# Stereochemical differentiation in the reactions of organometallic reagents with levoglucosenone and some of its dihydro derivatives

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The reactions of methylmanganese iodide with levoglucosenone, its dihydro derivative, and 1,6-anhydro-3-deoxy-4-*O*-methyl-β-D-*erythro*-hexopyran-2-ulose were found to be highly diastereoselective compared to the reactions of Li-, Mg-, and Cu-based reagents. This specific feature of the manganese reagent is due to the enhanced tendency of manganese for chelation.

**Key words**: levoglucosenone, chelate control, organometallic reagent, diastereoselectivity.

In continuation of our studies[1,2] dealing with the diastereofacial selectivity of organomanganese reagents in reactions with carbonyl compounds, we investigated the reactions of methylmanganese iodide, similar lithium and magnesium derivatives, and copper "ate-complexes" with levoglucosenone (**1**) and its dihydro derivatives, *viz.*, 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hexopyran-2-ulose (**2**) and 1,6-anhydro-3-deoxy-4-*O*-methyl-β-D-*erythro*-hexopyran-2-ulose (**3**), and compared the diastereoselectivities of the corresponding reactions. The reaction products are compounds **4a,b**,[3] **5**,[3] **6a,b**,[3] and **7** (Scheme 1). Organic derivatives of $Mn^{II}$, like those of $Ti^{IV}$,[1,4] exhibit higher chelating capacity than organometallic reagents traditionally used for alkylation at a carbonyl group. This provides grounds for expecting a high degree of diastereoselectivity in reactions with substrates containing an α-ketoacetal fragment, capable of effective coordination to a metal.

$^{13}C$ NMR spectroscopy proved to be the most informative method for stereochemical identification of diastereomers. The criterion used to assign the products of methylation of levoglucosenone to the *erythro*-series is an upfield shift of the signals of C(2), C(5), and C(6) caused by the *syn*-interaction of the substituents at C(2)

**Scheme 1**

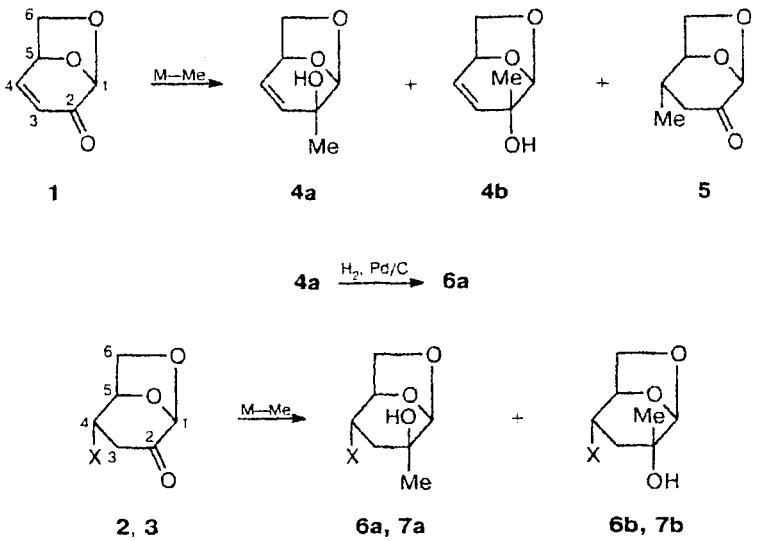


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**Table 1.** $^{13}C$ NMR chemical shifts for compounds **4**—**7** ($CDCl_3$, δ)

| Compound | C(1) | C(2) | C(3) | C(4) | C(5) | C(6) | Me |
|---|---|---|---|---|---|---|---|
| **4a** | 105.3 | 73.3 | 133.3 | 127.8 | 71.4 | 69.7 | 23.2 |
| **4b** | 104.9 | 68.6 | 131.8 | 128.7 | 70.6 | 68.7 | 21.0 |
| **5** | 101.5 | 200.7 | 36.0 | 38.7 | 77.8 | 68.0 | 18.7 |
| **6a** | 106.0 | 70.6 | 32.2 | 27.3 | 73.2 | 67.5 | 21.7 |
| **6b** | 105.5 | 70.0 | 29.7 | 25.6 | 72.7 | 67.2 | 23.9 |
| **7** | 106.0 | 70.0 | 35.7 | 76.6 | 74.2 | 66.0 | 23.3 |

