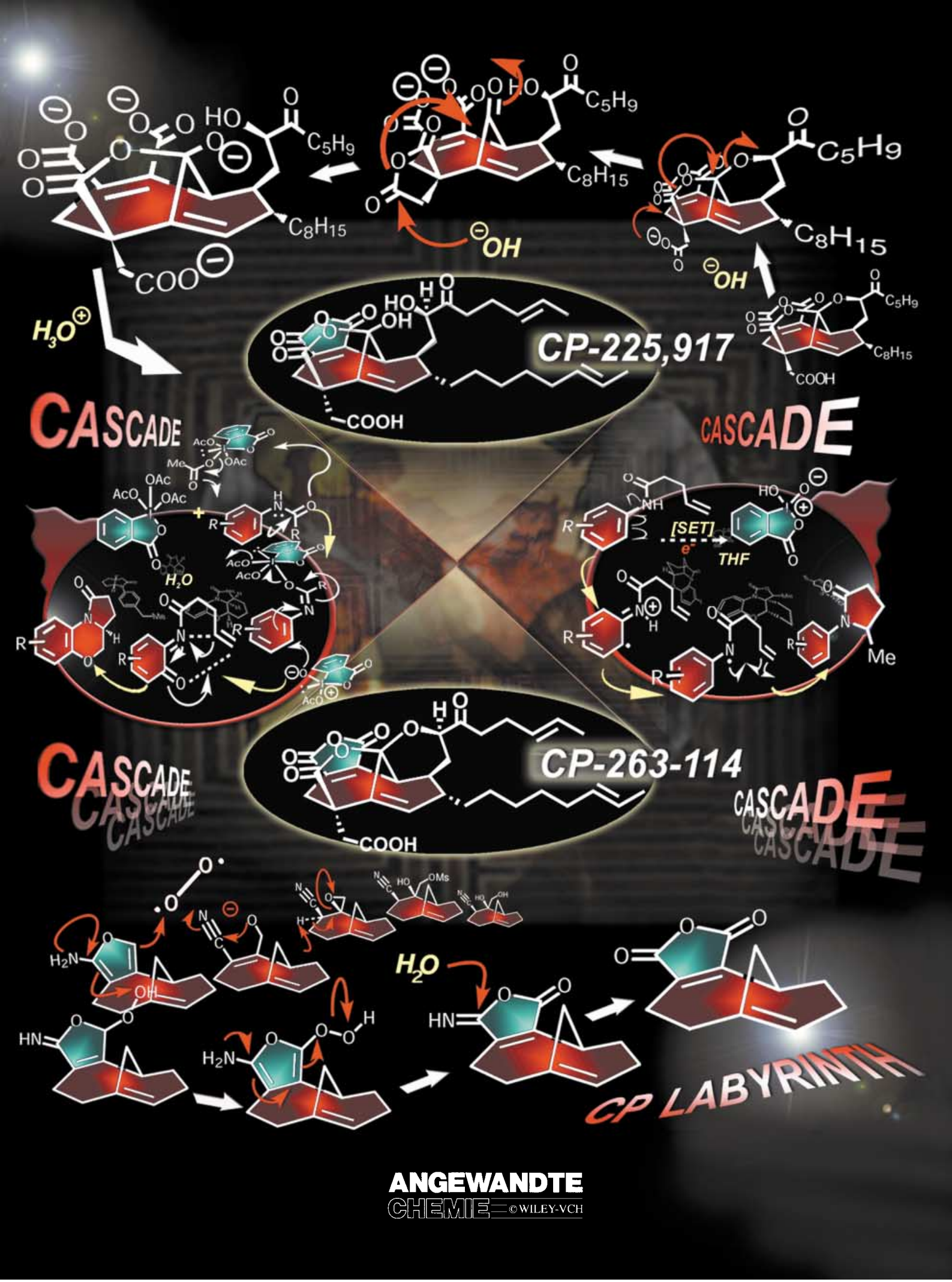
CP-225,917
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The CP Molecule Labyrinth: A Paradigm of How Endeavors in Total Synthesis Lead to Discoveries and Inventions in Organic Synthesis

K. C. Nicolaou* and Phil S. Baran

Dedicated to Mrs. Niki Goulandris for her outstanding contributions to humanity and Planet Earth on the occasion of the opening of the GAIA Center for Environmental Research and Education at the Goulandris Natural History Museum in Athens, Greece.

Imagine an artist carving a sculpture from a marble slab and finding gold nuggets in the process. This thought is not a far-fetched description of the work of a synthetic chemist pursuing the total synthesis of a natural product. At the end of the day, he or she will be judged by the artistry of the final work and the weight of the gold discovered in the process. However, as colorful as this description of total synthesis may be, it does not entirely capture the essence of the endeavor, for there is much more to be told, especially with regard to the contrast of frustrating failures and exhilarating moments of discovery. To fully appreciate the often Herculean nature of the task and the rewards that accompany it, one must sense the details of the enterprise behind the scenes. A more vivid description of total synthesis as a struggle against a tough opponent is perhaps appropriate to dramatize these elements of the experience. In this article we describe one such endeavor of total synthesis which, in addition to reaching the target molecule, resulted in a wealth of new synthetic strategies and technologies for chemical synthesis. The total synthesis of the CP molecules is compared to Theseus' most celebrated athlos (Greek for exploit, accomplishment): the conquest of the dreaded Minotaur, which he accomplished through brilliance, skill, and bravery having traversed the famous labyrinth with the help of Ariadne. This story from Greek mythology comes alive in modern synthetic expeditions toward natural products as exemplified by the total synthesis of the CP molecules which serve as a paradigm for modern total synthesis endeavors, where the objectives are discovery and invention in the broader sense of organic synthesis.

Keywords: CP molecules · natural products · synthetic methods · total synthesis

1. Prologue

"Athens had been at war with Crete. Although the war was over, Minos (King of Crete), ruled the seas and Athens had to pay an awful tribute as a condition for peace. Minos sought revenge for the death of his son and demanded that every nine years the Athenians send him fourteen of their children—7 girls and 7 boys. Once in Crete, the young men and women were sent into the maze-like labyrinth to face the deadly Minotaur who was half man, half bull.

Each year the children were selected by lot, and as all of Athens mourned they set sail for Crete on a ship with black sails. Theseus, the son of Aegeus (King of Athens), was very brave and had had many adventures already. Theseus resolved to become one of the young men chosen, so that he might slay the Minotaur and put an end to the horrible sacrifice. Aegeus reluctantly agreed to let Theseus go, and asked that Theseus change the sails to white for the journey home if he was successful in his plan to kill the Minotaur.

When the fourteen arrived in Crete, they were entertained at the enormous and colourful palace of Minos. The next day, they were to be sent into the intricate mazes of the labyrinth, home of the deadly Minotaur, from which there was no escape…

That night at dinner, listening to the exploits and adventures of Theseus, Ariadne—daughter of King Minos—fell in love with him. Not wanting to see Theseus killed, Ariadne vowed to find a way to help him. The next morning, as they

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were being led to the labyrinth, Ariadne gave Theseus a ball of string. She told Theseus to tie the string to the inside of the door, and it would help him find his way back if he was able to kill the Minotaur. She also brought him a sword, which he hid underneath his cape.

After winding his way through twists and turns, Theseus came upon the lair of the Minotaur. In the narrow passageways, they battled until Theseus was triumphant. Theseus began to rewind the ball of string, retracing his steps until he found his way back to the entrance and the other young men and women. Ariadne was waiting for them on the other side. She hid them until nightfall, and in the dark helped them escape to their ship. In exchange for helping him, Ariadne asked that Theseus take her with him and make her his wife, and Theseus happily agreed.

On their return trip to Athens, the ship stopped at the island of Naxos for the night. What happened next, and why it happened is a bit unclear. Either through trickery or too much frivolity (for Naxos was the island of Dionysus, after all) the group became forgetful. The next morning, Theseus set sail with the other Athenians leaving poor Ariadne asleep on the beach. At this point, there are two distinctly different versions of the tale. One version finds Ariadne so distraught that she takes her own life. The other version, which I like to believe, leaves Ariadne happy with Dionysus, living out her days on Naxos.

Away from Naxos, Theseus' forgetfulness remained, and despite his promise to his father, he neglected to change the sails on his ship from black to white. At Cape Sounion, Aegeus watched hopefully every day for the safe return of his son. Spotting the ship, with black sails flying, Aegeus presumed the worst and threw himself from the cliffs to his death and the water below. Today this water is known as the Aegean Sea."[1]

This tale from Greek Mythology has inspired writers as well as artisans from the days of classical Greece to the twentieth century (Figure 1). Many morals can be found in this story, but in total synthesis, perhaps, the play comes alive more vividly and truly than in other endeavors. The virtues of total synthesis and its practice have been amply discussed in a recent account from our group.[2] The purpose of this article is to dramatize the endeavor by relating its characters to those of the Theseus and Minotaur myth and, in so doing, offer valuable lessons and inspirations to ensuing generations of chemists. Most importantly, we wish to add to this tale the elements of discovery and invention in the face of adversity. The conquest of the demonic molecule (the Minotaur) by total synthesis (the labyrinth) represents not only an isolated, albeit creative, accomplishment, but moreover one which is accompanied by often abrupt twists and turns and showers of scientific discoveries, inventions, and technological advances (treasures found, tricks invented, skills developed in the labyrinth) with associated rewards and benefits (Ariadne, freeing Athens from the awful sacrifice). Most practitioners of the art of total synthesis, particularly graduate students and postdoctoral fellows, may identify with Theseus and his teammates. They may also recognize their supervisor in the form of King Aegeus. Some may even hint at the evil King Minos as a more fitting description of their supervisors! Many more comparisons and experiences may come alive later on in the article as you read on.

We will now introduce the main characters of the play as it often unfolds in laboratories engaged in total synthesis endeavors. The mighty "molecular Minotaur," the CP molecules, were discovered by a group at Pfizer headed by Takushi Kaneko in the 1990s. Here is how the world at large learned of these compounds in 1995:

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K. C. Nicolaou

P. S. Baran

Phil S. Baran was born in Denville, New Jersey in 1977. He received his B.S. in chemistry from New York University while conducting research under the guidance of Professors D. I. Schuster and S. R. Wilson, exploring new realms in fullerene science. Upon entering The Scripps Research Institute as a graduate student in chemistry in 1997, he joined the laboratory of Professor K. C. Nicolaou where he immediately embarked on the total synthesis of the CP molecules. His primary research interest involves natural product synthesis as an enabling endeavor for the discovery of new fundamental concepts in chemistry and their application to chemical biology. He is currently engaged in a postdoctoral position with Professor E. J. Corey at Harvard University.

"New natural products have unusual structures

Fermentation broths of a still-unidentified fungus have yielded two compounds that are promising leads to drugs for lowering serum cholesterol and treating cancer. In addition to their medicinal promise, the two compounds have unusual structures that make them attractive synthetic targets.

Takushi Kaneko, manager of natural products discovery at Pfizer's research laboratories, Groton, Conn., reported the discoveries and structure proofs made by 15 of the firm's researchers at the April International Conference on Biotechnology of Microbial Products in Oiso, Japan. The two compounds are known so far only by their Pfizer code numbers, CP-225,917 and CP-263,114. The Pfizer workers call the microorganism that elaborates the compounds, "an unidentified fungus isolated from juniper twigs in Texas." They have deposited samples of the organism at the American Type Culture Collection under the accession number ATCC 74256. Both compounds inhibit the enzymes squalene synthase and farnesyl protein transferase. Squalene synthase catalyzes condensation of two molecules of the C15 sesquiterpenoid farnesyl pyrophosphate to squalene, with presqualene pyrophosphate as a step on the way. This reaction is one in the overall biosynthesis of cholesterol. The hope is that such compounds will lead to new cholesterol-lowering drugs.

Farnesyl protein 1 transferase mediates farnesylation of the protein p21, which is the product of the *ras* oncogene. A one-amino acid mutation of p21 renders it permanently activated, so that it pushes regulation of cell growth and division out of control. Here, the hope is that the Pfizer compounds will inhibit a step that may be essential to p21 activity and thus to the carcinogenic process.

Both compounds are members of a class called nonadrides, which are natural products featuring nine-membered rings with carboxylic acid groups on adjacent carbons cyclized to anhydrides. The Pfizer team determined the structures of the compounds from high-resolution fast-atom-bombardment mass spectrometry and two-dimensional nuclear magnetic resonance techniques.

In addition, the compounds are bicyclic and violate Bredt's rule, which states that bridgehead atoms of polycyclic compounds cannot be double-bonded. The rule was put forth in 1902 by organic chemistry professor Julius Bredt at the University of Aachen, Germany. Kaneko notes that synthetic chemists have since devised ingenious ways to violate Bredt's rule, but that such compounds are rare in nature.

Another source of strain in the molecules occurs because the apical carbon atom of the bicyclic structure is a carbonyl. But this strain is relieved by conversion to an sp^3 hybridized carbon atom by formation of a lactol ring with a neighboring carboxyl group of one compound, and by formation of a lactol/ketal with the carboxyl and a neighboring hydroxyl group in the other compound."[3]

To say the least, this report[3] was intriguing to us as it was to many other synthetic chemists, but our enthusiasm for a total synthesis program was curtailed by the lack of a hard-core publication committed to their structures. Indeed, the very unusual connectivities revealed in the *C&E News* article[3] cast a shadow of doubt over their structures. Prudence dictated that we should wait for a while; besides, the group was busy with several other projects including a number dealing with much larger molecules and, therefore, these small "guys" could be put on the shelf for a time.

Figure 1. a) Representations of the exploits of Theseus. In the center, the hero is confronting the Minotaur (440–430 BC, interior of a red-figure kyliz, British Museum, London). Copyright The British Museum. b) Minotaur, Paris, January 1, 1928 by Pablo Picasso, Musée National d'Art Moderne, Centre National d'Art et de Culture Georges Pompidou, Paris. Copyright CNAC/MNAM/Dist. Réunion des Musées Nationaux/Art Resource, NY, Musée National d'Art Moderne, Centre Georges Pompidou, Paris, France. 2001 Estate of Pablo Picasso/Artists Rights Society (ARS), New York.

Little did we know then how much these small "guys" had in store for us when we finally paid proper attention to them. That occurred in 1997 when the definitive paper[4] on the CP molecules from the Kaneko group appeared in the *Journal of the American Chemical Society*. Approximately two years later, the battle against the Minotaur was over with the triumphant Theseus having succeeded in the "kill."[5] Here is how *Science* magazine described the athlos in its *News of the Week* section in 1999:

"**40 Steps to a Chemical Synthesis Summit**

Like mountaineers who set off to scale ever more challenging peaks, organic chemists over the past half-century have tested the limits of their skills by attempting to synthesize increasingly complicated natural molecules, such as antibiotics and steroid hormones. The most fiendishly complex targets have taken synthesis labs a decade or more to conquer. With the completion of each new project, labs scan the horizon for even higher peaks. And in the past 2 years, few mountaintops were more tantalizing than a pair of jellyfish-shaped molecules found in 1997 in a fungus.

One enticement was the anticancer and cholesterol-lowering properties of the natural compounds, called CP molecules. The other was their complexity. The molecules' compact structure, crammed with chemical groups, made them "diabolical" targets, says K. C. Nicolaou, an organic chemist at The Scripps Research Institute in La Jolla and the University of California, San Diego. But in the 1 June issue of *Angewandte Chemie*, Nicolaou and his colleagues report having scaled that demonic peak: They have performed the first-ever complete synthesis of the CP molecules.

"It's an extremely impressive accomplishment," says Samuel Danishefsky, whose own group at Columbia University in New York City was closing in on the same goal. Other recently synthesized molecules have been more than four times the size of the CPs, which have 31 carbon atoms each. But Danishefsky says the CP molecules require particular finesse. "The functional groups bump into each other so that it's difficult to work on one portion of the molecule without affecting another part," he says.

"The CP molecules originally attracted attention when researchers at the pharmaceutical giant Pfizer showed that they inhibited the work of a cancer-causing gene known as *Ras*, which is overactive in up to 80% of human cancers. CP molecules, it turns out, block the addition of a chemical group known as a farnesyl group onto the *Ras* gene, a key step in its activation. Other more potent farnesyl blockers have been discovered, says Takushi Kaneko, a medicinal chemist at Pfizer's research center in Groton, Connecticut, who helped nail down the structure of the CP molecules. However, the new synthetic work could still prove vital, he says, by allowing chemists to manufacture CP analogues that may prove even more potent and also easier to produce than the CPs themselves.

Getting this far was a nearly two-year slog. In all, it took more than 40 chemical steps and many grams of starting materials to make milligrams of the molecules, which consist of a core ring of nine carbon atoms bearing three more oxygen-containing ring systems. On two occasions the group had progressed to key intermediate compounds along the way, only to find that although they were only a few bonds away from the complete structure they could not forge the final links.

The final attempt that got them to the summit took three key steps. First, the researchers had to convert a linear hydrocarbon precursor molecule into the nine-membered ring at the core of each CP molecule. They turned to a well-known ring-forming process known as an intramolecular Diels–Alder reaction and tweaked the reaction conditions to coax the precursor to adopt the correct ring-shaped structure.

For the next step, the Scripps researchers developed a set of novel "cascade" reactions. Cascade reactions run through a staccato of intermediate steps, each one automatically producing the right materials and conditions for the next, before ending up at a final product. The researchers used two of their cascade reactions to fuse two additional five-membered carbon- and oxygen-containing ring systems to opposite sides of the core. A final summit push, which consisted of a flurry of reactions provided them with CP-263,114, the more stable of the pair of CP molecules.

However, they also wanted to make its partner, CP-225,917, which differs only in that one of the three attached rings is broken, and the frayed ends capped with hydroxy groups. Trying to coax the stable CP-263,114 into a more unstable form proved very difficult. After numerous attempts, the team designed another cascade reaction which finished the job. When the resulting compound passed muster in a structure-determining NMR spectrometer, the climb was complete. Atop the mountain, says Scripps Ph.D. student Phil Baran, "it feels like a 200-ton anvil has lifted off my back."

Yet in some ways the work was just beginning. Now the hunt is on to come up with CP analogues that are more potent and simpler to make. The Scripps team is also launching studies of the detailed biological effects of the CPs and their derivatives. Of course, the search is also on for new molecular mountains to climb."[6]

How did it all happen and what was discovered and developed in the process? The answers to these and other intriguing questions will be found below as we take you behind the scenes and into the trenches of this battle against the CP molecules, the "molecular Minotaur" of our story.

2. The Intrigue and Lure of the CP Molecules to the Synthetic Chemist

Within the realm of molecular architectures of natural products, the CP molecules (**1** and **2**, Figure 2) occupy an intriguing position not because of their size but instead by virtue of the bond connectivities they display. Thus, the core structure of CP-263,114 (**1**), which consists of only 18 atoms, masters two five-membered rings, two six-membered rings, one seven-membered ring, and one nine-membered ring as well as several unusual and sensitive functionalities, including a maleic anhydride moiety, a γ-hydroxylactone, an internal ketal, a tetrahydropyran system, a bridgehead double bond, and a quaternary center (Scheme 1). While each of these structural features and the five stereogenic centers adorning this target poses its own synthetic challenge, it is the orchestration of the sequence by which one would have to construct them within the whole and maintain their integrity until the end that would present the major challenge to the molecule's total synthesis. In other words, this demonic molecular structure was well fortified and defended by a panoply of barricades whose defensive shield the synthetic chemist would have to overcome in a fierce struggle (see

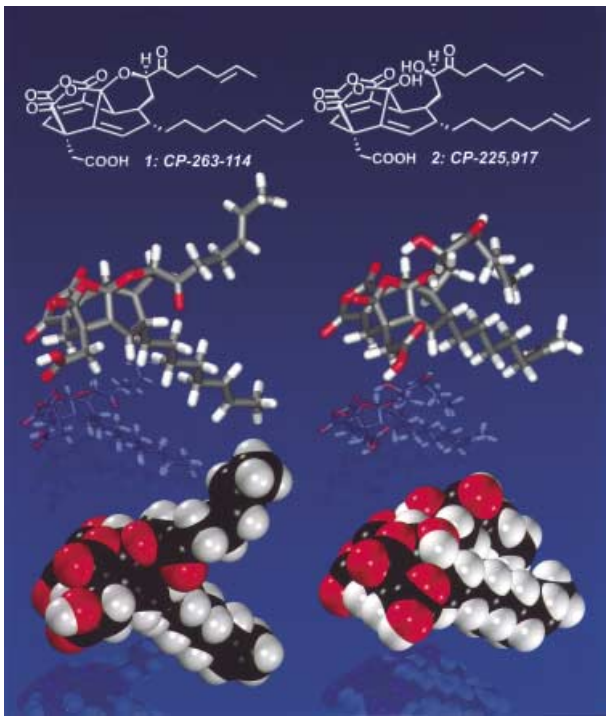
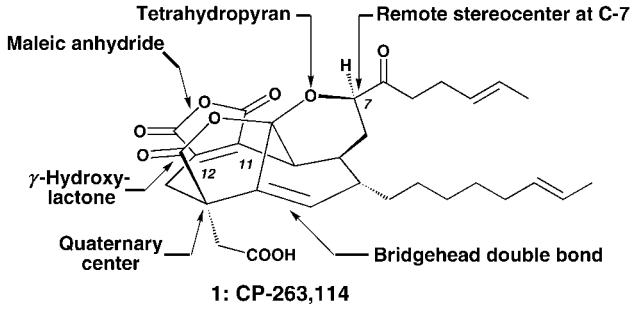


Figure 2. Molecular structures and computer-generated models of the CP molecules.



Scheme 1. Challenging structural elements of the CP molecules.

Figure 3). The outcome of the contest would surely depend on the resourcefulness, courage, and stamina of the daring, "would be conqueror", chemist. Our first shy steps toward the CP molecules were taken in 1996 with the intention of exploring possible pathways to their general core structure.

3. Entry to the Labyrinth: An Intramolecular Diels–Alder Approach versus a Divinylcyclopropane [3,3] Sigmatropic Rearrangement Strategy

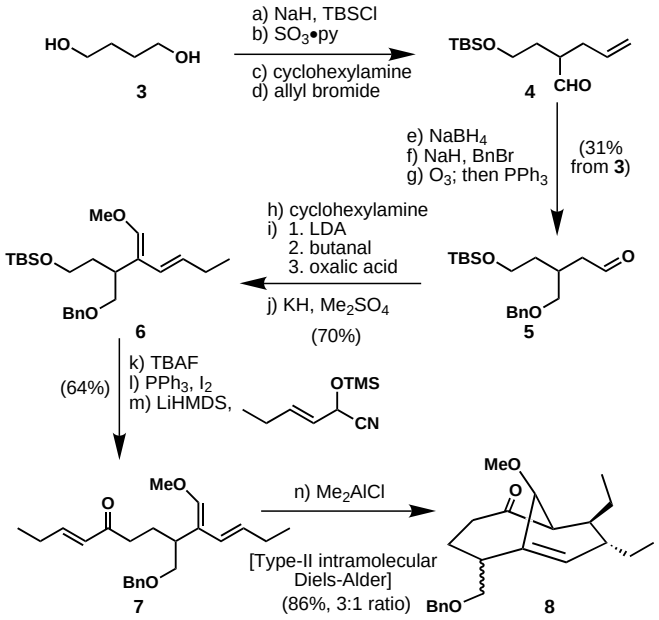
As with many molecules, entry into the synthetic labyrinth of the CP molecules was possible from several gates (exit would prove another matter, of course!). We chose two approaches for initial scouting and feasibility evaluation.

The first approach to the core of the CP molecules called upon the venerable Diels–Alder reaction, specifically a type-II version,[7] to weave an appropriately designed open-chain precursor into a bicyclo[4.3.1] system **8** whose resemblance to

Figure 3. The "graduate student's view" of the CP molecules guarded by the dreaded Minotaur.

the CP-molecule structure was not only credible but also encouraging (Scheme 2).[8] The high yield and exclusive stereochemical outcome of this cycloaddition reaction leading to the desired carbon framework added considerable weight to the potential and possible virtues of such an entry into the anticipated synthetic campaign.

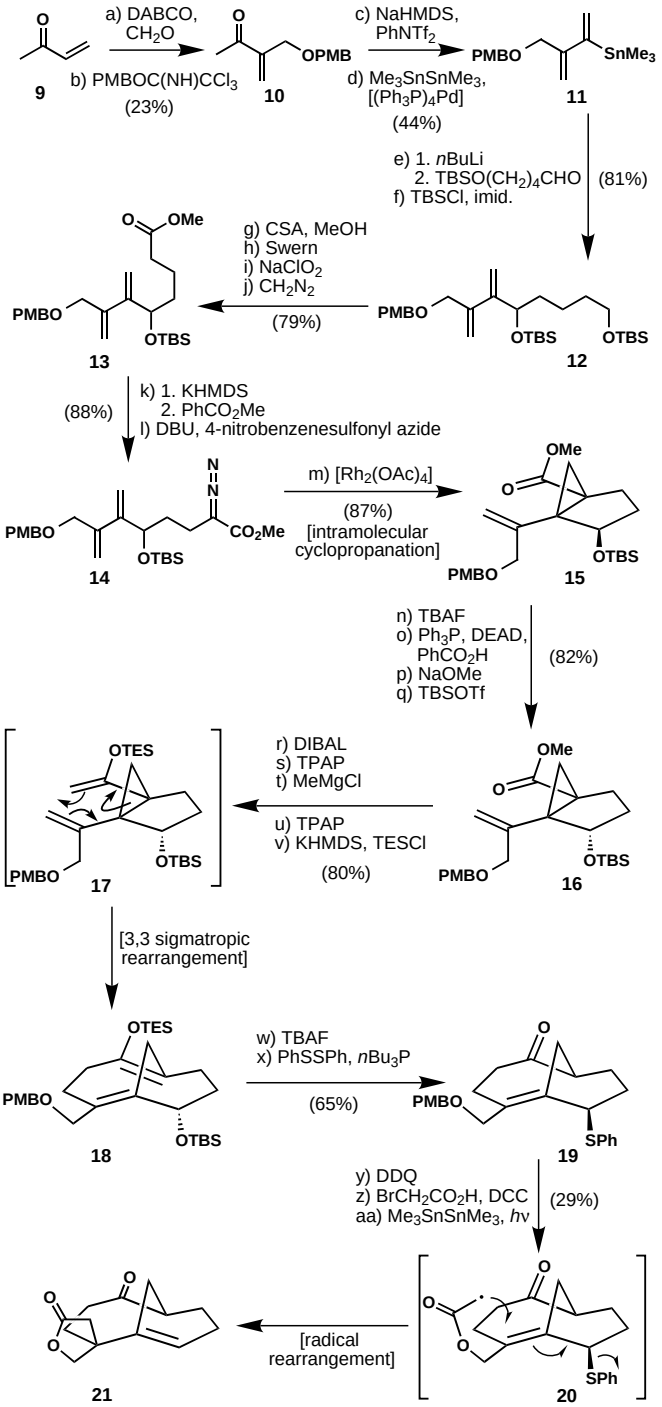
In the meantime, a second foray into the labyrinth was being explored (Scheme 3).[9] This strategy was designed



Scheme 2. The Diels–Alder approach to the CP core: a model study.

based on an initial carbenoid addition to a double bond followed by a Claisen rearrangement and a final S_H2 reaction. This rather elegant sequence proved rewarding in that all key steps proceeded as planned, but somewhat disappointing with regard to the stereochemical outcome of the final, radical-based S_H2 process. That step led to the wrong stereochemical arrangement at the quaternary center (**21**, Scheme 3).

