Pergamon

Tetrahedron Letters 42 (2001) 6615–6618

TETRAHEDRON LETTERS

Synthesis of D-arabinofuranosides using propane-1,3-diyl phosphate as the anomeric leaving group

Yuan Li and Gurdial Singh*

Department of Chemistry, University of Sunderland, Sunderland SR1 3SD, UK

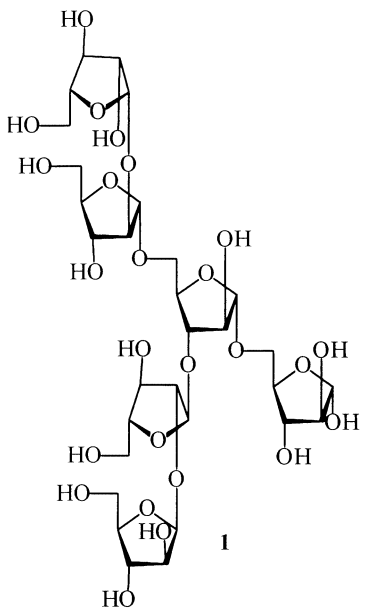
Received 20 June 2001; revised 9 July 2001; accepted 20 July 2001

Abstract—2′,3′,5′-Tri-*O*-benzyl-D-arbinofurano-1-*O*-propane-1,3-diylphosphate was activated with TMSOTf to afford 1-*O*-linked arabinofuranosides with good stereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

The fight against bacterial infections has become severely compromised by the ability of bacterial organisms, in particular, to mutate rapidly and become resistant to the drugs employed. The design of new pharmaceutical agents to deal with various disease states has led to a thriving pharmaceutical industry. The role played by chemists in the development of new agents is seen as being pivotal to the continued success of these endeavours. This role has been further strengthened by the advances made in understanding the mechanisms that pertain in infection processes at the molecular level. In this regard the importance of carbohydrate structures in such events has come to the fore during the last two decades, which has been directly responsible for the re-emergence of interest in their chemistry.

Currently the two diseases most prevalent in both the developing and developed countries are malaria and tuberculosis (TB), with HIV currently following in their footsteps. In the case of TB, there has been no significant decrease in world-wide mortality despite the advent of sanatoria and chemotherapy. It is estimated that about one third of the world population is infected with *Mycobacterium tuberculosis* and that each year there are three million deaths as a result of this infection.[1] The drug resistance of mycobacteria is due to their cell walls having unusually low permeability which makes it difficult to deliver therapeutic agents. Their cell walls contain large amounts of C_{60}–C_{90} fatty acids, mycolic acids, that are covalently linked to arabinogalactan.[2] As a direct consequence of this a great deal of effort has focused on the synthesis of the hexa-saccharide epitope **1**[3] so as to understand the importance of this motif, and has resulted in an examination of the glycosylation reaction of arabinose. Central to the synthesis of the arabinose epitope is the ability of forming disaccharides that are 1,5-α-linked in a stereochemical manner with good efficiency.[4]

We have previously reported that the displacement of diphenylphosphinates derived from tri-*O*-benzyl-D-ribofuranose invariably resulted in poor stereoselectivity in its coupling reaction with a range of glycosyl acceptors.[5] In our recent investigations we have successfully used propane-1,3-diyl phosphates to prepare a wide range of pyranosides with excellent stereochemical control.[6]



1

* Corresponding author. Tel.: +44 191 515 3094; fax: +44 191 515 3148; e-mail: gurdial.singh@sunderland.ac.uk

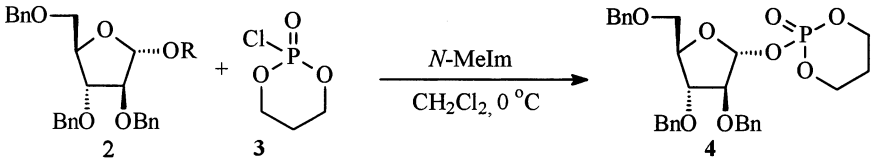
PII: S0040-4039(01)01327-2

In order to extend the scope of this methodology to form glycofuranosides, we investigated the possibility of using propane-1,3-diyl phosphate as the leaving group at the anomeric centre of tri-*O*-benzyl-D-arabinofuranose. Additionally, we believed the use of the propane-1,3-diyl phosphate activating group would allow us to determine the significance of steric interactions in the subsequent transition states, as the anomeric effect in furanoses is equal in the stabilisation of both α- and β-anomers. In this paper we present our findings aimed at establishing this linkage efficiently. Treatment of tri-*O*-benzyl-D-arabinofuranose **2** with propane-1,3-diyl phosphoryl chloride **3** afforded the phosphate **4** in 80% yield after flash column chromatography on silica, as a colourless oil. Unlike the pyranose case, propane-1,3-diyl phosphate **4** proved to be relatively unstable and was used within 14 days of preparation and storage at –23°C.

phosphate **4** had a single resonance at δ_P –8.7 indicating that the reaction had proceeded with excellent stereocontrol.

