Strategies and Tactics in Organic Synthesis

Volume 9

Edited by

MICHAEL HARMATA

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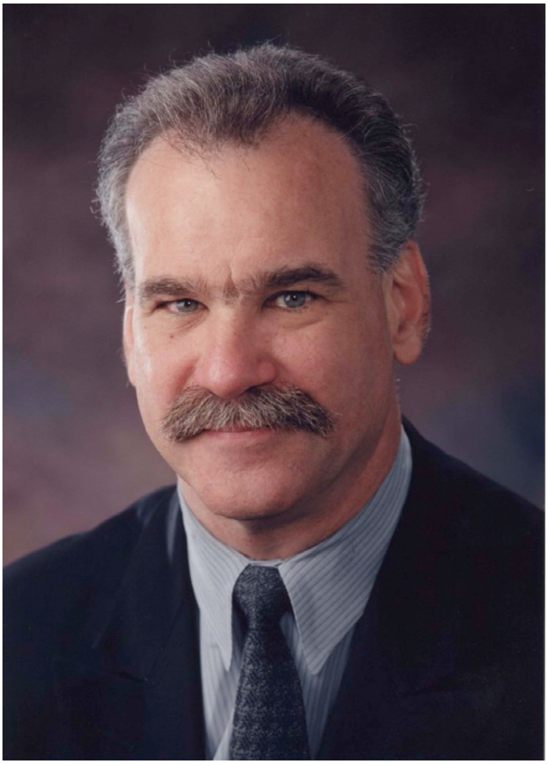
Dedication

This volume is dedicated to my mentor and friend Professor Scott E. Denmark on the occasion of his 60th birthday and in recognition of his dedication to organic chemistry and the beautiful science that dedication has produced.



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Foreword

How could a chemist and former teacher not wholeheartedly agree when he is gently asked by one of his chemical grandsons to write a foreword in a book dedicated to the grandson's former PhD supervisor on the occasion of his 60th birthday? Writing for and about Scott Denmark, my brilliant former PhD student from America, will be a delightful duty and even be a kind of adventure, since neither the personality nor the achievements of the man are "mainstream." In the 1970s, with golden medals in his pocket, awarded to him by the school of his hometown Lynbrook (NY), and a Sigma-Chi Award from MIT for having been an "outstanding undergraduate," he changed continents for his PhD studies and came to the "Eidgenössische Technische Hochschule (ETH)": a move from big America to small Switzerland, "far from mainstream" indeed. When he arrived at the ETH, the B_{12}-adventure was behind us, and so I naturally assumed that he wanted to join our group because he was interested in working on a problem of total synthesis. No, he insisted, what he wants is to work on a problem of reaction mechanism. What at that time also happened to be behind us was our work on *endo*- versus *exco*cyclic S_N2-type reactions; in its wake, another rather general question had come up, namely, whether Pauling's bent-bond model of the carbon–carbon double bond might not be more discriminative on the level of the organic chemist's qualitative reasoning than the conventional sigma/pi model in describing and predicting the stereochemistry of allylic reactions. Scott's struggle with this question in his thesis work led eventually to 367 pages entitled "On the Stereochemistry of the S_N2' Reaction." To me, the thesis represented an analysis of the topic unprecedented in depth and comprehension. The ways that Scott navigated through the problem and the absolutely exceptional, clearly inborn meticulousness by which he analyzed the outcome of experiments made one thing clear: this man is indeed born to study mechanisms.

Genuinely, if not obsessively, interested in understanding molecular behavior, blessed with sustained creativity and success in his research, pragmatic in knowing that studies on the reactivity of molecules should remain connected to chemical synthesis, competent and courageous to do both—this is what Scott has been ever since. Courage is one of his strengths he should be proud of; it triggers many of his activities. So it was, when he decided to do his PhD studies abroad, so it is today and by no means only in his research, as his predilection for racing motor cars and riding fast motorcycles reveals. "Taking risks"—the title of an essay in this volume referring to the field of natural products synthesis—is one of the basic challenges a scientist has to deal with if he wants to “go beyond.” In chemistry, handling the challenge wisely requires the virtues of mountaineers: in order to survive you need—apart from knowledge and skills—sound judgment, caution, discipline, and—as an organic chemist—empathy for molecules. I am simplifying, but may not be exaggerating, when I state that Scott has them all. And, by all means, he is one of those who are eager to “go beyond.” So he did, most importantly so in his exploration of a novel type of catalysts, the “Denmark catalysts.”

For an advanced octogenarian, it is of course quite impossible to keep up-to-date with modern organic synthesis, be it the development of new methods or be it the never ending flow of total syntheses of “marvelously” complex and exotically looking natural products. He is overwhelmed by the myriad of *chemo*-, *regio*-, *diastereo*-, and *enantio*-selective reactions that could never have been even dreamed of at the time he himself was active in chemical synthesis. Equally impossible for him was to follow in deserving detail all the work Scott accomplished over the decades. This, so he felt, is shameful and therefore embarked in some chemical fitness training for the sake of this foreword, trying to brush up his knowledge of Denmark chemistry and to revisit in some detail the conceptual essentials of Scott’s opus magnum, his seminal work on enantio-selective catalysis by hypervalent Lewis base/main-group Lewis acid complexes in (mostly, but not only) C,C-bond formation. These essentials cannot be repeated often enough, and when I try this once more, it is now Scott who—more than 30 years after his promotion at ETH—may generously smile at the senior’s effort to pass the exam.

In a typical example of this kind of Denmark chemistry, two achiral reactants—a nucleophile (such as an silyl enol ether) and an electrophile (such as an aldehyde group)—undergo a chirogenic addition reaction under the control of a Denmark catalyst to afford a chiral product in high yield and high degree of enantio-selectivity. A Denmark catalyst is a hypervalent complex formed *in situ* through the interaction of a *chiral* Lewis base with an *achiral* Lewis acid, whereby, by virtue of this interaction, the complex will act as a stronger Lewis acid than it would without the base. The coordination center of the achiral Lewis acid is a main group element, most often silicon, that can be part either of the prospective electron-donating leaving group of the substrate molecule that acts as the nucleophile or of a Lewis acid that participates as a co-reactant. The degree of activation imposed on the Lewis acid by the Lewis base is such that the Lewis base/Lewis acid complex, and not the achiral Lewis acid, will catalytically activate the reactant that acts as the electrophile. It is the judiciously structured *chiral* Lewis base, most prominently a bidentate bis-phosphoramide, that imposes chirality on the catalytically active species and, by dissociating after bond formation between the substrates, closes the catalytic cycle.

Denmark’s catalysis concept has intellectual appeal with a tickling component: counterintuitiveness, an emblem for undeniable nontriviality of a research contribution. That the electrophilicity of a Lewis acid should be increased through the interaction with an electron donor is—to an organic chemist—counterintuitive. However, by reading Scott's lesson, bafflement changes into approbation, even on maintaining the level of qualitative reasoning. Denmark's belongs to the kind of lessons through which progress in organic chemistry proceeds; it does so in seemingly small but significant steps: by looking more closely, there may be order, where before there was none, and a chemist may be granted, bit by bit, new insight into the almost unlimited diversity of molecular behavior.

How could I pay tribute to Scott Denmark for his work on his catalytic systems without explicitly pointing to his and Gregory Beutner's monumental review in *Angewandte Chemie* of the year 2008, entitled "Lewis Base Catalysis in Organic Synthesis." In itself a tribute to the great Gilbert Newton Lewis, Scott's scientific hero, the article is a grand overview on organocatalysis by Lewis bases in organic chemistry, terms are rigorously defined, the immense diversity of the topic is systematically structured, and his own contributions are lucidly embedded in the discussion of the work of others; it is a paragon in scholarship. I suppose, if *Angewandte Chemie* would be offering a prize for "The Best Review of the Year," the one on "Lewis Base Catalysis ..." might well have been the front runner and quite probably not only for that specific year. This seems safe a prognosis in retrospect, since in the year that followed, the community of organic chemists of the United States made Scott Denmark the 2009 ACS National Award Winner of the "Herbert C. Brown Award for Creative Research in Synthetic Methods," the laudation pointing to "his insightful and scholarly analysis of reaction mechanisms" and "his creative approach and rigorous development of novel synthetic transformations of broad utility." A few years before, Scott had already won the ACS Award for "Creative Work in Synthetic Chemistry." The probability to find the term "creative" in connection with the name Scott Denmark is conspicuously high. Well deservedly so. In science, technology, and art, the term retains its important meaning, in deplorable contrast to other worlds, where one can find it downgraded to a slogan.

Hardly any "Matterhorn" of research achievement stands alone; there will be other peaks, distributed over a less or more distant neighborhood. Besides the seminal work on Lewis base/Lewis acid catalysis, Scott's panorama of achievements shows many further peaks, the ones perhaps best known are the Eiger, Mönch, and Jungfrau—I am keeping the allegorical language in order to induce in Scott some nostalgia by reminding him of the beauty of the Swiss Alps. Located rather distant from the Matterhorn, that mountain massif in the Berner Oberland seems a worthy metaphor of Scott's successes in that other major research topic of his: the [4+2] cycloaddition reactions of nitroso- and nitroolefins, which so powerfully evolved into his tandem [4+2]/[3+2] cycloaddition chemistry. Furthermore, there are mountains also in the foothills of the Alps, from where one can also have a great view:

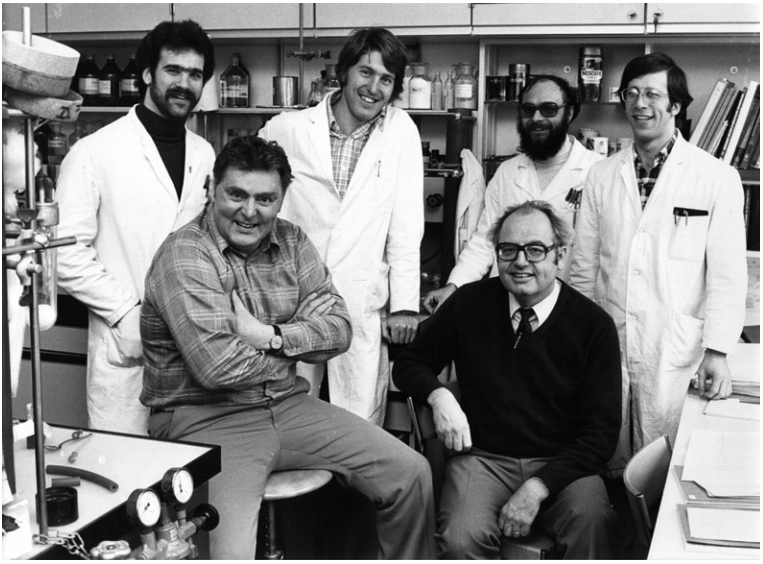
carbanion-accelerated Claisen rearrangements, structure and reactions of halomethyl-zinc reagents, asymmetric addition of organolithium reagents to imines, enantio-selective tin-mediated additions to carbonyl groups, enantio-selective cyclopropanation of allylic alcohols, catalytic enantio-selective vinylogous aldol reactions, catalytic epoxidation of alkenes, chemistry of silyloxyclobutanes, palladium-catalyzed cross-couplings of organosilicon derivatives, and more; a beautiful landscape it is. A very special mountain in the foothills of the Alps is the "Rigi," climbed by Mark Twain in 1879. From up there one has a truly gorgeous view, famously described in Twain's *A Tramp Abroad*. Scott also, so to say, "climbed the Rigi" very early in his career, and up there, as a young chemist, he had a vision: silicon! The picture stands for Scott's silicon-directed *Nazarov* reaction from the early 1980s, a beautifully elegant way of circumventing an organic reaction's intrinsic regio-ambiguity. I vividly remember that Scott had conceived and planned this work while still a PhD student. His plan for the research project was part of the "Arabian flying carpet" that carried him over the Atlantic back to the United States from the level of a PhD student directly into the position of an assistant professor. Silicon remained one of his preferred chemical elements ever since.

Among Scott Denmark's scientific contributions, we find a remarkable collection of total syntheses of natural product structures. As Scott himself describes it, his total syntheses of natural products are undertaken as "vehicle to illustrate and test the limits of a newly developed method." On the basis of the relationship between design and execution, we may distinguish between three types of total syntheses: of the first type are syntheses that are realized along a pathway derived from a retrosynthetic analysis of the target structure, thereby requiring disconnections to correspond to known reactions. The second type is the one referred to above in Scott's own words, where an independently developed new reaction or method allows for correspondingly new retrosynthetic disconnections and, in turn, for a potentially more efficient synthesis. A third type of synthesis is one in which it is the target structure that induces the conception and development of a new reaction for the sake of being able to reach the target via a pathway that—thus far—was considered impossible. At the outset of such a synthesis stands a violation of the central rule of retrosynthetic analysis. Needless to say that in reality hybrids of the three types can and do occur. Regarding scientific merit (not utility), a synthesis of the first type can reveal exciting new insights into the diversity of possible pathways to a target structure within the framework of known reactions. There can be great art in this. What, in addition, synthetic projects of the second and third type contribute are extensions of the conceptual and methodological armamentarium of organic synthesis. The syntheses realized in Scott's laboratory are without exception prototypical examples of the second type: the total synthesis of RK-397, illustrating the power of Lewis base-catalyzed aldol additions and silicon-based cross-coupling reactions, or the (+)-papulacandin D synthesis, featuring (in Scott's own terms) "a palladium-catalyzed, organosilanolate-based cross-coupling reaction with an electron-rich and sterically hindered aromatic iodide" and "a Lewis base-catalyzed, enantioselective allylation reaction of a dienal and allyltrichlorosilane." And there are the syntheses that reflect the synthetic versatility of the Denmark cycloaddition chemistry: for example, the syntheses of the natural products (+)-mesembrine or daphnilactone B (see below) and not least the nonnatural but nevertheless demanding structure of 1-aza-fenestrane. In contrast to total syntheses of the first type, examples of which are legion, of the second type they are much less numerous, and those of the third type are bound to be rare. Most comfortably familiar to the author—he may be forgiven—are the two variants of B_{12} synthesis: the one proceeding via a seco-corrin→corrin ring closure between rings A and B is an example of the first type; the one via the ring closure between rings A and D is an example of the third.

"Studies on various end-game strategies for introducing the hydroazulene portion of daphnilactone B and completion of the total synthesis are in progress" is the final sentence in Denmark's 2009 *Tetrahedron* paper on the construction of the pentacyclic core structure of the hexacylic alkaloid daphnilactone B. The synthesis is an outstanding exemplification of the potential of Scott's tandem [4+2]/[3+2] cycloadditions of nitroalkenes for the construction of complex polycyclic system and as such represents a significant contribution to chemical synthesis, irrespective of whether the "end-game" will reach its goal. Yet, there is something behind this work—so it seems to me—that may be seen as pointing to one of the underlying characteristics in Scott Denmark being an organic chemist. Daphniphyllum alkaloids derive biosynthetically from mevalonate, and Clayton Heathcock in the early 1990s had shown in a classic series of papers how representatives of this group of alkaloids can be efficiently synthesized via pathways that were conceived as being biomimetic. In contrast, Scott's approach to these complex targets is radically chemical, without any allusions to biosynthesis, as if he had decided to make the very point of showing that chemistry can do without having to be inspired by biology. Indeed, Scott's entire scientific work is "aseptically" chemical throughout; there are no signs that his interest would ever have philandered with biological problems. Keeping away from the ongoing intrusion of biology into chemistry is "not mainstream" once again. Organic molecules and their properties, and above all, *catalysis*, that all important phenomenon in chemistry and beyond—this is what Scott Denmark is compassionately interested in. The depth and breadth of his insight and his achievements in this field make him the leading scientist and teacher he is today. Whoever wants to have a closer look into the inner workings of this extraordinary personality in contemporary organic chemistry should read his unique 2009 *JOC* perspective entitled "The Interplay of Invention, Discovery, Development, and Application in Organic Synthetic Methodology: A Case Study." Much can be learned from it about the man and the way he is doing science.

In 2007, at the occasion of Scott receiving the golden Prelog medal of ETH for his contributions to stereochemistry, I had the privilege to comment on the importance of being a "pure organic chemist," and since there is some evidence that in some quarters the comment hit a sensitive spot, I am concluding this foreword by echoing it here again: "Neither Biology, nor Chemistry would be served best by a development in which all organic chemists would simply become biological such that, as a consequence, research at the core of organic chemistry and, therefore, progress in understanding the reactivity of organic molecules, would dry out. Progress at its core in understanding and reasoning is not only essential for organic chemistry, but for life science as a whole. Life science needs an Organic Chemistry that remains strong."

Albert Eschenmoser



From Scott Denmark's days at the ETH (February 23, 1977). In back from left to right: Scott Denmark, Ernst Vogel, Fritz Jaisli, and Daniel Sternbach. In front: Jakob Schreiber and Albert Eschenmoser.

Preface

When I first saw him, I thought Scott Denmark was just another graduate student, endowed with more facial hair than most (*the* eyebrow), but still just another guy close to getting out. It was early August 1980; he was 27 at the time. As I recall, he was just outside the lab in which Chemistry 338 was conducted, talking to Dan Dess of Dess-Martin periodinane fame. I was a newbie, not aware that Scott had interviewed at Illinois and landed the job, so his presence at that moment had no effect on me. I came to Illinois interested in the work of a few of the people there and had some time to think about joining a group; classes and TA duties beckoned.

In 1980, if not now, I don't really know; new graduate students at Illinois were required to do a number of things, one of which was to listen to research presentations given by the faculty, the organic faculty in my case. The idea was to give everyone a fair shake at getting students and to allow students to get some perspective as to the research programs of individual professors. To make what could be a long story short, what Scott did with a piece of white chalk and a blackboard blew the minds of at least four new students. His enthusiasm was unbridled and the intensity and joy with which he described the things he wanted to accomplish were astounding. In a very real sense, you had to be there to get a feel of how palpable the energy in that room was when he spoke. P.T. Barnum said, "There's a graduate student born every minute." But we needed no more convincing than that one talk. We were no doubt nervous, but also very excited.

Well, the four youngsters whom Scott managed to recruit that day were Eric Weber, Mike Dappen, Todd Jones, and I! What were we thinking? This Scott Denmark guy had no publications from his doctoral work and no postdoc. He appeared out of thin air and swept us off our feet. Luckily, I was too naïve to have even thought about the possible negatives, enamored as I was with organic chemistry and Scott's raw energy. I don't know if my friends had any concerns. We jumped in and the rest is history. As you know now, we needn't have had any worries.

Let's be frank. Scott's intensity was inspiring, but it could be very intimidating. I found it, along with his knowledge, very challenging, and that served to make me a better chemist. To be able to banter about chemistry at his level was a nice goal to have. Whether I really ever achieved it, I can't quite say (but I'm the editor so I'll say I did). Others saw that intensity and wanted to run! Here's where joining his group really came in handy. We soon learned that Scott had the habit of shaking his head back and forth when people gave chemistry talks. This little factoid was not always appreciated by other students in the department. Imagine giving a literature seminar and seeing Scott Denmark in the front row shaking his head "no" at almost everything you said. You *knew* he would ask a question; he always did. It would be a difficult question, one requiring deep thought. And there he sat, shaking his head in apparent disagreement with everything you were saying. Would this seminar have to be repeated if you fell apart during questioning?

Comedy is cruel and I have to admit that members of the Denmark group occasionally found this scenario pretty funny. While Scott was never mean, he was always challenging, challenging people to think. There is a quote attributed to Don Marquis: "If you make people think they're thinking, they'll love you; but if you really make them think, they'll hate you." I can't help but recall that when I remember Scott, especially when he was charged with the exuberance of youth. The quote is cynical, but it is true in my experience. However, certain people eventually have an epiphany, or are possessed of a little something special to begin with, and realize that finding someone who makes them think is a very good thing and they deeply appreciate the opportunity to learn how to do it. Thanks, Scott!

We had some intense, rewarding, and fun times during the early 1980s. Scott's initial projects included (1) the silicon-directed Nazarov cyclization, (2) the nitroso-olefin cycloaddition, (3) models for uncovering the intrinsic stereoelectronic preference for allyl metal additions to aldehydes, and my personal favorite, (4) the carbanion-accelerated Claisen rearrangement. They all ultimately succeeded, something that still impresses me. The best stories are the ones I will not divulge in this venue. Todd Jones was my lab partner for a number of years in those days and suffice it to say that we were kind of crazy. I think popular opinion would state that I was the craziest of all; would that it were still so, crazy and creative go well together.

One of my best ideas along those lines was deciding that we needed a group T-shirt. Having grown up on the south side of Chicago, I was acquainted with certain aspects of life that were foreign to many others, particularly those from small towns. It was easy jump to come up with a group nickname based on my Chicago days: Denmark's Disciples. Todd Jones' wife, Tracy, created an attractive logo and we had T-shirts. In those days, we noted that Scott had a propensity for using words that ended in "-ous" when describing how things should or should not be in a proper organic chemistry lab. One must be rigorous, meticulous, industrious, ambitious ... One must not be dangerous, ambiguous, calamitous, cumbrous ... Well, we all took names based on the "-ous" theme, a nice team-building experience. I was Ambiguous. It figures.

Over the years, Scott has continued to provide me with support, both generally and specifically as a sounding board for chemistry. Among many pieces of advice, he gave me two that were particularly important. He first said that I should focus. I probably should have listened, but what can one do when there is so much chemistry to be explored and ultimately so little time? And what about those chickens over there? Pass the Ritalin, please. The other bit of sagacity was even more important, however. Perhaps mindful of the biblical passage Ruth 1:20 ("Call me not Naomi, that is sweet, but call me Mara, that is bitter, for the Study Section hath quite filled me with bitterness."), he warned me to avoid becoming bitter over the disappointments that would be inevitable in an academic career. It has not always been easy, but this little gem of wisdom remains one of the most important things I have learned from Scott, in addition to the mountains and mountains of chemistry.

Regrettably, I don't have the time to write a real story and am not sure I have the talent to do so if I had the time. Scott Denmark started his career under what especially today would be considered unusual circumstances: he was not well known; he had the support of only a few individuals, one of whom happened to be his doctoral mentor, Albert Eschenmoser, and he had no record. But Illinois placed a bet and won big time, perhaps relying on Eschenmoser's assessment of this young Denmark character. Scott's intelligence and ambition turned him into an award-winning chemist and, by the way, an excellent teacher. And he's only 60 years old! Great things lie ahead. So Scott I wish you a heartfelt Happy Birthday! May you have many more years of great chemistry, fast racecars and motorcycles, and all else that brings you fun and fulfillment!

And now on to the business of the book ...

I am grateful to all of the authors who have contributed to this book. Not only do they provide scientific insight into the ongoing developments in the world of synthetic organic chemistry, they often also allow us glimpses into the reality of research and the fact that it is executed by people, often by those who are just beginning their journey into this fascinating area of science. To be allowed access to the thoughts and hopes of principal investigators and to see how obstacles can be overcome by strategic decision-making, tenacity, and good old dumb luck give readers (young ones especially) the knowledge that we have or can develop what we need to create new science. That creation is a cornerstone of what synthetic organic chemists do and it places us not only at the center of science but all the way up to its forefront as well. The principles of mechanism, structure, and reactivity that form the foundation of synthesis are the keys to all other molecular science involving organic compounds. And so, most generally, chemistry is not the central science; it is *the* forefront science. More people at the forefront need to learn it.

This series was born from the hard work of Tom Lindberg. It was born again because I loved that series and wanted to see it go on. With support from community members such as Erik Sorensen, Dirk Trauner, and others, I had the hope that a continuing series dedicated to organic synthesis could be maintained. So far, so good! I'm grateful to Elsevier for their support of this series and particularly grateful to Derek Coleman and Susan Dennis for their continuing assistance and enthusiasm for this ongoing project.

Finally, I make it a point, while I remain funded, to thank those agencies responsible for keeping my research program alive. This "broader impact" is facilitated by such funding and my gratitude goes out to the National Science Foundation for their continued support.

MICHAEL HARMATA

Chapter 1

Total Synthesis of *Strychnos* Alkaloids Akuammicine, Strychnine, and Leuconicines A and B

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Chapter Outline

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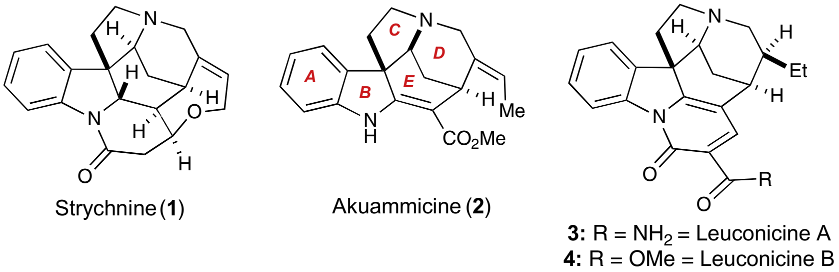
1 INTRODUCTION AND OVERVIEW

In the great tradition of Organic Chemistry, there is no mistaking that we are impacted (often deeply) by our experiences with undergraduate, graduate, and postdoctoral mentors. The individual styles, philosophies, approaches to problem solving, and selection of research projects or targets (in the case of total synthesis) affect our points of view and shape how we, in turn, carry out research. I had the good fortune of carrying out postdoctoral studies with Professor Steve Martin at the University of Texas at Austin, working on the synthesis of alkaloids from 2003 to 2006, and the experience had a profound impact on me. To be sure, Steve's elegant biomimetic syntheses of strychnine (and akuammicine) continue to inspire. However, I did not seriously consider strychnine (and its provincial cousin akuammicine) as synthetic targets until 1 year into my independent career at Temple University. In the fall of 2007, Professor Al Padwa came to give a seminar in the chemistry department. As is the custom at Temple, several faculty (including myself) took him to lunch before the afternoon seminar. Somehow the topic of strychnine (and the varied syntheses thereof) came up, and Al quickly informed me his lab had just successfully completed the molecule; moreover, he would disclose the specifics (and tell the story) in his lecture! True to form, the seminar was magnificent and from that point on, I began feverishly coming up with different routes and entertaining outlandish chemical fantasies, which will be spared in this account. Dr. Tapas Paul, a postdoc in my group, carried out early studies that ultimately were unsuccessful. At this point, Gopal Sirasani (one of my first two graduate students) had just completed a total synthesis project (crocacin C) and was looking for a new one. We discussed it briefly, and he began studies immediately. After several months grappling with frustratingly recalcitrant iminium chemistry, he deployed a completely different route featuring new chemistry inspired by the rich prior art. This approach was ultimately successful (*vide infra*).

This account details: (1) our overall approach to the *Strychnos* alkaloids and relevant prior art; (2) the development of novel synthetic methodology toward the preparation of the ABCE tetracyclic framework of the *Strychnos* alkaloids



Strychnine (**1**)

Akuammicine (**2**)

3: R = NH_2 = Leuconicine A
4: R = OMe = Leuconicine B

FIGURE 1 Representative *Strychnos* alkaloids.

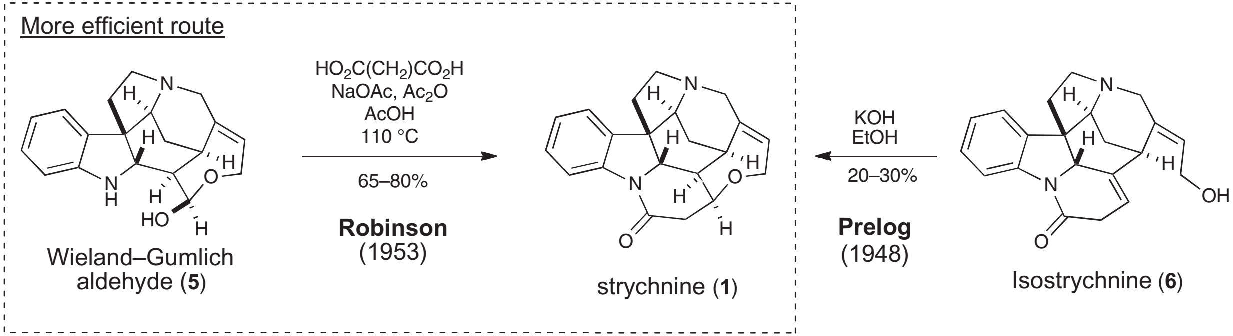
(Figure 1); and (3) the application of this method toward the successful syntheses of strychnine (**1**),[1] akuammicine (**2**),[2] leuconicines A (**3**) and B (**4**).[3]

2 BACKGROUND ON THE SYNTHESIS OF STRYCHNINE AND OUR RETROSYNTHESIS

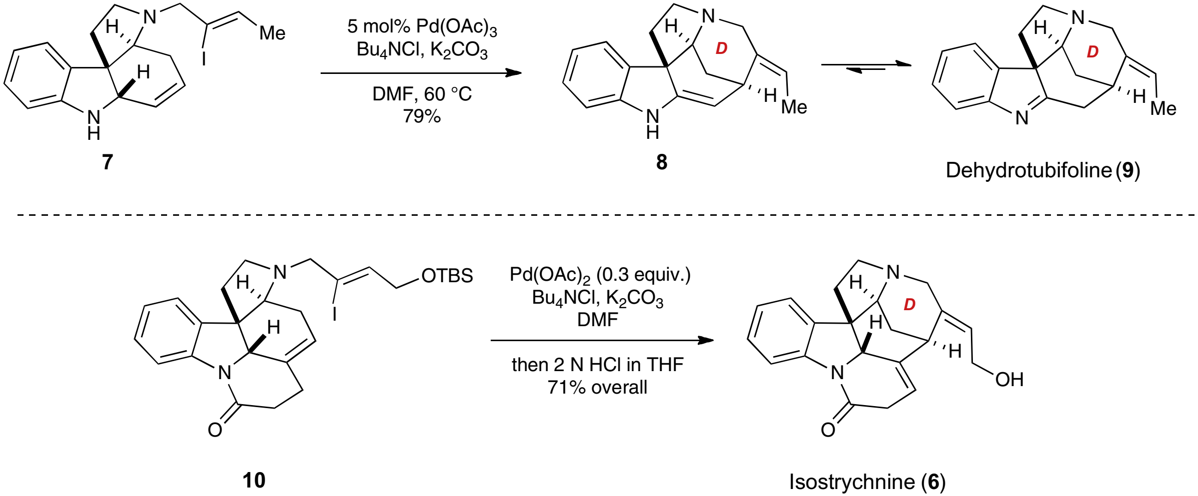
The abundance of strychnine and its ease of isolation were critical to its structure elucidation in 1948, which required over a century of work chronicled in several hundreds of papers.[4] The vast amount of prior art also contained two routes to prepare strychnine from two distinct degradation products: isostrychnine (**6**) and the Wieland–Gumlich aldehyde (**5**) (Scheme 1). Historically, the first route was reported by Prelog and coworkers in 1948 wherein heating isostrychnine (**6**) and KOH in ethanol produced strychnine in low yields (20–30%) with the mass balance being largely **6**.[5] Woodward employed this route in his landmark synthesis of strychnine in 1954.[6] However, Robinson reported a much more efficient conversion of the Wieland–Gumlich aldehyde to strychnine (65–80%) in 1953 by heating the former in a mixture of malonic acid, sodium acetate, and acetic anhydride in acetic acid as solvent.[7]

It is important to note that *all 19 syntheses of strychnine* reported to date have targeted either isostrychnine or the Wieland–Gumlich aldehyde as their penultimate precursor to the natural product.[8] Based on the efficiency of Robinson's method, most have targeted the Wieland–Gumlich aldehyde, and this is the path we also took.

In 1991, Viresh Rawal published a brilliant, general method for preparing the piperidine D-ring of the *Strychnos* alkaloids by means of an intramolecular Heck reaction of a vinyl halide tethered to a cyclohexenyl amine.[9] This efficient tactic solved several synthetic challenges posed by the *Strychnos* alkaloids, particularly the bridged-bicyclic [3.3.1] DE ring system with pendant (*E*)-hydroxyethylidene moiety. Rawal showcased his method in the synthesis of *Strychnos* alkaloids dehydrotubifolidine (**9**) in 1993[10] and strychnine (**1**) in 1994 (Scheme 2).[11] The step- and yield-efficiency of this overall



SCHEME 1 Two paths lead to strychnine.



SCHEME 2 Rawal's intramolecular Heck route to dehydrotubifoline (1993) and strychnine (1994).

process appealed to us and left a deep impression on our retrosynthetic thinking about strychnine and *Strychnos* alkaloids in general.

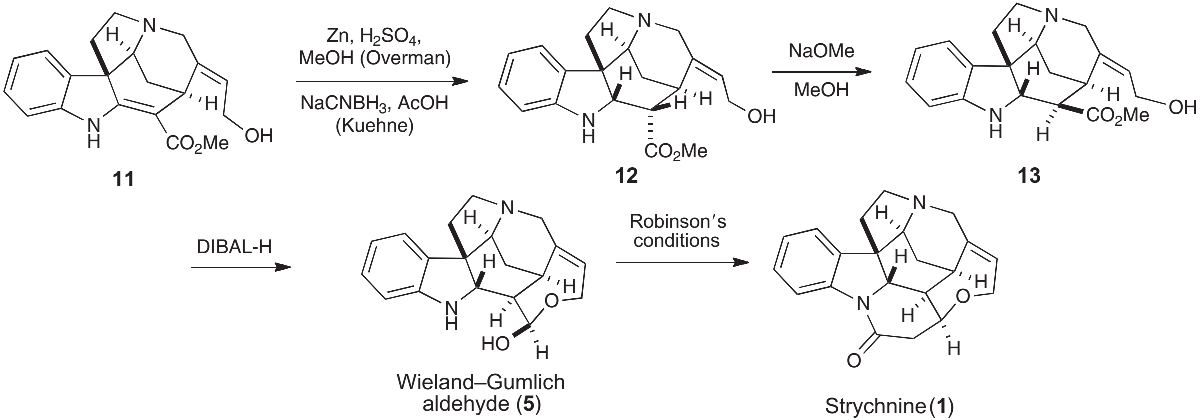
As mentioned above, many syntheses of strychnine employed Robinson's protocol and therefore targeted the Wieland–Gumlich aldehyde (**5**). Two key examples come from the laboratories of Overman and Kuehne, who each transformed pentacyclic (ABCDE) intermediate 18-hydroxyakuammicine (**11**) ultimately into the natural product. Overman first reduced vinylogous carbamate **11** with Zn, H_2SO_4, and methanol, whereas Kuehne employed sodium cyanoborohydride in AcOH. As the reaction produced a mixture of diastereomeric methyl esters **12** and **13**, equilibration to the more favorable (and requisite) β-epimer **13** was easily accomplished by stirring with sodium methoxide in methanol. Reduction of **13** with DIBAL-H secured Wieland–Gumlich aldehyde (**5**), which was converted to **1** with Robinson's protocol (Scheme 3).

Combining the endgame tactics of Overman and Kuehne with Rawal's intramolecular Heck approach to the DE bicyclic ring system naturally led to the identification of subgoal (**14**) as our target for synthesis (Scheme 4), which would be derived from 18-hydroxyakuammicine (**11**). Retrosynthetic analysis of **14** produced an intriguing opportunity to effect an intramolecular aza-Baylis–Hillman reaction of an appropriately functionalized spiroindolenine **16** bearing both electrophilic (i.e., imine) and nucleophilic (i.e., enoate) components (see synthon **15**). This would lead to gramine derivative **17**, which would feature both an appropriately spaced leaving group and an alkenyl halide to close the D-ring using Rawal's Heck tactic.

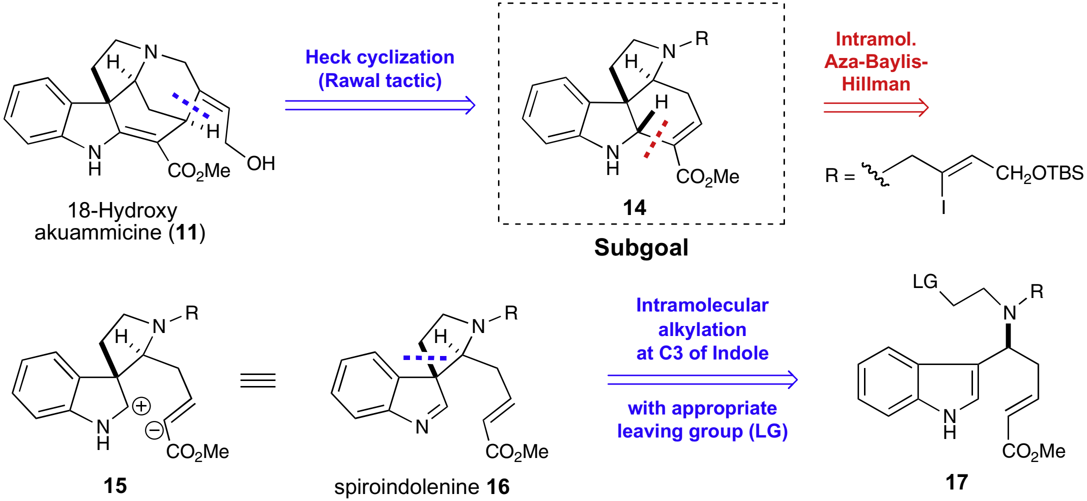
An important component of the spirocyclization to form the C-ring (i.e., connecting the C3 position of the indole and the carbon bearing the leaving group) was that it is a stereochemistry-forming event. In other words, it was critical the reaction proceed in a manner such that pendant enoate was proximal to the C2 position of indole in order for the E-ring to be prepared. A survey of the literature sheds light on the matter. Woodward prepared the C-ring by means of a Pictet–Spengler reaction between 2-veratryltryptamine **18** and ethyl glyoxaldehyde in the presence of *p*-toluenesulfonyl chloride (Scheme 5).[6] In the event, diastereomer **20** was isolated in 64% yield, which is the isomer possessing the opposite configuration for strychnine. In fact, in order to cyclize the E-ring, Woodward had to epimerize this center later in the synthesis. The rationale for this stereoselectivity lies in the bulky nature of the C-2 veratryl group, which sterically steers the reaction so as to avoid a steric clash with the ester moiety in **21** at the newly formed stereocenter.

3 SELECTED STRATEGIES FOR PREPARING THE ABCE TETRACYCLIC FRAMEWORK OF *STRYCHNOS* AND *ASPIDOSPERMA* ALKALOIDS

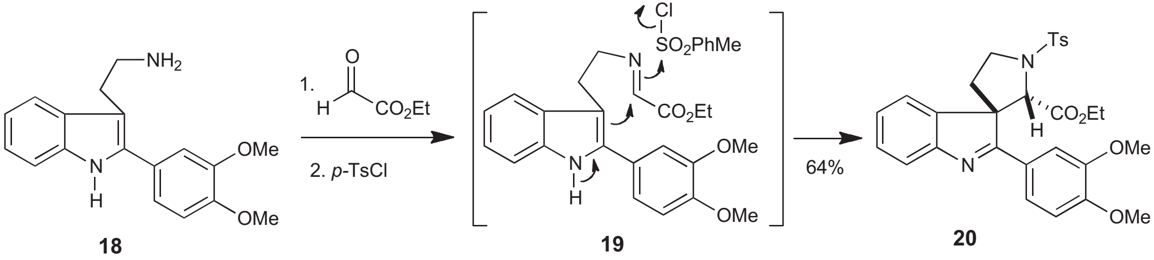
Before proceeding to the discussion of our approach to the ABCE framework of the *Strychnos* and *Aspidosperma* alkaloids, it is instructive to discuss the



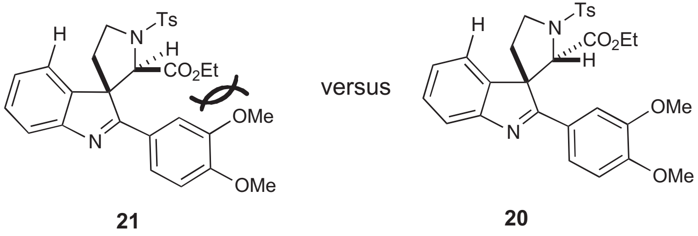
SCHEME 3 Endgame in Overman (1993) and Kuehne (1998) syntheses of strychnine.



SCHEME 4 Retrosynthetic analysis revealing ABCE subgoal.



Rationale for spirocyclization stereoselectivity

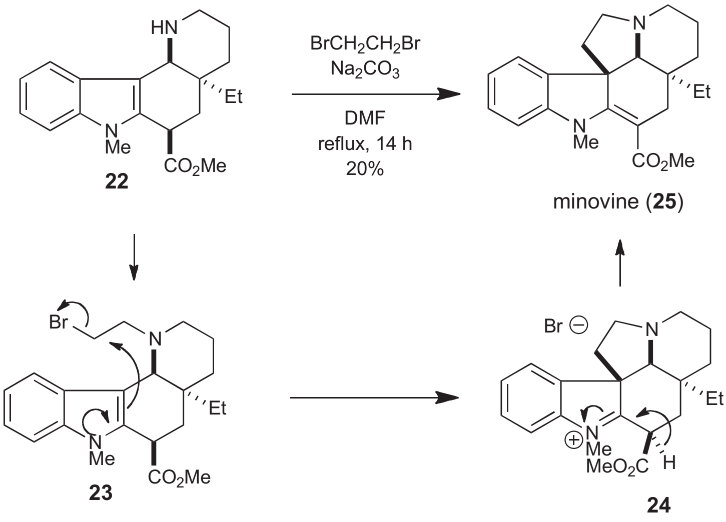


SCHEME 5 Woodward's C-ring cyclization (strychnine, 1954).

rich prior art. The following selections have been made based on their relevance to our approach. The organization is as follows: first, approaches to the C-ring of both the *Strychnos* and *Aspidosperma* alkaloids from gramine precursors will be presented; second, bis-cyclization approaches (i.e., wherein two rings are formed sequentially in one operation) will be discussed. Finally, each route is presented in chronological order.

3.1 Ziegler's 1,2-Dibromoethane Linchpin Approach

In 1970, Ziegler reported an elegant synthesis of the *Aspidosperma* alkaloid minovine (**25**), which was inspired by established biogenetic pathways.[12] After preparing tetracyclic gramine derivative **22**, an intriguing bis-alkylation linchpin strategy was employed to access the C-ring (Scheme 6). Treatment of **22** with 1,2-dibromoethane and sodium carbonate in refluxing DMF for 14 h afforded minovine (**25**) in 20% yield. The sequential process featured alkylation of the more basic piperidine nitrogen to form 2-bromoethylamino intermediate **23**. Spirocyclization of **23** at C3 of the indole nucleus stereoselectively gave **24**; deprotonation installed the β-amino acrylate moiety of minovine (**25**). Ziegler predicated the second step on a favorable orbital overlap of the indole π-system with C–Br σ* despite the modest yield. Magnus argued that the modest yield in such a transformation resulted from difficulty in accessing the challenging pentacoordinate transition state required for the spirocyclization; this led to his deployment of the Pummerer reaction to realize such a tactic.[13] Nevertheless, this was a bold and innovative approach to forging the C-ring of the *Strychnos* and *Aspidosperma* alkaloids that paved the way for (inspired) similar tactics (*vide infra*).



SCHEME 6 Ziegler's synthesis of C-ring (minovine, 1970).

3.2 Potier–Wenkert 2-Haloacetyl-Gramine Approach

Months after Ziegler communicated his elegant synthesis of minovine, Potier and Wenkert reported a similar two-carbon linchpin approach albeit at a higher (i.e., amide) oxidation state.[14] Treatment of tetracyclic amide **26** with bromoacetyl bromide afforded 2-haloacetamide **27** (Scheme 7). Heating a solution of **27** in DMF with sodium bicarbonate in DMF afforded a meager 10% yield of 5-oxo-deethylvincadifformamide (**28**). Again the authors attribute the low yields to an "unfavorable stereochemical environment." These pioneering approaches of Ziegler, Potier, and Wenkert to the C-ring of *Aspidosperma* and *Strychnos* alkaloids from gramine derivatives preceded the work of Natsume, Magnus, Bosch, Rubiralta, Rawal, Martin, and Andrade (*vide infra*).

3.3 Magnus' Pummerer Approach

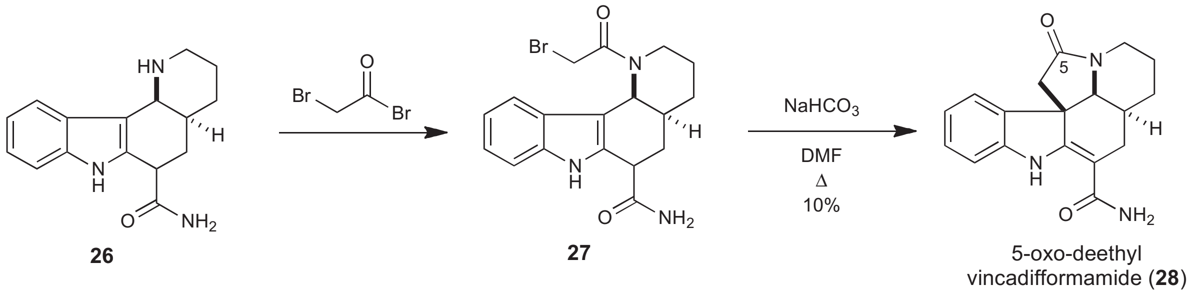
The low yields of C-ring formation by Ziegler and Potier–Wenkert prompted Magnus to devise an alternate strategy. Changing the reactive electrophilic group from sp^3 to sp^2 would both facilitate the process of cyclization and position a functional handle at that position for further manipulation (i.e., synthesis of congested kopsane *Aspidosperma* alkaloids). The realization of this strategy was the use of the potent thionium ion intermediate of the Pummerer reaction. Treatment of sulfoxide **29** with trifluoroacetic anhydride furnished pentacycle **30** in 91% yield. Desulfurization with Raney Ni (60% yield) afforded **31**; subsequent lithium aluminum hydride reduction gave aspidospermidine (**32**) in 70% yield (Scheme 8).

3.4 Natsume's 2-Chloroethylgramine Approach

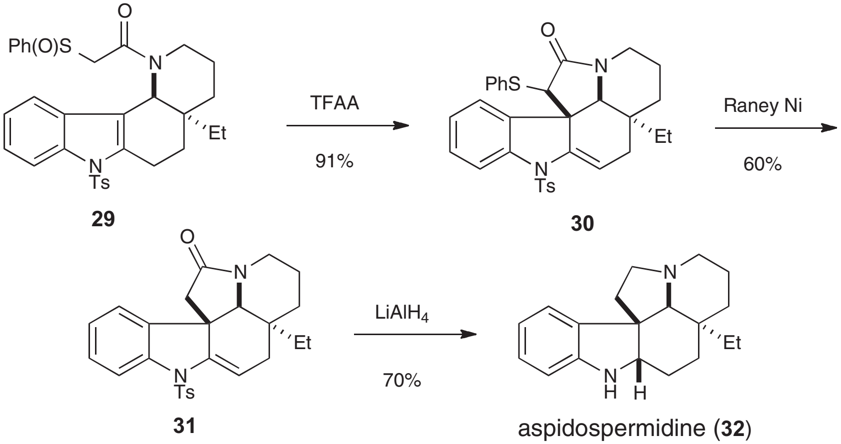
The synthesis of vindorosine in 1984 by Natsume and coworkers featured a brilliant bis-cyclization of 2-chloroethylgramine intermediate **33** reminiscent of Ziegler's approach, albeit in a stepwise fashion.[15] Mesylation of aminoethanol **33** furnished an intermediary chloride **34** that was subsequently reacted with KHMDS in THF at −70 °C then at room temperature for 1 h to stereoselectively afford pentacycle **35** in 60% yield whereby both C- and E-rings were prepared in a single operation (Scheme 9A). Optimization of this sequence was realized via the use of a β-keto ester moiety **36** as the pendant nucleophile as opposed to the methyl ketone (Scheme 9B). As such, Natsume transformed substrate **37** into **38** in 91% yield, which was carried to kopsinine in 1987.[16]

3.5 Bosch's Thionium Approach

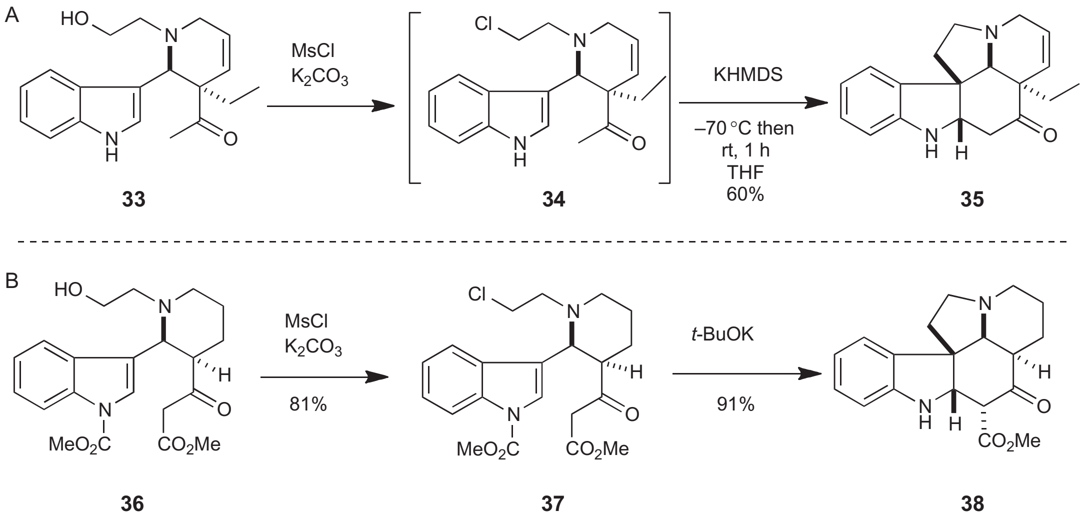
The synthesis of the C-ring of tubifolidine (**41**), a member of the *Strychnos* family, by Bosch and coworkers also leveraged elegant thionium chemistry (Scheme 10).[17] An appropriately functionalized dithioacetal tethered to the



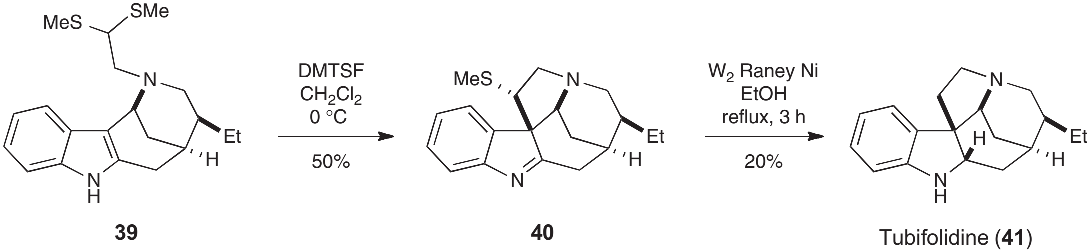
SCHEME 7 Potier–Wenkert synthesis of C-ring (5-oxo-deethylvincadifformine, 1970).



SCHEME 8 Magnus' synthesis of C-ring (aspidospermidine, 1982).



SCHEME 9 Natsume's bis-cyclization approach to C- and E-rings (vindorosine, 1984 and kopsinine, 1987).



SCHEME 10 Bosch's synthesis of C-ring (tubifolidine, 1988).

piperidine D-ring **39** when treated with the thiophilic reagent dimethyl (methyl-1-thio)sulfonium tetrafluoroborate[18] generated a thionium intermediate that spirocyclized at the C3 position to afford indolenine **40** in 50% yield.

Reductive desulfurization of **40** with Raney Ni and concomitant reduction of the carbon nitrogen double bond delivered tubifolidine (**41**) in 20% isolated yield.[19]

3.6 Rubiralta's 2-Hydroxyethyl Gramine Approach

In 1996, Rubiralta and coworkers reported a clever approach to the C-ring of the *Aspidosperma* alkaloids.[20] Starting with readily available 2-hydroxyethyl gramine derivative **42**, treatment with potassium *t*-butoxide and *p*-toluenesulfonyl chloride gave pentacyclic intermediate **43** in 77% yield via (1) tosylation of the primary alcohol and (2) spirocyclization to stereoselectively form the C-ring (Scheme 11).

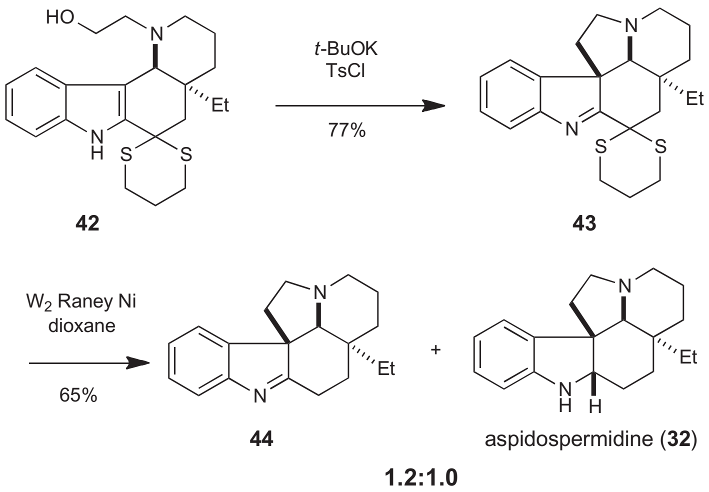
Reduction of dithiane **43** was accomplished with Raney Ni to afford indolenine **44** and aspidospermidine (**32**) in 65% yield (1.2:1 ratio).

3.7 Heathcock's 2-Iodoacetylgramine Approach

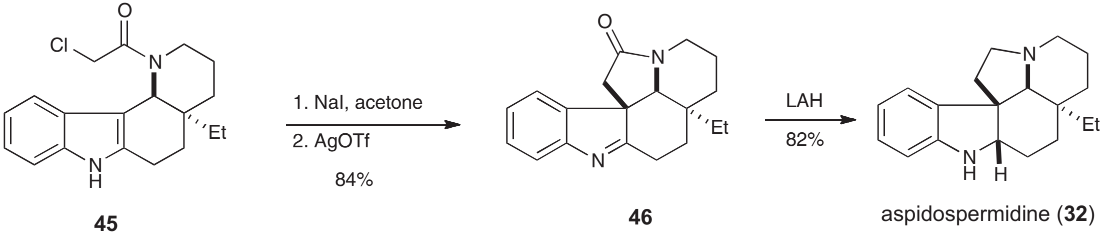
Heathcock's synthesis of aspidospermidine (**32**) employed the Potier–Wenkert tactic (i.e., 2-haloacetamide of a gramine derivative) for preparing the C-ring (Scheme 12).[21] However, there were several differences between the two approaches. First, his system lacked an additional primary amide that likely contributed to low yield with the Potier–Wenkert substrate. Second, he employed the more reactive iodo functionality in the spirocyclization (vs. the bromo analog). Thirdly and most significantly, he employed AgOTf to activate the α-halo functionality. Overall, the process furnished pentacycle **46** in 84% yield over two steps. LAH reduction of the lactam and the indolenine in **46** delivered aspidospermidine (**32**) in 82% yield.

3.8 Rawal's 2-Chloroethylgramine Approach

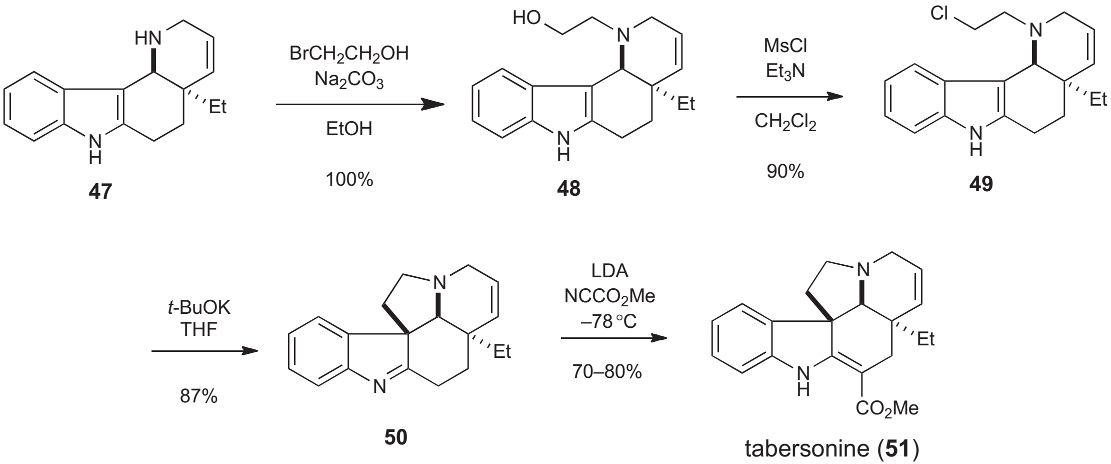
In 2002, Rawal reported elegant syntheses of various *Aspidosperma* alkaloids including tabersonine (**51**).[22] His approach to the C-ring was a blend of previous approaches, most prominently Natsume's and Rubiralta's. Installation of the 2-hydroxyethyl moiety was achieved by alkylation of gramine **47** with 2-bromoethanol and sodium carbonate (Scheme 13). Reaction of the primary alcohol in **48** with MsCl and Et_3N furnished 2-chloroethyl intermediate **49** in 90% yield. Treatment of **49** with *t*-BuOK in THF cleanly afforded the C-ring in 87% yield. To access tabersonine (**51**), Rawal modified a tactic initially reported by Overman in his synthesis of akuammicine (i.e., generation of aza-enolate with LDA and trapping with methyl chloroformate).[23] Specifically, Rawal employed Mander's reagent in place of methyl chloroformate, which gave excellent yields (70–80%) even on gram scale.



SCHEME 11 Rubiralta’s synthesis of C-ring (aspidospermidine, 1996).



SCHEME 12 Heathcock’s synthesis of C-ring (aspidospermidine, 2001).



SCHEME 13 Rawal's synthesis of C-ring (tabersonine, 2002).

3.9 Martin's 2-Hydroxyethyl Gramine Approach

The synthesis of the C-ring of pseudotabersonine (**54**) in 2010 by Martin and coworkers was inspired by Bosch and Rubiralta, who first reported the remarkable sequence of reactions toward the indolo[2,3-*a*]quinolizidine ring system in 1989.[24] The method as applied by Martin began with 2-hydroxyethyl gramine **52** bearing a phenylsulfonyl protecting group on the indole nitrogen (Scheme 14). Treatment of **52** with *t*-BuOK in THF/DME at low temperatures triggered a cascade of events: (1) removal of the sulfonyl group to generate *t*-$BuOSO_2Ph$ and an indole anion; (2) transfer of the sulfonyl group from *t*-$BuOSO_2Ph$ to the alcohol; and (3) spirocyclization of the indolyl anion and the primary benzenesulfonate intermediate to generate pentacycle **53** in 66% yield. Subjecting **53** to Rawal's LDA/Mander's reagent combination delivered pseudotabersonine (**54**) in 61% yield.[22]

4 SELECTED BIS-CYCLIZATION APPROACHES

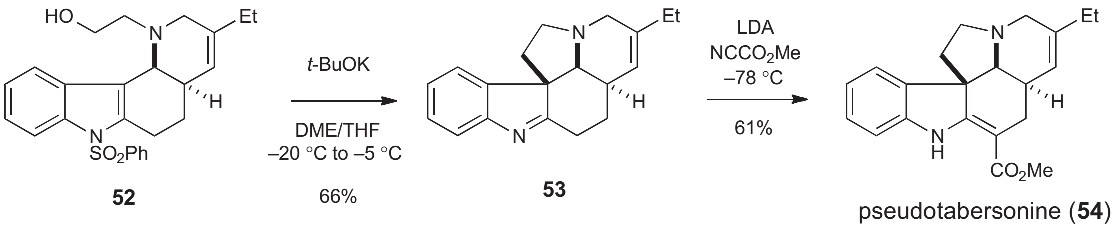
An exhaustive review of bis-cyclization reactions in the area of *Aspidosperma* and *Strychnos* alkaloids unfortunately cannot be done, but we have selected a few bis-cyclization approaches that do punctuate the history of chemical synthesis of complex alkaloids, showing the broad scope of creativity and innovation on the part of the chemist (and his/her laboratory). I apologize to those whose beautiful chemistry is not covered here due to space limitations, particularly in the *Strychnos* area, for which I refer readers to several excellent reviews.[4,25]

4.1 Harley-Mason's Approach

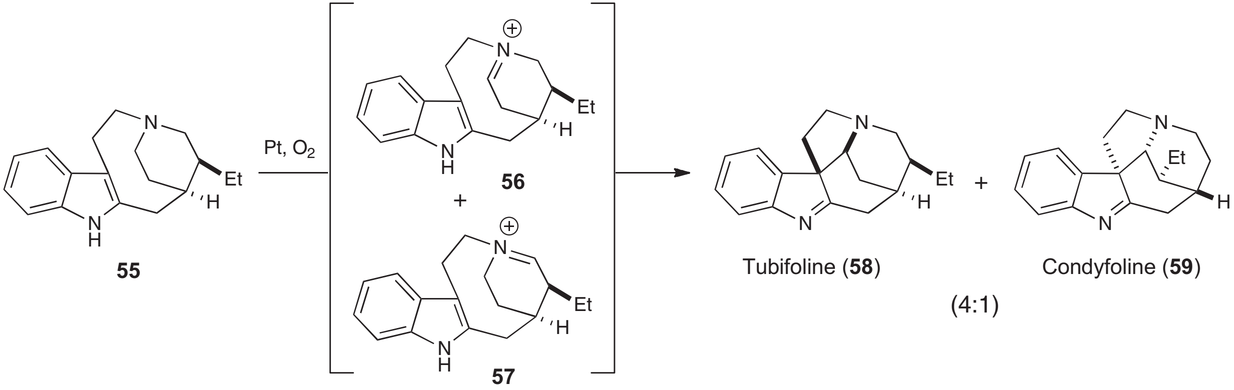
The concise and elegant synthesis of pentacyclic *Strychnos* alkaloids tubifoline (**58**) and condyfoline (**59**) by Harley-Mason in 1968 is a bona fide classic in alkaloid synthesis.[26] Harley-Mason discovered a concise route to the 9-membered stemmadenine system **55** and from this intermediate completed the syntheses of many *Strychnos* alkaloids, including tubifoline (**58**), which was the first pentacyclic *Strychnos* alkaloid to be prepared by chemical synthesis.[27] He was also keenly aware that in 1963 Schumann and Schmid had converted stemmadenine intermediate **55** (obtained from akuammicine (**2**) by degradation) into a mixture of tubifoline (**58**) and condyfoline (**59**) by aerial oxidation over platinum.[28] This tactic was successfully employed on fully synthetic, racemic material (Scheme 15). The process occurred via (1) formation of regioisomeric iminium ions **56** and **57** in a 4:1 ratio and (2) transannular attack at C3 of indole in a Mannich fashion.

4.2 Büchi's Approach

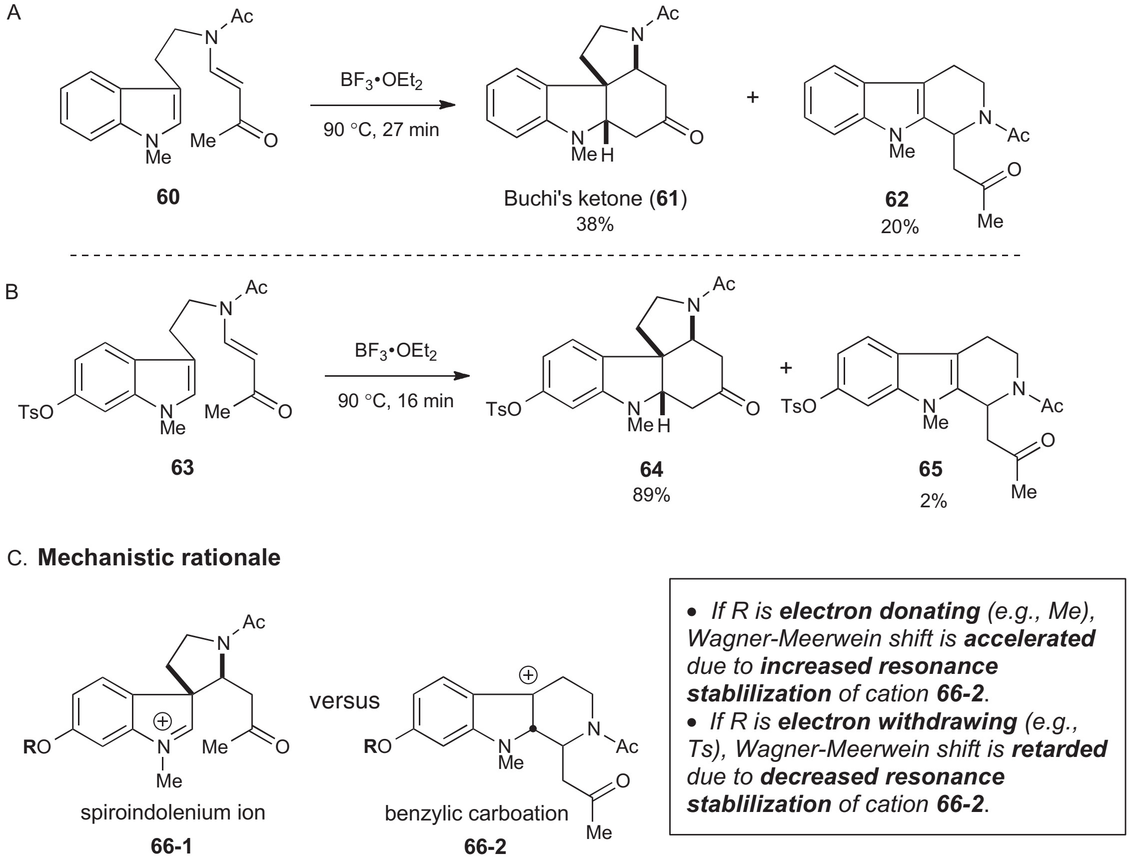
Büchi's approach to *Aspidosperma* alkaloids vindorosine and vindoline began with a brilliant bis-cyclization reaction wherein the C- and E-rings were prepared in the same operation (Scheme 16). Vindoline makes up the "southern



SCHEME 14 Martin's synthesis of C-ring (pseudotabersonine, 2010).



SCHEME 15 Harley–Mason's synthesis of tubifoline and condyfoline (1968).



- *If R is **electron donating** (e.g., Me), Wagner-Meerwein shift is **accelerated** due to **increased resonance stablilization** of cation **66-2**.*
- *If R is **electron withdrawing** (e.g., Ts), Wagner-Meerwein shift is **retarded** due to **decreased resonance stablilization** of cation **66-2**.*

SCHEME 16 Büchi's route to vindorosine (1971) and vindoline (1975).

half" of the *Vinca* alkaloid vinblastine used in cancer chemotherapy regimens and has always been a popular target for synthesis due to the architectural challenge and biological relevance. A series of reactions quickly prepared vinylogous imide **60** as substrate for the bis-cyclization reaction. When **60** was heated in BF_3·etherate at 90 °C for 27 min, two compounds were isolated: tetracyclic ketone **61** in 38% yield, which is now referred to as "Büchi's ketone" and tetrahydro-β-carboline **62** in 20% yield as an undesired by-product (Scheme 16A). The latter is derived from a competing Wagner–Meerwein (W–M) shift of the spiroindolenium intermediate (e.g., **66**), as the compound enters the venerable Pictet–Spengler reaction manifold.[29] Ketone **61** was carried onto vindorosine.[30] When imide substrate **63** was prepared bearing the correct oxidation state on the benzene moiety and subjected to the same conditions for bis-cyclization, an impressive 89% yield of ABCE tetracycle **64** was isolated along with only 2% of the Pictet–Spengler by-product **65** (Scheme 16B). When a methoxy group was employed at that position, which maps onto vindoline, a meager 9% yield of the corresponding ABCE tetracycle was isolated.[31]

Büchi rationalized this by looking at the intermediary spiroindolenium ion **66-1** and benzylic carbocation **66-2** (Scheme 16C). With electron-donating groups (e.g., methoxy) on the benzene ring, the W–M shift is accelerated by virtue of increased resonance stabilization. On the other hand, with electron-withdrawing groups (e.g., arenesulfonate), the W–M shift is retarded as resonance participation by the oxygen is attenuated, which leads to less stabilization of **66-2**.

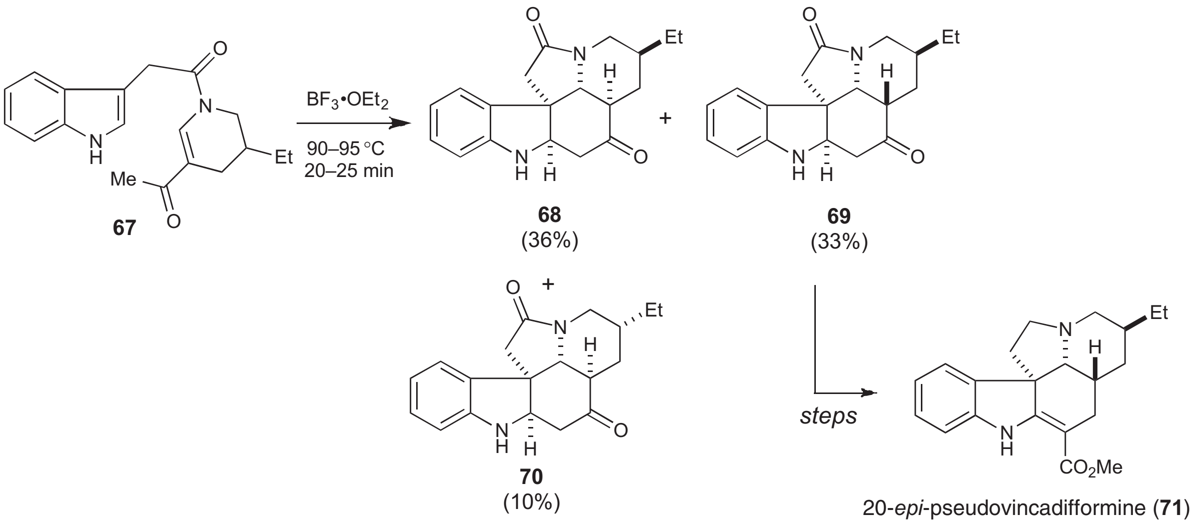
4.3 Wenkert's Approach

Wenkert pioneered the 3-acylpyridine approach to complex indole alkaloids, resulting in beautiful syntheses of many *Strychnos* and *Aspidosperma* alkaloids.[32] A poignant example is in his 1984 synthesis of 20-*epi*-pseudovincadifformine (**71**), which featured his signature Lewis acid-catalyzed bis-cyclization of vinylogous imide **67** (Scheme 17).[33] Curiously similar to Büchi's approach, heating a solution of **67** in neat BF_3·etherate at 90–95 °C resulted in a mixture of three products, **68**, **69**, and **70** in a 4:4:1 ratio. Intermediate **69** was carried further to 20-*epi*-pseudovincadifformine (**71**).

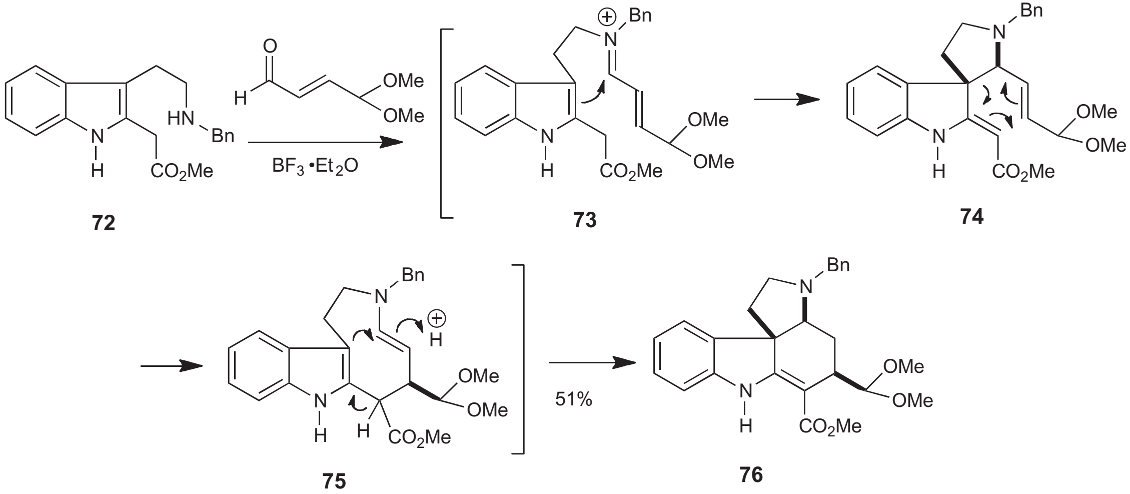
4.4 Kuehne's Approach

In 1993, Kuehne reported a remarkable domino condensation/Mannich/sigmatropic rearrangement/Mannich sequence to rapidly and efficiently assemble an elaborated ABCE framework characteristic of the *Strychnos* alkaloids (Scheme 18).[34]

Substrate **72** was prepared in five steps from commercial tryptamine. Condensation of **72**, 4,4-dimethoxy-2-butenal, and catalytic BF_3·etherate gave



SCHEME 17 Wenkert's route to 20-*epi*-pseudovincadifformine (1984).



SCHEME 18 Kuehne's route to strychnine (1998).

tetracycle **76** in a single operation in 51% isolated yield. This striking multistep process is thought to proceed via (1) an initial Mannich condensation of **73**, (2) spirocyclization to form **74**, (3) [3,3]-sigmatropic rearrangement to give **75**, and, finally (4) a transannular Mannich reaction in **75** to deliver ABCE tetracycle **76**. Kuehne leveraged this strategy in his concise syntheses of strychnine and related alkaloids.[35]

4.5 Padwa's Approach

In 2007, Padwa and coworkers reported a concise synthesis of strychnine based on an intramolecular Diels–Alder reaction/rearrangement cascade (Scheme 19).[36]

Tethered indolyl furan **77** was prepared in four steps from known starting materials. The rationale behind the bulky 2-methylbenzyl group for the amido nitrogen was to favor the *s-trans* rotamer **78** and therefore promote the intramolecular Diels–Alder reaction. Indeed, heating **77** in a microwave reactor with a catalytic MgI_2 gave ABCE tetracycle **81** in 95% yield. Padwa's domino sequence presumably proceeds via (1) nitrogen-assisted ring opening of cycloadduct **79**, (2) deprotonation of **80**, and (3) tautomerization thereof to give ketone **81**.

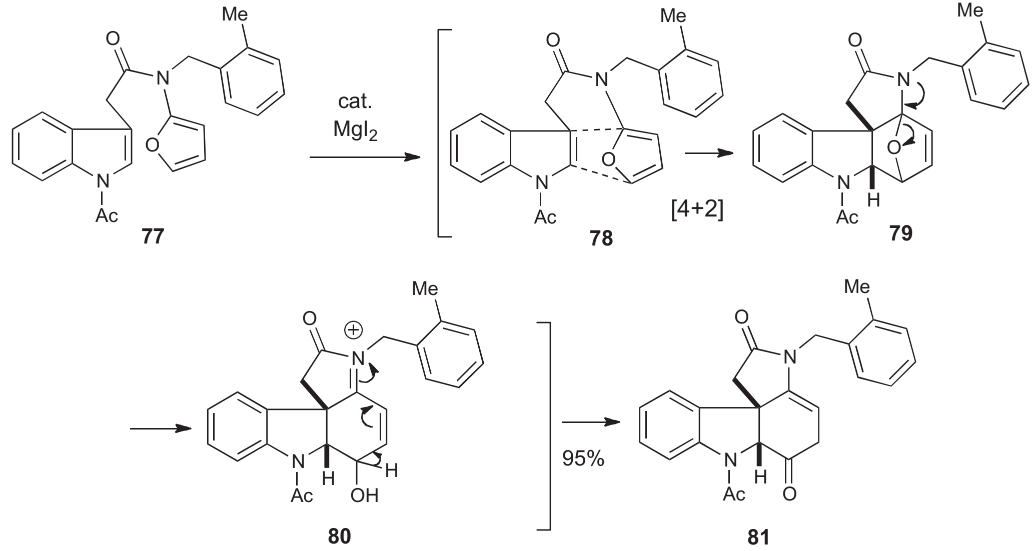
4.6 Vanderwal's Approach

Vanderwal and coworkers have shown the versatility of Zincke aldehyde chemistry.[37] In 2009, they reported an elegant, concise synthesis of *Strychnos* alkaloid norfluorocurarine featuring a bis-cyclization approach to the ABCE core **83** from **82**, which was readily prepared from N_b-benzyltrytpamine (Scheme 20).[38] Inspired by the work of Marko,[39] treatment of **82** with *t*-BuOK in a sealed tube at 80 °C for <2 h gave tetracycle **83** in 82% yield. The formal [4+2] cycloaddition process is thought to proceed via a stepwise intramolecular Michael/Mannich sequence (i.e., **84** and **85**) and final isomerization sequence of β,γ-unsaturated enal **85** into α,β-unsaturated enal **83** via dienolate **86**.[37] Evidence for this came from the failed cyclization of a substrate bearing a methyl group in the α-position of the dienamide, which precluded the final isomerization step.[40]

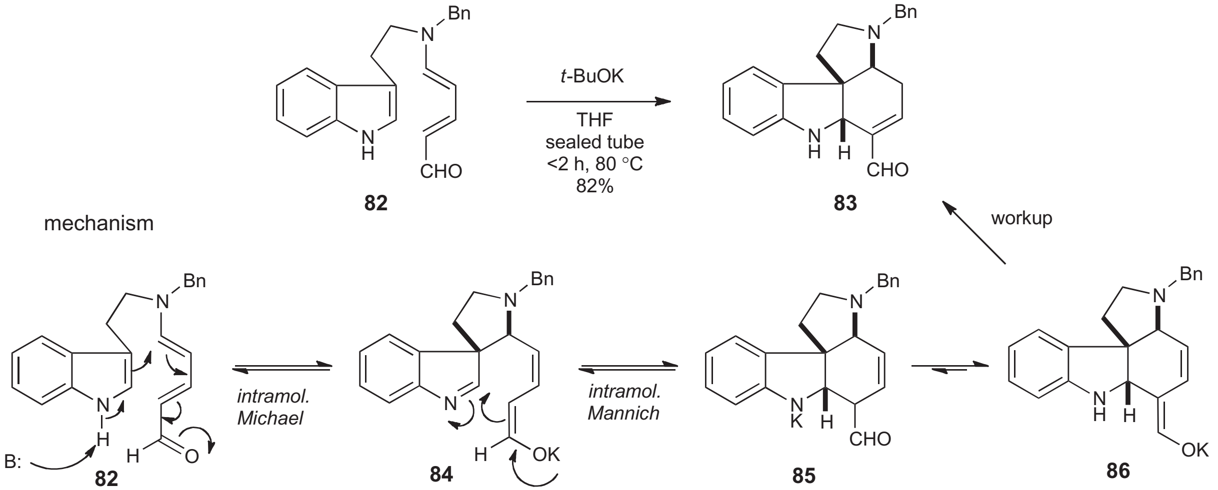
Tetracycle **83** was transformed into the *Strychnos* alkaloid norfluorocurarine[38] and 2 years later into strychnine.[41]

5 OUR APPROACH TO THE ABCE TETRACYCLE

Scheme 4 illustrates our retrosynthetic thinking involved in constructing the ABCE tetracycle. Thus, the first task was, in fact, to determine if the spirocyclization at C3 of indole **17** would proceed in the desired fashion (i.e., mapping onto the *Strychnos* framework) or not. To that end, we condensed



SCHEME 19 Padwa's route to strychnine (2007).



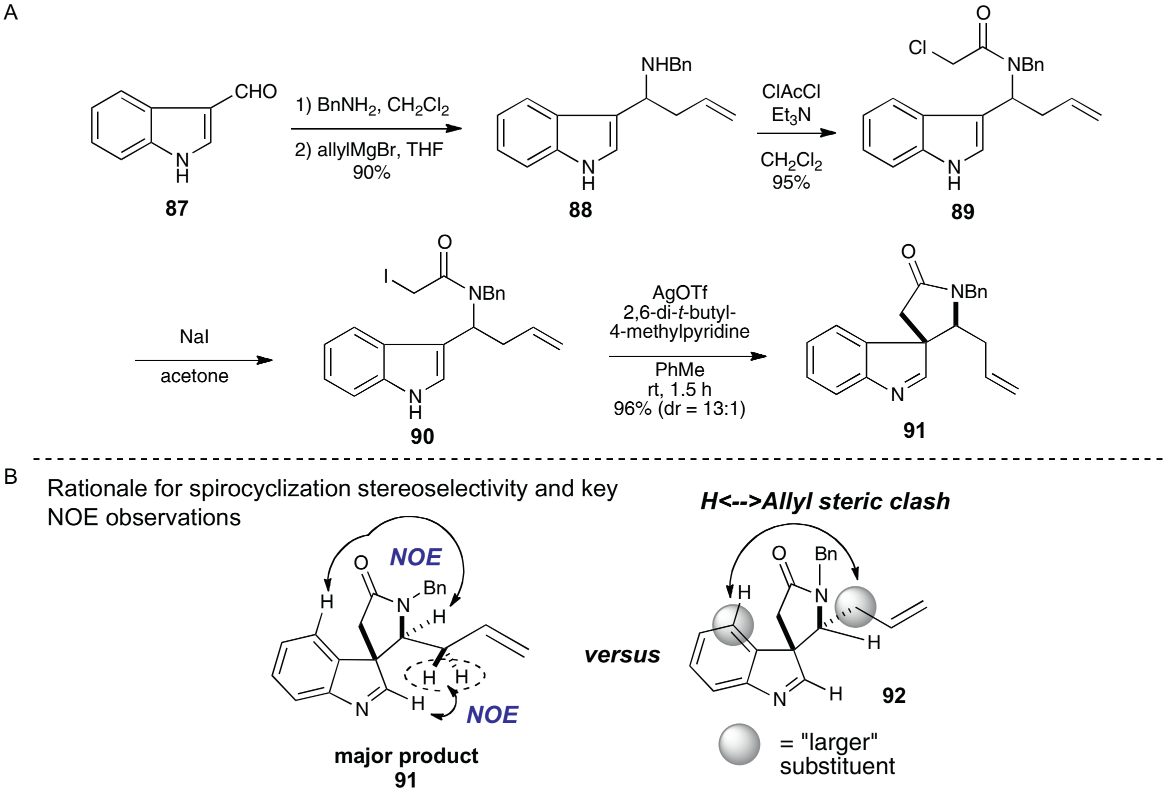
SCHEME 20 Vanderwal's route to norfluorocurarine (2009).

indole 3-carboxaldehyde (**87**) with benzylamine and treated this imine with an excess of allylmagnesium bromide to give homoallylic amine **88** in 90% yield over two steps (Scheme 21A). The rationale behind the choice of allyl was to enable functionalization via cross-metathesis (CM) (*vide infra*). At this stage, we opted to employ Heathcock's approach toward the C-ring (see Scheme 11). Acylation of **88** with chloroacetyl chloride furnished amide **89** in 95% yield. The Finkelstein reaction of **89** (i.e., NaI in acetone) afforded spirocyclization precursor **90**. Attempted spirocyclization using Heathcock's original conditions (i.e., only AgOTf; no base) lead to substantial decomposition of substrate. This is not surprising as TfOH is generated in the process. To rectify this, we employed the hindered base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). In the event, we obtained a 96% yield of indolenine **91** (dr = 13:1). While we screened other bases (e.g., 2,6-lutidine, pyridine, Et_3N, *i*-Pr_2NEt), DTBMP gave the highest yields. Additionally, the reaction proceeded in both THF and CH_2Cl_2. Stronger bases (e.g., NaH, *t*-BuOK) also cyclized **90** albeit at the expense of both yield and diastereoselectivity.[42]

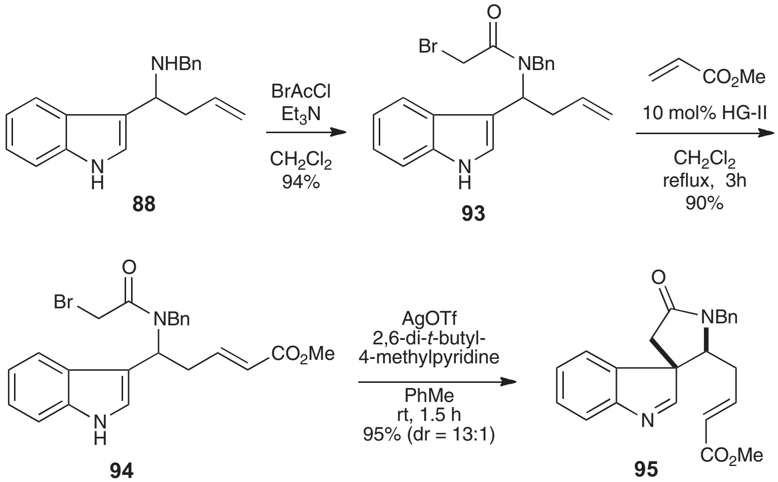
We reasoned that the major diastereomer was the desired **91** and not **92**; this was largely based on a steric argument resulting from a "steric clash" of the C4 hydrogen (indole) and the allylic methylene group. Initial evidence in favor of this hypothesis came from clear NOE analyses, specifically enhancements between (1) the C4 hydrogen on the indole and the methine α to nitrogen; and (2) the C2 hydrogen on the indole and the allylic methylene hydrogens (Scheme 21B).

With the C-ring secured, we turned our attention to preparing the D-ring. En route, we investigated whether a 2-bromoacetamide could spirocyclize rather than the 2-chloro to save a step (i.e., obviate the Finkelstein reaction). Indeed, Potier and Wenkert had employed a bromoacetamide in their C-ring synthesis (Scheme 7). Thus, homoallylic amine **88** was acylated with bromoacetyl chloride in 94% yield to afford **93** (Scheme 22). A CM reaction was recruited to install the desired enoate functionality for the D-ring.[43] Phosphine-free Hoveyda-Grubbs II catalyst[44] proved effective for this transformation, affording enoate **94** in 90% yield. To our delight, the subsequent spirocyclization proceeded almost identically to the iodo model system, furnishing the functionalized ABCD system **95** in 95% yield (dr = 13:1).

With tricycle **95** in hand, we were poised to evaluate whether an intramolecular aza-Morita[45] or aza-Baylis–Hillman (IABH)[46] reaction could indeed close the D-ring. This tactic was predicated on the electrophilic nature of spiroindolenine **95**, which was further enhanced by the *N*-phenyl substituent. To the best of our knowledge, this specific transformation was unprecedented.[47] Altogether, we screened a variety of conditions to effect either the intramolecular aza-Morita or IABH reaction. We observed no reaction of **95** with Bu_3P, Et_3N, *i*-Pr_2NEt, DMAP, or DABCO regardless of the solvent used (e.g., CH_2Cl_2, THF, PhMe). However, treatment of **95** with 2–2.5 equiv. of 1,8-diazabicycloundec-7-ene (DBU) in toluene at room temperature for 12 h cleanly afforded ABCE tetracycle **96** in 90% yield (Scheme 23A). The use of less DBU translated into longer reaction times. Performing the reaction in THF gave **96** in slightly lower yield



SCHEME 21 DTBMP-mediated spirocyclization to form C-ring.

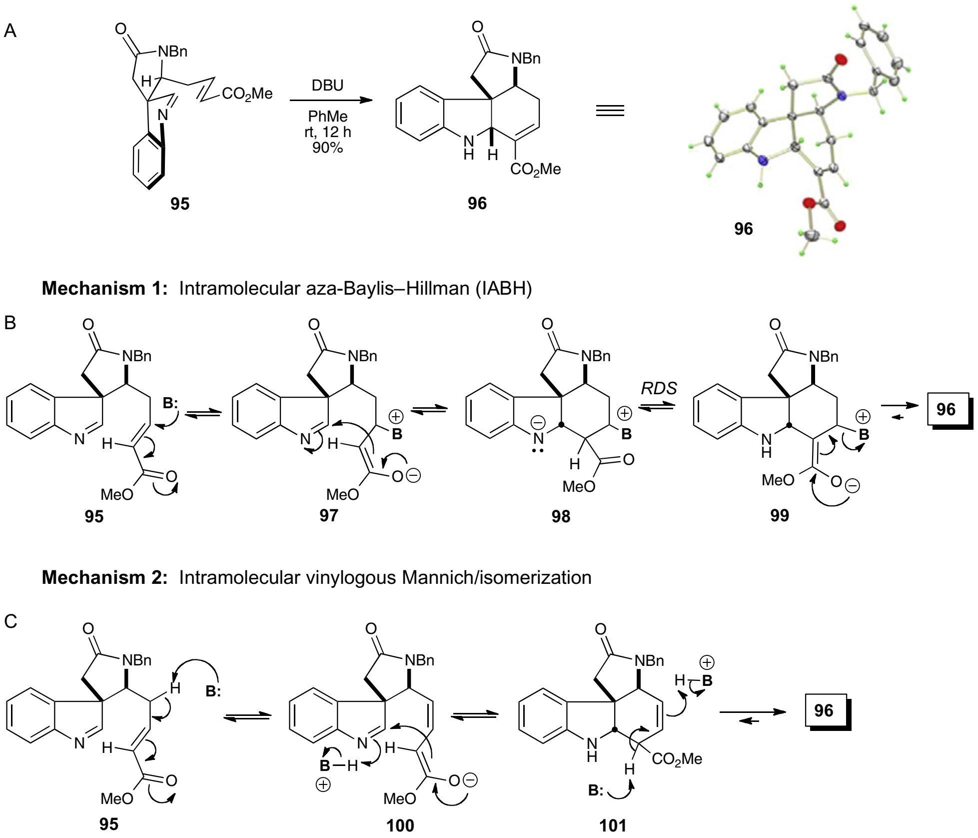


SCHEME 22 Streamlined synthesis of functionalized ABC system.

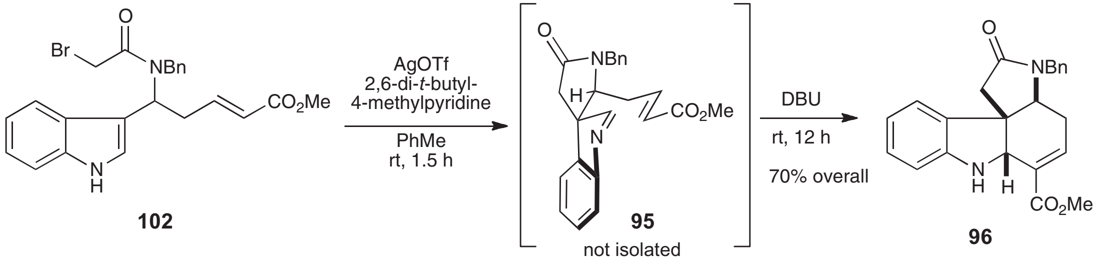
(83%). Recrystallization of **96** from EtOAc afforded material for single-crystal X-ray analysis, which confirmed previous spectroscopic assignments.

A priori, there are two mechanistic proposals to rationalize the D-ring cyclization. The fact that DBU was the only effective base in the D-ring cyclization reaction (Scheme 23A), coupled with its strong basicity, undermines the IABH mechanism (Scheme 23B) and suggests that γ-deprotonation of the enoate/cyclization/isomerization (Scheme 23C) may be operative. Scheme 23B describes the discrete steps along the pathway of the IABH reaction consistent with mechanistic studies of the *intermolecular* variant by Jacobsen[48] and Leitner.[49] Those steps include: (1) a Michael addition of the amine base to the enoate of **95**, (2) cyclization of the ammonium enolate zwitterion onto the imine in **97**, (3) proton transfer (the RDS) in **98**, and, finally, (4) β-elimination of the ammonium species **99** to deliver product **96**. On the other hand, Scheme 23C shows the steps involved in the alternative γ-deprotonation/cyclization/isomerization mechanism. Therein, DBU can deprotonate the γ-position of enoate **95** and generate dienolate **100**. (*Z*)-β,γ-Enoate intermediate **100**, which is in equilibrium with its (*E*) isomer (not shown), can cyclize onto the imine moiety in a Mannich fashion. Attendant DBU-mediated isomerization of β,γ-enoate **101** to the more energetically favorable α,β-enoate **96** completes the sequence. Mechanistic studies are currently in progress to help rationalize this interesting process.

To further increase efficiency, we wondered if both C- and D-ring cyclizations could be accomplished in a single pot (i.e., operation) without isolating the spiroindolenine. In the event, treatment of bromoacetamide **102** with AgOTf and DTBMP in toluene at room temperature for 1.5 h followed by the addition of DBU (2.5 equiv.) and additional stirring (12 h) afforded **96** in 70% yield after flash silica gel chromatography (Scheme 24).[50]



SCHEME 23 E-ring cyclization and two mechanistic proposals.



SCHEME 24 One-pot bis-cyclization (our approach).

