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Electronic Supporting Information

Convergent Synthesis of Oligosaccharides in Gram-Scale Using Cetyl Thioglycoside Based on Hydrophobically Assisted Switching Phase Method

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Synthesis of compound 1



4-Tolyl 3,4-O-[(1'S,2'S)-1',2'-dimethoxy-1',2'-dimethyl-1',2'-ethylene]-1-thio-α-D-mannopyranoside (S-1)

400mL Ac₂O stirred by a mechanical agitator in a 1L bottom was cooled in an ice bar. 1mL HClO₄ was added slowly and the solution became light yellow. 100g D-mannose was added in five portions during 2h. The reaction was complete after 5h and the solution was poured into 0.5L ice-water in a 2L beaker. The mixture was stirred vigorously for 1h and then 500mL CH₂Cl₂ was added. The mixture was poured into a 2L separating funnel. The organic layer was separated, washed by saturated NaHCO₃ solution and brine three times and then dried over MgSO₄. The filtrate was evaporated and 216.0g light yellow syrup was obtained.

The syrup was dissolved in 500mL CH_2Cl_2 and 82.6g 4-tolyl mercaptan was added. Then 140mL $BF_3 Et_2O$ was added and the solution was stirred for 8h. To the vigorously stirred solution, 100mL brine was added and the mixture was poured into separating funnel after 1h. The organic layer was separated, washed by saturated Na_2CO_3 solution and brine three times and then dried over MgSO₄. The filtrate was evaporated

and 500mL MeOH with 5.0g NaOMe was added to the residue. The mixture was stirred at room temperature for 5h and concentrated. The residue was recrystallized with MeOH and 108.2g 4-tolyl 1-thio- α -D-mannopyranoside was obtained in white solid.

The 4-tolyl 1-thio- α -D-mannopyranoside was suspended in 400mL dry MeOH. 82.0mL 2,3-butanedione and 206.0mL trimethyl orthoformate were poured into the suspension. The mixture was heated at 40°C until the solid was dissolved completely. Then 10.0mL BF₃Et₂O was added and the solution was stirred at 80°C for 6h while the color became dark red. 50mL Et₃N was added slowly and the mixture was evaporated. The residue was dissolved in 500mL CH₂Cl₂ and washed by brine for three times. The organic layer was dried over MgSO₄ and filtered. The filtrate was evaporated and the residue was recrystallized with MeOH. 120.0g compound **S-1** was obtained in white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H,), 5.44 (d, *J* = 1.2 Hz, 1H), 4.24-4.14 (m, 3H), 4.01 (dd, *J* = 3.0 Hz, 9.6 Hz), 3.76 (dd, *J* = 2.8 Hz, 6.3 Hz), 3.61 (d, *J* = 3.0 Hz, 1H), 3.29 (s, 3H), 3.22 (s, 3H), 2.57 (t, *J* = 6.3 Hz, 1H), 2.30 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 137.8, 132.5, 129.8, 129.8, 100.4, 99.8, 88.5, 71.6, 70.9, 68.7, 62.8, 60.9, 48.0, 47.9, 21.1, 17.7, 17.6.

4-Tolyl 2-benzoyl-3,4-*O*-**[(1'5,2'5)-1',2'-dimethoxy-1',2'-dimethyl-1',2'-ethylene]-6-***O*-**[(tert-butyl-diphenyl)-silyl]-1-thio**-*a*-**D-mannopyranoside** (S-2) 50.0g compound **S-1** and 0.75g DMAP was dissolved in 100mL dry pyridine. 35.7mL TBDPSCl was added at 0°C in tree portions. The mixture was stirred at room temperature for 6h and 50mL pyridine was poured in. The mixture was cooled in an ice bar and 17.3mL BzCl was added dropwise. The mixture was stirred for 3h and then quenched with 10mL MeOH. The mixture was evaporated and the residue was dissolved in 300mL CH₂Cl₂. The solution was washed by 1M HCl and then saturated NaHCO₃ and brine, each for tree times and dried over MgSO₄. The filtrate was evaporated and the residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 15:1) to give compound **S-2** (82.5g, 89%) in light yellow syrup. ¹H NMR (400 MHz, CDCl₃) δ 8.20 – 7.98 (m, 2H), 7.79 – 7.63 (m, 4H), 7.60 – 7.49 (m, 1H), 7.47 – 7.29 (m, 8H), 7.29 – 7.17 (m, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 5.64 – 5.48 (m, 2H), 4.57 (t, *J* = 10.1 Hz, 1H), 4.35 – 4.27 (m, 1H), 4.21 (dd, *J* = 10.3, 3.1 Hz, 1H), 4.09 (dd, *J* = 11.5, 3.1 Hz, 1H), 3.88 (dd, *J* = 11.5, 1.9 Hz, 1H), 3.32 (s, 6H), 2.32 (s,

