ORGANIC
LETTERS

2004
Vol. 6, No. 18
3051−3054

Preparation, Properties, and Applications of *n*-Pentenyl Arabinofuranosyl Donors[†]

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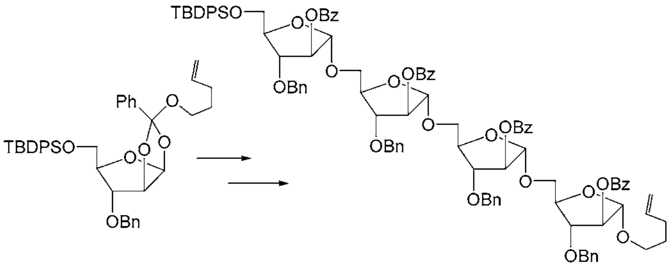
Received May 20, 2004

ABSTRACT



The development of *n*-pentenyl furanosyl donors has been tested using arabinose as a model. The readily prepared ortho ester (NPOE) is converted into disarmed (NPG_{AC}) and thence armed (NPG_{ALK}) *n*-pentenyl arabinofuranosides. The reactivities of these furanosyl donors and pyranosyl counterparts have been assessed by allowing pairs of both to compete for an acceptor. For the NPOE and armed (NPG_{ALK}) pairs, coupling products were obtained from donors, whereas for the disarmed (NPG_{AC}) pair, only the *arabinofurano* coupled product was obtained. To probe their synthetic utility, the NPOE was shown to be the only precursor needed to prepare an α-1,5-linked arabinan segment of the complex lipoarabinomannan cell wall array of *Mycobacterium* tuberculosis.

In the past, comparatively little attention has been paid to glycosyl donors for furanosides[1] undoubtedly because of the greater abundance of pyranosidic structures in nature. However, the recent discovery of furanoside components in a wide range natural products of biological importance such as glycosylphosphatidyl inositol,[2] helminthosporium toxins,[3] and most abundantly as mycobacterial cell wall components[4] suggests that greater effort will be directed at oligofuranoside synthesis now that mild, modern isolation methods are allowing such molecules to be discovered with ever increasing frequency.

In an early attempt to apply *n*-pentenyl methodology to furanoside coupling, Plusquellec and co-workers,[5] and subsequently Arasappan and Fraser-Reid,[6] relied on the well-established technique of Fischer glycosidation,[7] i.e., aldose → furanoside → pyranoside, which can be interrupted at optimal furanoside accumulation. By this protocol, *n*-pentenyl

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[†] We dedicate this paper to the memory of Professor Christian Pederson.

[‡] An independent, nonprofit research facility with laboratories at Centennial Campus (North Carolina State University), Raleigh, NC.

(1) For a recent summary of developments in furanosyl donors, see: Lowary, T. L. In *Glycoscience: Chemistry and Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Heildelberg, 2001; Vol. 3, p 1696.

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(4) See for example: Kordulakova, J.; Gilleron, M.; Puzo, G.; Brennan, P. J.; Gicquel, B.; Mikusova, K.; Jackson, M. *J. Biol. Chem.* **2003**, *278*, 36285. Patterson, J. H.; Waller, R. F.; Jeevarajan, D.; Billman-Jacobs, H.; McConville, M. J. *Biochem. J.* **2003**, *372*, 77. Nigou, J.; Gilleron. M.; Puzo, G. *Biochimie* **2003**, *85*, 153. Schaeffer, M. L.; Khoo, K. H.; Besra, G. S.; Chatterjee, D.; Brennan, P. J.; Belisle, J. T.; Inamine, J. M. *J. Biol. Chem.* **1999**, *274*, 31625.

