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Observations on the State of Synthesis: Some Magic Moments Revisited

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Introduction There are many considerations that might entice chemists to undertake the synthesis of target systems of some complexity. Historically, rational synthesis was perceived to provide the ultimate confirmation of structure. It was tacitly assumed that synthesis could not deliver the goal substance unless the structural assignment around which the plan had been organized was correct. Implicit in this line of reasoning is the presumption of unfailing rationality in the conduct of a synthesis and in the assessment of the information loop arising from synthetic experiments. I shall return to this matter shortly.

Another type of incentive is that of augmenting access to a substance, otherwise available through natural sources such as phytochemistry or fermentation. If this is to be the primary motivation in conducting the experiments, careful and realistic assessments are in order. It is necessary to be clear minded about the complexity level of the target, the state of development of the field of chemical synthesis, the number of steps contemplated in the venture, the sorts of reagents and reaction conditions under consideration (even assuming all went well) and the sorts of measures that would be likely for purification of intermediates as one goes along. It is well to bear in mind that the exploitability of natural sources for reaching a natural product is not necessarily a constant. For instance, fermentation yields may also be subject to major improvements in response to strong economic or public health incentives. Hence, synthesis may have to compete with alternative sources that are, themselves, becoming more efficient.[1]

Of course, there are naturally occurring structures that will presumably never be readily available from their native sources. For instance, cell surface complex carbohydrate tumor antigens constitute a subclass of natural products that can not be obtained in more than trace quantities from natural habitats. Chemical synthesis (with or without assistance from the repertoire of enzymatically mediated steps) is indispensable for the availability of such carbohydrate motifs.[2]

There may also be interest in structures that are not in themselves available through nature and do not connect in history or concept with known natural products. Such goal compounds may address medicinal issues at the level of structure activity relationships (SAR). Perhaps the structures might be of theoretical importance. Alternatively, their enchantment value might arise from their esthetically appealing symmetry. The challenge may also lie in dealing with compounds at the very margins of chemical viability. In ventures into the

world of "unnatural products," synthesis emerges as the sole source of the target and provides unique insights as to the chemical personality of the goal system.

Alternatively, a total synthesis exercise may serve as a setting for testing either new reaction modalities or (alas more commonly!) the boundary limits of already recorded transformation types. Of course, it is prudent to conduct proof of principle experiments in the context of relatively simple privileged structures. Having accomplished such a feasibility demonstration in the sanctuary of minimal functionality, it is well to challenge the presumed advance in a less controlled but, ultimately, more informative multifaceted context. Thus, an expedition in total synthesis often provides a realistic context to better evaluate the scope of applicability of a projected methodological advance.

Not the least satisfaction of total synthesis (though one of the most difficult to convey to skeptics) is that of taking on and mastering a difficult scientific challenge. The fascination lies in the complex dimensions of the problem. In dealing with intricate goal structures, one may well gain a unique perspective as to the limits of design and methodology. In favorable instances, the daunting nature of an undertaking could serve as a prod for innovative strategies. In other instances, the technology and the planning capacity was really there all the time (perhaps all the way back to Diels and Alder, Dieckmann and Michael) if only the vision were clear. Such syntheses may still be of great teaching value, since they provide a deeper appreciation of the strategy-level resources available to those who can make suitable connections.

Although the successful reaching of "mountain tops" that have not been scaled before can be quite satisfying to the investigators, achievement of the climb is surely not the most important result of the effort. Of minimal enduring meaning (except to some of the climbers themselves) is the speed with which the goal was reached. Rather, the benefit of the research lies in the vision and wisdom gained along the way, and in the sharing of the discovery process with the scientific community. Accordingly, the privilege for a laboratory to conduct complex scientific undertakings carries with it a particularly heavy responsibility on the part of the explorers to record their findings in a fashion that conveys setbacks as well as forward movements. Only in this way will the attainment of the objective be of general value.

Organic synthesis is all of the above and even more. Advances in cognate disciplines have opened up hitherto unimagined challenges and opportunities for chemists with vision and steadfastness of purpose. I shall return to my perception of the sorts of challenges which will engage the field of synthesis in the future. Presently, it is difficult to resist a rare opportunity for selective retrospection, made possible through the invitation to write this paper. These recollections are best structured around some particularly happy memories of events already well documented in the open literature.

It is not without foreboding and anticipation of misunderstanding on the part of some readers, that I have chosen to characterize the objects of these recollections as "magic moments." Needless to say, synthesis places a very high premium on methodical planning and organization. One must attempt to be mindful of all relevant precedents and coldly realistic in evaluating their pertinence to the case under study. Thus, at first glance, there

would seem to be no relationship between the systematics - intensive field of synthesis and any perception of "magic." However, even after all of the advances in theory, and all of the massive data banks (now readily accessible through computer-driven retrieval regimens), organic chemistry retains a large measure of non-predictability. Those who look upon synthesis as a mature and standardized science are apt to miss out on the excitement of discovery. The "magic moments" we recall here followed syntheses which were venturesome, yet successful. It is in explorations of the poorly illuminated corners of organic chemistry that we can learn the most. "Magic moments" are most likely to be encountered in contexts which defy confident prediction.

Before relating a few of these episodes, some important cautionary notes and attributions are in order. For those schooled in the art, there will be little need for either. The experienced practitioner is well aware that the pathways of synthesis are circuitous, bumpy, and even treacherous. Seldom do straight lines suffice to connect points in a synthesis of real consequence. Hence, the seasoned chemist will appreciate that along with these "magic moments" of success, one could have reported a litany of setbacks and reversals. However, for younger and more optimistic enthusiasts, it is appropriate to underscore the uncertainties, the detours and, yes, the frustrations associated with organic synthesis. Success is often a prize reserved for those who temper noble ideas with appropriate measures of realism and skepticism. Given the episodic nature of our science, wisdom may well be more valuable than cleverness. The ability to plumb the implications of each experiment, positive and negative, is central to the process of learning as we go along. Our quest to reach the promised land should not render us insensitive to opportunities for discovery, even as we find our way through the desert.

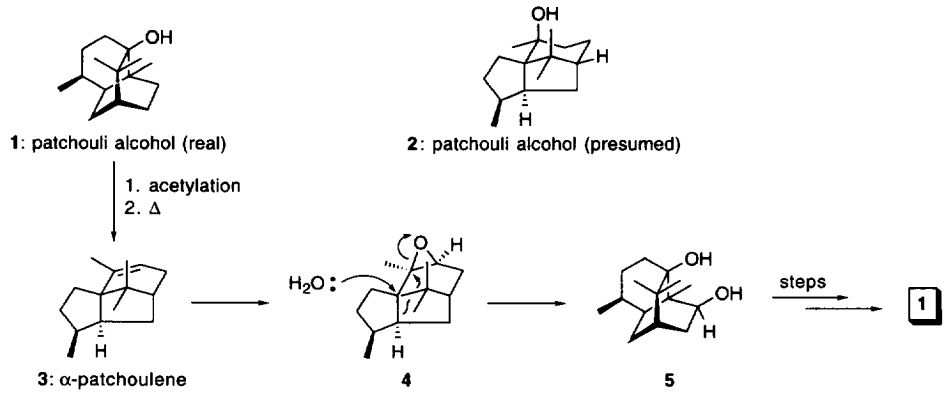
At the risk of belaboring the obvious, one can not overemphasize the collaborative nature of the undertakings recorded here. None of these "magic moments" would have been possible, but for the imagination, vision, focus and toughness of my colleagues. To have had the opportunity to work in academic settings, and to have been able to help in the advancement of the careers of young scientists, has surely been the greatest privilege of my career.

In this spirit it is well to confess, particularly to former collaborators on projects not cited below, that the process of selecting these "magic moments" was not without a large measure of arbitrariness. Perhaps, the future will provide opportunities for a fuller rendering of exciting times from bygone days, and from ongoing synthetic forays, with graduate students and postdoctorals all of whom are near and dear.

(I) <u>The Patchouli Alcohol Venture - Some Lessons Learned</u>

The first total synthesis undertaking of my laboratory at the University of Pittsburgh was directed at patchouli alcohol (**1**) (Scheme 1). Without going into the full and fascinating chemical history of this naturally occurring perfume, suffice it to say that in the case of patchouli alcohol, the surmise that a successful total synthesis necessarily reveals the structure of its target was not correct. Thus, the best indications from the literature flowing from the degradative chemistry of patchouli alcohol occasioned the assignment of its structure to be that shown in formula **2**.[3] On the basis of this assignment, a characteristically brilliant and rational synthesis was designed and implemented by Büchi and associates.[4] The M.I.T. synthesis did indeed produce

patchouli alcohol, *even though it was subsequently shown that its actual structure is 1 rather than 2*. In time, it was recognized that during the dehydration of the "real" patchouli alcohol (**1**), α-patchoulene (**3**) is produced through a rearrangement. Similarly, in the reconstruction of patchouli alcohol from **3**, there was another unrecognized rearrangement (cf. **4** → **5**).



