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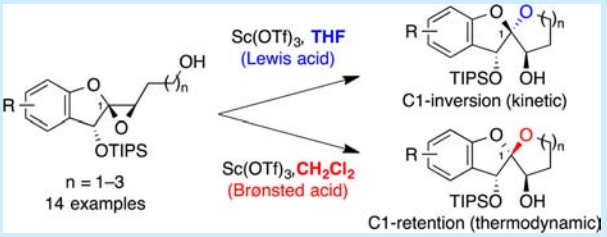
Solvent-Dependent Divergent Functions of $Sc(OTf)_3$ in Stereoselective Epoxide-Opening Spiroketalizations

Indrajeet Sharma,[†] Jacqueline M. Wurst,[‡] and Derek S. Tan*[,†,‡]

[†]Molecular Pharmacology & Chemistry Program, [‡]Tri-Institutional PhD Program in Chemical Biology, and Tri-Institutional Research Program, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York 10065, United States

Supporting Information

ABSTRACT: A stereocontrolled synthesis of benzannulated spiroketals has been developed using solvent-dependent Sc-$(OTf)_3$-mediated spirocyclizations of *exo*-glycal epoxides having alcohol side chains. In THF, the reaction proceeds via Lewis acid catalysis under kinetic control with inversion of configuration at the anomeric carbon. In contrast, in CH_2Cl_2, Brønsted acid catalysis under thermodynamic control leads to retention of configuration. The reactions accommodate a variety of aryl substituents and ring sizes and provide stereochemically diverse spiroketals.



Benzannulated spiroketal natural products exhibit a broad array of biological activities.[1] Examples include the matrix metalloproteinase inhibitor berkelic acid,[2] the fungal cell wall glucan synthase inhibitory papulacandins,[3] and the anti-inflammatory aquilarinoside A.[4] Bisbenzannulated spiroketals include the rubromycin family of human telomerase and HIV reverse transcriptase inhibitors,[5] the DNA helicase inhibitor heliquinomycin, and the antibiotic purpuromycin, which inhibits aminoacyl-tRNA synthesis by a novel mechanism involving direct binding to the tRNA substrate.[6] Notably, the benzannulated spiroketal core is essential for telomerase inhibition in the rubromycin family.[7] Numerous approaches to the synthesis of benzannulated spiroketals have been reported.[8,9] Despite these notable advances, most strategies rely upon thermodynamically controlled reactions that often lead to stereoisomeric mixtures at the anomeric carbon.[1]

We have previously developed stereocontrolled approaches to aliphatic spiroketals using stereocomplementary kinetic spirocyclization reactions of *endo*-glycal epoxides that proceed with either inversion or retention of configuration at the anomeric carbon, independent of thermodynamic preferences.[10] We have also extended this approach to benzannulated spiroketals via incorporation of aromatic rings on the cyclizing side chain.[11] Unfortunately, this approach provides low diastereoselectivity in spirocyclization reactions with phenolic nucleophiles (45:55 to 58:42 dr).[11]

To address this problem, we envisioned an alternative entry to phenolic spiroketals involving stereoselective spirocyclizations of benzannulated *exo*-glycal epoxides (dihydrobenzofuran spiroepoxides). Spirocyclizations of exocyclic enol ether epoxides have apparently not been explored previously, although classical acid-catalyzed spiroketalizations of the parent exocyclic enol ethers are well-known,[12] and the corresponding epoxides[13] have been used in intermolecular alcohol additions.[14]

Thus, the requisite benzannulated *exo*-glycal epoxide substrates were synthesized from salicylaldehydes **1** via alkyne additions to form propargyl alcohols **2a–h** (Figure 1).[15] Au(I)-mediated cycloisomerization, previously restricted to aromatic alkynes,[15,16] then afforded *exo*-glycals **5a–h**. Diastereoselective *anti*-epoxidation with dimethyldioxirane (DMDO)[17] provided *exo*-glycal epoxides **6a–h**. Interestingly, these epoxides were

