Lessons from Natural Product Total Synthesis: Macrocyclization and Postcyclization Strategies

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CONSPECTUS: Macrocyclic natural products are plentiful in the bacteria, archaea, and eukaryote domains of life. For the significant advantages that they provide to the producing organisms, evolution has learned how to implement various types of macrocyclization reactions into the different biosynthetic pathways and how to effect them with remarkable ease. Mankind greatly benefits from nature’s pool, not least because naturally occurring macrocycles or derivatives thereof serve as important drugs for the treatment of many serious ailments.

In stark contrast, macrocyclization reactions are usually perceived as difficult to accomplish by purely chemical means. While it is true that ring closure necessarily entails an entropic loss and may result in the buildup of (considerable) ring strain that must be compensated for in one way or the other, it is also fair to note tremendous methodological advances during the last decades that greatly alleviated this traditional ”macrocycle challenge”. It is therefore increasingly possible to explore the advantages provided by large as well as medium-size ring systems in a more systematic manner. This venture also holds the promise of increasing the ”chemical space” amenable to drug development to a considerable extent.

In consideration of this and other important long-term perspectives, it is appropriate to revisit the current state of the art. To this end, a number of vignettes are presented, each of which summarizes a total synthesis project targeting macrocyclic natural products of greatly different chemotypes using a variety of transformations to reach these goals. Although we were occasionally facing ”dead ends”, which are also delineated for the sake of a complete picture, these case studies illustrate the notion that the formation of a certain macrocyclic perimeter is (usually) no longer seriously limiting. In addition to substantial progress in the “classical” repertoire (macrolactonization and macrolactamization (pateamine A, spirastrellolide, and belizentrin)), various metal-catalyzed reactions have arguably led to the greatest leaps forward. Among them, palladium-catalyzed C−C bond formation (roseophilin and nominal xestocyclamine A) and, in particular, alkene and alkyne metathesis stand out (iejimalide, spirastrellolide, enigmazole, ingenamine, and sinulariadiolide). In some cases, different methods were pursued in parallel, thus allowing for a critical assessment and comparison.

To the extent that the macrocyclic challenge is vanishing, the opportunity arises to focus attention on the postmacrocyclization phase. One may stipulate that a well-designed cyclization precursor does not only ensure efficient macrocyclization reaction but also fosters and streamlines the steps that come after the event. One way to do so is dual (multiple) use in that the functional groups serving the actual cyclization reaction also find productive applications downstream from it rather than being subject to simple defunctionalization. In this context, better insight into the conformational peculiarities of large rings and the growing confidence in their accessibility in a stereochemically well defined format rejuvenate the implementation of transannular reactions or reaction cascades that can lead to rapid and substantial increases in molecular complexity. The examples summarized herein showcase such possibilities, with special emphasis on tranannular gold catalysis and the emerging ruthenium-catalyzed trans-hydrometalation chemistry for the selective functionalization of alkynes.

KEY REFERENCES

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palladium catalysis, but also is equally enabling in the postmacrocyclization phase.

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■ INTRODUCTION

Nature does not know about Lipinski’s empirical “rule of five” that is thought to roughly determine the spectrum of druglike small molecules. Many secondary metabolites of the highest biological significance have molecular weights of >500 Da and exhibit polar surfaces far beyond the range deemed acceptable in medicinal chemistry. One strategy by which nature gets away is macrocyclization: in essence, the shape and reduced conformational space of a medium or large ring entail a certain preorientation of the H-bond acceptor/donor substituents toward reciprocal functionality on the target protein. While this preorganization reduces the entropic penalty to be paid upon docking to a receptor, most cyclic frameworks remain sufficiently adaptive as needed for an optimal fit; the net results are high selectivity and affinity. For these reasons, macrocycles often allow even rather shallow binding sites to be addressed. Moreover, they contain fewer rotatable bonds than their acyclic analogues, which may lead to improved (oral) bioavailability and (metabolic) stability.

