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Pattern Recognition in Retrosynthetic Analysis: Snapshots in Total Synthesis

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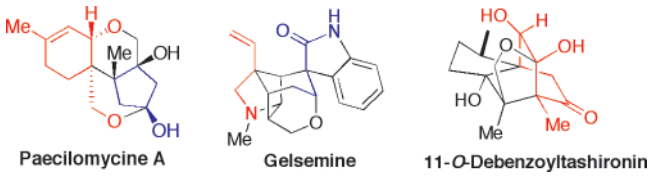

In this Perspective, the value of small molecule natural products (SMNPs) in the discovery of active biological agents is discussed. The usefulness of the natural products-based method of potential pharma discovery is much augmented by the capacities of chemical synthesis. The great advances in synthetic methodology allow for major editing of the natural product in the hopes of optimizing potency and therapeutic index. As a consequence of the enormous increase in the power of multistep chemical synthesis, one can now approach structures of previously impractical complexity. In constructing a plan for a multistep synthesis, two complementary thought styles are often encountered. One is the traditional and extremely powerful concept of prioritized strategic bond disconnections. The other, which we term "pattern recognition," involves the identification of moieties within the target, which are associated with reliable chemistry, and can serve to facilitate progress to the target. Recognition of such targets may require substantial recasting of the target structure to connect it to well-established types of transformations. Some of our older ventures, where ideas about pattern recognition were first being fashioned and used productively, are revisited. In addition, we provide snapshots of recently achieved total syntheses of SMNPs of novel biological potential. These vignettes serve to harmonize insights occasioned by pattern recognition, in concert with transformations enabled by the enormous growth in the power of synthesis.

I. Introduction

In a recent Perspective,[1] we attempted to demonstrate that the small molecule natural product (SMNP) estate has been an important source of discovery of valuable pharmaceutical agents, including blockbuster drugs. Interestingly, although big pharma has (unwisely!) de-emphasized SMNPs as potential resources in drug discovery, many of the most interesting compounds in the pipelines—particularly in oncology pipelines—are themselves SMNPs. Others drugs have been derived by chemical modification of natural products. Still others, which may be termed "natural product inspired" (such as Lipitor), arise from a more casual, though still unmistakable, SMNP connection.[2] The modification of SMNPs by chemical means, or by the total synthesis of structures inspired by SMNPs, accomplishes what may be termed "molecular editing." Underlying the rationale of molecular editing of SMNPs is the supposition that many natural products constitute high-pedigree, relatively privileged structures. The thought is that recourse to SMNPs results in entering the drug discovery progression at a more advanced stage than is the case through traditional medicinal chemistry. Obviously, the identification, isolation, and structural determi-

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nation of SMNPs and the maintenance of natural product collections involve significant commitment and expense. The real question is whether the advantages of working with privileged, high-pedigree structures can compete with the much larger numbers of samples accessible through traditional medicinal chemistry, not to speak of the more recent techniques of combinatorial chemistry.

A serious concern about SMNP-based discovery has been that of compound availability. Even for the laboratory which first discovers the active SMNP, the source of the natural product must be secure and the isolation yield must be manageable. Given that these conditions are met, an efficient program in partial synthesis is then required, for the purposes of optimizing the therapeutic index of the eventual clinical agent. Fine-tuning, which might entail the addition or reduction of molecular complexity, may be circumscribed by existing noncompatible functionality of the SMNP.

Laboratories which might attempt to build upon a published or potential account of a new SMNP, following reports of the initial discovery elsewhere, face additional problems. For understandable reasons, the discoverers may be reluctant to distribute workable amounts of the SMNP to other laboratories. Moreover, in a pharma business context, there may be apprehensions regarding the sustainability of claims to ensure "intellectual property" control.

Fortunately, concurrently with the identification of the concerns described above, came the means for rejuvenating SMNPs as starting points for biological exploration. Thus, chemical synthesis is now an increasingly critical enabler in leveraging the value of SMNPs. As we have shown in recent reviews, chemical synthesis allows for the potential underlying messages from SMNPs to be vastly extended and woven into the discovery fabric.

There has been, in our judgment, a quiet revolution in the capacities of chemical synthesis (so quiet that it has not been properly appreciated). Before our eyes, tremendous advances in the methodology of preparative chemistry (and, to some extent, in its underlying logic) now render synthesis a practical resource in exploring and exploiting the lead value of SMNPs. The complexity level of structures which are now accessible through synthesis for drug discovery programs has increased dramatically, and the timelines for accomplishing total syntheses of targets of significant complexity have correspondingly been decreased.

There is, of course, an underlying assumption "out there" to the effect that the best chances for discovery lie in the screening of large numbers of structures, via the medium of high-throughput screening. No one should contest the potential benefits to be had from evaluating ever-increasing numbers of chemical agents. Chemistry and medicinal chemistry are empirical sciences. The notion of high-throughput screening of large numbers of structures is in keeping with the relatively immature level of contemporary de novo theory. SMNPs will indeed provide far fewer and more difficultly accessible entries than will the general pharma sample collections. However, while SMNPs cannot compete at the "head count" level with medicinal/combinatorial chemistry, natural product-derived collections may well yield a much higher candidate "hit rate" than the traditional pharma or combichem-derived sample collection.

Since chemical synthesis is so central to the fuller development of SMNPs, we thought it well to focus in this Perspective on some of the underpinnings of systematic planning for multistep ventures. We suspect that, from the beginning of the subject of complex molecule total synthesis, some form of retrosynthetic analysis was inherently involved in the planning phase. It would be improbable, to say the least, to plan the synthesis of a complex target structure through a cognitive process which is fully progressive in nature. Given the stupefying number of ways in which one might begin and proceed, it would seem unlikely that the human mind would go anywhere but in the retrosynthetic direction wherein, at least generally, complexity is reduced as the planning exercise goes on.

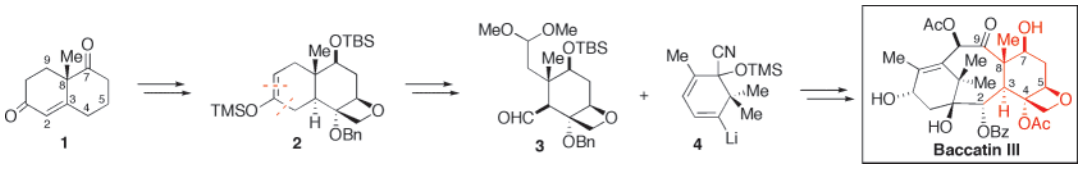
While there certainly is an artistic dimension in the building of complex molecules (vide infra), there are important boundary conditions. In artistic experiences, the goal itself may be initially perceived at a fairly imprecise level. The goal of a creative artistic enterprise often unfolds as the exercise moves forward. At some point, a coherent target begins to emerge. Different artists, depending on their creative styles, perceive different visions. At least in the early stages of the undertaking, the artist enjoys the prerogative of a "work in progress," which can be idealized, fashioned, and ultimately sculpted through artistic mastery.

Not so in the case of the chemical synthesis of a SMNP. Here, the goal structure is very clear and stubbornly inflexible. To be of any great interest to those who are serious about synthesis, the goal is quite likely to be complex. The planning process tends to be one of continuing reduction of complexity, to the point where one arrives at correspondence between the retrosynthetic starting material and that which is either known or likely to be quite available. *When the retrosynthetic analysis converges with a feasible starting material, a synthesis plan is at hand.* Of course, there will be many such plans to consider. However, coalescence of retrosynthetic analysis with available starting materials does constitute, in principle, a solution to the planning problem.

Critical to the actual plan is the feasibility of conducting the presumed retrosynthetic steps in the forward direction. The analysis is heavily dependent on the massive database of chemical synthesis. Fortunately, the collection of available transformations is not a static one. In fact, huge advances in the methodology of chemical synthesis, and thus in the ability of retrosynthetic steps to chart in the forward direction, are being made all the time. Moreover, it is not uncommon for powerful new methodologies to be uncovered in the context of planning and executing a difficult total synthesis. A major challenge in planning a synthesis lies in the management of the reams of information, and in identifying the pertinence of some element of the information morass to the precise problem at hand.

The last two decades have been particularly fruitful in enhancing the realm of the feasible. The most dramatic advances have surely been registered by astute recognition of the critical role of transition metals, in exploitable oxidation states and appropriately connected to ligands, in the catalysis of a range of carbon−carbon bond formations, as well as functional group interchanges. Another huge advance is to be found in the capacity to generate enantiopure or highly enantiocontrolled substances through reagent control. An extension of this application is the ability to exploit the same sort of reagent-lodged dominant stereoselectivity patterns, even in the presence of existing elements of chirality. Accordingly, the value of powerful reagents with major stereo biases may go beyond the introduction of de novo chirality and venture into the control of relative stereochemistry. Thus, retrosynthetic analysis through

SCHEME 1. Total Synthesis of Baccatin III



appropriate bond disconnections, strongly augmented by the Corey concepts of strategic prioritization, is surely a key platform for synthetic planning.[3]

It is perhaps well to use the occasion of this Adams Perspective to point out another modality of retrosynthetic analysis, which we describe as "pattern recognition." In this form of conjecture, a structure is viewed with an eye to discerning substructural units, which we call patterns. Pattern recognition differs in a subtle but real way from bond disconnection analysis, wherein one begins by evaluating the implications of disconnecting the various existing linkages. Impressive as are the sorting capacities of the human mind, the response cannot be stochastic. By some difficultly articulatable mental process, the synthetic chemist is drawn to assess the implications of various plausible retrosynthetic disconnections and to rank, however non-explicitly, their likely productivities. What prompts various synthetic chemists to develop vastly different bond disconnection schemes toward a fixed target is in itself a fascinating question. Surely, the increasing molecular complexity with which we deal these days leads to a proliferation of potentially relevant bond disconnections, whose prioritization can be continuously debated.

