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A comprehensive glycosylation system for the elaboration of oligoarabinofuranosides

Sylvie Sanchez,[a] Toufiq Bamhaoud[b] and Jacques Prandi[a,*]

[a]*Institut de Pharmacologie et de Biologie Structurale du CNRS, 205 route de Narbonne, F-31077 Toulouse Cedex, France*

[b]*Laboratoire de Chimie Organique et Bioorganique, Université Chouaib Doukkali, BP 20 El Jadida, Morocco*

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Abstract

1,2,5-Orthoesters of D-arabinose are key compounds for the construction of a glycosylation system that allows the stereoselective synthesis of any interglycosidic linkage between arabinofuranosidic units. Application to the synthesis of a pentaarabinofuranoside of the mycobacterial cell wall is also described.

Keywords: glycosylation; arabinofuranoside; mycobacterium.

1. Introduction

Mycobacteria form a class of microorganisms where two major pathogens are found, *Mycobacterium leprae*, the etiologic agent of leprosy and *Mycobacterium tuberculosis*, responsible for human tuberculosis. They make intensive use of D-arabinose for the construction of their cell wall where it is found as homopolymers in the furanoside form with α-(1→5), α-(1→3) and β-(1→2) linkages.[1] As D-arabinose is not used by the human host, the biosynthetic pathway of mycobacterial arabinans is a potential target for the development of new therapeutic agents against tuberculosis and other mycobacterial infections.[2] For this, small synthetic oligoarabinofuranosides are powerful tools for the search and characterization of enzymatic activities and their synthesis has prompted renewed interest in arabinofuranoside chemistry.[3,4] Pursuing our work on the construction of arabinofuranosides,[5,6] we now present our preliminary results on a comprehensive glycosylation system which allows the efficient elaboration of any possible glycosidic linkage between arabinofuranosidic units.

* Corresponding author. Tel: +33 (0)5 61 17 54 85; fax: +33 (0)5 61 17 59 94; e-mail: prandi@ipbs.fr

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2. Preparation of arabinofuranosidic donors and acceptors

In order to shorten the lengthy protection/deprotection sequences usually associated with oligosaccharide synthesis, we looked for a common synthetic intermediate which could be easily transformed into donors and acceptors. As the group on the carbon 2 of the donor controls the stereoselectivity of the glycosylation reaction (see Fig. 1), this position had to be differentiated from the others for the introduction of a participating group (α-donors) or of a *p*-methoxylbenzyl group (β-donors).[7] We also needed fast and regioselective access to partially protected acceptors.

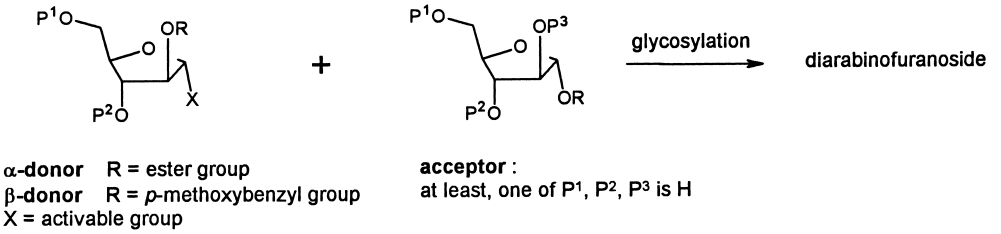


Figure 1. Schematic representation of the formation of a diarabinofuranoside

1,2,5-Benzylidene D-arabinose (**1**),[8] its 3-*O*-benzyl ether **2**[6] and 3-*O*-benzyl-1,2,5-dichloroethylidene D-arabinose (**3**)[9,6] were submitted to acid-catalyzed ring opening with oxy-, thio- and seleno-nucleophiles to obtain the corresponding α-glycosides **4**–**12** in good yields (see Fig. 2).

