Tetrahedron Letters, Vol. 34, No. 31, pp. 4897-4900, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

STEREOSELECTIVE SYNTHESIS OF DIPYRANYL C-DISACCHARIDES

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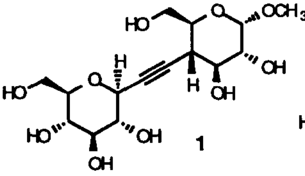
Abstract: *The synthesis of trans-fused dipyranyl sugars containing an acetylenic moiety at C-1 has been completed starting from D-glucose. Formation of the β-substituted C-disaccharide provides a water soluble sugar-based linker spanning approximately 12.8 Å.*

The design and synthesis of polycyclic frameworks which can be used to control the spatial relationship of functional groups has provided useful applications in diverse areas including polymerizations, electron transfer processes and molecular recognition events.[1] In aqueous media, the extensive use of cross-linking agents which act as tethers to covalently link biopolymers and their more recent application to smaller molecules has focused our interest in the generation of water-soluble "linear" C-oligosacharides. The use of carbohydrates as rigid frameworks in probing the spatial relationship of appendant sugars has been described in relationship to the generation of antiviral agents which require polydentate interactions.[2] We have reported[3] on the syntheses of glucose-derived C-dissacharide **1**, which can be converted to water soluble oligomers of the general formula **2**.[4] In an effort to expand the versatility of these tethers, we were interested in synthesizing fused dipyranose C-oligosacharides (**3**)[5,6] which possess increased rigidity with respect to **1** and which contain two anomeric carbons available for simultaneous functionalization. Described herein is the stereoselective synthesis of disaccharide **3**.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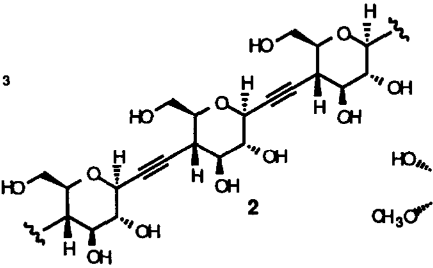
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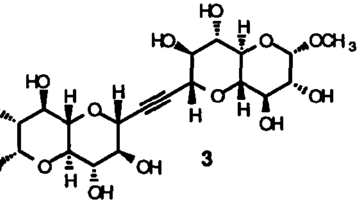
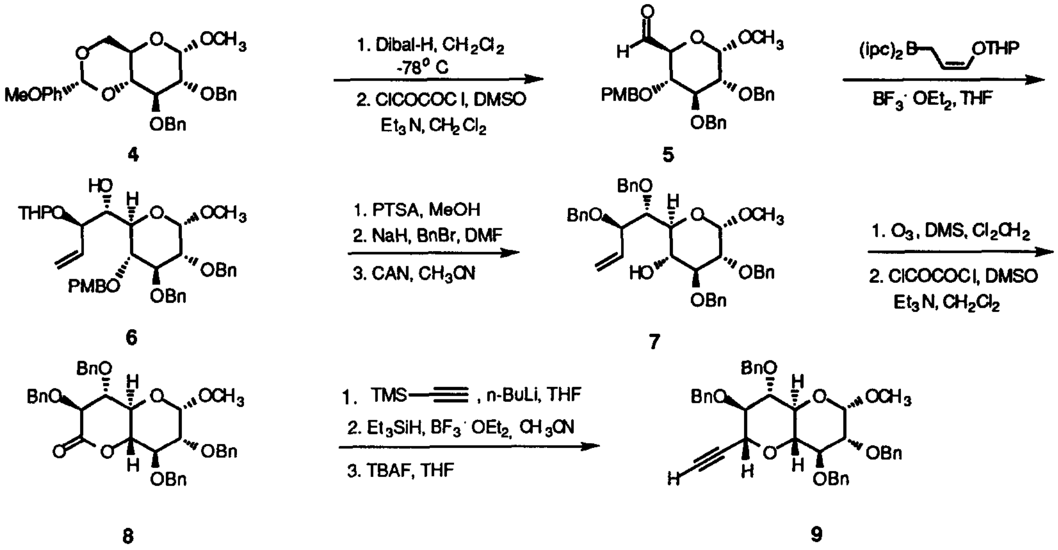

3

Formation of a suitably functionalized dipyranyl species focused on the allylborane coupling to a C-6 aldehyde derived from D-glucose. Initially, benzylidine 4 was synthesized from methyl glucopyranoside according to literature precedent.[7] . Selective reduction of the benzylidine ring with Dibal-H (3.0 equiv., CH_2Cl_2) afforded the C-6 alcohol in 95% yield.[8] Subsequent Swern oxidation afforded aldehyde 5 which was condensed with [(2)-γ-(tetrahydropyranyl)allyl]diisopinocampheylborane[9] derived from (+)-pinene without further purification. The overall yield of 6 for this two step transformation was 52% with >95% diastereoselectivity (by ^1H NMR analysis of the THP hydrolysis product of 6).

