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Highly Selective Reduction of Acyclic β-Alkoxy Ketones to Protected *syn*-1,3-Diols

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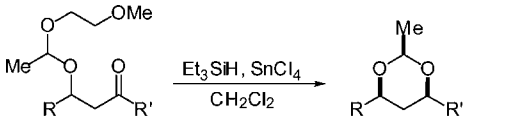
ABSTRACT



dr= >200:1 (*syn* : *anti*)

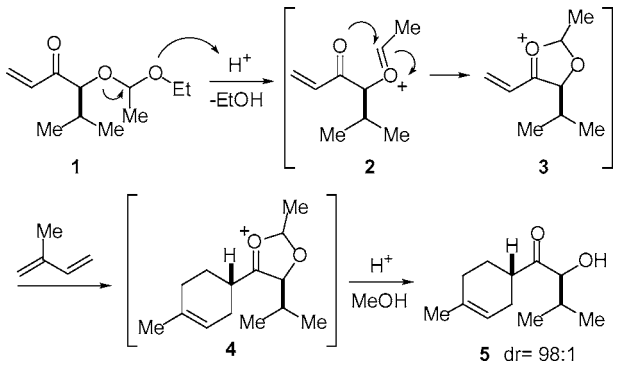
The conversion of 1-(2-methoxyethoxy)ethyl-protected β-hydroxy ketones to *syn*-1,3-ethylidene acetals is effected by Et_3SiH and $SnCl_4$. This reaction is proposed to proceed via a cyclic oxocarbenium ion intermediate and provides the products in yields that range from 69 to 94% and with diastereoselectivities that are >200:1.

Some time ago, we described an asymmetric ionic Diels−Alder reaction that proceeds by way of a cyclic oxocarbenium ion (Scheme 1).[1] In this reaction, treatment of **1** with HBF_4 induces ionization of the acetal to generate the acyclic oxocarbenium ion **2**. This compound then undergoes intramolecular attack by the proximal carbonyl to provide the cyclic oxocarbenium ion[2] **3**, which then undergoes an ionic Diels−Alder reaction with excellent diastereoselection due to the structural rigidity of **3**. We sought to expand this method to include the stereoselective synthesis of 1,3-diols. Extended 1,3-polyol units are found in many biologically active oxo polyene macrolides, and for the construction of such polyol chains,[3] we viewed the reduction of cyclic oxocarbenium ions derived from β-alkoxy ketones as a concise means of accessing protected 1,3-diol units.[4] In this Letter, we describe the implementation of this strategy.

In analogy with our Diels−Alder studies, we wished to study the reaction sequence shown in Scheme 2. We envisioned that Lewis or protic acid-catalyzed ionization of the acetal in a compound such as **6** would provide acyclic oxocarbenium ion **7**, which would undergo intramolecular attack by the ketone to provide the cyclic oxocarbenium ion **8**. Reduction of **8** by a reducing agent that is compatible with the reaction conditions should proceed via axial delivery of hydride,[5] and provide the all-*syn*-ethylidene acetal **9**.

In our initial investigations, we studied the ethoxyethyl-protected ketone **10**, which was prepared by aldol addition

Scheme 1. Asymmetric Diels−Alder Reaction via Cyclic Oxocarbenium Ion



(1) Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1995**, *60*, 6652.

(2) For selected examples of chiral oxocarbenium ions in synthesis, see: (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931. (c) Hashimoto, Y.; Saigo, K.; Machida, S.; Hasegawa, M. *Tetrahedron Lett.* **1990**, *31*, 5625. (d) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208.

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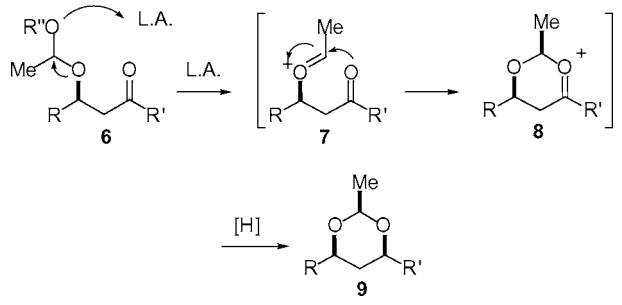
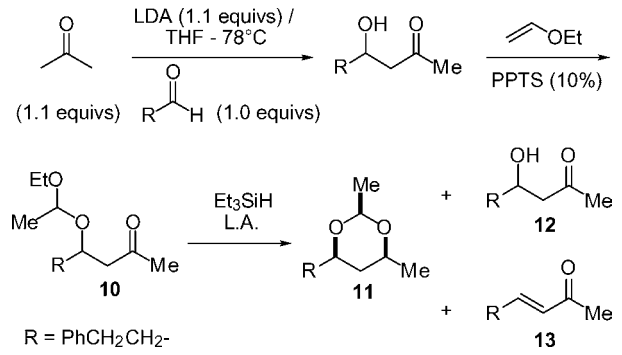
Scheme 2. Proposed Reduction via Cyclic Oxocarbenium Ion



