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STEREOSELECTIVE SYNTHESIS OF "LINEAR" C-DISACCHARIDES

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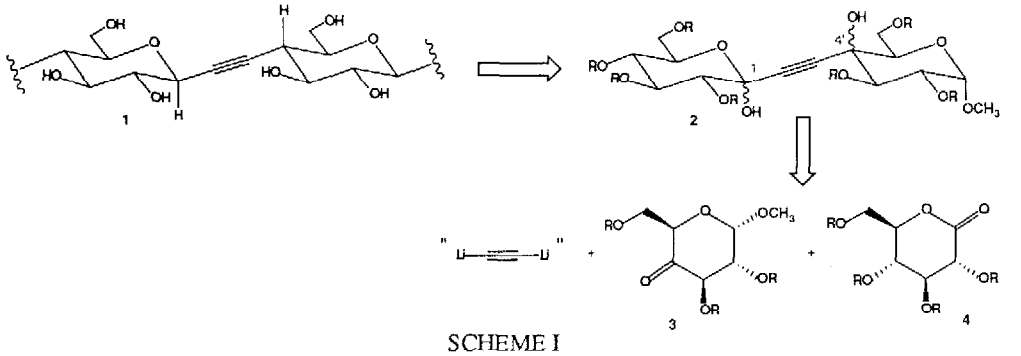
*Abstract: A 1,4'-C-disaccharide (**20**) containing an acetylenic linkage was synthesized from D-glucose via a homologation of a 4-ulose derivative (**6a**) followed by condensation with 2,3,4,6-tetrabenzyl pyranolactone. Subsequent reduction afforded isomerically pure β-C-disaccharide in good overall yield.*

We are currently investigating the use of C-oligosaccharides (**1**) as readily accessible substrates for the introduction of functional groups with fixed (and predictable) distance relationships to one another. By varying the number of monomers and C-1/C-4' substitution of the terminal pyranoses, we envision utilizing these substrates to study interactions of macromolecules in aqueous solutions. Herein we report the stereoselective synthesis of an alkynyl substituted C-dissaccharide (**20**).[1]

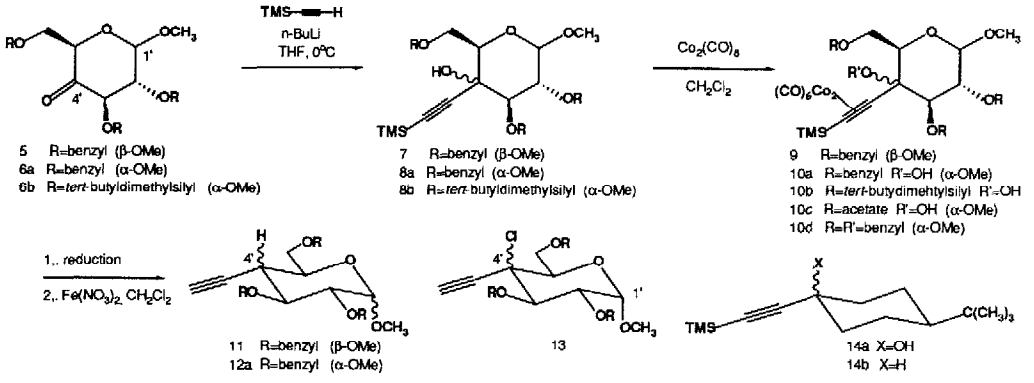


SCHEME I

Our initial attempts were focused on the sequential generation of the alkylidene anions obtained from bis-trimethylsilyl acetylene. Addition to a suitably functionalized lactone **4** followed by ketone **3** would afford a diol (**2**) which we hoped could be stereoselectively reduced to **1**. The stereoselective reduction of C-1 hemiketals has been extensively investigated for alkyl, aryl, and alkynyl substituents,[2] affording excellent yields of the desired β-C-glycosides. However, stereoelectronic effects which govern axial addition of reducing agents at C-1 (in the

glucose series) would no longer be in effect at C-4' thus complicating selective reduction at this center.[3] We reasoned that converting the acetylene to the more bulky cobalt complex followed by axial addition of a reducing agent to the cobalt-stabilized carbocation might favor the equatorial conformation of this group and afford the desired stereochemistry.