and C(5). The possibility of this influence is supported by the results of MM+ molecular mechanics calculations performed using the HyperChem 5.01 program package (1996); according to these calculations, the distance between $H^{endo}(6)$ and the methyl group proton is sufficient for this and amounts to 3.4 Å. The validity of the assignment of signals of dihydro derivative **6a** is additionally confirmed by the fact that its spectrum is identical to that of the hydrogenation product obtained from individual *threo*-isomer **4a**. The ratio of *erythro*- and *threo*-isomers is retained during hydrogenation of the diastereomer mixture. It is of interest that the $^{13}C$ NMR signals for the methyl groups, which occur at 23.2 ppm in the *threo*-isomer **4a** and at 21.0 ppm in the *erythro*-isomer **4b**, are observed at 21.7 ppm and 23.9 ppm, respectively, after hydrogenation. This is consistent with general features[5,6] of shielding of substituents in a six-membered ring occurring in the $^1C_4$ conformation. After hydrogenation of the double bond in *threo*-isomer **4a**, the pyranose ring acquires the $^1C_4$ conformation and the methyl group occupies an axial position. This is accompanied by an upfield shift of the $CH_3$ signal in the $^{13}C$ NMR spectra. Correspondingly, upon hydrogenation of the double bond in *erythro*-isomer **4b**, the methyl group assumes an equatorial orientation, which results in a downfield shift of its $^{13}C$ NMR signal (Table 1).

The shielding effect of the anhydro bridge on the methyl-group protons is manifested in the $^1H$ NMR spectra of both methylated derivatives of levoglucosenone **4a,b** and their saturated analogs **6a,b**. Whereas the singlet due to the $CH_3$ group in *threo*-diastereomers **4a** and **6a** is exhibited at ~1.2 ppm, the signals for the methyl groups in *erythro*-isomers **4b**, **6b** are shifted upfield and occur at 1.18 ppm and 1.14 ppm, respectively (Table 2).

The reaction of levoglucosenone (**1**) with the Grignard reagent MeMgI proceeds diastereoselectively, regardless of the temperature (20 °C or −78 °C), to give *threo*-isomer **4a**[3] (Table 3). However, this process is not regiospecific; the content of the addition product **5** at −78 °C reaches 14%. At −20 °C, the yield of this compound is 6%.[3]

The reaction of MeLi with levoglucosenone (**1**) at −78 °C, which is the reference reaction regarding determination of the direction of the attack, occurs, as expected, regiospecifically but its stereoselectivity is relatively low and reverse to that observed with the Grignard reagent MeMgI; the *threo*-**4a** : *erythro*-**4b** ratio is ~45 : 55 (see Table 3). The use of MeMnI results in the stereospecific formation of a mixture of 1,2- and 1,4-addition products in 52 : 48 ratio. As in the case of MeMgI, raising the temperature (to −5 °C) resulted in a higher regioselectivity: the **4a** : **5** ratio increased to 24 : 1. The reaction of $LiCuMe_2$ proceeds as diastereospecific 1,4-addition, as opposed to a previous study[3]; no 1,2-addition products were detected.

Although approach of the chelating agent from the *Si*- and *Re*-sides is seemingly equivalent, the reaction

**Table 2.** $^1H$ NMR ($CDCl_3$) chemical shifts (δ) and spin-spin coupling constants (*J*/Hz) of compounds **4**—**7**

| Compound | δ (*J*/Hz) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | H(1) | OH | $H^{ax}(3)$ | $H^{eq}(3)$ | $H^{ax}(4)$ | $H^{eq}(4)$ | H(5) | $H^{exo}(6)$ | $H^{endo}(6)$ | $CH_3$ |
| **4a** | 5.13 d (2.0) | 2.68 br.s | 5.52 dd (2.0, 9.8) | | 5.90 dd (4.4, 9.8) | | 4.58 m | 3.64 dd (4.0, 6.7) | 3.72 d (6.7) | 1.20 s |
| **4b** | 5.17 d (2.0) | 2.51 br.s | 5.60 dd (2.0, 9.8) | | 5.98 dd (4.4, 9.8) | | 4.58 m | 3.60 m | | 1.18 s |
| **5** | 5.04 s | — | 2.80 dd (7.9, 16.2) | 2.04 dd (1.0, 16.2) | 2.30 ddd (1.0, 7.2, 7.9) | | 4.40 dd (1.0, 5.0) | 3.95 dd (5.0, 7.5) | 4.02 dd (1.0, 7.5) | 1.18 d (7.2) |
| **6a** | 4.98 s | 2.25 br.s | 1.85 ddd (5.5, 10.8, 11.4) | 1.68 dd (5.5, 11.4) | 1.72 ddd (5.5, 10.08, 13.0) | 1.54 dd (5.5, 13.0) | 4.50 br.s | 3.78 dd (2.0, 7.1) | 3.85 d (7.1) | 1.21 s |
| **6b** | 4.98 s | 2.68 br.s | 2.20 m | | 1.50—1.75 m (3H) | | 4.48 br.s | 3.76 m | 3.87 d (7.2) | 1.12 s |
| **7*** | 5.95 s 5.96 | 2.60 br.s | 1.60 dd (4.7, 14.7) | 1.96 d (14.7) | — — | 3.22 d (4.7) | 4.33 d (5.3) | 3.75 dd (5.3, 7.7) | 3.68 d (7.7) | 1.28 s |

