Solid Phase Synthesis of New *S*-Glycoamino Acid Building Blocks.

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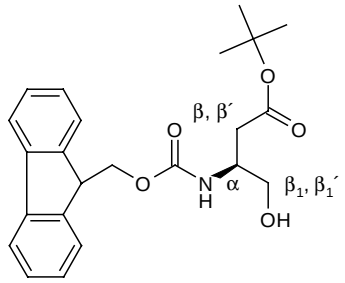
SUPPORTING INFORMATION

Experimental Section

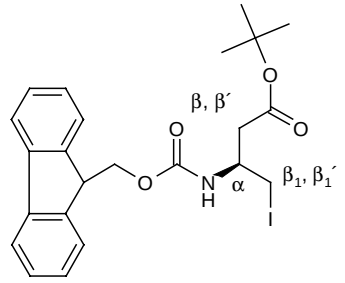


2

3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-hydroxy-butyric acid *tert*-butyl ester **2**.

Fmoc Asp(O-^{t}Bu) (1 g, 2.43 mmol) and triethylamine (340 μL, 2.43 mmol) were dissolved in 10 mL of dry THF. A solution of ethyl chloroformate (229 μL, 2.55 mmol) in 3 mL of dry THF was added dropwise to the reaction at –10°C. The resulting suspension was stirred at room temperature for 30 min and then filtered. The filtrate was added dropwise at 0°C to a solution of sodium borohydride (190 mg, 5.05 mmol) in 2 mL of water. The reaction was stirred at room temperature for 4 h, acidified to pH 2 with 1 N HCl and then diluted with EtOAc. The organic layer was washed with saturated sodium hydrogencarbonate, and brine, dried ($MgSO_4$) and concentrated. The residue was eluted from a column of silica gel with 3:2 hexane-ethyl acetate to give the corresponding alcohol **2** (723 mg, 74%).

NMR-^{1}H ($CDCl_3$) δ = 1.45 (s, 9 H, C(C*H*$_3$)$_3$), 2.56 (m, 2 H, H$_{\beta,\beta'}$), 3.72 (m, 2 H, H$_{\beta1,\beta1'}$), 4.01 (m, 1 H, H$_\alpha$), 4.22 (m, 1 H, Fmoc-CH), 4.40 (m, 2 H, Fmoc-CH_2), 5.47 (d, 1 H, *J* = 7.3 Hz, NH), 7.31 (dd, 2 H, H-3), 7.40 (dd, 2 H, H-2), 7.59 (d, 2 H, *J* = 7.4 Hz, H-4), 7.76 (d, 2 H, *J* = 7.3 Hz, H-1).



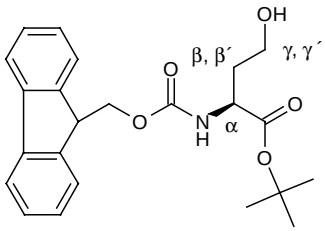
3

3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-iodo-butyric acid *tert*-butyl ester **3**.

A mixture of **2** (452 mg, 1.14 mmol) and triphenylphosphine (445 mg, 1.71 mmol) in toluene (30 mL) was refluxed, and solvent (5 mL) was distilled off. The mixture was cooled

to room temperature, imidazole (232 mg, 3.41 mmol) and I_2 (377 mg, 1.48 mmol) were added. The resulting mixture was stirred for 30 min at 120°C, then cooled and concentrated. The residue was diluted with EtOAc, washed with brine, and water, dried over $MgSO_4$ and concentrated. The residue was eluted from a column of silica gel with 5:1 hexane-ethyl acetate to give the title compound **3** (319 mg, 80%), mp 145-146°C (EtOAc/hexane).

NMR-^{1}H ($CDCl_3$) δ = 1.45 (s, 9 H, C(CH_3)$_3$), 2.61 (ddd, 2 H, H$_{\beta, \beta'}$), 3.42 (m, 2 H, H$_{\beta 1, \beta 1'}$), 3.95 (m, 1 H, H$_\alpha$), 4.22 (m, 1 H, Fmoc-CH), 4.41 (m, 2 H, Fmoc-CH_2), 5.36 (d, 1 H, *J* = 8.8 Hz, NH), 7.31 (dd, 2 H, H-3), 7.40 (dd, 2 H, H-2), 7.59 (d, 2 H, *J* = 7.3 Hz, H-4), 7.77 (d, 2 H, *J* = 7.8 Hz, H-1).

