Tetrahedron Letters 53 (2012) 5667–5670

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Glycosylations with a septanosyl fluoride donor lacking a C2 protecting group

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ARTICLE INFO

Article history:
Received 27 July 2012
Revised 8 August 2012
Accepted 9 August 2012
Available online 16 August 2012

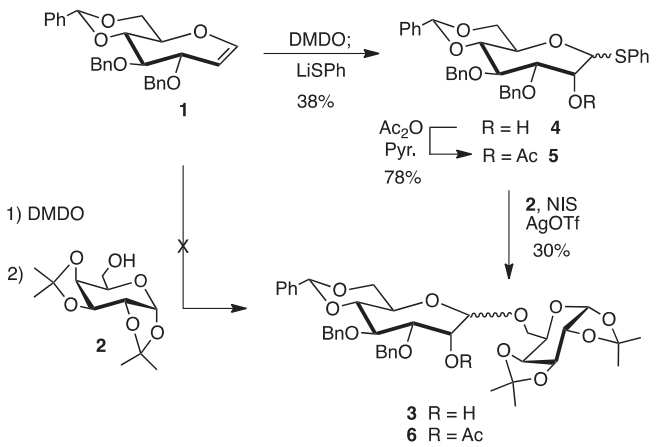
Keywords:
Glycosylation
Septanose carbohydrate
Glycosyl fluoride

ABSTRACT

Septanosyl fluorides, prepared from protected pyranoses, were used as donors in glycosylation reactions. The fluorides were synthesized by the addition of vinyl Grignard to the pyranoses followed by ozonolysis and then DAST-mediated fluorination. Activation in the presence of nucleophiles then provided the product glycosides. High α-stereoselectivity was observed for glycosylations using a donor that had a free C2 hydroxyl group; a model where the hydroxyl group participates to guide the stereochemical outcome is proposed.

Efficient methods for the preparation of septanose glycoconjugates are required to properly assess their utility in glycobiology.[1] Septanose carbohydrates have been incorporated into oligonucleotides,[2] evaluated as substrates[3,4] or inhibitors[5] of glycosidase enzymes and as ligands of lectins.[6] Methods for glycosylations involving septanoses have ranged from donor strategies co-opted from the pyranose literature[3,7–9] to ring expansion and functionalization sequences.[10,11] Despite these successes, glycosylation reactions involving septanoses are still being actively investigated. Currently, key challenges are to suppress undesired, transannular reactions that have been observed and to identify methods that are sufficiently general with respect to the acceptors that can be used. Our work has largely aimed at applying glycosylation strategies from pyranose chemistry to the world of septanosides. Here we report on a method that converts a pyranose lactol to the corresponding septanosyl fluoride. The fluoride, which lacks a protecting group on the C2 hydroxyl group, is then utilized as a glycosyl donor in model glycosylation reactions.

In earlier work from our lab, oxepines (ring expanded glycals) were epoxidized with dimethyldioxirane (DMDO); the product of epoxidation, a transient 1,2-anhydroseptanose, when in the presence of an acceptor and under appropriate conditions was converted to septanose-containing glycoconjugates. This method exploited the glycal-like reactivity of the oxepines.[7] Moreover, we and others have converted 1,2-anhydroseptanoses to their corresponding *S*-phenyl septanosides which were subsequently used as donors.[8] Notably, both of those methods were used with donors that lacked a C6 hydroxymethyl group. Our recent studies on ConA binding to septanosides[6] indicated that the hydroxymethyl group is essential for such interactions to mimic pyranoses. Accordingly, we focused our attention on the preparation of septanose glycoconjugates containing this key structural element. We therefore attempted glycosylation of 1,2:3,4-di-*O*-isopropylidene-D-galactose **2** under Lewis acidic conditions with the 1,2-anhydrosugar (not shown) prepared from oxepine **1** but this was unsuccessful (Scheme 1). Alternatively, we converted oxepine **1**[8a] to *S*-phenyl glycoside **4**. The yield of **4** was significantly lower than other instances where the starting materials lacked a C6 substituent. Glycoside **4** was isolated in 38% yield over two steps as a mixture of α- and β-anomers. Varying the temperature, solvent, or Lewis acid failed to improve the yield. The C2 hydroxyl group of **4** was protected as the acetate, providing **5** in 78% yield. The donating ability of **5** was then tested using **2** as a model acceptor under standard



Scheme 1. Glycosylations involving oxepine 1 as donor.

