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Stereocontrolled Synthesis of Spiroketal: An Engine for Chemical and Biological Discovery

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Abstract

Spiroketal is a key structural motif found in diverse natural products with compelling biological activities. However, stereocontrolled synthetic access to spiroketals, independent of their inherent thermodynamic preferences, is a classical challenge in organic synthesis that has limited in-depth biological exploration of this intriguing class. Herein, we review our laboratory's efforts to advance the glycol epoxide approach to the stereocontrolled synthesis of spiroketals via kinetically controlled spirocyclization reactions. This work has provided new synthetic methodologies with applications in both diversity- and target-oriented synthesis, fundamental insights into structure and reactivity, and efficient access to spiroketal libraries and natural products for biological evaluation.

Keywords

catalysis; diversity-oriented synthesis; glycol epoxide; kinetic spiroketalization; spiro compounds

1. Introduction

Spiroketal is found in a wide range of natural products with diverse biological activities.¹ This motif can serve both as a pharmacophore that directly engages in specific interactions with biological targets as well as a rigid scaffold that presents side chains along well-defined vectors in three-dimensional space. Prominent examples of the spiroketal pharmacophores include olean, sex pheromones of the olive fruit fly *Dacus oleae*, wherein the *R* enantiomer is active on the male while the *S* enantiomer is active on the female;² and the avermectin family of antiparasitic agents, in which the spiroketal motif engages in specific binding interactions with glutamate-gated chloride channels (Figure 1).³ Scaffolding functions are seen in calyculin A, a protein phosphatase inhibitor that directs its phosphate, cationic, and hydrophobic side chains into complementary binding sites in the enzyme;⁴ and bistramide A, an actin disruptor in which the spiroketal acts as a saddle-like 90° turn element.⁵ Indeed,

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Dedicated to Professor Stuart L. Schreiber and Professor K. C. Nicolaou in honor of their receipt of the 2016 Wolf Prize in Chemistry

these scaffolding capabilities of spiroketals have been leveraged in medicinal chemistry to develop potent, stereochemistry-dependent NK₁ receptor antagonists as antiemetics with CNS activity in a mouse model.⁶ A variety of benzannulated spiroketal natural products have also been identified, such as the rubromycin telomerase inhibitors, in which the central spiroketal motif is essential to activity, and related heliquinomycin DNA helicase inhibitors.⁷

As a result of these diverse biological activities, as well as the intriguing stereochemical and stereoelectronic features of spiroketals,⁸ this class has long attracted the attention of synthetic chemists, and several excellent reviews have been published previously.^{1,9} Readers are referred to those articles for comprehensive discussion and review of the field. Herein, we summarize our laboratory's efforts to develop novel, stereocontrolled approaches to spiroketals, with applications in both diversity-oriented synthesis and natural product total synthesis. In addition to providing efficient access to these molecules for biological evaluation, this program has led to new synthetic methods of broad potential utility and fundamental insights into structure and reactivity.

2. The Glycol Epoxide Approach to Stereocontrolled Synthesis of Spiroketal

At the outset of our studies, we were inspired by two early reports of the synthesis of spiroketals by spirocyclization of cyclic epoxides having alcohol side chains. Cremins and Wallace reported the synthesis of chromanone spiroketals **3** and **4** by spirocyclizations of chromenone epoxide **2** in 1986 (Figure 2a).¹⁰ Subsequently, Friesen and Sturino described a related approach to access the spiroketal core of the papulacandin natural products (**9**), via treatment of a glycol substrate **7** with dimethyldioxirane (DMDO)¹¹ followed by spontaneous spirocyclization of the intermediate glycol epoxide (Figure 2b).¹² In both cases, the spirocyclization reactions proceeded under kinetic control, but afforded mixtures of anomeric diastereomers.

Thus, building upon these reports, we envisioned that the development of kinetic spirocyclization reactions that proceed with either inversion (**13**) or retention (**14**) of configuration of epoxides **12** would provide stereocontrolled access to either spiroketal anomer individually (Figure 3), and ideally independently of thermodynamic product stability considerations that govern the stereochemical outcome of classical acid-catalyzed spiroketalization reactions.^{1,8} In the context of diversity-oriented synthesis, systematic stereochemical diversification at neighboring carbons would then provide access to collections of spiroketals with a wide range of three-dimensional structures.

2.1. Enantioselective synthesis of *threo*- and *erythro*-glycol substrates

Toward this end, we first developed asymmetric syntheses of all four diastereomers of the requisite glycol substrates, in which the C3-alcohol substituent would be used as a directing group to control the stereochemistry of the epoxidation reaction. The *threo*-glycol substrates **18** were readily accessed via asymmetric hetero-Diels–Alder reaction of protected aldehyde **15** with the Danishefsky diene,¹³ using Jacobsen's chromium iminoindanol catalyst **16**¹⁴ (Figure 4a).¹⁵ The C5-hydroxyethyl side chain was designed to maintain 1,3-polyol spacing of oxygen functionalities seen in polyketide natural products, with the TBDPS protecting group envisioned as a surrogate for an analogous silyl linker that we developed for solid-

phase synthesis applications,¹⁶ or as a handle for tagging of the final products with various reporter groups for biological studies. Luche reduction of the ketone proceeded with complete diastereoselectivity for the *threo* configuration to afford **18**.¹⁷

