

Published in final edited form as:

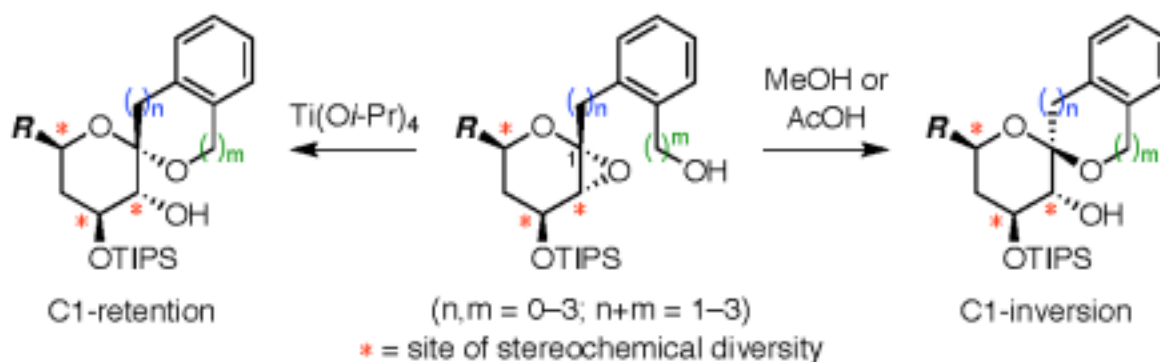
Org Lett. 2009 August 20; 11(16): 3670–3673. doi:10.1021/ol901437f.

Stereoselective Synthesis of Benzannulated Spiroketal: Influence of the Aromatic Ring on Reactivity and Conformation

 Guodong Liu[†], Jacqueline M. Wurst[‡], and Derek S. Tan^{*,†,‡}
[†] Molecular Pharmacology & Chemistry Program, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York 10065

[‡] Tri-Institutional Training Program in Chemical Biology, and Tri-Institutional Research Program, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York 10065

Abstract



A systematic stereocontrolled synthesis of benzannulated spiroketals has been developed, using kinetic spirocyclization reactions of glycol epoxides, leading to a new AcOH-induced cyclization and valuable insights into the reactivity and conformations of these systems. One stereochemical series accommodates axial positioning of the aromatic ring while another adopts an alternative ¹C₄ chair conformation to avoid it. Equatorial aromatic rings also participate in non-obvious steric interactions that impact thermodynamic stability. A discovery library of 68 benzannulated spiroketals with systematic variations in stereochemistry, ring size, and positioning of the aromatic substituent has been synthesized for broad biological evaluation.

Benzannulated spiroketals are found in a variety of natural products with diverse, compelling biological activities. Key examples include the rubromycin family of telomerase inhibitors, the related DNA helicase inhibitor heliquinomycin, the papulacandin family of fungal cell wall glucan synthase inhibitors, the griseusin class of antibacterial agents, the antimetabolic paecilospirone, and the novel matrix metalloproteinase inhibitor berkelic acid.¹ As the benzannulated spiroketal motif has been directly implicated in the biological activity of several of these compounds, this class is an attractive target for the diversity-oriented synthesis of natural product-based libraries for use in discovery screening.² In this vein, the aromatic ring can be expected to influence the reactivity, three-dimensional conformation, and

tand@mskcc.org.

 Supporting Information **Available:** 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>.

physicochemical properties of these molecules relative to aliphatic spiroketals. To evaluate the impact of the aromatic ring on the chemistry and biology of benzannulated spiroketals, we have carried out a systematic study of their stereocontrolled synthesis using kinetic spirocyclization reactions. This work has revealed unexpected reactivity patterns and conformational preferences and paves the way to comprehensive biological evaluation of this class.

