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STEREOSELECTIVE REDUCTION OF α-ALKOXY ACETYLENIC KETONES WITH ZINC BOROHYDRIDE AND K-SELECTRIDE.

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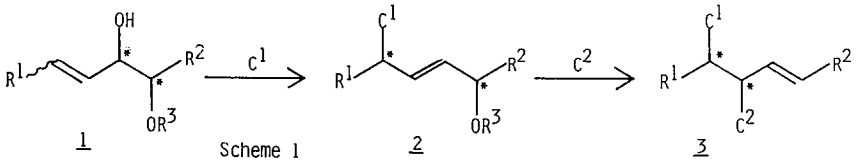
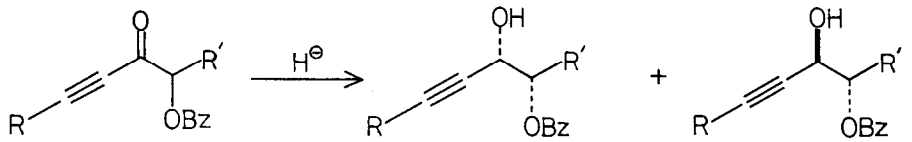
Summary: Reduction of α-benzyloxy acetylenic ketones with zinc borohydride afforded the erythro-acetylenic vicinal diols in 95% stereoselectivity, while reduction with K-selectride gave the isomeric threo-diols in 90% stereoselectivity.

Repetition of 1,3-chiral transfer reaction by palladium catalyzed allylation[1], coupling reaction of organocuprate[2], and [3,3]- or [2,3]-sigmatropic rearrangements of allylic compounds[3], as shown in scheme 1, offer a powerful method for construction of the vicinal carbon asymmetric centers.



1 Scheme 1 2 3

In these overall transformations, choices of E-(or Z-) configuration of the double bond and the threo- (or erythro-) stereochemistry of the vicinal diol **1** are crucial to induce the desired stereochemistry on the newly formed C-C bond in **3**. The selective protection of diols is also important for the introduction of different nucleophiles C^1 and C^2. Thus the question is how to prepare selectively four possible isomers **1** (E-,Z-double bonds, erythro-, threo-diols). Obviously it is efficient if all isomers of allylic diol **1** can be derived from a single intermediate. The α-alkoxy ketones **4** are suitable intermediates[4], if the stereoselective reduction of **4** is possible. The triple bond in the product **5** (or **6**) can be reduced to either E- or Z-double bond by

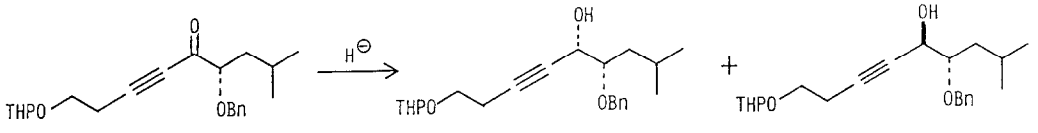


4 Scheme 2 5 6

the reduction with $LiAlH_4$ or catalytic hydrogenation. We have investigated the stereoselectivity in the reduction of α-alkoxy acetylene ketones **4** with various hydride reagents.

Recently, Nakata and Oishi[5] examined the stereoselectivity in the reduction of ketones having oxygen substituents and found the erythro-selection of α-hydroxy ketone with $Zn(BH_4)_2$ and the threo-selection of its α-silyoxy ketone with $NaAlH_2(OCH_2CH_2OMe)_2$ (Red-Al). Hiyama[6] also reported the Bu_4NF catalyzed threo-selection and the CF_3CO_2H catalyzed erythro-selection in the reduction of the α-benzyloxy ketones with hydrosilane. So far stereoselectivities in the reduction of α-alkoxy ketones with $Zn(BH_4)_2$ and K-selectride have not been reported.

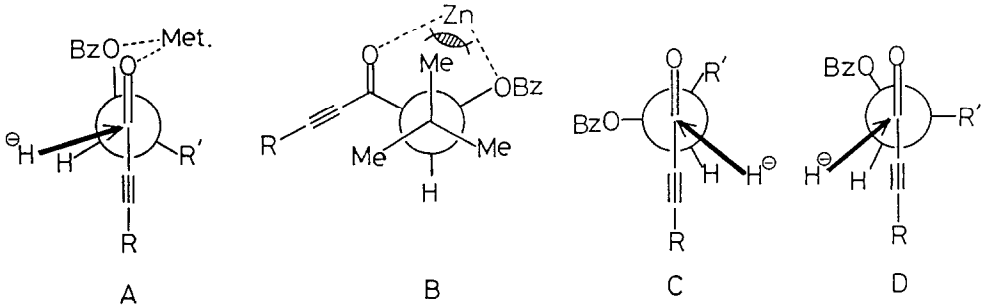
At first, we have examined the stereoselectivity in reductions of the α-benzyloxy ketone **4a** with various hydride reagents (Scheme 3; Table 1). The $Zn(BH_4)_2$ reduction proceeded with high stereoselectivity (95%) through the cyclic model **A** to give the erythro product **6a**. The Red-Al reduction of α-benzyloxy ketone **4a** also gave the erythro-**6a** as the major product. These results are very different from the threo-selective reduction of α-silyoxy ketone with Red-Al through the open model **C** reported by Nakata and Oishi. The



