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General Synthesis of *C*-Glycosyl Amino Acids via Proline-Catalyzed Direct Electrophilic α-Amination of *C*-Glycosylalkyl Aldehydes

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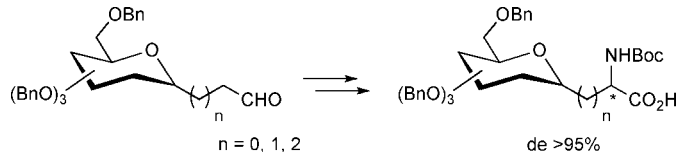
ABSTRACT



Non-natural axially and equatorially linked *C*-glycosyl α-amino acids (glycines, alanines, and CH_2-serine isosteres) with either *S* or *R* α-configuration were prepared by D- and L-proline-catalyzed (de >95%) α-amination of *C*-glycosylalkyl aldehydes using dibenzyl azodicarboxylate as the electrophilic reagent.

Out of infancy and now enjoying a renaissance,[1] asymmetric organocatalysis has firmly established itself in recent years as a powerful tool in drug and natural product synthesis, as in the transformation of readily available simple compounds into chiral building blocks for the synthesis of more complex molecular targets. Quite surprisingly, however, organocatalysis has scarcely been used in carbohydrate chemistry. The only significant contribution is represented by the biomimetic de novo synthesis of common and rare carbohydrates.[2] Studies in glycobiology and glycomedicine are posing a pressing need for natural and non-natural oligosaccharides and glycoconjugates in meaningful amounts and with a well-established structure and composition. These compounds may serve as probes in studies aimed at clarifying the complex functions at a molecular level that carbohydrates exert in living systems,[3a] in addition to serving as new leads for the development of carbohydrate-based drugs.[3b] It is in this context, we report herein an organocatalytic-based synthetic scheme for the asymmetric synthesis of carbon-linked sugar amino acids such as *C*-glycosyl glycines, alanines, and methylene isosteres of serines. The importance of non-natural *C*-glycosyl α-amino acids[4] relies mainly on their use as building blocks for the cotranslational modification of natural glycopeptides.[5] A general method for the synthesis of these amino acids with different chain length between the carbohydrate and the glycinyl moiety has not so far been reported

(1) For a focus review of recent and significant synthetic acquisitions of organocatalysis, see: Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660.

(2) A selection: (a) Córdova, A.; Notz, W.; Barbas, C. F., III *Chem. Commun.* **2002**, 3024–3025. (b) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752–1755. (c) Enders, D.; Grondal, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210–1212. (d) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III *J. Org. Chem.* **2006**, *71*, 3822–3828. (e) Ibrahem, I.; Zou, W.; Xu, Y.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348*, 211–222. (f) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas, C. F., III *Org. Lett.* **2007**, *9*, 3445–3448.

(3) (a) Varki, A.; Cummings, R.; Esko, J.; Freeze, H.; Hart, G.; Marth, J. *Essentials of Glycobiology*; Cold Spring Harbor Laboratory Press: New York, 1999. (b) Wong, C.-H. *Carbohydrate-based Drug Discovery*; Wiley-VCH: Weinheim, 2003; Vols. 1 and 5.

(4) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395–4421.

(5) For a brief introduction to this topic and leading references, see: Dondoni, A.; Massi, A. Synthesis of Heterocycle-Linked *C*-Glycosyl α-Amino Acids and *C*-Glycopeptides In *Current Frontiers in Asymmetric Synthesis and Application of a-Amino Acids, ACS Symposium Series*; Soloshonok, V. A., Izawa, K., Eds.; Oxford University Press, to be published in 2008.

(6) Dondoni, A.; Massi, A.; Nuzzi, A *Synlett* **2007**, 303–307, and references therein.

