Synthesis of Lewis a Trisaccharide Based on Anomeric Silyl Fluorous Tag

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Supporting Information Available

^1H - and ^{13}C -NMR spectra were recorded in CDCl_3 solution as indicated, at 200 (or 300, 400) and 50.3 MHz, respectively. The chemical shift values are given in ppm and the coupling constants in Hz. – MALDI spectra were recorded with the OMNIFLEX Bruker apparatus. – Thin-layer chromatography (TLC) was carried out using Merck precoated silica gel F-254 plates. Flash chromatography was carried out using Macherey-Nagel silica gel 60, 230-400 mesh. – Solvents were dried according to standard procedures, and reactions requiring anhydrous conditions were performed under nitrogen or argon. Solutions containing the final products were dried with Na_2SO_4 , filtered, and concentrated under reduced pressure using a rotary evaporator. – Elemental analyses were performed by the staff of the microanalytical laboratory in our department. – The FluoroFlash Columns have been purchased from Fluorous Technologies, Inc. – *tert*-butyl-phenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl bromide was synthesized as described in Röver, S.; Wipf, P. *Tetrahedron Lett.* **1999**, 40, 5667.

All fluorous tagged compounds are isomeric mixtures because the silicon atom is a stereogenic center. Isomer ratio was 10:6.3 determined by NMR.

All new compounds have been characterised by NMR experiments (COSY, TOCSY, HETCOR).

***tert*-Butyl-phenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-trichloroethoxycarbonyl- β -*D*-glucopyranoside** **6**. *tert*-butyl-phenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl bromide (2.930 g, 4.154 mmol) was dissolved in CH_2Cl_2 (20.0 mL). **5** (0.885 g, 1.896 mmol), triethylamine (0.580 mL, 4.161 mmol), and dimethylaminopyridine (0.023 g, 0.188 mmol) were added and the mixture was stirred under nitrogen at rt overnight. CH_2Cl_2 was added and the mixture was washed with NaHCO_3 solution. The organic phase was dried over Na_2SO_4 , the solvent was removed under reduced pressure and the residue purified by flash chromatography (toluene/acetone 9:1) to afford

2.053 g (98%) of **6** as a white foam. – ^1H NMR (mixture of diastereoisomers) (400 MHz, CDCl_3): δ 0.98, 1.18 (2 s, 18 H, t-Bu), 1.90-2.13 (6 s, 18 H, $\text{CH}_3\text{CO-}$), 2.42 (m, 4 H, $-\text{CH}_2\text{C}_8\text{F}_{17}$), 3.59 (m, 1.22 H, H5), 3.65 (m, 0.78 H, H5'), 3.81 (m, 2 H, H2, H2'), 3.88 (t, 2.44 H, $J = 6.7$ Hz, $-\text{CH}_2\text{OSi-}$), 4.02-4.26 (m, 5.56 H, H6, H6', $-\text{CH}_2'\text{OSi-}$), 4.48-4.84 (m, 4 H, $-\text{CH}_2\text{Cl}_3$), 4.91 (d, 1.22 H, H1), 5.03-5.31 (m, 4.78 H, H1', H4, H4', H3, H3'), 5.50, 5.55 (2d, 2 H, $J = 3.1$ Hz, $J = 3.3$ Hz, NH), 7.32-7.82 (m, 10 H, aromatics). – ^{13}C NMR (mixture of diastereoisomers) (100.6 MHz, HETCOR, CDCl_3): δ 136.0, 131.0, 128.8, 126.9, 95.9, 96.0, 75.1, 72.7, 72.6, 72.3, 69.0, 62.5, 62.4, 58.8, 55.8, 56.7, 34.8, 27.5, 26.5, 21.4 – MS (MALDI-TOF): calcd. For $\text{C}_{35}\text{H}_{37}\text{Cl}_3\text{F}_{17}\text{NO}_{11}\text{Si}$ 1103.09; found 1126 (M+Na). – $\text{C}_{35}\text{H}_{37}\text{Cl}_3\text{F}_{17}\text{NO}_{11}\text{Si}$ (1105.08): calcd. C 38.04, H 3.37, N 1.27; found C 38.12, H 3.38, N 1.27

