Pergamon

Tetrahedron Letters, Vol. 38, No. 51, pp. 8845-8848, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10389-6

Stereocontrolled Access to Carba-C-disaccharides Via Functionalized Dienylsilanes.

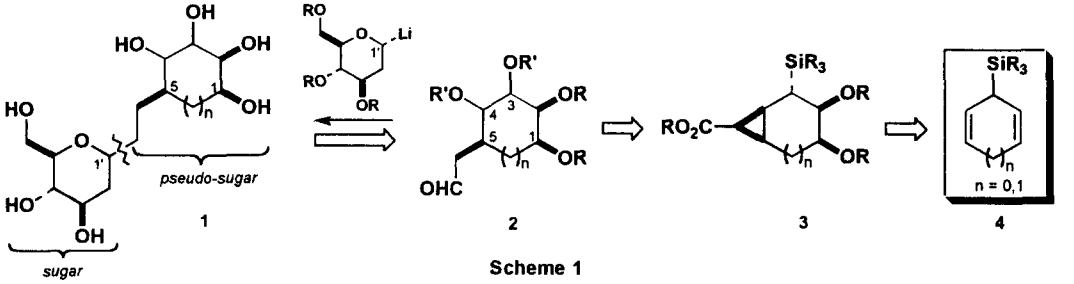
Rémy Angelaud, Yannick Landais,* Liliana Parra-Rapado

Institut de Chimie Organique, Université de Lausanne
Collège Propédeutique, 1015 Lausanne-Dorigny, Switzerland.
Fax: (33) 05 56 84 66 46. email : yannick.landais@ico.unil.ch

Abstract : We report here the total synthesis of a class of C1→ C6 Carba-C-disaccharide, formed by the association between a 2-deoxyglucose as the sugar unit and a *pseudo*-pyranose or a *pseudo*-furanose as the carba-sugar moiety. The carba-sugar fragments were assembled from the corresponding dienylsilanes through a dihydroxylation-cyclopropanation sequence. © 1997 Elsevier Science Ltd.

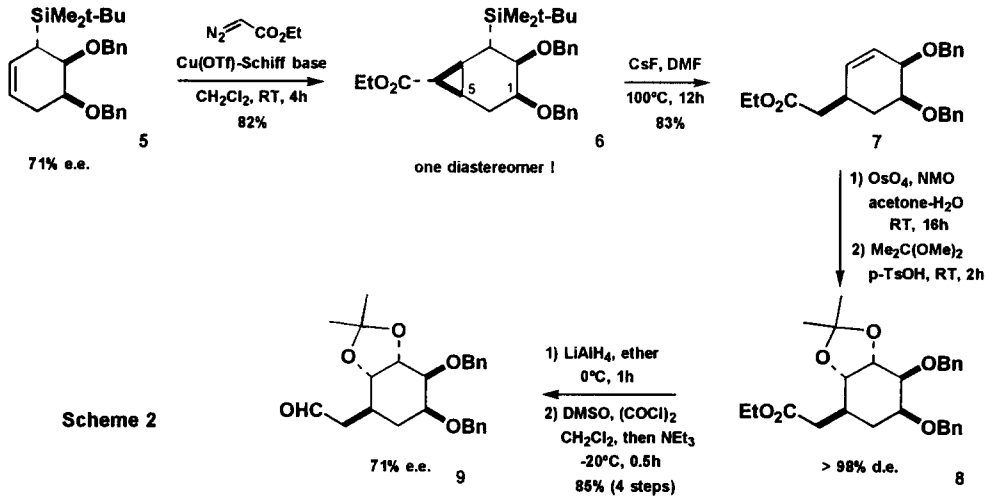
Carba-C-disaccharides such as **1** have received a great deal of attention recently, due to their potential use in the treatment of viral infections, diabetes and cancer (Scheme 1).[1] Their structural and conformational resemblance to related natural sugars suggests that they might be able to inhibit oligosaccharide processing enzymes, *i.e.* glycosidases and glycosyltransferases.[2] Their structure consists of a *pseudo*-sugar and a sugar unit linked together by one (or two) methylene groups instead of the oxygen found in the parent disaccharides. As a consequence, they are endowed with relatively greater stability towards glycosidase-induced hydrolysis. The large number of possible connections between two sugar units also implies that great potential exists for the discovery of specific glycosidase inhibitors. In this context, several approaches to the synthesis of C-disaccharides have recently appeared, illustrating some of the possible combinations mentioned above.[3]

