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The Art of Total Synthesis Through Cascade Reactions

K. C. Nicolaou and Jason S. Chen

Abstract

The growing importance of cascade reactions reflects and imparts advances in the state of the art of organic synthesis and underscores the desire of synthetic chemists to achieve higher levels of elegance and efficiency. Besides their aesthetic appeal, cascade processes offer economical and environmentally friendly means for generating molecular complexity. Because of their many advantages, these reactions have found numerous applications in the synthesis of complex molecules, both natural and designed. In this Tutorial Review, we highlight the design and execution of cascade reactions within the context of total synthesis as demonstrated with selected examples from these laboratories.

Introduction

Chemical synthesis is, at its core, an endeavor in composition, and, as such, is a creative field of almost limitless scope, especially when applied to complex molecules whose primary element is carbon, collectively known as organic compounds. Total synthesis refers to the laboratory construction of naturally occurring substances, often complex organic compounds with important biological activities, some of which eventually find their way into the clinic as useful medicines. In a broader sense, the term may also be applied to the synthesis of designed molecules of significant complexity for multifaceted intents and purposes, whether in biology and medicine, or materials science and nanotechnology. Total synthesis has been hailed as a highly demanding and exacting science, but it is also recognized in its finest form as an art. The artistic nature of total synthesis manifests itself in the selection of the synthetic maneuvers that lead to the target molecule (the strategy) and the design of the structural variations of the target that are synthesized (the analogues).

In the eyes of the connoisseur of the art of total synthesis, the emergence of molecular complexity from simpler molecular assemblies becomes a choreographed event wherein, although each move is appreciated, it is their combinations in sequence that solicit the louder applause. In chemical synthesis, such combinations, commonly known as cascade reactions,¹ are often aesthetically pleasing and can be highly efficient. Cascade reactions are sequences of chemical transformations in which the starting substrate is designed so as to (or happens to) undergo a reaction whose product becomes the substrate for the next step, whose product again becomes the substrate for the next step, and so on, until a product stable to the reaction conditions is reached. In addition to the obvious benefits of reducing the number of manipulations required, cascade reactions also expand our repertoire of reactions and strategies by allowing the use of synthetically enabling intermediates that may or may not be practical or possible to isolate. Indeed, many catalytic processes, such as palladium-catalyzed cross coupling reactions² and olefin metathesis reactions,³ are in their very nature cascade reactions and have become key components of the synthetic toolbox. Cascade reactions, besides being artistically appealing, are often associated with cost savings in terms of reagents, catalysts, and solvents, as well as time and effort. They are, therefore, a means to achieve green chemistry

and a way to develop economical processes for the manufacture of pharmaceuticals and other fine chemicals.

In this article, we will attempt to demonstrate the present power of cascade reactions in total synthesis and point out their future potential, with particular emphasis on the art and science involved in achieving molecular complexity and diversity. As cascade reactions in total synthesis have been thoroughly reviewed elsewhere,¹ we shall confine ourselves only to cascade sequences discovered during selected synthetic campaigns in these laboratories, namely those directed toward the total syntheses of the endiandric acids [see endiandric acid A (**1**, Figure 1)], hybocarpone (**2**), thiostrepton (**3**), the C_2 -symmetric bisanthraquinones [see 2,2'-*epi*-cytoskyrin A (**4**)], biyouyanagin A (**5**), and antibiotic BE-43472B (**6**).

Endiandric acids

Endiandric acids A–C (**1**, **7**, **8**, Figure 2) were discovered from the Australian tree *Endiandra introrsa* and reported by Black, Gatehouse, and coworkers in 1980.^{4,5} Interestingly, these polycyclic systems exist naturally as racemic mixtures. Based on this observation and by virtue of their molecular structures, Black proposed an intriguing biosynthetic hypothesis whereby the endiandric acids are formed from linear, achiral polyunsaturated precursors through a sequence of thermally allowed pericyclic reactions independent of the influence of any enzymes.⁵ Thus, as shown in Scheme 1, polyunsaturated carboxylic acids **10** and **11** might suffer spontaneous conrotatory $8\pi e$ electrocyclization to form cyclooctatriene systems **12** and **13**, differing only in their ring conformation. In turn, these proposed intermediates (**12** and **13**) were expected to readily undergo a disrotatory $6\pi e$ electrocyclization to furnish the bicyclic structures shown (**9**, **14**–**16**). The putative compounds **14**–**16** (since named endiandric acids E, F, and G, respectively) could further react to generate endiandric acids A, B, and C (**1**, **7**, and **8**, respectively) through intramolecular Diels–Alder cycloadditions,⁶ as indicated in Scheme 1. In contrast, compound **9** (named endiandric acid D), being incapable of a further pericyclic reaction, was predicted to be a stable chemical entity,⁵ a fact that was later confirmed when it was both synthesized in the laboratory⁷ and isolated from nature.⁸

