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A Ring Expansion–Glycosylation Strategy toward the Synthesis of Septano-oligosaccharides

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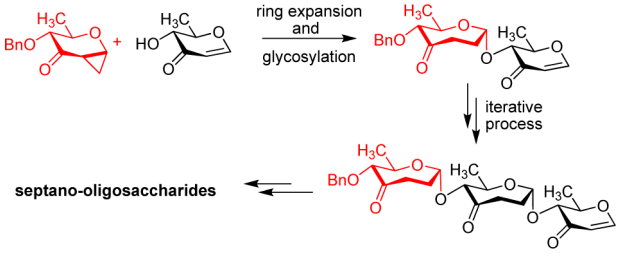
ABSTRACT



A one-pot ring-expansion–glycosylation reaction was performed using 1,2-cyclopropanated sugars as glycosyl donors and carbohydrate *O*-nucleophiles as acceptors to provide septanohexose mimics of pyranose and furanose derivatives. The methodology was successfully extended to the synthesis of septano-oligosaccharides by adopting a divergent strategy as well as an iterative protocol.

Mimicking natural glycans[1] is one of the intellectual ways of misleading microorganisms and enzymes that are responsible for a variety of diseases. An important method of mimicking natural carbohydrates is by expanding or contracting the ring size. The ring-expanded versions of hexoses are the so-called septanoses/carbohydrate-based oxepanes,[2] which have been shown to be very important mimics of carbohydrates. Structure–activity studies on oral antithrombotic beciparcil derivatives revealed that ring-expansion to a seven-membered thio sugar exhibited a 10-fold increase in activity relative to the reference compound, beciparcil.[3] Protein–carbohydrate interaction studies by Peczuh et al., involving concanavalin A and methyl septanosides, provided preliminary evidence that septanosides can resemble pyranosides.[4] Septanose mimics of nucleosides[5] and nucleic acids[6] have also been synthesized and evaluated for their antiviral and RNA-cleavage[7] properties. Even though several methods are available for the synthesis of septanose monosaccharides,[8] not many reports have been published on the preparation of septanose containing oligo- and polysaccharides.[9,8b] In this context, stereoselective construction of glycosidic linkage is a central challenge in the formation of di- and oligosaccharides.

(1) (a) Chapleur, Y. *Carbohydrate Mimics: Concepts and Methods*; Wiley-VCH: Weinheim, 1998. (b) Koester, D. C.; Holkenbrink, A.; Werz, D. B. *Synthesis* **2010**, 3217–3242.

(2) For reviews on oxepanes, see: (a) Pakulski, Z. *Pol. J. Chem.* **1996**, *70*, 667. (b) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631–12670. (c) Pakulski, Z. *Pol. J. Chem.* **2006**, *80*, 1293–1326. For a review on septanoses, see: Jaideep, S.; Peczuh, M. W. *Advances in Carbohydrate Chemistry and Biochemistry*; Academic Press: New York, 2011; Vol 66, pp 121 – 186.

(3) (a) Bozo, E.; Medgyes, A.; Boros, S.; Kuszmann, J. *Carbohydr. Res.* **2000**, *329*, 25–40. (b) Bozo, E.; Boros, S.; Parkanyi, L.; Kuszmann, J. *Carbohydr. Res.* **2000**, *329*, 269–286.

(4) (a) Castro, S.; Duff, M.; Snyder, N. L.; Morton, M.; Kumar, C. V.; Peczuh, M. W. *Org. Biomol. Chem.* **2005**, *3*, 3869–3872. (b) Duff, M. R.; Fyvie, W. S.; Markad, S. D.; Frankel, A. E.; Kumar, C. V.; Gascon, J. A.; Peczuh, M. W. *Org. Biomol. Chem.* **2011**, *9*, 154–164.

(5) Richard, S.; Gilles, G.; David, D.; Frederic, L.; Jean-Christophe, M.; Thierry, C. WO 2007/025043 A2 and references cited therein.

(6) (a) Sabatino, D.; Damha, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8259–8270. (b) Sabatino, D.; Damha, M. J. *Nucleosides Nucleotides Nucleic acids* **2007**, *26*, 1185–1188.

(7) Mangos, M. M.; Min, K. L.; Viazovkina, E.; Galarneau, A.; Elzagheid, M. I.; Parniak, M. A.; Damha, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 654–661.

