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A VERSATILE AND NEW HIGHLY STEREOSELECTIVE APPROACH TO THE SYNTHESIS OF L-*GLYCERO*-D-*MANNO*-HEPTOPYRANOSIDES

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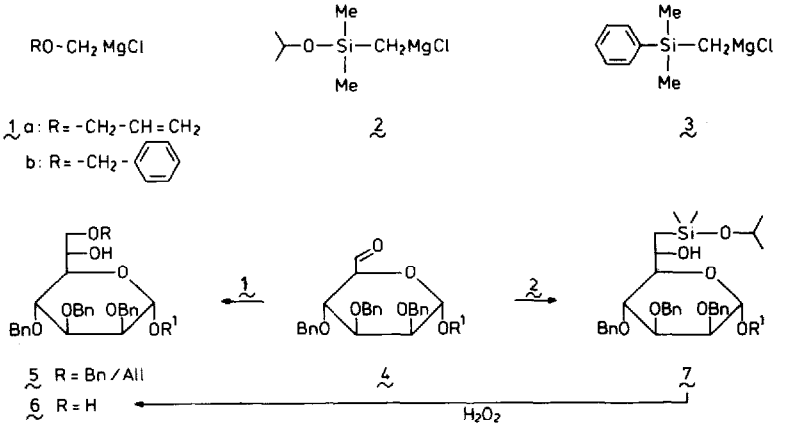
Abstract: The reaction of (phenyldimethyl)silylmethylmagnesium chloride with benzyl 2,3,4-tri-O-benzyl-α-D-manno-hexodialdo-1,5-pyranoside affords the corresponding L-*glycero*-D-*manno*-addition product having at C-7 the phenyldimethylsilyl (PDMSi) group. The latter silanyl compound survived benzylation as well as glycosylation at OH-6, and the PDMSi group could be unmasked with overall retention of configuration to give a free hydroxyl.

It is well-established now that L-*glycero*-D-*manno*-heptopyranose (L-D-Hepp) is an important component of the core region of many polysaccharides of gram-negative bacteria[1]. It has also been proposed that the core region can induce immunological reactions[2].

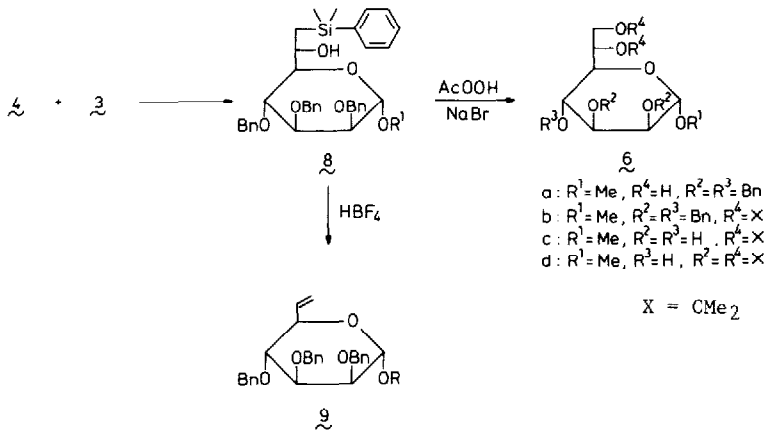
In a preliminary paper[3] we reported that the benzyl-protected L-*glycero*-D-*manno*-heptose derivative **6** (R=H, R^1=Bn) could be prepared *via* the two-step Tamao procedure[4] by reaction of benzyl 2,3,4-tri-O-benzyl-α-D-manno-hexodialdo-1,5-pyranoside (**4**) with (isopropoxydimethylsilyl)methylmagnesium chloride **2** followed by oxidation of the intermediate silane **7** with hydrogen peroxide. It was also pointed out that the above mentioned hydroxymethylation procedure was more reliable than the earlier proposed one-step method of Dziewiszek *et al.*[5] which consisted of a Grignard reaction of the rather unstable[6] allyl- or benzyloxymethylmagnesium chloride (**1**) with **4** to give **5**. However, the general usefulness of the Tamao hydroxymethylene extension method is, despite the high diastereoselective outcome of the reaction, not completely satisfactory to meet the demands for a wide variety of partially and suitably protected L-*glycero*-D-*manno*-heptopyranose derivatives.



