# Glucose-based spiro-oxathiazoles as *in vivo* anti-hyperglycemic agents through glycogen phosphorylase inhibition

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## CHEMICAL SYNTHESIS

**Method A: General procedure for the preparation of acetylated hydroximothioates 2.**

The conventional method using a hydroximoyl chloride was applied. Per-*O*-acetylated-1-thio-β-D-glucopyranose **1** (1 mmol) dissolved in $CH_2Cl_2$ (5 mL) and $Et_3N$ (3 mmol) was added under Ar atmosphere with continuous stirring to a solution of a hydroximoyl chloride (1.5 mmol) in $Et_2O$ or $CH_2Cl_2$ (5 mL). Immediate precipitation of $Et_3N{\cdot}HCl$ occurred. The mixture was stirred further at rt. When TLC (1:2 EtOAc-hexane) indicated completion of the transformation (~1-3 h), 0.5 M $H_2SO_4$ (20 mL) was added, and the organic phase was separated, washed with water (2×20 mL), and dried ($MgSO_4$). After removal of the solvent under diminished pressure, the residue was purified by crystallization or column chromatography.

**Method B: General procedure for the preparation of spiro-oxathiazoles 3.**

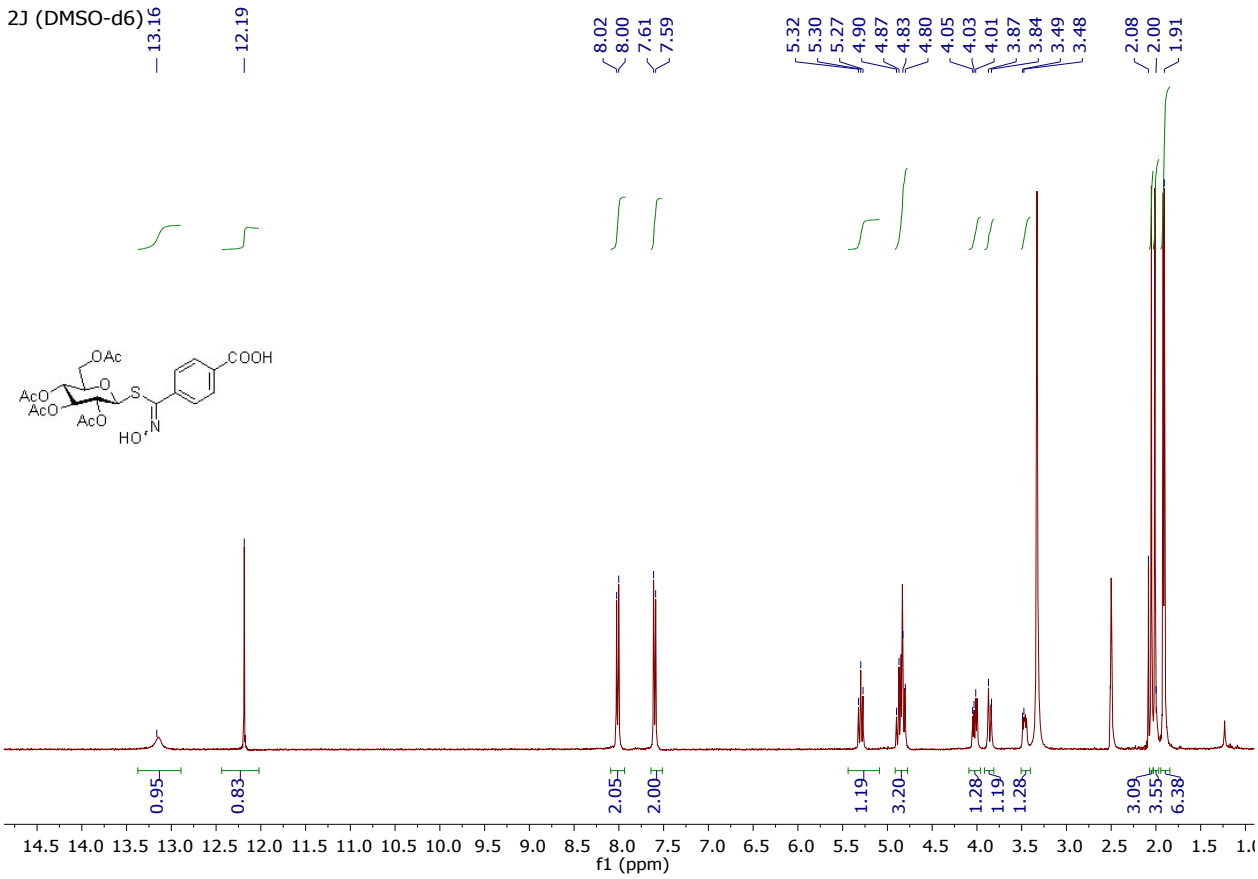
A flask containing the selected hydroximothioate **2** (200 mg) and NBS (4 eq) and dry $CCl_4$ (5 mL) was placed over a 60W tungsten lamp and illuminated for 30-45 min. Progress of the reaction in refluxing $CCl_4$ was followed by TLC. The mixture was diluted with EtOAc (100 mL) and washed with a saturated solution of $Na_2S_2O_3$ (3 x 50 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (PE/EtOAc 7:3) to afford the spiro-oxathiazoles **3j-l**. $CCl_4$ can be replaced by $CHCl_3$. For larger scale experiments, a 250W tungsten lamp was used.

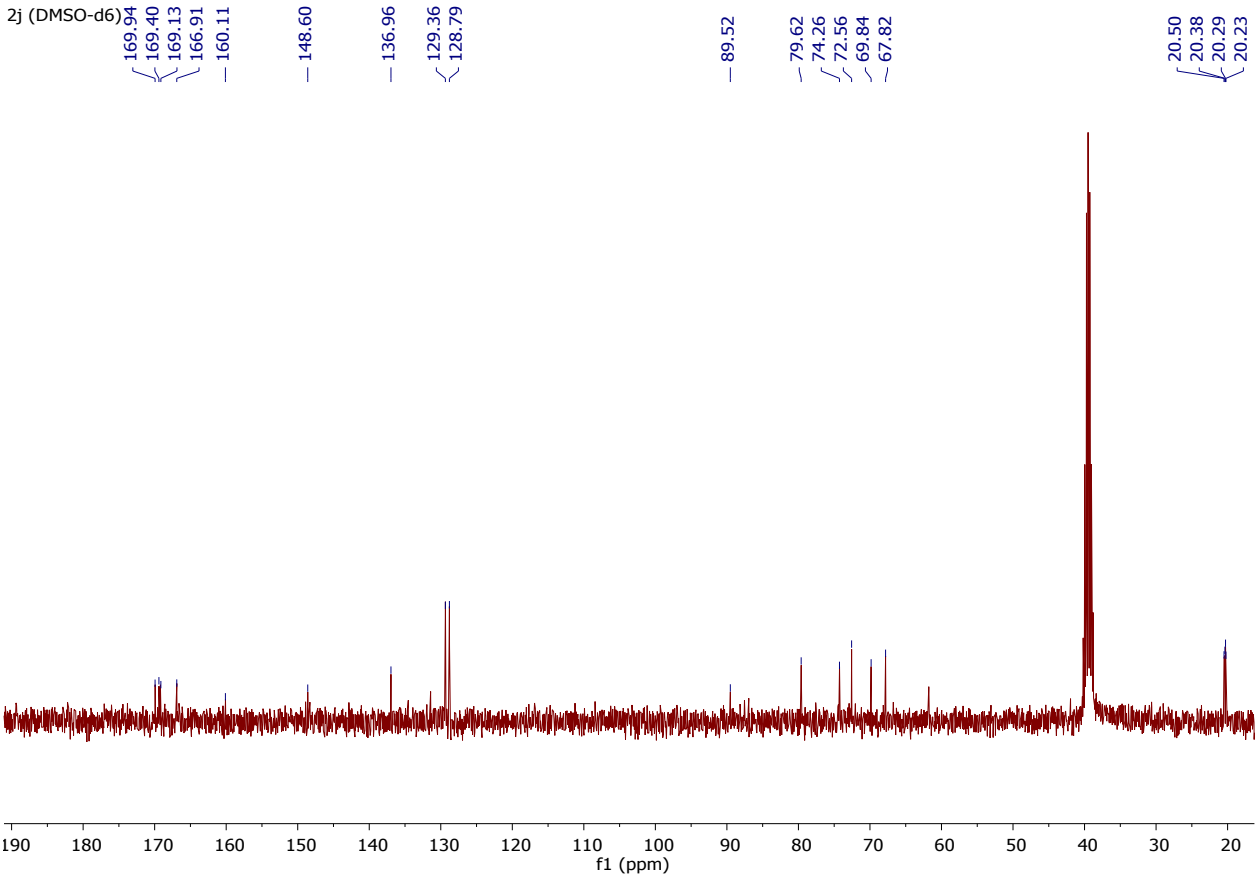
**Method C: General procedure for the Zemplén deacetylation.**

Methanolic MeONa (0.4 eq) was added to a suspension of acetylated compound **3** (1 eq) in dry MeOH (5 mL/0.2 mmol). If the acetylated compound was not soluble in MeOH, $CH_2Cl_2$ was added to reach reasonable solubility. The mixture was stirred at rt until TLC monitoring (1:1 $CHCl_3$-MeOH) showed completion of the transformation. After neutralization with Amberlite IR 120 resin and filtration, concentration *in vacuo* of the organic medium afforded the corresponding deacetylated product **5**.

**2,3,4,6-Tetra-*O*-acetyl-1-*S*-(*Z*)-4-carboxybenzhydroximoyl-1-thio-β-D-glucopyranose 2j.**

Prepared from 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **1** (0.5 g, 1.37 mmol) according to method **A** yielding **2j** (0.38 g, 53%) as a white crystalline product, Mp: 203-205°C; $[\alpha]_D$ + 61 (*c* 0.17, DMSO); $^1$H NMR (360 MHz, DMSO-$d_6$) δ 13.13 (s, 1H, COOH), 12.18 (s, 1H, OH), 8.00 (d, 2H, *J* 7.9 Hz, ArH), 7.59 (d, 2H, *J* 7.9 Hz, ArH), 5.29 (t, 1H, $J_{1,2}$ 9.2 Hz, $J_{2,3}$ 9.2 Hz, H-2), 4.89-4.80 (m, 3H, H-1, H-3, H-4), 4.01 (dd, 1H, $J_{6,6'}$11.9 Hz, $J_{5,6}$ 5.3 Hz, H-6), 3.85 (dd, 1H, $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$ 1.3 Hz, H-6'), 3.47 (ddd, 1H, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 5.3 Hz, $J_{5,6'}$ 1.3 Hz, H-5), 2.07, 2.00, 1.90 (2) (3s, 12H, $COCH_3$); $^{13}$C NMR (90 MHz, DMSO-$d_6$) δ 182.6 (*C*OOH), 169.8, 169.1, 169.0 (2) (*C*O), 148.5 (*C*=N), 136.8-128.7 (CAr), 79.5 (C-1), 74.2, 72.5, 69.7, 67.7 (C-2 - C-5), 61.7 (C-6), 20.1, 20.2 (3) ($COCH_3$); Anal. Calcd. for $C_{22}H_{25}NO_{12}S$ (527.50): C, 50.09; H, 4.78; N, 2.76. Found: C, 50.19; H, 4.85; N, 2.79.






