JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

Ready Preparation of Furanosyl *n*-Pentenyl Orthoesters from Corresponding Methyl Furanosides

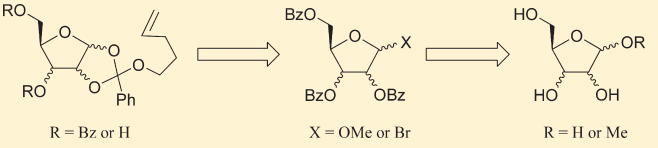
Changalvala V. S. Ramamurty,[†] Parimala Ganney,[†] C. Srinivas Rao,[‡] and Bert Fraser-Reid*[,†]

[†]Natural Products and Glycotechnology Research Institute, Inc., 595 F Weathersfield Road, Pittsboro, North Carolina 27312, United States

[‡]CiVentiCHEM, P.O. Box 12041, Research Triangle Park, North Carolina 27709, United States

Supporting Information

ABSTRACT: The 3,5-di-*O*-benzoyl *n*-pentenyl orthoesters of the four pentofuranoses have been prepared. The first key intermediate in each case is the methyl pentofuranoside(s), and a user-friendly procedure for the preparation of each, based on the Callam−Lowary precedent, is described, whereby formation of the crucial α/β anomeric mixture is optimized. The mixture is used directly to prepare the corresponding perbenzoylated pentofuranosyl bromide(s) and then the title compounds.



Recent work in our laboratory has been concerned with the antigenic glycolipid found on the cell surface matrix of *Mycobacterium tuberculosis*.[1] Attention was focused on the oligoarabinofuranan array, which has been identified as the seat of antigenic activity.[2] This structure exists as a totally carbohydrate-based dendrimer which, in a recent nanoscale rendition, can be seen to tower over the complex cell surface saccharide matrix.[3] Our synthetic approach to this dendritic domain employed chemo- and regioselective couplings of arabinose donors and acceptors, all of these building blocks being readily available from the *n*-pentenyl orthoester (NPOE) of arabinose **9**.[4] This achievement has sparked our interest in extending NPOE chemistry to the other pentofuranoses.

NPOEs of the hexopyranoses, used extensively in our studies,[5] require perbenzoylated pyranosyl bromide precursors as key intermediates. The corresponding furanosyl arabinose derivative **4a** (Scheme 1a) was therefore seen as an appropriate intermediate, and fortunately its synthesis had previously been reported originally by Fletcher[6] and more recently by Hatanaka and Kuzuhara.[7] These routes required prior formation of the methyl furanoside **2a** under kinetic conditions to establish the five-membered ring and perbenzoylation to **3a** to secure the system against ring expansion during the subsequent acid-catalyzed bromination.

Formation of the perbenzoylated methyl furanoside intermediates was therefore seen as the key step. Some of these derivatives are commercially available, but the costs are beyond our economic resources. A survey of the literature failed to disclose simple, generalizable syntheses of the corresponding methyl furanosides. One popular strategy is to establish the furanose ring by affixing an isopropylidene acetal[8] with subsequent methylation at the anomeric center.[9] However, a more direct route was preferable, and thus, we have adapted the user-friendly procedure for preparation of **2a** to the other methyl pentofuranosides.

We had obtained methyl arabinofuranoside **2a** by use of the modern procedure described by Callam and Lowary,[10] which employs an easier Fischer glycosidation procedure than that used earlier by Fletcher.[6] Accordingly, a general procedure based on the Callam−Lowary protocol was applied to the pentofuranoses. As seen in Scheme 1, the sugar was dissolved in a methanol/acetyl chloride solution (step 1) and the time for its disappearance determined by TLC (EtOAc/MeOH/H_2O/nBuOH 2:1:1:1). The new material, which was usually not resolved with this solvent system, was presumed to be methyl α/β furanosides. However, if the reaction was allowed to stand longer, and a less polar solvent system (EtOAc/MeOH/nBuOH 2:1:1) used, TLC monitors showed eventual conversion to, presumably, the α/β pyranosides.

