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Pyranone Natural Products as Inspirations for Catalytic Reaction Discovery and Development

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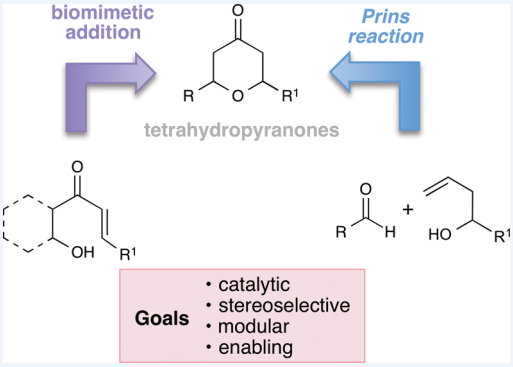
CONSPECTUS: Natural products continue to provide a wealth of opportunities in the areas of chemical and therapeutic development. These structures are effective measuring sticks for the current state of chemical synthesis as a field and constantly inspire new approaches and strategies. Tetrahydropryans and tetrahydropyran-4-ones are found in numerous bioactive marine natural products and medicinal compounds. Our interest in exploring the therapeutic potential of natural products containing these motifs provided the impetus to explore new methods to access highly functionalized, chiral pyran molecules in the most direct and rapid fashion possible. This goal led to exploration and development of a Lewis acid-mediated Prins reaction between a chiral β-hydroxy-dioxinone and aldehyde to produce a pyran−dioxinone fused product that can be processed in a single pot operation to the desired tetrahydropyran-4-ones in excellent yield and stereoselectivity. Although the Prins reaction is a commonly employed approach toward pyrans, this method uniquely provides a 3-carboxy-trisubstituted pyran and utilizes dioxinones in a manner that was underexplored at the time. The 3-carboxy substituent served as a key synthetic handhold when this method was applied to the synthesis of highly functionalized pyrans within the macrocyclic natural products neopeltolide, okilactiomycin, and exiguolide. When employed in challenging macrocyclizations, this tetrahydropyranone forming reaction proved highly stereoselective and robust.



Another major thrust in our lab has been the synthesis of benzopyranone natural products, specifically flavonoids, because this broad and diverse family of compounds possesses an equally broad range of biological and medicinal applications. With the goal of developing a broad platform toward the synthesis of enantioenriched flavonoid analogs and natural products, a biomimetic, asymmetric catalytic approach toward the synthesis of 2-aryl benzopyranones was developed. A bifunctional hydrogen bonding/Brønstead base catalyst was ultimately found to enable this transformation in analogous manner to the biosynthesis via the enzyme chalcone isomerase. Employing thiourea catalysts derived from the pseudoenantiomeric quinine and quinidine, alkylidene β-ketoesters can be isomerized to 3-carboxy flavanones and decarboxylated in a single pot operation to stereodivergently provide highly enantioenriched flavanones in excellent yield. This method was applied to the synthesis of the abyssinone family of natural products, as well as the rotenoid, deguelin. An analogous method to isomerize chalcones was developed and applied to the synthesis of isosilybin A. In both of these related endeavors, the need for novel enabling methodologies toward the efficient creation of targeted molecular complexity drove the discovery, development and deployment of these stereoselective catalytic transformations.

1. INTRODUCTION

Tetrahydropryans and tetrahydropyran-4-ones are found in many bioactive natural products and medicinal compounds.[1,2] Hence, a variety of strategies have been devised over the last century to construct these six-membered heterocycles, including Prins cyclizations,[3−7] hetero-Diels−Alder reactions,[8,9] and intramolecular nucleophilic reactions.[10,11] The tetrahydropyran-4-one containing natural product okilactomycin (**1**) has been of great interest since the establishment of our laboratory in 2002. Our interest in this natural product and related structures, combined with the limits of specific catalytic reactions to craft the key pyran core at the time, led to the multifaceted reaction discovery and development platform described in this Account.

2. LEWIS ACID MEDIATED PYRANONE SYNTHESIS

Our original retrosynthesis of okilactomcyin required the creation of a 3-carboxy substituted tetrahydropyran-4-one (**2**). This seemingly small requirement had large, unintended consequences, and precipitated a completely new approach. Unfortunately, this added substituent precluded the use of a hetero-Diels−Alder strategy, despite exhaustive screening of reaction conditions (eq 1).[12]

We quickly turned to a Prins cyclization strategy, which would form the tetrahydropyran ring with good control over

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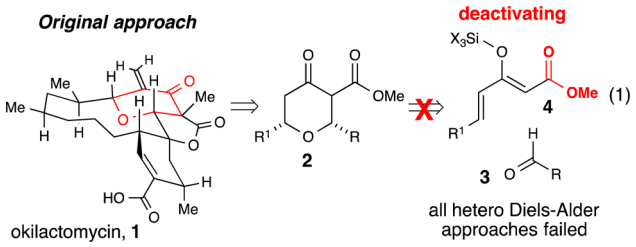
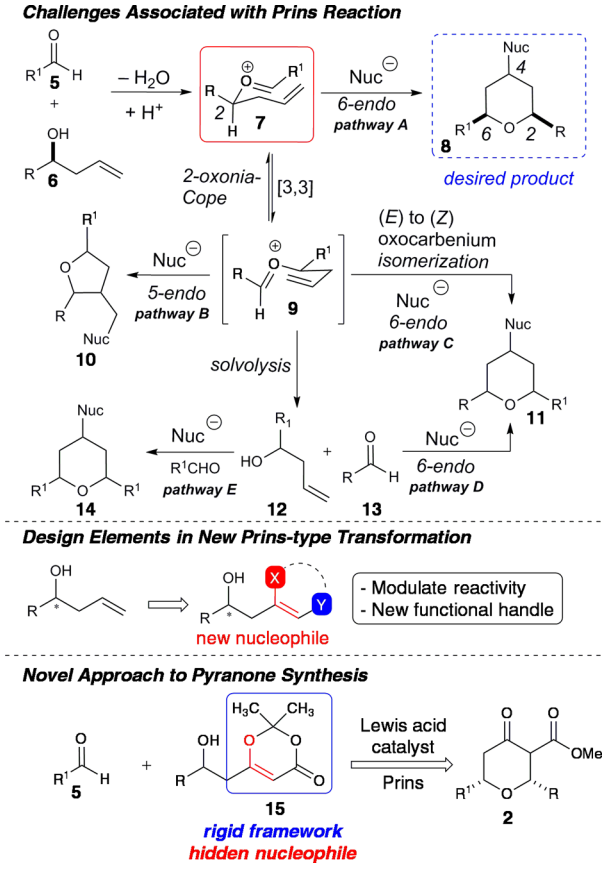


the required 2,6-cis diastereoselectivity.[13] The C−C bond forming event in the Prins reaction is believed to occur via a chair-like transition state, with the C-2 substituent located equatorially and an *E* configuration about the oxocarbenium (Scheme 1).[14,15] This highly organized structure allows the

Scheme 1. Design of a New Prins-type Reaction



chirality at the C-2 position to be transferred to the newly formed chiral center at C-6. The resulting carbocation at C-4 undergoes equatorial attack by a nucleophile to provide the desired tetrahydropyran (pathway A, Scheme 1). A significant pitfall of Prins approaches toward tetrahydropyrans is the vast array of unproductive pathways accessible from the high-energy intermediates (pathways B−E, Scheme 1). Unexpected racemic products have been observed as a number of pathways result in scrambling of the C-2 stereocenter or the formation of undesired products. Of particular concern is the loss of stereochemical information at the C-2 stereocenter via a tandem oxonia-Cope/oxocarbenium isomerization process (pathway C, Scheme 1).[16−18] Prudent substrate design allows for destabilization of the oxocarbenium intermediate (**7**) or stabilization of the C-4 carbocation species, making the desired Prins pathway the kinetically favored outcome.[19−21]

