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# Chemical investigations in the synthesis of *O*-serinyl aminoribosides

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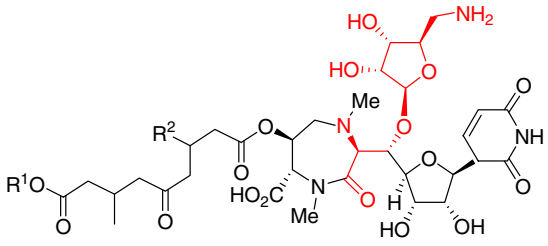
**Abstract**—Glycosylation involving D-ribose derivatives and various *N*-protected *tert*-butyl L-serinates can be achieved efficiently by careful choice of the activation method at the anomeric position and of the Lewis acid promoter. The conditions described allow the major formation of the β-anomer required for further elaboration to liposidomycin and caprazamycin analogues.


## 1. Introduction

A concise and efficient synthesis of glycoconjugates is a significant challenge for the better understanding of biological events, such as cell–cell recognition, cell adhesion, host pathogen interactions, and tumor cell metastasis.[1] Furthermore, glycosyl aminoacids can also be part of complex natural products.[2] For example, *O*-serinyl aminoriboside is a key fragment of the naturally occurring family of lipo-uridinyl antibiotics, such as liposidomycins[3] and caprazamycins[4] (Fig. 1), for which several synthetic approaches have been studied.[5,6] These biologically active compounds are formed from common structural fragments: 1,4-diazepan-3-one heterocycle, aminoribosyl, and uridinyl moieties and lipophilic side chains, eventually substituted by a fucosyl derivative in the case of caprazamycins. In the context of an ongoing program dealing with the synthesis of liposidomycins analogues using the diazepanone core as a versatile scaffold with high and orthogonal functionalization, we aimed at synthesizing *O*-serinyl aminoriboside for further transformation into *O*-serinyl aminoriboside diazepanones. Indeed, it has been shown[7] that the aminoribose moiety of the liposidomycins is essential for biological activity. Although numerous methods of glycosylation[8] related to the synthesis of pyranosyl aminoacids[9] have been described, only few examples are dedicated to the apparented *O*-glycoside derivatives of furanose.[10] Furanosyl derivatives are mainly involved in *N*-glycosylation reactions with either purine or pyrimidine moieties to afford nucleosidic compounds. The synthesis of such *O*-linked furanosyl aminoacids is complicated both by the acid lability of glycosides in general, and by the base sensitivity of the *O*-serinyl glycosides, involving retro-Michael reaction, in particular.[11] In this context, we embarked on the synthesis of *O*-serinyl aminoriboside according to efficient routes. Part of our results involving commercially available *O*-protected derivatives of D-ribose has already been published in a preliminary form.[12] Herein we report the totality of our work in this field, notably including access to an *O*-serinyl azidoriboside, a key building block for further elaboration.




liposidomycins : $R^1$ = H, $R^2$ = alkyl or alkenyl chain

caprazamycins : $R^1$ = fucose derivative, $R^2$ = alkyl chain

**Figure 1.** Structure of liposidomycins and caprazamycins, naturally occurring compounds with antibacterial activity.

Retrosynthetic analysis of the targeted compound (Fig. 2) involves a *tert*-butyl *N*-protected-L-serinate as a glycosyl acceptor and various D-ribose derivatives activated at the anomeric position as glycosyl donnors. For this purpose, access to orthogonally *N*- and *O*-protected

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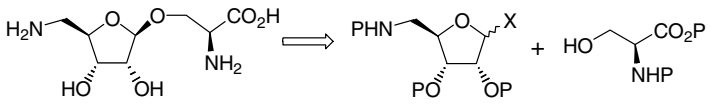
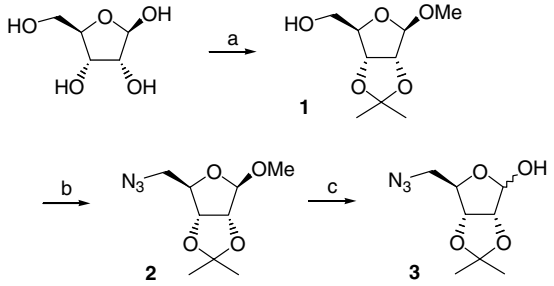


**Figure 2.** Retrosynthetic analysis.

derivatives with predominant or exclusive β-*O*-glycosidic linkage has been targeted.

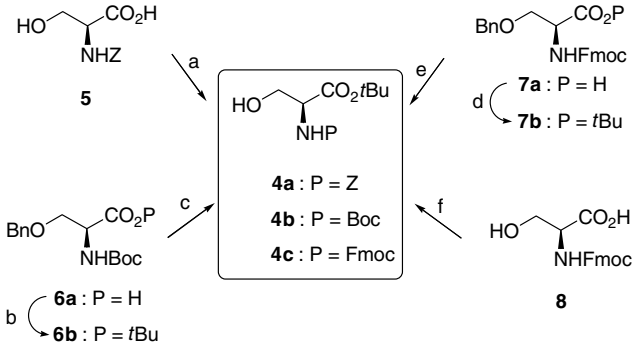
## 2. Results and discussion

Before studying the glycosylation reaction, various derivatives of both counterparts have been synthesized. With the goal of further elaboration of liposidomycin analogues in mind, we focused on the preparation of an azidoribose derivative for which the secondary alcohol functions at the 2- and 3-positions were protected as an acetonide. Thus, the commercially available D-ribose was first submitted to concomitant protection of the anomeric hydroxy group and secondary alcohols (Scheme 1) to give **1** in 75% yield.[13] Subsequent Mitsunobu reaction[14] with hydrazoic acid afforded the corresponding methyl 5-azidofuranoside derivative **2** in 98% yield. Further acidic hydrolysis of the protecting groups at 85 °C, followed by selected protection of the 2,3-diol by 2,2-dimethoxypropane in acetone in the presence of camphor sulfonic acid yielded the expected precursor **3** (40%).



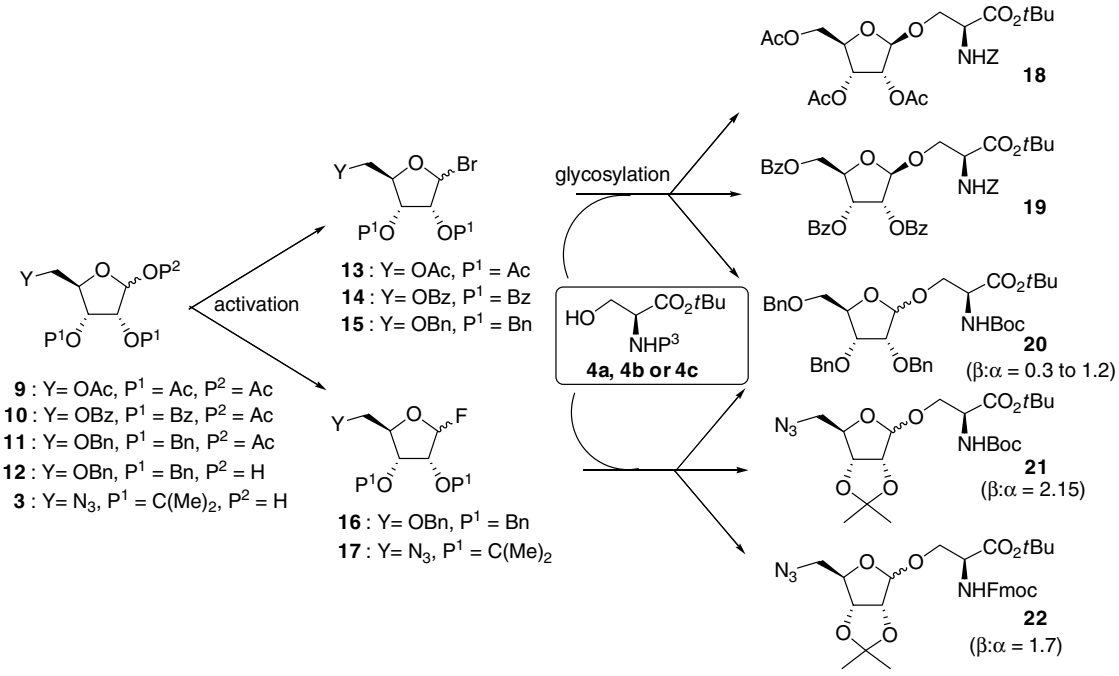
**Scheme 1.** Reagents and conditions: $Me_2CO$, MeOH, $HCl_g$, 75%; (b) $HN_3$, $Ph_3P$, DIAD, THF, 0 °C, 98%; (c) (i): $H_2SO_4$, 85 °C, (ii): $Me_2C(OMe)_2$, $Me_2CO$, CSA, 50 °C, 40% (β/α = 9:1).