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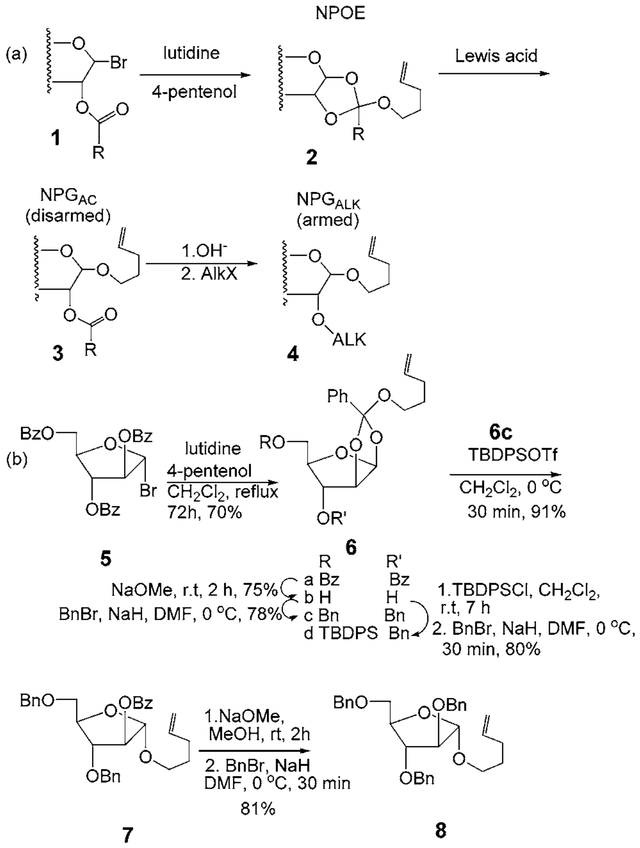
10.1021/ol0490680 CCC: $27.50

Scheme 1



galactofuranosides were obtained in good yield and shown to be very good donors.[5,6,8]

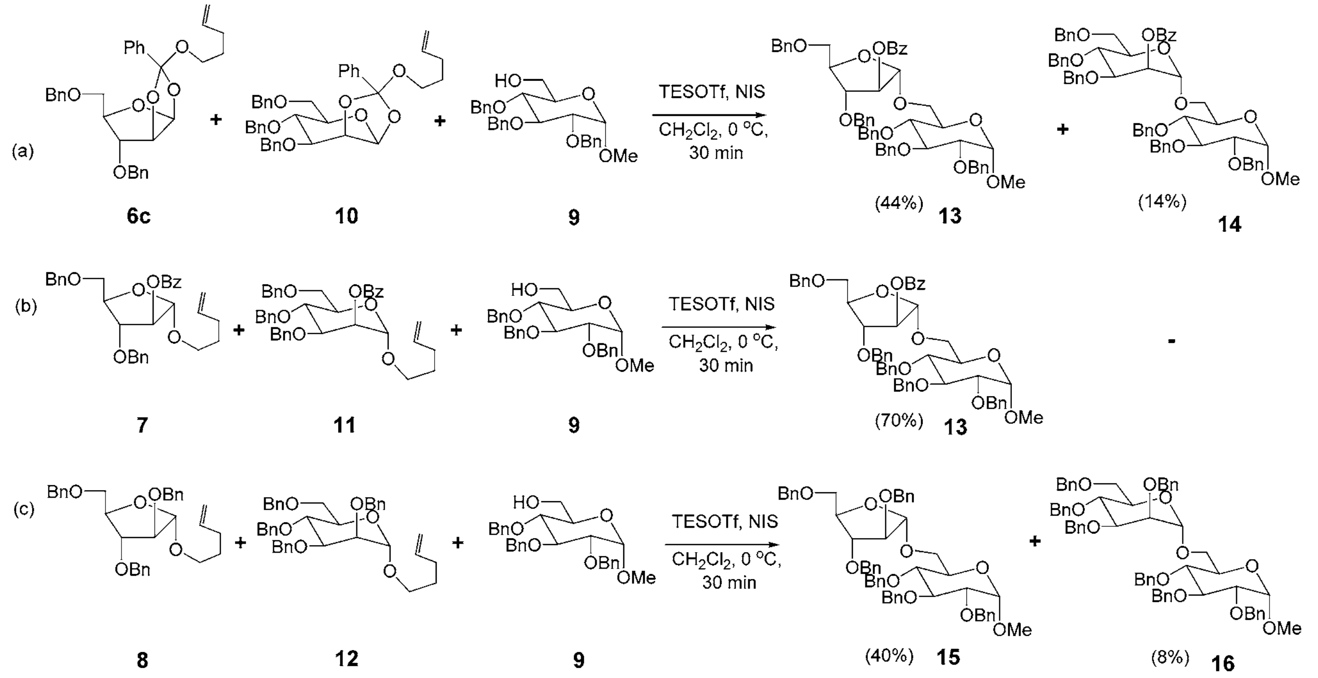
Mereyala, Hotha, and Gurjar,[9] in an experiment reminiscent of an earlier van Boom strategy,[10] used an *n*-pentenyl furanoside bearing a free-OH as an acceptor for a thiofuranoside donor. The resulting disaccharide, itself an *n*-pentenyl glycoside, could then function as a donor for further elaboration.

