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SYNTHESIS OF 2-VINYL-1,3-DIOLS VIA HIGHLY STEREOSELECTIVE REDUCTION OF 2-VINYL ALDOLS USING TRIMETHYLSILYL STEREO-DIRECTING GROUP

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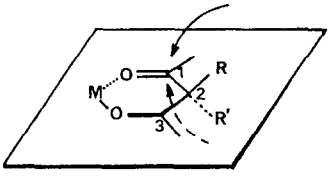
Summary: Stereo-defined 2-vinyl-1,3-diols are synthesized by the reduction of aldol derivatives bearing α-trimethylsilylvinyl group at C(2) ($LiBEt_3H$ / THF, -78°C), which proceeds highly stereoselectively to give 1,2-syn isomer as the sole product.

1,3-Diols constitute a class of structural subunits in macrolide or ionophore antibiotics. As a synthetic approach to these units, stereoselective addition of nucleophiles (including H^-) to the aldol derivatives has attracted much recent interest, where two factors (below) are concerned as shown in Fig. 1.[1)]

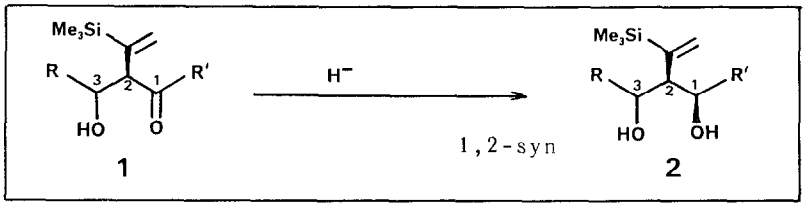
(i) the chelation effect (1,3-chelation)
(ii) the Cram selectivity (1,2-relationship)

Fig. 1



Type I : R = R' = H
Type II : R or R' ≠ H

Use of Lewis-acidic metal chelates (e.g. B, Zn, Al) is effective in the reduction of Type I substrates (free of the Cram problem), while the Type II cases are sensitive to the structural change of the substrate depending on the balance of the above two factors.[2)]



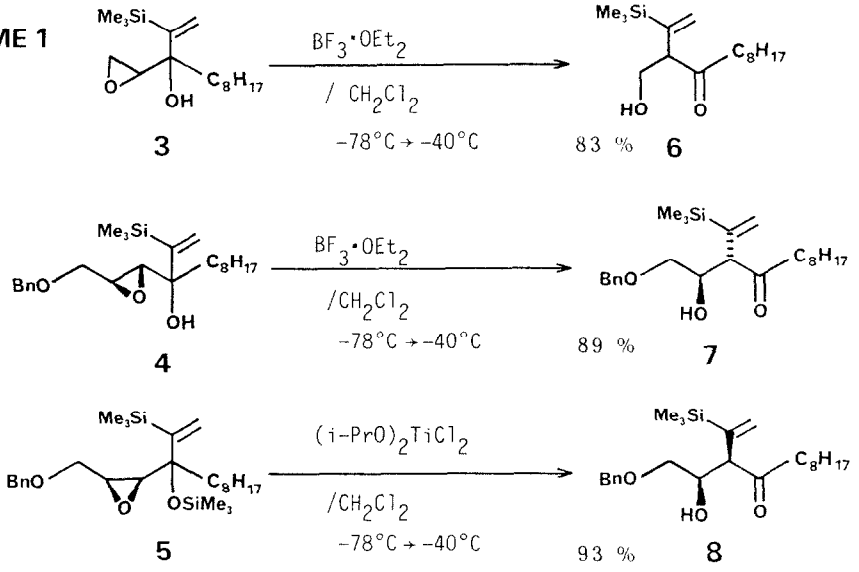
(eq. 1)

During the course of our synthetic program, we were interested in the reduction of a structurally unique class of aldols, that is, 2-vinyl aldols,[3)] which are readily available in enantio- and diastereo-controlled manner by the novel 1,2-rearrangement of the epoxyalcohol derivatives.[4)] We have disclosed a large stereo-directing effect of α-trimethylsilylvinyl group, which provides an effective solution to the Cram / anti-Cram problem in the macrolide synthesis.[5)] Herein, we wish to report that this directing effect serves as the decisive factor in the reduction of the 2-vinyl aldols 1 with the Me_3Si-group: a specific example of Type II reduction where the steric effect[6)] overrides the chelation effect leading uniformly to the 1,2-*syn* diols 2.[3)]

The model aldols were prepared via the Lewis acid-promoted 1,2-rearrangement

of epoxyalcohol derivatives (Scheme 1).[4] By the treatment with $BF_3 \cdot OEt_2$, smooth 1,2-migration of the TMS-substituted vinyl group occurred for the epoxyalcohols 3 and 4.[7] Reaction of *cis*-epoxyalcohol was plagued by the side reactions, however, which was cleanly circumvented by the prior conversion to the TMS ether 5 followed by treatment with $(i\text{-PrO})_2TiCl_2$. The rearrangements were rigorously stereospecific to afford the *anti* isomer 7 (from 4) and the *syn* isomer 8 (from 5), respectively.[8]