In pattern recognition, the entire structure is the focus of the search. The exercise may well be less "activist" than strategic bond disconnection. The total structure is mentally scanned and rescanned as one seeks to discover an exploitable substructural motif around which to organize first the thought process and then the synthesis. The cognitive challenge lies in the recognition of productive patterns, even in the presence of endless apparent decoys. A still higher level challenge is that of creating, de novo, a body of chemistry which makes the pattern synthetically accessible or productive in a forward sense. There is often a great challenge in fashioning a plan to close the gap between the patterns and the target.

We emphasize that pattern recognition goes well beyond the scanning of a structure, seeking familiar substructures. The most fascinating cases arise when the target itself must actually be modified, mentally, before a staple pattern is revealed. There are many levels of opportunity for creativity in deeply disguised patterns. We will first attempt to illustrate the idea of pattern recognition by revisiting some of our battlegrounds from years ago.

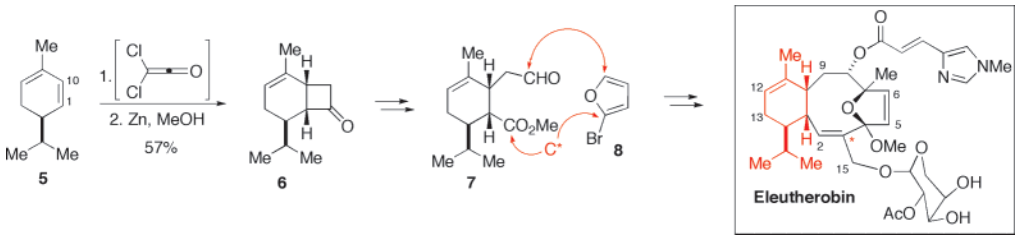
Before browsing through our album, it is well (though it should not be necessary) to underscore a key point in the relationship between the charting of a synthetic plan and the achievement of a total synthesis on a target of some complexity. The theory of organic chemistry, and thus the predictability of reactions, particularly as one attempts to advance beyond the well trodden norms, is surprisingly shaky. Accordingly, it is well to look upon a plan as a broad organizational prospectus. More often than not, the so-called "reduction to practice" phase, in reality, involves recasting and restructuring of the plan. A fine plan is one which has the elasticity and staying power to survive the inevitable setbacks and frustrations along the way. Retrosynthetic analysis produces not a precisely defined blueprint, but rather a strategic framework. The most successful plans lend themselves to modification based on actual laboratory findings. Undoubtedly, someday down the road, there will be a higher correspondence between the strategic plan and the unfolding synthesis. However, for the more immediate future, the interfacing of a plan of synthesis with the unfolding synthesis is one of feedback loops, as the plan is being iterated in the context of experimental findings. It is to be hoped (but is not always the case) that papers addressed to the realization of a total synthesis would accurately reflect the many frustrations which had to be overcome en route to the target. With these preliminaries well understood, we now go on to recall some of our older efforts. These will hopefully bring home, by example, the nature of pattern recognition in the total synthesis planning process.

We start with the taxol problem. In studying the baccatin III moiety of taxol,[4] we came to discern a conceivably exploitable relationship to the mono-reduced form of the Wieland−Miescher (WM) ketone (see **1**, Scheme 1).[5] The WM ketone has a strong history as a valuable intermediate, whose established synthetic potential could be mined and then expanded. The homology between the WM ketone and baccatin III obviously encompasses carbons 3, 7, and 8. The homology deepens as we recognize how functionality inherent in **1** might also be expanded to encompass C_2, C_9 (by late stage oxidation), as well as C_4 and C_5 (by deconjugation of the α,β-enone double bond to the β,γ-slot). The reader is advised to revisit the original paper to assimilate the chemistry which, in fact, enabled progression from **1**→**3**. Coupling of **3** with **4** set the stage, after considerable travail, to reach baccatin III.

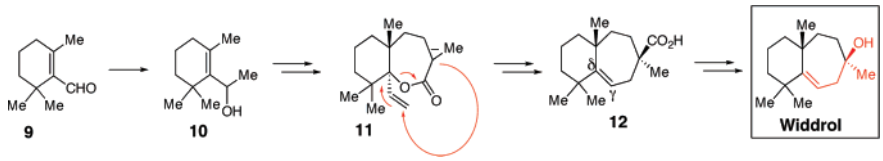
Our total synthesis of eleutherobin also illustrates the application of pattern analysis to a starting material which provided the required chirality (Scheme 2).[6] In studying the structure of our target, we were struck by a possible connection to the known monoterpene α-phellandrene (**5**). Even with that realization, there was a need to append a differentiated two-carbon unit to C_{10} (eleutherobin numbering) and a one-carbon unit to C_1 of the phellandrene (**5**). This progression was initiated in practice by a [2 + 2] cycloaddition of dichloroketene to the phellandrene. The regiochemistry of this reaction is undoubtedly related to the propensity of the electrophilic component of the dichloroketene to attack the diene system at its terminus with the proviso that the dichloro-bearing carbon be joined to an unalkylated carbon. This reaction modality led to structure **6**. The methylene group of the cyclobutanone was susceptible to one-carbon extension. Fragmentation of the resultant structure eventually gave rise to a viable coupling partner, **7**. Substrate **7** serves as a subunit for merger with **8**, leading eventually to the eleutherobin target.

A more sophisticated pattern recognition can perhaps be discerned in our total synthesis of widdrol (Scheme 3).[7] As one scans the seven-membered ring of widdrol, the mind quickly recognizes a homoallylic alcohol. This recognition might

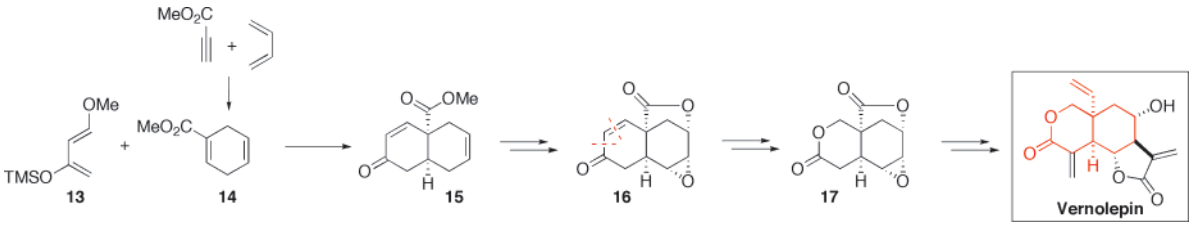
SCHEME 2. Total Synthesis of Eleutherobin



SCHEME 3. Total Synthesis of Widdrol



SCHEME 4. Total Synthesis of Vernolepin



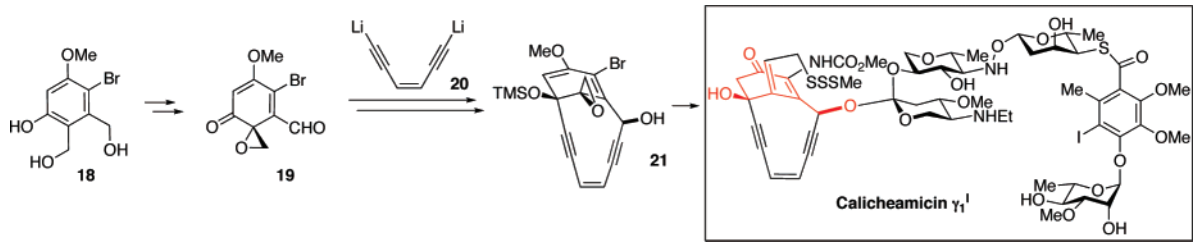
suggest, in the first instance, formation of a tertiary alcohol by nucleophilic methylation of the corresponding β,γ-unsaturated ketone. Obviously such a proposal brings with it concerns as to the degree of diastereocontrol in the nucleophilic alkylation step. We sought a solution which would be insulated from this type of uncertainty. This line of conjecture led to suggestion of a possibly exploitable pattern (see **10**, derivable from cyclohexenal **9**). However, to connect this type of pattern to the actual structure of the target, it was necessary, *in the mind's eye*, to imagine that the hydroxyl group of widdrol would have arisen from degradation of a carboxylic acid (cf. **12**). It would be necessary that sound stereochemical principles govern the relationship of the carboxyl group of **12** with the emerging hydroxyl of widdrol. The solution we proposed was that the hydroxyl group would have been generated from a "carboxy-inversion" sequence which started with the corresponding β-oriented carboxylic acid (see **12**). At that point, one could discern a γ,δ relationship of the carboxylic acid with its double bond. In the mind of the pattern analyst, this arrangement would conjure up the possibility of a Claisen-type rearrangement. What was also fascinating about this idea at the time is that the [3,3]-sigmatropic rearrangement would occur not on the usual allyl ester but on a then novel vinyl lactone moiety (see **11**). Given the α-orientation of the vinyl group of **11**, the rearrangement would necessarily create a β-disposed carboxylic acid in **12**. In the degradative sense, the carboxy inversion (which actually occurs with retention of configuration) would then install the tertiary alcohol in the appropriate β-face stereochemistry (see **12**→widdrol).