Stereoselective reductions at C-4' were investigated on the propargyl monomers **9** and **10**.[4] Addition of trimethylsilyl lithium acetylide to 4-ulose derivatives[5] **5** (R=benzyl, β-anomer), **6a** (R=benzyl, α-anomer), and **6b** (R=*tert*-butyldimethylsilyl, α-anomer) afforded exclusive axial addition (**8b**) to the silyl protected substrate or a 4:1 and 1.5:1 mixture by ^{1}H NMR analysis of axial to equatorial isomers (**7** and **8a** respectively) in the less sterically hindered benzyl series. The cobalt complexes ($Co_2(CO)_8$, CH_2Cl_2, rt) were prepared according to Nicholas[6] and were either isolated (flash silica gel chromatography) or carried on to the next step as a crude mixture. Initial attempts at reduction were carried out on **9** using $NaBH_4/CF_3COOH$[7] in dichloromethane at O°C. After decomplexation ($Fe(NO_3)_2$, CH_2Cl_2, rt), only a small amount of the desired product **11** was obtained (<5%). In the case of the α-anomer **10a**, treatment with $Et_3SiH/BF_3{\cdot}OEt_2/CH_2Cl_2$[8] resulted in a small amount (<10% after decomplexation) of the desired product **12a** as a 1:1 mixture of diastereomers at C-4'. Upon introduction of excess reagents or increase in the reaction temperature, a mixture of debenzylated products was observed. When **10a** was reacted with $HBF_4{\cdot}Me_2O/Et_3SiH/CH_2Cl_2$ followed by cobalt decomplexation, exclusive formation of the desired equatorial isomer **12a** was obtained in low yields (<10%). The stereochemical outcome of the reaction was readily determined by analysis of the ^{1}H NMR where the large coupling constant of the C-4' methine triplet is a result of the trans-diaxial relationship to the C-3' and C-5' hydrogens. Treatment of the tetrabenzyl derivative **10d** with $Et_3SiH/TiCl_4/CH_2Cl_2$,[6] afforded chloride **13** as one of several products. It should be noted that reductions of the C-1 acetylenic hemiketals ($BF_3.Et_2O$, CH_3CN, 0°C) results in virtually quantitative conversion to the C-glycosides in a matter of minutes at ice-bath temperatures.[1]

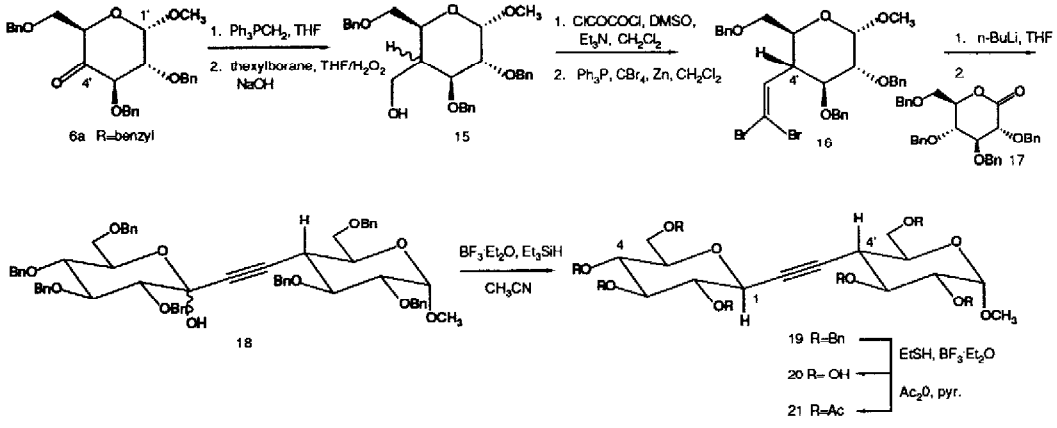


SCHEME II

In an effort to increase the acid stability of the protecting groups, silyl ether **8b** was deprotected (HF·CH_3CN, rt.) and converted to its triacetate (Ac_2O, pyridine, 60°C) and complexed with cobalt to afford **10c**. Treatment under a variety of conditions including $HBF_4.Me_2O/Et_3SiH/CH_2Cl_2$, $CF_3COOH/Et_3SiH/CH_2Cl_2$, $NaBH_4/CF_3COOH/CH_2Cl_2$, resulted in recovery of starting material. The lack of reactivity is likely a result of the steric hindrance of the substituted carbohydrate and the competing basicity of the ether oxygens which make