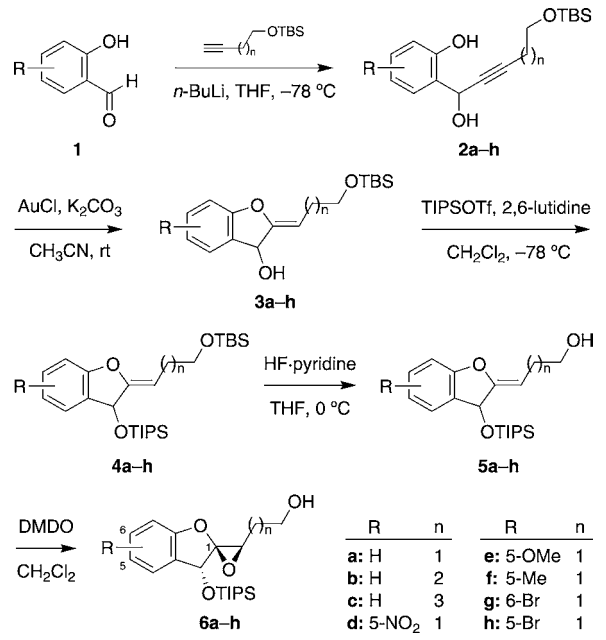


Figure 1. Synthesis of *exo*-glycal epoxide substrates **6a–h**.

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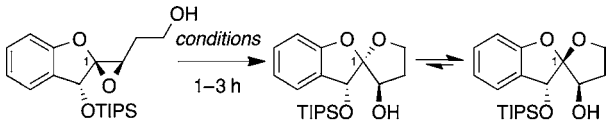
stable upon warming to rt, in stark contrast to the corresponding *endo*-glycal epoxides, which cyclize spontaneously at −35 °C.[18]

We next explored spirocyclization reactions of benzannulated *exo*-glycal epoxide **6a** (Table 1). Notably, **6a** proved unreactive

Table 1. Spirocyclization Reactions of *exo*-Glycal Epoxide 6a[a]



6a **7a** (C1-inversion) **8a** (C1-retention)

entry	reagent (equiv)	solvent, temp (°C)	7a:8a
1	MeOH (excess)	MeOH, rt	NR
2	$Ti(O^iPr)_4$ (2.0)	CH_2Cl_2, rt	NR
3		toluene, 120	NR
4	$Sc(OTf)_3$ (2.0)	CH_2Cl_2, −78 → 0	75:25
5	$Sc(OTf)_3$ (2.0)	THF, −78 → 0	>98:2
6	$Sc(OTf)_3$ (1.0)	THF, −78 → 0	>98:2
7	$Sc(OTf)_3$ (0.1)	THF, −78 → 0	93:7
8	**$Sc(OTf)_3$ (1.0)**	**THF, −20**	**>98:2**
9	$Sc(OTf)_3$ (1.0)	THF, rt	90:10
10	$Sc(OTf)_3$ (1.0)	CH_2Cl_2, 0 → rt	<2:98
11	**$Sc(OTf)_3$ (0.5)**	**CH_2Cl_2, 0 → rt**	**<2:98**
12	$Sc(OTf)_3$ + DTBMP (1.0 + 1.0)	THF, −20	>98:2
13	$ScCl_3$ (1.0)	THF, rt	>98:2
14	TfOH (1.0)	THF, −20	30:70
15	$Sc(OTf)_3$ + DTBMP (0.5 + 0.5)	CH_2Cl_2, 0 → rt	75:25
16	TfOH (0.5)	CH_2Cl_2, 0 → rt	<2:98
17	TfOH + DTBMP (0.5 + 0.5)	CH_2Cl_2, 0 → rt	51:49

[a]Product ratios determined by ^{1}H NMR analysis of crude reaction products. NR = no reaction; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine. See the Supporting Information for the complete table.

under our previously reported MeOH and $Ti(O\text{-}i\text{-}Pr)_4$ spirocyclization conditions, as well as upon heating to 120 °C in toluene (entries 1−3). After investigating a wide range of Lewis acids,[16] we were encouraged to find that $Sc(OTf)_3$ favored the inversion product **7a** (entry 4), which could be formed exclusively by changing the reaction solvent from CH_2Cl_2 to THF (entry 5). The diastereoselectivity decreased slightly with substoichiometric $Sc(OTf)_3$ (entries 6 and 7). Other Lewis acids gave lower or even reversed diastereoselectivity.[16]

In low-temperature ^{1}H NMR experiments, we found that the $Sc(OTf)_3$-mediated spirocyclization begins to occur at −35 °C.[16] Complete selectivity for spirocyclization with inversion of configuration was maintained when the reaction was run at −20 °C (entry 8), but selectivity decreased at higher temperatures (entry 9), suggesting that the reaction proceeds under kinetic control between −35 and −20 °C.

Strikingly, when the room-temperature reaction was carried out in CH_2Cl_2 instead of THF, thermodynamic equilibration of an initially formed diastereomeric mixture afforded the retention product **8a** with complete stereoselectivity (entries 10, 11).[19] A structural rationale for the observed thermodynamic preference is nonobvious, due to the conformational flexibility of 5-membered rings,[20] and remains a subject for further investigation. However, on the basis of these results, it is apparent that $Sc(OTf)_3$ plays divergent roles in the spirocyclization reactions depending upon solvent selection (THF vs CH_2Cl_2, entry 9 vs 10).