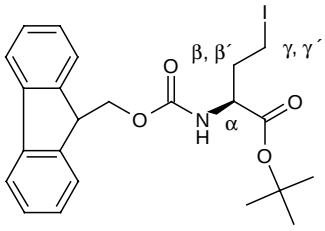


4

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-hydroxy-butyric acid *tert*-butyl ester **4**.

Fmoc Asp-O^{t}Bu was treated as described for the preparation of **2** to give **4** (783 mg, 81%).

NMR-^{1}H ($CDCl_3$) δ = 1.48 (s, 9 H, C(CH_3)$_3$), 1.60 (m, 1 H, H$_{\beta'}$), 2.15 (m, 1 H, H$_\beta$), 3.60 (m, 1 H, H$_{\gamma'}$), 3.68 (m, 1 H, H$_\gamma$), 4.22 (m, 1 H, Fmoc-CH), 4.39 (m, 2 H, Fmoc-CH_2), 4.46 (m, 1 H, H$_\alpha$), 5.53 (d, 1 H, *J* = 6.7 Hz, NH), 7.32 (dd, 2 H, H-3), 7.40 (dd, 2 H, H-2), 7.60 (d, 2 H, *J* = 7.4 Hz, H-4), 7.76 (d, 2 H, *J* = 7.7 Hz, H-1).

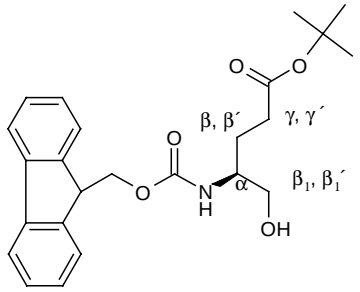


5

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-iodo-butyric acid *tert*-butyl ester **5**.

4 was treated as described for the preparation of **3** to give **5** (469 mg, 81%), mp 87-88°C (EtOAc/hexane).

NMR-^{1}H ($CDCl_3$) δ=1.48 (s, 9 H, C(CH_3)$_3$), 2.18 (m, 1 H, $H_{\beta'}$), 2.42 (m, 1 H, H_β), 3.13 (m, 2 H, $H_{\gamma,\gamma'}$), 4.22 (m, 1 H, Fmoc-CH), 4.27 (m, 1 H, H_α), 4.43 (m, 2 H, Fmoc-CH_2), 5.33 (d, 1 H, *J* = 7.8 Hz, NH), 7.35 (dd, 2 H, H-3), 7.41 (dd, 2 H, H-2), 7.60 (d, 2 H, *J* = 7.3 Hz, H-4), 7.77 (d, 2 H, *J* = 7.4 Hz, H-1).

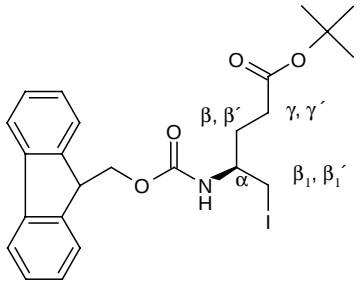


6

4-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5-hydroxy-pentanoic acid *tert*-butyl ester **6**.

Fmoc Glu(O^{t}Bu) was treated as described for the preparation of **2** to give **6** (832 mg, 86%).

NMR-^{1}H ($CDCl_3$) δ = 1.45 (s, 9 H, C(CH_3)$_3$), 1.65 (m, 1 H, $H_{\beta'}$), 1.86 (m, 1 H, H_β), 2.32 (m, 2 H, $H_{\gamma,\gamma'}$), 3.56-3.67 (m, 3 H, $H_{\beta1,\beta1',\alpha}$), 4.21 (m, 1 H, Fmoc-CH), 4.41 (m, 2 H, Fmoc-CH_2), 5.17 (d, 1 H, *J* = 7.3 Hz, NH), 7.32 (dd, 2 H, H-3), 7.40 (dd, 2 H, H-2), 7.59 (d, 2 H, *J* = 7.3 Hz, H-4), 7.76 (d, 2 H, *J* = 7.3 Hz, H-1).

