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Small Molecule Natural Products in the Discovery of Therapeutic Agents: The Synthesis Connection†

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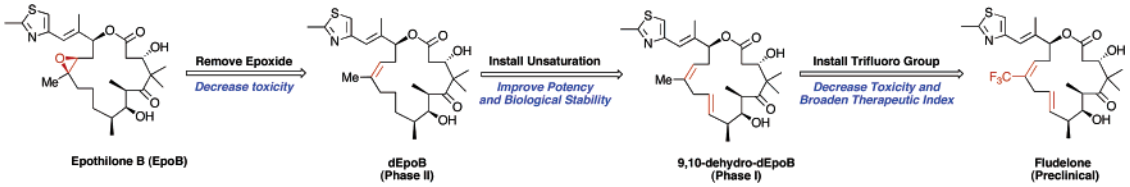

Natural products have been a rich source of agents of value in medicine. They have also inspired, at various levels, the fashioning of nonnatural agents of pharmaceutical import. Hitherto, these nonnatural derivatives have been primarily synthesized by manipulating the natural product. As a consequence of major innovations in the subscience of synthetic methodology, the capacity of synthesis to deal with molecules of considerable complexity has increased dramatically. In this paper, we show by example some total syntheses which draw from strategy-enabling advances in methodology. Moreover, we show how these capabilities can be used to discover and develop new agents of potential pharmaceutical value without recourse to the natural product itself.

I. Introduction

"Small molecule" natural products (SMNPs) have played a major role in the intellectual and experimental development of organic chemistry.[1] The engagement of the two fields started with the challenge of isolating pure products from complex naturally derived mixtures. As the theory of organic chemistry began to grow and mature, the basis for structure elucidation of SMNPs based on profiling of chemical behavior emerged. The creative interactivity between the proof of structure of SMNPs and the maturing of the general theories of what we now consider organic chemistry is a remarkable instance of intellectual synergism. The massive collection of descriptive chemistry including new reactions exhibited by small-molecule natural products (cf. inter alia camphor, quinine, strychnine, morphine, cholesterol) formed a key part of the database of organic chemistry. In fact, it would be hard to imagine how what we call organic chemistry would have developed without exciting inputs from SMNPs. The growing database of SMNP reactions helped to drive the development of descriptive theory. With the theory came the enablement of pattern analyses by reconciliation of observed chemical properties with expectations based on precedent. This reasoning allowed for the assignment of ever more complex structures. In this way, a whole new world of fascinating molecules insinuated itself into the mindsets of organic chemists. At first, the assignments were unable to deal with the full stereochemical details of the SMNP. As insight regarding the way in which functional groups within a molecule communicate matured, increasing definition at the stereochemical level became possible, but progress was still slow. The

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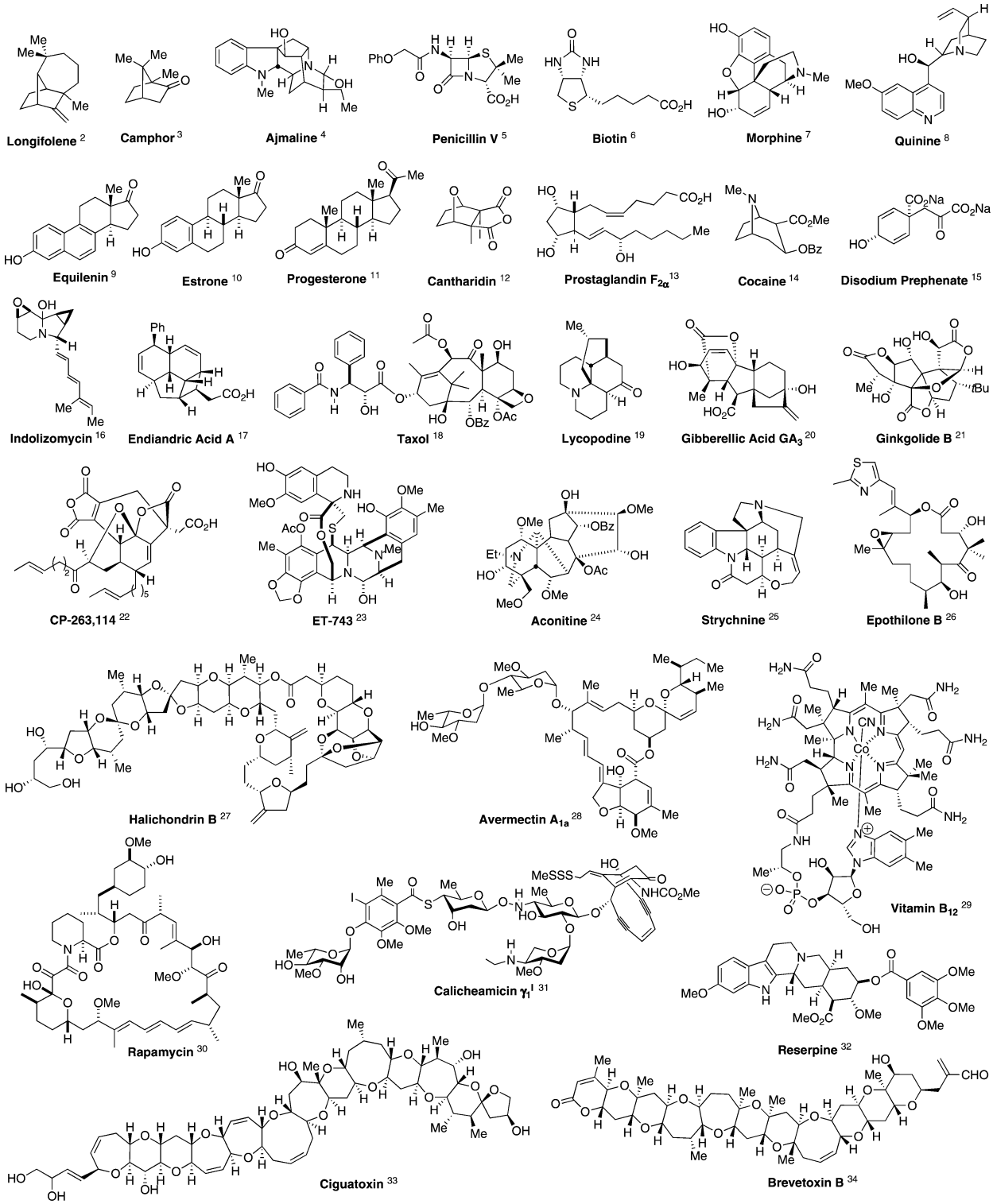
SCHEME 1. Structures of Natural Products[2−34]

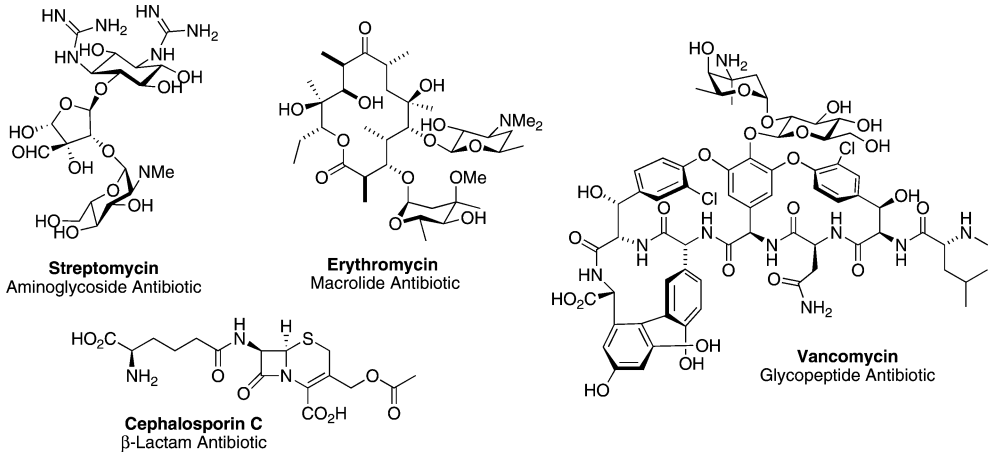


process of structure determination, including stereochemistry, was massively accelerated with major advances in spectroscopy and eventually with the advent of pre-emptory crystallography-based elucidations. A remarkable galaxy of pure compounds isolated from plants, bacteria, fungi, marine sources, and in time, humans ensued. This collection proved to be at once mind-teasing and mind-expanding in its power to provoke the imaginations of organic chemists. A sampling of some of these natural products, including compounds of historic interest and some of particularly novel structure, is offered in Scheme 1. In summary, the fields of natural products chemistry and the development of descriptive organic chemistry grew up together in close rapport.

II. SMNPs as a Source of New Pharmaceuticals

The natural product estate has proven itself to be an invaluable resource in the search for new lead agents of medicinal import.[35]

SCHEME 2. Natural Products as Antibiotic Agents



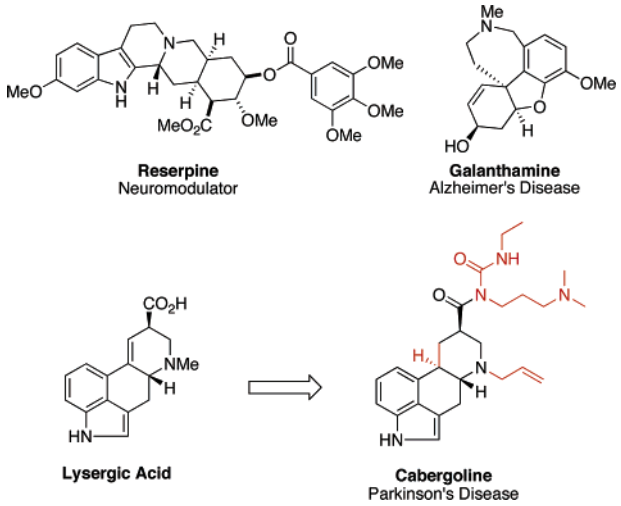
Indeed, despite the puzzling (and, we think, disastrous) decision of Big Pharma organizations to significantly downplay the role of small molecule natural products in Medicinal Research in favor of far less validated discovery platforms,[36] a disproportionate number of new chemical entities (NCE) approved even over the past 20 years have in fact been natural products or natural product-based.[35a]

The natural product landscape offers entry into the drug discovery process in a number of ways. In the most direct case, a natural product may itself possess all of the potency, selectivity, and pharmacokinetic traits required to render it a clinically useful drug agent. More often are the instances where the natural products themselves serve as lead agents, providing the chemist with a structural platform which can be elaborated upon, or simplified, to yield a therapeutically valuable pharmaceutical. Analogues that can be accessed through modification of the natural product itself are considered to be "natural product-derived." Alternatively, a biologically active natural product may serve as an inspiration for the medicinal discovery chemist, by providing insight into types of structural features that may prove valuable. A drug candidate that has been designed on the basis of the teachings of a natural product, but which is not itself synthesized from that compound, is, in our language, "natural product-inspired." This latter classification may encompass a vast range of connectivities ranging from those which essentially retain nearly all of the structural features of the natural compound to those in which only hints of the natural product structure have been preserved.

All would agree that the de novo discovery of a new registrable drug of value in medicine is a daunting task, the risks of which are virtually prohibitive. The main case for SMNPs as a means of discovering valuable leads is that *such structures often allow for entry into the discovery progression at a much more advanced stage than does the screening of standard diversity libraries which lack comparable pedigree or intellectual coherence*. This accessibility to "advanced standing" is surely a major factor in the extraordinary record of success of SMNPs in the discovery of new agents, often of enormous value.

The impact of natural products on drug development can be felt across virtually every major therapeutic area. For instance, between 1981 and 2002, of the 90 antibacterial new chemical entities (NCE) approved by the FDA, 10% were natural products while another 68% were natural product-derived.[35a] Indeed, many of the most prevalent antibiotic agents in use today are

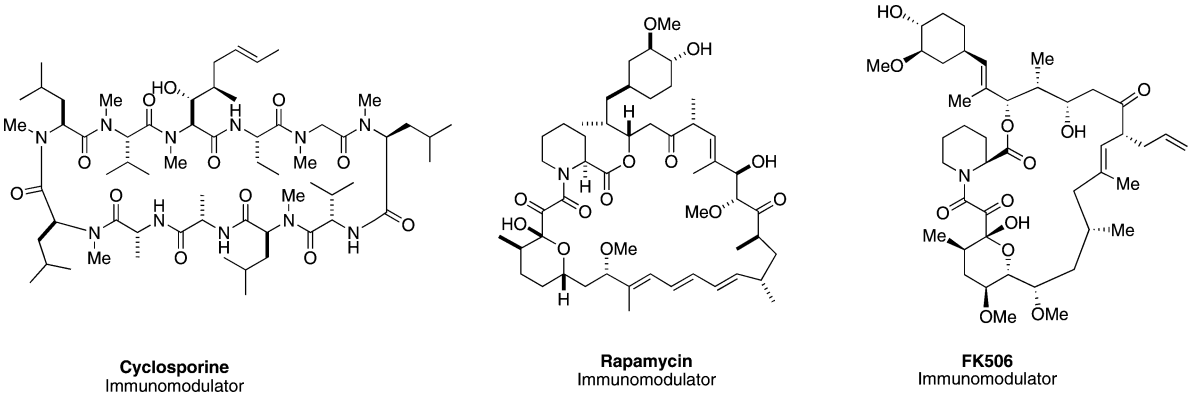
SCHEME 3. Natural Products as CNS-Based Agents