Intrigued by these reports, we set out to test Black's intriguing hypothesis, and, in 1982, published our results that provided its experimental verification.⁷ We first synthesized each of the polycyclic frameworks through sequential pericyclic reactions in order to test the viability of each step in the proposed cascade process. Having successfully prepared all the endiandric acids through stepwise syntheses, we then turned our attention to a more direct mimicry of the proposed biosynthesis. Polyunsaturated methyl ester **17** (Scheme 2), possessing a conjugated diyne moiety and the proper olefinic geometries, was subjected to Lindlar reduction conditions in order to form the highly conjugated polyene system **18** with the requisite *cis*-disposed central olefinic bonds. The latter intermediate proved transient, undergoing a spontaneous $8\pi e$ electrocyclization followed by a second $6\pi e$ electrocyclization⁹ to yield a mixture of endiandric acids D and E methyl esters (**19** and **20**). As expected, endiandric acid A methyl ester (**21**) was obtained upon heating, but surprisingly, endiandric acid D methyl ester (**19**) was no longer observed. Rather than being the dead end product predicted in Black's hypothesis, endiandric acid D methyl ester (**19**) was evidently capable of undergoing a $6\pi e$ ring opening, ring flip, and subsequent $6\pi e$ electrocyclization (all reversible processes), finally being trapped irreversibly through an intramolecular Diels–Alder cycloaddition to deliver endiandric acid A methyl ester (**21**), as illustrated by the sequence **9**→**13**→**12**→**14**→**1** (see Scheme 1). Indeed, this proposed explanation was verified by following the fate of pure endiandric acid D methyl ester (**19**) under the same reaction conditions through ¹H NMR spectroscopic analysis. Thus, heating a solution of endiandric acid D methyl ester (**19**) led to the formation of endiandric acid A methyl ester (**21**) via endiandric acid E methyl ester (**20**) (see Scheme 2).

As shown in Scheme 3, polyunsaturated methyl ester **22** was subjected to the same Lindlar reduction conditions to effect formation of endiandric acids F and G methyl esters (**23** and **24**). As anticipated, endiandric acids B and C methyl esters (**25** and **26**) were produced upon heating. As in the formation of endiandric acid A methyl ester (**21**, Scheme 2), at elevated temperatures, endiandric acids F and G methyl esters (**23** and **24**) interconverted reversibly and, finally, trapped irreversibly, as shown by the sequences **15**→**12**→**13**→**16**→**8** and **16**→**13**→**12**→**15**→**7** (see Scheme 1). Thus, exposure of a pure sample of either compound (**23** or **24**) to heat led to the formation of both endiandric acids B and C methyl esters (**25** and **26**).

In the endiandric acid cascades, the simplest of reagents (H₂ gas, Lindlar catalyst, and heat) effected formation of up to four rings and generation of up to eight contiguous stereogenic centers with complete stereocontrol. Considering the striking operational simplicity of these cascade reactions and the impressive molecular complexity so formed, it is indeed difficult to imagine a more efficient strategy to synthesize the endiandric acids and other molecules like them.

Hybocarpone

Hybocarpone (**2**, Figure 3) is a cytotoxic compound isolated from *Lecanora hybocarpa*, a lichen found in the Louisiana woodland, and reported by Elix and coworkers in 1999.¹⁰ Hybocarpone is a C₂-symmetric compound, and the suspiciously related monomeric structure **27** (6-methylchristazarin, Scheme 4) is also naturally occurring.¹¹ Although there is no proof of the biosynthetic proposal shown in Scheme 4, it seemed reasonable to us that nature may oxidatively dimerize 6-methylchristazarin (**27**) in an enantio- and diastereoselective manner to form a dimeric structure such as **28**. We further reasoned that spontaneous hydration of **28** may yield hybocarpone (**2**) in a cascade fashion. It was after failing to synthesize hybocarpone through the use of a Claisen rearrangement to install its highly hindered all-carbon quaternary centers that we turned to this postulated, but highly speculative, biosynthetic hypothesis as a means to construct the molecule. In 2001, we reported a total synthesis of hybocarpone (**2**) based on this approach.¹²