Efforts to access the C3-epimeric *erythro*-glycals **24** by inversion of the C3-alcohol in the *threo*-glycals above using a variety of classical approaches were unsuccessful.¹⁸ Thus, we turned to an alternative approach involving asymmetric synthesis of an alkynediol substrate **23** followed by alkynol cycloisomerization (Figure 4b). Initial stereoinduction was achieved using asymmetric allylation of aldehyde **15** using Leighton's chiral allylsilane reagent **19**¹⁹ followed by homologation to install the desired terminal alkyne in **23**. McDonald's tungsten-mediated photocycloisomerization²⁰ then afforded the desired *erythro*-glycals **24**.

2.2. Installation of C1-alkyl side chains on the glycal substrates

Next, we sought to install C1-alkyl side chains bearing protected alcohol nucleophiles on these glycal substrates. Direct base-mediated alkylation with alkyl iodides proved challenging due to the poor nucleophilicity and high basicity of the corresponding C1-lithioglycals, which led to competing elimination of the alkyl iodide partners.²¹ To overcome this problem, we developed an alternative approach involving conversion of glycals **25** to the corresponding C1-iodides **27** followed by *B*-alkyl Suzuki–Miyaura cross-coupling with alkene-derived side chains to afford a variety of C1-alkylated products **29** (Figure 5).²¹ In the course of this work, we found that preincubation of the 9-BBN-derived alkyl borane intermediate with aqueous NaOH was critical to avoid competing protodemetalation regenerating **25**, which we attributed to disproportionation of an undesired glycal palladium hydroxide intermediate.

2.3. Methanol-induced kinetic spirocyclization with inversion of configuration

With efficient synthetic access to a variety of glycal substrates in hand, we next explored approaches to achieve kinetic spirocyclization of the corresponding glycal epoxides **12** (Figure 3). We focused our initial efforts on epoxide opening with inversion of configuration. At the outset, we recognized several challenges in achieving such reactivity: (1) S_N2 inversion was expected to be challenging at the quaternary anomeric center, (2) competing S_N1 reaction manifolds via oxocarbenium intermediates would remove the C1 stereocenter and could lead to poor stereoselectivity or other undesired products, and (3) unfavorable net *trans*-diequatorial epoxide opening would be required in some cases. Nonetheless, initial studies yielded promising results, with *threo*-glycal **30** undergoing efficient *anti*-epoxidation with DMDO to form epoxide intermediate **31**, followed upon warming to room temperature by spontaneous spirocyclization to a 70:30 mixture of spiroketals **32** and **33** (Figure 6a).¹⁵ Notably, the “inversion” spiroketal **32**, which has only a single anomeric stabilization, was formed with equatorial installation of the side chain nucleophile. This is in contrast to most previously reported approaches to monoanomeric spiroketals, which rely upon axial attack.²² Equilibration of this mixture with TsOH yielded exclusively the “retention” spiroketal **33** (99%, >98:2 dr), which is thermodynamically favored due to double anomeric stabilization.

Encouraged by these results, we sought to improve the stereoselectivity of this reaction for the contrathermodynamic inversion spiroketal **32**. In a key control experiment, we added a large excess of MeOH to the nascent glycal epoxide **31** at $-78\text{ }^{\circ}\text{C}$ in an effort to evaluate the stereochemical outcome of the corresponding intermolecular glycosylation. However, we were surprised to discover that the major product was the inversion spiroketal **32** (80%), formed with complete diastereo-selectivity, while the expected methyl glycosides **34** were formed only as minor products (20%, $\approx 1:1$ dr). Building upon this serendipitous discovery, we found that selectivity for the intramolecular spirocyclization could be improved further to 92:8 (**32**:**34**) by adding the MeOH at $-63\text{ }^{\circ}\text{C}$ (dry ice/chloroform), consistent with entropic considerations, while higher temperatures led to decreased diastereoselectivity in spiroketal formation. Control experiments indicated that the reaction proceeds under kinetic control and that the methyl glycosides are not intermediates *en route* to the spiroketals. Surprisingly, use of more hindered alcohols led to increased competing intermolecular glycosylation, as did decreasing the concentration of the alcohol. A mechanistic explanation for these seemingly paradoxical findings was not immediately apparent, and would await future mechanistic studies (*vide infra*).

Using these optimized reaction conditions, we examined the scope of this MeOH-induced kinetic spirocyclization. Spirocyclization of *threo*-glycal substrates was effective in forming both 5- and 6-membered rings with inversion of configuration, but not 7-membered rings, with only the corresponding methyl glycosides recovered. Importantly, secondary alcohol side chains also underwent efficient spirocyclization independent of side chain stereochemistry to afford substituted spiroketals that access distinct three-dimensional vectors. The MeOH-induced spirocyclization was also effective in the corresponding *erythro*-glycal series, albeit with slightly reduced stereoselectivity in 5-membered ring cyclizations.