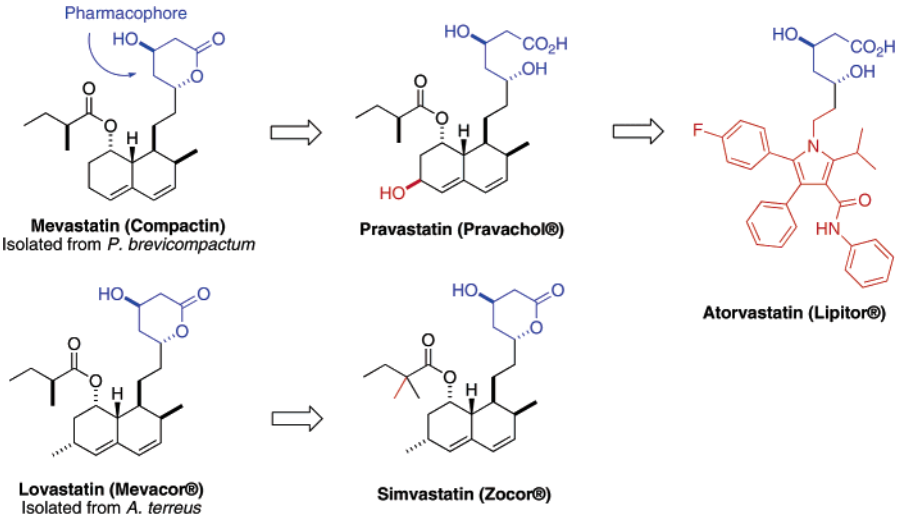
members of well-known natural product classes, including β-lactams (cf. penicillins and cephalosporin C), macrolides (such as erythromycin), aminoglycosides (such as streptomycin), and glycopeptides (including vancomycin) (Scheme 2).[37]

A number of clinically important CNS-active drugs are readily traceable to natural sources (Scheme 3). Notable examples include the naturally occurring yohimbine alkaloid reserpine, synthesized as described by Woodward in a manner which also had significant teaching consequences.[32d] Reserpine had found application as an antihypertensive agent and a tranquilizer. More recently, galanthamine, originally isolated from *Galanthus nivalis*, has been approved for the treatment of Alzheimer's disease, though the impact of this registration is by no means established.[38] Cabergoline, a long-lasting dopamine D2 receptor agonist that is used in the treatment of Parkinson's disease, is another example of a natural product-inspired drug agent. Cabergoline is an analogue of the naturally occurring ergot alkaloids, a class of biologically active molecules whose membership includes lysergic acid[39] (itself synthesized by Woodward in collaboration with a group at the Eli Lilly laboratories[39d]). The natural ergot alkaloids per se have not found wide clinical application due to their complexity of action. However, cabergoline, whose core structural backbone is quite similar to that of lysergic acid, is one of a number of ergot-inspired derivatives that have demonstrated broad, clinically useful activity.

SCHEME 4. Natural Products as Immunomodulators



SCHEME 5. Natural Product-Based Statins



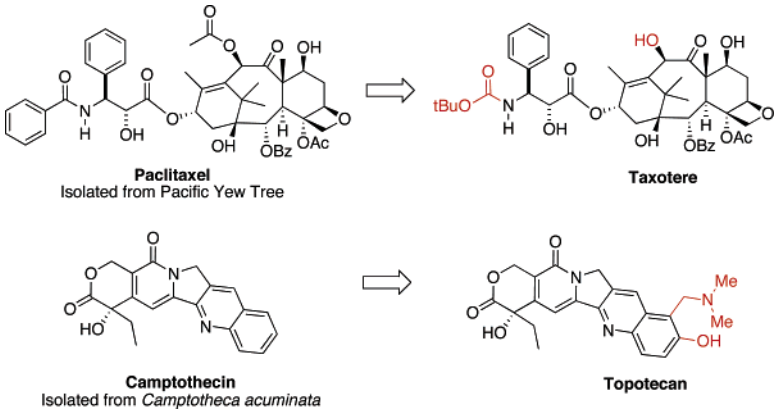
Several of the most widely employed immunosuppressive agents also arose from a SMNP connection. The immunosuppressive action of the naturally occurring cyclosporine A has been widely credited with the significant increase in the success of organ transplantations. More recently, the natural products FK-506[40] and rapamycin[30] have entered the market as immunosuppressive agents, thereby enhancing the chances for favorable outcomes in organ transplantations (Scheme 4).

The statins, inhibitors of the HMG CoA reductase enzyme, are widely prescribed as anti-hypercholesteremic agents, with long-term cardiotonic benefits.[41] It is widely agreed that the statins represent an invaluable class of drug agents with major commercial implications. As shown, mevastatin (compactin)[42] and lovastatin (Mevacor)[43] are natural products isolated from *Penicillium brevicompactin* and *Aspergillus terreus*, respectively (Scheme 5). Simvastatin (Zocor)[44] is a semisynthetic analogue, closely related to lovastatin. This agent incorporates only one additional methyl group in the acyl sector of the ester, as shown. Similarly, pravastatin (Pravachol) incorporates a hydroxyl group on the decalin system and displays the pharmacophore in ring-opened form. Atorvastatin (Lipitor),[45] certainly among the most commercially successful drugs ever used, differs substantially from both natural products, and its structure can be considered to have been creatively inspired by the parent compounds lovastatin and mevastatin. Clearly, though the presumed central statin pharmacophore is retained in the mega blockbuster Lipitor, the extensive periphery of the molecule has been completely reconfigured.

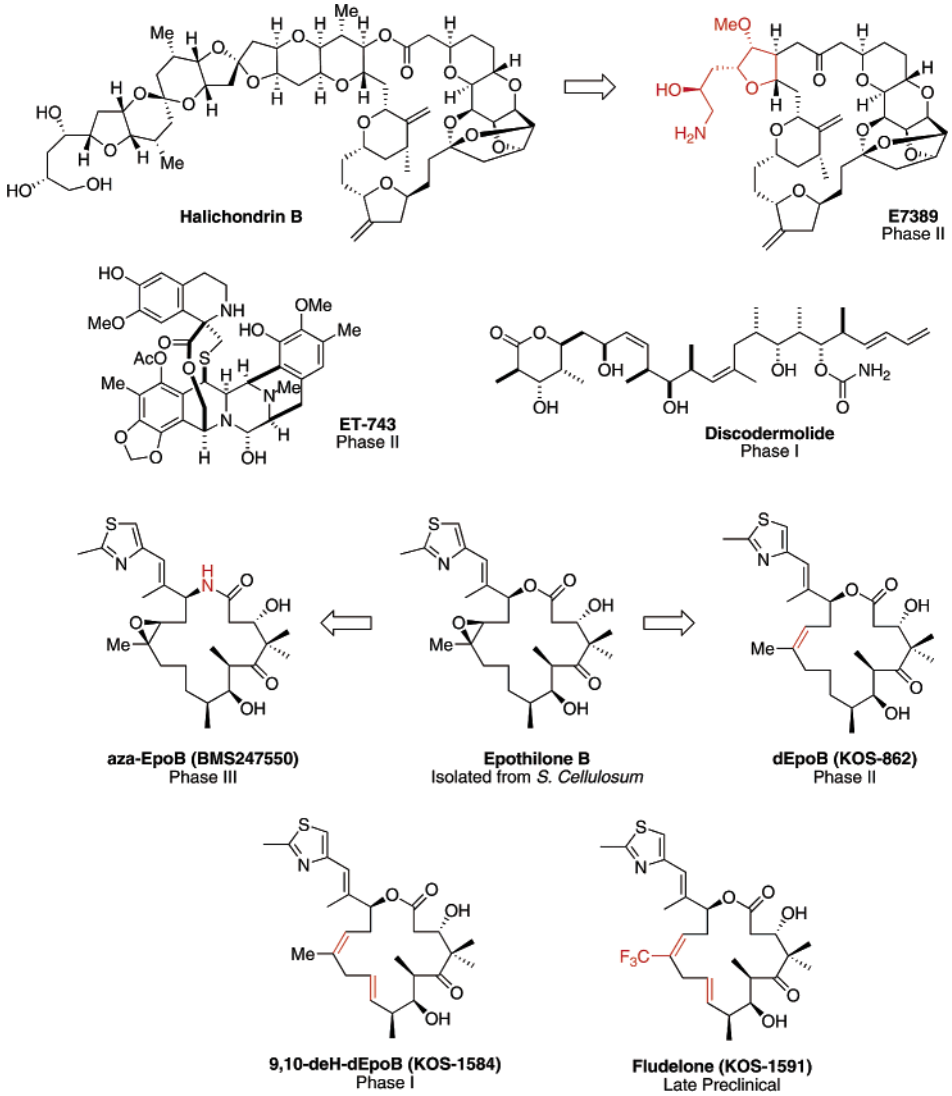
The natural product reservoir has proven to be a particularly rich source of anticancer lead compounds (Scheme 6). A full 74% of anticancer agents approved between 1981 and 2002 were natural products, natural product-derived, or natural product-inspired. The majority of commonly used anticancer agents on the market today, including the sometimes curative vinblastine, vincristine, and paclitaxel (Taxol), were originally isolated from natural sources. Taxotere, another widely prescribed antitumor agent, is a semisynthetic derivative of Taxol, while topotecan was clearly derived from the natural product camptothecin (Scheme 6).[46] The anthracyclines,[47] the etoposides,[48] and the mitomycins,[49] not to mention bleomycin,[50] are further examples of applications of SMNPs to oncology.

In this connection, we digress to briefly comment on the state of the natural product-based anticancer pipeline. It is notable that development in this field via SMNPs is particularly vibrant, despite the virtual abandonment of the field by major Pharma organizations. Some particularly promising anticancer agents currently in clinical evaluation are E7389,[51] a derivative of the naturally occurring halichondrin B,[27] the natural products discodermolide[52] and ET-743,[23] and several analogues of the epothilone family of natural products, including BMS247550 (aza-EpoB) and KOS-862 (dEpoB), as well as KOS-1584 (9,-10-deH-dEpoB). These latter two compounds were both reported from our laboratory. KOS-1584 is the lead member of a promising class of compounds in the epothilone series that contain an additional 9,10-double bond. Indeed, the 26-trifluoromethyl derivative in this family, which we have termed

SCHEME 6. Natural Product-Based Anticancer Agents



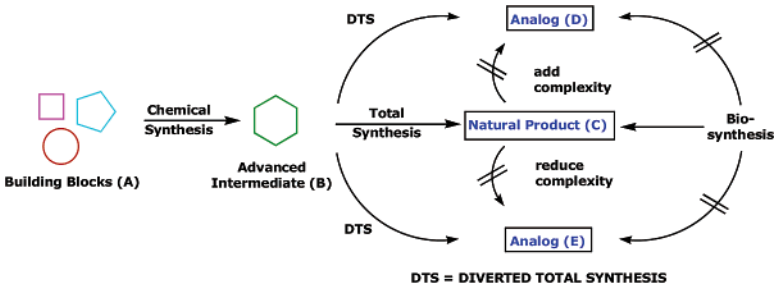
SCHEME 7. The Anticancer Pipeline



fludelone,[53] exhibits a most favorable therapeutic index. Based on extensive in vivo models, fludelone is a unique compound in its curative properties with respect to xenografts and its wide therapeutic index. It will hopefully mature into "breakthrough" status in the field (Scheme 7).

Finally, even in this cursory overview, the extraordinary impact of steroids in inflammation (corticosteroid[54]), in reproductive regulation (19-norsteroids[55]), and in dermatology (vitamin D metabolites[56]) can hardly be overlooked. In summary, by every reasonable yardstick, SMNPs have played a very large role in the discovery of new agents of major value to medicine. We would further argue that the decision to downgrade or even end small molecule natural products research was particularly regrettable since the great advances in chemical synthesis

SCHEME 8. Diverted Total Synthesis



rendered the setting particularly conducive to success. To appreciate these positions, it is first necessary to think about why SMNPs have been such a rich source in the discovery of pharmaceuticals of value to human health and welfare.

III. Some Thoughts on the SMNP/Useful Drug Correlation

To what are we to ascribe this remarkable record of connectivity between SMNPs and agents of interest as potential pharmaceuticals? We start with a reality check. Of course, while a remarkably high percentage of drugs have been identified through SMNP-related research, it is important to realize that only a small percentage of SMNPs emerge as candidates for further development from a pharma perspective. Still, upon guesstimation of the number of all known compounds which are themselves SMNPs, or that have been inspired from the primary SMNP isolates as a function of all known compounds, the propinquity factor, while not quantifiable, must be staggering.

Unfortunately, we are still largely uninformed as to why most SMNPs are being biosynthesized in the first place. In all but a small number of cases, structurally fascinating SMNPs appear to the chemist as extravagances, often enabled by extraordinarily sophisticated and "creative" biosynthetic pathways (cf. inter alia polyketides, polyisoprenoids, eicosanoids, mevalonate, alkaloidal constructions, chlorophyll-corrin assemblies, etc....). While the purpose of their biosynthesis is far from clear and presumably varies from case to case, on the whole it is fair to say that SMNPs are primarily built and evolutionarily optimized to interact with proteins such as enzymes or receptors. As such, SMNPs benefit from the wisdom of lessons which nature has learned. In addition to appropriate size, the often ornate stereochemical patterns of the SMNPs must be there for reasons other than challenging the inventiveness of aspiring organic chemists. It is not unlikely that the rich three-dimensional detail of the SMNPs provides complementarity to enable their recognition as ligands by larger biomolecular targets of action. This affinity to proteins and other biomacromolecules (nucleic acids and carbohydrates) already is a major step forward in establishing a putative SMNP-pharmaceutical connection. Moreover, SMNPs have a further advantage in that they tend to have the molecular size suitable for cell permeability and also that they been biosynthesized largely through protein-based machinery. Particularly in the last stages of its biosynthesis, the SMNP-like structure serves as a viable substrate in some enzymatically mediated process. It goes without saying that the overwhelming majority of pharmaceuticals are directed to a protein-type target.

We further observe that the SMNP also starts life with the advantage that it was effectively housed in a living system. Although the biological settings which prompted the biosynthesis and allowed for the maintenance of the SMNP are much different from those which will be required of a drug, the prescreening of a SMNP by a naturally occurring host as to function and "pharmacoviability" is significantly greater than the typical synthesized pharma aspirant. In summary, in three areas: (i) wisdom of the ages, (ii) proclivity of SMNPs to interact with proteins and other biomolecules arising from their appropriate size and fine-tuned stereochemical nuances, and (iii) demonstrated accommodatability in a living system, a SMNP may start life with a substantial initial advantage not readily overcome by brute force numbers of random compounds lacking comparable pedigrees.