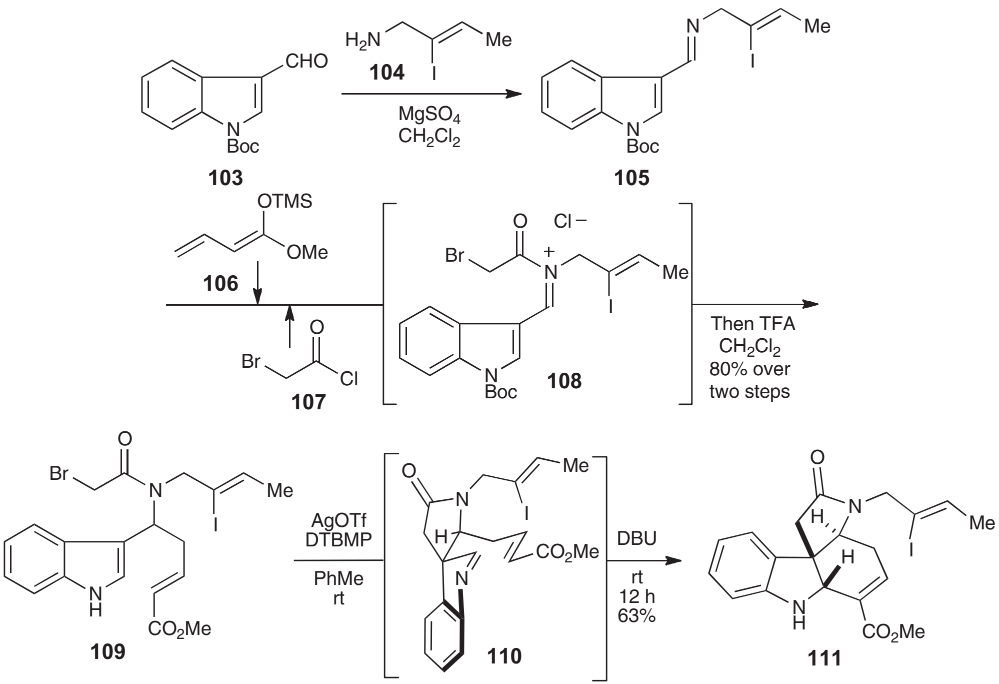
6 RACEMIC SYNTHESES OF AKUAMMICINE AND STRYCHNINE

With a route to the ABCE framework in hand, we were poised to launch syntheses of two classic *Strychnos* targets akuammicine (**2**) and strychnine (**3**). However, we wanted to increase step-efficiency vis-à-vis the first route (Scheme 22). Toward this goal, we employed the vinylogous Mannich reaction.[51] The condensation of *N*-Boc indole 3-carboxaldehyde (**103**) with known allylic amine **104** gave imine **105** (Scheme 25).[52] In the event, treatment of **105** with vinyl silyl ketene acetal **106** and bromoacetyl chloride (**107**) effected the vinylogous Mannich (via the intermediary *N*-acyliminium species **108**).[51] Addition of TFA removed the *N*-Boc protecting group and afforded **109** in 80% yield (two steps). Subjecting **109** to our sequential bis-cyclization protocol: (1) AgOTf and DTBMP to give spiroindolenine **110** bearing the C-ring; and (2) subsequent addition of 3 equiv. of DBU to afford ABCE tetracycle **111** took place in 63% overall yield. Importantly, the reaction proceeded in the presence of the vinyl iodide side chain with no issues.

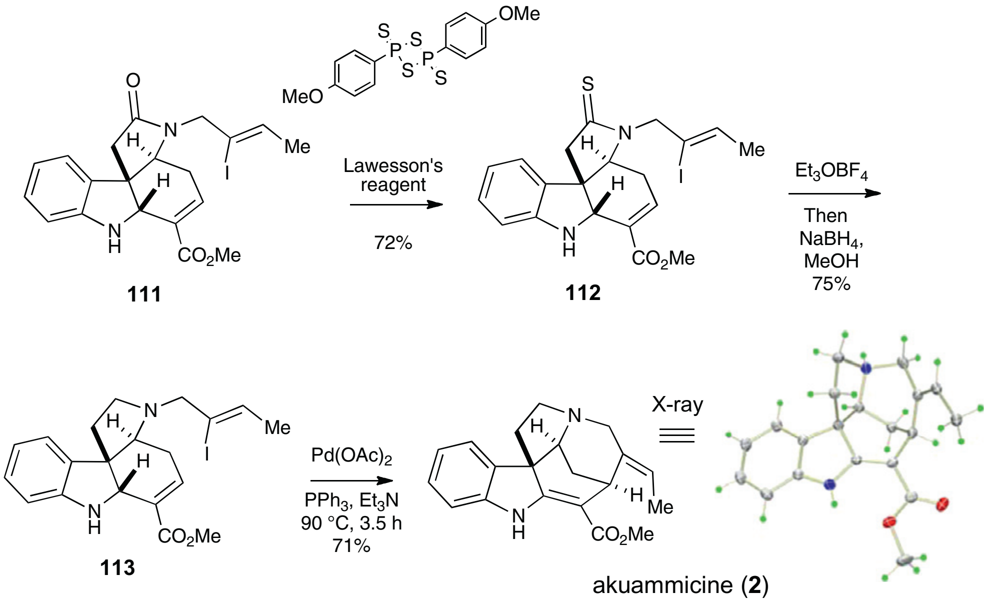
The endgame for akuammicine (**2**) began with adjustment of the oxidation state of the C-ring. The presence of vinyl iodide and conjugated ester functional groups precluded hydride reduction or similar reducing agents; thus, recourse to the classical Borch protocol (i.e., amide *O*-alkylation with Meerwein's salt followed borohydride reduction of the imidate intermediate) was made.[53] Unfortunately, this reaction was ineffective in our hands as the indoline nitrogen in **111** suffered from significant alkylation. A solution to our problem was found in Raucher's modification of the Borch method.[54] Specifically, converting the amide/lactam to the corresponding thioamide/lactam resulted in improved alkylation yields due to the softness of sulfur vis-à-vis oxygen. Thus, treatment of **111** with Lawesson's reagent afforded thiolactam **112** in 76% yield (Scheme 26). Alkylation of **112** with Et_3OBF_4 and subsequent reduction with $NaBH_4$ and methanol furnished tetracycle **113** in 75% yield. The use of Me_3OBF_4 resulted in additional methylation at the N_a-position, which was ameliorated by employing the bulkier ethyl variant. With **113** in hand, the endgame inspired by Rawal's intramolecular Heck reaction was engaged.[9] We were pleased that heating a solution of **113**, catalytic $Pd(OAc)_2$ and PPh_3 in Et_3N as solvent at 90 °C for 3.5 h secured akuammicine (**2**) in 71% yield. The use of other solvents and variants of the Heck reaction resulted in lower yields.

Treatment of **2** with HCl and slow evaporation of the salt from dichloromethane afforded material suitable for single-crystal X-ray analysis, which served to further confirm the structure. In summary, the total synthesis of akuammicine (**2**) was accomplished in six steps (20% overall yield) from commercial *N*-Boc indole 3-carboxaldehyde **103**.[55]

The total synthesis of strychnine (**1**) required slight modifications of the route employed for **2**. First and foremost, we required a more functionalized



SCHEME 25 Application of method toward synthesis of akuammicine.



SCHEME 26 Akuammicine synthesis endgame.

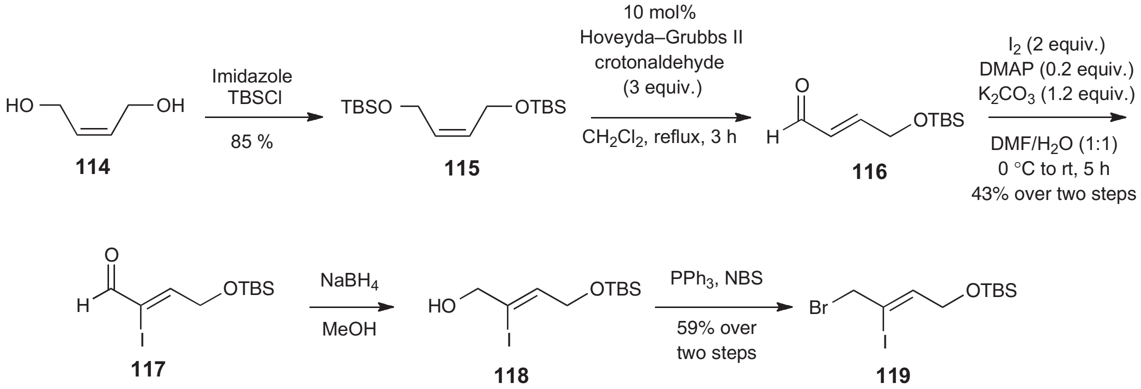
side chain, the synthesis of which is shown in Scheme 27. Protection of commercial (*Z*)-2-butenediol (**114**) with TBSCl and imidazole furnished **115**. Next, a CM reaction with crotonaldehyde and bis-*O*-TBS ether **115** (inspired by Taber's CM methodology of (*Z*)-2-butenediol and various alkenes)[56] yielded (*E*)-enal (**116**), which was subjected to Krafft's α-iodination protocol featuring DMAP, iodine, and K_2CO_3, to furnish vinyl iodide **117** (43% over two steps).[57] Reduction with $NaBH_4$ afforded alcohol **118**. Subsequent bromination (i.e., PPh_3 and NBS) gave the required bromide **119** in 59% over two steps.

To increase the convergence of the route to **1**, we postponed side chain installation to later in the synthesis and used the *N*-benzyl protecting group (Scheme 28). Condensation of benzylamine and **103**, vinylogous Mannich reaction, and the key bis-cyclization procedure furnished tetracycle **120** in 54% overall yield. Previously described lactam reduction delivered **122** via thiolactam **121**. After various attempts at removing the *N*-benzyl group in **122**, we discovered that optimal conditions included (1) stepwise protection of the indoline nitrogen with α-chloroethyl chloroformate (ACE-Cl)[58] and (2) reflux with neat ACE-Cl for 48 h. These conditions furnished diamine **124** in 75% yield from **123**. Alkylation with requisite bromide **119**[11] delivered Heck cyclization precursor **125** in 63% yield. In the event, we obtained **126** in a satisfactory 85% yield.[59] At this stage, we followed the Overman and Kuehne endgame discussed in Scheme 3. Reduction of the vinylogous carbamate and epimerization of the methyl ester afforded **13** in 80% overall yield.[60] Treatment of **13** with DIBAL-H delivered the W–G aldehyde (**5**), which was transformed into strychnine (**1**) using Robinson's protocol in 49% yield.

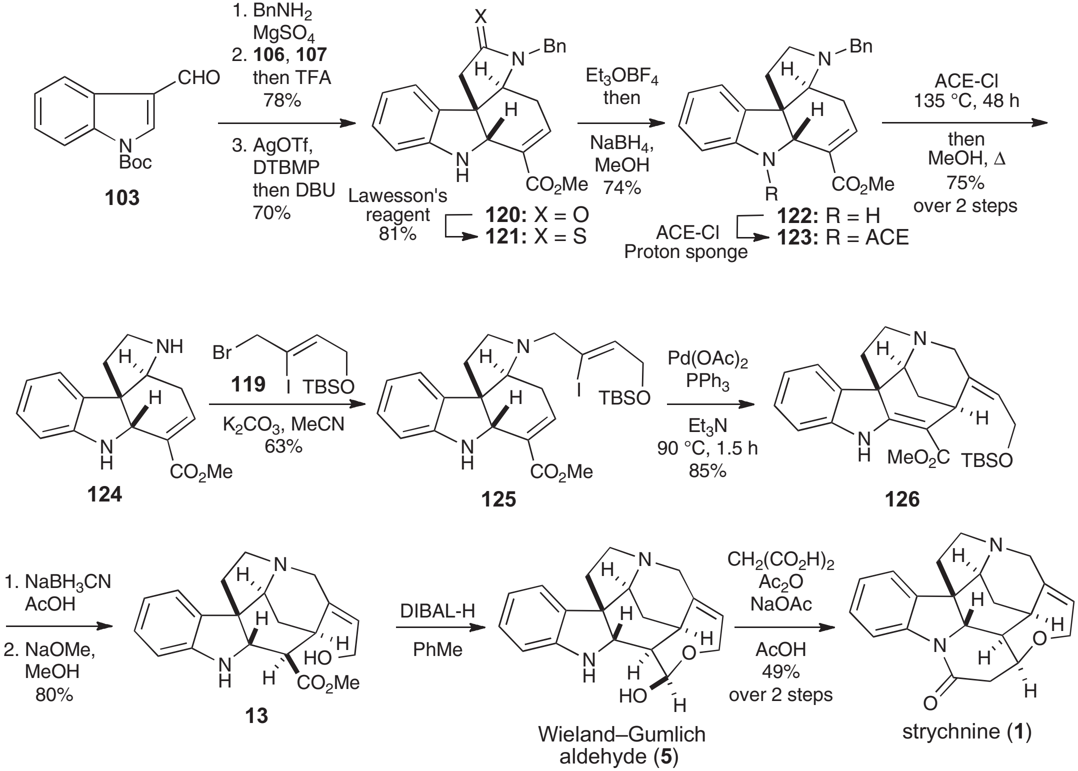
7 ASYMMETRIC PREPARATION OF THE ABCE TETRACYCLE

In order to realize the asymmetric syntheses of *Strychnos* alkaloids **1–4** (Figure 1), the enantioselective synthesis of a common building block was required. To that end, we condensed indole 3-carboxaldehyde (**87**) with commercially available (*S*)-phyenylglycinol (Scheme 29). Treatment of imine **127** with allylmagnesium chloride afforded homoallylic amine **128** in 92% yield (dr > *95:5*) over two steps. In order to confirm the stereochemical outcome of the reaction, we prepared material suitable for single-crystal X-ray analysis. Reaction of amino alcohol **128** with carbonyldiimidazole and Et_3N afforded an oxazolidinone that was acylated with ethyl carbamate to furnish **129** (36% yield over two steps). Recrystallization of **129** from CH_2Cl_2 and single-crystal X-ray analysis unambiguously confirmed the desired (*S*)-configuration at C3 (Scheme 29).

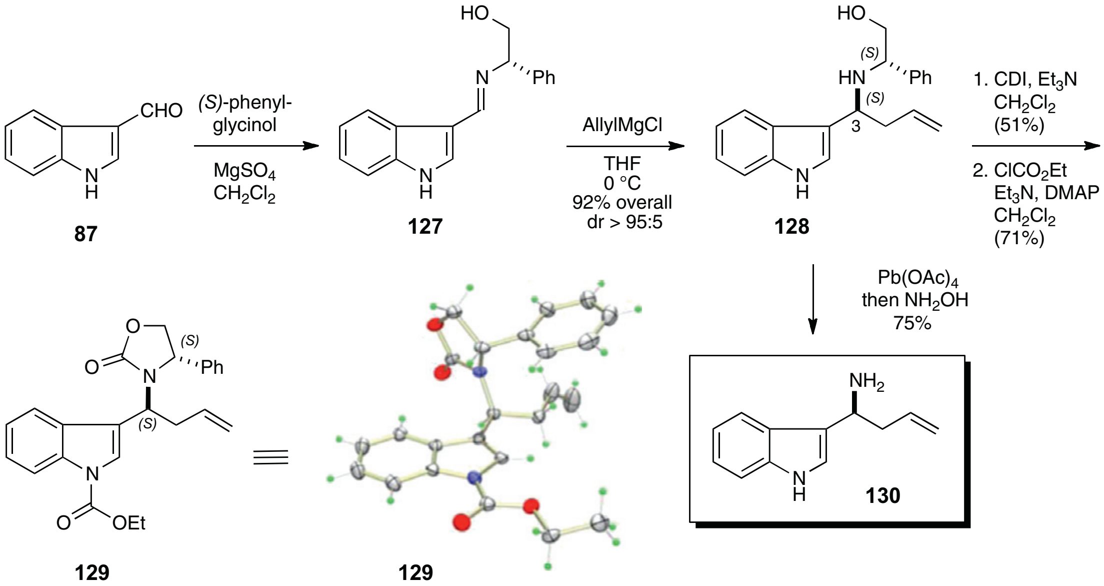
Removal of the auxiliary with $Pb(OAc)_4$ and hydroxylamine afforded the homoallylic amine **130** in 75% unoptimized yield.[61] A problem with this method, beyond the use of toxic lead tetraacetate in stoichiometric quantity,



SCHEME 27 Synthesis of strychnine side chain.



SCHEME 28 Synthesis of strychnine.



SCHEME 29 First-generation asymmetric synthesis of key intermediate.

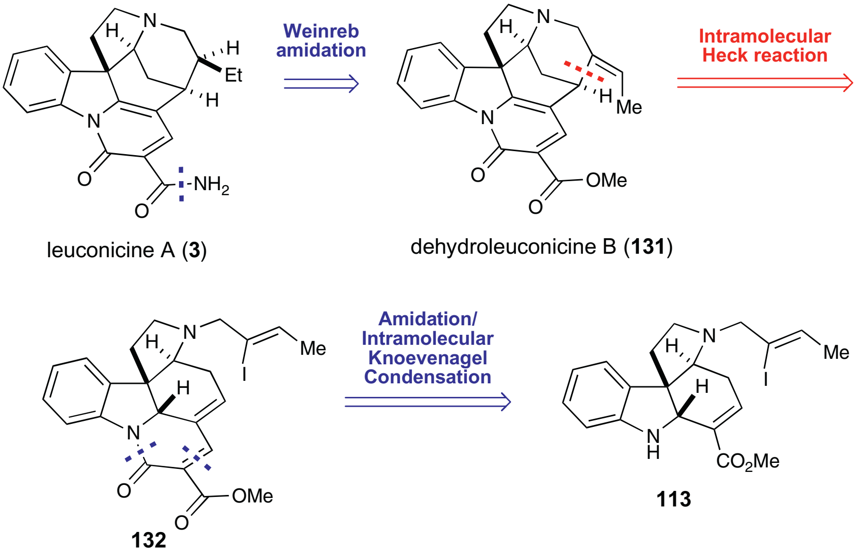
was that purification of **130** was painfully difficult on large scale. Thus, we abandoned this process in search of a better one (*vide infra*).

8 ASYMMETRIC SYNTHESES OF LEUCONICINES A AND B

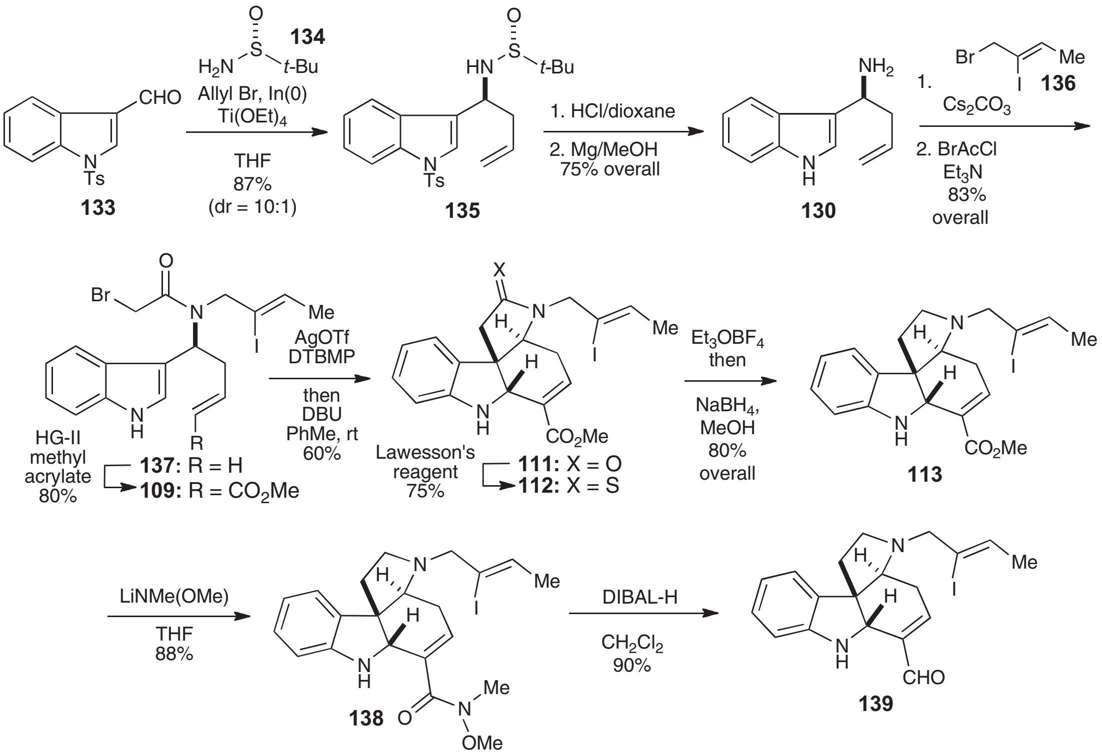
Novel hexacyclic *Strychnos* alkaloids (−)-leuconicine A (**3**) and B (**4**) were isolated in 2009 by Kam and coworkers from the Malaysian plant *Leuconotis maingayi* (Figure 1).[3] The leuconicines resemble a curious hybrid of classic *Strychnos* alkaloids akuammicine (**2**)[2] and strychnine (**1**),[1] yet distinguish themselves by virtue of (1) an 3-acyl-2-pyridone F-ring and (2) an ethyl (not ethylidene) substituent on the D-ring. We were intrigued by this and launched a total synthesis campaign: the retrosynthesis of **3** and **4** is shown in Scheme 30.

Leuconicine A (**3**) would be prepared from leuconicine B (**4**) via Weinreb amidation (i.e., ammonia and trimethylalane) and chemoselective reduction of the ethylidene moiety in **131**.[62] Dehydroeuconicine B (**131**) would, in turn, be prepared via the intramolecular Heck reaction of pentacycle **132**. The 3-acylpyridone in **132** would be prepared by a novel amidation/intramolecular Knoevenagel condensation reaction. This would then lead us to akuammicine precursor **113**, which was prepared in Scheme 26.

To realize the asymmetric syntheses of (−)-**3** and (−)-**4**, we employed the method of Yus[63] wherein Ellman's *N*-*tert*-butyl sulfinimines[64] are prepared and allylated *in situ* to afford homoallylic amines in high yields and diastereoselectivites (Scheme 31). To this end, commercial *N*-tosyl



SCHEME 30 Retrosynthesis of leuconicines A and B.



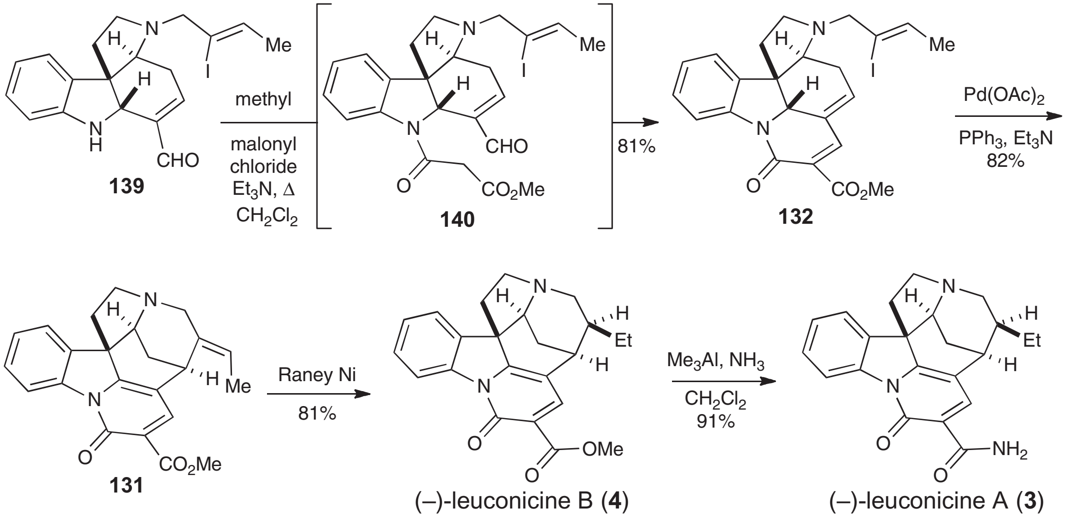
SCHEME 31 Second-generation asymmetric synthesis of ABCE intermediate.

indole-3-carboxaldehyde (**133**) was treated with (*R*)-*N*-*tert*-butanesulfinamide (**134**), $Ti(OEt)_4$, allyl bromide, and indium(0) to give homoallylic amine **135** in 87% yield (dr = 10:1). Removal of both sulfinyl and sulfonyl groups was accomplished by treatment with 4 M HCl then Mg/MeOH, respectively, to afford **130** in 75% yield (one-pot). Alkylation with bromide **136** and acylation with bromoacetyl chloride afforded amide **137** in 83% yield (two steps).

Chemoselective CM between **137** and methyl acrylate was accomplished with 10 mol% of Hoveyda–Grubbs second-generation catalyst[44] affording an 80% yield of **109**, which was carried to akuammicine (**2**) as shown in Schemes 25 and 26. The synthesis of the F-ring via the amidation/intramolecular Knoevenagel condensation protocol required the conversion of methyl ester **113** into aldehyde **139**. To this end, we transformed **113** into Weinreb amide **138** with LiN(OMe)Me in THF and subsequently reduced it to the aldehyde with DIBAL-H to access **139** in 89% yield (two steps).[65] Importantly, the alternate route to enal **139** featuring first DIBAL-H reduction followed by an oxidation reaction (e.g., Swern, Dess-Martin) proceeded with low yields.

With the bis-cyclization precursor in hand, we began thinking about tactics for accessing the F-ring. To effectively amidate the indoline in the first reaction, it was necessary to use a powerful electrophile, and ketene came immediately to mind. Once the amidation was complete, the Knoevenagel condensation reaction would make the critical C—C bond and install the requisite methyloxycarbonyl unit in the 3-position of the pyridone ring. Thus, methyl malonyl chloride was selected to accomplish the task. Gratifyingly, refluxing a solution of **139**, methyl malonyl chloride and Et_3N in CH_2Cl_2 for 3 h furnished pentacycle **132** in 82% yield. At this stage, we employed the intramolecular Heck reaction to prepare the D-ring. Thus, treatment of **132** with catalytic $Pd(OAc)_2$, PPh_3 in Et_3N to gave dehydroleuconicine B (**131**) in 81% yield.[66] All attempts to hydrogenate the ethylidene moiety using catalytic Pd or Pt were unsuccessful. Ultimately, chemoselective reduction of the ethylidene moiety was achieved with Raney Ni, which afforded (−)-leuconicine B (**4**) in 82% yield. The conversion of **4** into (−)-leuconicine A (**3**) was accomplished with the Weinreb procedure using dimethylaluminum amide in 91% yield.[62,67] (Scheme 32).

In summary, the *Strychnos* alkaloid (−)-leuconicine A (**3**) was synthesized in 14 steps (9% overall yield), whereas (−)-leuconicine B (**4**) was synthesized in 13 steps (10% overall yield) from commercial starting materials. Key steps included (1) our bis-cyclization method to assemble the ABCE framework, (2) a novel domino acylation/intramolecular Knoevenagel condensation to prepare the F-ring, and (3) an intramolecular Heck reaction to access the D-ring.[68]



SCHEME 32 Asymmetric syntheses of (−)-leuconicines A and B.

ACKNOWLEDGMENTS

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Chapter 2

Total Synthesis of the Unusual Peptide Celogentin C

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Chapter Outline

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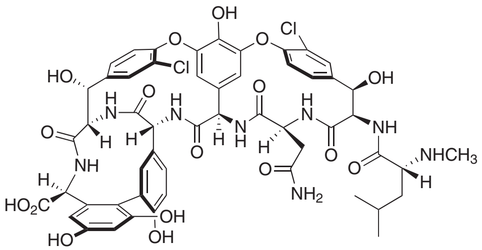
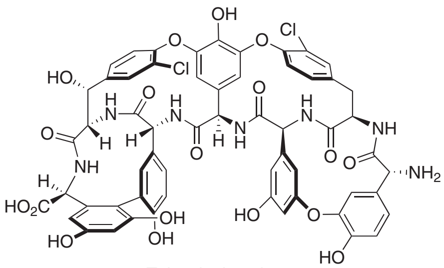
1 INTRODUCTION

The lead author's fascination with unusual peptide natural products began in the late 1990s as a graduate student in the laboratory of Dale Boger at The Scripps Research Institute. During that time, he was privileged to participate in total syntheses of the vancomycin[1] and teicoplanin[2] aglycons (Figure 1). These experiences cultivated an appreciation for the exquisite molecular architecture and potent bioactivity characteristic of unusual peptides that continues to this day. These compounds typically contain uncommon amino acids or cross-links between amino acid side chains that present substantial synthetic challenges. Accordingly, their synthesis serves as a crucible for the development of new and useful synthetic methodology. Moreover, the ability to generate unnatural analogues of the target compounds enables important studies of their modes of action. The thorough investigation of the vancomycin aglycon conducted by the Boger group[3] is one of many excellent examples of a total synthesis-based research program with strong positive impacts on the fields of organic synthesis and chemical biology.

In late 2001, the lead author was a postdoctoral researcher in the laboratory of Larry Overman at UC Irvine. While searching the scientific literature for complex natural products capable of launching an academic career, he came across a report from the group of Professor Jun'ichi Kobayashi of Hokkaido University, describing the isolation and structure determination of celogentins A–C (Figure 2).[4] These bicyclic peptides were obtained from the seeds of *Celosia argentea*, a flowering plant commonly known as cockscomb.

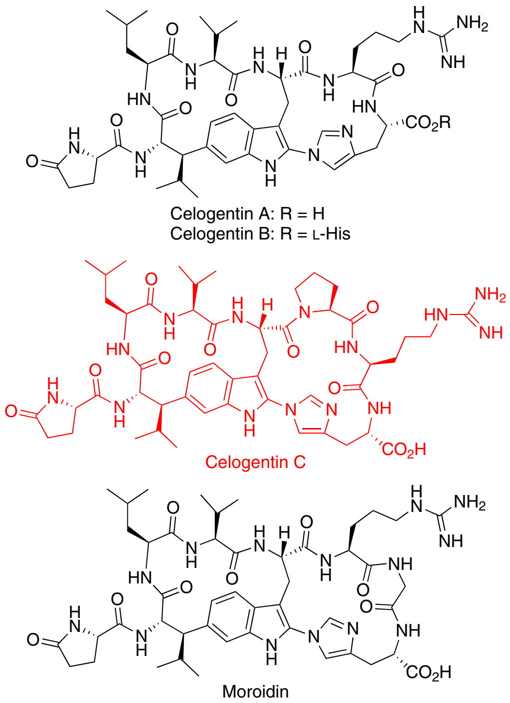


Vancomycin aglycon



Teicoplanin aglycon

FIGURE 1 Vancomycin and Teicoplanin Aglycons.



Celogentin A: R = H
Celogentin B: R = L-His

Celogentin C

Moroidin

FIGURE 2 Celogentins A–C and Moroidin.

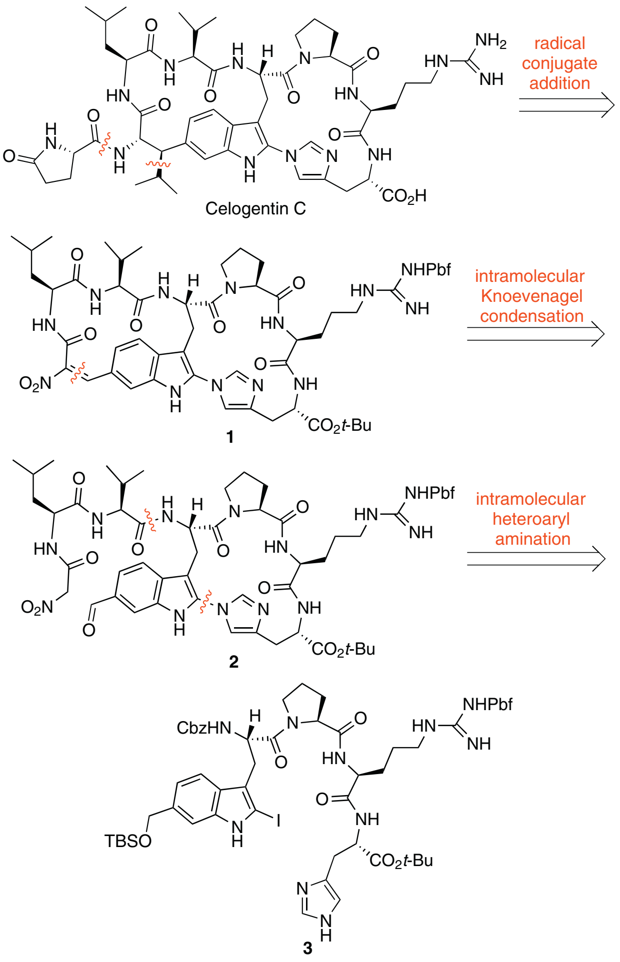
Celogentins A–C share an unusual structural motif comprised of two cross-links: a C—C bond joining the leucine β-carbon with the C-6 position of the tryptophan indole moiety, and a C—N bond connecting the indole C-2 atom with the imidazole N-1 of histidine. This striking architectural feature creates a left-hand macrocycle that is common to all three natural products and a right-hand macrocycle that differs slightly in each case. Celogentins A–C are closely related to moroidin (Figure 2), which was first isolated from the Australian bush *Laportea moroides*[5] and later found in the *C. argentea* seeds.[4] Since its discovery in 1986, moroidin had largely escaped the attention of organic chemists, with Moody's construction of the tryptophan–histidine cross-link[6] representing the only synthetic studies that were published prior to Kobayashi's paper describing the celogentins.

Biological assays of moroidin and celogentins A–C conducted by the Kobayashi group revealed that these peptides inhibit tubulin polymerization.[7] Significantly, celogentin C is a more potent antimitotic agent than the well-known anticancer drug vinblastine (IC_{50} of 0.8 μM vs. 3.0 μM).[4] In addition to their utility in treating cancer, compounds that inhibit tubulin polymerization have found use as anti-inflammatory, antifungal, and antiparasitic agents.[8] Recognizing that celogentin C possessed all of the necessary ingredients (i.e., unusual and challenging structure, dearth of related synthetic studies, useful biological activity) for spawning a high-impact research program, the lead author selected it as a total synthesis target. Others were also inspired by Kobayashi's report, as the groups of Moody,[9] Hutton,[10] Campagne,[11] and Wandless[12] disclosed progress toward constructing celogentin C or moroidin in the following years.

2 FIRST SYNTHETIC PLAN AND INITIAL STUDIES

2.1 First-Generation Retrosynthesis

During the early stages of planning the total synthesis of celogentin C, it became apparent that the key to constructing the target compound would be devising efficient methods of forming the aforementioned cross-links. A conjugate addition appeared to be a logical method of generating the leucine–tryptophan linkage, but the strongly basic nature of the requisite organocuprate or Grignard reagent would likely necessitate protection of all amide N—H groups present in the peptide substrate. While considering this problem, the lead author attended a seminar at UC Irvine presented by Mukund Sibi. Professor Sibi described some stereoselective radical conjugate additions that his group had recently discovered.[13] This outstanding lecture provided a straightforward means of circumventing the protecting group problems associated with standard conjugate additions to peptides. With this in mind, the lead author devised the retrosynthetic plan shown in Scheme 1. Based on molecular modeling studies, it was envisioned that diastereoselective addition of a nucleophilic isopropyl radical to the electron-deficient α,β-unsaturated α-nitro amide present in **1** and subsequent hydrogen atom abstraction could be accomplished with substrate-derived stereocontrol, affording celogentin C after a few straightforward manipulations of the adduct. Alternatively, a chiral Lewis acid might be able to direct the stereochemical course of the radical conjugate addition. In dissecting bicyclic peptide **1**, the lead author was mindful of his early experiences as a graduate student, which taught him that macrolactamizations are often plagued by epimerization of the activated carboxylate intermediates.[14] Motivated by a desire to develop alternative strategies for the synthesis of cyclic peptides, he decided to explore the intramolecular Knoevenagel condensation of α-nitroacetamide **2** as a method of fashioning the left-hand macrocycle of **1**. Continuing this line of reasoning, he planned to construct the remaining macrocycle in **2** via an intramolecular aryl amination of tetrapeptide **3**. This disconnection was inspired by the Cu-and Pd-catalyzed aryl aminations developed by Buchwald and coworkers, which included both intramolecular examples[15] and arylations of imidazole.[16] Tetrapeptide **3** could presumably be readily assembled from its amino acid constituents, but a concise synthesis of a tryptophan derivative bearing

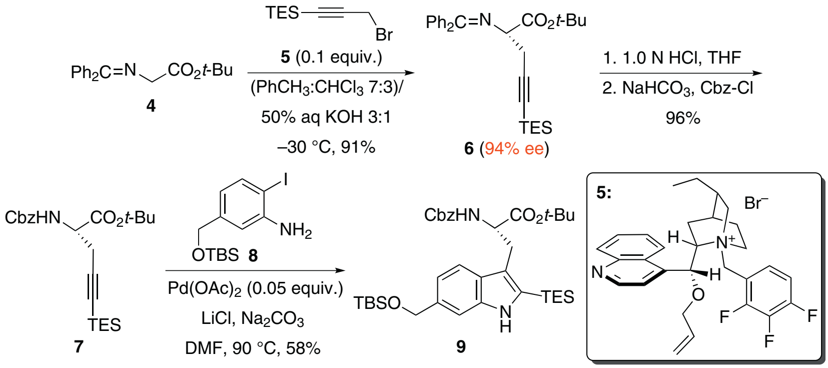


SCHEME 1 First-generation retrosynthesis.

appropriate substituents at the indole C-2 and C-6 positions was required in order to realize this plan.

2.2 Catalytic Asymmetric Synthesis of Functionalized Tryptophan Derivative

In August 2002, the lead author began his independent academic career at Brigham Young University by exploring the enantioselective synthesis of the central tryptophan residue of celogentin C. In 2001, Cook and coworkers published an attractive protocol for constructing substituted tryptophans[17]



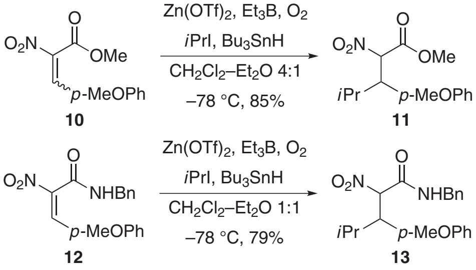
SCHEME 2 Enantioselective synthesis of tryptophan **9**.

based on the Larock heteroannulation[18] of *o*-iodoanilines with an enantioenriched propargylglycine species derived from diastereoselective alkylation of the Schöllkopf reagent.[19] This route was attractive, but its reliance on a stoichiometric amount of an expensive chiral auxiliary was a concern. Prompted by an excellent seminar on chiral phase-transfer catalysis[20] given at UC Irvine by Keiji Maruoka, the lead author decided to apply this technique to the enantioselective preparation of a propargylglycine derivative, which would then be subjected to the Larock heteroannulation according to Cook's procedure. Working together with newly arrived postdoctoral fellow G. S. C. Srikanth, he surveyed several propargylic electrophiles and chiral phase-transfer catalysts in alkylations of glycinate Schiff base **4** (Scheme 2). We found that the combination of triethylsilylpropargyl bromide and the trifluorobenzyl-substituted dihydrocinchonidine derivative **5**[21] was uniquely effective at furnishing propargylglycine **6** in excellent yield and ee. Exchange of the relatively labile benzophenone imine for the more robust Cbz group transformed **6** into **7**, and coupling of **7** with *o*-iodoaniline **8** utilizing a slight modification of Cook's conditions delivered functionalized tryptophan **9** in moderate but reproducible yield.[22] Importantly, no racemization occurred under the basic reaction conditions. The TES group on the alkyne is required for achieving regiocontrol in the Larock heteroannulation.[17] Moreover, it was envisioned to function as a handle for subsequent installation of an iodide[23] at the indole C-2 position in preparation for the key heteroaryl amination.

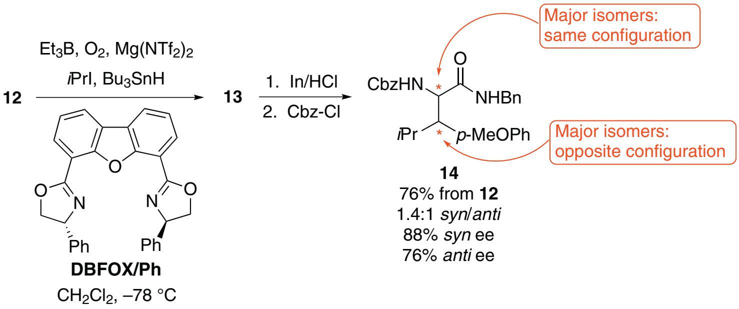
2.3 Radical Conjugate Addition Model Studies

In addition to helping with the tryptophan synthesis, Srikanth explored the viability of the proposed radical conjugate addition. α,β-Unsaturated α-nitro ester **10** and amide **12** were selected as model substrates, as the *p*-methoxyphenyl group was expected to serve as a suitable mimic of the electron-rich indole moiety present in celogentin C (Scheme 3). $Zn(OTf)_2$-promoted radical conjugate additions to **10** and **12** were facile, occurring rapidly (≤3 h) at −78 °C and affording adducts **11** and **13** in good yields. Although ester **10** was employed as a 1:1 mixture of *E* and *Z* isomers and amide *E*-**12** was used in pure form, both **11** and **13** were obtained as 1:1 mixtures of diastereomers. Reactions enlisting Bu_3SnD instead of Bu_3SnH revealed that deuterium could be installed and retained at the α-positions of **11** and **13**, as long as appropriate care was taken in the workup and amide **13** was not subjected to SiO_2 chromatography.[24] This important finding suggested the feasibility of an enantio- and diastereoselective radical conjugate addition that would be free of epimerization.

Postdoctoral fellow Liwen He continued Srikanth's work by examining a variety of chiral Lewis acids in radical conjugate additions to **12**. After considerable experimentation, he discovered that the DBFOX/Ph ligand[25] in conjunction with $Mg(NTf_2)_2$-promoted additions to **12** with good enantioselectivity but poor diastereoselectivity (Scheme 4). The diastereomeric adducts **13** were reduced and protected prior to purification in order to avoid epimerization of the sensitive α-stereocenter. Further studies indicated that the



SCHEME 3 Radical conjugate addition model studies.

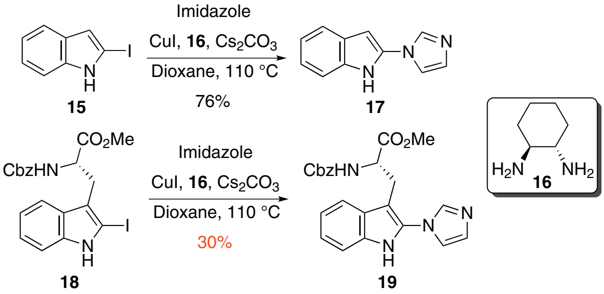


SCHEME 4 Chiral Lewis acid-promoted radical conjugate addition.

major enantiomers of each diastereomer of **14** possessed identical configurations at the α-carbon but differed at the β-carbon. This demonstrated that the hydrogen atom abstraction step was proceeding with good stereoselectivity and that epimerization was not problematic. However, the radical addition step was occurring with marginal selectivity.[26] We tentatively attributed these results to poor shielding of the β-carbon in radical acceptor **12** by the chiral Lewis acid. We hypothesized that second-generation versions of DBFOX/Ph containing larger aryl groups would more effectively shield the β-carbon, thereby improving the diastereoselectivity of the radical conjugate addition. A variety of such ligands were prepared and evaluated, but only modest improvements (≤2:1 dr) were observed.[27] Nonetheless, the good enantiomeric excesses obtained for both diastereomers in all cases (76–97%) provided some cause for optimism in the event that a chiral Lewis acid-promoted radical conjugate addition would be required in the total synthesis of celogentin C.

2.4 Attempted Metal-Catalyzed Aryl Aminations

While Srikanth and Liwen were addressing the radical conjugate addition, graduate student Liping Yang was investigating formation of the indole–imidazole linkage of the natural product using metal-catalyzed aryl amination. Initial results were promising, as she found that 2-iodoindole (**15**) could be coupled to imidazole using CuI as the catalyst and racemic *trans*-1,2-diaminocyclohexane (**16**) as the ligand, furnishing heterobiaryl **17** in good yield (Scheme 5). Unfortunately, the yield dropped significantly when tryptophan derivative **18** was used in place of **15**. Attempts to employ other copper or palladium catalysts were unsuccessful.[28] Presumably, the presence of a substituent adjacent to the site of coupling hinders the amination of **18** relative to **15**. Faced with this negative result, we began to search for alternative methods of creating the indole–imidazole cross-link of celogentin C.



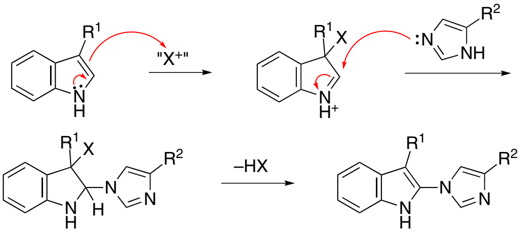
SCHEME 5 Cu-catalyzed couplings of Imidazole with 2-iodoindoles.

3 SYNTHESIS OF THE RIGHT-HAND RING VIA OXIDATIVE COUPLING

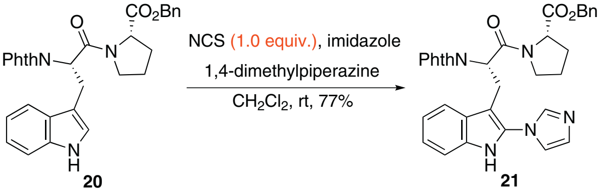
3.1 Model Studies

Based on an insightful suggestion from Paul Wender, who visited BYU in 2005, we examined an oxidative coupling reaction as a means of fashioning the right-hand ring of celogentin C. The concept is shown in Scheme 6. Upon exposure to a suitable electrophilic reagent (“X^+”), the indole subunit of a tryptophan derivative should react to form an iminium ion intermediate. Trapping of this species with the nucleophilic imidazole from a histidine residue and subsequent elimination of “HX” would afford the indole–imidazole linkage characteristic of the right-hand ring of celogentin C. Reports from Booker-Milburn[29] and Bergman[30] describing indole oxidative couplings with various nucleophiles provided reason for optimism, but we were unsure of the viability of imidazole in this process. Furthermore, we recognized that the indole present in the heterobiaryl adduct might react with the electrophilic agent, leading to destruction of the product. With these two concerns in mind, Liwen He commenced a model study.

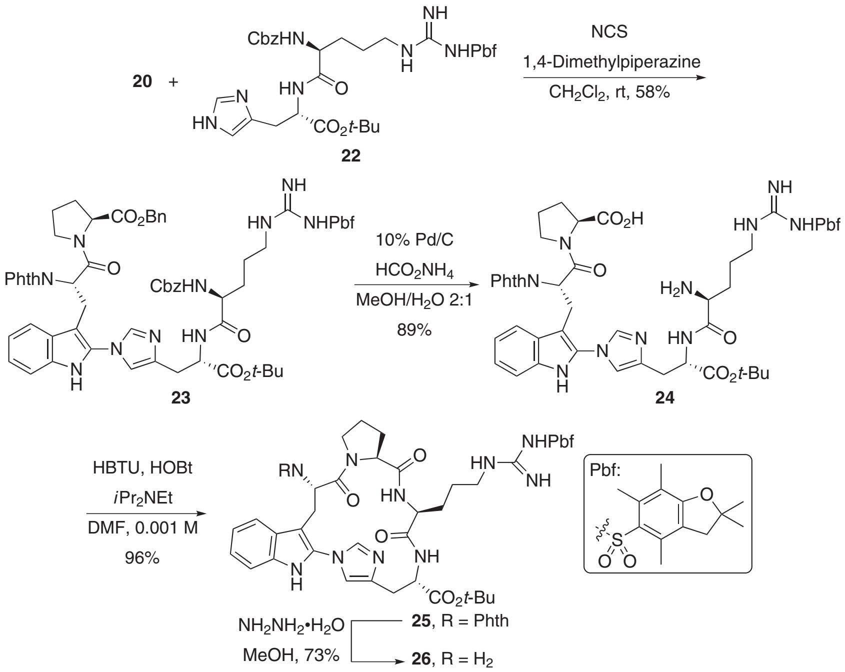
Liwen began by investigating the coupling of tryptophan–proline dipeptide **20** with imidazole (Scheme 7). A survey of reagents capable of serving as “X^+” equivalents revealed the utility of *N*-chlorosuccinimide. 1,4-Dimethylpiperazine was selected as the base because of its utility in Bergman’s work.[30] A 77% yield of heterobiaryl **21** was obtained when 1 equivalent of NCS was employed, but the yield decreased with increasing amounts of NCS, presumably due to consumption of the product.[31] The phthalimide



SCHEME 6 Proposed indole–imidazole oxidative coupling.



SCHEME 7 Oxidative coupling model reaction.



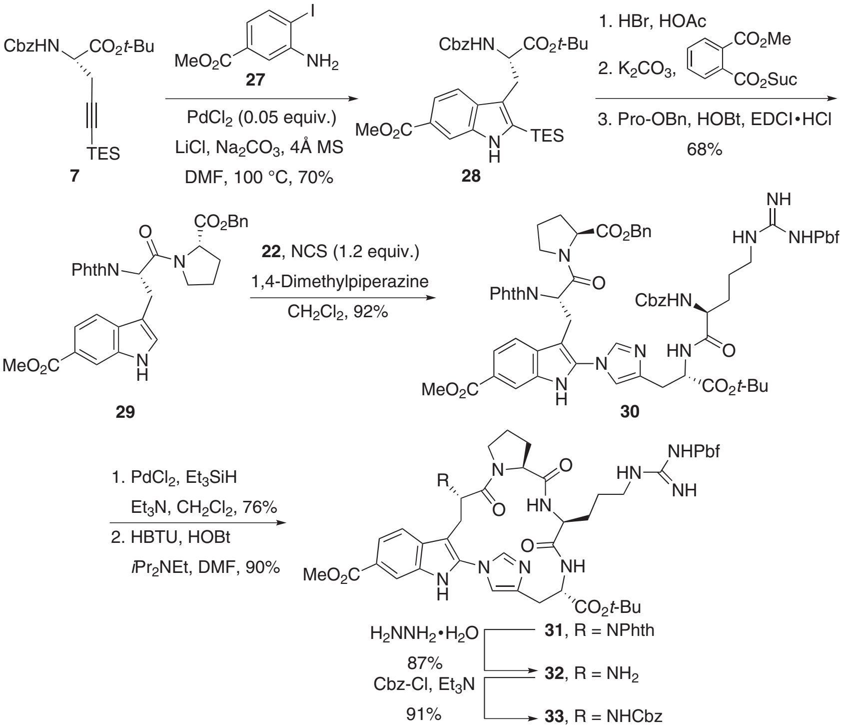
SCHEME 8 Simplified right-hand ring synthesis.

protecting group was critical, as significantly lower yields were obtained when the N-terminus of **20** was masked as a carbamate. It is likely that the carbamate is sufficiently nucleophilic to cyclize onto the putative iminium intermediate, thereby preventing the desired coupling with imidazole.

This positive result encouraged us to use this methodology to construct a simplified version of the right-hand ring. Thus, oxidative coupling of **20** with dipeptide **22** under the established conditions provided heterobiaryl-linked tetrapeptide **23** in 58% yield (Scheme 8). The reaction did not proceed to completion, as 25–30% of both starting materials could be recovered. However, increasing the reaction time or the equivalents of NCS did not improve the yield. Simultaneous removal of the Cbz group and the benzyl ester of **23** was accomplished via transfer hydrogenation. Then, we were relieved to find that macrolactamization under high dilution conditions was very efficient, producing macrocycle **25** in excellent yield without evidence of epimerization. Cleavage of the phthalimide furnished amine **26**, representative of the right-hand ring of celogentin C.[31]

3.2 Synthesis of Functionalized Right-Hand Ring

Although the macrolactamization of **24** was facile, our desire to explore alternatives for cyclic peptide formation led us to attempt construction of macrocycle **25** by means of an intramolecular oxidative coupling. Unfortunately, this reaction failed to deliver any of the desired product. Accordingly, graduate student Bing Ma decided to use the intermolecular oxidative coupling to prepare a functionalized version of the right-hand ring suitable for subsequent left-hand ring annulation. Tryptophan derivative **9** (Scheme 2) was a feasible starting point for this endeavor, but a C-6 methyl ester was deemed to be more desirable than the protected hydroxymethyl group contained in this substrate. Thus, Larock heteroannulation of propargylglycine **7** with *o*-iodoaniline **27** afforded tryptophan **28** in good yield (Scheme 9). Notably, the use of $PdCl_2$ as catalyst instead of $Pd(OAc)_2$ and the inclusion of 4 Å molecular sieves were essential to obtaining good yields. Treatment of **28** with HBr in acetic acid served to cleave the Cbz group, the *tert*-butyl ester, and the triethylsilyl moiety, and phthalimide formation followed by peptide coupling delivered dipeptide **29**. Bing was pleased to discover that oxidative coupling of **29** with arginine–histidine dipeptide **22** was significantly higher yielding than the coupling of **20** with **22**, as acyclic tetrapeptide **30** was obtained in 92% yield. In contrast to the previous reaction, this



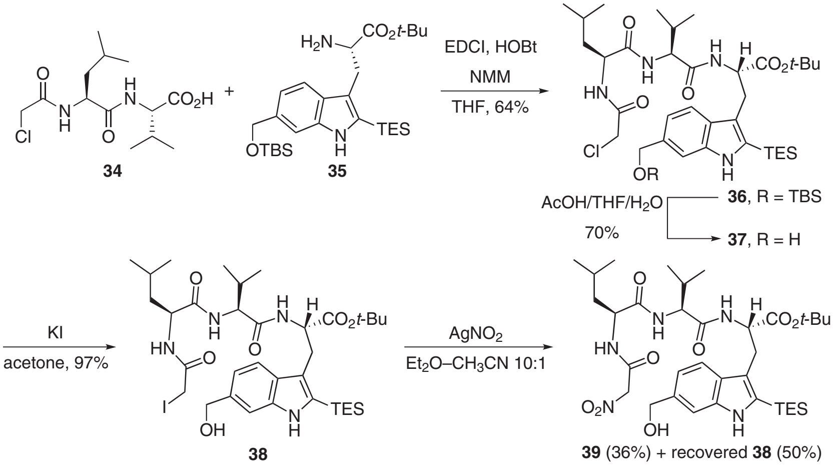
SCHEME 9 Functionalized right-hand ring synthesis.

transformation could be performed with a slight excess of NCS without any detectable consumption of the product. Perhaps, the presence of the electron-withdrawing methyl ester renders **30** less reactive than **23** to NCS. Surprisingly, transfer hydrogenation of **30** failed to promote *N*-Cbz cleavage. Fortunately, the combination of $PdCl_2$ and triethylsilane[32] caused scission of both the Cbz and benzyl ester moieties, furnishing the macrolactamization substrate. Analogous to Liwen's prior experience, a high-yielding macrolactamization proceeded under the influence of HBTU and HOBt, providing functionalized right-hand ring derivative **31** in 90% yield. The somewhat labile phthalimide could be exchanged for a more robust benzyl carbamate in two simple, high-yielding steps.[33] The resulting product **33** was primed for annulation of the left-hand ring by virtue of the methyl ester situated at C-6 of the tryptophan indole moiety.

4 EARLY ATTEMPTS TO FORM THE LEFT-HAND RING

4.1 Intramolecular Knoevenagel Condensation and Alkylation Strategies

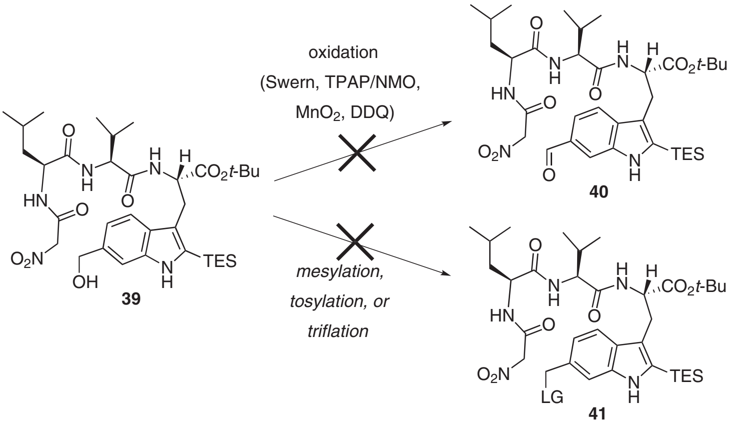
The partial success of our radical conjugate addition model studies prompted us to address the synthesis of an α,β-unsaturated α-nitro amide corresponding to the left-hand ring of celogentin C. Graduate student Dmitry Litvinov attempted to prepare substrates for an intramolecular Knoevenagel condensation or an intramolecular nitroacetamide alkylation–dehydrogenation sequence. Coupling of chloroacetyl-capped dipeptide **34** with tryptophan amine **35** (prepared by hydrogenation of benzyl carbamate **9**) furnished peptide **36**, which was treated with AcOH to effect cleavage of the silyl ether (Scheme 10). The resulting product **37** was converted into an iodide via a



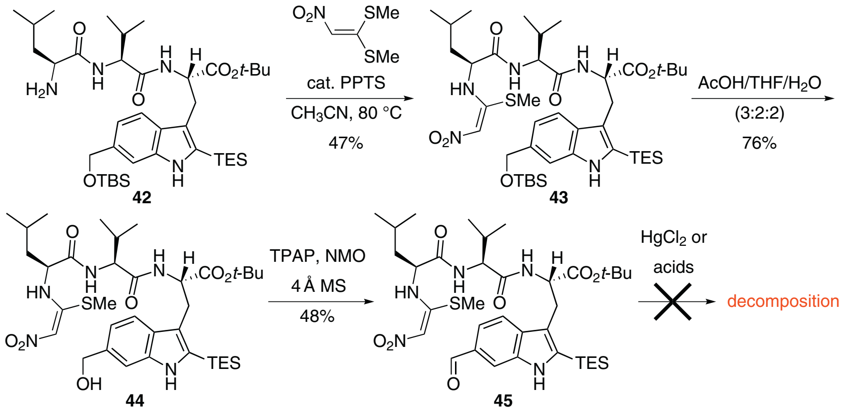
SCHEME 10 Preparation of α-nitroacetamide **39**.

Finkelstein reaction. Transformation of iodide **38** into the desired nitro compound was fraught with difficulty, as complex mixtures were generated under a variety of conditions. The ambident nucleophilicity of nitrite ion was primarily responsible for these problems, as alcohol byproducts presumably derived from nitrite ester hydrolysis or decomposition were frequently observed. A modification to Kornblum's conditions[34] involving acetonitrile as a cosolvent to increase the solubility of $AgNO_2$ afforded modest yields of nitroacetamide **39** along with substantial amounts of recovered starting material. Attempts to push the reaction to completion merely resulted in elevated levels of byproducts.[35] Unfortunately, efforts to oxidize **39** to the corresponding aldehyde **40** (in preparation for an intramolecular Knoevenagel condensation) or to install a leaving group at the indole C-6 position (in preparation for an intramolecular alkylation) were unsuccessful (Scheme 11).[36]

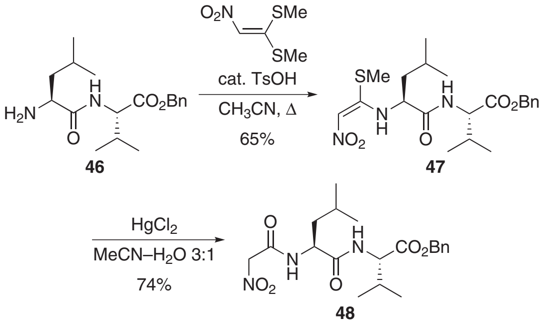
Reasoning that the nitroacetamide was interfering with the oxidation, Dmitry decided to postpone its installation until after the aldehyde had been generated. Accordingly, reaction of amine **42** with Rajappa's commercially available dithioketene acetal[37] afforded masked nitroacetamide **43** in modest yield as a single isomer of undetermined alkene stereochemistry (Scheme 12). Silyl ether deprotection proceeded uneventfully, and we were pleased to find that the resulting alcohol **44** could be oxidized with TPAP and NMO. Unfortunately, all attempts to unveil the nitroacetamide from **45** using either $HgCl_2$ or acids resulted in decomposition of the starting material.[36] Continually faced with obstacles in generating substrates for an intramolecular Knoevenagel condensation or a related alkylation, at this stage we elected to examine an intermolecular Knoevenagel condensation instead.



SCHEME 11 Failed attempts to functionalize **39.**



SCHEME 12 Unsuccessful approach to intramolecular Knoevenagel substrate.

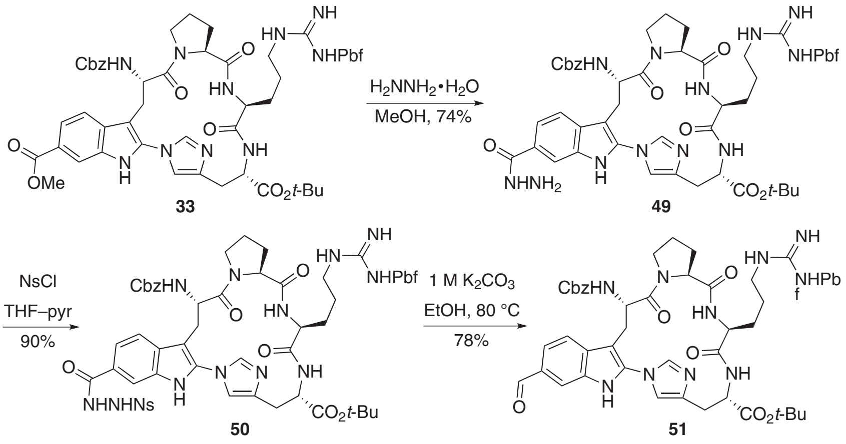


SCHEME 13 Synthesis of nitroacetyl dipeptide **48.**

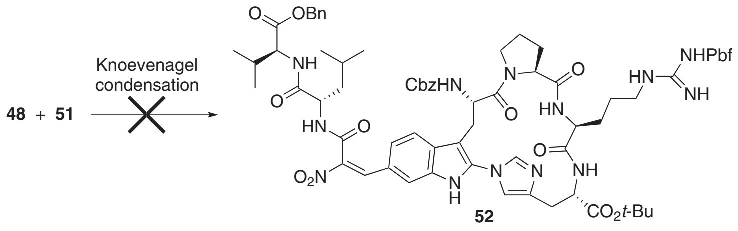
4.2 Intermolecular Knoevenagel Condensation and Change in Overall Strategy

Synthesis of the nitroacetyl-capped dipeptide **48** required for this alternative strategy was accomplished readily as shown in Scheme 13. Treatment of amine **46** with Rajappa's dithioketene acetal afforded vinyl sulfide **47**. In contrast to the attempted deprotection of **45** described above, exposure of **47** to $HgCl_2$ in aqueous acetonitrile provided nitroacetamide **48** in good yield. We intended to couple this compound to an aldehyde derived from functionalized right-hand ring derivative **33**, but to our great surprise the C-6 methyl ester of **33** was inert to common reduction and hydrolysis methods. Apparently, the electron-rich indole ring significantly reduces the electrophilicity of this functional group. After extensive investigations enlisting tryptophan derivative **28** (see Scheme 9 for structure) as a more abundant substrate than **33**, Bing Ma discovered that Braslau's practical modification[38] of the McFadyen–Stevens reduction[39] was uniquely effective at facilitating methyl ester reduction. He applied this protocol to right-hand ring derivative **33** by first transforming its methyl ester moiety into an acyl hydrazine through exposure to hydrazine hydrate (Scheme 14). Prevention of diacyl hydrazine formation caused by reaction of the *tert*-butyl ester was accomplished by concentrating the crude mixture under high vacuum at 0 °C. Nosylation of acyl hydrazine **49** then furnished key intermediate **50**, which underwent base-promoted fragmentation at 80 °C to deliver the desired aldehyde **51**. The use of a nosyl group in place of a tosyl group allows this step to proceed at a significantly lower temperature than the classical McFadyen–Stevens reduction, which typically takes place at ca. 160 °C.[39] Although this three-step sequence is unlikely to become a common method of reducing esters to aldehydes, it is quite useful with recalcitrant esters that do not respond to typical reduction protocols.

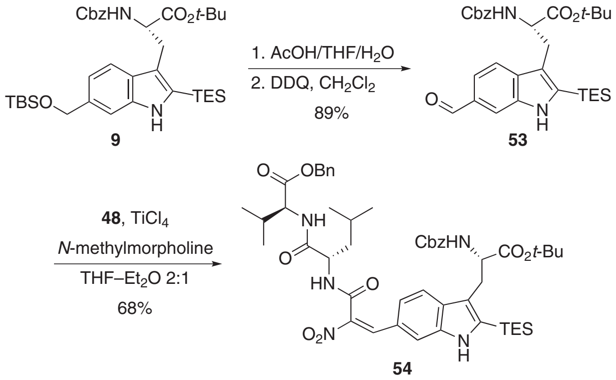
With aldehyde **51** finally in hand, we attempted its much-anticipated intermolecular Knoevenagel condensation with nitroacetamide **48**. To our dismay, Dmitry was unable to achieve the required coupling despite multiple attempts under both acidic and basic conditions (Scheme 15). We posited that the numerous functional groups present in **51**, including several Lewis bases, were preventing



SCHEME 14 Modified McFadyen–Stevens reduction.



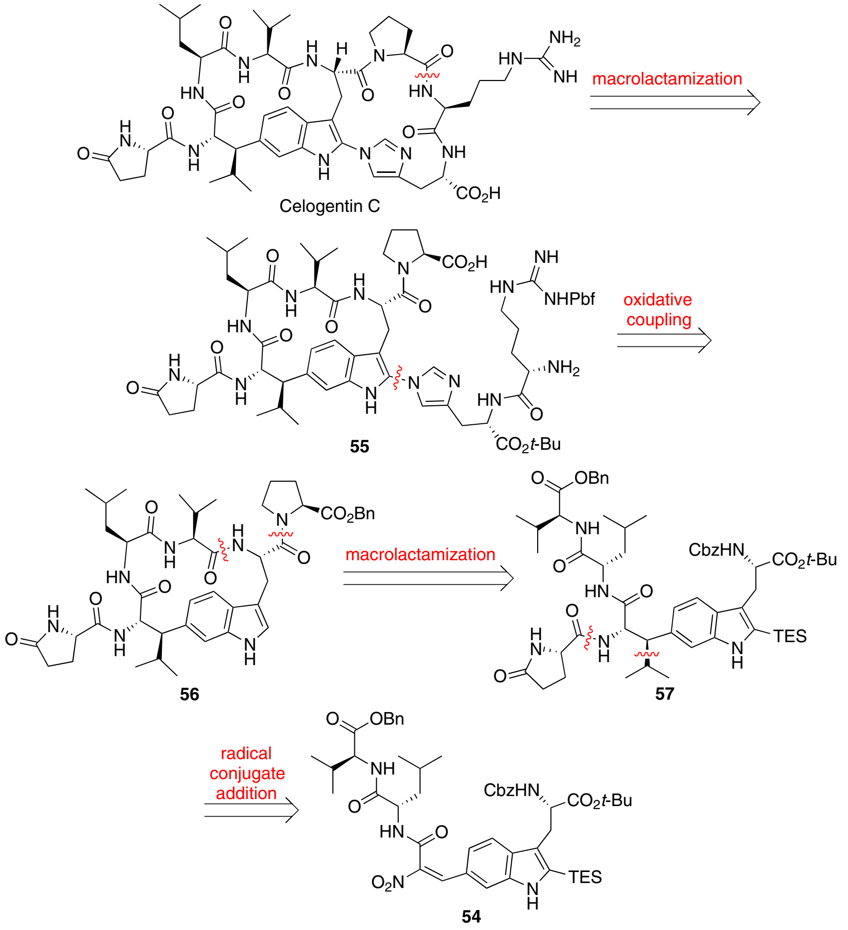
SCHEME 15 Failed intermolecular Knoevenagel condensation.



SCHEME 16 Successful intermolecular Knoevenagel condensation.

the Knoevenagel condensation. Accordingly, we decided to perform the reaction with a simpler aldehyde. Cleavage of the silyl ether moiety of tryptophan derivative **9** and oxidation of the resulting benzylic alcohol with DDQ[40] proceeded smoothly, delivering aldehyde **53** in 89% yield (Scheme 16). Fortunately, condensation of **53** with **48** occurred in the presence of $TiCl_4$ and *N*-methylmorpholine. Substantial optimization studies demonstrated that a mixed THF–Et_2O solvent system was necessary in order to obtain reproducible yields. Interestingly, alkene **54** was produced as a single isomer, a phenomenon first observed in the synthesis of radical conjugate addition model substrate **12** (Scheme 3). The *E* configuration of **12** was established by X-ray crystallography,[26] and the stereochemistry of **54** was assigned by analogy since both compounds were constructed under similar conditions. We are unsure of the underlying reasons for the stereoselective Knoevenagel condensation, but it appears that selectivity is only achieved with nitroacetamides. When an α-nitro ester was used to prepare model compound **10** (Scheme 3), a 1:1 mixture of *E* and *Z* isomers was furnished. These contrasting results make the Knoevenagel condensations of nitroacetamides and α-nitro esters a subject worthy of further study.

The successful coupling of nitroacetamide **48** and aldehyde **53** caused us to change the order of macrocyclizations in the total synthesis of celogentin C. Our modified strategy is shown in retrosynthetic format in Scheme 17. The new plan involved forming the natural product by macrolactamization of **55** to fashion the right-hand ring and subsequent deprotection. Disconnection of the arginine–histidine dipeptide from **55** using the oxidative coupling reaction reveals left-hand ring hexapeptide **56**. This intermediate would be created by macrolactamization of a substrate derived from the deprotection of **57**, which would, in turn, be accessible via radical conjugate addition to Knoevenagel adduct **54**. We were optimistic that this revised plan would enable us to achieve the total synthesis of celogentin C. Nevertheless, two issues concerned us. We worried that the indole moiety of **56**, which is imbedded within a macrocycle, would be significantly less reactive toward the



SCHEME 17 Revised synthetic strategy.

oxidative coupling than the less-hindered indoles contained in dipeptides **20** (Scheme 8) and **29** (Scheme 9). Additionally, we were uncertain about the prospects for achieving stereoselectivity in the radical conjugate addition to **54**. With these potential pitfalls in mind, Bing Ma began exploring our new synthetic route.

5 CONSTRUCTION OF THE LEFT-HAND RING

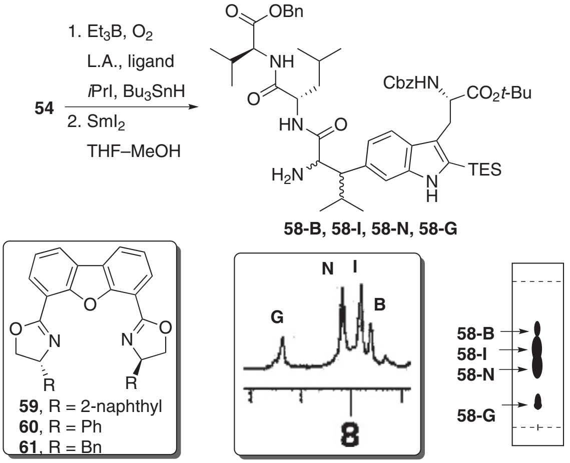
5.1 Radical Conjugate Addition and Nitro Reduction

The radical conjugate addition model studies conducted previously by Liwen He demonstrated that chiral Mg–DBFOX Lewis acids could provide good stereocontrol over the hydrogen atom abstraction step but poor stereocontrol over the radical addition step (see Scheme 4).[26] Thus, we anticipated that these Lewis acids would promote the addition of isopropyl radical to α,β-unsaturated α-nitroacetamide **54** with moderate diastereoselectivity, affording two of the four possible products in a ca. 1–2:1 ratio as epimers at the leucine β-carbon. Our model studies also taught us the importance of reducing the nitro group without purification in order to preserve the configuration of the sensitive α-carbon. While this reduction could be accomplished by In/HCl with simple adducts (see Scheme 4),[26] attempts to reduce the nitro group of a saturated congener of **54** (generated by $NaBH_4$ reduction) showed the ineffectiveness of these conditions with a more complex substrate. Of the numerous methods examined by Bing, SmI_2 in THF–MeOH[41] was the only protocol that cleanly produced the desired amine. Accordingly, we selected these conditions for use in reducing the radical conjugate addition product.

To our surprise and dismay, radical conjugate addition to **54** in the presence of Mg–DBFOX Lewis acids and subsequent nitro reduction provided substantial quantities of all four possible diastereomers of adduct **58** (Table 1, entries 1–4).[33,42] In an attempt to find some humor in this disappointing result, Bing named the isomers after himself. Therefore, the four products were dubbed "B," "I," "N," and "G" in order of increasing polarity. The indole N–H signals of these compounds were well resolved in the crude ^1H NMR spectra, allowing easy determination of the product ratios. The contrasting results in radical conjugate additions to acceptors **12** and **54** demonstrate that the chiral Lewis acids are not binding to the complex substrate in the same fashion that they interact with the simple substrate.

In contrast to model substrate **12**, compound **54** is chiral. To evaluate the possibility of achieving substrate-derived stereocontrol, Bing performed the radical conjugate addition to **54** with an achiral Lewis acid ($Zn(OTf)_2$, entry 5) and in the absence of a Lewis acid (entry 6). Both reactions proceeded smoothly, with the latter result establishing that Lewis acid promotion is not essential for addition of nucleophilic radicals to electrophilic acceptor **54**. Interestingly, the product ratios were slightly more favorable than those obtained from the chiral Lewis acid-mediated reactions. In particular, we were intrigued by the $Zn(OTf)_2$-promoted reaction (entry 5), in which the major isomer **58-I** comprised almost half (43%) of the product mixture. Although the four products were not completely separable (see inset of TLC plate in Table 1), SiO_2 chromatography allowed removal of the two minor products (least polar isomer **58-B** and most polar isomer **58-G**). By purifying a preparative scale reaction, Bing discovered that the combined yield of the radical conjugate addition and nitro reduction was 90%.[33,42] We believed that the yield of major isomer **58-I** (36% over these two steps, see footnote b of Table 1), while not stellar, was high enough to enable completion of the total synthesis of celogentin C *as long as this compound possessed the requisite configuration at the two newly created stereocenters*. Consequently, we moved forward with the goal of separating isomers I and N and determining their stereochemistry.

TABLE 1 Conjugate Additions of Isopropyl Radical to 54

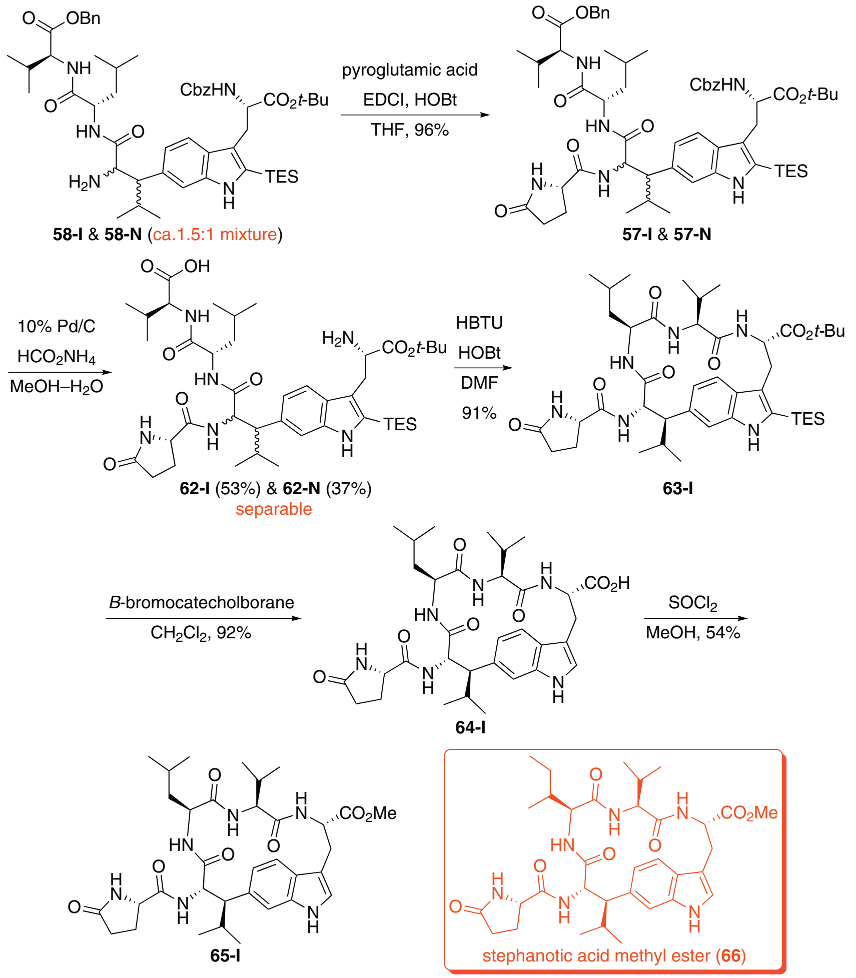


Entry	Lewis acid/ligand	Equivalents	*B*:I:N:G[a]
1	$Mg(NTf_2)_2$/**59**	2.0	1:2:1:1
2	$Mg(NTf_2)_2$/**60**	2.0	1:2:2:1
3	$Mg(NTf_2)_2$/**60**	5.0	2:2:2:1
4	$Mg(NTf_2)_2$/**61**	2.0	3:2:2:1
5	$Zn(OTf)_2$/none	2.0	1:3:2:1[b]
6	None/none	–	3:4:4:1

[a] *Calculated from ^{1}H NMR spectra of the crude reaction mixtures (see inset above).*
[b] *When run on a preparative scale (0.4 mmol), 90% of a 1.0:2.9:2.0:1.2 mixture was obtained.*

5.2 Macrolactamization and Determination of Stereochemistry

Coupling of the mixture of amines **58-I** and **58-N** with pyroglutamic acid delivered **57-I** and **57-N** in 96% yield, but unfortunately, these two compounds were also inseparable (Scheme 18). Gratifyingly, transfer hydrogenolysis effected smooth cleavage of the benzyl esters and Cbz groups, and the resulting peptides **62-I** and **62-N** could be separated on silica gel. Bing was able to isolate major isomer **62-I** in 31% yield over the four steps consisting of radical conjugate addition, nitro reduction, peptide coupling, and tandem deprotection. This result is remarkable given the low diastereoselectivity of the radical conjugate addition and is reflective of the outstanding yields of these reactions. Then, we were thrilled to find that macrolactamization of **62-I** furnished left-hand ring derivative **63-I** in 91% yield with no evidence



SCHEME 18 Left-hand ring synthesis and comparison to stephanotic acid methyl ester.

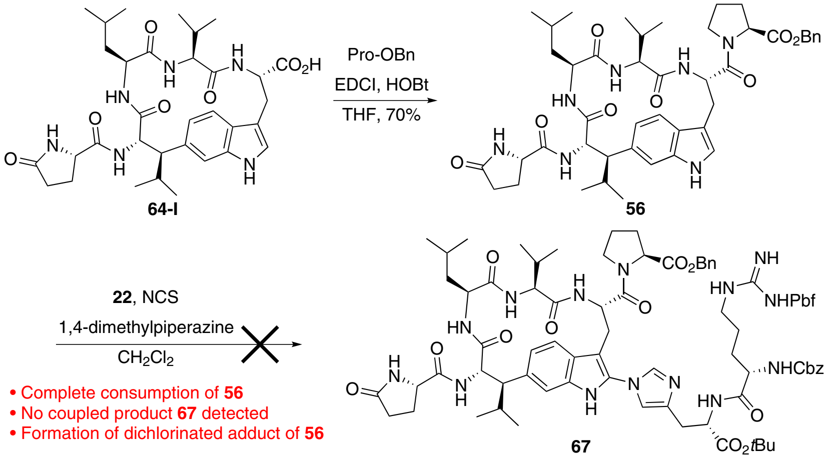
of epimerization.[33,42] This result contrasts that of Moody and coworkers, who observed extensive epimerization in forming the closely related cyclic peptide stephanotic acid methyl ester (**66**) via macrolactamization at a different site in the ring.[9c]

With left-hand macrocyclization accomplished, our focus turned toward determining the stereochemistry of the "I" series of compounds. We noted that the configurations of **66** and the left-hand ring of celogentin C are identical, with the only structural difference derived from the position of a single methyl group (i.e., isoleucine in **66** is replaced by leucine in celogentin C). Thus, we enlisted *B*-bromocatecholborane to cleave the *tert*-butyl ester and triethylsilyl groups of **63-I** and transformed the resulting acid into methyl ester **65-I** for the purpose of comparing NMR data with **66**. *We were delighted to discover that the data matched very well, with only minor differences in the* ^{1}*H and* ^{13}*C NMR spectra that could be attributed to the isoleucine→leucine substitution!* Our excitement grew when we learned that methyl ester **65-G**, which was prepared by subjecting minor isomer **58-G** to the sequence shown in Scheme 18, was distinct from **65-I** and quite similar to a known diastereomer of **66** (i.e., the alternative *trans* isomer at the leucine–tryptophan junction) prepared by Moody and coworkers.[9c] Moreover, the spectral data of methyl ester **65-N** were readily distinguishable from those of **65-I** and **65-G**. Unfortunately, insufficient quantities of minor isomer **58-B** were produced to enable its transformation into **65-B**.[33] This evidence, although circumstantial, gave us confidence that the major "I" series of compounds was of the correct configuration for synthesizing celogentin C. Nonetheless, we recognized that constructing the natural product was the only way to prove this supposition.

6 OXIDATIVE COUPLING IS ENABLED BY AN UNEXPECTED ADDITIVE

6.1 The Serendipitous Discovery

In preparation for the critical indole–imidazole oxidative coupling reaction, Bing generated hexapeptide **56** by coupling acid **64-I** with proline benzyl ester (Pro-OBn, Scheme 19). We approached the oxidative coupling with great anticipation, but Bing's initial results were very disappointing. Exposure of **56** to NCS and 1,4-dimethylpiperazine induced consumption of the starting

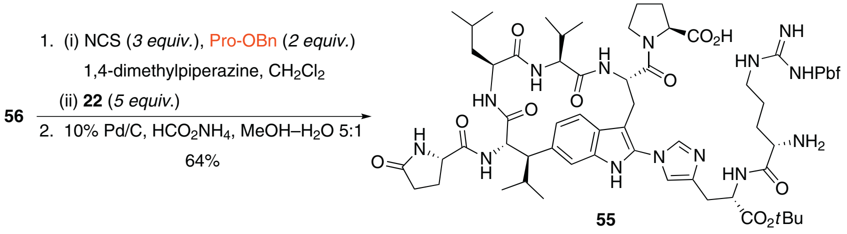


- Complete consumption of **56**
- No coupled product **67** detected
- Formation of dichlorinated adduct of **56**

SCHEME 19 Unsuccessful oxidative coupling of **56** and 22.

material, but the desired product **67** was not formed upon addition of arginine–histidine dipeptide **22**. Analysis of the reaction mixture by mass spectrometry revealed the presence of a dichlorinated adduct of **56** rather than the monochlorinated species required for oxidative coupling to occur. When compared to the ^{1}H NMR spectrum of **56**, the spectrum of this crude adduct showed measurable differences in the signals derived from the proline residue. This observation suggested that the second chlorination might be occurring on the tryptophan–proline tertiary amide. The dichlorinated adduct was surprisingly unreactive, as Bing was unable to coax it to couple with **22** despite increasing the temperature, time, and concentration of the reaction. Apparently, our earlier fears regarding the reactivity (or lack thereof) of the hindered indole ring imbedded within the left-hand macrocycle were being realized.

Undaunted, Bing made further changes to the reaction conditions. After several futile attempts, he finally obtained the desired product. In order to reproduce this exciting result, he needed to determine which modification enabled the success of the reaction. Upon considering each step of the process as well as the quality of reagents and starting materials, he recognized that the batch of hexapeptide **56** enlisted in the successful oxidative coupling was contaminated with Pro-OBn, which had been used in excess during the peptide coupling with precious acid **64-I** (see Scheme 19). *Further investigations revealed that the oxidative coupling only proceeded when this "contaminant" was present in the reaction mixture!* An excess of NCS relative to Pro-OBn was necessary, with three equivalents of the former and two equivalents of the latter proving to be optimal (Scheme 20). A large excess of the base 1,4-dimethylpiperazine was also included, and these three components were stirred in the presence of **56** at ambient temperature for 6 h prior to the addition of dipeptide **22**. The oxidative coupling was slow, requiring large quantities of **22** (5 equiv.) and a relatively long reaction time (24 h) in order to furnish a reasonable amount of the product. The excesses of reagents and the coupling partner made purification quite challenging. Fortunately, subjection of the crude product to transfer hydrogenation induced cleavage of the benzyl ester and Cbz groups, and the resulting product **55** could be readily

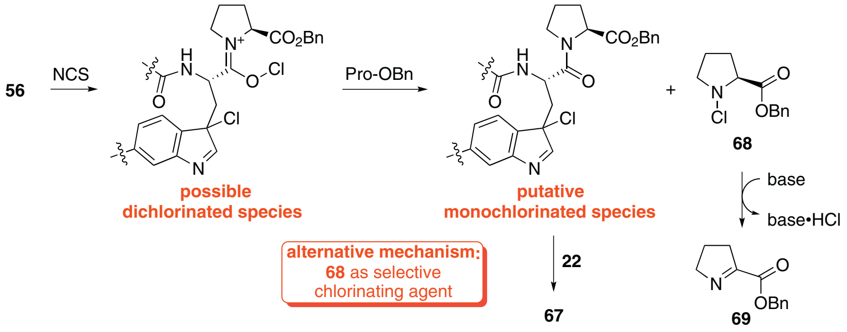


SCHEME 20 Pro-OBn-promoted oxidative coupling.

separated from the other reaction mixture components. Bing was able to obtain this key late-stage intermediate in a respectable 64% yield over these two steps.[33,42]

6.2 Mechanistic Studies

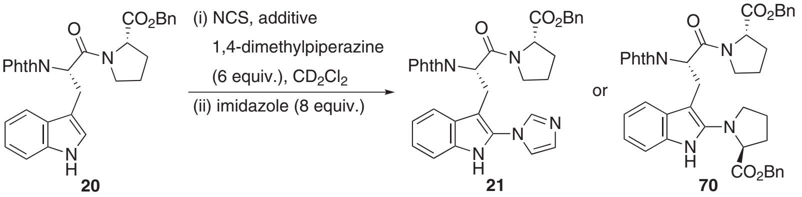
We were extremely grateful for the serendipitous discovery of Pro-OBn as a necessary additive in the indole–imidazole oxidative coupling. Never in our wildest dreams would we have imagined that some sloppy chromatography (i.e., Bing's inability to remove unreacted Pro-OBn from the peptide coupling reaction mixture) would provide the key to solving the puzzle of this difficult reaction. The end of the total synthesis was now in sight, but in order to take full advantage of our unusual finding, we needed to understand the role of the additive in the oxidative coupling process. Thus, we formulated the preliminary mechanistic hypothesis shown in Scheme 21 for the purpose of focusing our mechanistic studies. We reasoned that the hindered nature of the indole present in left-hand ring hexapeptide **56** would slow its chlorination at C-3 significantly compared to chlorinations of smaller substrates (e.g., indoles **20** and **29**, Schemes 8 and 9). This would allow a second chlorination, possibly at the tryptophan–proline tertiary amide, to take place competitively. We posited that the undesired chlorine atom of the dichlorinated species might be transferred to the nucleophilic amine of Pro-OBn, affording *N*-chloroamine **68** along with the desired monochlorinated species. Base-promoted elimination of HCl from **68** would generate imine **69** and an HCl salt. Free of the unwanted second chlorine atom, the monochlorinated intermediate would then be attacked by arginine–histidine dipeptide **22**, delivering the product **67** after elimination of HCl. In addition to this scenario, we also considered the possibility that NCS could react directly with Pro-OBn to form **68**, which might function as a more selective electrophile by delivering a single chlorine atom to **56**.



SCHEME 21 Preliminary mechanistic hypothesis.

Our efforts to study the mechanism of the Pro-OBn-promoted oxidative coupling were hampered by the scarcity of precious intermediate **56**. Unwilling to divert a substantial amount of this compound from the total synthesis effort, we searched for a suitable, readily available model substrate. In contrast to **56**, simple dipeptide **20** underwent clean and rapid oxidative couplings in the absence of Pro-OBn, with no evidence of dichlorination (Schemes 7 and 8). Presumably, the fast rate of indole chlorination obviated the need for an additive with this substrate. Accordingly, we were skeptical regarding its utility for probing the role of Pro-OBn in the oxidative coupling of **56**. Fortunately, postdoctoral fellow Biplab Banerjee discovered that **20** could be dichlorinated by excess NCS. With hopes that oxidative couplings of **20** conducted under these conditions would be informative, Biplab performed the experiments summarized in Table 2. To closely mimic the conditions employed with substrate **56**, reactions with **20** involved excess 1,4-dimethylpiperazine (6 equiv.) and imidazole

TABLE 2 Mechanistic Studies with Dipeptide 20



Entry	Equivalents of NCS	Additive (equiv.)	Product[a]
1	3	Pro-OBn (2)	**21**
2	2	Pro-OBn (2)	Recovered **20** (major), **21** (minor)
3	3	Pro-OBn (2)[b]	**70**+2Cl (major), **21**+Cl (minor)
4	3	Pro-OMe (2)	**21**
5	3	Pyrrolidine (2)	**21** (major), **21**+Cl (minor)
6	3	Pro-OBn (2)	**21** (68%)
7	3	Pro-OMe (2)	**21** (79%)
8	3	Pyrrolidine (2)	**21** (41%)
9	3	None	**21** (47%)

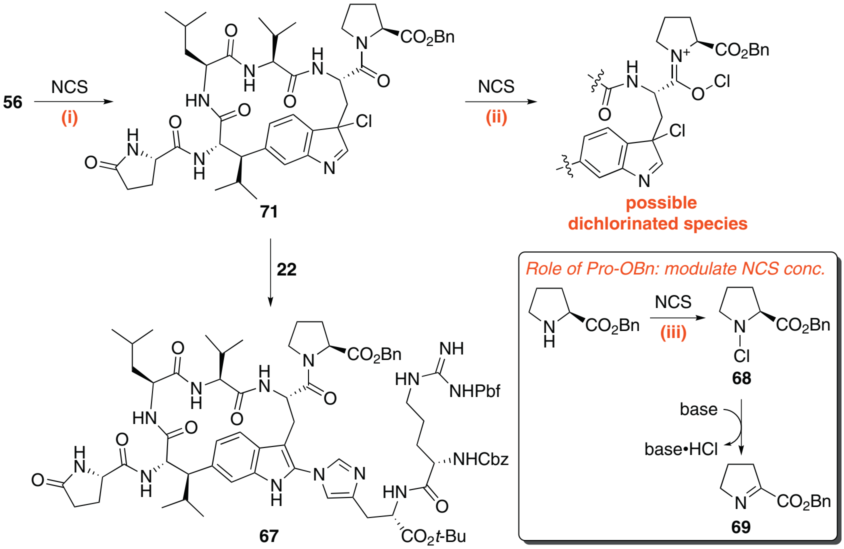
[a] *Values in parentheses refer to isolated yields of product.*
[b] *Added 3 h after addition of NCS and 1,4-dimethylpiperazine.*

(8 equiv.). Biplab used CD_2Cl_2 as solvent for the purpose of monitoring the reactions by NMR spectroscopy. In practice, mass spectrometry data (ESI-MS) were more informative; however, deuterated solvent was utilized in all reactions for consistency.

The first set of experiments was conducted on a small scale and analyzed qualitatively by ESI-MS. When NCS and Pro-OBn were utilized in the same 3:2 ratio employed in the oxidative coupling of **56**, the expected adduct **21** was obtained (entry 1). In contrast, equimolar quantities of these two components led to only minor amounts of **21** (entry 2), demonstrating that an excess of NCS relative to Pro-OBn is necessary for facile oxidative coupling to occur. This result casts doubt on our alternative theory that invoked *N*-chloroamine **68** as the chlorinating agent. The next experiment was designed to test the validity of our primary hypothesis. If Pro-OBn was scavenging the undesired chlorine from the dichlorinated species, then its presence at the outset of the reaction would not be essential. However, when Biplab waited 3 h to inject the additive, the anticipated product **21** was not observed. Instead, minor amounts of a chlorinated adduct of **21** were detected, and the major product was a dichlorinated adduct of **70**, which was produced by nucleophilic attack of Pro-OBn rather than imidazole (entry 3). From this result, we learned that overchlorinated species derived from **20** are able to participate in oxidative couplings, unlike the dichlorinated intermediate obtained from complex substrate **56**. More importantly, we found that Pro-OBn *cannot* function as a scavenger of chlorine atoms unless it is present at the beginning of the reaction. If this additive is injected at a later stage (presumably after the NCS has been consumed by reaction with **20**), then it acts as a nucleophile instead. Clearly, Pro-OBn is unable to remove a chlorine atom from a dichlorinated species derived from **20**. This finding demanded a revision of our mechanistic rationale, but more experiments were necessary before a new hypothesis could be advanced.