Before we could attempt the proposed oxidative dimerization, we first had to prepare 6-methylchristazarin (**27**), or a masked equivalent of this monomeric unit. Toward this end, a mixture of aromatic aldehyde **29** (Scheme 5) and α,β -unsaturated ester **30** was irradiated with UV light to effect photoenolization¹³ of **29**, thus providing access to the highly reactive *o*-quinonedimethide **31**, which underwent rapid Diels–Alder cycloaddition⁶ with dienophile **30** to afford bicyclic system **32**. A series of oxidations and a decarboxylation then yielded trimethoxy naphthoquinone **33**, from which 6-methylchristazarin (**27**) was generated through the action of BBr₃.

Initial attempts to effect the desired oxidative dimerization of 6-methylchristazarin (**27**) to directly yield hybocarpone (**2**) were unsuccessful. Experimentation with its protected form **33**, however, proved more fruitful. Thus, as shown in Scheme 6, a solution of **33** was exposed to cerium(IV) ammonium nitrate (CAN) to effect a single electron oxidation, generating radical cation **34**. The latter species proved to be transient, rapidly dimerizing with ease to afford hexaketone **35**, selectively, with the *trans* stereochemistry shown. The high degree of stereocontrol observed in this carbon–carbon bond forming reaction is presumably due to minimization of severe steric interactions at this congested site. The resulting reaction mixture was rapidly quenched with a solution of aqueous 5 M KOH, a process that resulted in hydration of the reactive polyketone **35** (which acts as an anhydride), thus casting the oxygen ring of the molecule and furnishing a mixture of the desired product **37** and its diastereoisomer **36**. This strongly basic quenching process was essential to the successful isolation of the dimeric

products **36** and **37**. Though the combined yield (19%) was modest, recycling of the starting material (**35**), which was recovered in 60% yield by simple acid–base extraction, greatly enhanced the material throughput of this dimerization process. Upon prolonged standing in CDCl_3 , the undesired product **36** was found to cleanly isomerize to the desired stereoisomer **37**, a conversion that could be accelerated by the addition of acetic acid. The aryl methyl ether groups of **37** were finally cleaved (AlBr_3 , 60% yield) to complete the total synthesis of hybocarpone (**2**).

The ease and rapidity of formation of the dimeric structure of hybocarpone and the high degree of stereocontrol in this cascade sequence suggest this oxidative dimerization may indeed represent a biosynthetic pathway, as postulated. It represents an unusually mild method of forging a highly hindered carbon–carbon bond in a diastereoselective manner and achieves an impressive increase in molecular complexity through an attractive sequence of synthetic transformations.

Thiostrepton

Thiostrepton (**3**, Figure 4) is the flagship member of the thiopeptide family of antibiotics.¹⁴ First described in 1956 by scientists at The Squibb Institute for Medical Research (now a subsidiary of Bristol-Myers Squibb),¹⁵ thiostrepton has found use as a topical antibiotic in veterinary medicine. Floss and coworkers have elucidated many details of the biosynthesis of thiostrepton.¹⁶ Of particular interest to us was the putative biosynthesis of the central dehydropiperidine core of the molecule, summarized in Scheme 7. Thus, a biosynthetic intermediate such as **38**, possessing a dehydroalanine-derived domain (formed by dehydration of a serine residue) and a serine-derived moiety, likely undergoes a dehydration and tautomerization to afford azadiene **39**, which is proposed to undergo a spontaneous aza-Diels–Alder cycloaddition to form dehydropiperidine system **40**. According to this biosynthetic hypothesis, subsequent reduction of the latter compound completes the formation of the dehydropiperidine core of thiostrepton (**41**).