Was there an error in the planning of this last operation? Specifically, what would the outcome have been in this reaction had we utilized the epimer of the precursor **19**? The answer to this question will remain unknown in the absence of the experiment, even though one can hypothesize that if the radical S_H2' process proceeds by a *syn* mechanism (as appears from the observed stereochemistry of the product) then reversing the stereochemistry of the leaving group (assuming no other factor intervenes) may result in the formation of the desired product.[9] On the other hand, it is likely that regardless of the absolute configuration of the carbon atom carrying the phenylthio group, approach of the acetate radical would take place from the convex face of the molecule. While insufficient information in the literature then and now prevents us from "betting the ranch" on such a prediction, the incident underscores the importance of mechanistically driven rational synthetic design. Incidentally, we may now revisit this question as a part of our recent interests in the chemistry initiated by related S_N2'-type reactions of *cis*-1,2-dichlorocyclobutene as an entry into novel molecular diversity.[10]



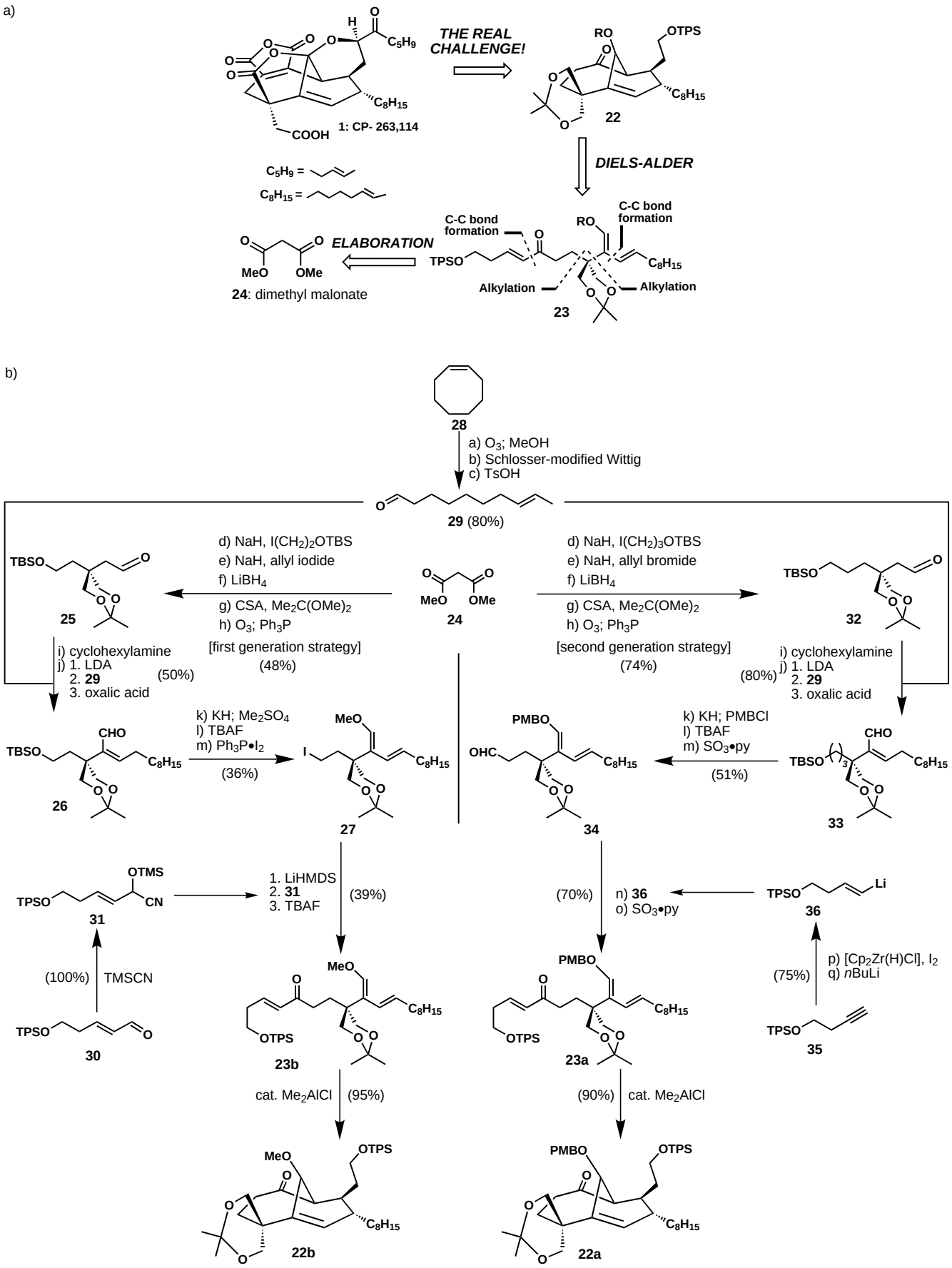
Scheme 3. The sigmatropic rearrangement approach to the CP core: a model study.

As for the choice of entrance into the CP-molecule labyrinth, the dilemma was solved by the disappointing stereochemical result of the latter approach, which tilted the balance in favor of the intramolecular type-II Diels–Alder reaction. In the meantime, the definitive paper and the Kaneko structures of the CP molecules was about to appear in the literature,[4] so the commitment was made to pursue the molecules as worthy challenges for total synthesis. It was both fortunate and timely (for me, K.C.N.) that a young man by the name of Phil S. Baran was entering the graduate program at Scripps in the same year. At the age of 19, Phil Baran decided to join my group and willingly accepted the CP-molecule challenge. He was destined to become the "Theseus" of this total synthesis story.

4. Evolution of the Intramolecular Type-II Diels–Alder Strategy to the CP-Molecule Core Structure

Armed with the positive results of the Diels–Alder model study described above, we proceeded to design a more appropriate intermediate for eventual incorporation into a synthetic blueprint capable of reaching the target natural products and streamlining a synthetic route. The general retrosynthetic strategy and the evolution of this plan are shown in Scheme 4.

Our original retrosynthetic analysis entailed the use of the key intermediate **22** whose disassembly to the prochiral precursor **23** became apparent upon recalling the intramolecular type-II Diels–Alder reaction. The obligatory simplification of precursor **23** relied upon two alkylation reactions, two crucial carbon–carbon bond-forming reactions, and a directed aldol reaction to disconnect the molecule as indicated in Scheme 4a. The execution of this plan is shown in Scheme 4b (left). The requisite building blocks **25**, **29**, and **31** were constructed expeditiously from dimethylmalonate (**24**), cyclooctene (**28**), and aldehyde **30**, respectively. Anion formation from the imine generated from aldehyde **25** and cyclohexylamine followed by addition of aldehyde **29** and elimination of H_2O from the resulting product led to the α,β-



Scheme 4. a) General retrosynthetic analysis of the CP molecules. b) First and second generation intramolecular type-II Diels – Alder routes to the CP-core structures **22a** and **22b**.

unsaturated aldehyde **26**, whose elaboration to iodide **27** required a second anion generation, quenching with Me_2SO_4, and desilylation-iodonation. The alkylation of the anion of cyanohydrin **31** with iodide **27** was accomplished only in low yield to afford, upon hydrolysis, enone-diene **23b**, whose Me_2AlCl-catalyzed Diels–Alder reaction proceeded smoothly to give the coveted bicyclo[4.3.1] system **22b**.

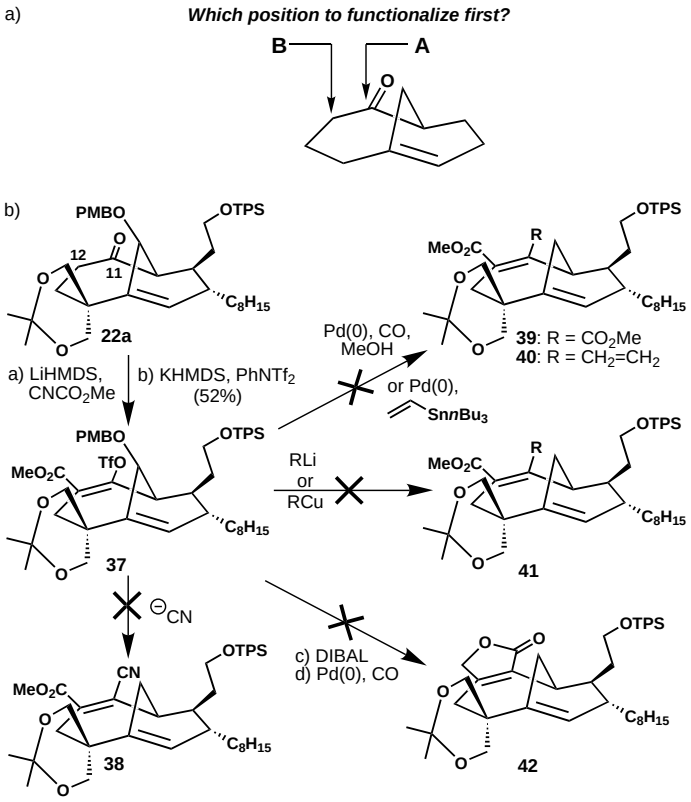
This early success gave us the confidence that a sufficiently elaborated system such as **22** could be reached by the chosen route. However, this route needed to be refined because of the low yielding alkylation step involving the sterically encumbered iodide **27** and because of questions regarding the suitability of the methoxy group as a surrogate to the required bridgehead functionality.

Accordingly, a second approach (Scheme 4b, right) in which a different coupling strategy for the initial building blocks was devised and executed, this time targeting a PMB derivative of the bridgehead hydroxy group. A similar sequence was followed as before except for the final connection which was now made by coupling vinyllithium **36** with aldehyde **34**. The efficiency of the overall scheme proved quite satisfactory, and hundreds of grams of the key bicyclic system **22a** were synthesized, thus keeping the supply lines for waging battle constantly filled.

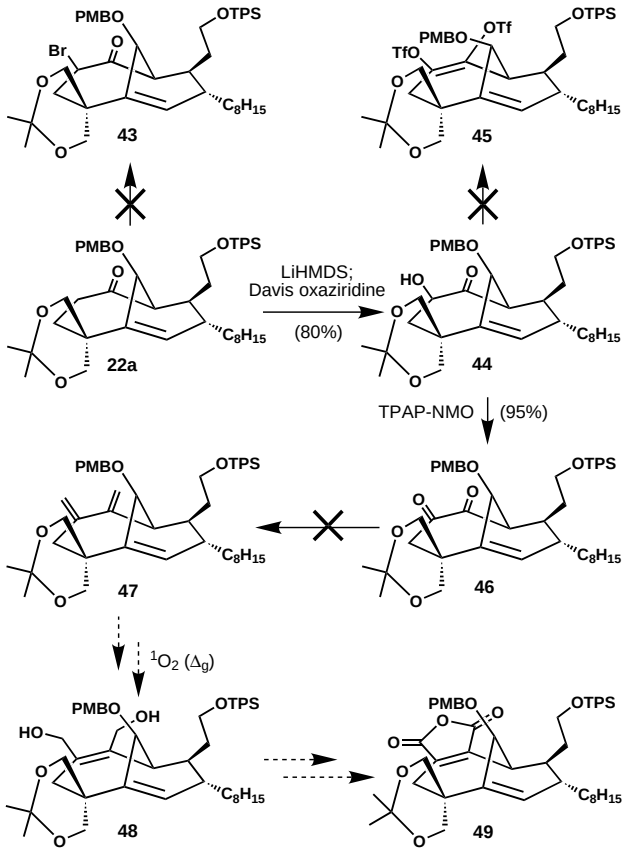
5. The Maleic Anhydride Hurdle

Of the various functionalities adorning the periphery of the CP skeleton, we first decided to investigate and develop a reliable method for the synthesis of the maleic anhydride moiety. Little did we know that this seemingly innocent structural unit would pose one of the most arduous challenges in the CP synthetic labyrinth. Our initial approaches were all flawed in that they attempted to operate first on the more hindered position A (Scheme 5a) after the less hindered carbon atom adjacent to the ketone moiety (position B) had been functionalized. This strategy occupied us for several months because of the ease of alkylation of the ketone enolate with a variety of electrophiles. Several attempts to convert vinyl triflate **37** (easily obtained from ketone **22a**) into suitable anhydride precursors were plagued with unpredicted failures (Scheme 5b), despite success in simple model systems. For several weeks, in parallel to the streamlining of the Diels–Alder sequence (see Section 4), these studies continued as multiple reaction conditions and catalysts were screened in hopes of opening one of the reaction pathways. Thus, conjugate addition–elimination reactions[11] on **37** (for example, **37**→**38**) failed, as did palladium-catalyzed coupling reactions[12] (for example, **37**→**39** or **40**), organometallic additions (**37**→**41**), and a DIBAL reduction–carboxymethylation[13] pathway (**37**→**42**).

Other strategies were then pursued from **22a** and the easily accessible hydroxyketone **44**, as shown in Scheme 6. Having failed to selectively brominate **22a** to **43**, we turned to the hydroxylation of **22a**, a transformation that was smoothly carried out with Davis' oxaziridine[14] to generate **44**. Formation of ditriflate **45** as an attempt to advance intermediate **44** failed, but oxidation of the latter compound (**44**) with



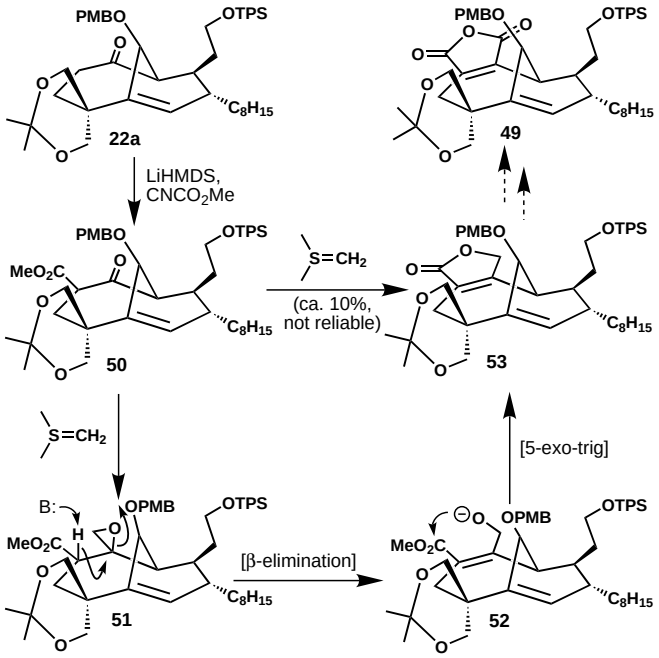
Scheme 5. a) Installation of the maleic anhydride moiety (substituents deleted for clarity). b) Unsuccessful attempts to functionalize triflate **37** toward the maleic anhydride moiety.



Scheme 6. Other failed attempts to access potentially useful precursors to the maleic anhydride moiety.

TPAP/NMO[15] led to diketone **46**. Hopes that diketone **46** could be funneled into a pathway leading to a maleic anhydride intermediate (**46** → **47** → **48** → **49**) were, however, dashed by failure at the start: diketone **46** was unwilling to be a player in this scenario, resulting in another dead-end situation.

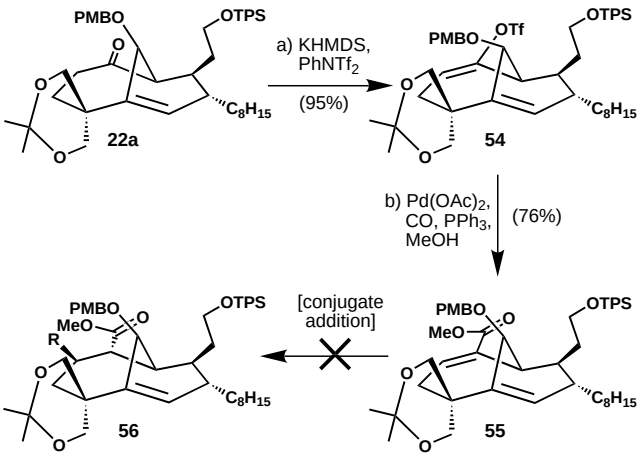
A sulfur ylide-based epoxidation[17] of keto-ester **50** (readily obtained from ketone **22a**, Scheme 7) then shed a glimpse of light on our endeavors. The expectation was that the initially formed epoxide **51** would suffer β-elimination to furnish



Scheme 7. Attempted epoxidation of ketone **50** leads to butenolide **53**, albeit in low yield, which forced us to abandon this route.

alkoxy ester **52**, whose collapse to the potential maleic anhydride precursor **53** was deemed inevitable. This hypothesis was indeed borne out by the initial experiments, with butenolide **53** being observed in about 10% yield. The euphoric feeling of finally arriving at something resembling the anhydride moiety was soon squelched, however, as we were unable to improve the reaction, despite several repeated attempts. It was now mid-September, 1997.

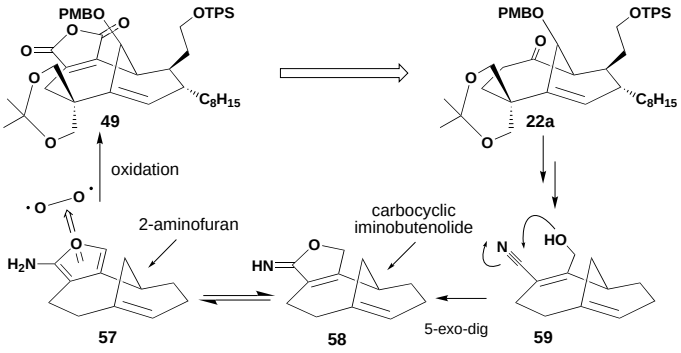
Studies to construct the anhydride were then temporarily halted as finishing touches and optimization of the 13-step sequence to the Diels–Alder product **22a** were undertaken (Scheme 4b). Studies directed toward solving the maleic anhydride problem resumed in the beginning of December, 1997, and continued in the same fashion (functionalization of position A and then position B, Scheme 5a) until Christmas eve of that year when we decided to explore the functionalization of position B first (Scheme 8). Thus, ketone **22a** was converted into the vinyl triflate **54** which was then submitted to Pd-catalyzed carboxymethylation to furnish the α,β-unsaturated ester **55**. This transformation represented the first reliable synthesis of a compound (that is, **55**) bearing a useful carbon functionality at position B, and, at this point, conjugate addition strategies[11] to provide intermediates of type **56** were



Scheme 8. Successful synthesis of the α,β-unsaturated ester **55**, which, however, turns out to be another dead-end.

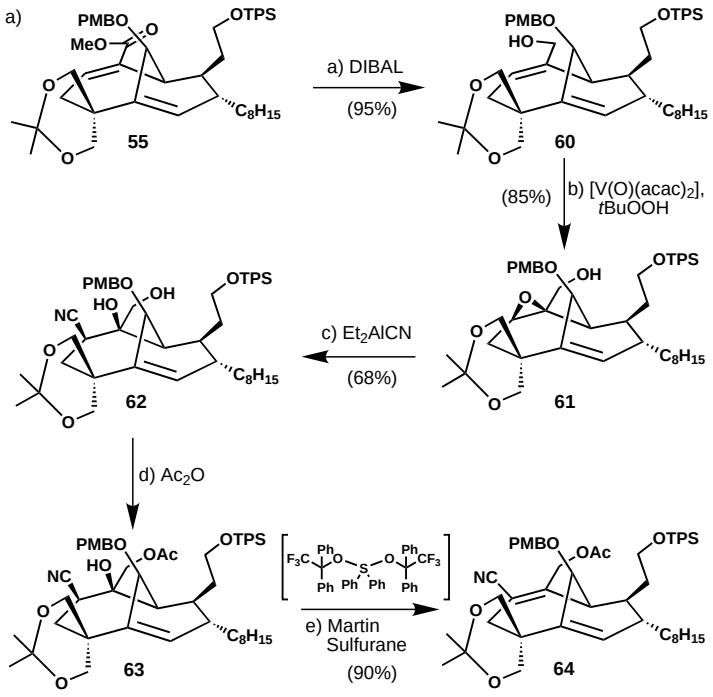
evaluated. All attempts toward this goal failed, however, adding further frustration to those gloomy days. A new plan was clearly needed to extricate ourselves from this rather miserable predicament.

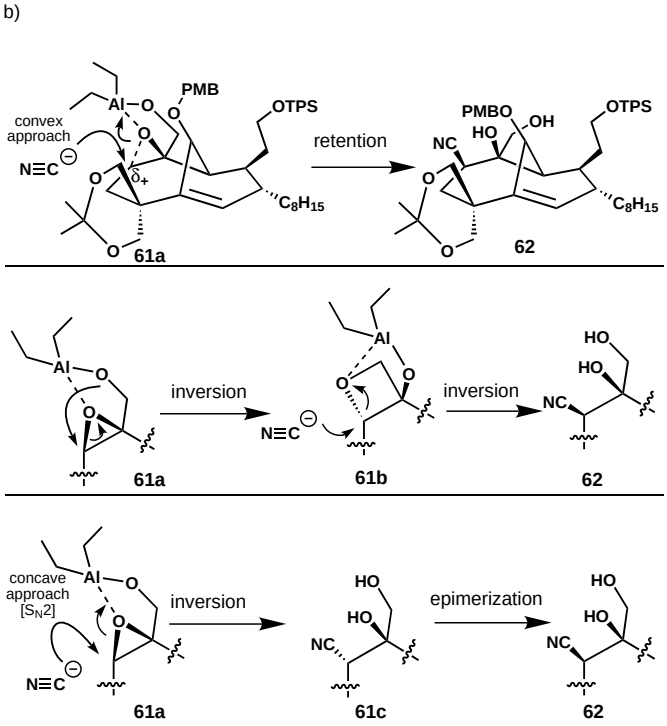
Shortly before New Year's eve, 1997, a rather daring strategy towards the anhydride moiety was conceived of as shown in Scheme 9. We envisaged the use of an unprecedented 2-aminofuran[17] moiety as a "molecular sponge" to



Scheme 9. Novel designed strategy for the conversion of ketone **22a** into anhydride **49**. (Substituents in structures **57**–**59** have been deleted for clarity.)

harvest oxygen and lead to the maleic anhydride moiety after expulsion of ammonia. On the basis of Dewar's pioneering calculations,[18] access to the requisite 2-aminofuran (**57**) was envisaged from the iminobutenolide **58**. This idea was inspired by the previous observation of butenolide **53** (Scheme 7) which suggested that a β-elimination pathway could, in principle, permit access to this rare chemical species. Thus, the projected synthetic pathway was directed towards **59** whose generation from ketone **22a** was considered feasible. With the α,β-unsaturated ester in hand, we proceeded at a furious pace which reached a climax at 2:00 a.m. on January 1, 1998, wherein we had synthesized the cyanodiol **62** (Scheme 10a). Soon thereafter, and much to our surprise, we established the unorthodox stereochemistry (-CN, -OH *cis* to each other) of the compound as suggested by NOE experiments. There are three possible mechanistic rationales



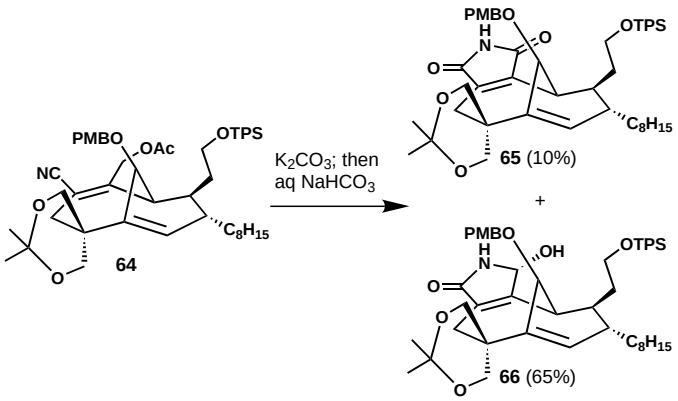


Scheme 10. a) Arrival at the cyanoacetate **64**. b) Three possible mechanistic explanations for the observed "unorthodox" stereoselectivity of the cyanide addition to **61a**.

for this unexpected stereochemical outcome: in the first (Scheme 10b, top), our favored scenario, a molecule of Et_2AlCN[19] reacts with the hydroxyl group of **61** furnishing complex **61a**, which suffers nucleophilic attack by cyanide from the more accessible convex site made possible by considerable weakening of one of the epoxide C–O bonds. This mode of attack would then be accompanied by the observed retention of stereochemistry at C-12 (CP numbering). In the second scenario, the initially formed complex **61a** (Scheme 10b) is envisioned to undergo intramolecular rearrangement, by inversion of configuration, to afford oxetane **61b**, whose reaction with cyanide by inversion is expected to lead to the observed product **62**. In the third scenario (Scheme 10b, bottom) a concave mode of attack by cyanide on complex **61a** is postulated to afford the now inverted cyanodiol **61c** which, under the reaction conditions, suffers epimerization to the observed cyanodiol **62**.

Irrespective of the mechanism of this transformation, formation of **62** was good news because we could now test our iminobutenolide hypothesis. In anticipation of that event, and after scaling up the sequence, the push forward was uninterrupted, and within two days we arrived at the precious acetoxycyanide precursor **64** by mono-acetylation of **62**, followed by a dehydration facilitated by the Martin sulfurane[20] (**62** → **63** → **64**, Scheme 10a). One of us (K.C.N.) will never forget the scene in the laboratory on that day in January 1998, who upon arrival at 8:00 a.m. found the other (P.S.B.) fast asleep on his desk with a clean NMR spectrum of compound **64** by his side. It was classic brilliance and characteristic dedication from the team working on this project!

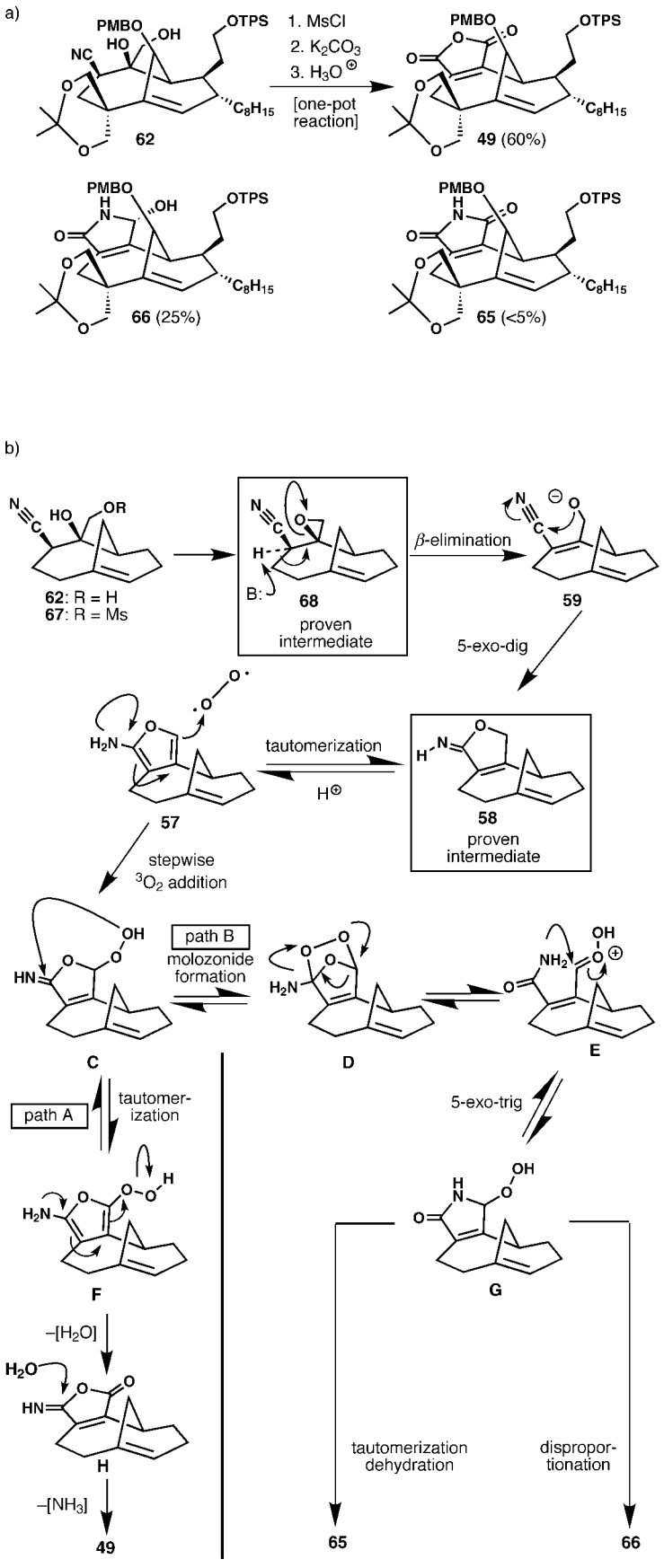
Later that day, the crucial experiment towards iminobutenolide **58** (Scheme 9) was carried out. Scheme 11 tells the rest of the story—disappointing, but interesting! Basic (K_2CO_3) hydrolysis of **64** followed by mildly basic workup ($NaHCO_3$)



Scheme 11. First attempt to reach the anhydride leads to the maleimide **65** and an unknown by-product, which was later determined to be **66**.

led to two compounds, neither of which was the coveted maleic anhydride **49**. Instead, we discovered that we synthesized maleimide **65** (ca. 10% yield) along with an unknown major product, which was later characterized as a single isomer of the hydroxyamide **66**.

We shall return shortly to the discussion of the mechanistic aspects of these remarkable transformations; but first back to the main issue at hand, the maleic anhydride moiety and its construction. It would take another seven weeks before we finally found reliable conditions for the conversion of cyanodiol **62** into maleic anhydride **49** (Scheme 12a). In this one-pot reaction involving exposure of **62** to mesyl chloride/triethylamine followed by addition of K_2CO_3 and oxalic acid



Scheme 12. a) The "magic" of the maleic anhydride cascade. Conversion of **62** into **49**. b) Proposed mechanistic underpinnings in the conversion of **62** into **49**, **65**, and **66**. (Substituents have been deleted from the structures for clarity.)

