Cascade reactions in total synthesis

Recent advances

K.C. Nicolaou and Scott A. Snyder

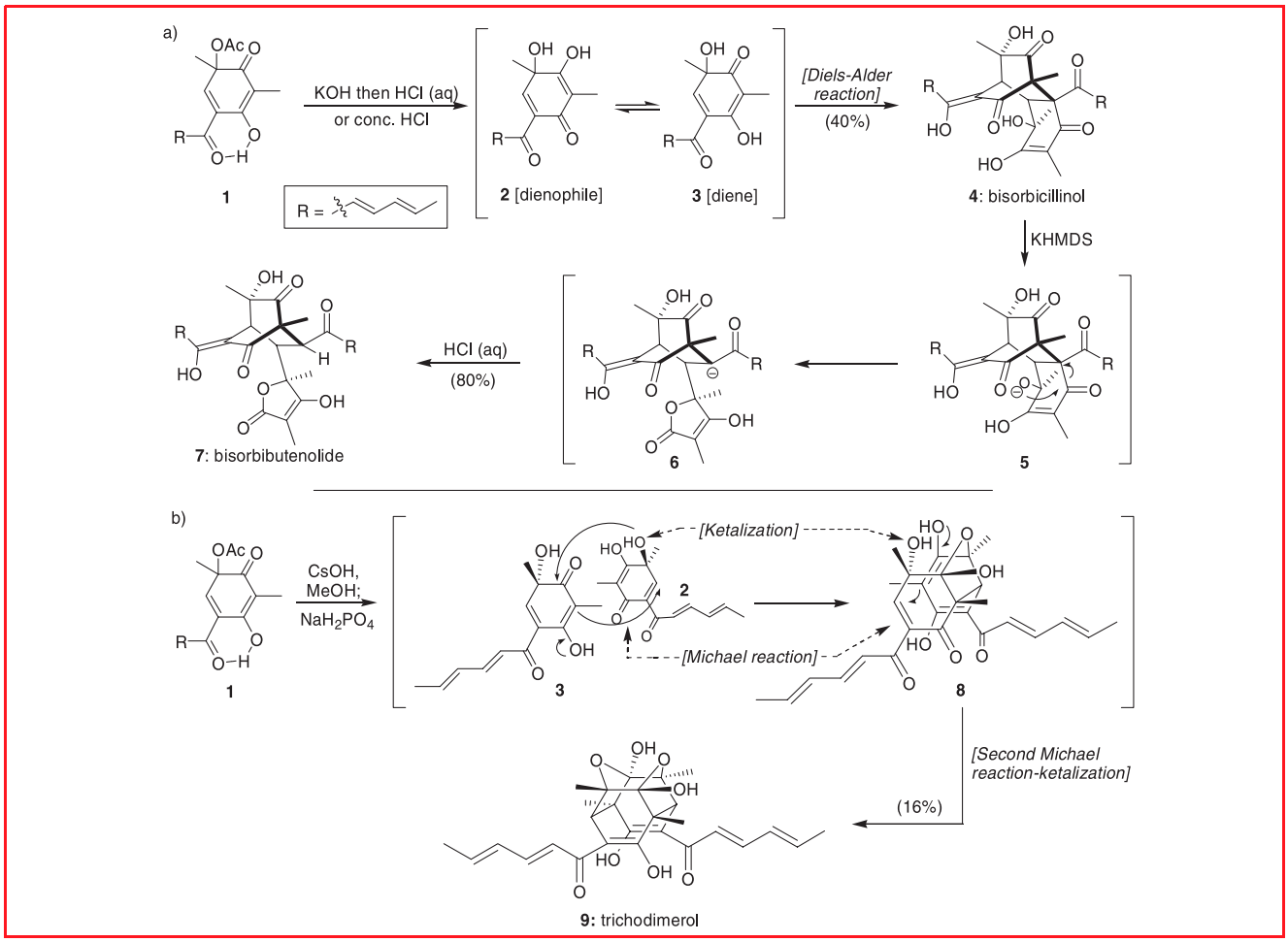
Résumé **Réactions en cascade en synthèse organique : avancées récentes**
L'un des objectifs les plus importants de la synthèse organique au XXI^{e} siècle est sans aucun doute de trouver des méthodes permettant d'élaborer des architectures moléculaires complexes et variées de manière plus efficace et plus sélective. Bien que différentes approches peuvent répondre à ce besoin, des réactions-tandem, des réactions en cascade ou encore des stratégies biomimétiques offrent souvent les solutions les plus attrayantes à cet égard. Cet article souligne quelques-unes de ces tactiques mises au point dans notre laboratoire dans le cadre de programmes de recherche orientés vers la synthèse de produits naturels complexes.

