Carbohydrate Research 346 (2011) 2862–2871

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

# Preparation of 2-amino-2-*C*-glycosyl-acetonitriles from *C*-glycosyl aldehydes by Strecker reaction

Szabolcs Sipos, István Jablonkai *, Orsolya Egyed, Mátyás Czugler

*Institute of Biomolecular Chemistry, Chemical Research Center, Hungarian Academy of Sciences, PO Box 17, 1525 Budapest, Hungary*

ARTICLE INFO

*Article history:*
Received 23 May 2011
Received in revised form 13 October 2011
Accepted 14 October 2011
Available online 20 October 2011

*Keywords:*
1-*C*-Glycosyl aldehyde
Strecker reaction
2-Amino-2-*C*-D-glycosyl-acetonitrile
Double asymmetric induction

ABSTRACT

Synthesis of new 2-amino-2-*C*-D-glycosyl-acetonitriles in a Strecker reaction from various *C*-glycosyl aldehydes, chiral amines, and HCN was carried out. While aminonitriles from glycal and 2-deoxy-β-D-glycosyl aldehydes were prepared in satisfactory yields, lower yields were obtained with *C*-glycosyl aldehydes. Strecker reaction with the benzyl-protected 1-*C*-formyl-D-galactal and *S*- or *R*-1-phenylethylamine (*S*-PEA or *R*-PEA) yielded predominantly the *R*-configured *C*-glycosyl aminoacetonitrile. The direction of the nucleophilic addition appears to be governed by the configuration of the anomeric carbon with β-linked sugars. Since the stereochemistry of the transition state is unknown according to the configuration of the major product a Felkin–Ahn selectivity can be mainly presumed.



## 1. Introduction

2-Amino-2-*C*-D-glycosyl-acetonitriles (*C*-glycosyl aminoacetonitriles) carrying an α-aminonitrile moiety directly linked to the anomeric carbon of carbohydrates are challenging bifunctional intermediates which can be applied in various organic transformations. By hydrolysis these compounds can be converted into *C*-glycosyl glycine building blocks applicable in the synthesis of biologically important glyco-peptidomimetics. Reduction of the nitrile functionality may result in 1,2-diamino derivatives as starting materials for the preparation of carbohydrate linked nitrogen heterocycles. Also, deprotonated α-aminonitriles have been applied as valuable and readily accessible synthetic equivalents of acyl anions and α-aminocarbanions.[1] Typically, α-aminonitriles are prepared by Strecker synthesis involving the reaction of aldehydes with amines and cyanides such as HCN, KCN, TMSCN, $(EtO)_2P(O)CN$, $Et_2AlCN$, $Bu_3SnCN$, acetone cyanohydrin, or acyl cyanides.[2,3] Preformed imines which are intermediates of α-aminonitrile formation during the Strecker synthesis are widely used starting materials in catalytic asymmetric Strecker syntheses.[4] Despite their importance only few synthetic methods have been described for *C*-glycosyl aminoacetonitriles. Strecker-type transformations of sugar derived aldehydes in 'anomeric like' positions to *C*-glycosyl aminoacetonitriles have been described.[5–8] A ribofuranose-linked α-aminonitrile (2-amino-2-ribofuranosyl acetonitrile) was prepared from chiral sulfinimine derived from 2′,3′-O-protected 5′-formyluridine and *R*- or *S*-*tert*-butyl sulfinamide in a reaction with TMSCN using boron trifluoride.[9] In situ $H_2O_2$ oxidation of the cyanohydrin formed from benzyl-protected formyl *C*-ribofuranoside by treatment with aqueous NaCN and $K_2CO_3$ provided the corresponding α-hydroxy amide as appropriate intermediate for the synthesis of β-D-ribofuranosyl glycine.[10] In another example, dehydration of a β-D-ribofuranose-linked Cbz-protected glycine amide carried out with trifluoroacetic anhydride and pyridine provided the α-aminonitrile connected to the anomeric carbon.[11,12] *C*-Glycosyl-L-alanine precursor 2-amino-2-(α-D-glycopyranosyl)propanenitrile derivatives were synthesized by asymmetric Strecker synthesis from perbenzylated 2-*C*-(α-D-glycopyranosyl)acetaldehydes employing *S*-1-phenylethylamine as chiral inducer.[13]

Nevertheless, no information on the preparation of α-aminoacetonitriles directly linked to the anomeric center of D-glycopyranose derivatives as *C*-glycosyl glycine precursors has been available. Our objective was to prepare various glycopyranose-linked aminoacetonitriles from 1-*C*-formyl-glycosyl derivatives such as D-glycal-, 2-deoxy-β-D-glycosyl-, and α- and β-D-glycosyl aldehydes by asymmetric Strecker reaction using *S*- and *R*-1-phenylethylamines. Since 1-*C*-formyl-glycosides have been reported as unstable derivatives due to their decomposition by 2-benzyloxy elimination[14] it was not trivial that these compounds can tolerate the conditions employed in the Strecker reaction of 2-*C*-(α-D-glycopyranosyl)acetaldehydes.[13] In the stereoselective formation of *C*-glycosyl aminonitriles in addition to chiral amine the sugar aldehyde reactant can also influence the stereochemical outcome of the reaction and therefore the double asymmetric induction by these chiral auxiliaries can also be studied. The effect of reaction conditions such as solvents, cyanide source, and amines on yields and diastereomeric ratios (dr) will be also discussed.

* Corresponding author.
*E-mail address:* jabi@chemres.hu (I. Jablonkai).

0008-6215/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2011.10.023

## 2. Results and discussion

### 2.1. Preparation of 1-*C*-formyl glycosyl derivatives

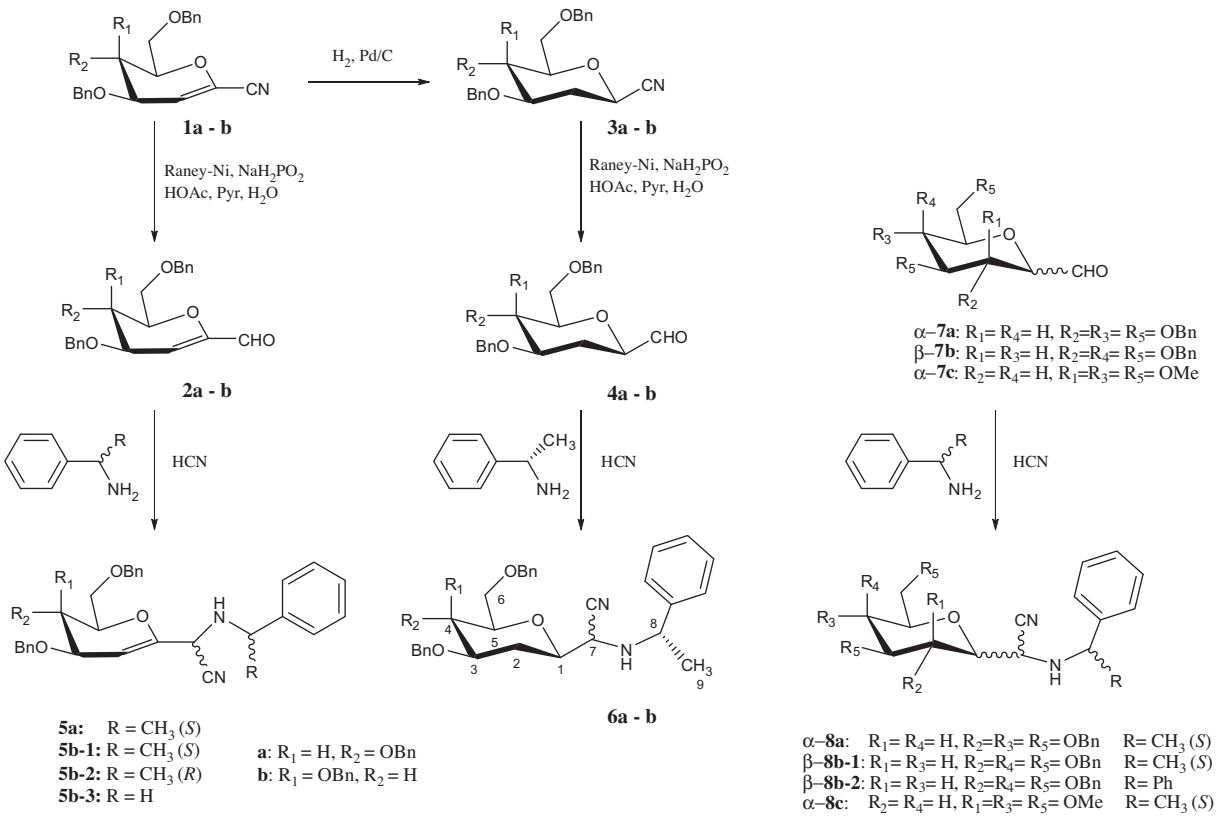
Our synthetic approach for the preparation of *C*-glycosyl aminoacetonitriles (**5a–b**, **6a–b**) by Strecker synthesis via 1-*C*-formyl-D-glycal (**2a–b**) and 2-deoxy-β-D-glycosyl aldehyde (**4a–b**) intermediates is outlined in Scheme 1. 1-Cyano-D-glycals (**1a–b**) were considered as common starting materials for these sugar aldehydes. Benzyl-protected glycal nitriles (**1a–b**) were available in our laboratory from previous work as unexpected by-products during the standard benzylation (NaH, benzylbromide, DMF) of β-D-glucopyranosyl, β-D-galactopyranosyl, and α-D-mannopyranosyl cyanides by 2-benzyloxy elimination.[15] 2-Deoxy-β-D-glucopyranosyl (**3a**) and galactopyranosyl (**3b**) cyanides were prepared from the respective glycal cyanide by hydrogenation over palladium on charcoal at atmospheric pressure in moderate yields (50–60%).[15] An attempt to use a diimide reduction failed since no reaction took place with *o*-nitrobenzenesulfonyl-hydrazide (NBSH)[16] as diimide precursor. Nevertheless, NBSH was reported as a useful diimide source in the preparation of 2,3-dideoxyhexoses from derivatives having non-polarized double bond.[17]

Benzylated 1-*C*-formyl-glycals (**2a–b**) and 2-deoxy-glycosyl formaldehydes (**4a–b**) were prepared from the corresponding nitriles (**1a–b**, **3a–b**) by reductive hydrolysis carried out with Raney nickel and $NaH_2PO_2$ in acetic acid/pyridine/water at room temperature. Yields (55–72%) obtained were similar to those reported for the same transformation of peracetylated sugar nitriles.[18,19] The reported direct lithiation of 2-phenylsulfinyl- and 2-phenylsulfonyl-3,4,6-tri-*O*-benzyl-galactals followed by a reaction with DMF as electrophile affording 1-*C*-formyl-glycals[20] seemed to be less convenient procedure than the reductive hydrolysis. *C*-Glycosyl formaldehydes (**7a–c**, Scheme 1) were prepared from glyconolactone derivatives by an established literature method[21] introducing aldehyde equivalent thiazole functionality at the anomeric position followed by unmasking the formyl group in several steps.