approach of excess reagent to the tertiary alcohol more difficult. The lability of the protecting groups at high acid concentrations results in a large mixture of compounds at which point the course of the reaction is difficult to determine. Selective activation of the tertiary alcohol in the highly oxygenated sugars is in stark contrast to the facile reduction (5 min) of the cobalt complex of **14a** (mixture of isomers) with $NaBH_4/CF_3COOH/CH_2Cl_2/0°C$ (SCHEME II) which resulted in a 91% yield of **14b** favoring the equatorial product (1.2:1).

In an attempt to obtain a reliable method for formation of these dimers, we directed our attention to the one-carbon homologation at C-4' (SCHEME III). Several routes are known for the stereoselective introduction of carbon which involve the intermediacy of 1,6-3,4-dianhydroglucose. Lewis-acid catalyzed addition of dimethylcyanoaluminum[9] or allyl silane[10] affords good yields of the resulting alcohols. We chose the 4-ulose derivative of glucose since we felt that all intermediates in the series **6a-16** would be useful for further manipulation of the terminal C-pyranosides in the C-oligosaccharide. Wittig condensation (Ph_3PCH_2, THF, 0°C-rt) followed



SCHEME III

by hydroboration/oxidation afforded alcohol **15** in 45% from the C-4' alcohol. We found that the regiochemistry of addition of borane (BH_3) to the exomethylene resulted in a 1:1 mixture of primary to tertiary alcohols after oxidation. The use of more bulky reagents (9-BBN, thexyl borane) resulted in a lower yield and substantial increase in time required. We observed that addition of BH_3 to a thexyl borane/olefin mixture which had been stirring for 12 hours decreases the reaction time and results in exclusive formation of the desired primary alcohol. Swern oxidation (ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, -78°C to -40°C, 98%) afforded a 2:1 mixture of axial to equatorial aldehydes, a ratio which could be inverted upon addition of excess Et_3N. Further equilibration in the formation of the dibromo olefin (PPh_3, CBr_4, Zn, CH_2Cl_2, rt)[11] resulted in a >80% yield of the desired diastereomer (**16**) which was readily separated by flash silica gel chromatography.

The lithium acetylide obtained from n-BuLi addition to **16** (n-BuLi, THF, -78°C to -40°C) was quenched with lactone **17**[12] to afford dimer **18** in 80% yield as an inseparable mixture of diastereomers at C-1. Reduction of the hemiketal (Et_3SiH, $BF_3{\cdot}Et_2O$, CH_3CN, 0°C,99%) resulted in isomerically pure benzyl C-disaccharide (**19**)with none of the α-isomer being detected by ^1H NMR. Deprotection of the benzyl ethers under Lewis acid conditions[13] ($BF_3{\cdot}Et_2O$, CH_2Cl_2, EtSH, rt, 63%) afforded methyl glycoside **20.** Polyol **20** was converted to heptaacetate **21** (Ac_2O, pyridinc, 50°C, 90%) for further characterization.[14]

Analysis of the ^1H NMR of **20** in D_2O established unequivocally the stereochemical integrity at C-1 and C-4' and compared well with the C-4' monomer (**12a**) and a C-1 β-acetylenic C-glycoside (**22**) prepared from glucose by a separate route.[15] The propargyl hydrogens at C-1 and C-4' are readily identified by the spin-spin coupling (J=1.6 Hz) to one another. The diaxial relationship of C-4' methine to the hydrogens at C-3' and C-5' results in similar coupling constants ($J_{4'-3'}$=10.5Hz, $J_{4'-5'}$=10.8Hz) to each as is the case of the benzyl (**19**, J=10.4-10.7Hz)[16], acetate (**21**, $J_{4'-3'}$=10.2Hz, $J_{4'-5'}$=10.9Hz), and monomer (**12a**, J=10.6-10.7Hz) intermediates. A similar analysis of the H-1/H-2 coupling (**20**, J_{1-2}=9.1Hz, **21**, J_{1-2}=9.4Hz, 22, J_{1-2}=9.0Hz) confirms the stereochemical assignment at C-1. Further synthesis of C-oligosaccharides and the incorporation of peptides at the termini are currently under investigation in these laboratories.