**2,3,4,6-Tetra-*O*-acetyl-1-*S*-(Z)-2-quinolinyl-hydroximoyl-1-thio-β-D-glucopyranose 2k.** Prepared from **1** (0.5g, 1.37 mmol) according to method **A** yielding **2k** (0.25 g, 35%) as a yellow crystalline product, Mp: 140-142°C; $[\alpha]_D$ -99 (*c* 0.44, $CHCl_3$); $^1H$ NMR (360 MHz, $CDCl_3$) δ 9.42 (s, 1H, OH), 8.24-7.60 (m, 6H, ArH), 5.78 (pseudo t, 1H, $J_{1,2}$ 9.2 Hz, $J_{2,3}$ 7.9 Hz, H-2), 5.16-5.10 (m, 2H, H-1, H-3), 4.98 (t, 1H, $J_{3,4}$ 9.2 Hz, $J_{4,5}$ 9.2 Hz, H-4), 3.81 (dd, 1H, $J_{6,6'}$11.9 Hz, $J_{5,6}$ 4.0 Hz, H-6), 3.47 (dd, 1H, $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$ 2.6 Hz, H-6'), 2.91 (ddd, 1H, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 4.0 Hz, $J_{5,6'}$ 2.6 Hz, H-5), 2.10, 1.99, 1.92 (2) (3s, 12H, $COCH_3$); $^{13}$ C NMR (90 MHz, $CDCl_3$) δ 170.5, 170.3, 169.5, 169.2 (*C*O), 152.1 (*C*=N), 150.4-120.9 (CAr), 79.9 (C-1), 75.5, 73.9, 70.4, 67.7 (C-2 - C-5), 61.2 (C-6), 20.7, 20.5, 20.4 (2) (CO*C*$H_3$); Anal. Calcd. for $C_{24}H_{26}N_2O_{10}S$ (534.54): C, 53.93; H, 4.90; N, 5.24. Found: C, 53.98; H, 4.96; N, 5.27.

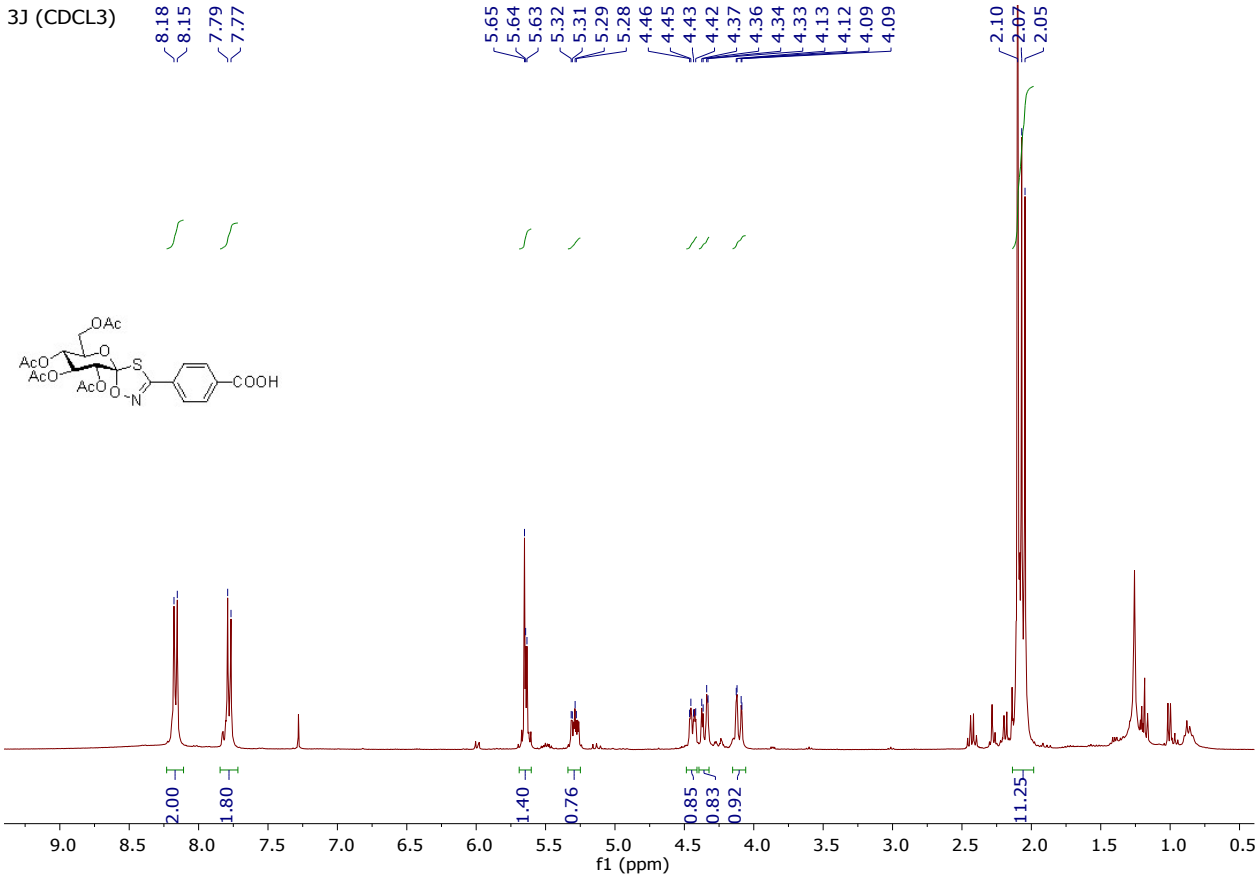
**2,3,4,6-Tetra-*O*-acetyl-1-*S*-(Z)-9-phenantryl-hydroximoyl-1-thio-β-D-glucopyranose 2l.** Prepared from **1** (1.0 g, 2.75 mmol) according to method **A** yielding **2l** (1.38 g, 86%) as a white foam, $R_f$.= 0.62 (1:1 EtOAc-hexane); $[\alpha]_D$ +53 (*c* 0.50, $CHCl_3$); $^1H$ NMR (360 MHz, $CDCl_3$) δ 9.65 (s, 1H, OH), 8.72-7.59 (m, 9H, ArH), 4.98 (t, 1H, $J_{1,2}$ 9.2 Hz, $J_{2,3}$ 9.2 Hz, H-2), 4.88

(pseudo t, 1H, $J_{2,3}$ 9.2 Hz, $J_{3,4}$ 9.3 Hz, H-3), 4.67 (t, 1H, $J_{3,4}$ 9.3 Hz, $J_{4,5}$ 9.2 Hz, H-4), 4.14 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1), 3.47 (dd, 1H, $J_{6,6'}$ 12.3 Hz, $J_{5,6}$ 2.9 Hz, H-6), 3.95 (dd, 1H, $J_{6,6'}$ 12.3 Hz, $J_{5,6'}$ 1.4 Hz, H-6'), 2.22 (ddd, 1H, $J_{4,5}$ 9.3 Hz, $J_{5,6}$ 2.9 Hz, $J_{5,6'}$ 1.4 Hz, H-5), 2.08 (2), 1.87, 1.77 (3s, 12H, $COCH_3$); $^{13}$ C NMR (90 MHz, $CDCl_3$) δ 170.6, 170.2, 169.2, 169.0 (*C*O), 151.9 (*C*=N), 130.6-122.7 (CAr), 81.2 (C-1), 75.1, 73.6, 69.1, 67.0 (C-2 - C-5), 60.3 (C-6), 20.6, 20.5, 20.3, 20.2 (CO*C*$H_3$); Anal. Calcd. for $C_{29}H_{29}NO_{10}S$ (583.61): C, 59.68; H, 5.01; N, 2.40. Found: C, 59.61; H, 5.11; N, 2.47.

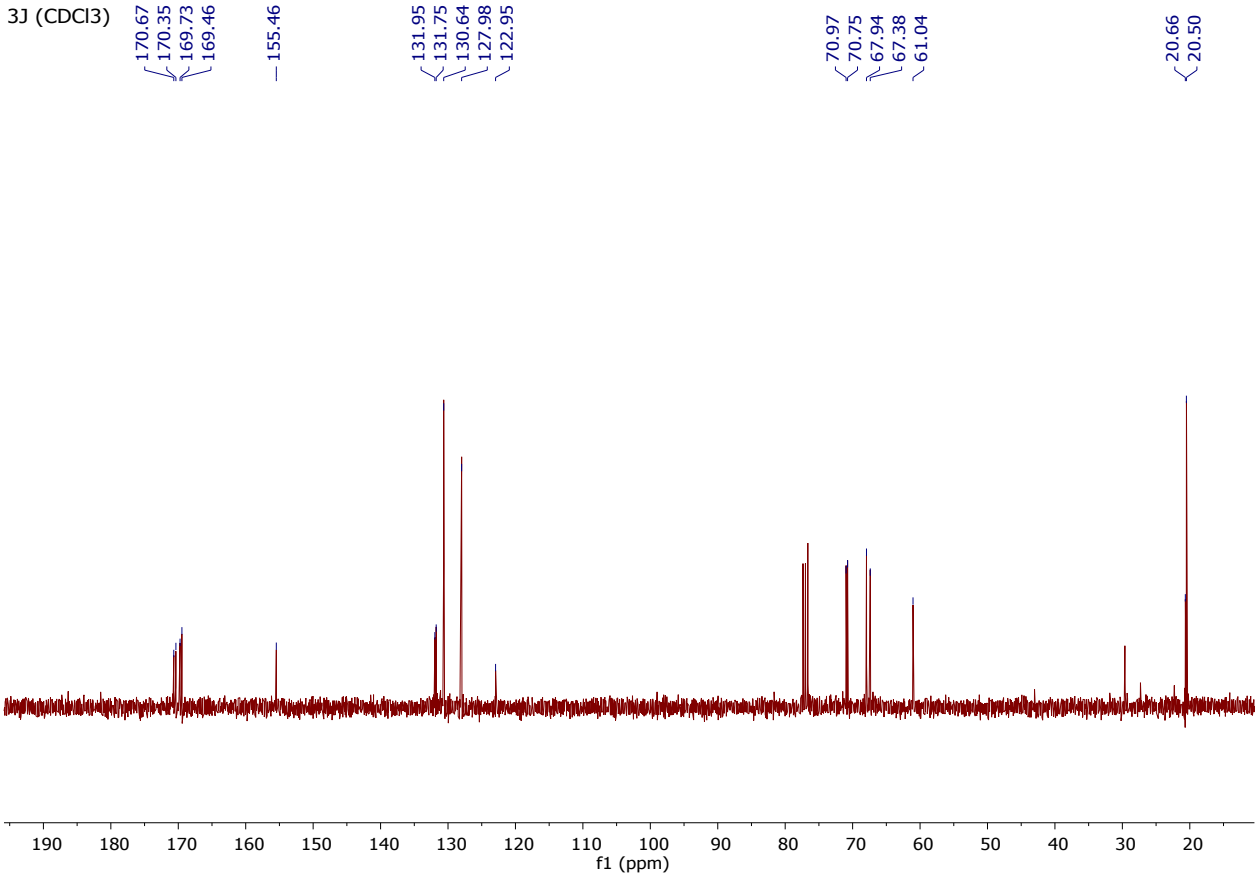
**(1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol-spiro[1,5]-3-(4-carboxyphenyl)-1,4,2-oxathiazole 3j.**

