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A Novel Synthesis of Chain-Extended Amino Sugar Derivatives through Aza-Cope Rearrangement of *N*-Galactosyl-*N*-Homoallylamines

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Abstract: Chain-extended amino sugars are synthesized via stereocontrolled Lewis acid-catalyzed aza-Cope rearrangement of *N*-glycosyl homoallylamines in high yield and stereoselectivity.

In recent years, so-called "higher sugars" have been receiving increasing attention, because several of these 7-11 carbon carbohydrates play prominent roles in biological processes. Important representatives of these higher sugars are KDO[1] (3-deoxy-D-manno-2-octulosonic acid) and L-glycero-D-manno-heptopyranose,[2] essential components of bacterial lipopolysaccharides, and the amino sugar *N*-acetylneuraminic acid,[3] an important component of human and animal glycoconjugates. A number of strategies for the carbon chain extension of appropriate aldoses have been developed,[4] including syntheses of C-glycosides and C-nucleosides.[5] The interest in higher sugars was further enforced by the observation that a 4-guanidino-*N*-acetylneuraminic acid derivative proved to be an effective inhibitor of the influenza virus sialidase and therewith a promising antiviral agent.[6] Only a few chain-extending reactions on carbohydrates have been described in which amino-substituted stereogenic centers are formed. These are the Strecker syntheses on aldoses[7] and the recently reported reactions of Grignard reagents with N-alkyl glycosylamines.[8]

We here describe an alternative stereoselective synthesis of chain-extended amino sugars achieved by an aza-Cope rearrangement of *N*-galactosyl-*N*-homoallylamines. This method avoids basic conditions. Simple *O*-acyl protecting groups can therefore be applied. *N*-Galactosyl-*N*-homoallylamines **2**[9] were obtained with high asymmetric induction by $SnCl_4$-induced addition of allyltrimethylsilane or allyltributylstannane to aromatic and aliphatic Schiff bases **1** of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (Scheme 1). We were initially interested in a Lewis acid-induced Cope rearrangement of the (*S*)-unsaturated homoallylamine **2a** obtained from the (*E*)-*N*-cinnamylidene derivative **1a** with a high diastereomeric ratio (d.r. = 16-19 :1). This rearrangement was expected to yield the isomeric 1,5-diene containing a new stereogenic center. However, this Cope rearrangement could not be achieved under thermal conditions or by Lewis base- or Lewis acid-catalysis. Notwithstanding, with two of the investigated Lewis acid catalysts, BF_3 etherate and $TiCl_4$, an immaculate conversion of **1a** occurred yielding quantitatively the unexpected chain-extended imino derivative **3a** (Scheme 1). In a simple procedure, BF_3 etherate was added to a solution of the homoallylamine **2a** in xylene at room temperature. After completion of the reaction (t.l.c. control) and hydrolysis, the imine **3a**[10] was obtained with a high diastereoselectivity (d.r. > 15:1, Table 1).

Various Lewis acids were tested on the *N*-galactosyl-*N*-homoallylamine **2a** under different conditions. Titanium tetrachloride also produced the imine **3a** in quantitative yield but with lower diastereoselectivity. The tin tetrachloride-induced reaction proceeded only at high temperature (refluxing tetrahydrofuran) with concomitant decrease in yield and diastereoselectivity. Zinc chloride was unable to catalyze the reaction. The obtained results are summarized in Table 1.

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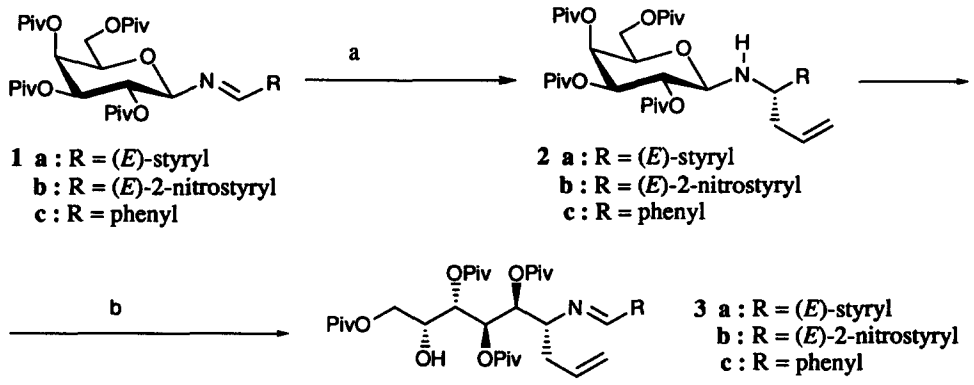
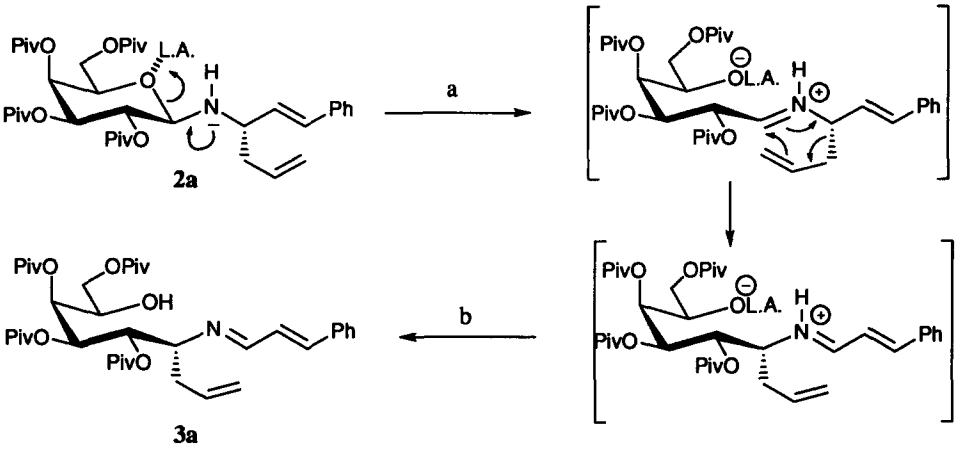