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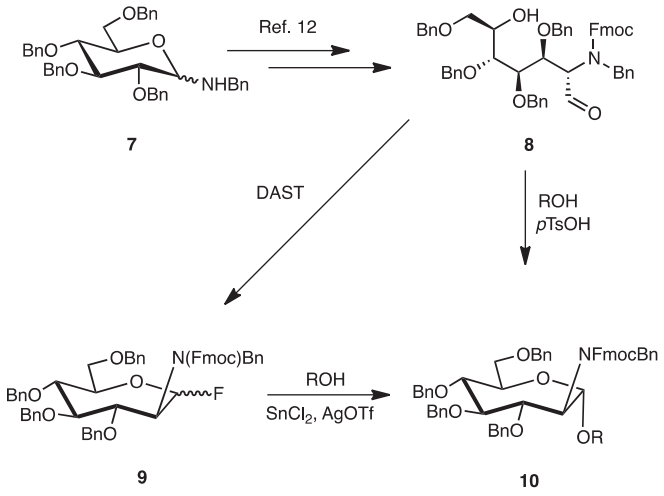
http://dx.doi.org/10.1016/j.tetlet.2012.08.039

glycosylation conditions. Disaccharide **6** was obtained in 30% yield as a mixture of anomers. Poor efficiency in both the preparation of donor **5** and in its utilization as a glycosyl donor leads us to explore an alternative strategy.

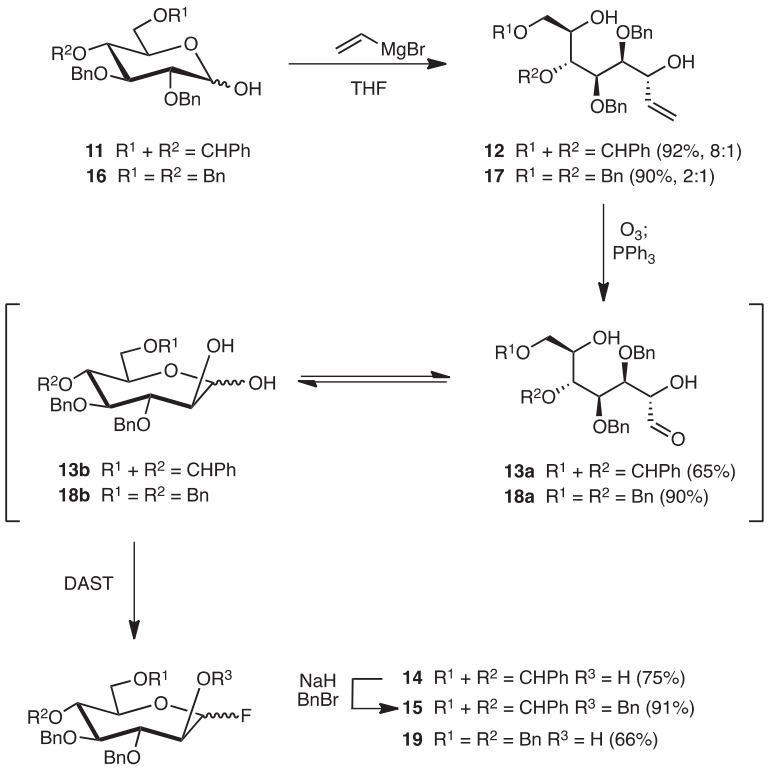
We recently reported a method for the preparation of 2-amino septanosides that utilized septanosyl fluorides as donors.[9] As shown in Scheme 2, septanosyl fluoride **9** was synthesized from hydroxy aldehyde **8** using DAST as the fluoride source. Hydroxy aldehyde **8** was itself prepared from glucosyl amine **7**.[12] Primary and secondary alcohol acceptors as well as azide were glycosylated by fluoride **9** in yields that ranged from 40–70%. The approach proved to be relatively general; in addition to **9**, which was prepared from glucosyl amine **7**, fluorides from the corresponding galactosyl and mannosyl amines were similarly synthesized. Glycosylations using septanosyl fluorides were superior to our initial method where hydroxy aldehydes were used to make septanosides via an acid mediated cyclization and glycosylation.[12] That method was limited by the large excess of acceptor required (acceptors were solvents or cosolvents) and its reliance on protic acid. Instead, we envisioned that, with some modifications, the fluoride strategy could be extended to the preparation of septanosides that are oxygenated at C2.



Scheme 2. Synthesis and glycosylations of 2-amino septanosyl fluorides.

