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Synthesis of a branched chain aza-*C*-disaccharide via the cycloaddition of a chiral nitrone to an alkene, both sugar derivatives

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Abstract—A multistep synthesis of a protected aza-*C*-disaccharide derivative with a pyrrolidine ring as the azasugar component is described. The key step is a stereoselective cycloaddition reaction of a chiral nitrone derived from D-ribose and a sugar alkene derived from D-galactose. An intramolecular *N*-alkylation followed by a reductive cleavage of the isoxazolidine N–O bond, in one pot, gave the final product.

Aza-*C*-disaccharides are a relatively new class of sugar mimics in which an azasugar unit (polyhydroxylated pyrrolidines or piperidines) is linked to a second monosaccharide unit by a methylene group. It is expected that these sugar mimics may improve the effectiveness and selectivity of the well known inhibition properties of aza sugars.[1,2] This assumption is based mainly on the fact that incorporation of a nonhydrolyzable monosaccharide unit into the azasugar may provide all the steric information of the glycosidic moiety including that of the aglycon, thus combining the features of both azasugars and *C*-glycosides.

Several synthetic approaches towards this class of compounds have been reported. Johnson and co-workers obtained various $(1\rightarrow6)$, $(1\rightarrow4)$ and $(1\rightarrow1)$ linked compounds, using alkyl boron compounds generated from hydroboration of olefinated sugar precursors and a vinyl compound via a Suzuki coupling as the key step.[3,4] Another methodology utilized a Barbier coupling of an aldehydo sugar and an aza sugar,[5] while others built up the *C*-linked bridge by a Wittig olefination.[6] Other approaches utilized double reductive aminations either of a carbohydrate-derived acetylenic diketone,[7] or an appropriate 1,5-diketone obtained from a C1-substituted galactal.[8] Vogel and co-workers introduced the 'naked sugar' methodology for the total synthesis of several imino-*C*-disaccharides and other analogues, starting from an iminosugar substrate and an enantiomerically pure 7-oxabicyclo[2.2.1]heptyl derivative via a cross aldolization reaction.[9–14] According to another approach, also introduced by Vogel's group, various $(1\rightarrow2)$ and $(1\rightarrow4)$ *C*-linked iminodisaccharides were obtained from leavoglucosenone or isoleavoglucosene and iminosugars using either a Nozaki–Kishi coupling[15,16] or an aldol condensation reaction.[17] In another approach, which appeared during the course of our study on the subject, linear $(1\rightarrow6)$ aza-*C*-disaccharides were obtained by cycloaddition of six-membered chiral nitrones and sugar derived alkenes.[18] The synthesis of $(1\rightarrow2)$ pseudo-aza-*C*-disaccharides by cycloaddition reactions of cyclic nitrones to glycals is also relevant.[19]

Our approach is based on a cycloaddition reaction of an open chain nitrone and an alkene both obtained from sugar precursors. The nitrone has a protected hydroxyl group that could be transformed to a good leaving group (e.g. a mesylate), to give the desired pyrrolidine nucleus by an intramolecular *N*-alkylation followed by the reductive cleavage of the isoxazolidine cycloadduct.

The synthesis of the nitrone is outlined in Scheme 1. Starting from L-erythrose monoacetonide, alkene **2** was obtained by a Wittig olefination[20] and a subsequent protection of the resulting hydroxy group as a *t*-butyl dimethylsilyl ether (TBDMS). Compound **2** was then transformed into the desired nitrone **3** without isolation of intermediates, by the illustrated three step sequence,

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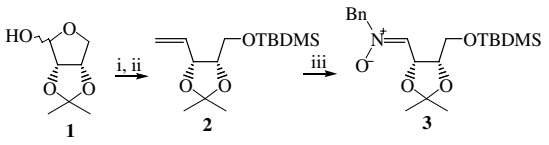


Scheme 1. Reagents and conditions: (i) $Ph_3P^+CH_2Br^-$, *n*-BuLi, THF, −78 °C, 90%, (ii) TBDMSCl, imidazole, DMF, overnight, rt, 92%, (iii) OsO_4 (4% H_2O), NMO, CH_3COCH_3, H_2O, 5 h, rt, then $NaIO_4$, THF, H_2O, overnight, rt, then BnNHOH·HCl, Et_3N, CH_2Cl_2, overnight, rt, 3%.