(8) (a) Castro, S.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 3312–3315. (b) Peczuh, M. W.; Snyder, N. L.; Fyvie, W. S. *Carbohydr. Res.* **2004**, *339*, 1163–1171. (c) Ovaa, H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boom, J. A. *Tetrahedron Lett.* **1998**, *39*, 3025–3028. (d) Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.* **1994**, *35*, 7249–7252.

(9) Using anomeric chlorides: (a) Micheel, F.; Suckfüll, F. *Ann. Chim.* **1933**, *507*, 138. Using acyclic chlorothioethyl acetals: (b) McAuliffe, J. C.; Hindsgaul, O. *Synlett* **1998**, 307–309. Using *S*-phenyl septanosides (c) Castro, S.; Fyvie, W. S.; Hatcher, S. A.; Peczuh, M. W. *Org. Lett.* **2005**, *7*, 4709–4712. (d) Boone, M. A.; McDonald, F. E.; Lichter, J.; Lutz, S.; Cao, R.; Hardcastle, K. I. *Org. Lett.* **2009**, *11*, 851–854.

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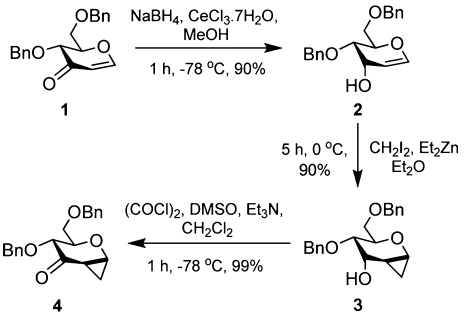
In our efforts to explore the application of 1,2-cyclopropanated sugars in the synthesis of unnatural glycoanalogues,[10] herein we report the stereoselective synthesis of 2,3-dideoxyseptanohexoses by TMSOTf-mediated one-step ring-expansion−glycosylation of sugar-derived 1,2-cyclopropanated donors with a series of carbohydrate acceptors.

The use of 1,2-cyclopropanated sugars for the synthesis of carbohydrate-based oxepanes has been reported via either the standard Ferrier rearrangement conditions[11] or by nucleophilic ring-opening of geminal dihalocyclopropanated sugar derivatives.[12] However, to the best of our knowledge, no reports are available for the synthesis of di- and oligoseptanosides from this type of glycosyl donor.

We envisaged that incorporating an electron-withdrawing functionality at the C-3 position of 1,2-cyclopropanated sugar derivatives would provide access to cyclic donor−acceptor cyclopropanes, which might undergo a regioselective electrophilic ring-opening reactions, assisted by the endocyclic oxygen, to give oxepane derivatives. Based on this protocol, we herein present stereoselective ring-opening of 3-oxo-1,2-cyclopropanated sugar derivatives, with carbohydrate *O*-nucleophilic glycosyl acceptors. Even though this kind of donor−acceptor cyclopropanes have been shown to undergo Lewis acid promoted ring-expansion with silyl enolates,[13] to the best of our knowledge, this is the first report of using these sugar derivatives as glycosyl donors in oligosaccharide synthesis. Further, an iterative glycosylation technology has been developed and utilized for the synthesis of a diseptanohexose oligosaccharide.

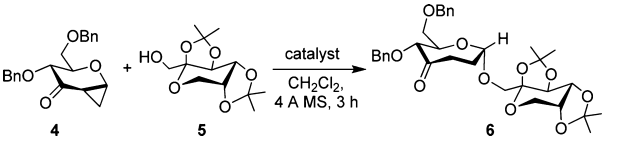
The 1,2-cyclopropanated glycosyl donors were prepared from known sugar-derived enones.[14] Luche reduction[15] of **1**[14] produced the allal derivative **2**[16] as a single diastereomer. Hydroxyl-directed cyclopropanation[11d] of **2** using CH_2I_2 and Et_2Zn under Simmons−Smith reaction conditions[17] produced 1,2-cyclopropanated allose derivative **3**, which upon Swern oxidation[18] provided the 1,2-cyclopropa-3-pyranone **4** in excellent yield (Scheme 1).[13]

