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COMPLETELY STEREOSPECIFIC 1,2-MIGRATION OF ALKYL GROUPS IN Et_2AlCl PROMOTED PINACOL-TYPE REARRANGEMENT

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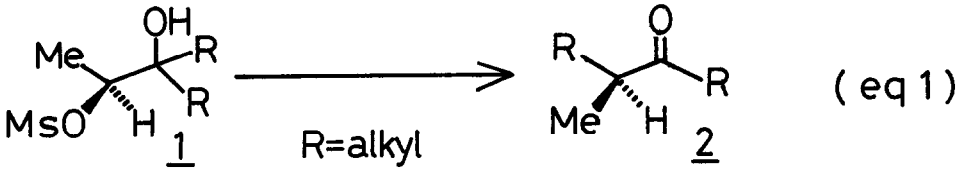
Summary: *Completely stereospecific 1,2-migration of alkyl groups was achieved in Et_2AlCl-promoted pinacol-type rearrangement of chiral β-mesyloxy alcohols to give optically pure α-alkyl ketones including both enantiomers of 4-methyl-3-hexanone, an alarm pheromone of ant.*

In biosynthetic pathways, stereospecific 1,2-migration of hydride or alkyl groups constitutes one of the fundamental processes for the construction of the complex framework of natural products. On the other hand, the stereospecificity is substantially lost in the related chemical reactions mainly through the intermediacy of free carbocation. Thus, exploitation of such a chemical process attracts much interests from both theoretical and synthetic standpoints.

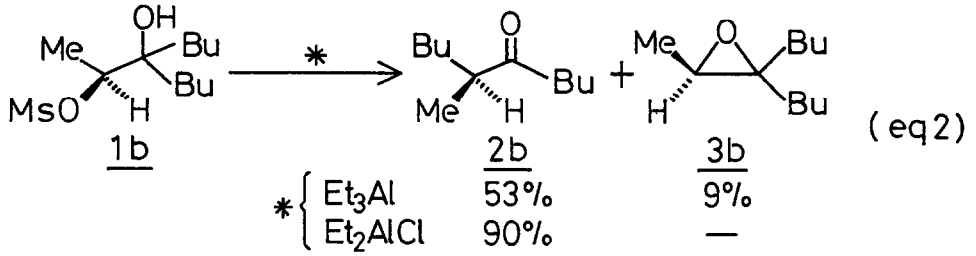
In our continuing research on the exploitation of facile access to the *optically pure* compounds, we reported the stereospecific (asymmetric) pinacol-type rearrangement promoted by Et_3Al.[1] In this process, aryl or alkenyl groups participated in the ready 1,2-migration, whereas alkyl group behaved as the "staying group" reflecting its low migratory aptitude. We examined the migration of the latter group intrigued by the following points of view; i) the requisite reaction conditions for the smooth migration to take place compensating the low migratory aptitude, and ii) the extent of the stereospecificity under the conditions stated above. These two precarious points turned to be easily surmounted by a subtle change of the organoaluminum reaction promoter.



(eq 1)

In this communication, we wish to report the realization of the smooth and completely stereospecific 1,2-shift of alkyl groups by employing a more Lewis-acidic promoter Et_2AlCl in place of Et_3Al and its successful application to the chiral synthesis of both enantiomers of 4-methyl-3-hexanone, an alarm pheromone of ant starting from (R)- and (S)-lactate.

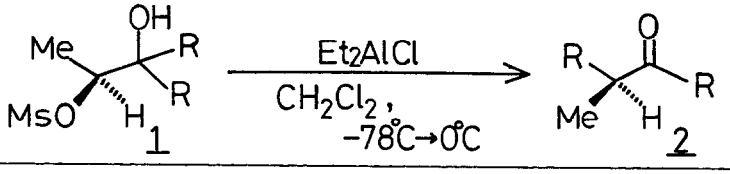
Et_3Al was ineffective as a promoter of the alkyl-shift; treatment of the β-mesyloxy alcohol 1b with Et_3Al (-78°C → 0°C / CH_2Cl_2) resulted in a sluggish 1,2-migration of butyl group which was accompanied by a serious side reaction, epoxide formation (eq 2). This result could be ascribable to the low migratory aptitude of the alkyl group compared with aryl or alkenyl groups, wherein the raised reaction temperature rendered the nucleophilicity of the diethylaluminum alkoxide no longer negligible to result in the internal S_N2 ring closure.