With these design parameters and challenges in mind, we envisioned dioxinones as a novel functional handhold to execute our desired Prins transformation. Dioxinones have been used as masked *β*-ketoesters and as precursors to extended enolates.[22,23] However, their use as nucleophiles is quite uncommon, with only one example when our Prins approach was initially disclosed.[24]

We sought to exploit two features with this new strategy: first, the embedded enol ether functionality could afford a nucleophilic handle at the *α*-position; second, the entire dioxinone framework should provide a rigid platform to engender stereoselectivity (Scheme 1). Furthermore, the requisite enol character is essentially "locked" in dioxinones, and the expected tautomeric-related challenges of related *β*-ketoesters are sidestepped. Finally, dioxinones are easily accessed from catalytic asymmetric additions of dienolates to aldehydes, allowing for facile access to diverse functionality.[25,26]

A brief survey of Lewis acids revealed that scandium(III) triflate afforded the desired pyran−dioxinone at loadings as low as 10 mol %, while other metal triflate salts failed to yield significant amounts of product. Notably, selection of dehydrating reagent is crucial because calcium sulfate exclusively enables formation of the desired pyranone product in high yield. Subjecting a variety of aldehydes and dioxinones to the reaction conditions delineated the strengths and limitations of this approach.

Reactions with saturated and unsaturated aldehydes generally proceed in good yield; however, the overall diastereoselectivity of the transformation is sensitive to aldehyde functionality (Table 1). Branched aliphatic aldehydes (Table 1, entry 3) and aryl substituents such as phenyl (Table 1, entry 4) and 1-naphthyl generally lead to lower diastereoselectivities; however, electron deficient aryl groups (Table 1, entry 5) display excellent diastereoselectivity. Dioxinone substitution is broadly tolerated.

While the pyran−dioxinones (**18**−**25**) can be isolated in good yield, the related *β*-keto esters can be obtained with excellent diastereoselectivity in a single-pot operation. Upon exposure to heat, a highly reactive acylketene **32** is likely formed. This can be trapped with an amine to yield the corresponding *β*-keto amide **33**, or the use of wet DMSO promotes decarboxylation, affording the disubstituted tetrahydropyran-4-ones **34** with complete retention of stereochemistry.

3. DEPLOYMENT OF TETRAHYDROPYRAN-4-ONE FORMING METHODS IN TOTAL SYNTHESIS

With a versatile platform in hand, we sought to apply this method toward the synthesis of biologically and medicinally relevant targets of interest. The application toward okilactomycin proved more challenging than expected (see below), but during these studies another potential target appeared in early 2007, which captured our immediate attention.

3.1. Neopeltolide

Neopeltolide, a highly cytotoxic macrolide isolated from sponges related to the *Daedalopelta* genus, was disclosed by Wright and co-workers in 2007.[27] The reported structure consisted of a 14-member macrolactone embedded with a trisubstituted 2,6-*cis*-tetrahydropyran and a oxazole side chain appended to this pyran. Excitingly, our Lewis acid-catalyzed

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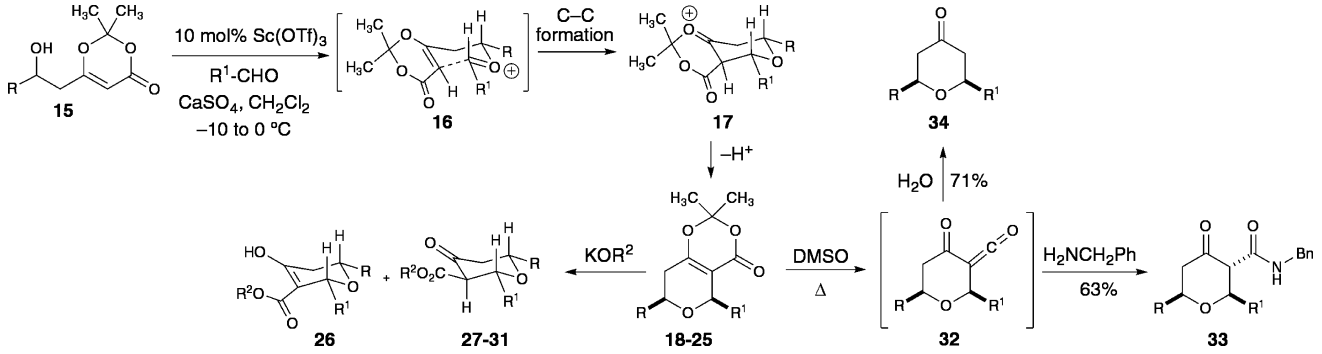
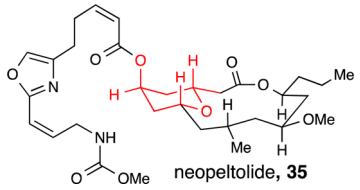
Table 1. Scope of Lewis Acid Mediated Prins Reaction[12]



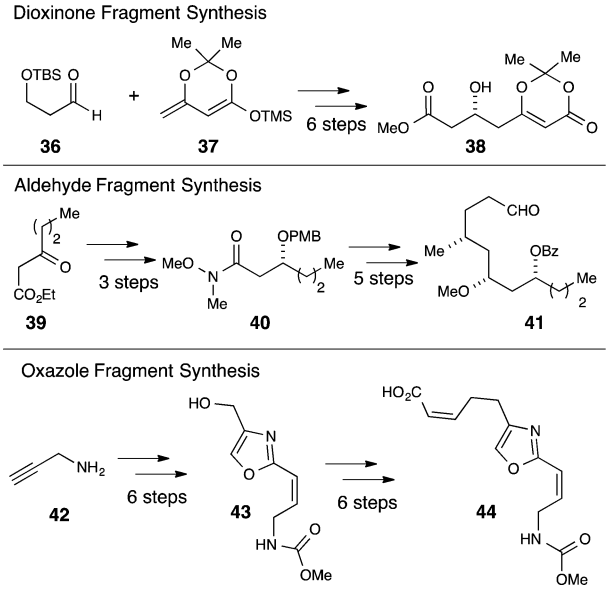
scope of $Sc(OTf)_3$-catalyzed cyclization						ring-opening functionalization						
entry	R^1	R^2	yield (%)	dr	product	entry	substrate	Nuc	yield (%)	dr (*cis*–*trans*)	keto/enol	product
1	benzyl	benzyl	80	20:1	**18**	9	**18**	KOEt	78	95:5	4:1	**27**
2	benzyl	*n*-hexyl	85	20:1	**19**	10	**21**	KOEt	67	93:7	2:1	**28**
3	benzyl	*i*-Pr	75	2:1	**20**	11	**24**	KOEt	72	95:5	4:1	**29**
4	benzyl	Ph	71	6:1	**21**	12	**25**	KOEt	60	95:5	6:1	**30**
5	benzyl	4-F-Ph	83	20:1	**22**	13	**18**	$KOCH_2Ph$	82	94:6	4:1	**31**
6	benzyl	4-MeO-Ph	54	2:1	**23**	14	**18**	H_2NCH_2Ph	63	20:1	N/A	**33**
7	cyclohexyl	benzyl	70	20:1	**24**	15	**18**	N/A	71	20:1	N/A	**34**
8	Ph	benzyl	64	20:1	**25**							



cyclization was ideally suited to setting the 2,6-*cis* stereochemistry and would further provide a handhold to install the highly functionalized oxazole side chain. We further envisioned a highly convergent and flexible synthetic plan where pyran formation could be employed in an intermolecular setting to form a seco acid precursor or, alternatively, in an intramolecular sense in the macrolide forming step. Importantly, when this work was initiated, the use of a Prins cyclization as a macrocyclization reaction had only been reported a single time.[28] As time would demonstrate, other groups were also independently pursuing this general strategy, for example, Wender with the bryostatins, and a full account of these activities have been summarized elsewhere.[13] We viewed this target as a means to expand the venerable Prins into a new type of enabling transformation while simultaneously highlighting the power of our dioxinone mediated cyclizations.