Prepared from **2j** (0.2 g, 0.38 mmol) according to method **B** ($CHCl_3$ as solvent) resulted in 0.10 g, 50% of **3j** as a colourless oil, $R_f$= 0.20 (1:1 EtOAc-hexane); $[\alpha]_D$ +119 (*c* 0.14, DMSO); $^1$H NMR (360 MHz, $CDCl_3$) δ 8.42 (s 1H, COOH), 8.16 (d, 2H, *J* 8.3 Hz, ArH), 7.78 (d, 2H, *J* 8.3 Hz, ArH), 5.67-5.61 (m, 2H, H-2, H-3), 5.29 (pseudo t, 1H, $J_{3,4}$ 9.8 Hz, $J_{4,5}$ 10.6 Hz, H-4), 4.44 (1H, ddd, $J_{4,5}$ 10.6 Hz, $J_{5,6}$ 3.4 Hz, $J_{5,6'}$ 1.9 Hz, H-5), 4.35 (1H, dd, $J_{6,6'}$ 12.6 Hz, $J_{5,6'}$ 3.4 Hz, H-6), 4.10 (1H, dd, $J_{6,6'}$ 12.6 Hz, $J_{5,6'}$ 1.9 Hz, H-6'), 2.09 (2), 2.07, 2.05 (3s, 12H, $COCH_3$); $^{13}$ C NMR (90 MHz, $CDCl_3$) δ 170.6 (*C*OOH), 170.3, 169.7, 169.4 (2) (*C*O), 155.4 (C=N spiro), 131.9-128.0 (*C*Ar), 122.9 (C-1 spiro), 70.9, 70.7, 67.9, 67.4 (C-2 - C-5), 61.0 (C-6), 20.6, 20.5 (3) (CO*C*$H_3$); Anal. Calcd. for $C_{22}H_{23}NO_{12}S$ (525.48): C, 50.28; H, 4.41; N, 2.67. Found: C, 50.35; H, 4.46; N, 2.73.

3J (CDCL3)




3J (CDCl3)

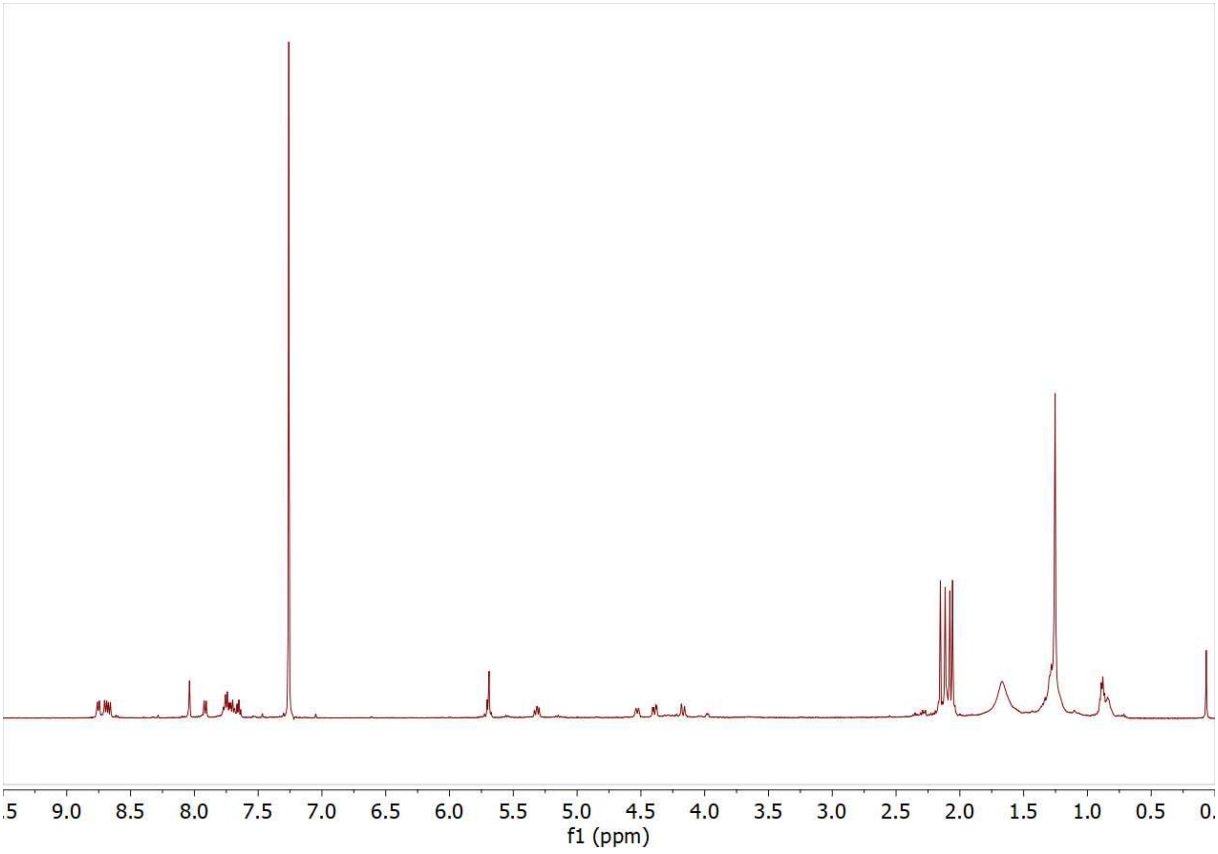


**(1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol-spiro[1,5]-3-(2-quinolinyl)-1,4,2-oxathiazole 3k.**

Prepared from **2k** (0.15 g, 0.28 mmol) according to method **B** ($CHCl_3$ as solvent) resulted in **3k** as first fraction 0.05 g, 36% (next, a 32 mg fraction was a complex mixture). Yellow powder, Mp: 172-174 °C; $[\alpha]_D$ +100 (*c* 0.15; $CHCl_3$); $^1$H NMR (360 MHz, $CDCl_3$) δ 8.24-7.60 (m, 6H, ArH), 5.70-5.62 (m, 2H, H-2, H-3), 5.30 (t, 1H, $J_{3,4}$ 9.2 Hz, $J_{4,5}$ 9.2 Hz, H-4), 4.47 (1H, ddd, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 2.6 Hz, $J_{5,6'}$ 1.1 Hz, H-5), 4.33 (1H, dd, $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$ 2.6 Hz, H-6), 4.11 (1H, dd, $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$ 1.1 Hz, H-6'), 2.08, 2.07, 2.04 (2) (3s, 12H, $COCH_3$); $^{13}$ C NMR (90 MHz, $CDCl_3$) δ 170.6 (*C*OOH), 169.3 (3), 169.6 (*C*O), 151.5 (C=N), 136.8-116.9 (*C*Ar), 122.4 (C-1 spiro), 71.1, 70.5, 68.1, 67.6 (C-2 - C-5), 61.2 (C-6), 20.7 (3), 20.5 (CO*C*$H_3$); Anal. Calcd. for $C_{24}H_{24}NO_{10}S$ (532.52): C, 54.13; H, 4.54; N, 5.26. Found: C, 54.13; H, 4.54; N, 5.26.

