Stereoselective Synthesis of β-C-Allyl- and β-C-Propargyl-D-arabinofuranosides

C. V. Ramana,* Sachin B. Narute, Rajesh G. Gonnade, Rahul S. Patil
National Chemical Laboratory, Pune 411 008, India
Fax +91(20)25902629; E-mail: vr.chepuri@ncl.res.in
Received 30 October 2007; revised 25 February 2008

Abstract: The stereoselective synthesis of β-configured C-allyl- and C-propargyl-D-arabinofuranosides (4,7-anhydro-1,2,3-deoxy-D-gluco-oct-1-enitols and -oct-1-ynitols) was addressed by employing allylation/propargylation of a dialdofuranose under aqueous Barbier reaction conditions and acid-catalyzed furan ring transposition of 5-O-mesyl-manno-oct-7-enol- or 5-O-mesyl-manno-oct-7-ynofuranoside derivatives.

Key words: C-glycoside, D-mannose, Barbier reaction, allylation, propargylation, ring transposition

The cell wall components of Mycobacterium tuberculosis and other mycobacterial species are characterized by the presence of arabinogalactan (AG) and lipoarabinomannan (LAM) polysaccharides consisting of D-arabinose and D-galactose in their furanose form. Since its absence in mammalian cells, combined with the fact that the well-known antitubercular drug ethambutanol inhibits arabinofuranosyl transferases (AraT’s),2 the biosynthesis and activation of D-arabinose represent excellent potential sites for drug intervention.3 Arabinofuranosyl transferases are the key enzymes involved in the biosynthesis of cell wall arabinan polysaccharides.4

β-D-Arabinofuranosyl-l-monophosphoryldecaprenol (β-DPA, Figure 1) is an immediate substrate for many of these enzymes and is an attractive target for the development of various long chain alkyl arabinosides as inhibitors of AraT’s.5 C-Glycosides, which entail methylene substitution for the anomeric oxygen, are isosteric mimics of their O-glycoside counterparts, which offer a great deal of stability without substantial conformational amendment.6 Amongst the various approaches, cross metathesis7 employing C-allyl glycosides and [3+2]-azide-alkyne cycloaddition8 with propargyl glycosides were shown to be versatile and simple methods for the construction of glycoconjugates like glycosyl amino acids, glycosyl phosphonates, and glycosyl lipids.

Dealing with a program to develop inhibitors for the arabinofuranosyl transferases, β-C-allyl- and β-C-propargyl D-arabinofuranosides (1 and 2, respectively) have been identified as key precursors. Synthesis of differently protected α- and β-C-allylarabinofuranosides is already documented. In general, C-allylarabinofuranosides were prepared by treatment of a protected arabinofuranoside with allyltrimethylsilane in the presence of a Lewis acid,7h,9 which results either in an inseparable anomeric mixture or exclusively in the β-anomer depending upon the protecting groups employed. The synthesis of either of the C-propargyl arabinofuranosides is not yet documented. Since these derivatives are key intermediates, their stereoselective preparation is an important synthetic task in our program that led us to seek a general route. Herein, we report a stereoselective synthesis of β-C-allyl-D-arabinofuranoside 1 and β-C-propargyl-D-arabinofuranoside 2 from D-mannose.

Figure 1 depicts the general strategy for the construction of C-arabinofuranosides based on the stereoselective alkylation of methyl diazo-D-lyxofuranoside 310 and subsequent acid-mediated ring isomerization.11 Propargylation of 3 under Barbier conditions is known and occurs exclusively from the Re face of the carbonyl group.12 The intended synthesis of 1 and 2 started with the preparation of 3 according to the literature procedure. Thus, periodate cleavage of 413 afforded the aldehyde 3, which was used without purification (Scheme 1). Allylation of 3
under aqueous Barbier conditions using zinc and allyl bromide gave exclusively diastereomer 5 (86%) whose stereochemical assignment was made by analogy. Treatment of 5 with methanesulfonyl chloride in the presence of triethylamine afforded mesylate 6.

After a careful examination of various reaction conditions (acid, temperature, time) we found that the best result for the intended acid-catalyzed ring transposition of 6 was obtained by using 4-toluenesulfonic acid in methanol at reflux temperature, which afforded the furan 7 in 93% yield. Hydrolysis of the dimethyl acetal using 50% aqueous trifluoroacetic acid followed by sodium borohydride reduction gave 1 (72% 2 steps). Compound 1 was converted into the known triacetate 8. The spectral and analytical data of triacetate 8 were in good agreement with reported data.