Neopeltolide can be reduced to three segments, dioxinone **38** and aldehyde **41** for the Prins cyclization and an oxazole side chain **44** (Scheme 2). The dioxinone fragment was prepared via a vinylagous Mukiyama aldol reaction in good yield and enantioselectivity (63% yield, 88% ee) with further functional group manipulations yielding the desired dioxinone. The aldehyde fragment was prepared from the readily available ethyl 3-oxohexanoate **39**. Noyori asymmetric reduction followed by conversion of the terminal ester to the Weinreb amide and protection with a *para*-methoxy benzyl group produces amide **40** in 64% yield and 97% ee on gram scale, which was elaborated to the desired aldehyde fragment **41**. Finally, the oxazole fragment **44** was prepared from propargyl amine according to the reports of Leighton[29] and Kozmin,[30] with minor alterations.

Scheme 2. Synthesis of Neopeltolide Fragments[31]



With all the necessary fragments in hand, the respective pathways toward neopeltolide were investigated. The scandium triflate catalyzed Prins methodology was first deployed in an intermolecular fashion, with the macrocycle to be formed by Yamaguchi macrolactonization. Subjection of aldehyde fragement **41** and dioxinone **38** to our cyclization conditions yielded the desired bicyclic dioxinone as a single diastereomer in 55% yield (Scheme 3), and subsequent decarboxylation yielded pyranone **45** in good yield (87%). While we believed that this intermediate could be easily elaborated to neopeltolide, we were eager to deploy the Lewis acid catalyzed cyclization reaction in a more elegant and challenging manner, simultaneously forming the macrocyle and the stereodefined, highly functionalized pyranone in an intramolecular macrocyclization.

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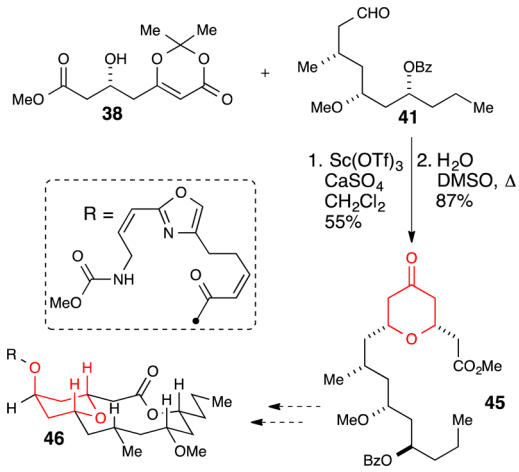
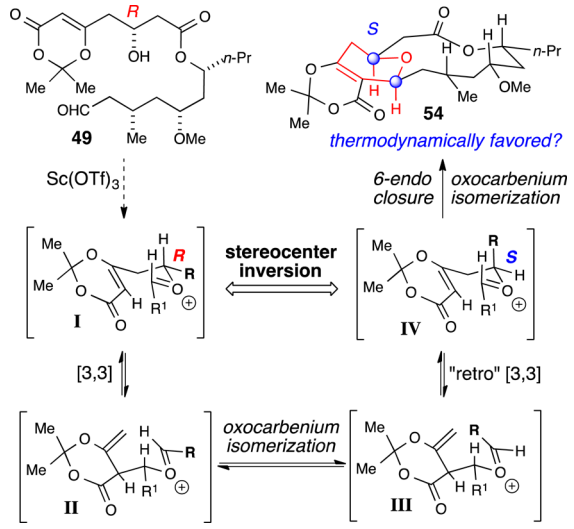
Scheme 3. Intermolecular Prins Approach to Neopeltolide



Aldehyde fragment **47** and acid fragment **48** were coupled by Yamaguchi esterification, silyl protecting groups were globally removed, and selective oxidation yielded cyclization precursor **49**.[32] Gratifyingly, treatment of **49** with 10 mol % scandium triflate furnished the 14-membered tricyclic macrocycle **51** in an unoptimized 25% yield and greater than 20:1 dr (Scheme 4). Upon formation of the pyranone, a stereoselective reduction and Mitsunobu reaction with oxazole fragment **44** yielded what was ostensibly the reported structure of neopeltolide **53**. However, comparison of NMR spectral data revealed that the synthetic material was similar but not identical to the material obtained in the isolation of neopeltolide. Extensive NOE experiments on synthetic precursors, advanced intermediates, and the final product indicated that key protons of the pyran and macrolide possessed a *syn* relationship, as was reported by Wright and co-workers.

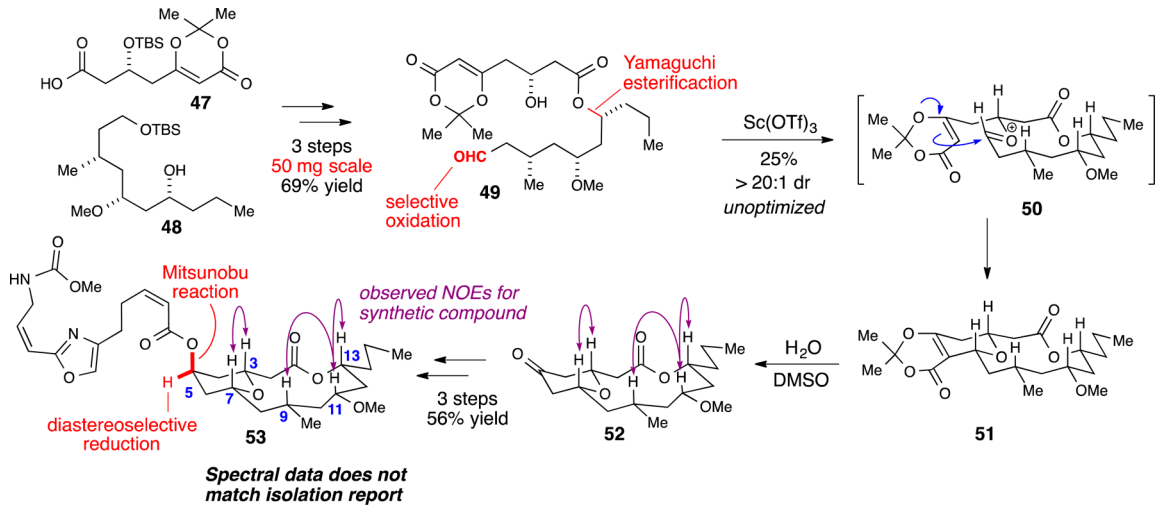
At this juncture, two hypotheses could be advanced to account for the discrepancies between our synthetic material and isolated natural product. First, alternate pathways could be operative due to the higher strain energy associated with macrocyle formation. Previously discussed side reactions of the Prins reaction, namely, the tandem oxonia-Cope/oxocarbenium isomerization process, could be operative, providing inverted stereochemistry at the C-3 and C-7 positions (Scheme 5). Rapid interconversion between oxocarbenium intermediates would allow for racemization and funneling to a thermodynamically favored product **54**.

