Asymmetric Strecker Synthesis of C-Glycopeptide

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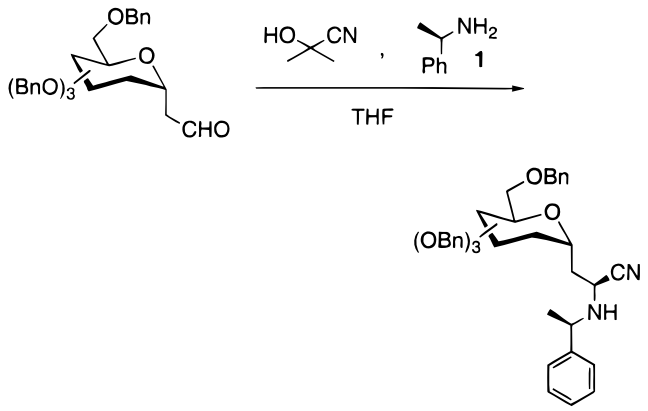
Glycopeptides serve not only as key components in cellular recognition processes but also as modulators of protein function.[1,2] Small glycopeptides have also become attractive therapeutic targets as exemplified by the recent preparation of a glycopeptide-based vaccine that is now in clinical trials against prostate cancer.[3] Nevertheless, the use of glycopeptides as pharmaceuticals is limited by their chemical and enzymatic instability in vivo. This drawback can be overcome by the use of C-glycosides.[4]

Several procedures have been reported for the asymmetric synthesis of C-linked serine[5] and asparagine[6] glycoconjugates. The strategies developed include the coupling of an activated chiral amino acid analogue,[7−9] the use of asymmetric reactions such as catalytic hydrogenation,[10] the Wittig rearrangement,[11] or the chiral auxiliary based enolate methodology.[12] In the course of developing new sialyl Lewis x mimics,[13−15] we were interested in the synthesis of glycopeptide analogues with the amino acid function closer to the sugar moiety. To date, however, only a few are available to provide such structures that involve either a Sharpless asymmetric dihydroxylation of allyl glycosides or a free-radical addition of bromo glycosides to dehydroalanine derivatives.[16,17] Here, we report our investigation on the Strecker reaction as a general stereoselective method for C-glycopeptide synthesis.

Scheme 1



Our strategy relies on the coupling of a fully benzylated C-glycoside[18,19] with a benzylic amine in the presence of acetone cyanohydrin as a cyanide donor (Scheme 1). The starting aldehydes, obtained in three steps following known procedures,[20,21] have already been used in numerous synthetic procedures.[12,22−28] To our surprise, the sugar did not induce any chirality (see Table 1, entries 6 and 10) in the mannose and the galactose series, although 1-amino sugars have previously been successfully employed as chiral auxiliaries.[29,30] Thus, we turned our attention to the use of (*S*)-α-methylbenzylamine, which has been described as one of the best chiral auxiliaries for the Strecker synthesis and always gives the expected (*S*)-configurated amino acid.[31−33] The intermediate imine is first formed at room temperature with magnesium sulfate or molecular sieves as a desiccant and then allowed to react with acetone cyanohydrin. The diastereoisomeric excess of each reaction was determined by NMR. As expected, in any solvent the selectivity was always enhanced by lowering the reaction temperature. We were able to separate the resulting α-aminonitrile mixture by standard silica gel chromatography only in the fucose and glucose series. However, in each case, pure

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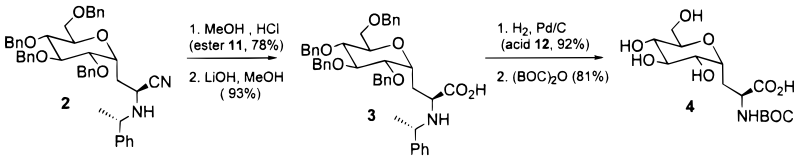
Table 1

