A Concise and Highly Efficient Synthesis of Trehazolin and Trehalamine Starting from D-Mannose

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Supporting Information

General. NMR spectra were recorded at 200 MHz, 300 MHz, 400 MHz or 500 MHz (^{1}H frequency) and at 30 ˚C. In some cases, the intensities observed in ^{13}C DEPT 135˚ experiments are included as follows: "0" (carbons without directly attached protons), "+" (CH and CH_3 carbons), "-" (CH_2 carbons). Tetrahydrofuran (THF) was distilled under argon from sodium-benzophenone ketyl, and CH_2Cl_2 from CaH_2. All reactions were performed under argon with anhydrous freshly distilled solvents. Samarium diiodide was prepared immediately before use by adding ICH_2CH_2I in one portion to a suspension of samarium metal powder (1.2 equiv) in THF (10 mL/mmol of ICH_2CH_2I) under argon, and stirring vigorously the resultant suspension for 1-2h.[1] The reductive carbocyclizations were performed in the presence of the slight excess of samarium metal used in the preparation of the reagent. Analytical thin-layer chromatography was carried out using Merck Kieselgel 60 F_{254} plates. Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh).

Phenyl 4,6-*O*-Isopropylidene-1-thio-α-D-mannopyranoside (6). To a solution of **5**[2] (7.0 g, 15.3 mmol) in MeOH (50 mL) was added Na (50 mg, 2.17 mmol). After stirring at rt for 4h, the mixture was neutralized with Amberlite IR-120 H^+, filtered and concentrated at reduced pressure. The crude was dissolved in anhydrous DMF (11 mL), Drierite (1 g) was added and the mixture was stirred at rt for 30 min. The mixture was cooled to 0 ˚C and *p*-TsOH (20 mg, 0.1 mmol) and 2-methoxypropene (2.4 mL, 24.9 mmol) were added. After stirring for 70h at 0 ˚C, was added Et_3N (1 mL), the mixture was filtered, the filter was rinsed with CH_2Cl_2/MeOH (10:1), and the filtrate was concentrated at reduced pressure. The crude was purified by flash chromatography (EtOAc/hexane 2:5) to afford **6** (3.62 g, 73%) as a colourless oil. Phenyl 1,2:4,6-di-*O*-isopropyliden-1-thio-α-D-mannopyranoside was isolated as a by-product (350 mg, 6.2%). **6:** ^{1}H NMR ($CDCl_3$) δ 7.51-7.23 (m), 5.80 (d, *J*=0.6 Hz), 4.37 (dd, 1H, *J*=0.8, 5.6 Hz), 4.27-3.75 (m), 3.1 (br s), 3.0 (br s); ^{13}C NMR ($CDCl_3$) δ 133.3 (0), 132-127.5 (+), 100 (0), 88.0 (+), 72.3 (+), 71.4 (+), 69.3 (+), 65.0 (+), 61.7 (-), 29.0 (+), 19.1 (+).

Phenyl 3-*O*-Benzyl-4,6-*O*-isopropylidene-1-thio-α- D-mannopyranoside (7). To a solution of **6** (260 mg, 0.83 mmol) in acetonitrile (42 mL), was added 4Å MS (200 mg), Bu_4NBr (268.25 mg,

0.83 mmol), Bu_2SnO (207 mg, 0.83 mmol) and $PhCH_2Br$ (509 μL, 4.16 mmol). The reaction was stirred at reflux for 20h, filtered through Celite and the filter was rinsed with CH_2Cl_2. The filtrate was concentrated at reduced pressure and the crude was purified by flash chromatography (EtOAc/hexane 1:3) to afford **7** (330 mg, 98%) as a white solid. Mp 75-77 ˚C; $[\alpha]_D^{22}$ +206.3 (*c* 1.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.5-7.23 (m, 10H), 5.53 (d, 1H, *J*=1Hz), 4.90 (d, 1H, *J*=11.8 Hz), 4.73 (d, 1H, *J*=11.8 Hz), 4.55-4.08 (m, 3H), 3.87-3.75 (m, 3H), 2.94 (d, 1H, *J*=13.4 Hz), 1.51 (s, H), 1.45 (s, H); ^{13}C NMR ($CDCl_3$) δ 138 (0), 133.5 (0), 131.5-127.5 (+), 99.7 (0), 87.9 (+), 76.2 (+), 73.1 (-), 71.6 (+), 71.5 (+), 65.6 (+), 62.0 (-), 29.2 (+), 19.2 (+).

