cocktail in a process that involves 17 steps and the formation of nine stereocenters in a single reaction vessel![13] A further four chemical transformations enable the elaboration of hydrogenobyrinic acid to vitamin B_{12} (**27**).[14]

Before tackling the chosen examples, however, some discussion regarding the terminology and organization of this Review is warranted. Different authors use varying definitions as to what constitutes a cascade process. A variety of terms, including "cascade", "domino", "tandem", and "sequential", are used in the literature, often seemingly interchangeably and with liberal abandon, although efforts have been made to restore order to this area of reaction terminology.[1b,c] For our subjective purposes, we shall employ the term "cascade" to encompass all of the above descriptors. We have also adopted a rather inclusive attitude in order to capture as broad a spectrum of creative reaction design as possible. For example, the strictest definition of a cascade process would discount any example in which the reaction conditions are altered during the process; we will include not only these but also sequences in which further reagents are added at various points ("one-pot" transformations). We will, however, exclude multidirectional reactions (also sometimes termed "tandem" reactions) in which two or more reactions occur on the same substrate, but essentially in isolation of one another.

Paul G. Bulger was born in London (UK) in 1978. He completed his MChem degree in 2000 at the University of Oxford, where he carried out undergraduate research under the supervision of M. G. Moloney. He remained at the University of Oxford for his graduate studies, obtaining his DPhil in Chemistry in 2003 for research conducted under the supervision of Professor Sir J. E. Baldwin. In late 2003, he joined Professor K. C. Nicolaou's group at The Scripps Research Institute as a postdoctoral researcher. His research interests encompass reaction mechanism and design, and their application to complex natural product synthesis and chemical biology.



Scheme 6. The enzymatic synthesis of hydrogenobyrinic acid (**26**; Scott et al., 1994).[13]

Many of the examples highlighted here are based on the use of biosynthetic considerations to guide synthetic strategy (biomimetic synthesis), a paradigm that has witnessed a renaissance in recent years.[15] Others feature novel strategies by combining several known reactions that would normally be executed independently into a single-pot cascade, or by developing completely new reaction pathways altogether. Nevertheless, the common feature of all these examples is their inspired use of cascade reactions to generate molecular complexity in a concise fashion. It is hoped that this Review will serve not only to put into perspective recent accomplishments in the field but also to provide further impetus and inspiration for the implementation of new cascade strategies of broader generality and scope in the future.

2. Nucleophilic Cascades

In defining a nucleophilic cascade, we have adopted a policy whereby the key step in each case involves a nucleophilic attack. This section includes a variety of conjugate addition reactions, which are often employed in conjunction with other reactions.[16] Also included here are several organometallic addition processes, which are followed by pericyclic or anionic rearrangements, such as the anionic oxy-Cope reaction or Brook rearrangement.

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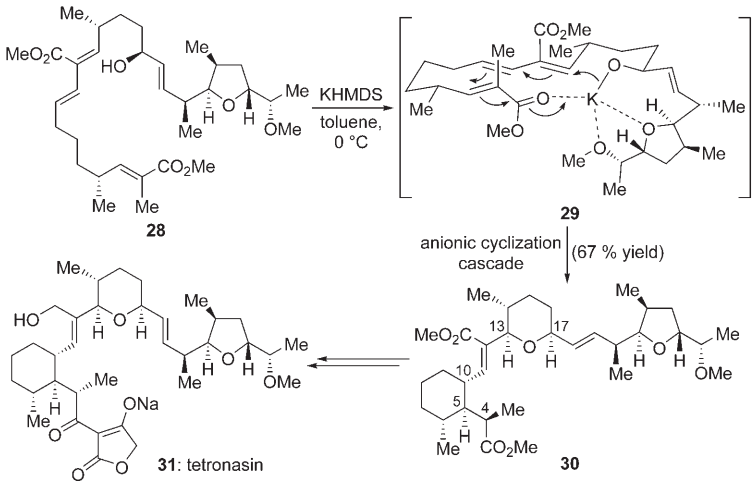
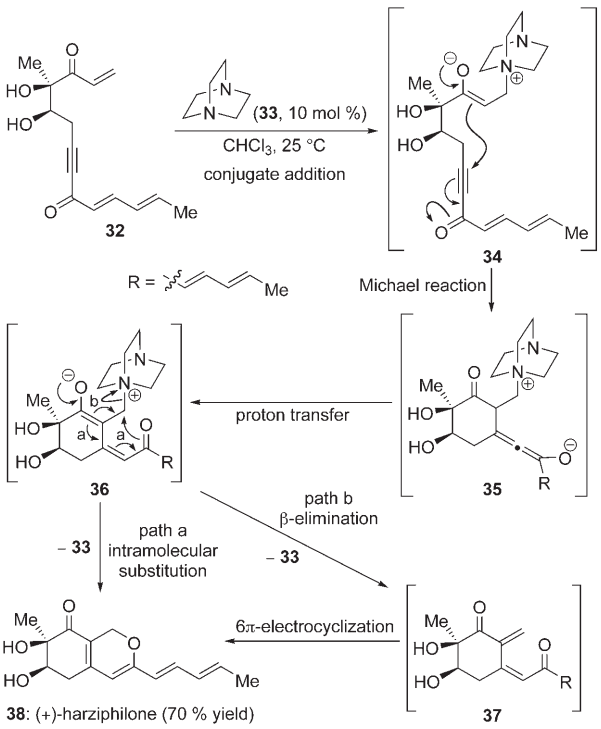
The polyketide ionophore natural product tetronasin (**31**, Scheme 7) is of commercial importance as an antibiotic, antiparasitic, and growth-promoting agent for use in ruminants. The interesting structure of tetronasin, which includes



Scheme 7. An anionic cyclization cascade in the total synthesis of tetronasin (**31**; Ley et al., 1998).[18]



Scheme 8. Total synthesis of (+)-harziphilone (**38**) via a nucleophile-catalyzed cycloisomerization (Sorensen et al., 2004).[20]

tetronic acid, tetrahydrofuran, tetrahydropyran, and cyclohexane rings, prompted the groups of Ley and Staunton to investigate its biosynthesis. They proposed that both the tetrahydropyran and cyclohexane six-membered rings might be formed in a single step, and with the correct configuration, through a nucleophilic cascade triggered by the addition of an alcohol group to a suitably disposed activated triene.[17] The intriguing question of whether this process could be replicated in the laboratory was also answered by Ley and coworkers, who developed a biomimetic total synthesis of tetronasin incorporating the proposed biosynthetic cyclization cascade (Scheme 7).[18] They found that exposure of the putative cascade precursor **28** to potassium hexamethyldisilazide (1.1 equiv) in toluene at 0 °C indeed led to efficient cyclization to give **30** in a respectable yield of 67 %. This cyclization is thought to proceed via potassium salt **29**, in which the oxygen-based functional groups coordinate to the metal center in a manner resembling the ionophoric characteristics of the natural product, orienting the reacting groups in a favorable manner for cyclization. The structural order in this intermediate led to formation of **30** as a single diastereoisomer, in which three of the newly formed stereogenic centers (at C5, C10, and C13) were installed with the required configuration as found in the natural product **31**. Although the stereogenic center at C4 was formed with the incorrect *R* configuration, this site was readily epimerized to the natural *S* configuration in the closing stages of the synthesis.[19]

The group of Sorensen recently reported the nucleophilic catalysis of a cascade reaction in the enantioselective total synthesis of harziphilone (**38**, Scheme 8).[20] They devised a clever strategy for the construction of the required bicyclic ring system of the target molecule through the conjugate addition of a ketone enolate onto an acetylenic ketone to form the cyclohexane ring, followed by a 6π-electrocyclization of a dienone to generate the pyran ring. This second step was based on precedent from work by Büchi and Marvell on the cycloisomerization of *cis*-dienones.[21] Thus, treatment of enone **32** with DABCO (**33**, 10 mol %) in $CHCl_3$ at ambient temperature led to the initial formation of enolate **34** in a process resembling the first step of the Baylis–Hillman reaction.[22] Subsequent conjugate addition of enolate **34** onto the proximal triple bond established the cyclohexane ring (**34**→**35**), and was presumably followed by proton transfer to give the isomeric enolate **36**. A further cyclization process then generated the target natural product **38** and concomitantly liberated a molecule of DABCO (**33**), which could then re-enter the catalytic cycle. Two mechanistic pathways can be envisaged for this second ring formation. The first involves a single step, intramolecular substitution of the quaternary ammonium ion by the ketone carbonyl oxygen atom (path a). Alternatively, elimination of DABCO from **36** would give *cis*-dienone **37**, which would be expected to undergo a facile 6π-electrocyclization (path b).[21] Interestingly, model studies indicated that the cyclization cascade proceeded significantly faster in substrate **32**, which bears an unprotected 1,2-diol, as opposed to one in which the diol group was protected as the corresponding acetonide. This disparity may be due to activation of the enone to 1,4-addition by intramolecular hydrogen bonding.

The growing family of bisanthraquinone natural products includes a number of dimeric structures, such as rugulosin (**47**, Scheme 9), in which the monomeric anthraquinone units are united by between one and four single bonds to form cagelike skeletons. Following the biosynthetic proposals and prelimi-

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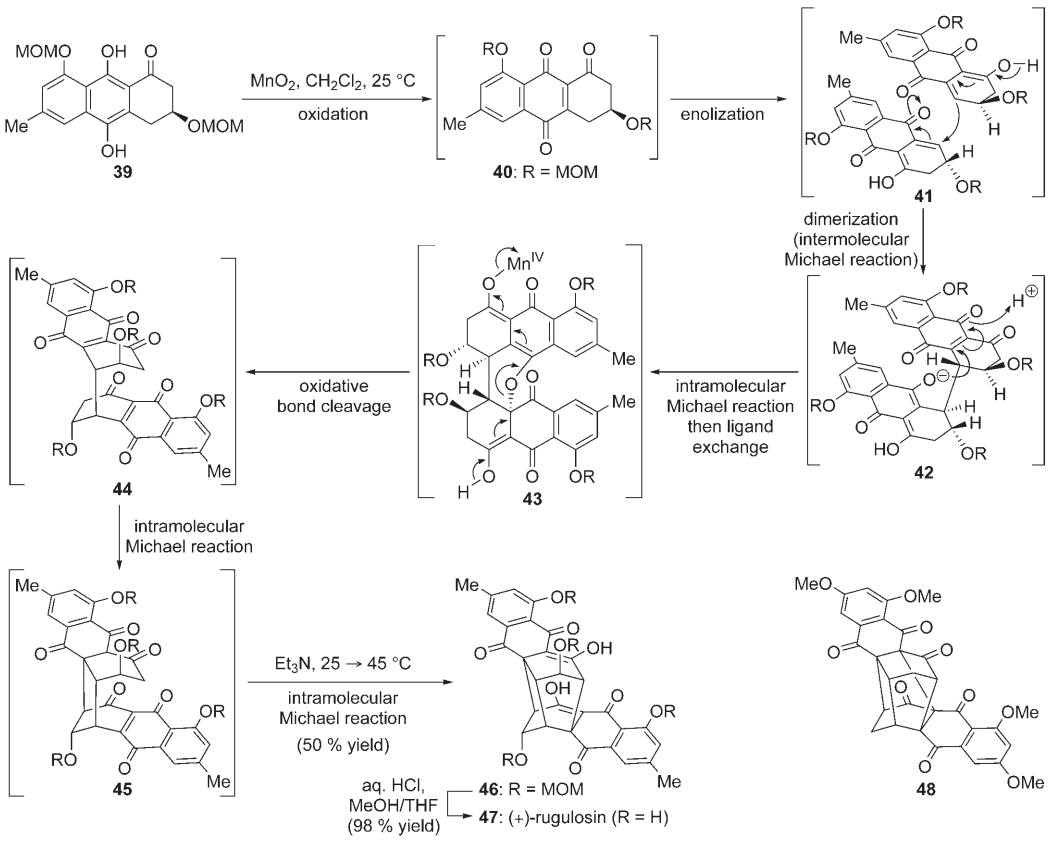

Scheme 9. The total synthesis of (+)-rugulosin (**47**) through an oxidative coupling/Michael reaction cascade (Nicolaou et al., 2005).[26]

nary experimental results of Shibata and co-workers,[23] the groups of Nicolaou[24] and Snider[25] independently developed biomimetic approaches to this class of natural products by employing cascade sequences to prepare model systems and analogues. A major obstacle to the preparation of the natural compounds is the presence of β-hydroxy or alkoxy ketone groups in both the monomeric tricyclic units (such as **39**) and the dimeric intermediates, as these motifs are very prone to elimination and subsequent aromatization of the resulting cyclohexenone ring. The conditions developed by Nicolaou et al. proved to be mild enough to overcome this hurdle and allowed for the preparation of (+)-rugulosin (**47**) in a highly efficient cascade process.[26] It was found that the complete polycyclic architecture of the target compound, **47**, could be prepared from readily available ketone **39** in a single reaction vessel through a sequence of oxidative, bond-forming and bond-breaking events (Scheme 9). Exposure of monomeric ketone **39** to MnO_2 in CH_2Cl_2 resulted in oxidation to the corresponding anthraquinone, **40**, followed by dimerization to give heptacyclic compound **43**. Although **43** is formally the product of a hetero-Diels–Alder reaction between two molecules of the corresponding enolized species **41** of anthraquinone **40**, compound **43** is believed to be formed via sequential inter- and intramolecular Michael reactions (i.e. **40**→**41**→**42**→**43**), as the use of the bulkier TBS hydroxy-protecting group (R = TBS) allows for the isolation of the first Michael adduct (corresponding to **42**). Oxidative bond cleavage (**43**→**44**) and Michael reaction steps then led to the formation of doubly bridged structure **45**. Addition of Et_3N to the reaction mixture at this point, followed by gentle warming to 45 °C, not only facilitated the final intramolecular Michael reaction to establish the complete core structure (**45**→**46**) but also hindered further oxidative carbon–carbon bond formation between the enol groups. In earlier model studies,[24] Nicolaou et al. observed a related oxidative bond formation in the absence of Et_3N to form the strained product **48**, which comprises the carbon framework of the related natural product rugulin. With compound **46** in hand, acidic hydrolysis of the hydroxy-protecting groups then completed the total synthesis of (+)-rugulosin (**47**). If so desired, any one of **43**, **44**, or **45** could be isolated at the appropriate stage. In this case, however, the rugulosin structure **46** was the desired endpoint, and it transpired that it was, in fact, more efficient to conduct the whole seven-step sequence (**39**→**46**) in one pot rather than to adopt a stepwise approach to bond construction.

The facile dimerization of the alkaloid avrainvillamide (**49**) has been exploited by the groups of Myers and Baran in their total syntheses of stephacidin B (**51**, Scheme 10).[27] Both groups observed that **49** dimerized upon treatment with triethylamine at room temperature. The interconversion of **49** and **51** was also observed during preparative TLC or upon concentration or dissolution. A plausible mechanism for this dimerization involves the nucleophilic attack by the amide nitrogen atom of one molecule of **49** onto the α,β-unsaturated nitrone group of another to give **50**, with conjugate addition of the resulting hydroxyenamine onto the other α,β-unsaturated nitrone then forming the second bond.[27a,28] An alternative

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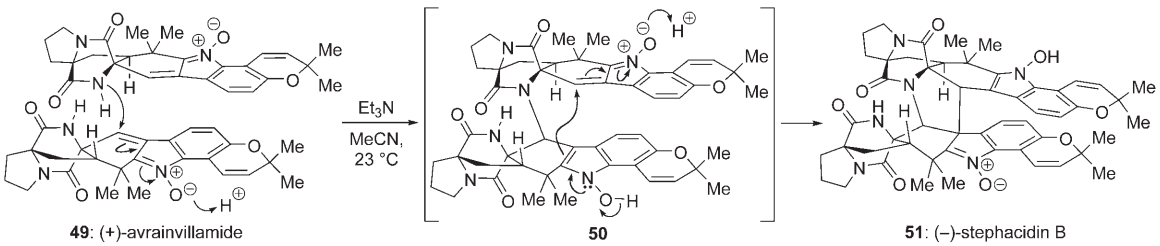
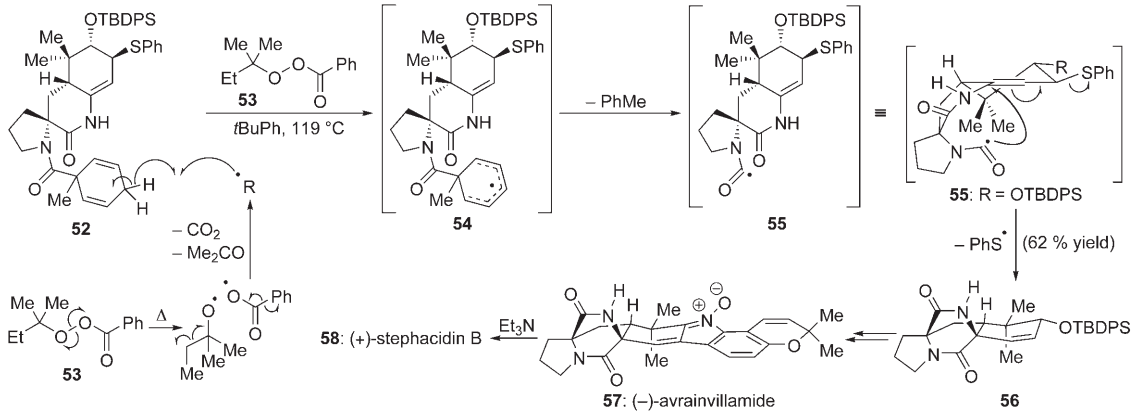


Scheme 10. Dimerization of (+)-avrainvillamide (**49**) to give (−)-stephacidin B (**51**) through a double conjugate addition (Herzon and Myers, 2005; Baran et al., 2005).[27]

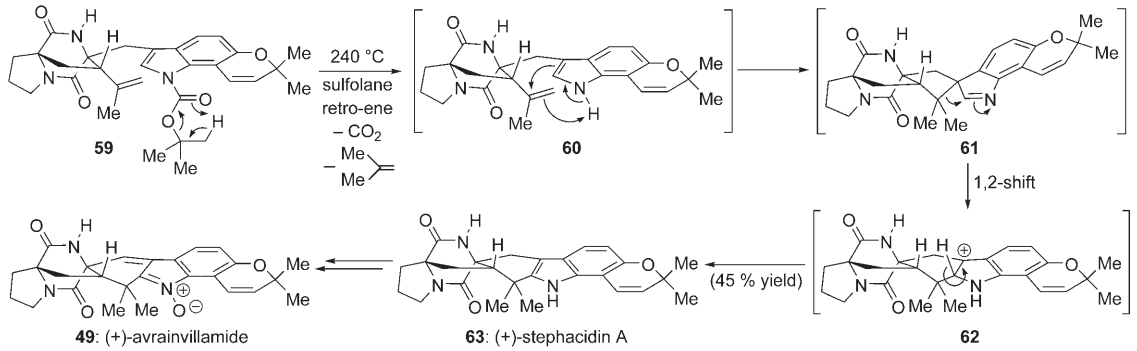
mechanism in which the two bonds are formed in the reverse order has also been proposed,[29] however, this seems less likely in light of the observations by Myers and Herzon regarding the electrophilicity of the α,β-unsaturated nitrone functionality.[30]

The groups of Myers and Baran both also employed cascade reactions in their respective routes to avrainvillamide (Scheme 11 and Scheme 12). The synthesis by Herzon and Myers (Scheme 11),[27a] which led to the unnatural enantiomers (−)-avrainvillamide (**57**) and (+)-stephacidin B (**58**), featured a radical cyclization cascade approach to the diazabicyclooctane ring system. Acyl radical **55** was generated from cyclohexadienyl carboxamide **52** by employing a method developed by Walton and co-workers.[31] Heating of a mixture of amide **52** and peroxide-based initiator **53** resulted in radical generation followed by hydrogen-atom abstraction from the bis-allylic methylene site in **52** to generate cyclohexadienyl radical **54**. The latter species fragments through the enthalpically and entropically favored loss of a molecule of toluene to give acyl radical **55**; 6-*exo*-trig cyclization and expulsion of a phenylsulfinyl radical then furnished the desired tetracyclic product **56** in good overall yield (62%). Fusion of the remaining three rings of the avrainvillamide structure onto compound **56**, over the course of five more steps, then completed the synthesis of the monomeric unit **57**.[32]

The synthesis of (+)-avrainvillamide (**49**) by Baran et al. involved a deprotection–cyclization cascade initiated by heating of **59** at 240 °C (Scheme 12).[27b,33] The first step is the loss of the Boc protecting group from the indole nitrogen atom, which occurs by a retro-ene mechanism under thermal



Scheme 11. Acyl radical generation and cyclization in the total synthesis of (−)-avrainvillamide (**57**) and (+)-stephacidin B (**58**; Herzon and Myers, 2005).[27a]



Scheme 12. The total synthesis of (+)-stephacidin A (**63**) and (+)-avrainvillamide (**49**) by a thermal cascade (Baran et al., 2005).[27b]

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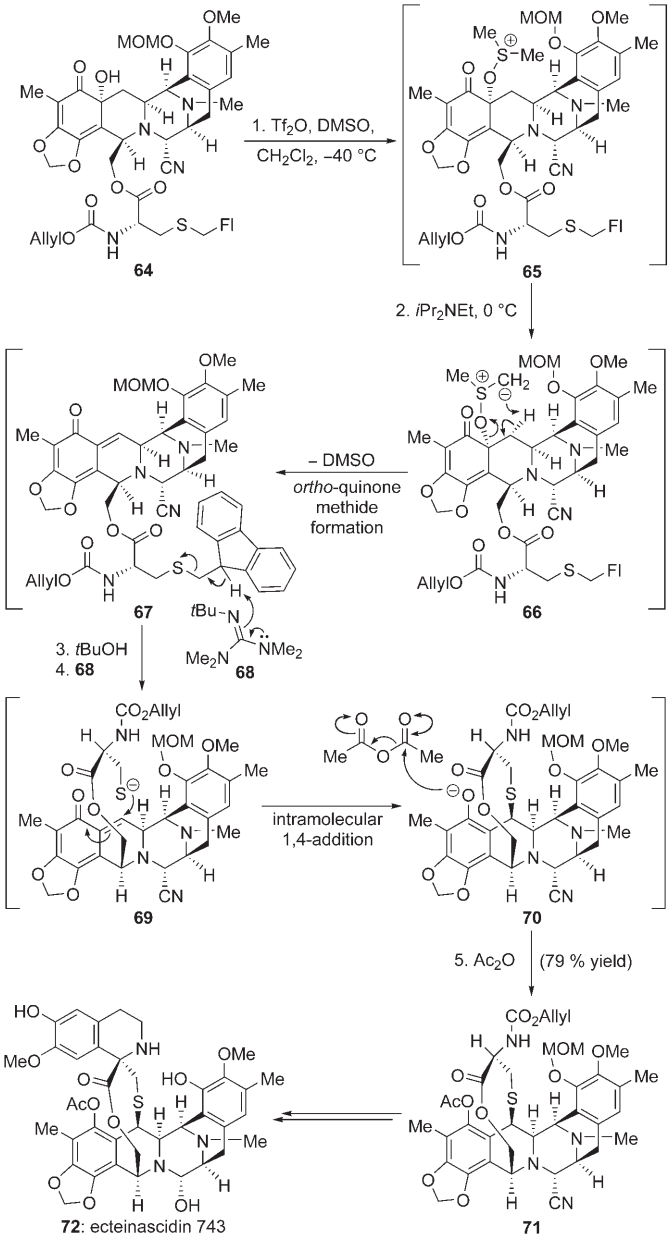
conditions with the extrusion of isobutene and carbon dioxide to afford **60**. At the elevated temperature of the reaction, a formal ene reaction between the indole ring and the isopropenyl group of **60** then ensues, yielding spirocyclic imine **61** as a fleeting intermediate, which then undergoes a selective 1,2-shift of the more highly substituted alkyl group to give (+)-stephacidin A (**63**). This material was converted into the natural enantiomers of avrainvillamide (**49**) and stephacidin B (**51**), thus establishing their absolute configurations as those shown in Scheme 10.[34]

Ecteinascidin 743 (**72**, Scheme 13) is a marine-derived natural product isolated from the Caribbean tunicate *Ecteinascidia turbinata*.[35,36] It is a potent antitumor agent and has entered clinical trials for the treatment of a number of different types of human cancer.[37] Inspired by its promising biological activity, scarcity, and intriguing molecular structure, the Corey group initiated investigations that culminated in the efficient total synthesis of ecteinascidin 743 (**72**).[38] A prominent feature of the route was the ingenious method devised for the installation of the unusual bridging 10-membered sulfur-containing ring, as shown in Scheme 13. Advanced hexacyclic intermediate **64** was prepared from two amino acid derivatives through a series of iminium ion cyclizations. This set the stage for the introduction of the bridging sulfide through the 1,4-addition of a thiolate anion to an intermediate *ortho*-quinone methide (**67**).[39] This highly reactive species was generated by treatment of hydroxy ketone **64** with a Swern-type reagent to generate the *O*-dimethylsulfonium ion intermediate **65**. Triflic anhydride was used in place of the more conventional oxalyl chloride in order to avoid any interference by chloride ions during subsequent steps. The addition of an amine base (iPr$_2$NEt) led to the cyclo-elimination of DMSO, via ylide species **66**, to afford *ortho*-quinone methide **67**. Following the addition of tBuOH to quench any excess Swern reagent, a guanidine base **68** was used to release a thiolate anion from the fluorenyl sulfide moiety. The liberated thiolate anion **69** was then trapped by the *ortho*-quinone methide to give the 10-membered sulfide ring. This intramolecular conjugate addition was rendered irreversible by the addition of acetic anhydride, to trap the resulting phenolate **70** as the corresponding acetate **71**. This amazing one-pot cascade proceeded in excellent overall yield (79%) and, significantly, without the need for isolation of any of the sensitive intermediates along the pathway. A similar cascade sequence has since been employed in an efficient semisynthesis of ecteinascidin 743 (**72**), thereby securing the supply of larger quantities of this previously scarce compound.[40]



Scheme 13. *ortho*-Quinone methide generation and trapping in the total synthesis of ecteinascidin 743 (**72**; Corey et al., 1996).[38]

Multicomponent reactions offer means to construct complex and structurally diverse compounds rapidly from relatively simple building blocks.[41,42] The Ugi reaction is a powerful four-component coupling reaction and one of several such processes that employ an isocyanide as one of the reactants.[43] Although popular in the field of combinatorial synthesis,[44] applications of Ugi reactions in total synthesis are comparatively rare.[45] One of the most advanced applications of an Ugi reaction to date can be found in the total synthesis of ecteinascidin 743 (**72**) by Fukuyama and coworkers, who employed this four-component process to couple two major fragments, whilst simultaneously incorporating the remaining three carbon atoms needed for the hexacyclic core structure of the target.[46] Amine **73**, carboxylic acid **74**, isocyanide **75**, and acetaldehyde (**76**) were heated in methanol to give amide **80** (Scheme 14). Reversible acid-catalyzed iminium ion formation (**73** + **76** → **77**) is followed by nucleophilic attack of the isocyanide component and capture of the resulting nitrilium ion **78** by the carboxylate anion to generate neutral intermediate **79**. This species then undergoes a rapid O → N acyl transfer to afford **80** as the observed product. Amide **80** was formed in high yield (90%), albeit as a mixture of epimers at the newly generated C4 stereocenter. Indeed, satisfactory control of the stereochemistry of the newly formed stereocenter in the Ugi reaction remains an