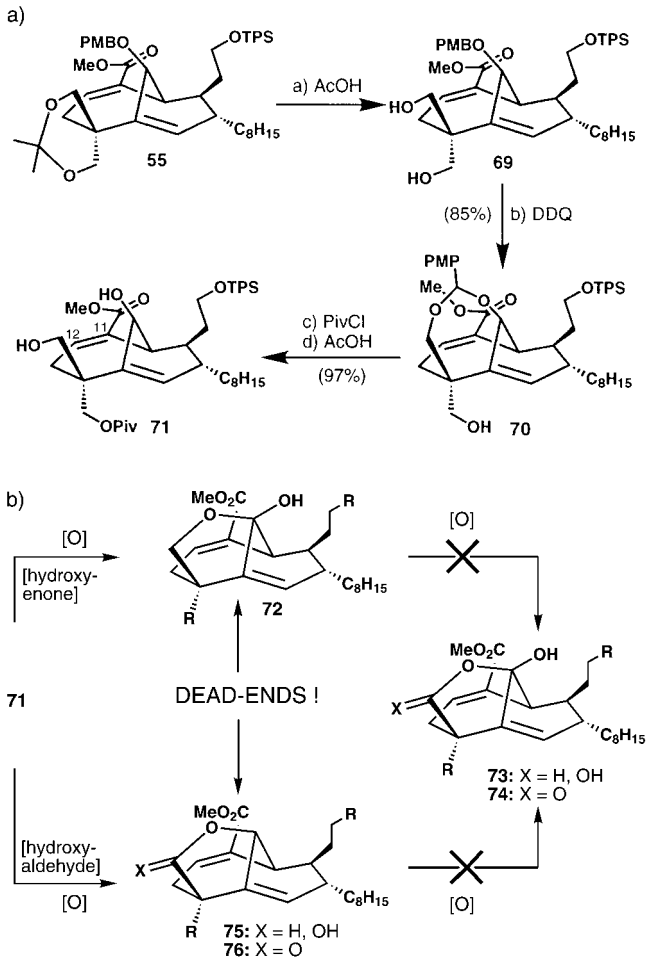
workup, the following chemical transformations were accomplished: 1) primary mesylate formation; 2) epoxide formation; 3) β-elimination rupturing the epoxide; 4) 5-exo-dig cyclization to an iminobutenolide; 5) double oxygenation; and 6) hydrolysis/expulsion of ammonia. Scheme 12b presents a plausible mechanistic rationale for these transformations which explain the formation of the observed final products **49**, **65**, and **66**.

Despite the extraordinary chemistry involved in this cascade in which maleic anhydride is formed,[21] we restrained ourselves from submitting a paper describing the work until later on in 1998 when further progress toward the CP molecules was made. Notwithstanding the relief and excitement of designing and executing a remarkable cascade reaction to synthesize the maleic anhydride moiety within the CP molecule, we were cognizant of the fact that we were still far away from the center of the CP labyrinth. Sure enough, more challenging hurdles and unpredictable twists, turns, and puzzles were waiting ahead of us, as we shall see in the upcoming sections of the tale.

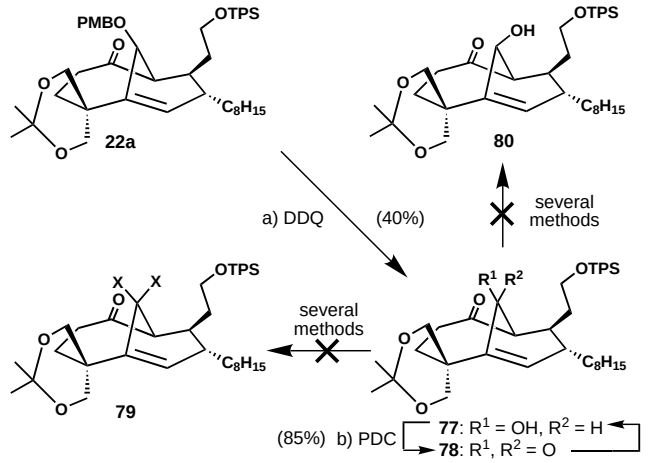
6. The γ-Hydroxylactone Hurdle

Having secured the maleic anhydride moiety, we then decided to turn our attention to the γ-hydroxylactone system of the CP molecules. Seemingly, the construction of this moiety boils down to oxidizing the appropriate carbon atoms to their highest oxidation state. This task turned out, however, not to be so trivial. The underlying challenges of the γ-hydroxylactone construction surfaced rather quickly after synthesizing the model 1,4-diol **71** (Scheme 13a). As shown in Scheme 13b, we were only able to isolate partially oxidized, yet unproductive, forms of the γ-hydroxylactone upon attempted oxidation of this 1,2-diol. For example, if we used oxidants capable of selective oxidation of the bridgehead position, rapid closure to hemiketal **72** was always observed. Alternative oxidants capable of selectively oxidizing the primary alcohol also led to dead-ends in the form of lactol **75** and lactone **76**, which were resistant to further oxidation at the bridgehead position. Other 1,4-diols that differed at positions C-11 and C-12 exhibited similar stubbornness toward oxidizing agents, which forced us, ultimately, to search for an alternative pathway.

Since the stereochemistry of the bridgehead hydroxy group was crucial to the "locked" structures **75** and **76** (Scheme 13b), our first impulse was to invert the stereochemistry at that center. Another option to avoid the "locking up" of partially oxidized intermediates would have been a sequence in which the bridgehead carbon atom was oxidized to the ketone and protected while the primary alcohol was still engaged in the acetonide functionality. These ideas were tested starting with ketone **22a** as shown in Scheme 14, but unfortunately failed. Thus, the bridgehead hydroxy group could not be inverted, neither by a Mitsunobu reaction[22] nor through an oxidation/reduction sequence, with the latter protocol



Scheme 13. a) Synthesis of the model 1,4-diol system **71**, in preparation for the construction of the γ-hydroxylactone moiety. b) The "lock-up" problem of oxidizing the 1,4-diol system to a γ-hydroxylactone moiety.



Scheme 14. Failed attempts to protect the bridgehead enone or invert the bridgehead hydroxy group.

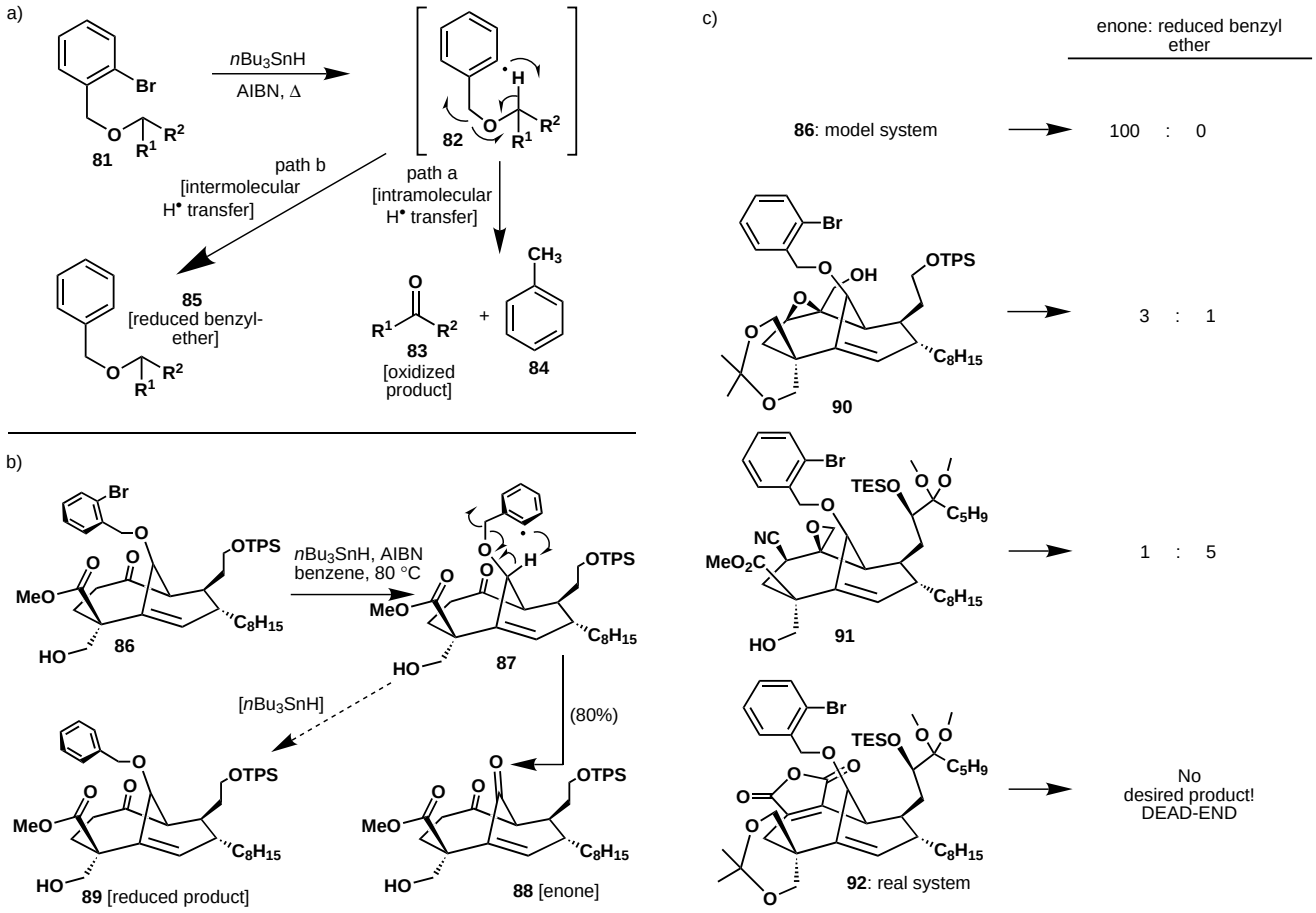
leading to the same starting alcohol. Furthermore, enone **78** could not be protected under a variety of conditions.

When one of us took a trip downstairs to discuss this problem with Professor Erik Sorensen, he drew our attention to a paper by D. P. Curran and H. Yu which introduced a unique self-oxidizing protecting group to organic synthesis based on the radical chemistry of the *o*-bromobenzyl ether group (Scheme 15a).[23] Without the intermediacy of a free hydroxy group at the bridgehead position we would no longer have to worry about "locked" structures! Eager to implement this novel idea to the solution of the thorny γ-hydroxylactone problem, we synthesized substrate **86** as a model system and subjected it to the Curran conditions (Scheme 15c). Much to our delight upon exposure of **86** to the radical debromination conditions we observed a clean oxidation to enone **88** which was exclusively formed in 80% yield. No detectable amounts of the undesired reduced benzyl ether **89** could be seen. The path now appeared clear towards the γ-hydroxylactone! Unfortunately, as is often the case in total synthesis, our hopes were soon crushed when we found that more advanced substrates containing the maleic anhydride moiety, or its progenitor functionalities, failed to follow the same path, but led instead to either the reduced benzyl ether or decomposition products. Scheme 15c summarizes the results with a number of such substrates, with the real intermediate **92** leading to no desired product whatsoever, bringing us once again to a halt.

We went back to the drawing board and devised a strategy which was predicated on the ring-chain tautomerization of hydroxy ketones (Scheme 16a).[24] Specifically, we reasoned that the locked hemiketal (for example, **94**, Scheme 16a), readily available from structures of type **93**, might be intercepted by an oxidant in its open hydroxy-enone form (**95**) and lead to a dicarbonyl system (namely, **96**) which, after hydration, would lead to the γ-hydroxylactol **97** or even possibly to the γ-hydroxylactone **98** after further oxidation. To test this hypothesis we subjected the easily obtainable 1,4-diol **99** (Scheme 16b) to excess DMP[25] in CH_2Cl_2 for 16 h, at which point we were delighted to encounter the desired γ-hydroxylactol **100**. We then found that TEMPO/NaOCl[26] was a suitable oxidant to carry out the further oxidation to the corresponding γ-hydroxylactone **101**. In a custom with which we soon became all too familiar, this simple model study failed to prepare us for the surprise that lay ahead. When we employed as a substrate the more advanced 1,4-diol system **102**, which was identical to the model compound **99** except for the fact that it was now harboring the maleic anhydride moiety, the DMP-mediated oxidation failed to proceed beyond the hemiketal "locked" stage (Scheme 16c). After a number of failed attempts to coax this reaction in the right direction, a linear path to construct the γ-hydroxylactone moiety was pursued (see Scheme 17a).[27] In retrospect, this strategy, which was based on conventional protecting-group manipulations, set us back a number of months even though it succeeded in furnishing the most advanced CP intermediate (namely, **107**) at the time.[27] Soon afterwards, however, we were to realize that the anhydride moiety would not tolerate the conditions required to install the "upper" side chain, as indicated in substrates **108** and **109** (Scheme 17b). It was time for a new strategy and the team retreated to earlier intermediates for some serious planning.

7. Selecting a Strategy for the First Serious Assault on the CP Molecules

After coming to the realization that the "upper" side chain would have to be installed prior to maleic anhydride



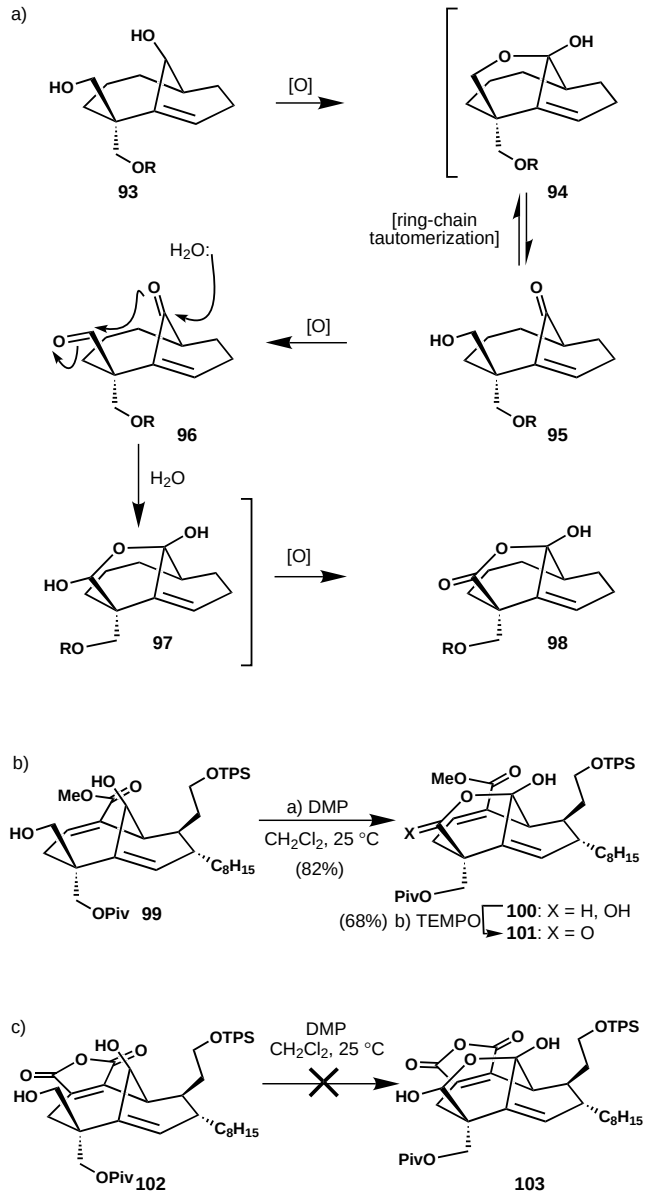
Scheme 15. a) Curran's self-oxidizing protecting group. b) Model study to reach a bridgehead enone utilizing Curran's self-oxidizing protecting group proves successful. c) Summary of attempts to reach the bridgehead enone utilizing the self-oxidizing protecting group.

formation, and with two potential methods to construct the γ-hydroxylactone at our disposal (DMP-mediated cascade and the linear approach), we prepared, starting from the Diels–Alder product **22a**, a series of CP-core aldehydes (**111**–**114**, Scheme 18a) for coupling with lithiodithiane **110a**. In our first attempt, we employed ketoaldehyde **111**, which mainly gave us one diastereomeric product (ca. 11:1 ratio of diastereomers) of the corresponding hydroxyketone (**115**). To determine the configuration of the newly generated center at C-7 of the latter compound it was necessary to prepare tetrahydropyran derivative **122**, via intermediates **120** and **121** (Scheme 18b). The NOE signals observed in the ^{1}H NMR spectrum of this rigidified structure (**122**) confirmed our wish for the 7(*R*) configuration as desired for the CP molecules. This remarkable degree of stereocontrol may be explained by commissioning lithium complexation with both carbonyl groups of **111**, thereby fixing the conformation of the aldehyde in a favorable position to yield the desired product (Figure 4).[28] As seen in Scheme 18a, the selectivities observed in other cases (aldehydes **112**–**114**) where such a chelation possibility does not exist were either diminished or skewed in the direction of the wrong, 7(*S*) isomer (**117** and **118**).

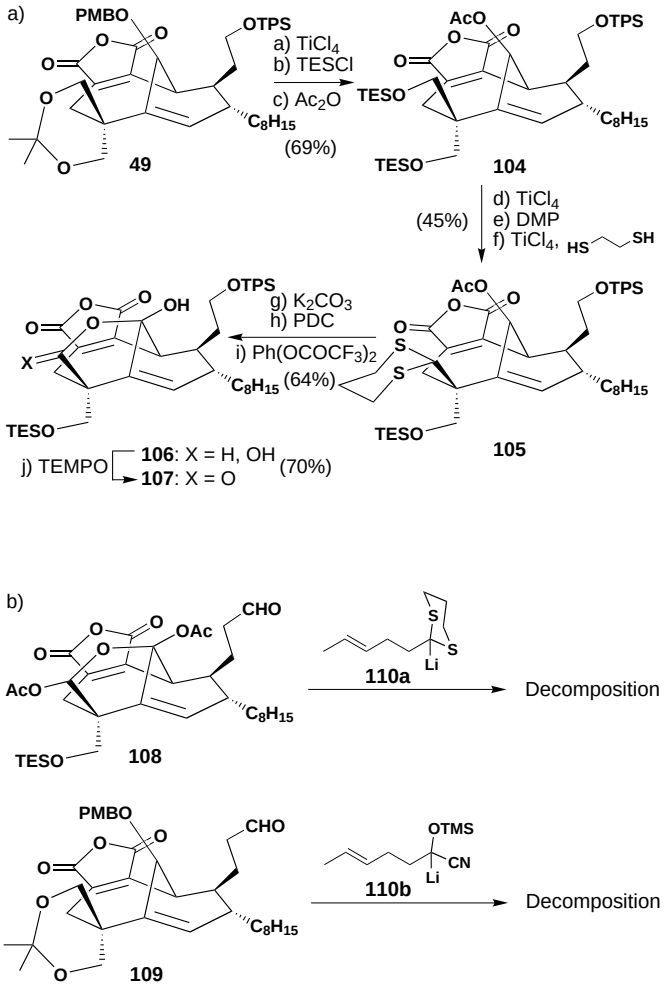
With a reliable method for the attachment of the "upper" side chain at our disposal, we were now able to charter a route towards the advanced key intermediate **129** (Scheme 19). Key events en route to **129** included a Pd-catalyzed carboxymethylation of the vinyl triflate derived from ketone **123**, a highly stereoselective epoxidation of the allylic double bond of **125**, and, of course, the efficient formation of the maleic anhydride moiety (**127**→**128**). The structure of **129** was firmly established by X-ray crystallographic analysis.

Arrival at key intermediate **129** constituted a somewhat historical event in the CP project, in that we marked this compound as the embarking point for any new excursions. The decision to use **129** as the "beachhead" for all future operations was taken not only because of the intermediate's attractiveness as a readily available and fertile substrate, but also partly because of our frustrating failures with numerous other plans to make substantial forward progress. Indeed, more than ten variations of such strategies were devised and explored, only to lead to dead-ends as summarized in Scheme 20.

The decision to abandon the linear, protecting group-based route to the γ-hydroxylactone moiety was critical, because it allowed us to focus on a more daring and concise approach to this functionality. Given the risky nature of the new scheme, part of the research group remained loyal to the linear approach for a while longer, only to return later to join the main effort on the new strategy. What happened next is a notable example of rational design, although the ideas were considered risky and long-shots. However, a good mix of rational thinking, intuition, desperation, and courage brought us victorious to the next stage. Intuitively we felt that the DMP-based oxidation cascade to produce the γ-hydroxylac-



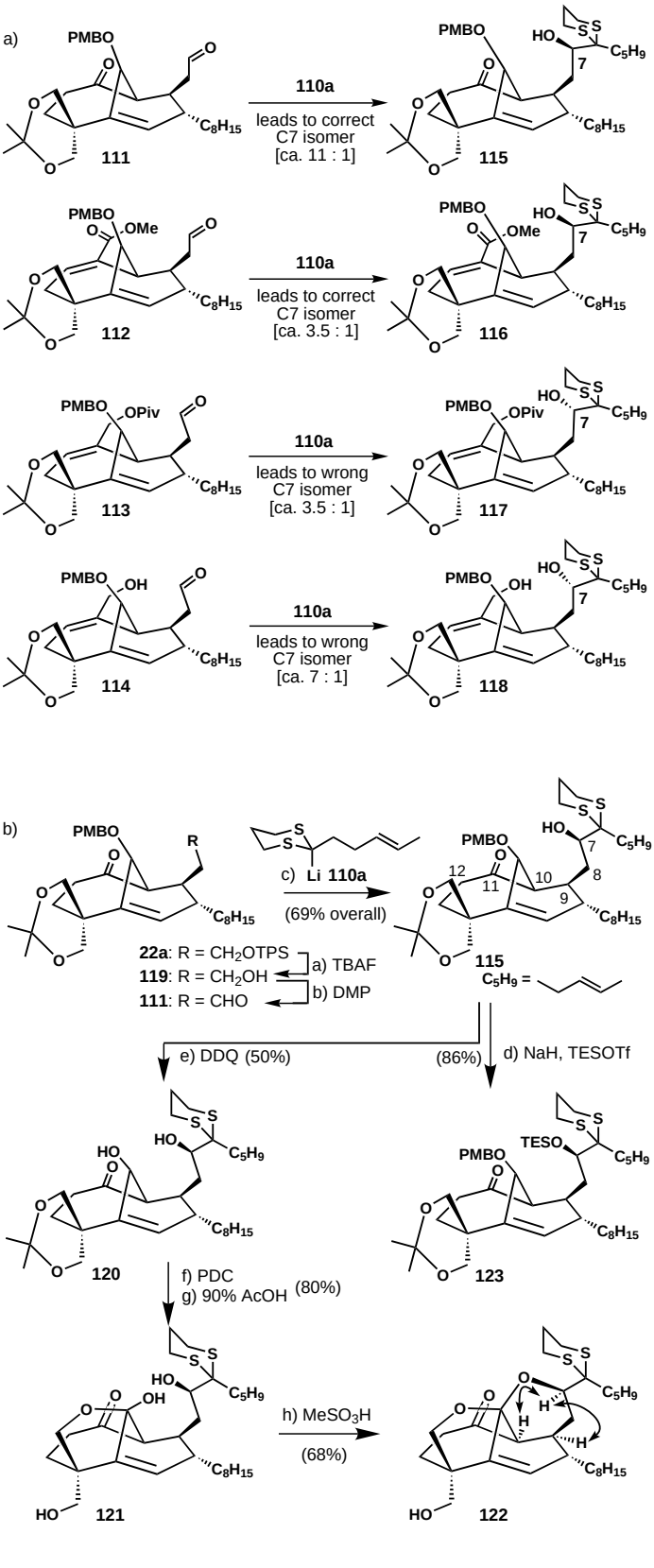
Scheme 16. a) General concept for tandem oxidation of **93** to the corresponding γ-hydroxylactone (**98**) based on the ring-open chain tautomerization of hemiketals. (Substituents have been deleted for clarity, [O] = oxidant.) b) The DMP oxidation cascade of 1,4-diols: proof of principle. c) DMP oxidation cascade of 1,4-diols fails in the presence of the maleic anhydride moiety.



Scheme 17. a) Stepwise construction of the γ-hydroxylactone moiety in the presence of the maleic anhydride moiety. b) Chemical reactivity of the anhydride moiety renders side-chain extension by organometallic addition to aldehydes a nonpractical proposition.

tone system deserved another chance. Our inspiration to try again (having failed before, see Scheme 16) was drawn from the prior observation of the influence the upper side chain had on the reactivity of the core's functionalities and vice versa. Specifically, it was reasoned by analogy that, perhaps, a complete upper side chain such as in **129**, our "beachhead" compound, might exert enough remote influence so as to favorably coax the equilibrium between the closed and open forms of the lactol chain involved in the DMP-oxidation cascade (in contrast to the case with a truncated upper side chain where the lactol remained stubbornly closed, Scheme 16). Unlikely as it seemed, this proposition was viewed almost as a last resort, but since it would only take five steps from **129** to test it, we considered it worthy of pursuit.

At the beginning of November, 1998, we arrived at the coveted hydroxylactol **132** by the route shown in Scheme 21 a. However, no matter how large an excess of DMP in CH_2Cl_2 at room temperature was used in our attempts to oxidize this intermediate further than the lactolaldehyde stage, its hemiketal moiety remained defiantly closed and intact (Scheme 21 b, top). In the midst of their desperation and hope, Yong-Li Zhong and Phil postulated that raising the temperature might persuade the lactol to reveal its primary alcohol, thus rendering it susceptible to oxidation by DMP. They proceeded to design, in complete secrecy (from K.C.N.), an experiment in which hydroxylactol **132** was to be heated in refluxing benzene with excess DMP! It is fair to say at this junction that had they informed me of their intention to heat DMP at such temperatures, I would have most likely instructed them against this course of action in light of the assumption that DMP could possibly be explosive at high temperatures. Their plot was, therefore, perfect and they got away with it. The first signs of success came when traces of the desired γ-hydroxylactol aldehyde **134** (Scheme 21 b, middle) were detected by NMR spectroscopy despite a rather messy and distressing thin-layer chromatography (TLC) picture.



Scheme 18. a) Extending the upper side-chain. The addition of lithium dithiane to CP-core aldehydes occurs with remarkable remote stereocontrol. b) Construction of key intermediate **115** and confirmation of its C-7 stereochemistry by NOE studies on a rigid descendant (**122**). Arrows in structure **122** indicate observed NOEs.

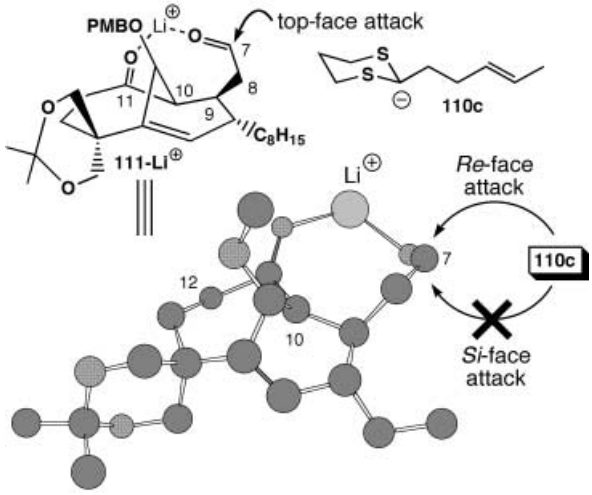
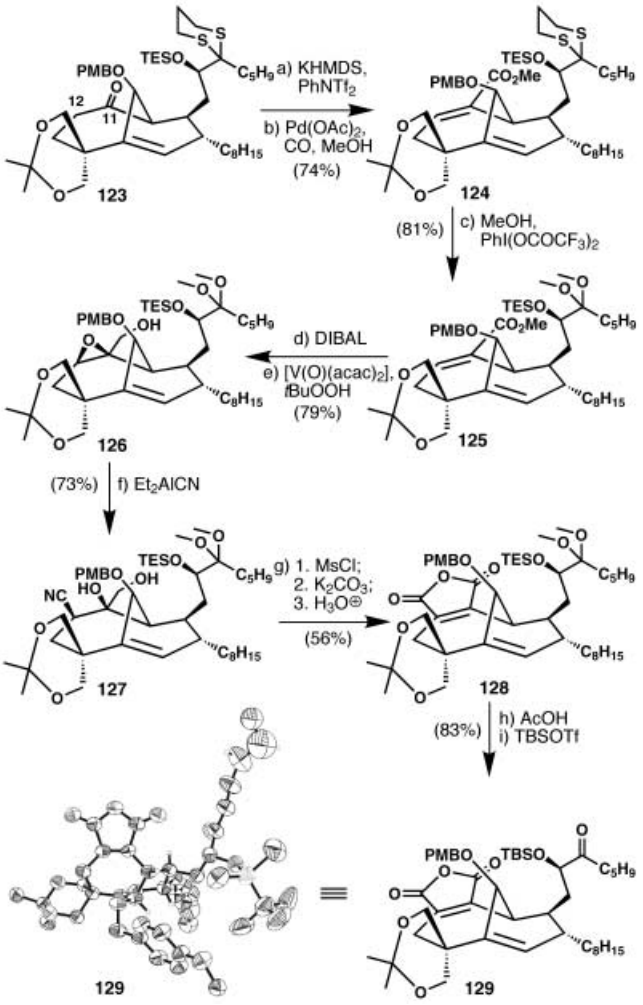


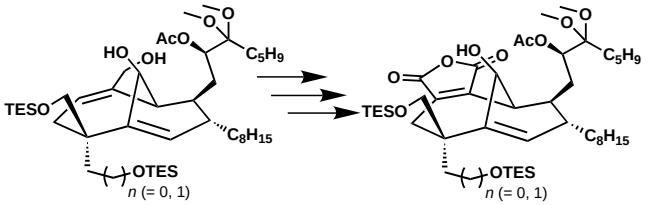
Figure 4. MM3-minimized structure of keto-aldehyde **111** chelated to a lithium cation (Li^+). Such an interaction explains why the *Si*-face is blocked from attack of the incoming dithiane anion.



