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Total synthesis of complex heterocyclic natural products*,**

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Abstract: Total synthesis campaigns toward complex heterocyclic natural products are a prime source of inspiration for the design and execution of complex cascade sequences, powerful reactions, and efficient synthetic strategies. We highlight selected examples of such innovations in the course of our total syntheses of diazonamide A, azaspiracid-1, thiostrepton, 2,2'-*epi*-cytoskyrin A and rugulosin, abyssomicin C, platensimycin, and uncialamycin.

Keywords: total synthesis; natural products; marine neurotoxins; antibiotics; antitumor agents.

INTRODUCTION

Complex natural products have always served as a prime source of inspiration for the synthetic organic chemist and continue to do so to this day. The seemingly limitless structural variations of the secondary metabolites found in nature provide a wealth of synthetic challenges that play a major role in developing and testing the universe of strategies and reactions available for the synthesis of complex organic molecules.

In recent years, our laboratory has been inspired by a diverse array of heterocyclic natural products. Their beautiful molecular architectures provided us with opportunities to ponder their biosynthesis, design complex cascade sequences [1], apply powerful reactions, and devise efficient strategies for their construction. Among the many target molecules that have inspired our research over the last few years are the natural products discussed in this review: diazonamide A (**1**), azaspiracid-1 (**2**), thiostrepton (**3**), 2,2'-*epi*-cytoskyrin A (**4**) and rugulosin (**5**), abyssomicin C (**6**), platensimycin (**7**), and uncialamycin (**8**), all shown in Fig. 1.

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**Dedicated to Prof. Madeleine M. Joullié on the occasion of her 80th birthday.
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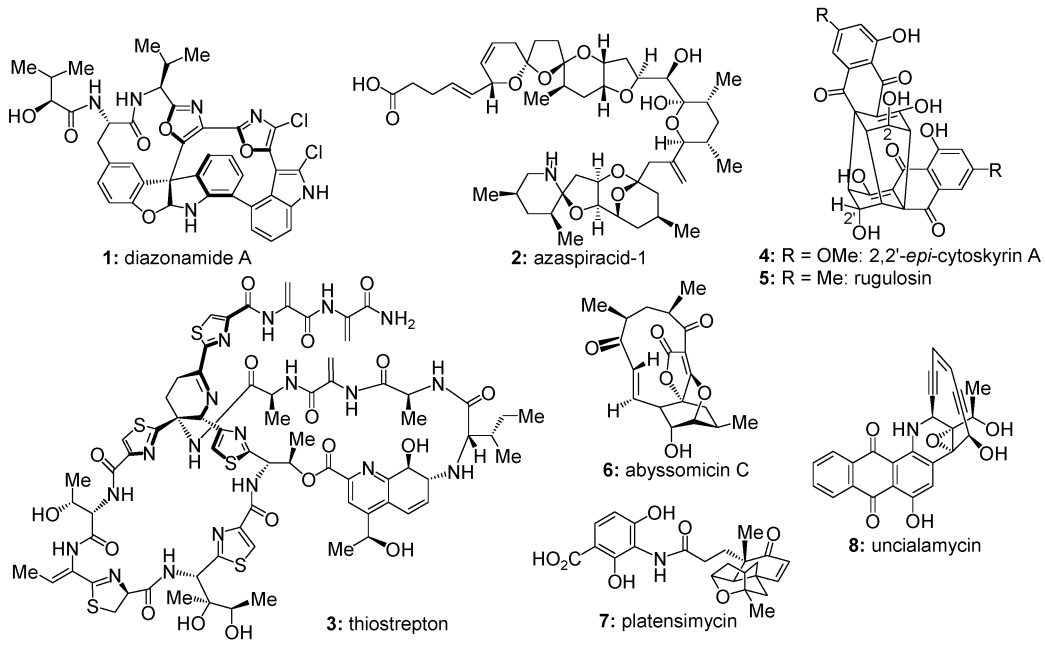


Fig. 1 Selected molecules from nature's molecular diversity library as synthetic targets.