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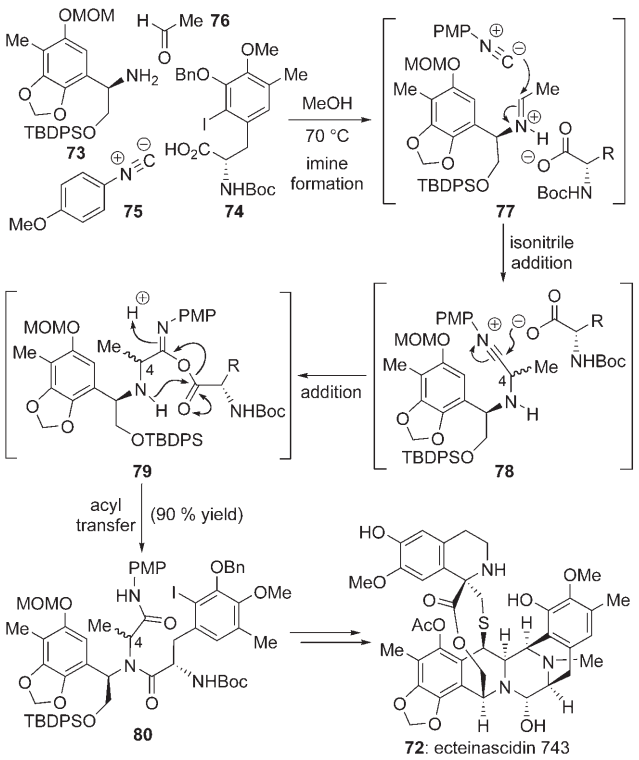
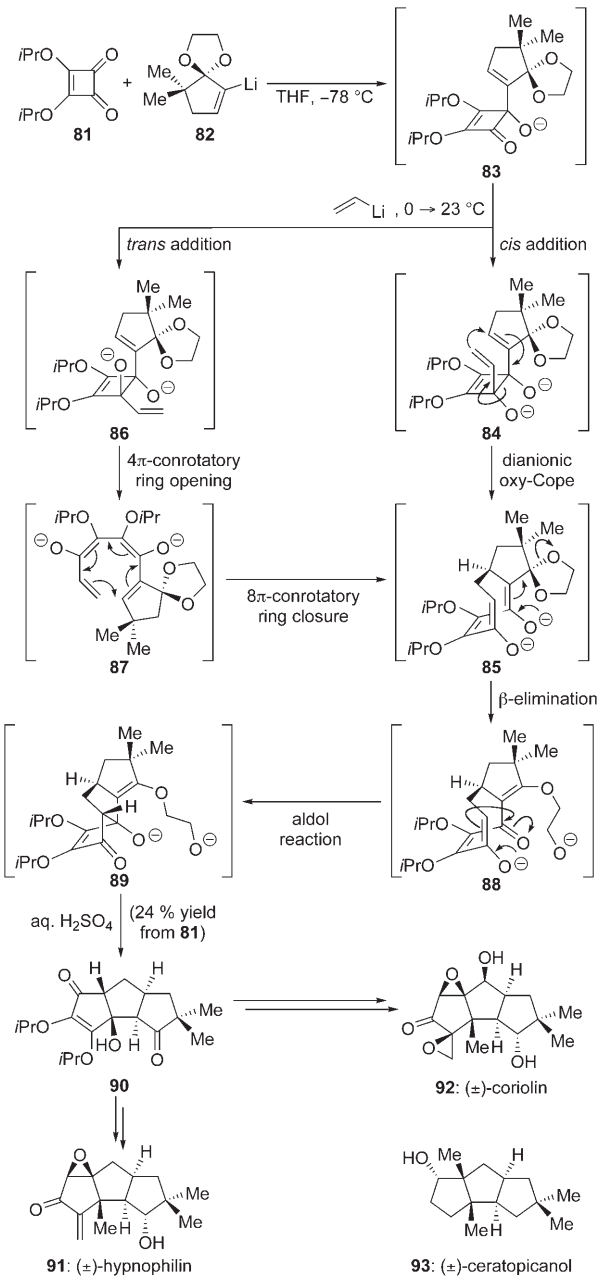


Scheme 14. The Ugi four-component coupling reaction in the total synthesis of ecteinascidin 743 (**72**; Fukuyama et al., 2002).[46]

unresolved problem in general. In the context of this synthesis, however, this lack of stereocontrol was immaterial, as the planned route required the subsequent destruction of this stereocenter followed by its later reinstallation with the required configuration.[47]

Triquinane natural products, such as hypnophilin (**91**), coriolin (**92**), and ceratopicanol (**93**, Scheme 15) have been, and continue to be, popular targets for total synthesis endeavors, inspiring the development of a number of cascade processes.[48] The Paquette group has exploited the squarate ester cascade[49] for the total syntheses of all three of the aforementioned targets, as shown in Scheme 15.[50] This anionic cascade is triggered by the addition of two vinyllithium species to the squarate ester **81**, and can proceed by two pathways, depending on whether the second nucleophile adds in a *cis* or *trans* fashion relative to the first. With a *cis* mode of addition, favored by chelation between the incoming nucleophile and the ketal oxygen atoms, the 1,5-diene-dialkoxide **84** is formed. This undergoes a facile dianionic oxy-Cope rearrangement, via a boatlike transition state, to form cyclooctatriene species **85**. Alternatively, a *trans* mode of addition, favored by steric considerations, leads to dialkoxide **86**, which, on stereoelectronic grounds, cannot undergo a [3,3] sigmatropic reaction. Instead, a charge-driven 4π-conrotatory electrocyclic ring opening occurs, with electrostatic repulsion favoring rotation of the two alkoxide oxygen centers away from each other. The resulting octatetraene **87** then converges on cyclooctatriene intermediate **85** through an 8π-conrotatory ring closure. In cases where both



Scheme 15. The squarate ester cascade as used in the total synthesis of (±)-hypnophilin (**91**) and (±)-coriolin (**92**), and the structure of (±)-ceratopicanol (**93**; Paquette and Geng, 2002).[50]

vinyllithium species are substituted on the distal end of the olefin, it is possible to distinguish between these mechanisms and, to some extent, control which pathway is followed.[49] In this case, it is likely that both modes are operative, each giving the same final product. From dianion intermediate **85**, the cascade continues with the β-elimination of one of the ketal oxygen groups by the adjacent enolate, leading to regioselective formation of ketone **88**. An intramolecular aldol reaction between this ketone and the remaining enolate, followed by hydrolysis, then gave tricyclic product **90**, which could be converted into hypnophilin (**91**) or coriolin (**92**) over

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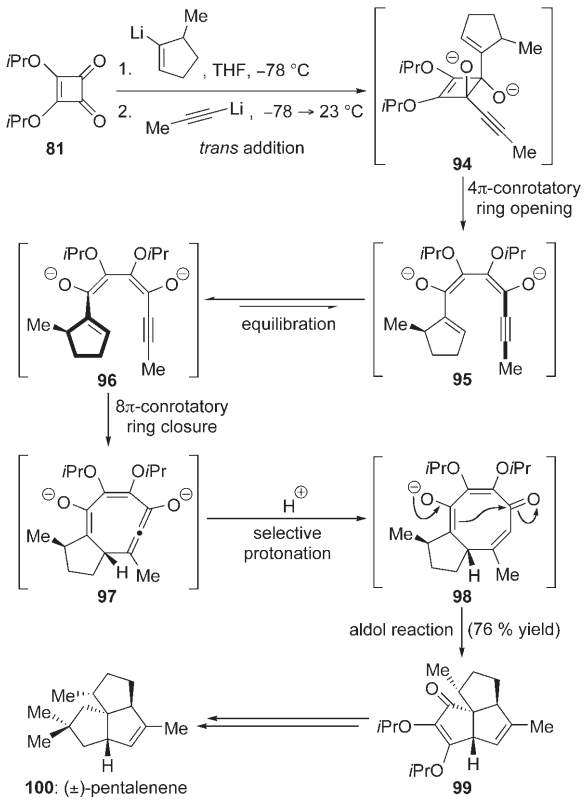
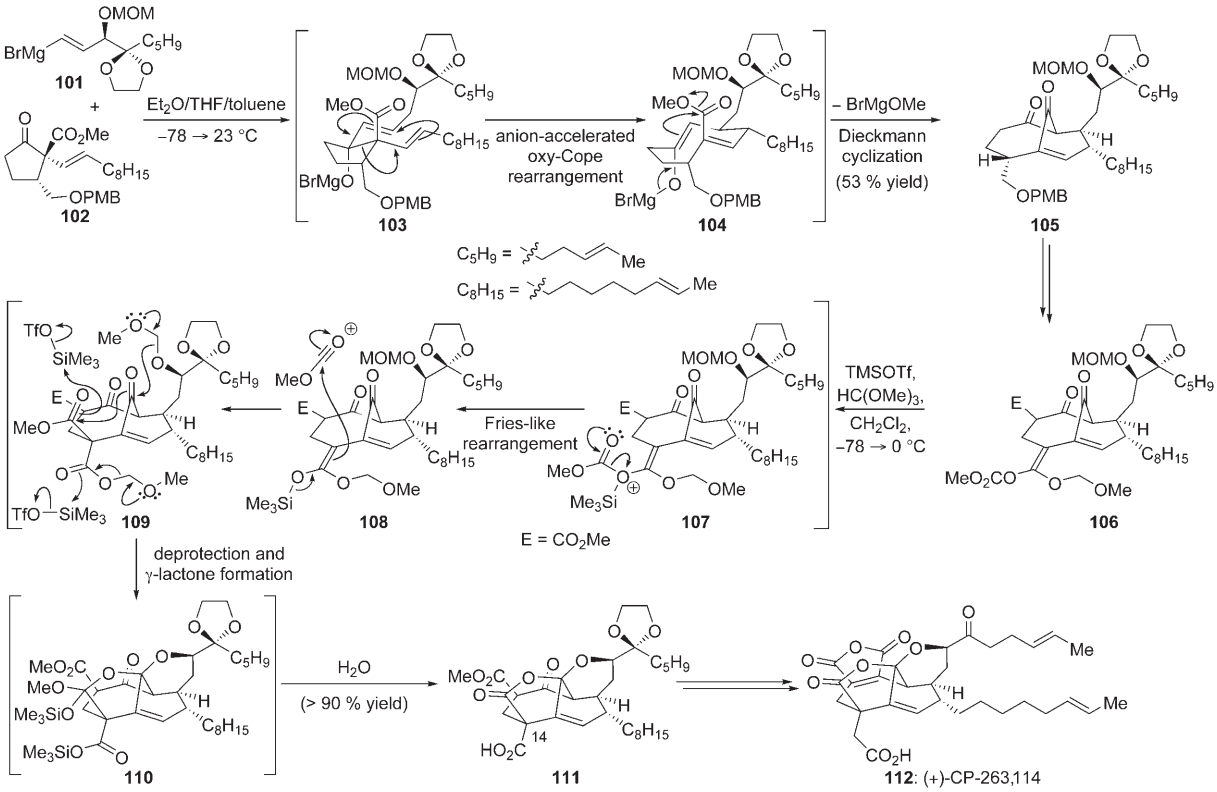
several more steps. A similar cascade led to the total synthesis of ceratopicanol (**93**).[50b]

Paquette and Geng employed a related approach for the preparation of the angular triquinane pentalenene (**100**, Scheme 16).[51] In this cascade, the second nucleophile is an acetylide anion and the *trans* addition route dominates, generating the highly strained 1,2,4,6-cyclooctatetraene intermediate **97**. As expected, this species was formed with high stereoselectivity due to the more facile 8π-conrotatory electrocyclic ring closure of conformer **96**, in which the cyclopentane methyl substituent is on the exterior of the helical pitch of the dienolate. In this case, there is no leaving group available to differentiate the two enolate groups, but relief of strain favors the selective protonation of the allenoate to give ketone **98**. A transannular aldol reaction then gives the product **99**, which was elaborated to give the target natural product **100**.[52]

In their approach to (+)-CP-263,114 (phomoidride B, **112**), Shair and co-workers also employed an organometallic addition/Cope rearrangement strategy.[53a] Their variant involved the addition of Grignard reagent **101** to β-keto ester **102** (Scheme 17). The addition proceeds with complete selectivity for the desired diastereoisomer **103** under chelation control. 1,5-Diene **103** then undergoes a facile oxy-Cope rearrangement upon warming to room temperature to give the cyclononene enolate **104**. Interestingly, the use of organolithium or organocerium reagents in model studies of this addition step failed to give the desired products.[53b] The final step in this cascade is the transannular Dieckmann cyclization of **104** to form ketone **105** and generate the characteristic



Scheme 16. The total synthesis of (±)-pentalenene (**100**) using the squarate ester cascade (Paquette and Geng, 2002).[51]



Scheme 17. Anionic oxy-Cope/Dieckmann cascade and Fries-like rearrangement in the total synthesis of (+)-CP-263,114 (**112**; Shair et al., 2000).[53]

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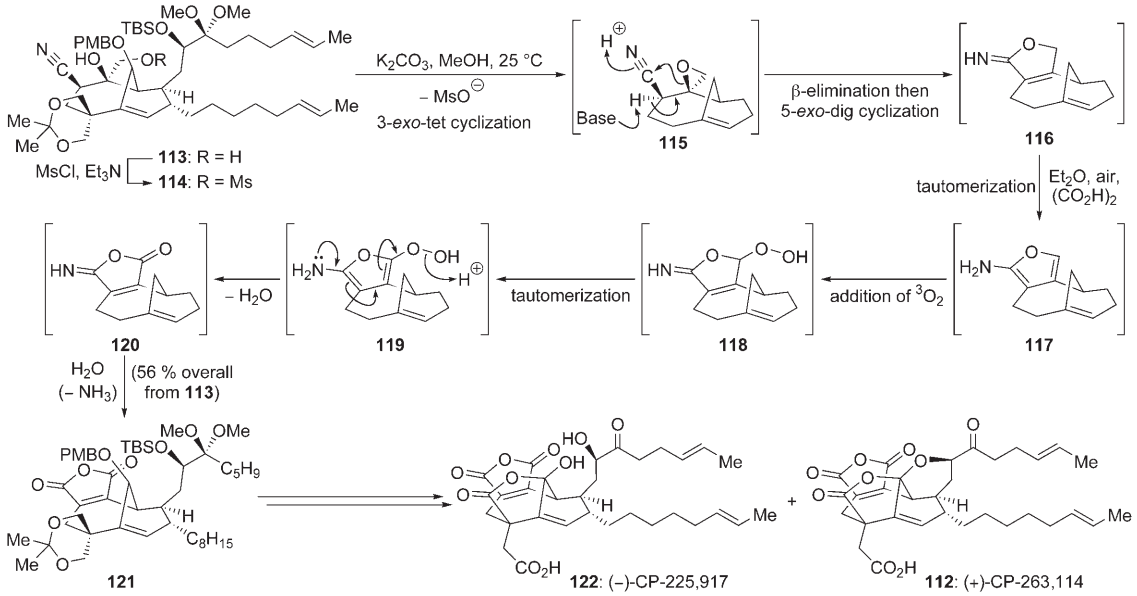
strained bicyclic core of the target compound. Following the advancement of ketone **105** to β-ketoester **106**, a novel electrophilic cascade was effected by treatment of this material with TMSOTf (2.0 equiv) and $HC(OMe)_3$ (2.0 equiv) in CH_2Cl_2 to give lactone **111** in over 90% yield. A plausible mechanism for this transformation is shown in Scheme 17 and commences with the initial ionization of the enol carbonate with TMSOTf to provide silylketeneacetal **108**, a species poised for reaction with the liberated acylium ion, leading to the assembly of **109**. Lewis acid mediated deprotection of the MOM groups and hydrolytic workup then gave the product **111**. In addition to providing an interesting solution to the problem of generating the γ-lactone cage structure, the concomitant unveiling of the carboxylic acid group at C14 during the conversion of **106** into **111** provided a convenient handle for the installation of the one remaining carbon atom required to reach the target structure **112** through a modified Arndt–Eistert protocol. Subsequent studies by Shair and co-workers of this addition/Cope rearrangement strategy using related systems revealed the potential for retro-aldol/aldol equilibration of the organometallic addition product (corresponding to magnesium alkoxide **103**), with implications for the dynamic kinetic resolution of substrates with chiral all-carbon quaternary stereocenters.[54]

Nicolaou et al. also employed a cascade reaction in their total synthesis of CP-225,917 (phomoidride A, **122**) and CP-263,114 (phomoidride B, **112**).[55] This cascade was used to introduce the challenging maleic anhydride moiety from nitrile precursor **114**. In preparation for the cascade process, **113** was selectively mesylated on the primary alcohol group. Mesylate **114** was then exposed to mildly basic conditions, which initiated the presumed chain of events delineated in Scheme 18. Base-induced epoxide formation (**114**→**115**) is followed by fragmentation to give an intermediate alkoxide, which immediately closes onto the proximal nitrile functionality to give iminobutenolide **116**. Subsequent tautomerization, oxidation, and hydrolysis steps afforded maleic anhydride **121** via intermediates **117**–**120**. Several further functional group manipulations then completed the syntheses of both CP-225917 (**122**) and CP-263114 (**112**).[56]

The dithiane lynchpin strategy,[57] developed by the Smith group based on precedent noted by Tietze et al.,[58] makes use of the Brook rearrangement[59] to regenerate a lithiated dithiane, following the opening of an epoxide by a lithiated silyl dithiane nucleophile. The new lithiated dithiane can then capture a second, different electrophile, provided that the timing of migration of the silyl group can be controlled. Smith and Kim recently extended this strategy to the synthesis of the poison frog alkaloids (−)-indolizidine 223AB and (−)-205B (**129**, Scheme 19) by using an aziridine electrophile in the second step.[60] Thus, lithiation of silyl dithiane **123** with *t*BuLi in diethyl ether and addition of epoxide **124** led to lithium alkoxide **125** (Scheme 19). Aziridine **126** was then added in a mixture of THF and DME, the polar solvent triggering a 1,4-Brook rearrangement to generate lithiated dithiane **127**. Nucleophilic opening of the aziridine then gave the sulfonamide product **128**, which was subsequently converted into alkaloid (−)-205B (**129**).[61]

3. Electrophilic Cascades

The first synthesis described in this section could equally have been included in the previous section, as it includes both nucleophilic and electrophilic cascades. The approach of Corey and co-workers to the dimeric triterpene (+)-α-onocerin (**137**, Scheme 20) involved a sequential addition/dimerization, four-component coupling sequence to assemble a precursor for a two-directional electrophilic tetracyclization.[62] Addition of vinyllithium to acyl silane **130** gave



Scheme 18. Construction of the maleic anhydride unit during the total synthesis of the CP molecules (Nicolaou et al., 1999).[55] Substituents in intermediates **115**–**120** are omitted for clarity.

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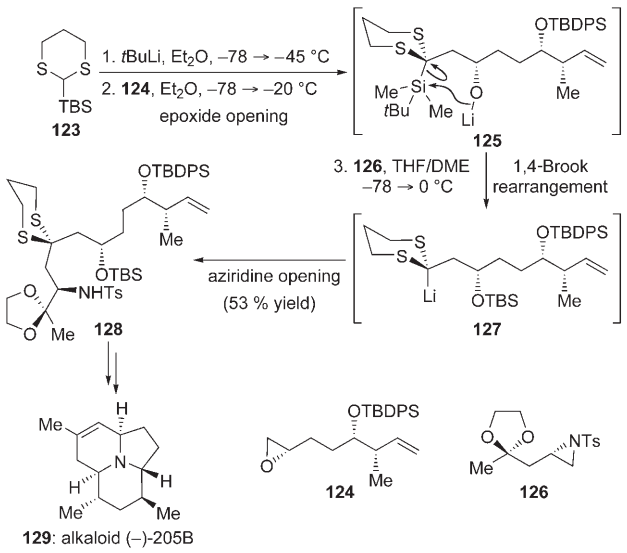
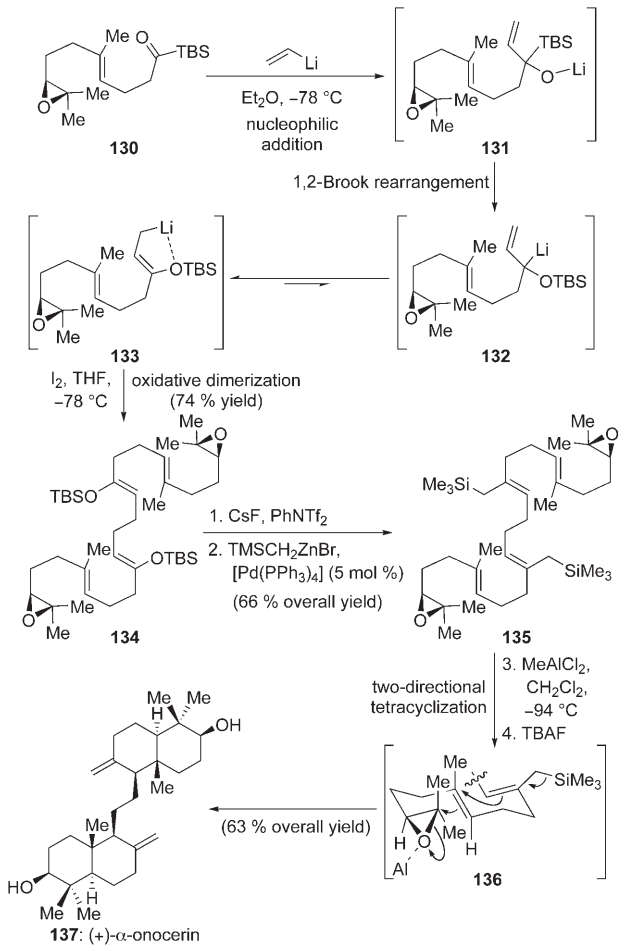


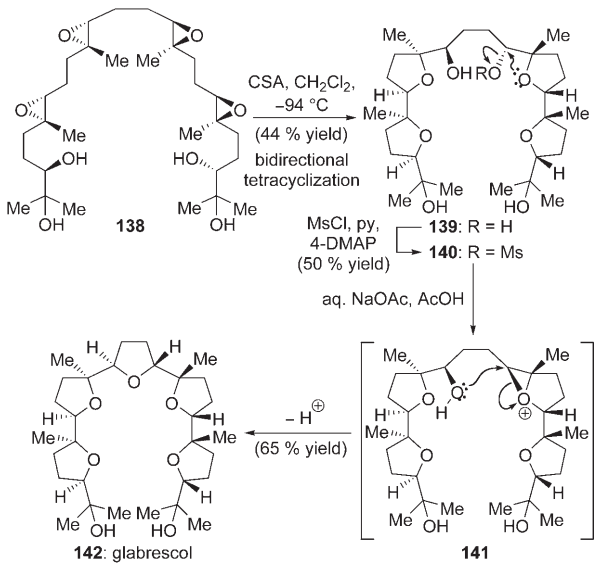
Scheme 19. Dithiane linchpin coupling through a 1,4-Brook rearrangement, as applied to the total synthesis of poison-frog alkaloid (–)-205B (**129**; Smith and Kim, 2005).[60]



Scheme 20. Application of the 1,2-Brook rearrangement and a two-directional epoxy-olefin cyclization in the total synthesis of (+)-α-onocerin (**137**; Corey et al., 2002).[62]

chelated *Z*-allylic lithium intermediate **133** through the 1,2-Brook rearrangement of alkoxide **131** followed by allylic rearrangement (**132**→**133**).[63] Addition of iodine gave the dimer **134** in excellent yield (74%). Conversion of the silyl enol ether groups into the corresponding enol triflates was accomplished in a single operation through the action of cesium fluoride and phenyl ditriflimide, and was followed by Negishi coupling to give dimeric allylsilane **135** in 66% yield from **134**. Exposure of **135** to $MeAlCl_2$ (2.5 equiv) in CH_2Cl_2 at −94°C followed by treatment with TBAF (to cleave any TMS ethers of **137** which may have been present) then gave (+)-α-onocerin (**137**, 63% yield from **135**). In addition to the desired tetracyclic product, which arose from the chair–chair transition-state arrangement **136**, a minor non-C_2-symmetric product (not shown) was also formed in 9% yield, presumably as a result of one cyclization proceeding through a chair–boat transition state. This remarkable synthesis demonstrates the great power of cascade reactions in the rapid construction of complex molecules; indeed, the two cascades described here enabled the formation of four rings, nine carbon–carbon bonds, and six new stereogenic centers in just four steps.[64]

The opening of epoxide rings under (Brønsted or Lewis) acidic catalysis forms the basis of many spectacular cascade processes. Corey and Xiong used a two-directional epoxide-opening cascade in their total synthesis of the C_2-symmetric pentacyclic tetrahydrofuran natural product glabrescol (**142**), in an endeavor which also served to determine the true stereochemical identity of the natural material.[65] They had previously prepared several *meso* isomers, including that originally proposed for the natural product, and found that the original structure was incorrect.[66] All the isomers were prepared by using cascade cyclizations of polyepoxides; the cascade used to prepare natural glabrescol is illustrated in Scheme 21. The tetra-epoxide precursor **138** was prepared by oxidative dimerization and epoxidation using the protocol of Shi and co-workers.[67] Treatment of **138** with camphorsulfonic acid gave the desired tetracyclic product **139** in good overall



Scheme 21. Poly-epoxide cyclizations in the total synthesis of glabrescol (**142**; Xiong and Corey, 2000).[65]

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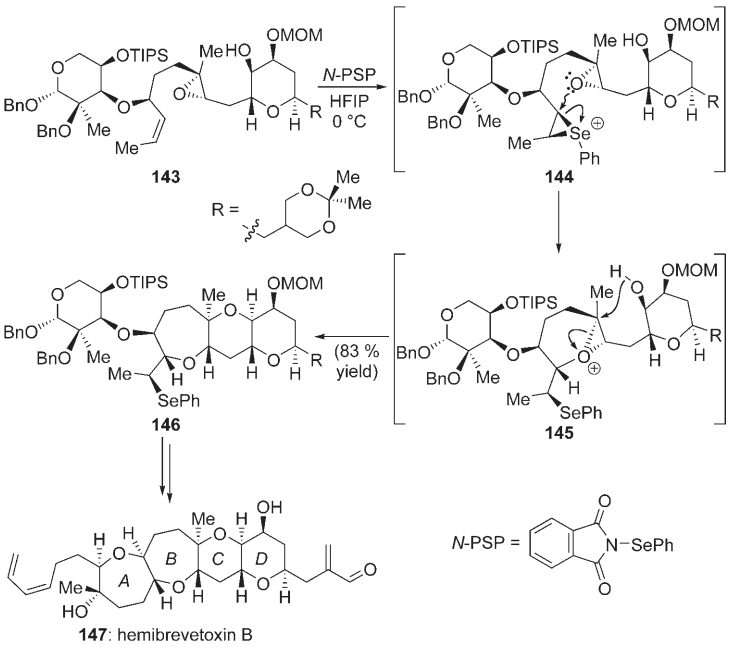
yield. At each site, opening of the corresponding epoxide ring occurred at the more substituted terminus, a corollary of the stereoelectronic preference for five-membered-ring formation, and with inversion of configuration. Selective monomesylation of **139**, followed by treatment with acetic acid gave the desired C_2-symmetric product **142** by the double-inversion mechanism shown (**140**→**141**→**142**). The use of acetic acid, a good ionizing solvent, combined with the steric shielding around the secondary mesylate group, discourages the direct S_N2-type displacement by the hydroxy group (which would form the undesired product stereochemistry as the result of a single inversion), and enables neighboring-group participation from the vicinal ether oxygen to form epoxonium ion intermediate **141**. This species is then opened in a kinetically favored 5-*exo* mode by the pendant hydroxy group. Comparison of synthetic **142** and natural glabrescol revealed the two materials to be identical.[68]

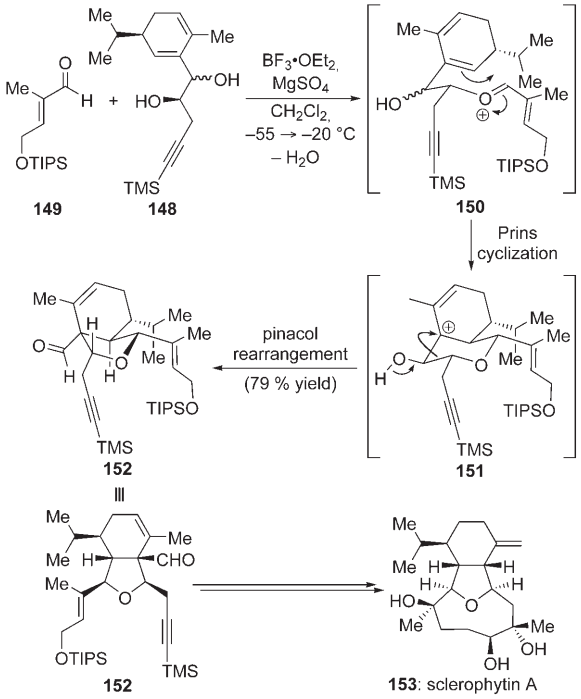
A biomimetic electrophilic cascade[69] was employed by Holton and co-workers in their total synthesis of hemibrevetoxin B (**147**, Scheme 22).[70] Their plan of attack called for the formation of the B and C rings of the target structure through the double cyclization of a suitable hydroxy epoxide precursor.[71] They eventually settled on epoxy alkene **143** as a suitable substrate, with the alkene serving as a trigger for the cascade upon activation by an electrophile. In the event, treatment of **143** with *N*-phenylselenophthalimide led to sequential ring closure to give the advanced intermediate **146** in 83% yield and as a single stereoisomer. This cyclization is thought to proceed through attack of the epoxide oxygen atom on the *epi*-selenonium ion of intermediate **144** to generate a bicyclic epoxonium ion **145**. Subsequent attack by the hydroxy group then proceeds selectively to give the *trans*-fused oxepane product **146**. The highly polar but non-



Scheme 22. Total synthesis of hemibrevetoxin B (**147**) using an epoxy-olefin cyclization (Holton et al., 2003).[70]

nucleophilic solvent 1,1,1,3,3,3-hexafluoro-2-propanol was chosen for its ability to stabilize such charged species without interfering in the progress of the reaction. Fusion of the oxepane A ring onto intermediate **146** followed by the appropriate side-chain manipulations then completed the total synthesis.[72]

The pinacol-terminated Prins cyclization was developed by the group of Overman as an effective technology for the synthesis of natural products.[73] One such application is found in their general approach to the cladiellin family of diterpene metabolites, as represented by the synthesis of the revised structure of sclerophytin A (**153**, Scheme 23.[74] The sequence



Scheme 23. The Prins-pinacol reaction in the total synthesis of sclerophytin A (**153**; Overman et al., 2001).[74]

begins with the Lewis acid catalyzed condensation of diol **148** with aldehyde **149** to form oxocarbenium ion **150**. It is not necessary to specifically control which alcohol group engages the aldehyde in this step, as only **150** can participate in the Prins cyclization reaction and all the possible condensation products are in equilibrium. The Prins cyclization of **150** proceeds stereoselectively, with the approach of the oxocarbenium ion dictated by the bulky isopropyl substituent. The cyclization generates stabilized allylic carbocation **151**, which undergoes a pinacol rearrangement to give the bicyclic product **152** in 79% isolated yield. Tetrahydrofuran **152** proved to be a versatile platform for the synthesis of various members of this class of natural products, including sclerophytin A (**153**), its originally proposed structure, deacetoxyalcyonin acetate, and cladiell-11-ene-3,6,7-triol.[74–76]