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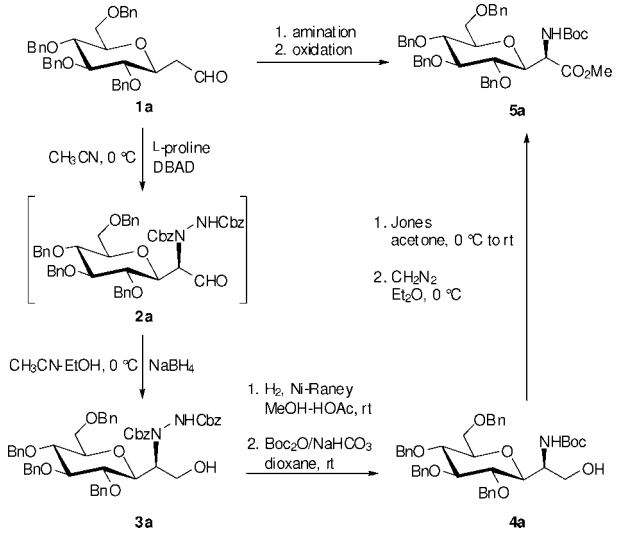
to the best of our knowledge. Hence, we first considered the class of *C*-glycosyl glycines wherein a single carbon−carbon bond is holding the two molecular fragments.[6] We envisaged a direct entry to these compounds with either *R*- or *S*-configuration by stereospecific α-amination of glycosyl acetaldehydes via an organocatalyzed asymmetric carbon−nitrogen bond-forming reaction.[7] The ready access to α (axial) *C*-glycopyranosyl acetaldehydes by double bond oxidative cleavage of allyl *C*-glycopyranosides and the proline-catalyzed epimerization of α to *β* (equatorial) anomers developed in our laboratory[8] furnished the required substrates for our synthetic program. The execution of this plan starting from *β*-*C*-glucopyranosyl ethanal **1a** to give the corresponding *R*-configured *C*-glucosyl glycine **5a** under the effect of the simplest organocatalyst such as L-proline is presented in Scheme 1. Guided by previous studies on direct

Scheme 1. L-Proline-Catalyzed α-Amination of Model Perbenzylated *β*-*C*-Glucosyl Acetaldehyde **1a**



electrophilic α-amination of simple α-enolizable ketones and aldehydes by using enamine catalysis,[9] the sugar aldehyde **1a** was allowed to react in acetonitrile at 0 °C with a typical electrophilic nitrogen source such as dibenzyl azodicarboxylate (DBAD) in the presence of 30 mol % of L-proline as the catalyst. To our great delight, this coupling process turned out to be highly effective because it afforded exclusively the α-hydrazino aldehyde **2a** as judged by TLC and NMR analyses of the reaction mixture. This product, however, was reduced in situ by sodium borohydride and ethanol to give the nonepimerizable alcohol **3a** which was isolated in very good yield and high diastereomeric purity (de >95%).[10] Hydrogenation of **3a** over Raney Nickel selectively removed the Cbz protective groups and cleaved the N−N bond to give the free amine.[11] Treatment of crude amine with Boc_2O furnished the *N*-Boc protected amino alcohol **4a** (Scheme 1). This was readily transformed into the target α-amino ester **5a** by oxidation with Jones reagent and esterification with diazomethane. The configuration of the carbon stereocenter of the glycinyl group of **5a** was assigned[7] as *R* by the Dale−Mosher NMR method.[12] To this end, the ^{1}H NMR analysis of the pair of Mosher amides derived from **5a** allowed us to calculate $\Delta\delta^{RS}$ values (see Supporting Information) as previously performed in our[13a,b] and other[13c] laboratories for other *C*-glycosyl amino acids.

To firmly establish the key role of L-proline on the stereochemical outcome of the aldehyde **1a** and DBAD asymmetric coupling, the reaction was carried out in MeCN at 0 °C in the presence of an achiral base and a Brønsted acid. To this aim, the couples pyrrolidine/acetic acid and pyrrolidine/trifluoroacetic acid were employed. In both cases, the reaction afforded a mixture of α-hydrazino aldehyde diastereoisomers as shown by the isolation of alcohols **3a** and epimer **6a** in a 1:1 ratio (Table 1). Hence, an internal asymmetric induction by the chiral glycoside moiety was reasonably excluded while the presence of proline appeared to be crucial. Accordingly, a reversal of diastereoselectivity was observed by performing the reaction of **1a** with DBAD in the presence of D-proline as the catalyst (Table 1). This reaction led to the *S* configured α-hydrazino alcohol **6a** as a single product in 73% isolated yield. This alcohol was processed as described for **3a** in Scheme 1 and transformed into the corresponding *β*-*C*-glucosyl amino ester **7a** (Table 1).

