Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1113–1116
Tetrahedron Letters

Hydrolytically stable arabinofuranoside analogs for the synthesis of arabinosyltransferase inhibitors

Manon Chaumontet, Valérie Pons, Karine Marotte and Jacques Prandi*

Institut de Pharmacologie et de Biologie Structurale du CNRS, UMR 5089, 205 route de Narbonne, 31077 Toulouse Cedex 04, France

Received 8 November 2005; revised 6 December 2005; accepted 6 December 2005
Available online 27 December 2005

Abstract—The first members of two new families of arabinosyltransferase inhibitors, derived from previously reported hybrid compounds covalently associating an iminoalditol with an α-D-arabinofuranoside, have been prepared. In place of the arabinofuranoside moiety, they incorporate in their structure a suitably substituted tetrahydrofuran (C-glycoside family) or a cyclopentane (*carba*-sugar family) for mimicking the α-D-arabinofuranoside ring.

1. Introduction

Despite the availability of numerous antibiotics effective against *Mycobacterium tuberculosis*, the causative agent of human tuberculosis, the disease remains a major world-wide health problem, taking millions of lives annually. New therapeutic strategies for fighting the disease are urgently needed because of emergence and slow increase of infections by multi-drug resistant strains of the bacillus. Biosynthesis of the mycobacterial cell wall is a validated target for the development of new therapeutic agents against tuberculosis.[1] It is already the site of action of three major antituberculosis drugs: isoniazid and ethionamide block the mycolic acid synthesis[2,3] while ethambutol interferes with the biosynthesis of arabinogalactan, a major structural element of the cell wall.[4–7] Glycosyltransferases of the mycobacterial cell wall have been identified many years ago as good targets for the development of new antimycobacterial drugs[8] and the field has been active during recent years.[9,10]

We recently described a new family of hybrid molecules, which showed good arabinosyltransferase inhibitory properties[11] and very promising in vitro activity against *M. tuberculosis*.[12] These molecules were built from a 1,4-dideoxy-1,4-anhydro-D-pentitol (five-membered aza-sugar) covalently linked to a small oligo-α-D-arabinofuranoside, acting as an addressor for the iminosugar (see compound **1**, Fig. 1).

A drawback of these compounds is the presence of an acid-sensitive arabinofuranosidic linkage in their structure, which shortens their half-life in biological medium and impairs their potential use as antibiotics.

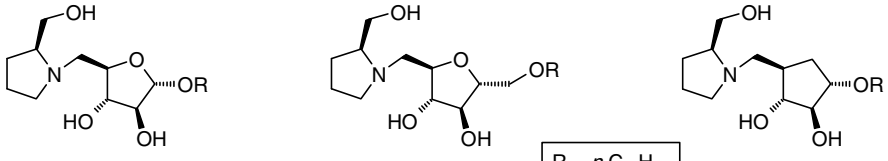
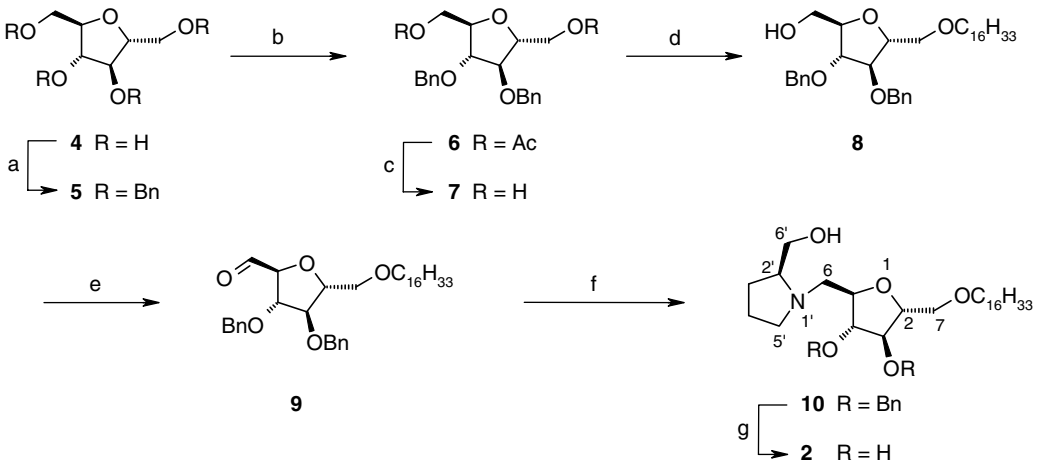


Figure 1. Arabinosyltransferase inhibitor **1** and its analogs: C-glycoside **2** and *carba*-sugar **3**.