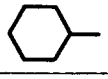


To suppress this undesirable side reaction, we examined more Lewis-acidic promoter in expectation of i) the increased level of the activation and ii) the decreased nucleophilicity of the alkoxide. After some experimentation, Et_2AlCl was found to be a highly efficient promoter for this purpose; the alcohol 1b was treated with Et_2AlCl (2.1 equiv / CH_2Cl_2) at -78°C for 1.5 h and the temperature was slowly raised during 2h to 0°C to give (S)-6-methyl-5-decanone(2b) in 90% yield without any contamination with the epoxide 3b. Thus, the perplexity was cleanly solved by the modulation of the reaction promoter.

Under the similar conditions, the Et_2AlCl-promoted pinacol-type rearrangements of alkyl groups were examined and the results are summarized in Table I.

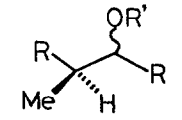
TABLE I. Asymmetric Pinacol Rearrangement of Alkyl Groups



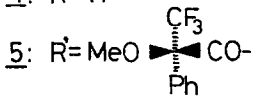
1	R-	Yield (%)[a]	ee (%)[d]	$[\alpha]_D$ (c, temp.)[f]
a	C_2H_5-	72[b] (99)[c]	> 95	+ 26.1° (neat, 18)[g]
b	n-C_4H_9-	90	> 95	+ 22.3° (2.44, 17)
c	n-C_8H_{17}-	90	> 95	+ 15.1° (5.17, 18)
d		92	> 99[e]	+ 58.9° (5.17, 18)

a) Isolated yields after purification on silica-gel column chromatography. b) Yield after distillation (ref 10). c) By GLC (PEG 20M; 2-octanone as standard). d) By ^{13}C NMR (ref 2,3). e) By HPLC (ref 2). f) Measured in $CHCl_3$. g) Lit. $[\alpha]_D^{25}$ +24.08° (neat) (ref 8).

It is noteworthy that the smooth migration of alkyl groups including cyclohexyl group was effected by this procedure to give the α-alkyl-substituted chiral ketones 2 in excellent yields and any of the epoxide congener was not detected in every case.



4: R'=H



5: R'=MeO CO-Ph

In addition and more importantly, the chiral ketones 2 were proved to be *enantiomerically pure* within the limit of the analyses: Reduction of 2 with DIBAL gave 1/1 mixture of the alcohols 4 which was converted to (+)-MTPA esters 5 and analyzed with 100 MHz ^{13}C NMR (5a,b,c) or HPLC (5d).[2,3] Thus, the mode of the 1,2-migration of the alkyl groups was confirmed to proceed *in a stereospecific manner*. To our knowledge, this is the first example of the acyclic pinacol-type rearrangement wherein the *stereospecific 1,2-migration of alkyl group* was proved.[4] This positive result stems from two factors, i) efficacy of Et_2AlCl as a reaction promoter by *push-pull* sense,[1] and ii) the σ participation of alkyl groups to exclude the intermediacy of the open carbocation.[5] We assume that these two factors are of indispensable relationship since the HOMO level of the migrating alkyl group is adequately highered by the aluminum alkoxide (*push*) so as to have an effective interaction with the LUMO of the developing carbocation generated by the *pull* of the Lewis-acidic aluminum. In other word, the σ participation is embodied by the ambidextrous action of the organoaluminum promoter as depicted in Fig I.[6]

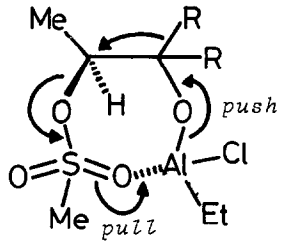
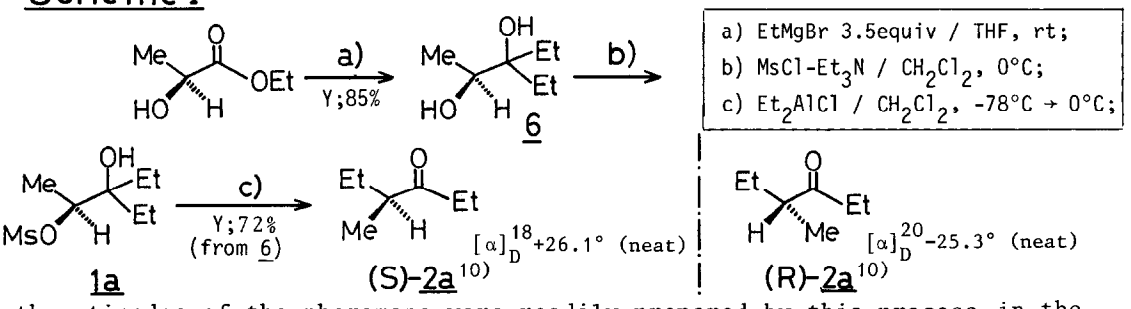


