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Perspective

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Natural Products and Their Mimics as Targets of Opportunity for Discovery

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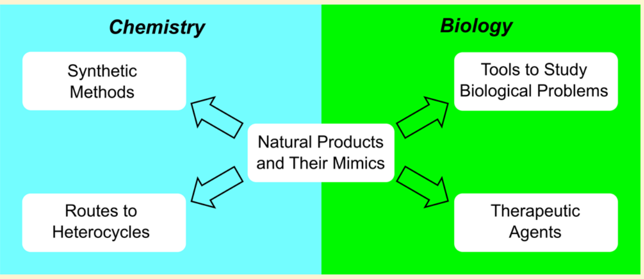
ABSTRACT: Diverse structural types of natural products and their mimics have served as targets of opportunity in our laboratory to inspire the discovery and development of new methods and strategies to assemble polyfunctional and polycyclic molecular architectures. Furthermore, our efforts toward identifying novel compounds having useful biological properties led to the creation of new targets, many of which posed synthetic challenges that required the invention of new methodology. In this Perspective, selected examples of how we have exploited a diverse range of natural products and their mimics to create, explore, and solve a variety of problems in chemistry and biology will be discussed. The journey was not without its twists and turns, but the unexpected often led to new revelations and insights. Indeed, in our recent excursion into applications of synthetic organic chemistry to neuroscience, avoiding the more-traveled paths was richly rewarding.



> *Success consists of going from failure to failure without loss of enthusiasm.*
>
> Winston Churchill

■ INTRODUCTION

In conjunction with receiving the Ernest Guenther Award in Natural Products Chemistry for 2017, I was asked to write a Perspective article summarizing some of our research that led to this award, which is indeed a great honor. However, this award is really a tribute to a team effort that recognizes the outstanding achievements of members of my research group over the years, and I am deeply indebted to all of them; I was merely their conductor. This Perspective is thus a partial account of their accomplishments, and I apologize to those whose stories I was unable to tell.

Natural products have long played a major role in medicine and science. For example, naturally occurring compounds are arguably the single most important source for new drugs to treat human disease.[1] Efforts directed toward their synthesis have led to the discovery of new chemistry and reactivity and to the invention and development of new strategies for generating skeletal frameworks and for forming new chemical bonds. The remarkable diversity of natural products offers a virtually limitless playing field for discovery in chemistry, biology, and medicine, and we have explored only a small fraction of that space.

In thinking about presenting how we have used natural products and their mimics as targets of opportunity to address chemical and biological problems, I decided to organize the discussion primarily along thematic lines, but with a chronological suborganization. Accordingly, I will first present some results in the area of oxygenated natural products, which comprises work directed toward the syntheses of macrolide antibiotics and related compounds, *C*-aryl glycoside natural products, and polycyclic xanthone natural products. One theme of work in this area is the use of substituted furans and pyrans as building blocks. Next, some results in the synthesis of alkaloid natural products, arguably the cornerstone of our efforts over the years, will be discussed. Work in this area features developing methods for the synthesis of quaternary carbon atoms and the use of Diels—Alder, vinylogous Mannich, ring-closing metathesis, and dipolar cycloaddition reactions to construct subunits common to a wide variety of alkaloid natural products.

We have not restricted our attention to compounds that fit the common definition of a natural product as being a secondary metabolite. Rather, we have long believed in a broader definition that regards a natural product as being any compound of natural origin. In that context, we have focused on the design and development of natural product mimics as tools to interrogate biology. We thus became interested in phospholipid analogues and cyclopropane-derived analogues of peptides. At the outset, we were attracted to these natural product mimics as potential enzyme inhibitors, but we pivoted over time to using peptide mimics to probe complex questions of energetics and structure in protein—ligand interactions. Finally, an interesting journey will be discussed that commenced with solving a problem in alkaloid synthesis and ended with the design of a general platform for the synthesis of a diverse array of functionalized heterocyclic scaffolds. This program evolved to the discovery of new compounds that show significant promise as potential therapeutic leads to treat neurodegenerative and neurological conditions.

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SYNTHESIS OF OXYGENATED NATURAL PRODUCTS

Furans and Hydropyrans as Templates. In the early days at The University of Texas, we were drawn to the challenges associated with developing short and efficient approaches to the synthesis of oxygenated natural products, including those having functionally and structurally complex frameworks. Some oxygenated natural products that captured our interest included Prelog−Djerassi lactone,[2] 3-deoxy-D-manno-2-octulosonic acid [(+)-KDO],[3] 1-deoxycastanospermine,[4] tirandamycin A,[5] macbecin I,[6] herbimycin A,[7] and erythromycin B (Figure 1).[8,9]

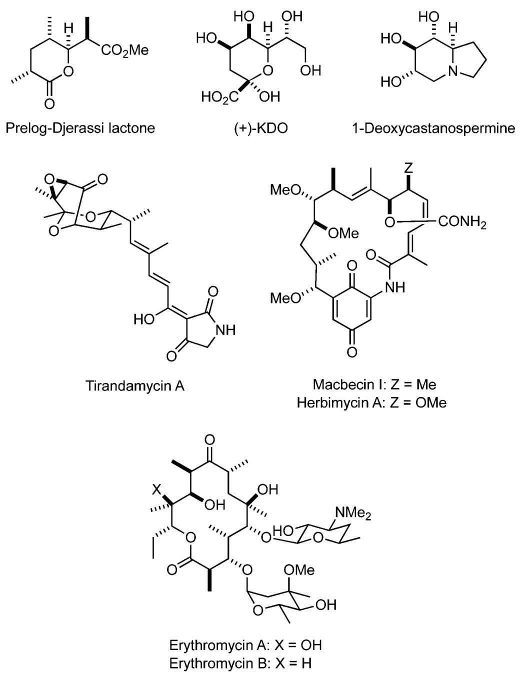
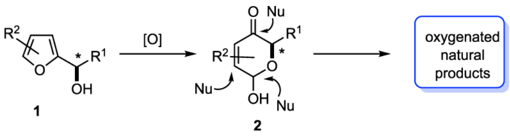


Figure 1. Some representative oxygenated natural products.

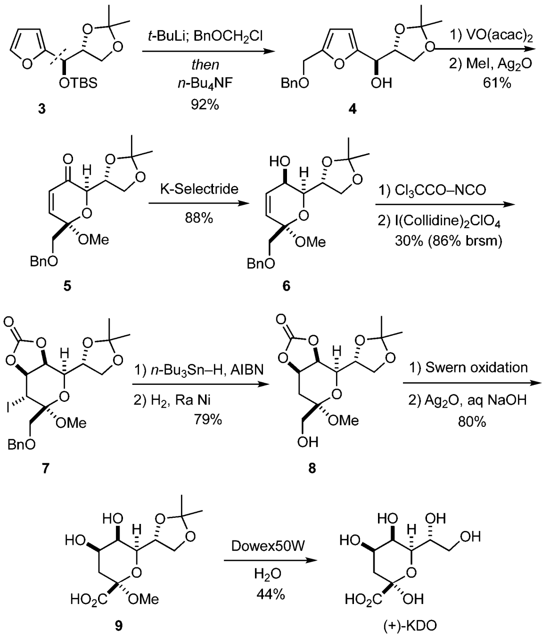
Toward developing a general approach to solve the stereochemical problems presented by these natural products, it occurred to us that the oxidative transformation of substituted furans **1** by an Achmatowicz or related reaction would provide hydropyrans of the general form **2** (Scheme 1). We reasoned that these hydropyrans **2** would nicely serve as conformationally rigid templates that could be modified by stereoselective reactions to introduce new substituents. These elaborated hydropyrans would then serve as key intermediates in the synthesis of oxygenated natural products, such as those depicted in Figure 1.

Scheme 1



One use of a furan as a starting material to prepare oxygenated natural products is exemplified by our synthesis of (+)-KDO, a higher monosaccharide that forms the link between lipid A and the hydrophilic polysaccharide subunits in the outer membrane lipopolysaccharides of Gram-negative bacteria (Scheme 2).[10] Notably, analogues of (+)-KDO had been developed as antibacterial agents. The point of departure for the synthesis of (+)-KDO was **3**, which was prepared in 53% yield in a one-pot operation from Garner's aldehyde. The derived intermediate **4** was then oxidatively processed into the hydropyran **5** together with 14% of its anomer. Stereoselective hydride reduction of the enone followed by an iodonium ion-initiated cyclization of a carbamate led to the key intermediate **7**. The yield of this cyclization was severely compromised by the fact that considerable amounts of recovered starting material were isolated, and despite extensive efforts, it was not possible to identify conditions that led to high conversion. Nevertheless, the starting material **6** could be recycled, so the overall process was reasonably efficient. Sequential removal of the iodo and benzyl groups led to **8**, which was converted by Swern oxidation and hydrolysis of the cyclic carbonate to **9**. Removal of the acetonide protecting group furnished (+)-KDO. This short synthesis of (+)-KDO highlights the utility of our approach for the preparation of higher monosaccharides and densely hydroxylated hydropyrans.

Scheme 2



Herbimycin A is a representative member of the ansamycin antibiotics that exhibits a broad spectrum of biological activities, including antiangiogenic and antitumor properties. Our synthesis of this novel antibiotic, which is outlined in Schemes 3−5,[11] is exemplary of how we typically tried to use natural products as targets of opportunity to discover and develop new chemistry. Namely, we first employed our strategy to use furans and hydropyrans derived therefrom as templates to create the C3−C8 and C9−C15 subunits of the natural product. Our plan then called for coupling these two fragments by stereoselective formation of the C8−C9 double bond (Figure 2). Because

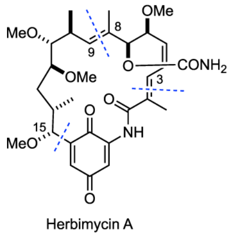


Figure 2. Key disconnections in herbimycin A.

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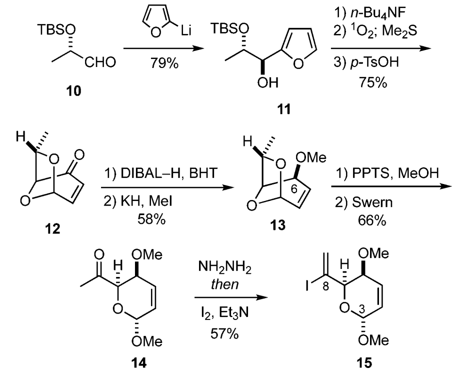
J. Org. Chem. 2017, 82, 10757−10794

methodology for such constructions was severely limited, we knew it would be necessary to develop a new process for the stereoselective synthesis of trisubstituted olefins to address this deficiency. Along the way, we also encountered several other unexpected challenges that required the development of new methods.

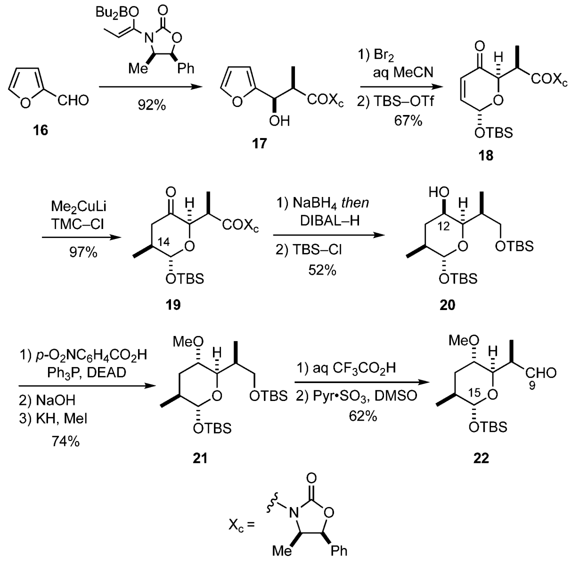
The synthesis of the vinyl iodide **15**, which comprises C3–C8 of herbimycin A, commenced with the addition of 2-lithiofuran to the protected aldehyde **10** to give **11** (Scheme 3). Processing of **11** led to the bicyclic intermediate **12**, which is conformationally biased to enable highly stereoselective reduction of the keto group leading to **13**. The bridged bicyclic framework had thus served its purpose as a rigid template to enable stereochemical control at C6, so **13** was converted in three operations to the monocyclic hydropyran **15**.

Scheme 3



The C9–C15 subunit was then prepared from furfuraldehyde (**16**) via an Evans aldol reaction to deliver **17**, which was oxidatively transformed into the hydropyranone **18** (Scheme 4).

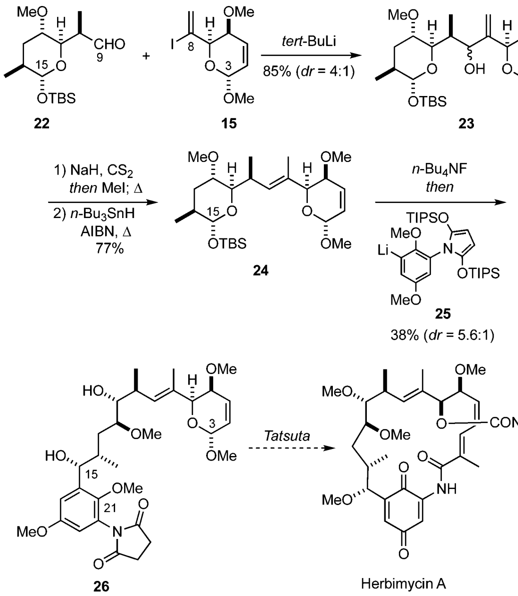
Scheme 4



The stereoselective introduction of the requisite methyl group at C14 was achieved by a cuprate addition providing **19**. Because of the axial orientation of the methyl group at C14 of **19**, it was not possible to stereoselectively reduce the ketone moiety to give the requisite equatorial alcohol at C12. However, treatment of **19** with sodium borohydride gave an intermediate lactone that was reduced to give a diol, the primary alcohol of which was selectively protected to give **20**. Although a seemingly straightforward transformation, inversion of the alcohol at C12 of **20** was unexpectedly problematic. We ultimately discovered that a modified Mitsunobu reaction in which *p*-nitrobenzoic acid was used as the nucleophile proceeded smoothly and in excellent yield to invert the stereochemistry at C12 leading to **21**,[12] which was transformed in two straightforward steps to the aldehyde **22**. This new method for effecting the inversion of secondary alcohols is widely applicable, especially for sterically encumbered alcohol substrates, and it has been broadly utilized by others.

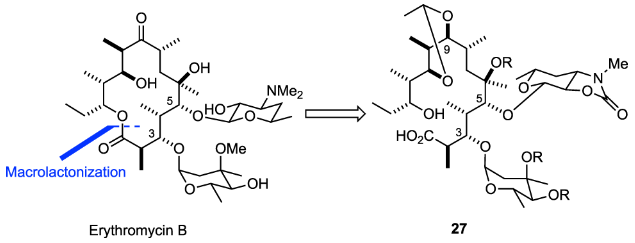
As mentioned previously, our plan to assemble the C3–C15 subunit of herbimycin A entailed joining these two subunits stereoselectively to form an *E*-trisubstituted olefin. Although the Julia olefination and other reactions work well in conjunctive processes to form *E*-disubstituted olefins, they tend to proceed in low yields and diastereoselectivities when applied to the construction of trisubstituted alkenes. Knowing in advance that the methodology for such transformations was severely limited, we developed a general and effective procedure for preparing trisubstituted olefins that is illustrated by the conversion of **22** and **15** into **24** via the allylic alcohol **23**; no detectible amounts of the *Z*-olefin were observed (Scheme 5).[13] The key intermediate **24** was converted into **26** by selective unmasking of the C15 aldehyde in **24** followed by a reaction with the aryllithium **25**. In related work in the ansa antibiotic arena, the aniline moiety of compounds related to **25** had been protected as a 2,5-dimethylpyrrole. Because the procedure to convert such *N*-arylpyrroles to anilines requires somewhat vigorous conditions, we developed an alternative way of diprotecting anilines as their 1-aryl-2,5-bis-triisopropylsilyloxypyrrole derivatives, which are easier to remove.[14] The intermediate **26** is closely related to a compound Tatsuta previously converted into herbimycin A.[15] At this juncture, it made little sense to simply repeat these reactions, so we terminated our efforts with the synthesis of **26**.

Scheme 5



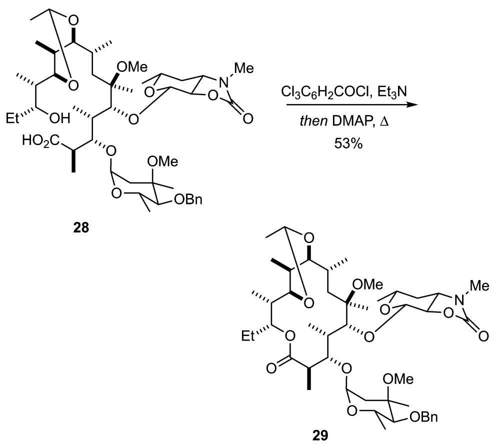
From the very outset of our work in the area of oxygenated natural products, we were attracted to the considerable challenges associated with the total synthesis of the erythromycin antibiotics. These important antibiotics owe their activity to their ability to inhibit ribosomal-dependent protein biosynthesis by binding to the 50S ribosomal subunit;[16] erythromycin A remains in clinical use for treating bacterial infections. In addition to using a furan as a key building block for the stereoselective creation of a subsection of the macrocyclic backbone, we were also interested in developing an "abiotic" approach to these compounds. Namely, all of the contemporaneous approaches to macrolide antibiotics were patterned after their biosynthesis, which involves formation of a macrolide ring, followed by the introduction of the requisite carbohydrate groups onto pendant hydroxyl groups by glycosyl transfer enzymes. Indeed, in the landmark synthesis of erythromycin A in 1981, the Woodward group employed this strategy.[17] During the course of these efforts, the Woodward group explored in some detail the conformational features of the seco acid backbone that were required for cyclization. We took the opposite approach. Namely, we queried whether a glycosylated seco acid derivative, such as **27**, might undergo macrolactonization to give an intermediate that could be transformed after appropriate refunctionalizations into erythromycin B (Scheme 6). If such a strategy were feasible, the cladinose residues at C3 and a desosamine group at C5 of **27** might then nicely serve as surrogates of hydroxyl protecting groups, thereby resulting in a shorter synthesis because traditional protection of these hydroxyl groups would be unnecessary.

Scheme 6



In order to establish the underlying feasibility of this rather speculative plan, we set to the task of establishing proof-of-principle for the macrocyclization in a critical model study.[18] Accordingly, erythromycin B was degraded into the seco acid derivative **28**, drawing largely on considerable literature precedent in the field. Gratifyingly, we discovered that cyclization of **28** using the Yamaguchi cyclization conditions afforded **29** (Scheme 7);[19] other standard tactics to induce macrocyclizations were less effective.

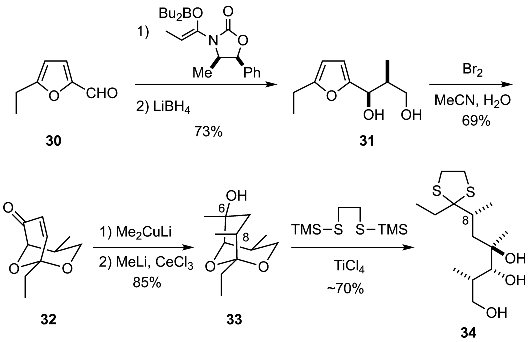
Scheme 7



As a prelude to the eventual implementation of this strategy, we engaged in a variety of support studies that revealed important information about a number of steps. One of these efforts led to the successful synthesis of seco acid derivatives of erythromycin A and erythromycin B.[20] In our first attempt to prepare erythromycin B according to the plan in Scheme 6, we prepared a protected seco acid derivative having an intact carbon backbone, but all attempts to introduce a cladinose residue onto this framework were unsuccessful.[8] Given the late-stage nature of this failure, we opted at the time for an expedient solution that led to the first total synthesis of erythromycin B via a classical approach in which the two carbohydrate residues were introduced onto a preformed macrocyclic lactone. This synthesis of erythromycin B required only 30 steps in the longest linear sequence. As a fringe benefit, we also finished a 23-step synthesis of 9(*S*)-dihydroerythronolide B, one of the shortest to date.

Although we were not able to implement our original plan as set forth in Scheme 6, we developed an alternative embodiment of that approach that was successful. The synthesis commenced with an Evans aldol reaction of 5-ethylfurfuraldehyde (**30**) leading to **31** (Scheme 8).[9] Oxidative transformation of the diol **31** led to the conformationally biased bicycle **32**. Stereoselective introduction of the two methyl groups at C8 and C6 was easily achieved by additions of Me$_2$CuLi and then MeLi under Luche conditions to give **33** with high stereochemical efficiency. Having served its key role as a stereochemically biased template, the bicyclic ketal **33** was unraveled to give the thioketal **34**, albeit with some unavoidable erosion of the stereochemistry at C8.

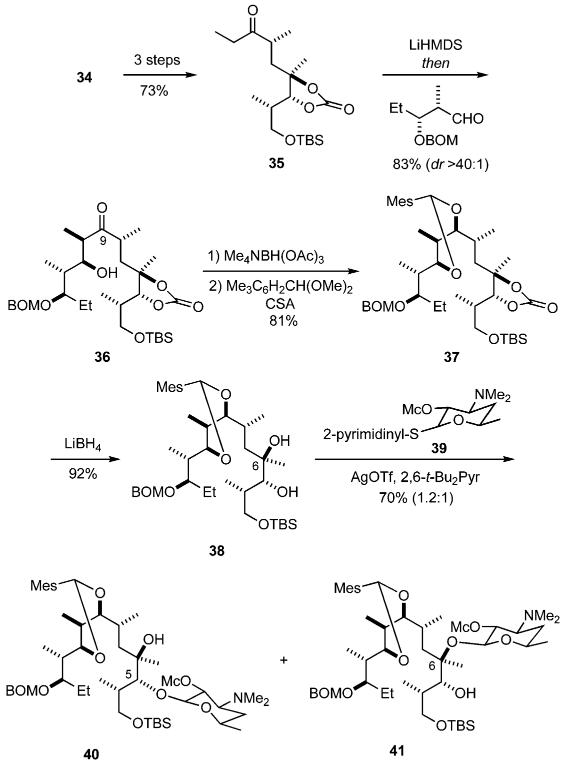
Scheme 8



Refunctionalization of **34** led to **35**, and this ketone underwent a highly diastereoselective aldol reaction to give **36** (Scheme 9). Stereoselective hydride reduction of the C9 ketone followed by acetal formation and removal of the cyclic carbonate protecting group led to **38**. Introduction of a protected desosamine residue at C5 using the glycosyl donor **39** proceeded with poor regioselectivity giving substantial quantities of the C6 glycosylated derivative **41** in addition to the desired **40**. When we tried to obviate glycosylation at C6 by protection of the C6 tertiary hydroxyl group, glycosylation of the C5 hydroxyl group was unsuccessful; we were thus obliged to accept this result. It is noteworthy that the introduction of a desosamine residue at C5 in macrocyclic intermediates in our first synthesis of erythromycin B was not accompanied by significant amounts of glycosylation at C6.[8]

With **40** in hand, completion of the erythronolide backbone remained. Refunctionalization of **40** led to **42**, setting the stage to introduce the remaining three carbon atoms via

Scheme 9

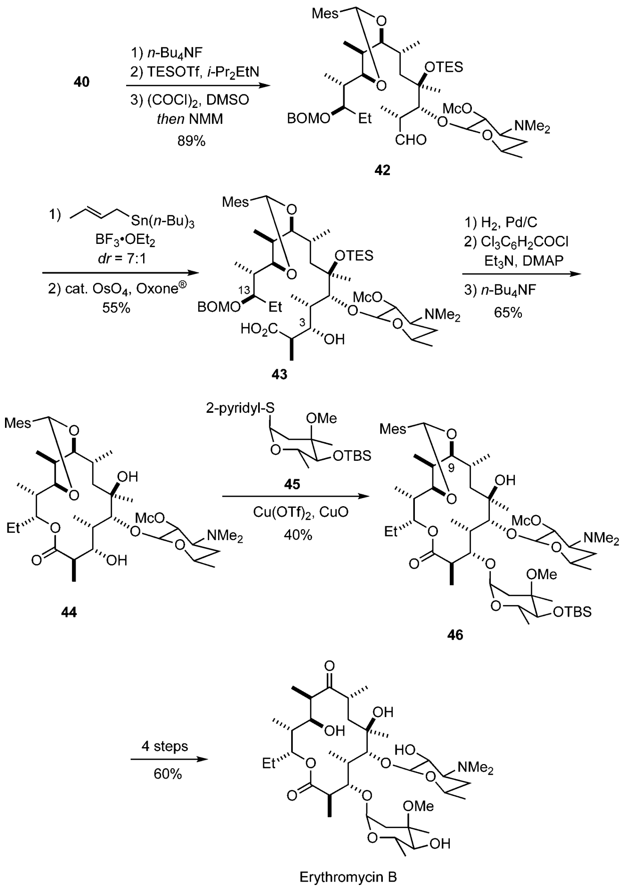


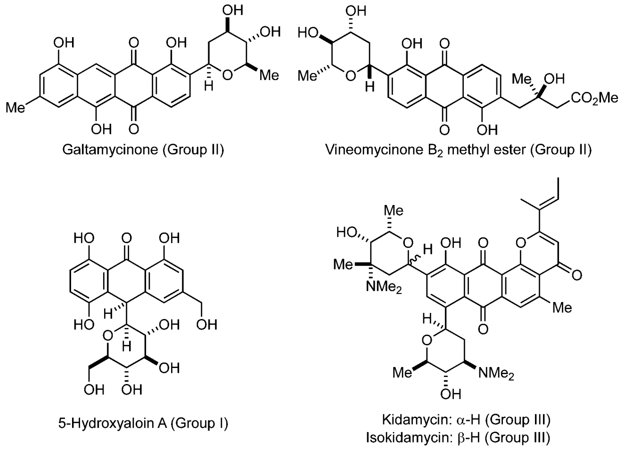
stereoselective crotyl stannylation, followed by oxidative cleavage of the terminal olefin to give **43** (Scheme 10). Initial attempts to introduce the cladinose residue at the C3 hydroxyl group in **43**, or its immediate olefin precursor, were unsuccessful. Because material was in short supply, we opted to see whether we might be able to induce macrolactonization on a substrate lacking the cladinose moiety. Toward this goal, selective removal of the C13 hydroxyl protecting group and cyclization of the intermediate hydroxy acid according to the Yamaguchi protocol led to lactone **44**.[19] Reaction of **44** with the glycosyl donor **45** furnished the bisglycosylated lactone **46**. This synthesis of erythromycin B was completed in four steps that were developed during our first synthesis[8] and involved global deprotection and selective oxidation of the hydroxyl group at C9. This route to erythromycin B, which required only 27 steps in the longest linear sequence, is three steps shorter than our first synthesis wherein the carbohydrate residues were introduced *after* macrolide formation. Moreover, this synthesis represents the first time any macrolide antibiotic had been prepared by an "abiotic" approach in which a sugar residue was appended as a surrogate hydroxyl protecting group prior to the macrolactonization step.