Mots-clés **Synthèse totale, réactions en cascade, produits naturels, synthèse biomimétique, réactions-domino.**
Key-words **Total synthesis, cascade reactions, natural products, biomimetic synthesis, domino sequences.**

The principle of cascade reactions in organic synthesis has a long and proud lineage, whose roots can be traced forward to the present day from such landmark achievements as Sir Robert Robinson's elegant union of succindialdehyde, methylamine, and acetone in a one-pot biomimetic formation of tropinone in 1917 [1], and W.S. Johnson's synthesis of progesterone in 1971 which defined polyolefinic cation-π cyclizations as an invaluable synthetic tool [2]. Today, with ever increasing pressure to create molecular complexity rapidly, through efficient and atom-economical [3] processes with high degrees of selectivity, cascade transformations offer a magical level of power that is unsurpassed by any other weapon in the current synthetic arsenal.
In order to advance the state of the art of cascade reactions, however, contemporary as well as future generations of practitioners of the art of chemical synthesis will require increasingly advanced mechanistic understanding of organic transformations combined with a large dose of intellectual flexibility and creativity. In this mini review, we have elected to focus on cascade sequences developed in our laboratories over the past two years as part of our efforts directed towards the expedient total synthesis of natural products. Our goal is not only to demonstrate the effectiveness (or limits) of current synthetic technology in the context of some of the most advanced synthetic problems presently facing the chemical community, but also to provide inspiration that will hopefully lead to the design and development of even more impressive tandem reaction processes in the future.

Synthetic approaches based on biogenetic cascade hypotheses have long been a mainstay of retrosynthetic analysis in our group, in view of the extremely concise and elegant construction of molecular complexity that often results by adopting such strategies. Indeed, these sequences represent the closest that chemists can currently come to emulating nature's efficient and seemingly effortless construction of complex molecules. Recent examples along these lines include our program directed towards the biomimetic synthesis of three members of the bisorbicillinoids (*scheme 1*), natural products with potent inhibitory activity against lipopolysaccharide-induced production of tumor necrosis factor α.
Careful examination of these dodecaketides has led to several biosynthetic hypotheses which uniformly implicate an expected highly reactive intermediate quinol (masked as its acetate in **1**, *scheme 1a*) as the key building block leading to the biosynthesis of all members of this family of natural products [4].
In 1999, our group was the first to achieve verification of this concept when exposure of a THF/H_2O solution of **1** to NaOH, followed by an aqueous HCl quench, led to the Diels-Alder adduct **4** (bisorbicillinol) in 40% yield with complete regio- and diastereocontrol deriving from the *endo* selectivity of the union [4b, 5]. NMR spectroscopic studies verified the course of the reaction as deacetylation followed by formation of a quinolate system which rapidly equilibrated to a mixture of dienophile (**2**) and diene (**3**) units; these monomers then united in a Diels-Alder fashion to form **4** with concomitant generation of four chiral centers, two of which are quaternary. With compound **4** in hand, subsequent exposure to KHMDS in THF at ambient temperature with eventual acidic work-up smoothly led to the formation of bisorbibutenolide (**7**) in 80% yield, presumably through the delineated mechanism. As such, this successful conversion completed the original biosynthetic hypothesis for the formation of **4** and **7** first advanced by Abe [4a].

