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Silicon-directed Stereocontrolled Cyclization. Possible Route to Functionalized Tetrahydrofurans

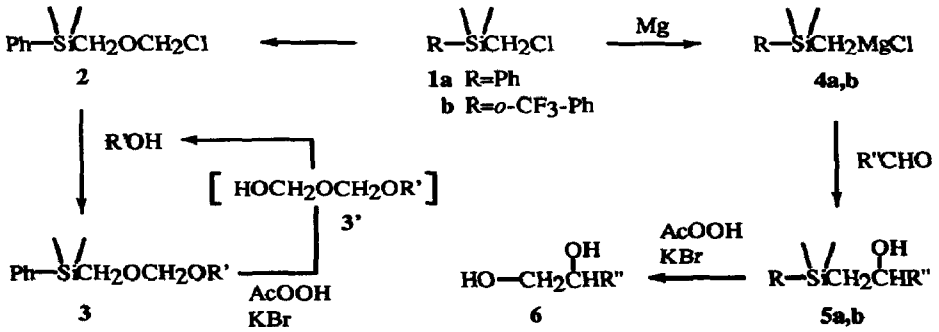
F.L. van Delft, G.A. van der Marel and J.H. van Boom*

Gorlaeus Laboratories, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Abstract: *Cyclization of 3,4,6-tri-O-benzyl-1-deoxy-1-phenyldimethylsilyl-L-glucitol using a slight excess of $BF_3.Et_2O$ or a catalytic amount of H_2SO_4 gives access to the 2,5-anhydro-L-glucitol or 2,5-anhydro-L-mannitol derivative, respectively.*

Earlier studies from this laboratory[1] revealed that (phenyldimethylsilyl)methoxymethyl chloride (**2** in Scheme 1), prepared from commercially available (chloromethyl)dimethylphenylsilane (**1a**), reacts smoothly with primary and secondary hydroxyl groups to yield the corresponding ether derivatives **3**. More importantly, it was found that the Grignard derivative **4a**, derived from **1a**, adds with a high degree of *syn*-selectivity to carbohydrate aldehydes[2] (*e.g.* methyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-hexodialdo-1,5-pyranoside[2a,b]) resulting in the β-hydroxysilane adducts **5a**. The newly introduced phenyldimethylsilane (PDMS) moiety, which is compatible with a wide range of protective group manipulations and glycosylation protocols, can be readily transformed[3] into a primary hydroxyl (*i.e.* conversion of **3**, *via* intermediate **3'**, into R'OH and **5a** into **6**) at a suitable stage of the synthesis. The synthetic usefulness of