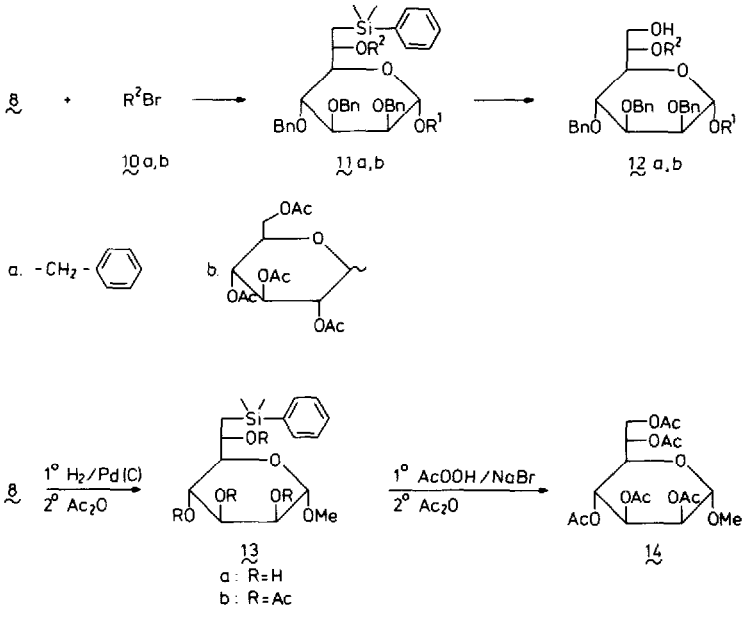
As part of a programme to study in detail the immunological reactions of the L-D-Hepp containing core region[7] of *Neisseria meningitides*, we report, for the first time, that (phenyldimethylsilyl)methylmagnesium chloride (**3**) is a very convenient reagent for the syn-

thesis of partially protected L-*glycero*-D-*manno*-heptopyranosides (L-D-Hepp) in which the phenyldimethylsilyl at C-7 (*e.g.* **8**) may function as a masked form of a hydroxyl group.

The reaction of **4** (R^1=Bn), with reagent **2** gives **7** containing the intrinsically labile isopropoxydimethylsilyl group which, for this reason, has to be desilylated *in situ* with hydrogen peroxide resulting in **6** having a free diol system. On the basis of earlier studies by Fleming *et al.*[8] on silafunctional compounds, we reasoned that the corresponding more stable phenyldimethylsilyl (PDMSi) group could serve as a masked form of the hydroxy group. Thus reaction of fully-protected **4** with **3** would give **8** the C-6 hydroxy group of which will then be amenable to further processing (*i.e.* protection or interglycosydic bond formation to give **11a** and **11b**, respectively). Unmasking of the PDMSi group from **11a,b** thus obtained by the recently developed two-step one-pot Fleming method[8c] would result in the corresponding L-D-Hepp derivatives **12a,b**.



The feasibility of the above mentioned approach was elaborated as follows. The aldehyde **4** (R^1=Me, 30 mmol, THF, 45 ml) was added to a cooled (0°C) solution of the easily accessible[9] Grignard reagent **3** (60 mmol, THF, 45 ml). Work-up, after 1.5 h at 0°C, and purification (Silica gel chromatography) afforded chiral pure **8**[10] (R^1=Me, $[\alpha]_D^{20}$ + 11.5°, c 1, $CHCl_3$) in a yield of 70%. The sense of the diastereoselectivity was the same (*i.e.* predominant formation[11] of the L-D-Hepp derivative **8**, R^1=Me), as corroborated earlier[3] for **7** obtained by the reaction of **4** (R^1=Bn) with **2**. Unmasking of the silyl group from **8** (R^1=Me) was easily accomplished[8c] with AcOOH/NaBr/NaOAc to furnish homogeneous[12] **6a** in a yield of 85%. In this respect it is of interest to note that acidolysis of **8** (R^1=Me) in CH_2Cl_2 with tetrafluoroboric acid resulted in the quantitative formation of the Peterson[13] elimination product **9** (R^1=Me, $[\alpha]_D^{20}$ + 24.6°, c 1; $CHCl_3$). The stability of the PDMSi group was further demonstrated by the preparation of the benzylated and glycosylated L-D-Hepp derivatives **11a** and **11b**. Thus benzylation of **8** (R^1=Me, 1 mmol) in DMF with sodium hydride (1.1 mmol) and benzyl bromide (**10a**, 1.2 mmol) in the presence of a catalytic amount of tetrabutylammonium iodide[14] gave, after 1 h at 20°C and purification, homogeneous **11a** ($[\alpha]_D^{20}$ + 24.6°, c 1, $CHCl_3$) in 95% yield. No trace of the elimination[13] product **9** (R^1=Me) was formed under these mild benzylation conditions. Further, Koenigs-Knorr ($HgCN_2/HgBr_2$)-mediated glycosylation of **8** (R^1=Me, 1 mmol) in acetonitrile (10 ml) with the α-glucosyl bromide **10b** (1.5 mmol)



