HETEROCYCLES, Vol. 54, No. 2, pp. 585-588, Received, 12th June, 2000

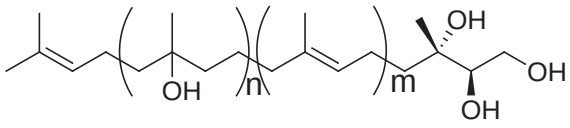
# DIASTEREOCONTROL IN THE REACTION OF (*R*)-2,2-DIMETHYL-4-ACYL-1,3-DIOXOLANES WITH ALKYLMETALS: A FACILE ENTRY TO ENANTIOPURE TERPENETRIOLS[#]

**Hisashi Mikoshiba, Koichi Mikami, and Takeshi Nakai***

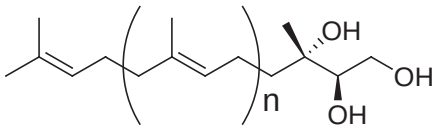
Department of Applied Chemistry, Tokyo Institute of Technology,
Meguro-ku, Tokyo 152-8552, Japan

*Abstract*-The reactions of the 4-acetyldioxolane with terpenoid Grignard reagents are shown to proceed predominantly through the α-chelation model to give the *syn*-triol derivatives in ~70% selectivity. A novel and efficient protocol to effect the stereoselective methylation onto the terpenoid-derived 4-acyldioxolanes has been developed which affords the desired *anti*-terpenetriols in high stereopurities.

In conjuntion with the asymmetric synthesis of gymnoprenols (**1**)[1] and terpenetriols (**2**)[2] which have attracted much interest as water-soluble hydrated terpenoids, we became intrigued by the reactions of (*R*)-2,2-dimethyl-4-acyl-1,3-dioxolanes (**3**, "glycerketone acetonides") with organometallic reagents (Scheme 1). However, the stereochemistry of the organometallic addition reaction onto ketone (**3**) remains largely unexplored, while the similar addition reaction onto glyceraldehyde acetonide has been extensively studied and highly stereoselective protocols have been developed which afford either the *syn*- or *anti*-adducts.[3] Disclosed herein are the stereochemical feature of the addition reaction of ketone (**3**) with alkylmetals and a novel procedure which affords the desired *syn*-terpenetriols in highly diastereofacial selectivity.

