Pergamon

Tetrahedron Letters 41 (2000) 6195–6199

TETRAHEDRON LETTERS

Convergent synthesis of pyrrolidine-based (1→6)- and (1→5)-aza-*C*-disaccharides

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Received 12 May 2000; accepted 14 June 2000

Abstract

A new entry to (1→6)- and (1→5)-aza-*C*-disaccharides featuring the pyrrolidine ring as the imino sugar component is described via Wittig condensation of polyhydroxylated 2-formylpyrrolidines with galacto-pyranose 6-phosphorane and ribofuranose 5-phosphorane, respectively.

Keywords: glycomimetics; azasugars; glycosidase inhibitors; Wittig reactions.

The application of the Wittig reaction[1] in synthetic routes to complex molecules is greatly favoured by the ready preparation of the relevant reagents, the aldehyde and phosphorous ylide. Accordingly, the access to various formyl *C*-glycosides by a scalable preparative method developed in our laboratory,[2] prompted us to employ these sugar aldehydes in a new synthetic approach to (1→6)-linked *C*-disaccharides via Wittig-type coupling to sugar phosphoranes.[3] Work is now underway to obtain higher oligomers by iterative repetition of this coupling reaction.[4] A similar Wittig-based synthesis of *C*-disaccharides containing an azasugar component (aza-*C*-disaccharides) is reported here. This work follows our recent extension to furanoses[5] of the thiazole-based aminohomologation protocol of aldehydes through their nitrones.[6] Specifically, D-arabinose was transformed[5] into the polyhydroxylated 2-formylpyrrolidine **1**, a formyl aza-*C*-glycoside (Scheme 1). In contrast to our previous observation,[7] the aldehyde **1** turned out to be a stable compound when generated from the corresponding thiazole precursor by some improvements of the unmasking protocol. Also the isomer **2** which was obtained from D-ribose by the same aminohomologation protocol proved to be a sufficiently stable and manipulatable product. Hence, with the aldehydes **1** and **2** in hand, we have foreseen their Wittig-type coupling with sugar phosphoranes as an entry to (1→6)- and (1→5)-aza-*C*-disaccharides featuring the polyhydroxylated pyrrolidine ring as the azasugar component. While azasugars are

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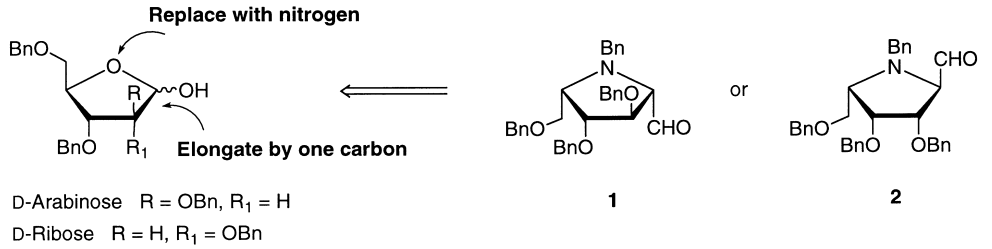
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01005-4

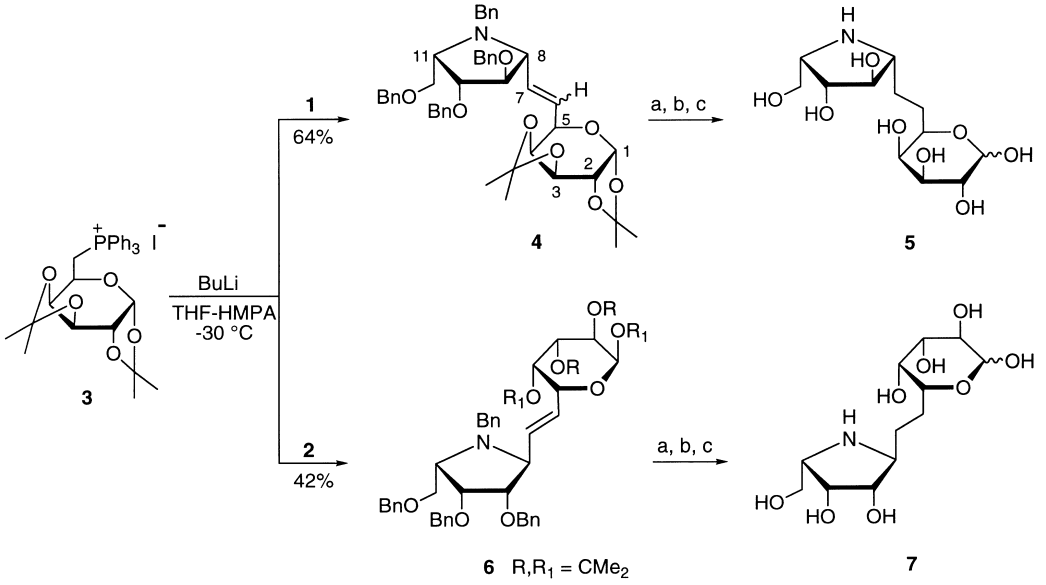
well-known inhibitors of oligosaccharide processing enzymes,[8] there is current interest in the synthesis of aza-*C*-glycoconjugates since these compounds are expected to be more potent than the parent azasugars.[9] Moreover, the configurational stability at the anomeric carbon of the azasugar moiety should provide increased selectivity toward a specific glycosidase.[10] Hence aza-*C*-disaccharides with different (1→*x*)-linkages have been prepared[11] although very few are genuine isosteres of *O*-disaccharides. Surprisingly, methods based on Wittig-type coupling have not been reported.