Despite the foregoing successes, we were interested in developing alternative procedures, because not all aldoses are as obliging as galactose toward furanoside formation in Fischer glycosidations.[11] We have therefore been trying to adapt recent innovations[12,13] with *n*-pentenyl ortho ester donors, **2**, to furanoses. In the case of pyranosyl systems, the NPOE **2** is obtainable in three steps from the aldose, via the glycosyl bromide, **1**.[12] As is typical of such glycosyl ortho esters,[14] mild treatment with acid effects rearrangement to the disarmed *n*-pentenyl glycoside (NPG$_{AC}$), **3**, from which the armed counterpart (NPG$_{ALK}$), **4**, is obtained routinely.[12]

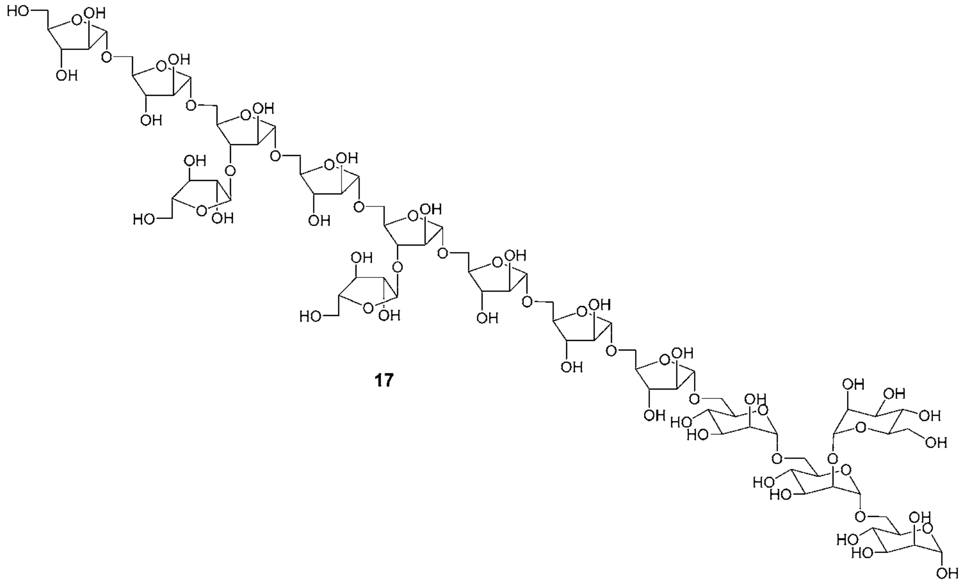
Donors **2** and **3** are capable of furnishing the same coupling product(s). However, a pyranose NPOE (a) is infinitely more reactive than the NPG$_{AC}$ derived from it and (b) usually couples with exclusive stereoselectivity.[12] Furthermore, recent reports from our laboratory on the use of Lewis acid salts to generate iodonium ions from *N*-iodosuccinimide (NIS) have shown that ytterbium triflate, Yb(OTf)$_3$, is *chemospecific* for the NPOE, leaving disarmed (NPG$_{AC}$) and armed (NPG$_{ALK}$) donors untouched.[15]