***tert*-Butyl-phenyl-1H,1H,2H,2H-heptadecafluorodecyloxysilyl 2-deoxy-2-N-trichloroethoxycarbonyl- β -D-glucopyranoside **7**.** Compound **6** (1.105 g, 1.000 mmol) was dissolved in dry MeOH (10 mL) and MeONa-MeOH (0.290 mL, 0.355M) was added. The mixture was then stirred under nitrogen for 2 hours at rt and then neutralized with Amberlite IRC 50 H^+ resin. The mixture was filtered and the solvent evaporated under reduced pressure to give 0.960 g (98%) of **7** as white foam. The crude was submitted to next reaction without further purification. – ^1H NMR (mixture of diastereoisomers) (400 MHz, CDCl_3): δ 0.98, 1.00 (2 s, 18 H, t-Bu), 2.47 (m, 2.44 H, $-\text{CH}_2\text{C}_8\text{F}_{17}$), 2.75 (m, 1.56 H, $-\text{CH}_2'\text{C}_8\text{F}_{17}$), 3.31 (m, 1.22 H, H5), 3.39 (m, 0.78 H, H5'), 3.46-3.87 (m, 10 H, H2, H2', H3, H3', H4, H4', H6, H6'), 4.17 (t, 2.44 H, $J = 6.6$ Hz, $-\text{CH}_2\text{OSi}$), 4.22 (t, 1.56 H, $J = 6.6$ Hz, $-\text{CH}_2'\text{OSi}$), 4.67-4.82 (m, 4 H, CH_2CCl_3 , $\text{CH}_2'\text{CCl}_3$), 4.89 (d, 1.22 H, $J = 7.9$ Hz, H1), 5.10 (d, 0.78 H, $J = 7.9$ Hz, H1'), 5.21 (bs, NH), 5.36 (bs, NH'), 7.37-7.70 (m, 10 H, aromatics) – ^{13}C NMR (mixture of diastereoisomers) (100.6 MHz, HETCOR, CDCl_3): δ 135.0, 128.3, 96.1, 76.0, 75.6, 75.4, 72.6, 63.0, 61.1, 56.9, 34.5, 26.7. – MS (MALDI-TOF): calcd. For $\text{C}_{29}\text{H}_{31}\text{Cl}_3\text{F}_{17}\text{NO}_8\text{Si}$ 977.06; found 1000.3 (M+Na). – $\text{C}_{29}\text{H}_{31}\text{Cl}_3\text{F}_{17}\text{NO}_8\text{Si}$ (978.97): calcd. C 35.58, H 3.19, N 1.43; found C 35.38, H 3.20, N 1.43.