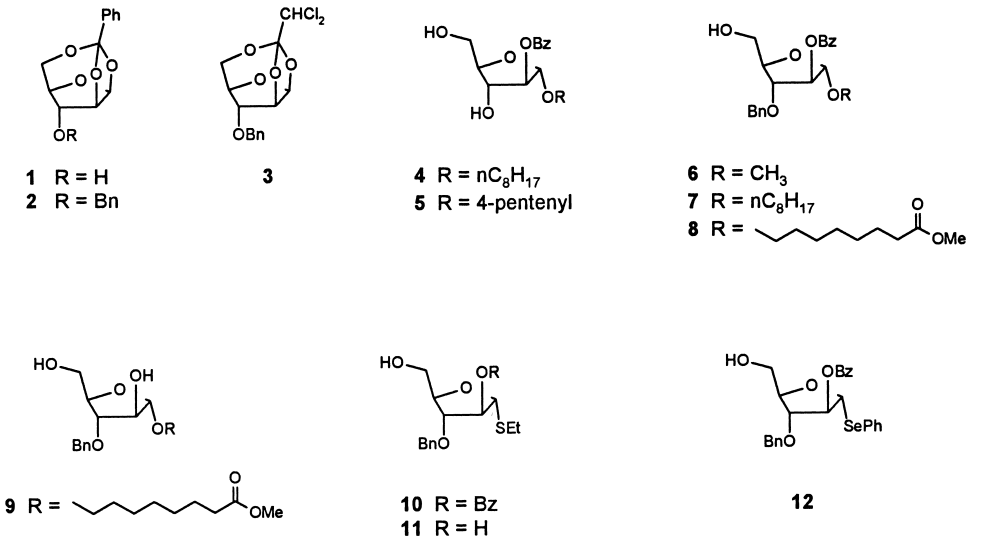


Figure 2. Compounds **1**–**12**

Some representative results are summarized in Table 1.

For ring opening with alcohols, a fivefold excess of reagent had to be used to avoid oligomerization of the orthoester,[10] whereas for the other nucleophiles, only a slight excess (1.1–1.5 equiv.) of reagent was used. No significant influence of the Lewis acid was observed for the ring opening of **2** provided that a strong acid was used (see Table 1). The use of $HgBr_2$ as

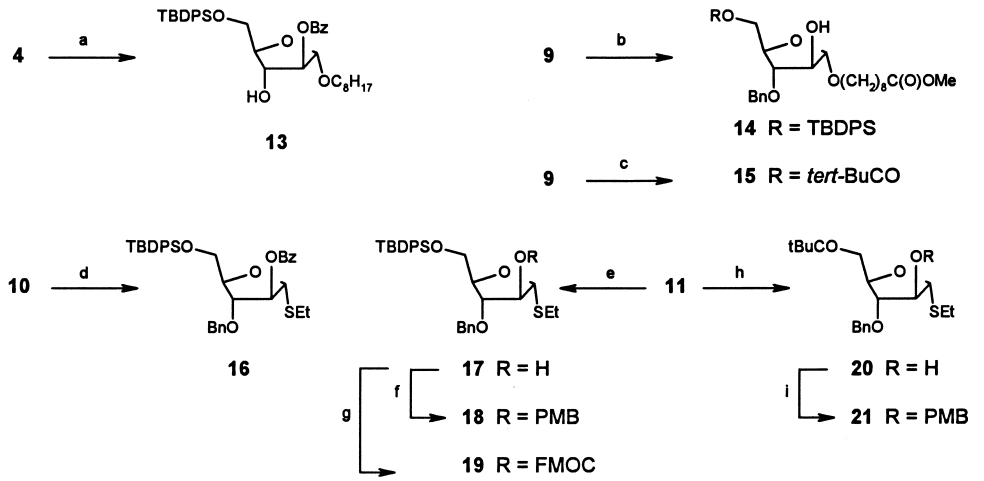
Table 1

Substrate[a]	Nucleophile	Acid (equiv.)	Product[a]	Yield[b] (%)
1	Octanol	$SnCl_4$ (0.1)	**4**	95
1	4-Pentenol	$SnCl_4$ (0.1)	**5**	74
2	Methanol	$SnCl_4$ (0.1)	**6**	96
2	Octanol	BF_3:OEt_2 (0.15)	**7**	89
2	Octanol	TMSOTf (0.1)	**7**	90
2	$HO(CH_2)_8C(O)OMe$	$SnCl_4$ (0.1)	**8**	76
3	$HO(CH_2)_8C(O)OMe$	$SnCl_4$ (2.0)	**9**	60
2	EtSH	$SnCl_4$ (0.1)	**10**	80
3	EtSH	$SnCl_4$ (0.2)	**11**	64
2	PhSeH	$SnCl_4$ (0.1)	**12**	61

