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. 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

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

Figure 1. Some representative oxygenated natural products.

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.

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).
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.

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).

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.

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...
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. 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. 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 S-ethylfurfuraldehyde (30) leading to 31 (Scheme 8). 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 Me2CuLi and then MeLi under Luche conditions to give 33 with high stereoselective efficiency. Having served its key role as a stereocnemically biased template, the bicyclic ketal 33 was unraveled to give the thiketal 34, albeit with some unavoidable erosion of the stereochemistry at C8.

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 proceeded with poor regioselectivity giving substantial quantities of the C6 glycosylated derivative in addition to the desired 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.

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 a highly diastereoselective aldol reaction to give 46 (Scheme 10). Introduction of a protected desosamine residue at C5 using the glycosyl donor proceeded with moderate stereoselectivity giving substantial quantities of the C6 glycosylated derivative 49 in addition to the desired 50. 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.
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 synthesis8 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 B2 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).

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.

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to provide C-aryl glycosides. 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. 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).

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).

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.

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.

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 benzyynes are known to undergo regioselective cycloadditions with unsymmetrical furans, the process is not general. Hence, the question arose: How can one control the regiochemistry in the cycloaddition of furfuryl glycosides with unsymmetrical benzyynes? 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 benzyynes 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. 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.
An application of a palladium-catalyzed ring-opening reaction of benzene–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). 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.

We prepared galtamycinone22 and a precursor of 5-hydroxyaloin A24 using this benzene−glycosyl furan cycloaddition strategy, but the syntheses of vineomycinone B2 methyl ester23 and isokidamycin25 best illustrate the scope and potential of this novel approach to C-aryl glycoside natural products.

Vineomycinone B2 methyl ester is a degradation product of vineomycin B2, 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 the furan ring of 75 was easily achieved by regioselective metalation, followed by appending a functionalized silyl side chain to furnish 77.

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 metatalate 80, it did undergo regioselective bromination, and subsequent metal halogen-exchange and introduction of the silyl tethering moiety provided 81.

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 benzene–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 B2 methyl ester.

Scheme 16

Scheme 17

Scheme 18

Scheme 19

Figure 4. Furan-derived subunits of vineomycinone B2 methyl ester.
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. Given its planar tetracyclic core structure, it is not surprising that kidamycin, like other pluramycin antibiotics, binds to DNA leading to single strand cleavage. 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).

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. 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).

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 enyne 98 by a carbonylative cross coupling reaction we had developed in ancillary work and had already successfully applied to the synthesis of luteolin. 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, there was precedent...
suggesting that this undesired pathway might be avoided by first converting the ynone into a vinylogous amide. Fortunately, we discovered that the vinylogous diethylamide derived from 98 did undergo acid-catalyzed cyclization to form the diepyranone 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. 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).

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, 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 vancomamine 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-dideoxyxqualistatin H5, we had occasion to use a furan in an intramolecular vinylogous aldol reaction. 6,7-Dideoxyxqualistatin 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.

In order to set the stage for the pivotal vinylogous aldol reaction in our synthesis of 6,7-dideoxyxqualistatin H5, 103, which was prepared in three steps from dimethyl L-tartrate, was esterified with the known acid 104, and removal of the tetrahydropyranyl protecting group followed by oxidation gave 105 (Scheme 24). The key cyclization of 105 proceeded efficiently using TiCl₄ 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-dideoxyxqualistatin H5 was then simply achieved by oxidation of the primary alcohol function in 110, followed by global saponification of the methyl ester groups.
**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 to the polycyclic representatives IB-00208, citreamixin η, 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.

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. In particular, we envisioned that the Moore reaction of disubstituted acetylene 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 reasoned that the requisite disubstituted acetylene would provide an intermediate quinone that would undergo cyclization to generate the xanthone (Scheme 25). 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. In order to set the stage for the pivotal Moore rearrangement, it was first necessary to prepare \( \text{Scheme 25} \) (Scheme 27).

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.

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. 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). 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 formulation, 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.