We next turned our attention to the preparation of variously protected L-serine derivatives. Thus, the corresponding *N*-Cbz, *N*-Boc and *N*-Fmoc compounds **4** were prepared (Scheme 2) from commercially available reagents. The *N*-Cbz compound **4a** was readily obtained in 88% yield by esterification of *N*-Cbz serine with *tert*-butyl bromide in the presence of potassium carbonate and benzyl triethylammonium chloride.[15] The related *N*-Boc derivative **4b** was prepared in two steps from the *O*-benzyl *N*-Boc serine **6a**. Esterification with *tert*-butyl trichloroacetimidate in the presence of boron trifluoride etherate afforded the corresponding *tert*-butyl ester in 96% yield and was followed by *O*-benzyl hydrogenolysis in the presence of Pearlman's catalyst in a quantitative yield.[16] Finally, the synthesis of the *N*-Fmoc derivative **4c** could be achieved according to two different ways. The first one involved a similar strategy as that described for the preparation of **4b**, however in this case *O*-benzyl hydrogenolysis occurred in a lower yield (29%). The second method involving direct esterification of the *N*-Fmoc serine **8** in the presence of *tert*-butyl trichloroacetimidate[17] was achieved in an improved 84% yield.



**Scheme 2.** Reagents and conditions: (a) *t*BuBr, $K_2CO_3$, $BnEt_3NCl$, $CH_3CN$, 50 °C, 88%; (b) $Cl_3CC(=NH)OtBu$, $BF_3{\cdot}OEt_2$, $C_6H_{12}$, $CH_2Cl_2$, 96%; (c) $H_2$, $Pd(OH)_2/C$, EtOH, AcOH, 99%; (d) $Cl_3C(=NH)OtBu$, $CH_2Cl_2$, $C_6H_{12}$, 40 °C, 100%; (e) $H_2$, Pd/C, EtOH, AcOH, 29%; (f) $Cl_3C(=NH)OtBu$, $C_6H_{12}$, EtOAc, 84%.

With these building blocks in hand, the key glycosylation step was then studied (Scheme 3). Due to the possible anchimeric assistance of a participating group at the 2-position of the glycosyl derivatives to direct the reaction toward a single anomer, commercially available D-ribose derivatives displaying either an acetyl **9** or a benzoyl **10** group were included herein. Moreover, in order to examine the diastereoselectivity, the glycosylation was also carried out with the C2 *O*-benzyl derivative **11**, which was easily available from **12** by acetylation in anomeric position ($Ac_2O$, DMAP, $CH_2Cl_2$, 93%). In all cases, the glycosylation was carried out through activation of the anomeric position as a halide. On one hand, bromide derivatives of C2-*O*-acetyl **9**, -benzoyl **10** and -benzyl **11** were prepared by reaction with an excess of trimethylsilyl bromide[18] in dichloromethane. Due to the instability of these bromides[19] they could not be purified by flash chromatography. Nevertheless $^1H$ NMR of the crude showed the major formation of the expected β-anomer (over 95%). On the other hand, fluorination by DAST[20] [(diethylamino)sulfur trifluoride] was carried out either on **12** or on azidoacetonide **3**. In these cases, the resulting β/α mixture of fluorinated compounds **16** and **17** were more stable, and could be isolated by flash chromatography in about a 5.3 ratio in 84% yield. Careful choice of the Lewis acid used to promote the glycosylation[8] revealed that the best conditions were either silver triflate in dichloromethane at −15 °C for compounds activated as a bromide, or stannous dichloride in the presence of silver perchlorate from −15 °C




**Scheme 3.** Reagents and conditions: see text and Table 1.

to rt, for derivatives activated as a fluoride. In each case, the success of the reaction depends on the presence of a large excess of molecular sieves.[21] According to the nature of both the ribosyl and serinyl derivatives, the yield and the diastereoselectivity of the reaction are gathered in Table 1. As expected, with a participating group at the C2 position of the ribose (entries 1 and 2) the exclusive formation of the β-anomer was observed. Glycoside **19** was isolated in an excellent overall yield (92%) after flash chromatography, while its acetate analogue **18** was isolated in a lower yield (32%). In the latter case, 2,3,5-tri-*O*-acetyl ribose was isolated in yields of up to 62% revealing in situ hydrolysis of the bromide intermediate **13**. For the C2 benzyl or acetonide derivative (unable to promote anchimeric assistance) the formation of a mixture of α,β-anomers was observed. For benzyl derivatives **11** and **12** (entries 3 and 4) according to the nature of both the halide in anomeric position (**15** and **16**) and the Lewis acid used in the glycosylation step, the yield and diastereoselectivity for the formation of **20** varied. As expected with the non-participating group and with bromide activation (entry 3), the major formation of the α-anomer was observed (β/α = 0.3, 69% yield of **20**). Nevertheless, fluoride activation allowed the inversion of the diastereoselectivity to give the major formation of the β-anomer (β/α = 1.2, entry 4). However in that case, the yield of **20** decreased to 44%. With regards to azidoribose compound **3** (entries 5 and 6), its fluoride derivative was involved in glycosylation with either *tert*-butyl *N*-Boc or *N*-Fmoc serinate, **4b** or **4c**, to afford the glycosylated compound **21** or **22**, respectively, in good to excellent yields. In each case, the major formation of the β-anomer was observed and was unambiguously assigned by $^1$H NMR analysis (Table 2), singlet or doublet for H1 in the β- or α-anomer, respectively. Indeed, we were delighted to observe that for entries 4–6, the experimental conditions allowed the predominant formation of the desired β-anomer. In these cases, increasing both the temperature and duration of the reaction increased the β-anomer formation as observed by TLC. These observations seem to be in agreement with the formation of the α-anomer as a kinetic product, and β-anomer as a thermodynamic product. Unfortunately, exclusive formation of either one or the other anomer could not be achieved under these conditions.

**Table 1.** Synthesis of *O*-serinyl riboside derivatives via Scheme 3

| Entry | Compd | Activation | Compd | Yield | Aminoacid | Glycosylation | Compd | Ratio β:α | Yield[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **9** | TMSBr, $CH_2Cl_2$, −40 °C to rt | **13**[a] | — | **4a** | AgOTf, $CH_2Cl_2$, −15 °C | **18** | β: 100% | 32[b,c] |
| 2 | **10** | TMSBr, $CH_2Cl_2$, −40 °C to rt | **14**[a] | — | **4a** | AgOTf, $CH_2Cl_2$, −15 °C | **19** | β: 100% | 92[b] |
| 3 | **11**[d] | TMSBr, $CH_2Cl_2$, −40 °C to rt | **15**[a] | — | **4b** | AgOTf, $CH_2Cl_2$, −15 °C | **20** | 0.3 | 69[b] |
| 4 | **12** | DAST, THF, −30 °C to rt | **16** | 84 | **4b** | $SnCl_2$, $AgClO_4$, −15 °C to rt | **20** | 1.2 | 44 |
| 5 | **3** | DAST, THF, −30 °C to rt | **17** | 95 | **4b** | $SnCl_2$, $AgClO_4$, −15 °C to rt | **21** | 2.15 | 64 |
| 6 | **3** | DAST, THF, −30 °C to rt | **17** | 95 | **4c** | $SnCl_2$, $AgClO_4$, −15 °C to rt | **22** | 1.7 | 100 |

[a] Unstable compound.
[b] Overall yield for the two steps.
[c] Corrected yield.
[d] Available from **12** by acetylation: $Ac_2O$, DMAP, $CH_2Cl_2$, 93%.