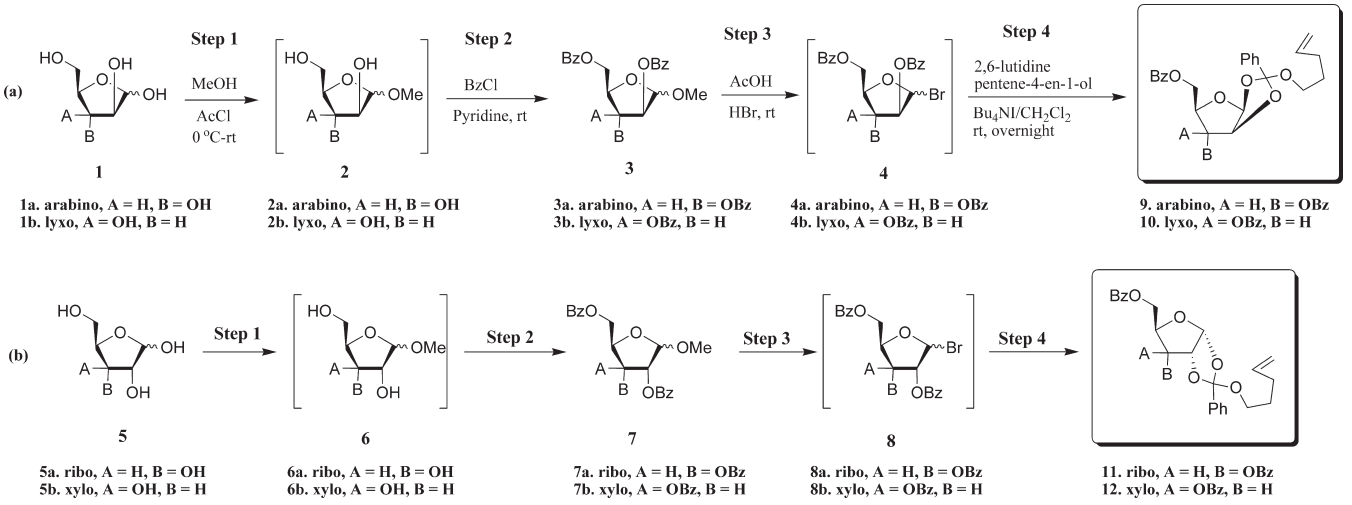
The reaction was usually stopped at the furanoside formation stage, and since both anomers would be useful for eventual orthoester formation, no attempt was made at separation. Instead, the solution was neutralized with pyridine, and after coevaporation with methylene chloride, the crude product was treated directly with benzoyl chloride and pyridine overnight (step 2) to give the desired perbenzoylated methyl furanoside.

As seen from the data in Scheme 1, generalization of the glycosidation (i.e., step 1) proved to be very substrate-sensitive. In the case of arabinose, step 1 required 7 h for the α/β mixture (R_f 0.8) to be optimized. Employing step 2 afforded benzoylated material, which gave evidence of imminent crystallization. The material was therefore dissolved in ethanol which upon cooling deposited α**3a** as a crystalline material in 50% yield, mp 100−102 °C, in agreement with the literature value.[11]

With regard to lyxose, van Boom and co-workers[12] had previously applied a similar Fischer glycosylation for 24 h which afforded a complex mixture. Because such complexity could be

Received: October 27, 2010
Published: March 07, 2011

Scheme 1. Preparation of Pentose Pentenyl Orthoesters[a]



[a] For details about steps 1−4 for each transformation, see the Experimental Section.

problematic for us, a systematic study was undertaken to optimize furanose formation.

Experiments showed that 0.2 mL of acetyl chloride was required for 1 g of lyxose to gradually disappear in 3 h, as monitored by TLC (EtOAc/MeOH/nBuOH 2:1:1). At this time, an apparently single new material was evident, and this was perbenzoylated in the usual way. The product **3b** was isolated by chromatography in approximately 66% yield (Table 1).