entry	substrate	solvent	desiccant	compd	*T* (°C)	amine	*R*/*S*[a]	yield (%)
1	fucose	THF	$MgSO_4$	**5**	−20	**1**	1/5.2	79
2	fucose	CH_2Cl_2	$MgSO_4$	**5**	−85	**1**	1/1.3	73
3	galactose	THF	$MgSO_4$	**6**	−20	**1**	1/3.5	82
4	galactose	CH_2Cl_2	MS 4 Å	**6**	−70	**1**	2.1/1	67
5	galactose	CH_2Cl_2	$MgSO_4$	**6**	−15	**1**	7/1	69
6	galactose	THF	MS 4 Å	**6**	−20	$BnNH_2$	1/1	85
7	glucose	THF	$MgSO_4$	**2**	−20	**1**	1/1.8	89
8	glucose	CH_2Cl_2	MS 4 Å	**2**	−70	**1**	2/1	81
9	glucose	CH_2Cl_2	$MgSO_4$	**2**	−70	**1**	4.1/1	80
10	mannose	THF	$MgSO_4$	**7**	−20	$BnNH_2$	1/1	78
11	mannose	THF	$MgSO_4$	**7**	−40	**1**	ND	no reaction
12	mannose	CH_2Cl_2	MS 4 Å	**7**	−70	**1**	3/1	75
13	mannose	THF	$MgSO_4$	**7**	−20	**1**	1/1.1	84

[a] Determined by ^{1}H NMR.

Scheme 2

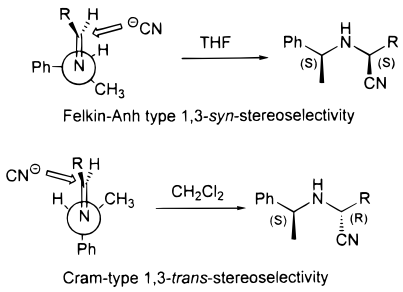


diastereoisomers could be obtained as methyl esters after methanolysis of the nitrile function. The absolute stereochemistry of the formed stereocenter was determined by ^{1}H NMR according to the well-established rules described by Stout et al.[32−34] We further confirmed the stereochemistry by converting **3** to the known *C*-glucoL-alanine analogue **4** (Scheme 2).[17] Therefore, asymmetric Strecker reactions, employing **1** as chiral inducer and *C*-glycosylacetaldehydes, give in THF the expected aminonitrile with the (*S*) configuration.

Solvent Effect. To improve the selectivity, we tried several other conditions and found that when performing the reaction in CH_2Cl_2, the diastereoselectivities were reversed as exemplified in entries 3, 5, 7, 9, 12, and 13. In the mannose, glucose, and galactose series, the reactions gave opposite stereoselectivities when carried out in CH_2Cl_2 vs THF. Table 1 collects representative data taken from experiments for which the best diastereoselectivities have been obtained as well as experiments showing the characteristics of the reaction. In CH_2Cl_2, the temperature can be significantly lowered (entries 11 and 12) to improve the selectivity. In both solvents, we obtained good stereoselectivities, especially in the reaction of the fucosyl and the galactosyl imines. It is, however, unclear why the mannose derivatives gave poorer selectivities considering that neither the mannosyl nor the galactosyl moieties induce any stereoselectivities with benzylamine (entries 6 and 10). Furthermore, we found that the use of magnesium sulfate in place of molecular sieves increased the stereoselectivities in the glucose and galactose series (entries 4, 5, 8, and 9).

Rationalization of the Stereoselectivity. The 1,3-syn-stereoselectivity was obtained when the Strecker reaction was performed in THF, corresponding to a Felkin−Ahn model (see Scheme 3).[35] This Felkin−Ahn selectivity had previously been observed in water−alcoholic mixtures containing sodium[36] or potassium

Scheme 3



cyanide.[32,33] So far, this selectivity had only been described for the Strecker reaction involving **1** as chiral inducer. Surprisingly, in CH_2Cl_2, the 1,3-trans-selectivity was observed, corresponding to a Cram-type stereoinduction.[37] In the fucose series, even if the Cram product ratio is increased from CH_2Cl_2 to THF, the Felkin−Anh product, with the *S* configuration, is still predominantly formed (Table 1, entry 2). It is still unclear why the Strecker reaction proceeds through different transition states from a solvent to another but this phenomenon seems to be quite general.