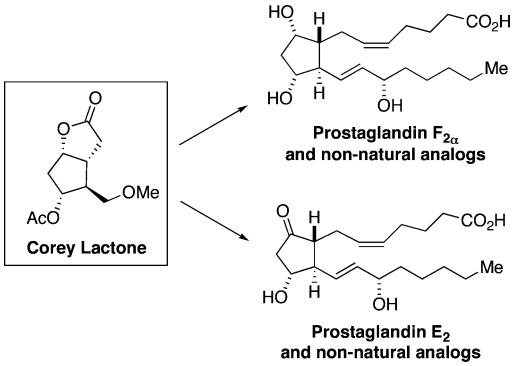
Having said this, it is also appropriate to recognize that the SMNP was presumably not optimized for the same purpose as it will serve in a pharmaceutical setting. The appearance of the SMNP on the scene required the evolution of an enabling and feasible biosynthetic pathway. *Hence, the SMNP may well represent a balance between biological optimization and biosynthesizability*. Although a great deal has been accomplished in adjusting biosynthetic pathways at the gene/enzyme level,[57] allowing for much greater control than is available by the traditional nutrient modification methods, the world of small molecule biosynthesis is still one with its own normative guidelines. These pathways are not always readily administered from "without."

IV. Diverted Total Synthesis of SMNPs

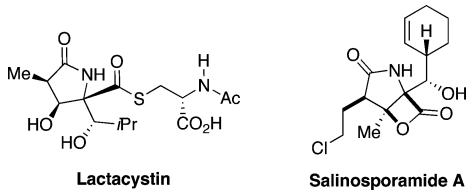
It is with a view toward using target-oriented synthesis to take advantage of the valuable but not necessarily optimized pharmacophoric space of SMNPs that the notion of diverted total synthesis (DTS) was developed.[90] The central proposition is that, as indicated above, there is no reason to believe that the natural products themselves have been fine-tuned with respect to the properties sought after in the eventual drug. As stated above, SMNP optimization requires the existence of a workable biosynthetic pathway and maintenance of balance within the host system. Yet, there is more than ample reason, based on experience, to believe that the natural products exhibit, at some level, the key pharmacophoric properties of value in attacking their targets. Diverted total synthesis also takes due cognizance of the fact that many transformations of natural products which might be considered for optimization cannot be accomplished due to the requirements and vulnerabilities of resident functional groups or due to a lack of feasible reactions.

The central notion of diverted total synthesis is a simple one. Consider a program directed to the total synthesis of a natural product (Scheme 8). Before reaching the product itself, one may well have progressed to level **B**. It could be of great interest to use **B** to reach point **D**, which represents chemical space of a

SCHEME 9. Prostaglandins from the "Corey Lactone"



SCHEME 10. Lactacystin and Salinosporamide A



higher order of chemical complexity than is encountered in the natural product itself, or point **E**, which is of a lower order of complexity. As stated above, often neither of these structure types can be reached from the natural product, for reasons arising from chemical limitations. We also note that access to useful amounts of the SMNP may not be available to anyone outside of the discovery laboratory. By contrast, DTS is available to all with the appropriate skills. Moreover, in the case of chemically inaccessible analogues, it may not be possible in a reasonable time scale to reprogram the natural biosynthetic order of things to gain access to either points **D** or **E**. It is here also that diverted total synthesis can manifest its great potential. In Section VI, we will show by example how some major advanced preclinical successes have been realized by using diverted total synthesis as a means of "molecular editing" of unnecessary or even undesirable structural features.

We emphasize that the central idea formalized under the rubric of diverted total synthesis is by no means original. A famous and clearly discernible example of this line of thinking came in the prostaglandins field (Scheme 9). Thus, the "Corey lactone," prepared by total synthesis,[58] became a springboard to reach and evaluate a myriad of prostaglandins, many of which could not have been obtained from any known natural prostaglandin.[13g] Indeed, diverted total synthesis, starting from the "Corey lactone," was helpful in establishing the SAR profile of prostaglandins[59] (perhaps more so than through partial synthesis starting from naturally occurring prostaglandins).

A more recent ongoing example, again from the Corey laboratory, involved the building of fully synthetic, chemically flexible intermediates of the extremely potent lactacystin[60] and salinosporamide proteasome inhibitors (Scheme 10).[61] Given the inaccessibility of these compounds to all but the laboratories in which they were discovered, diverted total synthesis and total synthesis constitute a powerful means for extensive and wide-ranging new lead development.

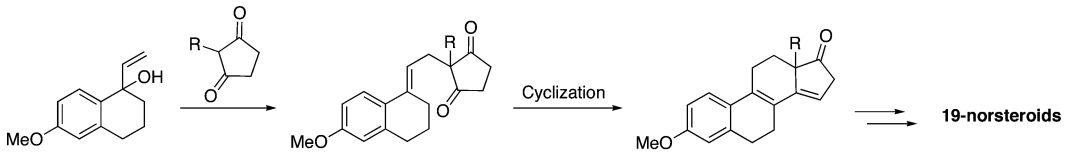
Another fascinating example of DTS came in the synthesis of the nonnatural, clinically useful anti-ovulatory 19-norsteroid family containing a 13-ethyl function, the norgestrels.[55] The synthesis of the 13-ethyl series via partial synthesis of the natural 13-methyl structures would have been more challenging than was its total synthesis by "diverting" the classical Torgov route to steroids (Scheme 11).

V. SMNPs and Total Synthesis

Given the interest of our laboratory in total synthesis, as well as the diverted total synthesis of SMNPs, it is appropriate to digress briefly into the history of this field and its future prospects. In two previous publications,[62] it was observed that the announcement of the first total synthesis of equilenin by Bachmann, Cole, and Wilds, which appeared in 1939,[9] was pivotal in ushering in the era of natural product total synthesis. Many of the elements we look for today in a total synthesis paper, such as target selection, discussion of the strategy to be followed, and an account of the execution, were in place in that effort. Equilenin is a naturally occurring hormone (albeit a bit player in the large universe of endocrinology). It has what was, at that time, considered to be a challenging tetracyclic molecular architecture. The announcement of the achievement of the total synthesis of equilenin was indeed an impressive harbinger of things to come.

The enterprise grew rapidly from this launching. Success in accomplishing the total synthesis of estrone, which is a far more central hormone in mediating human physiology than equilenin, was another important milestone.[10] From the perspective of the complexity of chemical challenge, the rather more elaborate stereochemical dictates inherent in the structure of estrone made its early conquests, most notably by Johnson and associates[10b] as well as by Anner and Miescher,[10c−e] all the more impressive. Surely, from the perspective of garnering attention from the broader society, the synthesis of quinine by Woodward and Doering must be regarded as a significant milestone.[8c] Another aspect of this quinine effort should be noted. There was an implication (though never stated in a specific way) that a total synthesis of quinine would impact on the insecure availability of this medicinally vital antimalarial agent from natural sources (cinchona). Although the claimed formal total synthesis of quinine in reality never carried with it any consequences for the availability of this particular drug, the concept that total synthesis, *in principle*, had such a potential, helped to fuel interest in this fledgling field.

SCHEME 11. Natural and Nonnatural Norsteroids



With ongoing enhancements in the sophistication of strategy level thinking, the growth of synthetic methodology, and "quantum jump" improvements in analytical capabilities to validate the assignment of structures in the course of a synthetic progression (particularly ultraviolet, infrared, and most dramatically NMR and mass spectroscopy) came conquests of significantly more complex structures. These included nonaromatic steroids (containing minimally six stereogenic centers undergirding their saturated tetracyclic framework, not to speak of additional sites of stereogenicity) and, particularly, the complex alkaloid strychnine.[25]

As was painfully obvious in the quinine effort,[8] as well as in the late 1940s/early 1950s skirmishing with steroids,[63] the lack of control in stereodefining reactions (particularly those which give rise to sp^3 carbons) constituted a major impediment to progress. A notable advance in demonstrating the implications of full stereocontrol in the context of a difficult molecular structure was recited in the landmark total synthesis of cantharidin by Stork and co-workers.[12c] In short order, the goal of stereospecificity became central to the growing, but still select, community of devotees of total synthesis. Highly stereoselective total syntheses of the yohimbine alkaloids, culminating in Woodward's historic stereocontrolled total synthesis of reserpine[32d]—a then promising CNS agent for mediating depression—were important milestones. The stereoselective total synthesis of cortisone by a Merck group headed by Sarett[64] was surely another major event, rendered more dramatic by the perception that the corticosteroids were miracle drugs of the future. Total synthesis of highly active structures such as morphine[7] and the penicillins[5] continued to drive progress.

In retrospect, it is fair to observe that these early total syntheses brought with them relatively modest advances in the methodology of synthesis. In those earlier days, excellence in total synthesis tended to reflect clever exploitation of the existing corpus of then known reactions. Instances of systematically and independently pursued advances in methodology driven by the context of total synthesis were still quite rare.

In our judgment, the huge advances in the power of total synthesis have been fueled primarily by advances in synthetic methodology. While it is often more aesthetically pleasing to focus on strategy level issues, in reality, new strategic insights and increasingly powerful retrosynthetic analyses are inextricably interwoven with the development of enhancing reaction methodology.[65] Most exciting from our perspective is the creative synergism of methodology and target pursuits. Thus, opportunities in natural product total synthesis open up major prospects and incentives for accomplishments in methodology. Correspondingly, the emergence of new reactions, which provide new enablements, prompt more daring "strategies".

Indeed, the growth in the power of synthetic methodology has been explosive. Much was accomplished even within the confines of the rather restricted segment of the periodic table with which organic chemists were comfortable (e.g., C, H, O, N, Li, K, Ca, and the halogens). Dramatic advances in this confining context were mediated by a growth in the predictive powers of qualitative mechanistic thinking (arrow pushing!). It is from this type of thinking that key advances in the practice of synthesis (cf. inter alia enamines,[66] silyl enol ethers,[67] site-specific alkylations,[68] umpolung,[69] and free-radical cyclizations[70]) were accomplished. The opening up of additional elements (cf. inter alia B,[71] S,[72] Se,[73] Si,[74] Sn,[75] P[76]), in concert with the growing predictive capacity of qualitative mechanistic thinking, led to much growth in reagent development. Included among these are what were then novel departures (for instance, ylides,[77] routes to carbenes,[78] benzynes,[79] Diels–Alder components,[80] dipolar cycloadditions,[81] organoboranes[82]).

The last 25 years have witnessed particularly revolutionary advances in the form of new, enabling reactions. Many of these developments—including cross-coupling processes,[83] trans metal-driven cyclizations,[84] olefin metathesis,[85] as well as enantiospecific oxidations[86] and reductions[87]—arose from the opening of virtually all transition and lanthanide metals and their derived reagents to exploitation in the context of synthesis. The development of chiral auxiliaries[88] for the control of relative stereochemistry, which then translates to absolute stereochemistry, was certainly among the major advances.

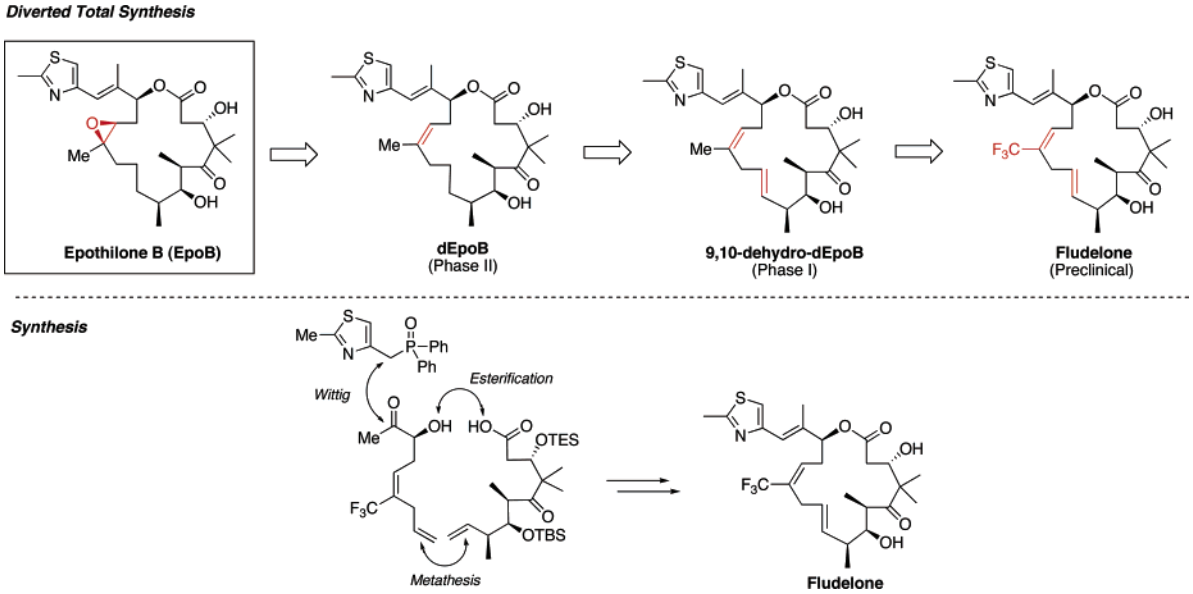
Similarly, large strides were accomplished in the synthesis of agents for biology and in the interfacing of enzymatic steps in primarily chemical synthesis programs.[89] Also, advances in the synthesis of polypeptides and oligonucleotides and, more recently, huge steps forward in the synthesis of oligosaccharides, render such structures within the purview of chemical synthesis. The goal in practical synthesis is to "get there" and to do so in the most time-efficient and economy-efficient fashion. Whether this involves purely chemical methodology or whether it involves recourse to enzymatically mediated processes, including bioreplicative synthesis, is a decision that should be driven by purely practical considerations, which take into account time, cost, and scale.