Glycosidation of ribose under the conditions for step 1 was much faster, with the conversion **5a** → **6a** being complete in 1 h (R_f 0.8). Benzoylation in the usual way afforded **7a** in 72% yield after chromatography.

With regard to xylose, our earliest approach to the methyl furanoside had been to repeat the work of Fletcher.[14] But in our hands, the methyl pyranoside was the only product. A subsequent paper with Diehl[13] recommended that "the procedure involving the methyl glycosides is superior", the latter being the previously described preparation.[14] In our hands, the "improved procedure" gave a mixture of furanose and pyranose products. The general procedure was therefore employed. Three hours were required for optimal xylofuranoside formation (R_f 0.75). This process was three times slower than of ribose but, notably, two times faster than arabinose.

Conversion of the benzoylated methyl furanosides to the corresponding furanosyl bromides (step 3, Scheme 1) was also structure-sensitive. Treatment of the arabinosyl substrate **3a** with hydrobromic acid in acetic acid at room temperature required 45 min for conversion to the glycosyl bromide **4a**. For ribose and xylose, the process was complete in 10 min.

However, the generalized reaction did not work in the case of lyxose. Success required changing the solvent from acetic acid to dichloroethane, which afforded the perbenzoylated lyxosyl bromide **4b**.

In all cases, the glycosyl bromides turned out to be syrups, and these were used directly in step 4 (Scheme 1). Treatment with 2,6-lutidine and pent-4-en-1-ol in methylene chloride solution at room temperature overnight under the agency of tetrabutylammonium iodide gave the desired *n*-pentenyl orthoesters **9**−**12** in yields ranging from 60 to 90% for the last two steps.

Proton 500 MHz and carbon 80 MHz spectra indicate that orthoesters **9**−**12** exist as single diastereomers in each case. We

Table 1. Summary of Converting Furanoses to *n*-Pentenyl Orthoesters

entry	substrate	reaction conditions[a]	time	product	yield (%)
1	**1a**	A	7 h	**2a**	NI
2	**2a**	B	12 h	**3a**	50
3	**3a**	C	45 min	**4a**	NI
4	**4a**	D	12 h	**9**	90
5	**1b**	A	3 h	**2b**	NI
6	**2b**	B	12 h	**3b**	66
7	**3b**	C*	30 min	**4b**	NI
8	**4b**	D	12 h	**10**	60
9	**5a**	A	1 h	**6a**	NI
10	**6a**	B	12 h	**7a**	73
11	**7a**	C	10 min	**8a**	NI
12	**8a**	D	12 h	**11**	90
13	**5b**	A	3 h	**6b**	NI
14	**6b**	B	12 h	**7b**	66
15	**7b**	C	10 min	**8b**	NI
16	**8b**	D	12 h	**12**	60

[a] Conditions: (A) MeOH, AcCl, 0 °C to rt; (B) BzCl, pyridine, 0 °C to rt; (C) AcOH, HBr (45% in AcOH), rt; (D) 2,6-lutidine, pent-4-en-1-ol, Bu_4NI, CH_2Cl_2. *Dichloroethane was used as a solvent instead of acetic acid. NI: not isolated.

opine that the phenyl ring is over or under the sugar nucleus, as is the case with the corresponding pyranose derivatives.[5a] The availability of all the pentofuranoside *n*-pentenylorthoester analogues provides an opportunity to explore their potential as glycosyl donors. In addition, a preliminary examination of their NMR spectra indicates interesting conformational characteristics of these 3:3:0 bicyclic systems, notably with regard to the C5 methylene protons. A detailed study of these aspects is underway and will be reported in due course.