Scheme 19. Synthesis and X-ray structure of advanced key intermediate **129**.

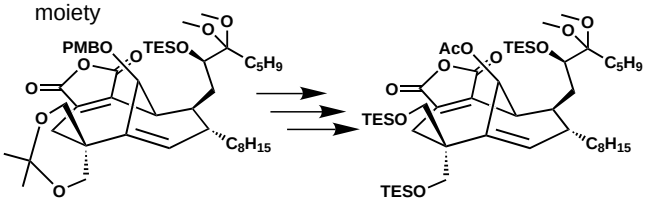
Guided by their impulses, they rushed to perform the next logical experiment which was to employ the TES-protected lactol **135** (Scheme 21 b, bottom) as a substrate in the reaction.

A
- Plan: to linearly construct the γ-hydroxylactone and maleic anhydride moieties



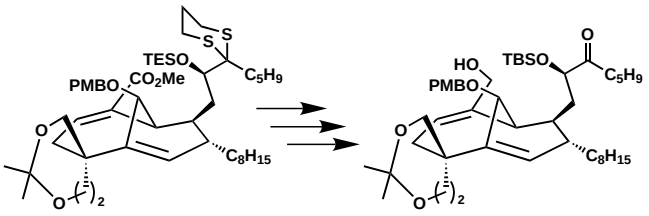
- Several variations of the strategy failed because of low yielding anhydride-formation step, instability of side-chain protecting groups, and low overall yield for certain sequences

B
- Plan: to linearly construct the γ-hydroxylactone moiety after the efficient installment of the maleic anhydride moiety



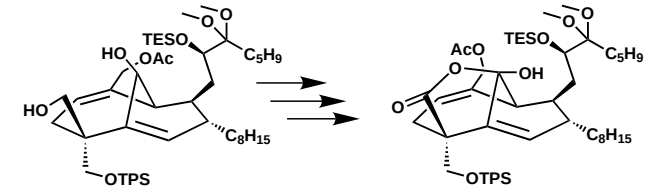
- Several variations of the strategy failed because of protecting group conflicts and maleic anhydride instability

C
- Plan: to utilize a 7-membered ring acetonide substrate to build linearly and sequentially the γ-hydroxylactone and anhydride moieties



- Strategy failed because of protecting-group complications and instability of 7-membered acetonide

D
- Plan: to construct linearly the γ-hydroxylactone first and then install the maleic anhydride moiety

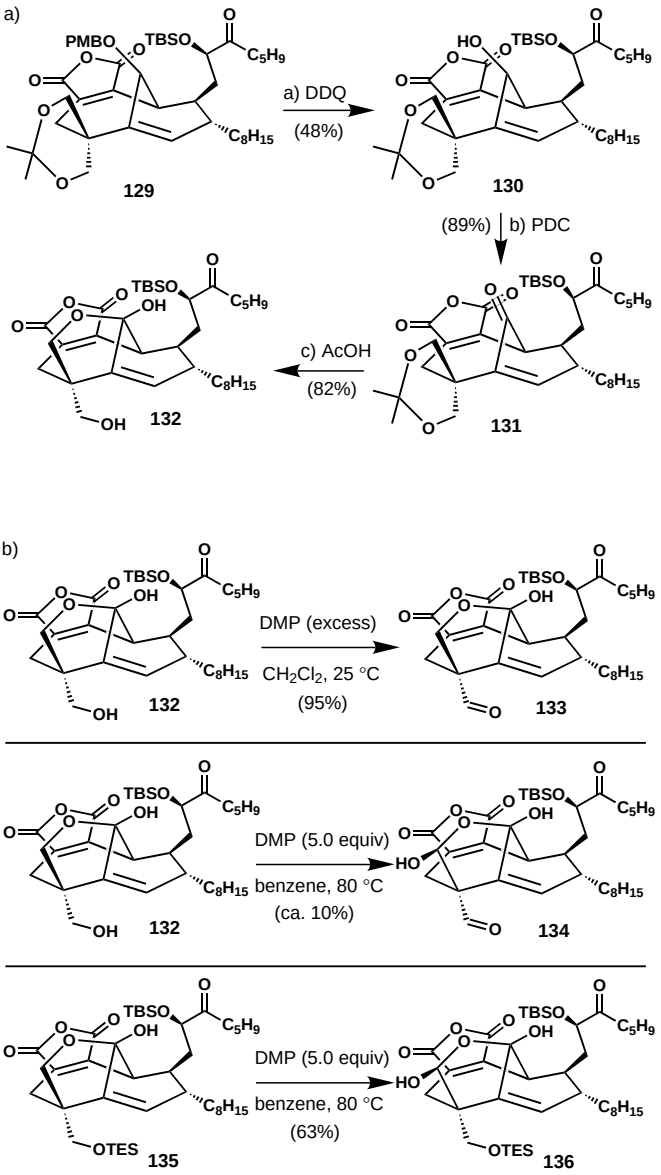


- Several variations of the plan failed because of difficulty in homologation and failure to construct the anhydride moiety after the γ-hydroxylactone

Scheme 20. Summary of selected failed attempts to break through a stalemate.

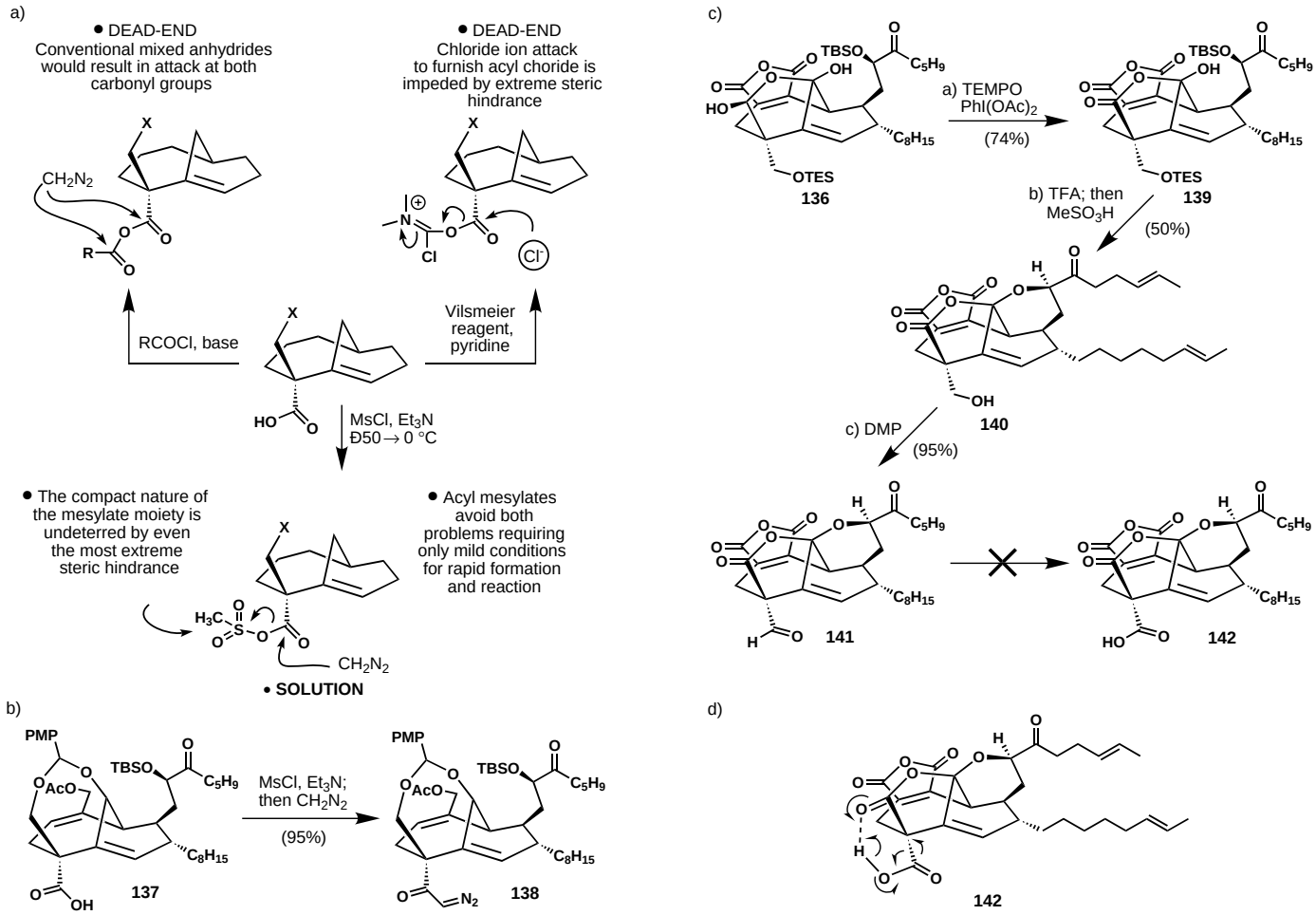
Happily they observed the formation of the desired product, compound **136**, in 63 % yield. That was when I (K.C.N.) heard about their daring escapades with high-temperature DMP oxidations. In retrospect I am, of course, glad that I did not interfere with this part of the expedition which brought us within striking distance of the "Minotaur," the CP molecules.

From the last intermediate (**136**, Scheme 21 b, bottom) all that remained to reach the target molecules was only a few functional group adjustments and a one-carbon homologation of the projected carboxylic acid side chain, or so it seemed.



Scheme 21. a) Synthesis of **132** from **129**. b) Discovery of the DMP-mediated cascade of **135**. Top: excess DMP at ambient temperature oxidizes the primary alcohol but fails to produce any γ-hydroxylactol; middle: DMP at 80°C gives encouraging signs with hydroxylactol **132**; bottom: DMP at 80°C produces γ-hydroxylactol **136** in satisfactory yield from protected lactol **135**.

In anticipation of the upcoming Arndt–Eistert homologation[29] (the last important operation of projected synthesis) we had been simultaneously conducting model studies with relevant systems to streamline the process. We soon realized that the toolbox of known carboxyl-activation methods which were needed in order to access a diazoketone from a carboxylic acid was inadequate for addressing the sterically demanding CP-based systems (Scheme 22 a). Faced with this challenge we resorted to what synthetic chemists have learned they must do in such circumstances: invent a new and improved method. We rationalized that a relatively small reagent such as a sulfene (generated in situ from MsCl and Et_3N) would not only be able to penetrate the steric shield of the CP system and engage the carboxylic acid as an acyl sulfonate, but also that the latter moiety would be at least as



Scheme 22. a) Difficulties in producing the required sterically hindered diazoketone for Arndt–Eistert homologation lead to the consideration of mixed acyl mesylates as candidates for carboxyl activation. b) Demonstration of the principle of the activation of hindered carboxylic acids by mesylation and synthesis of sterically congested diazoketones from mixed acyl mesylates. c) Synthesis of "Christmas compound" **141** and the elusive carboxylic acid **142**. d) Proposed mechanism (most likely radical) for the rapid decomposition of the γ-hydroxylactone-carboxylic acid **142**.

reactive as the corresponding acyl chloride. Thus, on December 14, 1998, the model compound **137** (Scheme 22b) was exposed to MsCl/Et_3N at 0°C for 10 minutes at which point an ethereal solution of CH_2N_2 was added and the resulting mixture was stirred for another 20 minutes at that temperature. To our delight, a clean conversion of **137** into the corresponding diazoketone (**138**, Scheme 22b) was obtained in 95% yield. With an expedient solution to the problem at hand and eager to engage the "Minotaur" in a final battle, we postponed exploration of the scope and generality of this new method until the synthesis was complete (see Section 11.1).

Returning to the total synthesis, the oxidation of γ-hydroxylactone **136** proceeded in the presence of TEMPO/$PhI(OAc)_2$[30] to furnish the γ-hydroxylactone **139** in good yield (Scheme 22c). Acid-induced removal of both silicon protecting groups from **139**, followed by dehydration under the Pfizer conditions[4] led to the formation of the pyran-alcohol system **140**. The excitement was now hard to contain!

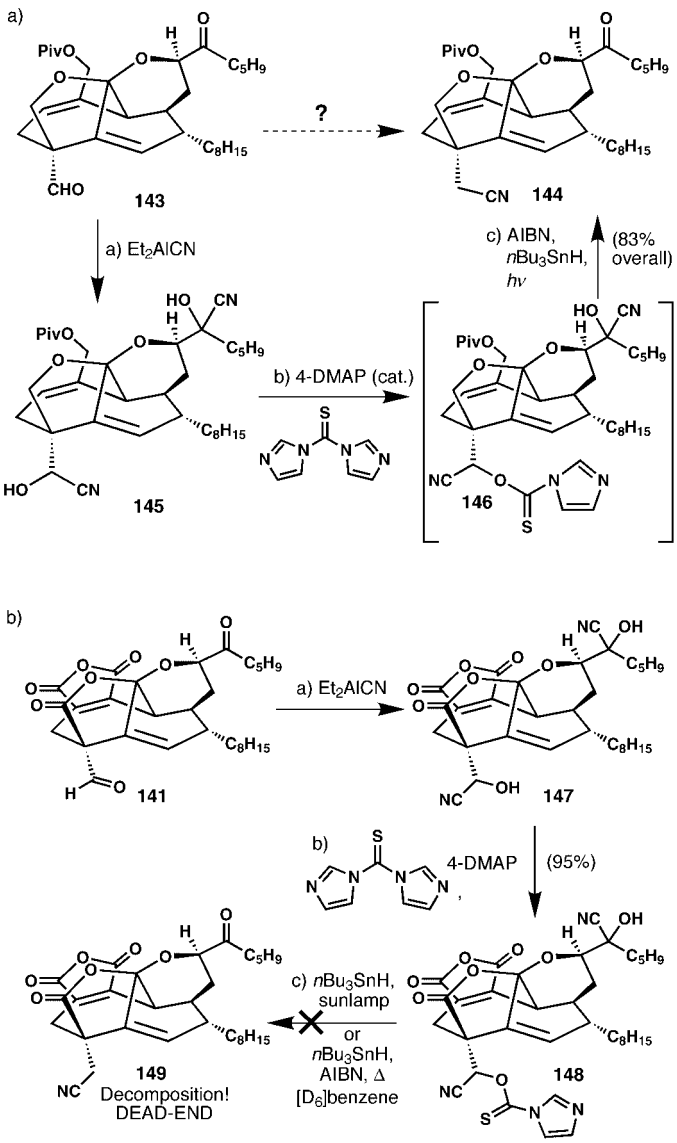
With full confidence that we would soon be finished with the CP molecules (**1** and **2**) at our feet, our plan was to strive for **1** first and then investigate proper protecting groups to access **2**. In fact, we were so sure of our imminent success that we drafted a communication detailing the total synthesis; it was only missing the yield of the last two steps. The "Minotaur" was finally engaged (Figure 5)! Unfortunately, that was not to be, at least not yet! What we expected to be a nice Christmas present turned out to be the agony of defeat. Once again the "Minotaur" proved defiant. Thus, alcohol **140** was converted into aldehyde **141**, the so-called "Christmas compound" (Scheme 22c). This aldehyde seemed to be endowed with a peculiar instability toward oxidation conditions aimed at its conversion into the coveted carboxylic acid (**142**). Even the mildest of methods, such as the $NaClO_2$-based procedure, proved futile and on Christmas eve, 1998, all we had in our hands was an NMR spectrum of what appeared to be a mixture of at least 30 compounds resulting from extensive decomposition. My (K.C.N.) first reaction was to attribute this failure to the "inadequate" experimental skills of my co-workers; after all, I said, "This is a textbook example of the easiest transformations in organic chemistry!" However, despite repeated attempts, including the use of alternative oxidants and trials to trap the carboxylic acid as the methyl ester, we were consistently unsuccessful. I was wrong and I apologized profusely to my very capable co-workers! A possible explanation for this catastrophe is shown in Scheme 22d. An intramolecular hydrogen bond could activate

Figure 5. "Christmas compound" **141**. A final blow at the "Minotaur" misses its mark.

both functional groups involved and lead to a nucleophilic attack or decarboxylation.

Convinced of our inability to secure the desired carboxylic acid **142** by direct oxidation of the aldehyde **141** or through other conventional and disadvantage-laden sequences, we quickly formulated an alternative strategy which required a new method for its implementation. Since aldehyde **141** was relatively stable, why not attempt to homologate it without ever going through the intermediate carboxylic acid, which, after all, was at the root of the problem. A mild method for deoxygenating a cyanohydrin would be sufficient to test this hypothesis and so a model study (Scheme 23a) was designed for this purpose.

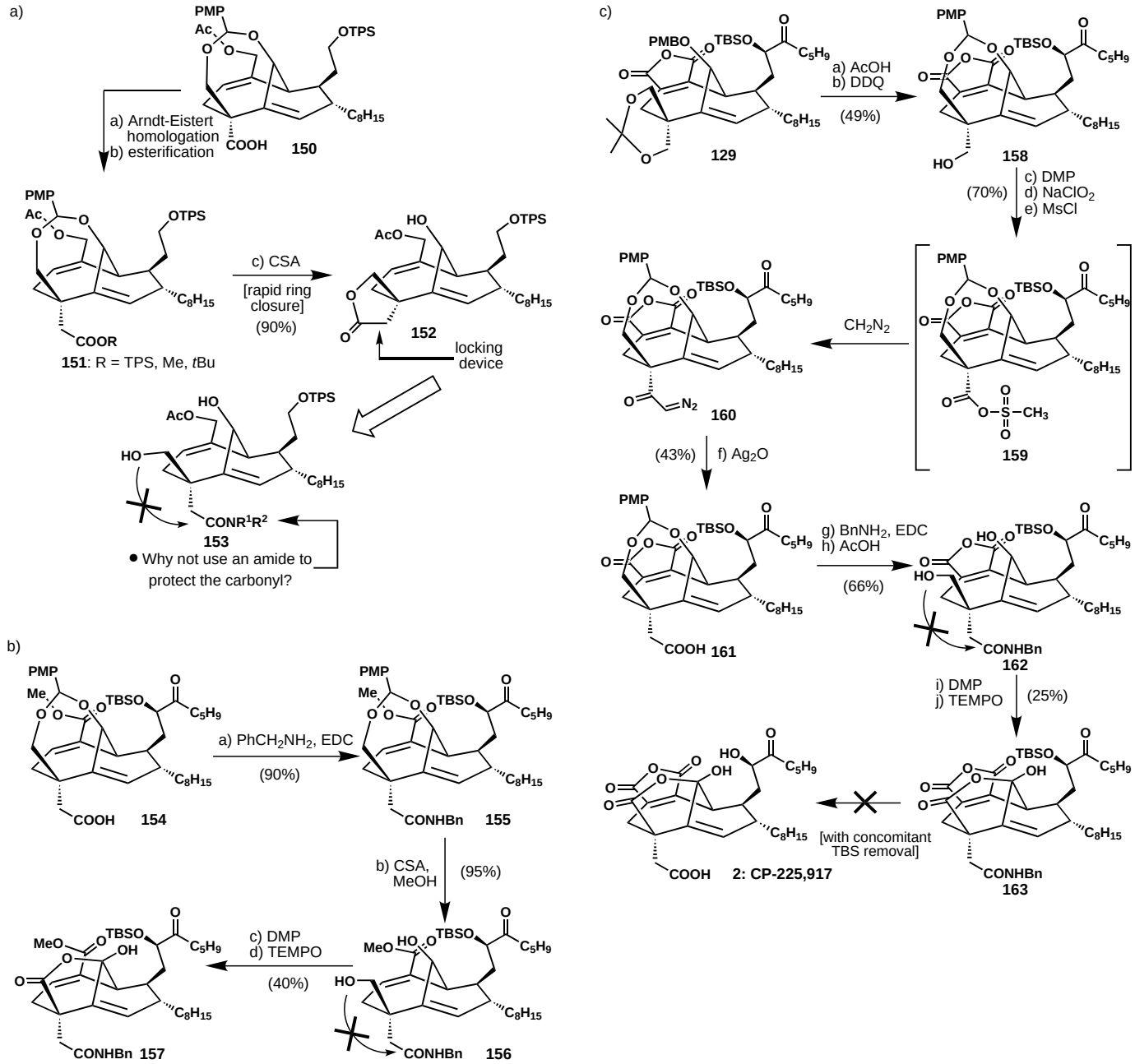
The idea worked beyond our wildest imagination in that not only the cyanohydrin formation/deoxygenation sequence proceeded in excellent overall yield, but the initially interfering ketone functionality was regenerated smoothly during the radical-induced deoxygenation step. Armed with this key information, we rushed to apply the method to the real system, aldehyde **141**, only to be reminded of the lesson that many had learned before us: "model is model, real is real." As shown in Scheme 23b, although the first two steps of the newly developed sequence worked beautifully (**141** → **147** → **148**), the method failed miserably in its final stage and left us confronted with yet another dead end. By then we knew that the maleic anhydride moiety was intolerant of radical chemistry and so we learned to stay away from it in the future. Nevertheless, the experience was rewarding in that it led us to develop a rather general method for the mild homologation of hindered aldehydes in the presence of ketones, as well as providing us with some interesting insights into the reactivity of cyanohydrins and the mechanisms involved. We will return to a description of this methodology later in this article. After a few days of frustrating, last-resort experiments with aldehyde **143**, we decided that it was time for a drastically new approach which we would base on the latest reconnaissance information available.



Scheme 23. a) A successful model study for the one-carbon homologation of aldehydes to nitriles brings new hope for the completion of the CP-molecule total synthesis. b) Failure in the real system: the maleic anhydride moiety proves too sensitive for radical chemistry involved in deoxygenation.

8. The Second Assault at the CP Molecules

With the latest string of failures, most of the CP-team members were rather depressed; some were even convinced that the "beachhead" compound **129** would never lead to the CP molecules. These feelings persisted only for a few days at the beginning of 1999 while we were scrutinizing our problems and contemplating new plans. Upon realizing that homologation would have to precede lactol construction, we proceeded to investigate several esters of the general type **151** (Scheme 24a) which were easily derived from compound



Scheme 24. a) Dead-end locked structures led us to the amide strategy. b) This strategy allowed the 1,4-diol system to be kept open. c) One-step away from the CP molecules: failure to hydrolyze the benzyl amide **163**.

150 by Arndt–Eistert homologation and esterification. The idea was to see whether we could liberate the 1,4-diol system of **151** and construct from it the γ-hydroxylactone. However, as soon as the benzylidine group was removed from such esters, the structure would rapidly collapse into the γ-lactone system **152**. This result was again a dead-end, another "check" by the molecule, for no matter what we tried, this locking device would not open! If a way existed to shield the homologated carboxylic acid function from attack by the nearby primary alcohol, it would certainly solve this problem. Several options were evaluated, including complete reduction of the carboxylic acid group to the corresponding alcohol followed by protection, as well as a number of other homologation protocols. All of these options either added significantly to the length of the synthesis or were plagued by low yields relative to the venerable Arndt–Eistert homologation sequence. In the midst of this chaos when everyone was following their own intuition, I (K.C.N.) approached Phil and asked what strategy he was following. "I have an idea," he said. "It's simple." What he had in mind was the use of an amide as a protecting group for the carboxylic acid—a much less reactive functionality than an ester and, therefore, one that would, hopefully, restrain the structure of the 1,4-diol into an open form.

Since there was precedent for mild activation and cleavage of benzyl amides[31] we targeted first the 1,4-diol system **156**. Within 24 hours of its conception, Phil and Zhong demonstrated the viability of this strategy with the synthesis, on

February 8, 1999, of model benzyl amide γ-hydroxylactone **157** as shown in Scheme 24b. With this success, a great new hope was given to the team and the project had a new lease on life. Efforts began in earnest to construct the real system **163** (Scheme 24c). Within a week the team had reached this new "beachhead" starting from advanced key intermediate **129** following the route shown in Scheme 24c. With 30 mg of benzylamide **162**, we felt confident that we would soon arrive at the CP molecules. Our excitement was heightened even further when we successfully arrived at compound **163** and secured conditions to remove the benzylamide group from appropriate CP model systems. Only a single step was now separating us from the Minotaur. However, once again he deftly evaded our sword, cleverly maneuvering his way out of its path (Figure 6). The fragility of the intact CP molecule was simply too much for any hydrolysis conditions to succeed and we were left in "check" once again, with only a protected form of CP-225,917 (**2**). Further strategies and tactics were needed to continue the campaign.

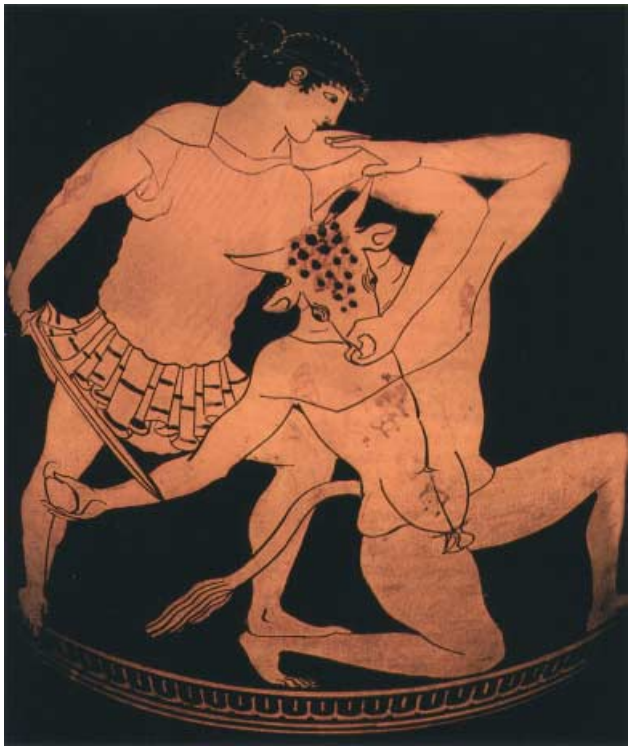


Figure 6. Final dashes at the Minotaur (benzylamide **162** and heterocycle **208**) are thwarted by unanticipated maneuvers by the monster.

