

REDUCTIVE PINACOL-TYPE REARRANGEMENT OF CHIRAL α -MESYLOXY KETONES
PROMOTED BY ORGANOALUMINUM COMPOUNDS

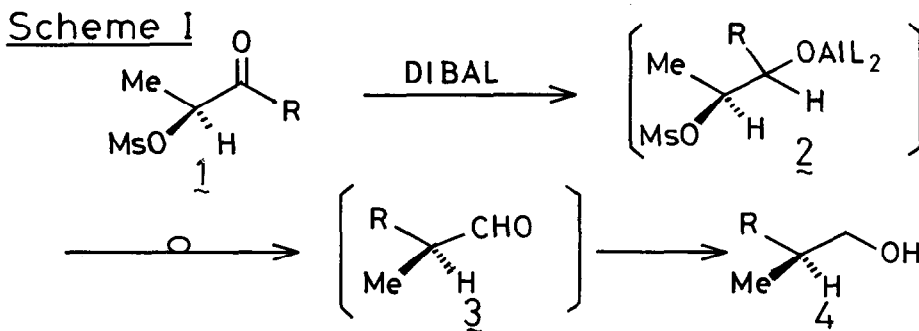
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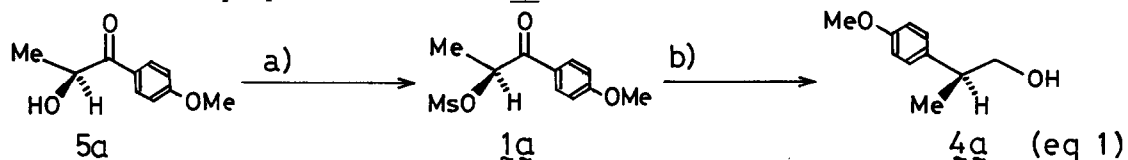
Summary: Reductive pinacol-type rearrangement of chiral α -mesyloxy ketones was effected by organoaluminums (DIBAL in combination with Et_3Al or Et_2AlCl) leading to enantiomerically pure 2-aryl- or 2-alkenyl-1-propanols.

π -Face selection of acyclic molecules has received remarkable interest in connection with the synthesis of macrolide and related natural products. For the starting material of such reactions, following criteria must be fulfilled; the geometrical purity (in case alkenyl groups are concerned) and the enantiomeric purity. Ready availability of the starting compounds with high stereochemical purities enlarges the perspective of acyclic stereoselection.

For this purpose, we investigated the possibility to utilize the stereospecific rearrangement as a reliable tool and already reported novel method for the synthesis of α -aryl ketones,^{1a)} α -alkenyl ketones,^{1b)} and *threo* β -methyl homoallylic alcohols^{1c)} based on the Et_3Al -mediated asymmetric pinacol-type rearrangement. In order to widen the scope of this novel rearrangement, we introduced a new concept "the reductive pinacol-type rearrangement"; the key species β -mesyloxy alkoxide 2 was generated *in situ* by the action of DIBAL to the α -mesyloxy ketone 1, which underwent rearrangement followed by reduction of the resulting aldehyde 3 to give enantiomerically pure 2-substituted-1-propanol derivative 4 as shown in Scheme I. In this communication, we wish to describe an efficient method for the synthesis of optically pure 2-aryl- or 2-alkenyl-1-propanols based on the reductive pinacol-type rearrangement.



Mesylation of α -hydroxy ketone 5a²⁾ was effected by sulfene without any difficulty ($\text{MsCl-Et}_3\text{N} / \text{CH}_2\text{Cl}_2$, -45°C) to give the corresponding mesylate 1a³⁾ in essentially quantitative yield. The α -mesyloxy ketone 1a, thus formed, was dissolved in CH_2Cl_2 and treated at -78°C with 2.5 equiv of diisobutylaluminum hydride (DIBAL) where immediate reduction of the carbonyl group took place to form the alkoxide 2a. Upon further addition of Et_3Al (1.0 equiv) into this reaction mixture, the alkoxide intermediate was smoothly converted to alcohol 4a. This conversion consists of the Et_3Al -promoted 1,2-migration of p-anisyl group followed by the reduction of the resulting aldehyde. Thus, (S)-2-(p-anisyl)-1-propanol 4a was obtained in 83 % yield. Moreover, the alcohol 4a was proved to be optically pure as evidenced by ^1H NMR shift study of (+)-MTPA ester (Mosher-Yamaguchi method)⁴⁾ employing $\text{Eu}(\text{FOD})_3$ ⁵⁾ as a shift reagent. It was indicated that none of the racemization problems was encountered not only at the rearrangement step but also during the manipulation of the ketones 5a and 1a. In this way by the combinational use of organoaluminum compounds, there was realized a one-pot reaction of three successive steps, i) reduction of the starting ketone 1a, ii) 1,2-migration of the aryl moiety, and iii) reduction of the resulting aldehyde, furnishing the enantiomerically pure 2-substituted-1-propanol derivative 4a in high yield (eq. 1).