***tert*-Butyl-phenyl-1H,1H,2H,2H-heptadecafluorodecyloxysilyl 3,4-O-benzylidene-2-deoxy-2-N-trichloroethoxycarbonil- β -D-glucopyranoside 8.** Compound **7** (0.944 g, 0.964 mmol) was dissolved in dry CH₃CN (10.0 mL), then were added benzaldehyde dimethylacetal (0.440 mL, 2.932 mmol) and camphorsulfonic acid (0.022 g, 0.095 mmol). The mixture was stirred for 3 h at room temperature and neutralised with TEA. To the mixture was added water (7.0 ml) and extracted with CH₂Cl₂. The collected organic phases were dried over Na₂SO₄ and evaporated under reduced pressure. The resulting residue was passed through fluorosilica gel in a two-stage extraction eluting first with 80% MeOH/H₂O (to remove the benzaldehyde byproducts) and then with MeOH to recover the reaction product and the unreacted tagged substrate. The MeOH fraction was evaporated and the MALDI-TOF analysis showed the presence of a small quantity of non reacted starting materials. The mixture was submitted to a second cycle of reaction with the same condition described above to give 0.885 g of **8** as white foam (86% over two cycles). ¹H NMR (mixture of diastereoisomers) (400 MHz, CDCl₃): δ 0.98, 1.00 (2 s, 18 H, t-Bu), 2.48 (m, 4 H, -CH₂C₈F₁₇), 3.39 (m, 1.22 H, H5), 3.52 (m, 0.78 H, H5'), 3.61 (t, 1.22 H, J = 7.9 Hz, H2), 3.76 (t, 0.78 H, J = 8.4 Hz, H2'), 3.92-4.31 (m, 12 H, H3, H3', H4, H4', H6, H6' -CH₂OSi, -CH₂'OSi), 4.66-4.82 (m, 4 H, CH₂CCl₃, CH₂'CCl₃), 4.96 (d, 1.22 H, J = 7.9 Hz, H1), 5.14 (bd, 1.22 H, NH), 5.19 (d, 0.78 H, J = 8.4 Hz, H1'), 5.28 (bd, 0.78 H, NH'), 5.54 (s, 1.22 H, CHPh), 5.57 (s, 0.78 H, CH'Ph) 7.37-7.70 (m, 20 H, aromatics) – ¹³C NMR (mixture of diastereoisomers) (100.6 MHz, HETCOR, CDCl₃): δ 135.2, 128.5, 126.4, 102.3, 96.1, 81.8, 75.4, 71.7, 68.9, 68.7, 66.8, 61.1, 60.9, 56.7, 34.3, 26.1. – MS (MALDI-TOF): calcd. For C₃₆H₃₅Cl₃F₁₇NO₈Si 1065.09; found 1088 (M+Na). – C₃₆H₃₅Cl₃F₁₇NO₈Si (1067.08): calcd. C 40.52, H 3.31, N 1.31; found C 40.56, H 3.30, N 1.31.

Compound 10. TMSOTf (0.022 mL, 0.114 mmol) was added to a solution of **8** (1.209 g, 1.133 mmol) and **9** (1.304 g, 2.721 mmol) in dry CH₂Cl₂ (10 mL) in presence of molecular sieves (UOP type AW), under Argon atmosphere at –30°C. After 45 min TEA was added, and the mixture was filtered

and extracted with CH₂Cl₂. The organic layers has been collected, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was passed through fluorosilica gel in a two-stage extraction eluting first with 80% MeOH/H₂O and then with MeOH. The MeOH fraction gave 1.108 g of **10** as white foam (70%). – ¹H NMR (major diastereoisomer) (400 MHz, CDCl₃): δ 0.98, (s, 9 H, t-Bu), 1.90-2.18 (4 s, 12 H, CH₃CO-), 2.43 (m, 2 H, -CH₂C₈F₁₇), 3.30-5.70 [m, 20 H, H,H-COSY: 3.40 (m, 1 H, H5a), 3.50 (m, 1 H, H5b), 3.58 (m, 1 H, H2a), 3.77 (m, 2 H, H4a, H6'a), 3.79 (m, 1 H, H6'b), 4.08 (m, 2 H, -CH₂OSi) 4.15 (m, 2 H, H3a, H6a), 4.31 (m, 1 H, H6b) 4.71 (m, 3 H, H1b, CH₂CCl₃), 4.87 (m, 1 H, H3b), 5.1 (m, 1 H, H1a), 5.22 (m, 1 H, H2b), 5.30 (m, 1 H, H4b), 5.61 (m, 1 H, NH), 5.53 (m, 1 H, -CHPh)], 7.35-7.80 (m, 10 H, aromatics) – ¹³C NMR (major diastereoisomers) (100.6 MHz, HETCOR, CDCl₃): δ 135.3, 130.8, 128.5, 129.4, 126.3, 101.9, 101.3, 95.6, 80.6, 78.6, 75.2, 71.3, 71.1, 69.9, 68.8, 67.3, 66.7, 61.2, 60.6, 56.6, 56.4, 34.2, 26.2, 21.1. – MS (MALDI-TOF): calcd. For C₅₀H₅₃Cl₃F₁₇NO₁₇Si 1395.19; found 1434 (M+K). – C₅₀H₅₃Cl₃F₁₇NO₁₇Si (1397.37): calcd. C 42.98, H 3.82, N 1.00, found C 43.01, H 3.83, N 1.00.

