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1,3-Diastereocontrolled *O*-Displacement of Enolates

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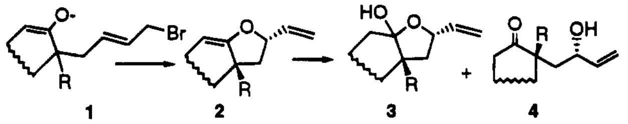
Acyclic diastereoselection of 1,3-relative centers is a topic of great interest[1] and has important implication in the synthesis of polyether and macrolide antibiotics.[2] Impressive progress has been made in special cases such as in the conversion of metal-chelated β-hydroxyl ketones to 1,3-diol derivatives.[3] However, high levels of asymmetric induction are less documented for substrates which do not involve metal-chelated complexes.[4] Geometrical constraints imposed by intramolecular cyclization reactions provide attractive means to control the newly-formed asymmetric centers in the process of ring assembly,[5] and *acyclic* stereocontrol would then result if the temporary ring can be subsequently elaborated.

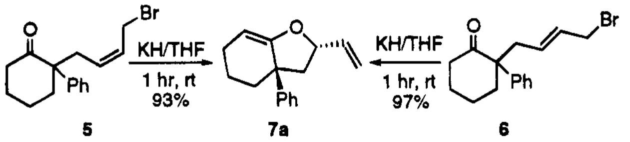
We describe here a new approach employing rigid five-membered ring systems for diastereoselective constitution of stereocenters via intramolecular S_N' reactions. It was presumed that enolates **1** would undergo *O*-displacement[6] with the formation of enol ethers **2** which, after simple hydrolysis, would afford hemiacetals **3** or γ-hydroxy ketones **4** with resulting stereocontrol of remote stereogenic centers (Scheme 1).

We were initially intrigued with the possibility of stereoselective formation of bicyclic enol ether **7a** via intramolecular S_N' displacements (Scheme 2). In fact, treatment of cyclohexanone derivative **5**[7] with potassium hydride gave a *single* isomer of vinyl ether product **7a** which was similarly obtained from trans olefin **6**.[7] Thus, the olefin geometry of the starting materials has little influence on the resulting stereochemistry of the final product. The preference for *O*- rather than *C*-alkylation, which derives from stereoelectronic considerations, has been well documented for the process of five-membered ring formations.[8]

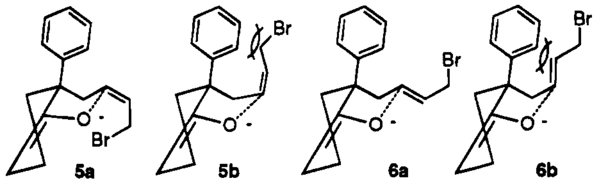
Scheme 1



Scheme 2



Scheme 3



Molecular modeling studies[9] were performed to elucidate the nature of these results. In assessing the contribution of various transition states, we have chosen early transition state structures in which the new bond formation is stereodetermining (Scheme 3). In structures **5b** and **6b**, there are strong 1,3-interactions between phenyl and vinyl groups regardless of the geometry of the double bond. Therefore, the preferred transition states are **5a** and **6a** in which the vinyl group is oriented away from the phenyl during the five-membered ring formation, thus leading to an efficient 1,3-diastereoselection.

An interesting feature of this enolate approach to bicyclic systems is that the ketone alkylation and cyclic vinyl ether formation can be carried out in a one-pot operation (Scheme 4). For example,[10] the treatment of 2-phenylcyclohexanone (**10a**) with potassium hydride[11] and subsequent reaction with 1,4-dibromo-*trans*-2-butene[12] gave the anticipated vinyl ether **7a**. Reaction of this unsymmetric ketone **10a** with the first equivalent of potassium hydride produces predominantly thermody-

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[1] For reviews, see: (a) Bartlett, P. A. *Tetrahedron* **1980,** *36,* 3. (b) Heathcock, C. H. *Aldrichemica Acta* **1990,** *23,* 99. (c) Roush, W. R. In *Comprehensive Organic Synthesis,* Volume II; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxord, 1991; Chapter 1.1. (d) Fleming, I. In *Comprehensive Organic Synthesis,* Volume II; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Chapter 2.2. (e) Gennari, C. In *Comprehensive Organic Synthesis,* Volume II; Trost, B. M., Flemming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Chapter 2.4.