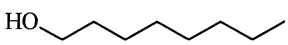
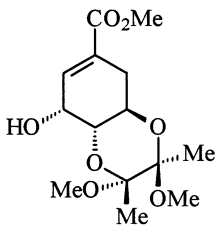
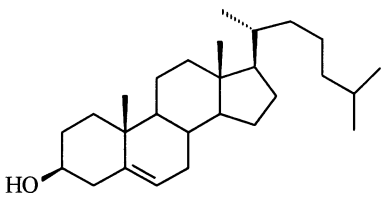
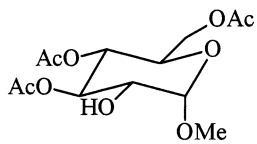
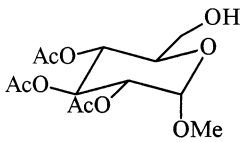
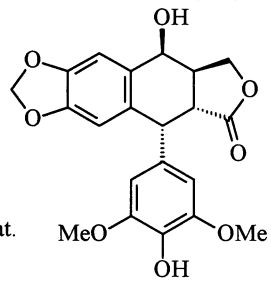
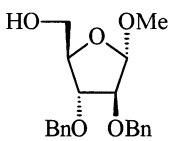
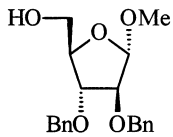
With the availability of the phosphate **4** we proceeded to investigate the displacement of the propane-1,3-diyl phosphate group with a range of acceptors. In the first instance we studied the displacement reaction of phosphate **4** with *n*-octanol as the acceptor, in the presence of a catalytic amount of trimethylsilyl triflate as the activator.

We were gratified to observe that the reaction proceeded in a yield of 67% with the β-isomer being the major product, Table 1; {$[\alpha]_D$ –45.9 (*c* 1.1, $CHCl_3$); lit.[7] $[\alpha]_D$ –49.6 (*c* 1.4, $CHCl_3$)}. Similarly, using isopropanol as the acceptor afforded the corresponding α- and β-furanosides. Support for the assignment of the stereo-



The stereochemistry of phosphate **4** was assigned on the basis of its ^{1}H NMR spectrum, wherein a $J_{H\text{-}P}$ 4.3 Hz was observed for the anomeric proton which had a resonance at δ 5.98. In its ^{31}P NMR spectrum the chemistry at the anomeric centre followed from the ^{1}H NMR of **5α** in that the H-1 signal was found to resonate at δ 5.16 and appeared as a singlet, whilst for **5β** the H-1 resonance occurred at δ 5.02 and appeared

Table 1.

Acceptors[9]	5α : 5β (%yield)	Acceptors[9]	5α : 5β (%yield)
	1 : 4 (67%)		1 : 0 (62%)
	1 : 3 (92%)		
	1 : 4 (87%)		3 : 1 (82%)
	2 : 1 (70%) 1 : 0 (89%) 1eq cat.		4 : 1 (70%)
	6 : 1 (90%) 1eq cat.		1 : 3 (93%)

as a doublet with J 4.1 Hz. Additional support for this assignment was gained from its ^{13}C NMR[8] spectrum, where a resonance at δ_C 104.18 was indicative of an α-linkage at the anomeric centre of the 2,3,5-tri-*O*-benzylarabinofuranose, whilst for the β-linkage[9] this was found at 98.71. Changing the acceptors to more heavily oxygenated substrates including those derived from carbohydrates had an unexpected outcome, in that the stereoselectivity of the coupling reaction changed from being β-selective and became α-selective. For the acceptor 4-*epi*-podophyllotoxin, glycosylation occurred regioselectively at the secondary alcohol. In the case of the methyl shikimate derivative we obtained exclusively the α-isomer. All of the coupling reactions that we investigated proceeded in good yields. In the case where we formed a C-5 arabinofuranoside linkage with a catalytic amount of TMSOTf we obtained the β-isomer as the major product. This stereoselectivity could be changed to provide the α-disaccharide by the use of one equivalent of TMSOTf as the activator. In the latter case the reaction is most likely proceeding via an oxonium ion intermediate,[10] whilst in the reactions with 'simple' alcohols the reaction occurs via a mixed pathway with the S_N2 process dominating.