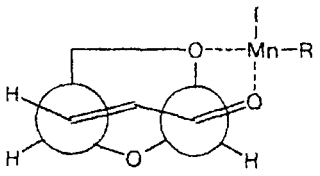
* The signal of OMe, δ 3.31 s (3 H); the integral intensities of signals correspond to expected values.

**Table 3.** Reactions of organometallic reagents with ketones **1**, **2**, and **3** ($Et_2O$, −78→20 °C, 3 h, 20 °C, 20 h, $[reagent]_0$ : $[substrate]_0$ = 1.5 : 1)

| Reagent | Substrate | Reagent products | Isomer ratio[a] (%) | | | Yield (%) |
|---|---|---|---|---|---|---|
| | | | **a** | **b** | **5** | |
| MeLi | **1** | **4a,b** | 45 | 55 | — | 94 |
| MeMgI | **1** | **4a,b** + **5** | 82 | 4 | 14 | 70 |
| MeMgI[b] | **1** | **4a,b** + **5** | 90 | 6 | 4 | 67 |
| MeMnI | **1** | **4a** + **5** | 52 | — | 48 | 67 |
| MeMnI[c] | **1** | **4a** + **5** | 96 | — | 4 | 68 |
| $LiCuMe_2$ | **1** | **5** | — | — | 100 | 75 |
| MeLi | **2** | **6a,b** | 63 | 37 | — | 82 |
| MeMgI | **2** | **6a,b** | 75 | 25 | — | 85 |
| MeMgI[b] | **2** | **6a,b** | 74 | 26 | — | 82 |
| MeMnI | **2** | **6a,b** | 92 | 8 | — | 69 |
| MeLi | **3** | **7a** | 100 | — | — | 78 |
| $LiCuMe_2$ | **3** | **7a** | 100 | — | — | 52 |
| MeMgI | **3** | **7a** | 100 | — | — | 70 |
| MeMnI | **3** | **7a** | 100 | — | — | 66 |

[a] According to $^1H$ NMR spectroscopy.
[b] The reaction was carried out at 20 °C.
[c] The reaction was carried out at −5 °C.

pathway is evidently governed by α-chelate control from the side of the oxygen atom of the anhydro bridge, which is located closer and is less shielded (according to MM+ calculations in the HyperChem 5.01 package (1996)). The alternative coordination of the reagent on the *Si*-side, to a more "stretched" fragment to give a five-membered cyclic transition state is unlikely, from the energy standpoint, for the rigid bicyclic structure of the 1,6-anhydro sugar. In this case, an increase in the coordination capacity of the reagent should increase the process diastereoselectivity and the content of the *threo*-isomer **4a**, due to the attack of the carbonyl group by the nucleophile from the side opposite to the anhydro bridge.[7]




Indeed, whereas the reaction of MeLi gives the Cram product with low diastereoselectivity, the reactions of levoglucosenone with MeMgI and MeMnI are termed diastereoselective and diastereospecific processes, respectively, with respect to the chelate control product. The slight predominance of the *erythro*-isomer in the case of MeLi is due to the fact that the equatorial attack is somewhat more preferred owing to the flattening of the pyran ring.[8] The inversion of the diastereoselectivity of the 1,2-addition of MeLi to dihydrogenated derivative **2** is due to the fact that the $^1C_4$ conformation is more susceptible to an axial attack; this is also facilitated by the antiperiplanar effect, which forces the more polar hydroxy group to an equatorial position[8,9] (*cf.* Ref. 10). The introduction of the methoxy group to C(4) adds a more rigorous stereocontrol factor; compound **3** is converted into the final product upon 1,3-diaxial interaction; no *erythro*-diastereomer **7b** was detected after the reaction with MeLi or even with $LiCuMe_2$, which is known[11] to be susceptible for β-chelation.