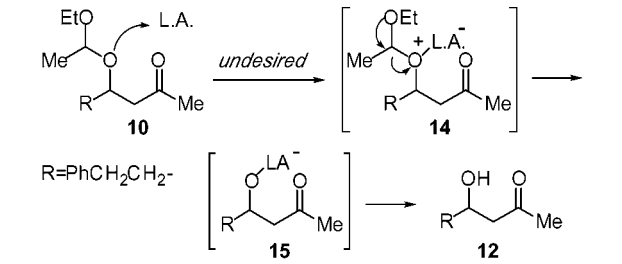
of acetone to hydrocinnamaldehyde[6] as shown in Scheme 3. We examined the reduction of this compound using Et_3-SiH and a variety of Lewis acids in numerous solvents and

Scheme 3. Initial Studies



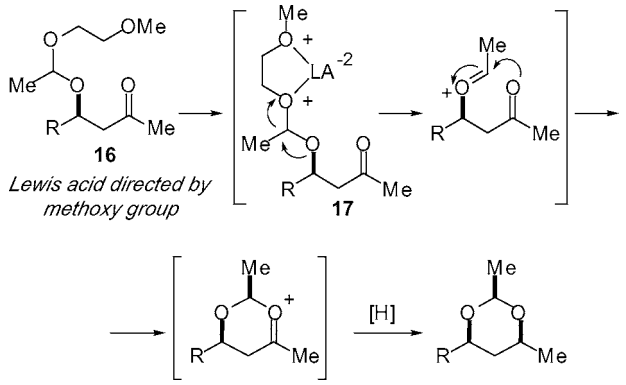
at different temperatures, and while we were able to observe the desired acetal **11**, the best yield we could consistently obtain was about 55%. The reaction typically produced two side products, **12**, the product of hydrolysis of the acetal, and **13**, the product of elimination of the β-alkoxy group. The generation of **12** likely stems from complexation of the Lewis acid to the internal oxygen of the acetal (**14**, Scheme 4), and we, therefore, sought to direct complexation to the

Scheme 4. Undesired Pathway



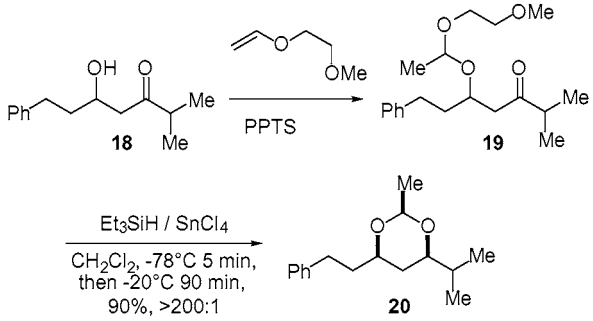
desired oxygen of the acetal. Our strategy was to introduce a coordinating heteroatom in the ethyl group of the acetal and to then use a Lewis acid capable of chelation such that binding to the desired oxygen of the acetal is preferred (**16**, **17**, Scheme 5).[7]

Scheme 5. Directed Ionization



This simple modification proved fruitful. Conversion of β-hydroxy ketone **18** to the 1-(2-methoxyethoxy)ethyl-protected ketone **19** was accomplished in good yield by treatment with 2-methoxyethyl vinyl ether[8] and PPTS in dichloromethane at room temperature. Treatment of a dichloromethane solution of **19** with triethylsilane (1.05 equiv) and tin(IV) chloride (1.0 equiv) at −78 °C for 5 min, followed by warming to −25 °C for 90 min, provided the desired all-*syn*-ethylidene acetal **20** in 90% yield and in >200:1 diastereoselectivity (Scheme 6).

Scheme 6. Reduction via Cyclic Oxocarbenium Ion

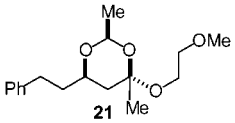
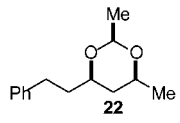
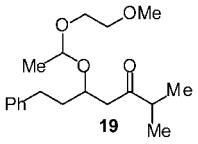
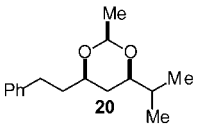
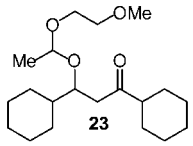
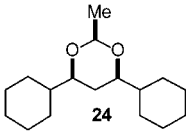
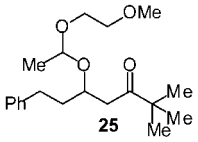
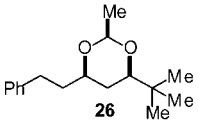
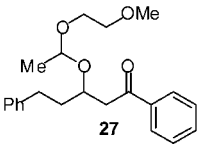
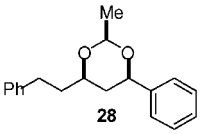
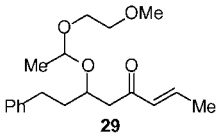
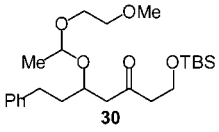
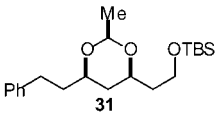
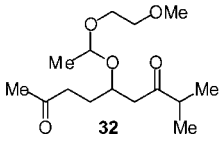
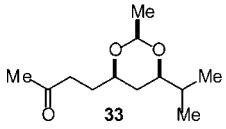