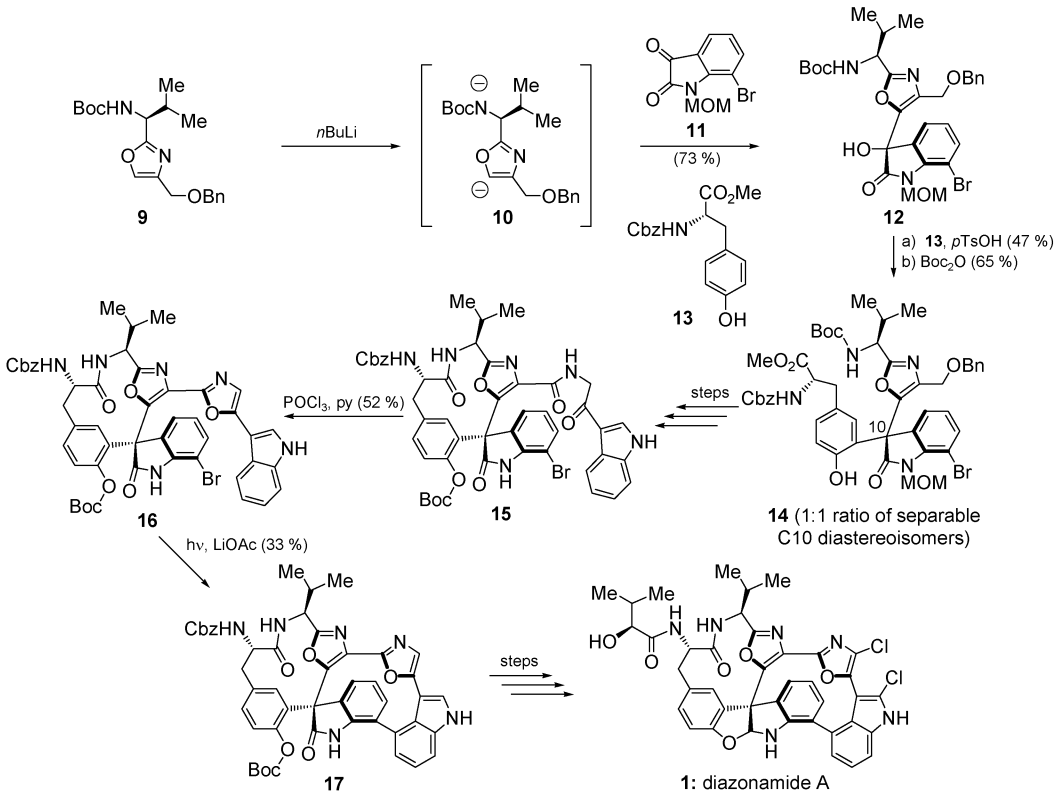
TOTAL SYNTHESIS CASE STUDIES

Diazonamide A

Diazonamide A (**1**) is a cytotoxic compound containing a peptidic macrocyclic domain fused to a polyaromatic macrocyclic structural motif. It was isolated and characterized by the Fenical camp in collaboration with the Clardy group in 1991 [2]. Its striking molecular architecture and important biological activity prompted total synthesis efforts by many groups around the world [3,4], including ours [5–7]. In 2001, the Harran group reported the total synthesis of the initially proposed structure of diazonamide A and proposed a revised structure [3a,b]. With nontrivial changes in the core of the molecule, the revised structure forced a reevaluation of our synthetic strategy toward diazonamide A. Two strategies were followed, with one tending to the polyaromatic macrocyclic domain first and the other placing the peptidic macrocycle at the front end of the synthetic sequence.

Our first total synthesis of diazonamide A (**1**) [6] utilized a bisarylation of an isatin derivative to synthesize the all-carbon quaternary center at the core of the molecule's structure. While acid-promoted bisarylations of isatin at C3 were known [8], the existing methodology did not allow for selective sequential arylation, a challenge that was met as part of the campaign to synthesize diazonamide A. Indeed, in the course of synthesizing diazonamide A, a stepwise bisarylation of isatin derivatives was developed (Scheme 1). Thus, oxazole derivative **9** was exposed to *n*BuLi to afford bisanion **10**, which attacked isatin derivative **11** to yield monoarylated intermediate **12**. Acid-promoted arylation with tyrosine derivative **13** then yielded, after Boc protection, differentially bisarylated intermediate **14**.

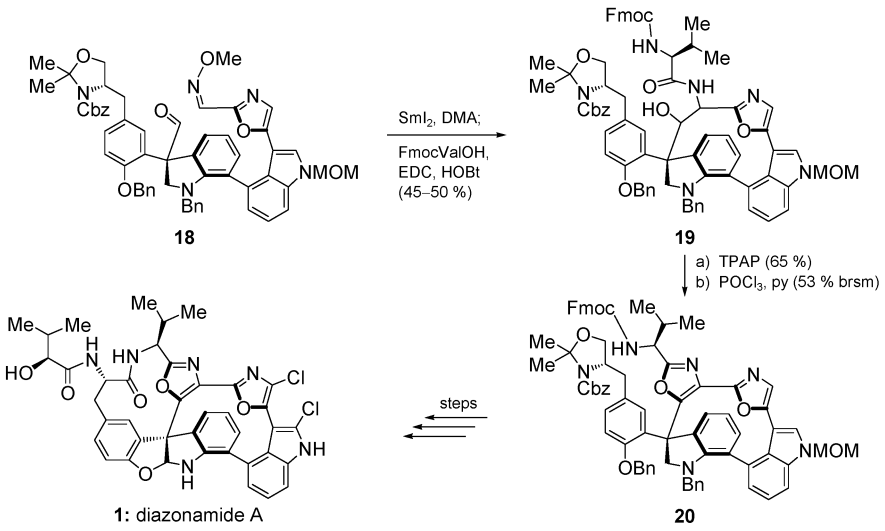
Completion of the peptidic macrocycle and attachment of the indole moiety yielded intermediate **15**, at which point our attention turned to synthesizing the requisite oxazole ring in the polyaromatic macrocyclic section to be followed by closure of the polyaromatic macrocycle. While subjecting intermediate **15** to standard Robinson–Gabriel cyclodehydration conditions afforded the desired oxazole derivative **16** in low yields, none of the other conditions afforded as high a yield as the use of pyridine-buffered $POCl_3$, a reaction modification developed during our campaign toward the originally proposed structure of diazonamide A [5]. Subjecting this product to a Witkop-type photocyclization [3a,9] af-



Scheme 1 Highlights of the first total synthesis of diazonamide A (**1**).

forded compound **17**. This advanced intermediate was then converted in five steps to diazonamide A (**1**), whose spectroscopic data matched those of the natural product [2].

Our second total synthesis of diazonamide A (**1**) [7] was patterned after our initial forays toward the originally proposed structure [5]. In this strategy, the synthesis of a central oxazole ring system would play a key role, closing the polyaromatic macrocycle and providing a point of attachment for a fragment of the peptidic macrocycle (Scheme 2). Closure of the polyaromatic macrocycle was effected by a SmI_2-promoted heteropinnacol reduction of aldehyde oxime ether **18** to yield, after in situ amide coupling, macrocyclic compound **19** [10]. After tetrapropylammonium perruthenate (TPAP) oxidation of the resulting secondary hydroxyl group, the above-described use of pyridine-buffered $POCl_3$ to effect a Robinson–Gabriel cyclodehydration [5] furnished oxazole intermediate **20**. No other conditions yielded the desired oxazole intermediate, providing further evidence for the mildness and generality of the newly developed conditions. Oxazole intermediate **20** was then successfully converted to diazonamide A (**1**), completing our second total synthesis of this uniquely challenging natural product that, together with the first total synthesis, demonstrated the power of chemical synthesis in complex molecule construction and structural elucidation.



Scheme 2 Highlights of the second total synthesis of diazonamide A (**1**).

Azaspiracid-1

Azaspiracid-1 (**2**) is a marine biotoxin found in contaminated mussels that causes a toxic syndrome known as azaspiracid poisoning (AZP), with symptoms that include nausea, vomiting, and severe diarrhea [11]. In 1998, Yasumoto, Satake, and coworkers isolated and characterized azaspiracid-1 as one of two possible diastereoisomers [12], one of which (**21**) is shown in Fig. 2. In light of the importance of this marine toxin, our laboratory pursued its total synthesis, only to find out, in 2003, that the proposed structure was in error [13]. It was only after a campaign whose narrative resembles a detective story that the true nature of this fascinating natural product was elucidated as structure **2** [14].