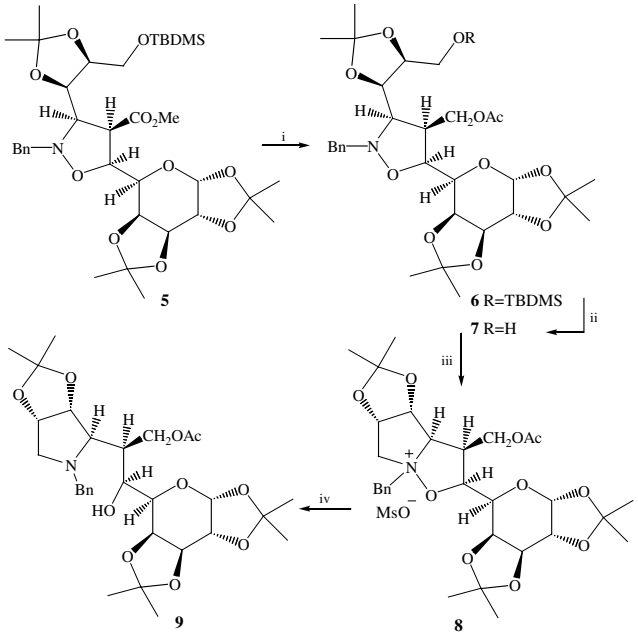
in 93% overall yield. All steps of this synthetic scheme were optimized so that a reasonably good overall yield was attained.[21]

The cycloaddition step was performed using a slight excess (1:1.2) of nitrone **3** and the known alkene **4**.[22] Preliminary experiments showed that after prolonged heating (five days) in refluxing toluene, besides cycloadduct **5**, two other stereoisomers of unknown stereochemistry were also formed. Meanwhile, considerable amounts of the nitrone **3** were decomposed so additional quantities needed to be added in order to get the reaction to go to completion. Interestingly the reaction was enhanced by the addition of a catalytic amount of triethylamine and was complete after two days heating in refluxing benzene. A remarkable stereo-selectivity was observed and only stereoisomer **5** was formed in very good yield. We cannot yet evaluate the exact catalytic effect of the added triethylamine. One possibility is that it may prevent *Z*- to *E*-isomerization of the reacting nitrone. This hypothesis is supported by blank experiments, carried out by heating nitrone **3** in refluxing benzene and by adding a catalytic amount of triethylamine. In the first experiment, after heating for 4 h, a new peak at δ 6.8 appeared in the ^{1}H NMR spectrum, which was attributed to the methine proton of the *E*-isomer of nitrone **3**, when the experiment was repeated, and adding a catalytic amount of triethylamine, no appreciable change in the ^{1}H NMR spectrum was observed.

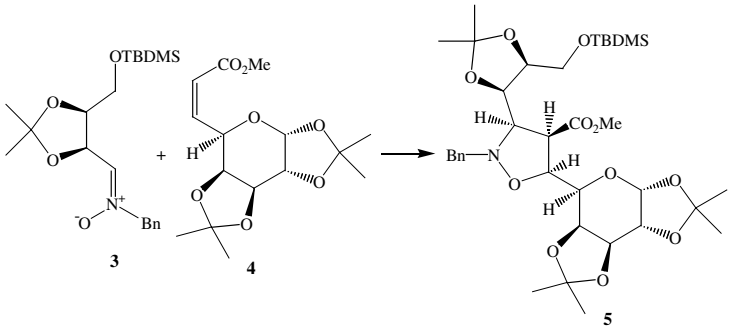
Attempts to selectively deprotect the primary hydroxyl group of cycloadduct **5**, using standard procedures, with tetrabutylammonium fluoride did not proceed well and resulted in complex mixtures. Also, attempts to carry out the deprotection using acetic acid resulted in partial removal of the acetonide group prior to the completion of the deprotection.

At this point crucial removal of the TBDMS group was left for a later stage and the reduction of the ester group was carried out instead. This was done using $LiBH_4$ and the resulting primary hydroxy group was protected as an acetate by reaction with Ac_2O/pyridine. Compound **6**, thus obtained was subjected to selective removal of the TBDMS group, carried out by short treatment with dilute acetic acid to give compound **7**,[23] fortunately without affecting the acetonide. This compound after treatment with MsCl in pyridine gave compound **8** as a mesylate salt; analogous intermediates have been previously reported.[24,25] Without isolation, catalytic hydrogenolysis using Pd/C gave the desired final product **9**,[26] in an 65% overall yield (from compound **7**) (Scheme 3).