In an attempt to probe the structural requirements of the additive, Pro-OMe and pyrrolidine were used instead of Pro-OBn. In qualitative experiments, both enabled the formation of product **21** (entries 4 and 5), although Pro-OMe appeared to be somewhat more effective than pyrrolidine. Intrigued by the possibility that the acidic α-hydrogen of the proline esters might not be necessary, Biplab performed four preparative scale reactions to obtain quantitative data regarding the effectiveness of these additives. Pro-OBn and Pro-OMe mediated the production of **21** in 68% and 79% yields, respectively (entries 6 and 7), suggesting that a range of proline esters might be useful additives. Contrastingly, the use of pyrrolidine afforded a lower yield (41%, entry 8) than a reaction conducted with no additive (47%, entry 9). These two reactions taught us that a proline ester additive is beneficial but not essential when excess NCS is employed in the oxidative coupling of **20**, and that no benefit is derived from using pyrrolidine as the additive.

Based on the results summarized in Table 2, we crafted a new mechanistic hypothesis for the oxidative coupling of **56** and **22**, which is illustrated in



SCHEME 22 Revised mechanistic hypothesis.

Scheme 22. Attack of the indole moiety of **56** on NCS presumably leads to chloroindolenine **71** (step i). This step is relatively slow due to the hindered nature of the indole, and a second chlorination (step ii) is competitive. In the absence of Pro-OBn, the dichlorinated species predominates and the desired adduct **67** does not form upon addition of dipeptide **22**. Although we have not determined the structure of the dichlorinated species, ^{1}H NMR data implicate the tryptophan–proline tertiary amide in the second chlorination event. When Pro-OBn is present at the beginning of the reaction, its nucleophilic secondary amine reacts with NCS, generating *N*-chloroamine **68** (step iii). Subsequent elimination of HCl from **68** furnishes imine **69** and sequesters the electrophilic chlorine atom originating from NCS in a relatively benign HCl salt. *Apparently, the rates of the three processes that consume NCS (i.e., steps i–iii) are finely balanced in a manner that maximizes the concentration of **71** and minimizes the concentration of the dichlorinated species when the proper amounts of the electrophilic reagent and additive are employed.* Attack of the imidazole subunit of dipeptide **22** on **71** followed by elimination of HCl delivers the final product **67**. Thus, the role of the Pro-OBn additive is to favor the production of **71** and disfavor formation of the dichlorinated species by modulating the concentration of NCS. In support of this rationale, oxidative couplings conducted in the presence of Pro-OBn exhibited high levels of **71** according to ESI-MS, whereas reactions performed in its absence were characterized by large amounts of the undesired dichlorinated adduct.

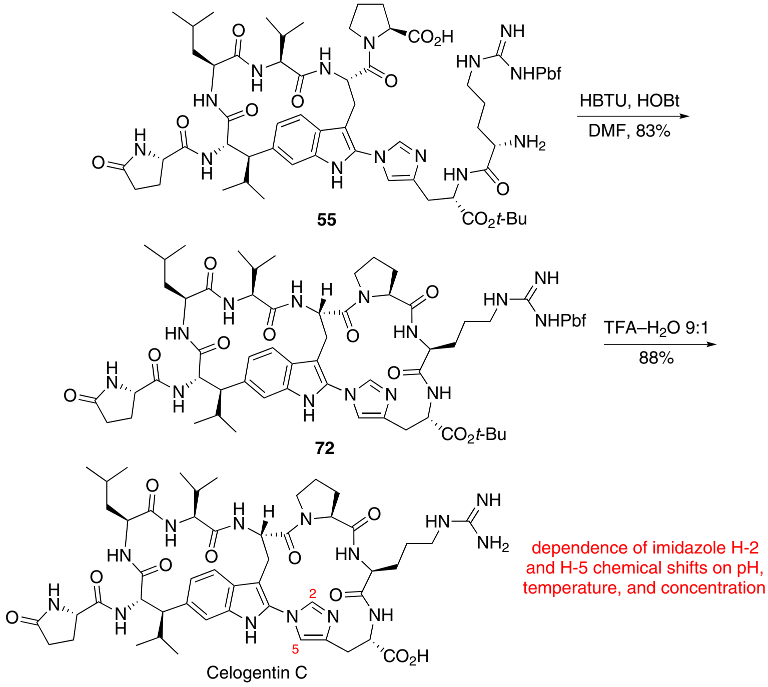
To gain more support for this hypothesis, Biplab monitored the reaction of Pro-OBn and NCS by ^{1}H NMR and ESI-MS. Gratifyingly, the starting material was consumed and *N*-chloroamine **68** was produced. Then, addition of 1,4-dimethylpiperazine to the solution induced elimination and formation of imine **69** as predicted. At this point, we were fairly confident in the veracity of our mechanistic proposal. This experiment highlighted the necessity of the nucleophilic amine and the acidic α-hydrogen present in Pro-OBn, and reminded us of how fortunate we were that an additive with the correct structure for controlling the NCS concentration was a starting material of the previous reaction in the synthetic route.

Our new hypothesis for the role of Pro-OBn suggested that a similar effect could be achieved by simply adding the NCS slowly (i.e., as a solution via syringe pump) rather than all at once. We wanted to test this idea, but practical considerations prevented us from doing so. By the time we made this realization, virtually our entire supply of left-hand hexapeptide **56** had been used to produce sufficient quantities of celogentin C for anticancer testing (*vide infra*). Also, Bing had graduated and Biplab had moved on to a new position. Sadly, our limited resources combined with the finite tenure of these two critical group members precluded exploration of a slow addition protocol in the oxidative coupling of **56**.

One final point related to the indole–imidazole oxidative coupling is worthy of mention. About 6–7 months after our initial disclosure of the total synthesis of celogentin C,[42] total syntheses of this natural product were published by the groups of Gong Chen at Penn State University[43] and Yanxing Jia at Peking University.[44] Both of these groups devised highly innovative and stereoselective strategies for constructing the left-hand ring, and both utilized our oxidative coupling and subsequent endgame chemistry by intercepting our route at the stage of carboxylic acid **64-I** (see Scheme 18 for structure). These reports were gratifying to us, as they demonstrated that others recognized the value of the oxidative coupling for creating indole–imidazole linkages, and that our unconventional procedure employing Pro-OBn as an additive could be readily reproduced outside our laboratory. Additionally, the work of the Chen and Jia groups provided independent confirmation that the “I” series of compounds derived from the major diastereomer of the radical conjugate addition were stereochemically identical to the natural product.

7 RIGHT-HAND MACROLACTAMIZATION AND ONE FINAL SURPRISE

With right-hand ring precursor **55** in hand, we were two steps away from accomplishing the total synthesis of celogentin C. We were again relieved to find that another macrolactamization proceeded smoothly, furnishing bicycle **72** in good yield with no evidence of epimerization (Scheme 23). Simultaneous deprotection of the Pbf sulfonamide and *tert*-butyl ester groups was



SCHEME 23 Completion of total synthesis.

facile, delivering the natural product in high yield. Notably, no alkylation of the tryptophan indole by the electrophilic byproducts of the Pbf deprotection took place, an observation that was in harmony with prior reports[45] and validated our rationale for using this protecting group. Isolation of celogentin C proved challenging, but Bing discovered that a pure sample of the natural product could be obtained without recourse to chromatography as long as the protected precursor **72** was of sufficient purity.[33,42] The ^{1}H NMR spectrum of our synthetic material matched the published spectrum of the natural product[4] extremely well, with the exception of the imidazole H-2 (δ 9.16 ppm synthetic vs. 9.41 ppm natural) and H-5 (δ 7.72 ppm synthetic vs. 7.79 ppm natural) signals. This discrepancy was an unexpected surprise and a major cause for concern.

At first, we considered the possibility that macrolactamization had somehow given rise to the unnatural configuration about the indole–imidazole heterobiaryl axis. Accordingly, Bing acquired NOESY data on our synthetic material and found the same diagnostic correlations (i.e., indole N—H to imidazole H-2, tryptophan β-H to imidazole H-5) that were reported for the natural product.[4] These data allowed us to rule out the possibility of an unnatural atropisomer but did not lessen our confusion regarding the structural identity of our synthetic material. A breakthrough came when Bing noticed that the chemical shifts of the H-2 and H-5 atoms were dependent on temperature and concentration. Spectra of our synthetic material acquired at a range of temperatures (16–44 °C) and concentrations (ca. 12 mg/mL to ca. 0.6 mg/mL) showed a very large variation in the H-2 chemical shift (8.04–9.22 ppm) and a smaller variation in the H-5 chemical shift (7.40–7.73 ppm). Although encouraging, the fact that these ranges did *not* encompass the H-2 and H-5 chemical shifts reported for the natural product (9.41 and 7.79 ppm, respectively) prevented us from claiming success in our quest to synthesize celogentin C. Unfortunately, the observed trends indicated that a colder and/or more concentrated sample would give the desired chemical shifts, and the high freezing point of DMSO-d_6 along with the relatively small amount of synthetic material prevented us from acquiring NMR spectra under the required conditions.

The final piece of the puzzle was revealed in a correspondence with Phil Baran. He noticed the presence of a common contaminant of trifluoroacetic acid in the ^{1}H NMR spectrum of natural celogentin C, and suggested that the published data had been acquired at a low pH. Excitingly, when ca. 2 μL of TFA was added to a room-temperature solution of our synthetic material in DMSO-d_6 at a concentration of ca. 12 mg/mL, the H-2 and H-5 chemical shifts increased dramatically (9.53 and 7.83 ppm, respectively), giving us a range of chemical shifts for each imidazole hydrogen (8.04–9.53 and 7.40–7.83 ppm) that encompassed the reported values for the natural product (9.41 and 7.79 ppm). Presumably, these variable chemical shifts indicate the existence of either intermolecular hydrogen bonding or acid–base chemistry at the basic N-3 atom of imidazole. At this point, we were very confident that our synthetic material was identical to celogentin C. We were able to confirm this belief when Professor Hiroshi Morita of Hoshi University (a former staff member in the Kobayashi group who was a coauthor of the celogentin C isolation paper) kindly sent us a small (ca. 0.1 mg) sample of the natural product. Synthetic and natural celogentin C were shown to be identical by HPLC coinjection of the two samples.[33,42] At last, we knew that we had achieved our goal of synthesizing this beautiful and challenging natural product.

8 ANTICANCER SCREENING

One of our aims in pursuing the total synthesis of celogentin C was to prepare sufficient quantities of the natural product to enable anticancer screening. Kobayashi and coworkers demonstrated its potency as an antimitotic agent,[4] but prior to our work, there were no reports of its efficacy in antiproliferative assays employing cancer cells. We were able to synthesize a batch of material that was large enough for screening against the 60-cell-line panel of the National Cancer Institute. Unfortunately, the overall result was disappointing, as celogentin C did not significantly impact the growth of most of the cell lines at 10 μM concentration. Promising levels of growth inhibition at this concentration were exhibited in only four cancer cell lines: the SR leukemia line (35% growth), the MDA-MB-435 melanoma line (23% growth), the HS 578T breast cancer line (30% growth), and the MDA-MB-468 breast cancer line (34% growth). It is possible that future studies of the activity of celogentin C against these and related cancer cell lines would be worthwhile.

9 CONCLUSION

Completion of the total synthesis of celogentin C represented the culmination of an almost 8-year journey that began in late 2001. As is often the case in total synthesis ventures, some of our initial goals, such as the development of alternatives to macrolactamization, were not achieved. Although our first-generation plan underwent several modifications; it served its purpose by placing us on the pathway to discovery. As a result, many interesting and useful findings emerged from this endeavor. The indole–imidazole oxidative coupling, which was critical to the synthesis of the right-hand ring of celogentin C, has already been utilized by other research groups. We believe that more applications of this process are likely to be disclosed in the future. Radical conjugate additions to α,β-unsaturated α-nitroamide acceptors, while not as stereoselective as envisioned, enabled the construction of the left-hand ring of the natural product and provide rapid access to valuable β-substituted amino acids in high yields. Even the dead-end routes produced important results, as our application of the Braslau modification of the McFadyen–Stevens reaction (Scheme 14) and our observations pertaining to stereoselective Knoevenagel condensations (Scheme 16) and alkylnitro chemistry (Schemes 10–13) should be helpful to the organic synthesis community.

The celogentin C total synthesis was the first project launched in our research group, and we learned many valuable lessons while carrying out this work. Two specific lessons are particularly noteworthy. We benefited greatly from luck at two stages in the synthesis: the radical conjugate addition to α,β-unsaturated α-nitroacetamide **54** (the major isomer **58-I** was of identical configuration to the natural product), and the oxidative coupling of indole **56** with imidazole **22** (the Pro-OBn contaminant left over as a starting material from the previous reaction was necessary for the coupling to proceed). We believe that luck plays a role in the majority of scientific endeavors, and that successful projects often result from capitalizing fully on these serendipitous events. We also received valuable input and inspiration from several eminent organic chemists at various stages of the work. As a result, we have strong feelings about the importance of scientific discourse. In our opinion, listening to and learning from seminars and engaging in conversations and correspondence with other scientists is critical to achieving success in research. It is often said that science is not conducted in a vacuum, and in our experience it is extremely rare to solve a challenging problem alone without input from others. Thus, we believe that researchers should take advantage of every opportunity to interact with scientists in their own and related fields. We fully intend to exploit the useful synthetic methods and important lessons derived from the celogentin C project in our future work, and it is our hope that others will find value in them as well.

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Chapter 3

The Upside of Panic: Developing a Synthesis of Englerin A

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Chapter Outline

1 INTRODUCTION: CARBONYLS AND TARGET SELECTION

1.1 Working with Carbonyl Chemistry

As a graduate student in the laboratories of Professor Andrew Myers at Harvard University and a postdoctoral researcher in the laboratories of Professor Erik Sorensen at Princeton University, I developed a great respect and affinity for the chemistry of the carbonyl group.[1] At Harvard, my work was focused on the alkylation of α,α-disubstituted pseudoephedrine amide enolates and the analyses of the resultant products.[2] This was a continuation of many years of methodological development in the group.[3] My colleagues in

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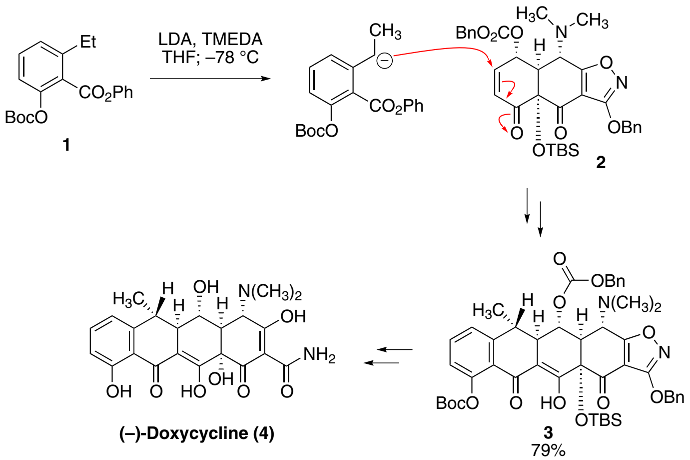
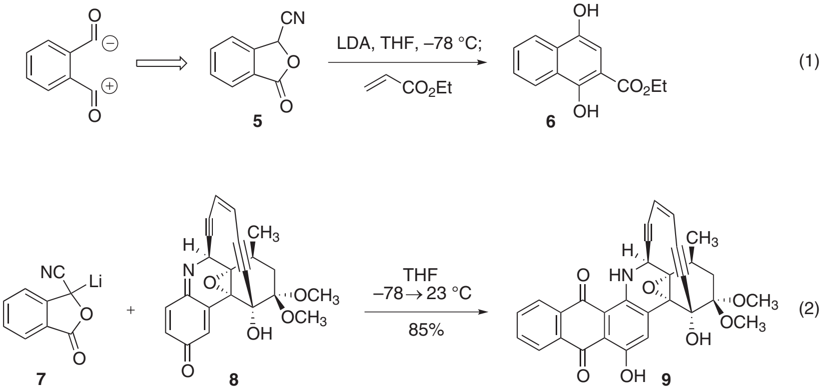
the Myers group at that time, such as the team that completed the tetracycline antibiotics[4] and those who worked in the elegant syntheses of various alkaloids by the directed condensation of α-aminoaldehydes,[5] were also deeply invested in the chemistry of the carbonyl. One result that always impressed me as a benchmark of elegance and simplicity in complex target synthesis was the development of the Michael–Claisen cyclization sequence to form the C-ring of many of the tetracyclines.[4] For example, in this work, a *t*-butoxycarbonyl-protected phenyl ester **1** was metalated with lithium *N*,*N*-diisopropylamide (LDA) at low temperature in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Treatment of the resultant anion with a solution of the enone **2** resulted in a rapid and highly diastereoselective Michael addition reaction (Scheme 1): one of four possible diastereoisomers forms predominantly. The intermediate enolate (which could be intercepted by the careful addition of a proton source) then underwent a much slower Claisen condensation with the neighboring phenyl ester to complete the C-ring of the target to give **3**, which was subsequently deprotected to give (−)-doxycycline (**4**).

There are many examples of this type of ring formation in the chemical literature,[6] but one of particular note is that described by Kraus and Sugimoto[6] wherein a cyanophthalide anion (**7**) was joined with ethyl acrylate in a similar sequence (Scheme 2, Equation 1) to give a substituted naphthalene (**6**). This particular reagent (which itself can be considered the equivalent of an electrophilic and a nucleophilic carbonyl within the same molecule) and bond-forming strategy had been employed in the Myers group previously in the context of the dynemicins (Scheme 2, Equation 2).[7]



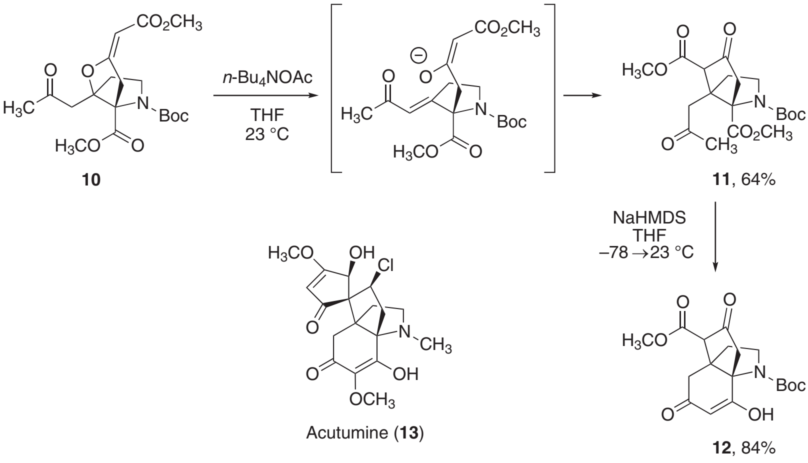
SCHEME 1 A Michael–Claisen sequence to form tetracycline antibiotics. Boc, *t*-butoxycarbonyl; LDA, lithium *N*,*N*-diisopropylamide; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; THF, tetrahydrofuran; Bn, benzyl; TBS, *t*-butyldimethylsilyl.



SCHEME 2 Cyanophthalide anions in Michael–Dieckmann ring forming cascades. LDA, lithium *N*,*N*-diisopropylamide; THF, tetrahydrofuran.

One of the most beneficial aspects of conducting research with Professor Erik Sorensen is the frequent and often passionate discussions of the classic total syntheses that have inspired and continue to inspire us.[8] It is impossible to escape without a deep admiration of Professors Woodward, Corey, Stork, Eschenmoser, Danishefsky, and Nicolaou, just to name a few.

Right around the time I arrived in Princeton, Sorensen and Moreau described a wonderful sequence of simple reactions that built most of the core structure of the alkaloid acutumine (**13**).[9] In their work, an elimination–Michael addition–Dieckmann cyclization converted a bicyclic vinylogous carbonate (**10**) into the tricyclic core of the natural product (**12**, Scheme 3). The elimination reaction revealed a stabilized enolate, which cyclized back upon the tethered



SCHEME 3 A carbonyl-enabled synthesis of the acutumine core structure. Boc, *t*-butoxycarbonyl; THF, tetrahydrofuran; NaHMDS, sodium bis(trimethylsilyl)amide.

enone to form a carbon–carbon bond and give **11**. A second operation under the action of sodium bis(trimethylsilyl)amide induced a Dieckmann cyclization between the methyl ketone and the pendant methyl ester to give **12**.

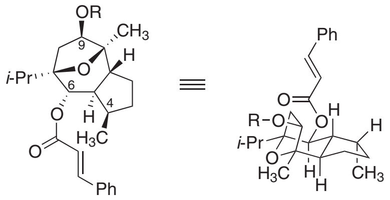
I view new targets for synthesis in my own laboratories with the elegant applications of fundamental reactions of carbonyls like those described above ever present in my mind as a benchmark for success; they are constant reminders that complex problems do not always require complex solutions.

1.2 Englerin A, Englerin B, and Englerin B Acetate

I began my independent career at the University of Hawaii during the late summer of 2009. I entered terminal C at Newark Airport in July of that summer, dragging behind me a bag containing nearly every earthly possession. I promptly handed that bag to a complete stranger who traded me the bag for a boarding pass, straight up. After passing through the various security checkpoints, my mood could only be described as "panic." It was an exciting time—I was embarking on a new and independent career, but at the same time, I was flying as far away from home as one could without leaving American soil. I proceeded straight past the gate waiting area and into an establishment that catered to those in special states of mind with an odd mixture of automotive magazines and chemistry literature tucked casually under my arm. After placing an order with the nice smiling face behind the counter, I slapped down the pile of papers onto the bar, and by happenstance the article on top was a little structure that had recently appeared in *Organic Letters*. So there it was, a little guaiane sesquiterpene staring me in the face on what was the first day of the rest of my life.

1.2.1 Structure and Biological Activity of the Natural Product

Englerin A (**14**) was attractive straightaway. The englerins were isolated by Beutler and coworkers from an extract of the stem bark of *Phyllanthus engleri*, which is a plant indigenous to east Africa (particularly Tanzania and Zimbabwe) and used in many traditional medicines (Figure 1).[10]



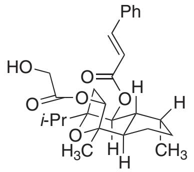
Englerin A, 14, R = $HOCH_2C(O)$–
Englerin B, 15, R = H–
Englerin B Acetate, 16, R = $CH_3C(O)$–

FIGURE 1 Structures of englerin A (**14**), englerin B (**15**), and englerin B acetate (**16**).

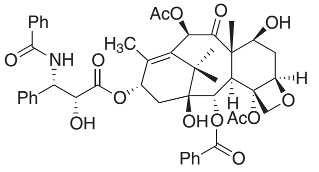
This plant in particular, and the natural products so derived, carry the name of the eminent botanist Adolf Engler (1844–1930), who spent the majority of his life working in the areas of plant taxonomy and phytogeography.[11] The extract from which the englerins were isolated was identified as part of a study searching for selective inhibitors of human cancers. It was determined that englerin A was the active component, and its activity against five of the eight renal lines in the NCI 60-cell panel (GI_{50} values under 20 nM, see Table 1) was cause for excitement.

Upon isolation, the natural products had a few surprises. There was of course the typical 5–7 hydroazulene ring system present in other guaiane sesquiterpenes, but the englerins were special. The englerins contained an

TABLE 1 **Renal Cancer Cell Growth Inhibition Activity for Englerin A (14) and Taxol® (Mean GI_{50} in μM)**



Englerin A, 14



Taxol®

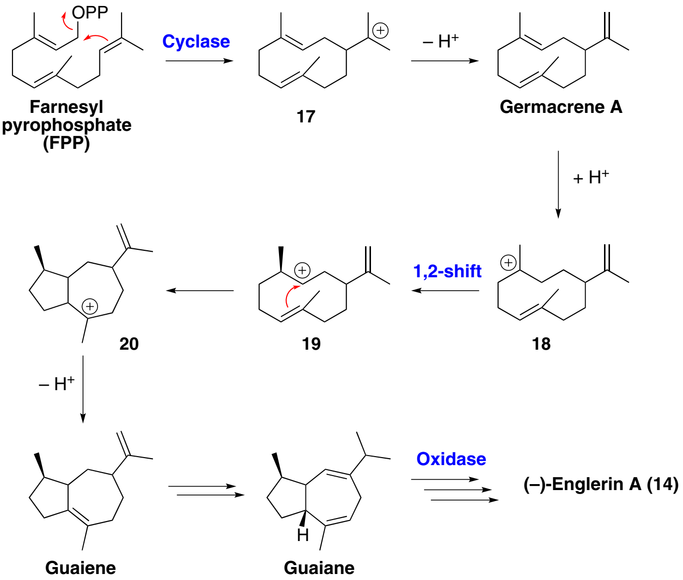
Renal cell line	Englerin A	Taxol®
786–0	<0.01	0.034
A498	<0.01	0.1
ACHN	<0.01	0.65
CAKI-1	15.5	0.35
RXF-393	0.011	0.041
SN12C	0.087	0.018
TK-10	15.5	0.11
UO-31	<0.01	0.45

unusual C7–C10 oxo bridge, present in a few other guaiane sesquiterpenes such as the orientalols[12] and the purbinernoids,[13] a structural feature that renders the hydroazulene system an exquisite 5,6,5-fused tricyclic system. In addition, the englerins possessed two oxygen-bearing stereogenic centers at C6 and C9, and moreover, englerin A was found to contain the highly unusual glycolate residue at C9. The glycolate residue is known in only three other natural products (saframycin R,[14] pleuromutilin,[15] and an ecdysteroid[16]), none of which exhibit the wonderfully potent and selective activity against human renal cancer cell lines like englerin A. This is particularly interesting if one considers that glycolic acid itself exhibits acute renal toxicity to mammals.[17] Beuter and his group also determined that the natural product is active in mouse xenografts and appears to exhibit relatively low toxicity (a maximum tolerated dose of 5 mg/kg i.p. in mice), which suggests the possibility of a large therapeutic window. Englerin B (**15**), which lacks the C9 glycolate residue, and its acylated derivative englerin B acetate (**16**) are essentially inactive and this implicates the glycolate residue in anticancer activity.

Natural products rarely emerge with such exciting activity and such an exciting structure, but when they do, the synthetic community takes notice.[18] In the time since the first disclosure of the gross structure and activity of the englerins, several structure–function studies have been reported[19] that discuss the structural modifications that can be tolerated in active compounds; with some exceptions, those structures that retain the glycolate residue but have been modified elsewhere (most notably at the C6 ester side chain) are the most promising of the agents reported thus far in the development of compounds like englerin A as potential therapeutics.

1.2.2 Proposed Biosynthesis of the Natural Product

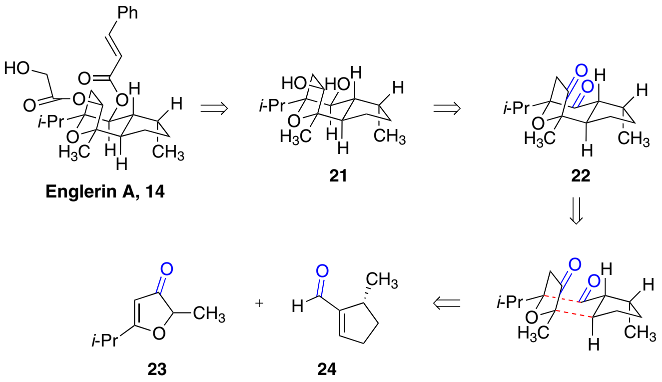
The natural product likely arises in a fashion typical of many sesquiterpenes (Scheme 4).[12] Farnesyl pyrophosphate (FPP) is cyclized to give **17**, followed by a loss of a proton to give germacrene A. Protonation to give **18** and a subsequent 1,2-hydride shift establishes the C4 methyl-bearing stereogenic center to give **19** and sets the stage for the cation-π closure of the 5–7 ring system. Loss of a proton from the resultant cation (**20**) gives the guaiene structure, which is a few alkene isomerization operations away from the guaiane skeleton. Presumably, a series of oxidases then transforms the guaiane core into the exquisitely decorated natural product, including installation of the C7–C10 oxo bridge and the unusual glycolate residue at C9. No bench chemist is likely to approach Nature's efficiency at building the englerins, but the laboratories of Professors Ma[18] and Echavarren[18] independently reported elegant syntheses of englerin A that are no doubt inspired by such cascades of bond formations, which was the subject of a recent highlight.[20] But something else about these structures caught my eye, however, glassy and awash in solicitude as it may have been at the time.



SCHEME 4 Proposed biosynthesis of the englerins.

1.2.3 *The Big Idea: Putting Together the Natural Product*

I moved my libation to the left to reveal a napkin, flipped over the napkin, and began to draw. Drawing englerin A crudely in three dimensions, and focusing upon the oxo bridge allows one to consider the chair-like, six-membered ring embedded within the core structure. The oxo bridge is part of an appended five-membered ring occupying pseudoaxial positions, with the remaining five-membered ring bearing the C4 methyl group sitting nicely in a pseudoequatorial position. The acyl groups were natural disconnections to consider, as late stage acylations were not anticipated to be any trouble. With those removed, the resultant diol (**21**, Scheme 5) suggested that this structure could be put together using a very simple idea. The C6 and C9 alcohols could certainly arise from diastereoselective reductions of the corresponding diketone (**22**, key carbonyl functions highlighted in blue), and at the carbonyl oxidation level, two special relationships are established. The C6/C9 diketone places the carbonyl functions in a 1,5-relationship in one direction, and a 1,4-relationship in the other. This suggested that the core structure could arise by a sequence of simple carbonyl-dependent operations—a Michael addition[21] of a 3-furanone-derived enolate to an unsaturated aliphatic aldehyde followed by an intramolecular Stetter reaction,[22] or vice versa, a Stetter reaction of an unsaturated aliphatic aldehyde and a 3-furanone followed by an intramolecular Michael addition. In either sequence, the problem of the core



SCHEME 5 A concept for the synthesis of englerin A (**14**).

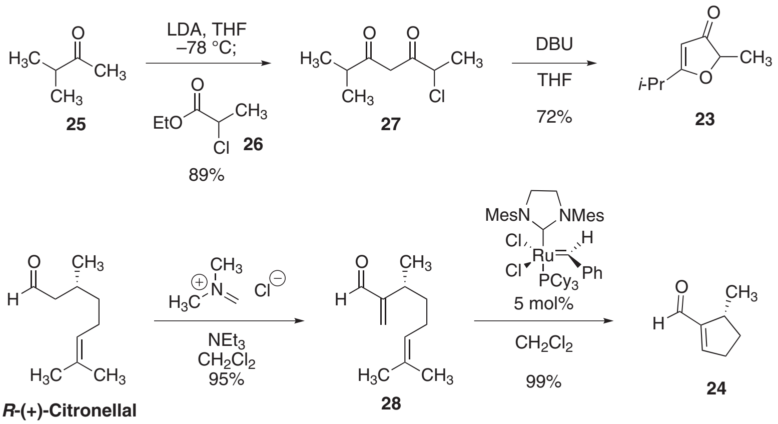
structure of englerin A is simplified to a 2,5-dialkyl substituted 3-furanone (**23**) and 5-methylcyclopentenecarboxaldehyde (**24**), both of which are readily available from inexpensive commodity chemicals. The idea fit neatly on the back of the napkin, which I hastily stuffed into my shirt pocket as a boarding announcement was made for a flight to Honolulu.

2 PUTTING THE PIECES TOGETHER: DEVELOPING A CARBONYL-BASED SYNTHESIS OF ENGLERIN A

2.1 Synthesis of the Building Blocks and Liabilities of Their Union

With the central idea in hand and a new laboratory in which to play, we set about synthesizing the 2,5-dialkyl-3-furanone (**23**) and 5-methylcyclopentenecarboxaldehyde (**24**) we required, and identifying the liabilities we would need to address and overcome in order to join these pieces as we saw fit.

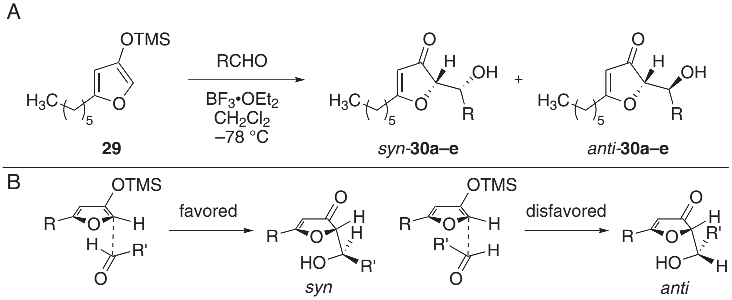
The 2,5-dialkyl-3-furanone (**23**) was a known compound at the outset of our study,[23] but Winkler and his group had described an efficient two-step preparation of simpler 3-furanones[24]—their syntheses joined ketones and chloroesters via a Claisen condensation, followed by base-mediated cyclizations of the resultant dicarbonyls. In our hands, the conversion of 3-methyl-2-butanone (methyl isopropyl ketone, **25**) and ethyl 2-chloropropionate (**26**) to the corresponding 3-furanone **23** proceeded in the same manner (Scheme 6). We joined the kinetic lithium enolate derived from 3-methyl-2-butanone (**25**) with ethyl 2-chloropropionate (**26**) in a Claisen condensation, and treatment of the resultant diketone (**27**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF afforded the 3-furanone **23** quite efficiently.



SCHEME 6 Preparation of the 3-furanone **23** and the aldehyde **24**. LDA, lithium *N*,*N*-diisopropylamide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; THF, tetrahydrofuran; NEt_3, triethylamine; Mes, 2,4,6-trimethylphenyl; Cy, cyclohexyl.

The 5-methylcyclopentenecarboxaldehyde (**24**) had been described before the outset of our study.[25] We elected to prepare the aldehyde in optically enriched form by the procedure described by Jacobsen and his group.[25] Citronellal was treated with Eschenmoser's salt (dimethylmethylideneammonium chloride)[26] to give the corresponding α,β-unsaturated aldehyde **28**, which was then transformed into the desired product **24** via a ring-closing metathesis[27] under the action of the second-generation Grubbs catalyst. With judicious choice of chromatography conditions and careful attention during handling, the volatile aldehyde was produced cleanly and efficiently using this procedure.

The question then became which sequence would ultimately assemble the core structure of englerin A. Though we had simple and efficient access to our building blocks, it was not readily apparent what the behavior of an ostensibly aromatic and diene-like 3-furanone-derived enolate would be toward an α,β-unsaturated aldehyde, nor was it clear how we might control the stereochemical outcome of the desired Michael addition. Winkler and his group had demonstrated that enolates and 3-silyloxyfurans derived from simpler 3-furanones underwent efficient Lewis acid-mediated aldol-type additions and conventional alkylation reactions (Scheme 7A).[24] The Winkler group developed serviceable levels of diastereocontrol with bulky aldehydes and they advanced some simple steric models that account for their results (Scheme 7B), but no Michael additions of these substrates had been reported at the time. The stereochemical models for similar additions advanced by Seebach[28] and Heathcock[29] were encouraging; however, the additional functionality of our putative enolate intermediate complicated matters.[30] It was not clear how the 3-furanone enolate might interact with an α,β-unsaturated



Entry	R	Product	*syn:anti*	Yield (%)
1	$(CH_2)_4CH_3$	**30a**	50:50	100
2	CH_2CH_2OBn	**30b**	50:50	42
3	Ph	**30c**	62:38	95
4	*i*-Pr	**30d**	>95:5	60
5	*t*-Bu	**30e**	>95:5	99

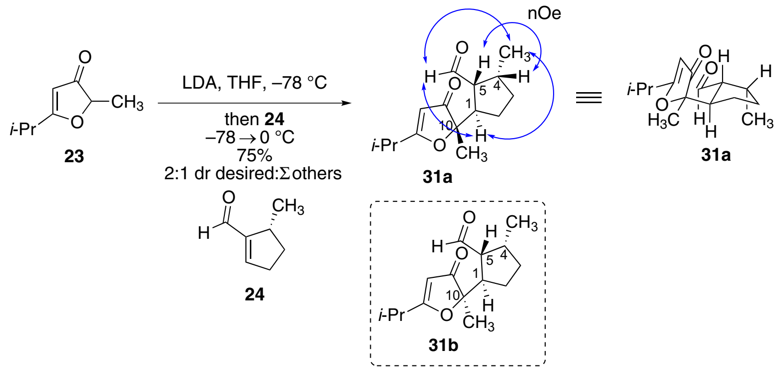
SCHEME 7 Aldol reactions of 3-silyloxyfurans under the influence of a Lewis acid. TMS, trimethylsilyl.

aldehyde in the presence of Lewis acidic atoms, though we hoped to take advantage of stereocontrol mediated by metal chelation.

We were also concerned about the C6–C7 bond formation—though many other similar acyclic vinylogous esters had been successfully engaged[31] under umpolung[32] conditions, Stetter-type[22] additions of aliphatic aldehydes with 3-furanones were unknown at the time. Both the steric and electronic properties of the 3-furanone were working against us for any intramolecular cyclization reaction. Lastly, once the desired sequence was executed, we would be faced with distinguishing the C6 and C9 ketone functions in subsequent reduction and acylation operations. We made a list of all these risks and reasons not to trifle with this strategy, then we ignored the list and forged ahead anyway.

2.2 A Diastereoselective Michael Addition

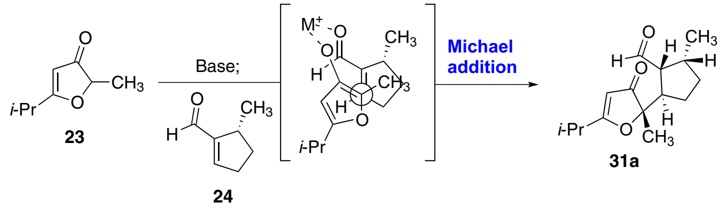
Our first set of experiments focused on a Michael addition–Stetter reaction sequence to assemble the target diketone (Scheme 8). Though we were uncertain as to the degree to which we might control the stereochemical outcome of a Michael addition of an enolate derived from **23**, we started with a simple set of experiments. Deprotonation of the 3-furanone **23** by treatment LDA proceeded uneventfully; exposure of the resultant lithium enolate to a solution of 5-methyl-cyclopentenecarboxyaldehyde (**24**) at low temperature cleanly produced a new product. Remarkably, our first experiment appeared to afford the desired Michael adduct **31** exclusively (we observed no evidence of the



SCHEME 8 A diastereoselective Michael addition. Key NOE observations made on the major diastereoisomer are noted with blue arrows. LDA, lithium *N*,*N*-diisopropylamine; THF, tetrahydrofuran; NOE, nuclear Overhauser effect.

direct aldol addition), and in what was a very pleasant surprise, the reaction appeared to be quite diastereoselective (75% yield, 2:1 dr major (**31a**):Σ others). The successful Michael addition forged the C1–C10 bond of the natural product and addressed the stereochemistry at C1, C5, and C10 during the course of the reaction, thus six possible diastereomers could result from this operation. Though these diastereomers were not separable by conventional silica gel chromatography, the signals for the protons at C1, C4 (the methyl-bearing stereogenic center introduced as citronellal), C5, the aldehyde proton, and the C10 methyl group in ^{1}H NMR spectrum of the Michael adducts were distinguished enough to permit detailed stereochemical analysis of the major product. We were able to conclusively establish the relative stereochemistry of C1, C4, and C5 using NOE studies, which was consistent with the relative stereochemistry at these positions in the natural product—we observed clear correlations between the protons at C4 and C5, and between the aldehyde proton and the proton at C1. Unfortunately, at this point in our study, we were unable to determine the relative stereochemistry at C10 as the structure did not permit any conclusive cross-relaxation with the C10-methyl group. Interestingly, however, we found the stereochemical outcome of the Michael addition reaction with respect to C10 to be quite sensitive to additives commonly used in enolate chemistry. For example, addition of excess lithium chloride, hexamethylphosphoramide (HMPA), or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) to Michael addition reactions that were conducted otherwise identically to that described above favored the opposite stereochemistry at C10 (**31b**).

On the basis of these data, we formulated a stereochemical model for the Michael addition reaction in which the C4 methyl-bearing stereogenic center serves as a key stereocontrolling element. In this model, the stereochemical outcome with respect to C10 matches that of the natural product by virtue



SCHEME 9 A stereochemical model for the diastereoselective Michael addition.

of a chelated assembly that disposes the bulky isopropyl group away from the rest of the structure. In the presence of chelation-disrupting additives, the opposite enolate π-face may be presented to the aldehyde, again disposing the bulky isopropyl group away from the rest of the structure. Though this model is speculative, the stereochemistry at C10 in the Michael adducts **31a** and **31b** was later established to be that shown in Schemes 8 and 9 based on the successful elaboration of **31a** into the natural product.

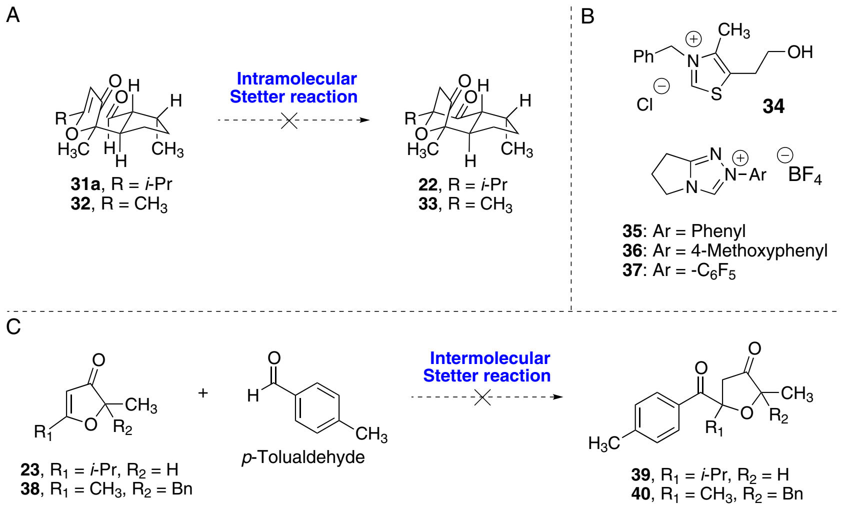
We briefly screened other standard reaction parameters by varying solvents, temperature profiles, concentrations, and addition sequences but we did not improve on our initial result in the Michael addition reaction—a remarkably diastereoselective process that set us on our path toward the natural product.

2.3 Umpolung Chemistry to Close the Core Structure

It was right about this time that Professor Christmann and his group reported the first synthesis of englerin A.[18] It was a conflicting moment to be sure—we were rather disappointed that we would not be the first to synthesize the natural product, but at the same time Professor Christmann's report set the bar very high and invigorated us to complete our work. It was also right about this time that a new postdoctoral researcher by the name of Zhenwu Li joined the group, and he set right to work on completing the core structure of the englerins with the help of a young undergraduate, Mika Nakashige. With quick access to the Michael adduct **31a** in hand, and Mika furiously building up a lifetime supply, we set about forging the C6–C7 bond. As discussed above, we wondered if we could render C6 nucleophilic in some fashion, and in doing so, engage the 3-furanone at the β-position. We faced a clear set of challenges, but several options lay before us to achieve the desired bond formation. We focused on three general strategies—cyclization under neutral conditions (Stetter-type chemistry), cyclization under anionic (basic) conditions, and cyclization under reductive conditions.

2.3.1 Cyclization Under Neutral Conditions

We were initially attracted to an umpolung[32] strategy that employed a proximity-favored intramolecular Stetter reaction,[22] owing to the identification



SCHEME 10 Attempts toward intra- and intermolecular Stetter reactions with 3-furanones.

of the dicarbonyl intermediate **22** in our retrosynthetic analysis (Scheme 10A). The Stetter reaction has been developed in several manifolds, including those consisting of vinylogous esters similar to our own, and has enjoyed a storied history in complex target synthesis. A number of highly effective thiazolium-, imidazolium-, and triazolium-based catalyst systems are known, most of which are easily prepared and/or commercially available.

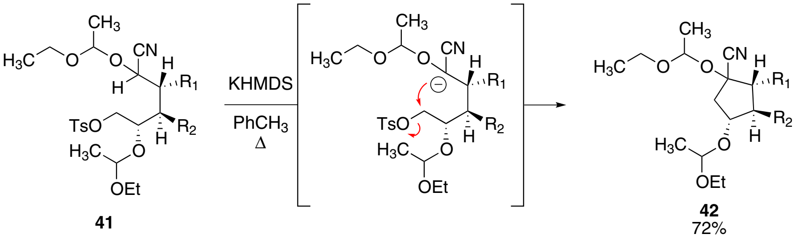
In our first experiments in this area, we attempted to form the C6–C7 bond using the commercially available thiazolium catalyst **34** (Scheme 10B). Our confidence was bolstered by the work of Professor Trost and his group during the course of their synthesis of hirsutic acid where they demonstrated that the thiazolium **34** was capable of engaging an aliphatic aldehyde and a β,β-disubstituted-α,β-unsaturated methyl ester in an intramolecular reaction to form a small ring.[33] Exposure of the aldehyde **31a** to the catalyst **34** (and an appropriate proton shuttle such as triethylamine) in a variety of solvents at ambient and elevated temperatures (including those conditions described by Trost) returned the starting material largely unchanged. We noted at this time that the aldehyde **31a** was sensitive to oxidation (presumably by adventitious oxygen), but we observed no formation of the desired C6–C7 bond. To address our concerns about the bulky isopropyl group hindering access to the β-position of the 3-furanone, we prepared the methyl analog **32** with the expectation of accessing the diketone **33** under the same reaction conditions. Unfortunately, after many experiments, we again observed no evidence of the desired intramolecular Stetter reaction.

We were hopeful that one of the more active triazolium-based catalyst systems like **35–37** (Scheme 10B) might allow access to **22**, based on the successes of Rovis and his group.[34,35] In their work, the Rovis group has successfully engaged vinylogous esters in other contexts, including the formation of quaternary centers, and the development of chiral variants of **35–37**. However, to our disappointment, treatment of our aldehydes **31a** or **32** with any of the triazolium catalysts **35–37** under the conditions described by Rovis (e.g., in the presence of potassium bis(trimethylsilyl)amide in hot toluene) resulted in no formation of the desired carbon–carbon bond. Humbled by all these results, we executed a series of control experiments wherein we attempted to engage our starting 3-furanone **23** and a less hindered analog **38** in intermolecular Stetter reactions. Employing the catalysts described above along with *p*-tolualdehyde as the nucleophilic component, we observed no evidence of the formation of **39** or **40**; the 3-furanones were recovered unchanged. We were simply unable to engage our 3-furanones under the conditions described above, which pushed us to think about more aggressive bond-forming strategies.

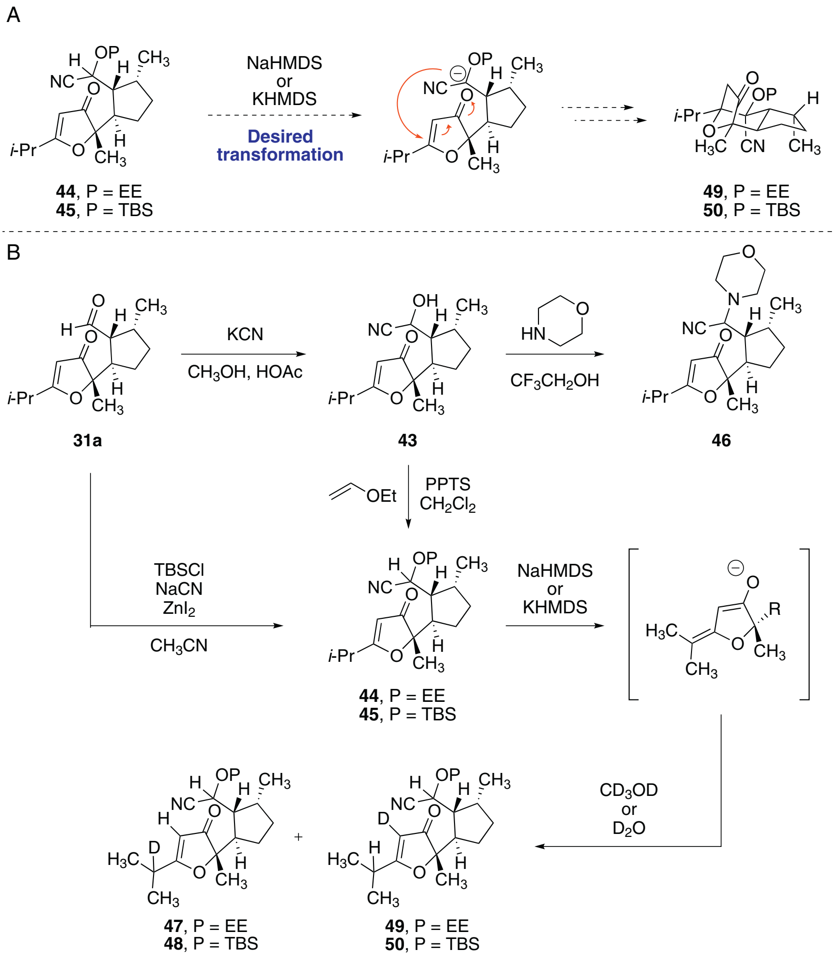
2.3.2 Cyclization Under Anionic Conditions

We were mindful that we had to somehow increase the nucleophilicity of our aldehyde carbon or the electrophilicity of the 3-furanone, or perhaps both of these. We chose to focus upon manipulating the aldehyde component of the reaction pair, although we were aware of Lewis acids that might enhance the reactivity of the 3-furanone that are compatible with the Stetter chemistry we had explored.[36] We were encouraged by the classic chemistry developed by Stork and his group in the course of their synthesis of the prostaglandins.[37] In their work, the Stork group described aldehyde-derived protected cyanohydrins (of type **41**) that can be metalated under the action of an appropriate base to give a stabilized anion. The anions then underwent alkylation reactions with electrophiles, and in the case of the prostaglandins, a tethered electrophile engaged the anion to give a small carbocycle (products of type **42**, Scheme 11).

In the course of our Stetter experiments, we learned that transforming our aldehyde into the corresponding cyanohydrin **43** was achievable; treatment of **31a** with methanolic potassium cyanide in the presence of acetic acid gave **43**



SCHEME 11 A key cyclization event in the synthesis of prostaglandins by Stork and coworkers. KHMDS, potassium bis(trimethylsilyl)amide; TsO, *p*-toluenesulfonate.



SCHEME 12 (A) An acyl anion undergoes a Michael addition to the 3-furanone. (B) Preparation and use of acyl anion equivalents. EE, ethoxyethyl; TBS, *t*-butyldimethylsilyl; NaHMDS, sodium bis(trimethylsilyl)amide; KHMDS, potassium bis(trimethylsilyl)amide; PPTS, pyridinium *p*-toluenesulfonate.

in low, but serviceable yields (Scheme 12B). Protection of **43** as the corresponding ethoxyethyl acetal **44** was also achievable but again in low yield. We also had access to a *t*-butyldimethylsilyl-protected cyanohydrin (**45**) in a single pot reaction by treatment of the aldehyde with *t*-butylchlorodimethylsilane, and sodium cyanide in the presence of zinc iodide.[38] Though these additional steps came at the cost of inconsistent yields and complicated spectroscopic analyses owing to the unselective addition of yet two more (albeit temporary) stereogenic centers, we felt this strategy might address two issues simultaneously—it would allow us to form the desired carbon–carbon to complete to core structure of the englerins, and at the same time distinguish one of the carbonyl functions for future manipulation. We subjected the protected cyanohydrins to the action of potassium and sodium bis(trimethylsilyl)amide in warm benzene as described by Stork in the hope that the resultant stabilized anion might engage the furanone in a conjugate addition reaction (Scheme 12A). Unfortunately, we were undermined by the acidity of the furanone moiety; the isopropyl group methine proton proved more acidic than the latent aldehyde proton at C6, precluding productive bond formation; we observed deuterium incorporation at the α- and γ-positions of the furanone upon quenching of the anion with d_4-methanol or deuterium oxide (**47–50**, Scheme 12B).

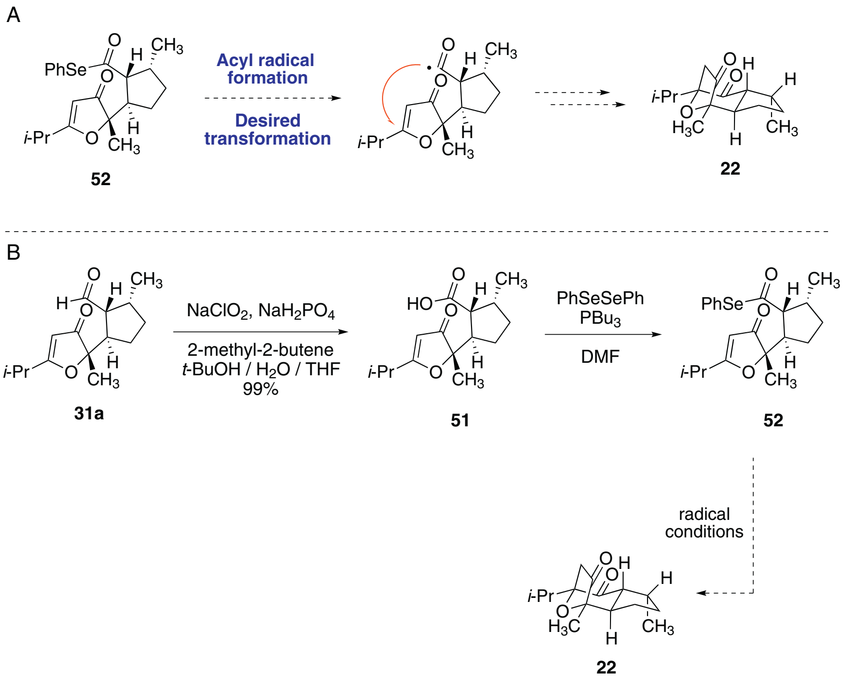
In parallel, we prepared other acyl anion equivalents such as morpholinonitriles (by treatment of the cyanohydrin with morpholine in trifluoroethanol—Scheme 12B, compound **46**), and dithianes (by treatment of the Michael adduct with 1,3-propanedithiol and boron trifluoride etherate—not shown) but cyclization experiments with all of these were again undermined by the acidity of the 3-furanone function. We reluctantly retreated from the idea of an acyl anion equivalent and began to consider chemistry that would not suffer from the liabilities of acid/base chemistry.

2.3.3 Cyclization Under Reductive Conditions

We wondered if we could generate a radical at C6 under reductive conditions and ask that radical to engage the furanone at the β-position (Scheme 13A). We considered this strategy with substrates at both the aldehyde and carboxylic acid oxidation levels—strategies that might employ a stabilized alkyl radical or an acyl radical.

Acyl radicals are well-studied intermediates in organic chemistry and continue to find use in modern synthesis.[39] A classical, and perhaps the preferred means of generating an acyl radical is via the corresponding acyl selenium compound. Several methods for the synthesis of acyl selenium compounds have been described, and most involve the treatment of a carboxylic acid with a trialkylphosphine and an electrophilic aryl selenium source such as diphenyl diselenide or phenylselenium halides.[40] We transformed the Michael adduct **31a** into the corresponding acyl selenium compound **52** using such standard chemistry (Scheme 13B)—oxidation to the corresponding carboxylic acid (**51**) was easily accomplished in nearly perfect yield using the Pinnick protocol,[41] and conversion of the acid into the acyl selenium species (**52**) under the action of tri-*n*-butylphosphine and diphenyldiselenide in *N*,*N*-dimethylformamide (DMF) was straightforward though the yields were low.

We subjected the acyl selenide to the action of tri-*n*-butylstannane and azobisisobutyronitrile in hot benzene; however, even after extended exposure to these typical radical conditions, we did not detect any of the desired

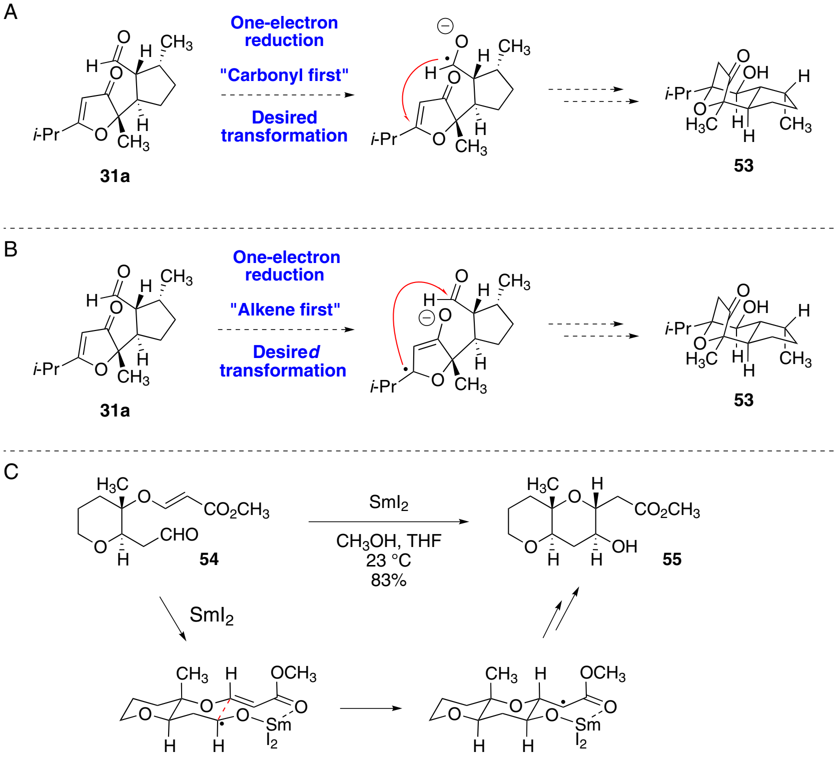


SCHEME 13 (A) An acyl radical undergoes a Michael addition to the 3-furanone. (B) Preparation of the acyl selenide **52**.

diketone **22**. Instead, we recovered some starting material unchanged, trace amounts of the Michael adduct **31a**, and observed some decomposition. Though disappointing, the observation of **31a** at least provided (albeit trace) evidence that we had indeed generated a radical at C6. We screened other radical initiators such as triethylborane in the presence of air, but we again observed no evidence of the desired diketone. Increasing the reaction temperature or prolonging the reaction time with either initiator also did not afford us any improvement, but we remained encouraged by the evidence that we could generate a radical at C6 even if we did not successfully engage the 3-furanone.

We considered accessing radical intermediates directly from the Michael adduct **31a**; this chemistry would generate a stabilized alkyl radical. In so doing, these reactions would afford us the oxidation level at C6 required for natural product and preclude the need for distinguishing homologous functionality in the previously targeted diketone. Furthermore, by judicious choice of reducing agents, we might locate a species capable of increasing the reactivity of the 3-furanone. We focused upon one-electron reducing agents that might also serve as a Lewis acid—reagents like samarium(II) iodide,[42] titanium(III) chloride,[43] vanadium(II) chloride,[44] and lithium naphthalenide.[45]

Samarium(II) iodide, or Kagan's reagent, has become an essential tool for a synthetic organic chemist since its introduction in the late 1970s.[42] This reagent finds use as a reductant in a variety of chemistry, such as Barbier-type processes and various radical-mediated couplings and fragmentations including carbonyl-alkene cyclizations. The desired samarium-mediated carbonyl-alkene cyclization can be considered to proceed in one of two ways, depending on the reduction event that occurs at the substrate. One might consider the traditional mechanism of the "carbonyl first" pathway wherein the aldehyde undergoes a one-electron reduction, followed by cyclization onto the alkene (Scheme 14A). It is also equally plausible to consider the alternative "alkene first" pathway wherein the alkene undergoes a one-electron reduction, followed by cyclization onto the aldehyde (Scheme 14B). Prior to our work, there were no examples of carbonyl-alkene cyclizations involving 3-furanones, but other similar cyclizations that employ α,β-unsaturated



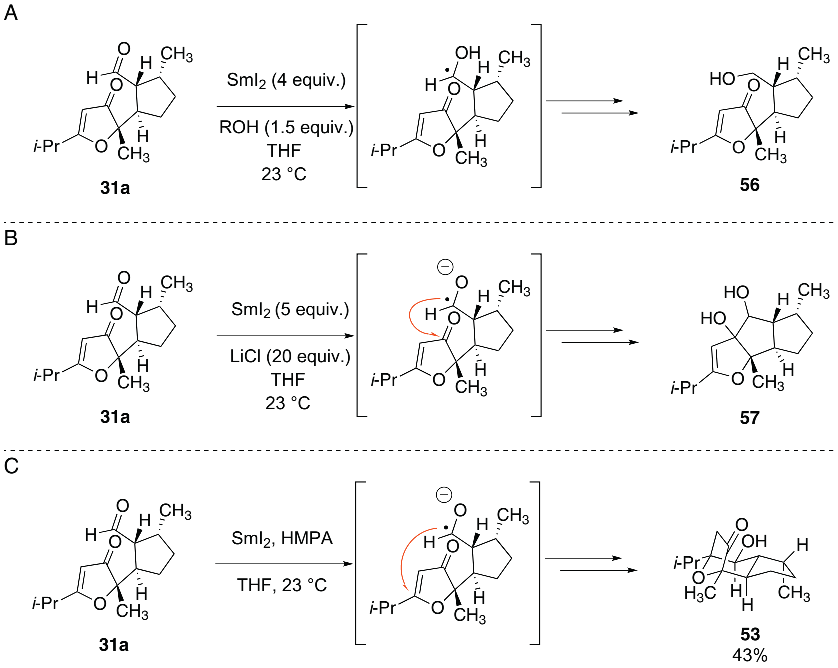
SCHEME 14 (A) Single electron reduction "carbonyl first" pathway to the ketoalcohol **53**. (B) Single electron reduction "alkene first" pathway to the ketoalcohol **53**. (C) A samarium(II) iodide-mediated carbonyl-alkene coupling of an aliphatic aldehyde with a β-heteroatom-α,β-unsaturated ester. THF, tetrahydrofuran.

carbonyls containing β-heteroatoms were known. We were very encouraged by a report by Nakata and coworkers in which several fused oxanes were constructed by successive samarium-mediated carbonyl-alkene cyclizations involving β-oxy-α,β-unsaturated esters as the alkene component (Scheme 14C).[46] For example, the transformation of ester aldehyde **54** into the hydroxyl ester **55** was remarkably efficient and diastereoselective. The authors suggested that the observed stereochemical outcomes of their cyclizations may have benefitted from chelate-organization within the samarium-bound radical anion intermediates, as evinced by the effect of chelation-disrupting additives like HMPA; the influence of such an additive on the reduction potential of the samarium was not mentioned.

We experienced success immediately with samarium(II) iodide.[47] We started with the conditions described by Nakata and coworkers that were so successful with their carbonyl-alkene couplings. Treatment of a solution of the Michael adduct **31a** in tetrahydrofuran with freshly prepared samarium (II) iodide in the presence of methanol afforded us a primary alcohol (**56**) as the major product resulting from reduction of the aldehyde moiety, presumably via protonation of the putative ketyl radical intermediate. Other protic additives such as *t*-butanol, isopropanol, trifluoroethanol, hexafluoroisopropanol, and water afforded similar mixtures containing the primary alcohol **56** as the major product (this product also dominates if the reaction media is not rigorously anhydrous). Though we had not formed the desired C6–C7 carbon–carbon bond, we were pleased that we had successfully manipulated the aldehyde the presence of other reducible functionality—we were confident that the desired bond formation was a simple reaction parameter change away (Scheme 15).

We examined some common additives associated with samarium chemistry, additives known to have influence upon the reduction potential of the reagent. For example, addition of lithium chloride (LiCl) is thought to generate samarium(II) chloride,[48] a much stronger reducing agent than samarium (II) iodide. In our hands, exposure of the Michael adduct **31a** to samarium (II) iodide and lithium chloride in THF provided a new product—a pinacol-type coupling joined the aldehyde and the furanone carbonyl carbons to give a diol and a tricyclic scaffold (**57**). This reaction presumably proceeds via the same ketyl radical that afforded the primary alcohol, and at long last, we had engaged the furanone, albeit directly at the carbonyl carbon.

We then eagerly examined HMPA in our system. The samarium(II) iodide/HMPA mixture is reported to have a reduction potential between those of samarium(II) iodide and samarium(II) chloride.[48,49] Exposure of a solution of the Michael adduct **31a** and HMPA in THF to samarium(II) iodide at room temperature afforded that which we had been chasing for months—we had successfully engaged the furanone again, but this time at the β-position, forging the C6–C7 carbon–carbon bond to complete the core structure of the englerins (**53**). The hydroxyketone product **53** was formed in 43% yield



SCHEME 15 (A) A samarium(II) iodide-mediated reduction of the aldehyde. (ROH, proton source such as methanol, *t*-butanol, isopropanol, trifluoroethanol, hexafluoroisopropanol, or water). (B) A samarium(II) iodide-mediated pinacol-type coupling. (C) A samarium(II) iodide-mediated carbonyl-alkene coupling to complete the core structure of the englerins. THF, tetrahydrofuran.

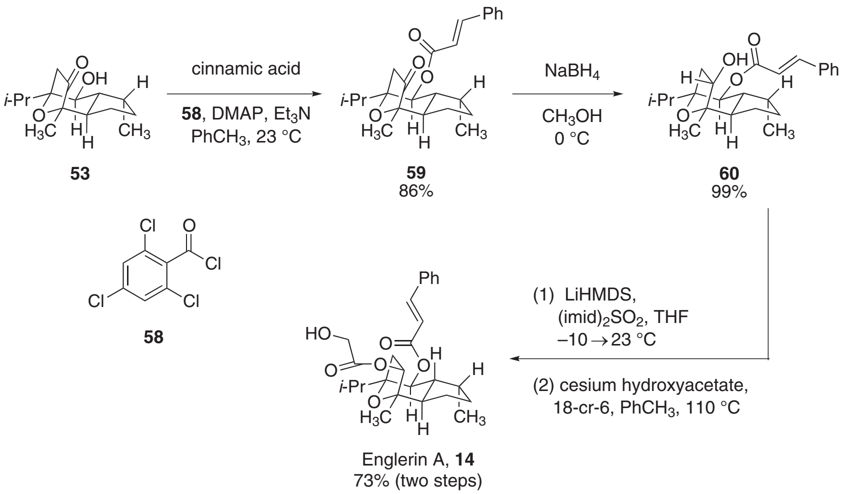
and had the correct stereochemistry at C6. Moreover, we were finally able to confirm the stereochemistry at C10 established in the Michael addition reaction. Thus, the stage was set to complete the natural product, and we no longer needed to distinguish between ketones at C6 and C9 as originally planned. We presume this reaction proceeds via the same "carbonyl first" reduction event followed by attack of the ketyl radical upon the α,β-unsaturated carbonyl at the β-position. A second one-electron reduction event followed by a proton transfer gives the cyclized product. The yield may seem disappointing, but it is actually rather remarkable—not only did we establish the correct stereochemistry at C6, but we also treated a diastereomeric mixture of Michael adducts **31a** (2:1 dr shown:Σ others) with the reducing agent in this carbonyl-alkene cyclization. Thus, the maximum yield of **53** in this reaction was 66%.

We briefly explored the other one-electron reducing agents described above in an effort to avoid the use of HMPA, but samarium(II) was uniquely capable of producing the hydroxyketone **53**; other reagents were either ineffective or caused unproductive decomposition of the Michael adduct.

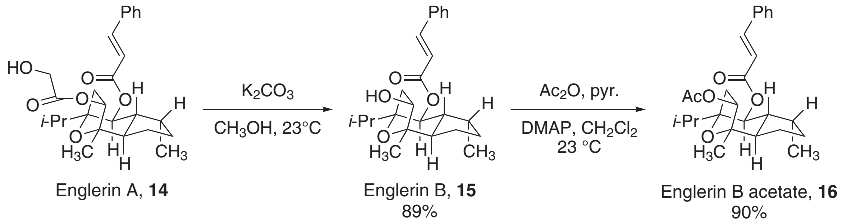
3 COMPLETING ENGLERIN A

With the hydroxyketone **53** in hand, completion of the natural product was straightforward (Scheme 16). The ketoalcohol **53** was described by Professor Ma and his group during the course of their synthesis of englerin A, and we were able to advance our material to the natural product using their chemistry.[18]

Installation of the C6 cinnamate ester was accomplished using the Yamaguchi protocol.[50] Treatment of **53** with cinnamic acid, 2,4,6-trichlorobenzoyl chloride (**58**), 4-(*N*,*N*-dimethylamino)pyridine (DMAP), and triethylamine in toluene at room temperature gave the ester **59** in 86% yield. We have found that some acid chlorides in the presence of base are as effective for the acylation of the C6 alcohol, which has been convenient in our structure–function studies. Massaging the C9 carbonyl of ester **59** into the corresponding C9 glycolate ester (to give englerin A, **14**) was also uneventful. Reduction of the C9 carbonyl in **59** to the corresponding secondary alcohol with sodium borohydride in methanol proceeded in nearly quantitative yield to give **60** as a single diastereoisomer. Conversion of the alcohol into a leaving group (to give the sulfonate imidazole, not shown) by treatment with lithium bis(trimethylsilyl) amide followed by 1,1′-sulfonyldiimidazole in THF also proceeded in nearly quantitative yield. Finally, displacement of the leaving group with cesium hydroxyacetate in the presence of 18-crown-6 in hot toluene afforded englerin A (**14**) in 74% yield. Thus, our synthesis of the natural product proceeds in six steps from the 3-furanone **23** and the aldehyde **24** (eight steps from commercially available commodity chemicals) and 20% overall yield (Scheme 17).



SCHEME 16 Completion of englerin A (**14**). DMAP, 4-(*N*,*N*-dimethylamino)pyridine; LiHMDS, lithium bis(trimethylsilyl)amide; THF, tetrahydrofuran.



SCHEME 17 Conversion of englerin A (**14**) into englerin B (**15**) and englerin B acetate (**16**). Ac_2O, acetic anhydride; pyr., pyridine; DMAP, 4-(*N*,*N*-dimethylamino)pyridine.

Englerin B and englerin B acetate are easy to prepare from englerin A—the glycolate residue can be sensitive and its removal is facile under mildly acidic or basic conditions to give englerin B. We have found it convenient to remove the glycolate under the action of methanolic potassium carbonate to give englerin B (**15**) in 89% yield. Acylation of the resultant C9 alcohol to give englerin B acetate is also uncomplicated; treatment of englerin B (**15**) under standard acetylation conditions (acetic anhydride, pyridine, and 4-[*N*,*N*-dimethylamino]pyridine in dichloromethane) gave englerin B acetate (**16**) in 90% yield.

4 CONCLUSIONS, THOUGHTS, AND FUTURE DIRECTIONS

The englerin project has been an exciting ride for us. I hope this modest document conveys the process by which we developed our thoughts and arrived at our synthetic route. Our final solution to the englerin problem is not quite as we originally planned (and rightly so), but it has been a wonderful experience to witness the project evolve from an idea scribbled on the back of a napkin during an emotional episode into an elegant piece of science. In contributing to the growing body of work surrounding this exciting molecule, my students and I have gotten to stand shoulder to shoulder with a group of chemists whom we respect and admire. Our work,[51] combined with that described by our colleagues, has begun to unravel the biological potential of the englerins, and using the compounds that we have synthesized, we eventually expect to fully characterize the mode of action of these natural products and contribute further to the development of the englerins in the context of human health.

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I am deeply grateful to the students that made all the work described here possible. I initiated the synthesis of englerin A in the fall of 2009, but it would not have been brought to completion without the great effort of Dr. Zhenwu Li with the help of Ms. Mika Nakashige, and the intellectual contributions from other members of the Chain group. The project and synthesis of materials to tease out the biological details of the englerins are now in the hands of Dr. David M. Fash. We thank Professor Marcus Tius (University of Hawai'i at Manoa) for many helpful discussions and support during the course of our synthetic efforts. We are indebted to our biological collaborators Professor Joe W. Ramos and Mr. Florian J. Sulzmaier at the University of Hawai'i Cancer Center. We thank Wes Yoshida (University of Hawai'i at Manoa) for his patient and endless assistance with NMR data collection, and Materia, Inc. for generous donations of ruthenium catalysts. We gratefully acknowledge the financial support for this work from the University of Hawai'i, the University of Hawai'i Cancer Center, and the Victoria S. and Bradley L. Geist Foundation (47030).

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Chapter 4

Total Synthesis of (±)-Anislactone A and (±)-Merrilactone A

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Chapter Outline

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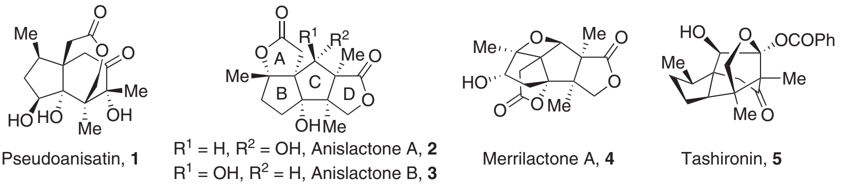
1 INTRODUCTION

1.1 Background to the Natural Products

Plants of the *Illicium* genus are widely distributed across eastern North America, Mexico, the West Indies, and eastern Asia, with the area spanning southern China and northern Myanmar being home to 35 of the 40 species described to date. *Illicium* plants are rich sources of biologically active sesquiterpenes, producing numerous intricate architectures that have been extensively characterized.[1] Categories of *Illicium seco*-prezizaane-type sesquiterpenes include the anisatins, pseudoanisatins, majucins, cycloparvifloralones, and anislactones, with representative structures shown in Figure 1. The structural complexity of these sesquiterpenes, allied with often important biological activities, has made them popular and challenging targets for total synthesis.[2] We will describe our efforts toward two members of the anislactone group of *Illicium* sesquiterpenes, the canonical anislactone A structure along with the related natural product merrilactone A.

Anislactone A and B (**2** and **3**) were isolated in 1989 by Kouno from the pericarps of *Illicium anisatum*.[3] The structure of anislactone A was established from spectral data and X-ray crystallographic analysis, with that of anislactone B determined by spectroscopic analysis in relation to anislactone A. At the time of isolation, the carbon skeleton was unique, featuring a fused 5,5 system, two γ-lactones and a *cis*-arrangement of the two angular methyl groups at the C–D-ring junction. The natural product displays a high degree of steric congestion, featuring five contiguous fully substituted carbon centers and an additional secondary alcohol stereocenter. In spite of these challenging and provocative features, synthetic studies on the anislactones were slow to materialize. This was likely due to the unknown biological activity of the natural products, with preliminary biological assays not reported at the time of isolation. Subsequent work has identified anislactone B as having neuroprotective activity, prolonging cell survival when assayed against SH-SY5Y cells treated with peroxide.[4]

Interest in the anislactone class of *Illicium* sesquiterpenes was ignited following Fukuyama's discovery of merrilactone A (**4**).[5] Isolated in 2000 from the methanol extract of the dried pericarps of *Illicium merrillianum* (0.004% yield), its structure was elucidated by means of extensive spectroscopic and X-ray crystallographic analysis and the absolute configuration was established



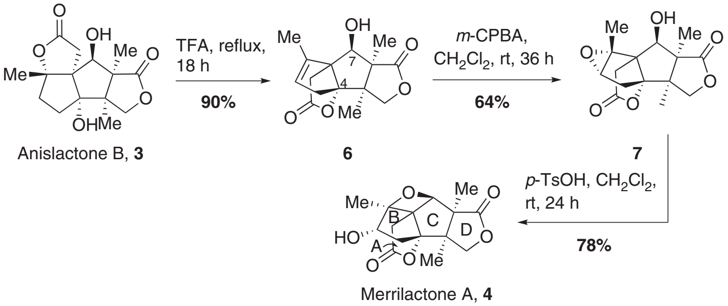
Pseudoanisatin, **1**

R^1 = H, R^2 = OH, Anislactone A, **2**
R^1 = OH, R^2 = H, Anislactone B, **3**

Merrilactone A, **4**

Tashironin, **5**

FIGURE 1 *Illicium* natural products.



SCHEME 1 Chemical conversion of anislactone B to merrilactone A.

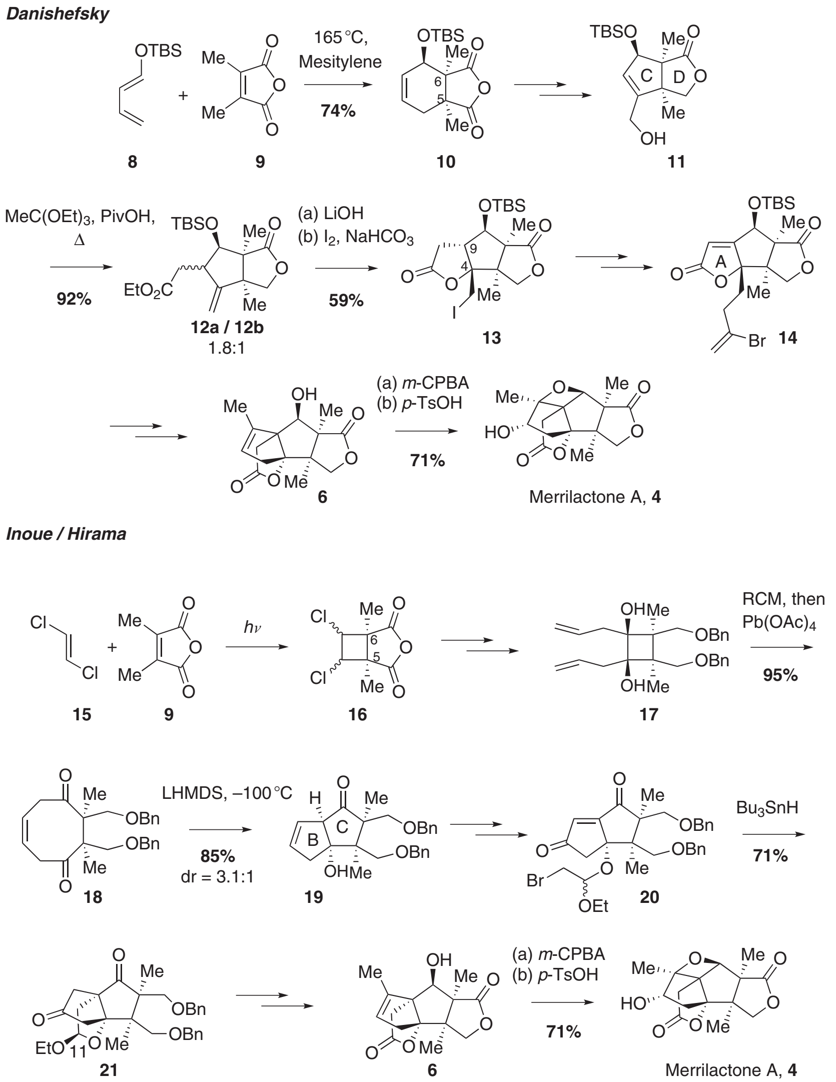
using the modified Mosher method. Merrilactone A has a unique pentacyclic anislactone-type sesquiterpene structure, featuring an eye-catching central oxetane ring, two γ-lactones, as well as seven stereocenters, of which five are contiguous fully substituted carbon atoms. This densely oxygenated molecule forms a compact yet complex cage-like structure, thereby presenting a highly attractive and challenging target for total synthesis. In addition to its intriguing molecular structure, merrilactone A has also been shown to possess neurotrophic activity. In nerve-growth assays, merrilactone A was found to promote neurite outgrowth in primary cultures of fetal rat cortical neurons at very low concentrations, ranging from 10 to 0.1 μmol/L.[6] Nonpeptidic small molecules with neurotrophic activity are important lead compounds for drug design in neurodegenerative diseases (e.g., Alzheimer's) where administration of neurotrophins has been identified as a possible therapeutic strategy. The endogenous neurotrophins are small proteins termed nerve-growth factors; small molecules that can mimic their neurotrophic activity have the advantages of more tractable pharmacokinetic properties such as plasma stability and ability to penetrate the blood–brain barrier.[7]

Fukuyama also showed that merrilactone A could be synthesized in a simple three-step procedure from anislactone B, co-isolated from *I. merrillianum* in greater quantities (Scheme 1).[5b] Acid treatment effected elimination and relactonization at the C4 tertiary alcohol. Epoxidation was then quite selective for the α-face in **6**, which could be transformed to the oxetane-containing natural product through homo-Payne rearrangement using mild acid. This process, which is likely the biosynthetic origin of the oxetane functional group in merrilactone, became very influential to route design in subsequent total syntheses. It demonstrates that the ostensibly challenging oxetane ring can be accessed quite simply, *if* the precursor **6** can be synthesized containing the requisite trisubstituted B-ring alkene and C7 secondary alcohol.

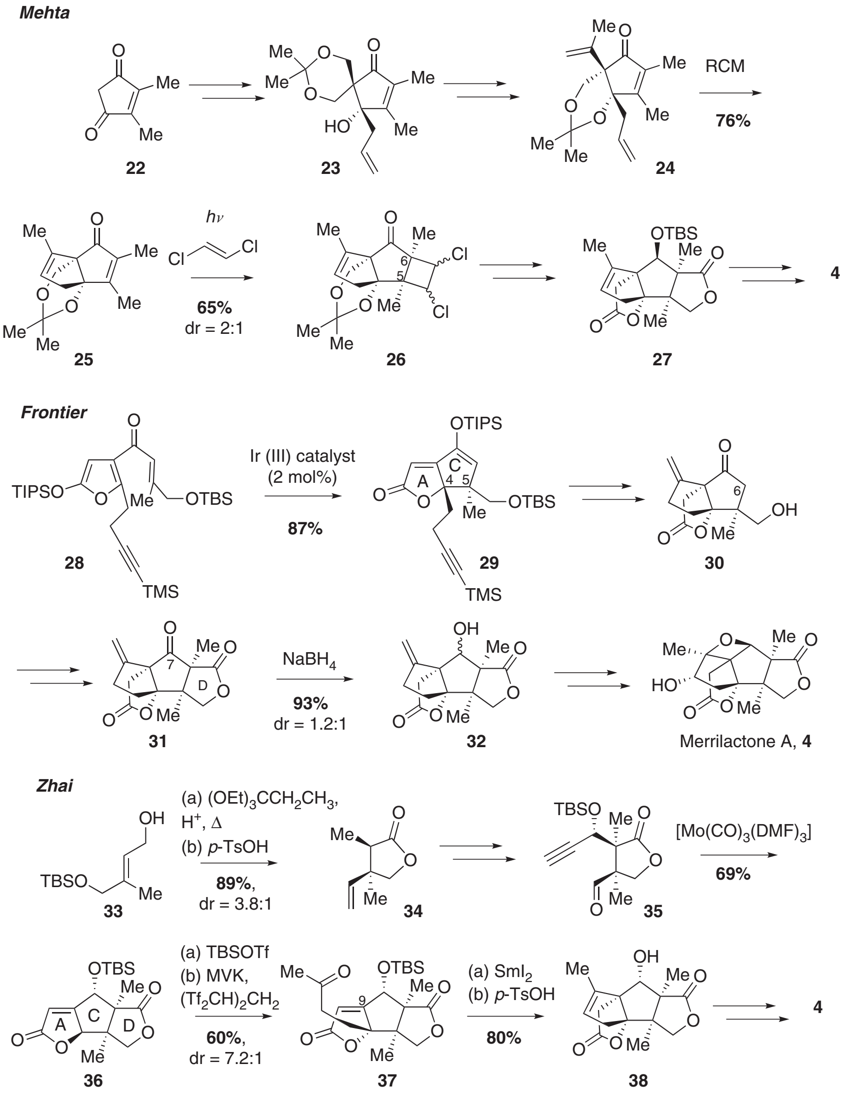
1.2 Previous Syntheses

Several laboratories around the world have worked on merrilactone A, with the following groups completing total syntheses: Danishefsky (2002, racemic;

2005, asymmetric),[8] Inoue and Hirama (2003, racemic; 2006, asymmetric),[9] Mehta (2006, racemic),[10] Frontier (2007, racemic),[11] and most recently Zhai (2012, racemic).[12] Along with his isolation work, Fukuyama has also reported approaches to functionalized bicyclic components of the merrilactone A structure.[13] As a detailed review of this work is beyond the scope of this chapter, we have briefly summarized the key steps in each total synthesis in Schemes 2 and 3 in terms of the important C—C bond forming steps employed *en route*. Construction of the cyclopentane C-ring is fundamental to synthetic strategy for



SCHEME 2 Previous syntheses of merrilactone A.



SCHEME 3 Previous syntheses of merrilactone A.

merrilactone—sitting at the heart of the molecule and containing five stereocenters, it is the principal challenge for C—C bond formation in the natural product.

In the first total synthesis of merrilactone A, completed less than 2 years following the isolation paper, Danishefsky and Birman used a Diels–Alder reaction between diene **8** and dimethyl maleic anhydride **9** to set the two quaternary centers in step 1 (Scheme 2).[8a] The anhydride **10** could be selectively reduced to the D-ring lactone, and the cyclohexanol contracted to the C-ring cyclopentene using an ozonolysis/aldol process. The C9 and C4 B-ring stereochemistry was then tackled via a Johnson–Claisen rearrangement, effecting C—C bond formation at C9 but with modest stereocontrol. Hydrolysis and iodolactonization enabled the correct stereoisomer of iodide **13** to be isolated. This underwent C-allylation and further functionalization to the vinyl bromide **14**. Conjugate addition of the vinyl radical (Bu_3SnH treatment) to the A-ring butenolide created the full merrilactone A carbon skeleton, which was readily functionalized to the final natural product. Danishefsky subsequently reported the asymmetric synthesis of intermediate **13** (in 20 steps), representing the first enantiocontrolled route to merrilactone A.[8b]

Inoue and Hirama likewise elected to tackle the C5 and C6 quaternary centers in step 1 but used a [2+2] photocycloaddition with **9** to form a cyclobutane that could be subsequently enlarged to, initially, an eight-membered ring **18**.[9a] This medium ring compound was the substrate for a creative approach to the C4 and C9 cyclopentane stereocenters, whereby transannular aldol reaction gave the 5–5 BC carbocycle. Desymmetrization with LiHMDS afforded the BC bicycle **19** in high yield as a 3.1:1 ratio of diastereoisomers (minor component having a *cis* BC-ring junction in the opposite sense to C5 and C6). An intramolecular radical conjugate addition to the B-ring enone (cf. radical addition to the A-ring enoate in the Danishefsky route) then afforded the full carbon skeleton, which was transformed into merrilactone A. The Inoue/Hirama team subsequently developed an asymmetric approach based around their transannular aldol chemistry. Their initial report in this area described the synthesis of a chiral analog of diketone **18** having different protecting groups at the C12 and C14 alcohols. Regio- and diastereoselective aldol reaction then afforded the analog of **19** as a single enantiomer, which was advanced to natural merrilactone A.[9b] This work was then further extended to an enantioselective desymmetrization of **18** using a chiral lithium base (79% yield, 57% ee; 42% yield, 99% ee after one recrystallization), which was used to synthesize the unnatural congener of the natural product.[9c] Interestingly, the unnatural enantiomer had similar activity to its mirror image in neurite outgrowth assays.

Mehta and Singh also used a [2+2] photocycloaddition with dichloroethylene to create the C5 and C6 stereocenters but did so later in the synthesis (step 12 of 25) on tricyclic intermediate **25** (Scheme 3).[10] The tricycle **25** could be assembled with excellent stereocontrol via an alkylation approach from dione **22**, setting up an RCM reaction to form the B-ring. The enone double bond was then the subject of the [2+2] reaction, forming the two quaternary stereocenters with modest dr(2:1) in favor of the desired β-cyclobutane **26**. Reduction to the cyclobutene set up a selective ozonolysis procedure to install the final D-ring lactone, which could be elaborated to the racemic natural product using established protocols.

Frontier's synthesis is distinct in using a stepwise installation of the two C5 and C6 quaternary stereocenters.[11] The furan substrate **28**, containing an *E*-alkene, underwent a novel Ir-catalyzed Nazarov reaction to set both C4 and C5 in a stereospecific fashion. This transformation enabled a highly concise synthesis of the natural product: First, the A-ring butenolide in **29** was nicely disposed to undergo conjugate addition of the vinyl radical derived from Bu_3SnH treatment of the alkyne. Second, subsequent acylation at C6, followed by stereoselective methylation of the resultant ketolactone, then supplied the second quaternary methyl stereocenter at C6 and the complete carbon skeleton of merrilactone A. Stereocontrol in C—C bond formation was perfect throughout the synthesis, but the late-stage reduction of ketone **32** proved unselective. An efficient reoxidation/reduction sequence mitigated this problem, affording an overall sequence of 18 steps in 19% overall yield, which is the most efficient approach to date for merrilactone A.

Zhai's approach to merrilactone A used an acyclic substrate for the installation of C5 and C6, in contrast to the cyclic substrates used by other groups.[12] Johnson–Claisen rearrangement on **33** and cyclization gave lactone **34** in 4:1 dr. Functionalization with a propynal side chain then set up a novel hetero-Pauson–Khand reaction (mediated by $Mo(CO)_3$) to synthesize the A-ring lactone **36**. The B-ring cyclopentane was then built by an initial vinylogous Mukaiyama–Michael addition of a silyloxyfuran to methyl vinyl ketone, which was selective for the top face of **37**. The ring system was completed by conjugate addition of a ketyl radical to C9 and dehydration of the resultant tertiary alcohol. Inversion at C7 was required, and as with Frontier's synthesis, reduction of the requisite ketone was unselective, but amenable to a reoxidation/reduction recycling strategy to complete the synthesis.

The completed syntheses feature a rich selection of chemistry, testament to the challenging architecture of merrilactone A that demands stereoselective C—C bond constructions in very sterically hindered environments. Despite the variety of inventive, stereocontrolled synthesis on display, the difficulties in constructing the anislactone skeleton are apparent in the fact that all syntheses suffered from a lapse in stereocontrol in one or more instances. The syntheses showcase some very distinctive C—C bond forming steps, but there is also some commonality of synthetic strategy. Installation of the two *cis*-quaternary methyl stereocenters at C5 and C6 has been achieved using pericyclic reactions for four of the five routes, with three groups electing to tackle this challenging feature in the very first step of the synthesis. Radical addition to create the C9 quaternary center has also been a productive tactic, with addition to either an A-ring enoate or a B-ring cyclopentenone being a key step in four of the five routes.

2 FIRST-GENERATION SYNTHESIS OF (±)-MERRILACTONE A AND (±)-ANISLACTONE A

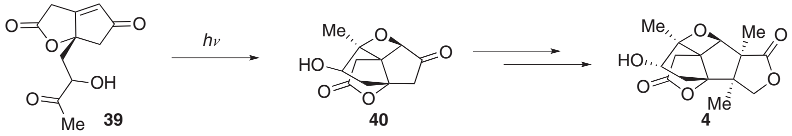
2.1 Paternò–Büchi Approach

We began work on merrilactone A in late 2002, as the first project in the corresponding author's laboratory at the University of Edinburgh, UK.

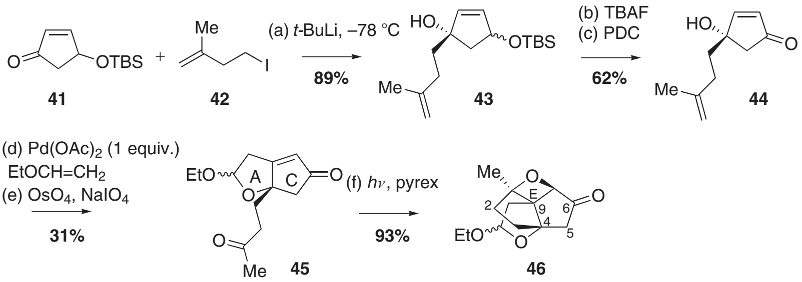
At the time, the Danishefsky racemic synthesis was the only extant work in the literature, and numerous approaches could be contemplated to the natural product's unique architecture. Our initial approach to the molecule would attempt an alternative construction of the oxetane ring to the biomimetic sequence demonstrated by Fukuyama. We wanted to explore the Paternò–Büchi carbonyl alkene photocycloaddition as a possible route, whereby a cyclopentenone such as **39** could undergo reaction with a pendant alkene, forming the C9 quaternary stereocenter, the B-ring cyclopentane, as well as the oxetane (Scheme 4).[14]

To investigate this idea, Ph.D. students Jone Iriondo and Jesus Perea developed a short synthesis of a Paternò–Büchi substrate starting from the TBS-protected 3-hydroxy-cyclopentenone **41**, a well-known building block in terpene synthesis. This material can be prepared on a large scale from the cheap feedstock furfuryl alcohol through treatment with mild acid (Piancatelli rearrangement) and subsequent silyl protection.[15] Addition of the organolithium prepared from the homoallylic iodide **42** is quite selective for the *trans*-diol, but this stereorelationship vanishes on desilylation and oxidation to the enone **44**. We then carried out an interesting tandem reaction to install the A-ring, whereby the C4 tertiary alcohol reacts with ethyl vinyl ether and palladium (II) in an oxy-palladation reaction, and the resultant organopalladium intermediate is then set up for a 5-*exo* Heck reaction (a sequence first demonstrated by Utimoto/Oshima and Larock in the 1980s).[16] Carbopalladation with the enone double bond leads to an initial *anti*-disposition between the Pd atom and the β-hydrogen atom at C9; however, it is reasonable to posit the *syn* relationship required for elimination to arise through carbon/oxygen/carbon equilibration of the Pd-enolate. The reaction used stoichiometric Pd—in principle, a catalytic reaction is possible through inclusion of a stoichiometric oxidant to reoxidize the Pd(0) eliminated from the Heck reaction. An initial screen of oxidant conditions did not immediately bear fruit, so we elected to move on with the synthesis and revisit this issue, if necessary, in subsequent iterations of the route. Oxidative cleavage of the alkene then afforded the Paternò–Büchi substrate **45**. Pleasingly, irradiation of a degassed acetonitrile solution of **45** (400 W medium-pressure mercury lamp, Pyrex filter) gave a clean cyclization to the tetracyclic oxetane **46** in excellent yield (Scheme 5).[17]

The Paternò–Büchi approach demonstrated a rapid assembly of the ABCE merrilactone tetracycle—in just six steps from **41**. To develop the route further, we first needed a strategy for D-ring synthesis—annulation of a



SCHEME 4 Proposed Paternò–Büchi route to merrilactone A.