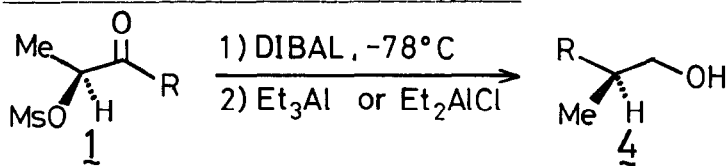
Key: a) MsCl (1.2 equiv), Et_3N (1.5 equiv) / CH_2Cl_2 , -45°C .
 b) DIBAL (2.5 equiv) / CH_2Cl_2 , -78°C , 10 min;
 Et_3Al (1.0 equiv), -78°C , 30 min.

Under the similar conditions, the reductive pinacol-type rearrangement of the related substrates was carried out and the results are shown in Table I. In these reactions, the additional use of the second organoaluminum compound (Et_3Al or Et_2AlCl) was necessary for the smooth conversion of the alkoxide intermediate 2 to the alcohol 4 via the aldehyde 3, suggesting the binary activation by the Al-alkoxide and the second Lewis-acidic promoter. On the other hand, the rearrangement had proceeded only sluggishly in the absence of the second promoter. Even when a large excess of DIBAL (up to 5.0 equiv) was used at the initial stage, the reaction had mainly stopped at the alkoxide 2.

It is noteworthy that the present rearrangement is not limited to the aryl group migration but also feasible for the migration of the alkenyl groups activated by silicon.^{1b,6)} This fact implies that the initial reduction of the $\alpha,8$ -enones proceeded in a 1,2- but not 1,4-sense⁷⁾ to form the requisite aluminum alkoxide 2 ready for the alkenyl-group migration. It is also worthy of comment that the geometries of the alkenyl moieties were retained during the rearrangement suggesting the highly concerted nature of the rearrangement.¹⁾

Concerning the relative migratory aptitude, the normal tendency for the cationic migration was observed, that is, $\text{p-MeOC}_6\text{H}_4\text{-} > \text{C}_6\text{H}_5\text{-}$: For the completion

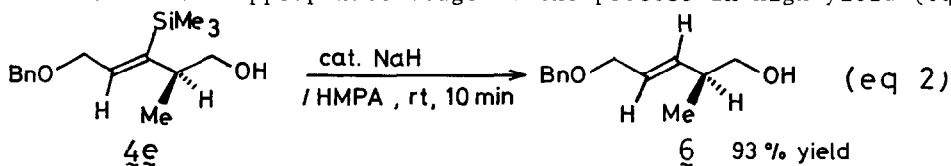
Table I. Reductive Pinacol-Type Rearrangement



<u>4</u>	R	Yield (%) ^e	ee (%) ^d	$[\alpha]_D$ (c, temp.) ^e
<u>a</u>		83 ^a	> 95	-14° (0.82, 17)
<u>b</u>		80 ^b	> 95	-19° (0.83, 19)
<u>c</u>		77 ^a	> 95	-2.4° (1.4, 16)
<u>d</u>		67 ^a	> 95	-2.6° (1.7, 18)
<u>e</u>		91 ^a	> 95	-16° (0.39, 16)
<u>f</u>		78 ^a	> 95	-15° (1.0, 20)

a) Carried out in CH_2Cl_2 at -78°C with DIBAL (2.5 equiv) followed by Et_3Al (1.0 equiv). b) Et_2AlCl was used in place of Et_3Al ; other conditions were the same as above. c) Measured in CHCl_3 except 4b (in C_6H_6 , see ref 9). d) Determined by the analysis of (+)-MTPA ester of 4 (For a,b: ^1H NMR-shift study with $\text{Eu}(\text{FOD})_3$; for c,d: 100 MHz ^{13}C NMR; for e,f: ^{19}F NMR). e) Isolated yield after purification on silica-gel TLC.⁸⁾