FURANS AS BUILDING BLOCKS FOR *C*-ARYL GLYCOSIDE SYNTHESIS

Another area of inquiry arose because we recognized the significant challenges associated with synthesizing natural products of the *C*-aryl glycoside class.[21] This important family of compounds has long attracted interest because of their broad range of biological activities and their resistance to enzymatic hydrolysis. Some *C*-aryl glycosides that were of interest included galtamycinone[22] and vineomycinone B_2 methyl ester,[23] two representative members of the Group II *C*-aryl glycosides, 5-hydroxyaloin A,[24] a Group I *C*-aryl glycoside, as well as kidamycin and its isomer isokidamycin,[25] which belong to the Group III *C*-aryl glycoside family (Figure 3).

Scheme 10





Galtamycinone (Group II)

Vineomycinone B_2 methyl ester (Group II)

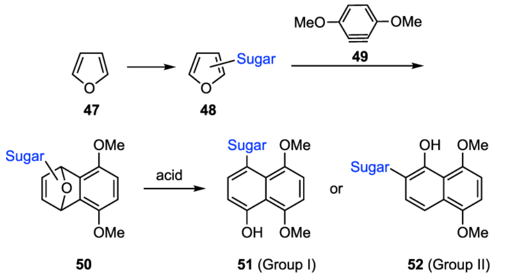
5-Hydroxyaloin A (Group I)

Kidamycin: α-H (Group III)
Isokidamycin: β-H (Group III)

Figure 3. Representative *C*-aryl glycoside antibiotics.

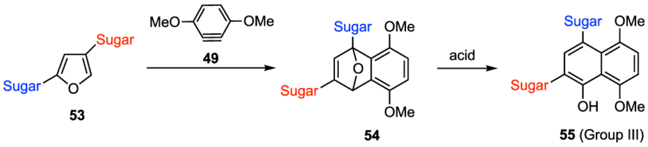
In keeping with our broad synthetic objectives, a central goal was to develop a unified approach to the major classes of *C*-aryl glycosides that was concise and general, so it could be broadly applied to the syntheses of any member of this family of natural products. The strategy that thus evolved is illustrated in Schemes 11−13. The essence of the approach features the cycloaddition of furfuryl glycosides with substituted benzynes to give cycloadducts that undergo acid-catalyzed rearrangement to provide *C*-aryl glycosides.[26] For example, furfuryl glycosides such as **48** are readily available from furan (**47**). The cycloaddition of **48** with benzyne **49**, which was generated in situ by deprotonation/elimination of 2-chloro-1,4-dimethoxybenzene, yields **50**, analogues of which were known to undergo facile acid-catalyzed reorganization to provide 1-naphthol derivatives.[26] In the present case, this rearrangement would deliver **51**, a Group I *C*-aryl glycoside, or **52**, a Group II *C*-aryl glycoside, depending upon the orientation of the sugar residue on **50** (Scheme 11).

Scheme 11

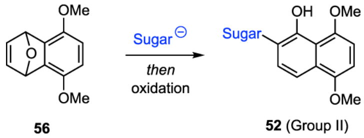


Similarly, the bis-glycosylated furan **53** can be envisioned as a precursor of **55**, a representative Group III *C*-aryl glycoside (Scheme 12) via cycloaddition with **49** and subsequent rearrangement of the intermediate **54**. We also envisioned the possibility of inducing ring opening reactions of furan-benzyne cycloadducts such as **56** leading to compounds such as **52**, thereby offering an alternative route to Group II *C*-aryl glycosides (Scheme 13).

Scheme 12



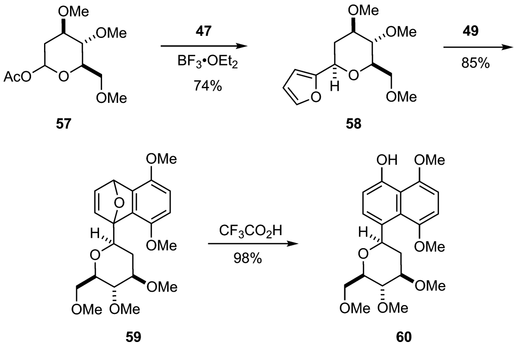
Scheme 13



Inspection of the sequences shown in Schemes 11−13 highlights an important feature of this approach. Namely, the introduction of the *C*-aryl glycoside moiety is performed in tandem with the annelation of a new aromatic ring. Because the formation of the *C*-aryl glycoside is coupled with an increase in skeletal complexity, we envisioned that this new entry to *C*-aryl glycosides would lead to more concise syntheses of these natural products.

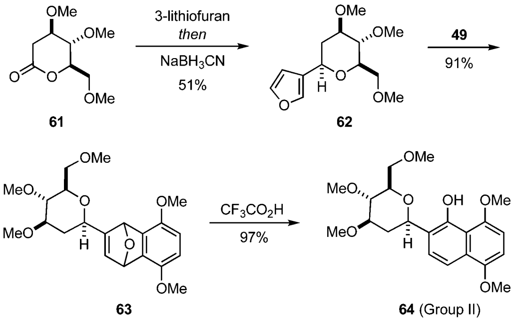
With an overall strategy in mind, it remained to demonstrate proof-of-principle. The ease with which furfuryl glycosides can be assembled is nicely illustrated by the conversion of the readily available **57** into **58** (Scheme 14).[27] Cycloaddition of **58** with benzyne **49** provided **59**, which underwent acid-catalyzed rearrangement to generate the exemplary Group I *C*-aryl glycoside **60**.

Scheme 14



Similarly, the furfuryl glycoside **62** can be readily assembled from **61** by sequential addition of 3-furyllithium, followed by stereoselective hydride reduction (Scheme 15). Transformation of **62** via cycloaddition with benzyne **49** and acid-catalyzed rearrangement of the intermediate cycloadduct **63** delivered the model Group II *C*-aryl glycoside **64**.

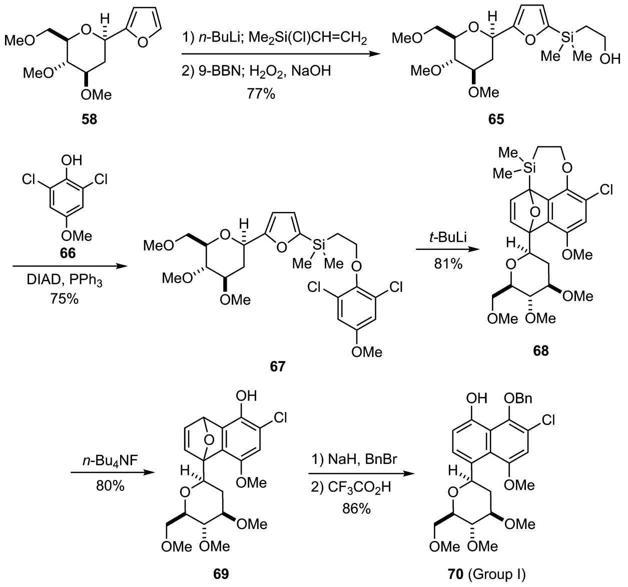
Scheme 15



Examination of the processes of Schemes 14 and 15 reveals a limitation of this approach to *C*-aryl glycosides. In particular, the benzyne intermediate **49** in each of these examples is symmetrical. However, a mere glance at the natural products in Figure 3 reveals that the benzyne precursors that would be required to synthesize any of these *C*-aryl glycosides must necessarily be unsymmetrical. Although unsymmetrical benzynes are known to undergo regioselective cycloadditions with unsymmetrical furans,[28] the process is not general.[29] Hence, the question arose: How can one control the regiochemistry in the cycloaddition of furfuryl glycosides with unsymmetrical benzynes? We briefly examined the possibility of placing a bulky protecting group on one of the oxygen atoms of the hydroquinone precursor of the benzyne; however, it became quickly apparent that the regiochemical course of cycloadditions of unsymmetrical benzynes could not be controlled through simple steric effects. Accordingly, it was necessary to develop an alternate strategy to solve this regioselectivity issue.

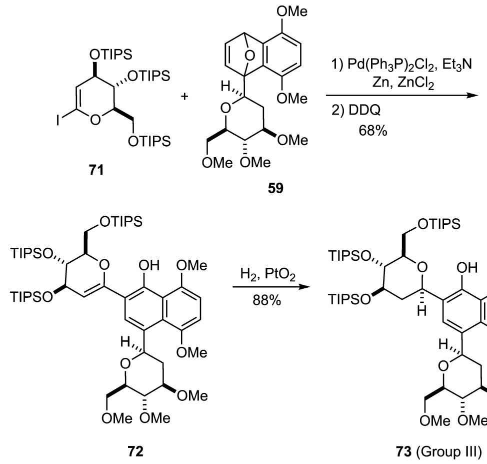
Toward that end, we developed a tethering strategy in which the benzyne precursor and the furan are linked together with a removable tether prior to generation of the benzyne.[30] For example, regioselective deprotonation of the furan ring of **58**, followed by appending a functionalized silyl group led to **65** (Scheme 16). Coupling **65** with the phenol **66** via a Mitsunobu reaction provided **67**. Generation of a benzyne from **67** was easily accomplished using *tert*-BuLi, leading to the cycloadduct **68**. Removal of the temporary silyl tether and sequential protection and acid-catalyzed rearrangement furnished the model Group I *C*-aryl glycoside **70**.

Scheme 16



An application of a palladium-catalyzed ring-opening reaction of benzyne−furan cycloadducts to generate *C*-aryl glycosides (see Scheme 13) is exemplified for the formation of the model Group III *C*-aryl glycoside **73** (Scheme 17).[27] In the event, ring opening of **59** with the iodo glycal **71** proceeded with high regioselectivity, presumably directed by steric effects, to give **72**, and catalytic hydrogenation of the enol ether moiety in **72** yielded **73** as a single diastereomer.

Scheme 17



We prepared galtamycinone[22] and a precursor of 5-hydroxyaloin A[24] using this benzyne−glycosyl furan cycloaddition strategy, but the syntheses of vineomycinone B_2 methyl ester[23] and isokidamycin[25] best illustrate the scope and potential of this novel approach to *C*-aryl glycoside natural products. Vineomycinone B_2 methyl ester is a degradation product of vineomycin B_2, which was isolated from a culture of a *Streptomyces* and found to exhibit anticancer and antibiotic activity.[31] Examination of its structure (Figure 4), reveals that the central quinone ring is flanked by two aromatic rings, bearing on one side a carbohydrate residue and a hydroxy ester group on the other. It occurred to us that we might be able to simultaneously annelate *both* of the benzene rings in vineomycinone B_2 methyl ester concomitant with introducing the appropriate side chains using a variation of the general plan depicted in Scheme 11.

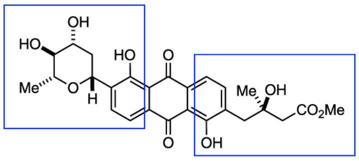
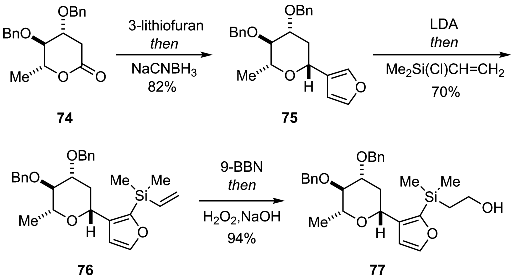


Figure 4. Furan-derived subunits of vineomycinone B_2 methyl ester.

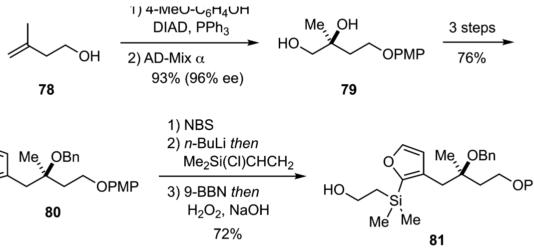
As the first step toward implementing this plan, the furfuryl glycoside **75** was prepared from the readily available lactone **74**, which was an intermediate in our synthesis of galtamycinone (Scheme 18).[22] Introduction of the silyl tethering group onto the furan ring of **75** was easily achieved by regioselective metalation, followed by appending a functionalized silyl side chain to furnish **77**.

Scheme 18



The synthesis of the furan **81** commenced with the protection and Sharpless dihydroxylation of the commercially available homoallylic alcohol **78** (Scheme 19). Conversion of **79** into **80** featured a step involving epoxide formation and ring opening. Although it was not possible to regioselectively metalate **80**, it did undergo regioselective bromination, and subsequent metal halogen-exchange and introduction of the silyl tethering moiety provided **81**.

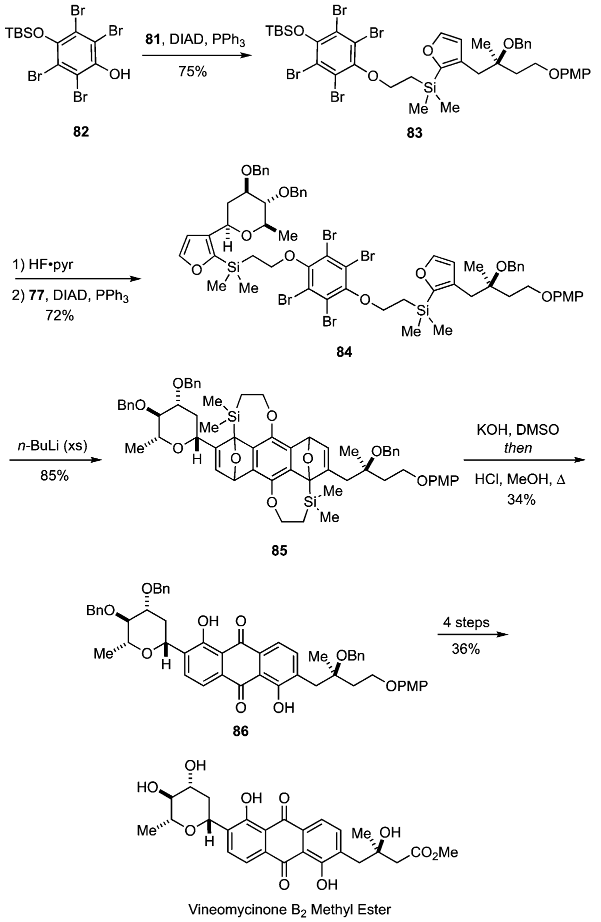
Scheme 19



Furan intermediates **81** and **77** were then sequentially attached to the tetrabromohydroquinone **82** leading to **84** (Scheme 20). In the key step of the synthesis, **84** was treated with excess *n*-BuLi to deliver **85** in a single operation that involved two intramolecular benzyne−furan cycloadditions. Although **85** was produced as a complex mixture of stereoisomers, removal of the tethering groups and ring opening of the two bicycloheptadiene rings furnished **86**. It then remained to remove the protecting groups and oxidize the primary alcohol to deliver vineomycinone B_2 methyl ester.

DOI: 10.1021/acs.joc.7b01368
J. Org. Chem. 2017, 82, 10757−10794

Scheme 20



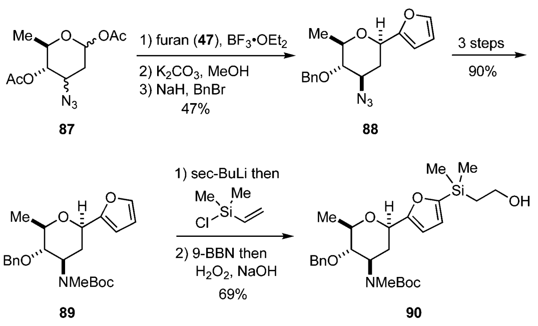
This synthesis highlights the ease with which complex skeletal systems can be rapidly assembled using our benzyne−furan cycloaddition methodology to produce a *C*-aryl glycoside moiety in tandem with forming a new aromatic ring.

We then turned to the significantly greater challenge of the synthesis of kidamycin, which is a member of the pluramycin class of *C*-aryl glycoside antibiotics and displays a broad range of antibacterial, antifungal, and anticancer activities.[32] Given its planar tetracyclic core structure, it is not surprising that kidamycin, like other pluramycin antibiotics, binds to DNA leading to single strand cleavage.[33]

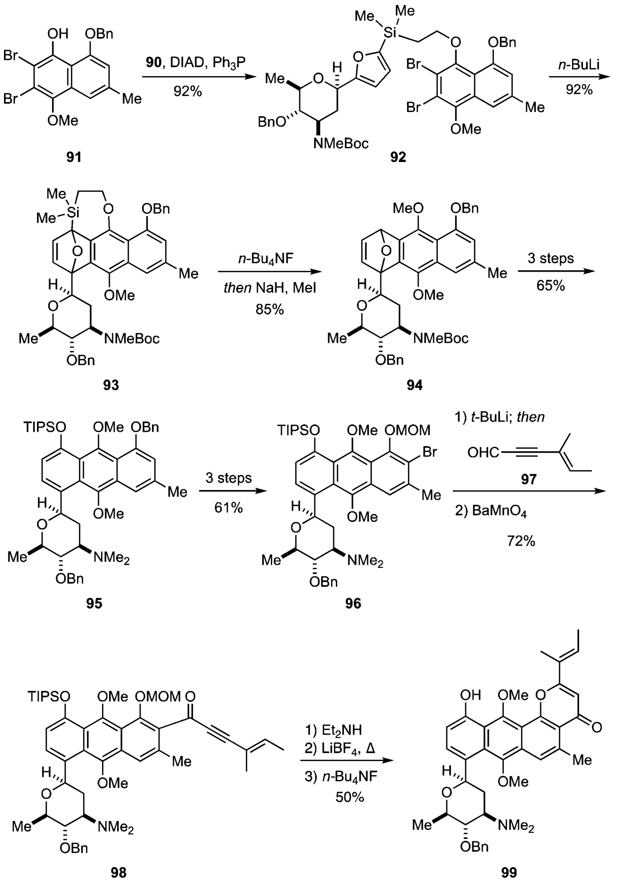
Because of the unsymmetrical nature of kidamycin, it was again necessary to employ a tethering approach to control regiochemistry in the benzyne−furan cycloaddition (Scheme 21).[25] Toward this end, the first stage of the synthesis involved making the glycosyl furan **88** from the known carbohydrate derivative **87**, which was prepared from D-rhamnal according to the protocol reported by Brimble.[34] Refunctionalization of **88** led to **89**, and introduction of the silyl tethering group to give **90** followed previous work (see Scheme 18).

The highly substituted naphthalene **91** was then coupled with **90** via a Mitsunobu reaction to generate **92**, which underwent an intramolecular benzyne−furan cycloaddition upon treatment with *n*-BuLi to provide **93** (Scheme 22).

Scheme 21



Scheme 22

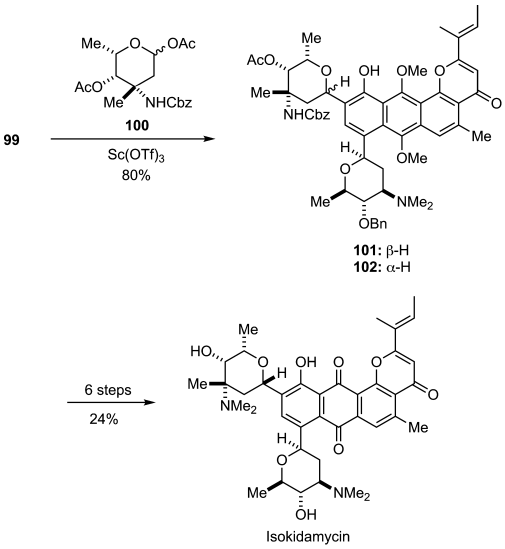


Processing of **93** via cleavage of the silyl tether, acid-catalyzed ring opening of the oxabicycle, and a series of refunctionalizations then led to **96**. We had originally intended to convert **96** into the enynone **98** by a carbonylative cross coupling reaction we had developed in ancillary work and had already successfully applied to the synthesis of luteolin.[35] Unfortunately, this method could not be applied to the conversion **96** → **98**, and we were forced to adopt a stepwise strategy. In the event, reaction of the anion generated from **96** by metal−halogen exchange with the ynal **97** followed by oxidation of the intermediate alcohol gave **98**.

We then turned our attention to forming the pyranone ring. We had originally anticipated that removal of the MOM protecting group followed by cyclization via a 6-*endo*-digonal pathway would lead to **99**; however, our optimism would not be rewarded. We discovered that treating **98** with Lewis and Brønsted acids led to the formation of a five-membered ring benzofuranone via a 5-*exo*-digonal cyclization, not the desired hydropyranone **99**. Although similar cyclizations were also known to give benzofuranones,[36] there was precedent suggesting that this undesired pathway might be avoided by first converting the ynone into a vinylogous amide.[37] Fortunately, we discovered that the vinylogous diethylamide derived from **98** did undergo acid-catalyzed cyclization to form the hydropyranone ring in **99**.

At this juncture, it was necessary to introduce the remaining carbohydrate residue, and we briefly considered the possibility of a glycal-induced ring opening reaction of **94** in analogy with chemistry developed in Scheme 17. However, we quickly realized such a tactic would not be applicable to the task at hand because this procedure would likely have led to the *β*-anomeric *C*-aryl glycoside, not the *α*-anomer as required. Accordingly, we planned to introduce the remaining carbohydrate residue via an *O* → *C* glycosyl transfer process that had been developed by Suzuki and that we believed would furnish the correct *α*-anomer via a kinetically controlled rearrangement.[38] Reaction of **99** with **100**, which was prepared in four steps (54% yield) from L-vancomycin, in the presence of $Sc(OTf)_3$ furnished a single diastereomeric product (Scheme 23).

Scheme 23



Our initial excitement that the *O* → *C* glycoside rearrangement had occurred quickly evaporated, however, when we discovered that the product was the *β*-anomer **101**, not the desired *α*-anomer **102**. Although it is possible that **102** was kinetically formed and underwent rapid epimerization to **101** under the reaction conditions, we never observed any trace of **102** in the mixture. A detailed discussion may be found in our original paper,[25] but suffice it to say we now believe that the intermediate oxonium ion formed during the rearrangement likely exists preferentially in a twist boat conformation, not a half chair conformation as originally predicted. If the *O* → *C* glycosyl transfer process occurs via a twist-boat transition state, the observed *β*-anomer would be expected. Although it is possible that an alternate protecting group strategy for the vancosamine residue might favor formation of the desired *α*-anomer, we did not perform any experiments to address this question.