Scheme 1

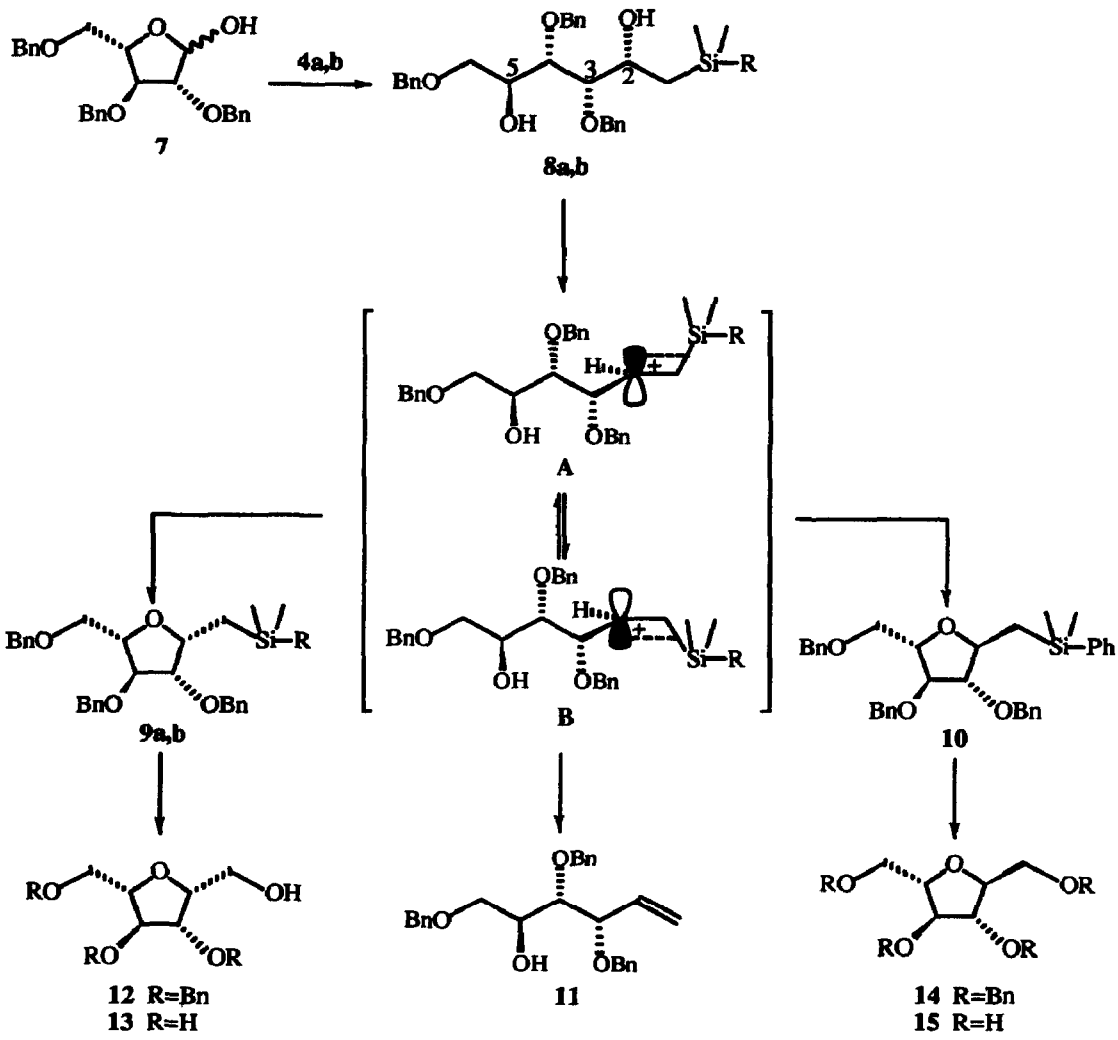


the Grignard reagent **4a** was further demonstrated[4] (see Scheme 2) in its stereoselective condensation with 2,3,5-tri-*O*-benzyl-α/β-L-arabinose (**7**) to yield exclusively the *syn*-adduct 3,4,6-tri-*O*-benzyl-1-deoxy-1-phenyldimethylsilyl-L-glucitol (**8a**, R=Ph).

As part of an ongoing program[2,4,5] to use carbohydrates as chiral synthons, we here report that acid-

mediated cyclization of the L-glucitol derivative **8a** (R=Ph) gives access to either the 2,5-anhydro-L-glucitol derivative **9a** (R=Ph) or the 2,5-anhydro-L-mannitol derivative **10**.

Scheme 2



In analogy with previously reported[6] routes to 2,5-disubstituted tetrahydrofurans *via* a silyl-stabilized carbenium ion, generated in the course of a $BF_3{\cdot}Et_2O$-mediated addition of chiral (E)-crotylsilanes to achiral aldehydes[6d], the silane adduct **8a** (R=Ph, see Scheme 2) in dichloromethane was treated with a slight excess (1.2 equiv.) of $BF_3{\cdot}Et_2O$ at 0° to 20°C. TLC-analysis of the reaction mixture, after one hour at 20°C, showed the presence of a minor and a more lipophilic major product. Work-up and purification by silica gel chromatography afforded the lower-running compound (28% yield), the structure of which was in complete accordance with the Peterson elimination[7] (PE) product **11**[8]. Further, the ^1H and ^{13}C NMR data of the major product, which was obtained in 60% yield, were in agreement with the structure of one of the two possible diastereoisomers **9a** (R=Ph) and **10**. The newly introduced stereocentre at C-2 of the