Scheme 5. Possible Pathway for Isomerization under Prins Conditions



Our second hypothesis was that we had indeed prepared the proposed structure and that the current structure of neopeltolide was incorrect. We felt that prudent experimental design could allow for the concurrent investigation of both hypotheses. Preparation of oppositely configured dioxinone **ent-47** enabled synthesis of the diastereomeric cyclization precursor **56** (Scheme 6). Exposure of **56** to cyclization conditions yielded a single diastereomer, and elaboration to the final product enabled a comprehensive comparison of the isomeric cyclization products and neopeltolide diastereomers. NOE data collected on intermediates and the final product revealed that the C-3 and C-7 positions had been inverted, indicating conservation of stereochemical information during the Prins macrolactionization. We could thus exclude our first hypothesis and concluded that we had likely synthesized the reported structure.

Scheme 4. Prins-Macrolactonization Approach to Neopeltolide



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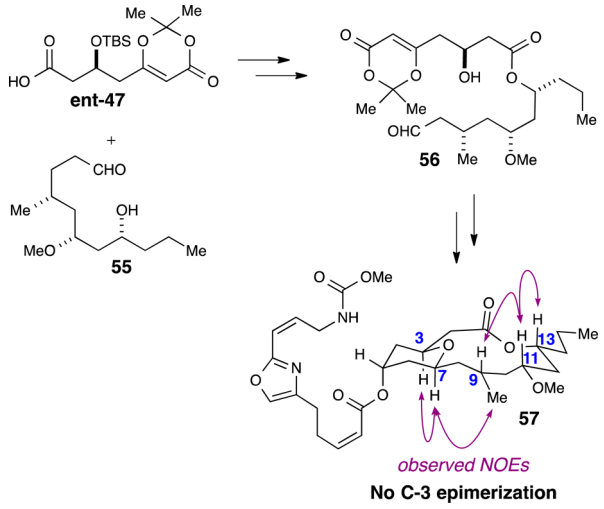
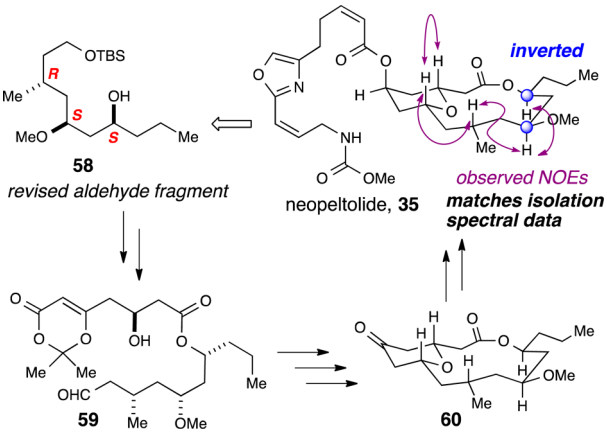
Scheme 6. Synthesis of a Neopeltolide Diastereomer[31]



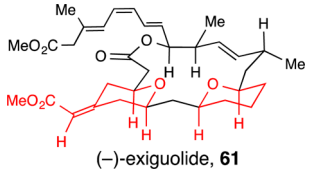
Careful comparison of isolation data with the wealth of information provided by our synthetic efforts led to our hypothesis that the C-11 and C-13 stereocenters were inverted. Again, the flexibility of our synthetic plan lent itself to the facile preparation of the revised alcohol fragment **58**. Elaboration of this fragment to the final product (via the same tranformations) yielded a product that fully matches reported isolation data. Two-dimensional NOESY, HRMS, and optical rotation data confirmed that we had successfully synthesized the natural product (+)-neopeltolide, **35** (Scheme 7). Our findings corroborated those of Panek and co-workers whose elegant independent studies were published shortly before our own.[33]

Scheme 7. Completion of Neopeltolide[31]



3.2. Exigulide

We then sought to extend our Lewis acid catalyzed Prins cyclization strategy in an iterative fashion to form both pyran rings in the macrocylic natural product exiguolide, **61**. Isolated by Ohta, Ikegami, and co-workers in 2006 from the marine sponge *Geodia exigua* Thiele, this molecule possesses potentially useful anticancer activity.[34] From a structural perspective, this target was suited to a unified strategy in which the Prins methodology would be employed to construct the pyran units first in a intermolecular and subsequently in an intramolecular fashion to afford maximum convergency and flexibility, thus enabling structure–activity based biological studies. Notably, the same dioxinone fragment could be used in both Prins cyclizations and the overall approach offered the chance to employ our Prins macrocyclization strategy on a larger macrocycle than neopeltolide.

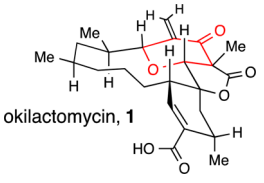


Our synthesis commenced with the aluminum catalyzed, asymmetric acyl halide/aldehyde cycloaddition developed by Nelson and co-workers[35] of alkynyl aldehyde **62** and propionyl bromide **63** to yield a β-lactone, which was processed to enone **64**. Corey–Bakashi–Shibita-type reduction of **65** and a subsequent Eschenmoser–Claisen rearrangement[36] with *N*,*N*-dimethylacetamide dimethyl acetal established the olefin geometry and the stereocenter of the eastern most methyl group; subsequent oxidation state manipulation afforded aldehyde fragment **65** for the first Prins cyclization. Dioxinone **66** was prepared as discussed previously.

With the appropriate fragments in hand, attention was turned to the first Prins cyclization. Unfortunately, scandium triflate proved unable to promote the desired cyclization (see Table 1). More potent Lewis acids were required, which in turn required judicious selection of robust protecting groups. Use of $BF_3 \cdot OEt_2$ and calcium sulfate as Lewis acid and dehydrating reagent, respectively, afforded the desired pyran–dioxinones **67** and **68** in a combined 63% yield on gram scale, which were elaborated to tetrahydropyran **69**. With the stage set for the key Prins macrocylization, conditions were assessed to enable this transformation. Unlike the previous Prins cyclization, scandium triflate proved to be the most effective catalyst, providing the 16-member macrocycle and second pyran unit as a single diastereomer in a noteworthy 66% yield. Following decarboxylation of the dioxinone product, removal of the trimethylsilyl protecting group provided a terminal alkene that was selectively hydrostannylated via a Pd^0 mediated process. This coupling partner was situated to provide a variety of side chains for biological evaluation. Ultimately, a Liebeskind Cu^I mediated coupling enabled the completion of (–)-exiguolide and a host of analogs for biological evaluation (Scheme 8).

