A Straightforward Route to Novel α,α-Disubstituted Tetrahydrofuran β-Amino Acids and Spirodiketopiperazines from Sugar Lactones

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Abstract: Indium-mediated Reformatsky reactions of aldonolactones with ethyl α-bromoisobutyrate allowed the synthesis of ulosonic acid esters, which were readily transformed into the corresponding tetrahydrofuran β-azido esters in a stereoselective fashion. This approach provided monomeric components suitable for oligomerization to the carbopeptoid class of foldamers and prompted the total synthesis of the attractive novel spiro diketopiperazine, which can be regarded as a spironucleoside.

Key words: indium, Reformatsky reaction, sugar amino acids (SAA), β-amino acids, spirodiketopiperazines

Sugar amino acids (SAA)[1] constitute a large family of hybrid carbohydrate derivatives that bear an amino and a carboxylic acid group and these compounds include naturally occurring members such as neuraminic acid and muraminic acid.[2] Among them, sugar amino acids arising from the direct incorporation of the amino acid moiety on the cyclic carbohydrate scaffold have emerged as a new class of promising hybrids that have played an important role in drug design and development. In fact, since the first reported synthesis of a SAA,[3] a vast number of these amino acids have been prepared for use as glycosidase inhibitors and as starting materials of great interest for the preparation of peptidomimetics.[4] The rigid furan or pyran rings make these systems ideal nonpeptididic scaffolds for incorporation into peptides in order to induce conformational restrictions[5] and enhance metabolic stability in pharmacologically active peptides.[6] In addition, the presence of several stereogenic centers on these rings[7] can be exploited to create chemical diversity and, furthermore, protection or deprotection of the hydroxy substituents opens opportunities to access hydrophobic or hydrophilic peptidomimetics.[8]

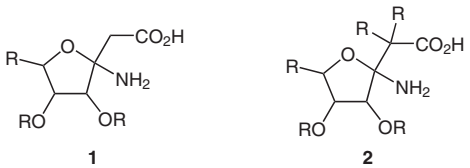
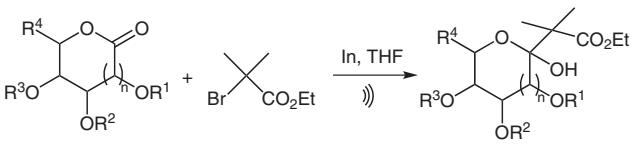


Figure 1 Sugar β-amino acids

The special folding properties of β-peptides has in recent times prompted exhaustive studies into the preparation of conformationally restricted β-amino acids, including type **1** furanoid β-amino acids. In this context, the related β,β-disubstituted β-amino acids **2** (Figure 1) could be novel, more convenient candidates for the preparation of stabilized peptidomimetic type **1** β-amino acids that are structurally related to α,α-disubstituted α-amino acids, which have also been used for the preparation of conformationally stabilized peptides.

Furanoid sugar β-amino acids **1** have been synthesized by a Wittig reaction involving a sugar-derived lactone, followed by a 1,4-addition of benzylamine.[9] However, this approach is not suitable to give the target amino acids **2** reported here.



Scheme 1 Preparation of ulosonic acid esters

As a part of our current studies on the synthetic usefulness of indium in carbohydrate chemistry,[10] we recently reported a highly efficient indium-mediated Reformatsky reaction between ethyl α-bromoisobutyrate and aldonolactones.[10a] This approach allowed us to access 2-deoxy-2,2′-dimethyl-3-ulosonates, which should provide an easy access to the target SAA **2**. Thus, diverse 2-deoxy-2,2′-dimethyl-3-ulosonates were prepared by indium-mediated reaction of ethyl α-bromoisobutyrate with D-manno, D-ribo, L-gulo and D-allo lactones **3**–**7** (Scheme 1, Table 1).

In order to explore the transformation of sugar-based β-hydroxyesters **8**–**12** into the corresponding β-amino acid esters, we first attempted the N-glycosylation of D-manno configured ulosonate **8** by acetylation of the free anomeric hydroxy group followed by treatment of the crude acetate with trimethylsilyl azide in the presence of trimethylsilyl triflate.[11]

The reaction proceeds stereoselectively to give the corresponding azido ester **14** in good yield (Scheme 2).

