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ENANTIO- AND DIASTEREOMERICALLY PURE *THREO*-HOMOALLYLIC ALCOHOLS *VIA* HIGHLY STEREOSELECTIVE REDUCTION OF α-METHYL-β,γ-UNSATURATED KETONES

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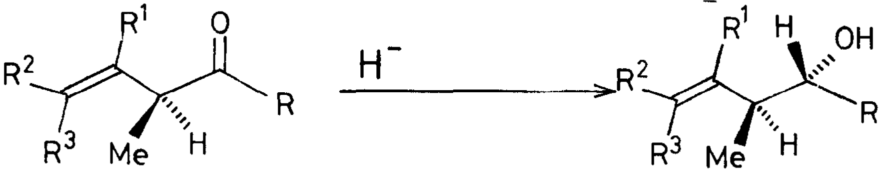
Summary: Reduction of α-methyl-β,γ-unsaturated ketones with L-Selectride proceeded with high threo-selectivity to afford threo-β-methyl homoallylic alcohols of high enantio- and diastereomerical purities.

Acyclic stereocontrol has received a broad and intense interest in the past decade,[1)] and especially, a wide variety of examples have been documented concerning the 1,2-asymmetric induction of the carbonyl compounds, so-called the Cram vs *anti*-Cram problems.[2)] However, there have been reported no systematic investigations on the stereochemical course of the nucleophilic attack to α-substituted-β,γ-unsaturated carbonyl compounds, presumably due to the lack of the general access to these compounds. In our preceding communication,[3)] we have reported a versatile approach to the optically pure α-methyl-β,γ-unsaturated ketones 1 by virtue of the Et_3Al-mediated pinacol-type rearrangement. Prompted by the stereochemical interests stated above and with a hope to extend the synthetic potential of the process, we have investigated the stereochemical course of the reduction of ketones 1. It was found that the alkenyl groups exert high steric bias to permit stereoselective reductions. In this communication, we wish to report a versatile method for the synthesis of the optically pure *threo* β-methyl homoallylic alcohols of general formula 2 based on the highly stereoselective reduction of ketones 1.



1 threo-2

In order to elucidate the general aspects of the reduction of the α-methyl-β,γ-unsaturated ketones, we examined the stereoselectivities of the reduction of the ketones possessing variously substituted alkenyl groups, namely 1a-1h, which are now readily available (in optically pure form) by the Et_3Al-mediated pinacol-type rearrangement of β-mesyloxy alcohols.[3)]

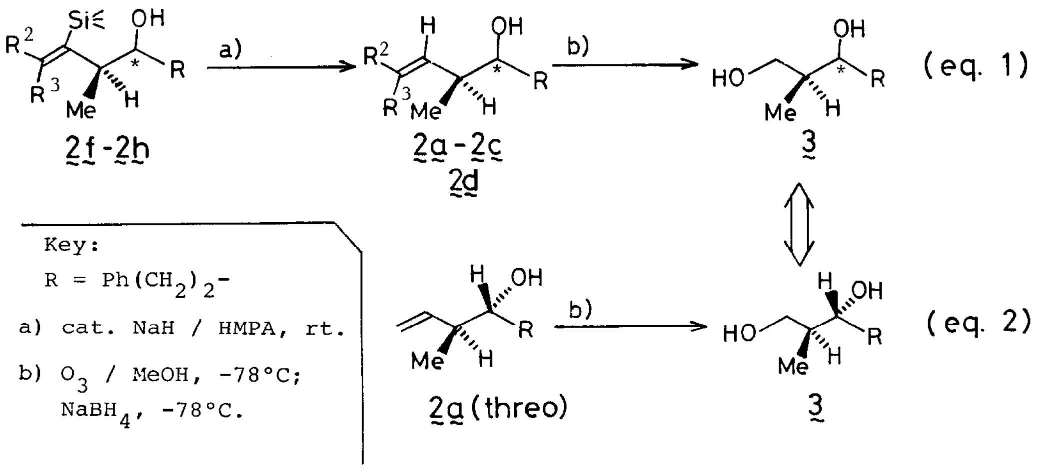
The reductions were performed in THF at -78°C with diisobutylaluminum hydride (DIBAL) or lithium tri-s-butylborohydride (L-Selectride) followed by the usual work-up to afford the homoallylic alcohols 2a-2h in high yields. The epimeric alcohols were easily separated on silica-gel TLC except for the case of the alcohols 2a.[7] The relative stereochemistry of these alcohols was determined by the extensive correlation study as shown in Scheme I: The trimethylsilyl groups in 2f-2h were easily removed under Sato's conditions[4] (cat. NaH / HMPA, rt, 10 min) to correlate them to 2a-2c. The alcohols were further transformed to the diol-3 whose HPLC analyses[8] revealed the relative stereochemistry (eq. 1).[5] The authentic sample of the *threo*-2a was obtained by the crotylation of 3-phenylpropanal (Hiyama's procedure; $Ph(CH_2)_2CHO$, $CH_3CH{=}CHCH_2Br$, $CrCl_3$-$LiAlH_4$/THF).[6] The stereostructure of 2e was tentatively assigned by the comparison of the ^1H NMR spectra with those of the alcohols 2f and the analogical consideration of the course of the reduction.