The synthesis of benzannulated spiroketals has depended largely upon thermodynamically controlled transketalization reactions of glycoside or ketoalcohol precursors.^{3,4} Several kinetically controlled approaches have also been developed, but still generally do not provide selective access to contrathermodynamic products. Fully stereocontrolled access to either diastereomer at the anomeric carbon is preferable both for total synthesis applications and to leverage stereochemical diversity in spiroketal libraries.⁵ Early work by Wallace suggested the feasibility of overcoming inherent thermodynamic preferences in kinetic chromone epoxide spirocyclizations, albeit with limited stereoselectivity.⁶ Recently, Pettus has also advanced elegant cycloaddition-based approaches to the stereoselective synthesis of rubromycin family members.⁷ We have previously developed a stereocontrolled approach to aliphatic spiroketals using two complementary kinetic spirocyclization reactions of glycal epoxides that proceed with either inversion or retention of configuration at the anomeric carbon, independently of thermodynamic considerations.⁸ We envisioned that these reactions might also be useful for the synthesis of benzannulated spiroketals.

Our overall synthetic strategy is outlined in Figure 1.⁹ The *threo*- and *erythro*-glycal stannanes **1**^{8a,10} were functionalized at C1, either by direct Stille cross couplings of aryl and benzyl bromides,¹¹ or via conversion to the corresponding glycal iodides followed by *B*-alkyl Suzuki–Miyaura cross couplings with styrenes and allylbenzenes.¹² Stille couplings of benzyl bromide substrates required copper iodide to suppress glycal dimer formation and yields were further increased by protection from light.¹³ Deacetylation then provided all nine precursors to 5-, 6-, and 7-membered rings with the aromatic ring systematically positioned along the sidechain (**2a–r**).

Stereoselective *anti*-epoxidation at low temperature afforded glycal epoxide intermediates **3a–r**, which were subjected *in situ* to various spirocyclization conditions (Figures 2 and 3). Warming the glycal epoxides (−78 °C → rt) resulted in spontaneous cyclization with variable selectivity for retention of configuration (**4a–r**). Acid-catalyzed spirocyclization with TsOH (−78 °C → rt) led to **4a–r** exclusively, although these reactions were often compromised by side reactions.¹⁴ In contrast, our Ti(Oi-Pr)₄-mediated spirocyclization (−78 °C → 0 °C)^{8b} afforded **4a–r** in high yields and with complete stereocontrol for all substrates.⁹ Notably, the conformational constraint provided by the aromatic ring allowed highly efficient formation of 7-membered rings (**4c,e,f,i,l,n,o,r**), which was not the case for the corresponding aliphatic systems.^{8b}

Conversely, our MeOH-induced spirocyclization (−63 °C)^{8a} provided stereocontrol for the inherently thermodynamically and kinetically disfavored inversion products in several cases (**5a,b,d–f,j,m,n**). The aromatic ring constraint provided reduced competing intermolecular formation of methyl glycoside side products (**6**) compared to the corresponding aliphatic systems,^{8a} and again allowed several 7-membered rings to be formed (**5e,f,n**). Two additional reactivity trends were noted in these MeOH-induced spirocyclizations. C1-Aryl substrates yielded decreased selectivity for inversion of configuration (**5b** vs. **5d**; **5c** vs. **5e,f**; **5k** vs. **5m**; **5l** vs. **5n**), which we attributed to stabilization of a cyclic oxocarbenium intermediate leading to the retention products. Phenolic substrates also afforded decreased stereoselectivity (**5g–i,p–r**) and increased methyl glycoside formation, presumably due to the lower nucleophilicity of the phenol sidechains.

To achieve more efficient access to the inversion products, we explored alternative Brønsted acids and were gratified to find that AcOH (10 equiv., $-63\text{ }^{\circ}\text{C} \rightarrow -44\text{ }^{\circ}\text{C}$) provided increased yields for both the problematic 7-membered ring and phenolic systems (**5e-i,n-r**).^{15,16} Treatment of the isolated products with AcOH confirmed that this reaction remains under kinetic control. The increased yields could be attributed largely to the absence of competing intermolecular glycosylation. AcOH may also provide increased epoxide reactivity for less-reactive phenol nucleophiles, consistent with our previous proposal that the MeOH-induced spirocyclization proceeds via activation of the epoxide by MeOH hydrogen bonding.^{8a,17}