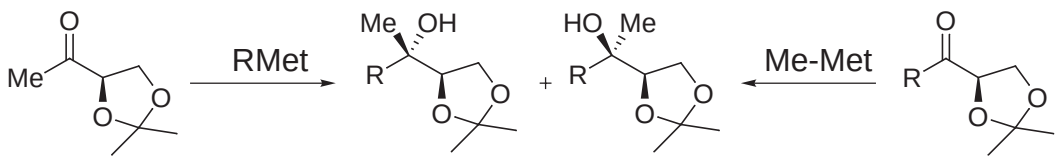



**1**, n=5-6, m=2




**2a,** n=0; **2b,** n=1

**Scheme 1**

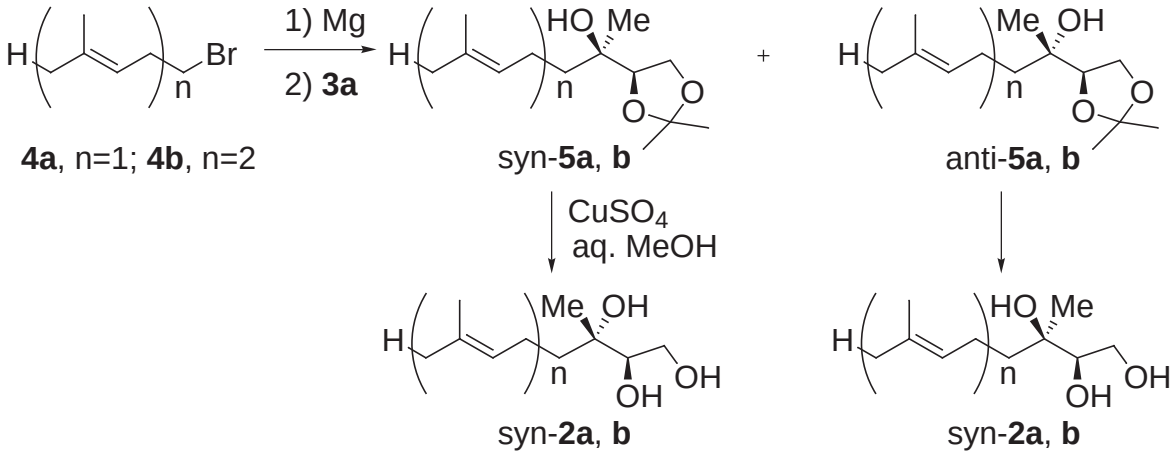



**3a** anti (R>Me) syn **3b~d**

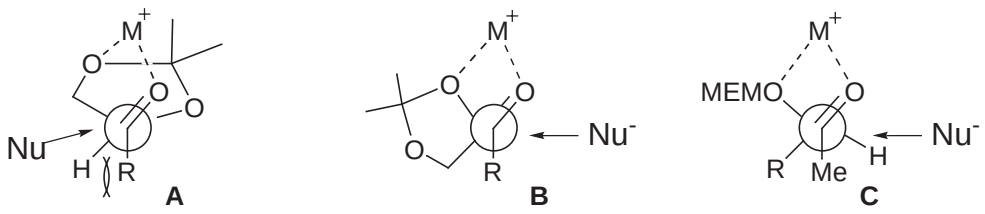
[#] Dedicated to Professor Sho Ito on the occasion of his 77th birthday.

At first, we examined the diastereoselectivity of the methyl ketone (**3a**)[4] with the Grignard reagents prepared *in situ* from homoprenyl bromide (**4a**) and homogeranyl bromide (**4b**) (Scheme 2). Thus, the Grignard reagent generated from **4a** in THF reacted with **3a** in THF at –70 ℃ to afford 80% yield of the tertiary alcohol (**5a**) as a 70 : 30 mixture of the diastereomer as determined by NMR analyses.[5] Hydrolysis of the mixture gave the terpenetriol (**2a**) as a mixture of the diastereomers which are distinguishable by $^1$H NMR spectrum ($CDCl_3$). On the basis of comparison of the observed δ-values due to the 3-Me with the reported values,[1c,d] the major diastereomer (δ 1.13) was assigned to the undesired *syn*-isomer with (3*R*)-configuration, and the minor one (δ 1.20) to the desired *anti*-isomer with (3*S*)-configuration. A similar reaction of **3a** with the **4b**-derived Grignard reagent provided a diastereomeric mixture of adduct (**5b**) in the same ratio (70:30), again, favoring the undesired *syn*-isomer.[6]

**Scheme 2**



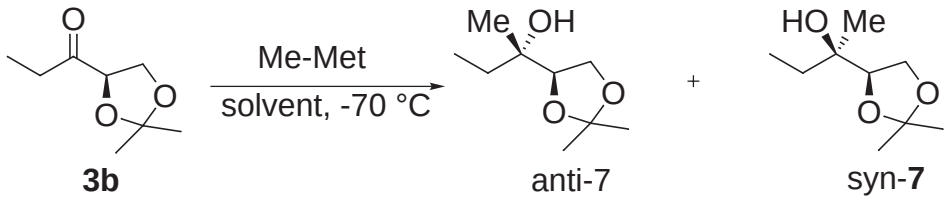

The stereochemical trend is of mechanistic interest, since the predominant formation of the *syn*-isomers in the present Grignard reactions is in stark contrast to the selective formation of the *anti*-isomer often observed in similar additions onto glyceradehyde acetonide (**6**),[3] thus revealing that the steric courses of the two reactions are different. While the *anti*-selective additions onto aldehyde (**6**) have been well rationalized in terms of the β-chelation model (**A**) (R=H), the *anti*-selectivity observed in the present additions onto ketone (**3a**) is best explained as a result of the α-chelation model (**B**) (R=Me), similar to the α-chelation model (**C**) previously proposed for the *syn*-selective Grignard reaction onto α-(methoxymethoxy)alkyl methyl ketones.[7] Thus, it appears likely that the β-chelation species (**A**) (R=Me) involved in the present reaction would suffer the steric repulsion between the methyl and 4-hydrogen as depicted below.




