Merging Strategy, Improvisation, and Conversation to Solve Problems in Target Synthesis

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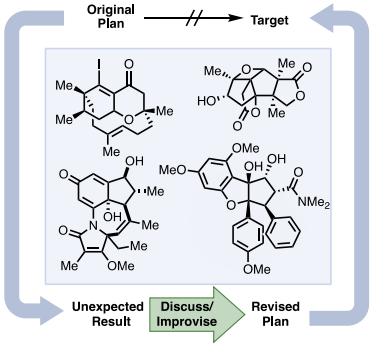


Conspectus: Total synthesis has long been depicted as the quest to conquer the structures created by nature, requiring an unflinching, single–minded devotion to the task. The goal is achieved by chemists with grit, strength of will and a competitive spirit. While there is some truth to this viewpoint, it does not fully capture the rich experiences gained in this research realm. In our lab, strategic planning, improvisation and conversation have worked in concert to enable progress. This account summarizes our efforts to synthesize four different bioactive targets: merrilactone A, rocaglamide, phomactin A and tetrapetalone A. Certain missteps were integral to success in these synthetic projects. As such, we include the hiccups, and their roles in the evolution of the strategies, along with the results that aligned with our expectations.

Two of these projects (merrilactone A and rocaglamide) culminated in the total synthesis of the targets. The challenges presented by merrilactone A spawned a new design strategy for pentannulation using Nazarov cyclization chemistry. This work demonstrated that Lewis acid catalysis is often a viable electrocyclization strategy in activated, polarized pentadienyl cation intermediates. We sought to apply the same logic to the rocaglamide target, but precursors we prepared did not behave according to plan. This situation pushed us to adapt our approach in order to match the innate reactivity of the substrate, resulting in an on–the–spot improvisation that was not only integral to the success of the project but also expanded our understanding of pentadienyl cation chemistry. In the other two projects, (phomactin A and tetrapetalone A) we did not complete a total synthesis,but did build the polycyclic core of the target. Even though the hetero [4+2] cycloaddition plan for assembling the macrocyclic oxadecalin ring system of phomactin A failed, the original experimental design still enabled us to solve the problem. Through a wholly unanticipated series of events, our focus on the oxadecalin ring system primed us for the discovery of a sequential iodoaldol/ oxa–Michael sequence, using the original [4+2] building blocks. Then, the bridging ring present in phomactin A demanded we implement this sequence in a transannular environment. Finally, our successful synthesis of the tetrapetalone core was enabled by consultations with others in the community. Each bond in our strategy seemed to require different expertise and in three separate instances (C–N cross–coupling, diastereoselective ring–closing metathesis, and oxidative dearomatization) synthetic challenges were overcome through conversation and collaboration.

In our experience, the amount of creative power we summon during a target synthesis project correlates directly with the magnitude of the structural challenges we face. When reactivity surprises us, we analyze the problem anew, consult with colleagues, and improvise with the tools at hand. The inevitable misbehavior of a complex system is a strong motivating force, and one that has helped to shape our research program for nearly two decades.

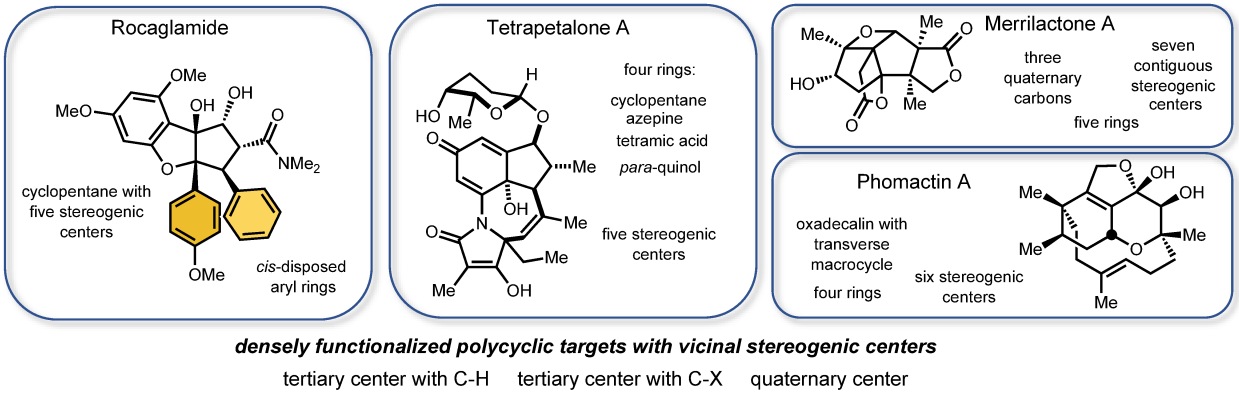
Key References:

1. Hei, W.; Huang, J.; Sun, X.; Frontier, A. J. Total Synthesis of (±)–Merrilactone A. *J. Am. Chem. Soc*. **2008** 130, 300–308.[1] *Investigations into the polarized Nazarov cyclization aid in the construction of functionalized cyclopentanoid rings and culminate in the total synthesis of (±)–Merrilactone A.*

2. Malona, J. A.; Cariou, K.; Spencer, III, W. T.; Frontier, A. J. Total Synthesis of (±)–Rocaglamide via Oxidation–Initiated Nazarov Cyclization. *J. Org. Chem.* **2012**, 77, 1891–2908.[2] *A pentadienyl cation is generated via oxidation of an alkoxyallene, enabing Nazarov cyclization and eventual total synthesis of (±)–rocaglamide.*
3. Ciesielski, J.; Gandon, V.; Frontier, A. J. Cascade Cyclizations of Acyclic and Macrocyclic Alkynones: Studies toward the Synthesis of Phomactin A. *J. Org. Chem.* **2013**, 78, 9541–9552.[3] *A novel transannular annulation strategy (iodo-aldol/ oxa-Michael addition) is leveraged to construct the ABD ring system of phomactin A.*
4. Carlsen, P. N.; Mann T. J.; Hoveyda, A. H.; Frontier, A. J. Synthesis of (±)–Tetrapetalone A–Me Aglycon *Angew. Chem. Int. Ed.* **2014**, 53, 9334–9338; *Angew. Chem.* **2014**, 126, 9488–9492.[4] *Nazarov cyclization, C-N coupling, and diastereoselective ring-closing metathesis are employed in the synthesis of (±)–Tetrapetalone A–Me Aglycon.*

Introduction: The challenging stereochemical features and functional group arrays found in polycyclic natural products has provided the inspiration for all of the chemistry discovered and developed in our lab since its inception in 2002. We focused on four heterocyclic targets (Figure 1), all with interesting bioactivity profiles,[5] unusual patterns of ring fusion, as well as dense stereochemical arrays of functionality on saturated carbon scaffolds. Merrilactone A has seven stereocenters situated on contiguous carbons on the pentacyclic system. Rocaglamide contains a *syn*–disposed pair of aryl rings and a stereocenter on every carbon of the cyclopentanoid ring. Phomactin A has a long carbon bridge spanning an oxadecalin system. In tetrapetalone A, a central nitrogen anchors an aniline, a saturated azepine ring and a tetramic acid moiety. The quaternary carbon atoms embedded in these systems, and the arrays of vicinal stereogenic centers were features of particular interest to us. In this Account, we will describe how the study of these complex molecules has guided our research efforts, enabling the development of stereocontrolled cyclization methods for the installation of vicinal stereocenters, including quaternary, oxa- and aza-tertiary centers. The reader will notice that we include a number of unexpected results in the narrative, because unanticipated reactivity played a central role in the evolution of these syntheses. If we left out these wrong turns and surprises, we would be telling only half the story.