The regioselectivity of the cycloadduct **5** as well as the stereochemical course of the cycloaddition step was deduced from the ^{1}H and ^{13}C NMR data of compounds **7** and **9**. These compounds show well-defined signals so that it was possible to unambiguously assign them. As expected, the regiochemistry of cycloadduct **5** is as



Scheme 3. Reagents and conditions: (i) (a) $LiBH_4$, THF, overnight, rt, 98% (b) Ac_2O/Py, overnight, rt, 90%; (ii) AcOH; 3 h, rt, 95%, (iii) MsCl/Py, 0 °C, 1 h, 90%; (iv) H_2, Pd/C, EtOH, 12 h, rt, 65%.



Scheme 2. Reagents and conditions: benzene, NEt_3 (cat.), reflux, two days, 75%.

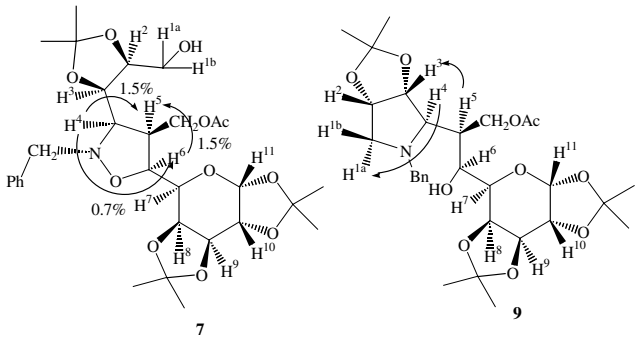


Figure 1. Representative NOE and ROESY interactions observed for cycloadduct **7** and aza-*C*-disaccharide derivative **9**.

illustrated in Scheme 2 and is in accordance with that observed from other analogous reactions of nitrones with α,β-unsaturated esters.[27]

The stereochemistry of the final product is obviously determined by the stereochemical course of the cycloaddition step, in particular by the reacting form of nitrone **3** (*Z* or *E*) in combination with a possible *exo*/*endo* and π facial selectivity. In principle four diastereomers are possible, by altering either the nitrone stereochemistry or the approaching mode.

The stereochemistry of the starting nitrone **3** was determined by NOE experiments. Irradiation of the azomethine proton resulted in a significant enhancement (∼12%) of the benzylic proton signals, indicative of a *Z*-form of nitrone **3**.

The absolute configuration of the new stereogenic centre at the C-3 of the isoxazolidine ring was assigned using proton decoupling, NOE and ROESY experiments, carried out on compounds **7** and **9** (Fig. 1). ROESY correlation peaks were observed between H-4 and H-6 of compound **7**, which indicated their *cis* arrangement. On the other hand, the absence of coupling between H-3 and H-4 in compound **9** suggests a dihedral angle of ∼90° consistent with a *trans* arrangement. This is also supported by the observed NOE interactions between H-3 and H-5.

All these data are in accordance with the assumption that the cycloaddition step follows an *exo*-attack of the sugar alkene to the *Re* face of sugar *Z*-nitrone **3**, although the alternative *endo* mode to the *Re* face of sugar *E*-nitrone can not be excluded.

Further work is in progress using other sugar alkenes in order to clarify the stereochemical consequences in this synthetic scheme and to obtain other branched chain aza-*C*-disaccharide derivatives.

References and notes

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21. Selected spectroscopic data for compound **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.95 (9H, s, $C(CH_3)_3$), 1.36 (3H, s, CH_3), 1.47 (3H, s, CH_3), 3.51 (1H, dd, $J = 3.9$, 11.5 Hz, CH_2OTBDMS), 3.67 (1H, dd, $J = 3.4$, 11.5 Hz, CH_2OTBDMS), 4.51 (1H, ddd, $J = 3.4$, 3.9, 6.4 Hz, CH–O), 4.86 (1H, s, NCHPh), 4.87 (1H, s, NCHPh), 5.36 (1H, dd, $J = 5.4$, 6.4 Hz, CH–O), 6.93 (1H, d, $J = 5.4$ Hz, CH=N), 7.39–7.47 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4, −5.3, 18.2, 24.5, 25.9, 26.7, 62.3, 69.0, 72.5, 78.9, 109.2, 128.3, 128.9, 129.3, 132.4, 138.1. HRMS (MALDI-FTMS) *m*/*z* obsd. 402.2087 calcd for $C_{20}H_{33}NO_4SiNa$ (MNa^+) 402.2071 $[\alpha]_D$ −106.8 (*c* 1.96, $CHCl_3$).
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FTMS) m/z obsd 594.2908 calcd for $C_{30}H_{44}NO_{11}$ (MH^+) 594.2909. $[\alpha]_D$ −4.0 (*c* 2.70, $CHCl_3$).

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