Phenyl 2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-isopropylidene-1-thio-α-D-mannopyranoside (8). To a solution of **7** (60 mg, 0.149 mmol) in pyridine (0.6 mL) was added Ac_2O (0.3 mL) and the reaction was stirred at rt for 14h. The solvent was removed under reduced pressure, coevaporating with toluene. The crude was purified by flash chromatography (EtOAc/hexane 1:3) to afford **8** (65 mg, 98%) as a colourless oil. R_f = 0.22 (EtOAc/hexane 1:3); $[\alpha]_D^{22}$ +98.8 (*c* 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.44-7.26 (m, 10H), 5.54 (dd, 1H, *J*=1.4, 3.4 Hz), 5.04 (d, 1H, *J*=1.4 Hz), 4.69 (s, 2H), 4.19-4.08 (m, 2H), 3.87-3.81 (m, 3H), 2.14 (s, 3H), 1.56, 1.55 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 170,1 (0), 138.1 (0), 133.2 (0), 132-127.5 (+), 99.9 (0), 87.3 (+), 74.6 (+), 72.3 (-), 71.7 (+), 71.3 (+), 66.2 (+), 61.9 (-), 29.2 (+), 21.0 (+), 19.4 (+).

2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-isopropylidene-α-D-mannopyranose (9). To a solution of **8** (3.0 g, 6.75 mmol) in acetone (65 mL) at -15 ˚C was added NBS (115 mg, 0.644 mmol). After stirring at -15 ˚C for 15 min, the mixture was diluted with CH_2Cl_2 (100 mL) and washed with an aqueous saturated solution of $NaHCO_3$ (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x50 mL). The combined organic fractions were washed with an aqueous 10% solution of $Na_2S_2O_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (EtOAc/hexane 1:3) to afford **9** (2.25 g, 95%) as a mixture of anomers. R_f= 0.33 (EtOAc/hexane 1:1); $[\alpha]_D^{22}$ -9.4 (*c* 0.7, $CHCl_3$); **α–anomer**: ^{1}H NMR ($CDCl_3$) δ 7.36–7.23 (m, 5H), 5.49 (dd, *J*=1.5, 3.5 Hz), 4.85 (dd, 1H, *J*=1.5, 9.3 Hz), 3.57 (dd, *J*=3.5, 9.6 Hz), 3.36 (d, *J*=9.3 Hz), 3.23 (td, *J*=5.6, 9.9 Hz), 2.22 (s), 1.28 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.3, 128.4-127.5, 93.7, 77.6-73.6, 71.9, 70.0, 67.5, 61.9, 29.1, 21.0. **β-anomer**: ^{1}H NMR ($CDCl_3$) δ 7.36-7.23 (m, 5H), 5.33 (dd, 1H, *J*=1.7, 3.5 Hz), 5.14 (dd, *J*=1.6, 3.8 Hz), 4.67 (s, 2H), 4.15-4.04 (m, 2H), 3.99-3.80 (m, 3H), 2.89 (d, 1H, *J*=3.8 Hz,), 2.04 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H); ^{13}C NMR δ 170.3 (0), 138.3 (0), 128.4-127.5 (+), 99.9 (0), 93.6 (+), 73.6 (+), 72.2 (-), 71.2 (+), 70.3 (+), 64.6 (+), 62.2 (-), 29.2 (+), 21.0 (+), 19.2 (+).

2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-isopropylidene-D-mannose *O*-Benzyl Oxime Ether (10). To a solution **9** (175 mg, 0.5 mmol) in MeOH (5 mL) was added a solution of $BnONH_2$·HCl (96 mg, 0.6 mmol) and pyridine (202 μL, 2.5 mmol) in MeOH (1 mL). The mixture was stirred at reflux for 3h,

concentrated at reduced pressure and the crude was purified flash chromatography (EtOAc/hexane 1:1) to afford **10** (222 mg, 97%) as a colourless oil (mixture of oximes: *E/Z* = 8:1). R_f = 0.24 (EtOAc/hexane 1:1); ***E:*** ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 1H, *J*=6.23 Hz), 7.32-7.23 (m, 10H), 5.67 (dd, 1H, *J*=6.2, 5.2 Hz), 5.1 (s, 2H), 4.73 (d, 1H, *J*=11.8 Hz), 4.54 (d, 1H, *J*=11.8 Hz), 3.95 (dd, 1H, *J*=5.2, 3.3 Hz), 3.93-3.66 (m, 3H), 3.43 (m, 1H), 2.06 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2 (0), 147.3 (0), 137.6 (0), 137.3 (0), 128-127.0 (+), 99.0(0), 77.5 (-), 77.4 (-), 73.6 (+), 70.5 (+), 64.8 (-), 63.5 (+), 28.0 (+), 19.2 (+). ***Z*****:** ^{1}H NMR ($CDCl_3$) δ 7.32-7.24 (m, 10H), 6.87 (d, 1H, *J*=5.6 Hz), 6.34 (dd, 1H, *J*=5.6, 3.5 Hz), 5.13 (s, 2H), 4.75 (d, 1H, *J*=11.8 Hz), 4.51 (d, 1H, *J*=11.8 Hz), 4.04 (t, 1H, *J*=4 Hz), 2.04 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H).