Figure 1. Challenging structural features in four polycyclic natural product targets.

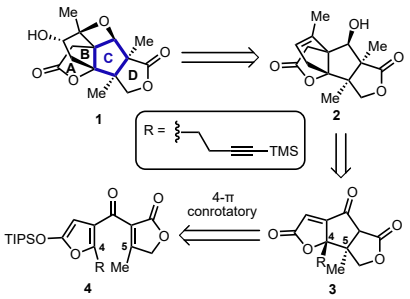


Total Synthesis of (±)–Merrilactone A

Merrilactone A is a sesquiterpene dilactone that was isolated from *Illicium merrilianum* by Fukuyama and co–workers in 2000 (Figure 1).[6] It possesses an unusually dense skeleton containing a propellane motif and seven stereogenic centers (three quaternary) within a total of total of five rings. Merrilactone A also promotes the growth of fetal rat neurons at concentrations of 0.1 μmol/L.[5] Since its isolation, the highly oxygenated pentacyclic framework has inspired a number of racemic and enantioselective total syntheses.[7] In our lab, the challenges presented by the structure of merrilactone A focused our attention on Nazarov electrocyclization chemistry, launching a research program that has persisted for eighteen years.

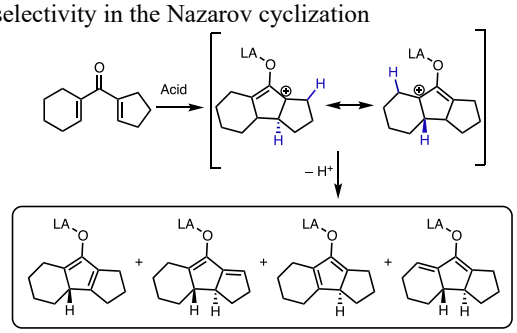
Few methods allow rapid assembly of rings that are as densely substituted as the C ring of merrilactone A. Any useful strategy must install all five stereogenic centers. Remarkably, the C ring is fused to four other rings, adding another element of difficulty to the synthesis. We hoped to leverage a Nazarov cyclization to build merrilactone A from the inside out, imagining that the 4π conrotatory ring closure dictated by the electrocyclization would enable the creation of the core cyclopentane (C ring) and simultaneously install the C4 and C5 stereogenic centers (Scheme 1).

Scheme 1. Initial retrosynthetic analysis of merrilactone A



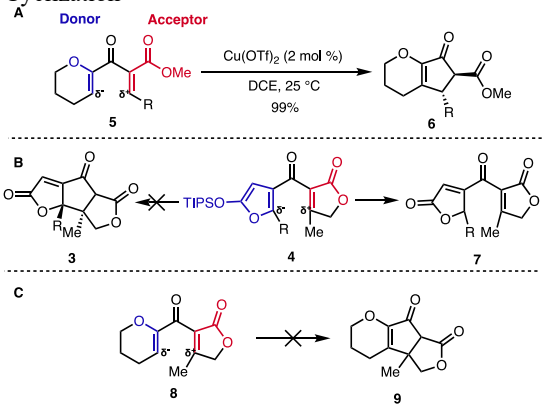
While the synthetic potential of the Nazarov cyclization had been appreciated for years, the reaction suffered from several significant drawbacks at the time our studies began.[8] Firstly, harsh Lewis or Brønsted acidic conditions were needed to overcome the high barrier to electrocyclization. Secondly, a stoichiometric amount of acid was often needed to promote the cyclization. Finally, elimination of a proton from the intermediate oxyallyl cation often occurred with poor regioselectivity, leading to a mixture of products (Scheme 2).[9] Furthermore, there was no precedent for electrocyclization of a substrate like **4**, which is fully substituted at both termini (cf. C4 and C5; Scheme 1) and contains an acid-sensitive silyloxyfuran moiety.

Scheme 2. The problem with regioselectivity in the Nazarov cyclization

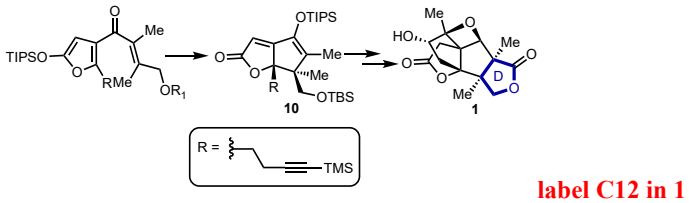


Despite this discouraging backdrop, the interesting electronic juxtaposition of substituents in silyloxyfuran **4** convinced us to pursue the strategy anyway. Specifically, we wondered whether the inherent polarization of this molecule, containing an electron–rich silyloxyfuran π–system and an electron–poor butenolide π–system, would provide enhanced reactivity. A similar idea of pairing of electron–poor and electron–rich substrates is effective in the Diels–Alder cycloaddition strategies popularized by Danishefsky and others.[10] When we tested this hypothesis on simplified systems **5** we confirmed that polarizing the Nazarov cyclization renders the conditions mild and catalytic (Scheme 3A).[11] Unfortunately, we were never able to effect the cyclization of silyloxyfuran **4** as it only gives desilylation product **7** under the reaction conditions (Scheme 3B). The failed cyclization of **8** pointed to the butenolide as the source of the problem rather than the silyloxyfuran (Scheme 3C). We therefore revised the synthetic strategy by removing the D ring from the Nazarov substrate in favor of installing it after the cyclizaton (Scheme 4).

Scheme 3. The Polarized Nazarov Cyclization



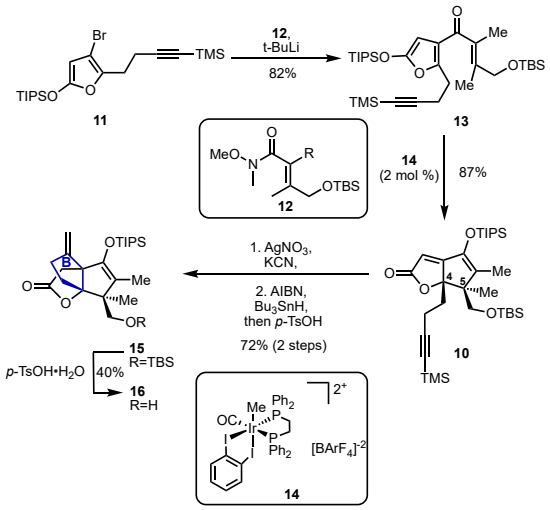
Scheme 4. Revising the strategy



label C12 in 1

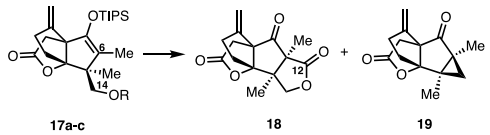
The successful approach is summarized in Scheme 5. Silyloxyfuran **11** (which was synthesized in 4 steps from known compounds[12]) underwent lithium/halogen exchange and addition to Weinreb amide **12** to yield the Nazarov precursor **13** (Scheme 5**)**. Treatment of **13** with cationic iridium complex **14**, previously identified as a uniquely active catalyst for polarized Nazarov cyclizations, led to smooth cyclization with transfer of the silyl protecting group in a manner analogous to a Mukaiyama–Michael reaction.[3,14] The cyclization thus delivers silyl enol ether **10** *as a single diastereoisomer* with the desired C4/C5 stereochemistry as dictated by the constraints of the 4-π conrotatory electrocyclization. The B ring was installed next by an AIBN initiated radical cyclization. This sequence completed the assembly of the ABC propellane system of merrilactone A. Acidic conditions enabled chemoselective deprotection of the primary silyl ether, delivering alcohol **16** in 40% yield.