In our hands 1-*C*-formyl-glycal formation by 2-benzyloxy elimination always occurred during the regeneration of aldehyde functionality therefore the yields for 1-*C*-formyl derivatives (α-**7a** 31% and glucal aldehyde 35%; β-**7b** 35% and galactal aldehyde 26%) were always less than the literature[21] values. When the benzyl protecting groups were replaced with methyl groups somewhat improved yield (α-**7a**, 46%) with concomitant glycal aldehyde formation was obtained. Reductive hydrolysis of perbenzylated α-glucopyranosyl cyanide with $LiAlH_4$ in THF followed by hydrolysis of the intermediate aldimine was reported to afford the respective 1-*C*-formyl derivative with good yields (75%).[22] However, in the reported $^1H$ NMR spectrum of the product the chemical shift (9.20 ppm) of the CHO proton is rather consistent with the formation of 1-*C*-formyl-3,4,6-tri-*O*-benzyl-D-glucal since in all 1-formyl-*C*-glycosyl derivatives of the *gluco, galacto*, and *manno* series higher chemical shifts (9.60–9.98 ppm) were reported.[15,21] Due to this contradiction and the ability of $LiAlH_4$ to reduce nitriles to primary amines we did not attempt to prepare the aldehydes by this way.

### 2.2. Strecker synthesis of various *C*-glycosyl aminoacetonitriles

Strecker-reaction for the preparation of *C*-glycosyl aminoacetonitriles (**5a–b**, **6a–b,** and **8a–c**, Scheme 1) was carried out with 1-*C*-formyl-glycals (**2a–b**), as well as 2-deoxy-glycosyl- (**4a–b**) and glycosyl-formaldehydes (**7a–c**) using chiral amines such as *S*- or *R*-PEA or achiral (benzylamine (BA), benzhydrylamine (BHA)) amines and various cyanide donors. Acetone cyanohydrine (ACH) was used initially as a cyanide source but due to by-product formation it was replaced later with NaCN/$NH_4Br$ or TMSCN in methanol. The




**Scheme 1.** Preparation of glycal-(**5a–b**), 2-deoxy-glycosyl-(**6a–b**) and α- and β-glycosyl-linked (**8a–c**) aminoacetonitriles.

by-product, 2-methyl-2-(1-phenylethylamino)propene-nitrile, formed in the reaction of acetone cyanohydrin and *S*-PEA,[23] contaminated the *C*-glycosyl aminoacetonitrile products due to its similar elution pattern which made the determination of the dr values complicated. By the use of ACH a catalytic amount (0.1 equiv) of triethylamine was always added in order to increase the dissociation of ACH into acetone and HCN.[24] Diastereomeric mixtures of aminonitriles **5a**–**b** and **6a**–**b** formed in the Strecker reactions were inseparable by chromatography and therefore dr values were calculated from the $^1$H NMR integral values of the CH protons at the new stereogenic center (C-7 as indicated on the numbered structure of **6a**–**b** on Scheme 1) as well as those of the $CH_3$ protons (C-9) due to the chiral amine. On the other hand, **8a**–**c** diastereomeric aminonitriles could be separated by column chromatography. Yields and dr values of the Strecker reaction with protected 1-*C*-formyl-D-galactal **2b** were superior to those with 1-*C*-formyl-D-glucal **2a** (Table 1, entries 1–5). The reaction exhibited higher stereoselectivity when *S*-PEA was used as compared to *R*-PEA (Table 1, entries 3 and 4) indicating that in the imine intermediate formed with the *S*-configured amine one of the diastereotopic faces at the prochiral CH=N group was preferred. While no stereodifferentiations were reported[13] in the Strecker reaction of 2-*C*-α-D-glycosyl acetaldehydes with BA and ACH, the reaction performed with **2b** and BA yielded **5b-3** with dr 2.78 (entry 5). Similarly, in the reaction of β-**7b** with achiral BHA similar dr value was found indicating the stereodifferentiating effect of these sugar aldehydes. As stereodiscriminating auxiliaries carbohydrates offer a variety of possibilities for spatial differentiation at various stereoselective syntheses.[25,26] The O-pivaloylated-β-D-galactosylamine proved to be an effective chiral auxilary in Strecker synthesis of aminonitriles.[27] Strecker reactions carried out with 2-deoxy-β-D-glycosyl aldehydes (**4a**–**b**) and *S*-PEA employing TMSCN in $CH_2Cl_2$ (entry 6) or ACH in THF (entry 7) exhibited higher dr values (8.25 and 5.17, respectively). However, low yields and diastereoselectivities were obtained when the reaction was carried out with α- and β-linked aldehydes (**7a**–**c**) derived from glucose, galactose, and mannose (entries 8–11). The low yields can be attributed to the decomposition of these unstable aldehydes by 2-alkyloxy elimination. Higher dr values were obtained with β-linked aldehydes as compared to those from the α-linked derivatives.

### 2.3. Configuration of the new stereocenter

The assignment of the configuration at the newly formed stereocenter was a crucial problem in our work. While diastereomers of benzyl-protected glycal- and 2-deoxy-glycosyl-linked aminonitriles (**5** and **6**) were inseparable, isolated diastereomers of benzyl-protected *C*-glycosyl-acetonitriles (α-**8a** and β-**8b**) were oily materials unsuitable for an X-ray crystallographic structure determination. However, the absolute configuration of the new stereocenter in the crystalline major product of α-**8c** derived from permethyl α-mannopyranosyl aldehyde α-**7c** (Table 2, entry 11) was established *R* by X-ray crystallography. In this diastereomer the methine proton (H-7) is located above the benzene ring (Fig. 1). For all other compounds, the configurations of the major and minor diastereomeric products were determined by comparing the $^1$H NMR chemical shifts of methine protons (H-7) at the new stereocenter as described in the literature.[13,28–30] In the aminonitriles formed from achiral aldehydes, the signals due to the methine protons of the new stereocenter in the major isomers always appeared at a higher field than those in the minor isomers. The observed upfield methine shift is due to the magnetic shielding effect by the phenyl group from the

**Table 1**
Preparation of *C*-glycosyl aminoacetonitriles from glycal-, 2-deoxy-glycosyl-, and glycosyl aldehydes and effects of the reaction conditions on yields and diastereomeric ratios

| Entry | Aldehyde | Amine (equiv) | HCN source (equiv) | Aminonitriles | Solvent | Yield (%) | dr |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | *S*-PEA (1.1) | ACH (1.3) | **5a** | $CH_3CN$ | 38 | 1.44 |
| 2 | **2a** | *S*-PEA (1.5) | ACH (2.5) | **5a** | $CH_2Cl_2$ | 48 | 1.24 |
| 3 | **2b** | *S*-PEA (2.0) | ACH (5.0) | **5b-1** | $CH_2Cl_2$ | 78 | 3.00 |
| 4 | **2b** | *R*-PEA (2.0) | ACH (5.0) | **5b-2** | $CH_2Cl_2$ | 72 | 2.06 |
| 5 | **2b** | BA (2.0) | ACH (5.0) | **5b-3** | $CH_2Cl_2$ | 74 | 2.78 |
| 6 | **4a** | *S*-PEA (2.0) | TMSCN (2.0) | **6a** | $CH_2Cl_2$ | 70 | 8.25 |
| 7 | **4b** | *S*-PEA (2.0) | ACH (5.0) | **6b** | THF | 67 | 5.17 |
| 8 | α-**7a** | *S*-PEA (1.5) | ACH (2.5) | α-**8a** | $CH_3CN$ | 47 | 1.35 |
| 9 | β-**7b** | *S*-PEA (2.0) | TMSCN (2.0) | β-**8b-1** | $CH_2Cl_2$ | 34 | 3.30 |
| 10 | β-**7b** | BHA (3.0) | NaCN (3.0) | β-**8b-2** | $CH_2Cl_2$ | 43 | 2.79 |
| 11 | α-**7c** | *S*-PEA (2.0) | ACH (5.0) | α-**8c** | $CH_2Cl_2$ | 30 | 2.00 |

**Table 2**
$^1$H NMR shifts of anisochronous protons and the suggested configuration of the new stereocenter in the major diastereomers of various aminonitriles

| Entry | Aminonitrile | Amine | $^1$H NMR chemical shifts (ppm) | | | | | | Configuration of N–CH–CN in major product |
|---|---|---|---|---|---|---|---|---|---|
| | | | N–CH–*CH*$_3$ (H-9) | | N–*CH*–CH$_3$ (H-8) | | N–*CH*–CN (H-7) | | |
| | | | Major | Minor | Major | Minor | Major | Minor | |
| 1 | **10** | *S*-PEA | 1.47 | 1.42 | 4.17 | 4.13 | 3.56 | 4.04 | *R* |
| 2 | **5a** | *S*-PEA | 1.36 | 1.31 | 4.10 | 3.97 | 3.81 | 4.04 | *R* |
| 3 | **5b-1** | *S*-PEA | 1.36 | 1.31 | 4.05 | 3.97 | 3.76 | 4.01 | *R* |
| 4 | **5b-2** | *R*-PEA | 1.19 | 1.38 | 3.89 | 4.07 | 3.86 | 3.75 | *R* |
| 5 | **5b-3** | BA | — | — | — | — | 3.87 | 3.91 | *R*[a] |
| 6 | **6a** | *S*-PEA | 1.38 | 1.34 | 4.05 | 4.06 | 3.29 | 3.69 | *R* |
| 7 | **6b** | *S*-PEA | 1.38 | 1.33 | 4.04 | 4.06 | 3.26 | 3.63 | *R* |
| 8 | α-**8a** | *S*-PEA | 1.30 | 1.32 | 4.02 | 4.06 | 4.03 | 3.58 | *S* |
| 9 | β-**8b-1** | *S*-PEA | 1.39 | 1.25 | 4.04 | 3.99 | 3.64 | 4.02 | *R* |
| 10 | β-**8b-2** | BHA | — | — | — | — | 3.79 | 3.86 | *R*[a] |
| 11 | α-**8c** | *S*-PEA | 1.35 | 1.33 | 4.06 | 4.04 | 3.59 | 4.04 | *R*[b] |

[a] Suggested configuration based on preferred *re*-face attack by $^-$CN in case galactal and β-D-galactosyl derivatives.
[b] Configuration confirmed by X-ray crystallography.

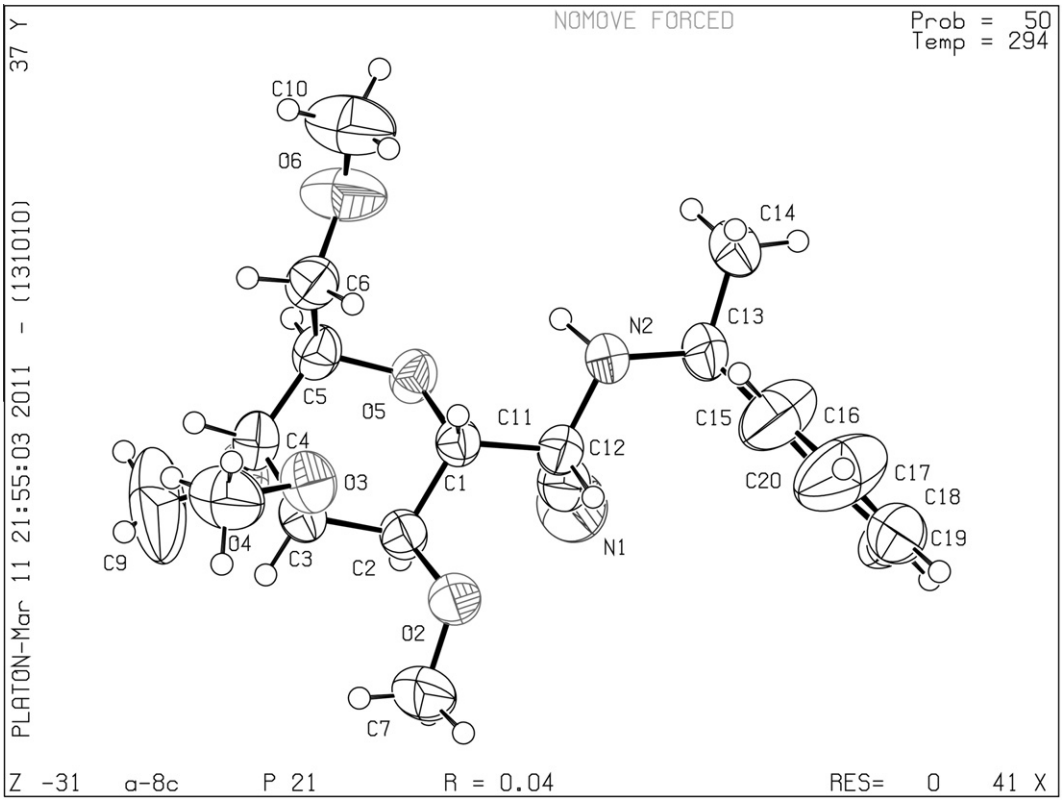
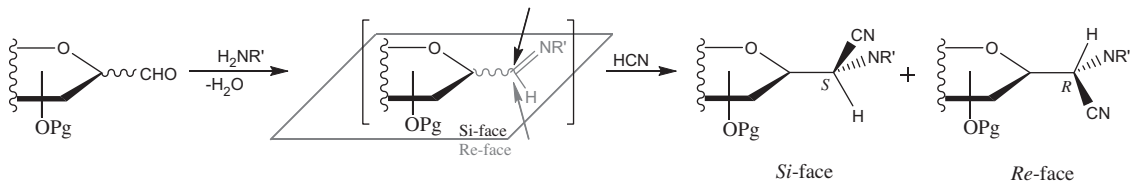



