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Synthesis of Benzylated *(R)*- and *(S)*-Aminoethyl-*C*-α-D-Mannosides as Conformationally Restricted Building Blocks for the Preparation of E- and P-Selectin Antagonists

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Abstract: A straightforward synthesis for the aminoethyl-*C*-α-D-mannosides ***(R)*-1** and ***(S)*-1** has been developed. The conformationally restricted mannosides serve as building blocks for the synthesis of a new class of selectin antagonists of type **A**.

The migration of neutrophiles from the intravascular space to sites of inflammation or tissue injury is initiated by their rolling on the activated vascular endothelium.[1] This adhesion process is mediated by the interaction of cell adhesion molecules, the so-called selectins, with their physiological glycoprotein ligands.[2] All the three selectins recognize a common carbohydrate epitope, the sialyl Lewis^x tetrasaccharide (sLe^x, *Figure 1*), albeit with different affinities. The sLe^x/E-selectin binding has been shown to be strongly dependent on the presence of the sialic acid carboxylate and the fucosyl hydroxyl groups.[3]

In the course of our research aimed at the design of novel selectin antagonists,[4] we became interested in the synthesis of glycomimetics of the general structure **A** (*Figure 1*) based on a *C*-mannoside building block ***(R)*-1** .

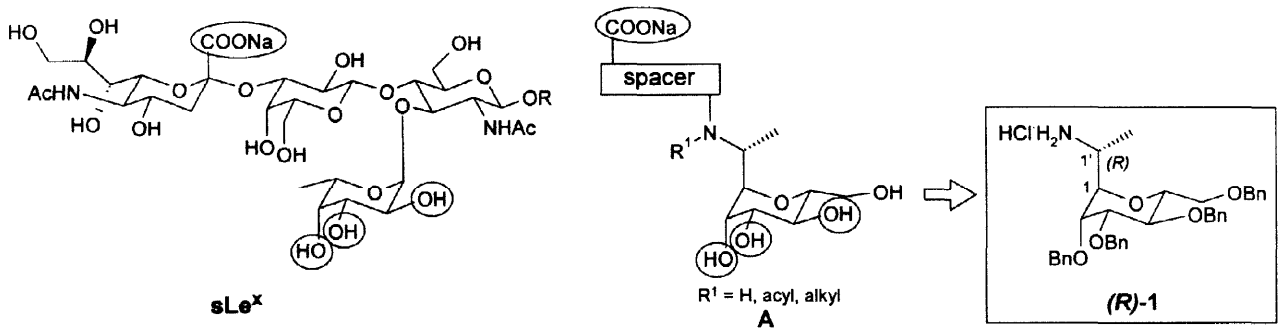

Figure 1.

In order to favor the spatial arrangement of the essential carboxylate and the three hydroxyl groups found in sLe^x,[5] it appeared important to choose a conformationally restricted building block like ***(R)*-1** with a defined N-C(1')-C(1)-O torsion angle. Molecular modeling studies indicated that an *(R)*-configurated methyl substituent at C(1') could more ideally serve this purpose than the corresponding *(S)*-configurated substituent. Our effort was thus directed towards the selective synthesis of the conformationally restricted aminoethyl-*C*-α-D-mannoside building block ***(R)*-1**.

Aminomethyl-*C*-glycosides are usually prepared by *Henry* condensation of hexoses or pentoses with nitromethane, followed by reduction of the nitro group.[6] The reaction is known to proceed through the addition of the nitromethane enolate to the sugar aldehyde form, dehydration of the Henry adduct to a nitroalkene and cyclization by β-addition of the C(5) hydroxyl group. This reaction sequence yields predominantly the thermodynamically more stable β-anomer. α-Selectivity has been reported in the reaction of silyl enol ethers derived

