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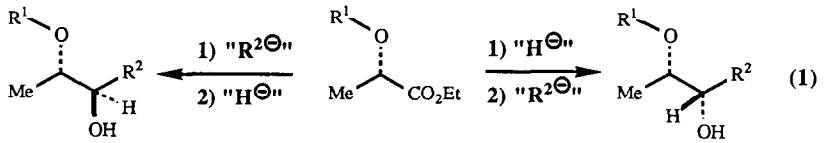
STEREOCONTROLLED ONE-POT CONVERSIONS OF α-ALKOXY ESTERS TO *SYN*- AND *ANTI*-1,2-DIOL DERIVATIVES

Steven D. Burke,*[1] David N. Deaton, Robert J. Olsen,[2] David M. Armistead, and Bruce E. Blough
Department of Chemistry, University of South Carolina
Columbia, South Carolina 29208 USA

Summary: Complementary one-pot methods for the sequential addition of carbon and hydride nucleophiles to α-alkoxy esters leading to syn or anti mono-protected vicinal glycol derivatives are described.

In the course of synthesizing natural antibiotics of the ionophore and macrolide classes, we have encountered the need for simple, complementary methods to selectively produce *syn*- or *anti*-1,2-diol derivatives. Conversion of the (*S*)-ethyl lactate ether **1** (eq. 1) to the anti glycol diastereomer **2** would require the sequential addition of carbon- and hydride nucleophiles to the ester, the latter via α-chelation control.[3] Reversal of these bond-forming steps, with "$R^{2\ominus}$" adding second via α-chelation control, would lead to the syn glycol derivative **3**.



2 (anti) **1** **3 (syn)** (1)

TABLE I. *STEREOSELECTIVE CONVERSION OF ESTER* 1 *TO* 2 *OR* 3

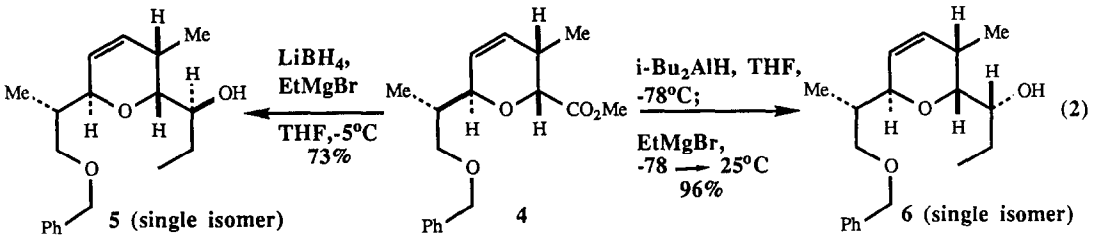
Entry	R^1	R^2	Conditions[(1)]	% Yield	Ratio 2/3 (anti/syn)[6]
1	$PhCH_2$	Me	a	87	6:1
2	$PhCH_2$	Et	a	74	6:1
3	$PhCH_2$	*i*-Pr	a	71	5.1:1
4	$PhCH_2$	Ph	b	59	11:1
5	$PhCH_2$	2-propenyl	b	51	20:1
6	$PhCH_2OCH_2$	*i*-Pr	a	93	6.3:1
7	$PhCH_2OCH_2$	2-propenyl	b	63	30:1
8	$PhCH_2$	Me	c	72	1:15
9	$PhCH_2$	Et	c	79	1:10
10	$PhCH_2$	*i*-Pr	c	82	1:13
11	$PhCH_2$	Ph	c	87	1:7
12	$PhCH_2$	2-propenyl	c	79	1:6

(1) a: α-alkoxy ester 1 (1 mmol) in 7 mL Et_2O added to $LiBH_4$ (1 mmol) and R^2MgX (2 mmol) in 50 mL Et_2O at -20°C.
b: R^2MgX (2 mmol) added to α-alkoxy ester 1 (1 mmol) and $LiBH_4$ (1 mmol) in 60 mL THF at 0°C.
c: *i*-Bu_2AlH (1.2 mmol in hexanes) added to α-alkoxy ester 1 (1.0 mmol) in 60 mL Et_2O at -78°C; R^2MgX (3.0 mmol) added at -78°C when TLC showed complete consumption of 1.

The ample precedent for stereoselective, chelation-controlled nucleophilic additions to α-alkoxy ketones and aldehydes,[3] together with isolated reports by Comins[4] and Kelly[5] prompted our systematic study. The 1984 report by Comins showed that simple esters could be converted to secondary alcohols in one step with a mixture of a Grignard reagent (R^2MgX) and $LiBH_4$ in tetrahydrofuran. This demon-

strated that, although $LiBH_4$ reduces esters very slowly at low temperatures and thus *does not* compete effectively with the Grignard reagent for the ester carbonyl, it *does* compete effectively in the addition to the intermediate ketone. Primary and tertiary alcohols were very minor by-products in this one-step ester → secondary alcohol conversion. Kelly reported[5] a synthesis of rhodinose from (*S*)-ethyl lactate via $(i\text{-Bu})_2AlH$ reduction of **1** ($R^1 = MeOCH_2CH_2OCH_2-$), isolation of the aldehyde, and chelation-controlled addition of 2-(2-bromomagnesioethyl)-1,3-dioxane in a second step. The general tendency of α-alkoxy aldehydes to form hydrates and to be configurationally unstable relative to the corresponding α-alkoxy esters led us to attempt the reduction/Grignard addition tandem as a one-pot procedure.

The results of these modifications and extensions of the Comins and Kelly procedures are summarized in Table I.[6] A more elaborate example of these methods is illustrated in eq. 2, wherein the α-alkoxy ester **4** is converted to the anti derivative **5** or the syn diastereomer **6** in high selectivity (>20:1).



(2)

It is thus apparent that one can convert α-alkoxy esters in one pot via complementary procedures to the corresponding anti or syn 1,2-diol derivatives in good-to-excellent yields and diastereoselectivities. Since the minor products are usually readily separable by flash chromatography[7] from the desired major isomer, these methods provide preparatively useful reactions for carbon chain extension with 1,2-chirality transfer.

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References and Notes

1. National Science Foundation Presidential Young Investigator, 1984-89; Research Fellow of the Alfred P. Sloan Foundation, 1984-88. Address correspondence to this author at Department of Chemistry, University of Wisconsin-Madison, Madison, WI 53706 USA.
2. On leave from Wabash College, Crawfordsville, IN 47933.
3. (a) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035. (b) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769, and references cited in each.
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6. The ratios were determined by integration of distinctive resonances in the 300 MHz ^1H NMR spectra of the mixtures containing **2** and **3**. The separated diastereomers (flash chromatography[7] on silica gel) were fully characterized by IR, ^1H NMR, ^{13}C NMR, and mass spectrometric and combustion analyses. The syn and anti stereochemical assignments were confirmed by conversion of the separated diastereomers to cyclic derivatives (*trans*- and *cis*-5,6-disubstituted 1,4-dioxan-2-ones) with characteristic vicinal H(5)-H(6) ^1H NMR coupling constants. See: Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787.
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