We next set out to achieve the synthesis of trichodimerol (**9**) from **1** via our own biosynthetic hypothesis [4b] based



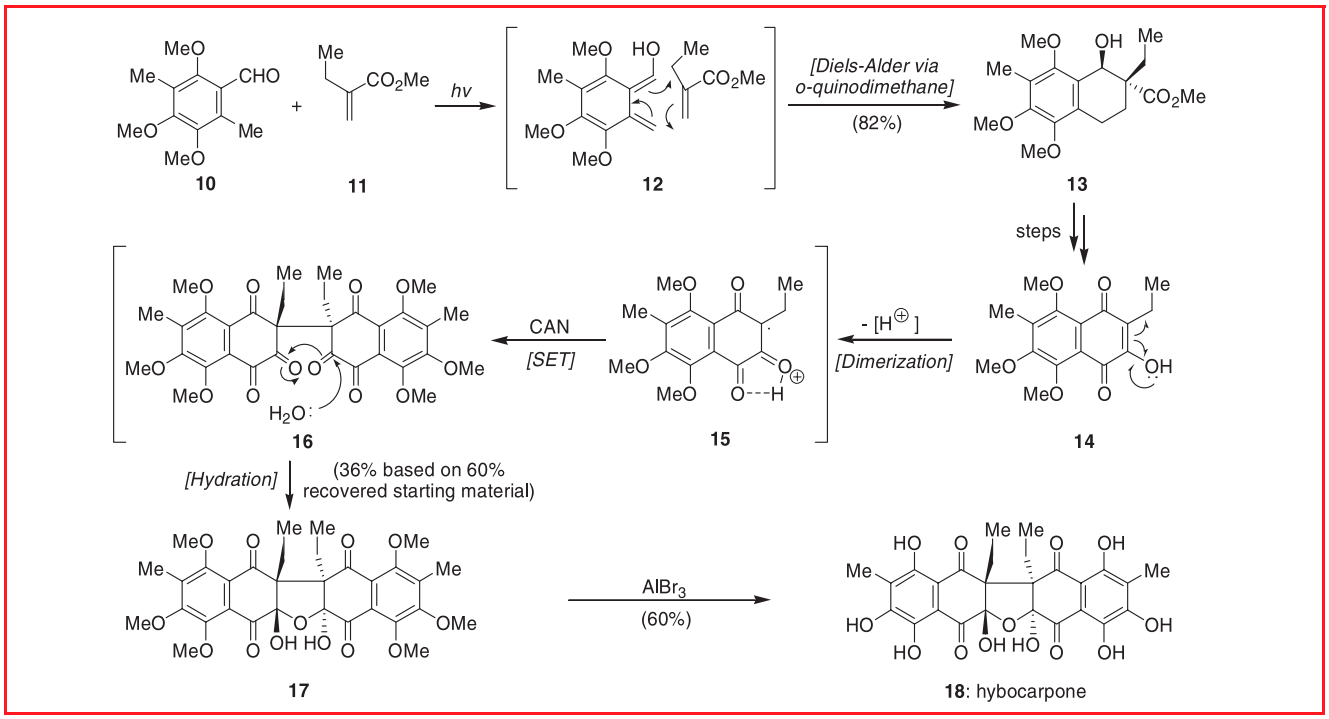
Scheme 1 - Cascade sequences features in the biomimetic syntheses of the bisorbicillinoids.
a) cascade transformation of bisorbicillinol (**4**) to bisorbibutenolide (**7**); b) synthesis of trichodimerol (**9**) from **1**.

on an oxidation-Michael reaction-ketalization cascade (*scheme 1b*). Success in this endeavor was realized by treating **1** with CsOH•H_2O in MeOH, followed by neutralization with finely powdered NaH_2PO_4•H_2O and further stirring at ambient temperature, providing **9** in an isolated yield of 16%. Overall, this extraordinary dimerization provided eight chiral centers, no less than six of which are fully substituted. Moreover, extension of this cascade to generate novel analogs of the parent structure was readily achieved, furnishing new tools with which to explore the chemical biology of this important class of natural products. The key to the success of this cascade sequence, as well as those events leading to **4**, rested in the reliable generation of the desired quinolates (**2** and **3**) under protic conditions, with minimal water present, followed by slow neutralization. Additionally, we should note that the synthesis of enantiomerically pure **9** was elegantly achieved in a similar manner from **1** by Corey and Barnes-Seeman prior to the full disclosure of our work [6].

