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Improving the stereoselectivity of one-carbon atom homologation of hexoses at the terminal position

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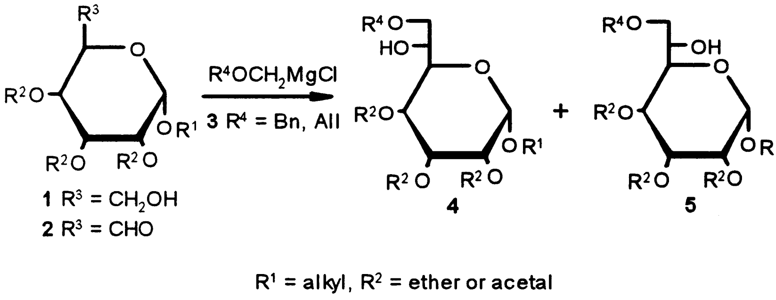
Abstract—A number of modifications of the original Grignard C_1 homologation of hexoses was examined, e.g. reactions of protected hexodialdo-1,5-pyranosides with benzyloxymethyllithium, transmetalation, precomplexation of the aldehydes. Some of the modifications, e.g. benzyloxymethyl Grignard addition in the presence of *tert* amines showed good to very good stereoselectivity of the heptoside formation. © 2002 Elsevier Science Ltd. All rights reserved.

A practical method of homologation of hexoses **1**, preserving their natural D configuration, consists of a reaction between an alkoxymethyl Grignard reagent **3** and a C-6 aldehyde **2** (Scheme 1).[1] Although the yields of heptosides **4** D,D and **5** L,D are generally high or very high, the stereoselectivities of the reactions are usually in the range 1.5–4:1.[1] Only (phenyldimethylsilyl)methylmagnesium chloride, a reagent introduced by van Boom,[2] secures very high yields of L,D-heptosides.

Benzyloxymethyllithium, readily available from (benzyloxymethyl)tributylstannane,[3,4] reacted with four hexopyranose 6-aldehydes **6**–**9** to yield the expected D,D and L,D-heptoses in good yields (72–76%)(Table 1, entry 2). The stereoselectivity of the reactions was substantially improved (9–10:1) in the *galacto* series **8**,**9**, slightly improved in the case of the *allo* aldehyde **6** (2:1), whereas no improvement was noted for the *gluco* aldehyde **7**. Transmetalation[5] of benzyloxymethyllithium with $Ti(OiPr)_4$ or CuCN in reactions with the *galacto* aldehyde **8** led to the corresponding heptosides in low yield. Only with $Al(OiPr)_3$, the D,D and L,D-heptosides were obtained in high yield and with good (10:1) stereoselectivity. Attempts at transmetalation of the lithium reagent with $ZnCl_2$, $ZrCp_2Cl_2$, $TiCl_4$, $Ti(OiPr)_3Cl$, $CuBr\cdot Me_2S$, $CeCl_3$ and Et_2AlCl led to completely unreactive reagents.

We next examined precomplexation[6] of the hexose aldehydes with some metal compounds. Moderate to good yields (37–57%) of the corresponding D,D and L,D-heptosides were obtained when all four hexose aldehydes were precomplexed with Et_2AlCl and reacted next with benzyloxymethyllithium (Table 1, entry 3). The reaction of benzyloxymethyllithium with $Ti(OiPr)_3Cl$, $Ti(OiPr)_4$ or $ZnCl_2$-precomplexed *galacto* aldehyde **8** led to D,D and L,D-heptosides with high (9–15:1) stereoselectivity but in low yields. The stereoselectivity of the heptoside formation in the case of the *allo* aldehyde **6** was increased to 1:2 and for both *galacto* aldehydes **8** and **9**



Scheme 1.

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Table 1. Stereoselectivity in chain-elongation reactions of terminal hexose-derived aldehydes **6**–**9** with a benzyloxymethyl unit under different conditions

Entry no.	Reagent	**6** (*allo*)			**7** (*gluco*)			**8** (*galacto*[d])			**9** (*galacto*)		
		Yield (%)	D,D	L,D	Yield (%)	D,D	L,D	Yield (%)	D,D	L,D	Yield (%)	D,D	L,D
1	BnOCH$_2$MgCl[a]	84[b]	38	51	89	60	40	80	60	40	80	54	46
2	BnOCH$_2$Li	76	34	66	72	48	52	74	91	9	76	89	11
3	BnOCH$_2$Li+Et$_2$AlCl[c]	52	31	69	37	48	52	49[e]	87	13	57	93	7
4	BnOCH$_2$MgCl+TMEDA	79	14	86	78	20	80	71	84	16	74	81	19
5	BnOCH$_2$MgCl+(*R*)-Me$_2$N-CHPh-CH$_3$	90	21	79	79	30	70	87	74	26	76	64	36
6	BnOCH$_2$MgCl+(*S*)-Me$_2$N-CHPh-CH$_3$	86	35	65	80	47	53	83	62	38	74	60	40
7	BnOCH$_2$MgCl+(*S*)-1-methyl-2-(piperidinemethyl)-pyrrolidine	–	–	–	57	2	98	–	–	–	–	–	–

[a] Data from Ref. 1.