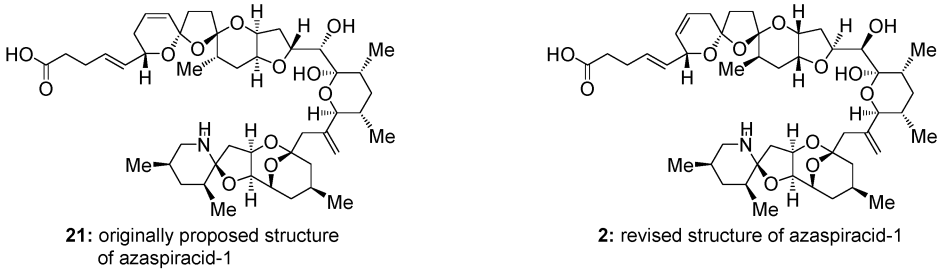
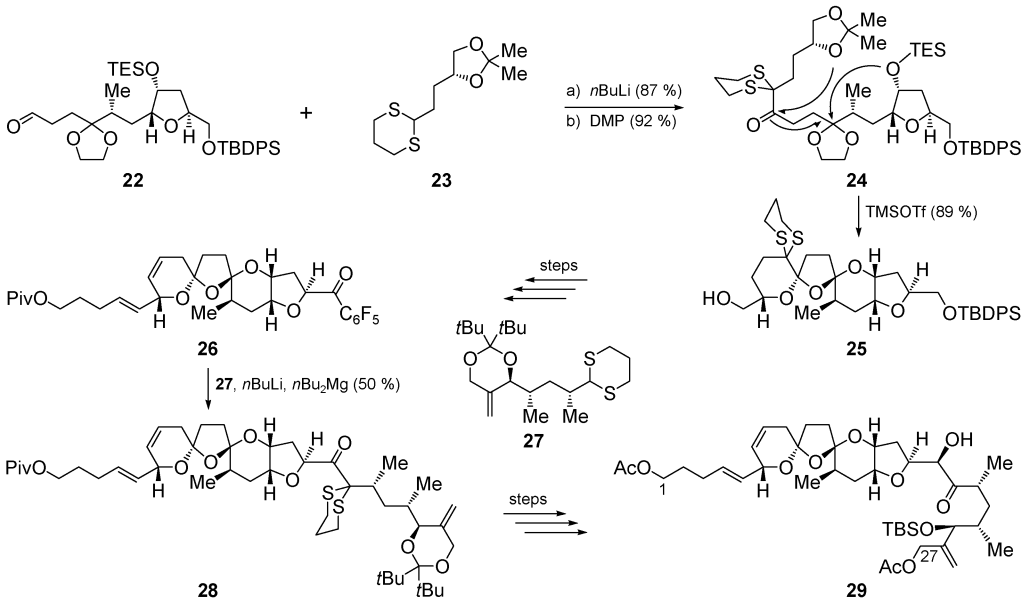


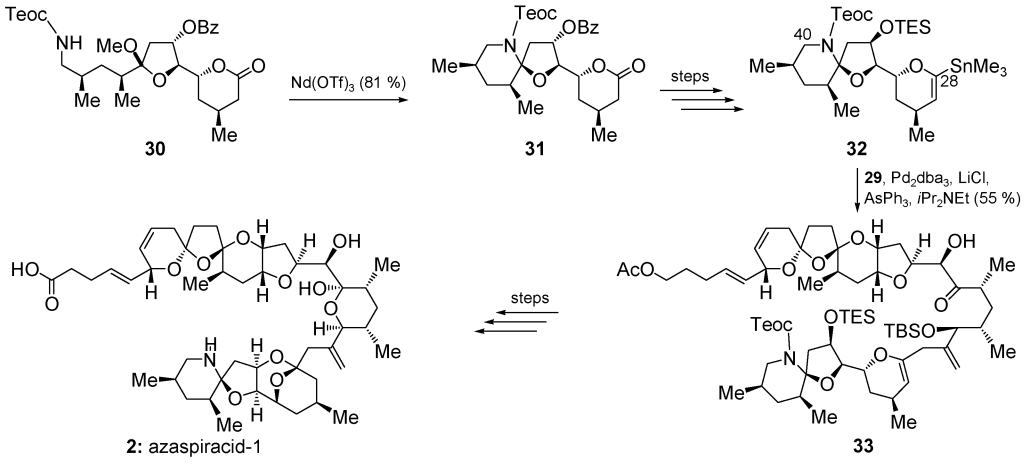
Fig. 2 Originally proposed and revised structures of azaspiracid-1.

The synthesis of the bis-spiroketal moiety utilized a coupling of aldehyde **22** with dithiane **23** to yield, after oxidation, ketone **24** (Scheme 3). A TMSOTf-initiated cascade sequence led, from ketone **24**, to the tetracyclic bis-spiroketal **25** stereoselectively and in excellent yield. This intermediate was converted into pentafluorophenyl ester **26**, which was coupled with the anion derived from dithiane **27** to yield intermediate **28**. A few functional group transformations yielded the C1–C27 fragment (**29**).



Scheme 3 Highlights of the total synthesis of azaspiracid-1 (**2**). Construction of the C1–C27 fragment.

Synthesis of the aminol moiety of the C28–C40 fragment (**32**) proved to be surprisingly problematic, for initial attempts to promote the cyclization of carbamate **30** to afford protected aminal **31** using Brønsted or Lewis acids were unsuccessful (Scheme 4). Fortunately, extensive screening of Lewis acids ultimately led to the discovery of catalytic $Nd(OTf)_3$ as a suitable initiator of the required ring closure. Protected aminol **31** was converted into organostannane **32**, which was coupled with allylic acetate **29** to yield advanced intermediate **33** [15], a molecule that contained the entire carbon skeleton of azaspiracid-1. A series of functional group manipulations led to synthetic azaspiracid-1 (**2**) possessing identical spectroscopic data to those of the authentic substance [12]. Thus, through extensive total synthesis efforts, the structure of this marine toxin was finally fully elucidated. An improved, second-generation total synthesis of azaspiracid-1 was successfully extended to the synthesis of its siblings, azaspiracid-2 and -3 [16].