In some cases, we were also able to access the diastereomeric retention spiroketals (*e.g.*, **33**) by thermodynamic equilibration with TsOH. However, this was not the case for many substituent patterns for which the kinetic spirocyclization products were also thermodynamically favored, particularly in the *erythro*-series (Figure 6b). This highlighted the need for a second, kinetically-controlled spirocyclization reaction to access retention spiroketals in a stereocontrolled fashion.

2.4. $\text{Ti}(\text{O}i\text{-Pr})_4$ -mediated kinetic spirocyclization with retention of configuration

We next sought to develop a stereocomplementary kinetic spirocyclization that proceeded with retention of configuration at the anomeric carbon. We recognized that this could be particularly challenging in the *erythro*-series for both thermodynamic and kinetic reasons. The acid equilibration studies above indicated that the inversion products are thermodynamically favored in most cases, due to double anomeric stabilization. Furthermore, the *erythro*-glycal epoxides would be expected to have a kinetic preference for *trans*-diaxial epoxide opening to give inversion products. We noted parallels to the key challenges in the synthesis of β -mannosides. This problem has been solved elegantly by using covalent tethers to deliver nucleophiles *syn* to the axial C2-hydroxyl of mannose.²³ Accordingly, we hypothesized that a similar tethering effect could be invoked in the

spirocyclization of glycal epoxides using a multidentate Lewis acid to coordinate both the epoxide oxygen and side chain hydroxyl (**39**), thus activating the epoxide to promote oxocarbenium formation (**40**) while chelating the pendant nucleophile to direct *syn* addition with retention of configuration at the anomeric carbon (**41**) (Figure 7a).²⁴

In initial studies with *erythro*-glycal **42**, *anti*-epoxidation with DMDO proceeded efficiently to give glycal epoxide **43**, which spontaneously cyclized even at low temperatures (NMR, –65 °C) to favor the inversion spiroketal **37** (75:25 dr) (Figure 7b).²⁴ In hopes of reversing this stereoselectivity, we added various multidentate Lewis acids directly to the nascent epoxide **43** at –78 °C, followed by warming to room temperature. We were encouraged to find that all of the Lewis acids tested improved the ratio towards the desired retention spiroketal **38**. After some optimization, addition of Ti(*Oi*-Pr)₄ (2 equiv.) to the nascent epoxide **43** at –78 °C and warming to 0 °C provided retention spiroketal **38** in 81% yield and complete diastereoselectivity.

Exploration of the scope of this reaction revealed that spirocyclizations of stereochemically diverse substrates in both the *erythro* and *threo* series proceed effectively. In particular, the reaction provided contrathermodynamic 5- and 6-membered ring products with complete stereocontrol for retention of configuration and in good yields, including cases in which spiroketals exhibited no anomeric stabilization. Seven-membered rings were also formed stereoselectively, albeit in low yields. Conformational analysis of early (half-chair) and late (chair/boat) transition state models suggested that the observed stereochemical outcome could not be rationalized by alternate, non-chelated mechanisms, nor by a double-inversion mechanism proceeding via an intermediate isopropyl glycoside.

Collectively, this Ti(*Oi*-Pr)₄-mediated spirocyclization (C1-retention) and the MeOH-induced spirocyclization (C1-inversion) described in the preceding section provide stereocomplementary, kinetically-controlled access to diastereomeric spiroketals. This enabled the synthesis of pilot-scale libraries that were submitted to the NIH Molecular Libraries Program for biological evaluation, and also set the stage for extension to the stereocontrolled synthesis of benzannulated spiroketals below.

3. Extension of Glycal Epoxide Approach to Benzannulated Spiroketals

Benzannulated spiroketals are important structural motifs found in a variety of natural products with diverse biological activities. This privileged scaffold can bind to multiple classes of biological targets, and importantly, the aromatic ring can impact activity, three-dimensional conformation, and physicochemical properties compared to aliphatic spiroketals. As such, this class is an attractive target for diversity-oriented synthesis of natural product-based libraries for discovery screening. Building upon our earlier discoveries of stereocomplementary kinetically controlled spirocyclizations of glycal epoxides above, we sought to extend this approach to the synthesis of benzannulated spiroketals.

To access the requisite C1-functionalized glycal substrates, we devised an efficient synthetic approach that was amenable to systematic structural diversification in which the aryl moiety could be positioned anywhere along the side chain (Figure 8a). C1-Functionalization of

threo- and *erythro*-glycal stannanes **44** was achieved by direct Stille cross-couplings of aryl and benzyl bromides, or via *B*-alkyl Suzuki–Miyaura cross-couplings of the corresponding glycal iodides with styrenes and allylbenzenes.²⁵ Deacetylation then provided glycal precursors **45** with the aromatic ring systematically positioned along the side chain to give all possible iterations of 5-, 6-, and 7-membered rings. With these glycal precursors in hand, we set out to evaluate thermodynamic and kinetic spirocyclizations to form benzannulated spiroketals **47** and **48**.