3.3. Okilactomycin

In 2011, we disclosed the synthesis of (–)-okilactomycin **1**, an antitumor and antibiotic agent[38] with promising nanomolar



growth inhibition activity against multiple tumor lines.[39] In addition to the biological activity, our interest was further piqued by the intriguing architecture; okilactomycin possesses a unique tricyclic core made up of a 6,5-fused tetrahydropyranone γ-lactone bicycle, the latter of which is fused to a highly substituted cyclohexene. This cyclohexene is further linked to the pyranone through a deoxygenated dipropionate chain, resulting in a rigid, tetracyclic macrocycle. It was these

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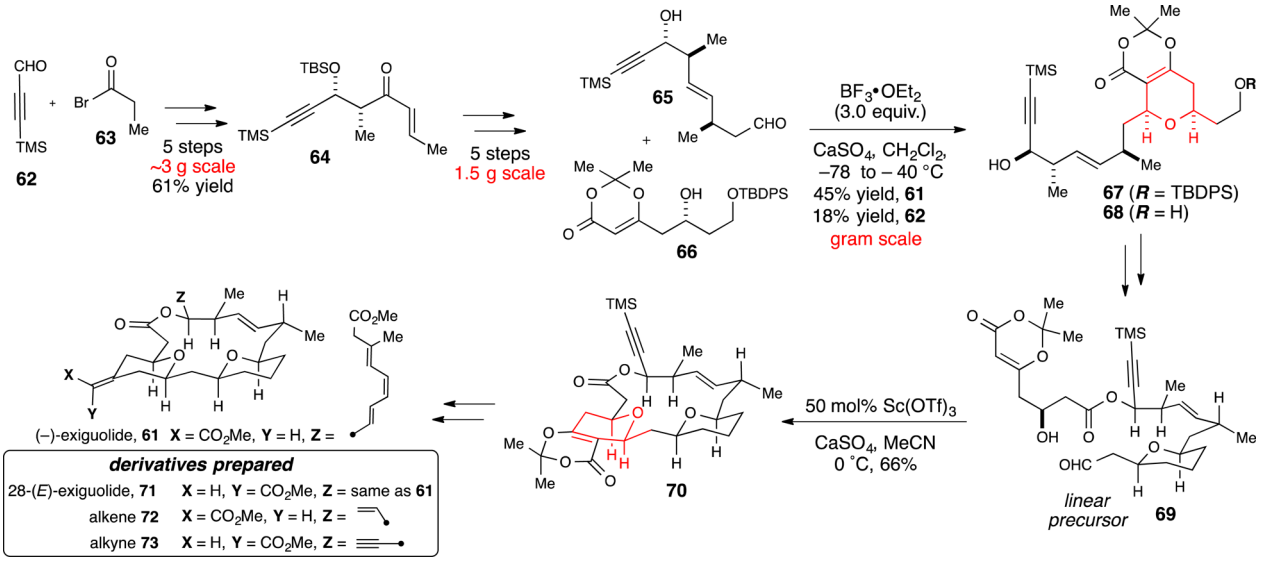
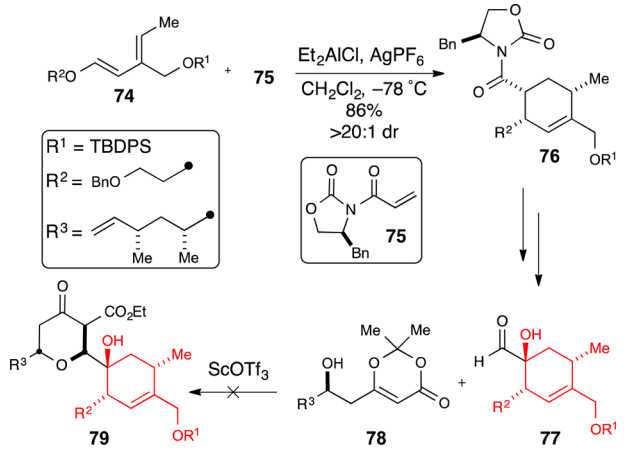
Scheme 8. Total Synthesis of (−)-Exiguolide[37]



structural elements, along with the lack of available methods to construct okilactomycin, that drew us to pursue this target when our laboratory started.[40] Our Prins cyclization was uniquely positioned to provide the pyranone core, along with an ester functionality that with the correct aldehyde substitution (α-hydroxyl) would allow facile formation of the 6,5-fused tetrahydropyranone δ-lactone bicycle. Our convergent route commenced with the parallel synthesis of the cyclohexene aldehyde fragment **77** and dioxinone **78** The key step in the preparation of the former is a highly diastereoselective Lewis acid-mediated Diels–Alder cycloaddition (Scheme 9).[41] The use of silver hexafluorophosphate

Scheme 9. Synthesis of Cyclohexene Fragment

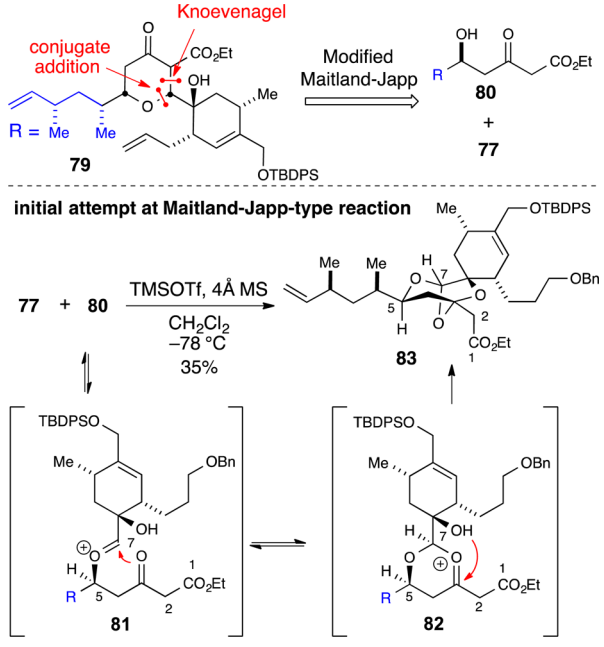


to activate the aluminum catalyst proved to be crucial to the efficiency of the reaction. The imide product **76** is facilely processed to the desired α-hydroxyl alcohol by cleavage of the oxazolidinone auxiliary, conversion of the resulting acid to the aldehyde and Rubottom oxidation with dimethyl dioxirane.

The requisite dioxinone **78** was obtained similarly to earlier efforts through an asymmetric dienolate aldol addition to a known aldehyde,[42] employing conditions developed by the Carreira labratory.[26] However, to our dismay, dioxinone **78** and aldehyde **77** proved unreactive when subjected to scandium triflate conditions (Scheme 9). We took inspiration from Clarke and co-workers who employed a modified Maitland–Japp reaction to effect a similar transformation with δ-hydroxy-β-ketoesters.[43]

The desired pyranone structure could be formed by a Knoevenagel–conjugate addition cascade (Scheme 10).

Scheme 10. Initial Efforts towards a Maitland–Japp Reaction



Hydrolysis and deprotection of dioxinone **78** provided the requisite δ-hydroxy-β-ketoester **80**. Subjecting **77** and **80** to TMSOTf unexpectedly yielded the trioxabicylo[3.2.1]octane **83** in 35% yield (Scheme 10). Interestingly, this suggests that the typical mechanism of condensation followed by oxo-conjugate addition is not operative and a Prins-like reaction is occurring. A proposed mechanism for this process is seen in Scheme 10. Condensation of the δ-hydroxy-β-ketoester **80** with aldehyde **77** yields oxocarbenium **81**. Instead of enol addition, the ketone carbonyl adds to create another oxocarbenium **82**

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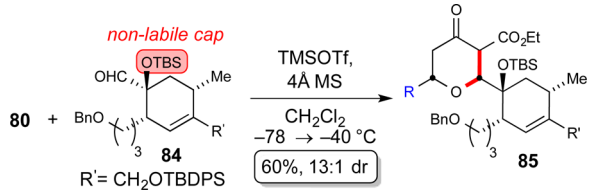
that is trapped by the α-alcohol of the aldehyde fragment to form the observed trioxabicylo[3.2.1]octane **83**. We hypothesized that simply capping the alcohol could suppress this pathway, given that the ketone addition into the oxocarbenium was likely reversible.