2-*O*-Acetyl-3-*O*-benzyl-1-(*O*-benzyloximino)-4,6-*O*-isopropylidene-D-*lyxo*-hexos-5-ulose (11). To a solution of Dess-Martin periodinane (662 mg, 1.56 mmol) in CH_2Cl_2 (22 mL) was added a solution of **10** (510 mg, 1.15 mmol) in CH_2Cl_2 (6 mL). After stirring at rt for 30 min, Et_2O (100 mL) and a 10% aqueous solution of $Na_2S_2O_3$ (10 mL) were added, and the mixture was vigorously stirred for 10 min. The mixture was extracted with Et_2O, the combined organic layers were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude was purified by flash chromatography (EtOAc/hexane 1:3) to afford **11** (450 mg, 85%) as a colourless oil (mixture of oximes: *E/Z* = 4:1). R_f = 0.6 (EtOAc/hexane 1:1); ***E:*** ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1H, *J*=6.2 Hz), 7.2-7.4 (m, 10H), 5.56 (t, 1H, *J*=6.3 Hz), 5.11 (s, 2H), 4.54 (s, 2H), 4.43-4.38 (m, 2H), 4.26 (dd, 1H, *J*=1.3, 16.5 Hz), 3.94 (d, 1H, *J*=16.5 Hz), 2.05 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.5 (0), 169.0 (0), 146.4 (+), 128.4-127.7 (+), 101.0 (0), 76.7 (+), 76.4 (-), 75.0 (-), 74.8 (+), 70.1 (+), 66.1 (-), 23.9 (-), 23.2 (+), 20.8 (+). ***Z*****:** ^{1}H NMR ($CDCl_3$) δ 7.2-7.4 (m, 10H), 6.85 (d, 1H, *J*=6.0 Hz), 6.15 (dd, 1H, *J*=6.1, 4.1 Hz), 5.11 (s, 2H), 4,6 (s, 2H), 4.36-4.31 (m, 2H), 4.23 (dd, 1H, *J*=1.3, 16.6 Hz), 3.84 (d, 1H, *J*=16.6 Hz), 2.02 (s, 3H), 1.36, 1.33 (2s, 6H).

[1*R*(1α,2β,3α,4α,5β)-3-Acetoxy-4-benzyloxy-2-(*O*-benzylhydroxylamino)-1',5-(isopropylidenedioxy)-1-methyl-1-cyclopentanol (12). To a 0.1M solution of SmI_2 in THF (20 mL, 2 mmol) and *t*-BuOH (316 μL, 3.3 mmol) at –30 ˚C was added dropwise a solution of **11** (300 mg, 0.66 mmol) in THF (26.5 mL). After stirring at –30 ˚C for 1h, the flask was opened to the air to oxidize excess SmI_2 and the crude reaction mixture was filtered through Florisil, eluting with CH_2Cl_2/MeOH (10:1). The filtrate was evaporated at reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 1:2) to afford **12** (260 mg, 86%)**.** R_f= 0.2 (EtOAc/hexane 1:2); $[\alpha]_D^{22}$ +46.5 (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36-7.25 (m, 10H), 5.99 (br s, 1H, NH), 5.02 (ddd, 1H, *J*=0.5, 4.5, 9.1 Hz, H-2), 4.72 (d, 1H, *J*=11.6 Hz), 4.69 (d, 1H, *J*=11.6 Hz), 4.67 (d, 1H, *J*=11.7), 4.63 (d, 1H, *J*=11.7), 4.21 (d, 1H, *J*=12.2 Hz, H-6b), 4.06 (ddd, 1H, *J*=0.5, 1, 4.5 Hz, H-3), 3.96 (s, 1H, H-4), 3.89 (d, 1H, *J*=9.5 Hz, H-1), 3.69 (d, 1H, *J*=12.2 Hz, H-6a), 2.9 (br s, 1H, OH), 2.04 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 137.5, 137.3, 128.4, 128.4,

128.3, 127.9, 127.8, 127.7, 99.2, 80.3, 78.2, 76.7, 75.9, 75.7, 73.0, 72.1, 63.6, 26.8, 21.1, 20.8. Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.64; H, 6.78; N, 3.06. Found: C, 65.45; H, 6.99; N, 3.06.

