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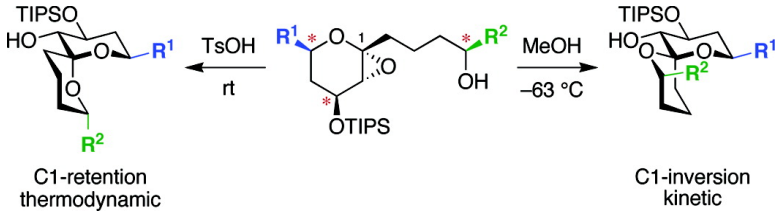

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Stereocontrolled Synthesis of Spiroketals via a Remarkable Methanol-Induced Kinetic Spirocyclization Reaction

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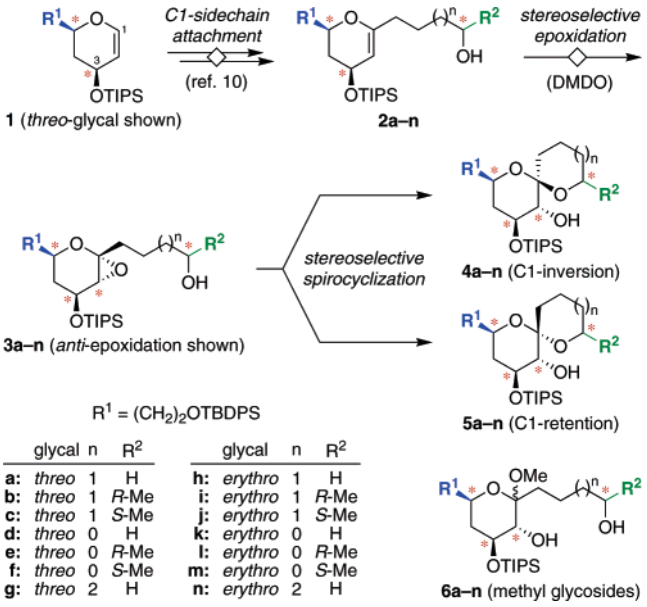
The spiroketal motif is found in myriad natural products, and this privileged structure can bind to multiple classes of biological targets.[1,2] Thus, spiroketals have attracted considerable attention in both target- and diversity-oriented synthesis.[1,3] In the latter context, spiroketals present the opportunity to exploit extensive stereochemical diversity,[4] wherein these rigid scaffolds display substituents along well-defined three-dimensional vectors.[5] However, exploration of this concept has been limited by the constraints of the existing approaches to spiroketals. In particular, there is still no general method to synthesize *systematically* stereodiversified spiroketals. We describe herein our early endeavors to develop such a method and, toward that end, the discovery of a novel kinetic spiroketalization reaction.

Classically, spiroketals have been synthesized using acid-catalyzed spiroketalizations in which the stereochemical outcome at the anomeric carbon is governed by thermodynamic product stability.[1,6] Several kinetic spirocyclization reactions have been developed to access contrathermodynamic spiroketals, particularly those stabilized by only one anomeric effect. However, these are often dependent upon spirocyclization of an oxygen nucleophile along an axial trajectory.[7] As a result, these thermodynamic and kinetic reactions are not completely stereocomplementary.

We envisioned a conceptually different approach (Figure 1), in which the stereochemical configuration at the anomeric carbon is controlled by an initial stereoselective epoxidation reaction (**2** → **3**). Systematic stereodiversification is then accomplished using kinetic spirocyclization reactions that proceed with either inversion (**4**) or retention (**5**) of configuration at the anomeric carbon, independent of thermodynamic considerations or cyclization trajectory. We recognized that achieving epoxide opening with faithful inversion of configuration is by no means trivial in this system. Net *trans*-diequatorial opening would be required in some cases, and oxonium-stabilized S_N1-type reaction manifolds might also have undesirable stereochemical consequences. Thus, our first attentions have focused on addressing this challenge.