[2] (a) Nicolaou, K. C. *Tetrahedron* **1977**, 683. (b) Back, T. G. *Tetrahedron* **1977**, 3041. (c) Wierenga, M. In *The total Synthesis of Natural Products,* Volume 4; Apsimon, J., Ed.; John Wiley & Sons, Inc.: New York, 1981; p 263. (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985,** *41,* 3569. (e) Boeckman, R. H.; Goldstein, M. In *The total Synthesis of Natural Products,* Volume 7; Apsimon, J., Ed.; John Wiley & Sons, Inc.: New York, 1988, p 1.

[3] (a) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992,** *57,* 2235. (b) Mohr, P. *Tetrahedron Lett.* **1991,** *32,* 2219. (c) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990,** *55,* 5190. (d) Oishi, T.; Nakata, T. *Synlett* **1990**, 635 and references therein.

[4] (a) Molander, G. A.; Bobbitt, K. L.; Murray, C. K. *J. Am. Chem. Soc.* **1992,** *114,* 2759. (b) Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988,** *29,* 4245. (c) Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982,** *23,* 4577.

[5] For recent examples, see: (a) Hanassian, S.; Fabio, R. D.; Marcoux, J.-F.; Prud'homme, M. *J. Org. Chem.* **1990,** *55,* 3436. (b) Koreeda, M.; Hamann, L. G. *J. Am. Chem. Soc.* **1990,** *112,* 8175. (c) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991,** *113,* 8036. (d) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P.; Ito, Y. *J. Am. Chem. Soc.* **1993,** *115,* 6487.

[6] For palladium-catalyzed *O*-displacment of acetoacetate derivatives, see: Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981,** *103,* 7550 and 7559.

[7] By using 1 equiv of sodium hydride at 0 °C, monoalkylation of 2-phenylcyclohexanone with *cis*- or *trans*-1,4-dibromide-2-butene gave the corresponding intermediates **5** and **6** in 45% and 65% yields, respectively.

[8] Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977,** 233.

[9] Still, W. C. *MacroModel Version 4.5,* **1994.**

[10] A general procedure for the preparation of vinyl enol ethers 7 and hemiacetals 8. A stirred suspension of KH (2−3 mmol) in dry THF (85 mL) was treated at room temperature under argon with 2-substituted cyclohexanone (1 mmol) in dry THF (10 mL). The reaction mixture was stirred for 30 min, followed by one-portion addition of 1,4-dibromo-2-butene (1.5 mmol) in dry THF (5 mL). The reaction was stirred for 2 to 3 days and quenched with saturated NH_4Cl (50 mL). Aqueous workup (Et_2O) and silica gel chromatography (flash silica, 2−5% EtOAc/hexanes) gave stable enol ether (**7a,e,f**). Or the residue was dissolved in THF/10% HCl (2:1) and stirred for 8 h. Normal workup and silica gel chromatography (10−15% EtOAc/hexanes) provided hemiacetals 8.

[11] (a) Brown, C. A. *J. Org. Chem.* **1974,** *39,* 1324. (b) Pinnick, H. W. *Org. Prep. Proc. Int.* **1983,** *15,* 199.

[12] References involving the use of 1,4-dibromo-2-butene for carbon−carbon bond formations: (a) Näf, F.; Decorzant, R. *Chem. Abstr.* **1979,** *90,* 186489. (b) Näf, F.; Decorzant, R. *Helv. Chim. Acta* **1978,** *61,* 2524. (c) Cekovic, Z.; Matovic, R. *J. Chem. Soc., Chem. Commun.* **1991,** 294. (d) Fuchs, P. L.; Lamothe, M. *J. Am. Chem. Soc.* **1993,** *115,* 4483.

