Pergamon

Tetrahedron Letters, Vol. 38, No. 13, pp. 2215-2218, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00327-4

C-Disaccharides I. Stereoselective Approach to β-(1-4)-3-Deoxy-C-Disaccharides from Levoglucosenone.[1]

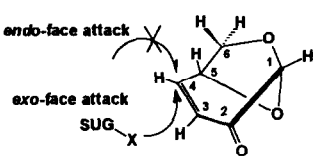
Zbigniew J. Witczak,* Renu Chhabra, Joanna Chojnacki

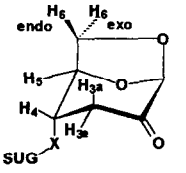
School of Pharmacy, Department of Pharmaceutical Sciences,
University of Connecticut, Storrs, Connecticut 06269-2092. U.S.A.

Abstract: β -(1-4)-C-Disaccharides have been synthesized in four steps by stereoselective base catalyzed Michael addition reaction of glucosyl nitromethane to the chiral synthon, levoglucosenone followed by radical removal of the nitro group with tributyltinhydride.

C-Disaccharides are a class of unnatural and nonhydrolyzable mimics of disaccharides and potential glycosidase inhibitors for the treatment of metabolic diseases. In response to our continuous interest in C-glycosyl compounds and C-disaccharides,[2] we have focused our attention on the development of new strategies for the synthesis of (1-4)-C-disaccharides and (1-4)-S-thiodisaccharides.[3a]

Existing synthetic methods to C-glycosyl compounds are multistep and low overall yield approaches.[4] The new approach developed in our laboratory and presented here supports the ongoing studies on the utility of the convenient chiral "synthon" levoglucosenone.[5] These approaches are based on the Michael addition reaction of glucosyl nitronates and radical coupling of iodo derivatives to levoglucosenone.





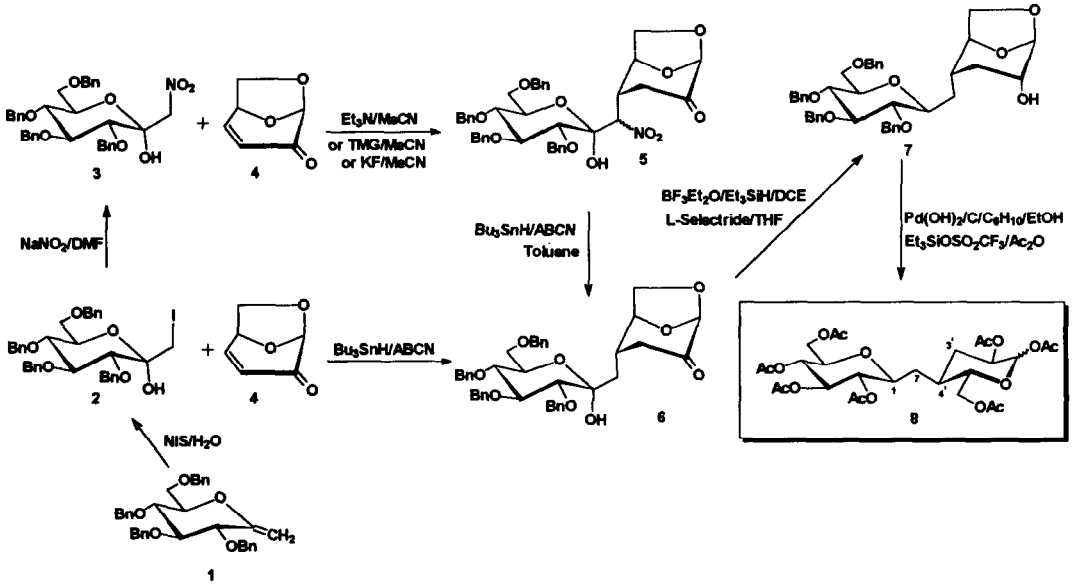
X = SH, CH_2NO_2,CHO X = S, $CHNO_2$, CHOH,