Scheme 5. Iterative cyclizations for installation of merrilactone A core



Intermediate **16** contains all of the carbons in the merrilactone A skeleton except C12 (in ring D; see Scheme 4). Installation of this carbon required extensive experimentation (Table 1). Our initial strategy was to install C12 through intramolecular acylation of the silyl enol ether, wherein the acyl partner would be situated on the C14 oxygen (see **17**). To that end, alcohol **16** was converted into several different electrophilic species **17** in preparation for cyclization. However, cyclopropane product **19** was the only product obtained from these experiments. Unexpectedly, it appears that C14 is better aligned than C12 for nucleophilic attack by the enol for either steric or stereoelectronic reasons. Minimizing the steric hindrance at C6 by removing the TIPS group and performing the ring closing under basic conditions also gives rise to cyclopropane **19**.

Table 1.

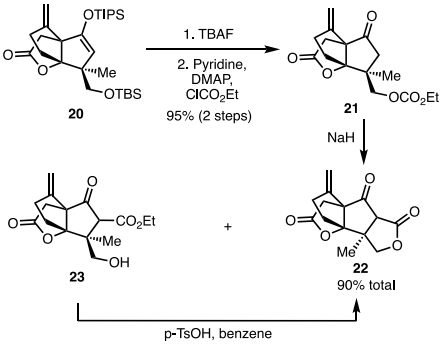


entry	substrate	R	conditions	yield (pdt)

1	**17a**	CO_2Et	TMSOTf,	72% (**19**)
2	**17a**	CO_2Ph	TMSOTf	72% (**19**)
3	**17b**	COCl	AgOTf	88% (**17b**)
4	**17c**	$CH(OMe)_2$	$TiCl_4$	68% (**19**)

Given the challenges associated with the intramolecular acylation of **17**, we shifted our focus to **20** which was prepared in an analogous manner to **17,** reasoning that this reactant should present less steric demand in the cyclization. Global deprotection of **20** followed by treatment with ethylchloroformate produces carbonate **21** (Scheme 6). Generation of the sodium enolate does enable the desired addition to the carbonate, giving a mixture of ring closure product **22** and carbonyl transfer product **23**. β–Ketoester **23** could be transformed to **22** by reaction with *para*-toluenesulfonic acid in benzene, giving a combined 90% yield of **22** from **21**.

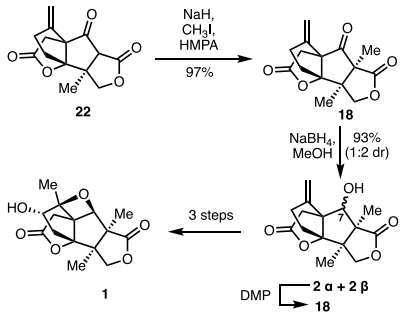
Scheme 6. Installation of D ring



The final carbon was installed via addition of the enolate of **22** to methyl iodide in a diastereoselective fashion to create the desired *cis* CD ring fusion (Scheme 7). Sodium borohydride reduction of **18** gives **2** as a 1:2 ratio of C7 α:β epimers. The undesired α isomer could be recycled back to **18** by DMP oxidation, such that subsequent reduction could generate more **2β**. From **2β**, the precedent of Danishefsky allowed completion of the synthesis in three more steps.

Scheme 7. Endgame of merrilactone A synthesis

I think alpha and beta were reversed in the text, I corrected it. To make the recycling more clear, I'd put 2α and 2β on different lines, and point the arrow with DMP to the structure 18 above. Also, the ratio 1:2 (or 2:1) should appear under structure 2 I think,



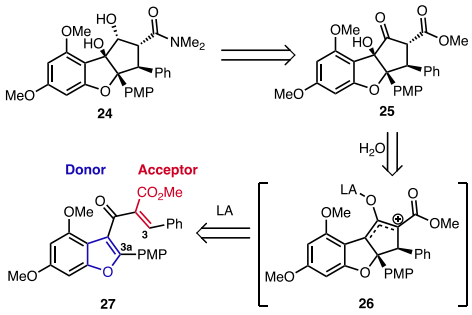
In retrospect, the complex cyclopentane at the core of merrilactone A demanded that we expand the capabilities of the Nazarov cyclization, while the unique electronic composition of the system suggested a solution to the problem. The specific features of this molecule thus guided and inspired us, ultimately leading to the development of a new, *general* strategy for Nazarov electrocyclization focused on polarization of the pentadienyl cation. This project illustrates how complex natural products require us to innovate, and how even within the strict focus on one specific target structure, we can extract valuable strategic ideas that have impact beyond the total synthesis exercise.

Total Synthesis of (±)–rocaglamide

Rocaglamide was first isolated by King and co–workers in 1982 from *Aglaia elliptifolia*, a plant native to the Philippines.[15] Since its isolation, rocaglamide has been identified as a potent cytostatic agent with activity against leukemia and other cancer cell lines (IC_{50} values <10 ng/mL).[15,16] The cyclopenta[b]tetrahydrobenzofuran core of the rocaglate natural products provides a formidable challenge for synthetic chemists. It contains five contiguous stereogenic centers, including vicinal cis aryl moieties (Figure 2). A number of different approaches to rocaglates have been reported, spanning the years 1990–2020, which serves to underline the enduring role of the molecule as a compelling target.[20]