Our transfer of NPOE technology to furanoses began with the known arabinofuranosyl bromide **5**[18] (Scheme 1b). (In this connection, it is appropriate to note that Backinowsky and co-workers[16] have used 1,2-*O*-(1-cyanoethylidene) derivatives of furanoses for glycosidations. These ortho ester-like componds are excellent donors,[17] although not as

Scheme 2. Competition of Pairs of Donors to Glycosidate Methyl 2,3,4-Tri-*O*-benzyl α,D-glucopyranoside, **9**[a]



[a] Equivalent amounts of the pairs of donors and 1 equiv of the acceptor in CH$_2$Cl$_2$ were treated with NIS (1 equiv) and TESOTf at 0 °C for 30 min.



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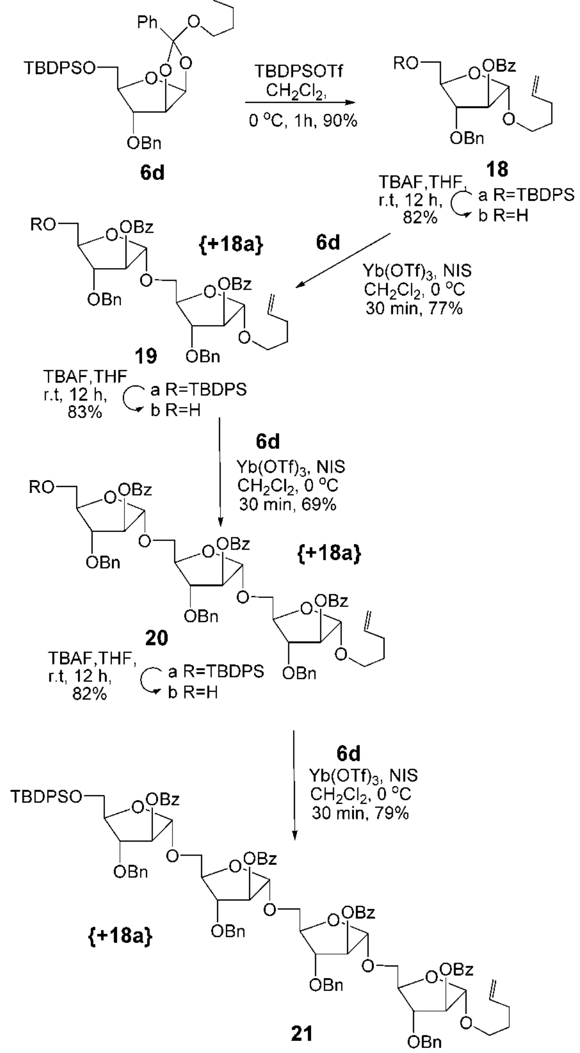
versatile as NPOEs.) Upon treatment with 4-pentenol in dichloromethane containing 2,6-lutidine and tetra-*n*-butylammonium iodide for 72 h, an inseparable mixture (3:1) of products was obtained in 70% yield. The presence of two ester carbonyl signals (^{13}C NMR at 166.1 and 165.5 ppm) along with an aromatic multiplet for 15 protons (i.e., three phenyl rings in the ^{1}H NMR spectrum between 7.34 and 8.06 ppm) was consistent with formation of the desired ortho ester product **6a**. Further support for this assignment came from treatment with sodium methoxide at room temperature for 2 h, whereupon the definitive ^{13}C NMR ester signals, noted above, disappeared, and the aromatic proton multiplet was reduced in intensity from 15 to 5, consistent with the loss of two benzoyl groups leading to diol **6b**. The di-*O*-benzyl ether **6c** was then prepared.