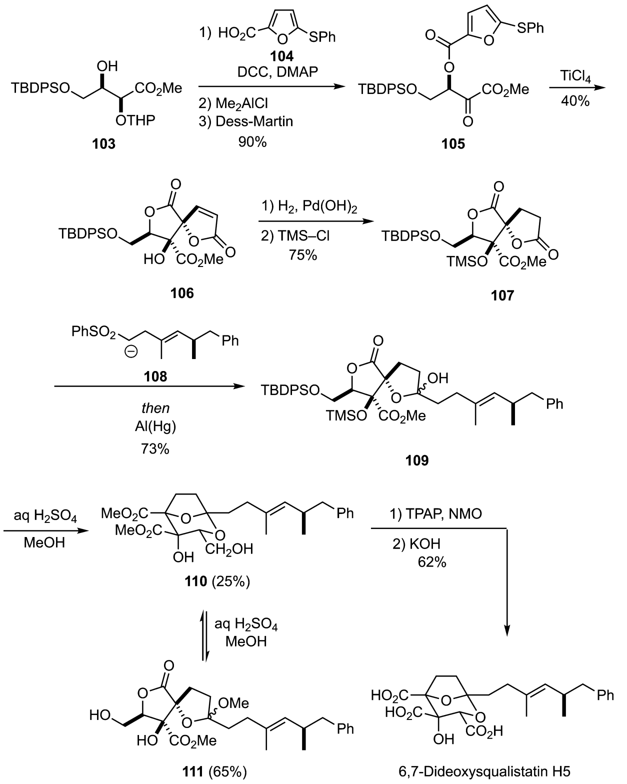
Having been given a lemon, we resorted to making lemonade, and **101** was transformed in six steps, largely involving refunctionalization operations, into isokidamycin, the structure of which was verified by comparison of its spectra with those of an authentic sample. This achievement represents the first total synthesis of a bis-*C*-aryl glycoside natural product in the pluramycin family.

■ FURANS AS *π*-NUCLEOPHILES IN VINYLOGOUS ALDOL REACTIONS

Over the years, we have explored the use of furan intermediates in a number of applications, some of which have been presented previously. We have also been interested in the use of furans as *π*-nucleophiles, especially in vinylogous Mannich reactions, which will be discussed in more detail later. However, in planning an approach to 6,7-dideoxysqualistatin H5,[39] we had occasion to use a furan in an intramolecular vinylogous aldol reaction.[40] 6,7-Dideoxysqualistatin H5 is a natural product related to the zaragozic acids and squalistatins, which had attracted considerable attention because of their activity as squalene synthase inhibitors.[41]

In order to set the stage for the pivotal vinylogous aldol reaction in our synthesis of 6,7-dideoxysqualistatin H5, **103**, which was prepared in three steps from dimethyl D-tartrate, was esterified with the known acid **104**, and removal of the tetrahydropyranyl protecting group followed by oxidation gave **105** (Scheme 24).[42] The key cyclization of **105** proceeded efficiently using $TiCl_4$ as the catalyst to give **106** together with less than 5% of other diastereomers. The spirocyclic lactone **106** was then converted into **107**, thereby setting the stage for coupling with the side chain subunit **108** to produce **109**. Treatment of **109** with methanolic acid then furnished a separable mixture of **110** and **111**. The undesired ketals **111** could be re-equilibrated to give additional quantities of **110**. The conversion of **110** into 6,7-dideoxysqualistatin H5 was then simply achieved by oxidation of the primary alcohol function in **110**, followed by global saponification of the methyl ester groups.

Scheme 24



■ GENERAL ROUTE TO POLYCYCLIC XANTHONE NATURAL PRODUCTS

A more recent foray into the arena of oxygenated natural products was directed toward developing a general approach to polycyclic xanthone natural products. Such compounds range in structural complexity from the tricyclic tetramethoxyxanthone[43] to the polycyclic representatives IB-00208,[44] citreamicin η,[45] and kibdelone C (Figure 5, xanthone rings highlighted in blue). Many compounds of this class exhibit potent antibacterial and anticancer activity. As was often the case in our group, we were drawn by both the structural features and the biological activities of members of this class of natural products.

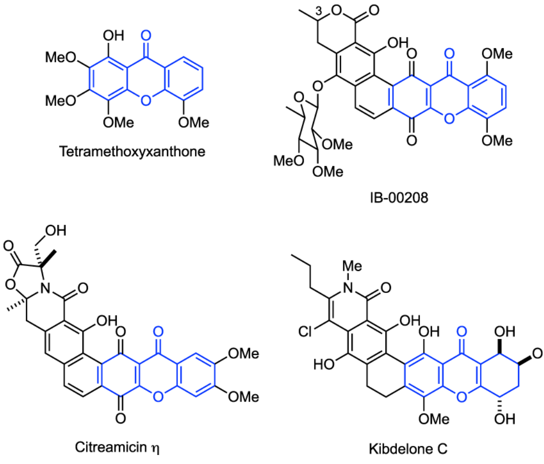
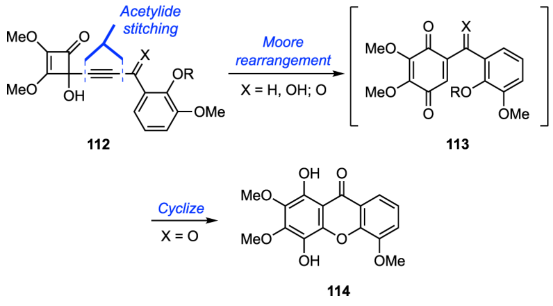


Figure 5. Representative polycyclic xanthone natural products.

Toward developing a general entry to polycyclic xanthone natural products, we were intrigued by the possibility of exploiting a novel variant of the well-known Moore rearrangement.[46] In particular, we envisioned that the Moore reaction of **112** would provide an intermediate quinone **113** that would undergo cyclization to generate the xanthone **114** (Scheme 25).[43]

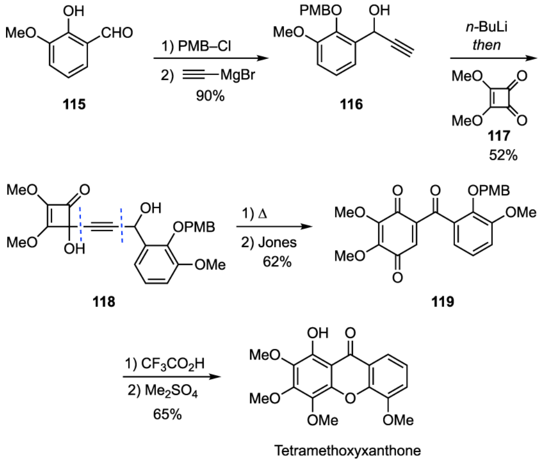
Scheme 25



We reasoned that the requisite disubstituted acetylene **112** might be rapidly assembled by an "acetylide stitching" process in which a squaric acid derivative and either an aldehyde or activated carboxylic acid derivative would serve as electrophilic partners in reactions with acetylide anions.

We first performed a series of simple model experiments to validate the underlying feasibility of this new approach to substituted xanthones, and we then applied it to a facile synthesis of tetramethoxyxanthone (Scheme 26).[43] The key intermediate **118** was readily assembled by the acetylide stitching process using the aldehyde **115** and dimethyl squarate (**117**). Rearrangement of **118**, followed by Jones oxidation of the secondary alcohol provided **119**, which underwent facile cyclization upon acid-catalyzed removal of the PMB protecting group; regioselective methylation of the less hindered phenolic hydroxyl group then furnished tetramethoxyxanthone.

Scheme 26

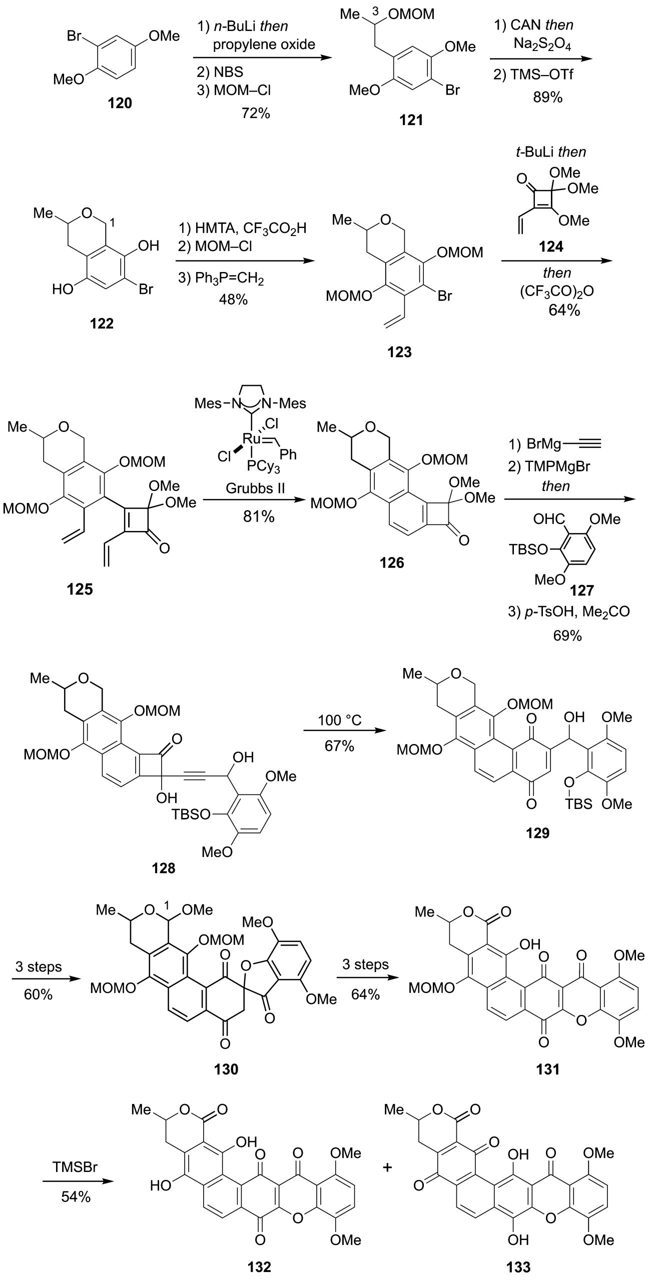


Although the synthesis of tetramethoxyxanthone was sufficient to establish proof-of-principle, it remained to demonstrate the applicability of the approach in a more complex setting. We thus set to the challenging task of synthesizing IB-00208, which displays strong antibiotic activity against Gram-positive bacteria and potent anticancer activity against several cancer cell lines.[47] In order to set the stage for the pivotal Moore rearrangement, it was first necessary to prepare **128** (Scheme 27). We envisioned that **128** could be prepared by joining the squaric acid derivative **126** with the aldehyde **127** via an acetylide stitching process similar to that shown in Schemes 25 and 26. However, methods for preparing angularly fused benzocyclobutenones such as **126** were not available, thus demanding the development of new methodology that would feature a new application of ring-closing metathesis (e.g., **125** → **126**).

The synthesis of the benzocyclobutenone **126** commenced with the transformation of **120** into **121**, wherein the MOM group not only serves as a protecting group but also the eventual source of the C1 carbon atom in the hydropyran ring (Scheme 27).[44] Because both enantiomers of propylene oxide are commercially available, we would be able to introduce the correct stereochemistry at C3 once the absolute configuration in IB-00208 was known. After removal of the two *O*-methyl groups from **121**, acid-catalyzed cyclization furnished **122**, which was converted via a Duff formylation, followed by protection and Wittig olefination to give **123**. Union of **123** and **124** led to **125**, which underwent ring-closing metathesis in the presence of Grubbs II catalyst to provide **126**. This approach to **126** appears to be general and has been applied to the synthesis of other angularly fused benzocyclobutenones.[44b]

With **126** in hand, acetylide stitching with **127** followed by cleavage of the dimethyl acetal delivered **128**, which underwent Moore rearrangement upon heating to give the tetracyclic intermediate **129**. Following oxidation of **129** to introduce a methoxy group at C1, removal of the TBS protecting group and cyclization furnished the spirocyclic product **130** rather than the desired fused ring system. This mode of ring closure did not occasion surprise because we had previously observed that 2,6-disubstituted benzoyl substrates similar to **129** underwent

Scheme 27



kinetically controlled cyclizations to give spirocyclic products that could be isomerized to the desired fused ring systems.[43] Processing **130** via oxidation at C1 and thermal rearrangement then provided **131**. Removal of the MOM-protecting group gave an inseparable mixture of **132**, the aglycone of IB-00208, and its tautomer **133**. In retrospect, the formation of **132** and **133** is perhaps not unexpected because the redox potentials of the two compounds might be predicted to be similar. Because all efforts to separate these compounds failed and because they underwent facile interconversion as well as transformation by unknown decomposition pathways, we were unable to characterize these compounds individually nor were we able to convert **132** into IB-00208. Nevertheless, our general strategy for the synthesis of polycyclic xanthone natural products generally worked as planned, and we have applied a similar approach to the synthesis of a pentacyclic precursor of citreamicin η.[45]

■ SYNTHESIS OF QUATERNARY CARBON ATOMS

Another significant challenge that captured our attention in the early days at The University of Texas involved the formation of quaternary carbon atoms, a structural motif that occurs widely in a diverse array of natural products of biological interest. The methodology for forming fully substituted carbon atoms was rather limited at the time,[48] so we sought to discover general strategies for assembling quaternary carbon centers. Part of the motivation to invent and develop such procedures arose from our specific interest in spirocyclic sesquiterpenes such as acorone,[49] as well as in several Amaryllidaceae and related alkaloids that included *O*-methyljoubertiamine,[50,51] mesembrine,[51] lycoramine,[52] crinine,[53] and pretazettine[54] (Figure 6).

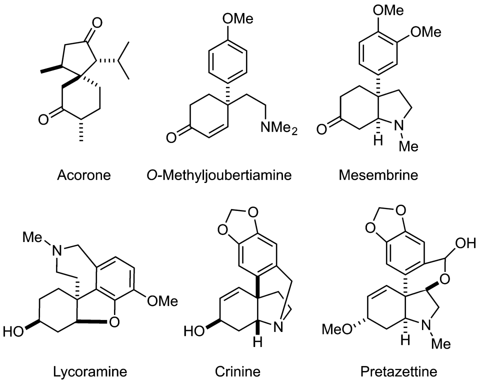
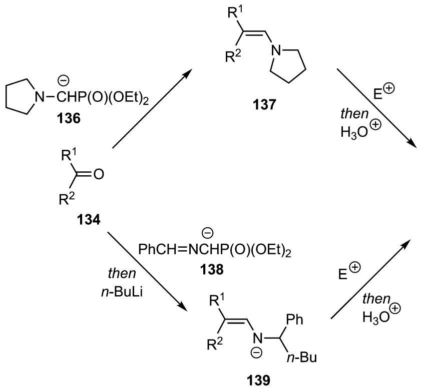


Figure 6. Selected natural products having quaternary carbon atoms.

In one appealing approach to the construction of quaternary carbon atoms, we envisioned replacing both of the carbon–oxygen bonds of a ketone **134** with carbon–carbon bonds leading to **135** (Scheme 28). In this novel process for geminal acylation–alkylation, the first step corresponds to a carbonyl homologation reaction,[55] whereas the second step involves the introduction of an electrophile at the carbon-atom α to the newly added aldehyde group. It occurred to us that the reaction of **134** with the phosphonate anion **136** would generate an enamine **137** that could be elaborated by reaction with an electrophile, followed by an aqueous acid workup to produce **135**.[56] This procedure for effecting the geminal acylation–alkylation of ketone was successfully applied to a synthesis of *O*-methyljoubertiamine,[50,51] but not unexpectedly, the limitations of this approach for the synthesis of more complex alkaloids became quickly apparent

Scheme 28

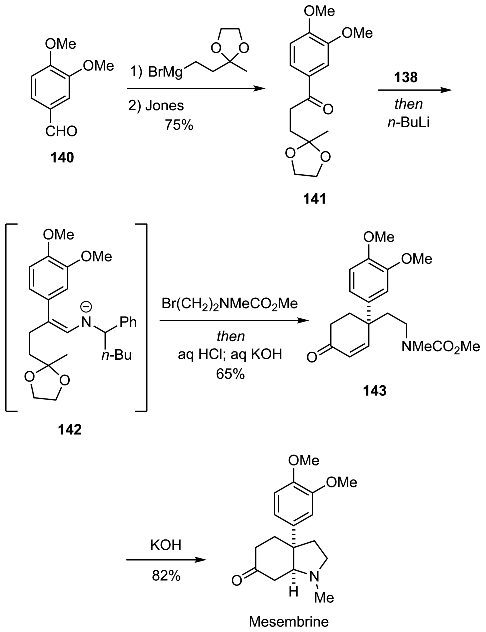


because enamines react with only a limited number of reactive electrophiles.

In contrast to the modest reactivity of enamines, imine anions, which are also known as metalloenamines, such as **139** react with a wide variety of electrophiles. Hence, a procedure that enabled the conversion of ketones **134** into imine anions **139** would have broader utility (Scheme 28). It is noteworthy that at the time we were interested in developing applications of Diels–Alder reactions (vide infra) of dienes, including 2-azadienes. It thus occurred to us that reaction of the phosphonate anion **138** with **134** would produce a 2-azadiene that would undergo 1,2-addition of *n*-BuLi to generate the metalloenamine **139**. Subsequent reaction of **139** with different electrophiles would deliver *α*-trisubstituted aldehydes **135** bearing functionalized substituents.[57,58] We were gratified to discover that this procedure for the one-pot geminal acylation–alkylation of ketones to create quaternary carbon atoms worked extremely well. That a solution to a pending synthetic problem was inspired by another area of inquiry in the group stands as one example of how cross-fertilization has benefited discovery.

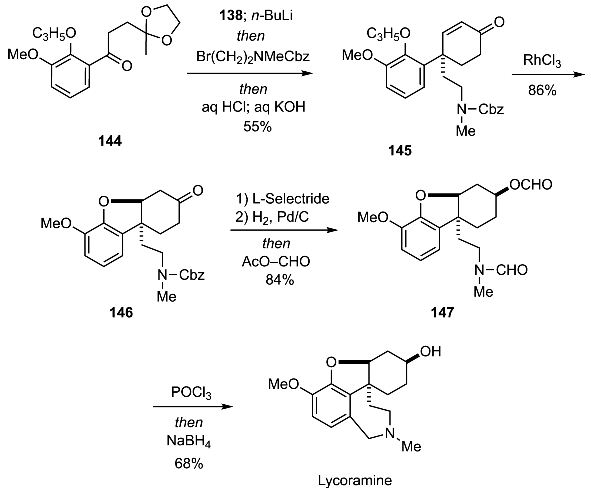
The utility of this method to generate a new quaternary carbon center is nicely illustrated by its application to a very concise synthesis of mesembrine, a representative member of the *Sceletium* genus of alkaloids. The extracts of plants of this family have long been used in traditional medicine for sedation and analgesia,[59] and over the years, mesembrine has arguably become one of the most synthesized alkaloids.[60] Our approach to mesembrine commenced with the reaction of the protected 1,4-dione of **141**, which was prepared in two steps from **140**, with the phosphonate anion **138** to give an intermediate 2-azadiene that was treated with *n*-BuLi to generate the metalloenamine **142** (Scheme 29).[51] Alkylation of **142**, followed by sequential processing with aqueous acid and then base afforded **143** in a single operation. Removal of the carbamate protecting group then furnished mesembrine in a sequence comprising only five linear steps from a commercially available starting material. Of the more than 40 total syntheses of mesembrine reported to date,[60] this remains one of the shortest.

Scheme 29



This general process for creating quaternary carbon atoms was also applied to several more complex alkaloids of the Amaryllidaceae family, which comprises a number of biologically active members.[61] For example, our synthesis of lycoramine featured the geminal acylation–alkylation of the *O*-allyl protected ketone **144**, which was easily prepared in three steps from *o*-vanillin, to give **145** (Scheme 30).[52] Removal of the *O*-allyl protecting group followed by cyclization gave **146**, which was transformed by stereoselective hydride reduction and refunctionalization to give the *N*-formyl compound **147**. Subsequent Bischler–Napieralski reaction of **147** followed by reduction gave lycoramine; attempts to form the seven-membered ring via a Pictet-Spengler reaction were unsuccessful. The general applicability of this methodology was further established in syntheses of other Amaryllidaceae, including crinine and buphanasine as well as pretazettine and the related alkaloid haemanthidine.[53,54]

Scheme 30



■ APPLICATIONS OF DIELS–ALDER REACTIONS TO ALKALOID SYNTHESIS

A major driving force for discovery in our laboratories has been developing new and efficient approaches to generate substructures commonly found in alkaloid natural products, because such strategies are applicable to the synthesis of alkaloids belonging to numerous different families. Examination of the structures of many alkaloids reveals that cyclohexane rings fused to pyrrolidine or piperidine rings are common motifs. For example, the tricyclic hydrolulolidine ring system in aspidospermine[62] (Figure 7) is found in many *Aspidosperma* alkaloids, and the hydroindole ring subunit in lycorine[63] (Figure 7) is present in a number of Amaryllidaceae and other alkaloids, including dendrobine[64] (Figure 7). The hydroisoquinoline ring system occurs in numerous alkaloids of the yohimbine family,[65] including reserpine and *α*-yohimbine[66] as well as in the manzamine alkaloid manzamine A[67,68] (Figure 7). Although less-common, oxahydroisoquinolines are found in indole alkaloids of the heteroyohimbine class such as tetrahydroalstonine[69,70] (Figure 7). One powerful construction to fabricate six-membered rings is the Diels–Alder reaction, so we queried whether intramolecular Diels–Alder reactions might be used to create these heterocyclic ring systems. Intramolecular Diels–Alder reactions were, of course, well-known,[71] so we carefully selected our targets in order to develop variants that expanded the scope of these cycloadditions.

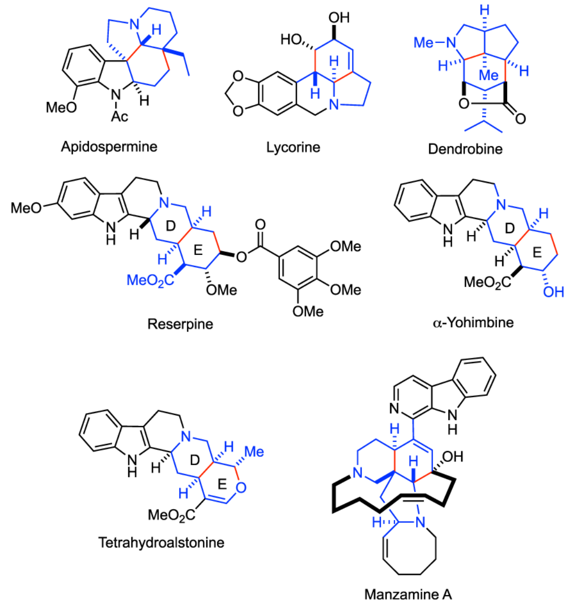
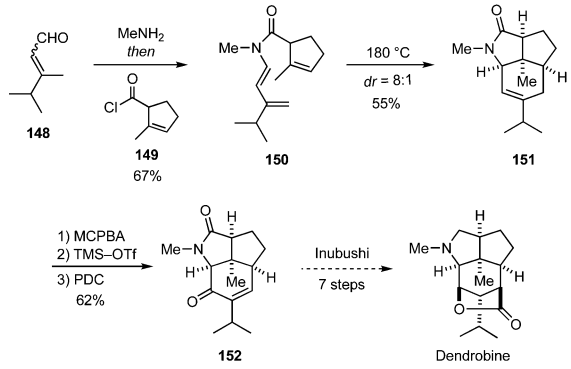


Figure 7. Common structural subunits (highlighted in blue) found in representative alkaloids and accessible by intramolecular Diels–Alder reactions (newly formed bonds in red).

