Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information

Thioctic acid amides: Convenient tethers for achieving low nonspecific protein binding to carbohydrates presented on gold surfaces†

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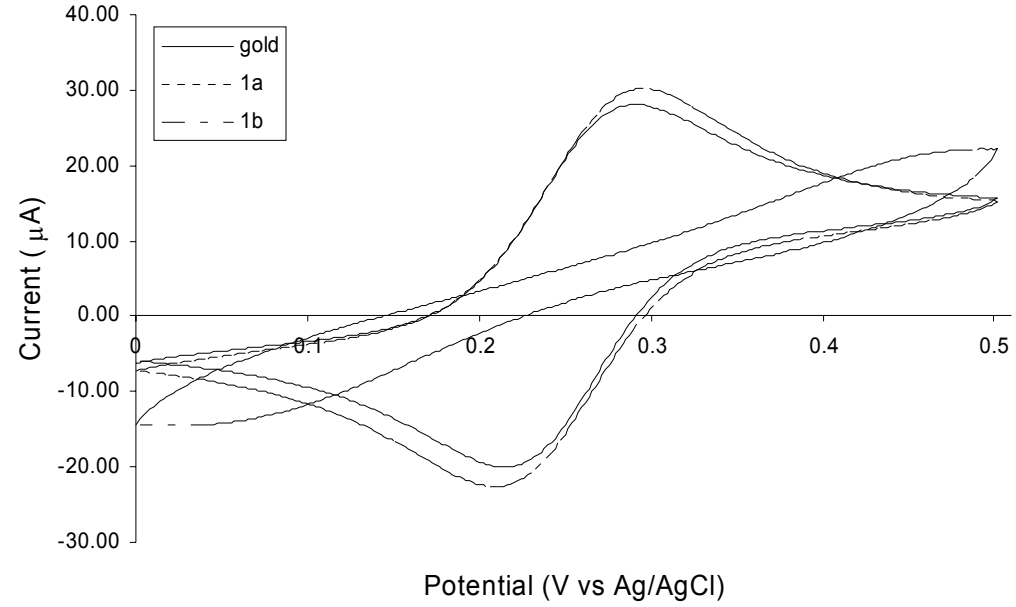


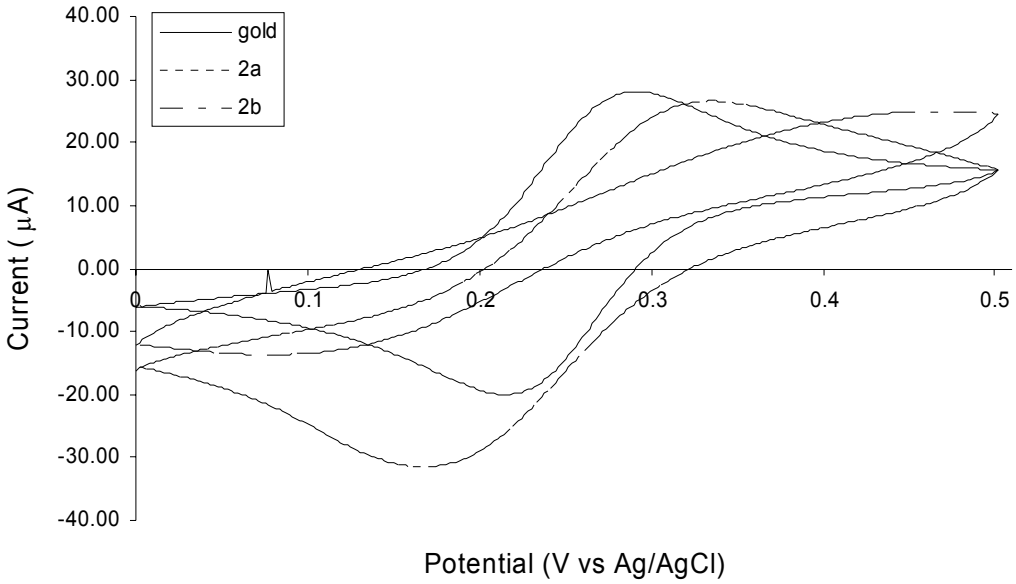


Figure 1. Cyclic voltammograms (scan rate = 50 mV s^{-1}) of gold, **1a**, **1b**, **2a** and **2b** monolayers in the presence of 1 mM $K_3Fe(CN)_6$