A previously reported observation from the Wulff group¹⁷ provided an encouraging precedent for our proposed biomimetic dehydropiperidine core construction in the laboratory. Thus, azadiene **42** (Scheme 8), isolated as a crystalline solid at $-90\text{ }^\circ\text{C}$, was conceived as a building block for α -amino acid synthesis.¹⁷ Upon warming, azadiene **42** spontaneously dimerized to give aza-Diels–Alder⁶ adduct **44**, presumably through *exo* transition state **43**. Under appropriate conditions, the aryl imine of **44** was preferentially hydrolyzed to afford primary amine **45**.¹⁷ Although this precedent differed in key details from what we proposed to attempt (notably in that our proposed aza-Diels–Alder dimerization required an *endo* transition state), it nonetheless provided inspiration for our thiostrepton campaign, which we successfully completed in 2004.¹⁸

Scheme 9 depicts our thiostrepton cascade, developed for the construction of the dehydropiperidine core of the molecule. Thus, thiazolidine **46** (prepared from threonine and cysteine) was exposed to Ag_2CO_3 and DBU in pyridine at $-12\text{ }^\circ\text{C}$ (conditions A, Scheme 9) to effect extrusion of the sulfur atom and generate transient azadiene **47**.¹⁹ The latter species proceeded to dimerize in a Diels–Alder fashion, as expected. The yield of the desired imine hydrolysis product **49**, however, was a modest 22%, with bridged polycyclic byproduct **52** representing the lion's share of the isolated material (63% yield). This rather annoying side reaction was the result of a tautomerization of the initially formed *endo* aza-Diels–Alder dimerization product **48** to provide enamine **51**, which apparently underwent an aza-Mannich cyclization reaction to afford the undesired product **52**. After considerable experimentation, we discovered that the imine hydrolysis reaction manifold could be facilitated by simple addition of BnNH_2 (conditions B, Scheme 9), which raised the yield of dehydropiperidine

49 to a satisfying 60%. Aldehyde **50** was also recovered from this process in 68% yield, and could be recycled.

This would not be the only instance of an undesired cascade pathway in our thioistrepton campaign that had to be suppressed. Indeed, as shown in Scheme 10, in the subsequent manipulation, coupling of dehydropiperidine **49** with protected alanine **53** (EDC, HOAt) gave not the expected amide product, but rather imine ring contracted system **55**. Presumably, this transformation proceeded through the intermediacy of bridged bicyclic amina **54**. It was after considerable experimentation that we discovered that the use of the sterically small acylating agent **56** in the absence of any activating agents (e.g. 4-DMAP) could effect direct amidation of the sterically hindered primary amine moiety of **49**. The resulting amide product (**57**) was subsequently elaborated to synthetic thioistrepton (**3**).

The cascade reactions of the thioistrepton total synthesis discussed above had to be carefully optimized since minor changes to the reaction conditions induced wildly different reactions yielding unexpected products. Indeed, this is one of the challenges faced in developing and executing such complex sequences. Thorough and exquisite experimentation is, therefore, required to achieve and control the desired reaction pathways. However, as demonstrated here, such efforts can reap rich dividends.

C₂-Symmetric bisanthraquinone natural products

The bisanthraquinone natural products are a large class of complex secondary metabolites possessing a broad array of biological activities. Our attention was drawn to the cytoskyrin family of C₂-symmetric bisanthraquinone compounds, such as 2,2'-*epi*-cytoskyrin A (**4**, Figure 5),²⁰ rugulosin (**58**),²¹ and rugulin (**59**).²² Although anthraquinone monomers are readily identified within the polycyclic molecular architectures of these compounds, it was not evident at first glance how these structures might arise from their monomeric precursors. Careful analysis of these cage-like structures, however, revealed a logical pathway for their construction from simple monomeric anthraquinones. Thus, and as shown in Figure 6, retrosynthetic disconnection of the C4a–C4a' bond of rugulin (**59**) suggested structure **60**, possessing the same ring system as that of 2,2'-*epi*-cytoskyrin A (**4**) and rugulosin (**58**), as a possible advanced subtarget. Two of the three carbon–carbon bonds that join the two monomeric units within this carbon skeleton may be disconnected through retrosynthetic application of two sequential Michael additions, thus revealing simplified dimers **61–63** as potential intermediates. The latter structures may be formed through oxidation and dimerization of monomeric anthraquinones **64–66**, which, in turn, may arise from the oxidation of dihydroanthraquinones **67–69**. Indeed, Shibata and coworkers had previously demonstrated the feasibility of such transformations, albeit in low yield.²³ It seemed reasonable that nature may employ a similar sequence of events for the construction of these fascinating compounds.

