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gem-Dimethyl 4-Pentenyl Glycosides: Novel Glycosylating Agents and Anomeric Protecting Groups

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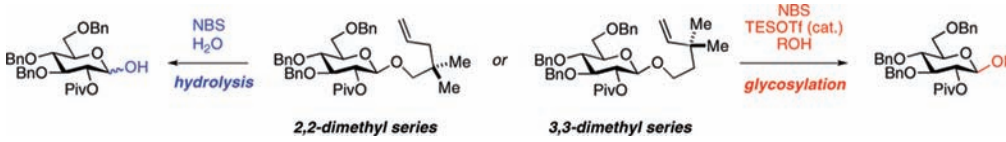
ABSTRACT



Two classes of *gem*-dimethyl 4-*n*-pentenyl glycosides (i.e., C2-series and C3-series) have been prepared and studied in both the glycosylation and hydrolysis manifolds utilizing NBS as the sole stoichiometric activator. These novel glycosylating agents, which are analogues of Fraser-Reid's 4-*n*-pentenyl glycosyl donors, show increased reactivity in side-by-side studies by virtue of the *gem*-dimethyl effect.

The biological significance of oligosaccharides and their glycoconjugates, coupled with the need for reliable access to structurally defined material for study, continues to drive oligosaccharide synthesis.[1] Remarkable advances in the field have been made since the venerable Koenigs−Knorr method was discovered over a century ago.[2] Since then, many glycosyl donors have been developed including the following: orthoesters,[3] trichloroacetimidates,[4] thioglycosides,[5] fluorides,[6] glycals,[7] sulfoxides,[8] 4-*n*-pentenyl glycosides (NPGs),[9] phosphates,[10] 1-hydroxy glycosides,[11] and thioimidates,[12] among others.[13] The labor-intensive and multistep nature of oligosaccharide synthesis is largely derived from the high density of functionality decorating the furanose and pyranose scaffolds (e.g., hydroxy and amino groups), mandating the use of protecting groups. Thioglycosides, 4-*n*-pentenyl glycosides, and more recently thioimidates distinguish themselves in that they serve both as glycosyl donors and anomeric protecting groups, thus minimizing the overall number of operations employed in the synthesis.[14]

Our efforts in the area of oligosaccharide synthesis have been focused on synthetic efficiency and inspired by Fraser-Reid's NPG donor **1**, whose mechanism of activation is

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(2) Koenigs, W.; Knorr, E. *Ber.* **1901**, *34*, 957.

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(5) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.

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(8) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

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(12) (a) Demchenko, A. V.; Malysheva, N. N.; De Meo, C. *Org. Lett.* **2003**, *5*, 455. (b) Pornsuriyasak, P.; Demchenko, A. V. *Chem.—Eur. J.* **2006**, *12*, 6630.

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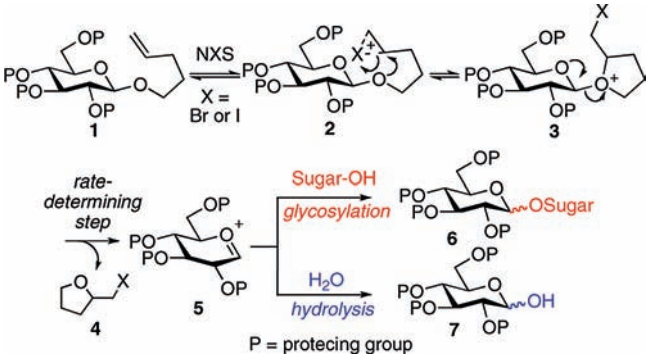
detailed in Scheme 1.[15] Electrophilic attack of a halonium ion (e.g., Br^+ or I^+) on the olefin of **1** generates intermediate **2** in a reversible manner.