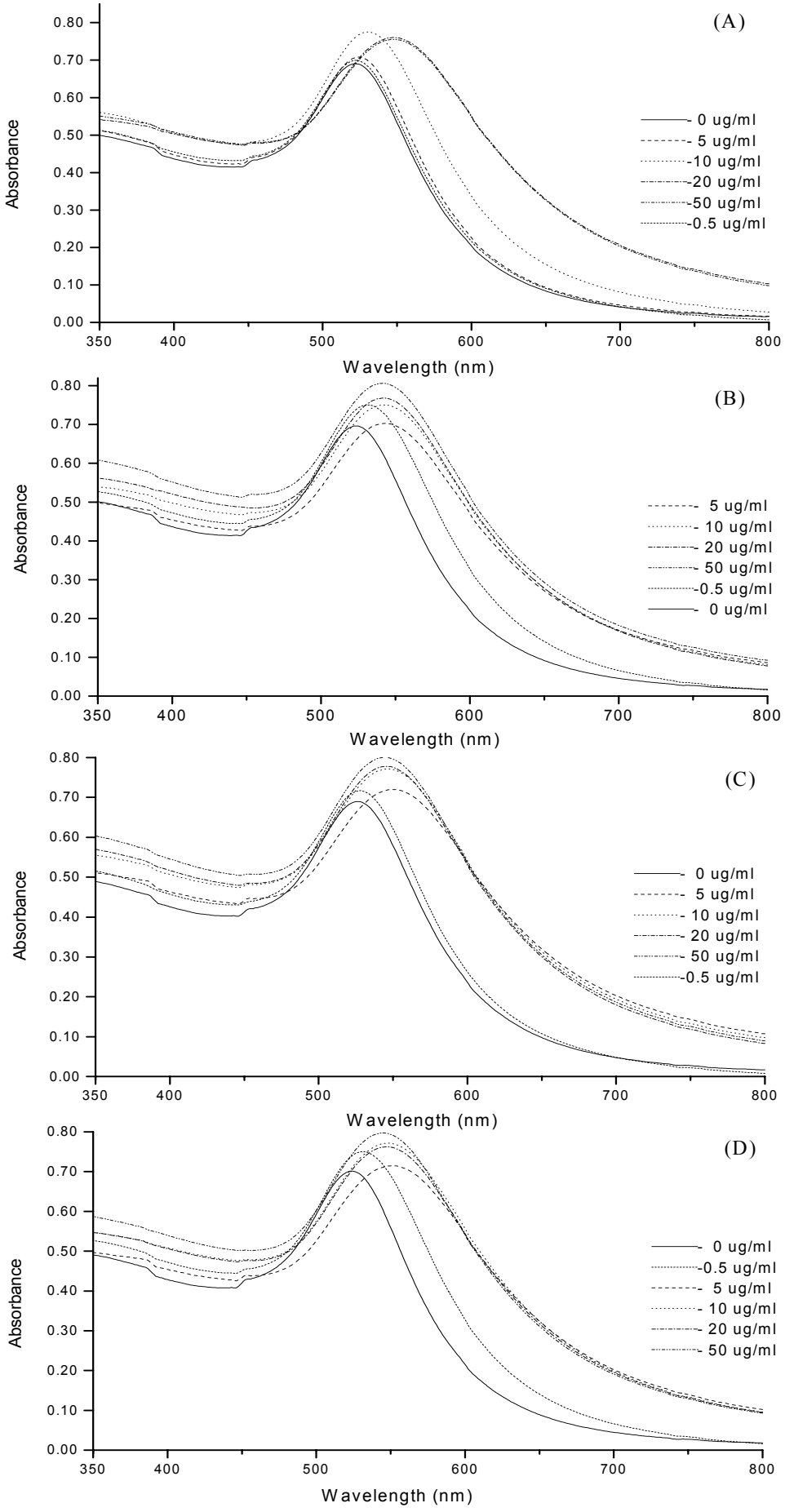


Figure 2. Changes in UV-vis spectra of gold-mannoside particles after interaction with different concentrations of Con A (0-50 μg/ml): (A) **1a**; (B) **2a**; (C) **1b** and (D) **2b** derivatised particles