Fig I

Synthetic aspect of this stereospecific 1,2-migration of alkyl groups was demonstrated by a facile synthesis of *both enantiomers* of 4-methyl-3-hexanone (2a), an alarm pheromone of ant (*Manica mutica, Manica bradleyi*),[7,8] starting from (S)-ethyl lactate and (R)-methyl lactate as shown in Scheme I.[9] Thus,

Scheme I



both antipodes of the pheromone were readily prepared by this process in the enantiomerically pure forms as evidenced by ^{13}C NMR analysis.[2,3] Since the chirality *vs* the pheromone activity relationship of this substance has not been specified yet,[11,12] availability of both enantiomers of 2a would attract biological and ecological interests.

In summary, completely stereospecific 1,2-migration of alkyl groups in the pinacol-type rearrangement of lactate-derived chiral β-mesyloxy alcohols 1

was accomplished by employing Lewis acidic promoter Et_2AlCl to furnish the enantiomerically pure α-alkyl-substituted chiral ketones 2 including (R)- and (S)-4-methyl-3-hexanone, both enantiomers of an ant alarm pheromone.

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References and Notes

1) a) K. Suzuki, E. Katayama, and G. Tsuchihashi, Tetrahedron Lett., 24, 4997 (1983).
b) K. Suzuki, E. Katayama, and G. Tsuchihashi, ibid., 25, 1817 (1984).

2) Comparison of (+)-MTPA ester 5 prepared via the present process starting from (S)- and (RS)-ethyl lactate revealed diagnostic ^{13}C NMR signals by 100.40 MHz off resonance spectra. In case of 5d, clean separation of diastereomers was effected by HPLC (ODS-5 column, Nomura Chem. Co., $MeOH/H_2O = 85/15$).

δ, $CDCl_3$	MTPAO 5a	MTPAO 5b	MTPAO 5c
S	37.99, 37.78	81.17, 80.54	81.21, 80.60
RS	38.06, 37.99 37.78, 37.66	81.29, 81.17 80.72, 80.54	81.32, 81.21 80.78, 80.60

3) The ee's of (S)- and (R)-2a were estimated to be at least 95%; the Mosher ester 5a derived from (S)-2a showed a pair of ^{13}C signals (37.78, 37.99) and the other pair (37.66, 38.06) was completely absent, and *vice versa* for the ester derived from (R)-2a.

4) Y. Pocker, "Molecular Rearrangements," P. de Mayo ed., Intersci., NY, (1963), 1, pp 15-25.

5) So far, argument on the existence of σ participation by the adjacent C-C single bond has been essentially limited to Wagner-Meerwein rearrangement of 2-norbornyl systems (see J. B. Lambert, H. W. Mark, A. G. Holcomb, and E. S. Magyar, Acc. Chem. Res., 12, 317 (1979).). On the other hand, possibility of σ participation is more plausible in our case by virtue of the molecular orbital preference (energy matching) as stated in text.

6) At present, it is not clear whether these modes of activations are governed by a monomeric aluminum, and intensive study on this point is now under way.

7) H. M. Fales, M. S. Blum, R. M. Crewe, and J. M. Brand, J. Insect Physiol., 18, 1077 (1977).

8) O. Pieroni, F. Ciardelli, C. Botteghi, L. Lardicci, P. Salvadori, and P. Pino, J. Polymer Sci. (C), 22, 993 (1969).

9) (S)-Ethyl lactate was purchased from Aldrich Chem. Co. and (R)-methyl lactate was a kind gift from Daicel Chem. Ind., Ltd. ($[\alpha]_D^{20}$ +8.52°) which is greatly appreciated.

10) After usual extractive workup, the extract was passed through Al_2O_3 short column (Woelm neutral, deactivated by 10% H_2O) and distilled (80-85°C/170 Torr (bath temp.)). This procedure avoids racemization during distillation caused by the acidic aluminum residue.

11) One-carbon homolog of this substance, 4-methyl-3-heptanone, is the alarm pheromone of ant (*Atta texana*) where its (S)-antipode was shown to possess more activity by 400 times than its (R)-counterpart; R. G. Riley and R. M. Silverstein, Tetrahedron, 30, 1171 (1974).

12) Attempted asymmetric synthesis of this pheromone has been reported; D. Enders and H. Eichenauer, Angew. Chem., Int. Ed. Engl., 18, 397 (1979); H. C. Brown, P. K. Jadhav, and M. C. Desai, J. Am. Chem. Soc., 104, 6844 (1982).

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