Application to the Synthesis of Fucopeptides Mimetics. One application of this methodology is illustrated in Scheme 4, where the amino nitrile **7** resulting from the asymmetric Strecker reaction was transformed into the methyl ester. Saponification then gives the *C*-fucopeptide **8**, which could be hydrogenolysed to the fully deprotected analogue **9**. This *C*-fucosyl alanine derivative can be further functionalyzed and used as core structure to generate libraries of biologically relevant fucopeptide mimetics.

In conclusion, we developed a new stereoselective way to synthesize glycoalanine derivatives using the Strecker reaction. An interesting solvent-dependent reversal of

(34) In all cases, in THF with (*S*)-(−)-α-methylbenzylamine **1**, the protons vicinal to the nitrile of the major isomer were always upfield, compared to the minor isomer, in the NMR spectra. The (*S*) stereochemistry was therefore assigned to the major isomer.

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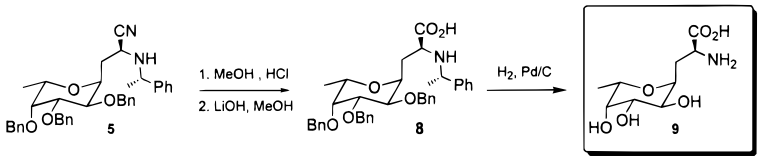
Scheme 4



stereoinduction was observed from THF to CH_2Cl_2, allowing the preparation of both epimers using the same chiral inducer (*S*)-methylbenzylamine.

Experimental Section

General Procedures. Strecker Reaction. To an aldehyde (prepared by standard procedure) in the appropriate solvent (see Table 1, $c = 0.2$ M) was added the desiccant and (*S*)-phenylethylamine (2.0 equiv) at room temperature. The reaction mixture was then cooled to the temperature indicated in Table 1, and acetone cyanohydrin (5.0 equiv) was injected. After the reaction was complete, the mixture was poured onto ice−water, saturated with sodium bicarbonate, and extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvent removed in vacuo. The product was purified by column chromatography on silica gel.

Aminonitrile Conversion to the Corresponding α-Amino Methyl Ester. Dry methanol was added to aminonitriles ($c = 0.1$ M). The solution was saturated with HCl gas at 0 °C and kept at this temperature for an additional 2 h. The reaction mixture was then poured on ice−water and neutralized with sodium hydroxide and sodium bicarbonate until pH 7.5. After extraction, the combined organic layers were dried over magnesium sulfate and the solvent removed in vacuo. The residual mixture was purified by column chromatography on silica gel.

Conversion of the Methyl Ester to the Corresponding Acid. The methyl ester was dissolved in a 10:1 methanol/water mixture. Lithium hydroxide was added (apparent pH = 9.5−10.5), the mixture was stirred at room temperature for 16 h, the solution was reacidified to pH 1, and the aqueous layer was extracted three times with ethyl acetate. The combined organic fractions were dried with magnesium sulfate, and the solvent was removed in vacuo.

Deprotection of the Benzyl Groups. A solution of benzylated compound in MeOH/H_2O (10:1) was treated with H_2 at 60 psi in the presence of $Pd(OH)_2$/C (Degussa type, 20% $Pd(OH)_2$ on activated carbon) at 23 °C overnight. The reaction was filtered through Celite and washed with MeOH/H_2O/AcOH (10:1:1), and the solvent was removed under reduced pressure.