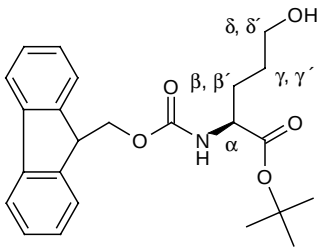


7

4-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5-iodo-pentanoic acid *tert*-butyl ester **7**.

5 was treated as described for the preparation of **3** to give **7** (402 mg, 95%).

NMR-^{1}H ($CDCl_3$) δ = 1.45 (s, 9 H, C(CH_3)$_3$), 1.85 (m, 2 H, $H_{\beta,\beta'}$), 2.30 (m, 2 H, $H_{\gamma,\gamma'}$), 3.29 (m, 1 H, $H_{\beta1}$), 3.43 (m, 1 H, $H_{\beta1'}$), 3.47 (m, 1 H, H_α), 4.22 (t, 1 H, *J* = 6.9 Hz, Fmoc-CH), 4.42 (m, 2 H, Fmoc-CH_2), 5.05 (d, 1 H, *J* = 7.3 Hz, NH), 7.31 (dd, 2 H, H-3), 7.40 (dd, 2 H, H-2), 7.59 (d, 2 H, *J* = 7.3 Hz, H-4), 7.76 (d, 2 H, *J* = 7.8 Hz, H-1).

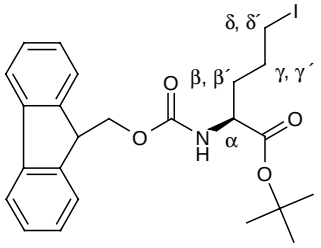


8

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5-hydroxy-pentanoic acid *tert*-butyl ester **8**.

Fmoc Glu-O^{t}Bu was treated as described for the preparation of **2** to give **8** (800 mg, 83%).

NMR-^{1}H ($CDCl_3$) δ = 1.48 (s, 9 H, C(CH_3)$_3$), 1.67 (m, 2 H, $H_{\beta,\beta'}$), 1.76 (m, 1 H, $H_{\gamma'}$), 1.92 (m, 1 H, H_{γ}), 3.68 (m, 2 H, $H_{\delta,\delta'}$), 4.22 (m, 1 H, Fmoc-CH), 4.30 (m, 1 H, H_{α}), 4.39 (m, 2 H, Fmoc-CH_2), 5.48 (d, 1 H, *J* = 7.3 Hz, NH), 7.32 (dd, 2 H, H-3), 7.40 (dd, 2 H, H-2), 7.60 (d, 2 H, *J* = 7.3 Hz, H-4), 7.76 (d, 2 H, *J* = 7.3 Hz, H-1).

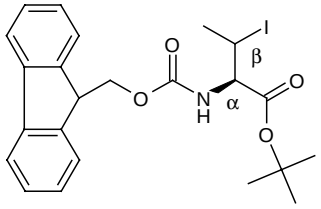


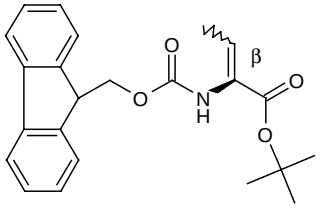
9

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5-iodo-pentanoic acid *tert*-butyl ester **9**.

8 was treated as described for the preparation of **3** to give **9** (350 mg, 76%).

NMR-^{1}H ($CDCl_3$) δ = 1.49 (s, 9 H, C(CH_3)$_3$), 1.77-1.96 (m, 4 H, $H_{\beta,\beta',\gamma,\gamma'}$), 3.22 (m, 2 H, $H_{\delta,\delta'}$), 4.22 (m, 1 H, Fmoc-CH), 4.28 (m, 1 H, H_{α}), 4.40 (m, 2 H, Fmoc-CH_2), 5.34 (d, 1 H, *J* = 8.3 Hz, NH), 7.33 (dd, 2 H, H-3), 7.41 (dd, 2 H, H-2), 7.60 (d, 2 H, *J* = 7.3 Hz, H-4), 7.77 (d, 2 H, *J* = 7.4 Hz, H-1).