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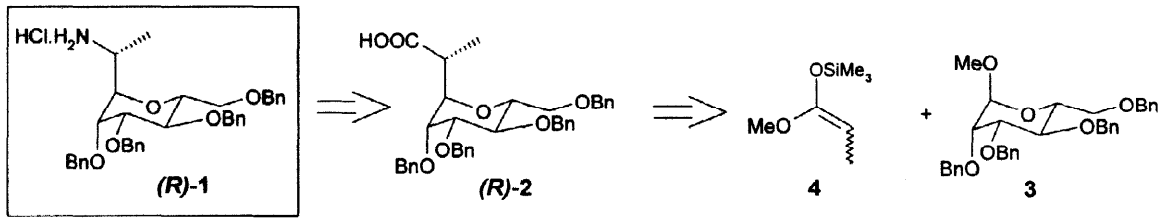
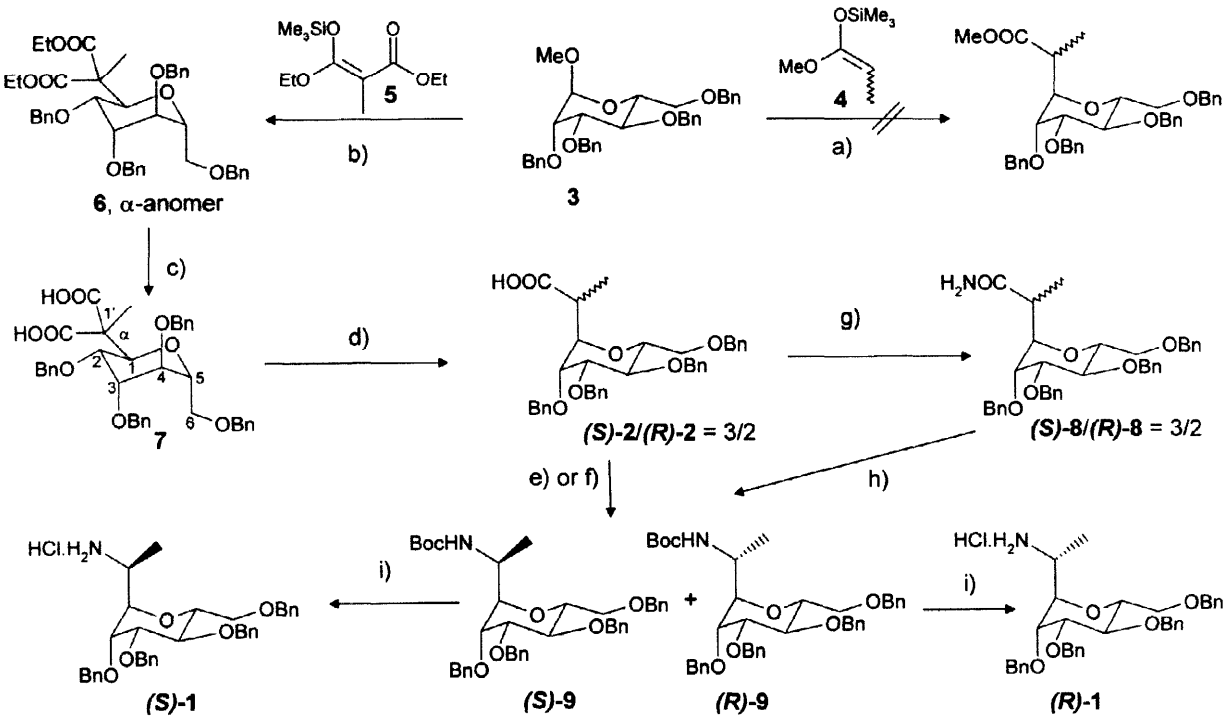
from ketones or esters with glycofuranosides[7] or pyranosides.[8] Examining this methodology, we arrived at the retro-synthetic analysis of **(*R*)-1** depicted in *Scheme 1*. While the amino function would be introduced by *Curtius* rearrangement of **(*R*)-2**, the *C*-glycosylation of a mannose derivative **3** was to be performed using the silyl ketene acetal **4**[9] as the glycosyl acceptor.



Scheme 1. Retrosynthetic analysis

Thus the reaction of silyl ketene acetal **4** with the mannoside **3** was investigated (*Scheme 2*). However, no reaction or degradation products were observed under various conditions (TMSOTf, BF_3Et_2O, $SnCl_4$, or $TiCl_4$ in CH_2Cl_2 or CH_3CN).