Thus, the diastereomer ratios of the alcohols 2a-2h were determined by the TLC separation and the HPLC analysis[8] of their *threo/erythro* mixtures and the results are summarized in Table I.

In the reductions with DIBAL, the substituent of the alkenyl group R^1 (Me- or Me_3Si-) exerted a marked stereo-directing effect where high degrees of *threo*-selectivity were observed (1e-1h), whereas virtually non-stereoselective reductions had occurred in cases lacking this substituent R^1 (1a-1d). Since easily removed to produce 2a-2c, the trimethylsilyl groups of 2f-2h act as the "template" for the stereoregulation in the present reduction.

On the other hand, the reductions with L-Selectride proceeded in uniformly excellent *threo* selectivities irrespective of the substitution pattern of the alkenyl group of the substrates. Especially, exclusive formation of the *threo*-alcohols was observed in the substrates bearing R^1 and/or R^3 substituents. Thus, properly substituted alkenyl group offers a sufficiently large steric bias for essentially complete 1,2-asymmetric induction to be achieved.[9]

Scheme I



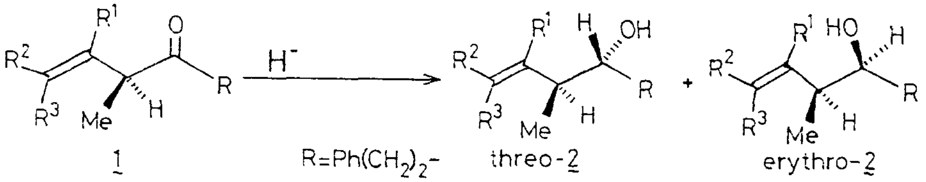
Key:

R = $Ph(CH_2)_2$-

a) cat. NaH / HMPA, rt.

b) O_3 / MeOH, -78°C; $NaBH_4$, -78°C.

TABLE I. Stereoselective Reduction of β,γ-Unsaturated Ketones



Ketone $\underline{1}$	R^1	R^2	R^3	$\underline{2}$: *threo/erythro* [a,b,c] DIBAL [d]	L-Selectride [d]	$[\alpha]_D$ (c, temp.) [e]
a	H	H	H	47 / 53	96 / 4	+ 18° (0.62, 24) [f]
b	H	Bu	H	52 / 48	93 / 7	-1.6° (2.4, 22)
c	H	H	Bu	60 / 40	>99 / 1	+ 24° (0.36, 27)
d	H	Me	Me	55 / 45	>99 / 1	- 6° (0.5, 27)
e	Me	H	H	88 / 12	>99 / 1	+ 32° (1.7, 20)
f	Me_3Si	H	H	89 / 11	>99 / 1	+ 12° (1.1, 23)
g	Me_3Si	Bu	H	94 / 6	>99 / 1	+9.0° (1.0, 25)
h	Me_3Si	H	Bu	>99 / 1	>99 / 1	+ 17° (0.80, 25)

a) Ratios were determined by HPLC.[8] *b)* Yields are 85-95%. *c)* Separable on SiO_2 TLC (hexane-AcOEt) except $\underline{2a}$.[7] *d)* Carried out in THF at -78°C. *e)* Optical rotation of optically pure *threo*-$\underline{2}$ in $CHCl_3$.[13] *f)* See ref. 7).