The approach was adapted by starting the synthesis from a protected lactol rather than a glycosylamine. We expected that an aldehydo-diol, akin to hydroxy aldehyde intermediate **8** in the 2-amino septanoside synthesis, could be similarly parlayed into a septanosyl fluoride. There was some risk in targeting this intermediate though. Unlike the addition to the glycosyl amine which delivered an allylic amine, addition to the lactol would give an allylic alcohol. Selectively protecting the allylic alcohol in the presence of the C6 alcohol would be problematic. Also, upon ozonolysis, the allylic alcohol would be transformed into an α-hydroxy aldehyde which would further offer challenge for the acid mediated manipulation of the functionality because of its propensity to isomerize to an α-hydroxy ketone.

Confident that these potential challenges could be surmounted if they arose, we set about the investigation. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidine glucopyranose **11** was used as the lactol in our preliminary investigations (Scheme 3). Addition of vinyl Grignard to **11** delivered an 8:1 mixture of diastereomers (92%). The major isomer was tentatively assigned as **12**. The stereochemical assignment was based on a reported addition to glucopyranose[13] which used a Cram-chelate model.[12] Addition to lactol **11** was less diastereoselective than addition to glycosyl amines such as **7**. We attributed this to variations in the occupancy of the open-chain hydroxyaldehyde (versus closed hemiacetal) of the electrophile. Specifically, under the basic conditions of the reaction, a lower population of the open-chain form (as in the case of the glycosyl amine) at a given instance would favor a higher selectivity of the



11 $R^1 + R^2$ = CHPh
16 $R^1 = R^2$ = Bn

12 $R^1 + R^2$ = CHPh (92%, 8:1)
17 $R^1 = R^2$ = Bn (90%, 2:1)

13b $R^1 + R^2$ = CHPh
18b $R^1 = R^2$ = Bn

13a $R^1 + R^2$ = CHPh (65%)
18a $R^1 = R^2$ = Bn (90%)

14 $R^1 + R^2$ = CHPh R^3 = H (75%)
15 $R^1 + R^2$ = CHPh R^3 = Bn (91%)
19 $R^1 = R^2$ = Bn R^3 = H (66%)

Scheme 3. Preparation of septanosyl fluorides from protected pyranoses.

addition.[14] Ozonolysis of **12** provided **13** in 65% yield. Inspection of the NMR spectra of **13** showed that the hemiacetal form (**13b**) was adopted almost exclusively as mixture of anomers. Similarly, tetra-*O*-benzyl glucopyranose **16** was transformed to allylic alcohol **17** and isolated in 90% yield. The major diastereomer of **17** was then converted into **18** in 90% yield.[15]

Encouraged by the fact that **13** and **18** both favored the cyclic lactol form (i.e., **13b** and **18b**), we set about the task of converting them into their respective septanosyl fluorides. One concern however, was the possibility that fluorination at C2 followed by stereospecific migration of the C1 hydroxyl group[16] might compete with the desired fluorination at C1. In our case, this would lead to partial or complete epimerization at the C2 stereocenter.[17] In such a scenario, four different anomeric fluorides, two from direct fluorination at C1 (α and β) and two by epimerization of the hydroxyl at C2 could form. Reasoning that the C1 hydroxyl group would be more reactive as a nucleophile,[18] we anticipated that products arising from reaction at this position would dominate. Fluorination of **13** and **18** at −78 °C was sensitive to different reaction parameters as summarized in Table 1. For example, switching the reaction solvent from THF to dichloromethane (DCM) improved the yield for converting **13** to **14** from 32% to 55% (entries 1 and 2); we had observed the same solvent dependence in our previous work.[9] The reaction also showed a significant dependence on the number of equivalents of DAST used and the reaction time (entries 2–5). Cutting the reaction time to five minutes and using 1.5 equiv of DAST proved to be most efficient, providing **14** and **19** in 75 and 66% yields, respectively (entries 3 and 5).