**Figure 1.** An ORTEP view of the *R*-diastereomer of aminoacetonitrile α-**8c**.

chiral amine in the major diastereomers.[28–30] In case of aminonitriles prepared from *C*-glycosyl aldehydes similar pattern was established using *S*-PEA chiral auxiliary except for α-**8a** (Table 2). Consistent differences in the range of 0.2–0.4 ppm were noticed. In asymmetric Strecker reaction with *S*-PEA and achiral aliphatic or substituted benzaldehydes *re*-face selectivity was observed.[28,31] *Re*-face addition of the cyano group to the prochiral center yields *R*-configured major product since the Cahn-Ingold-Prelog priority of C-1 (anomeric carbon) is higher than that of CN. NMR data suggest preferred *R*-configured new stereocenters in the major diastereomers of all *C*-glycosyl aminoacetonitriles except **8a**-α indicating a predominant *re*-face attack by the nucleophile (Scheme 2, Table 2). Employing *R*-PEA in the Strecker reaction with achiral aldehydes *si* selectivity was reported.[28] However, in case of **5b-2** using *R*-PEA the chemical shifts of the methine protons in the major and minor isomers appeared in a reversed order suggesting *R*-configured C-7 formed by *re*-face attack.

Lower dr values obtained with *R*-PEA as compared to *S*-PEA under the same conditions suggest that **2b** and *S*-PEA react in a matched pair reaction (Tables 1 and 3). This indicates that the asymmetric induction by the reacting sugar is dominant over the 1,3-asymmetric induction by the *R*-PEA. By the use of achiral amines (BA, BHA) the C-7 configuration was not predictable, however *re*-face control by the sugar strongly suggests the formation of *R*-diastereomers. The major products formed from β-deoxy-D-glycosyl aldehydes in highly diastereoselective CN addition possess *R*-configured new stereocenter (Table 2, entries 6 and 7). In the Strecker reaction with glucopyranosyl aldehyde α-**7a** CH proton of the new stereocenter in the major isomer appeared at a lower field than that in the minor isomer indicating *si*-face selectivity by the formation of *S*-configured major product (entry 8). With β-D-galactopyranosyl aldehyde β-**7b** and *S*-PEA the reaction provided predominantly *R*-configured product. *Re*-face selectivity was also observed in the reaction of dry HCN and imines prepared from pivaloyl-β-D-galactosylamine as chiral template and various achiral aldehydes in $CHCl_3$.[31] *Re*-face selectivities in Mannich- and Reformatsky-type reactions were also reported with β-linked sugar aldehydes and were explained by the polar Felkin–Ahn and Cram-chelate models.[32] The direction of the nucleophilic addition appears to be governed by the configuration of the anomeric carbon in case of β-linked sugars. Since the stereochemistry of the transition state is unknown according to the configuration of the major product a Felkin–Ahn selectivity can be presumed in most cases.




**Scheme 2.** Stereochemistry of the nucleophilic cyanide addition to the intermediate glycosyl imines.

**Table 3**
Diastereoselectivity of Strecker reaction depending on the chirality of the amine and the effect of thiourea bifunctional organocatalysts in the hydrocyanation of preformed imines

| Entry | Substrate | Amine (1 equiv) | HCN donor (1.25 equiv) | Catalyst (0.02 equiv) | Solvent | Product (C-7 config.) | Yield (%) | dr |
|---|---|---|---|---|---|---|---|---|
| 1 | **2b** | *S*-PEA | TMSCN | — | $CH_2Cl_2$ | **5b-1** (*R*) | 65 | 5.82 |
| 2 | **9b-1** | — | TMSCN | **10** | $CH_2Cl_2$ | **5b-1** (*R*) | 78 | 4.80 |
| 3 | **2b** | *R*-PEA | TMSCN | — | $CH_2Cl_2$ | **5b-2** (*R*) | 61 | 2.44 |
| 4 | **9b-2** | — | TMSCN | **10** | $CH_2Cl_2$ | **5b-2** (*R*) | 77 | 2.11 |
| 5 | **2b** | BA | TMSCN | — | $CH_2Cl_2$ | **5b-3** (*R*)[b] | 72 | 3.36 |
| 6 | **9b-3** | — | TMSCN | **11**[a] | $CH_2Cl_2$ | **5b-3** (*R*)[b] | 77 | 2.85 |

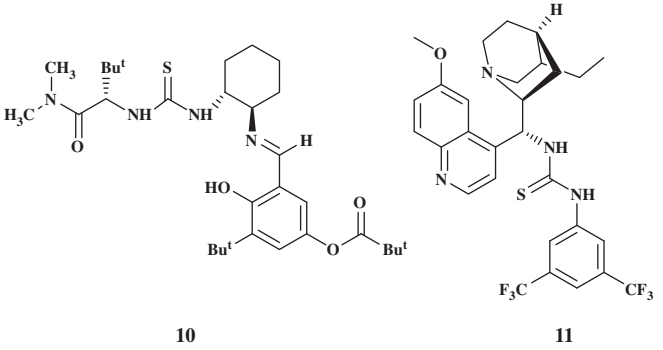
[a] 0.10 equiv of catalyst was used.
[b] Suggested configuration based on preferred *re*-face attack by $^{-}$CN.

## 2.4. Studies on double asymmetric induction and the use of organocatalysts to improve diastereoselectivities

In order to gain stereocontrol of the asymmetric Strecker reaction resulting *C*-glycosyl aminoacetonitriles we conducted experiments with chiral aldehyde **2b** and *S*- as well as *R*-PEA to reveal which is the matched and the mismatched pair in this asymmetric Strecker reaction (Scheme 1). Moreover, in order to improve diastereoselectivities, the hydrocyanation of previously unreported preformed glycosyl-imines (**9b-1**, **9b-2**, **9b-3**) was studied in the presence of thiourea organocatalysts (**10–11**, Schemes 3 and 4). The ability of thioureas to activate electrophiles such as imines bearing a wide variety of protecting groups has been demonstrated in several enantioselective C–C bond-forming reactions.[33]

In the reaction of **2b** with chiral amines and TMSCN predominantly *R*-configured products were obtained in both cases. Higher dr value was achieved with *S*-PEA (dr 5.82, Table 3, entry 1) than with *R*-PEA (dr 2.44, Table 3, entry 3) indicating that in the Strecker reaction **2b** and S-PEA react as a matched pair. It is noteworthy that employing TMSCN as cyanide donor resulted in higher diastereoselectivities as compared to reactions carried out with ACH (Table 1).The origin of the double asymmetric induction is presently unknown. With achiral benzylamine dr 3.66 was observed (Table 3, entry 5).

For studying thiourea organocatalysts preformed imines (**9b-1**, **9b-2**, **9b-3**) were prepared from 1-*C*-formyl-tri-*O*-benzyl-D-galactal **2b** employing stoichiometric amounts of *S*- or *R*-PEA as well as benzylamine in the presence of molecular sieves (Scheme 3). These glycal imines were unstable during column chromatography therefore used without purification in the aminonitrile formation. Nucleophilic HCN addition to these imines employing thiourea catalysts was performed in $CH_2Cl_2$ using a slight excess of TMSCN (Table 3, entries 2, 4 and 6). Thiourea **10** (Scheme 4) has been shown to promote proton transfer from HCN to imine to generate diastereomeric iminium/cyanide ion pair that are bound to the catalyst via multiple noncovalent interactions followed by a collapse of ion pairs resulting in (*R*)-α-aminonitrile products.[34] However, in our conditions this highly enantioselective catalyst showed no activity with either of *S*- or *R*-configured galactal imines and even lower dr values were found by the addition of the catalyst. In a literature example, by the use of chiral bicyclic guanidine catalyst in the hydrocyanation of imines from benzaldehyde and *S*-PEA and *R*-PEA greatly different *R*/*S* diastereoselectivities were obtained.[35]

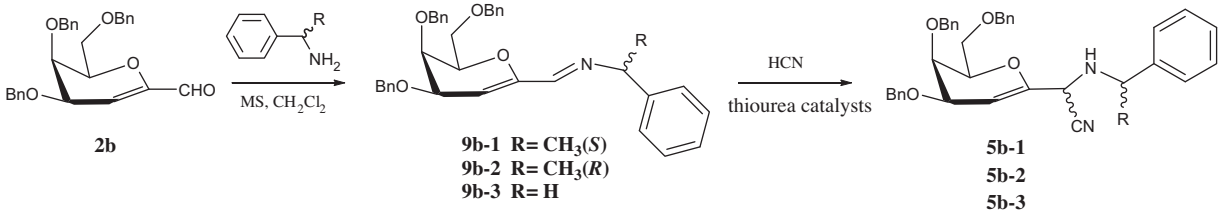



**Scheme 4.** Structure of thiourea organocatalysts.

The *R*/*S* dr value with the *S*-configured imine was 14.4 while with the *R*-imine was 1.38 indicating that the pre-transition state assembly of the catalyst and the *S*-imine favors for *re*-face attack by the cyanide leading to predominant *R*-enantiomer. The ineffectiveness of thiourea **10** in our case may be explained by the lack of interaction between the sugar imine and the catalyst. The cinchona-based thiourea catalyst **11** (Scheme 4) successfully applied in a Michael addition reaction[36] was also ineffective in the hydrocyanation of the imine prepared from the galactal aldehyde **2b** and benzylamine. Nevertheless **11** contains no amide moiety which in addition to the thiourea moiety of **11** actively participates in the stabilization of the iminium ion by hydrogen bonding.[34]

## 3. Conclusions

In summary, synthesis and structure elucidation of new 2-amino-2-*C*-D-glycosyl-acetonitriles in a Strecker reaction from various *C*-glycosyl aldehydes, chiral amines, and HCN were carried out. While aminonitriles from glycal and 2-deoxy-β-glycosyl aldehydes were prepared in satisfactory yields, lower yields were obtained with *C*-glycosyl aldehydes due to the decomposition of these aldehydes by β-elimination. In the reactions from 1-*C*-formyl-galactal improved stereoselectivities were noticed when ACH was replaced with TMSCN. The configurations of the major and minor diastereomeric products were assigned based on the $^1$H NMR chemical shifts of methine protons (H-7) at the new stereocenter. Strecker reaction with the benzyl-protected 1-*C*-formyl-D-galactal and *S*-PEA or *R*-PEA




**Scheme 3.** Preparation of D-galactal-linked α-aminonitriles via preformed galactal imines.

yielded predominantly the *R*-configured *C*-glycosyl aminoacetonitrile via *re*-face nucleophilic addition of HCN in both cases. Since higher dr values were obtained with *S*-PEA as compared to *R*-PEA, we can conclude that the aminonitrile formation from the 1-*C*-formyl-D-galactal derivative, *S*-PEA and TMSCN takes place in a matched pair reaction. Diastereoselectivity of the reaction from preformed imines prepared from galactal aldehyde was not influenced by the use of thiourea organocatalysts. The direction of the nucleophilic addition appears to be governed by the configuration of the anomeric carbon with β-linked sugars. Since the stereochemistry of the transition state is unknown according to the configuration of the major product a Felkin–Ahn selectivity can be presumed in most cases.