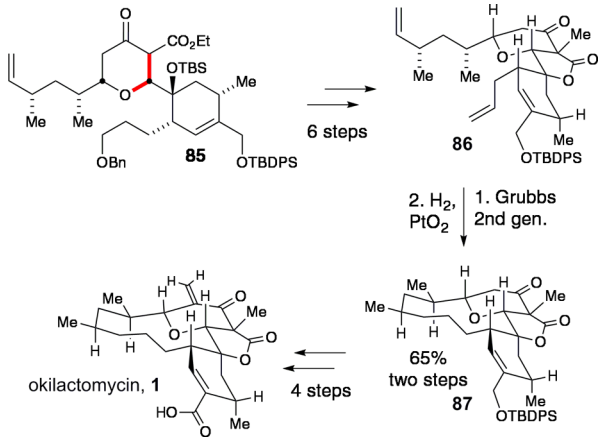
Gratifyingly subjection of α-silyl ether aldehyde **84** and δ-hydroxy-β-ketoester **80** to the same Lewis acid conditions provided the desired pyranone **85** in good yield and excellent diastereoselectivity (Scheme 11).

Scheme 11. Successful Deployment of the Modified Maitland–Japp Reaction



With the key fragment in hand, the okilactomycin was well within reach. Ring-closing metathesis precursor **86** was obtained in 20% yield over six steps (Scheme 12) from **85**.

Scheme 12. Completion of Okilactomycin[44]



Treatment with Grubbs second generation catalyst (40 mol %, 40 °C) followed by platinum catalyzed hydrogentation yielded **87** in 65% yield (two steps). Silyl group cleavage, methylenation, and oxidation provided (−)-okilactomycin **1** in 1% yield over 26 steps (longest linear).

4. BIOMIMETIC CATALYTIC APPROACHES TO PYRANONES

Complementary to our interest in forming highly functionalized pyranones, we have also pursued the catalytic asymmetric synthesis of benzopyranones, the core structures of flavonoids, a broad class of plant secondary metabolites that possess a diverse array of biological activity and medicinal applications.[45] Interestingly, the biosynthesis occurs via the annulation of a 2′-OH chalcone to a flavanone via the chalcone isomerase enzyme (CHI).[46,47] This enzyme impressively performs the isomerization in an estimated S/R ratio of 100 000:1 (ee = 99.998%).[48] The simple flavanone product is then processed to the wide variety of flavonoids found by a series of oxidations and other transformations. We sought to mimic this impressive biosynthetic transformation via a bifunctional H-bonding/Brønsted base catalyst in direct analogy to CHI (Figure 1).

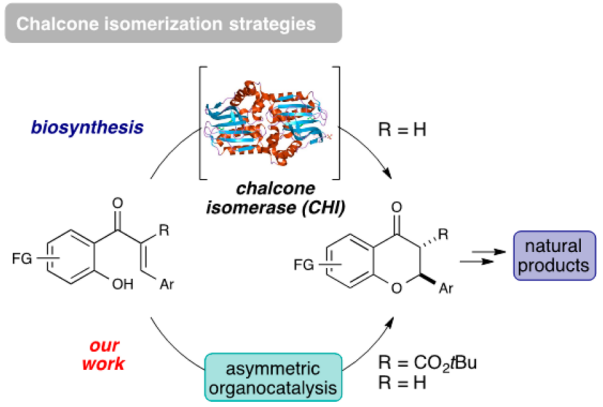


Figure 1. Biosynthetic and Biomimetic Approaches toward Flavanone.

4.1. Development of Small Molecule CHI Analog

A review of asymmetric approaches to flavanones reveals that options are still far from perfect.[49] At the time of our initial disclosure in 2007, the selection of approaches was severely limited. We sought to directly synthesize these compounds from readily prepared precursors. The previously described biosynthetic approach provides great inspiration as the preparation of chalcones, or the related alkylidene β-ketoesters, is generally facile and robust. *A challenge with reconstituting the chalcone cyclization under laboratory settings is the ease of which the flavanone undergoes the reverse reaction, phenoxide elimination.* As such, mild conditions, analogous to physiological conditions, are required. With these design parameters in mind, neutral hydrogen bonding organocatalysis stood out as an attractive option. We felt that activated unsaturated ketones (e.g., alkylidene β-ketoesters) would further gear the system toward cyclization, while being easily removed to afford the desired benzopyranone. Furthermore, a second electron-withdrawing group could provide two-point binding for a hydrogen bonding catalyst (Table 2).

Since alkylidene β-ketoesters could be facilely prepared by Knoevenagel condensations in >95:5 E/Z ratio from aryl aldehydes, they were the substrate of choice for initial investigations. Cinchona alkaloid thioureas had been highly explored as bifunctional catalysts[50] and were chosen due to their ease of preparation. Surveying three such catalysts (Table 2) demonstrated that these were promising catalysts for this transformation, particularly with respect to the fact that catalysts yielding equivalent and complementary stereocontrol were identified (entries 1–3, Table 2). The effect of temperature on selectivity was examined and surprisingly only affected catalyst **C**. Further investigation of catalyst **C** revealed a dependence on concentration, with 10 mol % at −25 °C promoting the isomerization reaction with a yield of 85%. The sensitivity of thiourea catalysts to concentration has been previously observed.[51,52] Finally, it should be noted that the corresponding chalcone substrate *does not react* when exposed to catalysts **A**, **B**, or **C** under these conditions.

As seen in Table 3, the reaction proved amenable to a variety of substitution, including electron-rich (entry 5), extended aromatic (entry 3), and cycloalkyl (entry 9).

Conditions to effect the removal of the 3-carboxy group were then identified: the exposure of the product to *p*-TsOH in

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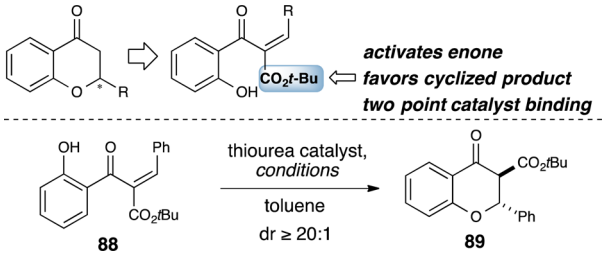
Table 2. Development of Biomimetic Chalcone Annulation[53]



entry	catalyst[a]	mol %	temp (° C)	ee (%)	yield (%)
1	**A**	20	22	−80	97
2	**B**	20	22	80	82
3	**C**	20	22	71	88
4	**A**	20	−25	−80	78
5	**B**	20	−25	80	nd
6	**C**	20	−25	88	nd
7	**C**	10	−25	92	85

a

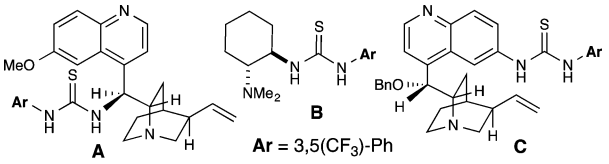
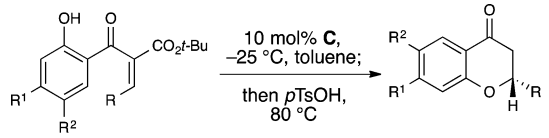


Table 3. Scope of Chalcone Annulation



entry	R	R^1	R^2	ee (%)	yield (%)
1	Ph	H	H	94	92
2	4-BrPh	H	H	92	65
3	2-naphthyl	H	H	91	89
4	4-CH_3-Ph	H	H	90	83
5	4-OMe-Ph	H	H	91	94
6	Ph	OMe	H	89	71
7	Ph	Me	H	90	97
8	Ph	−$(CH)_4$−		89	78
9	cyclohexyl	H	H	80	65

toluene following cyclization in a single pot operation at 80 °C affords the decarboxylated benzopyranone in excellent yield and with complete retention of stereochemistry at the C-2 position. Interestingly, the 3-carboxy flavanone was often formed as a mixture of *cis* and *trans* isomers but yielded highly enantioenriched flavanones upon decarboxylation.