In summary, the intervening 70 years since Bachmann[9] have certainly seen basic advances in what one might refer to as the strategy of synthesis. A seminal innovation in this regard was the formalization of retrosynthesis, particularly by E. J. Corey and associates, including the evaluation of criteria for selection of optimal total synthesis pathways. The longifolene total synthesis by Corey[2d] was pivotal in the promulgation of contemporary systematic retrosynthetic analysis. Needless to say, each advance enabling simplification in structure assignment, not to mention advances in separation sciences, has expanded the capabilities of organic synthesis beyond the imagination of its early enthusiasts. We refer to the aggregate explosive events in synthesis and in its cognate sciences as the "quiet revolution."

That being the case, it is appropriate to ask where we go from here. Obviously, one direction to follow is "more of the same." There is still no shortage of extraordinarily interesting problems in the distinct science of chemical synthesis which will continue to entice those of a scholarly, as well as creative, bent. No one can reasonably think that we have "enough" good methodology on hand. There are still many vexatious problems that confound the best synthesizers. Even with all of the advances, ours is a fickle science of limited predictive capacity. The fact that so much success has been accomplished should not obscure the fact that there is so much that we do not know how to do at all, or can do only poorly. Hence, that school of synthesis that focuses almost entirely on enlarging the capabilities and successes of the "quiet revolution" in methodology will continue to play a profound role in the evolution of the science. It is research of this type that clarifies the realities of what can and cannot be done well, and provides solutions which, in the aggregate, revolutionize the thinking of the so-called "strategist."

However, we are convinced that the massive advances in the "know-how" of synthesis, both methodological and strategic, set the stage for exciting ventures which could not even have

SCHEME 12. Diverted Total Synthesis of the Epothilones



been imagined in the Bachmann era.[9] As a consequence of the quiet revolution, synthesis emerges as the central resource in bridging the gap between natural product studies (focusing primarily on merging isolation and structural deduction) and drug discovery. In short, the awesome power and potentialities of chemical synthesis arising from the quiet revolution have perhaps not been appropriately fathomed even by its architects, who were busily focusing on their particular scientific breakthroughs. However, with the benefit of retrospective assessment, it seems likely that with the massive enhancements from the science of synthesis, the natural products enterprise can and should reemerge as an exciting forum for pharma level discoveries, many of which could well be of value to humanity.

In this Perspective, we have attempted to underscore this forward vision, by highlighting, if only in a cursory fashion, the remarkable role which natural products have played in the fashioning of agents for human, veterinary, or agricultural applications and the way in which chemical synthesis can amplify the value of SMNPs.

VI. Personal Vignettes from Diverted Total Synthesis

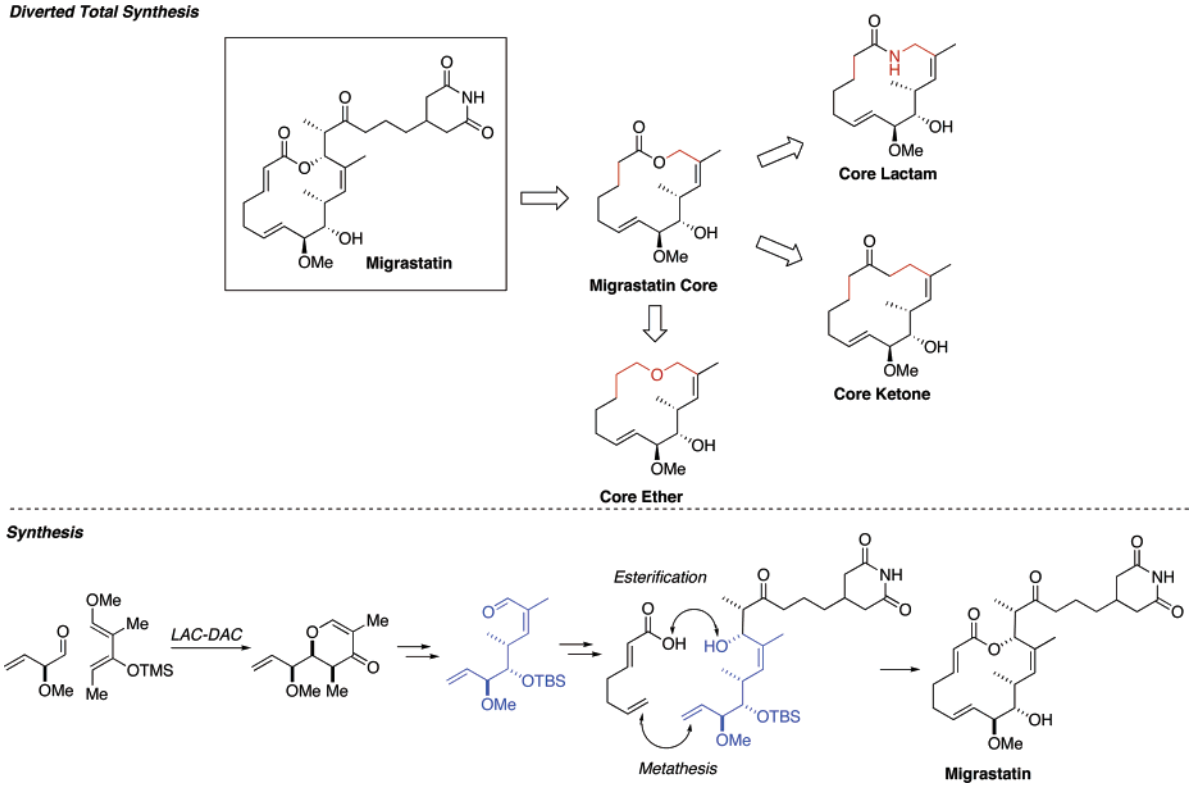
Here, we focus on a few choice examples from our own recent work from the field of diverted total synthesis. We begin by combing the literature in search of SMNPs of challenging structure and promising biological properties. In many instances, the biological profile of the natural product itself may not suffice for further development. In several of the happy cases shown below, diverted total synthesis has enabled major advances of pre-clinical promise, via structures which could not have been derived from the SMNP itself.

A. Epothilones.[53] In 1997, our laboratory disclosed the first total synthesis of Epothilone B (EpoB),[26c] a highly cytotoxic natural product with demonstrated activity against multidrug resistant (MDR) cell lines.[26] Preliminary in vivo studies with our synthetic material revealed EpoB to be highly toxic in mice, even at low doses. Suspecting the epoxide of EpoB to be a likely culprit in the observed nonselective toxicity, we prepared an analogue, dEpoB, in which the erstwhile epoxide had been deleted. Indeed, this compound has been shown to be much better tolerated in a variety of in vivo settings. Although significantly less potent than the parent compound, dEpoB retains activity against MDR cell lines. On the basis of its strong preclinical performance, this candidate has been advanced to clinical trials and is currently being evaluated in late Phase II undertakings against breast cancer.

In the meantime, our laboratory also explored the effects of various structural edits in the epothilone framework by preparing a collection of analogues through diverted total synthesis (Scheme 12). In particular, we found that the incorporation of a 9,10-double bond has positive implications in terms of restoring some of the potency that had been lost in the removal of the epoxide. 9,10-Dehydro-dEpoB, which is substantially more potent than dEpoB itself, is currently in Phase I clinical trials. Fludelone, a congener of 9,10-dehydro-dEpoB which incorporates a trifluoromethyl group at C_{26}, is an extremely promising lead candidate. Currently in late preclinical investigations, fludelone appears to possess the qualities of a true breakthrough compound. Its low toxicity, broad therapeutic index, and excellent pharmacokinetic properties are most impressive. Moreover, it is curative in the elimination of tumors in xenografts, without recurrence for periods approaching a year. Although it remains to be seen whether the promise of fludelone will be translatable to a clinical context, we have reason to be optimistic on the basis of its astounding performance in a variety of mouse xenograft models.[53]

B. Migrastatins.[90] Isolated from a cultured broth of *Streptomyces*, migrastatin has been reported to inhibit tumor cell migration with an IC_{50} of 29 μM.[91] Despite this rather modest inhibitory activity, we hoped that migrastatin might serve as a viable lead compound from which more potent analogues could be derived. Having completed the total synthesis of migrastatin and confirmed its reported activity, we began to prepare a number of structurally simplified synthetic analogues. We were particularly encouraged to find the 2,3-dihydromigrastatin core to be more potent than the natural product itself *by 3 orders of magnitude* (IC_{50} of 24 nM). Needless to say, this structurally simplified core structure cannot be easily accessed from the natural product itself, although it is readily prepared from an advanced intermediate in the synthesis of migrastatin. Despite

SCHEME 13. Diverted Total Synthesis of the Migrastatins



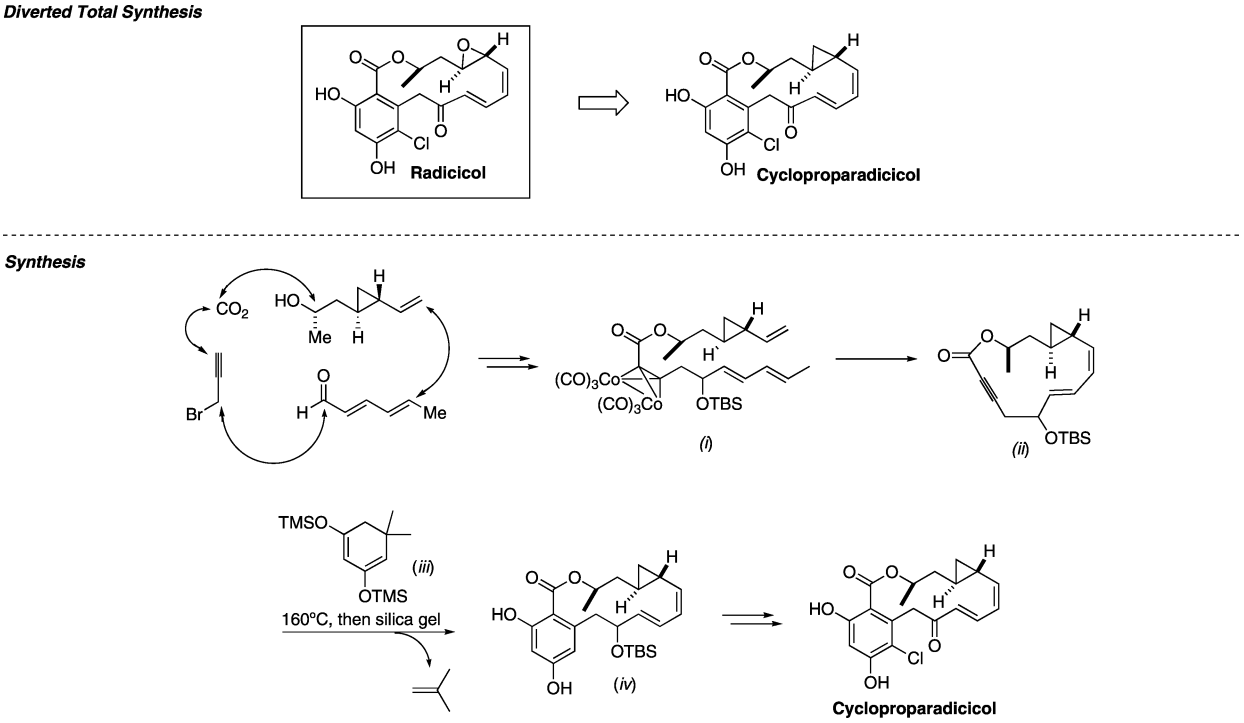
its excellent in vitro activity, the migrastatin core did not perform well in mouse plasma stability studies, presumably as a result of the lactone functionality, which renders the molecule susceptible to the action of esterases. With this consideration in mind, we synthesized a family of core analogues in which the lactone moiety was "edited" and replaced with a lactam, a ketone, and, more recently, an ether functionality. Indeed, each of these analogues was found to retain tumor cell migration inhibitory activity at nanomolar levels. Importantly, both the lactam and ketone groups exhibit markedly enhanced mouse plasma stability compared with the core lactone. Encouraging stability and efficacy studies are currently underway. At this writing, the possibility of exploiting fully synthetic products derived from DTS in the migrastatin series is being pursued in a focused manner (Scheme 13).

C. Cyclopropradicicol.[92] Radicicol, isolated from *Monocillium nordinii*, binds to and inhibits the molecular chaperone heat shock protein 90 (Hsp90) at very low concentrations (20 nM).[93] Given its role in mediating the folding of a number of oncogenic proteins, Hsp90 is considered to be an attractive target for inhibition by anticancer agents. Our laboratory developed a highly convergent enantioselective synthesis of radicicol and was able to confirm its remarkable inhibitory activity against the Hsp90 chaperone. However, biological evaluations revealed radicicol to be ineffective in the setting of in vivo animal models. We suspected that this failure might be attributable to nonspecific cytotoxicity arising from the epoxide functionality of radicicol, which could prohibitively limit the exploitable margin of the therapeutic index. The presence of the dienylepoxide moiety also raised concerns with regard to the shelf stability and pharmacostability of nonedited wild-type drugs. With these considerations in mind, we sought to design an analogue that would retain much of the potency of radicicol while alleviating some of the observed in vivo complications. We elected to exchange the epoxide moiety for a cyclopropyl group through diverted total synthesis. Thus, our first-generation analogue, termed cyclopropradicicol, was synthesized. Not the least interesting element of the DTS came in the ring-closing metathesis step. Thus, prior complexation of the acetylene linkage was critical in orchestration of the ring-closing metathesis reaction. The presentation of the acetylenic linkage in the context of the ynolide enhances its dienophilicity (see formation of *ii*). Following extrusion of isobutylene and desilylation, *iv* is produced and, shortly thereafter, cyclopropradicicol itself. The chemistry developed in this program is broadly applicable to the synthesis of a range of macrolactones based on an orsenillic acid format.

