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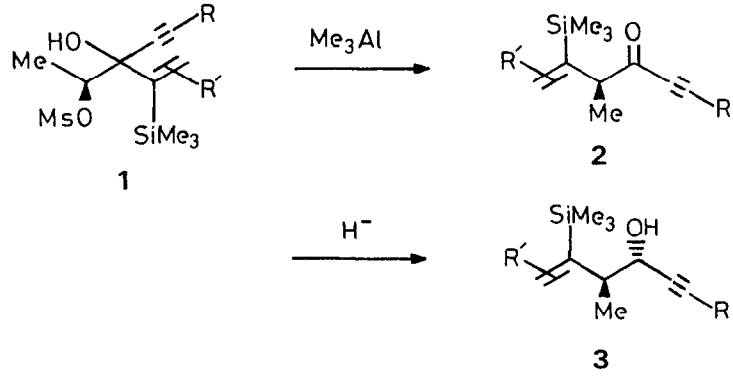
ASYMMETRIC SYNTHESIS OF CHIRAL SYNTHONS BEARING ALKYNYL GROUP VIA ORGANOALUMINUM-PROMOTED PINACOL-TYPE REARRANGEMENT

Keisuke Suzuki, Takeshi Ohkuma, Mayumi Miyazawa, and Gen-ichi Tsuchihashi*

Department of Chemistry, Faculty of Science and Technology,
Keio University, Hiyoshi, Yokohama 223, Japan

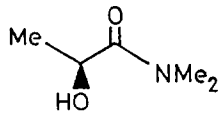
Summary: A method is described for the synthesis of chiral alkynyl ketones and alkynols via trimethylaluminum-promoted pinacol-type rearrangement where alkynyl groups behave as "the staying group", followed by stereoselective reduction leading to the latter.

Chiral building blocks possessing C≡C bonds have shown high versatility in the synthesis of biologically active substances. Accordingly, a number of methodologies have been developed toward this class of compounds, for example, asymmetric reduction,[1a] addition,[1b] microbial resolution,[1c] sigmatropic rearrangement[1d] and so on. We envisaged the possible use of the stereospecific 1,2-rearrangement, recently reported from our laboratory,[2] for an approach to chiral alkynyl synthons. Herein, we wish to report a ready and stereoselective access to such chiral synthons, alkynyl ketones 2 and threo-alkynols 3. The method relies on the low migratory aptitude of the alkynyl groups[3] which renders them "the staying group" in the 1,2-migration process, and the exclusive migration of Me_3Si-activated alkenyl group gives rise to the alkynyl ketones 2. In addition, the Me_3Si-directed stereoselective reduction of α-methyl-β,γ-unsaturated ketones 2 opens an entry to the threo-alkynols 3.[4]



1 2 3

The starting chiral β-mesyloxy alcohols 1 were prepared from the (S)-lactamide 4 in three steps [(1) R'C≡CLi / THF, (2) RCH=C(SiMe$_3$)Li / THF, (3) MsCl-Et$_3$N / CH$_2$Cl$_2$, -45 °C].[2,3] The attempted rearrangement of 1 was relatively sluggish under the standard conditions previously described (Et$_3$Al / CH$_2$Cl$_2$).[2] This retardation may be derived from the π-complexation of the alkynyl (and the alkenyl) moiety in 1 to the Et$_3$Al-promoter.[4] After some experimentation, suitable reaction conditions for the present rearrangement were found: The use of the mixed solvent CHCl$_3$-toluene [5/1 (v/v)] gave rise to the clean rearrangement of the alkenyl group to afford 2. Slightly better yields (~5%) were realized using Me$_3$Al as the reaction promoter, rather than Et$_3$Al which caused some β-hydride reduction of the resultant alkynyl ketone 2.



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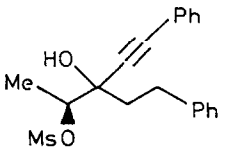
A representative procedure is described for the synthesis of 2a: Under an argon atmosphere, Me$_3$Al (1.0M /hexane, 0.72 ml) was slowly added to a solution of the β-mesyloxy alcohol 1a (96 mg, 0.24 mmol) in CHCl$_3$/toluene (1.5ml/0.3ml) at -45 °C. After the temperature was gradually raised to -10 °C during 2 h, the reaction was stopped by the careful addition of dil. NH$_4$Cl aq. solution. The remaining organoaluminums were destroyed by 1N HCl at 0 °C, and the product was extracted with ether, washed with brine, and dried over Na$_2$SO$_4$. Purification on silica-gel PTLC (hexane-AcOEt = 93/7) gave the alkynyl ketone 2a as a colorless oil (60 mg, 88%).[5]

Under the similar conditions, the 1,2-rearrangement of various mesylates 1 was performed, and the results are summarized in Table I. Concerning the stereochemical integrity of the reaction, the enantio-specificity of the chiral center (see Run 3),[6] and the geometrical specificity of the migrating group (see Run 3 and 4) were notified. In the present cases, the products derived from the alkynyl-migration were not detected, even though the starting β-mesyloxy alcohols 1 were the diastereomeric mixtures.[7] This selective migration could be understood by the low migratory aptitude of the alkynyl groups as was obviated in the related rearrangement of acetylenic chlorohydrins by P. A. Wender et al.[8] Experimentally, the low migratory aptitude of the alkynyl group in the present 1,2-rearrangement was indicated by the almost complete recovery of 5 after its treatment with R$_3$Al under variety of reaction conditions.[9]