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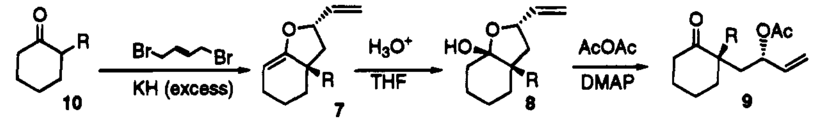
Table 1



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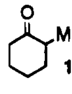
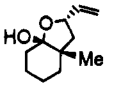
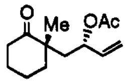
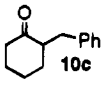
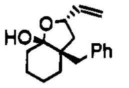
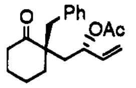
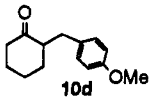
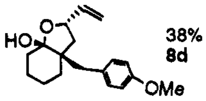
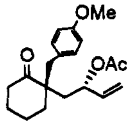
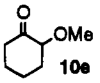
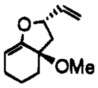
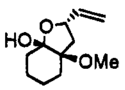
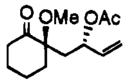
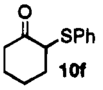
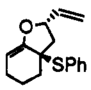
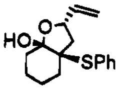
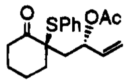
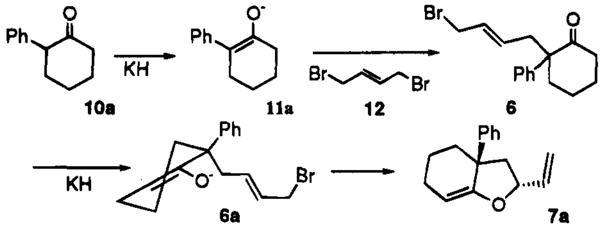
1	 10b				62% 8b		97% 9b
2	 10c				77% 8c		92% 9c
3	 10d				38% 8d		80% 9d
4	 10e		36% 7e		91% 8e		96% 9e
5	 10f		96% 7f		99% 8f		99% 9f

a. Isolated yields.

Scheme 4



namic enolate **11a**, monoalkylation of which with dibromide **12** then occurs to give ketone **6**. The second equivalent of base converts **6** to intermediate **6a**, which then reacts intramolecularly to afford bicyclic ether **7a**.

The results in Table 1 show that this new method is versatile and efficient for the preparation of a variety of cyclic vinyl ethers **7**, hemiacetals **8**, and γ-hydroxy ketone derivatives **9**. Vinyl ethers **7** can be purified by flash chromatography but can be directly subjected to aqueous hydrolysis to give hemiacetals **8** which can be either isolated or converted without isolation to γ-hydroxy ketones **9** by a reported procedure.[13] Enolization of 2-*alkyl-substituted* cyclohexanones[14] produces a mixture of thermodynamic enolates (entries 1–3),[11] but the more substituted enolate is presumably more reactive toward bromide **12**. Further reaction of the resulting intermediates gives enol ethers which are readily hydrolyzed to **8b–f**, respectively, in the process of silica gel chromatographic purification. The decreased yield of 2-dialkylated compound from 2-methoxycyclohexanone enolate is attributed to nonregioselective alkylation (entry 4), but **7e** has been cleanly converted to 2,4-dialkoxy ketone derivatives **8e** and **9e**. The successful preparation of **8f** and **9f** in high yields (entry 5) further broadens the utility of this method to 2-thio-substituted ketones.

The stereochemistry of compound **8d** (Table 1) was determined by single-crystal X-ray diffractometry,[15] which clearly shows that the vinyl and 4-methoxybenzyl groups are on opposite faces of the five-membered furan ring. The stereochemistry of the products **8a–c** and **8e,f** was assigned by comparative analysis of ^{1}H and ^{13}C NMR spectra, and thus the observed 1,3-diastereocontrol is consistent with our original proposal for the cyclization.

The method reported here has proven to be successful for the preparation of 2-alkyl-2-(2-acetoxy-3-butenyl)-cyclohexanones in terms of its simplicity and its attainment of uniformly high diastereoselectivity. In fact, this transformation allows for the stereoselective construction of 1,3-relative acyclic centers and provides functionalities for further elaboration to more complicated molecules. We are actively pursuing the extension of this method to other cyclic or acyclic ketone systems, as well as to the synthesis of macrolides.[16]

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Supplementary Material Available: Experimental procedures and characterization data (60 pages).

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[13] Bartlett, P. A.; Holm, K. H.; Morimoto, A. *J. Org. Chem.* **1985**, *50*, 5179.

[14] Compounds **10a,b,e** were purchased from Aldrich. **10c,d** were prepared through enamine alkylation. For the preparation of **10f**, see: Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4487.

[15] Gi, H.; Wang, T.; Zhao, K. *Acta Crystallogr. C*, in press. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

[16] Wang, T.; Chen, J; Landry, D. W.; Zhao, K. *Synlett.*, in press.