Keywords: Inhibitor; Arabinosyltransferase; Mycobacteria; C-Glycoside; *Carba*-sugar.
* Corresponding author. Tel.: +33 (0)5 61 17 54 85; fax: +33 (0)5 61 17 59 94; e-mail: Jacques.Prandi@ipbs.fr

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.029



Scheme 1. Reagents and conditions: (a) 6.5 equiv BnBr, 10.0 equiv NaH, DMF, 4 h, 77%; (b) TFA, Ac_2O, room temp, 1.5 h; (c) MeONa, MeOH, room temp, 4 h, 77%, two steps; (d) 1.0 equiv $C_{16}H_{33}I$, 1.3 equiv NaH, DMF, room temp, 18 h, 42%; (e) $(COCl)_2$, DMSO, NEt_3, −78 °C, 0.5 h; (f) 2.0 equiv prolinol, 6.0 equiv $NaBH_3CN$, MeOH, AcOH, reflux, 1.5 h, 48%, two steps; (g) H_2, Pd/C, 0.5 M HCl in MeOH, room temp, 4 h, 87%.

Replacement of this glycosidic bond with a more stable ether bond should give inhibitors with improved stability and, possibly, greater potency. Depending on which oxygen atom of the glycosidic bond is replaced by a carbon atom, *exo*-cyclic or *endo*-cyclic oxygen, two families of hydrolytically stable compounds are obtained, a tetrahydrofuran family (or C-glycosides) and a cyclopentane family (or *carba*-sugars). The conformational analysis of these arabinofuranoside analogs had been carried out[13,14] and showed them to be of possible potential as arabinofuranoside analogs. There has been recent interest in the synthesis of oligo-*C*-arabinofuranosidic compounds and the first members of this series have been prepared.[15,16]

We now report the preparation of two hydrolytically stable analogs of **1**, a simple but representative example of our previously described arabinosyltransferase inhibitors: C-glycoside **2** and *carba*-arabinofuranoside **3**, where the 1,4-dideoxy-1,4-anhydro-D-pentitol moiety is the commercially available (*S*)-2-pyrrolidinemethanol ((*S*)-prolinol).

2. Synthesis of C-glycoside 2

The most simple C-glycoside of α-D-arabinofuranoside is 2,5-anhydro-D-mannitol **4** (Scheme 1), which is readily available from D-glucosamine by a two-step procedure.[17] So, **4** was benzylated in 73% yield with benzyl bromide and sodium hydride in DMF to afford the tetrabenzyl derivative **5** and the primary benzyl groups of **5** were then selectively acetolyzed with trifluoroacetic acid in acetic anhydride to give diacetate **6**.[18] Crude **6** was taken up in basic methanol (MeONa, MeOH) to remove the ester groups and diol **7** was isolated in 77% yield for the two steps. Despite the report[15] of the successful selective monobenzylation of diol **7** in 84% yield, monoalkylation of **7** with 1-iodohexadecane was found to be difficult to control, mainly because of the very low solubility of 1-iodohexadecane in DMF (or THF) at temperatures below 0 °C. The reaction had to be run at room temperature and alcohol **8** was isolated in only 40% yield, together with the recovered starting material and some dialkylated product. Swern oxidation of the alcohol, immediately followed by reductive amination of aldehyde **9** with (*S*)-prolinol and $NaBH_3CN$ in acidic methanol[19,20] gave the coupling product **10** in 48% yield (two steps). Catalytic hydrogenation of **10** (H_2, Pd/C, MeOH, HCl) afforded the targeted compound **2**[†] in 87% yield, completing the synthesis of the first C-glycoside analog of **1**.