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
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

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,52 lycoramine,53 crinine,53 and pretazettine54 (Figure 6).

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.

Figure 6. Selected natural products having quaternary carbon atoms.

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 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 Scelletium 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, this remains one of the shortest.

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 refuctionalization 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.55,54

**Scheme 29**

**Scheme 30**

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 hydrolulidine ring system in aspidospermine62 (Figure 7) is found in many Aspidosperma alkaloids, and the hydroindole ring subunit in lycorine63 (Figure 7) is present in a number of Amaryllidaceae and other alkaloids, including dendrobine64 (Figure 7).

The hydroisoquinoline ring system occurs in numerous alkaloids of the yohimbine family,65 including reserpine and α-yohimbine66 as well as in the manzamine alkaloid manzamine A67,68 (Figure 7). Although less-common, oxahydroisoquinolines are found in indole alkaloids of the heteroyohimbine class such as tetrahydroalstonine69,70 (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, so we carefully selected our targets in order to develop variants that expanded the scope of these cycloadditions.
Our syntheses of aspidospermine and lycorine featured intramolecular Diels–Alder reactions of simple enamides with unactivated dienes,\textsuperscript{62,63} whereas our synthesis of dendrobine involved the intramolecular Diels–Alder reaction of a dienamide with an unactivated olefin.\textsuperscript{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.\textsuperscript{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).\textsuperscript{64} Compound 151 was swiftly converted into 152, which had been previously transformed in seven steps into dendrobine by Inubushi.\textsuperscript{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.

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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{66} The requisite hydroxyl groups at C17 and C18 were introduced stereoselectively by sequential epoxide formation/ring opening to give 158.

Scheme 31

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

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 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 oxahydroisouquinoline 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 the lactam moiety provided geissoschizine (Scheme 33).\(^70\) 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.\(^79\) Selective reduction of the lactam ring in 168 proceeded without event to provide tetrahydroalstonine. Alternatively, we found that base-induced \(\beta\)-elimination of 168 followed by selective reduction of the lactam moiety provided geissoschizine (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).

![Scheme 33](image-url)
hindered by the SnCl₄ 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. We then applied a similar strategy to a synthesis of strychnine. Knowledge of the biosynthesis of indole alkaloids 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. A key step in the plan involved cyclization of 178 (Scheme 35). Although some experimental support for this step is found in van Tamelen’s synthesis of ajmaline, subsequent reports by Lounasmaa and co-workers cast serious doubt on the feasibility of such a cyclization. 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. 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 A₁,3-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 marine sponge that exhibits potent antitumor activity. More recently, it was found that manzamine A also displays antimalarial and antituberculosis activity. 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).

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). 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, it 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. 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 S-, 6-, and 7-membered nitrogen heterocyclic rings could be readily formed by ring closing metathesis (RCM) reactions using the Schrock precatalyst. 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.

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).\textsuperscript{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,\textsuperscript{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.

\section*{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 acid102 (Figure 9).

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.

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).105 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.

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).106 Zirconocene dichloride and EtMgBr were then simply added to the reaction mixture to induce a carbomagnesation107 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...
cis-2,5-disubstituted pyrrolidines. Using this procedure, 211 was converted with high diastereoselectivity into 212 (Scheme 42).

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). 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, 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.

There is a long-standing problem in the synthesis of (+)-lysergic acid, arguably the most notorious member of the Ergot alkaloid family, and we sought to address this issue using an RCM reaction to create the piperidine D-ring (Figure 10).
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 Donohoe113 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.

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.
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). Catalytic hydrogenation of 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. Inasmuch as 241 had been converted by Gallagher and co-workers into pumiliotoxin 251D, 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. 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, in the presence of TIPSOTf gave the threo-adduct 245 as the major product (Scheme 47). Somewhat surprisingly, 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.

Thus, treatment of 246 with POCl₃ 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, were originally isolated in racemic form, and they were observed to interconvert upon warming. Based upon these findings, it was proposed that rugulovasines A and B undergo facile interconversion via the achiral intermediate 250. (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.