[a] See Fig. 1 for structural formulas.
[b] Yields are for isolated, chromatographically homogeneous and analytically pure products.

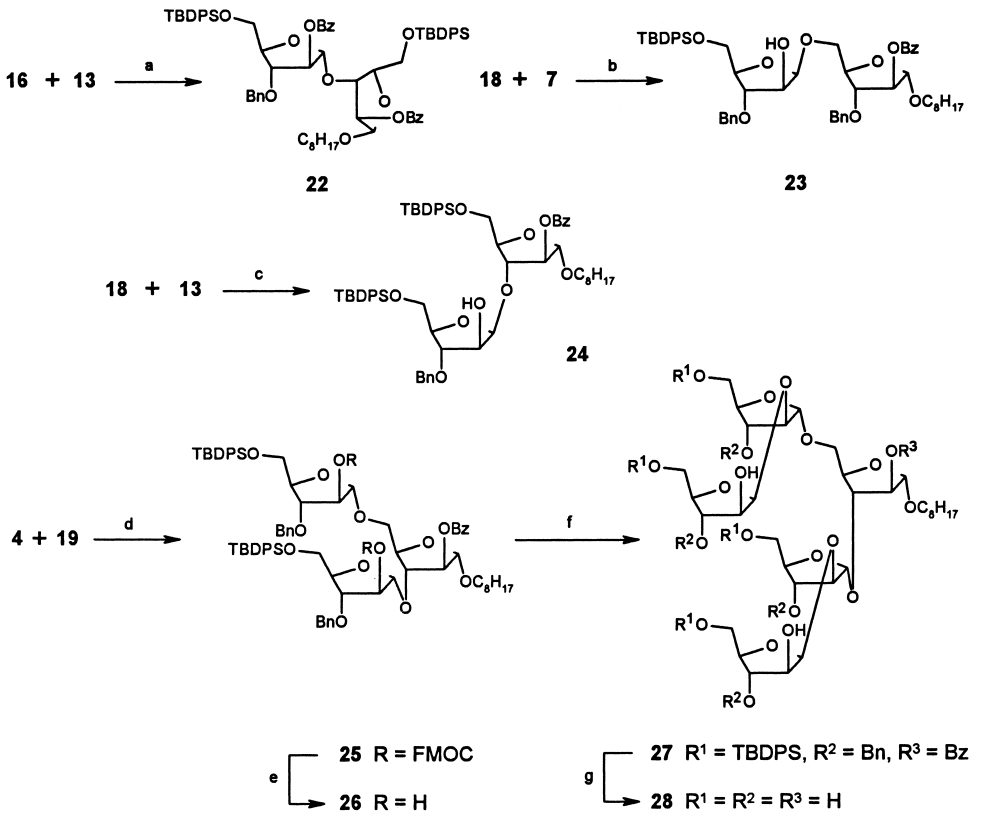
promoter[10] with compound **2** gave sluggish reactions and long reaction times. Opening of the orthoester of the dichloroethylidene derivative **3** was found to be more difficult and gave lower yields than for **1** and **2**, but could be obtained with a higher amount of acid catalyst. The successful opening of **2** with selenophenol gave access to selenoglycoside donors, which are known to be selectively activated in the presence of thioglycosides.[11] 4-Pentenyl glycosides, another type of donor,[12] were also easily made from orthoester **2** and 4-pentenol.