[1*R*(1α,2β,3α,4α,5β)-2-Acetamido-3-acetoxy-4-benzyloxy-1',5-(isopropylidenedioxy)-1-methyl-1-cyclopentanol (13). To a 0.1M solution of SmI_2 in THF (19 mL, 1.9 mmol) and *t*-BuOH (147 μL, 1.54 mmol) at –30 ˚C was added dropwise a solution of **11** (140 mg, 0.31 mmol) in THF (12.5 mL) dropwise. After stirring at –30 ˚C for 0.5h, water (166 μL, 9.23 mmol) was added and the reaction mixture was allowed to attain rt. After stirring at rt for 0.5h, the flask was opened to the air to oxidize excess SmI_2 and pyridine (2 mL, 12.3 mmol) and Ac_2O (1 mL, 4.6 mmol) were added. After stirring 14h, the mixture was diluted with EtOAc (50 mL) and aqueous saturated $NaHCO_3$ (20 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic layers were washed with a 10% aqueous solution of $Na_2S_2O_3$ (10 mL), brine, dried over Na_2SO_4 and the solvent was removed at reduced pressure. The crude was purified by flash chromatography (EtOAc) to afford **13** (120 mg, 99%) as a colorless oil. R_f= 0.26 (EtOAc); $[\alpha]_D^{22}$ +37.8 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39-7.25 (m, 5H), 6.62 (d,1H, *J*=4.5 Hz), 5.20 (dd, 1H, *J*=4.6, 4.3 Hz), 4.75 (d, 1H, *J*=12.1 Hz), 4.63 (d, 1H, *J*=12.1 Hz), 4.53 (s, 1H), 4.49 (t, *J*=4.6 Hz), 4.53 (s, 1H), 3.89 (d, 1H, *J*=4.3 Hz), 3.68 (d, 1H, *J*=12.2 Hz), 3.46 (d, 1H, *J*=12.2 Hz), 2.13 (s, 3H), 2.01 (s, 3H), 1.42 (s, 3H), 1.29 (s, 3H). Anal. Calcd for $C_{20}H_{27}NO_7$: C, 60.06; H, 6.51; N, 3.56. Found: C, 60.06; H, 6.51; N, 3.26.

[1*R*(1α,2β,3α,4α,5β)-2-Amino-4-benzyloxy-1',5-(isopropylidenedioxy)-1-methyl-1,3-cyclopentanodiol (14). To a 0.1 M solution of SmI_2 in THF (185 mL, 18.5 mmol) and *t*-BuOH (1.4 mL, 15.4 mmol) at -30 ˚C was added dropwise the solution of **11** (1.4 g, 3.1 mmol) in THF (123 mL). After stirring at –30 ˚C for 0.5h, the cooling bath was removed and the reaction mixture was allowed to attain rt. Water (1.7 mL, 92.3 mmol) was added and stirring continued for 2h. The flask was opened to the air and an aqueous 5M solution of LiOH (77 mL) was added. After stirring for 5h, the reaction mixture was diluted with CH_2Cl_2 (250 mL) and a 10% aqueous solution of K_2CO_3 and Rochelle's salt was added (200 mL).[3] The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated at reduced pressure. The crude residue was purified by flash chromatography on Florisil (CH_2Cl_2/MeOH 5:1) to afford **14** (932 mg, 98%) as a colorless oil. R_f= 0.28 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{22}$ +29.3 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34-7.24 (m, 5H), 4.71 (d, 1H, *J*=11.6 Hz), 4.59 (d, 1H, *J*=11.6 Hz), 3.96-3.92 (m, 2H), 3.83 (d, 1H, *J*=12.3 Hz), 3.60 (d, 1H, *J*=12.3 Hz), 3.59 (s, 1H), 3.31 (d, 1H, *J*=8 Hz), 2.66 (br s, 3H), 1.38 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.4 (0), 128.6-126.9 (+), 99.3 (0), 83.1 (+), 79.5 (+), 78.5 (+), 76.8 (0), 72.6 (-), 65.3 (+), 64.1 (-), 26.7 (+), 21.8 (+). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.47; H, 7.57; N, 4.31.

[1*R*(1α,2β,3α,4α,5β)-4-benzyloxy-2-(*O*-benzylhydroxylamino)-1',5-(isopropylidenedioxy)-1-methyl-1,3-cyclopentanodiol (15). To a solution of **12** (50 mg, 0.1 mmol) in THF (0.3 mL) was added a saturated solution of NH_3 in MeOH (0.5 mL). After stirring at rt for 2h, the solvent was removed at reduced pressure and the crude was purified by flash chromatography (EtOAc) affording **15** (41 mg, 99%) as a colorless oil. R_f= 0.3 (EtOAc/hexane 1:1); ^{1}H NMR δ 7.38-7.25 (m, 10H), 5.87 (d, 1H, *J*=5.6 Hz), 4.79-4.58 (m, 4H), 4.06 (dd, 1H, *J*=8.7, 5.7 Hz), 4.03 (d, 1H, *J*=12.4 Hz), 3.93 (s, 1H), 3.81 (d, 1H, *J*=4.7 Hz), 3.61 (dd, 1H, *J*=8.8, 5.4 Hz), 3.63 (d, 1H, *J*=12.4 Hz), 1.40 (s, 3H), 1.31 (s, 3H).