To evaluate the impact of the aromatic ring upon the conformation of benzannulated spiroketals, we carried out detailed structural analyses of several products (Figure 4).⁹ Analyses of NOESY spectra and *J* values¹⁸ indicated that both *threo* series products **4a** and **5a** adopt standard ⁴C₁ chair conformations. Notably, this is despite the axial orientation of the aromatic ring in **5a**, due to unfavorable 1,3,5-triaxial interactions in the alternative ¹C₄ conformation (**5a'**). In contrast, the corresponding *erythro* series product **4j** adopts the alternative ¹C₄ conformation, due to the additional steric impact of the C3-OTIPS group (**4j'**). While both **4j** and **5j** have anomeric stabilization and comparable 1,3-diaxial interactions involving C1-O, the thermodynamic preference for **4j** can be rationalized by an additional, non-obvious steric interaction between the *ortho*-proton of the aromatic ring and C2-OH in **5j**. Strikingly, after desilylation (R' = H), the thermodynamic preference is reversed, with **8** stabilized by an intramolecular hydrogen bond. These results highlight the profound impact of the aromatic ring upon both the conformational and thermodynamic preferences of benzannulated spiroketals and the increased conformational diversity in this class compared to the corresponding aliphatic spiroketals.

Desilylation of all products provided a discovery library of 68 out of the 72 possible benzannulated spiroketals (both enantiomeric series) having all combinations of five-, six-, and seven-membered rings and aromatic ring positions, with nearly comprehensive stereochemical diversity. These compounds have been deposited in the NIH Molecular Libraries Small Molecule Repository¹⁹ and are undergoing biological evaluation to assess the effectiveness of this structural class against a wide range of targets. Analysis of those results will be reported in due course.

In conclusion, we have carried out a systematic analysis of kinetic and thermodynamic spirocyclization reactions to form benzannulated spiroketals, leading to the development of a new AcOH-induced kinetic spirocyclization. Notably, the systematic nature of this study, mandated by our interest in diversity-oriented synthesis applications, has revealed significant reactivity changes and conformational effects imparted by the aromatic ring, which may be useful in the design and synthesis of a broad range of molecules with related structural motifs. Finally, this work sets the stage for further biological investigation of this compelling class of molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Prof. Ian Fairlamb (University of York) for helpful discussions and Dr. George Sukenick, Dr. Hui Liu, Hui Fang, and Dr. Sylvia Rusli for expert mass spectral analyses. D.S.T. is an Alfred P. Sloan Research Fellow. Financial support from the NIH (P41 GM076267), NYSTAR Watson Investigator Program, William H. Goodwin and Alice Goodwin and the Commonwealth Foundation for Cancer Research, and MSKCC Experimental Therapeutics Center is gratefully acknowledged.