Stereoselective *anti*-epoxidation of glycals **45** with DMDO afforded glycal epoxide intermediates **46**, which were subjected to various spirocyclization conditions *in situ*. Acid-catalyzed cyclization with TsOH (−78 to 0 °C) led exclusively to the thermodynamic retention spiroketals **48** in all cases, although these reactions often suffered from formation of side products, particularly in the *erythro*-series, which was prone to Ferrier-type elimination pathways. In contrast, our Ti(*O*-i-Pr)₄-mediated spirocyclization²⁴ provided all 36 retention spiroketals **48** with complete stereocontrol and in high yields (81–99%), demonstrating the mild nature of this reaction. Notably, in stark contrast to the corresponding aliphatic systems, 7-membered rings formed efficiently due to the conformational constraint conferred by the aromatic ring.

On the other hand, our MeOH-induced spirocyclization¹⁵ provided stereocontrol for the contra-thermo-dynamic inversion products **47** in only a few cases. Despite the reduced diastereoselectivity, we noted several important reactivity trends. The aromatic ring constraint allowed formation of several 7-membered rings (*n*+*m* = 3), while no cyclization was observed for the corresponding aliphatic systems. Attempted cyclizations of C1-aryl substrates (*n* = 0) resulted in lower stereoselectivity for inversion of configuration, potentially due to stabilization of an oxocarbenium intermediate that can lead to retention products **48**. Reduced selectivity and increased methyl glycoside formation was also observed for phenolic substrates (*m* = 0), which we attributed to the lower nucleophilicity of the phenol side chains.

With these reactivity trends in mind, we explored alternative Brønsted acids and discovered that treatment of the glycal epoxides **46** with AcOH (10 equiv.) provided increased diastereoselectivity for the desired inversion spiroketals **47** in both the 7-membered ring (*n* + *m* = 3) and phenolic (*m* = 0) systems. This was attributed to the absence of competing intermolecular glycosylation in the 7-membered ring systems, and increased epoxide activation in the less-reactive phenol systems. While diastereoselectivities remained modest, the spiroketal products could be separated chromatographically to afford serviceable yields of 32 out of the 36 targeted inversion spiroketals **47**.

To evaluate the impact of the aromatic ring upon the conformations of the benzannulated spiroketal products, we carried out detailed structural analyses of several products (Figure 8b). This revealed that both *threo*-series diastereomers **49** and **50** adopted the standard ⁴C₁ conformation of the non-benzannulated ring, despite the axial orientation of the aromatic ring in inversion spiroketal **49**. In contrast, in the corresponding *erythro*-series products, the retention spiroketal **52** adopted a ¹C₄ conformation to avoid 1,3-diaxial interactions between the aromatic ring and the C3-OTIPS group. The thermodynamic preference (TsOH) for **52**

was attributed to a non-obvious steric interaction in **51** ($R' = \text{OTIPS}$) between the *ortho*-proton of the aromatic ring and the axial C2-hydroxyl group. Strikingly, the thermodynamic preference was reversed after desilylation of the C3-OTIPS group, attributed to a favorable intramolecular hydrogen bond in **51** ($R' = \text{H}$).

These systematic studies underscored the distinctive effects of the aromatic ring on reactivity, conformation, and thermodynamic preferences of benzannulated spiroketals. This chemistry was used to synthesize pilot-scale libraries for the NIH Molecular Libraries Program and also paved the way to further mechanistic studies of the MeOH-induced kinetic spirocyclization below.

4. Mechanism of MeOH-catalyzed Kinetic Spirocyclization

We next turned our attention to investigating the mechanistic basis for our novel MeOH-induced kinetic spirocyclization with inversion of configuration, described above (Figure 6).¹⁵ We had previously confirmed that the reaction proceeds under kinetic control, as exposure of thermodynamically favored retention spiroketal **33** to the reaction conditions did not generate the contra-thermo-dynamic inversion spiroketal **32**. In addition, we had ruled out nucleophilic catalysis by MeOH as a potential mechanism, as reexposure of methyl glycoside side products **34** to the reaction conditions did not yield spiroketals. Finally, addition of other polar aprotic solvents did not induce spirocyclization of epoxide **31**, suggesting that the reaction is not driven simply by solvent polarity effects. Based on these experimental observations, we postulated that the kinetic spirocyclization reaction might proceed via MeOH hydrogen-bonding catalysis.

The observed stereoselectivity for inversion of configuration may be attributed to either S_N2 or S_N1 reaction manifolds (Figure 9). To distinguish between these two pathways, we carried out detailed kinetic studies of a series of electronically tuned glycal epoxide substrates (Figure 10a).²⁶ Importantly, our systematic studies above on the synthesis of benzannulated spiroketals provided access to a series of C1-aryl glycal substrates **55a–f** in which the electronic character of the anomeric carbon could be modulated using various aryl substituents.

In initial studies, these substrates were converted to the corresponding glycal epoxides **56a–f** *in situ* and exposed to spontaneous thermal or MeOH-induced spirocyclization conditions (not shown). As expected, MeOH provided increased selectivity for inversion of configuration compared to the thermal cyclizations. Interestingly, for both thermal and MeOH reaction conditions, electron-donating substituents trended toward increased levels of retention products, while electron-withdrawing substituents instead favored inversion products. This reactivity trend is consistent with formation of retention products via an S_N1 mechanism, in which a discrete oxocarbenium intermediate is stabilized by electron-donating substituents or destabilized by electron-withdrawing substituents. Conversely, these observations are also consistent with a proposed S_N2 pathway for formation of the inversion products, as oxocarbenium formation should be strongly disfavored in substrates with electron-withdrawing C1-aryl substituents.