In order to improve stereoselectivity of the Strecker reaction the complex-forming ability of carbohydrates can be exploited. Coordination of Lewis acids to glycosyl imines formed from glycosyl amines has been found to have strong influence on the stereodifferentiation in the nucleophilic cyanide addition.[37] Further studies on applying Lewis acid catalysts in asymmetric Strecker reaction will be performed.

## 4. Experimental

### 4.1. General methods

All chemicals and solvents were purchased from Sigma–Aldrich Kft. (Budapest, Hungary). TLC aluminum sheets (Silica Gel 60 $F_{254}$, 0.2 mm layer thickness) for following the proceeding of the reactions and silica gel for column chromatography (Silica Gel 60, 0.040–0.063 mm) was from Merck Kft. (Budapest, Hungary). Spots of compounds were visualized under UV light or heating the plates after immersion in 5% (v/v) $H_2SO_4$ in EtOH or 0.4% (w/v) 2,4-dinitrophenylhydrazine in 2 N HCl or 0.2% (w/v) ninhydrin in EtOH. Melting points were determined by a Boetius PHMK05 melting point apparatus (MLW, Dresden, Germany) and are uncorrected. The NMR spectra were recorded with Varian Gemini-3000 (300 MHz for $^1$H and 75 MHz for $^{13}$C) spectrometer (Varian Inc., Palo Alto, CA, USA). Mass spectrometric measurements were run on an Applied Biosystems 3200QTrap hybrid mass spectrometer in electrospray ionization mode. Optical rotations were measured using an Optical Activity AA-10R polarimeter (Optical Activity Ltd, Ramsey, UK) at 20 °C.

### 4.2. General procedure for the preparation of 1-formyl-3,4,6-tri-*O*-benzyl-D-glycals (2a–b) and 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glycopyranosyl formaldehydes (4a–b) and 2,3,4,6-tetra-*O*-benzyl/methyl-α/β-D-glycopyranosyl formaldehydes (α-7a, β-7b, α-7c)

A mixture of pyridine (4 ml), acetic acid (4 ml) and water (4 ml) was added to the respective nitrile **1a–b**, **3a–b** (1 mmol) in a pressure bottle and placed in an ice-bath. Sodium hypophosphite (10 mmol) then Raney-nickel (6 ml, 10% w/v in water) was added and the mixture was shaken for 3 h at room temperature. The reaction mixture was filtered and the filtrate was diluted with dichloromethane and washed successively with saturated sodium hydrocarbonate solution, 1 N HCl and again using saturated sodium hydrocarbonate solution. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel with hexanes–EtOAc (8:2 for **2a**–**b** and 6:4 for **4a–b**) eluent to afford the corresponding aldehyde.

#### 4.2.1. 1-Formyl-3,4,6-tri-*O*-benzyl-D-glucal (2a)

Compound **2a** was obtained from **1a**[15] as colorless syrup; yield 52%. $[\alpha]_D^{20}$ −23.90 (*c* 0.50, $CHCl_3$); $R_f$ = 0.20 (hexanes–EtOAc, 85:15); $^1$H NMR (400 MHz, $CDCl_3$), δ ppm: 3.85 (m, 2H, H-6′, H-6″), 3.99 (dd, *J* = 8.7, 6.4 Hz, 1H, H-4), 4.16 (m, 1H, H-5), 4.27 (dd, *J* = 6.4, 2.7 Hz, 1H, H-3), 4.50–4.80 (m, 6H, $PhCH_2$), 5.82 (d, *J* = 2.7 Hz, 1H, H-2), 7.19–7.36 (m, 15H, Ph), 9.21 (s, 1H, CHO); $^{13}$C NMR (75 MHz, $CDCl_3$), δ (ppm): 68.0 (C-6), 71.8 ($PhCH_2$), 73.8 ($PhCH_2$), 73.9 (C-4), 74.3 ($PhCH_2$), 75.9 (C-3), 77.90 (C-5), 117.3 (C-2), 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 128.7, 128.8 (Ph-CH), 137.9, 138.1, 138.2 (Ph-Cq), 151.8 (C-1), 186.4 (CHO); MS (ESI): *m/z* = 467.4 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{28}O_5$: C, 75.65; H, 6.35. Found: C, 75.74; H, 6.29.

#### 4.2.2. 1-Formyl-3,4,6-tri-*O*-benzyl-D-galactal (2b)

Compound **2b** was obtained from **1b**[15] as colorless syrup; yield 63%. $[\alpha]_D^{20}$ −84.0 (*c* 1.10, $CHCl_3$); $R_f$ = 0.15 (hexanes–EtOAc, 8:2); $^1$H NMR (400 MHz, $CDCl_3$), δ (ppm): 3.75 (m, 2H, H-6′, H-6″), 4.10 (dd, *J* = 3.5, 2.2 Hz, 1H, H-3), 4.17 (ddd, *J* = 7.6, 6.0, 1.0 Hz, 1H, H-5), 4.41 (m, 1H, H-4), 4.30–5.00 (m, 6H, $PhCH_2$), 5.81 (dd, *J* = 2.2, 2.0 Hz, 1H, H-2), 7.20–7.40 (m, 15H, Ph), 9.16 (s, 1H, CHO); $^{13}$C NMR (100 MHz, $CDCl_3$), δ (ppm): 67.7 (C-6), 69.5 (C-4), 71.6 ($PhCH_2$), 73.0 (C-3), 73.8 ($PhCH_2$), 74.6 ($PhCH_2$), 76.8 (C-5), 119.3 (C-2), 127.8, 128.0, 128.1, 128.2, 128.3, 128.6, 128.7, 128.8 (Ph-CH), 137.8, 137.9, 138.4 (Ph-Cq), 151.6 (C-1), 186.3 (CHO); MS (ESI): *m/z* = 467.4 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{28}O_5$: C, 75.65; H, 6.35. Found: C, 75.81; H, 6.21.

#### 4.2.3. 3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl formaldehyde (4a)

Compound **4a** was obtained from **3a**[15] as colorless syrup; yield 59%. $[\alpha]_D^{20}$ +17.0 (*c* 0.94, $CHCl_3$); $R_f$ = 0.15 (hexanes–EtOAc, 6:4); $^1$H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.50 (ddd, *J* = 13.0, 11.7, 11.0 Hz, 1H, H-2ax), 2.39 (ddd, *J* = 13.0, 4.7, 2.2 Hz, 1H, H-2eq), 3.41–3.82 (m, 6H, H-1, H-3, H-4, H-5, H-6′, H-6″), 4.42–4.93 (m, 6H, $PhCH_2$), 7.17–7.34 (m, 15H, Ph), 9.70 (s, 1H, CHO); $^{13}$C NMR (75 MHz, $CDCl_3$), δ (ppm): 29.7 (C-2), 69.1 (C-6), 71.4 ($PhCH_2$), 73.6 ($PhCH_2$), 75.2 ($PhCH_2$), 77.7 (C–H), 79.1 (C-H), 79.4 (C–H), 80.3 (C–H), 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 138.4, 128.4, 128.5 (Ph-CH), 137.9, 138.1, 138.2 (Ph-$C_q$), 200.8 (CHO); MS (ESI): *m/z* = 469.4 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.54; H, 6.59.

#### 4.2.4. 3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-galactopyranosyl formaldehyde (4b)

Compound **4b** was obtained from **3b**[15] as colorless syrup; yield 53%. $[\alpha]_D^{20}$ +5.50 (*c* 0.37, $CHCl_3$); $R_f$ = 0.27 (hexanes–EtOAc, 6:4); $^1$H NMR (300 MHz, $CDCl_3$), δ (ppm) 1.99 (m, 1H, H-2′), 2.11 (m, 1H, 1H, H-2″), 3.59 (m, 2H, H-6′, H-6″), 3.60 (m, 1H, CH), 3.62 (m, 1H, CH), 3.80 (m, 1H, 1H, CH), 3.86 (m, 1H, CH), 4.41–4.96 (m, 6H, $PhCH_2$), 7.18–7.39 (m, 15H, Ph), 9.68 (s, 1H, CHO); $^{13}$C NMR (75 MHz, $CDCl_3$), δ (ppm) 27.4 (C-2), 69.8 (C-6), 70.5 ($PhCH_2$), 72.9 (C-4), 73.9 ($PhCH_2$), 74.7 ($PhCH_2$), 78.1 (CH), 78.2 (C-5), 80.3 (CH), 127.5, 127.6, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, (Ph-CH), 138.1, 138.3, 138.8 (Ph-$C_q$), 201.4 (CHO); MS (ESI): *m/z* = 469.4 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.57; H, 6.56.

#### 4.2.5. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl formaldehyde (α-7a)

Compound α-**7a** was prepared from perbenzylated D-gluconolactone according to an established literature method.[21] $R_f$ = 0.18 (hexanes–EtOAc, 6:4); $^1$H NMR spectrum was identical with the reported one. MS (ESI): *m/z* 553.4 $[M+H]^+$. Anal. Calcd for $C_{35}H_{36}O_6$: C, 76.06; H, 6.57. Found: C, 76.27; H, 6.51.

#### 4.2.6. 2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl formaldehyde (β-7b)

Compound β-**7b** was prepared from perbenzylated D-galactonolactone according to an established literature method.[21] $R_f$ = 0.17 (hexanes–EtOAc, 6:4); $^1$H NMR (300 MHz, $CDCl_3$), δ (ppm) 3.50–3.65 (m, 3H, H-5, H-6′, H-6″), 3.66 (dd, 1H, $J_{3,4}$ = 2.7 Hz, H-3),

3.75 (dd, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 3.98 (d, 1H, H-4), 4.05 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.42–4.99 (m, 8H, $PhCH_2$), 7.03–7.41 (m, 20H, Ph), 9.64 (d, 1H, $J$ = 1.4 Hz, CHO); MS (ESI): $m/z$ 585.4 $[M+Na]^+$. Anal. Calcd for $C_{35}H_{36}O_6$: C, 76.06; H, 6.57. Found: C, 76.19; H, 6.53.

