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Synthesis of Pseudo-Sugars Based On Desymmetrization of Dienylsilanes.

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Abstract: A synthesis of *pseudo*-sugars using the desymmetrization of a dienylsilane, followed by a stereocontrolled introduction of the hydroxymethyl group at C5, is described. The CH_2OH group at C5 was elaborated using either a regioselective cyclopropane-ring opening or a [2,3]-Wittig rearrangement.
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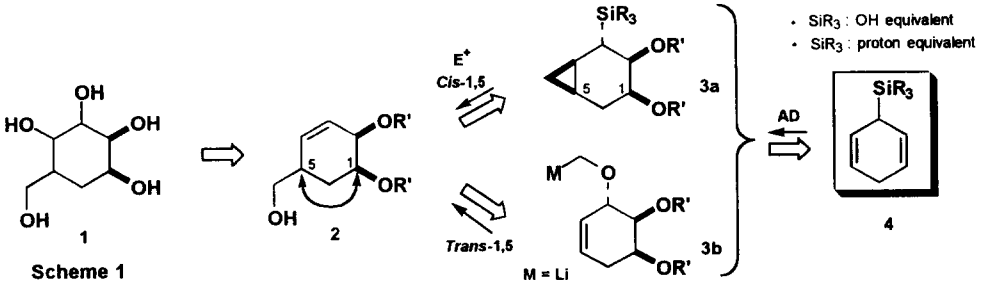
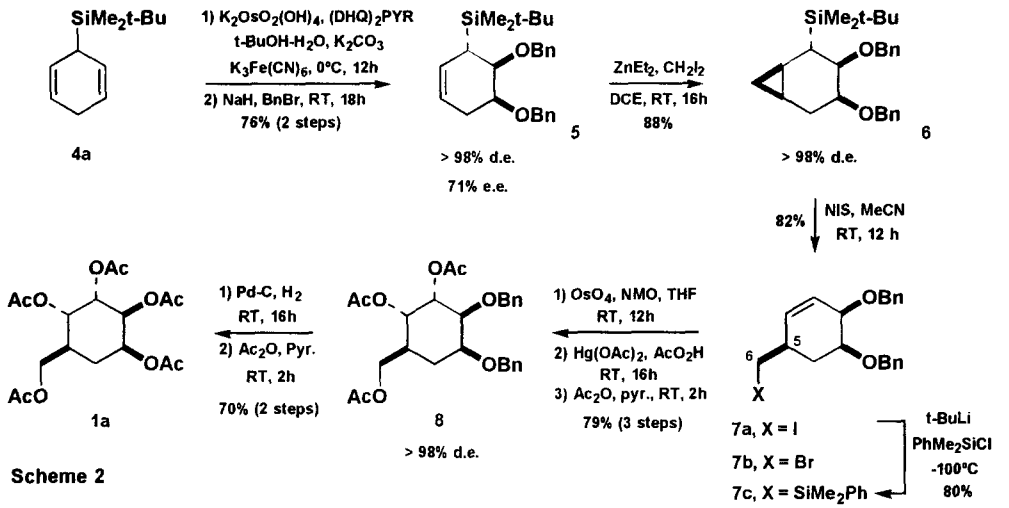
The term *pseudo*-sugar has been given to compounds having the same structure and substitution pattern as that of the parent carbohydrate, but possessing an endocyclic methylene group instead of an oxygen (*i.e.* **1**, Scheme 1).[1] *Pseudo*-sugars have recently received a high degree of attention due to their potential biological activity as antibiotics,[2a] inhibitors of glucose-stimulated insulin release[2b] and more recently as inhibitors of glycosidases.[2c] Their ability to mimic the polarity and the conformation of the parent sugars along with their inertness towards glycosidase hydrolysis make them potential candidates for the inhibition of oligosaccharide processing enzymes.

Different approaches towards these substrates have been devised in the past, including transformation of natural sugars[3a] and more recently the modification of microbial metabolites.[3b-d] We report here a general approach towards the synthesis of *pseudo*-sugars involving, as key-steps, the desymmetrization of a dienylsilane (*i.e.* **4**) and the stereocontrolled introduction of a hydroxymethyl group at C5 (Scheme 1). Differentiation of the enantiotopic double bonds of **4** was anticipated using Sharpless asymmetric dihydroxylation (AD).[4] We showed recently that this approach gives rise to the corresponding diol with complete diastereocontrol (*anti*) and reasonable enantioselectivity.[5] Addition of the CH_2OH fragment would then rely on the stereocontrolled functionalization of the remaining double bond which forms part of an allylsilane. Using the silicon group as either a proton equivalent[6] or as a latent hydroxy group,[7] we anticipated that we could access both *cis*- and *trans*-C1-C5 relative configurations. Cyclopropanation of allylsilanes is known to occur *anti* relative to the silicon group[8] and should thus lead to **3a** having the desired *cis*-1,5 stereochemistry. Electrophilic cyclopropane-ring opening[9] of **3a** would then give rise regioselectively to **2** having the same *cis*-1,5 relative configuration. On the other hand, oxidation of the C-Si bond with retention of configuration, followed by a [2,3]-Wittig rearrangement[3c,10] of **3b** should afford the complementary diastereomer having the *trans*-1,5 relationship. An illustration of these concepts is proposed here with the synthesis of both *pseudo*-β-L-altropyranose **1a**[3d-e] and naturally occurring *pseudo*-α-D-galactopyranose **1b**.[1]



