The Synthesis of Disaccharides Terminating in D-Septanosyl Residues Using Acyclic Intermediates

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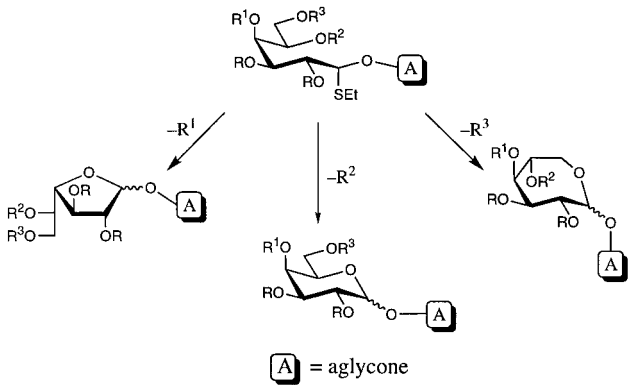
Abstract: A general method for the construction of disaccharides containing D-septanosyl residues from acyclic intermediates has been developed. The synthesis of an analogue of *N*-acetyl D-lactosamine with a D-galactoseptanosyl unit has also been accomplished with the aim of determining the behaviour of this compound as a substrate for several glycosyltransferases.

The role of carbohydrates in biochemical processes is eliciting much attention recently.[2] Accordingly, the demand for synthetic carbohydrates and their analogues has grown. The properties of seven-membered sugars have remained mostly unexplored to date, in contrast to five- and six-membered sugars.[3] Aside from the challenge in constructing such molecules, there is also the potential to derive information about carbohydrate-protein interaction. This letter describes the synthesis of disaccharides terminating in D-*galacto*-, D-*gluco*- and D-*manno*-septanosyl residues. The synthesis of an analogue of *N*-acetyl D-lactosamine (Galβ(1→4)GlcNAc, LacNAc) containing a D-galactoseptanosyl residue is also presented.

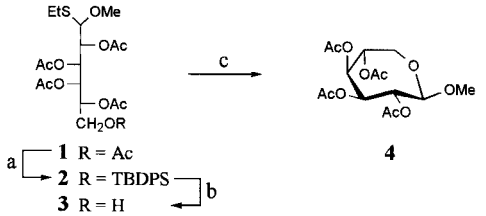
The synthesis of D-hexoseptanosides has not been extended beyond monosaccharide derivatives of D-galactose and D-glucose. D-Glucoseptanoses have been obtained either by isopropylidination of D-glucose,[4] ring expansion of methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside[5] or from D-glucose diethyl dithioacetal.[6] The synthesis of methyl D-galactoseptanoside was also achieved from acyclic intermediates.[7] In general these methods suffer from either low yields or a lack of applicability to more complex substrates. Elaboration of the acyclic approach could allow the synthesis of seven-membered sugars with a range of aglycones.

We recently presented a method for the synthesis of D-hexofuranosides from acyclic precursors in which an unprotected *O*,*S*-acetal could be cyclized to a D-furanoside with high stereo- and regioselectivity.[8] The cyclization of differentially protected intermediates clearly presents the possibility of access to sugars of other ring sizes (**Scheme 1**). With regard to seven-membered rings, this strategy involved the synthesis of an *O*,*S*-acetal selectively protected at the primary alcohol. Following selective deprotection, treatment with a thiophilic promotor would be expected to result in the formation of a septanoside.