#### 4.2.7. 2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranosyl formaldehyde (α-7c)

Compound α-**7c** was prepared from permethyl D-mannonolactone according to an established literature method.[21] $R_f$ 0.14 (hexanes–EtOAc, 1:1); $^1$H NMR ($CDCl_3$), $\delta$ ppm 3.07 (dd, 1H, $J_{3,4}$ 9.0 Hz, H-3), 3.39 (dd, 1H, $J_{4,5}$ 8.8 Hz, H-4), 3.38, 3.42, 3.44, 3.46 (s, 12H, $CH_3$), 3.53 (m, 1H, H-5), 3.58 (dd, 1H, $J_{5,6}$ = 5.2 Hz, $J_{6',6''}$ 9.9 Hz, H-6′), 3.63 (dd, 1H, $J_{5,6''}$ 1.6 Hz, H-6″), 3.98 (dd, 1H, $J_{2,3}$ = 3.3 Hz, H-2), 4.39 (d, 1H, $J_{1,2}$ = 2.8 Hz, H-1), 9.87 (s, 1H, CHO); $^{13}$C NMR ($CDCl_3$), $\delta$ (ppm) 57.6, 58.1, 59.2, 60.6 ($CH_3$), 71.8 (C-6), 74.9 (C-2), 75.6 (C-4), 76.9 (C-5), 79.1 (C-1), 81.6 (C-3), 202.90 (CHO); MS (ESI): $m/z$ 271.4 $[M+Na]^+$. Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12. Found: C, 53.37; H, 8.04.

### 4.3. General procedure for the preparation of *C*-glycosyl aminoacetonitriles 5a–b, 6a–b and 8a–c

*Method A:* To a solution of the aldehydes (**2a–b**, **4b**, α-**7a** and α-**7c**) (0.5 mmol in 6 ml of solvent as specified in Table 1) was added molecular sieves (100 mg) and the respective amine at ice-bath temperature under nitrogen and the mixture was stirred for 1 h. To this solution was added acetone cyanohydrin then $Et_3N$ (0.1 M equiv of the cyanohydrin) and the solution was stirred at 0 °C for 1 h followed by stirring at room temperature overnight. The reaction was filtered through Celite and the solvents were removed in vacuum. The resulting residue was purified by silica gel column chromatography using hexanes–EtOAc eluents.

*Method B:* To a solution of the aldehydes (**2b**, **4a** and β-**7b**) (0.5 mmol in 6 ml of $CH_2Cl_2$) was added molecular sieves (100 mg) and the respective amine at ice-bath temperature under nitrogen and the mixture was stirred for 1 h. In a teflon-capped reaction vial equipped with stir bar methanol (same molar equivalent as TMSCN) was added to a solution of TMSCN in dry $CH_2Cl_2$ (1 ml). The solution was allowed to stir for 1 h at ice-bath temperature and then added to the reaction flask by slow syringe addition. After 1 h at 0 °C the reaction was allowed to warm to room temperature and was stirred overnight. The work-up and isolation of the product were the same as described in Method A.

*Method C:* To a solution of β-**7b** (0.5 mmol in 4 ml of $CH_2Cl_2$) was added molecular sieves (100 mg) and the respective amine at ice-bath temperature under nitrogen and the mixture was stirred for 1 h. To this solution was added dropwise the methanol (3 ml) solution of NaCN (1.5 mmol) and $NH_4Br$ (1.5 mmol). After the addition the mixture was stirred at 0 °C for 1 h followed by stirring at room temperature overnight. The work-up and isolation of the product were the same as described in Method A.

#### 4.3.1. Determination of diastereomeric ratios from NMR spectra

The assignment of the diastereomers was performed by $^1$H–$^{13}$C heterocorrelation (HSQC, HMBC) measurements. In contrast to the H-7 proton shifts, the C-7 carbon shifts were not remarkably influenced by the stereochemistry (*R* or *S* configuration) in the two diastereomers. The two H-7,C-7 cross-peaks at ~50 ppm carbon shift in the HSQC spectrum of the diastereomeric mixtures provided the basis for the differentiation of the two stereoisomers.

#### 4.3.2. (*S*/*R*)-2-((S)-Phenylethylamino)-2-*C*-(3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranosyl)acetonitrile (5a)

Compound **5a** was obtained as from **2a** colorless syrup by Method A; yield 33%, dr = 1.44 in $CH_3CN$ and 43%, dr = 1.24 in $CH_2Cl_2$. $R_f$ = 0.21 (hexanes–EtOAc, 8:2) for both diastereomers. Major diastereomer (*R* at C-7): $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm): 1.36 (d, $J$ = 6.3 Hz, 3H, H-9), 3.78 (m, 1H, H6′), 3.81 (s, 1H, H-7), 3.84 (m, 1H, H-6″), 3.89 (m, 1H, H-5), 4.10 (q, $J$ = 6.3 Hz, 1H, H-8), 4.16 (m, 1H, H-4), 4.19 (m, 1H, H-3), 4.50–4.90 (m, 6H, $PhCH_2$), 5.12 (d, $J$ = 3.0 Hz, 1H, H-2), 7.18–7.42 (m, 20H, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm): 24.7 (C-9), 50.8 (C-7), 56.3 (C-8), 68.1 (C-6), 71.0 ($PhCH_2$), 73.5 ($PhCH_2$), 73.8 ($PhCH_2$), 74.4 (C-5), 75.9 (C-3), 78.2 (C-4), 99.3 (C-2), 117.6 (CN), 127.2, 127.4, 127.8, 127.9, 128.0, 128.07, 128.2, 128.5, 128.6, 128.7, 128.9, 129.0 (Ph-CH), 138.2, 138.4, 138.5, 143.1 (Ph-Cq), 148.0 (C-1). Minor diastereomer (*S* at C-7): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 1.31 (d, $J$ = 6.3 Hz, 3H, H-9), 3.75 (m, 2H, H-6′, H-6″), 3.97 (q, $J$ = 6.3 Hz, 1H, H-8), 4.04 (s, 1H, H-7), 4.12 (m, 1H, CH), 4.18 (m, 1H, CH), 4.24 (m, 1H, CH), 4.50–4.90 (m, 6H, $PhCH_2$), 5.02 (d, $J$ = 3.0 Hz, 1H, H-2), 7.18–7.42 (m, 20H, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm): 23.4 (C-9), 50.3 (C-7), 55.6 (C-8), 68.0 (C-6), 71.2, 71.3, 71.6, 73.5, 73.8, 76.8, 99.7 (C-2), 117.7 (CN), 127.2, 127.4, 127.8, 127.9, 128.0, 128.1, 128.2, 128.6, 128.7, 128.9, 129.0 (Ph-CH), 138.4, 138.5, 143.9 (Ph-Cq), 148.2 (C-1); MS (ESI): $m/z$ = 575.1 $[M+H]^+$. Anal. Calcd for $C_{37}H_{38}N_2O_4$: C, 77.33; H, 6.66; N, 4.87. Found: C, 77.51; H, 6.50; N, 4.94.

#### 4.3.3. (*S*/*R*)-2-((S)-Phenylethylamino)-2-*C*-(3,4,6-tri-*O*-benzyl-2-deoxy-D-*lyxo*-hex-1-enopyranosyl) acetonitrile (5b-1)

Compound **5b-1** was obtained from **2b** as colorless syrup by Method A (in $CH_2Cl_2$, 73%, dr = 3.0) or B (65%, dr = 5.82). $R_f$ = 0.22 (hexanes–EtOAc, 8:2) for both diastereomers. Major diastereomer (*R* at C-7): $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm): 1.36 (d, $J$ = 6.3 Hz, 1H, H-9), 3.76 (m, 3H, H-6′, H-6″, H-7), 3.97 (m, 1H, H-4), 4.05 (q, $J$ = 6.3 Hz, 1H, H-8), 4.16 (t, $J$ = 2.7 Hz, 1H, H-3), 4.28 (ddd, $J$ = 6.7, 6,6, 1,0 Hz, 1H, H5), 4.42–4.89 (m, 6H, $PhCH_2$), 5.08 (d, $J$ = 2.7 Hz, 1H, H-2), 7.18–7.42 (m, 20H, Ph). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 24.7 (C-9), 50.8 (C-7), 56.3 (C-8), 68.0 (C-6), 71.2 (C-3), 71.3 (C-4), 71.6 ($PhCH_2$), 73.5 ($PhCH_2$), 73.7 ($PhCH_2$), 76.9 (C-5), 99.3 (C-2), 117.6 (CN), 127.2, 127.4, 127.8, 127.9, 128.0, 128.1, 128.2, 128.6, 128.7, 128.9, 129.0 (Ph-CH), 138.2, 138.4, 138.5, 143.1 (Ph-Cq), 148.0 (C-1). Minor diastereomer (*S* at C-7): $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm): 1.31 (d, $J$ = 6.3 Hz, 3H, H-9), 3.75 (m, 2H, H-6′, H-6″), 3.97 (q, $J$ = 6.3 Hz, 1H, H-8), 3.99 (m, 1H, H-4), 4.01 (s, 1H, H-7), 4.18 (t, $J$ = 3.0 Hz, 1H, H-3), 4.28 (m, 1H, H-5), 4.40–4.90 (m, 6H, $PhCH_2$), 5.07 (d, $J$ = 3.0 Hz, 1H, H-2), 7.18–7.42 (m, 20H, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm): 23.3 (C-9), 50.4 (C-7), 56.0 (C-8), 68.1 (C-6), 71.2 (C-3), 71.3 (C-4), 71.6 ($PhCH_2$), 73.5 ($PhCH_2$), 73.8 ($PhCH_2$), 76.8 (C-5), 99.7 (C-2), 117.7 (CN), 127.2, 127.4, 127.8, 127.9, 128.0, 128.2, 128.6, 128.7, 128.9, 129.0 (Ph-CH), 138.4, 138.5, 138.6, 144.0 (Ph-Cq), 148.12 (C-1); MS (ESI): $m/z$ = 575.4 $[M+H]^+$. Anal. Calcd for $C_{37}H_{38}N_2O_4$: C, 77.33; H, 6.66; N, 4.87. Found: C, 77.53; H, 6.56; N, 4.75.

#### 4.3.4. (*S*/*R*)-2-((*R*)-Phenylethylamino)-2-*C*-(3,4,6-tri-*O*-benzyl-2-deoxy-D-*lyxo*-hex-1-enopyranosyl) acetonitrile (5b-2)

Compound **5b-2** was obtained from **2b** as colorless syrup by Method A (in $CH_2Cl_2$ 67%, dr = 2.06) or B (61%, dr = 2.44). $R_f$ = 0.22 (hexanes–EtOAc, 8:2) for both diastereomers. Major diastereomer (*R* at C-7): $^1$H NMR (300 MHz, $CDCl_3$), $\delta$ ppm: 1.19 (d, $J$ = 6.6 Hz, 3H, H-9), 3.78 (m, 2H, H-6′, H-6″), 3.86 (s, 1H, H-7), 3.89 (q, $J$ = 6.6 Hz, 1H, H-8), 3.97 (m, 1H, CH), 4.12 (t, $J$ = 3.0 Hz, 1H, CH), 4.18 (m, 1H, CH), 4.41–4.94 (m, 6H, $PhCH_2$), 4.81 (m, 1H, H-2), 7.18–7.42 (m, 20H, Ph); $^{13}$C NMR (75 MHz, $CDCl_3$), $\delta$ ppm: 24.2 (C-9), 50.4 (C-7), 55.1 (C-8), 67.9 (C-6), 71.0 (CH), 71.3 ($PhCH_2$), 71.8 (CH), 73.7 ($PhCH_2$), 73.9 ($PhCH_2$), 76.5 (CH), 101.1 (C-2), 117.9 (CN), 127.4, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, (Ph-CH), 138.1, 138.4, 138.7, 143.8 (Ph-$C_q$), 146.6 (C-1). Minor diastereomer (*S* at C-7): $^1$H NMR (300 MHz, $CDCl_3$), $\delta$ (ppm) 1.38 (d, $J$ = 6.6 Hz, 3H, H-9), 3.75 (s,

1H, H-7), 3.76 (m, 2H, H-6′, H-6″), 3.97 (m, 1H, CH), 4.07 (q, $J$ = 6.6 Hz, 1H, H-8), 4.13 (m, 1H, CH), 4.31 (m, 1H, CH), 4.41–4.94 (m, 6H, $PhCH_2$), 5.05 (d, $J$ = 3.3 Hz, 1H, H-2), 7.18–7.42 (m, 20H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm) 24.9 (C-9), 51.0 (C-7), 56.4 (C-8), 68.0 (C-6), 70.6 (CH), 71.4 ($PhCH_2$), 71.6 (CH), 73.8 ($PhCH_2$), 73.82 ($PhCH_2$), 76.8 (CH), 99.3 (C-2), 117.4 (CN), 127.7, 127.74, 127.9, 127.97, 128.0, 128.1, 128.2, 128.4, 128.6, 128.64, 128.7, 128.74 (Ph-CH), 138.2, 138.4, 138.6, 142.9 (Ph-$C_q$), 148.0 (C-1); MS (ESI): $m/z$ = 575.4 $[M+H]^+$. Anal. Calcd for $C_{37}H_{38}N_2O_4$: C, 77.33; H, 6.66; N, 4.87. Found: C, 77.44; H, 6.58; N, 4.91.