**Table 2.** $^1$H NMR data, chemical shift and coupling constants, for H1 of α and β-anomers of the fluorinated derivatives **16** and **17** and the glycosylated products **18–22**

| | | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|
| α | δ | 5.61 | 5.70 | — | — | 4.85 | 5.09 | 4.99 |
| | multiplicity | dd ($^2J_{H1,F} = 64$, $^3J_{H1,H2} = 3.1$) | dd ($^2J_{H1,F} = 64$, $^3J_{H1,H2} = 3.5$) | — | — | d ($^3J_{H1,H2} = 3.1$) | d ($^3J_{H1,H2} = 4.4$) | d ($^3J_{H1,H2} = 4.0$) |
| β | δ | 5.84 | 5.83 | 4.98 | 5.30 | 5.02 | 5.01 | 5.13 |
| | multiplicity | d ($^2J_{H1,F} = 61$) | d ($^2J_{H1,F} = 61$) | s | s | s | s | s |

## 3. Conclusion

The glycosylation involving ribose derivatives and variously *N*-protected *tert*-butyl L-serinate could be achieved efficiently by careful choice of the activation method at the anomeric position and of the Lewis acid promoter. The conditions described allow the major formation of the β-anomer required for further elaboration to liposidomycin and caprazamycin analogues. Their obtention will take advantage of the orthogonally protected functional groups of the synthesized *O*-serinyl aminoribosides. These results make a contribution to the already reported methods for the obtention of *O*-glycosylated aminoacids which are, to the best of our knowledge, seldom described in furanosyl series.

## 4. Experimental

$^1$H NMR (250 or 500 MHz) and $^{13}$C NMR (63 MHz) spectra were recorded on a Bruker AM250 in $CDCl_3$ (unless indicated). Chemical shifts ($\delta$) are reported in ppm and coupling constants given in Hz. Optical rotations were measured on a Perkin–Elmer 241C polarimeter with a sodium (589 nm) or mercury (365 nm) lamp at 20 °C. Mass spectra, chemical ionization (CI), and high resolution (HRMS) were recorded by the Service de Spectrométrie de Masse, Ecole Normale Supérieure, Paris. All reactions were carried out under an argon atmosphere, and monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Unless indicated, flash chromatography was performed with Merck Kieselgel 60 (0.2–0.5 mm); the solvent system was given v/v. Spectroscopic ($^1$H and $^{13}$C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

### 4.1. Methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside 2

To a solution of triphenylphosphine, dried in vacuo (14.26 g, 2.2 equiv, 54.4 mmol), in THF (120 mL) at 0 °C, was added dropwise diisopropyl azodicarboxylate (10.52 mL, 2.2 equiv, 54.4 mmol) and the mixture stirred for 5 min prior to the sequential dropwise addition of a benzene solution of hydrazoic acid[22] (2.8 M, 69.3 mL, 2.1 equiv, 52.6 mmol) and a solution of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside **1** (5 g, 1 equiv, 24.6 mmol) in THF (10 mL). After 3 h stirring, the mixture was concentrated in vacuo and flash chromatography (cyclohexane/EtOAc 9:1) of the residue afforded the expected methyl azido-ribofuranoside **2** (5.54 g) as a yellow oil in 98% yield. $[\alpha]_D = -53$ (*c* 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 4.98 (s, 1H, $H_1$), 4.56 (s, 2H, $H_2$, $H_3$), 4.27 (dd, 1H, $J_{H4-H5a} = 7.6$ Hz, $J_{H4-H5b} = 6.8$ Hz $H_4$), 3.43 (dd, 1H, $J_{H5a-H4} = 7.6$ Hz, $J_{H5a-H5b} = 12.6$ Hz, $H_{5a}$), 3.36 (s, 3H, OMe); 3.22 (dd, 1H, $J_{H5b-H4} = 6.8$ Hz, $J_{H5b-H5a} = 12.6$ Hz, $H_{5b}$), 1.47, 1.30 (2s, 6H, $CMe_2$); $^{13}$C NMR $\delta$ 112.7 ($CMe_2$), 109.8 ($C_1$), 85.4 ($C_4$), 85.1 ($C_2$), 82.1 ($C_3$), 55.2 (MeO), 53.8 ($C_5$), 26.4, 24.9 ($CMe_2$); MS (CI, $NH_3$): 247 $(M+NH_4)^+$; HMRS for $C_9H_{19}N_4O_4$ $(M+NH_4)^+$: calcd 247.1406; found 247.1407.

### 4.2. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranose 3

To azidoribofuranoside **2** (150 mg, 1 equiv, 0.66 mmol) was added a 0.1 M solution of sulfuric acid (3.1 mL) and the mixture stirred at 85 °C for 4 h. After cooling to 20 °C, the solution was neutralized by the addition of 1X8-400 Dowex® resin until pH ≈ 7.5. After filtration and concentration in vacuo, the residual water was azeotropically removed with toluene and the residue concentrated in vacuo. To the resulting residue in acetone (2.7 mL) were then added camphor sulfonic acid (15.5 mg, 0.1 equiv, 0.067 mmol) and 2,2-dimethoxypropane (0.535 mL, 6.7 equiv, 4.39 mmol). After heating at 50 °C for 30 min, the temperature was decreased to 20 °C and a saturated aqueous solution of sodium bicarbonate added. Evaporation of the acetone was followed by the addition of ethyl acetate and the organic layer successively washed with water and brine, then dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc 7:3) gave an unseparable β/α-anomers mixture (9:1) of the ribofuranose **3** (57 mg) as a colorless oil in 40% yield. $^1$H NMR $\delta$ 5.49 (s, 1H, $H_{1\beta}$), 5.43 (sl, 1H, $H_{1\alpha}$), 4.65 (m, 2H, $H_2$, $H_3$), 4.35 (ddd, 1H, $J_{H4-H3} = 0.7$ Hz, $J_{H4-H5a} = 7.1$ Hz, $J_{H4-H5b} = 5.7$ Hz, $H_4$), 3.58 (dd, 1H, $J_{H5a-H4} = 7.1$ Hz, $J_{H5a-H5b} = 8.9$ Hz, $H_{5a}$), 3.41 (dd, 1H, $J_{H5b-H4} = 5.7$ Hz, $J_{H5b-H5a} = 8.9$ Hz, $H_{5b}$), 1.50, 1.34 (2s, 6H, $CMe_2$); $^{13}$C $\delta$ 112.8 ($CMe_2$), 103.4 ($C_1$), 86.0 ($C_2$), 85.4 ($C_4$), 82.1 ($C_3$), 53.9 ($C_5$), 26.2, 24.7 ($CMe_2$); MS (CI, $NH_3$): 215 $(M-H_2O+NH_4^+)$; HMRS for $C_8H_{13}N_3O_4$ $(M^+-H_2O+NH_4^+)$: calcd 215.1144; found 215.1148.

### 4.3. *tert*-Butyl *N*-benzyloxycarbonyl-L-serinate 4a

To a solution of the commercially available *N*-benzyloxycarbonyl-L-serine (500 mg, 1 equiv, 2.09 mmol) in

acetonitrile (16 mL) were successively added benzyl triethylammonium chloride (477 mg, 1 equiv, 2.09 mmol), potassium carbonate (7.50 g, 26 equiv, 54.3 mmol) and finally *tert*-butyl bromide (11.3 mL, 48 equiv, 0.1 mol) at 20 °C. After 24 h stirring at 48 °C and cooling to 20 °C, cold water (2.1 mL) was added to the mixture which was then concentrated in vacuo. The resulting residue was extracted with ethyl acetate, (5 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue (Merck Kieselgel 60H, cyclohexane/EtOAc 1:1) furnished the *N*-Cbz-protected serinate **4a** (539 mg) as a white solid in 88% yield. $[\alpha]_D = -16$ (*c* 1.1, EtOH abs.), Lit.[15] $[\alpha]_D = -16.0$ (*c* 1.1, EtOH), Lit[23]: $[\alpha]_D = -16.3$ (*c* 1.03, EtOH); Mp 95 °C, Lit.[15] Mp 94 °C, Lit.[23] Mp 93–95 °C; $^1$H NMR $\delta$ 7.29 (s, 5H, Ph), 5.92 (d, 1H, $J_{NH-H2} = 7.4$ Hz, NH), 5.06 (s, 2H, $CH_2Ph$), 4.27 (m, 1H, $H_2$), 3.85 (m, 2H, $H_3$), 3.20 (s, 1H, OH), 1.42 (s, 9H, *t*Bu); $^{13}$C NMR $\delta$ 169.7 ($C_1$), 156.4 (NHCO), 136.2–128.1 ($C_{ar}$), 82.5 (*t*Bu), 67.0, 63.3 ($C_3$, $CH_2Ph$), 55.0 ($C_2$), 27.9 (*t*Bu); MS (CI, $NH_3$): 296 $(M+H)^+$, 295 $(M-H_2O+NH_4^+)$; HRMS for $C_{15}H_{22}NO_5$ $(M+H)^+$: calcd 296.1498; found 296.1502; for $C_{15}H_{23}N_2O_4$ $(M-H_2O+NH_4^+)$: calcd 295.1658; found 295.1660; Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found C, 61.26; H, 7.26; N, 4.86.