We report herein the total synthesis of a class of C1→ C6 Carba-C-disaccharide **1**, formed by the association between a 2-deoxyglucose as the sugar unit and a *pseudo*-pyranose (**2**, n = 1) or a *pseudo*-furanose (**2**, n = 0) as the carba-sugar moiety (Scheme 1). The connection between the two fragments could be carried out through an aldol condensation between a glucosyl-lithium and the aldehydic function of the carba-sugar, following the methodology of Sinaÿ and Beau.[4] This approach should ensure the control of the stereochemistry at the anomeric centre (C1'), since this reaction is known to occur with *retention of configuration* at this position. The *pseudo*-sugar fragment could be assembled either from 2,5-cyclohexadienyl- or 2,4-cyclopentadienylsilanes **4** using a dihydroxylation-cyclopropanation sequence. As the cyclopropane in **3** is activated by an ester group, we anticipated that a nucleophilic attack at the silicon centre would assist the ring-opening[5] leading to the required chain at C5, along with a new endocyclic double bond (C3-C4) which could then be further functionalized. The strategy could be equally applied to 5- and 6-membered ring systems. The stereochemistry of the *pseudo*-sugar unit should be controlled by the silicon group during dihydroxylation and cyclopropanation, both processes being known to proceed *anti* relative to the silicon group.[6]



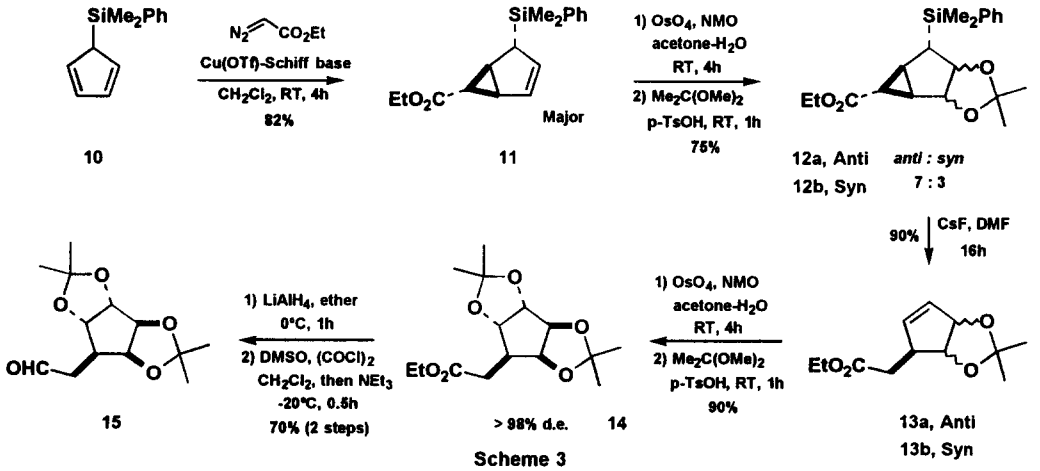
Scheme 1

The allylsilane **5**, prepared as previously reported,[7] was treated with ethyldiazoacetate in the presence of a catalytic amount of Cu(I)OTf-Schiff-base[8] to afford the cyclopropane **6** as a single diastereomer (Scheme 2). As expected, the reaction had taken place *anti* relative to the silicon moiety,[6] thus leading to the relative *cis*-C1-C5 configuration. **6** was then transformed into the olefin **7** in the presence of CsF (8 eq.) in DMF.[5] It must be emphasized that contrary to what was observed with methylene-cyclopropane,[7a] electrophilic reagents such as NIS or NBS do not react with **6**. Subsequent osmylation of **7** occurred with complete diastereocontrol, and, as expected, *anti* relative to the benzyloxy groups. The resulting diol was then protected as an acetonide and the ester function of **8** was converted, using standard methods, into the required aldehyde to give **9** in 58% overall yield from **5**.