Scheme 1. *Aminohomologation*: (a) BnNHOH; (b) 2-lithiothiazole; (c) Zn, $Cu(OAc)_2$; (d) Tf_2O; (e) TfOMe, then $NaBH_4$, then $AgNO_3/H_2O$

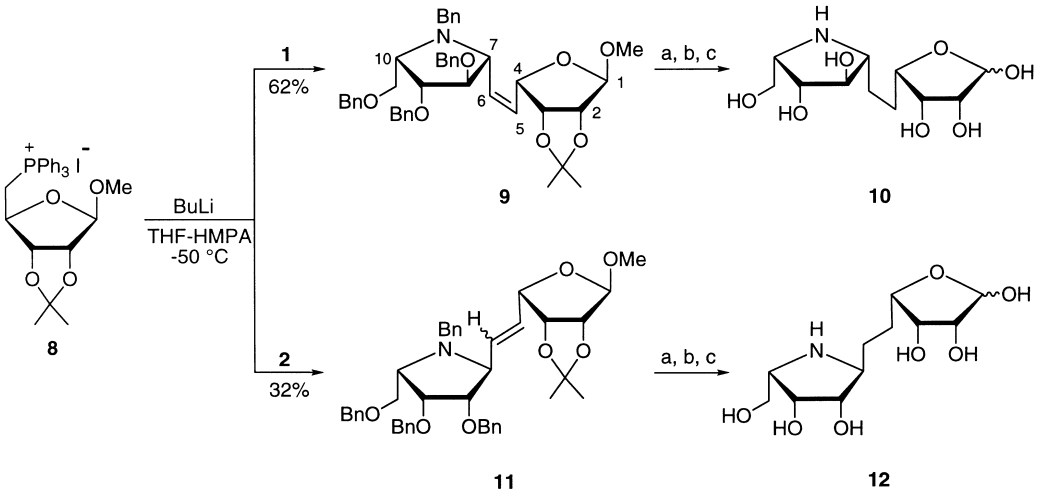
The polyhydroxylated 2-formylpyrrolidines **1** and **2** were prepared in 10 mmol scale from D-arabinose and D-ribose, respectively, by some improvements of the aminohomologation protocol.[12] While **1** was purified and stored at low temperature for some days without appreciable decomposition, the isomer **2** was used as crude material within 1–2 hours after preparation. The Wittig reaction of aldehydes **1** and **2** with 1.2 equiv. of the ylide generated in situ from the D-galactopyranose phosphonium iodide[13] **3** occurred smoothly at –30°C in 2:1 THF:HMPA (Scheme 2) to give, after 2 hours, the corresponding olefins[14] **4** and **6** in 64 and 42% isolated yield, respectively[15] (flash column chromatography, 5:1 cyclohexane:AcOEt). Although it was scarcely relevant in the context of the present project, we noticed that the alkene **4** was formed as a mixture of *E*- and *Z*-isomers in ca. 1:1 ratio by NMR analysis while **6** was present exclusively as *E*-isomer ($J_{6,7}=15.6$ Hz). The ^{1}H NMR data also confirmed the stereochemistry of the α-D-galactopyranose moiety.[16] This finding is in line with earlier observations[3,4] showing the conservation of the configuration at C-5 in the galactose 6-phosphorane generated from **3**. Based on our previous work on *C*-disaccharide synthesis,[3] the subsequent elaboration of the coupling products **4** and **6** was almost routine. The reduction of the double bond was carried out at first by in situ-generated diimide from *p*-toluenesulfonhydrazide (PTSH). Then the resulting alkane was subjected to the catalytic hydrogenation over $Pd(OH)_2$ for debenzylation and to treatment with Amberlite IR 120 for deacetonization. The (1→6) aza-*C*-disaccharides **5** and **7** were released from the resin with aqueous HCl and purified as hydrochlorides by column chromatography on Sephadex LH20 (9:1 MeOH:H_2O).[14] Both compounds gave consistent MALDI-TOF mass spectra. However, it is worth noting that some condensation products were also isolated (MS analysis), very likely arising from intermolecular glycosidation reactions.