With an efficacious catalytic system developed that tolerated a variety of substrates, efforts were turned to applying this to the synthesis of biologically and medicinally relevant natural products.

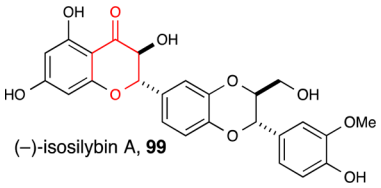
4.1. Abyssinones

The abyssinones are a group of enantioenriched flavanones historically used in traditional remedies[54] that possess a diverse range of promising biological activity.[55−57] Since no asymmetric synthesis or evaluation of anticancer progression properties had been reported, we saw this as an excellent opportunity to deploy our biomimetic chalcone annulation reaction. We envisioned that our methodology would yield both the natural (*S*) and unnatural (*R*) antipode for biological testing via a uniform sequence of Knoevenagel condensation, catalytic annulation, and subsequent deprotection.

Conversion of aryl aldehydes to the corresponding bismorpholine aminal enabled smooth condensation with *β*-ketoester **94** to deliver the desired alkylidines with minimal amounts of racemic cyclized material (Scheme 13). Exposure of the product to 10 mol % of quinidine derived catalyst **D** or quinine derived catalyst **C** smoothly afforded the cyclized product (natural (*S*) and unnatural (*R*), respectively) in good yield and excellent stereoselectivity. Use of allyl ester functionality, as well as allyl protecting groups, allowed for a convenient Pd^0 catalyzed tandem deallylative decarboxylation/deprotection, which smoothly affords the abyssinone final product with yields of 65−76% over the cyclization and deallylation steps (Scheme 13).

4.2. The Silybins: Synthesis of Isosilybin A

With our methodology toward flavanone natural products validated, we turned our attention to more structurally complex flavonoids, the silybins. Isolated as extracts from the milk thistle



(*Silybum marianum*), known as silymarin, the mixture of these natural products has historically been employed as an ethnomedicine for acute mushroom poisoning.[58] Silymarin is a complex mixture of flavonolignans and flavonoids, including silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin, and taxifolin (Figure 2).[59]

Congruent with our ongoing interest in prostate cancer (PCa) therapies, the silybins and isosilybins have shown promising activity against PCa.[60] On the basis of reports accessing the corresponding benzodioxane aldehyde developed by Gu,[61] we felt that we could rapidly obtain the precursor for the cyclization reaction. Yet in attempting to follow this route, we observed subtle differences between isomeric intermediates during a critical ring-forming step. For example, the critical regioselectivity of an intramolecular epoxide opening reaction with a phenol group was dictated by the placement of an electron-withdrawing group (*para* versus *meta* relationship). This unanticipated aspect highlights the challenges with synthesis in general and forced us to develop a new solution specifically tailored for the silybins. The inexpensive and readily available vanillin was elaborated to an enantioenriched epoxide and coupled to an isovanillin derivative via Mitsunobu reaction to yield cyclization precursor **101** on gram scale. Treatment of **101** with mild base (K_2CO_3, MeOH) was expected to yield dioxane **103**, via a spiro TS, in analogous fashion to the many reports using regioisomeric precursors (1,4-aldehyde phenol relationship in contrast to the 1,3-relationship of **101**) (Scheme 14). However, to our surprise, careful analysis of the product revealed that dioxopine product **102** had been exclusively produced via a fused-type transition state. This was verified by single-crystal X-ray analysis of a downstream intermediate. An alternative route was developed in which epoxide **104** was hydrolyzed, the terminal diol was regioselectively protected, and the desired dioxane **105** was formed with a second,

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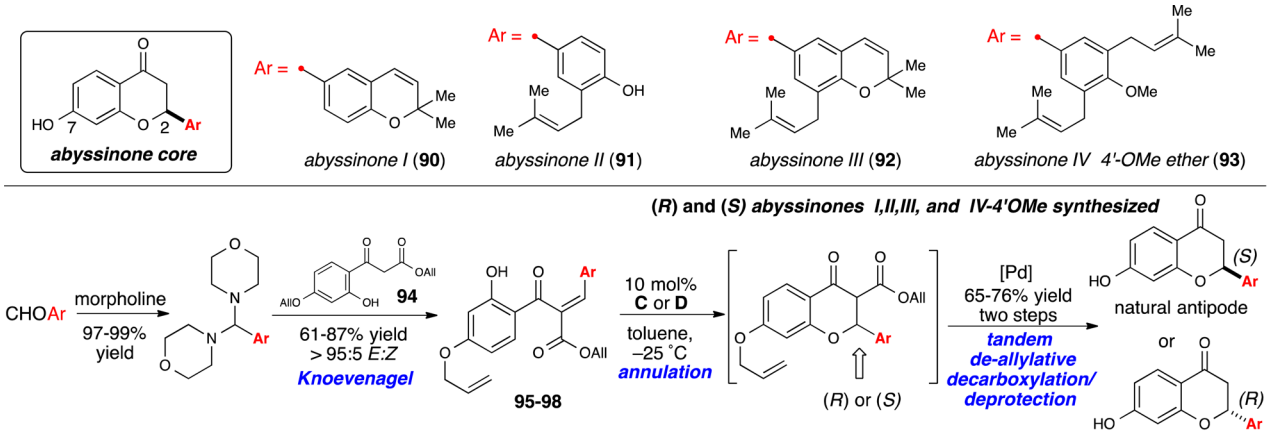
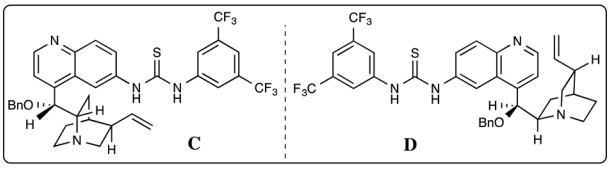
Scheme 13. Synthesis of the Abyssinone Family of Natural Products



Completed Abyssinones

entry	catalyst	alkene	ee (%)[c]	yield (%)[d]	product	
1	**C**	**95**	87	70	*(R)*-**90**	*ent*-abys. I
2	**D**	**95**	82	76	*(S)*-**90**	abys. I
3	**C**	**96**	88	61	*(R)*-**91**	*ent*-abys. II
4	**D**	**96**	89	72	*(S)*-**91**	abys. II
5	**C**	**97**	86	75	*(R)*-**92**	*ent*-abys. III
6	**D**	**97**	84	70	*(S)*-**92**	abys. III
7	**C**	**98**	95	65	*(R)*-**93**	*ent*-abys. IV 4'-OMe
8	**D**	**98**	94	65	*(S)*-**93**	abys. IV 4'-OMe