The organocatalytic enamine−enamine tandem sequence which involved the proline-catalyzed anomerization of α-*C*-glucosyl acetaldehyde **1b** to the *β*-anomer **1a** and the subsequent α-amination of the latter was also investigated (see Scheme S1 in Supporting Information). The combination

(7) Preliminary data have been succinctly reported in ref 1. It has to be noted, however, that because of a misprinting the representative *β*-*C*-glucosyl glycine reported therein was erroneously depicted as having the *S* configuration.

(8) Massi, A.; Nuzzi, A.; Dondoni, A. *J. Org. Chem.* **2007**, *72*, 10279–10282.

(9) A selection: (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5667. (b) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790–1793. (c) Liu, T.-Y.; Cui, H.-L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 3671–3674. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

(10) The diastereomeric purity of hydrazino-alcohols **3** was evaluated by ^{1}H NMR analysis (DMSO-d_6, 120−160 °C) of crude reaction mixtures and by comparison with spectra of authentic samples of the corresponding α-epimers. These were isolated from epimeric mixtures of **3** which were obtained by treatment of crude aldehydes **2** with imidazole (CH_2Cl_2, rt, 72 h) and then with $NaBH_4$. The diastereomeric purity of **3** was also confirmed by ^{1}H NMR analysis of crude *N*-Boc amino alcohols **4**. The same analysis was extended to hydrazino-alcohols **9a**, **11a**, **14a**, and **16a** (Table 2).

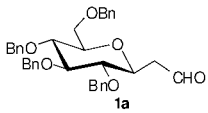
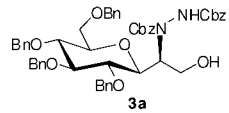
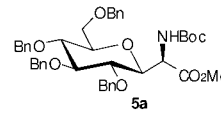
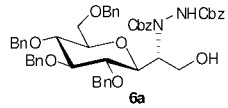
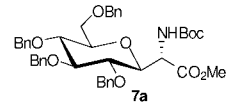
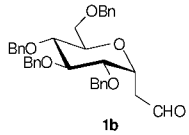
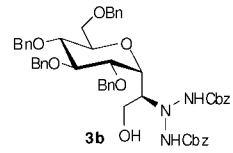
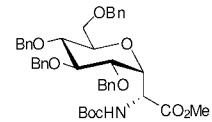
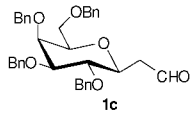
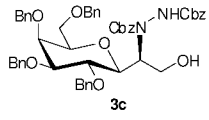
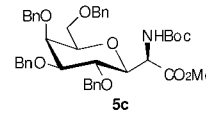
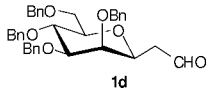
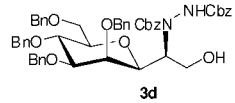
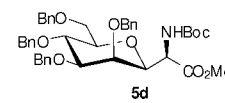
(11) Crucial for the effective execution of this synthetic pathway was the cleavage of the hydrazino group by the use of high-quality Raney Nickel catalyst. Apparently deteriorated batches of this catalyst resulted in partial or total debenzylation of the sugar moiety and the formation of hardly processable intermediates.

(12) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.

(13) (a) Dondoni, A.; Massi, A.; Sabbatini, S. *Chem.−Eur. J.* **2005**, *11*, 7110–7125. (b) Dondoni, A.; Massi, A.; Minghini, E. *Synlett* **2006**, 539–542. (c) Röhrig, C. H.; Takhi, M.; Schmidt, R. R. *Synlett* **2001**, 1170–1172.

(14) Attempts to perform both proline-catalyzed cycles in either MeOH or MeCN produced poorer results as confirmed by the lower yields of isolated **3a**. For a detailed scheme showing all the species involved, see Scheme S1 in the Supporting Information.