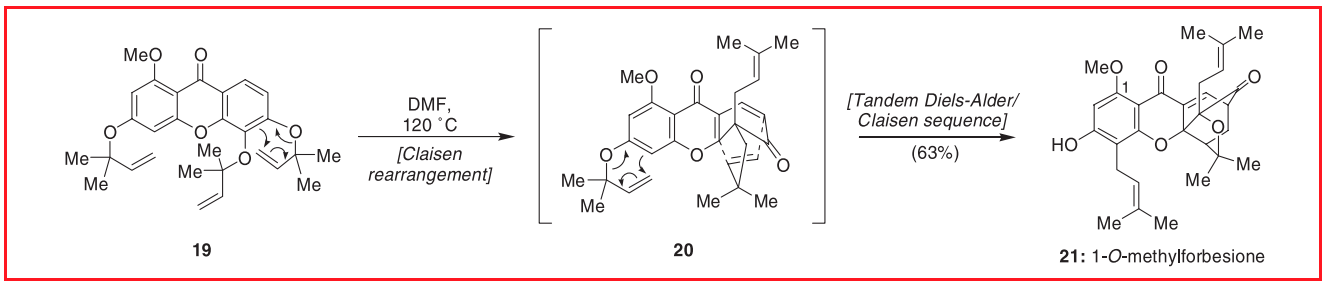
Along related lines, we were enticed by the unique and cytotoxic natural product hybocarpone (**18**, *scheme 2*) which possesses an aesthetically pleasing C_2-symmetric molecular structure. One can readily envision a plausible biosynthetic origin of this compound as dimerization of a precursor naphtharazin (**14**) initiated by a single-electron transfer (SET) process followed by a hydration event. This hypothesis was confirmed in 2001 with an expedient total synthesis of hybocarpone guided by this concept [7].

After an exhaustive search of suitable SET reagents, it was discovered that use of cerium ammonium nitrate (CAN), followed by a basic work-up, led to the desired parent structure in protected form (**17**) in 36% yield which was then readily converted to the natural product (**18**) upon treatment with $AlBr_3$. This SET-initiated cascade sequence is particularly impressive, as it enabled concomitant formation of a highly hindered carbon-carbon bond and the selective installation of four stereogenic centers.
Among the steps employed to prepare the dimerization precursor (**14**), one transformation of note was the generation of an intermediate hydroxy-*o*-quinodimethane (**12**) from an aromatic aldehyde (**10**) using ultraviolent irradiation, followed by its successfully engagement of methyl-2-ethylacrylate (**11**) in a Diels-Alder reaction to form the requisite bicyclic system. Although scant reports of this latter cascade process are reported in the chemical literature on simple precursors, the sequence has been virtually ignored in total synthesis endeavors. As such, this particular example of photogeneration and trapping of quinodimethanes in the context of hybocarpone represents one of the most complex applications of this technology achieved to date. Further optimization of this technology for both intra- and intermolecular cycloadditions has recently enabled us to synthesize several members of the hamigeran family of natural products [8].

As a final biomimetic entry, we note our recently achieved verification [9] of a biosynthetic hypothesis first advanced by



Scheme 2 - Dimerization-hydration cascade of a naphtharazin (**14**) to hybocarpone hexamethyl ether (**17**) initiated by single-electron transfer (SET).



Scheme 3 - A Claisen rearrangement/Diels-Alder cycloaddition/Claisen rearrangement sequence in a biomimetic cascade, generating 1-*O*-methylforbesione (**21**) from **19**.

Quillinan and Scheinmann over thirty years ago [10] in which a Claisen rearrangement followed by an intramolecular Diels-Alder reaction was postulated for the formation of the 4-oxatricyclo[4.3.1.0]decan-2-one ring system found in numerous natural products isolated from the Guttiferae family of plants, which include forbesione (the C-1 phenol analog of **21**, *scheme 3*). Thus, an expedient synthesis of the tri-prenylated derivative **19** was followed by heating of the latter compound in DMF at 120 °C for 20 minutes, furnishing *O*-methylforbesione (**21**) in 63% yield, presumably via the anticipated biosynthetic route involving a double Claisen/ Diels-Alder sequence. The successful development of this technology bodes well for the future construction of the entire functionalized skeleton of other members of this constantly expanding class of important natural products.