EXPERIMENTAL SECTION

Methyl 2,3,5-Tri-*O*-benzoyl-α,β-D-ribofuranoside (7a). A suspension of ribose **5a** (5.0 g, 33.3 mmol) in anhydrous methanol (120 mL) was treated slowly with acetyl chloride (2.1 mL) at 0 °C via syringe

dx.doi.org/10.1021/jo1021376 |J. Org. Chem. 2011, 76, 2245–2247

(~30 min). The mixture was stirred at rt, and progress of the reaction was monitored by TLC in EtOAc/MeOH/nBuOH/H_2O (2:1:1:1) until disappearance of the starting material, which was ~1 h. At this time, a faster running material which appeared as a single "spot" was evident. (If at this time, TLC was run in the less polar solvent mixture such as EtOAc/MeOH/nBuOH 2:1:1, the new material, presumed to be the α/β furanoside, still appeared as a single "spot". However, if the reaction time was extended, a newer material started to form which became dominant, signaling formation of the corresponding α/β pyranoside). The reaction mixture, after 1 h, was quenched with pyridine, evaporated, and then coevaporated with dichloromethane to give a crude product that was dried overnight under high vacuum. The material was then dissolved in pyridine, cooled to 0 °C, and treated with benzoyl chloride (15 mL, 120 mmol), and the mixture was stirred overnight at room temperature. Water was added, and after being stirred for 30 min, the mixture was extracted with CH_2Cl_2. The extract was washed with water, 3 N sulfuric acid, saturated $NaHCO_3$ solution, and brine and dried over Na_2SO_4. Purification was effected by *flash column* chromatography using hexanes/ethyl acetate (8:2), which gave compound **7a** as a syrupy material (11.5 g, 72%) as a mixture of anomers.

3,5-Di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enylorthobenzoate) (11). The perbenzoylated methyl ribofuranoside **7a** (5 g, 10.5 mmol) was dissolved in acetic acid (25 mL), and HBr (18 mL, 45% in acetic acid) was added. The reaction vessel was tightly stoppered and stirred at rt for 10 min, diluted with CH_2Cl_2 (100 mL), and washed with ice-cold water (500 mL), $NaHCO_3$ (satd) (3 × 50 mL), and brine (25 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo at 20 °C to give a crude product (5.1 g), which was submitted to the next step immediately without further purification. This mixture was dissolved in CH_2Cl_2 (75 mL), 4-penten-1-ol (2.0 mL, 19.4 mmol) and 2,6-lutidine (2.48 mL, 21.3 mmol) were added followed by Bu_4NI in three lots (358 mg, 0.97 mmol) in 30 min intervals at rt. The reaction mixture was stirred at rt overnight, *when TLC (hexanes−EtOAc 4:1) indicated completion*. The reaction mixture was washed with water (3 × 100 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The obtained crude was purified by *flash column* chromatography on silica gel using hexanes/EtOAc (9:1) to give compound **11** (3.95 g, 71% over two steps): $[\alpha]^{26}_D$ +128.28 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.0−7.96 (m, 4H), 7.66−7.64 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.40−7.36 (m, 5H), 6.20 (d, *J* = 4.5 Hz, 1H), 5.76 (tqt, *J* = 7.0 Hz, *J* = 6.5 Hz, *J* = 4.0 Hz, 1H), 5.25 (t, *J* = 5.0 Hz, 1H), 5.05 (app.t, *J* = 5.5 Hz, *J* = 5.5 Hz, 1H), 4.96 (m, 2H), 4.60 (dd, *J* = 3.0 Hz, *J* = 3.5 Hz, 1H), 4.37 (dd, *J* = 5.0 Hz, *J* = 5.5 Hz, 1H), 4.18−4.15 (m, 1H), 3.45−3.38 (m, 2H), 2.08 (q, *J* = 6.5 Hz, 2H), 1.61 (pent, *J* = 7.0 Hz, 2H); ^{13}C NMR (80 MHz, $CDCl_3$): δ 166.2, 165.8, 138.2, 137.7, 133.8, 133.4, 130.2 (2C), 129.9 (2C), 129.5, 129.2, 128.7 (2C), 128.6 (2C), 128.3 (2C), 126.4 (2C), 124.2, 115.1, 104.7, 78.1, 76.4, 73.4, 62.9, 62.6, 30.4, 28.8; HRMS (ESI) calcd for $C_{31}H_{30}O_8$ Na $[(M + Na)^+]$ 553.1833, found 553.1834.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures for compounds **9**−**12** along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dglucose@aol.com.