These advantages are so significant that evolution has learned to integrate macrocyclization into the biosynthesis machinery in many different ways. As a result, large rings are common in the peptide, polyketide, terpene, fatty acid, glycolipid, and alkaloid series. Since natural products have been and continue to be a major starting point for drug development, many macrocyclic compounds have reached the bedside. Drugs as emblematic as erythromycin and vancomycin (antibiotics), amphothericin (antifungal agent), FK-506, cyclosporine (immunotherapeutic agents), avermectin (river blindness; also agro business and animal health), and eribulin (anticancer agent) may illustrate the point. Although this list is by no means comprehensive, it shows yet another important aspect: most of the cited compounds are available from the natural source, usually by fermentation (sometimes followed by chemical modification); eribulin is probably the most impressive exception. Anyway, the tendency to let nature forge the macrocyclic ring for us is prevalent. This notion also transpires from the fact that compounds comprising medium or large rings are usually underrepresented in the compound collections of (big) pharma companies, even though the last decades have seen many...
dedicated forays trying to address this imbalance for the sake of an increased chemical space amenable to drug development.\textsuperscript{10,11}

There are certainly good reasons that macrocyclization reactions are commonly perceived as difficult to accomplish. The entropic loss caused by ring closure and/or possible strain of the incipient macrocycle must be compensated for in one way or the other, usually by recourse to high-dilution conditions.\textsuperscript{12} This aspect notwithstanding, it is equally correct to note tremendous methodological advances during the last several decades. We are arguably no longer (seriously) limited by the ability to forge a medium or macrocyclic perimeter. Rather, a stage is reached where the focus can be increasingly shifted to the postmacrocyclization stage, raising the question as to how creative use can be made of the functionality installed during ring closure; transannular chemistry is among the most intriguing of such possibilities.\textsuperscript{13} The following vignettes describe a few selected examples from my laboratory: they showcase various enabling methodologies for macrocycle formation and illustrate different strategies to be considered prior to or downstream of the actual ring-closure event.

\section*{ROSEOPHILIN}

For its intriguing topology and promising biological properties, the pentacyclic alkaloid roseophilin (8) has attracted considerable attention.\textsuperscript{14–16} In 1998, our group reported the first total synthesis, which, though racemic, illustrated how a palladium-catalyzed macrocyclization can institute subsequent transannular events and, in doing so, allows all substituents to be used for an expedient assembly of the target.\textsuperscript{1}

Desilylation of resulting 13-membered ring 2 entailed lactonization, which upgraded the previously unreactive site to a premium substrate for the next palladium-catalyzed event. To this end, the alcohol was first oxidized and corresponding ketolactone 3 then reacted with benzylamine and catalytic [Pd(PPh\textsubscript{3})\textsubscript{4}] to give pyrrole 4. Because the carboxylate leaving group is retained in the product, it could be used to form the target framework: specifically, the derived acid chloride was engaged in a Friedel–Crafts acylation to forge tricyclic core structure 5. At this stage, the remaining sulfone served as a handle for the introduction of the yet missing isopropyl group in the adjacent position. This goal was reached by a cascade commencing with the base-induced elimination of phenyl sulfinate followed by instant trapping of resulting antiaromatic cyclopentadieneone \textit{A} with an isopropyl donor reagent. Only the combination of \textit{t}BuOK and \textit{i}PrMe\textsubscript{2}ZnMgCl (generated in situ from ZnCl\textsubscript{2}·tmda, 2MeLi, and \textit{i}PrMgCl) proved capable of effecting this taxing maneuver. Importantly, the rigid \textit{ansa}-chain provided facial guidance, forcing the zincate to attack transient \textit{A} from the front side. Likewise, the protonation of resulting enolate \textit{B} occurs from the same face, thus furnishing product 6 as a single isomer. Adjustment of the protecting group followed by reaction with metalated side-chain segment 7 and the acid-catalyzed elimination of water installed the azafulvene chromophore and completed the total synthesis of roseophilin (8).\textsuperscript{1}

In a second-generation approach, we pursued the same overall strategy but replaced the palladium-catalyzed macrocyclization by the then-emerging ring-closing alkene metathesis (RCM).\textsuperscript{17} Although the formation of the 13-membered ring was higher-yielding, the need to saturate the additional double bond adds an extra step. In terms of overall yield, the two approaches proved fairly equivalent.
PATEAMINE A

In the roseophilin case, the leaving groups of the cyclization precursor were not defunctionalized but were used for the assembly of the target. A recent total synthesis of cytotoxic marine macrolide pateamine A (13) reiterates this theme, although the chemical context is very different.2,18

Pateamine is a potent cytotoxic agent of marine origin but in extremely short supply.19,20 It exhibits differential activity in xenograft melanoma models in vivo and serves as a valuable probe molecule for investigations into protein biosynthesis because it binds selectively to eukaryotic initiation factor 4A.21 This biological profile is contingent on the presence of an intact Z,E-dienoate spanning the macrodiolide ring: this particular subunit, however, is prone to isomerization to the thermodynamically favored E,E isomer. Therefore it seemed advisable to unravel this pharmacophore as late as possible on the way to 13.