Compound 11. To a solution of **10** (0.181 g, 0.130 mmol) in dry CH₂Cl₂ was added triethylsilane (0.100 ml, 0.626 mmol) at 0°C. The mixture was stirred for 20 min under nitrogen, then trifluoroacetic acid (0.050 ml, 0.652 mmol) and trifluoroacetic anhydride (0.018 ml, 0.127 mmol) were added. The reaction was completed (TLC) in 5 h, while the temperature slowly rose up to rt, then aqueous NaHCO₃ was added. The mixture was extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄ and evaporated under reduced pressure and gave 0.157 g of **11** (86%) as white foam. – ¹H NMR (major diastereoisomer) (400 MHz, CDCl₃): δ 0.98, (s, 9 H, t-Bu), 2.00-2.25 (4 s, 12 H, CH₃CO-), 2.34 (m, 2 H, -CH₂C₈F₁₇), 3.20-5.55 [m, 21 H, H,H-COSY: 3.28 (m, 1 H, H2a), 3.37 (m, 1 H, H5a), 3.57 (m, 1 H, H6a), 3.58 (m, 1 H, H4a), 3.65 (m, 1 H, H6'a), 4.00-4.19 (m, 6 H, H3a, H5b, H6b, H6'b, CH₂OSi), 4.46 (m, 2 H, CH₂Ph), 4.59 (m, 1 H, H1b), 4.71 (m, 2 H, CH₂CCl₃) 4.9-5.52 (m, 5 H, H1a, H2b, H3b, H4b, NH)], 7.35-7.7 (m, 10 H, aromatics) – ¹³C NMR (major diastereoisomer) (100.6 MHz, HETCOR,

CDCl₃): δ 135.2, 128.5, 128.0, 127.8, 102.0, 75.2, 73.8, 71.9, 71.2, 70.1, 69.3, 67.2, 62.1, 56.6, 34.1, 26.2, 21.1. – MS (MALDI-TOF): calcd. For C₅₀H₅₅Cl₃F₁₇NO₁₇Si 1397.20; found 1420 (M+Na). – C₅₀H₅₅Cl₃F₁₇NO₁₇Si (1399.38): calcd. C 42.91, H 3.96, N 1.00, found C 43.83, H 3.95, N 1.00.

