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Stereocontrolled Synthesis of Spiroketals via Ti(O*i*-Pr)$_4$-Mediated Kinetic Spirocyclization of Glycal Epoxides with Retention of Configuration

Sirkka B. Moilanen[†], **Justin S. Potuzak**[‡], and **Derek S. Tan**[*,†,‡,§]
Tri-Institutional Training Program in Chemical Biology, Pharmacology Program, Weill Graduate School of Medical Sciences of Cornell University, and Tri-Institutional Research Program and Molecular Pharmacology & Chemistry Program, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York, 10021

The stereocontrolled synthesis of spiroketals continues to present a stimulating challenge in target- and diversity-oriented synthesis.[1] With a view toward exploiting stereochemical diversity in spiroketal libraries, we recently developed a synthetic approach to spiroketals in which the stereochemical configuration at the anomeric carbon is dictated by an initial stereoselective epoxidation of a C1-alkylglycal **1** (Figure 1).[2] The intermediate epoxide **2** can then undergo a methanol-induced kinetic epoxide-opening spirocyclization (spirocycloisomerization) to **4** with *inversion* of configuration at the anomeric carbon. To access systematically stereochemically diversified spiroketals, we also required a method to effect the complementary spirocyclization to **3**, in an unusual epoxide opening with *retention* of configuration. We report herein our solution to this problem, involving a new Ti(O*i*-Pr)$_4$-mediated kinetic spirocyclization reaction.

We noted at the outset that access to 'retention' spiroketals in the *erythro*-glycal series (**3a–g**) is particularly challenging. The corresponding 'inversion' spiroketals (**4**) are thermodynamically favored in most cases,[2] owing to double anomeric stabilization.[3] Further, the *erythro*-glycal epoxides **2a–g** should be kinetically predisposed to spirocyclization with inversion of configuration via favorable *trans*-diaxial epoxide opening. However, we recognized that the problem at hand bears a notable similarity to a key challenge in carbohydrate synthesis, namely the synthesis of β-mannosides.[4] One effective solution has been to direct the desired β-glycosylation reaction *syn* to the axial C2-hydroxyl group of mannose using a covalent tether to the nucleophile.[5] By analogy, we reasoned that, in our spiroketal synthesis, an appropriate multidentate Lewis acid might serve as a non-covalent tether between the epoxide oxygen and the sidechain hydroxyl of **2** (Figure 2). The Lewis acid could then activate the epoxide electrophile (**5**) to form an oxonium intermediate (**6**), then deliver the sidechain nucleophile to the desired β-face of the anomeric carbon (**7**). In this manner, the required epoxide opening with retention of configuration might be achieved in a kinetically controlled reaction, overriding the inherent thermodynamic and kinetic preferences of the system.

To explore this hypothesis, we carried out initial experiments with *erythro*-glycal **1a**.[2,6] Epoxidation with DMDO provided the reactive glycal epoxide **2a**, which began to cyclize spontaneously even at reduced temperatures (NMR, −65 °C). Since isolation of **2a** was, thus,

E-mail: tand@mskcc.org.
[†]Tri-Institutional Training Program in Chemical Biology.
[‡]Weill Graduate School of Medical Sciences of Cornell University.
[§]Tri-Institutional Research Program and Molecular Pharmacology & Chemistry Program.

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precluded, we added various multidentate Lewis acids directly to the nascent epoxide at −78 °C and analyzed the resulting product ratios after warming to room temperature (Table 1).[7] Despite our initial concerns that the acetone cosolvent used in the epoxidation reaction might interfere with substrate coordination by these Lewis acids, we were encouraged to find that all of the reagents tested provided an improved ratio of **3a:4a** compared to the spontaneous cyclization (entry 1). In particular, Ti(O*i*-Pr)$_4$ provided the retention spiroketal **3a** as a single stereoisomer (entry 6), albeit in low purity (≈55%). Further investigations revealed that warming the reaction to 0 °C immediately after addition of Ti(O*i*-Pr)$_4$ dramatically improved the yield of **3a** by avoiding the formation of various glycoside and overoxidation products (2 equiv Ti(O*i*-Pr)$_4$, −78 °C; then 0 °C, ≤ h; >98:2 dr, 81% isolated yield). Importantly, exposure of the inversion spiroketal **4a** to the reaction conditions did not result in equilibration to **3a,** establishing that this Ti(O*i*-Pr)$_4$-mediated spkocyclization is, indeed, kinetically controlled.[8] We observed reduced stereoselectivity using substoichiometric amounts of Ti(O*i*-Pr)$_4$, suggesting that the metal may remain coordinated to the product (**7**), although this complex is not responsible for the stereochemical outcome of this kinetically controlled reaction.