SCHEME 1



Reduction of these 2-vinyl aldols were carried out and the ratios of the resulting diols were determined by ^1H NMR (400 MHz) and / or HPLC.[8] For comparison, following two different types of reducing agents were tested:

(1) $LiBEt_3H$ as a nucleophilic and non-chelating reagent,[9a]

(2) DIBAL as an electrophilic and chelating reagent,[9b]

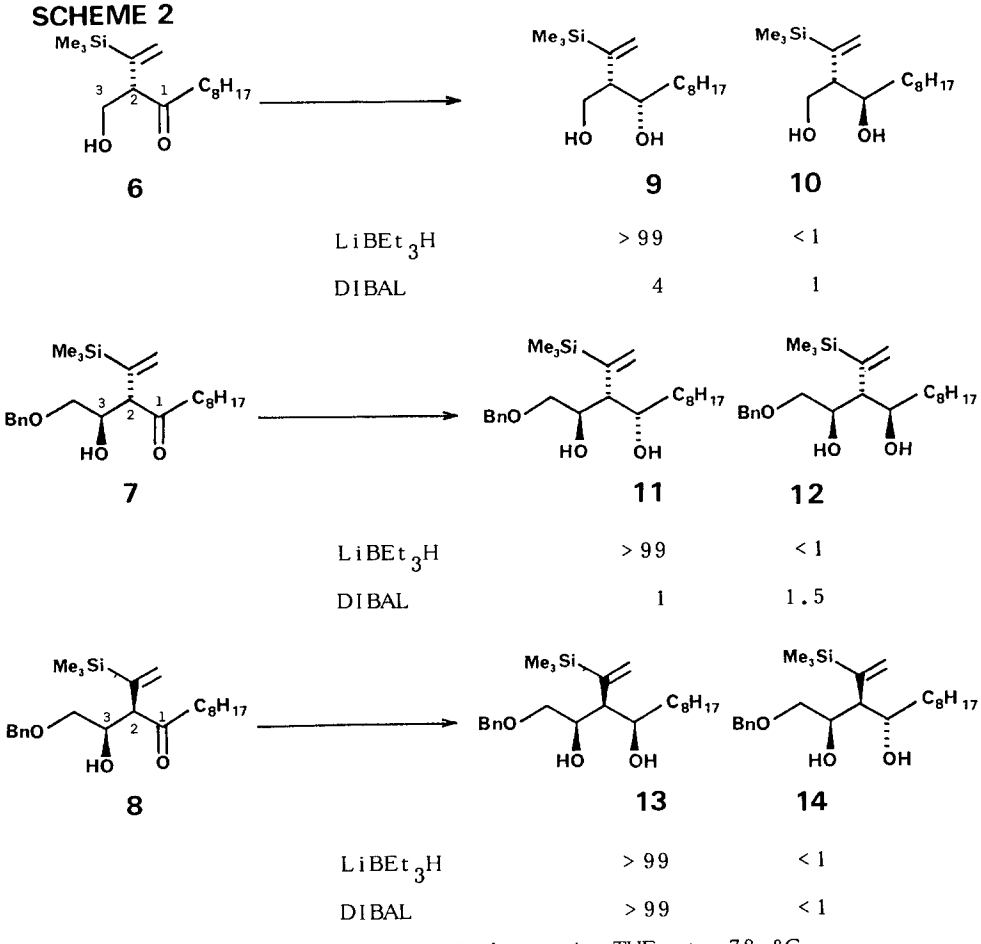
and the results are summarized in Scheme 2.[10]

Remarkably, the reductions with $LiBEt_3H$ uniformly led to the excellent selectivity in each of the cases and any trace of the *anti* isomer was not detectable. Especially noteworthy is the fact that the 1,2-*syn* isomers were produced exclusively without regard to the substituent or the configuration at the C(3) position of the starting aldols. In sharp contrast, the C(3) substituents have significant effects on the selectivity in the DIBAL cases (Cf. 7 and 8), which suggests the involvement of the chelation effect.

These observations are rationalized as follows: As for the uniformly high *syn*-selectivities with $LiBEt_3H$, of the primary importance is the extremely large steric bias[6] posed by the TMS-bearing vinyl group,[5] which strongly favors the Felkin-Anh-type transition state A*.[11] The weak chelating ability of $LiBEt_3H$[12] well suits for the achievement of this acyclic transition state A* which selectively leads to the 1,2-*syn* diol without influenced by the C(3) substituent or the configuration of the starting aldol compounds.