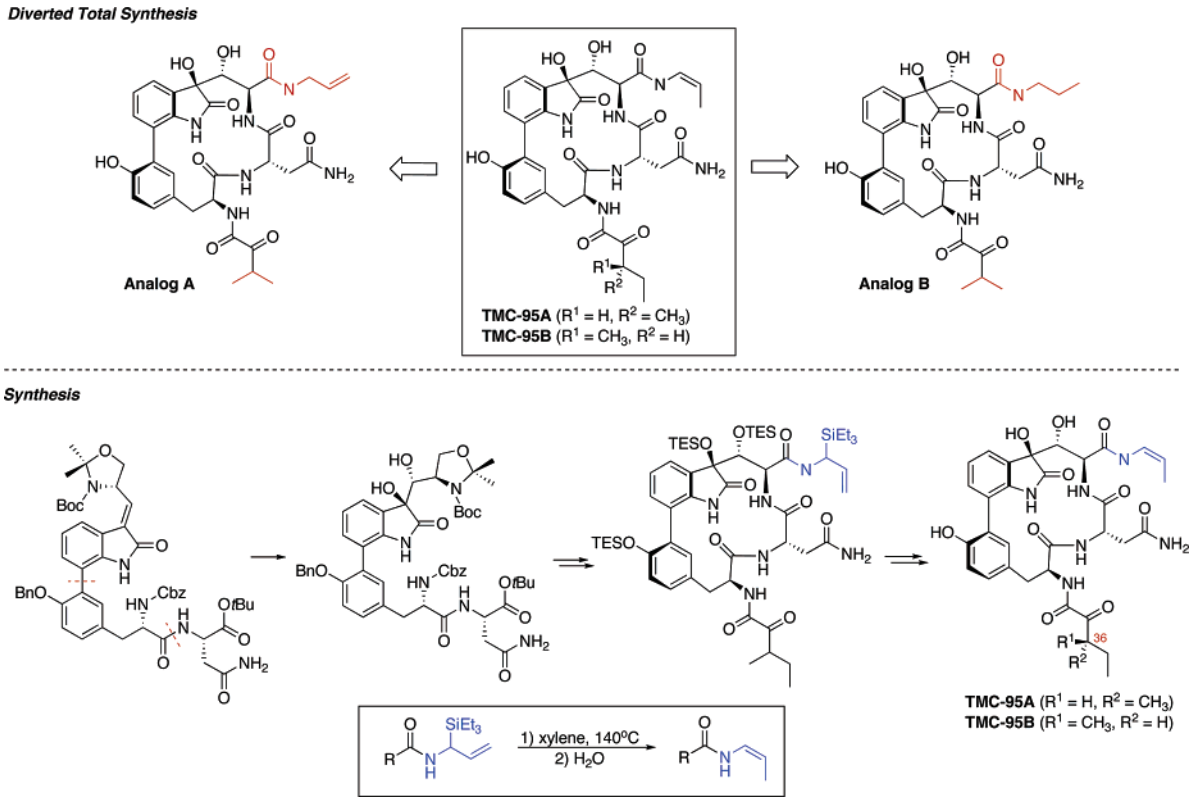
Preliminary investigations reveal that the epoxide functionality of radicicol is not critical for inhibitory activity, as cyclopropradicicol inhibits Hsp90 at 160 nM. Furthermore, introduction of cyclopropradicicol to cancer cells leads to a decrease in the expression of the Hsp90 client oncogenic proteins, Raf-1 and Her-2, and in an in vitro evaluation, cyclopropradicicol was found to inhibit MCF-7 breast cancer cells with an IC_{50} of 49 nM. Based on these results, cyclopropradicicol has been identified as a promising candidate for preclinical development. In a preliminary in vivo study against mice implanted with human colon carcinoma (HCT-116), cyclopropradicicol (75 mg/kg, QDx7, administered through i.v.-infusion) was found to effect 68% tumor growth suppression (Scheme 14).

D. TMC-95A and TMC-95B.[94] First isolated as fermentation products from *Apoispora montagnei* in soil samples, TMC-95A and TMC-95B (which differ only in the stereochemistry at C_{36}) are potent inhibitors of the 20S proteasome, with IC_{50} values in the nanomolar range. Both TMC-95A and TMC-95B were shown to inhibit three important 20S proteasome activities—chymotrypsin-like (CT-L), trypsin-like (TL), and post-glutamyl peptide hydrolytic (PGPH)—each at nanomolar levels. Inspired

SCHEME 14. Diverted Total Synthesis of Radicicol and Cycloproparadicicol



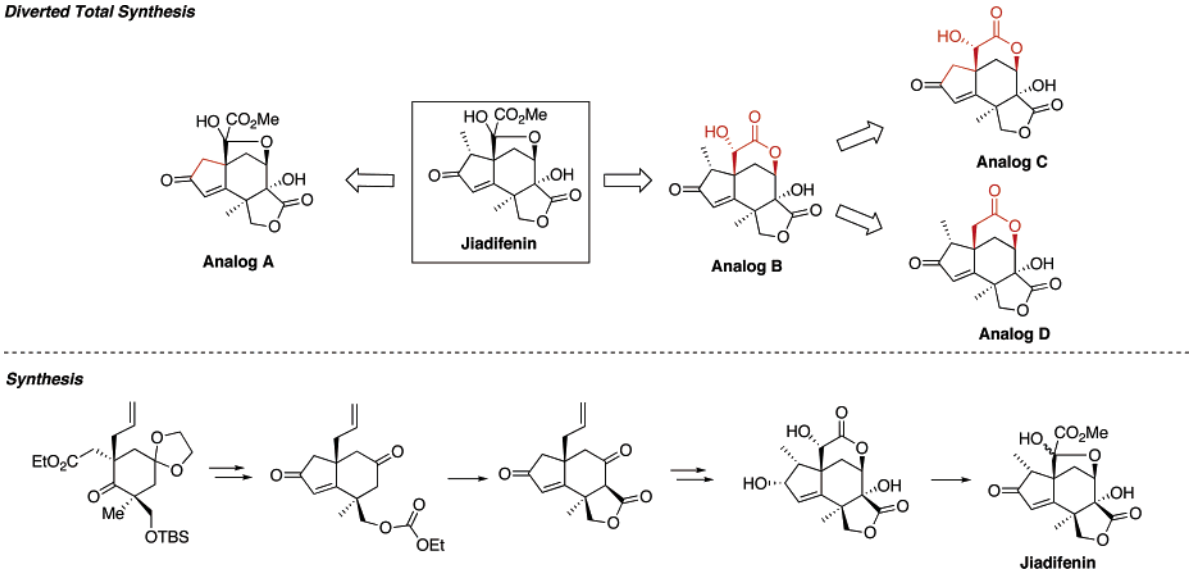
SCHEME 15. Diverted Total Synthesis of TMC-95A, TMC-95B, and Analogues



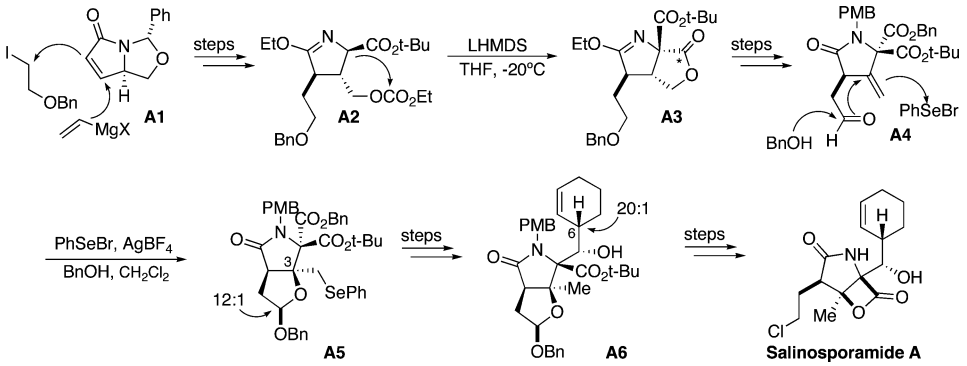
by the therapeutic potential of these cyclic peptides, we undertook the synthesis of TMC-95A and TMC-95B. This was accomplished, and, with synthetic material in hand, we were able to confirm the biological activity reported for both TMC-95A and -B (Scheme 15).

We next sought to prepare and evaluate structurally simplified TMC-95 analogues. Two obvious sectors presented themselves for structural simplification. First, we were interested in evaluating the impact of removal of the C_{36} stereocenter. Our current route required separation of TMC-95A from TMC-95B in the last stage of the synthesis. Thus, the elimination of this stereocenter through conversion of the ethyl to a methyl group would constitute a significant simplification of the synthetic route. In addition, we sought to evaluate the role of the

SCHEME 16. Diverted Total Synthesis of Jiadifenin and Analogues



SCHEME 17. Total Synthesis of Salinosporamide

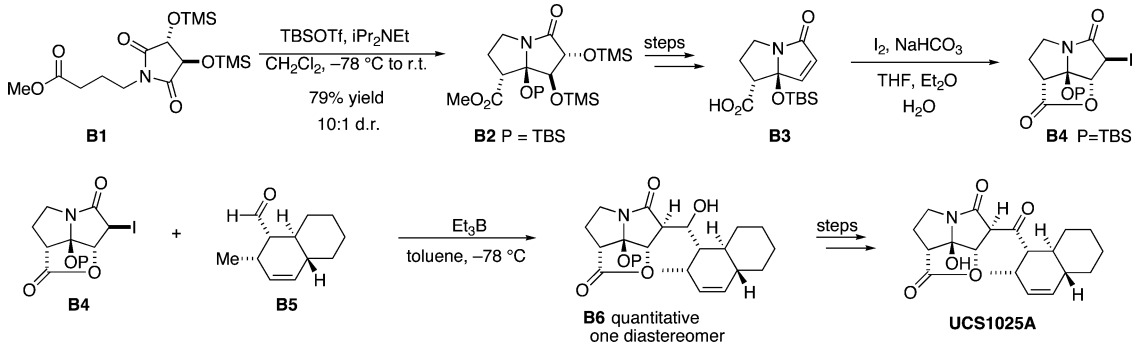


Z-enamide in the biological activity of TMC-95A and -B. Two analogues were prepared. Each compound was then compared with the natural products for inhibition of the three types of 20S proteasome activities described above (CTL, TL, and PGPH activity). Interestingly, analogue **A** preserved the full inhibition potency against each of the three types of proteases, thus suggesting that the presence of the C_{36} stereocenter is not a requirement for biological activity. Compound **B**, however, was markedly less potent than were the natural compounds, indicating that the amide side chain requires a certain level of rigidity. In the case of TMC-95A, it would be necessary to achieve still further simplifications of structure if diverted total synthesis were to be practiced. However, these results already serve to further highlight the important role that total synthesis and diverted total synthesis can play in the charting of constructive directions for drug discovery.

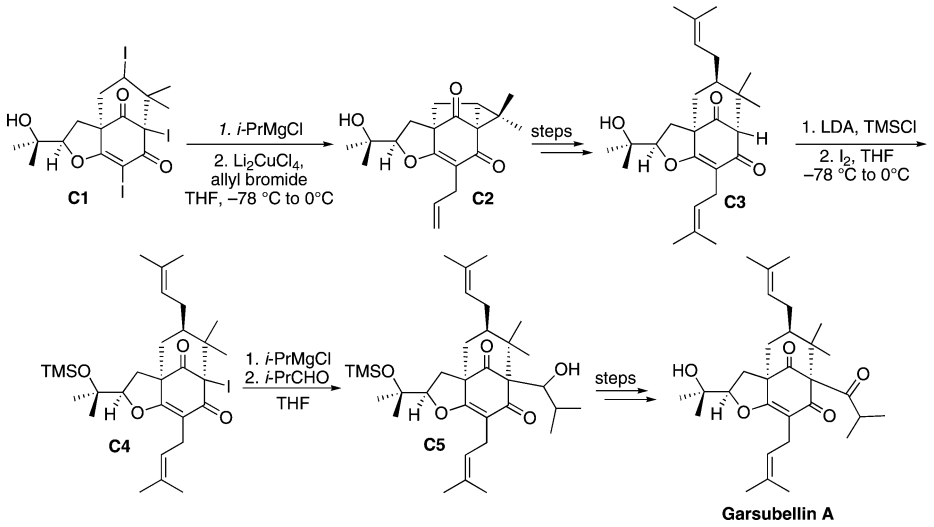
E. Jiadifenin.[95] Isolated from the *Illicium jiadifengpi* species of China, jiadifenin has been reported to promote neurite outgrowth in rat cortical neurons.[96] In the context of our broad-based program devoted to the total synthesis of neurotrophically active compounds that might serve as lead agents in the development of treatments of neurodegenerative disorders, we undertook to synthesize jiadifenin (Scheme 16). With this task accomplished, we were able to corroborate the reported activity with our synthetic material. Thus, in the presence of NGF, jiadifenin enhanced neurite lengths by 162%, while in the absence of NGF, no neurite outgrowth was observed. This suggests that jiadifenin operates by upregulating the action of NGF rather than functioning independently. In addition to the natural product itself, we were able to modify our synthetic pathway to gain access to a number of analogues. Notably, compound **B** (a direct synthetic precursor to the natural product) was found to be more active than jiadifenin itself, increasing neurite lengths by as much as 184%. The normethyl congener (**A**) was similarly potent, providing an enhancement of 181%. Interestingly, the unrearranged normethyl analogue (**C**) displayed only moderate activity in this assay, suggesting a somewhat complex SAR profile for jiadifenin. We also found that the congener in which C_{10} is unoxidized (**D**) exhibits no neurite length enhancement. Once more, it is of note that these analogues represent manipulations of chemical space that would not be readily accessed from the natural product itself, even if it were available. However, through slight modifications of the synthetic route to jiadifenin, we were able to obtain sufficient quantities of a variety of interesting congeners, which will themselves serve as valuable lead compounds for development. Of course, the translation of in vitro level findings to the discovery of CNS-active drugs in humans is at a very early stage. However, the work already shows how chemical synthesis can be a valuable and "doable" resource in the discovery of early lead structures.