[1*R*(1α,2β,3α,4α,5β)-2-Acetamido-4-benzyloxy-1',5-(isopropylidenedioxy)-1-methyl-1,3-cyclopentanediol (16). To a solution of **13** (100 mg, 0.25 mmol) in THF (0.5 mL) was added a saturated solution of NH_3 in MeOH (0.5 mL). After stirring at rt for 2h, the solvent was removed at reduced pressure and the crude was purified by flash chromatography (EtOAc) affording **16** (80 mg, 90%) as a colorless oil. R_f= 0.25 (EtOAc); $[\alpha]_D^{22}$ +48.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36-7.25 (m, 5H), 6.31 (br s, 1H), 4.80 (d, 1H, *J*=11.6 Hz), 4.60 (d, 1H, *J*=11.6 Hz), 4.14-4.13 (m, 2H), 4.04 (s, 1H); 3.82-3.81 (m, 1H), 3.64 (d, 1H, *J*=12.1 Hz), 3.50 (d, 1H, *J*=12.1 Hz), 2.03 (s, 3H), 1.43 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.0 (0), 137.2 (0), 128.5-128.0 (+), 99.3 (0), 82.1 (+), 76.8 (0), 76.3 (+), 76.1 (+), 75.7 (+), 72.4 (-), 66.7 (+), 64.4 (-), 26.6 (+), 22.6 (+), 22.2 (+).

Oxazoline 18. To a solution of **16** (124 mg, 0.35 mmol) in CH_2Cl_2 (3.5 mL) at –20 °C was added pyridine (113 μL, 1.4mmol) and Tf_2O (89 μL, 0.52 mmol). The reaction was stirred at this temperature for 20 min. The mixture was diluted with CH_2Cl_2 (20 mL) and aqueous saturated $NaHCO_3$ (5 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude was purified by flash chromatography (EtOAc/MeOH 9:1) affording **18** (38.7 mg, 82%) as a colourless oil. R_f= 0.1 (EtOAc); $[\alpha]_D^{22}$ –2.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40-7.26 (m, 5H), 4.95 (dd, 1H, *J*=1.1, 8.2 Hz), 4.64 (d, *J*= 11.7 Hz), 4.52 (d, 1H, *J*=8.2 Hz), 4.26 (d, 1H, *J*=12 Hz), 4.06 (d, 1H, *J*=0.9 Hz), 4.01 (s, 1H), 3.85 (d, 1H, *J*=12 Hz), 2.85 (br s), 1.93 (d, 3H, *J*=1.4 Hz), 1.43 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.5 (0), 136.7 (0), 128.6 (+), 128.3 (+), 127.9 (+), 98.3 (0), 87.4 (+), 87.3 (+), 86.6 (+), 80.8 (+), 79.4 (0), 79.3 (+), 72.0 (-), 63.8 (-), 53.4 (0), 27.1 (+), 20.2 (+), 13.7 (+).

Trehazolamine (3). To a solution of **18** (20 mg, 0.06 mmol) in EtOH (3.0 mL) at rt were added CF_3CO_2H (23 μL, 0.3 mmol) and 25% $Pd(OH)_2$ on charcoal (27 mg). The mixture was stirred under H_2 (2 atm) at rt for 5 h. The reaction mixture was filtered through Celite and the filter was washed with MeOH and water. The solvent was removed at reduced pressure and the residue was dissolved in 3N HCl (3 mL) and the solution was stirred at reflux for 12 h. The reaction was diluted with water and concentrated at reduced pressure. The residue was purified by ion-exchange chromatography on Dowex-50W-H^+ eluting with 0.5 M aqueous NH_4OH to afford **3** (8.9 mg, 83%)

after freeze-drying. R_f= 0.5 (MeCN/AcOH/H_2O 6:1:3); $[\alpha]_D^{22}$ +2.0 (*c* 0.5, H_2O); ^{1}H NMR (D_2O) δ 4.12 (dd, 1H, *J*=6.8, 5.7 Hz), 4.01 (dd, 1H, *J*=6.6, 5.7 Hz), 3.78 (d,, 1H, *J*=11.9 Hz), 3.78 (d, 1H, *J*=11.9 Hz), 3.28 (d, 1H, *J*=6.8 Hz); ^{13}C NMR (D_2O) δ 82.2, 81.9, 79.7, 73.7, 61.9, 58.5.

Urea 19. To a solution of **14** (90 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was added benzyl isocyanate (100 μL, 0.48 mmol) and the mixture was stirred at rt for 1.5h. The solvent was removed at reduced pressure and the crude was purified by flash chromatography (EtOAc/hexane 1:1) to afford **19** (120 mg, 93%) as a colourless oil. R_f= 0.2 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 7.25-7.09 (m, 10H), 5.84 (br s, 1H), 5.65 (br s, 1H), 4.64 (d, 1H, *J*=11.8 Hz), 4.46 (d, 1H, *J*=11.8 Hz), 4.17 (dd, 1H, *J*=5.8, 15 Hz), 4.10 (dd, 1H, *J*=5.8, 15 Hz), 3.98 (dd, 1H, *J*=2.9, 10.4 Hz), 3.93 (dd, 1H, *J*=4.1, 10.4 Hz), 3.83 (s, 1H), 3.62 (d, 1H, *J*=4.1 Hz), 3.53 (d, 1H, *J*=12.2 Hz), 3.36 (d, 1H, *J*=12.2 Hz), 1.28 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.1 (0), 138.9 (0), 137.4 (0), 128.5-127.2 (+), 99.6 (0), 81.8 (+), 77.4 (0), 76.8 (+), 75.0 (+), 72.1 (-), 65.9 (+), 64.6 (-), 26.1 (+), 22.8 (+). Anal.Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.08; H, 6.63; N, 6.76.

