Polish J. Chem., **77**, 257–281 (2003) **REVIEW ARTICLE**

Homologation of Protected Monosaccharides at the Terminal Position with Grignard C_1 Reagents

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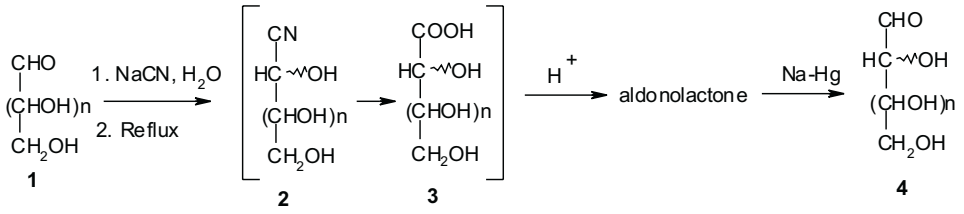
The survey presents details of the recently introduced general method of homologation of monosaccharides. This method is based on chain-elongation of a protected monosaccharide from the terminal carbon atom. The terminal CH_2OH group is oxidized to the aldehyde grouping and next reacted with an alkoxymethylmagnesium chloride (C_1 Grignard) to form directly stereoisomeric homologues. The yields of the homologation products are high. Experiments aiming at improvement of the stereoselectivity of the reactions are described. The application of another C_1 Grignard reagent, (phenyldimethylsilyl)methylmagnesium chloride, is presented. The advantages and disadvantages of the method are discussed. All syntheses connected with the important bacterial heptose, L-*glycero*-D-*manno*-heptose and its oligosaccharides are described.

Key words: homologation, pentoses, hexoses, heptoses, bacterial oligosaccharides, alkoxymethylmagnesium chlorides, (phenyldimethylsilyl)methylmagnesium chloride, Grignard reaction

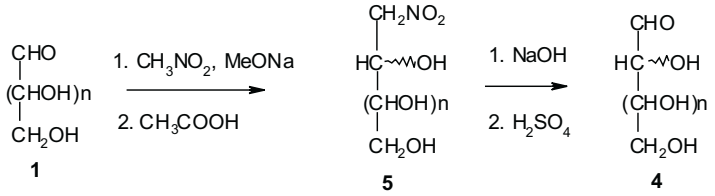
Homologation of monosaccharides belongs to the classical problems of carbohydrate chemistry. In short, it refers to procedures enabling introduction of a CHOH grouping into the OCH-$(CHOH)_nCH_2OH$ molecule, thus, forming a higher homologue, OCH-$(CHOH)_{n+1}CH_2OH$. Essentially two basic approaches are discerned in the synthetic procedures. The first takes the advantage of the carbonyl group present the substrate **1**. Thus, formation of a cyanohydrin **2**, a reaction which can be readily performed in an aqueous solution with the unprotected substrate, followed by hydrolysis of the aldononitrile to aldonic acid **3**, and reduction of the carbonyl group in the transient aldonolactone to the aldehyde stage, leads to a new sugar **4**, one CHOH grouping richer. This is the oldest, classical Kiliani-Fischer method [1–3], mentioned in practically all textbooks of organic chemistry. Another general method, elaborated mainly by Sowden [4], is based on condensation of a free sugar (**1**) with nitromethane under basic conditions to form nitroalditol **5**, followed by Nef reaction, converting the introduced nitromethyl group into the formyl grouping in **4**. A third homologation method, recently introduced by Dondoni [5], makes the use of a facile reaction between 2-(trimethylsilyl)-thiazole (**7**) and an aldehyde (*e.g.* **6**) to form a 2-hydroxymethyl-thiazole **8**. In the next steps the thiazole ring is N-methylated (→ **9**), hydrogenated to thiazolidine (→ **10**), and finally hydrolyzed, liberating the formyl group, thus, forming the homologue of the starting sugar (**11**). These are the three general methods, proven in homologation of many sugars (Scheme 1).

Scheme 1

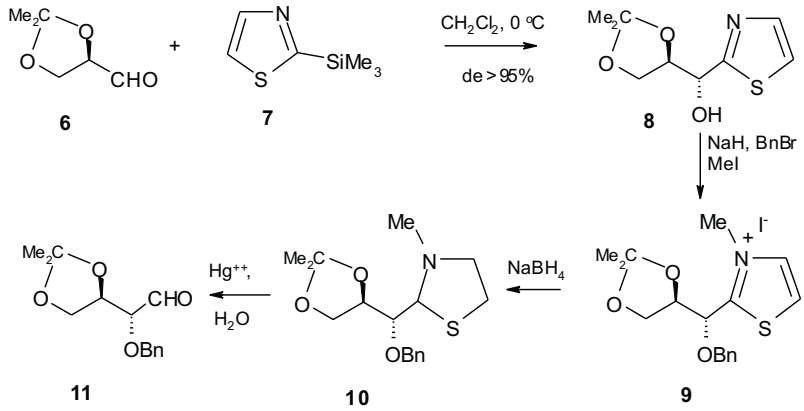
Kiliani-Fischer homologation



Sowden homologation



Dondoni synthesis

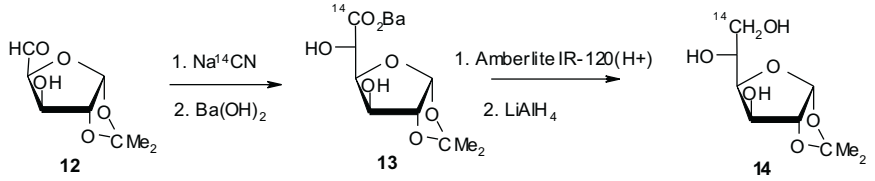


The second approach is based on chain elongation of a monosaccharide from the terminal position. This requires a suitable preparation of the substrate as *e.g.* protection of the original aldehyde at C-1 and protection of the remaining hydroxyl groups except the terminal one. The CH_2OH grouping must be converted to the reactive formyl group by oxidation. Thus, a dialdo-furanose or -pyranose is obtained, which is next reacted with an elongating reagent. This pathway did not gain a more extended

application in the past compared with the first approach. In a limited number of examples the Kiliani-Fischer method was employed, *e.g.* **12→13→14** [6,7], (main isolated product), Dondoni (*e.g.* **15→16→17** [8,9], exclusive diastereoisomer), and methods based on dihydroxylation of olefinic sugars [10,11] or on ozone cleavage followed by reduction of the terminal formyl group to CH_2OH (*e.g.* **18→19→20**) [12,13] (Scheme 2).

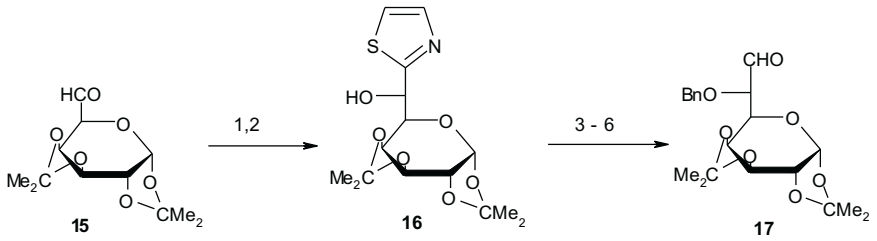
The development of the synthetic methodology described in this article was connected with the need of elaboration of a practical approach to a specific heptose, L-*glycero*-D-*manno*-heptose (LD-*man*Hep*p*, **21**), a bacterial sugar occurring in many lipopolysaccharides (LPS) [14,15]. This heptose is found in the inner core of LPS of many Gram-negative bacteria in form of an oligosaccharide. Scheme 3 shows a tri-heptoses (**22**) with 1,7 and 1,3 linkages, one of the trisaccharides often found within LPS.

Scheme 2



12 **13** **14**

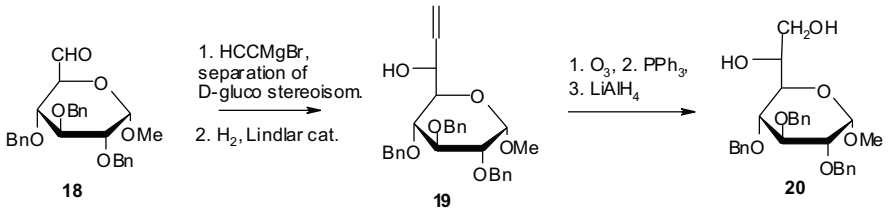
R. Schaffer and H. S. Isbell, [7].



15 **16** **17**

1. 2-Trimethylsilylthiazole, 2. Bu_4NF, 3. NaH, BnBr, 4. MeI, 5. $NaBH_4$, 6. $HgCl_2$-H_2O

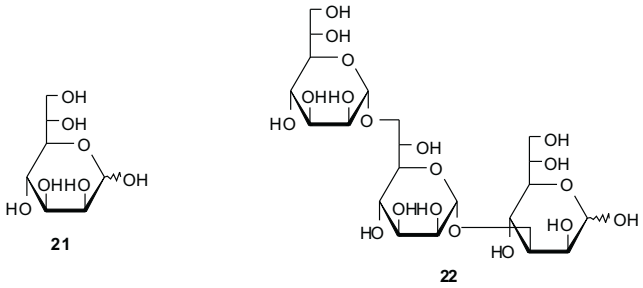
A. Dondoni *et al.,* [8].