**(1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol-spiro[1.5]-3-(9-phenanthryl)-1,4,2-oxathiazole 3l.**

Prepared according to method **B**. White powder (97 mg, 0.17 mmol, 49%); $R_f$ = 0.63 (PE/EtOAc 6:4); Mp = 123-124°C ($CH_2Cl_2$/PE); $[\alpha]_D^{20}$ = +56 (*c* 1, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 500 MHz) δ 8.74-8.76 (m, 1H, H-Ar), 8.66-8.70 (m, 2H, H-Ar), 8.04 (s, 1H, H-Ar), 7.91-7.92 (m, 1H, H-Ar), 7.70-7.77 (m, 3H, H-Ar), 7.64-7.67 (m, 1H, H-Ar), 5.69-5.72 (m, 2H, H-2, H-3), 5.29-5.33 (m, 1H, H-4), 4.53 (ddd, 1H, *J* = 10.4, 3.7, 2.2 Hz, H-5), 4.39 (dd, 1H, *J* = 12.7, 3.9 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.7, 2.0 Hz, H-6b), 2.15, 2.12, 2.08, 2.06 (4s, 12H, acetyl); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 170.5, 169.6, 169.4, 169.4 (4C, C=O), 155.8 (C-3'), 131.9 (CH-Ar), 131.4 (C-Ar), 130.7 (C-Ar), 130.2 (C-Ar), 129.3 (CH-Ar), 128.7 (CH-Ar), 128.5 (C-Ar), 127.5 (CH-Ar), 127.4 (CH-Ar), 127.3 (CH-Ar), 126.4 (CH-Ar), 123.0 (CH-Ar), 122.6 (CH-Ar), 122.4 (C-Ar), 121.7 (C-1), 71.1 (C-3), 70.6 (C-5), 67.2 (C-2), 67.6 (C-4), 61.2 (C-6), 20.7, 20.5, 20.5, 20.5 (4$CH_3$, acetyl); HRMS [ESI+] *m/z* $[M+Na]^+$ calcd. for $C_{29}H_{27}NNaO_{10}S$ 604.1248; found 604.1223.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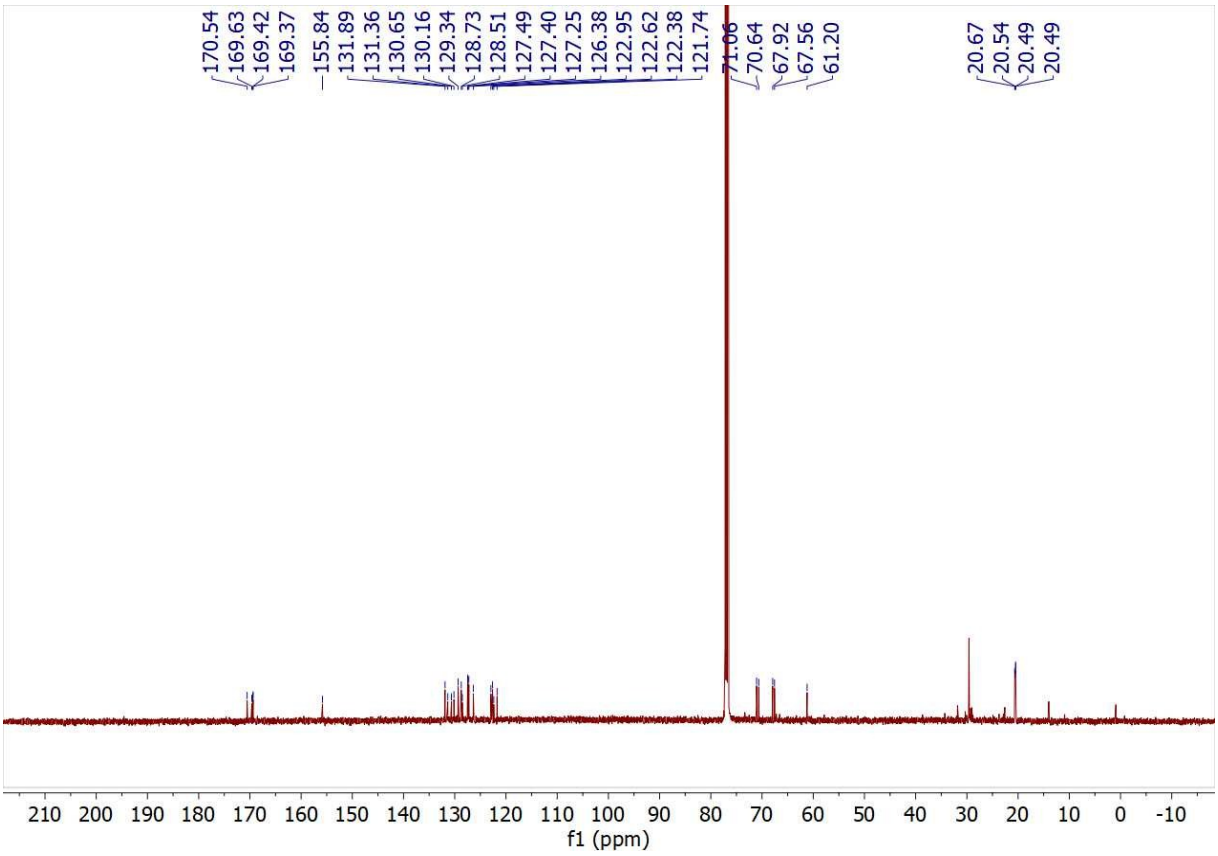
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70.64
67.92
67.56
61.20
20.67
20.54
20.49
20.49
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

**(1*S*)-1,5-Anhydro-D-glucitol-spiro[1,5]-3-(4-carboxyphenyl)-1,4,2-oxathiazole 5j.**

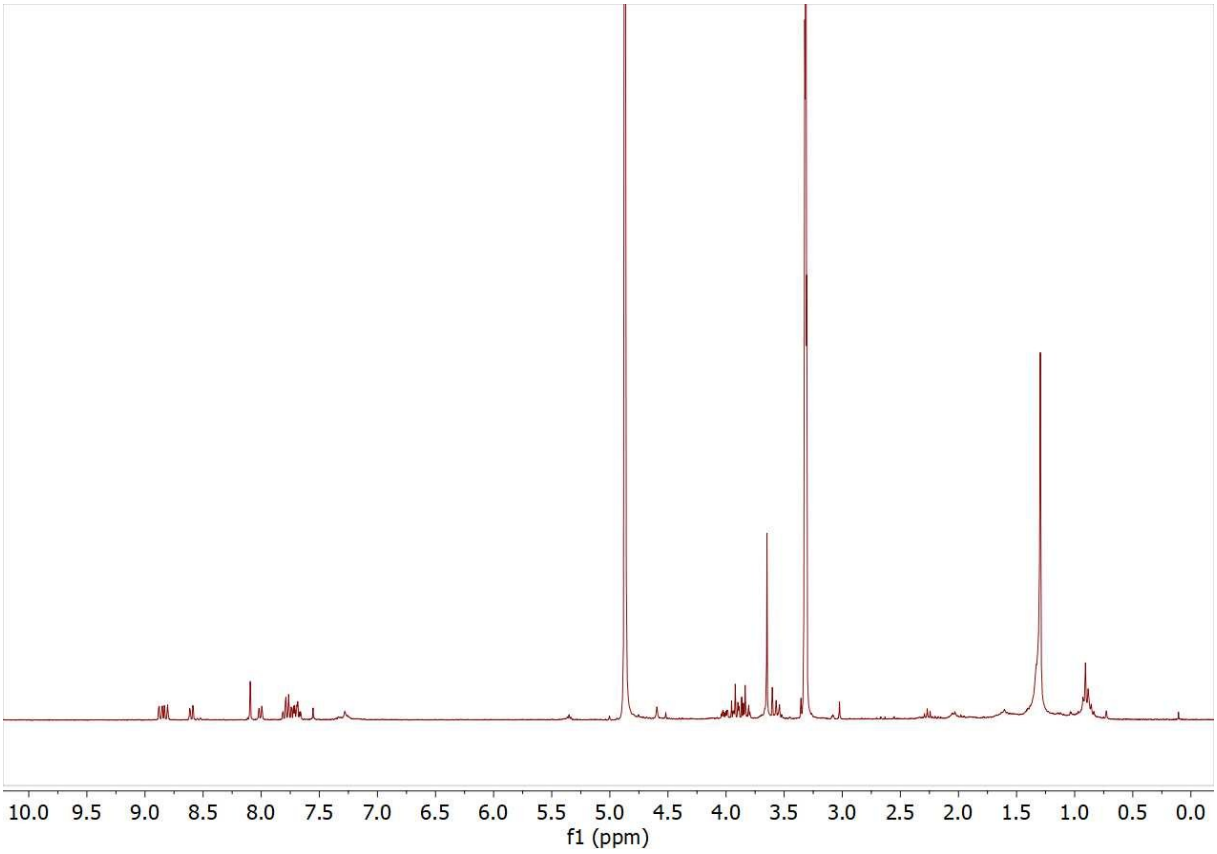
Prepared from **3j** (0.05 g, 0.10 mmol) according to method **C** resulted in **5j** (0.03 g, 73%) as a greyish powder, Mp: 182-184 °C, $[\alpha]_D$ +159 (*c* 0.10, DMSO); $^1$H NMR (360 MHz, $CD_3OD$) δ 8.08 (d, 2H, *J* 7.3 Hz, ArH), 7.77 (d, 2H, *J* 7.3 Hz, ArH), 4.10-3.85 (m, 2H, H-2, H-5), 3.79-3.71 (3H, m, H-3, H-6, H-6'), 3.50 (pseudo t, 1H, $J_{4,5}$ 9.7 Hz, $J_{3,4}$ 9.2 Hz, H-4); $^{13}$C NMR (90 MHz, $CD_3OD$) δ 168.7 (COOH), 134.4-128.7 (ArC), 128.3 (C-1 spiro), 77.5, 76.1, 72.8, 70.7 (C-2 - C-5), 62.0 (C-6) ; Anal. Calc. for $C_{14}H_{15}NO_8S$ (357.34): C, 47.0; H, 4.23; N, 3.92. Found: C, 47.8; H, 4.33; N, 3.98.

**(1*S*)-1,5-Anhydro-D-glucitol-spiro[1,5]-3-(2-quinolinyl)-1,4,2-oxathiazole 5k.**

Prepared from **3k** (0.03 g, 0.06 mmol) according to method **C** resulted in **5k** (0.02 g, 88%) as a yellow powder, Mp: 204-207°C, $[\alpha]_D$ +76 (*c* 0.05, MeOH); $^1$H NMR (360 MHz, $CD_3OD$) δ 8.43-7.69 (m, 6H, ArH), 3.98 (ddd, 1H, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 2.4 Hz, $J_{5,6'}$ 1.9 Hz, H-5), 3.93 (d, 1H, $J_{2,3}$ 9.2 Hz, H-2), 3.87 (dd, 1H, $J_{6,6'}$ 12.1 Hz, $J_{5,6}$ 2.4 Hz, H-6), 3.86 (t, 1H, $J_{2,3}$ 9.2 Hz, $J_{3,4}$ 9.2 Hz, H-3), 3.82 (dd, 1H, $J_{6,6'}$ 12.1 Hz, $J_{5,6'}$ 1.9 Hz, H-6'), 3.58 (t, 1H, $J_{4,5}$ 9.2 Hz, $J_{3,4}$ 9.2 Hz, H-4); $^{13}$C NMR (90 MHz, $CD_3OD$) δ 145.4-119.0 (ArC), 125.8 (C-1 spiro), 77.4, 76.1, 73.0, 70.8 (C-2 - C-5), 62.1 (C-6) ; Anal. Calc. for $C_{16}H_{16}N_2O_6S$ (364.37): C, 52.74; H, 4.43; N, 7.69. Found: C, 52.77; H, 4.49; N, 7.75.