The challenges associated with the total synthesis of vernolepin carried with them opportunities for extended pattern analysis (Scheme 4).[8] A provocative substructure in vernolepin is the *cis*-fused δ-lactone. At the time, there was no orderly method for synthesizing such a moiety, further complicated by the presence of the angular vinyl group. We struggled with potentially direct solutions to this problem. However, in the end, they were rejected on the grounds of being overly speculative. Instead, we sought to retreat to at least a more familiar port, that is, that of a *cis*-fused hexalin system. The hexalin (**15**) would carry an angular carbomethoxy group. This group, destined to become a vinyl function, would influence the functionalization of the nonconjugated double bond, thereby eventually producing the vicinal *trans*, *trans*-hydroxy γ-lactone, en route to the introduction of the two conjugated α-methylene functions. Those were to be implemented at a very late stage of the synthesis. A problem engendered by this analysis was that at the time there were no established and concise ways for reaching such a *cis*-fused hexalin system. The thought was that we would try to do so by a new extension of the Diels−Alder reaction, invoking cycloaddition of the then unknown diene **13** with dienophile **14**, itself the product of the Diels−Alder reaction of butadiene with methyl propynoate. Since **14** is not a very powerful dienophile, we needed a diene which would be sufficiently reactive to allow for the cycloaddition. We also needed the diene to possess the functionality which would lead to the ready introduction of the enone of compound **15**. It was this context which obliged us to think about the then unknown diene **13**. Indeed, this synergistically substituted diene proved to be very reactive, and cycloadditions with many hitherto sluggish dienophiles became an active possibility.

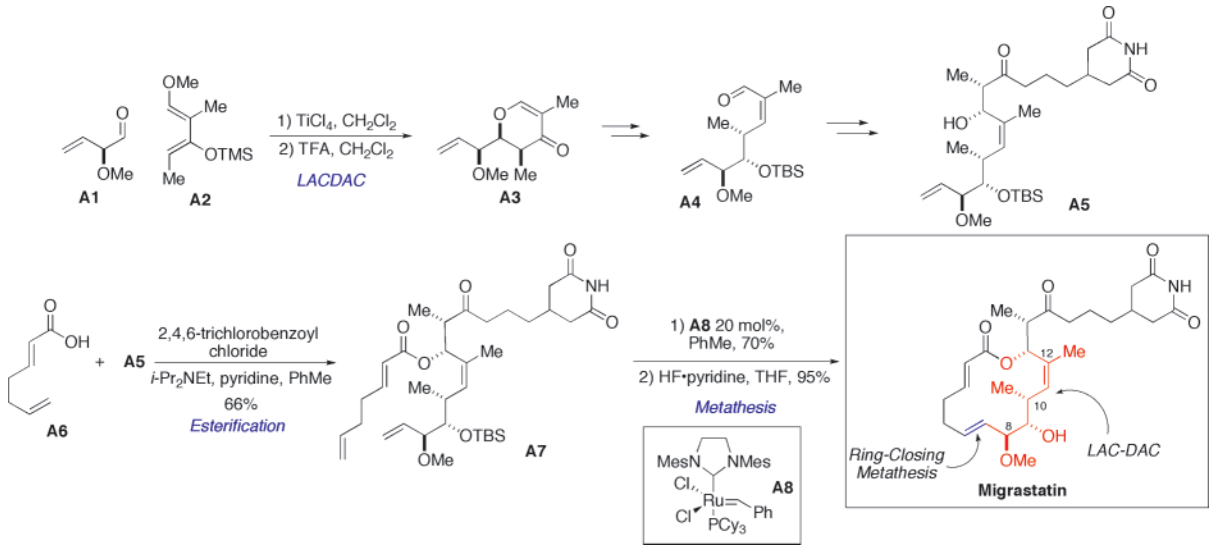
In the case at hand, at a later stage of the synthesis, the α,β-unsaturated ketone in **15** was used as a conduit to the δ-lactone (cf. **16** to **17**). This involved excision of a one-carbon fragment, as well as reductive cyclization of an aldehyde. Intermediate **17** contained the required functionality to carry us to vernolepin.

As a final example in this introductory section on pattern analysis, we discuss the case of calicheamicin (Scheme 5).[9] The non-glycoside core region of this molecule (i.e., calicheamicinone) was, at the time, considered rather complicated, and its complexity prompted us to seek a relatively safe substructural

SCHEME 5. Total Synthesis of Calicheamicin γ_1^I



SCHEME 6. Total Synthesis of Migrastatin



pattern, such as an aromatic system. We could discern within the aglycon sector a potentially exciting possibility. The aromatic structure which we selected (i.e., **18**) would be converted to **19**. We note that the α-spiroepoxyketone of **19** corresponds to an otherwise difficultly manageable α-dicarbonyl system. The aldehyde function, as well as the keto function, would serve as electrophilic termini in a highly convergent but technically demanding 2-fold addition with the enediyne **20**. There was particular need to orchestrate the sequence in this coupling event (see original paper). The Becker−Adler reaction[10] was invoked as a route from **18** to the spiroepoxide **19**. We came to view the Becker−Adler reaction in the broader context of oxidative dearomatization. The thinking implied in Scheme 5 was implementable, though not without considerable challenges along the way.

We close this introduction on earlier examples of pattern recognition and move on to some rather recent synthetic successes, which benefited from this retrosynthetic mode. Through the medium of these snapshots, the usefulness of pattern analysis is shown as a complement to strategic bond disconnection.

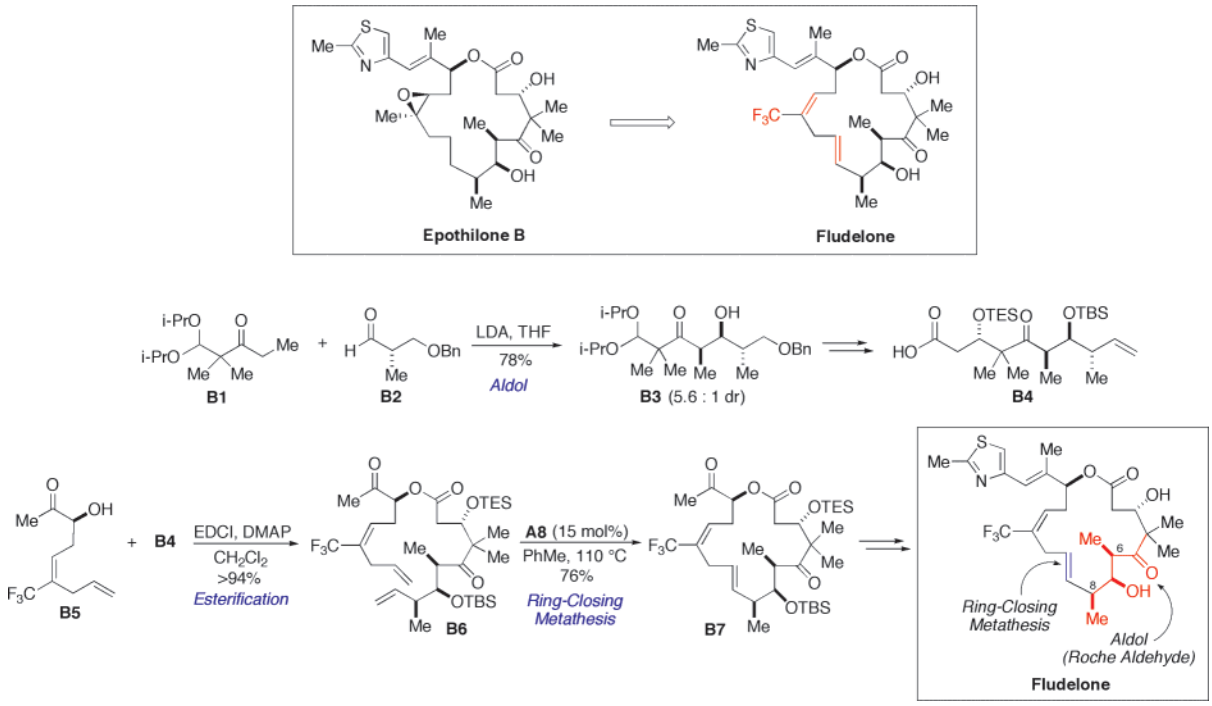
II. Discussion: Snapshots In Recent Total Synthesis

A. Migrastatin. Migrastatin is a tumor cell migration inhibitor isolated from two different strains of *Streptomyces*.[11] Upon studying this molecule, we took particular note of the cryptopolypropionate sector of the macrolactone, incorporating three contiguous stereocenters at C_8, C_9, and C_{10}, as well as a C_{11}−C_{12} *Z*-olefin (Scheme 6). To our eye, this pattern might well be accessible through recourse to a chelation-controlled Lewis acid catalyzed diene aldehyde cyclocondensation (LACDAC) reaction. We further anticipated that the macrolactone ring might be fashioned through a ring-closing metathesis (RCM), which would make use of the terminating olefin arising from the LACDAC sequence. Having thus identified a central structural pattern of the migrastatin system, we next sought to adopt a synthetic plan based upon the proposed LACDAC transformation.[12]

As outlined in Scheme 6, the key chelation-controlled LACDAC reaction, between the optically active dienophile, **A1**, and synergistically activated diene, **A2**, proceeded with excellent stereocontrol to provide intermediate **A3**. The latter was advanced to aldehyde **A4** and eventually to the coupling partner, **A5**. Esterification with the carboxylic acid, **A6**, provided the key intermediate, **A7**. At this stage, we were able to implement a ring-closing metathesis strategy, using the Grubbs' catalyst, **A8**, to provide, following deprotection, the natural product migrastatin.

