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Diastereoselective Formation of Cyclic Acetals *via* an Intramolecular Fluoride-Catalyzed Hetero-Michael Reaction

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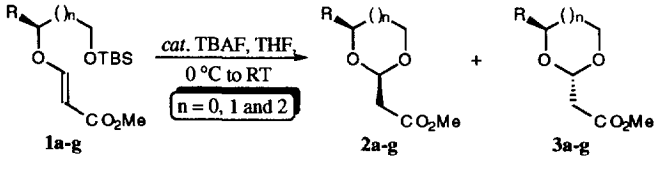
Abstract: *Treatment of the* tert-*butyldimethylsilyl ethers* ***1a-g*** *with tetra*-N-*butylammonium fluoride furnished the corresponding cyclic acetals* ***2/3a-g*** *in 82-90% yield and with excellent diastereoselectivity for* $n = 1$ *and* 2. Copyright © 1996 Elsevier Science Ltd

Cyclic acetals have been studied extensively, and represent important synthons for target directed synthesis.[1] They serve as versatile protecting groups for diols, particularly in carbohydrate chemistry,[2] and as chiral auxiliaries that may be transformed into an array of complementary functionality.[1,3] Cyclic acetals have also been utilized as chiral intermediates for the synthesis of polyol chains,[4] which are directly applicable to the polyene macrolide antibiotics.[5] Furthermore, the conformational analysis of these systems has attracted significant attention,[6] and has led to greater insight into the stereoelectronic factors that are responsible for the stereocontrol obtained within these systems. Although several methods have emerged for the preparation of cyclic acetals, these generally involve an acid or Lewis acid catalyst,[1,2] making them unsuitable for molecules that contain acid labile functionality. In this letter, we report a new method for the synthesis of 5-, 6-, and 7-membered cyclic acetals, involving a fluoride-catalyzed intramolecular hetero-Michael reaction (**Scheme 1**).[7,8]

Scheme 1

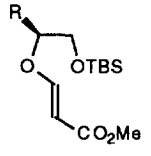
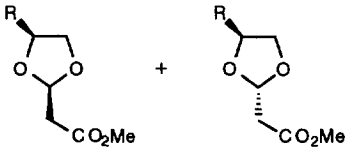
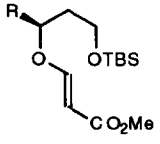
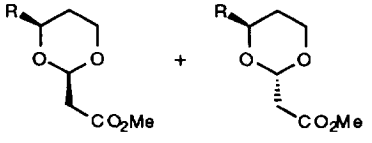
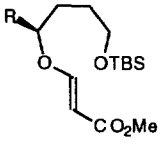
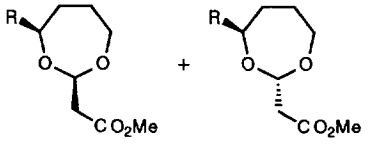


1a-g **2a-g** **3a-g**

In the course of our synthetic studies, the desilylation of the *tert*-butyldimethylsilyl ether **1c** to the corresponding primary alcohol was required. However, treatment of **1c** with tetra-*N*-butylammonium fluoride (TBAF) furnished the cyclic acetal **2c** in 88% yield, as a single diastereoisomer. **Table 1** summarizes the results for the application of this protocol to other ring sizes and substituents. Preliminary work demonstrated that the reaction could be effected by a catalytic amount of TBAF, provided the *tert*-

butyldimethylsilyl ether was the only silyl group present in the molecule. Treatment of the silyl ethers **1a-b**[9,10] with a catalytic amount of TBAF furnished the 2,4-disubstituted dioxolanes **2/3a-b** in 84-86% yield, as a 1.2 : 1 mixture, favoring the *cis*-diastereoisomer. However, treatment of the *tert*-butyldimethylsilyl ethers **1d-f** under analogous conditions afforded the cyclic acetals **2d-f** in 82-90% yield, in which the *cis*-diastereoisomer for both the 2,4-disubstituted 1,3-dioxanes **2d-e** and 1,3-dioxepin **2f** was the exclusive stereoisomer. Cyclization of **1g** also proceeded with high diastereocontrol. The stereochemical outcome of the cyclization reactions was determined by a series of n.O.e. studies.[11]

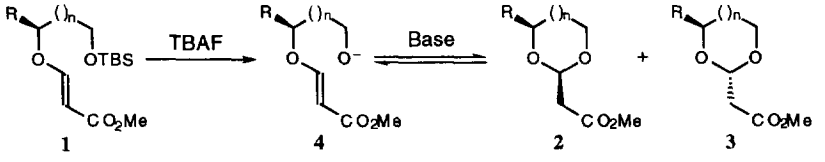
Table 1: Intramolecular Fluoride Induced Cyclization of *tert*-Butyldimethylsilyl Ethers **1a-g**

Entry	*tert*-Butyldimethylsilyl Ether **1**[a,b]	Cyclic Acetal **2/3**	Time (hours)	Ratio of **2** : **3**[c]	Yield (%)[d]
					
1	**1a** R = Me	**2/3a** R = Me	1.25	1.2 : 1	86
2	**1b** R = Ph	**2/3b** R = Ph	0.5	1.2 : 1	84
					
3	**1c** R = TMS-C≡C-CH_2	**2/3c** R = H-C≡C-CH_2	1.0	≥19 : 1	88[e]
4	**1d** R = Me	**2/3d** R = Me	1.5	≥19 : 1	90
5	**1e** R = Ph	**2/3e** R = Ph	1.0	≥19 : 1	90
					
6	**1f** R = Me	**2/3f** R = Me	29	≥19 : 1	84
7	**1g** R = Ph	**2/3g** R = Ph	23	12 : 1	82

[a] All the reactions were carried out on a 0.5 mmol reaction scale except where indicated to the contrary.[10,12] [b]TBAF (0.2 eq.) THF, RT. [c]Ratios of diastereoisomers determined by ^{1}H-NMR integration. [d]Isolated yields. [e]1.25 eq of TBAF on a 0.25 mmol reaction scale.