We next examined TsOH-catalyzed epimerization of contrathermodynamic inversion spiroketals **57a–f** to the corresponding thermodynamic retention spiroketals **59a–f** (Figure 10b). This epimerization reaction is known to proceed by an S_N1 mechanism and the rate of conversion would serve as a benchmark against which to compare our proposed S_N2 MeOH-catalyzed epoxide-opening spirocyclization. As expected, the electron-donating *p*-methoxy-substituted inversion spiroketal **57a** ($X = \text{OMe}$) underwent rapid epimerization to retention spiroketal **59a** within 2.5 min, while the electron-withdrawing *p*-nitro-substituted inversion spiroketal **57f** ($X = \text{NO}_2$) showed no conversion over 72 h. Intermediate rates were observed for spiroketals with substituents having intermediate electronic properties. Rate constants for these reactions were determined to define the Hammett correlation, giving a ρ value (slope) of -5.1 , indicative of a distinctly positive S_N1 transition state.

With a benchmark for S_N1 reactions established, we examined reaction rates for MeOH-induced kinetic spirocyclizations of glycol epoxides **55a–f** (Figure 10a). We anticipated that, if the spirocyclization reaction proceeds via an S_N2 mechanism, the ρ value should be closer to zero than that observed for the TsOH epimerization, reflecting less buildup of positive charge at the reactive anomeric center. Thus, CD_3OD -catalyzed spirocyclizations of glycols **55a–f** were monitored by low temperature NMR, and initial rate constants were determined. The resulting Hammett correlation provided a ρ value of -1.3 , indicative of an S_N2 (or S_N2 -like) transition state.

We next carried out additional kinetic studies to evaluate the role of MeOH in catalysis. To determine the kinetic order of MeOH in the transition state, we measured the initial rates of spirocyclization of glycol epoxide **55c** ($R = \text{H}$) in the presence of varying concentrations of CD_3OD . Intriguingly, this analysis indicated that the spirocyclization reaction is second order in MeOH. In contrast, the corresponding intermolecular glycosylation reaction was found to be first order in MeOH. This provided a mechanistic explanation for the seemingly paradoxical finding earlier¹⁵ that increased MeOH concentration leads to increased spiroketal formation and decreased methyl glycoside formation.

Two additional experiments provided support for a role for hydrogen bonding in catalysis. Use of DMDO as an oxidant necessarily introduces acetone as a cosolvent in the spirocyclization reaction. Kinetic analysis revealed that acetone is a first-order inhibitor of the spirocyclization reaction, suggesting that it may compete as a hydrogen-bonding acceptor. Furthermore, spiroetherification of an analogous cyclohexene oxide substrate lacking the glycol ring oxygen (not shown) proceeded with fractional-order catalysis by MeOH ($n = 0.59$), suggesting that the ring oxygen in the corresponding glycol epoxides **55a–f** may interact with MeOH in second-order catalysis of the spiroketal-forming reaction.

Taken together, these data support a proposed S_N2 transition state **61** in which one equivalent of MeOH activates the epoxide oxygen as an electrophile, while a second equivalent of MeOH activates the side chain alcohol as a nucleophile (Figure 11). Hydrogen bonding of the second equivalent of MeOH to the ring oxygen may enhance reaction selectivity by disfavoring oxocarbenium formation in competing S_N1 pathways (*i.e.*: forming retention spiroketals and methyl glycosides), while also directing the nucleophile to *anti*-attack to afford inversion of configuration at the anomeric carbon.

In summary, detailed kinetic studies revealed a unique ability of MeOH to act as a hydrogen-bonding catalyst in epoxide-opening spirocyclization reactions, both controlling stereoselectivity and avoiding competing S_N1 -reaction pathways. Indeed, Jamison and coworkers have reported related catalytic functions of water in their epoxide-opening cascades to form ladder polyethers, with differential kinetic orders of hydrogen-bonding catalysis proposed to provide selectivity for competing *endo* and *exo* reaction manifolds.²⁷ Taken together, these studies reveal the dramatic and specific roles that simple solvents can play in hydrogen-bonding catalysis of epoxide-opening reactions and raise the possibility that specific solvent catalysis may play as yet unappreciated roles in other reactions as well.

5. Solvent-dependent $\text{Sc}(\text{OTf})_3$ -catalyzed Spirocyclization of *exo*-Glycal Epoxides to Form Benzannulated Spiroketal

In our original *endo*-glycal epoxide approach to benzannulated spiroketals, spirocyclization of side chains with phenol nucleophiles was particularly problematic, proceeding with low diastereoselectivity for inversion of configuration.²⁵ To overcome this problem, we envisioned an alternative approach to benzannulated spiroketals in which the benzannulated ring system would be built into the substrate from the outset, with spirocyclization of a simple aliphatic side chain.