SUG = GLU, GAL FUC,

Glycosyl nitromethanes[6] were convenient starting materials for the synthesis of C-disaccharides in Martin's laboratories[7] and others[8]. Our new approach also utilizes glycosyl nitromethanes as reactive donors in the stereoselective Michael 1,4-addition reaction to the conjugated system of levoglucosenone.[9] The advantage of the stereoselective 1,4-addition is the exclusive formation of an *exo*-adduct *via* formation of 1,4-C-linkage from the less hindered face of the molecule (see A). The shielding effect of the 1,6-anhydro bridge in levoglucosenone effectively prevents the formation of the 4-equatorial (*e*) product, and only the 4-axial (*a*) product was routinely obtained. The most direct way to prove the correct stereochemistry of the 1,4-adduct is to measure the coupling constants, $J_{3ax,4}$ and $J_{3e,4}$ (see B), which range from 5.0-8.0 Hz and 1.0-1.5 Hz, respectively. Lack of coupling between H-4 and H-5 indicates that the pyranose ring of the adduct is in a $^1C_4$

conformation and is slightly distorted due to the presence of a carbonyl function at C-2 with an axial substituent at the 4-position. Due to long range couplings of 1-2 Hz, the complex multiplicity of the signals for H-3e is consistent with "W" planar arrangements of H-1, H-3, as well as H-5.These important facts prompted us to explore the synthetic utility of levoglucosenone by stereoselectively introducing a methylene bridge connecting two sugar rings at C-(1-4). Indeed, the ^{1}H-NMR coupling constants of the addition product **5** $J_{3ax,4}$= 6.2 Hz and $J_{3e,4}$=1.2 Hz indicate the axial disposition of the new C-4 substituent. This particular rule is highly predictable and has been observed by other authors[5] during the course of the Michael conjugate addition, as well as proved by us during the base-catalyzed addition reaction of 1-thiosugars[3a] and sugar aldehydes[3b] to levoglucosenone. Furthermore, in contrast to the existing methods of C-disaccharide synthesis, our method does not require a multistep procedure or special protection of functional groups.

The starting glycosyl nitromethane **3**[9] was prepared by nucleophilic displacement of iodide **2** synthesized from exocyclic glucal **1** according to the Van Boom methodology.[10] The Michael 1,4-addition reactions of glycosyl nitromethane **3** to levoglucosenone **4** were run in polar solvents (acetonitrile) in the presence of potassium fluoride or triethylamine or tetramethylguanidine (TMG). These mildly basic conditions[7-8] form a nitronate anion and avoid concurrent β-elimination of the neighboring benzyl group. The isolation of the



Scheme 1.

diastereoisomeric mixture of C-disaccharide **5**[11] proceeds in 43% yield due to the recovery of starting **4**. Removing the nitro group of the methylene bridge of C-disaccharide **5** was achieved by reacting it with tributyltin hydride[12] in the presence of the radical initiator 1,1'-azobis(cyclohexanecarbonitrile), (ABCN). The resulting 2-keto-2,3-dideoxy-C-disaccharide **6** was obtained in good (68%) yields after purification by flash-column chromatography. Alternatively, the radical coupling of iodide **2** with levoglucosenone in the presence of radical initiator ABCN also gave C-disaccharide **6**[13], however in a low (26% yield) due to concurrent

formation of direct reduction product of **2**. The removal of the anomeric hydroxyl of **6** was achieved by treatment with triethyl silane (Et_3SiH), borontrifluoride (BF_3-Et_2O) in a 1,2-dichloromethane (DCE) solution[10] followed by stereoselective reduction of the keto function[14] at C-2 with the formation of **7**[15] in 89% and 41% overall yield from **4**. Debenzylation was performed according to the Hanessian methodology[16] followed by acetolysis[17] of the 1,6-anhydro ring which produced the peracetylated target C-disaccharide **8**[18] in 19% overall yield from **4**.