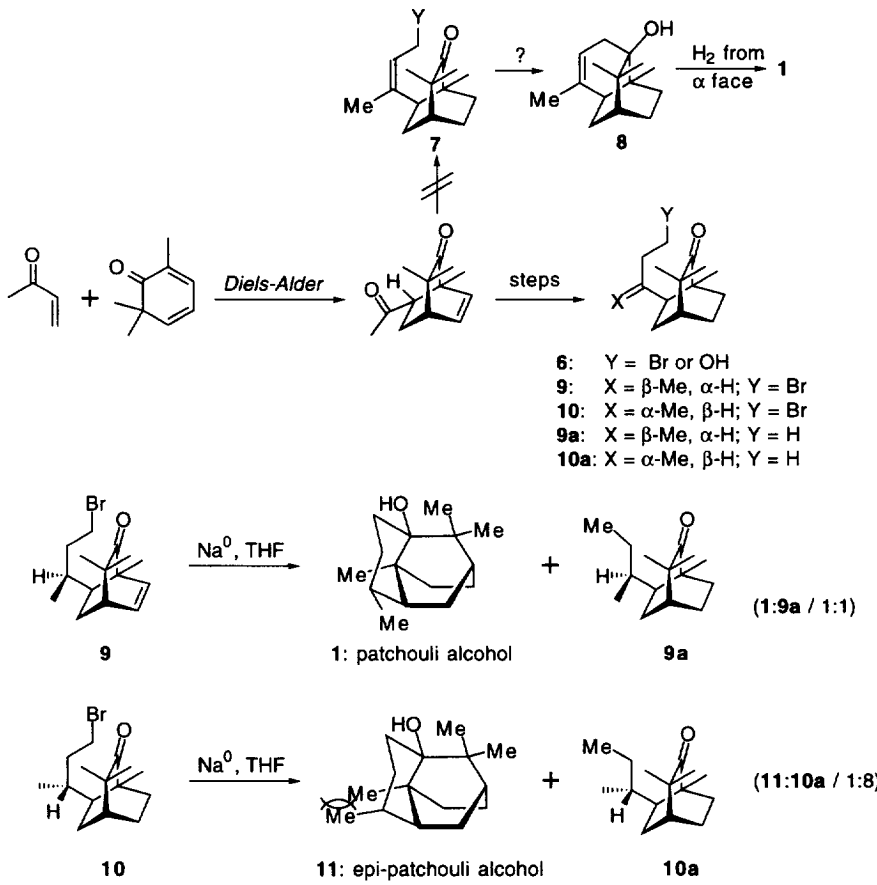
Scheme 1. Büchi's synthesis of patchouli alcohol (**1**).

Armed with this information, from what was then recent literature, we undertook a planned synthesis of **1**[5] (Scheme 2). We perceived that the β-stereochemistry of the secondary methyl group required for **1** could be reached by hydrogenation of **8** from its α-face. We hoped to reach **8** by cyclization of a *Z*-configured haloketone of the type **7**. It is fair to say that in projecting this kind of cyclization, David Dumas was anticipating what is now a widely practiced strategy of reductive cyclization.[6] Of course, we did not have available to us the contemporary reagents (such as samarium[II] iodide or surface active zinc-copper combinations) for achieving the desired bond construction.

Unfortunately, at that time we were unable to reach the required *Z*-system **7**. Not surprisingly, *E* constructs (cf. **6**, Y = halide) did not lend themselves to cyclization. We were therefore obliged to accept poor stereoselectivity in the catalytic reduction of the open *E*-compound, **6** (Y = OH). In this way, we eventually arrived at bromides **9** and **10**. Under a variety of conditions, compound **9** resisted conversion to its corresponding Grignard reagent, frustrating the projected cyclization to **1**. In sheer desperation, the bromide **9** was treated with sodium in THF. A reaction occurred, producing an approximately 1:1 (separable) mixture of patchouli alcohol **1** and non-cyclized **9a**. In contrast, attempted cyclization of **10** under the same conditions afforded a *ca.* 1:8 mixture of epi-patchouli alcohol (**11**) and the reduced epi seco system **10a**. We argued that in the case of epi bromide **10**, reductive cyclization would introduce a destabilizing 1,3 - diaxial methyl: methyl contact. In the epi-series, such a ring closure is, therefore, disfavored relative to the non- suppressible (and still

somewhat mysterious!) reduction leading to **10a**. In the reductive cyclization of bromide **9**, this de-stabilizing abutment is not encountered in the product **1**.

While this planned synthesis of patchouli alcohol was far from ideal in terms of stereoselectivity and cyclization yields, the congruence of fully synthetic material with the natural product, through a rational, but then rather new type of reductive cyclization scheme,[6] constituted for our laboratory a magic moment. Though Dumas and I would have hoped that the lesson could have been conveyed more gently, the patchouli venture taught us that synthesis does, on occasion, test one's powers of stamina and survival skills as well as intellect.



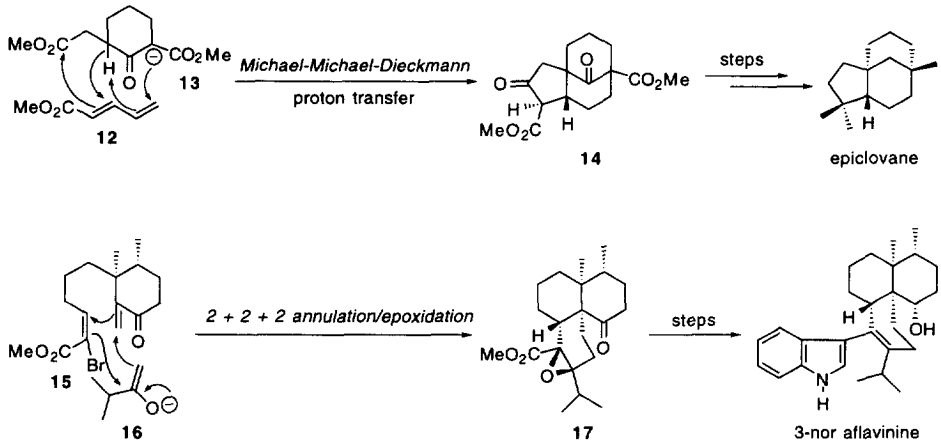
Scheme 2. A reductive cyclization approach to a synthesis of patchouli alcohol (**1**).

(II) Early Attempts At Multistep Orchestrations - The Michael and Cyclopropane Phase

Significant efforts in our laboratory in those days were allocated to exploration of highly active and multifunctional Michael acceptor agents. The reactions of methyl β-vinylacrylate (**12**) (Scheme 3) with various

β-dicarbonyl systems engaged our attention. Perhaps the high point of that effort - a real "magic moment" - arose when Ellis Hatch worked out a 1-step assembly of the epiclovane ring system (cf. **14**) by convergence of **12** and **13**.[7] The structure and stereochemistry of **14** was proven to our satisfaction only through crystallographic means (at that time, with the facilities available to us, this confirmation was *ca.* a 5 month proposition!). The anticipated sequence of intermolecular 1,6-addition, proton transfer, intramolecular 1,4 - addition and regio-defined Dieckmann closure had actually occurred.

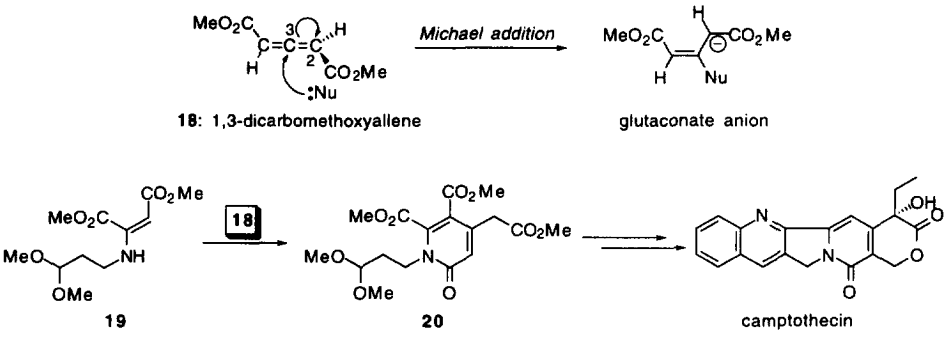
Another instance of successful reaction choreography came in the coupling of **15** with the anion **16** (Scheme 3). It will be noted that **17** is produced following four bond forming reactions and one carbon-bromine heterolysis. The product was transformed in a few steps to 3-nor aflavinine.[8] In retrospect, the orchestration of such entirely classical reactions in these one step assemblies, foreshadowed the current interest in "tandem" or "cascade" constructions.[9] No doubt, the future will bear witness to ever more efficient and encompassing demonstrations of the power of creating (or fragmenting) many bonds in a single reaction.



Scheme 3. Early instances of cascade syntheses in connection with the clovane and aflavinine problems.

In this era of involvement with Michael acceptors, the laboratory also concerned itself with 1,3-dicarbomethoxyallene (**18**) (Scheme 4). Curiously, the electrophilic potential of this compound had not been recognized, at least in the recorded literature. It seemed likely that Michael addition to the central carbon of such an allene could generate a stereoelectronically competent glutaconate anion, provided that rehybridization of the sp carbon (C3) and rotation about the C2-C3 bond would occur early along the reaction trajectory.

A pleasing outcome in this regard was the development by James Eggler, Robert Volkmann, Sarah Jane Etheredge and James Quick of a new route to α-pyridones (cf. **20**)[10] *en route* to camptothecin.[11] Some years later, camptothecin and its analogs gained considerable clinical attention when it was shown that they operate at the level of stabilizing the complex between topoisomerase I and its DNA target. When this was recognized, the then newly constituted Sloan-Kettering group[12] adjusted the earlier Pittsburgh synthesis to provide a more efficient route to the drugs, still retaining the central logic of the 1971 "magic moment."

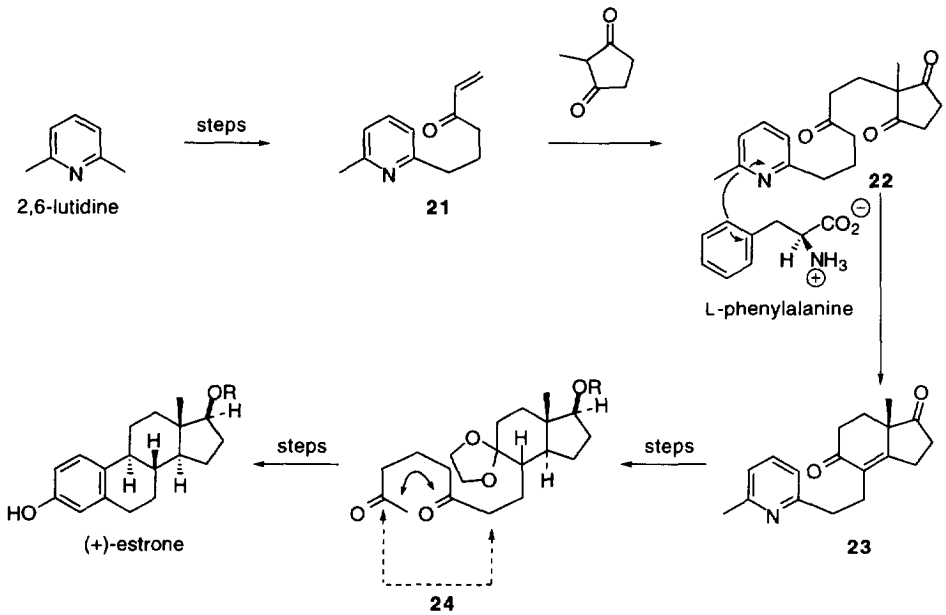


Scheme 4. A synthesis of camptothecin (**21**) based on Michael addition to 1,3-dicarbomethoxyallene (**18**).