With this approach in mind, we devised a flexible synthetic route to access a variety of benzannulated *exo*-glycal epoxide (dihydrobenzofuran spiroepoxide) substrates **67** (Figure 12).²⁸ From salicylaldehydes **63**, alkyne additions afforded propargyl alcohols **64**. Au(I)-mediated cycloisomerizations²⁹ yielded *exo*-glycals **65**. Protecting group manipulations were followed by diastereoselective *anti*-epoxidation with DMDO to provide *exo*-glycal epoxides **67**.

We next focused on developing stereoselective spirocyclization reactions of *exo*-glycal epoxide **67** ($R = \text{H}$, $n = 1$). This epoxide was remarkably stable, even upon heating to 120 °C, in stark contrast to the corresponding *endo*-glycal epoxides, which cyclize spontaneously at –35 °C.²⁶ In addition, the epoxide was unreactive under our MeOH- and $\text{Ti}(\text{O}i\text{-Pr})_4$ -induced spirocyclization conditions.^{15,24} After investigation of a wide range of Lewis acids, we discovered that treatment with $\text{Sc}(\text{OTf})_3$ favored the inversion spiroketal **68** ($R = \text{H}$, $n = 1$), which could be formed exclusively using a stoichiometric amount of catalyst in THF at –20 °C. Other Lewis acids gave lower or even reversed diastereoselectivity. Low-temperature ^1H -NMR experiments revealed that the $\text{Sc}(\text{OTf})_3$ -catalyzed spirocyclization reaction proceeds under kinetic control between –35 and –20 °C, while higher temperatures lead to reduced diastereoselectivity. Interestingly, exposure of a diastereomeric mixture of spiroketals to $\text{Sc}(\text{OTf})_3$ in CH_2Cl_2 led to exclusive formation of the thermodynamically-favored retention spiroketal **69** ($R = \text{H}$, $n = 1$). Based on these results, it was apparent that $\text{Sc}(\text{OTf})_3$ plays divergent roles in the spirocyclization reaction depending on solvent selection (THF vs CH_2Cl_2).

We carried out mechanistic studies to investigate this striking phenomenon further. We noted that $\text{Sc}(\text{OTf})_3$ may act as either a Lewis acid or as a mild source of triflic acid.³⁰ To differentiate between these two activities in the inversion reaction in THF, we added 2,6-di-

tert-butyl-4-methylpyridine (DTBMP) and found that dia-stereo-selectivity favoring the inversion spiroketal **68** was unaffected. Treatment with the Lewis acid ScCl_3 also resulted in exclusive formation of the inversion spiroketal **68**. Conversely, treatment with TfOH gave a diastereomeric mixture favoring the retention product **69**. Thus, these studies suggest that $\text{Sc}(\text{OTf})_3$ acts as a Lewis acid in THF, effecting kinetic spirocyclization to form the contra-thermodynamic inversion spiroketal **68**.

In parallel studies of the retention reaction in CH_2Cl_2 , we found that addition of DTBMP led to a reversal of selectivity, forming a diastereomeric mixture favoring the inversion product **68**. However, TfOH provided the retention spiroketal **69**. Taken together, these studies suggest that $\text{Sc}(\text{OTf})_3$ acts as a mild source of Brønsted acid in CH_2Cl_2 to catalyze thermodynamically-controlled spirocyclization to retention spiroketal **69**.

We next explored the scope of these stereocomplementary spirocyclization reactions. Spirocyclizations of substrates with longer side chains ($n = 2-3$) provided 6- and 7-membered ring spiroketals with complete diastereoselectivity under both solvent conditions. However, the 7-membered ring cyclization proceeded with lower yield due to an unexpected anti-Markovnikov 6-*exo* epoxide opening side reaction. Spirocyclizations of substrates with a variety of electron-withdrawing and -donating aryl substituents (*R*) also maintained high diastereoselectivities in all cases, demonstrating that the $\text{Sc}(\text{OTf})_3$ -catalyzed reactions tolerate a wide range of functional groups. Consistent with electronic considerations, inclusion of a nitro group *para* to the phenol oxygen decreased reactivity at the anomeric spiroepoxide center, requiring heating to room temperature to induce spirocyclization in THF, while inclusion of a methoxy substituent at this position increased reactivity and decreased diastereoselectivity to 93:7 (**68:69**) in THF.

This new *exo*-glycal epoxide approach to benzannulated spiroketals highlighted the divergent catalytic activities of $\text{Sc}(\text{OTf})_3$ depending on solvent selection. In THF, the reaction proceeds via Lewis acid catalysis under kinetic control to provide contrathermodynamic inversion spiroketals. In contrast, in CH_2Cl_2 , Brønsted acid catalysis under thermodynamic control produces retention spiroketals. While a structural rationale for the observed thermodynamic preference for retention spiroketals in this system requires further investigation, the reactions tolerate a wide range of functionalities and ring sizes. Importantly, this *exo*-glycal-based approach provides stereocontrolled access to contrathermodynamic phenolic spiroketals, which were difficult to obtain using our original *endo*-glycal-based approach.²⁵ Applications of this method to the diversity-oriented synthesis of benzannulated spiroketal libraries are ongoing.

