# Acyclic Stereoselection using Relative 1,2-Asymmetric Induction. A Convenient Method for the Stereoselective Construction of α,γ-Dimethyl-α,β-dihydroxy Compounds, Useful Intermediates for Synthesis of Erythronolides

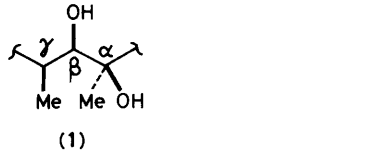
**Ashis K. Samaddar, Tsunehisa Chiba, Yuichi Kobayashi, and Fumie Sato***

*Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan*

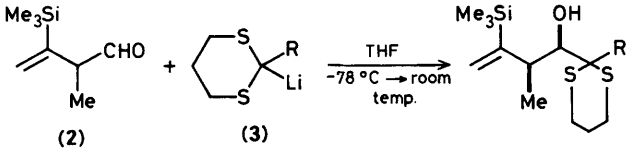
Highly stereoselective addition of dithiane anions with 2-methyl-3-trimethylsilylbut-3-enal combined with the stereoselective addition of Grignard reagents to chiral α-alkoxyketones affords a practical and efficient method for the construction of the title compounds.

Stereochemical construction in acyclic systems is of great importance for the total synthesis of macrolide and ionophore antibiotics. Although quite a number of elegant approaches have been developed and some of these have led to the completion of several total syntheses,[1] the investigation of new synthetic methodologies to achieve promising practical routes in this area is still being actively pursued. Stereoselective construction of the structural unit having the configuration shown in (**1**) is of considerable value in the synthesis of erythronolides.[2]

Recently, we reported that racemic and also optically active 2-methyl-3-trimethylsilylbut-3-enal (**2**) reacts with Grignard reagents[3,4] and enolate anions[5] highly selectively to afford the corresponding *syn* addition products.[6] Because of the versatility and reactivity of the vinylsilane moiety, such adducts could be used to achieve an extension in acyclic chain systems. In this communication, we report that dithiane anions also add to the aldehyde (**2**) with extremely high stereoselectivity. This can be successfully applied to the known observation that chiral α-alkoxyketones undergo reaction with Grignard reagents selectively,[7] to achieve an efficient strategy for the stereoselective construction of (**1**).

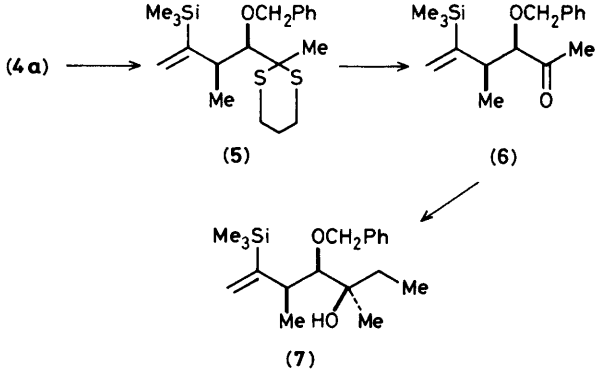


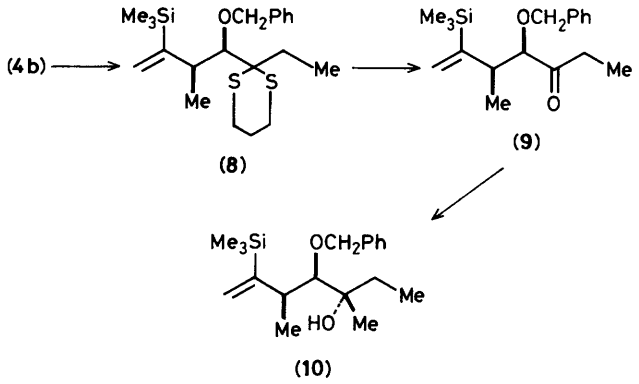

(1)




**a**; R = Me
**b**; R = Et
**c**; R = H

Carbanion (**3a**) generated from 2-methyl-1,3-dithiane by the action of Bu$^n$Li was treated with (**2**) at −78 °C in tetrahydrofuran (THF) with excellent selectivity (>99%) to furnish the adduct (**4a**) in 83% yield. $^1$H and $^{13}$C n.m.r. spectra of the product were homogenous indicating 'Cram' product (**4a**) as the only product formed. This was further confirmed by conversion of (**4a**) into *syn*-4-methyl-5-trimethylsilylhex-5-en-3-ol by desulphurization with Raney nickel.[8] The $^1$H n.m.r. spectrum of the product was compared with that of an authentic sample prepared by the reaction of (**2**) with ethylmagnesium bromide.[3] No *anti*-isomer was detected by g.l.c. analysis. Similarly, 2-ethyl-1,3-dithiane and 1,3-dithiane anions (**3b**) and (**3c**) also reacted with (**2**) to provide the corresponding *syn*-adducts (**4b**) and (**4c**) exclusively in 91 and 84% yields, respectively.