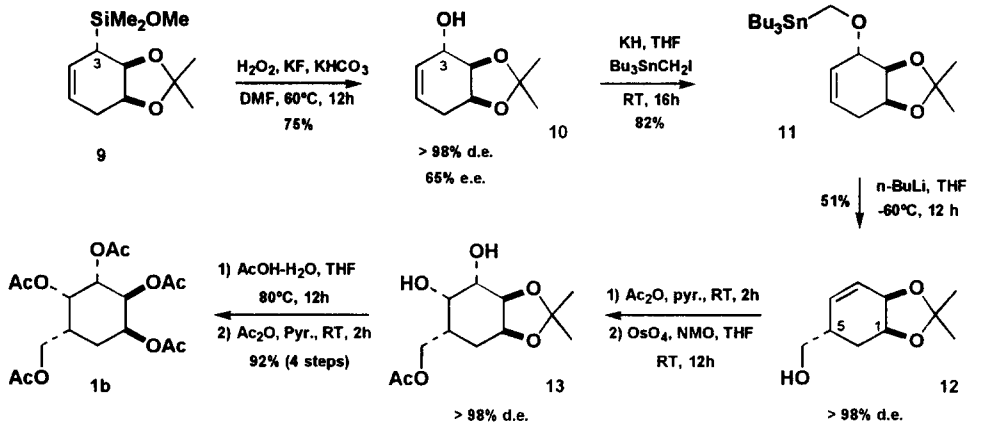
Scheme 1

In the cyclopropanation route we chose the $SiMe_2t$-Bu group instead of the $SiMe_2OH$ group used in our previous studies since it was envisaged that the former would be more able to survive the cyclopropanation conditions. Dienylsilane **4a** was therefore prepared in 94% yield from the corresponding arylsilane using a Birch reduction (Li, NH_3).[11] Sharpless asymmetric dihydroxylation[4] of **4a** with $(DHQ)_2PYR$ as chiral ligand, afforded the desired diol as a single diastereomer in 71% e.e. (Scheme 2). As expected, only the attack of the osmium reagent *anti* relative to the silicon group was observed. Protection of the diol as its bis-benzyl ether (*i.e.* **5**), followed by cyclopropanation using Furukawa conditions,[12] afforded **6** as a single diastereomer. NOESY experiments indicated that, again, the cyclopropanation had taken place *anti* to the silicon group. The cyclopropane-ring opening using $Hg(NO_3)_2$ produced the corresponding olefin (**7**, X = $HgNO_3$) but with a low and irreproducible yield (29%), contrasting with our recent results on acyclic systems.[9] Fortunately, it turned out that N-iodo- and N-bromosuccinimide could also open the cyclopropane ring with concomitant desilylation to afford **7a-b**, but under milder conditions and in much better yields (> 80%). The conversion of the C6-X bond (X = I, Br) into the corresponding C-OH bond was also found to be particularly troublesome. After several attempts using various conditions,[13] the CH_2OH fragment was finally introduced through a two-step sequence involving silylation and oxidation of the C6-Si bond. The silylation was carried out by iodine-lithium exchange with t-BuLi in the presence of $PhMe_2SiCl$ at -100°C (internal quench) to afford the homoallylsilane **7c** in 80% yield. **7c** was then submitted to catalytic osmylation producing the diol with complete diastereofacial selectivity (*anti*). The oxidative unmasking of the $PhMe_2Si$ group using Fleming's conditions[7] followed by acetylation afforded the *pseudo*-sugar **8** which was subsequently debenzylated and fully acetylated to give the known *pseudo*-β-L-altropyranose **1a** in 23% overall yield (from $PhSiMe_2t$-Bu).[3d-e,15]