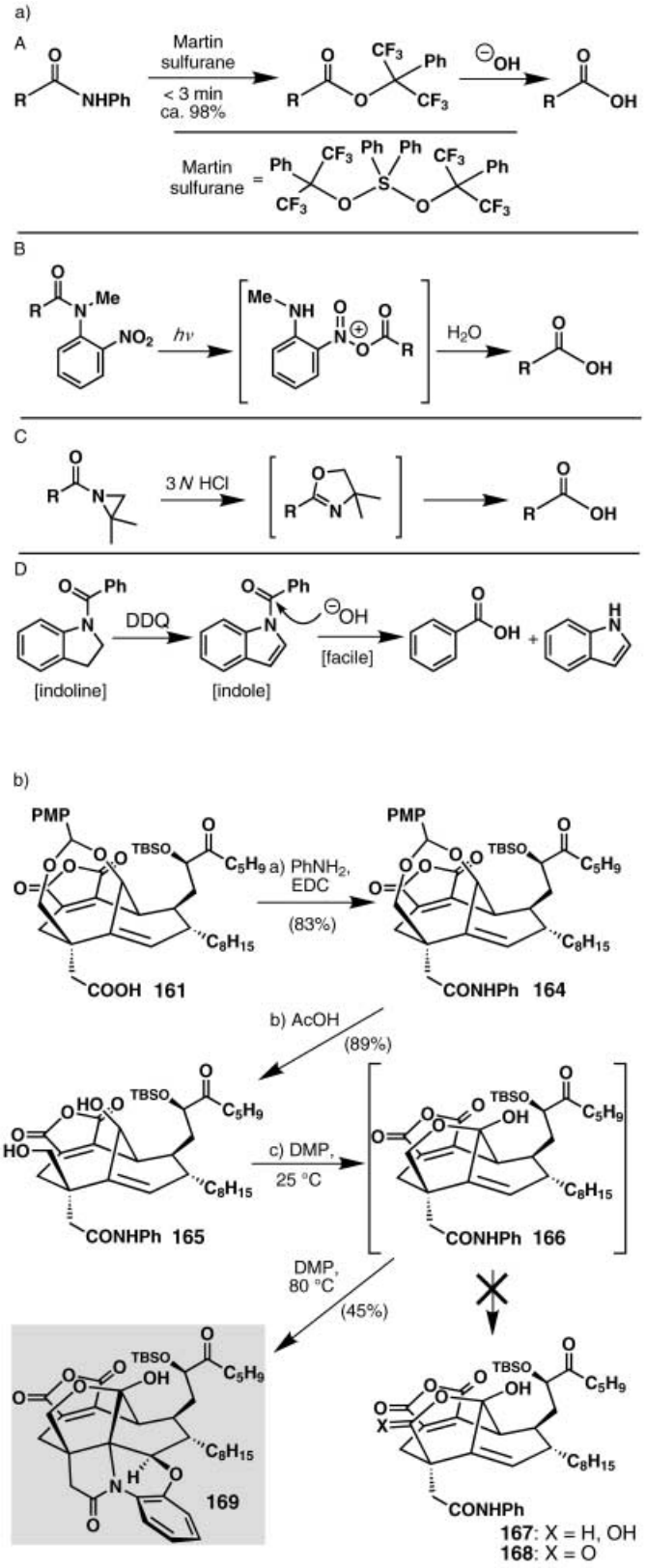
A thorough literature search led to a number of other possible amides[32–35] as alternatives for what we had in mind (Scheme 25a). We first investigated the aniline amide (anilide) since the conditions reported by Martin and Franz[32] for its cleavage were remarkably mild. As shown in Scheme 25b, we arrived at the anilide-diol **165** in short order, and upon treatment of the latter compound with DMP we isolated a compound with polarity (TLC) and HRMS data that were consistent with those expected for the γ-hydroxylactone **168** (oxidation of **167**, Scheme 25b)! Analysis of the ^{1}H NMR spectrum of this product, however, raised serious doubts, since not only was the bridgehead olefinic proton missing but there seemed to be one extra proton. After scaling up the reaction, we were able to obtain clean ^{1}H and ^{13}C NMR spectra which definitely led us to conclude that we did not have anything resembling lactone **168**. The Minotaur remained unscathed once again (Figure 6)! What, however, was the structure of this strange compound? After several 2D NMR experiments and careful mechanistic reasoning we finally secured the structure of the "mystery compound" as the remarkable polycycle **169**. Was this the Minotaur's hidden treasure, or simply another road block? Either way, it did not help us at the time and we decided to put this strange discovery on the shelf (but not under the carpet!) until after the total synthesis was complete. Even more disheartening were the failures shown in Scheme 25c, which cast further doubt on the wisdom of the amide strategy and its potential for success.

Early one morning, after another failure, I (K.C.N.) called Phil to my office, sat him down and said, "This project is always in shambles, and it is very painful to everyone. I think we should cut our losses and just forget about the CP molecules. I would not think any less of you if you stop now." Phil's eyes widened and he immediately declared, "Impossible, I will never stop until CP has fallen and I know Zhong feels the same way. This is what a PhD is all about, isn't it?" "OK, good, you passed the test. Now you can go back to work…"

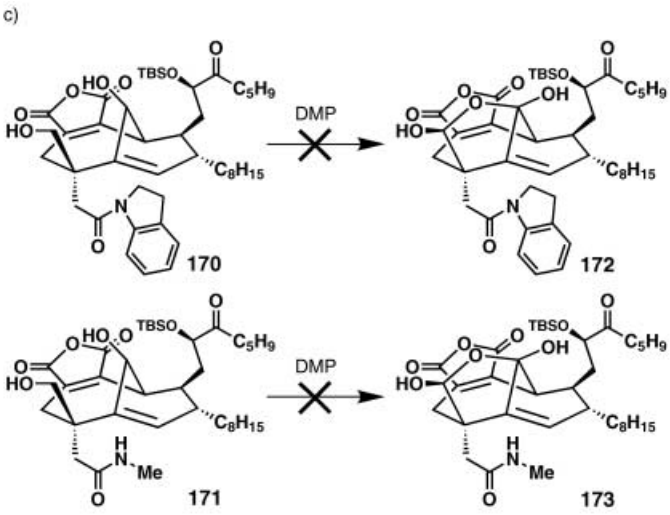
9. Third and Final Assault on the CP Molecules

It was now the beginning of March, 1999, and we were desperately searching for a new strategy. Before another retrosynthetic analysis could be drafted, however, we needed answers to a number of strategic questions as shown in Scheme 26. Since we realized that the DMP cascade to construct the γ-hydroxylactone moiety would have to precede homologation of the carboxylic acid side chain, our concerns now focused on suitable protecting groups for lactol **136** (Scheme 26). After experimenting with a variety of different protecting groups for about a week we realized that it was not such a straightforward proposition, and we were sent back to the drawing board for yet another re-evaluation by the very failures of such strategies (some explorations in that direction that ended in dead-ends are shown in Scheme 26). In the meantime, we dispatched a communication to *Organic Letters* detailing our explorations in the CP project leading to an advanced model compound, but we did not mention the revised protocol for γ-hydroxylactone construction involving DMP at high temperatures.[27] At this juncture, we had no idea that we would confront the Minotaur and conquer the CP labyrinth in only a couple of weeks!

The key insight which led us out of the maze was hidden within the structure of one of the CP molecules itself. Suddenly we came to realize that, perhaps, nature herself had been giving us a clue on how to answer our protecting-group problems all along! Throughout the campaign we had observed that CP structures in the open lactol form (CP-225,917, **2**) were less stable on silica gel and to most reaction conditions than the corresponding closed pyran derivatives (CP-263,114, **1**). Therefore, we targeted the easily accessible and less-fragile "closed" lactol **177** for synthesis (Scheme 26).



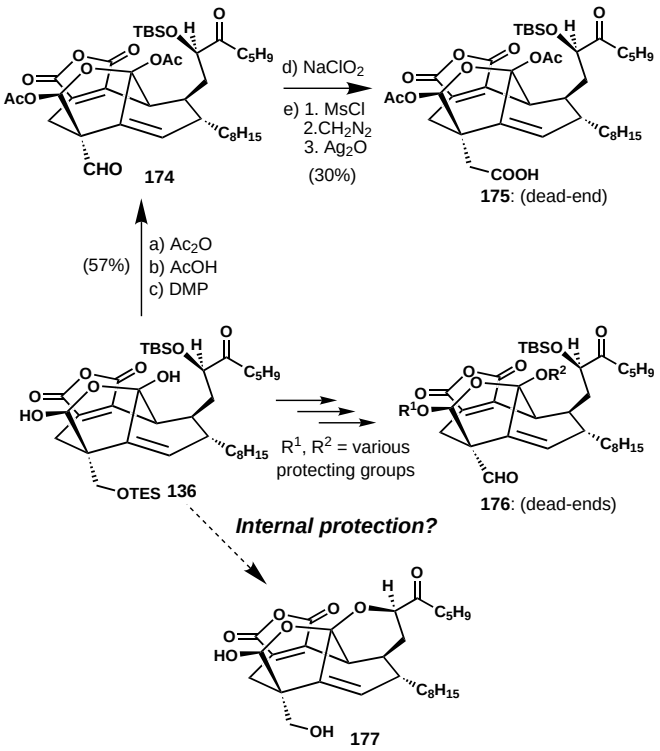
Scheme 25. a) Alternative amide-based protection strategies which were evaluated: A) use of Martin sulfurane for the conversion of anilides into esters and carboxylic acids;[32] B) a photolabile amide group;[33] C) the Meyer's aziridine ring-expansion method;[34] and D) Barton's "latent" heteroaromaticity principle for the protection/deprotection of carboxylic acids.[35] b) Another roadblock or a hidden treasure? Serendipitous isolation of the unusual polycycle **169**. c) Additional failures of the amide strategy led to re-evaluation of the plans.



The clear risk associated with this strategy was that we would, most likely, only be able to access CP-263,114 (**1**), since the conversion of **1** into **2** was not known at that time.

Nevertheless, we proceeded forward thinking that, after all, accessing one of the CP molecules would be better than none at all! The final retrosynthesis was drafted as shown in Scheme 27a. Thus, based on all our intelligence gathering we projected CP-263,114 (**1**) arising from indoline derivative **178** (see Scheme 25a D for the rationale), whose origins were traced back to compounds **177** and **136**. We began, starting in late March 1999, working at a furious pace towards the implementation of the new plan. During this period, I (K.C.N.) would often find Zhong and Phil either fast asleep in the mornings or working in eight-hour shifts exchanging material back and forth. As one rested, the other worked; my contribution was to bring them occasional sustenance in the form of sandwiches in the lab! The drive to the indoline amide **185** is depicted in Scheme 27b. A key discovery occurred when we submitted lactol **177** to a DMP oxidation in dichloromethane, and upon workup we isolated the desired product **179** along with a substantial amount of the ill-fated "Christmas compound" **141**. Although we clearly had no use for the latter compound (**141**) its isolation indicated to us that the hydroxy compound **179** was behaving as a normal lactol, and thus we would not have to employ TEMPO (see Section 6) in the late stage of the synthesis to convert it into the desired lactone. The latter oxidant, although mild, is not as easy to handle, while DMP and its by-products are rather conveniently removed upon completion of the reaction. Capitalizing on our previous observations with DMP, we then proceeded to employ benzene as solvent instead of dichloromethane in an effort to "tame" its reactivity and permit the isolation of lactol **179** as the major product and thus avoid the extraneous, albeit informative, lactone **141**.

In the days approaching the synthesis of the indoline **185** we were all camped out in the laboratory with great expectations. We eagerly anticipated the synthesis of this compound (**185**) since we had prepared an authentic sample from natural CP-263,114 (**1**) (Scheme 27c). Identical samples would give us the



Scheme 26. The evolution of the internal protection strategy.

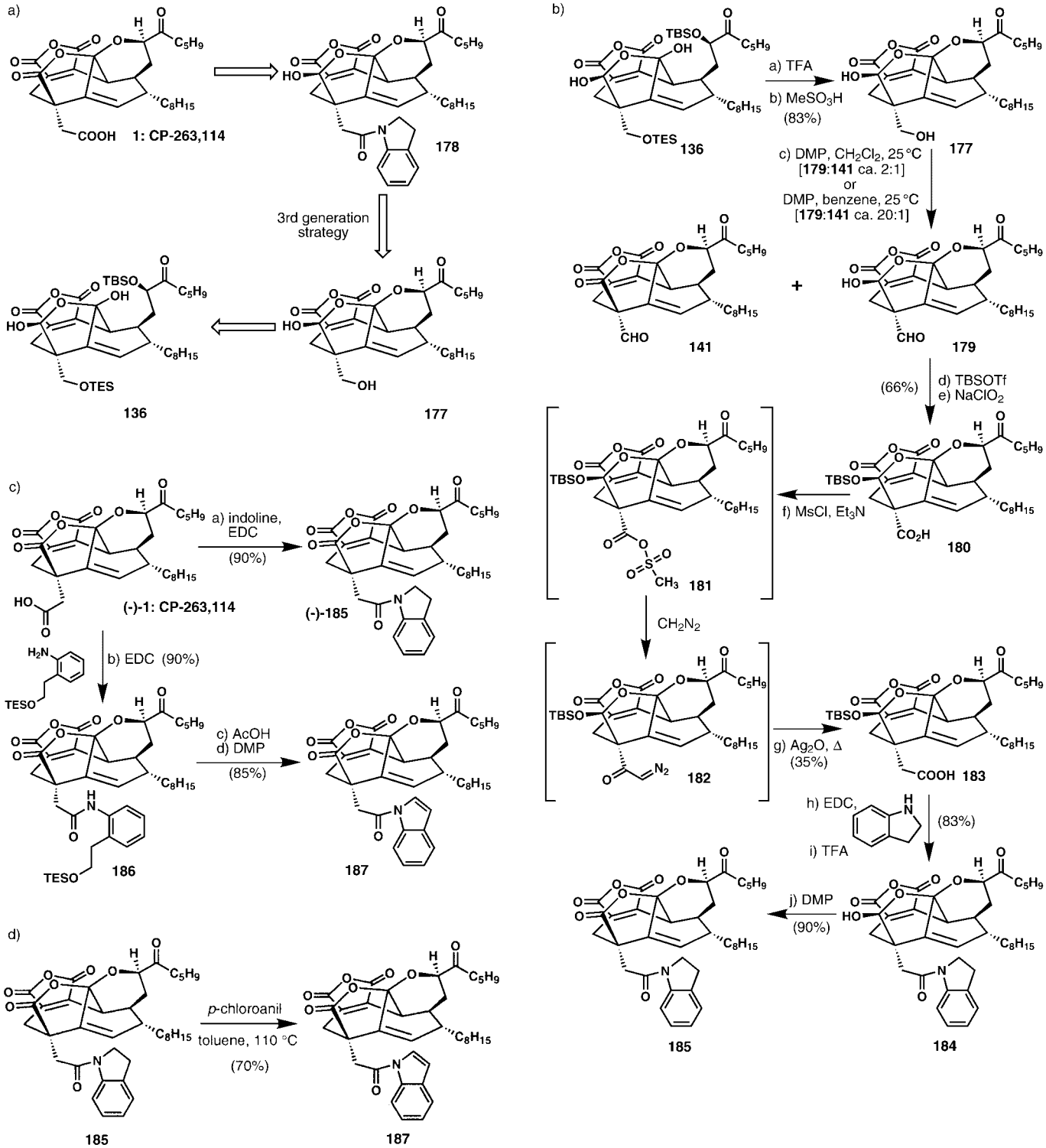
Figure 7. Synthetic indoline amide **185** matches a naturally derived sample (**185**). The deadly wounded Minotaur is falling![71]

first indication that the total synthesis was in sight, and that the Pfizer structural assignment,[4] based on NMR spectroscopy alone, was correct. At 8:30 pm on April 7, 1999, the CP team dragged me (K.C.N.) down to the first floor of the Beckman building in front of the NMR instrument. "You have to see this," said Phil with a big smile on his face. "This had better be good," I said as we were riding the elevator en route to the NMR room. On the screen were two spectra side by side; the upper spectrum was that of the naturally derived while the lower spectrum reflected the signals of a 1:1 mixture of synthetic indoline lactol **184** and indoline lactone **185**. Although that final reaction was performed only on a 100 μg scale and the NMR spectrum showed a 1:1 mixture of starting material and product, it was clear from the spectra and from TLC and HPLC analysis that synthetic **185** was identical to naturally derived **185**! The Minotaur was, this time, not only sighted in the still misty horizon (see Figure 3) but, as it turned out, fatally wounded (see bleeding Minotaur, Figure 7).

But there was still much more work to be completed before we could declare victory. We immediately began a barrage of model studies focusing on the key oxidative conversion of the indoline to its indole counterpart. Simultaneously, we prepared the authentic indole (**187**) from the natural product (CP-263,114, **1**) for comparison purposes. After about 30 hours of continuous searching, we identified *p*-chloroanil as the most mild and likely candidate for the key conversion of **185** into **187**. With more of the synthetic indoline **185** in hand, we set up the reaction in refluxing toluene using excess *p*-chloroanil and to our delight we obtained the coveted synthetic indole **187** (Scheme 27 d) which was identical to that prepared from the natural product (Scheme 27 c).

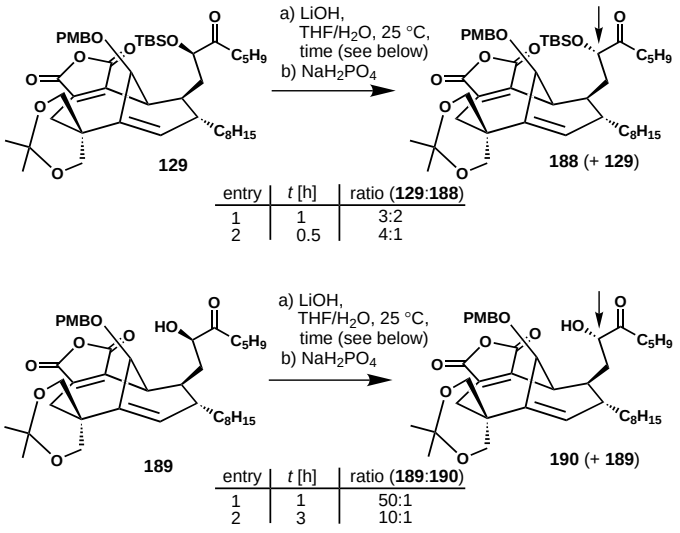
It was April 10, 1999, and we were poised to complete the total synthesis. Only one step remained: hydrolysis of the indole moiety. We reasoned that LiOH would be the most appropriate reagent to accomplish this transformation by virtue of its mild nature and unique solubility and nucleophilicity. Before attempting the reaction with the precious sample of synthetic indole **187**, we decided to conduct a number of model studies. These rather simple experiments, whose primary aim was to probe the stability of the maleic anhydride and hydroxy ketone moieties, turned out to be surprisingly informative. There were several issues which needed to be addressed concerning the treatment of these compounds with base, namely: 1) to what extent, if any, would epimerization of the carefully installed C-7 center take place?; 2) would destructive enolization of the α-hydroxy ketone occur to give a mixture of regioisomeric hydroxy ketones?; and 3) how would the fragile maleic anhydride moiety hold up to the basic conditions? To our dismay we found that treatment of the advanced key intermediate **129** with LiOH (10 equiv) in THF/water followed by workup with NaH_2PO_4 led to a 3:2 mixture of C-7 epimers (**129**:**188**) as observed by ^{1}H NMR spectroscopy after only 1 h of exposure (Scheme 28). Halting the reaction after 30 minutes afforded a 4:1 mixture of epimers, the major of which was still **129**. As troubling as this result was, it was likely to get worse we thought, for in the real system we would also be faced with the potentially destructive isomerization of the α-hydroxy ketone system. With these issues in mind, we submitted the hydroxy ketone **189** to the same conditions (LiOH, 10 equiv, THF/water; then workup with NaH_2PO_4), and much to our delight found that the α-hydroxy ketone system was still intact with almost no epimerization (>50:1 **189**:**190** by ^{1}H NMR spectroscopy) after 1 h. After 3 h the ratio was still a remarkable 10:1 in favor of **189**.

Based on these reassuring model studies, we next proceeded to test the robustness of CP-263,114 (**1**) itself under the



Scheme 27. a) Third generation retrosynthetic analysis of the CP molecules (**1** and **2**). b) Synthesis of indoline amide **185**. c) Synthesis of **185** and **187** from the natural product **1**. d) Synthesis of **187** from **185** through the action of *p*-chloroanil.

basic conditions of the projected final hydrolysis step. Although we were optimistic about the result of this experiment, we were not fully prepared for its outcome. The starting CP molecule (**1**) did not survive the reaction conditions at all, being rapidly transformed to its sister CP molecule (**2**)! Pleasingly the C-7 stereocenter of the CP structure remained intact. Furthermore, since a method existed for the conversion of **2** into **1**, we immediately realized that this time, perhaps, we had the "Gods" on our side (just as Theseus had in his battle against the Minotaur) in our final assault against the dreaded Minotaur. Before we tell, however, the final tale, we must draw attention to the fascinating mechanistic underpinnings of this interesting base-induced transformation of CP-263,114 (**1**) to CP-225,917 (**2**) as shown in Scheme 29a. This operation commencing with **1** represents a unique cascade reaction sequence since it accomplishes



Scheme 28. Model studies before the final LiOH hydrolysis of the indole derivative to CP-225,917 (**2**).

temporary masking of the maleic anhydride (as its dianion), basic opening of the γ-hydroxylactone, deprotonation of the C-29 carboxylic acid, and reconstitution of **2** upon acidic quench.

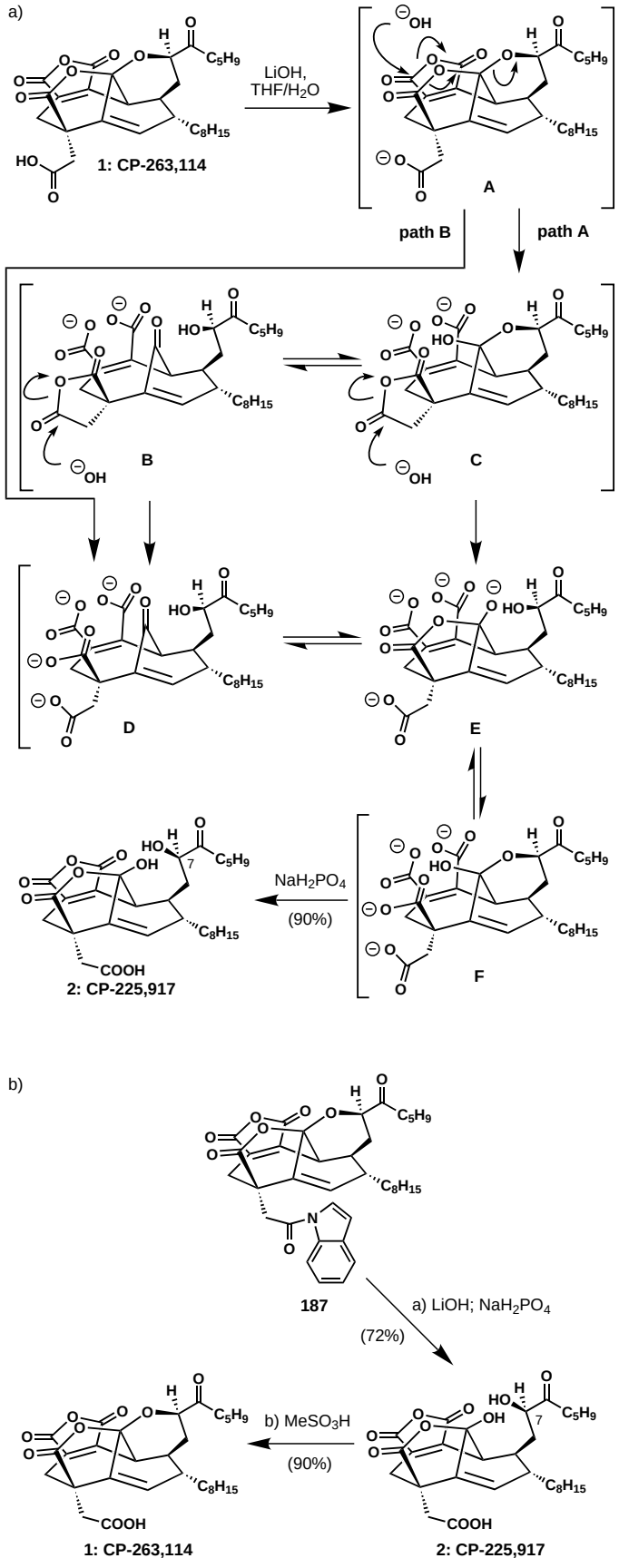
Having practiced the final act, with all the necessary preparations complete, we sharpened our sword and engaged with the Minotaur for the last time. The final reaction was set up at 1:00 a.m. on April 12, 1999.A few hours later it was done (Scheme 29b)! I (K.C.N.) was to learn of the athlos upon my arrival in the lab at 8:00 a.m. that day. Needless to say, pure adrenaline kept Phil and Zhong awake past the successful isolation of CP-225,917 (**2**) and its subsequent conversion into CP-263,114 (**1**).

Within 24 hours of that final blow, two communications were dispatched to *Angewandte Chemie*.[5a,b] The triumphant team is shown in Figure 8b celebrating their accomplishment with smiles and grins.

Frequently in the endeavors of total synthesis, arrival at the target molecule marks the final act, but not in this case, for it was clear that we had struck gold on several occasions during our journey to the center of the labyrinth. It was time to consolidate the gains made during the campaign and to fully exploit the many inventions and discoveries found during this campaign. In the next sections we will discuss some of these exploits and new synthetic technologies, beginning with the establishment of the absolute configuration of the CP molecules by asymmetric synthesis.

10. Asymmetric Synthesis of CP Molecules

Attempts by ourselves and others to crystallize naturally derived heavy-atom derivatives of the CP molecules to decipher their absolute configuration by X-ray crystallographic analysis had been thwarted by the inability to grow suitably ordered crystals. Therefore, we turned our attention



Scheme 29. a) Conversion of CP-263,114 (**1**) into CP-225,917 (**2**). The remarkable LiOH cascade hydrolysis and postulated mechanistic underpinnings. b) April 12, 1999: The total synthesis of the CP molecules (**1** and **2**) is complete.

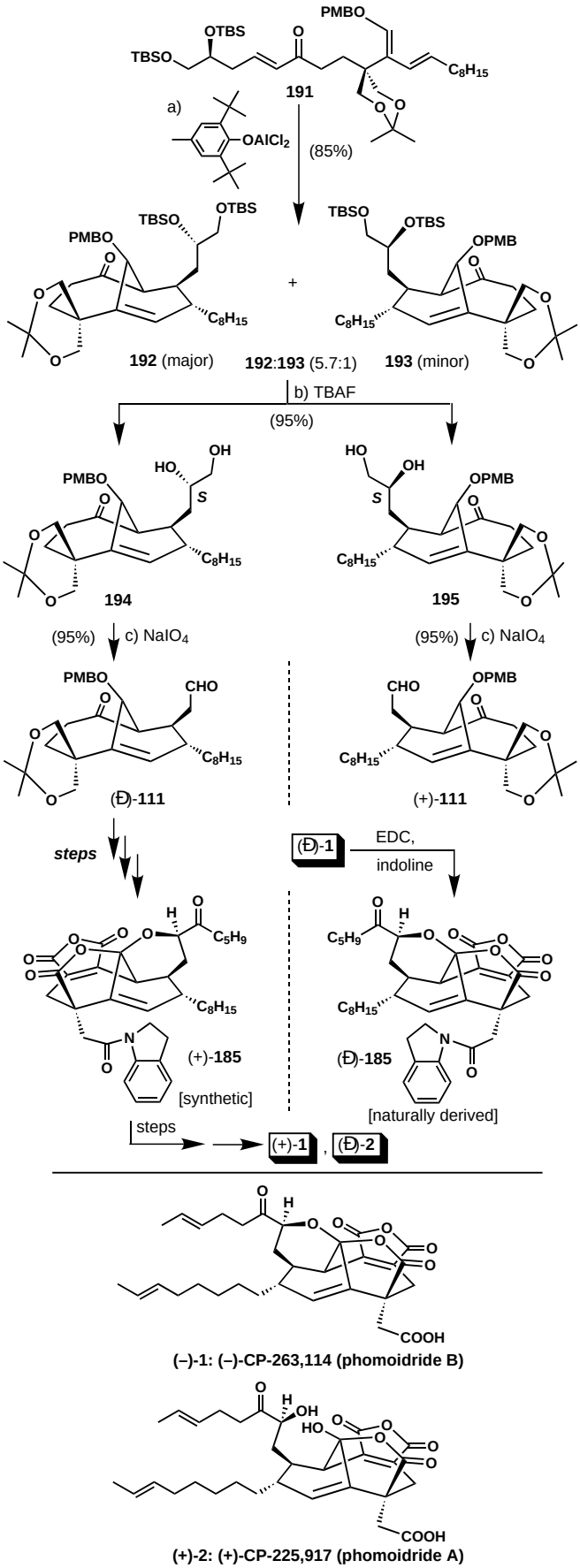
Figure 8. Top: left: In front of the "CP battlefield", K. C. Nicolaou (left) and Phil S. Baran (right); right: Conquest outside the lab, Phil S. Baran (left) and Yong-Li Zhong (right). Bottom: The triumphant "CP team" shortly after the completion of the feat (from left to right): Ha-Soon Choi, Won-Hyung Yoon, Kin Chiu Fong, Yong-Li Zhong, Phil S. Baran, and Yun He. K. C. Nicolaou is seated.

to determining the absolute configuration of these compounds through chemical synthesis. Our asymmetric total synthesis of the CP molecules, which served to establish their absolute configuration, is summarized in Scheme 30.[5c] The hallmark of this strategy is the combined use of substrate- and reagent-based control of stereoselectivity.

Shortly after this disclosure, three additional syntheses of the CP molecules appeared from the Shair,[36] Fukuyama,[37] and Danishefsky[28] groups. All three of these syntheses were elegantly conceived and masterfully executed. The syntheses by the groups of Shair[36] and Fukuyama[37] also confirmed our absolute configuration assignments.