### 4.4. *tert*-Butyl *N*-*tert*-butyloxycarbonyl-L-serinate 4b

To a solution of the commercially available *N*-Boc-*O*-benzyl-L-serine (2 g, 1 equiv, 6.77 mmol) in dichloromethane (7 mL) were added a solution of *tert*-butyl trichloroacetimidate (2.95 g, 2 equiv, 13.54 mmol) in cyclohexane (14 mL) and boron trifluoride etherate (0.136 mL, 0.16 equiv, 1.08 mmol) and the mixture stirred for 20 h at 20 °C. Neutralization by the addition of solid sodium hydrogen carbonate, was followed by concentration in vacuo and flash purification of the residue (Merck Kieselgel 60H, toluene/EtOAc 9:1) to afford the corresponding ester **6b** (2.28 g) in 96% yield. $[\alpha]_D = -4$ (*c* 1.05, EtOH abs.); $^1$H NMR $\delta$ 7.36–7.23 (m, 5H, Ph), 5.35 (d, 1H, $J_{NH-H2} = 8.1$ Hz, NH), 4.55, 4.45 (AB, 2H, $J_{AB} = 12.1$ Hz, $CH_2$Ph), 4.30 (dd, 1H, $J_{H2-H3a} \approx J_{H2-H3b} \approx 3.2$ Hz, $H_2$), 3.83 (dd, 1H, $J_{H3a-H3b} = 9.3$ Hz, $J_{H3a-H2} = 3.2$ Hz, $H_{3a}$), 3.64 (dd, 1H, $J_{H3b-H3a} = 9.3$ Hz, $J_{H3b-H2} = 3.2$ Hz, $H_{3b}$), 1.45–1.33 (m, 18H, *t*Bu); $^{13}$C NMR $\delta$ 169.6 ($C_1$), 155.5 (NH*C*O), 137.8, 137.6, 129.0, 128.3, 128.2, 127.7, 127.6, 125.4 ($C_{Ph}$), 81.6, 79.4 (2 *t*Bu), 73.2 ($CH_2$Ph), 70.4 ($C_3$), 54.6 ($C_2$), 28.3, 27.9, 20.6 (2 × *t*Bu).

Hydrogenolysis of the *O*-benzyl protective group of **6b** was then carried out by adding to a solution of the ester (2.28 g, 1 equiv, 6.51 mmol) in a 5:1 mixture of ethanol/acetic acid (24 mL) the Pearlman's catalyst (228 mg, 10% w/w) in the presence of dihydrogen. After 36 h stirring at 20 °C, filtration through a Celite pad and concentration in vacuo, the expected *tert*-butyl *N*-Boc-serinate **4b** (1.67 g) was isolated in 99% yield as a white solid. $[\alpha]_D = -22$ (*c* 1.8, EtOH abs.), Lit[16]: $[\alpha]_D = -22.5$ (*c* 1.8, EtOH abs.), Lit[24]: $[\alpha]_D = -20.0$ (*c* 1.8, EtOH); Mp 80 °C, Lit[16]: 80 °C, Lit[24]: 76–78 °C; $^1$H NMR $\delta$ 5.40 (br s, 1H, NH), 4.22 (m, 1H, $H_2$), 3.87 (s, 2H, $H_{3a}$, $H_{3b}$), 1.46, 1.43 (2s, 18H, *t*Bu); MS (FAB): 284 $(M+Na)^+$; HMRS for $C_{12}H_{24}NO_5$ $(M+H^+)$: calcd 262.1654; found 262.1651.

### 4.5. *tert*-Butyl *N*-fluorenylmethoxycarbonyl-L-serinate 4c

To a solution of the commercially available *N*-Fmoc-serine (350 mg, 1 equiv, 1.07 mmol) in ethyl acetate (10 mL) was dropwise added a solution of *tert*-butyl trichloroacetimidate (0.766 mL, 4 equiv, 4.28 mmol) in cyclohexane (1 M, 4.3 mL) and the mixture was stirred for 24 h at 20 °C. Concentration in vacuo was then followed by flash chromatography of the residue (Merck Kieselgel 60H, cyclohexane /EtOAc 6:4) to give the *tert*-butyl *N*-Fmoc-L-serinate **4c** (344 mg) in 84% yield. $[\alpha]_D = +2$ (*c* 1.0, $CH_2Cl_2$); Mp 130 °C; $^1$H NMR $\delta$ 7.81–7.21 (m, 8H, Ph), 5.78 (d, 1H, $J_{NH-H2} = 5.7$ Hz, NH), 4.45 (d, 2H, $J_{H1'-H2'} = 6.9$ Hz, H1′), 4.35 (m, 1H, $H_2$), 4.25 (t, 1H, $J_{H2'-H1'} = 6.9$ Hz, $H_{2'}$), 3.98–3.94 (m, 2H, $H_3$), 1.52 (s, 9H, *t*Bu); $^{13}$C NMR $\delta$ 170.0 ($C_1$), 156.8 (NHCO), 144.1–120.4 ($C_{ar}$), 83.3 (*t*Bu), 67.6 ($C_{1'}$), 64.0 ($C_3$), 57.1 ($C_2$), 47.5 ($C_{2'}$), 28.4 (*t*Bu); MS (CI, $NH_3$): 401 $(M+NH_4^+)$; HMRS for $C_{22}H_{29}N_2O_5$ $(M+NH_4^+)$: calcd 401.2076; found 401.2079; Anal. Calcd for $C_{22}H_{29}N_2O_5$: C, 68.91; H, 6.59; N, 3.65. Found: C, 68.41; H, 6.58; N, 3.58.

### 4.6. Acetyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside 11

To a solution of the commercially available 2,3,5-tri-*O*-benzyl-D-ribofuranose (100 mg, 1 equiv, 0.24 mmol) and 4,4-dimethylaminopyridine (87.5 mg, 3 equiv, 0.71 mmol) in dichloromethane (1 mL) at 20 °C was added acetic anhydride (0.068 mL, 3 equiv, 0.71 mmol). After 3 h stirring, a saturated aqueous solution of ammonium chloride (3 mL) was added and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the crude (cyclohexane/EtOAc 1:1) afforded an unseparable β/α-anomers mixture (4:1) of the acetyl ribofuranoside **11** (101.9 mg) in 93% yield, as a colorless oil.

**11β**: $^1$H NMR $\delta$ 7.39–7.25 (m, 15H, Ph), 6.27 (s, 1H, $H_1$), 4.73–4.55 (m, 6H, $CH_2Ph$), 4.39 (ddd, 1H, $J_{H4-H3} = 5.6$ Hz, $J_{H4-H5} = 5.2$ Hz, $H_4$), 4.11 (d, 1H, $J_{H2-H3} = 1.9$ Hz, $H_2$), 4.00 (dd, 1H, $J_{H3-H2} = 1.9$ Hz, $J_{H3-H4} = 5.6$ Hz, $H_3$), 3.64 (d, 2H, $J_{H5-H4} = 5.1$ Hz, $H_5$), 2.05 (s, 3H, OAc); $^{13}$C NMR $\delta$ 170.0 (OAc), 138.0, 137.7, 137.3 ($3C_{q\ (ar)}$), 128.5–127.7 ($C_{ar}$), 100.6 ($C_1$), 87.1 ($C_2$), 83.8 ($C_3$), 83.4 ($C_4$), 73.5, 72.2, 72.0 ($CH_2Ph$), 69.7 ($C_5$), 21.3 (OMe).