Urea 20. To a solution of **14** (20 mg, 0.06 mmol) in CH_2Cl_2 (0.5 mL) was added phenyl isocyanate (11 μL, 0.12 mmol) and the mixture was stirred at rt for 1h. The solvent was removed at reduced pressure and the crude was purified by flash chromatography (EtOAc/hexane 1:1) to afford **20** (30 mg, 99%) as a colorless oil. R_f = 0.2 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 8.12-6.96 (m, 10H), 6.0 (br s), 4.76 (d, 1H, *J*=11.6 Hz), 4.58 (d, 1H, *J*=11.7 Hz), 4.16-4.09 (m, 2H), 3.99 (s, 1H), 3.77 (br s, 1H), 3.69(d, 1H, *J*=12.2 Hz), 3.56 (d, 1H, *J*=12.3 Hz), 3.11 (s), 1.26 (s, 3H), 1.24 (s, 3H).

Aminooxazoline 21. To a solution of **19** (60 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL) at –20 °C was added pyridine (44 μL, 0.54 mmol) and Tf_2O (32 μL, 0.60 mmol). After stirring at this temperature for 30 min, the mixture was diluted with CH_2Cl_2 (20 mL) and aqueous saturated $NaHCO_3$ was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude was purified by flash chromatography (EtOAc) affording **21** (55 mg, 99%) as a colourless oil. R_f= 0.3 (EtOAc); $[\alpha]_D^{22}$ +34.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35-7.16 (m, 10H), 5.07 (d, 1H, *J*= 7.6 Hz), 4.62 (d, 1H, *J*=11.8 Hz), 4.58 (d, 1H, *J*=11.8 Hz), 4.48 (d, 1H, *J*=7.6 Hz), 4.32 (d, 1H, *J*=14.5 Hz), 4.25 (d, 1H, *J*=14.5 Hz), 4.13 (d, 1H, *J*=12.2 Hz), 4.03 (d, 1H, *J*=0.7 Hz), 3.98 (s, 1H), 3.72 (d, 1H, *J*=12.2 Hz), 1.33 (s, 3H), 1.11 (s, 3H).

Aminooxazoline 22. To a solution of **20** (30 mg, 0.07 mmol) in CH_2Cl_2 (0.7 mL) at –20 °C was added pyridine (23 μL, 0.09 mmol) and Tf_2O (15 μL, 0.09 mmol). After stirring at this temperature for 1h, the mixture was diluted with CH_2Cl_2 (20 mL) and aqueous saturated $NaHCO_3$ was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and

concentrated at reduced pressure. The crude was purified by flash chromatography (EtOAc) to afford **22** (20 mg, 67%) as a colourless oil. R_f=0.13 (EtOAc); $[\alpha]_D^{22}$ +49.7 (*c* 5.7, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ 7.64–6.86 (m, 10H), 5.00 (dt, 1H, *J*=1, 7.6 Hz), 4.68 (s, 2H), 4.46 (ddd, 1H, *J*=0.6, 1.2, 7.7 Hz), 4.27 (d, 1H, *J*=11.8 Hz), 4.15 (d, 1H, *J*=1.1 Hz), 3.97 (d, 1H, *J*=0.6 Hz), 3.75 (d, *J*=11.8 Hz), 1.37 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (CD_3COCD_3) δ 155.5 (0), 139.9 (0), 129.2-128.4 (+), 122.1 (+), 119.2 (+), 98.9 (0), 90.0 (0),86.8 (+), 81.1 (+), 72.3 (-), 65.9 (0), 26.9 (+), 21.17 (+).

Trehalamine (4). To a solution of **21** (28 mg, 0.07 mmol) in EtOH (3 mL) at rt was added CF_3CO_2H (25 μL, 0.33 mmol) and 25% $Pd(OH)_2$ on charcoal (30 mg) and the mixture was stirred under H_2 (2 atm) at 60 °C for 5h. The reaction mixture was filtered through Celite and the filter was washed with MeOH and water. The crude was concentrated at reduced pressure. The residue was purified by ion-exchange chromatography on Dowex 50W-H^+ eluting with 0.5M NH_4OH to afford **4** (11.4 mg, 85 %). ^{1}H NMR (D_2O) δ 5.02 (dd, 1H, *J*=1.5, 8.4 Hz), 4.37 (d, 1H, *J*=8.5 Hz), 4.24 (dd, 1H, *J*= 2.5, 4.3 Hz), 3.98 (d, 1H, *J*= 4.3 Hz), 3.84 (d, 1H, *J*= 11.8 Hz), 3.75 (d, 1H, *J*= 11.9 Hz); ^{13}C NMR ($CDCl_3$) δ 164.9, 90.5, 85.7, 83.3, 83.0, 76.6, 64.8.