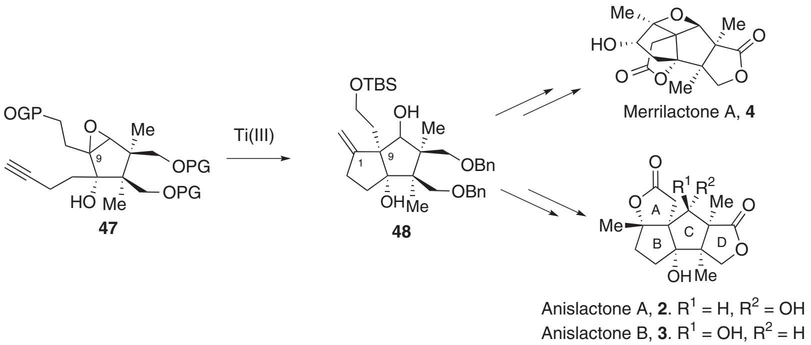
SCHEME 5 Paternò–Büchi photoaddition in the synthesis of the core of merrilactone A. Conditions: (a) *t*-BuLi, Et_2O, −78 °C, 89%; (b) TBAF, THF, 88%; (c) PDC, DCM, 70%; (d) $Pd(OAc)_2$ (1 equiv.), $EtOCH{=}CH_2$ (neat), 65%; (e) OsO_4 (4 mol% aq. solution), CH_2Cl_2, $NaIO_4$, dioxane/water, 47%; (f) *hν* (pyrex), MeCN, 93%.

γ-lactone at C5 and C6 along with two quaternary methyl stereocenters, and second, a method for installing the missing secondary alcohol at C2. While the first of these challenges is clearly the bigger job, it is the second that is arguably the more fundamental challenge to incorporate into the route. Inclusion of secondary alcohol functionality from the outset on an analog of iodide **42** dictates the development of an asymmetric route—a chiral iodohydrin or its equivalent would need to be added to a single enantiomer of enone **41** to afford the addition product as a single diastereoisomer. Alternatively, we could maintain the racemic approach and attempt to install the C2 alcohol later in the synthesis from a B-ring alkene using substrate control. This would also require addition of more functionalized organometallic precursors to the enone **41**. While some progress was made along the latter of these lines,[18] we were unable to synthesize a precursor having real or incipient C2 alcohol functionality that could undergo both successful photocycloaddition *and* be compatible with a workable D-ring synthetic strategy. As a result, we redesigned our synthesis to one that would approach Fukuyama's compound **6** and thus access the oxetane in the last two steps of the synthesis.

2.2 Reductive Epoxide Ring-Opening Approach: Background and Model Study

Our strategy coalesced around the idea of using a reductive epoxide ring opening/cyclization[19] for constructing the pivotal C1–C9 bond. We envisaged the synthesis of a fully elaborated cyclopentane C-ring (**47**) containing an epoxide and pendant alkyne group. Treatment with Ti(III) would then effect reductive epoxide cleavage and 5-*exo*-dig cyclization of the resultant C4 radical, affording the full carbon skeleton **48** of both the merrilactone and anislactone natural products (Scheme 6).

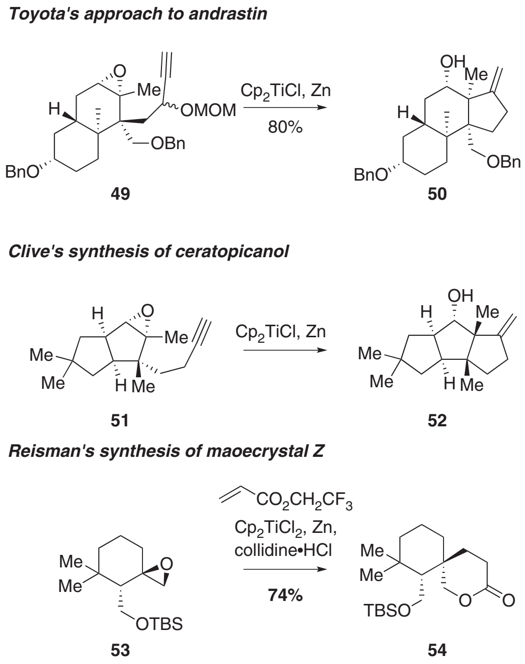
The reductive epoxide cyclization has a number of compelling features for the proposed C—C bond formation. Epoxides are highly versatile functional



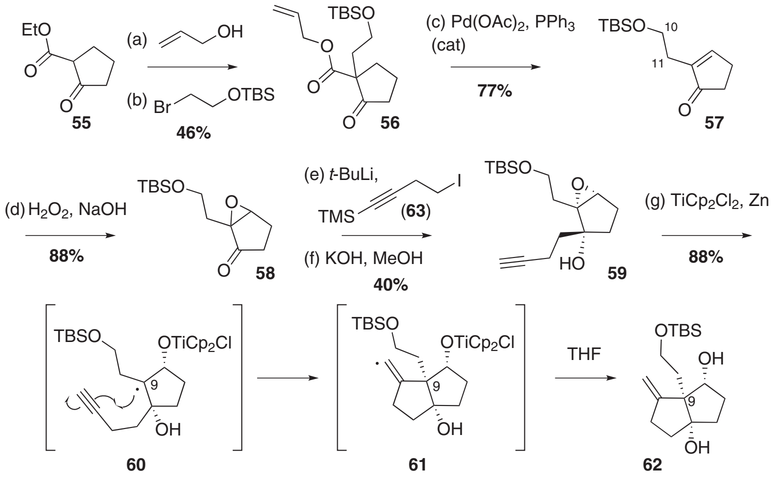
SCHEME 6 Proposed reductive epoxide cyclization.

groups with a wealth of methods available for their stereocontrolled installation in hindered environments. One electron reduction then reliably cleaves the more substituted C—O bond to form the more stable radical intermediate, which itself can undergo a range of chemistries including C—C bond formation. These radical reactions have the well-known characteristic of better tolerating sterically encumbered substrates relative to polar reactions, due to the lack of solvation around the radical intermediate. Taken with the tolerance of radical chemistry to acid- and base-sensitive functional groups, it is no surprise that this reaction has seen application as a key C—C bond forming method in complex molecule synthesis (Scheme 7).[20]

Ph.D. students Karsten Meyer and Lei Shi designed a model system to investigate the feasibility of the proposed reductive epoxide cyclization, based on the BC bicycle of merrilactone A (Scheme 8). In addition to familiarizing ourselves with the epoxide reduction chemistry, we wanted to develop a route to the requisite epoxide alkyne substrate that would translate to the total synthesis. We began with the commercially available ethyl 2-oxocyclopentanecarboxylate **55**, which would act as the C-ring cyclopentane of the natural product. Simple heating of this material in toluene and allyl alcohol without any catalyst afforded the allylic β-ketoester as essentially pure material following removal of solvents. Taking this crude product forward, alkylation of the β-ketoester was then required to install C10 and C11 of the natural product. Using TBS-protected 2-bromoethanol in the presence of K_2CO_3 gave a slow conversion to **56** in a rather low yield. A subsequent Tsuji–Trost reaction transformed the allyl ester **56** into the enone **57**. Under conditions of catalytic $Pd(OAc)_2$ and PPh_3 (1:1 ratio) in acetonitrile,[24] the intermediate palladium enolate formed by decarboxylation undergoes β-hydride elimination to the enone in high yield. Exposure of cyclopentanone **57** to basic H_2O_2 in MeOH then installed the key epoxide functional group in good yield. A 1,2-addition to the ketone was then necessary to install the pendant alkyne group. The reaction proceeded smoothly by treating epoxycyclopentanone **58** with the organolithium generated *in situ* from (4-iodobut-1-ynyl)-trimethylsilane **63** and *t*-butyllithium at −78 °C in ethyl



SCHEME 7 Application of reductive epoxide ring opening and radical C—C bond formation in natural product synthesis.[21–23]



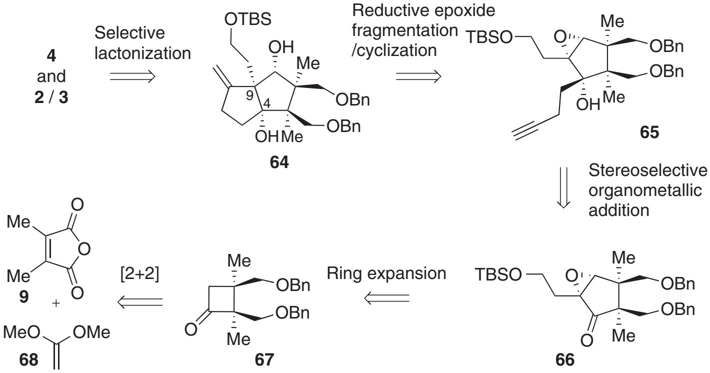
SCHEME 8 Model study: (a) allyl alcohol, toluene, reflux; (b) K_2CO_3, acetone, reflux, 46% over two steps; (c) $Pd(OAc)_2$ (5 mol%), PPh_3 (5 mol%), MeCN, reflux, 77%; (d) H_2O_2, NaOH, MeOH, 88%; (e) *t*-BuLi, **63**, Et_2O, −78 °C; (f) K_2CO_3, MeOH, 40% over two steps; (g) $TiCp_2Cl_2$, Zn, THF, 88%.

ether, followed by desilylation using methanolic KOH. The stereoselectivity of the 1,2-addition was exclusively in favor of the *cis*-epoxy alcohol product **59**, a well-precedented outcome for organometallic addition to simple epoxycyclopentanones.[25] The selectivity of this reaction would be a major consideration in the design of the total synthesis (*vide infra*).

With the radical cyclization substrate **59** in hand, we attempted the key step of the model study by treating it with Ti(III). The Ti(III) reagent was prepared by stirring a red THF solution of commercially available titanocene dichloride with activated powdered zinc metal. After 30 min, the red solution turned to lime green indicating formation of titanium(III). The clear green solution of titanium(III) was then transferred via cannula to a solution of **59** in THF. As expected, selective scission of the C—O bond to form the more stable tertiary radical preceded 5-*exo*-dig cyclization onto the pendant alkyne, furnishing bicyclic product **62** in excellent yield (88%). It is thought that the vinyl radical **61** formed on cyclization rapidly abstracts a hydrogen atom from the THF solvent to give the product **62**.

2.3 Reductive Epoxide Ring-Opening Approach: Total Synthesis

Translation of the successful model study into a total synthesis of merrilactone A required the construction of a more elaborate cyclopentane C-ring, specifically one containing the quaternary stereocenters at C5 and C6. Our full synthetic plan is shown below, whereby we hoped to implement the reductive epoxide cyclization on a suitably protected alkyne epoxide **65** (Scheme 9). The tertiary alcohol in **65** arises from a stereocontrolled 1,2-addition to a ketone, as per the model study, and we planned to form the cyclopentanone **66** via a regioselective ring enlargement of the cyclobutanone **67**. The cyclobutane structure would enable a [2+2] photocycloaddition to set the two *cis*-quaternary methyl groups as the first step in the synthesis. Inoue and Hirama had pursued a similar tactic in their merrilactone A synthesis,[9]



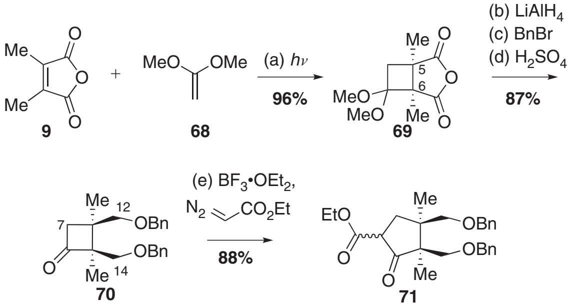
SCHEME 9 Retrosynthesis of merrilactone A and anislactone A.

demonstrating the value of installing two potentially difficult stereocenters at an early stage in the route.

The synthesis began with [2+2] photocycloaddition reaction of the commercially available compounds 2,3-dimethylmaleic anhydride **9** and dimethylketene acetal **68** (Scheme 10). Irradiation in a mixed solvent of degassed acetone and acetonitrile, using a 400 W medium-pressure mercury lamp with a pyrex filter under water cooling, gave excellent yields of the photoadduct **69**. The scale of the reaction, however, was not optimal with runs above ca. 15 mmol of the anhydride **9** becoming low yielding—a typical problem with immersion well scale-up. Nonetheless, running the reaction batchwise and pooling the crude product allowed direct crystallization from diethyl ether and hexane, avoiding silica gel column chromatography and producing gram quantities of material to take on in the synthesis.

A simple, high-yielding three-step manipulation of photoadduct **69** afforded the cyclobutanone **70**, the substrate for ring enlargement (over 30 g of **70** were prepared in this fashion). We elected to install benzyl groups as our first choice to protect the primary alcohols at C12 and C14—we felt that a robust group was needed at this early stage as deprotection was not planned until much later in the route. Ring enlargement was attempted using a well-known variant of the Tiffeneau–Demjanov rearrangement (TDR). The original TDR describes the reaction of 1-aminomethyl-cycloalkanols with nitrous acid to form an enlarged cycloketone, via an *in situ*-formed diazonium species.[26] Here, we treated the ketone **70** with ethyl diazoacetate to form the alkoxy diazonium *in situ*, which rearranged to the desired cyclopentenone **71** in the presence of a stoichiometric amount of $BF_3 \cdot OEt_2$. The less-substituted carbon center (C7) migrated in this reaction, in line with literature precedent for TDRs under these conditions.[27]

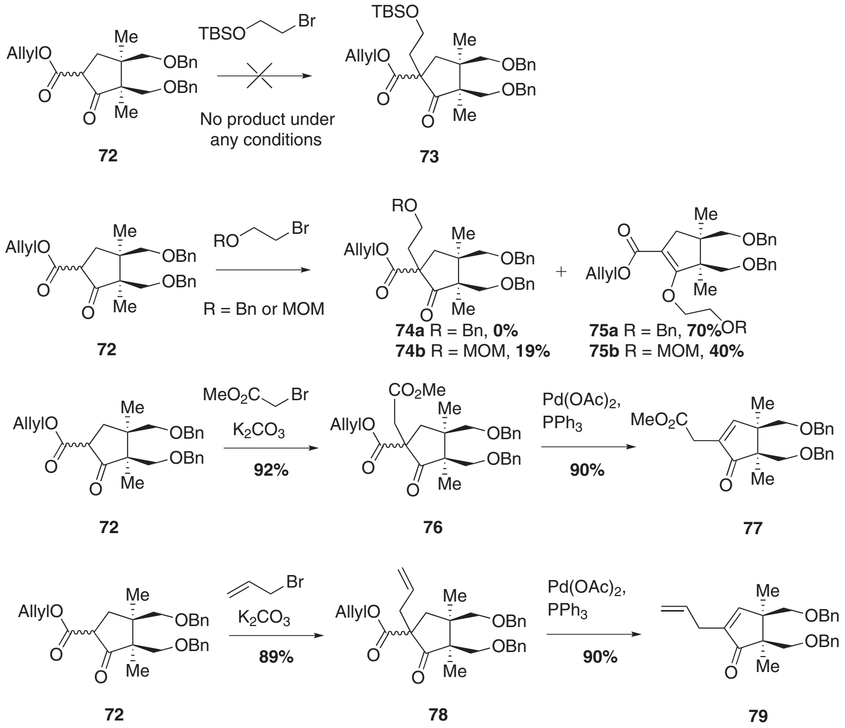
The β-ketoester **71** is the fully elaborated analog of the model system starting material **55** (Scheme 8), and we attempted the same sequence of reactions



SCHEME 10 Synthesis of cyclopentenone C-ring, **72** (principle reagents shown in scheme): (a) *hν*, pyrex, MeCN/acetone (9:1), 96%; (b) $LiAlH_4$, Et_2O, 0 °C, 97%; (c) BnBr, TBAI, NaH, THF; (d) H_2SO_4 (aq.), MeCN, 90% (two steps); (e) N_2CHCO_2Et, $BF_3 \cdot Et_2O$ (2.5 equiv.), CH_2Cl_2, 0 °C, 88%.

as previously developed. Initial transesterification with allyl alcohol worked as before, but we immediately encountered difficulties in the alkylation step (Scheme 11). The additional steric hindrance arising from the existing quaternary stereocenters at C5 and C6 made installation of a third one quite challenging—TBS-protected 2-bromoethanol, which was used in the model system successfully, gave no product under a range of conditions. Changing to a smaller protecting group on the alkylating agent improved matters to a small extent, with MOM- and Bn-protected bromoethanols producing low yields of the desired products **74a** and **74b**. *O*-Alkylation proved highly competitive, however, and this proved insurmountable under a variety of alkylating conditions. Success came by increasing the reactivity of the alkylating agent. Moving from alkyl halides to methyl bromoacetate and allyl bromide gave excellent yields of alkylated product in both cases. Furthermore, both diesters (**76** and **78**) were good substrates for the ensuing Tsuji–Trost reaction, producing the cyclopentenones **77** and **79** in high yield.

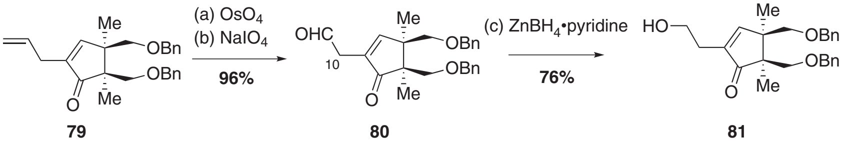
We initially concentrated on manipulating ester **77** in the synthesis, as alkene **79** has an extraneous carbon atom on the allyl moiety that would require excision. Unfortunately, the presence of ester and (hindered) ketone carbonyl functionality caused difficulties and we were not able to advance **77** much



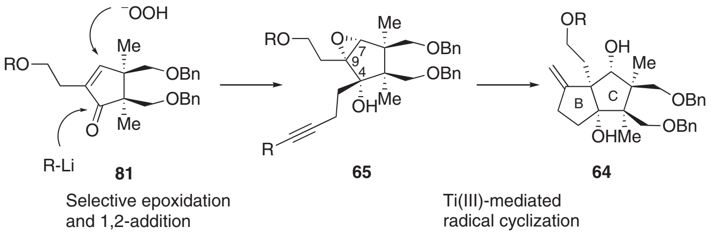
SCHEME 11 Alkylation of 1,3-ketoester in the model system.

further. 1,2-Addition of organometallics to the ketone was compromised by substantial ester cross-reactivity, and attempts at selective reduction were fruitless. The allyl substrate, however, proved more tractable and we were able to develop an efficient cleavage sequence to the protected alcohol **81** (Scheme 12). Initial dihydroxylation of the primary alkene in **79**, with careful control of the NMO oxidant stoichiometry, worked well and was followed by oxidative cleavage to aldehyde **80**. Reduction of the aldehyde proved to be one of the more difficult functional group manipulations in the synthesis, due to the presence of the enone group and the rather acidic C10 position. Furthermore, the 1,4-relationship between the two carbonyl groups appeared to activate the ketone to reduction once the aldehyde had undergone initial reduction—a phenomenon observed with a variety of hydride reducing agents. After considerable experimentation, selective reduction could be achieved using the pyridine complex of $Zn(BH_4)_2$. This reagent is known to show excellent selectivity between aldehyde and ketones;[28] using *iso*-propanol or *tert*-butanol as solvents gave good yields of the desired alcohol **81**.

With an efficient synthesis of cyclopentenone **81** established, we next investigated the epoxidation and 1,2-nucleophilic addition reactions that were required to set up the substrate for radical epoxide opening and cyclization. Installation of these two groups represents the stereochemical crux of the synthesis—it is critical that the 1,2-nucleophilic addition occurs on the same face as the protected diol functionality of the cyclopentenone, to set the correct stereochemistry at C4 (Scheme 13). The relative stereochemistry of the epoxide is less important when considered in isolation—C—O bond cleavage in the reductive cyclization will correctly set the *cis*-BC-ring junction, and the configuration of the C7 secondary alcohol could likely be inverted at a subsequent stage. As seen from the model study, however, the epoxide



SCHEME 12 Transformation of alkene to alcohol. Conditions: (a) OsO_4, NMO, H_2O, acetone, 96% yield; (b) $NaIO_4$, THF, quant; (c) $Zn(BH_4)_2$·py, *i*-PrOH, 76%.

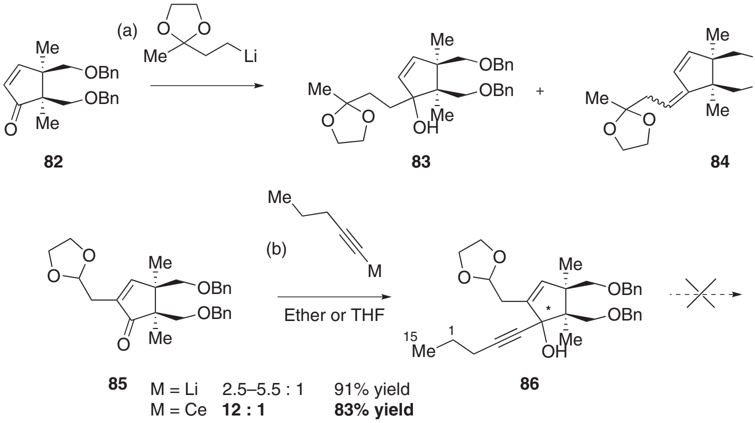


SCHEME 13 Selectivity in epoxidation and 1,2-organometallic addition.

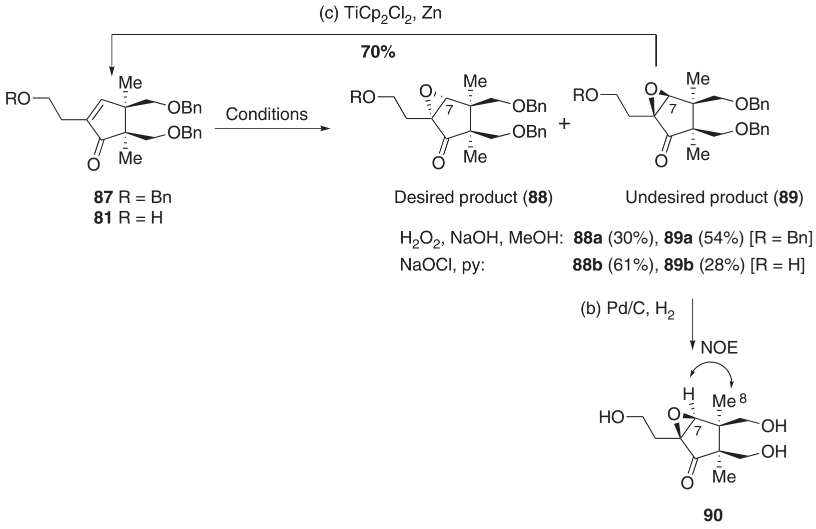
stereochemistry can act as a powerful element of stereocontrol for the 1,2-addition to the ketone.

To begin our studies on the cyclopentenone functionalization, Karsten Meyer had noted in earlier work on related cyclopentenone systems that 1,2-addition of sp^3-hybridized organolithiums was plagued with elimination difficulties (e.g., **82** in Scheme 14)—unsurprisingly, given the product alcohol is tertiary, allylic, and next to a quaternary stereocenter. Some effort was expended on removing the elimination pathway by using sp-hybridized organolithiums (e.g., **85** → **86**); while these additions generally worked well, useful functionalization of the resulting alkyne (including an ambitious zipper reaction[29] to isomerize it to the required position at C15 and C1) did not prove possible. As a result, it was necessary for epoxidation to precede 1,2-addition. On the basis of both the model results and literature precedent for simple epoxycyclopentanones,[25] epoxidation from the lower face of **81** should direct the ensuing 1,2-addition to the correct face of the ketone to afford the *cis*-epoxy alcohol. The impact of the two quaternary centers at C5 and C6 on both of these reactions, in terms of stereocontrol and steric crowding, was difficult to predict.[30]

In the event, treatment of the benzyl-protected cyclopentenone **87** with alkaline hydrogen peroxide in methanol afforded a very clean epoxidation reaction in 84% yield, furnishing the two diastereomers **88a** and **89a** in a 1:1.8 ratio (Scheme 15). The two isomers were readily separated through column chromatography and the stereochemistry was assigned based on NOESY analysis of the downstream intermediate **90**. The key NOESY interaction observed was between the proton at C7 and the C8 methyl group. The facial selectivity apparent in the epoxidation reaction slightly favored the formation of undesired product **89a**, in which the epoxide is introduced on the same face as the bis-benzyl-protected diol. We speculated that this stereoselectivity could arise from the weak interaction of hydrogen bonding between hydrogen



SCHEME 14 Selective 1,2-organometallic addition and epoxidation.



SCHEME 15 Epoxidation studies on enones **81** and **87**.

peroxide and the BnO groups, countering their larger steric demand. A screen of other common epoxidizing agents (*m*-CPBA, *t*-BuOOH, and VO(acac)$_2$/*t*-BuOOH system) gave no reaction at all, illustrating the sterically hindered nature of the double bond. Treatment of the primary alcohol substrate (**81**) with NaOCl (bleach) in the presence of pyridine, however, gave a high yield of the two epoxide isomers in the more useful ratio of 2.2:1 in favor of the desired **88b**. It appears that the larger OCl^- anion, with no H-bonding donor facility, favored attack at the less-hindered α-face.

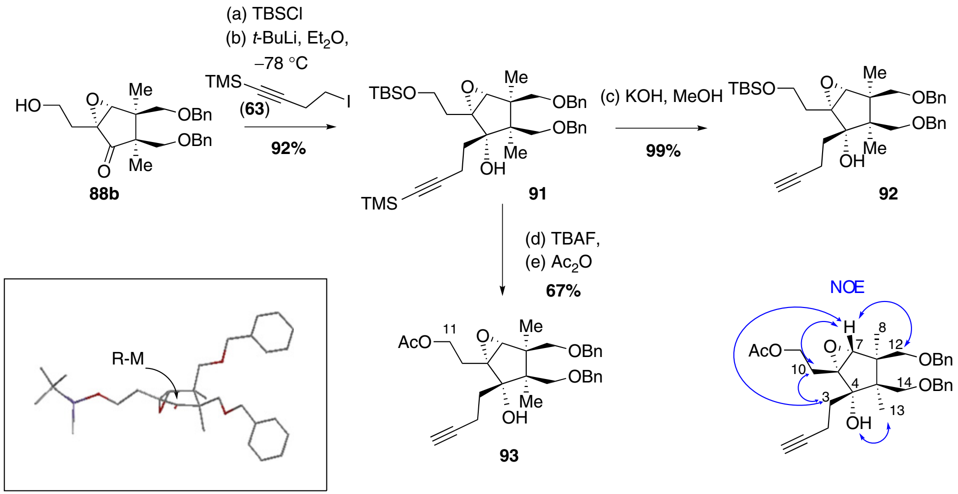
While the stereoselectivity of epoxidation was modest, the efficiency of the overall transformation could be improved by recycling the unwanted minor β-epoxide **89b** through reductive deoxygenation. This transformation can be achieved by a number of methods,[31] one of the more popular employing the same Ti(III) reagent as used in our reductive epoxide cyclization reaction.[32] In the absence of any intramolecular radicalophile, treatment of epoxides with Cp_2TiCl_2/Zn would be expected to promote deoxygenation, particularly (as here) if the resultant double bond is stabilized by conjugation. This proved to be the case; treatment of **89b** with $TiCp_2Cl_2$ and zinc in THF for 10 h gave the deoxygenation product **81** in 70% yield.

With adequate quantities of α-epoxide **88b** in hand, we turned to the introduction of the C15–C1–C2–C3 side chain via organometallic addition. The primary alcohol was protected as a TBS ether and then treated with an excess of the organolithium prepared from iodide **63** and *t*-BuLi. Pleasingly, we isolated tertiary alcohol **91** as a single diastereoisomer in excellent yield. The epoxide is acting as the dominant element of stereocontrol, and as with the simple model, the 5–3 bicycle must be offering a considerably less-hindered convex face for attack by the organometallic (MM2 minimized structure shown in Scheme 16). We removed the TMS group on the alkyne selectively (KOH, MeOH) to secure the substrate for reductive epoxide cyclization. To help optimize the reaction, we also removed both silyl groups on **91** to enable variation of the protecting group at the C11 alcohol. The acetate **93** was a convenient substrate for NOESY studies to ascertain the relative stereochemistry of the 1,2-addition.

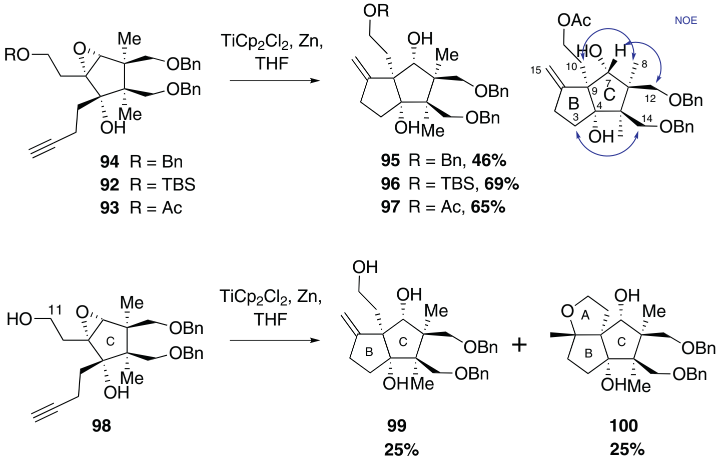
We had four substrates at our disposal for epoxide cleavage, each differing at the C11 primary alcohol—benzyl and TBS ether, acetate, and free OH. Our first attempt used the benzyl ether **94**, and we were delighted to find that the reaction was successful: Addition of **94** in THF to a green solution of $TiCp_2Cl_2$ and zinc in THF under argon afforded the bicycle **95** in an encouraging 46% yield (Scheme 17). In order to optimize the reaction, we observed that some of the by-products appeared to include deoxygenated materials (alkene signal in ^1H NMR). Working with the TBS- and Ac-protected substrates **92** and **93**, we found that running the reaction at more dilute concentration (0.04 and 0.2 M for **94**), and using an inverse addition protocol where the Ti(III) solution was added to the substrate, led to enhanced yields of the product bicycles **96** and **97**. (The stereochemistry of the cyclized products was again assigned by NOESY analysis, using compound **97**.)

Finally, the free alcohol **98** was also viable in the reaction, producing the expected bicycle **99** in a low 25% yield along with a similar amount of the unexpected tricycle **100**. It appears that the Lewis acidic conditions of the reductive epoxide cyclization, whereby 1 equiv. of $ZnCl_2$ is formed *in situ*, are promoting a 5-*exo* etherification reaction of the free alcohol. We also observed slow conversion of **99** into **100** when standing in $CDCl_3$ over a period of weeks. Given that the newly formed tetrahydrofuran ring corresponds to the A-ring in the anislactone series, this was a promising result and one we would capitalize on in our final route design to complete the synthesis (*vide infra*).

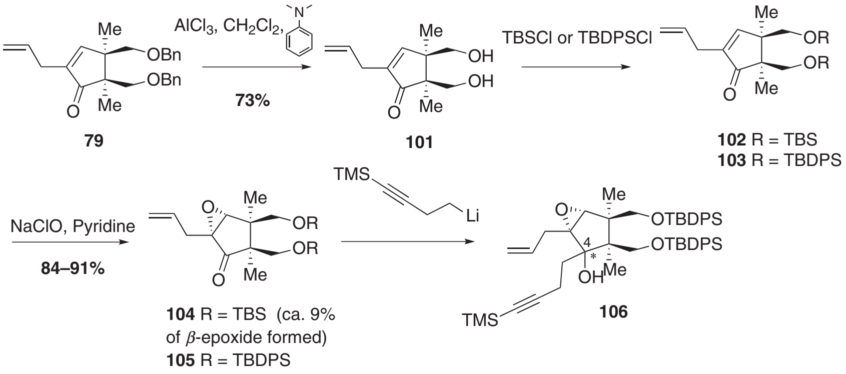
Before tackling the endgame of the synthesis, we reexamined the epoxidation reaction (Scheme 15) with a view to improving stereocontrol. Bulkier protecting groups on the C12 and C14 primary alcohols would be expected to improve diastereoselectivity, so we experimented with the TBS- and TBDPS-containing substrates **102** and **103** (Scheme 18). As expected, both compounds gave excellent conversions to the desired α-epoxides **104** and **105**. Furthermore, compound **105** was also a good substrate for 1,2-addition, affording high yields of the cyclopentanol **106** as a single stereoisomer. This compound did not lend itself to NOESY analysis, so we were unable to ascertain whether the epoxide was still controlling the facial selectivity of addition or whether the introduction of the large silyl groups had reversed the facial selectivity of the addition. The question became moot, however, as exposure of **106** to the Ti(III) reductive epoxide cyclization conditions produced no reaction with only recovery of starting material. It was apparent that the addition of more steric bulk to an already hindered system could not be tolerated



SCHEME 16 Stereoselective 1,2-addition for B-ring synthesis. Conditions: (a) TBSCl, imidazole, CH_2Cl_2, 0 °C, 98%; (b) *t*-BuLi, **63**, Et_2O, −78 °C, 94%; (c) KOH, MeOH, 99%; (c) TBAF, CH_2Cl_2; (d) Ac_2O, pyridine, CH_2Cl_2, 67%, two steps.



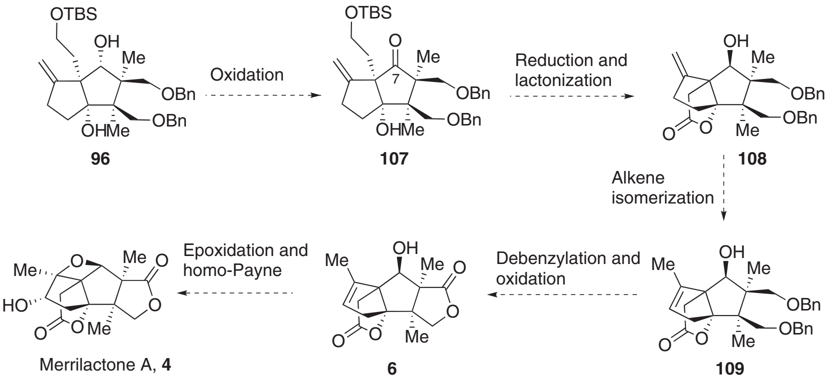
SCHEME 17 Radical cyclization to form the BC-ring system.



SCHEME 18 Epoxidation with bulky protecting groups.

and reaction was not possible. Furthermore, trial attempts at removing the large TBDPS groups from the two neopentyl alcohols were not promising, persuading us to abandon this avenue of enquiry and retain benzylation as the most productive overall protection strategy for the totality of the synthesis.

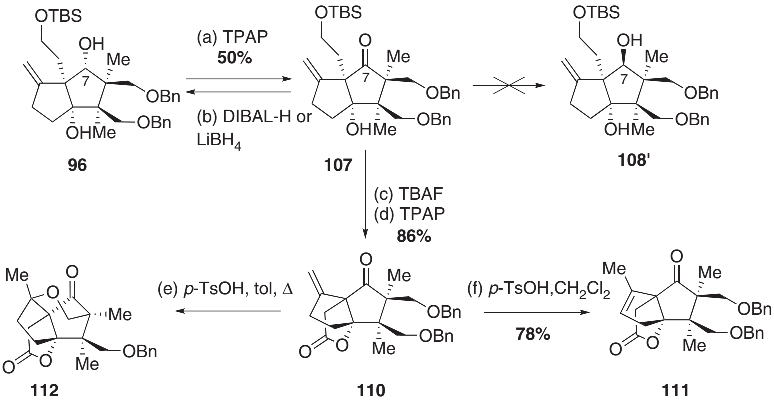
With the full anislactone carbon skeleton in hand, we planned to direct it to both the merrilactone A and anislactone A and B structures. The synthetic plan for merrilactone is shown below in Scheme 19; we felt the inversion of stereochemistry at C7 could be tackled first with a simple oxidation–reduction protocol, as the back face of the BC bicycle in **107** appeared considerably less hindered to hydride addition. Lactonization and alkene isomerization would then follow, with debenzylation and selective oxidative lactonization completing the synthesis.



SCHEME 19 Synthesis plan for merrilactone A.

Oxidation of alcohol **96** was best carried out with TPAP, forming ketone **107** in good yield. To our surprise, reduction of this molecule with both DIBAL-H and $LiBH_4$ gave the starting alcohol **96**, where hydride has been delivered from the ostensibly more hindered upper face. Alternative reducing agents such as $NaBH_4$, $ZnBH_4$, or SmI_2 gave no reaction, meaning that ketone reduction would need to be considered on an alternative substrate. Precedent from Inoue and Hirama's merrilactone synthesis suggested that the C7 ketone would undergo dissolving metal reduction with the A-ring lactone in place.[9b] Accordingly, desilylation of **107** and subsequent oxidative lactonization with TPAP and excess NMO furnished the A-ring γ-lactone **110** in 86% yield over two steps (Scheme 20). Isomerization of the alkene into the B-ring was then necessary (attempted dissolving metal reduction at this stage led to competitive reaction with the *exo*-alkene). This transformation had some precedent in Danishefsky's merrilactone route, where a similar substrate (variable at the C-ring) was isomerized using *p*-TsOH in refluxing toluene.[8a] Unfortunately, ketone **110** proved more sensitive to acidic conditions; the major product isolated had undergone debenzylation and was tentatively characterized as the bridged ether **112**. This unwanted debenzylation pathway could be observed at lower temperatures, conditions considered easily tolerable by the benzyl group under normal circumstances, suggesting that the neighboring ketone group could be accelerating the reaction by offering a well-placed protonation site. After considerable optimization, we could suppress the debenzylation using conditions of *p*-TsOH in AcOH and CH_2Cl_2 at 30 °C, successfully switching the alkene into the B-ring in 78% yield.

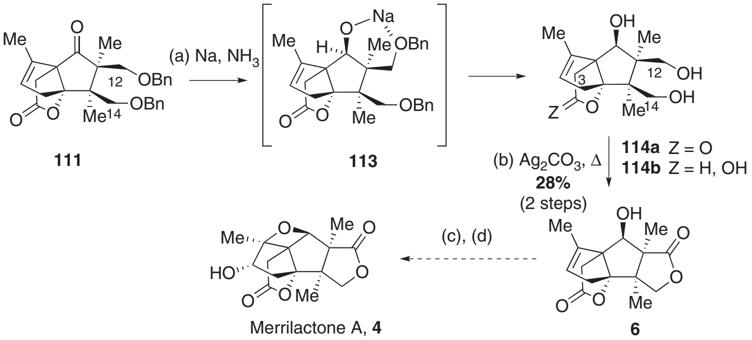
Compound **111** is very similar to a late-stage intermediate in Inoue and Hirama's synthesis,[9b] differing only slightly in the protecting group at C14 (benzyl vs. substituted benzyl). Lei Shi was able to apply Hirama's two-step protocol of sodium in ammonia followed by Fetizon's reagent to effect three transformations: First, the dissolving metal reduction effects debenzylation



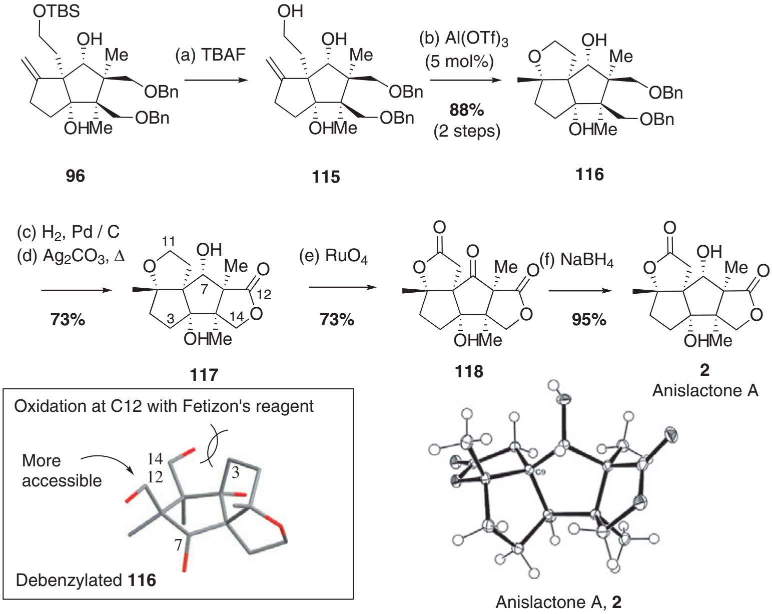
SCHEME 20 A-ring synthesis. Conditions: (a) TPAP (50 mol%), NMO (10 equiv.), DCM, 10 h, 76%; (b) DIBAL-H or LiBH$_4$; (c) TBAF, THF; (d) TPAP (10 mol%), NMO (5 equiv.), CH$_2$Cl$_2$, 86% over two steps; (e) *p*-TsOH, tol, Δ; (f) *p*-TsOH, AcOH (1:1), CH$_2$Cl$_2$, 30 °C, 78% (5% SM recovered).

and subsequent stereoselective reduction of the hindered ketone at C7 to the β-hydroxy group, presumably via **113** through a six-membered chelate (Scheme 21). It is likely that the lactone A-ring is also reduced to a lactol at this stage. Second, the mixture of lactols **114a/b** is oxidized with Fetizon's reagent, with the weak oxidizing agent being selective for the sterically most accessible C12 primary alcohol, to produce the desired bis-γ-lactone **6** as a single isomer. This selectivity in the oxidative lactonization step is crucial to the success for the synthesis and was precedented in Inoue/Hirama's work—molecular models of **111** show that the C14 position is occluded by the sp^3 C3 atom on the other side of the molecule. Unfortunately, the isolated yield over the two steps was a rather poor 28% (cf. 41% reported by Hirama), and we did not have the material to optimize this reaction further. Nevertheless, we had successfully arrived at Fukuyama's tetracycle (**6**), the antepenultimate compound in all merrilactone A syntheses to date. The ^{1}H NMR, ^{13}C NMR, IR, and HRMS data of **6** matched that reported in the literature,[5b] thus representing a formal total synthesis of the natural product.

In order to access the anislactone series of natural products, it was necessary to install the regioisomeric γ-lactone between C1 and C9, as opposed to C4 and C9 in merrilactone A. A hint on how to achieve this transformation came from our development of the earlier epoxide fragmentation/cyclization, where we observed a small amount of alkene etherification product being formed from substrates having a free C11-OH group. The resulting five-membered cyclic ether could in principle be further oxidized to the γ-lactone D-ring of anislactone A and B with a strong oxidant. In order to optimize the etherification reaction, we screened various acid catalysts using alcohol **115** as substrate. Strong Brønsted acids (TfOH, MsOH, TFA) led to rapid decomposition, but we were



SCHEME 21 Formal total synthesis of merrilactone A. Conditions: (a) Na, NH_3, EtOH/THF, −78 °C; (b) Ag_2CO_3, toluene, reflux, 28% over two steps; (c) *m*-CBPA, CH_2Cl_2; (d) *p*-TsOH, CH_2Cl_2.[5b]



SCHEME 22 Completion of anislactone A synthesis. Conditions: (a) TBAF, CH_2Cl_2/THF (5:1); (b) Al(OTf)$_3$ (5 mol%), CH_2Cl_2, 88% (two steps); (c) H_2, Pd/C, MeOH; (d) Ag_2CO_3 on celite, toluene, 130 °C, 73% over two steps; (e) $RuCl_3$ (0.5 equiv.), $NaIO_4$, MeCN/CCl_4/H_2O (1:1:1), 73%; (f) $NaBH_4$, THF, 95% (dr = 5:1).

pleased to find that the Lewis acid Al(OTf)$_3$, introduced by Dunach for intramolecular hydroalkoxylation,[33] was highly effective for the transformation. Treatment of **115** with Al(OTf)$_3$ at room temperature gave an excellent yield of the tricycle **116** having the correct ring structure for the anislactones (Scheme 22).

The absence of any alkene functionality meant that the benzyl groups could be smoothly removed using hydrogenolysis, setting the stage for two selective lactone installations. First, the γ-lactone D-ring was formed by regioselective oxidation of debenzylated **116** with Fetizon's reagent. As with the merrilactone A synthesis, it appeared that the reactivity of the hydroxy group at C12 toward oxidation was higher than the one at C14. Molecular modeling (shown in Scheme 22 for an MM2-minimized structure of debenzylated **116**) suggested that the steric hindrance between the protons at C3 and C14 impeded the attack of the bulky Fetizon's reagent; thus the weak oxidizing agent was selective for the sterically most accessible C12 primary alcohol. The remaining γ-lactone was then accessed through oxidation at C11 of the cyclic ether. Using catalytic ruthenium tetroxide (RuO_4) and excess $NaIO_4$ in carbon tetrachloride (CCl_4) gave a good yield of the lactone **118** with concomitant oxidation of the secondary alcohol to a ketone. Reduction with $NaBH_4$ was found to be straightforward, delivering hydride from the more accessible β-face and producing anislactones A and B in 95% yield as a 5:1 mixture, from which anislactone A could be purified as a single diastereoisomer. Synthetic **2** had identical ^{1}H NMR, ^{13}C NMR, IR, and HRMS data to the natural product,[3a] and the structure was confirmed unambiguously through X-ray crystallography of a single crystal that formed following chromatography.[34]

3 CONCLUSIONS

The formal synthesis of merrilactone A was completed in 22 steps and 2.4% overall yield, and the total synthesis of anislactone A in 21 steps and 5.6% overall yield, from the common intermediate **96**. Strategically, the strengths of the route rest, first, on a direct approach to the cyclopentane C-ring **92** containing five stereocenters (secondary, two tertiary, and two quaternary) and, second, on the facility of reductive epoxide ring opening to take this molecule forward with an efficient C—C bond formation in a highly hindered environment. The strategy of using a stereospecific [2+2] cycloaddition to set two quaternary centers in a cyclobutane as the first step worked well, thanks to an effective Tiffeneau–Demjanov ring enlargement to the requisite cyclopentane. Subsequently, the use of the 5–3 epoxycyclopentanone ring system to effectively control addition to the carbonyl was critical to the eventual success of the synthesis. The product from reductive epoxide cyclization (**96**) was also versatile enough to be directed toward both natural product structures, enabling the first total synthesis of anislactone A.

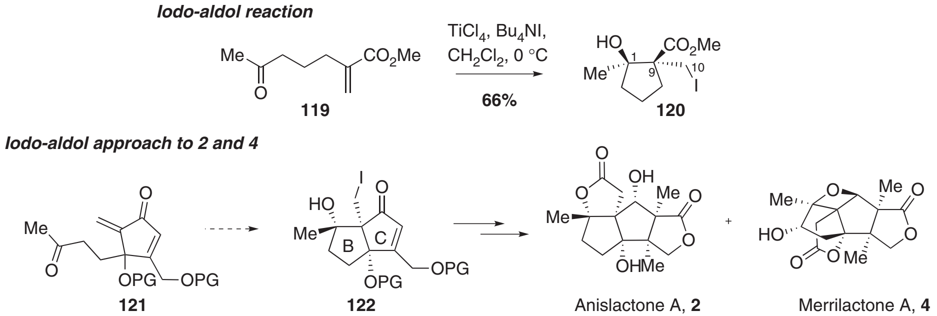
Our merrilactone A synthesis suffered from a low yield in the final stages of the debenzylation/reduction/oxidative lactonization cascade. This was a consequence of lack of material preventing further optimization, and we feel given more time this reaction could be significantly improved in our hands. Stereocontrol throughout the synthesis was high, but there was a single instance of rather weak selectivity in the epoxidation step (Scheme 15), whereby the C5 and C6 quaternary stereocenter functionality did not strongly distinguish between both faces of the C-ring enone **87**. While this issue could be solved practically through a recycling protocol, it remains a strategic flaw in the synthesis. It could be overcome in microcosm through the use of bulky protecting groups, but that approach led to excessively hindered substrates that could not be advanced. The benzyl protecting groups used in the sequence proved best from an overall perspective—they represented a good balance of stability to the wide variety of chemistries employed (installed in step 3, removed in step 21) versus ease of removal.

4 MERRILACTONE A: SECOND-GENERATION SYNTHESIS

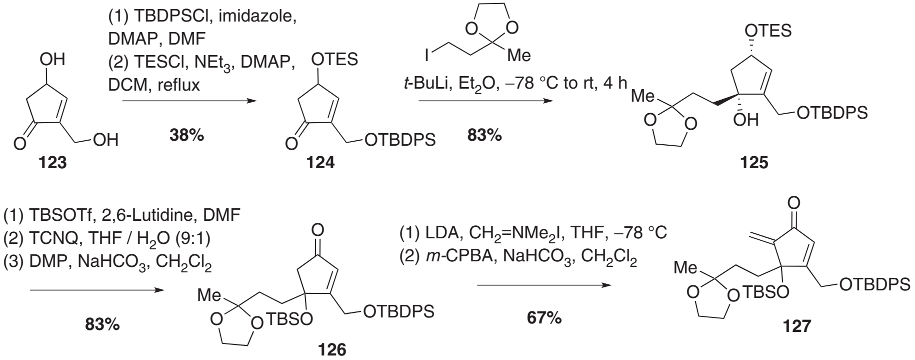
4.1 Tandem Iodo-Aldol Chemistry: Background and Application to Merrilactone A Synthesis

During the course of our first-generation synthesis of merrilactone A, we became interested in the general problem of cyclopentannulation in organic synthesis.[35] Five-membered ring synthesis is a well-studied field that encompasses a vast scope of reaction classes but continues to develop due to the importance of cyclopentanes in natural product structures.[36] As part of our efforts in this area, Ph.D. student Frederic Douelle developed a tandem iodo-aldol reaction for accessing sterically congested carbocycles. The halo-aldol is a well-known transformation that uses conjugate addition of halide anion to generate enolates, which undergo subsequent inter- or intramolecular aldol reaction. Frederic developed a stereoselective iodo-aldol reaction using substrates branched at the α-position of the Michael acceptor, affording products containing a quaternary center *vicinal* to a secondary or tertiary center (e.g., **120** in Scheme 23).[35b] The structure of the products prevents elimination of the nucleophile as would be seen in a Morita–Baylis–Hilman (MBH) reaction, retaining it in the product for further elaboration. Structures such as **120** overlap perfectly onto the anislactone skeleton with respect to the C1 and C9 stereocenters, suggesting an iodo-aldol approach could produce a direct, stereocontrolled route to the natural product. Naim Nazef joined the group in September 2007 with this objective of developing tandem-aldol approaches to merrilactone and anislactone as the focus of his Ph.D. To test this idea, we conceived structure **121** as an appropriate target in the first instance. Iodo-aldol cyclization would afford the BC bicycle **122**, with good prospects for stereocontrol across the critical tertiary–quaternary–tertiary stereotriad of C1, C9, and C4. The B-ring enone contains sufficient functionality for further advancement to the anislactone family of natural products.

Our experience with cyclopentenone synthesis and manipulation in our earlier work informed a relatively straightforward synthesis of **127** (Scheme 24). The parent hydroxymethyl-substituted cyclopentenone is a literature compound accessed via furan-cyclopentenone rearrangement chemistry[37] and could be prepared on a large scale. Problems were encountered in the first step where selective protection of the primary alcohol proved difficult, with the secondary alcohol



SCHEME 23 Iodo-aldol chemistry for anislactone synthesis.

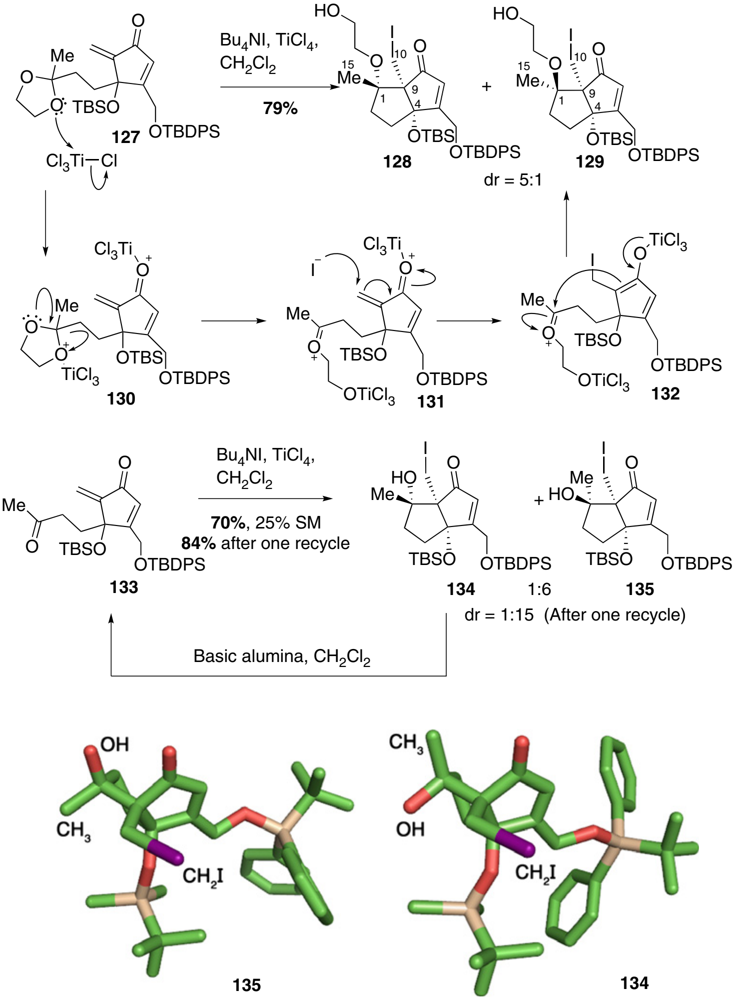


SCHEME 24 Preparation of iodo-aldol substrate.

competing under a range of protection conditions. A selective capping with the TBDPS group in a rather low 40% yield was deemed sufficient to move material along at this inchoate stage in the proceedings. From this point, however, an efficient route was established involving protection of the secondary alcohol as a TES ether, 1,2-addition, TBS protection of the tertiary alcohol, selective desilylation of the C7 secondary alcohol with tetracyanoquinone (TCNQ), and Dess–Martin oxidation, and then methylenation at C4 via Eschenmoser's protocol, each step proceeding in good to excellent yield.

The ketal **127** is then a suitable substrate for iodo-aldol cyclization. We were pleased to find that treatment with Bu_4NI and $TiCl_4$ in CH_2Cl_2 at 0 °C gave the desired adduct as a separable mixture of diastereoisomers **128** and **129** (5:1) in high yield. The reaction creates the B–C carbocyclic ring system of the natural product with the required *cis*-geometry at the ring fusion, along with moderate selectivity for the *trans*-relationship between the C1 tertiary alcohol functionality and the iodomethyl group (stereochemistry assigned by NOESY NMR). We were interested in exploring the iodo-aldol method on the ketone substrate **133** (prepared through simple DDQ treatment of the ketal **127**), as a comparison of ketal versus ketone activity in the aldol component of the reaction. The ketone substrate also offers the potential of saving a step in the synthesis. The tertiary alcohol functional group is formed directly in the tandem aldol, whereas the ketal-derived product (**128**) requires a two-step deprotection of the hydroxyethyl moiety.

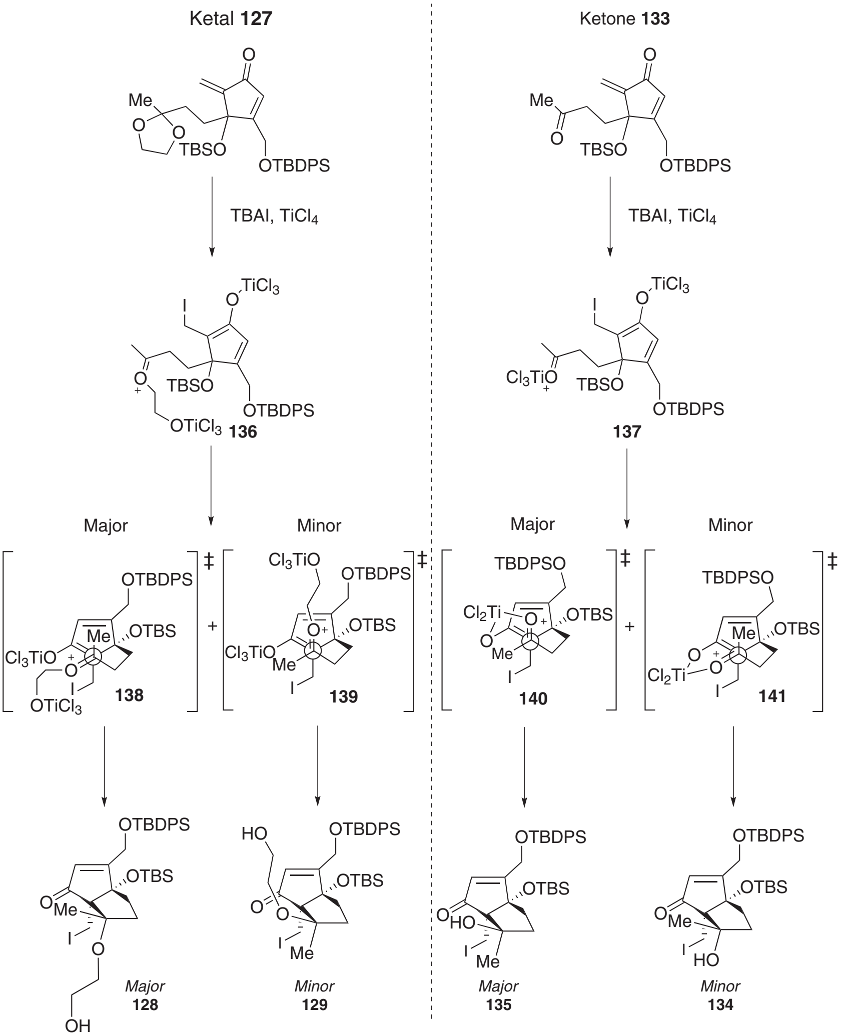
Application of the iodo-aldol conditions to **133** gave a very clean transformation to the aldol adducts **134** and **135** in 70% yield (25% unreacted starting material), again as a separable pair of diastereoisomers (6:1). Both alcohols were solids and yielded crystals suitable for X-ray analysis, securing the structures shown in Scheme 25. The crystal structure for major diastereomer **135** clearly shows a *trans* stereochemical relationship between the C1 alcohol and the C10 iodomethyl group, in contrast to that obtained from the ketal substrate. The steric environment around the C1 oxonium cation intermediate must be the pivotal factor in directing the stereochemical course of the reaction—a possible rationale is outlined in Scheme 26. Initial conjugate addition of the iodide nucleophile generates a (*Z*)-enolate followed by a diastereoselective aldol reaction. In the case of the ketal substrate **127**, discrimination between transition states **138** and **139** arises from the orientation of the bulky ketal side chain, which is pointing away from the hindered concave face of the incipient 5–5 system in **138**, rather than pointing toward the more sterically crowded concave face in **139**. The C15 methyl substituent occupies the more hindered position as it offers less steric congestion as compared to the bulkier ketal side chain. The differentiated concave and convex faces of the ensuing bicycles in **138** and **139** are proposed to drive the observed diastereoselectivity leading to the preferential formation of C1,C9-*cis*-diastereomer **128**. The iodo-aldol reaction with methyl ketone **133** resulted in reversal of diastereoselectivity. In this scenario, which may proceed through a chelated transition



SCHEME 25 Key intramolecular tandem iodo-aldol cyclization reaction.

state, the C15 methyl group is considered to be bulkier than the developing C1 tertiary alcohol, favoring transition state **140** with the methyl substituent pointing away from the concave bicycle. This results in reversed diastereoselectivity affording C1,C9-*trans* **135** as the major diastereomer.

Purification of the adducts **134** and **135** by column chromatography led to the interesting observation that diastereoisomer **135** was isolated accompanied with small amounts of the minor diastereoisomer **134**, even after repeated columns and despite both isomers being well separated on the TLC plate. Additionally, purple-colored fractions were noted in some cases, indicating the release of



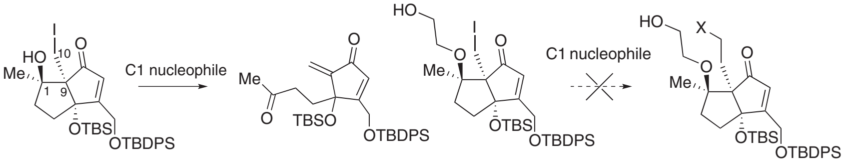
SCHEME 26 Proposed stereochemical model for the iodo-aldol cyclization on ketal **127** and ketone **133**.

iodide, pointing to a retro-aldol/elimination process being active and converting some of the major isomer **135** to **134** via the starting enone **133** on the column. We could take advantage of this equilibration process to recycle the minor diastereoisomer **134**. Exposure of **134** to basic alumina at room temperature overnight led to the clean formation of the starting enone **133**. Pooling with the previously recovered starting material and resubmission to the iodo-aldol reaction conditions gave a cumulative diastereomeric ratio of 15:1, with **135** isolated in a combined 79% yield and a diminished 5% yield for **134**. Although a pleasing result, this facile retro-aldol process pointed to possible problems in taking **135** further in the synthesis.

Logical progression of the synthesis from either of the iodo-aldol adducts **134** or **135** requires the installation of the A-ring γ-lactone, meaning a one-carbon homologation at the C10 alkyl iodide position. Unfortunately, the fragmentation pathway of these adducts proved too facile, with attempts at iodide displacement from **135** using nucleophiles such as cyanide being plagued with retro-aldol reaction under a variety of conditions. There is clearly a substantial release of steric strain following rupture of the C1–C9 bond, making it difficult to manipulate the intact iodo-aldol adduct. As a result, we shifted attention to the ketal-derived adduct **128**, where retro-aldol fragmentation should be impossible due to the hydroxyethyl remnant capping the tertiary alcohol. The tertiary alcohol is also correctly configured for A-ring lactonization. Unfortunately, the iodo group proved impervious to manipulation in this compound under a range of conditions. Extensive cyanidation, carbonylation, organometallic, and radical addition reactions were screened, but none managed successful displacement of iodide. The iodo group is clearly very sterically hindered, being neopentyl and shielded by further tertiary centers at C1 and C4—while initially conceived as a feature of iodo-aldol chemistry that would power further synthesis, we were forced to conclude that iodide incorporation in this particular architecture was not going to be productive (Scheme 27).

4.2 Tandem Cyanide Addition/Aldol Cyclization Approach to Anislactone A

A logical solution to the iodide functionalization problem, however, readily presented itself-rather than attempt a subsequent one-carbon homologation of the installed iodide, an alternative carbon-centered nucleophile in the tandem-aldol process would afford all of the requisite carbon atoms of the ABC anislactone tricycle. Cyanide, the subject of previous efforts to displace iodide, would be the perfect choice as it presents the correct oxidation level for subsequent lactonization with the C1 tertiary alcohol. Furthermore, there were just two isolated reports in the literature of tandem cyanide addition/aldol reaction, presenting an opportunity to develop a new reaction on a complex substrate.[38] One reason for this dearth of examples could be the tendency



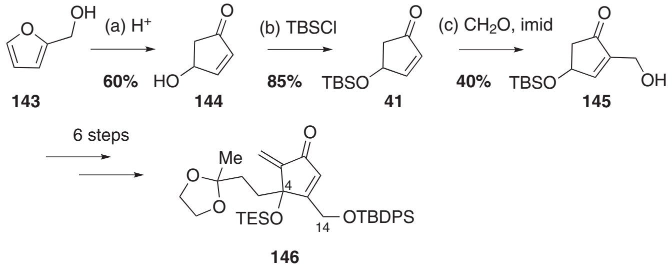
135 *Retro-aldol product*, **133** **128** **142**

SCHEME 27 Attempts at iodide displacement.

of cyanide to add in a 1,2-sense to Michael acceptors, making the enone substrate **127** an interesting test case for the conjugate addition/aldol pathway.

In preparation for the cyanide tandem aldol, we took the opportunity to develop a more efficient approach to the tandem-aldol substrate, avoiding the selective protection issues that arose in our preparation of substrate **124**. The known TBS-protected cyclopentenone **41**, prepared as before via Piancatelli rearrangement from furfuryl alcohol, proved a good substrate for MBH reaction with formaldehyde (Scheme 28). Using modified conditions from the work of Gatri and El Gaïed,[39] exposure of **41** to imidazole and excess formaldehyde over 6 days at room temperature resulted in the formation of primary alcohol **145** in moderate yield with a small amount of unwanted dialkylated by-product. Although the yield was moderate, the reaction was very amenable to scale-up as multigram batches of crude product could be pooled together and purified without difficulty. The MBH reaction avoids the problem of selective protection at C14, setting up a very similar sequence to that used earlier for the preparation of the tandem-aldol reaction (**124–127**, Scheme 24). We chose to protect the C4 tertiary alcohol as a TES ether, rather than a TBS ether as used previously, to enhance the prospects of removal from what would be quite a hindered structure later in the synthesis.

We began with a simple addition of Bu$_4$NCN to the enone **146** to familiarize ourselves with cyanide conjugate addition chemistry. No reaction could be observed and starting materials were recovered, indicating Lewis acid activation would be required. Switching to diethylaluminum cyanide yielded immediate results, affording the conjugate addition product **149** in 60% yield. The ketone substrate **147** behaved similarly, giving a 57% yield of the cyano adduct **150**. The tandem-aldol reaction was not taking place under the reaction conditions, a somewhat surprising result given the strong Lewis acid character of the Et$_2$AlCN reagent. We turned to TiCl$_4$ to activate the substrate, given its success in the iodo-aldol and other halo-aldol transformations. Using the same procedure as the successful iodo-aldol reaction established previously



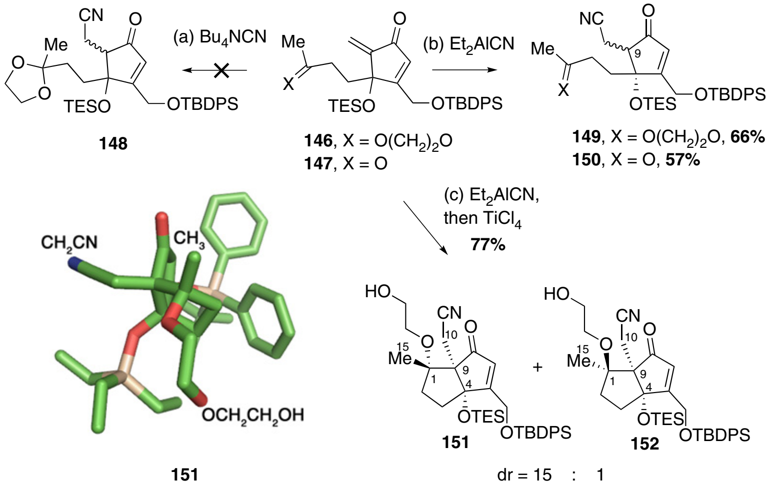
SCHEME 28 Morita–Baylis–Hillman route to starting cyclopentenone **146**. Conditions: (a) hydroquinone, NaH$_2$PO$_4$, H$_2$O, 1,4-dioxane, pH 4.1, reflux, 60%; (b) TBSCl, DMAP, NEt$_3$, CH$_2$Cl$_2$, reflux, 85%; (c) HCOH (aq.), imidazole, THF:H$_2$O (1:1), rt, 40%.

(Scheme 25), but swapping Bu_4NI for Et_2AlCN, was not immediately effective and led to extensive decomposition. A delayed addition of $TiCl_4$, however, successfully delivered the tandem-aldol reaction. Treating a solution of **146** in toluene at 0 °C with diethylaluminum cyanide, followed in 10 min by the addition of a toluene solution of $TiCl_4$, gave a separable 15:1 diastereomeric mixture of the desired adducts **151** and **152** with a good overall yield of 77% (Scheme 29).

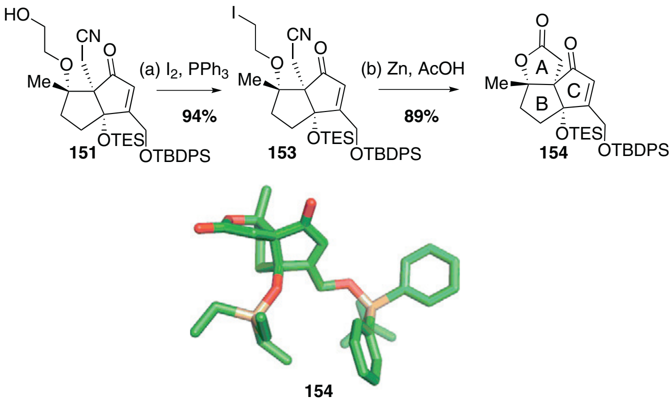
As expected, the diastereoselectivity for the cyclization was the same as the iodo-aldol cyclization with ketal **126** as the substrate (cf. Scheme 25). The major diastereoisomer **151** was isolated as a solid and yielded crystals suitable for X-ray diffraction, illustrating the *cis* stereochemical relationship between the C1 alkoxy group and the cyanomethyl group at C10.

The cyano group quickly proved its effectiveness as a functional handle. Iodination of the primary alcohol in **151** proceeded without incident. Subsequent treatment of the resultant ethyl iodide with activated zinc dust in a solvent mixture of THF:0.1 M acetic acid (9:1) gave a clean transformation to the desired γ-lactone **154** in an excellent yield of 89%. The X-ray crystal structure (Scheme 30) confirmed the tricyclic structure having the desired relative stereochemistries at C1, C4, and C9 for the anislactones.

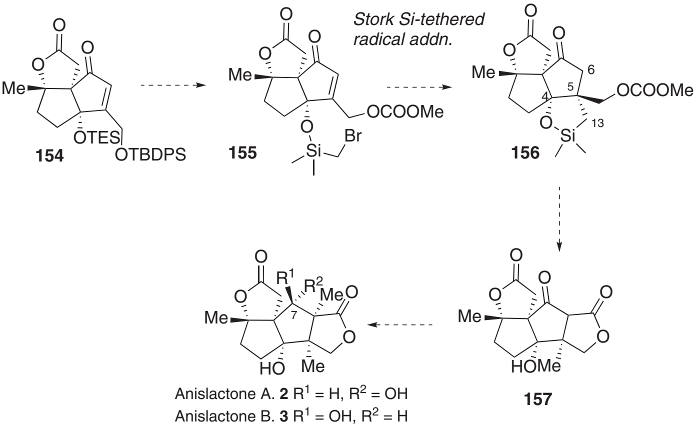
Tricycle **154** represented a key milestone in the second-generation approach—its synthesis involved 13 steps, using a novel cyanide tandem-aldol reaction to set up the challenging C1–C9–C4 stereotriad. Evolving this compound to the complete anislactone skeleton required installation of the D-ring



SCHEME 29 Cyanide tandem-aldol reaction: Feasibility studies and successful cyclization. Conditions: (a) Bu_4NCN, CH_2Cl_2, rt; (b) Et_2AlCN, CH_2Cl_2, rt (from **146**, 66%, dr = 1.1:1, from **147**, 57%); (c) Et_2AlCN, then $TiCl_4$, toluene, 0 °C, 77% combined, 72% **151**, 5% **152**, dr = 15:1.

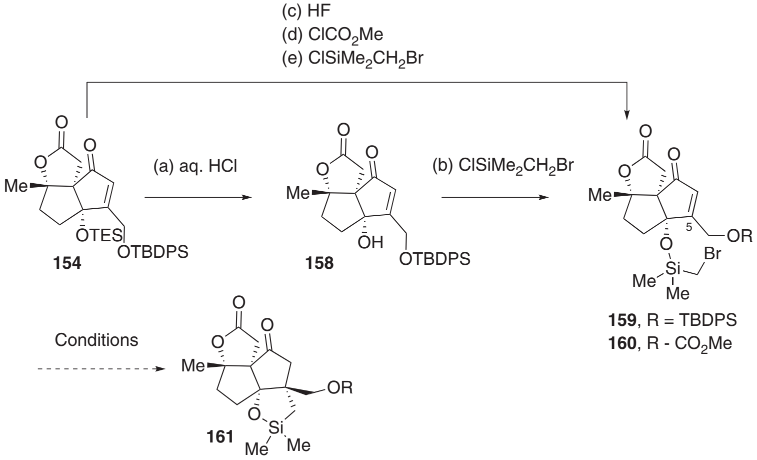


SCHEME 30 Synthesis of the tricyclic core of anislactones A/B. Conditions: (a) I_2, imidazole, PPh_3, CH_2Cl_2, rt, 94%; (b) zinc dust, THF:0.1 M AcOH (9:1), reflux, 89%.



SCHEME 31 Endgame strategy for anislactones A/B.

with attendant quaternary centers at C5 and C6, with methylation at C5 being the pivotal transformation. We planned to use a Stork silicon-tethered radical addition[40] for this task, as the steric hindrance around the β-substituted Michael acceptor favored an intramolecular strategy (Scheme 31). We would functionalize the C4 alcohol with a bromomethylsilyl group, a precursor to intramolecular radical conjugate addition. Successful reaction would afford the silacycle **156**, which could be cleaved by fluoride to yield the quaternary methyl group at C5. Completion of the synthesis from this point was anticipated to be straightforward using well-precedented acylation and alkylation reactions at C6.



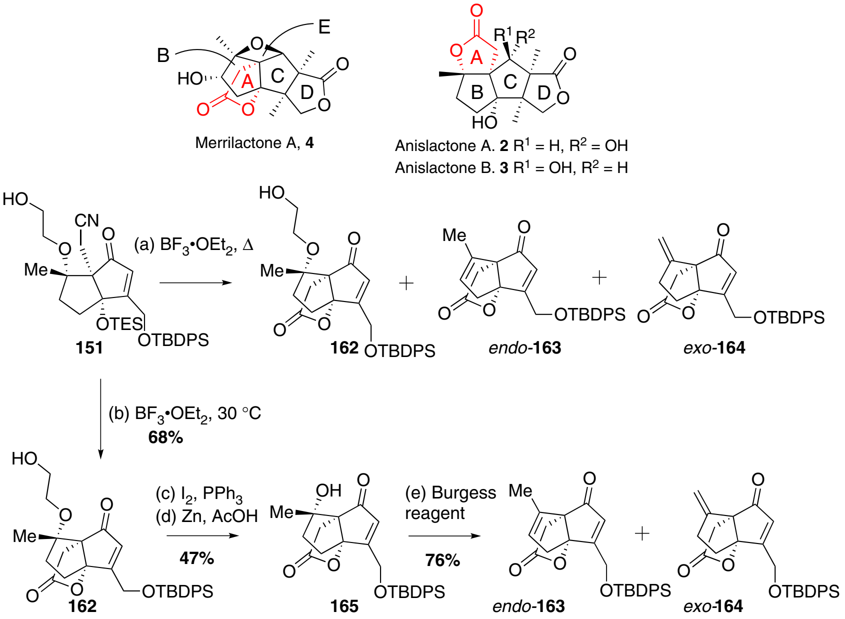
SCHEME 32 Attempted Stork silicon-tethered radical addition. Conditions: (a) HCl (0.05 M), THF, Δ, 71%; (b) $ClSiMe_2CH_2Br$, imidazole, DMAP, CH_2Cl_2, reflux, 95%; (c) 48% aq. HF: MeCN (1:5), 50 °C, 89%; (d) ClCOOMe, NEt_3, DMAP, THF, reflux, 82%; (e) $ClSiMe_2CH_2Br$, imidazole, DMAP, CH_2Cl_2, reflux, 82%.

Desilylation of **154** was complicated by the compound's being sensitive to base. Careful treatment with dilute acid could, however, selectively remove the tertiary TES group in good yield, enabling the functionalization of the tertiary alcohol with the requisite bromomethylsilyl group to give **159** (Scheme 32). We could also remove both silyl groups from **154** using HF in MeCN to give a diol, which was then functionalized with a carbonate and bromomethylsilyl group, respectively, to give the alternative substrate **160**.

Unfortunately, both of these substrates failed under numerous conditions for intramolecular radical addition. Stork's original conditions of AIBN and Bu_3SnH were ineffective in a variety of solvents, with product isolation complicated by the presence of tin residues dominating the small scale of the reactions. Catalytic Bu_3SnH protocols[41] failed to give any clean transformation, as did photochemical initiation of $Bu_3SnSnBu_3$. Finally, we investigated the formation of a Grignard from the alkyl bromide of the silicon tether; despite observing consumption of starting materials, no identifiable products could be isolated. We then turned to an intermolecular strategy, whereby a methylmetal reagent would be expected to add to the lower *exo* face of the AB-ring system in molecules such as **158**. Furthermore, the directing effect of neighboring alcohols is a well-described phenomenon in conjugate addition chemistry.[42] In the event, this strategy was likewise unsuccessful with a variety of lithium-, magnesium-, copper-, aluminum-, and zinc-based methyl reagents failing to react, even under vigorous conditions of heating or Lewis acid promotion.

4.3 Accessing the Merrilactone A Skeleton from the Tandem Cyanide Addition/Aldol Reaction

The failure of the conjugate addition approach was disappointing, with the C-ring enone functionality proving too sterically hindered and unreactive. We remained optimistic, however, that the cyanide tandem-aldol reaction could provide the platform for an efficient synthesis. To increase our chances of capitalizing on this reaction, we developed a short sequence of functional group interconversion that would give us the option of directing the tandem-aldol adducts toward the merrilactone structure. Merrilactone A differs from the anislactone A structure with respect to the linkage of the A-ring lactone and the presence of the oxetane E-ring (Scheme 33). A selective TES deprotection would enable A-ring lactonization, and elimination of the hydroxyethyl group would lead to the B-ring alkene **163**, a precursor for oxetane synthesis. We were able to observe the first of these transformations by treating the TES ether **151** with excess $BF_3 \cdot Et_2O$ in refluxing CH_2Cl_2. This gave low yields of the tricycle **162**, along with the formation of small amounts of the *exo*- and *endo*-alkene products **163** and **164**.

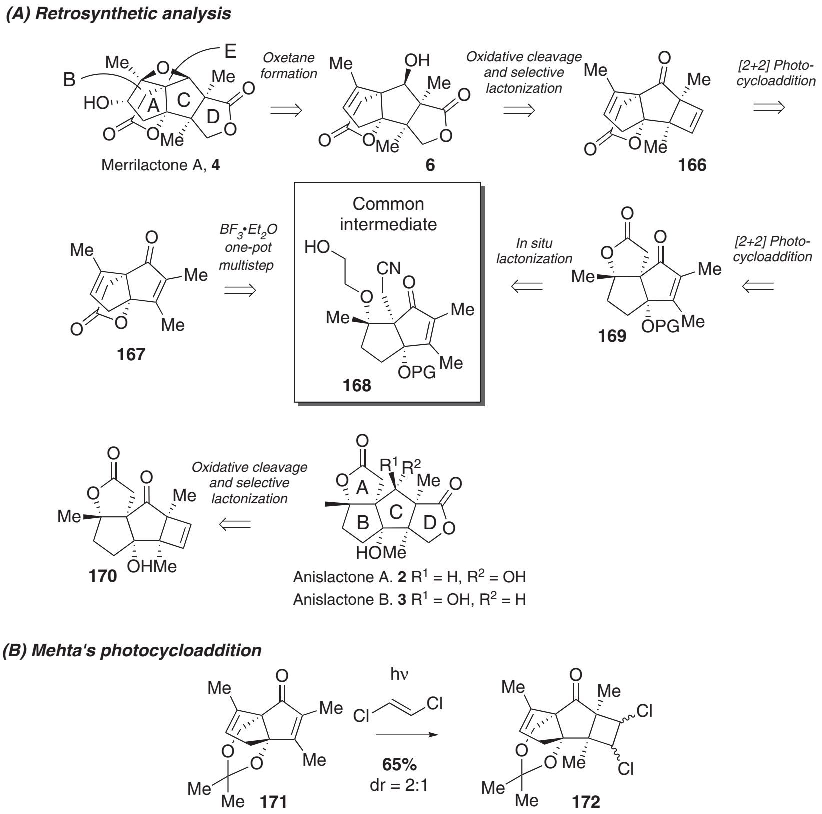


SCHEME 33 Accession of the merrilactone A skeleton from cyanide tandem-aldol product **151**. Conditions: (a) $BF_3 \cdot Et_2O$, CH_2Cl_2, reflux, 13% **162**, 7% *endo*-**163** and *exo*-**164** (1:0.6), 7% recovered **151**; (b) $BF_3 \cdot Et_2O$, CH_2Cl_2, 30 °C, 68%; (c) I_2, PPh_3, imidazole, CH_2Cl_2, rt, 73%; (d) Zn dust, THF:0.1 M AcOH (9:1), reflux, 65% yield; (e) Burgess reagent, CH_2Cl_2, reflux, *endo*-**163** and *exo*-**164**, 76%, 1:1.2 mixture of regioisomers.

Observation of the eliminated product **163** was an exciting result, as it suggested the possibility of a multistep (selective TES deprotection, cyclization and imidate hydrolysis, selective elimination of ethane diol), one-pot transformation of **151** into a merrilactone A precursor. For the time being, however, we focused on optimizing the yield of **162**. Lowering the reaction temperature gave a 65% yield of the lactone, which was then iodinated, reduced to the tertiary alcohol **165**, and then treated with the Burgess reagent to give the merrilactone [3.3.3] system as a mixture of alkene isomers (**163** and **164**).

4.4 Late-Stage [2+2] Approach to Anislactone A

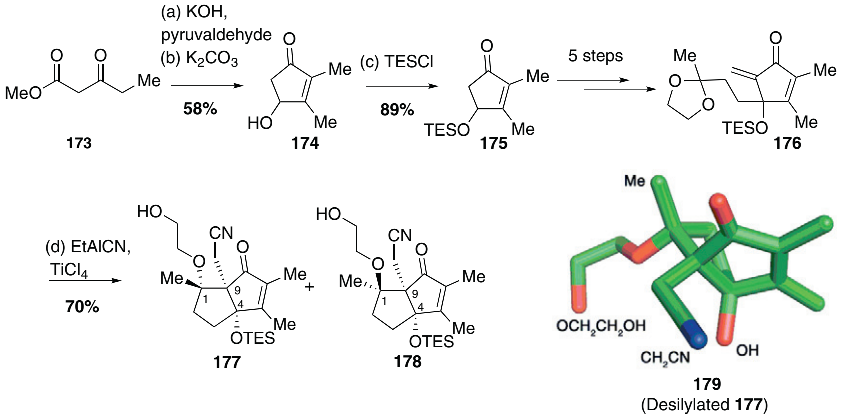
The availability of routes toward both anislactone and merrilactone structures was important in light of our eventual strategy for C-ring synthesis. We envisaged a [2+2] photocycloaddition of dichloroethylene onto a disubstituted enone as the key step to solve the D-ring problem (Scheme 34). Successful



SCHEME 34 (A) Retrosynthetic analysis for the regiodivergent approach to merrilactone A and anislactones A and B. (B) Mehta's photocycloaddition.

synthesis of the cyanide tandem-aldol product **168**, containing the dimethyl-substituted enone, would enable a regiodivergent approach to both natural products, via the functionalization sequences already established. Late-stage [2+2] cycloaddition raises a stereocontrol issue with respect to the facial selectivity of dichloroethylene addition to **168**, something not relevant in the early stage photocycloaddition we used in our first-generation synthesis. Metha's merrilactone A synthesis was instructive in this regard, as it featured dichloroethylene [2+2] addition to a more advanced, tricyclic intermediate.[10] He demonstrated that enone **171** could undergo photocycloaddition with dichloroethylene, but with only moderate selectivity in favor of addition to the desired β-face of the [4.3.3] enone system. Stereodifferentiation of the two B-ring faces is evidently challenging; having two different architectures (**167** and **169**) available for photocycloaddition would enhance our prospects of success.

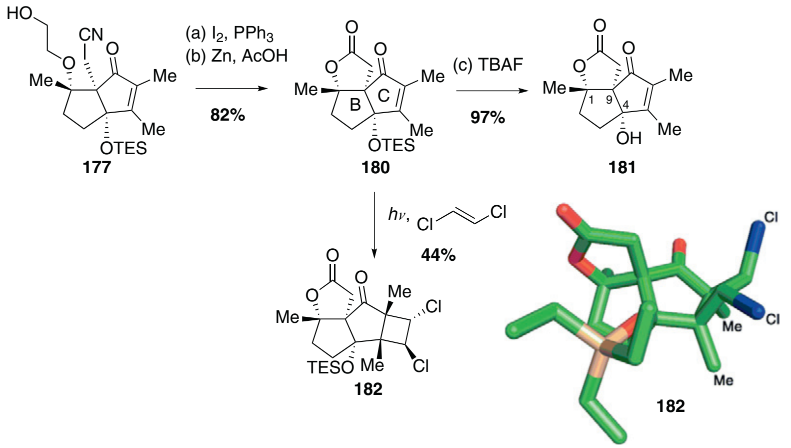
The first task was to access a suitably methylated cyclopentenone starting material from which to build the cyanide tandem-aldol substrate. Fortunately, dimethylcyclopentenone **174** is a literature compound that could be prepared via a straightforward two-step synthesis from the simple ketoester **173** (Scheme 35).[43] From this point, we synthesized enone **176** using chemistry that by now was well established in our group, taking five steps, all of which proceeded in good to excellent yield. Pleasingly, the cyanide tandem aldol proved indifferent to the alternative C-ring functionality and proceeded as before to give **177** and **178** as a separable 7:1 mixture of diastereomers in 70% combined yield. The configuration of the major diastereoisomer was confirmed on the desilylated derivative **179**, having the expected *cis*-geometry between C1 and C10.



SCHEME 35 Synthesis and cyano-addition-cyclization of substrate **176**. Conditions: (a) KOH, H_2O, then CO_2, 4 °C to rt, then pyruvaldehyde 58%; (b) K_2CO_3, MeOH, 0 °C to rt, 72%; (c) TESCl, NEt_3, DMAP, rt, 89%; (d) Et_2AlCN, then $TiCl_4$, toluene, 0 °C, 70% combined, 62% **177**, 8% **178**, dr = 7:1.

With the key cyano-aldol cyclization reaction now established, we first prepared a photocycloaddition substrate in the anislactone A series (Scheme 36). Iodination and treatment of the resultant ethyl iodide with zinc led to de-ethylation and *in situ* lactonization as before, affording tricycle **180** in high yield. We noted that TES removal was easier than for the previous series of compounds, with simple treatment with TBAF affording a clean transformation to alcohol **181**. However, we elected to retain the TES group in the substrate for photocycloaddition for its presumed steric shielding of the lower face of the enone.

As might be expected, [2+2] photocycloaddition of **180** proved a far tougher reaction to develop than the analogous transformation of dimethylmaleic anhydride used in the first-generation synthesis. Initial attempts using pyrex immersion well reactors and a medium-pressure mercury vapor lamp were unproductive under a range of solvents and dichloroethylene stoichiometries. The recovery of starting material in most cases indicated an issue with accessing the triplet state of the enone, usually addressed through the use of sensitizers or a change of irradiation wavelength. The latter provided the breakthrough, with immediate success coming from the use of a Rayonet photochemical reactor equipped with 254-nm bulbs (6 × 10 W) and a quartz filter. After 4 h of irradiation in cyclohexane, we successfully obtained tetracyclic **182** in a fair 42% yield, purified with difficulty from a rather dirty reaction mixture. Using neat *trans*-dichloroethylene at a substrate concentration of 0.07 mM significantly reduced the amount of reaction by-products, furnishing the product cyclobutane as a clean, single diastereomer in a reasonable 44% yield. Compound **182** was a solid and, in common with several compounds

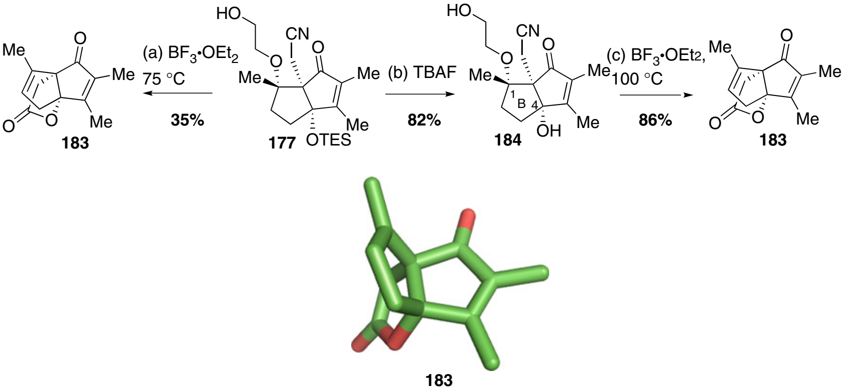


SCHEME 36 Photocycloaddition approach to anislactone. Conditions: (a) I_2, PPh_3, imidazole, CH_2Cl_2, rt, 94%; (b) Zn dust, THF:0.1 M AcOH (79:1), reflux, 87%; (c) TBAF, THF, rt, 97%; (d) *hv* (quartz), dichloroethylene (neat), 44%.

in this second-generation approach, yielded good crystals for X-ray analysis. Unfortunately, the X-ray bore bad tidings as it showed unequivocally that the dichloroethylene had added to the same face as the OTES group and A-ring lactone to give the unwanted stereoisomer. The OTES group can be seen to impart little if any steric shielding to the lower α-face, the course of the reaction being controlled by the slightly cupped BC bicycle geometry.

4.5 Late-Stage [2+2] Approach to Merrilactone A

As the anislactone architecture appeared unsuitable to the [2+2] C-ring approach, we turned our attention to a merrilactone A precursor. We anticipated that the $BF_3{\cdot}Et_2O$ multistep reaction protocol developed on cyanide tandem-aldol product **151** would be more effective for **177**, as it lacks the TBDPS group that was previously shown to be labile at elevated temperatures in the presence of $BF_3{\cdot}Et_2O$ (cf. Scheme 33). This proved to be the case, as treatment of **177** with $BF_3{\cdot}Et_2O$ in toluene at 75 °C furnished the desired *endo*-alkene tricycle **183** in 35% yield as a single double-bond regioisomer, a significant step forward (Scheme 37). It eventually proved most efficient to desilylate in a separate step (82% yield) and then treat the alcohol **184** with $BF_3{\cdot}Et_2O$ at 100 °C, followed by an aqueous quench, affording a very good 86% yield of the oxa-triquinane structure **183** (characterized by X-ray). This treatment effected four transformations in one pot—cyclization of the C4 alcohol to form an imidate, elimination of the ethylene glycol moiety, equilibration of the resultant alkene into the B-ring, and hydrolysis of the imidate into the final lactone **183**. A corollary to this approach is that the destruction of the C1

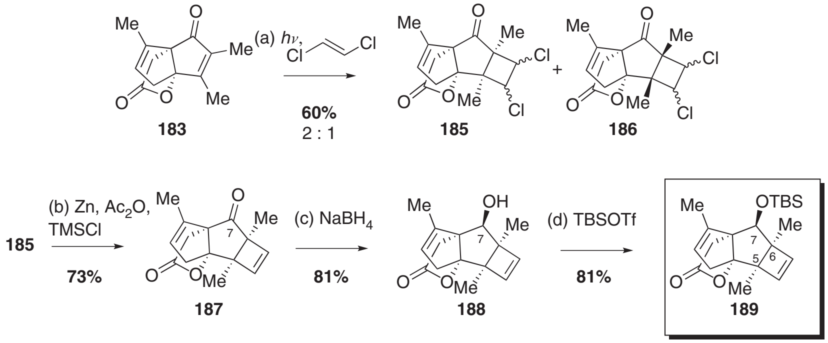


SCHEME 37 Lewis acid-assisted one-pot reaction for the synthesis of the tricyclic ABC core of merrilactone A. Conditions: (a) $BF_3{\cdot}Et_2O$, toluene, 75 °C, 35%; (b) TBAF, THF, rt, 82%; (c) $BF_3{\cdot}Et_2O$, toluene, 100 °C, 86%.

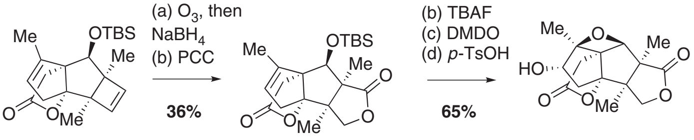
stereocenter makes the minor isomer **178** in the preceding aldol reaction a productive compound, and it could be pooled with **177** and taken forward.

[2+2] Photocycloaddition of **183** was then attempted under the previously optimized conditions (rayonet lamp, quartz filter, neat ClHC=CHCl). On our first attempt, we isolated cyclobutanes **185** and **186** as a 2:1 mixture of diastereomers in a reasonable combined yield of 60% (Scheme 38). Stereochemical assignment was not possible at this stage, as both cyclobutanes were oils and did not yield unequivocal NOESY NMR data. It did appear, however, that both isomers featured a single arrangement of chlorine atoms (unassigned). Both cycloadducts were then reductively dechlorinated with activated zinc, to give two separate cyclobutenes. At this point in our research, we were very short of advanced intermediates and decided to intercept a known intermediate in Mehta's synthesis to confirm the stereochemistry of photocycloaddition.