Scheme 1. a: Allyltrimethylsilane or allyltributylstannane, $SnCl_4$, THF. Piv = $(CH_3)_3C$-CO; b: 1.1 eq. Lewis acid (conditions see Table 1).

Single crystals of the *N*-cinnamylidene imine **3a** were obtained by recrystallization from n-pentane. The X-ray analysis revealed that the major diastereomer **3a** possessed (*R*)-configuration at the new chiral center.[11] The stereoselective formation of the chain-extended imino derivatives can be explained by a two step reaction: Coordination of the Lewis acid to the ring-oxygen atom of the carbohydrate moiety results in ring opening and is followed by a 2-azonia-[3,3]-sigmatropic rearrangement (cationic aza-Cope rearrangement[12]) of the intermediate iminium ion[13] (Scheme 2).



Scheme 2: a: Lewis acid L.A.; b: Hydrolysis.

The attack of the allyl group from the *Re*-side of the iminium ion is obviously controlled by the configuration of the homoallylamine in a chair-like transition state.

The Lewis acid-catalyzed chain extension was also applied to two other aromatic *N*-galactosyl-*N*-homoallylamines **2b** and **2c**, prepared from the Schiff bases **1b** and **1c**, respectively. The reactions were conducted using boron trifluoride etherate or titanium tetrachloride as Lewis acids under different conditions

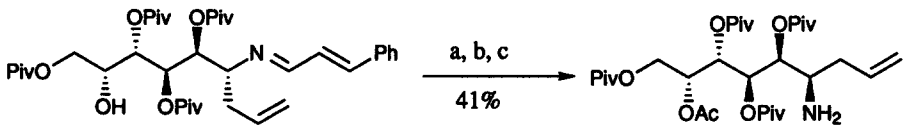
(Table 1). In both cases, the expected chain-extended imino compounds **3b** and **3c** were formed in high yield and diastereoselectivity (Scheme 1). Enrichment of the major diastereomer **3b** was achieved by a single recrystallization from n-hexane.

Table 1. Synthesis of the chain-extended amino sugar derivatives **3** according to Scheme 1.

Educt **2**	Lewis acid	Solvent	*T*/°C	*t*	Product **3**	Yield [%]	d.r.[a]
2a	$BF_3{\cdot}Et_2O$	xylene	r. t.	12h	**3a**	99[b]	>15:1
2a	$BF_3{\cdot}Et_2O$	THF	reflux	9h	**3a**	40[c]	11:1
2a	$TiCl_4$	toluene	1) -30 to -10 2) r.t.	1)1h 2)5min	**3a**	97[b]	>9:1
2a	$TiCl_4$	CH_2Cl_2	-30 to r. t.	5h	**3a**	96[b]	11:1
2a	$SnCl_4$	THF	reflux	3.5h	**3a**	69[c]	4:1
2a	$ZnCl_2$	THF	-30 to reflux	24h	---	—	---
2b	$BF_3{\cdot}Et_2O$	xylene	r. t.	12h	**3b**	74[c]	6:1
2b	$TiCl_4$	toluene	-30 to r. t.	3h	**3b**	96[b]	9:1
2c	$BF_3{\cdot}Et_2O$	xylene	r. t.	12h	**3c**	99[b]	>20:1

[a] Diastereomeric ratio determined from the crude product by ^1H NMR. [b] Further purification not necessary. [c] Yield after preparative thin layer chromatography.

In order to prepare the chain-extended amino sugar derivative **4**, the *N*-cinnamylidene derivative **3a** was *N*-deprotected. In a not yet optimized procedure, the imine **3a** was first *O*-acetylated with acetic anhydride in pyridine. Treatment of the obtained crude mixture with aqueous 1N HCl in the presence of 2,4-dinitrophenylhydrazine and subsequent deprotonation with sodium hydrogencarbonate furnished the free amine **4**[14] in an overall yield of 41% (scheme 3).