Intrigued by the relatively simple chemistry postulated to lead to these complex cage-like systems, we set out to discover an efficient cascade pathway to cytoskyrin-type molecules in the laboratory, and reported the so-called cytoskyrin cascades in 2005.²⁴ In our model study with a substrate lacking the C2-hydroxyl group (see **67**, Figure 6), we discovered that each of the requisite transformations could be accomplished through judicious use of only the simplest of reagents, namely MnO₂, CSA, and/or Et₃N. Furthermore, through careful tuning of reaction conditions, any or all of the synthetic steps could be combined in a cascade sequence. In our ultimate synthetic strategy toward these natural products, we employed protected C2-hydroxyl groups in spite of the potential complication of elimination reactions. As shown in Scheme 11, dihydroanthraquinone **67** was exposed to the action of MnO₂, which initially effected oxidation to anthraquinone **64**. Tautomerization of this intermediate gave access to enol **70**, which dimerized through two sequential Michael additions to give, through the intermediacy of **73**,

isolable oxygen-bridged intermediate **76**. Further oxidation (see **79**) effected collapse of the oxygen bridge, giving rise to compound **61**. An intramolecular Michael addition within the latter molecule then generated intermediate **79**, lacking only one carbon–carbon bond of the cage-like framework of the targeted molecules. Upon addition of Et₃N and gentle warming, a second Michael addition effected the closure of the cage, furnishing protected 2,2'-*epi*-cytoskyrin A (**82**) in a highly gratifying 60% overall yield for the entire cascade starting from simple dihydroanthraquinone **67**. Subjecting dihydroanthraquinone **68** to the same reaction conditions afforded protected rugulosin (**83**) in 50% overall yield. Similarly, exposure of dihydroanthraquinone **69** to these reaction conditions provided cage system **60** in 40% overall yield.

The total syntheses of the targeted natural products were completed as shown in Scheme 12. Thus, cleavage of the MOM ethers from intermediates **82** and **83** revealed 2,2'-*epi*-cytoskyrin A (**4**) and rugulosin (**58**), respectively. Cage compound **60** was further oxidized with MnO₂ to give rugulin derivative **84**. Removal of the two MOM protecting groups from the latter compound afforded a substance with the alleged structure of rugulin (i.e. **59**), but its NMR spectral data did not match those reported for natural rugulin. The structure assigned to our synthetic material was verified by X-ray crystallographic analysis and, therefore, we concluded that the molecular structure of natural rugulin is not **59**. Unfortunately, as an authentic sample was not available, the true structure of rugulin still remains an unsolved mystery.

The cytoskyrin cascades are striking for both the expedient introduction of significant molecular complexity and the ease with which the reactions were induced. In total, the cytoskyrin cascade involves four bond-forming reactions and one bond-breaking event, and sets six stereogenic centers with complete stereochemical fidelity. Yet, the only reagents required to bring about this significant increase in molecular complexity were a common oxidant (MnO₂), a simple base (Et₃N), and a little warmth. It is indeed difficult to imagine a more direct means of accessing these complex cage-like molecules.

Biyouyanagin A

The anti-HIV agent biyouyanagin A was isolated from *Hypericum chinense* L. var. *salicifolium* (biyouyanagi in Japanese), a plant used in traditional Japanese medicine and reported in 2005, by Takaishi and colleagues.²⁵ Biyouyanagin A was assigned the molecular structure **85** or **86** (Figure 7) by NMR spectroscopy. This structure contains a striking and unusual all-*cis* cyclobutane ring system, which was proposed to arise biosynthetically from a [2+2] photocycloaddition reaction. Drawn to the promising biological activity, intriguing molecular architecture, and appealing biosynthetic hypothesis for biyouyanagin A, we evaluated the proposed [2+2] photocycloaddition through manual molecular modeling. We reasoned that the *endo* product (**85** or **86**) was disfavored because of significant steric repulsion in the transition state. Therefore, in our view, the *exo* product (**5** or **87**; Figure 7) represented the most likely structure of biyouyanagin A. As shown in Figure 8, we envisioned a synthesis of both **5** and **87** through a biomimetic [2+2] photocycloaddition reaction between hyperolactone C (**90**, naturally occurring)^{26,27} and either *ent*-zingiberene (**88**; *ent*-**88** is naturally occurring),²⁸ or *ent*-7-*epi*-zingiberene (**89**; *ent*-**89** is naturally occurring),²⁸ respectively. In 2007, we completed total syntheses of both **5** and **87**, and demonstrated conclusively that the true structure of biyouyanagin A is **5**.²⁹