Thus, high diastereoselectivity of the 1,2-addition of MeMnI to levoglucosenone and some its derivatives, which must be due to the high chelating capacity of manganese, characterizes MeMnI as the most efficient reagent for this type of reaction.

## Experimental

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM 300 spectrometer (300.13 and 75.47 MHz, respectively) in $CDCl_3$ using $Me_4Si$ as the internal standard. IR spectra were measured on a UR-20 instrument in thin films. Optical rotation was measured on a Perkin—Elmer-141 instrument.

Carbonyl substrates **2** and **3** were synthesized from levoglucosenone using published procedures.[12,13] Known procedures were also used to prepare ethereal solutions of organolithium[14] and organomagnesium[15] compounds, $MnI_2$,[16] and $LiMe_2Cu$.[17] All the reactions were carried out under argon; $Et_2O$ was distilled over $LiAlH_4$ immediately before the reaction.

**Reaction of substrates 1, 2, and 3 with MeMnI (general procedure).** A 1.11 *M* ethereal solution of MeLi (2.72 mL, 3.02 mmol) was added with stirring and cooling to −10 °C to a suspension of $MnI_2$ (0.933 g, 3.02 mmol) in 8 mL of anhydrous $Et_2O$. The mixture was stirred for 30 min at −5 °C. After cooling the mixture to −78 °C, a solution of the corresponding ketone (2.02 mmol) in 5 mL of $Et_2O$ was added. The reaction mixture was stirred for 1 h at −78 °C, heated to −20 °C for 3 h, kept for 20 °C for an additional 20 h, and hydrolyzed with a saturated solution of $NH_4Cl$. The products were extracted with EtOAc (3×5 mL) and the combined extracts were dried with $MgSO_4$ and concentrated. The residue was chromatographed on $SiO_2$ (elution with hexane—AcOEt = 2 : 1, or 1 : 1 for compound **7a**).

**Reaction of substrates 1, 2, and 3 with MeLi (general procedure).** A 0.85 *M* ethereal solution of MeLi (2.36 mL, 2.01 mmol) was added with stirring and cooling to −78 °C to a solution of the corresponding ketone (1.34 mmol) in 8 mL of anhydrous $Et_2O$. The reaction mixture was stirred for 1 h at −78 °C, heated to 20 °C over a period of 3 h, kept at 20 °C for 20 h, and hydrolyzed with a saturated solution of $NH_4Cl$. The products were extracted with EtOAc (3×5 mL) and the combined extracts were dried with $MgSO_4$ and concentrated. The residue was chromatographed on $SiO_2$ (elution with hexane—AcOEt, 2 : 1, or 1 : 1 for compound **7a**).

**Reaction of substrates 1, 2, and 3 with MeMgI (general procedure).** A 2.44 *M* ethereal solution of MeMgI (1.04 mL, 2.5 mmol) was added with stirring and cooling to −78 °C to a solution of the corresponding ketone (1.7 mmol) in 8 mL of anhydrous $Et_2O$. The reaction mixture was stirred for 1 h at −78 °C, heated to 20 °C over a period of 3 h, kept at 20 °C for 20 h, and hydrolyzed with a saturated solution of $NH_4Cl$. The products were extracted with EtOAc (3×5 mL) and the combined extracts were dried with $MgSO_4$ and concentrated. The residue was chromatographed on $SiO_2$ (elution with hexane—AcOEt, 2 : 1, or 1 : 1 for compound **7a**).

**1,6-Anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*threo*-hex-3-enopyranose (4a)**, 36%, oil, $R_f$ 0.30 (hexane : AcOEt = 2 : 1),

$[\alpha]_D^{20}$ −78.2° (*c* 1.0, $CHCl_3$). IR, $\nu/cm^{-1}$: 830, 905 (C=C), 1010, 1140 (C—O—C), 3500 (OH).

**1,6-Anhydro-3,4-dideoxy-4-*C*-methyl-β-D-*erythro*-hexopyran-2-ulose (5)**, 31%, oil, $R_f$ 0.64 (hexane : AcOEt = 2 : 1), $[\alpha]_D^{20}$ −234.7° (*c* 1.0, $CHCl_3$). IR, $\nu/cm^{-1}$: 1010, 1130 (C—O—C), 1740 (C=O).