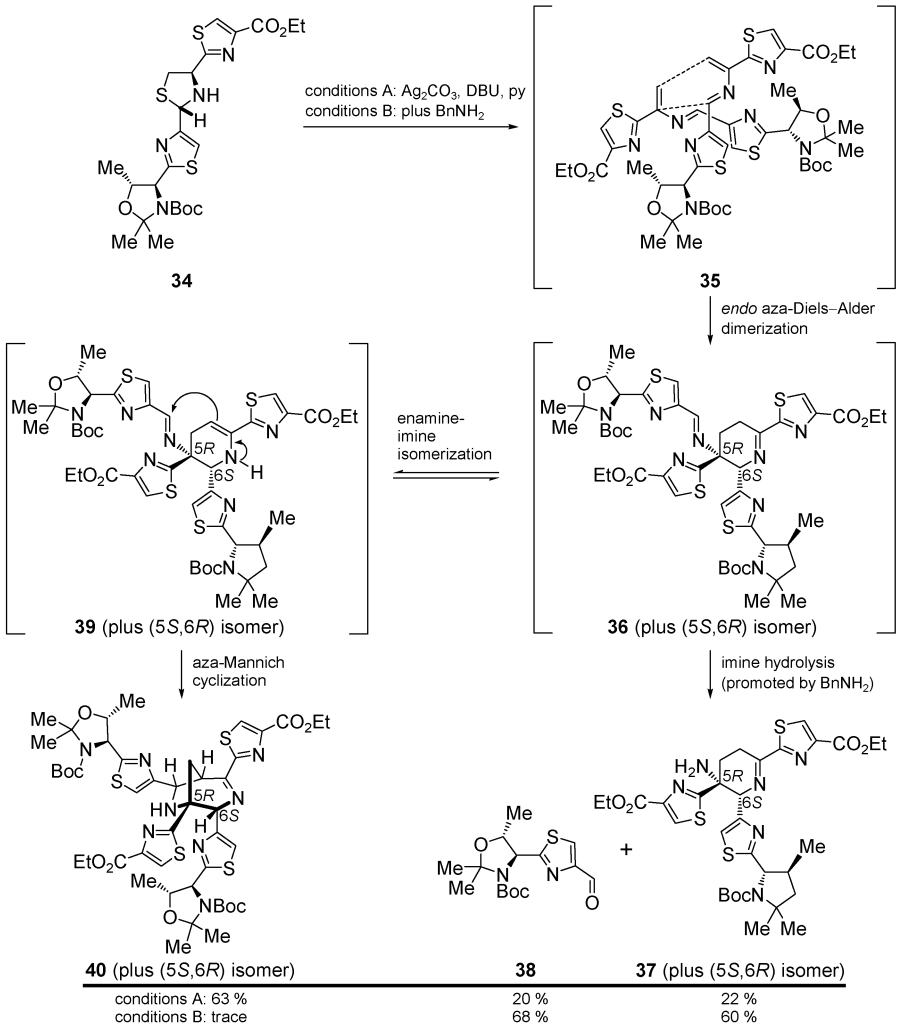


Scheme 4 Highlights of the total synthesis of azaspiracid-1 (**2**). Completion of the synthesis.

Thiostrepton

First isolated in 1954, thiostrepton (**3**) is the flagship of the thiopeptide class of natural products [17]. It is active against Gram-positive bacteria [18] and *Plasmodium falciparum* (the parasite responsible for the majority of malaria cases) [19], and possesses potent immunosuppressive properties [20]. Studies on the biosynthetic origins of thiostrepton have revealed that all structural motifs of the molecule have amino acid origins [21]. Most fascinating, these studies implicated the aza-Diels–Alder reaction in the biogenesis of the dehydropiperidine moiety found at the core of the molecule.

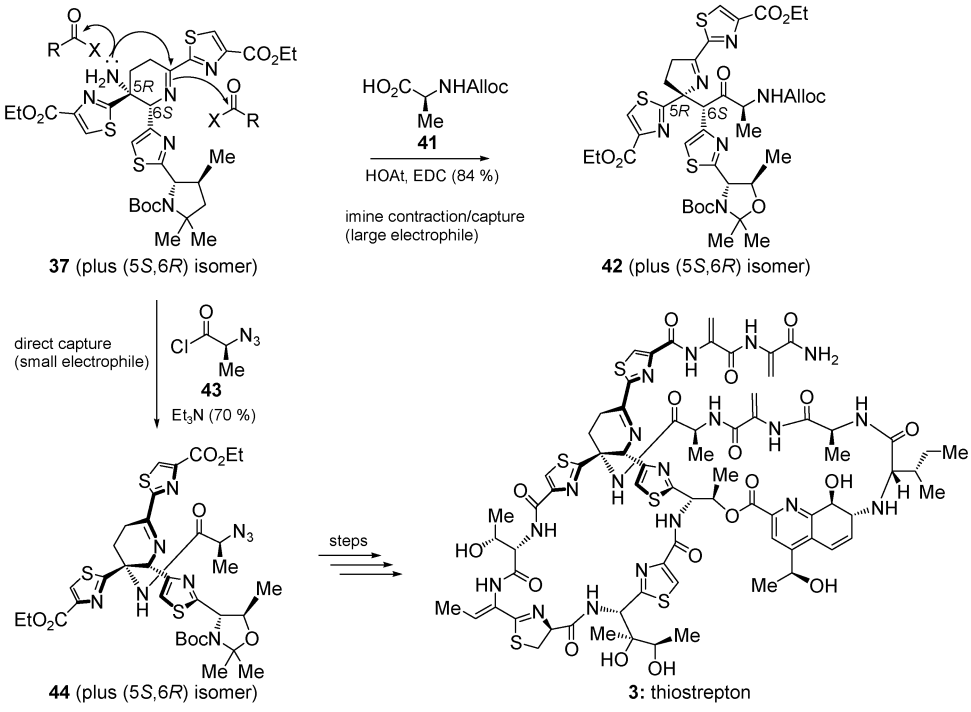
Inspired by the intriguing biosynthesis of the core dehydropiperidine moiety, our strategy for the total synthesis of thiostrepton [22] focused on an aza-Diels–Alder based dimerization of a suitable azadiene system [23] (Scheme 5). Thus, reaction of thiazolidine derivative **34** with Ag_2CO_3, DBU, and pyridine (conditions A) led to a transient azadiene (**35**) whose rapid dimerization furnished, upon selective imine rupture, the desired tetrahydropiperidine intermediate **37** and aldehyde **38**, which could be recycled. However, under these conditions, the major product was the complex heterocycle **40**, presumably formed by isomerization of intermediate **36** to tautomeric enamine **39** and subsequent aza-



Scheme 5 Highlights of the total synthesis of thiostrepton. Construction of the tetrahydropiperidine core.