Table 1. α-Amination of *C*-Glycosyl Acetaldehydes with DBAD to Give Glycines **5a**−**d** and **7a** through Hydrazino Alcohols **3a**−**d** and **6a**

aldehyde	catalyst	hydrazino alcohol	yield (%),[b] de (%)[c]	glycine	yield (%)[b]
 **1a**	L-proline	 **3a**	80, >95	 **5a**	71
1a	D-proline	 **6a**	73, >95	 **7a**	61
1a	pyrrolidine/AcOH (1:1)	**3a** + **6a**	69, 0	/	/
1a	pyrrolidine/TFA (1:1)	**3a** + **6a**	74, 0	/	/
 **1b**	L-proline	 **3b**	68, >95	 **5b**	63
 **1c**	L-proline	 **3c**	75, >95	 **5c**	58
 **1d**	L-proline	 **3d**	73, >95	 **5d**	66

[a] All reactions were run with 0.40 mmol of aldehyde and 30 mol % of catalyst. [b] Isolated yield. [c] See ref 10.

of the two catalytic cycles produced optimal results by changing the reaction solvent, i.e., MeOH in the first cycle and MeCN in the second. In this way, the alcohol **3a** obtained by reduction of the aldehyde **2a** was prepared in 75% overall yield from **1b**.[14] This value is identical to that registered in the stepwise protocol, thus demonstrating the maintenance of proline activity during the two catalytic cycles.

The scope of the above α-amination protocol was extended to other perbenzylated *C*-glycosyl acetaldehydes, i.e., the α-*C*-glucosyl **1b**, *β*-*C*-galactosyl **1c**, and *β*-*C*-mannosyl **1d** derivatives (Table 1). In all cases, the key asymmetric C−N bond-forming reaction between the aldehyde and DBAD proceeded readily under the conditions described in Scheme 1 to give after reduction with $NaBH_4$ the corresponding hydrazino alcohols **3** in good yield and complete diastereoselectivity.[10] Then, alcohols **3b**−**d** were transformed into the *N*-Boc methyl glycinates **5b**−**d** whose configuration was assigned as *R* by the Dale−Mosher method.[12,15]

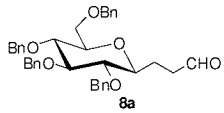
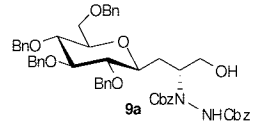
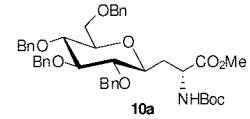
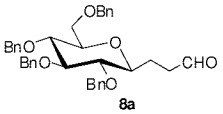
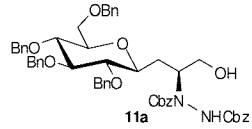
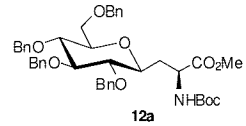
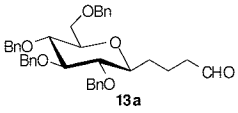
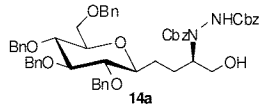
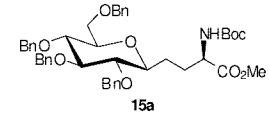
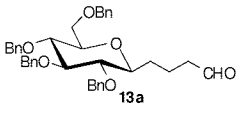
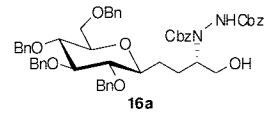
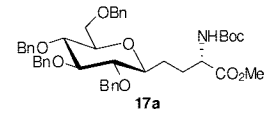
By analogy to the *C*-glycosyl glycine synthesis, we also prepared the chain-lengthened *β*-*C*-glucosyl alanines **10a** and **12a** and CH_2-serine isosteres **15a** and **17a**. The *R* and *S* α-configuration in these compounds was achieved by using L- and D-proline catalysis, respectively (Table 2). *C*-Glycosyl alanines of type **10a** and **12a** are challenging synthetic targets as demonstrated by low stereoselectivity and lack of generality of previously reported synthetic methods.[16] Compounds **15a** and **17a** are methylene isosteres of *O*-glycosyl serines that are largely diffused in natural O-linked glycoproteins. Therefore, these isosteres bear special importance for the preparation of *C*-glycopeptides[4,13a] since these will offer substantial resistance to chemical and enzymatic degradation while showing minimal steric variance and unaltered biological activity. The starting sugar aldehydes *C*-glucosyl propanal **8a** and butanal **13a** were conveniently prepared by elaboration of the same precursor, the butenyl *β*-*C*-glucopyranoside (see Supporting Information). Each aldehyde was reacted with DBAD in the presence of either L- or D-proline, and the α-hydrazino aldehyde that formed was converted into the corresponding sugar amino ester by the same reaction sequence described in Scheme 1. The glycinyl group configuration was assigned by the Dale−Mosher method[12] and confirmed by the identical properties of products **15a**