We synthesized *threo*-glycal **1** enantioselectively according to literature precedents.[8] The diastereomeric *erythro*-glycal (not shown) was synthesized using our recently reported route.[9] We next attached C1 side chains using our *B*-alkyl Suzuki−Miyaura cross-coupling methodology to form **2a**−**n**.[10] We then carried out preliminary studies on *threo*-glycal **2a**, which underwent efficient *anti*-epoxidation with DMDO[11] (100%, >98:2 dr; NMR, −60 °C). We were encouraged to find that warming glycal epoxide **3a** to room temperature caused spontaneous spirocyclization to a 70:30 mixture of spiroketals **4a** and **5a**.[12] Equilibration of this mixture with TsOH



	glycal	n	R^2		glycal	n	R^2
a:	*threo*	1	H	**h:**	*erythro*	1	H
b:	*threo*	1	*R*-Me	**i:**	*erythro*	1	*R*-Me
c:	*threo*	1	*S*-Me	**j:**	*erythro*	1	*S*-Me
d:	*threo*	0	H	**k:**	*erythro*	0	H
e:	*threo*	0	*R*-Me	**l:**	*erythro*	0	*R*-Me
f:	*threo*	0	*S*-Me	**m:**	*erythro*	0	*S*-Me
g:	*threo*	2	H	**n:**	*erythro*	2	H

Figure 1. Epoxide-based approach to the stereocontrolled synthesis of spiroketals. Potential sites of stereochemical diversity are highlighted (∗).

yielded the thermodynamically favored "retention" spiroketal **5a** (99%, >98:2 dr), benefitting from double anomeric stabilization.[6]

In the course of our efforts to achieve spirocyclization to the contrathermodynamic "inversion" spiroketal **4a** with greater stereocontrol, we were pleasantly surprised to discover that addition of a large excess of MeOH to the nascent epoxide **3a** at −78 °C resulted in stereospecific spirocyclization to **4a** (Table 1, entry 1). Meanwhile, the expected methyl glycosides **6a** were formed as minor products. In keeping with entropic considerations, the intermolecular glycosylation was less competitive at higher temperatures, although the stereoselectivity of the intramolecular spirocyclization was also decreased (entries 3 and 4). Reactions using other alcohols or lower alcohol concentrations proved to be less selective (entries 5−12). Our best results were achieved with MeOH at −63 °C, where **4a** was formed with complete stereocontrol, along with only a small amount of readily separable **6a** (entry 2). Notably, this reaction allows equatorial installation of the oxygen nucleophile, in contrast to most existing kinetic spiroketalization reactions.[7]

We carried out several experiments to probe the mechanism of this intriguing reaction. Exposure of the retention spiroketal **5a** to the same conditions (DMDO, −78 °C; then MeOH, −63 °C) did not produce any inversion spiroketal **4a**, confirming that the MeOH-induced spirocyclization is kinetically controlled. Likewise, the isolated methyl glycosides **6a** were unchanged under these conditions, thus eliminating them as possible intermediates in mechanisms

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Table 1. Alcohol-Induced Spirocyclizations of Glycal Epoxide **3a**[a]

entry	ROH	vol[b]	temp (°C)	time (h)	**4a** (%)	**5a** (%)	**6a**[c] (%)
1	MeOH	5	−78	1	80	0	20
2	MeOH	5	−63	1	92	0	8
3	MeOH	5	−44	1	92	3	5
4	MeOH	5	0	1	71	21	8
5	CH_3OD	5	−63	1	87	0	13
6	EtOH	5	−63	2	77	0	23
7	*i*-PrOH	5	−63	2	72	4	24
8	MeOH	0.5	−63	1	50	8	42
9	EtOH	0.5	−63	2	59	6	35
10	*i*-PrOH	0.5	−63	2	69	8	23
11	CF_3CH_2OH	0.5	−63	2	70	14	16
12	$(CF_3)_2CHOH$	0.5	−63	2	70	30	0

[a] Product ratios determined by NMR. [b] Volume of alcohol added to **3a** relative to the initial volume of 1:1 acetone/CH_2Cl_2 used in the preceding epoxidation reaction. [c] Formed as a ≈1:1 mixture of α- and β-anomers.