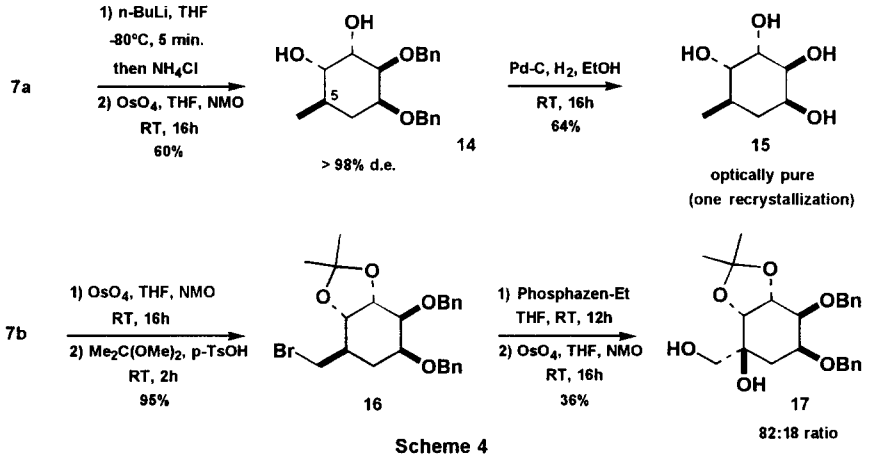
Scheme 2

In the second and complementary approach, the CH_2OH moiety was introduced through a [2,3]-Wittig sigmatropic rearrangement.[10] In this strategy the silicon group is oxidized into a OH group using the Tamao-Kumada conditions[7] which allow a retention of configuration at C3 (Scheme 3). As it is known from precedent in the literature[3c,10] that Wittig rearrangement on such rings occurs in a *syn* fashion, a *trans*-C1-C5 relative configuration was expected in our case. The tin precursor **11** was obtained in 82% yield by alkylation of the allylic alcohol **10**, itself prepared in two-steps starting from a dienylsilanol, following our recently reported procedure.[5] The [2,3]-Wittig rearrangement was then carried out by tin-lithium exchange with n-BuLi at -80°C and the resulting lithium species was stirred overnight at - 60°C, to afford the homoallylic alcohol **12** as a single diastereomer in moderate yield. As expected, the transfer had occurred through a *syn* mode, leading to the desired *trans*-C1-C5 configuration. Acetylation of **12** followed by osmylation, afforded the diol **13** with complete diastereocontrol, *anti* relative to the acetonide group. Removal of the acetonide and complete acetylation eventually gave the pentaacetate derivative of the naturally occurring *pseudo*-α-D-galactopyranose **1b**[1] in 20% overall yield (from commercially available $PhMe_2SiCl$).[16]



Scheme 3

Halogenated intermediates **7a** and **7b** were found to be useful substrates for the synthesis of other *pseudo*-sugars as illustrated in Scheme 4. For example, **7a** was converted via a 3 step sequence into **15**, an isomer of the biologically relevant *pseudo*-fucopyranose.[17] **7a** was easily transformed into the C5 methyl intermediate which was directly osmylated to afford **14** as a single diastereomer. Removal of the benzyl groups then afforded **15**, in homochiral form after one recrystallization (20% overall yield from $PhSiMe_2t$-Bu).[18] In parallel, osmylation of **7b** followed by protection of the resulting diol as an acetonide gave the bromo-*pseudo*-sugar **16**, which was then submitted to elimination conditions in the presence of the strong uncharged nitrogen base, phosphazen-Et.[19] The *exo*-olefin was obtained in moderate yield and was then treated with OsO_4/NMO to produce the corresponding isomer of 1-oxy-*pseudo*-fructopyranose **17** as a 82:18 mixture of separable diastereomers, the major one resulting from an attack of the osmium reagent *anti* relative to the acetonide, according to NOESY experiments.



Scheme 4

In summary, we have shown that the biologically relevant class of *pseudo*-sugars is available in just a few steps and good overall yield from dienylsilanes using our methodology. This approach should theoretically afford both enantiomers of each compound, which is not always the case with other methodologies.[1,3] Interestingly, the same dienylsilane can afford isomeric *pseudo*-sugars at C5, using the silicon group as either a latent hydroxy group or as a proton equivalent. The functionalization of the second double bond (*i.e.* as in **7** and **12**) also offers many variations, enhancing the value of our strategy.

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References and Notes

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15. The optical rotation of **1a** ($[\alpha]_D^{25}$ = + 6.7° (C 1, CH_2Cl_2) (Lit.[3d] : $[\alpha]_D^{24}$ = - 8° (C 1, CH_2Cl_2)) (Lit.[3e] : $[\alpha]_D^{24}$ = + 7° (C 1, CH_2Cl_2)) does not match exactly that of the literature, even after the recrystallization of one of the intermediates (*i.e.* **8**). The optical purity of **1a** can be expressed as 87% (*i.e.* $[\alpha]_{obs}/[\alpha]_{pure}$ x 100). This suggest that **1a** has been enantiomerically enriched during recrystallization and is obtained with a e.e. superior to 71%, the value measured for its precursor **5**.
16. The optical rotation of **1b** ($[\alpha]_D^{25}$ = + 30.6° (C 1, $CHCl_3$) (Lit.[1b] : $[\alpha]_D^{25}$ = + 35° (C 1, $CHCl_3$)) does not match that of the literature, in spite of the careful recrystallization of **1b**. An optical purity of 87% was calculated as above. Again, this may suggest that **1b** has been enantiomerically enriched during recrystallization and is obtained with a e.e. superior to 65%, the value measured for its precursor **10**.
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