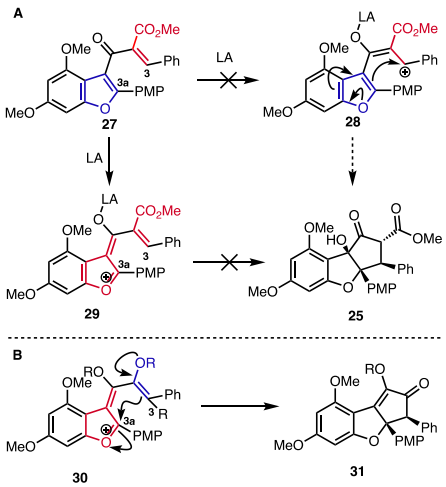
Given our previous experience with merrilactone A, in which a silyloxyfuran ring engaged in Nazarov cyclization, we considered a similar strategy for the synthesis of rocaglamide (Scheme 8). Specifically, we expected cyclization of **27** followed by trapping of oxyallyl cation **26** with water to install the densely functionalized cyclopentanoid ring in **25**, which could be elaborated to **24**. Most importantly, the conrotatory nature of the cyclization would enable us to install *stereospecifically* the cis–disposed aromatic rings in a single step. Additionally, we believed both the benzofuran and alkylidene β–ketoester moieties would lend themselves to a polarized cyclization according to the model discussed above and under development in our group at the time. Just as we were starting the project, AJF (to her astonishment) received a phone call, out of the blue, from Professor Philip Magnus at UT Austin. This is how Prof. Magnus started the conversation [paraphrased]: "We are working on the total synthesis of rocaglamide, and based on your recent publications, I imagine you are too. I have always believed that the molecule is our adversary when we engage in synthesis, and we chemists should work together, rather than compete against each other, to solve the problems encountered along the way. So I propose we share our findings as our two labs pursue this target."[22] Following this phone call was a rapid description of the Magnus approach, described using chemical naming schemes that went by very fast, as well as some observations related to unwanted reactions experienced during routine transformations. AJF did her best to capture the scientific content, and so began a conversation that culminated in two successful routes to the target rocaglamide. The entire experience flies in the face of the stereotypical depiction of a total synthesis venture, which is done alone, in cut–throat competition with others racing to finish first.

Scheme 8. Initial retrosynthesis of rocaglamide: polarized Nazarov cyclization/oxyallyl cation captured by water
The positive charge in 26 should be at the C-OLA carbon



Unfortunately, despite extensive experimentation, no evidence for cyclization of compound **27** was ever found. To rationalize this behavior, we hypothesized that **29**, in which C3a has the properties of an acceptor, is more dominant than **28**, where electrophilic character is more localized on C3 (Scheme 9A). This analysis reveals **27** as a system with two acceptors, rendering it unreactive. At this point, the project demanded improvisation, or we faced certain failure. With the molecule's natural tendencies acting as our guide, we adapted our approach to compensate for the hypothesized electrophilic character of C3a. Following this logic, we opted to attempt cyclization of **30**, with nucleophilic character at C3 (Scheme 9B). In principle, this strategy reverses the roles of the C3a and C3 carbons, restoring the polarity match, and indeed, cyclization of the redesigned system does occur.

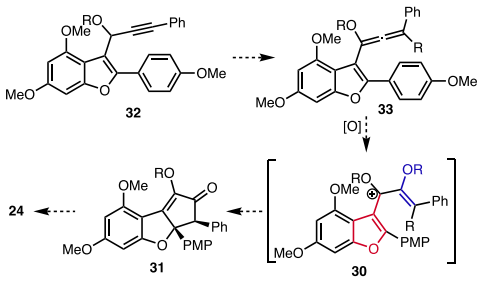
Scheme 9. A) Different conceptualizations of charge distribution in **27**. B) Improvisation: adjusting substrate polarization to compensate for unexpected behavior



the plus in 30 is overlapping the bond

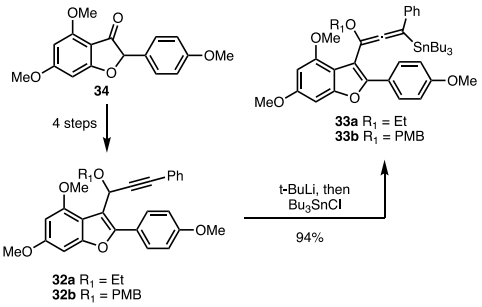
Our new synthetic plan hinged on the oxidation of an alkoxyallene to generate the correctly polarized pentadienyl cation (Scheme 10). While Nazarov cyclizations initiated by oxidation of vinylallenes had been reported, vinyl alkoxyallenes had not been studied in this context.[23]

Scheme 10. Revised synthetic plan to access the tricyclic core of rocaglamide via an alkoxyallene



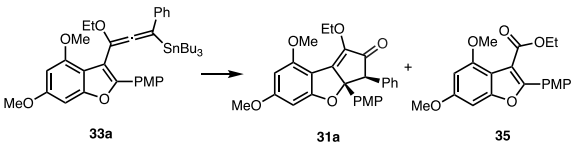
The synthesis began with compound **35** (prepared in 2 steps from known compounds),[20d] which was elaborated in four steps to **33** (Scheme 11). Initial attempts at base promoted isomerization of **30** met with little success due to protonation at the carbon bearing the ether rather than at the vinyl position. To circumvent this, we investigated trapping the allenylanion with an electrophile that could later be removed and found that trapping with tributyltin chloride gives excellent yield of the allenylstannane **34**.

Scheme 11. Synthesis of allenylstannane Nazarov precursor



We then explored the oxidative Nazarov cyclization of **33**. As shown in Table 2, oxidation of **33** with *m*–CPBA gives the desired product **31** along with the unexpected ester **35**. DMF is the best solvent for this reaction and increasing the amount of oxidant to 3.5 equivalents gives the best yields of **32** **(wrong number? Also in Table 2).** Ester **35** is likely the result of a reaction pathway stemming from an undesired oxidation event. The proposed mechanism for the formation of **31** is shown in Scheme 12.

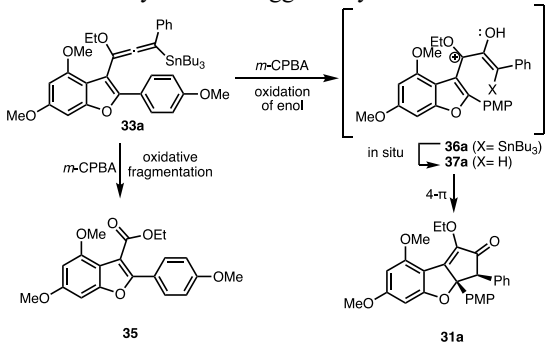
Table 2. Optimization of oxidative Nazarov Cyclization[a]



entry	solvent	ratio **(32:33)**
1	DCM/Hexane (1 : 1)	1 : 1.2
3	toluene	1 : 4
3	DMF	1.6 : 1
4[b, c]	DMF	1 : 2
5[b, d]	**DMF**	**4.3 : 1**
6[b, e]	DMF	1 : 6
7	sulfolane	1.2 : 1

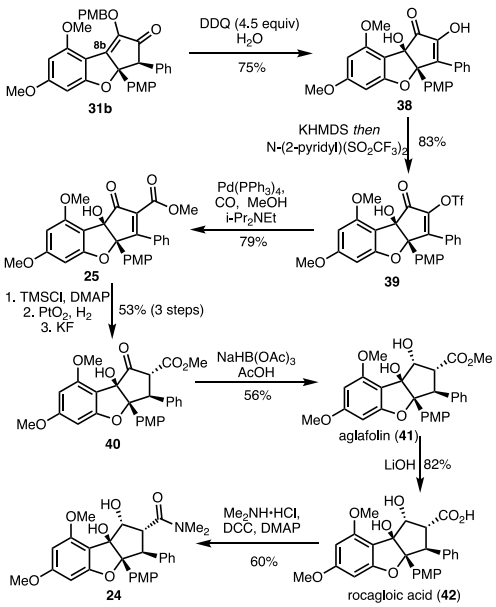
[a]Conditions: *m*–CPBA (1 equiv.), r.t. [b]0 °C [c]5 mol % *p*–TSA was added [d]3.5 equiv. of *m*–CPBA were used [e]TFA (1 equiv.) was used

