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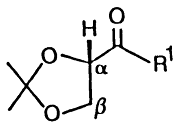
Diastereoselective Addition of Organometallics to 3,4-*O*-Isopropylidene-L-*glycero*-2-tetrulose Derivatives

Hajime NAGANO,* Mina OHNO, and Yoko MIYAMAE
Department of Chemistry, Faculty of Science,
Ochanomizu University, Otsuka, Bunkyo-ku, Tokyo 112

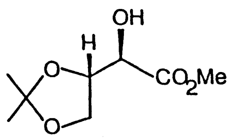
Diastereoselectivity in the addition of Grignard reagents (RMgX) to 1-*O*-benzoyl-3,4-*O*-isopropylidene-L-*glycero*-2-tetrulose and 3,4-*O*-isopropylidene-1-*O*-triphenylmethyl-L-*glycero*-2-tetrulose (**2**) depended remarkably on X, R, and the reaction temperature. The addition of EtMgBr, *i*-PrMgBr, and BuMgCl to **2** at 0 °C gave (2*R*,3*S*)-adducts with high diastereoselectivity (≧ 94% de).

Chiral tertiary alcohols are quite frequent in nature and a number of methods for their synthesis has been developed. In particular highly diastereoselective chelation controlled nucleophilic addition of Grignard reagents to α-chiral α-alkoxy ketones is an efficient method for the synthesis of chiral tertiary alcohols.[1)] The usefulness of this method would be enhanced if diastereoselectivity could be controlled even in the presence of an additional α'-oxygen containing function. To our knowledge, however, very few investigations on the diastereoselectivity in the nucleophilic addition to α-chiral α,α'-dialkoxy ketones have been reported.[2)] We now wish to report the diastereoselectivity in the nucleophilic addition of organometallics to 1-*O*-benzoyl-3,4-*O*-isopropylidene-L-*glycero*-2-tetrulose (**1**)[3)] and 3,4-*O*-isopropylidene-1-*O*-triphenylmethyl-L-*glycero*-2-tetrulose (**2**),[4)] i.e., ketones having an α asymmetric center and α-, β-, and α'-oxygen substituents.

Compound **1** was prepared from methyl 3,4-*O*-isopropylidene-L-threonate (**3**)[5)] [(i) $LiAlH_4$ (77%), (ii) PhCOCl (58%), and (iii) $CrO_3 2pyr$ (90%)].



1 $R^1 = CH_2OCOPh$
2 $R^1 = CH_2OCPh_3$
17 R^1= alkyl, aryl



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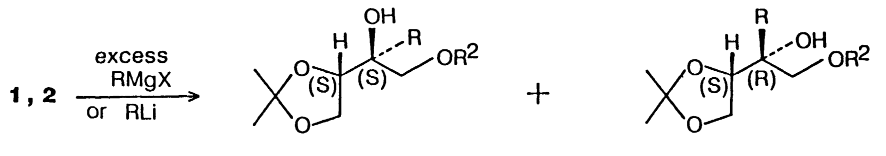
The results of the nucleophilic addition of Grignard reagents and alkyllithiums to ketones **1** and **2** are summarized in Table 1.