B. Fludelone. Epothilone B (EpoB) is a naturally occurring cytotoxic macrolide, which was first isolated from the myxobacterium, *Sorangium cellulosum*.[13] In 1997, we reported the inaugural total synthesis of EpoB.[14] Although our early studies revealed the natural product, EpoB, to be highly toxic in in vivo settings, we subsequently prepared a number of synthetic EpoB derivatives, several of which have exhibited great promise in preclinical settings. In the context of this ongoing effort directed toward the diverted total synthesis and biological evaluation of EpoB analogues, we sought access to a particular congener of interest, which we term fludelone. As shown in Scheme 7, fludelone differs from the parent natural product (EpoB) in a number of its structural features. Upon studying the structure

SCHEME 7. Total Synthesis of Fludelone



of fludelone, it was seen that the strategy so well employed for the total synthesis of EpoB would not be directly translatable to our newly conceived congener. In this evaluation, we noted the pattern of contiguous C_6, C_7, and C_8 stereocenters lodged in the polypropionate domain. This pattern might conceivably arise from a diastereoselective aldol reaction with the optically active Roche aldehyde (**B2**). Furthermore, the macrolide might be fashioned through ring-closing metathesis.

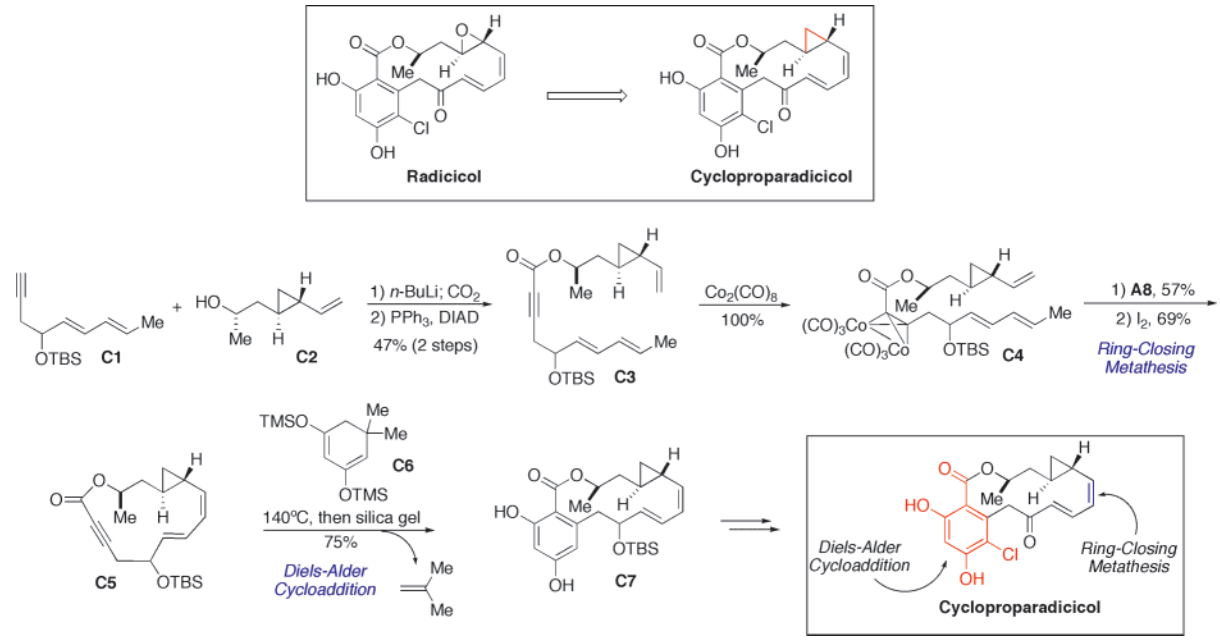
Indeed, the synthesis of fludelone was accomplished, as outlined in Scheme 7.[15] As hoped, **B1** and **B2** readily participated in an aldol coupling to provide the β-hydroxyketone, **B3**, properly presenting the three contiguous stereocenters required for fludelone. This intermediate was ultimately advanced, through a second aldol reaction, to the carboxylic acid coupling partner, **B4**. Esterification with alcohol **B5** provided the metathesis precursor, **B6**. In the event, the desired ring-closing metathesis proceeded smoothly to furnish a macrolide ketone, which, following installation of the heteroaromatic sector, afforded the target epothilone congener, fludelone. Although a full accounting of the highly exciting biological activity of fludelone is beyond the purview of this disclosure, we note that this compound, arising from diverted total synthesis, has indeed revealed itself to be an exceptionally promising candidate for further development.

C. Cyclopropparadicicol. Radicicol, a resorcinylic macrolide isolated from *M. bonorden*, initially came to our attention as a consequence of its reported high affinity binding to, and inhibition of, the heat shock protein 90 (Hsp90) molecular chaperone.[16] The Hsp90 protein is considered these days to be a promising target for cancer chemotherapy, and on the basis of these in vitro findings, we first launched a program directed to the synthesis of radicicol.[17] Upon completion of our first total synthesis of radicicol, we went on to confirm its excellent in vitro activity. However, the results of preliminary studies in mouse models were quite disappointing, suggesting that radicicol is not effectively able to manifest its pharma potential in in vivo settings. We postulated that the epoxide moiety of the natural product was perhaps serving to undermine its stability and efficacy in vivo. Accordingly, we designed a synthetic analogue, termed cyclopropparadicicol, in which the possibly offending epoxide functionality would be edited and replaced with a more stable cyclopropyl group (Scheme 8). Although our first-generation synthesis of cyclopropparadicicol was achieved by analogy to the original radicicol route, this synthesis was somewhat cumbersome and inefficient.[18] On the basis of some promising findings in in vivo models, we sought to redesign the synthetic route to cyclopropparadicicol in order to secure access to larger quantities of material for more extensive evaluations.

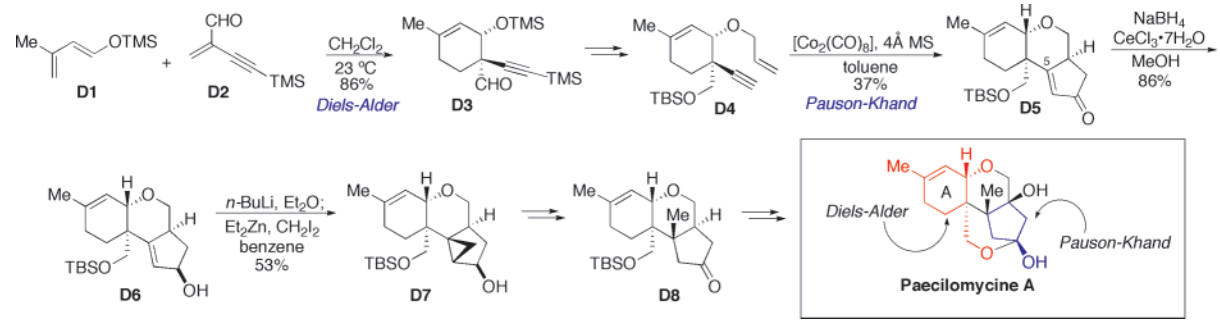
As is our custom, we approached the design of our second-generation route by first attempting to identify useful patterns in the target structure around which we might design a viable synthesis. In our first-generation route, we had encountered difficulties in attempting to perform synthetic manipulations with the resorcinylic functionality intact. We thus wondered whether this particular unit could be installed at a late stage of the synthesis through an ynolide−Diels−Alder cycloaddition. According to this formulation, the tractable resorcinylic moiety would be "masked" as an ynolide until the concluding phases of the synthesis. The macrolide formation would be accomplished at an earlier stage through ring-closing metathesis.[19]

The much improved, second-generation cyclopropparadicicol synthesis is presented in brief form in Scheme 8. Thus, key intermediate **C3** was reached from fragments **C1** and **C2**, as shown. Interestingly, we had observed that **C3** was itself unable to function properly in the requisite RCM, presumably as a consequence of geometric constraints imposed by the rigid ynoate moiety. To circumvent this reactivity problem, we temporarily masked the alkyne functionality as a cobalt complex, as shown (cf. **C4**). Gratifyingly, this intermediate readily underwent metathesis, under the influence of the Grubbs' catalyst (**A8**), to provide, following I_2-mediated removal of the