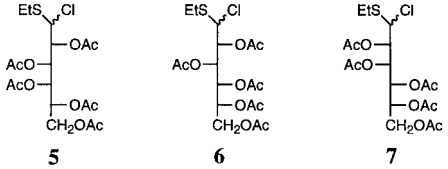
Scheme 1

In order to test the feasibility of this scheme, the *O*,*S*-acetal **1**[9] was chosen as the model compound (**Scheme 2**). Following deacetylation (NaOMe/MeOH), sequential treatment with excess *t*-butyldiphenylsilyl chloride (TBDPS-Cl) in pyridine and then Ac_2O/DMAP gave the 6-*O*-silyl ether **2** in high yield (86%). Careful desilylation with excess HF/pyridine in THF[10] gave the 6-OH compound **3** and was accompanied by minimal acetyl group migration. Treatment of this compound with NIS/TfOH in CH_2Cl_2 at -30°C gave the septanoside **4** as anticipated. The ^{1}H NMR spectrum of **4** allowed unambiguous assignment of a seven-membered ring owing to the presence of downfield signals attributed to H-2, -3, -4 and -5.[11] The signals corresponding to the H-6 protons were observed at 3.69 and 4.15 ppm with a geminal coupling constant of 14.1 Hz. Long-range coupling between H-4 and one of the H-6 protons (J = 2.4 Hz) was also evident. With this result in hand our attention was turned to the synthesis of selectively protected intermediates bearing saccharide aglycones.

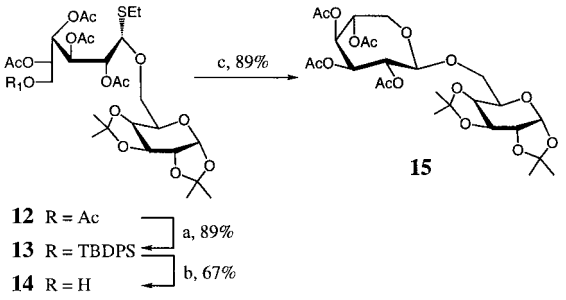


Scheme 2. a) 1. NaOMe, MeOH; 2. *t*-BuPh$_2$SiCl, pyr.; 3. Ac_2O, 86%; b) HF/pyr, THF, 0 °C→ RT, 70%; c) NIS/TfOH, CH_2CH_2, –30 °C→ RT, 85%

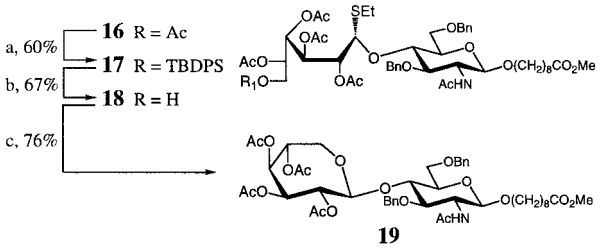
The 1-chloro-1-(ethylthio) compounds **5**-**7**[12] were synthesized from the corresponding diethyl dithioacetals by treatment with AcCl/BF_3·Et_2O (100:1) at reflux.[8] Glycosylation of the acceptor **8** with **5**, promoted by AgOTf and 2,6-di-*t*-butyl-4-methyl pyridine (DTBMP) in CH_2Cl_2 at -30°C, gave the *O*,*S*-acetal **12** (81%) (**Scheme 3**). Conversion of this compound into the 6′-*O*-TBDPS derivative **13**, and then the 6′-OH compound **14**, was accomplished as for the monosaccharide **1**. Likewise, the cyclization of **14** proceeded smoothly to give the D-galactoseptanoside **15** in excellent yield (89%). The 4-OH acceptor **9** was also glycosylated by **5** to give **16** (56%). In this case however, the conversion of **16** to the 6′-*O*-TBDPS derivative **17** was not easily accomplished, requiring over 24 h to go to completion. Desilylation gave **18** (65%) which was in turn converted into the septanoside **19** in good yield (76%). The ^{1}H NMR spectra of **15** and **19** confirmed the selective formation of the D-galactoseptanosyl residue.[13]



Attention was next turned to derivatives of D-glucose and D-mannose. The D-*gluco* donor **6** was coupled to the acceptor **10** with AgOTf promotion, and the product **20** was elaborated to the D-glucoseptanoside **23** (**Scheme 5**). Glycosylation of the D-manno acceptor **11** with the

