Pergamon

Tetrahedron Letters 40 (1999) 9375–9378

TETRAHEDRON LETTERS

New entry to pyrrolidine homoazasugars: conversion of D-arabinose into 2,5-anhydro-2,5-imino-D-glucitol via aminohomologation

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Received 27 September 1999; accepted 19 October 1999

Abstract

The title homoazasugar, also referred as (2*R*,5*S*)-bis(hydroxymethyl)-(3*R*,4*R*)-dihydroxypyrrolidine, has been synthesized by addition of 2-lithiothiazole to the 2,3,5-tri-*O*-benzyl-D-arabinofuranose-derived nitrone–hydroxylamine mixture followed by reductive *N*-dehydroxylation and conversion of the thiazole ring into the hydroxymethyl group.

Keywords: homoazasugars; sugar nitrones; 2-lithiothiazole.

Recent work from our research group illustrated the high yielding and stereoselective addition reaction of C-2 metalated thiazoles to *N*-benzyl nitrones of chiral aldehydes.[1] The reduction of the resulting hydroxylamine adducts to amines and the facile transformation of the thiazole ring into the formyl group afforded one-carbon higher α-amino aldehyde homologues as the final products (aminohomologation). The synthetic utility of this method was demonstrated by the conversion of polyalkoxy aldehydes derived from aldoses into various natural amino- and imino-sugars (D-mannosamine, lincosamine, destomic acid, D-nojirimycin)[1] as well as carbon-linked glycosyl amino acids.[2] We would like to report here a convenient variant of the above aminohomologation procedure that employs C-1 unprotected aldofuranoses as starting material and allows a new pyrrolidine homoazasugar synthesis.[3] The method is illustrated below by the synthesis of 2,5-anhydro-2,5-imino-D-glucitol **2** from 2,3,5-tri-*O*-benzyl-D-arabinofuranose **1**. Earlier syntheses of this compound include chemical[4] and enzymatic[5] methods and it has been shown to be an effective inhibitor of α- and β-glucosidases. The search for good inhibitors of oligosaccharide processing enzymes has promoted intense research over the last 10 years in the synthesis of azasugars of both pyrrolidine and piperidine families.[6] These compounds have various therapeutic potential as antiviral, antimethastatic, antibacterial, antiadhesive, and antihyperglycemic agents.

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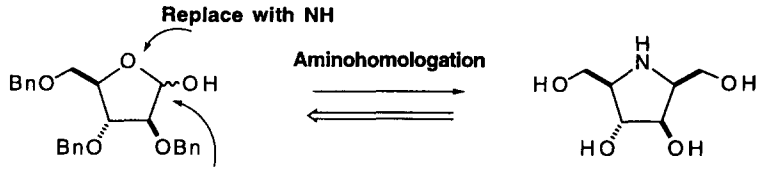
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01987-5