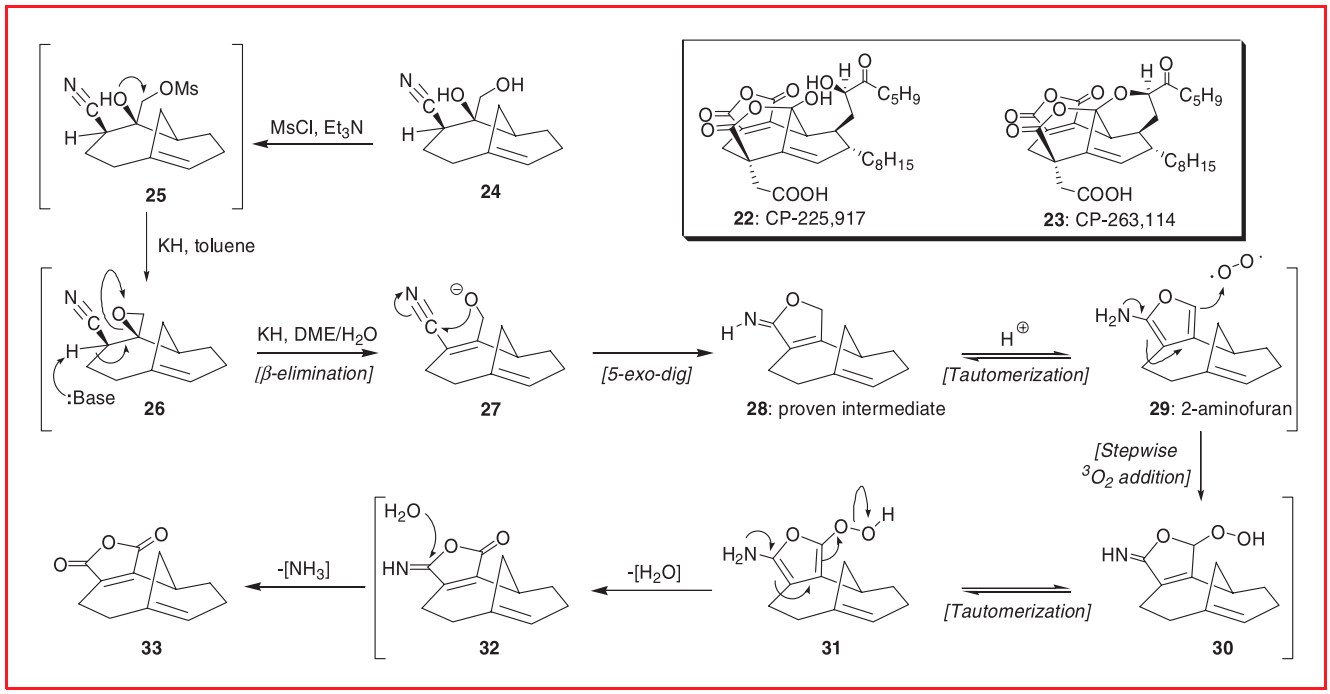
Besides biomimetic routes, unique molecular motifs in complex natural products typically afford golden opportunities for cascade development, as conventional and laborious step-wise syntheses often prove inadequate to overcome the synthetic challenge at hand. A seminal example of this concept includes our successful total synthesis of the CP-molecules (**22** and **23**, *scheme 4*), accomplished in 1999 [11]. In addition to a novel, base-induced cascade sequence which was developed to successfully convert **23** to **22**, a key transformation in the drive to complete the carbogenic skeleton was the formation of the maleic anhydride, a structural unit of the molecule which posed a persistent and unique challenge throughout the synthetic campaign.

After considerable experimentation and deep mechanistic analysis, it was shown that diol **24** could be converted to the coveted anhydride domain (**33**) in 60% yield through a one-pot operation. In the event, initial treatment with mesyl chloride, followed by exposure to base, induced a domino sequence of epoxide formation and β-elimination to alkoxide derivative **27**, with eventual conversion to **28** achieved through a favored 5-*exo*-dig cyclization.