Scheme 1. Mechanism of NPG **1** Activation



Proximity effects permit a cyclization to occur whereby the anomeric hydroxyl generates a tetrahydrofuranyl oxonium intermediate **3**. At this point, the pyranose oxygen can assist in ejecting the THF moiety and form the reactive oxocarbenium ion **5**, which can react with a suitably protected acceptor to form glycoside **6** or water to yield lactol **7**.[16] Our attention was focused on the first two steps in the cascade process, and we set about modifying the 4-*n*-pentenyl aglycon to arrive at a donor system that (1) was efficiently prepared from commercial sources, (2) displayed increased reactivity under electrophilic activation, (3) would withstand the routine battery of protecting group conditions, and (4)

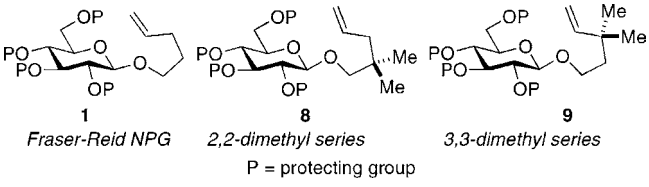
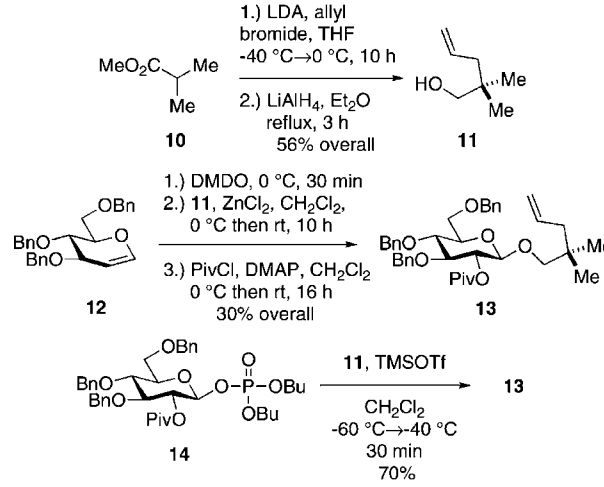


Figure 1. NPG **1** and *gem*-dimethyl analogues **8** and **9**.

utilized inexpensive NBS rather than NIS as the sole stoichiometric activator.[17] Toward this end, we conceived and prepared two series of *gem*-dimethyl analogues of **1**: 2,2-dimethyl-4-pentenyl (**8**) and 3,3-dimethyl-4-pentenyl glycosides (**9**), hypothesizing that an attendant *gem*-dimethyl effect would accelerate the ring-closure (Figure 1).[18] The 1,1-dimethyl congener was not considered as it would preclude the use of acid, which is often employed during protecting group manipulation.

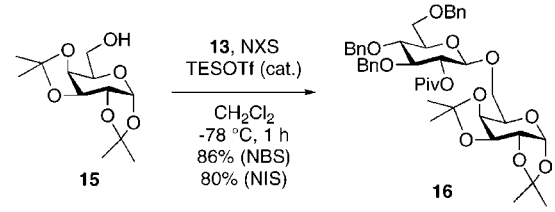
Scheme 2. Synthesis of 2,2-Dimethyl-4-pentenyl Donor **13**



The preparation of C2-*gem*-dimethyl donor **13** is shown in Scheme 2 and began with the synthesis of known 2,2-dimethyl-4-pentenol (**11**).[19] Treatment of the lithium enolate of methyl isobutyrate (**10**) with allyl bromide and subsequent LAH reduction of the ester afforded alcohol **11** in 56% yield after a single distillation.

We first employed the glycal assembly method to rapidly access C2-*gem*-dimethyl donor **13**.[7] Not surprisingly, neopentyl acceptor **11** reacted sluggishly with the intermediary 1,2-anhydrosugar even in excess (>5 equiv) to yield donor **13** in 30% overall yield from glycal **12**,[20] despite an excess of $ZnCl_2$. Recourse to the more reactive glycosyl phosphate donor **14**[21] delivered **13** in an acceptable 70% yield under the agency of stoichiometric TMSOTf.