To this end, the Z,E-dienoate was encoded in the form of a robust 2-pyrone ring, which provides internal protection and can be carried through the synthesis without problems up to product 9 as the penultimate compound prior to macrocyclization (Scheme 2). When treated with MeMgBr and catalytic Fe(acac)₃ at low temperature, the pyrone formally behaves as a cyclic enol ester that succumbs to cross coupling with the retention of configuration; the iron-catalyzed reaction entails ring opening while stitching the missing C22 methyl substituent into the framework.22 Since the carboxylate leaving group is retained as a constituent of the resulting seco-acid, the resulting product is primed for macrolactonization, thus minimizing the risk of isomerization of the fragile Z,E-dienoate entity. The fact that only bromopyridinium salt 11 escorted by a non-nucleophilic counterion23 proved capable of forging lactone 12 without jeopardizing the integrity of the dienoate illustrates the delicacy of this maneuver. Product 12 thus formed could be readily elaborated into pateamine A (13).2,18

Since a detailed discussion of iron catalysis is beyond the scope of this Account,24 it may suffice to mention that the ring cleavage is not the outcome of canonical cross coupling. Rather, it is the net result of an iron-catalyzed 1,6-addition of the methyl donor to the heterocyclic system, followed by ring opening of the resulting enolate (Scheme 2). Whether this step follows an electrocyclic course or an ionic mechanism remains currently unclear.2,22

BELIZENTRIN

Inherent instability also overshadowed our pursuit of the methyl ester of potent neurotoxic, dinoflagellate-derived compound belizentrin (22).25 Its scaffold provides several opportunities for macrocyclization:26 after careful consideration, we opted for macrolactamization rather than macrolactonization or C–C bond formation, not the least because we saw a possibility to effect this step by an intramolecular aminolysis of a lactone precursor; such a tactic is exceedingly rare in the literature.

To this end, alkyl bromide 15 was converted to polyfunctionalized organozinc derivative 16, which was cross-coupled with alkenyl iodide 14 comprising a partially skipped and hence highly sensitive polyene sector (Scheme 3). Attempted isolation of free amine 18 derived from coupling product 17 led to a substantial loss of material, likely because of incipient oligomerization by intermolecular amide formation upon removal of the solvent. Although this process prevented the rigorous purification of 18, it actually augured well for the projected macrolactamization. Therefore, crude 18 was diluted with toluene, and the mixture was stirred at 90 °C in the presence of 2-pyridone; this additive serves as a proton shuttle that promotes the breakdown of the tetrahedral intermediate formed upon attack of the amine onto the lactone carbonyl group. Desired macro lactam 19 was indeed cleanly formed, but the reaction invariably stalled at about 60% conversion. Control experiments proved that this outcome is due to reversible amide bond formation in this case:26 the alcohol group in 19 is poised to snap back and close the original spirolactone. Despite the formation of an equilibrium mixture,
this key step proved robust and allowed the first total synthesis of this intricate natural product to be completed. The most challenging step was actually faced downstream from macrocyclization: the extreme base sensitivity of the skipped polyene subunit in aldehyde thwarted all attempts to attach the hydrophilic side chain to the core by classical olefination reactions; only upon tempering the basicity of lithiated sulfone could a modified Kocienski olefination be achieved in a rather low but well-reproducible yield (25–30%).

IEJIMALIDE

The remarkable cytotoxicity of iejimalide B (30) had already been noticed by the isolation team, but it was only a decade later that a more detailed assay by the National Cancer Institute indicated that this marine macrolide deserved careful study. Our group was committed to this task in that we completed the first total synthesis of the iejimalides, optimized the route for gram-scale delivery, prepared numerous analogues and hybrids for SAR studies, and investigated their biological and pharmacological properties in vitro and in vivo. Although further preclinical development was ultimately abandoned because of insufficient metabolic stability, several important lessons were learned during this campaign.