2-[(1(*S*)-Phenylethyl)amino]-3-[2,3,4,6-tetrabenzyl-α-D-glucopyranosyl]propanenitrile (2). The general procedure was used for the synthesis. The desired pure (**S**)-derivative was obtained. The (*R*)-aminonitrile was still contaminated with its diastereoisomer (Table 1, entry 7:89% yield): ^{1}H NMR (400 MHz, $CDCl_3$) *S* diastereoisomer (50.9%) δ 7.32−7.08 (m, 25H), 4.90−4.30 (m, 8H), 4.20 (td, $J = 5.2$ Hz $J = 3.9$ Hz, 1H), 4.06 (q, $J = 6.6$ Hz, 1H), 3.75−3.55 (m, 5H), 3.37 (bd, $J = 9.3$ Hz, 1H), 2.12 (m, 2H), 1.76 (bs, 1H), 1.33 (d, $J = 6.6$ Hz, 3H); *R* diastereoisomer (38.1% *R*/*S* = 84/16) δ 7.32−7.08 (m, 25H), 4.90−4.30 (m, 8H), 3.98 (q, $J = 6.6$ Hz, 1H), 3.84 (dd, $J = 8.2$ Hz $J = 3.9$ Hz, 1H), 3.75−3.55 (m, 5H), 3.48 (bd, $J = 8.8$ Hz, 1H), 2.24 (ddd, $J = 15.0$ Hz $J = 11.6$ Hz $J = 3.8$ Hz, 1H), 2.01 (ddd, $J = 15.0$ Hz $J = 8.1$ Hz $J = 2.4$ Hz, 1H), 1.27 (bs, 1H), 1.29 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.75, 143.24, 138.5−137.7; 128.7−127.5, 126.73, 120.18, 119.94, 82.00, 81.98, 79.13, 79.98, 77.63, 77.42, 75.40, 75.02, 74.26, 71.78, 71.64, 70.95, 70.56, 68.54, 68.00, 56.52, 56.14, 45.29, 45.02, 29.69, 28.57. 24.73, 21.70; HRMS (M + Na^+) calcd for $C_{45}H_{48}N_2O_5$ 719.3461, found 719.3479.

2(*S*)-[(1(*S*)-Phenylethyl)amino]-3-[2,3,4,6-tetrabenzyl-α-D-glucopyranosyl]propanoic Acid (3). The general procedure was used for the synthesis (93% yield): ^{1}H NMR (600 MHz, CD_3-OD) δ 7.50−7.11 (m, 25H), 4.77 (d, $J = 11.4$ Hz, 1H), 4.67 (m, 2H), 4.56 (AB system, $\nu_A = 4.58$ $\nu_B = 4.53$, $J_{AB} = 11.4$ Hz, 2H), 4.49 (m, 1H), 4.41 (m, 2H), 4.15 (btd, $J = 4.8$ Hz $J = 10.4$ Hz, 1H), 3.74 (m, 1H), 3.61 (m, 2H), 3.45 (m, 3H), 3.29 (m, 1H), 2.46 (btd, $J = 16.0$ Hz $J = 5.1$ Hz, 1H), 2.21 (bt, $J = 16.0$ Hz, 1H), 1.65 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.52, 139.69, 139.34, 139.14, 138.93, 136.81, 130−128, 81.44, 79.57, 78.38, 75.71, 75.25, 74.24, 74.02, 72.96, 72.32, 69.73, 59.55, 30.88, 20.67; HRMS (MaldiFTMS) calcd for $C_{45}H_{49}N_1O_7$ 716.3587, found 716.3606.

2(S)-[(1(S)-Phenylethyl)amino]-3-[2,3,4,6-tetrabenzyl-α-L-fucopyranosyl]propanenitrile (5). The general procedure was used for the synthesis (66% yield in pure (*S*) isomer): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45−7.16 (m, 20H), 4.74 (m, 2H), 4.63 (m, 3H), 4.48 (d, $J = 11.8$ Hz, 1H), 4.38 (td, $J = 7.3$ Hz $J = 3.2$ Hz, 1H), 4.04 (q, $J = 6.6$ Hz, 1H), 3.82 (dd, $J = 7.1$, 3.0 Hz, 1H), 3.79 (m, 1H), 3.71 (t, $J = 3.0$ Hz, 1H), 3.69 (dd, $J = 7.1$, 2.8 Hz, 1H), 3.33 (dd, $J = 8.7$, 3.3 Hz, 1H), 2.11 (ddd, $J = 14.7$, 11.1, 3.3 Hz, 1H), 1.75 (ddd, $J = 14.7$, 8.9, 2.0 Hz, 1H), 1.72 (bs, 1H), 1.32 (d, $J = 6.6$ Hz, 3H), 1.19 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.02, 138.47, 138.67, 138.5, 137.76, 136.50, 129.63, 128−127, 125.85, 120.28, 73.27, 75.80, 73.32, 73.17, 73.14, 73.04, 68.86, 63.03, 56.37, 45.81, 25.14, 15.36; HRMS (M + Cs^+) calcd for $C_{38}H_{42}N_2O_4$ 723.2199, found 723.2221.