Aminooxazoline 23. To a solution of **22** (16 mg, 0.04 mmol) in EtOH (2.5 mL) at rt was added CF_3CO_2H (19μL, 0.25 mmol) and 25% $Pd(OH)_2$ on charcoal (25 mg) and the mixture was stirred under H_2 (2 atm) at rt for 5h. The reaction mixture was filtered through Celite and the filter was washed with MeOH and water. The crude was concentrated at reduced pressure and the residue was purified by ion-exchange chromatography on Dowex-50W-H^+ eluting with 0.5 M NH_4OH to afford **23** (7 mg, 65 %). R_f= 0.2 (EtOAc); $[\alpha]_D^{22}$ +87.8 (*c* 1.3, MeOH); ^{1}H NMR (D_2O) δ 7.44-7.15 (m, 5H), 5.00 (dd, 1H, *J*= 2.4, 8.4 Hz), 4.40 (d, 1H, *J*=8.4 Hz), 4.28 (dd 1H, *J*=2.4, 43 Hz), 4.02 (dd, 1H, *J*=1.4, 4.4 Hz), 3.91 (d, 1H, *J*=11.8 Hz), 3.63 (d, 1H, *J*=11.8 Hz).

Thiourea 25. To a solution of **14** (121 mg, 0.39 mmol) in THF (6 mL) was added dropwise a solution of 24[4] (227 mg, 0.39 mmol) in THF (4 mL). After stirring for 4h at 30 ºC, the solvent was removed at reduced pressure and the crude was purified by flash chromatography (EtOAc/hexane 1:2) to afford **25** (334 mg, 96%) as a white solid. R_f = 0.42 (EtOAc/hexane 1:1); mp 81-82 ºC. $[\alpha]^{22}_D$ +149.1 (*c* 0.9, $CHCl_3$); IR (KBr) 3400, 3000, 1545, 1370, 1080, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 1H, *J* = 6.0 Hz), 7.40-7.23 (m, 22H), 7.14-7.11 (m, 2H), 6.65 (d, 1H, *J* = 1.6 Hz), 5.17 (dd, 1H, *J* = 4.8, 1.7 Hz), 5.08 (s, 1H), 4.90 (d, 1H, *J* = 11.0 Hz), 4.85-4.77 (m, 3H), 4.64 (s, 2H), 4.58 (d, 1H, *J* = 11.6 Hz), 4.58 (d, 1H, *J* = 11.6 Hz), 4.53 (dd, 1H, *J* = 9.9, 6.0 Hz), 4.45 (d, 1H, *J* = 11.6 Hz), 4.45 (d, 1H, *J* = 11.6 Hz), 4.16 (td, 1H, *J* = 10.4, 4.4 Hz), 4.03 (s, 1H), 3.85-3.67 (m, 4H), 3.66 (s, 2H), 3.58 (dd, 1H, *J* = 10.4, 1.9 Hz), 3.53-3.44 (m, 2H), 2.67 (d, 1H, *J* = 10.7 Hz), 1.70 (s, 1H), 1.41 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 186.0, 138.1, 137.7, 137.3, 137.2, 136.7, 128.6-127.7 (25C), 99.3, 81.7, 81.3, 79.8, 77.5, 77.3, 77.0, 76.4, 76.1, 75.9, 75.0, 73.4, 72.3, 72.1, 71.0, 70.8, 68.2, 64.5, 26.3, 22.3. Anal. Calcd for $C_{51}H_{58}N_2O_{10}S$: C, 68.74; H, 6.56; N, 3.14; S, 3.60. Found: C, 68.71; H, 6.80; N, 3.41; S, 3.52.

Urea 26.

To a solution of **25** (89 mg, 0.10 mmol) in MeCN/H_2O 2:1 (3.5 mL) was added freshly prepared yellow HgO (150 mg, 0.69 mmol). After stirring for 24h at rt, the reaction mixture was filtered through celite, the solvent was removed at reduced pressure and the crude was purified by flash chromatography (EtOAc/hexane 1:1) to afford **26** (17 mg, 98%) as a white solid: R_f = 0.22 (EtOAc/hexane 1:1); mp 94-95 ºC; $[\alpha]^{22}_D$ +89.7 (*c* 0.9, $CHCl_3$); IR (KBr) 3300, 2900, 1640, 1530, 1050, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37-7.23 (m, 23H), 7.19-7.12 (m, 2H), 6.09 (br s, 1H), 5.34 (br s, 1H), 5.19 (d, 1H, *J* = 2.7 Hz), 4.89 (d, 1H, *J* = 11.0 Hz), 4.83-4.76 (m, 3H), 4.62 (s, 2H), 4.56 (d, 1H, *J* = 10.9 Hz), 4.56 (d, 1H, *J* = 13.2 Hz), 4.46 (d, 1H, *J* = 10.8 Hz), 4.46 (d, 1H, *J* = 13.2 Hz), 4.04 (dd, 1H, *J* = 10.4, 4.6 Hz) 3.99 (s, 1H), 3.95 (dd, 1H, *J* = 10.4, 4.4 Hz), 3.89-3.84 (m, 1H), 3.77-3.57 (m, 4H), 3.52-3.40 (m, 4H), 2.53 (d, 1H, *J* = 10.5 Hz), 1.62 (s, 1H), 1.41 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.2, 138.2, 137.8, 137.4 (2C), 136.9, 128.6-127.8 (25C), 99.4, 81.9, 81.7, 78.0 (2C), 77.5, 77.3, 76.4, 75.8, 75.0 (2C), 73.5, 72.9, 72.1, 70.1, 68.7, 66.7, 64.5, 26.3, 23.0. Anal. Calcd for $C_{51}H_{58}N_2O_{11}$: C, 70.00; H, 6.68; N, 3.20. Found: C, 69.75; H, 6.92; N, 3.45.