**(1*S*)-1,5-Anhydro-D-glucitol-spiro-[1.5]-3-(9-phenanthryl)-1,4,2-oxathiazole 5l.**

Prepared from **3l** according to method **C** to afford **5l** (>95%). White powder; $R_f$ = 0.16 ($CH_2Cl_2$/MeOH 9:1); Mp = 196-197°C (MeOH/$CH_2Cl_2$); $[\alpha]_D$ = +52 (*c* 1, MeOH); $^1$H NMR ($CD_3OD$, 400 MHz) δ 8.87 (d, 1H, *J* = 8.4 Hz, H-Ar), 8.82 (d, 1H, *J* = 8.3 Hz, H-Ar), 8.60 (dd, 1H, *J* = 8.3, 1.4 Hz, H-Ar), 8.09 (s, 1H, H-Ar), 8.00 (dd, 1H, *J* = 7.9, 1.4 Hz, H-Ar), 7.77 (m, 4H, H-Ar), 4.01 (ddd, 1H, *J* = 10.1, 4.7, 2.3 Hz, H-5), 3.93 (d, 1H, *J* = 9.7 Hz, H-2), 3.91 (dd, 1H, *J* = 12.3, 2.3 Hz, H-6a), 3.83 (m, 2H, H-6b, H-3), 3.60 (d, 1H, *J* = 5.4 Hz, H-4); $^{13}$C NMR ($CD_3OD$, 100 MHz) δ 156.5 (C-3'), 132.6 (C-Ar), 132.0 (C-Ar), 131.9 (CH-Ar), 130.8 (C-Ar), 130.4 (CH-Ar), 130.2 (C-Ar), 129.8 (CH-Ar), 128.6 (CH-Ar), 128.5 (CH-Ar), 128.4 (CH-Ar), 127.6 (C-1), 127.6 (CH-Ar), 124.7 (C-Ar), 124.2 (CH-Ar), 123.9 (CH-Ar), 77.5 (C-5), 76.2 (C-3), 72.7 (C-2), 70.8 (C-4), 62.1 (C-6) – *Note:* The second 13C NMR spectrum with a "wavy" baseline was recorded with a cryoprobe at 150 MHz frequency to obtained the resonance peak of the quaternary oxathiazole carbon atom at 156.5 ppm.; HRMS [ESI+] *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{19}NNaO_6S$ 436.0825; found 436.0824.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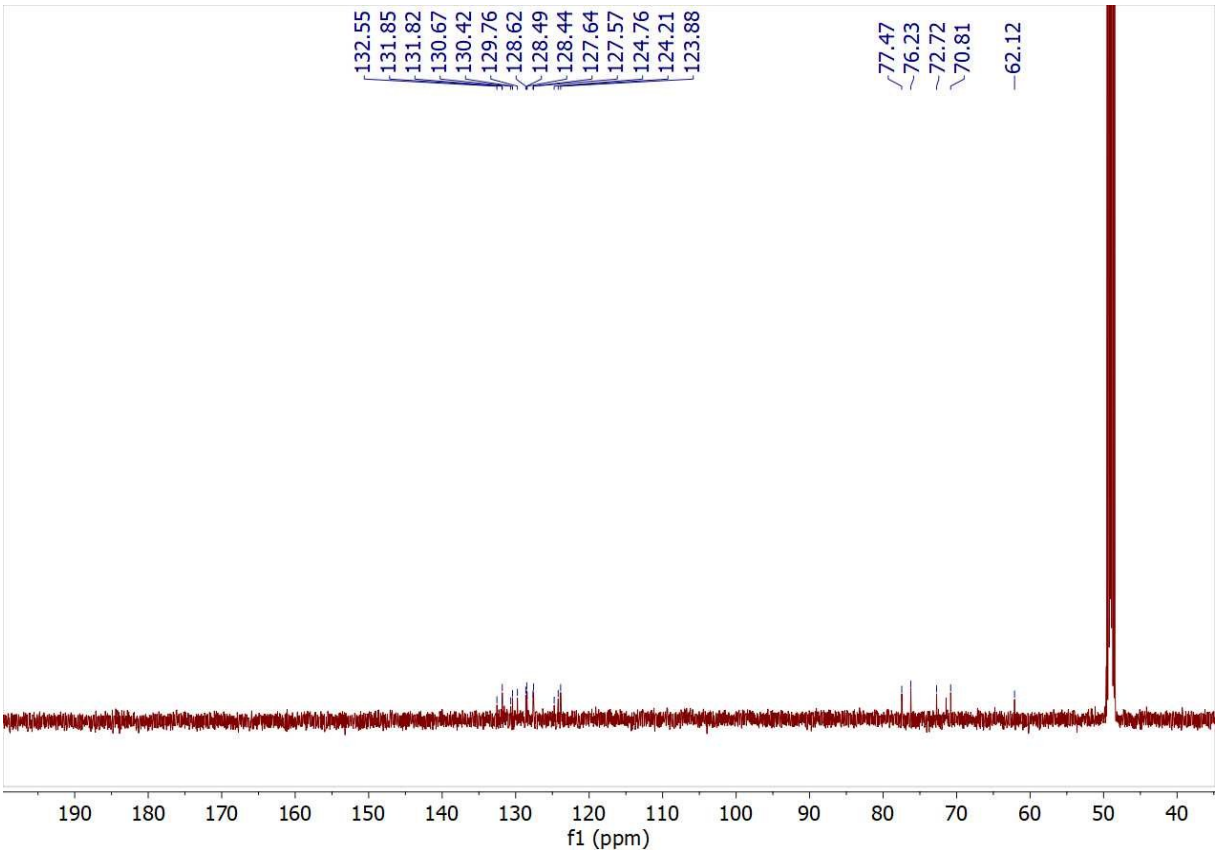
f1 (ppm)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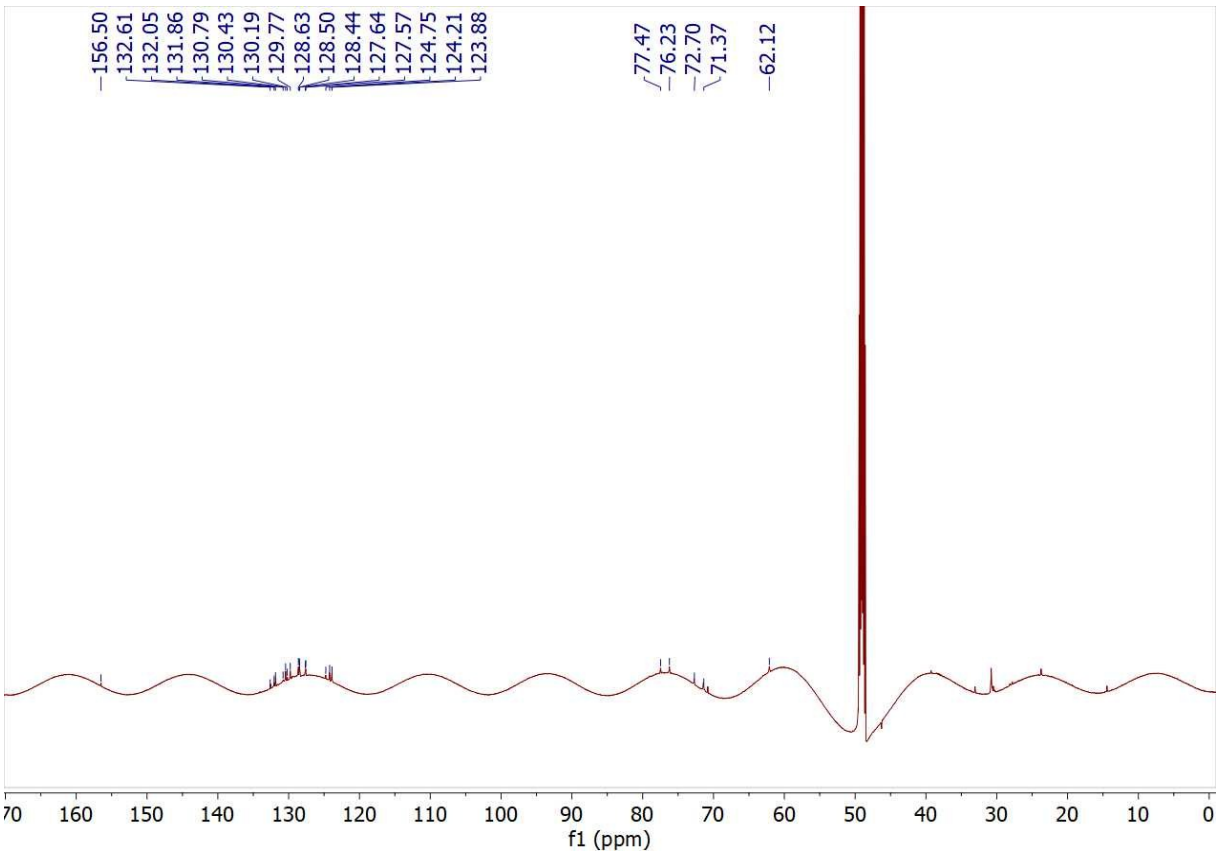



***O*-Ethyl-*S*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-dithiocarbonate 8.**

To a solution of 2,3,4,6-tetra-*O*-benzyl-glucopyranose **6** (10.0 g, 18.49 mmol) and carbon tetrachloride (3.57 mL, 36.99 mmol, 2 eq) in anhydrous $CH_2Cl_2$ (80 mL) at -40°C was added dropwise HMPT (5.04 mL, 27.74 mmol, 1.5 eq). The mixture was stirred for 30 min. at -40°C and potassium ethyl-dithiocarbonate (5.92 g, 36.99 mmol, 2 eq) was added. The mixture was stirred for 2 h at -40°C, allowed to warm up to rt, and filtered through Celite. The filtrate was concentrated *in vacuo* and purified over silica gel chromatography (PE/EtOAc 90:10) to afford **8** (2:8 α/β anomeric mixture) as a white solid.

**2,3,4,6-Tetra-*O*-benzyl-1-thio-D-glucopyranose 9.**

*O*-Ethyl-*S*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-dithiocarbonate **8** was suspended in anhydrous methanol (100 mL) and metallic sodium was added portionwise to the suspension until it became a clear solution. The mixture was stirred at rt for an additional 2 h, neutralized with a 10% aqueous solution of acetic acid (50 mL), extracted with $CH_2Cl_2$ (3×50 mL), washed with $H_2O$ (3×50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product (pale