Oxocarbenium ion species are commonly employed in total synthesis as intermediates in the preparation of acetal and ketal protecting groups, and also in the formation of spiroketal structural units.[77,78] The construction of such

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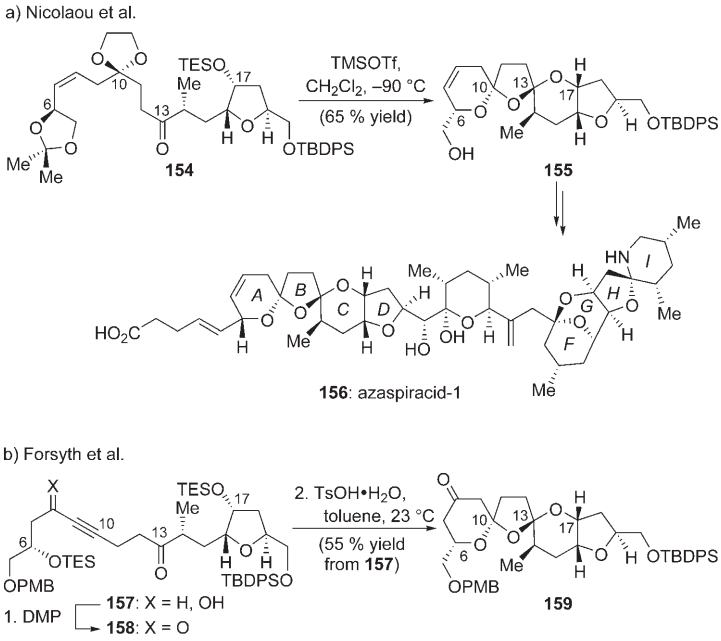
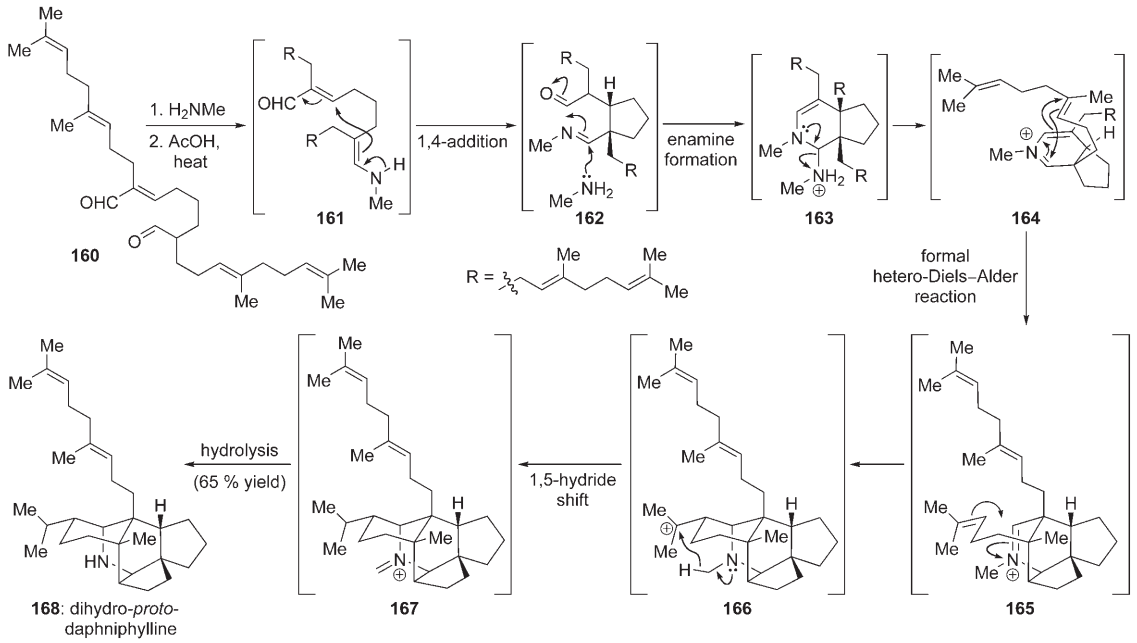
motifs using cascade processes is exemplified by two syntheses of the trioxadispiroketal ABCD-ring fragment of the shellfish toxin azaspiracid-1 (**156**, Scheme 24). In their second-generation synthesis of the azaspiracids, Nicolaou et al. prepared bis-spiroketal **155** from precursor **154** in a one-step deprotection–cyclization cascade sequence.[79] Treatment of **154** with excess TMSOTf at low temperature effected removal of the TES ether, acetonide, and dioxolane protecting groups, and the formation of three rings, with the thermodynamically favored anomeric configuration at the C10 and C13 positions, to give **155** in 65% yield.[80] In a conceptually different approach to the ABCD-ring fragment, Forsyth and co-workers prepared acetylenic ketone **158**, which, upon exposure to $TsOH{\cdot}H_2O$ (1.0 equiv) in toluene at room temperature, underwent cleavage of the two TES protecting groups followed by a double intramolecular conjugate addition.[81] The use of acid catalysis under equilibrating conditions ensured the formation of the desired, thermodynamically favored ketal **159**, which was isolated as a single stereoisomer in 55% yield from alcohol **157**.[81–83]

Heathcock and co-worker's famous one-step synthesis of dihydro-*proto*-daphniphylline (**168**), the proposed biogenetic precursor to the *Daphniphylum* polycyclic alkaloids, is perhaps the most striking example of a cascade involving iminium ion intermediates.[84] The process begins with dihydrosqualene dialdehyde **160** (Scheme 25) and represents the culmination of several years of careful development combined with a chance discovery.[85] Treatment of acyclic di-aldehyde **160** with methylamine and warm acetic acid gave the target compound **168** in 65% yield through a process that formed five new rings and installed eight new stereogenic centers in a completely diastereoselective fashion. The first step in the cascade involves the condensation of methylamine with the most reactive aldehyde group to give secondary enamine **161**. Intramolecular Michael addition of enamine **161** onto the enal group establishes the first carbon–carbon bond and ring of the sequence (**161**→**162**), and is followed by further condensation and cyclization events to form iminium ion **164**. A formal hetero-Diels–Alder reaction then gives tetracyclic



Scheme 24. a) Use of a deprotective polycyclization en route to the total synthesis of azaspiracid-1 (**156**; Nicolaou et al., 2006).[79] b) Construction of the azaspiracid-1 ABCD ring framework through an acid-catalyzed nucleophilic addition cascade (Forsyth et al., 2004).[81]



Scheme 25. Biomimetic synthesis of dihydro-*proto*-daphniphylline (**168**; Heathcock et al., 1992).[84]

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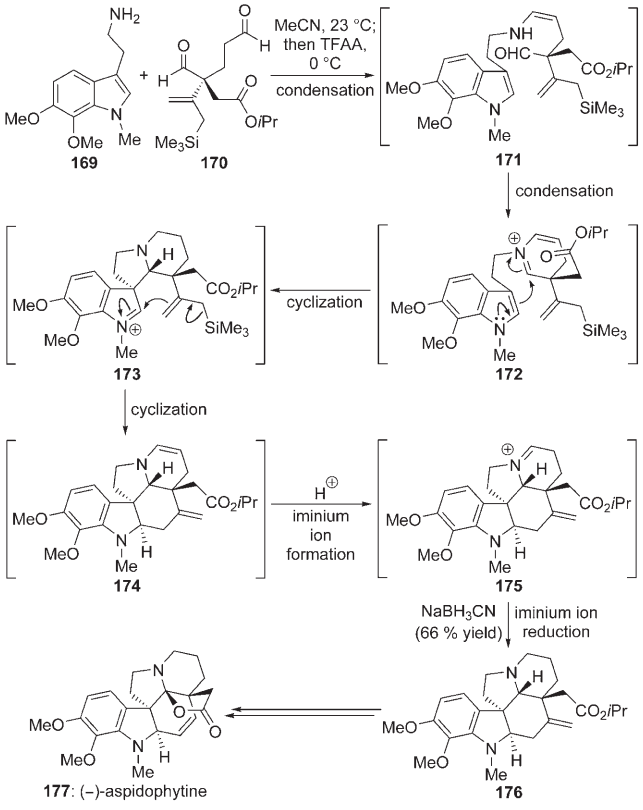
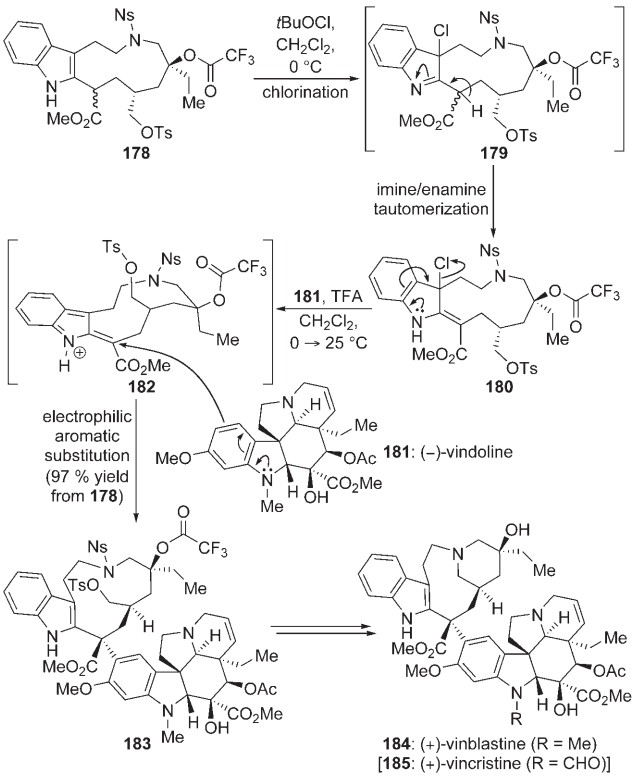
iminium ion **165**, although this step most likely proceeds in a stepwise manner through a Prins cyclization to form the second five-membered ring, followed by ring closure between the resulting enamine and tertiary carbocation species. The final ring is then formed by another Prins cyclization to generate carbocation **166**. A 1,5-hydride shift from the methyl group of the tertiary amine to the carbocation, followed by hydrolysis on workup, completes the synthesis of dihydro-*proto*-daphniphylline (**168**). When ammonia is used in place of methylamine, the dehydro product with an isopropenyl side chain in place of the isopropyl group, is formed in a rather lower yield. Thus, in addition to differentiating what would be one of three similar olefins in the polycyclic product, the use of methylamine also aids the progress of the cascade as the substituted imine and enamine intermediates are more stable.

Another example of the power of iminium ions as intermediates in cascade reactions can be found in the highly efficient and convergent synthesis of aspidophytine (**177**, Scheme 26) by Corey and co-workers. Reductive condensation of tryptamine derivative **169** and chiral di-aldehyde **170** gave pentacyclic amine **176** with the formation of three new rings, three new stereogenic centers, and four new sigma bonds.[86] This transformation proceeds through condensation of primary amine **169** with dialdehyde **170** to give the cyclic iminium ion **172**, presumably via enamine **171**. A Pictet–Spengler cyclization generates the pyrrolidine ring and the new quaternary stereocenter. The stereocontrol obtained in this step is notable and may arise through interaction between the iminium ion carbon atom and the ester carbonyl oxygen atom of **172**, leading to preferential attack by the indole from the opposite face of the molecule. The stereochemistry of the resulting spirocyclic intermediate **173** then governs the facial selectivity in the attack of the allylsilane substituent[87] on the newly formed iminium ion to generate the pentacyclic system **174**. Following completion of this cascade, sodium cyanoborohydride was added to effect reduction of the enamine group to give **176**, which was converted into aspidophytine.[88]



Scheme 26. The total synthesis of (−)-aspidophytine (**177**) through a series of iminium ion cyclizations (Corey et al., 1999).[86]

The total synthesis of (+)-vinblastine (**184**, Scheme 27) by Fukuyama and co-workers makes use of an electrophilic aromatic substitution reaction for the late-stage coupling of the "northern" and "southern" halves of the target (**178** and **181**, respectively), along the lines of the biosynthesis of this clinically important anticancer drug.[89] Treatment of indole **178** with *t*BuOCl in CH_2Cl_2 led to the initial formation of imine **179**, followed by tautomerization to the corresponding chloroindolene species **180**. Exposure of a mixture of chloroindolene **180** and synthetic indole **181** (itself a natural product, (−)-vindoline, which had previously been synthesized by the Fukuyama group)[90] in CH_2Cl_2 to excess TFA led to the formation of the desired adduct **183** as a single regio- and stereoisomer in remarkable yield (97% for the two steps from "northern" indole **178**) by addition of the vindoline aromatic nucleus to the highly reactive electrophilic species **182**.[91] The stereochemical outcome of the coupling was anticipated not only on the basis of precedent provided by model studies from Schill and co-workers,[92] but also by molecular modeling calculations, which suggested that the 11-membered ring of intermediate **182** would preferentially



Scheme 27. The total synthesis of (+)-vinblastine (**184**) through electrophilic aromatic substitution (Fukuyama et al., 2002).[89]

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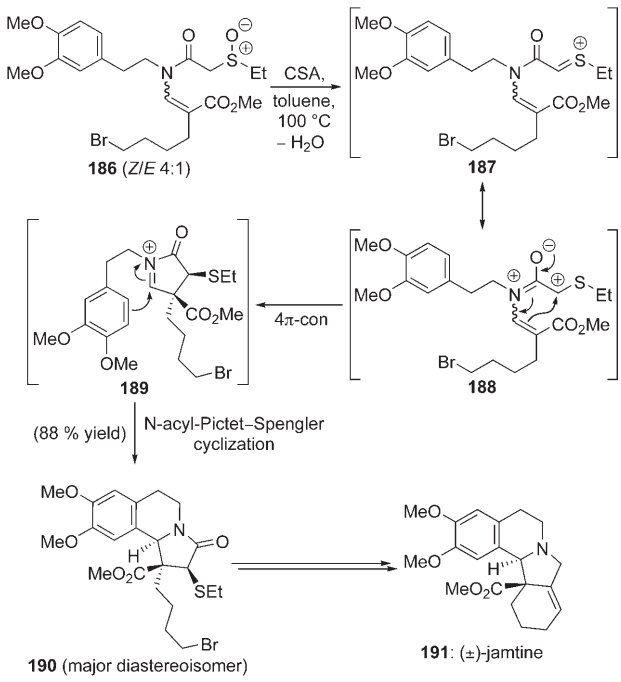
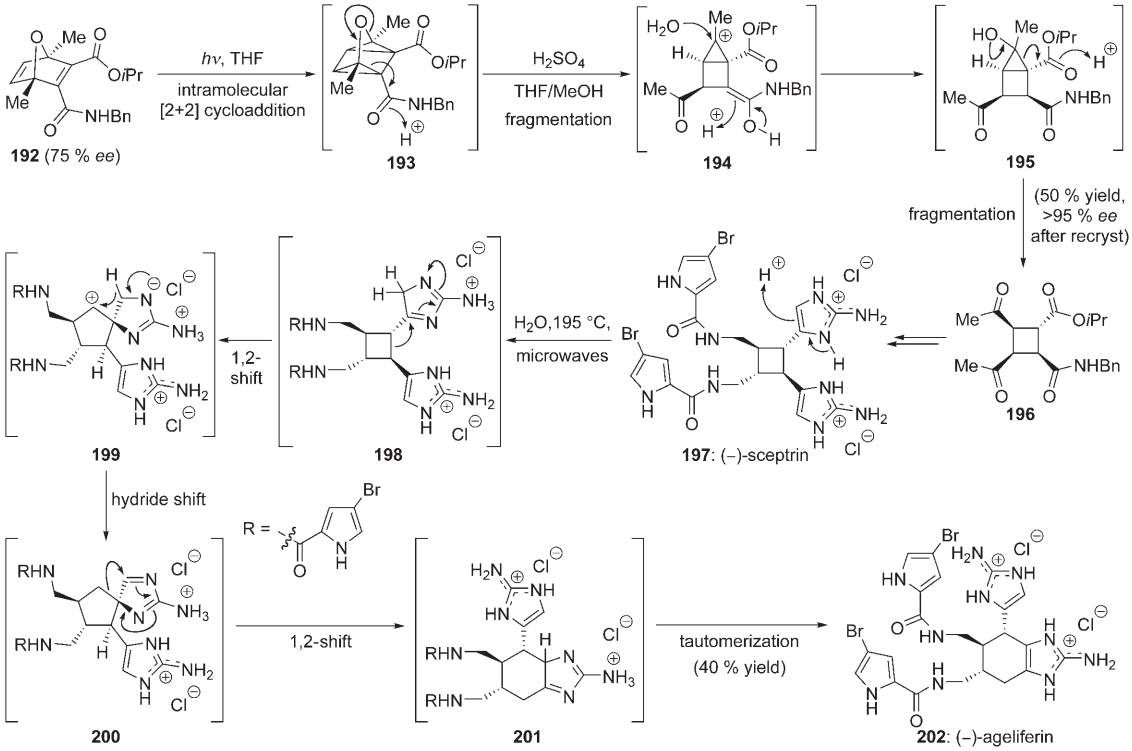
adopt the conformation shown. Attack of (−)-vindoline (**181**) from the convex face of this ring would then lead to the formation of coupled product **183** with the correct stereochemistry at the C16 position as required for the target natural product **184**.[93] Fukuyama and co-workers have also applied this strategy to the synthesis of the related alkaloid (+)-vincristine (**185**).[94]

The Padwa group has employed a Pummerer/Pictet–Spengler cascade reaction,[95–97] involving both thionium and iminium ion intermediates, in the preparation of the alkaloid jamtine (**191**, Scheme 28).[98] This synthesis also serves to demonstrate the versatility of sulfoxides in total synthesis. Treatment of sulfoxide **186** (as a 4:1 mixture of *Z*/*E* isomers) with CSA in refluxing toluene generated sulfonium ion **187**, which underwent cyclization to form *N*-acyl iminium ion **189**. This species was then intercepted by the electron-rich aromatic ring in a Pictet–Spengler cyclization to form the tricyclic core of the target natural product **191**. This cyclization cascade in fact led to the formation of a 5:2:1:1 mixture of diastereoisomers in an overall yield of 88%, with the major product being the desired diastereoisomer **190**. To rationalize the preferential formation of tricyclic stereoisomer **190**, Padwa et al. suggested that a 4π-Nazarov-type electrocyclization controls the direction of ring closure from the α-acylthionium ion intermediate (i.e. **188**→**189**). The subsequent Pictet–Spengler step involves attack of the aromatic ring from the less hindered side of the iminium ion framework. The resulting sulfide group in cascade product **190** was put to further use later in the synthetic route to introduce the trisubstituted alkene through the thermal elimination of a sulfoxide. This strategy allowed the rapid construction of the polycyclic alkaloid jamtine (**191**) from simple building blocks.[99]



Scheme 28. The total synthesis of (±)-jamtine (**191**) through a Pummerer/Pictet–Spengler cascade (Padwa and Danca, 2002).[98]

Two distinct cascade reactions involving carbocationic intermediates can be found in the total syntheses of sceptrin (**197**) and ageliferin (**202**, Scheme 29), reported by Baran and



Scheme 29. The total synthesis of (−)-sceptrin (**197**) and (−)-ageliferin (**202**) by a controlled quadricyclane fragmentation and cationic ring expansion (Baran et al., 2006).[103]

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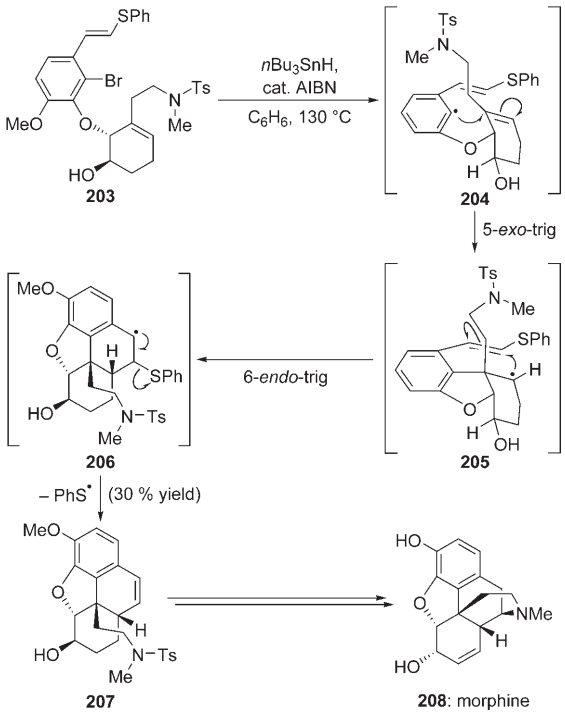
co-workers. In their synthesis of racemic sceptrin,[100] they made use of the fragmentation of a 3-oxaquadricyclane system, first reported by the groups of McInnes[101] and Nelson,[102] to prepare the required all-*trans*-tetrasubstituted cyclobutane ring. The problem of preparing enantiopure sceptrin by an analogous route was far from simple, especially in light of the poorly understood mechanism of the quadricyclane fragmentation. Indeed, initial attempts to prepare non-racemic cyclobutanes from enantiomerically enriched chiral 3-oxaquadricyclanes resulted in significant loss of enantiopurity. However, by employing monobenzylamide **193**, prepared in situ by irradiation of non-racemic diene **192**, Baran et al. were able to access tetrasubstituted cyclobutane **196** with clean transfer of chirality (Scheme 29).[103] They proposed a mechanism involving initial cleavage of the oxygen bridge to give cyclopropyl carbocation **194**. The regioselectivity of this step is crucial to the transfer of chirality during the cascade and is correlated with the greater stability of amide enols as compared to ester enols.[104] Addition of a molecule of water to **194** yields cyclopropanol **195**, which subsequently undergoes retroaldol fragmentation, driven by relief of ring strain, to give cyclobutane **196**. Interestingly, the product of this cascade has the *cis*,*trans*,*trans* configuration, in contrast to that observed earlier using *meso*-quadricyclanes. Fortunately, a facile epimerization gave the correct all-*trans* arrangement required for natural (−)-sceptrin (**197**).[105] Suspecting that (−)-sceptrin (**197**) may be the true natural precursor of the related natural product (−)-ageliferin (**202**), rather than a product of a divergent pathway, Baran et al. began to investigate the rearrangement of **197** to **202**. After screening a number of conditions, they discovered that the required transformation could be achieved by brief heating of an aqueous solution of **197** under microwave irradiation.[106,107] The most direct route from **197** to **202** would involve a concerted [1,3]-sigmatropic shift followed by tautomerization, but the possibility of this pathway occurring can be excluded on the basis that it would require inversion of configuration at the migrating center, whereas retention is observed experimentally. Several other more plausible mechanisms for the conversion of **197** into **202** can be envisioned, including the one illustrated in Scheme 29 which features a series of 1,2-shifts. Initial enamine–imine tautomerization of (−)-sceptrin (**197**) gives **198**, which undergoes the first alkyl 1,2-shift to give 5,5-spiro carbocation **199**. A hydride shift followed by a second alkyl 1,2-shift gives cyclohexane **201**, and a final tautomerization affords (−)-ageliferin (**202**) in moderate overall yield (40% from **197**). The synthesis by Baran et al. of (−)-sceptrin (**197**) and (−)-ageliferin (**202**) served to highlight a new possibility for the biosynthetic relationship of these natural products and to define the absolute stereochemistry of natural (−)-ageliferin.

4. Radical Cascades

The reactivity profiles of organic radicals[108] are well suited to the development of cascade reactions, and a wide variety have been designed and executed.[109] In this section, we will discuss a selection of radical-based cascades from recent total synthesis campaigns, with the aim of highlighting a broad scope of radical processes. The use of carbon- and heteroatom-centered radicals is exemplified, as are a range of methods for radical generation, including single electron transfer and photochemical processes in addition to the more traditional AIBN/tin hydride protocols.

In their synthesis of (−)-morphine (**208**, Scheme 30), Parker and Fokas used a cascade radical process to form two rings and install the all-carbon quaternary stereocenter in a single step. Treatment of bromide **203** with tri-*n*-butyltin hydride and AIBN in refluxing benzene gave tetracyclic



Scheme 30. Radical cyclizations in the total synthesis of (−)-morphine (**208**; Parker and Fokas, 2006).[110]

product **207** in moderate yield.[110] The reaction proceeds by the initial generation of aryl radical **204**, which cyclizes onto the tethered cyclohexene to form the dihydrobenzofuran system and the quaternary center. The approach of the aryl radical to the lower face of the alkene (as drawn in **204**) is governed by the stereochemistry of the ether linkage. Secondary radical **205** then cyclizes in a 6-*endo*-trig fashion to generate benzylic radical **206**. The geometric constraints imposed by the tricyclic framework of **205** discourage the alternative, and otherwise generally kinetically favored, 5-*exo*-trig mode of cyclization. Finally, elimination of phenylsulfinyl radical forms the olefin required for completion of this formal total synthesis of morphine.[111] Notably, a model substrate that lacks the vinylic 2-aminoethyl substituent underwent an analogous radical-based cyclization to generate the corresponding tetracyclic system in a much improved yield of 85%, illustrating the difficulties often encountered in the installation of congested all-carbon quaternary centers.