Acceptors **13** and **14** were then obtained from **4** and **9** in 77 and 69% yields, respectively, by selective protection of the primary position of the ring as a *tert*-butyldiphenylsilyl ether (Scheme 1). Monopivaloylation of **9** gave compound **15**[6] in 80% yield.



Scheme 1. a: 1.4 equiv. TBDPSCl, imidazole, DMF, 0°C to rt, 1 h, 77%. b: 1.4 equiv. TBDPSCl, imidazole, DMF, rt, 2 h, 69%. c: 1.5 equiv. *tert*-BuCOCl, 0.1 equiv. DMAP, pyridine, 0°C, 1.5 h, 80%. d: 1.5 equiv. TBDPSCl, imidazole, DMF, rt, 1 h, 93%. e: 1.5 equiv. TBDPSCl, imidazole, DMF, rt, 3 h, 80%. f: 2.5 equiv. *p*-$MeOPhCH_2Br$, 2.5 equiv. BEMP, 0°C to rt, acetonitrile, 2 h, 71%. g: 1.5 equiv. FMOC-Cl, pyridine, CH_2Cl_2, rt, 1 h, 82%. h: 1.3 equiv. *tert*-BuCOCl, DMAP, pyridine, 0°C to rt, 2.5 h, 65%. i: same as f, 67%

Thioglycoside donors were also easily derived from the opening products of **2** and **3** with ethanethiol. Silylation of **10** gave the α-donor **16** in 93% yield. Elaboration of donors from **11** is of particular interest: first, both α- and β-donors could be made in only two steps from **11**, and second, different α-directing groups could be introduced on **17** (or **20**), which gave another level of flexibility for the further elaboration of oligoarabinofuranosides. Monoprotection of the primary position of **11** could be carried out with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in DMF to give **17** in 80% yield or with pivaloyl chloride in pyridine to give **20** in 65% yield. Introduction of the *p*-methoxybenzyl group on **17** and **20** was effected as previously described[5,6] with *p*-methoxybenzyl bromide and 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine[13] (BEMP) in acetonitrile and gave the β-donors **18** and **21** in 71 and 67% yields, respectively. α-Donor **19** was obtained in 82% yield from the reaction of **17** with 9-fluorenylmethyl chloroformate (FMOC-Cl) and pyridine in CH_2Cl_2. It should be emphasized that many of these compounds could be used as donors as well as acceptors depending on the reaction conditions: for example, **5** is an acceptor on the 3 and 5 positions and an α-donor once



Scheme 2. a: 1.0 equiv. **13**, 1.3 equiv. **16**, 1.7 equiv. NIS, 0.1 equiv. TMSOTf, MS 4 Å, CH_2Cl_2, 0°C, 1 h, 94%. b: 1.0 equiv. **18**, 1.05 equiv. **7**, 1.5 equiv. DDQ, MS 4 Å, CH_2Cl_2, rt, 3 h, 53%; 1.2 equiv. IDCP, MS 4 Å, CH_2Cl_2, rt, 1.5 h, then 5% DDQ in CH_3CN/H_2O 9/1, 79%. c: 1.0 equiv. **13**, 1.2 equiv. **18**, 1.5 equiv. DDQ, MS 4 Å, CH_2Cl_2, rt, 3.5 h; 1.3 equiv. IDCP, MS 4 Å, CH_2Cl_2, 0°C to rt, 3 h, then 5% DDQ in CH_3CN/H_2O 9/1, 74% overall. d: 1.0 equiv. **4**, 2.5 equiv. **19**, 3.7 equiv. NIS, 0.25 equiv. TMSOTf, MS 4 Å, CH_2Cl_2, 0°C to rt, 79%. e: Et_3N/THF 1/4, rt, 9 h, 97%. f: 2.5 equiv. **18**, 2.8 equiv. DDQ, MS 4 Å, CH_2Cl_2, 0°C to rt, 75%; 2.7 equiv. IDCP, MS 4 Å, CH_2Cl_2, rt, 22 h, then 1 equiv. DDQ in CH_3CN/H_2O 9/1, 23% (two steps). g: 6 equiv. NBu_4F, THF, rt, 2 h; MeONa, MeOH, rt, 18 h; H_2, Pd/C, MeOH, rt, 2 h; 52% (three steps)

these positions are protected (or glycosylated); thioglycosides **10**, **11**, **17** and **20** are donor precursors, but may be used as acceptors versus selenoglycoside donors derived from **12**.