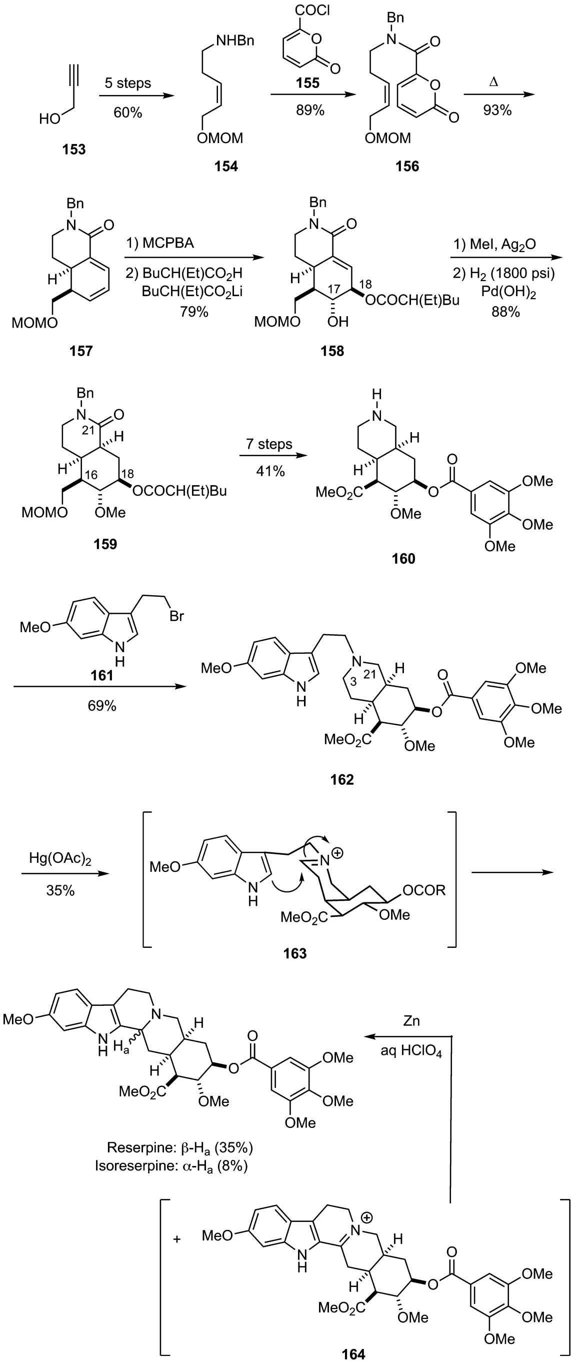
Our syntheses of aspidospermine and lycorine featured intramolecular Diels–Alder reactions of simple enamides with unactivated dienes,[62,63] whereas our synthesis of dendrobine involved the intramolecular Diels–Alder reaction of a dienamide with an unactivated olefin.[64] Because there was little contemporaneous precedent for these types of [4 + 2] cycloadditions, we would necessarily probe new chemistry. For example, dendrobine is a structurally compact natural product that exhibits antipyretic and hypotensive activity and is the major alkaloid component of the ornamental orchid *Jinchai shihu* used in traditional Chinese medicine.[72] Our synthesis of dendrobine commenced with converting the unsaturated aldehyde **148** into the dienamido alkene **150**, heating of which afforded the cycloadduct **151** in good diastereoselectivity (Scheme 31).[64] Compound **151** was swiftly converted into **152**, which had been previously transformed in seven steps into dendrobine by Inubushi.[73] We had thus not only completed a short formal synthesis of an unusual alkaloid but also discovered and applied a novel intramolecular Diels–Alder reaction to solve a challenging problem.

Scheme 31



The D/E ring system of the monoterpenoid indole alkaloids of the yohimboid family is a hydroisoquinoline ring, so we conducted an exploratory study to assess the applicability of intramolecular Diels–Alder reactions to provide this and related heterocycles.[74] The utility of this approach was then reduced to practice in a synthesis of the "classic" alkaloid in this family—reserpine, a natural product that was first isolated from Indian snake root and achieved clinical prominence as a hypotensive agent that also exhibits significant sedative and tranquilizing activity.[75] In the event, heating the triene **156**, which was readily prepared in six steps from propargyl alcohol (**153**) delivered the cycloadduct **157** (Scheme 32).[66] The requisite hydroxyl groups at C17 and C18 were introduced stereoselectively by sequential epoxide formation/ring opening to give **158**. When I presented our synthetic approach to

Scheme 32

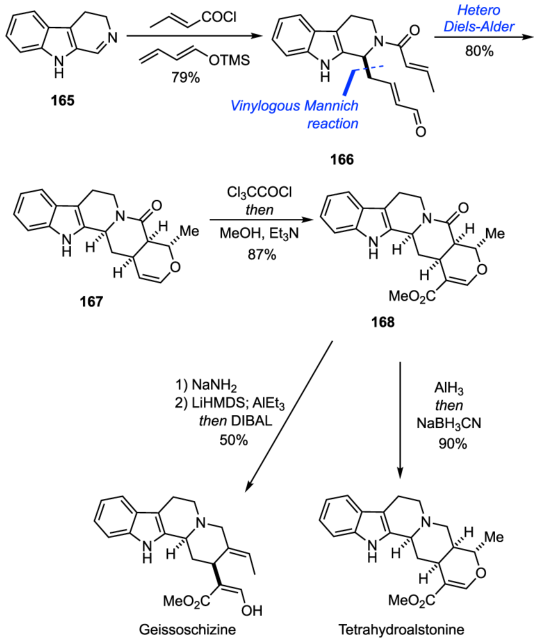


reserpine in lectures, I was often asked why we chose such an unusual carboxylic acid as a nucleophile. There was, of course, a good reason. Namely, the regioselectivity of the epoxide ring opening reaction with smaller carboxylic acids such as acetic acid was not as selective (85:15 mixture of isomers), and acyl migration was observed to produce mixtures of isomeric acetates. Although *O*-methylation of **158** proceeded smoothly, the subsequent stereoselective reduction of the carbon−carbon double bond to give **159** was initially highly problematic. We eventually discovered that Pearlman's catalyst, which Bill Pearlman at Parke-Davis/Warner-Lambert generously donated to us, and high pressures of hydrogen gas were required in order to avoid double bond isomerization and nonstereoselective reduction of the tetrasubstituted olefin. The **159** thus obtained was then transformed in seven straightforward steps into **160** (18 steps and 17% overall yield), which was alkylated with **161** to give **162**.

The oxidation and cyclization of compounds similar to **162** leading to indole alkaloids was well established in the literature, so we were confident that the oxidation at C3 of **162** would give **163**, together with the regioisomeric iminium ion derived from the undesired oxidation at C21 (not shown). We envisioned that axial attack of the indole ring onto the preferred conformation of the D/E ring subunit as shown in **163** would produce reserpine as the major product. This stereochemical outcome was predicted based upon the principle of stereoelectronic control in additions to cyclic iminium ions, which that was well-known at the time.[76] Stork later also relied upon a similar analysis in his synthesis of reserpine.[77] Unfortunately, some of the reserpine thus produced underwent oxidation under the reaction conditions to generate the iminium ion **164**. Although reduction of **164** with hydride ion provides isoreserpine with high stereoselectivity, the zinc metal promoted reduction of **164** had been reported to give reserpine with high selectivity under certain conditions.[78] However, we found that when the mixture obtained upon mercuric acetate oxidation of **162** was treated with zinc metal under these and a number of other conditions, mixtures of reserpine and isoreserpine were inevitably obtained; under optimized conditions, a mixture of reserpine (35% yield) and isoreserpine (8% yield) was isolated.

In our initial approach to the heteroyohimboid alkaloid tetrahydroalstonine (Figure 7), we discovered a novel hetero Diels−Alder reaction that generated the oxahydroisoquinoline ring subunit.[69] Although this D/E ring precursor was eventually transformed into tetrahydroalstonine using an approach similar to that outlined in Scheme 32 for reserpine, this synthesis was just too long and inefficient. Accordingly, we designed a second-generation approach to tetrahydroalstonine that required **166** as the key intermediate (Scheme 33).[70] After some experimentation, we discovered a simple, one-step procedure for the synthesis of **166** that featured a vinylogous Mannich reaction of **165**. The subsequent hetero Diels−Alder reaction of **166** then furnished the pentacyclic intermediate **167**. Introduction of the carbomethoxy group onto **167** using a procedure we previously developed specifically for this purpose gave the key intermediate **168**.[69] Selective reduction of the lactam ring in **168** proceeded without event to provide tetrahydroalstonine. Alternatively, we found that base-induced *β*-elimination of **168** followed by selective reduction of the lactam moiety provided geissoschizine (Scheme 33).

Scheme 33



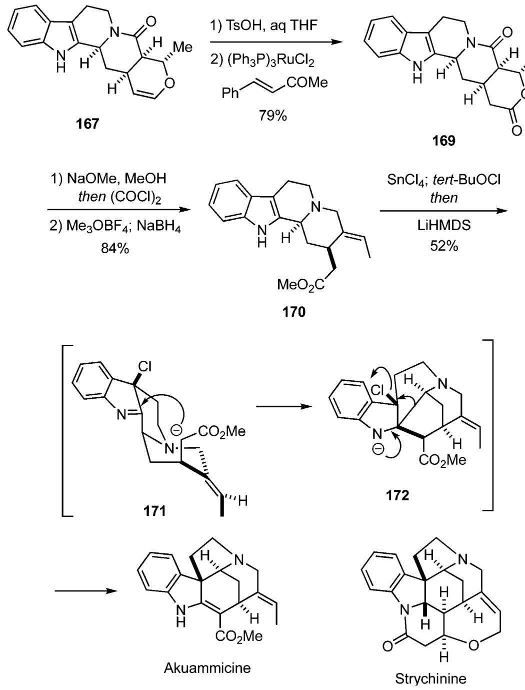
It is significant that these short syntheses of tetrahydroalstonine and geissoschizine inspired major new ventures in our group that were completely unanticipated. First, we discovered the power of using vinylogous Mannich reactions to rapidly assemble structural subunits in alkaloids, and we subsequently developed a program exploiting this construction to solve problems in alkaloid synthesis (vide infra). Second, these syntheses highlight the extraordinary potential of combining a vinylogous Mannich reaction and a hetero Diels−Alder reaction in tandem to generate molecular complexity. This realization led to the design and development of a general platform to create molecular libraries that features cyclizations of intermediates that are produced by Mannich or related reactions (vide infra).

■ BIOMIMETIC SYNTHESIS OF INDOLE ALKALOIDS

Knowledge of the biosynthesis of alkaloids and other natural products can lead to biomimetically inspired strategies for their synthesis that can be remarkably short.[79] Indeed, we were keenly aware of the pivotal role geissoschizine was known to play in the biogenesis of indole alkaloids of the *Strychnos* family.[80] That we were able to prepare geissoschizine in only five operations from **165** encouraged us to see whether we might be able to divert intermediates in its synthesis to access representative *Strychnos* alkaloids such as akuammicine and its more notorious analogue strychnine. Strychnine owes its toxicity to its interaction with a glycine receptor in the lower brain stem and spinal cord that can disrupt normal nerve signaling, thereby leading to overexcitation and intense muscular convulsions.[81]

In order to assess the feasibility of our biomimetic approach to akuammicine, cycloadduct **167** was converted in four steps into desformyl geissoschizine (**170**) (Scheme 34).[82] The biogenetically patterned transformation of **170** into akuammicine was then effected in a one-pot operation via the putative intermediates **171** and **172**. Briefly, in accord with ample precedent,[83] **170** was oxidized with electropositive chlorine to give a mixture of chloroindolinines. We believe chlorination occurred preferentially on the requisite *β*-face in the presence of $SnCl_4$ because approach from the *α*-face was sterically

Scheme 34

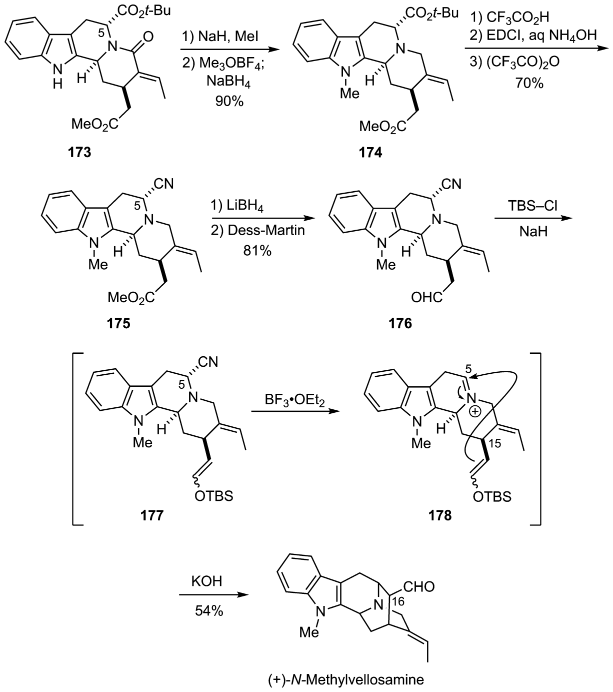


hindered by the $SnCl_4$ coordinated to the basic nitrogen atom. Deprotonation of the major chloroindolinine furnished **171**, cyclization of which to **172** followed by a 1,2-rearrangement delivered akuammicine. This skeletal reorganization is reminiscent of a related process that generated the *Aspidosperma* skeleton.[84] We then applied a similar strategy to a synthesis of strychnine.[82b]

Knowledge of the biosynthesis of indole alkaloids[80] also led us to consider the possibility of elaborating a compound related to **170** into (+)-*N*-methylvellosamine, a representative member of the sarpagine family that has been used in traditional medicine as an emetic and cathartic.[85] A key step in the plan involved cyclization of **178** (Scheme 35).[86] Although some experimental support for this step is found in van Tamelen's synthesis of ajmaline,[87] subsequent reports by Lounasmaa and co-workers cast serious doubt on the feasibility of such a cyclization.[88] Fortunately, it was easy to test our hypothesis because we had prepared **173**, which bears functionality at C5 that would eventually serve as a handle for regioselective generation of the requisite iminium ion, as a key intermediate in an enantioselective synthesis of geissoschizine.[89] In the event, **173** was converted into **175** via a straightforward sequence of reactions. Although it was our original intention to form an iminium ion at C5 on **175**, we were unable to induce the requisite ionization/cyclization. In an alternative approach, **175** was converted into the enol ether **177**, which underwent Lewis acid-induced cyclization via the putative intermediate **178** to give (+)-*N*-methylvellosamine. In light of the reports of Lounasmaa, we believe the success of this cyclization owes its origin to the preferred axial orientation of the side chain at C15 of **178** that is enforced by $A^{1,3}$-strain. It is notable that the transformation of **178** into (+)-*N*-methylvellosamine also provides compelling experimental support for the involvement of such a cyclization in the biosynthesis of the sarpagine and ajmaline alkaloids.

Another natural product that captured our attention was manzamine A, a novel polycyclic alkaloid isolated from a

Scheme 35



marine sponge that exhibits potent antitumor activity.[90] More recently, it was found that manzamine A also displays antimalarial and antituberculosis activity.[91] The structural complexity presented by manzamine A clearly offered a number of challenges that would require new chemistry as detailed below. A central element in our plan for the synthesis of manzamine A involved an intramolecular Diels–Alder reaction that would create the tricyclic ABC ring subunit by forming the bonds highlighted in red (Figure 8).

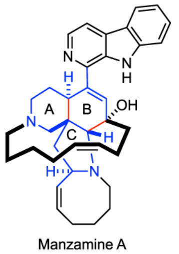
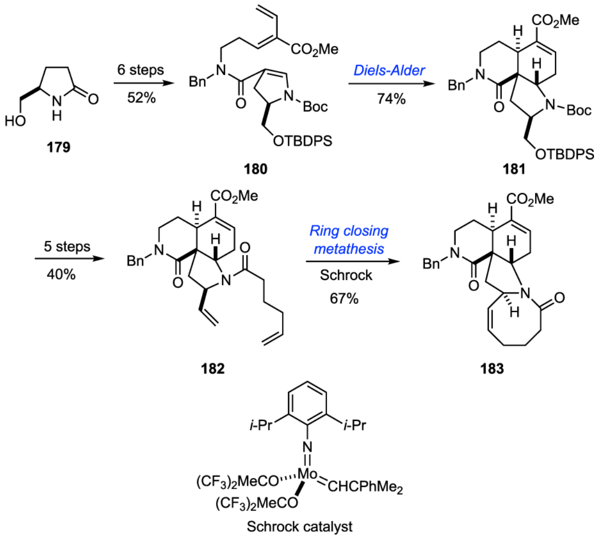


Figure 8. Diels–Alder route to form tricyclic core (blue) of manzamine A.

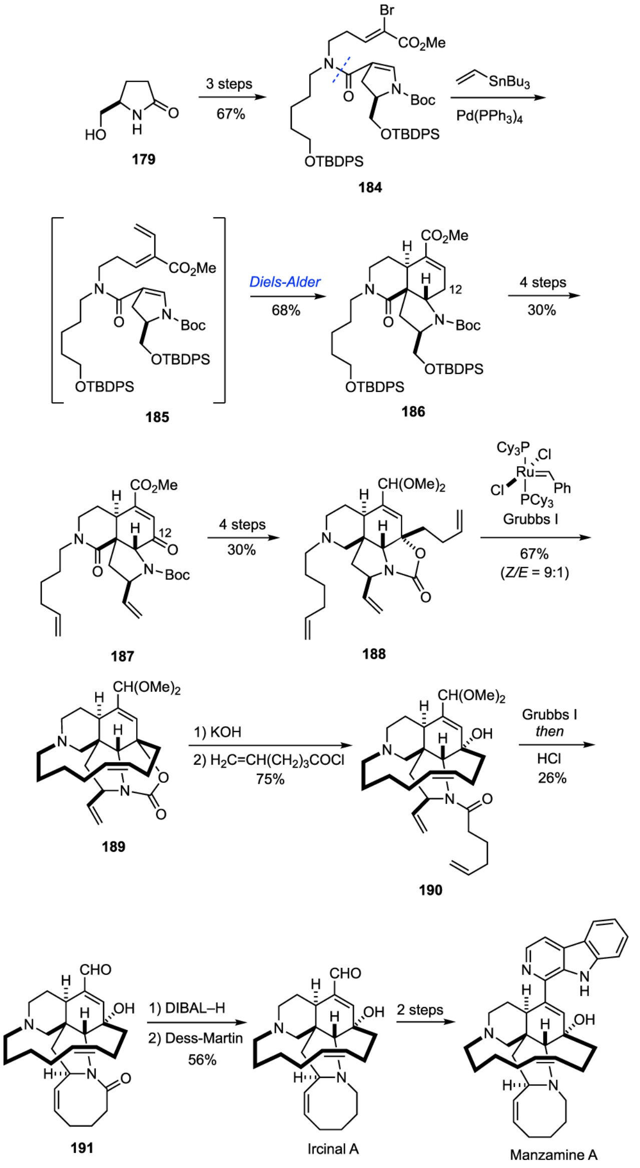
In order to establish the underlying feasibility of this key cycloaddition, triene **180** was prepared in six steps from the readily available chiral starting material **179** (Scheme 36).[67] The intramolecular Diels–Alder reaction of **180** proceeded smoothly to give **181**. In the context of our general objectives of expanding the scope of intramolecular Diels–Alder reactions, is notable that [4 + 2] cycloadditions involving vinylogous *N*-acyl ureas were unknown at the time, although there were a few examples wherein vinylogous amides served as dienophiles.[92]

Our initial plan for forming the 8-membered ring in manzamine A involved cyclizations via Wittig- or McMurry-type reductive coupling reactions. However, contemporaneous with our preparation of **181**, Fu and Grubbs published their seminal finding that 5-, 6-, and 7-membered nitrogen heterocyclic rings could be readily formed by ring closing metathesis (RCM) reactions using the Schrock precatalyst.[93] We were thus excited to test whether such a process might be applied to the cyclization of **182**. Toward this end, I telephoned Bob Grubbs, explaining our idea, and I asked him whether he could provide us with a sample of the Schrock catalyst—he graciously did. We then discovered that treating **182** with Schrock catalyst led to the rapid formation of **183** in good yield. The fact that such a reactive catalyst was tolerant of the multiple functional groups in **182**, selectively inducing an efficient RCM was a stunning finding. To our knowledge, this cyclization represents the first reported application of RCM to complex molecule synthesis.

Scheme 36



Scheme 37



We then turned our attention to the considerably more difficult challenge of applying the lessons from our model work (Scheme 36) to the total synthesis of manzamine A. In the event, **184** was prepared via a streamlined procedure requiring only three steps from readily available **179** (Scheme 37).[68] Heating **184** with vinyl tributylstannane eventuated in a novel domino Stille/Diels−Alder sequence that delivered **186** in a single operation. In this novel sequence of reactions, three new carbon−carbon bonds were produced in a single operation, and the lone stereocenter in **184** dictated the absolute and relative stereochemistry at the three newly created stereocenters. Introduction of the carbonyl group at C12 of **186** via allylic oxidation, followed by parallel processing of the protected primary alcohol groups led to the diene **187**. The triene **188**, which was formed in four steps from **187**, then underwent facile RCM in the presence of Grubbs I catalyst to generate the 13-membered ring in **189** with very good stereoselectivity. Conversion of **189** into **190** was easily achieved, thereby setting the stage for the formation of the 8-membered ring via a second RCM reaction. Given the success with the RCM of **182** (Scheme 36), this cyclization was surprisingly difficult, and it was only after extensive experimentation that we were finally able to convert **190** into **191**, albeit in modest yield. Although we used every known RCM catalyst, the best results were obtained using Grubbs I catalyst; protonation of the basic amino group offered no improvement. We surmised at the time that the double bond in the 13-membered ring in either **190** or **191** might be undergoing ring opening metathesis reactions, but we did not secure sufficient experimental evidence to support this conjecture. Notably, Winkler later reported that manzamine A itself undergoes ring opening metathesis,[94] thereby lending some support to our hypothesis. The conversion of **191** into ircinal A and manzamine A was then easily achieved by straightforward reactions.

In completing this synthesis of manzamine A, we achieved our goal of expanding the scope of the Diels−Alder reaction, and we exploited a novel domino Stille/Diels−Alder reaction to generate the tricyclic core of the natural product in a single operation. Unexpected at the outset of our journey, however, we also discovered that RCM reactions could be exploited to form 13- and 8-membered nitrogen heterocycles. This important finding revealed the potential of RCM as a useful construct in the design of new approaches to natural products. This realization captured our attention and opened the door to an entirely new area of inquiry for research in our group.

■ OLEFIN METATHESIS AS A CONSTRUCT FOR NATURAL PRODUCT SYNTHESIS

Having been introduced to the significant potential of RCM reactions in our synthesis of manzamine A, we were inspired to explore such constructions more generally. However, we wanted to avoid the lure of using a RCM reaction followed by a reduction simply to form a new ring because we viewed such a tactic as being inefficient from the functional group perspective. A central design element in developing our approaches to natural products by olefin metathesis thus required the carbon−carbon double bond formed by the RCM either to be present in the natural product or to be used in a subsequent transformation leading to the natural product. With this limitation in mind, some targets we selected include FR-900482,[95] dihydrocorynantheol,[96] hirsutine,[96b] peduncularine,[97] anatoxin-a,[98] 8-*epi*-xanthatin,[99] pseudotabersonine,[100] isolysergol,[101] and pinnaic acid[102] (Figure 9).

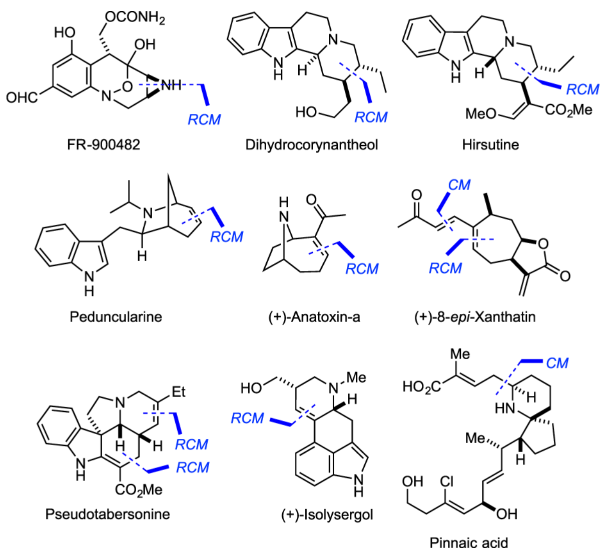
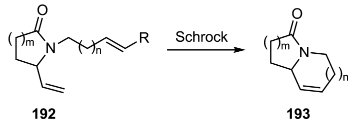


Figure 9. Representative natural products prepared by olefin metathesis (bonds formed by RCM indicated by dashed blue lines).

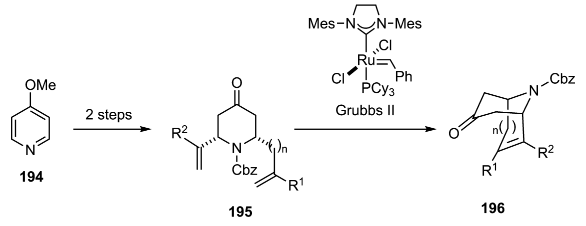
As a prelude to embarking on these syntheses, we performed several studies to examine the scope and utility of using RCM to form fused heterocycles (Scheme 38)[103] and bridged heterocycles (Scheme 39).[104] These early studies helped establish RCM as a useful reaction for the elaboration of functionalized nitrogen heterocycles that are structural subunits in a diverse array of alkaloid natural products, some applications of which are summarized herein.