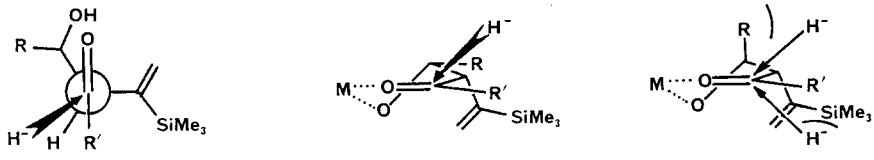
On the other hand, the DIBAL cases are clearly dependent on the balance of

SCHEME 2



*Reactions were carried out in THF at -78 °C.

the steric and the chelation effects. In the reduction of *syn* aldol 8, the two factors can cooperate as shown in B* to give rise to the high level of selectivity. In contrast, the chelate of *anti* aldol 7 fails to adopt any suitable conformations which selectively expose the one diastereotopic face due to the conflict of the two factors as shown in C* leading to the loss of the selectivity.[12]



A* B* (from 8) C* (from 7)

In summary, reduction of 2-vinyl aldols is efficiently controlled by the TMS stereo-directing group, which offers a *syn*-selective approach to 2-vinyl-1,3-diols, where the use of the non-chelating reducing agent, $LiBEt_3H$, reinforces the diastereogenic effect. The synthetic applications as well as the complementary *anti*-selective reduction are presented in the accompanying paper.

Acknowledgments: The authors are grateful to Prof. H. Yamamoto and Dr. K. Maruoka, Nagoya Univ., for the fruitful collaboration for the development of the new rearrangement reaction of the epoxyalcohol derivatives.

References and Notes

1) For the importance of the stereoselective synthesis of 1,2- and 1,3-diols, see, S. Masamune & W. Choy, Aldrichimica Acta, 15, 47 (1982). For chelation vs non-chelation control, see M. T. Reetz, Angew. Chem., Int. Edn. Engl., 23, 556 (1984).

2) a) B: K. Narasaka & F.-C. Pai, Tetrahedron, 40, 2233 (1984). b) Zn: T. Oishi & T. Nakata, Acc. Chem. Res., 17, 338 (1984). c) Al: S. Kiyooka, H. Kuroda, & Y. Shimasaki, Tetrahedron Lett., 27, 3009 (1986).

3) This arbitrary numbering is used throughout the discussions in this paper.

4) K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki, & G. Tsuchihashi, J. Am. Chem. Soc., 108, 3827 (1986).

5) a) K. Suzuki, E. Katayama, & G. Tsuchihashi, Tetrahedron Lett., 25, 2479 (1984); b) K. Suzuki, E. Katayama, K. Tomooka, T. Matsumoto, & G. Tsuchihashi, ibid., 26, 3707 (1985); c) K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, & G. Tsuchihashi, J. Am. Chem. Soc., 108, 5221 (1986).

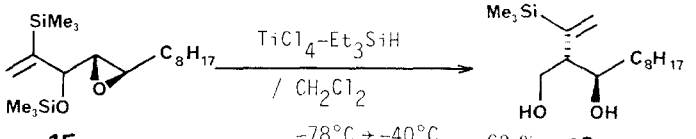
6) Herein, the term "steric effect" is used as the antonym of "chelation effect", without refer to the true origin of the effect. For the possible involvement of the orbital control in the present vinylsilane-directed stereoselection, see refs. 5a) and 11b).

7) Facilitation of the 1,2-rearrangement by the TMS-substituent, see K. Suzuki, E. Katayama, & G. Tsuchihashi, Tetrahedron Lett., 25, 1817 (1984).

8) All new compounds were fully characterized by 400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, IR and high-resolution mass spectra.

9) a) H. C. Brown, S. C. Kim, & S. Krishnamurthy, J. Org. Chem., 45, 1 (1980). b) N. M. Yoon & Y. S. Gyoung, ibid., 50, 2443 (1985).

10) Structural assignments of the diols are based on the coupling constants of their acetonides or carbonates.[8] Samples of the minor isomers were obtained by the TLC separation (11/12 and 13/14) or by the reductive rearrangement (for 10: eq. 2).[4] An isomeric mixture of 13/14 (=4/1) was prepared by reducing 8 with $LiAlH_4$ in refluxing THF.



15 63 % 10 (eq. 2)

11) a) M. Chérest, H. Felkin, & N. Prudent, Tetrahedron Lett., 1968, 2199. b) N. T. Anh & O. Eisenstein, Nouv. J. Chim., 1, 61 (1977).

12) We presume that $LiBEt_3H$ reduces the aldol itself, whereas another path competes in DIBAL cases, the prior aldolate formation followed by the H^- attack, judging from the markedly different rates of the alcoholysis of these reductants. Upon reaction with sec-BuOH (1 equiv/THF, -78°C, 5 min), the H_2 evolutions were ~100% (DIBAL) and <5% ($LiBEt_3H$). Besides the difference of the Lewis acidities, the extent of the aldolate formation may partly contribute to the difference of the chelating properties of these reagents.

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