4a Scheme 3 threo-5a erythro-6a

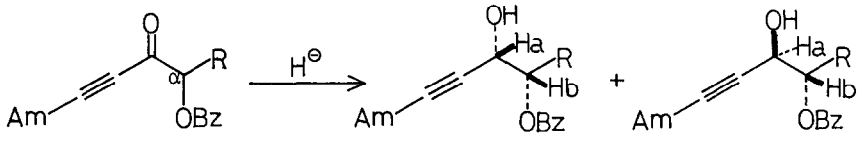
Table 1

Reagent	Solvent	Temp. (°C)	Ratio (5a : 6a)
$Zn(BH_4)_2$	Et_2O	-30	5 : 95
Red-Al	Toluene	-78	16 : 84
$LiAlH_4$	THF	-30	32 : 68
$^iBu_2AlH$	THF	-78	48 : 52
L-selectride	THF	-78	73 : 27
K-selectride	THF	-78	85 : 15
K-selectride	THF	-95	90 : 10



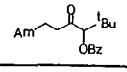
erythro-selection with Red-Al can be explained by the cyclic model **A**. The relatively poor selectivity with $LiAlH_4$ and the nonselectivity with Dibal-H were observed. On the other hand, the reduction with K-(or L-) selectride gave the threo product **5a** with high stereoselectivity(90%). The threo-selection found with K-selectride, having low coordinating ability, can be explained by the open model **C**.

To establish the generality of $Zn(BH_4)_2$ and K-selectride reduction, we have examined reduction of a number of α-benzyloxy ketones (scheme 4; Table 2) and found the erythro-selection with $Zn(BH_4)_2$ and the threo-selection with K-selectride. Interestingly, β-substitution in **4** has significant effect on stereoselectivity in $Zn(BH_4)_2$ reduction. If β-carbon was sufficiently hindered (entry **5**), then chelation-directed stereoselectivity was completely lost (see the cyclic model **B**). While the less hindered substitution at β-carbon (entry **1**) can have the weaker control on hydride addition course in the cyclic model **A**. Therefore a moderately bulky nature at β-carbon is necessary for efficient erythro-selection with $Zn(BH_4)_2$. In K-selectride reduction, however, the secondary carbon at β-position (entries **8,9**) led to two types of open models **C** and **D** and thus lowered the stereoselectivity. Moreover, tertiary butyl group (entry **10**) blocked the 1,2-reduction and only the 1,4-reduction was observed.



4(b-f) Scheme 4 5(b-f) 6(b-f)

Table 2

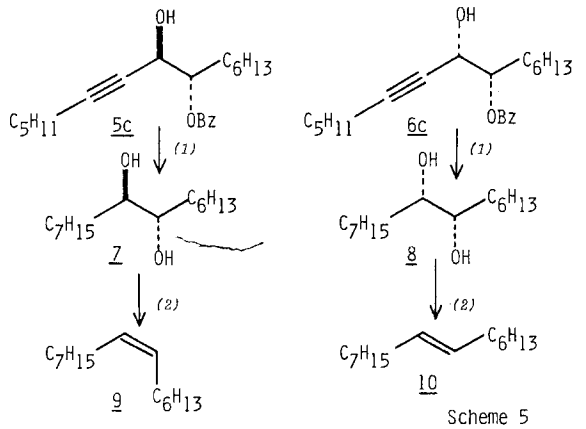
Ketone	R	Entry	$Zn(BH_4)_2$ / Ether Yield(%)	Ratio(5:6)	Entry	K-Selectride / THF Yield(%)	Ratio(5:6)
4b	Me	1	94	17 : 87	6	99	90 : 10
4c	$n\text{-}C_6H_{13}$	2	95	6 : 94	7	99	89 : 11
4d	^iPr	3	90	8 : 92	8	99	75 : 25
4e	PhMeCH-	4	98	10 : 90	9	98	69 : 31
4f	^tBu	5	64	50 : 50	10	78	

The stereostructures of erythro-**5** and threo-**6** were determined by the ^{1}H-NMR coupling constants (Table 3) based on the general rule that J_{ab} of the threo-form is larger than J_{ab} of the erythro-form when substitution on the vicinal carbon atoms are capable of forming a hydrogen bond. Moreover, the structures of **5c** and **6c**, obtained by $Zn(BH_4)_2$ and K-selectride reductions respectively, were confirmed by the selective conversions to the Z- and E-olefins **9** and **10** (Scheme 5). The chemical shift in ^{13}C-NMR of the Z-allylic carbon in **9** showed lower shift than that of the E-allylic carbon.

Table 3

Compound	J_{ab} (Hz) threo-5	erythro-6
a	5.29*	3.33*
b	6.84	3.53
c	5.98	3.75
d	4.86	4.41
e	—	—
f	3.33	1.98

* These coupling constants were observed after the THP was removed.



Scheme 5

Conditions: (1) H_2 (1 atm), PtO_2, AcOEt, r.t.
(2) i) $(MeO)_2CHNMe_2$, Toluene, 100°C; ii) Ac_2O, 160°C

References and Notes

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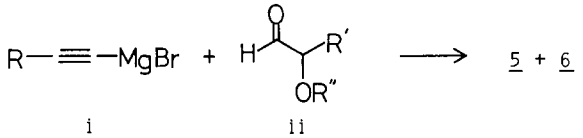
4) Based on Still's results, (W.C.Still, J.A.Schneider, Tetrehedron Lett., **21**, 1035 (1980), that threo-selection was observed in the nucleophilic addition of Grignard reagent to α-alkoxy aldehyde, we first examined the reaction of Grignard reagent **i** with the α-alkoxy aldehyde **ii** . However all attempts, changing the reaction temperature (-30°C -110°C), the protecting groups and additive metals, gave roughly 1:1 mixture of products.



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