Scheme 12. Proposed mechanism for Nazarov cyclization triggered by the oxidation of an allenol ether



Having finally executed the Nazarov cyclization, with creation of the C3/C3a stereocenters of rocaglamide, it remained to install the requisite functionality on the cyclopentane core. DDQ oxidation of **33b** (bearing a para–methoxybenzyl protecting group) achieves both deprotection and installation of the hydroxyl group at the ring junction (Scheme 13). Conversion of alcohol **38** to vinyl triflate **39** followed by palladium(0) mediated carbonylation installs the final carbon atom of rocaglamide. The hydroxy group of alkylidene β–ketoester **25** was temporarily protected with a trimethylsilyl group, allowing clean PtO_2–catalyzed hydrogenation of the electron–deficient olefin. Removal of the TMS protecting group gave **40** which was reduced in a diastereoselective fashion to 2give aglafolin (**41**). **41** was hydrolyzed to afford rocagloic acid (**43**), and coupling with dimethylamine afforded (±)–rocaglamide in 18 steps.

Scheme 13. Completion of rocaglamide synthesis

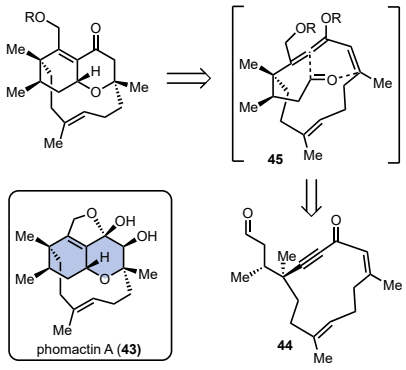


Our synthetic journey *en route* to rocaglamide is a story of success through failure. Because we were unable to achieve the key cyclization as originally planned, we were forced to improvise within very specific constraints as dictated by the target. We were obligated to re–evaluate our understanding of pentadienyl cation behavior as it presented itself in the highly electron–rich benzofuran system central to our strategy. The success of the enol ether oxidation encouraged us to think seriously about alternative means to generate the pentadienyl cation intermediates for electrocyclic processes. This project led us to shift our focus away from divinyl ketones as reactants, spawning new methodological advances in our lab with potentially broad impact for cyclopentene synthesis.[24]

Studies Towards the Total Synthesis of Phomactin A

The phomactin class of natural products were isolated from *phoma* sp. a marine fungus that grows on the shell of a crab off the coast of Japan.[25] Phomactin A is the most structurally complex of the phomactin family, possessing a bicyclo [9.3.1]pentadecane core and a reduced furanochroman. The phomactins were found to be platelet–activating factor (PAF) antagonists, with phomactin A showing an IC_{50} of 10 μM. At the time of our work, four total syntheses of phomactin A had been completed along with a number of studies towards the carbocyclic skeleton.[27] The initial strategy targeting the oxadecalin core of phomactin A hinged upon an intramolecular hetero–Diels–Alder reaction of a macrocyclic vinyl allenol ether **45** (Scheme 14).

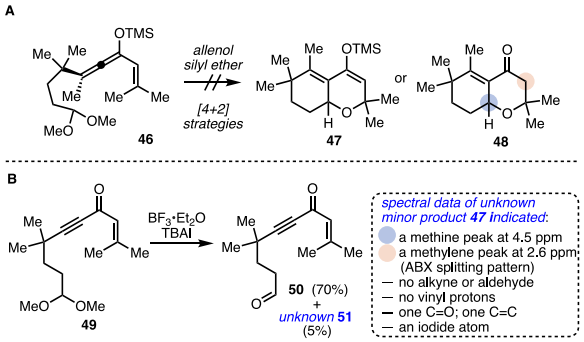
Scheme 14. Hetero Diels–Alder route to phomactin A



Plans to use model silylallenol ether **46** to assess the viability of the strategy were foiled due to an inability to unmask the aldehyde without destroying the diene moiety. Simple acetal deprotection of **49** produced mostly **50**, along with a minor

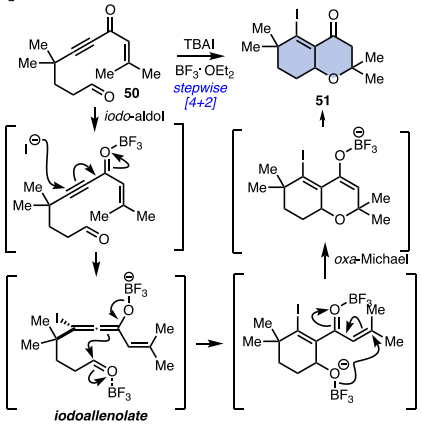
product **51**, which was noted with excitement because ^{1}H NMR peaks consistent with an oxadecalin system were detected (Scheme 15).

Scheme 15 A) A Model for the Hetero-[4+2] Cycloaddition B) An Exciting Observation
Numbering problem? Unknown is 51, not 47



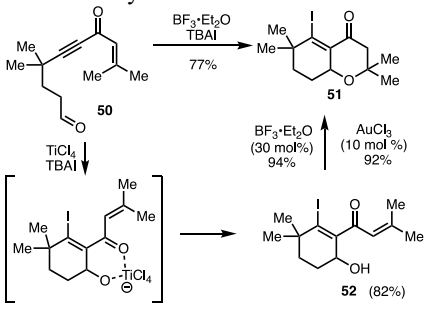
Finally, additional spectral data allowed the assignment of unknown **51**: an oxadecalin bearing a vinyl iodide (Scheme 16). Remarkably, the experimental design underlying the original hetero [4+2] cycloaddition strategy primed us for the discovery of this sequential iodoaldol/ oxa–Michael sequence. The proposed mechanism of this transformation is shown in **S**cheme 16. 1,4-addition of the iodide to the alkynone produces an iodoallenolate, aligned to participate in intramolecular iodoaldol reaction.[28] The Lewis acid then promotes oxa–Michael addition and delivers oxadecalin **51**.