**1,6-Anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*threo*-hexopyranose (6a)** and **1,6-anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*erythro*-hexopyranose (6b)** were prepared as oils in a ratio of 92 : 8 to 63 : 37, $R_f$ 0.33 (hexane : AcOEt = 2 : 1), $[\alpha]_D^{20}$ −227.8° (for the 92 : 8 ratio) (*c* 1.0, $CHCl_3$). IR, $\nu/cm^{-1}$: 1010, 1130 (C—O—C), 3500 (OH).

**1,6-Anhydro-3-deoxy-2-*C*-methyl-4-*O*-methyl-β-D-*arabino*-hexopyranose (7a)**, oil, $R_f$ 0.40 (hexane : AcOEt = 1 : 1), $[\alpha]_D^{20}$ −80.0° (*c* 1.0, $CHCl_3$). IR, $\nu/cm^{-1}$: 1110, 1140 (C—O—C), 1750 (O—$CH_3$), 3400 (OH). Found (%): C, 54.6; H, 7.9. $C_8H_{14}O_4$. Calculated (%): C, 55.1; H, 8.0.

**1,6-Anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*threo*-hexopyranose (6a)** and **1,6-anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*erythro*-hexopyranose (6b).** 5% Pd/C (0.011 g) was added to a solution of a 7 : 3 mixture of **4a** and **4b** (0.22 g, 1.53 mmol) in 15 mL of anhydrous AcOEt and the mixture was stirred in a hydrogen atmosphere. After completion of the reaction (TLC monitoring), the reaction mixture was filtered off, the filtrate was concentrated, and the residue was chromatographed on $SiO_2$ (hexane : AcOEt = 2 : 1) to give a mixture of **6b** and **6a** in 7 : 3 ratio and in 95% yield, $[\alpha]_D^{20}$ −270.2° (*c* 1.0, $CHCl_3$).

## References


1. A. N. Kasatkin, R. Kh. Biktimirov, I. P. Podlipchuk, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 178 [*Russ. Chem. Bull.*, 1993, **42**, 161 (Engl. Transl.)].
2. A. N. Kasatkin, R. Kh. Biktimirov, I. P. Podlipchuk, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1122 [*Russ. Chem. Bull.*, 1993, **42**, 1078 (Engl. Transl.)].
3. F. Shafizaden and P. P. S. Chin, *Carbohydr. Res.*, 1977, **58**, 79.
4. M. T. Reetz, *Organotitanium Reagents in Organic Synthesis*, Springer Verlag, Berlin—Heidelberg, 1986, 236 c.
5. G. C. Levy and G. C. Nelson, *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Wiley, New York, 1972.
6. E. Pretsch, T. Clers, J. Seibl, and W. Simon, *in Tables of Spectral Data for Structure Determination of Organic Compounds*, Springer Verlag, Berlin, 1983, C60.
7. D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, 1959, **81**, 2748.
8. M. Nogrady, *Stereoselective Synthesis*, VCH Verlagsgessellschaft Weinheim, 1987.
9. V. M. Potapov, *Stereokhimiya* [*Stereochemistry*], Khimiya, Moscow, 1988, 463 pp. (in Russian)
10. A. C. Forsyth, R. M. Paton, and I. Watt, *Tetrahedron Lett.*, 1989, **8**, 993.
11. W. C. Still and J. A. Schneider, *Tetrahedron Lett.*, 1980, **21**, 1035.
12. G. A. Tolstikov, M. E. Adler, I. N. Gaisina, F. A. Valeev, and M. S. Miftakhov, *Zh. Org. Khim.*, 1993, **29**, 417 [*Russ. J. Org. Chem.*, 1993, **29** (Engl. Transl.)].
13. F. Shafizaden, R. H. Furneaux, and T. T. Stevenson, *Carbohydr. Res.*, 1979, **71**, 169.
14. T. V. Talalaeva and K. A. Kocheshkov, *Metody elementoorganicheskoi khimii* [*Methods of Organoelement Chemistry*], Nauka, Moscow, 1971, **1**, 87 (in Russian).
15. *Organikum. Organish-chemisches Grundpraktikum*, Veb Deutscher Verlag der Wissenschaften, Berlin, 1976.
16. F. Normant and G. Cahiez, *Modern Synthetic Methods*, Ed. R. Scheffold, J. Wiley & Sons, New York, 1983, **3**, 173.
17. H. O. House, W. L. Respecc, and G. M. Whitesides, *J. Org. Chem.*, 1966, **31**, 3128.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