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Enantioselective reduction of esters: synthesis of optically active α-acetoxy ethers

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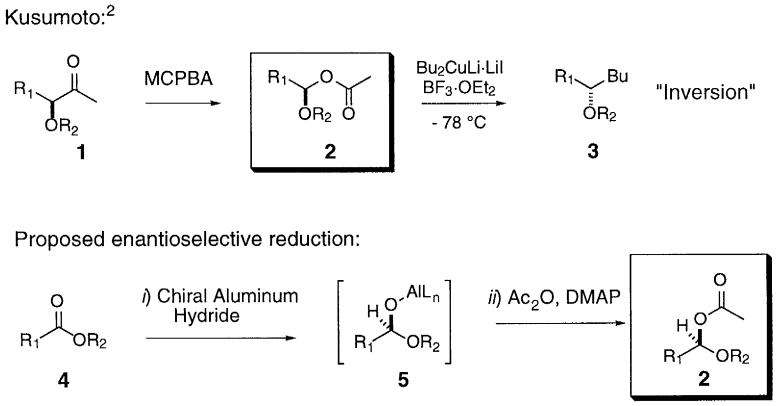
Abstract

An enantioselective reduction and acetylation of esters to α-acetoxy ethers is described. Reduction with a $NaAlH_4$–ephedrine reagent followed by in situ acetylation gives **2** with good enantiomeric excess. This reaction is limited in scope, but it demonstrates that enantioselective reductions of esters are possible.

The stereoselective alkylation of acetals to form new C–C bonds is a widely used reaction that usually proceeds by an S_N1 pathway.[1] Recently, Kusumoto has reported an S_N2-like alkylation of enantiopure acetals (**2**) with cuprates that proceeds with inversion of configuration.[2] Kusumoto's chiral acetals were synthesized by Baeyer–Villager oxidations of the enantiopure α-alkoxy ketones **1**. An alternative approach to Kusumoto's optically pure α-acetoxy ethers can be envisioned using an enantioselective reductive-acetylation of simple esters. We have recently reported a DIBAL-H reduction and in situ acetylation of esters to racemic α-acetoxy ethers.[3] The first example of an *enantioselective* reductive-acetylation of an ester is reported in Scheme 1.



Scheme 1.

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For an enantioselective reduction and acetylation to be effective, the aluminum hemiacetal must be configurationally stable. We have reported[3] that the reduction and acetylation of the macrocyclic lactone oxacyclohexadecan-2-one gave 2-acetoxyoxacyclohexadecane in 71% yield. If the intermediate aluminum hemiacetal had been susceptible to loss of configuration by reversible opening and closing, none of the macrocycle would have been formed: polymerization would predominate over reclosing a 16-membered hemiacetal ring. We concluded that the intermediate aluminum hemiacetals are acetylated without opening to the aldehyde and without significant loss of configuration.[4]

The most conservative modification of our reductive-acetylation procedure would be to use a chiral analogue of DIBAL-H. Chiral analogs of DIBAL-H are known, but are not easily accessible.[5] Instead we focused on modified sodium aluminum hydrides ($NaAlH_{4-n}X_n$), which have been used for the selective reduction of esters to aldehydes.[6] Ethyl *O*-benzylglycolate (**7**) is a simple, prochiral ester that was selected to screen for enantioselective reductive-acetylation by chiral reagents. Several bishydrido aluminum species were prepared from $NaAlH_4$ and a chiral diol or an amino alcohol. Reduction of **7** and in situ acetylation gave the α-acetoxy ester **8** (Table 1).[7] The optical purity of **8** was assayed by HPLC on a Chiracel OJ column.

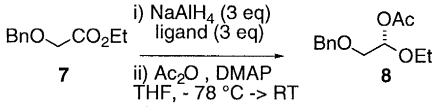
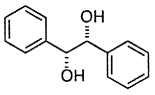
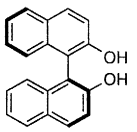
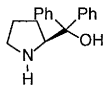
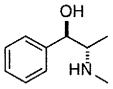
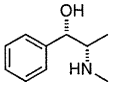


Table 1
Enantioselective reduction and in situ acetylation of ester **7**

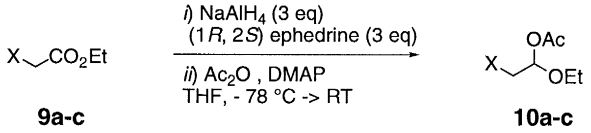
entry	ligand	yield %	e.e	Configuration
1		30[a]	30	*S*
2		75[a]	35	*S*
3		30	20	*R*
4		55	83	*S*
5		65	5	*S*

[a]Yields based on NMR analysis of a mixture of product and recovered starting material.

Reagents analogous to TADDOL[8] and BINAL-H[9] (entries 1 and 2) did give optically active **8**, but the reaction did not go to completion, and the optical purity of the product was modest. The best results were found using (1*R*,2*S*)-(−)-ephedrine (entry 4), where the product was isolated in 55% yield and 83% ee.[10] Pseudoephedrine gave almost racemic product under the same reaction conditions. The reduction of

ester **7** with ephedrine shows that good enantioselectivities are possible using ligand-modified $NaAlH_4$ reagents.

The ephedrine system was successful in the enantioselective reduction of closely related substrates, but it is not general. Table 2 shows the results with three esters analogous to the ester **7**. The reaction works well with the PMB ether **9a**, but gave unacceptably low yields with the other two substrates. The reduction of **9c** was very slow, and the majority of the starting material was recovered unchanged. Product **10c** was isolated in 17% ee, demonstrating that an adjacent heteroatom is not necessary for modest enantioselectivity. While the hydride/ephedrine system reduces aliphatic esters slowly, it does not reduce aromatic or unsaturated esters at −78°C.