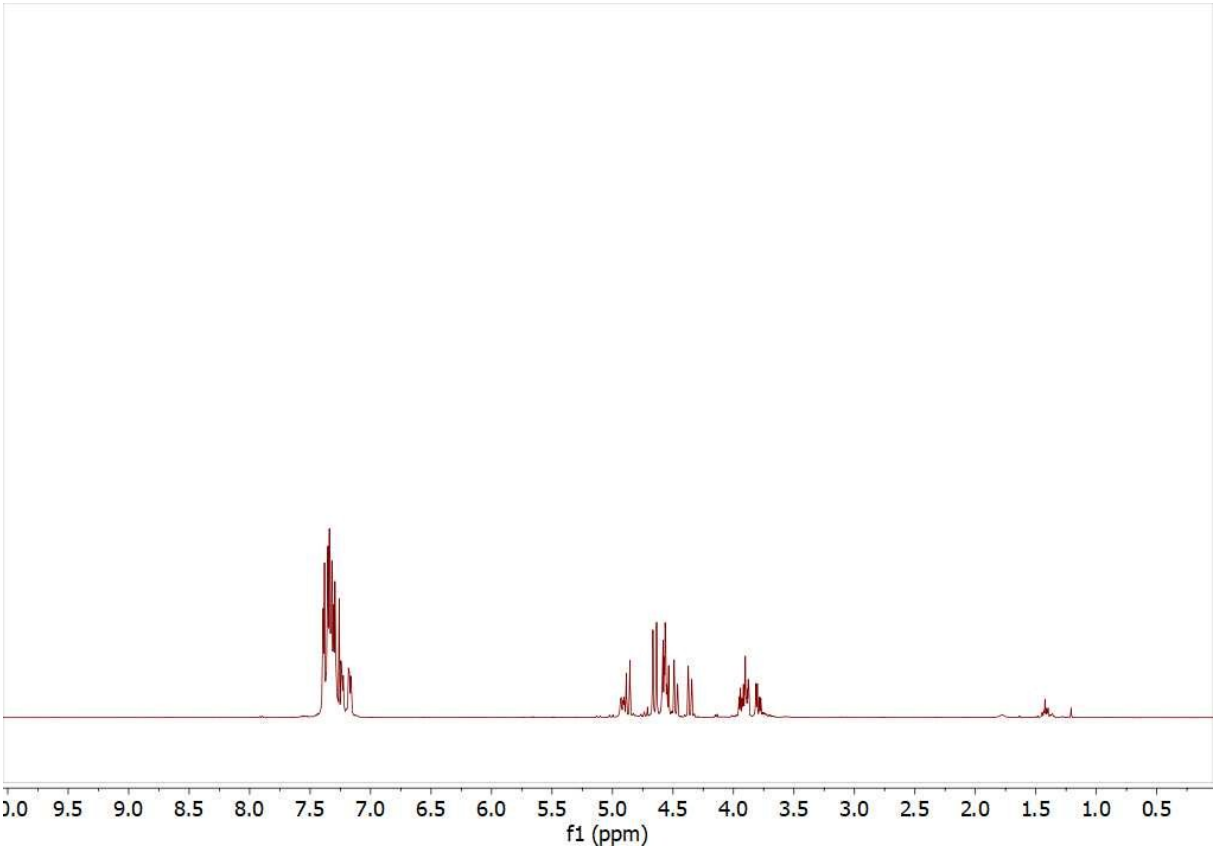
yellow oil) was purified over silica gel chromatography (PE/EtOAc 5:95) to afford **9** as a colourless oil that crystallized upon drying (8.75 g, 15.72 mmol, 85% over two steps).

**1-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-*tert*-butyl-sulfinothioate 10.**

To a solution of **9** (18.34 g, 32.95 mmol) and freshly distilled $Et_3N$ (4.99 mL, 32.95 mmol, 1 eq) in anhydrous toluene under $N_2$ was added *tert*-butyl-sulfinyl chloride (4.34 mL, 39.54 mmol, 1.2 eq). The mixture was stirred at rt for 20 min and concentrated *in vacuo* at 20°C. The crude mixture was suspended in a minimum of $Et_2O$ and filtered. The solid was discarded and the filtrate was concentrated *in vacuo* at 20°C. The residual pale yellow oil was purified over silica gel chromatography (PE/EtOAc 15:85) to afford **10** as a 1:1 mixture of diastereoisomers (pale yellow oil, 19.60 g, 29.66 mmol, 90%).

**2,3,4,6-Tetra-*O*-benzyl-D-glucono-δ-thionolactone 12.**

A solution of **10** (19.60 g, 29.66 mmol) in anhydrous toluene (100 mL) under $N_2$ was gently heated to reflux (110°C). The reaction was carefully monitored and heating was stopped when TLC (PE/EtOAc 20:80) showed complete conversion of the less polar thiosulfinate **10**. The mixture was concentrated *in vacuo* at 20°C and the crude yellow oil was purified by silica gel flash chromatography (PE/EtOAc 5:95) to afford the thionolactone **12** as a bright yellow oil (7.40 g, 13.35 mmol, 45%). As this purification entailed partial loss of thionolactone **12**, the crude lactone mixture was used without purification for the cycloaddition step. An analytically pure sample of thionolactone **12** was also obtained to provide the analytical data. Yellow oil; $R_f$ = 0.67 (Cyclohexane/EtOAc 80:20) ; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.28 (m, 16H, H-Ar), 7.26-7.15 (m, 4H, H-Ar), 4.92 (ddd, *J* = 9.7, 4.0, 2.0 Hz, 1H, H-5), 4.87 (d, *J* = 11.8 Hz, 1H, $CH_2$), 4.65 (d, *J* = 12.1 Hz, 2H, $CH_2$), 4.60-4.53 (m, 4H, $CH_2$), 4.48 (d, *J* = 11.4 Hz, 1H, $CH_2$), 4.36 (d, *J* = 11.7 Hz, 1H), 3.96-3.86 (m, 3H, H-3, H-4, H-6), 3.79 (dd, *J* = 11.4, 4.1 Hz, 1H, H-6'); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 215.6, 138.2, 137.9, 137.5, 137.2, 129.0, 128.93, 128.90, 128.85, 128.83, 128.63, 128.57, 128.50, 128.41, 128.36, 128.30, 128.2, 83.1, 81.3, 80.9, 74.0, 73.4, 72.2, 72.1, 68.5.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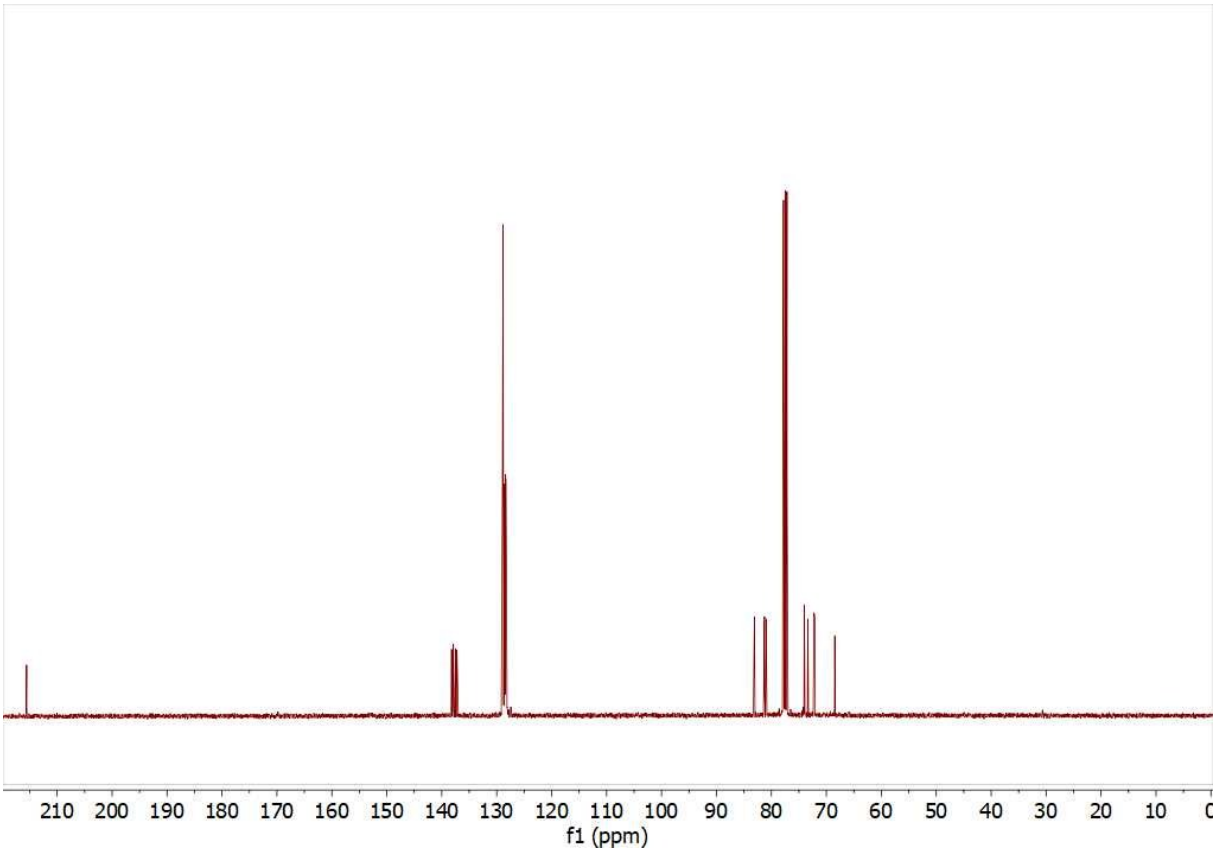
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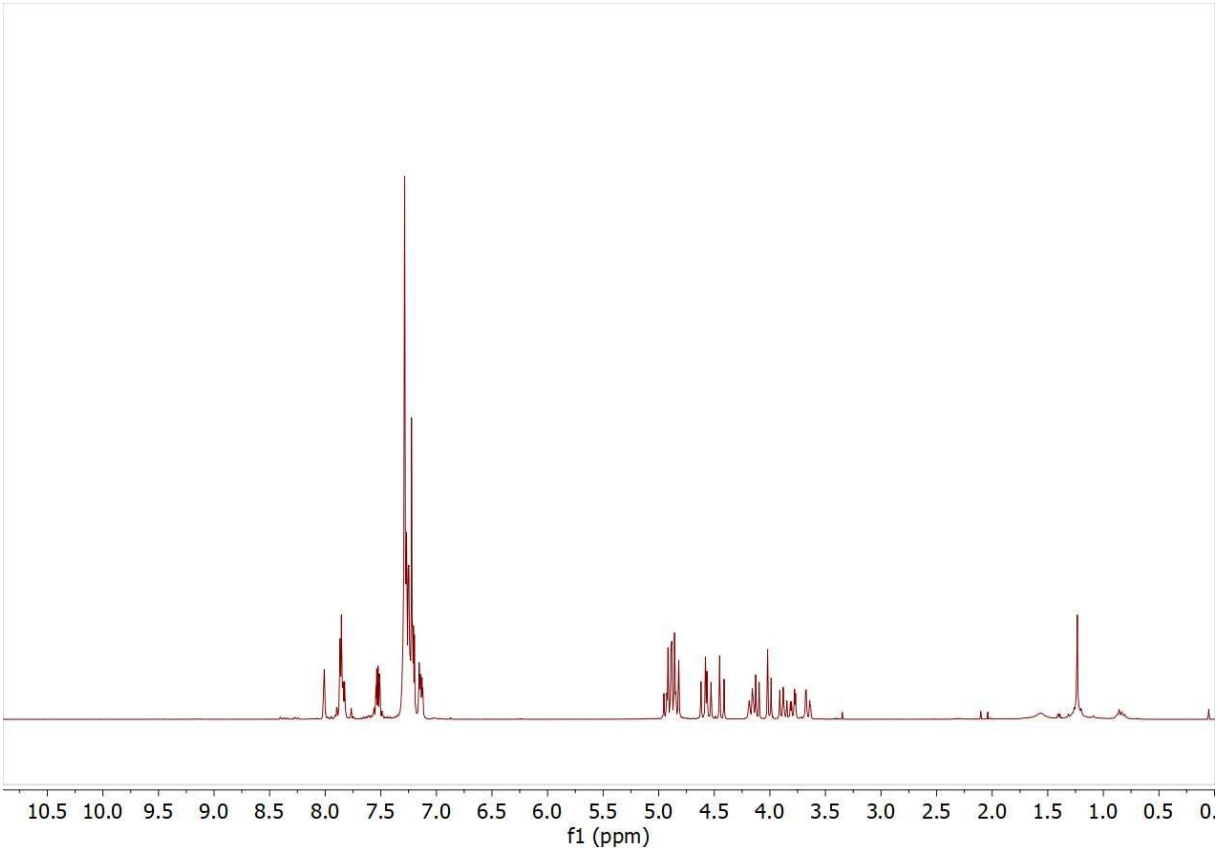
**(1*S*)-2,3,4,6-Tetra-*O*-benzyl-1,5-anhydro-D-glucitol-spiro[1,5]-3-(2-naphthyl)-1,4,2-oxathiazole 13.**