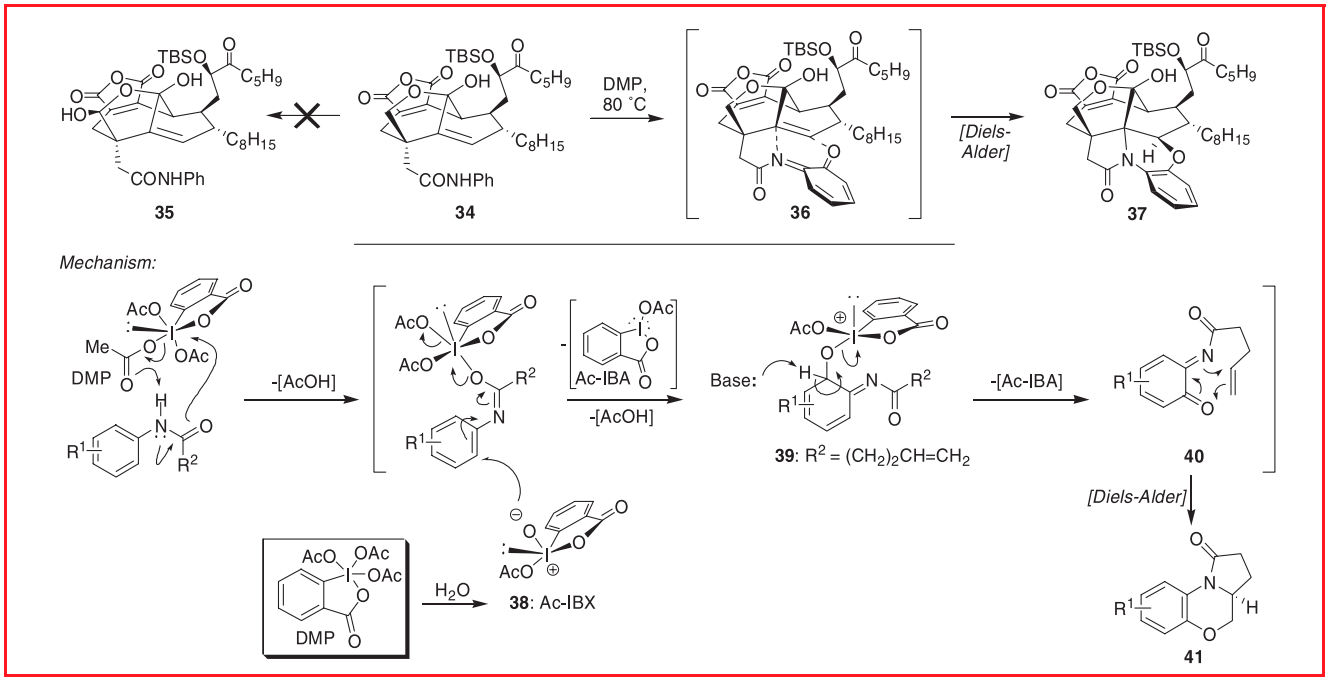
Next, it was anticipated, and realized, that mildly acidic conditions would promote the tautomerization of **28** to the highly reactive 2-aminofuran (**29**), an intermediate which combined with triplet oxygen immediately upon formation to afford hydroperoxide **30**. A second, rapid tautomerization

followed by the loss of water then furnished intermediate **32**, which ultimately provided the desired anhydride surrogate **33** after expulsion of ammonia facilitated by hydrolytic collapse. Extensive mechanistic studies verified the existence of intermediates **26** and **28** along this cascade sequence, lending credence to the proposed set of conversions as defined in *scheme 4*.

In addition to designed sequences, the complex and multifaceted campaign toward the CP-molecules also demonstrated the opportunistic development of cascade reactions based on serendipitous discoveries. For example, as shown in *scheme 5*, treatment of **34** with Dess-Martin periodinane (DMP) at elevated temperatures was expected to provide **35**; instead, the sole product of the reaction was



Scheme 4 - The designed cascade sequence enabling generation of the coveted maleic anhydride portion (**33**) of the CP-molecules (**22** and **23**).
Note: appendages on the core have been removed for clarity.