References

1. Rubromycins/heliquinomycin: (a)Brasholz M, Sörgel S, Azap C, Reißig HU. Eur J Org Chem 2007;3801–3814.3814. Papulacandins: (b)Traxler P, Fritz H, Fuhrer H, Richter WJ. J Antibiot 1980;33:967–978.978 [PubMed: 7440418](c)Varona R, Perez P, Duran A. FEMS Microbiol Lett 1983;20:243–247.247. Griseusins: (d)Tsuji N, Kobayashi M, Wakisaka Y, Kawamura Y, Mayama M, Matsumoto K. J Antibiot 1976;29:7–9.9 [PubMed: 819406]. Paecilospirone: (e)Namikoshi M, Kobayashi H, Yoshimoto T, Meguro S. Chem Lett 2000:308–309.309. Berkelic acid: (f)Stierle AA, Stierle DB, Kelly K. J Org Chem 2006;71:5357–5360.5360 [PubMed: 16808526]
2. Tan DS. Nat Chem Biol 2005;1:74–84. [PubMed: 16408003]
3. For examples from natural product total synthesis, see: Rubromycins: (a) Reviewed in ref. 1a. (b)Akai S, Kakiguchi K, Nakamura Y, Kuriwaki I, Dohi T, Harada S, Kubo O, Morita N, Kita Y. Angew Chem, Int Ed 2007;46:7458–7461.7461. Heliquinomycinone: (c)Siu T, Qin D, Danishefsky SJ. Angew Chem, Int Ed 2001;40:4713–4716.4716. Papulacandins: (d)Denmark SE, Regens CS, Kobayashi T. J Am Chem Soc 2007;129:2774–2776.2776 [PubMed: 17305346]. Griseusins: (e)Kometani T, Takeuchi Y, Yoshii E. J Org Chem 1983;48:2311–2314.2314. Berkelic acid: (f)Wu X, Zhou J, Snider BB. Angew Chem, Int Ed 2009;48:1283–1286.1286(g)Buchgraber P, Snaddon TN, Wirtz C, Mynott R, Goddard R, Fürstner A. Angew Chem, Int Ed 2008;47:8450–8454.8454
4. For other approaches to benzannulated spiroketals, see: Alkoxyseleation: (a)Elsley DA, MacLeod D, Miller JA, Quayle P, Davies GM. Tetrahedron Lett 1992;33:409–412.412. Alkyne cyclotrimerization: (b)McDonald FE, Zhu HYH, Holmquist CR. J Am Chem Soc 1995;117:6605–6606.6606. Glycoside rearrangement: (c)Kumazawa T, Asahi N, Matsuba S, Sato S, Furuhashi K, Onodera JI. Carbohydr Res 1998;308:213–216.216. Michael addition: (d)Carretero JC, De Diego JE, Hamdouchi C. Tetrahedron 1999;55:15159–15166.15166(e)Choi PJ, Rathwell DCK, Brimble MA. Tetrahedron Lett 2009;50:3245–3248.3248. Ring-closing metathesis: (f)Van Hooft PAV, Van Swieten PF, Van der Marel GA, Van Boeckel CAA, Van Boom JH. Synlett 2001:269–271.271. *o*-Quinone methide hetero-Diels–Alder: (g)Zhou G, Zheng D, Da S, Xie Z, Li Y. Tetrahedron Lett 2006;47:3349–3352.3352(h) Lindsey CC, Wu KL, Pettus TRR. Org Lett 2006;8:2365–2367.2367 [PubMed: 16706527]. Alkyne hydroalkoxylation: (i)Messerle BA, Vuong KQ. Organometallics 2007;26:3031–3040.3040(j)Zhang Y, Xue J, Xin Z, Xie Z, Li Y. Synlett 2008:940–944.944. Radical cyclization: (k)Liu YC, Sperry J, Rathwell DCK, Brimble MA. Synlett 2009:793–797.797
5. For a recent review of non-anomeric spiroketal synthesis, see: Aho JE, Pihko PM, Rissa TK. Chem Rev 2005;105:4406–4440.4440 [PubMed: 16351049]
6. Cremins PJ, Wallace TW. J Chem Soc, Chem Commun 1986:1602–1603.
7. (a) Wu KL, Wilkinson S, Reich NO, Pettus TRR. Org Lett 2007;9:5537–5540. [PubMed: 18044909] (b) Marsini MA, Huang Y, Lindsey CC, Wu KL, Pettus TRR. Org Lett 2008;10:1477–1480. [PubMed: 18336038]
8. (a) Potuzak JS, Moilanen SB, Tan DS. J Am Chem Soc 2005;127:13796–13797. [PubMed: 16201793] (b) Moilanen SB, Potuzak JS, Tan DS. J Am Chem Soc 2006;128:1792–1793. [PubMed: 16464069]
9. See Supporting Information for full details.
10. Moilanen SB, Tan DS. Org Biomol Chem 2005;3:798–803. [PubMed: 15731865]
11. (a) Friesen RW, Sturino CF. J Org Chem 1990;55:2572–2574. (b) Milstein D, Stille JK. J Am Chem Soc 1979;101:4992–4998. (c) Farina V, Kapadia S, Krishnan B, Wang C, Liebeskind LS. J Org Chem 1994;59:5905–5911.
12. Potuzak JS, Tan DS. Tetrahedron Lett 2004;45:1797–1801.
13. Crawforth CM, Burling S, Fairlamb IJS, Kapdi AR, Taylor RJK, Whitwood AC. Tetrahedron 2005;61:9736–9751.
14. In particular, for *erythro* series substrates (**3j–r**), loss of the C3-OTIPS group with concomitant oxidation of the C2-OH group was observed. This may occur via enolization (C2-deprotonation) of the intermediate cyclic oxocarbenium species, followed by Ferrier type elimination of the C3-substituent, tautomerization of the resulting C2 enol to a ketone, and ring reclosure at C1.
15. *p*-NO₂PhOH provided comparable **4i:5i** selectivity, while weaker (PhOH) and stronger acids (HCO₂H, *p*-NO₂PhCO₂H, TFA) led to decreased amounts of the desired inversion product **5i**. Larger amounts of AcOH (100–1000 equiv.) led to increased formation of the retention products **4**, presumably due to increased competing oxocarbenium formation.