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 NaBH₃CN 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.124 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.

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 Cs₂CO₃ 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 268 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 carboxylative cross-coupling procedure we had developed,135 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

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Scheme 49

Scheme 50
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 S1, 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 enantiomorph 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-methyl-welwitindolinone 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 S2).126

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-acloxy 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 welwitindolinone C isothiocyanate (Scheme S2).142

Scheme S1

Scheme S2
synthesis of N-methylwelwitindolinone C isothiocyanate from 278.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.

**Scheme 54**

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.\textsuperscript{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.\textsuperscript{127} Notably, 285 (IC\textsubscript{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\textsubscript{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 (−)-astlcrone, a member of the macrolone/sarpagine alkaloids that has been reported to exhibit cytotoxic activity against two human lung cancer cell lines.\textsuperscript{145} For example, reaction of trimethylallylsilane with the N-acyl iminium ion 286 furnished 287, which was transformed into the diene 288 in a single operation (Scheme 54).\textsuperscript{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 cyclopentone 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 dihydropyran in our synthesis of tetrahydroalstonine (See Scheme 33), thereby completing an enantioselective total synthesis of (−)-astlcrone 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.

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

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 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.

### 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).\(^ {154}\)

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 Rh₂(OAc)₄ to give 305; none of the regioisomeric cycloadduct was observed. Surprisingly, 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 S160 and solandелactone E161 (Figure 14). 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 Rh₂[S(S)-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 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.

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 Rh₂[S(S)-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.

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

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 Rh₂[S(S)-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 Rh₂[5(S)-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). 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, whereas the opposite trend is observed for the corresponding palladium-catalyzed reactions. 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, cycloisomerizations, and [5 + 2] cycloadditions. 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 R¹ 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). 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.

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). 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...
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. 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, 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.

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 site-selective π-allylation at the carbon atom bearing the leaving group. 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 Bronsted 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. 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.

**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.

**Phospholipid Analogue**. 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). Because activation of PKC is relevant to cancer,
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-prefering PLC from *B. cereus* (PLC<sub>BC</sub>), 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<sub>BC</sub> complex. 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. The goal was to transform PLC<sub>BC</sub> 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<sub>BC</sub>–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<sub>BC</sub>.

**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. 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. 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<sub>i</sub>*'s, IC<sub>50</sub>'s, and EC<sub>50</sub>'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). 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<sup>2</sup> group in 348 is oriented so it occupies a region in space relative to the backbone atoms that approximates a gauche (−) conformation.

Much of our work in this area has been reviewed elsewhere, 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 reorganization 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](image-url)

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).

Scheme 66

![Scheme 66](image)

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.

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.

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

Figure 18. Peptide mimics as HIV protease inhibitors.

Figure 19. Peptide mimics of Src SH2 domain binding ligands.
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). 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. 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. 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). 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. 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. This stunning finding is contrary to the prevailing conventional wisdom regarding the putative entropic effects 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. 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!

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. 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. However, there are cases wherein increasing the hydrophobic surface area of a ligand leads to increased affinity because of a more favorable binding entropy, a phenomenon that was first observed in host–guest interactions and termed a “nonclassical” hydrophobic effect by Diederich. 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-Echeverria 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). In order to investigate the energetic origin of these potency enhancements, we prepared 362 (n = 1–4) and determined the binding enthalpies and entropies for their complexation with the Grb2 SH2 domain. In accord with the results of Garcia-Echeverria, 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.

Figure 20. 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. 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, of introducing macrocyclic constraints in a peptide, as well as the effect of cation–π interactions. 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. 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**

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, 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, and the biology oriented synthesis (BIOS) approach described by Waldmann. 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, we applied this approach to the synthesis of numerous heterocyclic scaffolds that could be easily diversified.

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
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 identity 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 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).

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...
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, 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 with other researchers 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 phospho-diester mimics 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 coworkers 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 seize 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.
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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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