#### 4.3.5. (*S*/*R*)-2-(Benzylamino)-2-*C*-(3,4,6-tri-*O*-benzyl-2-deoxy-D-*lyxo*-hex-1-enopyranosyl) acetonitrile (5b-3)

Compound **5b-3** was obtained as colorless from **2b** syrup by Method A (in $CH_2Cl_2$ 69%, dr = 2.78) or B (72%, dr = 3.36). $R_f$ = 0.27 (hexanes–EtOAc, 7:3) for both diastereomers. Major diastereomer (assigned *R* at C-7): $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ ppm: 3.76 (m, 2H, H-6′, H-6″), 3.82 (m, 1H, H-8′), 3.87 (s, 1H, H-7), 3.98 (m, 1H, CH), 4.06 (m, 1H, H-8″), 4.18 (m, 1H, CH), 4.25 (t, $J$ = 6.0 Hz, 1H, CH), 4.40–4.89 (m, 6H, $PhCH_2$), 5.10 (d, $J$ = 2.4 Hz, 1H, H-2), 7.19–7.41 (m, 20H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm) 50.6 (C-8), 51.6 (C-7), 67.7 (C-6), 70.6 (CH), 71.1 (CH), 71.2 ($PhCH_2$), 73.4 ($PhCH_2$), 73.5 ($PhCH_2$), 76.6 (CH), 100.1 (C-2), 117.1 (CN), 127.4, 127.7, 127.8, 127.9, 127.94, 127.98, 128.1, 128.3, 128.4, 128.42, 128.47, 128.5, 128.7 (Ph-CH), 137.8, 138.0, 138.1, 138.2 (Ph-$C_q$), 147.0 (C-1). Minor diasteromer (assigned *S* at C-7): $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm) 3.76 (m, 2H, H-6′, H-6″), 3.80 (m, 1H, H-8′), 3.91 (s, 1H, H-7), 3.95 (m, 1H, CH), 4.09 (m, 1H, H-8″), 4.20 (m, 1H, CH), 4.28 (m, 1H, CH), 4.40–4.94 (m, 6H, $PhCH_2$), 5.19 (d, $J$ = 2.4 Hz, 1H, H-2), 7.19–7.41 (m, 20H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm) 50.6 ($PhCH_2N$), 51.7 (C-7), 67.8 (C-6), 70.8 (CH), 71.2 (CH), 71.3 ($PhCH_2$), 73.34 ($PhCH_2$), 73.5 ($PhCH_2$), 76.7 (CH), 99.5 (C-2), 117.1(CN), 127.4, 127.7, 127.77, 127.9, 127.94, 127.98, 128.1, 128.3, 128.4, 128.42, 128.47, 128.5, 128.7 (Ph-CH),137.8, 138.0, 138.1, 138.2, (Ph-$C_q$), 147.2 (C-1); MS (ESI): $m/z$ = 561.8 $[M+H]^+$. Anal. Calcd for $C_{36}H_{36}N_2O_4$: C, 77.12; H, 6.47; N, 5.00. Found: C, 77.31; H, 6.55; N, 4.93.

#### 4.3.6. (*S*/*R*)-2-[(*S*)-Phenylethylamino]-2-*C*-(3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl) acetonitrile (6a)

Compound **6a** was obtained from **4a** as colorless syrup by Method B; yield 65%; dr = 8.25. $R_f$ = 0.60 (hexanes–EtOAc, 1:1) for both diastereomers. Major diastereomer (*R* at C-7): $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ (ppm) 1.38 (d, $J$ = 6.6 Hz, 3H, H-9), 1.80 (br s, 1H, NH), 1.93 (ddd, $J$ = 12.6, 11.5, 10.9 Hz, 1H, H2′), 2.02 (ddd, $J$ = 12.6, 5.2, 2.7 Hz, 1H, H2″), 3.29 (d, $J$ = 3.3 Hz, 1H, H-7), 3.43 (dt, $J$ = 9.3, 3.0 Hz, 1H, H-5), 3.48–3.70 (m, 3H, H-1, H-3, H-4), 3.74 (m, 2H, H-6′, H-6″), 4.05 (q, $J$ = 6.6 Hz, 1H, H-8), 4.50–4.92 (m, 6H, $PhCH_2$), 7.18–7.38 (m, 20H, Ph); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ (ppm): 24.9 (C-9), 32.3 (C-2), 52.0 (C-7), 56.3 (CH, C-8), 69.2 (C-6), 71.7 ($PhCH_2$), 73.4 ($PhCH_2$), 74.7 (CH), 75.1 ($PhCH_2$), 77.9 (CH), 79.3 (C-5), 80.3 (CH), 118.5 (CN), 126.9, 127.5, 127.7, 128.3, 128.4, 128.8 (Ph-CH), 138.3, 138.4, 143.1 (Ph-$C_q$). Minor diasteromer (*S* at C-7): $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ (ppm): 1.34 (d, $J$ = 6.6 Hz, 3H, H-9), 1.71 (m, 1H, H-2′), 2.22 (m, 1H, H-2″), 3.38–3.82 (m, 6H, CH), 3.69 (m,1H, H7), 4.06 (q, $J$ = 6.6 Hz, 1H, H-8), 4.50–4.92 (m, 6H, $PhCH_2$), 7.18–7.38 (m, 20H, Ph); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ ppm: 22.1 (C-9), 33.9 (C-2), 53.0 (C-7), 55.9 (C-8), 68.9 (C-6), 71.8 ($PhCH_2$), 73.1 ($PhCH_2$), 74.8 (CH), 75.2 ($PhCH_2$), 77.9 (CH), 79.3 (CH), 80.4 (CH), 117.6 (CN), 126.6, 126.7, 127.2, 127.8, 128.1, 128.7 (Ph-CH), 138.1, 138.3, 144.4 (Ph-$C_q$); MS (ESI): $m/z$ = 577.5 $[M+H]^+$. Anal. Calcd for $C_{36}H_{38}N_2O_4$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.01; H, 6.75; N, 4.87.

#### 4.3.7. (*S*/*R*)-2-[(*S*)-Phenylethylamino]-2-*C*-(3,4,6-tri-*O*-benzyl-2-deoxy-β-D-galactopyranosyl) acetonitrile (6b)

Compound **6b** was obtained from **4b** as colorless syrup by Method A; in THF yield 62%; dr = 5.17. $R_f$ = 0.41 (hexanes–EtOAc, 7:3) for both diastereomers. Major diastereomer (*R* at C-7): $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ ppm: 1.38 (d, $J$ = 6.3 Hz, 3H, H-9), 1.66 (m, 1H, H-2′), 2.45 (ddd, $J$ = 12.0, 12.0, 11.8 Hz, 1H, H-2″), 3.26 (d, $J$ = 3.6 Hz, 1H, H-7), 3.49–3.70 (m, 4H, CH, H-6′, H-6″), 3.90 (m, 1H, CH), 4.04 (q, $J$ = 6.3 Hz, 1H, H-8), 4.40–5.00 (m, 6H, $PhCH_2$), 7.19–7.39 (m, 20H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ ppm: 25.2 (C-9), 28.5 (C-2), 52.5 (C-7), 56.4 (C-8), 69.2 (C-6), 70.5 ($PhCH_2$), 72.3 (CH), 73.7 ($PhCH_2$), 74.3 ($PhCH_2$), 75.8 (CH), 78.1 (CH), 78.3 (CH), 118.8 (CN), 127.2, 127.6, 127.8, 127.9, 128.1, 128.4, 128.7, 129.0 (Ph-CH), 138.2, 138.4, 139.3, 143.6 (Ph-$C_q$). Minor diasteromer (*S* at C-7): $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ ppm: 1.33 (d, $J$ = 6.6 Hz, 3H, H-9), 1.99 (m, 1H, H-2), 2.15 (ddd, $J$ = 12.0, 12.0, 11.8 Hz, 1H, H-2′), 3.63 (m, 1H, H-7), 3.49–3.71 (m, 4H, CH, H-6′, H-6″), 3.90 (m, 1H, CH), 4.06 (q, $J$ = 6.6 Hz, 1H, H-8), 4.40–4.97 (m, 6H, $PhCH_2$), 7.20–7.40 (m, 20H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ ppm: 22.3 (C-9), 29.9 (C-2), 53.3 (C-7), 56.2 (C-8), 69.2 (C-6), 70.5 ($PhCH_2$), 72.6 (CH), 73.7 ($PhCH_2$), 74.3 ($PhCH_2$), 75.6 (CH), 77.3 (CH), 78.4 (CH), 118.8 (CN), 127.1, 127.6, 127.8, 127.9, 128.1, 128.4, 128.7, 128.7, 128.9 (Ph-CH), 138.2, 138.4, 139.1, 144.7 (Ph-$C_q$); MS (ESI): $m/z$ = 577.1 $[M+H]^+$. Anal. Calcd for $C_{36}H_{38}N_2O_4$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.93; H, 6.72; N, 4.91.

#### 4.3.8. (*S*/*R*)-2-((S)-Phenylethylamino)-2-*C*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)acetonitrile (α-8a)

Compound **α-8a** was obtained from **α-8a** as colorless syrup by Method A; in $CH_3CN$ yield 42%; dr = 1.35. Major diastereomer (*S* at C-7): $[\alpha]_D^{20}$ +12.6 (*c* 0.95, $CHCl_3$); $R_f$ = 0.18 (hexanes–EtOAc, 8:2); $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm): 1.30 (d, $J$ = 6.3 Hz, 3H, H-9), 3.56 (m, 1H, CH), 3.63 (m, 2H, H-6′, H-6″), 3.88 (m, 3H, CH), 4.02 (q, $J$ = 6.3 Hz, 1H, H-8), 4.03 (d, $J$ = 8.4 Hz, 1H, H-7), 4.22 (dd, $J$ = 8.4, 3.0 Hz, 1H, H-1), 4.42–4.76 (m, 8H, $PhCH_2$), 7.08–7.40 (m, 25H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm) 22.7 (C-9), 48.2 (C-7), 57.2 (C-8), 69.1 (C-6), 73.1 (C-1), 73.7 ($PhCH_2$), 73.9 ($PhCH_2$), 74.0 (CH), 74.1 ($PhCH_2$), 74.3 ($PhCH_2$), 76.5 (CH), 77.1 (CH), 79.1 (CH), 119.2 (CN), 127.1, 127.7, 128.1, 128.2, 128.3, 128.5, 128.7, 128.9 (Ph-CH), 137.5, 138.1, 138.3, 138.5, 144.7 (Ph-$C_q$); MS (ESI): $m/z$ = 683.6 $[M+H]^+$. Anal. Calcd for $C_{44}H_{46}N_2O_5$: C, 77.39; H, 6.79; N, 4.10. Found: C, 77.58; H, 6.68; N, 4.08. Minor diastereomer (*R* at C-7): $R_f$ = 0.20 (hexanes–EtOAc, 8:2).$^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm): 1.32 (d, 3H, $J$ = 6.6 Hz, H-9), 3.58 (m, 1H, H-7), 3.63 (m, 3H, CH, H-6′, H-6″), 3.81 (m, 1H, CH), 4.01–4.08 (m, 3H, CH), 4.06 (q, $J$ = 6.6 Hz, 1H, H-8) 4.42–4.76 (m, 8H, $PhCH_2$), 7.09–7.38 (m, 25H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm): 24.8 (C-9), 48.5 (C-7), 56.4 (C-8), 69.2 (C-6), 73.1 (C-1), 73.7 ($PhCH_2$), 73.8 ($PhCH_2$), 74.1 (CH), 74.2 ($PhCH_2$), 74.24 ($PhCH_2$), 76.3 (CH), 77.5 (CH), 81.1 (CH), 119.5 (CN), 127.0, 127.4, 127.46, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.7 (Ph-CH), 137.5, 137.9, 138.1, 138.3, 146.6 (Ph-$C_q$); MS (ESI): $m/z$ = 683.6 $[M+H]^+$. Anal. Calcd for $C_{44}H_{46}N_2O_5$: C, 77.39; H, 6.79; N, 4.10. Found: C, 77.53; H, 6.72; N, 3.97.