SCHEME 8. Total Synthesis of Cycloproparadicicol



SCHEME 9. Total Synthesis of Paecilomycine A



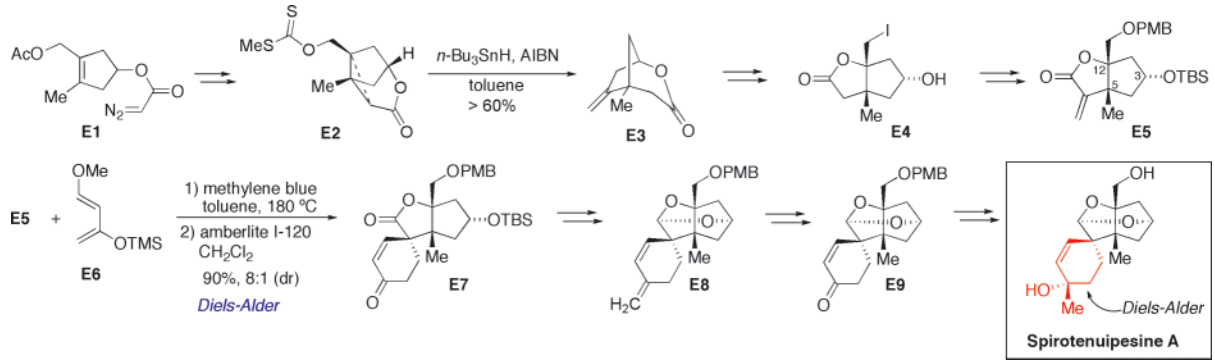
cobalt, the key ynoate macrolide, **C5**. At this stage, the crucial Diels−Alder reaction with diene **C6** proceeded smoothly to afford, following retro-Diels−Alder excision of isobutylene, the resorcinylic macrolactone, **C7**. The latter was readily advanced to cycloproparadicicol.

D. Paecilomycine A. Paecilomycine A is a terpenoid-derived natural product, isolated from *Isoria japonica*.[20] Our interest in this compound arose from reports of its potent neurite outgrowth activity in rat pheochromocytoma (PC_{12}) cells. In the context of our ongoing program devoted to the synthesis and evaluation of neurotrophic factors,[21] we targeted paecilomycine A for synthetic investigations. Our examination of the natural product revealed two substructural patterns that we anticipated could arise from well-established cyclization reactions (Scheme 9). Thus, the "cyclopenta" sector of the molecule suggested to us a Pauson-Khand pattern, while the A-ring might be perceived through a Diels−Alder type lens. For maximal convergency, the Diels−Alder adduct would ideally incorporate the terminal alkyne necessary for the subsequent Pauson-Khand transformation.[22]

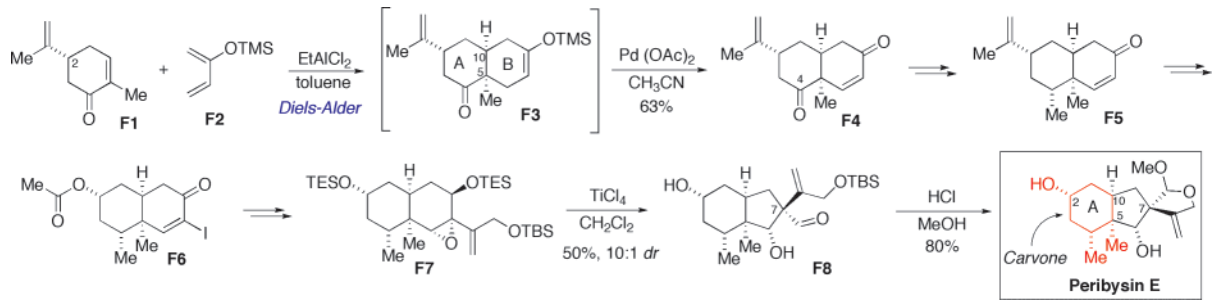
Indeed, this plan could be reduced to practice in a pleasingly concise manner. Thus, we found that diene **D1** readily undergoes cycloaddition with the α-disubstituted aldehyde dienophile, **D2**, to provide adduct **D3** in high yield, as a single observed diastereomer (Scheme 9). The ability of the Diels−Alder reaction to accommodate the resident alkynyl functionality and to proceed with such high levels of *endo* selectivity was, to us, a most welcome surprise. Indeed, intermediate **D3** was rapidly advanced to the key substrate **D4**. The latter readily underwent the anticipated Pauson-Khand reaction, as shown, to provide the tricyclic adduct, **D5**. Even at this late stage, some not fully anticipated difficulties ensued in attempting to install the angular C_5 methyl group in a stereoselective fashion. After some investigation, we settled upon a route, outlined below, wherein the enone was diastereoselectively reduced to the *β*-allylic alcohol, according to the logic originally set forth by Corey and Virgil some years ago.[23] Directed cyclopropanation afforded **D7**, which could indeed be advanced to **D8** and, ultimately, to the natural product itself.

E. Spirotenuipesine A. Isolated from the entomopathogenic fungus, *Paecilomyces tenuipes*, spirotenuipesine A has been found to promote the expression of neurotrophic factors and to effect neuronal differentiation in rat PC_{12} cells.[24] We undertook the synthesis of spirotenuipesine A in the hopes of gaining access to sufficient quantities of material for extensive in vitro and in vivo investigations (Scheme 10). Close survey of the structural topography of spirotenuipesine A helped to identify a pattern that served to provoke a *spiro*-Diels−Alder cycloaddition between a core α-methylene lactonic dienophile and a synergistic diene. It was our conjecture that this transformation would proceed in the desired sense, such that the diene would approach the dienophile from the less hindered *exo* face of the

SCHEME 10. Total Synthesis of Spirotenuipesine A



SCHEME 11. Total Synthesis of Peribysin E



bicyclic system. Under this formulation, the synthesis problem would then be reduced to the stereoselective preparation of the dienophilic component (cf. **E5**).[25]

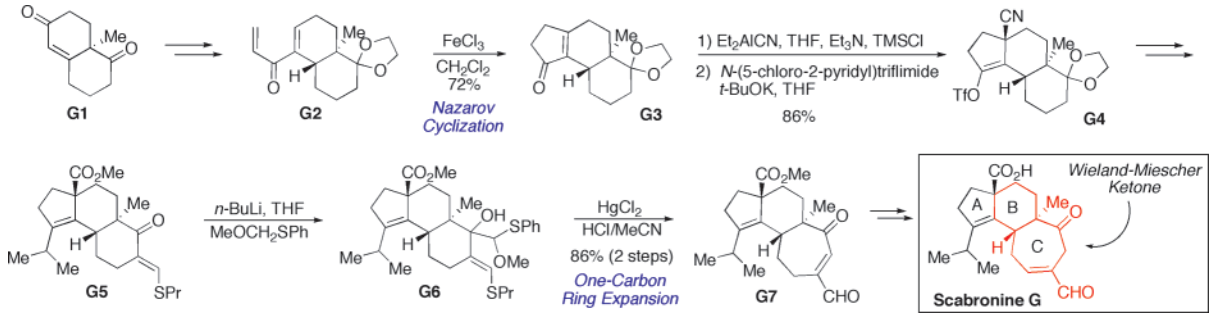
Our initial attempts to establish the relative stereochemistry of **E5** through a diastereoselective Claisen rearrangement had, surprisingly, failed. The [3,3] bond reorganization was virtually stereorandom. Accordingly, we devised an alternative strategy which would take advantage of the benefits of intramolecularity in establishing the relative configurations at carbons 3, 5, and 12. In the key transformation, diazoacetyl intermediate **E1** underwent intramolecular cyclopropanation to ultimately afford the activated cyclopropane, **E2** (Scheme 10). Under this protocol, the demands of intramolecularity had effectively dictated the establishment of the relative C_3, C_5, and C_{12} stereocenters in the desired sense. Free-radical-mediated Barton−McCombie cleavage provided intermediate **E3** which was readily advanced to iodolactone **E4**. The latter was converted to the requisite dienophile (**E5**) in straightforward fashion. At this stage, we were pleased to find that the key *spiro*-Diels−Alder reaction between **E5** and diene **E6** indeed progressed in the desired stereochemical fashion to provide, following workup, the spiroenone **E7**. This compound was advanced to spirotenuipesine A in due course.