**11α**: $^1$H NMR $\delta$ 7.39–7.27 (m, 15H, Ph), 6.31 (d, 1H, $J_{H1-H2} = 3.5$ Hz, $H_1$), 4.52 (m, 6H, $CH_2Ph$), 4.22–4.17 (m, 3H, $H_2$, $H_3$, $H_4$), 3.59 (d, 2H, $J_{H5-H4} = 4.5$ Hz, $H_5$), 1.99 (s, 3H, OAc); $^{13}$C NMR $\delta$ 170.0 (OAc), 138.0, 137.7, 137.3 ($3C_{q\ (ar)}$), 128.5–127.7 ($C_{ar}$), 100.6 ($C_1$), 87.1 ($C_2$), 83.8 ($C_3$), 83.4 ($C_4$), 73.5, 72.2, 72.0 ($CH_2Ph$), 69.7 ($C_5$), 21.3 (OMe); MS (CI, $NH_3$): 480 $(M+NH_4)^+$; HRMS for $C_{28}H_{34}NO_6$ $(M+NH_4)^+$: calcd 480.2386; found: 480.2383.

### 4.7. 2,3,5-Tri-*O*-benzyl-1-fluoro-D-ribofuranose 16

To a solution of the commercially available 2,3,5-tri-*O*-benzyl-D-ribofuranose (291 mg, 1 equiv, 0.69 mmol) in THF (5 mL) at −30 °C was rapidly added (diethylamino)sulfur trifluoride (0.11 mL, 1.2 equiv, 0.83 mmol). The cooling bath was then immediately removed and TLC analysis (cyclohexane/EtOAc 9:1) revealed that the reaction was complete within 30 min. The mixture was again cooled to −30 °C prior to the addition of methanol (0.470 mL). After concentration in vacuo, the resulting residue was taken up in dichloromethane and the organic layer washed with brine. The aqueous layer was further extracted with dichloromethane (3 × 20 mL) and the combined extracts dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the crude (Merck Kieselgel 60H, cyclohexane/EtOAc 9:1) afforded a β/α-anomers mixture (95:5 to 99:1) of the fluoro ribofuranose **16** (276.4 mg) in 95% yield, as a pale oil.

**16β**: $[\alpha]_D = +22$ (*c* 1.0, $CH_2Cl_2$); $^1H$ NMR $\delta$ 7.44–7.33 (m, 15H, Ph), 5.84 (d, 1H, $J_{H1-F} = 61.5$ Hz, $H_1$), 4.60–4.50 (m, 7H, $H_4$, $CH_2Ph$), 4.22 (dd, 1H, $J_{H2-H3} = 1.9$ Hz, $J_{H2-F} = 9.2$ Hz, $H_2$), 4.05 (dd, 1H, $J_{H3-H2} = 1.9$ Hz, $J_{H3-H4} = 5.1$ Hz, $H_3$), 3.67 (d, 2H, $J_{H5-H4} = 4.8$ Hz, $H_5$); $^{13}C$ NMR $\delta$ 137.9, 137.5, 137.0 ($3C_{q\ (ar)}$), 128.6–127.8 ($C_{ar}$), 113.6 (d, $J_{C1-F} = 225$ Hz, $C_1$), 86.9 (d, $J_{C2-F} = 33.7$ Hz, $C_2$), 84.2 ($C_4$), 82.6 ($C_3$), 73.5–72.2 ($CH_2Ph$), 69.4 ($C_5$), MS (CI, $NH_3$): 440 $(M+NH_4)^+$; HRMS for $C_{26}FH_{31}NO_4$ $(M+NH_4)^+$: calcd: 440.2237; found 440.2231.

**16α**: $^1H$ NMR $\delta$ 7.34–7.18 (m, 15H, Ph), 5.61 (dd, 1H, $J_{H1-F} = 64$ Hz, $J_{H1-H2} = 3.1$ Hz, $H_1$), 4.85–4.50 (m, 7H, $H_4$, $CH_2Ph$), 4.22–4.06 (m, 2H, $H_2$, $H_3$), 3.58 (m, 2H, $H_5$); MS (CI, $NH_3$): 440 $(M+NH_4)^+$; HRMS for $C_{26}FH_{31}NO_4$ $(M+NH_4)^+$: calcd 440.2237; found 440.2235.

### 4.8. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-1-fluoro-D-ribofuranose 17

The preparation of fluoro derivative **17** was carried out from the 5-azido-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranose **3** (2.38 g, 1 equiv, 11 mmol) according to the experimental procedure described above for the preparation of the fluoro compound **16**. Flash chromatographic purification of the crude (cyclohexane/EtOAc 9:1) gave a β/α-anomers mixture (84:16) of the fluoro ribofuranose **17** (2.06 g) in 86% yield. Each anomer could be isolated as a pure compound.

**17β**: $[\alpha]_D = +24$ (*c* 1.0, $CH_2Cl_2$); $^1H$ NMR $\delta$ 5.83 (d, 1H, $J_{H1-F} = 61.3$ Hz, $H_1$), 4.83 (dd, 1H, $J_{H3-H2} = J_{H3-H4} = 5.9$ Hz, $H_3$), 4.69 (d, 1H, $J_{H2-H3} = 5.9$ Hz, $H_2$), 4.48 (ddd, 1H, $J_{H4-H5a} = 7.5$ Hz, $J_{H4-H5b} = 6.7$ Hz, $J_{H4-H3} = 5.9$ Hz, $H_4$), 3.53 (dd, 1H, $J_{H5a-H4} = 7.5$ Hz, $J_{H5a-H5b} = 12.9$ Hz, $H_{5a}$), 3.26 (dd, 1H, $J_{H5b-H4} = 6.7$ Hz, $J_{H5b-H5a} = 12.9$ Hz, $H_{5b}$), 1.61, 1.36 (2 s, 6H, $CMe_2$); $^{13}C$ $\delta$ 115.3 (d, $J_{C1-F} = 245$ Hz, $C_1$), 113.7 ($CMe_2$), 87.8 ($C_4$), 84.9 ($C_3$), 81.4 ($C_2$), 53.6 ($C_5$), 26.6, 25.7 ($CMe_2$); MS (CI, $NH_3$): 235 $(M+NH_4)^+$; HMRS for $C_8FH_{16}N_4O_3$ $(M+NH_4)^+$: calcd 235.1206; found 235.1210.

**17α**: $[\alpha]_D = +98$ (*c* 1.0, $CH_2Cl_2$); $^1H$ NMR $\delta$ 5.70 (dd, 1H, $J_{H1-F} = 64.1$ Hz, $J_{H1-H2} = 3.5$ Hz, $H_1$), 4.76 (ddd, 1H, $J_{H2-H1} = 3.5$ Hz, $J_{H2-F} = 15.6$ Hz, $H_2$), 4.64 (dd, 1H, $J_{H3-H2} = 6.8$ Hz, $J_{H3-H4} = 2.3$ Hz, $H_3$), 4.57 (ddd, 1H, $J_{H4-H5a} = J_{H4-H5b} = 3.5$ Hz, $J_{H4-H3} = 2.3$ Hz, $H_4$), 3.66 (dd, 1H, $J_{H5a-H4} = 3.5$ Hz, $J_{H5a-H5b} = 13.3$ Hz, $H_{5a}$), 3.45 (dd, 1H, $J_{H5b-H4} = 3.5$ Hz, $J_{H5b-H5a} = 13.3$ Hz, $H_{5b}$), 1.59, 1.40 (2s, 6H, $C(Me_2)$); $^{13}C$ $\delta$ 116.5 ($CMe_2$), 110.4, 106.6 (d, $J_{C1-F} = 236$ Hz, $C_1$), 83.0 ($C_4$), 81.7, 81.4 (d, $J_{C1-F} = 20.3$ Hz, $C_2$), 80.1 ($C_3$), 52.6 ($C_5$), 26.1 ($CMe_2$); HMRS for $C_8FH_{16}N_4O_3$ $(M+NH_4)^+$: calcd 235.1206; found 235.1211.

### 4.9. General procedure for glycosylation

#### 4.9.1. Glycosylation according to path A

**4.9.1.1. Preparation of the bromide derivatives 13, 14, and 15.** To a solution of 1-acetyl ribofuranose **9**, **10**, or **11** (1.57 mmol) in dichloromethane (2 mL), at −40 °C, was dropwise added trimethylsilyl bromide (0.735 mL, 3.7 equiv, 5.8 mmol) and the temperature raised to 20 °C. Monitoring of the reaction by thin layer chromatography often revealed incomplete bromination. As a result, the mixture was again cooled to −40 °C prior to further addition of TMSBr followed by increasing the temperature to 20 °C and stirred again. Several successive additions of TMSBr were usually required to obtain total transformation into the corresponding 1-bromo derivative. The excess of TMSBr and the trimethylsilyl acetate were then removed by concentration in vacuo and the resulting crude bromide **13**, **14**, or **15** was then used for the next glycosylation step without purification.