This new methodology will prove very useful for synthesizing a wider range of 3-deoxy-C-disaccharides with various linkages while using levoglucosenone as a convenient synthon to control the stereoselectivity. The readily procured β-(1-4)-linked C-disaccharides are versatile synthons that may be employed in a variety of transformations to amino- thio- and branch-chain sugars by functionalization of the remaining functional groups.

ACKNOWLEDGMENT -Financial support from the University of Connecticut Research Foundation and American Cancer Society, Institutional Grant to University of Connecticut Health Center # ACSIN 152L-132 is gratefully acknowledged.

REFERENCES AND NOTES

1. Presented in part during XVIIth International Carbohydrate Symposium, Ottawa, Canada, July 17-22, **1994**, Abstract No. B1.96; Witczak, Z. J., *Abstract Am. Soc. Meet.* 208, **1994**, : Abstract: CARB. 58.
2. Witczak, Z. J., in *Studies in Natural Products Chemistry, Vol. 3B*, Atta-ur-Rahman Ed., Elsevier Science Publishers, Amsterdam, **1989**, pp. 209-232; Witczak, Z. J. *Pure & Appl. Chem.* **1994**, *66*, 2189-2192.
3. a) Witczak, Z. J.; Sun, J.; Mielguj, R., *Bioorg.Med.Chem.Lett.* **1995**, *5*, 2169-2174; b) Witczak, Z.J.; Sun, J., Unpublished data
4. For review see; Postema, M. H. D., *Tetrahedron* **1992**, *48*, 8545-8599. For different approaches to (1-4)-C-disaccharides see: Xin, Y. C.; Mallet, J. M.; Sinaÿ, P., *J.Chem.Soc. Chem. Commun.* **1993**, 864-865; Vauzeilles, B.; Cravo, D.; Mallet, J. M.; Sinaÿ, P., *Synlett* **1993**, 522-523; Schmidt, R. R.; Preuss R., *Tetrahedron Lett.* **1989**, *30*, 3409-3412; Armstrong , R. W.; Teegarden, B. R., *J.Org.Chem.*, **1992** , *57*, 915-922; For (1-3)-C-disaccharides synthesis see: Dawson, J. M.; Johnson, T.; Paton, R. M.; Rennie, R. A., *J.Chem. Soc.Chem.Commun.* **1988**, 1339-1340; Preuss, R.; Jung, K.H.; Schmidt, R.R., *Liebigs Ann. Chem.* **1992**, 377-382; *Liebigs Ann. Chem.* **1992**, 983-986.
5. Shafizadeh, F.; Chin, P. P. P., *Carbohydr. Res.* **1977**, *58*, 79-89; For review see: Witczak, Z.J., in *"Studies in Natural Products Chemistry" Vol. 14*, Atta-ur-Rahman Ed., Elsevier, Amsterdam, **1994**, pp. 268-282; *"Levoglucosenone and Levoglucosans Chemistry and Applications"* Witczak, Z. J., Ed., ATL Press Inc. Science Publishers, Mount Prospect, Illinois, **1994.**
6. Förstch, A.; Kogelberg, P.; Köll, P., *Carbohydr. Res.* **1987**, *164*, 391-402.
7. Martin, O. R.; Khamis, F. E.; El-Shenawy H.; Rao S. P., *Tetrahedron Lett.* **1989**, *30*, 6139-6142,: Martin, O. R., Khamis, F. E.; Rao, S. P., *Tetrahedron Lett.* **1989**, *30*, 6143-6146: Martin, O. R.; Lai,W., *J.Org.Chem.* **1990**, *55*, 5188-5190, *J.Org.Chem.* **1993**, *58*, 176-185.
8. Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M., *J.Org.Chem.* **1996**, *61*, 1894-1897.
9. Compound **3**, 3,4,5,7-tetra-*O*-benzyl-1-C-methanenitro-α-D-*gluco*-heptulopyranose, syrup $[\alpha]^{23}+16.5°$ (c1.00 $CHCl_3$). ^{13}C NMR: ($CDCl_3$):δ 68.5, 72.8 (C-1 and C-7), 69.9, 74.2, 75.5, 80.5 (C-3,C-5, C-6), 73.0, 73.6,

74.4, 75.0 (4x CH_2 -benzyl), 97.6 (C-2), 127.4-128.6 (CH-arom), 137.8-138.8 (C-arom).