Compound 13. TMSOTf (0.007 mL, 0.036 mmol) was added to a solution of **11** (0.480 g, 0.343 mmol) and **12** (0.489 g, 1.013 mmol) in dry CH₂Cl₂ (4 mL) in presence of molecular sieves (UOP type AW), under Argon atmosphere at –40°C. After 2 h TEA was added, and the mixture was filtered and extracted with CH₂Cl₂. The organic layers has been collected, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was passed through fluorous silica gel in a two-stage extraction eluting first with 80% MeOH/H₂O and then with MeOH. The MALDI spectrum of the MeOH fraction showed the presence of a discrete amount of unreacted glycosyl acceptor. The mixture was then submitted to a second cycle of reaction in the same conditions described for the first cycle. After the subsequent F-SPE, the MeOH fraction gave 0.354 g of **13** as white foam (60% over two cycles). – ¹H NMR (major diastereoisomer) (400 MHz, CDCl₃): δ 0.92, (s, 9 H, t-Bu), 1.27 (d, 3 H, J = 6.5 Hz, H6c), 1.96, 1.97, 2.07, 2.12, 2.16, 2.18 (6 s, 18 H, CH₃CO-), 2.29 (m, 2 H, -CH₂C₈F₁₇), 3.23-5.45 [m, 27 H, H,H-COSY: 3.29 (m, 1 H, H5a), 3.39, 3.76 (2 m, 2 H, H6a), 3.86 (m, 1 H, H2c), 3.88 (m, 1 H, H2a), 4.00 (m, 2 H, H3a, H4a), 4.11 (m, 1 H, H5b), 4.17 (m, 2 H, CH₂OSi), 4.30 (m, 2 H, H6b), 4.51 (m, 2 H, CH₂Ph), 4.66 (m, 1 H, H1a), 4.72 (m, 2 H, CH₂CCl₃) 4.85 (m, 1 H, H1b), 4.90 (m, 1 H, H3b), 5.05 (m, 1 H, H5c), 5.12 (m, 2 H, H2b, H1c), 5.20 (m, 2 H, H3c, NH), 5.38 (m, 1 H, H4b), 5.40 (m, 1 H, H4c)], 7.30-7.70 (m, 15 H, aromatics). – ¹³C NMR (major diastereoisomer) (100.6 MHz, HETCOR, CDCl₃): δ 135.1, 128.4, 128.2, 128.1, 101.4, 97.3, 96.0, 75.6, 75.3, 75.0, 74.6, 73.7, 73.9, 72.5, 72.4, 71.1, 67.3, 64.8, 61.2, 56.5, 34.0, 29.8, 21.2, 16.3. – MS (MALDI-TOF): calcd. For C₆₇H₇₅Cl₃F₁₇NO₂₃Si 1717.33; found 1740 (M+Na). – C₅₀H₅₃Cl₃F₁₇NO₁₇Si (1719.72): calcd. C 46.79, H 4.40, N 0.81, found C 46.88, H 4.41, N 0.81.

Compound 14. To a solution of **13** (0.221 g, 0.129 mmol) in THF (2 ml), at 0°C, was added a solution of TBAF in THF (1 M, 0.193 mmol, 0.193 mL). The solution was stirred for 5 min., then brine (1 mL) was added and the resulting mixture was extracted with EtOAc. The combined organic phases were dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was passed through fluorous silica gel eluting with MeOH/H₂O 80% to obtain the non tagged product. The MeOH/H₂O was evaporated to give 0.106 g of **14** (75%) as white foam. – ¹H NMR (major epimer) (400 MHz, CDCl₃): δ 1.28 (s, 3 H, H6c), 1.96, 1.99, 2.08, 2.17 (4 s, 18 H, CH₃CO-), 3.50-5.50 [m, 26 H, H,H-COSY: 3.55 (m, 1 H, H5a), 3.87 (m, 2 H, H6a), 3.94 (m, 3 H, H3a, H6b), 4.00 (m, 1 H, H2c), 4.02 (m, 1 H, H4a), 4.04 (m, 1 H, H5b), 4.05 (m, 1 H, H2a), 4.27 (m, 2 H, CH₂Ph), 4.42, 4.5, 4.6 (m, 2 H, CH₂CCl₃), 4.52 (m, 2 H, CH₂'Ph), 4.80 (m, 1 H, H1b), 4.95 (m, 1 H, H3b), 5.03 (m, 1 H, H5c), 5.12 (m, 1 H, H1c), 5.15 (m, 2 H, H1a, H2b), 5.25 (m, 1 H, H4c), 5.40 (m, 3 H, H3c, H4b, NH)], 7.32-7.40 (m, 10 H, aromatics). – ¹³C NMR (major epimer) (100.6 MHz, HETCOR, CDCl₃): δ 128.2, 101.55, 97.5, 92.6, 75.7, 75.2, 74.6, 73.9, 72.7, 71.6, 71.3, 70.9, 69.1, 67.9, 67.2, 64.8, 62.2, 61.4, 57.4, 56.2, 46.2, 21.1 – MS (MALDI-TOF): calcd. For C₄₇H₅₈Cl₃NO₂₂ 1093.25; found 1116 (M + Na). – C₄₇H₅₈Cl₃NO₂₂ (1095.32): calcd. C 51.54, H 5.34, N 1.28; found C 51.67, H 5.33, N 1.28.