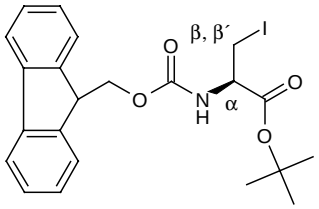
11 **12**

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-iodo-butyric acid *tert*-butyl ester **11**.

I_2 (682 mg, 2,68 mmol) was added to a suspension of triphenylphosphine polymer (1,00 g, 2,68mmol) in anhydrous CH_2Cl_2 (20 mL). The reaction was stirred at RT. After 15 min, imidazole (195 mg, 3,05 mmol) was added at RT and the stirring was continued for additional 15 min. A solution of *N*-(9*H*-fluoren-9-ylmethoxycarbonylamino)-D-threonine 1-*tert*-butyl ester **10** (488 mg, 1,23 mmol) in anhydrous CH_2Cl_2 (5 mL) was then adden to the suspension. The reaction was refluxed 3 h. After filtration on Celite and washing with CH_2Cl_2, the mixture was washed with sodium thiosulfate and water, dried over $MgSO_4$ and concentrated. The residue was eluted from a column of silica gel with 5:1 hexane-ethyl acetate to give first the elimination derivative **12** (37 mg, 8%). NMR-^{1}H ($CDCl_3$) δ = 1.50 (s, 9 H, C(C*H*$_3$)$_3$), 1.78 (d, 3 H, *J* = 7.4 Hz, C*H*$_3$), 4.25 (m, 1 H, Fmoc-CH), 4.43 (m, 2 H, Fmoc-CH_2), 6.24 (bs, 1 H, NH), 6.68 (q, 1 H, H$_\beta$), 7.33 (dd, 2 H, H-3), 7.40 (dd, 2 H, H-2), 7.61 (d, 2 H, *J* = 7.3 Hz, H-4), 7.76 (d, 2 H, *J* = 7.8 Hz, H-1).

Next eluted was the iodo **11** (549 mg, 88%).

NMR-^{1}H ($CDCl_3$) δ = 1.55 (s, 9 H, C(C*H*$_3$)$_3$), 2.05 (d, 3 H, *J* = 6.9 Hz, C*H*$_3$), 4.17-4.26 (m, 2 H, H$_\alpha$, Fmoc-CH), 4.36-4.44 (m, 3 H, H$_\beta$, Fmoc-CH_2), 6.24 (d, 1 H, *J* = 7.4 Hz, NH), 7.34 (dd, 2 H, H-3), 7.40 (dd, 2 H, H-2), 7.60 (d, 2 H, *J* = 7.3 Hz, H-4), 7.77 (d, 2 H, *J* = 7.4 Hz, H-1).

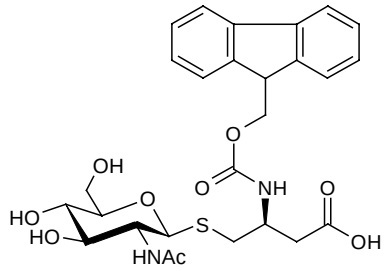


14

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-iodo-propyric acid *tert*-butyl ester **14**.

13 was treated as described for the preparation of **11** to give **14** (382 mg, 99%). The reaction was refluxed 30 min. The compound was used without further purification.

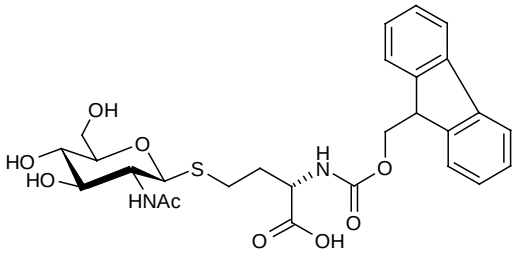
NMR-^{1}H ($CDCl_3$) δ = 1.52 (s, 9 H, C(C*H*$_3$)$_3$), 3.60 (m, 2 H, C*H*$_2$I), 4.25 (m, 1 H, Fmoc-CH), 4.35-4.46 (m, 3 H, H$_\alpha$, Fmoc-CH_2), 5.68 (d, 1 H, *J* = 6.8 Hz, NH), 7.34 (dd, 2 H, H-3), 7.41 (dd, 2 H, H-2), 7.62 (d, 2 H, *J* = 7.3 Hz, H-4), 7.77 (d, 2 H, *J* = 7.3 Hz, H-1).