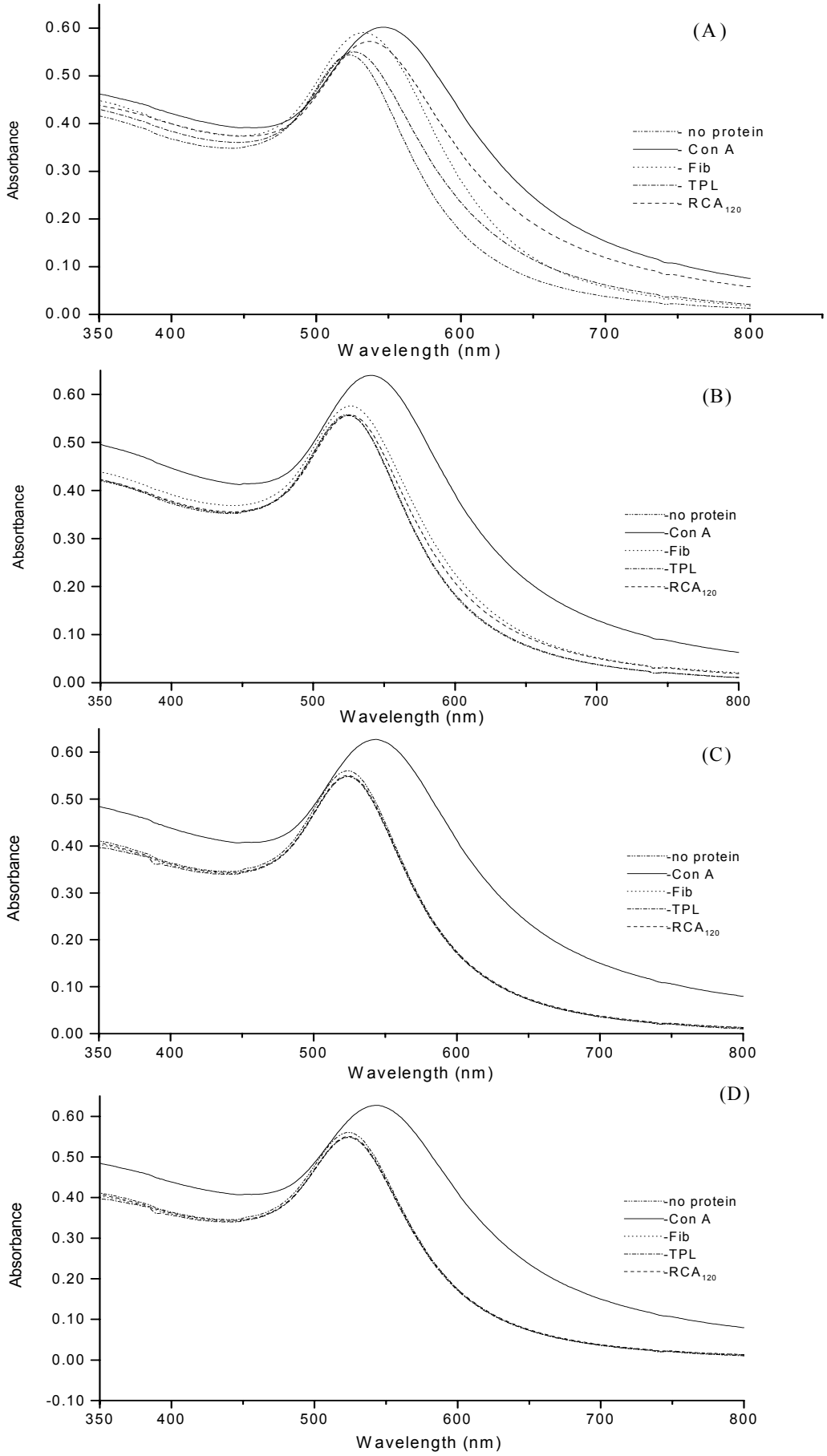


Figure 3. Comparison of specific and non-specific binding of mannoside-gold particles with 50 μg/ml lectins (Con A, RCA_{120} and TPL) and Fibrinogen; (A) **1a**; (B) **2a**; (C) **1b** and (D) **2b**.

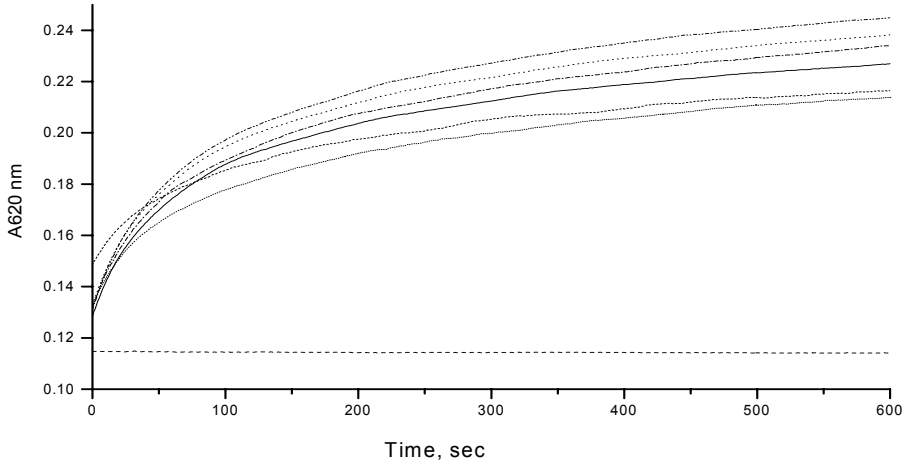
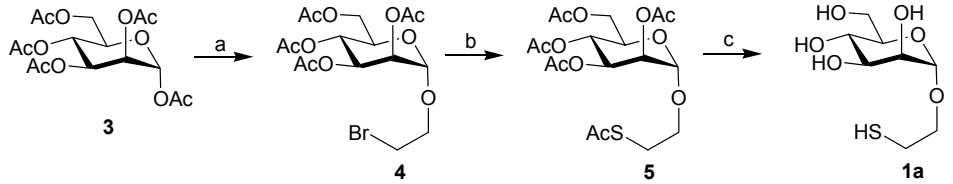