2-[(1(*S*)-Phenylethyl)amino]-3-[2,3,4,6-tetrabenzyl-α-D-galactopyranosyl]propanenitrile (6). The general procedure was used for the synthesis. This compound was isolated as a diastereoisomeric mixture (82% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.05 (m, 25H), 4.75−4.45 (m, 8H), 4.20 (td, $J = 10.3$, 4.0 Hz, 1H), 4.01 (q, $J = 6.6$ Hz, 1H), 3.94 (m, 1H), 3.90 (m, 1H), 3.71 (m, 1H), 3.65 (dd, $J = 7.0$, 2.6 Hz, 1H), 3.59 (dd, $J = 10.6$, 5.1 Hz, 1H), 3.26 (dd, $J = 8.4$, 5.9 Hz, 1H), 2.08 (ddd, $J = 14.0$, 10.2, 5.9 Hz, 1H), 1.87 (ddd, $J = 14.0$ Hz, 1H), 1.72 (bs, 1H), 1.29 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.44, 138.43, 138.41, 138.39, 138.33, 138.31, 137.90, 128−125, 120.28, 76.48, 76.13, 74.03, 73.33, 73.27, 73.24, 73.18, 73.02, 72.99, 72.52, 67.31 (*S*), 66.28 (*R*), 56.58 (*S*), 56.05 (*R*), 45.83 (*S*), 45.54 (*R*), 31.88, 24.68; HRMS (M + Cs^+) calcd for $C_{45}H_{48}N_2O_5$ 829.2618, found 829.2648.

2-[(1(*S*)-Phenylethyl)amino]-3-[2,3,4,6-tetrabenzyl-α-D-mannopyranosyl]propanenitrile (7). The general procedure was used for the synthesis. This compound was isolated as a diastereoisomeric mixture (84% yield): ^{1}H NMR (400 MHz, $CDCl_3$) (*R*) diastereoisomer δ 7.31−7.14 (m, 25H), 4.85−4.42 (m, 8H), 4.34 (ddd, $J = 10.3$ Hz $J = 7.3$ Hz $J = 3.5$ Hz, 1H), 3.97 (q, $J = 6.5$ Hz, 1H), 3.91 (bt, $J = 4.3$ Hz, 1H), 3.79−3.61 (m, 5H), 3.51 (m, 1H), 1.95 (m, 2H), 1.58 (bs, 1H), 1.26 (d, $J = 6.5$ Hz, 3H); (*S*) diastereoisomer δ 7.31−7.14 (m, 25H), 4.85−4.42 (m, 8H), 4.17 (bq, $J = 7.0$ Hz, 1H), 4.05 (q, $J = 6.2$ Hz, 1H), 3.79−3.61 (m, 5H), 3.51 (m, 1H), 3.43 (bt, $J = 7.6$ Hz, 1H), 1.95 (m, 2H), 1.58 (bs, 1H), 1.33 (d, $J = 6.2$ Hz, 3H).

2(*S*)-[(1(*S*)-Phenylethyl)amino]-3-[2,3,4,6-tetrabenzyl-α-L-fucopyranosyl]propanoic Acid (8). The general procedure was used for the synthesis (95% yield): ^{1}H NMR (600 MHz, CD_3-OD) δ 7.37−7.10 (m, 20H), 4.88 (bs, 2H), 4.65 (m, 2H), 4.48 (m, 3H), 4.21 (td, $J = 10.1$, 3.9 Hz, 1H), 3.85 (m, 1H), 3.82 (dd, $J = 6.2$, 2.9 Hz, 1H), 3.74 (bt, $J = 3.8$ Hz, 1H), 3.71 (dd, $J = 6.2$, 3.8 Hz, 1H), 3.46 (bd, $J = 5.4$ Hz, 1H), 2.29 (m, 1H), 2.00 (m, 1H), 1.64 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 177.62, 139.37, 139.28, 138.90, 136.93, 130.10, 130.01, 128.9−128.1, 77.33, 76.37, 75.39, 73.43, 73.41, 73.32, 73.22, 70.21, 67.25, 58.64, 29.99, 19.39, 14.65; HRMS (M + Cs^+) calcd for $C_{39}H_{45}NO_6$ 756.2301, found 756.2321.