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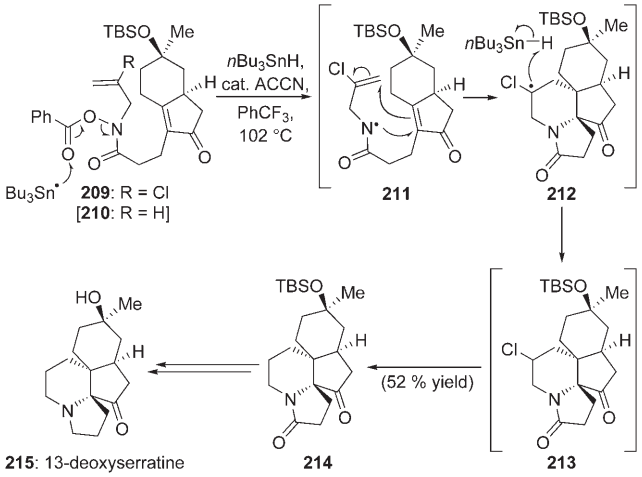
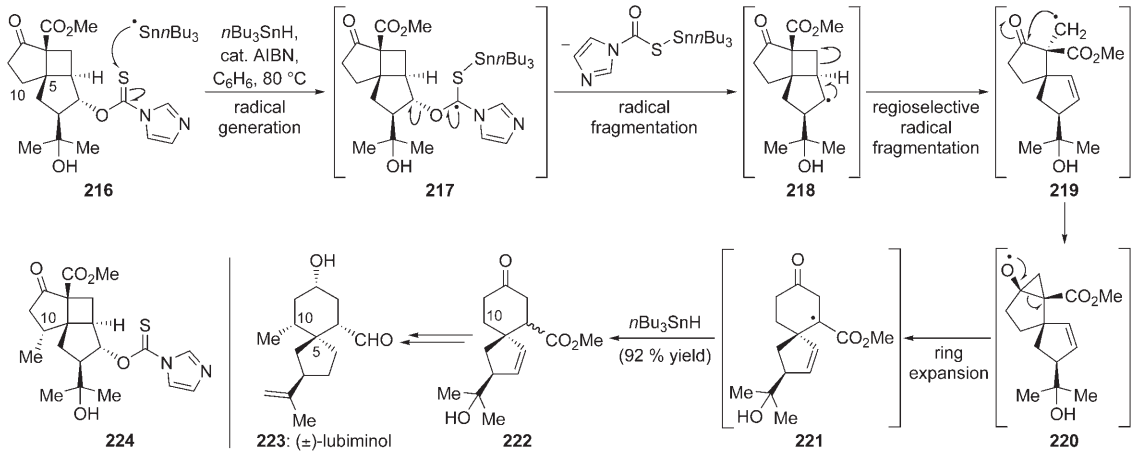
Zard and co-workers have developed a mild method for the generation of nitrogen-centered amidyl radicals from *O*-acyl hydroxamic acids.[112] This technology was central to their synthesis of the *Lycopodium* alkaloid 13-deoxyserratine (**215**, Scheme 31).[113] Treatment of benzoate **209** with tri-*n*-butyltin



Scheme 31. Nitrogen-centered radical cyclization in the total synthesis of 13-deoxyserratine (**215**; Zard et al., 2002).[113]

hydride and the radical initiator 1,1′-azobis(cyclohexanecarbonitrile) led to generation of amidyl radical **211**. This species underwent sequential 5-*exo*-trig and 6-*endo*-trig cyclizations, followed by hydrogen abstraction from tri-*n*-butyltin hydride, to furnish a tetracyclic intermediate (**211**→**212**→**213**). In this reaction, the vinyl chloride substituent acts as a disposable directing group.[114] Substrate **210**, which lacks this control element, was found to give the product arising from two 5-*exo*-trig cyclizations. The chlorine atom encourages the desired switch in regiochemical outcome by disfavoring the 5-*exo*-trig ring closure on steric grounds and by stabilizing the radical that results from the 6-*endo* cyclization. The overall efficiency of the synthesis does not suffer as a result of this tactic, as no extra step was required for the introduction of the chlorine substituent and it is cleanly removed in situ to give **214**, which was converted into 13-deoxyserratine (**215**) in just a few more steps. The yield for this cascade is impressive if it is considered that two vicinal quaternary stereocenters are formed in a single step from a relatively simple starting material. Zard and Sharp have recently applied a similar strategy to the total synthesis of the alkaloid aspidospermidine.[115]

The use of radical rearrangements and fragmentations can allow for the construction of complex systems in remarkable ways, providing that the timing of the elementary steps in the cascade can be controlled in the desired manner.[109] One instructive example can be found in the synthesis of lubiminol (**223**, Scheme 32) by Crimmins et al.[116] The synthetic strategy called for a radical fragmentation/ring expansion of a tricyclic cyclobutane such as **216**. This plan allowed for the formation of the spirocyclic system, including the challenging C5 quaternary center, by a stereocontrolled [2+2] photocycloaddition. Indeed, the cyclobutane substrate **216** could be prepared as a single diastereoisomer in this manner. Treatment of **216** with tri-*n*-butyltin hydride and AIBN led to fragmentation of the thiocarbamate to give secondary radical **218**. This process is driven by the affinity of tin for the sulfur atom of the thiocarbonyl group and the formation of a stronger C=O bond in place of the C=S linkage. Strain-driven fragmentation of the cyclobutane ring in **218** then proceeded regioselectively to give the primary radical **219**. This species then underwent a Dowd–Beckwith ring expansion,[117] involving 3-*exo*-trig cyclization onto the ketone carbonyl group followed by fragmentation of the resulting oxygen-centered radical **220**, with regioselective cleavage giving the observed cyclohexanone product **222** after reduction of **221**. Ketone **222** was then converted into (±)-lubiminol (**223**).[118] A more direct approach to this target would involve the radical fragmentation of substrate **224**, in which the required C10 methyl substituent has already been installed. Surprisingly, under the conditions that worked so effectively for **216**, cyclobutane **224** failed to give any cyclohexanone products.[116] The reason for the dramatic and deleterious effect of this seemingly benign methyl group on the radical process is not clear. It may be that the Dowd–Beckwith fragmentation step is disfavored by the increased steric hindrance imposed



Scheme 32. The total synthesis of lubiminol (**223**) through a cyclobutane fragmentation/ring-expansion cascade (Crimmins et al., 1998).[116]

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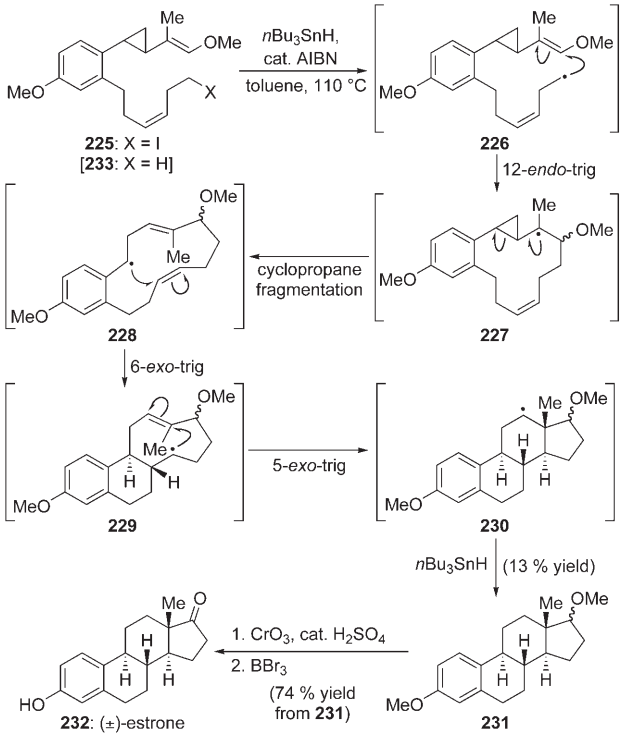
by the methyl group, or that intramolecular hydrogen-atom transfer from this group is a competing process. However, as another substrate bearing the epimeric 10*S*-methyl-substituted center also failed to proceed efficiently through the cascade, more subtle conformational effects may also be at work.

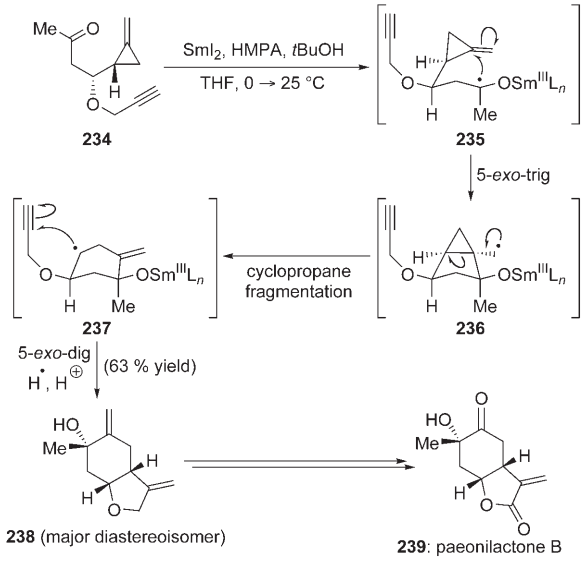
The chemical synthesis of steroids has been a central feature of organic chemistry research for much of the last century.[119] The rigid steroid framework has inspired a number of elegant and inventive cascade reactions, from the landmark biomimetic synthesis of progesterone (**11**) by Johnson and co-workers (see Scheme 2),[5] and the cobalt-catalyzed synthesis of estrone (**232**) by Vollhardt and co-workers,[120] to more recent accomplishments, including the palladium-catalyzed sequences developed by the groups of Tietze[121] and Negishi,[122] and Grubbs and co-workers' enyne metathesis cascade.[123] Pattenden et al. recently completed a short synthesis of (±)-estrone (**232**) using an imaginative radical cascade (Scheme 33).[124] Radical precursor **225** was



Scheme 33. Total synthesis of (±)-estrone (**232**) through a radical cascade cyclization (Pattenden et al., 2004).[124]

treated with AIBN and tri-*n*-butyltin hydride to give the tetracyclic steroid precursor **231**. This reaction proceeds by the initial macrocyclization of the primary radical **226** to give tertiary radical **227** (note that, in contrast to carbanion chemistry, carbon-centered radicals generally tolerate oxygenated functionality in the β-position). Fragmentation of the cyclopropane ring (**227**→**228**) then serves to move the radical site to the benzylic position. Two sequential transannular cyclizations (**228**→**229**→**230**) followed by quenching of the resulting secondary radical (**230**) then gave **231**. Although the overall yield of this cascade was very modest, it nevertheless enabled the diastereoselective formation of three rings and four stereocenters in a single maneuver. From tetracyclic compound **231**, a simple two-step procedure then led to (±)-estrone (**232**).[125] The low overall yield of this cascade can be attributed largely to the difficulty in achieving the initial macrocyclization step. The relatively slow rate of macrocyclization allows side reactions, such as simple quenching of primary radical **226** by tri-*n*-butyltin hydride, to compete. Indeed, the major product of this reaction was the reduced species **233**, which was isolated in 52% yield. However, once the macrocyclization event had occurred, the remaining steps of the cascade were comparatively efficient.

Radical cascades can also be initiated by treating suitable substrates with various single-electron-transfer reagents. Samarium(II) iodide has been employed as a mild and selective reductant in many cascade reactions, in which it can mediate both radical and anionic processes.[126] Kilburn and co-workers employed this reagent in the synthesis of paeonilactone B (**239**, Scheme 34),[127] which featured a cascade



Scheme 34. The use of a Sm^{II}-mediated cyclization/fragmentation cascade in the total synthesis of paeonilactone B (**239**; Kilburn et al., 2001).[127]

cyclization involving a methylene cyclopropane group. Treatment of ketone **234** with samarium(II) iodide in the presence of HMPA and *t*BuOH results in one-electron reduction to give ketyl radical anion **235**. A 5-*exo*-trig cyclization of **235** onto the methylene cyclopropane unit generates cyclopropyl carbinyl radical **236**, which undergoes a facile ring-expanding fragmentation to give homoallylic radical species **237**. Subsequent 5-*exo*-dig cyclization of **237**, followed by hydrogen-atom capture, gives the bicyclic product **238** in good yield (63%) as a 10:1 mixture of diastereoisomers at the hydroxy-substituted center (only the major diastereoisomer is shown in Scheme 34). Elaboration of bicyclic product **238** over a short sequence of steps then completed the total synthesis.[128] The relatively high level of diastereoselectivity observed in the conversion of **235** to **236** was found to be critically dependent

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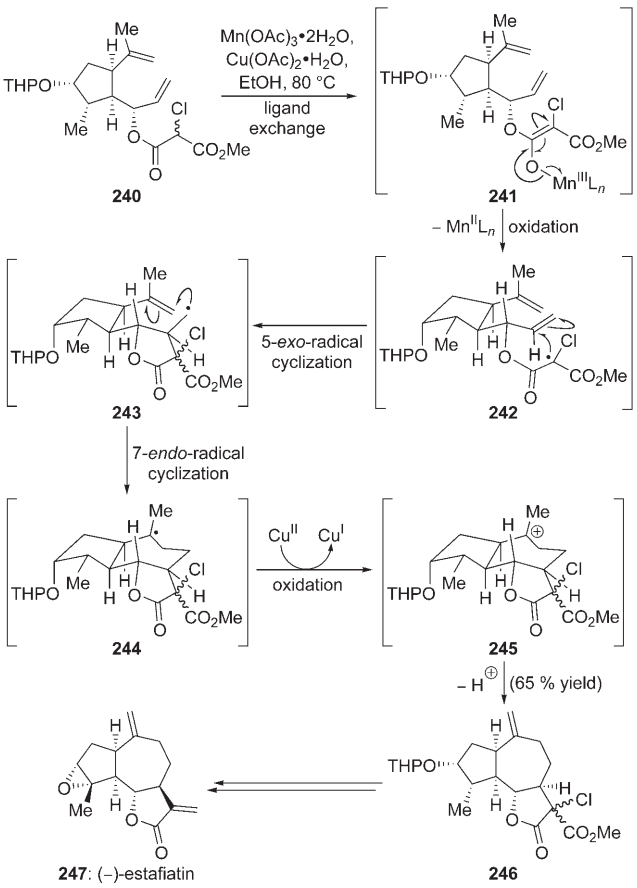
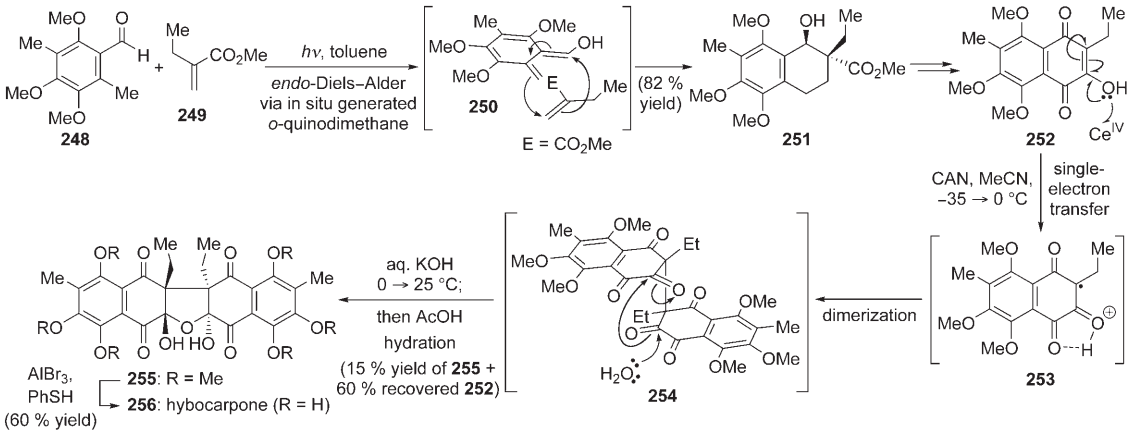
on the reaction solvent mixture. The use of the highly coordinating cosolvent HMPA was crucial, with the selectivity thought to result from the bulky solvated samarium alkoxide adopting a pseudoequatorial position in the cyclization of **235**.[129]

Radical species can also be generated oxidatively by one-electron transfer from the substrate to a metal center. Lee et al. employed the Mn^{III}–Cu^{II} system in their total synthesis of the guaianolide sesquiterpene (−)-estafiatin (**247**, Scheme 35).[130] Treatment of allylic chloromalonate **240** with a mixture of manganese(III) acetate and copper(II) acetate in ethanol at 80 °C led to a stereoselective 5-*exo*-trig,7-*endo*-trig radical cyclization cascade, which gave tricyclic product **246** in 65% yield. The chloride substituent was specifically incorporated into cascade precursor **240** in order to prevent further oxidation of product lactone by the excess manganese(III) acetate and was easily removed during the subsequent completion of the total synthesis of (−)-estafiatin (**247**).[131] The radical cyclization proceeds by ligand exchange to generate the manganese(III) enolate **241** in the rate-determining step.[132] A rapid redox reaction then generates the electrophilic radical **242**, which undergoes a 5-*exo*-trig cyclization to generate primary radical **243**. This species then undergoes a selective 7-*endo*-trig cyclization to afford tertiary radical **244**. The generally moderate intrinsic *endo* selectivity found in related reactions[133] is enhanced in this case by the presence of the vinylic methyl substituent, which hinders the trajectory of approach required for 6-*exo* cyclization and encourages the 7-*endo* pathway. A reluctance towards formation of a more strained *trans*-fused 6,5-ring system may also contribute to the high *endo* selectivity in this case. In the final step, tertiary radical **244** is oxidized by the copper(II) acetate to give the tertiary carbocation **245**, which loses a proton to give the *exo*-methylene product **246**.



Scheme 35. Total synthesis of (−)-estafiatin (**247**) through an oxidative radical cyclization cascade (Lee et al., 1997).[130]

The lanthanide salt, cerium(IV) ammonium nitrate (CAN), is another single-electron oxidant that is widely used in organic synthesis.[126,134] Nicolaou and Gray employed CAN to effect the key dimerization step in their total synthesis of hybocarpone (**256**).[135] Their approach involved the use of two separate cascade sequences, as shown in Scheme 36. The first was used to prepare the monomeric naphthazarin unit of hybocarpone (**256**) through photoenolization of benzaldehyde derivative **248** in the presence of acrylate **249**. Thus, irradiation of **248** generated *ortho*-quinodimethane enol **250**, which was trapped in situ by dienophile **249** to give the cyclohexanol product **251** in high yield.[136] Alcohol **251** was then converted into quinone **252** in preparation for the crucial dimerization event. After screening a range of electron-transfer agents, it was discovered that



Scheme 36. Total synthesis of hybocarpone (**256**) through photochemical enolization/Diels–Alder and oxidative coupling cascades (Nicolaou and Gray, 2001).[135]

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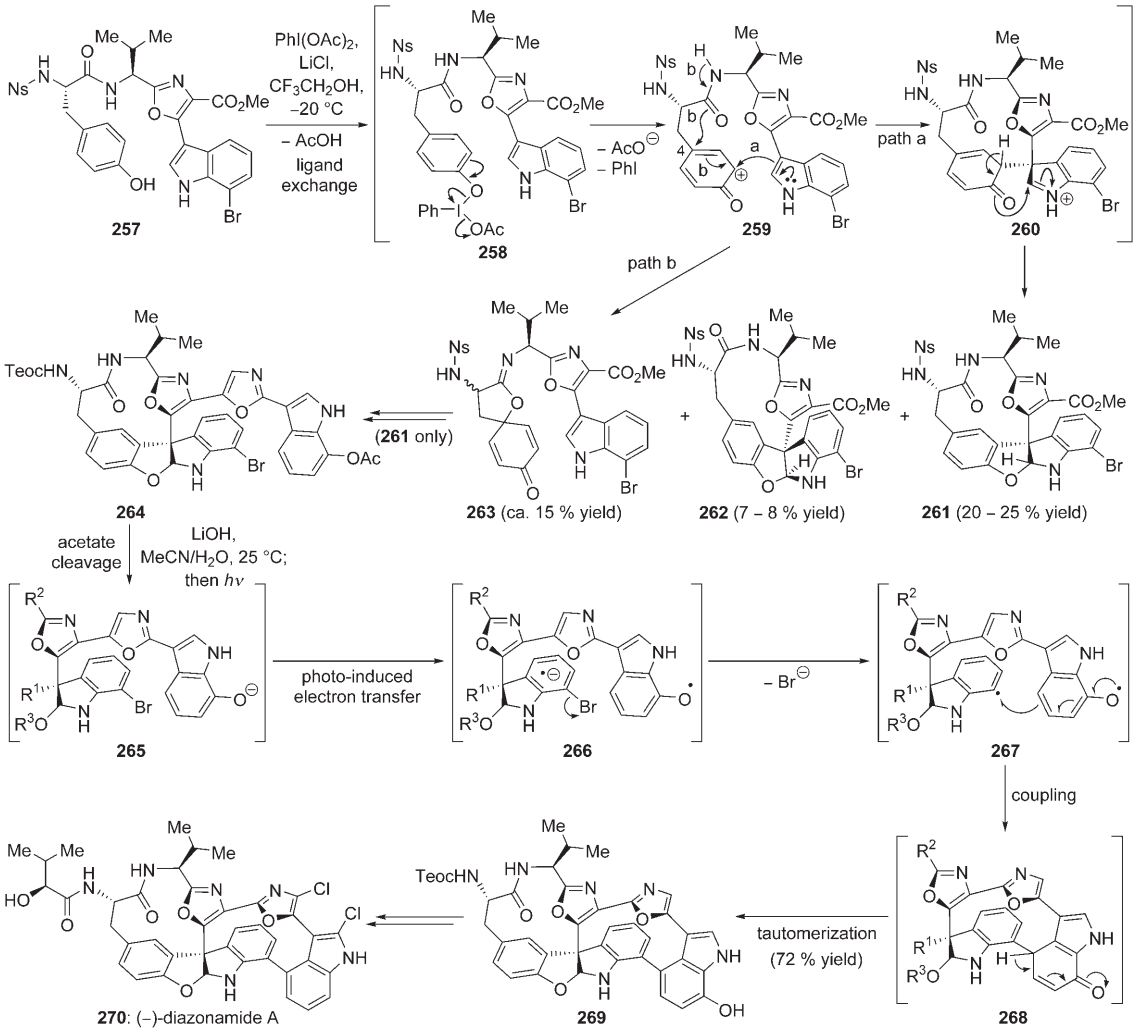
brief treatment of **252** with CAN at low temperature effected the desired carbon–carbon bond-forming reaction. Oxidation of **252** by CAN is believed to lead to tertiary radical **253**, which undergoes stereoselective dimerization to give the C_2-symmetric diketone **254**. Quenching of the reaction with base completed the process by triggering hydration of the 1,4-diketone to give pentacyclic product **255**. Hydrate **255** was formed along with a minor quantity of an unsymmetrical stereoisomer, as predicted by molecular modeling studies, which could be epimerized to give **255** on treatment with mild acid. Global deprotection of **255** with aluminum bromide and benzene thiol gave hybocarpone (**256**).[137]

Harran and co-workers employed a photochemically initiated radical coupling in the total synthesis of the revised structure of diazonamide A (**270**, Scheme 37).[138] They also made use of an oxidative annulation reaction of a phenol precursor, mediated by a hypervalent iodine(III) reagent. The core architecture of diazonamide A (**270**) comprises two macrocyclic domains: the "left-hand" macrolactam peptide-containing portion and the "right-hand" heterocyclic sector. The macrolactam portion of the target was prepared first, through the oxidative cyclization of peptidic precursor **257**. Thus, treatment of **257** with $PhI(OAc)_2$ and LiCl in CF_3CH_2OH gave the desired macrocycle **261** in moderate yield (20–25%), accompanied by lesser amounts of the diastereomeric product **262** (7–8%) and a mixture of epimeric spirodienones **263** (ca. 15%). A number of mechanistic pathways could be invoked to explain this result,[139] but a likely pathway[140] involves the reaction of the phenol group with the iodoso species to generate **258**, which fragments with the loss of acetate and iodobenzene to give phenonium ion intermediate **259**. Reaction of **259** through path b (Scheme 37) involves attack of the amide group at C4 of the phenonium ion, leading to spirocycle **263**. Alternatively, attack of the nucleophilic indole (path a) gives macrocyclic intermediate **260**, which re-aromatizes with concomitant ring closure to generate the required aminal ring system in **261**. The minor diastereomeric product **262** arises from attack of the indole ring and subsequent ring closure occurring on the opposite face of the indole C2–C3 double bond to that depicted in Scheme 37. The observed stereocontrol in the formation of the macrocyclic products is thought to be relayed



Scheme 37. Oxidative phenolic coupling and photolytic aromatic coupling reactions in the total synthesis of (−)-diazonamide A (**270**; Harran et al., 2003).[138]

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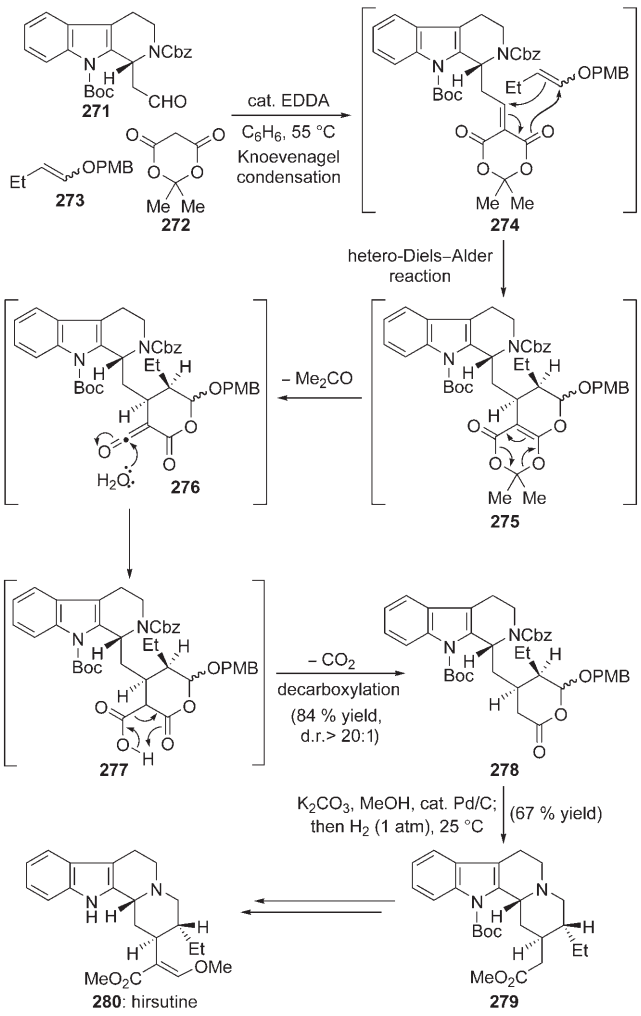
from the two backbone stereocenters, which endow precursor **257** with a helical character. This helical character also brings the phenol and indole rings into close proximity to one another, enabling macrocyclization to dominate over an ostensibly more favorable five-membered ring closure to afford spirodienones **263**. After separation from the accompanying by-products, macrocycle **261** was elaborated to give bromide **264**, in preparation for the photochemical macrocyclization event. Treatment of compound **264** with aqueous lithium hydroxide in acetonitrile served to cleave the phenolic acetate group and afford phenolate anion **265**. Irradiation of this solution then triggered the crucial Witkop cyclization[141] to generate macrocyclic product **269** in 72% overall yield. This process involves a photoinduced electron transfer between the phenoxide group and the less electron-rich bromoindoline aromatic ring. Loss of bromide from the resulting radical anion **266** then gives a radical pair **267**, which couples (**267**→**268**) and tautomerizes (**268**→**269**) to generate the required biaryl linkage in high yield and complete the macrocyclic framework.[142] These two very different cyclization procedures therefore provided both elegant and creative solutions to the synthesis of the respective macrocyclic domains of diazonamide A (**270**). Having reached the advanced staging area represented by compound **269** in this concise manner, Harran and co-workers were able to complete the total synthesis of this fascinating target in short order.[143]

5. Pericyclic Cascades

Pericyclic reactions are perhaps the most common processes encountered in cascade reactions. This broad class includes cycloadditions, sigmatropic rearrangements, and electrocyclic reactions, all of which have been employed in cascades en route to natural product targets. This section begins with cascades that incorporate Diels–Alder reactions,[144] coupled with a variety of other pericyclic and nonpericyclic processes, in both inter- and intramolecular settings. Several other cascades that hinge upon sigmatropic and electrocyclic transformations then follow. Additionally, a number of pericyclic reactions can be found throughout this Review as components of other cascades.

The first example in this section is taken from the total synthesis of the indole alkaloid hirsutine (**280**, Scheme 38) by Tietze and Zhou.[145] As with several of the reactions covered in this Review, this process is rather difficult to classify, as it combines several individual reaction types in an elegant cascade. The first step in this three-component coupling reaction is the Knoevenagel condensation of chiral aldehyde **271** with Meldrum's acid (**272**), which proceeds under very mild conditions.[146] The resulting alkylidene intermediate **274** then reacts with enol-ether **273** in an intermolecular hetero-Diels–Alder reaction to give dihydropyran **275** with excellent diastereoselectivity. This is then followed by a retro-[4+2] cycloaddition reaction to expel a molecule of acetone and generate a reactive ketene intermediate **276**. Hydration of **276** gives a new 1,3-diacid derivative **277**, which undergoes thermal decarboxylation to form **278** in excellent overall yield



Scheme 38. Knoevenagel/hetero-Diels–Alder reaction cascade in the total synthesis of hirsutine (**280**; Tietze and Zhou, 1999).[145]

(84%). In a second cascade step, treatment of **278** with K_2CO_3 in methanol followed by hydrogenation under palladium catalysis led to methanolysis of the lactone, loss of the PMB and Cbz protecting groups, iminium ion formation, and finally reduction to form tetracyclic amine **279**, a precursor to hirsutine (**280**).[147]

Another cascade sequence involving a hetero-Diels–Alder reaction can be found in the total synthesis by Nicolaou et al. of the veterinary antibiotic thiostrepton (**289**, Scheme 39),[148] the most structurally complex member of the thiopeptide class of natural products.[149] Inspired by the biosynthetic proposals of Floss and co-workers,[150] Nicolaou et al. began investigating the [4+2] dimerization of azadienes for the construction of the dehydropiperidine core structure that lies at the heart of the target natural product. It was found that treatment of thiazolidine **281** with silver(I) carbonate and a catalytic amount of DBU in pyridine led to a formal elimination of hydrogen sulfide to generate the highly reactive aza-diene **282**. The Diels–Alder dimerization of **282** then proceeded through an *endo* transition state to give the dihydropiperidine system **283** with excellent control of stereoselectivity at the newly formed piperidine C5 and C6

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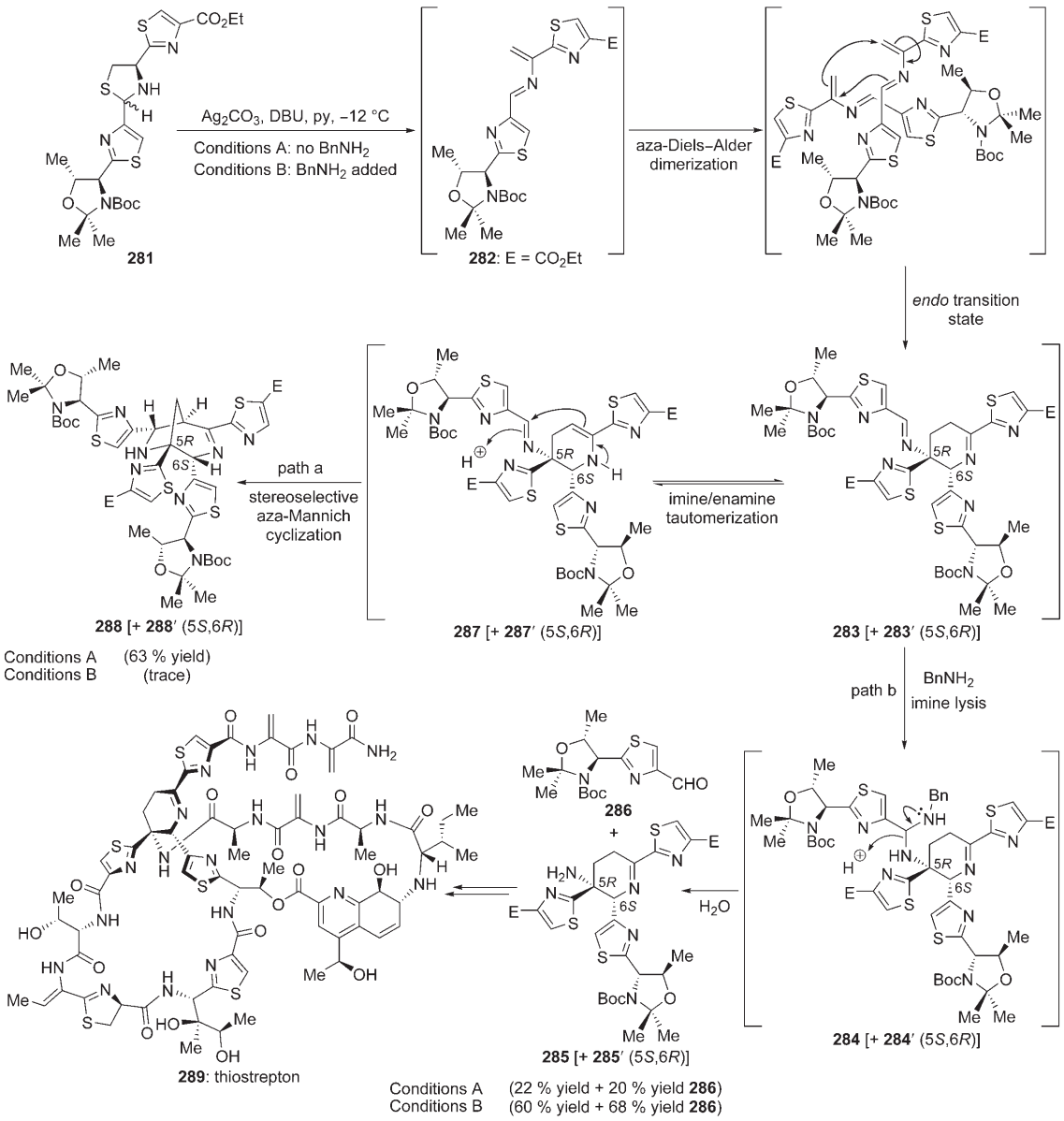