Total syntheses of hyperolactone C (**90**) had previously been reported, but we hoped to improve on the Kinoshita synthesis,²⁷ which was not stereoselective with regards to C4. Our efforts to install the C4 stereogenic center in a selective manner led us to apply an interesting palladium-mediated cascade reaction first reported by Inuoe and coworkers³⁰ that had not previously seen use in total synthesis. Thus, as shown in Scheme 13, tertiary alcohol **91** (readily prepared by

an adaptation of the Kinoshita route) was heated with iodobenzene and catalytic amounts of $\text{Pd}(\text{PPh}_3)_4$ in Et_3N under an atmosphere of CO and CO_2 to deliver the desired product **98** in 79% yield. This cascade process presumably proceeded through an initial carbonylative Sonogashira-type cross coupling² to afford ynone **92**, which then engaged a molecule of CO_2 to form carbonic acid **93**. Intramolecular Michael addition then gave cyclic carbonate **94**, which reacted with the palladium catalyst to generate palladium-allyl species **95**. The η^1 complex **96**, in equilibrium with η^3 complex **95**, underwent ring closure to palladacycle **97**. Reductive elimination from palladacycle **97** delivered the observed product **98** and regenerated the active $\text{Pd}(0)$ catalyst. By virtue of the above mechanism, the formation of spirocycle **98** was stereospecific, with complete retention of stereochemistry at C4, as verified by X-ray crystallographic analysis.

Spirocycle **98** was smoothly converted into hyperlactone C (**90**) through a standard sequence of manipulations as shown in Scheme 14. A biomimetic [2+2] photocyclization reaction of hyperlactone C (**90**) and *ent*-zingiberene (**88**) then gave synthetic biyouyanagin A (**5**), which was identical to the natural substance. X-Ray crystallographic analysis confirmed the assigned stereochemistry of **5**, validating our structural reassignment of this secondary metabolite. 24-*epi*-Biyouyanagin A (**87**, Figure 7) was also synthesized in the same manner during this study.

The application of Inoue's palladium-mediated cascade sequence to the synthesis of hyperlactone C (**90**) provided exquisite stereocontrol in a situation where no such control was previously observed. The elimination of a tedious chromatographic separation of diastereoisomers significantly improved the practicality of the total synthesis of hyperlactone C (**90**) and, in turn, biyouyanagin A (**5**). Indeed, several biyouyanagin A analogues were synthesized for chemical biology studies through the developed synthetic technology.

Bisanthraquinone antibiotic BE-43472B

BE-43472B (**6**, Figure 9) is a structurally unique bisanthraquinone natural product first described (with no stereochemical details) in a Japanese patent in 1996 as an antitumor agent.³¹ It was rediscovered in 2006 by Rowley and coworkers³² as a bactericidal antibiotic with potency against a broad panel of drug-resistant bacterial strains, including methicillin-susceptible, methicillin-resistant, and tetracycline-resistant *Staphylococcus aureus* (MSSA, MRSA, and TRSA, respectively) and vancomycin-resistant *Enterococcus faecium* (VRE). The relative stereochemistry of the substance was elucidated, but the absolute configuration was left undetermined. Drawn to this combination of promising biological activity and exquisite molecular architecture, we initiated a program directed towards the laboratory construction of this molecule. We recently reported the total synthesis of both enantiomeric forms of BE-43472B and the assignment of its absolute configuration as that depicted in structure **6**.³³ Our synthetic strategy focused on a Diels–Alder-based assembly of the bisanthraquinone system. Thus, and as shown in Figure 10, advanced intermediate **99**, containing the complete octacyclic skeleton of BE-43472B, was envisioned as the product of an $\text{S}_{\text{N}}(\text{Ar})$ reaction of hemiketal **100**, which was anticipated to arise spontaneously from its ketone isomer (i.e. **101**). The latter structure was proposed to be formed through a Diels–Alder cycloaddition⁶ of silyl enol ether **103** and naphthoquinone system **102**.