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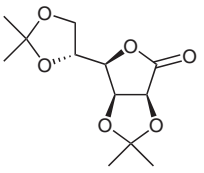
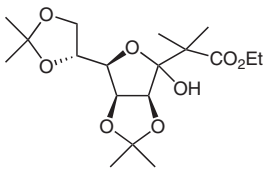
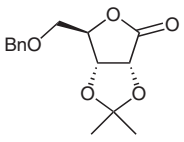
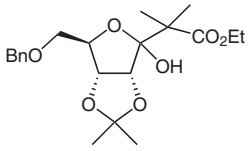
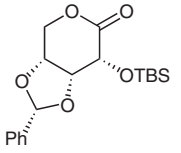
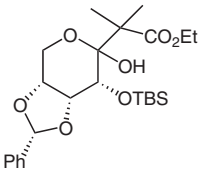
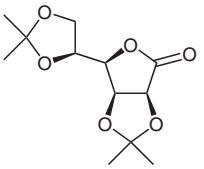
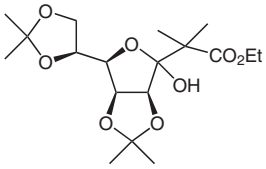
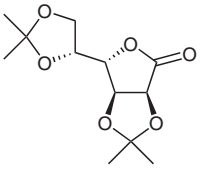
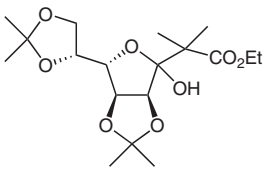
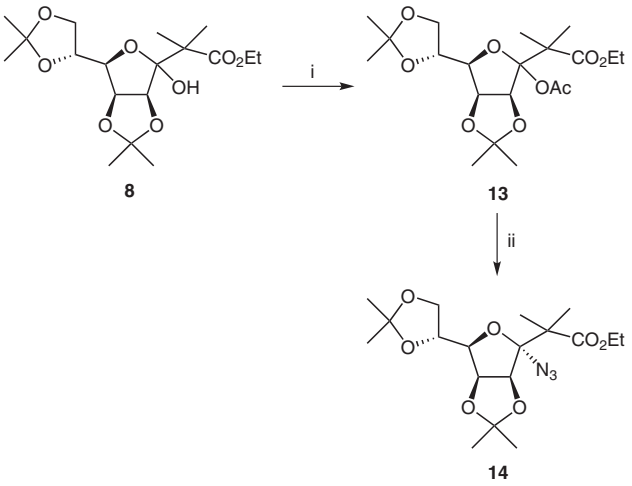
Table 1 Indium-Mediated Reformatsky-Type Reaction between Aldonolactones and Ethyl α-Bromoisobutyrate

Lactone	Uronate	Yield (%)
 **3**	 **8**	87
 **4**	 **9**	80
 **5**	 **10**	78
 **6**	 **11**	82
 **7**	 **12**	85



Scheme 2 *Reagents and conditions*: (i) Ac_2O, Et_3N, CH_2Cl_2, r.t., 14 h; (ii) $TMSN_3$, TMSOTf, powdered MS, CH_2Cl_2, r.t., 14 h, (71% over two steps).

The configuration of the anomeric center was firmly established by X-ray diffraction analysis (Figure 2).

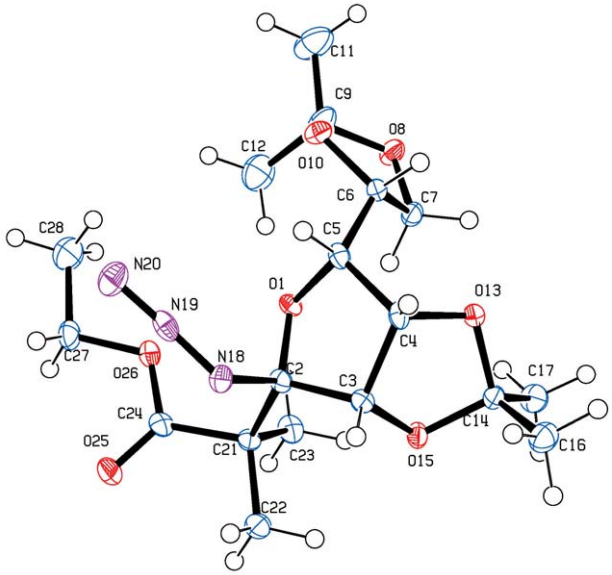
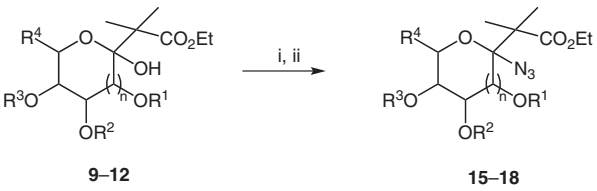