**4.9.1.2. Glycosylation.** To a solution of *tert*-butyl *N*-carbamoyl-serinate (1.2 mmol, 0.76 equiv related to the 1-acetyl ribofuranose) in dichloromethane (3 mL), in the presence of 4 Å molecular sieves (0.465 g, Lancaster®) at −20 °C, was added silver triflate (398 mg, 1 equiv). After 1 h stirring, a solution of the bromide derivative **13**, **14**, or **15** (1.57 mmol) in dichloromethane (2 mL) was slowly added at −10 °C and the mixture stirred for 24 h at −10 °C. Triethylamine (2 mL) was then added and the mixture filtered through a Celite® pad. A saturated aqueous solution of sodium hydrogenocarbonate was then added and the aqueous layer was extracted with dichloromethane (4 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo prior to flash chromatographic purification. According to the starting compounds, the results are given below.

**4.9.1.3. (*tert*-Butyl *N*-benzyloxycarbonyl-L-serinate-3′-yl)2,3,5-tri-*O*-acetyl-β-D-ribofuranoside 18.** From the *tert*-butyl *N*-benzyloxycarbonyl-L-serinate **4a** (354 mg, 1.2 mmol) and the 2,3,5-tri-*O*-acetyl-1-bromo-D-ribofuranose **13** (1.57 mmol), the described procedure followed by flash chromatography (cyclohexane/EtOAc 1:1) afforded the target glycosylated compound **18** (275 mg) as a colorless oil in 32% yield. $R_f$ 0.24 (cyclohexane/

EtOAc 1:1); $[\alpha]_D = -20$ ($c$ 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 7.33–7.24 (m, 5H, Ph), 5.57 (d, $J_{NH-H2} = 8.0$ Hz, 1H, NH), 5.18 (m, 2H, $H_2$, $H_3$), 5.10, 5.08 (AB, 2H, $J_{AB} = 11.8$ Hz, $H_{4'}$), 4.98 (s, 1H, $H_1$), 4.36 (ddd, $J_{H2'-NH} = 8.0$ Hz, $J_{H2'-H_{3'a}} = 5.5$ Hz, $J_{H2'-H_{3'b}} = 2.5$ Hz, $H_{2'}$), 4.29–4.19 (m, 2H, $J_{H4-H5a} = 4.5$ Hz, $H_{5a}$, $H_4$), 4.14–4.09 (m, 2H, $J_{H3'a-H_{2'}} = 5.5$ Hz, $J_{H5b-H4} = 2.4$ Hz, $J_{H5b-H5a} = 12$ Hz, $H_{5b}$, $H_{3'a}$), 3.64 (dd, $J_{H3'b-H_{3'a}} = 9.8$ Hz, $J_{H3'b-H_{2'}} = 2.5$ Hz, $H_{3'b}$), 2.07, 2.05, 2.02 (3 s, 9H, OAc), 1.44 (s, 9H, $t$Bu); $^{13}$C NMR $\delta$ 170.5 ($C_{1'}$), 169.8, 168.8, 168.7 (O-$CO$CH$_3$), 155.9 (NH$CO$), 136.3, 128.5, 128.0, 124.4, 124.2 ($C_{ar}$), 104.1 ($C_1$), 82.3 ($t$Bu), 78.2 ($C_4$), 76.1 ($C_3$), 72.1 ($C_2$), 70.5 ($C_{3'}$), 66.8 ($C$H$_2$-Ph), 62.2 ($C_5$), 54.6 ($C_{2'}$), 27.8 ($t$Bu), 22.9, 22.4, 20.6 (OAc); MS (CI, $NH_3$): 554 $(M+H)^+$: HRMS for $C_{26}H_{36}NO_{12}$ $(M+H)^+$: calcd 554.2238; found 554.2237.

**4.9.1.4. ($tert$-Butyl *N*-benzyloxycarbonyl-L-serinate-3′-yl)2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside 19.** From the $tert$-butyl *N*-benzyloxycarbonyl-L-serinate **4a** (190 mg, 0.644 mmol) and the 2,3,5-tri-*O*-benzoyl-1-bromo-D-ribofuranose **14** (0.5 mmol), the described procedure followed by flash chromatography (cyclohexane/EtOAc/$Et_3N$ 8:2:3) afforded the targeted glycosylated compound **19** (338.2 mg) as a white foam in 92% yield. $R_f$ 0.25 (cyclohexane/EtOAc 8:2); $[\alpha]_D = +18$ ($c$ 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 8.04–7.28 (m, 20H, Ph), 5.79 (d, 1H, $J_{NH-H2'} = 7.5$ Hz, NH), 5.70 (d, 1H, $J_{H2-H3} = 4.7$ Hz, $H_2$), 5.68 (dd, 1H, $J_{H3-H2} = 4.7$ Hz, $J_{H3-H4} = 5.6$ Hz, $H_3$), 5.30 (s, 1H, $H_1$), 5.08, 5.06 (AB, 2H, $J_{AB} = 13.9$ Hz, $2H_{4'}$), 4.75 (ddd, 1H, $J_{H4-H3} = 5.6$ Hz, $J_{H4-H5b} = 5.8$ Hz, $J_{H4-H5a} = 9.4$ Hz, $H_4$), 4.60 (dd, 1H, $J_{H5a-H4} = 9.4$ Hz, $J_{H5a-H5b} = 14.7$ Hz, $H_{5a}$), 4.50 (dd, 1H, $J_{H5b-H4} = 5.8$ Hz, $J_{H5b-H5a} = 14.7$ Hz, $H_{5b}$), 4.48 (m, 1H, $H_{2'}$), 4.25 (dd, 1H, $J_{H3'a-H2'} = 2.4$ Hz, $J_{H3'a-H3'b} = 9.6$ Hz, $H_{3'a}$), 3.80 (dd, 1H, $J_{H3'b-H2'} = 2$ Hz, $J_{H3'b-H3'a} = 9.6$ Hz, $H_{3'b}$), 1.49 (s, 9H, $t$Bu); $^{13}$C NMR $\delta$ 168.7 ($C_{1'}$), 166.1, 165.3, 165.2 (Ph$CO$), 156.0 (NH$CO$), 136.4–128.1 ($C_{ar}$), 106.0 ($C_1$), 82.8 ($t$Bu), 79.2 ($C_4$), 75.4 ($C_3$), 72.8 ($C_2$), 68.8 ($C_{3'}$), 67.0 ($C'_4$), 63.7 ($C_5$), 54.7 ($C_{2'}$), 28.0 ($t$Bu); MS (CI, $NH_3$): 757 $(M+NH_4)^+$; HRMS for $C_{41}H_{45}N_2O_{12}$ $(M+NH_4)^+$: calcd 757.2973; found 757.2980; Anal. Calcd for $C_{41}H_{41}NO_{12}$: C, 66.57; H, 5.59; N, 1.89. Found C, 66.66; H, 5.63; N, 1.95.

**4.9.1.5. ($tert$-Butyl *N*-$tert$-butyloxycarbonyl-L-serinate-3′-yl)2,3,5-tri-*O*-benzyl-β-D-ribofuranoside 20.** From the $tert$-butyl *N*-$tert$-butyloxycarbonyl-L-serinate **4b** (42 mg, 0.16 mmol) and the 2,3,5-tri-*O*-benzyl-1-bromo-D-ribofuranose **15** (0.18 mmol), the described procedure followed by flash chromatography (cyclohexane/EtOAc 8:2) afforded the targeted glycosylated compound **20** in 69% overall yield as a mixture of α-epimer (62 mg, oil) and β-epimer (19 mg, oil), which could be isolated as pure compounds.