6. Synthesis of Pyrrolomorpholine Spiroketal Natural Products

With an arsenal of methods for the stereocontrolled synthesis of spiroketals in hand, we sought to apply these approaches to the synthesis of pyrrolomorpholine spiroketal natural products. This novel family of naturally-occurring alkaloids includes both furanose and pyranose isomeric forms, as well as both epimeric α - and β -configurations at the anomeric carbon (Figure 13).³¹ These natural products were isolated from a variety of different plant species (*Acorus tatarinowii*, *Brassica campestris*, and *Capparis spinosa*, Shensong Yangxin

capsules), as well as a fungus (*Xylaria nigripes*), all of which have been used in traditional Chinese medicines for the treatment of a variety of diseases. Notably, the acortatarins exhibit significant antioxidant activity against hyperglycemia-induced oxidative stress in kidney cells,^{31a} and similarly, the xylapyrrosides protect against peroxide-induced cytotoxicity in vascular smooth muscle cells.^{31f} These antioxidant effects suggest that the pyrrolomorpholine spiroketals may have therapeutic potential for the treatment of diabetic nephropathy and other oxidative stress-related pathologies. However, due to the extremely limited quantities available from the natural sources, efficient synthetic access is needed for comprehensive biological studies. Accordingly, this family of natural products has attracted considerable attention from the synthetic community.^{31b,f,32} We envisioned that we might access the natural products and analogues efficiently using our glycal epoxide rubric and related glycal-based approaches.

Our initial efforts focused on the development of concise, highly stereoselective syntheses of the furanose natural products acortatarins A (**70**) and B (**73**).³³ Retrosynthetically, we envisioned that both acortatarins A and B could be synthesized via spirocyclizations of a glycal intermediate **76** (Figure 14). This glycal precursor could be accessed in a modular fashion via coupling of pyrrole **77** with ribal **79**, derived from commercially available D-thymidine (**80**).

Thus, we synthesized the pyrrole-functionalized glycal substrate **81** (Figure 15a) in 6 steps and 58% yield from D-thymidine (not shown). In line with our glycal epoxide approach established above, we pursued an epoxidation–spirocyclization route to acortatarin B. After extensive optimization, we found that β -selective *anti*-epoxidation of diformylpyrrole-substituted glycal **81** with DMDO, followed by addition of Bu₄NBH₄ to effect *in situ* aldehyde reduction provided the desired β -spiroketal **82** with complete diastereoselectivity. The diformylpyrrole glycal **81** proved to be the ideal substrate for the reaction, as the electron-withdrawing aldehydes protected the pyrrole from undesired oxidation in the epoxidation step. Use of alternative reducing agents generally led to formation of other side products or decomposition. Interestingly, however, reductive spirocyclization with NaBH₃CN under acidic conditions yielded the corresponding C1-epimeric α -spiroketal as a single diastereomer. Desilylation of β -spiroketal **82** provided acortatarin B (**73**) while C1-*epi*-acortatarin B (**71**, later isolated as the natural product shensongine C^{31e}) was accessed by desilylation of the corresponding protected α -spiroketal (not shown).

To synthesize acortatarin A, we pursued a mercury-mediated spirocyclization approach pioneered by Danishefsky and Pearson.³⁴ In initial studies, we found that treatment of hydroxymethylpyrrole-functionalized glycal **83** with Hg(OAc)₂, followed by NaBH₄ reduction of the resulting 2-mercurial acetal, produced the desired α -spiroketal **84** with modest stereoselectivity (2:1 dr). Further studies revealed that pretreatment of glycal **83** with sodium hexamethyldisilazide improved diastereoselectivity for the α -spiroketal **84**, presumably by forming a more reactive alkoxide nucleophile for cyclization. Use of weaker, non-nucleophilic bases provided lower diastereoselectivity. Moreover, allowing the initial oxymercuration reaction to proceed for longer times prior to NaBH₄ reduction led to further increased diastereoselectivity to 9:1 dr favoring the α -spiroketal **84**, suggestive of an equilibrium effect in this reaction. Desilylation of the 9:1 mixture of α - and β -spiroketals

then provided separable acortatarin A (**70**) and C1-*epi*-acortatarin A (**72**, later isolated as the natural products shensongine B^{31e} and xylapyrroside B^{31f}) (Figure 13).

With the natural products and their C1 epimers in hand, we investigated their thermodynamic preferences via acid-catalyzed equilibration (Figure 15b). In both cases, the α -anomer was favored by a 65:35 ratio. Notably, this corresponds with the unnatural anomer of acortatarin B. To investigate the underlying structural bases for these thermodynamic preferences, we obtained an X-ray crystal structure of synthetic acortatarin B, and compared it to the previously reported crystal structure of acortatarin A^{31a} (Figure 15c). This revealed that the two natural products adopt distinct conformations in both the furanose and morpholine rings, allowing double anomeric stabilization in both systems despite their opposite stereochemical configurations at the anomeric carbon.