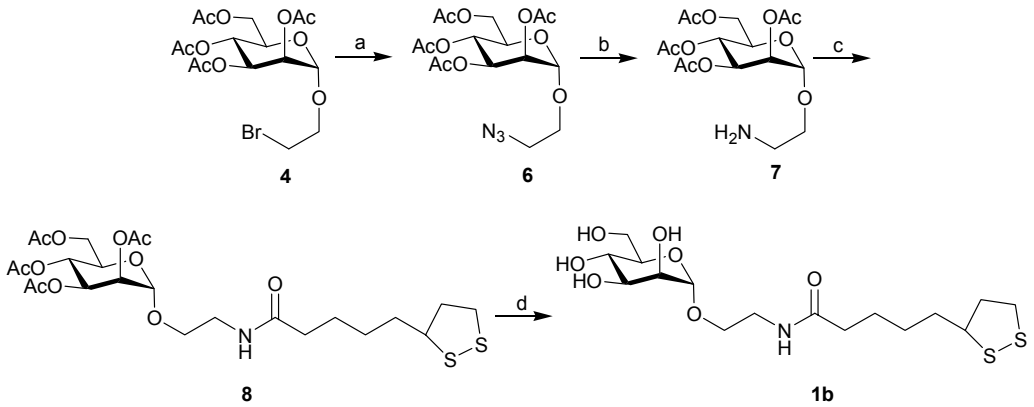
Figure 4. Interaction of **2b** modified gold particles with 2.5 µg/ml Con A plus 0-50 µg/ml Fibrinogen. Particles only (dash); particles+Con A only (solid); particles+Con A+2.5µg/ml Fib (dot); particles+Con A+5µg/ml Fib (dash dot dot); particles+Con A+10 µg/ml Fib (dash dot); particles+Con A+25µg/ml Fib (short dot); particles+Con A+50µg/ml Fib (short dash)

Scheme 1. Synthesis of **1a**



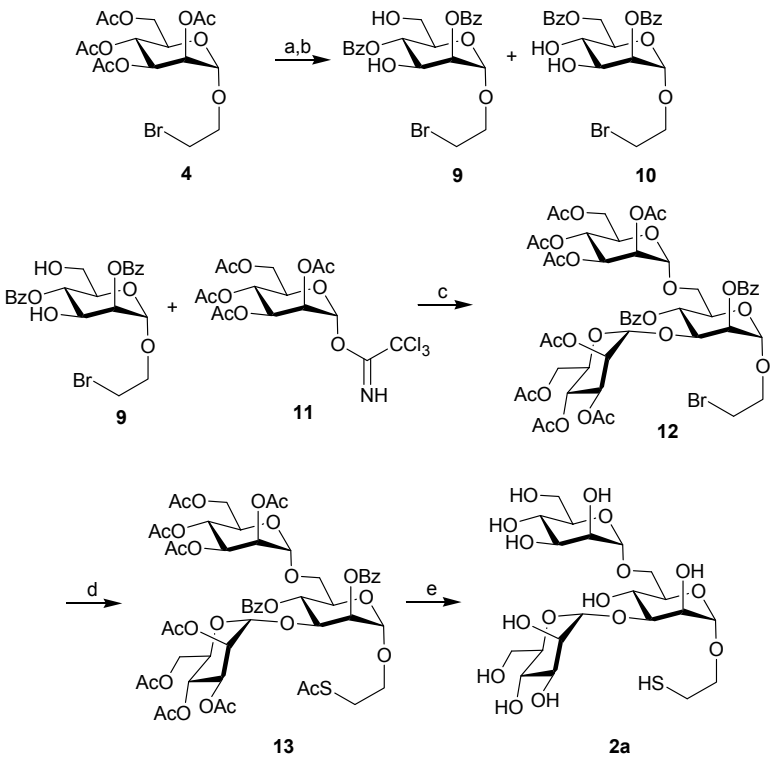
Reagents and conditions: a. 2-bromo propanol, $BF_3.Et_2O$, CH_2Cl_2, 12h, rt, 65%; b. KSAc, 2-butanone, reflux, 3h, 97%; c. NaOMe, MeOH, 93%.