With the general stereochemical trend in mind, we next turned our attention to the methylation reactions of

4-acyldioxolanes (**3**) other than **3a** using a variety of methyl-organometallic reagents. Thus, we first examined the reaction of the ethyl ketone (**3b**)[8] with a series of methyl-metallic species as a model reaction (Scheme 3). As expected, the simple additions of MeMgBr and MeLi resulted in the selective formation of the desired *anti*-**7**,[9] although the selectivity was still moderate. Unfortunately, most of the combined uses of MeLi/Lewis acid examined did not provide increased selectivity, while the addition of $ZnI_2$ led to the opposite selectivity. Interestingly, the reaction with the cuprate species showed slightly enhanced selectivity. Most significantly, the combined use of MeLi (4.0 equiv.) and $SnCl_4$ (1.0 equiv.) in dichloromethane was found to provide over 95% of *anti*-selectivity . This novel methylation protocol deserves special comment. The use of a large excess of MeLi relative to $SnCl_4$ and the use of dichloromethane as solvent are essential for obtainig high yield and/or selectivity. While the exact role of $SnCl_4$ is unclear at present, it seems that it not only coordinates to the ketone to form the α-chelated species, but also reacts with MeLi at least partially to generate a new Me-metallic species, thus leading to the high anti-selectivity.

**Scheme 3**



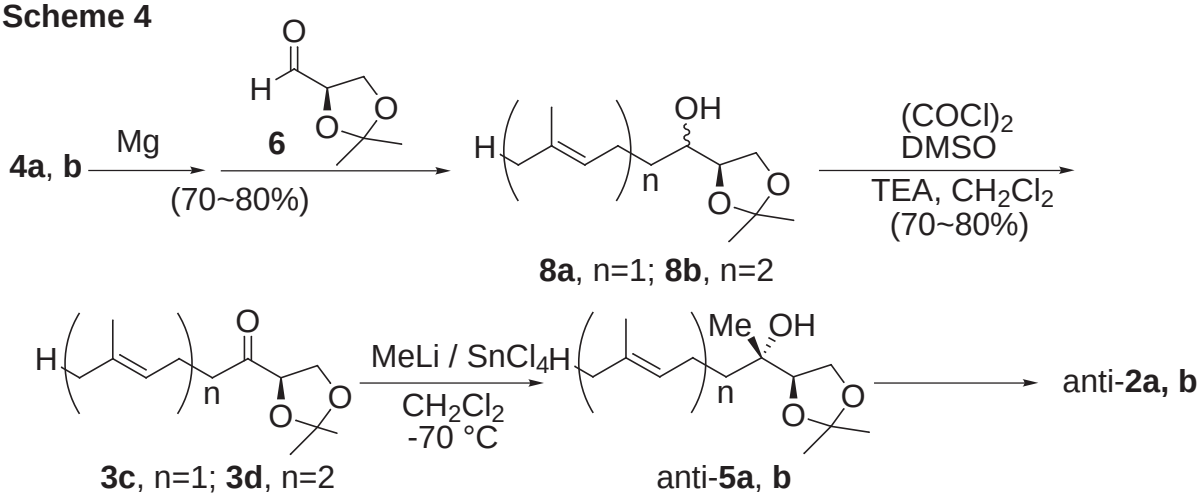

**3b** anti-7 syn-**7**

"Me-metal"(solvent, %yield, anti/syn): MeMgBr (THF, >95%, 81:19); MeLi (THF, >95%, 81:19); MeLi/$ZnI_2$ (THF, >95%, 40:60); MeLi/$BF_3OEt_2$ (ether, 96%, 61:39); MeLi/$TiCl_4$ (toluene, 30%, 81:19); MeLi/Ti(O-*i*-Pr)$_4$ ($CH_2Cl_2$, 80%, 85:15); $Me_2CuLi$ (THF, 83%, 90:10); MeLi/$SnCl_4$ ($CH_2Cl_2$, 91%, >95:<5).