18 **19** **20**

S. Jarosz, [12].

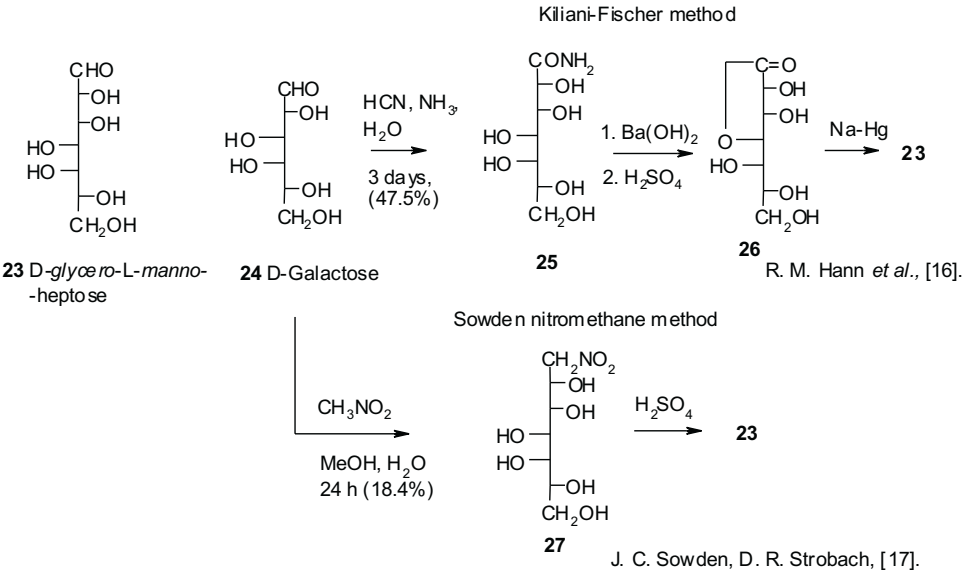
Scheme 3

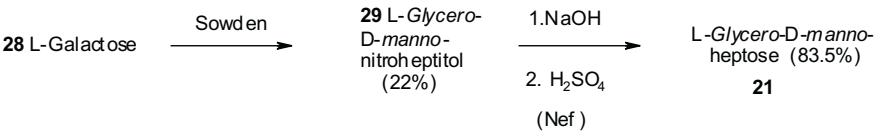


21 **22**

The negligible amounts of this heptose available from natural sources and difficulties in its isolation in the pure form prompted the development of syntheses. Early syntheses, based on Kiliani-Fischer: **24→25→26→23** [16] or Sowden: **24→27→23** [17] elongation of D-galactose (**24**), led to the enantiomeric heptose (**23**) of D-*glycero*-L-*manno* configuration. The proper enantiomer **21** was obtained first by Osborn [18] from L-galactose (**28**) by the Sowden method: **28→29→21** (Scheme 4).

Scheme 4



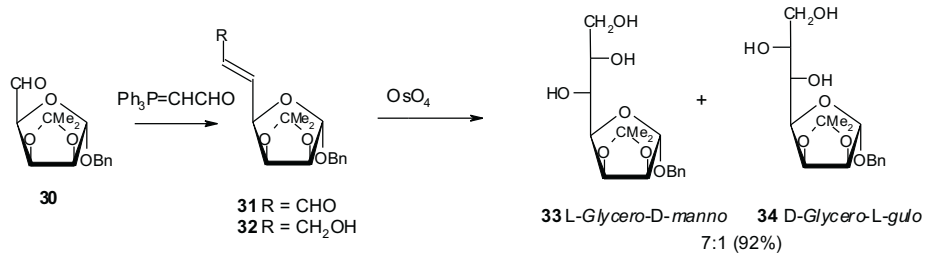


M. Teuber, R. D. Bevill, M. J. Osborn, [18].

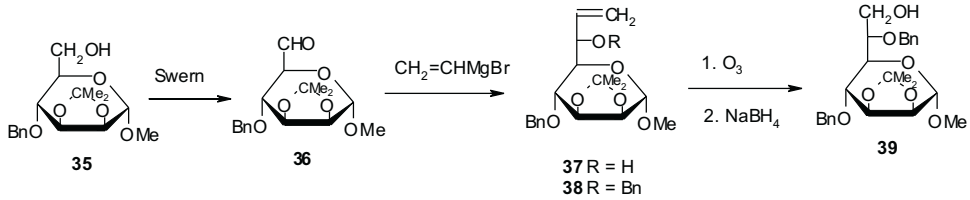
Later, few other syntheses were elaborated. Paulsen *et al.* [19,20] obtained the desired heptose by chain elongation performed on 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose with 2-lithio-1,3-dithiane and subsequent rather complicated transformations. Brimacombe [21] synthesized benzyl 2,3-*O*-isopropylidene-β-L-*glycero*-D-*manno*-heptofuranoside (**33**) starting from benzyl 2,3-*O*-isopropylidene-α-D-*lyxo*-dialdo-1,4-furanoside (**30**), Wittig reaction with formylmethylylide to form **31**, reduction (→**32**) and *cis*-hydroxylation to benzyl heptofuranosides **33** and **34** in 7:1 proportion (Scheme 5). Using benzyl 5,6,7-tri-*O*-acetyl-2,3-*O*-isopropylidene-L-*glycero*-α-D-*manno*-heptofuranoside prepared on that way, Paulsen [22] synthesized a disaccharide, α-D-Glc*p*N-(1→7)-L-α-D-*man*Hep*p* representing a partial structure of the core region of *Aeromonas hydrophila* and *Bordetella pertussis* LPS and the same disaccharide with aβ linkage, occurring within the core of *Vibrio ordalii* LPS.

Chapleur [23] prepared methyl 4,6-di-*O*-benzyl-2,3-*O*-isopropylidene-L-*glycero*-α-D-*manno*-heptopyranoside (**39**) starting from methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (**35**), oxidation to 6-aldehyde (diulose, **36**), reaction with vinylmagnesium bromide (leading to a single stereoisomeric olefin **37**), benzylation (→ **38**), ozonolysis and reduction of the aldehyde formed to the heptoside **39** (Scheme 5).

Scheme 5



J. S. Brimacombe, A. K. M. S. Kabir, [21].

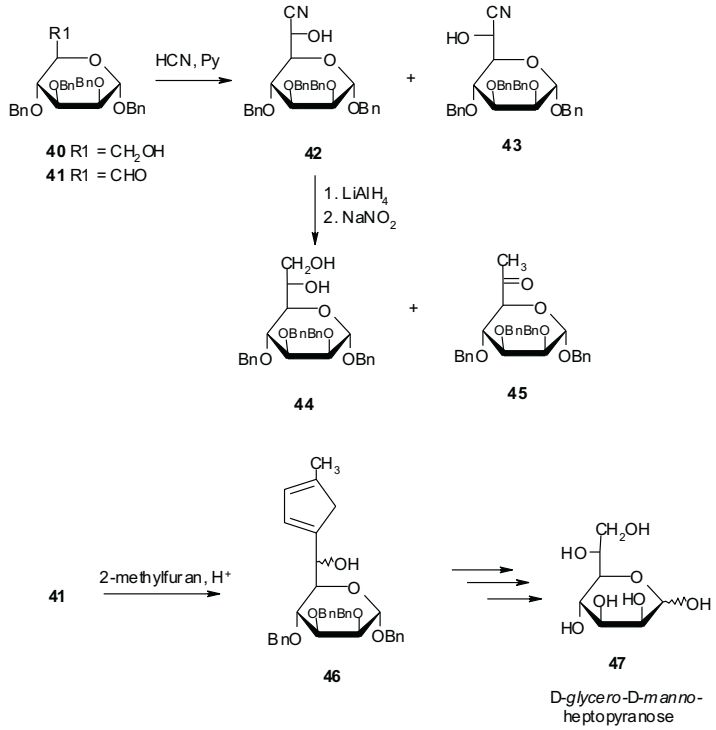


M. Dasser, F. Chretien, Y. Chapleur, [23].

In 1985 we undertook the task of elaboration of a practical approach to this particular heptose. The main idea was based on elongation of the carbon atom chain of D-mannose from the terminal position just to preserve the original D configuration of the substrate. D-Mannose had to be used in a protected form. Benzyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **40** [24,25] was selected as the substrate of choice. Its oxidation, according to Swern, afforded benzyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-hexodialdo-1,5-pyranoside (**41**) in a quantitative yield. Reaction of the dialdose with hydrogen cyanide in pyridine led to two pyranurononitriles **42** (34%) and **43** (19%), which were separated. Both products were characterized as 6-*O*-acetates. Reduction of the main product **42** with lithium aluminum hydride led to 7-amino-7-deoxy derivative, which was *in situ* de-aminated with sodium nitrite in acetate buffer to yield benzyl 2,3,4-tri-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside (**44**) in 18% yield. The second product of the de-amination, obtained in higher 36% yield, was benzyl 2,3,4-tri-*O*-benzyl-7-deoxy-α-D-*manno*-hexopyranosid-6-ulose (**45**). Thus, the desired product was obtained, but in a low yield and accompanied by an undesired side-product.