3H), 1.33 (s, 3H), 1.27 (s, 3H), 0.98 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 166.14, 137.75, 136.13, 135.58, 134.92, 134.20, 133.21, 132.95, 132.35, 130.59, 130.16, 129.89, 129.79, 129.61, 129.57, 128.46, 127.85, 127.74, 127.55, 100.42, 99.93, 87.15, 72.99, 72.44, 67.46, 63.18, 61.73, 48.28, 48.26, 26.83, 26.69, 21.28, 19.50, 17.97, 17.76. HRMS(ESI) m/z calcd for C₄₂H₅₈NO₈SSi [M+NH₄]⁺: 760.3334, found: 760.3372.

2-Benzoyl-3,4-*O***-[(1'***S***,2'***S***)-1',2'-dimethoxy-1',2'-dimethyl-1',2'-ethylene]-6-***O***-[(tert-butyl-diphenyl)-silyl]-1-thio-***α***/β-D-mannopyranose (S-3) 82.0g compound S-2 was dissolved in 300mL acetone. To the vigorously stirred solution, 30mL water was added and the mixture was cooled to 0°C in an ice bar. 21.8g NBS was added in darkness and the mixture was stirred at 0°C for 4h while the solution became light yellow. Then the reaction was quenched by 50mL 40% Na₂S₂O₃ solution. 300mL CH₂Cl₂ was added after the acetone was removed by evaporation. The organic layer was separated, washed by saturated NaHCO₃ and brine, and dried over MgSO₄. The filtrate was evaporated and the residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 5:1) to give compound S-3 (56.23g, 80%) in white solid. The α isomer was major product while the β isomer was not separated for the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.17 – 8.05 (m, 2H), 7.70 (m, 4H), 7.58 – 7.48 (m, 1H), 7.44 – 7.31 (m, 6H), 7.30 – 7.22 (m, 2H), 5.32 (ddd,** *J* **= 9.9, 3.3, 1.6 Hz, 2H), 4.48 (t,** *J* **= 10.1 Hz, 1H), 4.32 (dd,** *J* **= 10.4, 3.1 Hz, 1H), 4.10 – 3.96 (m, 2H), 3.86 (dd,** *J* **= 11.2, 1.7 Hz, 1H), 3.27 (s, 6H), 3.04 (d,** *J* **= 3.6 Hz, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 1.02 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 166.32, 136.11, 135.93, 135.66, 134.30, 133.30, 133.14, 130.29, 130.17, 129.66, 128.49, 128.44, 127.70, 127.64, 127.57, 100.33, 99.86, 92.96, 71.74, 66.15, 63.12, 62.26, 48.29, 48.18, 26.96, 19.54, 17.94, 17.80. HRMS(ESI) m/z calcd for C₃₅H₄₈NO₉Si [M+NH₄]⁺: 654.3093, found: 654.3079.**

2-*O*-Benzoyl-3,4-*O*-[(1'*S*,2'*S*)-1',2'-dimethoxy-1',2'-dimethyl-1',2'-ethylene]- 6-*O*-[(*tert*-butyl-diphenyl)-silyl]-α-D-mannopyranose 2,2,2-trichloroethanimidate (1)

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56.0g compound **S-3** was dissolved in 200mL dry CH₂Cl₂ and cooled to 0°C under N₂. 44.0mL trichloroacetonitrile was added and followed by 1.3mL DBU. The solution was stirred at 0°C for 2h while the color became brown. The solution was evaporated and the residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 10:1) to give compound **1** (59.0g, 86%) in white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 8.19 – 8.06 (m, 2H), 7.77 – 7.67 (m, 4H), 7.62 – 7.51 (m, 1H), 7.48 – 7.26 (m, 8H), 6.48 (d, *J* = 1.8 Hz, 1H), 5.63 – 5.45 (m, 1H), 4.58 (t, *J* = 10.3 Hz, 1H), 4.35 (ddd, *J* = 10.4, 3.4, 1.1 Hz, 1H), 4.13 – 3.99 (m, 1H), 3.99 – 3.88 (m, 1H), 3.28 (s, 6H), 1.32 (s, 3H), 1.24 (s, 3H), 1.03 (d, *J* = 1.3 Hz, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 165.85, 160.11, 136.08, 135.66, 134.07, 133.31, 133.09, 130.24, 129.97, 129.69, 129.65, 128.48, 127.78, 127.72, 127.66, 100.33, 99.93, 95.89, 91.13, 74.70, 69.67, 66.69, 62.53, 61.68, 48.37, 48.07, 26.88, 19.54, 17.92, 17.74. HRMS(ESI) m/z calcd for C₃₅H₄₃O₈Si [M-OC(NH)CCl₃]⁺: 619.2722, found: 619.2784. **Synthesis of compound 2 and 3**