With the newly-developed methylation protocol in hand, we next carried out the stereocontrolled synthesis of terpenetriols *via* methylation of the terpenoid-derived 4-acyldioxolanes (**3c** and **3d)** (Scheme 4). Thus, the requisite ketone (**3c**)[10] was prepared *via* reaction of glyceraldehyde (**6**)with the Grignard reaction generated from bromide (**4a**) followed by the Swern oxidation of the resulting alcohol (**8**).[10] Application of the methylation protocol using MeLi/$SnCl_4$ to ketone (**3c**) was found to afford the *anti*-isomer of **5a** as the single stereoisomer as judged from $^1H$ and $^{13}C$ NMR comparisons[5] with the *syn*-enriched mixture obtained above; any appreciable amount of *syn*-**5a** was not detected in the spectra. Indeed, deprotection of **5a** furnished the desired *anti*-terpenetriol (**2a**) in diastereo- and enantiomerically pure form. Further application of the methylation protocol to ketone (**3d**),[10] prepared analogously from glyceraldehyde (**6**) and bromide (**4b**), provided *anti*-**5b**, again, as the single stereoisomer.[6] Hydrolysis of **5b** afforded the desired *anti*-terpenetriol (**2b**) in high diastereo- and enantio-purity.

In summary, we have shown that the reaction of (*R*)-acyl-1,3-dioxolanes (**3**) with alkylmetals proceeds predominantly through the α-chelation model, in contrast to the β-chelation model previously proposed for most of the similar reactions of glyceraldehyde acetonide. Furthermore, a highly *anti*-diastereoselective

**Scheme 4**




protocol for the methylation onto ketones (**3**) has been developed and successfully applied to the highly stereocontrolled synthesis of *anti*-terpenetriols (**2**). Further application of the novel methylation protocol for the asymmetric synthesis of other tertiary alcohols is in progress.


## ACKNOWLEDGMENT

We are grateful to Drs. M. Shiono and Y. Fujita of Kuraray Co. for the gifts of bromides (**4a, b**) and their helpful discussions.


## REFERENCES AND NOTES


1. a) Isolation: S. Nozoe, Y. Koike, E. Tsuji, G. Kusano, and H. Seto, *Tetrahedron Lett.*, 1983, **24**, 1731. b) Partial synthesis: S. Nozoe, Y. Koike, and G. Kusano, *Ibid.*, 1984, **25**, 1371. c) R. M. Hanson, *Ibid.*, 1984, **25**, 3783. d) S. Nozoe, T. Ohta, T. Koike, and G. Kusano, *Ibid.*, 1984, **25**, 4023.
2. S. Suzuki, Y. Fujita, Y. Kobayashi, and F. Sato, *Tetrahedron Lett.*, 1986, **27**, 69, and references cited therein.
3. G. J. McGarvey, M. Kimura, T. Oh, and J. M. Williams, *J. Carbohydrate Chem.*, 1984, **3**, 125.
4. E. Baer and H. O. L. Fisher, *J. Biol. Chem.*, 1939, **128**, 463. bp 43 °C/5 mmHg; $[\alpha]_D$ +74.7° (*c* 1.56, $CHCl_3$, 20 °C).
5. $^1$H NMR ($CDCl_3$): the δ-value for 3-Me, 1.08 (major) and 1.20 (minor). $^{13}$C NMR ($CDCl_3$): the peaks due to 1-, 2-, and 3-C; 64.7, 81.0, 72.2 ppm (major) and 64.6, 81.4, 71.5 ppm (minor).
6. The stereochemical assignment was made by the NMR similarity: the δ-value for 3-Me, 1.08 (major) and 1.20 (minor); the δ-values for 1-, 2- and 3-C, 64.9, 81.1, 71.3 (major) and 64.7, 81.5, 71.7 (minor).
7. W. C. Still and J. R. McDonald, III, *Tetrahedron Lett.*, 1980, **21**, 1031.
8. Prepared *via* reaction of aldehyde (**6**) with EtMgBr followed by the Swern oxidation in 73% yield.
9. The two isomers were distinguishable by $^1$H NMR: the δ-value for 3-Me, 1.03 (syn) and 1.19 (anti).
10. The $^1$H NMR spectrum is in agreement with the assigned structure.