Scheme 2. a) TMSOTf or BF_3Et_2O or $SnCl_4$ or $TiCl_4$ (1-3 eq.), CH_2Cl_2 or CH_3CN, -78 °C - rt, 1 h - 4 days; b) TMSOTf (1 eq.), CH_3CN, rt, 18 h, 96%; c) 1. NaOH 3 N, MeOH, 80 °C, 3 h, 2. HCl 3 N, rt, 5 min, quant; d) Cu_2O cat., CH_3CN, 80 °C, 2 h, 91%; e) DPPA (diphenylphosphoryl azide) (1 eq.), Et_3N (1 eq.), tBuOH, 88 °C, 20 h, 16%; f) 1. $ClCO_2Et$ (2 eq.), Et_3N (1.5 eq.), NaN_3 (2.6 eq.), THF/H_2O 2/1, -10 °C, 1 h, 2. *p*TsOH.H_2O (cat.), *t*BuOH, 100 °C, 12 h, 26%; g) EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) (1.1 eq.), NH_4HCO_3 (3 eq.), $CHCl_3$, rt, 12 h, 82%; h) $Pb(OAc)_4$ (1.3 eq.), *t*BuOH, 100 °C, 2.5 h, 62%; i) 3 M dry HCl in EtOAc, rt, 30 min, ((*S*)-1 : 97%, (*R*)-1 : 95%).

Therefore, the C-glycosylation of **3** was examined with the more stable silyl ketene acetal **5**,[10] derived from 2-methyl-diethylmalonate. Whereas the reaction failed using $SnCl_4$ or BF_3Et_2O in CH_2Cl_2 or CH_3CN, **3** was completely consumed within 18 h using 1 eq. of TMSOTf in CH_3CN yielding 96% of **6** as a single α-anomer. The stereochemistry of **6** was determined on the saponified product **7** (*figure 2*). Among the characteristic $J_{H\text{-}H}$ values, H4 appeared as a doublet ($J_{H3\text{-}H4}$ = 1.8; $J_{H4\text{-}H5}$ = 0 Hz) instead of the expected triplet if H4 was axial ($J_{H3\text{-}H4} = J_{H4\text{-}H5} \approx 10$ Hz). The small $J_{H2\text{-}H3}$ and $J_{H3\text{-}H4}$ (2 and 1.8 Hz) and the large $J_{H1\text{-}H2}$ (9.8

Hz) indicated a *trans*-diaxial arrangement of H1 and H2. The NOE observed between H1 and H6 confirms the proposed conformation

Taking the steric bulk of the 2-methyl ethylmalonate moiety into account, the α-anomeric selectivity obtained is remarkable. The intermediate oxonium triflate appears to react with the nucleophilic ketene acetal exclusively from the axial side presumably under the influence of the anomeric effect.[11] However, due to the steric bulk of the substituent, the α-*C*-mannoside ring is inverted. Molecular mechanics energy minimization showed that the preferred α-$^1C_4$-conformation of **7** (drawn in *Figure 2*) was 4 kcal/mol lower in energy than the corresponding α-$^4C_1$-conformation. It is worth noting that the reaction is irreversible and the presence of the quaternary carbon C(1') excludes an epimerization of the anomeric center through β-elimination.

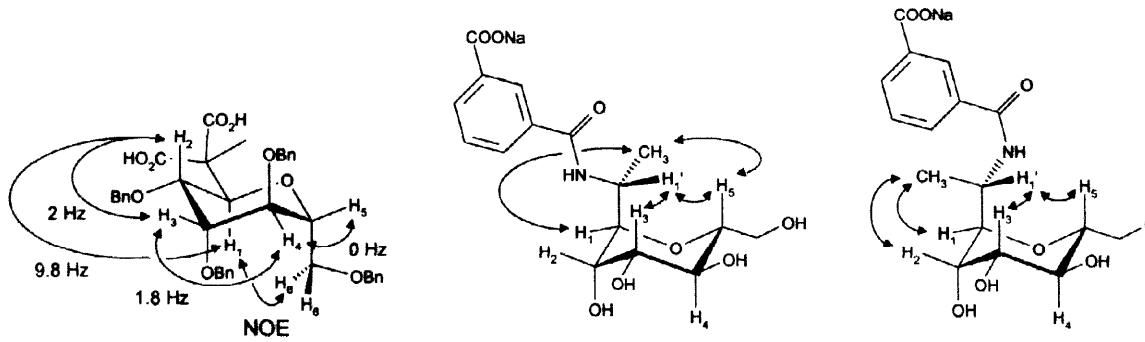
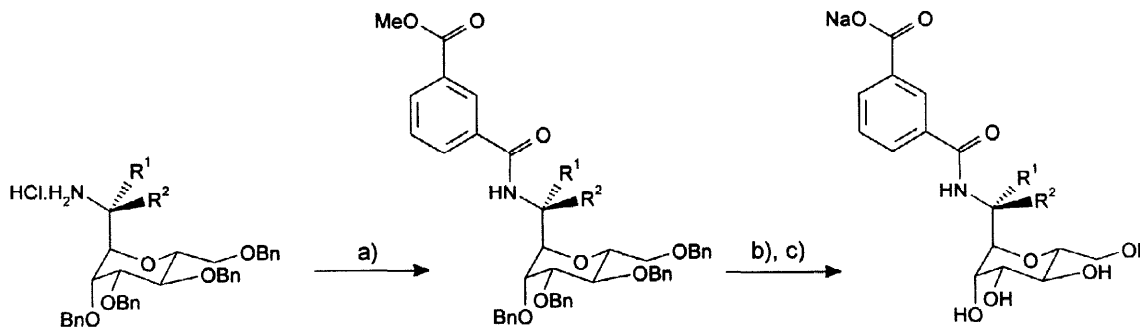