Bi-functional Catalysts Employed



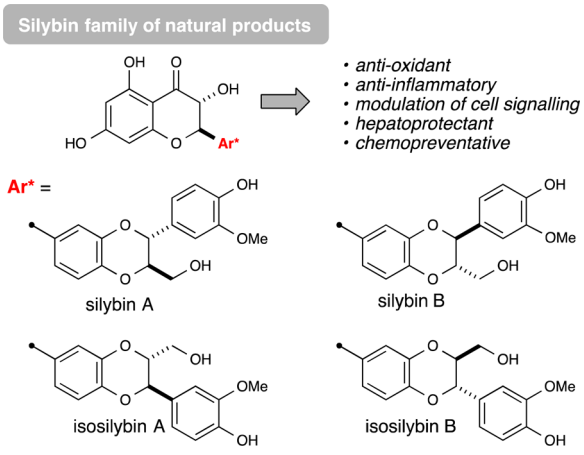


Figure 2. Silybin Family of Natural Products.

annulative Mitsunobu reaction (Scheme 14). At this juncture, it was determined that the aryl aldehyde (or activated derivatives) would not undergo Knoevenagel condensation with β-ketoester, due to the 2,6-functionalization about the aryl ring engendering an unfavorable distortion of the aryl ring. Undaunted, we believed that a similar bifunctional catalytic system could be developed for the analogous chalcone. A simple aldol condensation and p-TsOH·H_2O mediated deprotection provided a chalcone as a substrate for chalcone isomerization. The 2,6-functionalization that precluded the Knoevenagel condensation, proved to be a further design challenge in the cyclization. After extensive screening, we observed that the 2,6-hydroxyl groups must remain unfunctionalized to generate competent reactivity.[62]

In analogous fashion to the issues with the Knoevenagel condensation, bulky substituents at the 2 and 6 positions likely engender an orthogonal relationship between the aryl ring and enone system, preventing cyclization. It has also been proposed that internal hydrogen bonding is necessary to activate the enone system for this oxy-conjugate addition, either electronically activating the enone or planarizing the aryl and enone systems (or potentially both), effectively serving as a template toward the benzopyranone product.

The quinine and quinidine derived catalysts previously used in our abyssinone studies proved most active; however, on the chalcone substrates, the pseudoenantomeric catalysts no longer provided the antipodes with equivalent selectivity. Studies are ongoing to identify a system to provide the opposite flavanone enantiomer with comparable selectivity.[63] Urea catalyst **E** proved most active and provided good selectivity (85:15 dr) on scale. It is important to note that with Schreiner's achiral thiourea catalyst, *no* diastereoselectivty was observed, indicating that stereocenters present in the benzodioxane do not greatly influence the outcome of the cyclization.

With the cyclized flavanone in hand, α-oxidation of the ketone remained. Prudent selection of protecting group was key to enabling this oxidation. While Boc protection proved facile and enabled the purification of the flavanone product, efforts toward the Rubottom oxidation were met with failure. Methoxy methyl ether (MOM) was selected, and oxidation of the corresponding trimethylsilyl enol ether with dimethyldioxoirane proved high yielding and highly diastereoselective (Scheme 15); however the previously discussed sensitivity of flavanones toward basic conditions was observed, with some epimerization of the C-2 position observed when enantiopure flavanone (90:10 dr) was used.

Cleavage of MOM acetals provided (−)-isosilybin A, the unnatural antipode. However, this strategy still is a general entry into the family of silybins and should drive further inquiry into structure−activity relationships, as well as the molecular pharmacology, of these natural products.

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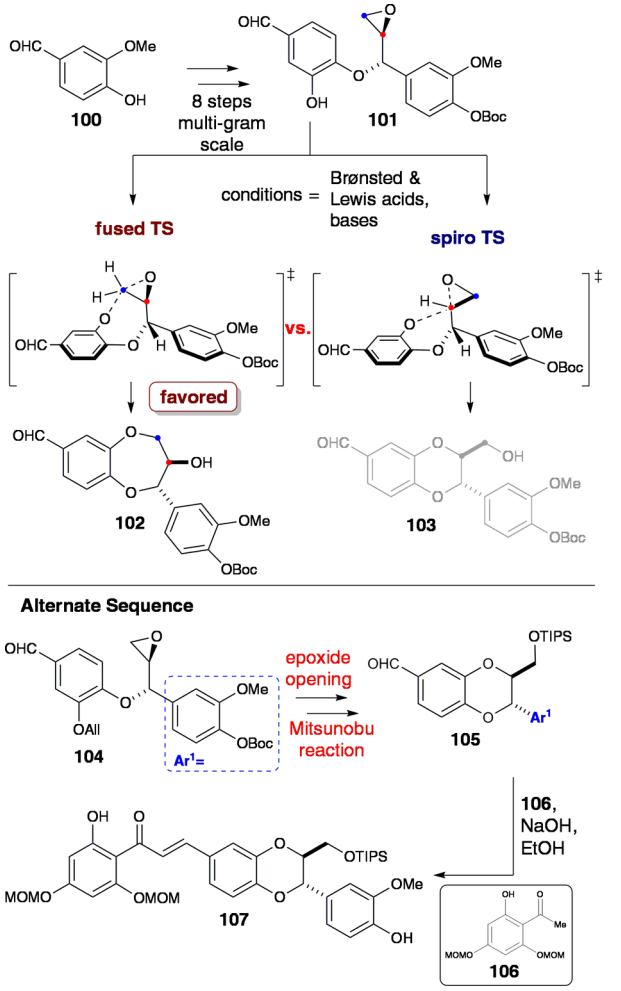
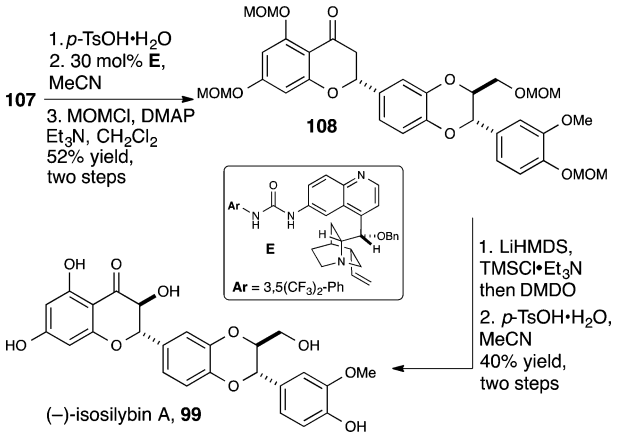
Scheme 14. Preparation of Cyclization Precursor



Scheme 15. Completion of (−)-Isosilybin A[64]



5. CONCLUSIONS

Pyrans are ubiquitous motifs in biologically active and medicinally relevant molecules and continue to provide challenges and inspirations for catalytic reaction development. Since its inception, our research program has been engaged in the development and application of two complementary approaches to the preparation of highly functionalized, chiral pyrans: a highly stereoselective, Lewis acid-catalyzed Prins reaction to produce highly functionalized pyranones and biomimetic catalytic approaches to benzopyrananones. These pursuits to date have entailed a broad range of new methodological strategies and their deployment in complex total synthesis. Both related activities have been successfully applied to the synthesis of privileged natural products and subsequently fueled biological studies involving these compounds. While many exciting challenges and opportunities remain in these areas, we feel that the most important are (1) a pressing need for further reaction discovery and development of catalytic methods with broad scope and high selectivity to construct these oxygen-containing motifs and (2) the continued leveraging of these methods toward functional-oriented synthesis for more expansive biological and ultimately *clinical* investigations of pyranone-containing small molecules inspired by natural products. We look forward to these pursuits and their impact on the broader scientific and medical communities.

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Notes

The authors declare no competing financial interest.

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Karl Scheidt is currently the Dow Chemical Company Professor, the Department of Chemistry at Northwestern University, and Director of the Center for Molecular Innovation and Drug Discovery. Since 2002, his laboratory has been exploring new concepts and strategies for catalysis, chemical synthesis, and therapeutic science.

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