Acid-catalyzed condensation of dialdose **41** with 2-methylfuran yielded a mixture of stereoisomeric 6-C-(2-methyl-5-furyl) derivatives **46** in 1:6 proportion and 30% yield. The furyl ring in the main product was degraded by ozonolysis and after suitable work-up 11% of a derivative of benzyl D-*glycero*-α-D-*manno*-heptopyranoside (**47**) was isolated.

Scheme 6



The third, and eventually successful elongation method was based on direct introduction of an alkoxymethyl group by reacting an alkyl dialdo-pyranoside with alkoxymethylmagnesium chloride.

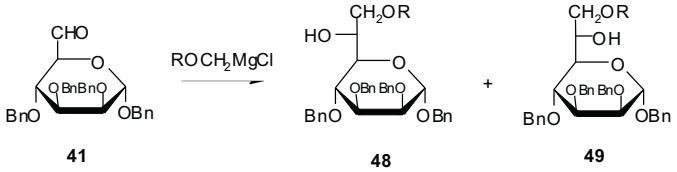
Alkoxymethyl Grignard reagents were introduced by Sommelet in 1907 [26]. Sixty years later Castro [27–29] studied several reagents of this type in detail and elaborated preparative procedures, enabling their use in organic synthesis. In fact, preparation of alkoxymethyl Grignards and their handling is not trivial and their successful use requires a precise observation of reaction conditions. First of all, alkoxymethyl chlorides, which are the typical and most common substrates for the reaction with magnesium, must be freshly prepared and carefully distilled just before the reaction with Mg turnings. Reagents of commercial origin or even own preparations, stored for a few weeks in the fridge, are unsuitable. Our extended experience has shown that a successful Grignard can be obtained when the alkoxymethyl chloride (typically allyloxymethyl, benzyloxymethyl or methoxymethyl) is prepared freshly (a few days before the reaction), and distilled directly before the reaction with magnesium. The activation of magnesium with iodine is unsuitable. Freshly sublimed mercuric chloride is the best activator. Below a typical prescription [30], proven in many preparations, is presented:

To dry magnesium turnings (474 mg, 19.5 mmol) covered with freshly distilled tetrahydrofuran (1 ml) under dry argon was added sublimed mercuric(II) chloride (18 mg), and a few drops of neat, freshly prepared alkoxymethyl chloride were added while lowering the temperature to –15°C (for allyloxymethyl chloride), 0 to –5°C (for benzyloxymethyl chloride) or –20°C (for methoxymethyl chloride). When formation of the Grignard reagent has started, the rest of the alkoxymethyl chloride (19.5 mmol) in abs. THF (2 ml) was slowly added. At –20°C (for allyloxymethyl chloride), –10°C (for benzyloxymethyl chloride) or –25°C (for methoxymethyl chloride) and stirring was continued for 2 h. The temperature was then lowered to –78°C and a solution of the dialdo-pyranoside (3.25 mmol) in abs. THF (8 ml) was added dropwise and stirring at this temperature was continued for 2 h. Afterwards the reaction mixture was allowed to attain room temperature and additionally stirred for 12 h. Cold (0°C) aq. NH_4Cl (82 ml) was added and the products were extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to dryness. The residue was separated on a silicagel column with hexane-ethyl acetate as eluent. In the case of difficult separable products, HPLC was used.

Following this procedure, benzyl dialdo-pyranoside **41** was reacted with benzyloxymethylmagnesium chloride to furnish 65% of a mixture of stereoisomeric benzyl 2,3,4,7-tetra-*O*-benzyl-α-D- and -L-*glycero*-D-*manno*-heptopyranosides (**48** and **49**, R = Bn) in 1:3 proportion, but we did not succeed in its separation. However, condensation of **41** with allyloxymethylmagnesium chloride gave 67.5% of benzyl 7-*O*-allyl-2,3,4-tri-*O*-benzyl-α-D- and –L-*glycero*-D-*manno*-heptopyranosides (**48** and **49**, R = All, 1:3.2), which could be readily fractionated by flash chromatography to yield pure components. Their identification was based on full deprotection to free heptoses and formation of diethyl dithioacetals, known from literature (*e.g.* [18]).

A facile access to preparative amounts of LD-*man*Hep*p* enabled the synthesis of di- and tri-heptoses, forming the heptose region of the core oligosaccharides isolated from many Gram-negative bacteria [14]. Thus, two diheptoses linked α1-7 (**50**) and α1-3 (**51**) and a trisaccharide **22** linked α1-7 and α1-3 were synthesized [31,32].

Scheme 7

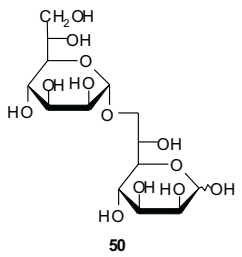


41 48 49

R = Bn, All.

These products were characterized as partially methylated and acetylated derivatives by GLC-MS method [33]. A disaccharide, 6-*O*-(L-*glycero*-α-D-*manno*-heptopyranosyl)-D-glucopyranose (**52**) has been synthesized [34] to prove a structural fragment of the heptose/hexose region of the lipopolysaccharide from *Escherichia coli* K-12 strain W3100* [35]. The synthesis of a trisaccharide: 2-*O*-(6-*O*-L-*glycero*-α-D-*manno*-heptopyranosyl-α-D-glucopyranosyl)-α,β-glucopyranose (**53**) substantiated further the structural conclusions [36]. Further syntheses in this field aimed a LD-*man*Hep*p*-containing oligosaccharides **54**–**56** as substrates for synthetic antigens (Scheme 8) [37,38].

Scheme 8



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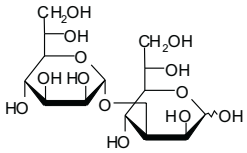

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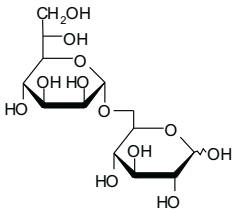

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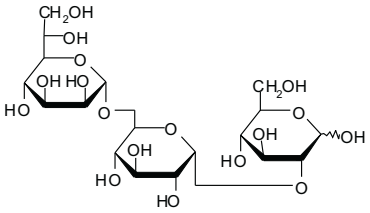

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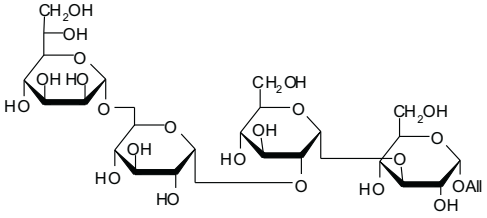

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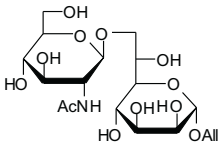

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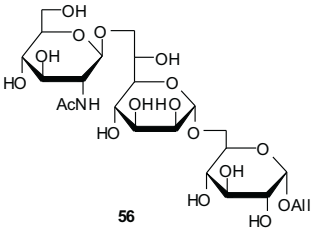

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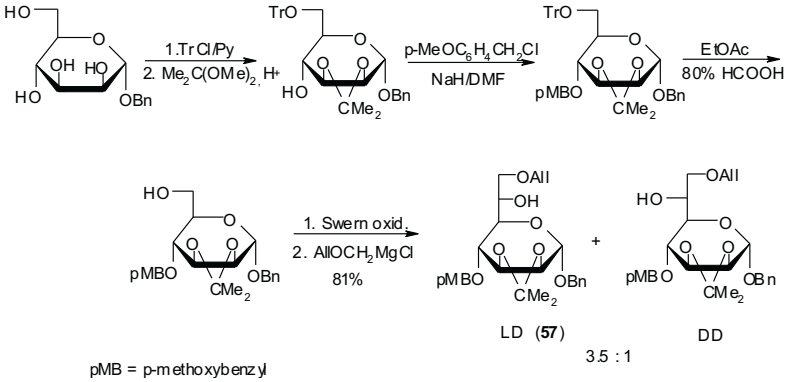
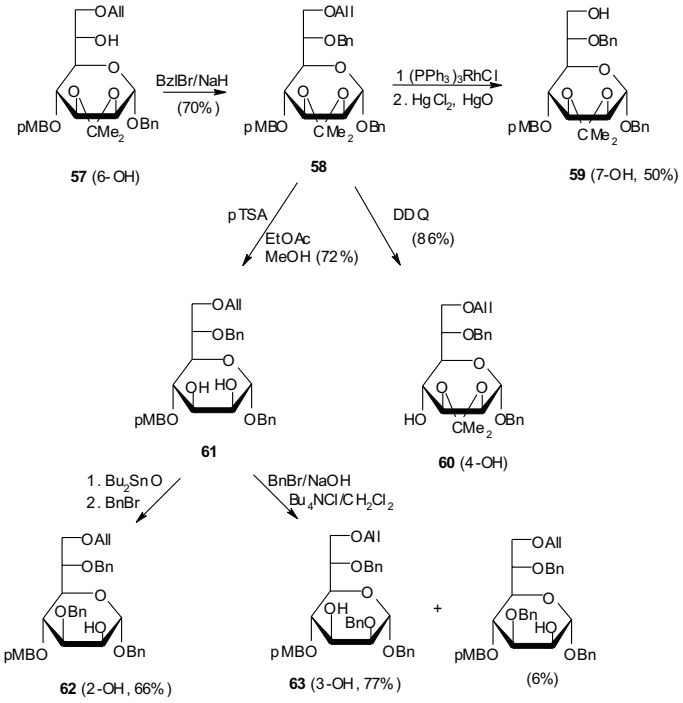
Scheme 9