The major diastereoisomer from the photocycloaddition was reductively dechlorinated and then reduced to the secondary alcohol at C7 with $NaBH_4$, affording a single diastereomer in a high 81% yield. Protection of the newly formed secondary alcohol was then possible using TBSOTf, the steric congestion dictating a reaction time of 5 days before the reaction was predominantly complete, furnishing TBS ether **189**. Naim Nazef established that this compound was identical to a late-stage intermediate in Mehta's synthesis, subjecting it to a thorough 1D- and 2D-NMR analysis, correlating its structure to the literature compound and confirming that the photocycloaddition was selective for the desired top face of enone **183**. Mehta prepared compound **189** in 20 steps and converted it into merrilactone A via the five-step sequence shown in Scheme 39. Our second-generation approach thus represents a formal synthesis of the natural product taking 15 synthetic steps to **189**, making 20 in total to access merrilactone A.[44]



SCHEME 38 Formal total synthesis of merrilactone A. Conditions: (a) neat *trans*-1,2-dichloroethylene, *hv* (254 nm, quartz), rt, 41% **185**, 19% **186**, dr = 2:1; (b) Zn dust, Ac_2O, TMSCl, toluene, 100 °C, 73%; (c) $NaBH_4$, MeOH, rt, 81%; (b) TBSOTf, NEt_3, CH_2Cl_2, 30 °C, 81%.



189 **190** Merrilactone A, **4**

SCHEME 39 Mehta's synthesis of merrilactone A from known intermediate **189**. Conditions: (a) (i) O_3, MeOH, 78 °C; (ii) $NaBH_4$, MeOH, 78 °C, 45%; (b) PCC, CH_2Cl_2, 80%; (c) TBAF, AcOH, THF, 85%; (d) DMDO, 95%: (i) *p*-TsOH, CH_2Cl_2, 80%.

5 CONCLUSIONS

The second-generation approach was built around novel tandem-aldol reactions as the key step of the synthesis, chemistry that proved to be a very productive and rewarding area of study. The reactions were reliably clean and high yielding, forming two rings and setting three contiguous, fully substituted, stereocenters with good to excellent levels of stereocontrol. The cyanide variant, in particular, was perfectly suited to building the tricyclic ABC-rings of the anislactone skeleton and offers exciting possibilities for complex molecule synthesis in general. The synthesis as a whole also benefited from knowledge accrued in our earlier work with respect to functional group and protecting group chemistry, with few problems encountered in these areas.

Elaboration of the two quaternary centers at the C–D-ring fusion at a late stage proved a major tactical challenge, requiring several failed approaches before the highly hindered system could be successfully synthesized. The failure of the Stork silicon-tethered radical addition, in particular, was a significant setback as it dictated substantial alterations to our strategy at a late stage in proceedings. While the [2+2] photocycloaddition overcame this obstacle, stereocontrol was a modest 2:1 in favor of the desired isomer. The oxa-triquinane [3.3.3] structure **183** was unable to provide strong stereodifferentiation between α- and β-faces of the B-ring enone, making photocycloaddition only weakly selective. This impacted the overall efficiency of the route; while representing one of the shortest approaches to merrilactone A, at 20 steps, it is less efficient than both Danishefsky's (20 steps, 11% overall yield) and Frontier's (18 steps, 19% overall yield) syntheses. Nonetheless, the power of the cyanide tandem-aldol reaction as a strategy for stereocontrolled carbocyclization is clear, and we hope to develop this reaction further in other complex molecule settings.

ACKNOWLEDGMENTS

We thank all of the coworkers in the Greaney group who worked on the merrilactone A and anislactone A projects, whose contributions have been mentioned by name throughout the chapter. The work was supported by the University of Edinburgh, the EPSRC, and the Government of the Basque Country (Ph.D. fellowship to Jone Iriondo).

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Chapter 5

Symmetry-Driven Total Synthesis of Merrilactone A and Resolvin E2

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Chapter Outline

1 INTRODUCTION

Complex natural products often contain intrinsic symmetric elements within their structures, such as *meso* or C_2-symmetric substructures. Utilization of these symmetrical properties in the target natural products generally minimizes the overall number of steps for their total syntheses.[1] For instance, one could start from a small *meso* or C_2-symmetric compound, the core structure, and transform the two functional groups simultaneously by pairwise functionalizations, which significantly reduce synthetic manipulations en route to the more functionalized

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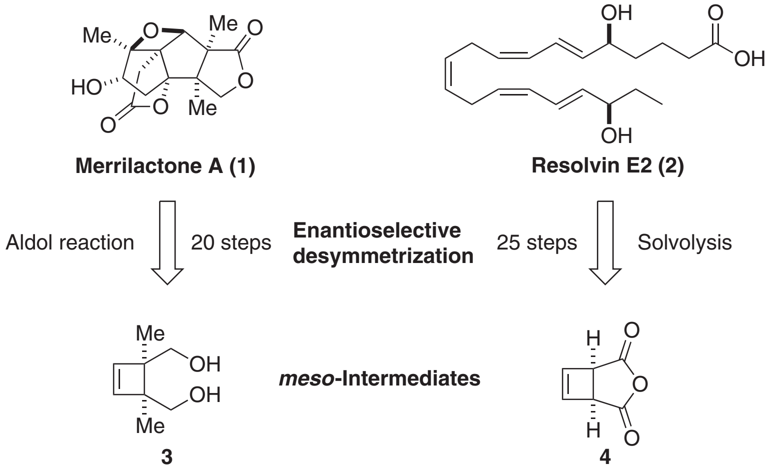


SCHEME 1 Symmetry-driven total synthesis of merrilactone A and resolvin E2.

symmetric intermediates. As most of the target natural products possess dissimilar structures, an effective method for desymmetrization of the intermediates is required for executing the symmetry-driven synthesis. To synthesize the targets in an enantiomerically pure manner, enantioselective differentiation of the two functional groups is usually employed as a desymmetrization step for *meso* compounds, while a C_2-symmetric compound prepared in an enantioselective fashion is desymmetrized via simple mono-functionalization of the two groups.

In order to generalize the symmetry-driven strategy for asymmetric total syntheses of complex natural products, we have applied the strategy to both linear and multicyclic natural products. Namely, *meso* intermediates were retrosynthetically designed from the nonsymmetric substructures, and the enantioselective desymmetrization reactions were successfully utilized to generate the enantiopure intermediates. In this account, we report in detail the enantioselective total syntheses of both enantiomers of pentacyclic merrilactone A (**1**)[2] from *meso*-**3** in a total of 20 steps and linear resolvin E2 (**2**)[3] from *meso*-**4** in a total of 25 steps (Scheme 1). While the enantio- and diastereoselective transannular aldol reaction was developed as the novel desymmetrization step of the *meso* intermediate in the synthesis of **1**, the two pseudo-enantiomeric diene structures of **2** were effectively constructed from *meso*-**4** through enantioselective solvolysis and then were coupled to construct the entire carboskeleton.[4]

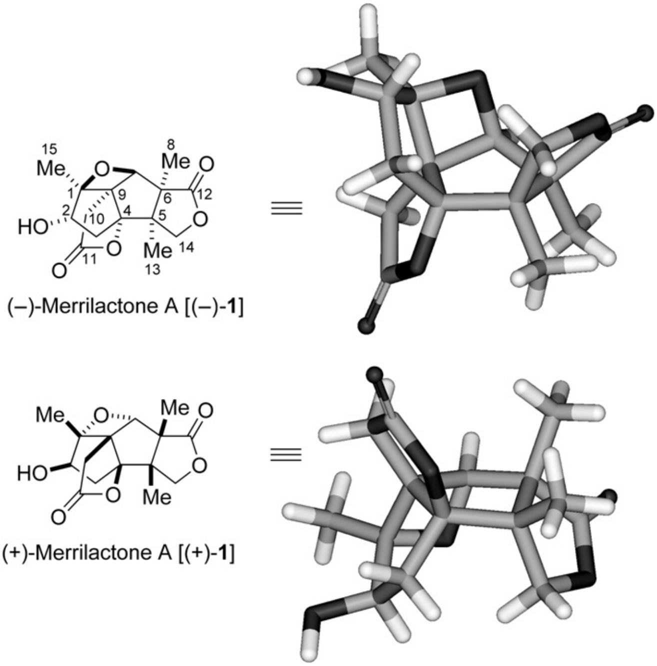
2 TOTAL SYNTHESIS OF MERRILACTONE A

2.1 Merrilactone A

Neurotrophic factors (NTFs) are endogenous proteins that regulate neuronal survival and neurite outgrowth,[5] and NTFs have served as potent therapeutic agents for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. However, their clinical use has been limited due to their relatively poor bioavailability and pharmacokinetics: NTF proteins are easily metabolized and unable to cross the blood–brain barrier. Thus, stable, nonpeptidal small molecules have been the subject of intense attention as NTF alternatives.[6]

Accordingly, Fukuyama and coworkers isolated and determined the structure of a series of natural products with NTF-like activities.[7] One of the most potent compounds, (−)-merrilactone A [(−)-**1**, Figure 1], promoted neurite outgrowth and exerted a neuroprotective effect at low concentrations (0.1–10 μM) in primary cultures of fetal rat cortical neurons.[8] Despite its promising activity, its mode of action in neuronal cells and the structural features necessary for activity have not been elucidated.

In addition to significant biological activity, **1** possesses an interesting architecture from a synthetic point of view. The highly oxygenated caged structure is composed of a central *cis*-bicyclo[3.3.0]octane carbon framework, two γ-lactones, a unique oxetane ring, and seven contiguous stereogenic carbon centers, three of which are quaternary carbons (C5, C6, C9). This challenging structure has been the target of intense synthetic investigations,[9] which led to the total synthesis of (±)-merrilactone A independently by our group in 2003,[2] and the



(−)-Merrilactone A [(−)-**1**]

(+)-Merrilactone A [(+)-**1**]

FIGURE 1 Structures of both enantiomers of merrilactone A.

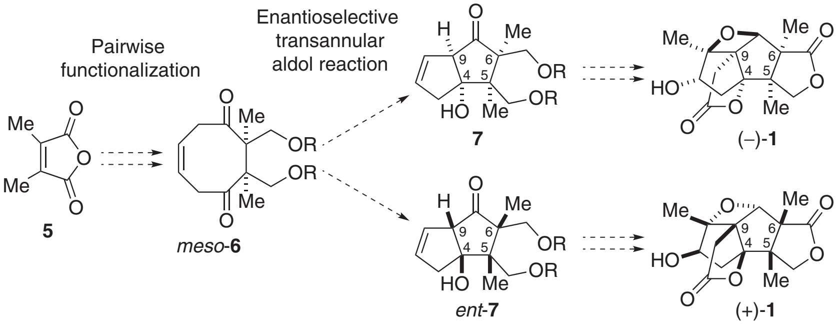
laboratories of Danishefsky in 2002,[10] Mehta in 2006,[11] Frontier in 2007,[12] Greaney in 2010,[13] and Zhai in 2012.[14] The asymmetric synthesis of **1** was accomplished by Danishefsky *et al.* in 2005.[15] We also achieved the asymmetric total syntheses of the natural enantiomer (−)-**1** in 2006[2] and unnatural (+)-**1** in 2007[2] and found equal neurite outgrowth activity for both natural and unnatural enantiomers. Here, we describe the details of our total synthesis of both enantiomers of merrilactone A on the basis of a pairwise functionalization and an enantioselective desymmetrization.[16]

2.2 Synthetic Plan

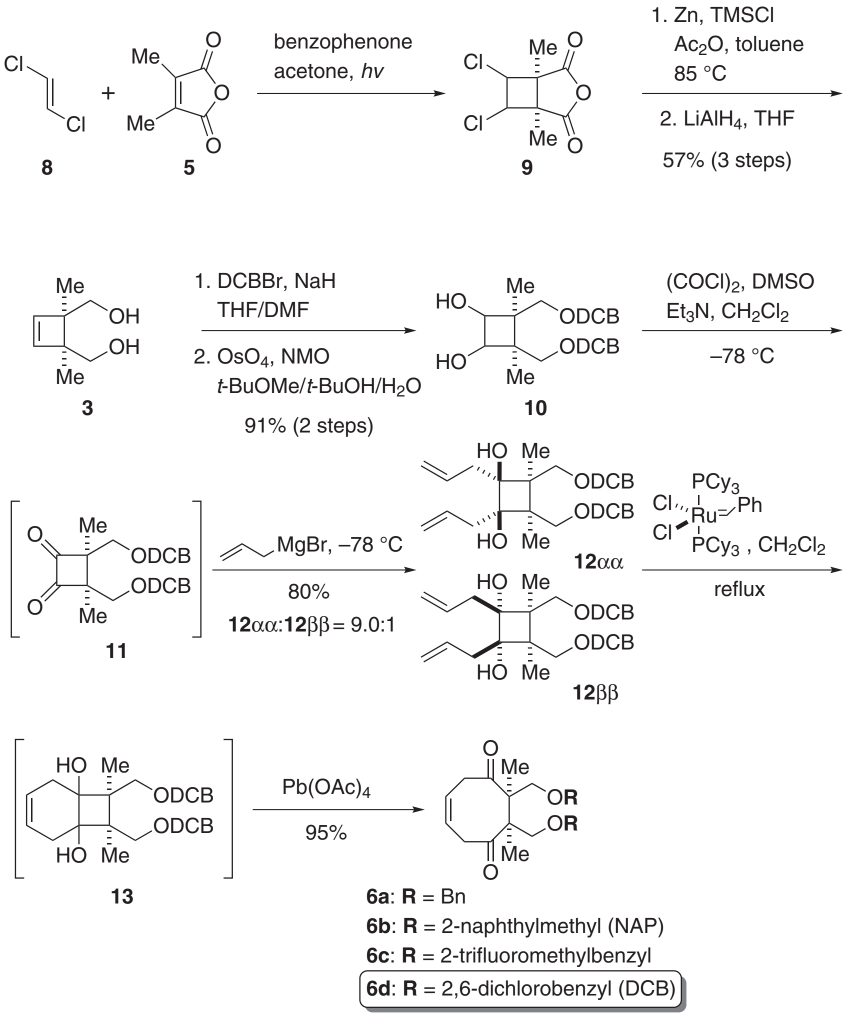
Merrilactone A (**1**) possesses a densely oxygenated carbon framework fused with two γ-lactones and an oxetane ring (Scheme 2). To develop an asymmetric synthetic route to both enantiomers of **1**, we exploited a hidden structural symmetry in the framework of **1**. The plan involved assembly of the pivotal *cis*-bicyclo[3.3.0]octane skeleton **7** or *ent*-**7** by an enantioselective transannular aldol reaction of the common *meso* eight-membered diketone **6**.[17,18] Installation of the absolute stereochemistry of four centers (C4, C5, C6, C9) from an achiral material was considered the most prominent, yet challenging, feature of this reaction.[19] By taking advantage of its symmetry, an efficient synthesis of *meso*-**6** could be attained by applying pairwise functionalization to the *meso*-intermediates starting with **5**. This strategy allows readily available **7** and *ent*-**7** to serve as platform structures for subsequent functional group transformations necessary for the chemical construction of not only natural merrilactone A (−)-**1** but also its unnatural enantiomer *ent*-(+)-**1**, respectively.

2.3 Synthesis of Eight-Membered *meso* Diketone

As shown in Scheme 3, synthesis of **6** started with a [2+2] photocycloaddition between 2,3-dimethylmaleic anhydride **5**[20] and *trans*-dichloroethylene



SCHEME 2 Synthetic plan of both enantiomers of merrilactone A.

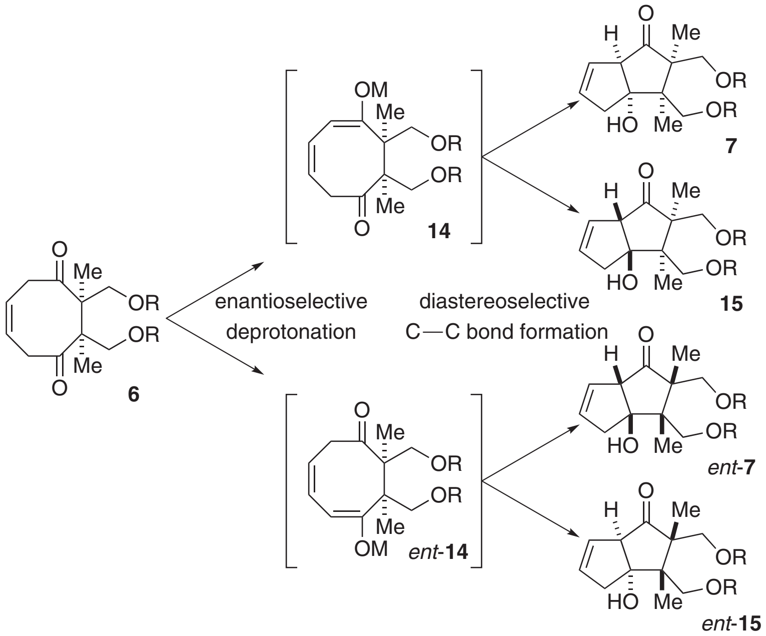


SCHEME 3 Synthesis of *meso* eight-membered diketone.

8 to install the two contiguous quaternary stereocenters (C5, C6).[21] Reductive dechlorination of **9** with Zn/AcOH, followed by $LiAlH_4$ reduction of the anhydride, provided *meso*-diol **3**. After protection of the primary alcohols of **3** as their dichlorobenzyl (DCB) ethers, dihydroxylation of the olefin afforded **10**. Although Swern oxidation of the obtained diol **10** generated diketone **11**, the aqueous workup of **11** readily resulted in its hydrated form, which turned out to be unreactive toward various nucleophilic reagents. Thus, allyl magnesium bromide was added directly to the Swern oxidation mixture containing **11**,[22] leading to **12αα** and **12ββ** as major isomers in high yield. The *cis*-arrangement of allyl groups effectively facilitated the ring-closing metathesis reaction[23] of **12** to produce the bicyclo[4.2.0]octyl system **13**, which was treated with $Pb(OAc)_4$ *in situ*[24] to yield the *meso* eight-membered diketone **6d**. Therefore, **6d** was synthesized in only seven steps through pairwise symmetrical functionalization. To evaluate the effect of the protective group on the outcome of the next aldol reaction, various other *meso* eight-membered diketones **6a–c** were prepared in a similar manner.

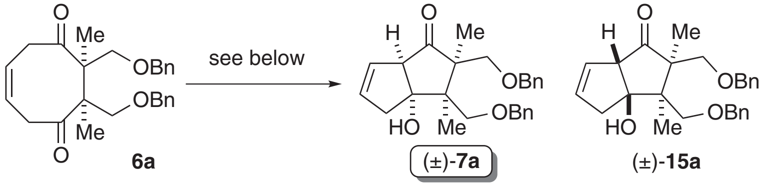
2.4 Desymmetrization by the Enantioselective Transannular Aldol Reaction

As shown in Scheme 4, the crucial asymmetric aldol reaction of **6** contained two distinct steps: enantioselective deprotonation and diastereoselective C—C bond formation, both of which need to be highly selective for obtaining **7** or *ent*-**7** out of the four possible *cis*-fused isomers.[25] First, we evaluated the outcome of the C—C bond formation (the second step) by varying two elements: the reaction conditions (Table 1) and the protective group of the primary alcohols (Table 2). As shown in Table 1, treatment of **6a** with LiN(TMS)$_2$ in THF at −100 °C led to the *cis*-fused products (±)-**7a** and (±)-**15a**, favoring the desired isomer (±)-**7a** (entry 1). The kinetic formation of (±)-**7a** under these conditions was reinforced by the absence of isomerization of **7a** to **15a** upon retreatment with LiN(TMS)$_2$. Interestingly, both



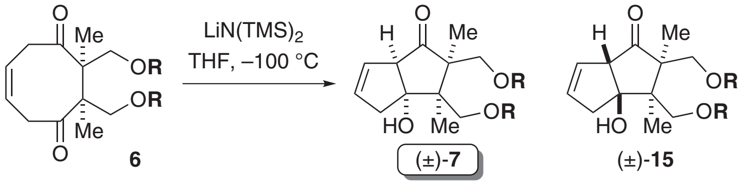
SCHEME 4 Two distinct steps in enantioselective transannular aldol reaction.

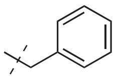
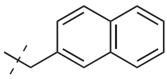
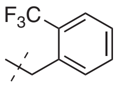
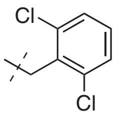
TABLE 1 Diastereoselective C—C Bond Formation: Effect of Base



Entry	Reagents and conditions	(±)-7a:(±)-15a	Combined yield
1	$LiN(TMS)_2$, THF, −100 °C	3.1:1	85%
2	$MgBrN(TMS)_2$, Et_2O, rt	1:3.0	81%
3	$LiN(TMS)_2/Et_3N$, toluene, −78 °C	1:5.1	79%
4	DBU, CH_2Cl_2, 0 °C	1.1:1	63%
5	LiNMe(*p*-ClPh), THF, −100 °C	11.2:1	89%

TABLE 2 Diastereoselective C—C Bond Formation: Protecting Group Effect



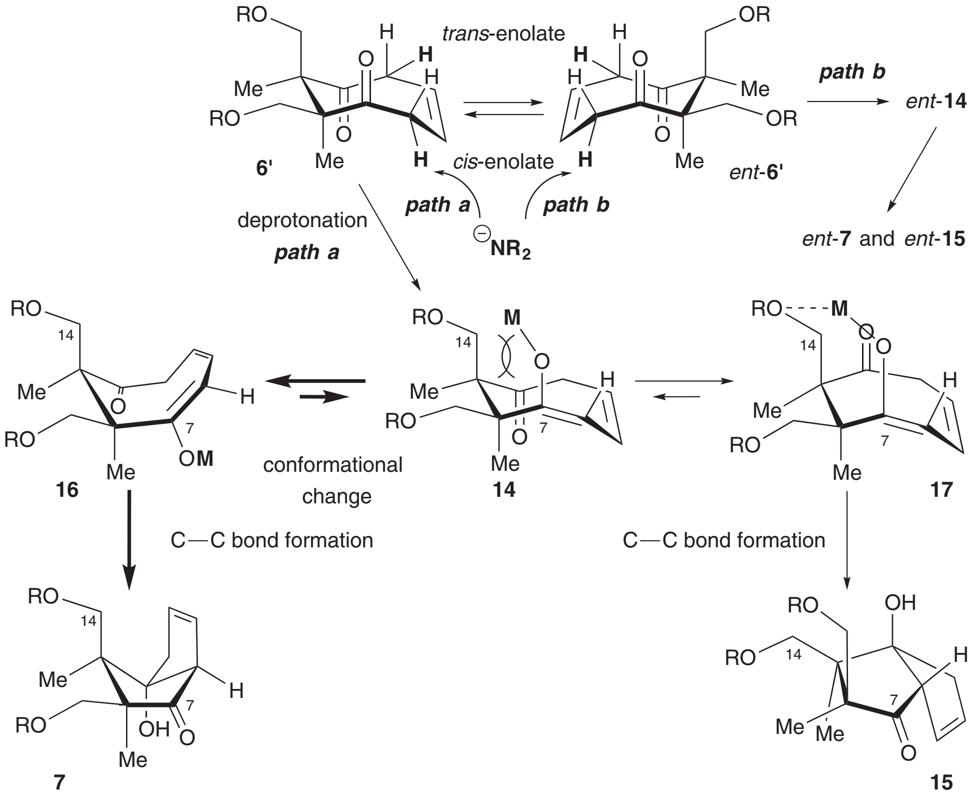
Entry	R		(±)-7:(±)-15	Combined yield
1		**6a**	3.1:1	85%
2		**6b**	3.2:1	92%
3		**6c**	3.9:1	93%
4		**6d**	6.0:1	88%

$MgBrN(TMS)_2$ (entry 2) and $LiN(TMS)_2/Et_3N$[26] in toluene (entry 3) induced the opposite selectivity, favoring the undesirable diastereomer (±)-**15a**, whereas DBU did not exhibit a preference for either product (entry 4). As the lithium amide in THF (entry 1) gave the most promising result, a number of other lithium bases were applied to **6a**. After several experiments, lithium 4-chloro-*N*-methylanilide[27] was found to provide the best results [(±)-**7a**:(±)-**15a** = 11.2:1, entry 5].

As shown in Table 2, the yield of (±)-**7** was also improved by increasing the steric bulk of the protective group (R). Whereas replacement of the benzyl group with a 2-naphthyl group (NAP) (entry 2) gave a result comparable to that shown in entry 1 under the same conditions [$LiN(TMS)_2$, THF], **6c** bearing a 2-trifluoromethylbenzyl group showed higher selectivity for (±)-**7c** (entry 3). The preference for (±)-**7** was improved further when substrates with doubly *ortho*-substituted benzyl groups, 2,6-dichlorobenzyl (DCB, entry 4), were subjected to the same reaction conditions. In this way, we successfully developed highly diastereoselective C—C bond formation by controlling the reaction conditions and protective groups.

A possible mechanism of the present transannular reaction can be formulated by examining the conformations of **6** and subsequent enolate intermediates. Based on the spectroscopic data,[28] it is very likely that the eight-membered ring **6** exists as an equimolar mixture of the two enantiomeric conformers **6**' and *ent*-**6**' (Scheme 5). As *cis*-enolate formation from the eight-membered ring is energetically more favorable than *trans*-enolate formation, only one of the two protons orthogonal to the C═O bonds (indicated in bold face) is considered to be abstracted by the base ($^{-}NR_2$). Consequently, conformers **6**' and *ent*-**6**' would lead to **7**/**15** and *ent*-**7**/*ent*-**15** via **14** and *ent*-**14**, respectively (only the former path is shown in Scheme 5). After enolate formation from **6**', the strong 1,3-diaxial-like steric interaction between the bulky protected oxymethylene and C7—O bond in **14** would enforce a conformational flip of the olefin to form **16**, from which the enolate reacts with the ketone to generate the desired *cis*-fused 5-5 ring system **7**. The proposed mechanism agrees well with the observation that a bulkier protecting group is beneficial in obtaining **7** (Table 2). However, metal chelation could fix the orientation between C7—O and C14—O in intermediate **17**, which leads to the undesired diastereomer **15**. In fact, **15** was obtained selectively in entries 2 and 3 (Table 1), where Mg^{2+} and Li^{+}, respectively, in a nonpolar solvent would stabilize the seven-membered chelate in **17**, unlike Li^{+} in THF. Hence, the diastereoselectivity of the C—C bond formation appears to be controlled by a balance between steric interaction and chelation of C7—OM and C14—oxymethylene.

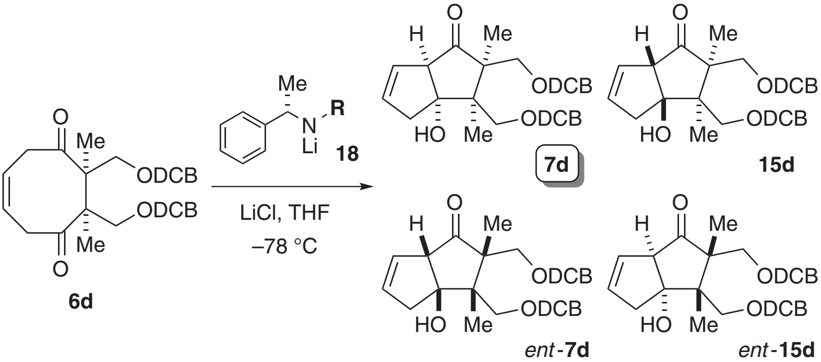
With the establishment of an efficient procedure for the synthesis of (±)-**7** using bulky protective groups and a lithium amide as controlling elements, efforts turned toward the development of a procedure for synthesis of either **7** or *ent*-**7** via an enantioselective deprotonation[29] (**path a** or **path b** in

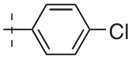
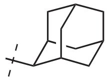
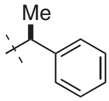
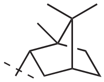
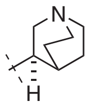


SCHEME 5 Mechanistic consideration of aldol reaction.

Scheme 5). We envisaged that a chiral lithium amide would differentiate **path a** and **path b** through selective recognition of the two enantiomeric conformers **6**’ and *ent*-**6**’, respectively. To realize the enantioselective transformation, DCB-protected diketone **6d** was treated with substituted lithium (*R*)-1-phenylethylamides **18a–g** with lithium chloride[30] in THF (Table 3). As expected, all entries showed a diastereoselectivity preference for **7d** + *ent*-**7d**

TABLE 3 Enantioselective Transannular Aldol Reaction



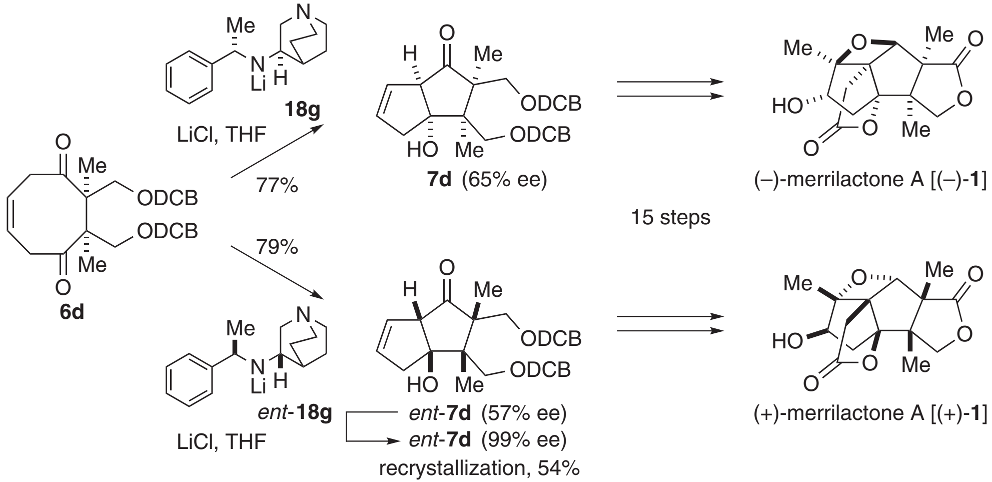
Entry	R		(7d + *ent*-7d):(15d + *ent*-15d)	7d:*ent*-7d	Combined yield
1		**18a**	19:1	1:2.4	87%
2	$\text{SiMe}_2t\text{-Bu}$	**18b**	15:1	1:1.3	73%
3		**18c**	6.0:1	1:1	100%
4		**18d**	7.0:1	1.9:1	88%
5		**18e**	8.1:1	2.2:1	94%
6		**18f**	3.0:1	2.7:1	94%
7		**18g**	6.0:1	4.7:1	90%

over **15d** + *ent*-**15d**. In contrast, the enantiomer ratio between **7d** and *ent*-**7d** was highly sensitive to the lithium amide structures. While enantioselectivity was not observed upon treatment of **6d** with **18b**[31] and **18c**[32] (entries 2 and 3), **18d**,[33] **18e**,[34] **18f**,[33] and **18g**[35] selectively generated **7d**[36] (entries 4–7), and **18a**[37] induced the opposite selectivity (entry 1). Most importantly, the enantiomer ratio obtained in the case of **18g** (**7d**:*ent*-**7d** = 4.7:1, entry 7) was practically sufficient for the asymmetric total synthesis of enantiopure merrilactone because of the crystalline nature of **7d**; one recrystallization afforded enantiopure **7d**. Thus, we established the novel enantioselective desymmetrization for the selective formation of both **7** and *ent*-**7** from *meso*-**6d** by the transannular aldol reaction with the chiral lithium amide **18g** and *ent*-**18g** (Scheme 6). Both **7** and *ent*-**7** served as intermediates of (−)- and (+)-merrilactone A, respectively, and the 15-step route to natural merrilactone A (**1**) is shown in Schemes 7 and 8.

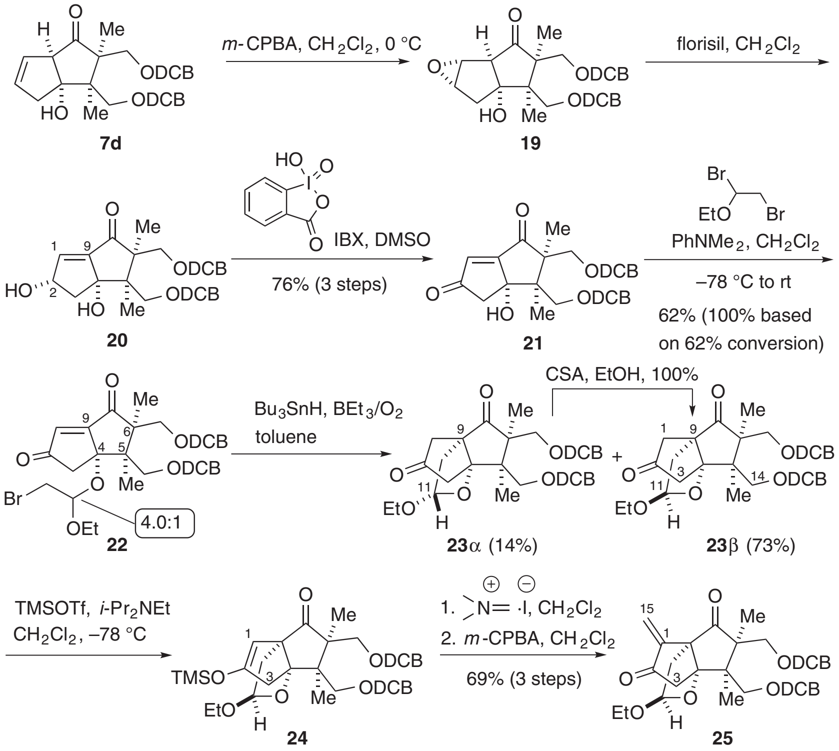
2.5 Total Synthesis of (−)-Merrilactone A

The carboskeleton of (−)-merrilactone A (**1**) was constructed from **7d** (Scheme 7). The C1–C9 olefin and C2–oxygen functionality were introduced in two steps: α-selective epoxidation of **7d** and subsequent florisil-mediated epoxide opening of **19**, to provide allylic alcohol **20**. To synthesize the entire carboskeleton of **1**, introduction of the C9–quaternary center and a C15–carbon was necessary. The former was particularly problematic, owing to the large steric hindrance of three proximal tetra-substituted carbon centers (C4, C5, C6). After attempting a number of unsuccessful reactions, we conducted intramolecular radical cyclization of α-bromoacetal **22**[38,39] because of its powerful yet mild nature. Thus, oxidation of allylic alcohol **20** was accomplished using IBX[40] to yield enedione **21**. α-Bromoacetal was then introduced to the hindered tertiary alcohol **21** using 1,2-dibromoethyl ethyl ether and *N*,*N*-dimethylaniline to provide **22**. Treatment of **22** with Bu_3SnH and BEt_3 in an atmosphere of air[41] at room temperature successfully led to 5-*exo* product **23α** and C11-epimer **23**β in 87% combined yield. When subjected to acidic conditions, **23α** was selectively isomerized to **23β**. NOE experiments suggested the three-dimensional structure of **23β**, with the C11-*O*-ethyl and C14-*O*-benzyl groups located in spatial proximity to the C3 carbon center. This arrangement of functional groups was beneficial for the next site-selective installation of C15 at C1. A combination of TMSOTf and *i*-Pr_2NEt enabled the regioselective enolization of ketone **23β** at the C1 position in the presence of the sterically shielded C3 methylene, leading to silyl enol ether **24** as a single isomer. Finally, exposure of **24** to Eschenmoser's salt and subsequent elimination of amine via its *N*-oxide furnished the carboskeleton **25**.[42]

Seven selective functional group transformations yielded the targeted (−)-**1** from **25** (Scheme 8). Ethyl acetal **25** was converted to lactone **26** by



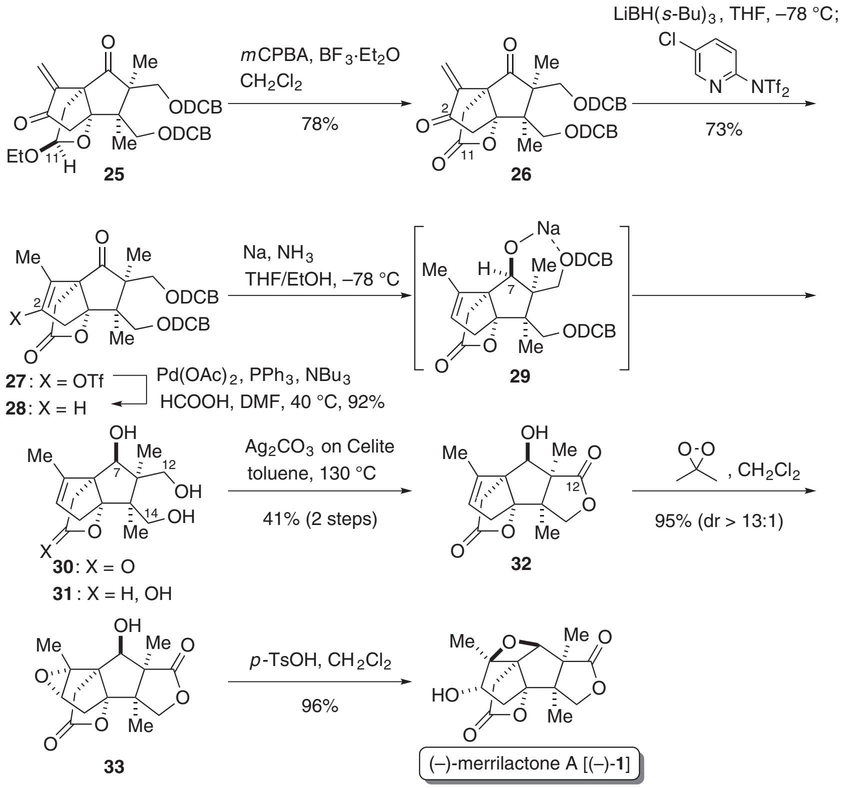
SCHEME 6 Enantioselective desymmetrization for total syntheses of both enantiomers of merrilactone A.



SCHEME 7 Synthesis of carboskeleton of merrilactone A.

the action of *m*CPBA in the presence of $BF_3{\cdot}Et_2O$.[43] Lithium enolate formation from enone **26** using LiBH(*s*-Bu)$_3$, followed by *in situ* triflation,[44,45] afforded enol triflate **27**, whose palladium-mediated hydrogenolysis proceeded smoothly to give trisubstituted olefin **28**.[46,47] Exposure of **28** to Na in NH_3[48] effected stereoselective reduction of the hindered C7-ketone to the β-alcohol, presumably via six-membered chelate **29**. The removal of both DCB groups gave rise to lactol **31** along with lactone **30**. This mixture was subjected to Fetizon oxidation[49] to produce the desired bis-γ-lactone **32** as the exclusive isomer via **30**. It appears that the reactivity toward oxidation of the pseudoequatorial C12 alcohol of **30** is greater than that toward the pseudoaxial C7 and C14 alcohols because of its more exposed nature (Scheme 9).[50] This C12-chemoselectivity was found to be sensitive to the substitution patterns. For instance, PDC oxidation of the TBS-protected **34** provided C14-lactone **35** preferentially over C12-lactone **36**, presumably due to the conformational change of the central five-membered ring induced by the C7-bulky TBS ether.

Lastly, epoxidation of **32** with dimethyldioxirane[51] selectively furnished **33**, which was subjected to acid-promoted oxetane formation to produce (−)-**1**.

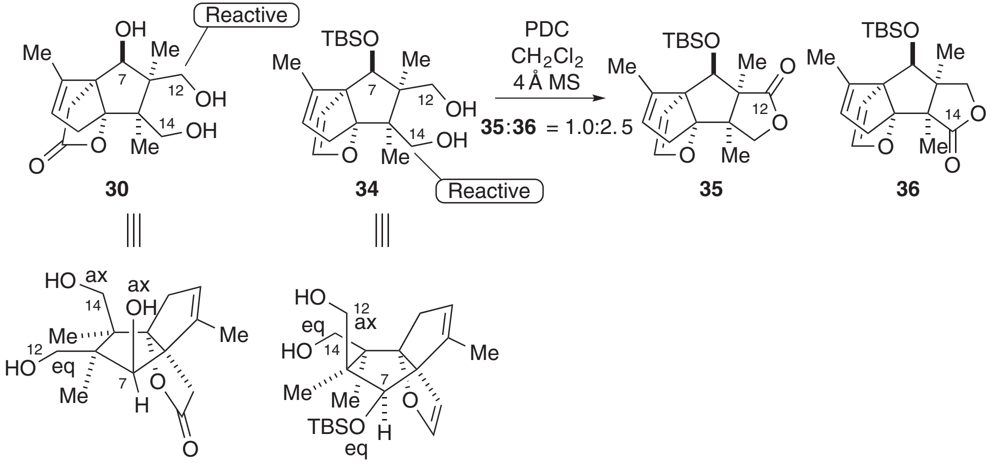


SCHEME 8 Total synthesis of (−)-merrilactone A.

The flexible asymmetric route described here also allowed practical access to unnatural enantiomer (+)-**1** from *ent*-**7d**.

2.6 Summary

A concise total synthesis of (−)- and (+)-merrilactone A (**1**) has been achieved based on a novel enantioselective desymmetrization strategy (1.3% overall yield, 23 steps from **5**). Key transformations in the total synthesis included: (i) seven-step pairwise symmetrical functionalization to synthesize **6d** by taking advantage of its *meso*-symmetry; (ii) a new enantioselective transannular aldol reaction of *meso*-**6d** to construct the bicyclo[3.3.0]octane core **7d**; (iii) radical cyclization to establish the sterically congested C9-quaternary carbon of **23β**; and (iv) highly selective substrate-controlled reactions to introduce three functional groups, the C15-methylene of **25**, C7-α-alcohol of **31**, and C12-γ-lactone of **32**.

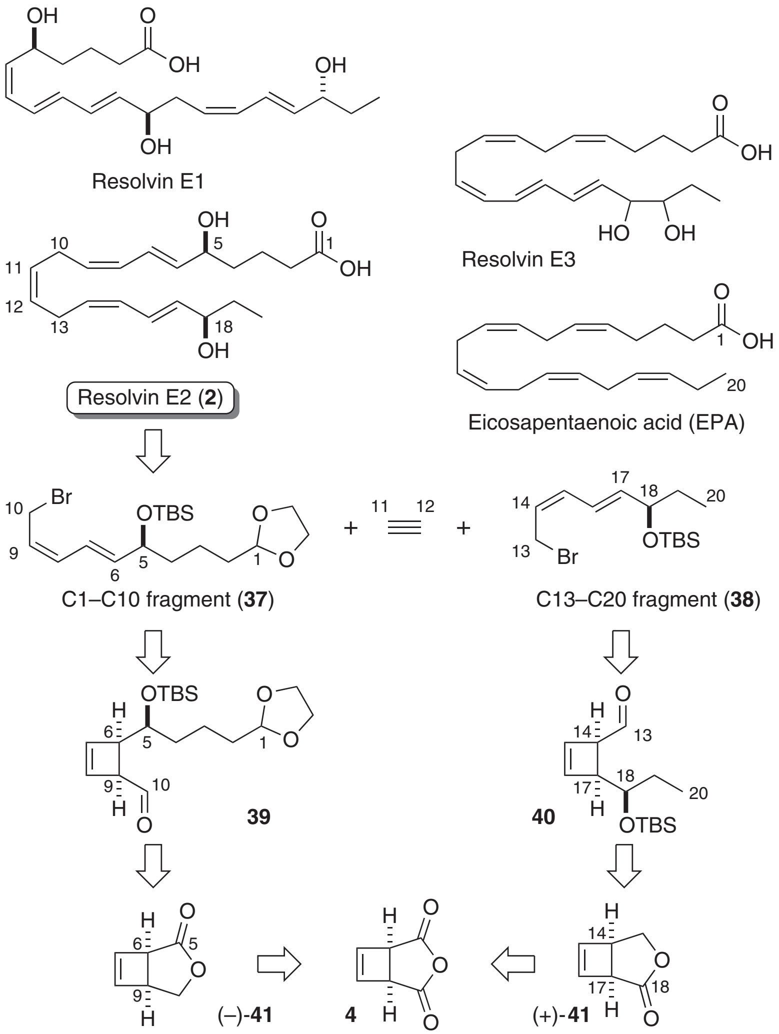


SCHEME 9 The explanation of regioselective oxidation.

3 TOTAL SYNTHESIS OF RESOLVIN E2

3.1 Resolvin E2

Resolvins are a new family of lipid mediators derived from omega-3 polyunsaturated fatty acids, namely, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are generated during the resolution phase of acute inflammation.[52] The resolvin E series (resolvin E1,[53] E2,[54] and E3,[55] Scheme 10) is biosynthesized from a common intermediate, 18-hydroxy eicosapentaenoic acid (18-HEPE), generated by cyclooxygenase (COX)-2-mediated conversion of



SCHEME 10 Structures of resolvins and EPA, and retrosynthesis of resolvin E2.

EPA, and has been shown to possess significant anti-inflammatory properties, thereby protecting organs from collateral damage. It has thus been hypothesized that these E series resolvins contribute to the beneficial actions that have been attributed to EPA in certain human diseases, particularly those in which inflammation is suspected as a key component in pathogenesis. Motivated by their potential for new therapeutic treatments of human disorders associated with aberrant inflammation, we launched the synthetic studies of resolvins as well as other lipid mediators.[56] In conjunction with our program for the symmetry-driven total synthesis of natural products, we designed and developed an efficient synthetic route to resolvin E2.[3,57]

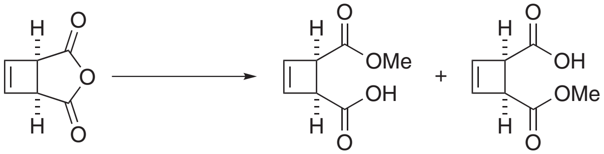
3.2 Synthetic Plan

We planned to simplify the synthetic route to resolvin E2 (**2**) by taking advantage of its two enantiomeric substructures at C5–C10 and C13–C18 (Scheme 10). Retrosynthetic disconnections at C10–C11 and C12–C13 provided a C11–C12 unit together with pseudo-enantiomeric fragments, **37** and **38**, both of which have the *E*,*Z*-conjugated olefin and allylic alcohol groups. Because of their structural similarity, **37** and **38** would be prepared from enantiomers of **41** by applying the same strategy. Specifically, the stereocenters at C5 of **37** and C18 of **38** would be generated by substrate-controlled stereoselective addition of the corresponding carbon nucleophiles, while the *E*,*Z*-olefins at C6 of **37** and C17 of **38** would be constructed using a torquoselective thermal electrocyclic ring-opening reaction[58] of cyclobutene aldehydes **39** and **40**, respectively.[59] Hence, the stereochemistry of the cyclobutane of (−)- or (+)-**41** was envisioned to be transferred to the stereochemistries of the hydroxy group at C5 or C18 and the diene at C6 or C17. A pair of optically active six-carbon units **41**[60] would be obtained from the known achiral *meso*-anhydride **4**[61] by enantioselective desymmetrization.

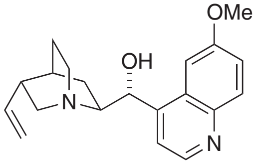
3.3 Syntheses of C1–C10 and C13–C20 Fragments

To synthesize both enantiomers of lactone **41**, the enantioselective methanolysis of *meso*-**4** to (+)- and (−)-methyl ester **42** was first explored (Table 4).[62] A stoichiometric amount of quinine **A** and quinidine **B** induced the highly enantioselective desymmetrization of *meso*-**4** to afford (+)- and (−)-**42**, respectively (entries 1 and 2). The catalytic enantioselective desymmetrization developed by Song was then utilized.[63,64] Namely, 1 mol% of the quinine derivative **C** and 10 equiv. of methanol were applied to **4** in Et_2O to generate (+)-**42** in highly enantioselective fashion (95% yield, 87% ee, entry 3). Interestingly, methanolysis of the same **4** using the quinidine derivative **D**, the pseudoenantiomer of **C**, indeed gave the enantiomeric (−)-**42**, albeit with lower enantioselectivity (64% ee, entry 4). Based on these results, we decided to synthesize (−)- and (+)-**41** from the same (+)-**42** obtained from the

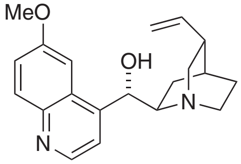
TABLE 4 Enantioselective Methanolysis



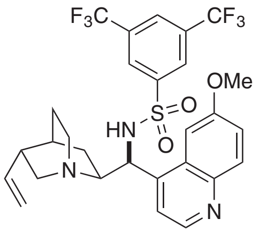
***meso*-4** (+)-**42** (−)-**42**



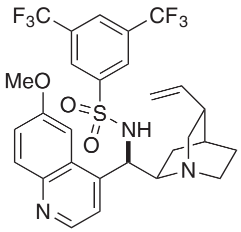
A (quinine)



B (quinidine)



C

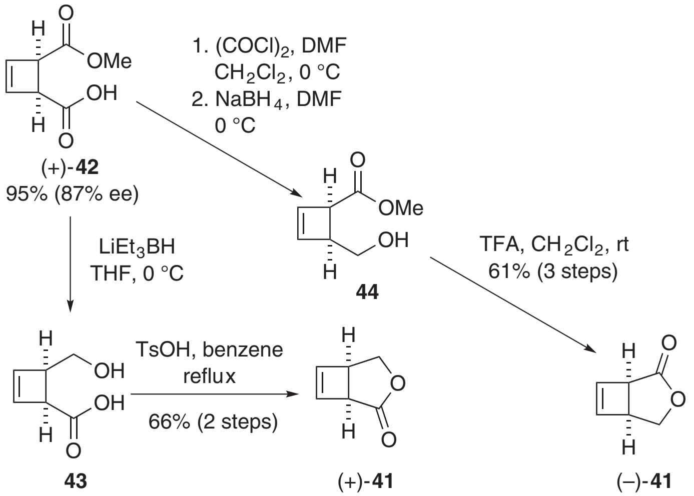


D

				Results	
Entry	**Amine (mol%)**	**MeOH**	**Solvent**	***Yield (product)***	***ee***
1	**A** (100 mol%)	3 equiv.	Toluene/CCl_4	99% ((+)-**42**)	89%
2	**B** (100 mol%)	3 equiv.	Toluene/CCl_4	99% ((−)-**42**)	92%
3	**C** (1 mol%)	10 equiv.	Et_2O	95% ((+)-**42**)	87%
4	**D** (1 mol%)	10 equiv.	Et_2O	100% ((−)-**42**)	64%

catalytic conditions in entry 3 using chemoselective reduction of either the carboxylic acid or the ester. Lactone (−)-**41** was prepared in three steps: conversion of the carboxylic acid of (+)-**42** into the acid chloride, followed by chemoselective $NaBH_4$ reduction,[65] and subsequent acid-mediated cyclization of methyl ester **44** (Scheme 11). The enantiomer (+)-**41** was in turn synthesized by $LiEt_3BH$ reduction[66] of the methyl ester of (+)-**42** and subsequent cyclization of carboxylic acid **43** under acidic conditions.

Synthesis of the C1–C10 fragment **37** started with reduction of (−)-**41** by DIBAL-H, followed by addition of Grignard reagent **46** in one pot,[67] resulting

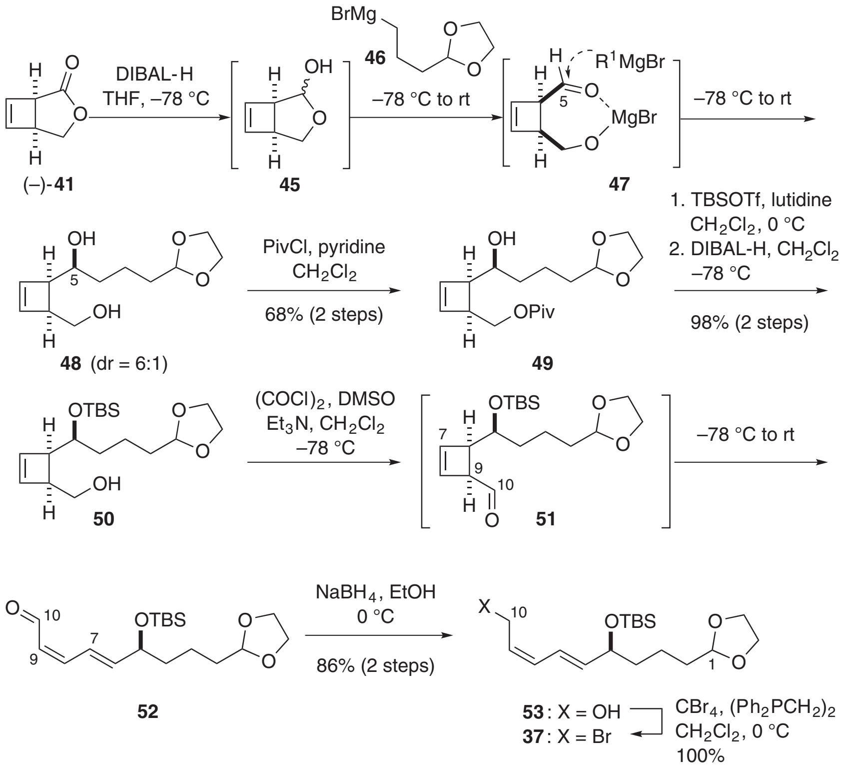


SCHEME 11 Synthesis of both enantiomers of **41**.

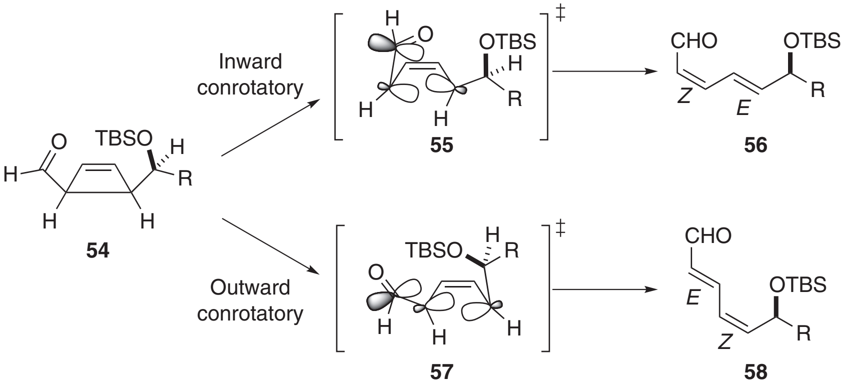
in stereoselective introduction of the C5-hydroxy group of **48** (dr = 6:1, Scheme 12). The high diastereoselectivity is attributable to chelation between the magnesium alkoxide and the aldehyde, and subsequent nucleophilic attack from the convex face of the 4/7-fused ring system **47**.[59] Next, 1,4-diol **48** was transformed to alcohol **50** by a protection/deprotection procedure: stepwise introduction of Piv and TBS to the primary and the secondary alcohols, respectively, and subsequent reductive removal of the Piv ester from **49**.

Swern oxidation of alcohol **50** at −78 °C generated aldehyde **51**, which underwent the crucial torquoselective electrocyclic ring-opening reaction even at room temperature to deliver *E*,*Z*-diene **52** as a single isomer. The stereoselective formation of **52** originates from the inward rotation of the electron-accepting aldehyde moiety of **51** through the favorable secondary orbital interaction with the HOMO of cyclobutane (Scheme 13).[58,59] Because of its chemical instability, the resulting α,β,γ,δ-unsaturated aldehyde **52** was immediately subjected to $NaBH_4$ reduction without purification to give allylic alcohol **53**.[68] Finally, bromination of the chemically sensitive allylic alcohol was realized by the action of CBr_4 and $(CH_2PPh_2)_2$ to give the C1–C10 fragment **37**.[69,70]

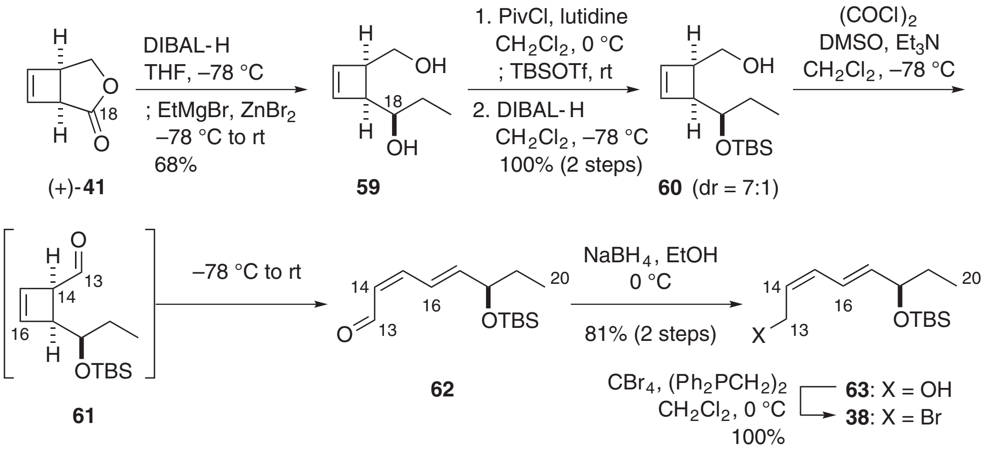
The C13–C20 fragment **38** was synthesized from (+)-**41** similar to the C1–C10 fragment **37** (Scheme 14). Reduction of (+)-lactone **41** with DIBAL-H was followed by stereoselective addition of ethyl magnesium bromide in the presence of zinc bromide to afford **59** with the desired C18 stereochemistry (dr = 7:1). After protecting group manipulations from **59** to **60** in two steps, Swern oxidation of the primary alcohol of **60** to aldehyde **61** accelerated the thermal ring-opening reaction to produce *E*,*Z*-diene **62** as a single isomer. Reduction of the resulting aldehyde of **62** to alcohol **63**, followed by bromination, led to the C13–C20 fragment **38**.



SCHEME 12 Synthesis of C1–C10 fragment.



SCHEME 13 Torquoselective ring-opening of **54**.

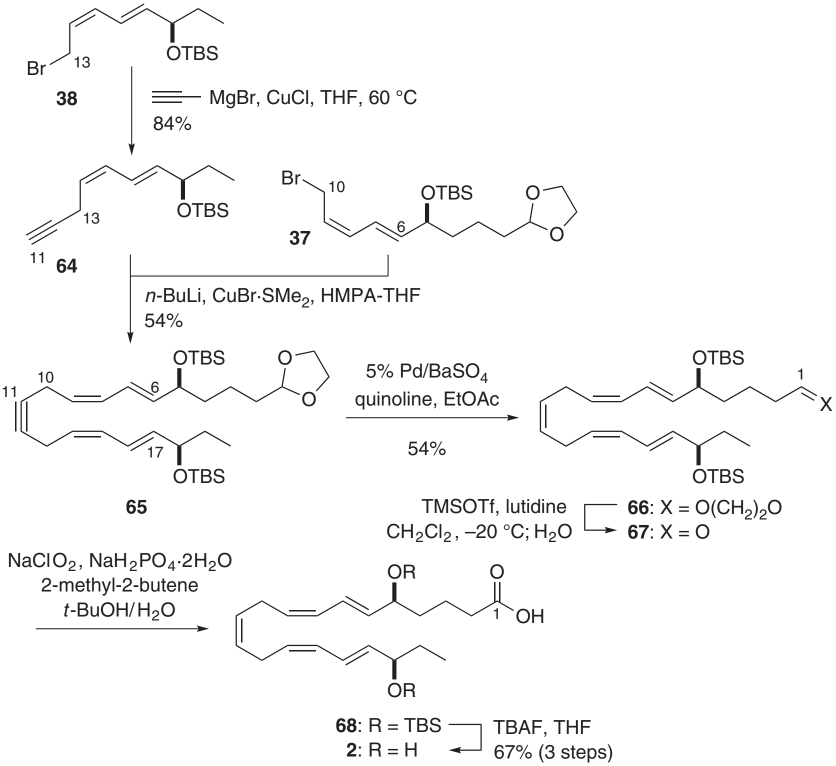


SCHEME 14 Synthesis of C13–C20 fragment.

3.4 Total Synthesis of Resolvin E2

Final convergent assemblies of the three partial structures utilized two copper-mediated couplings (Scheme 15). The bromide of **38** was first displaced with the copper acetylide, generated from ethynyl magnesium bromide and CuCl,[71] delivering the C11–C20 fragment **64**. Deprotonation of the C11-proton of **64** by *n*-BuLi in the presence of CuBr·SMe_2[72] at −78 °C then afforded the corresponding copper acetylide, which was treated with the C1–C10 fragment **37**, giving rise to the entire structure **65**. Intriguingly, only these particular conditions produced a sufficient amount of the adduct **65**. For instance, use of copper iodide instead of copper bromide for the coupling only gave a mixture of byproducts, in which the C6-*E*,*Z*-olefins were reacted or isomerized.

Four transformations from **65** led to the targeted resolvin E2. Lindlar conditions[73] enabled partial reduction of the alkyne of **65** into alkene **66** without reduction and/or isomerization of the reactive C6- and C17-*E*,*Z*-olefins. Acid-mediated removal of the ketal of **66** was troublesome because of the presence of the acid-labile allylic TBS ethers. After many attempts, we found that the conditions reported by Fujioka and Kita[74] were effective for selective



SCHEME 15 Total synthesis of resolvin E2.

reaction of the cyclic ketal. Treatment of **66** with an excess amount of TMSOTf and lutidine provided aldehyde **67** in high yield. Lastly, $NaClO_2$-mediated oxidation of the obtained aldehyde **67** into a carboxylic acid and subsequent desilylation with TBAF gave rise to resolvin E2 (**2**).

3.5 Summary

The efficient total synthesis of resolvin E2 (**2**) was achieved by utilizing the intrinsic pseudo-enantiomeric nature of the key fragments **37** and **38**. Most importantly, the two stereochemistries of **41** introduced via the desymmetrization of *meso*-**4** effectively transferred to those of the hydroxy group and the diene for preparing **37** and **38**. The obtained fragments were assembled into **2** in a convergent fashion.

4 CONCLUSION

The symmetry-driven total syntheses of merrilactone A (**1**) and resolvin E2 (**2**) were achieved in an efficient fashion. The retrosynthetic design of the simple *meso* intermediates and development of the enantioselective desymmetrization reactions enabled the efficient total syntheses of both enantiomers of merrilactone A in a total of 20 steps from *meso*-**3**, and the assembly of the pseudo-enantiomeric fragments, generated through desymmetrization of *meso* lactone **4**, resulted in convergent total synthesis of resolvin E2 in a total of 25 steps from **4**. These successful total syntheses clearly demonstrate the power and generality of this strategy for construction of both linear and multicyclic natural products. Further applications of the symmetry-driven strategy for synthesis of complex natural products with potent biological activities are underway in our laboratory.

ACKNOWLEDGMENTS

We are pleased to acknowledge an inspiring and dedicated group of co-workers whose names and contribution are referenced.

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Chapter 6

The Circuitous Journey from Malonamides to BTPhens: Ligands for Separating Actinides from Lanthanides

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Chapter Outline

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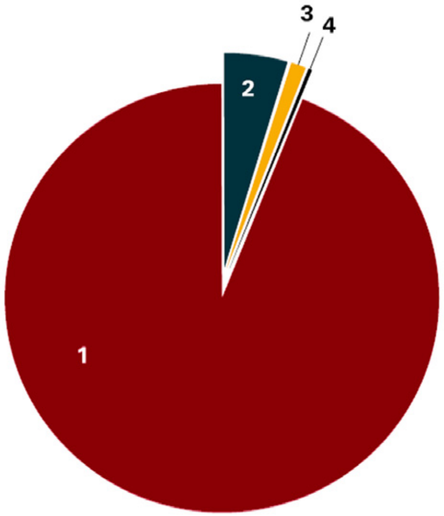
1 INTRODUCTION: PARTITIONING OF MINOR ACTINIDES AND SOME FISSION PRODUCTS WITHIN THE NUCLEAR FUEL CYCLE

The initiator of this project (Michael Hudson) studied coordination chemistry in the 1960s with Ron Nyholm and then was appointed to the School of Chemistry at the University of Reading in 1972. The research group initially focused on ion exchange and solvent extraction in relation to environmental problems. Alan Dyer at the University of Salford introduced him to the environmental problems concerning radionuclides, particularly technetium and ruthenium, for which several selective resins were devised. Claude Musikas of the CEA (France) helped to initiate funding from the European Commission for joint studies between Reading and the CEA. This work, which started in 1980 and included a long and happy collaboration with the energetic and enthusiastic Charles Madic of the CEA, has continued to the present time with separate European Commission grants from EURATOM. The high value of these European collaborations was evident from the quantity and quality of the publications. In fact, the contracts were so well subscribed that, by 2005, the number of research groups was over 30 with a substantial number involved in partitioning (i.e., chemical separations).

The focus of the research has been concerned with the partitioning (separation) of minor actinides (An) such as americium(III) from the rare earth elements (Ln) such as europium(III) from nitric acid solutions derived from the PUREX process. The PUREX (or Plutonium and URanium EXtraction) process arose out of research conducted in the Manhattan project and is currently used worldwide to separate and recycle the plutonium and uranium from spent fuel rods from nuclear power plants.[1] The requirements included separating Am(III) and Eu(III) from three molar nitric acid using solvents such as hydrogenated tetrapropene (TPH). TPH, a branched chain aliphatic diluent, is an industrial mixture of branched dodecanes. In the 1980s, such a separation was regarded as being difficult, if not downright impossible, to achieve.

2 SOME FUNDAMENTAL ASPECTS OF THE CHEMISTRY OF MINOR ACTINIDES

The approximate composition of spent nuclear fuel is shown in Figure 1. As is evident, the majority of the waste is made up of uranium, which is recovered in the PUREX process. Its removal reduces the long-lived radiotoxicity of the remaining waste from approximately 300,000 to 9000 years (as judged by the amount of time it would take for the radioactivity to decay to the level of natural uranium). However, if the minor actinides are subsequently removed, the remaining waste takes approximately 300 years to reach the level of natural uranium and is also much more manageable in terms of reduced heat generation, making storage in a geological depository a much more



Spent fuel contains approximately:

1 94% by mass of uranium (U) with an enrichment level at or slightly above that of natural uranium.

2 4–5% of fission products, including strontium (Sr), caesium (Cs), iodine (I) and technetium (Tc).

3 1% plutonium (Pu).

4 0.1% other minor actinides, such as neptunium (Np), americium (Am), and curium (Cm).

Key

1 Uranium	–94%	3 Plutonium	–1%
U-235	–0.7%	Pu-238	0.04%
U-238	–93%	Pu-239	0.7%
		Pu-240	0.3%
2 Fission products	**–4–5%**	Pu-241	0.2%
Sr-90	0.1%	Pu-242	0.1%
Cs-137	0.2%		
I-129	0.03%	**4 Minor actinides**	**–0.1%**
Tc-99	0.1%	Np-237	0.07%
		Am-241	0.03%
		Cm-244	0.01%

FIGURE 1 Approximate composition of spent nuclear fuel. *Reproduced with permission from The Royal Society Science Policy Centre Report 10/11, October 2011.*

tractable proposition. Thus, the minor actinides are responsible for much of the long-lived radiotoxicity of used nuclear fuel, even though they only account for about 0.1% by mass of the waste.[2] Americium and curium are two of the principal elements that give rise to the long-term radioactivity of the nuclear waste. They arise from the irradiation of uranium and plutonium during the production of energy from nuclear power. Therefore, one scheme to reduce the radiotoxicity of the nuclear waste is to remove these elements using solvent extraction, after which the Am(III) is converted to the oxide, which can then be transmuted to short-lived radionuclides or stable nonradioactive elements using high-energy neutrons in the Generation IV reactors due to come on-stream in the next decade.[3] This process is referred to as partitioning and transmutation. The solvent extraction of these actinides (Am and Cm) requires the remote automated separation from a 40-fold excess of lanthanide fission products; no mean task as both are present as the trivalent M(III) cations and their properties and chemistries are very similar.[4]

3 THE REQUIRED PROPERTIES OF THE SOLVENT EXTRACTION REAGENTS

A short review of solvent extraction was written at the commencement of these studies.[5] A series of exacting requirements for the chemical and physical properties of any successful ligand include good distribution ratios (*D*, a measure of extraction efficiency) and separation factors (SFs, a measure of extraction selectivity), solubility in appropriate solvents, resistance to acid hydrolysis, radiolysis, and third-phase formation and, finally, show efficient and rapid back extraction (stripping). Furthermore, the ligand should ideally be "CHON" (i.e., composed of only carbon, hydrogen, oxygen, and nitrogen so that any waste solvents can be completely incinerated to gases), and its synthesis amenable to economical scale-up.[6] Unfortunately, many of these requirements are incompatible with each other, requiring compromises. For example, an acceptable solubility in the type of hydrocarbon solvent likely to be used on the plant requires an alkyl side chain, which means that the kinetics of extraction and stripping could be slower than required.

Recent reviews have covered in detail the development of ligands suitable for the separation of actinides from lanthanides,[7] and many of the classes of molecules to be considered in this chapter are shown in Figure 2.

4 COEXTRACTION OF AMERICIUM(III) AND EUROPIUM(III): THE "EASY BIT"

4.1 Malondiamides

Historically, many countries have pursued a two-step strategy for the removal of the minor actinides from PUREX waste solutions[8] where in the first step,

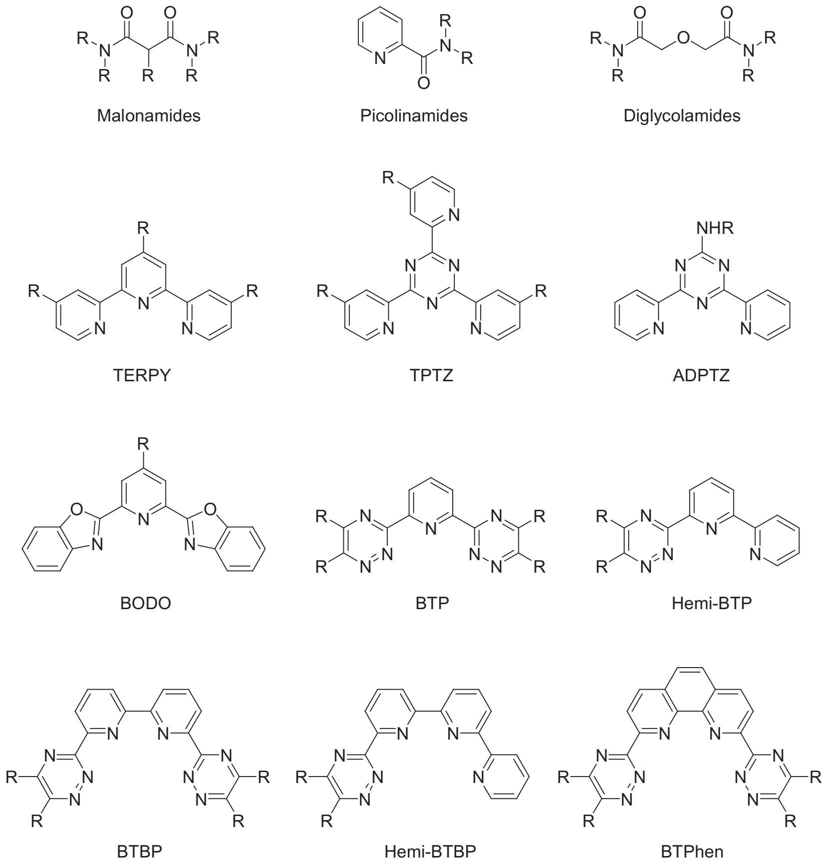
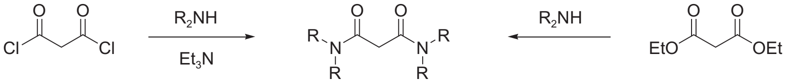


FIGURE 2 Structures of selected molecules for the partitioning of actinides from lanthanides.

An(III) and Ln(III) are coextracted from the remaining waste. In Europe, this step has been coined the DIAMEX (DIAMide EXtraction) process. In the second step, the plan is for the An(III) species to be selectively removed from Ln(III). This second step is referred to as the SANEX (Selective ActiNide EXtraction) process. Pearson's hard/soft acid/base theory[9] may be used to infer that ligands composed of hard *O*-donor atoms would be suitable candidates for the coextraction of trivalent cations such as An(III) and Ln(III). One component of the research thus commenced with the synthesis of new bidentate malondiamide ligands that have two ligating donor oxygen atoms, while another component was to establish an understanding of the chemistries involved. However, in spite of the plethora of insightful scientific papers that have appeared over the course of these studies, it is still true to say that experimental developments have outstripped our comprehension of the more fundamental theoretical aspects of the chemistry involved and much remains to be understood, with empiricism still leading theory.



1 **2**

SCHEME 1 Synthesis of malonamide ligands.

At the outset, potential extractants were synthesized at Reading and all of the solvent extraction and radiochemical studies were carried out at the CEA. In subsequent projects, other partner laboratories also performed radiochemical studies. The malondiamide ligands are readily synthesized from malonyl chloride **1** or from diethyl malonate **2** as shown in Scheme 1.

There have been significant advances since several malondiamide ligands were shown to be efficient for the coextraction of Am(III) and Eu(III) from nitric acid solutions,[10] with the nature of the extracted species involved being indicated by elucidation of the crystal structure of the lanthanum tetraethyl malondiamide nitrate complex.[11] In the crystal, the lanthanum ion is 10-coordinate overall and is bound to two bidentate malondiamide ligands and three bidentate nitrates. Thus, both diamide and nitrate are coextracted with the lanthanide. Picolinamides, which are bidentate mixed *N*- and *O*-donors, were also shown to be effective reagents for the coseparation of Am(III) and Eu(III).[12] It was shown that the mechanism of coseparation changed from a coordination mechanism at concentrations below 1 molar nitric acid to an ion-pair mechanism at higher acidities. In other words, the protonated ligand LH^+ ion pairs with an $[M(NO_3)_5]^{2-}$ anion at higher acidities to form an extractable ion-pair complex (M = metal ion). This paper had some personal significance because it was the only paper that Claude Musikas, Charles Madic, and Michael Hudson published together. Charles was subsequently to take over from Claude, who retired just before the paper was published. In subsequent contracts, the team was joined by the Swedish Group at Chalmers University led initially by Jan-Olov Liljenzin.

Since these early pioneering studies, the more hydrophobic malonamides *N*,*N*′-dimethyl-*N*,*N*′-dibutyltetradecylmalonamide (DMDBTDMA) **3**[13] and *N*,*N*′-dimethyl-*N*,*N*′-dioctylhexoxyethylmalonamide (DMDOHEMA) **4**[14] have been developed (Figure 3), and show promising properties for use in a process for the coextraction of actinides and lanthanides. Currently, the ligand of choice for the coextraction of actinides and lanthanides in the DIAMEX process is *N*,*N*,*N*′,*N*′-tetraoctyldiglycolamide (TODGA) **5**, which shows superior performance compared to the other malonamide ligands in laboratory demonstration tests on genuine PUREX raffinate.[15]

4.2 Nitrogen Heterocycles Such as 1,3,5-Triazines

Once the coextraction of Am(III) and Eu(III) could be achieved with hydrophobic malonamide or diglycolamide ligands, the principal focus of

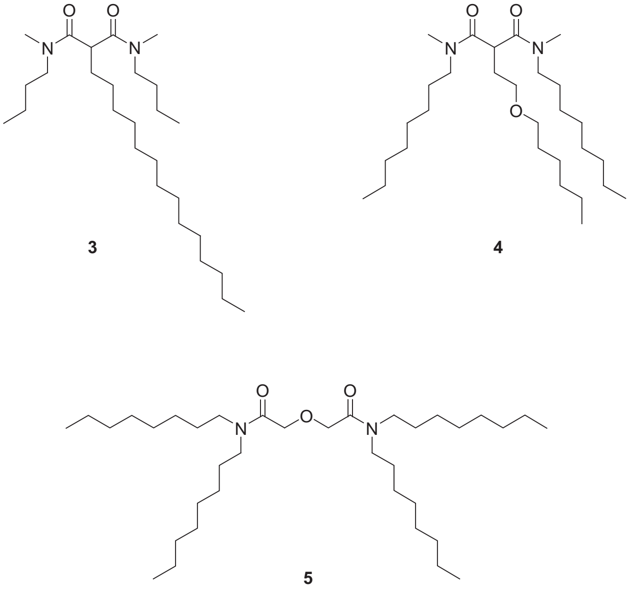
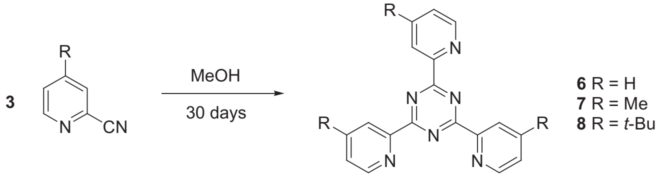


FIGURE 3 Structures of hydrophobic diamide ligands **3**–**5**.



SCHEME 2 Synthesis of the TPTZ ligands.

the research studies turned to ligands composed of soft *N*-donor atoms. The d and f orbitals of the actinides are more diffuse than the 4f orbitals of the lanthanides and there is a small but significantly greater degree of covalency in the bonding between a ligand lone electron pair and the actinides than there is with the lanthanides. Although the exact origins of this covalency are still the subject of ongoing debate,[16] it was proposed that *N*-donor ligands would be able to exploit this covalency difference and thus would be capable of performing the challenging separation of An(III) from Ln(III). The first ligand family synthesized at Reading for this purpose was the 2,4,6-tri(2-pyridyl)-1,3,5-triazine (TPTZ) system. The principal symmetrical 1,3,5-triazine studied was 2,4,6-tri(2-pyridyl)-1,3,5-triazine (TPTZ) **6**, in which three pyridines are bound at C-2 to the central triazine ring. The parent molecule can be synthesized by the cyclotrimerization of 2-cyanopyridines in methanol (Scheme 2). However, it was found that this molecule protonates in acidic media and is sufficiently soluble in 3 M nitric acid to render it inefficient for solvent extraction. In order to increase the solubility of the ligand in the organic phase, it was decided to look at alkylated derivatives. The synthesis of the methyl derivative MeTPTZ **7** by cyclization of 4-methyl-2-cyanopyridine was found to be inefficient at ambient pressures. However, Neil Isaacs, a physical organic chemist at Reading, suggested the use of ultra-high-pressure conditions (>10 kbar) and it was found that when these substrates were squeezed, the yields of the cyclizations were typically above 60%. However, even this technique proved limited as all attempts to prepare the ethyl derivative EtTPTZ from 4-ethyl-2-cyanopyridine were unsuccessful even using ultra-high pressures.

In TPTZ **6** itself, there are three identical cavities with two nitrogen atoms.[17] When protonated or bound to a metal cation, there are three different cavities with three, two, or one heterocyclic nitrogen (Figure 4). The hydrophobicity of the extracted metal species can be increased by using a hydrophobic synergist such as α-bromodecanoic acid. In this process, the term "synergist" is used for an agent that assists in the extraction of metal complexes from aqueous solutions by ion pairing with the $[L_nM]^{3+}$ complex cation to form a more hydrophobic complex that is more easily extracted into the organic phase. Indeed, for a long time, popular wisdom had it that it would be essential to have a synergist in the mix. One of the nitrogens in the 2N-cavity is protonated and it is probable that the α-bromodecanoate anion is bound in this cavity (Figure 4).[18] The synergistic extraction of Am(III) and Eu(III) was studied with TPTZ and α-bromodecanoic acid. At pH 1, the optimum SF for Am(III) over Eu(III) ($SF_{Am/Eu}$) value was found to be 7 using *tert*-butylbenzene as the diluent.[19] Although dwarfed by today's standards, in the 1980s, an SF for Am(III) over Eu(III) of 5 or higher was thought to be impossible to achieve; so, this was a real breakthrough. However, even with a synergist, the Am(III) and Eu(III) were not coextracted below pH 1—presumably due to competing protonation of the pyridine rings of TPTZ preventing metal ion coordination.

A variety of synergists was tried with a range of heterocyclic nitrogen donor molecules such as 2,2′:6′,2″-terpyridines (TERPYs) and TPTZs. In each case, however, the extractions of Am(III) and Eu(III) were limited to weakly acidic nitric acid solutions of pH greater than 1.[20] The protonation

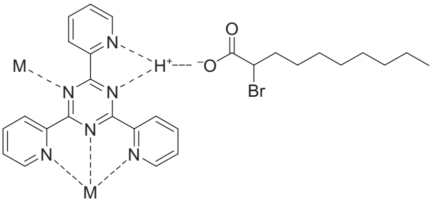


FIGURE 4 The three coordination cavities of the TPTZ ligand **6**. The 2N-cavity is shown in its protonated form with the proton hydrogen bonding to a 2-bromodecanoate anion.

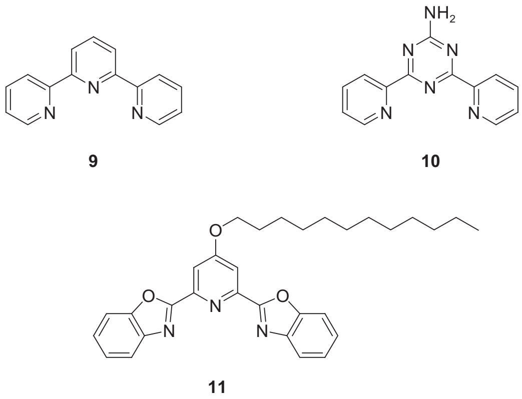


FIGURE 5 Structures of the ligands terpyridine **9**, ADPTZ **10**, and BODO **11**.

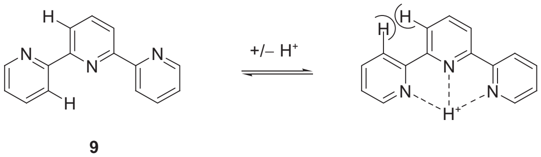


FIGURE 6 Conformations of 2,2′:6′,2″-terpyridine **9** in its unprotonated and protonated forms.

of terpyridine **9** (Figure 5) was studied in detail and it was confirmed that the unprotonated molecule adopted the *trans*-conformation of the N—C—C—N groups. In this conformation, the *ortho*-protons do not sterically clash with each other but, when protonated, intramolecular hydrogen bonds stabilize the *cis*-conformation (Figure 6).[21] There was also clear evidence of water molecules bound by hydrogen bonds being present. Thus, protonation of *N*-donor ligands such as the terpyridines and TPTZs competes with the required metal ion complexation and so impedes the extraction of the metals from nitric acid solutions of concentrations greater than 0.1 M. These poor extractions from acidic media were also true of ligands based on 4-amino-2,6-di-2-pyridyl-1,3,5-triazine (ADPTZ) **10** (Figure 5) that were subsequently studied and for which very promising selectivities were observed ($SF_{Am/Eu} \leq 12$) at higher pH.[22]

Ligands based on 2,6-bis(benzoxazol-2-yl)-4-dodecyloxypyridine (BODO) **11** (Figure 5) and their benzimidazole and benzothiazole counterparts showed encouraging extraction results. The selectivities for Am(III) over Eu(III) of some of these ligands even exceeded 70. However, they still suffered from the drawback of being unable to extract either Am(III) or Eu(III) from the 1–4 M nitric acid solutions that would be encountered in the SANEX process and could only extract from dilute nitric acid solutions even in the presence of a synergist.[23] Again, competing protonation of these ligands at low pH was the most likely reason for their inability to extract from more concentrated nitric acid solutions.

5 SELECTIVE SEPARATION OF AMERICIUM(III) FROM EUROPIUM(III) AT HIGH ACIDITY: THE "HARD BIT"

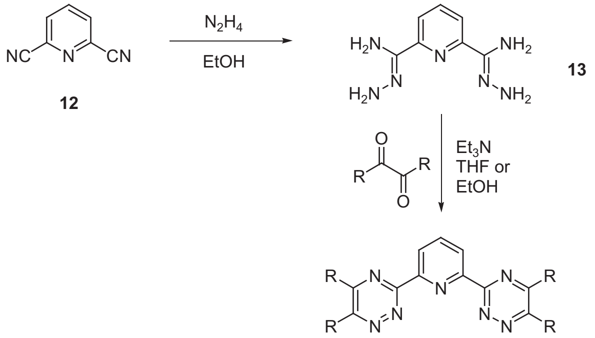
5.1 Nitrogen Heterocycles Including the α-Effect with Adjacent Nitrogens

At this stage, we were becoming concerned by the fact that the heterocyclic nitrogen had a greater affinity for protons than for trivalent cations. Fortunately, Neil Isaacs came to our rescue by drawing our attention to the α-effect that occurs when atoms with nonbonding electron pairs are adjacent to each other. With respect to adjacent heterocyclic nitrogen atoms, the α-effect leads to a diminution of the affinity of the nitrogens for protons and a concomitant increase in the affinity for "soft" cations[24] as overlap of the adjacent noncoordinating nitrogen lone pair of the triazine ring with the coordinating lone pair increases the covalent contribution to bonding of the latter. This was proposed to lead to a greater orbital overlap with the more diffuse 5f orbitals of the actinides than with the 4f orbitals of the lanthanides and consequently, a wide range of 1,2,X-triazine ligands containing adjacent nitrogens in the ring was studied with the 1,2,4-triazine-based ligands being by far the most interesting. The current optimum molecules are the BTBP (6,6′-bis(1,2,4-triazin-3-yl)-2,2′-bipyridine) and the BTPhen (2,9-bis (1,2,4-triazin-3-yl)-1,10-phenanthroline) families, but the story started with the synthesis of the BTP (2,6-bis(1,2,4-triazin-3-yl)pyridine) system.

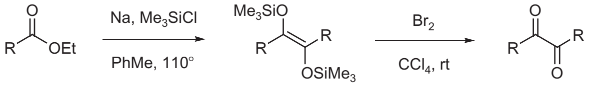
5.2 2,6-bis(1,2,4-triazin-3-yl)pyridines

Running with the notion that the α-effect could be useful, Zdenek Kolarik at the Karlsruhe Institute of Technology (KIT-INE) found that the 2,6-bis (1,2,4-triazin-3-yl)pyridine (BTP) ligands were able to separate Am(III) and Eu(III) from concentrated (1–4 M) nitric acid solutions without the aid of a synergist, and that it was possible to achieve very high separation selectivity ($SF_{Am/Eu} > 100$).[25] Thus, for the first time, an *N*-donor heterocyclic molecule was able to extract Am(III) over Eu(III) with high selectivity from the sorts of nitric acid concentrations that would be encountered in a realistic SANEX process (i.e., 1–4 M HNO_3). The BTPs also had the virtue that they could be readily synthesized by the reaction of an α-diketone with pyridine-2,6-dicarbohydrazonamide **13** (Scheme 3), which is itself made by the reaction of 2,6-dicyanopyridine **12** with hydrazine hydrate. The α-diketones were also readily synthesized by the intermolecular acyloin reaction of esters with sodium in the presence of chlorotrimethylsilane.[26] This reaction afforded the enediolate bis-silyl ethers, which were then oxidized to the diketones with bromine (Scheme 4).

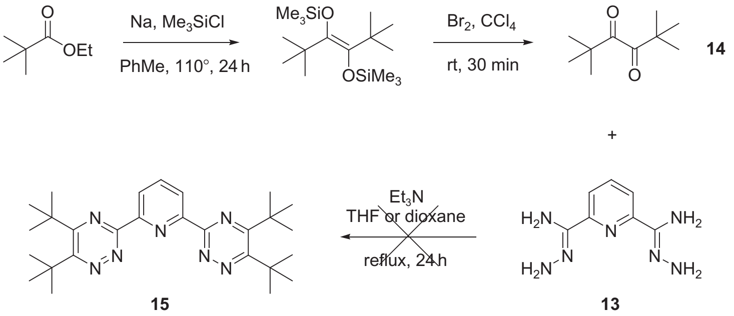
However, although the BTPs showed very useful distribution ratios and SFs, it was not possible to strip the bound metal cations easily and quickly—a conundrum that was always to bedevil these studies.



SCHEME 3 Synthesis of the BTPs.



SCHEME 4 Synthesis of α-diketones by intermolecular acyloin reactions of esters.



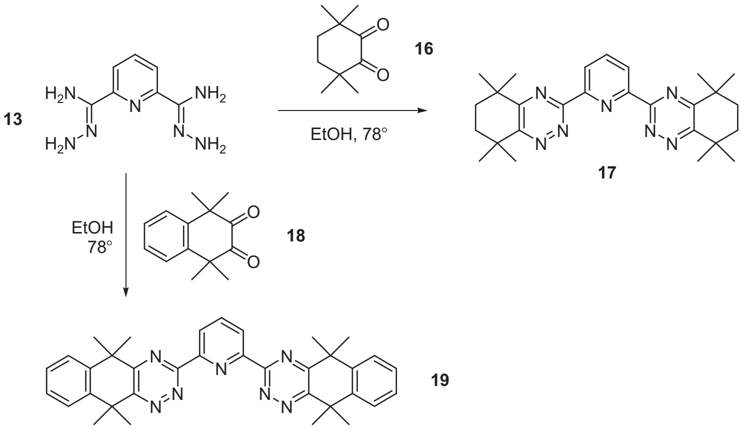
SCHEME 5 Attempted synthesis of *tert*-butyl substituted BTP **15**.

One further requirement of any ligand is that it must be able to resist radiolytic degradation and, when the tetrapropyl-BTP was tested using genuine PUREX raffinate, it was found that it was degraded during the attempted extraction. With the appearance of a card-carrying synthetic organic chemist on the scene in the form of Laurence Harwood, it was proposed that BTPs with side chains containing benzylic hydrogens would be susceptible to degradation by reacting with hydroxyl radicals generated by radiolysis, and so he suggested that the BTPs would need to have solubilizing alkyl side groups with no benzylic hydrogens.[27] As a consequence, one of the early target molecules proposed was BTP **15** which has four *tert*-butyl groups attached to the triazine rings.

However, in these early stages, it did not prove possible to synthesize this molecule because the corresponding pivalyl diketone **14** did not react with the diamide dihydrazide **13** (Scheme 5). This was proposed to be due to the fact that the diketone resides so predominantly as its *trans* conformer with a high-energy barrier for the formation of the *cis* conformer that the cycloaromatization to form the triazine rings could not take place.

BTP **15** remains a target molecule and the Reading group still has it on the "to do" list but, in the meantime, it was reasoned that by tying the *tert*-butyl groups of diketone **14** back into a six-membered ring, the result would be a more reactive diketone that could react with the diamide dihydrazide **13**. Attention was thus focused at Reading on "CyMe$_4$-diketone" **16** and related cyclic α-diketones. Thus, diketone **16** and its benzannulated derivative **18** were synthesized. Pleasingly, the reactions of diketones **16** and **18** with diamide dihydrazide **13** proceeded efficiently to afford CyMe$_4$-BTP **17** and its benzannulated derivative BzCyMe$_4$-BTP **19** in high yield (Scheme 6).[28] What was totally unexpected however was that, in solvent extraction tests, CyMe$_4$-BTP **17** showed far higher selectivities ($SF_{Am/Eu} \leq 5000$) than related alkyl-BTPs, as well as an increase in extraction efficiency ($D_{Am} \leq 500$). Both BTPs **17** and **19** were also resistant to acid hydrolysis (boiling 3 M HNO_3), while BTP **19** was resistant to low doses (100 kGy) of gamma radiation. Unfortunately, back extraction (stripping) of the metal from the ligands **17** and **19** once again proved impossible to achieve, limiting the recycling and reuse of these ligands in a real SANEX separation process.

The X-ray crystal structure of the cation of the 1:3 complex formed between CyMe$_4$-BTP **17** and Y(III) is presented in Figure 7. The metal center is 9-coordinate and is completely enclosed by three ligands **17** that each bind in a terdentate fashion.[28] There are no additional ligands such as water or nitrate ion in the inner coordination sphere of the metal, and this structure provides evidence for the hydrophobic nature of the extracted metal species.



SCHEME 6 Synthesis of CyMe$_4$-BTP **17** and BzCyMe$_4$-BTP **19**.