10. Noort, D.; Veeneman, G.H.; Boons, G-J. P. H.; van der Marel, G. A.; Mulder, G. J.; van Boom, J. H., *Synlett* **1990**, 205-206; Heskamp, B. M.; Noort, D.; van der Marel, G. A.; van Boom, J. H.; *Synlett* **1992**, 713-715.
11. Compound **5**, 1,6-anhydro-2,3-dideoxy-4-deoxy-4-C-(3,4,5,7-tetra-*O*-benzyl-1-deoxy-1'-nitro-α-D-*gluco*-2-heptulopyranos-1-yl)-D-*glycero*-hexo-pyranos-2-ulose, syrup $[\alpha]^{23}$-15.3° (c1.00 $CHCl_3$); ^{13}C NMR: ($CDCl_3$): δ 29.8 (C-3'), 39.8 (C-3), 73.0, 73.6, 74.4, 75.0 (4x CH_2 benzyl), 73.8 (C-6'), 76.0 (C-6), 77.6 (C-5), 77.9 (C-4'), 82.7 (C-5'), 83.3 (C-2'), 89.3 (C-7), 96.6 (C-1), 97.6 (C-2), 123.3 (C-1), 127.4-128.6 (CH-arom), 137.8-138.8 (C-arom), 207.1 (C-2). HRMS $(M)^+$ *m/z*: Calcd for $C_{41}H_{43}NO_{11}$: 725.79. Found: 725.28.
12. The radical removal of the nitro group was performed according to Martin's protocol[7] with Kocienski's [*Carbohydr.Res.* **1982**, *110*, 330-333.] modification to remove tributyltin compounds by treatment with 25% aqueous solution of potassium fluoride.
13. Compound **6**, 1,6-anhydro-2,3,4-trideoxy-4-C-(3,4,5,7-tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-2-heptulopyranos-1-yl)-D-*glycero*-hexo-pyranos-2-ulose, syrup $[\alpha]^{23}$-16.5° (c1.00 $CHCl_3$).^{13}C NMR ($CDCl_3$):δ 29.8 (C-3'), 39.8 (C-3), 73.0, 73.6, 74.4, 75.0 (4x CH_2 benzyl), 74.8 (C-6'), 76.0 (C-6), 77.6 (C-5), 77.9 (C-4'), 82.7 (C-5'), 83.3 (C-2'), 79.3 (C-7), 96.6 (C-1), 97.6 (C-2), 123.3 (C-1), 127.4-128.6 (CH-arom), 137.8-138.8 (C-arom), 207.1 (C-2). HRMS $(M)^+$ *m/z*: Calcd for $C_{41}H_{44}O_9$: 680.79. Found: 680.29.
14. Okano, K.; Ebata,T.; Koseki, K.; Kawakami, H.; Matsumoto, K.; Matsushita, H., *Chem. Pharm. Bull.* **1993**, *41*, 861-865.
15. Compound **7**, 1,6-anhydro-3,4-dideoxy-4-C-(3,4,5,7-tetra-*O*-benzyl-2,6-anhydro-1-deoxy-β-D-*gluco*-2-heptulopyranos-1-yl)-D-glucopyranose, syrup $[\alpha]^{23}$-18.9° (c 1.00 $CHCl_3$); ^1H NMR (250MHz, $CDCl_3$): δ 8.10-6.86 (m, 20H), 5.51 (d,1H-1', $J_{1',2'}$=5.2Hz,), 4.5 (d, 1H-1, $J_{1,2}$=8.4Hz), $J_{1,7}$=9.2Hz, $J_{7,4'}$=4Hz, 4.83 (q, 