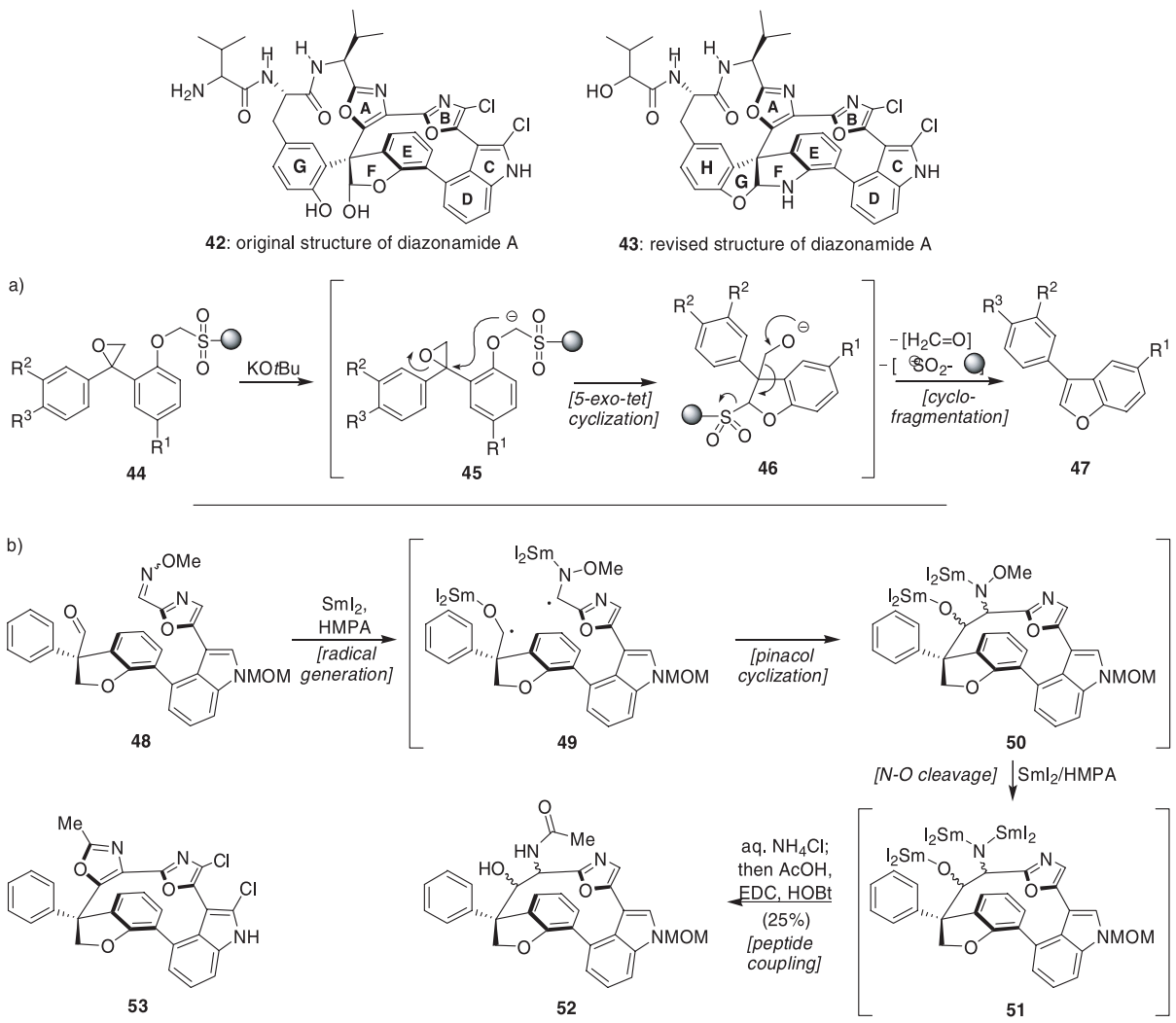


Scheme 5 - Cascade sequence discovered by serendipity as part of the CP-campaign.
Dess-Martin periodinane-initiated polycyclization reaction through the intermediacy of *o*-quinodimethanes (**36**) and proposed mechanism for the series of transformations.

the polycyclic adduct **37**. The determined pursuit of the mechanistic underpinnings of this reaction led to the recognition of a cascade reaction sequence initiated by Dess-Martin periodinane (DMP) and involving Ac-IBX (**38**) in which initial generation of an intermediate *o*-quinodimethane (**36**) was followed by a merger with the pendent dienophile in an intramolecular cycloaddition reaction. These mechanistic insights, in turn, have led to the design of further reactions based on the chemistry of hypervalent iodine reagents, including the formation of α,β-unsaturated compounds, *cis*-aminosugars, and aromatic aldehydes and ketones [13].

