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Rational Synthesis of Contra-Thermodynamic Spiroacetals by Reductive Cyclizations

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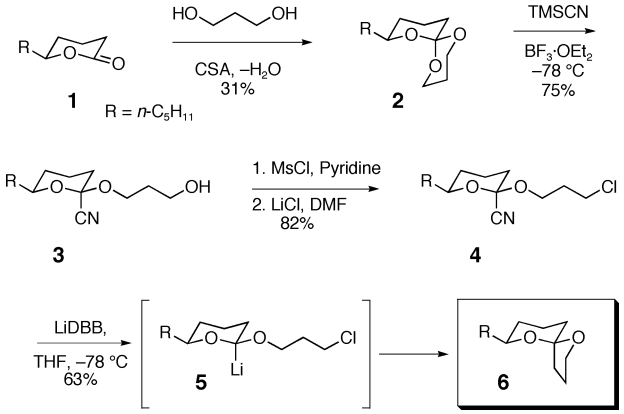
Spiroacetal structures are widely distributed in natural products, and there are many methods that have been developed for their synthesis.[1] Most methods rely on an acid-catalyzed cyclization and thus lead to a thermodynamic mixture of spiroacetals. The most stable spiroacetal configuration usually has both oxygens positioned to favor anomeric stabilization.[2] A number of natural products contain spiroacetals with only a single anomeric stabilization possible, and these contra-thermodynamic acetals have been more difficult to access.[3] These spiroacetals have most often been prepared by setting up an equilibrium, preferably with solvent effects, the addition of metal salts, or protecting group motifs that shift the equilibrium in the desired direction, and then separating the two spiroacetals.[4] We describe herein the first rational and general synthetic approach to spiroacetal structures with only a single anomeric stabilization.

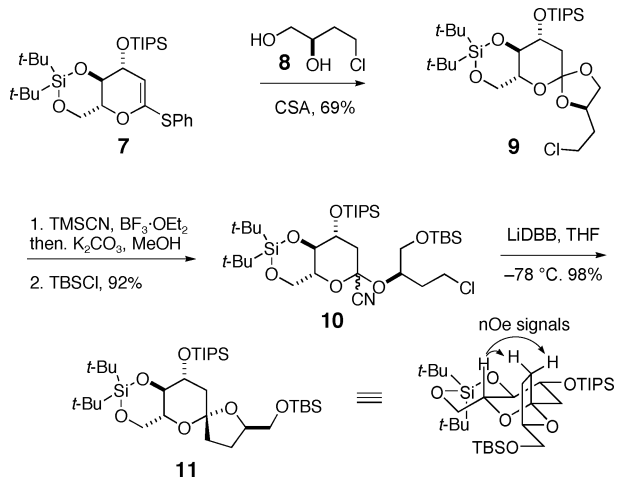
The spiroacetal synthesis is based on a reductive cyclization of 2-cyanotetrahydropyrans.[5] The strategy is outlined in Scheme 1. Spiro ortho ester **2** was prepared from lactone **1** and 1,3-propanediol under acidic conditions.[6] The ortho ester was cleaved on treatment with TMSCN and $BF_3{\cdot}OEt_2$ to produce the axial nitrile **3**.[7] The nitrile was fragile and, on standing at −20 °C, slowly equilibrated to the other acetal stereoisomer. The alcohol was replaced with a chloride by treatment with MsCl and then LiCl. Reduction generated an intermediate dialkoxylithium reagent[8] in the expected axial configuration,[9] and intramolecular alkylation produced the spiroacetal **6** as a single diastereomer. Compound **6** has only one anomeric stabilization possible because one oxygen is equatorial on the tetrahydropyran ring. As expected, spiroacetal **6** is contra-thermodynamic, and it was equilibrated quantitatively to the other spiroacetal epimer on treatment with CSA in dichloromethane.[10] Stereoselective reduction to the axial alkylithium reagent **5** and alkylation with retention of configuration accounts for the generation of the contra-thermodynamic spiroacetal with a single anomeric stabilization.

While the reaction sequence in Scheme 1 did produce the contra-thermodynamic acetal **6**, there were difficulties. Foremost among them was the problematic preparation of the spiro ortho ester. Seeking to expand the scope of the reaction, we attempted to prepare more highly substituted spiro ortho esters using these conditions and by other methods with very little success.[6,11] The acid-catalyzed condensation approach is not tolerant of substitution of other functional groups. After much frustration, we developed a new route to spiro ortho esters that is general and takes place under mild conditions.[12] The key intermediate is an α-thiophenyl ketene acetal such as **7** (Scheme 2), which was prepared by deprotonation of the enol ether with *tert*-BuLi, followed by quenching with diphenyl disulfide.[13] These hemithio ketene acetals react with diols in the presence of an acid catalyst to produce spiro ortho esters in good yield.[12] For example, reaction of **7** with optically pure diol **8** led to the spiro ortho ester **9** as a 2:1 mixture of diastereomers at the

Scheme 1. Synthesis of Contra-Thermodynamic Spiroacetal **6** by Stereoselective Reductive Lithiation and Cyclization



Scheme 2. Synthesis of a Monoanomeric Stabilized Spiroacetal **11** from Spiro Ortho Ester **9**



ortho ester center. This new route to spiro ortho esters enabled us to evaluate the scope of the contra-thermodynamic spiroacetal synthesis.