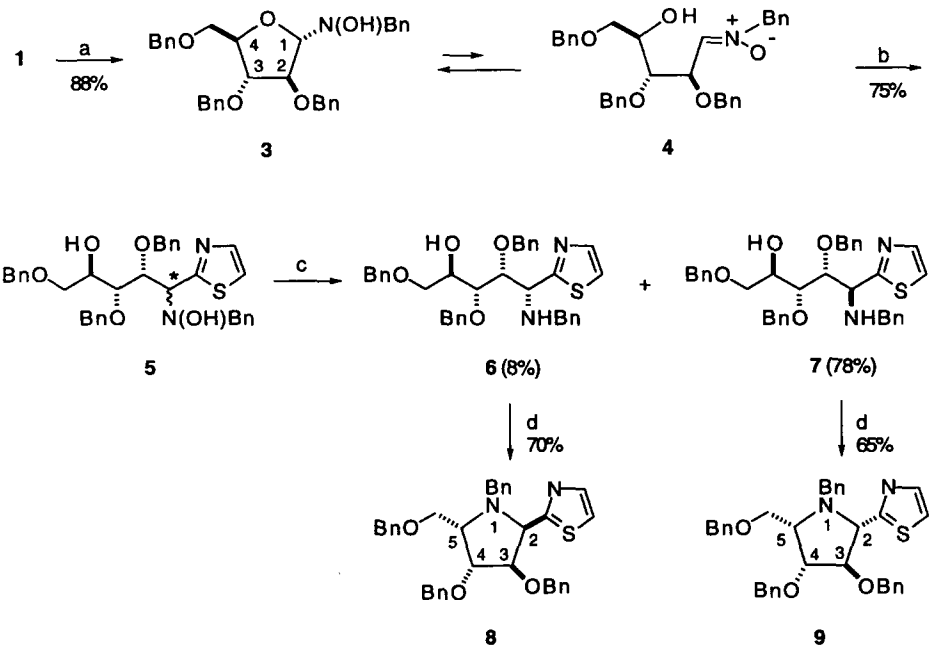


1 2

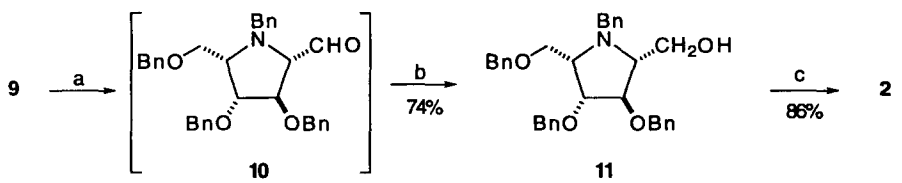
Formally, compound **2** can be considered to be derived from **1** by replacement of the furanose ring oxygen by the amino group and substitution of the anomeric hydroxyl by the hydroxymethyl group (one-carbon elongation). These transformations have been efficiently carried out by the aminohomologation process with high levels of stereochemical control at C-1 (sugar numbering). Stirring a mixture of the protected D-arabinose[7] **1** with *N*-benzylhydroxylamine and anhydrous $MgSO_4$ afforded, after 48 h, the arabinosylhydroxylamine **3** as a single anomer (mp 68–70°C) in fairly good yield (88%) (Scheme 1). The stereochemistry at the anomeric center was assigned on the basis of a strong NOE between H-1 and H-3 and the absence of NOE between H-1 and H-4. Treatment of **3** with 2-lithiothiazole (5.5 equiv.) generated in situ as described,[1] at −78°C and then allowing the reaction mixture to warm up to −70°C for 6 h, provided the open-chain thiazolylhydroxylamine **5** as a mixture of diastereomers (9:1 ratio by NMR analysis) in 75% combined yield. Due to the difficult separation of the diastereomers, the above mixture was subjected to reductive dehydroxylation using a Zn–Cu couple as we have described in related work.[8] The resulting amines **6** (8%) and **7** (78%) were individually isolated by flash chromatography (cyclohexane:EtOAc, 3:2). The configuration at the carbon atom bearing the amino group in these compounds was established following their transformation into pyrrolidines. To this aim, the free hydroxyl group of **6** and **7** was converted to the trifluoromethanesulfonyl group and the product heated in pyridine to give the *N*-benzylpyrrolidines **8** (70%) and **9** (65%), respectively, in satisfactory isolated yields.[9] The *cis*-relationship between the thiazole ring and the CH_2OBn group in **9** was assigned on the basis of strong NOE of H-2 with H-4 and H-5 while these effects were not observed in the *trans*-isomer **8**. Consequently, on the basis of the reasonable assumption that the ring closure occurred via an S_N2-like mechanism involving displacement of the OSO_2CF_3 group with inversion, the stereochemistry of the aminoalcohols **6** and **7** was assigned as shown. It thus appears that the major isomer (90%) in the mixture of hydroxylamines **5** is the *anti* adduct. Although no appreciable quantity of the open-chain nitrone **4** in equilibrium with **3** could be determined by NMR spectroscopy, it is conceivable that the addition of 2-lithiothiazole occurs to the alkoxyiminium ion equivalent **4** existing in a preferential conformation by lithium coordination to the nitrone oxygen and the free hydroxy group. However, it is worth pointing out that *syn* selectivity has been reported for the Grignard addition to amines derived from the same protected D-arabinose derivative **1**.[10]

The completion of the aminohomologation process required the unmasking of the formyl group from the thiazole ring as the final step. Only the pyrrolidine **9** arising from the main stereochemical course of the amination step was considered for this conclusive operation (Scheme 2). The submission of this compound to the usual thiazole-to-formyl conversion protocol[11] afforded the 2-formylpyrrolidine **10**, a rather unstable product that was reduced in situ to the alcohol **11**. Finally, the removal of the *O*- and *N*-benzyl groups by hydrogenation and purification over Dowex (OH^-) afforded the target homoazasugar **2** ((2*R*,5*S*)-bis(hydroxymethyl)-(3*R*,4*R*)-dihydroxypyrrolidine) showing identical characteristics (mp 138–140°C, lit.[4] mp 139–142.5°C; $[\alpha]_D$=+25.1 (*c* 1.5, H_2O), lit.[5] $[\alpha]_D$=+25.75 (*c* 4, H_2O)) with those of the literature.