In conclusion, the stereoselective synthesis of acortatarin A was achieved in 9 steps and 30% overall yield from D-thymidine with 9:1 dr in the key spirocyclization step, while acortatarin B was synthesized in 8 steps and 41% overall yield with complete diastereoselectivity in the key spirocyclization step. This compares favorably to previous syntheses and provides practical access to both the natural products and analogues for biological evaluation. Ongoing efforts are focused on expanding this approach to a family-level synthesis of the pyrrolomorpholine spiroketals and evaluating the biological activity and mechanisms of action of the natural products and analogues.

7. Conclusions

The stereocontrolled synthesis of spiroketals represents a classical challenge in organic synthesis and has presented fertile ground for both chemical and biological discoveries. In our own efforts to advance the glycol epoxide approach to spiroketals, we have developed new chemical methodologies of broad potential utility and fundamental insights into structure and reactivity. Efficient, systematic access to this chemotype now sets the stage for biological evaluation of spiroketals in the contexts of both diversity libraries and natural products and analogues.

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Derek S. Tan received his BS in Chemistry from Stanford University in 1995, working with Prof. Dale G. Drueckhammer. He went onto graduate studies with Prof. Stuart L. Schreiber at Harvard University, receiving his PhD in Chemistry in 2000. He then joined the lab of Prof. Samuel J. Danishefsky at Memorial Sloan Kettering Cancer Center (MSKCC) for his post-doctoral studies. He began his independent career at MSKCC in 2002 in the Molecular Pharmacology & Chemistry Program, with joint appointments at the Rockefeller University and Weill Cornell Medical College. He is currently a tenured Member and Tri-Institutional Professor. In 2015, he was appointed Chairman of the newly formed Chemical Biology Program at MSKCC. Since 2012, he has also been the Director of the Tri-Institutional PhD Program in Chemical Biology.

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Figure 1. Spiroketal is found in a wide range of natural products as well as synthetic compounds with diverse biological activities, serving as both binding pharmacophores and rigid scaffolds.

Figure 2.

Synthesis of spiroketals by spirocyclization of cyclic epoxides. (a) Wallace and Cremins' synthesis of spiroketals from a chromenone epoxide. (b) Friesen and Sturino's synthesis of the spiroketal core of the papulacandins via DMDO epoxidation of a glycal.

Figure 3.

The glycol epoxide approach to stereocontrolled spiroketal synthesis using stereocomplementary kinetic spirocyclization reactions. * = site of potential stereochemical diversity.

Figure 4. Enantioselective synthesis of (a) *threo*-glycal (**18**) and (b) *erythro*-glycal (**24**) substrates.

Figure 5.

C1-alkylation of glycals via *B*-alkyl Suzuki–Miyaura cross-coupling of glycal iodides with alkene-derived side chains.

Figure 6.

Discovery of a methanol-induced kinetic spirocyclization with inversion of configuration. (a) Epoxidation of *threo*-glycal **30** (derived from the corresponding side chain acetate, not shown) and MeOH-induced spirocyclization provides contra-thermo-dynamic inversion spiroketal **32**. (b) Examples of *threo*-series (left) and *erythro*-series (right) spiroketals in which TsOH equilibration does not favor the stereocomplementary retention product. ^a Remainder methylglycosides (*cf.* **34**). ^b C3-desilylated product recovered.

Figure 7.

Discovery of a Ti(O*i*-Pr)₄-mediated kinetic spirocyclization with retention of configuration. (a) Mechanistic hypothesis for Lewis acid-tethered epoxide opening spirocyclization. (b) Epoxidation of *erythro*-glycol **42** and Ti(O*i*-Pr)₄-mediated spirocyclization provides contra-thermo-dynamic retention spiroketal **38**. ^a C3-desilylated product recovered.

Figure 8. Stereocontrolled synthesis of benzannulated spiroketals. (a) Stille and *B*-alkyl Suzuki–Miyaura cross couplings were used to install various arene-containing C1 side chains, followed by epoxidation and kinetic spirocyclization. (b) Conformational analysis of diastereomeric benzannulated spiroketals. * = site of stereochemical diversity.

Figure 9. Possible $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$ reaction mechanisms for the MeOH-induced kinetic spirocyclization of glycal epoxides leading to inversion of configuration at the anomeric carbon.

Figure 10. Mechanistic studies of (a) MeOH-induced kinetic spirocyclization reactions and (b) acid-catalyzed spiroketal equilibration. **55–59a–f**: X = OMe (**a**), Me (**b**), H (**c**), Cl (**d**), CF₃ (**e**), NO₂ (**f**).

Figure 11.
Proposed hydrogen-bonding mechanism for MeOH-induced kinetic spirocyclization reaction.

Figure 12.

Synthesis of benzannulated spiroketals via solvent-dependent stereoselective spirocyclizations of *exo*-glycal epoxides.

Figure 13.
The pyrrolomorpholine spiroketal family of natural products.

Figure 14.
Retrosynthetic approach to acortatarins A and B.

Figure 15.

Stereoselective synthesis and thermodynamic preferences of acortatarins A and B. (a) Synthesis of acortatarin B via reductive epoxide-opening spirocyclization and of acortatarin A via Hg-mediated spirocyclization. (b) Acid equilibration favors the α -anomer in both systems. (c) Acortatarins A and B exhibit distinct ring conformations to enable double anomeric stabilization.