Another program which developed during this "orchestration" phase of our research involved an approach to the total synthesis of steroid hormones from pyridine matrices (Scheme 5). It was speculated that Birch type reduction of the pyridine ring (there had been one example of such a reaction when we started) would give rise to 1,4-dihydro products and thence, on hydrolysis, to 1,5-diketones. Steroid-like tetracyclic systems could then be obtained from staged aldolizations. For instance, from the coal tar product 2,6-lutidine, Paul Cain (following earlier exploratory studies by Robert Cavanaugh and Arthur Nagel) handily synthesized the tris-annulating agent **21**.[13] Michael addition of 2-methylcyclopentane 1,3-dione to **21** afforded the pro-chiral **22**. Earlier, Zoltan Hajos, in a landmark paper,[14] had demonstrated the use of L-proline to catalyze cyclodehydrations of pro-chiral triones to afford products with a high degree of enantiomeric enrichment. We attempted to apply the Hajos finding to the case at hand. Unfortunately, L-proline failed to provide a high margin of enantioselectivity. However, we could reach the then quite respectable range of 86% ee for formation of compound **23** through the use of L-phenylalanine.[15] The thought that time had been that "π stacking" types of contacts between the aromatic rings of the L-phenylalanine with the pyridine segment of **22** would augment enantioselection.[16] This thought may well have been an early (and not appropriately documented) instance of exploiting such weak associations in synthesis.

From compound **23** we made our way to **24**. As discussed by Alyce Zimmer,[17] the sense of aldolization of **24** needed for our synthesis (see curved arrow) was counter to many early precedents, wherein it

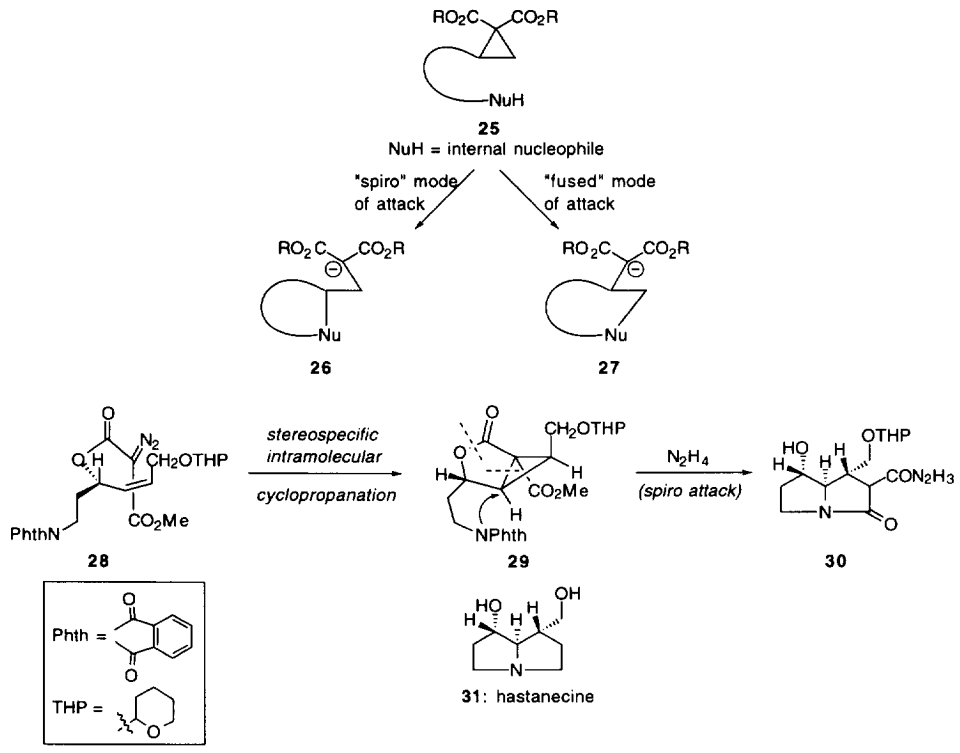
might have been anticipated that formation of the tetrasubstituted cyclohexenone (see dotted arrow) would prevail. Fortunately, we elected to ignore this discouraging body of information, in the hope that the proximal ketal might decisively direct the cyclohexenone formation in the desired sense. This turned out to be the case. The controlled polycarbonyl condensation strategy to reach estrone using novel chemistry certainly qualified as a magic moment. We emphasize that in the evaluation of the pertinence of experiments from the literature, it is well to assess in detail the extent of structural homology between the recorded and projected cases. In doing so, one might realize that prior art may not govern the molecular circumstances at hand. Opportunities that would otherwise be rejected as contrary to conventional wisdom could well prove to be feasible in the appropriate context.



Scheme 5. A synthesis of (+)-estrone from 2,6-lutidine.

In this general time frame, we were investigating the applicability of cyclization and fragmentation reactions of activated cyclopropanes in synthesis.[18] The question of the site of ring opening was framed at that time in terms of "spiro" vs. "fused" modes of attack (see **25** → **26** or **27**, Scheme 6). During this work, John Dynak[19] was able to expound some principles which were subsequently encompassed in the conceptual framework of the Baldwin rules for displacement reactions by proximal intramolecular nucleophiles.[20,21] A magic moment arose in the course of a synthesis of hastanecine (**31**). Robert McKee nicely exploited the then predictable spiro sense attack in the case of a three carbon tether between the nucleophile and the nearest carbon

of the cyclopropane. The general theme of orchestration had thus been demonstrated with homoconjugate addition as the initiation event (see **29** → **30** *en route* to **31**).[22]



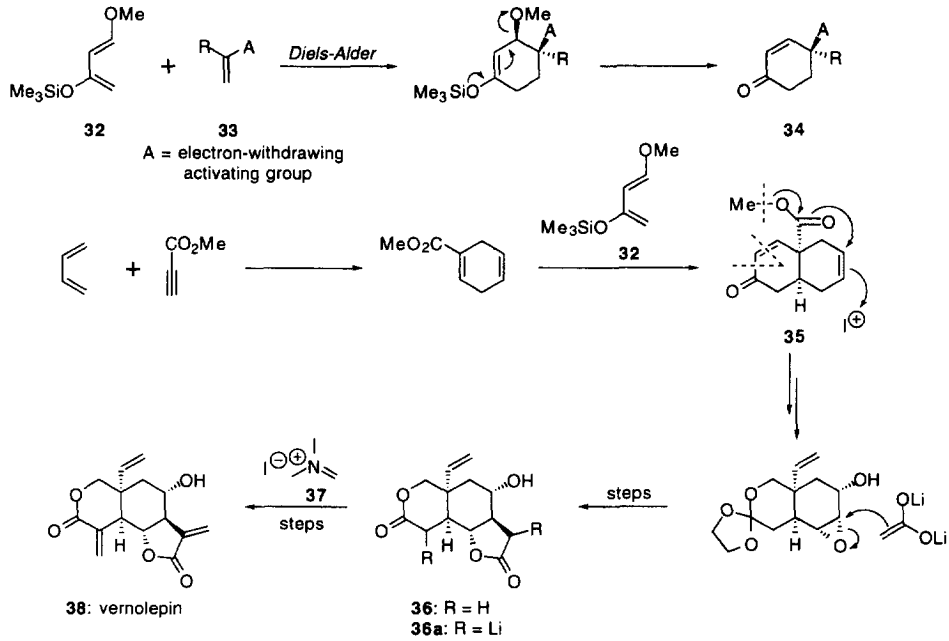
Scheme 6. Ring mutations of activated cyclopropanes.

(III) The Cycloaddition and Cyclocondensation Phases: Early steps *en route* to Glycal Assembly -

In the early 1970's, an effort directed toward the total synthesis of vernolepin (**38**) constituted a serious preoccupation of our laboratory as well as others (Scheme 7).[23] In retrospect, the vernolepin problem can be seen to have attracted far greater attention than should have been warranted by the rather meager tissue culture level cytotoxicity findings. Of course, from the perspective of a chemist, the structure of this bis α-methylenelactonic sesquiterpene was in itself of interest. Fortunately, our infatuation with vernolepin led to some new and productive forays.