16. For related reactions of glycals and glycosides, see: (a)Pothier N, Goldstein S, Deslongchamps P. *Helv Chim Acta* 1992;75:604–620.620(b)Castagnolo D, Breuer I, Pihko PM. *J Org Chem* 2007;72:10081–10087.10087 [PubMed: 18004871]
17. Related effects have been proposed in epoxide-opening cascades leading to ladder polyethers: (a) Vilotijevic I, Jamison TF. *Science* 2007;317:1189–1192.1192 [PubMed: 17761875](b)Byers JA, Jamison TF. *J Am Chem Soc* 2009;131:6383–6385.6385 [PubMed: 19385615]
18. Karplus M. *J Chem Phys* 1959;30:11–15.
19. PubChem Substance Identifiers (SID): “DST_SK2_*”; <http://pubchem.ncbi.nlm.nih.gov/>

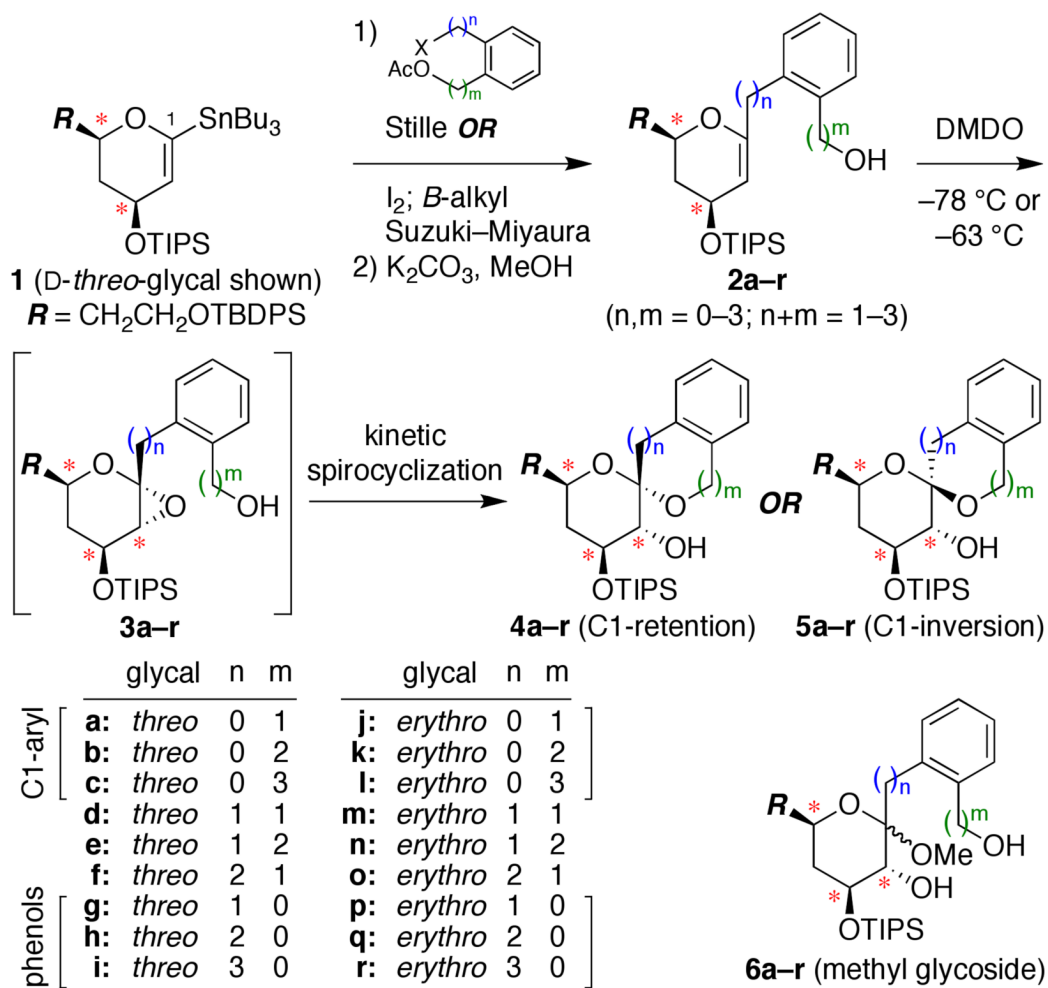
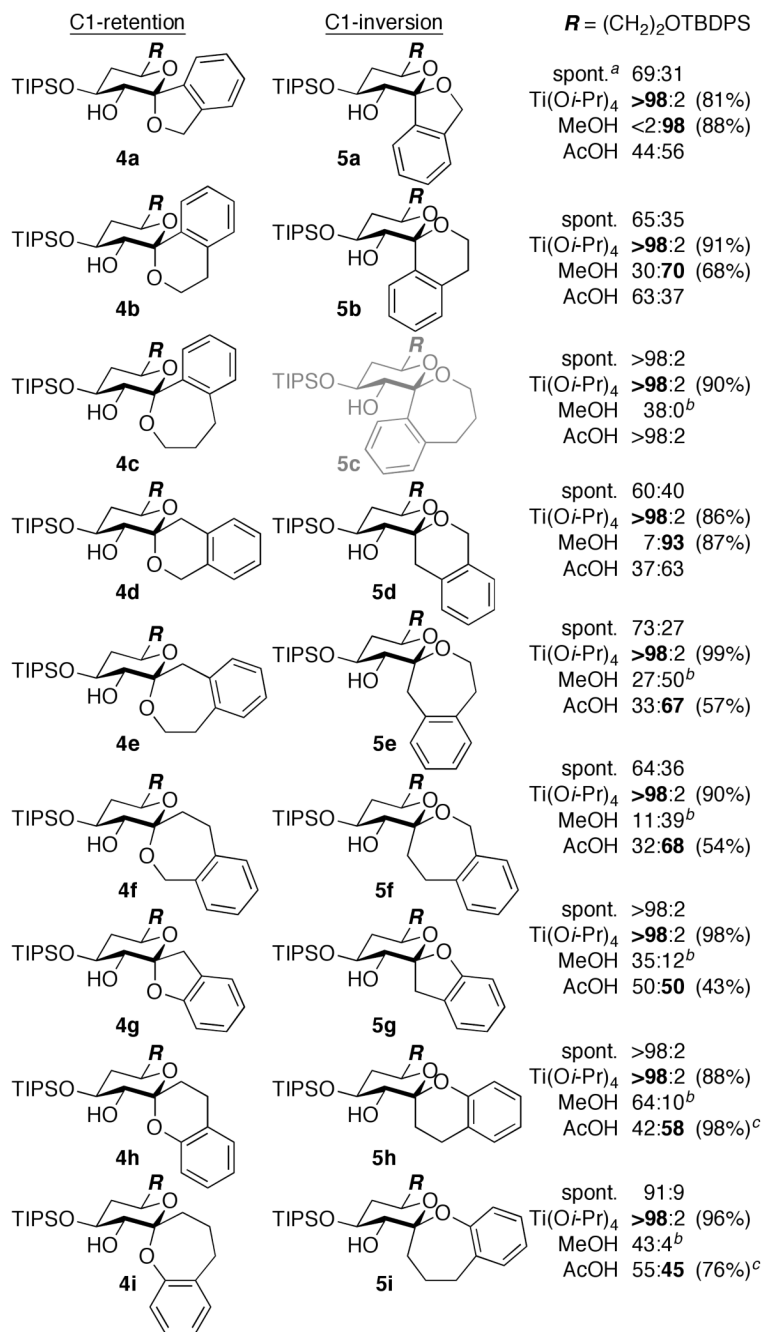


Figure 1. Overall approach to stereocontrolled synthesis of benzannulated spiroketals using kinetic spirocyclization reactions. (*) = site of stereochemical diversity.