In closing, we emphasize the need for sensible project selection if DTS is to be practiced. For those who, like ourselves, insist on chemical novelty in our synthetic ventures, inciteful

SCHEME 18. Total Synthesis of UCS1025A



SCHEME 19. Total Synthesis of Garsubellin A



structural complexity is a necessary condition. The reported biological profile should be testable. The synthesis, while challenging and of teaching value to the cognoscenti, should not be of such a multistep nature as to disincentivize (perhaps by sheer exhaustion!) the biological follow-up. As in all good science, in the practice of DTS there is no substitute for judgment.

VII. Recent Vignettes from Our Laboratory: Studies of the Total Synthesis of Natural Products

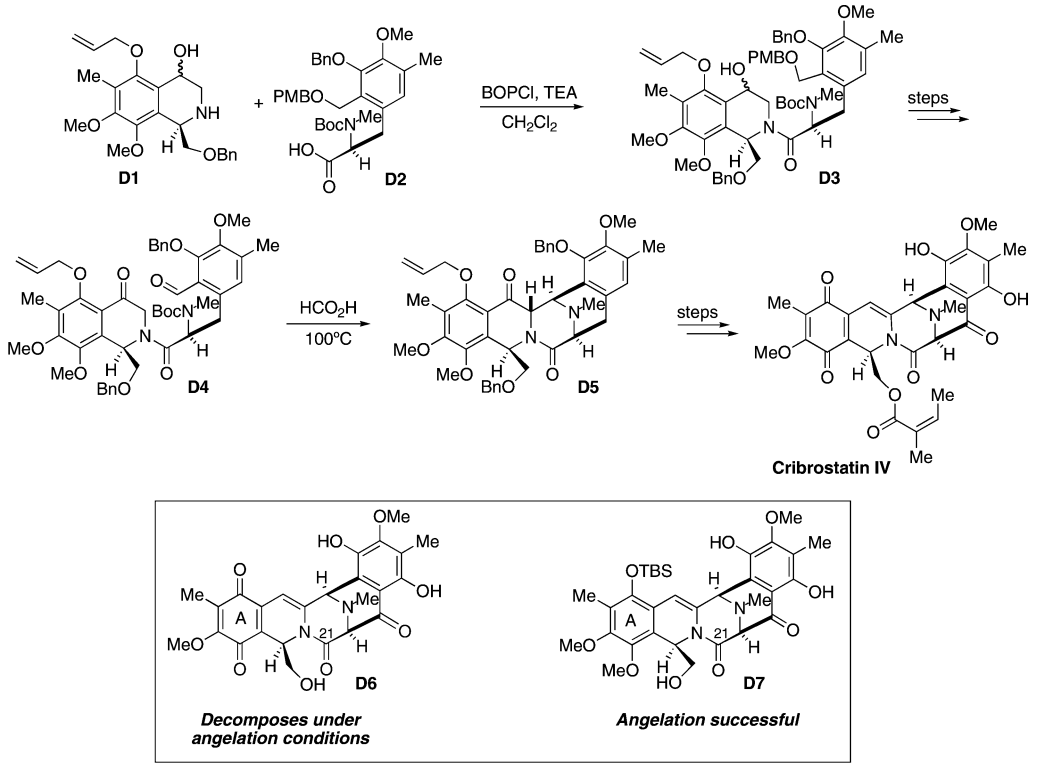
Remarkably to us, even after the nearly 70 years following the historic disclosure of Bachmann,[9] the field of total synthesis of natural products retains all of the excitement, vibrancy, drama, and fascination that it must have held for its early brave pioneers. To say this is not to lose perspective regarding the emergence of other opportunities for organic chemistry, which surely provide formidable competition for the commitments and affiliations of aspiring scientists. Clearly, there are great opportunities "out there", for instance in material sciences, in imaging as well as other forms of bio-diagnostics, in computation, and in the elucidation of the labyrinthine complexities of proteomics. Nonetheless, huge advances in the separation sciences and in the capacity for elucidation of gross, as well as three-dimensional, structures on tiny amounts of materials[97] point to the robustness of inexhaustible reserves of fascinating, mind-expanding structures which challenge those who are not only willing to live dangerously *but also, perhaps, secretly enjoy doing so*.

Total synthesis offers a clear-cut challenge, not only to the putative synthesizer but, more importantly, to the field itself. Each successful total synthesis underscores in a small but meaningful way the state of the art of the science we call organic chemistry. The quality and style of a total synthesis serve parenthetically as a report card, not only on the scientist but on the science itself.

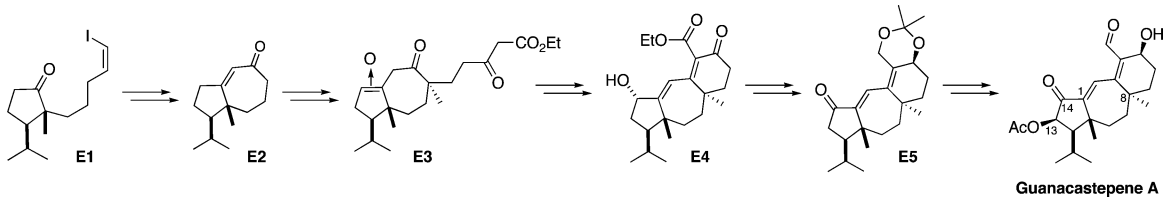
No one in 2006 and beyond can doubt that, in principle, virtually every structure within reason can be synthesized if enough resources (including time!) are applied to the problem. The stunning record of successes from equilenin[9] to ciguatoxin[33] suggest that no SMNP structure is inaccessible to total synthesis. Though many goal systems are still very difficult, and success in a foreseeable time span cannot be assured, we would assert that total synthesis has outgrown the mountain climbing phase, though the challenges may still be severe.

If this obvious point is accepted, the emphasis on finishing first, which was so prevalent during the earlier stages of total synthesis, should be "down-regulated." Since the feasibility, in principle, of complex molecule total synthesis is no longer under challenge, the imperative to finish first, although in keeping with human nature, is correspondingly diminished. The real issues of contemporary total synthesis are more subtle and more sophisticated than sheer demonstrations of feasibility and order of crossing the finish line, however exhausted. The major determinants of contemporary total synthesis may well be in problem selection, synthetic style, and teaching potential—in summary, quality. A great goal remains that of creating new

SCHEME 20. Total Synthesis of Cribrostatin IV



SCHEME 21. Total Synthesis of Guanacastepene A



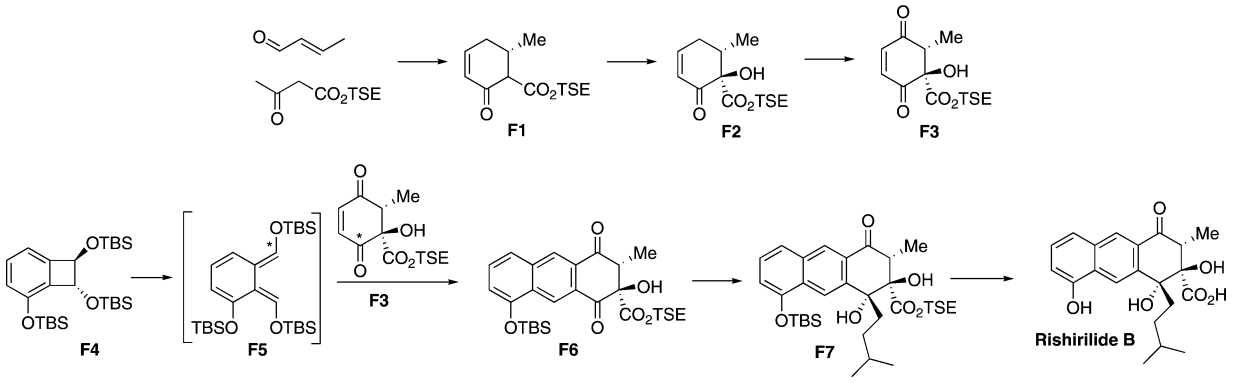
science as we go along. The prod value of these structures to create broadly useful chemistry will no doubt contribute to the freshness and vitality of synergism between synthetic methodology and total synthesis. From our admittedly personal perspective, the ultimate "big picture" challenge is that of reintegrating natural products in the advancement of medicine via the increasingly awesome power of chemical synthesis.

The closing section of this Perspective provides brief accounts of key elements of some recently completed total syntheses from our laboratory. In each instance, at least one paper has been published which can help direct the reader to initial circumstances of isolation and the early biological profile of the SMNP. Hence, in this section, we hope to focus on some key transformations (magic moments!) which were enabling and central in the realization of the total synthesis goal. The reader we hope to reach will, of course, realize that these vignettes correspond to snapshots of particularly pleasing elements of complex undertakings. That reader will also appreciate that total synthesis is not for the fainthearted. It is a field of great challenge and complexity. With the great uncertainties, as steps depart from the norm, come long intervals of disappointment and even angst. However, for those who have the staying power to see these matters through, there are great advances to be achieved for the field of synthesis itself and, as discussed above, for applications to the broad and critical field of drug discovery.

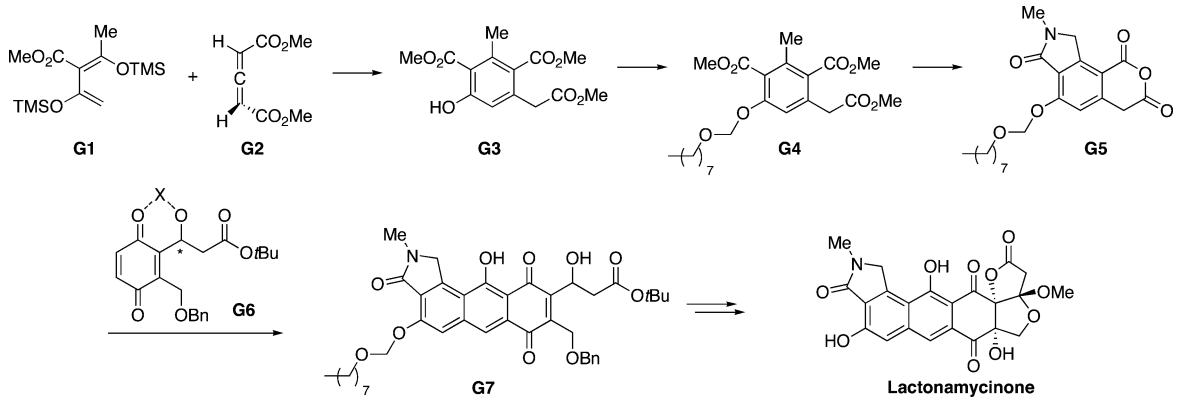
A. Salinosporamide.[98] There were several key teachings in this synthesis (Scheme 17). First, we note the use of the pyroglutamate-derived unsaturated lactam (**A1**). Successive nucleophilic and electrophilic alkylations led eventually to **A2**. This led to a critical phase of the study, i.e., differentiation of the two acyl groups of the malonyl equivalent at C_5 (see asterisk, **A3**). Happily, we were able to fashion the terminal methyl group in this compound by an intramolecular oxy-selenation. The nucleophile formally corresponds to the aldehyde of **A4** or perhaps its benzyl alcohol-derived hemiacetal. In any case, this methodology leads to **A5**, which carried sufficient elements to reach salinosporamide. Clearly, the closing phases of our salinosporamide synthesis were heavily mortgaged to the spectacular total synthesis of this compound first accomplished by Corey and associates.[61]

B. UCS1025A.[99] The key enabling cyclization is that of **B1** to **B2**, which occurs via the silyl ketene acetal derived from the ester carbonyl group of **B1**, as implicit in the work of Hoye and Dvornikovs.[100] The tartramide chirality of **B1** has, in effect, been transferred to C_{2a} as well as to the tertiary alcohol center at C_2. Ultimately, the tartramide centered stereogenicity is removed, though not without difficulties, to create the unsaturated lactam shown as **B3**. This compound serves as a substrate for iodolactonization, leading to **B4**. The latter undergoes a quite novel and remarkable (but predicted) boron-mediated coupling

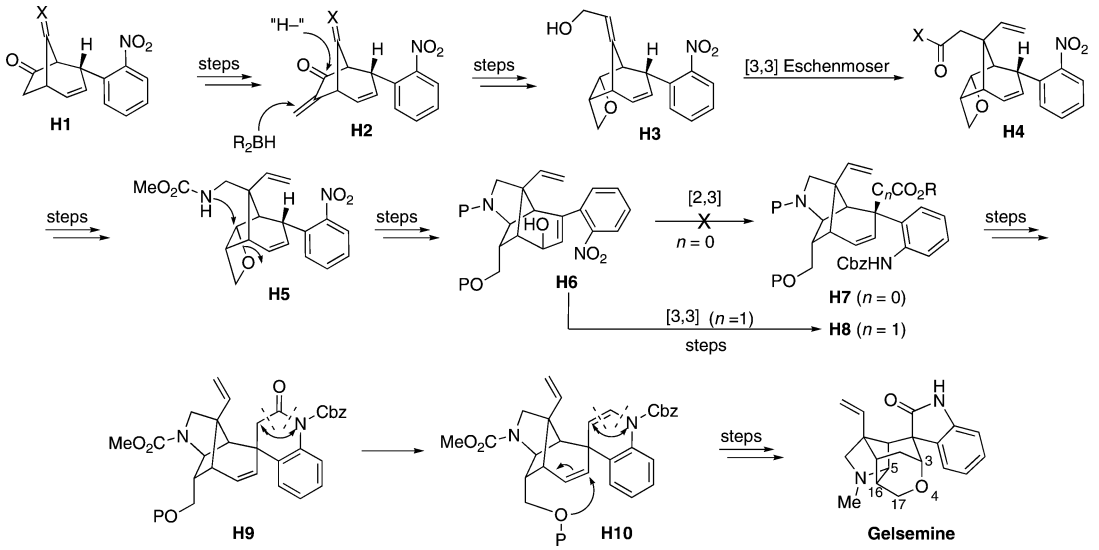
SCHEME 22. Total Synthesis of Rishirilide B



SCHEME 23. Total Synthesis of Lactonamycinone



SCHEME 24. Total Synthesis of Gelsemine

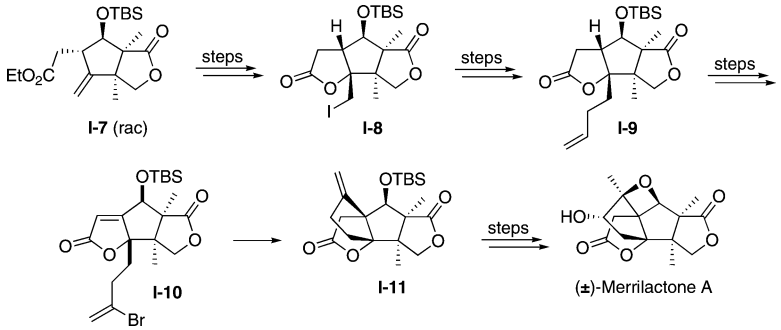


reaction with aldehyde **B5** to provide the aldol product **B6** and, soon thereafter, the SMNP UCS1025A (Scheme 18).