We have thus demonstrated that tri-*O*-benzyl-L-arabinofuranose can be converted into *O*-linked arbinofuranosides with high stereoselectivity where the anomeric centre bears a propane-1,3-diylphosphate function as the leaving group, which further added to the versatility of the type of activation for the preparation of glycosides.

Acknowledgements

We thank EPSRC for financial support and for access to the high resolution mass spectrometry service at the University of Wales, Swansea (director Professor D. E. Games). We express our thanks to Dr. B. Harrison (Bristol-Myers Squibb, Ireland) for providing the 4-*epi*-podophyllotoxin used in these studies.

References

1. Enarson, D. A.; Murry, J. F. In *Tuberculosis*; Rom, W. M.; Garay, S., Eds.; Little, Brown and Co.: Boston, 1996; pp. 57–75.
2. (a) Brennan, P. J.; Nikaodo, H. *Annu. Rev. Biochem.* **1995**, *64*, 29–63; (b) Besra, G. S.; Brennan, P. J. *Biochem. Soc. Trans.* **1997**, *25*, 845–850.
3. (a) Chatterjee, D.; Khoo, K. H. *Glycobiology* **1998**, *8*, 113–120; (b) Schlesinger, L. S. *Curr. Top. Microbiol.* **1996**, *215*, 71.
4. (a) Ayers, J. D.; Lowary, T. L.; Morehouse, C. B.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 437–442; (b) D'Souza, F. W.; Cheshev, P. E.; Ayers, J. D.; Lowary, T. L. *J. Org. Chem.* **1998**, *63*, 9037–9044; (c) Mereyala, H. B.; Hotha, S.; Gurjar, M. K. *J. Chem. Soc., Chem. Commun.* **1998**, 685–686; (d) D'Souza, F. W.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 1493–1495; (e) Gujar, M. K.; Reddy, L. K.; Hotha, S. *Org. Lett.* **2001**, *3*, 321–323; (f) D'Souza, F. W.; Ayers, J. D.; McCarren, P. R.; Lowary, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 1251–1260.
5. Singh, G.; Tranoy, I. *Carbohydr. Lett.* **1998**, *3*, 79–84.
6. (a) Vankayalapati, H.; Singh, G.; Tranoy, I. *J. Chem. Soc., Chem. Commun.* **1998**, 2129–2130; (b) Vankayalapati, H.; Singh, G. *Tetrahedron Lett.* **1999**, *40*, 3925–3928; (c) Vankayalapati, H.; Singh, G. *Tetrahedron: Asymmetry* **2000**, *11*, 125–138; (d) Vankayalapati, H.; Singh, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2187–2193.
7. Subramanian, V.; Lowary, T. L. *Tetrahedron* **1999**, *55*, 5965–5976.
8. Mizutani, K.; Kasai, R.; Nakamura, M.; Tanaka, O.; Matsuura, H. *Carbohydr. Res.* **1989**, *185*, 27–38; anomeric carbons in β-arabinofuranosides resonate between 100 and 104 ppm whilst those in α-arabinofuranosides resonate between 105 and 110 ppm.
9. All new compounds gave satisfactory spectral, microanalytical and/or high-resolution mass spectral data. The ratios and yields in parentheses refer to isolated yields of compounds after column chromatography. Selected data: **4** $[\alpha]_D$ +19.5 (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 1610; δ_H (270 MHz, $CDCl_3$) 1.49–1.56 (1H, m), 2.12–2.20 (1H, m), 3.57–3.68 (2H, m), 3.96 (1H, dd, *J* 4.8, 1.0 Hz), 4.20–4.42 (5H, m), 4.41–4.68 (7H, m), 5.98 (1H, d, $J_{H\text{-}P}$ 4.3 Hz), 7.21–7.37 (15H, m); δ_C (67.8 MHz, $CDCl_3$) 25.60 ($J_{C\text{-}P}$ 7.3 Hz), 68.52 ($J_{C\text{-}P}$ 7.0 Hz), 68.81 ($J_{C\text{-}P}$ 7.3 Hz), 69.43, 71.77, 71.79, 73.17, 83.14, 84.04, 86.77 ($J_{C\text{-}P}$ 7.5 Hz), 