Scheme 1. Synthesis of Glucose-Derived 1,2-Cyclopropanated Donor



Our preliminary investigations focused on optimization of the glycosylation reaction conditions using **4** as the glycosyl donor and sugar-derived *O*-nucleophiles as glycosyl acceptors. Toward this end, **4** (1 mmol) was glycosylated with 2,3;4,5-di-*O*-isopropylidene-α-D-fructopyranose **5** (1.1 mmol) as an acceptor in CH_2Cl_2 at −78 °C using catalytic $BF_3 \cdot Et_2O$ (0.2 equiv) as Lewis acid. The glycosylation reaction proceeded smoothly and provided the septanohexose disaccharide **6** in 65% yeild, respectively (Table 1, entry 1). A slight improvement that favored the α-glycoside formation was observed by using $(CF_3SO_2)_2O$ or $InCl_3$ as Lewis acids under similar reaction conditions (Table 1, entries 2−4). Interestingly, when TMSOTf was used as a catalyst, the ring-expansion glycosylation proceeded fruitfully, with excellent α-selectivity, providing the disaccharide **6** with 1:0.11 α:*β* selectivity in excellent yield (Table 1, entry 5). Carrying out the reaction either at −78 °C or from −10 to 0 °C did not improve the stereoselectivity of the glycosylation reaction (Table 1, entries 6 and 7).

Table 1. Optimization of Reaction Conditions for One-Step Ring-Expansion-Glycosylation Reaction Using 1,2-Cyclopropanated Sugar Donor **4**



entry	catalyst (0.2 equiv)	temp conditions (°C)	yield[a] (%)	α:*β*[c]
1	BF_3 OEt_2	−78 to +25	65	1:0.71
2	$(CF_3SO_2)_2O$	−78 to +25	60	1:0.57
3	$lnCI_3$	−78 to +25	<5	
4	$lnCI_3$[b]	−78 to +25	50	1:0.45
5	TMSOTf	−78 to +25	89	1:.0.11
6	TMSOTf	−78	72	1:0.71
7	TMSOTf	−10 to 0	82	1:0.42

[a] Yield represents pure and isolated products. [b] 1 equiv of catalyst was used. [c] Based on septanosyl anomeric proton ratio.

(10) (a) Sridhar, P. R.; Ashalu, K. C.; Chandrasekaran, S. *Org. Lett.* **2004**, *6*, 1777–1779. (b) Sridhar, P. R.; Kumar, P. V.; Seshadri, K.; Satyavathi, R. *Chem.—Eur. J.* **2009**, *15*, 7526–7529. (c) Sridhar, P. R.; Seshadri, K.; Reddy, G. M. *Chem. Commun.* **2012**, *48*, 756–758.

(11) (a) Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831–6834. (b) Batchelor, R.; Harvey, J. E.; Northcote, P. T.; Teesdale-Spittle, P.; Hoberg, J. O. *J. Org. Chem.* **2009**, *74*, 7627–7632. (c) Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165–174. (d) Hoberg, J. O. *J. Org. Chem.* **1997**, *62*, 6615–6618.

(12) (a) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694–7703. (b) Ganesh, N. V.; Raghothama, S.; Sonti, R.; Jayaraman, N. *J. Org. Chem.* **2010**, *75*, 215–218. (c) Hewitt, R. J.; Harvey, J. E. *Chem. Commun.* **2011**, *47*, 421–423. (d) Hewitt, R. J.; Harvey, J. E. *J. Org. Chem.* **2010**, *75*, 955–958.

(13) Sugita, Y.; Kimura, C.; Hosoya, H.; Yamadoi, S.; Yokoe, I. *Tetrahedron Lett.* **2001**, *42*, 1095–1098.

(14) Kirschning, A. *J. Org. Chem.* **1995**, *60*, 1228–1232.

(15) Luche, J. −L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848–5849.

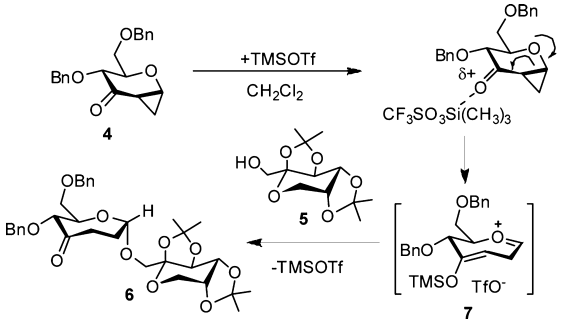
(16) Kirschning, A.; Hary, J.; Plumeier, C.; Ries, M.; Rose, L. *J. Chem. Soc., Perkin Trans 1* **1999**, 519–528.

(17) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256–4264.