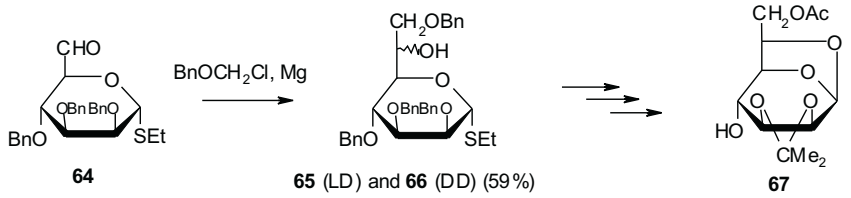
A specifically blocked derivative of LD-*man*Hep*p* (**57**) has been synthesized (Scheme 9) [39]. This derivative, by using proper de-blocking reagents, enables an access to all positions of L-*glycero*-D-*manno*-heptopyranoside system. Thus, **57** itself offers position 6 for glycosidation or other transformations. Benzylation leads to **58**, which can be de-allylated opening an access to 7-OH (**59**). Oxidative removal of the *p*-methoxybenzyl group from **58** gives **60** having the free 4-OH group. De-isopropylidenation of **58** leads to 2,3-diol **61**, which, in turn, can be selectively blocked at C-3 leaving 2-OH group (**62**), or can be benzylated in a two phase system to yield predominantly ether **63** with the free 3-OH group. Scheme 10 illustrates the methods employed.

Scheme 10



Another methodology for the synthesis of LD-*man*Hep*p* was proposed [40]. Ethylthio 2,3,4-tri-*O*-benzyl-α-D-*manno*-hexodialdo-1,5-pyranoside (**64**) was benzyloxymethylated, using the Barbier conditions (addition of benzyloxymethyl chloride simultaneously with the dialdo-pyranoside to the magnesium turnings). The yield and proportion of stereoisomeric products, **65** and **66**, were similar to those observed under the Grignard condition, however, less halide could be used. The ethylthio LD-heptoside obtained was converted into 1,6-anhydro derivative **67**, used subsequently in the synthesis of oligosaccharides of the core region of *Haemophilus influenzae* lipopolysaccharide: β-D-Glc*p*-(1→4)-L-α-D-*man*Hep*p*-(1→3)-L-α-D-*man*Hep*p*-(1→5)-α-D-KDO (**68**) and β-D-Glc*p*-(1→4)-L-α-D-*man*Hep*p*-(1→3)-L-α-D-*man*Hep*p* (**69**) as glycosides of 2-(4-aminophenyl)ethanol (Scheme 11) [40].

Scheme 11



β-D-Glcp-(1-4)-L-α-D-manHepp-(1-3)-L-α-D-manHepp-(1-5)-α-D-Kdo (**68**)

β-D-Glcp-(1-4)-L-α-D-manHepp-(1-3)-L-α-D-manHepp (**69**)

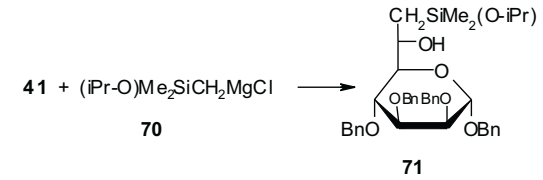
Ch. Berlind, S. Oscarson, [40].

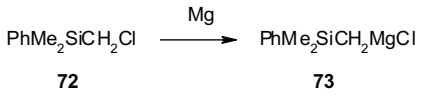
Silyl Grignards

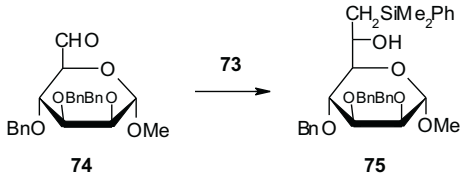
In the search for a more stable (than alkoxymethyl Grignard) C_1 reagent Boons [41] used (isopropoxydimethylsilyl)methylmagnesium chloride (**70**) for reaction with **41**. After hydrolytic work-up the product was oxidized with H_2O_2. Column chromatographic separation gave 60% of the desired LD-*man*Hep*p* derivative (**71**), accompanied by only 3% of the DD-stereoisomer. The heptoside prepared on this way was next used for the syntheses of disaccharide β-D-Glc*p*-(1→4)-L-α-D-*man*Hep*p*-OMe (and also as -O-$(CH_2)_2NH_2$ glycoside) [42] and a trisaccharide 3-*O*-(α-D-Glc*p*)-7-*O*-(L-α-D-*man*Hep*p*)-L-α-D-*man*Hep*p*-OMe [43]. A next report from van Boom's laboratory introduced (phenyldimethylsilyl)methylmagnesium chloride (**73**) as a convenient reagent for chain elongation of manno-dialdosides, *e.g.* **41** [44]. (Chloromethyl)dimethylphenylsilane (**72**) is a commercial product, which reacts with magnesium under typical conditions to form a Grignard reagent [45]. Phenyldimethylsilyl group can be converted to a hydroxy group by oxidation with peroxyacetic acid, sodium bromide and sodium acetate. Thus, reaction of **73** with methyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-hexodialdo-1,5-pyranoside (**74**), followed by oxidative removal of the silyl group, led to the corresponding LD—Hep*p* derivative **75** in 85% yield. The corresponding DD stereoisomer was not found in the reaction mixture.

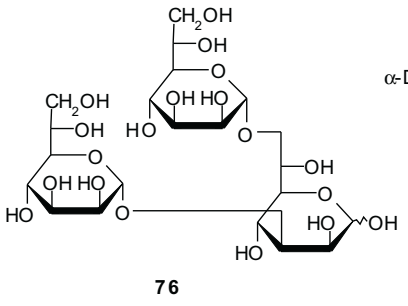
The convenient access to LD-Hep*p* derivatives prompted van Boom's group to perform the syntheses of another series of heptose-containing oligosaccharides. Thus, a branched-chain triheptose from the inner core of *Citrobacter PCM* 187 lipopolysaccharide, 3,7-di-*O*-(L-*glycero*-α-D-*manno*-heptopyranosyl)-L-*glycero*-α-D-*manno*-heptopyranose (**76**) has been synthesized as α-methyl glycoside [46]. Next, α-D-Glc*p*NAc-(1→2)-L-α-D-*man*Hep*p*-(1→3)-L-α-D-*man*Hep*p* (**77**), a trisaccharide from the core region of *Neisseria meningitides* was synthetically prepared [47]. Two LD-*man*Hep*p*-containing disaccharides were obtained: α-D-Glc*p*N-(1→7)-L-α-D-*man*Hep*p*-OMe (**78**) and L-α-D-*man*Hep*p*-(1→6)-L-α-D-*man*Hep*p*-OMe (**79**), being potential immunogenic inner core fragments [48] (Scheme 12).

Scheme 12









α-D-GlcpNAc-(1-2)- L-α–D-*man*Hepp-(1-3)-L-α–D-*man*Hepp (**77**)

G. J. P. H. Boons *et al*. [47].

α-D-GlcpN-(1-7)- L-α–D-*man*Hepp-OMe (**78**)

L-α–D-*man*Hepp-(1-6)-L-α–D-*man*Hepp-OMe (**79**)

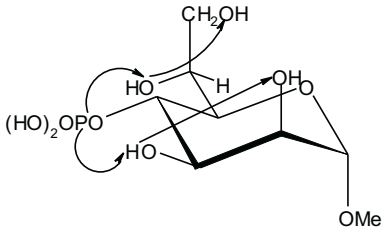
G. J. P. H. Boons *et al*. [48].

Phenyldimethylsilyl group, being a masked form of the hydroxyl group, permits a number of chemical transformations, *e.g.* glycoside coupling, NaOMe/MeOH treatment, H_2/Pd-C hydrogenation, $(n\text{-}Bu)_4NF$, *etc.* These observations gave rise to elaboration of new blocking groups: (phenyldimethylsilyl)methoxymethyl and (phenyldimethylsilyl)methyl enabling protection of carbohydrate OH groups [49]. However, up to the present time these groups do not enjoy a wider application.