3a **4**

Scheme 3: a: Ac_2O, pyridine; b: 1N HCl, 2,4-dinitrophenylhydrazine, MeOH, CH_2Cl_2, r.t.; c: $NaHCO_3$

More detailed studies are required in order to improve the hydrolytic deprotection of the imines **3**. However, the high efficiency and diastereoselectivity of the three carbon homologation on chiral *N*-glycosyl-*N*-homoallylamines via an asymmetric cationic aza-Cope rearrangement should provide an interesting access to chain-extented amino sugars of varied substitution patterns by oxidative functionalization of the C=C double bond.

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10. **3a**: M.p. 97-98°C; $[a]_D^{22}$ = -20.3 (c = 0.95, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$): d = 2.40 (m, 2H, 2H-3), 3.13 (dt, ^3J = 8.0 Hz, ^3J = 4.0 Hz, 1H, H-4), 3.71 (t, ^3J = 6.0 Hz, 1H, H-8), 3.88 (dd, ^2J = 11.3 Hz, ^3J = 5.8 Hz, 1H, H-9a), 3.99 (dd, ^2J = 11.3 Hz, ^3J = 7.5 Hz, 1H, H-9b), 5.01 (m, 3H, 2H-1, H-7), 5.30 (dd, ^3J = 8.6 Hz, ^3J = 1.4 Hz, 1H, H-5), 5.62 (m, 1H, H-2), 5.64 (dd, ^3J = 7.5 Hz, ^3J = 1.8 Hz, 1H, H-6), 6.87 (m, 2H, H-1', H-2'), 7.78 (d, 1H, ^3J = 7.5 Hz, H-3'); ^{13}C NMR (100.6 MHz, ^1H-^{13}C-COSY, $CDCl_3$): d = 36.12 (C-3), 64.18 (C-9), 67.85 (C-8), 68.14 (C-7), 68.70 (C-6), 71.03 (C-5), 71.53 (C-4), 118.02 (C-1), 129.28 (C-1'), 134.06 (C-2), 142.47 (C-2'), 163.74 (C-3').
11. Monoclinic, space group $P2_1$ with a = 12.349(1)Å , b = 8.589(3)Å, c = 19.982(1)Å and b = 103.839(6). Crystal dimensions : 0.064 x 0.128 x 0.800 mm^3. Density amounts to 1.084gcm^{-3} with a volume of 2057.8(7)$Å^3$, z = 2. $2q_{max}$ = 150°. Cu-Ka Graphitmonochromator. Wavelength : 1.54061. Scan mode : w/2q. Temp. : 296 K. 8962 measured and independent reflections, 8309 included in the refinement. All reflections are used in refinement. Lorentzian polarization corrections applied. No absorption corrections were performed. Direct methods of structure solution with SIR92. Method of refinement: full least squares with SHELXL-93. 459 parameters. Except hydrogens of pivaloyl groups all atoms found in difference Fourier maps, isotropic refinement assumed a riding motion model. Refined against F^2. Residual electron density : max. 0.16, min. -0.11e$Å^{-3}$. Flack parameter : -0.06(20). Further details are available on request from the Fachinformationszentrum Karlsruhe GmbH, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the deposit number CSD-406759, the names of the authors and journal citation.We thank Dr. D. Schollmeyer, Institut für Organische Chemie, Universität Mainz, for the X-ray analysis and calculations.
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14. **4**: $[a]_D^{22}$ = +51.3 (c = 0.61, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): d = 2.03 (s, 3H, CH_3CO), 2.19 (dd, ^2J = 14.0 Hz, ^3J = 7.2 Hz, 1H, H-3a), 2.33 (m, ^2J = 14.0 Hz, 1H, H-3b), 3.68 (m, 1H, H-4), 3.86 (dd, ^2J = 11.3 Hz, ^3J = 7.8 Hz, 1H, H-9a), 4.06 (dd, ^2J = 11.3 Hz, ^3J = 5.8 Hz, 1H, H-9b), 4.15 (dd, ^3J = 5.5 Hz, ^3J = 1.4 Hz, 1H, H-5), 5.10 (dd, ^3J = 9.6 Hz, ^3J = 1.4 Hz, 1H, H-6), 5.18 (dt, ^3J = 7.5 Hz, ^3J = 1.7 Hz, 1H, H-8), 5.43 (dd, ^3J = 9.6 Hz, ^3J = 2.0 Hz, 1H, H-7); ^{13}C NMR (100.6 MHz, $CDCl_3$): d = 20.71 (CH_3CO), 39.41 (C-3), 61.81 (C-9), 66.18, 68.18, 68.33, 69.47 (C-5, C-6, C-7, C-8), 80.09 (C-4).