#### 4.3.9. (*S*/*R*)-2-((S)-Phenylethylamino)-2-*C*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl) acetonitrile (β-8b-1)

Compound β-**8b-1** was obtained from β-**7b** as colorless syrup by Method B; yield 29%; dr = 3.3. Major diastereomer (*R* at C-7): $R_f$ = 0.23 (hexanes–EtOAc, 8:2); $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm): 1.39 (d, $J$ = 6.6 Hz, 3H, H-9), 2.12 (br s, 1H, NH), 3.49 (dd, $J$ = 9.3, 1.5 Hz, 1H, CH), 3.58 (dd, $J$ = 9.3, 2.7 Hz, 1H, CH), 3.60 (m, 1H, CH), 3.62 (m, 2H, H-6′, H-6″), 3.64 (m, 1H, H-7), 4.03 (m, 1H, CH), 4.04 (q, $J$ = 6.6 Hz, 1H, H-8), 4.27 (dd, $J$ = 9.3, 9.3 Hz, 1H, CH), 4.22–5.02 (m, 8H, $PhCH_2$), 6.81–6.85 (m, 2H, Ph), 7.13–7.37 (m, 23H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ ppm: 24.6 (C-9), 49.4 (C-7),

56.3 (C-8), 68.4 (C-6), 72.3 ($PhCH_2$), 73.4 (CH), 73.8 ($PhCH_2$), 74.2 (CH), 74.4 ($PhCH_2$), 75.4 ($PhCH_2$), 77.4 (CH), 79.1 (CH), 85.0 (CH), 119.3 (CN), 127.6, 127.62, 127.67, 127.8, 127.9, 128.0, 128.04, 128.1, 128.2, 128.5, 128.69, 128.7, 129.9 (Ph-CH), 138.1, 138.12, 138.23, 139.26, 143.3 (Ph-$C_q$); MS (ESI): $m/z$ = 683.5 $[M+H]^+$. Anal. Calcd for $C_{44}H_{46}N_2O_5$: C, 77.39; H, 6.79; N, 4.10. Found: C, 77.50; H, 6.69; N, 4.13. Minor diastereomer (*S* at C-7): $R_f$ = 0.17 (hexanes–EtOAc, 8:2). $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm): 1.25 (d, $J$ = 6.3 Hz, 3H, H-9), 1.87 (br s, 1H, NH), 3.51 (m, 1H, CH), 3.55 (m, 2H, H-6′, H-6″), 3.59 (m, 1H, CH), 3.62 (dd, $J$ = 9.3, 2.7 Hz, 1H, CH), 3.99 (q, $J$ = 6.3 Hz, 1H, H-8), 4.00 (m, 1H, CH), 4.02 (m, 1H, H-7), 4.10 (dd, $J$ = 9.3, 9.3 Hz, 1H, CH), 4.36–5.01 (m, 8H, $PhCH_2$), 7.17–7.35 (m, 25H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ ppm : 21.9 (C-9), 49.8 (C-7), 55.9 (C-8), 68.7 (C-6), 72.7 ($PhCH_2$), 73.4 (CH), 73.7 ($PhCH_2$), 75.4 ($PhCH_2$), 75.9 ($PhCH_2$), 76.1 (CH), 77.6 (CH), 78.8 (CH), 84.7 (CH), 117.4 (CN), 127.1, 127.2, 127.5, 127.6, 127.8, 128.0, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 129.6, 128.7, 128.9 (Ph-CH), 138.0, 138.2, 138.3, 139.1, 144.7 (Ph-$C_q$); MS (ESI): $m/z$ = 683.5 $[M+H]^+$. Anal. Calcd for $C_{44}H_{46}N_2O_5$: C, 77.39; H, 6.79; N, 4.10. Found: C, 77.57; H, 6.62; N, 4.05.

#### 4.3.10. (*S*/*R*)-2-(Benzhydrylamino)-2-*C*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)acetonitrile (β-8b-2)

Compound β-**8b-2** was obtained from β-**7b** as colorless syrup by Method C; yield 38%; dr = 2.79. $R_f$ = 0.30 (hexanes–EtOAc, 8:2) for both diastereomers. Major diastereomer (assigned *R* at C-7): $^1H$ NMR (300 MHz, $CDCl_3$), δppm: 2.63 d, $J$ = 12.9 Hz, 1H, NH, 3.44–3.70 (m, 5H, CH, H-6′, H-6″), 3.79 (d, $J$ = 12.9 Hz, 1H, H-7), 3.92 (d, $J$ = 2.4 Hz, 1H, CH), 4.01 (m, 1H, CH), 5.11 (s, 1H, H-8), 4.34–5.06 (m, 8H, $PhCH_2$), 6.80 (m, 2H, Ph), 7.17–7.54 (m, 28H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ ppm: 49.3 (C-7), 65.1 (C-8), 68.3 (C-6), 73.5 ($PhCH_2$), 73.9 (CH), 74.5 ($PhCH_2$), 74.6 ($PhCH_2$), 76.5 ($PhCH_2$), 77.3 (CH), 78.9 (CH), 84.9 (CH), 119.0 (CN), 126.9, 127.3, 127.6, 127.9, 128.2, 128.4, 128.5, 128.7, 128.8 (Ph-CH), 138.1, 138.2, 138.4, 139.3, 141.5, 143.6 (Ph-$C_q$). Minor diasteromer (assigned *S* at C-7): $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ ppm: 2.48 (d, $J$ = 11.6 Hz, 1H, NH), 3.57–3.68 (m, 5H, CH, H-6′, H-6″), 3.86 (d, $J$ = 11.6 Hz, 1H, H-7), 3.92 (d, $J$ = 2.4 Hz, 1H, CH), 4.01 (m, 1H, CH), 5.11 (s, 1H, H-8), 4.34–5.06 (m, 8H, $PhCH_2$), 6.80 (m, 2H, Ph), 7.17–7.54 (m, 28H, Ph). $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm): 50.3 (C-7), 65.6 (C-8), 68.6 (C-6), 73.6 ($PhCH_2$), 74.2 (CH), 74.5 ($PhCH_2$), 74.6 ($PhCH_2$), 76.3 ($PhCH_2$), 77.7 (CH), 79.5 (CH), 84.6 (CH), 118.4 (CN), 126.9, 127.3, 127.6, 127.9, 128.2, 128.4, 128.5, 128.8, (Ph-CH), 137.6, 137.9, 138.1, 139.3, 141.3, 143.4 (Ph-$C_q$); MS (ESI): $m/z$ = 745.5 $[M+H]^+$. Anal. Calcd for $C_{49}H_{48}N_2O_5$: C, 79.01; H, 6.49; N, 3.76. Found: C, 79.16; H, 6.42; N, 3.68.

#### 4.3.11. (*S*/*R*)-2-((S)-Phenylethylamino)-2-*C*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl) acetonitrile (α-8c)

Compound α-**8c** was obtained from α-**7c** as colorless syrup by Method A; in $CH_2Cl_2$ yield 21%; dr = 2.0. Major diastereomer (*R* at C-7): Mp 105–107 °C; $[\alpha]_D^{20}$ −36.2 (*c* 0.94, $CHCl_3$); $R_f$ = 0.24 (hexanes–EtOAc, 1:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ (ppm): 1.35 (d, $J$ = 6.6 Hz, 3H, H-9), 2.08 (d, $J$ = 12.9 Hz, 1H, NH), 3.31 (s, 3H, $OCH_3$), 3.40 (s, 3H, $OCH_3$), 3.42 (s, 3H, $OCH_3$), 3.47 (s, 3H, $OCH_3$), 3.53 (dd, $J$ = 3.6, 2.4 Hz, 1H, H-2), 3.59 (m, 1H, H-7), 3.60 (1H, m, H-4), 3.64 (m, 2H, H-6′, H-6″), 3.67 (m, 1H, H-3), 3.89 (dd, $J$ = 9.1, 3.6 Hz, 1H, H-1), 4.05 (1H, m, H-5), 4.06 (q, $J$ = 6.6 Hz, 1H, H-8), 7.24–7.37 (m, 5H, Ph). $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ (ppm): 25.1 (C-9), 50.0 (C-7), 56.1 (C-8), 56.7 ($OCH_3$), 57.7 ($OCH_3$), 58.4 ($OCH_3$), 59.1 ($OCH_3$), 69.9 (C-1), 70.1 (C-6), 73.5 (C-5), 75.0 (C-2), 75.1 (C-4), 75.2 (C-3), 117.7 (CN), 126.9, 127.5, 128.7(Ph), 143.2 ($C_q$); MS (ESI): $m/z$ = 379.1 $[M+H]^+$. Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.53; H, 7.87; N, 7.31. Minor diastereomer (*S* at C-7): $[\alpha]_D^{20}$ +31.2 (*c* 0.94, $CHCl_3$); $R_f$ = 0.26 (hexanes–EtOAc, 1:1); $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm): 1.33 (d, $J$ = 6.4 Hz, 3H, H-9), 2.11 (br s, 1H, NH), 3.38 (s, 3H, $OCH_3$), 3.40 (s, 3H, $OCH_3$), 3.48 (s, 3H, $OCH_3$) 3.51 (s, 3H, $OCH_3$), 3.52 (m, 1H, CH), 3.67 (m, 2H, H-6′, H-6″), 3.79 (m, 1H, CH), 3.82 (m, 1H, CH), 4.04 (m, 4H, CH, H-7, H-8), 7.21–7.38 (m, 5H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm): 21.8 (C-9), 49.2 (C-7), 56.1 (C-8), 57.3 ($OCH_3$), 57.9 ($OCH_3$), 59.0 ($OCH_3$), 59.4 ($OCH_3$), 70.2 (CH), 70.2 (C-6), 74.2 (CH), 74.3 (CH), 75.6 (CH), 75.9 (CH), 119.1 (CN), 127.1, 127.7, 128.8 (Ph-CH), 145.0 (Ph-$C_q$); MS (ESI): $m/z$ = 379.1 $[M+H]^+$. Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.56; H, 7.82; N, 7.28.