Scheme 2. Synthesis of thioctic amide derivative **1b**



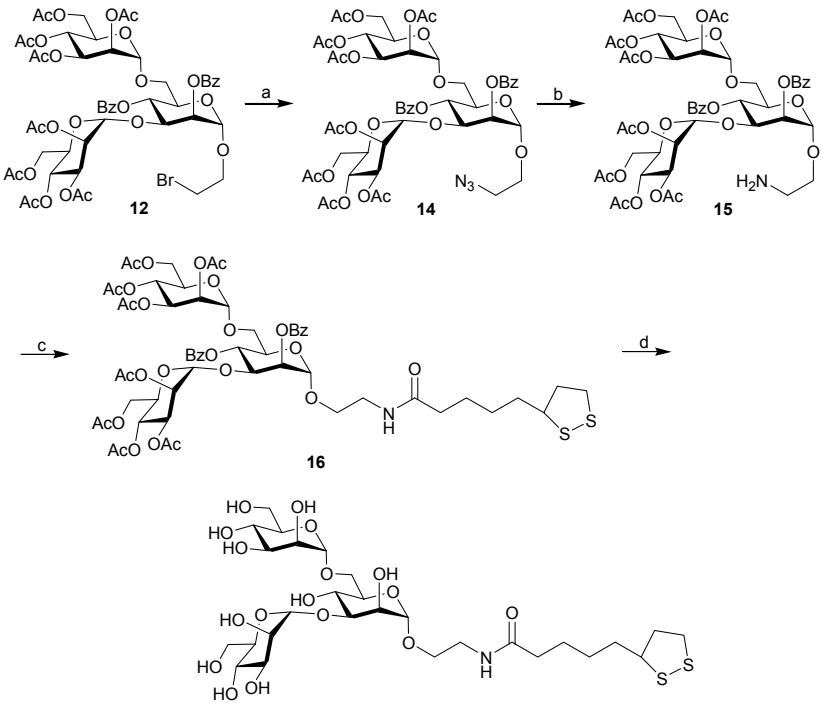
Reagents and conditions: a. NaN_3, Bu_4NOTf, DMF, rt, 3h, 91%; b. H_2-Pd, MeOH-$CHCl_3$, 74%; c. thioctic acid, HOBt, EDCI, Et_3N, DMF, rt, 12h, 67%; d. NaOMe, MeOH, 89%.

Scheme 3. Synthesis of **2a**



Reagents and conditions: a. NaOMe, MeOH, 93%; b. trimethyl orthobenzoate, (S)-10-camphorsulfonic acid, CH_3CN, rt, 2h then H_2O, 30 min, 78%, **9**:**10** = 1.5:1; c. TMSOTf, CH_2Cl_2, rt, 30 min, 76%; d. KSAc, 2-butanone, reflux, 3h, 87%; e. NaOMe, MeOH, 93%.

Scheme 4. Synthesis of **2b**



Reagents and conditions: a. NaN_3, Bu_4NOTf, DMF, rt, 3h, 87%; b. H_2, Pd-C, MeOH-$CHCl_3$, 72%; c. Thioctic acid, HOBt, EDCI, DMF, 12h, 76%, d. NaOMe, MeOH, 83%.

Experimental

Compounds **2**,[i] **3**,[ii] **4**,[iii] **5**[iv] and **6**[v] were made by following literature procedure and products were fully characterized and compared with reported data.

***N*-(2-[2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy]ethyl) thioctamide (8)**. A solution of compound **7** (1.0g, 2.6 mmol), HOBt (350 mg, 2.6 mmol), EDCI (500 mg, 2.6 mmol) and Et_3N (100 μL) in dry DMF (20 mL) was stirred at rt for 12 hours. The solution was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (3 × 20 mL). The organic layer was dried with Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash chromatography (*n*-hexane-EtOAc 1:2) to afford **Compound 8** (990 mg, 67%) as foam. $[\alpha]_D^{25}$ +38° (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 6.21 (t, 1H), 5.23-5.09 (m, 3H), 4.72 (d, 1H), 4.15 (dd, 1H), 3.99 (dd, 1H), 3.87 (m, 1H), 3.50-3.42 (m, 3H), 3.29 (m, 1H), 3.10-2.95 (m, 2H), 2.28 (m, 1H), 2.15 (t, 2H), 2.04, 1.98, 1.93, 1.88 (4s, 12H), 1.80 (m, 1H), 1.71 (m, 4H), 1.38 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 172.9, 170.4, 169.9 (2), 169.5, 97.4, 69.0, 68.7, 68.3, 67.0, 65.8, 62.1, 56.0, 39.9, 38.6, 38.1, 35.8, 34.2, 28.5, 25.0, 20.4, 20.3, 20.2. HRMS $[M+NH_4]^+$ calcd. for $C_{24}H_{41}O_{11}N_2S_2$ 597.2152, found 597.2149.

