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Diastereofacial Selection in the 1,2-Addition of MeMgX and MeLi to 4-Oxo sugar: Efficient Synthesis of 4-C-Methyl-1-S-β-D-Gluco- and Galactopyranoside Building Blocks of Moenomycin

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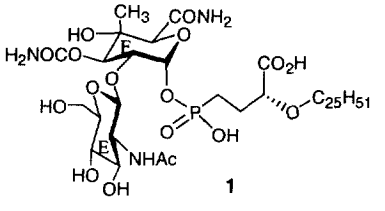
Abstract: The stereochemical course of the 1,2-addition upon treatment of various 1-thio-4-oxo sugars with MeMgX and MeLi has been determined. The effects of reagent, solvent, and neighboring functionalities in the gluco/galacto (non-chelation/chelation controlled) product distribution are detailed. Stereocontrolled 1,2-addition to these 4-oxo sugars provide access to a number of differently functionalized F unit building blocks of the moenomycin family, and demonstrate the versatility of this transformation.

The phosphoglycolipid antibiotic, moenomycin A,[1] is a potent inhibitor of bacterial cell wall biosynthesis.[2] The minimum structural unit required for antibiotic activity is the disaccharide **1**[3-5] which contains the 4-C-methyl-β-D-glucopyranoside building block as one of its important features. In a program to generate a library around the core active disaccharide unit **1** involving solid-phase combinatorial chemistry,[6] we required a synthesis of building block **2**. To accomplish the synthesis of **2** we needed a stereoselective method for the conversion of 4-oxo-1-thioglycosides to the corresponding 4-C-methyl derivatives by 1,2-addition of organometallic methylating agents.



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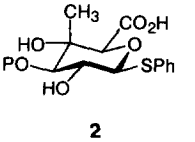

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The stereochemical course of the 1,2-addition of unhindered organometallic reagents to conformationally rigid cyclohexanones preferentially from the axial direction has been extensively documented,[7] and several mechanistic models for the understanding of this phenomenon have appeared in the literature.[8] However, with neighboring polar substituents such as alkoxy groups, equatorial attack predominates due to the intervention of a chelate complex[9] (chelation control) unless the equatorial surface is blocked by complex formation with a bulky reagent.[10] Although addition of an organometallic reagent such as Grignard or organolithium species to the carbonyl group of an oxosugar is often highly stereoselective, rational prediction of the stereochemical outcome of the 1,2-addition in such highly oxygenated systems is difficult. This lack of predictability relates to the inability to define the scope and limitations of the process, in terms of substrate structure, reagents, solvents, and conditions. We report herein the results of our studies directed toward the selective formation of C-4-substituted gluco- and galactopyranosyl derivatives starting from the corresponding 4-oxo sugars along

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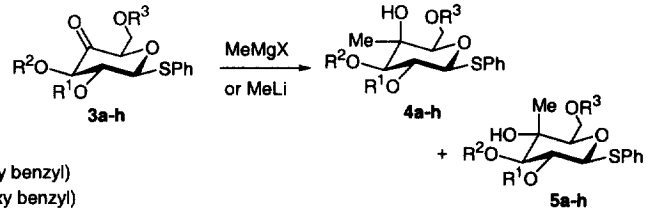
with a mechanistic discussion of transition state metal chelate models to help rationalize the observed stereochemical outcomes.

The results of the addition of Grignard reagents to the oxosugars **3a-h** are summarized in Table 1. Nucleophilic addition of methyl magnesium iodide to the ketone **3a** at low temperature in ether afforded the branched galactose derivative **4a** in 97% yield (Entry 1). Although undetectable by ^{1}H NMR, ^{13}C NMR analysis of the crude reaction mixture indicated small amount of the C-4 epimer (gluco) which could be isolated only in trace amounts. This result could be rationalized considering chelation of the magnesium atom (Figure 1) of the Grignard reagent with the C-4 carbonyl oxygen and the C-3 oxygen[11] atom (chelation-controlled). Equatorial attack of the nucleophile dominates due to the sterically hindered axial face of the chelated conformation of the oxo sugar. Structure of **4a** was unequivocally assigned by ^{13}C NMR experiments which showed characteristic 4-C-methyl carbon signal at ~21ppm. Similar galacto/gluco selectivities were observed for compounds **3b** and **3c** when treated with ethereal Grignard reagents at -78°C (entries 5 and 8) to produce **4b** and **4c** in excellent yield (>97%). With MeLi in ether (entries 3, 6 and 9; compounds **3a-c**), axial attack predominated (ca. 90%) indicating a more flexible (non-chelation controlled) transition state conformation for the formation of **5a-c**. Compared to MeMgI-ether reagent system, the yields of addition with MeLi-ether were slightly lower (entries 1 vs 3, 5 vs 6, 8 vs 9).