Scheme 16. Mechanism of stepwise [4+2] annulation



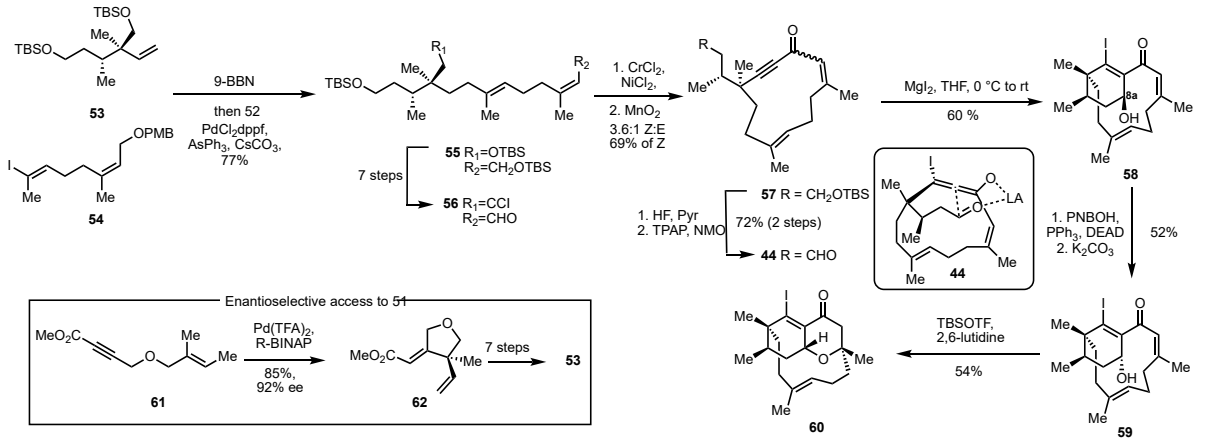
When we evaluated the scope and limitations of the annulation, we found that (a) the process was reasonably general and (b) the identity of the Lewis acid has a strong influence on chemoselectivity. While $BF_3{\cdot}OEt_2$ promotes the stepwise [4+2] annulation, chelating Lewis acids arrest the sequence before the oxa-Michael reaction, affording monocyclic alcohol products **49** (Scheme 17).[29] Consistent with this analysis, enone **52** can be induced to undergo oxa-Michael addition with $BF_3{\cdot}OEt_2$, or with catalytic gold(III) chloride.[30]

Scheme 17. Effect of Lewis Acid on chemoselectivity



Could this novel, stepwise [4+2] annulation enable assembly of the oxadecalin system in phomactin A? This revised strategy would make use of the original macrocyclic reactant **44**, envisioned as part of the hetero-Diels-Alder route (Scheme 14). An attractive feature of the newly discovered annulation was the potential utility of the vinyl iodide as a functional handle for installation of the dihydrofuran moiety. However, success rested on our ability to implement the iodoallenolate aldol reaction in a *transannular* fashion for the first time. Scheme 18 shows the asymmetric synthesis of the crucial macrocyclic reactant **44.** The enantioenriched building block **53** (synthesized as shown in the inset) and achiral **54** can be joined together by hydroboration of **53** with 9–borabicyclo(3.3.1)nonane (9–BBN) and subsequent Suzuki–Miyaura cross coupling to deliver **55**. Execution of a series of functional group manipulations affords **56**, which can be cyclized via intramolecular Nozaki–Hiyama–Kishi coupling. After oxidation (manganese dioxide), the desired keto-aldehyde **44** is obtained as a 3.6:1 ratio (*Z*:*E*).

Scheme 18. Synthesis of the macrocycle of phomactin A **(box overlaps number 51; and should it be 53?)**



Unfortunately, extensive experimentation with **44** revealed that neither the $TiCl_4$ nor BF_3•Et_2O conditions developed previously (see Scheme 16) can catalyze the desired cyclization. Exposure to either Lewis acid leads to complex mixtures of products and degradation, so we focused our attention on identifying milder conditions to achieve the critical annulation sequence. Pleasingly, magnesium diiodide is a competent promoter of the cyclization, leading to 60% yield of the alcohol product **58**. The drawback to this reaction, however, is that the product is isolated as a 10:1 diastereomeric mixture favoring the undesired alcohol isomer at C8a. The diastereoselectivity is attributed to chelation–controlled cyclization (Scheme 18). The alcohol can be inverted by performing a Mitsunobu reaction with p–nitrobenzyl alcohol and subsequently removal of the *p*–nitrobenzyl group. Finally, *t*–butyldimethylsilyl trifluoromethyl sulfonate in the presence of 2,6–lutidine delivered the oxadecalin core of phomactin A (Scheme 18).

It is important to acknowledge that the weakest aspect of our route is the preparation of building block **53**. The project makes clear how difficult it is to achieve the enantioselective assembly of an all–carbon quaternary–tertiary stereodiad, and thus identifies an unsolved problem in organic synthesis.

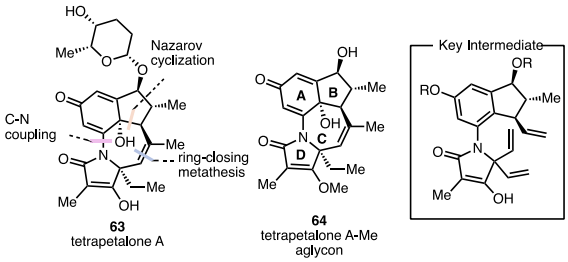
This work highlights the different ways that a total synthesis project can spark the development of new methods. In performing total synthesis, we synthesize exotic molecules with specific arrays of functional groups, necessarily aligned with the target structure. For example, if we had not been experimenting with reactant **49** as a prerequisite for our phomactin A strategy, we would not have stumbled upon the sequential iodoaldol/oxa–Michael sequence. Similarly, reactant **44** demanded we examine and optimize the sequence in a transannular environment. Therefore, we can draw a direct line connecting the structural challenge presented by phomactin A to the expanded applications of the halo–aldol reaction developed in our lab. We can draw another line connecting our experiences synthesizing vinylhalides in the phomactin project to an entire body of recent work in our lab focused on novel *halo*–Nazarov cyclization strategies.[24b–d] This second connection to a seemingly unrelated project demonstrates how ideas explored during total synthesis endeavors influence subsequent research directions – in completely unanticipated ways.

Total Synthesis of Tetrapetalone A–Me Aglycon

Tetrapetalones A–D were first isolated by Hirota and co-workers from *Streptomyces* sp. USF–4727, a bacterial strain found in Japanese soil.[31] The initial structure of tetrapetalone A **63** was misassigned, and to help correct it, a degradation product known as tetrapetalone A–Me Aglycon **64** was produced (Figure 3). These natural products present a unique fused tetracyclic core that contains a tetramic acid, a *para*–quinol, and four contiguous stereogenic centers. At the time of our

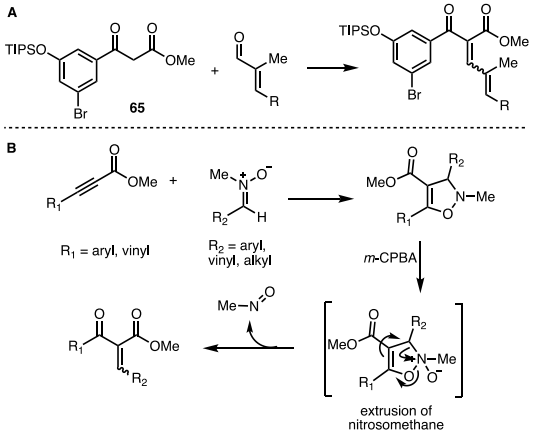
studies, synthetic approaches had been disclosed by Porco,[32] Sarpong,[33] Hong,[34] and Pettus[35] but no synthesis of the tetracyclic core had been achieved. Several years after our report, tetrapetalone A was finally conquered in an elegant synthesis by the Wood group.[36] Given our familiarity with the Nazarov reaction, we chose to engage this cyclization for construction of the AB ring system of tetrapetalone A. We then envisioned use of C-N coupling method to install a tetramic acid surrogate bearing symmetric vinyl groups (see key intermediate, Figure 4), and subsequent diastereoselective ring closing metathesis to create ring C.