The above reaction sequences were followed in the synthesis of the (1→5)-linked aza-*C*-disaccharides **10** and **12** using the ribofuranosyl phosphonium iodide **8** as starting material[17] (Scheme 3). The Wittig coupling of the aldehydes **1** and crude **2** with the in situ generated ribose 5-phosphorane derived from **8** afforded the corresponding alkenes **9** (62%, *Z*-isomer, $J_{5,6}=11.2$ Hz) and **11** (32%, 5:1 *E*:*Z* mixture).[14,15] The relatively low yield of **11** could not be improved by



Scheme 2. Reagents and conditions: (a) $TsNHNH_2$, AcONa, DME–H_2O, 85°C, 5 h; (b) H_2, $Pd(OH)_2$, 8 bar, AcOH, rt, 12 h; (c) Amberlite IR 120, H_2O, 70°C, 2 h

the use of purified aldehyde **2** and some changes of the reaction conditions, while a substantial decomposition of **2** was observed in all cases. The transformations of **9** and **11** to the hydroxy free final products **10** and **12** were carried out using the above three-step procedure involving the diimide reduction of the double bond, the debenzylation by hydrogenolysis, and the deacetonization by acid hydrolysis, followed by purification of the hydrochlorides by Sephadex LH20.[14] Also these compounds were characterized through their MALDI-TOF mass spectra. Special care was taken for the assignment of the structures of these compounds since the original D-*ribo* configuration of the phosphonium salt **8** was reported as not retained in Wittig reactions.[17,18] Accordingly, the $J_{3,4}$



Scheme 3. Reagents and conditions as in Scheme 2

of 3.6 Hz in **9** and **11** confirmed the presence of an α-L-*lyxo* furanose ring.[19] As already suggested,[17] a rapid epimerization of the furanose ring of the ylide should take place through an open-chain intermediate. On the other hand, the NMR analysis confirmed that the configuration at the anomeric carbon of the azasugar moiety in both products **9** and **11** was identical to that of the aldehyde precursors **1** and **2**.

A Wittig-based route to aza-*C*-disaccharides containing a polyhydroxylated pyrrolidine ring linked to a pyranose or furanose residue by an ethylene bridge has been described. The scope of this approach should be extensible for the preparation of other compounds featuring a variety of structural diversities in both carbohydrate moieties. Other formyl aza-*C*-glycosides as intermediates in the synthesis of other pyrrolidine homoazasugar are available in our laboratory via the aminohomologation route of furanoses.[20]

Acknowledgements

Financial support from MURST COFIN-98 (Italy) is gratefully acknowledged. We thank Mr. Paolo Formaglio for assistance in the NMR analysis.