2(*S*)-Amino-3-α-L-fucopyranosylpropanoic Acid (9). The general procedure was used for the synthesis (94% yield): ^{1}H NMR (600 MHz, D_2O) δ 4.11 (ddd, $J = 11.2$, 5.6, 3.0 Hz, 1H), 3.94 (dd, $J = 9.7$, 5.9 Hz, 1H), 3.91 (q, $J = 6.0$ Hz, 1H), 3.79 (dd, $J = 3.4$, 1.6 Hz, 1H), 3.76 (bdd, $J = 9.6$, 3.4 Hz, 2H), 2.26 (ddd, $J = 15.3$, 11.7, 3.5 Hz,), 1.94 (ddd, $J = 15.3$, 12.0, 3.2 Hz, 1H), 1.11 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, D_2O) δ 178.12, 71.02, 70.23, 69.11, 67.08, 66.69, 51.64, 25.19, 14.81; electrospray (MH^+) 236.

2(*S*)-[(1(*S*)-Phenylethyl)amino]-3-[2,3,4,6-tetrabenzyl-α-L-fucopyranosyl]propanoic Acid, Methyl Ester (10). The general procedure was used for the synthesis (81% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46−7.12 (m, 20H), 4.90−4.50 (m, 6H), 4.28 (td, J = 11.5, 3.3 Hz, 1H), 3.91 (bs, 1H), 3.77 (bs, 1H), 3.79 (m, 1H), 3.71 (m, 6H), 3.11 (dd, J = 9.3, 4.4 Hz, 1H), 1.95 (ddd, J = 14.8, 10.8, 4.5 Hz, 1H), 1.63 (m, 2H), 1.29 (d, J = 6.5 Hz, 3H), 1.16 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.62, 145.62, 139.67, 139.39, 139.23, 129−127, 77.77, 77.00, 74.24, 74.01, 73.91, 73.89, 73.85, 73.71, 69.22, 57.19, 57.00, 52.49, 26.48, 16.39; HRMS (M + Cs^+) calcd for $C_{39}H_{45}NO_6$ 756.2301, found 756.2321.

2(*S*)-[(1(*S*)-Phenylethyl)amino]-3-[2,3,4,6-tetrabenzyl-α-D-glucopyranosyl]propanoic Acid, Methyl Ester (11). The general procedure was used for the synthesis (78% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.11 (m, 25H), 4.90 (m, 1H), 4.77 (m, 2H), 4.56 (m, 2H), 4.42 (m, 3H), 4.17 (td, J = 5.2, 9.7 Hz, 1H), 3.73 (m, 2H), 3.68 (s, 3H), 3.66 (m, 2H), 3.61 (m, 2H), 3.43 (bd, J = 9.4 Hz, 1H), 3.35 (dd, J = 10.5, 1.9 Hz, 1H), 3.17 (t, J = 6.2 Hz, 1H), 2.02 (m, 2H), 1.83 (bs, 1H), 1.31 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.79, 145.09, 138.66, 138.23, 138.08, 128−126, 82.16, 79.53, 77.71, 75.43, 74.93, 73.42, 72.86, 71.50, 71.18, 68.43, 56.85, 55.88, 51.72, 29.26, 25.21; HRMS (MaldiFTMS) calcd for $C_{46}H_{51}N_1O_7$ 730.3744, found 730.3744.

2(*S*)-Amino-3-[α-D-glucopyranosyl]propanoic Acid Acetate Salt (12). The general procedure was used for the synthesis except that 5% AcOH was added to the solvent mixture): ^{1}H NMR (600 MHz, D_2O) δ 4.22 (btd, J = 4.8, 10.1 Hz, 1H), 3.77 (m, 2H), 3.67 (dd, J = 6.1, 9.7 Hz, 1H), 3.64 (dd, J = 4.8 Hz, J_{AB} = 12.3 Hz, 1H), 3.56 (bt, J = 9.2 Hz, 2H), 3.30 (t, J = 9.2 Hz, 1H), 2.15 (m, 2H), 1.95 (); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.75, 74.48, 74.14, 73.70, 71.28, 70.71, 61.65, 54.07, 26.58, 23.77; HRMS (MaldiFTMS) calcd for $C_9H_{18}NO_7$ 252.1083 (MH^+), found 252.1079.

Supporting Information Available: NMR spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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