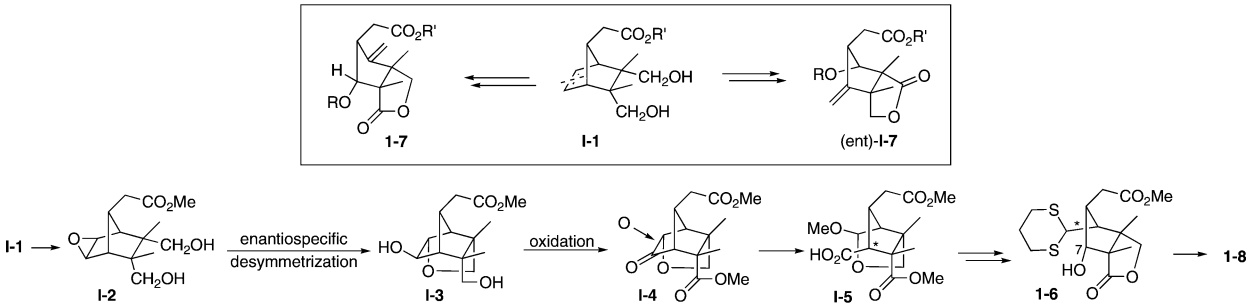
C. Garsubellin A.[101] Many fascinating transformations were involved in achieving the total synthesis of garsubellin A. Not the least interesting among them was the formation of the spiro-activated cyclopropane, **C2**, by a reductive cyclization of **C1**. The pathway from **C2** to **C3** involved a Keck-type allylation of a secondary iodo-function derived from **C2**, as well as a 2-fold cross-metathesis reaction to convert allyl functions to the required prenyl groups. Success was eventually attained by a rather novel β-dicarbonyl flanked bridgehead dicarbanion derived from **C4**. The aldol product, **C5**, was soon converted to garsubellin A (Scheme 19).

D. Cribrostatin IV.[102] The total synthesis of cribrostatin IV involved several demonstrations of novel chemistry (Scheme 20). The defining step was the cyclization of **D4** to **D5** by an intramolecular lynchpin Mannich-type cyclization. Another interesting feature of cribrostatin is worth noting in passing. Having reached intermediate **D6**, we discovered that the anticipated concluding angelation reaction could not be carried out in practice, thereby threatening the whole enterprise. Upon further analysis of the problem, it was recognized that inter-

SCHEME 25. Total Synthesis of Racemic Merrilactone A



SCHEME 26. Access to Enantioenriched Merrilactone A



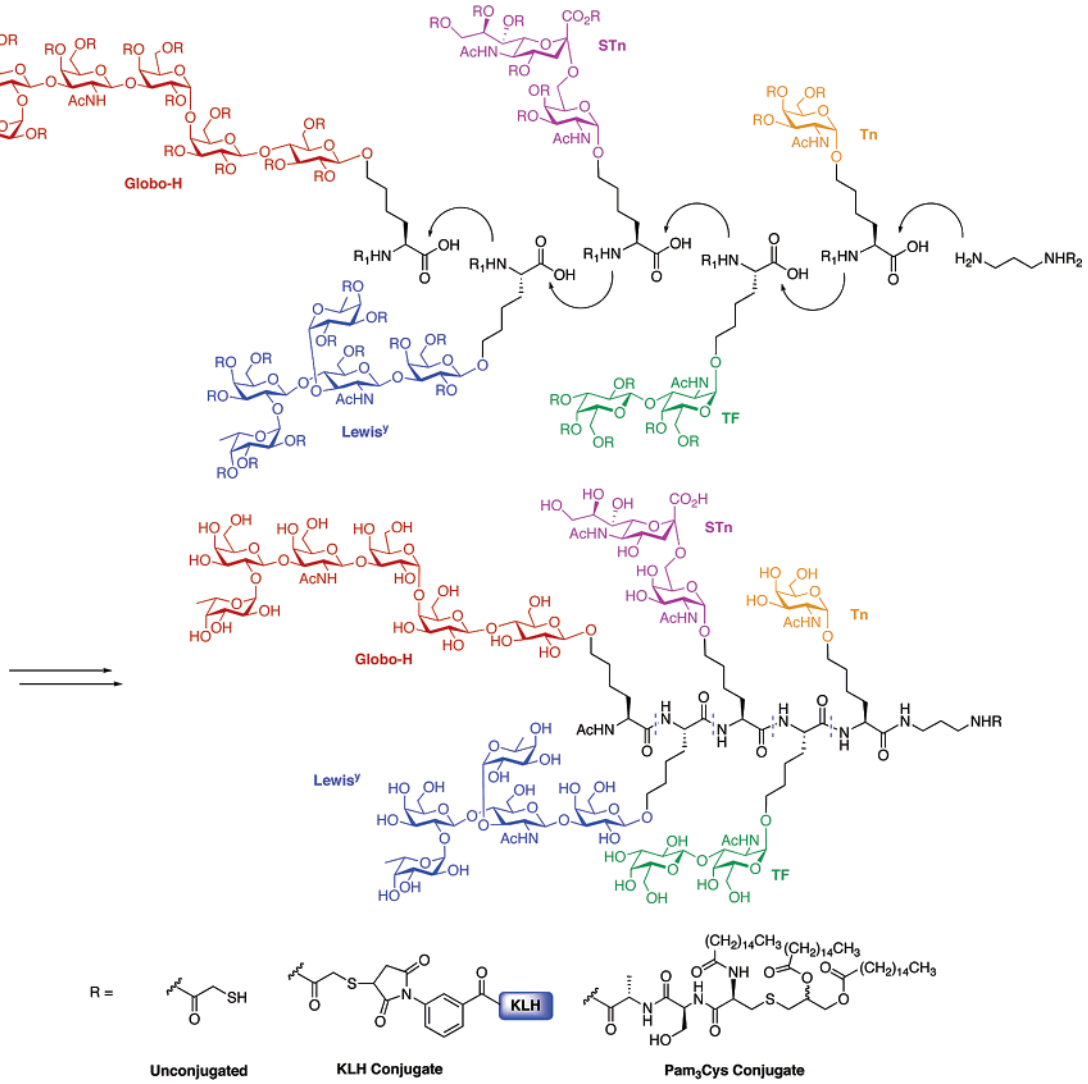
mediate **D6** contains at once vinylogous imide and β-dicarbonyl linkages. Accordingly, its vulnerability to reverse Dieckmann-like reaction could be readily rationalized. The problem was solved by modifying the synthesis such as to conduct angelation at the stage of **D7**. In essence, we used the A ring as a switch to modulate the character of the C_{21} carbonyl function. With ring A quinonoidal, as in **D6**, C_{21} is a vulnerable vinylogous imide linkage. On the other hand, with the A ring in protected hydroquinoidal form, as in **D7**, the C_{21} carbonyl function is amidic in nature and, not surprisingly, quite robust. The cribrostatin effort in its terminating phase was an exercise in fine-tuning of chemical character by remote control. The reader is referred to the original paper, which teaches how the nontrivial differentiation of the southwest and northeast aromatic sectors was accomplished, and how all of the diverse functionalities of cribrostatin IV were orchestrated in the synthesis.

E. Guanacastepene A.[103] The total synthesis of guanacastepene A was recently accomplished, though not without the need to overcome some significant hurdles (Scheme 21). Surely, one of the key phases of the synthesis involved reaching **E2** by reductive cyclization of **E1**. The issues associated with this nontrivial step are described in our full treatment of the synthesis.[103i] The stereospecific construction of the quaternary asymmetric center at C_8 was a novel feature of the synthesis (see **E3**). A seemingly straightforward cyclization which would have been expected to readily establish the six-membered ring, required, in practice, prior oxidation of the $C_{14}-C_1$ double bond. Epoxidation set the stage for β-elimination of the C_1 oxido bond, enabling a high-yielding Knoevenagel-like cyclization. Not the least element of interest in the total synthesis of guanacastepene A was the late-stage acetoxylation at C_{13}, wherein attack had occurred on the β-face syn to existing isopropyl and angular methyl functionalities. This matter has recently been rationalized at the computational level.[104]

F. Rishirilide B.[105] This synthesis was undertaken to investigate the use of 1,2-silyloxybenzylcyclobutenes in organic synthesis (Scheme 22). The notion is that the silyloxy groups will prompt opening of the benzocyclobutene to generate the "out, out" stereoisomer (see **F5**). We further sought to study whether even a highly reactive Diels–Alder diene, such as 1,2-bisquinonedimethide, might be perturbed in a systematic way by the presence of the silyloxy function in the aromatic ring. In the case of **F5**, the resident silyloxy group on the aromatic ring is so positioned to favor initial bond formation at the meta double bond of diene system (see asterisk). At the same time, we hoped to explore another interesting question. Consider the ene–dione linkage of putative dienophile **F3**. The issue we hoped to address was whether the hydroxyl function, by hydrogen bonding to its *o*-carbonyl group, would serve to activate the double bond in a selective way, such that the ketone of the β-keto ester linkage (see asterisk) would be the dominant activating function of the ene-dione. Were these contingencies to transpire, the alignment of **F3** synthesized by classical chemistry, as indicated above, would occur in a fashion such as to lead specifically to **F6**. Happily, this in fact occurred. That the free hydroxyl group was strategic to the outcome is inferable from the fact that reaction of the corresponding silyl ether results in the formation of a one-to-one mixture of cycloaddition products. Another pleasing feature of the synthesis is that the same hydroxyl group, which we believe directed the Diels–Alder reaction, serves to direct nucleophilic addition to its proximal ketone leading to the formation of **F7** and, shortly thereafter, rishirilide B itself.

G. Lactonamycinone.[106] As in the case of rishirilide B, the total synthesis of lactonamycinone, the aglycone of lactonamycin, was undertaken with a view toward clarifying some issues and exploring some new possibilities in the Diels–Alder reaction which seemed very interesting to us (Scheme 23). We had studied the dienophilicity of the symmetrical allene, **G2**, many years earlier, with synergistically activated dienes.[107] In this effort, we came to wonder whether a complex diene of the type **G1**, which carried potential vulnerabilities of 1,1-disub-

SCHEME 27. Unimolecular Pentavalent Vaccine Construct

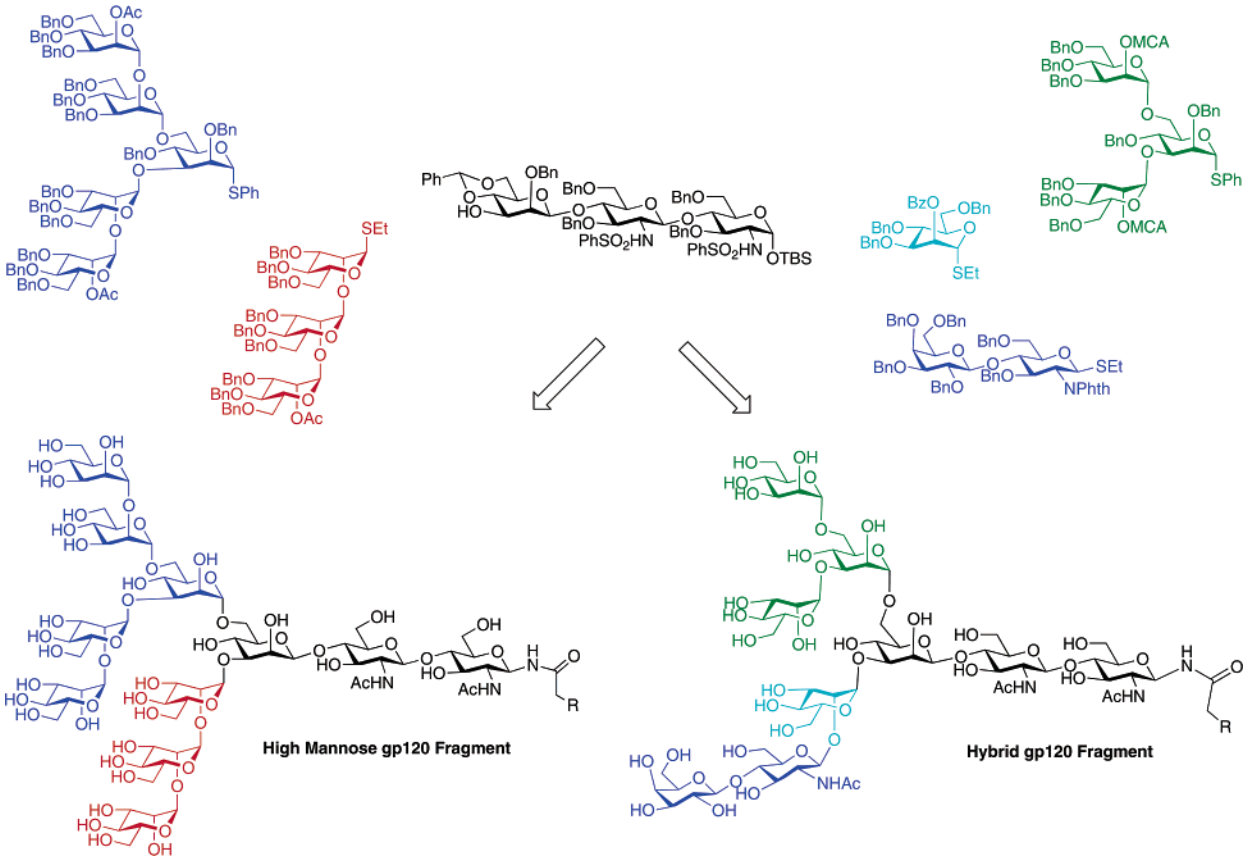


stitution as well as potential deactivation by the presence of the ester group, would function in a Diels−Alder setting. In the event, cycloaddition occurred in a satisfactory fashion, yielding **G3**. The availability of this complex aromatic structure in such a concise fashion prompted us to ask another Diels−Alder-level question. Thus, **G3** was converted to **G5** by straightforward steps. As a complementary dienophile, we synthesized **G6**, bearing a hydroxyl group on the side chain of a 1,2-disubstituted quinone (see asterisk). We wondered whether the hydrogen bonding (or metal chelation) possibilities of this strategically placed oxygen function (see asterisk) would perturb the quinone linkage to the point where the *o*-carbonyl group (see asterisk) would be selectively activated through hydrogen bonding, thereby enabling it to emerge as the dominant carbonyl group in controlling the sense of Diels−Alder reaction of the unsubstituted double bond of the quinone. Happily, this turned out to be the case as **G5** and **G6** coupled smoothly in a Diels−Alder like fashion, generating in one step **G7**. The conversion of **G7** to lactonamycinone was itself a surprisingly difficult undertaking but, in the end, proved to be doable, thereby allowing for the achievement of the total synthesis of this aglycon.