of the migration of phenyl group, a more Lewis-acidic promoter Et_2AlCl in place of Et_3Al was required. Also, the migratory aptitude of 1-trimethylsilyl alkenyl groups is notable, which is qualitatively comparable to that of p-anisyl group. This high level of migratory aptitude of these groups is attributed to the β -effect inherent in silicon⁶⁾ as we demonstrated previously.^{1b)} Thus, trimethylsilyl group acts as a temporary activating group for the rearrangement, easily removed at the appropriate stage of the process in high yield (eq. 2).¹⁰⁾



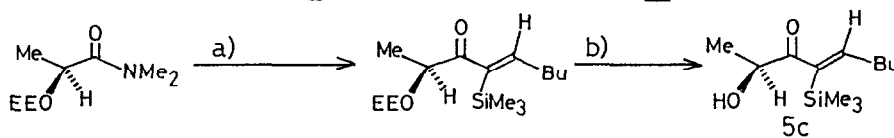
As for the enantiomeric purities the chiral alcohols 4 were all proved to be enantiomerically pure within the limit of the analysis of their Mosher esters (^1H NMR shift study, ^{13}C NMR, ^{19}F NMR, see Table).

As a consequence, *enantiomerically* pure 2-aryl- or 2-alkenyl-1-propanols 4 were easily obtained by the organoaluminums-promoted reductive pinacol-type rearrangement. The olefinic alcohols 4 possessing high *geometrical* purity are useful compounds in natural product synthesis based on acyclic stereoselection.¹¹⁾

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References and Notes

- 1) a) K. Suzuki, E. Katayama, and G. Tsuchihashi, *Tetrahedron Lett.*, **24**, 4997 (1983).
b) *Idem.*, *Ibid.*, **25**, 1817 (1984). c) *Idem.*, *Ibid.*, in press.
- 2) Preparation of α -hydroxy ketone 5 is illustrated by that of 5c. Isomerization of the



olefin geometry during the deprotection of ethoxyethyl group was suppressed by employing the acid of low nucleophilicity such as H₂SO₄. As for the requisite alkenyllithiums, see G. Zweifel, R. E. Murray, and H. P. On, *J. Org. Chem.*, **46**, 1292 (1981); H. P. On, W. Lewis, and G. Zweifel, *Synthesis*, **1981**, 999.

a) (Z)-Bu(H)C=C(SiMe₃)Li / THF, -78°C, 30 min
b) 1N H₂SO₄-DME (1:5), rt, 30 min.

- 3) α -Mesyloxy ketone 1 may be used either with or without purification on silica gel. No racemization of 1 was observed during this procedure.
- 4) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969). For the shift study of Mosher esters, see F. Yasuhara and S. Yamaguchi, *Tetrahedron Lett.*, **1977**, 4085.
- 5) Tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium(III).
- 6) E. Colvin, "Silicon in Organic Synthesis" Butterworths, London, 1981, pp 15-20.
- 7) DIBAL is known to behave as a 1,2-reducing agent on α,β -enones; for example, see K. E. Wilson, R. T. Seidner, and S. Masamune, *J. Chem. Soc., Chem. Commun.*, **1970**, 213.
- 8) All new compounds gave satisfactory analytical data.
- 9) E. L. Eliel and J. P. Freeman, *J. Am. Chem. Soc.*, **74**, 923 (1952); S. Mitsui, S. Imaizumi, and Y. Takahashi, *J. Chem. Soc. Jpn.*, **84**, 842 (1963). The absolute configuration of (+)-2-phenyl-1-propanol was assigned to be (R).
- 10) Trimethylsilyl group in this sequence also contributed to the stereoregulation of the alkenyl geometry; E/Z isomerization problem was encountered at the stages of α,β -enones 1 and 5 in the absence of this grouping on the alkenyl moiety.
- 11) Elaboration of this type of molecules is expected to be stereoselective since the stereoelectronic environment of the two π -faces are discriminated due to A(1,3) strain. For example, see I. Hasan and Y. Kishi, *Tetrahedron Lett.*, **21**, 4229 (1980).

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