The compound (**4a**) was protected to (**5**) with benzyl bromide in the presence of NaH in THF (83% yield). The resultant (**5**) was changed to the ketone (**6**) (70%) by treatment with $HgCl_2$–$CaCO_3$ in 80% aqueous acetonitrile.[9] The Grignard addition reaction of (**6**) with ethylmagnesium bromide in diethyl ether at −78 °C afforded only the α,β-*syn*-isomer (**7**) (judged by $^1H$ and $^{13}C$ n.m.r. spectra);† no detectable amount of the α,β-*anti*-isomer was observed (*vide infra*). As illustrated by Still *et al.*,[7] the configuration of this product should be as shown in structure (**7**) assuming a cyclic transition state model in which the nucleophile added to the less hindered face of a chelated carbonyl. The α,β-*anti*-isomer of (**7**) was prepared exclusively by the reaction of the ketone (**9**) [obtained from the reaction of (**2**) with (**3b**)] with methylmagnesium bromide in diethyl ether; the $^{13}C$ n.m.r. spectrum of this compound, (**10**),† was completely different from that of (**7**). It is noteworthy that in contrast to the observation of Still *et al.*,[7] Grignard reagents add to chiral α-alkoxyketones such as (**6**) and (**9**) highly selectively even in diethyl ether.

† The $^{13}C$ n.m.r. spectra ($CDCl_3$) of (**7**) and (**10**) are as follows: (**7**) δ −0.5, 8.2, 15.9, 22.2, 33.0, 39.0, 76.0, 76.1, 85.0, 125.5, 127.3, 127.5, 128.4, 138.7, 156.5. (**10**) δ −0.4, 7.8, 17.1, 24.0, 30.8, 39.8, 75.9, 76.1, 86.6, 125.5, 127.3, 127.4, 128.3, 138.7, 157.2.

In conclusion, we succeeded in a highly stereoselective construction of (**1**). This method can be effectively used for the preparation of either α,β-*syn*-β,γ-*syn*- or α,β-*anti*-β,γ-*syn*-α,γ-dimethyl-α,β-dihydroxy compounds. The configuration of the β-hydroxy group can be inverted easily by oxidation followed by reduction[3] and hence this reaction sequence can be used for the preparation of all the diastereoisomers of the title compounds.

*Received, 12th November 1984; Com. 1597*

## References

1 J. D. Morrison, 'Asymmetric Synthesis, Vol. 3, Stereodifferentiating Addition Reactions, Part B,' Academic Press, New York, 1984; D. A. Evans, J. V. Nelson, and T. R. Taber, *Top. Stereochem.*, 1982, **13**, 1; D. A. Evans, *Aldrichimica Acta*, 1982, **15**, 23; S. Masamune and W. Choy, *ibid.*, 1982, **15**, 47; C. H. Heathcock, in 'Current Trends in Organic Synthesis,' ed. H. Nozaki, Pergamon Press, New York, 1983, p. 27.
2 Recent publications in this area: E. Vedejs, J. M. Dolphin, and H. Mastalerz, *J. Am. Chem. Soc.*, 1983, **105**, 1271; I. Paterson, S. K. Patel, and J. R. Porter, *Tetrahedron Lett.*, 1983, **24**, 3395; Y. Oikawa, T. Nishi, and O. Yonemitsu, *ibid.*, p. 3635.
3 F. Sato, M. Kusakabe, and Y. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1984, 1130.
4 Y. Kobayashi, Y. Kitano, and F. Sato, *J. Chem. Soc., Chem. Commun.*, 1984, 1329.
5 F. Sato, M. Kusakabe, T. Kato, and Y. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1984, 1331.
6 The stereoconfiguration was classified as '*syn*' and '*anti*' according to the definition of Masamune: S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 557; S. Masamune, T. Kaiho, and D. S. Garvey, *J. Am. Chem. Soc.*, 1982, **104**, 5521.
7 W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, 1980, **21**, 1031.
8 H. R. Billica and H. Adkins, *Org. Synth.*, Coll. Vol. III, 1955, p. 176.
9 E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 1975, 2643.