Figure 2. J values and NOE data of compounds **7**, ***(R)*-11** and ***(S)*-11**.

Decarboxylation of **7** using catalytic amount of copper (I) oxide[12] led to the monoacid **2** as a 3/2 mixture of isomers. In contrast to **7**, the decarboxylation product **2** prefers an α-$^4C_1$-conformation, presumably caused by the release of steric bulk at C(1'). The observed J values in both isomers ***(R)*-2** and ***(S)*-2** indicated that H4 and H5 are *trans*-diaxial, while H1 and H2 are both equatorial. It is worth noting that no epimerization to the β-anomer was observed.

Our first attempt to prepare **9** from **2** *via* a Curtius rearrangement using Shiori's conditions[13] or through the mixed anhydride method, gave poor yields (16% and 26%). Consequently, **2** was converted to the corresponding carboxamide **8**, which underwent Hofmann rearrangement[14] to give the desired Boc-protected amine **9** (62% yield). The isomers ***(R)*-9** and ***(S)*-9** could be separated by flash chromatography. Acidic cleavage of the Boc protection gave the desired building block ***(R)*-1**[15] (15% overall yield from **3**). The diastereomer ***(S)*-1**[15] was analogously obtained in 25% yield from **3**.



Scheme 3. a) EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) (1.2 eq.), DIPEA (1 eq.), $CHCl_3$, rt, 12 h, ***(R)*-10**, 71%; ***(S)*-10**, 78%; b) H_2 (1 atm.), Pd/C 10% (cat.), AcOH (cat.), MeOH, rt, 5 days; c) 1 N NaOH (2 - 3 eq.), THF/H_2O 1/1, 0 °C - rt, 1 h, ***(R)*-11**, 88%; ***(S)*-11**.

The absolute stereochemistry at C(1') in ***(R)*-1** and ***(S)*-1** was determined by NMR on isomers **11** (*vide supra, Scheme 3*). Acylation of the individual isomers of **1** with monomethylisophthalate acid using EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) as coupling reagent, hydrogenation and saponification led to the isomers of **11** (*Scheme 3*). NOE data are presented in *Figure 2*: In both isomers **11**, strong NOE's were observed between H1' and H3 as well as H1' and H5, confirming the α-stereochemistry and the α-$^4C_1$-conformation of the mannose ring. The ***(R)*-**configuration was then attributed to the isomer having strong NOE's between the C(1')-methyl and H1 as well as with H5, whereas in the ***(S)*-**isomer, strong NOE's appeared between the C(1')-methyl and H1 and H2. In addition, no significant NOE is observed in ***(R)*-11** between the C(1') methyl and H-2 and in ***(S)*-11** between the C(1') methyl and H-5, respectively. These NOE data confirmed our prediction based on molecular modeling concerning the conformational preference introduced by the C(1')-methyl substituent.

In summary, we have achieved the first synthesis of a new class of aminoalkyl-C-α-mannosides ***(R)*-1** and ***(S)*-1** in 6 steps with a 15% resp. 25% overall yield from commercially available methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside **3**. The chiral center in C(1') introduces a conformational preference around the glycosidic bond which is normally not present in *C*-glycosides. These building blocks have been used for the synthesis of E- and P-selectin antagonists of type **A** (*Figure 1*). Results will be communicated in due course.

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15 $[\alpha]_D$ of ***(R)*-1** = +34.1° (c = 0.98 in ethanol) and $[\alpha]_D$ of ***(S)*-1** = +23.4° (c = 1.05 in ethanol).