Deprotection of the THP ether afforded the intermediate diol in 66% yield. Following benzylation, selective removal of the PMB protecting group with CAN in CH_3CN/H_2O (9:1) afforded the C-4 hydroxyl tetrabenzylated glycoside 7 in 88%. Ozonolysis of the terminal olefin and subsequent work-up led to isolation of the C-8 hemiacetal. Oxidation under Swern conditions gave the stable lactone 8 in 90% yield. Addition of TMS acetylide anion to lactone 8 yielded a mixture of diastereomers (73%). Treatment with 15 equivalents of $BF_3 \cdot OEt_2$ and Et_3SiH at 0 C for 5 min. stereoselectively reduced the C-8 hemiketal to the beta anomer[10] which was subsequently desilated to afford 9 in 78% yield.



Scheme I

Confirmation of the stereochemical outcome of the allylboration reaction involving the C-6 aldehyde (5→6) was established by X-ray analysis of the bicyclic trans-fused pyran 9 (Figure 1).

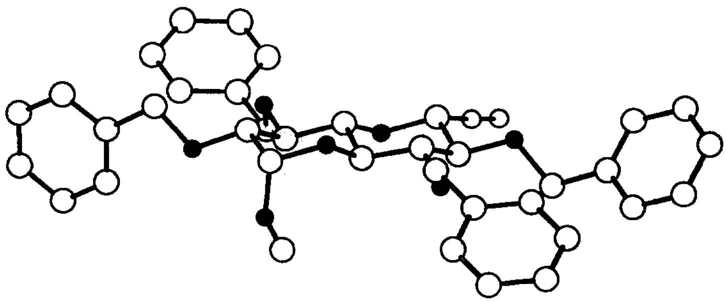
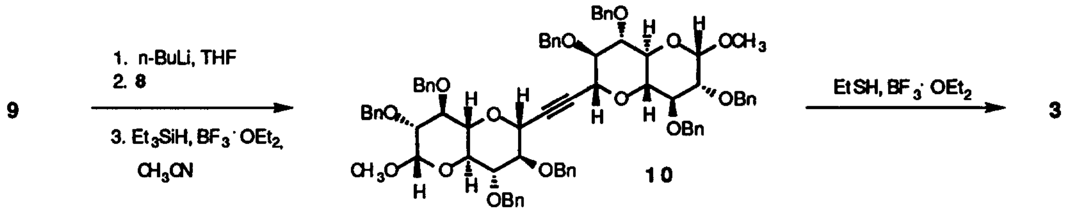


Figure 1. X-ray structure of acetylenic C-glycoside **9**.

Generation of the lithium acetylide of **9** followed by condensation with lactone **8** proceeded to yield an inseparable mixture of diastereomers. Subsequent reduction of the hemiketal with $BF_3{\cdot}OEt_2/Et_3SiH$ (rt. for 45 min) afforded dimer **10** in 54 % overall yield from **9**. No alpha anomer was detected by ^1H NMR analysis. Deprotection of the benzyl ethers was accomplished using Lewis acid conditions (BF_3OEt_2, EtSH)[11] to afford the tetraol **3**.



Scheme II

The ^1H NMR spectrum of **3** (D_2O, 360 MHz) is remarkably simple due to the C_2 symmetry of the molecule. The trans diaxial relationship of all of the ring hydrogens results in an average 9.37 Hz coupling constant. As a consequence, hydrogens at C3 to C7 appear as triplets. Further elaboration of these targets is an ongoing project in these laboratories.

ACKNOWLEDGEMENT: We thank the National Institututes of Health for financial support of this work (GM 39512). We also thank Dr. Saeed Khan for solving the X-ray structure of **9**.

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(Received in USA 10 May 1993)