Figure 4. Tetrapetalone A with key disconnections (there is a methyl missing on the vinyl group in the key intermediate. Also I would put the key intermediate in the middle, instead of on the right, and put an R on the tetramic acid oxygen in the intermediate, and straighten that C-O bond.)



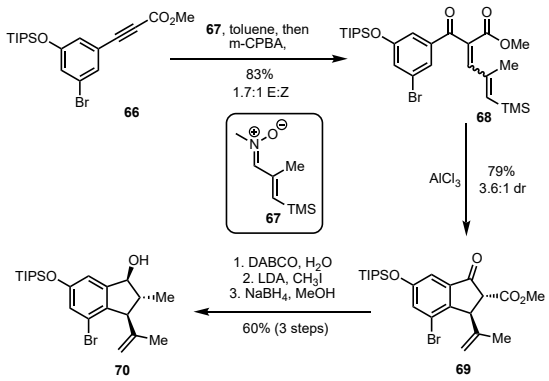
Early in our investigation, we discovered that Knoevenagel condensation of vinyl aldehydes and β–ketoester **65** is not a viable method for synthesizing alkylidene β–ketoesters, the precursors for the Nazarov pentannulation (Scheme 19A).[37, 38] The circumstances required that we invent an alternative method for alkylidene β–ketoester synthesis that replaces the Knoevenagel condensation in our proposed strategy. Inspired by the work of Padwa,[39] the successful new procedure that emerged from our study involves heating nitrones and alkynyl esters to initiate a [3+2] dipolar cycloaddition. Upon cooling and the addition of *m*–CPBA, the nitrogen is oxidized, and the system extrudes nitrosomethane to generate the aryl vinyl ketones in good yields (Scheme 19B).[40]

Scheme 19. (A) The challenges of preparing Nazarov precursors inspire (B) A new method for synthesizing alkylidene β–ketoesters should the arrow in A be hashed (doesn't work?); should the final structure in A have a number (68?) structures in A need alignment; I gave A and B different titles?



This new method enabled the efficient synthesis of the Nazarov precursor **68** **(if we call structure in Scheme 19A 68 this could be 68a)**. Treatment of **68** with stoichiometric $AlCl_3$ gave 79% of the desired product (Scheme 20). The silyl group is also cleaved under the acidic conditions of the cyclization. Krapcho decarboxylation, methylation and reduction of the indanone afforded **70**. The sequence from **68**-**70** paralleled that of the Sarpong group.ref again

Scheme 20. Synthesis of A–B Ring system



Despite extensive experimentation with different aryl halide/amide cross–coupling protocols, we were unable to achieve the direct conversion of aryl bromide **70** to an amide derivative. It is likely that the congestion around the crucial sp^2 carbon compromised reaction efficiency. Fortuitously, AJF visited Dalhousie University during this period of struggle, and Professor Stradiotto suggested that we try his conditions for ammonia cross coupling, which can engage otherwise unreactive aryl halides.[41] This method indeed promoted the elusive C–N cross–coupling, affording aniline derivative **71** in 97% yield from the corresponding bromide **(**Scheme 21).

Next, it was necessary to convert the primary aniline into a substrate bearing symmetrical vinyl groups, in preparation for the planned ring-closing metathesis (see Figure 3). We chose to target oxazolidinone **74**, which could be constructed efficiently through palladium(0)–catalyzed intramolecular allylic amination of dienyl carbamate **73**.[42] ~~Conventional methods enable preparation of cyclization precursor **73**, which indeed cyclizes smoothly upon treatment with palladium(0)~~ (Scheme 20). **(if this reads ok, go ahead and delete crossed out sentence)** This transformation, which presumably proceeds through a π–pentadienyl palladium intermediate, represents a unique cycloamidation manifold. Regarding the closure of ring C, we quickly discovered that the ring–closing metathesis can be achieved with respectable diastereoselectivity using conventional ruthenium catalysts (Table 3 entry 2). However, turnover does not occur with any efficiency. This serious problem (and expense) led AJF to approach Prof. Hoveyda to inquire about molybdenum catalysts, which had been instrumental in the successful RCM of structurally similar divinyl reactants.[43] The inquiry initiated a fruitful collaboration with the Hoveyda group, which ultimately identified the biaryl catalyst **79b**. Using 25 mol% of **79b**, desired tetracycle **75a** is obtained in 82% yield as a single diastereoisomer.

Scheme 21. Construction of symmetrical divinyl system via ammonia coupling and palladium mediated cyclization

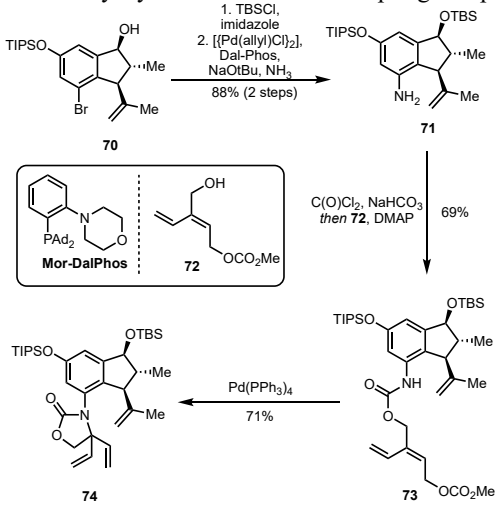
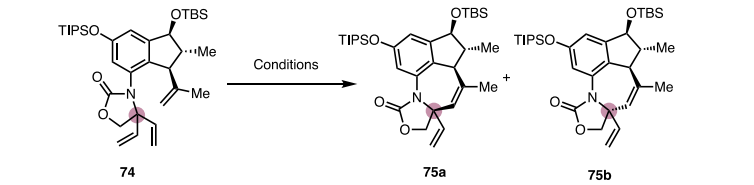
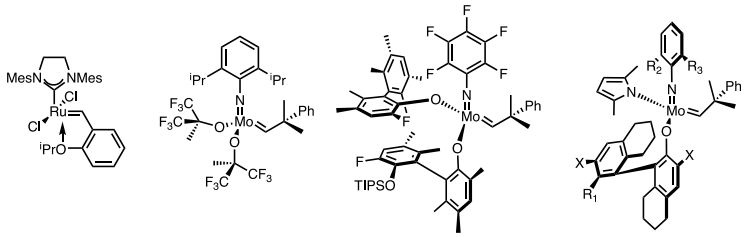


Table 3. Olefin Metathesis Catalyst Screen performed in collaboration with Hoveyda