Scheme 38



m = 1, 2; n = 0–3; R = Me, H

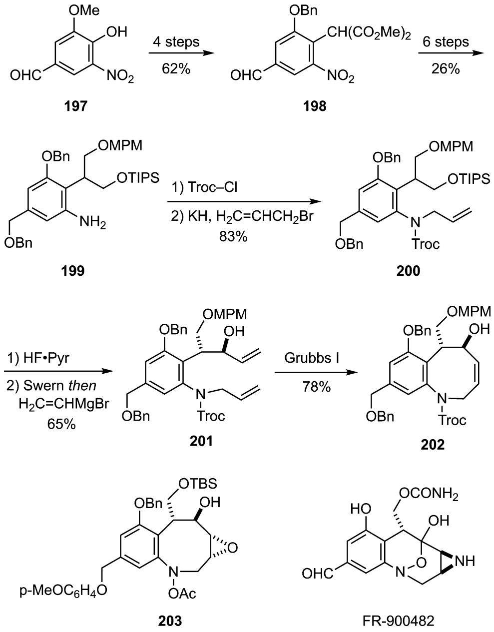
Scheme 39



n = 0, 1; R^1, R^2 = H, CH_3 combinations

FR-900482, a potent antitumor antibiotic that was isolated from the fermentation broth of a *Streptomyces* bacteria,[105] was one of our early targets. We envisioned that the double bond formed by a RCM reaction would be used as the precursor of the aziridine ring (see Figure 9). The synthesis of the key intermediate diene **201** was readily achieved by a relatively straightforward sequence of reactions (Scheme 40).[95] The RCM of **201** proceeded smoothly to create the 8-membered ring in **202**, in spite of the highly functionalized nature of **201**. Unfortunately, all of our attempts to introduce the requisite aziridine ring stereoselectively onto a compound derived from **202** were unsuccessful. We thus elected to transform **202** into **203**, which had been previously converted into FR-900482 by Fukuyama and co-workers.[106] Although we had to settle for a formal synthesis of FR-900482, the use of a RCM as a key step validated the central element in our original plan.

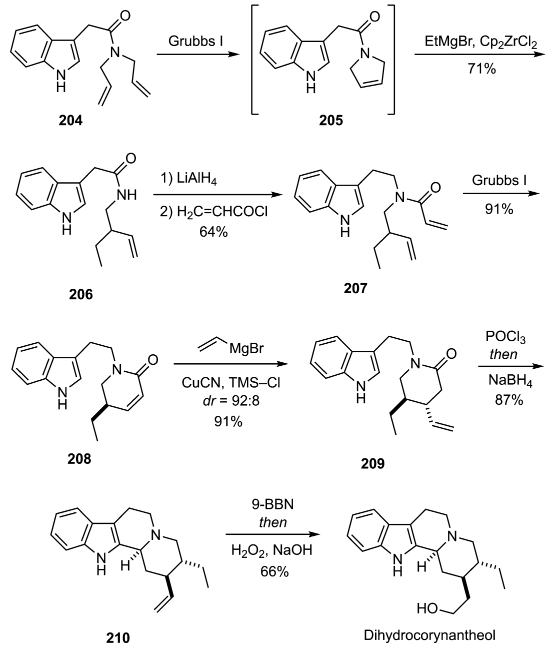
Scheme 40



Our approach to dihydrocorynantheol, an archetypal corynantheoid alkaloid and a popular synthetic target, features two RCM steps to generate key intermediates. The readily available amide **204** was first converted into the homoallylic amide **206** in a novel one-pot sequence in which **204** was first cyclized via RCM to furnish the amide **205** (Scheme 41).[96] Zirconocene dichloride and EtMgBr were then simply added to the reaction mixture to induce a carbomagnesation[107] that provided **206**. Conversion of **206** into **207** followed by a RCM delivered the unsaturated lactam **208**. The highly stereoselective 1,4-addition of a vinyl group to **208** gave **209**, which was then converted via a Bischler−Napieralski reaction into **210**; hydroboration/oxidation of the vinyl group then delivered dihydrocorynantheol.

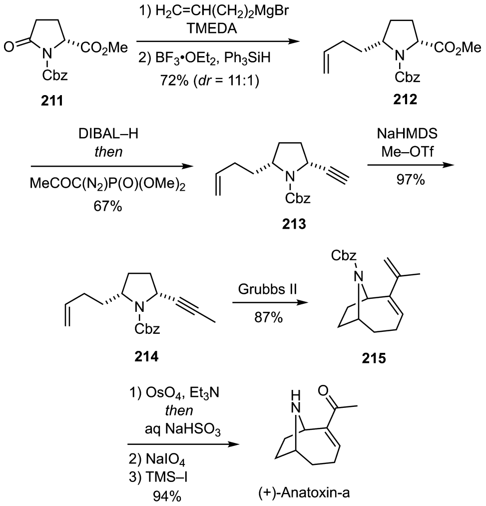
Our general interest in the synthesis of bridged bicyclic alkaloids using RCM as a key construction led us to anatoxin-a, which was isolated from the toxic blooms of a blue-green algae and is one of the most potent nicotinic acetylcholine receptor agonists known.[108] In order to prepare **214**, the substrate for the planned enyne RCM reaction, it was first necessary to develop a method for the stereoselective synthesis of

Scheme 41



cis-2,5-disubstituted pyrrolidines.[109] Using this procedure, **211** was converted with high diastereoselectivity into **212** (Scheme 42).[98]

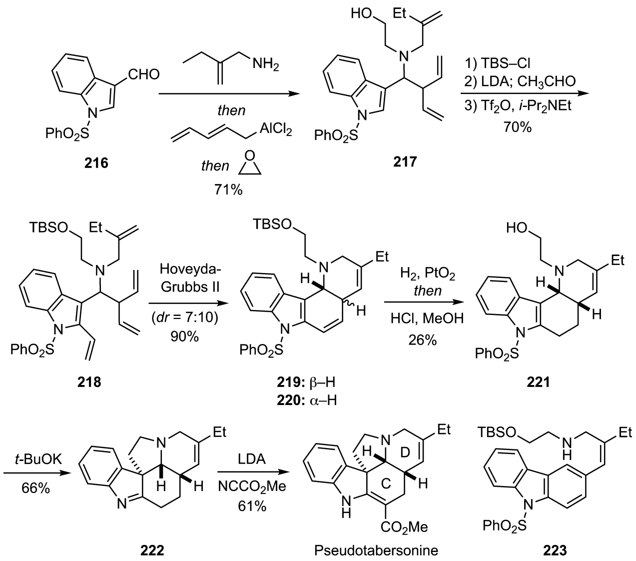
Scheme 42



In the first step of this sequence, it was necessary use TMEDA as an additive in order to increase the regioselectivity of the nucleophilic attack of the Grignard reagent upon the lactam carbonyl group. A bulky silane reducing agent was also needed to achieve stereoselective reduction of the acyl iminium ion precursor of **212**. Transformation of **212** into **214** followed by an enyne RCM cyclization in the presence of Grubbs II catalyst gave **215**. The selective oxidation of the disubstituted olefin in **215** proved to be somewhat vexing. However, we eventually found that this double bond could be selectively functionalized using stoichiometric amounts of osmium tetroxide. Oxidative cleavage of the intermediate diol, followed by removal of the *N*-protecting group provided anatoxin-a.

We were drawn to the synthesis of pseudotabersonine, which is a member of the small pandoline subgroup of *Aspidosperma* alkaloids, because it presented a novel opportunity to construct the C and D rings simultaneously by the double ring-closing metathesis of the tetraene **218** (Scheme 43).[100] The synthesis of **218** featured a multicomponent assembly process to convert **216** into **217** together with about 10% of the corresponding linear adduct. A vinyl group was then introduced at C2 of the indole ring in three steps, thereby giving **218**. The double RCM of **218** was induced by Hoveyda−Grubbs II catalyst to give a mixture of the *cis*- and *trans*-hydroquinolines **219** and **220**. The stereoselectivity in the cyclization, which was presumably initiated by catalyst loading onto one of the vinyl groups in the skipped diene, was somewhat disappointing because an inseparable mixture (7:10) of *cis*- and *trans*-hydroquinolines was formed with the desired *cis*-product being the minor product. Exacerbating this problem was the discovery that **219** underwent facile fragmentation under the reaction conditions to provide **223**. We did not investigate the possibility of using a chiral RCM precatalyst to assess whether enhanced diastereoselectivity might be achieved. Rather, the mixture of **219** and **220** was converted by catalytic hydrogenation, followed by deprotection of the primary alcohol group into a readily separable mixture of **221** (26%) and its *trans*-isomer (44%). The conversion of **221** to **222** featured a novel process inspired by the work of Bosch,[110] and subsequent introduction of the remaining carbomethoxy group proceeded without event to give pseudotabersonine. Although we achieved the goal of elaborating the hydroquinoline ring in pseudotabersonine by a double RCM reaction, the formation of stereoisomers unveiled a significant challenge in the field.

Scheme 43



There is a long-standing problem in the synthesis of (+)-lysergic acid, arguably the most notorious member of the *Ergot* alkaloid family,[111] and we sought to address this issue using an RCM reaction to create the piperidine D-ring (Figure 10).

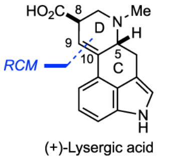


Figure 10. Challenges in the synthesis of (+)-lysergic acid.

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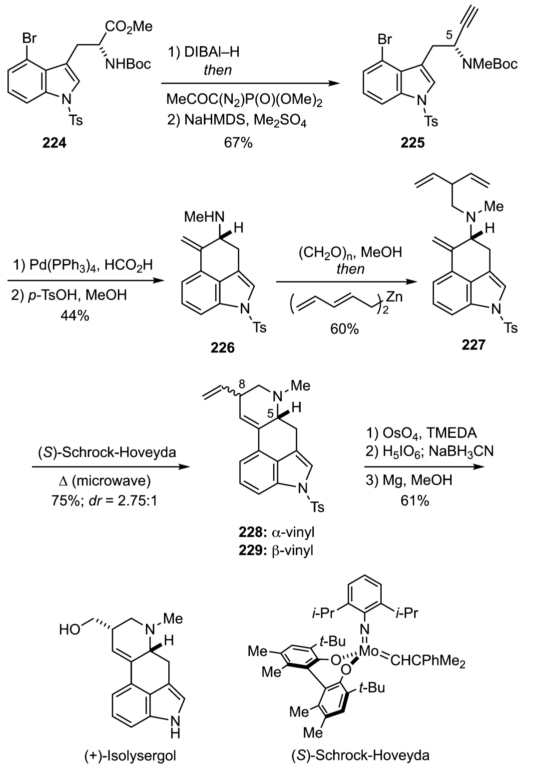
J. Org. Chem. 2017, 82, 10757−10794

Namely, in all of the approaches to (+)-lysergic acid, controlling the stereochemistry at C8 and C5 in both an absolute and relative sense is an unsolved problem. Maintaining the position of the carbon−carbon double bond at C9−C10 is associated with this challenge. Our intention was to generate the C9−C10 double bond by a RCM reaction of a substrate in which the stereocenters at C5 and C8 had either been previously set or would be established by a diastereoselective RCM cyclization.

In order to test the feasibility of our plan, the bromotryptophan derivative **224,** which was prepared according to the reported procedure for the synthesis of its enantiomer,[112] was converted into the acetylene **225** (Scheme 44).[101b] An intramolecular reductive Heck cyclization then led to **226**. Preliminary attempts to alkylate the nitrogen atom of **226** with groups suitable for the eventual RCM step were unsuccessful. However, the Mannich-type reaction of **226** with pentadienyl zinc provided the branched triene **227** together with its separable linear regioisomer in about 30% yield. Initial experiments using the achiral Schrock catalyst to induce the RCM of **227** gave a mixture of **228** (36% yield) and **229** (8% yield). Although we optimistically hoped that a chiral catalyst might load preferentially onto one of the vinyl groups of the skipped diene moiety in **227**, this was sadly not to be. Namely, the RCM of **227** in the presence of (*S*)-Schrock−Hoveyda catalyst did proceed in substantially better yield, but **228** was still formed as the major product, albeit with slightly lower diastereoselectivity. The (*R*)-Schrock−Hoveyda catalyst did not grant significant favoritism to either **228** or **229** and gave only small quantities of cyclized product, presumably as a consequence of being mismatched for the substrate. Although we examined other RCM precatalysts, none surpassed the effectiveness of the (*S*)-Schrock−Hoveyda catalyst. Our troubles did not end with this RCM reaction, because all of our attempts to convert either **228** or **229** into lysergic acid or isolysergic acid via selective oxidative cleavage of the vinyl group were unsuccessful. We attributed these difficulties to the instability of the intermediate aldehyde, which had not been isolated and characterized. After some experimentation, however, **228** was converted into (+)-isolysergol by selective dihydroxylation of the vinyl group at C8 using the protocol of Donohoe,[113] followed by oxidative cleavage of the resultant diol, reduction of the aldehyde, and removal of the indole protecting group. Our disappointments notwithstanding, this first enantioselective synthesis of (+)-isolysergol required only 12 steps from commercially available 4-bromoindole.

Scheme 44

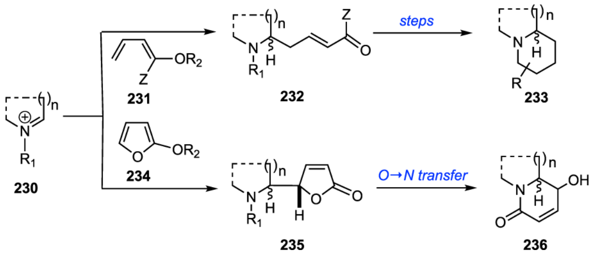


It is perhaps notable that our syntheses of pseudotabersonine and isolysergol revealed deficiencies in methods for controlling the diastereoselectivity in RCM processes. Clearly there remain opportunities for future advances that will likely be solved by new catalyst design.

APPLICATIONS OF VINYLOGOUS MANNICH AND RELATED REACTIONS

The discovery of the vinylogous Mannich reaction, which we had invented to solve a problem encountered during our concise syntheses of tetrahydroalstonine and geissoschizine (see Scheme 33), inspired us to expand the utility of this powerful construction and apply it to the syntheses of other alkaloid natural products.[114] More generally vinylogous Mannich reactions can be depicted as shown in Scheme 45 wherein cyclic and acyclic iminium ions **230** undergo reaction with acyclic and cyclic dienes **231** and **234**, respectively, to give the corresponding adducts **232** and **235**.[115] One can then envision conversions of **232** into compounds such as **233** and the transformation of **235** by *O*→*N* transfer reactions to give lactams such as **236**. Intramolecular variants of the vinylogous Mannich reaction were also examined.[116] As part of our general work in the area, we also developed an enantioselective process,[117] and we studied the basis for the diastereoselectivity in the reactions of furans **234** with iminium ions.[118]

Scheme 45



The applicability of vinylogous Mannich reactions to the syntheses of natural products can be readily appreciated upon realizing that structural subunits found in **233**, **235**, and **236** abound in alkaloids as exemplified by pumiliotoxin 251D,[119] (−)-A58365A,[120] croomine,[121] rugulovasine A and B,[122] setoclavine,[122b] and citrinadin A[123,124] (Figure 11, blue dashed lines highlight bond formed). Although these structural subunits are not present in *N*-methylwelwitindolinone C isothiocyanate[125,126] and actinophyllic acid,[127] related transformations can also be readily applied to the syntheses of these complex alkaloids.

The key step in the synthesis of (−)-pumiliotoxin 251D, which was isolated from an Ecuadoran poison-arrow frog,[128]

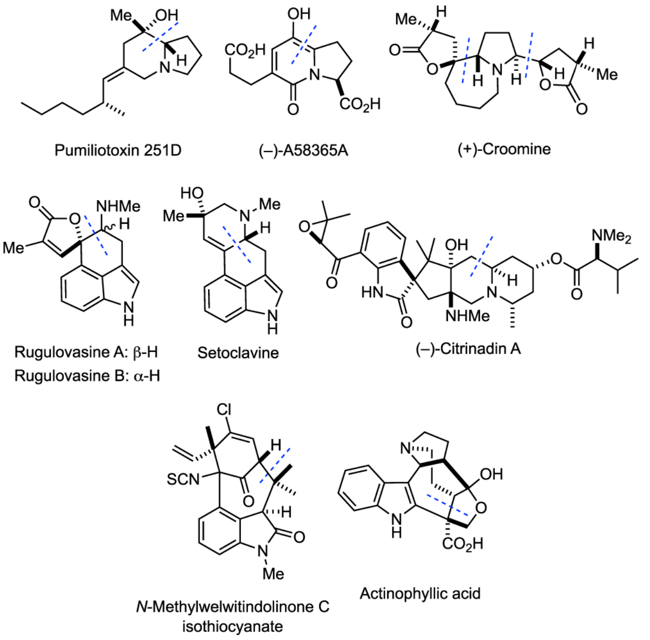
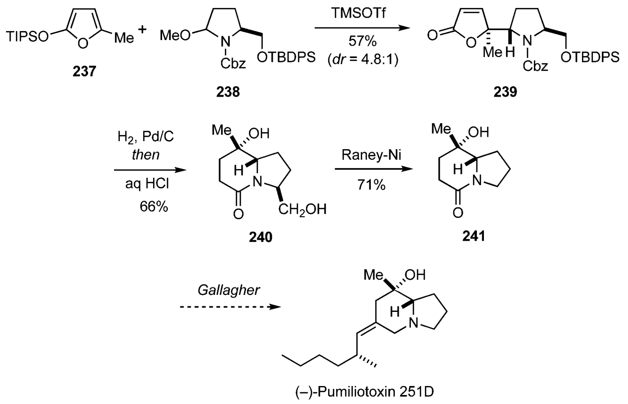


Figure 11. Representative alkaloids prepared by vinylogous Mannich and related reactions (new bonds indicated by dashed blue line).

involves the vinylogous Mannich reaction of **237** with **238**, which was prepared in three steps (71% overall yield) from commercially available material, to furnish **239** with good diastereoselectivity (Scheme 46).[119] Catalytic hydrogenation of

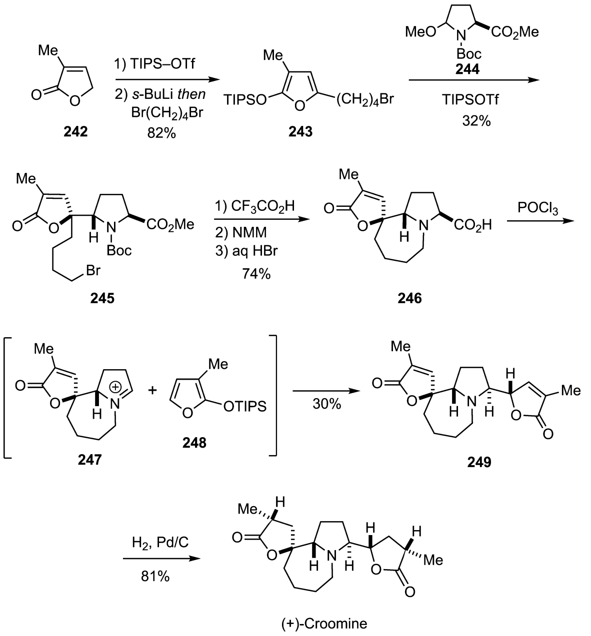
Scheme 46



239, followed by a lactone−lactam rearrangement delivered **240**. The hydroxymethyl group in **240**, which had fittingly served its purpose of directing facial selectivity in the vinylogous Mannich reaction, was removed using Raney-Ni according to the method of Kraft to give **241**.[129] Inasmuch as **241** had been converted by Gallagher and co-workers into pumiliotoxin 251D,[130] its preparation represents a short formal synthesis of this indolizidine alkaloid.

Perhaps no alkaloid better serves to exemplify the utility of the vinylogous Mannich reaction than the *Stemona* alkaloid croomine, which was isolated from plants of the Stemonaceae family used in traditional Chinese and Japanese medicine to treat respiratory disorders such as pulmonary tuberculosis and bronchitis.[131] Croomine bears two butyrolactone rings appended to a central pyrrolidine ring, and because this array is found in the vinylogous Mannich adduct **235** (Scheme 45), it occurred to us that two vinylogous Mannich reactions involving furans might be employed in its synthesis. Indeed, reaction of **243** with **244**, which is readily available from pyroglutamic acid,[132] in the presence of TIPSOTf gave the *threo*-adduct **245** as the major product (Scheme 47).[121] Somewhat surprisingly,

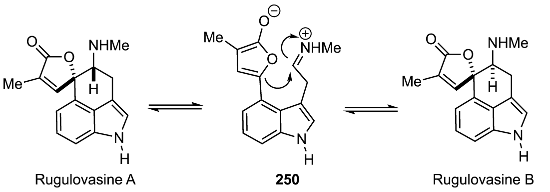
Scheme 47



no *erythro*-products were observed, and the only other product isolated from the reaction was the *threo*-adduct (1%) derived from attack on the more hindered face of the intermediate acyl iminium ion. Compound **245** was then easily converted into **246** in three steps. The carboxylic acid moiety in **246** had already served a critical role in controlling the facial selectivity in the vinylogous Mannich reaction, and it would now serve as a functional handle for the regioselective creation of the iminium ion **247** using a protocol reported by Rapoport.[133] Thus, treatment of **246** with $POCl_3$ led to the formation of **247** that was trapped with the furan **248** to provide a mixture (2:1) of **249** and its *erythro*-diastereomer. Simultaneous catalytic hydrogenation of both butenolide moieties in **249** then delivered (+)-croomine in only eight steps in the longest linear sequence and in a total of 10 steps from commercially available starting materials. The brevity of this synthesis is notable and underscores the power of vinylogous Mannich reactions to rapidly assemble complex molecular architectures.

Rugulovasine A and rugulovasine B, which represent unusual structural types within the *Ergot* alkaloid family,[111] were originally isolated in racemic form, and they were observed to interconvert upon warming.[134] Based upon these findings, it was proposed that rugulovasines A and B undergo facile interconversion via the achiral intermediate **250**. (Scheme 48).

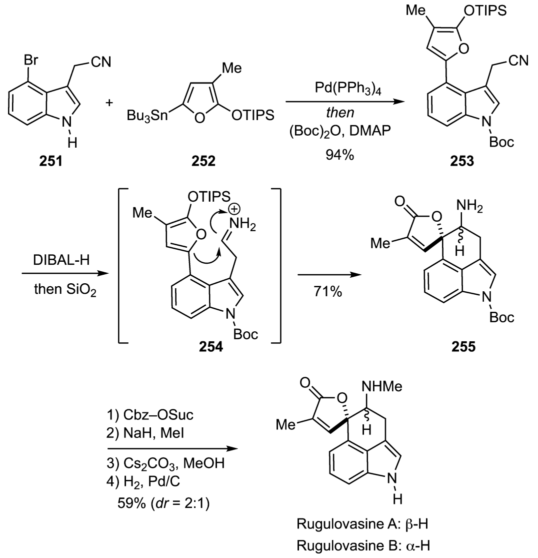
Scheme 48



The veracity of this hypothesis was convincingly demonstrated by Rebek, who first prepared rugulovasine A in optically pure form and showed that it equilibrated to form a mixture of racemic rugulovasine A and rugulovasine B.[135]

Examination of the conversion of **250** into either rugulovasine A or B reveals this process is a vinylogous Mannich reaction (see Scheme 45). We therefore reasoned that if we could develop a short synthesis of an intermediate such as **250**, we would be able to complete a concise synthesis of the rugulovasines. In the event, **251**, which was available in two steps from commercially available 4-bromoindole, was coupled with the furylstannane **252** to give the key intermediate **253** (Scheme 49).[122] Hydride reduction of **253** generated an intermediate iminium ion that underwent facile cyclization upon exposure to silica gel to provide **255**. *N*-Methylation of **255** followed by removal of the protecting group on the indole nitrogen atom gave a mixture (2:1) of rugulovasine A and B.

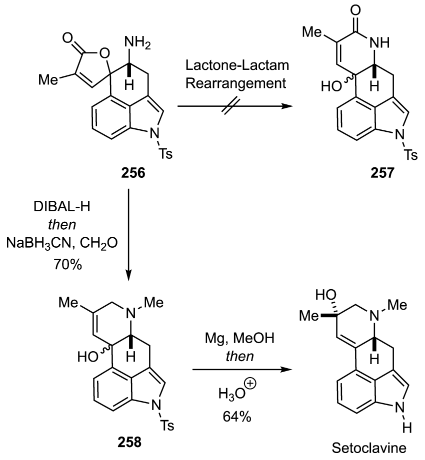
Scheme 49



We then queried whether we might be able to transform an intermediate such as **255** via a lactone-lactam rearrangement into a precursor of setoclavine, which possesses the tetracyclic skeleton characteristic of lysergic acid and other *Ergot* alkaloids. Inasmuch as we discovered that the *N*-Boc protecting group on the indole ring of **253** was somewhat labile under conditions required to convert it into **255**, we prepared the *N*-tosyl analogue **256** by a sequence of reactions similar to that used to make **255**. However, we were unable to induce the desired lactone-lactam rearrangement of **256** to furnish **257** (Scheme 50),[122b] so we had to adopt an alternative strategy. Accordingly, **256** was converted to **258** by reduction of the lactone moiety to give an intermediate amino alcohol that underwent facile isomerization and dehydration to give a mixture of epimeric dihydropyridines that were simply reduced with excess $NaBH_3CN$ in aqueous formaldehyde to give an inconsequential mixture of the diastereomeric amino alcohols **258**. Removal of the *N*-tosyl protecting group followed by acid catalyzed rearrangement of the allylic alcohol array provided setoclavine as a single stereoisomer.