Mannich cyclization. With this mechanistic rationale for the formation of undesired product **40** in mind, benzylamine was added (conditions B) to enhance the rate of imine hydrolysis, thus avoiding the undesired pathway. Pleasingly, this simple procedural change led to the suppression of the undesired reaction pathway and an increase of the yield of the desired tetrahydropiperidine product (**37**) from 22 to 60 %.

With the key construction accomplished, another challenge lay in wait (Scheme 6). Attempted amide coupling of the hindered primary amine in intermediate **37** with protected alanine **41** yielded imine ring-contracted product **42**. While the mechanistic course of this undesired reaction was clear, the means to suppress it was not so evident. However, through systematic experimentation, it was discovered that small electrophiles were directly captured by the hindered primary amine without changing the ring size, whereas large electrophiles reacted with concomitant imine ring contraction. Therefore, acid chloride **43** was chosen as a masked alanine unit by virtue of its relatively small size, resulting in the formation of the desired amide bond to yield intermediate **44**, which upon further elaboration was successfully transformed into thiostrepton (**3**) [24].



Scheme 6 Highlights of the total synthesis of thiostrepton (**3**). Completion of the synthesis.

2,2'-*epi*-Cytoskyrin A and rugulosin

The bisanthraquinones are an impressive class of compounds isolated from a variety of fungi and lichens that possess a broad array of biological activities. Structurally, they are characterized by the presence of two identical monomeric units with varying degrees of oxidation and bonding joining them together. Examples of this family of natural products include cytoskyrin A (**45**) [25], 2,2'-*epi*-cytoskyrin A (**4**) [26], rugulosin (**5**) [27], rugulin (**46**) [28], and flavoskyrin (**47**) [27d] (Fig. 3). Flavoskyrin is the only true heterocyclic compound of this series, but one serving as the precursor of all the others. In the course of our model studies toward cytoskyrin A (**45**) [29,30b], it was discovered that all the bonding

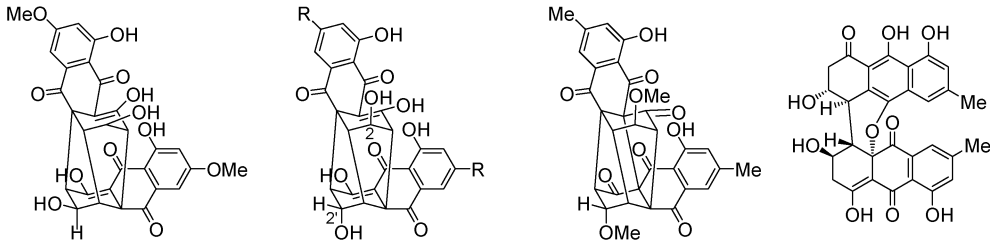
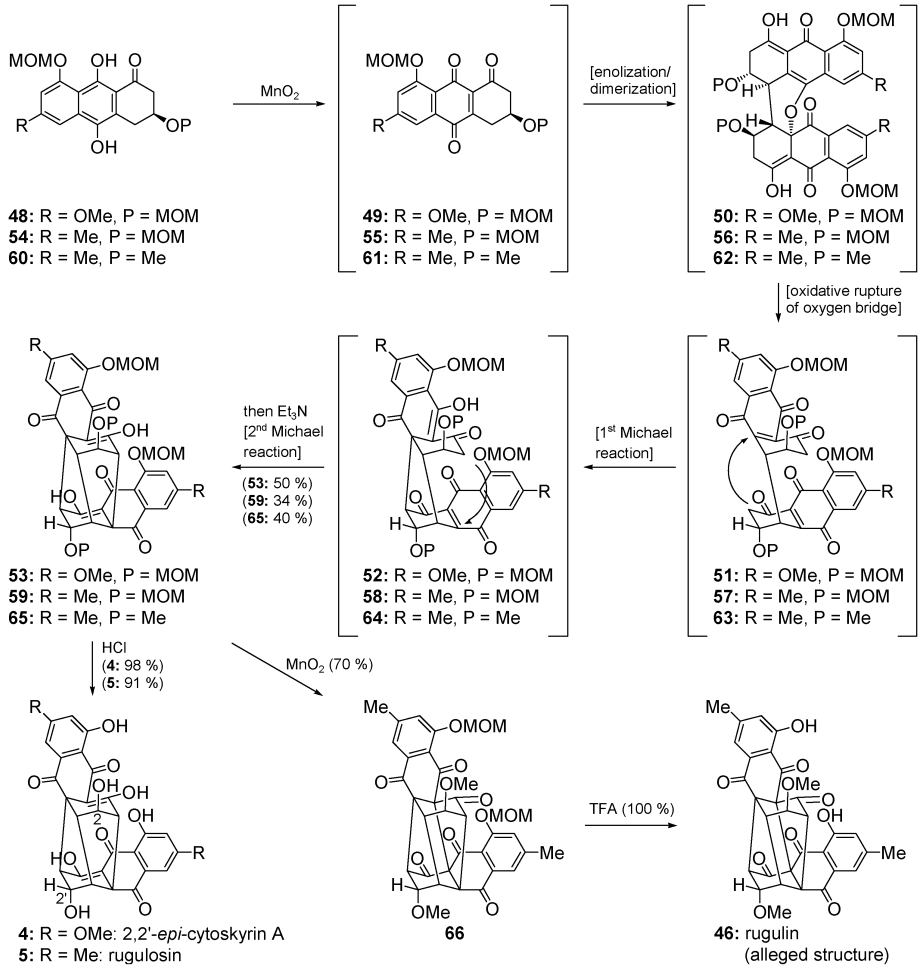


Fig. 3 Structures of selected members of the bisanthraquinone class of natural products.

patterns found within this compound class could be selectively formed by controlled, one-pot cascade reactions starting with the monomeric precursor unit.

Emboldened by our successful model studies, we set out to synthesize selected members of the bisanthraquinone class of natural products via ambitious cascade sequences [30] (Scheme 7).



Scheme 7 Highlights of the total synthesis of 2,2'-*epi*-cytoskyrin A (**4**), rugulosin (**5**), and the alleged structure of rugulin (**46**).