In focusing on a synthesis of **38**, we came to favor a Diels-Alder strategy using synergistic diene **32**. Takeshi Kitahara hoped that Diels Alder reactions of **32** (or related dienes) with dienophiles of the type **33** would lead to systems of the type **34** which we looked upon, broadly, as 4-acylcyclohexenones.[24] This turned out to be the case.[25] The use of synergistically activated dienes with appropriate all carbon dienophiles has, indeed, had

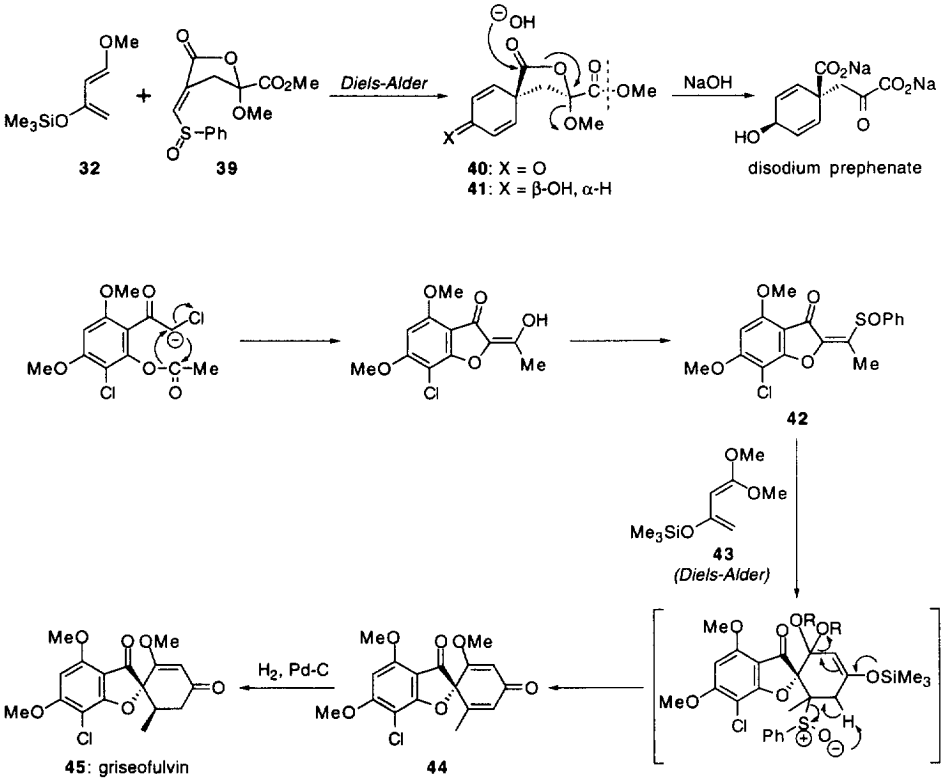
helpful consequences in synthesis. For the vernolepin case, Takeshi was joined by Paul Schuda and Sarah Jane Etheredge. System **35** was generated. From there, by stereospecific reactions, my colleagues could advance to system **36**. To complete the total synthesis of **38**, they made recourse to the then unknown reaction of an enolate (or silyl enol ether) with the Eschenmoser salt[26,27] (**37**) resulting in the overall methylenation of an ester.



Scheme 7. Synthesis of vernolepin (**38**).

With vernolepin safely behind us, our laboratory entered a phase of natural products synthesis driven by newly discovered findings demonstrating the value of synergistic dienes. Two particularly interesting cases come to mind. In struggling to reach prephenic acid, Masahiro Hirama constructed dienophile **39** following an earlier lead of Takashi Harayama (Scheme 8).[28] Diels-Alder reaction between **32** and **39** led to **40** and, thence, to **41**. It was not by chance that the functionality of the highly unstable projected target had been stored in base labile form. Treatment of **41** with alkali delivered, for the first time, pure prephenate as its di-sodium salt.[29] (The magic of the moment was not diminished by the fact that Masahiro achieved success the weekend before the gathering of many scientists to the 1977 Organic Symposium at Morgantown, West Virginia. In the audience, to which I lectured on the subject, was an approving R.B. Woodward).

Another particularly pleasing case was a concise synthesis of dehydrogriseofulvin (**44**) and shortly thereafter griseofulvin (**45**). For the griseofulvin synthesis, Fred Walker[30] and Sarah Jane Etheredge[31] had occasion to prepare and exploit the reactive, novel dienophile **42** in a cycloaddition reaction with dienes **32** and **43** (Scheme 8).

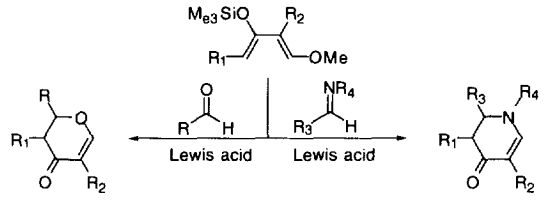


Scheme 8.Diels-Alder reactions of electron-rich dienes in syntheses of disodium prephenate and griseofulvin (**45**).

Happily, the use of siloxydienes in synthesis was adapted by many other chemists. While we could easily anticipate additional applications of this chemistry, it seemed appropriate for our group to move on to other questions. In this connection, an important finding was realized shortly after we reconstituted our laboratory at Yale University. We had begun to investigate possible cycloadditions of synergistic siloxydienes with heterodienophiles under Lewis Acid catalysis. This chemistry was developed by James Kerwin. In the case of aldehydes, Kerwin obtained dihydropyrones of the type **46** (Scheme 9).[32a] He also found that Lewis Acid catalyzed cycloadditions of such dienes with imino heterodienophiles led to dihydropryidones (see **47**).[32b] Given the sensitivity of these dienes to the action of Lewis Acids, the demonstrations of the feasibility, let alone the generality of this chemistry, were particularly exciting.

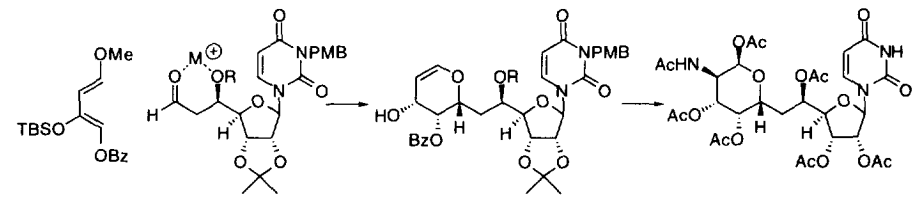
In the course of following up Kerwin's work, Mark Bednarski[33] recorded a seminal finding, i.e. that soluble lanthanide catalysts bearing chiral ligands confer significant enantioselection on such cycloaddtions. While the degree of the selectivity in these early (shotgun!) experiments never exceeded 60%, Mark had anticipated what are now large subfields in organic synthesis ((i) lanthanides as Lewis Acid catalysts in carbon-carbon bond construction and (ii) chiral ligands as devices for conferring enantioselection on such catalysis).

Access to systems such as **46** and **47** through simple chemistry of this sort has had broad impact in heterocyclic synthesis. Both reactions are quite tolerant of extensive substitutions both in the dienes and in the heterodienophiles. Particularly in the aldehyde cases, we focused on natural product goals. In so doing, we had excellent incentives and opportunities to explore the scope of the cyclocondensation reaction in considerable detail. Indeed, the Lewis Acid catalyzed diene aldehyde cyclocondensation reaction provided entry points to a range of unusual higher order monosaccharides (cf. peracetyl tunicaminyluracil (**48**),[34] the hikosamine family **49**[35] and octosyl acid (**50**)).[36, 37]



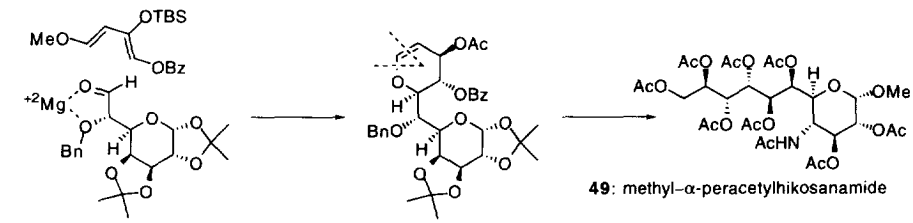
46: dihydropyrone

47: dihydro-γ-pyridone

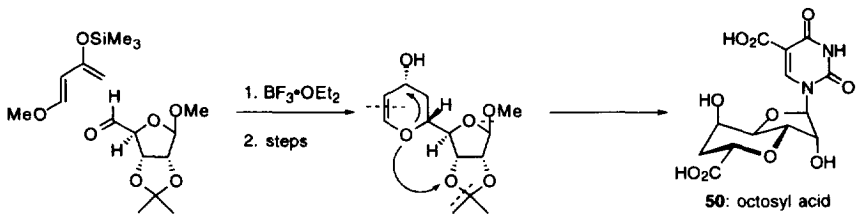


TBS = Si*t*-BuMe$_2$ R = CH_2OMe
Bz = $C(O)C_6H_5$ PMB = $CH_2C_6H_4$-*p*-OMe

48: peracetyltunicaminyluracil

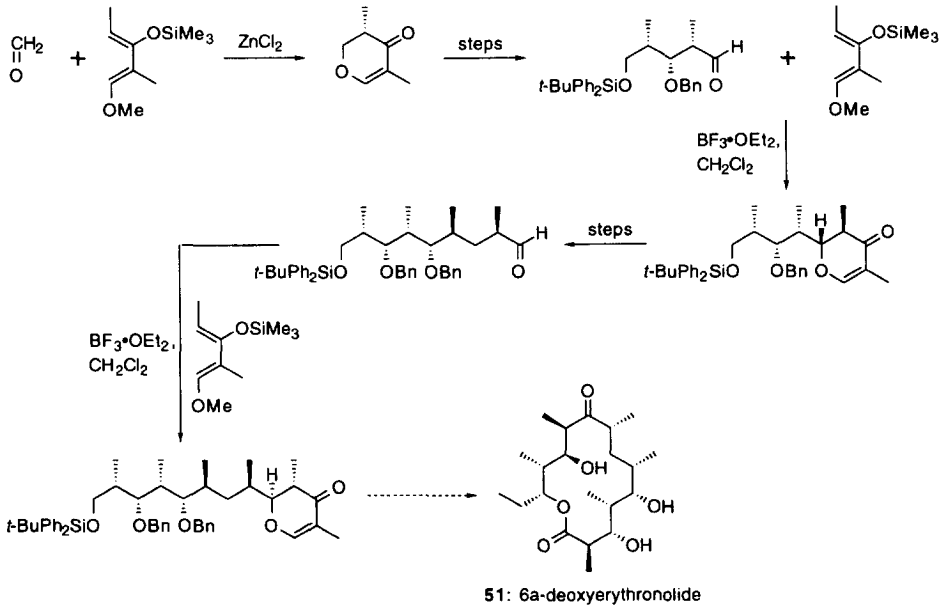


49: methyl-α-peracetylhikosanamide



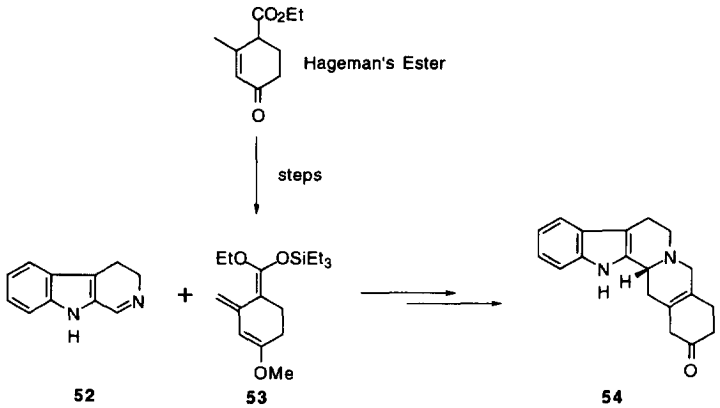
Scheme 9. Lewis acid-catalyzed cyclocondensations of synergistic dienes with heterodienophiles. A general route to the higher order monosaccharides.