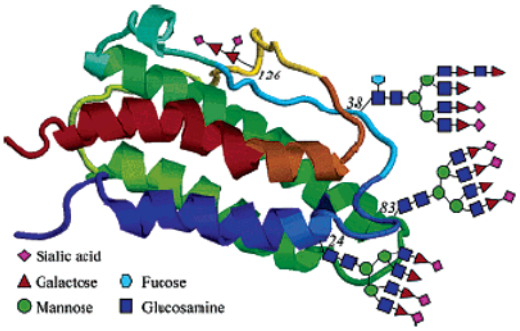
H. Gelsemine.[108] The total synthesis of gelsemine was undertaken, not in the search of new leads for medicine, but to explore some issues which, while speculative, were intriguing to us (Scheme 24). The crux of the problem of building gelsemine in the laboratory in the $C_{16}-C_{17}-O_4$ area is that the latter two atoms are found in a very hindered circumstance. Our notion was that the required *endo*-centered hydroxymethyl group at C_{16} would be produced from an *endo*-oxetane embracing C_5 and C_{16}. A nitrogen-based nucleophile, housed at C_{21}, would displace the oxetane C−O bond at C_5, thereby generating the C_{16} hydroxymethyl on the hindered *endo* face. In the later stages, the hydroxyethyl group would join to C_3 by an intramolecular hydroxymercuration.

The oxetane would be generated from an earlier C_5 ketone, which would be advanced to an α-methylene lactone, as we described almost three decades earlier.[109] The reduction of the ketone at C_5 and hydroboration of the methylene group at C_{16} would each occur from the *exo*-face, thereby creating the basis for building the key *endo*-situated oxetane. The nitrogen nucleophile to establish the $N-C_5$ bond was introduced by Shiori−Curtius degradation of a two-carbon acid. The latter, in turn, arose from a [3,3]-sigmatropic rearrangement of a genre anticipated many years earlier by the late W. S. Johnson and collaborators.[110] Happily, these extended speculations could be realized as shown by the cyclization of **H5**, which enabled

SCHEME 28. High-Mannose and Hybrid gp120 Fragments



SCHEME 29. Structure of Erythropoietin (EPO)



eventual access to **H6**, bearing a β-situated allylic alcohol at the future C_{14}.

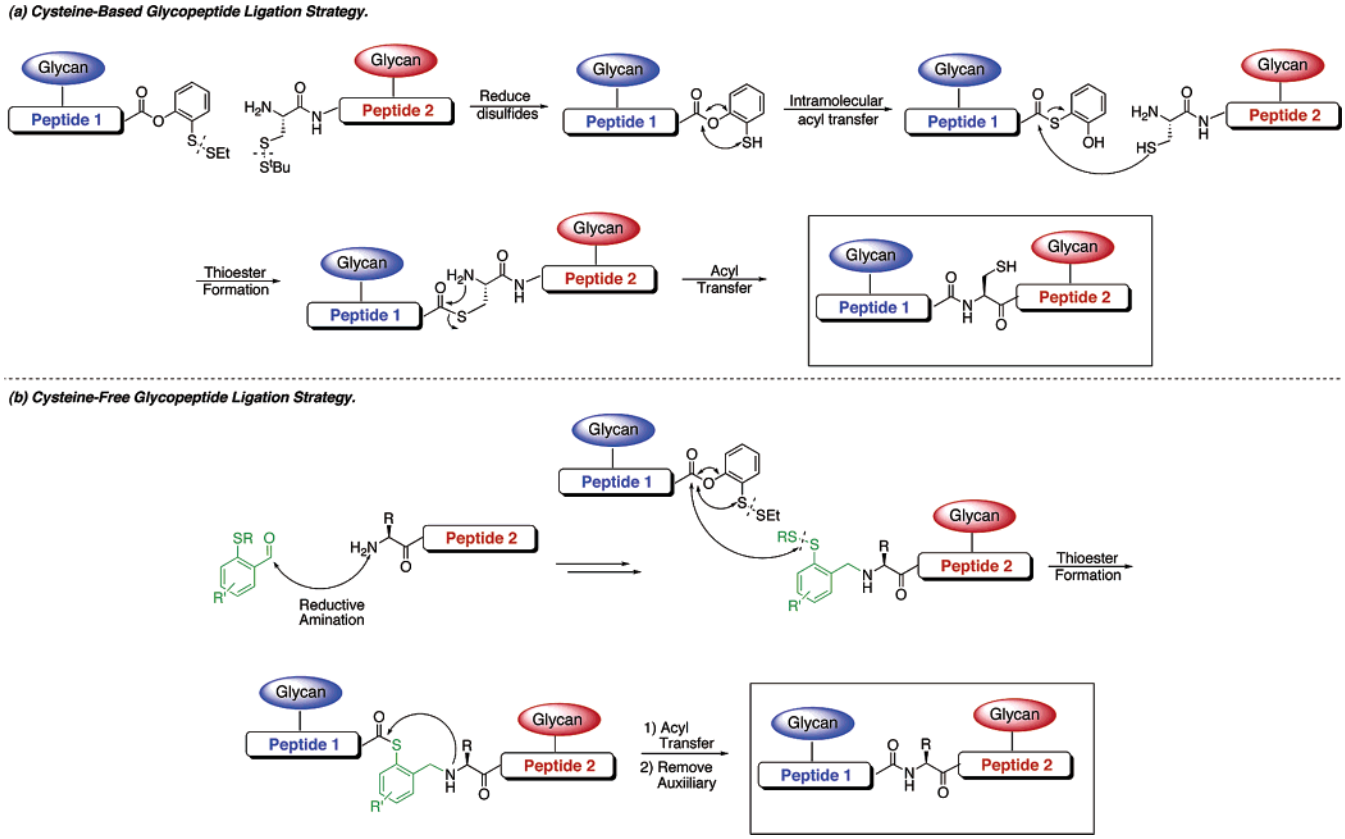
Now it was our original plan to achieve, with compound **H6**, transformation to **H7** by some version of a [2,3]-sigmatropic rearrangement. Were this to have been successful, there would have been established a properly β-situated C_1 ester ($n = 0$), which would have been well-positioned to generate stereospecifically the spiro-oxindole of our target structure. Unfortunately, we were unable to achieve any [2,3]-sigmatropic rearrangement which would be in keeping with the original synthetic plan. Frustrated but not defeated, we turned our attention to salvaging the basic elements of our blueprint. Happily, it was possible to achieve a [3,3]-sigmatropic rearrangement under protocols pioneered many years earlier by Eschenmoser and associates (see conversion of **H6** to **H8**).[111] Following lactam formation, compound **H9** was in hand. The conversion of **H9** to the spiro-oxindole, even in the context of potentially competing functionality, was not of a type that could be confidently projected in advance (see carbonyl group to be excised in structure **H9**). Fortunately, it was possible to convert **H9** to its derived "ene-urethane" by reduction and dehydration (see **H10**). This linkage lent itself to dihydroxylation and cleavage, generating an imide-like formamide which further hydrolyzed and cyclized, leading, eventually to gelsemine itself.

I. Merrilactone A.[112] A key phase in our total synthesis of the nonpeptidyl neurotrophically active natural product, merrilactone A, started with an iodolactonization step (**I-7** to **I-8**) (Scheme 25). This step was followed by a Keck-type free radical driven allylative chain extension[113] (see **I-8** to **I-9**). In a concise way, **I-9** was converted to **I-10**. It was envisioned and, in turn, demonstrated that free-radical mediated cyclization of **I-10** would give rise to the propeller-like structure, **I-11**.

Not surprisingly, **I-11** could be converted, in time, to racemic merrilactone A itself. Though the total synthesis had been completed, the total synthesis problem was revisited for the purpose of providing a more selective route to **I-7**. We also sought a route which would be capable of delivering either enantiomer of this γ,δ-unsaturated acid.

A plan emerged to accomplish this goal. An interesting Diels−Alder alkylation sequence was fashioned to reach **I-1**. For our purposes, it would be necessary to go from **I-1** to **I-2**. Such a transformation inherently posed an issue of regiocontrol. The degradative scheme, at the end, had to place the −OTBS group β to the lactonic carbonyl function. Correspondingly, the exocyclic methylene group must appear β to the methylene carbon of the γ-lactone. At the level of relative stereochemistry, the oxygen introduced at the future C_7 must be *anti* to the two tertiary methyl functions. Finally, at the level of absolute

SCHEME 30. Cysteine-Based and Cysteine-Free Glycopeptide Ligations[112]



stereochemistry, we wanted to be able to reach a compound of the type **I-7** or ent-**I-7**.

A pleasing solution to these multiple issues presented itself and proved to be implementable. *Exo*-face epoxidation of **I-1** leads to **I-2** (Scheme 26). Enantioselective desymmetrization of achiral **I-2** (itself prepared by a Diels−Alder *C*-methylation sequence) was accomplished by the use of the two antipodes of [Co(III)(salen)] as pioneered in the elegant studies of Jacobsen and associates.[114] For instance, use of the *S,S*-catalyst led to **I-3** with high enantioselection. This set the stage for a regiodefined and pleasing degradative sequence. The progression started with oxidation of **I-3**, both at its primary and secondary alcohol centers, leading to keto-acid **I-4**. Perhaps not surprisingly, it proved possible to interpolate oxygen in a Baeyer−Villiger sense, as shown (see arrow in **I-4**). The Baeyer−Villiger product generates, in effect, aldehydo- and acyl-like differentiation in the oxidation levels of the formal ester linkage. Indeed, the resultant "lactone" could be manipulated so as to store the aldehyde in the form of its cyclic methyl glycoside, while revealing a strategic and stereodefined carboxyl function (see asterisk in **I-5**). This set the stage for a carboxy-inversion reaction which generated the appropriate secondary alcohol. Conversion of the aldehydo center, earlier stored as its dithiane derivative (see asterisk in **I-6**), led eventually to the *exo*-methylene group (see **I-7**), and, following iodolactonization, to **I-8**. Not surprisingly, use of the antipodal Jacobsen catalyst led to *ent*-**I-8**. Thus, access was gained to either antipode of merrilactone A, enabling a more searching evaluation of its biological properties and their dependence on absolute stereochemistry.

We conclude this section with a most cursory overview of our activities in the oligosaccharide area. While, from a purely chemical perspective, many issues remain as one attempts to synthesize complex oligosaccharides, the total syntheses already accomplished open up major possibilities for biological follow-through studies. A few particularly exciting possibilities are shown below.

J. Unimolecular Pentavalent Anticancer Vaccine.[62b,115] One of our long-standing goals is to create a clinically useful *fully synthetic* anticancer vaccine based on carbohydrate tumor antigens. In Scheme 27, we show how such a vaccine has been put together using glycosido amino acid spacers. In this way, a complex peptide containing all of the antigenic components currently known to be associated with breast cancer has been assembled. Clinical trials of this construct, shown in Scheme 27, are planned for 2007.

K. HIV Vaccine.[116] Still another possibility is the building of complex agents that might be used in an anti-HIV vaccine. The thought in this project was to simulate the characteristics of gp120, in the context of a relevant glycopeptide. The glycopeptide is selected to present what we perceive to be a simulation of the natural architecture of gp120. As has been reported,[116] these total syntheses have been accomplished. Constructs arising from these syntheses are in early preclinical evaluation with respect to applicability to an HIV vaccine (Scheme 28).

L. Erythropoietin (EPO).[117] In our view, the ultimate benchmark in the synthesis of oligosaccharides arises when the complex carbohydrate is incorporated into the context of a biologically relevant glycoconjugate, such as a glycoprotein or glycolipid. An overarching challenge to our laboratory in that respect is the total synthesis of homogeneous erythropoietin (Scheme 29). Though we are still far from accomplishing this formidable goal, our laboratory has made substantial progress

in building enabling technologies which render a total synthesis of EPO an entertainable prospect. *The chemistry shown in Scheme 30 is already applicable to the construction of complex glycopolypeptides with complete structural definition.*

We close this Perspective by reiterating a few general observations. First, it is our contention that the opportunities for total synthesis have never been greater. It is clear that these opportunities are realizable only in the context of continuing advances in the allied field of synthetic methodology. It is such methodological advances which enable evolution of synthetic logic directed to complex targets. The range of possibilities still challenges the capacity of even the most inquisitive of minds. No doubt, future generations of synthetic organic chemists will be tackling even more complicated problems at the frontier of organic chemistry which touch on fascinating issues in biology and even medicine. In short, complex molecule total synthesis is not only alive and well but, indeed, prospering all the time.

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