resulted in the isolation of the β(1-6)-linked disaccharide **11b** (R^1=Me, $[\alpha]_D^{20}$ + 17.1°, c 1, $CHCl_3$) in a yield of 60%. Unmasking of the PDMSi from **11a** and **11b** obtained above, under the conditions mentioned before, afforded the corresponding derivatives **12a** ($[\alpha]_D^{20}$ + 37.8°, c 1, $CHCl_3$) and **12b** ($[\alpha]_D^{20}$ + 99.3°, c 1, $CHCl_3$), respectively, in a yield of 70%. Briefly summarized, the approach illustrated in this paper gives an easy access to L-D-Hepp building blocks, which may be glycosylated at C-6 (*i.e.*, compound **8**, R^1= Me) or C-7 (*i.e.* compound **12a**, R^1=Me). On the other hand, compound **6a** could be converted in an overall high yield by the following sequence of well-established reactions, *i.e.* acetonation (**6a** to **6b**), hydrogenolysis (**6b** to **6c**) and subsequent acetonation into the L-D-Hepp derivative **6d** ($[\alpha]_D^{20}$ + 13.6°, c 1, $CHCl_3$) having a free C-4 hydroxy group. Finally, the stability of the PDMSi-group was further demonstrated by the smooth hydrogenolysis[8b] ($Pd(C)/H_2$) of **8** (R^1=Me) resulting into **13a**, which was then acetylated to give **13b** ($[\alpha]_D^{20}$ + 23.5°, c 1, $CHCl_3$) in an excellent yield. The identity of **13b** thus obtained was further corroborated by unmasking the PDMSi-function and subsequently acetylation to furnish **14** ($[\alpha]_D^{20}$ + 19.8°, c 1, $CHCl_3$) in an overall yield of 60%. At present we are studying in detail whether the PDMSi function in the non-acetylated product **13a** survives acid-catalyzed acetalisation conditions which are required for the preparation of other protected L-D-Hepp derivatives.

In conclusion, the synthetic protocol described in this paper promises[15] to be of great value for the preparation of antigenic oligosaccharides containing L-D-Hepp sugar units.

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10. Satisfactory elemental analytical data were obtained for compounds **6d, 8, 9, 11a,b, 12a,b, 13b** and **14**.
    Relevant ^{1}H-NMR ($CDCl_3$) data of compound: **6d**; δ 4.94 (s, 1H, H1), 4.39 (dt, 1H, H_6, $J_{5,6}$ = 5.0 Hz, $J_{6,7}$ = 7.0 Hz), 4.07 (dd, 1H, H7, $J_{7,7'}$ = 8.5 Hz), 3.96 (dd, 1H, H7'). **8**; δ 4.71 (d, 1H, H1, $J_{1,2}$ = 2.0 Hz), 1.37 (dd, 1H), H7, $J_{7,7'}$ = 17.0 Hz, $J_{6,7}$ = 12.0 Hz), 0.94 (dd, 1 H, $J_{7'}$, $J_{6,7'}$ = 5.0 Hz) 0.36, 0.35 (2xS, 6H, $S_1(CH_3)_2$). **9**; δ 6.02 (M, 1H, H_6), 5.37 (M, 2H, H_7, $H_{7'}$), 4.71 (d, 1H, H_1, $J_{1,2}$ = 2.0 Hz). **11a**; δ 4.85 (d, 1H, H_1, $J_{1,2}$ = 2.0 Hz), 1.42 (m, 2H, H_7, $H_{7'}$), 0.33 (s, 6H, $Si(CH_3)_2$). **11b**; δ 4.93 (d, 1H, $H_{1'}$), 4.79 (d, 1H, H_1, $J_{1,2}$ = 2.0 Hz), 1.55 (M, 2H, H_7, $H_{7'}$). **12a**; δ 4.84 (d, 1H, H_1, $J_{1,2}$ = 2.0 Hz, 3.98 - 3.90 (m, 4H, H_3, H_6, H_7, $H_{7'}$). **14**; δ 4.74 (d, 1H, H_1, $J_{1,2}$ = 1.5 Hz), 4.36 - 4.21 (m, 2H, H_7, $H_{7'}$), 1.92 - 2.21 (5xs, 15H, 5xCH_3Ac).
    Relevant ^{13}C-NMR ($CDCl_3$) data of compound: **6d**; δ 98.37 (C1), 65.58 (C7). **8**; δ 99.39 (C1), 21.72 (C7), -2.45 ($Si(CH_3)_2$. **9**; δ 135.43 (C6), 117.88 (C7), 99.04 (C1). **11a**; δ 99.08 (C1), 17.02 (C7), -2.13, -2.33 ($SiCH_3)_2$). **11b**; δ 101.91 (C1'), 98.64 (C1), 20.03 (C7), -2.21 ($Si(CH_3)_2$. **12a**; δ 98.84 (C1), 62.05 (C7). **12b**; δ 101.50 (C1'), 98.35 (C1), 64.18, 61.70 (C6', C7). **13b**; δ 98.93 (C1), 19.80 (C7), 1.05, 0.76 ($Si(CH_3)_2$). **14**; δ 98.93 (C1), 61.67 (C7).
11. In this particular case the formation of the D-D-Hepp stereoisomer was neglible.
12. Conversion of **8** into **6a** proceeded as expected (ref. 8c) with retention of configuration. The latter was confirmed by hydrogenolysis followed by conversion of the de-benzylated product into the known diethyldithioacetal (see ref. 15a).
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15. Apart from the synthesis of L-D-Hepp derivatives by Dziewiszek *et al.* (ref. 5), two other rather time-consuming approaches have been published. See: (a) H. Teuber *et al.*, Biochemistry, 7, 3303 (1968), and (b) H. Paulsen *et al.*, Liebigs Ann. Chem., 675 (1986).

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