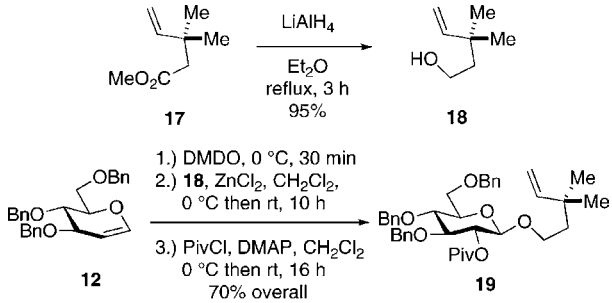
Scheme 3. Glycosylation of **13** with Acceptor **15**



With 2,2-dimethyl-4-pentenyl glycoside **13** in hand, we examined how this novel reagent performed under the typical NPG glycosylation conditions.[9] In the event, treatment of

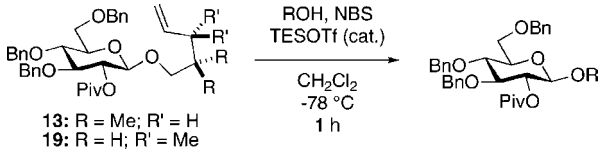
(15) Fraser-Reid, B.; Merritt, J. R.; Handlon, A. L.; Andrews, C. W. *Pure Appl. Chem.* **1993**, *65*, 779.
(16) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662, and references cited therein.
(17) 2008 Prices from Aldrich: NBS (99%), 1 kg, $90.80 ($0.09 per gram); NIS (97%), 100 g, $392 ($3.92 per gram) .
(18) Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205, and references cited therein.
(19) Crimmins, M. T.; Carroll, C. A.; Wells, A. J. *Tetrahedron Lett.* **1998**, *39*, 7005.
(20) Bovin, N. V.; Zurabyan, S. E.; Khorline, A. Y. *Carbohydr. Res.* **1981**, *98*, 25.
(21) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545.

Scheme 4. Synthesis of 3,3-Dimethyl-4-pentenyl Donor **19**



donor **13** and galactose acceptor **15** with equimolar NBS or NIS and catalytic TESOTf in CH_2Cl_2 at −78 °C for 1 h resulted in 86% and 80% yields of disaccharide **16**,[10c]

Table 1. Glycosylation and Hydrolysis of C2-*gem*-Dimethyl Donor **13** and C3-*gem*-Dimethyl Donor **19**



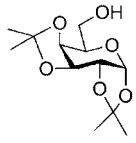
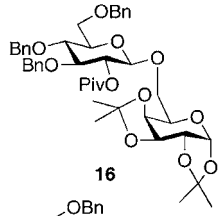
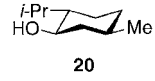
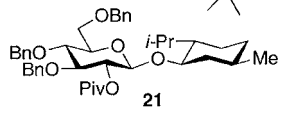
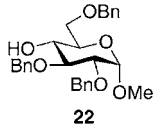
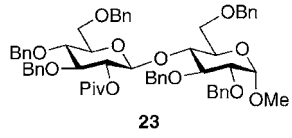
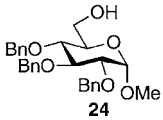
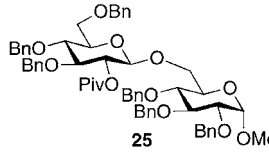
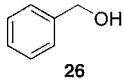
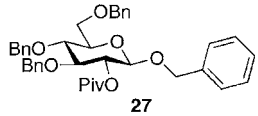
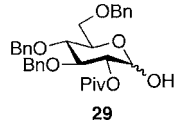
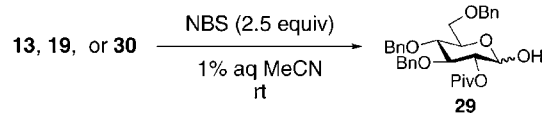
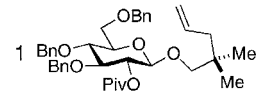
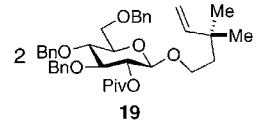
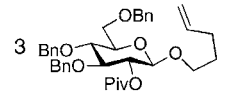
entry	acceptor (ROH)	product	yield (%) donor: **13**	**19**
1	 **15**	 **16**	86	81
2	 **20**	 **21**	80	78
3	 **22**	 **23**	74	80
4	 **24**	 **25**	81	82
5	 **26**	 **27**	80	74
6	H_2O	 **29**	85	90

Table 2. Side-by-Side Hydrolysis of 4-Pentenyl Donors



entry	donor	time (min)[a]	k_{rel}[b]	k (min^{-1})[c]	$t_{1/2}$ (min)[d]	yield
1	 **13**	30	1	--[e]	4.62[f]	85%
2	 **19**	105	3.5	0.0429	16.18	90%
3	 **30**	330	11	0.0144	48.14	83%

