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ASYMMETRIC SYNTHESIS OF OPTICALLY PURE α-METHYL-β,γ-UNSATURATED KETONES VIA TRIETHYLALUMINUM-MEDIATED STEREOSPECIFIC PINACOL REARRANGEMENT OF ALKENYL GROUPS

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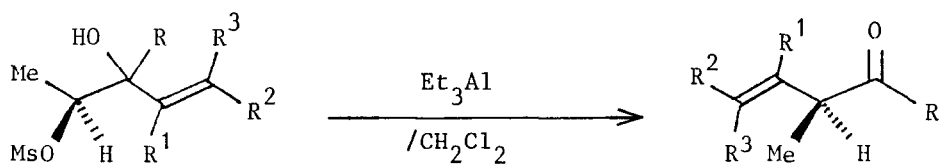
Summary: Optically pure α-methyl-β,γ-unsaturated ketones are synthesized by the Et_3Al-mediated pinacol-type rearrangement where alkenyl groups migrate stereospecifically with complete retention of the olefin-geometry.

Optically active β,γ-unsaturated ketones such as 1 have high versatility and wide potentiality in natural product synthesis. However, there have been reported no general preparative methods of them, mainly due to their lability to acid and base to result in the conjugation. Thus, the reaction conditions have to be as mild as possible for the asymmetric synthesis of this class of compounds. In our previous communication,[1] we have demonstrated the complete stereospecificity in the pinacol-type rearrangement of chiral β-mesyloxy alcohols by employing Et_3Al as the reaction promoter. Considering the milder conditions ensured by the organoaluminum and the high efficacy of the chirality transfer, we decided to exploit the possibility of the chiral synthesis of 1 by

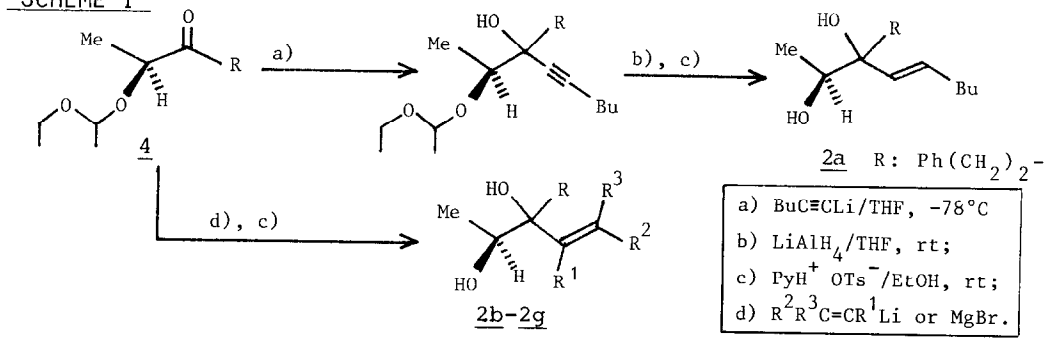


3 1

the stereospecific rearrangement. In this communication, we wish to report a highly efficient method for the preparation of optically and geometrically pure α-methyl-β,γ-unsaturated ketones *via* stereospecific 1,2-migration of the alkenyl groups of the lactate-derived chiral β-mesyloxy alcohols.[2]

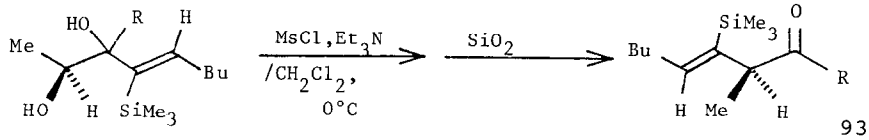
The (E)-olefinic diol 2a was prepared from the chiral ketone 4[2] *via* the acetylide-addition and hydroalumination[3] sequence. Other olefinic diols were prepared in a straightforward manner by the reaction of the stereo-defined alkenyllithium[4] or magnesium[5] reagents with the ketone 4 and the subsequent deprotection of the ethoxyethyl protecting group (Scheme I).

SCHEME I



The chiral β-mesyloxy alcohol 3a, readily prepared from 2a,[1] was treated with Et_3Al (1.2 equiv, 1 M/hexane) at -42 °C for 1 h to afford the rearranged product 1a in 67 % yield from 2a after purification on silica-gel TLC. The ketone 1a was free from the α,β-unsaturated isomers, and its double-bond geometry was solely E judged from ^1H NMR and HPLC analysis of the crude reaction products. Also, in the rearrangement of the (Z)-isomer 3b, the stereochemical integrity of the alkenyl group was completely retained during the migration to furnish the (Z)-olefinic ketone 1b in 64 % yield from 2b. Under the similar conditions, the pinacol rearrangements of the other alkenyl substrates were performed and the results are summarized in Table I.[6]

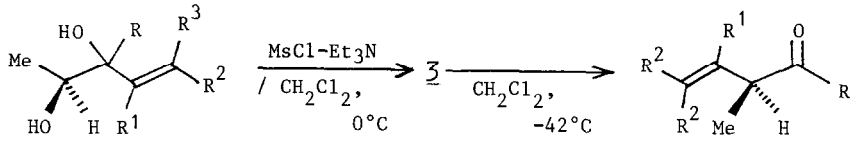
Concerning the substituent effect of the migrating alkenyl group, notable phenomenon was observed; the rate of the migration is much faster when Me_3Si-substituent is present at the α-position of the alkenyl group compared with non-substituted cases. In an extreme case, a spontaneous rearrangement had occurred upon mesylation; when 2f was mesylated (CH_3SO_2Cl/CH_2Cl_2, 0°C) in the presence of 3.5 equiv of Et_3N, immediate formation of the rearranged product 1f was detected by TLC and an addition of silica gel into the reaction mixture drived the reaction to completion within 30 min at 0°C. The ketone 1f was obtained in 93 % yield and also proved to be geometrically pure. This rate-enhancement effect by trimethylsilyl group could be explained in terms of the pronounced β-effect of silicon[7] where partially developing positive charge is effectively stabilized at the transition state to facilitate the 1,2-migration of the alkenyl group.