Although the sequence of events anticipated by our retrosynthetic analysis likely could be achieved in a sequential manner, we were pleased to find that under optimized conditions, the formation of octacyclic intermediate **99** could be effected in a single operation by simple heating. Thus, and as shown in Scheme 15, a solution of diene **103** and naphthoquinone system **102** in CH_2Cl_2 was initially heated at 85 °C in a sealed tube, conditions that induced the expected Diels–Alder cycloaddition reaction, presumably by way of *endo* transition state **104**, to provide an equilibrating mixture of adduct **101** and its hemiketal isomer (i.e. **100**). Upon

further heating in toluene at reflux in a reaction vessel equipped with a Dean–Stark trap (to azeotropically remove the generated MeOH), an intramolecular Michael-type addition occurred to afford **105**, which spontaneously proceeded to furnish the targeted octacyclic product in a gratifying 98% overall yield for the entire cascade sequence. Interestingly, the resulting product was obtained as a ca. 2:1 mixture of inconsequential C9a epimers **107** and **99**. The unexpected isomer **107** probably formed through a spontaneous isomerization of hemiketal **100** to the epimeric system **106**.

The mixture of **99** and **107** was transformed into enone **108** (Scheme 16) through a standard sequence of manipulations. All that now remained for the completion of the total synthesis of BE-43472B (**6**) was the installation of one oxygen atom at the proper position. After considerable experimentation, we discovered that the requisite oxygen could be installed through nucleophilic epoxidation (*t*-BuOOH, DBU) to afford epoxide **109** as the predominant diastereoisomer (12:1 *dr*). Distressingly, all attempts at thermal or acid-promoted isomerization of this epoxide to antibiotic BE-43472B (**6**) yielded either no reaction, or decomposition. We finally called upon the rarely used photoinduced isomerization of α,β -epoxy ketones³⁴ as a means to achieve the desired rearrangement. Gratifyingly, irradiating a benzene solution of epoxide **109** with UV light effected the desired isomerization and delivered BE-43472B (**6**) in a satisfying 83% yield (based on 92% conversion). This solution to the problem at hand was striking and pleasing for both its simplicity and efficiency. The reaction was proposed to proceed through initial photo-excitation ($n \rightarrow \pi^*$) of the carbonyl moiety adjacent to the epoxide unit of **109** to generate diradical **110**. As shown in the partial structure of **110**, the neighboring epoxide C–O bond is appropriately aligned with the benzylic radical so as to undergo a facile bond cleavage to afford ring-opened intermediate **111**. A subsequent 1,4-shift of the pseudoequatorial β -hydrogen, favored by good n,σ -orbital overlap, then results in enol **112**, tautomerization of which provides the targeted molecule, antibiotic BE-42472B (**6**). Though none of the putative intermediates (**110**–**112**) are isolable, treatment of this reaction as a cascade sequence was useful to our understanding of the outcome, especially in view of the fact that the α -epoxide diastereoisomer of **109** refused to undergo the same rearrangement, presumably due to poor orbital overlap in the transient species corresponding to **110**.

The total synthesis of bisanthraquinone antibiotic BE-43472B highlights the utility of cascade reactions in both planned and unplanned situations. The developed Diels–Alder cascade sequence resulted in the formation of three rings and the controlled installation of three stereogenic centers. The unusual photoisomerization process employed in the final step was adopted in response to an unanticipated challenge, and its successful execution enabled the completion of this synthetic campaign in a highly rewarding manner. Employing only heat or light, both cascade processes are shining examples of green chemistry.

Conclusion

The cascade reactions employed in the case studies presented herein are not the only conceivable means of synthesizing the target molecules under construction. However, these sequences possess many practical advantages in addition to their undeniable aesthetic appeal. Well designed and executed cascades are effective solutions to challenging problems in organic synthesis, and, in certain cases, only the simplest of conditions and reagents, such as heat, light, acid, or base, are needed. The significant molecular complexity generated, combined with a remarkable simplicity of operation, renders cascade reactions potentially cost-effective and environmentally friendly. As synthetic chemists take on ever more ambitious targets, the design and execution of cascade sequences will no doubt play a crucial role in reaching their goals of elegance and practicality.