Compound **6c**, upon treatment with *tert*-butyldiphenylsilyl triflate (TBDPSOTf) in dichloromethane for 1 h, was transformed into a single new product in 90% yield. Notably, this treatment caused disappearance of a low-intensity peak in the 75 MHz ^{13}C NMR spectrum of **6c** in $CDCl_3$ at 122.6 ppm and appearance of a strong signal at 165.5, consistent with the ortho ester to ester transformation, **6c** → **7**. Further support for the structure of compound **7** came from the benzoyl resonances in the ^{1}H NMR spectrum in $CDCl_3$ (2H ~7.95 and 3H 7.49−7.67). The tri-*O*-benzyl analogue **8** was obtained from **7** routinely.

With the *furano* series (Scheme 1b) in hand, comparisons could be drawn with the pyranose counterparts. That furanoses are generally more reactive than pyranoses is well established;[19] however, it was of interest to see if these reactivities would be amenable to substituent effects.

Scheme 3



First, donors[20] **6c**, **8**, **10**, and **12** were coupled separately with methyl 2,3,4-tri-*O*-benzyl α,D-glucopyranoside, **9**. The

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resultant disaccharide products **13**, **15**, **14**, and **16**, respectively, were characterized. Fortuitiously, all four were sufficiently well resolved on TLC (hexane/EtOAc (4:1) R_f = 0.34, 0.37, 0.35, and 0.29, respectively) to enable preliminary identification.

With this information in hand, we then allowed pairs of donors in equimolar amounts (Scheme 2) to compete for 1 equiv of the glucoside acceptor in a reaction medium containing NIS (1 equiv) and TESOTf (0.3 equiv) for 30 min, this time having been shown (TLC) to be adequate for completion of all reactions. The products were identified by the above-noted R_f values, and then they were isolated by chromatography and matched with the authentic materials, **13**, **14**, **15**, or **16**, prepared in the prior experiments.

The product percentages in Scheme 2 indicate that furanosyl donors are always preferred for coupling, but to different extents. Thus, with the most reactive donors (NPOEs), **6c** and **10**, the coupling products were **13** and **14** in a 3:1 ratio (Scheme 2a). With the least reactive (disarmed) donors, **7** and **11**, only furanose-coupled product **13** was observed (Scheme 2b).

The armed donors **8** and **12**, which are of intermediate reactivity, gave furanose and pyranose products **15** and **16**, respectively, in a 5:1 ratio (Scheme 2c).

An attractive context for probing for nuanced selectivities of these *n*-pentenyl donors is the arabinan segment, **17**, from the lipoarabinomannan complex of complex from *Mycobacterium* tuberculosis.[1,4] The diol **6b** was silylated and benzylated in sequence to obtain NPOE **6d**, which was rearranged with TBDPSOTf to NPG **18a** (Scheme 3). Desilylation gave acceptor **18b**, which was then presented with 1.5−2.0 equiv of NPOE **6d** in order to optimize formation of the coupled product **19a**. *Notably, for this exercise Yb(OTf)$_3$ was used to decompose NIS, because the residual NPOE, **6d**, would be converted into the NPG **18a** and recovered as such, since Yb(OTf)$_3$/NIS is chemospecific for NPOEs.*[15] This “byproduct” would then be desilylated to obtain the initial acceptor, **18b**, for use in future experiments.

The *chemo* and *stereoselective* processes leading from **18** → **19** offered a simple strategy for arabinan assembly involving desilylation/coupling iterations. This idea was reduced to practice with the conversions **19** → **20** → **21** (Scheme 3). Being an NPG, the tetraarabinofuranoside **21** can now serve as a donor on the basis of earlier work in our[6] and other[5,8] laboratories.

Acknowledgment. We are grateful to the National Science Foundation and the Human Frontier Science Program Organization.

Supporting Information Available: Experimental details for preparation and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For donors **10**−**12**, see ref 12 and references therein.