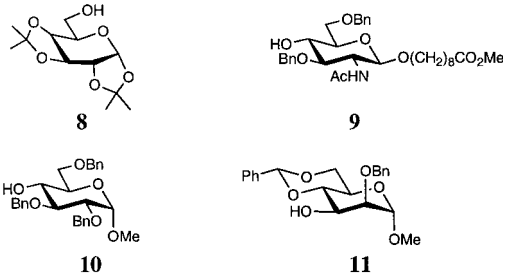


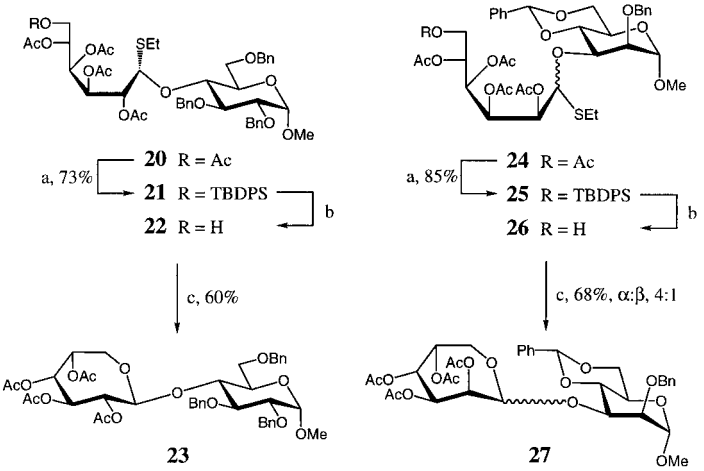
Scheme 3. a) 1. NaOMe, MeOH; 2. *t*-BuPh$_2$SiCl, pyr.; 3. Ac$_2$O; b) HF/pyr, THF, 0°C → RT; c) NIS/TfOH, CH_2CH_2, –30°C → RT



Scheme 4. a) 1. NaOMe, MeOH; 2. *t*-BuPh$_2$SiCl, pyr.; 3. Ac$_2$O; b) HF/pyr, THF, 0°C → RT; c) NIS/TfOH, CH_2CH_2, –30°C → RT

donor **7** proceeded in acceptable yield (58%), however the product **24** was obtained as a mixture (4:3) of diastereoisomers. This outcome was in contrast to a previous result in which the treatment of the acceptor **8** with **7** gave rise to only one compound.[8] Cyclization of the 6′-OH intermediate **26** also gave rise to a mixture of D-mannoseptanosides **27**. Interestingly, the ratio of anomers was now determined to be 4:1 in favor of the α-anomer.

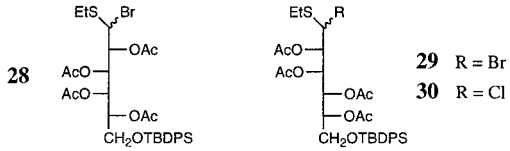




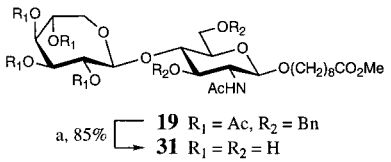
Scheme 5. a) 1. NaOMe, MeOH; 2. *t*-BuPh$_2$SiCl, pyr.; 3. Ac$_2$O; b) HF/pyr, THF, 0°C → RT; c) NIS/TfOH, CH_2CH_2, –30°C → RT

In both cases, the 6′-OH intermediates **22** and **26** were not isolated but cyclized directly to the D-septanosides **23** and **27**, respectively. This greatly reduced acetyl migration and hence the presence of by-products corresponding to other ring-sizes. In contrast to the D-galactoseptanosides, the ^{1}H NMR spectra of **23** and **27** did not exhibit long range coupling between H-4′ and -6′.[13]

The use of donors prefunctionalised at the primary alcohol was also examined. Glycosylation of acceptors **8** and **10** with the 1-bromo-1-(ethylthio) donor **28**[14] resulted in average to low yields of the corresponding *O*,*S*-acetals, **16** (65%) and **28** (37%), respectively. In contrast, the D-mannose derivative **29** was not effective in glycosylating the acceptor **10**. The corresponding 1-chloro compound **30**[15] however, glycosylated **10** to give **25**, with virtually the same yield (63%) and stereoselectivity (4:3) as the pentaacetate donor **7**.