The high degree of stereocontrol observed in the formation of the 6- and 7-membered cyclic acetals is presumably due to the reversibility of the hetero-Michael reaction, as illustrated in **Scheme 2**. Hence, the *trans*-diastereoisomer is equilibrated to the thermodynamically most stable *cis*-diastereoisomer.[6,8]

Scheme 2



The poor diastereoselectivity obtained in the formation of the 1,3-dioxolanes **2/3a-b** indicates the relatively small difference in energy between the *cis*- and *trans*-isomers.[13] In order to provide additional evidence in support of this hypothesis the reaction was carried out under kinetic conditions. Treatment of the *tert*-butyldimethylsilyl ether **1b** with TBAF at –50 °C afforded the 1,3-dioxolanes **2b/3b** in an improved 2.1 : 1 ratio, favoring the *cis*-diastereoisomer. However, when this mixture of cyclic acetals **2b/3b** was resubmitted to the reaction conditions, the 1,3-dioxolanes **2b/3b** were recovered as a 1.2 : 1 ratio of diastereoisomers in near quantitative yield.[2,14]

In conclusion, we have developed a new method for the stereoselective synthesis of *cis*-2,4-disubstituted 6- and 7-membered cyclic acetals. The advantage of this protocol is the extremely mild reaction conditions, which should be particularly useful for acid labile molecules, and the ability to introduce useful functionality at the C-1 position of the cyclic acetal.

Acknowledgments

We would like to thank the University of Delaware Research Foundation and the Donors of the Petroleum Research Foundation, administered by the American Chemical Society, for generous financial support.

References and Footnotes

1. For a recent review on cyclic acetals, see Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

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6. Gordillo, B.; Juaristi, E.; Martínez, R.; Toscano, R. A.; White, P. S.; Eliel, E. L. *J. Am. Chem. Soc.* **1992**, *114*, 2157 and references cited therein.

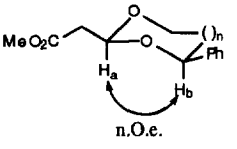
7. For an example of a fluoride induced hetero-Michael reaction for the synthesis of cyclic ethers, see: Palazón, J. M.; Soler, M. A.; Ramírez, M. A.; Martín, V. S. *Tetrahedron Lett.* **1993**, *34*, 5471.

8. For an example of the synthesis of *syn*-1,3-benzylidene acetals using a hetero-Michael reaction, see: Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

9. The vinylogous carbonates **1a-g** were prepared, in 78-91% yield, from the corresponding secondary alcohols using tributylphosphine and methyl propiolate at room temperature: Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241.

10. All new compounds exhibited spectroscopic (IR, ^{1}H and ^{13}C-NMR) and analytical (HRMS) data in accord with the assigned structure.

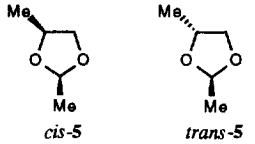
11. The stereochemistry of the major diastereoisomer was assigned from the n.O.e.'s observed between H_a and H_b for the 5-, 6- and 7-membered cyclic acetals.



		% n.O.e	
2b	n = 0	H_a to H_b = 1%	H_b to H_a = na
2e	n = 1	" = 8%	" = 7%
2g	n = 2	" = 6%	" = 9%

12. *Typical Cyclization Procedure:* The enol ether **1e** (0.168 g, 0.48 mmol) was dissolved in anhydrous THF (4.8 ml) and cooled with stirring to 0 °C. TBAF (96 µl, 96 µmol, 0.2 eq, 1M soln. in THF) was then added *via* syringe and the pale yellow solution was allowed to warm to room temperature and stirred for an additional hour (TLC control). The reaction mixture was then poured into saturated $NaHCO_3$ solution (10 ml) and extracted with diethyl ether (3 x 15 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 1 : 4 diethyl ether/hexane) afforded the cyclic acetal **2e** (0.102 g, 90%) as a colorless oil.

13. Molecular mechanics as implemented on the Tektronix CAChe workstation for 2,4-dimethyl-1,3-dioxolane **5** confirm the *cis*-isomer to be the most stable diastereoisomer. However, the relatively small experimental difference between the two diastereoisomers may be attributed to electronic factors not considered in the calculations.



cis-**5** *trans*-**5**

MM2 7.79 kcal/mol 8.53 kcal/mol

14. A survey of the literature reveals that the equilibrium ratio of 2,4-disubstituted 1,3-dioxolanes, formed under acid catalysis, often leads to mixtures of diastereoisomers.[2]

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