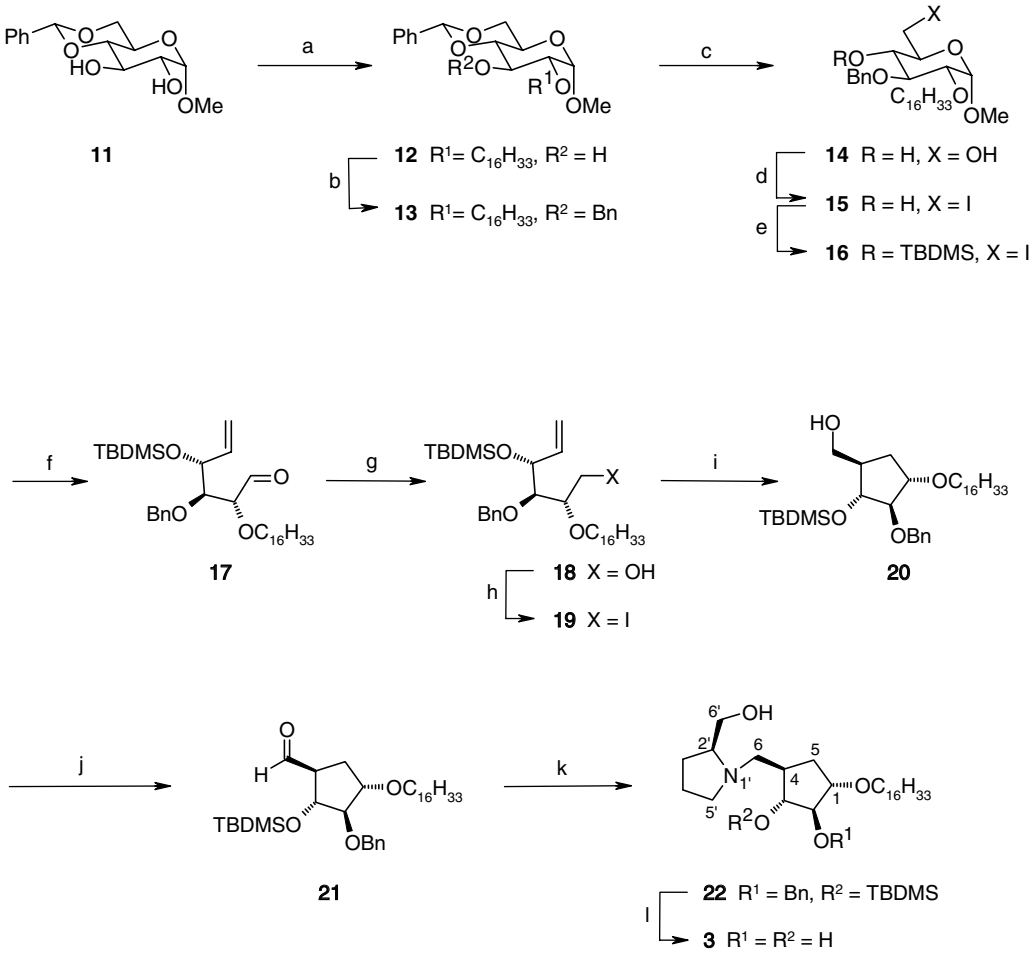
3. Synthesis of cyclopentane 3

The elaboration of the carbocyclic analog of the α-D-arabinofuranoside ring relies on the cobalt-mediated oxygenative radical cyclization of suitably protected polyhydroxylated 6-iodohex-1-enitols-1-hexenitols to cyclopentane methanols.[21,22] As we wanted the configurations of the various substituents of cyclopentane **3** (two hydroxyls, an alkoxy, and the aminomethyl group) to be identical to those in α-D-arabinofuranoside, the hex-1-enitol to be chosen for the radical cyclization had to be derived from any D-glucopyranoside. Alkyl-