(15) Consistent with the configurational assignment by the NMR method, compound **5c** turned out to be identical with the *R*-configured *β*-*C*-galactosyl glycinate whose structure was previously assigned from circular dichroism spectra: Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Scherrmann, M.-C.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5484–5496.

(16) Nolen, E. G.; Kurish, A. J.; Potter, J. M.; Donahue, L. A.; Orlando, M. D. *Org. Lett.* **2005**, *7*, 3383–3386, and references therein.

(17) (a) For **15a**, see: Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1323–1336. For **17a**, see: (b) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1999**, *64*, 933–944.

Table 2. α-Amination of *C*-Glucosyl Alkylaldehydes **8a** and **13a** with DBAD to Give Alanines **10a** and **12a**, and Serines **15a** and **17a**

aldehyde	catalyst	hydrazino alcohol	yield (%),[b] de (%)[c]	amino ester	yield (%)[b]
 **8a**	L-proline	 **9a**	68, >95	 **10a**	69
 **8a**	D-proline	 **11a**	65, >95	 **12a**	61
 **13a**	L-proline	 **14a**	61, >95	 **15a**	65
 **13a**	D-proline	 **16a**	62, >95	 **17a**	71

[a] All reactions were run with 0.40 mmol of aldehyde and 30 mol % of catalyst. [b] Isolated yield. [c] See ref 10.

and **17a** with those of known compounds.[17] Gratifyingly, the results of Table 2 were similar in terms of yield and diastereoselectivity to those obtained with glycosyl glycines and therefore provide evidence of the broad scope and effectiveness of the whole reaction scheme leading to *C*-glycosyl amino acids with carbon tethers of variable length.

To account for the formation of *R*-configured α-aminated products **5a**−**d**, **10a**, and **15a**, we propose transition state (TS) model **A** (Figure 1). This is similar to other models

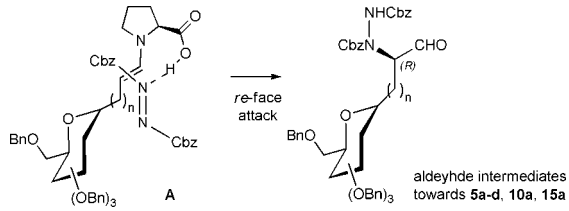


Figure 1. Proposed transition state model **A**.

that have been previously introduced to rationalize proline-catalyzed electrophilic aminations of simple aldehydes with DBAD.[9] Accordingly, DBAD is connected by hydrogen bonding to the carboxylic group of the pyrrolidine moiety and attacks the *re* face of the sugar (*E*)-enamine *anti* conformer. The high (and unexpected) level of diastereoselectivity (de > 95%) registered in all cases investigated indicates the preferential formation of a single TS structure regardless of the sugar configuration and distance from the prochiral carbon atom.

In conclusion, we have paved the way for an efficient and general organocatalytic route to orthogonally protected *C*-glycosyl α-amino acids which are suitable for cotranslational incorporation into peptide sequences. The practicality of the synthetic procedures represents a further advantage of the described methodology as it requires simple reaction conditions and an inexpensive chiral catalyst such as proline. Therefore, we believe our organocatalytic strategy is more convenient than the previosly reported DBAD-based asymmetric α-hydrazination of glycosylalkyl carbonyls[18] via Evans' asymmetric oxazolidinone enolate methodology.[19]

Acknowledgment. We gratefully acknowledge the University of Ferrara for financial support.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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