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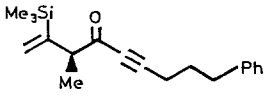
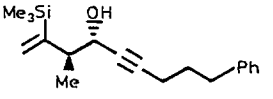
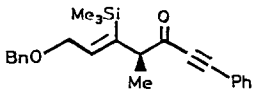
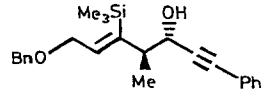
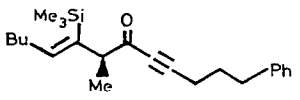
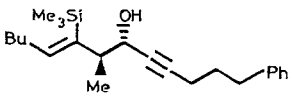
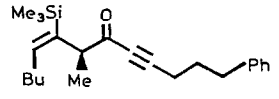
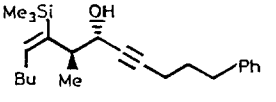
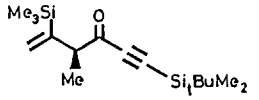
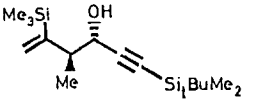
The chiral alkynyl ketones 1 could function as the useful chiral building blocks, when coupled with the acyclic stereoselection. In this context, we next examined the stereoselectivity of the reduction of the alkynyl ketone 2, and the results are also summarized in Table I.

Table I. Synthesis of Chiral Synthons 2 and 3.[5)]

Run	Ketone 2	Yield $[\alpha]_D$/$CHCl_3$	Alcohol 3	*threo*/*erythro*[a)] $[\alpha]_D$/$CHCl_3$
1		88 % $[\alpha]_D^{29}$ - 29° (c 0.43)		> 99 / 1 $[\alpha]_D^{29}$ - 22° (c 1.2)
2		79 % $[\alpha]_D^{26}$ - 8.4° (c 1.0)		> 99 / 1 $[\alpha]_D^{27}$ - 6.7° (c 0.91)
3		85 % $[\alpha]_D^{30}$ + 35° (c 0.53)		60 / 1 b) $[\alpha]_D^{31}$ - 15° (c 0.54)
4		89 % $[\alpha]_D^{29}$ + 150° (c 1.1)		8 / 1[c)] $[\alpha]_D^{31}$ - 60° (c 0.59)
5		83 % $[\alpha]_D^{33}$ + 29° (c 0.54)		40 / 1[d)] $[\alpha]_D^{30}$ - 23° (c 0.82)

a) Determined by HPLC; Develosil 60-3, 4.6 x 250 (hexane-CH_2Cl_2).
b) Determined to be over 95 %ee by HPLC analysis of the Mosher's ester (Develosil 60-3, hexane-CH_2Cl_2).
c) The ratio was 16 / 1 with $LiAlH_4$ in Et_2O at -100°C.
d) Determined by HPLC after conversion to the benzoyl derivative.

Due to the strong directive effect by the Me_3Si-bearing alkenyl group, the reduction of 2 proceeded in good to excellent threo-selectivities, although more sensitive to the substitution pattern of the substrate compared with the (non-alkynyl-containing) model cases in our previous paper.[4)]

The chiral alkynyl ketones 2 and alkynols 3 possess functional groups properly disposed ready to the further elaboration. Synthetic study of the chiral natural products utilizing these chiral synthons is now under way in our laboratory.

References and Notes

1) a) R. Noyori, I. Tomino, Y. Tanimoto, & M. Nishizawa, J. Am. Chem. Soc., 106, 6709(1984). b) T. Mukaiyama & K. Suzuki, Chem. Lett., 1980, 255. c) K. Mori & H. Akao, Tetrahedron, 36, 91(1980). d) K. Mikami, K. Azuma, & T. Nakai, Chem. Lett., 1983, 1379.

2) K. Suzuki, E. Katayama, & G. Tsuchihashi, Tetrahedron Lett., 25, 1817(1984).

3) K. Suzuki, E. Katayama, & G. Tsuchihashi, Tetrahedron Lett., 25, 2479(1984). The use of the non-protected lactamide 4 was benefitial for the present purpose because of the highly acid-sensitive nature of the tertiary hydroxyl during the unravelling when the acetal-type protection was used.

4) J. J. Eisch, "Comprehensive Organometallic Chemistry", ed. by G. Wilkinson, Pergamon, Oxford (1982), Vol. 1, Chap. 6, p 555.

5) All new compounds were fully characterized by ^{1}H NMR, IR, and high-resolution MS.

6) The enantiomerical purity was inspected only in one case (for 2c and 3c) to be pure within the limit of HPLC analysis. Since the stereospecificity of the related 1,2-migration has been established in our recent study (see ref. 2), the rest of the products in the present study are presumed to be enantiomerically pure.

7) The conformational effects on the migration course were recently clarified; see K. Suzuki, K. Tomooka, M. Shimazaki, & G. Tsuchihashi, Tetrahedron Lett., 26, 4781(1985).

8) P. A. Wender, D. A. Holt, & S. M. Sieburth, J. Am. Chem. Soc., 105, 3348 (1983).

9) The low migratory aptitude of the alkynyl group in the present rearrangement could be ascribable to the low participation ability derived from the bond angle; the linearity of the alkynyl group renders it poor in the participation to the homopropargylic $\delta+$ center. For the aspect of the solvolytic behavior of the activated homopropargyl alcohol derivatives, see G. Aucher, E. Kunzmann, and M. Hanack, Tetrahedron Lett., 24, 577(1983), and the references cited therein.

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