Phosphates of LD-*man*Hep*p*

L-*glycero*-D-*manno*-Heptopyranose units, occurring within the inner core of bacterial lipopolysaccharides, are often esterified by a phosphate, β-aminoethylphosphate or -pyrophosphate rests [14]. Location of these groups may cause difficulties, because of migration or removal during the purification procedures. In order to obtain unambiguous models of a LD-*man*Hep*p* system having a firm location of the phosphate groups at O-2, -3, -4, -6, or -7, five L-α-D-*man*Hep*p* monophosphates have been synthesized and characterized by NMR [50]. An analogous series of phosphates of methyl glycoside, L-α-D-*man*Hep*p*-OMe, permitted a study of migration of the phosphoryl grouping [51]. It was shown that $PO(OH)_2$ group is stable under basic conditions but in acidic medium, besides undergoing hydrolysis, can readily migrate along the heptoside chain, the primary phosphate (at C-7 OH) being the most stable [51]. Scheme 13 illustrates the fate of the phosphoryl residue in 4-*O*-phosphate when hydrolysed in 1 M hydrochloric acid (Scheme 13).

Scheme 13



Migration of the phosphoryl group in methyl L-*glycero*-α-D-*manno*-heptopyranoside 4-O-phosphate (1 M HCl, 100 °C, 2 h):
2-O-phosphate 6.7%,
3-O-phosphate 19.3%,
7-O-phosphate 11.2%,
free heptose 62.8%

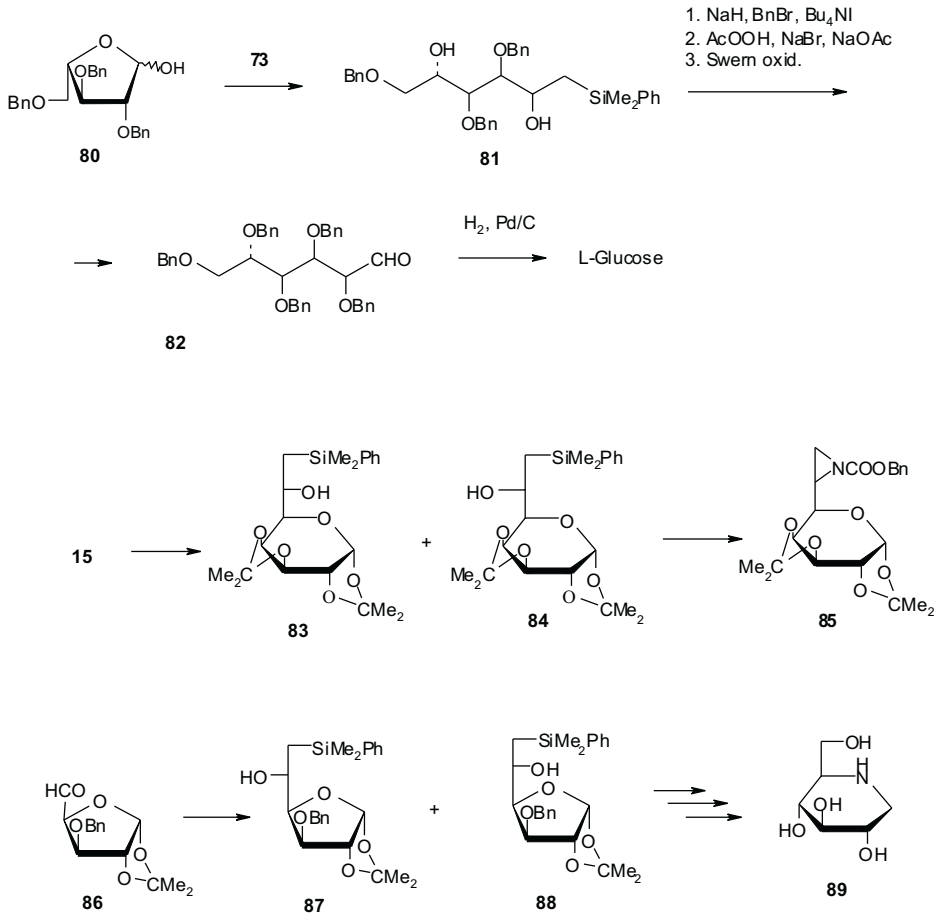
Synthetic phosphates of L-*glycero*-D-*manno*-heptopyranose are only little known. 1-Phosphate [18], 7′-(β-aminoethyl)phosphate [52], and 4- and/or 4′-phosphates of LD-*man*Hep*p*-(1→3)-L-α-D-*man*Hep*p* [53] have been described. 7-Phosphate of enantiomeric DL-*man*Hep*p* was obtained by P. Szabó [54].

Syntheses beyond LD-*man*Hep*p*

Chain-elongation methods, described for alkyl α-D-*manno*-hexodialdo-1,5-pyranosides possess evidently a larger, general potential, *i.e.* can be applied for the synthesis of homologues of different stereoisomeric monosaccharides. Van Boom's group [55] used (phenyldimethylsilyl)methylmagnesium chloride (**73**) for chain extension of 2,3,5-tri-*O*-benzyl-L-arabinose (**80**), thus producing 3,4,6-tri-*O*-benzyl-1-deoxy-1-phenyldimethylsilyl-L-glucitol (**81**) as the exclusive product of the reaction. This product was next benzylated (at positions 2 and 5), de-silylated, and

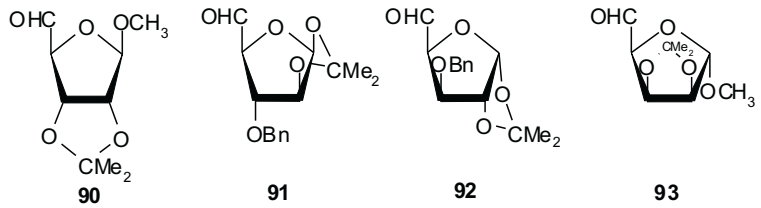
the liberated CH_2OH group was oxidized to the aldehyde stage this forming a per-benzylated derivative of L-glucose (**82**). The same silyl Grignard reagent was used for chain elongation of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**15**) to form 80% of 3:2 stereoisomeric L- and D-*glycero*-D-*galacto*-heptose derivatives, **83** and **84** [56]. The same reaction performed in the presence of $ZnCl_2$ led to 85% of both stereoisomers in 1:19 proportion. The D-*glycero*-D-*galacto* stereoisomer **84** was desilylated, the 6,7-diol formed was converted into a cyclic sulphite, oxidized next to sulphate. The sulphate was reacted with lithium azide, followed by reductive formation of 6,7-epimino derivative **85**, identical (after protection of the N-atom) with a transient product in the successful synthesis of destomic acid. An analogous cycle of reactions was also performed with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**86**), culminating in the preparation of 1-deoxy-nojirimycin (**89**) [56]. The outcome of the chain-elongation reaction must be mentioned: two stereoisomeric products, **87** and **88**, have been obtained of D-*gluco* and L-*ido* configuration in 6:94 proportion and 80% yield (Scheme 14).

Scheme 14



These examples illustrated the application of the "dialdose-Grignard C_1" methodology for the synthesis of some selected sugar-derived compounds. In our extended study we wanted to examine the application of several C_1 Grignards to chain elongation of suitably protected pentose and hexose systems.

Scheme 15



$BnOCH_2MgCl$ (**94**), $MeOCH_2MgCl$ (**95**), $AllOCH_2MgCl$ (**96**), $PhMe_2SiCH_2MgCl$ (**97**)

Our study started with homologation of pentoses to hexoses [57]. Four stereoisomeric pentose-derived aldehydes (Scheme 15): methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**90**), 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*arabino*-pentodialdo-1,4-furanose (**91**), 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**92**) and methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**93**) were prepared by conventional methods. The aldehydes were reacted with four freshly prepared Grignard reagents **94**–**97**, as shown schematically in Scheme 16. The results of chain elongation reaction of pentodialdo-1,4-furanoses are shown in Table 1. The yields of the Grignard reactions are generally high and very high. The products could be readily separated by simple column chromatography. Their identification was based mainly on comparison with authentic hexose samples.

Scheme 16

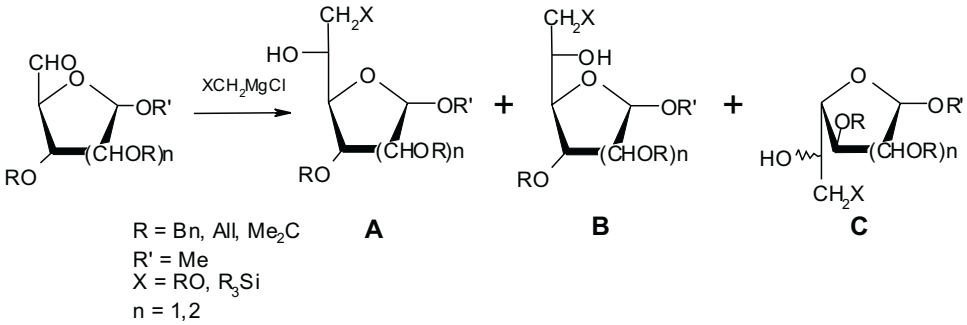
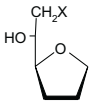
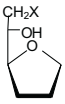


Table 1. Chain elongation reaction between pentodialdo-1,4-furanoses **90**–**93** and Grignard reagents **94**–**97**[a].