***N*-(2-[α-D-mannopyranosyloxy]ethyl) thioctamide (1b)**. To a solution of compound **8** (700 mg, 1.2 mmol) in dry MeOH (15 mL), methanolic NaOMe (150 μL, 0.5M) was added and the mixture was stirred at rt for 2 hours. After neutralization with DOWEX 50W H^+ resin, the mixture was filtered and evaporated *in vacuo* to give **Compound 1b** (630 mg, 89%) as foam. $[\alpha]_D^{25}$ +17° (*c* 1.0, MeOH). ^{1}H

NMR (D_2O) δ: 4.72 (s, 1H), 3.81-3.38 (m, 6H), 3.27 (m, 2H), 3.12-2.93 (m, 2H), 2.31 (m, 1H), 2.15 (t, 2H), 1.81 (m, 1H), 1.67-1.32 (m, 4H), 1.28 (m, 2H). ^{13}C NMR (D_2O) δ: 178.1, 99.9, 73.8, 70.3, 70.2, 68.1, 67.7, 61.1, 57.3, 40.4, 39.7, 39.3, 37.9, 35.6, 28.4, 26.7. HRMS $[M+H]^+$ calcd. for $C_{16}H_{30}O_7NS_2$ 412.1464, found 412.1462.

Bromoethyl 2,4-di-*O*-benzoyl-α-D-mannopyranoside (9) and Bromoethyl 2,6-di-*O*-benzoyl-α-D-mannopyranoside (10). Compound **4** (2.5g, 5.5 mmol) was de-*O*-acetylated as described for compound **1b**. After drying *in vacuo*, the de-*O*-acetylated product was dissolved in dry CH_3CN (20 mL), trimethyl orthobenzoate (2.8 mL, 16.5 mmol) and CSA (100 mg) were added and stirred at rt until TLC (2:1 *n*-hexane-EtOAc) showed complete conversion to a faster running compound. Then H_2O (2 mL) was added and stirring continued for another 30 min the mixture was neutralized with Et_3N. After evaporation *in vacuo*, the crude product was purified by flash chromatography (*n*-hexane-EtOAc 1:1) to afford **Compound 9** (1.3g, 47%) and **Compound 10** (850 mg, 31%).

Bromoethyl 2,4-di-*O*-benzoyl-α-D-mannopyranoside (9): $[\alpha]_D^{25}$ +107° (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 8.05 (m, 4H), 7.63-7.39 (m, 6H), 5.52 (t, 1H), 5.43 (dd, 1H), 5.11 (s, 1H), 4.45 (dd, 1H), 4.07 (m, 1H), 4.03 (t, 1H), 3.91 (dd, 1H), 3.80 (dd, 1H), 3.73 (dd, 1H), 3.56 (t, 2H), 2,45 (bs, 2H). ^{13}C NMR ($CDCl_3$) δ: 166.9, 166.1, 133.3, 133.1, 129.7, 129.6, 129.3, 128.4, 128.3, 97.7, 72.1, 71.0, 69.7, 67.9, 67.5, 63.4, 29.8. HRMS $[M+NH_4]^+$ calcd. for $C_{22}H_{27}BrO_8N$ 512.0915, found 512.0919.

Bromoethyl 2,6-di-*O*-benzoyl-α-D-mannopyranoside (10): $[\alpha]_D^{25}$ +106° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 8.11-7.83 (2d, 4H), 7.61-7.19 (m, 6H), 5.34 (dd, 1H), 4.93 (s, 1H), 4.61 (dd, 1H), 4.51 (d, 1H), 4.16 (m, 1H), 4.05-3.82 (m, 3H), 3.74 (m, 1H), 3.65 (bs, 2H), 3.42 (t, 2H). ^{13}C NMR ($CDCl_3$) δ: 166.9, 166.1, 133.3, 133.1, 129.7, 129.6, 129.3, 128.4, 128.3, 97.7, 72.1, 71.0, 69.7, 67.9, 67.5, 63.4, 29.8. HRMS $[M+NH_4]^+$ calcd. for $C_{22}H_{27}BrO_8N$ 512.0915, found 512.0919.

Bromoethyl 3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-2,4-di-*O*-benzoyl- α-D-mannopyranoside (12). A mixture of compound **9** (1 g, 2.0 mmol), 2,3,4,6-tetra-*O*-acetyl- α-D-mannopyranosyl trichloroacetimidate (**11**) (3 g, 6.0 mmol) and MS 4Å (3 g) in dry CH_2Cl_2 (30 mL) was stirred under N_2 for 3 hours. TMSOTf (7.0 µL, 0.04 mmol) was added and stirring was continued for another 30 minutes. After neutralizing with Et_3N, the mixture was filtered through Celite® and the filtrate was evaporated *in vacuo*. Flash chromatography (*n*-hexane-EtOAc 1:1) afforded pure **Compound 12** (1.8 g, 76%) as foam. $[\alpha]_D^{25}$ +39° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 8.10-7.98 (2d, 4H, *J*=5.5 Hz), 7.60-7.39 (m, 6H), 5.58 (t, 1H, *J*=10.0 Hz), 5.49 (dd, 1H, *J*=1.6 Hz, 3.2 Hz), 5.29 (dd, 1H, *J*=3.6 Hz, 10.4 Hz), 5.18 (t, 1H, *J*=10.0 Hz), 5.06 (m, 2H), 5.04 (d, 1H, *J*=1.6 Hz), 4.98 (d, 1H, *J*=2.0 Hz), 4.83 (m, 1H), 4.78 (d, 1H, *J*=1.6 Hz), 4.43 (dd, 1H, *J*=3.2 Hz, 9.2 Hz), 4.23 (m, 1H), 4.16-3.83 (m, 9H), 3.58-3.55 (m, 3H), 2.08, 2.02, 2.00, 1.94, 1.88, 1.87, 1.82, 1.78 (8s, 24H). ^{13}C NMR ($CDCl_3$) δ: 170.5, 170.4, 169.8, 169.6, 169.5, 169.4, 169.0, 168.9, 165.8, 165.2, 133.6, 133.5, 129.9, 129.8, 128.9, 128.7, 128.5, 128.4, 99.4, 97.3, 96.8, 75.5, 71.6, 69.6, 69.2, 69.1, 69.0, 68.7, 68.5, 68.4, 68.1, 68.0, 66.3, 65.8, 62.2, 62.0, 30.2, 20.7, 20.6, 20.5 (2), 20.4 (2), 20.3, 20.2. HRMS $[M+NH_4]^+$ calcd. for $C_{50}H_{63}BrO_{26}N$ 1172.2816, found 1172.2830.