We next explored the effectiveness of this reaction in spirocyclizations of stereochemically diverse substrates with various sidechain lengths (Figure 3 and Supporting Information). We were gratified to find that, in the *erythro* series, the reaction provided contrathermodynamic five- and six-membered ring retention spiroketals with complete stereocontrol and good yields (**3a–f**), including **3b,** which has no anomeric stabilizations. The seven-membered ring spiroketal **3g** was also formed stereoselectively, but in low yield. The reaction was similarly effective in the *threo* series (**3h–n**)[9] and, in particular, provided the retention spiroketal **3j**, which we have previously found to be contrathermodynamic in spite of double anomeric stabilization.[2]

To evaluate our proposed tethered spirocyclization mechanism (Figure 2), we carried out conformational analysis of transition state models developed by Deslongchamps for oxonium-based kinetic spiroketalizations.[9,10] In particular, our analysis revealed that alternate non-chelated mechanisms are inconsistent with the observed stereochemical preference for **3**. Conversely, a metal-chelated early transition state model (cf. **6**) appears energetically favorable and is consistent with formation of the retention spiroketals.

We recognized that this strategy might also provide a means to achieve the related intermolecular glycosylations of glycal epoxides to generate β-mannosides.[11] Indeed, early investigations of this idea have produced promising results, with β-selectivity as high as 10:1 achieved in a model system.[9]

In conclusion, we have developed a Ti(O*i*-Pr)$_4$-mediated kinetic spirocyclization for the stereocontrolled synthesis of spiroketals. To our knowledge, this is the first example of a *kinetic* spiroketalization that is controlled by metal chelation. This Ti(O*i*-Pr)$_4$-mediated cyclization (C1-retention) and our previously described MeOH-induced cyclization (C1-inversion) provide comprehensive access to systematically stereochemically diversified spiroketals. Application of this strategy to the synthesis of stereochemically diverse spiroketal libraries is ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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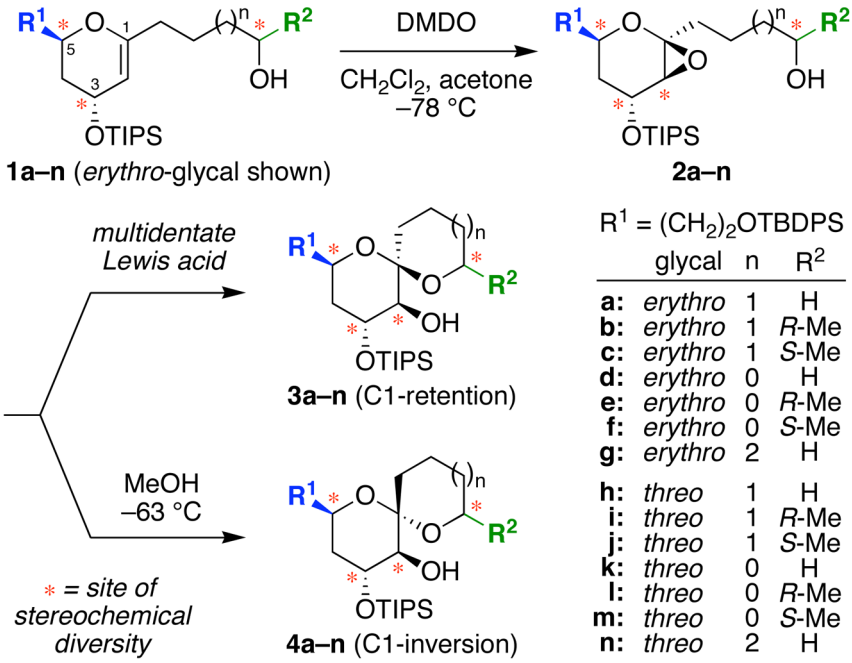

Figure 1.
Strategy for stereocontrolled synthesis of spiroketals via epoxide-opening spirocyclizations with retention (**3**) or inversion (**4**) of configuration at the anomeric carbon, (*erythro* = 3,5-*anti*; *threo* = 3,5-*syn*).

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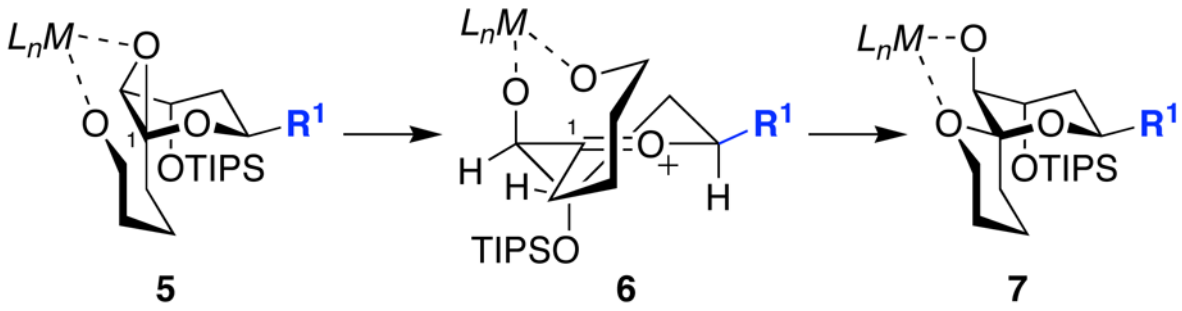

Figure 2.
Proposed tethered mechanism for kinetic spirocyclization of **2**.