11. Mining the Gold: Discovery and Invention of New Synthetic Technologies

After traversing the CP-synthetic labyrinth and having marked the points of interest, we set forth to investigate the scope, generality, and mechanistic aspects of the various designed and discovered reactions. These explorations snowballed, for as we garnered mechanistic insights we were able to move to the next step by designing further strategies and

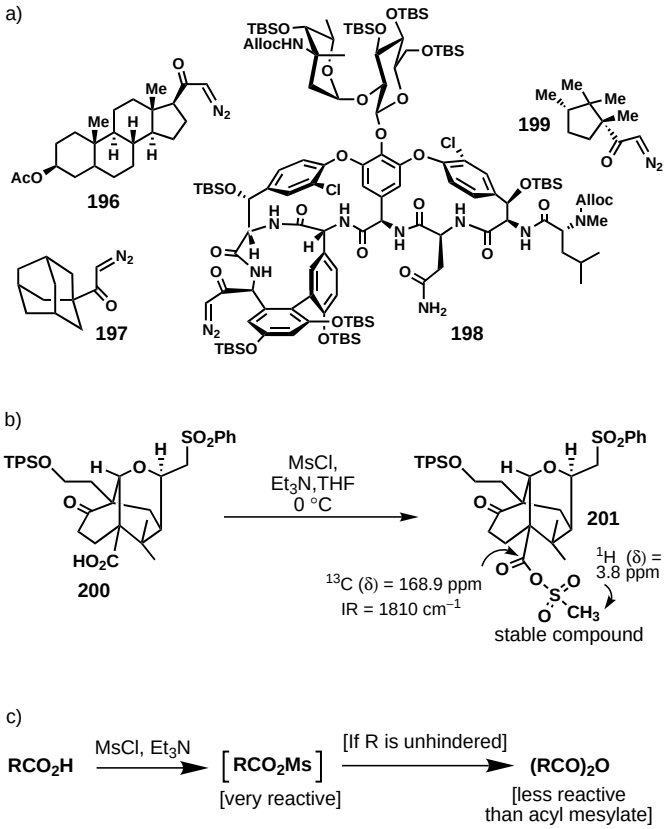


Scheme 30. Asymmetric total synthesis of the CP molecules (top) and assignment of their absolute configuration (bottom).

processes and by calling upon old reagents to perform new reactions. In the following sections we discuss, in approximate chronological order, the synthetic technologies developed during these investigations.

11.1. Acyl Mesylates and the Synthesis of Sterically Hindered Diazoketones

The use of acyl mesylates as novel acyl chloride surrogates for highly hindered carboxylic acids as mentioned above (Scheme 22b) was aptly demonstrated by the synthesis of a variety of hindered ketones (Scheme 31a) on molecular



Scheme 31. a) Examples of hindered diazoketones prepared by the acyl mesylate technology. b) First isolation and characterization of an acyl mesylate (**201**). c) Carbonyl activation, particularly useful in sterically hindered systems.

scaffolds of numerous types, including steroids (**196**) and the vancomycin family of antibiotics (**198**).[38] In addition, we were able to isolate the first stable acyl mesylate (**201**), enabling a full elucidation of the physical properties for this chemical entity (Scheme 31b).[38] These studies also shed light on the unexplored chemistry of these highly reactive species (shown in generalized format in Scheme 31c), indicating the differential products that one can expect based on the nature of the molecule onto which this reactive group is attached.[38]

11.2. Homologation of Sterically Hindered Aldehydes via Cyanohydrin Formation

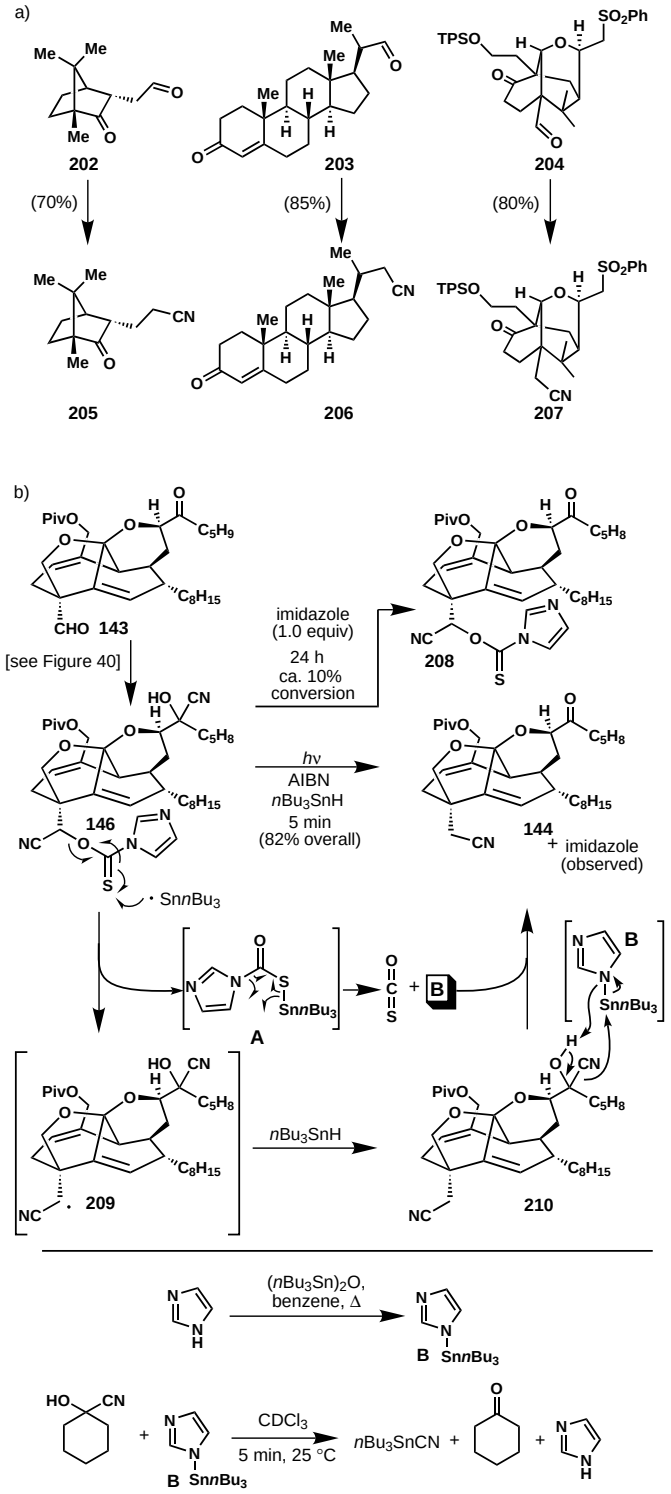
Our struggle to add one carbon to the "Christmas compound" **141**, led to the development of a novel strategy for the homologation of sterically hindered aldehydes even in the presence of ketones and other electrophilic functionalities as mentioned earlier in the context of Scheme 23a. After demonstrating the generality and scope of the process (Scheme 32a for selected examples in substrate classes of historical significance)[39] we also conducted experiments to confirm the unique mechanism by which it operates (Scheme 32b), providing validation of the specific role played by each reagent in the process, as well as insight into the reactivity of cyanohydrins and their potential use as masking devices for ketones.[39]

11.3. The DMP- and IBX-Cascade Reactions for the Synthesis of Heterocycles from Anilides, Urethanes and Ureas

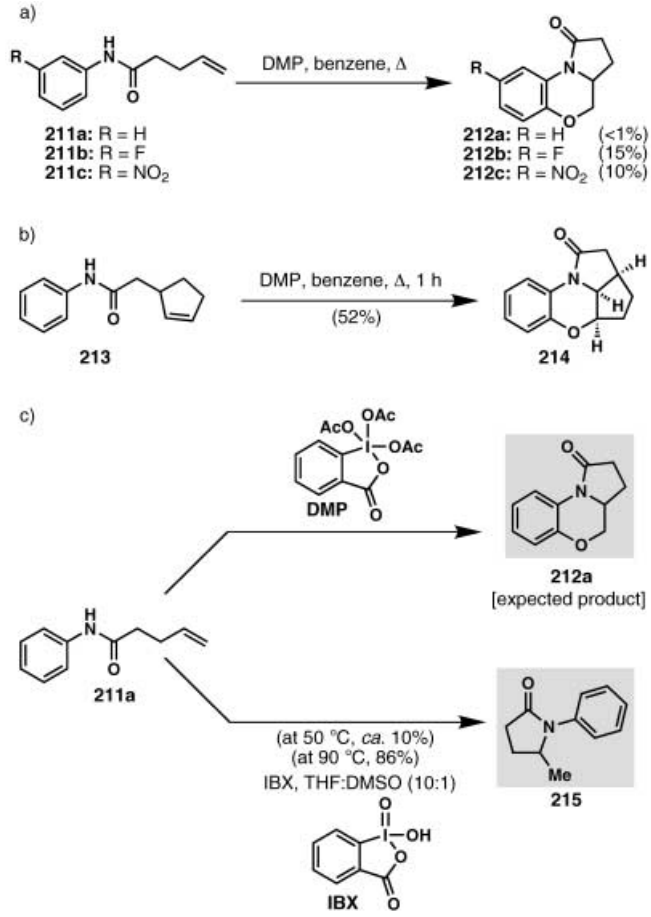
The intrigue of the unexpected reaction of DMP with substrate **166** producing the unusual heterocycle **169** (see, Scheme 25b) soon sent us out on an expedition to investigate it further. What was the mechanism of this unprecedented transformation, its prerequisites, scope and generality? Having suspected that the essential requirement for the substrate in this reaction were the anilide and olefinic functionalities, we focused on such substrates. Our first explorations were disappointing and gave only very low yields of the desired products (Scheme 33a). We reasoned that embedding the olefin portion in a ring system might boost the efficiency of the reaction due to reduced conformational freedom and increased electron density. Indeed, this modification proved to be crucial for accessing complex polycyclic systems in synthetically useful yields (Scheme 33b).

Simultaneously we investigated how the precursor to DMP, IBX (2-iodoxybenzoic acid), might react with such anilides. Perhaps these examples would furnish the same polycycles more efficiently. THF:DMSO (10:1), rather than benzene, was employed as a solvent due to solubility considerations and by analogy to alcohol oxidations performed with IBX. When we conducted the reaction at 50°C with the simple substrate **211a**, instead of forming the polycycle **212a**, we isolated the γ-lactam **215** in 10% yield (Scheme 33c). Upon increasing the reaction temperature to 90°C, remarkably efficient conversion to **215** was observed. In fact, this result was initially received with considerable skepticism by one us (KCN). Could it be that inadequate experimental technique led to this bizarre finding or had we discovered another unique reaction? And how is it that no one had ever reported such reactions with iodine(v)-based reagents or hypervalent iodine compounds in general? It was time to consider this issue from a more global perspective.

Scheme 34a depicts a sampling of iodine(III) and (v)-based reagents. While the chemistry of iodine(III)-based reagents has been extensively explored, iodine (v)-based reagents have been mainly relegated to the realm of alcohol oxidation and a



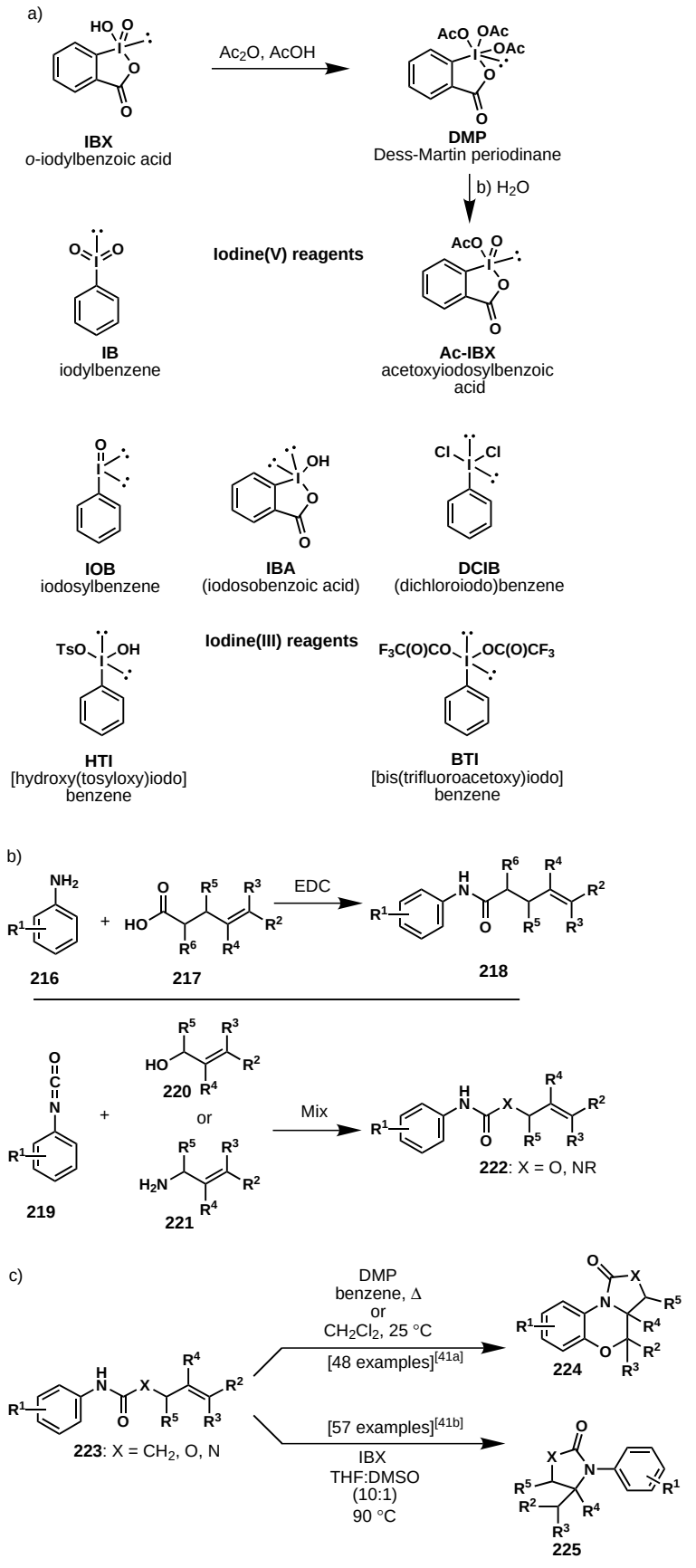
Scheme 32. a) Examples of selective homologation of ketoaldehydes using the cyanohydrin technology. b) Mechanistic aspects of the cyanohydrin-based homologation of sterically hindered aldehydes in the presence of ketones.



Scheme 33. a) First attempts to construct polycycles using DMP prove disappointing. b) Using more substituted olefins in the DMP cascade led to synthetically useful yields of heterocycles. c) Discovery of the IBX-cyclization reaction.

number of closely related processes. For instance, in Varvoglis' 223 page treatise[40] on hypervalent iodine reagents, only 10 pages are dedicated to the reactions of iodine(v)-based reagents (5 pages deal with alcohol oxidations and 5 pages deal with the use of these reagents as co-oxidants in selenium- and vanadium-catalyzed reactions); the remainder focuses on the more popular iodine(III)-manifold. Therefore, we proceeded to rapidly explore the scope and generality of these transformations to determine whether they were simply anomalies or more desirably, useful synthetic transformations.

Since the starting materials for DMP- and IBX-cyclizations were the same, we were able to evaluate the utility of both reactions in parallel. The library of anilides to be used as substrates was rapidly expanded by utilizing a series of simple building blocks as shown in Scheme 34b. We quickly and firmly established the structural parameters required for the reactions to proceed, namely the presence of an anilide moiety and an olefinic system in close proximity. We suspected, however, that the reaction could be extended into the realm of olefinic urethanes and ureas. Indeed, both the DMP- and IBX-cyclizations could be expanded to furnish diverse heterocycles using urethanes and ureas as starting materials (Scheme 34b and c). It took a few days before we realized the potential of the gold mine that we had unearthed![41] Because of the excitement which was generated from these discoveries our initial forays into this new territory were not entirely focused and we often went back and forth between studying new reactions of DMP and IBX, always having as our guide mechanistic hypotheses. We will attempt to recount these discoveries in the correct chronological order



Scheme 34. a) Selected hypervalent iodine (III and V) reagents and their relationships. b) The simple preparation of starting amide scaffolds (top) was then extended to the diverse and commercially available phenyl isocyanates and allylic alcohols/amines (bottom). c) General formulas for the remarkably general DMP and IBX reactions.

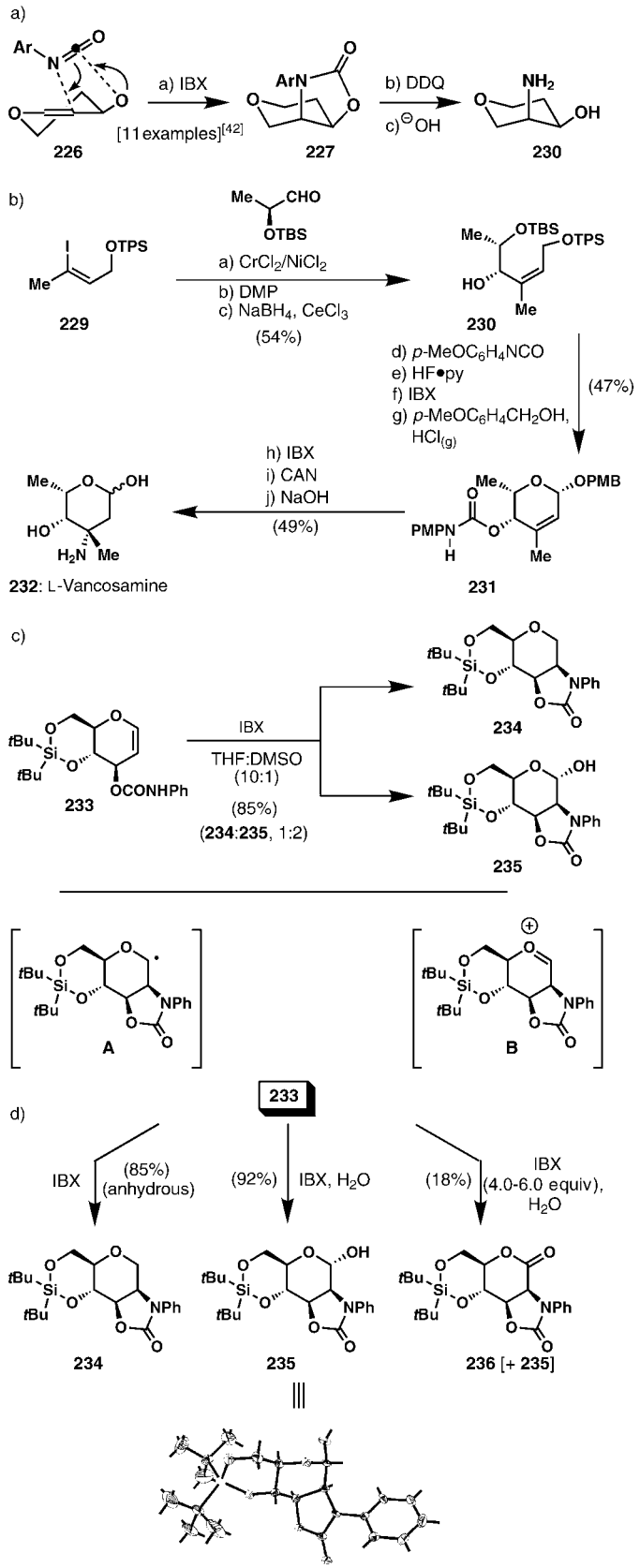
and, thus, we will return to the DMP-cyclization and its mechanism later on; for now we were intrigued by the IBX-cyclization.

11.4. IBX-Mediated Synthesis of Amino Sugars

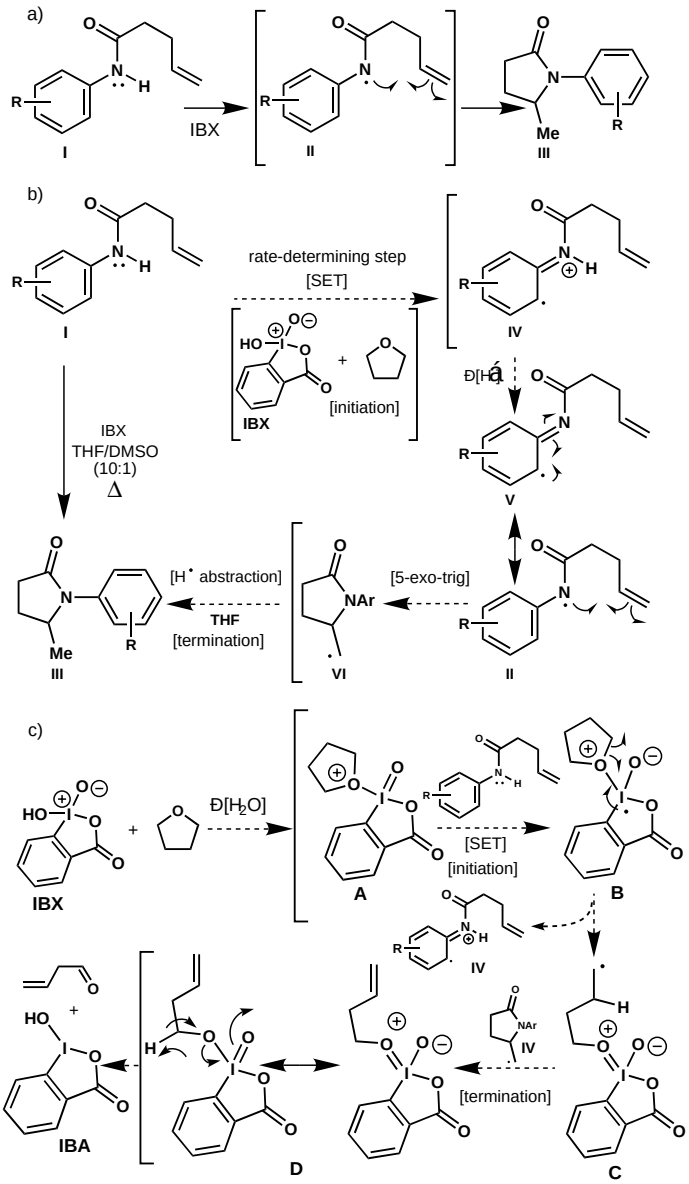
The efficiency with which a latent *cis*-1,2-amino alcohol functionality could be generated from an allylic alcohol by the newly discovered IBX reaction inspired us to investigate this process in the context of carbohydrate scaffolds (Scheme 35a). The expedient preparation of amino sugars and analogues thereof is a worthy synthetic goal since these compounds represent an important class of biologically active molecules. Thus, we were able to access a number of such amino sugars in high yield with complete stereocontrol by using the removable *p*-methoxyphenyl group on the nitrogen center. As a demonstration of its power, the reaction was employed in a concise and efficient synthesis of L-vancosamine (**232**) as shown in Scheme 35b.

The IBX reaction tantalized us further when we employed the glycal urethane **233** as a substrate (Scheme 35c). Instead of isolating 1-deoxyaminosugar **234** exclusively, as expected, we also observed formation of the aminosugar derivative **235** as a minor product (ca. 1:2 ratio). We hypothesized that the latter compound (**235**) must be arising from attack of water upon an oxonium species such as **B** (Scheme 35c). We then reasoned that if we controlled the amount of water in the reaction system, we might be able to direct the reaction pathway to either 1-deoxyamino sugars or amino sugars at will. Indeed, this line of reasoning was sound since glycal **233** (and a number of other glycal systems) could be reliably converted in high yield to a 1-deoxyamino sugar (for example, **234**) or amino sugar derivatives (for example, **235**) just by controlling the amount of water present (Scheme 35d). In addition, these tunable cascade reactions could be set to provide amino sugar lactones such as **236** by using additional oxidant; however, it was more efficient to oxidize the amino sugars in a separate operation to achieve the same goal (namely, **235** → **236**).

Following our work with amino sugars,[42] we began to think more deeply about the mechanism of the IBX-induced cyclization reaction. The evolution of our understanding of this reaction is shown in Scheme 36. Our first mechanistic postulate for this reaction involving amide-based radicals (Scheme 36a) was accurate, yet rather simplistic. It was H. Martin R. Hoffman that first alerted us to the possibility that these reactions may be following a single-electron transfer (SET) pathway and we, therefore, proposed the mechanism shown in Scheme 36b for this process. The formulation of the possible nature of the IBX·THF complex (Scheme 36c), and the isotope labeling, kinetic,



Scheme 35. a) Application of the IBX cyclization to amino sugar synthesis, Ar = *p*-methoxyphenyl. b) Synthesis of **232** using IBX-based amino sugar synthesis. c) Reaction of **233** with IBX leads to a mixture of **234** and **235**, presumably via radical **A** and oxonium species **B**. d) Synthesis of 1-deoxy amino sugars, amino sugars, and amino sugar lactones from **233** and glycalurethanes.

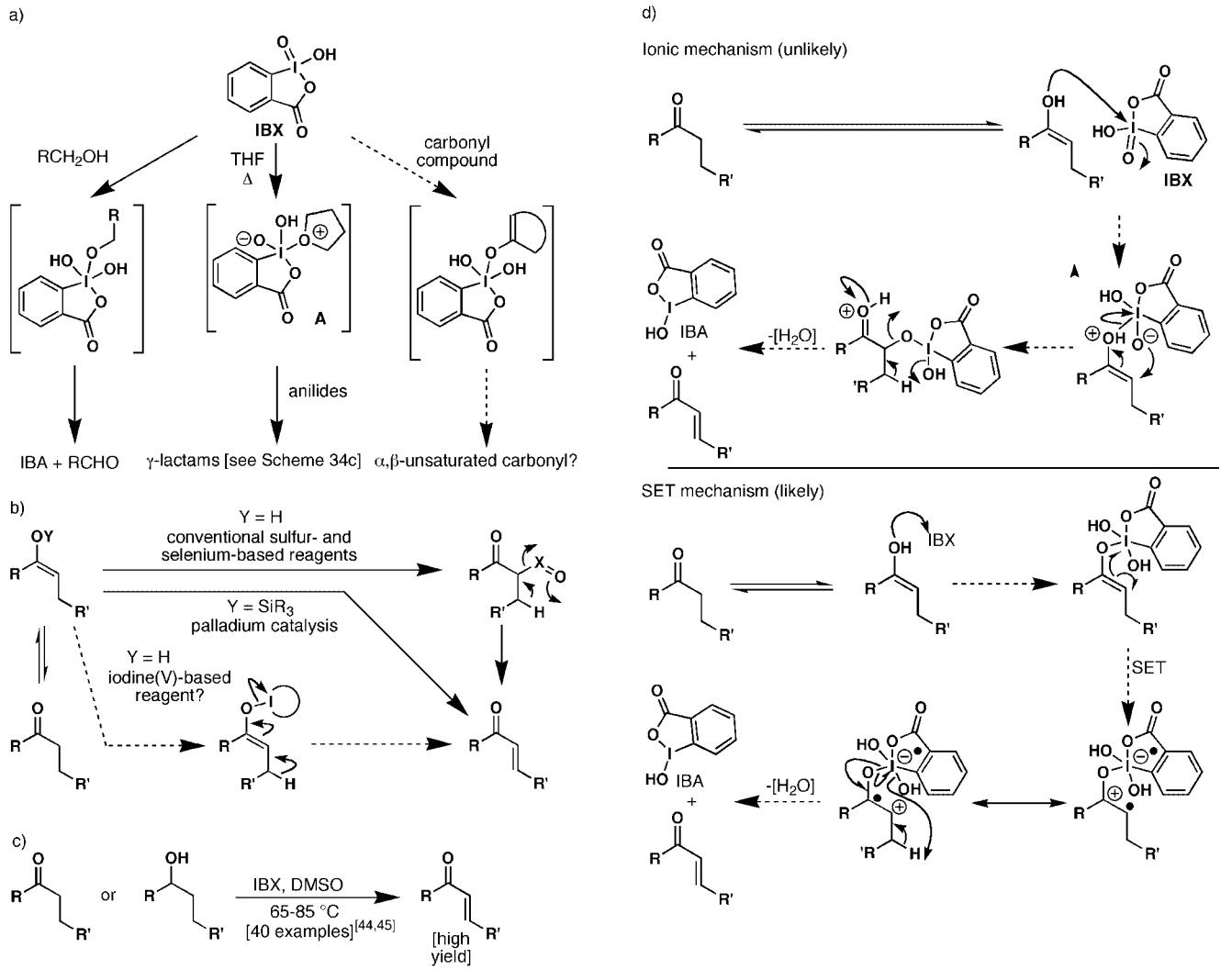


Scheme 36. Evolution of our mechanistic rationale for the SET-based IBX-mediated cyclization of anilides and related compounds (a and b) and plausible role of the solvent (THF) in these reactions (c).

electrochemical, and NMR studies would not come until a few months later.[43] Only then would we recognize the full potential of IBX as a general and highly controllable SET reagent.