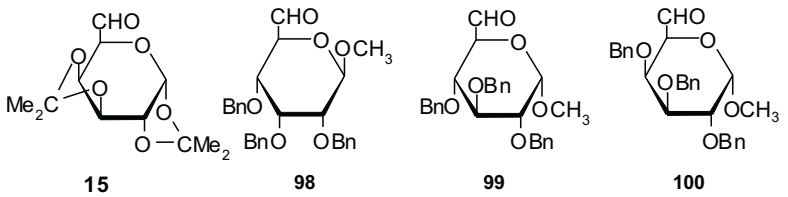
Entry No.	Dialdose	Grignard	X	Overall yield (%)	 Proportion (%)	 Proportion (%)
1	**90**	**94**	BnO	91.6	31	55[b]
2	**90**	**95**	AllO	89.0	11	89
3	**90**	**96**	MeO	76.2	c	
4	**90**	**97**	$PhMe_2Si$	81.0	66	14[d]
5	**91**	**94**	BnO	71.0	–	>95
6	**91**	**95**	AllO	71.8	24	75
7	**91**	**96**	MeO	89.3	–	90
8	**91**	**97**	$PhMe_2Si$	89.0	45	55
9	**92**	**94**	BnO	80.6	>95	–
10	**92**	**95**	AllO	79.8	81	11[e]
11	**92**	**96**	MeO	82.4	82	13
12	**92**	**97**	$PhMe_2Si$	95.0	7	93
13	**93**	**94**	BnO	75.2	57	43
14	**93**	**95**	AllO	81.3	86	14
15	**93**	**96**	MeO	69.2	60	40
16	**93**	**97**	$PhMe_2Si$	78.7	42	58

[a] 1 Mol equiv of dialdose **90**–**93** was reacted with 4 mol equiv of Grignard reagents **94**–**97** at –30°C in THF solution. [b] 14% of C-4 inverted products. [c] Only a mixture of C-4 inverted products was obtained. [d] 20% of C-4 inverted products. [e] 8% of C-4 inverted products.

From the practical point of view the next homologation, leading from hexoses to heptoses, was more important. Using the same four Grignard reagents, **94**–**97**, chain elongation of four hexodialdo-1,5-pyranoses of *allo* (**98**), *gluco* (**99**), and *galacto* (two substrates, **15** and **100**) configuration was performed (Table 2) [30].

The reactions opened an access to less common hexose derivatives, *e.g.* L-talose, L-galactose, L-gulose, *etc*., and a number of difficult available heptoses, *e.g.* D- and L-*glycero*-D-*allo*-, -D-*gluco*-heptopyranoses, *etc*. Several heptoses occur in nature, often as components of polysaccharides. This synthetic access to them, using this protocol may often be regarded as "the method of choice". On the other hand, the results of reactions collected in Tables 1 and 2 present also a contribution to the discussion on nucleophilic additions to chiral oxyaldehydes. All eight aldehydes

Scheme 17

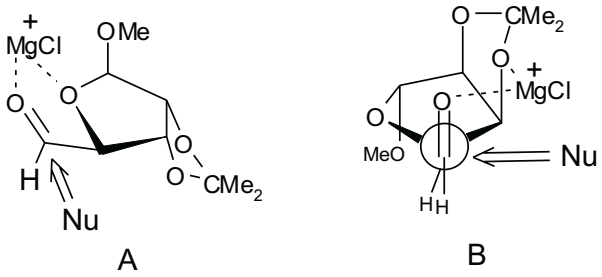


15 **98** **99** **100**

90–**93**, **15**, **98**–**100** contain an α-oxygen atom (furanose or pyranose ring oxygens) and β-oxygen atoms in the sterically defined positions: *trans* {**90** (*ribo*), **91** (*arabino*), **98** (*allo*), and **99** (*gluco*)} or *cis* {**92** (*xylo*), **93** (*lyxo*), **100** (*galacto*), and **15** (*galacto*)} in relation to the formyl group. It is expected that these atoms should influence the steric course of addition of nucleophiles, depending on the importance of α- or β-chelation [58]. In fact, from the data in Tables 1 and 2 it is evident that L stereoisomers (at C-5 or C-6) dominate over D counterparts in reactions of dialdoses **90**, **91** and **98** with alkoxymethyl Grignards. The *gluco* dialdoside **99** afforded both stereoisomeric heptosides – in two cases – with a slight preference for the D stereoisomer. On the other hand, D stereoisomers are formed preferentially from **92, 93, 100** and **15**. We assume that these results are connected α- or β-chelation of the alkoxymethylmagnesium reagents.

The problem of α- and β-chelation in α- and β-alkoxy-aldehydes and -ketones has been studied experimentally [59–63] and theoretically [64,65]. Most relevant experimental investigations have been performed by E.L. Eliel [66–68] and theoretical calculations by E. Nakamura and K. Morokuma [69]. From the experiments it is known that α-chelation has a profound impact on the stereochemical outcome of reactions [66]. β-Chelation seems not to provide a sufficient bias to achieve high stereoselectivities in nucleophilic additions [66,70]. However, *ab initio* calculations indicate that both types of chelation facilitate product formation through low-energy transition states (TS) [69].

Scheme 18

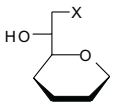
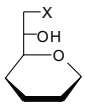


The interpretation of the results presented in Tables 1 and 2 rests on the assumption that both types of chelation play an essential role in determining the stereochemical outcome of reactions, not excluding the participation of a non-chelated reaction pathway. Thus, the main, normal (not „inverted") products of addition of alkoxymethyl Grignards **94**–**96** to *ribo*, *arabino*, and *allo* aldehydes (Table 1, entries 1–8, and Table 2, entries 5–8) are formed by intermediation of α-chelated transition states. In this case α-chelation forces the approach of the nucleophile from „below the ring" (Scheme 18, transition state A), this leading to L-configuration of the new CHOH grouping. Products of the D configuration at C-5 or C-6 are formed probably *via* the non-chelated TS.

For the *xylo, lyxo* and *galacto* aldehydes (**92** and **93**, Table 1, **15** and **100**, Table 2), having β-oxygens in *cis* disposition towards the formyl group, β-chelation becomes more important and the major products formed have D-configuration of the new CHOH grouping (Scheme 18, TS B). Incidentally, the attack of nucleophiles on β-chelated aldehydes **92** and **93** or **100** and **15** follows also the Felkin-Anh model: the *anti* approach towards the ring oxygen atom.

The dimethylphenylsilyl Grignard reagent **97** displays a distinct preference for the formation of hexose or heptose derivatives, having L-configuration at C-5 or C-6. This must be again interpreted with a preferred α-chelated TS in all seven aldehydes, the possibility of forming β-chelates being neglected. This indicates that besides the metal, reaction conditions and proportion of reagents [63,71], the kind of substitution on the alkyl of the organomagnesium compound ($PhMe_2Si$ instead of RO) also influences the course of addition to the carbonyl group. The "diacetonegalactose" derived aldehyde **15** is an exception, as the silyl Grignard does not add specifically to the carbonyl group and both stereoisomeric heptoses are formed in almost equal amounts (Table 2, entry 4). May be the distorted pyranose ring [72] does not allow the formation of an α-chelate? It was found also that the steric course of reaction between **97** and aldehyde **90** strongly depends on the proportion of reagents and the temperature [57].

Table 2. Chain elongation reaction between hexodialdo-1,5-pyranoses **15**, **98**–**100** and Grignard reagents **94**–**97**[a].

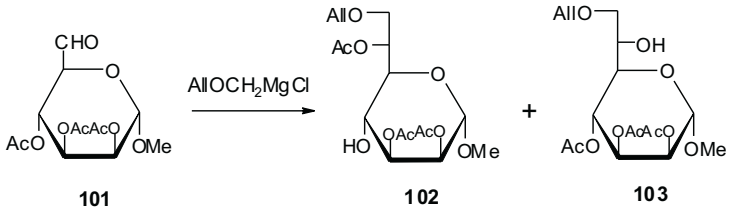
Entry No.	Dialdose	Grignard	X	Overall yield (%)		
					Proportion (%)	Proportion (%)
1	**15**	**94**	BnO	79.6	54	46
2	**15**	**95**	AllO	79.0	79	21
3	**15**	**96**	MeO	82.2	82	18
4	**15**	**97**	$PhMe_2Si$	76.0	52	48
5	**98**	**94**	BnO	84.0	38	51[b]
6	**98**	**95**	AllO	77.2	40	48[b]
7	**98**	**96**	MeO	90.2	31	55[b]
8	**98**	**97**	$PhMe_2Si$	70.2	–	100
9	**99**	**94**	BnO	88.5	60	40
10	**99**	**95**	AllO	91.5	55	45
11	**99**	**96**	MeO	89.1	45	55
12	**99**	**97**	$PhMe_2Si$	87.4	–	100
13	**100**	**94**	BnO	79.8	60	40
14	**100**	**95**	AllO	87.2	79	21
15	**100**	**96**	MeO	91.8	82	18
16	**100**	**97**	$PhMe_2Si$	82.1	2	98

[a] Cf. footnote a in Table 1. [b] entry 5: 6% of C-5 inverted products; also entry 6 – 12%; entry 7 – 14%.

