Pergamon

Tetrahedron Letters 41 (2000) 7801–7803

TETRAHEDRON LETTERS

Studies directed toward the synthesis of carba-D-arabinofuranose

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Received 14 June 2000; revised 3 August 2000; accepted 7 August 2000

Abstract

The key cyclopentene analog of carba-D-arabinofuranose was prepared in five steps from 2,3,5-tri-*O*-benzyl-D-arabinofuranose.

Keywords: cyclopentenes; metathesis; cyclization; cyclitols.

Infection by mycobacteria, such as *Mycobacterium tuberculosis*, causes tuberculosis.[1] The protective mycobacterial cell wall is composed of polysaccharide, proteins and lipids.[2] The major polysaccharide components are terminated with arabinofuranosyl hexasaccharide, which is fundamental to the structural integrity of the cell wall.[3] Recently, the biosynthesis of the arabinofuranosyl moiety has been studied and it was suggested that targeting one or more of the arabinose biosynthetic enzymes may result in a new drug for tuberculosis.[4] Inhibitors of these enzymes are an attractive approach since D-arabinofuranosyl residues are not found in mammalian glycoconjugates. During cell wall synthesis, D-arabinofuranosyl residues are enzymatically activated and transferred to the polysaccharide chain, therefore it was hypothesized that a pseudo sugar carba analog of D-arabinofuranose might provide stability to the activated form and consequently inhibit the transfer process. These pseudo sugars have enhanced metabolic and acid stability relative to the parent carbohydrate and have shown promising reaction profiles as antiviral agents[5] as well as glycosyl transferase substrates.[6] There have been several synthetic approaches to provide the pseudo sugar carba-D-arabinofuranose **1**,**2** (Scheme 1).[7] As part of our program directed towards the synthesis of carbocyclic analogs of carbohydrates,[8] we report herein an efficient formal synthesis of carba-D-arabinofuranose.

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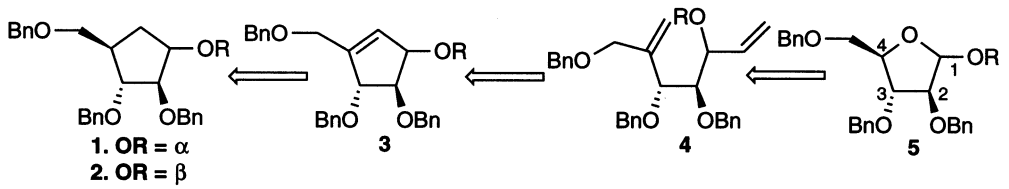
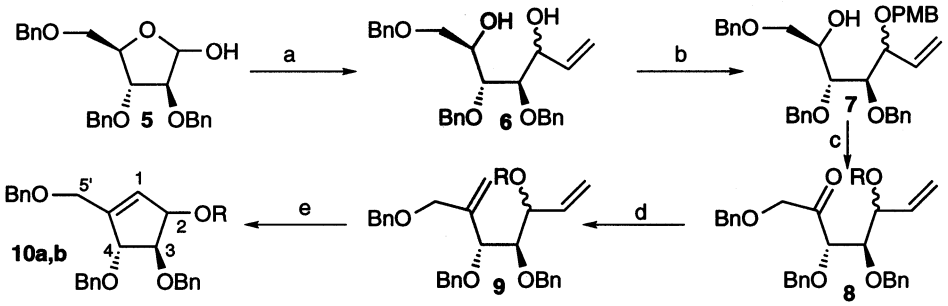
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01355-1



Scheme 1.

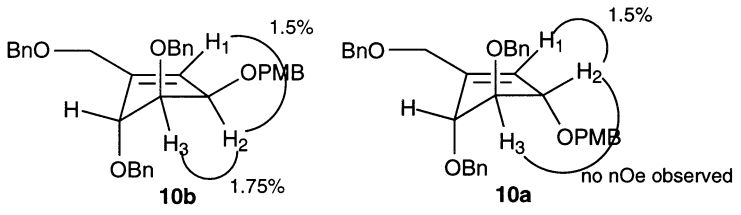
Logical retrosynthetic analysis suggests that carba-D-arabinofuranoside could be obtained via a hydrogenation on a cyclopentene intermediate **3**. The cyclopentene could be obtained from a ring closing metathesis (RCM)[9] of a suitable diene precursor **4** which is assembled from a carbohydrate source. The starting material of choice would be tri-*O*-benzyl-D-arabinofuranose **5**, since it possesses the key stereocenters at the C-2 and C-3 positions (Scheme 1).[10]

