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Synthesis of Conformationally Constrained *C*-Glycosyl α- and *β*-Amino Acids and Sugar–Carbamino Sugar Hybrids via Diels–Alder Reaction†

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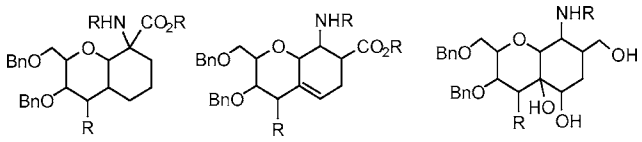
ABSTRACT



Sugar-derived dienes undergo Diels–Alder reactions with methyl α-nitro acrylate and ethyl *β*-nitro acrylate to form the corresponding cycloadducts which have been converted into conformationally constrained *C*-glycosyl α- and *β*-amino acids. Further, these *β*-amino acids are converted into sugar–carbamino sugar hybrid molecules.

Naturally occurring *O*- and *N*-glycoconjugates play key roles as carriers of biological information at the cellular level, such as the adhesion of bacteria and viruses to cells and cell−cell communication.[1] Owing to their limited chemical and enzymatic stabilities, recent efforts have been focused on the synthesis of unnatural *C*-glycosyl amino acids with the amino acid side chains connected to the sugar unit via linkers such as triazoles,[2a] isoxazoles,[2a,b] acetylenes,[2c] alkyl chains,[2d] phenyl ring,[2e,f] and spirolinkage.[2d,g] It is expected that these may lead to chemically and metabolically more stable and rigid analogues with potential biological activities. Encouraging results of very similar binding constants and biological properties of *C*-glycosides to those of oxygen counterparts have been reported.[3] In drug design, rigidity plays an important role for the binding of a glycopeptide (or) peptidomimetic to the target protein receptors. Compounds that are too flexible may pay high entropic penalties on binding such that the process becomes energetically unfavorable. Introducing annulation to the appropriate amino acid residue is one of the ways to rigidify glycopeptides.[4] Even though glycosyl α-amino acids are fragments of several natural products,[5] the same is not generally true of glycosyl *β*-amino acids. But *β*-peptides (non-natural oligomers of *β*-amino acids) have been shown to fold into helices, sheets, and turns, which are the main structural elements of proteins, and in some instances, it has been found that they possess even higher biological activities than their parent α-peptides.[6]

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† Dedicated to Prof. S. Chandrasekaran on the occasion of his 60th birthday.

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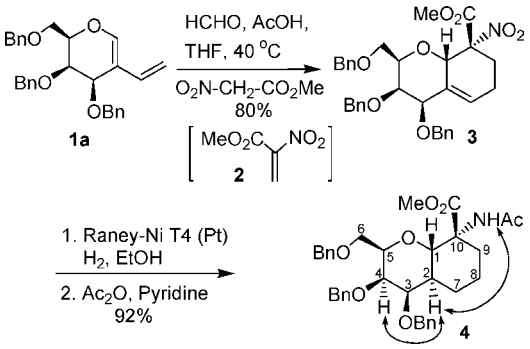
Also recently, certain *C*-glycosyl *β*-amino acids have been shown to be a new class of antitubercular agents.[7] In addition, some cyclic α-amino acid derivatives have been found to be valuable enzyme inhibitors[8a−c] and serve as "chiral auxiliaries" in asymmetric Diels−Alder reactions.[8d] On the other hand, some cyclic *β*-amino acids have a range of structural and biological properties[9a] including antifungal activity.[9b] In view of these important effects, we now report new methods to prepare some cyclic α- and *β*-amino acids fused to a sugar moiety via a *C*-glycosidic linkage. These molecules constitute another class of rigidified *C*-glycosyl α- and *β*-amino acids.

There are several notable contributions to the area of carbohydrate annulation involving ring-closing metathesis (especially by Jenkins);[10] Robinson annulation,[11] intramolecular aldol condensation,[12] radical cyclization,[13] and Diels−Alder cycloadditions have also been used for carbohydrate annulation.[14] Our approach to conformationally constrained (annulated)-*C*-glycosyl α- and *β*-amino acids would be based upon the Diels−Alder reaction of pyranose dienes with α- and *β*-nitro acrylic esters. Accordingly, the known pyranose diene **1a**[15] (Scheme 1) was reacted with