11.5. IBX-Mediated Introduction of Unsaturation Adjacent to Carbonyl Compounds

With an increased but still incomplete level of understanding of the reactivity of IBX, we pondered what other types of molecules might complex to IBX. Alcohols were known to form complexes with IBX to give the corresponding oxidized species (Scheme 37a). In addition, we had found that THF presumably forms some sort of complex with IBX (Scheme 37a). Would a carbonyl compound in its enol form



Scheme 37. a) Original considerations of IBX reactivity lead to a b) mechanistically inspired design of the IBX-based process for introduction of α,β-unsaturation adjacent to a carbonyl system. c) The IBX-mediated dehydrogenation of carbonyl compounds. d) Possible ionic- (top) and SET-based (bottom) mechanisms for the dehydrogenation of carbonyl compounds by IBX.

also form a complex with IBX? If so, would it lead to the corresponding α,β-unsaturated system? This expectation was probably far-fetched at the time. After all, if IBX could accomplish this transformation, why had no one reported it in the last hundred years of the reagent's history? The expectation was that if IBX could possibly trap a carbonyl compound in its enol tautomer, its fate just might be oxidation to the corresponding α,β-unsaturated compound.

The first example of introducing α,β-unsaturation adjacent to a carbonyl function with IBX was performed on May 9, 2000. When Zhong and Phil told me the news, I (K.C.N.) was again skeptical, but clandestinely excited at the same time! As shown in Scheme 37b, our mechanistic reasoning (right or wrong!) paid off with an efficient method for the synthesis of a variety of α,β-unsaturated compounds. Furthermore, since IBX is a very capable oxidant of alcohols, we could proceed in a one-pot process to form an α,β-unsaturated carbonyl compound from an alcohol in high overall yield (Scheme 37c). It was found that a large number of protecting groups and other sensitive functionalities are well tolerated including nitrogen-based heterocycles and amides. Simple primary alcohols can even be oxidized to the corresponding, often sensitive, α,β-unsaturated aldehydes in high yield.[44,45]

As it turned out, the initially proposed ionic pathway (Scheme 37d) had to be revised to a SET-based mechanism (Scheme 37d).[45] We shall now return to the DMP cyclization, and the detailed study of its mechanism which led to the development of a number of additional synthetic technologies.

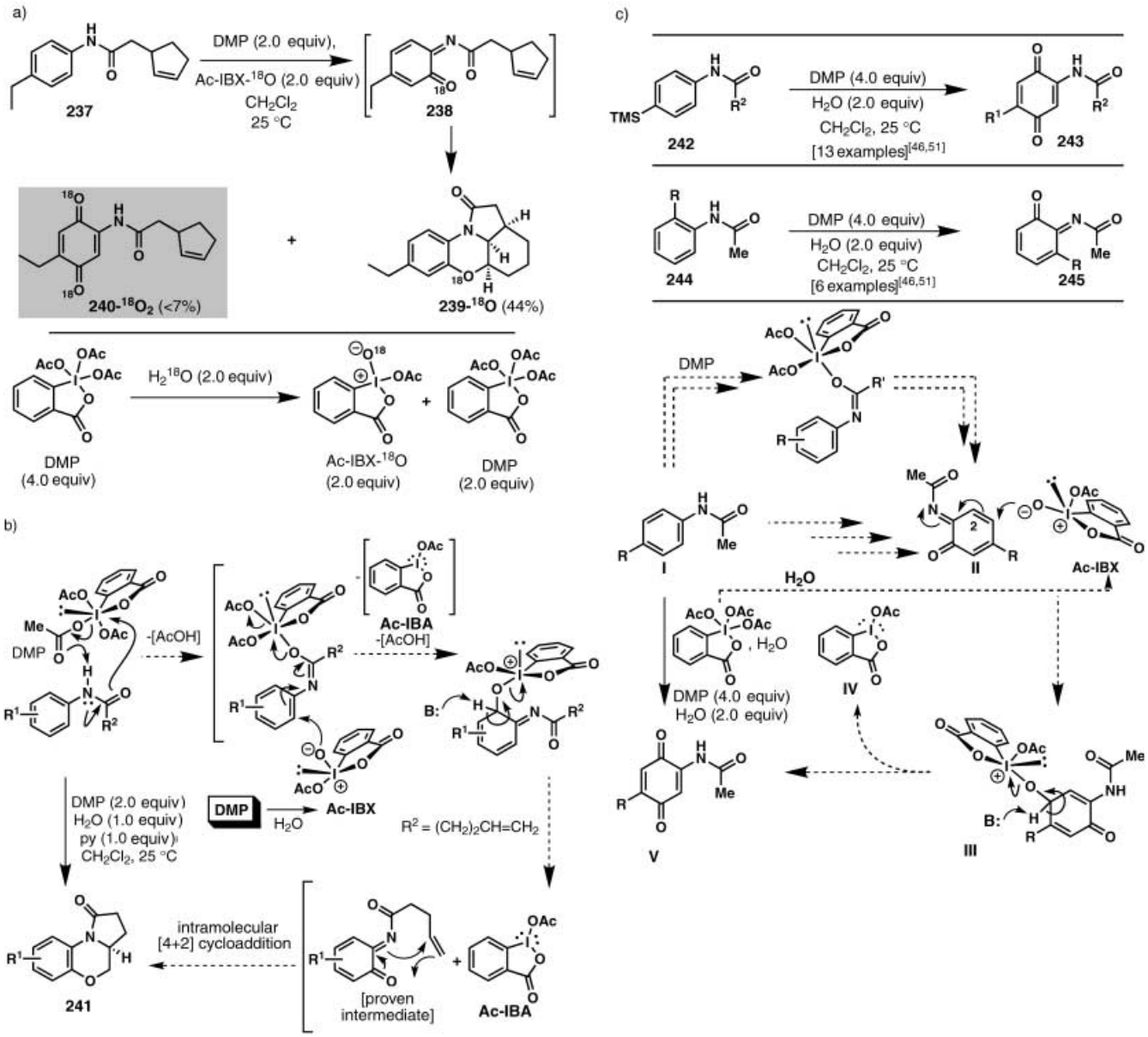
11.6. New Synthetic Technologies for the Construction of *p*-Quinones, *o*-Imidoquinones, and Complex Molecular Architectures Thereof

Without much data, we knew that our first analyses of the mechanism of the DMP cascade reaction were speculative and, indeed, were soon proven to be rather primitive. After extensive optimization studies we took note of the special influence of water on the reaction. Through control experi-

ments and isotope labeling studies (Scheme 38a) we were able to arrive at the mechanism shown in Scheme 38b. The remarkable feature of this reaction is that it involves two different iodine(v) reagents, DMP and Ac-IBX, working together. This synergistic reactivity was verified since no reaction occurs when an excess of DMP or Ac-IBX alone are employed. A detailed study of the DMP cyclization also led to a revised protocol which allows the reaction to proceed in dichloromethane at room temperature.[43]

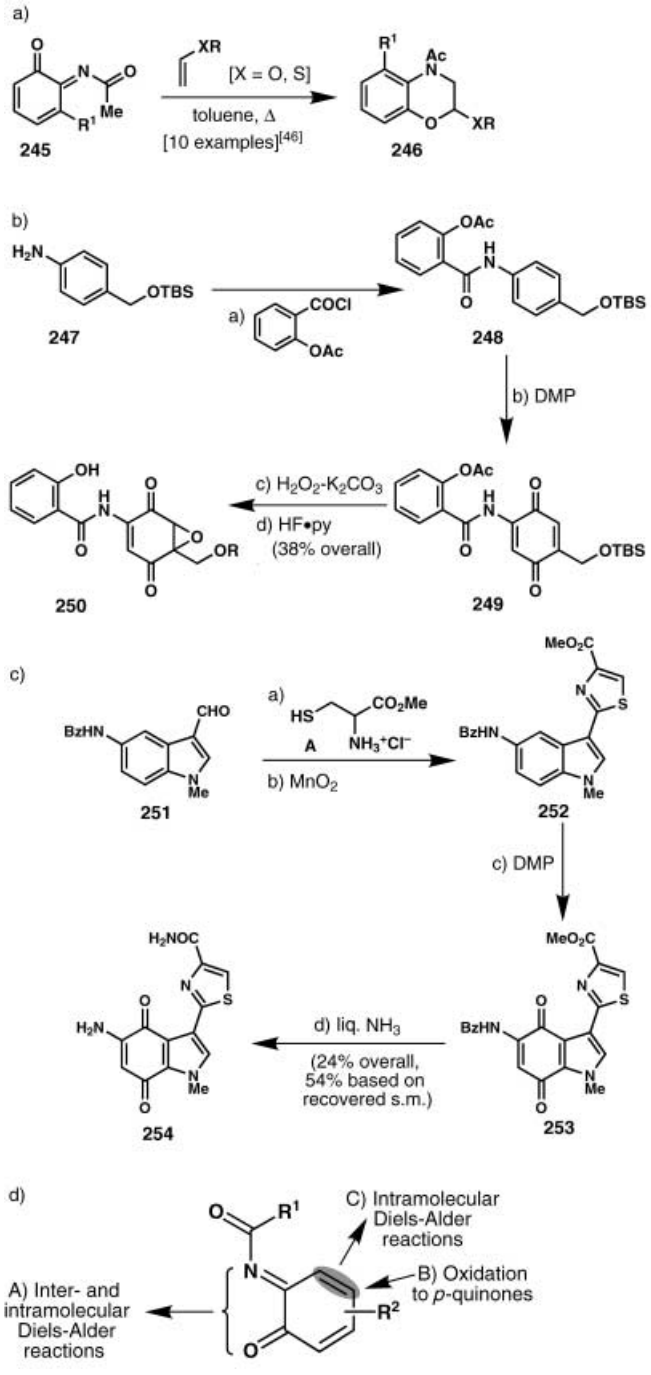
During the course of our mechanistic studies of the DMP reaction we stumbled onto the ^{18}O-labeled *p*-quinone byproduct **240-^{18}O** (Scheme 38a). We had not observed this type of product earlier because of the higher temperatures employed in the original conditions, which are apparently detrimental to the survival of such species. Logic dictated that if we deleted the appended olefin in the starting anilide we could, potentially, maximize the yield of the *p*-quinone compound. The pronounced utility and widespread occurrence of the quinone moiety in nature and medicinally important agents prompted us to explore this possibility. To our delight, we found that a number of 4-substituted anilides could be easily oxidized to the corresponding *p*-quinones in good yields (Scheme 38c top). Although 3-substituted anilides gave unpredictable results, their 2-substituted counterparts gave rise to the corresponding *o*-imidoquinones in high yield (Scheme 38c middle). This procedure represented the first general synthesis of these rather rare species.[46]

From labeling studies (Scheme 38a) it is clear that two molecules of Ac-IBX are involved in *p*-quinone formation. As shown in Scheme 38c bottom, we postulated that an *o*-imidoquinone (**II**) is actually the precursor to a *p*-quinone (**V**) upon attack of an additional molecule of Ac-IBX. In the



Scheme 38. a) ^{18}O-labeling studies with the DMP cascade reaction. b) Proposed mechanistic underpinnings of the DMP-mediated polycyclization of olefinic aryl amides. c) Synthesis of *p*-quinones from 4-substituted anilides (top), synthesis of *o*-imidoquinones from 2-substituted anilides (middle), and postulated mechanistic rationale for the oxidation of *o*-imidoquinones to *p*-quinones using DMP (bottom).

case of anilides substituted at the 2-position, the increased steric hindrance might prevent attack of the intermediate *o*-imidoquinone by Ac-IBX, and thus the inability of the latter compounds to yield *p*-quinone products. The *o*-imidoquinones were found to undergo intermolecular inverse electron demand Diels–Alder reactions efficiently, as shown in Scheme 39a. This reaction is the intermolecular variant of the original DMP-cascade cyclization reaction (Scheme 38b).[46]



Scheme 39. a) Employment of *o*-imidoquinones in intermolecular inverse electron demand Diels–Alder reactions. b) Total synthesis of epoxyquinomycin B (**250**, top) and BE-10988 (**254**, bottom) using DMP-mediated *p*-quinone generation. c) Analysis of the reactivity of *o*-azaquinones: A) Participation in inter- and intramolecular Diels–Alder reactions, B) oxidation to *p*-quinones, and C) proposed intramolecular Diels–Alder reactions.

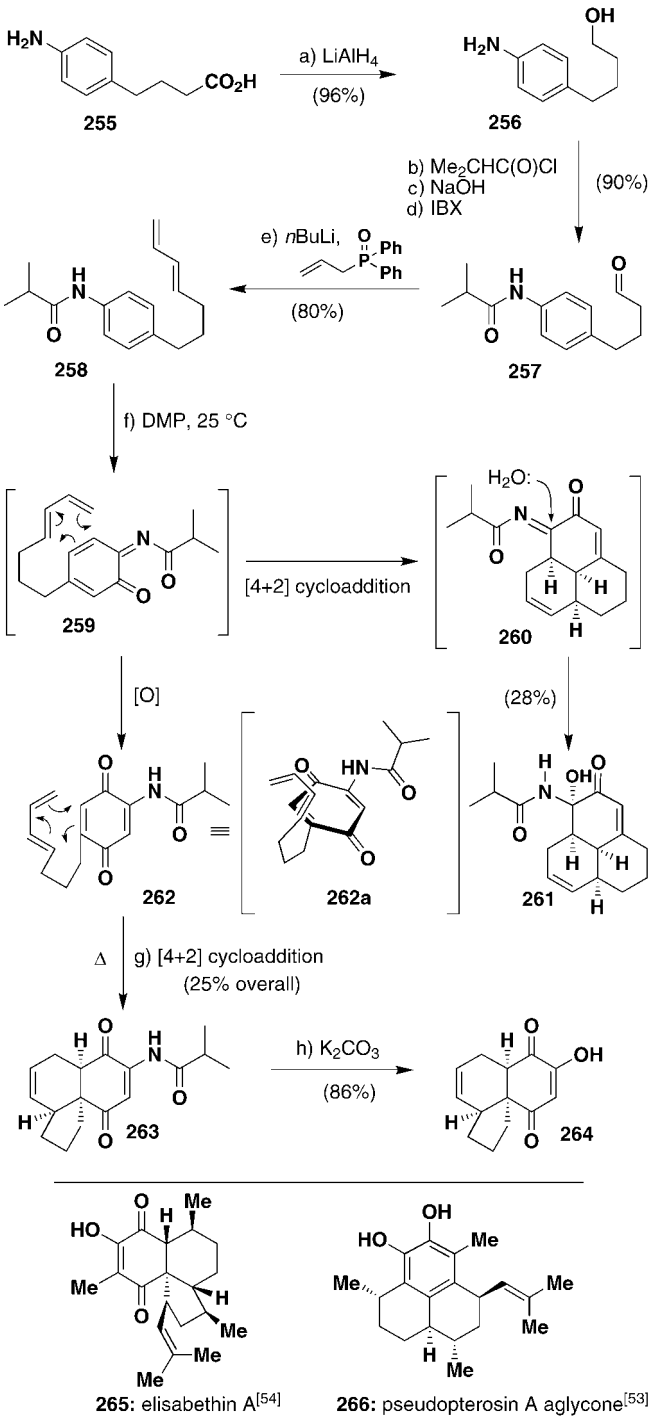
Soon after establishing the generality of *p*-quinone formation (Scheme 38a top), we realized that the direct synthesis of such compounds from anilides has important implications for organic synthesis. Specifically, in planning the construction of a *p*-quinone moiety from an aromatic nucleus, it is no longer necessary to include the normally obligatory one or two protected oxygen atoms in the starting material. In essence, an anilide moiety may be considered a latent *p*-quinone system, since both oxygen atoms may be installed concomitantly using DMP. To demonstrate the applicability of this synthetic technology in complex molecule construction, the naturally occurring and biologically active substances epoxyquinomycin B (**250**, Scheme 39b)[47] and BE-10988 (**254**, Scheme 39c)[48] were targeted for total synthesis.

The epoxyquinomycins, isolated from *Amycolatopsis* sp. MK299-95F4, are a class of structurally related antibiotics and anti-inflammatory agents.[47] As a consequence of their potential therapeutic applications as anti-inflammatory agents and for the treatment of rheumatoid arthritis, the epoxyquinomycins and related compounds have received considerable attention from the synthetic community.[49] Our total synthesis of epoxyquinomycin B (**250**),[46] the most potent member of this class, represents the shortest route to these compounds; it features only four synthetic operations from simple and readily available starting materials and proceeds in 38% overall yield (Scheme 39b).

BE-10988 (**254**, Scheme 39c) is a potent topoisomerase-II inhibitor, and as such has considerable potential in chemotherapy.[49, 50] The molecular structure of BE-10988 (**254**) contains a novel thiazole substituted indole-quinone and this provides a unique forum to test the utility and chemoselectivity of the tandem DMP cyclization.[50] Our total synthesis of BE-10988 (**254**)[51] (Scheme 39c represents the shortest and most efficient (24% yield overall, 54% yield based on recovered starting material) route to this important antitumor agent.

The facile generation of *o*-imidoquinone-type structures from anilides and DMP[46] and their demonstrated ability to undergo inter- and intramolecular Diels–Alder reactions as heterodienes (reactivity mode A, Scheme 39d) or to suffer further oxidation to *p*-quinones (reactivity mode B, Scheme 39c) set the stage for the development of yet another reaction pathway for these rather rare chemical species. Specifically, we reasoned that the electron-deficient olefin adjacent to the imide functionality of the *o*-imidoquinone moiety might also be capable of acting as a dienophile in an intramolecular Diels–Alder fusion (reactivity mode C, Scheme 39d) to provide novel and biologically relevant molecular diversity.[52]

To explore this novel prospect, we designed and synthesized anilide diene **258** as shown in Scheme 40. In line with our expectations, exposure of this substrate to DMP and H_2O in CH_2Cl_2 at ambient temperature led to ketohydroxyamide **261** and quinone **262** in 28 and 25% yield, respectively. The novel ketohydroxyamide **261** was presumably generated through hydration of the initially formed Diels–Alder adduct **260**. Interestingly, the ketohydroxyamide **261** and its derivatives closely resemble the pseudopterosin family of natural products (for example, pseudopserosin A aglycon, **266**,



Scheme 40. Rapid entry into complex molecular architectures resembling those of pseudopterosin A aglycon and elisabethin A from anilides and DMP.

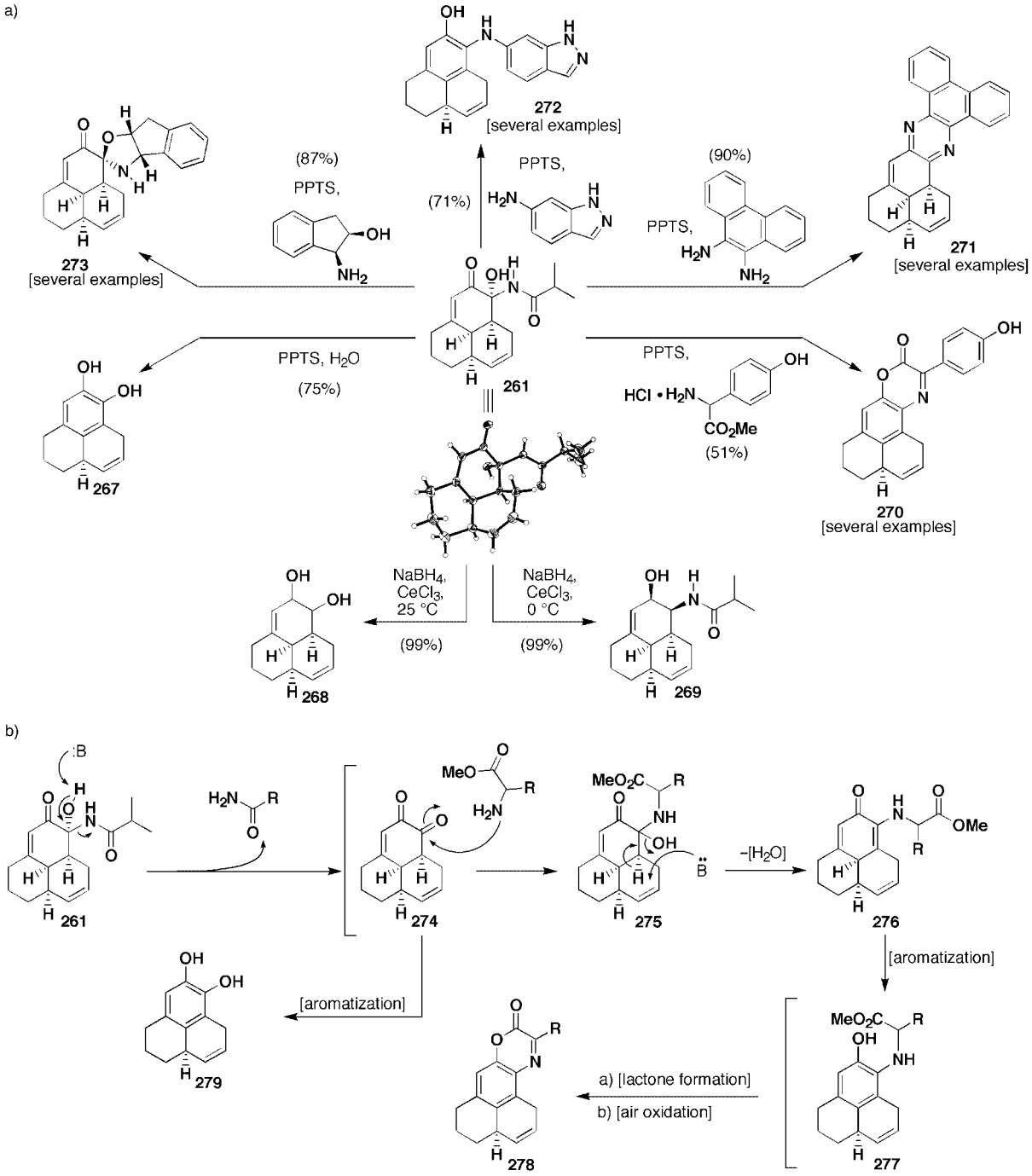
Scheme 40).[53] Upon heating, the initially formed quinone **262** was quantitatively converted, by an intramolecular Diels–Alder reaction, into the tricyclic system **263**. The latter framework embodies the full carbocyclic skeleton of the naturally occurring substance elisabethin A (**265**).[54] It is interesting to note that the structures of these two seemingly unrelated natural product classes (pseudopterosin A and elisabethin A) are produced by the same organism just as the present DMP-initiated cascade furnishes both complex pseudopterosin- and elisabethin-like structures (**261** and **263**) in the same pot.

The ready availability of ketohydroxyamide **261**, coupled with the scarcely investigated chemistry of this moiety,[55] enticed us to explore its reactivity and synthetic potential. It was soon found that ketohydroxyamide **261** undergoes a diverse range of novel transformations leading to a set of unusual products (Scheme 41a). These reactions revealed that, despite its misleading appearance, this substance does not always react as a simple protected α-diketone, but has its own chemical identity. Thus, exposure of ketohydroxyamide **261** to PPTS in aqueous media led to diphenol **267** in 75% yield, whereas treatment with sodium borohydride in the presence of cerium chloride furnished either a mixture of diastereomeric alcohols **268** (99%, ca. 1:1 ratio, 25 °C) or the hydroxyamide **269** (99%, single isomer, 0 °C) depending upon the temperature. Reaction of **261** with C-terminal-protected amino acid derivatives led, through an interesting cascade reaction (Scheme 41b), to heteroannulation, to furnish complex polycyclic scaffolds (**270**, **278**). The combination of ketohydroxyamide **261** with 1,2-diamines led smoothly to polycyclic pyrazines (**271**), whereas aromatic amines reacted with **261** to afford aniline derivatives (**272**) in high yield. Unusual heterocyclic spiro systems (**273**) were formed when 1,2-amino alcohols were employed in this reaction.

11.7. Benzylic Oxidation with IBX

Parallel to the extensive investigations in the DMP arena, we were also exploring new reactions mediated by IBX. Since we had come to the conclusion that IBX behaved as a general SET reagent, we rationalized that the oxidation of carbon atoms adjacent to aromatic systems should also be possible. As mechanistically illustrated in Scheme 42a, stepwise SET oxidation of a substituted toluene (**280**) leading to the stabilized benzylic cation (**283**) might trigger such a process by subsequent oxidation with another molecule of IBX to furnish the corresponding substituted benzaldehydes (**281**). The mild nature of IBX and its observed chemoselectivity in other transformations made this proposal particularly enticing.

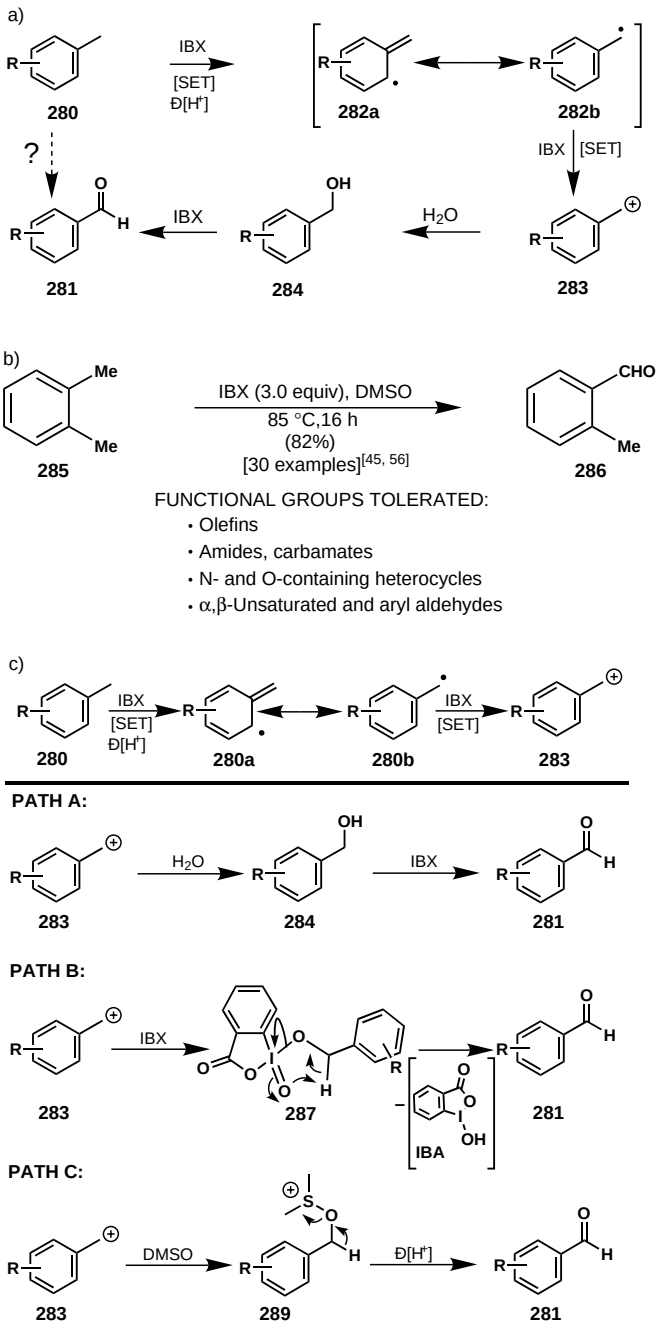
This plan worked (Scheme 42b)! Within a few weeks of its discovery, Phil and Zhong utilized this new reaction to complete a series of examples to demonstrate its scope and generality.[56] Significantly, and in contrast to conventional methods, the reaction tolerated the presence of a variety of sensitive and oxidation-prone functional groups (Scheme 42b). Moreover, over-oxidation of the resulting aldehydes was never observed. A subsequent, more-detailed mechanistic analysis of this process led us to consider several other possible pathways as shown in Scheme 42c.[45] It is also tempting to evolve our rationale and consider another mechanism for the IBX-mediated oxidation of benzylic positions based on literature precedent for aryl π–iodine complexes and their role in single electron transfer redox reactions[57] (Scheme 43).



Scheme 41. a) Remarkable reactivity of the unique ketohydroxyamide **261**, and b) postulated mechanism for the cascade heterocyclic annulation of **261** to polycycles **278**.