$Cetyl \ 2,3,4,6-tetra-\textit{O}-acetyl-1-thio-\alpha-D-mannopyranoside \ (S-4)/\ Cetyl \ 1-thio-\alpha-D-mannopyranoside \ ($

200mL Ac₂O stirred by a mechanical agitator in a 500L bottom was cooled in an ice bar. 0.5mL HClO₄ was added slowly and the solution became light yellow. 50g D-mannose was added in five portions during 2h. The reaction was complete after 5h and the solution was poured into 0.25L ice-water in a 1L beaker. The mixture was stirred vigorously for 1h and then 300mL CH₂Cl₂ was added. The mixture was poured into a 1L separating funnel. The organic layer was separated, washed by saturated NaHCO₃ solution and brine three times and then dried over MgSO₄. The filtrate was evaporated and 216.0g light yellow syrup was obtained.

The syrup was dissolved in 200mL CH_2Cl_2 and 85.0g *n*-hexadecyl mercaptan was added. Then 70mL BF_3Et_2O was added and the solution was stirred for 7h. To the vigorously stirred solution, 50mL brine was added and the mixture was poured into separating funnel after 1h. The organic layer was separated, washed by saturated Na_2CO_3 solution and brine three times and then dried over MgSO₄. The filtrate was evaporated and the yellow crude product was obtained

Compound **S-4** could be obtained in yellow syrup by chromatograph on silica gel (petroleum ether/ethyl acetate, 3:1). ¹H NMR (400 MHz, CDCl₃) δ 5.39 – 5.19 (m, 4H), 4.47 – 4.26 (m, 2H), 4.09 (dd, *J* = 12.2, 2.2 Hz, 1H), 2.76 – 2.50 (m, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.61 (q, *J*)

 $= 7.4 \text{ Hz}, 2\text{H}, 1.26 (s, 26\text{H}), 1.00 - 0.79 (m, 3\text{H}). {}^{13}\text{C NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 170.60, 170.00, 169.80, 169.77, 82.64, 71.28, 69.57, 69.00, 66.45, 62.53, 32.00, 31.44, 29.76, 29.74, 29.72, 29.66, 29.59, 29.51, 29.43, 29.22, 28.89, 22.77, 20.98, 20.78, 20.76, 20.69, 14.19. HRMS(ESI) m/z calcd for C₃₀H₅₉NO₉S [M+NH₄]⁺: 606.3670, found: 606.3698.$

In a more convenient way, the crude product was treated with 2.0g NaOMe in 150mL MeOH. The mixture was stirred overnight and a large number of white solids were separated out. The solid was filtered and washed by ethyl ether. 74.0g (63%, three steps) cetyl 1-thio-mannopyranoside was obtained in this way.



Cetyl 3, 6-di-O-[(tert-butyl)-dimethyl-silyl]-1-thio-a-D-mannopyranoside (S-5)

25.0g cetyl 1-thio-mannoside was dissolved in 60mL dry pyridine. 28.0g TBDMSCl and 0.5g DMAP were added and the mixture was stirred at 60°C for 6h. Then the reaction was quenched with 20mL MeOH and the solvent was removed by evaporation. 200mL CH₂Cl₂ was added to the residue and the organic layer was washed by 0.5M HCl, saturated NaHCO₃ and brine, each for three times. The CH₂Cl₂ layer was separated, dried over MgSO₄ and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 15:1) to give compound **S-5** (28.2g, 73%) in yellow syrup. ¹H NMR (400 MHz, CDCl₃) δ 5.30 (s, 1H), 3.97 (dt, *J* = 9.9, 5.4 Hz, 1H), 3.86 (m, 4H), 3.79 – 3.72 (m, 1H), 2.72 (s, 1H), 2.70 (d, *J* = 2.0 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.53 (m, 1H), 1.67 – 1.54 (m, 2H), 1.26 (s, 26H), 0.99 – 0.82 (m, 21H), 0.16 (s, 3H), 0.14 (s, 3H), 0.09 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 83.47, 73.73, 72.81, 71.29, 70.92, 64.97, 32.08, 30.90, 29.85, 29.81, 29.77, 29.69, 29.65, 29.51, 29.38, 29.00, 26.06, 25.96, 22.84, 18.47, 18.25, 14.26, -4.31, -4.70, -5.27, -5.30. HRMS(ESI) m/z calcd for C₃₄H₇₆NO₅SSi₂ [M+NH₄]⁺: 666.4977, found: 666.4002.