F. Peribysin E. Isolated from *Periconia byssoides* OUPS-N133, peribysin E has recently been reported to inhibit cell adhesion.[26] Guided by the admittedly unproven thesis that a small molecule adhesion inhibitor might potentially serve as an effective anticancer agent, we sought to design an efficient total synthesis of optically active peribysin E (Scheme 11). In examining the nature of the stereogenic centers which punctuate the tricyclic framework, we noted a potential homology between the A-ring of the natural product and the readily available, optically active, (*R*)-carvone (**F1**). Most importantly, we felt confident that the isopropenyl group on **F1** could serve as a convenient handle in the early stages of the synthesis, dictating the stereochemistry of critical transformations en route to peribysin E. At an appropriate time, this moiety would be converted to a secondary alcohol, under the guidance of a sequence through which the stereochemical integrity at C_2 would remain intact.[27]

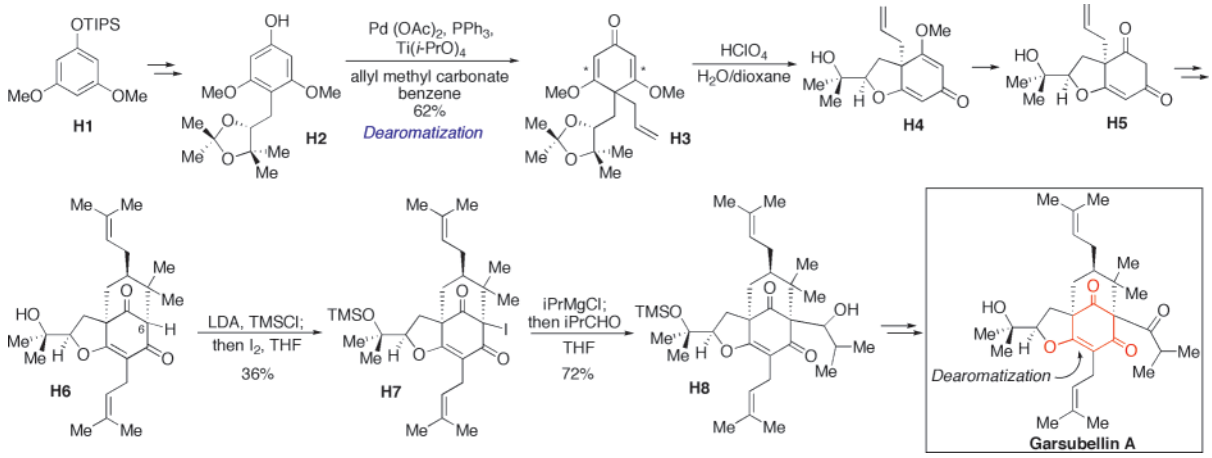
In the event, the synthesis of peribysin E commenced with a Diels−Alder cycloaddition reaction between (*R*)-carvone (**F1**) and diene **F2** (Scheme 11). As expected, the resident isopropenyl group of **F1** did indeed direct addition of the diene to the *β*-face of the molecule, thus establishing the future C_5 and C_{10} configurations in the desired sense. Saegusa oxidation of intermediate **F3** yielded enone **F4**, and the C_4 ketone of **F4** was stereoselectively converted to a methyl group (cf. **F5**). At this stage, we sought to convert the C_2 isopropenyl moiety to a hydroxyl functionality. This was accomplished through recourse to a Johnson−Lemieux oxidation with OsO_4, followed by Baeyer−Villiger oxidation, of course, with retention of stereochemistry. Following emplacement of a vinyl iodide, intermediate **F6** was in hand. The latter was readily advanced to **F7**, and at this stage, we were able to effect a critical ring-contracting reaction. Thus, following treatment with $TiCl_4$, intermediate **F7** underwent rearrangement to provide, as the principal adduct, **F8**, possessing the required configuration at the C_7 quaternary center. Treatment with HCl in methanol afforded the natural product peribysin E, as shown. We note, in passing, that as a consequence of this total synthesis, it was discovered that the original absolute configuration assignment of peribysin E had, in fact, been incorrect. The absolute configuration depicted in Scheme 11 represents the naturally occurring enantiomer of peribysin E.

G. Scabronine G. Scabronine G, a metabolite of the bitter mushroom *Sarcodon scabrosis*, is another member of the growing family of naturally occurring, small molecule neurotrophically active agents.[28] Thus, scabronine G and, to an even greater extent, its methyl ester derivative have been demonstrated to induce the production and release of nerve growth factor in 1321N1 human astroglial cells.[29] On the basis of these

SCHEME 12. Total Synthesis of Scabronine G



SCHEME 13. Total Synthesis of Garsubellin A



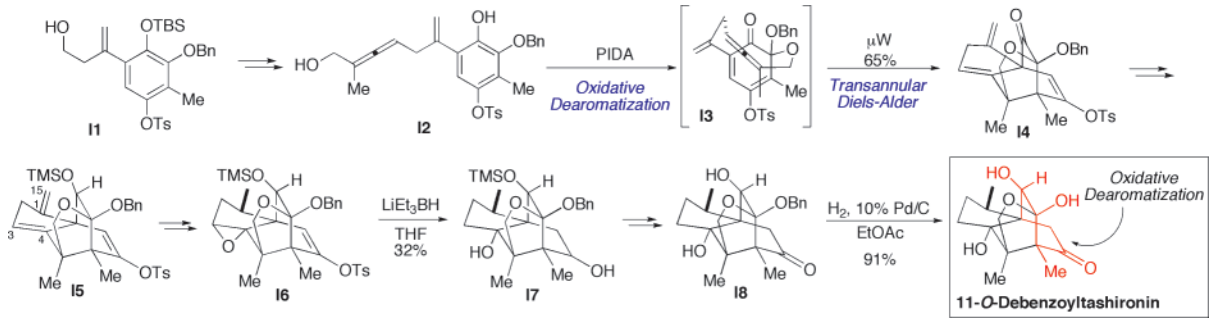
findings, we undertook the synthesis of this tricyclic diterpenoid (Scheme 12). Upon studying the structural framework of scabronine, we took note of a substructural pattern which to us suggested homology to the venerable Wieland−Miescher ketone (**G1**). Thus, our synthetic strategy was designed around the recognition that the B,C-ring system of scabronine G might be seen as a one-carbon ring-expanded version of the Wieland−Miescher ketone (**G1**). Importantly, **G1** can be readily obtained in optically active form and could presumably provide the means for an asymmetric synthesis of scabronine G. The A-ring of scabronine G would be established through a Nazarov cyclization.[30]

Thus, the Wieland−Miescher ketone (**G1**) was advanced to the Nazarov substrate, **G2** (Scheme 12). As hoped, upon exposure to $FeCl_3$, **G2** underwent cyclization to provide the tricyclic adduct **G3**. Diastereoselective conjugate addition with Nagata's reagent (Et_2AlCN), with subsequent TMSCl trapping, provided an intermediate silyl enol ether, which was readily transformed to the vinyl triflate, **G4**, as shown. The requisite isopropyl group was installed through a Negishi coupling and, following conversion of the nitrile to a methyl ester and appropriate functionalization of the C-ring, intermediate **G5** was in hand. We were now prepared to attempt the critical expansion of the C-ring. Thus, addition of lithiated methoxymethyl phenyl sulfide to the **G5** ketone provided **G6** as a diastereomeric mixture. We were pleased to find that, upon exposure to $HgCl_2$, **G6** indeed underwent the hoped-for one-carbon ring expansion to provide the cross-conjugated cycloheptenone **G7**. Thermodynamic isomerization of the olefin afforded scabronine G methyl ester, and upon ester hydrolysis, the naturally occurring scabronine G was in hand.

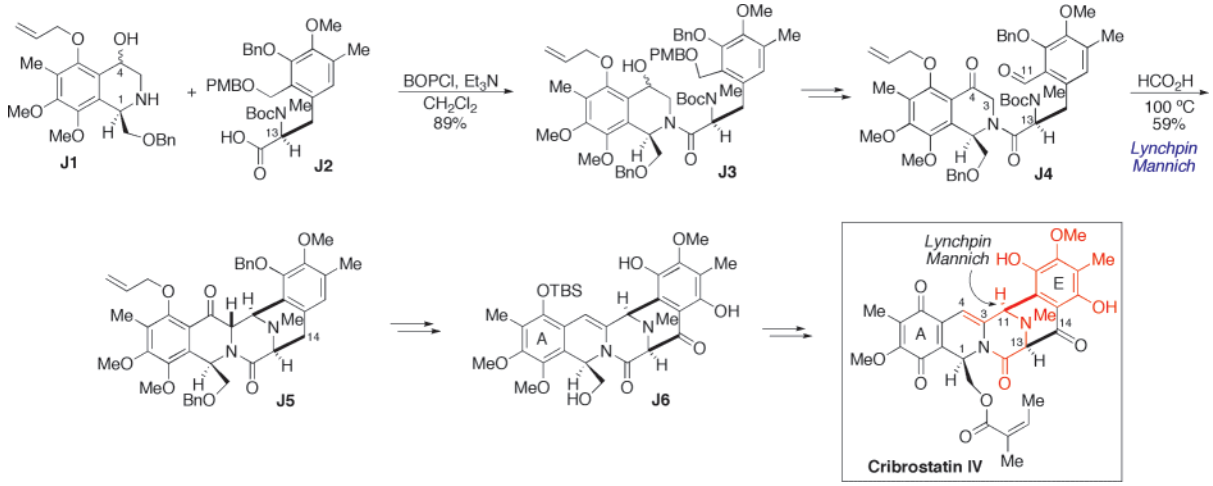
H. Garsubellin A. Garsubellin A first came to our attention on the basis of reports of its CNS activity. Isolated from the wood of *Garcinia subelliptica*, garsubellin A has been shown to enhance choline acetyltransferase (ChAT) activity by up to 154% in P10 rat septal neurons.[31] Taking note of reports that the progression of Alzheimer's disease is typically associated with an attenuated level of hippocampal ChAT activity, we sought to synthesize and evaluate garsubellin A in the context of our broad-based program directed at the development of potential lead candidates in the treatment of a range of neurotrophic disorders (Scheme 13). In our structural analysis of the natural product, we speculated that the central ring could be reached through an appropriately conceived dearomatization sequence. Increasingly, we have been drawn to dearomatized versions of highly functionalized arenes as valuable patterns in total synthesis. Aromatic chemistry is used to incorporate extensive and varied functionality. A dearomatization step removes the safety net of aromaticity, exposing a reactive multifunctionalized reactant for exploration.