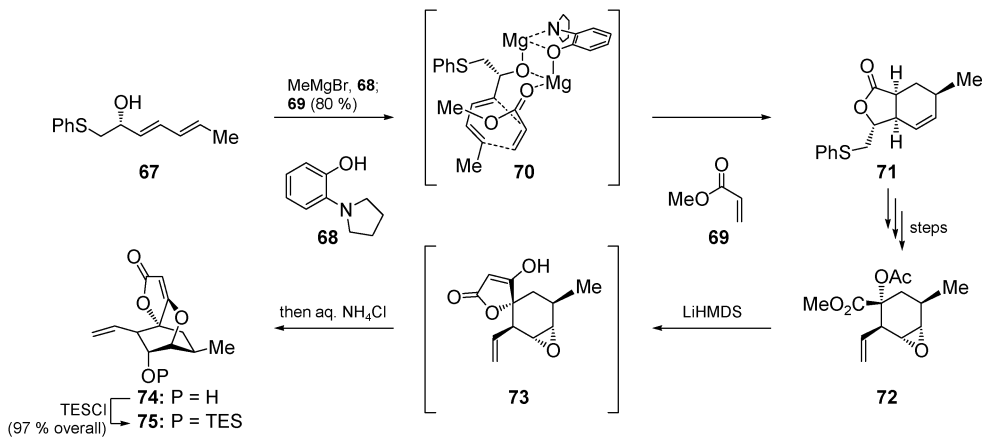
Subjecting dihydroquinone derivative **48** to the action of MnO_2 followed by the addition of Et_3N afforded cage-like compound **53** in a single operation. This cascade reaction occurred via oxidation of **48** to quinone derivative **49**, which upon enolization and formal hetero-Diels–Alder dimerization yielded isolable intermediate **50**. Further MnO_2-mediated oxidation ruptured the oxygen bridge of **50** to yield intermediate **51**, which under the reaction conditions underwent intramolecular Michael addition to yield compound **52**. Finally, addition of Et_3N to the reaction mixture promoted a second intramolecular Michael addition to yield cage-like compound **53**. Deprotection of **53** then afforded 2,2'-*epi*-cytoskyrin A (**4**).

Likewise, rugulosin (**5**) was successfully synthesized from dihydroquinone derivative **54**. Thus, exposure of the latter compound to MnO_2 and Et_3N afforded cage-like compound **59** by way of intermediates **55–58**. Acid-induced deprotection of compound **59** yielded rugulosin (**5**). Altering the choice of hydroxyl protecting group, dihydroquinone derivative **60** was converted to cage-like structure **65** by way of intermediates **61–64**. Further oxidation of **65** led to compound **66**, which was deprotected to furnish the alleged structure of rugulin (**46**). Although X-ray crystallographic analysis of the latter confirmed its structure, its spectroscopic data did not match those reported for the natural substance [28]. In the absence of an authentic sample of the natural product, the true structure of rugulin remains elusive. These studies also led to a family of flavoskyrin-like compounds, including **50**, **56**, and **62**.

Abyssomicin C

In 2004, Süssmuth and Fielder reported the isolation and structural determination of abyssomicin C (**6**) [31]. Abyssomicin C is the first known natural inhibitor of aminodeoxychorismate synthase and aminodeoxychorismate lyase, enzymes responsible for the biosynthesis of *p*-aminobenzoic acid (*p*ABA). Abyssomicin C was shown to inhibit the growth of both methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-intermediate *S. aureus* (VISA). The novel mechanism of action and interesting structure of abyssomicin C caught the attention of many synthetic groups [32], including ours [33].

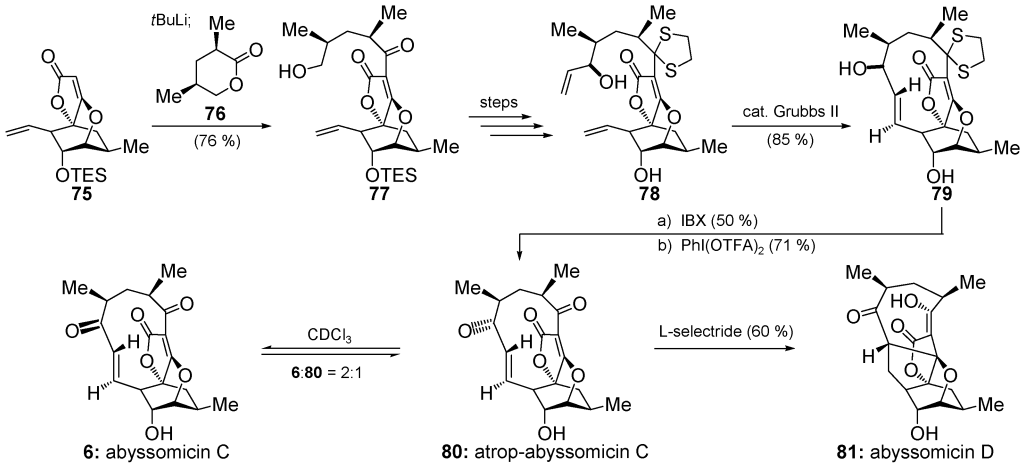
Our synthesis of abyssomicin C commenced with a Diels–Alder cycloaddition reaction [34] of diene **67** and methyl acrylate (**69**) to yield, after spontaneous lactonization, compound **71** (Scheme 8). This cycloaddition, initially promoted by MeMgBr, proved to be problematic, forcing a search for a means of improving the yield of this key step. Extensive screening of conditions ultimately led to the previously undescribed use of aminophenol derivative **68** as a means to improve this reaction.



Scheme 8 Highlights of the total synthesis of abyssomicin C (**6**). Construction of the heterocyclic core.

Presumably, the magnesium cation and the additive serve to template the cycloaddition partners as shown in **70**, and in so doing enhance reactivity and stereoselectivity. Intermediate **71** was converted to epoxyacetate **72**, which was exposed to LiHMDS to induce a Dieckmann cyclization to intermediate **73**. Intermediate **73** was not isolated, but rather was heated with aqueous NH_4Cl to effect intramolecular attack of the epoxide to yield tricycle **74**. The latter compound was found to be somewhat unstable to chromatography and was therefore protected as triethylsilyl (TES) ether **75**.