Figure 2 ORTEP diagram for **14**

This N-glycosylation protocol was next applied to ulosonates **9**–**12** (Scheme 3, Table 2). As expected, compounds **9**, **11**, and **12** afforded the corresponding azido esters **15**, **17**, and **18** in good yields and with excellent diastereoselectivities. However, derivative **10** afforded the *O*-acetyl derivative **16**, which remained unaltered under the N-glycosylation conditions. This lack of reactivity was related to the bulky protecting group present at the C-4 position.

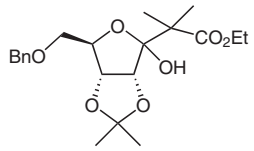
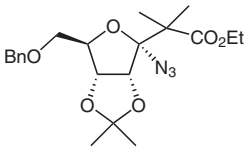
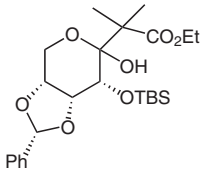
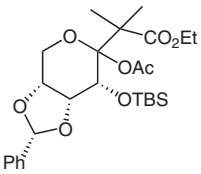
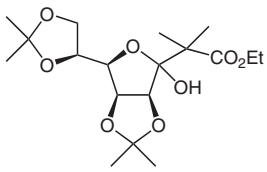
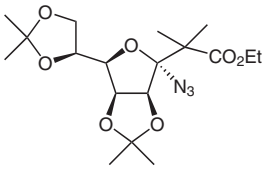
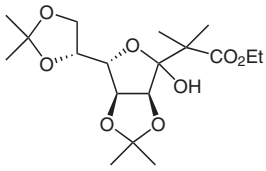
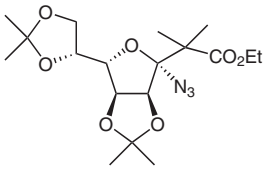


Scheme 3 *Reagents and conditions*: (i) Ac_2O, Et_3N, CH_2Cl_2, r.t., 14 h; (ii) $TMSN_3$, TMSOTf, powdered MS, CH_2Cl_2, r.t., 14 h.

The configuration of **17** at the anomeric center was unambiguously established by X-ray crystallographic analysis (Figure 3), while the absolute configuration of **15** and **18** was deduced from the strong NOE observed between one of the methyl groups at C-2 and a methyl group of the isopropylidene protecting group (Figure 4).

Catalytic hydrogenation of the azido esters **14**–**18** to give the corresponding amines led to loss of stereogenic integrity at the anomeric center; the epimeric amino esters equilibrate even in nonpolar solutions and all attempts to isolate deprotected equivalents of the amino esters were unsuccessful.[12] However, treatment of the amines with isocyanates should give anomeric ureas, which are likely

Table 2 Transformation of the Uronates in β-Azido Esters

Ulosonic ester	Azido ester	Yield (%)
 **9**	 **15**	58
 **10**	 **16**	92
 **11**	 **17**	61
 **12**	 **18**	62

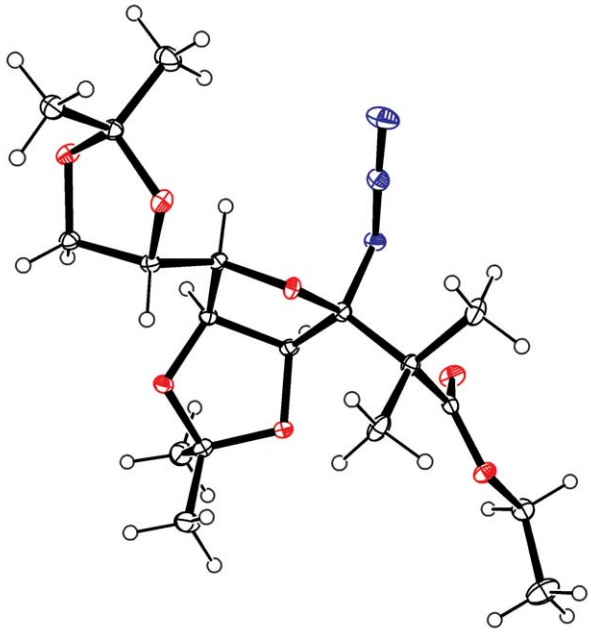


Figure 3 ORTEP diagram for **17**

to be much more stable as electron-withdrawing groups stabilize tetrahedral adducts relative to trigonal C=X systems. Accordingly, we decided to investigate the transformation of azido esters **14**–**18** into the corresponding ureas, which in turn could easily be transformed into novel and conformationally stable spiro diketopiperazine derivatives. The anomeric mixture of amino esters **19**, obtained from azido ester **14** by catalytic hydrogenation, was used as a model and thus reacted with phenyl isocyanate to afford derivative **20** as a single anomer (Scheme 4).