Cetyl 2,4-bis-O-(2-naphthalenylmethyl)-1-thio-α-D- mannopyranoside (2)

28.0g compound **S-5** and 23.8g 2-(bromomethyl)naphthalene were dissolved in 100mL dry DMF. 5.0g NaH (60% on silicone oil) was added at 0°C in five portions. The mixture was stirred for 3h and quenched with 10mL MeOH. The solvent was removed by evaporation and 400mL CH₂Cl₂ was added to the residue. The CH₂Cl₂ layer was washed with brineand dried over MgSO₄. The filtrate was evaporated and 200mL MeOH was added to the residue. 0.5g TsOH H₂O was added and the mixture was stirred at 70°C for 4h. The solution was neutralized with Et₃N and evaporated to give yellow residue, which was chromatographed on silica gel (petroleum ether/ethyl acetate, 4:1) to give compound **2** (18.2g, 60%) in colorless syrup. ¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.75 (m, 8H), 7.53 – 7.43 (m, 6H), 5.37 (d, *J* = 1.3 Hz, 1H), 5.07 (d, *J* = 11.3 Hz, 1H), 4.88 (d, *J* = 11.8 Hz, 1H), 4.84 (d, *J* = 11.3 Hz, 1H), 4.73 (d, *J* = 11.8 Hz, 1H), 4.06 – 3.98 (m, 2H), 3.92 (dd, *J* = 3.7, 1.3 Hz, 1H), 3.89 – 3.84 (m, 2H), 3.82 (t, *J* = 9.4 Hz, 1H), 2.61 – 2.45 (m, 2H), 2.43 (d, *J* = 9.3 Hz, 1H), 1.93 (t, *J* = 6.5 Hz, 1H), 1.57 – 1.46 (m, 2H), 1.24 (m, 26H), 0.88 (t, *J* = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 135.87, 134.97, 133.42, 133.33, 133.25, 133.14, 128.70, 128.39, 128.10, 128.07, 127.88, 127.81, 127.05, 126.84, 126.49, 126.35, 126.21, 126.10, 126.04, 125.83, 81.77, 80.20, 75.15, 72.83, 72.45, 71.82, 62.44, 32.07, 31.32, 29.84, 29.81, 29.75, 29.69, 29.67, 29.51, 29.31, 28.95, 22.84, 14.29. HRMS(ESI) m/z calcd for C₄₄H₆₄NO₅S [M+NH₄]⁺: 718.4500, found: 718.4488.

Cetyl 3,4-O-[(1'S,2'S)-1',2'-dimethoxy-1',2'-dimethyl-1',2'-ethylene]-1-thio-α-D-mannopyranoside (S-6)

22.5g cetyl 1-thio- α -D-mannopyranoside was suspended in 100mL dry MeOH. 9.5mL 2,3-butanedione and 24.0mL trimethyl orthoformate were poured into the suspension. The mixture was heated at 40°C until the solid was dissolved completely. Then 1.3mL BF₃Et₂O was added and the solution was stirred at 80°C for 6h while the color became dark red. 20mL Et₃N was added slowly and the mixture was evaporated. The residue was dissolved in 200mL CH₂Cl₂ and washed by brine for three times. The organic layer was dried over MgSO₄ and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 4:1) to give compound **S-5** (22.8g, 80%) in yellow syrup. ¹H NMR (400 MHz, CDCl₃) δ 5.28 (d, *J* = 1.1 Hz, 1H), 4.21 – 4.07 (m, 2H), 4.07 – 3.92 (m, 2H), 3.80 (dd, *J* = 6.5, 3.1 Hz, 2H), 3.27 (m, 6H), 3.09 (d, *J* = 1.9 Hz, 1H), 2.59 (m, 2H), 2.28 (t, *J* = 6.5 Hz, 1H), 1.68 – 1.51 (m, 2H), 1.41 – 1.19 (m, 26H), 0.88 (t, *J* = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 100.52, 99.97, 85.06, 71.34, 70.93, 68.88, 63.28, 61.31, 48.15, 48.01, 32.04, 31.40, 29.81, 29.77, 29.73, 29.66, 29.48, 29.32, 28.90, 22.80, 17.87, 17.76, 14.23. HRMS(ESI) m/z calcd for C₂₈H₅₈NO₇S [M+NH₄]⁺: 552.3928, found: 552.3944.