cyclic adduct was assigned the S-configuration as in stereoisomer **9a** (R=Ph) by the following procedure. Unmasking of the PDMS function with peracetic acid-sodium bromide[3], and subsequent hydrogenolysis of the benzyl groups of 2,5-anhydro-alditol **12**, gave homogeneous[9] **13**, having the same but opposite specific optical rotation (*i.e.* $[\alpha]_D$ +23°) as reported for 2,5-anhydro-D-glucitol[10]. The cyclization to the L-*gluco*-silane product **9a** (R=Ph) may proceed *via* cationic intermediate A formed by silicon-directed ionization of the carbon-oxygen bond at C-2. The observed retention of configuration at C-2 is probably due to a kinetically controlled attack of the C-5 hydroxyl *anti* to the C-Si bond in intermediate A in which rotation about the C-C bond (Scheme 2) is restricted by vertical stabilization[11].

In contrast with the forgoing cyclization, inversion of configuration at C-2 was, apart from formation of PE product **11**, the main stereochemical event when subjecting **8a** (R=Ph) to a catalytic amount of sulfuric acid in THF. Thus, work-up and purification of the H_2SO_4-mediated cyclization of **8a** (R=Ph), after 24 h at 60°C, yielded the PE product **11** (50% yield) together with an intractable mixture (45% yield) of two diastereomers (ratio 5:1), the minor component of which was identical with the L-*gluco*-silane derivative **9a** (R=Ph). The constitution of the major cyclization product was assigned the L-*manno* configuration as in **10** on the basis of the spectral and chiroptical data of the compounds resulting from a similar sequence of events as for the conversion of **9a** (R=Ph) into **13**. Consequently, unmasking of the PDMS group of both diastereomers, followed by benzylation and separation of the resulting fully benzylated epimers, gave the homogeneous product **14** (60% overall yield), the ^{13}C NMR data of which were in full accord with those reported[12] for perbenzylated 2,5-anhydro-D-mannitol. Moreover, hydrogenolysis of **14** yielded **15** having the L-*manno* configuration as evidenced by comparison of its $[\alpha]_D$-value with that of authentic[13] 2,5-anhydro-D-mannitol. The predominant formation of the L-mannitol derivative **10** in the H_2SO_4-mediated cyclization of **8a** (R=Ph) may be explained by a thermodynamically controlled attack of HO-5 at C-2 in the inverted intermediate B, which has lost its configurational identity by rotation of the silyl substituent to the position below the plane of the trigonal carbon[14,15].

At this stage, we explored the possibility whether the occurrence of the unwanted PE product **11** could be decreased by replacing the phenyl substituent at the silicon atom by the more electron withdrawing[16] *ortho*-CF_3-phenyl group. To this end, the L-arabinose derivative **7** was treated with the Grignard reagent **4b**[17] to afford (73% yield) the *syn*-adduct **8b** (R=*o*-CF_3-Ph), which was then cyclized under the influence of $BF_3{\cdot}Et_2O$. Monitoring of the process by TLC analysis revealed that the cyclization proceeded, in contrast with the $BF_3{\cdot}Et_2O$-mediated cyclization of **8a** (R=Ph), rather sluggishly[18] (reaction was complete after 4h at 20°C). In addition, spectral analysis of the purified products showed that the formation of the expected L-glucitol derivative **9b** (57%, R=*o*-CF_3-Ph) was nonetheless accompanied[19] by a substantial amount (27%) of the undesired elimination product **11**.

In conclusion, the results described in this paper indicate that the silicon-directed cyclization of β,ε-dihydroxysilanes may present a valuable asset in the preparation of 2,5-disubstituted tetrahydrofurans[20] which, in turn, are valuable starting compounds for the synthesis of biologically important C-glycosides[21].

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