Similarly, propargylation of 3 under Barbier conditions employing zinc and propargyl bromide, followed by mesylation afforded crystalline 10 (Scheme 2). The structure of 10 was confirmed with the help of single crystal X-ray analysis (Figure 2). Acid-catalyzed ring transposition of 10 followed by hydrolysis and sodium borohydride reduction of resulting dimethyl acetal 11 gave 2 in 54% yield.

To conclude, a general and stereoselective approach for the synthesis of b-configured C-allyl and C-propargyl D-arabinofuranosides was developed from easily available D-mannose through simple synthetic operations and with acid-catalyzed furan ring transposition as the key step. Experiments are in progress towards the synthesis of b-DPA analogues employing olefin cross metathesis with allyl glycoside 1 and azide-alkyne cycloadditions with 2.
with a soln of 4 (2 g, 8.54 mmol) in CH2Cl2 (20 mL) and stirring was continued at r.t. for an additional 1 h. The mixture was filtered through silica gel, which was washed with 10% MeOH–CH2Cl2. The combined filtrate was concentrated under reduced pressure to yield aldehyde 3 (1.7 g), which was used immediately without purification.

To a suspension of activated Zn dust (710 mg, 11 mmol) in THF (30 mL) was added a soln of allyl bromide (1.330 g, 11 mmol) in THF (12 mL). The mixture was allowed to stir at r.t. for 1 h. A soln of aldehyde 3 (1.7 g, 8.4 mmol) in THF (20 mL) was added dropwise. When the addition was complete, the mixture was allowed to stir at r.t. for 12 h, quenched with sat. NH4Cl (15 mL), and allowed to stir at r.t. for 1 h. The mixture was partitioned between EtOAc and H2O. The organic layers were washed with brine, dried (Na2SO4), and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane, 1:4) to afford 5 (1.765 g, 86%) as a colorless oil.

\[ \delta_{1} = 465.9 \text{ (c 1 CHCl3).} \]

1H NMR (200 MHz, CDCl3): \( \delta = 1.32 \text{ (s, 3 H, CH3), 1.47 \text{ (s, 3 H, CH3), 2.32 (ddt, } J = 1.1, 7.6, 14.3 \text{ Hz, 1 H, H6}), 2.38 \text{ (dddt, } J = 1.3, 4.2, 6.7, 14.3 \text{ Hz, 1 H, H6}), 2.76 \text{ (s, 3 H, OCH3), 3.78 (dd, } J = 3.7, 7.7 \text{ Hz, 1 H, H4}), 3.98 \text{ (dt, } J = 4.1, 7.8 \text{ Hz, 1 H, H5}), 4.56 \text{ (d, } J = 5.9 \text{ Hz, 1 H, H2}), 4.82 \text{ (dd, } J = 3.7, 5.9 \text{ Hz, 1 H, H3}), 4.91 \text{ (s, 1 H, H1)}, 5.12–5.33 \text{ (m, 2 H, CH=CH2)), 5.92 (ddddd, } J = 6.8, 7.7, 10.2, 17.2 \text{ Hz, 1 H, CH=CH2).} \]

13C NMR (50 MHz, CDCl3): \( \delta = 46.9 \text{ (t), 39.2 \text{ (d), 30.0 \text{ (s), 3 H, OCH3), 53.0 \text{ (s, 3 H, OCH3), 77.6 \text{ (d) 81.3 (d), 85.7 (d), 105.1 (d), 117.0 (t), 134.5 (d).} \}

MS (ESI): \( m/z = 241.4 \) (calcd for [M + Na]+ 241.1).


4,7-Anhydro-1,2,3-trideoxy-\( \beta \)-D-glucitol-1-enitol (1)

The dimethyl acetal 7 (300 mg, 1.38 mmol) was dissolved in ice-cold 50% aq TFA (2 mL) and stirred at r.t. for 4 h; TFA was removed under reduced pressure. The crude product was taken up in THF (5 mL) and was slowly added to a stirred soln of NaBH4 (700 mg, 18.5 mmol) in anhyd MeOH (25 mL) at 0 °C. When the addition was complete the mixture was stirred at 0 °C for 1 h monitored by TLC (10% MeOH–CHCl3). The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (MeOH–CHCl3, 1:9) to afford 1 (174 mg, 72%) as a colorless gum.

\[ \delta_{1} = 27.2 \text{ (c 1 MeOH).} \]