Aminooxazoline 27.

To a solution of **26** (69 mg, 0.08 mmol) in CH_2Cl_2 (2.6 mL) at –20 ºC was added pyridine (25 μL, 0.31 mmol) followed by Tf_2O (17 μL, 0.10 mmol). After stirring for 1 h at –20 ºC the reaction mixture was diluted with CH_2Cl_2 (2 mL) and aqueous saturated $NaHCO_3$ (2 mL) was added. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and concentrated at reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford **27** (62 mg, 92%) as a white solid. R_f = 0.10 (EtOAc); mp 54-55 ºC; $[\alpha]^{22}_D$ +46.3 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.44-7.25 (m, 23H), 7.16-7.11 (m, 2H), 5.41 (d, 1H, *J* = 4.5 Hz), 5.02 (d, 1H, *J* = 7.6 Hz), 4.88 (d, 1H, *J* = 11.0 Hz), 4.80 (d, 1H, *J* = 11.0 Hz), 4.77 (d, 1H, *J* = 10.9 Hz), 4.64 (s, 2H), 4.64-4.42 (m, 6H), 4.30 (d, 1H, *J* = 12.0 Hz), 4.05 (d, 2H, *J* = 5.0 Hz), 3.84-3.62 (m, 7H), 2.75 (br s, 1H), 1.42 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.2, 138.4, 138.2, 137.8, 137.3, 136.9, 128.6-127.7 (25C), 98.6, 87.5, 81.9, 79.9, 78.6-78.0 (5C), 77.6, 75.5, 74.8, 73.2, 72.7, 72.3, 70.0, 68.4, 64.5, 26.9, 20.6.

Trehazolin (2)

To a solution of **27** (10 mg, 0.012 mmol) in EtOH (1 mL) was added CF_3CO_2H (5 μL, 0.058 mmol) and 25% $Pd(OH)_2$ on charcoal (20 mg). The mixture was stirred under H_2 (1 atm) at rt overnight. The reaction mixture was filtered through Celite and the solvent was removed at reduced pressure. The residue was dissolved in 2M HCl (1 mL) and stirred at rt for 5 min. Evaporation of the solvent at reduced pressure afforded trehazolin hydrochloride (4 mg, 83%). The crude hydrochloride was filtered through a column of Dowex 50W-H^+ eluting with 0.5M NH_4OH to afford trehazolin (**2**) as a white solid after freeze-drying. R_f = 0.37 (CH_3CN/AcOH/H_2O 6:1:3); $[\alpha]^{22}_D$ +119.8 (*c* 0.42, H_2O);

^{1}H NMR (D_2O) δ 5.35 (d, 1H, *J* = 5.2 Hz), 4.97 (d, 1H, *J* = 8.5 Hz), 4.37 (d, 1H, *J* = 8.6 Hz), 4.22 (dd, 1H, *J* = 4.6, 2.5 Hz), 3.97 (d, 1H, *J* = 4.8 Hz), 3.84-3.72 (m, 5H), 3.66 (dd, 1H, *J* = 9.8, 9.3 Hz), 3.59-3.56 (m, 1H), 3.42 (dd, 1H, *J* = 9.6, 9.4 Hz); ^{13}C NMR (D_2O) δ 161.1, 87.3, 82.7, 80.2 (2C), 80.1, 73.0 (2C), 72.0, 69.9, 70.0, 61.9, 60.6.

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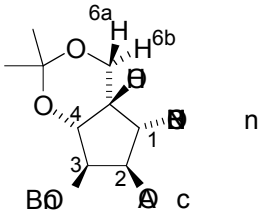
Table

Intensity of significant 2D-NOESY cross peaks for compound **12** in $CDCl_3$. Abbreviations: strong (s); medium (m); weak (w). For peak assignments, see experimental part.



	Relative Intensity
H-1/H-2	w
H-1/OH	m
H-2/H-3	s
H-2/H-6b	w
H-4/OH	m