It is known that metal triflates can serve as a mild source of triflic acid.[21] Thus, we carried out mechanistic studies to differentiate between the Lewis and Brønsted acid activities of $Sc(OTf)_3$. Inclusion of the noncoordinating Brønsted base, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP),[21a] in the reaction in THF did not affect diastereoselectivity (entry 8 vs 12). Treatment with $ScCl_3$ at rt also led to complete stereoselectivity for the contrathermodynamic spiroketal **7a** (entry 13). In contrast, spirocyclization with TfOH afforded a diastereomeric mixture favoring the retention product **8a** (entry 14). Taken together, these results suggest that $Sc(OTf)_3$ acts as a Lewis acid in THF at reduced temperatures, catalyzing formation of the contrathermodynamic spiroketal **7a** under kinetic control.

We next carried out the analogous experiments in CH_2Cl_2 where, upon warming to rt, $Sc(OTf)_3$ favors the retention product **8a** (entry 11). In contrast, inclusion of DTBMP resulted in a diastereomeric mixture favoring the inversion product **7a** (entry 15). However, spirocyclization with TfOH provided the retention product **8a** exclusively (entry 16). Treatment with both TfOH and DTBMP afforded a diastereomeric mixture of spiroketals, similar to the result observed with $Sc(OTf)_3$ and DTBMP (entry 17 vs 15). Collectively, these results suggest that $Sc(OTf)_3$ acts as a mild source of Brønsted acid in CH_2Cl_2 at rt, catalyzing formation of the thermodynamically favored spiroketal **8a** under equilibrium control.

We then investigated the scope of these stereocomplementary $Sc(OTf)_3$-catalyzed spirocyclization reactions. Substrates with longer side chains (**6b**, **6c**) and various aryl substituents (**6d**−**h**) were synthesized from the corresponding alkyne and salicylaldehyde precursors (Figure 1). The bromide intermediate **4h** was also used to introduce other substituents (aryl, alkyne, azide, aldehyde, ester, imide) in **4i**−**n** to examine the functional group tolerance of the spirocyclization reactions (Figure S2, Supporting Information).[16] The *exo*-glycals **4i**−**n** were then converted to the corresponding epoxide substrates **6i**−**n** (Figure S2, Supporting Information).[16]

In the spirocyclization reactions, both diastereomers of the larger 6- and 7-membered ring spiroketals (**7b**,**c** and **8b**,**c**) could be obtained with complete diastereoselectivity based on solvent selection (Figure 2). For **8b**, equilibration with $Sc(OTf)_3$ in CH_2Cl_2 required elevated temperature (60 °C). The 7-membered ring spiroketal **7c** was obtained in somewhat lower yield due to an unexpected anti-Markovnikov 6-*exo* epoxide opening side reaction leading to a benzofuran product.[16]

Next, we investigated the electronic effects of various aryl substituents. A wide range of electron-withdrawing and -donating groups were tolerated (**7d**−**n**, **8d**−**n**), and high diastereoselectivities were maintained. Notably, the nitro-substituted substrate **6d** was less reactive and required more forcing conditions (**7d**: rt; **8d**: 6 h). Conversely, the methoxy-substituted substrate **6e** was highly reactive, providing slightly decreased diastereoselectivity in the THF reaction (**7e**: 93:7 dr) and rapid equilibration in the CH_2Cl_2 reaction (**8e**: 1 h). These results are consistent with the expected electronic influence of these *para* substituents upon the reactive anomeric spiro-epoxide center.[18]

The reactions also tolerated other reactive functionalities including alkyne (**7j**, **8j**), azide (**7k**, **8k**), aldehyde (**7l**, **8l**), ester (**7m**, **8m**), and phthalimide (**7n**, **8n**) groups. In the case of