1H NMR (200 MHz, acetone-d6): \( \delta = 2.35–2.42 \text{ (m, 2 H, CH=CH2)}, 3.00 \text{ (br s, 1 H, OH)}, 3.68 \text{ (br s, 2 H, 2 OH), 3.76–3.80 \text{ (m, 2 H, H8)}, 3.95 \text{ (dt, } J = 2.9, 7.0 \text{ Hz, 1 H, H4}), 4.10 \text{ (br s, 1 H, H5)}, 4.32–4.45 \text{ (m, 2 H, H6, H7), 4.97–5.16 \text{ (m, 2 H, CH=CH2)}, 5.93 (dddt, } J = 7.0, 10.3, 17.2 \text{ Hz, 1 H, CH=CH2).} \]

13C NMR (125 MHz, acetone-d6): \( \delta = 34.0 \text{ (t), 63.2 (t), 78.2 (d), 80.2 (d), 82.0 (d), 87.3 (d) 116.5 (t), 136.6 (d).} \)

MS (ESI): \( m/z = 197.4 \) (calcd for [M + Na]+ 197.2).


5,6,8-Tri-O-acetyl-4,7-anhydro-\( \beta \)-D-glucal-1-enitol (8)

To a cooled (ice bath), stirred soln of I (200 mg 1.15 mmol) in pyridine (0.74 mL, 9.2 mmol) was added Ac2O (0.54 mL, 5.7 mmol) When the addition was complete, the mixture was allowed to stir at r.t. for 2 h. The mixture was partitioned between H2O and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat. NaHCO3, H2O, and brine, dried (Na2SO4), and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane, 1:1) to afford 8 (294 mg, 85%) as a colorless oil.

\[ \delta_{1} = 21.4 \text{ (c 1 CHCl3).} \]

1H NMR (200 MHz, CDCl3): \( \delta = 2.03 \text{ (s, 3 H, CO2CH3), 2.05 \text{ (s, 3 H, CO2CH3)}, 2.28 \text{ (dt, } J = 6.8, 14.0 \text{ Hz, 1 H, CH2(CH2)2CH2}), 2.37 \text{ (dt, } J = 7.0, 14.0 \text{ Hz, 1 H, CH2(CH2)2CH2)} \text{, 3.92 (ddd, } J = 3.4, 5.0, 6.5 \text{ Hz, 1 H, H7}), 4.03 \text{ (dt, } J = 3.6, 7.0 \text{ Hz, 1 H, H4), 4.10 \text{ (dd, } J = 6.5, 11.5 \text{ Hz, 1 H, H8}), 4.30 (dd, } J = 5.0, 11.5 \text{ Hz, 1 H, H8), 4.88 \text{ (br d, } J = 3.4 \text{ Hz, 1 H, H6), 5.00–5.07 \text{ (m, 2 H, CH=CH2), 5.15 (br d, } J = 3.6 \text{ Hz, 1 H, H5), 5.7 (dddt, } J = 7.0, 10.3, 17.2 \text{ Hz, 1 H, CH=CH2).} \]

Synthesis 2008, No. 11, 1783–1787 © Thieme Stuttgart · New York
**2.5-Anhydro-6,7,8-trideoxy-4-gulo-occt-7-ynose Dimethyl Acetal (11)**

To a soln of 10 (500 mg, 1.56 mmol) in anhyd MeOH (20 mL) at r.t. was added PTSA (50 mg) and the mixture was refuxed for 2 d. The mixture was neutralized by addition of solid NaHCO₃ and filtered through Celite. The Celite pad was washed repeatedly with MeOH and the combined filtrate was concentrated under reduced pressure.

The crude product was purified by column chromatography (EtOAc–hexane, 1:1) to afford 11 (220 mg, 65%) as a yellow oil.

**Methyl 6,7,8-trideoxy-2,3-O-isopropylidene-a-D-manno-occt-7-ynofuranoside (9)**

To a suspension of activated Zn dust (0.58 g, 8.8 mmol) in THF (20 mL) was added a soln of propargyl bromide (1.05 g, 8.8 mmol) in THF (5 mL). The mixture was allowed to stir for r.t. for 1 h. A soln of 3 (1.7 g, 8.8 mmol) in THF (10 mL) was added dropwise. When the addition was complete, the mixture was allowed to stir at r.t. for 12 h, quenched with sat. NH₄Cl (24 mL), and allowed to stir at r.t. for 1 h. The mixture was partitioned between EtOAc and H₂O. The organic layer was washed with H₂O and brine, dried (Na₂SO₄), and concentrated under reduced pressure.