Scheme 1



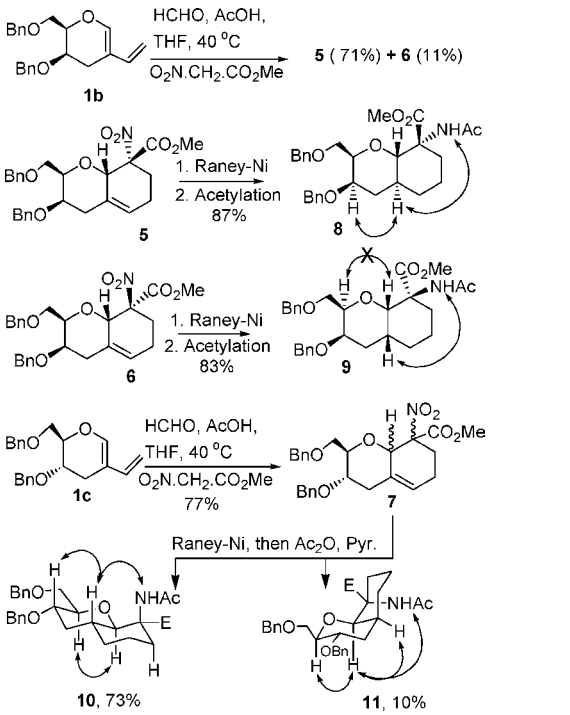
the *in situ* generated α-nitro methyl acrylate **2**[16a] to give the regio- and stereoselectively controlled cycloadduct **3** in 80% yield. The complete diastereoselectivity observed is noteworthy in view of the fact that cycloadditions of cyclopentadiene or Danishefsky diene to **2** lead[16a] to the corresponding cycloadducts as 85:15 and 70:30 mixtures of diastereomers in favor of the *endo* nitro group. This is possibly due to the presence of *β*-substituents at C-3, C-4, and C-5 which block the *β*-face for high *endo* nitro group selectivity. Reduction of the double bond as well as that of the nitro group was achieved with Pd−C under H_2 atmosphere, followed by acetylation of the free amine with pyridine-Ac_2O to obtain the fused bicyclic *C*-glycosyl α-amino acid **4** as a single stereoisomer in 53% yield. The moderate yield in the hydrogenation step led us to use platinized Raney-Ni T4[16b] in place of Pd−C which gave the *N*-acetyl α-amino ester **4** in 92% yield as the sole product.

The stereoselectivity of the reduction of the hindered double bond is consistent with similar reported observations,[17] and the overall stereochemistry was confirmed by 2D NMR experiments, particularly NOESY.

There was no NOE correlation between H-1 and H-2 in **4**, and $J_{1,2} = 10.0$ Hz revealed a *trans* diaxial relationship between these hydrogens (and a consequential diequatorial relationship between the C-substitutents at the ring junctions in **4**). Subsequent NOE correlations between H-2 and amide proton (NH) and H-2 and H-4 protons further suggested a *cis* relationship between them. Additionally, no NOE correlations were observed between H-1 and this NH, or H-1 and the H-5/H-3 protons, suggesting that these protons were all *trans* related.

Under the same conditions, the dienes **1b** and **1c** reacted with **2** (Scheme 2) to give a separable mixture (82% yield) of cycloadducts **5** and **6** in a 7:1 ratio. By way of contrast, the stereoisomeric mixture **7** (77% yield, 7:1 ratio) was

Scheme 2



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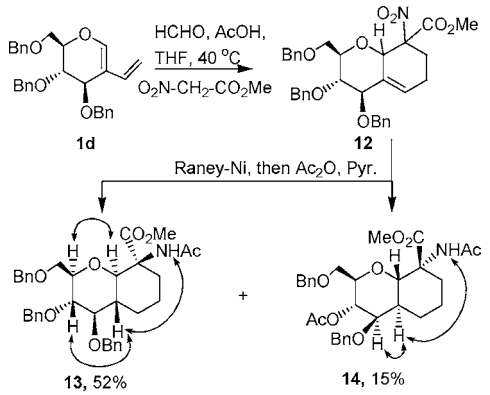
inseparable. Clearly, the absence of a substitutent at C-3 appears to be responsible for the low stereoselectivity observed. Compounds **5** and **6** were separated chromatographically and carried separately through the sequence of reactions as shown in Scheme-2. Single pot reduction of the nitro group and olefinic bond in compound **5** with Raney Ni followed by acetylation gave the α-linked *C*-glycosyl α-amino ester **8** (87%) and the *β*-linked *c*-glycosyl α-amino ester **9** (83%) respectively whose NOESY spectra[18a] were in accord with the stereochemical assignments made.