As a final set of examples, our recent forays directed towards the total synthesis of the marine-derived antitumor agent diazonamide A, whose originally proposed structure (**42**) has recently been revised to **43** (*scheme 6*), have afforded numerous opportunities for both the design and serendipitous discovery of cascade sequences in a manner similar to the CP-molecule expedition.
For instance, early efforts directed towards the generation of the quaternary center linking the AG and ABCDEF macrocycles were based on effecting a 5-*exo*-tet cyclization on a precursor such as **44**, leading to **46** (*scheme 6a*). Although this transformation was eventually realized, initial experiments brought about the discovery of a novel cyclofragmentation cascade sequence instead. The powerful process evidently proceeded from **46** *via* concomitant expulsion of formaldehyde and a sulfone unit, leading to the highly desirable 3-arylbenzofuran nucleus (**47**), a privileged structural motif found in numerous clinically-employed pharmaceuticals.
Based on the unique synthetic fertility of this novel transformation, the methodology was extended to split-and-pool combinatorial synthesis by linking the sulfone moiety to a polystyrene resin. This design enabled traceless cleavage of the final product from the resin and included a safety-catch feature as only the desired benzofuran skeleton could undergo release in the final cyclization cascade, thereby affording the ultimate compounds in high purity [14].

The opportunity to design and develop a *de novo* cascade sequence in the context of diazonamide came with roadblocks confronted in forging the A-ring oxazole after an initial macrocyclization event. Inspired by literature



Scheme 6 - Cascade sequences featured in synthetic efforts towards the originally disclosed structure of diazonamide A (**42**) in efforts targeting model system **53**.
a) creation of 3-arylbenzofurans by a cyclofragmentation sequence; b) closure of the 12-membered heterocyclic macrocycle.

precedent in systems of reduced complexity, we anticipated that a hetero pinacol coupling reaction could be enlisted to fashion a fully functionalized macrocyclic system directly suitable for A-ring oxazole formation through the use of SmI_2, a powerful reagent introduced to organic synthesis by Henri Kagan [15]. Specifically, it was envisioned that diradical generation from an aldehyde-oxime precursor could initiate an unprecedented domino sequence involving hetero pinacol macrocyclization, *in situ* N-O cleavage to generate an amino alcohol, and subsequent peptide formation.

After significant optimization, treatment of aldehyde-oxime **48** with a pre-mixed complex of SmI_2 and HMPA in THF at ambient temperature, followed by quenching with aqueous NH_4Cl, extraction, solvent removal, and subsequent peptide coupling using EDC and HOBt led to the formation of **52** as a mixture of stereoisomers in an isolated yield of 25% (63% per step). Significantly, this process was found to be applicable to other related systems in even higher overall yields. With functionality successfully installed in this cascade sequence, elaboration to the targeted model system **53** was readily achieved in just a few additional steps [16].

Not only does this example represent the first macrocyclization using a hetero pinacol reaction, but it also greatly extends our knowledge on the power of SmI_2 to achieve selective transformations on complex substrates.

This brief summary of recent advances in the field of cascade reactions in total synthesis reflects the stunning capacity of such processes to effect complex molecule construction. Although this concept has been practiced for nearly a century, its full potential has barely been tapped. It is our contention that the future of total synthesis will depend heavily on such programmed tandem sequences where the product of one reaction becomes the substrate for the next under the activating influence of heat, light, or various reagents and catalysts [17]. If we include the efficiency of multi-component reactions and the emerging field of multi-component catalysis, then one can only begin to imagine the anticipated power of artificial synthesis as it strives to approach nature's adeptness in fashioning its own molecules.

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