The most important and essential feature of the present process lies in its stereospecificity; the ketones 1 were optically pure as shown in Table I, within the limit of the analytical methods which are shown in Scheme II.

Each of the ketones 1 (except 1d) was transformed to the common diol 5,[8] which was doubly esterified with the chloride of (R)-(+)-MTPA[10] to give diester 6, whose HPLC analyses[9] showed over 99 %ee in each case. The ketone 1d was

TABLE I. Asymmetric Pinacol Rearrangement of Alkenyl Groups



2 1 R = $Ph(CH_2)_2$-

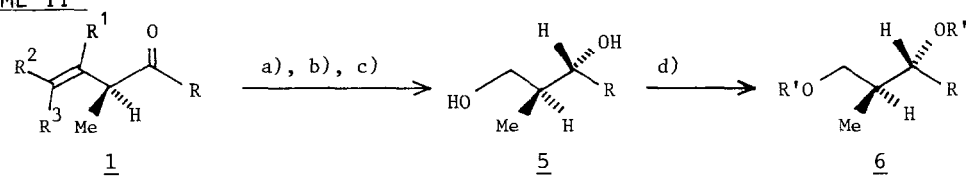
Diol 2	R^1	R^2	R^3	Yield (%)[a]	ee (%)	$[\alpha]_D$(c,temp.)[b]
a	H	Bu	H	67	> 99[d]	+150°(0.6 ,26)
b	H	H	Bu	64	> 99[d]	+293°(0.54,26)
c	H	Me	Me	65	> 99[d]	+204°(0.5 ,26)
d	Me	H	H	66	> 95[e]	+384°(0.2 ,27)
e	Me_3Si	H	H	75	> 99[d]	+131°(1.2 ,24)
f	Me_3Si	Bu	H	93[c]	> 99[d]	+110°(1.3 ,24)
g	Me_3Si	H	Bu	70	> 99[d]	+170°(1.1 ,27)

a) Isolated overall yield from 2 after purification on silica gel (hexane-AcOEt). *b)* In $CHCl_3$. *c)* Promoted by silica gel (see text). *d)* By HPLC analysis of (+)-MTPA diester 6 (Scheme II). *e)* By ^{19}F NMR analysis of the Mosher ester 6d (Scheme II).

also proved to be enantiomerically pure as evidenced by the ^{19}F NMR analysis of the Mosher ester 6d.[10] These results clearly indicate that no racemization took place during the course of the rearrangement as well as the whole derivation process starting from (S)-ethyl lactate.[2]

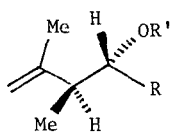
Thus, the migration of the alkenyl groups was proved to be *stereospecific with retention of (E),(Z)-geometries*, which implies the fully concerted nature of the present rearrangement. To our knowledge, this is the first example of

SCHEME II



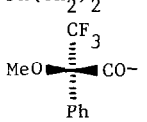
1 5 6

a) DIBAL / THF, -78°C, diastereomer sepn. on SiO_2.
b) cat. NaH / HMPA[12] (for series e, f, g).
c) O_3 / MeOH, -78°C; $NaBH_4$.
d) MTPA chloride / pyridine.



6d

R: $Ph(CH_2)_2$-

R': 

the acyclic pinacol rearrangement[11] in which the complete chirality transfer and the retention of the olefin-geometry are ascertained. These features, the enantiomerical and geometrical purity of ketones 1, are the essential requirement for the stereoselective further elaborations.

Acknowledgment

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Lithiation was effected by BuLi in Et_2O (-78°C, 30 min) and the subsequent reaction with 4 (-78°C, 30 min) afforded 2b, 2f and 2g, respectively, after deprotection.

5) Grignard reaction with 4 was performed in THF (0°C, 1 h). $H_2C=C(SiMe_3)Br$; see R. K. Boeckman Jr., D. M. Blum, B. Ganem, and N. Halvey, Org. Syn., 58, 152 (1978).

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8) The diastereomers were separated after the hydride reduction and transformed to the diol 5, among which the isomer depicted in Scheme II was employed for the analysis. The stereochemical feature of the reduction will be reported elsewhere. Racemic modification of 5 was prepared by Hiyama's procedure [(i) $CrCl_3$-$LiAlH_4$, $CH_3CH=CHCH_2Br$, $Ph(CH_2)_2CHO$, (ii) O_3/MeOH; $NaBH_4$] and transformed to 6; T. Hiyama, Y. Okude, K. Kimura, and H. Nozaki, Bull. Chem. Soc. Jpn., 55, 561 (1982).

9) Develosil ODS-5 46x250 (Nomura Chem. Co.) and Protesil 300 Diphenyl 46x250 (Whatman Co.) columns were used in sequence ($MeOH/H_2O$=79/21).

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