(18) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

The major α-glycosylated product can be envisaged arising by a preferential approach of the nucleophile along an axial trajectory toward the oxocarbonium ion intermediate.[19] As shown in Scheme 2, activation of the glycosyl donor **4** with TMSOTf would generate the oxocarbenium ion intermediate **7** via the cleavage of C1−C2 bond. The trimethylsilyl vinyl ether **7** would react with acceptor **5**, preferentially in the axial direction, due to the anomeric effect,[20] provide the α-selective septanohexose **6** as the major product.

Scheme 2. Proposed Mechanism for the Stereoselective Formation of α-Glycoside



After optimizing these conditions, the aforementioned ring expansion−glycosylation of sugar derived 1,2-cyclopropa-3-pyranone donors was extended to other carbohydrate-derived *O*-nucleophilic glycosyl bond acceptors. Thus, the reaction of acceptor **8** with 1,2-cyclopropanated donors **4** and **10** gave rise to septanohexose derivatives **9** and **11**, respectively, with modest diastereoselectivity at the newly formed C1″ anomeric center (α:*β* (7:3)) in excellent yield (Table 2, entries 1 and 2). The methodology was also applied to sugar acceptors possessing less reactive secondary alcohols. Thus, different 1,2-cyclopropa-3-pyranone donors, **4**, **10**, and **15** were glycosylated with the sugar acceptor **12**, possessing a free hydroxyl group at the C2 position (Table 2, entries 3−5). Interestingly, donors **4** and **15**, upon glycosylation with **12**, provided selectively the α-glycosylated septanohexoses **13** and **16**, whereas donor **10** with acceptor **12** provided a diastereomeric mixture of **14α** and **14*β*** in 7:3 ratio, respectively (Table 2, entry 4). The structure of the minor diastereomer **14*β*** was confirmed by X-ray crystallography.[21]

Glycosylation of donors **4**, **15**, and **20** with acceptor **17**, in which the free hydroxyl is at C3, provided the corresponding septanohexoses **18**, **19**, and **21** as single diastereomers with the α-configuration at the newly formed glycosidic center (Table 2, entries 6−8). The stereochemistry at C1″ for all the disaccharide derivatives was assigned

Table 2. Stereoselective Synthesis of Septanohexoses

entry	donor cyclopropane	acceptor	septano-hexose derivatives (%)[a]	α:β ratio
1	**4**	**8**	**9** (90)	7:3
2	**10**	**8**	**11** (85)	7:3
3	**4**	**12**	**13** (93)	Only α
4	**10**	**12**	**14** (89)	7:3
5	**15**	**12**	**16** (80)	Only α
6	**4**	**17**	**18** (95)	Only α
7	**15**	**17**	**19** (91)	Only α
8	**20**	**17**	**21** (93)	Only α
9	**20**	**22**	**23** (96)	Only α

[a] Isolated yield after column chromatography.

based on the chemical shift value of the anomeric carbon[22] ($\delta_{C1''}$ for α-septanosides ranges from 99 to 104 ppm while for *β*-septanosides it ranges from *δ* 104−111 ppm) as well as two-dimensional NMR experiments. For the septanohexoses possessing a *β*-glycosidic bond, a strong NOE was observed between the 1,3-diaxial hydrogens at C1″ and C6″ which was absent in the case of septanosides with α-glycosidic linkage. The sugar-derived enone acceptor **22** was also very reactive toward the one-step ring-expansion−glycosylation reaction with donor **20** and produced the disaccharide derivative **23** as a single diastereomer in excellent yield (Table 2, entry 9). It is well-known that

(19) (a) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032–7035. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983.

(20) Desilets, S., St.; Jacques, M. *J. Am. Chem. Soc.* **1987**, *109*, 1641–1648.

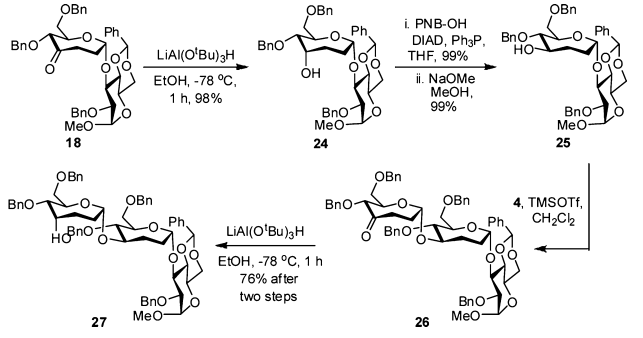
(21) CCDC deposition no. 903373.