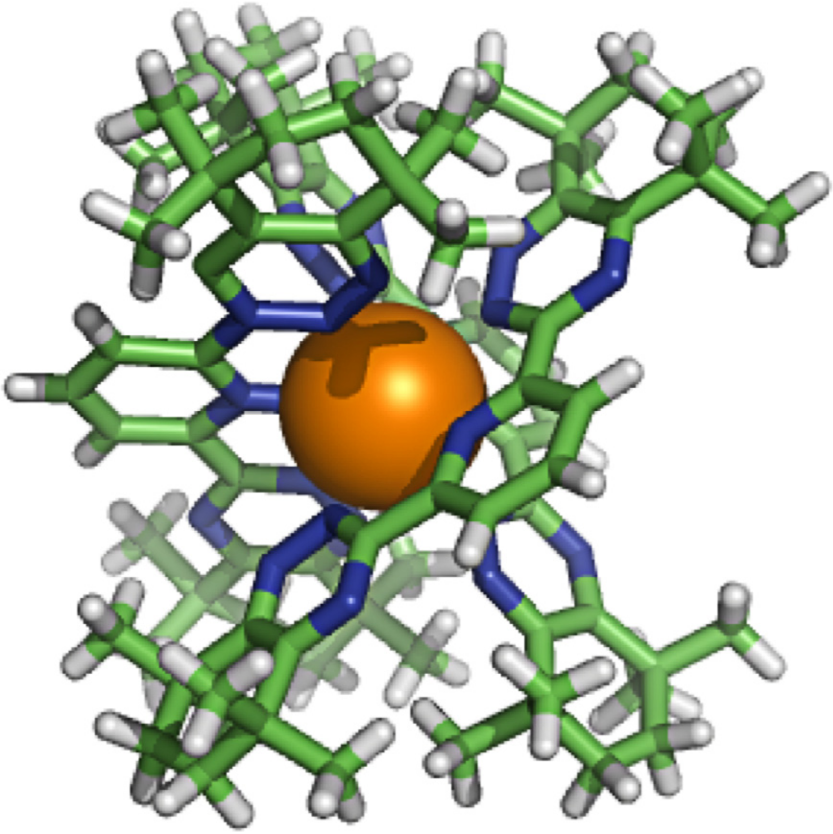
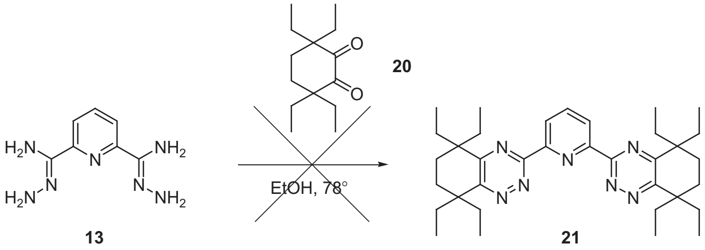


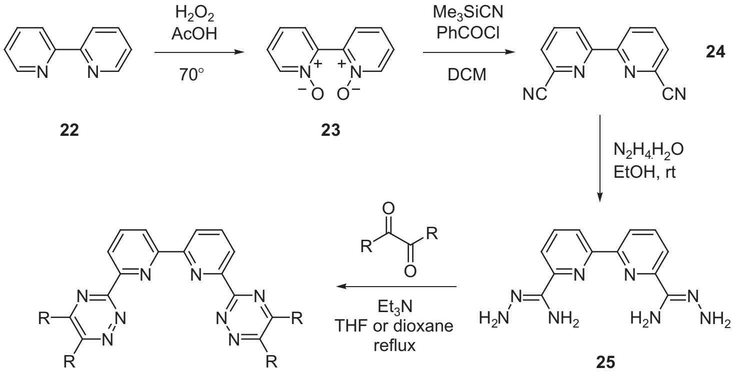
FIGURE 7 Depiction of the crystal structure of the $[Y(CyMe_4\text{-}BTP)_3]^{3+}$ cation.[28]

The formation of 1:3 complexes of the BTPs with trivalent lanthanides and actinides has also been observed in solution by TRLFS measurements and ESI-MS.[29] The ability of the BTPs to form hydrophobic 1:3 M:L complexes contrasts with earlier ligand designs (such as TERPY, TPTZ, BODO) for which only 1:1 complexes were observed in the solid state. The high extraction efficiency and selectivity of the BTPs is most likely related to their ability to form these hydrophobic 1:3 complexes under extraction conditions.

Another target ligand was one in which the aliphatic rings of BTP **17** contained ethyl groups at the benzylic positions, rather than methyl groups ($CyEt_4$-BTP **21**). Unfortunately, the corresponding diketone **20** proved to be unreactive toward the diamide dihydrazide **13**, even under forcing conditions and under ultra-high-pressure conditions (Scheme 7). The diketone **20** was obviously too sterically hindered to react with **13**, even though it was constrained in the reactive *cis*-conformation.



SCHEME 7 Attempted synthesis of CyEt$_4$-BTP **21**.



SCHEME 8 Synthesis of the BTBPs.

5.3 6,6′-bis(1,2,4-triazin-3-yl)-2,2′-bipyridines

The BTPs had proven to be good and selective ligands but the metals cannot be stripped once bound to the ligand. It was postulated that moving from a terdentate ligand to a quadridentate ligand would lead to a weaker ligand field, and thus permit better back extraction of the metal from the ligand's coordination cavity. This indeed proved to be the case and it has been shown that the quadridentate 6,6′-bis(1,2,4-triazin-3-yl)-2,2′-bipyridine (BTBP) ligands overcome the problems associated with the BTPs concerning stripping, while still allowing for selective separations of Am(III) from Eu(III). Consequently, the BTBPs remain one of the most important sets of molecules developed at Reading.[30] The BTBPs are synthesized by the condensation of 2,2′-bipyridine-6,6′-dicarbohydrazonamide **25** with α-diketones as shown in Scheme 8. Diamide dihydrazide **25** was readily synthesized from commercially available 2,2′-bipyridine **22** in three steps. Oxidation of **22** with hydrogen peroxide in acetic acid afforded in high yield the bis-*N*-oxide **23**, which was converted into dinitrile **24** by a Reissert–Henze cyanation reaction with trimethylsilyl cyanide and benzoyl chloride. Addition of hydrazine hydrate to **24** in ethanol generated the diamide dihydrazide **25** in excellent yield.

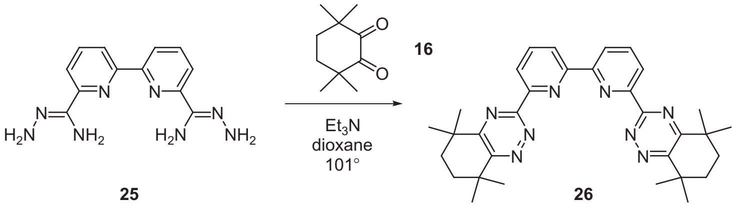
The current European reference molecule for the SANEX process is CyMe$_4$-BTBP **26**, for which there are some important design features, which may be summarized as follows:

1. Two adjacent nitrogens in the triazine rings (α-effect).
2. No benzylic hydrogens (resistance to radiolysis).
3. Annulated aromatic rings (resistance to radiolysis).
4. Coordination cavity approximates to 0.1 nm—the sizes of Am(III) and Eu(III).
5. Rotation between *cis*- and *trans*-conformers is possible. (Ligand is present in the *trans*-form, whereas the *cis*-form is required for binding to the metal cations).
6. Small dipole moment (much less than that of CyMe$_4$-BTPhen).

The CyMe$_4$-BTBP ligand **26** is synthesized by the condensation of diamide dihydrazide **25** with CyMe$_4$-diketone **16** (Scheme 9).

The CyMe$_4$-BTBP molecule **26** is able to extract Am(III) preferentially to Eu(III) even in 3 M nitric acid, it is resistant to radiolysis and hydrolysis (no decomposition occurred when in contact with 1M HNO_3 over 2 months), it is hydrophobic, but has a low concentration at the interface between the organic and aqueous phases. Furthermore, it is not a particularly strong ligand and the ligated metal cations can thus be back extracted using stripping agents like glycolic acid, allowing for the continuous recycling of the ligand in a separation process. However, the kinetics of extraction are limited by the low loading of the ligand in the solvent and therefore its concentration at the interface.

The BTBPs were first announced in 2006 when the coordination chemistry with lanthanides was first discussed.[31] The results of the high separation of Am(III) over Eu(III) without the requirement of an additional synergist were also first announced in this paper and detailed solvent extraction studies were published later in the same year.[32] As the CyMe$_4$-BTBP molecule **26** is hydrophobic, with a limited concentration at the interface, a malondiamide phase transfer reagent (DMDOHEMA **4**) was used in the extraction studies to accelerate the kinetics of extraction, and the Am(III) was subsequently stripped from the ligand using glycolic acid. The ligand was employed in a laboratory-scale SANEX demonstration test (hot test) with genuine PUREX raffinate at the Institute for Trans-Uranium elements (ITU) in Karlsruhe,



SCHEME 9 Synthesis of CyMe$_4$-BTBP **26**.

Germany in 2008, with extremely promising results.[33] A solution of CyMe$_4$-BTBP **26** and DMDOHEMA **4** in 1-octanol could separate more than 99.9% Am(III) and Cm(III) from the entire lanthanide series when used on the genuine waste solution. As this chapter is being written, further modifications of the SANEX process are being developed at Forschungszentrum Jülich (Germany) and at Chalmers University of Technology (Sweden) using CyMe$_4$-BTBP **26** as the principal extractant.[34]

In recent years, we have explored the effect of some systematic modifications to the structure of CyMe$_4$-BTBP **26** on the ligand's extraction properties. The aim was to obtain insights into the design features of the ligand necessary for efficient and selective extractions, and thus knowledge that could ultimately aid in future ligand design (Figure 8). Replacing the six-membered aliphatic rings of **26** with five-membered heterocyclic rings had detrimental effects on the solubilities and extraction properties of the resulting ligands **27** and **28**,[35] while the addition of alkyl groups to the pyridine rings of **26** resulted in similar selectivities, but slower rates of extraction by the ligands **29** and **30** compared to **26**.[36] The inclusion of an additional pyridine ring into

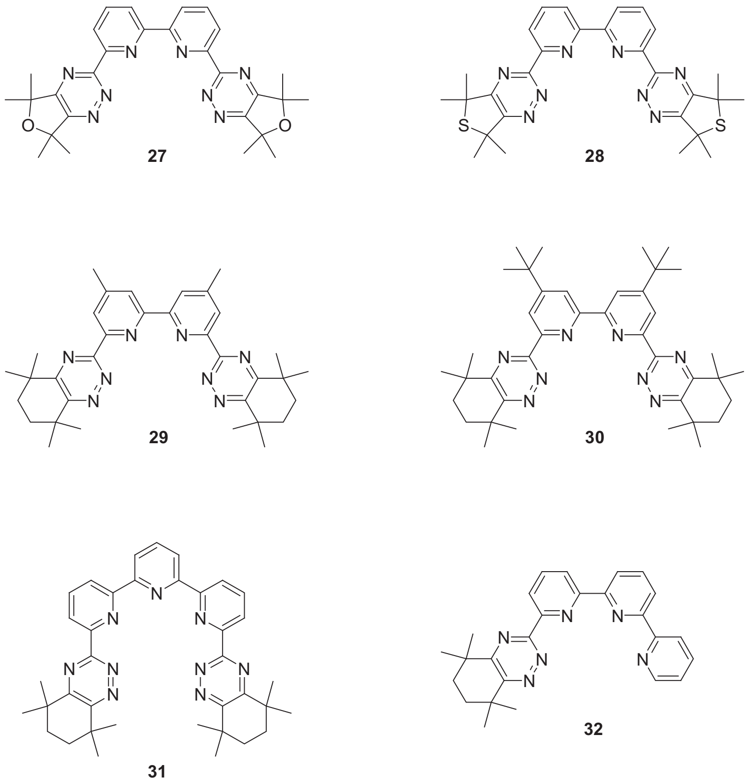
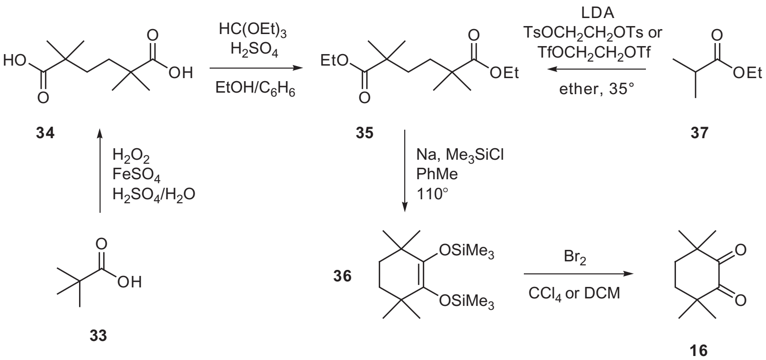

27 **28** **29** **30** **31** **32**

FIGURE 8 Structures of ligands closely related to CyMe$_4$-BTBP **26**.

the coordination cavity of CyMe$_4$-BTBP **26** (giving rise to the weaker field pentadentate CyMe$_4$-BTTP ligand **31**) resulted in extractions that were about two orders of magnitude weaker than those of CyMe$_4$-BTBP **26**.[37] This was attributed to the formation of less hydrophobic 1:1 complexes with lanthanides in nitrate media, as observed by NMR and ESI-MS. Interestingly, when one of the lateral 1,2,4-triazine rings of **26** is replaced by a pyridine ring (giving rise to the quadridentate CyMe$_4$-hemi-BTBP ligand **32**), the resulting ligand essentially does not extract Am(III) or Eu(III) at all![38] This illustrated that two 1,2,4-triazine rings are required for efficient and selective extractions with the BTBP ligands and are thus a very important ligand design feature. This work therefore did provide some insight into the basis of selectivity but also threw up as many, if not more, inexplicable results—empiricism still ruled.

Nevertheless, here at last was the basis for a potential process for partitioning Am(III) from Eu(III). However, there was a limitation to synthetic scale-up beyond about a gram of the ligand as the method used for the synthesis of the CyMe$_4$-diketone precursor **16** could only be performed on small scale, failing totally when attempting it on larger batches of starting material. The synthesis of **16** is shown in Scheme 10. The problematic step was the synthesis of 2,2,5,5-tetramethyladipic acid **34**, which was formed by the free-radical dimerization of pivalic acid using Fenton's reagent (essentially hydroxyl radicals formed *in situ* from the reaction of hydrogen peroxide with iron(II) sulfate). Although a yield of 35% of **34** is quoted in the literature,[39] the yields in our hands were far less. Esterification of **34** using triethyl orthoformate in ethanol in the presence of sulfuric acid formed diethyl 2,2,5,5-tetramethyladipate **35**. Intramolecular acyloin reaction of **35** generated the enediolate bis-silyl ether **36**, which can then be converted into CyMe$_4$-diketone **16** by oxidation with bromine. So, the overall yields of **16** were consistently less than 5% using this method—and then only on small scale. If CyMe$_4$-based ligands were ever to form the basis of an industrial SANEX process, we had to develop an improved method for the synthesis of CyMe$_4$-diketone **16**.



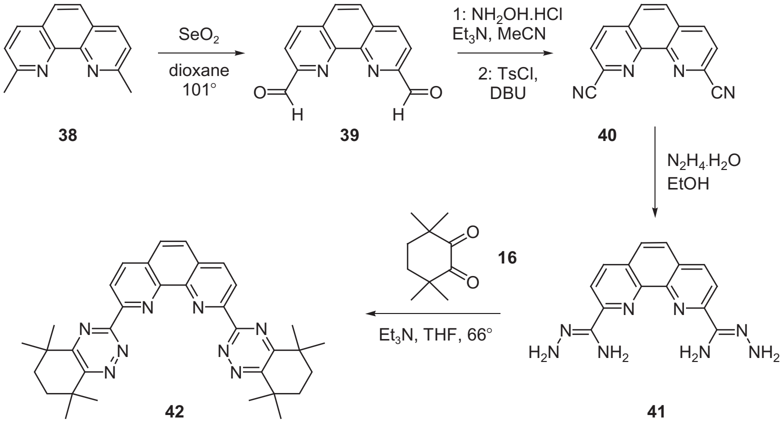
SCHEME 10 Old and new methods for the synthesis of CyMe$_4$-diketone **16**.

In 2008, postdoctoral research assistant Frank Lewis realized that symmetrical diester **35** had the potential to be synthesized by the alkylation of the enolate of ethyl isobutyrate **37** with a 1,2-bis-electrophile. However, the literature contains several reports that, with 1,2-dihalides, alkylation by the enolate of alkyl isobutyrates did not take place; instead, attack of the enolate of **37** on the bromine atom of the electrophile and subsequent expulsion of ethene occurred.[40] Frank's idea was that, by using disulfonate esters as the 1,2-bis-electrophile, this pathway would be circumvented and, just as predicted (for once), the desired diester **35** was obtained in 69–70% yield when the reaction was carried out using different ethane-1,2-disufonate esters (Scheme 10). Completion of the synthesis as before now led to a much improved overall yield of the diketone **16** of 43% that could be scaled up. With this new method of synthesis permitting scale-up and efficient production of CyMe$_4$-diketone **16**, a major obstacle to the possible industrial use of CyMe$_4$-based ligands was removed. The intellectual property has been protected and diketone **16**, and many of the ligands derived from it are now available commercially.[41]

5.4 2,9-bis(1,2,4-triazin-3-yl)-1,10-phenanthrolines

Although the BTBPs have been successful, there remain some limitations on their use. In particular, the rates of extraction are somewhat too slow—although the slow rates of extraction and stripping in a separation process may be improved by using mixer-settlers (solvent mixing chambers where both phases are vigorously mixed and allowed to settle) instead of centrifugal contactors (a sequence of mixing chambers where both phases flow past each other in opposite directions from one chamber to the next while being mixed). In addition, the solubilities of CyMe$_4$-BTBP **26** in solvents acceptable to the nuclear industry such as 1-octanol or hydrocarbon solvents are rather low.

It was thought that the conformational change of CyMe$_4$-BTBP **26** from its *trans*-conformation to its less favored *cis*-conformation could be responsible for the slow rates of extraction by CyMe$_4$-BTBP **26**. In order to overcome this problem, the 2,9-bis(1,2,4-triazin-3-yl)-1,10-phenanthroline (BTPhen) ligands were developed. Again, Frank Lewis stepped up to the plate. He reasoned that preorganization of the ligating nitrogens of CyMe$_4$-BTBP **26** using a rigid 1,10-phenanthroline moiety (rather than a freely rotating 2,2′-bipyridine moiety) would lock the *N*-donor atoms into the spatial arrangement required for metal binding and thus accelerate the rates of extraction. Consequently, CyMe$_4$-BTPhen **42** was synthesized as shown in Scheme 11.[42] Oxidation of 2,9-dimethyl-1,10-phenanthroline **38** with selenium dioxide afforded dialdehyde **39**, which was converted into dinitrile **40** in one pot in 62% overall yield by conversion of **39** to its dioxime followed by dehydration *in situ* using tosyl chloride and DBU. The addition of hydrazine to **40** generated the diamide



SCHEME 11 Synthesis of CyMe$_4$-BTPhen **42**.

dihydrazide **41** which, on treatment with CyMe$_4$-diketone **16** in hot THF, furnished CyMe$_4$-BTPhen **42**.

Extractions of Am(III) and Eu(III) by CyMe$_4$-BTPhen **42** proved to be about two orders of magnitude greater than those of CyMe$_4$-BTBP **26** ($D_{\mathrm{Am}} \leq 1000$), while the selectivity was quite similar or slightly higher ($\mathrm{SF}_{\mathrm{Am/Eu}} \leq 400$).[42] As predicted, the rates of extraction by **42** were significantly faster than those of **26**, allowing equilibrium to be reached within 15 min of phase mixing (compared to ca. 1 h for CyMe$_4$-BTBP **26**) *without the need for any added phase transfer agent*. These properties appear to overcome the criticisms leveled at the BTBPs; watch this space.

Probable evidence for the structures of the extracted metal complexes formed by CyMe$_4$-BTPhen **42** was obtained in the form of the X-ray structure of the cation [Eu(CyMe$_4$-BTPhen)$_2$]$^{3+}$ (Figure 9). The metal center is enclosed by two tetradentate CyMe$_4$-BTPhen ligands **42** and one bidentate nitrate ion, forming a hydrophobic complex cation.[42] The Eu(III) ion is 10-coordinate overall. Compared to the structure of the 1:3 complex of CyMe$_4$-BTP **17** with Y(III) shown in Figure 7, there is still ample room for water, nitrate ions, or stripping agents such as glycolic acid to coordinate to the metal center and displace the ligand **42**. A very similar crystal structure of the 1:2 complex of CyMe$_4$-BTBP **26** with Eu(III) was also recently reported.[43] This may explain why stripping can be achieved with the BTPhens (and the BTBPs) but not with the BTPs, as the extracted complexes of the former are less sterically hindered. The predominant formation of hydrophobic 1:2 complexes of CyMe$_4$-BTPhen **42** and CyMe$_4$-BTBP **26** with several lanthanides was also observed both in the solid state and in solution using a range of techniques, such as ^{1}H NMR spectroscopy, microcalorimetric titrations, electronic absorption titrations, X-ray absorption spectroscopy, and extended X-ray absorption fine structure.[44]

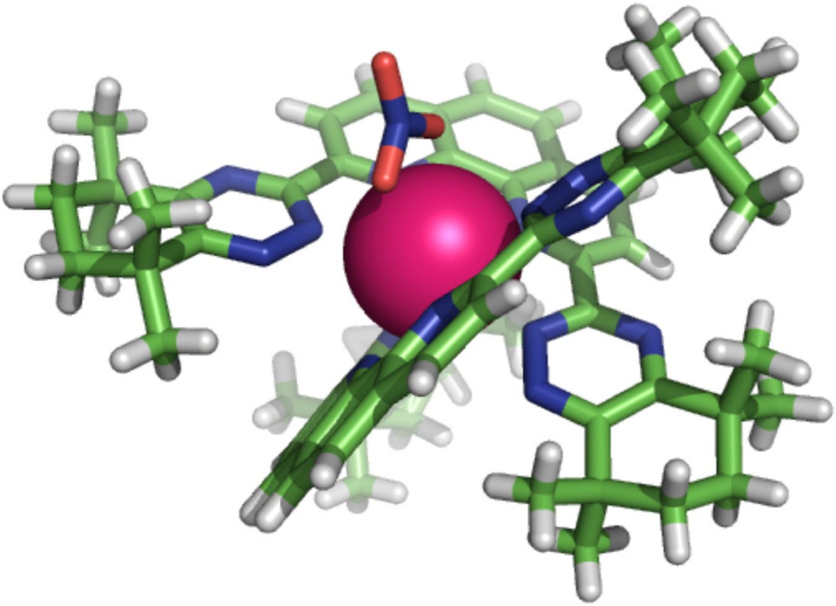


FIGURE 9 Depiction of the crystal structure of the $[Eu(CyMe_4\text{-}BTPhen)_2]^{3+}$ cation.[42]

The publication of the paper in the Fall of 2011 led to the celebratory drink mentioned in the Abstract and, at the time of writing (early 2013), that paper has been cited 25 times, so it seems that the BTPhens are making an impact. The range of BTPhen ligands has also been recently expanded by the reaction of **41** with several different aliphatic diketones.[45] Some of the advantageous features of $CyMe_4$-BTPhen **42** are:

1. Retains the advantages of the BTBPs.
2. $CyMe_4$-BTPhen **42** has a higher dipole moment than $CyMe_4$-BTBP **26** (leading to higher interfacial concentrations of $CyMe_4$-BTPhen **42**).
3. The preorganized molecule is present in the *cis*-form required for binding, extraction, and stripping of metal cations (faster rates of extraction with $CyMe_4$-BTPhen **42** than with $CyMe_4$-BTBP **26**).

As BTPhens have greater dipole moments than the corresponding BTBPs, it was predicted that there should be a greater concentration of the BTPhen at the organic/water interface. The concentrations at the interface may be inferred from surface tension measurements and Figure 10 shows the surface tensions of organic solutions of $CyMe_4$-BTBP **26** and $CyMe_4$-BTPhen **42** as a function of ligand concentration. A trend of decreasing surface tension with increasing ligand concentration indicates that the ligand is surface active. Since the extraction and stripping reactions occur at or near the interface, it was hoped that the corresponding rates with BTPhens should be greater than

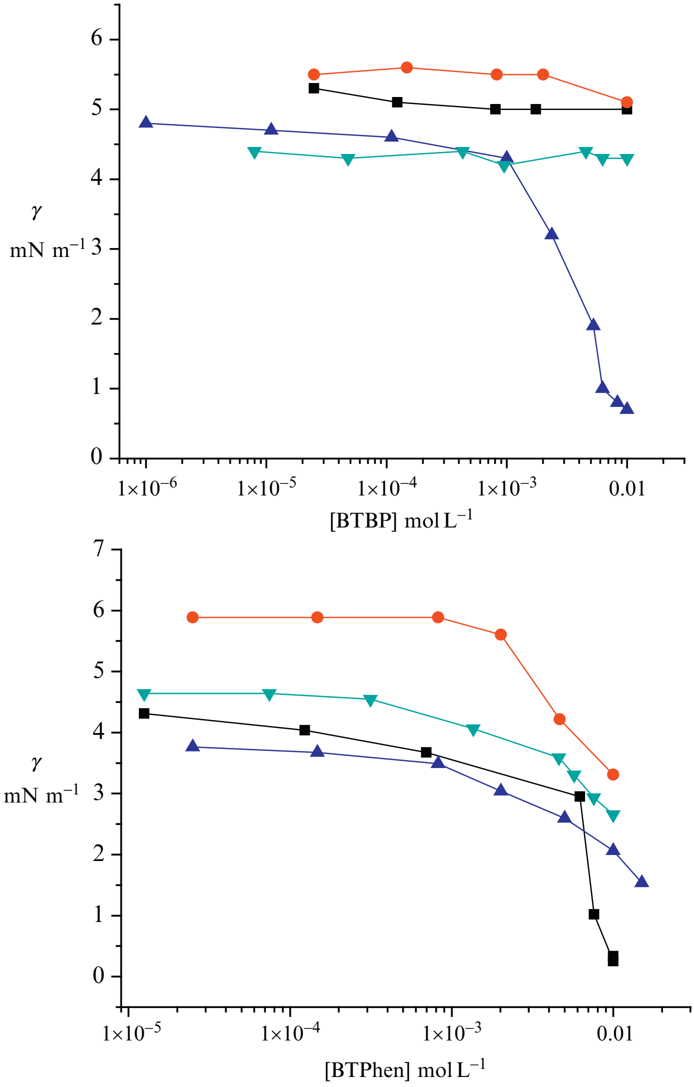


FIGURE 10 Surface tension measurements of CyMe$_4$-BTBP **26** (top) and CyMe$_4$-BTPhen **42** (bottom) as a function of ligand concentration in different diluents (■ = 1-octanol, ● = 2-methylcyclohexanone, ▲ = 3-methylcyclohexanone, ▼ = 4-methylcyclohexanone, aqueous phase: 1 M HNO_3).

with the BTBPs. Surface tension measurements revealed that the surface concentrations of CyMe$_4$-BTPhen **42** were indeed higher than those of CyMe$_4$-BTBP **26** in several solvents (Figure 10),[42] explaining why the rates of extraction were higher with CyMe$_4$-BTPhen **42**. Only in 3-methylcyclohexanone was CyMe$_4$-BTBP **26** found to be surface active. When studying a range of

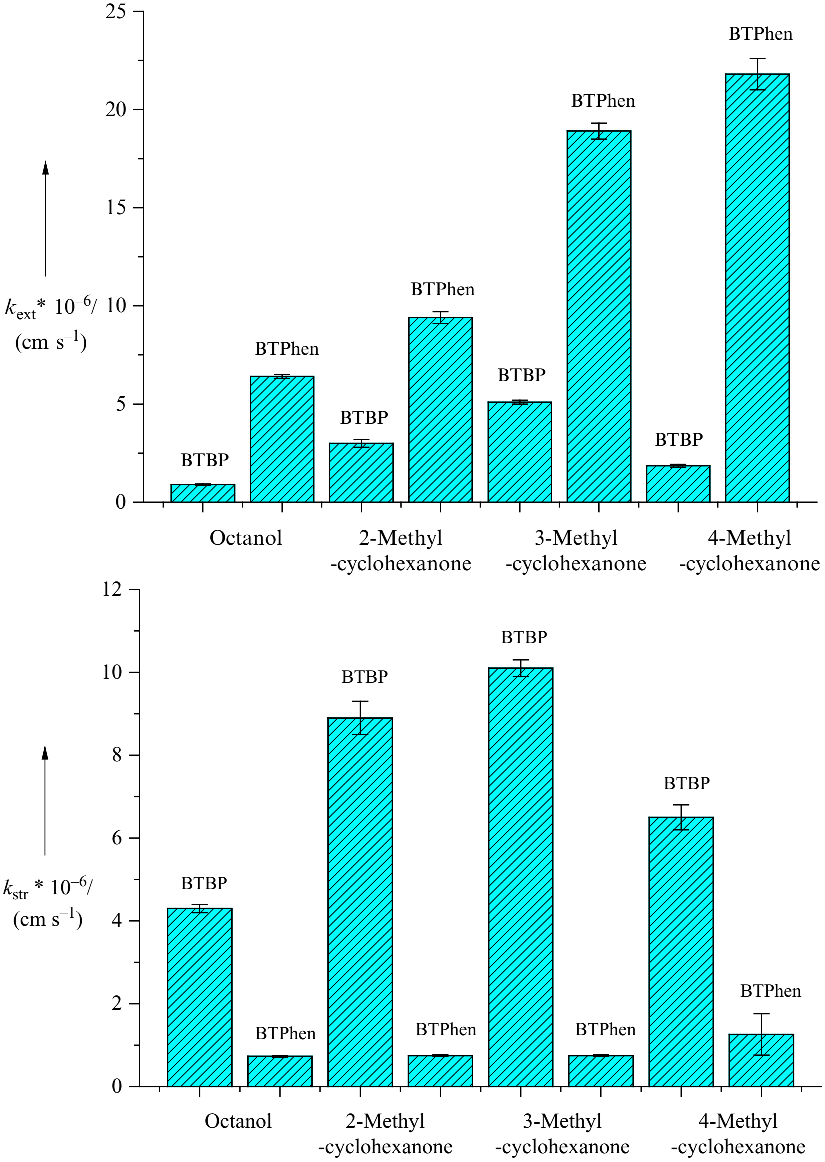


FIGURE 11 Extraction (top) and back-extraction (bottom) rate constants (*k*) of CyMe$_4$-BTBP **26** and CyMe$_4$-BTPhen **42** in different diluents.

alkyl-substituted cyclohexanones, this solvent was identified as a potential alternative to cyclohexanone.[46] Measurements of the extraction and back-extraction rate constants for Eu(III) across a range of solvents showed that CyMe$_4$-BTPhen **42** exhibited faster rates of extraction, while CyMe$_4$-BTBP **26** showed faster

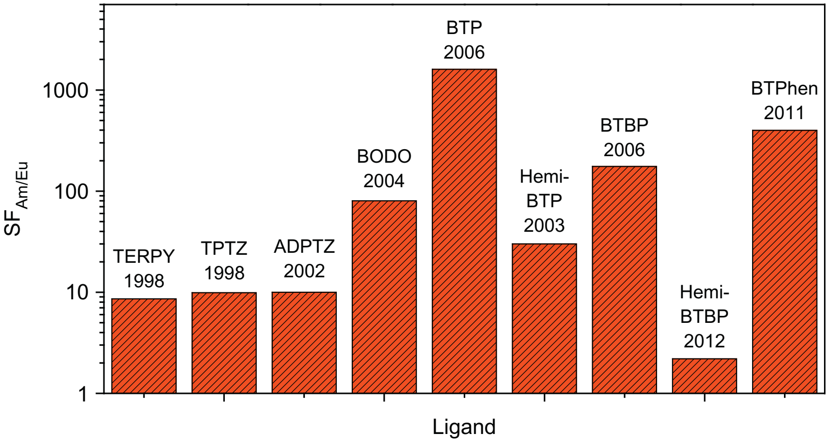


FIGURE 12 Am(III)/Eu(III) separation factors ($SF_{Am/Eu}$) for selected molecules over the years.

rates of stripping (Figure 11). For example, the extraction rate constants (k_{ext}) were higher for CyMe$_4$-BTPhen **42** than CyMe$_4$-BTBP **26** in octanol, 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone (Figure 11, top), while CyMe$_4$-BTBP **26** had the higher back-extraction rate constants (k_{str}) than CyMe$_4$-BTPhen **42** (Figure 11, bottom).

6 THE FUTURE PROSPECTS

It is clearly important to continue with developing the fundamental understanding of the relationship between structure, physical properties, and chemistry with regard to the partitioning of actinides from lanthanides. Very little is known about the formation of micelles in the above systems, for example. The evolution of the SF for Am(III) over Eu(III) ($SF_{Am/Eu}$) with different reagents over time is illustrated in Figure 12, but there is still room to synthesize new reagents and there are major challenges for the development of new reliable systems and extraction protocols. In addition, the proposed projects set new challenges for educating chemical engineers, who seem to think that the cost of chemicals is the principal criterion for the selection of a process. However, there are large cost savings to be made since the above reagents are far more selective than any previously developed. Therefore, the savings in the chemical plant could far outweigh the cost of chemicals.

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There are many European colleagues with whom we have worked and particular advances were made. The late Charles Madic of the CEA worked with M. J. H. for over 20 years, during which time over 100 joint papers were published. The EU financed much of this research under the EURATOM scheme and thanks go to the different desk officers,

especially Michel Hugon, who helped us to secure the funding. Special thanks must go to the different postgraduates and postdoctorates with whom we have worked over the years. Their names are mentioned in the references below. The studies continue!

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Chapter 7

Total Syntheses of Hamigeran B

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Chapter Outline

1 INTRODUCTION

Hamigera tarangaensis Berquist and Fromont (family Anchinoidae, syn. Phorbasidae) is a poecilosclerid sponge that grows near the Hen and Chicken islands lying east of Whangarei in New Zealand. The MeOH extract of the freeze-dried sponge afforded eight new compounds: hamigeran B **1**, 4-bromohamigeran B **2**, hamigeran A **3**, debromohamigeran A **4**, hamigeran C **5**, hamigeran D **6** isolated in, respectively, 0.63%, 0.07%, 0.46%, 0.32%, 0.09%, 0.09% yields, and hamigeran E **7**, and debromohamigeran **8**, which were isolated as their triethylderivatives **7a** and **8a** in, respectively, 0.93% and 0.11% yield. It still has to be established whether they are norditerpenoids or meroterpenoids (Figure 1).

The *in vitro* antitumor activity of these compounds against the P-388 cell line was evaluated and showed that hamigeran D **6** displayed the strongest activity with an IC_{50} of 8 mM. Hamigeran B **1** and 4-bromohamigeran B **2** showed similar activities, with IC_{50} values of 13.5 and 13.9 μM, respectively, while hamigeran C **5** and hamigeran A **4** had, respectively, an IC_{50} of 16.0 and 31.6 μM. None of the compounds tested showed any activity against the Gram-negative bacterium *Escherichia coli* or the yeast *Candida albicans*. However, against the Gram-positive bacterium *Bacillus subtilis*, compounds **5** and **6**

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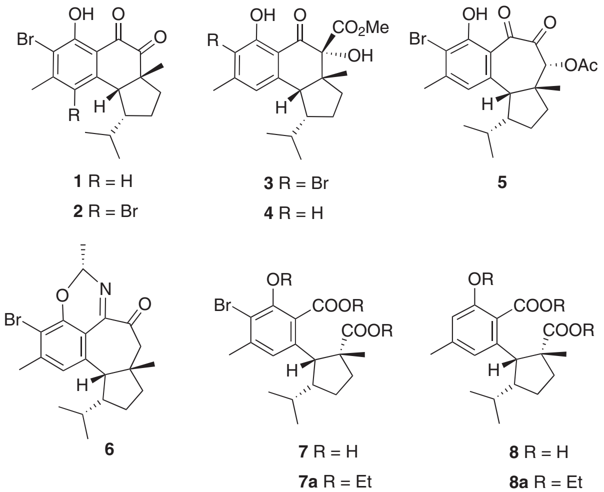


FIGURE 1 Compounds isolated from the sponge *Hamigera tarangaensis*.

showed a 3-mm inhibition zone outside the disk at assay loadings of 96, 150, and 156 μg, respectively. Compounds **1** and **2** both showed slight inhibition, while **3** and **8** (as the diethyl ester) showed no inhibition of bacterial growth. Compounds **1**, **5**, and **6** showed slight activity against *Trichophyton mentagrophytes*, although the rest were inactive. The most pronounced biological activity was observed in the antiviral assays. Hamigeran B **1** showed 100% virus inhibition against both herpes and polio viruses, with only slight cytotoxicity throughout the whole well at a concentration of 132 μg per disk. However, none of the other compounds showed any antiviral activity.[1]

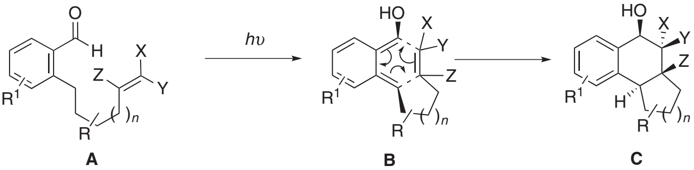
The synthesis of hamigerans, especially hamigeran B **1**, caught the attention of several chemists for two main reasons:

- their structural novelty: hamigeran B **1** has a unique carbon skeleton characterized by a substituted aromatic ring system fused to a [4.3.0] bicyclic system possessing a *cis* ring junction with three contiguous stereogenic centers and
- the exceptional biological activity of hamigeran B.

Nicolaou *et al.* reported in 2001 the first syntheses of hamigerans. Until 2011, six other syntheses have been disclosed using different strategies in each case.

2 NICOLAOU'S SYNTHESIS

The strategy developed by Nicolaou *et al.* is based on an IMPEDA (IntraMolecular PhotoEnolization Diels–Alder) cascade, comprising a photoinduced

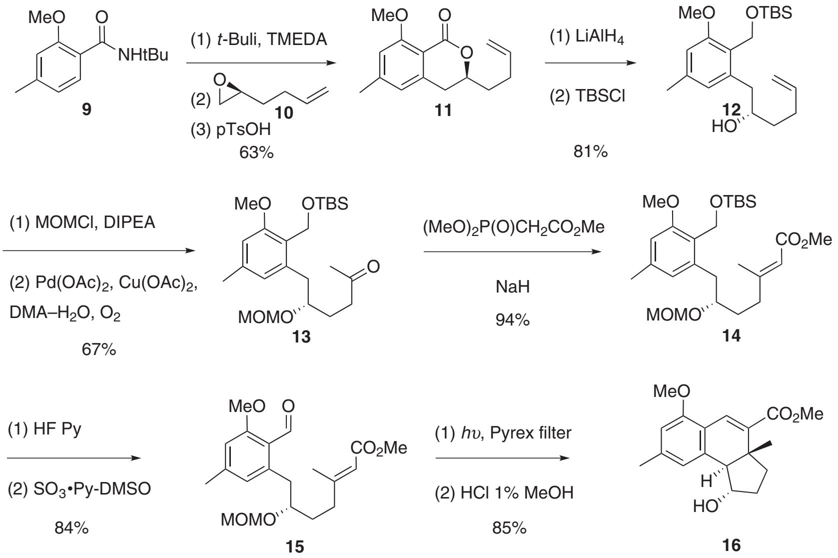


SCHEME 1 Nicolaou's IMPEDA cascade.

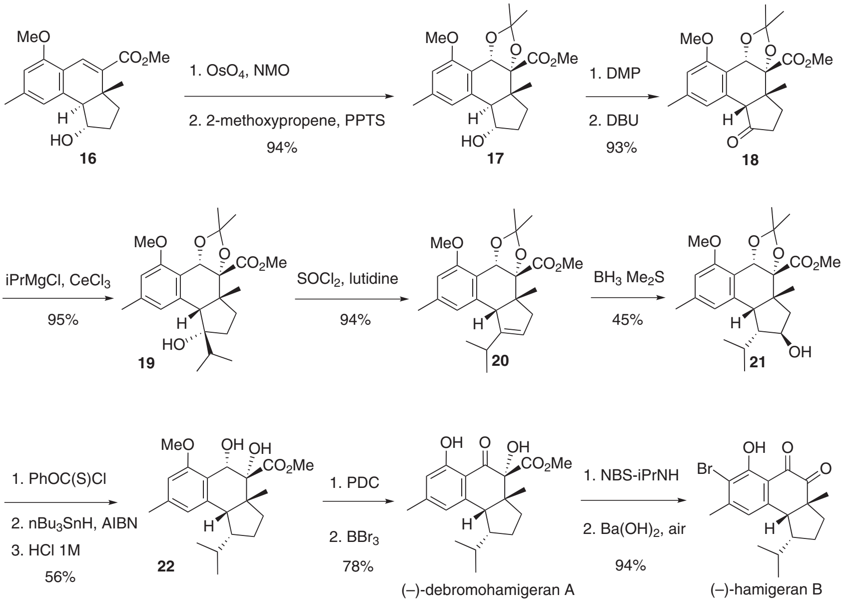
generation and trapping of hydroxy-*O*-quinodimethanes.[2–4] Thus, the general scheme for this methodology is the following: the photolysis of *O*-alkylbenzaldehyde **A** delivered a hydroxy-*O*-quinodimethane **B**, which in turn undergoes an intramolecular Diels–Alder reaction to deliver the corresponding tricyclic derivative **C** (Scheme 1).

Although Nicolaou *et al.* achieved the syntheses of several hamigerans; we will exclusively focus on the synthesis of hamigeran B. For that purpose, the enantiomerically enriched alcohol **12** was employed as starting material, the latter being readily available by treatment of amide **9** with 2 equiv. of *t*-BuLi to form a dianion that opened the terminal epoxide **10**, which was available according to Jacobsen's hydrolytic kinetic resolution method.[5] After reduction with $LiAlH_4$, the resulting diol was selectively monosilylated (TBSCl, NEt_3) to afford compound **12**. The protection of the latter as an MOM ether followed by Wacker oxidation ($Pd(OAc)_2$, $Cu(OAc)_2$, H_2O, O_2)[6] gave the methylketone **13**, which was homologated to the (*E*)-α,β-unsaturated ester **14** via a Horner–Wittig–Emmons reaction. After deprotection of the TBS ether with HF·pyridine, the resulting alcohol was oxidized by exposure to a $SO_3 \cdot$Py-DMSO protocol affording the photocyclized precursor **15**. The irradiation of the latter gave the expected tricyclic derivative **16** after acidic treatment (ee > 99%) (Scheme 2).

Afterward, compound **16** was dihydroxylated in the presence of NMO and a catalytic amount of OsO_4 leading to the corresponding triol with an excellent facial selectivity.[7] After selective protection of the vicinal hydroxy groups with 2-methoxypropene in the presence of a catalytic amount of PPTS, the resulting acetonide **17** was submitted to a Dess–Martin periodinane oxidation[8] to deliver the ketone derivative, which afforded, after a DBU-promoted, base-induced epimerization, compound **18** bearing a *cis* ring junction (Scheme 3). The entire carbon skeleton of hamigeran B was finally installed by addition of *i*-PrMgCl in the presence of $CeCl_3$ to give tertiary alcohol **19**. The regioselective elimination of the hydroxyl group was realized by addition of $SOCl_2$-lutidine to yield the trisubstituted olefin **20** as the major product. This was subjected to hydroboration with $BH_3 \cdot Me_2S$ under sonication conditions leading to the desired 6(*S*),7(*R*)-alcohol **21** (45%) arising from an *exo* addition, together with the 6(*R*),7(*S*)-stereoisomer (23%). A reaction sequence with PhOC(S)Cl-pyridine and *n*-Bu_3SnH–AIBN followed by removal of the



SCHEME 2 Synthesis of tricyclic derivative **16**.



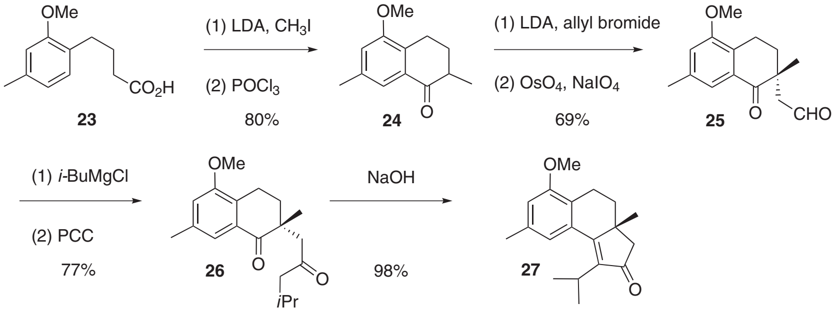
SCHEME 3 Nicolaou's synthesis of (−)-hamigeran B.

acetonide group under acidic conditions yielded compound **22**. An oxidation of the hydroxyl group with PDC followed by a demethylation reaction using BBr_3 gave (−)-debromohamigeran A. A cascade reaction initiated by $Ba(OH)_2$ under aerobic conditions promoted an initial saponification of the methyl ester followed by a decarboxylation reaction and an autoxidation leading finally to (−)-hamigeran B (Scheme 3).

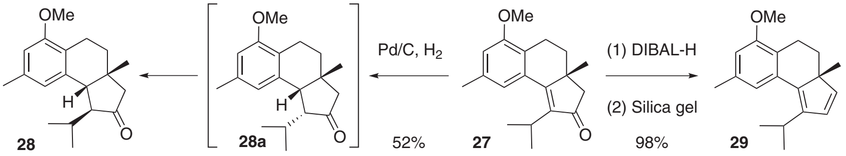
3 CLIVE AND WANG'S SYNTHESES

In their first synthesis of racemic hamigeran B, Clive and Wang turned their attention toward the formation of the tricyclic derivative **27**. However, it was not obvious that the hydrogenation of compound **27** would occur preferentially from the α- or the β-face. To check this point, the carboxylic acid **23** was transformed into the methyl tetralone **24**, which was submitted to an allylation reaction followed by an oxidative double bond cleavage to afford the keto aldehyde **25**. Addition of the Grignard reagent *i*-BuMgCl followed by a PCC oxidation delivered the 1,4-diketone **26**, which was cyclized under basic conditions to yield tricyclic derivative **27** (Scheme 4).[9–11]

Hydrogenation of compound **27** over Pd/C yielded the undesired β-stereoisomer **28**. Although the desired α-stereochemistry (formation of compound **28a**) was probably obtained, a carbonyl-mediated epimerization occurred in favor of compound **28**. In order to avoid this epimerization, the carbonyl group was reduced with DIBAL-H, leading to the corresponding



SCHEME 4 Clive and Wang's synthesis of intermediate **27**.



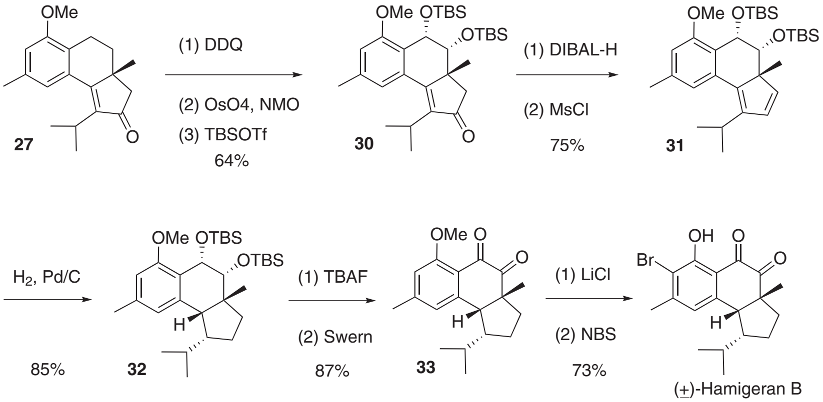
SCHEME 5 Hydrogenation and reduction of compound **27**.

allylic alcohol. However, the latter spontaneously underwent dehydration during silica gel chromatography, readily affording diene **29** (Scheme 5).

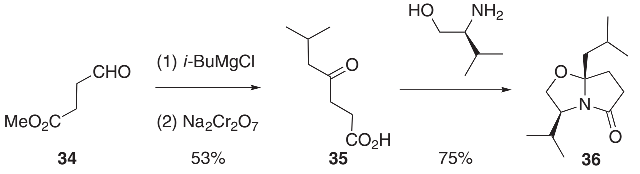
Due to a lack of facial selectivity, the hydrogenation of diene **29** led to an inseparable mixture of isomers. To promote the formation of the desired β-isomer, a bulky group was introduced on the α-face of the α,β-unsaturated ketone **27**. For that purpose, a DDQ oxidation followed by dihydroxylation with OsO_4 in the presence of NMO yielded the corresponding diol, which was protected as TBS ethers to afford compound **30**. A DIBAL-H reduction followed by mesylation of the resulting alcohol gave diene **31** after heating in refluxing dichloroethane. The hydrogenation of diene **31** in the presence of a catalytic amount of Pd/C took place readily to yield the desired isomer **32**. Finally, a desilylation with *n*-tetrabutylammonium fluoride (TBAF) and subsequent Swern oxidation delivered compound **33**, which was demethylated in the presence of LiCl and brominated with NBS to give (±)-hamigeran B (Scheme 6).

An asymmetric synthesis of key intermediate **27** was carried out as well by Clive and Wang. To this end, aldehyde ester **34**, easily available from γ-butyrolactone by methanolysis followed by PCC oxidation, was successively treated by *i*-BuMgCl and $Na_2Cr_2O_7$ to yield ketoacid **35**. Finally, condensation with (*S*)-valinol produced lactam **36** (Scheme 7).

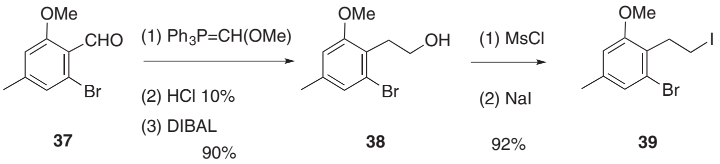
The aromatic moiety was built up as follows: aldehyde **37** was homologated by a Wittig reaction. After hydrolysis of the resulting enol ethers, a



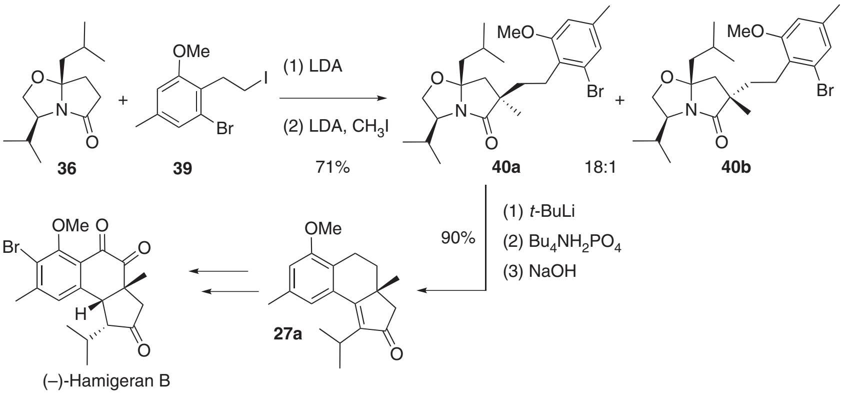
SCHEME 6 Clive and Wang's synthesis of (±)-hamigeran B.



SCHEME 7 Synthesis of lactam **36**.



SCHEME 8 Synthesis of the aromatic derivative **39**.



SCHEME 9 Clive and Wang's synthesis of (−)-hamigeran B.

DIBAL-H reduction afforded alcohol **38**, which was converted into its mesylate. Subsequent displacement of the leaving group by iodide yielded the desired compound **39** (Scheme 8).

The addition of LDA to lactam **36** followed by reaction with iodide **39** followed by a second alkylation with methyl iodide delivered the easily separable compounds **40a** and **40b** in an 18:1 ratio. Treatment of the major isomer **40a** with *t*-BuLi and *in situ* hydrolysis directly gave the tricyclic derivative **27a** as an enantiomerically pure compound. Procedures similar to those previously discussed led to (−)-hamigeran B (Scheme 9).

4 TROST'S SYNTHESIS

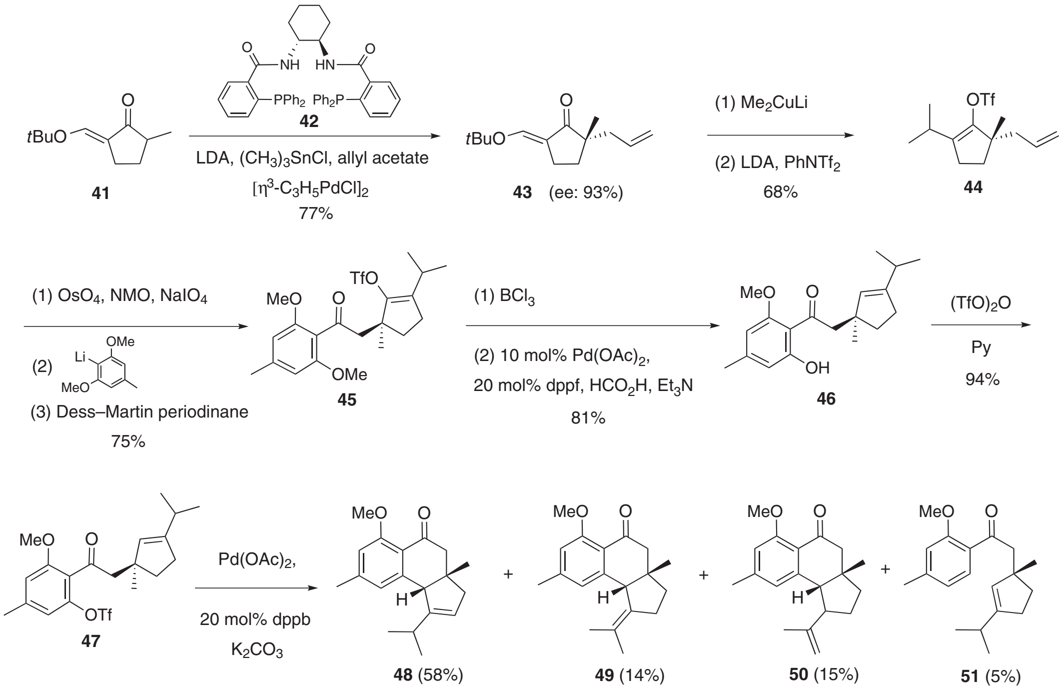
The synthetic route developed by Trost *et al.* was based on a palladium-catalyzed asymmetric allylic alkylation combined with an intramolecular Heck cyclization.[12,13] Cyclopentanone **41** was treated with [η^3-$C_3H_5PdCl]_2$, in the presence of the chiral ligand **42**, $(CH_3)_3SnCl$, LDA, and allyl acetate to give the corresponding enantiomerically enriched allylated ketone **43** (ee: 93%). The addition of lithium dimethylcuprate to the latter allowed the introduction of the isopropyl group. The resulting cyclopentanone was then converted into triflate **44** using standard conditions. After ozonolysis of the terminal double bond, reaction with lithiated orcinol dimethyl ether and a Dess–Martin oxidation, the expected ketone **45** was obtained. After mono-demethylation with BCl_3, the resulting product was subjected to a palladium-catalyzed reduction with formic acid. The resulting phenol derivative **46** was converted into triflate **47**. A Heck reaction on the latter led to a mixture of tricyclic derivatives **48**, **49**, and **50** together with compound **51** (Scheme 10).

At this stage, hydrogenation of compound **48** from the least hindered convex face seemed to be straightforward. To avoid reduction of the carbonyl group, a demethylation was first carried to generate phenol derivative **52**. However, hydrogenation over Pd/C afforded only compound **53** bearing a C-6 *epi* configuration. Trost *et al.* postulated that the epimerization at C-6 could occur by an equilibration in the semihydrogenation intermediate because of a slow final reductive elimination step. Therefore, the hydrogenation was carried out in the presence of iridium black, leading with complete diastereoselectivity to the desired tricyclic derivative **54**. Finally, a selenium dioxide oxidation followed by an NBS bromination delivered (−)-hamigeran B (ee > 93%) (Scheme 11).

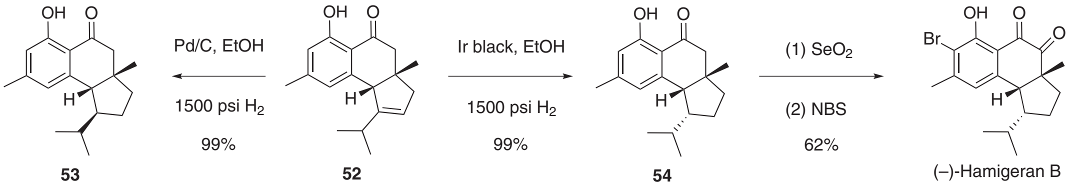
It has also to be noted that hydrogenation of the free phenol **55**, the product of a BBr_3-mediated demethylation of compound **49**, proved impossible under several reaction conditions. Similarly, the isomer of **49** with an endocyclic double bond, namely **56**, was also completely recalcitrant to hydrogenation (Scheme 12).

5 TABER'S SYNTHESIS

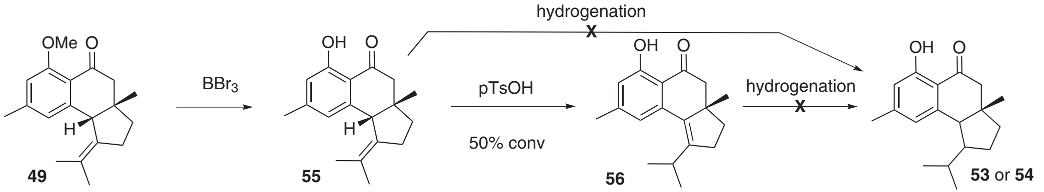
Taber *et al.* chose to develop a new approach to cyclopentane construction based on a rhodium-mediated, intramolecular C—H insertion of an α-aryl-α-diazoketones.[14] The starting material was aldehyde **57**, which was derived from (*R*)-citronellol. The benzylic deprotonation of 3,5-dimethylanisole, followed by addition of aldehyde **57**, afforded the corresponding alcohol as a mixture of two diastereomers. A catalytic PCC oxidation (with periodic acid as the stoichiometric oxidant) of the latter produced ketone **58**, which was submitted to a diazo transfer reaction with 2,4,6-triisopropylbenzenesulfonyl azide (TIBSA) and DBU in toluene to deliver diazoketone **59** as an unstable and light-sensitive compound. The rhodium-mediated C—H insertion proceeded efficiently in the presence of $Rh_2(pttl)_4$ (dirhodium (II) tetrakis[*N*-phthaloyl-(*S*)-*t*-leucinate]) to generate cyclopentanone **60** as a mixture of two diastereomers that were separable but interconverted on storage. A debenzylation reaction followed by a Dess–Martin oxidation produced aldehyde **61** still as a mixture of diastereomers. A $BF_3 \cdot Et_2O$-promoted intramolecular Friedel–Crafts reaction generated the benzylic alcohol, which underwent *in situ* dehydration to give the tricyclic derivative **62**. The cyclopropyl Petasis reagent was added to ketone **62** in the presence of sodium bicarbonate to avoid an *endo* isomerization of the double bond. The resulting alkene **63**



SCHEME 10 Trost's synthesis of (−)-hamigeran B precursor compound 48.



SCHEME 11 Trost's synthesis of (−)-hamigeran B.



SCHEME 12 Compounds **55** and **56** are recalcitrant to hydrogenation.

was hydrogenated in the presence of iridium black to minimize double bond migration, leading to compound **64** as a single diastereomer. A dihydroxylation was carried out to deliver diol **65** as a mixture of diastereomers. Hydrogenolysis of the cyclopropane ring installed the isopropyl group and also removed the benzylic alcohol to produce the tricyclic derivative **66**, which was oxidized with TPAP/NMO to compound **67**. Finally, a demethylation followed by a NBS bromination afforded (−)-hamigeran B (Scheme 13).

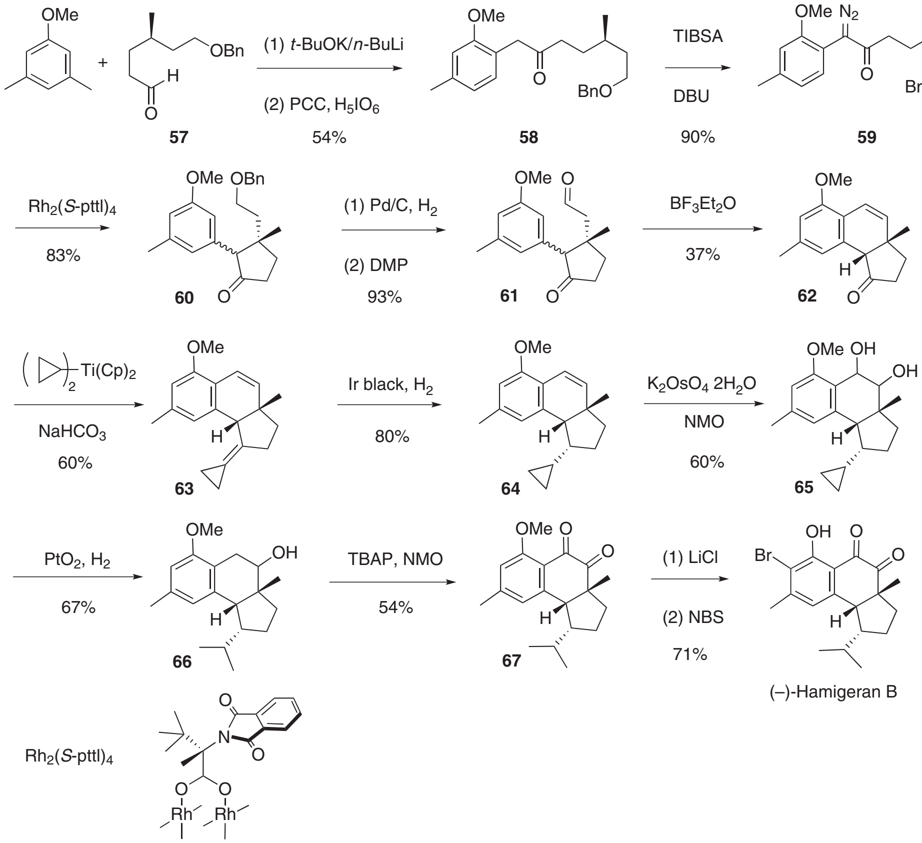
6 OUR APPROACHES

Our interest in the synthesis of hamigeran B **1** started in 2004, in conjunction with the work of Aurélie Klein, a Ph.D. student involved in a study of the reactivity of alkynoates tethered to cycloalkanones in the presence of TBAF. In this context, we showed that allenoate **69** bearing a *cis* ring junction was readily available when acetylenic ω-ketoester **68** was treated with TBAF at room temperature (Scheme 14).[15]

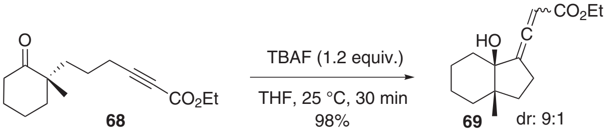
At that time, our interest was directed toward the synthesis of natural sesquiterpenes like lucinone.[16] Thus, we needed to have in our hands β-ketoester **70**, a precursor of lucinone. To that end, a model study was first carried out, as we wanted to see if hydroxy-β-ketoester **71** could be accessible starting from allenoate **69**. Indeed, a known procedure for the obtention of a β-ketoester is the addition of an amine to an allenoate followed by the hydrolysis of the resulting enamine (Figure 2).[17]

Thus, the protection of alcohol **69** as a silyl ether followed by addition of morpholine was achieved, leading quantitatively to the corresponding enamine **72**. However, the acidic hydrolysis of the latter did not deliver the expected hydroxy-β-ketoester **71**, but rather the α,β-unsaturated-β-ketoester **73** (Scheme 15). Furthermore, when morpholine was directly added to compound **69**, treatment of the resulting enamine **74** with formic acid generated the β-ketoester **75** and the α,β-unsaturated-β-ketoester **73**, which were, respectively, isolated in 32% and 34% yield (Scheme 15).[18] Ketoester **75** presumably resulted from a retro-aldol-type reaction of **71** or a similar species.

Despite many modifications of reaction conditions, compound **71** was never obtained. Consequently, we were never able to achieve the synthesis of lucinone. Nevertheless, an efficient access to the α,β-unsaturated β-ketoester **73** was developed. Taking into account this fact, we went looking for the synthesis of another natural product bearing such a 5–6-fused ring system as a substructure. It appeared that hamigeran B **1** fit this criterion and represented a goal that could be reached in a reasonable period of time. Unfortunately, Aurélie Klein was not in a position to start the synthesis of hamigeran B because she completed and presented her Ph.D. in November 2005. Therefore, the continuation of the hamigeran B synthesis was carried out by Tania Welsch, a Ph.D. student who started the benchwork on this subject in January 2006. In fact, we became interested in the synthesis of compound **54**, which



SCHEME 13 Taber's synthesis of (−)-hamigeran B.



SCHEME 14 Formation of allenoate **69**.

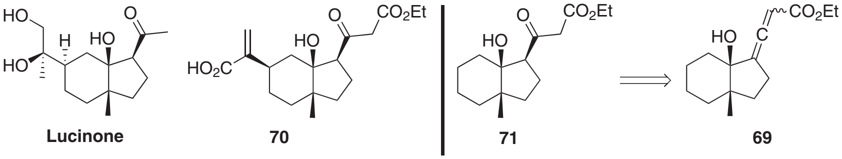


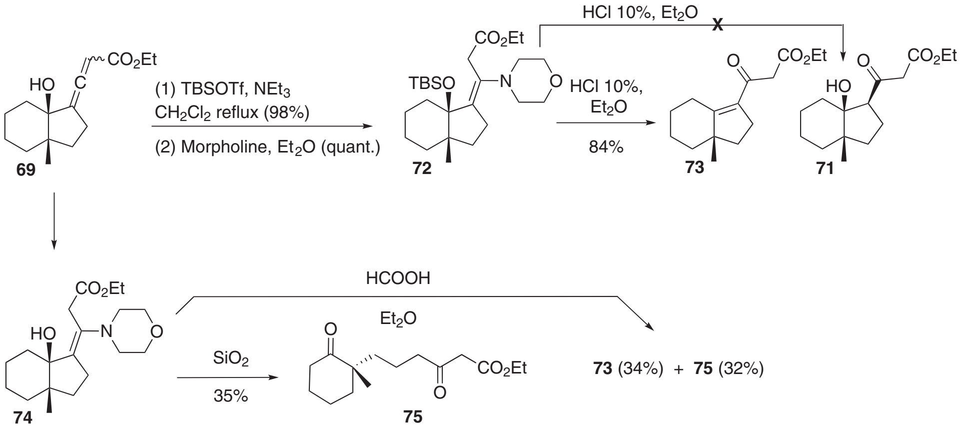
FIGURE 2 Lucinone and formal precursors of lucinone.

had already been transformed into hamigeran B by Trost *et al.*[13] It appeared that starting from a tetralone subunit, the construction of the missing five-membered ring present in hamigeran B could be achieved using our methodology involving the TBAF-mediated preparation of allenoates.

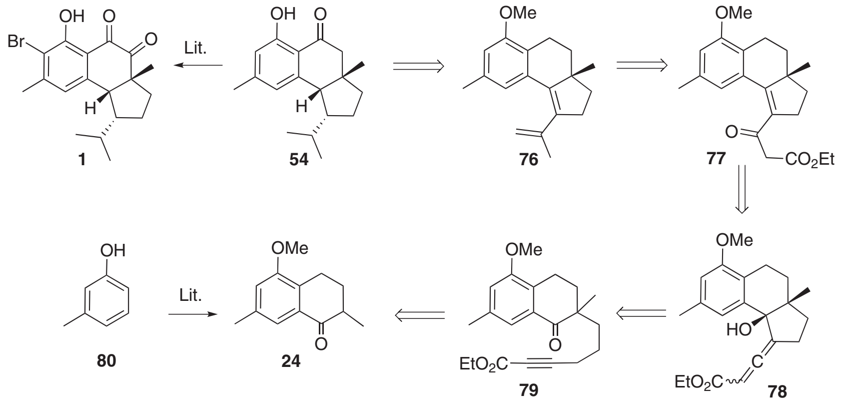
The retrosynthetic path was elaborated as depicted in Scheme 16. The tricyclic derivative **54** could result from diene **76** via a reduction–oxidation sequence. The latter compound would come from a decarboxylation–Wittig reaction sequence starting from the α,β-unsaturated-β-ketoester **77**. At this stage, our previously developed methodology could be useful. Indeed, compound **77** could arise from allenoate **78**, which should be available from acetylenic ω-ketoester **79** through a TBAF-promoted cascade reaction, the starting material being the substituted tetralone **24**, easily available from *m*-cresol **80** as shown by Clive *et al.* (Scheme 16).[10,11]

We were confident that we could prepare diene **76**, but the hydrogenation of the latter could have been troublesome. Indeed, the question was whether the hydrogenation would occur selectively from the convex or the concave face of the diene. As shown above, according to Clive *et al.*,[11] hydrogenation of compound **27** took place from the convex face to deliver **28a** as a primary product. This presumably undergoes an epimerization via an enol or enolate to yield compound **28** (see Scheme 5). On the other hand, Trost *et al.*[13] argued likewise that hydrogenation of compound **52** took place from the convex face when this reaction was carried out in the presence of iridium black, but in this case compounds **55** and **56** were unreactive under all hydrogenation reaction conditions. According to these results, it was reasonable to postulate that hydrogenation of compound **76** should occur from the convex face to deliver the required isomer, the hydrogenation catalyst being either Pd/C (see hydrogenation of compound **31**, Scheme 6) or Ir black (see hydrogenation of compound **52**, Scheme 11).

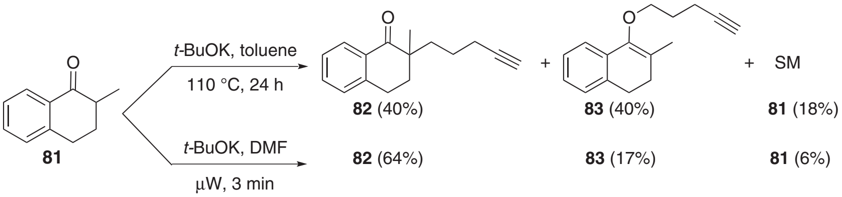
A model study was carried out starting from tetralone **81**. The alkylation reaction of the latter was run with 5-iodo-pentyne in the presence of *t*-BuOK as a base in refluxing toluene for 24 h. Under these reaction conditions, a



SCHEME 15 Unexpected reactions of allenoate **69** and enamine **74**.



SCHEME 16 Miesch's retrosynthetic analysis of hamigeran B.

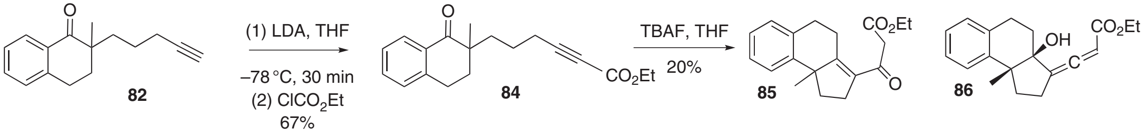


SCHEME 17 Alkylation of tetralone **81**.

1/1/0.45 mixture of compounds was obtained: the desired C-alkylated product **82**, the O-alkylated compound **83**, as well as unreacted starting material, isolated in 98% overall yield. In order to improve the reaction, the alkylation reaction was exposed to microwave activation in DMF to afford a similar mixture (ratio 11/3/1) that favored the desired compound **82**. The completion of the reaction took 3 min, well illustrating the usefulness of microwave activation in this case (Scheme 17).[19]

The introduction of the carbethoxy group was performed under the usual conditions providing the corresponding alkynoate **84**. The addition of TBAF to the latter did not afford the expected allenoate **86**, but instead gave the α,β-unsaturated β-ketoester **85**. Unfortunately, the latter was isolated in low yield (20%) from a complex mixture of compounds (Scheme 18).

Thus, our model study allowed the direct access to the α,β-unsaturated β-ketoester **85**, albeit in rather low yield. At this stage, it seemed obvious to us that the synthetic route depicted in Scheme 16 would not be tenable for the synthesis of hamigeran B. Fortunately, at this time, we were involved in a study of the reactivity of alkynoates tethered to bicyclo[*n*.2.0]alkanones.[20] Based on that work, we expected that a TBAF-promoted anionic cascade



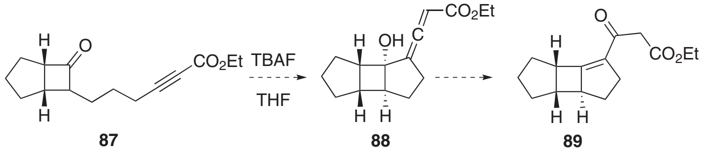
SCHEME 18 Formation of β-ketoester **87**.

reaction starting from bicyclo[3.2.0]heptanone **87** would afford tricyclic decane derivative **88**, a potential precursor of the α,β-unsaturated β-ketoester **89** (Scheme 19).

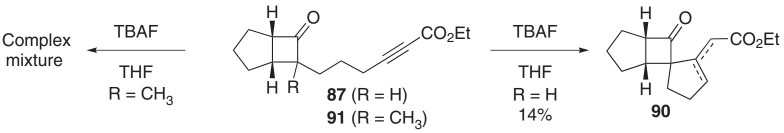
The preliminary results were frustrating. In this case, the expected allenoate **88** was never obtained, but the corresponding spiro derivative **90** was isolated (as a 1:1 mixture of *exo*:*endo* double bond isomers) in a very low yield (Scheme 20). Moreover, the addition of TBAF to the bicyclo[3.2.0]heptanone derivative **91**, bearing a quaternary stereogenic center at position 6, afforded a complex mixture of compounds.

In desperation, we next turned our attention toward our initial reaction conditions, which allowed us to discover the reactivity of alkynoates tethered to cycloalkanones in the presence of TBAF. We had previously shown that the addition of TBAF to alkynoates tethered to silyl enol ethers derived from (cyclo)alkanones allowed access to allenoate derivatives. For example, the addition of TBAF to silyl enol ether **92** afforded two compounds: the spiro derivative **93** together with allenoate **94** isolated in 15% and 45% yield, respectively (Scheme 21).[21]

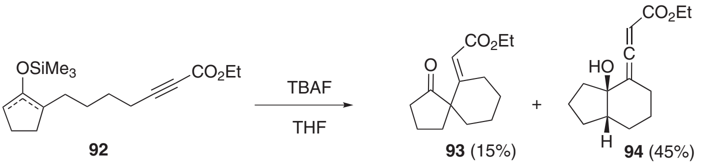
To apply this reaction sequence to bicyclo[3.2.0]heptanone **87**, we had first of all to transform **87** into the corresponding silyl enol ether. By using conventional reaction conditions (i.e., TBSOTf/NEt_3), the formation of the corresponding silyl enol ether was amazingly not observed. Two compounds were isolated: the spiro derivative **95** (mixture of *exo*–*endo* double bonds, ratio 2.5:1) and the tricyclic allenoate **96** (mixture of separable isomers, ratio 1.7:1) which were isolated in 35% and 36% yield, respectively (Scheme 22).



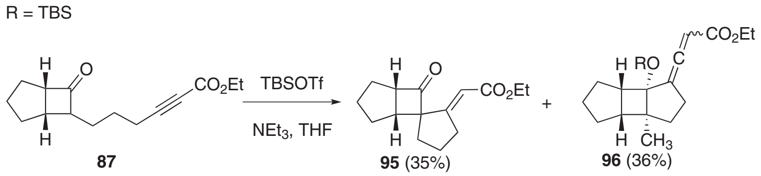
SCHEME 19 Predicted formation of allenoate **88** and β-ketoester **89**.



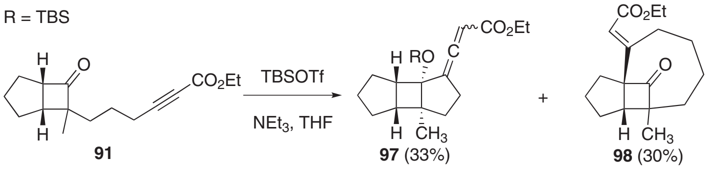
SCHEME 20 Formation of spiro derivative **90**.



SCHEME 21 Formation of spiro derivative **93** and allenoate **94**.



SCHEME 22 TBSOTf promoted alkynylogous Mukaiyama aldol reaction and intramolecular Michael addition.



SCHEME 23 TBSOTf promoted alkynylogous Mukaiyama aldol reaction and intramolecular Michael addition.

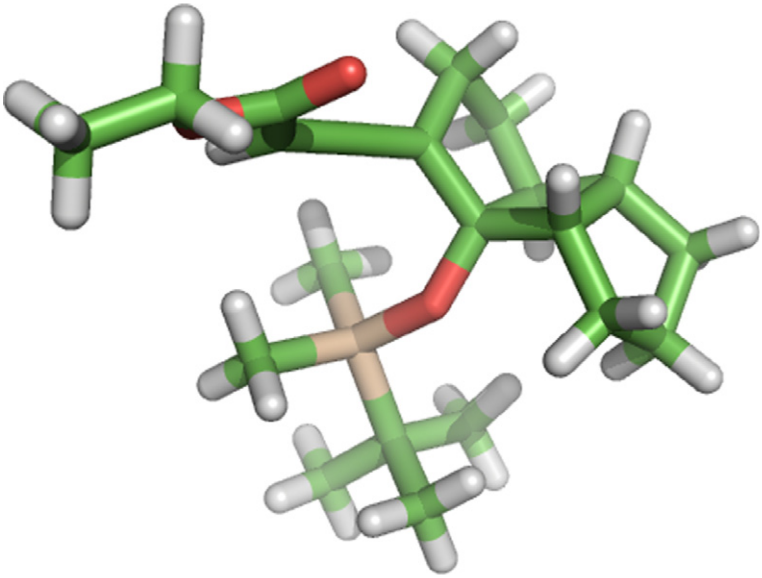
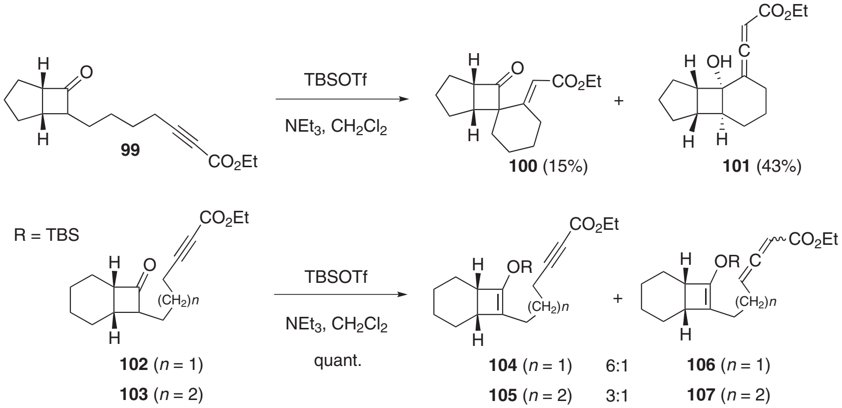
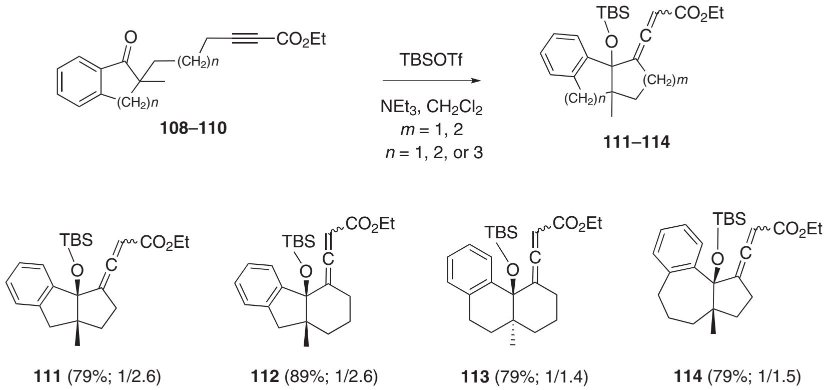


FIGURE 3 Crystal structure of allenoate **96**.

This outstanding reactivity was extended to α-disubstituted ketone **91**. The formation of the expected allenoate **97** took readily place, and surprisingly, it was also possible to isolate the strained tricyclic derivative **98** (Scheme 23). X-ray structure analysis made evidence for the structure of allenoate **96**, establishing the *cis–anti–cis* configuration of the latter (Figure 3).



SCHEME 24 Scope and limitations of the alkynylogous Mukaiyama aldol reaction.



SCHEME 25 The alkynylogous Mukaiyama aldol reaction starting from indanone, tetralone and suberone derivatives.

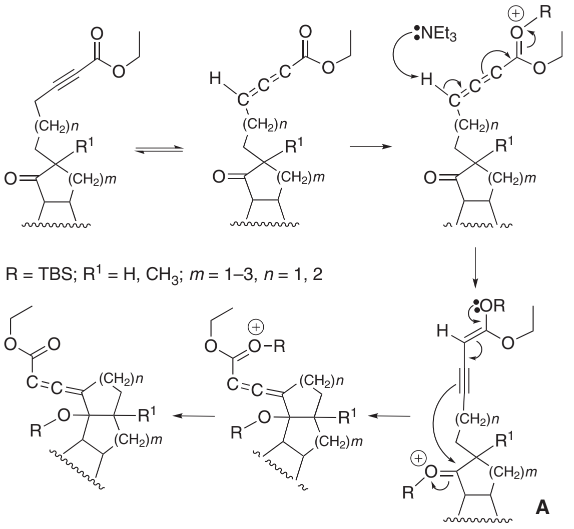
These results prompted us to study the scope and the limitations of this new cascade reaction. We found that a modification of the spacer length was tolerated, that is, starting from homologous alkynoate **99**, we observed the formation of the corresponding tricyclic derivative **101**. Unfortunately, the addition of TBSOTf to the bicyclo[4.2.0]octane derivatives **102** and **103** exclusively gave the silyl enol ethers **104–107**, containing either an alkynoate or an allenoate (Scheme 24).

However, when TBSOTf was added to alkynoates tethered to indanone, tetralone, and benzosuberone derivatives **108–110**, the corresponding allenoates **111–114** were readily obtained as a mixture of isomers and with a complete diastereoselectivity with respect to the ring junction (Scheme 25).

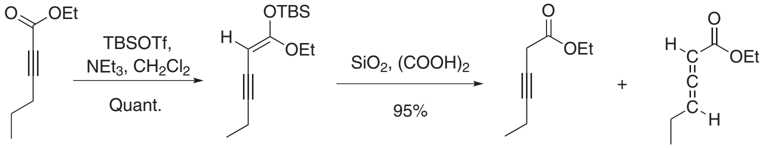
In order to explain the formation of the tricyclic derivatives **96**, **101**, and **111–114**, it was reasonable to consider that under our reaction conditions, the alkynoate could be in equilibrium with the corresponding allenoate. An initial TBSOTf activation of the allenoate led, in the presence of NEt_3, to a silylalkynylketene acetal **A**. An intramolecular alkynylogous Mukaiyama aldol-type reaction, induced by the concomitant Lewis acid activation of the cycloalkanone carbonyl group, then took place to afford the desired allenoate (Scheme 26).

To obtain evidence to support the mechanism proposed, ethyl hexynoate was treated with excess $TBSOTf/NEt_3$, leading to a compound whose spectroscopic data fully agree with silylalkynylketene acetal **115**. Before our discovery, the formation of this kind of silylalkynylketene acetal always required the use of strong bases, which is, of course, less convenient.[22] Interestingly, the acidic hydrolysis of compound **115** using Conia's conditions led to the deconjugated ester **116** together with allenoate **117** in a ratio 3:1 (Scheme 27).[23]

It was apparent to us that, in the context of a hamigeran B synthesis, our alkynylogous Mukaiyama aldol reaction would be of interest. These results led us to realize that access to the required tricyclic derivative **78** would be



SCHEME 26 Mechanism proposal for the alkynylogous Mukaiyama aldol reaction.



115 **116** 3:1 **117**

SCHEME 27 Formation of 3-alkynoate **116** and allenoate **117**.

possible. It was at this point that we renewed our effort toward the synthesis of hamigeran B.

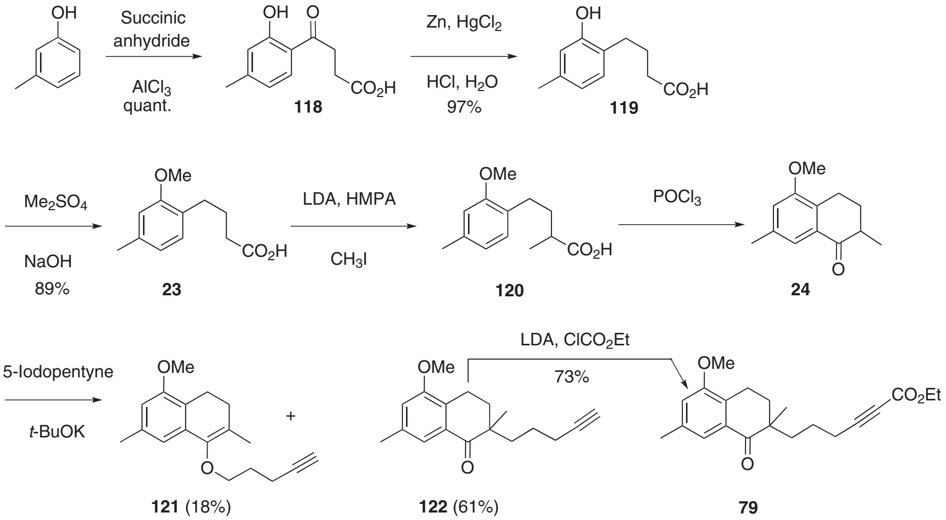
The synthesis of the key acetylenic ω-ketoester **79** was performed in a straightforward fashion. According to the procedure developed by Clive *et al.*,[10,11] a Friedel–Crafts reaction was carried out between *m*-cresol and succinic anhydride in the presence of $AlCl_3$, leading to the carboxyl derivative **118**. A Clemmensen reduction afforded compound **119**, which was transformed into methoxy derivative **23** using standard reaction conditions. An excess of LDA was added to compound **23** followed by the addition of methyl iodide to yield compound **120**. Cyclization upon treatment with phosphorus oxychloride led to the tetralone **24**. The addition of 5-iodo-1-pentyne to the latter was carried out under microwave activation to afford an easily separable mixture of O-alkylated product **121** together with alkyne **122** (Scheme 28). Finally, functionalization of alkyne **122** in the presence of LDA and ethyl chloroformate provided the desired alkynoate **79**.

Gratifyingly, the key steps of our synthesis readily took place. Indeed, starting from the alkynoate **79**, the alkynylogous intramolecular Mukaiyama aldol reaction afforded the desired allenoate **123** as an inseparable mixture of isomers (ratio 1.3:1) in 79% yield. The HBF_4-promoted acid hydrolysis of allenoate **123** yielded the expected α,β-unsaturated β-ketoester **124** (Scheme 29).

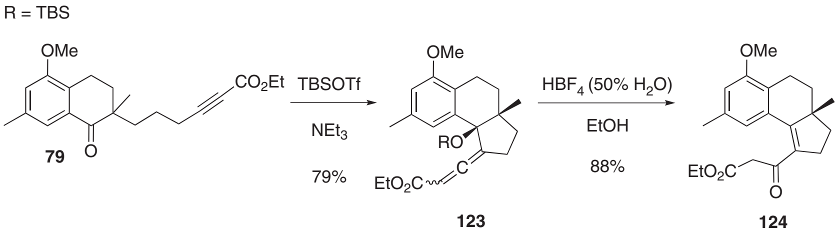
Using Krapcho's reaction conditions, a decarboxylation occurred, yielding the corresponding α,β-unsaturated ketone **125**. When a subsequent Wittig reaction was carried out in THF at room temperature, the corresponding diene **126** was isolated in a modest yield (25%). However, when the same reaction was executed in refluxing Me-THF, the yield could be increased to 86% (Scheme 30).

At this stage, we focused on the crucial reduction step of diene **126**. Hydrogenation of tricyclic compound **126** under an atmospheric pressure of hydrogen in the presence of a catalytic amount of Pd/C in AcOEt afforded exclusive reduction of the exocyclic double bond, giving alkene **127**. However, when the reaction was carried out under hydrogen pressure (45 bar) in MeOH, a 5:1 mixture of isomers **128a/128b** was obtained, the required isomer being the major compound. Finally, when the hydrogenation was run in acetic acid at atmospheric pressure in the presence of a catalytic amount of PtO_2, a 19:1 mixture of isomers **128a/128b** was obtained, the main isomer being the desired compound. It must also be noted that the starting material was quantitatively recovered when the hydrogenation was performed in the presence of iridium black (Scheme 31).

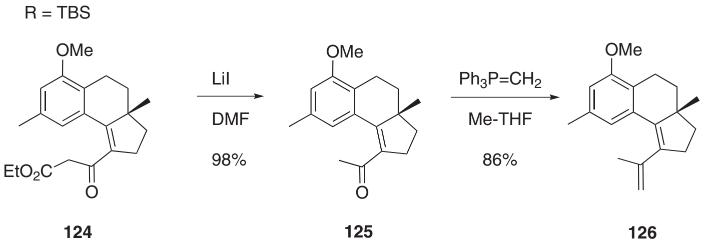
In order to achieve our synthesis, two synthetic routes were studied. First, a demethylation of isomers **128a/128b** was performed in the presence of BBr_3, followed by an oxidation in the presence of a mixture of DDQ and water. A benzylic oxidation occurred, but unfortunately together with an oxidation of the five-membered ring, leading to alkene **129**. The latter was unreactive toward different hydrogenation conditions, and this result is consistent with Trost's observations.[12] Therefore, the two steps were inverted. Thus,



SCHEME 28 Synthesis of alkynoate **80**.



SCHEME 29 Alkynologous Mukaiyama aldol reaction and acidic hydrolysis of allenoate **123**.



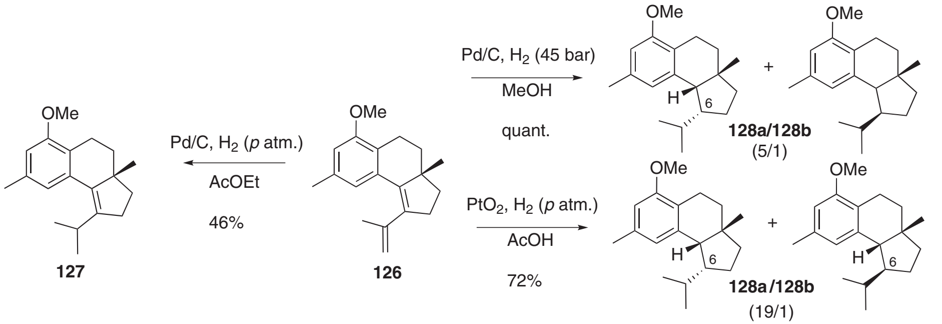
SCHEME 30 Synthesis of tricyclic derivative **130**.

the DDQ oxidation of compound **128a/128b** was performed first, immediately followed by addition of BBr_3 leading to the desired compound **54** along with compounds **130** and **129** (ratio 1:1.5:3). Compound **54** had already obtained by Trost *et al.* and converted into hamigeran B. Thus, our formal total synthesis of (±)-hamigeran B was achieved (Scheme 32).[23]

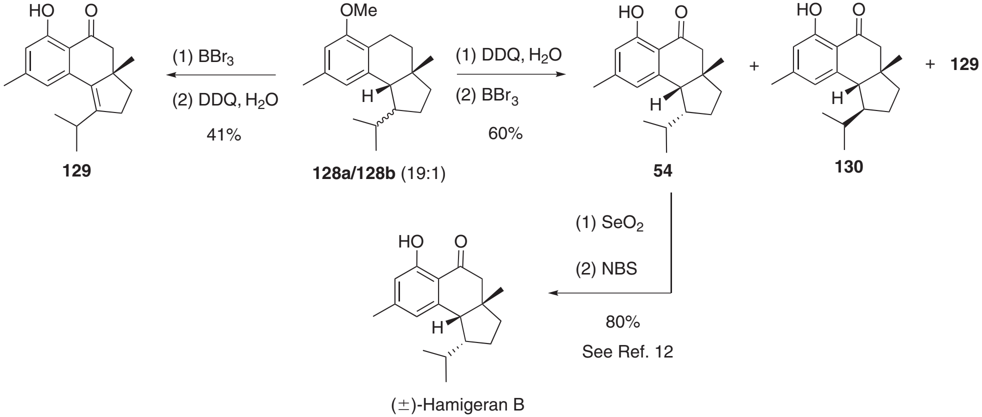
Further, we were pleased to see that the synthesis of highly enantiomerically enriched compound **54** was achieved by Stoltz *et al.* allowing them to achieve a formal total synthesis of (+)-hamigeran B. The synthetic route developed by the authors is described below.

7 STOLTZ'S SYNTHESIS

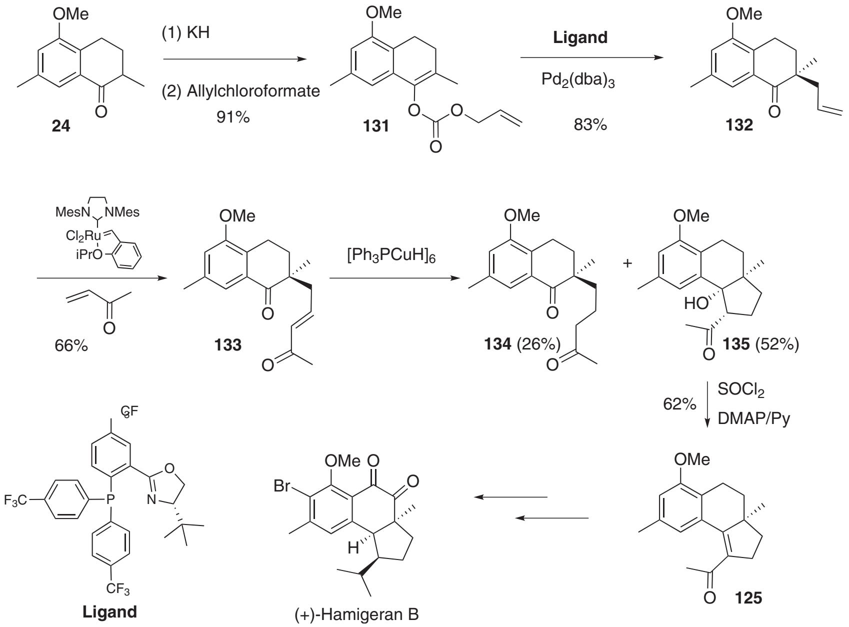
The key step in Stoltz's synthesis of (+)-hamigeran B was a Pd-catalyzed decarboxylative allylic alkylation allowing the introduction of the quaternary carbon center in excellent yield and stereoselectivity.[24] On this basis, tetralone **24** was transformed into allyl enol carbonate **131** by treatment with KH and addition of allyl chloroformate. Addition of $Pd_2(dba)_3$ in the presence of the trifluoromethylated derivative of (*S*)-*t*-BuPHOX as a ligand enabled the formation of compound **132** in 94% ee. To introduce the five-membered ring, a Ru-catalyzed cross-metathesis with methyl vinyl ketone was first performed in order to generate the 1,5-diketone **133**. However, after reduction of the α,β-unsaturated double bond, traditional aldol condensation reaction led to the formation of a complex mixture of products, this being probably due to nonselective enolization of the



SCHEME 31 Synthesis of tricyclic derivatives **128a/128b**.