A solution of $Et_3N$ (0.89 mL, 6.42 mmol, 2 eq) in $CH_2Cl_2$ (20 mL) was added dropwise overnight to a solution of **12** (7.40 g, 13.35 mmol, 1eq) and *N*-hydroxy-2-naphthimidoyl chloride (4.12 g, 20.03 mmol, 1.5 eq) in anhydrous $CH_2Cl_2$ (200 mL). The mixture was concentrated *in vacuo* and the crude mixture was suspended in a minimum of toluene. After the solid was discarded, the filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography (toluene/PE 6:4 to eliminate the less polar nitrile oxide dimer then PE/EtOAc 9:1) to afford cycloadduct **13** as a colorless oil (8.21 g, 25.35 mmol, 85%), and the minor *R*-configured analog (<10%). **13**: Colorless oil ; $R_f$ = 0.31 (PE/EtOAc 8:2) ; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 1H, H-Nap), 7.86-7.90 (m, 4H, H-Nap), 7.54-7.58 (m, 2H, H-Nap), 7.23-7.34 (m, 18H, H-Bn), 7.16-7.19 (m, 2H, H-Bn), 4.86-4.99 (m, 5H, H-Bn), 4.64 (d, 1H, *J* = 12.1 Hz, H-Bn), 4.58 (d, 1H, *J* = 10.9 Hz, H-Bn), 4.47 (d, 1H, *J* = 12.1 Hz, H-Bn), 4.19-4.23 (m, 1H, H-5), 4.16 (t, 1H, *J* = 9.3 Hz, H-3), 4.04 (d, 1H, *J* = 9.6 Hz, H-2), 3.92 (t, 1H, *J* = 9.6 Hz, H-4), 3.82 (dd, 1H, *J* = 11.1, 2.9 Hz, H-6a), 3.69 (dd, 1H, *J* = 11.1, 1.7 Hz, H-6b); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.9 (C-5'), 138.5, 138.2, 138.0, 137.5 (4C, Bn), 134.6 (C, Nap), 133.0 (C, Nap), 129.2 (CH, Nap), 128.8 (CH, Nap), 128.7 (CH, Nap), 128.6 (2CH, Bn), 128.5 (2CH, Bn), 128.5 (2CH, Bn), 128.5 (2CH, Bn), 128.4 (2CH, Bn), 128.1 (2CH, Bn), 128.0 (CH, Nap), 128.0 (2CH, Bn), 127.9 (2CH, Bn), 127.9 (CH, Bn), 127.8 (3CH, Bn), 127.8 (CH, Nap), 127.0 (CH, Nap), 125.5 (C, Nap), 124.8 (C-1), 124.0 (CH, Nap) 83.6 (C-3), 79.4 (C-2), 77.4 (C-4), 76.0, 75.5, 75.2 ($3CH_2Ph$) 73.9 (C-5), 73.6 ($CH_2Ph$), 68.0 (C-6); HRMS [ESI+] *m/z* $[M+H]^+$ calcd for $C_{45}H_{42}NO_6S$ 724.2733; found 724.2729.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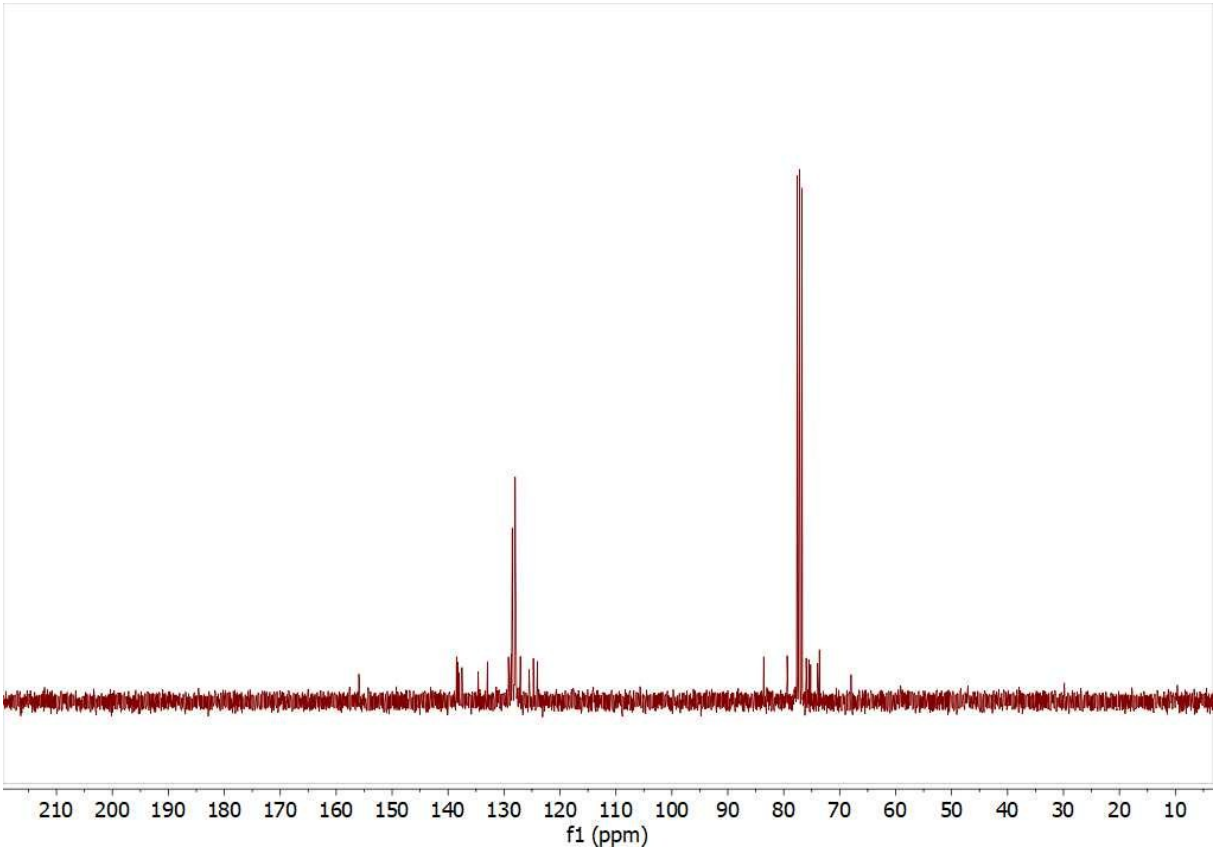
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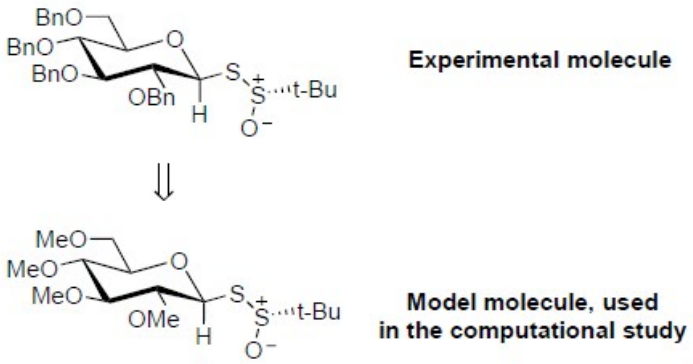
f1 (ppm)

**(1*S*)-1,5-Anhydro-D-glucitol-spiro-[1.5]-3-(2-naphthyl)-1,4,2-oxathiazole 5h.**

To a solution of **13** (2.50 g, 3.45 mmol) in $CH_2Cl_2$ (200 mL) at -60°C was added $BCl_3$ 1M in heptane (20.72 mL, 20.72 mmol, 6 eq). The mixture was stirred at -60°C until TLC showed complete conversion of the starting material (~30 min). MeOH (20 mL) and then $Et_3N$ (20 mL) were added to the mixture which was allowed to warm up to rt and then concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (95:5 $CH_2Cl_2$/MeOH) to afford **5h** as a white powder (815 mg, 2.24 mmol, 65%).

## COMPUTATIONAL DETAILS

Computational studies were conducted using G09 D.01 suite of programs.[1] DFT calculations were conducted using the WB97XD[2] functional. The O, C, H atoms were represented by a 6-311(d,p) basis set.[3] The S atom was represented by RECP from the Stuttgart group and the associated basis set,[4] augmented by a d polarization function (α= 0.503).[5] Full optimization of geometry was performed without any symmetry constraint, including implicit toluene (Tol) as solvent (PCM)[6] using SMD[7] solvation model, followed by analytical computation of the Hessian matrix to identify the nature of the located extrema as minima or transition states. Connection between reactant and product through a given transition state was checked by IRC (Intrinsic Reaction Coordinate) calculation. Gibbs free energies values G (T = 298 K, P = 1 atm) reported in the text are given in kcal $mol^{-1}$. Images were made using CYLview software.[8]




[1] Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2010**.