Scheme 39. aza-Diels–Alder dimerization and aza-Mannich reactions in the total synthesis of thiostrepton (**289**; Nicolaou et al., 2004).[148]

stereocenters. However, the reaction was not influenced by the remote stereocenters of the substrate, so **283** was formed as a 1:1 mixture of 5*R*,6*S*/5*S*,6*R* diastereoisomers (**283** and **284**, respectively). In the initial investigation of this reaction, the addition of water to the reaction mixture at the end of the cascade sequence, with the intention of hydrolyzing the exocyclic imine group of **283**, led to a low yield (20%) of the desired amine product **285**. Under these conditions, the major reaction product was found to be the interesting bicyclic imine **288**, which presumably arises as the result of tautomerization of the initial [4+2] adduct **283** to the corresponding enamine species **287**, followed by a highly stereoselective aza-Mannich cyclization (path a).[151] Fortunately, inclusion of benzylamine in the reaction mixture successfully diverted the course of the reaction in favor of the desired imine lysis pathway (path b). Thus, imine hydrolysis, through initial aminolysis (**283**→**284**→**285**), gave a good yield of the dihydropiperazine product **285** (60%), along with a similar quantity of aldehyde **286**, which could be recycled for the synthesis of thiazolidine **281**.[152,153]

The complex polycyclic architectures of the bisorbicillinoids belie their considerably simpler biosynthetic precursor. The groups of Nicolaou and Corey have investigated the biosynthesis and total synthesis of a number of these fascinating fungal metabolites.[154,155] Quinol **291** (Scheme 40) was identified as a potential precursor to several of these natural products, however, such a compound was anticipated to be highly unstable.[156] Therefore, acetate **290** was prepared through oxidation of the corresponding phenol using $Pb(OAc)_4$ in AcOH to serve as a more stable precursor to the required quinol species **291**. It was anticipated that hydrolysis of the acetate group, under either basic or acidic conditions, could then lead to the formation of reactive intermediate **291** in situ. As shown in Scheme 40, acid-

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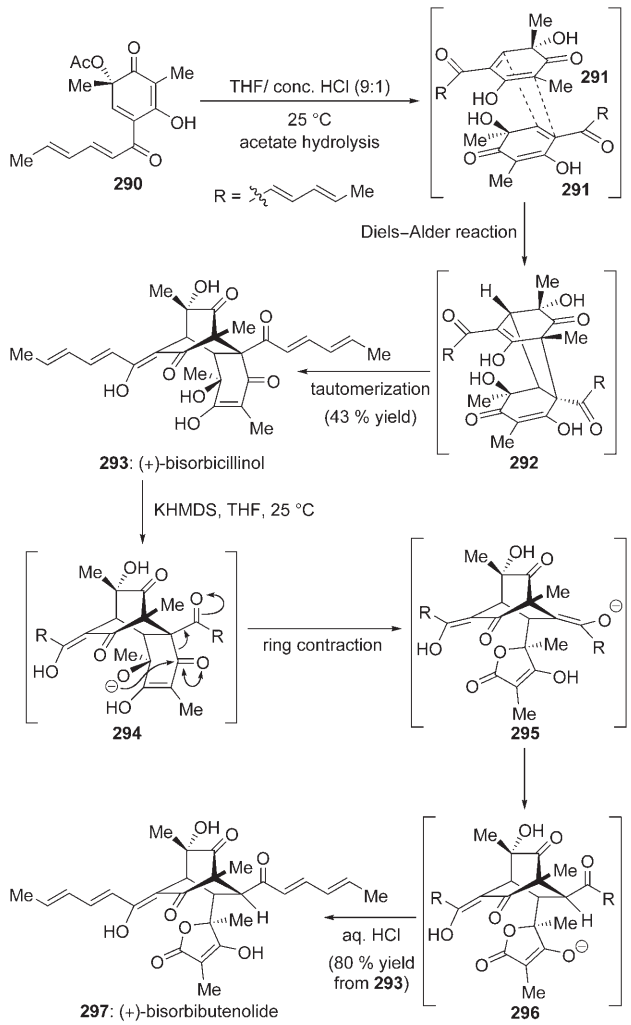
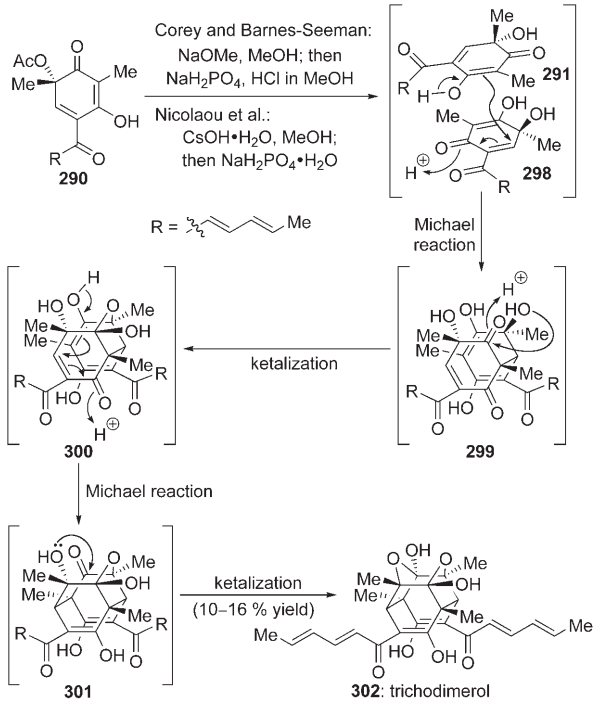


Scheme 40. Diels–Alder dimerization and base-catalyzed isomerization reactions to form (+)-bisorbicillinol (**293**) and (+)-bisorbibutenolide (**297**; Nicolaou et al., 1999).[154]

catalyzed hydrolysis of **290** led to the Diels–Alder dimerization of quinol **291** to give **292**, tautomerization of which afforded (+)-bisorbicillinol **293** in 43% yield.[154] Under basic conditions (10 equiv KOH, 9:1 THF/H_2O), the potassium salt of **291** could be observed by ^{1}H NMR spectroscopy, and only dimerized to give **293** on acidification, indicating the increased stability of the quinoxide. Nicolaou et al. also found that (+)-bisorbicillinol (**293**) could be converted into another member of this class through a base-mediated ring-contraction sequence. Deprotonation of **293** using KHMDS (1.1 equiv) in THF at room temperature led to intramolecular attack of the alkoxide group of anion **294** onto the ketone group, followed by a retro-aldol fragmentation to give butenolide anion **296**. Protonation of this species upon quenching the reaction mixture with 1N aqueous HCl then furnished (+)-bisorbibutenolide (**297**). The conversion of bisorbicillinol (**293**) into bisorbibutenolide (**297**) is attended by a significant relief in the ring strain and overall steric crowding present in the former compound, which provides the necessary driving force for this transformation.

The conditions under which acetate **290** is hydrolyzed and the resulting quinolate anion is neutralized have a dramatic impact on the product distribution. The groups of Corey and Nicolaou have both used **290** as a precursor to the intricate pentacyclic cage structure of trichodimerol (**302**, Scheme 41).



Scheme 41. A Michael reaction and ketalization cascade to form trichodimerol (**302**; Nicolaou et al., 1999; Corey and Barnes-Seeman, 1999).[154,155]

Basic hydrolysis of the acetate, followed by careful neutralization with sodium dihydrogen phosphate, gave the target natural product **302**. The yield of trichodimerol (**302**) isolated from this sequence may seem low (10–16%), but should be judged in light of the great molecular complexity generated; the sequence forms four new sigma bonds and generates eight new stereocenters (six of which are quaternary). Under these reaction conditions, quinol **291** enters a sequence of Michael additions and ketalizations rather than a Diels–Alder process. Addition of enol tautomer **291** to keto tautomer **298** initially yields dimeric species **299**. A ketalization event then provides tricyclic intermediate **300**, which is poised for a succession of Michael addition (**300**→**301**) and further ketalization steps (**301**→**302**) to afford the target product **302**. In addition to the formation of trichodimerol (**302**), Nicolaou et al. also isolated a similar proportion of bisorbicillinol (**293**) from the reaction mixture, indicating the degree of crossover between the competing Michael addition/ketalization and Diels–Alder dimerization pathways.

Aubé and co-workers have designed a number of cascade processes based on sequential Diels–Alder and intramolecular Schmidt reactions, using either keto-azides or azido-dienes under Lewis acid catalysis.[157] They applied this strategy for nitrogen heterocycle construction to the total synthesis of the *Stemona* alkaloid stenine (**310**, Scheme 42). Their first-

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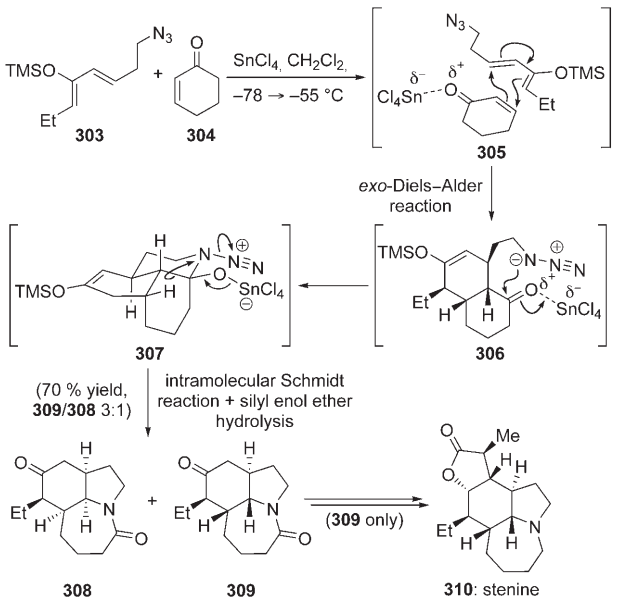
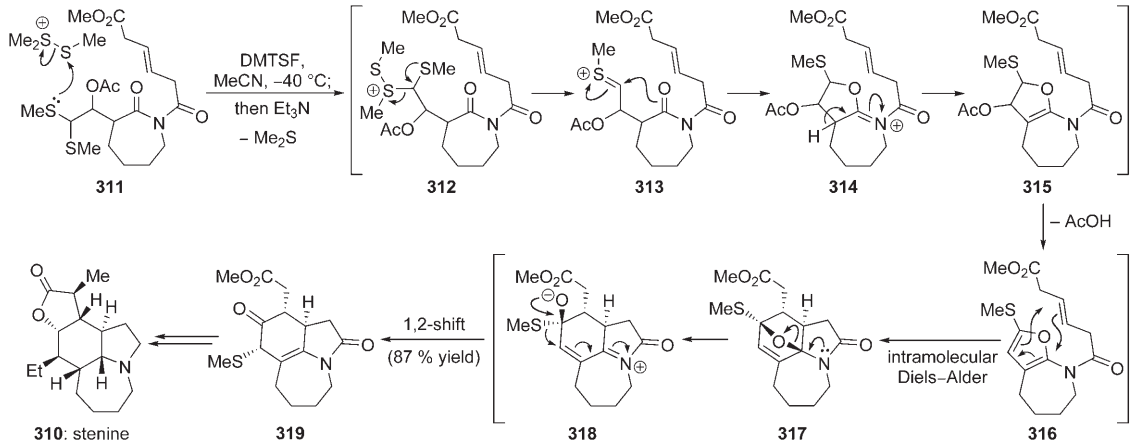


Scheme 42. Total synthesis of stenine (**310**) through a Diels–Alder/Schmidt cascade (Zeng and Aubé, 2005).[159]

generation approach to this target employed an intramolecular Diels–Alder/Schmidt reaction sequence,[158] however, not only was the cascade precursor difficult to prepare, but the cascade itself generated several undesired by-products, limiting its efficiency. In their second-generation synthesis,[159] a Lewis acid catalyzed intermolecular Diels–Alder reaction was utilized to couple azido-diene **303** with cyclohexenone **304** to give *cis*-decalin **306**, as shown in Scheme 42. The moderate *exo* selectivity of this reaction was ascribed to unfavorable steric interactions between the cyclic dienophile and the bulky TMS enol ether of the diene (only the *exo* mode of [4+2] cycloaddition is depicted in Scheme 42). Subsequent attack of the tethered azide onto the ketone proceeded stereoselectively due to the constraints of the fused ring system to give **307**.[160] Selective migration of the carbon–carbon bond antiperiplanar to the equatorially aligned N_2 leaving group in **307** led to formation of the desired tricyclic product **309**, accompanied by the corresponding diastereoisomer **308** (which results from the minor *endo* mode of [4+2] cycloaddition), in 3:1 ratio and a combined yield of 70%. After the separation of **308** and **309**, the latter could be converted into stenine (**310**) through a short sequence of steps.[161]

In their approach to the same target, Padwa and Ginn employed an intramolecular Diels–Alder reaction of a 2-methylthio-5-amido-substituted furan to fuse the 6,5-bicyclic system onto a preexisting seven-membered ring.[162] The required activated furan system was prepared in situ as part of an impressive cascade reaction (Scheme 43), which also included the rearrangement of the Diels–Alder product. The sequence begins with dithioacetal **311**, which was treated with DMTSF to form furan **316**. Methylsulfenylation of **311** by DMTSF gives methylthiosulfonium ion **312**, which fragments to give sulfonium ion **313**. A Pummerer cyclization of **313** with the nearby amide group, followed by loss of a proton and elimination of acetic acid, gives the required furan ring (**314**→**315**→**316**).[163] The electron-rich furan group then undergoes an intramolecular Diels–Alder reaction with the pendant olefin[164] to generate tetracyclic intermediate **317**. Interestingly, this Diels–Alder reaction proceeded smoothly at room temperature, while the reaction of the corresponding six-membered lactam substrate required heating at 110°C. The rate difference can be explained by the greater flexibility of the seven-membered lactam, which allows the furan to adopt a reactive conformation at ambient temperature.[165] Opening of the strained oxygen bridge (**317**→**318**), assisted by the nitrogen atom, is accompanied by a 1,2-shift of the methylthio substituent onto the activated iminium ion species to give tricyclic enamide **319**, a species which now comprised much of the structural and stereochemical complexity of the target natural product **310**.[166]

Boger et al. have developed a number of cascade processes based on the hetero-Diels–Alder reactions of azadienes.[167] Recent examples of this work can be found in their use of 1,3,4-oxadiazoles in the total syntheses of several alkaloid natural products, including that of vindorosine (**324**, Scheme 44) described here.[168] 1,3,4-Oxadiazoles had previously been employed in Diels–Alder reactions with olefins to



Scheme 43. A heterocyclization/Diels–Alder reaction/rearrangement cascade in the total synthesis of stenine (**310**; Ginn and Padwa, 2002).[162]

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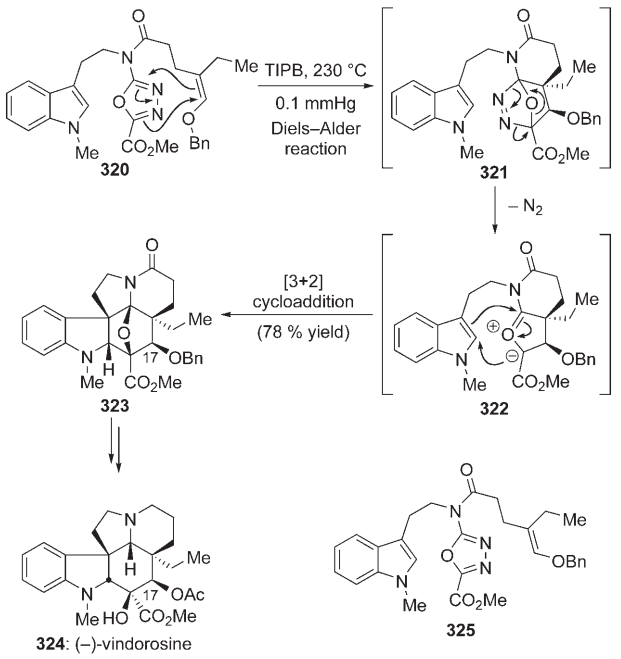
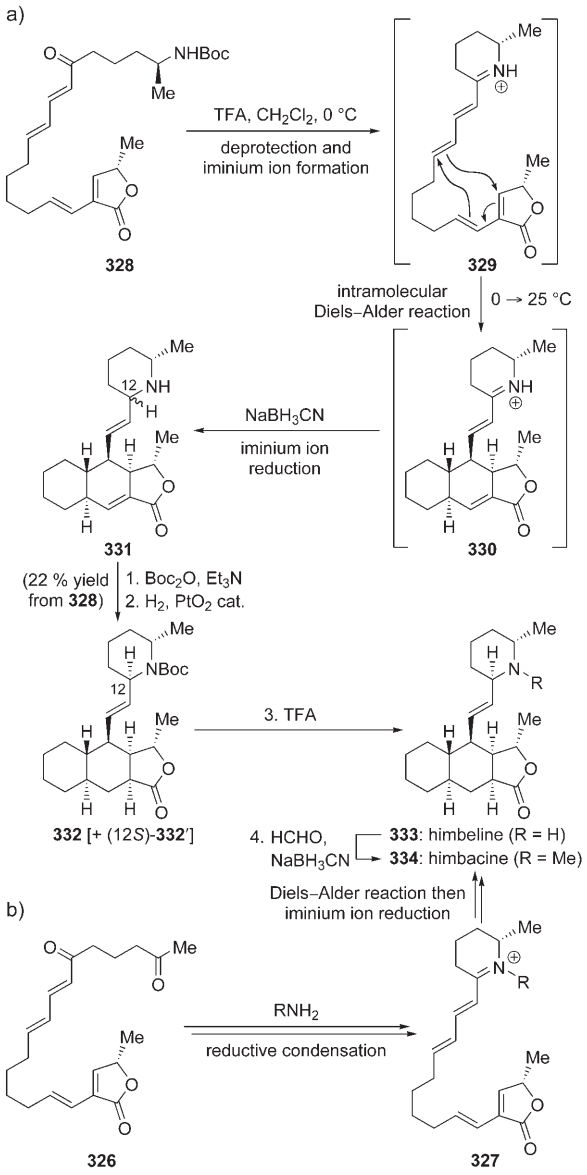


Scheme 44. Diels–Alder and [3+2] cycloadditions in the total synthesis of vindorosine (**324**; Boger et al., 2006).[168]

produce bicyclic intermediates. These intermediates lose nitrogen to generate 1,3-dipoles, which undergo a second cycloaddition with another equivalent of the olefin to give symmetrical 2:1 adducts.[169] Boger and co-workers have extended this technology by developing cascade processes in which 1,3,4-oxadiazoles are employed in intramolecular cycloadditions, giving access to nonsymmetrical products.[170] Work by Padwa and Price had demonstrated that vindorosine (**324**) and related alkaloids could be accessed through the 1,3-dipolar cycloaddition of a carbonyl ylide species and a tethered indole dipolarophile.[171] By tethering both the olefin and the indole ring to a suitably substituted 1,3,4-oxadiazole, Boger and co-workers found that the pentacyclic skeleton of vindorosine (**324**) could be accessed rapidly from the relatively simple precursor **320** in a single step.[172] Heating of a solution of **320** in triisopropylbenzene at 230 °C led to its slow, but efficient, conversion into hexacyclic product **323** (Scheme 44). An inverse-electron-demand Diels–Alder reaction between the oxadiazole ring and the tethered enol ether substituent leads to the initial formation of **321**, followed by extrusion of nitrogen to form carbonyl ylide intermediate **322**. A stereoselective 1,3-dipolar cycloaddition then ensues, to give the desired product **323**. In all, three rings, four carbon–carbon bonds, and six stereocenters (four of them quaternary) are formed in this cascade. The *endo* selectivity observed in this case,[172] and also in the work of Padwa and Price,[171] is attributed to the conformational preference of the tethered dipolarophile. Interestingly, the efficiency of this cascade sequence was found to be strongly dependent on the concentration of the reaction mixture, with dilute solutions giving the best results. The use of the corresponding *E*-enol ether **325** (which led to the formation of the undesired 17*S* epimer of hexacyclic product **323**) gave higher yields in the cascade sequence at higher reaction concentrations. As precursor **320** is achiral, hexacyclic product **323** was formed as a racemate; however, it could be resolved by HPLC on a chiral stationary phase, thus providing access to (−)-vindorosine.[171] Besides vindorosine, Boger and co-workers have used analogous cascades to prepare a number of other members of this class of alkaloids.[173,174]

Several groups have prepared the class 1 *Galbulimina* alkaloid himbacine (**334**) by means of an intramolecular Diels–Alder reaction.[175] In an extension of this approach, Baldwin et al. designed and executed a biomimetic cascade to install three of the four rings of the target molecule in a single step (Scheme 45 a). They postulated that reductive condensation of diketone **326** with an appropriate amine would generate a cyclic unsaturated iminium ion **327**, which would undergo a Diels–Alder reaction to form the tetracyclic structure (Scheme 45 b).[176,177] With this hypothesis as both



Scheme 45. Cyclization/cycloaddition cascades in the total synthesis of himbeline (**333**) and himbacine (**334**): a) biomimetic approach; b) proposed biosynthesis (Baldwin et al., 2005).[176]

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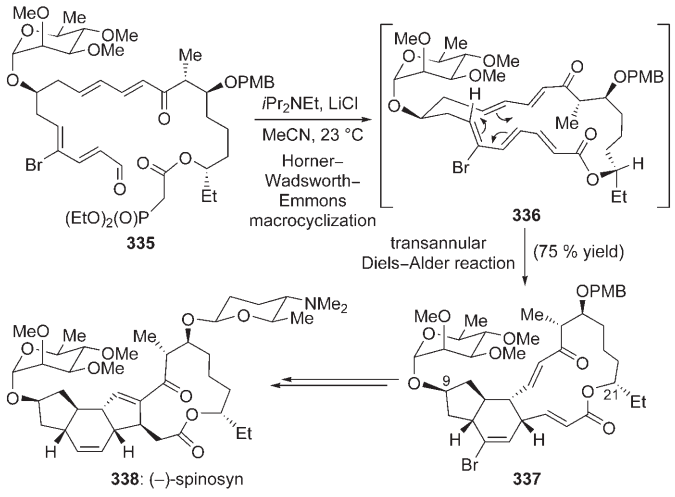
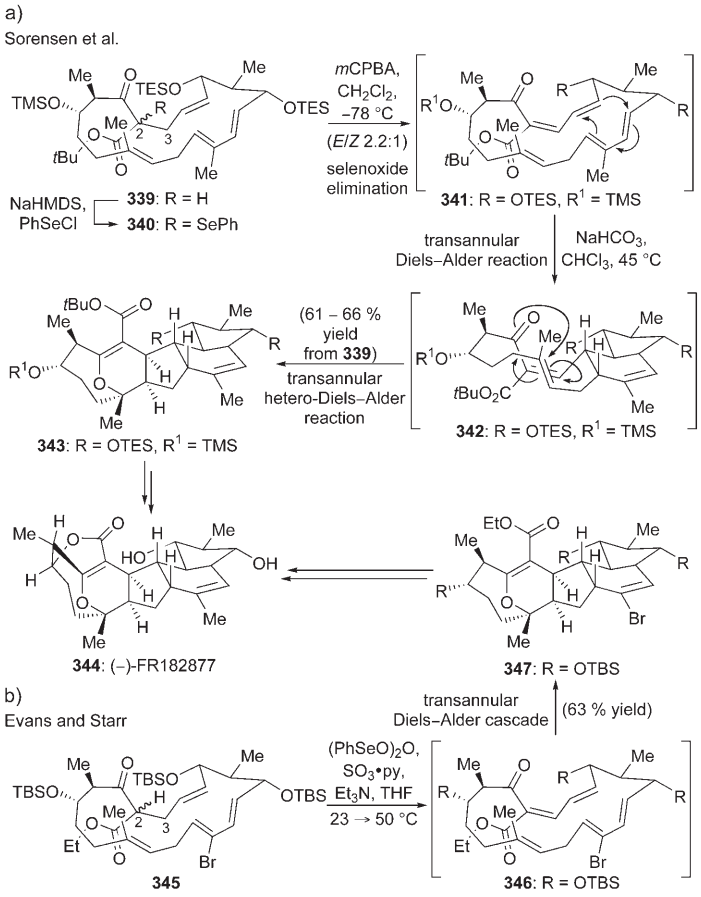
their guide and inspiration, the team prepared tetraene **328**, in which the chiral secondary amine was already incorporated in a protected form. Exposure of **328** to TFA in CH_2Cl_2 effected the cleavage of the Boc protecting group and catalyzed the formation of the cyclic iminium ion **329**. Conjugation with the iminium ion species served to activate the adjacent diene system (through the lowering of the LUMO energy) towards intramolecular Diels–Alder reaction with the other diene unit, forming tetracyclic species **330**. Brief treatment of the reaction mixture with sodium cyanoborohydride then gave amine **331**. While the Diels–Alder event was highly diastereoselective, forming a single 6,6,5-tricyclic system, the final reductive quench of iminium ion **330** displayed no facial selectivity, with amine **331** produced as a 1:1 mixture of epimers at the C12 position. Separation of this epimeric mixture was postponed until after Boc protection of the secondary amine and selective hydrogenation of the trisubstituted olefin to give **332**, along with its C12 epimer, in modest overall yield from **328**. Amine **332** was converted into himbeline (**333**) and then himbacine (**334**) through standard procedures. The other epimer of the cascade product, (12*S*)-**332′**, could similarly be transformed into another member of this class of natural products, namely himandravine (not shown), the C12 epimer of himbacine (**334**).[178]

Transannular Diels–Alder reactions have been used widely in the synthesis of complex natural products. The conformational constraints imposed by the macrocyclic nature of the substrates often provide a high degree of stereocontrol in these processes. This area was the subject of a recent review by Deslongchamps, a pioneer of the transannular Diels–Alder reaction.[179] Two striking examples that have appeared in the literature since that survey are included here to demonstrate the power of the reaction in cascade sequences. The first is the total synthesis of the insecticide spinosyn A (**338**, Scheme 46) by Roush and co-workers.[180] In their total synthesis of this target, Evans and Black had previously observed that the natural conformational preference of an intramolecular Diels–Alder substrate favored formation of the undesired *endo* adduct.[181] This was successfully overcome in their synthesis by the use of a chiral auxiliary, however, this strategy would not be possible in the context of a transannular cycloaddition. Roush and co-workers combined the use of a fully functionalized macrocyclic substrate with a bromide stereodirecting substituent on the diene to achieve excellent stereocontrol in favor of the correct isomer. As shown in Scheme 46, the cascade begins from the linear precursor **335**, which undergoes an *E*-selective Horner–Wadsworth–Emmons macrocyclization[182] to give pentaene **336**. This intermediate spontaneously undergoes a transannular Diels–Alder reaction to form **337**, with the correct stereochemistry for spinosyn A (**338**). Steric repulsion between the vinylic bromide and the C9 alkoxy substituent helps to ensure that **336** reacts through the conformation shown,[183] while the overall conformation of the macrocyclic ring improves the selectivity through the influence of distant stereogenic centers, such as that at C21. This highly efficient conversion (**335**→**337**) facilitated the completion of the total synthesis of (−)-spinosyn A (**338**).