2-*S*-Acetylthioethyl 3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-2,4-di-*O*-benzoyl- α-D-mannopyranoside (13). A solution of compound **12** (1 g, 0.9 mmol) and KSAc (g, 22.7 mmol) in 2-butanone (20 mL) was refluxed for 3 hours. After cooling at room temperature, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (3 × 30 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by flash chromatography (*n*-hexane-EtOAc 1:1) to afford pure **Compound 13** (900 mg, 87%).$[\alpha]_D^{25}$ +45° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 8.17-7.93 (2d, 4H, *J*=5.5 Hz), 7.61-7.38 (m, 6H), 5.60 (t, 1H, *J*=10.0 Hz), 5.45 (dd, 1H, *J*=1.6 Hz, 3.6 Hz), 5.29 (dd, 1H, *J*=1.6 Hz, 3.6 Hz), 5.25 (m, 1H), 5.21-5.16 (m, 2H), 5.06-5.04 (m, 2H), 5.01 (bs, 1H),

4.96 (bs, 1H), 4.83 (m, 1H), 4.76 (m, 1H), 4.40 (dd, 1H, *J*=2.8 Hz, 9.2 Hz), 4.18-4.04 (m, 3H), 4.01-3.90 (m, 3H), 3.85 (m, 1H), 3.66 (m, 1H), 3.55 (dd, 1H, *J*=1.2 Hz, 9.2 Hz), 3.15 (m, 2H), 2.37 (s, 3H), 2.15, 2.12, 2.01, 1.98, 1.96, 1.95, 1.91, 1.89 (8s, 24H). ^{13}C NMR ($CDCl_3$) δ: 195.0, 170.6, 170.5, 169.9, 169.8, 169.7, 169.5, 169.2, 169.1, 166.0, 165.3, 133.6, 133.5, 129.9, 129.8, 129.1, 128.8, 128.5, 99.4, 97.3, 97.1, 75.5, 71.6, 69.6, 69.3, 69.2, 68.8, 68.5, 68.2, 66.8, 66.5, 65.8, 62.2, 62.1, 30.4, 28.5, 20.7(2), 20.6, 20.5, 20.4 (2), 20.3, 20.2. HRMS $[M+NH_4]^+$ calcd. for $C_{52}H_{66}O_{27}SN$ 1168.3537, found 1168.3543.

Azidoethyl 3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-2,4-di-*O*-benzoyl- α-D-mannopyranoside (14). To a solution of compound **12** (1 g, 0.9 mmol) in dry DMF (20 mL), NaN_3 (585 mg, 9 mmol) and tetrabutylammonium triflate (350 mg, 0.9 mmol) were added and the mixture was stirred at room temperature for 3 hours. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (3 × 30 mL), the organic layer was collected, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by flash chromatography (*n*-hexane-EtOAc 1:1) to afford pure **Compound 14** (875 mg, 87%) as syrup. $[\alpha]_D^{25}$ +63° (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 8.17-7.92 (2d, 4H, *J*=5.5 Hz), 7.63-7.30 (m, 6H), 5.62 (t, 1H, *J*=10.0 Hz), 5.47 (dd, 1H, *J*=1.6 Hz, 3.6 Hz), 5.32 (dd, 1H, *J*=1.6 Hz, 3.6 Hz), 5.26 (m, 1H), 5.22-5.13 (m, 2H), 5.02-4.98 (m, 2H), 4.96 (bs, 1H), 4.81 (m, 1H), 4.73 (m, 1H), 4.41 (dd, 1H, J=2.4 Hz, 9.2 Hz), 4.19-4.03 (m, 3H), 3.99-3.89 (m, 3H), 3.84 (m, 1H), 3.63 (m, 1H), 3.58 (dd, 1H, *J*=1.2 Hz, 9.2 Hz), 3.51 (m, 2H), 2.11, 2.09, 2.08, 2.01, 1.98, 1.96, 1.91, 1.85 (8s, 24H). ^{13}C NMR ($CDCl_3$) δ: 170.5, 170.4, 169.8, 169.6, 169.5, 169.0, 168.9, 165.8, 165.2, 133.6, 133.5, 129.9, 129.8, 128.9, 128.7, 128.5, 128.4, 99.5, 97.2, 96.8, 75.3, 71.5, 69.5, 69.3, 69.1, 69.0, 68.7, 68.5, 68.4, 68.2, 66.9, 66.2, 65.8, 65.7, 62.2, 61.9, 50.3, 20.7, 20.6(2), 20.5, 20.4 (2), 20.3, 20.2. HRMS $[M+NH_4]^+$ calcd. for $C_{50}H_{63}O_{26}N_4$ 1135.3725, found 1135.3720.