Scheme 2

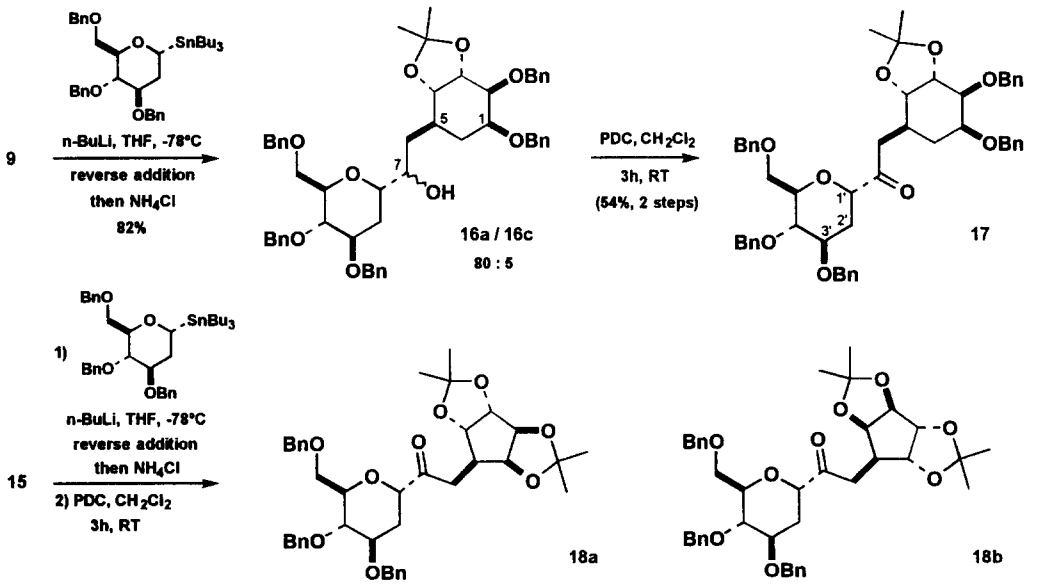
We first decided to follow a similar approach in the cyclopentadienylsilane series but soon abandoned this route where was found that the Sharpless asymmetric dihydroxylation[7] did not afford the desired diol but instead a siloxane residue resulting from desilylation of **10**.[9] Instead, we carried out the cyclopropanation of **10** first, as above, to produce cyclopropane **11** as a 95:5 mixture of two diastereomers (Scheme 3). Our different attempts to reproduce this reaction in a homochiral series[10] unfortunately failed, so we decided to carry out the whole sequence in racemic form with subsequent resolution of the racemic mixture after the glycosylation.



Scheme 3

Dihydroxylation of **11** with OsO_4 produced the desired diol in good yield, but with low diastereocontrol.[11] Protection of the diol as the acetonide gave both diastereomers **12a-b** which could be separated at this stage and treated independently with CsF (2 eq., 50°C) in DMF to afford the olefin **13a** and **13b**. We noticed that the cyclopropane-ring opening occurred in milder conditions with the *anti* isomer **12a**, compared to the *syn* isomer **12b** (CsF (8 eq.), 100°C).[12] Osmylation of **13a** and **13b**, occurring with complete diastereocontrol (*anti* relative to the acetonide), followed by protection of the resulting diol, produced the same pentasubstituted cyclopentane **14** as a consequence of its C_2-symmetry. Therefore, the whole sequence can be performed on the mixture of diastereomers **12a-b**. Reduction of the ester function of **14** followed by Swern oxidation of the alcohol as above afforded the aldehyde **15** in 35% overall yield from cyclopentadiene.

The aldehyde **9** was then condensed with 2-deoxyglucosyllithium, generated *in situ* from the corresponding tin-intermediate[4a] to afford, after aqueous workup, a mixture of three diastereomers **16a-c** in a 80:15:5 ratio (^{1}H NMR) (Scheme 4). The aldols **16a** and **16c**[13] could not be separated by chromatography and were directly oxidized with PDC[4a] to produce the protected carba-C-disaccharide **17** in 11 steps and 22% overall yield from $PhSiMe_2t$-Bu. Extensive NMR studies on **17** showed that retention of configuration at the anomeric centre had effectively occurred.[14] Similarly, condensation of aldehyde **15** with 2-deoxyglucosyllithium produced three aldol products (74% overall yield) which could not be separated and were directly oxidized to afford a 1:1 mixture (^{1}H NMR) of the ketones **18a** and **18b**.[15] These were readily separated by flash chromatography on silica and obtained in enantiomerically pure form, in 15% and 13% overall yield respectively, from cyclopentadiene.



Scheme 4

In summary, we have shown that our desymmetrization process affords a convenient and versatile access to carba-C-disaccharides, in optically pure form using a concise approach (11 steps) from readily available starting materials (cyclopentadiene or $PhSiMe_2t$-Bu). The silicon group is a key-element playing here two major roles. It initially controls the diastereofacial selectivity during dihydroxylation and cyclopropanation;[6] secondly, it assists the cyclopropane-ring opening process.[5,7a] Studies are now underway to extend this strategy to the synthesis of other carba-C-disaccharides, varying both the nature of the sugar unit and the substituents on the *pseudo*-sugar moiety.

Acknowledgements. We thank the *Swiss National Science Foundation* and the *Office Fédéral de l'Education et de la Science* for financial support through the CHiral2 and COST D2 programs. We also thank Dr. S. Ainge for proof-reading this article, Dr. P. Dumy for his help and advice during the ^{1}H NMR studies and C. Glanzmann for technical assistance.