**20β**: $R_f$ 0.61 (cyclohexane/EtOAc 8:2); $[\alpha]_D = +31$ ($c$ 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 7.37–7.18 (m, 15H, Ph), 5.52 (d, 1H, $J_{NH-H2'} = 9$ Hz, NH), 5.02 (s, 1H, $H_1$), 4.60–4.44 (3AB, 6H, $J_{AB} = 14.3$ Hz, $J_{A'B'} = 13.1$ Hz, $J_{A''B''} = 11.9$ Hz, $CH_2$Ph), 4.30 (m, 1H, $J_{H2'-NH} = 9$ Hz, $J_{H2'-H3'} = 2.6$ Hz, $H_{2'}$), 4.19 (ddd, 1H, $J_{H4-H5a} = 4.1$ Hz, $J_{H4-H5b} = 4.8$ Hz, $J_{H4-H3} = 6.5$ Hz, $H_4$), 3.96 (d, 1H, $J_{H3-H2} = 3.2$ Hz, $H_2$), 3.92 (dd, 1H, $J_{H3-H2} = 3.2$ Hz, $J_{H3-H4} = 6.5$ Hz, $H_3$), 3.89 (m, 2H, $H_{3'}$), 3.61 (dd, 1H, $J_{H5a-H4} = 4.1$ Hz, $J_{H5a-H5b} = 10.9$ Hz, $H_{5a}$), 3.59 (dd, 1H, $J_{H5b-H4} = 4.8$ Hz, $J_{H5b-H5a} = 10.9$ Hz, $H_{5b}$), 1.44, 1.43 (s, 18H, $t$Bu); $^{13}$C NMR $\delta$ 169.7 ($C_{1'}$), 155.6 (NH$CO$), 138.1, 137.8, 137.4 ($C_{q\ (ar)}$), 129.6, 128.5, 128.4, 127.9, 127.8, 127.6, 126.6 ($C_{ar}$), 106.3 ($C_1$), 88.0 ($C_2$), 83.8 ($C_3$), 81.9 ($CO_2t$Bu), 81.1 ($C_4$), 79.6 ($t$Bu), 73.4, 72.2, 71.9 ($C$H$_2$Ph), 69.5 ($C_5$), 68.1 ($C_{3'}$), 54.7 ($C_{2'}$), 28.4; 28.1 ($t$Bu); MS (CI, $NH_3$): 664 $(M+H)^+$; HRMS for $C_{38}H_{50}NO_9$ $(M+H)^+$: calcd 664.3486; found 664.3484.

**20α**: $R_f$ 0.56 (cyclohexane/EtOAc 8:2); $[\alpha]_D = -27$ ($c$ 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 7.39–7.24 (m, 15H, Ph); 5.60 (d, 1H, $J_{NH-H2'} = 8.1$ Hz, NH), 4.85 (d, 1H, $J_{H1-H2} = 3.1$ Hz, $H_1$), 4.64, 4.61, 4.59 (3AB, 6H, $J_{AB} = 11.3$ Hz, $J_{A'B'} = 12.1$ Hz, $J_{A''B''} = 14.3$ Hz, $CH_2$Ph), 4.33 (m, 1H, $J_{H2'-H3'a} = 4.3$ Hz, $J_{H2'-NH} = 8.1$ Hz, $H_{2'}$), 4.07 (m, 4H, $H_2$, $H_{3'a}$, $H_3$, $H_4$), 3.62 (dd, 1H, $J_{H3'b-H2'} = 3.7$ Hz, $J_{H3'b-H3'a} = 10.2$ Hz, $H_{3'b}$), 3.53 (m, 2H, $H_{5a}$, $H_{5b}$), 1.43, 1.42 (2s, 18H, $t$Bu); $^{13}$C NMR $\delta$ 169.4 ($C_{1'}$), 155.6 (NHCO), 138.2, 138.1, 137.8 ($C_{q\ (ar)}$), 128.5, 128.4, 128.0, 127.9, 127.8 ($C_{ar}$), 101.1 ($C_1$), 84.2 ($C_2$), 82.3 ($C_3$), 81.9 ($CO_2t$Bu), 80.1 ($C_4$), 79.6 ($t$Bu), 73.2, 72.4, 71.7 ($CH_2$Ph), 69.5 ($C_5$), 68.4 ($C_{3'}$), 54.5 ($C_{2'}$), 28.4, 28.0 ($t$Bu); MS (CI, $NH_3$): 664 $(M+H)^+$; HRMS for $C_{38}H_{50}NO_9$ $(M+H)^+$: calcd 664.3486; found 664.3496.

**4.9.2. Glycosylation according to path B.** To a solution of $tert$-butyl *N*-carbamoyl-L-serinate (0.85 equiv, 0.29 mmol), stannous chloride (65.4 mg, 1 equiv, 0.34 mmol) and silver perchlorate (71 mg, 1 equiv, 0.34 mmol) in ether (5 mL) at −15 °C, in the presence of 4 Å molecular sieves (1.5 g, Lancaster®) was added a solution of fluoride derivative **16** or **17** (1 equiv, 0.34 mmol) in ether (5 mL). After 2 h stirring, the temperature was raised to 20 °C and stirring continued for 48–72 h. The mixture was then filtered through a Celite® pad and a saturated aqueous solution of sodium hydrogen carbonate added. The aqueous layer was extracted with dichloromethane ($4 \times 25$ mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo prior to flash chromatographic purification. According to the starting compounds, the results are given below.

**4.9.2.1. ($tert$-Butyl *N*-$tert$-butyloxycarbonyl-L-serinate-3′-yl)2,3,5-tri-*O*-benzyl-β-D-ribofuranoside 20.** From the $tert$-butyl *N*-$tert$-butyloxycarbonyl-L-serinate **4b** (76 mg, 0.29 mmol) and the 2,3,5-tri-*O*-benzyl-1-fluoro-D-ribofuranose **16** (145 mg, 0.34 mmol), the described procedure followed by flash chromatography (cyclohexane/EtOAc 8:2) afforded the target glycosylated compound **20** in 44% overall yield as a mixture of the α-epimer (47 mg, oil) and the β-epimer (54 mg, oil), which could be isolated as pure compounds. For physical data of **20α** and **20β**, see above.

**4.9.2.2. ($tert$-Butyl *N*-$tert$-butyloxycarbonyl-L-serinate-3′-yl)5-azido-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranoside 21.** From the $tert$-butyl *N*-$tert$-butyloxy- carbonyl-L-serinate **4b** (204 mg, 0.78 mmol) and the 5-azido-5-deoxy-2,3-*O*-isopropylidene-1-fluoro-D-ribofuranose

**17** (200 mg, 0.92 mmol), the described procedure followed by flash chromatography (cyclohexane/EtOAc 9:1) afforded the targeted glycosylated compound **21** in 64% overall yield as a mixture of α-epimer (86 mg, oil) and β-epimer (184 mg, oil), which could be isolated as pure compounds.

**21β**: $R_f$ 0.49 (cyclohexane/EtOAc 7:3); $[\alpha]_D = -15$ (*c* 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 5.19 (d, 1H, $J_{NH-H2'} = 7.9$ Hz, NH), 5.01 (s, 1H, $H_1$), 4.58 (dd, 1H, $J_{H3-H2} = J_{H3-H4} = 6$ Hz, $H_3$), 4.50 (d, 1H, $J_{H2-H3} = 6$ Hz, $H_2$), 4.26–4.20 (m, 2H, $J_{H4-H5} = 7.5$ Hz, $H_{2'}$, $H_{4'}$), 3.99 (dd, 1H, $J_{H3'a-H2'} = 3.5$ Hz, $J_{H3'a-H3'b} = 10$ Hz, $H_{3'a}$), 3.53 (dd, 1H, $J_{H3'b-H2'} = 3.5$ Hz, $J_{H3'b-H3'a} = 10$ Hz, $H_{3'b}$), 3.34 (dd, 1H, $J_{H5a-H4} = 7.4$ Hz, $J_{H5a-H5b} = 12.6$ Hz, $H_{5a}$), 3.11 (dd, 1H, $J_{H5b-H4} = 7.5$ Hz, $J_{H5b-H5a} = 12.6$ Hz, $H_{5b}$), 1.41, 1.39, 1.33 (3s, 24H, *t*Bu, $CMe_2$); $^{13}$C NMR $\delta$ 169.6 ($C_{1'}$), 155.7 (NH*C*O), 113.2 ($CMe_2$), 109.6 ($C_1$), 85.9 ($C_4$), 85.4 ($C_3$), 82.8 ($CO_2$*t*Bu), 82.4 ($C_2$), 80.3 (*t*Bu), 69.1 ($C_{3'}$), 54.4 ($C_{2'}$), 53.7 ($C_5$), 28.7; 28.4 (*t*Bu), 26.7, 25.3 ($CMe_2$); MS (CI, $NH_3$): 459 $(M+H)^+$; HRMS for $C_{20}H_{35}N_4O_8$ $(M+H)^+$: calcd 459.2455; found 459.2453.