The total synthesis of the antitumor polyketide (−)-FR182877 (**344**, Scheme 47) was completed by the groups of Sorensen and Evans, with both employing a transannular Diels–Alder cascade sequence. Sorensen and co-workers proposed that the polycyclic ring system of (−)-FR182877 (**344**) could be formed through two Diels–Alder processes



Scheme 46. Total synthesis of spinosyn (**338**) using a macrocyclization/transannular Diels–Alder cascade (Roush et al., 2004).[180]



Scheme 47. Transannular Diels–Alder cascades in the total synthesis of (−)-FR182877 (**344**; Sorensen et al., 2002; Evans and Starr, 2002).[188,189]

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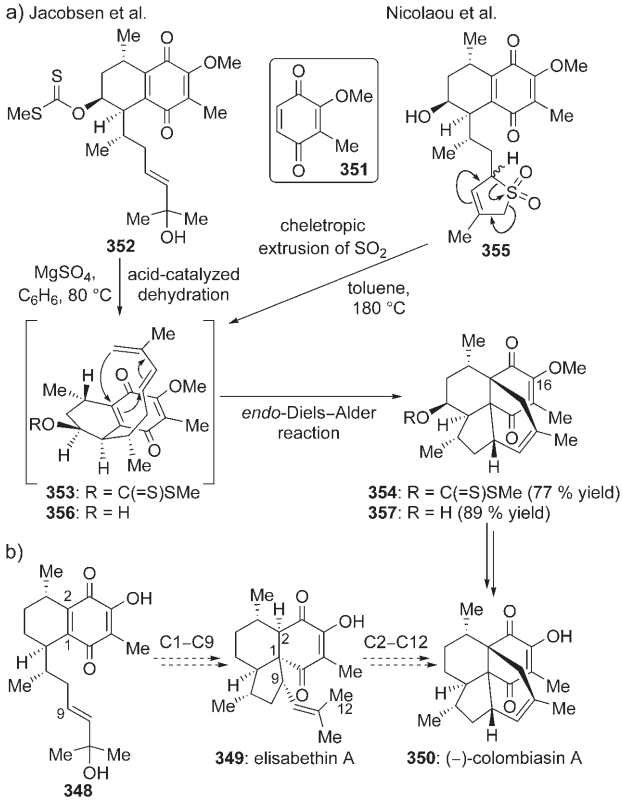
and a condensation event to form a large ring,[184] a hypothesis that was supported by the isolation and biosynthetic investigation of the related natural product hexacyclinic acid.[185] Their initial synthetic studies focused on a sequence involving an intramolecular Diels–Alder reaction followed by formation of a macrocycle and eventual hetero-Diels–Alder reaction.[186] Ultimately, their successful synthetic plan was based upon the construction of a polyketide macrocycle, which would undergo transannular Diels–Alder and hetero-Diels–Alder reactions to form the complex pentacyclic framework of the target compound. Their first total synthesis of FR182877 yielded the unnatural (+)-enantiomer,[187] however, their optimized sequence gave the natural (−)-antipode **344** (Scheme 47a).[188] The efficiency of the transannular Diels–Alder cascade hinged on the selectivity of the oxidation reaction used to introduce the crucial C2−C3 double bond into precursor **341**. In the absence of this element of unsaturation, macrocycle **339** did not undergo transannular cycloaddition, as the dienophile is not activated by conjugation. It was found that selenation of keto-ester **339**, using phenyl selenium chloride and sodium hexamethyldisilazide in diethyl ether at room temperature gave a 10:1 ratio of selenide products in favor of the desired epimer. Oxidation led to facile selenoxide elimination to generate pentaene **341**. Warming of the reaction mixture to 45 °C triggered the cycloaddition sequence (**341**→**342**→**343**), giving a good overall yield of the desired pentacyclic stereoisomer **343**. The selenoxide elimination step also formed a smaller amount of the alkene with a *Z*-configured C2=C3 bond (not shown), which in turn followed its own divergent cycloaddition pathways, yielding by-products which account for most of the mass balance in this reaction. Nevertheless, this optimized route allowed the Sorensen group to prepare multigram quantities of advanced intermediate **343**, ensuring a reliable supply of the natural product **344**.

Evans and Starr also identified a Diels–Alder cascade as a potential route to (−)-FR182877 (**344**).[189] They prepared a similar precursor, **345**, which underwent oxidation to **346** and the transannular Diels–Alder cascade in an efficient one-pot procedure (Scheme 47b). Their advanced cascade product **347** was formed as a single diastereoisomer in good yield. As both groups of researchers had observed poor selectivity in intramolecular Diels–Alder reactions of related substrates, Evans and Starr calculated the effect of the macrocycle on the selectivity of the cascade sequence. They found that the C6-C7-C8 stereotriad alone had little effect on the facial selectivity of the cycloaddition, even within a macrocyclic environment, due to its local symmetry. However, including either of the C18 or C19 stereocenters in the calculations led to a preference for the desired selectivity. The reinforcing effect of having both stereocenters present was shown to be responsible for the excellent selectivity observed in the initial transannular cycloaddition, further emphasizing the ability of a macrocyclic framework to transmit stereochemical control from seemingly remote stereocenters.

Highlighting the various syntheses of (−)-colombiasin A (**350**, Scheme 48–Scheme 50) serves to illustrate a compendium of pericyclic cascade processes. As shown in Scheme 48b, the final stages in the biosynthesis of **350** have been proposed to involve the stepwise formation of the bridged bicyclic system from bicyclic compound **348** through initial C1–C9 cyclization to give elisabethin A (**349**) followed by subsequent C2−C12 bond formation.[190] The concomitant isolation of **348**,[191] **349**,[192,193] and **350**,[190] all produced from the same organism (*Pseudopterogorgia elisabethae*), lends credence to this hypothesis (although, of course, not constituting definitive proof for it).



Scheme 48. a) Diene formation/Diels–Alder reactions in the synthesis of (−)-colombiasin A (**350**; Nicolaou et al., 2001; Jacobsen et al., 2005).[194,195] b) Proposed biosynthesis of elisabethin A (**349**) and (−)-colombiasin A (**350**) from bicyclic compound **348**.

Jacobsen and co-workers were keen to investigate a more direct method for the formation of the C1−C9 and C2−C12 bonds from a precursor such as **348**, and to this end they prepared advanced intermediate **352** (Scheme 48a). Heating a mixture of this material and $MgSO_4$ in benzene to reflux initiated a tandem dehydration/*endo*-intramolecular Diels–Alder reaction (**352**→**353**→**354**) to assemble the tetracyclic framework of the target natural product in 77% yield. Barton–McCombie reduction of the xanthate ester group to the corresponding alkane (nBu$_3$SnH/cat. AIBN) followed by demethylation of the C16 hydroxy group ($AlCl_3$, $PhNMe_2$) then completed the concise total synthesis of (−)-colombiasin A (**350**).[194] A related intramolecular Diels–Alder cascade approach had previously been employed by Nicolaou et al. in their approach to the same target.[195] In this case, the in situ generation of diene **353** was achieved through the cheletropic extrusion of SO_2 from sulfone **355**.[196] Note that the initial masking of the sensitive diene as the corresponding sulfone

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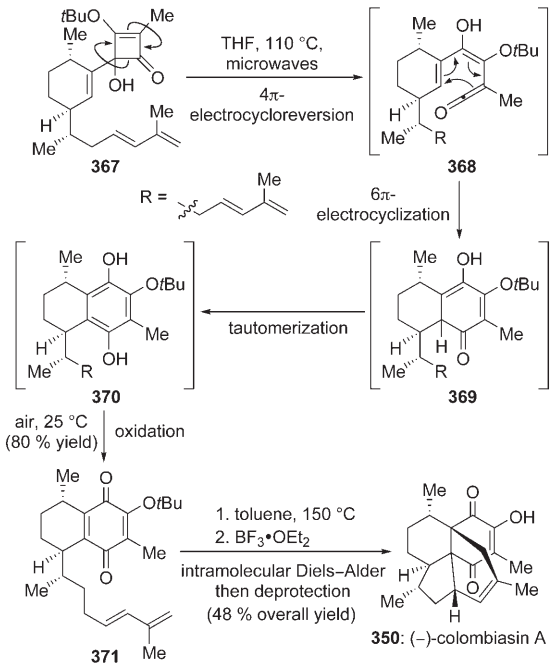
was essential in order to enable the generation of the quinone portion of the cascade precursor **355**.

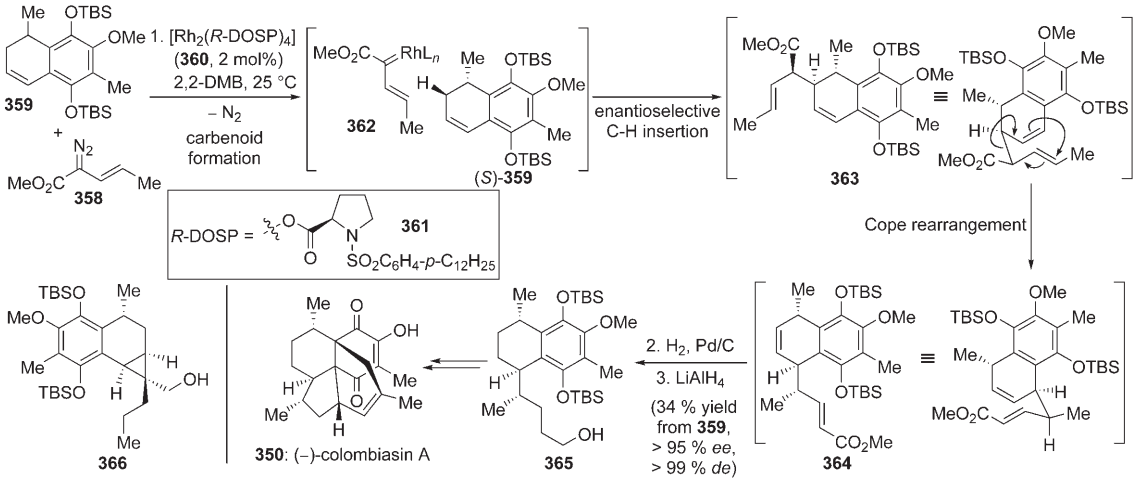
The most recently reported total synthesis of (−)-colombiasin A (**350**) came from Davies et al., who deployed their combined C–H insertion/Cope rearrangement methodology[197] as one of the defining transformations.[198] Slow addition of methyl vinyl diazoacetate (**358**, 3.0 equiv) to a solution of racemic dihydronaphthalene **359** and chiral rhodium(II) catalyst **360** (2 mol%) in 2,2-dimethylbutane at room temperature triggered the sequence of events shown in Scheme 49. Initial rhodium carbenoid formation (**358**→**362**) was followed by enantioselective intermolecular C–H insertion to give β,γ-unsaturated ester **363** as a fleeting intermediate which, under the conditions of the reaction, underwent Cope ([3,3] sigmatropic) rearrangement to form **364** (presumably via the expected chairlike transition conformation shown). Isolation of the cascade product was postponed until after hydrogenation of both alkenes and reduction of the ester group to the corresponding primary alcohol to give **365** in 34% overall yield from dihydronaphthalene **359** and, perhaps more significantly, as a single diastereoisomer and with over 95% *ee*! Three new stereogenic centers were therefore formed in a single operation from achiral starting materials employing only 2 mol% of a chiral catalyst, which demonstrates the enormous potential of this C–H activation methodology. The C–H functionalization step (**359**→**363**) is particularly noteworthy as a result of the discrimination between the two enantiomers of dihydronaphthalene **359** by the chiral rhodium carbenoid **362**. Thus, while the (*S*)-dihydronaphthalene enantiomer undergoes the desired C–H insertion, the corresponding *R* enantiomer preferentially undergoes cyclopropanation to give **366** in 36% yield and with over 95% *ee* following hydrogenation and ester reduction. As such, the conversion of racemic **359** into enantiomerically enriched **364** can be regarded as a kinetic resolution.[199]

The syntheses of (−)-colombiasin A (**350**) by the groups of Nicolaou, Jacobsen, and Davies all began with the same quinone starting material, **351** (Scheme 48), onto which the remainder of the polycyclic architecture was cleverly appended. In another highly original approach, Harrowven et al. introduced the quinone ring at a late stage in the synthetic sequence through the domino process illustrated in Scheme 50.[200] Heating of a solution of squarate derivative



Scheme 50. Electrocyclization reactions in the synthesis of (−)-colombiasin A (**350**; Harrowven et al., 2005).[200]

367 in THF to 110°C under microwave irradiation[107] triggered a Moore rearrangement,[201] involving sequential 4π-electrocycloreversion (**367**→**368**), 6π-electrocyclization (**368**→**369**), and tautomerization (**369**→**370**) steps to deliver the fully substituted aromatic derivative **370** as a single regioisomer. Following the complete conversion of **367** into **370**, exposure of the crude reaction mixture to air resulted in facile oxidation to form quinone **371**, which was isolated in



Scheme 49. Enantioselective C–H insertion/Cope rearrangement cascade in the synthesis of (−)-colombiasin A (**350**; Davies et al., 2006).[198]

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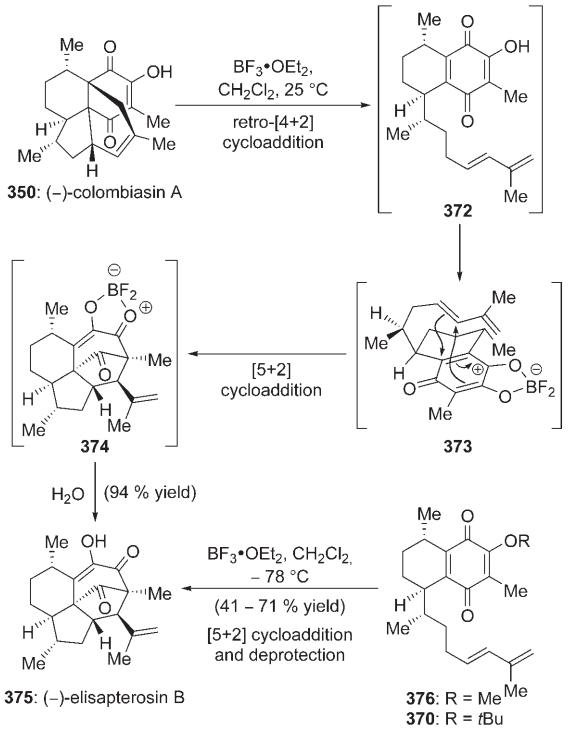
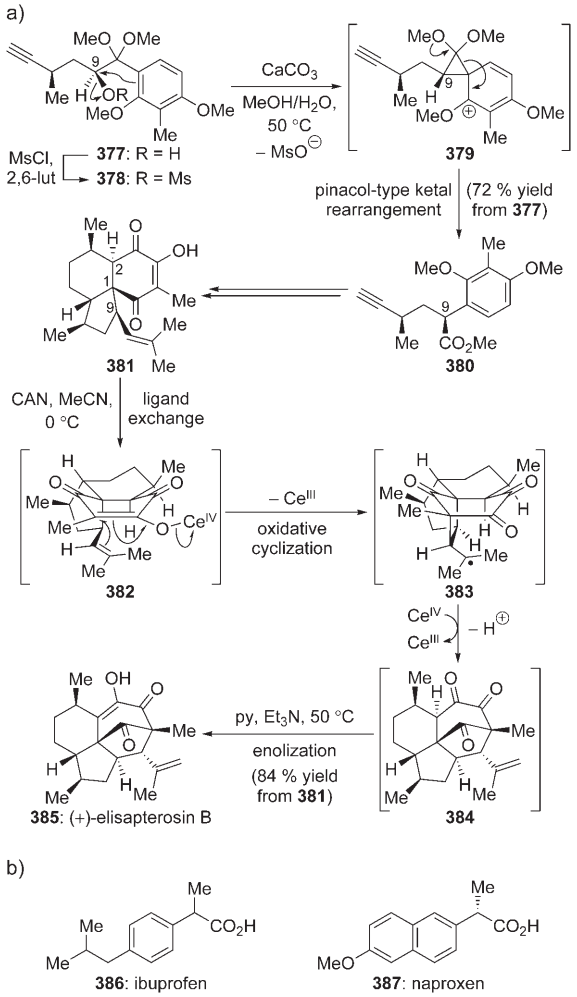
80% overall yield from cyclobutenone **367**. With **371** in hand, intramolecular Diels–Alder reaction followed by cleavage of the *tert*-butyl protecting group was all that was required to complete the total synthesis of this intriguing marine natural product.

The close structural relationships between various members of this family of marine-derived diterpenes was underscored by the conversion of (−)-colombiasin A (**350**) into (−)-elisapterosin B[202] (**375**, Scheme 51) reported by Jacobsen and co-workers.[194] One plausible mechanistic rationale for this transformation invokes a retro [4+2] cycloaddition to give quinone **372**, followed by Lewis acid catalyzed [5+2] cycloaddition[203] to generate the rearranged carbocyclic framework in a remarkable yield of 94%. Proof of the validity of the [5+2] cycloaddition step had already been provided in the pioneering total synthesis of (−)-elisapterosin B (**375**) by Rychnovsky and Kim,[204a] who converted quinone **376** into the natural product **375** in 41% yield by treatment with a large excess of $BF_3{\cdot}OEt_2$ (25 equiv) in CH_2Cl_2 at −78 °C. By analogy with Lewis acid catalysis of the Nazarov cyclization,[204b] Rychnovsky and Kim proposed that coordination of the boron species to the quinone generates a 4π-electron pentadienyl cation intermediate (e.g. **373**) which can undergo a thermally allowed cycloaddition with the pendant alkene. A similar protocol was subsequently applied by Harrowven and co-workers on the related *tert*-butyl ether **370**, to give (−)-elisapterosin B (**375**) in 71% yield.[200]



Scheme 51. Conversion of (−)-colombiasin A (**350**) into (−)-elisapterosin B (**374**) by a retro-Diels–Alder/[5+2] cycloaddition cascade (Jacobsen et al., 2005),[194] and formation of (−)-elisapterosin B from a quinone precursor (Rychnovsky and Kim, 2003; Harrowven et al., 2005; Davies et al., 2006).[198,200,204]

For the sake of completeness, we shall conclude our foray into the chemistry of gorgonian diterpene metabolites by highlighting the elegant biogenetically inspired synthesis of (+)-elisapterosin B (**385**, Scheme 52a) by Rawal and co-workers that features a conceptually different approach to formation of the bridged bicyclic system.[205] Treatment of tricyclic compound **381** (*ent*-2-*epi*-elisabethin A), in which the C1–C9 bond is already in place, with CAN in acetonitrile at 0 °C resulted in oxidative cyclization (possibly by the pathway shown)[206] to create the final ring junction and install the remaining two stereocenters, leading to the formation of triketone **384**. At this point, addition of pyridine and triethylamine to the reaction mixture, followed by gentle warming to 50 °C, resulted in enolization to give (+)-elisapterosin B (**385**, the enantiomer of the natural product) in 84% overall yield from **381**. A key step in the synthesis of tricyclic compound



Scheme 52. a) Pinacol-type rearrangement and oxidative cyclization cascades in the total synthesis of (+)-elisapterosin B (**385**; Rawal et al., 2003).[205] b) Structures of the nonsteroidal anti-inflammatory drugs ibuprofen (**386**) and naproxen (**387**).

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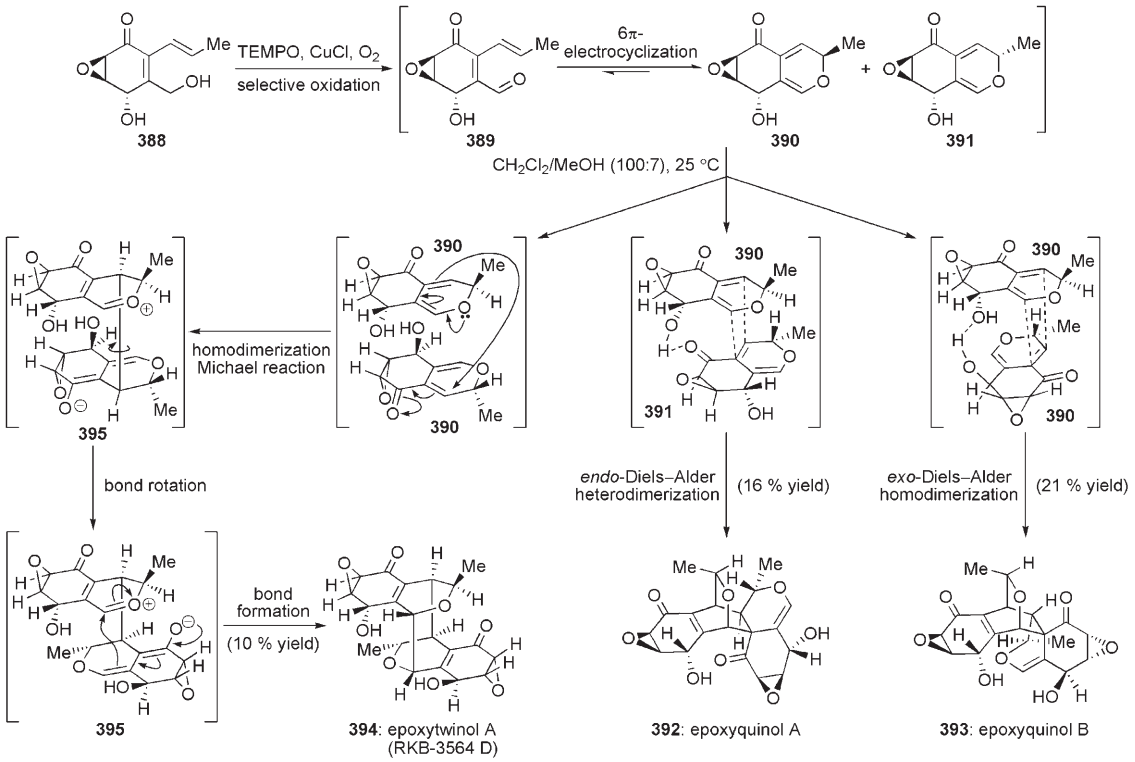
381 was the pinacol-type ketal rearrangement of mesylate **378** to give α-aryl ester **380**, involving migration of the electron-rich aryl ring (with inversion of stereochemistry at the C9 position) via bridged phenonium ion **379**. This type of rearrangement, initially developed by Tsuchihashi and co-workers,[207] provides a potentially useful stereocontrolled entry to the α-aryl alkanoic acid class of compounds, which includes the widely used nonsteroidal anti-inflammatory drugs ibuprofen (**386**) and naproxen (**387**) shown in Scheme 52b.[208]

As demonstrated by the syntheses of the endiandric acids (Scheme 3) and (−)-FR182877 (**344**, Scheme 47), the linking of sequential pericyclic processes into a single cascade can lead to rapid and dramatic increases in molecular complexity. Another example is provided by the novel anti-angiogenic fungal metabolites epoxyquinols A (**392**) and B (**393**, Scheme 53). These molecules have been proposed, by Osada and co-workers, to arise through oxidation of quinol **388** to give dienal **389**, followed by 6π-electrocyclization to give a mixture of diastereomeric 2*H*-pyrans **390** and **391** and subsequent intermolecular cycloaddition.[209] Epoxyquinol A (**392**) would be formed through an *endo*-Diels–Alder heterodimerization between one molecule of **390** and one molecule of **391**, while the formation of epoxyquinol B requires a [4+2] homodimerization between two molecules of **390** in an *exo* alignment. Interest in this class of compounds was heightened by the isolation, at a later date, of epoxytwinol A (**394**) from the same fungus.[210] This C_2-symmetric pentaketide dimer would arise from a formal [4+4] cycloaddition between two molecules of **390**.

The challenge of reducing these biosynthetic hypotheses to practice inspired a number of groups to tackle the total synthesis of these natural products. Hayashi and co-workers were the first to disclose their route to the epoxyquinols,[211] followed shortly thereafter by the groups of Porco,[212] Mehta,[213] and Kuwahara.[214,215] Each of these elegant syntheses featured a different route to the monomeric precursor **388**, but all then successfully employed the key oxidation/electrocyclization/Diels–Alder cascade.[216]

Studies by the groups of Hayashi[217] and Porco[218] also culminated in the enantioselective synthesis of epoxytwinol A (**394**). For the sake of brevity, however, we shall highlight only the results from Porco and co-workers, as summarized in Scheme 53 and Scheme 54. Selective oxidation of the primary hydroxy group in diol **388** using conditions developed by Semmelhack et al. (cat. TEMPO, cat. CuCl, 1 atm O_2, DMF, 25 °C)[219,220] provided a 9:1 equilibrium mixture of 2*H*-pyran epimers **390**/**391** and aldehyde **389**. Stirring this crude oxidation product mixture in CH_2Cl_2/MeOH (100:7) at room temperature triggered the various modes of dimerization, to give epoxyquinols A (**392**, 16% yield from **388**) and B (**393**, 21%) and epoxytwinol A (**394**, 10%). The fact that these oxidation/dimerization cascades occur spontaneously under ambient conditions suggest that they need not be enzyme-controlled.

Detailed mechanistic studies by Hayashi and co-workers indicate that the particular transition-state arrangements leading to epoxyquinols A (**392**) and B (**393**) are favored not only by approach of the larger methyl substituents *anti* to one another, but are also stabilized by intermolecular hydro-



Scheme 53. Pericyclic and Michael reaction cascades in the total synthesis of epoxyquinols A (**392**) and B (**393**) and epoxytwinol A (**394**; Hayashi et al., 2002; Porco et al., 2002).[211,212,218]

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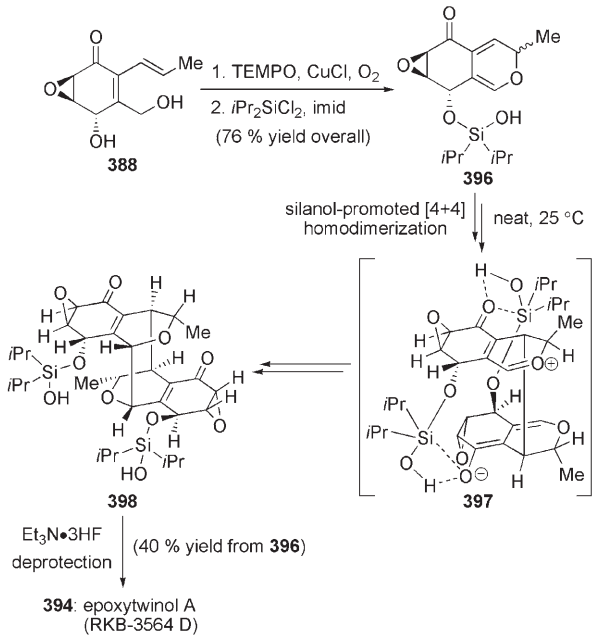
gen-bonding interactions as shown.[221] The [4+2] homodimerization of two molecules of 2*H*-pyran epimer **391** is apparently very unfavorable, and was not observed by Porco and co-workers.[222]

Of particular interest is the dimerization pathway leading to epoxytwinol A (**394**). [4+4] Cycloaddition reactions are electronically forbidden processes under thermal conditions and are generally conducted under photochemical irradiation[223] or with transition-metal catalysts.[224,225] A stepwise, ionic mechanism for the formation of epoxytwinol A (**394**) has therefore been invoked.[218] Intermolecular Michael reaction between two molecules of **390** initially gives zwitterionic intermediate **395**, which then undergoes rotation about the newly formed carbon–carbon bond to enable subsequent ring closure of the dienolate species onto the oxonium ion.

Whilst the cascades described above provided a concise approach to the target natural products (**392**, **393**, and **394**), Porco and co-workers were still interested in developing reaction conditions which would favor [4+4] cycloaddition over the predominant [4+2] Diels–Alder pathways. As shown in Scheme 54, it was found that the use of an alkoxysilanol



Scheme 54. Silanol-promoted formal [4+4] dimerization reaction for the selective formation of epoxytwinol A (**394**; Li and Porco, 2004).[226]

protecting group on the secondary alcohol redirected the inherently favored [4+2] dimerization pathway to a [4+4] manifold to exclusively generate the epoxytwinol molecular architecture in respectable overall yield.[226] The reasons behind the choice of a seemingly rather exotic silanol protecting group[227,228] are twofold: 1) the Diels–Alder reactions to form **392** or **393** (Scheme 53) place the hydroxy group(s) in more sterically encumbered positions than required in the corresponding [4+4] pathway, thus bulky protecting groups might be expected to discourage the [4+2] cycloadditions, and 2) formation of a templated intermediate such as **397** (Scheme 54), which is stabilized by both hydrogen bonding and interaction of the oxygen anion and carbonyl oxygen center with the electropositive silicon atoms, could facilitate the initial Michael addition in the [4+4] pathway. Whatever the precise mechanistic basis, this innovative use of a silanol as a directing group provided an elegant solution to the problem at hand.

The total syntheses of the immunosuppressant agents SNF4435 C (**399**) and D (**400**, Scheme 55), reported independently by the groups of Parker,[229] Baldwin,[230] and Trauner,[231] represent an "endiandric acid cascade" for the 21st century.[232] By analogy with the endiandric acids, the bicyclo[4.2.0]octadiene core of SNF4435 C (**399**) and D (**400**) would be derived from sequential 8π-conrotatory and 6π-disrotatory electrocyclizations of the appropriately configured tetraene precursor **401**.[233] In comparing the three total syntheses, one of the most striking observations is their common reliance on palladium-catalyzed cross-coupling reactions to assemble the tetraene backbone. These processes compare favorably with the more laborious preparation of the endiandric acid cascade precursor **13** (Scheme 3) more than twenty years earlier (when such cross-couplings were still a nascent technology) through a classical Glaser acetylene coupling[234,235] followed by several further manipulations (a route which in any case would not be amenable to the production of methyl-substituted derivatives of tetraene systems such as **13**).