### 4.4. General procedure for the preparation of galactal imines 9b

1-Formyl-3,4,6-tri-*O*-benzyl-D-galactal (**2b**) (1 mmol, 45 mg) was dissolved in dry $CH_2Cl_2$ (3 ml) and molecular sieves 4 Å (100 mg) then *S*-or *R*-PEA or benzylamine (1.02 mmol) were added during stirring. After 2 h the mixture was filtered and the filtrate was evaporated in vacuo and imines formed were used without purification for *C*-glycosyl aminoacetonitrile preparation in the presence of catalysts **11** and **12** as described in Method B.

#### 4.4.1. *N*-((*S*)-1-Phenylethyl)-(3,4,6-tri-*O*-benzyl-2-deoxy-D-*lyxo*-hex-2-enopyranosyl)formaldimine (9b-1)

Compound **9b-1** was obtained as colorless syrup; yield 99%. $R_f$ = 0.37 (hexanes–EtOAc, 6:4); $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm): 1.54 (d, $J$ = 6.6 Hz, 3H, H-9), 3.80 (m, 2H, H-6′, H-6″), 4.02 (m, 1H, CH), 4.22–4.26 (m, 2H, CH), 4.42 (q, $J$ = 6.6 Hz, 1H, H-8), 4.44–4.91 (m, 6H, $PhCH_2$), 5.37 (d, $J$ = 2.1 Hz, 1H, H-2), 7.18–7.39 (m, 20H, Ph), 7.60 (s, 1H, CH═N); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm): 24.4 (C-9), 67.7 (C-6), 69.6 (C-8), 70.9 (CH), 71.5 (CH), 71.8 ($PhCH_2$), 73.6 ($PhCH_2$), 73.8 ($PhCH_2$), 76.6 (CH), 108.2 (C-2), 127.1, 127.2, 127.7, 127.9, 128.1, 128.4, 128.5, 128.6, 128.7 (Ph-CH), 138.3, 138.4, 138.5, 144.4 (Ph-$C_q$), 150.5 (C-1), 155.4 (CH═N); MS (ESI): $m/z$ = 656.3 $[M+H]^+$. Anal. Calcd for $C_{43}H_{45}NO_5$: C, 78.75; H, 6.92; N, 2.14. Found: C, 78.96; H, 6.82; N, 2.28.

#### 4.4.2. *N*-((*R*)-1-Phenylethyl)-(3,4,6-tri-*O*-benzyl-2-deoxy-D-*lyxo*-hex-2-enopyranosyl)formaldimine (9b-2)

Compound **9b-2** was obtained as colorless syrup; yield 99%. $R_f$ = 0.37 (hexanes–EtOAc, 6:4); $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm): 1.54 (t, $J$ = 6.9 Hz, 3H, H-9), 3.80 (m, 2H, H-6′, H-6″), 4.02 (m, 1H, CH), 4.24 (m, 1H, CH), 4.29 (m, 1H, CH), 4.41 (q, $J$ = 6.9 Hz, 1H, H-8), 4.44–4.91 (m, 6H, $PhCH_2$), 5.37 (m, 1H, H-2), 7.18–7.38 (m, 20H, Ph), 7.59 (s, 1H, CH═N); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm) 24.3 (C-9), 68.0 (C-6), 69.5 (C-8), 70.5 (CH), 71.4 ($PhCH_2$), 72.3 (CH), 73.7 ($PhCH_2$), 74.1 ($PhCH_2$), 76.5 (C-3), 108.2 (C-2), 127.2, 127.7, 127.9, 128.0, 128.2, 128.5, 128.6, 128.7(Ph), 138.2, 138.4, 138.6, 144.4 ($C_q$), 150.7 (C-1), 155.6 (CH═N); MS (ESI): $m/z$ = 656.3 $[M+H]^+$. Anal. Calcd for $C_{43}H_{45}NO_5$: C, 78.75; H, 6.92; N, 2.14. Found: C, 78.90; H, 6.80; N, 2.26.

#### 4.4.3. *N*-Benzyl-(3,4,6-tri-*O*-benzyl-2-deoxy-D-*lyxo*-hex-2-enopyranosyl)formaldimine (9b-3)

Compound **9b-3** was obtained as colorless syrup; yield 99%. $R_f$ = 0.36 (hexanes–EtOAc, 6:4); $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ (ppm): 3.79 (d, $J$ = 6.6 Hz, 2H, H-6′, H-6″), 4.07 (m, 1H, H-4), 4.23 (dd, $J$ = 6.9, 6.6 Hz, 1H, H-5), 4.32 (m, 1H, H-3), 4.42 (m, 2H, $PhCH_2$), 4.64 (m, 2H, $PhCH_2$), 4.66 (d, $J$ = 12.0 Hz, 1H, H8′), 4.71 (m, 2H, $PhCH_2$), 4.90 (d, $J$ = 12.0 Hz, 1H, H8″), 5.35 (s, 1H, H-2), 7.20–7.37 (m, 20H, Ph), 7.59 (s, 1H, CH═N); $^{13}C$ NMR (75 MHz, $CDCl_3$), $\delta$ (ppm): 64.8 (C-8), 67.8 (C-6), 70.2 (CH), 71.3 ($PhCH_2$), 72.5 (CH), 73.6 ($PhCH_2$), 74.2 ($PhCH_2$), 76.4 (CH), 109.3 (C-2), 127.3, 127.7, 127.8, 127.9, 128.2, 128.4, 128.5, 128.6, 128.7 (Ph-CH), 137.1, 138.4, 138.6, 138.7 (Ph-$C_q$), 150.6 (C-1), 157.3 (CH═N) ; MS (ESI): $m/z$ = 642.3 $[M+H]^+$. Anal. Calcd for $C_{42}H_{43}NO_5$: C, 78.60; H, 6.75; N, 2.18. Found: C, 78.79; H, 6.68; N, 2.27.

### 4.5. Crystal structure determination of α-8c

Crystal data: $C_{20}H_{30}N_2O_5$, Fwt.: 378.46, colorless, prism, size: 0.66 × 0.60 × 0.30 mm, monoclinic, space group $P2_1$, $a$ = 8.704 (3) Å, $b$ = 12.873(3) Å, $c$ = 9.555(3) Å, $\beta$ = 92.735(6)°, $V$ = 1069.4 (6) Å$^3$, $T$ = 294(2) K, $Z$ = 2, $D_x$ = 1.175 Mg/m$^3$, $\mu$ = 0.084 mm$^{-1}$. A crystal of **α-8c** was mounted on a glass fiber. Cell parameters were determined by least-squares of the setting angles of 14,258 ($3.09 \leqslant \theta \leqslant 27.52°$) reflections. Intensity data were collected on a *R*-Axis RAPID diffractometer (graphite monochromator; Mo-Kα radiation, $\lambda$ = 0.71075 Å) at 294(2) K in the range $3.09 \leqslant \theta \leqslant 26.37°$ using $\omega$ oscillations. A total of 28641 reflections were collected of which 4359 were unique [$R$(int) = 0.0243, $R(\sigma)$ = 0.0201]; intensities of 3174 reflections were greater than $2\sigma(I)$. Completeness to $\theta$ = 0.998. An empirical absorption correction was applied to the data, minimum and maximum transmission factors were 0.947 and 0.975. The structure was solved by direct methods. Anisotropic full-matrix least-squares refinement on $F^2$ for all non-hydrogen atoms yielded $R_1$ = 0.0413 and $wR_2$ = 0.1056 for 3174 [$I > 2\sigma(I)$] and $R_1$ = 0.0573 and $wR_2$ = 0.1148 for all (4359) intensity data, (number of parameters = 249, goodness-of-fit = 1.088, Flack absolute structure parameter $x$ = 1.1(11), Hooft absolute structure parameter $y$ = 0.0(3). The maximum and minimum residual electron densities in the final difference map were 0.15 and −0.13 e Å$^{-3}$. Hydrogen atomic positions were calculated from assumed geometries and were included in structural factor calculations but they were not refined.

### Acknowledgements

The authors thank Dr. Pal Szabo for the mass spectrometry analyses. Excellent technical assistance by Janosne Keri and Eva Peter are gratefully acknowledged.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.10.023.

### References

1. Opatz, T. *Synthesis* **2009**, *12*, 1941–1959.
2. Paraskar, A. S.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 5759–5762.
3. Pan, S. C.; List, B. *Synlett* **2007**, 318–320.
4. Groger, H. *Chem. Rev.* **2003**, *103*, 2795–2827.
5. Boehm, J. C.; Kingsbury, W. D. *J. Org. Chem.* **1986**, *51*, 2307–2314.
6. Czernecki, S.; Valery, J.-M. *Carbohydr. Res.* **1988**, *184*, 121–130.
7. Prado, M. A. F.; Alves, R. J.; de Oliveira, A. B.; Filho, J. D. S. *Synth. Commun.* **1996**, *26*, 1015–1022.
8. Bae, C.; Lee, T.; Ahn, Y. *J. Korean Chem. Soc.* **2004**, *48*, 211–214.
9. Plant, A.; Thompson, P.; Williams, D. M. *J. Org. Chem.* **2008**, *73*, 3714–3724.
10. Robins, M. J.; Parker, J. M. *Can. J. Chem.* **1983**, *61*, 312–316.
11. Voegel, J. J.; Benner, S. A. *J. Am. Chem. Soc.* **1994**, *116*, 6929–6930.
12. Voegel, J. J.; Benner, S. A. *Helv. Chim. Acta* **1996**, *79*, 1863–1880.
13. Vincent, S. P.; Schleyer, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 4440–4443.
14. Dondoni, A. *Pure Appl. Chem.* **2000**, *72*, 1577–1588.
15. Sipos, S.; Jablonkai, I. *Carbohydr. Res.* **2011**, *346*, 1503–1510.
16. Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.
17. Haukaas, M.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771–1774.
18. Albrecht, H. P.; Repke, D. B.; Moffat, J. G. *J. Org. Chem.* **1972**, *38*, 1836–1840.
19. Dettinger, H.-M.; Kurz, G.; Lehmann, J. *Carbohydr. Res.* **1979**, *74*, 301–307.
20. Frische, K.; Schmidt, R. R. *Liebigs Ann. Chem.* **1994**, 297–303.
21. Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404–6412.
22. Lopez, G. M.-H.; Heras, F. G.; Felix, A. S. *J. Carbohydr. Chem.* **1987**, *6*, 273–279.
23. Jacobson, R. A. *J. Am. Chem. Soc.* **1945**, *67*, 1996–1998.
24. Stuart, T. D.; Fontana, J. *J. Am. Chem. Soc.* **1940**, *62*, 3281–3285.
25. Kunz, H.; Rück, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 336–358.
26. Totani, K.; Takao, K.-I.; Tadano, K.-I. *Synlett* **2004**, 2066–2080.
27. Kunz, H.; Sager, W.; Pfrengle, W.; Schanzenbach, D. *Tetrahedron Lett.* **1988**, *29*, 4397–4400.
28. Stout, D. M.; Black, L. A.; Matier, W. L. *J. Org. Chem.* **1983**, *48*, 5369–5373.
29. Inaba, T.; Fujita, M.; Ogura, K. *J. Org. Chem.* **1991**, *56*, 1274–1279.
30. Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179–9190.
31. Harada, K.; Fox, S. *Naturwissenschaften* **1964**, *51*, 106–107.
32. Dondoni, A.; Massi, A.; Sabbatini, S. *Chem. Eur. J.* **2005**, *11*, 7110–7125.
33. Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.
34. Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358–15374.
35. Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157–160.
36. Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967–1969.
37. Tietgen, H.; Schultz-Kukula, M.; Kunz, H. Glycosylamines as Auxiliaries in Stereoselective Synthesis of Chiral Amino Compounds. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; pp 103–128.