11.8. A Serendipitous Discovery Leads to an Exploration of the Chemistry of α-Sulfonated Ketones

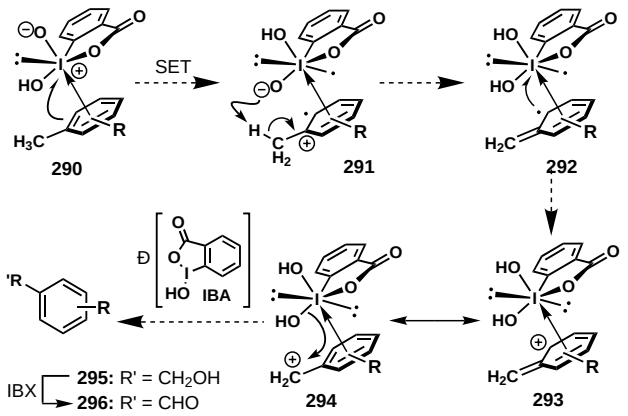
Around the same time that we had unearthed the ability of IBX to mediate the dehydrogenation of carbonyl compounds we had also discovered the potential of α-sulfonated ketones in organic synthesis. How does this seemingly unrelated finding relate to the study of iodine(v) reagents? Early one morning, I (K.C.N.) suggested to Phil and Zhong that they consider the reaction of IBX with epoxides. The hope, as illustrated in Scheme 44a, A, for the case of cyclooctene oxide, was that nucleophilic attack by IBX itself upon the epoxide moiety (**297**) followed by dehydrogenation would eventually lead to the highly oxidized system **298** in one pot. The proposed reaction was immediately set up with IBX, but there was no change. When we added catalytic amounts of TsOH we observed the formation of a trace amount of a new, strongly UV-active product. This compound turned out to be the α-tosylated ketone **299**. When the reaction was run again with stoichiometric amounts of TsOH we obtained sulfonyloxy ketone **299** in high yield. We were immediately excited by this finding and after a thorough literature search we



Scheme 42. a) Mechanistically inspired design of an IBX-mediated benzylic oxidation process. b) The IBX-mediated oxidation of benzylic positions. c) Alternative mechanisms postulated for the IBX-mediated benzylic oxidation.

confirmed our suspicions that indeed this was a new route to these types of compounds. It did not take long before we realized the potential of these now readily available intermediates in organic synthesis, particularly in solid-phase chemistry. Initial solution-phase studies (Scheme 44a, B) were promising; especially exciting was the unique synthesis of heterocycle **305**.

In considering the potential of the readily available α-sulfonated ketones, the well-known and fertile chemistry of α-halo ketones came to mind. Despite their versatile nature, however, α-halo ketones cannot easily be attached to solid



Scheme 43. Postulated concerted mechanism for the IBX-mediated benzylic oxidation.

supports for exploitation as precursors to molecular diversity by solid-phase and combinatorial methods. In contrast to the α-halo ketone solid-phase limitations, we found that α-sulfonated ketones can be readily formed on resins by employing sulfonic acid polymers. This advantage of α-sulfonated ketones, coupled with their stability and sometimes unique chemistry,[58] prompted us to investigate them further. Thus, by tapping into the rich chemistry of related sulfonyloxy ketones,[59] and by introducing our own modificaitons, we envisaged the naissance of a seamless and novel linker which would provide access to a wide ranging library of structural types.[60]

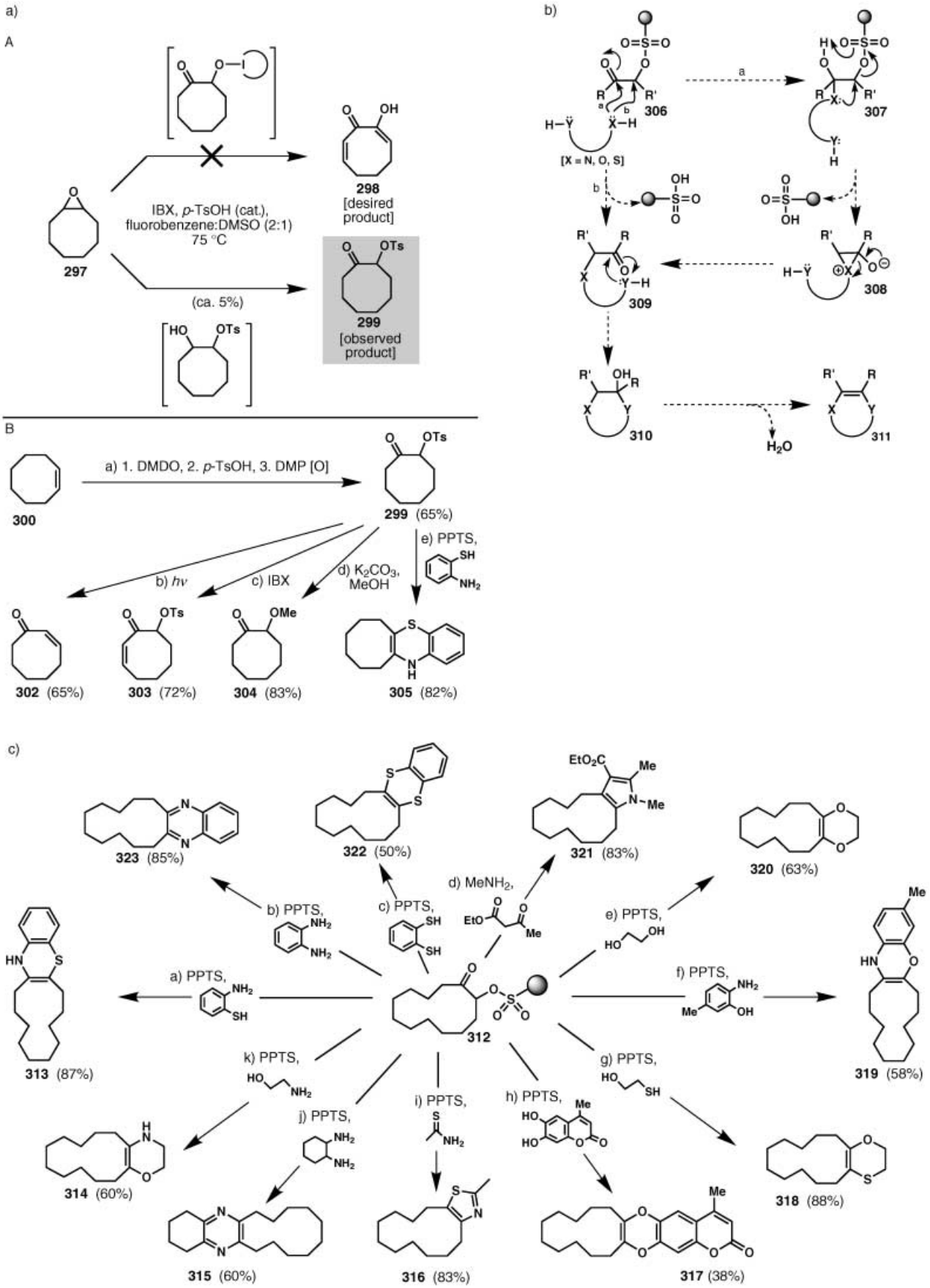
Confident that our solid-bound α-sulfonyloxy ketones were emulating their solution-phase relatives, we evaluated a strategy for the release of heterocycles from the solid support. Pleasingly, we found that this heterocycle-release concept, as depicted in Scheme 44b, allows for the generation of a plethora of ubiquitous heterocycles. Scheme 44c offers a snapshot of some of the explored possibilities.[60, 61]

We also investigated the efficiency of carbon–carbon bond forming reactions using α-sulfonyloxy ketones, and given the importance of enediynes and related systems, we set out to develop conditions which would permit the synthesis of such compounds. A unique strategy was then developed to generate libraries of dialkynols (stable precursors to enediynes). An example of this technology leading to the enediyne **329** is shown in Scheme 45.[61]

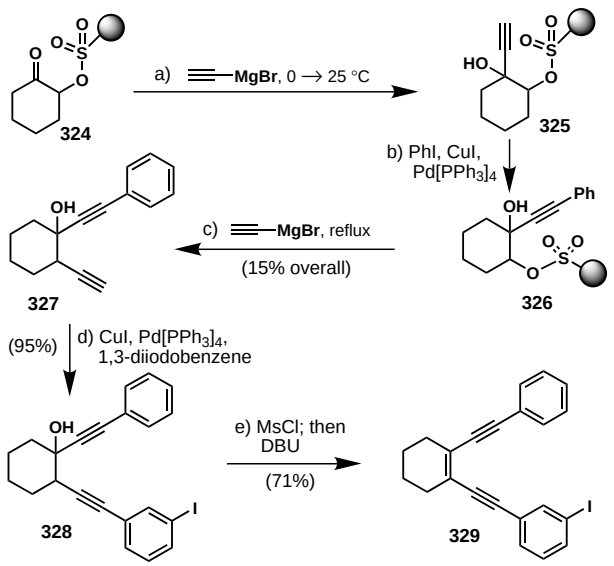
The story of α-sulfonyloxy ketones stands as an example of how an unexpected by-product and a little imagination can lead to the development of new chemistry. The moral of the story is that one should not be too quick to sweep unexpected observations under the carpet when they do not serve one's immediate purposes. Rather, one should look at such discoveries from a broader perspective and with curiosity to fuel further explorations into their mechanism and synthetic potential.

11.9. Selectivity in IBX-Mediated Reactions

The demonstrated ability of IBX to induce N-centered radical generation (from anilides and with subsequent cycli-

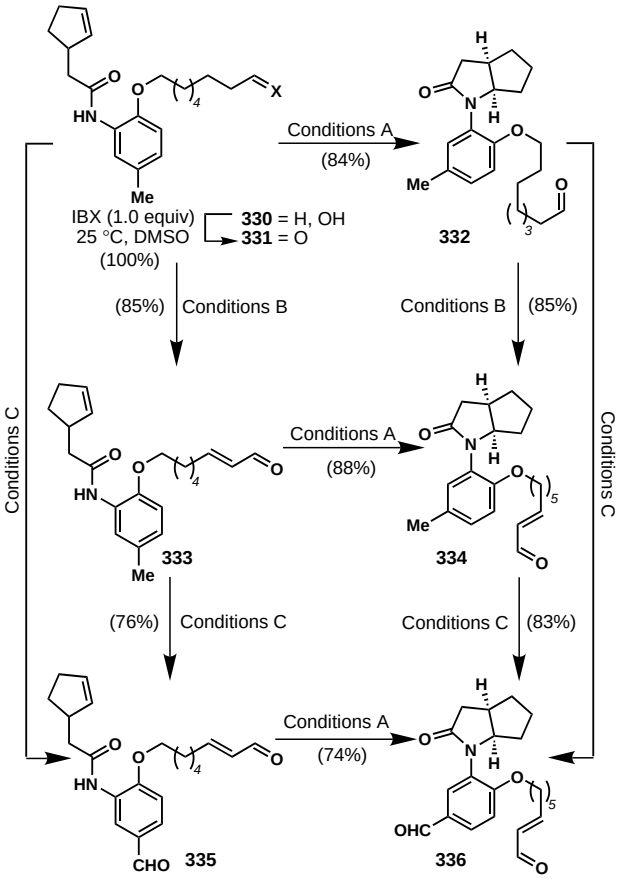


Scheme 44. a) Serendipitous discovery of a new method to synthesize α-tosyloxy ketones from epoxides (top); one-pot entry to α-tosyloxy ketones from olefins and preliminary exploration of their chemistry (bottom). b) Mechanistic rationale for the "heterocycle-release" strategy. c) "Heterocycle-release" applied to the α-sulfonyloxy ketone resin **312**.



Scheme 45. Synthesis of enediyne **329** from α-sulfonyloxy ketone **324**.

zation reactions), dehydrogenation of carbonyl compounds, and oxidation adjacent to aromatic systems dictated the need to determine the selectivity of the reagent in these reactions. How controllable are these processes in a setting where they are all conceivably possible? Scheme 46 answers this important question with the synthesis and reactions of alcohol-amide **330** which was designed to probe this issue. Using only three standard sets of conditions, substrate **330** could be easily converted into any of the compounds **331**–**336** as desired. This series of reactions ably illustrates the ease with which IBX-mediated oxidations can be manipulated to furnish a diverse spectrum of highly functionalized products.[56]



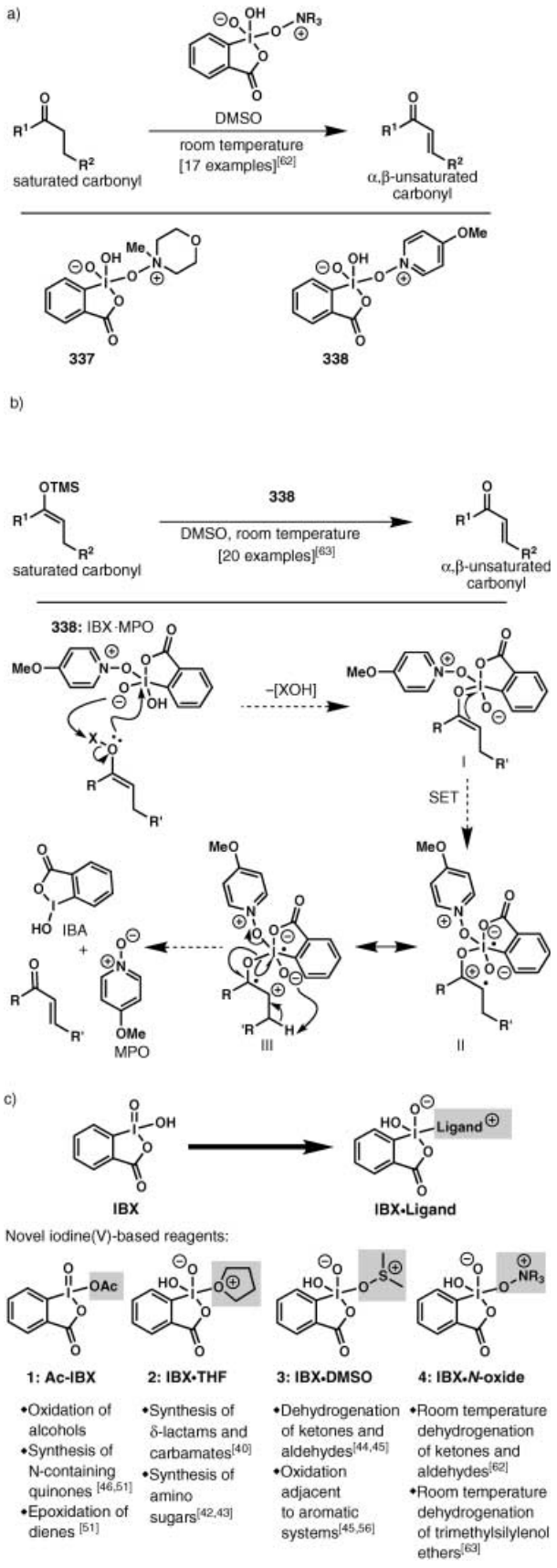
Scheme 46. Selective chemical transformations with IBX. Reaction conditions A: IBX (2.2 equiv), THF: DMSO (10:1), 85 °C, 8 h; B: IBX (2.0 equiv), TsOH (0.2 equiv), PhF:DMSO, 65 °C, 5 h; C: (3.0 equiv), DMSO, 90 °C, 2 h.

The fact that we could heat compound **333** (conditions A, Scheme 46) in a sealed tube with IBX at 90 °C in THF/DMSO and observe no benzylic oxidation or carbonyl dehydrogenation intrigued us. In the same vein, why, when there was no THF present (conditions B, Scheme 46), did the γ-lactam-forming process seem to shut off? Such questions piqued our earlier suspicions concerning the role of the solvent in these IBX reactions and led us to hypothesize that the solvent actually formed a discrete complex with IBX leading to the dramatic reactivity patterns observed.

11.10. Modifying the Iodine(v) Nucleus of IBX With Different Ligands: Room Temperature Dehydrogenation of Carbonyl Compounds

The possibility that a solvent molecule was forming a complex with IBX was first confirmed qualitatively. Thus, when a solution of IBX in DMSO was heated to 80 °C for a few minutes and then cooled down, the resulting complex was capable of carbonyl dehydrogenation at room temperature,[62] in contrast to IBX which had merely been dissolved in DMSO at room temperature. Since the conversion of this last reaction was not so high, we began to explore the effect of other ligands on the process. After extensive explorations we found that NMO is a suitable ligand for IBX; it forms a complex at room temperature (as clearly observed by ^{1}H NMR spectroscopy) and accomplishes room-temperature dehydrogenations in good yields. It was May 12, 2001, when Tamsyn Montagnon, a newly arrived postdoctoral fellow from England, informed me (K.C.N.) of this remarkable advance.[62]

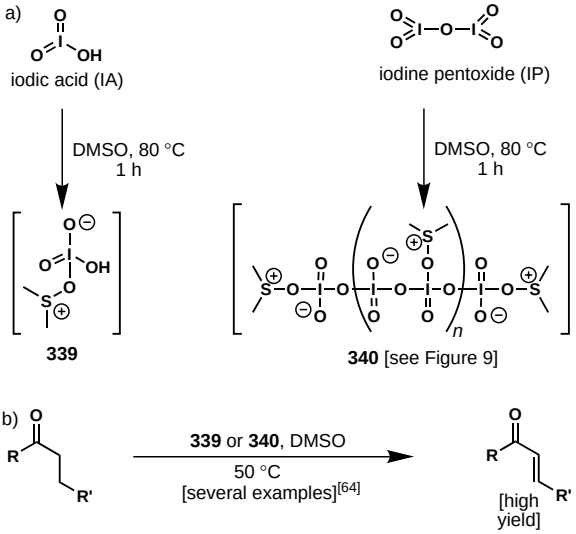
It was again hard to believe, but a clear ^{1}H NMR spectrum of the IBX · NMO complex left very little doubt of what was happening. Further optimization of the reaction led to the identification of 4-methoxypyridine-*N*-oxide (MPO) as a remarkably efficient ligand for effecting room-temperature dehydrogenation of a wide range of carbonyl compounds.[62] The applications of this new and mild reagent (IBX · MPO) were extended to encompass a highly efficient and rapid oxidation of trimethylsilylenol ethers to the corresponding enones (Scheme 47b).[63] Taken in combination, these new methods compliment each other's strengths and allow for a remarkably diverse set of ketones and aldehydes to be converted into their α,β-unsaturated congeners in high yields. Overall, these developments and the new appreciation they brought of the chemical characteristics of IBX ushered in a new paradigm for modifying the iodine(v) nucleus through ligand tailoring as a means to control its reactivity profile (Scheme 47c).



Scheme 47. a) N-oxide ligands on IBX allow for the room-temperature dehydrogenation of carbonyl compounds. b) New methodology extends the utility of *N*-oxide ligands on IBX to the room-temperature dehydrogenation of trimethylsilylenol ethers. c) Access to novel iodine(v)-based reagents by changing the ligand employed on IBX.

11.11. The Use of Iodic Acid and Iodine Pentoxide in Organic Synthesis

One day in July 2001, while pondering the reactivity of IBX we had an epiphany of sorts. It had always been bothersome to us that the use of IBX in industrial applications would likely be hampered by its high molecular weight, expense, and fear of detonation at high temperature (>200°C). What exactly is the role of the aromatic moiety in IBX, we asked. Could it's removal offer reagents with far higher atom efficiency? With the aromatic moiety simply deleted while maintaining the same oxidation state for iodine as in IBX, would we still be able to accomplish, for instance, carbonyl dehydrogenation? The most simple iodine(v) reagents, iodic acid (HIO_3, IA) and its anhydride, iodine pentoxide (I_2O_5, IA) were immediately acquired and investigated experimentally to answer these questions.[64] From our studies with IBX, we reasoned that our best chance for success would be to preform the corresponding DMSO complexes as shown in Scheme 48a. Remarkably and to our utter amazement, these DMSO complexes



Scheme 48. a) Preparation of IP- and IA-DMSO complexes. b) Their use to introduce α,β-unsaturation into carbonyl compounds.

(**339** and **340**) were indeed capable of the dehydrogenation of carbonyl compounds at rather moderate temperatures (45–65°C) and in high yield (Scheme 148b). Notwithstanding their extensive use in industrial applications[64] and their commercial availability,[65] IA and IP have rarely been employed in organic synthesis. Their industrial applications and studies conducted at elevated temperatures[66] strongly suggest these are particularly stable oxidants. This feature is perhaps related to the extensive secondary bonding networks present in these solids which is at least partially maintained in solution. To improve our understanding of the nature of these iodine(v)–DMSO complexes, we prepared crystalline **340** by lyophilization of a solution of IP in DMSO.[64] X-ray crystallographic analysis of this crystalline solid revealed its remarkable helical structure and provided the first physical confirmation of our long-held hypothesis that DMSO activates these species by acting as a ligand and complexing with the iodine(v) nucleus (Figure 9).

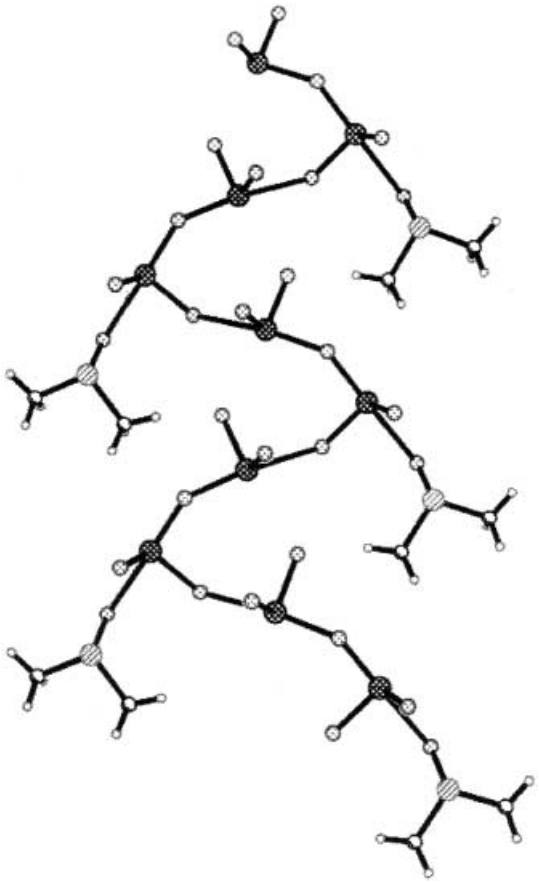


Figure 9. ORTEP representation of the helical IP-DMSO complex structure.

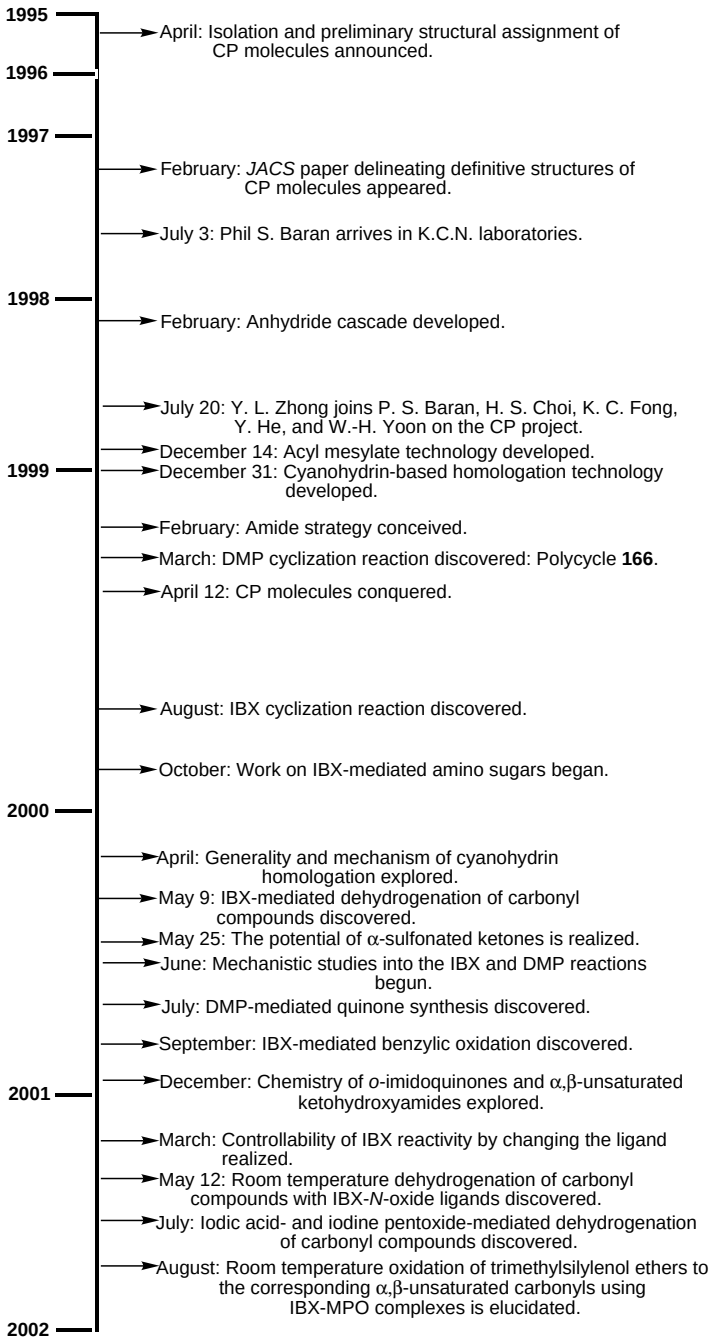


Figure 10. Timeline of an adventure in scientific discovery: The CP labyrinth.

12. Conclusion

In this article, we described our experiences with CP-263,114 (**1**) and CP-225,917 (**2**), two molecules whose conquest by total synthesis was enriched with a surplus of discoveries and inventions in organic synthesis (for a timeline of the main milestone events in this synthetic labyrinth, see Figure 10). Their unusual molecular connectivities and highly sensitive nature added to the lure of their challenge, and were instrumental in stimulating new chemistry by raising the bar at a level unattainable by existing methodology. Rising to this challenge, a team of dedicated graduate students and post-doctoral fellows battled for approximately two years through a "synthetic labyrinth" until the "Minotaur" fell in the face of their unwavering persistence and resourceful attacks. A number of new synthetic strategies and synthetic technologies were invented to get through and accomplish the final goal, and many more synthetic methods were discovered in the process and in follow-up studies. Among the most prominent of these reactions are the maleic anhydride cascade, the DMP-mediated cascade oxidation of 1,4-diols to construct the γ-hydroxylactone, the mixed acyl-sulfonyl anhydride method for activating sterically hindered carboxylic acids, the cyanohydrin-based homologation of sterically hindered aldehydes, the cascade hydrolysis of **1** to **2**, and finally the myriad of new reactions based on iodine(v) chemistry and spin-offs thereof.

The highly fertile and interwoven studies of synthetic strategy and synthetic methodology inspired by these "demonic" target molecules are a luminous example of how total synthesis should be performed these days. Indeed, this example provides ample demonstration of the attractiveness of total synthesis endeavors as a means to discover and develop science, particularly in the fields of new synthetic methodology and strategy. Another rich and rewarding approach to total synthesis of natural products is to blend it with chemical biology studies. Examples of such endeavors

from these laboratories include the enediyne,[68] epothilone,[69] and vancomycin[70] projects, all of which evolved and grew so that they were accompanied by a number of significant contributions to biology and medicine.

Overall, endeavors in total synthesis, if practiced wisely, are hard to match in terms of yield of basic science and the development of useful applications in biology and medicine, not to mention the opportunity they provide to train young men and women in the art of chemical synthesis. What determines the yield of such benefits is often encoded within the program and depends on many factors, admittedly including serendipity and good luck. However, the practitioner can optimize this yield by rational reasoning and imagination so as to maximize the opportunity, beginning with the prudent selection of the target molecule. The entire enterprise should be based on the premise of not only reaching the destination, but most importantly, collecting "goods and wisdom" along the way.

In closing this article we wish for more targets like the CP molecules, so that they can challenge and sharpen the minds and skills of new "Theseus".[71] Nature certainly has them, and it will be up to us to find them and pursue them, and in so doing learn the valuable lessons they hold in store for us. For nature, in her designs, is the supreme master, and thriving to mimic her efficiency and elegance is a most rewarding endeavor.

Abbreviations

Ac	acetyl
acac	acetylacetonyl
AIBN	2,2′-azobisisobutyronitrile
Alloc	allyloxycarbonyl
Bn	benzyl
Bz	benzoyl
CAN	cerium ammonium nitrate
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
4-DMAP	4-dimethylaminopyridine
DMDO	2,2-dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N*,*N*-dimethylpropyleneurea
DMSO	dimethylsulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
HMDS	bis(trimethylsilyl)amide
IBA	iodosobenzoic acid
IBX	*o*-iodoxybenzic acid
imid	imidazole
LDA	lithium diisopropylamide
Ms	methanesulfonyl
NMO	4-methylmorpholine-*N*-oxide
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium 4-toluenesulfonate
Ts	4-toluenesulfonyl
py	pyridine
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammoniumperruthenate
TPS	*tert*-butyldiphenylsilyl

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