In 2004, Kobayashi and co-workers reported the isolation of the spiro oxindole alkaloid (−)-citrinadin A from a marine fungus and found it had significant anticancer activity.[136] The unusual molecular architecture of (−)-citrinadin A intrigued us because it offered an opportunity to explore an enantioselective variant of the vinylogous Mannich reaction. We were destined to discover, however, that the structure originally assigned to (−)-citrinadin A was incorrect (vide infra). Hence, despite the many powerful advances in spectroscopic methods over the years, the enterprise of total synthesis still serves as a reliable means to verify or determine structures of natural products.

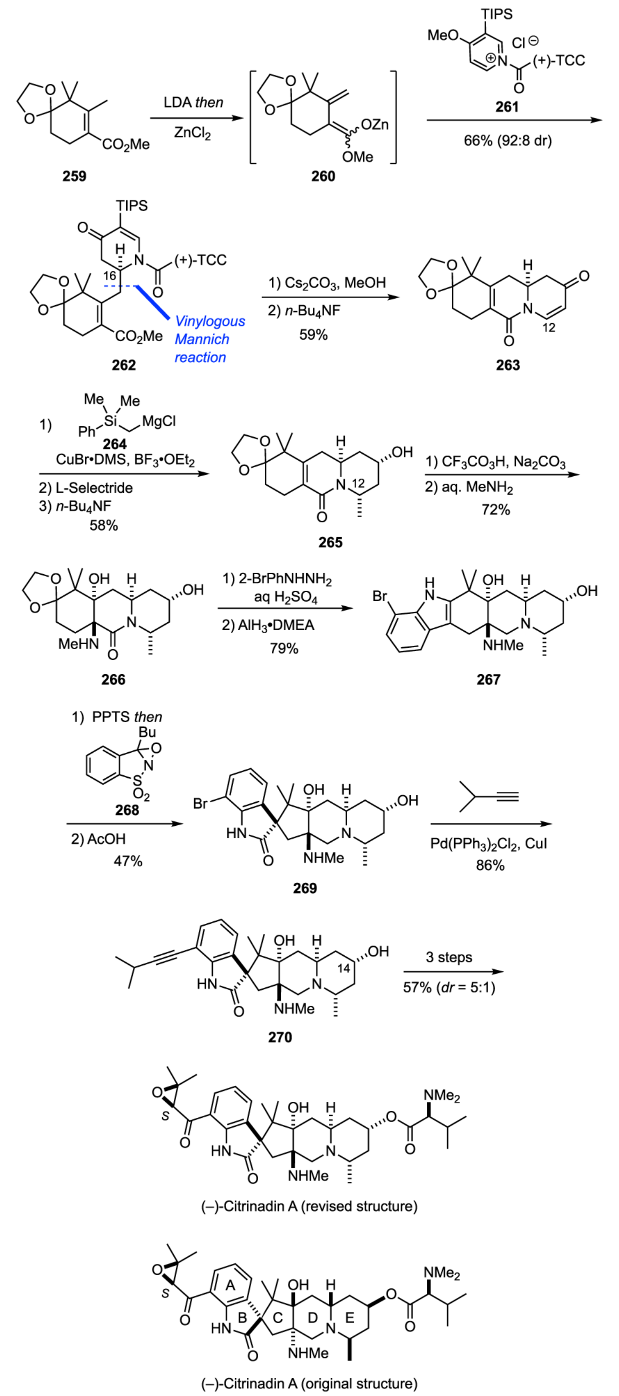
Scheme 50



The total synthesis of (−)-citrinadin A commenced with preparing **259** in four steps from commercially available 2,2-dimethylcyclohexane-1,3-dione (Scheme 51).[124] The zinc dienolate **260** was generated in situ from **259** and allowed to react with the chiral pyridinium ion **261** to give **262** with high diastereoselectivity in a process that is related to work of Comins and Sahn.[137] The newly created stereocenter at C16 of **262** would then serve as the origin of all the remaining stereocenters in the pentacyclic core of (−)-citrinadin A. Exposing **262** to Cs_2CO_3 in methanol led to the facile removal of the chiral auxiliary, which was recovered in good yield, followed by spontaneous cyclization; subsequent removal of the TIPS group provided the vinylogous imide **263**.

The challenge at this juncture was to introduce a methyl group at C12 of **263** with high diastereoselectivity, and after some experimentation it was discovered that the bulky methyl group equivalent **264** was best suited to the task at hand. Stereoselective reduction of the resultant ketone and removal of the silyl group furnished **265**. Resisting the impulsive temptation to protect the secondary hydroxyl group, **265** was converted directly via highly stereoselective epoxidation/ring opening to give **266**, which was elaborated to the pentacyclic intermediate **267** by sequential Fischer indole reaction and reduction of the lactam moiety. Conditions to effect the stereoselective rearrangement of **267** to form the spirooxindole **269** required extensive experimentation, the details of which can be found in our paper.[124b] However, we eventually discovered that treating the *p*-toluenesulfonate (PPTS) salt of **267** with Davis' oxaziridine **268**, followed by the acid-catalyzed rearrangement of the intermediate epoxide delivered **269**. It then remained to introduce the epoxy ketone moiety onto the aromatic ring. We initially examined the possibility of converting the aryl bromide in **269** directly into an *α,β*-unsaturated ketone via a carbonylative cross-coupling procedure we had developed,[35] but these efforts were unsuccessful. On the other hand, this construction was achieved by a Sonogashira reaction of **269** to give **270** that was then

Scheme 51

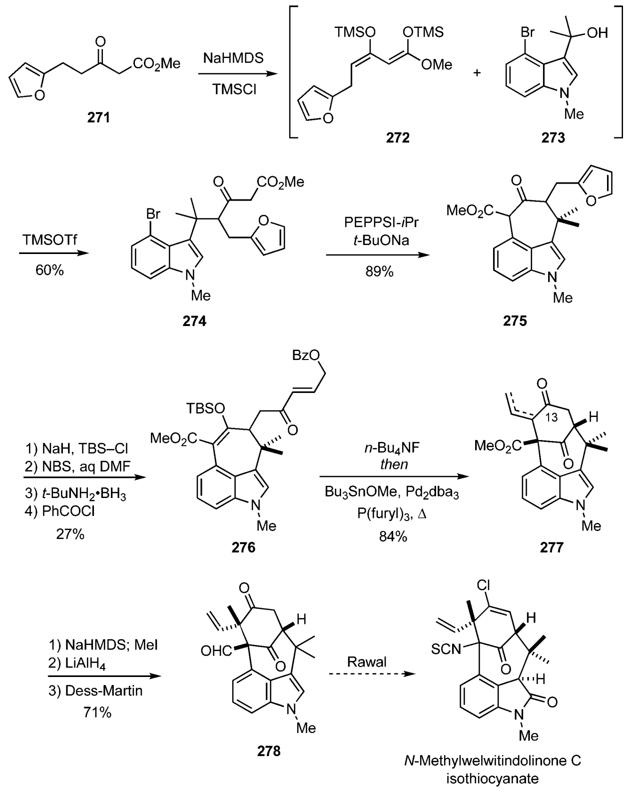


transformed to (−)-citrinadin A via a three-step sequence involving esterification of the C14 hydroxyl group, gold-promoted oxidation of the aryl acetylene group according to the method of Zhang,[138] and diastereoselective epoxidation of the resultant *α*,*β*-unsaturated ketone using the Enders protocol.[139] It is noteworthy that the advanced intermediate **265** also served as a precursor in our synthesis of (+)-citrinadin B, which had been previously prepared by Wood and co-workers.[140]

As mentioned previously, this synthesis of (−)-citrinadin A led to the revision of the structure reported by Kobayashi (see Scheme 51, bottom).[136] We discovered the error because we first made the isomer having the originally assigned structure and found that the CD spectra of the synthetic and natural materials did not match. The two structures of (−)-citrinadin A differ in the stereochemistry of the pentacyclic core, which is enantiomorphic to what was proposed by Kobayashi, who based his assignment upon a combination of ROESY correlations and the electronic circular dichroism (ECD) spectrum. Our finding serves as a useful reminder of the potential pitfalls that are associated with using spectroscopic techniques such as ROESY and ECD to assign absolute stereochemistry of compounds when other stereoisomers are not available for comparison.

We have explored variations of the vinylogous Mannich reaction as key steps in the syntheses of several other alkaloid natural products. For example, we were attracted by the significant challenges presented by the structure of *N*-methylwelwitindolinone C isothiocyanate, a novel alkaloid that was isolated in 1994 by Moore and co-workers from a Micronesian blue-green algae and found to reverse P-glycoprotein-mediated multiple drug resistance in human cancer cell lines.[141] Our synthetic approach to this intriguing alkaloid featured the reaction of the electron rich diene **272** with the stabilized cation generated upon ionization of **273**, which may be viewed as a vinylogous iminium ion, to provide **274** (Scheme 52).[126]

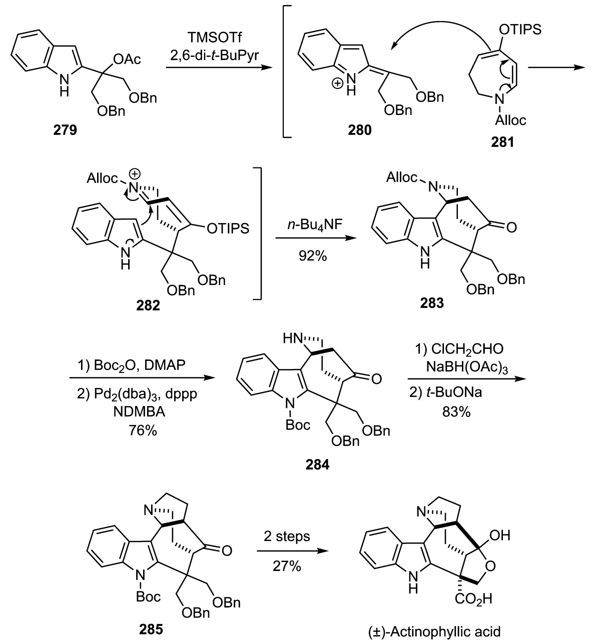
Scheme 52



Cyclization of **274** via a Pd(0)-catalyzed intramolecular enolate arylation provided **275**. Oxidative processing of the furan ring in **275** then led to the *γ*-acyloxy enone **276** that underwent a novel *π*-allylation reaction to deliver **277**, which possesses the bridged tetracyclic framework of the welwitindolinone alkaloids. Despite extensive experimentation, however, we were unable to convert the C13 ketone moiety of **277**, or any derivative thereof, into a vinyl chloride. Our frustrations were finally put to an end when Rawal reported the total synthesis of *N*-methylwelwitindolinone C isothiocyanate from **278**.[142] Accordingly, **277** was easily converted in three steps into **278**, thereby completing a formal total synthesis of this alkaloid.

The reaction of **272** with **273** (Scheme 52) served as an inspiration for the design of a novel entry to actinophyllic acid, an alkaloid with a unique structure that was isolated from the leaves of *Alstonia actinophylla* and exhibits potent activity as an inhibitor of carboxypeptidase U (CPU).[143] In the event, **279**, which is available in a one-pot operation from indole, underwent ionization to give the doubly vinylogous iminium ion **280** that was trapped with the dienamide **281**, which is available in three steps from *N*-vinylpyrrolidone, to give the key tetracyclic intermediate **283**, presumably via **282** (Scheme 53).[127]

Scheme 53



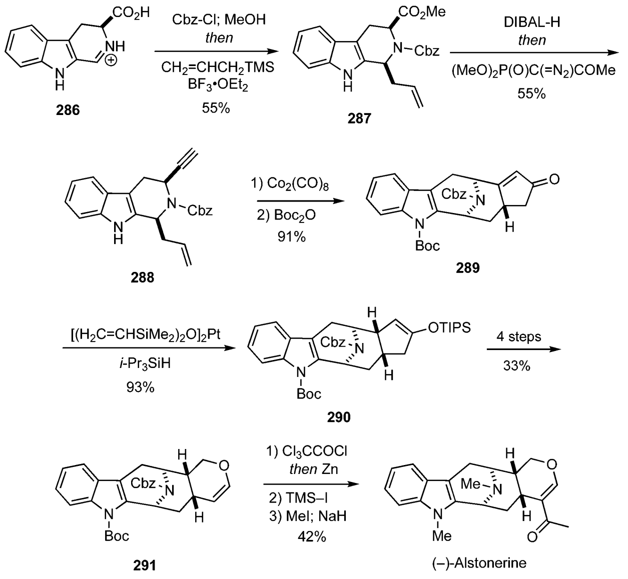
Although this cascade of reactions eventually proceeded in excellent yield, considerable experimentation was required to identify the optimal conditions, largely because **283** is remarkably acid labile. The stability of **283** was markedly enhanced by acylation of the indole nitrogen atom, and subsequent removal of the *N*-Alloc protecting group yielded **284**. Annelation of the pyrrolidine ring was achieved by reductive alkylation and cyclization to give **285**. Global deprotection of **285** followed by oxidation of the primary neopentyl alcohol led to actinophyllic acid. This seemingly straightforward oxidation proved to be unexpectedly challenging, and considerable effort was required to obtain even a modest yield.

Diversion of intermediates in the syntheses of complex natural products has become a popular strategy for creating unique compounds for biological screening that are otherwise inaccessible.[144] As part of an ongoing program to identify compounds having promising biological activities, we screened **284**, **285**, and several analogues for anticancer activity in Hs578t cells, a human breast cancer cell line.[127a] Notably, **285** (IC_{50} = 11.2 ± 1.9 μM) and several tetracyclic derivatives of **284** were active in this assay. The activities of these compounds were distinguished by their high Hill slopes and E_{max} values. Thus, the cascade sequence of reactions that featured a higher order vinylogous Mannich reaction gave rapid access to a collection of novel compounds that would have otherwise been unavailable and that exhibit unusual and promising anticancer activity. A series of related compounds are under current investigation as potential anticancer agents.

■ OTHER REACTIONS OF π-NUCLEOPHILES WITH IMINIUM IONS

Having explored the reactions of iminium ions with π-nucleophiles derived from alkoxy substituted dienes, we were intrigued by possible applications of reactions of iminium ions with other π-nucleophiles as a key construction for alkaloid synthesis. In one such endeavor, the reaction of an allylsilane with an *N*-acyl iminium ion was the first step in our synthesis of (−)-alstonerine, a member of the macroline/sarpagine alkaloids that has been reported to exhibit cytotoxic activity against two human lung cancer cell lines.[145] For example, reaction of trimethylallylsilane with the *N*-acyl iminium ion **286** furnished **287**, which was transformed into the α,ω-enyne **288** in a single operation (Scheme 54).[104b,146] The Pauson−Khand reaction of **288** led to the formation of the bridged pentacyclic intermediate **289**. The synthesis of **289** represents the first application of a Pauson−Khand reaction to the synthesis of an azabridged bicyclic structure. Elaboration of the cyclopentanone ring in **289** into the dihydropyran ring in **291** was initiated by hydrosilylation of **289** in the presence of Karstedt's catalyst to give the silyl enol ether **290**, which was transformed in four steps into **291**. The requisite acetyl group was installed onto the enol ether moiety of **291** by a variant of a reaction that we had developed earlier for the carbomethoxylation of dihydropyrans in our synthesis of tetrahydroalstonine (See Scheme 33), thereby completing an enantioselective total synthesis of (−)-alstonerine in only 15 chemical steps from L-tryptophan. The protocol developed in this synthesis to acetylate cyclic enol ethers to give vinylogous esters should also be generally useful because this functional group is commonly found in natural products.

Scheme 54



The quinolizidine and indolizidine ring systems comprise core structural subunits in a large number of alkaloid natural products.[147] Of these, epilupinine, tashiromine, and epimyrtine are some representative examples that have been targets of numerous synthetic efforts (Figure 12).

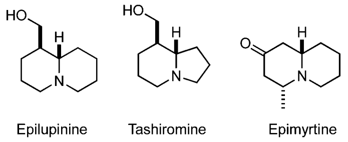
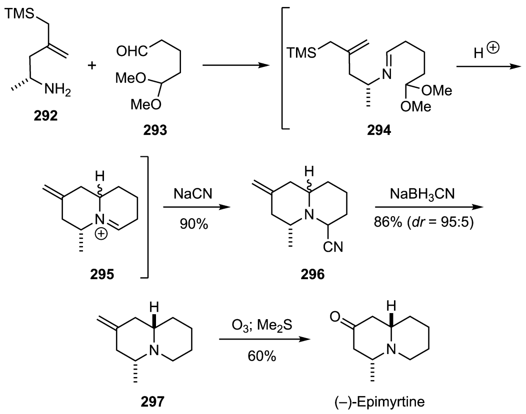


Figure 12. Representative quinolizidine and indolizidine alkaloids.

In thinking about designing a new and general approach to quinolizidine and indolizidine rings, we developed a novel iminium ion cascade reaction that is illustrated for the synthesis of (−)-epimyrtine (Scheme 55).[148] In the event, condensation of the known allylsilane **292**[149] with the monoprotected dialdehyde **293** in the presence of trifluoroacetic acid led to the formation of **296**, presumably via the intermediacy of **294** and **295**. A key step in this process is the cyclization of the iminium ion derived from **294** with the pendant allylsilane. The mixture of aminonitriles **296** thus obtained underwent hydride reduction to give **297**, and subsequent oxidative cleavage of the exocyclic methylene group of the salt of **297** delivered (−)-epimyrtine. This general approach for the rapid assembly of polycyclic systems represents a potentially useful strategy for the synthesis of compound libraries containing quinolizidine and indolizidine rings as structural subunits.

Scheme 55



APPLICATIONS OF DIPOLAR CYCLOADDITION REACTIONS

In addition to Diels−Alder reactions as a construct for alkaloid synthesis, we have also applied several dipolar cycloaddition reactions to the syntheses of natural products. For example, the cycloadditions of nitrile oxides with olefins followed by reductive cleavage can be used to generate β-hydroxy carbonyl compounds,[150] and such reactions were applied to generate substructures in phyllanthocin[151] and breynolide[152] (Figure 13). We also explored cycloadditions of azomethine ylides, and we developed a novel approach to didehydrostemofoline that featured construction of the tricyclic core of this natural product by the cycloaddition of an azomethine ylide related to **298**.[153,154]

Didehydrostemofoline is a member of the stemofoline family of alkaloids and one of the more complex representatives of the *Stemona* family.[131] Although many *Stemona* alkaloids exhibit insect acetylcholinesterase activity, didehydrostemofoline is among the most potent.[155] It also has in vivo antioxytocin activity and antitumor activity against gastric carcinoma.[156] We first established the underlying viability of intermolecular dipolar cycloadditions of substrates related to **298** to give the tricyclic framework characteristic of the stemofoline alkaloids in a series of preliminary studies.[153] The synthesis of didehydrostemofoline itself was then initiated with the transformation of 2-deoxy-D-ribose (**299**) in four steps into **300** (Scheme 56).[154]

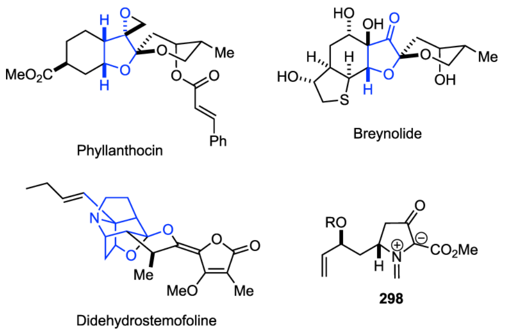
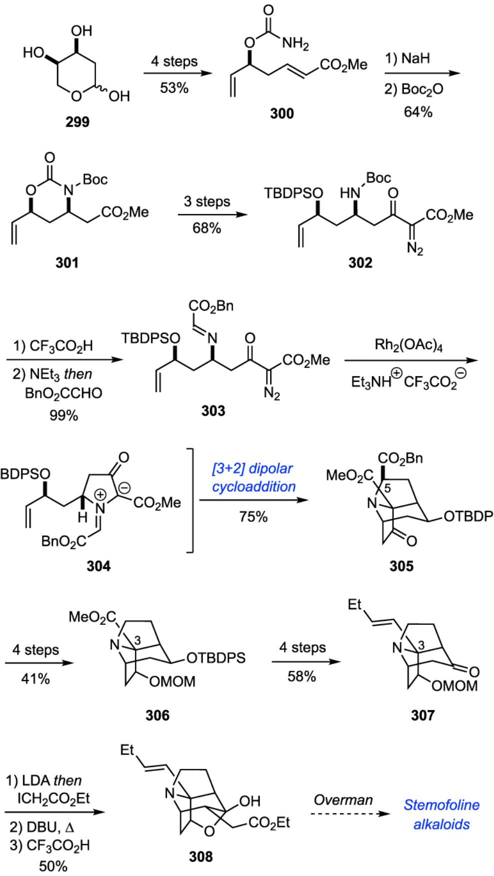


Figure 13. Skeletal subunits (blue highlight) accessible by dipolar cycloadditions.

Scheme 56



Cyclization of **300** using the Hirama−Itô protocol led to the cyclic carbamate **301**, exclusively as the *syn* diastereomer.[157] This carbamate was then converted in three steps into the diazo ketoester **302**, which underwent deprotection followed by condensation with benzyl glyoxylate to generate the imine **303**.

When we first tested the key cascade sequence that would deliver the tricyclic system of didehydrostemofoline, the diazo imine **303** was not purified. Rather, it was simply subjected immediately to heating with $Rh_2(OAc)_4$ to give **305**; none of the regioisomeric cycloadduct was observed. Surprisingly, however, we discovered that when **303** was purified and then subjected to the same conditions a mixture of cycloadducts was obtained. We eventually discovered that the presence of triethylammonium trifluoroacetate was key to the success of the reaction, presumably because it catalyzed the isomerization of the kinetically formed, U-shaped isomer of the intermediate azomethine ylide (not shown) into the more stable S-shaped isomer **304** as previously discussed in detail.[154] We were fortunate indeed that **303** was not purified when it was first prepared, and it was only careful experimental work that led to understanding how reaction conditions dramatically affected the regiochemical outcome. The tricyclic intermediate **305** was then processed by a sequence that involved removing the carboxyl functional group at C5 and introducing the alkenyl side chain at C3 to give **307**. Alkylation of the enolate derived from **307**, followed by epimerization and deprotection gave **308**, which had been previously converted by Overman into didehydrostemofoline and other stemofoline alkaloids.[158] This formal, enantioselective synthesis of didehydrostemofoline highlights the ease with which complex nitrogen heterocyclic systems can be rapidly assembled using cascade reactions involving cycloadditions of azomethine ylides generated in situ by cyclizations of diazo imines.[159]

■ APPLICATIONS OF ENANTIOSELECTIVE CYCLOPROPANATION REACTIONS

As a result of our interest in the design and use of trisubstituted cyclopropanes in conformationally constrained peptide mimics (vide infra), we also became interested in natural products containing cyclopropanes such as ambruticin S[160] and solandelactone E[161] (Figure 14).

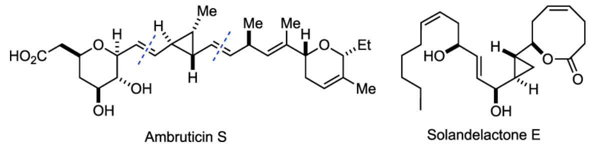
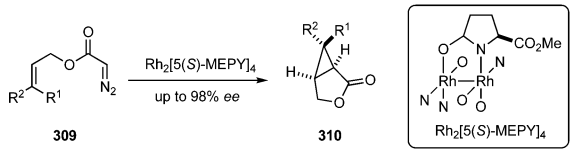


Figure 14. Representative cyclopropane ring-containing natural products.