Cetyl 2-O-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (S-7)

22.7g compound **S-6** was dissolved in 30mL pyridine. 14.2g TrtCl and 0.2g DMAP were added and the mixture was stirred at 50°C for 6h. The solvent was evaporated and the residue was dissolved in 150mL CH₂Cl₂. The solution was washed by 0.5M HCl, satarated NaHCO₃ and brine, each for three times. The organic layer was separated, dried over MgSO₄ and filtered. The filtrate was evaporated and the residue was dissolved in 80mL DMF. 6.9g 2-(bromomethyl)naphthalene and 2.1g NaH (60% on silicone oil) was added at 0°C in four portions. The mixture was stirred for 3h and quenched with 10mL MeOH. The solvent was removed by evaporation and 200mL CH₂Cl₂ was added to the residue. The mixture was washed with brine and dried over MgSO₄. After filtration, the solvent was evaporated to give light yellow syrup, which was then dissolved in 60mL CH₂Cl₂. 30mL TFA was added with 5mL water and the mixture was stirred for 4h. The solution was evaporated at 40°C and the residue was neutralized and chromatographed on silica gel (petroleum ether/ethyl acetate, 2:1) to give compound **S-7** (15.5g, 65%) in white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.95 – 7.69 (m, 4H), 7.58 – 7.38 (m, 3H), 5.38 (d, *J* = 1.1 Hz, 1H), 4.87 (d, *J* = 11.9 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.08 – 3.66 (m, 7H), 2.76 (d, *J* = 2.7 Hz, 1H), 2.64 – 2.43 (m, 3H), 2.13 (t, *J* = 6.3 Hz, 1H), 1.52 (m, 2H), 1.25 (m, 26H), 0.88 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 134.84, 133.36, 133.29, 128.73, 128.07, 127.89, 127.05, 126.53, 126.39, 125.79,

81.77, 79.73, 72.84, 72.18, 72.01, 69.70, 62.73, 32.08, 31.31, 29.85, 29.82, 29.76, 29.68, 29.51, 29.32, 28.98, 22.84, 14.27. HRMS(ESI) m/z calcd for C₃₃H₅₆NO₅S [M+NH₄]⁺: 578.3874, found: 578.3888..

Cetyl 2-*O*-(2-naphthalenylmethyl)-4,6-*O*-[(*R*)-phenylmethylene]-1-thio-α-D-mannopyranoside (3)

15.0g **S-7** was dissolved in 30mL dry DMF. 4.8mL benzaldehyde dimethylacetal and 0.2g TsOH H₂O were added and the mixture was stirred at room temperature for 4h. The solution was neutralized by Et₃N and evaporated. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 5:1) to give compound **3** (15.78g, 91%) in white solid ¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.79 (m, 4H), 7.54 – 7.45 (m, 5H), 7.38 – 7.32 (m, 3H), 5.57 (s, 1H), 5.35 (d, *J* = 1.0 Hz, 1H), 4.89 (d, *J* = 11.8 Hz, 1H), 4.81 (d, *J* = 11.8 Hz, 1H), 4.25 – 4.15 (m, 3H), 4.08 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.02 – 3.93 (m, 2H), 3.89 – 3.81 (m, 1H), 2.62 – 2.40 (m, 3H), 1.57 – 1.45 (m, 2H), 1.25 (m, 26H), 0.88 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 137.39, 134.92, 133.33, 133.25, 129.24, 128.64, 128.39, 128.06, 127.85, 127.12, 126.43, 126.31, 125.93, 102.25, 83.09, 80.32, 79.89, 73.49, 69.21, 68.73, 64.08, 32.06, 31.45, 29.83, 29.79, 29.74, 29.64, 29.50, 29.27, 28.89, 22.83, 14.27. HRMS(ESI) m/z calcd for C₄₀H₆₀NO₅S [M+NH₄]⁺: 666.4187, found: 666.4205.





































































