3a, R^1=TBS, R^2=allyl, R^3=Tr
3b, R^1=PMB, R^2=TBS, R^3=Tr
3c, R^1=3,5-dimethoxy benzyl, R^2=TBS, R^3=Tr
3d, R^1=R^3=3,5-dimethoxy benzyl, R^2=TBS
3e, R^1=Ac, R^2=TBS, R^3=Tr
3f, R^1=Bn, R^2=Ac, R^3=Bn
3g, R^1=Bn, R^2=TBS, R^3=PMB (PMB = 4-methoxy benzyl)
3h, R^1=MMB, R^2=TBS, R^3=Tr (MMB = 3-methoxy benzyl)



Reaction of oxo sugars **3a** with MeMgI using tetrahydrofuran as solvent (entry 2) showed only slight decrease in π-facial diastereoselection (92:8; **4a/5a**) compared to the reaction in ether. Similar solvent effect was observed with MeLi (entry 4) which afforded the gluco-derivative **5a** predominantly (6:94; **4a/5a**). Interestingly, when dichloromethane[12] was used as the solvent, the galacto-selectivity was considerably enhanced (>99:1; **4b/5b**), albeit in lower yield (entry 7).

A change in the nature of substituent on the neighboring hydroxy groups introduces several counterbalancing influences. Thus, replacement of the bulky 6-O-trityl protection with a 3,5-dimethoxy benzyl group (**3d,** entry 10) proved completely unselective towards MeMgI addition. A very interesting substrate-dependent selectivity was observed when we went to organocerium[13] reagents. Unlike in the case of MeMgI-ether reagent system (entries 1, 5 and 8), MeMgCl in the presence of $CeCl_3$ (THF-toluene; 1:8) favored gluco selectivity (4:1) with substrates **3e** and **3h** containing C-3-OTBS and C-6-OTr substitutions (entries 11 and 14). Apparently, unlike in the case of neighboring C-3 or C-6 oxygen substituents, the C-2 ester (Ac, **3e**) or ether (MMB, **3h**) functionalities have no effect on the facial selectivity of the addition. Under the same experimental conditions, however, the C-3-OAc derivative **3f** (entry 12) gave predominantly the galacto product. As in the cases of MeMgI addition to substrates **3a-d**, Mg-chelation could be a plausible explanation for the opposite stereoselectivity in this case. Although the C-6-OBn functionality of **3f** poses the possibility of β-chelation,[14] the acetate substiuent in the 3-position might be an even better ligand than the

ethereal C-3 oxygens in **3a-d** or its C-6-OBn group (Figure 2).[15] As in the case of **3d**, poor 'chelation-control selectivity' was observed for **3g** due to the presence of a sterically less demanding C-6-OPMB functionality.

Table 1. Diastereofacial Selectivity in Nucleophilic Additions to Oxosugars[a]

Entry	Oxosugar	MeMgX or MeLi	Reaction conditions[b]	Chelate/non-chelate (**4:5**)ratio	Yield[c], %
1	**3a**	MeMgI	Ether, -78°C	>97:3	97
2	**3a**	MeMgI	THF, -78°C	92:8	93
3	**3a**	MeLi	Ether, -78°C	10:90	82
4	**3a**	MeLi	THF, -78°C	6:94	85
5	**3b**	MeMgI	Ether, -78°C	>97:3	96
6	**3b**	MeLi	Ether, -78°C	~9:91	89
7	**3b**	MeMgI	CH_2Cl_2, -78°C	>99:1	76
8	**3c**	MeMgI	Ether, -78°C	>97:3	92
9	**3c**	MeLi	Ether, -78°C	10:90	78
10	**3d**	MeMgI	Ether, -78°C	50:50	89
11	**3e**	MeMgCl/ $CeCl_3$	THF-Toluene (1:8), -78°C to RT	20:80	88
12	**3f**	MeMgCl/ $CeCl_3$	THF-Toluene (1:8), -78°C to RT	87:13	82
13	**3g**	MeMgCl/ $CeCl_3$	THF-Toluene (1:8), -78°C to RT	70:30	70
14	**3h**	MeMgCl/ $CeCl_3$	THF-Toluene (1:8), -78°C to RT	20:80	85

[a] All new compounds showed characteristic spectral data and exact mass spectroscopic data.[16] The reported data represent the average of experiments conducted in duplicate. [b]The reaction mixtures were stirred for 2-3h before usual workup. For entries 11-14, the reactions were stirred at -78°C for 2h, and then allowed to warm up to room temperature. [c]Isolated yields are given.