In conclusion, a new chemical synthesis of homoazasugars of the pyrrolidine family has been traced by the synthesis of the imino-D-glucitol **2** from D-arabinose via a stereoselective amination and chain



Scheme 1. *Reagents and conditions*: (a) BnNHOH, $MgSO_4$, CH_2Cl_2, rt, 48 h; (b) 2-lithiothiazole, Et_2O, −78°C, 6 h; (c) $(AcO)_2Cu$, Zn, AcOH, H_2O, 70°C, 1 h; (d) Tf_2O, pyridine, 40°C, 30 min



Scheme 2. *Reagents and conditions*: (a) TfOMe, MeCN, rt; then $NaBH_4$, MeOH, rt; then $HgCl_2$, MeCN–H_2O, rt; (b) $NaBH_4$, rt; (c) 20% $Pd(OH)_2$/C, H_2, AcOH, 1 atm, rt, 18 h; then Dowex (OH^-)

elongation process. The reaction sequence can be applied to the synthesis of various stereoisomers starting from other aldofuranoses and/or suitable synthetic elaborations of intermediates. For instance, the preparation of the natural product 2,5-anhydro-2,5-imino-D-mannitol,[5,12] the 5-epimer of **2**, can be envisaged starting from either L-xylose or by inversion of the configuration at C-4 of the aminoalcohol **7**. Moreover, other organometalics, such as 2-lithiofuran (a carboxylate group equivalent), various Grignard reagents, and metalated acetylenes have been found to react readily and stereoselectively with **4**. Therefore, this methodology can be extended to the synthesis of various pyrrolidine azasugars having suitable side chains for further synthetic elaborations. This research program is underway in our laboratory.

Acknowledgements

Financial support from CNR (Rome) is gratefully acknowledged. We also thank Miss Gloria Borin for help with the synthetic work and Mr. Paolo Formaglio for assistance with NMR analysis.

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9. All new compounds gave satisfactory analytical and spectroscopical data. Some data are reported for selected compounds: **3**: $[\alpha]_D$ +29.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 3.59 (dd, 1H, J_{4-5}=5.2, $J_{5,5'}$=11.0 Hz, H-5), 3.70 (dd, 1H, $J_{4-5'}$=3.2 Hz, H-5′), 3.95 and 4.22 (2 d, 2H, *J*=13.0 Hz, PhCH_2N), 4.13 (dd, 1H, J_{2-3}=5.2, J_{3-4}=7.1 Hz, H-3), 4.33 (ddd, 1H, H-4), 4.48 (dd, 1H, J_{1-2}=4.5 Hz, H-2), 4.51–4.73 (m, 6H, 3 PhCH_2O), 4.78 (d, 1H, H-1), 7.20–7.50 (m, 20H). **7**: $[\alpha]_D$ +20.9 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 3.59 and 3.75 (2 d, 2H, *J*=13.0 Hz, PhCH_2N), 3.58–3.67 (m, 2H, H-5 and H-5′), 3.81 (dd, 1H, J_{2-3}=3.5, J_{3-4}=7.5 Hz, H-3), 3.93–4.01 (m, 1H, H-4), 4.04 (d, 1H, J_{1-2}=6.5 Hz, H-2), 4.28 and 4.52 (2 d, 2H, *J*=11.5 Hz, PhCH_2O), 4.45 and 4.63 (2 d, 2H, *J*=11.0 Hz, PhCH_2O), 4.46–4.52 (m, 3H, H-1 and PhCH_2O), 7.10–7.40 (m, 21H), 7.82 (d, 1H, *J*=3.2 Hz). **9**: $[\alpha]_D$ +28.7 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 3.53–3.61 (m, 2H, H-5 and H-6), 3.81 (dd, 1H, $J_{5-6'}$=8.9, $J_{6-6'}$=11.0 Hz, H-6′), 3.96 and 4.03 (2 d, 2H, *J*=13.0 Hz, PhCH_2N), 4.08 (dd, 1H, J_{3-4}=2.5, J_{4-5}=5.0 Hz, H-4), 4.25 (t, 1H, J_{2-3}=2.5 Hz, H-3), 4.35 and 4.40 (2 d, 2H, *J*=12.0 Hz, PhCH_2O), 4.42 (d, 1H, H-2), 4.45 (s, 2H, PhCH_2O), 4.53 and 4.67 (d, 2H, *J*=12.0 Hz, PhCH_2O), 7.00–7.10 (m, 2H), 7.17 (d, 1H, *J*=3.2 Hz), 7.20–7.40 (m, 18H), 7.67 (d, 1H, *J*=3.2 Hz).
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