In the event, phloroglucinol derivative **H1** was advanced to **H2**.[32] The key dearomatization event, depicted in Scheme 13, involved allylation of **H2** at the *para* position (cf. **H2** to **H3**). Fortunately, the diastereotopic olefins resulting from the dearomatization even lent themselves to differentiation in a pleasing fashion. Thus, upon treatment of **H3** with perchloric acid in water and dioxane, the acetonide was removed. The resultant secondary free hydroxyl group participated in Michael cyclization to afford, following elimination of methanol, the cyclized intermediate, **H4**, as a single diastereomer. Under prolonged reaction times, **H4** underwent removal of the vinylogous methyl ester to provide the desired adduct, **H5**. We note that, although

SCHEME 14. Total Synthesis of 11-*O*-Debenzoyltashironin



SCHEME 15. Total Synthesis of Cribrostatin IV



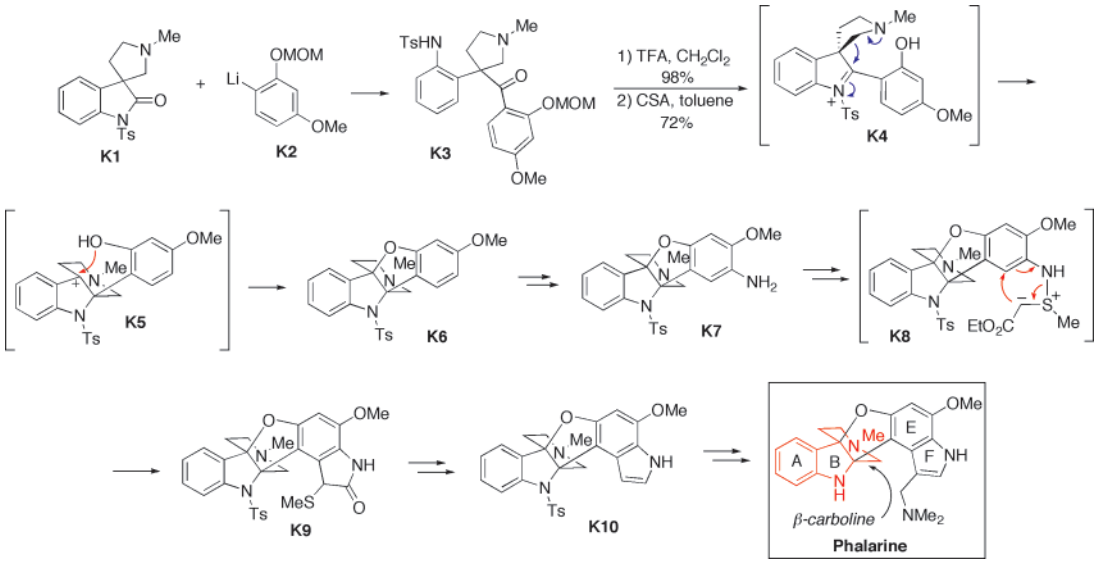
the product (**H5**) was isolated as a single diastereomer, there had been observed an equilibrating mixture of Michael-like cyclization products during the reaction. Presumably, only the desired diastereomer, wherein the allyl and 2-propanol moieties are positioned on opposite faces of the tetrahydrofuran ring, is well disposed for the subsequent methanol β-elimination. This elimination event would thus drive the diastereoselective cyclization process. In any case, this sequence had enabled both dearomatization and differentiation of the central ring of the natural product. Intermediate **H5** was subsequently advanced to the late stage compound, **H6**. At this point, the goal was the installation of the isobutyryl functionality at C_6. In fact, this task presented a significant challenge, due to the difficulties associated with generating a bridgehead anion such as would presumably be required. In the end, a workable solution was identified. First, **H6** was treated with LDA and TMSCl, followed by iodine to generate **H7**. A magnesium−iodide exchange generated the requisite bridgehead nucleophile which, upon treatment with isobutyraldehyde, smoothly underwent aldol reaction to afford **H8** in 72% yield. From this intermediate, garsubellin A was reached in two straightforward transformations.

I. 11-*O*-Debenzoyltashironin. Isolated from the pericarps of *Illicium merrillianum*, 11-*O*-debenzoyltashironin has been claimed to induce neurite outgrowth in rat cortical neurons at concentrations as low as 0.1 μM.[33] This highly oxygenated, densely functionalized natural product was targeted for total synthesis in our laboratory as part of our neurotrophin-based research program (Scheme 14). Upon examining the structure of 11-*O*-debenzoyltashironin, we formulated an overarching strategy, wherein virtually the entire tetracyclic framework of the target would be fashioned through a complexity-building oxidative dearomatization (**I2**→**I3**)−transannular Diels−Alder cascade sequence (**I3**→**I4**).[34]

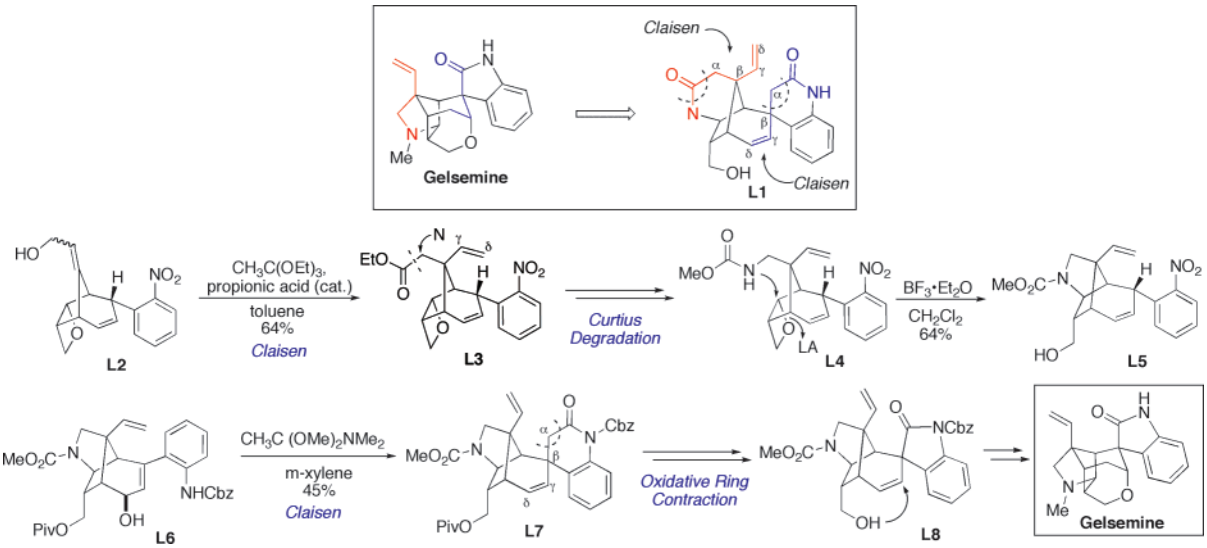
Thus in the tashironin synthesis, the relative stability of aromatic rings and the predictability of their reactions were exploited to build complex structure **I2**. It was now necessary to achieve high reactivity. To that purpose, **I2** was treated with an appropriate hypervalent oxidizing agent (phenyliodine(II) acetate (PIDA)), leading to the dearomatized structure **I3**. This structure indeed undergoes a spontaneous Diels−Alder reaction, producing **I4** containing all of the handles necessary to reach tashironin. While this progression was not a simple matter (particularly the conversion of **I6** to **I7**), in the end, it was possible, and this very complex sesquiterpene was reached by total synthesis.