ACKNOWLEDGEMENT: We would like to thank the National Institutes of Health for financial support (NIH FIRST GM 39512).

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(2) Lewis, M.D.; Cha, J.K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976; Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479.

(3) The monomer precursors are numbered as they would appear in the dimer.

(4) Satisfactory analytical data was obtained for all compounds.

(5) These were prepared as follows: **5**) starting from β-D-methylglucopyranose, a. α,α-dimethoxytoluene, p-TsOH (cat.), DMF, 80%; b. NaH, benzyl bromide, DMF, 95%; c. $NaCNBH_3$, HCl/Et20/THF, 90%; d. ClCOCOCl, Et_3N, DMSO, CH_2Cl_2, 80%; same procedure for **6a** from α-D-glucopyranose; **6b**) starting from α-D-methylgalactopyranose, a. TBDMSiCl, imidazole, DMF, 75%; b. ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, 95%.

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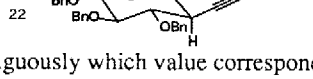
(11) Corey, E.J.; Fuchs, P.L. *Tetrahedron. Lett.* **1972**, *36*, 3769.

(12) Prepared by Swern oxidation (DMSO, Et_3N, ClCOCOCl, CH_2Cl_2, -78°C) of commercially available 2,3,4,6-tetrabenzyl glucose.

(13) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.

(14) 1H NMR (360Mz, $CDCl_3$) δ 1.99 (s,3), 2.01 (s, 3), 2.06 (s, 9), 2.10 (s, 3), 2.12 (s, 3), 2.84 (dt, 1, $J_{1-4'}$=1.6Hz, $J_{3'-4'}$=10.2Hz, $J_{4'-5'}$=10.8Hz, H4'), 3.39(s, 3, C1'-OCH3), 3.64 (ddd, 1, J_{5-6a}=2.18Hz, J_{5-6b}=4.48Hz, J_{4-5}=10.8Hz, H5), 4.00(ddd, 1, $J_{5'-6a'}$=2.2Hz, $J_{5'-6b'}$=4.9Hz, $J_{4'-5'}$=10.8Hz, H5'), 4.09 (dd, 1, J_{5-6a}=2.18Hz, J_{6a-6b}=12.40Hz, H6a), 4.15 (dd, 1, $J_{1-4'}$=1.6Hz, J_{1-2}=9.4Hz, H1), 4.22 (dd, 1, J_{5-6b}=4.49, J_{6a-6b}=12.4Hz, H6b), 4.24 (dd, 1, $J_{5'-6b'}$=4.9Hz, $J_{6a'-6b'}$=12.1Hz, H6b'), 4.25 (dd, 1, $J_{5'-6a'}$=2.2Hz, $J_{6a'-6b'}$=12.1Hz, H6a'), 4.78 (dd, 1, $J_{1'-2'}$=3.5Hz, $J_{2'-3'}$=10.2Hz, H2'), 4.90 (d, 1, $J_{1'-2'}$=3.5Hz, H1'), 5.01-5.09 (m, 3, H2, H3, H4), 5.45 (t, 1, $J_{2'-3'}$=$J_{3'-4'}$=10.2Hz, H3').

(15) C-glycoside **17** was prepared from **12** in two steps: 1. trimethylsilylacetylene, n-BuLi, THF, O°C, 95%; 2. Et_3SiH/BF_3·OEt_2, CH_2Cl_2, 0°C, 95%.

22 

(16) It is difficult to assign unambiguously which value corresponds to 3' vs. 5'.

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