Table 1. Nucleophilic addition of RMgX and RLi to ketones **1** and **2**

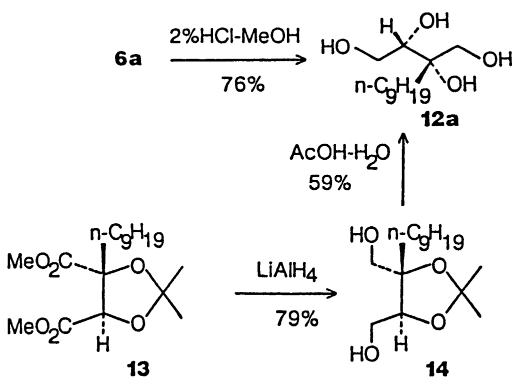


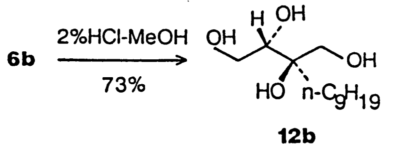
4a - 11a **4b - 11b**

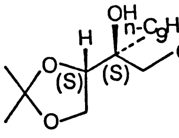
Entry	Ketone	RMgX RLi	Solvent	Temp °C	Product	R^2	Yield[a)] %	Diastereomer ratio (2*S*) : (2*R*)
1	**1**	MeMgI	ether	-78	**4a**, **4b**	COPh	89	62 : 38
2	**1**	EtMgI	ether	-78	**5a**, **5b**	COPh	61	77 : 23
3	**1**	EtMgBr	ether	-25	**5a**, **5b**	COPh	89	40 : 60
4	**1**	*n*-C_9H_{19}MgBr	ether	-78 → 0	**6a**, **6b**	H	81	68 : 32
5	**1**	MeLi	THF	-100	**7a**, **7b**	H	74	79 : 21
6	**2**	MeMgBr	b)	-78	**8a**, **8b**	CPh_3	92	16 : 84
7	**2**	MeMgBr	b)	0	**8a**, **8b**	CPh_3	93	28 : 72
8	**2**	EtMgI	ether	-78	**9a**, **9b**	CPh_3	89	53 : 47
9	**2**	EtMgI	ether	0	**9a**, **9b**	CPh_3	100	12 : 88
10	**2**	EtMgBr	ether	-78	**9a**, **9b**	CPh_3	86	11 : 89
11	**2**	EtMgBr	ether	0	**9a**, **9b**	CPh_3	94	3 : 97
12	**2**	*i*-PrMgI	ether	-78	**10a**, **10b**	CPh_3	75	2 : 98
13	**2**	*i*-PrMgI	ether	0	**10a**, **10b**	CPh_3	82	2 : 98
14	**2**	*i*-PrMgBr	ether	0	**10a**, **10b**	CPh_3	74	1 : 99
15	**2**	BuMgI	ether	-78	**11a**, **11b**	CPh_3	84	10 : 90
16	**2**	BuMgBr	ether	-78	**11a**, **11b**	CPh_3	94	13 : 87
17	**2**	BuMgCl	ether	-78	**11a**, **11b**	CPh_3	82	5 : 95
18	**2**	BuMgCl	ether	0	**11a**, **11b**	CPh_3	96	2 : 98
19	**2**	MeLi	THF	-78	**8a**, **8b**	CPh_3	100	63 : 37
20	**2**	BuLi	THF	-78	**11a**, **11b**	CPh_3	100	45 : 55

a) Isolation yield. b) Ether-THF (82 : 18 v/v).

The stereochemistry of the tertiary alcohols **4** - **11** was determined as follows. Nucleophilic addition of nonylmagnesium bromide to ketone **1** gave diols **6a** and **6b** in 55% and 26% yields, respectively. These diols were then hydrolyzed separately to give tetraols **12a** and **12b**.[6] On the other hand reduction of dimethyl (2*R*,3*R*)-2,3-*O*-isopropylidene-2-nonyltartrate (**13**) (96% ee)[7] with lithium aluminium hydride gave diol **14**. The diol was then hydrolyzed to give (2*S*,3*S*)-2-nonyl-1,2,3,4-butanetetraol, $[\alpha]_D$ - 8.7°, which was identical with the major tetraol **12a**, $[\alpha]_D$ - 8.9°. The stereochemistry of the diastereomeric pairs **4**, **5**, and **7** - **11** was determined in comparing their ^{13}C-NMR spectra with those of **6**, **15**, and **16**.[8] The diastereomer ratios were deduced by the integrations of ^{13}C-NMR spectra (entries 1 - 3, 5, 15, 16, 19, and 20) and/or HPLC analysis (entries 6 - 18).

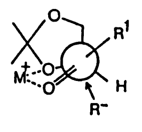






15a R^2= COPh

16a R^2= CPh$_3$



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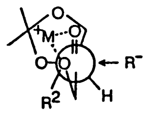
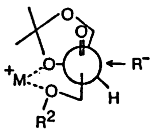
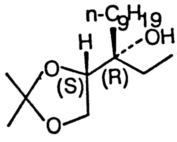