103.14 ($J_{C\text{-}P}$ 5.2 Hz), 127.48, 127.50, 127.64, 127.70, 127.79, 128.16, 128.19, 128.26, 136.84, 137.24, 137.72; δ_P (121.5 MHz, $CDCl_3$) −8.7; *m*/*z* (CI, NH_3). Found: MNH_4^+ 558.2256, $C_{29}H_{37}NO_8P$ requires 558.2257. **5α (Isopropyl)** $[\alpha]_D$ +57.2 (*c* 1.1, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.1 Hz), 1.22 (3H, d, *J* 6.3 Hz), 3.55–3.68 (2H, m), 3.90–4.01 (3H, m), 4.18–4.23 (1H, m), 4.45–4.61 (6H, m), 5.16 (1H, s), 7.21–7.34 (15H, m); δ_C (67.8 MHz, $CDCl_3$) 21.46, 23.59, 68.97, 69.73, 71.90, 72.04, 73.31, 80.09, 83.56, 88.80, 104.18, 127.53, 127.63, 127.72, 127.76, 127.79, 127.88, 128.29 (2C), 128.40, 137.69, 138.00, 138.18; *m*/*z* (CI, NH_3). Found: MNH_4^+ 480.2745, $C_{29}H_{38}NO_5$ requires 480.2750; **5β (Isopropyl)** $[\alpha]_D$ −55.0 (*c* 1.1, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.1 Hz), 1.16 (3H, d, *J* 6.4 Hz), 3.53–3.58 (2H, m), 3.83–3.92 (1H, m), 4.01–4.12 (3H, m), 4.52–4.70 (6H, m), 5.02 (1H, d, *J* 4.1 Hz), 7.20–7.37 (15H, m); δ_C (67.8 MHz, $CDCl_3$) 21.43, 23.38, 69.64, 72.15, 72.20, 72.82, 73.20, 79.86, 83.58, 83.92, 98.71, 127.48, 127.53, 127.61, 127.71, 127.78, 128.03, 128.23, 128.26, 128.32, 137.71, 138.03, 138.24; *m*/*z* (CI, NH_3). Found: MNH_4^+ 480.2754, $C_{29}H_{38}NO_5$ requires 480.2750. **5α (D-Arabinose)** $[\alpha]_D$ + 58.2 (*c* 1.6, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 3.36 (3H, s), 3.54–3.66 (2H, m), 3.70 (1H, dd, *J* 11.6, 3.6 Hz), 3.86–3.94 (2H, m), 3.98–4.07 (3H, m), 4.15–4.23 (2H, m), 4.40–4.60 (10H, m), 4.91 (1H, s), 5.16 (1H, s), 7.18–7.34 (25H, m); δ_C (67.8 MHz, $CDCl_3$) 54.87, 66.08, 69.63, 71.85, 71.90, 72.05, 72.31, 73.33, 80.53, 80.66, 83.22, 83.53, 88.08, 88.38, 106.40, 107.21, 127.54, 127.62, 127.67, 127.73, 127.79, 127.86, 128.17, 128.29, 128.34, 128.36, 137.57, 137.63, 137.93, 138.10; *m*/*z* (CI, NH_3). Found: MNH_4^+ 764.3799, $C_{46}H_{54}NO_9$ requires 764.3799. **5β (D-Arabinose)** $[\alpha]_D$ −9.2 (*c* 1.5, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 3.33 (3H, s), 3.51–3.61 (3H, m), 3.77–3.84 (2H, m), 3.98 (1H, d, *J* 1.8 Hz), 4.04–4.12 (3H, m), 4.22–4.28 (1H, m), 4.42–4.67 (10H, m), 4.92 (1H, s), 5.06 (1H, d, *J*

3.8 Hz), 7.17–7.36 (25H, m); δ_C (67.8 MHz, $CDCl_3$) 54.79, 67.73, 71.79, 71.87, 71.93, 72.04, 72.43, 73.11, 80.36, 81.11, 83.24, 83.49, 84.16, 87.89, 100.91, 107.20, 127.46, 127.58, 127.60, 127.63, 127.66, 127.71, 127.74, 127.77, 127.86, 128.21, 128.25, 128.27, 128.34, 137.41, 137.74, 138.06, 138.12; m/z (CI, NH_3). Found: MNH_4^+ 764.3789, $C_{46}H_{54}NO_9$ requires 764.3799.

10. The pure β-isomer (isopropyl) was treated with a catalytic amount of TMSOTf under the reactions conditions for 20 min, which indicated that no epimerisation was occurring at the anomeric centre. However, treatment with 1 equiv. of TMSOTf resulted in a substantial amount of the α-isomer being formed, further addition, after 20 min of activator (1.5 equiv.) resulted in complete conversion to the α-anomer within 40 min. The pure α-isomer was also subjected to the above reaction conditions and no conversion to the β-anomer was observed. We thank a referee for suggesting this additional experiment.