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Biographies

K. C. Nicolaou, born and raised in Cyprus, studied chemistry in England at the University of London (B.Sc., 1969, Bedford College, First Class Honors; Ph.D., 1972, University College, with Professors Sondheimer and Garratt). After postdoctoral appointments at Columbia University (1972–1973, Professor Katz) and Harvard University (1973–1976, Professor Corey), he joined the faculty at the University of Pennsylvania, where he eventually became the Rhodes–Thompson Professor. In 1989, he accepted joint appointments at the University of California, San Diego, where he is Distinguished Professor of Chemistry, and The Scripps Research Institute, where he is Chemistry Department Chairman and holds the Skaggs Professorship of Chemical Biology and the Darlene Shiley Chair in Chemistry.

Jason S. Chen received his A.B. and A.M. degrees in 2001 from Harvard University, where he performed research under the supervision of Professor Matthew D. Shair. He then joined Enanta Pharmaceuticals (Watertown, MA) as a medicinal chemist studying novel cyclosporine A analogues. He joined Professor K. C. Nicolaou's group at The Scripps Research Institute in 2003, where he was a National Defense Science and Engineering Graduate (NDSEG) Fellow. In 2008, he completed his Ph.D. studies on the total synthesis and biological evaluation of unciamycin. He is currently a research associate in Professor Nicolaou's laboratory.

Figure 1. Molecular structures of endiandric acid A (**1**), hybocarpone (**2**), thiostrepton (**3**), 2,2'-*epi*-cytoskyrin A (**4**), biyouyanagin A (**5**), and BE-43472B (**6**).

1: endiandric acid A

8: endiandric acid C

7: endiandric acid B

9: endiandric acid D

Figure 2.
Molecular structures of endiandric acids A–D (**1**, **7–9**).

Figure 3.
Molecular structure of hybocarpone (2).

Figure 4.
Molecular structure of thiostrepton (**3**).

4: 2,2'-*epi*-cytoskyrin A (R = OMe)

58: rugulosin (R = Me)

59: rugulin (proposed)

Figure 5. Molecular structures of 2,2'-*epi*-cytoskyrin A (**4**), rugulosin (**58**), and the proposed structure of rugulin (**59**).

Figure 6. Retrosynthetic analysis of 2,2'-*epi*-cytoskyrin A (**4**), rugulosin (**58**), and the proposed structure of rugulin (**59**).

a) originally proposed structures: Takaishi et al.

b) revised structures: Nicolaou et al.

Figure 7.
Originally proposed (a) and revised (b) structures of biyouyanagin A.

Figure 8.
Retrosynthetic analysis of the proposed structures for biyouyanagin A.

6: BE-43472B

Figure 9.
Molecular structure of BE-43472B (6).

Figure 10.
Retrosynthetic analysis of BE-43472B (**6**).

Scheme 1.

Black's hypothesis for the biosynthesis of the endiandric acids.

Scheme 2.

Biomimetic cascade total synthesis of endiandric acids A (**21**), D (**19**), and E (**20**) methyl esters.

Scheme 3.

Biomimetic cascade total synthesis of endiandric acids B (**25**), C (**26**), F (**23**), and G (**24**) methyl esters.

Scheme 4.

Proposed biosynthesis of hybocarpone (**2**) from 6-methylchristazarin (**27**).

Scheme 5.
Highlights of the photoenolization/Diels–Alder synthesis of 6-methylchristazarin (**27**)

Scheme 6.
Oxidative radical dimerization of **33** and total synthesis of hybocarpone (**2**).

Scheme 7.
Proposed biosynthesis of the dehydropiperidine core of thioestrepton.

Scheme 8.
Precedent for the proposed aza-Diels-Alder dimerization reaction.

Scheme 9.

Biomimetic aza-Diels-Alder dimerization cascade and construction of the dehydropiperidine core of thioestrepton (**49**).

Scheme 10.

Competing amide formation pathways and completion of the total synthesis of thiostrepton (**3**).

Scheme 11.
 Cascade synthesis of cage-like compounds **82**, **83**, and **60**.

Scheme 12.

Completion of the total syntheses of 2,2'-*epi*-cytoskyrin A (**4**), rugulosin (**58**), and the proposed structure of rugulin (**59**).

Scheme 13.
Palladium-catalyzed cascade synthesis of spirocycle **98**.

Scheme 14. Highlights of the completion of the total synthesis of biyouyanagin A (**5**).

Scheme 15. Diels-Alder/ $S_N(\text{Ar})$ cascade synthesis of the BE-43472B skeleton (**99** and **107**).

Scheme 16.
Photoisomerization and completion of the total synthesis of BE-43472B (**6**).