**21α**: $R_f$ 0.39 (cyclohexane/EtOAc 7:3); $[\alpha]_D = +32$ (*c* 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 5.73 (d, 1H, $J_{NH-H2'} = 8.6$ Hz, NH), 5.09 (d, 1H, $J_{H1-H2} = 4.4$ Hz, $H_1$), 4.80 (dd, 1H, $J_{H2-H1} = 4.4$ Hz, $J_{H2-H3} = 7.2$ Hz, $H_2$), 4.70 (dd, 1H, $J_{H3-H2} = 7.2$ Hz, $J_{H3-H4} = 3.2$ Hz, $H_3$), 4.50–4.41 (m, 2H, $J_{H4-H3} = 3.2$ Hz, $H_{2'}$, $H_4$), 4.20 (dd, 1H, $J_{H3'a-H2'} = 3.3$ Hz, $J_{H3'a-H3'b} = 10.7$ Hz, $H_{3'a}$), 4.07 (dd, 1H, $J_{H3'b-H2'} = 3.1$ Hz, $J_{H3'b-H3'a} = 10.7$ Hz, $H_{3'b}$), 3.73 (dd, 1H, $J_{H5a-H4} = 3.8$ Hz, $J_{H5a-H5b} = 8.8$ Hz, $H_{5a}$), 3.52 (dd, 1H, $J_{H5b-H4} = 4$ Hz, $J_{H5b-H5a} = 8.8$ Hz, $H_{5b}$), 1.66, 1.61, 1.59, 1.48 (4s, 24H, *t*Bu, $CMe_2$); $^{13}$C NMR $\delta$ 169.8 ($C_{1'}$), 156.0 (NH*C*O), 116.4 ($CMe_2$), 102.5 ($C_1$), 82.4 ($CO_2$*t*Bu), 81.1 ($C_2$), 80.5 ($C_3$), 80.0 ($C_4$), 70.1 ($C_{3'}$), 54.9 ($C_{2'}$), 52.7 ($C_5$), 28.7; 28.4 (*t*Bu), 26.4, 26.2 ($CMe_2$); MS (CI, $NH_3$): 459 $(M+H)^+$; HRMS for $C_{20}H_{35}N_4O_8$ $(M+H)^+$: calcd 459.2455; found 459.2461.

**4.9.2.3. (*tert*-Butyl *N*-fluorenylmethoxycarbonyl-L-serinate-3′-yl)5-azido-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranoside 22.** From the *tert*-butyl *N*-Fmoc-L-serinate **4c** (225 mg, 0.59 mmol) and the 5-azido-5-deoxy-2,3-*O*-isopropylidene-1-fluoro-D-ribofuranose **17** (150 mg, 0.69 mmol), the described procedure followed by flash chromatography (cyclohexane/EtOAc 7:3) afforded the target glycosylated compound **22** in 100% overall yield as a mixture of α-epimer (123 mg, oil) and β-epimer (214 mg, oil) which could be isolated as pure compounds.

**22β**: $R_f$ 0.37 (cyclohexane/EtOAc 7:3); $[\alpha]_D = -7$ (*c* 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 7.81–7.32 (m, 8H, $H_{ar.}$), 5.59 (d, 1H, $J_{NH-H2'} = 7.9$ Hz, NH), 5.13 (s, 1H, $H_1$), 4.68 (d, 1H, $J_{H3-H2} = 5.9$ Hz, $H_3$), 4.60 (d, 1H, $J_{H2-H3} = 5.9$ Hz, $H_2$), 4.46–4.43 (m, 3H, $J_{H4'-H5'} = 6.9$ Hz, $H_{2'}$, $H_{4'a}$, $H_{4'b}$), 4.35 (dd, 1H, $J_{H4-H5a} = J_{H4-H5b} = 7.4$ Hz, $H_4$), 4.27 (dd, 1H, $J_{H5'-H4'a} \approx J_{H5'-H4'b} = 6.9$ Hz, $H_{5'}$), 4.12 (dd, 1H, $J_{H3'a-H2'} = 3.3$ Hz, $J_{H3'a-H3'b} = 10$ Hz, $H_{3'a}$), 3.69 (dd, 1H, $J_{H3'b-H2'} = 2.8$ Hz, $J_{H3'b-H3'a} = 10$ Hz, $H_{3'b}$), 3.43 (dd, 1H, $J_{H5a-H4} = 7.4$ Hz, $J_{H5a-H5b} = 12.5$ Hz, $H_{5a}$), 3.22 (dd, 1H, $J_{H5b-H4} = 7.4$ Hz, $J_{H5b-H5a} = 12.5$ Hz, $H_{5b}$), 1.51 (s, 12H, *t*Bu, $CMe_2$), 1.35 (s, 3H, $CMe_2$); $^{13}$C NMR $\delta$ 169.6 ($C_{1'}$), 156.3 (NH*C*O), 144.2, 141.7, 128.1, 127.5, 125.5, 120.4 ($C_{ar.}$), 113.3 ($CMe_2$), 109.8 ($C_1$), 85.9 ($C_4$), 85.5 ($C_3$), 82.4 (*t*Bu), 82.4 ($C_2$), 68.9 ($C_{3'}$), 67.6 ($C_{4'}$), 54.9 ($C_{2'}$), 53.7 ($C_5$), 47.6 ($C_{5'}$), 28.4 (*t*Bu), 26.8, 25.3 ($CMe_2$); MS (CI, $NH_3$): 598 $(M+NH_4)^+$; HRMS for $C_{30}H_{40}N_5O_8$ $(M+NH_4)^+$: calcd 598.2877; found 598.2872.

**22α**: $R_f$ 0.31 (cyclohexane/EtOAc 7:3); $[\alpha]_D$ +21 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 7.93–7.29 (m, 8H, $H_{ar.}$), 6.03 (d, 1H, $^3J_{NH-H2'} = 8.4$ Hz, NH), 4.99 (d, 1H, $J_{H1-H2} = 4.0$ Hz, $H_1$), 4.69 (dd, 1H, $J_{H2-H3} = 6.9$ Hz, $J_{H2-H1} = 4.0$ Hz, $H_2$), 4.59 (dd, 1H, $J_{H3-H4} = 2.9$ Hz, $J_{H3-H2} = 6.9$ Hz, $H_3$), 4.48–4.31 (m, 3H, $J_{H4'-H5'} = 7$ Hz, $H_{2'}$, $H_{4'a}$, $H_{4'b}$), 4.30–4.10 (m, 3H, $J_{H5'-H4'a} = 7$ Hz, $J_{H4-H5b} = 3.2$ Hz, $H_4$, $H_{5'}$, $H_{3'a}$), 4.05 (dd, 1H, $J_{H3'b-H2'} = 3.2$ Hz, $J_{H3'b-H3'a} = 11$ Hz, $H_{3'b}$), 3.55 (dd, 1H, $J_{H5a-H4} = 2.6$ Hz, $J_{H5a-H5b} = 13$ Hz, $H_{5a}$), 3.35 (dd, 1H, $J_{H'b-H4} = 3.2$ Hz, $J_{H5b-H5a} = 13$ Hz, $H_{5b}$), 1.57, 1.38 (2s, 6H, $CMe_2$), 1.51 (s, 9H, *t*Bu); $^{13}$C NMR $\delta$ 169.6 ($C_{1'}$), 156.5 (NH*C*O), 144.2, 141.7, 128.0, 127.5, 125.5, 120.4 ($C_{ar.}$), 116.3 ($CMe_2$), 102.6 ($C_1$), 82.9 (*t*Bu), 81.1 ($C_2$, $C_3$), 80.6 ($C_4$), 70.0 ($C_{3'}$), 67.5 ($C_{4'}$), 55.3 ($C_{2'}$), 52.7 ($C_5$), 47.5 ($C_{5'}$), 28.4 (*t*Bu), 26.3, 26.1 ($CMe_2$); MS (CI, $NH_3$): 598 $(M+NH_4)^+$; HRMS for $C_{30}H_{40}N_5O_8$ $(M+NH_4)^+$: calcd 598.2877, found 598.2871.

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