With intermediate **75** in hand, we set about attaching the macrocyclic domain of the molecule (Scheme 9). Thus, lithiation of **75** and acylation with lactone **76** afforded compound **77**, which was converted through a short sequence of steps into bis-terminal alkene **78**. Ring-closing metathesis [35] within the latter compound afforded macrocyclic system **79**. Oxidation and thioketal cleavage led to compound **80**, whose spectroscopic data were similar to those of abyssomicin C [31], but not identical. Fortuitously, upon standing in unbuffered $CDCl_3$, a 2:1 ratio of abyssomicin C (**6**) and compound **80** was obtained. X-ray crystallographic analysis of the "mystery" compound revealed its identity as atrop-abyssomicin C (**80**). This unanticipated atropisomerism would prove to have consequences in reactivity that may lend insight into the biosynthesis of the abyssomicins. Thus, we found that atrop-abyssomicin C (**80**) was readily reduced to abyssomicin D (**81**) [31], whereas abyssomicin C (**6**) was reduced, under identical conditions, to afford a compound identified as a diastereoisomer of abyssomicin D. Based on this information, we hypothesized that abyssomicin D (**81**) may not be biosynthesized from abyssomicin C (**6**). Rather, it is likely that both atropisomers of abyssomicin C may be formed in nature, with atrop-abyssomicin C (**80**) being readily metabolized to abyssomicin D (**81**).

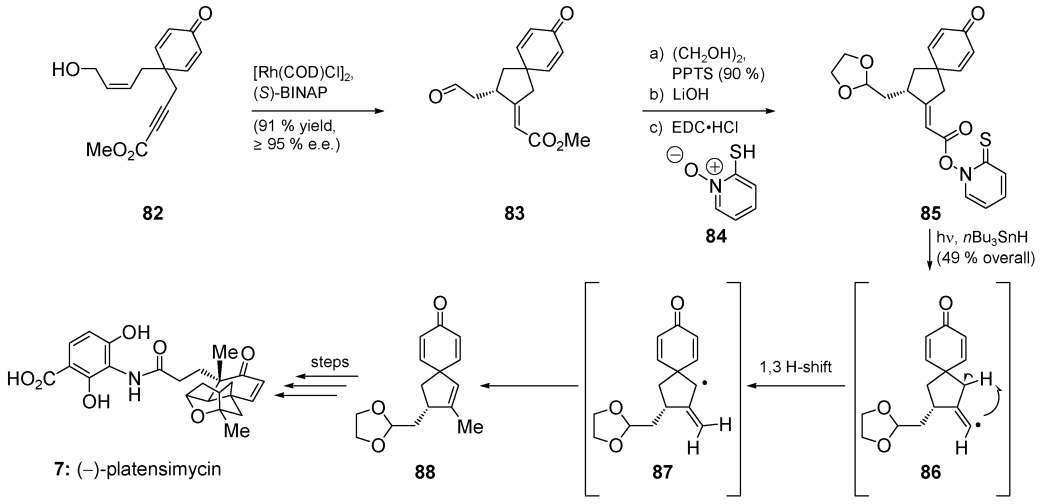


Scheme 9 Highlights of the total synthesis of abyssomicin C (**6**). Completion of the synthesis and synthesis of abyssomicin D (**81**).

Platensimycin

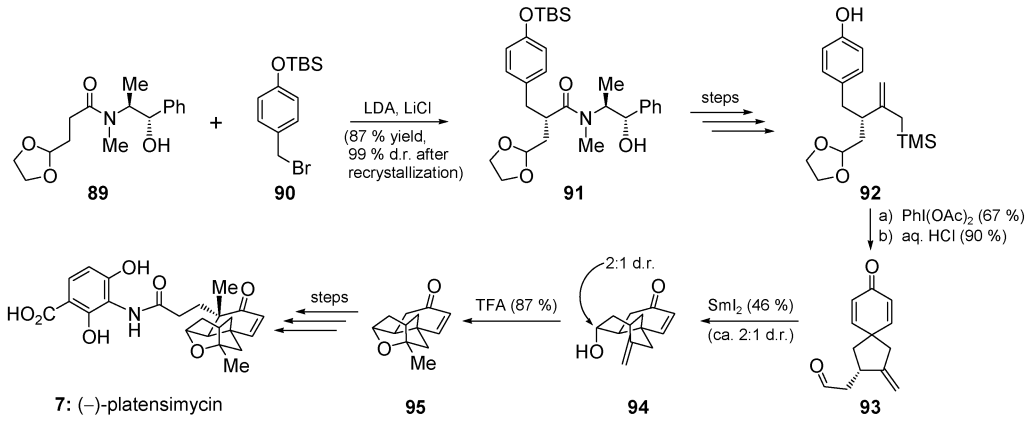
Platensimycin (**7**) was reported in 2006 by a team of Merck scientists [36]. Isolated from a strain of *Streptomyces platensis*, this molecule represents a new structural class of antibiotics with a novel mechanism of action, namely, the inhibition of the elongation-condensing enzymes β-ketoacyl-(acyl carrier protein) synthases I/II (FabF/B) in the type II bacterial fatty acid biosynthetic pathway. Platensimycin is the most potent inhibitor of these enzymes known and exhibits potent broad-spectrum antibacterial activity against Gram-positive bacteria, including methicillin- and vancomycin-resistant strains. Following our successful total synthesis of racemic platensimycin [37], we subsequently completed two conceptually distinct asymmetric syntheses [38].

Our first strategy for an asymmetric synthesis of platensimycin paralleled, to a large extent, our racemic synthesis (Scheme 10). Prochiral eneyne **82** was subjected to a rhodium-catalyzed asymmetric cycloisomerization [39] to yield chiral aldehyde **83** in 91 % yield and ≥95 % e.e. To converge with the racemic route, the ester moiety, which was obligatory for successful rhodium-catalyzed cycloisomerization, had to be excised. Protection of the aldehyde moiety and conversion of the methyl ester moiety into the Barton ester through coupling with pyridine *N*-oxide derivative **84** afforded intermediate **85**. Radical decarboxylation yielded internal alkene **88**, presumably because the initially generated vinyl radical intermediate **86** underwent a 1,3 hydride shift to yield allylic radical **87** before reacting with nBu$_3$SnH at the less hindered allylic position, to afford the observed product (**88**). This unexpected alkene shift was of no consequence, and intermediate **88** was taken through a similar sequence as the one developed for the synthesis of the racemic natural product to give (–)-platensimycin (**7**).



Scheme 10 Highlights of the first asymmetric synthesis of (–)-platensimycin (**7**) (catalytic asymmetric method).