[a] Reactions monitored by LC−MS until donor was no longer detected. [b] Based on data in "time (min)" column. [c] Determined as the average of two runs; see the Supporting Information. [d] See Supporting Information for half-life equations. [e] Not enough data points to reliably determine (i.e., reaction too fast). [f] Extrapolated from k_{rel} (entries 2 and 3).

respectively (Scheme 3). Reactions run at higher temperatures resulted in lower yields and more byproducts as per TLC analysis. The lower yield under NIS activation and/or higher temperature, which are conditions for the activation of **1**, suggest the *gem*-dimethyl analogues are more reactive vis-à-vis parent NPGs.

Encouraged by these initial results, we began exploring the scope of the method. In tandem, we pursued the C3-*gem*-dimethyl congener **9**. The preparation of 3,3-dimethyl-4-pentenyl donor **19** was achieved in a straightforward manner from cheap, commercially available methyl 3,3-dimethylpentenoate (**17**). Reduction of ester **17** with LAH in Et_2O yielded alcohol **18** in >97% purity by ^1H NMR after workup with no further purification (Scheme 4).

The glycal assembly method was favorably recruited to procure donor **19** in 70% yield overall.[7] Both *gem*-dimethyl 4-pentenyl donors **13** and **19** were subjected to a range of acceptors (including H_2O) to assess the scope of the method; those results are summarized in Table 1 below.

In general, both donors favorably glycosylated a range of acceptors, including primary alcohols (entries 1, 4, and 5) and secondary alcohols (entries 2 and 3) with synthetically useful yields (74−87%). Donor hydrolysis (entry 6) afforded known lactol **29**[22] in high yield, demonstrating the capacity of *gem*-dimethyl 4-pentenyl aglycons to serve as anomeric protecting groups.

Finally, to support our hypothesis that a *gem*-dimethyl effect is responsible for accelerating the reactions of **13** and

(22) Boebel, T. A.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 5874.

19, we conducted side-by-side studies of the NBS-mediated hydrolysis of said donors and parent NPG donor **30**, which was prepared via the glycal assembly method (see Scheme 4). The hydrolysis reaction was selected over the glycosylation reaction because of more manageable time scales (i.e., glycosylation rates are much faster due to the use of catatlyic TESOTf, which activates the NBS to rapidly generate Br^+).

All donors were subjected to oxidative hydrolysis conditions: NBS (2.5 equiv) in 1% H_2O/MeCN (0.025 M) at room temperature (Table 2). The progress of each reaction was monitored by LC−MS.[23] Our results showed that the C2-*gem*-dimethyl donor **13** (entry 1) hydrolyzed eleven times faster than the parent NPG **30** (entry 3) to furnish **29**. The C3-*gem*-dimethyl (entry 2), on the other hand, was approximately three times faster than **30**. These results were corroborated by half-live determination ($t_{1/2}$).[23]

In summary, we have developed novel *gem*-dimethyl analogues of Fraser-Reid's NPGs from readily available 2,2-dimethyl-4-pentenol (**11**) and 3,3-dimethyl-4-pentenol (**18**). These glycosylating agents utilize NBS as the sole stoichiometric activator for glycosylation and hydrolysis, allowing synthetic flexibility. We are currently expanding the study of these donors to include other monosaccharides (e.g., mannose, galactose, glucosamine, fucose, etc.) and exploring chemoselective (i.e., armed−disarmed) strategies for oligosaccharide synthesis. In addition, we will report alternative synthetic routes to these donors from the corresponding glycosyl bromide and acetate as per Fraser-Reid.[9] Those results will be reported in due course.

(23) See the Supporting Information for details.

Acknowledgment. Financial support of this work by the Department of Chemistry at Temple University is gratefully acknowledged. We thank Bristol-Myers Squibb for a BMS Summer Undergraduate Research Award in Organic Chemistry to K.P. We also thank Dr. Greg Foy (York College) for access to LC−MS instrumentation and helpful discussions.

Supporting Information Available: Experimental procedures, characterization of compounds **13**, **19**, **21**, **23**, **25**, and **27** (including ^1H and ^{13}C NMR spectra), LC−MS traces of hydrolysis reactions, and kinetics analysis of **13**, **19**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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