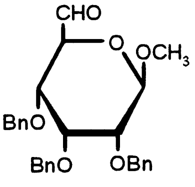
[b] C-5 inverted heptosides (11%) were also isolated.[1]

[c] Precomplexation of the aldehydes (**6**–**9**) with Et$_2$AlCl before reaction with BnOCH$_2$Li.

[d] When the solution of BnOCH$_2$Li was transmetalated before the reaction with aldehyde **8**, the following results were obtained (metal derivative/heptoside yield%/D,D:L,D):Ti(O*i*Pr)$_4$/14%/91:9, CuCN/9%/70:30, Al(O*i*Pr)$_3$/81%/91:9.

[e] Precomplexation of the aldehyde (**8**) with ZnCl$_2$ followed by the reaction with BnOCH$_2$Li led to 45% of D,D and L,D heptosides in 90:10 proportion. Analogous precomplexation of **8** with Ti(O*i*Pr)$_3$Cl gave 7% of heptosides in 94:6 proportion, and with Ti(O*i*Pr)$_4$—13% in 91:9 proportion.

was very high (7–14:1), leaving the proportion of heptosides obtained from the *gluco* aldehyde **7** unchanged.



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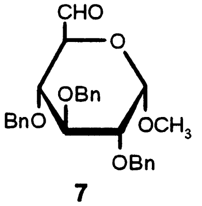

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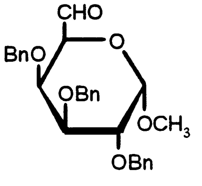

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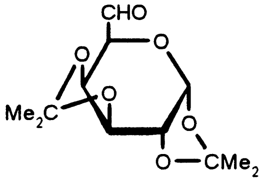

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Valuable results were obtained when tertiary amines were added to the Grignard reagent, benzyloxymethylmagnesium chloride, before the reaction with the four hexose aldehydes[7] (Table 1, entries 4–7). The corresponding heptosides were obtained in high yields and with good to very good stereoselectivities. An especially beneficial effect of amine addition was observed for the recalcitrant *gluco* aldehyde (**7**): the proportion of D,D:L,D heptosides was 1:4 with TMEDA and was raised to 1:49 in the presence of (*S*)-1-methyl-2-(piperidinomethyl)-pyrrolidine. With both enantiomeric monoamines of 1-*N*,*N*-dimethylamino-1-phenylethane, better stereoselectivities were found for the *R* enantiomer (Table 1, entries 5 and 6).

Discussion

The improved yields of D,D-heptoses when MgCl was replaced by Li in the BnOCH$_2$M reagent can be interpreted by the more effective, sterically accessible β-chelation control. An alternative explanation is based on the Felkin–Anh model of *anti* (towards ring oxygen atom) addition of the nucleophile to the carbonyl carbon atom. Several experimental studies[8–10] claim the negligible effect of chelation in the addition of organometallic reagents to aliphatic β-alkoxyaldehydes. However, theoretical work[11] underlines the importance of α- as well as β-chelation control in the addition of an organomagnesium reagent to a carbonyl group.

Precomplexation of the aldehydes[12] with Et$_2$AlCl was not stereoselective and did not exert any stereocontrol in the addition reaction. Lowered yields of products were observed which indicated hindered access of the reagent to the carbonyl groups.

Addition of tertiary amines to the Grignard reagent results in the replacing of the ether molecules in the coordination sphere of the Grignard reagent.[13–15] Enhanced reactivity[14] led to high yields of products. Coordination with TMEDA formed a reagent which improved the yield of L,D-heptosides in the *allo* and *gluco* aldehydes and D,D-stereoisomers in the *galacto* series. We tend to interpret these results in terms of α- and β-chelation control. Especially remarkable is the effect of optically active diamine (entry 7) in enhancing the yield of the D,D-*gluco*-heptoside. This result is in line with the observations of Mukaiyama[16] on similar addition reactions. Monoamines (entries 5 and 6 in Table 1), although producing reactive Grignard reagents, exert less steric control than diamines.

Acknowledgements

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5. To a solution of (benzyloxymethyl)tributylstannane (0.95 mmol) in THF (10 ml) butyllithium (1.0 mmol) was added at −78°C and stirred for 15 min. The metal compound was added and stirred for 30 min. Thereafter, a solution of the aldehyde **8** in THF was added, stirred for 2 h and worked-up.[1]
6. A solution of the aldehyde **8** (0.43 mmol) in THF (5 ml) was mixed with an equimolar amount Ti(O*i*Pr)$_4$ [Ti(O*i*Pr)$_3$Cl or ZnCl$_2$], cooled to −78°C and treated with a solution of benzyloxymethyllithium. After 2 h the reaction mixture was worked-up.[1] An analogous procedure was employed for the reactions of aldehydes **6**–**9** (precomplexed with Et$_2$AlCl) with BnOCH$_2$Li.
7. To a solution of benzyloxymethylmagnesium chloride[1] (6.1 mmol) in THF, cooled to −23°C, an equimolar amount of *tert*-amine was added and stirred at this temp. (1 h) and brought slowly to 0°C. After an additional 30 min the mixture was cooled to −78°C and aldehydes **6**–**9** (1 mmol) were added. Stirring was continued for 3 h at −78°C and 12 h at room temperature, after which the reaction was worked-up.[1]
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