Alongside our catalytic asymmetric synthesis, we engaged in an alternative asymmetric synthesis of platensimycin wherein the absolute stereochemistry was set by an asymmetric alkylation reaction (Scheme 11). Thus, Myers' alkylation [40] of (*S*,*S*)-pseudoephedrine amide **89** with bromide **90** yielded intermediate **91** (in 87 % yield and 99 % d.r. after recrystallization), which was converted into allylsilane derivative **92**. Though there was little precedent for the use of non-aromatic carbon nucleophiles in the hypervalent iodine-promoted oxidative dearomatization [41], we found that this reaction occurred smoothly with substrate **92** and PhI(OAc)$_2$ to yield, after acetal deprotection, aldehyde **93**, an intermediate in our synthesis of racemic platensimycin. This enantioselective total synthesis of (–)-platensimycin (**7**) was then completed as shown in Scheme 11 through intermediates **94** and **95**.

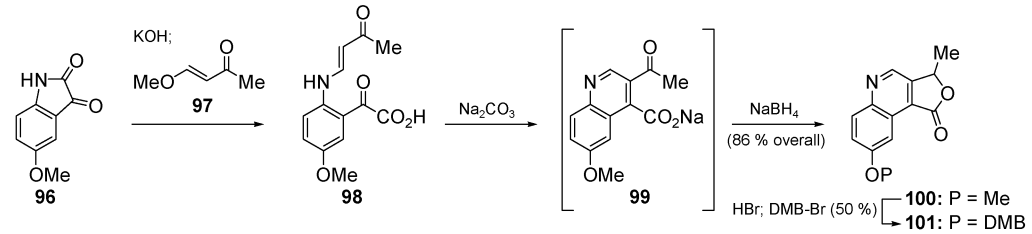


Scheme 11 Highlights of the second asymmetric synthesis of (–)-platensimycin (**7**) (chiral auxiliary method).

Uncialamycin

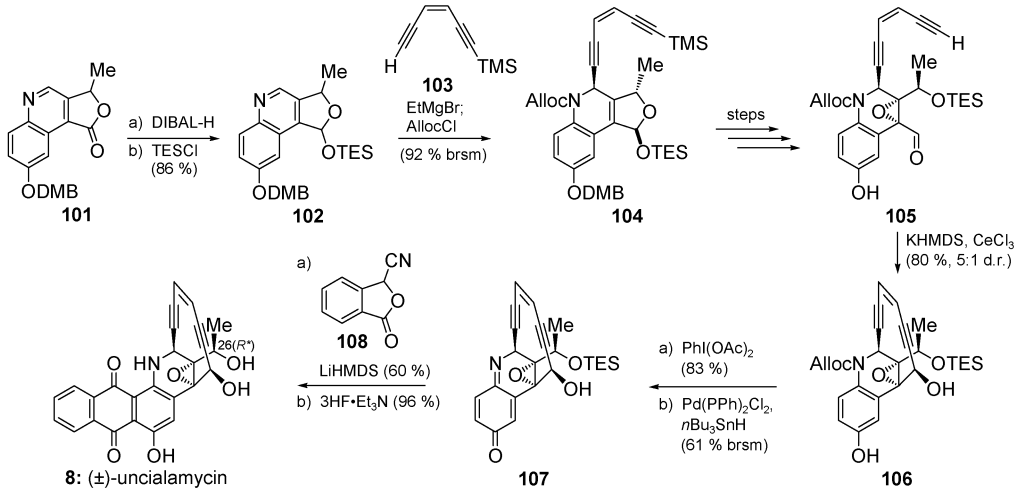
Uncialamycin (**8**, Scheme 13) is an enediyne antibiotic reported by the Davies and Andersen groups in 2005 [42]. The small quantity isolated (300 μg) of this naturally occurring substance was enough to allow determination of its extremely potent biological activity against *S. aureus* (MIC 0.0000064 μg/mL), *Escherichia coli* (MIC 0.002 μg/mL), and *Burkholderia cepacia* (MIC 0.001 μg/mL), but not sufficient to complete its structural elucidation. Specifically, the stereochemistry at the C26 stereocenter was not assigned. In light of this situation, we initiated a project directed toward the total synthesis of uncialamycin with the aim of determining its full structure and rendering it available for further biological investigations.

Our synthesis of uncialamycin [43] commenced with 5-methoxyisatin (**96**), which was subjected to a two-step Friedlander quinoline synthesis [44] (Scheme 12). Thus, exposure of **96** to KOH followed by addition of methoxyenone **97** yielded intermediate **98**. Base-promoted cycloaromatization of the latter intermediate yielded quinoline carboxylate **99**, which was reduced in situ to afford quinoline lactone **100**. Swapping the methyl ether for the more readily cleavable 3,4-dimethoxybenzyl (DMB) ether afforded lactone **101**.



Scheme 12 Highlights of the total synthesis of uncialamycin (**8**). Construction of the quinoline fragment.

Lactone **101** was converted into TES-protected lactol **102** as shown in Scheme 13. The pyridine moiety of this intermediate was then activated with AllocCl, and the resulting pyridinium species was trapped with the alkylidene generated from deprotonation of enediyne **103** to yield intermediate **104**. A series of functional group manipulations afforded aldehyde **105**, which was cyclized by treatment with potassium bis(trimethylsilyl)amide (KHMDS) in the presence of $CeCl_3$ to furnish 10-membered enediyne system **106**, a key intermediate along the synthetic pathway. Conversion of the latter com-



Scheme 13 Highlights of the total synthesis of uncialamycin (**8**). Completion of the synthesis.

pound to iminoquinone **107** made possible a Hauser cyclization utilizing lactone nitrile **108** as a reaction partner to afford, after desilylation, (±)-uncialamycin (**8**).

An asymmetric version of this total synthesis was subsequently developed in which a modified sequence was employed to prepare enantiomerically pure lactone **101** employing a Noyori reduction [45] of a methyl ketone intermediate.

CONCLUSION

Recent accomplishments in total synthesis highlighted major developments in heterocyclic chemistry and cascade reactions [1]. In this short review, a number of such highlights have been presented which underscore the importance of chemical synthesis in reaching complex molecular architectures defined by nature, assisting in their structural elucidation, and providing them in sufficient quantities for biological investigations. Given that so many interesting organic compounds encountered in nature and in the laboratory are heterocyclic and the fact that such constructs are usually structurally complex and synthetically challenging, the future of heterocyclic chemistry looks brighter than ever. Undoubtedly, major advances in chemistry, biology, and medicine will continue to emerge from endeavors in heterocyclic chemistry, a field that is proliferating as quickly as chemists are able to master its manifold intricacies, and as widely as chemists' imaginations can stretch it [46–48].

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