***N*-(2-[3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-2,4-di-*O*-benzoyl- α-D-mannopyranosyloxy]ethyl) thioctamide (16)**. To a solution of compound **14** (850 mg) in $CHCl_3$-MeOH (20 mL, 1:1), Pd-C (200 mg) was added and the mixture was stirred under H_2 for 12 hours. After filtration through Celite pad and evaporation of the solvents, the corresponding aminoethyl 3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-2,4-di-*O*-benzoyl- α-D-mannopyranoside **(15)** was formed as foam (600 mg, 72%) which was used for the next step without any further purification.

A solution of compound **15** (600 mg, 0.55 mmol), thioctic acid (210 mg, 0.55 mmol), HOBt (75 mg, 0.55 mmol), EDCI (105 mg, 0.55 mmol) and Et_3N (50 μL) in dry DMF (10 mL) was stirred at room temperature for 12 hours. The solution was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3×20 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by flash chromatography (*n*-hexane-EtOAc 1:1) to afford pure **Compound 16** (535 mg, 76%) as foam. $[\alpha]_D^{25}$ +18° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.87-7.07 (m, 10H), 6.24 (t, 1H), 5.27-5.01 (m, 6H), 4.76 (d, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 4.15 (m, 2H), 3.99 (m, 2H), 3.87 (m, 2H), 3.50-3.42 (m, 3H), 3.29 (m, 1H), 3.10-2.95 (m, 2H), 2.28 (m, 1H), 2.15 (t, 2H), 2.04, 2.02, 2.01, 2.00, 1.99, 1.98, 1.93, 1.88 (8s, 24H), 1.80 (m, 1H), 1.71 (m, 4H), 1.38 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 173.2, 172.7, 170.6, 170.0 (2), 169.9 (2), 169.7, 169.6, 169.5, 169.3, 98.0, 97.8, 97.4, 69.0, 68.9, 68.8, 68.7, 68.3, 67.6, 67.3, 67.0, 65.8, 63.2, 62.1, 56.0, 39.9, 38.6, 38.1, 35.8, 34.2, 28.5, 25.0, 20.4(2), 20.3(2), 20.2, 20.1(2), 20.0. HRMS $[M+NH_4]^+$ calcd. for $C_{58}H_{77}O_{27}N_2S_2$ 1297.4155, found 1297.4149.

***N*-(2-[3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranosyloxy]ethyl) thioctamide (2b)**. To a solution of compound **16** (500 mg, 0.4 mmol) in dry MeOH (20 mL), NaOMe (0.5 M, 1 mL) was added and the solution was stirred at room temperature for 3 hours. The solution was neutralized with DOWEX 50W H^+ resin and filtered through cotton. After evaporation the crude product was dissolved in H_2O and washed with CH_2Cl_2 to remove MeOBz. The aqueous layer was separated and freeze dried to afford pure **Compound 2b** as white foam (240 mg, 83%). $[\alpha]_D^{25}$ +21° (*c* 1.0, MeOH). ^{1}H NMR (D_2O) δ: 4.75 (s, 1H), 4.72 (s, 1H), 4.68 (s, 1H), 3.81-3.38 (m, 12H), 3.35-3.27 (m, 8H), 3.11-2.90 (m, 2H), 2.38 (m, 1H), 2.14 (t, 2H), 1.80 (m, 1H), 1.69-1.38 (m, 4H), 1.27 (m, 2H). ^{13}C NMR (D_2O) δ: 178.1,

99.9, 99.5, 98.6, 73.8, 73.5, 73.1, 70.3, 70.2, 70.0, 68.5, 68.3, 68.1, 67.9, 67.7, 61.3, 61.1, 60.9, 57.3, 40.4, 39.7, 39.3, 37.9, 35.6, 28.4, 26.7. HRMS $[M+H]^+$ calcd. for $C_{28}H_{53}O_{17}N_2S_2$ 753.2786, found 753.2781.

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