Notes

Natural Products and Glycotechnology Research Institute, Inc., is an independent nonprofit research facility with laboratories at CiVentiCHEM, P.O. Box 12041, Research Triangle Park, NC 27709.

■ ACKNOWLEDGMENT

We are grateful to the National Science Foundation (CHE 0717702) for financial support, Dr. George Dubay, Director of Instrument Operations in the Department of Chemistry, Duke University, for mass spectrometric and HRMS measurements, and Dr. D. Srinivas Reddy of the BRITE facility of North Carolina Central University for the 500 MHz NMR spectra of the compounds in Scheme 1.

■ REFERENCES

(1) (a) Jayaprakash, K. N.; Lu, J.; Fraser-Reid, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5894–5898. (b) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; Lopez, J. C. *Tetrahedron: Asymmetry* **2006**, *17*, 2449.(c) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; Chaudhuri, S. R. In *Carbohydrate Based Vaccines*; Roy, R., Ed.; ACS Symposium Series; American Chemical Society: Washington, DC, 2008; Vol. 989, p 199.

(2) See, for example: (a) Teitelbaum, R.; Flatman-Freedman, A.; Chen, B. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 15688. (b) Glatman-Freedman, A.; Casadevall, A. *Clin. Microbiol. Rev.* **1998**, *11*, 514. (c) Glatman-Freedman, A.; Casadevall, A.; Dai, Z.; Jacobs, W. R., Jr.; Li, A.; Morris, S. L.; Navoa, J. D.; Piperdi, S.; Robbins, J. B.; Schneerson, R.; Schwebach, J. R.; Shapiro, M. *J. Clin. Microbiol.* **2004**, *42*, 3225. (d) Riviere, M.; Molsand, A.; Lopez, A.; Puzo, G. *J. Mol. Biol.* **2004**, *344*, 907–915. (e) Costello, C. E.; Besra, G. S.; Porcelli, S. A. *Nature* **2000**, *404*, 884–888.

(3) Alsteens, D.; Verbelen, C.; Dague, E.; Raze, D.; Baulard, A. R.; Dufrene, Y. F. *Eur. J. Physiol.* **2008**, *456*, 117.

(4) Lu, J.; Fraser-Reid, B. *Org. Lett.* **2004**, *6*, 3051. Jun, L.; Fraser-Reid, B. *Chem. Commun.* **2005**, 862.

(5) (a) Mach, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B.; Hazen., K. C. *Tetrahedron* **2002**, *58*, 7345–7354.(b) , Fraser-Reid, B.; Cristobal Lopez, J. Orthoesters and Related Derivatives. In *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, 2008; pp 381−416.

(6) Fletcher, H. G. *Methods Carbohydr. Chem.* **1963**, *2*, 228.

(7) Hatanaka, K. L.; Kazuhara, H. *J. Carbohydr. Chem.* **1985**, 4333.

(8) See, for example: (a) Molina, J.; Malsen, H. L.; Simons, C. *Nucleosides, Nucleotides, Nucleic Acids* **2001**, *20*, 981. (b) Molina, J.; Malsen, H. L. *J. Carbohydr. Res.* **2000**, *19*, 991.

(9) Hirst, E. L.; Percival, E. L. *Methods Carbohydr. Chem.* **1963**, *2*, 349.

(10) (a) Callam, C. S; Lowary, T. L. *J. Chem. Educ.* **2001**, *78*, 73. (b) Liu., C.; Richards, M. R.; Lowary, T. L. *J. Org. Chem.* **2010**, *75*, 4992. (c) Joe, M.; Bai, Y.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 9885.

(11) Wright, R. S.; Khorana, H. G. *J. Am. Chem. Soc.* **1958**, *80*, 1994.

(12) Veeneman, G. H.; Gomes., L. J. F.; van Boom, J. H. *Tetrahedron* **1989**, *45*, 7433.

(13) Fletcher, H. G.; Diehl, H. W. *Carbohydr. Res.* **1967**, *4*, 438.

(14) Fletcher, H. G. *J. Am. Chem. Soc.* **1953**, *75*, 2624.