At the beginning, we had deliberately pursued a rather conservative approach for the sake of rapid access to a first crop of material for testing. Interestingly, this was presumably a safe route that failed at the stage of macrocyclization (Scheme 4) despite the favorable track record of the Yamaguchi method. Attempted lactonization of seco-acid afforded none of the desired lactone. Rather, phenol was the only defined compound isolated from the crude mixture; its formation is best explained by assuming the rapid formation of transient ketene intermediate, which undergoes 6π electrocyclic ring closure.

At this stage, the project had to be revisited and the synthesis blueprint had to be fundamentally changed. In the end, we opted for what appeared at the time to be a counterintuitive approach: in view of the polyunsaturated perimeter of 30, macrocyclization by RCM might seem overly risky because it mandates selective activation of 2 out of 10 different alkenes in the cyclization precursor. Moreover, conjugated 1,3-dienes are known to be capricious in that they can be activated by Grubbs-type catalysts on either site, thus opening the door for runaway ring contraction. Even if RCM was successful, control over the configuration of the newly formed olefin is yet another challenge because no kinetically E- or Z-selective alkene metathesis catalyst was known at the time. In consideration of these daunting issues, only the disubstituted and E-configured C11−C12 double bond was deemed a potentially viable site: it is sterically most accessible and E selectivity might eventually originate from thermodynamic control. However, there was no precedent of a similarly highly unsaturated target made by RCM available in the literature when this program was initiated.
In the end, this plan worked very well after an appropriate protecting group regime had been found and the assembly of the cyclization precursor been optimized. Scheme 5 shows the final version: treatment of 27 with ruthenium carbene 28 (10 mol %) in toluene ($10^{-3}$ M) at 50 °C consistently gave 24-membered polyene 29 in >70% yield as a single isomer, which was deprotected with TBAF to give eijimalide B (30).29,31 Numerous analogues were prepared analogously.32 Although Grubbs catalysis had served our long-term program on macrocycle formation exceedingly well on numerous occasions,38 we consider this particular example to be a highlight of our work.

SPIRASTREROLLOIDE F

Spoiled by these many successes, we had also planned to forge the intricate framework of the spirastrellolides by RCM. For their captivating structure and promising antimitotic activity, these phosphatase inhibitors attracted considerable attention from the synthesis community.39,40 Given the dense functionalization, it was the nonstereogenic C25−C26 bond that seemed to be the proper site for metathetic ring closure. Despite numerous attempts, however, this plan could not be reduced to practice; steric hindrance by the adjacent caged spirotricyclic DEF-ring system prevents the reaction from occurring, even in the format of an entrained “relay metathesis” process.41

To make the best use of northern building block 32 originally developed for the metathesis route,42 the strategy was changed and the critical assembly was delegated to an intermolecular alkyl-Suzuki reaction (Scheme 6). Specifically, 32 was subjected to hydroboration and the resulting 9-BBN derivative (33) was coupled to a slightly modified southern sector,31.32,43 Although Yamaguchi lactonization of the resulting seco-acid (34) required forcing conditions to override the stiffness of this compound and compensate for the incipient transannular strain, lactone 35 was obtained in high yield; with this key compound in hand, the door was open for the completion of the total synthesis of spirastrellolide F (36).45,46

Though successful, we could not help but pursue a second and perhaps more innovative approach (Scheme 7). For our long-standing interest in alkyne metathesis,47 we were tempted to scrutinize this transformation by the preparation of a target compound as complex as spirastrellolide. The fact that the C atoms of a triple bond have the same formal oxidation state as a carbonyl suggested that any of the spiro-ketal units punctuating the perimeter of 36 might be an adequate site to do so; the southern BC-ring system was our ultimate choice.3

In the forward sense, the same northern fragment (32) was elaborated into diyne 37, which succumbed to a remarkably facile ring-closing alkyne metathesis (RCAM) reaction on exposure to the molybdenum alkylidyne complex (38)48 in toluene at ambient temperature. This catalyst draws its activity and remarkable compatibility with the numerous donor substituents from a synergy between the high-valence Mo$^+6$ center and the ancillary silanolate ligands. This excellent
application profile also proved to be enabling in many other advanced applications and has recently been improved even further. The subsequent elaboration of cycloalkyne 39 into the target relied upon the ability of a carbophilic catalyst to activate the \( \pi \) system in the presence of numerous conventional Lewis base functional groups. The projected application required some optimization in order to engage the C13−OH group of 40 in the necessary 6-endo-dig cyclization mode with the formation of enol ether 42. Although spontaneous spiroketalization could not be achieved with the aid of catalyst 41, the treatment of 42 with PPTS in toluene at 80 °C closed the yet missing ring.