3. Synthesis of oligoarabinofuranosides

With donors and acceptors in hand, the construction of oligoarabinosides was straightforward. α-Arabinofuranosides were obtained in good yield and complete stereocontrol[14] from the reaction of α-donors **16** or **19** with acceptors. For example, coupling of **16** with alcohol **13** under *N*-iodosuccinimide/trimethylsilyl trifluoromethanesulfonate (NIS/TMSOTf) activation gave α-disaccharide **22** in 94% yield (Scheme 2).

The formation of β-diarabinofuranosides was equally effective from the two-step reaction of β-donor **18** with acceptors.[7] The 1,5-linked β-diarabinofuranoside **23** was obtained from the reaction of **18** with **7**; and **24** was obtained stereochemically pure in 74% yield from the coupling of **18** with **13**. The 1,2-linked β-diarabinofuranoside has already been described from the reaction of **15** with **18**.[6] Finally, the pentaarabinofuranoside **28**, the terminal motif of the mycobacterial arabinogalactan[1] was assembled. Bis α-glycosylation of diol **4** with 2.5 equiv. of donor **19** under NIS/TMSOTf activation gave in one step the trisaccharide **25** in 79% yield. Selective deprotection of the FMOC groups with triethylamine in THF afforded diol **26** (quantitative yield), which was submitted to a bis-β-glycosylation[7] with donor **18** to give the pentaarabinofuranoside **27**. Deprotection gave the desired compound **28** in only six steps from the monosaccharidic building blocks.[15]

In conclusion, we have shown the synthetic potential of 1,2,5-orthoesters of D-arabinose for the preparation of various arabinofuranosidic building blocks which could be used for the elaboration of complex oligoarabinofuranosides. Exploration of this system is currently being actively pursued.

References

1. Chatterjee, D. *Curr. Opin. Chem. Biol.* **1997**, *1*, 579–588. Daffé, M.; Draper, P. *Adv. Microb. Physiol.* **1998**, *39*, 131–203.
2. Lee, R. L.; Mikušová, K.; Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829–11832.
3. Ayers, J. D.; Lowary, T. L.; Morehouse, C. B.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 437–442.
4. Mereyala, H. B.; Hotha, S.; Gurjar, M. K. *Chem. Commun.* **1998**, 685–686.
5. Désiré, J.; Prandi, J. *Carbohydr. Res.* **1999**, *317*, 110–118.
6. Bamhaoud, T.; Sanchez, S.; Prandi, J. *Chem. Commun.* **2000**, 659–660.
7. Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765–1767. Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680–4681.
8. Kochetkov, N. K.; Khorlin, A. Ya.; Bochkov, A. F.; Yazlovetskii, I. G. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1966**, *11*, 2030–2032.
9. Salman, Y. G.; Makinabakan, Ö.; Yüceer, L. *Tetrahedron Lett.* **1994**, *35*, 9233–9236.
10. Kochetkov, N. K.; Bochkov, A. F.; Yazlovetsky, I. G. *Carbohydr. Res.* **1969**, *9*, 49–60.
11. Mehta, S.; Pinto, B. M. *Tetrahedron Lett.* **1991**, *32*, 4435–4438. *J. Org. Chem.* **1993**, *58*, 3269–3276.
12. Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc., Chem. Commun.* **1988**,

823–825. Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 270–272.
13. Sproat, B. S.; Beijer, B.; Iribarren, A. *Nucleic Acids Res.* **1990**, *18*, 41–49.
14. Kawabata, Y.; Kaneko, S.; Kusakabe, I.; Gama, Y. *Carbohydr. Res.* **1995**, *267*, 39–47.
15. While this manuscript was being written, another synthesis of this motif has been reported: D'Souza, F. W.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 1493–1495.