[†] Selected data for **2** (see Scheme 1 for numbering). $[\alpha]_D^{20}$ +18.5 (*c* 0.7, methanol). ^{1}H NMR (500 MHz); δ (CD_3OD): 0.93 (t, 3H, $^3J = 7.1$ Hz, CH_3 hexadecyl), 1.24–1.46 (m, 26H, CH_2 hexadecyl), 1.60 (m, 2H, O–CH_2–CH_2 hexadecyl), 1.90 (m, 1H, 3′-H), 2.10 (m, 1H, 4′-H), 2.09 (m, 1H, 4′-H), 2.20 (m, 1H, 3′-H), 3.21–3.35 (m, 2H, 5′-H, 6-H), 3.53 (m, 2H, O–CH_2 hexadecyl), 3.57–3.67 (m, 4H, 7-H, 2′-H, 7-H, 6-H), 3.72 (m, 1H, 5′-H), 3.75 (dd, 1H, $^2J_{6',6'} = 12.2$ Hz, $^3J_{6',5'} = 5.6$ Hz, 6′-H), 2.85 (dd, 1H, $^3J_{4,5} = 5.8$ Hz, $^3J_{4,3} = 5.1$ Hz, 4-H), 3.90 (dd, 1H, $^2J_{6',6'} = 12.2$ Hz, $^3J_{6',5'} = 4.0$; Hz, 6′-H), 3.98–4.05 (m, 2H, 2-H, 3-H), 4.19 (ddd, 1H, $^3J_{5,6} = 9.9$ Hz, $^3J_{5,4} = 5.8$ Hz, $^3J_{5,6} = 2.1$ Hz, 5-H) ppm. ^{13}C NMR (125.8 MHz); δ (CD_3OD): 13.1 (CH_3 hexadecyl), 22.3 (4′-C), 25.6 (3′-C), 55.8 (5′-C), 56.8 (6-C), 59.7 (6′-C), 69.0 (2′-C), 70.8 (7-C), 71.4 (O–CH_2 hexadecyl), 77.2 (2-C), 79.5 (4-C, 5-C), 83.2 (3-C) ppm. HRMS (FAB): $C_{27}H_{53}NO_5$ calcd 472.4002, found 472.4006.

ation of the stannylene acetal of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **11**[23] with 1-iodohexadecane and dibutyltin oxide[24] was very difficult in toluene under tetrabutylammonium bromide activation, only 16% of the 2-O-alkylated product **12** were isolated after 24 h at reflux temperature, together with an equal quantity of the 3-O-alkylated isomer and considerable amounts of recovered **11**. However, it was found that alkylation of the stannylene acetal of **11** could be smoothly obtained at 60 °C in DMF under cesium fluoride activation.[25] The conversion was complete after 14 h and **12** was obtained in 38% yield after chromatography. Once again, no regioselectivity was observed for the alkylation and an equal amount of the 3-O-alkylated isomer of **12** was also isolated from the reaction.

The 3-hydroxyl group of **12** was then protected as a benzyl ether (BnBr, NaH, DMF/THF, 72%) before acidic removal of the 4,6-*O*-benzylidene group (catalytic camphorsulfonic acid in refluxing MeOH) to afford **14** in quantitative yield. Selective iodination of the primary position of **14** was achieved under Garreg's conditions[26] with triphenylphosphine and 1.3 equiv of iodine in refluxing toluene, a 74% yield of **15** was obtained. A *tert*-butyldimethylsilyl ether was finally introduced under classical conditions (TBDMSOTf, pyridine, CH_2Cl_2) on the hydroxyl group of **15** and **16** was isolated in a quantitative yield. The protection of this hydroxyl group by the bulky silyl ether group was chosen to decrease, and possibly abolish the nucleophilicity of this oxygen atom during iodination of hexenitol **18** (to **19**, Scheme 2) and avoid competitive tetrahydrofuran formation during this step. With all protecting groups secured, 6-deoxy-6-iodo-glucopyranoside **16** was reductively opened with zinc powder in refluxing ethanol[27,28] and, after a rapid work-up of the reaction, the sensitive intermediate aldehyde **17** was immediately reduced to hexenitol **18** with methanolic sodium borohydride in fair yield (47% for the two steps). Introduction of the iodine atom, the radical precursor for the radical



Scheme 2. Reagents and conditions: (a) 1.0 equiv Bu_2SnO, toluene, reflux, then 1.0 equiv CsF, 1.4 equiv $C_{16}H_{33}I$, DMF, 60 °C, 14 h; (b) 1.5 equiv BnBr, 2.0 equiv NaH, DMF/THF 4/1 v/v, room temp, 3 h, 72%; (c) 0.04 equiv CSA, MeOH, reflux, 1 h, quant; (d) 1.2 equiv PPh_3, 3.0 equiv imidazole, 1.3 equiv I_2, toluene, reflux, 0.5 h, 74%; (e) 3.0 equiv TBDMSOTf, pyridine, CH_2Cl_2, room temp, 2.5 h, quant.; (f) 10.0 equiv Zn, 10.0 equiv pyridine, EtOH, reflux, 4 h; (g) $NaBH_4$, EtOH, room temp, 0.5 h, 47%, two steps; (h) 1.2 equiv PPh_3, 3.0 equiv imidazole, 1.3 equiv I_2, toluene, reflux, 0.5 h, 89%; (i) 4.0 equiv $NaBH_4$, 3.7 equiv NaOH, 0.08 equiv Co(salen), air, 95% EtOH, 40 °C, 3.5 h, 78%; (j) 3.0 equiv PCC, 5.0 equiv AcONa, 3 Å MS, CH_2Cl_2, room temp, 2 h; (k) 2.0 equiv (*S*)-prolinol, 6.0 equiv $NaBH_3CN$, AcOH, MeOH, reflux, 2 h, 62%, two steps; (l) H_2, $Pd(OH)_2$/C, 0.2 M HCl in MeOH, room temp, overnight, 82%.