A generalizable part of this chemistry was the finding that dihydropyran matrices could serve as microenvironments to control stereochemistry which is eventually expressed in acyclic arrays. In several instances, high margins of control of relative stereochemistry in acyclic domains could be accomplished. This chemistry, first rendered possible by exploratory studies of Daniel Harvey and William Pearson, was carried forward under the inspired aegis of David Myles.[38] He found the approach well suited for providing a stereoselective route to 6-deoxyerythronolide (**51**) (Scheme 10). Myles was able to achieve the construction using continuous asymmetric induction. In other words, in this synthesis, all stereochemistry accrued from operations conducted on various pyranoid matrices. David did not find it necessary to merge subunits with pre-arranged absolute stereochemistry in order to enforce desired relationships in chiral sectors.



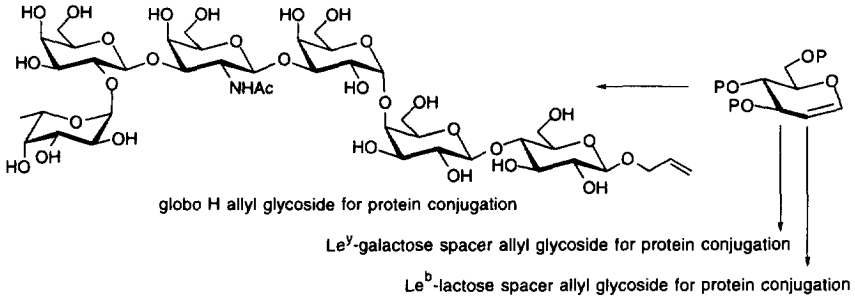
Scheme 10. Reiterative cyclocondensation strategy for a synthesis of 6a-deoxyerythronolide (**51**).

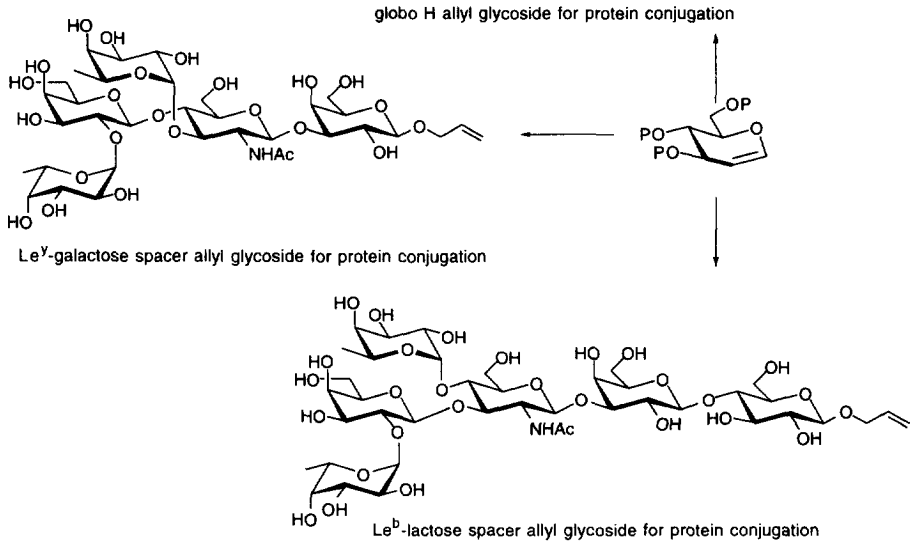
As noted above, the imino-diene cyclocondensation reaction can be carried out with a variety of substrates. Perhaps most exciting in this regard, was the chemistry of Matthew Langer and Claus Vogel, wherein β-carboline **52** combines with diene **53** to provide **54** *en route* to the yohimbines (cf. **54**)(Scheme 11).[39]



Scheme 11. Reaction of imino heterodienophile **52** with oxygenated diene **53** *en route* to the yohimbine system.

Recently, Marc Bilodeau and I described, in some detail, our progression from artificial dihydropyrones (cf. **46**) to oligosaccharides (Scheme 12).[40] This evolution gave rise to major efforts in the synthesis of carbohydrates and carbohydrate conjugates (see KLH conjugated Globo-H breast tumor antigen,[41] Lewis Y antigen,[42] Lewis B antigen,[43] polymer based carbohydrate synthesis,[44] as well as *N*-[45] and *O*-[46] linked glycopeptide constructions, all with their own magic moments). There can be little doubt that the assembly of oligosaccharides and their glycoconjugates constitutes one of the frontiers of synthesis. These kinds of goal structures provide their own opportunities for strategy-level innovations. Furthermore, synthesis serves as the indispensable element in furthering multidisciplinary collaboration with potential consequences in clinical contexts.[47] Since the subject of glycal assembly has been reviewed recently in some detail,[40] only a few cases are cited in Scheme 12.





Scheme 12. Assembly of oligosaccharides and glycoconjugates from glycals.

(IV) Some High Risk Solutions to Problems in Natural Product Synthesis -

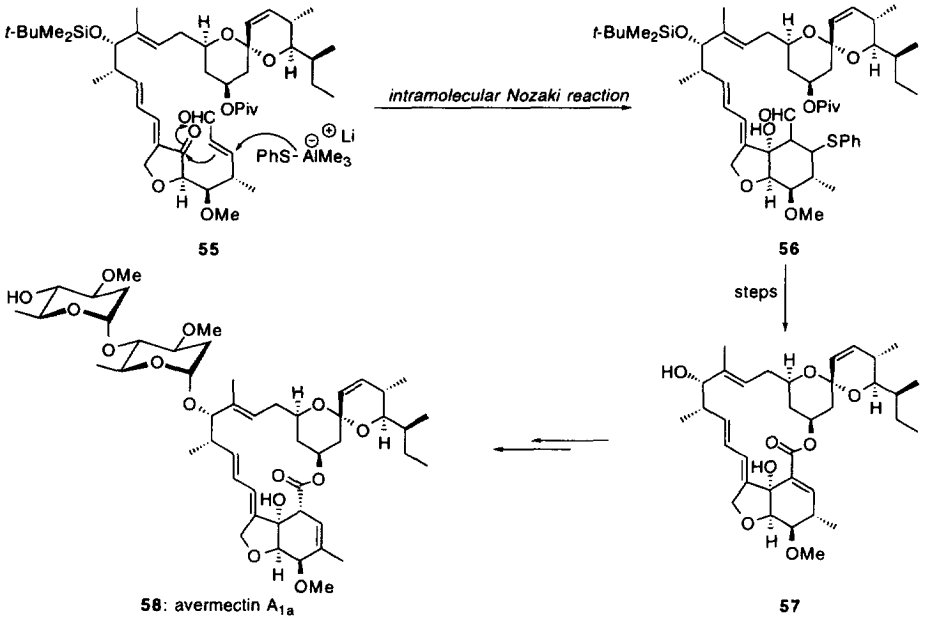
There are many points of view and styles that can be accommodated in synthesis. Given the hidden risks associated even with seemingly conservatively drawn blueprints, the tendency to gravitate toward well trodden sequences in search of workable propositions can be appreciated. That said and accepted, I would still urge investigators to take some far-out chances in their synthetic forays. The "if only" ideas are often the most exciting and memorable. The high-risk idea can well bring a seemingly remote and inaccessible target into range by directly attacking its most forbidding structural defenses.

Needless to say, the field of synthesis is much enriched by a continually advancing menu of sophisticated methods that are critical for progress. The massive and ongoing progress in methodology must be mastered and all available methodological resources should be considered in responding to problems at hand. Nonetheless, it is still possible to reduce many central problems to very simple and classical, if risky, propositions. We recall a few of these successful high risk ventures that led to some particularly treasured magic moments.