Compound 35 intercepts the previous route to spirastrellolide F (36), although a shortcut was also developed for the final attachment of the side chain.

**Scheme 7. Second-Generation Synthesis**

**Figure 1.** Selection of other targets formed by RCAM followed by \( \pi \)-acid-catalyzed transannular functionalization at the color-coded sites.

**ENIGMAZOLE A**

The second-generation synthesis of spirastrellolide illustrates the basic concept of inserting an oxygen (or nitrogen) substituent, in a highly regioselective manner, into a complex target framework via a \( \pi \)-acid-catalyzed transannular process. Different variations of this theme enabled the total syntheses of amphidinolide F, kendomycin, the polycavernoside aglycone, the formosalides, and piperidine alkaloid (−)-lythra-
nidine (Figure 1).\textsuperscript{55,56} It is, however, the conquest of enigmazole A (48) which arguably represents the most sophisticated manifestation to date.\textsuperscript{57} This phosphorylated marine natural product interferes with the c-Kit signaling pathway, which is deeply implicated in the regulation of cell proliferation, differentiation, and growth.\textsuperscript{58,59}

Although cyclization precursor 43 is smaller in size than 37 passed through en route to spirastrellolide, it is no less demanding or delicate (Scheme 8): not only is the oxazole ring a potential donor ligand for the molybdenum alkylidyne but the presence of propargylic acetate was also deemed a point of concern: if the metathesis catalyst comprising a high-valence Mo center acts as a Lewis acid and coordinates to this substituent (K), then elimination with the formation of a fully conjugated diene-yne is likely. Even if this fatal path can be suppressed and the triple bond can be activated, a second decomposition pathway is conceivable: any alkyne metathesis catalyst is a Schrock alkylidyne and hence nucleophilic and basic at carbon. This inherent polarization of the Mo–C bond in a complex such as L might cause the extrusion of the propargylic group and hence might lead to the decomposition of the catalyst and/or substrate.

In consideration of these daunting issues, it was gratifying that compound 43 reacted without incident to give cycloalkyne 44 in good yield, even though a fairly high catalyst loading was necessary. This example further illustrates the excellent application profile of the molybdenum alkylidyne catalysts at hand.\textsuperscript{47−49}

At this stage, the project entered the challenging phase of postmetathesis manipulation with the formation of the yet missing tetrahydropyran ring. As a prelude for a transannular reaction cascade, the −OTroc group was cleaved and the resulting alcohol (45) reacted with gold catalyst (R)-49 after ionization with AgSbF\textsubscript{6}. Coordination to the triple bond instigates a [3,3]-sigmatropic rearrangement that transforms the propargyl acetate entity of 45 into a transient allenyl acetate (J), which in turn gets activated by the very same complex that had led to its formation. Upon ligation, it gains Michael acceptor character as illustrated by resonance form N and is hence primed for transannular attack by the so-far bystanding C11−OH group. As this reaction proceeds via a highly ordered chairlike transition state, it affords the correct product stereochemistry. Methanalysis of the resulting enol ester (46) unmasked ketone 47 in readiness for completion of the total synthesis of enigmazole A (48).\textsuperscript{57}

Importantly, this suite of events required the use of chiral catalyst 49. Gold-catalyzed [3,3]-sigmatropic rearrangements are a priori reversible, and the resulting allenyl acetates are subject to racemization. It is believed that 49 forms a matching substrate/catalyst pair capable of overriding this bias and ensuring the correct orchestration of the individual steps.\textsuperscript{57}