Likewise, the inseparable nitro ester **7** was converted under the same conditions to the corresponding *C*-glycosyl α-amino esters **10** and **11** in 73% and 10% yield, respectively, which were readily separable by chromatography. Structures of these compounds were again assigned on the basis of NOESY and ^{1}H NMR data.[18a]

Diels−Alder reaction of glucal derived diene **1d**[15] (Scheme 3) with α-nitro methyl acrylate **2** under similar experimental

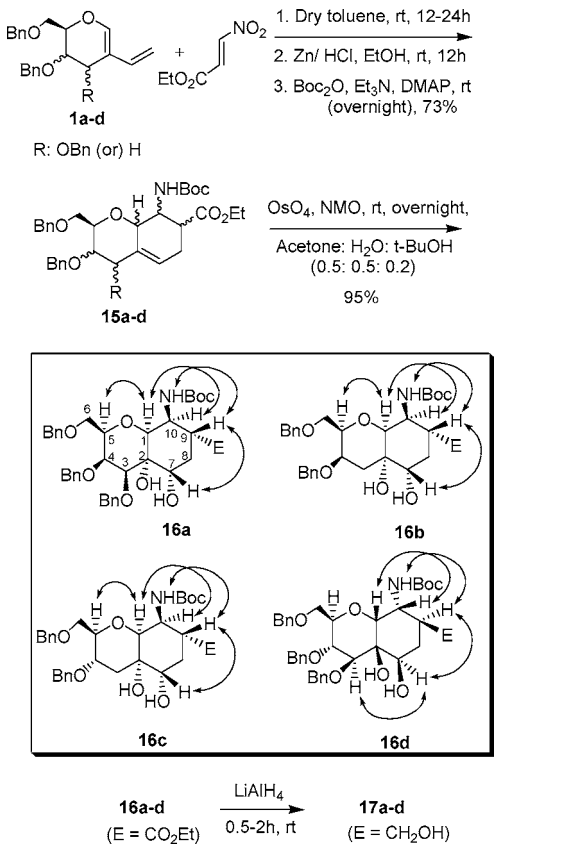
Scheme 3



conditions led to cycloadduct **12** as an inseparable stereoisomeric mixture. However, hydrogenation of **12** followed by acetylation gave chromatographically separable major product *β*-*C*-glycoside **13** and minor α-*C*-glycoside **14** in 52% and 15% yield, respectively, whose structures were established based on their ^{1}H NMR data and the NOESY experiments.[18a]

For the synthesis of annulated *β*-amino acids, dienes **1a**−**d** were reacted with ethyl *β*-nitro acrylate[19] (Scheme 4) to afford the corresponding cycloadducts as inseparable stereoisomers. The crude products were subsequently converted to the corresponding carbamates **15a**−**d** sequentially by

Scheme 4



reduction with Zn/HCl followed by addition of a large excess of Et_3N and Boc_2O in 73−84% yields through three steps. The major isomer in each case was separated from the inseparable mixture of minor diastereomers (8−10%) by SiO_2 column chromatography. Exposure of the unsaturated amino esters **15a**−**d** to OsO_4 and NMO led to dihydroxylation and the corresponding annulated *C*-glycosyl *β*-amino esters **16a**−**d** were obtained in good yields. Structures of these annulated products were assigned on the basis of their ^{1}H NMR and NOE data.[18a]

In every case, the H-9 proton showed a doublet ($J = 3-4$ Hz) of a triplet (which is basically an overlapping doublet of a doublet with $J = 11-12$ Hz) at $\delta \sim 2.73$, indicating that H-9 is flanked by two axial protons (H-10 and one of the H-8) and one equatorial proton (the other H-8) while H-9 itself being axial (structure **16d**,[18b] Scheme 4). On the other hand, H-1 appeared as a doublet with $J = 2.68$ Hz or as a broad singlet indicating that H-1 must be *cis* to H-10.

Reduction of compounds **16a**−**d** with $LiAlH_4$ led to the formation of the corresponding triols **17a**−**d**, whose structures were based on the spectral data obtained[18a] for these compounds. These molecules represent hybrid[20] structures of D-galactose or D-glucose with 4-deoxycarbasugars. In view of the fact that carbasugars and their hybrids act[21] as

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glycosidase inhibitors and our interest in synthesizing hybrid molecules[22] of sugars with azasugars, compounds **17a**−**d** appear interesting.

To the best of our knowledge, this is the first report of the synthesis of annulated *C*-glycosyl α- and *β*-amino acids. It is expected that these molecules would be useful in modifying the properties of certain oligopetides by virtue of their being rigid and metabolically stable (being annulated *C*-glycosides).

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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