Formation of the septanosyl fluorides was confirmed by NMR spectroscopy. Septanosyl fluoride **14** was obtained as an inseparable mixture of anomers whereas the two anomers of **19** were separable by column chromatography. For **19α**, the signal for the anomeric proton was characterized by a distinct downfield shift (δ_H 5.47 ppm) as a doublet of a doublets with the following coupling constants: J_{H-F} = 54.0 Hz, $^3J_{H1,H2}$ = 6.2 Hz. The α configuration was also confirmed by the downfield ^{13}C NMR chemical shift (δ_C 111.3 ppm) of the anomeric carbon with a $^1J_{C-F}$ coupling constant of 227 Hz. For **19**β, the anomeric proton appeared as doublet (δ_H 5.70 ppm) with a J_{H-F} 49.7 Hz. In the ^{13}C NMR, the δ_C was 110.0 ppm and the $^1J_{C-F}$ was 215 Hz. The lower $^1J_{C-F}$ value for the β anomer compared to the α is consistent with data reported for pyranosyl fluorides.[19] A ^{19}F NMR experiment performed on the β anomer showed a resonance at −138.0 ppm, unambiguously proving the C1 fluorination of the septanose lactol.[20] Proton coupled ^{19}F NMR data for the mixture of anomeric fluorides **14** was collected; chemical shifts of −134.1 and −134.5 ppm with J_{H-F} values of 50.2 and 50.6 Hz confirmed their structures.

With an established method to prepare septanosyl fluorides, we next evaluated their ability to act as donors in glycosylation reactions. We began by using 1,2:4,6-di-*O*-isopropylidene D-galactose **2** as a model acceptor. We previously reported that both TMSOTf or a combination of $SnCl_2$ and $AgClO_4$ could efficiently promote glycosylation when using 2-aminoseptanosyl fluorides (i.e., **9**) as donors. Accordingly, we attempted to use these promoters in reactions using donors **14**, **15**, and **19**.[21] Reaction of donor **14** using TMSOTf as promoter resulted in the formation of disaccharide **21** (Fig. 1) in 18% yield as mixture of anomers (Table 2, entry 1). The C2 benzyl protected donor **15** showed an improved yield (41% and 37% yields, respectively) although the stereoselectivity in glycoside bond formation was poor for both promoters (entries 2 and 3). Use of donor **19**, with a free C2 hydroxyl group, resulted in efficient glycosylation, providing **23** in 58% and 65% yields, depending on the promoter used. Notably, when using this donor, a single stereoisomer of the newly formed glycoside was isolated for several glycosyl acceptors (entries 4–9, 11). The product glycosides were assigned as the α-anomers based on ^{13}C chemical shifts, which were in the range of 98–103 ppm. Additional support came from a ^{13}C coupled HSQC experiment to determine the $^1J_{C-H}$ value for a selected compound. The measured $^1J_{C-H}$ measured for **26** was 167 Hz which is characteristic of the α-anomeric configuration of septanosides as has been reported.[7,10] High diastereoselectivity in glycosylation reactions involving partially protected donors is precedented.[22–24] We propose that a 1,2-anhydrosugar species such as **32** is sufficiently populated such that it blocks the β-face

Table 1
DAST conversion of septanose lactols **13** and **18** to the corresponding septanosyl fluorides[a]

Entry	Lactol	Product	Solvent	DAST (equiv.)	Time (min)	Yield (%)
1	**13**	**14**	THF	1.0	30	32
2	**13**	**14**	DCM	1.2	30	55
3	**13**	**14**	DCM	1.5	5	75
4	**18**	**19**	DCM	1.2	30	60
5	**18**	**19**	DCM	1.5	5	66

[a] All reactions done at −78 °C under N_2 atmosphere.