### INGENAMINE AND NOMINAL XESTOCYCLAMINE

Target molecules containing more than one medium/large ring pose the additional challenge of proper timing of the cyclization events. More often than not, the simultaneous formation of two (or more) macrocycles is difficult to accomplish (although not inconceivable). For any consecutive approach to be successful, it is quintessential that the chosen methods be chemically 

*Figure 2. Pseudo-enantiomeric relationship between xestocyclamine A and ingenamine as presumed in the literature.*

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Scheme 9. Conquest of Nominal Xestocyclamine A

Scheme 10. Total Synthesis of \textit{ent}-Ingenamine A
orthogonal. This aspect is illustrated in two different ways by our recent conquest of pentacyclic alkaloids ingenamine (51) and nominal xestocyclamine (50), the latter had been believed to be a pseudo-enantiomer of 51, differing in the position of the double bond within the 11-membered ring (Figure 2). By way of synthesis, we showed that this assignment is incorrect: natural xestocyclamine is actually the true enantiomer of ingenamine.

To solve the puzzle, it was necessary to develop an efficient yet flexible approach. To this end, the etheno-bridged diazadecaline core of these intricate targets was assembled by a Michael/Michael addition sequence, which we had originally hoped would proceed in one pot but ultimately had to be carried out in two operations (Scheme 9). Specifically, reaction of the lithium enolate derived from 52 with acceptor 53 failed to afford targeted caged compound 55 but stalled at the stage of 1,4-adduct 54 primarily formed. Gratifyingly though, 54 succumbed to the second Michael addition when treated with K₂CO₃ in refluxing MeCN to give 55 on a multigram scale. A palladium-catalyzed decarboxylicative alkylation allowed the challenging quarternary center at the bridgehead position to be set and, in doing so, a handle for the second macrocyclization to be installed. Compound 56 was then elaborated to 57 as necessary for the first macrocyclization, again by RCAM. All modern alkyne metathesis catalysts are able to distinguish between the π systems of triple bonds (reactive) and alkenes (inert); the active species generated in situ from complex 63 and trisilanol 64 proved most effective in the present case, furnishing strained cycloalkyne 58 in 85% yield.

Derived compound 59 was reacted with excess 9-H-9-BBN, causing hydroboration of the terminal alkenes and regioselective hydroboration of the internal triple bond, whereas the alkynyl iodide did not react under the chosen conditions. Next, dilute HOAc was added to the mixture, causing selective deprotection of the carbamate gave amino acid 66, which was directly subjected to macrolactamization to close the 11-membered ring. Since none of these transformations affect the triple bonds in 67, RCAM could follow. Semireduction of resulting cycloalkyne 68, reduction of the two amides, and deprotection of the silyl ether afforded ent-(−)-ingenamine. The data suggest that ent-51 is identical to natural xestocyclamine but enantiomeric to natural ingenamine.

This study hinged upon two different ways of effecting orthogonal macrocyclization reactions; the fact that alkyne metathesis can either come first or go second highlights the versatility and robustness of this method. In the past, the stereoselective semiredution of the cycloalkynes to the corresponding Z-alkenes, as also practiced en route to 50 and 51, was the most frequent way of harnessing the power of RCAM in the context of natural product synthesis. However, there are many other possibilities (see the examples discussed above using π-acid catalysis); most importantly, the recently developed trans-hydrogenation and trans-hydrometallation of internal alkenes open stereocomplementary access to E-alkenes and even to trisubstituted olefins. The final vignette showcases one such possibility.

**SINULARIADIOLIDE**

Propargyl alcohols are privileged substrates for ruthenium-catalyzed trans-hydrometallation because the −OH group is capable of steering the addition process. Detailed mechanistic studies showed that the effect is primarily due to hydrogen bonding between the −OH group and the polarized [Ru−Cl] unit of the catalyst, which locks the substrate in place; at the same time, the chloride ligand interacts with the incoming R₃E=H reagent (E = Si, Ge, Sn), thus leading to a highly ordered array of type O, which translates to generally excellent levels of regioselectivity (Scheme 11). The resulting products, P, can
be transformed into many different structural motifs, not least into stereodefined trisubstituted alkenes by cross coupling or carbonylation.\textsuperscript{66} Our total synthesis of the marine nor-cembranoid sinulariadiolide (69) illustrates the point (the synthetic product ultimately turned out to be the enantiomer).\textsuperscript{4,69} The tricyclic scaffold comprising a central nine-membered ring is highly strained and hence difficult to forge. We saw an opportunity to reach this compound by a transannular approach, which draws