A comment on the formation of the so-called „inverted" products (**C** in Scheme 16) is necessary. Their formation, first noted in the synthesis of L-*glycero*-D-*manno*-heptose derivatives [50], played a substantial role in the carbon atom chain extension of the *ribo* and to a lesser extent of the *xylo* (Table 1) and *allo* systems (Table 2). Reaction of **90** with methoxymethylmagnesium chloride led exclusively to two inverted products in spite of lowering the reaction temperature [57]. The interpretation is based on the assumption that aldehyde **90** is particularly sensitive to the basic medium of the Grignard reaction and readily undergoes epimerization [71] at C-4 before reacting with nucleophiles. This is apparently true also for other aldehydes although to a lesser extent. Although this seems to be a rational explanation, our isomerization experiments (isopropylidene-protected pentodialdo-1,4-furanosides treated with lithium diisopropylamide [73]) did not afford a convincing evidence.

Further studies aimed at the extension of the utility of this homologation method. The popular protection of the OH groups in hexosides is the ester grouping. Thus, three methyl D-hexopyranosides of the α-*manno,* α-*gluco*, and α-*galacto* configuration were conventionally tritylated, acetylated and de-tritylated to afford the proper substrates for oxidation at C-6. The dialdosides obtained were reacted with allyloxymethylmagnesium chloride (THF, –30°C, 1.5 h) to yield stereoisomeric methyl heptosides in moderate yield [74]. From the *manno* substrate **101** the D-*glycero*- and L-*glycero*-D-*manno* stereoisomers, **102** and **103**, were obtained in 21 and 17%. The stereoisomeric heptosides from the *gluco* dialdoside were obtained as a non-separable mixture in 35% (DD:LD = 1:1.4 from the NMR spectrum). The *galacto* dialdoside afforded four methyl heptosides, of the LD and DD configuration (overall yield 53%), but with different location of the acetyl groups. This study has shown that although chain elongation reaction in the presence of the ester groupings is feasible, nevertheless the yields are rather low and migration of the acetyl groups does not facilitate the identification of products.

Scheme 19

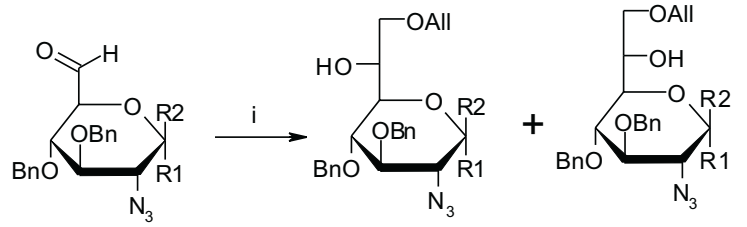


101 **102** **103**

Reactions of allyloxymethylmagnesium chloride with *gluco* (**104** and **105**) and *manno* (**106**) dialdosides are also successful when at C-2 an azido grouping is present [75]. Stereoisomeric heptosides (**107**–**112**, Scheme 20) are obtained in 58–60% and separated into components. Also, both anomeric methyl 2-acetamido-2-deoxy *gluco* dialdosides could be elongated with $AllOCH_2MgCl$ to furnish inseparable mixtures

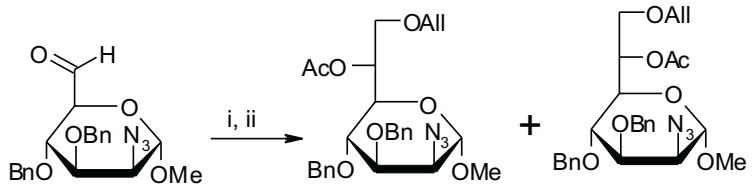
of the corresponding methyl heptosides. The application of the van Boom's reagent for the homologation reaction leads to a single heptoside of the L-*glycero*-D-*gluco* configuration [75].

Scheme 20



104,105 **107,109** **108,110**

104,107,108 R1 = OMe, R2 = H
105,109,110 R1 = H, R2 = OMe



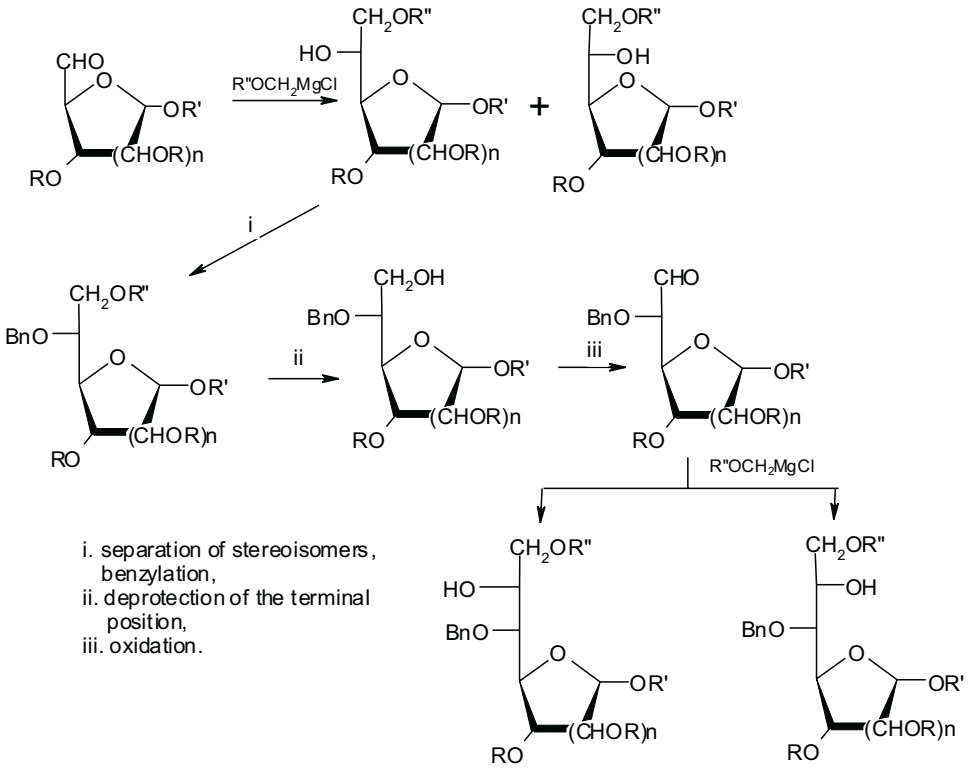
106 **111** **112**

i. $AllOCH_2MgCl$, THF, -20 °C, ii. Ac_2O, Py, DMAP.

The homologation sequence consisting of (i) oxidation of the terminal CH_2OH group to the aldehyde, (ii) reaction with the Grignard reagent, (iii) separation of the stereoisomeric homologues, can be adapted for the next elongation reaction. It would be enough to protect the free OH group and to liberate the primary hydroxymethyl grouping for the next oxidation step. This four-step procedure was used for the elongation of methyl mannosides to methyl octosides (Scheme 21) [76]. For comparison purposes methyl mannosides, protected with 2,3-*O*-ispropylidene and benzyl groups, in the furanose and pyranose forms were selected. Methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-α-*manno*-hexodialdo-1,4-furanoside (**113**) was reacted with allyloxymethylmagnesium chloride to yield 78% of DD and LD-heptosides (**114** and **115**) in 3.3:1 ratio. The DD stereoisomer was isolated, benzylated at C-6, and de-allylated. The DD-heptoside with the primary alcohol function was oxidized and again reacted with $AllOCH_2MgCl$. The octosides (**116**) were obtained in 71% yield, but their separation turned out to be impossible. Homologation of **113** with (phenyldimethyl)-

silylmethylmagnesium reagent afforded two stereoisomeric LD- and DD-heptosides, **117** and **118**, in 83% and in 4:1 proportion. The main product **117** of the LD configuration was benzylated at C-6, oxidatively desilylated, and oxidized to 7-aldehyde. A mixture (74.5%) of two stereoisomeric D-*threo*- and L-*erythro*-α-D-*manno*-octofuranosides, **119** and **120**, was obtained in 4.5:1 ratio (Scheme 22). Benzylation of the main product led to the 7-*O*-benzyl derivative in 18% yield only. The main product was an olefin **121**, stemming from the Peterson elimination. Protection of this group failed in spite of several modifications of the benzylation procedure attempted. In the pyranoside series, the chain elongation reaction of methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-α-D-*manno*-hexodialdo-1,5-pyranoside (**122**) with allyloxymethylmagnesium chloride led to the corresponding heptosides (**123** and **124**, 71%) of the L- and D-*glycero*-D-*manno* configuration in 2:1 proportion. After benzylation (at C-6) and de-allylation of the LD stereoisomer an unreactive aldehyde was obtained, which yielded only negligible amounts of the octosides (**125**) when treated with the Grignard reagent (Scheme 22). An analogous sequence of reaction with the silyl Grignard was unsuccessful due to the Peterson elimination. It is clear that a successful upward homologation must be preceded by a thorough study of the reaction conditions of each step.