(22) Demateo, M. P.; Snyder, N. L.; Morton, M.; Baldisseri, D. M.; Hadad, C. M.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 24–38.

the stereoselectivity in the glycosylation of hexose derived oxocarbenium ions is dictated by stereoelectronic effects in the glycosyl donor and nonbonding steric interactions from the glycosyl acceptors.[19,23] The above experimental results provide ample evidence that similar effects play a role in the glycosylation of septanosides as well.

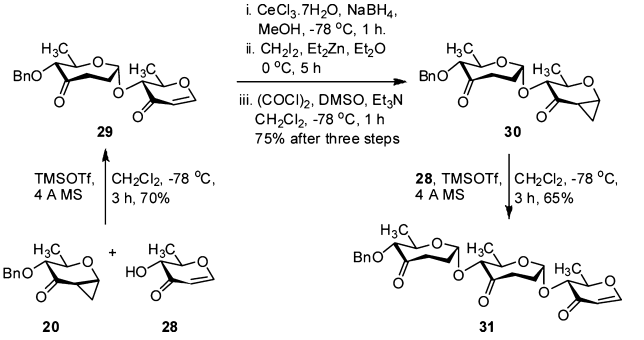
After successful synthesis of a series of septanohexose disaccharide derivatives, we focused our attention on the synthesis of diseptanohexose trisaccharides. Thus, stereoselective reduction of disaccharide **18** with lithium tri-*tert*-butoxyaluminum hydride in ethanol at −78 °C provided the acceptor alcohol **24**. However, glycosidation of donor **4** with acceptor **24** did not proceed under the optimized reaction conditions. We reasoned that the very low reactivity of the acceptor **24** might be due to the axial orientation of hydroxyl group. Therefore, inversion of the axial hydroxyl in **24** via the Mitsunobu reaction provided the acceptor **25**. Gratifyingly, glycosylation of **4** with acceptor disaccharide **25** proceeded smoothly, generating the diseptanohexose trisaccharide derivative **26** as a single diastereomer (Scheme 3). Stereoselective reduction of ketone provided the trisaccharide acceptor **27-α,α** which can be used further for the synthesis of septano-oligosaccharides.

Scheme 3. Synthesis of Diseptanohexose Trisaccharide



Finally, an iterative protocol for the synthesis of septano-oligosaccharides was investigated. Many biologically active natural products possess deoxysugar subunits in their structures.[24] Therefore, we planned to use 6-deoxy glucal derived 1,2-cyclopropanated sugar **20** as a glycosyl donor and alcohol **28** as an acceptor. Thus, glycosylation of **20** with **28** provided disaccharide **29** as a single diastereomer in good yield. Reduction of diketone **29** to the corresponding diol, followed by Simmons−Smith cyclopropanation and subsequent Swern oxidation of the diol provided the donor **30** as a mixture of α- and *β*-cyclopropanated products in 2:1 ratio, respectively, in 75% yield after three steps. Glycosidation of **30** with acceptor **28**, using TMSOTf in CH_2Cl_2 at −78 °C, provided the trisaccharide derivative **31** as a single diastereomer in which the second glycosylation was also α selective (Scheme 4).

Scheme 4. Iterative Protocol for the Synthesis of Septano-oligosaccharide



In conclusion, a novel ring expansion−glycosylation reaction has been developed for the synthesis of septanose derivatives which uses sugar-derived 1,2-cyclopropa-3-pyranones as glycosyl donors and carbohydrate-derived *O*-nucleophiles as acceptors. The generality of the reaction was evaluated by performing a number of glycosylation reactions and synthesizing several septanohexose derivatives. Two different methods (a divergent synthesis and an iterative technique) for the synthesis of septanose-derived oligosaccharides were successfully performed. Ligation of these ring-expanded sugar mimics to natural products and evaluation of their biological properties are presently under investigation.

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Supporting Information Available. Experimental procedures, full spectroscopic data, and ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) (a) Lemieux, R.; Hendriks, K. B.; Srick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062. (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531 and references cited therein. (d) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087and references cited therein.

(24) (a) Kirschning, A.; Bechthold, A.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1–84. (b) Thorson, J. S.; Hosted, T. J.; Jiang, J.; Biggins, J. B.; Ahlert, J. *Curr. Org. Chem.* **2001**, *5*, 139–167. (c) Salas, J.; Mendez, C. *Trends Microobiol.* **2007**, *15*, 219–232.

The authors declare no competing financial interest.