16

3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-*S*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-butyric acid **16**.

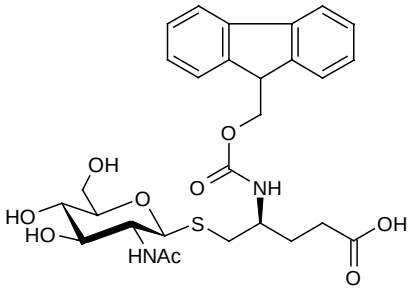
NMR-^{1}H (CD_3OD) δ = 1.96 (s, 3 H, CH_3CO), 2.51 (m, 1 H, Asp $H_{\beta'}$), 2.73 (m, 2 H, Asp $H_{\beta, \beta1'}$), 2.98 (dd, 1 H, $J_{\beta1,\beta1'}$ = 14.2, $J_{\beta1',\alpha}$ = 6.9 Hz, Asp $H_{\beta1}$), 3.35-3.45 (m, 2 H, H-3, H-5), 3.60-3.84 (m, 4 H, H-2, H-4, H-6a, H-6b), 4.22 (m, 2 H, H_α, Fmoc-CH), 4.32 (m, 2 H, Fmoc-CH_2), 4.50 (d, 1 H, $J_{1,2}$ = 10.2 Hz, H-1), 7.31 (dd, 2 H, H-3), 7.39 (dd, 2 H, H-2), 7.66 (d, 2 H, *J* = 7.3 Hz, H-4), 7.79 (d, 2 H, *J* = 7.3 Hz, H-1); MS: *m/z*: 560.9 [M^+].



17

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-*S*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-butyric acid **17**

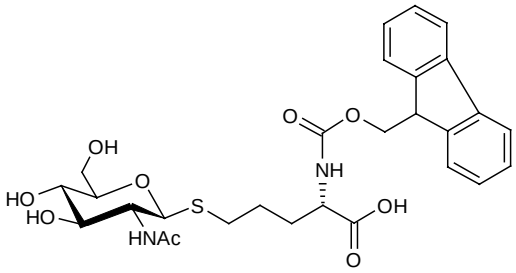
NMR-^{1}H (CD_3OD) δ = 1.97 (s, 3 H, CH_3CO), 2.00 (m, 1 H, Asp $H_{\beta'}$), 2.15 (m, 1 H, Asp H_β), 2.60 (m, 1 H, Asp $H_{\gamma'}$), 2.91 (m, 1 H, Asp H_γ), 3.34-3.48 (m, 2 H, H-3, H-5), 3.58-3.90 (m, 4 H, H-2, H-4, H-6, H-6´), 4.23 (m, 2 H, H_α, Fmoc-CH), 4.35 (m, 2 H, Fmoc-CH_2), 4.51 (d, 1 H, $J_{1,2}$ = 10.3 Hz, H-1), 7.31 (dd, 2 H, H-3), 7.39 (dd, 2 H, H-2), 7.68 (m, 2 H, H-4), 7.79 (d, 2 H, *J* = 7.3 Hz, H-1); MS: *m/z*: 560.8 [M^+].



18

4-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5-*S*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-pentanoic acid **18**.