This unusually high selectivity in the present reduction of α-methyl-β,γ-unsaturated ketones is unprecedented and deserves some mechanistic considerations. Although the precise mechanism has not been elucidated, the stereochemical aspects of the present reduction could be explained in terms of the Felkin-Anh's model[2c,d] where the alkenyl group behaves as the largest group, to which the hydride ion approaches in an antiperiplaner relationship as depicted in Fig I. The effective bulkiness of the alkenyl group is so much enhanced when the proximate sp^2 hybridized carbon possesses a bulky group.[10]

Since stereo-defined β-methyl homoallylic alcohols are valuable compounds in natural product synthesis, several methods have been devised for the diastereoselective synthesis of this class of compounds.[11] However, enantioselective version of the synthesis is lacking.[12] Thus, the present process in combination with the foregoing Et_3Al-mediated pinacol-type rearrangement offers a novel and efficient entry into the enantiomerically and diastereomerically pure *threo* β-methyl homoallylic alcohols of various substitution patterns.[13]

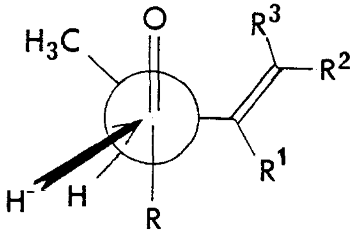


FIGURE I

References and Notes

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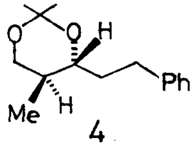
5) The relative stereochemistry was also ascertained by the literature procedure; the isopropylidene derivative 4 exhibited a distinct and diagnostic doublet (δ 0.7, J=7Hz); T. Nakata and T.Oishi, Tetrahedron Lett., 1980, 1641.



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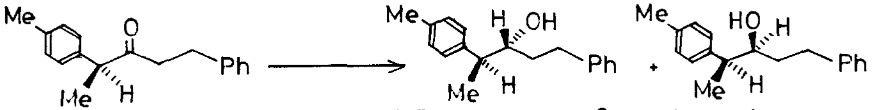
6) T. Hiyama, Y. Okude, K. Kimura, and H. Nozaki, Bull. Chem. Soc.Jpn., 55, 561 (1982).

7) Pure *threo-2a was obtained by the desilylation of threo-2f under Sato's conditions,*4) whose $[\alpha]_D$ value is shown.

8) Develosil ODS-5 column (46x250, Nomura Chem. Co.) was used ($MeOH-H_2O$).

9) Difference of the stereoselectivity between DIBAL and L-Selectride could be rationalized by the concept proposed by Midland *et al.*2f) In case of the Lewis-acidic reducing agent, namely DIBAL, 4-centered transition state might be operative where the conformation shown in Figure I is not necessarily a favored one leading to the decrease of the selectivity.

10) As Anh pointed out,2d) discussion on the basis of "effective size" must be cautiously done when the substituent has low-lying vacant orbitals. Thus, in the present case, an extra stabilization of the transition state is probable due to the π^*_{CO} - π^*_{CC} secondary orbital interaction. A similar tendency was observed in the reduction of α-aryl ketone 5.



5

DIBAL 2 / 1

L-Selectride >99 / 1

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12) Recently, several attempts have been reported on the asymmetric synthesis which, however, are accompanied by the lack of generality or unsatisfactory optical yields; T. Herold, U. Schrott, and R. W. Hoffmann, Chem. Ber., 114, 359 (1981); M. M. Midland and S. B. Preston, J. Am. Chm. Soc., 104, 2330 (1982); T. Hayashi, M. Konishi, and M. Kumada, *ibid.*, 104, 4963 (1982).

13) The alcohols 2 were all proved to be optically pure within the limit of the analytical method; the ee's of 2 were determined by HPLC and/or ^{19}F NMR analysis of the bis-MTPA ester derivative of 3. For detail, see the preceding paper, ref. 3).

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