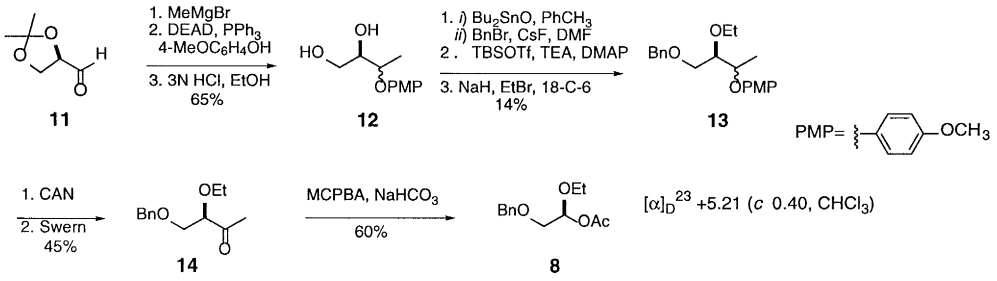
9a-c **10a-c**

Table 2
Reduction and in situ acetylation with a $NaAlH_4$-ephedrine reagent

compound	X	yield %	e.e.[a]
9a	4-$MeOC_6H_4CH_2O$	59	83
9b	$PhCH_2N(Me)$	25	–[b]
9c	$PhCH_2CH_2$	6	17

[a]Optical purity determined by HPLC on a CHIRACEL OJ column. Configurations of the products were not determined. [b]Compound **10b** was not resolved on any of the chiral columns investigated and the optical purity was not determined.

The configuration of α-acetoxy ether **8** was determined by correlation with D-glyceraldehyde acetonide (**11**),[11] using the method of Kusumoto.[2] Addition of MeMgBr followed by Mitsunobu etherification and hydrolysis of the acetonide afforded the diol **12** (Scheme 2). Selective alkylation of the 1° alcohol with Bu_2SnO and BnBr, followed by removal of the other isomer by silylation and separation gave the intermediate secondary alcohol in modest yield.[12] Alkylation of the alcohol with ethyl bromide gave **13**. Deprotection of the 4-methoxyphenyl ether with cerric ammonium nitrate, followed by Swern oxidation gave the ketone **14**. Baeyer–Villager oxidation of the ketone gave the α-acetoxy ether **8**, which was shown to have the same absolute configuration as compound **8** from Table 1 by HPLC and by optical rotation.[13]



11 **12** **13** **14** **8**

Scheme 2.

The first enantioselective reductive-acetylation of an ester to an α-acetoxy ether with good enantiomeric excess has been demonstrated.

References

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7. A 50 mL flask was charged with THF (2 mL) and $NaAlH_4$ (0.772 mL, 2.0 M in ether). To this mixture was added a solution of (1*R*,2*S*)-(−)-ephedrine (0.255 g, 1.54 mmol) in THF (2 mL) over 4 min. The solution was stirred for 15 min then cooled to −78°C. The ester **7** (100 mg, 0.514 mmol) was added to this solution neat and the mixture was stirred for 2 h at −78°C. Acetic anhydride (0.291 mL, 3.08 mmol) and DMAP (0.252 g, 2.06 mmol) were added to the reaction and the flask was warmed up to room temperature over 16 h. The yellow solution was diluted with ether and 1N HCl. The aqueous layer was extracted with ether (twice). The combined organic layers were washed successively with sat. K_2CO_3, brine, dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (5% ethyl acetate/hexanes) to give 64 mg of **8** as a clear oil (55%): $[\alpha]_D^{23}$ +4.0 (*c* 0.40, $CHCl_3$); IR (neat) 3031, 2979, 1743, 1239, 1115 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 5H), 6.01 (t, *J*=5.1 Hz, 1H), 4.64 (d, *J*=12.1 Hz, 1H), 4.59 (d, *J*=12.1 Hz, 1H), 3.80 (dq *J*=9.7, 7.1 Hz, 1H), 3.65 (dq *J*=9.7, 7.1 Hz, 1H), 3.61 (dd *J*=10.7, 5.1 Hz, 1H), 3.56 (dd *J*=10.7, 5.1 Hz, 1H), 2.11 (s, 3H), 1.25 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 137.8, 128.4, 127.7, 127.7, 95.7, 73.4, 70.3, 65.5, 21.2, 15.0; HRMS (CI-Isobutane) calcd for $C_{13}H_{17}O_4$ $(M-H)^+$: 237.1127, found: 237.1134. Anal. calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.77; H, 7.41. The product was determined to be 83% ee by analysis on a CHIRACEL OJ column (hexane:2-propanol=97:3 at a flow rate of 0.8 ml/min). The retention times were 12.5 min for the minor *R*-enantiomer and 13.5 min for the major *S*-enantiomer.
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10. An old bottle of ephedrine gave cloudy solutions with $NaAlH_4$ and lower yields and % ee, perhaps due to adventitious water.
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12. Ohno, M.; Nagashima, N. *Chem. Pharm. Bull.* **1991**, *39*, 1972–1982.
13. Both the sign and the magnitude of the optical rotations for the two samples of compound **8**, prepared in Table 1 and in Scheme 2, are consistent with them having the same absolute configuration. Both samples also showed the same retention time on a Chiracel OJ column.