Scheme 21



Scheme 22

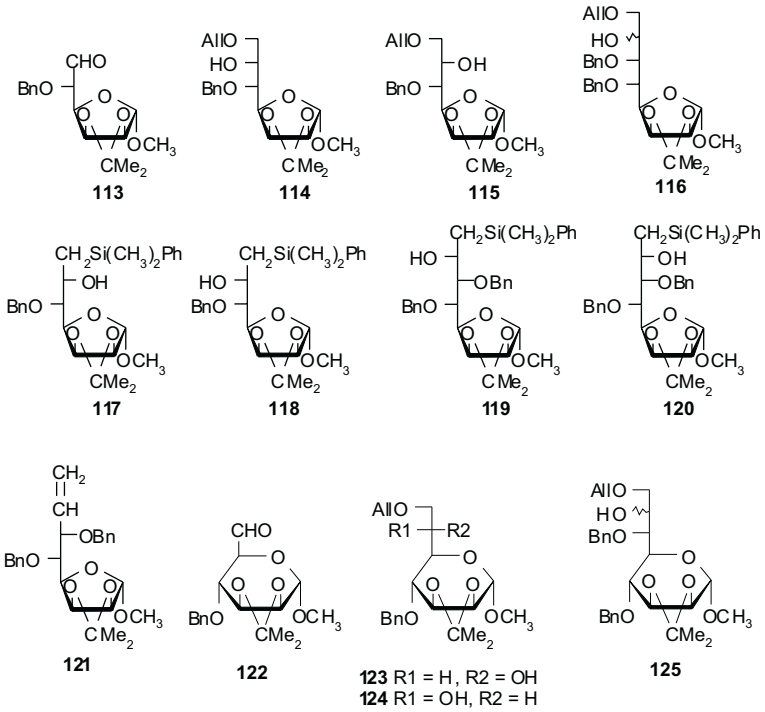


Table 3. Stereoselectivity in chain-elongation reactions of terminal hexose-derived aldehydes **15** and **98**–**100** with a benzyloxymethyl unit under different conditions.

Entry No.	Reagent	**98** (*allo*)			**99** (*gluco*)			**100** (*galacto*[d])			**15** (*galacto*)		
		Yield (%)	D,D	L,D	Yield (%)	D,D	L,D	Yield (%)	D,D	L,D	Yield (%)	D,D	L,D
1	$BnOCH_2MgCl$[a]	84[b]	38	51	89	60	40	80	60	40	80	54	46
2	$BnOCH_2Li$	76	34	66	72	48	52	74	91	9	76	89	11
3	$BnOCH_2Li$ $+Et_2AlCl$[c]	52	31	69	37	48	52	49[e]	87	13	57	93	7
4	$BnOCH_2MgCl$ + TMEDA	79	14	86	78	20	80	71	84	16	74	81	19
5	$BnOCH_2MgCl$ + (*R*)-Me_2N-CHPh-CH_3	90	21	79	79	30	70	87	74	26	76	64	36
6	$BnOCH_2MgCl$ + (*S*)-Me_2N-CHPh-CH_3	86	35	65	80	47	53	83	62	38	74	60	40
7	$BnOCH_2MgCl$ + (*S*)-1-Methyl-2-(piperidinemethyl)-pyrrolidine	–	–	–	57	2	98	–	–	–	–	–	–

a. Data from Ref. [30]. b. C-5 inverted heptosides (11%) were also isolated [30]. c. Precomplexation of the aldehydes (**98**–**100** and **15**) with Et_2AlCl before reaction with $BnOCH_2Li$. d. When the solution of $BnOCH_2Li$ was transmetalated before the reaction with aldehyde **100**, the following results have been obtained (metal derivative/heptoside yield%/D,D:L,D):$Ti(OiPr)_4$/14%/91:9, CuCN/9%/70:30, $Al(OiPr)_3$/81%/91:9. e. Precomplexation of the aldehyde (**100**) with $ZnCl_2$ followed by the reaction with $BnOCH_2Li$ led to 45% of D,D and L,D heptosides in 90:10 proportion. Analogous precomplexation of **100** with $Ti(OiPr)_3Cl$ gave 7% of heptosides in 94:6 proportion, and with $Ti(OiPr)_4$ – 13% in 91:9 proportion.

The last paper from this laboratory concerned attempts at improvement of the stereoselectivity in the homologation procedure by changing several reaction factors [77]. First, the Grignard reagent was replaced by a lithium organometallic counterpart. Reactions of the four hexopyranose 6-aldehydes **15**, **98**–**100** with benzyloxymethyllithium yielded the expected heptosides in good yields. A substantial improvement of the stereoselectivity was noted for the *galacto* aldehydes, slight improvement for the *allo,* and lack of stereoselectivity for the *gluco* aldehyde (Table 3). Transmetalation of this lithium reagent with tetra(isopropoxy)titanium or copper(I) cyanide led to less reactive reagents. Only tris(isopropoxy)aluminium led to a reactive and selective reagent. Several other metal salts did not afford reactive reagents when mixed with benzyloxymethyllithium. Precomplexation of the aldehydes with metal compounds did not lead to any substantial improvement of the stereoselectivity. However, addition of tertiary amines to benzyloxymethyl Grignard was important. With a diamine, TMEDA, the yields of heptosides were high and the stereoselectivity of reactions was improved. A particularly impressive result was obtained when the *gluco* aldehyde was reacted with benzyloxymethylmagnesium chloride in the presence of an enantiomeric diamine, (*S*)-1-methyl-2-(piperidinemethyl)-pyrrolidine: the LD heptoside was obtained in 49:1 domination over the DD counterpart (Table 3).

D-*glycero*-D-*manno*-Heptose

In almost all homologation processes performed for alkyl α-D-*manno*-hexodialdo-1,5-pyranoside besides the desired LD-heptoside some amounts of the DD-stereoisomer are usually formed.

D-*glycero*-D-*manno*-Heptose (**47**, DD-*man*Hep*p*) occurs in nature as a component of an extracellular polysaccharide of *Azotobacter indicum* [78]. In the last decade DD-*man*Hep was found in many bacterial polysaccharides, *e.g.* in LPS of *Yersinia* [79,80], *Proteus penneri* [81–84], *Klebsiella pneumoniae* [85], *Shewanella putrefaciens* [86], *Proteus vulgaris* [87], *Proteus mirabilis* [88], and *Coxiella burnetii* [89]. Recently it has been found that *Helicobacter pylori* strain D4 contains a homopolymer composed of the 1,2- and 1,3-linked D-*glycero*-D-*manno*-heptopyranose [90]. In the biosynthetic pathway leading to L-*glycero*-D-*manno*-heptose, the starting seduheptulose 6-phosphate is isomerized to D-*glycero*-D-*manno*-heptopyranose 6-phosphate, and in the final step DD-*man*Hep ADP is isomerized to LD-*man*Hep ADP [91].

The first synthesis of DD-*man*Hep*p* was reported by Hudson [92]. An improved method, based on the Sowden's approach, was presented by Jones [93]. A *de novo* synthesis of methyl D-*glycero*-α-D-*manno*-heptopyranoside started from furan, which was condensed with 2,3-*O*-isopropylidene-D-glyceraldehyde [94]. The seven-carbon atoms substrate was then converted in five steps into the product.

Conclusions

The practice of carbohydrate chemistry and biochemistry reveals often a need for higher sugars (seven carbon atoms and more). Scarce amounts of these compounds available from natural sources and complications connected with their isolation in the pure state make the synthesis (homologation) definitely advantageous. The synthetic approaches elaborated by Kiliani-Fischer and Sowden demonstrated their utility in the past. However, presently a need for larger amounts of higher homologous sugars of natural, usually D-configuration within the pyranose ring, demanded the elaboration of new methods. Undoubtedly, the homologation methodology, basing on elongation of the carbon atom chain *from the terminal* position, fulfills the needs of the synthesis. In short words, (i) it retains the original configuration of the starting sugar, (ii) it secures the necessary (or desired) protection of the non-participating hydroxyl groups, and (iii) it can be performed on the required, gram-quantity scale. The homologation method, based on alkoxymethyl Grignards, can be exploited on any desired scale, although it requires a careful observation of the experimental conditions, especially as concerns the formation of the Grignard reagent. The silyl Grignard, introduced by van Boom's group, is less demanding as concerns the experimental conditions and can be applied with success for the homologation reaction. The limitation is, however, the almost exclusive formation of the L-*glycero* stereoisomers at the new CHOH grouping. Certainly, for the synthesis of the popular L-*glycero*-D-*manno*-heptose, van Boom's reagent is the reagent of choice. But a wider spectrum of homologous sugars can be obtained with the alkoxymethyl Grignards!

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