Parker and Lim effected the Stille coupling of vinyl iodide **402** with stannane **403** to furnish the putative tetraene intermediate **401**, which, under the conditions of the reaction, spontaneously underwent the electrocyclization cascade to afford a 3.8:1 mixture of SNF3345 C (**399**) and D (**400**). Trauner and Beaudry subsequently coupled the complementary reaction partners **404** and **405** under modified Stille conditions[236] to provide the target products (**399** and **400**) in an improved overall yield. Baldwin and co-workers extended the proposed biosynthesis of SNF back a further step by speculating that the *Z*,*Z*,*Z*,*E*-tetraene **401** arises from isomerization of the corresponding *Z*,*E*,*E*,*E*-configured precursor **406**,[237] itself a natural product (named spectinabilin) isolated from the same actinomycete strain (*Streptomyces spectabilis*).[238] To their delight, they found that this extended cascade (**406**→**401**→**399** + **400**) could indeed be triggered by heating a solution of synthetic spectinabilin **406** (prepared through Suzuki coupling of **407** and **408** followed by a Negishi coupling to install the remaining vinyl methyl group) in DMF at 70 °C. The modest overall yield for this isomerization/electrocyclization cascade is counterbalanced by the more straightforward synthesis of the key cross-coupling fragments **407** and **408**, compared to that of **402** and **403** or **404** and **405**.

The ratio of synthetic SNF4435 C (**399**) and D (**400**) formed in these cascades (3.0–3.8:1.0) closely parallels that of the compounds found in nature.[239] The origin of this diastereoselectivity lies in the conrotatory 8π-electrocyclization of tetraene **401**, which can proceed through either of the helical transition states **410** or **412**;[240,241] the former is evidently favored to a degree, because in this arrangement the bulky pyrone substituent is orientated away from the interior of the helix. Related 8π-/6π-electrocyclization

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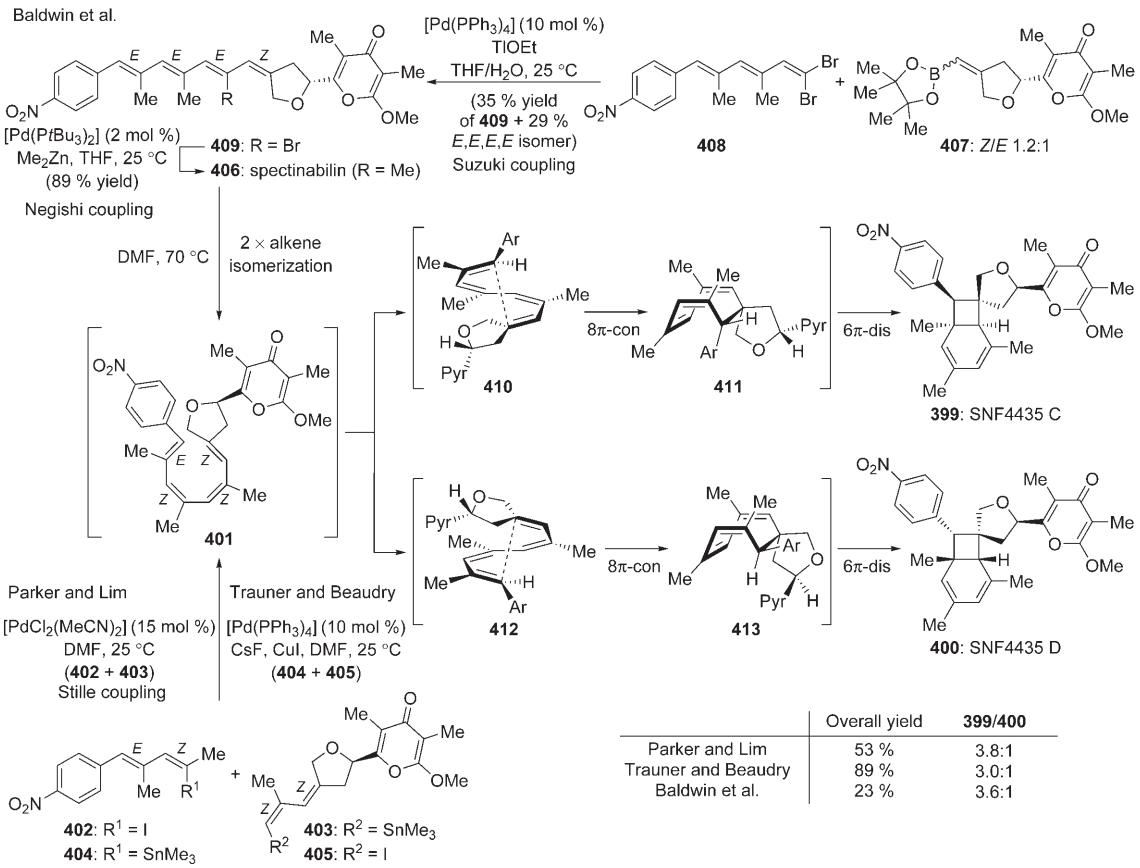

	Overall yield	399/400
Parker and Lim	53 %	3.8:1
Trauner and Beaudry	89 %	3.0:1
Baldwin et al.	23 %	3.6:1

Scheme 55. Total syntheses of SNF4435 C (**399**) and D (**400**) through electrocyclization cascades (Parker and Lim, 2004; Baldwin et al., 2005; Trauner et al., 2005).[229–231]

domino processes have been applied in the total syntheses of several other structurally intriguing natural products.[242–244]

Further proof, if any were needed, of the value of biomimetically inspired synthetic strategies towards natural products is provided by the total syntheses of 1-*O*-methylforbesione (**418**, Scheme 56) reported by Nicolaou and Li[245] and by Theodorakis and co-workers.[246] Heating a solution of readily available xanthone derivative **414** in DMF to 120 °C initiated the Claisen rearrangement/Diels–Alder/Claisen rearrangement cascade, illustrated in Scheme 56 a, to form four new stereogenic centers and two new rings to directly provide the target natural product (**418**) in 51–63 % yield. Most of the mass balance of this reaction comprised the regioisomeric polycyclic structure **419**, which results from the initial [3,3]-sigmatropic rearrangement of the C5, as opposed to C6, allyloxy group, followed by the corresponding intramolecular Diels–Alder reaction. Claisen rearrangement of the C3 allyloxy group was site-selective, with migration occurring exclusively towards the C4 terminus. Circumstantial evidence provided by both groups justifies the sequence of events being as depicted in Scheme 56 a, in which the Claisen/Diels–Alder cascade of ring C precedes the Claisen rearrangement of ring A. This biomimetic route to the 4-oxatricyclo[4.3.1.0]decan-2-one system, first proposed by Quillinan and Scheinmann in 1971,[247] provides access to this formidable cagelike structure with an unrivalled elegance and efficiency, and has found use in the synthesis of the related compounds gambogin[248] (**420**) and 1-*O*-methyllateriflorone (**421**, Scheme 56 b).[249]

The aza-Cope rearrangement/Mannich reaction cascade provides a useful access to 3-acylpyrrolidine systems (Scheme 57 a), which are a common substructure of a diverse collection of alkaloids.[250] Overman and co-workers employed this process in their recent synthesis of the *Stemona* alkaloids didehydrostemofoline (**429**) and isodidehydrostemofoline (**430**, Scheme 57 b).[251,252] Identification of an aza-Cope/Mannich cascade as a key operation en route to the rather unusual polycyclic framework of the target compounds **429** and **430** is aided by their retrosynthetic simplification to common precursor **428**, in which a 3-acylpyrrolidine motif is more clearly visible as part of the tricyclic skeleton. Despite being itself a formidable synthetic target, ketone **428** could be prepared in a single operation from the more readily available bicyclic compound **425**. Treatment of compound **425** with an excess of paraformaldehyde in toluene/MeCN (3:1) at 80 °C led to the initial formation of iminium ion **426**, which then underwent a (reversible) charge-accelerated [3,3]-sigmatropic arrangement[253] to afford enol **427**, with a subsequent irreversible and highly exothermic intramolecular Mannich reaction terminating the sequence. This cascade proceeded in a remarkable overall yield of 94 %, with the stereochemical information in bicyclic precursor **425** being transferred with high fidelity to the more structurally complex rearranged product **428**. Overman and co-workers have been instrumen-

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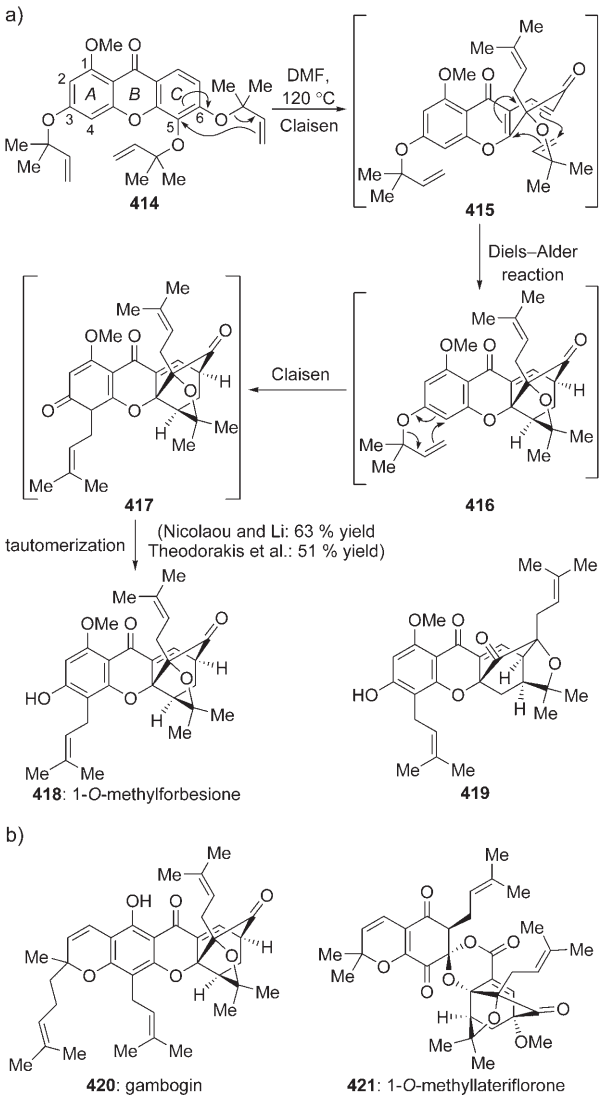
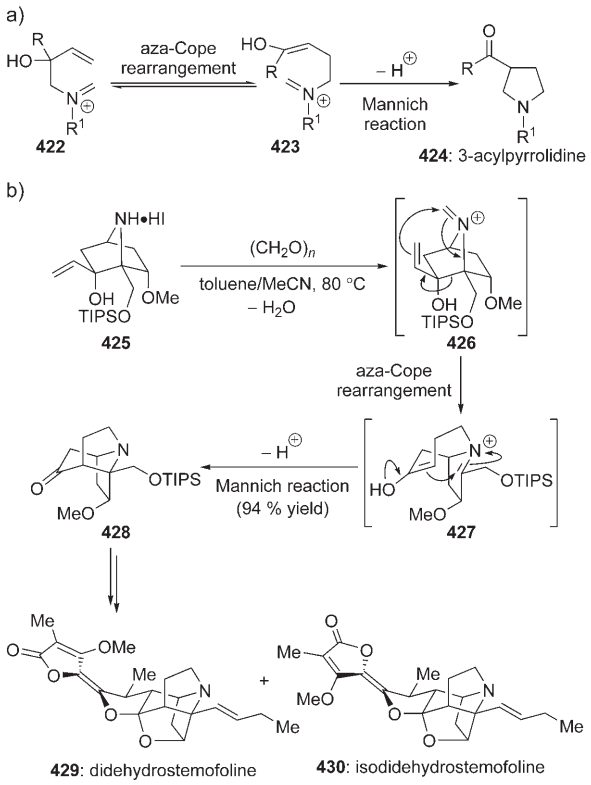


Scheme 56. a) A Claisen/Diels–Alder/Claisen cascade in the total synthesis of 1-*O*-methylforbesione (**418**; Nicolaou and Li, 2001; Theodorakis et al., 2004).[245,246] b) Structures of gambogin (**420**) and 1-*O*-methyllateriflorone (**421**).



Scheme 57. The aza-Cope/Mannich cascade approach to 3-acylpyrrolidine structures: a) general principles and b) application to the total synthesis of didehydrostemofoline (**429**) and isodidehydrostemofoline (**430**; Overman et al., 2003).[251]

tal in the design and development of the aza-Cope/Mannich cascade[254] and have demonstrated the utility of this methodology in the synthesis of a number of other structurally complex targets, including strychnine,[255] dehydrotubifoline,[256] and 16-methoxytabersonine.[257]

6. Transition-Metal-Catalyzed Cascades

The development of new transition-metal-catalyzed reactions is one of the most vibrant areas of chemical research, and one which is likely to become increasingly important in years to come.[258] Together with organocatalytic reactions[259] and enzymatic processes,[260] transition-metal-mediated reactions offer the potential for generating molecular complexity, and often in an enantioselective fashion, by employing only catalytic amounts of mediators. In doing so, they also meet many of the well-rehearsed criteria required to be labeled "atom-economical transformations".[2] Additionally, whilst many of the cascades described so far have been predicated on the use of biomimetic strategies, transition-metal-catalyzed processes provide synthetic chemists with tools for bond construction for which there are no direct parallels in nature. An enormous variety of transition-metal-mediated cascades have been developed in recent years, but our self-imposed restriction to applications in total synthesis will limit our discussion here to exemplars of just some of the more widely used processes.

It would certainly be hard to overstate the impact that the development of palladium-catalyzed cross-coupling reactions has had on synthetic organic chemistry. Within the last 25 years, these processes have blossomed into extraordinarily powerful tools for carbon–carbon and carbon–heteroatom bond formation, and research in this field continues apace.[261] A wide variety of highly inventive palladium-catalyzed cascades have been applied in total synthesis, but we shall limit our discussion here to just a few instructive examples. For more details on this topic, the reader is directed to several more specific reviews.[262]

Amongst the palladium-catalyzed carbon–carbon bond-forming reactions, the Heck reaction[263] has undoubtedly found the most applications in cascade processes. In particular, the utility of the intramolecular Heck reaction for the generation of tertiary or quaternary stereocenters (in both a

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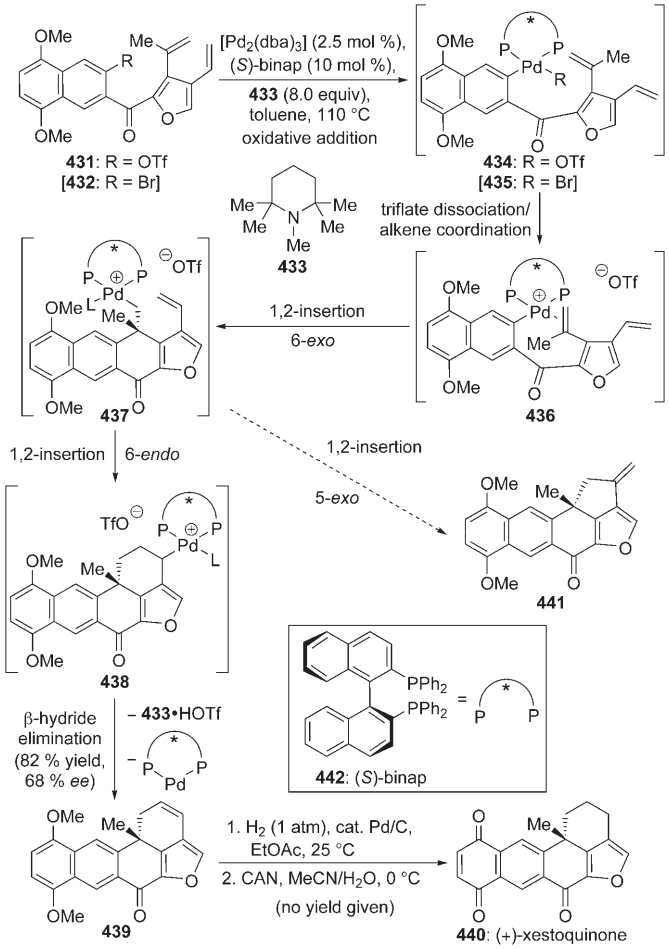
diastereo- and enantioselective fashion) and multiple-ring systems, even in sterically crowded environments, has been well documented.[264] Keay and co-workers employed an asymmetric polyene Heck cyclization in their enantioselective synthesis of (+)-xestoquinone[265] (**440**, Scheme 58), in which



Scheme 58. Use of a catalytic asymmetric Heck polyene cyclization in the total synthesis of (+)-xestoquinone (**440**; Keay et al., 1996).[266]

achiral aryl triflate **431** was converted in a single step into pentacyclic compound **439** under the conditions shown.[266,267] Although the enantioselectivity of this reaction was not optimal, the conversion of **431** into **439** nevertheless provided an elegant solution to both the problems of generation of the imposing polycyclic ring structure and the installation of the isolated all-carbon quaternary stereocenter. This polyene cyclization was originally attempted using aryl bromide **432**, which led to the formation of **439** with poor enantioselectivity (13% *ee* or less). Identification of the corresponding aryl triflate **431** as the optimal substrate for this reaction followed from insights provided by Hayashi and co-workers[268] and Cabri et al.[269] on the mechanism of Heck reactions of aryl triflates employing diphosphine ligands.[270] As shown in Scheme 58, oxidative addition of a Pd^0 species into aryl triflate **431** initially generates Pd^{II} complex **434**. Owing to the kinetic lability of the Pd–OTf bond, dissociation of the triflate counterion followed by alkene π coordination then yields cationic complex **436**. That the chiral binap ligand **442** remains anchored to the metal center through both the alkene coordination event and subsequent 1,2-insertion step to generate σ-alkylpalladium(II) intermediate **437** ensures a higher level of enantioselectivity. Once formed, intermediate **437** can then undergo another migratory insertion reaction (**437**→**438**) followed by β-hydride elimination to deliver pentacyclic compound **439** and regenerate the Pd^0 catalyst. Formation of the 5-*exo* product **441** during the second 1,2-insertion is apparently disfavored by the greater strain energy of the resulting ring system, to the extent that the 6-*endo* mode of ring closure predominates. In contrast, reaction of aryl bromide **432** presumably requires partial dissociation of the diphosphine ligand from the palladium center in the corresponding oxidative addition complex **435**, due to the lower lability of the Pd–Br bond, in order to generate a vacant coordination site for the pendant alkene. This can lead to the substantially diminished enantioselectivity observed experimentally.[271–273]

The Stille reaction has become a well-established method for effecting both intermolecular fragment couplings and intramolecular cyclizations of highly functionalized substrates under mild conditions.[274] The combination of these two processes into a single operation results in a Stille "stitching cyclization" cascade for the generation of macrocyclic structures. Pioneered by Nicolaou et al. in the total synthesis of rapamycin,[275] a more recent application of the stitching cyclization cascade can be found in the synthetic route to the novel ansamycin antibiotic mycotrienin I[276] (**447**, Scheme 59a) developed by Panek and co-workers.[277] Having overcome a number of unanticipated synthetic hurdles en route to bis-*E*,*E*-vinyl iodide **443**, the team was gratified to find that the most daring step in the whole sequence was to proceed with remarkable efficiency. Thus, sequential addition of bis-iodide **443**, enedistannane **444**[278] (1.2 equiv), and iPr_2NEt (1.5 equiv) to a solution of [$PdCl_2$-$(MeCN)_2$] (20 mol%) in DMF/THF (1:1) at room temperature led to the formation of macrocyclic triene **445** over the course of 24 h. Treatment of macrocycle **445** with TsOH in MeOH then resulted in the selective cleavage of the C11 TIPS protecting group (an outcome anticipated by the authors on the basis of earlier model studies, and a maneuver which would subsequently allow for the installation of the amino acid derived side chain on the correct hydroxy group) to give alcohol **446** in 90% overall yield from bis-iodide **443**. The crucial stitching cyclization therefore served to incorporate the missing C6–C7 unit, generate the complete macrocyclic structure, and form the C4–C9 triene with the required *E*,*E*,*E* geometry, all in a single operation![279]

A conceptually similar stitching cyclization cascade had been employed by Smith et al. two years earlier in their approach to the structurally related trienomycin family of metabolites,[280,281] in this case employing Wittig reactions as the key carbon–carbon bond-forming processes. As shown in Scheme 59b for the synthesis of (+)-trienomycin A (**451**), bis-olefination of dialdehyde **448** with phosphonium salt **449**[282] provided the macrocyclic *E*,*E*,*E*-triene in 21% yield, accompanied by a mixture of other triene isomers in a combined

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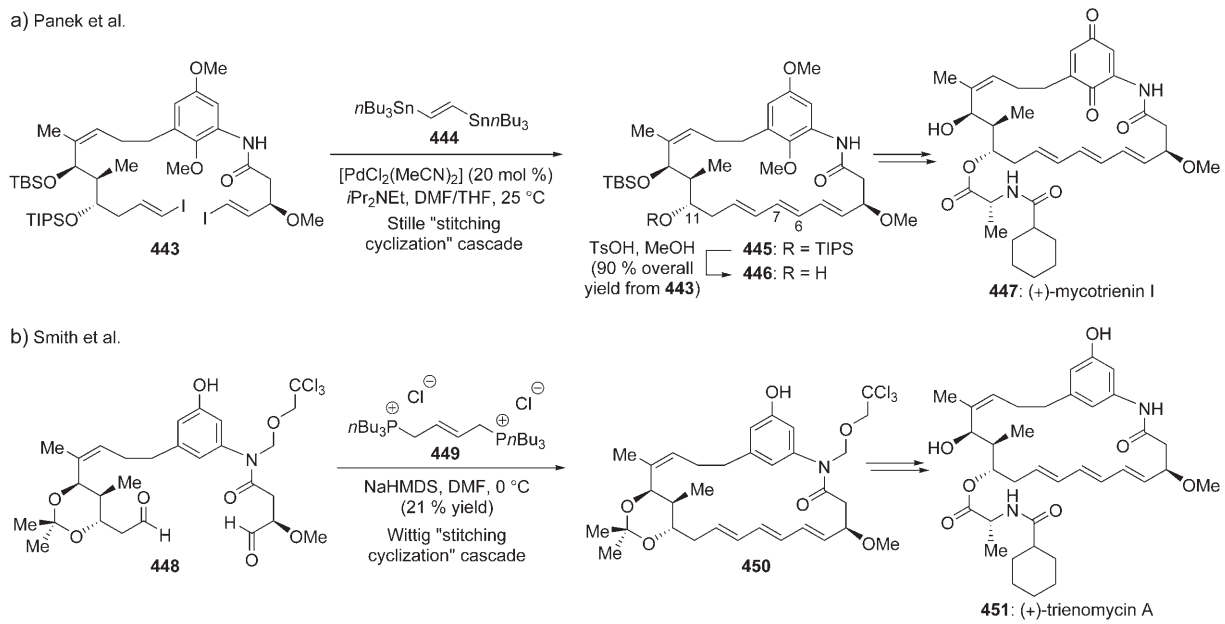
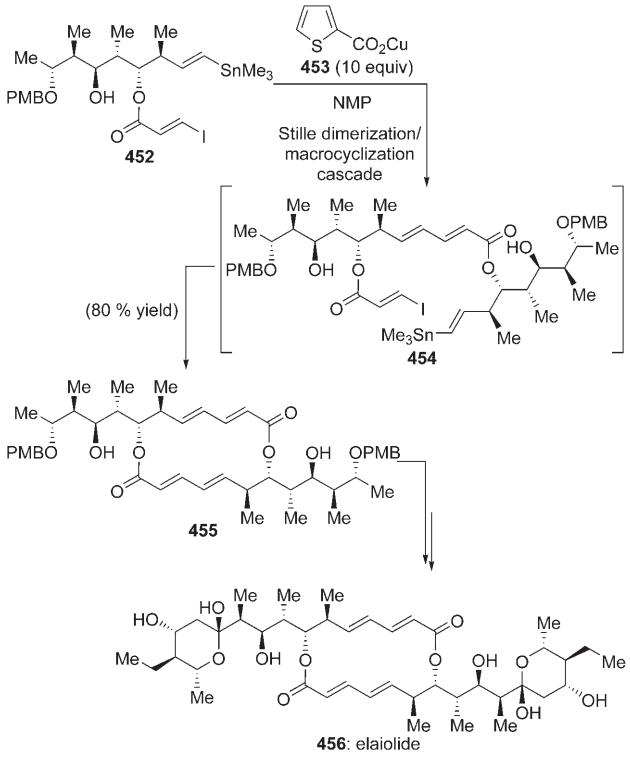


Scheme 59. a) A Stille "stitching cyclization" cascade in the total synthesis of (+)-mycotrienin I (**447**; Panek et al., 1998).[277] b) A Wittig "stitching cyclization" cascade approach to (+)-trienomycin A (**451**; Smith et al., 1996).[280]

yield of 34%. This case illustrates one potential advantage of cross-coupling reactions for the synthesis of polyene systems over more traditional olefination procedures, namely the (generally) reliable and predictable formation of alkene systems of well-defined geometry.

An alternative Stille-based cascade approach to macrocyclic structures, pioneered by Baldwin et al. in 1992[283] and exemplified by the synthesis of elaiolide (**456**, Scheme 60) by Paterson et al., involves the one-pot cyclodimerization of an α-iodo-ω-stannane monomeric precursor.[284] As illustrated in Scheme 60, treatment of ester **452** with copper(I) thiophene-2-carboxylate (10 equiv) in NMP (Liebeskind "palladium-free" Stille coupling conditions)[285,286] led to the formation of the 16-membered C_2-symmetric macrolide **455** in an impressive 80% yield. Note that the reaction proceeded to completion within 15 minutes at room temperature with no trace of the presumed intermediate **454** being isolated. Geometric constraints preclude intramolecular cyclization of precursor **452**, while intramolecular cyclization of the open-chain dimerization intermediate **454** is evidently faster than competing oligomerization processes, at least at the particular concentration used.[287] This one-step cyclodimerization approach to macrolides offers an appealing alternative to conventional esterification/macrolactonization strategies.[288]

One of the most widespread and versatile uses of palladium in organic synthesis is in the generation of heterocyclic ring systems.[289] Flynn and co-workers reported an interesting palladium-catalyzed multicomponent coupling approach to benzo[*b*]furan structures,[290,291] and subsequently applied this methodology to the synthesis of the norsesquiterpenoid frondosin B (**467**, Scheme 61).[292] This well-orchestrated sequence of events began with the treatment of a mixture of readily available *ortho*-bromophenol **457** and alkyne **458** with MeMgBr (2.1 equiv) in THF, leading to the initial formation of the corresponding magnesium phenolate **459** and magnesium acetylide **460**, respectively. Subsequent addition of $[PdCl_2(PPh_3)_2]$ (5 mol%) and heating to 65°C triggered a Kumada cross-coupling reaction[293,294] to give *ortho*-alkynylphenolate intermediate **461**. At this point, dilution of the reaction mixture with DMSO, addition of vinyl bromide **462**, and further heating to 80°C promoted the



Scheme 60. A "palladium-free" Stille dimerization/macrocyclization approach to the synthesis of elaiolide (**456**; Paterson et al., 1999).[284]

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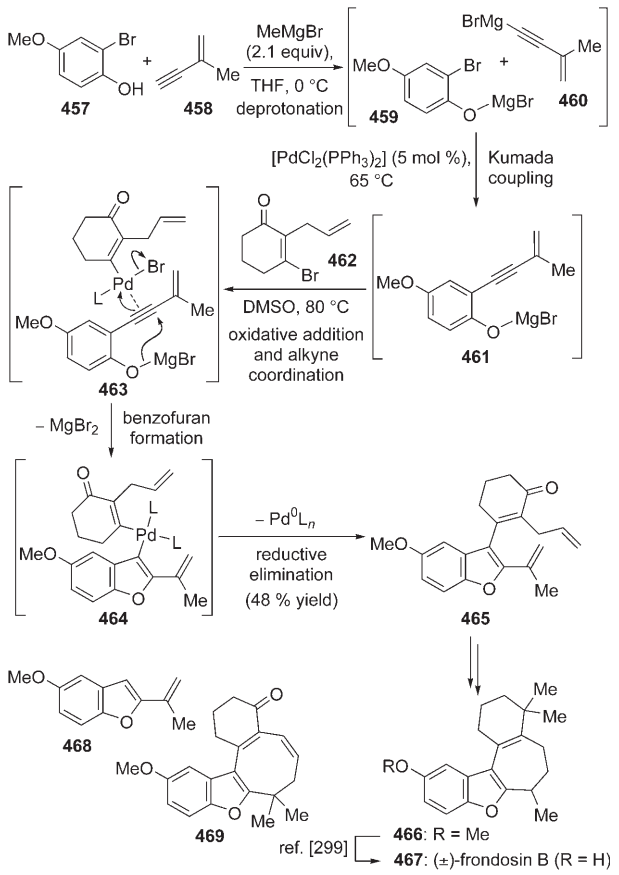
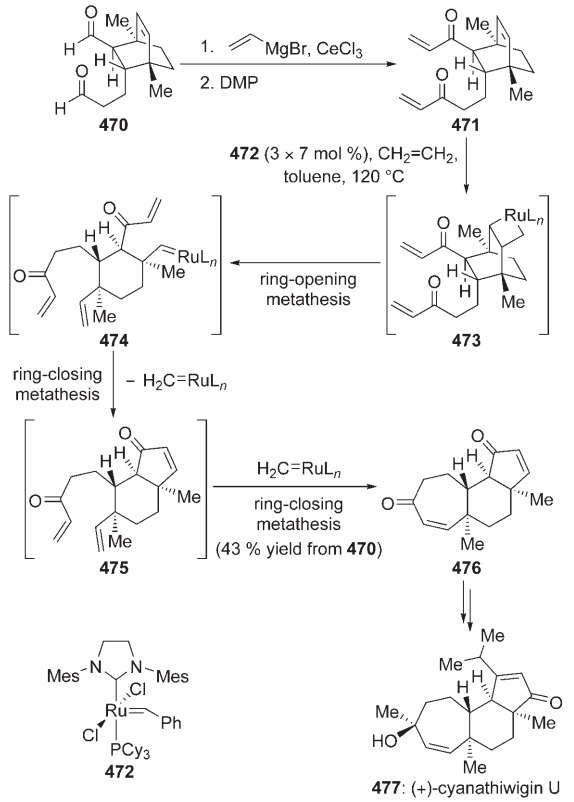


Scheme 61. A palladium-catalyzed multicomponent coupling approach to benzo[*b*]furan structures in the synthesis of (±)-frondosin B (**467**; Flynn et al., 2004).[292]

heteroannulation cascade, via the presumed intermediacy of species **463** and **464**, to afford the 2,3-disubstituted benzo[*b*]-furan product **465** in 48% overall yield.[295–297] Minor by-products concomitantly formed in this reaction were the protocyclized material **468** (12% yield) and tetracyclic compound **469** (11% yield); whilst the former would derive from the direct cyclization of *ortho*-alkynylphenolate intermediate **461**, the latter was speculated to arise from cascade product **465** by a further sequence consisting of an antarafacial 1,7-hydrogen shift followed by conrotatory 8π-electrocyclization.[298] Despite these competing side reactions, the multicomponent coupling cascade enabled the preparation of tricyclic compound **465** in just two steps from commercially available starting materials, with only a further three operations required to reach the complete framework of frondosin B (**467**), as represented by the phenolic methyl ether **466**. Deprotection of **466** to give the target natural product **467** had previously been reported by Danishefsky and co-workers[299] and by Trauner and Hughes[300] in their respective total syntheses.