References and Notes

1. (a) Winchester, B.; Fleet, G.W.J. *Glycobiology*, **1992**, *2*, 199-210; (b) Humphries, M.J.; Matsumoto, K.; White, S.L.; Olden, K. *Proc. Natl. Acad. Sci. U.S.A.*, **1986**, *46*, 1752-1756; (c) Anzeveno, P.B.; Creemer, L.J.; Daniel, J.K.; King, C.-H.R.; Liu, P.S. *J. Org. Chem.*, **1989**, *54*, 2539-2542.
2. (a) Sinott, M.L. *Chem. Rev.*, **1990**, *90*, 1171-1202; (b) Legler, G. *Adv. Carbohydr. Chem.*, **1990**, *48*, 319-384.
3. For comprehensive reviews on the total synthesis of C-glycosides, see : (a) Postema, M.H.D. *Tetrahedron*, **1992**, *48*, 8545-8599; (b) Levy, D.E.; Tang, C. in *The Chemistry of C-Glycosides*; Tetrahedron Organic Chemistry series, Pergamon, Elsevier Science Ltd., 1995.
4. (a) Lesimple, P.; Beau, J.-M.; Sinaÿ, P.J. *Carbohydr. Res.*, **1987**, *171*, 289-300; (b) See also : Wittmann, V.; Kessler, H. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 1091-1093.
5. Reichelt, I.; Reissig, H.-U. *Liebigs, Ann. Chem.*, **1984**, 828-830.
6. Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.*, **1989**, *37*, 57-575.
7. (a) Preceding communication in this issue; (b) Angelaud, R.; Landais, Y. *J. Org. Chem.*, **1996**, *61*, 5202-5203.
8. The Schiff-base was prepared from benzaldehyde and ethylenediamine, following our reported procedure : Andrey, O.; Landais, Y.; Planchenault, D.; Weber, V. *Tetrahedron*, **1995**, *51*, 12083-12096.
9. **10** was prepared in 95% yield by silylation of cyclopentadienyllithium (prepared from freshly distilled cyclopentadiene and n-BuLi (1.5 eq. at -80°C) with $PhMe_2SiCl$). ^{1}H NMR indicated that using this procedure, less than 5% of the undesired vinylsilanes were formed.
10. Our different attempts, using Cu(I)OTf with Evans or Pfaltz chiral ligands or Doyle's $Rh_2(MEPY)_4$, resulted in the formation of the desired cyclopropane in good yield but with no enantioselectivity. See : (a) Pfaltz, A. *Acc. Chem. Res.*, **1993**, *26*, 339-345; (b) Evans, D.A.; Woerpel, K.A.; Scott, M.J. *Angew. Chem. Int. Ed. Engl.*, **1992**, *31*, 430-432; (c) Protopopova, M.N.; Doyle, M.P.; Müller, P.; Ene, D. *J. Am. Chem. Soc.*, **1992**, *114*, 2755-2757.
11. The *anti* configuration was attributed to **12a** having the diol moiety *trans* relative to the silicon group. The lower diastereocontrol in the cyclopentadienyl series may be attributed to the close proximity of the cyclopropane moiety and the approaching osmium reagent which forces, to a certain extent, the dihydroxylation to proceed *syn* relative to the silicon group. Such a trend was not observed with cyclohexadienyl systems, where cyclopropanation, followed by dihydroxylation, afforded a single diastereomer, both processes occurring *anti* relative to the silicon group.
12. Landais, Y.; Parra-Rapado, L. *Tetrahedron Lett.*, **1996**, *37*, 1209-1212 and references cited therein.
13. As indicated by the oxidation with PDC, **16a,c** is a 80:5 mixture of the aldol epimers at C7 (implying a 88% d.e. for the aldolisation), formed from the major enantiomer of the *pseudo*-sugar **9**. The third aldol **16b**, obtained pure after chromatography (15%), is thus generated from the minor enantiomer of **9**, in good agreement with the enantiomeric excess measured for **5** (71% e.e.).
14. The stereochemistry of the anomeric centre (C1') in **17** was obtained from the coupling constant H1'-H2' ($J_{1\text{-}2'ax}$ = 5.8 Hz; $J_{2'ax\text{-}2'eq}$ = 13.2 Hz and $J_{2'ax\text{-}3'}$ = 10.2 Hz) of the 2-deoxyglucosyl moiety (Scheme 4).[4a] The stereochemistry at C7 in the major isomer **16a** could not be determined on the basis of ^{1}H NMR studies.
15. ^{1}H NMR studies unambiguously showed that retention of configuration at the anomeric centre occurred during the aldol-oxidation sequence leading to **18a-b**, similarly to what was observed for the preparation of **17**.

(*Received in France* 1 *September* 1997; *accepted* 13 *October* 1997)