The crude product was purified by column chromatography (EtOAc–hexane, 1:1 to afford 9 (1.59 g, 78%) as a colorless gum.

**Methyl 6,7,8-trideoxy-2,3-O-isopropylidene-5-O-(methyl-sulfonyl)-a-D-manno-occt-7-ynofuranoside (10)**

At 0 °C, a soln of 9 (1.2 g, 4.9 mmol) and Et₃N (1.58 mL, 11.3 mmol) in anhyd CH₂Cl₂ (15 mL) was treated with MsCl (0.52 g, 6.7 mmol) and the mixture was stirred at r.t. for 1 h. When the reaction was complete (TLC, 20% acetone–PE), the mixture was partitioned between CHCl₃ and H₂O. The organic layer was washed with aq NaHCO₃ soln and brine, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane, 1:4) to afford 10 (1.47 g, 92%) as a colorless oil. The crystals suitable for single crystal X-ray structural analysis were grown by slow evaporation of a soln of 10 (EtOAc–hexane; mp 93–94 °C).

**4,7-Anhydro-1,2,3-trideoxy-b-D-gluco-occt-1-ynitol (2)**

A soln of 11 (200 mg, 0.92 mmol) in 50% aq TFA (1 mL) was stirred at r.t. for 4 h. When the reaction was complete (TLC, 10% MeOH–CHCl₃), the mixture was concentrated under reduced pressure. To the resulting crude product in THF (5 mL) was added slowly to a stirred soln of NaBH₄ (500 mg, 13.2 mmol) in anhyd MeOH (25 mL) at 0 °C. When the addition was complete the mixture was stirred at 0 °C for 1 h. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (MeOH–CHCl₃, 1:9) to afford 2 (86 mg, 54%) as a colorless oil.

**Methyl 6,7,8-trideoxy-2,3-O-isopropylidene-5-O-(methyl-sulfonyl)-a-D-manno-occt-7-ynofuranoside (10)**

[α]D₀ 25 +48.2 (c 1, MeOH).

**1H NMR (400 MHz, aceton-d₆): δ = 2.34 (t, J = 2.7 Hz, 1 H, CH), 2.44 (dd, J = 2.7, 6.5, 16.5 Hz, 1 H, CH₂), 2.97 (br s, 2 H, 2 OH), 3.66 (dd, J = 3.3, 11.5 Hz, 1 H, H8), 3.70 (dd, J = 3.5, 11.5 Hz, 1 H, H8), 3.85 (dt, J = 1.9, 3.3 Hz, 1 H, H7), 3.87 (br d, J = 2.1 Hz, 1 H, H6), 4.11 (dd, J = 3.0, 6.5, 7.5 Hz, 1 H, H4), 4.09–4.14 (m, 1 H, H5), 4.48 (br s, 1 H, OH).

**13C NMR (100 MHz, aceton-d₆): δ = 19.0 (t), 63.1 (t), 70.4 (d), 77.7 (d), 79.9 (d), 81.1 (d), 82.3 (s), 87.8 (d).**


**5,6,8-Tri-O-acetyl-4,7-anhydro-1,2,3-trideoxy-b-D-gluco-occt-1-ynitol (12)**

To a cooled (0 °C), stirred soln of triol 2 (40 mg, 0.23 mmol) in pyridine (0.15 mL, 1.9 mmol) was added Ac₂O (0.11 mL, 1.2 mmol). When the addition was complete, the mixture was allowed to stir at r.t. for 2 h. The mixture was partitioned between H₂O and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat. NaHCO₃, H₂O, and brine, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane, 1:1) to afford 12 (54 mg, 78%) as a colorless oil.
Hz. 1 H, H4), 4.35 (dd, J = 4.8, 11.6 Hz, 1 H, H8), 4.95 (dd, J = 1.1, 3.3 Hz, 1 H, H6), 5.31 (dd, J = 1.1, 3.8 Hz, 1 H, H5).

13C NMR (100 MHz, CDCl3): δ = 18.9 (t), 20.6 (q), 20.7 (q), 20.8 (q), 63.6 (t), 70.2 (d), 76.4 (d), 78.4 (d), 78.7 (d), 79.1 (s), 81.8 (d), 169.5 (s), 169.6 (s), 170.7 (s).


Acknowledgment

R.S.P. thanks CSIR (New Delhi) for financial assistance in the form of a research fellowship.

References


(16) The crystallographic data of compound 10 has been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 676163. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)36033; e-mail: deposit@ccdc.cam.ac.uk].