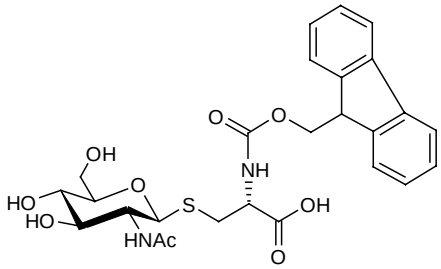
NMR-^{1}H (CD_3OD) δ = 1.65 (m, 1 H, $H_{\beta 1'}$), 1.95 (s, 3 H, CH_3CO), 1.98 (m, 1 H, $H_{\beta 1}$), 2.32 (m. 2 H. $H_{\beta, \beta'}$), 2.71 (m, 1 H, $H_{\gamma'}$), 2.85 (m, 1 H, H_{γ}), 3.31-3.44 (m, 2 H, H-3, H-5), 3.52-3.88 (m, 5 H, H-2, H-4, H-6, H-6´, H_{α}), 4.23 (m, 1 H, Fmoc-CH), 4.36 (m, 2 H, Fmoc-CH_2), 4.48 (d, 1 H, $J_{1,2}$ = 10.3 Hz, H-1), 7.32 (dd, 2 H, H-3), 7.39 (dd, 2 H, H-2), 7.68 (m, 2 H, H-4), 7.79 (d, 2 H, J = 7.3 Hz, H-1); MS: *m/z*: 574.9 [M^+].



19

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5-*S*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-pentanoic acid **19**.

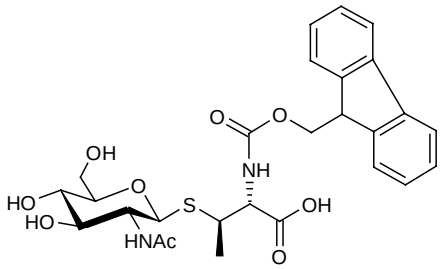
NMR-^{1}H (CD_3OD) δ = 1.62-1.83 (m, 4 H, $H_{\alpha 1, \alpha 1'}$, $H_{\beta,\beta'}$), 1.97 (s, 3 H, CH_3CO), 2.68 (m, 1 H, $H_{\gamma'}$), 2.80 (m, 1 H, H_{γ}), 3.31-3.46 (m, 2 H, H-3, H-5), 3.54-3.90 (m, 5 H, H-2, H-4, H-6, H-6´), 4.16 (m, 1 H, H_{α}), 4.23 (m, 1 H, Fmoc-CH), 4.36 (m, 2 H, Fmoc-CH_2), 4.49 (d, 1 H, $J_{1,2}$ = 10.3 Hz, H-1), 7.31 (dd, 2 H, H-3), 7.39 (dd, 2 H, H-2), 7.68 (m, 2 H, H-4), 7.79 (d, 2 H, J = 7.3 Hz, H-1); MS: *m/z*: 574.9 [M^+].



20

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-*S*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-propanoic acid **20**

NMR-^{1}H (CD_3OD) δ = 1.92 (s, 3 H, CH_3CO), 2.86 (dd, 1 H, $H_{\beta'}$), 3.07 (m. 1 H. H_β), 3.37-3.46 (m, 2 H, H-3, H-5), 3.53-3.87 (m, 5 H, H-2, H-4, H-6, H-6´), 4.25 (m, 1 H, Fmoc-CH), 4.34 (m, 2 H, Fmoc-CH_2), 4.44 (m, 1 H, H_α), 4.50 (d, 1 H, $J_{1,2}$ = 10.7 Hz, H-1), 7.32 (dd, 2 H, H-3), 7.39 (dd, 2 H, H-2), 7.69 (m, 2 H, H-4), 7.80 (d, 2 H, J = 7.3 Hz, H-1); MS: *m/z*: 546.9 [M^+].



21

2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-*S*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-3-methyl-propanoic acid **20**

NMR-^{1}H (CD_3OD) δ = 1.90 (d, 3 H, J = 6.9 Hz, CH_3), 1.93 (s, 3 H, CH_3CO), 2.86 (dd, 1 H, $H_{\beta'}$), 3.07 (m. 1 H. H_β), 3.36-3.48 (m, 2 H, H-3, H-5), 3.51-3.88 (m, 5 H, H-2, H-4, H-6, H-6´), 4.15-4.25 (m, 2 H, H_α, Fmoc-CH), 4.34 (m, 3 H, H_β, Fmoc-CH_2), 4.49 (d, 1 H, $J_{1,2}$ = 10.7 Hz, H-1), 7.31 (dd, 2 H, H-3), 7.38 (dd, 2 H, H-2), 7.68 (m, 2 H, H-4), 7.79 (d, 2 H, J = 7.3 Hz, H-1); MS: *m/z*: 561.0 [M^+].