B



C



15b R^2= COPh

16b R^2= CPh$_3$

While the addition of Grignard reagents to ketones **17** occurs stereoselectively *via* chelation of α-oxygen (**A**),[1,9] the diastereoselectivity in the reaction of **1** and **2** where the oxygen functions compete chelation depended remarkably on the halides (X), the bulk of alkyl (R) groups, and the reaction temperature. In the addition of MeMgI and EtMgI to ketone **1** (entries 1 and 2) and EtMgI to ketone **2** (entry 8) at - 78 °C were yielded (2*S*,3*S*)-diastereomers as the major products although the selectivity was low. These major alcohols may be yielded *via* chelate **B** (a variant of Felkin-Ahn model) and/or chelate **C** where the α'-oxygen carrying a benzoyl or a triphenylmethyl group participates in chelation. On the contrary, the stereoselectivity was reversed in the Grignard reactions of **2** shown in entries 6, 7, and 9 - 18. The α'-oxygen carrying a bulky triphenylmethyl group may be prevented to participate in chelation (**B** and **C**)[2] and the reactions may proceed *via* chelate **A** to give (2*R*,3*S*)-diastereomers. The proportion of (2*R*,3*S*)-diastereomers increased in the order of RMgI, RMgBr, and RMgCl. Furthermore, it was revealed that the reactions at 0 °C gave rise to higher selectivity than did the reactions at - 78 °C (entries 8 *versus* 9, 10 *versus* 11, and 17 *versus* 18). The formation of chelate **A** in ether may be favored at 0 °C over at - 78 °C.

Addition MeLi to **1** and **2** (entries 5 and 19) and BuLi to **2** (entry 20) did not show useful diastereoselectivity.

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2) S. V. Frye and E. L. Eliel, Tetrahedron Lett., 27, 3223 (1986).

3) Compound **1**: mp 58.5-59.0 °C; $[\alpha]_D^{26}$ - 83.2° (c 0.99, $CHCl_3$); IR(Nujol) 1750 and 1725 cm^{-1}; ^1H-NMR($CDCl_3$, 270 MHz) δ 8.09 (2H, d, J = 7.9 Hz), 7.58 (1H, t, J = 7.9 Hz), 7.46 (t, J = 7.9 Hz), 5.24 (1H, d, J = 17.5 Hz), 5.16 (1H, d, J = 17.5 Hz), 4.61 (1H, dd, J = 7.8 and 5.6 Hz), 4.22 (2H, m), 1.55 (3H, s), and 1.42 (3H, s); ^{13}C-NMR($CDCl_3$) δ 203.25, 165.84, 133.36, 129.43, 111.37, 79.19, 66.79, 66.53, 25.93, and 24.72; MS m/z 249 (3%, M^+ - Me), 105 (52), and 101 (100).

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5) K.- C. Luk and C.- C. Wei, Synthesis, 1988, 226.

6) Tetraol **12a**: mp 62.5-63.5 °C; IR(Nujol) 3300 cm^{-1}; ^{13}C-NMR(acetone-d_6) δ 75.45, 75.38, 65.74, 63.32, 35.28, 32.64, 31.26, 30.45, 30.37, 30.08, 23.47, 23.33, and 14.36; MS m/z 217 (20%, M^+ - CH_2OH) and 43 (100). Tetraol **12b**: mp 63.0-63.5 °C; IR(Nujol) 3300 cm^{-1}; ^{13}C-NMR(acetone-d_6) δ 76.30, 75.56, 65.69, 63.43, 34.46, 32.63, 31.30, 23.54, 23.33, and 14.36; MS m/z 217 (13%, M^+ - CH_2OH) and 43 (100).

7) Y. Tokunaga, H. Nagano, and M. Shiota, J. Chem. Soc., Perkin Trans. 1, 1986, 581.

8) The following ^{13}C-NMR signals were compared. [Δδ = δ(2*S*,3*S*) - δ(2*R*,3*S*)]. Compounds **6** and **7**: $\Delta\delta(\mathrm{Me_2\underline{C}O_2}) > 0$, $\Delta\delta(C_3) > 0$, $\Delta\delta(C_2) < 0$, $\Delta\delta(C_4) > 0$, and $\Delta\delta(C_1) < 0$. Compounds **4**, **5**, and **15**: $\Delta\delta(\mathrm{Me_2\underline{C}O_2}) > 0$, $\Delta\delta(C_3) < 0$, $\Delta\delta(C_2) < 0$, $\Delta\delta(C_4) > 0$, and $\Delta\delta(C_1) < 0$. Compounds **8** - **11**, and **16**: $\Delta\delta(\mathrm{Me_2\underline{C}O_2}) > 0$, $\Delta\delta(\mathrm{O\underline{C}Ph_3}) < 0$, $\Delta\delta(C_3) < 0$, and $\Delta\delta(C_2) < 0$.

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