**Figure 2.**

Diastereomeric ratios of benzannulated spiroketals formed from *D-threo*-glycal epoxides **3a–i**. Isolated yields of **4** (Ti[O*i*-Pr]₄) and **5** (MeOH or AcOH) shown in parentheses. ^a Spontaneous spirocyclization (–78 °C → rt). ^b Remainder methyl glycoside **6**. ^c Inseparable mixture of **4** and **5** (separable after desilylation).

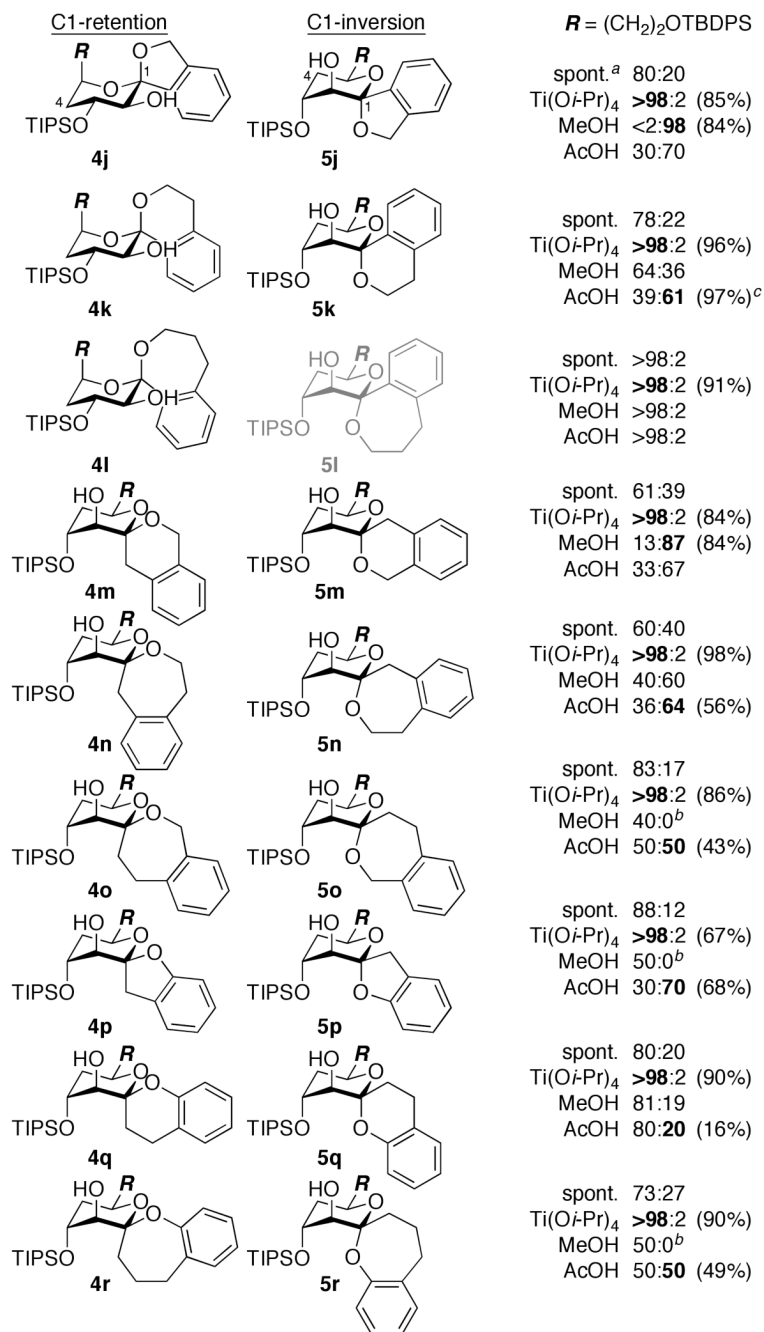


Figure 3. Diastereomeric ratios of benzannulated spiroketals formed from *D*-*erythro*-glycol epoxides **3j**–**r**. Isolated yields of **4** (Ti[O*i*-Pr]₄) and **5** (MeOH or AcOH) shown in parentheses.^a Spontaneous spirocyclization (−78 °C → rt).^b Remainder methyl glycoside **6**.^c Inseparable mixture of **4** and **5** (separable after desilylation).