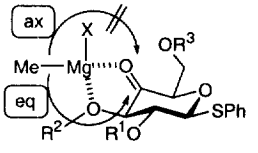


Figure 1

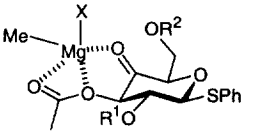


Figure 2

Other than the substituent effect, an appreciable level of solvent effect was also observed in these studies. Moderate gluco-selectivity was observed with diethyl ether as solvent using MeLi (non-chelation controlled). The better donor solvent THF competes with the substrate as a ligand of the metal center and diminishes or inhibits chelate formation. Thus, the gluco-selectivity is slightly improved (entry 3 vs. 4; MeLi), and galacto–selectivity is diminished (entry 1 vs. 2; MeMgI). The use of dichloromethane as the poor coordinating solvent probably enhances the formation and participation of chelates and leads to an even better selectivity in the reaction of **3b** (entry 7). This simplified interpretation does not take into account the Schlenk equilibria and the aggregation of the organometallic reagents, which could be responsible for cases where clear solvent effects are not observed. However, the experimental results support the effect of solvent on the stereochemical outcome.

These results demonstrate that proper combination of solvent and the counter cation of the Lewis acidic nucleophile could be used effectively to obtain either epimer of the 4-C-methyl sugars. The surrounding functionalities, especially the C-3 and C-6 oxygen functionalities, play major controlling factors that should be considered in reactions of Lewis acidic organometallic reagents with oxo sugars. These observations become important when considering the synthesis of 4-C-functionalized sugar derivatives that are essential constituent of several biologically active natural products.

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16) Compound **4a**: mp, 62-64 °C; ^{1}H NMR ($CDCl_3$) δ 7.58-7.08 (m, 20H), 5.84-5.71 (m, 1H), 5.12-4.99 (m, 2H), 4.43 (d, J = 9Hz, 1H), 4.27-4.21 (m, 1H), 3.89-3.83 (m, 1H), 3.75 (t, J = 9Hz, 1H), 3.41-3.27 (m, 2H), 3.11 (dd, J = 6.3, 2.4Hz, 1H), 2.78 (d, J = 9Hz, 1H), 0.82 (s, 12H), 0.01 and 0.14 (2s, 6H). Selected peaks in ^{13}C NMR ($CDCl_3$) δ 90.18, 87.26, 86.85, 81.52, 75.58, 73.89, 71.73, 63.16, 21.69 (4-C-Me).

Compound **5a**: mp, 72-75 °C; ^{1}H NMR ($CDCl_3$) δ 7.42-7.02 (m, 20H), 5.89-5.76 (m, 1H), 5.17-4.99 (m, 2H), 4.53 (d, J = 9.6Hz, 1H), 4.29-4.22 (m, 1H), 4.17-4.09 (m, 1H), 3.42-3.24 (m, 2H), 3.20-3.09 (m, 2H), 0.92 (s, 3H), 0.83 (s, 9H), 0.90 and 0.01 (2s, 6H). Selected peaks in ^{13}C NMR ($CDCl_3$/20%D_2O) δ 90.16, 88.50, 87.55, 80.06, 74.72, 74.32, 72.60, 62.89, 16.35 (4-C-Me).

Compound **4e** (R_1 = R_2 = H): mp, 74-76 °C; ^{1}H NMR ($CDCl_3$/20%D_2O) δ 7.69-7.22 (m, 20H), 4.56 (d, J = 9.6Hz, 1H), 3.65 (t, J = 9.6Hz), 3.57-3.25 (m, 3H), 3.17 (d, J = 9.6Hz, 1H), 0.95 (s, 3H). Selected peaks in ^{13}C NMR ($CDCl_3$/20%D_2O) δ 88.20, 87.12, 81.34, 78.08, 73.14, 70.35, 62.95, 20.65 (4-C-Me).

Compound **5e** (R_1 = H, R_2 = TBS): ^{1}H NMR ($CDCl_3$) δ 7.70-7.20 (m, 20H), 4.61 (d, J = 9.6Hz, 1H), 3.52-3.40 (m, 3H), 3.26-3.16 (m, 2H), 0.90 (s, 3H), 0.85 (s, 9H), 0.09 and 0.07 (2s, 6H). Selected peaks in ^{13}C NMR ($CDCl_3$) δ 88.89, 87.05, 81.51, 81.19, 73.09, 71.70, 62.66, 25.93, 18.34, 15.77 (4-C-Me).