Finally, the deprotection of **19** was carried out (NaOMe, MeOH; Pd/C, H_2, MeOH, AcOH) yielding the unprotected disaccharide **31** (**Scheme 6**).[16] This compound, an analogue of LacNAc, is under evaluation as a potential substrate for a series of glycosyltransferases.



Scheme 6. a) 1. NaOMe, MeOH; 2. Pd/C, H_2, MeOH, AcOH

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References and Notes

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11. ^{1}H NMR Data for **4**: δ 2.01-2.16 (4s, 12 H; COMe), 3.39 (s, 3 H; OMe), 3.69 (ddd, $J_{4,6}$ 2.4 Hz, $J_{5,6}$ 1.5 Hz, $J_{6,6}$ 14.1 Hz, 1 H; H-6), 4.15 (dd, $J_{5,6}$ 1.0 Hz, 1 H; H-6), 4.62 (d, $J_{1,2}$ 5.7 Hz, 1 H; H-1), 4.79 (ddd, $J_{4,5}$ 1.2 Hz, 1 H; H-5), 5.33 (ddd, $J_{3,4}$ 1.5 Hz, 1 H; H-4), 5.38 (dd, $J_{2,3}$ 9.6 Hz, 1 H; H-3), 5.47 (dd, 1 H; H-2).
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13. ^{1}H NMR of D-Septanosyl Residues

	15	**19**	**23**	***27α***	***27β***
H1′	4.80, d	4.81, d	4.84, d	4.91, d	5.11, d
$J_{1',2'}$	5.7 Hz	6.7 Hz	7.2 Hz	4.2 Hz	7.1 Hz
H2′	5.44, dd	5.40, dd	4.99, dd	5.60, dd	5.54, m
$J_{2',3'}$	9.6 Hz	9.5 Hz	8.4 Hz	1.7 Hz	
H3′	5.33, dd	5.28, dd	5.40, dd	5.40, dd	5.31-5.33
$J_{3',4'}$	1.6 Hz	1.8 Hz	9.6 Hz	10.2 Hz	m
H4′	5.28, dd	5.23, dd	5.09, dd	5.44, dd	5.31-5.33
$J_{4',5'}$	1.4 Hz	1.8 Hz	3.0 Hz	3.6 Hz	m
$J_{4',6'}$	4.1 Hz	3.6 Hz			
H5′	4.75, dt	4.64, ddd	5.04, dt	5.15, bt	5.12-5.18
$J_{5',6'}$	1.0, 1.4 Hz	0.5, 1.8 Hz	3.0, 3.7 Hz	0.4, 3.8 Hz	m
H6′	4.14, dd	3.93, dd	3.77, dd	4.03, bd	3.91, dd
	3.67, ddd	3.40, ddd	3.33, dd	3.40, dd	3.49, dd
$J_{6',6'}$	14.5 Hz	13.7 Hz	14.1 Hz	14.3 Hz	12.9 Hz

14. Synthesized from the corresponding diethyl dithioacetals upon treatment with bromine (0.55 eq.) in CH_2Cl_2 at –30°C followed by cyclohexene (1 eq).
15. Synthesized by treatment of **29** with AgOAc (2 eq) at –30°C, followed by HCl in ether.
16. **31**: Partial ^{1}H NMR (360 MHz, CD_3OD): δ = 3.64 (s, 3 H; OMe); 3.65 (m, 1 H; H-2); 4.40 (d, $J_{1,2}$ 8.4 Hz, 1 H; H-1); 4.58 (d, $J_{1',2'}$ 6.6 Hz, 1 H; H-1′).