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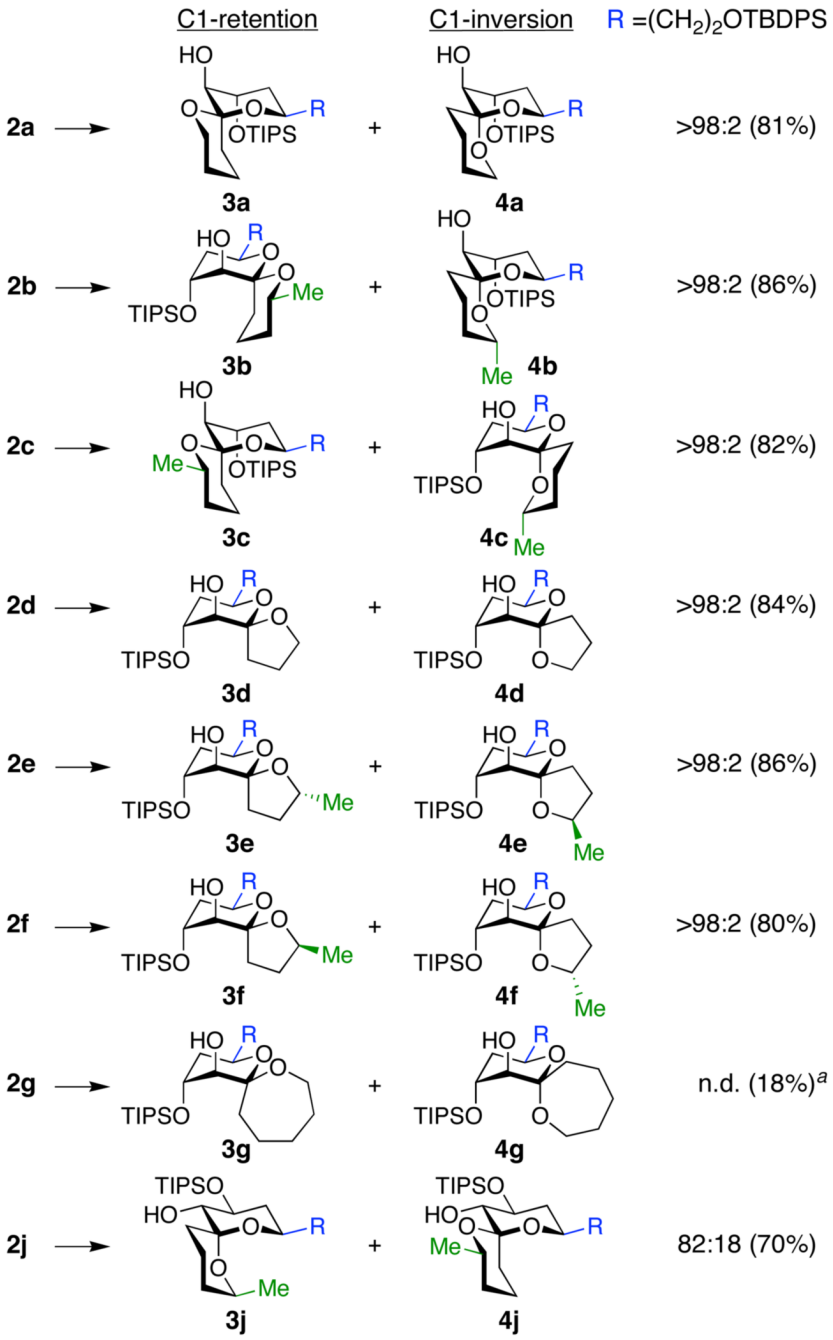

Figure 3.

Ti(O*i*-Pr)$_4$-mediated spirocyclizations. Isolated yields of retention spiroketals 3 shown in parentheses. Indicated favored conformations determined by NMR. Inversion spiroketals 4 were synthesized by MeOH-induced spirocyclization for comparison.[2] [a] Single stereoisomer **3g** recovered; remainder isopropyl glycoside and hydrolyzed **2g**.

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Table 1

Epoxide-opening spirocyclization reactions of **2a** with multidentate Lewis acids.[a,b]

entry	Lewis acid	3a (%)	4a (%)	entry	Lewis acid	3a (%)	4a (%)
1	none	25	75	4	$MgCl_2$	60	40
2	$Yb(OTf)_3$	43	57	5	$SnCl_4$	67	33[c]
3	$ZnCl_2$	43	57	6	$Ti(O\textit{i}\text{-}Pr)_4$	>98	<2

[a] **2** equiv Lewis acid, 1:1 CH_2Cl_2/acetone, −78 °C for 1 h, then warm to rt and quench with aq $NaHCO_3$. Ratios of **3a:4a** determined by NMR.

[b] Treatment of **2a** with TsOH yields the C3-desilylated congener of **4a** (<2:98 dr, 82%).[2]

[c] 1:3 mixture of **4a** and its C3-desilylated congener.

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