Over the last 15 years, metathesis-based reactions have made the transition from emerging methodologies to established synthetic techniques in the research laboratory, although, as with palladium-catalyzed cross-couplings, the field is still far from maturity.[301] The ring-opening metathesis polymerization of cyclic olefins, a well-established method for the industrial production of a variety of polymers, can in a sense be viewed as the pinnacle of metathesis-based cascades.[302] In the context of total synthesis, however, a number of elegant cascades triggered by the initial ring-opening metathesis of a strained ring system have also been developed. Selected examples include ring-opening metathesis/sigmatropic rearrangement processes,[303] ring-opening/cross-metathesis cascades,[304–306] and, in particular, ring-opening/ring-closing metathesis ("ring-rearrangement metathesis") strategies.[307] In their recent synthesis of (+)-cyanthiwigin U (**477**, Scheme 62), Phillips and Pfeiffer employed an elegant



Scheme 62. Total synthesis of (+)-cyanathiwigin U (**477**) via a two-directional ring-opening/ring-closing olefin-metathesis cascade (Pfeiffer and Phillips, 2005).[308]

two-directional ring-opening metathesis/ring-closing metathesis tandem reaction to fashion the tricyclic core structure of the targeted natural product.[308] A chiral-auxiliary-mediated asymmetric Diels–Alder reaction[309] was used to construct bicyclic dialdehyde **470** in enantiopure form, treatment of which with vinylmagnesium bromide and subsequent Dess–Martin oxidation gave bis-enone **471**. Exposure of **471** to ruthenium carbene **472**[310] in refluxing toluene under an atmosphere of ethylene[311] led to the desired rearrangement, giving tricyclic compound **476** in 43% overall yield from dialdehyde **470**. Tricyclic product **476** has the correct relative and absolute stereochemistry at the four contiguous stereogenic centers around the crowded cyclohexane ring required to complete the total synthesis, which was then achieved in only five further steps. There are several possible mechanistic scenarios for the conversion of **471** into **476**, of which only one

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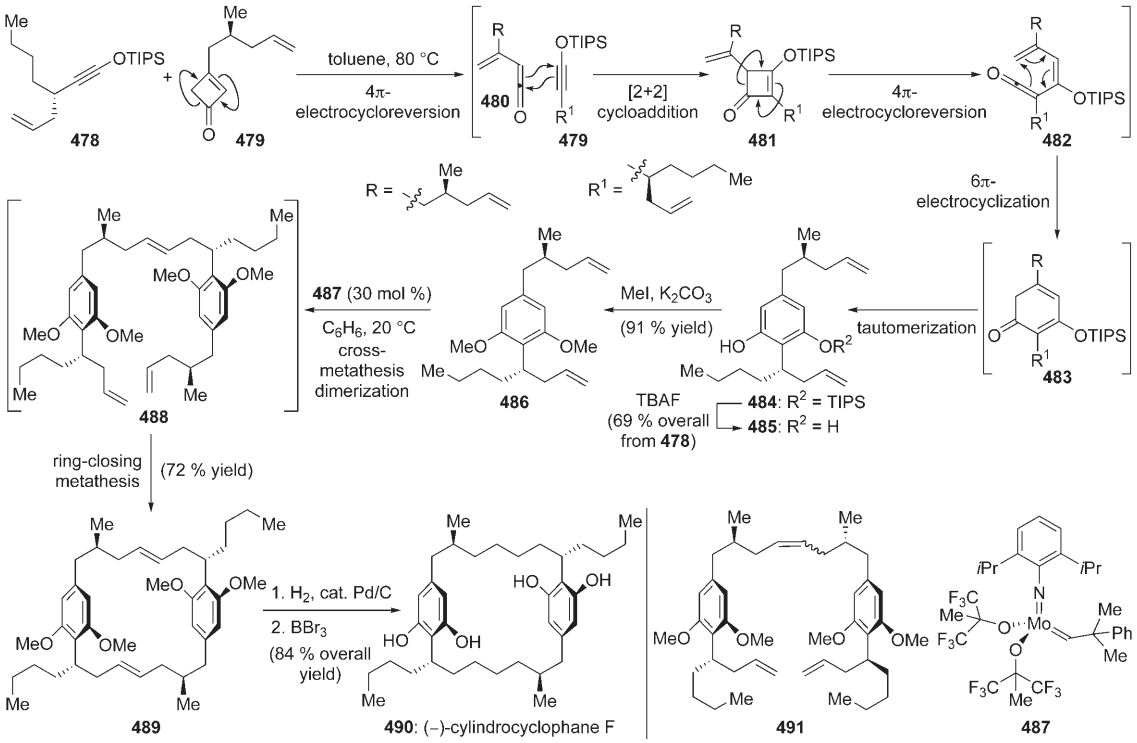
is illustrated in Scheme 62. Note that all the steps in the catalytic cycle are, in principle, reversible, but this reaction benefits from a powerful thermodynamic driving force with favorable contributions from both enthalpic (release of ring strain) and entropic (release of ethylene) terms. This example is illustrative of a key enabling ability of ring-rearrangement metathesis, namely the transfer of easily installed stereochemical information on a precursor molecule (in this case **471**) to a polycyclic product (**476**) in which such chiral information would be difficult to encode with equal facility.

Cascade reactions figure prominently in the masterful synthesis of (−)-cylindrocyclophane F (**490**, Scheme 63) reported by Smith et al. in 2000.[312,313] Having already synthesized this target through conventional stepwise approaches,[314] they turned to the far more challenging, but inherently more tantalizing, prospect of effecting the synthesis of the [7,7]-paracyclophane core structure through olefin-metathesis dimerization. Specifically, cross-metathesis between two molecules of functionalized rescorcinol monomer **486**, in a head-to-tail fashion, followed by a ring-closing metathesis event could afford the complete [7,7]-cyclophane skeleton, as represented by **489**, in a single operation. Monomeric precursor **486** was prepared by the thermal combination of silyloxyacetylene **478** and cyclobutenone **479** to give phenol **484**, followed by routine protecting-group adjustments. This initial annulation reaction, first developed by Danheiser et al.,[315] presents a convenient regiocontrolled approach to highly substituted aromatic compounds,[316] and proceeds through a cascade of four pericyclic reactions, as illustrated in Scheme 63.[317] To their delight, Smith et al. found that treatment of a solution of precursor **486** in benzene with the Schrock molybdenum carbene **487**[318] (30 mol%) cleanly generated the desired 22-membered macrocyclic compound **489** within two hours at 20°C in 72% yield and as a single *E*,*E* isomer. The same transformation could also be effected by using the Grubbs second-generation carbene **472** (15 mol% catalyst, benzene, 40°C, 27 h, 58% yield). Two further steps then completed the total synthesis of (−)-cylindrocyclophane F (**490**). To rationalize this remarkable metathesis cascade, the researchers performed molecular modeling calculations, which revealed that the observed product **489** was the thermodynamically most stable entity amongst the possible seven cyclic dimers of **486** (including head-to-head [8,6]-cyclophanes and *Z*-configured isomers). This suggested that the dimerization/macrocyclization of **486** actually proceeds through a cascade of reversible olefin metatheses,[319] which drives the reaction towards formation of the thermodynamically most stable product, *E*,*E*-[7,7]-paracyclophane **489**. Lending weight to this rationale was the observation that either the *E* or *Z* isomer of the tail-to-tail dimer **491** could be employed as a metathesis substrate, giving only the *E*,*E*-[7,7]-paracyclophane head-to-tail product **489**. This second-generation metathesis-based approach almost halved the number of steps (11 versus 20), and proceeded in nearly three times the overall yield (22% versus 8%) compared to the original stepwise strategy, once again highlighting the potential of cascade processes for the streamlining of synthetic routes.[320,321]

The spectacular results of the application of ruthenium carbine based systems such as **472** as olefin- and enyne-metathesis catalysts over the last decade has, to a certain degree, overshadowed the concomitant development of a number of other useful ruthenium-catalyzed carbon–carbon bond-forming reactions.[322] One such reaction is the ruthe-



Scheme 63. Selective olefin cross-metathesis/ring-closing metathesis in the synthesis of (−)-cyclindrocyclophane F (**490**; Smith et al., 2000).[312]

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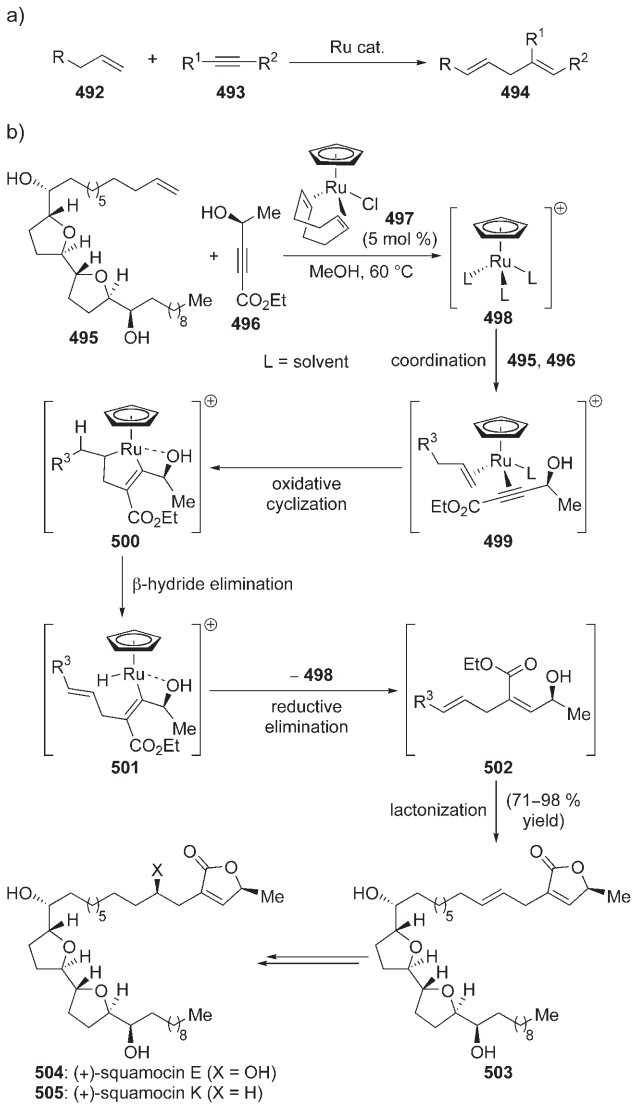
nium-catalyzed intermolecular coupling of alkynes and terminal alkenes to give 1,4-dienes (Scheme 64a) developed by Trost et al.[323] Through the judicious placement of appropriate functional groups on the alkene and alkyne partners, this coupling reaction has been extended to the one-step synthesis of substituted butenolides.[324,325] Trost et al. showcased this methodology in the total synthesis of squamocins E (**504**) and K (**505**, Scheme 64b),[326] whereby heating a solution of alkene **495** (1.0 equiv), γ-hydroxyalkynoate **496** (1.0–1.6 equiv), and ruthenium complex **497** (5 mol%) in MeOH at 60°C led to the formation of butenolide **503** as a single regioisomer and in yields of up to 98%! The mechanism of this protecting-group-free transformation is believed to proceed through the sequence shown in Scheme 64b. Formation of the presumed active ruthenium species **498** from precatalyst **497** is followed by ligand exchange and coordination of the alkene and alkyne components (**498**→**499**), oxidative cyclization to generate ruthenacyclopentene **500**, *syn*-β-hydride elimination (**500**→**501**), and then reductive elimination to extrude 1,4-diene **502** and regenerate catalyst **498**.[327] Diene **502** is suitably arranged to undergo lactonization to give butenolide **503** as the observed product. Simple manipulations of the 1,2-disubstituted alkene then completed the synthesis of the target natural products **504** and **505**.[328] The regioselectivity of butenolide formation is set during the coordination and cyclization steps of the catalytic cycle and is dictated primarily by coordination and steric effects, rather than electronic factors. This reaction provides a concise approach to the target butenolide ring system, a structural motif present in a large number of biologically active natural products.[329] In a more general context, the ruthenium-catalyzed alkene–alkyne coupling offers a mild, highly chemoselective, and atom-economical method for effecting fragment couplings.[330]



Scheme 64. Ruthenium-catalyzed alkene–alkyne coupling: a) general principles and b) application to butenolide formation in the total synthesis of (+)-squamocin E (**504**) and (+)-squamocin K (**505**; Trost et al., 1997).[326]

It is significant that the uncatalyzed reaction of simple alkenes with alkynes to give 1,4-dienes (Scheme 64a), a formal variant of the Alder-ene reaction, generally only occurs under forcing conditions ($T > 150$°C) and has consequently found little application in the synthesis of complex molecules.[331] Indeed, a notable feature of transition-metal catalysis is that it offers the potential for effecting a variety of pericyclic processes which would be difficult, if not impossible, to achieve under purely thermal conditions.[332]

In particular, a litany of higher-order and multicomponent [m+n+o…(+x)] cycloaddition reactions (where m, n, etc. refer to the number of atoms of each component participating in the reaction), many of which were unimaginable before the advent of transition-metal catalysis, have been, and continue to be, developed.[333] Classic examples include the [2+2+1] carbocyclization of an alkene, alkyne, and CO to generate cyclopentenones (the Pauson–Khand reaction),[334] and the [2+2+2] cyclotrimerization of alkynes to form benzenoid rings.[335–338] Wender et al. have been the key instigators in the development of a homologue of the venerable Diels–Alder reaction for the synthesis of seven-membered rings, namely the formal [5+2] cycloaddition between vinylcyclopropanes (VCPs) and π systems. Originally described as the intramolecular cyclization of alkynes and VCPs (e.g. **506**→**507**, Scheme 65a),[339] the scope of this reaction has subsequently been extended to include alkenes,[340] allenes,[341] and even intermolecular processes.[342] Given the prevalence of seven-membered rings in a wide range of natural and designed molecules,[343] it is perhaps unsurprising that this versatile reaction has begun to find application in target-oriented synthesis, an example of which being the approach to the bicyclo[5.3.0]decane skeleton of the tremulane sesquiterpenes recently reported by Martin and Ashfeld.[344] Exposure of alkyne **508** to dimeric rhodium species **509** (10 mol%) in refluxing toluene triggered the sequence of events depicted in Scheme 65b, leading to the formation of two new rings and two new stereocenters in a completely diastereoselective fashion and generating bicyclic aldehyde **514** in 85% yield. The initial steps in the mechanism bear close parallel to the ruthenium-catalyzed alkene–alkyne

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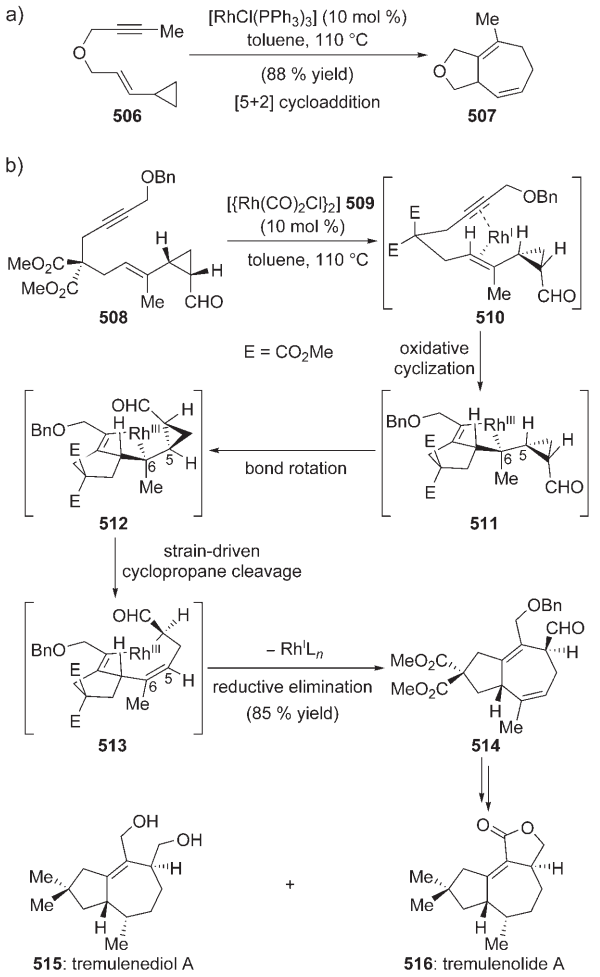
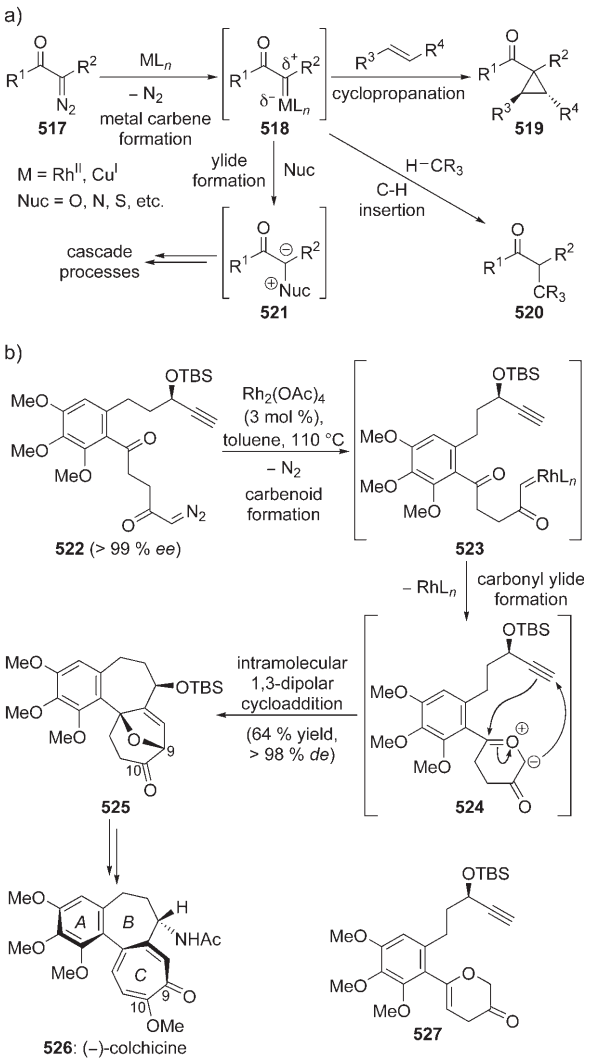


Scheme 65. Rhodium-catalyzed [5+2] cycloadditions: a) first examples (Wender et al., 1995)[339] and b) application to the total syntheses of tremulenediol (**515**) and tremulenolide A (**516**; Martin and Ashfeld, 2005).[344]

coupling discussed above (but this time occurring through a $Rh^{I}\leftrightarrow Rh^{III}$ manifold), that is, formation of a coordinatively unsaturated Rh^{I} species followed by complexation of the alkene and alkyne groups (**508**→**510**) and oxidative cyclization to give Rh^{III} metallacyclopentene **511**.[345] In this case, however, intermediate **511** can undergo a strain-driven cyclopropane cleavage reaction to form the ring-expanded metallacycle **513** and, finally, reductive elimination to provide bicyclic product **514**.[346] Importantly, note that cyclopropane cleavage from the initially formed metallacyclopentene **511** requires rotation about the C5–C6 bond to give the alternative conformer **512** (i.e. **511**→**512**→**513**). This ensures the correct alignment of not only the carbon–rhodium and carbon–carbon bonds required for concerted ring expansion, but also of the C5 hydrogen and C6 methyl substituents required for formation of the *Z*-configured C5–C6 double bond. The net result is that only one of the cyclopropyl carbon–carbon bonds undergoes cleavage to form **514** as a single regio- and diastereoisomer, an outcome anticipated by Martin and Ashfeld on the basis of elegant mechanistic studies by Wender et al.[347] Having assembled the bicyclic core structure in this manner, Martin and Ashfeld were then able to complete the enantioselective syntheses of tremulenediol A (**515**) and tremulenolide A (**516**) over the course of several more steps.[348–350]

The final class of transition-metal-catalyzed reactions that we shall highlight involves the formation and subsequent reactivity of metal carbenoid species from α-carbonyldiazo compounds. Coordination to the metal center (usually a Rh^{II} or Cu^{I} species) tempers, to a degree, the generally high reactivity associated with free carbenes and allows for potentially selective further transformations.[351] From a practical synthetic perspective, such metal carbenes undergo three main types of reaction, as summarized in a very simplistic form in Scheme 66 a. Cyclopropanation with alkenes and C–H insertion reactions are both areas that have witnessed spectacular advances in recent years, particularly with regards to intermolecular and asymmetric processes, and have been extensively reviewed.[352,353] An example of each was illustrated in the synthesis of (–)-colombiasin



Scheme 66. a) Formation and fate of metal–carbene species **518** derived from α-carbonyl diazo compounds **517**. b) A tandem carbonyl ylide formation/1,3-dipolar cycloaddition approach to the total synthesis of (–)-colchicine (**526**; Schmalz et al., 2005).[355]

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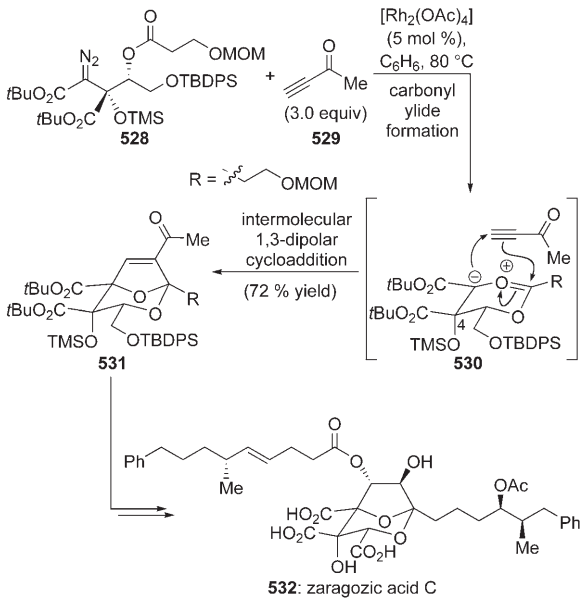
(**350**) by Davies et al. (Scheme 49). However, the electrophilic character of the metal-bound carbon atom also renders this site susceptible to nucleophilic attack to generate a variety of ylide species, which, in turn, can undergo subsequent reactions.

A number of elegant cascades have been designed on the basis of this sequence,[354] one of which was employed by Schmalz and co-workers in an enantioselective synthesis of (−)-colchicine (**526**, Scheme 66b) reported in 2005.[355,356] Colchicine (**526**) has proven to be a tempting target for generations of synthetic chemists and has inspired the development of many ingenious syntheses over the last 50 years.[357] However, a common feature of these routes is that they all adopt a stepwise linear approach to the construction of the tricyclic ring system (i.e. A→AB→ABC, A→AC→ABC, etc.), with the regiocontrolled synthesis of the tropolone C ring often being a particularly thorny issue.[358] As illustrated in Scheme 66b, Schmalz and co-workers employed a Rh-triggered cycloaddition cascade of α-diazoketone **522** to generate both the seven-membered B and C rings in a single step, and with complete control of diastereoselectivity, in a unique A→ABC ring approach. The mechanism of this transformation[359] begins with the generation of electrophilic rhodium carbene **523**, followed by intramolecular cyclization of the proximal Lewis basic carbonyl group to form a reactive carbonyl ylide **524**, which then undergoes intramolecular 1,3-dipolar cycloaddition onto the tethered alkyne to give the observed product **525** in 64% yield.[360] The elevated temperature (110°C) at which this reaction was run was crucial to the success of this venture, as at ambient temperature the uncyclized enol ether **527**, formally derived from carbonyl ylide **524** via a 1,4-hydrogen shift, was the exclusive product. In addition to establishing the complete carbon skeleton of the target natural product **526**, this sequence also regioselectively installed oxygen functionality at the C9 and C10 positions in what would become the tropolone C ring, thereby allowing the completion of the total synthesis in short order.[361]

An intermolecular variant of this cycloaddition cascade was applied by Hashimoto and co-workers en route to their second-generation synthesis of zaragozic acid C (**532**, Scheme 67).[362] Slow addition of a solution of the D-tartrate-derived α-diazoester **528** to a solution of alkyne **529** (3.0 equiv) and rhodium(II) acetate dimer (5 mol%) in refluxing benzene led to the formation of bicyclic compound **530** as a single stereoisomer in 72% yield. The stereoselectivity of this reaction is dictated by approach of the alkyne dipolarophile to the top face of carbonyl ylide intermediate **530** (as drawn in Scheme 67), so as to avoid steric interactions with the pseudoaxial OTMS group at C4. The regioselectivity of the cycloaddition can be rationalized in terms of frontier molecular orbital theory,[363] assuming that the dominant electronic interaction is between the ylide HOMO and alkyne LUMO.[364] This cycloaddition provides an concise approach to the densely functionalized 2,8-dioxabicyclo[3.2.1]octane core structure of the zaragozic acids, and avoids some of the potential problems associated with the formation of this motif through intramolecular acid-catalyzed ketalization of an open-chain 1,3-diol precursor.[365–367]



Scheme 67. Carbonyl ylide generation and cycloaddition in the total synthesis of zaragozic acid C (**532**; Hashimoto et al., 2003).[362]

7. Summary and Outlook

The enormous benefits associated with cascade reactions have ensured that they continue to be developed and exploited in organic synthesis. That most of the beautiful and ingenious examples described in this Review have been reported within only the last five years serves to emphasize this point. Of course, in highlighting only successful applications from total synthesis, we neglect a great many cascades developed for other applications, or without a natural product target in mind. Additionally, countless examples of cascades that have gone awry or failed altogether have been omitted. The synthesis of the cascade precursors themselves may also be far from trivial, and considerable experimental skill (and perseverance) is often required to unearth suitable conditions under which the desired cascade can be effected with success.

There are currently relatively few examples of catalytic enantioselective cascade reactions, and it is likely that asymmetric catalysis of cascade processes will become increasingly prominent in years to come, with enzymatic, organocatalytic, and transition-metal-catalyzed processes at the vanguard of this movement. With the increasing pressures to fashion diverse and increasingly complex molecular architectures rapidly through efficient and economical means, cascade reactions are destined to assume an integral position in many synthetic endeavors. In order to push the state of the art of these sequences, contemporary as well as future generations of synthetic practitioners will require an increasingly precise understanding of the mechanism and kinetics of organic transformations. Gains in this fundamental knowledge, combined with a large dose of intellectual flexibility and creativity, will undoubtedly lead to even more spectacular applications of cascade reactions in the future.

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Abbreviations

Ac	acetyl
ACCN	1,1′-azobis(cyclohexanecarbonitrile)
AIBN	2,2′-azobis(2-methylpropionitrile)
BINAP	2,2′-diphenylphosphino-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
CAN	ammonium cerium(IV) nitrate
Cbz	benzyloxycarbonyl
CSA	10-camphorsulfonic acid
2,2-DMB	2,2-dimethylbutane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
4-DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio)sulfonium tetrafluoroborate
EDDA	ethylenediamine diacetate
Fl	9-fluorenyl
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
imid	imidazole
KHMDS	potassium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
2,6-lut	2,6-lutidine
*m*CPBA	*meta*-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
NaHMDS	sodium bis(trimethylsilyl)amide
NMP	1-methyl-2-pyrrolidinone
Ns	2-nitrobenzenesulfonyl
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
N-PSP	*N*-(phenylseleno)phthalimide
py	pyridine
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxide
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPB	triisopropylbenzene
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
TsOH	4-toluenesulfonic acid

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