cyclization, on the primary position of **18** was readily accomplished, again under Garreg's conditions as above and gave 6-iodo-hex-1-enitol **19** in high yield (89%). Thanks to the silyl ether group on the 3-oxygen atom of **18**, and in contrast with previously reported examples where a more nucleophilic benzyl ether was at this position,[22,29] only very minor amounts (<2%) of cyclized tetrahydrofuran-type material could be isolated from the reaction mixture. Elaboration of the cyclopentanemethanol was then easily carried out using the oxygenative radical cyclization catalyzed by Co(salen) complex. Compound **19** was dissolved in basic 95% ethanol containing $NaBH_4$ and the cobalt catalyst at 40 °C. Air was continuously bubbled through the medium with a small pump and **19** cyclized smoothly to a mixture of cyclopentanemethanols in 2.5 h. Yield was 78% and the observed diastereoselectivity for the formation of the new C-4 asymmetric center of the cyclopentane ring was found to be 5.5/1. This mixture of diastereoisomers could be chromatographically resolved on silica and the absolute configuration of the major isomer, **20**, was established to be 4*R* by comparison of the NMR data of **20** with those of previously reported examples,[22] this configuration was expected from RajanBabu's stereochemical rules for these radical cyclizations.[30] The end of the synthesis was straightforward, oxidation of alcohol **20** was done with pyridinium chlorochromate (PCC, AcONa, CH_2Cl_2) and gave aldehyde **21**, which was immediately engaged in the reductive amination process with (*S*)-prolinol, as described above for the synthesis of **10**. Coupling product **22** was isolated in 62% yield for the two steps from alcohol **20**. Final deprotection was carried out by hydrogenolysis of **22** (H_2, $Pd(OH)_2/C$) in acidic methanol (HCl) at room temperature. This allowed smooth removal of both benzyl and TBDMS ether protecting groups in one step, and afforded a 82% yield of the final compound **3**.[‡]

4. Conclusion

The first members of two new families of potential arabinosyltransferase inhibitors have been prepared. They incorporate two different α-D-arabinofuranoside analogs in their structure, where the acido-labile glycosidic bond had been replaced by an hydrolytically resistant ether bond: a C-glycoside and a *carba*-sugar, respectively. The present synthetic routes are general and allow the preparation of two complete sets of potential new inhibitors with improved biological stability. Furthermore, in the preliminary in vitro testing on cultures of *M. tuberculosis*, C-glycoside **2** showed the same level of microbicidal activity as the original inhibitor **1**, showing the importance of this family of compounds. Results for **3** and other members of these families will be reported in the very near future.