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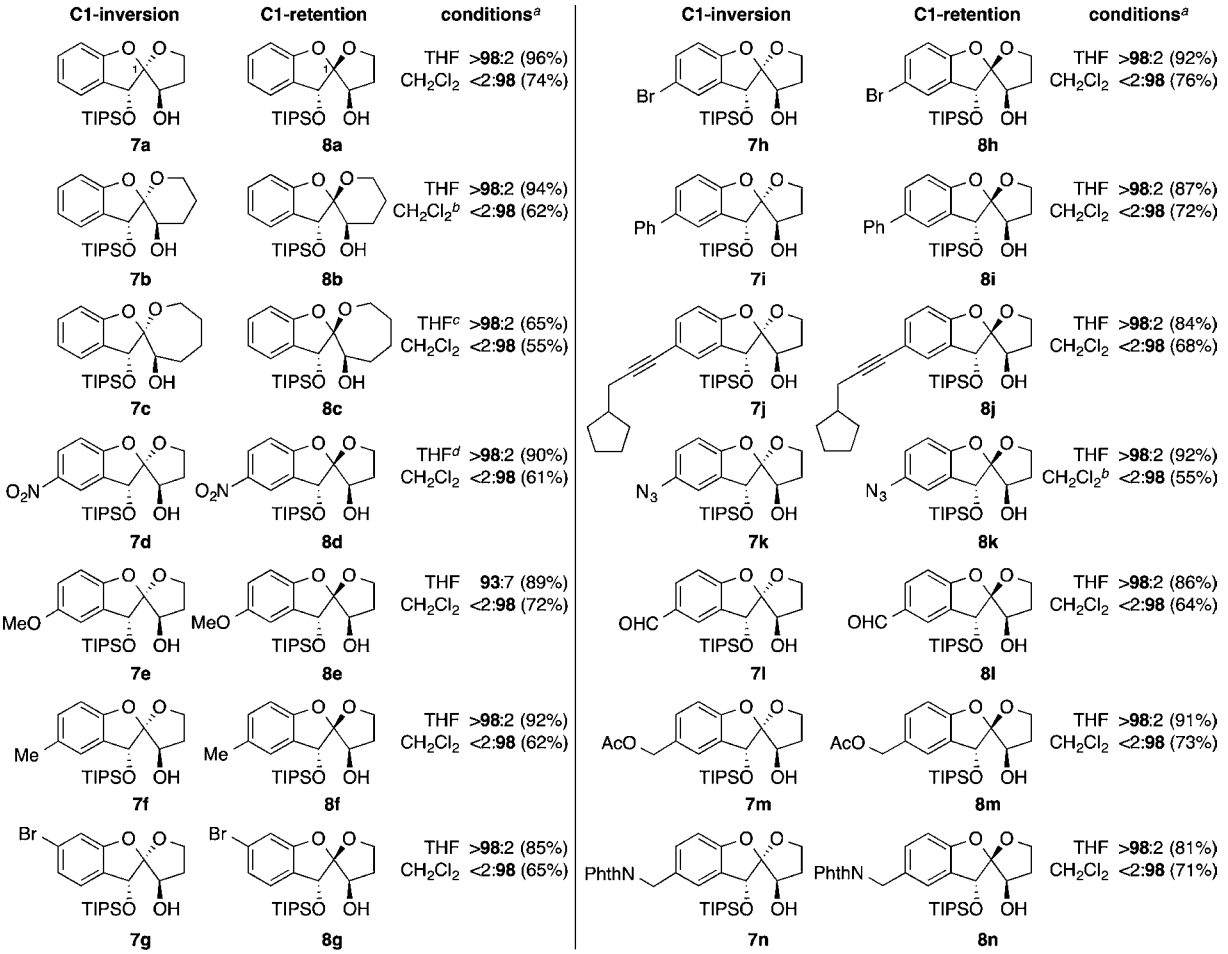

Figure 2. Scope of $Sc(OTf)_3$-mediated spirocyclization reactions. (a) THF: 1.0 equiv $Sc(OTf)_3$, THF, −20 °C, 2−3 h; CH_2Cl_2: 0.5 equiv $Sc(OTf)_3$, CH_2Cl_2, 0 °C to rt, 1−12 h; diastereomeric ratios determined by ^1H NMR analysis of crude reaction mixtures; stereochemistry assigned based on NOESY analysis except **8b**, which was determined by X-ray crystallography;[16] isolated yields after column chromatography shown in parentheses. (b) 60 °C. (c) 30% anti-Markovnikov 6-*exo*-cyclization side product also recovered.[16] (d) rt.

azide **8k**, $Sc(OTf)_3$ equilibration in CH_2Cl_2 required elevated temperature (60 °C).

In conclusion, we have developed novel, solvent-dependent $Sc(OTf)_3$-mediated spirocyclizations of *exo*-glycal epoxides for the stereocontrolled synthesis of benzannulated spiroketals. This *exo*-glycal-based approach overcomes a key limitation of our previous *endo*-glycal-based approach and tolerates a wide range of functionalities. Applications to the diversity-oriented synthesis of stereochemically diverse spiroketal libraries are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tand@mskcc.org.

Notes

The authors declare no competing financial interest.

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