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12. The quantitative conversion of the furanose into the *N*-benzylhydroxylamine–nitrone equilibrium mixture was carried out by heating the sugar and *N*-benzylhydroxylamine in the absence of solvent at 110°C for 30 min. No dehydrating agents were required under these conditions. The one pot thiazole-to-formyl group conversion was carried out using $AgNO_3$ instead of $HgCl_2$ in the final step. The aldehydes **1** and **2** were purified by filtration through a short column of silica gel with 8:1 cyclohexane:AcOEt. However, while **1** was stable to this treatment, compound **2** decomposed to a large extent. Compound **1**: ^{1}H NMR ($CDCl_3$) 9.27 (d, 1H, $J_{1,2}=1.2$ Hz, H-1), 7.40–7.19 (m, 20H, 4 Ph), 4.58 and 4.50 (2 d, 2H, $J=11.4$ Hz, PhCH_2O), 4.56 (s, 2H, PhCH_2O), 4.46 and 4.34 (2 d, 2H, $J=11.5$ Hz, PhCH_2O), 4.26 and 3.70 (2 d, 2H, $J=13.1$ Hz, PhCH_2N), 4.09 (dd, 1H, $J_{2,3}=J_{3,4}=1.2$ Hz, H-3), 4.07 (dd, 1H, $J_{4,5}=4.5$ Hz, H-4), 3.90 (dd, 1H, $J_{5,6a}=7.7$, $J_{6a,6b}=9.1$ Hz, H-6a), 3.74 (dd, 1H, $J_{5,6b}=5.1$ Hz, H-6b), 3.56 (ddd, 1H, H-5), 3.34 (dd, 1 H, H-2). Compound **2**: ^{1}H NMR ($CDCl_3$) 9.03 (d, 1H, $J_{1,2}=3.3$ Hz, H-1),

7.42–7.19 (m, 20H, 4 Ph), 4.66 and 4.60 (2 d, 2H, $J=12.5$ Hz, PhCH_2O), 4.60 and 4.54 (2 d, 2H, $J=11.3$ Hz, PhCH_2O), 4.53 (s, 2H, PhCH_2O), 4.33 and 3.75 (2 d, 2H, $J=13.2$ Hz, PhCH_2N), 4.01 (dd, 1H, $J_{3,4}=5.2$, $J_{4,5}=6.6$ Hz, H-4), 3.97–3.90 (m, 2 H, 2 H-6), 3.89 (dd, 1H, $J_{2,3}=2.2$ Hz, H-3), 3.79 (ddd, 1H, $J_{5,6a}=3.0$, $J_{5,6b}=6.4$ Hz, H-5), 3.52 (dd, 1H, H-2).

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14. Compound **4**: ^{1}H NMR ($CDCl_3$), *Z*-isomer: 5.78 (dd, 1H, $J=10.1$, 11.1 Hz), 5.65 (dd, 1H, $J=8.8$, 11.1 Hz). *E*-isomer: 5.94 (dd, 1H, $J=5.9$, 15.8 Hz), 5.80 (dd, 1H, $J=8.5$, 15.8 Hz). Compound **5·HCl**: $[\alpha]_D^{20}=+35.6$ (*c* 0.3, H_2O). Compound **6**: $[\alpha]_D^{20}=-42.0$ (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 5.76 (dd, 1H, $J_{5,6}=6.5$, $J_{6,7}=15.6$ Hz, H-6), 5.60 (dd, 1H, $J_{7,8}=8.8$ Hz, H-7 Hz). Compound **7·HCl**: $[\alpha]_D^{20}=+3.2$ (*c* 0.4, H_2O). Compound **9**: $[\alpha]_D^{20}=-20.8$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (C_6D_6) 6.12 (ddd, 1H, $J_{4,5}=8.7$, $J_{5,6}=11.2$, $J_{5,7}=0.9$ Hz, H-5), 5.84 (ddd, 1H, $J_{4,6}=1.0$, $J_{6,7}=9.3$ Hz, H-6). Compound **10·HCl**: $[\alpha]_D^{20}=+5.5$ (*c* 0.3, H_2O). Compound **11**: ^{1}H NMR ($CDCl_3$); *Z*-isomer: 5.82 (dd, 1H, $J_{4,5}=8.8$, $J_{5,6}=11.0$ Hz, H-5), 5.62 (dd, 1H, $J_{6,7}=10.5$ Hz, H-6); *E*-isomer: 5.87 (dd, 1H, $J=7.3$, 15.7 Hz), 5.66 (dd, 1H, $J=8.4$, 15.7 Hz). Compound **12·HCl**: $[\alpha]_D^{20}=-11.5$ (*c* 0.2, H_2O).
15. The yields of **6** and **11** were calculated with respect to the thiazole precursor since the aldehyde **2** was used as crude material.
16. This was essentially based on the almost identical values of all coupling constants, particularly that between H-4 and H-5 in the phosphonium salt **3** ($J_{4,5}=2.0$ Hz) and in the disaccharides ($J_{4,5}=1.8$ Hz).
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20. A full report is under preparation dealing with the synthesis of various pyrrolidine homoazasugars by the thiazole-based aminohomologation route of different furanoses.