[‡]Selected data for **3** (see Scheme 2 for numbering). $[\alpha]_D^{20}$ +12 (*c* 0.3, methanol). ^{1}H NMR (250 MHz); δ (4/1 $CDCl_3/CD_3OD$): 0.90 (t, 3H, $^3J = 7.1$ Hz, CH_3 hexadecyl), 1.22–1.33 (m, 26H, CH_2 hexadecyl), 1.56 (m, 2H, O–CH_2–CH_2 hexadecyl), 1.73 (ddd, 1H, $^2J_{5,5} = 13.5$ Hz, $^3J_{5,4} = 10.5$ Hz, $^3J_{5,1} = 8.0$ Hz, 5-H), 1.88 (ddd, 1H, $^2J_{5,5} = 13.5$ Hz, $^3J_{5,1} = 8.5$ Hz, $^3J_{5,4} = 3.0$ Hz, 5-H), 1.90–2.23 (m, 4H, 3′-H, 4′-H), 2.37 (m, 1H, 4-H), 3.01–3.13 (m, 2H, 2′H, 6-H), 3.43 (dt, 1H, $^2J = 9.0$ Hz, $^3J = 6.5$ Hz, O–CH_2 hexadecyl), 3.46–3.60 (m, 3H, 5′-H, 6-H, O–CH_2 hexadecyl), 3.66 (m, 1H, 1-H), 3.70 (dd, 1H, $^3J_{3,4} = 9.0$ Hz, $^3J_{3,2} = 7.5$ Hz, 3-H), 3.80–3.89 (m, 3H, 2-H, 5′-H, 6′-H), 3.95 (dd, 1H, $^2J_{6',6'} = 12.0$ Hz, $^3J_{6',2'} = 3.5$ Hz, 6′-H) ppm. ^{13}C NMR (62.9 MHz); δ (4/1 $CDCl_3/CD_3OD$): 13.8 (CH_3 hexadecyl), 22.4, 22.5, 25.9, 26.0, 29.1, 29.3, 29.4, 29.4, 29.5, 29.6, 30.5, 31.3, 31.7, 54.7 (5′C), 59.4 (6′-C), 69.4 (2′-C), 80.5, 81.5, 82.8 (1-C, 2-C, 3-C) ppm.

References and notes

1. Chatterjee, D. *Curr. Opin. Chem. Biol.* **1997**, *1*, 579–588.
2. Takayama, K. *Ann. N.Y. Acad. Sci.* **1974**, *235*, 426–438.
3. Zhang, Y.; Heym, B.; Allen, B.; Young, D.; Cole, S. T. *Nature* **1992**, *358*, 591–593.
4. Takayama, K.; Kilburn, J. O. *Antimicrob. Agents Chemother.* **1989**, *33*, 1493–1499.
5. Mikušová, K.; Slayden, R. A.; Besra, G. S.; Brennan, P. J. *Antimicrob. Agents Chemother.* **1995**, *39*, 2484–2489.
6. Lee, R. E.; Mikušová, K.; Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829–11832.
7. Khoo, K. H.; Douglas, E.; Azadi, P.; Inamine, J. M.; Besra, G. S.; Mikusova, K.; Brennan, P. J.; Chatterjee, D. *J. Biol. Chem.* **1996**, *271*, 28682–28690.
8. Maddry, J. A.; Suling, W. J.; Reynolds, R. C. *Res. Microbiol.* **1996**, *147*, 106–121.
9. Lowary, T. L. *Mini Rev. Med. Chem.* **2003**, *3*, 689–702.
10. Lee, R. E.; Protopopova, M.; Crooks, E.; Slayden, R. A.; Terrot, M.; Barry, C. E., III. *J. Comb. Chem.* **2003**, *5*, 172–187.
11. Marotte, K.; Ayad, T.; Génisson, Y.; Besra, G. S.; Baltas, M.; Prandi, J. *Eur. J. Org. Chem.* **2003**, 2557–2565.
12. Marotte, K.; Prandi, J., unpublished results.
13. O'Leary, D. J.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 6629–6636.
14. Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 8961–8972.
15. Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2002**, *43*, 7557–7559.
16. Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2003**, *44*, 4067–4071.
17. Horton, D.; Philips, K. D. *Carbohydr. Res.* **1973**, *30*, 367–374.
18. Eby, R.; Sondheimer, S. J.; Schuerch, C. *Carbohydr. Res.* **1979**, *73*, 273–276.
19. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
20. Lane, C. F. *Synthesis* **1975**, 135–146.
21. Désiré, J.; Prandi, J. *Tetrahedron Lett.* **1997**, *38*, 6189–6192.
22. Désiré, J.; Prandi, J. *Eur. J. Org. Chem.* **2000**, 3075–3084.
23. Evans, M. E. *Carbohydr. Res.* **1972**, *21*, 473–475.
24. David, S.; Thieffry, A.; Veyrières, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796–1801.
25. Nagashima, N.; Ohno, M. *Chem. Lett.* **1987**, 141–144.
26. Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866–2869.
27. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990–2016.
28. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1984**, *67*, 1328–1347.
29. Martin, O. R.; Yang, F.; Xie, F. *Tetrahedron Lett.* **1995**, *36*, 47–50.
30. Rajanbabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139–145.