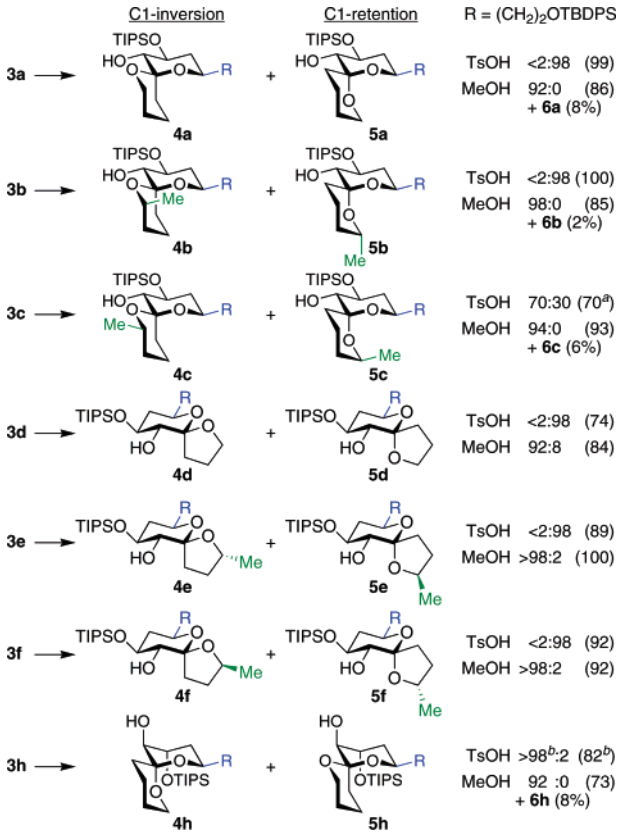

Figure 2. Spirocyclization product ratios. Isolated yields of major products are shown in parentheses. Indicated favored conformations were determined by NMR or predicted based on conformational analysis. [a] Inseparable mixture of spiroketals **4** and **5**; [b] C3-desilylated spiroketal **4**.

involving nucleophilic catalysis by MeOH. Addition of polar aprotic solvents (acetone, THF, EtOAc, or DMF; −78 °C) did not induce spirocyclization, suggesting that the reaction does not proceed simply as a result of increasing the solvent polarity. One remaining possibility is that this reaction proceeds by MeOH hydrogen-bonding catalysis. Similar alcohol catalysis has been reported previously in reactions of epoxides.[13]

Further efforts to understand the mechanism of this reaction are ongoing. However, with effective reaction conditions in hand (entry 2), we set out to explore spirocyclizations of additional C1-alkylglycal epoxide substrates (**3b**−**n**). For comparison, we also determined the thermodynamic ratio of spiroketals formed in each case by equilibration with TsOH. In the *threo*-glycal series (Figure 2), the MeOH-induced spirocyclization proved equally effective for producing spiroketals with substituted side chains (**4b**,**c**) and five-membered rings (**4d**−**f**). Notably, the resulting spiroketals have diverse three-dimensional structures. In the corresponding *erythro*-glycal series, TsOH-catalyzed equilibration generally led to inversion spiroketals (**4h**,**i**,**k**−**m**) having two anomeric stabilizations, albeit with concomitant desilylation of the C3-hydroxyl group (Figure 2 and Supporting Information). In contrast, MeOH-induced spirocyclization provided **4h**−**m** without compromising the C3-OTIPS group.[8] Attempted spirocyclizations of **3g**,**n** to form seven-membered rings produced only the methyl glycosides **6g**,**n**.

In conclusion, we have developed a novel MeOH-induced kinetic spiroketalization that provides stereocontrolled access to spiroketals based solely upon stereoinduction provided by a preceding epoxidation reaction. This epoxide-opening spirocyclization proceeds with inversion of configuration and appears to result from hydrogen-bonding catalysis. Efforts to develop stereocomplementary spirocyclizations that proceed with retention of configuration, but do not rely upon thermodynamic product stability, and to apply this route to the synthesis of systematically stereodiversified spiroketal libraries are progressing and will be reported in due course.

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Supporting Information Available: Complete ref 2, additional data on *erythro* series spirocyclizations, and experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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