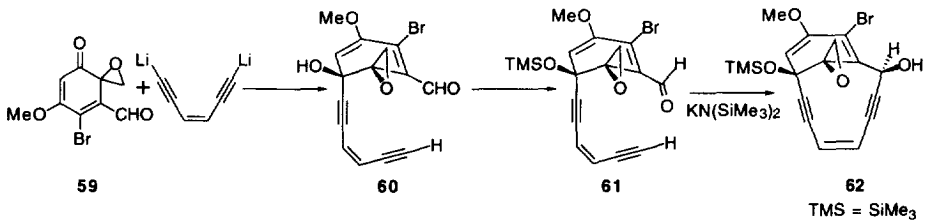
Thus, in the key step in our total synthesis of avermectin A1a (**58**) (Scheme 13), David Armistead[48] took advantage of a "thiolative Michael-aldol sequence" (see **55**→**56**→**57**), which was certainly a classical type of idea. In our total synthesis of calicheamicinone[49] (following highly pertinent leads developed in model systems by Nathan Mantlo, Dennis Yamashita and John Haseltine), my colleagues Maria Paz Cabal and Robert Coleman brought about a defining, yet conceptually classical solution. They exploited a simple nucleophilic acetylide motif in the context of the addition of an ene-diyne dianion (properly organized) to an aldehyde (see **59**→**60**→**61**→**62**, Scheme 14). In one form or another (*and with a widely varying range of appropriate*

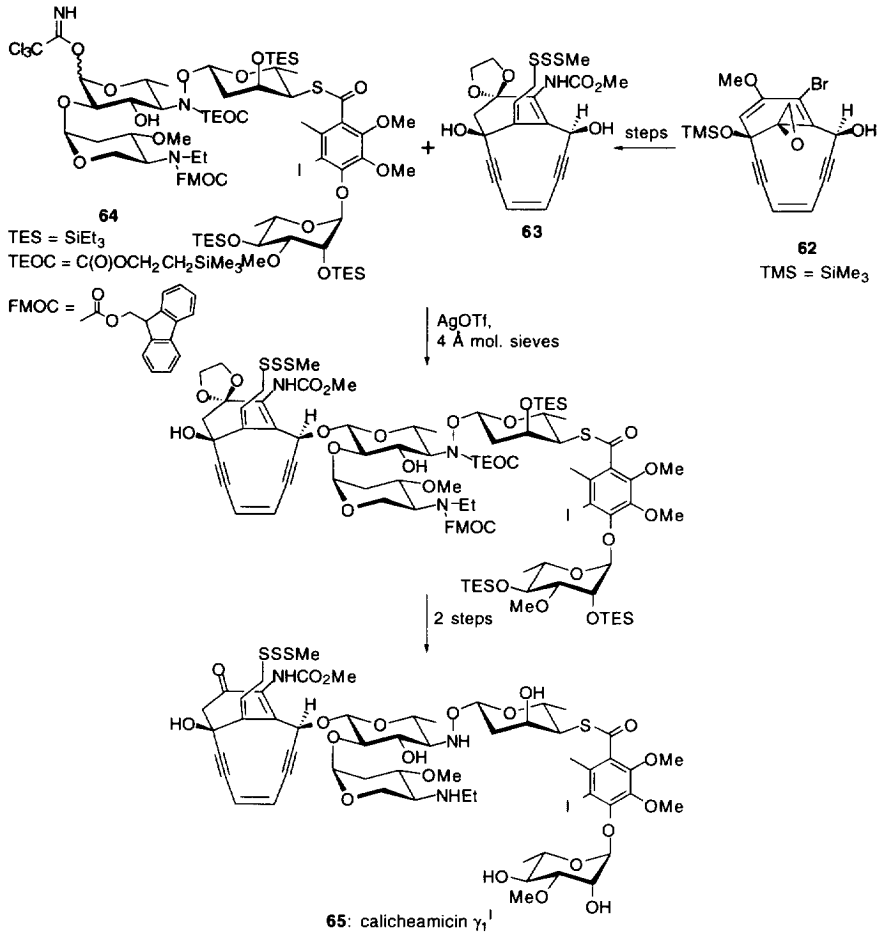
scholarly attribution) virtually every laboratory which is concerned with ene-diyne synthesis now practices this type of closure.[50]

A remarkably convergent glycosylation (see **63** and **64**), followed by a two step global deprotection of all blocking groups allowed Steven Hitchcock[51] to reach calicheamicin γ_1^I itself (see **65**). Thus, the merger of the carbohydrate and enediyne moieties had been fashioned when each domain was maximally advanced and carrying all of its vulnerable functionality. In its sheer boldness, it is hard to envision how the Hitchcock glycoslyation triumph could be surpassed.



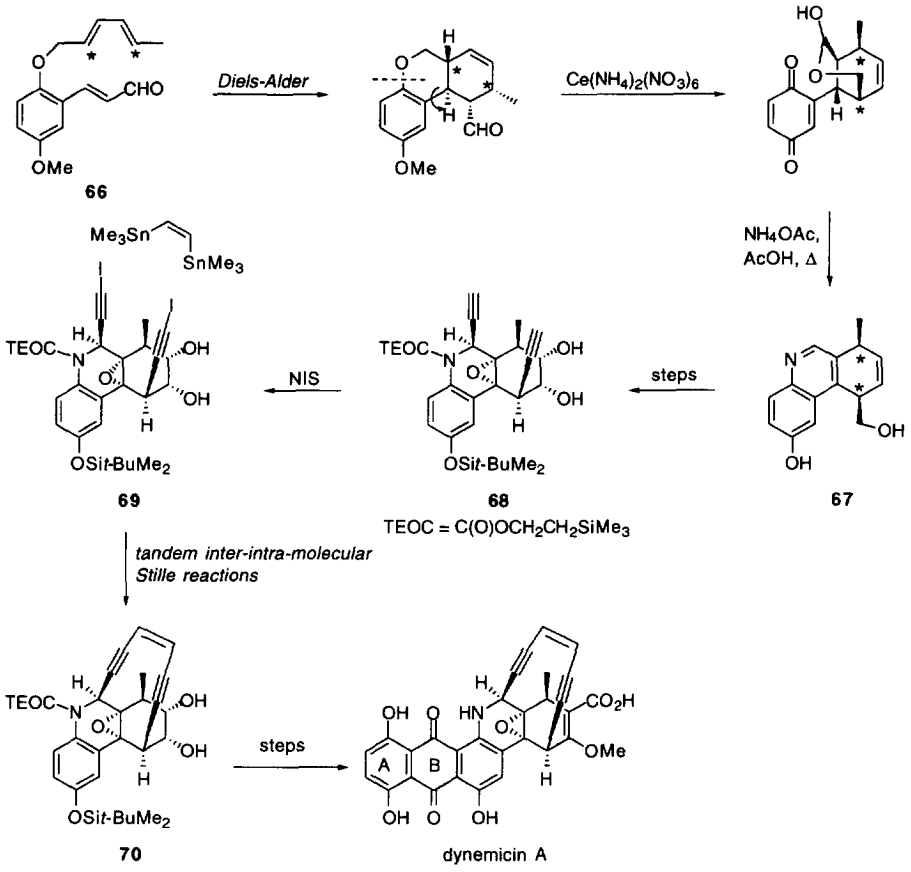
Scheme 13. Synthesis of avermectin A_{1a} (**58**).





Scheme 14. Synthesis of calicheamicin γ_1^I (**65**).

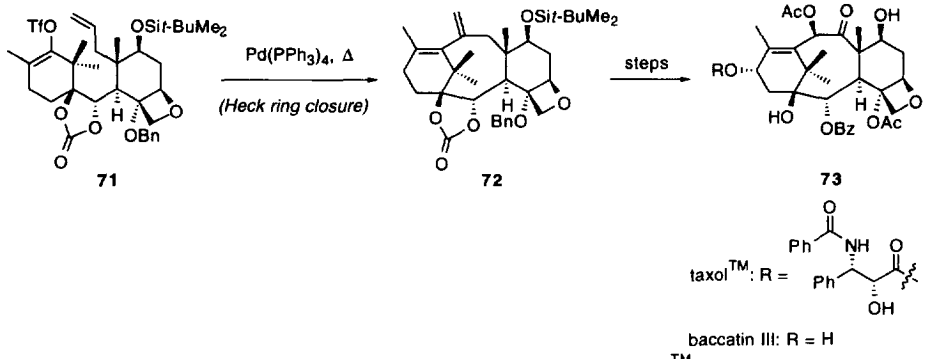
The total synthesis of dynemicin A brought with it many "magic moments." The program was initiated by Tae Young Yoon. The elegance of his perception benefited from its very traditional moorings (Scheme 15). Tae Young's graceful strategy provided much of the functionality needed to converge on our goal (see sequence **66**→**67**).[52] The stage was well prepared for the arrival of Matthew Shair. First, he provided a very nice solution for generating the required cis-disposed di-ethynyl linkages. This allowed him to realize a daring variation of the Stille reaction (see **68**→**69**→**70**).[53] Having reached compound **70**, Matt went on to solve the very difficult "AB problem" in an original way.



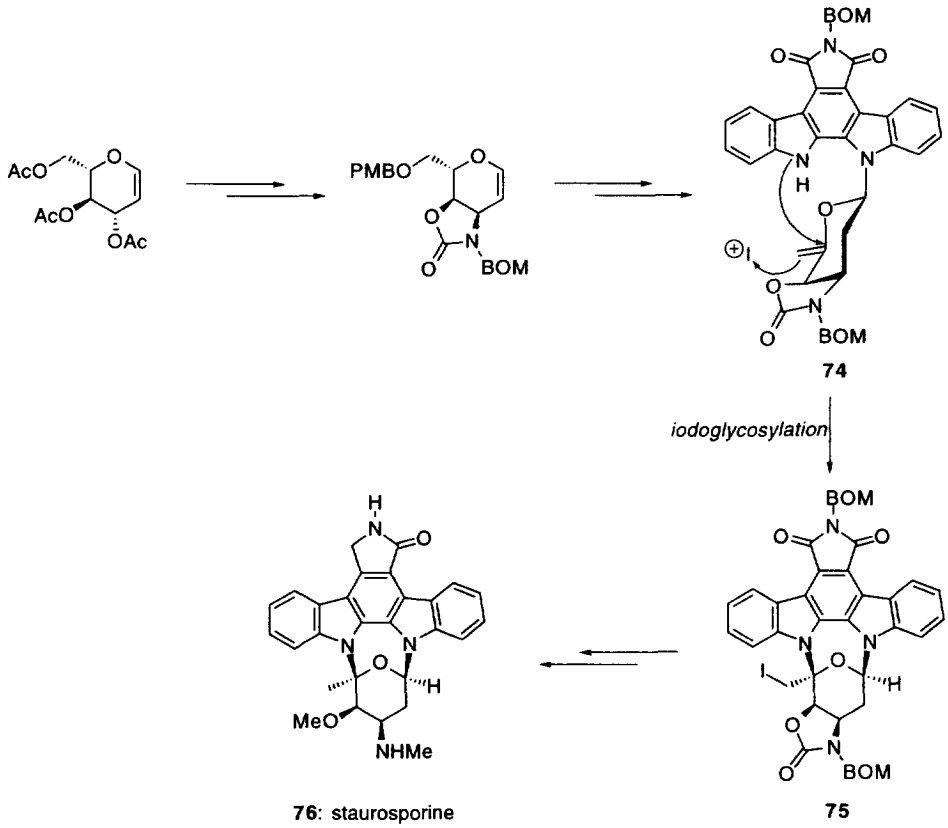
Scheme 15. Application of a tandem inter-intra-molecular Stille reaction in a synthesis of dynemicin A.