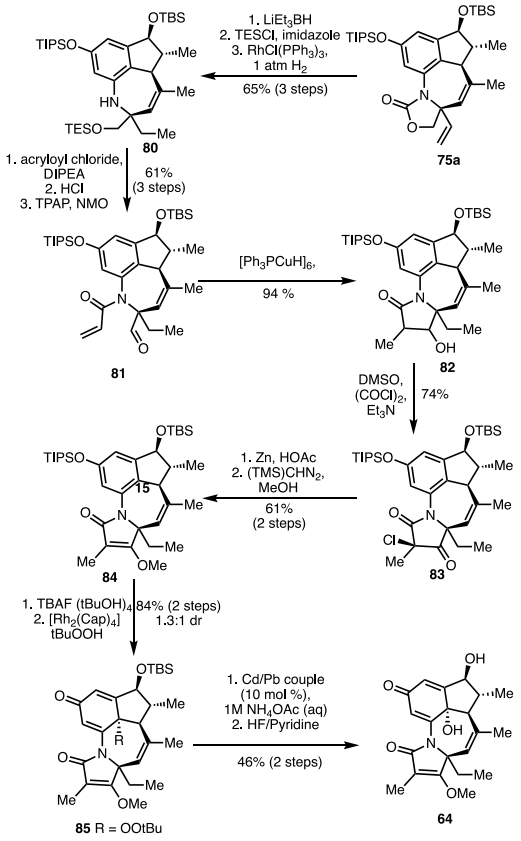


entry	catalyst (Mol %)	temp (°C)	conversion (%)	yield (%)	ratio (a**:b**)
1	**76** (25)	80	<2	–	–
2	**76** (90)	85	89	58	2.4 : 1
3	**77** (25)	22	12	n.d.	1 : 5
4	**78** (12.5)	22	98	90	1 : 3
5	**79a**[a] (25)	22	50	n.d.	>25 : 1
6	**79a**[a] (25)	40	63	63	>25 : 1
7	**79b**[b] (25)	22	58	n.d.	>25 : 1
8	**79b**[b] **(25)**	**65**	**83**	**82**	**>25 : 1**
9	**79c**[c] (25)	22	28	n.d.	>25 : 1
10	**79d**[d] (25)	22	49	40	1 : 1

[a] X=F, R_1=OTBDMS, R_2=R_3=Me
[b]X=F, R_1=OTES, R_2=R_3=Me
[c]X=Br, R_1=OTBDMS, R_2=R_3=Me
[d]X=Br, R_1=OTBDMS, R_2=H, R_3=CF_3

Conversion of **75a** into the tetramic acid target was fraught with unexpected challenges. First of all, both arylamide and aniline derivatives proved difficult to manipulate due to their inherently poor reactivity. Eventually, an exhaustive search led us to a 6-step procedure to access intermediate **81.** A conjugate reduction/ intramolecular aldol reaction sequence with Stryker's reagent gave **82**, closing the final ring of the tetrapetalone core (Scheme 22). Swern oxidation of tetracycle **82** invariably produces chloride **83**, the result of a–chlorination of the target tetramic acid. Reduction of the chloride is achieved with zinc, followed by methylation to afford **84**. The next challenge was oxidation at C15 to obtain the target *p*–quinol. With the endgame upon us, frontline material was precious, and it was not feasible to conduct a broad screen of oxidative dearomatization conditions. For help deciding which oxidation conditions to prioritize, AJF consulted Prof. Tom Pettus, world expert on methods for dearomatization of phenol derivatives.[44] He suggested that we use fairly exotic Rh/tBuOOH oxidation conditions, first disclosed by Doyle.[35,45] As predicted, the protocol is effective in the tetrapetalone context, giving the *para*–tert–butylperoxide **85** in 84% yield. However, our trials were not yet over. We found that conventional methods for reducing the *para*–peroxide to the desired *p*–quinol simply trigger rearomatization. We happened to have some Cd/Pb couple in the lab, recently prepared for the deprotection of a 2,2,2–trichloroethoxycarbonyl group in an unrelated project. We were enormously relieved to find that treatment of **85** with that unusual reducing agent achieves selective reduction of the O–O bond and delivers tetrapetalone A–Me aglycon after deprotection. This Cd/Pb reduction protocol was adopted by Wood et al, enabling their completion of the total synthesis of tetrapetalones A and C.[36]

Scheme 22. Completion of tetrapetalone A–Me Aglycon



Reflecting on this project, we encountered unexpected difficulties at every juncture. Each bond was a battle, and progress was only possible with successful improvisation. Furthermore, our quest to construct the core of tetrapetalone A connected us with other synthetic chemists, through discussions focused on especially challenging transformations. It was these conversations and collaborations, with Stradiotto on C–N cross–coupling, with Hoveyda on ring–closing metathesis, and with Pettus on oxidative dearomatization, that ultimately enabled us to succeed.

CONCLUSION

In our experience, the more insurmountable a problem appears, the more opportunities we find to try new things. In each case, a valuable finding emerged from the struggle to create a difficult bond. Merrilactone A encouraged us to innovate within the constraints of the Nazarov cyclization, which launched a long–term program focused on electrocyclization and a series of subsequent studies descended from this original problem. Phomatin A enabled the development of novel iodoallenolate annulations, reaction cascades that owe their discovery to the unusual oxadecalin scaffold of the target. In the case of rocaglamide, unfavorable results encouraged a conceptual shift in strategy, which led to the first successful execution of Nazarov cyclization induced by oxidation of an allenol ether. The tetrapetalone project in our lab was enriched by collaboration and conversations with colleagues with complementary expertise, ultimately allowing for the successful synthesis of the tetracyclic core. Our program has been profoundly shaped by these campaigns to assemble Nature's small molecules. The synthetic demands imposed by their structures has been the most important driving force for progress, innovation, and the acquisition of new chemical insight. Furthermore, the evolution of our research on cationic cascades and stereocontrolled cyclizations owes everything to the endeavors described in this Account.

CODA: *"I try to plan, in your sense of the word, but that isn't my basic mode, really. I improvise. It's my greatest talent. I prefer situations to plans you see… Really, I've had to deal with givens. "Neuromancer by William Gibson (1984).*

AJF recently encountered this quotation and thought it captured perfectly the practice of target synthesis. All too often, the success of our projects hinges upon our ability to improvise. When a complex intermediate does not react according to the synthetic plan, suddenly we are in a *situation,* improvising to adapt to the behavior ("givens") of the system we worked so hard to build. To find a way forward, we must consider all possible (and even some seemingly impossible) bond–forming

strategies. In this way, complex targets demand creative thinking, and provide opportunities for the discovery of new chemistry.

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Professor Alison J. Frontier received her AB from Harvard in 1992, then spent two years as an Associate Chemist at Merck Research Laboratories in Rahway, NJ. She earned her PhD in 1999 with Professor Danishefsky (Columbia University) and trained as a postdoc with Professor Trost (Stanford University) before joining the faculty at the University of Rochester in western New York, where she is now Professor of Chemistry. Her research focuses on the development of cationic cyclization cascades as strategies for the synthesis of complex natural product targets.

Paul Sinclair was raised in Pennsylvania before attending the University of Rochester, where he obtained a B.S. in Chemistry while conducting research into various cationic cyclizations with Prof. Alison Frontier. After graduating in 2020, Paul moved to Berkeley, CA, where he is currently a Ph.D. student studying complex molecule synthesis in the lab of Prof. Richmond Sarpong.

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