J. Cribrostatin. In planning our synthesis of the densely functionalized cribrostatin IV, we recognized C_{11} as possibly emanating from a precursory aldehyde (Scheme 15). If the C_3−C_4 double bond were to arise from a C_4 ketone, a potential Mannich pattern suggested itself. The key step to exploit the potential Mannich connection would be **J4**→**J5**. C_4 of **J4** would be presented as a ketone. The aldehyde carbon of **J4** would be interpolated between the *N*-methyl group and C_3, which is α to the keto group at C_4. The aldehyde carbon C_{11} is seen as a lynchpin, joining the *N*-methyl group to C_3 as a one-carbon bridge. Introduction of the oxygen at C_{14} would be postponed until after the formation of **J5**. The issue of relative stereochemistry simply involves the joining of the proper enantiomers (see **J1** and **J2**), corresponding to C_1 and C_{13}. Needless to say, the configuration which emerges at C_{11} is dictated by the configuration of C_{13}. It was necessary to merge **J1** as an

SCHEME 16. Total Synthesis of Phalarine



SCHEME 17. Total Synthesis of Gelsemine

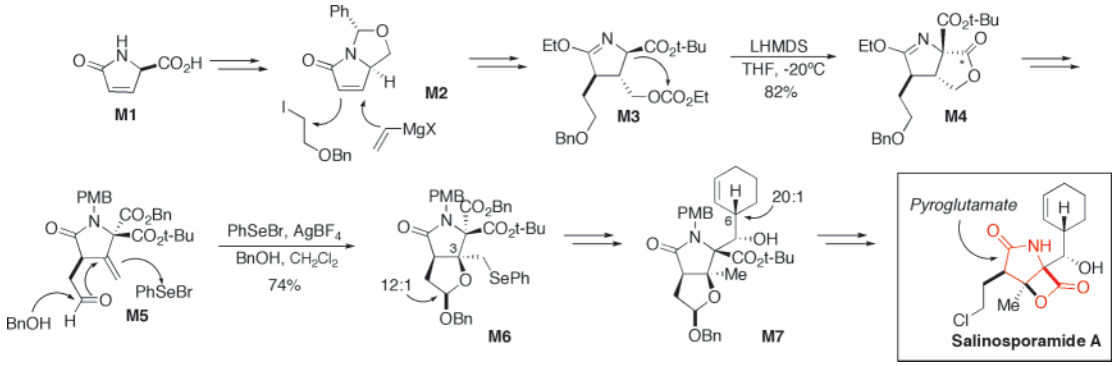


epimeric mixture of C_4 alcohols with **J2** since the attempted coupling failed with the corresponding keto version of **J1**. Happily, the signature step (see **J4**→**J5**), which we term a lynchpin Mannich reaction, worked reasonably well. The progression of **J5** to cribrostatin IV was nontrivial but, in the end, proved to be manageable.[35]

K. Phalarine. In studying and prioritizing various conceptions with respect to a projected total synthesis of phalarine, we came to favor one in which a tetrahydro β-carboline (AB indole) is joined through two critical bonds to a 4,5-disubstituted indole (EF indole) (Scheme 16). With the benefit of hindsight, fashioned by pitched trial-and-error empirical research, it would be necessary to present the EF indole in a segmental fashion (E then F). We moved on to a line of thinking adumbrated in Scheme 16. Coupling of **K1** with **K2** produced an intermediate, **K3** (in the actual case, a fully characterized *N*-tosylamino-ketone), which would go on to the fugitive **K4** (or a structural equivalent thereof). During this progression, the MOM protecting group was cleaved. We now come to the defining step. It was prompted at the conceptual level by focusing on the tetrahydro β-carboline moiety. We were struck by the recognition that this structure, in the context at hand, might well arise from a rearrangement of an uncharacterizable spiroindolenium ring framework, generating in its wake a cation at the β-carbon of the β-carboline (see **K5**). Happily, this plan worked, though a precise mechanistic description cannot yet be provided with appropriate rigor. Advancement of **K6** to phalarine was significantly enabled by application of the Gassman Indole synthesis, exploiting a [2,3]-sigmatropic rearrangement. In this way, **K7** progressed to **K9** and, in due course, to phalarine itself.[36]

L. Gelsemine. From the start of the planning exercise of the total synthesis of gelsemine, we envisioned that the tetrahydropyran ring would be established from a precedented ring closure of a bis-homoallylic alcohol (see **L8**→gelsemine, Scheme 17). We further speculated that perhaps the hindered hydroxymethyl group might arise from an internal alkylative opening of an oxetane electrophile, by a nitrogen-based nucleophile (see **L4**→**L5**). We took note that, in the projected **L8**, the disubstituted double bond is β,γ to the carbonyl group of the lactam function. Given the context, one was prompted to conjecture about the possibility of interpolating *in the mind's eye* an

SCHEME 18. Total Synthesis of Salinosporamide A



additional methylene group in **L8**, such that the disubstituted double bond would be γ,δ with respect to the lactam carbonyl group. By the same token, one could think about interpolating, through another gedanken experiment, a carbonyl function within the nitrogen nucleophile segment. The "reward" for doing so was that the vinyl group would then have a γ,δ relationship with respect to the carbonyl group of this formal lactam. Recollection that the disubstituted double bond would also have a γ,δ relationship to the carbonyl carbon of the cyclic anilide prompted the possibility of producing, in a properly sequenced fashion, each wing of the emerging system through a Johnson−Claisen rearrangement. At each end, there would be required, ultimately, excision of a single carbon atom. In each case, the raison d'être of the extraneous carbon was to enable compatibility with a Claisen-directed pattern. At the vinyl end, the excision would be through a Curtius rearrangement. At the anilide end, the excision would have been through oxidative fragmentation. We illustrate these notions in the context of a hypothetical entity **L1**. This structure is not intended to correspond, per se, to an actual synthetic subgoal. Rather it is a patterning device to bring out the notion of two Claisen-type transformations.[37]

These thoughts matured into the total synthesis shown in Scheme 17. The allylic alcohol **L2** was exploited for purposes of an *ortho*-acetate Claisen rearrangement, leading to the γ,δ-unsaturated ester **L3**. Indeed, the Curtius degradation scheme led to **L4**, which, happily, functioned as planned. Under Lewis acid catalysis, the nitrogen displaced the secondary carbon−oxygen bond of the oxetane to produce **L5**. After some manipulation, allylic hydroxylation was accomplished (see **L6**). Another Claisen-type rearrangement followed by cyclization led to pyradinone, **L7**. Following a one-carbon degradation, **L7** was converted to **L8**, and shortly thereafter, the total synthesis of gelsemine was accomplished.

M. Salinosporamide. In studying the structure of salinosporamide, we took note of a potentially productive pyroglutamate pattern (cf. **M1**, Scheme 18). This moiety would serve to provide a suitable enantiodefined starting material.[38] The pyroglutamate was to be converted by known steps to **M2** (Scheme 18). At this stage, it would be necessary to first accomplish an α,β-bisdialkylation of the conjugated double bond and then to protect the lactam center. In practice, this was done through imino ether formation. The vinyl group which was appended to the β-carbon of the unsaturated lactam would, in time, be converted to a mixed carbonate ester (see **M2**→**M3**). The carbonyl carbon of the mixed carbonate of **M3** corresponds to the all-critical carbon dioxide equivalent, which is then joined to the imino ether containing ring, through a base-induced Claisen-like condensation. The progression of **M4** to **M5** set the stage for a signature step. This important transformation involved intramolecular oxyselenation of the terminal methylene group of **M5** through the hydroxyl group of a fugitive hemiacetal. This step set the stage for presenting the all-critical methyl group at the base of the β-lactone. It is well to notice that the ester functions in **M6** are in effect differentiated by their protecting groups. The functional group distinction of the esters in **M6** could be exploited, allowing us to reach **M7** by the corresponding addition of cyclohexenyl zinc to the aldehyde function, derived from the benzyl ester of **M6**. This stereocontrol was borrowed from the E. J. Corey inaugural total synthesis of salinosporamide.[39]

III. Conclusions

Above we have attempted to make several points. The first is that SMNPs have proven to be valuable sources for the discovery of new and interesting biological agents, which, on some occasions, have matured into blockbuster drugs.[2] Prospecting in the SMNP area will produce fewer lead structures for potential pharmaceutical advancement than the unlimited terrain of medchem/combichem. However, judging by any fair reading of pharma history, particularly in oncology, anti-infectives, anti-inflammatories, and anti-hypercholestemic applications, SMNPs and SMNP-inspired structures have a most impressive track record.

We further argue that the revolutionary advances in the capacity of synthetic methodology over the last three decades allow for leveraging the already powerful SMNP estate, enabling much more profound molecular editing than was previously the case (cf. inter alia migrastatin, fludelones, and cycloproparadicicol). To a large extent, these advances in methodology are the pay-off of years of insufficiently appreciated scholarship and experimentation in transition-metal-mediated transformations.

The advances in the methodology of synthesis have had no small impact in the fashioning of the strategy of reaching relatively complex targets, including SMNPs themselves, or SMNP-inspired structural space. We have identified two styles in retrosynthetic analysis. The first is the established[3] and powerful concept of prioritized strategic bond disconnection. In principle, every complex target would fall within the scope of strategic bond disconnection. A complementary and, we think, worthwhile planning modality seeks out patterns in the form of substructural motifs. This line of analysis may perhaps follow a more holistic approach than strategic bond disconnection. Often the pattern is recognized only after substantial intellectual modification of the actual structure to connect the target with a

dominant exploitable motif. We emphasize that there is much opportunity for innovation in the recognition of the guiding pattern and in planning the progression from the governing motif to the complex target. Particularly fascinating and rewarding are the opportunities for creating new methodology level chemistry to enable access to the governing pattern and to smooth the pathway onto the target.

Again, we emphasize that these and other thought processes are really complementary, as the creative powers of the human mind are challenged by provocative structural targets. It is interesting to note that, in the area of synthetic analysis, the raw power of the human intellect has held its own with electronically driven capacities. Perhaps this is telling us that organic synthesis, particularly in the context of SMNPs, remains a fascinating blend of highly sophisticated science, mediated to a major extent by difficultly quantifiable but clearly discernible levels of sheer artistry. While the mind cannot compete with the computer in speed and efficiency, it still has huge contributions to offer in the domain of "close call" judgment and pristine elegance if we allow and even encourage it to roam about. Given the multifactorial nature of contemporary medical and material sciences, it seems safe to predict that the future will provide wrenching challenges as well as exciting opportunities for the "artscience" of organic total synthesis.

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