SCHEME 32 Miesch's synthesis of (±)-Hamigeran B.

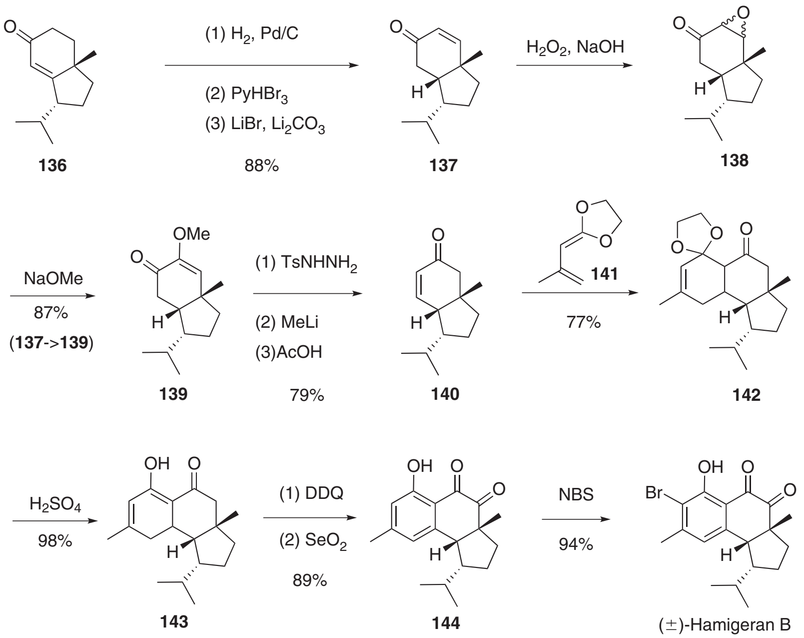


SCHEME 33 Stoltz's synthesis of (+)-hamigeran B.

diketone. To circumvent this problem, a CuH-mediated domino conjugate reduction–cyclization was carried out on compound **133** with Stryker's reagent to give the conjugated reduction product **134** and the desired keto-alcohol **135** as a single diastereomer. Finally, alcohol **135** was dehydrated to generate the enantiomerically enriched tricyclic derivative **125** (94% ee) a known precursor (see above) of (+)-hamigeran B (Scheme 33).

8 LAU'S SYNTHESIS

Lau's selected approach for the synthesis (±)-hamigeran B involved a Diels–Alder reaction allowing the introduction of the aromatic ring precursor and required no protecting group.[25] The bicyclic ketone **136** was used as starting material and was transformed into α,β-unsaturated ketone **137** by hydrogenation and regioselective bromination followed by elimination of HBr with lithium carbonate and lithium bromide. A Reusch enone migration was then performed on compound **138**. Toward this end, an epoxidation was first carried out and the resulting epoxide **138** was opened with sodium methoxide to provide α-methoxy enone **139**. After treatment of the latter with tosyl hydrazide, the resulting hydrazone was subjected to Shapiro reaction conditions to deliver the desired enone **140** after an *in situ* hydrolysis of the



SCHEME 34 Lau's synthesis of (+)-hamigeran B.

methyl enol ether. It has to be noted that the reaction sequence starting from compound **138** to compound **140** was performed without any purification of the different intermediates. A Diels–Alder reaction between enone **140** and ketene acetal **141** yielded the corresponding adduct **142** as a single diastereomer. No attempt was made to determine its configuration because the stereogenic centers would be destroyed through subsequent aromatization. Hydrolysis of the dioxolane ring gave enone **143**, which was aromatized by treatment with DDQ. Finally, a selenium dioxide oxidation provided 1,2-diketone **144** which, after treatment with NBS, provided (±)-hamigeran B (Scheme 34).

9 CONCLUSION

At this writing, three syntheses of (±)-hamigeran B, one synthesis of (+)-hamigeran B, and four syntheses of (−)-hamigeran B have been reported. Serendipity played an important role during our approach to hamigeran B. Indeed, none of the planned synthetic routes proved to be efficient to reach the final goal. Fortunately, a totally unexpected result allowed us to develop a new reaction, the alkynylogous Mukaiyama aldol reaction promoted by TBSOTf. The study of the scope and limitations of our reaction was very useful in devising an original synthetic route leading to a new formal total synthesis of (±)-hamigeran B.

ACKNOWLEDGMENTS

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Chapter 8

Exploring Prins Strategies for the Synthesis of Okilactomycin

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Chapter Outline

1 INTRODUCTION

The lead author's interest in natural product synthesis started as an undergraduate in the laboratory of Marvin Miller at the University of Notre Dame. While learning about science and chemistry starting at a young age from his patient father (inorganic chemistry Professor W. R. Scheidt), it was not until late in his bachelor degree studies while performing research in the Miller group that he started to fully appreciate the excitement and potential applications of organic chemistry and chemical synthesis. This interest led him to the laboratory of William Roush at Indiana University for his doctoral studies, where he focused on the synthesis of the ATPase inhibitor, bafilomycin A_1.[1] This successful endeavor instilled in him a fascination and appreciation for complex molecular architecture and polyketide macrolide natural products. In 2001, the lead author was evaluating potential research projects for

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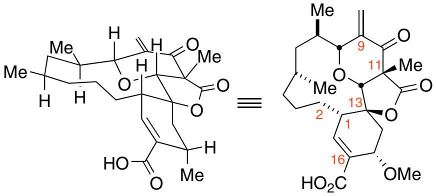
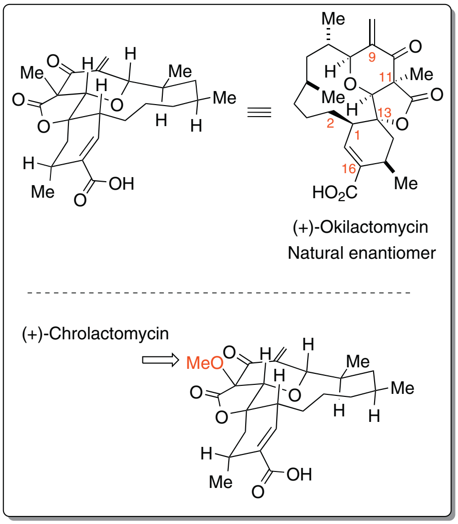
an independent career while a postdoctoral fellow with Prof. David Evans. A report from Yamashita and coworkers became interesting since it disclosed the structure of chrolactomycin, an intriguing natural product.[2] Further investigation of this potential target revealed that Omura and coworkers had reported the structure of an antibiotic okilactomycin (**1**) in 1987 (Figure 1). This compound was very closely related to chrolactomycin and isolated from a specific strain of *Streptomyces griseoflavus* cultured from an Okinawan soil sample.[3–5] Singh and coworkers have recently isolated okilactomycin and a number of congeners from *Streptomyces scabrisporus*.[6] Based on their structural similarity (chrolactomycin vs. okilactomycin), a successful route to either one would lead to success with the other related natural product. Like chrolactomycin, okilactomycin possesses a compact and challenging topology. A unique 6,5-fused tetrahydropyranone γ-lactone bicycle characterizes



1, (−)-Okilactomycin

- Four rings with spiro fusion
- Unusual 6/5-fused system
- Strained 11-membered ring
- Reactive *exo*-methylene



(+)-Okilactomycin
Natural enantiomer

(+)-Chrolactomycin

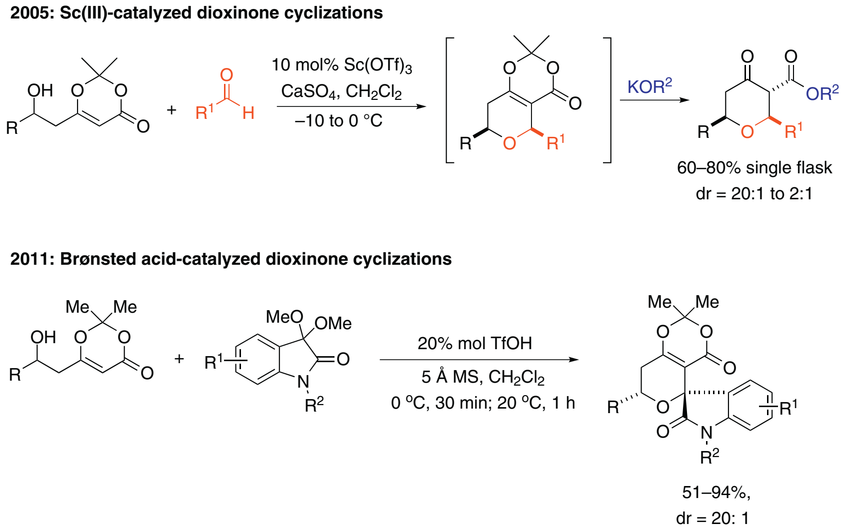
FIGURE 1 Structure of okilactomycin and chrolactomycin.

the tricyclic core with a spiro junction at a highly substituted cyclohexene. In addition to this unusual array, a strained deoxygenated bridge spans the cyclic framework to generate a rigid polycyclic architecture. In addition, okilactomycin exhibits antimicrobial and *in vitro* antiproliferative activity and inhibits Gram-positive organisms with MIC values ranging from 12.5 to 50 μg/mL.[5] Additionally, okilactomycin possesses nanomolar IC_{50} activity against leukemia tumor cells (L1210, P388). A number of previous synthetic efforts toward okilactomycin have been undertaken. The first reported synthetic studies on okilactomycin were by Takeda, Yoshii, and coworkers in 1992, who attempted a biomimetic intramolecular Diels–Alder cyclization strategy.[7] Paquette and coworkers also reported a partial synthesis of okilactomycin in 2002.[8,9] In 2007, Smith and coworkers accomplished the first total synthesis of (−)-okilactomycin and established the absolute stereochemistry by preparing the unnatural antipode.[10] Their synthetic route relied on a ring-closing metathesis (RCM) reaction and a Petasis–Ferrier rearrangement as the key transformations.[10,11]

2 OUR SYNTHETIC APPROACH

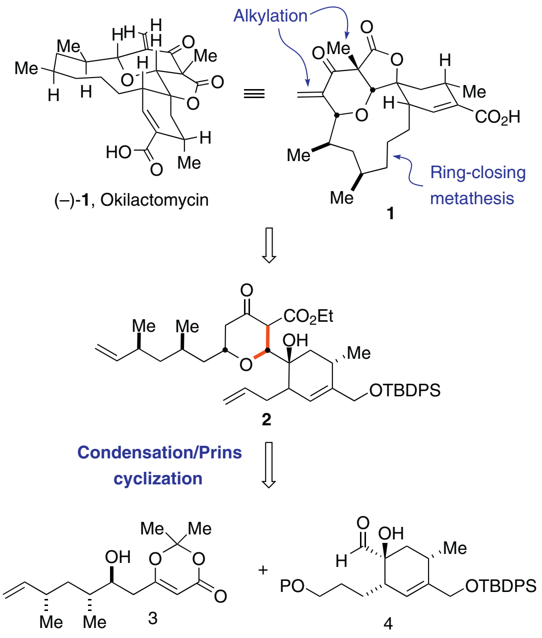
2.1 Synthesis Plan

The complexity and biological activity of okilactomycin was precisely the type of challenge we wished to tackle early in the establishment of our research group. There had been no total synthesis of either natural product as of 2002, and this opportunity seemed to be a perfect starting point to develop new chemical methodology for use in natural product synthesis. Significant strides have been made in the development of synthetic strategies toward tetrahydropyrans (along with related tetrahydropyran-4-ones) due to their prevalence in biologically active natural products and medicinal agents. Our interest in these classes of compounds has led us to discover a stereoselective and modular method for the direct formation of tetrahydropyran-4-ones through a Lewis acid-mediated condensation/Prins cyclization of β-hydroxydioxinones with aldehydes or isatins (Figure 2).[12,13] The Prins reaction has seen significant development over the past two decades, and this powerful process is poised for efficient and meaningful integration into complex synthesis with clinically relevant end points.[14–22] We have successfully applied our Prins strategy toward the total syntheses of neopeltolide and exiguolide, whose key steps both include ambitious Prins macrocyclization events.[23–26] The complex architecture of okilactomycin's 6,5-fused tetrahydropyranone γ-lactone bicycle presented a challenging target toward further extending our Prins methodology. Our initial 2002 plan toward okilactomycin is outlined in Scheme 1. Given the electrophilic nature of the *exo*-methylene unit, we elected to install it toward the end of the synthesis. We envisioned that the key tetracyclic precursor could be accessed from the lactonization


2005: Sc(III)-catalyzed dioxinone cyclizations

2011: Brønsted acid-catalyzed dioxinone cyclizations

FIGURE 2 Acid mediated condensation/Prins cyclization.



SCHEME 1 Retrosynthetic strategy.

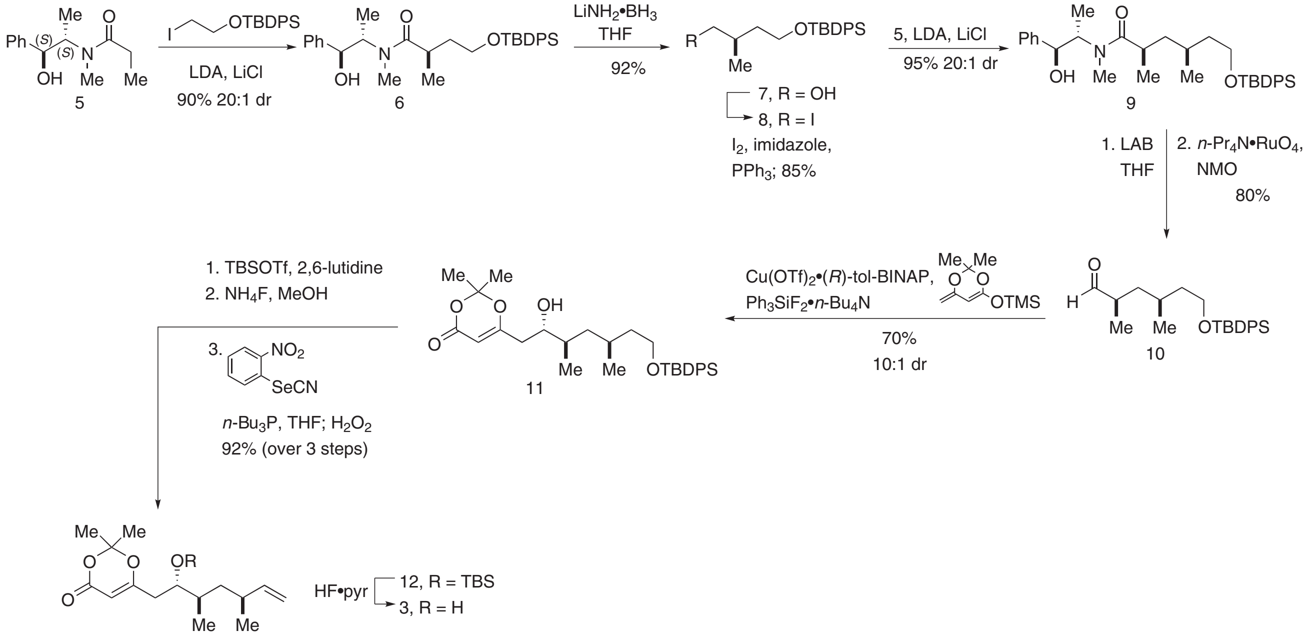
of *seco* ester **2** followed by an RCM reaction to install the 11-membered macrocycle. The tetrahydropyranone core would be formed from a highly convergent union of α-hydroxyaldehyde **4** and β-hydroxy dioxinone **3** through our condensation/Prins cyclization. This coupling represents an unprecedented attempt to extend our methodology to a highly encumbered tertiary aldehyde.

2.2 Construction of the Dioxinone Fragment

The synthesis of okilactomycin began with the development of high-yielding, reproducible routes to provide multigram quantities of key intermediates **3** and **4**. The synthesis of dioxinone **3** utilized two Myers–Larcheveque chiral amide alkylations[27–30] to install the 1,3-*syn* stereochemistry of the ansa chain (Scheme 2). The (+)-pseudoephedrine-derived chiral propionamide **5** was alkylated with TBDPS-protected iodoethanol to generate desired amide **6** in 90% yield and high diastereoselectivity (20:1 dr). With the proper documentation from Northwestern to the US Drug Enforcement Agency, 100 g of (+)-pseudoephedrine at a time could be obtained from Sigma-Aldrich to facilitate this work. Amide **6** underwent reductive removal of the chiral auxiliary with lithium (diisopropyl)amidoborohydride (LAB)[31] to provide primary alcohol **7** in 92% yield. Conversion of primary alcohol **7** to primary iodide **8** was accomplished with an Appel reaction using I_2 and PPh_3.[32] A second Myers–Larcheveque alkylation of iodide **8** and propionamide **5** gave amide **9** with the desired 1,3-*syn* substitution pattern. This particular bond-forming reaction needed optimization since early attempts provided only low to moderate yields. A minor breakthrough occurred when sampling a different concentration of *n*-BuLi to prepare the requisite LDA. In our hands, the use of any *n*-BuLi that was below 2.0 M to generate the amide base provided lower yields than expected. This phenomenon was observed only with the second alkylation and not the first one (i.e., **5–6**). A subsequent reductive cleavage of the chiral auxiliary with LAB went smoothly and oxidation of the resulting alcohol with tetrapropylammonium perruthenate (TPAP)[33] and NMO provided aldehyde **10**. The deployment of Carreira's Cu-catalyzed vinylogous aldol reaction afforded β-hydroxy dioxinone **11** in a 70% yield and 10:1 diastereomeric ratio.[34] The secondary alcohol was protected as a TBS ether, and the primary TBDPS group was removed upon treatment with NH_4F to afford the primary alcohol. The alcohol was converted to terminal olefin **12** with a Grieco elimination.[35] The deprotection of the secondary TBS ether with HF·pyridine revealed the requisite β-hydroxy dioxinone **3** in 93% yield.

2.3 Construction of the Cyclohexene Fragment

The synthesis of aldehyde **4** centered on an *endo*-selective Diels–Alder reaction to install the necessary substitution pattern. A variety of α-hydroxyaldehydes with various protecting groups on the primary aliphatic

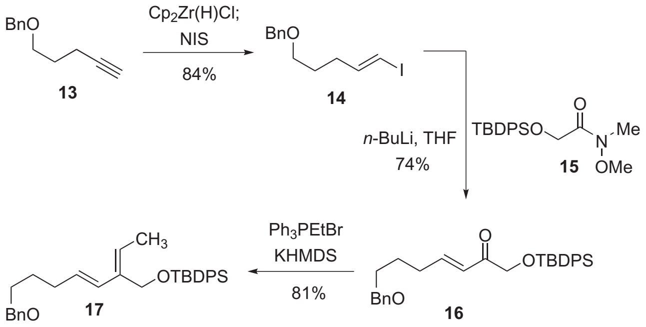


SCHEME 2 Synthesis of β-hydroxy dioxinone **3**.

alcohol were synthesized using this route. The formation of benzyl ether **17** is shown as a representative example. The requisite diene for this [4+2] strategy was constructed starting with the hydrozirconation/iodination reaction of benzyl-protected alkyne **13** derived from 4-pentyn-1-ol (Scheme 3).[36,37] The lithiation of vinyl iodide **14** with *n*-BuLi and subsequent treatment of the resulting vinyllithium species with Weinreb amide **15** (generated from TBDPS-protected ethyl glycolate) afforded the desired enone **16** in 75% yield as a >20:1 mixture of *E*/*Z* isomers. A selective Wittig olefination with ethyltriphenylphosphonium bromide provided diene **17** with >20:1 *E*/*Z* selectivity.[38]

In the first key step of the synthesis, we explored using a chiral acrylamide in the Diels–Alder reaction of diene **17** to furnish the core cyclohexene. Evans and coworkers reported that acrylic oxazolidinones treated with Et_2AlCl underwent an endo-selective Diels–Alder reaction with various dienes in significant excess (40–50 equiv.).[39,40] Treatment of diene **17** and acrylic oxazolidinone **18** with Et_2AlCl at −78 °C led to the Diels–Alder adduct **19** in a 25% yield (not shown). Attempts at using other dialkylaluminum halides or Lewis acids failed to improve the cyclization and rapid decomposition of the acrylamide was observed. This was a critical juncture of the project given that significant quantities of the cyclohexenyl fragment would be necessary for a successful campaign. As when any synthesis encounters a major roadblock, we were tempted by other possible avenues, including catalytic asymmetric methods (e.g., chiral Lewis acids, organocatalysis). However, these pursuits were challenged by the typical stoichiometries of these processes relying on massive excesses of diene. Unfortunately, the noncommercial aspect of diene **17** forced us to consider other options. We discovered that the addition of silver salts, particularly $AgPF_6$, allowed for the formation of the desired cyclohexene in high yield. We hypothesized that the excess Lewis acid, and specifically, chloride ion present from the coordination of the substrate to the aluminum(III) center, was interfering/adding to the reactive acrylate dienophile. Given the ability of silver(I) to precipitate chloride, we decided to add silver salts to the Diels–Alder reaction. Thus, exposure of **17** and **18** to Et_2AlCl with $AgPF_6$ as a critical additive at −78 °C in CH_2Cl_2 afforded cyclohexene **19** in 86% as the sole product with >20:1 diastereoselectivity (Scheme 4). The stereochemistry of the major product was elucidated by single-crystal X-ray diffraction analysis. Further investigation of this silver (I) additive benefit with acrylate Diels–Alder reactions is ongoing.

The reductive cleavage of the auxiliary in **19** with $LiBH_4$ and MeOH gave alcohol **20** in 83% yield (Scheme 4). Oxidation of the primary alcohol with Dess–Martin periodinane provided aldehyde **21** (90% yield). The installation of the α-hydroxyl group through a Rubottom oxidation produced α-hydroxy aldehyde **4** in 88% yield and 13:1 diastereoselectivity.[41–43] It is important to note that the choice of the silyl triflate for the formation of the enol silane was critical to both the yield and stereoselectivity of the reaction. Complete conversion was not observed when TMSCl was used to generate the silyl



SCHEME 3 Formation of diene **17**.

ether, presumably due to the lability of the TMS silyl enol ether. While use of TESOTf resulted in complete conversion, a mixture of two α-hydroxy aldehyde diastereomers was observed. Optimal yields and selectivities were seen when TBSOTf was used to generate the enol silane.

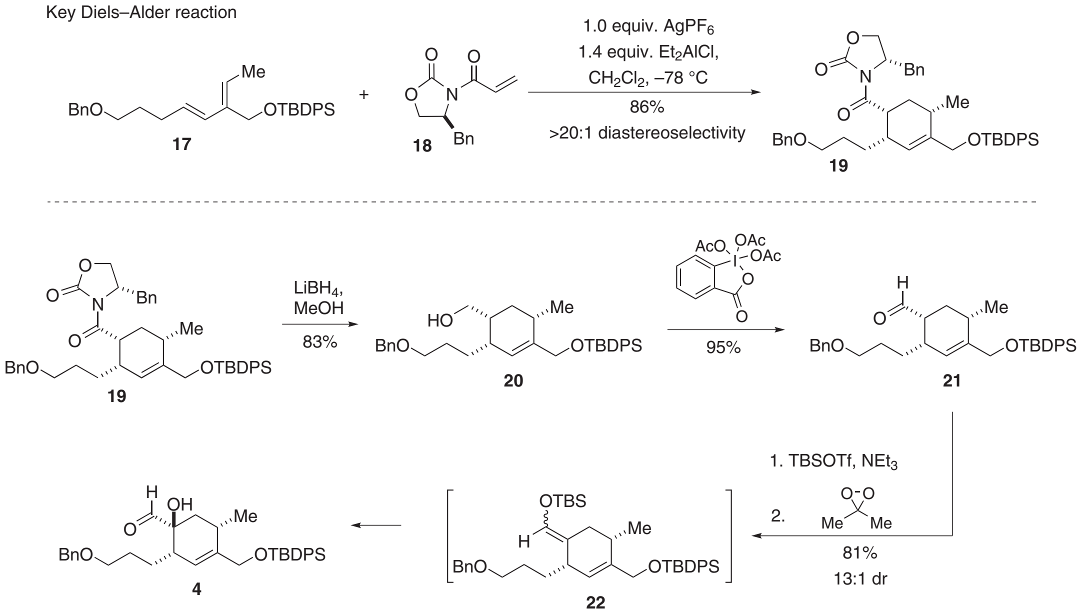
2.4 Initial Prins Assembly Strategy

We envisioned a tandem condensation/Prins cyclization reaction to construct the 6,5-fused bicyclic lactone. Our laboratory has reported on the development of this methodology catalyzed by mild Lewis acids.[12] We found that high yields and diastereoselectivities (>20:1 dr) could be achieved for formation of the 2,6-*cis*-tetrahydropyran-4-one product when using 10 mol% $Sc(OTf)_3$ and $CaSO_4$ in CH_2Cl_2 for a wide range of substrates. Our proposed mechanism begins with the condensation of a β-hydroxy dioxinone, such as **23**, with an aldehyde, such as **24**, to form an oxocarbenium ion **25** (Scheme 5). A subsequent Prins addition of the dioxinone enol ether to the oxocarbenium ion, followed by deprotonation of species **26**, forms the bicyclic dioxinone intermediate **27**. Treatment of **27** with a metal alkoxide induces fragmentation of the dioxinone to the corresponding tetrahydropyranone **28**.

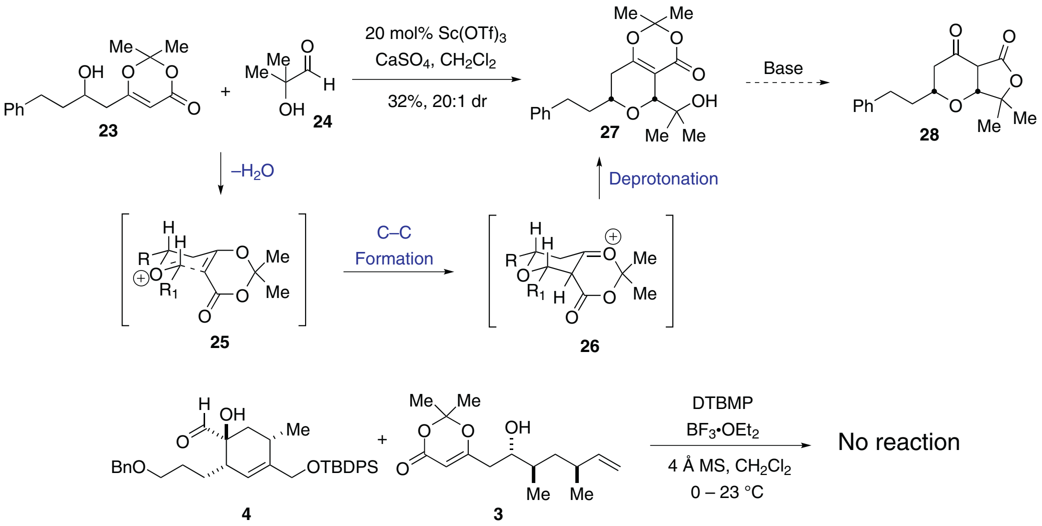
In anticipation of deploying this strategy toward okilactomycin, we demonstrated this transformation to be effective using tertiary α-hydroxyaldehyde **24**. Aldehyde **24** underwent $Sc(OTf)_3$-catalyzed cyclization with **23** in a 20:1 selectivity for the 2,6-*cis*-substituted product **27**, albeit in only 32% yield (Scheme 5). Based on this model study, we explored the condensation/Prins cyclization reaction of **3** and **4**. Unfortunately, β-hydroxydioxinone **3** was unreactive with the more complex α-hydroxy aldehyde **4** under a variety of Lewis acid conditions; no cyclization took place (Scheme 5).

2.5 Maitland–Japp Observation and Revised Approach

Disappointed with these unanticipated results, we were yet undeterred in demonstrating that strategies based on Prins-type bond-forming processes



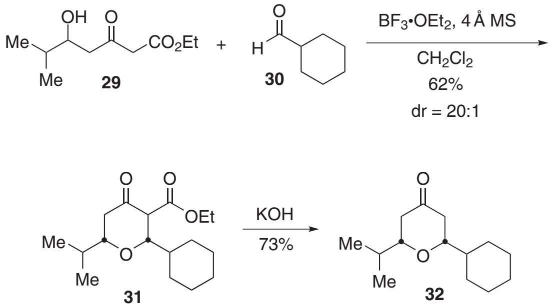
SCHEME 4 Diels–Alder and formation of α-hydroxyaldehyde **4**.



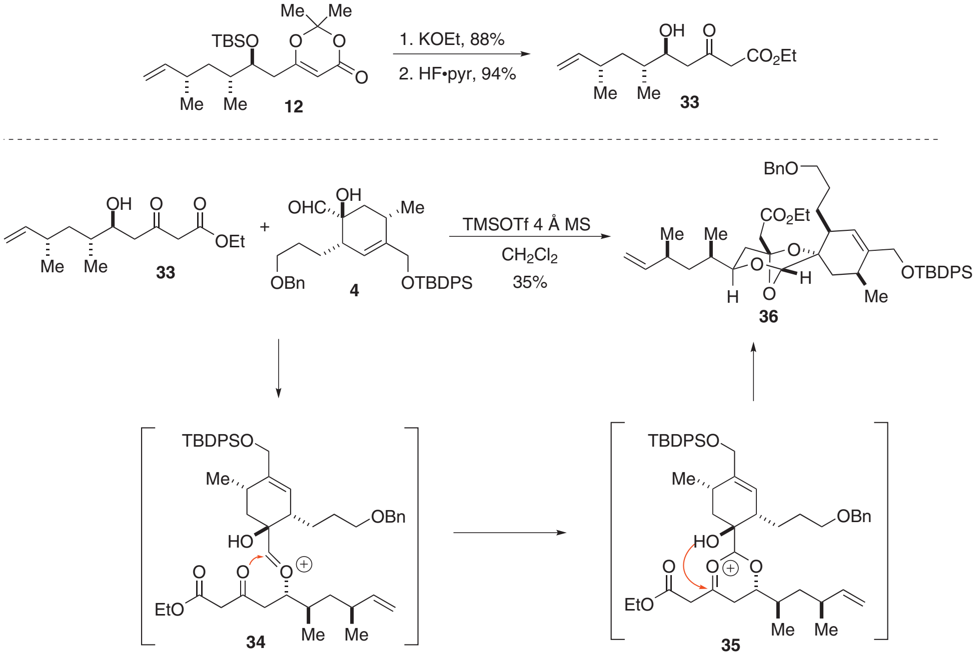
SCHEME 5 Condensation/Prins cyclization reactions.

could complete the desired coupling of the dioxinone and cyclohexenyl fragments. While exploring alternate means of constructing the 6,5-ring fusion from 2-cyclohexyl-3-carboxylate-tetrahydropyran substrates, we synthesized a number of test compounds using Clarke's modified Maitland–Japp reaction. Clarke and coworkers reported that a δ-hydroxy-β-ketoester undergoes a modified Maitland–Japp reaction with aldehydes to afford 2,6-*cis*-tetrahydropyran-4-ones in an analogous manner to our tandem condensation/Prins cyclization reaction.[44–46] An intriguing hypothesis emerged from combining this work with our own observations: a δ-hydroxy-β-ketoester would be more nucleophilic than a dioxinone such as **3** and this modulation of enol/keto structure might lead to a more successful Prins-type fragment coupling. Indeed, the treatment of δ-hydroxy-β-ketoester **29** and cyclohexane carboxaldehyde with $BF_3 \cdot OEt_2$ and 4 Å MS led to tetrahydropyranone **31** in 62% yield (Scheme 6). Saponification of the ester and subsequent decarboxylation led to **32** in 73% yield using aqueous KOH in ethanol.

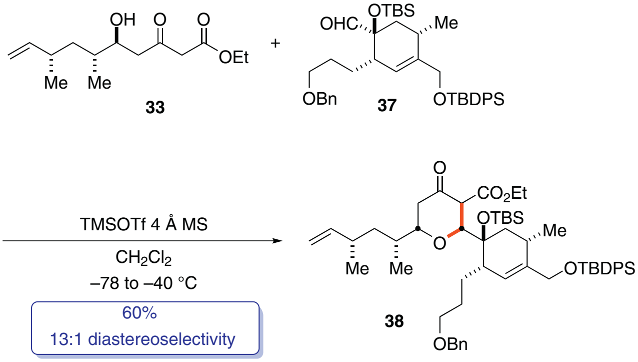
The success of this model system in the Maitland–Japp reaction circumvented our earlier difficulties and led us to speculate that this strategy might be extended to more complex partners, namely, tertiary α-hydroxy aldehyde **4** and δ-hydroxy-β-ketoester **33**.[44–46] To test this approach, the conversion of β-silyloxy dioxinone **12** into δ-hydroxy-β-ketoester **33** was accomplished in two steps (Scheme 7). Treatment of **12** with KOEt in CH_2Cl_2 led to the δ-silyloxy-β-ketoester in 88% yield. Deprotection of the silyl ether afforded the desired β-ketoester **33** in 94% yield. With this modified fragment in hand, the Maitland–Japp reaction of ketoester **33** and aldehyde **4** was examined. Unexpectedly, the Lewis acid-mediated coupling furnished trioxabicyclo[3.2.1]octane **36** in 35% yield instead of the desired tetrahydropyranone (Scheme 7). After significant detective work to establish the connectivity and structure of **36**, it became clear that the formation of this product is consistent with the condensation/Prins-type cyclization pathway found with β-hydroxy dioxinone instead of a Knoevenagel/oxo-conjugate addition mechanism for the modified Maitland–Japp reaction.[44,45] Our proposed mechanism is shown in Scheme 7. The condensation of δ-hydroxy-β-ketoester **33** with



SCHEME 6 Modified Maitland–Japp cyclization.



SCHEME 7 Modified Maitland–Japp reaction and formation of trioxabicyclo[3.2.1]octane **36**.



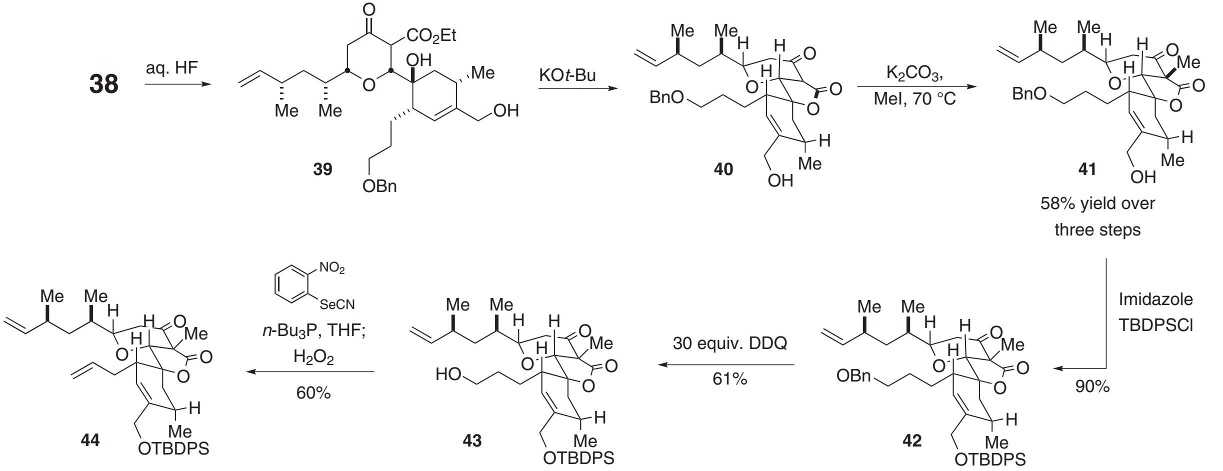
SCHEME 8 Key formation of cyclic core **38**.

aldehyde **4** forms transient oxocarbenium ion **34**. Instead of enol cyclization by the carbon atom, O-cyclization occurred to afford a second oxocarbenium ion **35**. Trapping of the oxocarbenium ion with the tertiary hydroxyl group afforded trioxabicyclo[3.2.1]octane **36**.

Despite the unexpected formation of **36**, we were encouraged that δ-hydroxy-β-ketoester **33** was a competent coupling partner for the sterically demanding α-hydroxy aldehyde **4**. We reasoned that protection of the tertiary alcohol in **33** with a robust silyl group might shift the O-cyclization pathway to the C-cyclization pathway since a final "trapping" of oxocarbenium **35** would not be possible. A number of protecting groups (TMS, TES, TBS, allyl, SEM) and Lewis acids (TMSOTf, $BF_3{\cdot}OEt_2$) were examined. Only the TBS ether of aldehyde **4** survived the Lewis acid-mediated conditions. We found that the optimal conditions for the cyclization of **33** and **37** were TMSOTf in CH_2Cl_2 at −78 to −40 °C, which led to the desired tetrahydropyranone **38** in a 60% yield and as a 13:1 mixture of diastereomers favoring the desired 2,6-*cis* isomer (Scheme 8).

2.6 Macrocycle Closure and Completion of the Synthesis

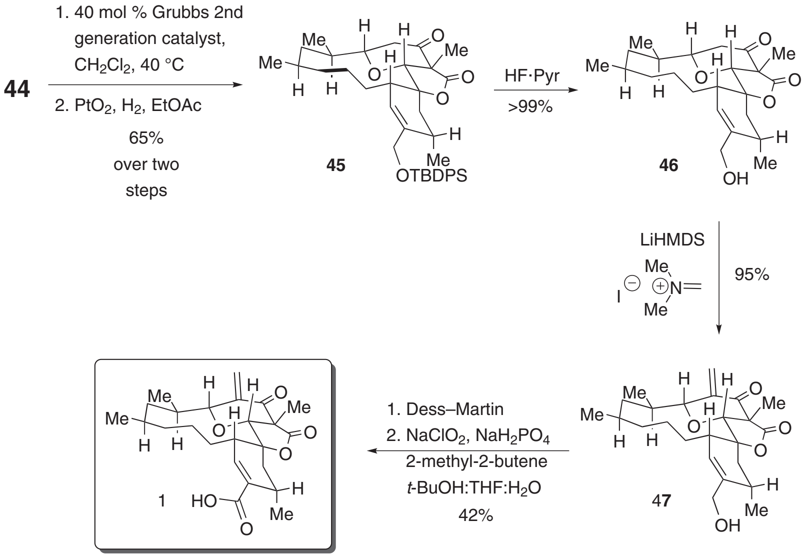
With the tetrahydropyranone ring installed, we expected some challenges in the deprotection of the tertiary TBS ether. Treatment of TBS ether **38** with a variety of fluoride sources (TBAF, TBAF buffered with AcOH, TASF, HF·pyr, $HF{\cdot}NEt_3$) led to only monodeprotection of the primary TBDPS. In some cases (HF·pyr at elevated temperatures), elimination and opening of the tetrahydropyranone to the butenolide were also observed. Treatment of silyl ether **38** with aqueous HF (48% in water) in CH_3CN led to a mixture of desired diol **39** as well as the lactonized product **40** (Scheme 9), though the mixture could not be purified without observing decomposition. The exposure of the unpurified mixture of **39** and **40** to KO*t*-Bu in THF for 10 min



SCHEME 9 Generation of diene for RCM.

converted diol **39** into tricyclic lactone **40**. Purification of lactone **40** itself was again not possible; attempts to isolate lactone **40** on silica gel also led to decomposition. Importantly, the observed decomposition during purification strongly suggested that bicyclic lactone **40** is unstable. Lactone **40**, also unpurified, was subjected to K_2CO_3 and MeI in CH_3CN at 70 °C,[47] and methylated lactone **41** was obtained in a 58% yield over the entire three-step sequence. It was unnecessary to protect the allylic alcohol; under the reaction conditions, no methyl ether formation was observed. With the formation of the tricyclic core of okilactomycin completed, we planned on an RCM reaction to complete the macrocycle. Allylic alcohol **41** was reprotected as the TBDPS ether in 90% yield (Scheme 9). The benzyl ether was cleaved with 30 equivalents of DDQ to afford primary alcohol **43** in 67% yield.[11,48] Our attempts to lower the number of equivalents of DDQ unfortunately resulted in incomplete conversion. Alcohol **43** was converted to terminal olefin **44** using Grieco's procedure, setting the stage for the RCM reaction followed by hydrogenation to form the macrocycle and complete the core of (−)-okilactomycin.

Grubbs second-generation and Hoveyda–Grubbs second-generation catalysts were both evaluated in the key RCM reaction (Scheme 10). While this approach had been successful in Smith's synthesis, the extra alkene in our approach could have potentially complicated the situation. Gratifyingly, the RCM of **44** with Grubbs second-generation catalyst followed by hydrogenation using PtO_2 gave desired macrocycle **45** in a 65% yield over two steps. Previous attempts to functionalize the alkene in the six-membered ring for a



SCHEME 10 Synthesis of (−)-okilactomycin.

failed route (not shown) had informed us that this particular olefin was resistant to reducing conditions so our RCM/reduction approach relied on that reconnaissance. The completion of the tetracyclic core of okilactomycin set the stage for the installation of the *exo*-methylene and the completion of the total synthesis. We were concerned that the *exo*-methylene unit would be incompatible with silyl deprotection conditions, so the silyl ether was removed and installation of the exocyclic olefin in the presence of the free allylic alcohol was attempted. Fortunately, silyl ether **45** was deprotected with HF·pyridine to yield allylic alcohol **46**, and treatment with LiHMDS and Eschenmoser's salt cleanly installed the exocyclic alkene (Scheme 10).[49,50] The installation of the *exo*-methylene prior to deprotection was not required. Finally, oxidation of allylic alcohol **47** to the enal with Dess–Martin periodinane (83% yield) followed by a Pinnick oxidation[51] afforded (−)-okilactomycin in 50% yield after purification. The analytical data of the synthetic material were consistent with that obtained for the natural material, except for the absolute value of the optical rotation, indicating we had synthesized the unnatural antipode of okilactomycin. Our synthesis was completed in 21 steps in the longest linear sequence with an overall yield of 1.0%.

3 CONCLUSIONS

The unique tetracyclic structure of okilactomycin has proven a formidable challenge since its discovery in 1987: only two of the four reported synthetic attempts have been successful. Our interest in this challenging target originated with the founding of our research laboratory in 2002, and our successful synthesis was the culmination of a circuitous, frustrating, educational, ambitious, and exhilarating 10-year experience! We were inspired by its unusual core to develop Prins-type methodology, and our success and interest in this powerful area of carbocation chemistry continue. Ultimately, our synthetic strategy began with an ambitious extension of our condensation/Prins cyclization methodology to a highly congested tertiary α-hydroxy aldehyde. While this strategy was unsuccessful, iterative stereoselective alkylations and a Diels–Alder cycloaddition facilitated rapid access to the δ-hydroxy β-ketoester and α-silyloxy aldehyde fragments, respectfully, and allowed us to explore a number of other synthetic approaches. We ultimately demonstrated that a Lewis acid-promoted Maitland–Japp reaction established the key tricyclic core with a high degree of diastereoselectivity for the 2,6-*cis*-tetrahydropyran motif. The ability to modify intermediates at an advanced stage to explore different modes of Prins-type reactivity (condensation/Prins cyclization for the β-hydroxydioxinone vs. Maitland–Japp for the δ-hydroxy β-ketoester) highlights the versatility and power of this chemistry for the total synthesis of tetrahydropyran-containing natural products. Our interest in oxygen-containing natural products and the new methods that arise from these challenges continues as does our efforts to translate these molecular accomplishments toward clinical endeavors.

ACKNOWLEDGMENTS

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Chapter 9

Taking Risks in Complex Synthesis Design

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Chapter Outline

1 INTRODUCTION

The birth of the structural language of organic chemistry may be traced to Archibald Scott Couper's, "On a New Chemical Theory," which was written in French and published in 1858.[1,2] In this influential manuscript, Couper portrayed organic compounds with drawings that closely resemble the style in which they are drawn today. Couper's depiction of chemical bonds as lines between atomic symbols is the foundation of the universal structural language of organic chemistry, a structural language that enables chemists to convey their thoughts and experimental advances with a unique precision. His work

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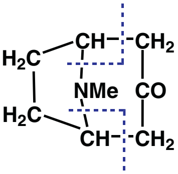


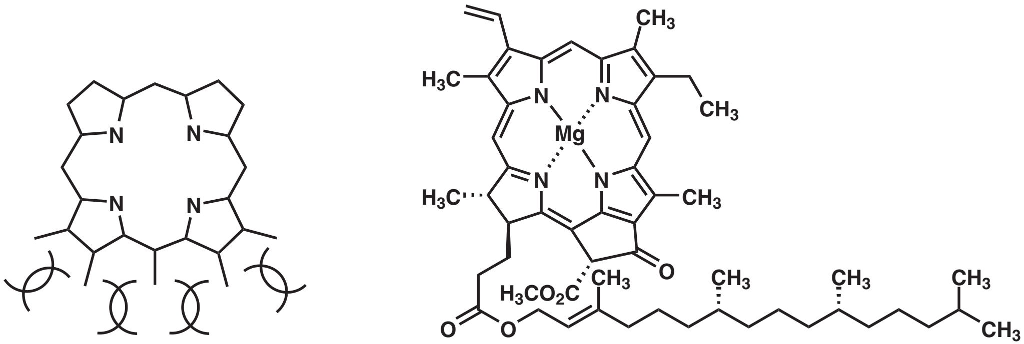
FIGURE 1 The constitution of tropinone and Robinson's reasoning that guided its synthesis. By imaginary hydrolysis at the points indicated by the dotted lines, the substance may be resolved into succindialdehyde, methylamine, and acetone, and this observation suggested a line of attack of the problem which has resulted in a direct synthesis (Robinson[3]).

was thus a significant contribution to one of the truly dominant conventions in the field of organic chemistry.

Figure 1 from Robert Robinson's landmark publication, "A Synthesis of Tropinone," provides a relatively early and powerful expression of Couper's convention.[3] This drawing and the associated text captured both the thinking that gave rise to Robinson's visionary design for synthesis and the essence of what we call today *retrosynthetic analysis*.[4] His self-assembly of the architecture of tropinone from succindialdehyde, methylamine, and acetone dicarboxylic acid was a solitary forerunner of the modern era of organic synthesis and inspired generations of organic chemists.[5]

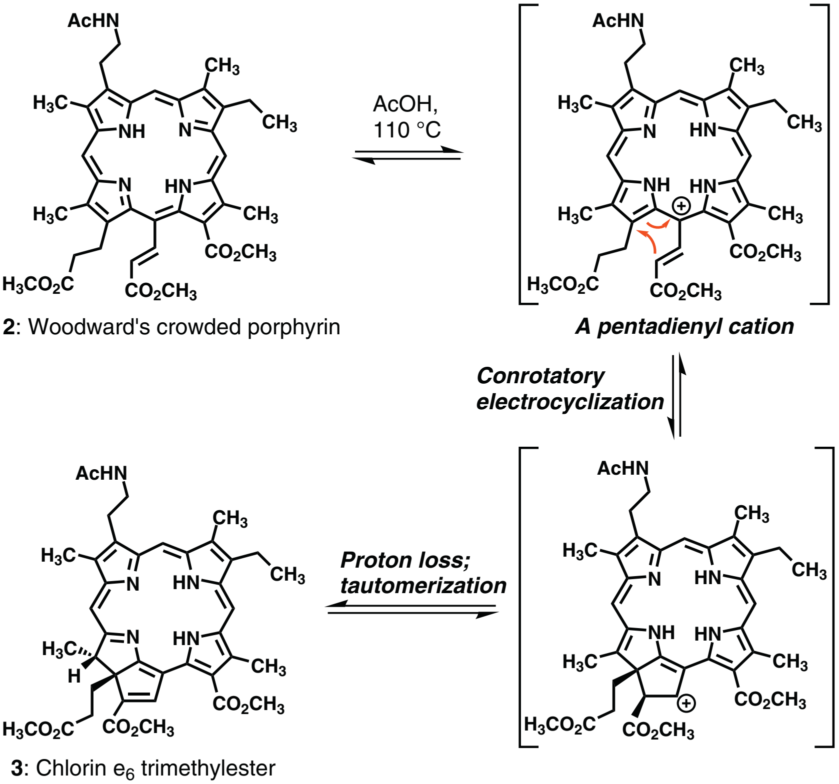
Robinson published his tropinone synthesis just a few months after the birth of Robert Burns Woodward, who, 44 years later, would describe his chemical reasoning and the structural transformations that allowed his laboratory to synthesize the green plant pigment chlorophyll *a* (**1**, Figure 2).[6] Woodward was supremely confident that a porphyrin with a sterically crowded periphery would lower its energy by converting itself to a chlorin. In hindsight, we conclude that the setup costs associated with the synthesis of the crowded porphyrin **2** were high and that Woodward's daring idea of a porphyrin → chlorin transformation was laced with risk. Nevertheless, a simple heating of the crowded porphyrin in acetic acid indeed effected a reversible interconversion with chlorin e_6 trimethylester (**3**), thus demonstrating, for the first time, a direct link between the porphyrin and chlorin ligand systems. This transformation, which had no precedent in the chemical literature, is still one of the boldest in the field of natural product synthesis (Scheme 1).[7]

This contribution to *Strategies and Tactics in Organic Synthesis* is about risk-taking in the design and execution of organic syntheses and the benefits that risk-taking can afford to the broader field of synthesis. A simple Google search reveals much about the psychology and merits of taking risks. According to About.com, "risk-taking refers to the tendency to engage in behaviors that have the potential to be harmful or dangerous, yet at the same time provide the opportunity for some kind of outcome that can be perceived as positive." The more negative connotation of risk-taking is reflected in the



1: Chlorophyll *a*

FIGURE 2 Reasoning and insight in organic chemistry: Woodward's approach to the chlorophyll problem. *Woodward's reasoning*: Steric crowding in a penta-substituted porphyrin would create a powerful driving force for a porphyrin → chlorin transformation. Constitution-dependent reactivity would thus establish a link between two ancient and biochemically significant classes of natural products.



SCHEME 1 The key porphyrin → chlorin transformation in the Woodward synthesis of chlorophyll *a* (**1**) [*K* (chlorin/porphyrin) ca. 1.7].

oxforddictionaries.com definition: "to expose someone or something valued to danger, harm, or loss." For this chapter, we will define risk-taking in organic synthesis as the deliberate pursuit of strategies that do not have close neighbors in the chemical literature; in these ventures into the unknown, predicting chemical behavior is difficult.

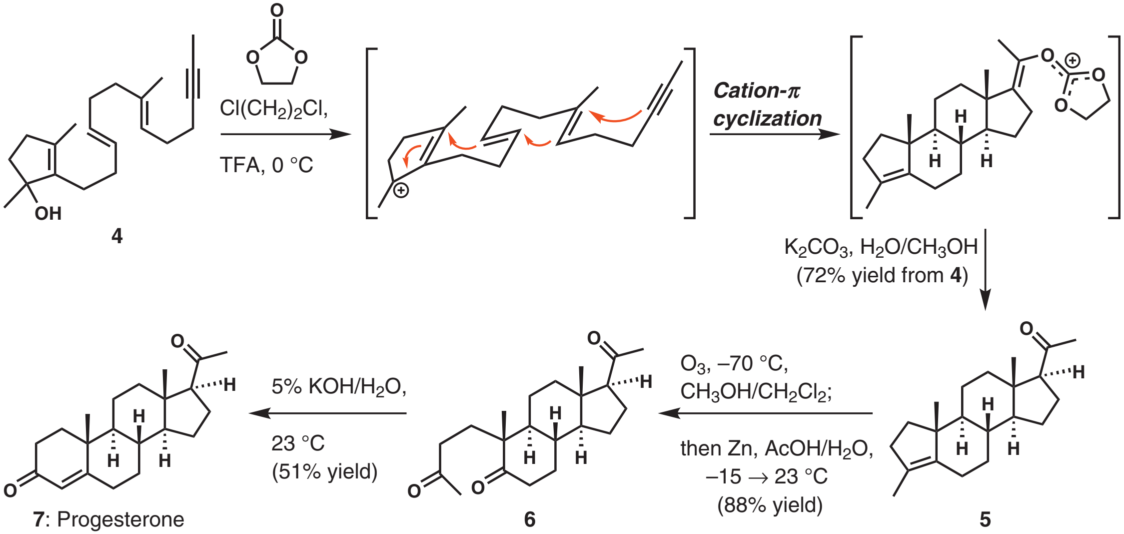
As a collective, the achievements addressed herein span a period of 89 years and offer creative chemical insights and solutions to a range of challenging problems in synthesis. Our only wish is that this chapter could have been more inclusive! The chemical literature is replete with achievements in organic synthesis that offer prime examples of bold risk-taking. Regrettably, our coverage is far from comprehensive, and we humbly and sincerely apologize to the readership for the unavoidable omissions in our narrative. From the moment we decided to pursue the theme reflected in the title for this chapter, we have had to live with the arbitrariness that goes with the process of selecting the literature examples for discussion and the fact that opinions will vary about the extent to which a particular achievement in synthesis is founded on risky propositions. Nevertheless, it is also our belief that some of the power, creativity, and planning capacity of organic synthesis are reflected in the historically significant and contemporary achievements addressed herein.

2 SOME EXAMPLES OF ARCHITECTURAL SELF-CONSTRUCTIONS AND THE POWER OF PROXIMITY IN COMPLEX SYNTHESIS DESIGN

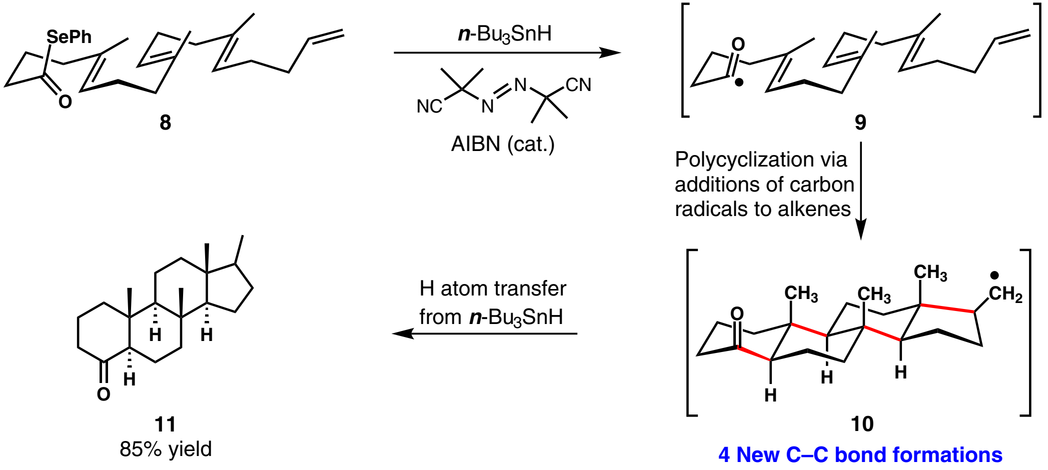
Nature generates the diverse structures of the polycyclic triterpenes from a single, acyclic chain of alkenes (i.e., squalene or oxidosqualene) by cascades of stereospecific cation-π cyclizations.[8] The enduring lesson from these impressive transformations is that the conformational diversity of the transition states for squalene polycyclizations translates into the constitutional and configurational diversity of the polycyclic triterpenes.[9] In nature, cyclase enzymes induce squalene and oxidosqualene to adopt particular conformations, trigger cation formation, and chaperone the ensuing cascade of stereospecific cation-π cyclizations. Given this impressive feat of biomolecular evolution, it is remarkable that organic chemists have been able to tap into the power of squalene-like reactivity in laboratory syntheses of natural products.[10] Using only trifluoroacetic acid (TFA) as an inducing agent, Johnson and his coworkers stereospecifically transmuted polyunsaturated alcohol **4** into the steroid precursor **5**.[11] The reasoning was that TFA would induce the formation of a tertiary, allylic carbocation as a prelude to a cascade of stereospecific ring formations and that the additive ethylene carbonate would capture the putative, linear vinyl cation (not shown). The stereochemical outcome of this nature-inspired transformation is fully consistent with the teachings of the Stork–Eschenmoser hypothesis[10] and a transition state having chair-like conformations for the nascent rings.

From compound **5**, all that remained to complete their synthesis of progesterone (**7**) was an oxidative cleavage of the cyclopentene ring (**5** → **6**) and a final aldol cyclocondensation (**6** → **7**) (Scheme 2).

This achievement by the Johnson laboratory is a paragon of "nature-inspired synthesis," and yet the broader field of chemical synthesis poses the challenge to consider the feasibility of chemical reactions that do not have counterparts in nature. A spectacular example is found in Pattenden's construction of the steroid architecture via a cascade of free radical cyclizations (Scheme 3).[12] In the pivotal step, a reduction of acyl selenide **8** with tri-*n*-butyl tin radical induced three consecutive 6-endo trigonal cyclizations and a terminal 5-*exo*-trigonal cyclization (**9** → **10**); a reduction of the intermediate radical **10** with tri-*n*-butyltin hydride terminated the tetracyclization cascade and afforded steroidal ketone **11** in an excellent yield of 85%. This is a dramatic example of the power of carbon-centered radical cyclizations in challenging undertakings in synthesis.[13]



SCHEME 2 Biomimetic, stereospecific cation-π cyclizations in the influential synthesis of progesterone (**7**) by the Johnson laboratory.

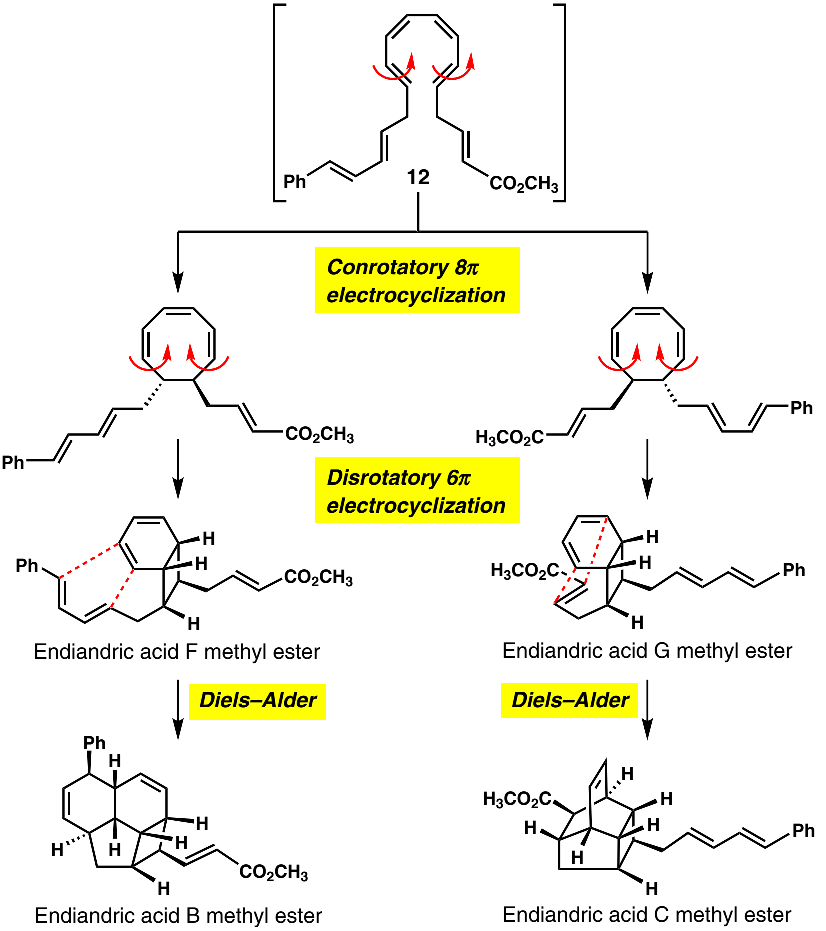


SCHEME 3 A direct construction of the steroid architecture via a cascade of radical cyclizations by the Pattenden laboratory.

The architectural self-constructions that allowed Nicolaou and coworkers to validate Black's hypothesis concerning the origin of the endiandric acids are striking examples of the idea that intricate, polycyclic compounds can be encoded in the relatively simple structure of an acyclic, polyunsaturated precursor.[9b] Black postulated that the endiandric acids, which are formed as racemates in nature, could originate from an achiral and highly unsaturated fatty acid-like compound by consecutive pericyclic reactions[14]; Nicolaou's lab provided the experimental verification of this intriguing idea and an early demonstration of the utility of electrocyclic reactions in natural product synthesis.[15] Racemic endiandric acid methyl esters B, C, F, and G were formed in a single experiment by heating compound **12**, the product of a twofold Lindlar hydrogenation of the corresponding bis-alkyne, to 100 °C in toluene (Scheme 4). Endiandric acid methyl esters F and G arise from **12** by successive conrotatory 8π- and disrotatory 6π-electrocyclizations and are capable of undergoing terminal Diels–Alder cyclizations to endiandric acid methyl esters B and C, respectively. An analogous cascade of stereospecific pericyclic reactions permitted syntheses of endiandric acid methyl esters A, D, and E from an acyclic precursor similar to compound **12**.

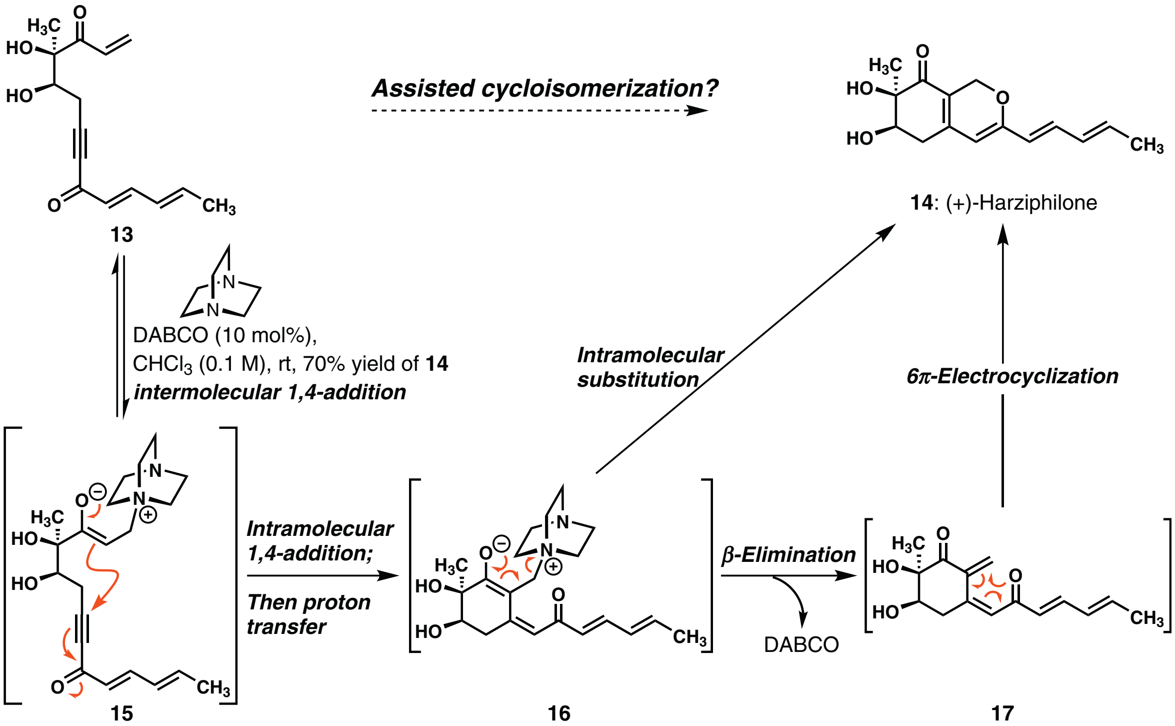
Looking back at some of our own work in the field of natural product synthesis, we are inclined to think that the design that guided our synthesis of (+)-harziphilone[16] was laced with risk (Scheme 5). Our aim was to channel the reactivity of the activated and highly unsaturated bis-ketone **13** in a direct construction of (+)-harziphilone (**14**). With six electron-deficient carbons, compound **13** could conceivably undergo a diversity of reactions, and it was not at all clear that we would be able to control its behavior. As it turns out, the desired cycloisomerization of **13–14** was accomplished with assistance from a small amount of the nucleophilic catalyst DABCO. We propose that a 1,4-conjugate addition of DABCO to the enone system of **13**, or perhaps to an enone system that is activated by an internal hydrogen bond, triggers an intramolecular Michael reaction (**15** → **16**). A proton transfer step and a β-elimination of neutral DABCO from intermediate **16** would then return the nucleophilic catalyst to the reaction milieu and afford intermediate **17**. If compound **17** is formed in this process, it exists only briefly, for it rapidly undergoes a Büchi/Marvell-type cycloisomerization[17] to form the α-pyran nucleus and complete the synthesis of (+)-harziphilone (**14**). The simplicity of the experimental procedure belies the mechanistic complexity of the overall transformation.

The facile conversion of dihydrosqualene dialdehyde (**18**) into dihydro-proto-daphniphylline (**23**) by the Heathcock laboratory comprises both ionic and pericyclic reactions and is one of the most exquisite examples of a cascade process (Scheme 6).[18] A simple condensation reaction between methylamine and the unconjugated aldehyde of **18** produces an enamine *in situ* that attacks the β-carbon of the nearby enal function to produce the five-membered ring and the two stereogenic centers in **19**.

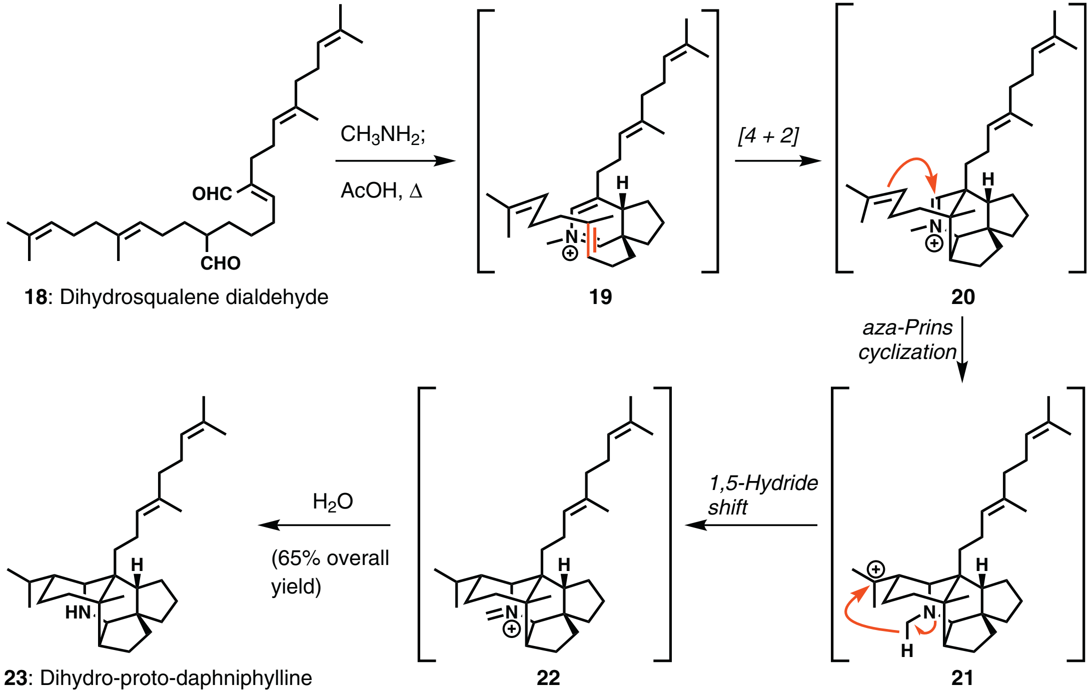


SCHEME 4 The experimental validation of the endiandric acid cascade by the Nicolaou laboratory.

On exposure to warm acetic acid, a second condensation occurs and the newly formed, well-placed azadiene moiety of **19** undergoes an intramolecular [4+2] cycloaddition reaction to the highlighted alkene to give the isomeric iminium ion **20**. The structure of **20** provides a perfect context for an intramolecular aza-Prins reaction, which yields the final ring. This aza-Prins reaction also instigates a fascinating, proximity-dependent hydride shift (see **21**), generating iminium ion **22** with the required isopropyl function on the six-membered ring. The internal redox mechanism that advanced **21–22** was a fortuitous discovery that served the synthesis remarkably well. A simple hydrolysis of the iminium function in **22** completed the construction of the multicyclic daphniphylline **23**. In all, seven new sigma bonds and five rings were formed in this inspiring transformation.



SCHEME 5 An instance of nucleophilic catalysis in the synthesis of (+)-harziphilone (**14**) by the Sorensen laboratory.



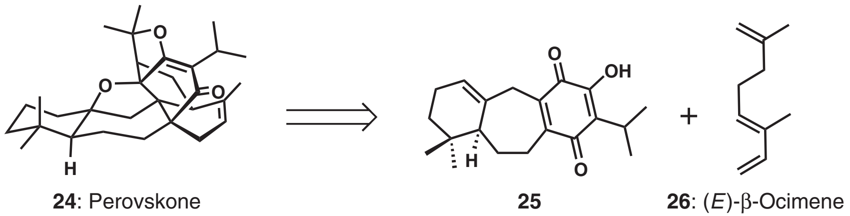
SCHEME 6 The conversion of dihydrosqualene dialdehyde (**18**) to dihydro-proto-daphniphylline (**23**) by the Heathcock laboratory, an artful orchestration of ionic and pericyclic reactivity.

The biomimetic synthesis of perovskone (**24**) by the Majetich laboratory offers another prime example of the advantages of functional group proximity and bold planning in natural product synthesis.[19] The molecular skeleton of perovskone comprises seven rings, both fused and bridged, as well as seven stereogenic centers (Scheme 7). The creative insight of Majetich and coworkers that a direct construction of **24** might be possible from the largely planar building blocks **25** and **26** definitely belongs in the "high-risk, high-reward" category. Under the conditions shown in Scheme 8, the merger of quinone **25** with (*E*)-β-ocimene (**26**) produced the perovskone precursor **29** via the following sequence of bond-forming reactions: (1) a diastereoface- and regioselective Diels–Alder reaction, (2) an alkene isomerization, (3) a ring-forming Prins reaction (**27** → **28**), and (4) a cycloetherification (**28** → **29**). A final, acid-induced ether ring formation afforded perovskone (**24**) in an excellent yield of 90%. In more recent studies, the Majetich laboratory achieved an asymmetric synthesis of tricyclic quinone **25** and subsequently joined it with the triene **26** under conditions that directly afforded (+)-perovskone in 50% yield.[20]

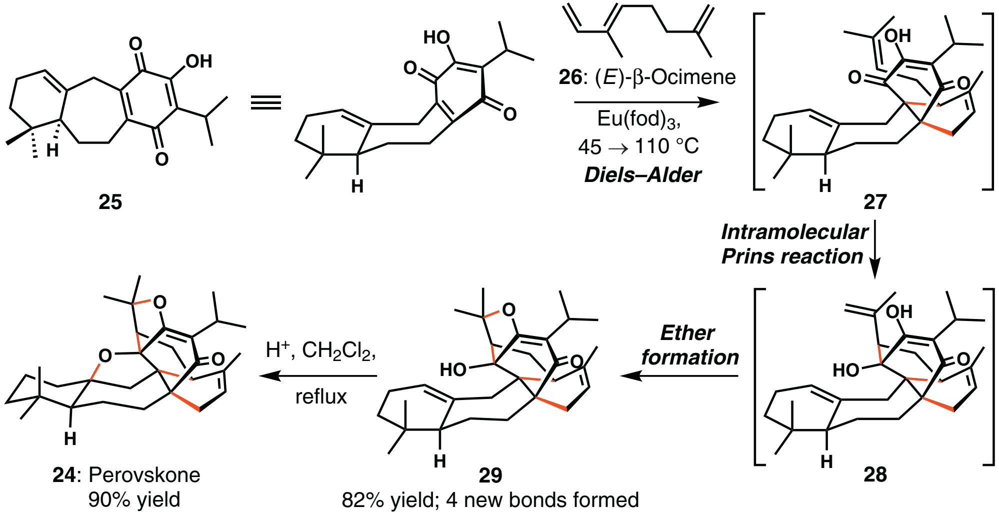
3 TARGETING THE TRULY FRAGILE: DANISHEFSKY'S SYNTHESIS OF DISODIUM PREPHENATE

Prephenic acid (**30**), nature's precursor to the aromatic amino acids phenylalanine and tyrosine, is noted for its proclivity to lose water and carbon dioxide, especially in the presence of acidic reagents, and be transformed to phenyl pyruvic acid (**32**) (Scheme 9).[21] In fact, prephenic acid is really only stable in its bis-carboxylate salt form. Of the problem that mitomycin poses to the field of synthesis, Danishefsky once wrote: "The synthesis of a mitomycin is the chemical equivalent of walking on egg shells."[22] He could have characterized the problem of synthesizing the delicate constitution of prephenate in an analogous way. In response to the prephenate structure, Danishefsky and Hirama conceived that an unraveling of lactonic ketal **33** under basic conditions (see arrows in **33**) and in the final step of the synthesis might permit the formation and isolation of disodium prephenate **31**.[23] The manner in which this ingenious concept for synthesis was brought to fruition is shown in Scheme 10.

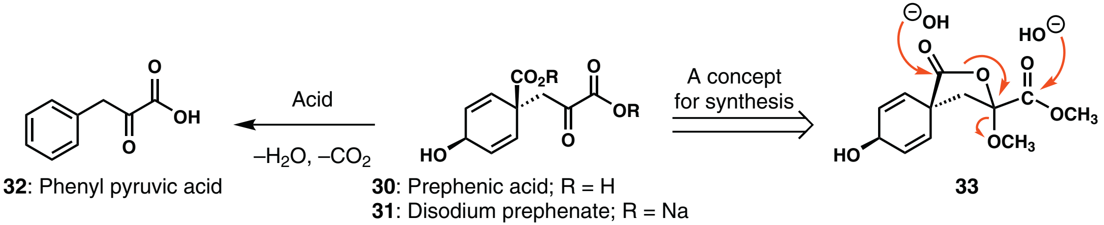
For the Danishefsky laboratory, part of the appeal of the prephenate system as an objective for synthesis stemmed from their interest in developing facile syntheses of 4,4-disubstituted cyclohexadienones via the chemistry of the Danishefsky/Kitahara diene (**34**).[24] Under the conditions shown, the "synergistic" diene **34** underwent a regiocontrolled Diels–Alder reaction with the doubly activated dienophile **35** and afforded the desired disubstituted cyclohexadienone **37** via the putative intermediate **36**. A chemoselective 1,2-reduction of the keto group in **37** with 9-borabicyclo[3.3.1]nonane (9-BBN) subsequently provided lactonic ketal **33** for the final, twofold saponification



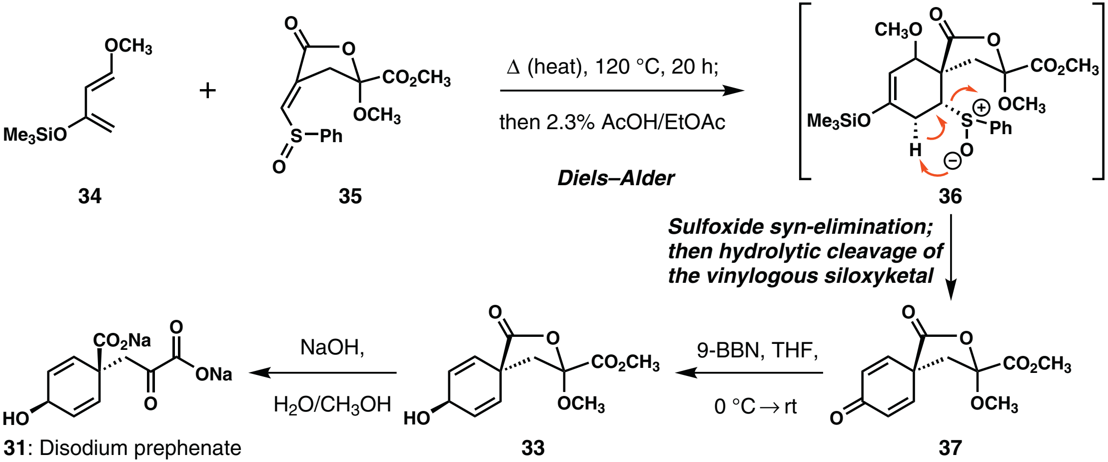
SCHEME 7 The Majetich retrosynthetic analysis of perovskone (**24**).



SCHEME 8 The power of proximity is expressed in Majetich's biomimetic synthesis of perovskone (**24**).



SCHEME 9 The concept of the base-labile ketal in Danishefsky's synthesis of disodium prephenate (**31**).



SCHEME 10 Key transformations of Danishefsky's impressive synthesis of disodium prephenate.

to disodium prephenate (**31**). Danishefsky's "base-labile ketal" is an enduring lesson from this achievement.

4 A LESSON ON HOW TO PRODUCE A "BENT BENZENE": BARAN'S SYNTHESIS OF HAOUAMINE

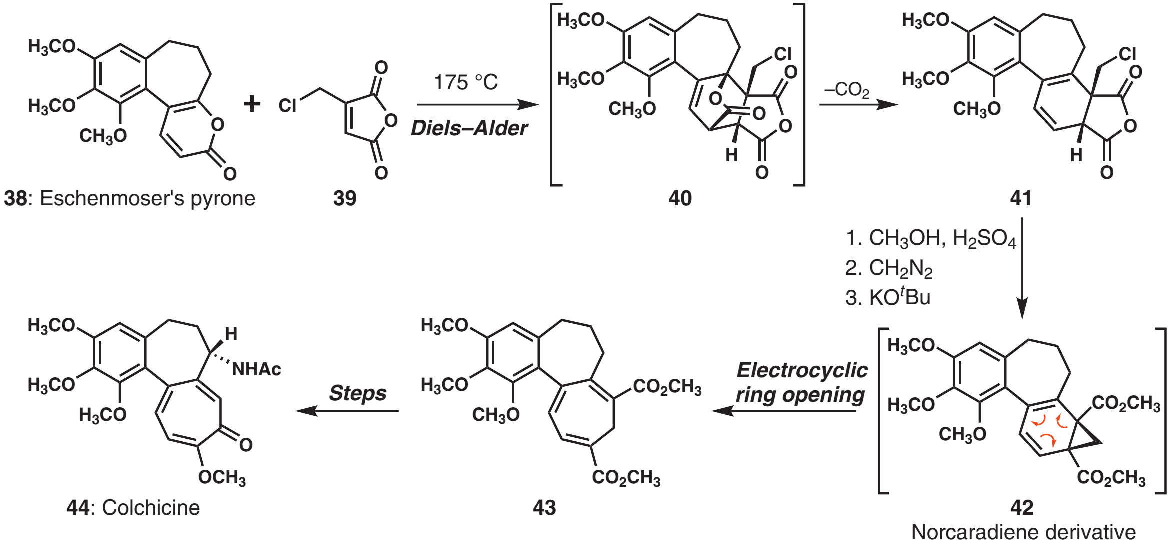
To the best of our knowledge, Eschenmoser's pioneering synthesis of colchicine (**44**), which was reported in 1959, provides the first example of a [4 + 2] cycloaddition reaction of a pyrone heterocycle in natural product synthesis.[25] This creative achievement featured a Diels–Alder reaction between pyrone **38** and chloromethyl maleic anhydride (**39**) with concomitant loss of carbon dioxide[26] (see **40** → **41**, Scheme 11) and a spontaneous, strain-releasing electrocyclic ring-opening (see **42** → **43**).

The formation and dismantling of a pyrone-derived bicyclo[2.2.2]octane structure was also a key concept in the recent synthesis of the complex alkaloid haouamine A by Baran and Burns.[27] They reasoned that the oxabicyclo [2.2.2] substructural element in **46**, which would arise from pyrone alkyne **45** via an intramolecular Diels–Alder reaction, could serve as a conformational mimic and precursor to the bent benzene ring of haouamine A (**47**); the formation of **46** by a thermal Diels–Alder reaction would be followed by the loss of a molecule of carbon dioxide in an irreversible, retro-hetero Diels–Alder reaction to give the aza-paracyclophane of the natural product. This intriguing concept for annulating haouamine A's strained, nonplanar benzene nucleus was probed in the penultimate step of the synthesis and brought to fruition under the conditions shown in Scheme 12. A final, base-induced methanolysis of the four acetate esters afforded the natural product.

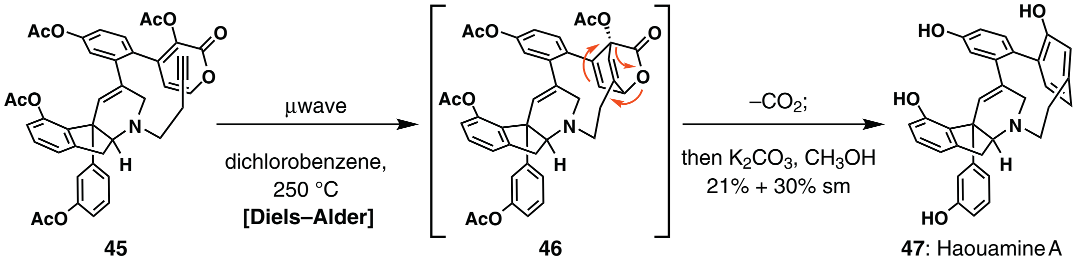
5 THE ALLYLIC DIAZENE REARRANGEMENT IN A SOPHISTICATED MOLECULAR CONTEXT: SCHREIBER'S SYNTHESIS OF DYNEMICIN A-LIKE COMPOUNDS

In the wake of their direct conversions of compounds **48** and **49** into the dynemicin A-like skeleton **51** featuring an impressive, room temperature transannular Diels–Alder reaction of the common intermediate **50**[28] (Scheme 13), the Schreiber laboratory needed to face the difficult problem of transposing the newly formed C3–C4 cyclohexenyl double bond to the C3–C11 position with control over the formation of the emerging, methyl-bearing stereocenter at C4. The ingenious tactic that solved this problem featured the formation and rearrangement of a fleeting allylic diazene (**53** → **54**, Scheme 14).[29]

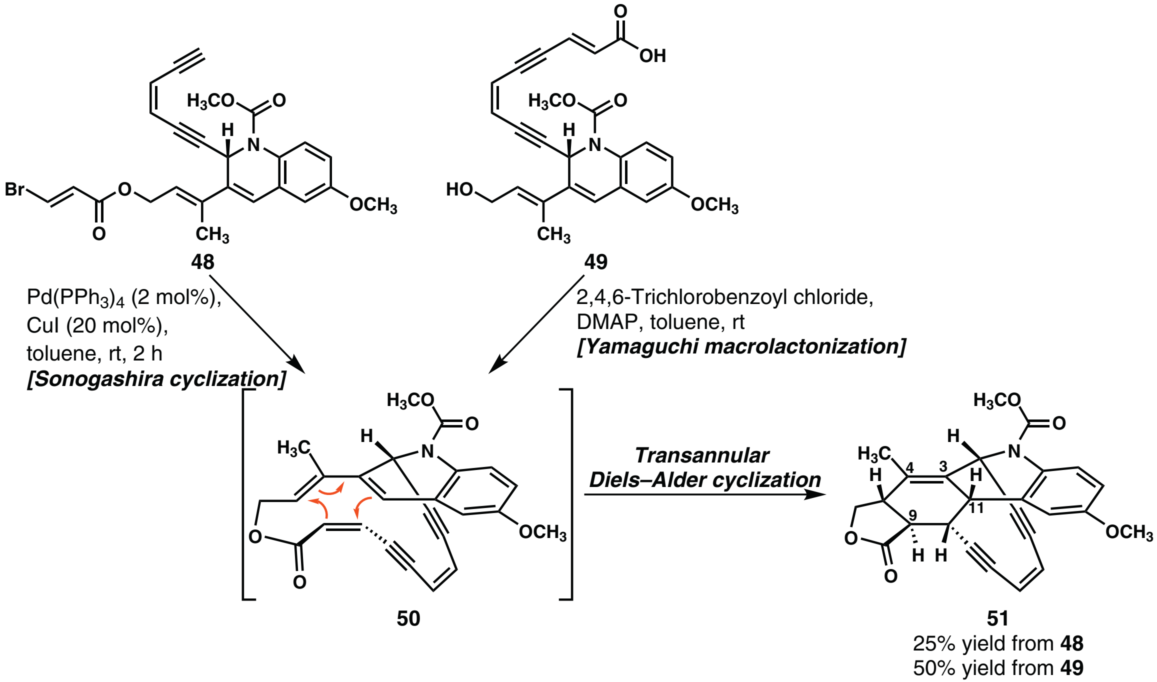
After a base-induced epimerization at C-9 of compound **51**, an allylic oxidation mediated by ceric ammonium nitrate (CAN) afforded tertiary, allylic alcohol **52**. In the pivotal step, this newly formed tertiary alcohol underwent a Lewis acid-induced ionization to a tertiary, allylic carbocation, which was subsequently trapped by mesitylenesulfonyl hydrazide. On warming to 0 °C,



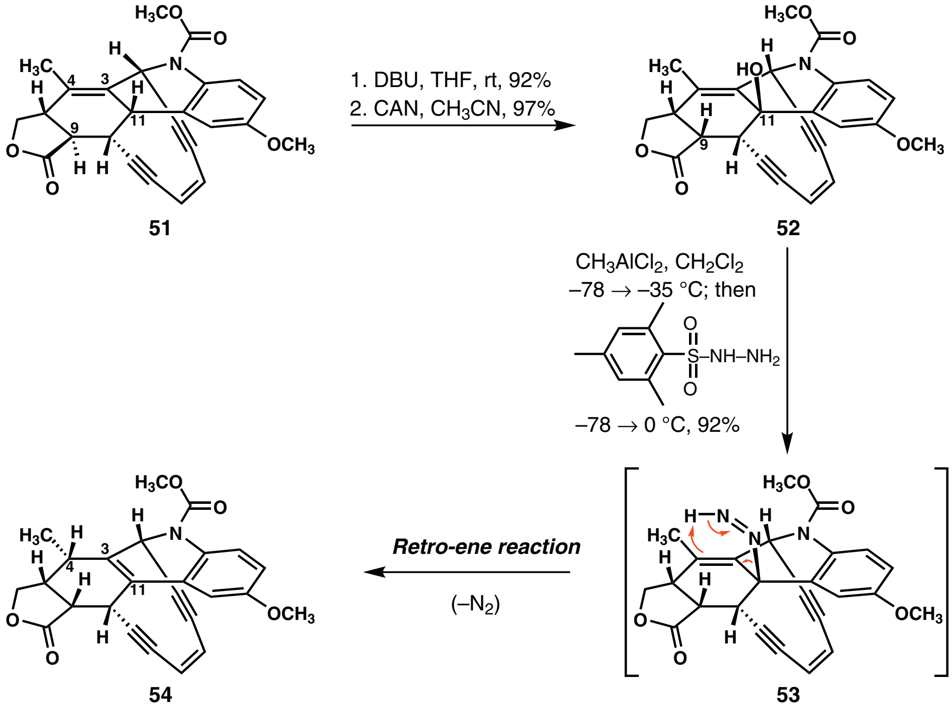
SCHEME 11 Some key transformations in Eschenmoser's landmark synthesis of colchicine (**44**).



SCHEME 12 The Baran/Burns strategy for constructing the strained, bent benzene nucleus of haouamine A (**47**).



SCHEME 13 Tandem cyclizations in the Schreiber synthesis of dynemicin A-like compounds.



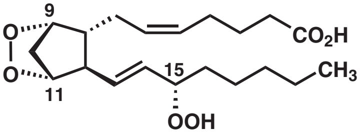
SCHEME 14 A stereospecific, reductive transposition of an allylic diazene in a synthesis of dynemicin A-like compounds by the Schreiber laboratory.

the adduct arising from this cation trapping step loses a molecule of mesityl sulfinic acid, thus giving rise to the putative allylic diazene **53**; this reactive species enables the desired reductive transposition to compound **54** through a stereospecific, retro-ene reaction with loss of molecular nitrogen. This chemical reaction beautifully solves the problem of establishing the desired stereochemistry at C-4 and is arguably the most impressive example of an allylic diazene rearrangement in complex natural product synthesis.

6 HARNESSING THE REACTIVITY OF PEROXYL RADICALS: COREY'S REMARKABLE SYNTHESIS OF PROSTAGLANDIN ENDOPEROXIDE PGG$_2$ METHYL ESTER

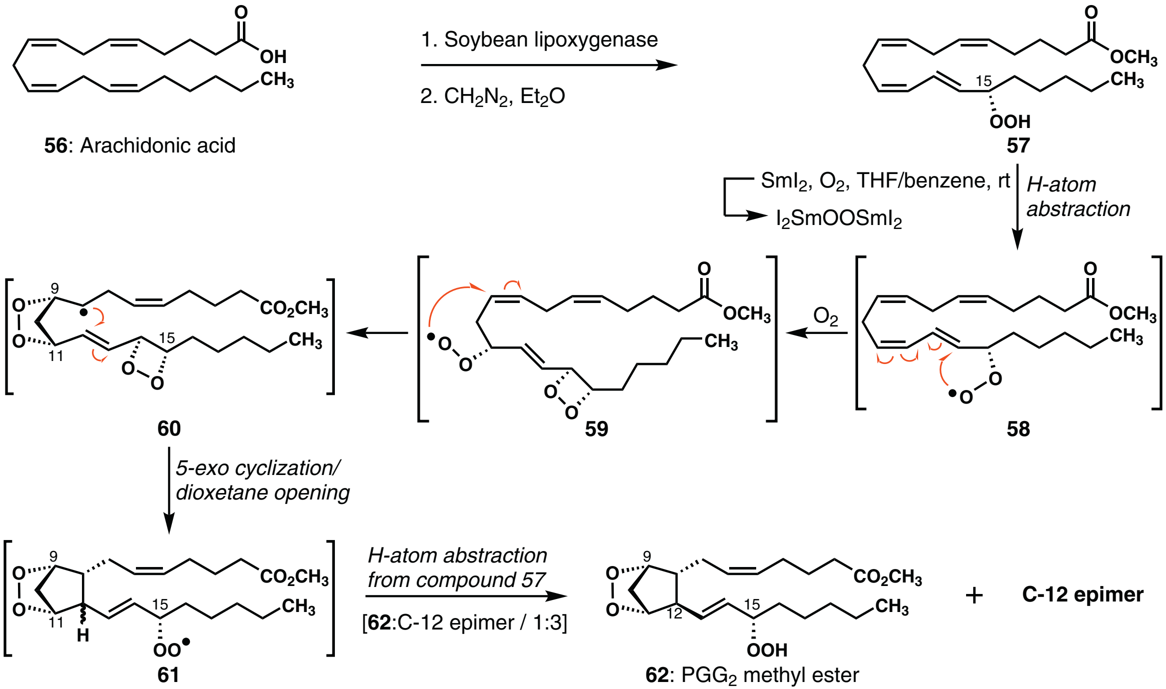
The endoperoxide, prostaglandin G$_2$ (PGG$_2$) (**55**) (Figure 3), plays an important role in the biochemistry of fatty acids because it is the first isolable intermediate on the path from arachadonic acid to the prostaglandins and thromboxanes.[30] The lability of its 9,11-endoperoxide bridge and the C-15 hydroperoxide group have complicated efforts to isolate this unique metabolite in a pure state from biological samples, as well as to achieve its synthesis. In 1994, Corey and Wang described an effective, new reagent for enabling the conversion of ROOH → ROO$^\bullet$ and its use in a creative, free radical-based synthesis of PGG$_2$ methyl ester (**62**) (Scheme 15).[31]

This impressive synthesis commenced with the soybean lipoxygenase-catalyzed oxidation of arachidonic acid (**56**); a simple esterification of the carboxyl group with diazomethane then gave hydroperoxide methyl ester **57**. The next and final step of the synthesis featured the chemistry of a new samarium peroxide initiator, which arises by the reaction of SmI$_2$ in THF with molecular oxygen. Corey and Wang suggest that this initiator may have the structure, I$_2$SmOOSmI$_2$, and that it may have special utility as a reagent for producing peroxyl radicals from hydroperoxides. In the pivotal transformation, the addition of 0.1 equiv. of this putative samarium peroxide initiator in THF to a solution of compound **57** in dry benzene at 6 °C resulted in the formation of a 1:3 mixture of the desired PGG$_2$ methyl ester (**62**) and an isomeric structure that was shown to be the C-12 epimer of **62** (43% total yield based on a 65% recovery of unreacted **57**). The generation of peroxyl radical **58** is believed to be the first step on the path to compound **62**; this initial, oxygen-centered radical engages the closest alkene in a 4-*exo*-trigonal cyclization, after which a site-selective trapping



55: PGG$_2$

FIGURE 3 The structure of prostaglandin G$_2$ (PGG$_2$) (**55**).