2,3,5-Tri-*O*-benzyl-D-arabinofuranose **5** was treated with vinylmagnesium bromide to afford an inseparable mixture of diastereomers **6**. The allylic center of the diol **6** was then selectively protected using *p*-methoxybenzyl chloride at 0°C. Compound **7** was then oxidized under Swern conditions to furnish **8** which was then converted via a Wittig reaction to the key diene intermediate **9**. Previously, we utilized Schrock's catalyst for the RCM of diene systems.[8] Using these conditions, the diene **9** was refluxed with Schrock's catalyst at 85°C for 10 h. Upon quenching the reaction, a mixture of cyclopentenes was obtained. This separable mixture was then subjected to flash column chromatography to afford the diastereomers **10b** and **10a** (62:38) in 95% yield (Scheme 2).



Scheme 2. (a) Vinylmagnesium bromide, THF, 87%; (b) *p*-methoxybenzyl chloride, NaH, DMF, 0°C, 83%; (c) $(COCl)_2$, DMSO, Et_3N, 77%; (d) methyltriphenylphosphonium bromide, *n*-BuLi, 89%; (e) Schrock's catalyst (0.4 equiv.), 95%

As shown below, nOe studies of compound **10b** and **10a** resulted in similar percentile around H_1/H_2. Interestingly, an nOe of 1.75% was observed between H_2/H_3 of compound **10b** whilst no nOe was observed for the same protons of **10a**. Therefore, we can confirm that the isomer **10b** is β while the other isomer **10a** is α.[11]



In summary, we have described a formal synthesis of carba-D-arabinofuranose, since compound **10b** was converted to β-carba-D-arabinofuranose via diastereoselective hydrogenation.[7a] Consequently it is expected that **10a** can be converted to the corresponding α isomer. Of note, our strategy provided an additional flexibility due to the selective protection of the pseudo anomeric group as the PMB ether allowing for easy removal, inversion or derivatization as required. The carba-arabinofuranose precursors **10b** and **10a** were prepared in five steps (47% overall yield) using RCM.

Acknowledgements

The authors would like to thank the Patterson Foundation for their support.

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10. This compound is available from Pfanstiehl Laboraties, Inc.
11. (a) Spectral data for **10a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.80 (s, 3H), 4.13 (ABq, $J=13.4$ Hz, $\Delta\delta=0.05$ ppm, 2H), 4.22 (t, $J=4.0$ Hz, 1H), 4.44 (m, 1H), 4.47 (m, 1H), 4.51 (ABq, $J=11.8$ Hz, $\Delta\delta=0.07$ ppm, 2H), 4.52 (ABq, $J=11.6$ Hz, $\Delta\delta=0.05$ ppm, 2H), 4.62 (ABq, $J=11.8$ Hz, $\Delta\delta=0.05$ ppm, 2H), 4.63 (ABq, $J=11.6$ Hz, $\Delta\delta=0.05$ ppm, 2H), 5.90 (s, 1H), 6.88 (d, $J=8.7$ Hz, 2H), 7.30 (m, 17H). ^{13}C NMR (C_6D_6, 67.5 MHz) δ 54.5, 66.8, 70.6, 71.7, 71.8, 72.5, 85.4, 85.8, 92.2, 113.8, 126–129 (several signals), 130.9, 138.8, 138.9, 139.0, 143.5, 159.5. MS (ES) m/z ($M+NH_4^+$), 554 (base peak), 391, 279. (b) Spectral data for **10b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.89 (s, 3H), 3.99 (t, $J=5.1$ Hz, 1H), 4.14 (ABq, $J=14.0$ Hz, $\Delta\delta=0.05$ ppm, 2H), 4.50 (m, 1H), 4.52 (ABq, $J=1.9$ Hz, $\Delta\delta=0.02$ ppm, 2H), 4.54 (ABq, $J=11.5$ Hz, $\Delta\delta=0.06$ ppm, 2H), 4.61 (ABq, $J=11.3$ Hz, $\Delta\delta=0.23$ ppm, 2H), 4.68 (ABq, $J=11.8$ Hz, $\Delta\delta=0.12$ ppm, 2H), 4.78 (d, $J=4.6$ Hz, 1H), 5.98 (s, 1H), 6.85 (d, $J=8.1$ Hz, 2H), 7.30 (m, 17H). ^{13}C NMR (C_6D_6, 67.5 MHz) δ 54.5, 66.9, 70.1, 71.6, 72.4, 72.6, 77.0, 85.8, 86.0, 113.8, 125.7, 126–128 (several signals), 129.4, 131.3, 138.7, 139.0, 139.2, 147.2, 159.4. MS (ES) m/z ($M+NH_4^+$), 554 (base peak), 391, 279.

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