Another high-risk organopalladium induced bond construction allowed John Masters to fashion and realize a total synthesis of baccatin III and taxol (see **71**→**72**→**73**), (Scheme 16).[54] The courage that John manifested in bringing off this Heck reaction, even in the face of a series of daunting obstacles and setbacks, remains as a profound personal inspiration to me.

In our synthesis of staurosporine, several high stakes risks were assumed. A striking example was the conceptually simple, but exciting, iodoglycosylation of an indolic nucleophile, first achieved by J.T. Link (**74**→**75**→**76**), Scheme 17.[55]

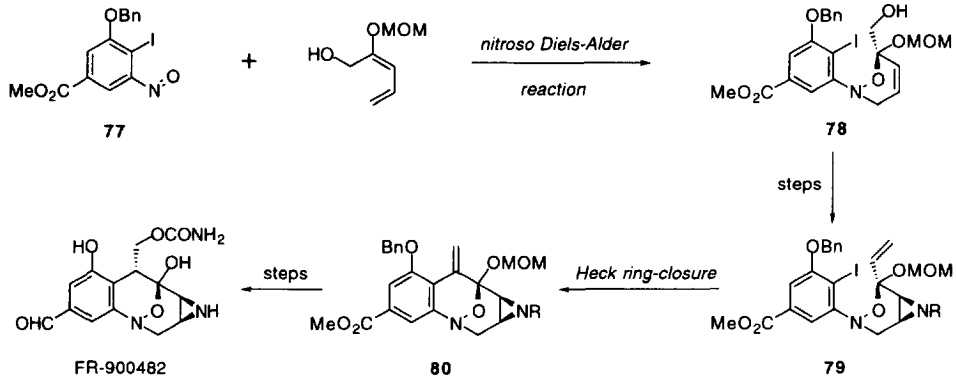


Scheme 16. Application of a Heck cyclization in a synthesis baccatin III and taxol™.

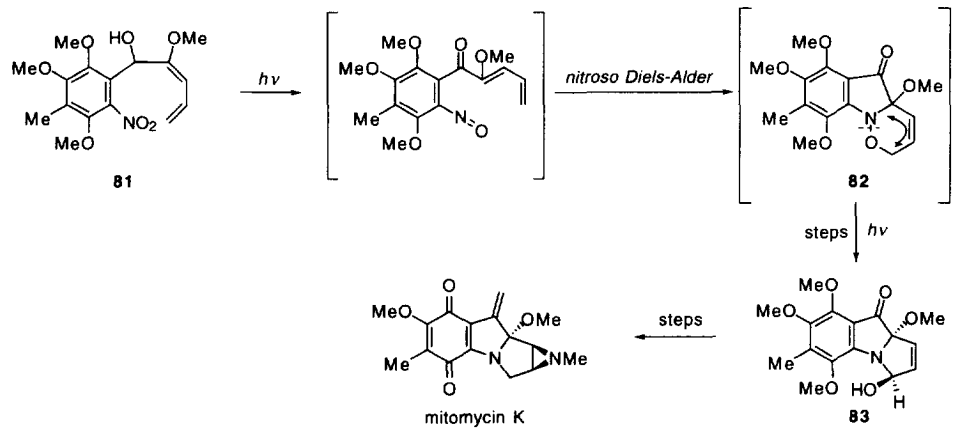


Scheme 17. Iodoglycosylation of an indole in a synthesis of staurosporine (**76**).

The total synthesis of FR-900482, realized by Kim McClure and Jeff Schkeryantz, began with a nitroso Diels-Alder cycloaddition reaction (**77** → **78**, Scheme 18) to set up another dicey but, in the end, highly gratifying Heck closure (**79** → **80**).[56] In this vein, we note that the seemingly forbidding character of the mitomycins[57] served to prompt a willingness to think in terms of "go for broke" strategies. The sequence **81**→**82**→**83** (Scheme 19), pioneered by Kim McClure and John Benbow *en route* to mitomycin K, is illustrative.[58]



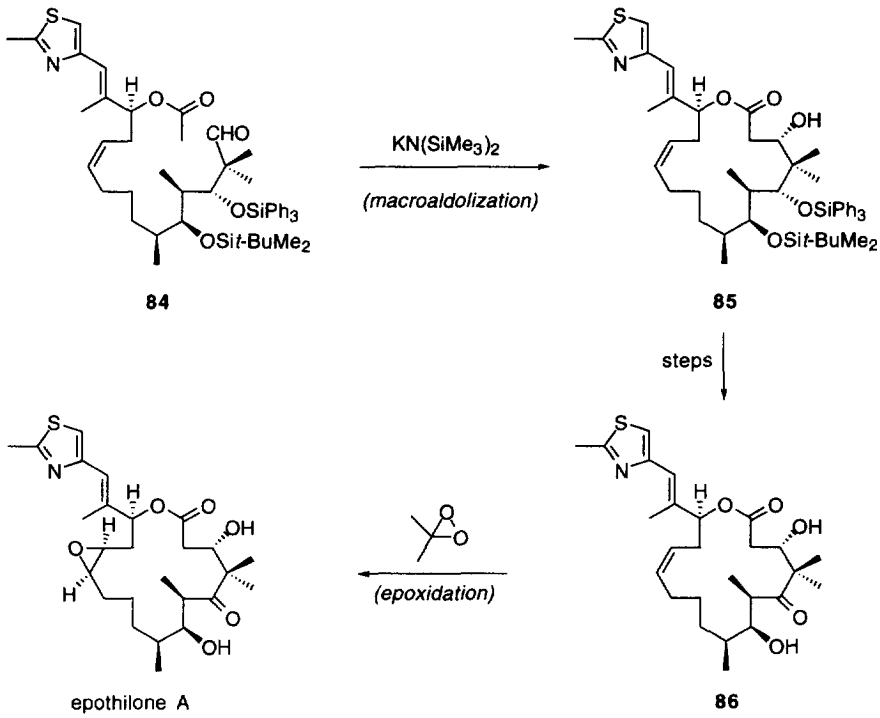
Scheme 18. Synthesis of FR-900482.



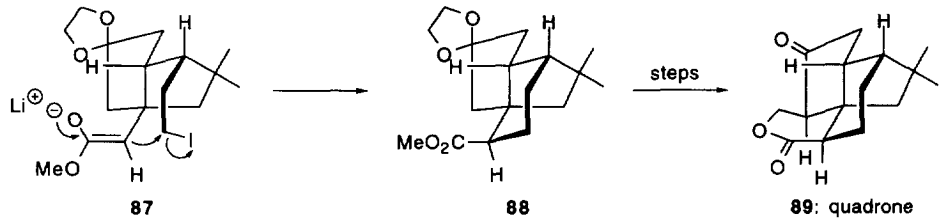
Scheme 19. Synthesis of mitomycin K.

A recent high-risk proposal which bore fruit is seen in the context of the closure of the 16-membered ring of epothilone A by macroaldolization[59] (**84**→**85**→**86**, Scheme 20). Recollection of another *a priori* risky ester enolate bond construction, by Ken Vaughan and colleagues,[60] *en route* to his stereospecific total synthesis of

quadrone (**87**→**88**→**89**, Scheme 21), helped to bolster our hopes that the macroaldol route to epothilone might succeed.



Scheme 20. Macroaldolization of an ester enolate in a synthesis of epothilone A.



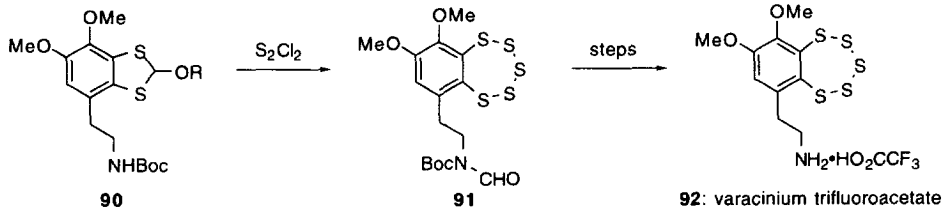
Scheme 21. Ester enolate alkylation in a synthesis of quadrone (**89**).

(V) Grace Under Pressure: Crisis as a Boon To Creativity - All of the cases in Section IV involved constructions that were contemplated at the planning stage of the synthesis. The reaction types were reasonably obvious and were rooted in well accepted mechanistic reasoning. The risk factors centered on whether the

particular reaction types would be operative even in a rather complex setting. Put differently, the risks that were assumed reflected, in each case, optimism that conditions could be developed to favor a desirable outcome even in the face of alternate possibilities. We close this section with an account of a different type of "gedanken" process *wherein the modus operandi that brought success was not even contemplated in the formulative phase of the grand undertaking.*

During the course of the synthesis of a complex target, it is not uncommon to reach an apparent impasse. (Certainly, this paper would have performed an inadvertent disservice to the field if the elements of struggle and disappointment were kept from view). Alas, there is much to be learned from attempts to extricate one's syntheses from such impasses - perhaps even more than from those situations where events come off according to plan. Crises in synthesis, born of impasses, may force new departures that would have been too speculative at the level of design. Crises may oblige recourse to reaction types which are not precedented or supported by a body of mechanistic scholarship. We close with three cases where apparent impasses gave rise to interesting solutions which were certainly not anticipated at the planning stage. Rather, responses to "molecular level emergencies" were devised while facing the harsh prospect of the collapse of a much cherished enterprise.