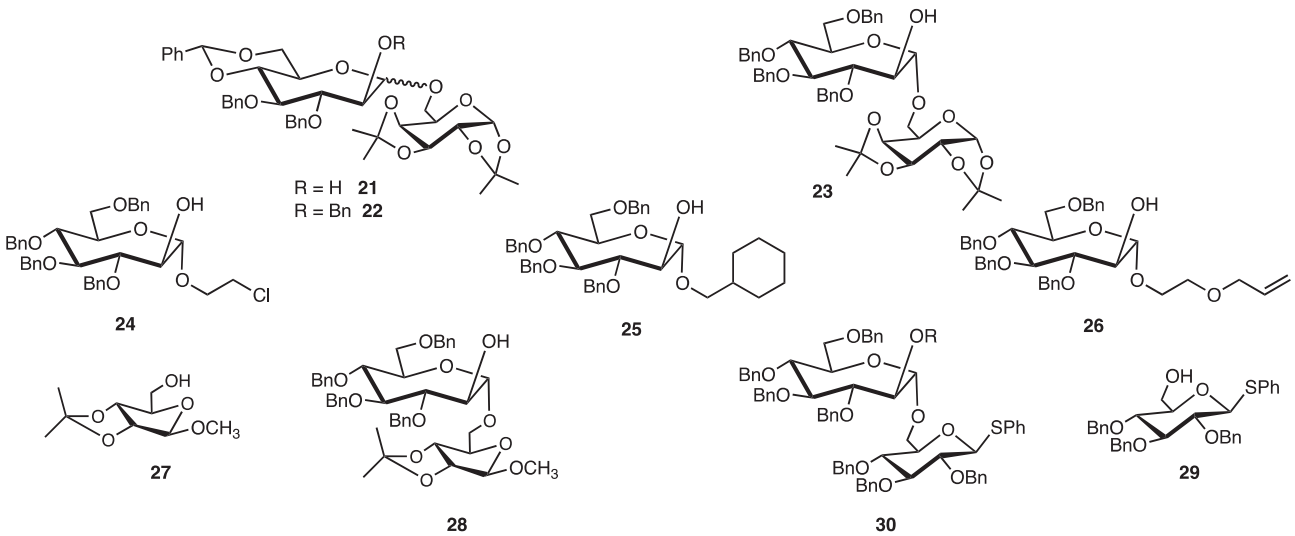


Figure 1. Products of glycosylation reactions described in Table 2.

Table 2
Glycosylations of several alcohols with septanosyl donors **14**, **15** and, **19**

Entry	Donor	Acceptor	Promoter	Product	Yield (%)	α:β
1	**14**	**2**	TMSOTf	**21**	18	1:1
2	**15**	**2**	TMSOTf	**22**	41	ND
3	**15**	**2**	$SnCl_2$–$AgClO_4$	**22**	37	ND
4	**19**	**2**	TMSOTf	**23**	58	α
5	**19**	**2**	$SnCl_2$–$AgClO_4$	**23**	65	α
6	**19**	Chloroethanol	TMSOTf	**24**	61	α
7	**19**	Cyclohexyl methanol	TMSOTf	**25**	52	α
8	**19**	Allyloxyethanol	TMSOTf	**26**	57	α
9	**19**	**27**	TMSOTf	**28**	60	α
10	**19**	**27**	$SnCl_2$–$AgClO_4$	**28**	49	ND
11	**19**	**29**	TMSOTf	**30**	54	α

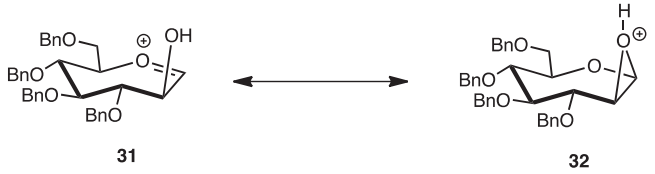


Figure 2. Oxocarbenium ion 31 and its 1,2-anhydrosugar resonance structure 32; 32 explains the high α-selectivity of the glycosylations in Table 2.

of the donor (Fig. 2) giving rise to the high α-selectivity observed.[22] Further, comparison of the glycosylation selectivities for **14** and **15** with those of **19** suggests that the flexibility within the ring is necessary to form **32**. The rigidity imposed by the benzylidine moiety on **14** and **15** presumably does not allow the 1,2-anhydrospecies to form and gives rise, therefore, to anomeric mixtures.

We have developed a glycosylation strategy that uses a C2 hydroxy (unprotected) septanosyl fluoride as donor in glycosylation reactions. Use of anomeric fluorides as donors has allowed the synthesis of septanosides that contain a substituent at the C6 position which had previously been cumbersome and inefficient. The new method overcomes the shortcomings associated with efficient preparation of thioglycoside donors (Scheme 1). It also simplifies an earlier route to prepare methyl septanosides through species akin to **13**.[25] This method was limited by stepwise synthesis with protecting group maneuvers. One of the major problems in that approach was to functionalize the anomeric group selectively in the presence of an unprotected C2 hydroxyl group. Compounds such as **13** (Scheme 3) are complicated by a propensity for the α-hydroxyaldehyde to equilibrate into an α-hydroxy ketone under the reaction conditions (via an ene-diol). Selective functionalization of the C1 hydroxyl in the new procedure provided the septanosyl fluoride donors in good yields. Furthermore, the glycosylations that were conducted without protecting the C2 hydroxyl group gave efficient yields and selectivity rendering shorter synthesis and provided more room to functionalize through C2 position for more complex septanose carbohydrates.

Acknowledgements

Bikash Surana is acknowledged for early investigations in the synthesis of compound **6**. This work was supported by a National Science Foundation CAREER Award (CHE-0546311) to M. W. P. NSF is also acknowledged for CRIF award to upgrade the 400 MHz NMR (CHE-1048717).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.039.

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