Scheme 12. Strategic Considerations

Scheme 13. Initial Foray

Scheme 14. Successful Transannular Reaction Cascade Affording ent-Sinulariadiolide
the necessary driving force from the proximity of the reacting sites, when properly positioned on a macrocyclic precursor (Scheme 12). In consideration of the β-ketoester subunit in 69, which is fully enolized despite the unfavorable bridgehead orientation, a transannular Michael addition of a reactive intermediate of type Q was deemed the way to go, despite the uncertainty about whether the involved enolate itself might be Z- or E-configured (cf. T versus U). This process should benefit from a favorable “Felkin-Anh-like” stereoelectronic alignment of the incipient C=C bond anti to the σ* orbital of the allylic −OR substituent.

This plan, however, bore considerable risk in that the allylic −OR group that supposedly facilitates the transannular Michael addition becomes a leaving group at the stage of resulting secondary enolate R, which might be extruded to give butenolide S before stereoselective protonation with the formation of 69 can occur. Use of a substrate with an unprotected −OH group (R = H) was thought to remedy the problem.

The required substrate was prepared from diyne 70, again relying on RCAM as the key step catalyzed by 63/64 (and, shortly thereafter, by new “canopy catalyst” 76 developed in parallel in our laboratory) (Scheme 13).49 The subsequent trans-hydrostannation of derived diol 72 worked as planned in a highly regio- and stereoselective manner,67,68 furnishing 73 as virtually the only product that underwent a palladium-catalyzed methoxycarbonylation70 to give enoate 74. Unfortunately, however, the elaboration of 74 into sinularadiolide met with failure: although C=C bond formation via Michael reaction did occur and the allylic −OH group was preserved, it was this latter substituent that thwarted the success by cleaving the incipient nine-membered ring via transactonization with the formation of 75.

To fix the problem, we resorted to a perhaps counterintuitive tactic: rather than trying to avoid the seemingly destructive extrusion of the allylic substituent, this process was deliberately sparked by converting the diol subunit to a cyclic carbonate leaving group (Scheme 14). Cleavage of the enol acetate in substrate 77 thus formed triggered the crucial transannular 1,4-addition of the resulting enolate; spontaneous cleavage of the allylic group, followed by the loss of CO2 and the attack of the released alkoxide on the adjacent ester furnished butenolide 78. The bridgehead enolate substructure comprised within this tricyclic scaffold is obviously sufficiently strained and hence poised for a spontaneous oxa-Michael reaction with methanol from the medium. Since the back side of the π system is shielded by the medium ring, the addition proceeded stereoselectively to give product 80 as the only isomer in 86% yield over the entire cascade. Cleavage of the methyl group with BBr3 at low temperature then furnished (−)-sinularadiolide (69).5 The recorded optical rotation of the synthetic sample also allowed the absolute configuration of the natural product to be assigned, which is dextro- rather than levorotatory.48,69

The interplay of RCAM, trans-hydrometallation, and methoxy-carbonylation manifested in the synthesis of 69 is only one way of harnessing the potential of this kind of chemistry. Once a C=E−ER3 (E = Si, Ge, Sn) group is set, it provides many opportunities for functionalization and can therefore also serve as a handle for late-stage diversification of a common intermediate (cf. Scheme 11). Focused product libraries modeled on the antibiotic 5,6-dihydrocineromycin B71 and cytotoxic cyclosporins A and Bx2 illustrate this possibility.

### CONCLUSIONS

The vignettes described above substantiate the notion that the formation of a densely decorated macrocyclic frame in a stereochemically well-defined format is, at least in many cases, no longer a limiting factor. To the extent that the former macrocycle challenge disappears, the opportunity arises to exploit the peculiar reactivity of medium and macrocyclic rings. Ring strain is a formidable driving force, and transannular reactions have long been recognized as a potential shortcut to molecular complexity.15 However, our ability to foresee whether macrocyclic stereocentrality will either enhance or outweigh reagent (catalyst) control is still limited. The increasingly powerful methodology for macrocycle formation available to us forms a sound basis for explorations into this underexplored yet highly promising field of research.

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