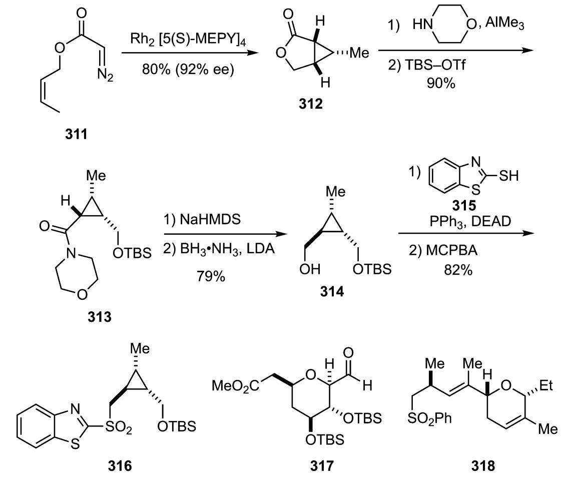
The first step toward any of these synthetic objectives required that we develop an enantioselective route to trisubstituted cyclopropanes. After trying several catalysts, we initiated a productive collaboration with Michael Doyle, then at Trinity University, who had reported that $Rh_2[5(S)\text{-MEPY}]_4$ was an effective catalyst for the enantioselective of cyclopropanes via bimolecular reactions.[162] We discovered that it was also an excellent catalyst for the intramolecular cyclopropanations of allylic diazo esters generally represented as **309** to give cyclopropyl lactones **310** (Scheme 57);[163] homoallylic diazo esters were also enantioselectively converted into the corresponding δ-lactones. Although both *Z*- and *E*-olefins were useful as substrates, enantioselectivities (ee) were better for *Z*-alkenes.

Scheme 57



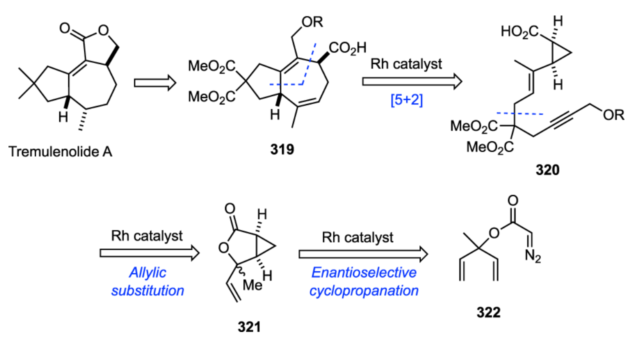
In developing an approach to ambruticin S, an orally active, antifungal antibiotic having low toxicity,[164] we envisioned a convergent strategy that involved coupling the three different subunits **316**–**318** as shown by the dashed blue lines in Figure 14. Although the details of our total synthesis of ambruticin S are not presented herein, the preparation of **316** is illustrative of the utility of our methodology for the enantioselective synthesis of trisubstituted cyclopropanes.[160] Briefly, the $Rh_2[5(S)\text{-MEPY}]_4$-catalyzed cyclization of **311** gave **312** that was converted in six steps to **316** (Scheme 58). Coupling **316** with **317** and **318** by carbon–carbon double-bond-forming reactions led to the synthesis of ambruticin S.

Scheme 58



Cyclopropane rings may also serve as versatile intermediates in the syntheses of other natural products.[165] For example, the sesquiterpene tremulenolide A, which was isolated from a fungal pathogen,[166] is not a particularly important sesquiterpene. However, it served us well as a platform for developing new chemistry when we adopted the unusual approach to the hydroazulene framework that is depicted in Scheme 59.[167]

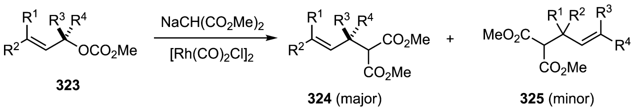
Scheme 59



The original strategy required the vinyl cyclopropyl lactone **321** as an early intermediate. Based upon our earlier work (see Scheme 57), it followed that **321** would be accessible by the enantioselective intramolecular cyclopropanation of the divinyl carbinol diazoacetate **322** using $Rh_2[5(S)\text{-MEPY}]_4$. It was at this point in the analysis, we became rather speculative. Rhodium catalysts were known to promote allylic substitutions and [5 + 2] cycloadditions of vinylcyclopropanes, so we dreamed optimistically that it might be feasible to convert **321** to **319** in one operation via **320** using a single rhodium catalyst. The conversion of **319** into tremulenolide A would then simply require a series of refunctionalizations.

Toward implementing the plan outlined in Scheme 59, we had already shown that $Rh_2[5(S)\text{-MEPY}]_4$ could be used for the first step, but we also surmised that this catalyst would not likely catalyze the other transformations. A few exploratory experiments quickly confirmed this prediction. We then discovered that the commercially available rhodium catalyst $[Rh(CO)_2Cl]_2$ promoted allylic substitutions in an unusual manner. In particular, $[Rh(CO)_2Cl]_2$ catalyzed allylic substitutions of substrates such as **323** by the regioselective introduction of the carbon nucleophile on the same carbon atom that bore the carbonate leaving group (Scheme 60).[168]

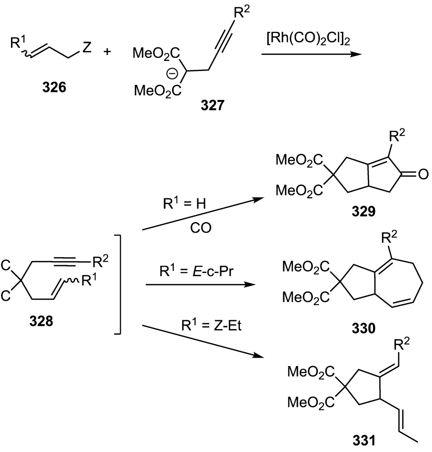
Scheme 60



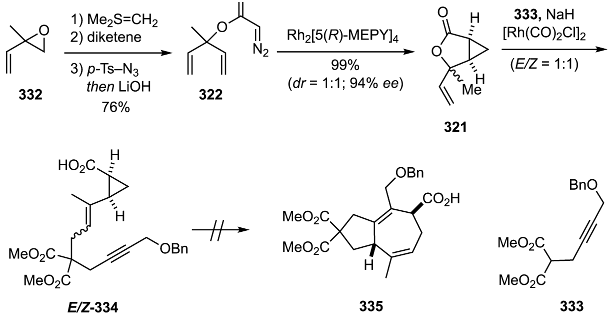
Namely, the structure of the starting material **323** maps directly onto the structure of the major product **324**, irrespective of substitution on the allylic array. This is a remarkable finding because rhodium catalysts typically give products derived from substitution at the more substituted terminus of the allylic subunit,[169] whereas the opposite trend is observed for the corresponding palladium-catalyzed reactions.[170] There are occasions when the lack of a direct correlation between the structure of the allylic starting material **323** and the preferred product may be a disadvantage.

The striking discovery that $[Rh(CO)_2Cl]_2$ selectively catalyzes the transformation of **323** into **324** suggested the possibility that such a catalyst might be useful in promoting cascade reactions because this and related rhodium catalysts were known to promote Pauson–Khand reactions,[171] cycloisomerizations,[172] and [5 + 2] cycloadditions.[173] We were thus gratified to discover that the reaction of allylic substrates **326** with the substituted malonates **327** in the presence of $[Rh(CO)_2Cl]_2$ gave the alkylated products **328**. Depending upon the nature of the R^1 substituent, **328** was directly transformed at higher temperatures into cyclopentanones **329** via a Pauson–Khand reaction, hydroazulenes **330** by a [5 + 2] cycloaddition, or cyclic dienes **331** via a cycloisomerization (Scheme 61).[168b,174] We believe these novel domino reactions represent the first examples of using a single catalyst to effect sequential reactions by simply increasing the temperature for the second reaction. Such processes have significant potential for the rapid assembly of structurally complex targets from simple starting materials.

Scheme 61



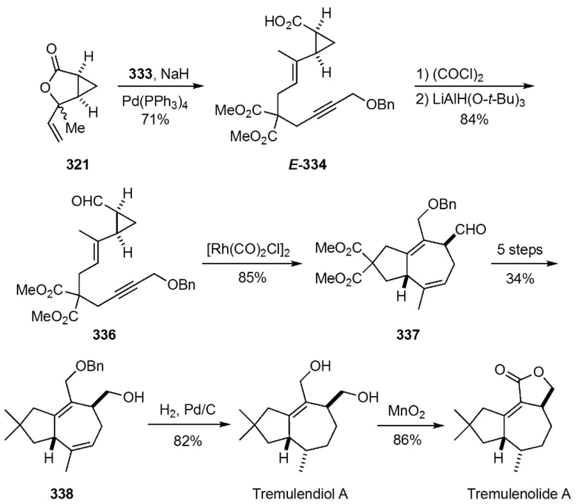
Scheme 62



Having established the underlying feasibility of inducing a rhodium-catalyzed cascade sequence leading to hydroazulenes, it remained to apply such a process to the synthesis of tremulenolide A. The divinyl diazo ester **322** was readily prepared from the allylic epoxide **332**, and the enantioselective cyclopropanation reaction proceeded with high ee to give a mixture (1:1) of epimeric vinyl cyclopropyl lactones **321** (Scheme 62).[167] The allylic substitution reaction of **321** using the anion derived from malonate **333**, which was obtained in three straightforward steps from 1,4-butynediol, produced a mixture (1:1) of ***E/Z*-334**. To our considerable dismay, we were unable to use $[Rh(CO)_2Cl]_2$ or any other Rh(I) catalyst to induce a [5 + 2] cycloaddition to give **335**. This unfortunate result did not come as a complete surprise because there were no examples of Rh(I)-catalyzed [5 + 2] cycloadditions of *cis*-vinylcyclopropane carboxylates. So much for dreams.

Turning to a more conservative approach, **321** was converted into ***E*-334** by a Pd(0)-catalyzed reaction with the anion derived from **333** (Scheme 63). Refunctionalization of the

Scheme 63



carboxylic acid moiety led to the aldehyde **336**, which underwent facile [5 + 2] cycloaddition with $[Rh(CO)_2Cl]_2$ to give **337**. Exhaustive reduction of the geminal diester moiety led to **338**, which was converted to tremulenediol A and tremulenolide A by straightforward redox transformations.

Even though the original strategy for synthesizing tremulenolide A could not be implemented, useful chemistry emerged. For example, we serendipitously discovered the unusual reactivity of $[Rh(CO)_2Cl]_2$ as a catalyst to promote site-selective π-allylations at the carbon atom bearing the leaving group. This finding led to the development of a series of novel cascade reactions wherein products initially obtained by π-allylic substitutions were transformed directly by a second $[Rh(CO)_2Cl]_2$ -catalyzed reaction to generate mono- and bicyclic products. Thinking outside of the box has its merits, even when dreams are not realized.

■ ENANTIOSELECTIVE HALOLACTONIZATION

More recently, we became interested in challenges associated with the synthesis of bromophycolide A (Figure 15), a novel bromine containing natural product having anticancer activity.[175] Examination of the structure of bromophycolide A reveals two bromohydrin subunits bearing stereogenic centers. Such functional arrays are typically accessed by electrophilic additions to alkenes, including bromolactonizations. Although enantioselective halolactonizations of unsaturated acids were known,[176] there were no examples of such reactions proceeding by an *exo*-mode of ring closure to generate a stereogenic carbon atom bearing a halogen substituent. Hence, controlling the absolute stereochemistry to form bromohydrins in which the bromine atom and the oxygen atom reside on stereogenic carbon atoms was an unsolved problem.

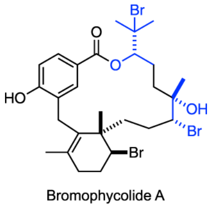
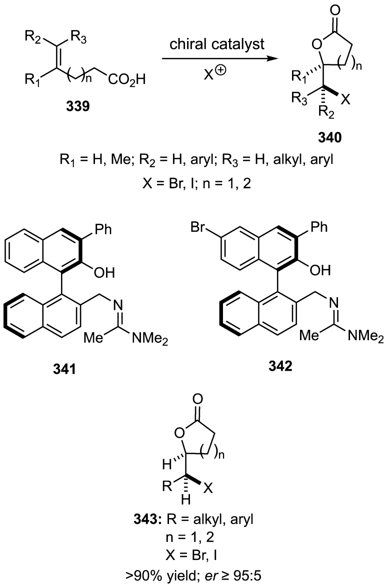


Figure 15. Bromohydrin subunits (highlighted in blue) of bromophycolide A.

In order to address this significant gap in methodology, we developed the BINOL-derived **341** and **342** as novel bifunctional catalysts (Scheme 64). Although the BINOL framework had been broadly employed to make catalysts that promote enantioselective reactions, it had not yet been used in catalysts for enantioselective halolactonizations. Our original design envisioned a thiocarbamate substituent as the Brønsted acid component of the bifunctional catalyst. However, because we were unable to introduce a thiocarbamate moiety onto the phenolic group of **341**, we reasoned that the phenol itself might serve as a Brønsted acid. Gratifyingly, we discovered this to be the case, and both **341** and **342**, which is formed upon bromination of **341**, induced highly enantioselective cyclizations of unsaturated acids of the general form **339** to give bromo or iodo halolactones **340** (Scheme 64). Notably, these cyclizations provided the first access to lactones such as **343** in which a halogen atom is on the newly created stereocenter.[177] This discovery, which was only possible because we ventured an experiment born from a failure, solved a longstanding problem in the field. Applications of this methodology to the synthesis of halogen-containing natural products such as bromophycolide A are under investigation.

Scheme 64



■ MIMICS OF NATURAL PRODUCTS

In chemistry circles, natural products are commonly regarded as being primary or secondary metabolites that occur in nature. However, a broader definition of a natural product is any compound that is produced by a living organism. Such a definition would include a variety of other naturally occurring materials such as peptides, proteins, nucleic acids, phospholipids, etc. Chemical interest in natural products has been driven by their structures and their biological activities, which are a manifestation of biological responses resulting from interactions of two or more naturally occurring compounds. Sadly, funding for traditional studies in natural products chemistry, which include isolation and synthesis, has declined significantly in recent years, and there is no compelling evidence that this unfortunate trend will be reversed in the near future. However, when one considers the broader definition of natural products, it quickly becomes apparent that mimics of natural products are equally important because such molecules might be developed into compounds of medical relevance, including enzyme inhibitors, nucleic acid binders, and receptor antagonists or agonists. Perhaps the organic chemistry community should consider the possible biological and medical applications of natural product mimics, which can be used as targets of opportunity to discover and develop new chemistry. Indeed, a number of synthetic chemists have already made substantial contributions in this area of inquiry.[178]

Phospholipid Analogues. In this spirit, a number of years ago we became interested in the chemistry and biology of phospholipids, which play vital roles in a number of cellular processes, including signaling pathways. For example, processing of different classes of phospholipids by enzymes of the phospholipase C (PLC) family leads to hydrolysis of the phosphodiester bond as shown in **344** (Figure 16) to produce a phosphorylated headgroup and a diacylglycerol, which functions as a second messenger by activating protein kinase C (PKC).[179] Because activation of PKC is relevant to cancer, we were lured by the possibility of using nonhydrolyzable phospholipid mimics as inhibitors of PLC as a potential strategy to discover novel anticancer agents.

Toward identifying PLC inhibitors, we developed a number of methods for the synthesis of analogues of phospholipids of the general type **345** and **346** (Figure 16).[180] Because of the nature of the phosphodiester replacements in these compounds, they were not expected to suffer cleavage by PLC enzymes. As a starting point, we examined the efficacy of using some of these analogues as inhibitors of the phosphatidylcholine-preferring PLC from *B. cereus* (PLC_{Bc}),[181] which had been cloned and was readily available in recombinant form. Once we had identified novel inhibitors, we collaborated with the Hough group in Norway to obtain the structure of an inhibitor−PLC_{Bc} complex.[182] Examination of this structure led us to query whether we might apply “rational” site-directed mutagenesis of the three key active-site residues (Glu4, Tyr56, and Phe66) that interact with the choline headgroup to modify substrate selectivity.[183] The goal was to transform PLC_{Bc} into a variant that selectively hydrolyzed phospholipids having ethanolamine and serine head groups. We were modestly successful in this endeavor, and we unraveled some of the details of how changing these three amino acids affected substrate specificity. The X-ray structure of the PLC_{Bc}−inhibitor complex also inspired a series of mechanistic studies in which we identified Asp55 as the general base in the hydrolysis step. Overall, our interest in inhibitors of phospholipid processing enzymes led to the development of useful methodology for the synthesis of phospholipid analogues as well as to some new structural and mechanistic insights into questions of substrate selectivity and catalysis of PLC_{Bc}.

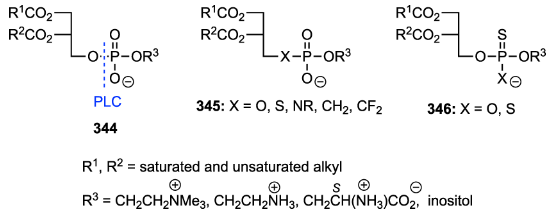


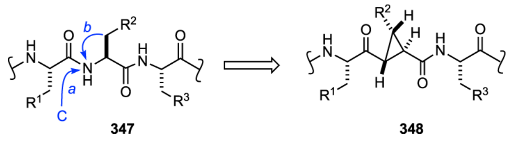
Figure 16. Phospholipid analogues as potential PLC inhibitors.

Peptide Mimics. In another area of chemical biology, we were drawn to peptide mimics, or peptidomimetics, which are biologically active peptides that have been modified to improve or modify their molecular properties, including stability and activity. Peptide mimics are typically derived from proteins, hormones, cytokines, and enzyme substrates, so they have long played an important role in the pharmaceutical industry in the design and development of novel enzyme inhibitors and receptor antagonists or agonists.

Of particular interest to us at the outset was the design of a new class of conformationally constrained peptide mimics. The rationale for developing such peptidomimetics arose from the prevailing belief that stabilizing the bound conformation of a ligand in solution would give a compound having higher affinity, provided the flexible and constrained molecules interacted in the same way with solvent and the protein.[184] The underlying assumption associated with this conventional wisdom is that the constrained ligand will benefit from a reduced entropic penalty upon binding. However, the increases in affinity of constrained molecules that are actually observed are often much less than the accepted energetic estimates of 0.7−1.6 kcal/mol for completely restricting independent rotors.[185] Surprisingly, *at the time we began these studies, there was no experimental evidence that actually supported this hypothesis* because binding entropies and enthalpies for flexible/constrained ligand pairs in protein−ligand interactions had never been determined. The only support for this widely held belief was based upon determinations of K_i’s, IC_{50}’s, and EC_{50}’s.

Toward inventing novel rigid peptide mimics, we modeled the bound conformations of peptide-like enzyme inhibitors and deduced that the cyclopropane-derived peptide mimic **348** might serve as a constrained analogue of the peptide **347** (Scheme 65).[186] Operationally, the cyclopropane ring in **348** arises from **347** by a side chain to backbone cyclization in which the backbone nitrogen atom is replaced with a carbon atom (*a*), and the new bond is formed between this atom and the *β*-carbon atom of the side chain (*b*). The *trans* relationship of the backbone substituents of **348** was envisioned to locally stabilize a *β*-strand. Moreover, the R^2 group in **348** is oriented so it occupies a region in space relative to the backbone atoms that approximates a *gauche* (−) conformation.

Scheme 65



Much of our work in this area has been reviewed elsewhere,[187,188] so the present discussion will focus upon lessons from our early work and how those studies led to our involvement in the biophysical aspects of protein−ligand interactions. Unbeknownst to us, we were destined to learn that the fundamental premise of ligand preorganization as a design strategy for identifying compounds having higher protein binding affinities because of more favorable binding entropies was flawed.

Our first foray into the field of conformationally constrained peptide mimics was in the design of novel inhibitors of renin, an aspartic protease involved in the angiotensin cascade. We hypothesized that the cyclopropane-derived peptidomimetic **350** might mimic the bound conformation of **349**, a potent renin inhibitor discovered at Abbott Laboratories (Figure 17).[189] Notably, **349** and **350** contain the same number and types of heavy atoms and the same number of hydrogen-bond donors and acceptors. We believe that meeting these criteria is critical because doing so increases the likelihood that desolvation parameters and binding interactions with solvent and the protein for the two compounds being

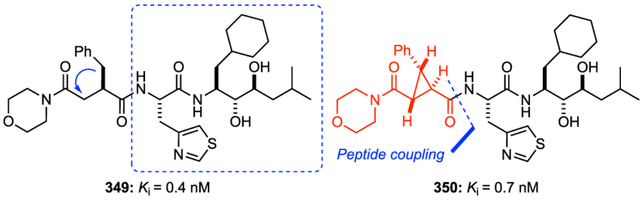
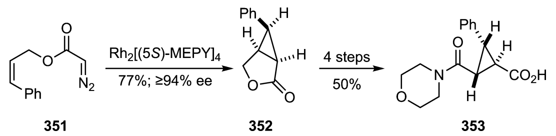


Figure 17. Peptide mimics as renin inhibitors showing transition-state isostere (blue dotted box).

compared will be closely similar. Indeed, a deficiency in the vast majority of studies of the effects of ligand preorganization is that they do not satisfy these simple requirements, making reliable comparisons of any kind problematic.

The synthesis of **350** commenced with transforming the allylic diazoacetate **351** into the cyclopropyl lactone **352** via an enantioselective intramolecular cyclopropanation, followed by a series of straightforward steps to give **353** (Scheme 66); standard peptide coupling of **353** with the tripeptide transition-state isostere in **349** then gave **350**. We found that **350** was approximately equipotent to the more flexible analogue **349** (see in Figure 17). Given the prevailing dogma that introducing a conformational constraint into a molecule should lead to higher affinity, we were initially somewhat disappointed by this result. Upon further reflection in a more positive mode, however, we surmised that the substituents on the cyclopropane ring in the bound conformation of **350** were likely oriented in a fashion similar to those substituents in the bound conformation of **349**. Hence, we reasoned that cyclopropanes might serve as stereochemical probes of the three-dimensional structure of bound ligands when X-ray crystallographic data of the protein−ligand complexes were not available, as was the case for **349**.

Scheme 66



In subsequent work, we studied conformationally constrained analogues of matrix metalloprotease inhibitors,[190] Ras-farnesyltransferase inhibitors,[191] and enkephalins.[192] In each of these investigations, we never observed more than a 10-fold enhancement in potency for the constrained analogue over its more flexible control. During this period, we also investigated cyclopropane-derived inhibitors of HIV protease, including **354** and **355**, close analogues of the Abbott inhibitor **A-75925** (Figure 18).[193] Crystallographic studies of **354** bound to HIV protease showed that it bound in a fashion highly similar to compounds closely related to **A-75925**. Subsequent studies conducted using NMR revealed that **355** adopted a conformation in solution closely comparable to that of the three-dimensional structure of **354** bound to the active site of HIV protease. It was thus clear that the cyclopropane rings in **354** and **355** do indeed stabilize the conformation in solution that corresponds to their conformation when bound to the protease. Accordingly, one would have anticipated that **354** and **355** would be more potent than **A-75925**; inexplicably, however, this was not the case.

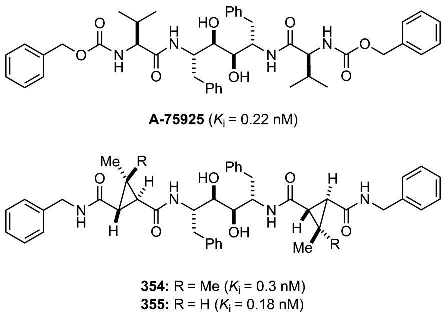
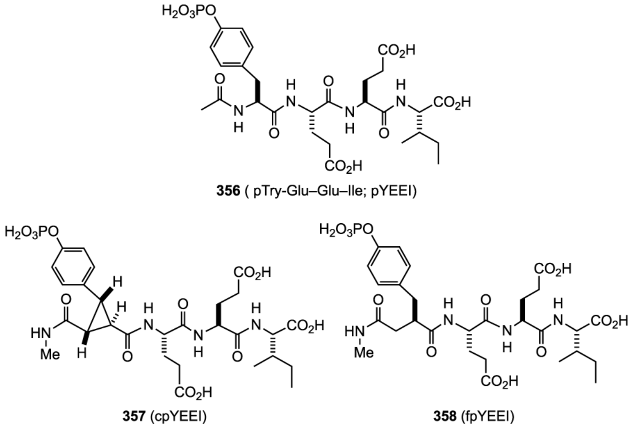


Figure 18. Peptide mimics as HIV protease inhibitors.

Collectively, our findings to this point suggested that cyclopropane-derived peptide mimics were suitable rigid replacements in a number of biologically active peptides. Unfortunately, few of the rigidified peptidomimetics we had prepared bound to the target protein with significantly greater affinity than their conformationally more flexible controls. But why? As noted earlier, there is a long tradition in medicinal and host−guest chemistry that is founded on the basic tenet that introducing a conformational constraint into a small molecule will result in a molecule having higher affinity. With the oft cited caveat that the two molecules interact in the same way with solvent and the protein or guest, the proclaimed origin of this enhanced affinity was that the preorganized molecule would benefit from a more favorable entropy of association. Certainly, a constrained molecule has a lower entropy than its corresponding flexible counterpart. However, is this reduction in ligand entropy really sufficient to guarantee a more favorable binding entropy? Because all of the data in the available literature relied solely upon experiments that measure parameters such as K_i or IC_{50}, we realized there was an unmet need to explore explicitly the detailed energetics of protein−ligand associations. This awareness drove us to design new experiments in which we would determine binding enthalpies and entropies in structurally well-defined systems.

