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

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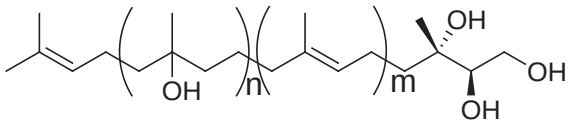
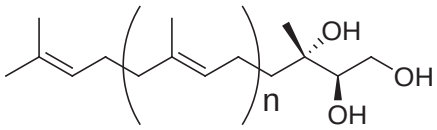
Abstract-The reactions of the 4-acetyldioxolane with terpenoid Grignard reagents are shown to proceed predominantly through the α-chelation model to give the *syn*-triol derivatives in ~70% selectivity. A novel and efficient protocol to effect the stereoselective methylation onto the terpenoid-derived 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.

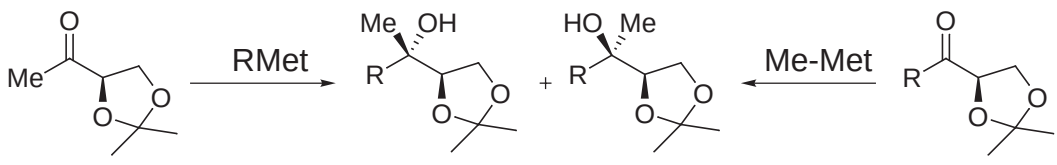


1, n=5-6, m=2



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

Scheme 1

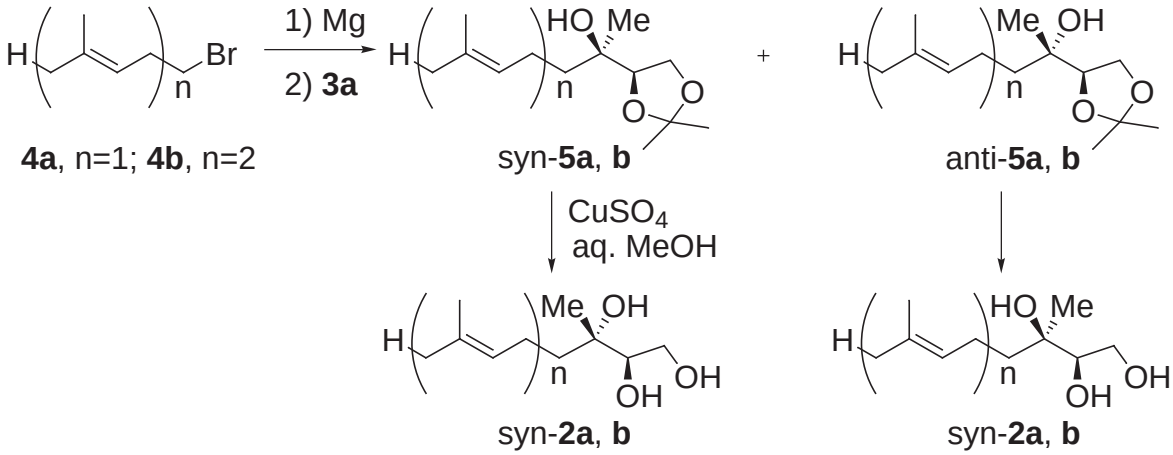


3a anti (R>Me) syn **3b~d**

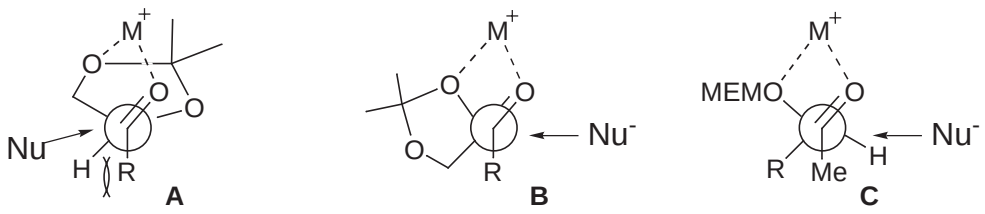
[#] Dedicated to Professor Sho Ito on the occasion of his 77th birthday.

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



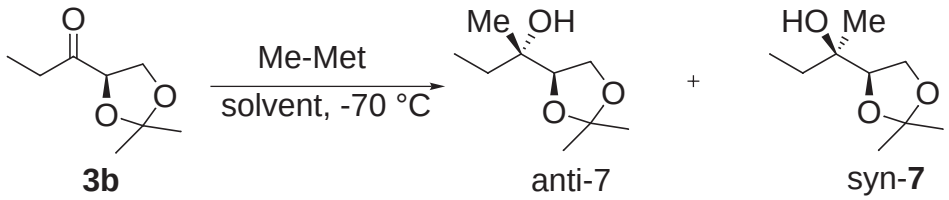
The stereochemical trend is of mechanistic interest, since the predominant formation of the *syn*-isomers in the present Grignard reactions is in stark contrast to the selective formation of the *anti*-isomer often observed in similar additions onto glyceradehyde acetonide (**6**),[3] thus revealing 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



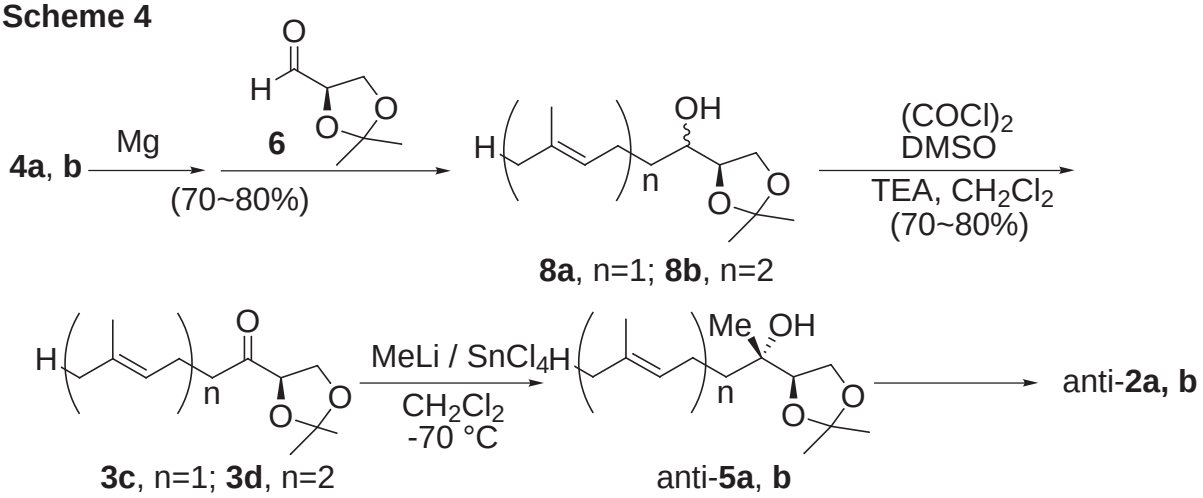
3b anti-7 syn-**7**

"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.