We have examined the scope and utility of this reaction as shown in Table 1. Steric and electronic modifications are well tolerated α to the ketone, affording the all-syn product with >200:1 selectivity and in excellent yield (entries 1−3 and 5). Reduction of *t*-butyl ketone-derived substrate **25**, although highly selective, suffered from diminished yields (69%, entry 4) due to significant amounts of elimination

(3) Reviews: (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (b) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375. (c) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. Recent polyol synthesis strategies: (d) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187. (e) Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341. (f) Smith, A. B.; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001. (g) Sinz, C. J.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3224. (h) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188.

(4) For related allylation reactions, see: Rychnovsky, S. D.; Skalitzky, D. J. *Synlett* **1995**, 555. Boons, G.-J.; Eveson, R.; Smith, S.; Stauch, T. *Synlett* **1996**, 536. Rychnovsky, S. D.; Frysman, O.; Khire, U. R. *Tetrahedron Lett.* **1999**, *40*, 41.

Table 1. Selective Reduction of Acyclic 1-(2-Methoxyethoxy)ethyl-Protected β-Hydroxy Ketones[a,b]

entry	ketone	product[c]	dr[d] (yield)[e]
1[f]			>200:1 (94%)
2			>200:1 (90%)
3			>200:1 (80%)
4[g]			>200:1 (69%)
5			>200:1 (81%)
6		— [h]	—
7			>200:1 (81%)
8[i]			>200:1 (76%)

[a] All starting ketones were prepared by a route analogous to that shown for the synthesis of compound **10** (Scheme 3). [b] For a representative procedure, see Supporting Information. [c] Stereochemistry determined by ^{1}H NOE. [d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [e] Isolated yield. [f] Ketone readily rearranges to the cyclic dioxane. [g] Elimination observed (~15%). [h] Complex mixture. [i] See Supporting Information for a modified reduction procedure.

(~15%) of the β-alkoxy group. Ketones possessing additional oxygen functionality, such as **30** and **32**, are potential polyol building blocks, and also furnished the desired products in good yield and with high selectivities (entries 7 and 8). Interestingly, unsymmetrical diketone **32** underwent reduction of the proximal ketone in preference to the distal one (entry 8). Unfortunately, attempted reduction of α,β-unsaturated ketone **29** provided a complex mixture of products under all conditions examined (entry 6).

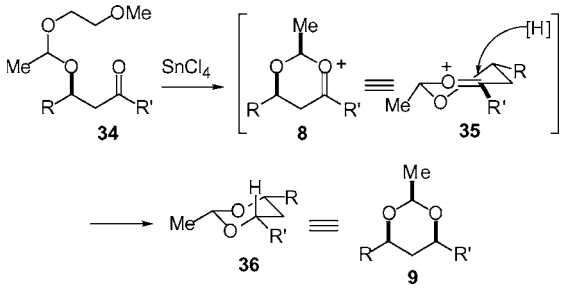


Figure 1. Proposed model accounting for the observed all-syn stereochemistry.

The stereochemical outcome of this reaction can be rationalized by a model in which the reduction proceeds via a half-chair conformation wherein the substituents occupy pseudoequatorial positions (**35**, Figure 1). Stereoelectronically preferred[5] axial delivery of hydride to the oxocarbenium ion carbon would provide the *syn*-1,3-diol **9**. This model is analogous to that for the chelation-controlled reduction of β-alkoxy ketones.[9,10]

In summary, we have described a direct and highly selective synthesis of protected *syn*-1,3-diols from the corresponding protected β-hydroxy ketones by way of a cyclic oxocarbenium ion. Additional studies of the use of oxocarbenium ions in synthesis are ongoing.

Acknowledgment. We wish to thank Dr. Mark Mitton-Fry for insightful discussions and early experimental work on this project and Dr. Richard Shoemaker for assistance in obtaining NOE spectra. This work was supported by the National Institutes of Health (GM48498) and Array Biopharma. NMR instrumentation used in this work was supported in part by the National Science Foundation CRIF program (CHE-0131003).

Supporting Information Available: Characterization data for all products, synthesis of 2-methoxyethyl vinyl ether, and representative procedures for the reduction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For a discussion, see: Deslongchamp, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; Chapter 6.

(6) For a general aldol procedure, see: Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.-b.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965.

(7) Itoh and Overman have reported the use of (2-methoxyethoxy)methyl (MEM) ether units as selective leaving groups in the Lewis acid-promoted ionization of mixed acetals. See: (a) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496. (b) Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695. (c) Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386.

(8) For the synthesis of this compound, see Supporting Information.

(9) (a) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233. (b) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. *Tetrahedron Lett.* **1987**, *28*, 155.

(10) Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, pp 1−24.