In achieving the total synthesis of varacinium trifluoroacetate (**92**, Scheme 22), Victor Behar reached compound **90**.[61] However, in attempting to progress from **90**, even Victor was unable to reach the pentasulfide by adaptations of traditional chemistry. In this trying context, Behar carried out an interesting and unprecedented kind of reaction of compound **90** with sulfur dichloride. Happily, this treatment resulted in construction of the pentasulfide ring, even as the formyl equivalent was being shuttled from the dithioorthoester linkage to the ureido nitrogen found in **91**. From compound **91**, Victor was able to reach his goal structure. The precise mechanistic details of the fascinating conversion of **90** to **91** still invite debate.

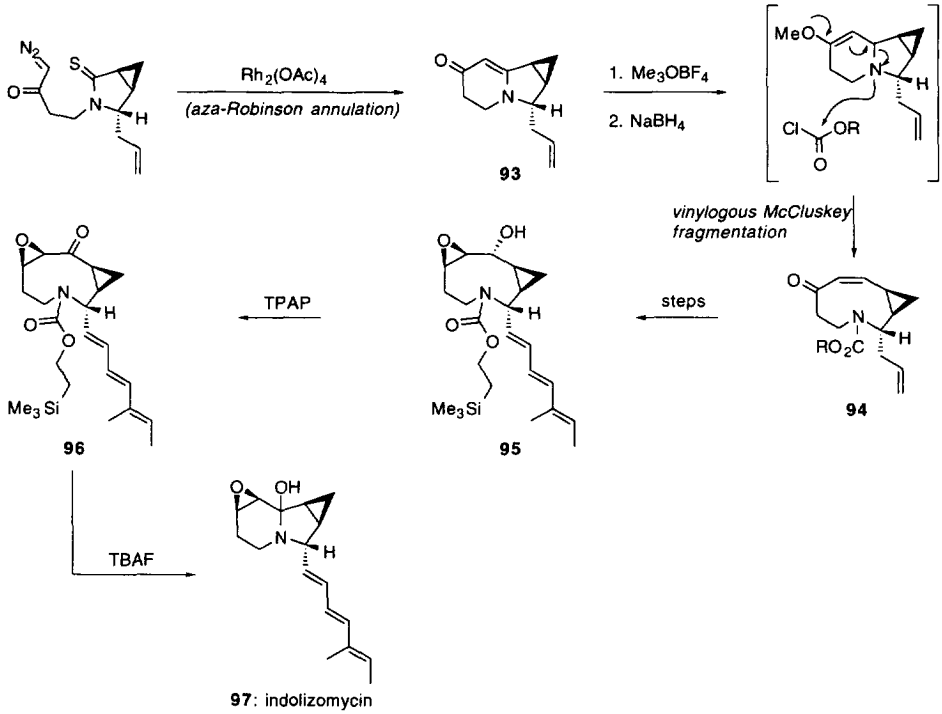


90 **91** **92**: varacinium trifluoroacetate

Scheme 22. Synthesis of varacinium trifluoroacetate (**92**).

In attempting to reach indolizomycin (**97**) (Scheme 23), *perhaps one of the most unstable natural compounds ever to be synthesized*, Guncheol Kim[62] confronted an apparent impasse. With great aplomb, he had earlier devised and implemented a route that brought him to the vinylogous amide **93**. From this point, Kim encountered a serious impediment to progress in attempting to introduce additional functionality with required

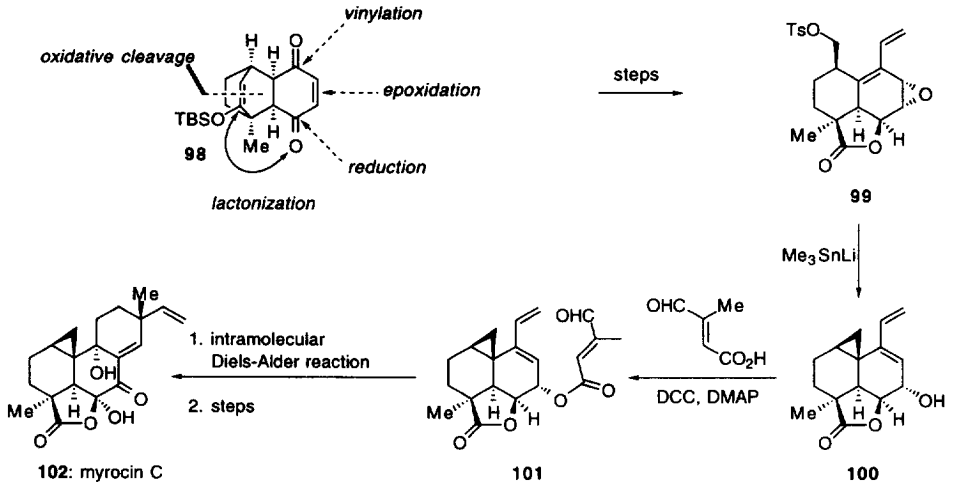
stereochemical control. It seemed that if a method could be devised for progressing from **93** to a nine-membered nitrogen-containing (azoninone system) depicted as **94**, perhaps the principles of medium ring conformational analysis could be tapped to introduce additional functionality in a stereochemically orderly way (see **95** and **93**). Guncheol then conceived of a brilliant solution to this subgoal. Methylation and conjugate reduction had apparently converted **96** to an enol ether system. It was hoped that treatment of this substance with a generic chloroformate would result in N-acylation. The chloride ion, thus liberated, would set in to motion a vinylogous McClusky type ring fragmentation to produce **94** (See **93** → **94**). This, in fact, occurred and Guncheol Kim, subsequently joined by Margaret Chu-Moyer, was able to reach the specific TEOC version **96** and, thereafter, indolizomycin itself.



Scheme 23. Synthesis of indolizomycin (**97**).

Another seemingly insurmountable obstacle confronted Margaret Chu Moyer in her synthesis of myrocin C (**102**) (Scheme 24).[63] Using esthetically pleasing chemistry, she had converted Diels-Alder adduct **98** to a system of the type **99**. At this stage, it was necessary to establish the fused cyclopropane ring. As outlined in our paper, many apparently conservative strategies directed toward this end were unsuccessful. Fortunately, a

fascinating solution was devised "on site." The tosylate **99**, on treatment with trimethylstannyllithium, gave rise to the required cyclopropane **100**. As matters transpired, this compound bore the requisite functionality for Margaret to complete the synthesis (see **100** → **101** → **102**).



Scheme 24. Synthesis of myrocin C (**102**).

Summary

In summary, the reader has been exposed to some of the issues involved in our synthesis program that has targeted biologically active natural products. Although much has been learned in the field since we took on the patchouli alcohol problem in 1966, the subject for us has lost none of its high purpose, intellectual ferment, or character - challenging drama. To the contrary, the opportunities for discovery are greater than ever for those who are willing to study and practice synthesis with scholarly dedication and experimental exactitude.

The playing field of synthesis today encompasses all but the rarest elements of the periodic table. The debt of total synthesis to methodology development goes well beyond the convenient availability of many new methods, important as they are. The new technologies liberate and, indeed, beckon the architects of synthesis to think in much broader and sweeping terms about tomorrow's problems. Clearly, the most dramatic advances have been registered from the mobilization of transition metals and other organometallic reagents to achieve specific transformations even in multifacted contexts. It is well to recognize that these breakthroughs were, on the whole, achieved by scholars of chemistry and even curiosity seekers - unconcerned with any apparent application to total synthesis. The synergism of methodology, mechanism, and strategy constitutes the core of synthesis.

There is diminishing need for the logistically intensive multistep assaults simply because the mountains are "there." The syntheses that will warrant the greatest interest are those which convey new ideas and new chemistry arising from a willingness to explore ambitious and risky propositions. It is in the context of

dreaming such dreams and, above all, in the struggle to reduce them to a "do able" state, that the power of our science, as well as its beauty, flourishes.

The devotees of synthesis have good reason to be particularly optimistic about their field. The opportunities in the design of high "value added" structures, of either theoretical, material science, or biological impact fire the imagination. Moreover, as bioassay systems become more and more sophisticated, and as more lead compound types, including structurally fascinating natural products, become increasingly amenable to deduction at the level of mode of action, the number of potential projects of high promise will continue to increase.

Another great opportunity is centered in the field of combinatorial chemistry. The mission here lies in the creation of designs and matching methodology that allow for rapid synthesis of diverse small, multifaceted structures, reminiscent of pharmaceuticals. Inspired synthesis will be required if the libraries of tomorrow are to be well stocked with valuable as opposed to convenient entries. The follow-up, in a combinatorial way, from lead structures of some complexity, to drug candidates is a significant challenge to the creative genius of synthesis.

Quite properly, organic synthesis will be drawn toward multidisciplinary undertakings. I would urge that, in these ventures, the synthetic organic chemist assume a significant leadership position. Those who accomplish the synthesis of a target are apt to have gained a privileged vantage point as to its true molecular nature. Synthesis is not unique among the sciences in its fostering of discovery. *However, it is in a class by itself in terms of its capacity for creation.* To fully exploit this power, chemists must be particularly well informed and venturesome in the broader contexts and applications of their accomplishments. Only through such activism can the formidable heuristics inherent in organic chemistry find full expression in multifield coalitions.

The future will be particularly bright for those who sort carefully and select wisely from an ever expanding menu. Again, I urge the emerging leaders of tomorrow to conduct their syntheses more with daring and imagination and less with reflexive recourse to well trodden paths. In such settings, synthesis will surely provide many more magic moments, first to its creative enthusiasts, thence to the larger scientific enterprise and, hopefully, to the public we all seek to serve.

Dedication. This paper is dedicated to Dr. Sarah Jane Etheredge for a lifetime of shared magic moments.

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