SCHEME 15 Corey's biomimetic synthesis of PGG$_2$ methyl ester (**58**) from arachidonic acid (**52**) featuring a cascade of free radical reactions.

of the intermediate allylic radical at C-11 with molecular oxygen occurs to give the novel dioxetane peroxyl radical **59**. A 5-*exo*-trigonal addition of the peroxyl radical in **59** to the C8–C9 alkene then generates carbon-centered radical **60** as a prelude to the final, 5-*exo*-trigonal radical cyclization to form the prostaglandin 5-membered ring. The rupture of the heterocyclic dioxetane and the formation of peroxyl radical **61** attend this last ring formation. A final H-atom transfer from hydroperoxide **57** to peroxyl radical **61** gives rise to PGG_2 methyl ester (**62**) and the chain-propagating peroxyl radical **58**.

7 CONCLUDING REMARKS

Every undertaking in organic synthesis starts with a plan. The plan might comprise sequences of well-known reactions and established concepts for synthesis, or it might require a venture into the unknown and the development of new chemical reactions and/or ideas for doing synthesis. R. B. Woodward once wrote, "Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in a general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective."[32] More recently, Albert Eschenmoser wrote, "The complexity in the behavior of organic molecules is such that the first execution of a complex synthesis based on design is almost always also a venture into the uncertain, an experiment run for finding out whether and under what conditions the elements of the design do correspond to reality."[33]

The achievements addressed in this account demonstrate the merits of creative risk-taking in the design and execution of organic syntheses. And yet one might wonder if risk-taking in organic chemical research is even worth the risk in an era when it is so challenging to gain financial support for research. The conservative nature of the peer review process is reflected in phrases like, "don't put it in your grant unless you know it will work." These are clearly challenging times, but there is reason for optimism. A relatively recent study by the American Academy of Arts and Sciences advocated for increases in support for early-career faculty and support for high-risk, high-reward, and potentially transformative research.[34] This study also drew the conclusion that high-risk, high-reward research must be supported even though the rate of progress will be uneven and the probability of success unknown.

Since it is not possible to "plan" significant discoveries in science, risk-taking will continue to beget innovation in the dynamic field of organic synthesis.[35] Of course, the state of this discipline is best demonstrated by way of example, and it is our sincere hope that the achievements addressed in this brief review will inspire you to embrace risk as you plan and execute your own undertakings in organic synthesis.

ACKNOWLEDGMENTS

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Chapter 10

Stereoselective Addition of Halogen to Conjugated Enynes and Its Application in the Total Synthesis of (–)-Kumausallene

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Chapter Outline

1 INTRODUCTION

Carbon–halogen bonds are widely present in marine natural products and pharmaceutical agents.[1–3] However, stereoselective introduction of halogens is often challenging and has received considerable attention recently in the total synthesis[4–8] and biosynthesis[9–14] of complex natural products. (−)-Kumausallene **1** belongs to a family of nonisoprenoid sesquiterpenes with an unusual bromoallene structural motif (Scheme 1).[15] The bromoallene moiety is present in a subcategory of about three dozen marine natural products.[16,17] Only a small fraction of them have been synthesized, including

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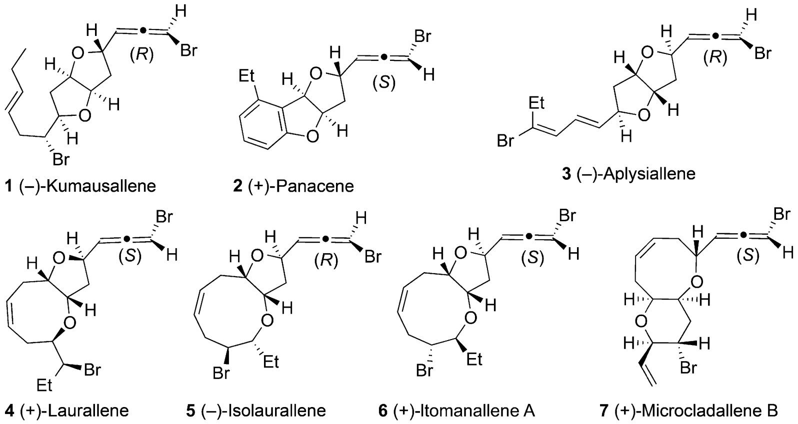


SCHEME 1 Selected bromoallene-containing natural products.

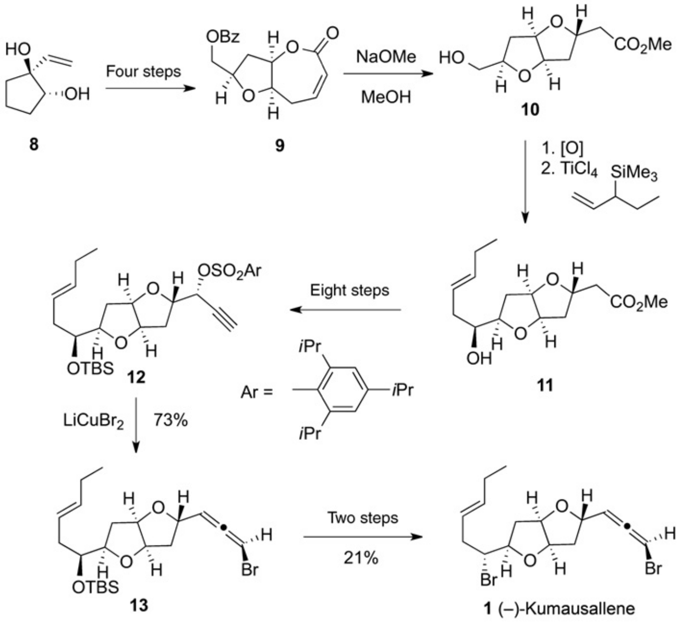
dioxabicyclic kumausallene **1**,[18–20] panacene **2**,[21–23] and aplysiallene **3**[24]; the eight- and nine-membered cyclic ethers laurallene **4**,[25,26] isolaurallene **5**,[27,28] itomanallene A **6**,[29] and microcladallene B **7**.[30]

The first total synthesis of (±)-kumausallene was accomplished by Overman in 1993.[18,31,32] In his synthesis, the complex dioxabicyclo[3.3.0]octane core was constructed by an elegant ring-expansion annulation strategy that was developed by his lab previously.[31,32] The bromoallene moiety was synthesized by stereoselective S_N2' displacement of propargylic sulfonate. This method was used earlier by Feldman for the synthesis of *epi*-panacene[21] and also was employed in most other syntheses of bromoallene-containing natural products.

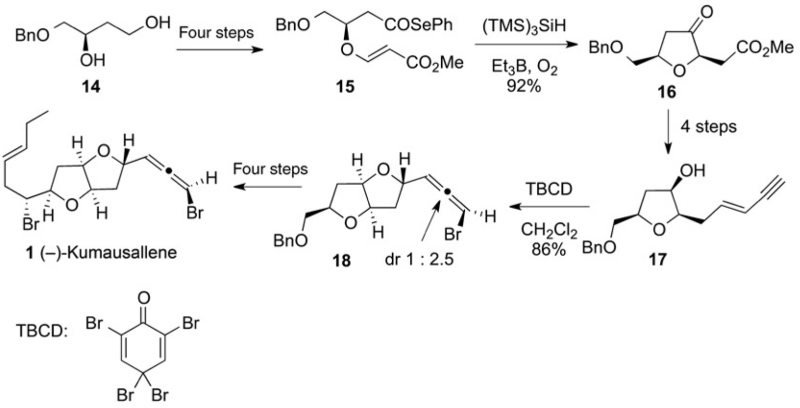
The key bicyclic lactone **9** was prepared in four steps from diol **8** (Scheme 2). The sequence included a Prins–pinacol rearrangement followed by a Baeyer–Villiger oxidation. This lactone underwent methanolysis to give the hydroxyl ester, which was immediately cyclized to give the desired *cis*-fused dioxabicycle **10**. The pentenyl side chain was installed through a Sakurai allylation[33,34] of the corresponding aldehyde. The methyl ester in compound **11** was then elaborated to propargyl sulfonate **12** in eight steps. The sulfonate was displaced with $LiCuBr_2$ to give the key bromoallenyl moiety of intermediate **13**. The final steps to the racemic natural product involved deprotection of the secondary alcohol followed by bromination. This first synthesis of kumausallene was completed in 20 steps.

Since Overman's first synthesis of kumausallene, numerous synthetic studies toward the preparation of the tetrahydrofuran ring in kumausallene and related natural products such as kumausyne have been reported.[35–47]

The Evans group reported the first enantioselective total synthesis of (−)-kumausallene in 1999 (Scheme 3).[19] The first tetrahydrofuran ring was prepared using an acyl radical cyclization method.[48,49] A biomimetic strategy



SCHEME 2 Overman's first total synthesis of (±)-kumausallene.



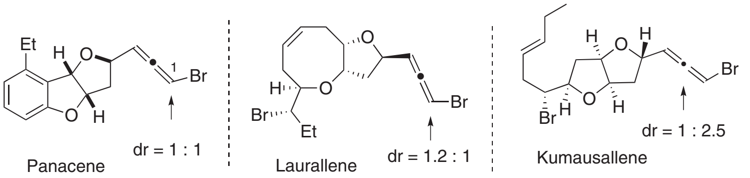
SCHEME 3 Evans' first enantioselective total synthesis of (−)-kumausallene.

was undertaken by Evans to forge the bromoallene and the second tetrahydrofuran ring simultaneously. Although the diastereoselectivity was high for the formation of tetrahydrofuran, two diastereomeric bromoallenes were produced and the major isomer was the unnatural epimer.

In Evans' synthesis, the enantioenriched diol **14**, available in three steps from commercially available materials, was converted to the key acyl selenide intermediate **15** in four steps. This intermediate was prepared as the precursor for the key radical cyclization, which was effected by using tris(trimethylsilyl) silane and triethylborane at −78 °C to give the desired cyclic ether **16** with almost complete diastereoselectivity. The 1,3-enyne side chain was installed in four steps to give a *trans*-enyne **17**. This enyne was then treated with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD) to give the bromoallene **18** in a 1:2.5 diastereomeric ratio (dr), favoring the unnatural allenic epimer. The desired bromoallene **18** could be converted to the final (−)-kumausallene product in four steps, including installation of the pentenyl side chain by Sakurai allylation.[33,34] The undesired epimer could be recycled by treatment with SmI_2. The first enantioselective synthesis of (−)-kumausallene was completed in 17 steps, and the absolute stereochemistry of the bromoallene was confirmed.

2 HALOGEN-PROMOTED 1,4-ADDITION TO 1,3-ENYNES

The first intramolecular 1,4-addition of alcohol and bromine (1,4-bromoetherification) to conjugated enynes was reported in 1982 by Feldman in the biomimetic synthesis of racemic *epi*-panacene.[22] A 1:1 dr was observed for the newly generated stereogenic center and axially chiral allene (Scheme 4). It was found later that the relative stereochemistry of (−)-panacene was assigned incorrectly and the first synthesis of (−)-panacene was completed in 2006 by Boukouvalas.[23] The 1,4-bromoetherification strategy was also applied to the synthesis of laurallene by Murai[50] and Crimmins[25] and the synthesis of (−)-kumausallene by Evans.[19] No diastereoselectivity was observed in the case of laurallene and a ratio of 2.5:1 favoring the undesired epimer through *anti*-addition was observed in the case of the (−)-kumausallene synthesis. Recently, Braddock studied the 1,4-bromoetherification of simple conjugated enynes without preexisting stereogenic centers by treating them with *N*-bromosuccinimide (NBS) at low temperature and observed improved diastereoselectivity favoring the *syn*-addition (dr = 6:1 for *trans*-enynes; dr = 7:1 for *cis*-enynes).[51] Canesi reported that high diastereoselectivity (dr > 20:1) could be obtained for 1,4-bromoetherification of conjugated enynes in nonpolar solvents.[52] However, the major diastereomer was the undesired epimer of natural product

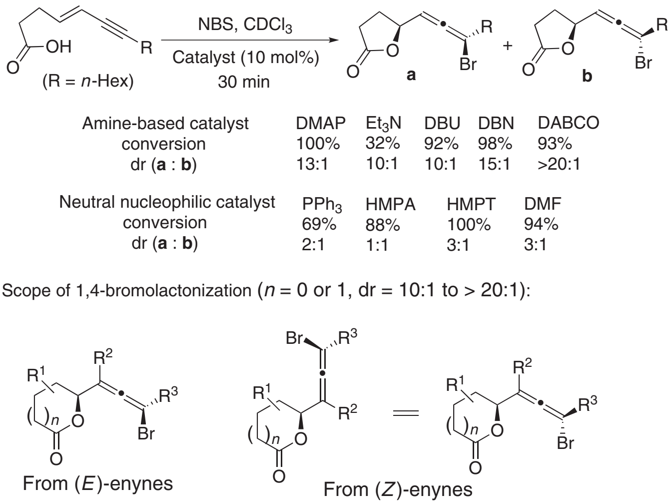


SCHEME 4 Diastereoselectivity for the bromoetherification of 1,3-enynes in natural product synthesis.

panacene. A $Hg(OAc)_2$-mediated cyclization of bromoenyne led to the synthesis of natural panacene.

Although several noncatalyst-mediated 1,4-additions of alcohols and bromine to conjugated enynes were reported in natural product synthesis, low diastereomeric ratios were generally observed for the newly generated stereogenic center and axially chiral allene. The diastereoselective 1,4-addition of various nucleophiles and electrophiles to conjugated enynes as a general method for the preparation of functionalized haloallenes had not been developed prior to our study. The enantioselectivity of the halogen-promoted 1,4-addition reaction to enynes had never been explored.

We first discovered that a highly diastereoselective 1,4-bromolactonization of conjugated enynes could be realized using DABCO as the catalyst (Scheme 5).[53] In contrast to the *anti*-1,2-addition of halogen and nucleophiles to simple alkenes, *syn*-addition occurred exclusively for the 1,4-addition to conjugated 1,3-enynes. The DABCO-catalyzed *syn*-1,4-bromolactonization works for both (*Z*)- and (*E*)-1,3-enynes and provided cyclization products with complementary stereochemistry. No reaction occurred in the absence of any catalyst. Interestingly, most amine-based catalysts (e.g., DMAP, Et_3N, DBU, DBN, DABCO) provided high diastereoselectivity, while neutral nucleophilic catalysts (i.e., Ph_3P, HMPA, HMPT, DMF) gave low dr as shown in Scheme 5. There are two potential activation modes for NBS: (1) activation of NBS by forming a catalyst–bromine adduct through Lewis base activation mechanism,[54] which is possible for all catalysts; (2) activation of NBS by forming a hydrogen bond between the protonated catalyst and the carbonyl group of NBS, which is only possible for amine-based catalyst. We hypothesized that the ionic interaction between the negatively charged carboxylate and the positively



Amine-based catalyst	DMAP	Et_3N	DBU	DBN	DABCO
conversion	100%	32%	92%	98%	93%
dr (**a** : **b**)	13:1	10:1	10:1	15:1	>20:1

Neutral nucleophilic catalyst	PPh_3	HMPA	HMPT	DMF
conversion	69%	88%	100%	94%
dr (**a** : **b**)	2:1	1:1	3:1	3:1

Scope of 1,4-bromolactonization (n = 0 or 1, dr = 10:1 to > 20:1):

SCHEME 5 Diastereoselective 1,4-*syn*-bromolactonization of 1,3-enynes.

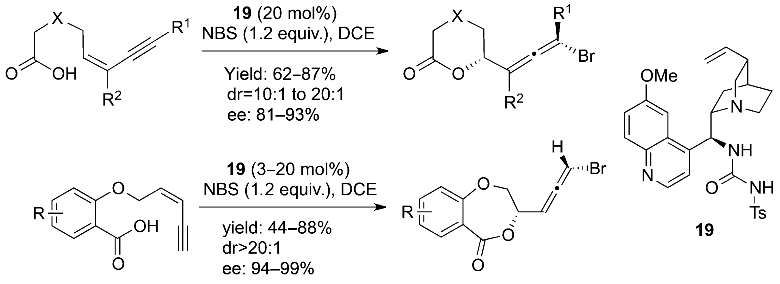
charged ammonium group complexed with NBS via hydrogen bonds might be the source of high *syn*-selectivity for amine-based catalysts.

In addition to carboxylate nucleophiles, we also examined different nitrogen nucleophiles for the halogen-promoted halocyclization of 1,3-enynes and observed correlations between the acidity of amide and the dr of cyclization products.[55]

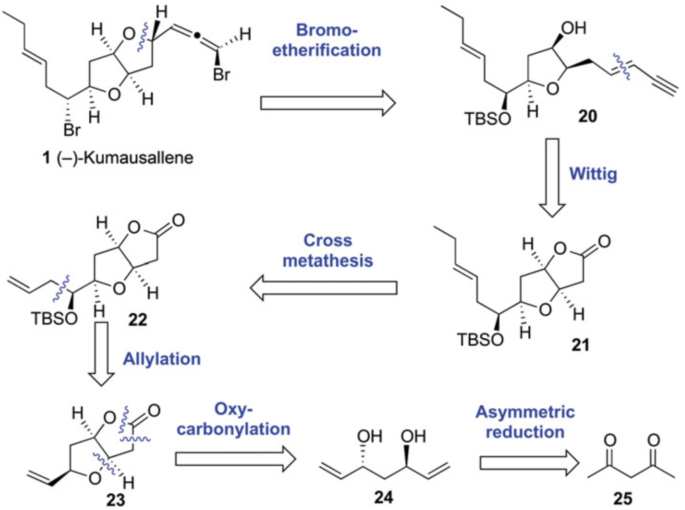
The structural similarity between cinchona alkaloids and DABCO prompted us to examine them as the catalysts for the enantioselective 1,4-bromolactonization of 1,3-enynes.[56] We indeed observed excellent diastereoselectivity for the bromocyclization of both (*E*)- and (*Z*)-enynes. While nearly racemic products were isolated for products derived from (*E*)-enynes, promising enantioselectivity (58% ee) was obtained for the bromoallenyl lactones derived from (*Z*)-enynes. We then prepared various cinchona alkaloid derivatives as catalysts for the enantioselective 1,4-bromolactonization of (*Z*)-1,3-enynes. Catalyst **19** with a urea group afforded over 80% ee for most (*Z*)-enynes (Scheme 6). Enynes tethered with a benzoic acid nucleophile generally provided higher enantioselectivity and required lower catalyst loading.

3 RETROSYNTHETIC ANALYSIS OF (–)-KUMAUSALLENE

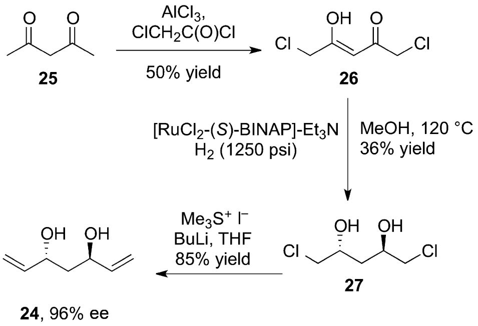
Based on the correlation of diastereoselectivity and catalyst in the bromolactonization of 1,3-enynes (Scheme 5), we hypothesized that the diastereoselectivity of bromoetherification may also be tuned by the catalyst. We proposed to use 1,4-bromoetherification of conjugated 1,3-enyne **20** as the key final step in our (–)-kumausallene synthesis (Scheme 7). Enyne **20** is available in two steps from bicyclic lactone **21** via reduction and Wittig olefination. The pentenyl side chain could be appended through cross metathesis of allylic alcohol **22**, which can be derived from bicyclic lactone **23**. We planned to access this lactone via palladium-catalyzed oxycarbonylation of the C_2-symmetric diol **24**, which, in turn, could be prepared from asymmetric reduction of acetylacetone **25**.



SCHEME 6 Enantioselective 1,4-bromolactonization of 1,3-(*Z*)-enynes.



SCHEME 7 Retrosynthetic plan for (−)-kumausallene.



SCHEME 8 Preparation of diol **24** for Pd-catalyzed cascade reaction.

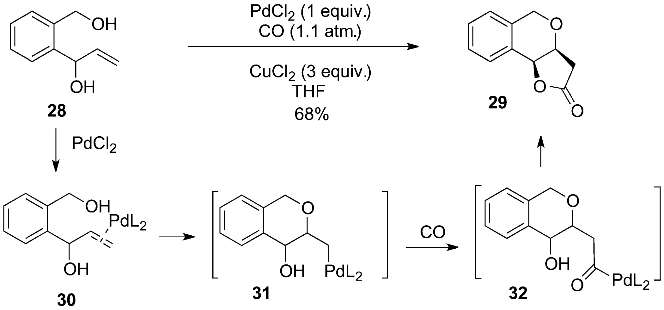
4 STEREOSELECTIVE SYNTHESIS OF (–)-KUMAUSALLENE

4.1 Pd-Catalyzed Oxycarbonylation–Lactonization Cascade

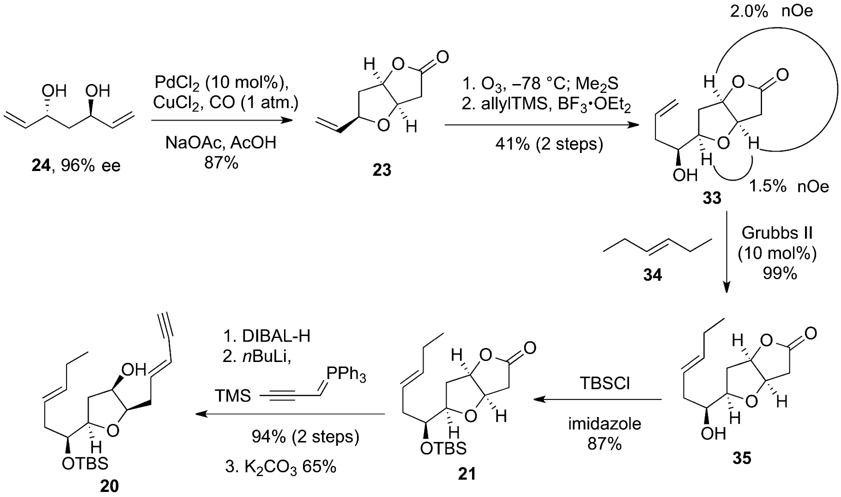
The synthesis began with the dichlorination of acetylacetone **25** by aluminum chloride and chloroacetyl chloride following known literature procedures.[57,58] The acetyl chloride side product was removed via distillation over 8–10 h, and the diketone product **26** was purified through its copper salt. As demonstrated by Rychnovsky,[57,58] this dione was reduced to diol **27** highly enantioselectively using Noyori's catalyst $[RuCl_2\text{-}(S)\text{-BINAP}]\text{-}Et_3N$ (Scheme 8). The catalyst is prepared by refluxing 1,5-cyclooctadieneruthenium(II) chloride, (*S*)-BINAP, and triethylamine in toluene for 16 h under an inert atmosphere.

Using this catalyst, pure crystalline diol **27** was prepared with excellent enantioselectivity, though we found the conditions of this hydrogenation reaction to be very sensitive. The pressure of the hydrogenation reaction must be kept above 1200 psi or the enantioselectivity is severely compromised, dropping from 96% ee to ~50% ee. The internal temperature must be carefully maintained at 65 °C, or the diol will cyclize to give 2-chloromethyl-4-hydroxytetrahydrofuran, which is extremely difficult to remove from the crystalline diol. We also attempted to prepare the enantiomer of diol **27** in an analogous fashion using the catalyst based on (*R*)-BINAP but found the product to be difficult to purify via recrystallization. The C_2-symmetric dichlorodiol **27** was converted to diene **24** via bis-olefination with Me_3SI and *n*-butyllithium, as shown by Hanson.[59] The enantiomeric excess of diene **24** was demonstrated through HPLC analysis to be 96% ee. This hydrogenation was the first true high-pressure reaction that was conducted in our lab. One thing the student learned was that the rating of a relief valve was significantly compromised when used at high temperature (theoretically, rather than through a burst valve—thankfully!).

The key oxycarbonylation step was founded on work done by the Semmelhack group in 1984.[60,61] They demonstrated that diol **28** could undergo an alkoxycarbonylation/lactonization cascade reaction with the incorporation of CO, promoted by palladium chloride, to give bicyclic lactone **29** (Scheme 9). The mechanism for this reaction likely involves the initial formation of the π-olefin palladium complex **30**, followed by intramolecular attack of the alcohol to generate the σ-alkylpalladium complex **31**. Insertion of CO to the Pd—C bond followed by lactonization liberates Pd^0, which is then reoxidized by an internal oxidant. This type of cascade reaction could be mediated by a catalytic amount of palladium and the first catalytic version appeared in 1985.[62] It has been applied to the total synthesis of *trans*-kumausyne,[39] and (−)-panacene,[23] and toward the synthesis of plakortones,[63] micrandilactone D,[64] and in the synthesis of C_{19} lipid diols.[65] Progress has also been made in the asymmetric oxycarbonylation under similar conditions.[66]



SCHEME 9 Semmelhack's Pd-mediated alkoxycarbonylation and lactonization cascade.



SCHEME 10 Pd-catalyzed alkoxycarbonylation/lactonization cascade and further elaborations.

We envisioned that this methodology could be extended to the desymmetrization of C_2-symmetric diol **24** for the construction of a tetrahydrofuran ring with a lactone and a vinyl group on the 2,5-positions for further manipulations. The key desymmetrization of C_2-symmetric diol **24**, via a palladium-catalyzed oxycarbonylation under an atmosphere of carbon monoxide, successfully yielded the bicyclic lactone **23** as a single isomer in 87% yield (Scheme 10).

The pentenyl side chain of (−)-kumausallene was appended via a four-step sequence, as outlined above in Scheme 10. Ozonolysis of the remaining alkene in **23** gave an aldehyde intermediate. Allylation of this aldehyde with allyltrimethylsilane[33,34] yielded a pair of diastereomers in a 4:1 ratio, which were separated by column chromatography to give the desired terminal alkene **33** in 41% yield over two steps. Our assignment for the secondary alcohol was based on the Felkin–Ahn model, and the selectivity of this reaction is consistent with that observed in Phillips' total synthesis of *trans*-kumausyne.[45] The stereochemistry of the bicyclic ring junction was confirmed by nuclear Overhauser effect (NOE) NMR experiments on compound **33**.

Cross metathesis with Grubbs II catalyst[67] and *trans*-3-hexene **34** installed the remaining carbon atoms on the side chain to give **35** in almost quantitative yield (Scheme 10). This allylation/cross metathesis route to the pentenyl side chain was also employed by Phillips in his synthesis of *trans*-kumausyne.[45] The free secondary alcohol **35** was protected by TBSCl. Reduction of the lactone in **35** by DIBALH followed by Wittig olefination led to a separable mixture (E:Z = 10:1) of conjugated enynes.[68] The trimethylsilyl group was removed using basic methanol to liberate terminal enyne **20**, the substrate for the key bromoetherification step.

4.2 Bromoetherification of Conjugated Enynes and Completion of the Synthesis

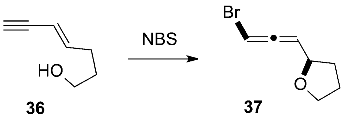
Bromoetherification of simple model enynes were conducted in different solvents (Scheme 11). When *E*-enyne **36** was treated with NBS in $CDCl_3$, the desired bromoallenyl ether **37** was formed in 74% yield and a 9:1 dr. In toluene, the dr was increased to 20:1, which was consistent with observations reported in literature.[51,52]

The key bromoetherification step was then investigated, using enyne **20** (Table 1). Unfortunately, under various bromoetherification conditions developed for the simple model system, the more complex enyne **20** failed to show any evidence of the desired allene product (entries 1 and 8). As previously discussed, Evans was able to effect the bromocyclization of enyne **17** using TBCD in methylene chloride (Scheme 3), but identical conditions led to a complex mixture with all evidence of olefin NMR signals gone (entry 2). The preparation of fresh TBCD or newly recrystallized NBS failed to show any improvement in the desired reaction.

In our previous studies on electrophilic brominations of conjugated enynes, we found that a variety of additives, including DABCO, DMAP, quinine, and HMPT, were able to facilitate the bromolactonization reaction (Scheme 5). We decided to explore the use of these additives in the case of alcohol nucleophiles. We found that when DABCO, quinine, HMPT, DMAP, and DMF were employed as the additives, either no reaction or a complex mixture was observed without any evidence of product formation (entries 3–7). Using toluene in place of chloroform led to disappearance of all olefin peaks within 2 h (entry 8), while addition of 10 equiv. of DABCO shut down the reaction once again (entry 9).

Gratifyingly, the use of HMPA as an additive in toluene finally led to the formation of some allenic products (entries 10). The ^{1}H NMR of product **38** appeared to be one compound and was almost identical to what had been reported in the literature. It looked like all we needed to do was the removal of the silyl protecting group, which has been realized by Overman's group.[18] This would then be the first total synthesis of a complex natural product completed in the Tang lab. We were almost ready to celebrate.

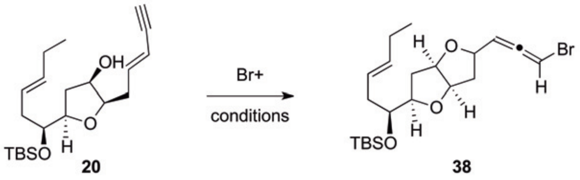
The next day was absolutely the worst day for us. Attempts to confirm the identity of intermediate **38** using ^{13}C NMR led to the surprising observation of



in $CDCl_3$, 74%, dr = 9:1
in toluene, 80%, dr = 20:1

SCHEME 11 Bromoetherification of model enyne **36**.

TABLE 1 **Attempted Bromoetherification of Enyne 20**[a]

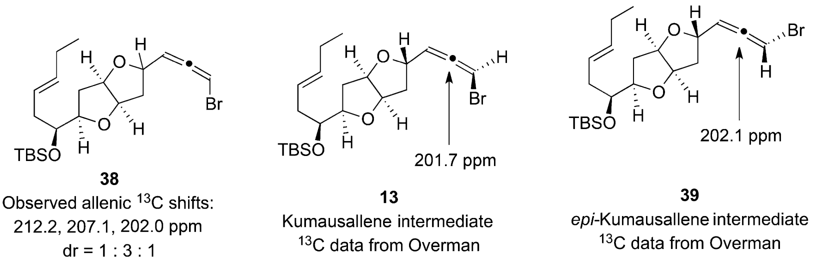


Entry	[Br$^+$]	Solvent	Additive	Time (h)	Ratio of 38/20[b]
1	NBS	$CDCl_3$	–	24	No reaction
2	TBCD	CH_2Cl_2	–	6.5	Complex mixture[c]
3	NBS	$CDCl_3$	DABCO	24	No reaction
4	NBS	$CDCl_3$	Quinine	24	No reaction
5	NBS	$CDCl_3$	HMPT	2	Complex mixture[c]
6	NBS	$CDCl_3$	DMAP	2	Complex mixture[c]
7	NBS	$CDCl_3$	DMF	2	Complex mixture[c]
8	NBS	Toluene	–	2	Complex mixture[c]
9	NBS	Toluene	DABCO	24	No reaction
10	NBS	Toluene	HMPA	24	1:2, dr=2:4:1[d]
11	NBS	Toluene	DMF	24	1:1, dr=1:3:1[d]
12	NBS	DMF	–	24	No reaction
13	NBS[e]	Toluene	DMF	24	4:1, dr=1:3:1[d]

[a] *Standard conditions: 1.2 equiv. [Br$^+$], 0.01 M, 10 equiv. of additive, rt.*
[b] *The ratio of* **38/20** *was estimated by* ^1H *NMR.*
[c] *All olefin signals completely disappeared.*
[d] *All drs were estimated by* ^{13}C *NMR.*
[e] *NBS was added in three portions.*

three characteristic allenic central carbons, at 212, 207, and 202 ppm, in a ratio of 2:4:1 (Scheme 12). Comparison to the previously reported ^{13}C data for compounds **13** and **39**[18] suggested that the minor isomer at 202 ppm might correspond to either the desired bromoallene **13** (201.7 ppm) or its epimer **39** (202.1 ppm). The other two diastereomers might be the result of low diastereoselectivity for the cyclization.

We could improve the conversion of the bromocyclization using DMF as the additive (entry 11). When DMF was employed as the solvent, the starting material was recovered (entry 12). Adding NBS in three portions over the



38
Observed allenic ^{13}C shifts:
212.2, 207.1, 202.0 ppm
dr = 1 : 3 : 1

13
Kumausallene intermediate
^{13}C data from Overman

39
epi-Kumausallene intermediate
^{13}C data from Overman

SCHEME 12 Comparison of ^{13}C chemical shifts of the allene moiety.

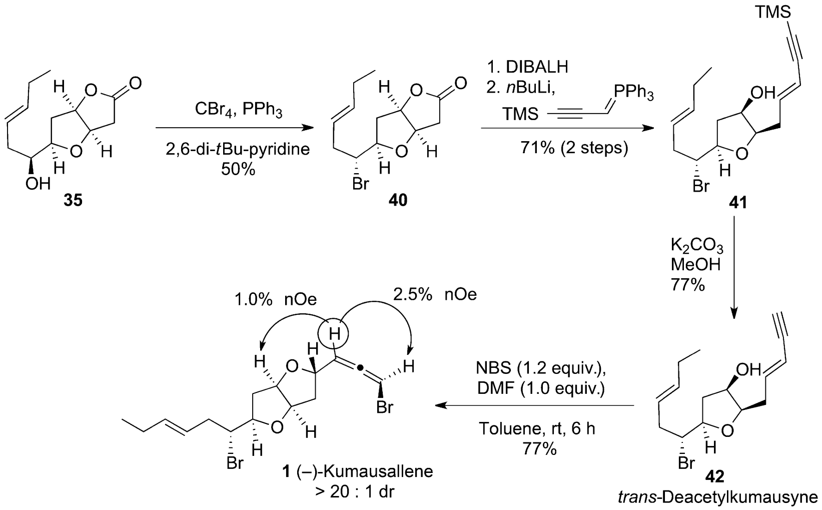
course of the reaction improved the conversion further (entry 13). The selectivity, however, remained about the same. At that time, we felt that this cyclization was like an insurmountable hurdle because the mixture just looked like one compound based on the ^{1}H NMR and we had to take a ^{13}C NMR for each analysis. In addition, it was also possible that none of the three isomers we had was the desired one. We decided to try a different substrate for the cyclization.

An earlier attempt at the bromocyclization of a conjugated enyne substrate in the pursuit of a total synthesis of kumausallene used a free diol derived from the deprotection of compound **20**. We had hoped to prevent the need for a protecting group, but it appeared that the *trans*-olefin on the pentenyl side chain underwent a reaction when exposed to NBS and led to unidentifiable products. This observation, as well as the results observed for enyne **20** and those reported by Evans, clearly demonstrated that the selectivity of the biomimetic bromoetherification was heavily dependent upon the effect of a remote directing group.

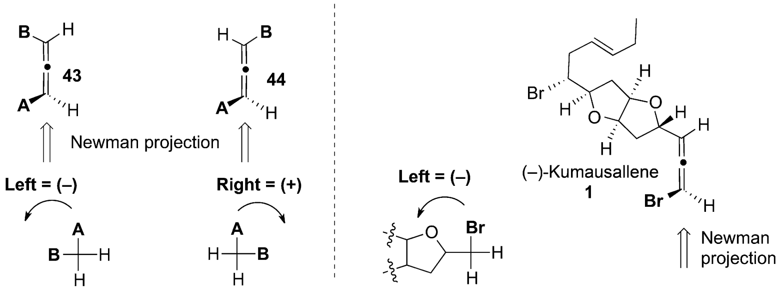
For these reasons, we elected to try to prepare *trans*-deacetylkumausyne **42** (Scheme 13), having a bromide on the pentenyl side chain in place of the protected alcohol. This compound could be the ideal candidate for our desired biomimetic bromoetherification, as it was originally isolated from the same red alga, *Laurencia nipponica* Yamada, and may be involved in the biosynthesis of kumausallene itself.[69]

As previously reported by Overman in his syntheses of kumausallene[18] and the related natural product kumausyne,[32] the bromination of a homoallylic alcohol such as **35** is known to be difficult, with yields averaging 30% with the use of CBr_4, PPh_3, and the bulky base 2,6-di-*tert*-butylpyridine. We were able to achieve yields around 50% through excessive purification of the carbon tetrabromide, to give the desired bromide **40**. Using the same series of steps as in Scheme 10, (−)-*trans*-deacetylkumausyne **42** was prepared in three steps through intermediate **41**.

Application of NBS in deuterated toluene with 10 equiv. of DMF effected the biomimetic 1,4-*syn*-bromoetherification of the enyne to give (−)-kumausallene **1** in 6 h. A larger scale reaction, using only 1 equiv. of



SCHEME 13 Biomimetic bromocyclization of (−)-*trans*-deacetylkumausyne.



SCHEME 14 The application of Lowe's rule to the prediction of absolute allene stereochemistry.

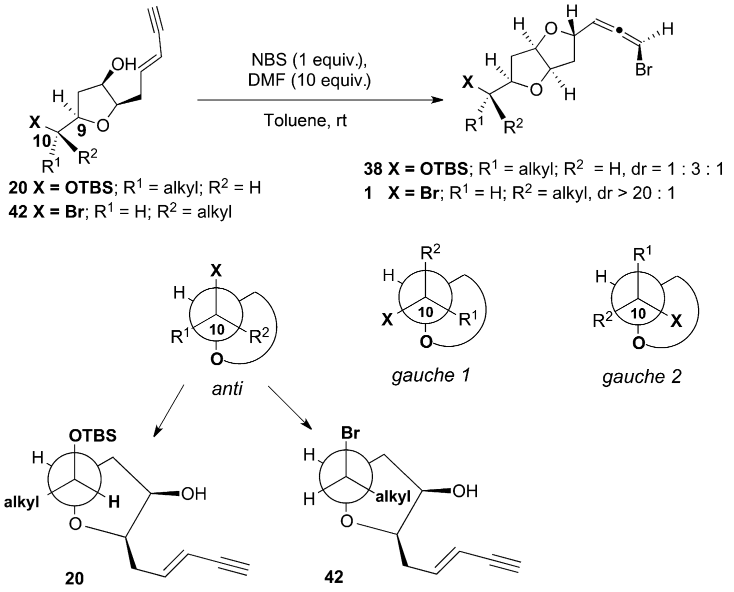
DMF, yielded the final product in 77% yield. We found the addition of DMF to be critical, because in its absence, the reaction of enyne **42** with NBS led to a complex mixture in 90 min without the formation of any desired bromoallene. The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) and optical rotation of our synthetic (−)-kumausallene **1** were identical to values reported in the literature.[20] The stereochemistry of the newly formed tetrahydrofuran ring in kumausallene **1** was further confirmed by NOE.

The correlation between the absolute stereochemistry of the bromoallene and its optical rotation is consistent with Lowe's rule,[70] as shown in Scheme 14. If allene **43** is viewed in a Newman projection with the most polarizable substituent on the top (**A**) and the second most polarizable substituent (**B**) is along the horizontal axis to the left, the allene is levorotary (left-handed) and its optical rotation will be negative. If **B** is to the right

(**44**), a positive optical rotation will be observed. This rule can also be extended to tri- and tetra-substituted allenes.

4.3 Rationalization of the Long-Range Stereochemical Effect

A drastic difference in diastereoselectivity was observed for the bromoetherification of the OTBS-substituted enyne **20** versus the bromine-substituted enyne **42**. While a single diastereomer **1** was isolated in 77% yield for the cyclization of **42**, three diastereomers of **38** were observed for the cyclization of **20** (Scheme 15). We hypothesized that the selectivity of the bromocyclization reaction might be influenced by the conformation around the C9—C10 bond. Of the three possible staggered conformations shown in Scheme 15, the positioning of oxygen and the X group (either Br or OTBS) in an *anti* orientation may be favored, due to the stabilization derived from opposing dipoles. In this *anti* configuration, the position of the pentenyl alkyl side chain can either be oriented away from the concave face in enyne **20**, or into the concave face in enyne **42**. In the latter case, the added steric constraint of the pentenyl alkyl side chain in **42** may exert a greater influence over the transition state of the bromoetherification reaction and force the resulting bromoallene group to be situated in the convex face in product **1**. The addition of alcohol nucleophile and bromine electrophile to 1,3-enyne **42** follows the *syn*-diastereoselectivity observed previously.



SCHEME 15 Effect of X group and its stereochemistry on the diastereoselectivity of bromoetherification of enynes.

5 CONCLUSION

In summary, the first diastereo- and enantioselective total synthesis of (−)-kumausallene was accomplished in 12 steps from acetylacetone after the development of diastereo- and enantioselective methods for 1,4-halocyclization of conjugated enynes. The core *cis*-dioxabicyclic ring structure was achieved through the desymmetrization of a C_2-symmetric diol via a palladium-catalyzed oxycarbonylation, uncovering the hidden symmetry of the kumausallene molecule. A remarkable long-range stereochemical effect was discovered for the DMF-promoted biomimetic 1,4-*syn*-bromoetherification of a conjugated 1,3-enyne. It may have broader implications not only for the synthesis of dozens of other bromoallene-containing natural products[16,17] but also for biomimetic synthesis in general.[71–74] In addition to the scientific accomplishments, it is very clear that the student involved in this total synthesis project became stronger and more mature after overcoming all the hurdles and frustrations.

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Chapter 11

Total Synthesis of Aspergillide C

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Chapter Outline

1 INTRODUCTION: IDENTIFICATION OF THE ASPERGILLIDES AS SYNTHETIC TARGETS

1.1 Isolation and Structural Determination

In 2008, three secondary metabolites aspergillides A, B, and C (Figure 1) were isolated from a marine-derived fungus, *Aspergillus ostianus* strain 01F313, found off the coast of Pohnpei.[1] Three chloride-containing antibacterial metabolites were previously isolated from this strain.[2] It was thought that chloride was incorporated into the compounds as a result of their cultivation in natural ocean water. Thus, it was anticipated in a parallel study that a cultivation medium of bromide-containing saltwater might give rise to the corresponding bromide-containing compounds, with possible new or improved biological activity. It was found, however, that this artificial

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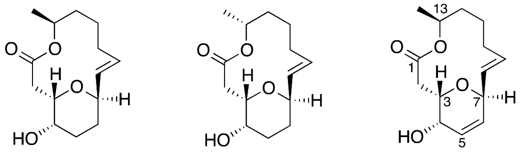


(−)-Aspergillide A (**1**) (−)-Aspergillide B (**2**) (+)-Aspergillide C (**3**)

FIGURE 1 Originally proposed structural assignments for aspergillides A, B, and C.

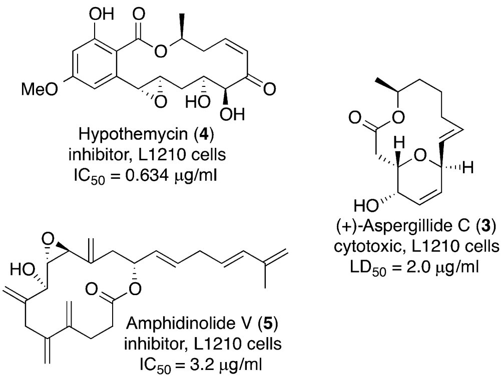
cultivation medium instead resulted in the production of the novel metabolites aspergillides A, B, and C.

The structures of these compounds were investigated through a combination of spectroscopic methods. Their absolute stereochemistries were determined through Mosher's ester analysis at C-4. Aspergillides A, B, and C were assigned a 2,6-*trans* relationship with regard to the alkyl substituents on the pyran ring. A tetrahydropyran ring was contained within the larger macrocyclic structure of aspergillides A and B, while a dihydropyran ring was present in (+)-aspergillide C with unsaturation occurring between C-5 and C-6. In addition, it was proposed that the singular difference between the structures of aspergillides A and B was a diastereomeric relationship of the methyl group at C-13.

1.2 Biological Activity

As a result of a preliminary biological assay, it was determined that aspergillides A, B, and C displayed cytotoxic activities against mouse lymphocytic leukemia cells (L1210) with LD_{50} values of 2.1, 71.0, and 2.0 μg/ml, respectively.[1] Other natural products containing 14-membered macrolactone rings have exhibited similar activity against the L1210 murine cell line, including hypothemycin (**4**, Figure 2) and amphidinolide V (**5**).[3,4] Although both hypothemycin and amphidinolide V feature oxygen-containing heterocycles within their respective macrocyclic frameworks, aspergillides A, B, and C are the first 14-membered macrolides to display this biological activity with a bridging oxygen-containing heterocycle embedded within the macrolactone.

Due to its promising biological activity as well as its interesting structural features, we and other researchers viewed (+)-aspergillide C as an attractive synthetic target. Until recently, there have been few reported syntheses of naturally occurring 14-membered macrolides containing a 2,6-*trans* pyran subunit.[5] Only one example of a nonnatural 14-membered macrolide containing this architecture had been reported.[6] In addition, it was thought that the (+)-aspergillide C motif could be amenable to the synthesis of biologically active analogues.



Hypothemycin (**4**)
inhibitor, L1210 cells
$IC_{50} = 0.634\ \mu g/ml$

(+)-Aspergillide C (**3**)
cytotoxic, L1210 cells
$LD_{50} = 2.0\ \mu g/ml$

Amphidinolide V (**5**)
inhibitor, L1210 cells
$IC_{50} = 3.2\ \mu g/ml$

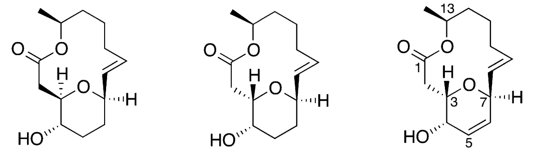
FIGURE 2 Biological activities of selected 14-membered macrolide natural products.

1.3 Structural Revisions

In 2009, the first syntheses of aspergillides A and B by Uenishi and coworkers suggested discrepancies in the relative stereochemistry originally assigned for these two compounds.[7] Shortly after, Kusumi and coworkers reported corrected structural assignments for aspergillides A and B via unambiguous X-ray crystallographic analysis of their C(4) *m*-bromobenzoate ester derivatives.[8] As a result of these structural investigations, aspergillides A and B were determined to be diastereomeric at C(3) rather than at C(13) as originally proposed. Supported by the unambiguous synthetic work of Uenishi and coworkers,[7] the originally proposed structure for aspergillide A was instead found to be that of (−)-aspergillide B, while the actual structure for (−)-aspergillide A was corrected to reflect a 2,6-*cis* relationship of the tetrahydropyran ring (Figure 3). However, one lingering problem remained: could the proposed structure of aspergillide C also be in question? Research groups already invested in synthetic campaigns toward aspergillide C (including the lead author's) were left with the uneasy feeling that they might not arrive at the correct structure. Ultimately, the synthetic work of Kuwahara and coworkers[9] as well as our own synthetic efforts, each reported in 2009, would confirm that the originally purported structure of aspergillide C was indeed correct (*vide infra*).

2 SYNTHETIC STUDIES ON ASPERGILLIDE C

Once the structural assignments of these three natural products were confirmed, the molecules quickly garnered the attention of many synthetic groups across the globe, including groups in Japan, China, Spain, India, and the United States. From 2009 to the time of this writing, there have been 11 syntheses of aspergillide A,[10] 11 syntheses of aspergillide B,[11] and 5 syntheses of aspergillide C, including the synthesis by our research group described



(–)-Aspergillide A (**6**) (–)-Aspergillide B (**1**) (+)-Aspergillide C (**3**)

FIGURE 3 Revised structural assignments for aspergillides A, B, and C.

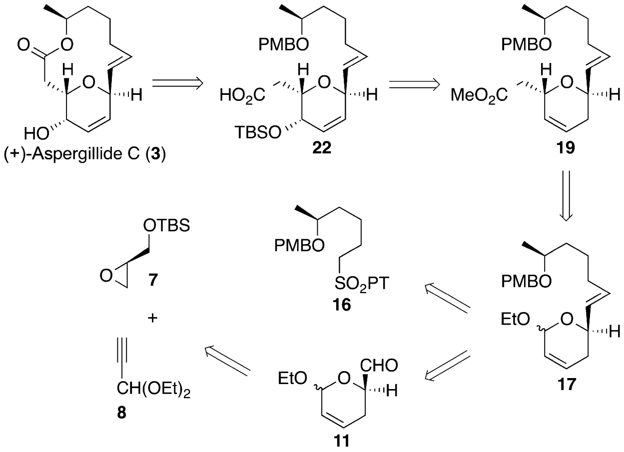


FIGURE 4 Kuwahara's retrosynthetic strategy.

herein.[12] Although these investigations constitute a noteworthy overall body of work, this account will focus solely on synthetic efforts toward (+)-aspergillide C.

2.1 Kuwahara's Synthesis of (+)-Aspergillide C

In 2009, Kuwahara and coworkers reported the first enantioselective synthesis of (+)-aspergillide C (Figure 4).[9] Their strategy centered on a Ferrier-type reaction of a silyl ketene acetal onto cyclic acetal **11**, derived from ring opening of epoxide **7** by alkyne **8** followed by chain elongation via a Kocienski-modified Julia olefination with sulfone **10**. An iodolactonization followed by deprotection and late-stage Yamaguchi macrolactonization[13] of PMB-protected *seco* acid **22** would complete the synthesis of the natural product.

The synthesis commenced with known TBS-protected glycidol **7** (Figure 5).[14] Exposure of this epoxide to the lithium acetylide of alkyne **8** in the presence of $BF_3 \cdot OEt_2$ afforded the desired disubstituted alkyne **9**. Semihydrogenation with Lindlar's catalyst followed by treatment with a catalytic amount of camphorsulfonic acid promoted the formation of cyclic acetal **10**. These mild acidic conditions also effected removal of the silyl ether

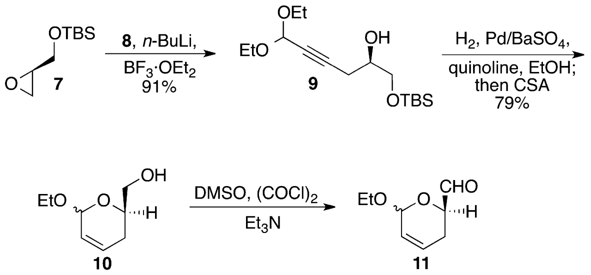


FIGURE 5 Synthesis of cyclic acetal fragment.

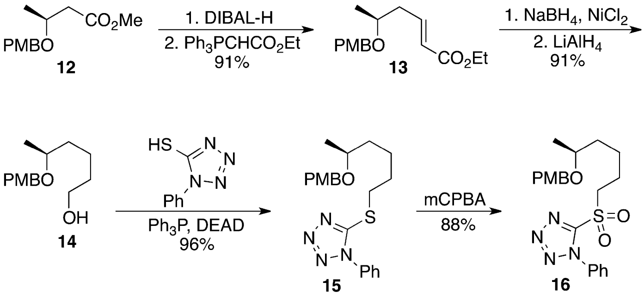


FIGURE 6 Preparation of olefination precursor.

protecting group, after which the resultant primary alcohol was oxidized to aldehyde **11** using Swern's protocol.

The sulfone-containing fragment required for a Kocienski-modified Julia olefination was obtained in a six-step sequence from known ester **12** (Figure 6).[15] DIBAL-H reduction of the methyl ester to the corresponding aldehyde followed by a two-carbon Horner–Wittig homologation gave *trans*-α,β-unsaturated ester **13** in 91% yield. Chemoselective reduction of the olefin in **13** employing $NiCl_2/NaBH_4$ in MeOH[16] gave an intermediate saturated ester, which was subsequently reduced to the primary alcohol **14** with $LiAlH_4$. Substitution of the alcohol function via a Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol gave sulfide **14**, which after oxidation with *m*-CPBA provided sulfone **16**.[17]

With each fragment in hand, cyclic acetal **17** was fashioned through the convergent Kocienski-modified Julia olefination of aldehyde **11** and sulfone **16** (Figure 7). The optimal solvent for this reaction was found to be DME, and the optimal base KHMDS. The coupling provided a 10:1 *E*/*Z* mixture of diastereomers favoring the desired *E* isomer. Interestingly, for reasons not disclosed by Kuwahara, aldehyde **11** were left uncharacterized, but rather used immediately in the Julia–Kocienski olefination sequence after it was produced through the Swern oxidation of alcohol **10**. Over these two steps, olefin **17** was produced in a 69% yield from primary alcohol **10**.

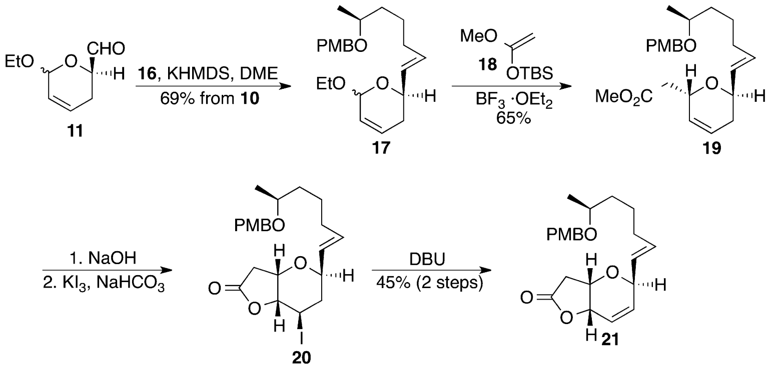


FIGURE 7 Key transformations in Kuwahara's synthesis.

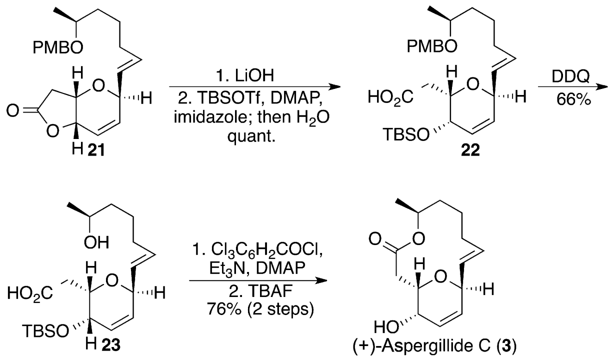


FIGURE 8 Kuwahara's end-game strategy.

After obtaining the desired (*E*)-olefin, it was necessary to install an acetate moiety at the anomeric position of dihydropyran **17**. This transformation was accomplished through a Ferrier-type addition of silyl ketene acetal **18**[18] onto the oxocarbenium ion generated from acetal **17**. The desired *trans* isomer was formed in 65% yield along with the *cis* isomer in 25% yield. The *trans* isomer was obtained in pure form following chromatographic separation from its *cis* counterpart. After basic hydrolysis of methyl ester in **19**, an iodolactonization protocol gave tetrahydropyran **20**. The stereochemical outcome of the iodolactonization was identified through NOE correlations. An elimination reaction was then conducted using DBU as base to give dihydropyran **21** in 45% yield, thereby installing the requisite olefin within the dihydropyran at the correct position.

The final stage of Kuwahara's synthesis of (+)-aspergillide C was completed in a five-step sequence from dihydropyran **21** (Figure 8). After saponification of the γ-lactone, the resultant secondary alcohol was protected as its corresponding TBS ether. Oxidative removal of the PMB ether was achieved with DDQ, which provided *seco* acid **23**. The Yamaguchi macrolactonization protocol gave TBS-protected (+)-aspergillide C as anticipated. Fluoride-mediated removal of the silyl ether gave the natural product. Overall, the Kuwahara synthesis was reported in 7.5% yield over the longest linear sequence of 15 steps.

2.2 Shishido's Syntheses of (+)-Aspergillide C

2.2.1 First-Generation Synthesis

In early 2011, Shishido reported what would become his first of two reported routes to (+)-aspergillide C (Figure 9).[12c] This first-generation synthesis would also rely on a late-stage macrolactonization of a *seco* acid to produce the natural product. The *seco* acid would ultimately be derived from tetrahydropyran **30** using a combination of tactics including Kocienski-modified Julia olefination and Noyori-type epoxide ring-opening.[19] In one of the key steps of the synthetic route, the tetrahydropyran ring would be constructed through an intramolecular oxy-Michael (IMOM) reaction of α,β-unsaturated ester **29**.[20] This ester would be prepared through a series of transformations originating from enantiopure glycidyl ether **24**.

In the forward synthesis, ring-opening of epoxide **24** with vinyl magnesium chloride produced homoallylic alcohol **25** (Figure 10). Acylation of the alcohol with acryloyl chloride furnished ester **26**. Ring closure employing Grubbs' second-generation catalyst gave the unsaturated lactone **27** in good yield. After diastereoselective epoxidation of **27** with basic hydrogen peroxide, the lactone function was reduced to a lactol with DIBAL-H and then subjected to Horner–Wadsworth–Emmons homologation conditions to furnish the acyclic, α,β-unsaturated ester **29**.

After construction of α,β-unsaturated ester **29**, investigations were centered on employing the IMOM reaction to secure the 2,6-*trans* relationship across the tetrahydropyran ring (Figure 11). Initial attempts were conducted

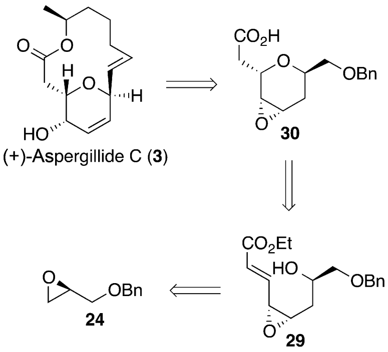


FIGURE 9 Shishido's retrosynthetic strategy.

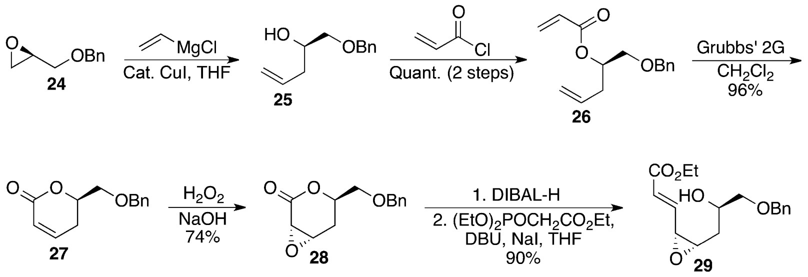


FIGURE 10 Preparation of an unsaturated ester.

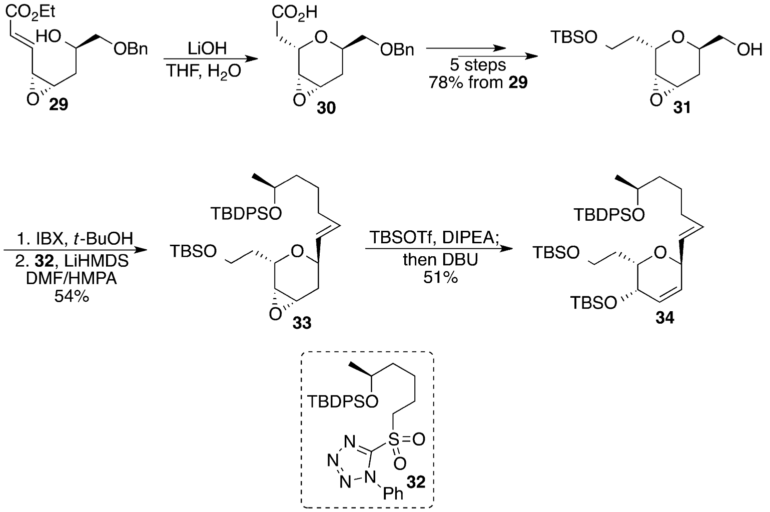


FIGURE 11 Utility of the IMOM reaction.

under anhydrous conditions with bases such as KH and NaHMDS. Although these conditions led to near equimolar mixtures of diastereomers, a slight but encouraging increase in diastereoselectivity was seen when LiHMDS was employed as base.

After these initial trials, it was determined that the use of lithium hydroxide in aqueous THF gave near-complete diastereoselectivity in the IMOM reaction. Exposure of **29** to these alkaline conditions provided tetrahydropyran **30**, now bearing a carboxylic acid group due to concomitant saponification of the ethyl ester. A further series of functional group adjustments furnished primary alcohol **31** in 78% yield over additional five steps. Oxidation of the alcohol function in **31** with IBX gave an intermediate aldehyde, which when subjected to Kocienski-modified Julia olefination[17] with sulfone **32** afforded (*E*)-olefin **33** in moderate yield. Ring-opening of the epoxide group in **33**

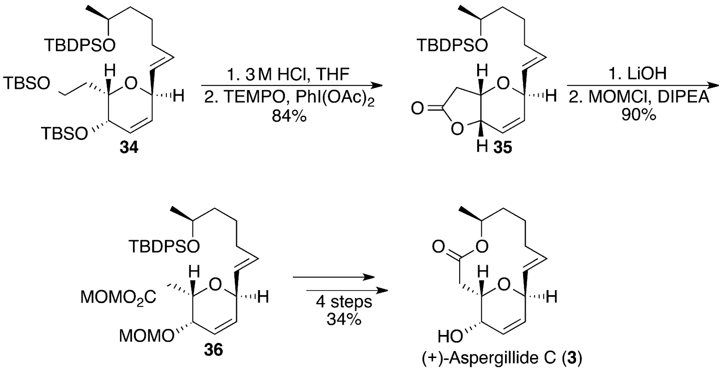


FIGURE 12 Shishido's end-game strategy.

following the protocol developed by Noyori and coworkers[19] gave silyl ether **34** in 51% yield.

To arrive at (+)-aspergillide C, Shishido and coworkers processed their advanced intermediate **34** through an eight-step sequence that commenced with chemoselective deprotection of the TBS ethers (Figure 12). A phenyliodine diacetate (PIDA)-mediated oxidation step furnished γ-lactone **35**, likely through the intermediacy of a cyclic hemiacetal. Basic hydrolysis of the lactone followed by MOM protection gave intermediate **36**. This intermediate was taken forward in four steps, consisting of a series of orthogonal deprotections and macrolactonization, to arrive at (+)-aspergillide C. In all, Shishido's synthesis relied on 23 synthetic steps to achieve a 3.5% overall yield.

2.2.2 Second-Generation Synthesis

Although Shishido's first-generation synthesis successfully demonstrated the utility of the IMOM reaction for the construction of the pyran ring in (+)-aspergillide C, it was clear that a more efficient synthetic route to reach this key step was desirable. To accomplish this goal, Shishido reported a second-generation route to (+)-aspergillide C[12b] shortly after his first disclosure.

Through use of a synthetic intermediate from their previously reported total syntheses of aspergillides A and B,[10d] an alternate approach to (+)-aspergillide C was undertaken (Figure 13). In their revised strategy, the IMOM reaction was placed toward the closing stages of the synthesis. The intermediate utilized, diol **45**, would be obtained from *seco* acid **44** through Shiina macrolactonization.[21] The α,β-unsaturated acid would be installed through a chain elongation involving Wittig olefination of cyclic hemiacetal **42**. The (*E*)-olefin function within compound **42** would be constructed through cross metathesis of acetate **41** and 1,4-diene **40**, which would be derived from bicyclic acetal **37**.[22]

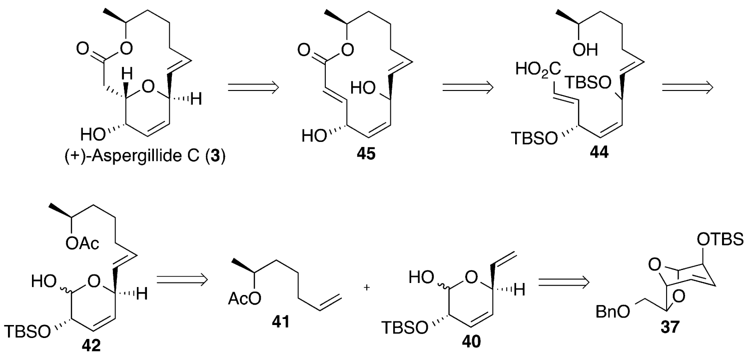


FIGURE 13 Shishido's second retrosynthetic analysis.

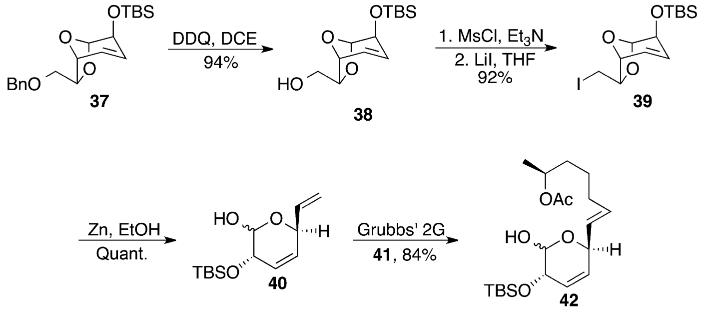


FIGURE 14 Functional group manipulation and cross metathesis.

The synthesis began with oxidative removal of the benzyl ether from their previously reported bicyclic acetal **37** (Figure 14). Mesylation of the primary alcohol in **38**, substitution by iodide, and subsequent zinc-mediated elimination provided hemiacetal **40** in 92% over three steps. Cross metathesis of the terminal olefin in **40** with alkene **41**,[23] employing Grubbs' second-generation catalyst, resulted in successful elongation of the C-7 side chain to give **42** bearing the desired (*E*)-olefin geometry. The remaining carbons were installed through a Horner–Wittig olefination onto hemiacetal **42** (Figure 15). This transformation came with some precedent; olefination of a similar hemiacetal intermediate was performed in Shishido's first-generation synthesis.

After Horner–Wittig olefination of hemiacetal **42**, a two-step procedure involving alcohol protection and ester hydrolysis provided *seco* acid **44**. Macrolactonization mediated by 2-methyl-6-nitrobenzoic anhydride (MNBA) gave rise to the requisite 14-membered ring, which was followed by fluoride-mediated deprotection of the two silyl ethers to give diol **45**. As the final step of the synthesis, the much-anticipated 6-*exo-trig* transannular IMOM reaction was successfully achieved with KH to provide (+)-aspergillide C in 86% yield.

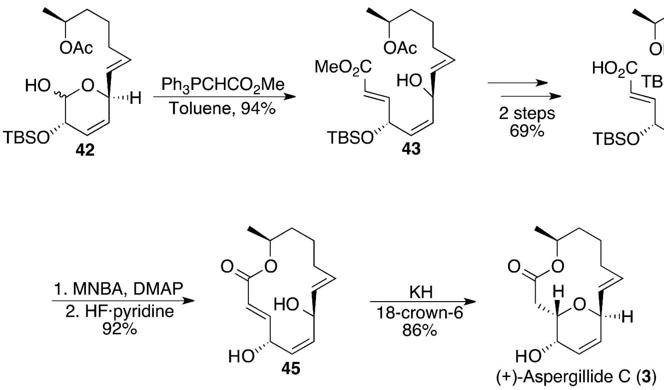


FIGURE 15 Shishido's second-generation end-game.

Overall, Shishido's second-generation synthesis of (+)-aspergillide C totaled 15 steps from a synthetically available chiral bicyclic acetal used in his synthesis of aspergillides A and B. This route offers a 19% overall yield to the natural product, which is a marked improvement over his first-generation synthesis.

2.3 Srihara's Synthesis of (+)-Aspergillide C

Also in 2011, a total synthesis of (+)-aspergillide C was reported by Srihari and coworkers.[12d] Their synthetic strategy not only provided the natural product but also enabled the preparation of the nonnatural (−)-aspergillide C and the C-4 epimer of (−)-aspergillide C. A unique approach to the construction of the requisite dihydropyran ring of (+)-aspergillide C involved an interesting oxidative rearrangement during the course of a Sharpless kinetic resolution of a racemic furfuryl alcohol.[24]

According to precedent, it was anticipated that (+)-aspergillide C could be obtained through Yamaguchi macrolactonization of the *seco* acid of intermediate **54** (Figure 16) after basic hydrolysis of the two ester groups. The MOM ether in **54** could be fashioned through a stereoselective Corey–Bakshi–Shibata reduction[25] of dihydropyranone **53**. The (*E*)-olefin of **53** could be produced through the stereoselective, partial reduction of the alkyne function in **52** via a hydrosilylation–protodesilylation sequence,[26] in turn generated through a Ferrier-type alkynylation between cyclic acetal **50** and TMS-protected alkyne **51**. A tandem kinetic resolution/oxidative rearrangement of furfuryl alcohol **48** would provide the required acetal **50**.

Addition of the lithium enolate of ethyl acetate (**47**, Figure 17) to 2-furfuraldehyde (**46**) afforded yield furfuryl alcohol **48**. In an effort to resolve this racemic mixture, alcohol **48** was subjected to Sharpless conditions, which after rearrangement furnished pyranone **49**.[24] After acetylation

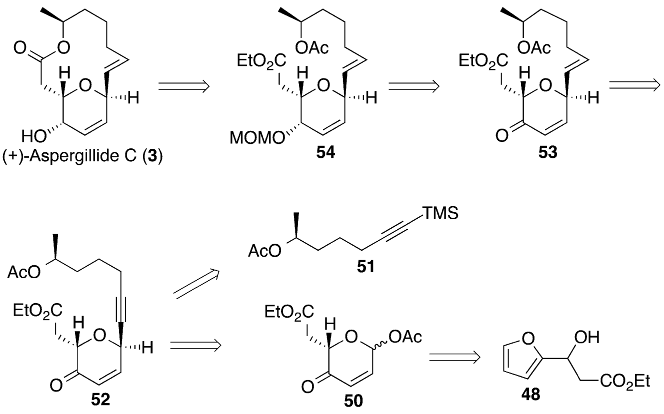


FIGURE 16 Srihari's retrosynthetic analysis.

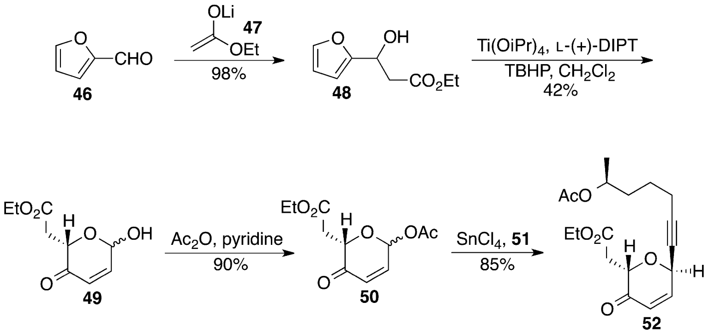


FIGURE 17 Construction of an advanced dihydropyranone.

at the anomeric position in **49** to give acetate **50**, alkyne **52** was produced through tin-mediated Ferrier-type alkynylation[27] with alkyne **51**, the latter prepared in a four-step sequence from a commercially available chiral epoxide. The diastereoselectivity of this addition was attributed to preferential approach of the nucleophile from the less-hindered face of the oxocarbenium ion derived from **50**.

A chemoselective reduction of the alkyne function in **52** was accomplished using Trost's *trans*-hydrosilylation/protodesilylation procedure[26] (Figure 18) to install the desired (*E*)-olefin. At this stage, although a synthetically desirable *seco* acid was theoretically only one step away from **53** through removal of the ester groups, attempts to obtain such a material under hydrolytic conditions all led to unidentifiable complex product mixtures. As a result, an alternative end-game strategy was deemed necessary.

Therefore, prior to operating on the ester functions in **53** (Figure 18), the enone group was reduced to an intermediate allylic alcohol with excellent

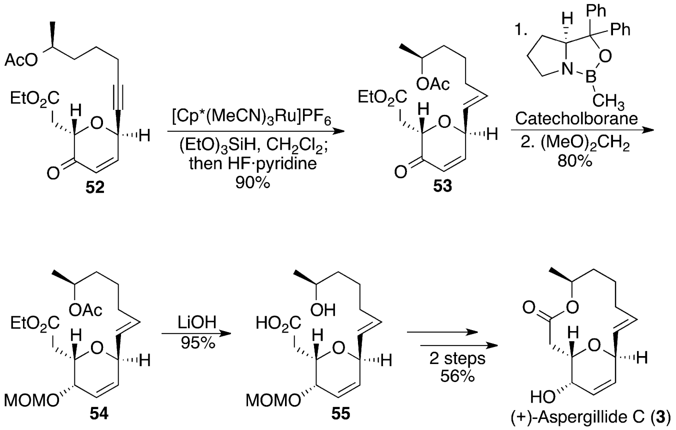


FIGURE 18 Srihari's end-game strategy.

diastereocontrol using the Corey–Bakshi–Shibata conditions.[25] Protection of this alcohol as its corresponding MOM ether was followed by successful saponification to give *seco* acid **55** in good yield. After macrolactonization of **55** using Yamaguchi's protocol,[13] removal of the MOM ether provided (+)-aspergillide C. The Srihari synthesis furnished (+)-aspergillide C in a 12% overall yield over 10 steps.

3 WATERS' SYNTHESIS OF (+)-ASPERGILLIDE C

3.1 Retrosynthetic Strategy

Our completed total synthesis of (+)-aspergillide C was described in 2009,[12e] just 1 year after the initial disclosure of the molecule's isolation and structural assignments. Our report followed closely on the heels of the report by Kuwahara and coworkers, whose late-stage synthetic transformations correlated with our own synthetic plans. Given the macrolide framework of the aspergillides, the vast majority of the successful synthetic routes to these metabolites invariably feature a late-stage macrolactonization to fashion the macrocyclic core, and it is at that stage where many of the later syntheses intersect with Kuwahara's and our own. In the early planning stages, we hypothesized that after hydrolysis of γ-lactone **21** (Figure 19), protecting group adjustment, and Yamaguchi macrolactonization of the corresponding *seco* acid **23** would constitute a suitable end-game strategy toward (+)-aspergillide C (**3**). We further envisioned that the (*E*)-olefin at C-8 and C-9 in lactone **21** could be obtained through Kocienski-modified Julia olefination of sulfone **16** and aldehyde **68** (Figure 19). Although our route and that of Kuwahara's each converge on intermediate **21**, the two routes differ in the tactics employed for the stereoselective construction of the dihydropyran core

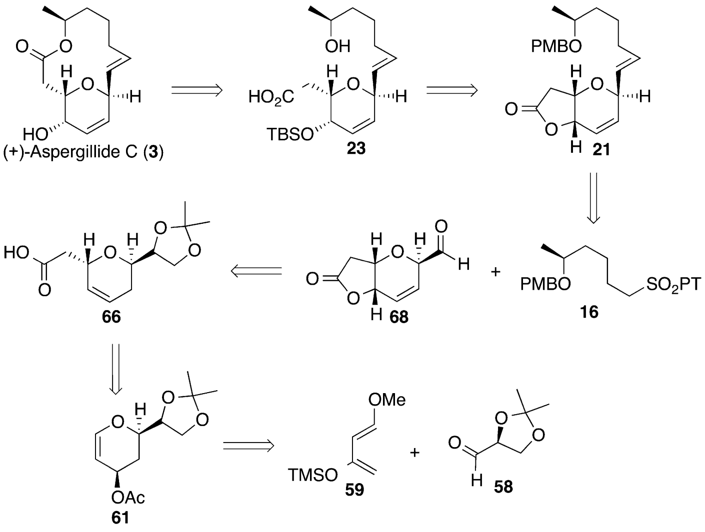


FIGURE 19 Retrosynthetic strategy for (+)-aspergillide C.

(cf., **68**). We anticipated that the γ-lactone of **68**, which was to be employed as a temporary means by which to secure functionality within the dihydropyran fragment, could be constructed through a palladium-catalyzed Wacker-type oxidative cyclization[28] of carboxylic acid **66**. In order to secure the 2,6-*trans* relationship of the substituents within the dihydropyran ring, installation of the side chain at C-3 would be established through a diastereoselective, Lewis acid-mediated Ferrier-type addition[29] of suitable two-carbon nucleophile onto allylic acetate **61**. The dihydropyranone framework of **61** would be constructed in short order through stereoselective cyclocondensation of the Danishefsky–Kitahara diene **59**[30] and optically active aldehyde **58**, in turn derived from a member of the pool of chiral building blocks, L-(+)-arabinose. Indeed, through the orchestration of a planned series of stereochemical relays, it was envisioned that the stereochemical information encoded in the one stereocenter of aldehyde **58** could be used to effectively secure all the other stereocenters within the natural product.

3.2 Forward Synthesis

3.2.1 Construction of the Dihydropyran Fragment

In keeping with our retrosynthetic plans, it was necessary to first produce gram-quantities of optically pure aldehyde **58**.[31] The optical purity of this intermediate would originate through its preparation from a readily obtainable, commercially available building block, L-(+)-arabinose (**56**, Figure 20). Treatment of this monosaccharide with benzyl mercaptan in an equal volume of

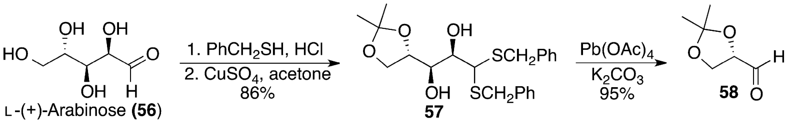


FIGURE 20 Preparation of the enantiopure aldehyde.

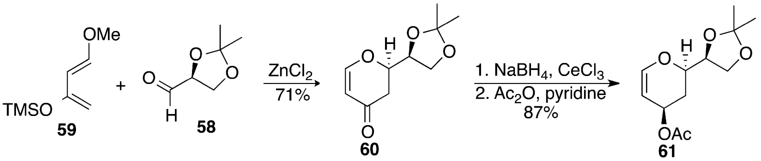


FIGURE 21 Construction of the functionalized dihydropyran.

concentrated HCl furnished a dithioacetal, which after regioselective ketalization of the terminal vicinal diol provided dibenzyl thioacetal mono-acetonide **57** on large scale. This suitably protected arabinose derivative was then subjected to oxidative scission under Criegee conditions to produce the unstable aldehyde **58**, which was best carried forward immediately after purification by vacuum distillation.

With enantiomerically pure aldehyde **58** in hand, construction of the dihydropyran fragment of (+)-aspergillide C could begin in earnest. Thus, allylic acetate **61** (Figure 21) was synthesized in a three-step procedure. A $ZnCl_2$-mediated cyclocondensation of aldehyde **58** and Danishefsky–Kitahara diene **59**, itself obtained through a one-step conversion from 1-methoxy-3-buten-2-one,[32] cleanly provided dihydropyranone **60**. Gratifyingly, this material was obtained as a single diastereomer as predicted by Felkin's model, thereby securing the requisite configuration at C-7. Conversion of enone **60** to allylic acetate **61** was achieved through reduction under Luche's conditions[33] to the corresponding allylic alcohol followed by acetylation with acetic anhydride and pyridine.

The incorporation of a functionalized substituent onto the pyran ring at C-3 proved to be more of a challenge than originally anticipated. It had been shown though the seminal work of Ferrier and coworkers that the Lewis acid-catalyzed formation of dihydropyran-based oxocarbenium ions can lead to functionalized 2,6-*trans* dihydropyran rings.[34] In addition, the elegant studies of Paterson of coworkers en route to swinholide A[35] demonstrated that the diastereoselectivity of such transformations was dependent upon the strength of the nucleophile employed, with allylsilanes providing exclusively *trans* isomers and more reactive silyl ketene acetals providing a mixture of diastereomers. In the case of (+)-aspergillide C, the desired functionality at this position was a carboxylic acid. Thus, a silyl enol ether was chosen as an agreeable compromise as the nucleophile due to its mild reactivity and, hopefully, high diastereoselectivity. After installation, the resultant aldehyde could

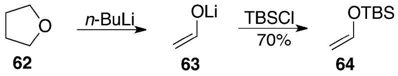


FIGURE 22 Preparation of silyl enol ether **64**.

then be readily oxidized to the desired carboxylic acid. The requisite silyl enol ether **64** (Figure 22), which could be viewed as a synthon for the enolate of acetaldehyde, was prepared in a two-step procedure from the base-mediated thermal decomposition of tetrahydrofuran.[36]

Our initial attempts to promote the Ferrier addition of **64** to allylic acetate **61** were met with significant complications. Though a variety of Lewis acids were investigated, including $BF_3 \cdot OEt_2$, $Cl_2Ti(O^iPr)_2$, and $Ti(O^iPr)_4$, none of these additives provided a satisfactory yield. In most cases, the undesired nucleophilic attack of the counterions supporting the Lewis acids (e.g., Cl^- and F^-) onto the oxocarbenium ion derived from **61** precluded the desired reaction with silyl enol ether **64**. It was evident at this stage that although the chosen Lewis acids provided necessary activation of the substrate, the nucleophilic character of their counterions had to be attenuated.

To meet this goal, a 3.0 M solution lithium perchlorate in EtOAc—the advantages of which were first described by Grieco and coworkers—was employed as a Lewis acidic medium with the expectation that it would promote the formation of the requisite oxocarbenium ion. More importantly, however, the low nucleophilicity of the perchlorate ion would suppress unwanted nucleophilic addition of the counterion. Gratifyingly, it was found that a solution of lithium perchlorate in ethyl acetate[29] at room temperature effectively promoted the Ferrier addition to furnish aldehyde **65** (Figure 23) as a single, 2,6-*trans* diastereomer. A subsequent Pinnick oxidation[37] furnished the carboxylic acid **66**.

Following the isolation of carboxylic acid **66**, we next sought to install the requisite hydroxyl function at C-4 through the construction of a fused γ-lactone ring. The cyclization of γ-unsaturated carboxylic acids to γ-lactones is most commonly accomplished through either a one- or two-step process.[28] The two-step process typically involves either an iodolactonization followed by base-induced dehydrohalogenation or a selenolactonization–oxidation protocol. The iodolactonization sequence often requires the use of a strong base to effect dehydrohalogenation; conditions that may be incompatible with base-sensitive functionality within the substrate. Selenolactonization procedures naturally require the use of toxic selenium reagents and produce toxic selenium byproducts.

To achieve this important transformation, we turned to the facile, one-step process to generate γ-lactones reported by Larock and coworkers using catalytic palladium under an oxygen atmosphere.[28a] This Wacker-type process may be modified by the addition of stoichiometric amounts of Cu(II) to serve as a sacrificial oxidant for palladium. We elected to use this efficient and

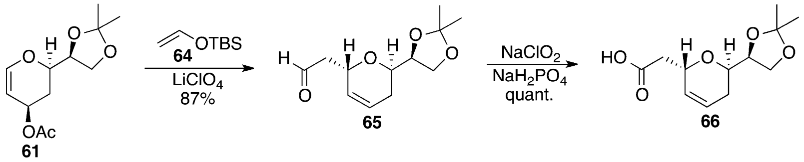


FIGURE 23 Installation of the side-chain appendage through Ferrier addition.

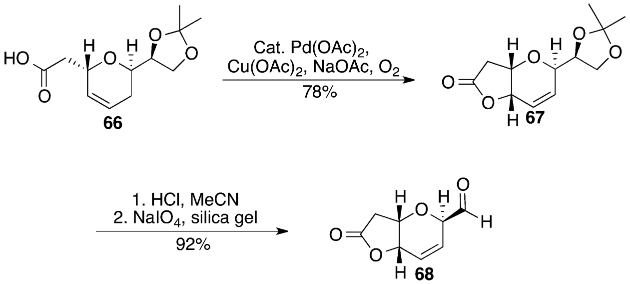


FIGURE 24 Diastereoselective synthesis of the dihydropyran core.

operationally simple one-step oxidative lactonization in our synthesis of (+)-aspergillide C (Figure 24). Our initial attempts to promote the cyclization of carboxylic acid **66** were originally conducted under an oxygen atmosphere as the sole reoxidant of Pd(0) to Pd(II). However, unsatisfactory yields were obtained under these conditions. Ultimately, the addition of Cu(II) as an oxidant for palladium at elevated temperatures greatly improved the efficiency of the transformation, furnishing lactone **67** in excellent yield.

The strategic construction of the γ-lactone overcame three important obstacles in our synthetic route toward (+)-aspergillide C. First, the requisite oxygen atom at C-4 was correctly placed at C-4 with strict stereochemical control. Second, the newly formed γ-lactone acted as an internal protecting group for both a secondary alcohol at C-4 and a carboxylic acid at C-3, which could be revealed at a later stage for a projected macrolactonization event. Third, as a result of reductive elimination of palladium, unsaturation in the dihydropyran ring correctly resided between C-5 and C-6. With these three tasks accomplished, removal of the acetonide function under aqueous acidic conditions followed by periodiate-mediated oxidative cleavage of the resultant 1,2-diol[38] provided aldehyde **68** (Figure 24), thereby completing our synthesis of the dihydropyran fragment of (+)-aspergillide C.

3.2.2 Construction of the Julia Coupling Fragment

Once the synthesis of aldehyde **68** was complete, it was necessary to obtain sulfone fragment **16** in order to investigate our convergent Kocienski-modified

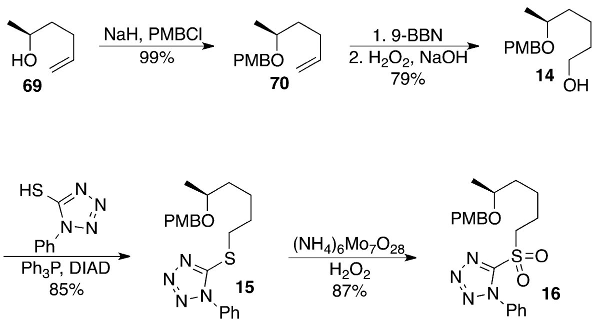


FIGURE 25 Synthesis of the Kocienski-modified Julia olefination fragment.

Julia olefination coupling strategy. Commercially available *S*-(+)-5-hexen-2-ol (**69**, Figure 25) was first protected as its corresponding PMB ether, **70**.[39] Hydroboration with 9-BBN in THF followed by oxidation with alkaline H_2O_2 provided primary alcohol **14** in good yield. In parallel with the procedure outlined by Kocienski, sulfide **15** was then fashioned in 85% yield through the Mitsunobu reaction of alcohol **14** with 1-phenyl-1*H*-tetrazole-5-thiol.[17] Subsequent oxidation of sulfide **15** employing catalytic ammonium heptamolybdate tetrahydrate in the presence of H_2O_2 gave sulfone **16** in 87% yield.

3.2.3 Fragment Coupling and Completion

The closing stages of our synthesis began with the coupling of sulfone **16** (Figure 25) and aldehyde **68** (Figure 24) through a modified-Julia olefination to produce γ-lactone **21**. In 1998, Kocienski reported that α-metalated phenyltetrazolyl sulfones reacted with both branched and straight chain aliphatic aldehydes to provide (*E*)-olefins as the major products. The selectivity and yield of the olefination could be tuned by changing the counterion of the base or by changing the solvent. Kocienski and coworkers demonstrated that (*E*)-olefins were produced almost exclusively by using KHMDS in DME with a modest yield. If a sacrifice in yield was not acceptable, NaHMDS in DME could be used to provide a higher yield with a slight sacrifice in stereoselectivity. The Kocienski-modified Julia olefination was therefore selected for our synthesis due to its high level of *trans*-selectivity.

Initially, KHMDS was used as the basic component and THF as the solvent in this transformation. Although *E*/*Z* selectivity was excellent, yields above 20% could not be achieved under these conditions. We hypothesized that competing retro-Michael elimination was likely taking place, resulting in a diminished yield of the desired product. In this mode, deprotonation could occur at the α-position of the lactone that would lead to the formation of an α,β-unsaturated lactone and ring opening of the dihydropyran.[40] We reasoned that the methylene protons at the α-position of sulfone **16** and those of lactone **68** had very similar pK_a values (of about 25). Therefore, we reasoned that the

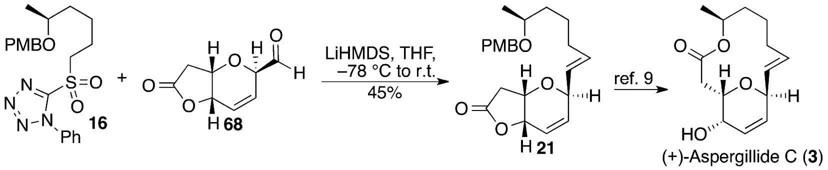


FIGURE 26 The convergent olefination reaction.

preformed potassium salt of sulfone **16** was likely abstracting the acidic protons of **68** located at the α-position of the lactone instead of engaging in nucleophilic addition to the aldehyde.

In an effort to minimize any competing retro-Michael-type processes, LiHMDS was employed as the base (Figure 26). It was thought that a smaller metal cation would favor coordination to the aldehyde of **68** instead of the ester, leading to the desired nucleophilic attack. Gratifyingly, formation of cleaner crude product mixtures was seen along with an increased isolated yield of γ-lactone **21**. Tetrahydrofuran was found to be the optimal solvent for this transformation, which afforded exclusively the (*E*)-olefin in 45% yield.

The final stage of the synthesis would require hydrolysis of the lactone in **21** (Figure 26), protecting group adjustment, and macrolactonization. Indeed, during the course of our work, an alternate path to **21** and its successful elaboration to (+)-aspergillide C by such a sequence was reported by Kuwahara.[9] Our synthetic route provided lactone **21** in 17% overall yield through a nine-step longest linear sequence from (*S*)-(−)-glyceraldehyde acetonide (**58**) and the Danishefsky–Kitahara diene (**59**). Key transformations in this synthesis included construction of the dihydropyran core through the Ferrier-type reaction of silyl enol ether **9** and allylic acetate **10** and the Kocienski-modified Julia olefination to produce γ-lactone **21**.

4 CONCLUSIONS AND FUTURE DIRECTIONS

One unifying theme in the syntheses of (+)-aspergillide C discussed above is the late-stage macrolactonization of an appropriate *seco* acid precursor, while the individual identities of each respective synthesis are distinguished through the creative tactics employed for the construction of the dihydropyran core.[41] Of the syntheses discussed, key reactions such as Achmatowicz-type rearrangement, IMOM, transacetalization, and heterocyclocondensation have been investigated to fashion the core of (+)-aspergillide C.

The good level of enantio- and diastereoselectivity of these synthetic pathways, together with their high-yielding and convergent natures, will now enable the preparation of synthetic analogues to further investigate the pharmacological activity of (+)-aspergillide C and, ultimately, reveal the biological mechanism by which this compound acts on L1210 cells. Through

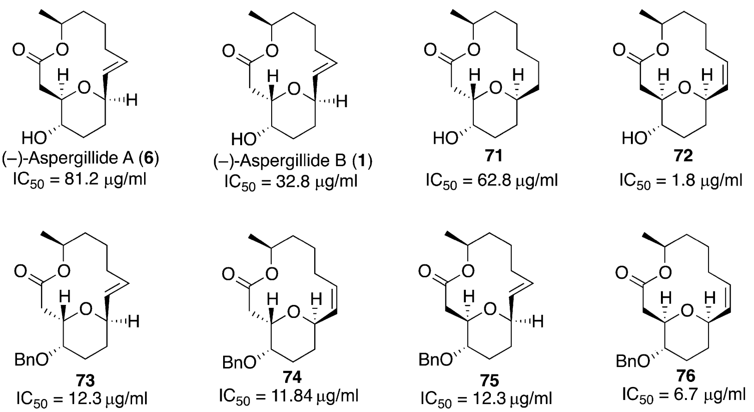

(−)-Aspergillide A (**6**)
IC_{50} = 81.2 μg/ml
(−)-Aspergillide B (**1**)
IC_{50} = 32.8 μg/ml
71
IC_{50} = 62.8 μg/ml
72
IC_{50} = 1.8 μg/ml
73
IC_{50} = 12.3 μg/ml
74
IC_{50} = 11.84 μg/ml
75
IC_{50} = 12.3 μg/ml
76
IC_{50} = 6.7 μg/ml

FIGURE 27 Biological activities of aspergillides A, B, and synthetic analogues against HL-60 cells.

an SAR-based medicinal chemistry program, information as to what structural changes on the molecule would provide increased potency would be determined. As different synthetic analogues are generated and assayed, new or improved biological activity may be achieved.

One advantage of having different synthetic approaches to the dihydropyran framework is that a comprehensive library of aspergillide analogues can now be generated. A study along these lines was recently initiated by Marco and coworkers,[10b] in which they synthesized and tested a small library of analogues of (−)-aspergillides A and B (Figure 27). Results indicate that (−)-aspergillides A and B and some structural analogues all showed some level of preferential cytotoxicity for human promyelocytic leukemia cells (HL-60) over other cell types, including nontransformed bovine aorta endothelial (BAE) cells. Several synthetic congeners displayed more potent activity than the natural products, with (*Z*)-analogue **72** being the most active. Interestingly, analogues bearing (*Z*)-olefin geometry show cytotoxicity similar to the clinically prescribed drug fludarabine.[42] We are hopeful that our report described herein will contribute similarly to further synthetic and biological studies on (+)-aspergillide C.

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