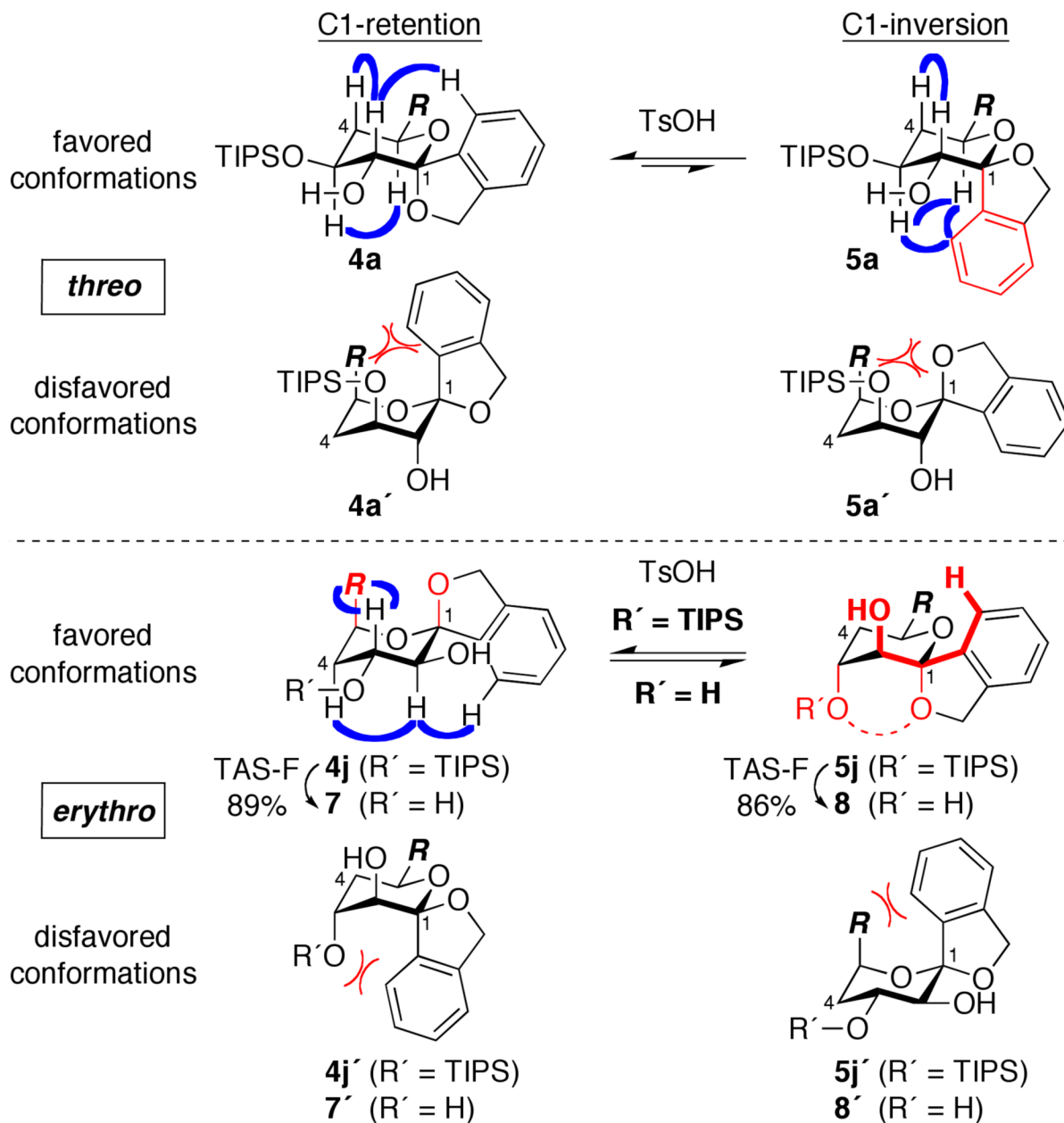


Figure 4.

Alternative conformations of benzannulated spiroketals **4a**, **5a**, **4j**, **5j** and desilylated congeners **7**, **8**. NOESY interactions are indicated in blue; steric interactions are indicated in red. A non-obvious steric interaction in **5j** between the *ortho*-proton of the aromatic ring and C2-OH is highlighted in bold red.