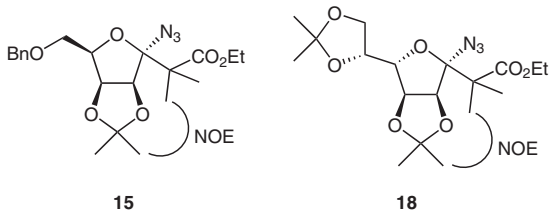
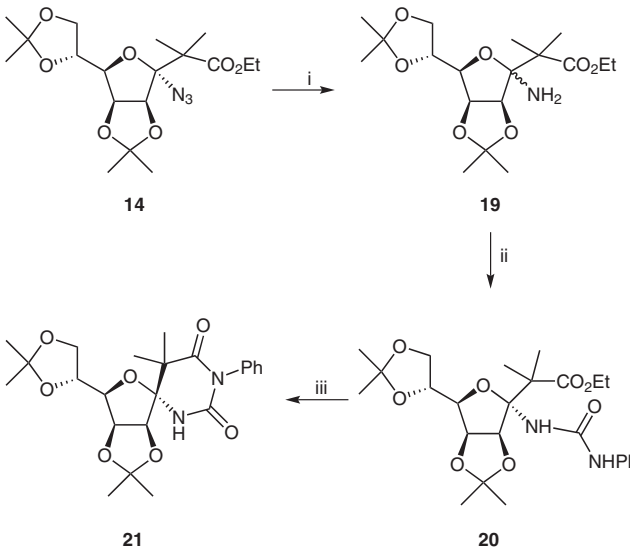


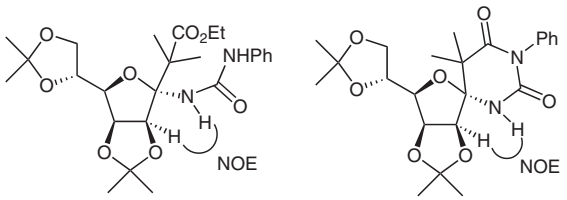
Figure 4 NOE experiments on **15** and **18**



Scheme 4 *Reagents and conditions*: (i) Pd/C, MeOH, r.t., 14 h; (ii) PhCON, toluene, r.t., 3 h; (iii) NaOMe, r.t., 14 h.

NOE measurements confirmed the proximity between the anomeric N–H of the urea and H-4 of the sugar ring, thus establishing the α configuration of urea **20** (Figure 5). The formation of the α urea from the anomeric mixture **19** is explained by a faster reaction of phenyl isocyanate with the less hindered – but less stable – α-anomer as compared to the β one, thus displacing the anomeric equilibrium toward the α-anomer and giving **20** in 85% yield.[13] Basic treatment of urea **20** easily gave the corresponding diketopiperazine **21** without any equilibration of anomers taking place. The absolute configuration of this spiro derivative was determined by NMR experiments, which showed an NOE between the N–H and the H-4 of the sugar ring (Figure 5).

In summary, the generation of THF β-carboxylates from carbohydrate lactones reported here has proven to be a short and efficient process. The process involves an easy and clean N-glycosylation of ulosonic acid esters, easily obtained by an indium-mediated Reformatsky reaction of aldonolactones with α-bromoisobutyrate, and provides



20 21

Figure 5 NOE experiments on **20** and **21**

access to α,α-disusbstituted THF β-amino acid derivatives. This approach provided monomeric components suitable for oligomerization to the carbopeptoid class of foldamers and prompted the total synthesis of the attractive novel spiro diketopiperazine, which can be regarded as a spironucleoside,[14] a type of *C*-nucleoside that has been of great interest[12,15] since the discovery of the herbicidal spironucleoside analogue hydantocidine.[16]

Work is in progress on the preparation and structural characterization of homopolymers based on these novel, promising β-amino acids. Further studies are also under way on the chemistry and biological activity of the novel type of sugar-derived spironucleosides reported here.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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