After surveying a number of biological systems, we first focused our attention on complexes of phosphotyrosine-derived peptides with the Src SH2 domain.[194] Not only were a number of crystal structures of such complexes known,[195] but binding enthalpies and entropies had been determined for interactions of the Src SH2 domain with different peptides.[196] Peptides that bind to the Src SH2 domain are characterized by having the pYEEI motif **356** (Figure 19). Examination of crystallographic data for complexes of this domain with peptides containing the pYEEI subunit suggested that the three-dimensional structure of the cyclopropane-derived phosphotyrosine (pY) replacement in **357** would closely approximate the bound conformation of the pY residue in **356**. Although the design of **357** relies upon



K_a (M^{-1}) (25 °C)	9.7×10^6	1.7×10^7
$\Delta G°$ (kcal/mol)	−9.5	−9.8
$\Delta H°$ (kcal/mol)	−4.6	−7.3
$\Delta S°$ (cal/mol.K)	17.0	8.3

Figure 19. Peptide mimics of Src SH2 domain binding ligands.

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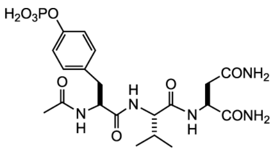
the peptide **356**, these two molecules contain different numbers of heavy atoms. As in the renin studies discussed previously, we adopted the guiding principle that ligands being compared should be as similar as possible. Accordingly, **358** is the appropriate control molecule for **357** because each has the same number of different heavy atom types and the same number of hydrogen bonding donors and acceptors.

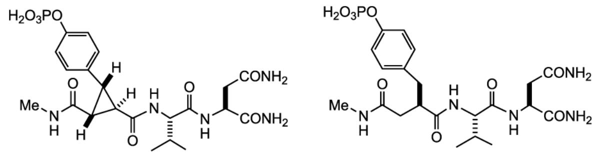
Compounds **357** and **358** were prepared, and their binding energetics were determined using isothermal titration calorimetry (ITC).[197] Both compounds bound with approximately the same affinity, and as expected the conformationally constrained **357** bound with a more favorable entropy than did **358**. We believe this finding represents the first time a conformationally constrained molecule was actually shown to bind to a protein with a more favorable binding entropy than its more flexible analogue. However, because the binding enthalpy of **357** was significantly less than **358**, both ligands bound with approximately equal affinity. This enthalpy−entropy compensation, the precise origin of which is not well understood, is actually a general phenomenon in protein−ligand interactions that is oftentimes balancing.[198]

At the time, we were unable to obtain a crystal structure of **358** bound to the Src SH2 domain, but examination of crystallographic data for **357** and an 11-mer analogue of **356** did not reveal any significant variations in binding interactions that might elucidate the origin of the enthalpic penalty for **357**. Indeed, the minor differences observed in comparing atomic positions and interactions in the structures of this 11-mer and **357** with the Src SH2 domain are comparable to the dissimilarities observed for coexisting complexes in the asymmetric unit of each structure.[197b] However, in subsequent NMR experiments performed in collaboration with Carol Post at Purdue University, we discovered that variations in hydrogen bonding interactions, which were detected by N−H chemical shift differences, between the Src SH2 domain and **356**−**358** correlated nicely with changes in binding enthalpies.[199] These studies suggest that NMR spectroscopy might be a better tool than X-ray crystallography for studying small differences in H-bonding interactions in protein complexes.

In another study of the effects of ligand preorganization upon binding energetics in protein−ligand interactions, we studied the binding of **359**−**361** to the SH2 domain of the growth receptor binding protein 2, Grb2 (Figure 20).[194] As was the case for the Src SH2 domain, crystallographic studies of the Grb2 SH2 domain complexed with peptides containing the consensus sequence pYVN suggested that the cyclopropane replacement of pY in **360** would mimic the bound conformation of the pY residue in **359**.[200] We prepared these compounds and discovered that the conformationally constrained peptide mimic **360** bound with higher affinity to the Grb2 SH2 domain than **361**, but the advantage was a consequence of a more favorable binding enthalpy, not a more favorable binding entropy.[201] *This stunning finding is contrary to the prevailing conventional wisdom regarding the putative entropic effects benefits of ligand preorganization in protein−ligand interactions!* This trend was also observed for several analogues having different amino acid replacements for the valine residue at pY+1 of **359**−**361**. In separate studies, we found that constraining linear peptides with macrocyclic constraints does not necessarily lead to more favorable binding entropies.[202,203] Based upon these revelations, one should no longer assert that ligand preorganization will lead to molecules that bind to proteins with more favorable entropies. So much for conventional wisdom!



359 (pTry–Val–Asn; pYVN)



360 (cpYVN) **361** (fpYVN)

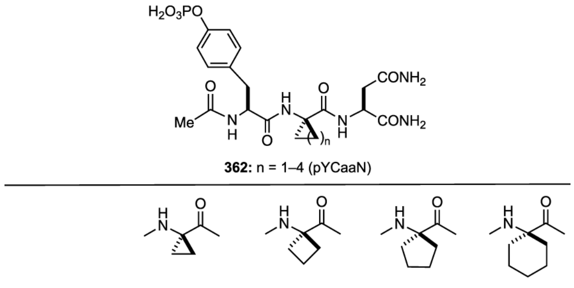
	360	361
K_a (M^{-1}) (25 °C)	2.8×10^6	4.5×10^5
ΔG° (kcal/mol)	−8.8	−7.7
ΔH° (kcal/mol)	−7.9	−5.4
ΔS° (cal/mol· K)	3.0	7.9

Figure 20. Peptide mimics of Grb2 SH2 domain binding ligands.

In an effort to identify the origin of the enthalpic advantage attending preorganization of **361**, we performed extensive structural studies of complexes of **360** and **361** and related constrained/flexible ligand pairs with the Grb2 SH2 domain.[201c] However, a detailed presentation of those results is beyond the scope of this Perspective. Suffice it to say that despite a number of observed differences in complexes of ligands such as **360** and **361** with the Grb2 SH2 domain, these variations are comparable to dissimilarities observed for coexisting complexes in the asymmetric unit of each structure. Hence, it is not possible to elucidate why the constrained ligands enjoyed an enthalpic benefit over their more flexible counterparts.

Another common assumption in protein−ligand interactions is that increasing nonpolar surface area in a molecule will lead to increased binding with a target protein because of the favorable entropic effects associated with desolvation and burial of hydrophobic surfaces.[204] However, there are cases wherein increasing the hydrophobic surface area of a ligand leads to increased affinity because of a more favorable binding enthalpy,[205,206] a phenomenon that was first observed in host−guest interactions and termed a "nonclassical" hydrophobic effect by Diederich.[207] More detailed studies of how adding nonpolar groups to ligands affects protein binding energetics are clearly needed.

Toward this goal, we were attracted to the work of Garcia-Echeverría and co-workers, who found that incremental increases in the ring size of a series of peptidomimetics represented by **362** (n = 1−4) led to corresponding decreases in IC$_{50}$ values (Figure 21).[208] In order to investigate the energetic origin of these potency enhancements, we prepared **362** (n = 1−4) and determined the binding entropies and enthalpies for their complexation with the Grb2 SH2 domain.[209] In accord with the results of Garcia-Echeverría, we found that the binding affinities increased upon the addition of methylene groups (see Figure 21). This trend resulted from increasingly more favorable binding enthalpies that dominated less favorable binding entropies. Hence, adding hydrophobic surface area did not enhance binding entropies as might have been expected based upon an entropy driven hydrophobic effect.



362: n = 1–4 (pYCaaN)

IC$_{50}$ (μM)	72.5	18.2	7.9	0.2
K_a (M^{-1}) (25 °C)	1.6x10^5	4.3x10^5	1.6x10^6	7.0x10^6
ΔG° (kcal/mol)	−7.1	−7.7	−8.5	−9.3
ΔH° (kcal/mol)	−3.3	−5.4	−6.3	−8.5
ΔS° (cal/mol•K)	13.0	7.5	7.4	2.7

Figure 21. Peptide mimics of Grb2 SH2 domain binding ligands.

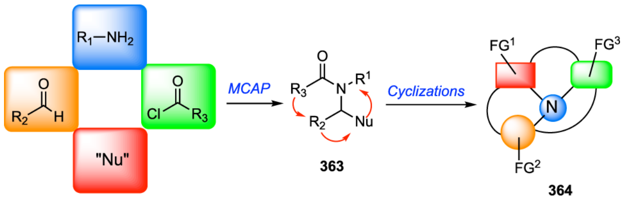
Crystallographic analysis of the four complexes of **362** (n = 1−4) with the Grb2 SH2 domain reveal that the positions of all atoms in the domain and in the backbone and side chain of the peptide mimics are identical within experimental error.[209] The only significant differences in these complexes are in the number of van der Waals contacts between the domain and the methylene groups ring at the pY+1 position. There is thus a positive correlation between buried nonpolar surface area and binding free energy *and* enthalpy, but not entropy as might have been expected.

In other studies involving ligand binding to the Grb2-SH2 domain we investigated the effects of increasing the length of an alkyl chain at the pY+1 position,[210] of introducing macrocyclic constraints in a peptide,[203] as well as the effect of cation−π interactions.[211] Collectively, these and other studies of protein−ligand interactions involving both the Grb2 and Src SH2 domains as well as numerous other biological systems reveal the difficulties of interpreting how even incremental structural changes in small molecules affect binding enthalpies and entropies in their interactions with a target protein.[188] However, it is only through detailed studies of structure and energetics in protein−ligand interactions that any real understanding will emerge. Given that such efforts involve the combined disciplines of synthetic organic chemistry, physical biochemistry, protein crystallography, NMR spectroscopy, and theoretical computations this is a significantly challenging interdisciplinary undertaking. There is much to do.

Collections of Natural Product Mimics. To suggest that phospholipid and peptide analogues of naturally occurring compounds are natural product mimics is relatively straightforward. However, if one thinks even more broadly, it follows that any small molecule that interacts with a biological target to elicit a response is likely mimicking an interaction that occurs in normal or diseased cells. Indeed, all drugs interact with some biological target and thus mimic some, perhaps unknown, natural ligand. This important realization opens the door to greatly expanding the scope of "natural products chemistry". Rational drug design can now be thought of as an exercise in the design and synthesis of natural product mimics. Such compounds, which can be structurally complex, can also provide an impetus for developing new synthetic methods and strategies and for discovering new chemical reactivity.

Our broad interest in natural product mimics led us to develop new platforms to prepare collections of such compounds for biological screening. The inspiration for what ultimately evolved into major effort in our laboratories is found in the conversion of **165** into **167**, a key sequence in our syntheses of tetrahydroalstonine and geissoschizine (Scheme 33). In a conceptual sense, this overall transformation involves the combination of three different reactants to form an intermediate that was rapidly converted into more complex structures of interest by ring forming reactions. Thinking about this process more broadly led us to design the general strategy to create libraries of small molecules that is outlined in Scheme 67.

Scheme 67



363

364

The first stage of this approach utilizes what we have since called a multicomponent assembly process (MCAP) in which four different inputs are combined to form an intermediate **363**. Because the functional groups resident in **363** are orthogonal, it is possible to transform **363** by various cyclizations to give a number of polycyclic nitrogen containing scaffolds of the general type **364**. Functional groups (FG) present in **364** can then be used to introduce various substituents onto the core structure.

Although we had envisioned this entry to the synthesis of small molecule libraries in the early 1990s, we did not actively pursue it until much later when we became involved in the NIH Roadmap Project. By that time, other related strategies for preparing collections of small molecules for biological screening had been reported. For example, Schreiber developed the general concept of diversity oriented synthesis (DOS) using a build-couple-pair approach,[212] which has been widely used. Other useful strategies for creating sets of novel compounds having biological activity include the diverted total synthesis approach of Danishefsky,[213] and the biology oriented synthesis (BIOS) approach described by Waldmann.[214] Given that the general strategy depicted in Scheme 67 was born from a problem in alkaloid synthesis, compounds of the general structure **364** having substructures present in biologically active alkaloids may be envisioned. Other privileged heterocyclic scaffolds found in drugs can also be accessed using this basic approach. Indeed, after unveiling the original concept,[215] we applied this approach to the synthesis of numerous heterocyclic scaffolds that could be easily diversified.[216,217]

We prepared more than 900 compounds derived from a diverse array of heterocyclic scaffolds (Figure 22), and these were distributed to various NIH screening centers that were also a part of the Roadmap Project. Although a number of hits in various assays emerged from these studies, several efforts to engage biologists who developed the screening assays in a collaborative project directed toward solving significant problems in biology and medicine were sadly unsuccessful. Accordingly, we cherry picked compounds from our collection and submitted them for screening at the Psychoactive Drug Screening Program that is run by Bryan Roth at the University of North Carolina with support from the National Institutes of Health. A number of these compounds bound with reasonable

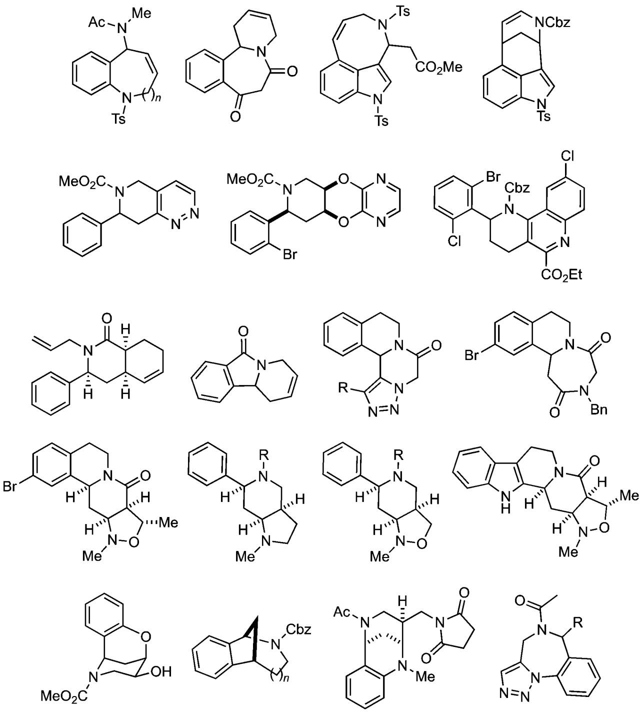


Figure 22. Some representative heterocyclic scaffolds accessible via MCAP approach.

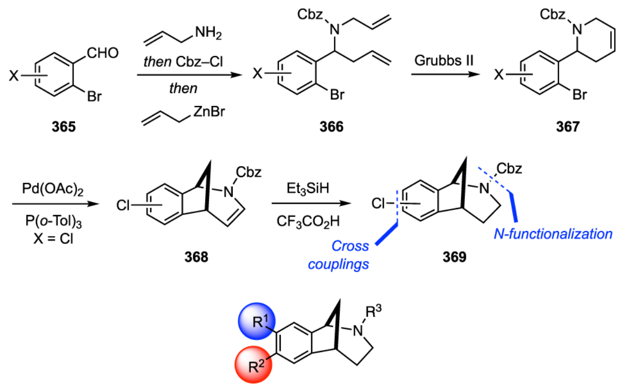
selectivity and affinity to a number of targets in the central nervous system (CNS), including opioid, dopamine, serotonin, muscarinic, and other receptors.

We could have used any of these initial hits to develop a new chemical biology or medicinal chemistry program, but we would have quickly found ourselves competing head-to-head with the pharmaceutical industry, a daunting challenge indeed for a small academic laboratory. Fortunately, we also identified compounds that bound with good selectivity and affinity to an interesting class of receptors called sigma receptors (σRs) for which there are two subtypes—the sigma 1 receptor (σ1R) and the sigma 2 receptor (σ2R). σRs are transmembrane, non-G protein coupled receptors that are expressed in the CNS and peripheral tissues and are involved in a variety of important cellular processes.[218] Although σ1R has been cloned and characterized by X-ray crystallography,[219] σ2R was enigmatic when we started and had not been cloned. The uncertainty regarding the molecular identify of σ2R is a serious handicap from the translational perspective.

The application of a multicomponent assembly process for the synthesis of some compounds that bind to σRs is illustrated by the synthesis of **369** (Scheme 68).[220,221] After making a number of analogues of **369**, we discovered that the orientation of substituents on the aromatic ring of the norbenzomorphan scaffold in **369** plays a key role in determining σ1R/σ2R selectivity.[222] For example, compounds generally represented by **370** tend to bind preferentially to σ2R, whereas compounds of the general form **371** tend to be selective for σ1R.

Armed with a set of compounds that bound with high affinity and selectively to σ1R and σ2R in hand, we needed to decide upon a plan for investigating the effects of modulating these receptors. Friends and former co-workers in the pharmaceutical industry hinted that we might want to avoid σ1R, so we accepted their informal advice and focused our attention upon σ2R. When we began our work, σ2R was known to be involved

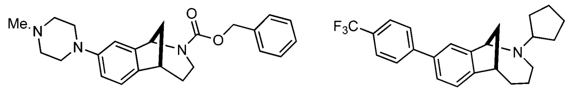
Scheme 68



370: R^1 = substituent; R^2 = H
371: R^1 = H; R^2 = substituent

in cell proliferation, and it was emerging as a target for the development of potential diagnostic and therapeutic agents for cancer.[223] Much less was known about its role in the CNS, but it has since been increasingly implicated in cellular processes relative to CNS disorders.[224]

We first queried whether ligands that bound to σ2R might be neuroprotective. By chance, I learned that Jon Pierce in the Department of Neuroscience at The University of Texas had developed a nice model for neurodegeneration in *Caenorhabditis elegans*. In collaboration with him and his group, we identified several compounds that had neuroprotective properties. We then wondered whether these compounds might have a beneficial effect in Alzheimer's disease (AD), so we initiated a collaboration with Mehrdad Shamloo at Stanford University. We found that **SAS-0132** (Figure 23) not only improved learning and memory in a transgenic animal model of AD, but it also enhanced performance in learning and memory tasks in wild-type animals.[225] This was an exciting finding because to our knowledge it was the first time σ2R had been associated with AD. We soon learned, however, that scientists at Cognition Therapeutics had made a similar discovery, and they published their work before we completed our studies for publication.[226] Subsequent investigations showed that **SAS-0132** reduces levels of proinflammatory cytokines, especially IL-1β. Moreover, **SAS-0132** suppresses the calcium transient induced by the σ2R modulator **DKR-1051** (Figure 23).



SAS-0132
σ1R = 841 ± 228 nM
σ2R = 90 ± 14 nM

DKR-1051
σ1R = 556 ± 99 nM
σ2R = 61 ± 23 nM

Figure 23. Selective σ2R modulators.

Because of the emerging importance of σ2R as a potential target in oncology and neuroscience, we initiated a collaboration with Andrew Kruse at Harvard University to see if we could clone the receptor, which had defied several previous attempts. We discovered certain aminotetralins bind with high affinity and selectivity to σ2R, so we prepared **JVW-1625** (Figure 24) and attached it to a resin for affinity purification of σ2R. These experiments led to identifying σ2R as being transmembrane protein 97 (TMEM97).[227] Notably, cloning σ2R resolves a longstanding mystery that will greatly facilitate

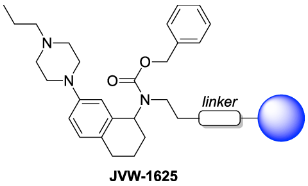


Figure 24. σ2R ligand-conjugate for pull-down experiments.

biological studies to discover the molecular mechanisms that are associated with small molecule modulation of σ2R/TMEM97.

In subsequent exploratory studies, we discovered that **SAS-0132** and another analogue exhibit promising activity in two models of traumatic brain injury. We have also identified compounds that bind to σ2R/TMEM97 and show promise in a mouse model of neuropathic pain,[228] whereas another is efficacious in a rat model of alcohol dependence. These findings represent the first time that σ2R/TMEM97 has been associated with these neurological conditions, so it is becoming increasingly apparent that modulating this receptor may have highly beneficial effects in treating a number of neurodegenerative and neurological conditions. This work has been truly rewarding as our discoveries might eventually have a beneficial impact on human health. We are exploring those possibilities as well as collaborating in studies with biologists to elucidate the physiological role of σ2R/TMEM97 using tool compounds.

CONCLUSIONS AND PROGNOSIS

The purpose of this Perspective is to illustrate how our group has used natural products and their mimics as targets of opportunity for discovering and developing new areas of chemistry and biology. Our approaches to many natural products were often guided by specific challenges posed by each class, but we sometimes purposefully created problems by design. At other times, we focused upon subunits commonly found in a number of natural products and developed strategies that enabled facile access to those substructures. These ventures resulted in the development of useful methods that filled synthetic gaps as well as general approaches to assemble a variety of polycyclic oxygen and nitrogen heterocycles. The diversity of the individual natural products we pursued enabled us to explore many aspects of synthetic organic chemistry, sometimes encountering unexpected problems. The numerous different projects that were being pursued at a given time led to an atmosphere where cross-fertilization among projects spurred new avenues of inquiry and inspired unusual solutions to problems we faced.

Our interest in biological applications of chemistry led us to study natural product mimics, which we broadly define as small molecules that interact with any biological target, including membranes, proteins, and nucleic acids. We were first drawn to mimics of phospholipids and peptides as potential enzyme inhibitors that might have medical applications. For example, we developed methods to prepare nonhydrolyzable phosphodiesters, and we implemented these in the synthesis of inhibitors of the PLC class of enzymes. We also designed a novel class of cyclopropane-derived peptide mimics to serve as conformationally constrained enzyme inhibitors. Because we did not observe the increases in affinity that were believed to attend ligand preorganization, we wanted to know why. Addressing this question required we adopt a highly multidisciplinary approach that led us to the startling finding that the prevailing conventional wisdom regarding the presumed entropic benefits of ligand preorganization in protein−ligand interactions are not always realized.

In the process of solving problems, we found ourselves being forcibly relocated into the arena of unknown unknowns. Although many examples can be cited, the one that most affects our current work began with solving a problem in alkaloid synthesis that led to the development of an effective platform for making focused libraries of functionalized nitrogen heterocycles for biological screening. From those collections, we identified a class of molecules that exhibited neuroprotective properties. Further encouraging work in several animal models motivated us to clone the receptor. We have recently pivoted and are now engaged in translational research directed toward identifying promising leads to treat neurodegenerative conditions and neurological disorders.

Our journey from natural products synthesis to addressing unmet medical needs in neuroscience has been one with many twists and turns. A willingness to dare to explore new avenues by allowing co-workers to follow their dreams and ideas took our research into unexpected and diverse directions that were rewarding and exciting. Pursuing so many different paths of inquiry may have had an impact on the total number of publications emerging from our efforts, but the invigorating environment created by a diverse research enterprise paid numerous educational dividends, and it inspired an intellectual curiosity within the group that would not have been possible had we stayed the narrow course of traditional natural products chemistry. I believe the many discoveries and contributions we made over the years substantiate the importance and continued relevance of natural products and their mimics in chemistry, biology, and medicine. If we as a community sieze the opportunity and more broadly embrace natural product mimics having medical relevance, the invention and development of new synthetic methods and strategies will continue to thrive for the foreseeable future, as they have since the days of Woodward. Targeting such compounds will enable us to create novel molecular frameworks that defy available technology and demand the invention of novel chemistry. Many unsolved problems and challenges, some of which are unknown and will only reveal themselves by continued exploration, await our discovery, attention, and resolution. Contrary to the opinions of some, there is still much we do not know about synthetic organic chemistry. As Mark Twain might have said were he a chemist: The reports of the death of synthetic organic and natural products chemistry are greatly exaggerated.

> *...We shall leave it that the evidence is overwhelming that the creative function of organic chemistry will continue to augment Nature, with great rewards, for mankind and the chemist in equal measure.*
>
> R. B. Woodward (1956)[229]

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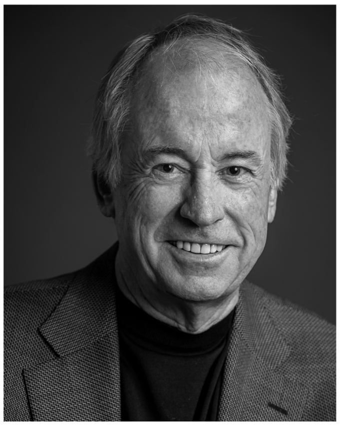
Notes

The author declares no competing financial interest.

Biography



A native of New Mexico, Stephen Martin received his B.S. degree from the University of New Mexico and his Ph.D. from Princeton University. After postdoctoral years at the University of Munich and Massachusetts Institute of Technology, he joined the faculty at The University of Texas at Austin in 1974, where he is the M. June and J. Virgil Waggoner Regents Chair in Chemistry.

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■ DEDICATION

This Perspective is dedicated to the late Professors Raymond C. Castle, Rudolf Gompper, and George Büchi and to Professor Edward C. Taylor for their invaluable mentoring.

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