1H-5', $J_{5',6'}$=6.0Hz,), 4.2-4.06 (m, 3H, H-6a, H-6'a, H-2'), 3.74 (d,1H-3, J=9.9Hz), 3.86 (dd, 1H-6'e, $J_{5,6a}$ = 5Hz, $J_{6a,6e}$=12Hz), 4.18 (d,1H-4, J=2.9Hz), 3.78 (d, 1H-4', $J_{3',4'}$= 2.6Hz), 3.71-3.52 (m, 3H, H-2,5,3'a), 2.74 (dd H-3'e, $J_{3'a,3'e}$= 16Hz, $J_{3'e,4'}$=7.9Hz), 2.76 (d, 1H-7, J= 15Hz), 1.96 (dd,1H-7, $J_{1,7}$=9.2Hz, $J_{7,4'}$=4Hz. ^{13}C NMR ($CDCl_3$): 21.5 (C-4), 30.8 (C-3), 31.9 (C-1'), 70.6 (C-5'), 71.9 (C-2), 72.1 (C-1'), 72.6 (C-6'), 3x 74.1, 76.0 (4x CH_2 benzyl), 75.3 (C-6), 74.6 (C-3'), 75.4 (C-4'), 87.5 (C-5), 115.6 (C-1), 127.4-128.6 (CH-arom), 137.8-138.8 (C-arom). HRMS $(M)^+$ *m/z*: Calcd for $C_{41}H_{46}O_8$: 666.81. Found: 666.29.
16. Hanessian, S.; Liak, T. J.; Vanase, B., *Synthesis* **1986**, 207-208.
17. Zotolla, M.; Venkateswara Rao, B.; Fraser-Reid, B., *J.Chem Soc. Chem.Commun.* **1991**, 969-970.
18. Compound **8**, 1,2,6-tri-*O*-acetyl-3,4-dideoxy-4-C-(3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*glycero*-D-gluco-heptitol-1-yl)-α,β-D-glucopyranose, syrup $[\alpha]^{23}$+51.2° (c 1.00 $CHCl_3$). ^1H NMR (500MHz, $CDCl_3$): δ 2.0-2.16 (m, 42H, AcO), 2.1 (ddd,1H-7, J=4.0, 9.5, 15.2 Hz, $J_{1,7}$ =9.2, 0.5Hz), 2.26 (dddd, 1H-4', J=3.6, 4.2, 10.6, 10.6Hz), 2.46 (ddd, 1H-2, J=2.3, 5.6, 10.2Hz), 2.66 (dd, 1H-7, J=3.7, 15.2Hz), 2.70 (d 1H-3'e, $J_{3'a,3'e}$=16Hz, $J_{3'e,}$=8Hz), 3.46 (dd, 1H-2', J=3.4, 9.1Hz), 3.72 (dd, 1H-5, J=4.1,7.4Hz), 3.89 (dd,1H-1, J=9.5, 10.2Hz), 3.96 (dd,1H-3, J=2.8, 9.6Hz), 4.08 (dd, 1H-6', J=5.2, 11.6Hz), 4.14 (dd,1H-6, J=4.0,11.4Hz), 4.18 (d,1H-4, J=2.8Hz, $J_{4,7}$=3.7, 4.0Hz), 4.32-4.46 (m,1H-5'), 4.46 (dd, 1H-6, J=7.4, 11.4Hz), 5.88 (d, 1H-1β, J=7.4 Hz), 6.36 (d, 1H-1α, J=3.4 Hz,); ^{13}C NMR ($CDCl_3$): δ 2x 17.3, 5x 17.6 (CH_3CO-), 29.7 (C-3), 33.9 (C-1'), 68.8 (C-6'), 69.6 (C-5'), 70.3 (C-2'), 71.6 (C-4), 72.6 (C-6), (C-4'), 73.7 (C-3'), 74.8 (C-2), 74.9 (C-5), 99.1 (C-1), (α-anomer): 102.6 (C-1), (β-anomer); HRMS $(M)^+$ *m/z*: Calcd for $C_{27}H_{38}O_{16}$: 618.58. Found: 618.21.

(*Received in USA* 20 *September* 1996; *revised* 7 *February* 1997; *accepted* 10 *February* 1997)