Scheme 2 illustrates the preparation of a much more complex spiroacetal. The spiro ortho ester **9** was cleaved by treatment with TMSCN and $BF_3{\cdot}OEt_2$ at −78 °C. The intermediate TMS ether was converted into a TBS ether by hydrolysis and reprotection to give cyano acetal **10** as a mixture of stereoisomers. The primary oxygen of **9** was cleaved selectively, presumably due to steric effects. Chloro diol **8** incorporates the leaving group for the reductive cyclization, eliminating the need to convert the alcohol to a chloride. Incorporating the leaving group into a diol is a more versatile approach to cyclization substrates than the original strategy outlined in Scheme 1. The reductive cyclization of **10** proceeds in almost quantitative yield on treatment with LiDBB at low temperature. NOE experiments confirm that the resulting spiroacetal **11**

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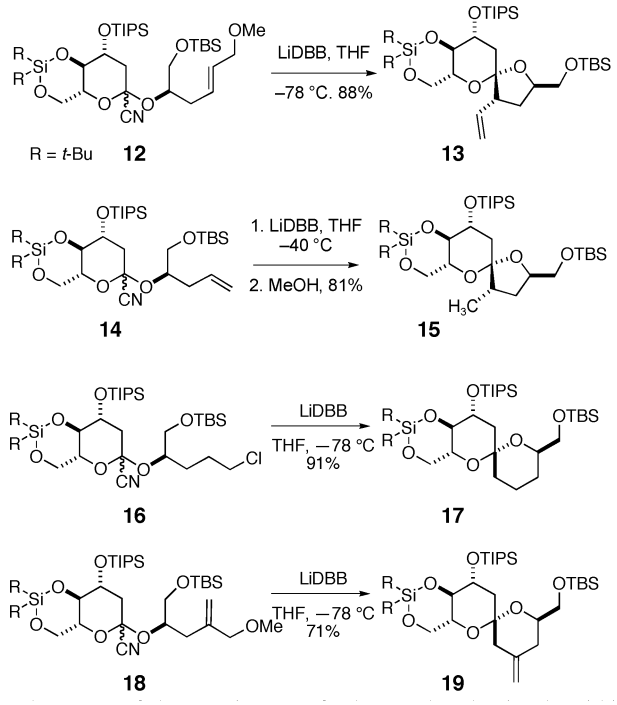
Scheme 3. Synthesis of Contra-Thermodynamic Spiroacetals by Reductive Cyclization



has the methylene rather than the oxygen axial to the pyran ring. Thus the monoanomeric stabilized spiroacetal was produced as expected.

The scope of the reaction was further explored using hemithio ketene acetal **7** and four other diols that incorporate a variety of leaving groups for the reductive cyclization. Each of the substrates in Scheme 3 was prepared by spiro ortho ester synthesis[14] followed by TMSCN treatment and alcohol reprotection following the protocol presented in Scheme 2.[15] Reductive lithiation of cyano acetal **12** followed by cyclization onto the methoxy alkene produced spiro ortho ester **13** in excellent yield as a single diastereomer. The alkene is cis to the pyran oxygen as expected,[5] and the oxygen is equatorial to the tetrahydropyran ring, confirming that this is a monoanomeric stabilized spiroacetal. On treatment with CSA in dichloromethane, spiroacetal **13** equilibrated quantitatively to the epimeric spiroacetal, confirming that **13** is a contra-thermodynamic spiroacetal. The cyclization of alkene **14** required higher temperature and proceeded in lower yield than that of **12** but once again led to a single diastereomer of spiroacetal **15** with the expected configurations at the two new stereogenic centers. Both of these substrates are sterically crowded and lead to more crowded products. Many reactions become problematic with increased steric hindrance, but reductive cyclizations, which are initiated by outer-sphere electron-transfer reactions, are relatively insensitive to steric bulk.

The strategy is also successful in producing [5.5]-spiroacetals. Cyclization of **16** produced **17** in excellent yield, and the structure of the product was confirmed by NMR and NOE analysis. Cyclization of methoxy alkene **18** gave the spiroacetal **19**, with only one anomeric stabilization present, in good yield as a single diastereomer. The structure of spiroacetal **19** was confirmed by NOE analysis. The examples in Scheme 3 demonstrate the impressive scope of this strategy for the synthesis of spiroacetals with single anomeric stabilization.

The first rational and general approach to contra-thermodynamic spiroacetals has been described. The strategy presented makes possible the synthesis of this previously inaccessible or poorly accessible class of compounds. The synthesis of spiroacetals is both convergent and compatible with complex structures. In two cases the initially formed spiroacetal was equilibrated to the thermodynamically more stable isomer. Thus, the reductive cyclization strategy presented can be used to prepare both contra-thermodynamic and thermodynamic spiroacetals. We are investigating the application of this strategy in natural product synthesis.

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Supporting Information Available: Experimental details for preparation of the cyclization substrates and the cyclization reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The spiroacetal carbon of **6** showed a ^{13}C NMR shift of 107.6 ppm. On equilibration to the more stable epimer, the chemical shift changed to 105.8 ppm. This change in chemical shift of the acetal carbon going from one anomeric stabilization to two is consistent with previous observations (ref 3e) and also was found in the equilibration of **13** (108.2 ppm) to its more stable epimer (106.7 ppm).

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(14) The spiro ortho esters precursors to **12**, **14**, **16**, and **18** were prepared from the appropriate diol and **7** in 67%, 81%, 93%, and 24% yields, respectively. The spiroacetals were mixtures of diastereomers that ranged from 1:1 to ca. 2:1.

(15) The cyano acetals **12**, **14**, **16**, and **18** were prepared from the spiro ortho esters in yields ranging from 81% to 95% and ranged from a 1:1 mixture to a 10:1 mixture of diastereomers.

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