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[8] "CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, **2009** (http://www.cylview.org)"

**Computed geometries**

**10**

50

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**12**

34

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**tert-butyl sulfenic acid tert-BuSOH**

16

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H 4.51411841 5.39724879 -2.45698705
H 3.12251717 6.39579343 -2.03880562
H 4.55803294 6.39602823 -0.99285143
O 1.17447113 6.13988992 -0.14873148
H 1.52988022 7.02789285 -0.24456062

**TS-b**

50

E: -1021.93170109 ; H: -1021.484047 ; G: -1021.570496

| | | | |
|---|---|---|---|
| C | -2.23489225 | -2.78965072 | 0.38163761 |
| C | -0.71990842 | -2.71449246 | 0.18786167 |
| C | -0.32334198 | -1.27348431 | -0.15881608 |
| C | -2.21976536 | -0.33188249 | 0.85098876 |
| C | -2.75041821 | -1.69390577 | 1.30355118 |
| H | -0.23010298 | -2.99681243 | 1.13004391 |
| H | -2.69886927 | -2.66071986 | -0.60589004 |
| H | -2.61031602 | -0.10981216 | -0.15453055 |
| H | -2.38585716 | -1.88117977 | 2.31857598 |
| H | -0.71120974 | -1.01591710 | -1.15322049 |
| O | -0.79938315 | -0.37967739 | 0.81073603 |
| C | -2.64436995 | 0.79623846 | 1.76287920 |
| H | -2.11698796 | 1.71295044 | 1.46349695 |
| H | -3.72331157 | 0.96129917 | 1.62814921 |
| O | -2.35957929 | 0.46952230 | 3.10003714 |
| O | -4.16441039 | -1.68191835 | 1.27599582 |
| O | -2.55581269 | -4.06321582 | 0.90492563 |
| O | -0.33065871 | -3.56592427 | -0.86151818 |
| S | 1.50161599 | -1.15584003 | -0.22775342 |
| S | 1.71830654 | 0.81477313 | -0.92124928 |
| C | 4.23523984 | 0.84883343 | -1.21071970 |
| C | 4.68247976 | -0.30960294 | -0.36786499 |
| H | 4.37132428 | -1.26813864 | -0.78740831 |
| H | 5.78031895 | -0.30303757 | -0.34693260 |
| H | 4.33704365 | -0.23510283 | 0.66527218 |
| C | 4.15831799 | 0.71356096 | -2.61506973 |
| H | 2.89379534 | 0.70123452 | -2.80046379 |
| H | 4.44560746 | 1.58854085 | -3.19830280 |
| H | 4.49622698 | -0.23513984 | -3.02965087 |
| C | 4.43913732 | 2.21251602 | -0.61379042 |
| H | 5.51412425 | 2.43523064 | -0.62457706 |

H 3.93609118 2.99006177 -1.19246330
H 4.10063335 2.26489041 0.42306631
O 1.60165920 0.79130090 -2.48726159
C -2.77667367 1.46943070 3.99214314
H -3.86091772 1.64459157 3.92745862
H -2.53372284 1.13271561 5.00089081
H -2.26011065 2.42156147 3.80410491
C -4.76482922 -1.96261691 2.52276904
H -5.84445119 -1.88975400 2.38161970
H -4.51781511 -2.97494637 2.86641120
H -4.45207582 -1.24065702 3.28730360
C -3.61432779 -4.71621225 0.23902197
H -3.36456008 -4.91509426 -0.81163871
H -3.77038809 -5.66969154 0.74683892
H -4.54081320 -4.13233115 0.28042587
C 0.24854948 -4.78559557 -0.44827310
H 1.18901874 -4.61891673 0.09444122
H -0.43517792 -5.36285742 0.18264504
H 0.46778178 -5.35259694 -1.35415016

**14**

38

E: -864.745117553 ; H: -864.410152 ; G: -864.482562

C -1.42597642 -2.06823853 0.27066615
C 0.01604657 -1.94279561 0.76350168
C 0.30749472 -0.47605158 1.10219259
C -1.94411549 0.06106553 1.48383705
C -2.40758610 -1.37005151 1.20162667
H 0.12975311 -2.54803956 1.67384772
H -1.47836870 -1.58813564 -0.71644081
H -1.94748015 0.63088252 0.54128266
H -2.44120158 -1.91211960 2.15204313
O -0.62531453 0.02736508 2.01571861
C -2.84031834 0.78999095 2.45859510

H -2.37563719 1.75245749 2.71456965
H -3.79941081 0.99330231 1.95998890
O -3.04020522 0.00862995 3.60921191
O -3.68543462 -1.34223138 0.59679550
O -1.74109245 -3.44117413 0.15932149
O 0.90821088 -2.35988524 -0.23944925
C -3.88609452 0.63514617 4.53860055
H -4.87450708 0.84977973 4.10591409
H -4.01097636 -0.04730665 5.38023633
H -3.45593321 1.57698652 4.90759715
C -4.68921700 -1.99749653 1.34260948
H -5.62419931 -1.88348694 0.79154980
H -4.47118188 -3.06676339 1.45620234
H -4.80331235 -1.55124485 2.33814997
C -2.39381797 -3.79358380 -1.04193644
H -1.75618418 -3.59823122 -1.91433036
H -2.59715214 -4.86462151 -0.99047718
H -3.33956333 -3.25392609 -1.16151385
C 1.42724564 -3.66216547 -0.06429506
H 2.01934291 -3.73548216 0.85803524
H 0.63040205 -4.41204772 -0.04123898
H 0.32222868 0.11658127 0.17804721
S 1.97798252 -0.35129690 1.85157471
S 2.31690894 1.66461459 1.83767093
O 2.98060843 1.99740863 0.31408235
H 3.92183027 1.80264641 0.36958048
H 2.08264220 -3.85740467 -0.91419544

**methyl-propene**

12

E: -157.218282580 ; H: -157.103770 ; G: -157.137028

C -0.24185113 -0.26835533 -0.19854694
C 1.07778127 -0.26536762 -0.02861218
H -0.79748324 0.65416309 -0.33816562

H -0.81031608 -1.19362731 -0.20438619
C 1.88273502 1.00451809 -0.01734309
H 2.64723558 0.98584654 -0.80202946
H 1.25636307 1.88577863 -0.16921880
H 2.41214097 1.11886757 0.93516962
C 1.86498308 -1.53111465 0.16647601
H 2.62975719 -1.63427170 -0.61154915
H 2.39327480 -1.51342348 1.12639352
H 1.22754377 -2.41732232 0.14183641

**TS-c**

50

E: -1021.91987407 ; H: -1021.467573 ; G: -1021.552254

C -2.08707950 -2.03650900 -0.33061702
C -0.90333015 -1.30389354 -0.95400209
C -1.10059315 0.17812850 -0.90925876
C -2.84170186 0.09641980 0.76140078
C -2.43573860 -1.35662653 0.99165361
H -0.01269170 -1.49366466 -0.33630541
H -2.94720565 -1.97390400 -1.01205504
H -3.83351519 0.14458661 0.30923560
H -1.55640327 -1.39258610 1.64660506
H -0.49233967 0.81503946 -1.54641455
O -1.97143247 0.77064215 -0.23505905
C -2.78876721 0.94626651 2.00492348
H -3.26740796 0.37367474 2.81362614
H -1.73693467 1.11989081 2.27194838
O -3.46738103 2.14374283 1.75499877
O -3.54266430 -1.97405641 1.59939524
O -1.72088333 -3.37565941 -0.12192051
O -0.67612976 -1.58761489 -2.30282763
S 0.92987059 0.20023721 1.72254684
S 1.98074206 1.39462909 0.40884408
C 3.35846443 0.27188248 -0.23881853

C 4.25797384 -0.10694643 0.92977480
H 3.72477103 -0.72039727 1.65852544
H 5.11707457 -0.67581513 0.55862095
H 4.64387553 0.77982829 1.44273223
C 2.74767690 -0.94386833 -0.91493214
H 2.00600917 -0.63291735 -1.65605814
H 3.52701661 -1.51511410 -1.43012354
H 2.27263452 -1.59839345 -0.18030821
C 4.10638402 1.13989959 -1.25071653
H 4.94905154 0.57674725 -1.66460907
H 3.45090431 1.43679810 -2.07183557
H 4.50643325 2.04575228 -0.78434228
O 1.13031993 1.64000507 -0.86054355
C -3.27276763 3.09200506 2.77992350
H -2.20917291 3.33279089 2.90465641
H -3.81142921 3.99464014 2.49085332
H -3.66913391 2.73310170 3.74037657
C -3.20973667 -2.80029271 2.70359982
H -4.14364158 -3.23245188 3.06330686
H -2.52523286 -3.60278321 2.41122183
H -2.75220521 -2.21715101 3.51206832
C -2.72298598 -4.31742665 -0.45823700
H -2.95693329 -4.28071201 -1.53024900
H -2.32038764 -5.30188459 -0.21945547
H -3.64250612 -4.15312961 0.11290908
C 0.04293890 -2.78650781 -2.56067921
H 0.85555012 -2.92405990 -1.84080226
H -0.61421304 -3.66004580 -2.52709354
H 0.46325065 -2.68587506 -3.56158980

**10’**

50

E: -1021.98689255 ; H: -1021.532294 ; G: -1021.618140

C -1.72368624 -2.19337486 0.32734692

| | | | |
|---|---|---|---|
| C | -0.26198176 | -2.36392284 | 0.74113000 |
| C | 0.33804994 | -0.99852497 | 1.09016985 |
| C | -1.73430680 | -0.03640083 | 1.61159867 |
| C | -2.49801533 | -1.32881726 | 1.31482807 |
| H | -0.22744594 | -2.99580271 | 1.63789378 |
| H | -1.75086972 | -1.69527180 | -0.65205316 |
| H | -1.66200385 | 0.55671192 | 0.68662150 |
| H | -2.61422606 | -1.87745131 | 2.25594500 |
| H | 0.39065967 | -0.36979090 | 0.18728047 |
| O | -0.43320104 | -0.36271437 | 2.07498100 |
| C | -2.42126746 | 0.82279755 | 2.64766457 |
| H | -1.80924595 | 1.71633169 | 2.83997461 |
| H | -3.38367241 | 1.15247044 | 2.23143805 |
| O | -2.61370844 | 0.08469884 | 3.82718234 |
| O | -3.75637429 | -0.98869999 | 0.77512623 |
| O | -2.35582118 | -3.45301574 | 0.24994216 |
| O | 0.43530411 | -2.95721408 | -0.32568890 |
| S | 2.33007120 | 1.38112008 | 0.18233015 |
| S | 2.81577427 | 0.02572140 | 1.52800145 |
| C | 2.66654720 | 0.78735822 | 3.26551520 |
| C | 4.02377155 | 1.47094236 | 3.44475680 |
| H | 4.16999861 | 2.27909817 | 2.72396217 |
| H | 4.06099838 | 1.90641910 | 4.44727684 |
| H | 4.85441542 | 0.76503378 | 3.35599434 |
| C | 1.52405693 | 1.77706884 | 3.37861265 |
| H | 0.56390488 | 1.27705704 | 3.25919889 |
| H | 1.56634805 | 2.23168776 | 4.37339770 |
| H | 1.60585879 | 2.57356643 | 2.63645306 |
| C | 2.50320409 | -0.38376048 | 4.22917083 |
| H | 2.58374337 | 0.00247456 | 5.24976562 |
| H | 1.52901757 | -0.85877622 | 4.11430884 |
| H | 3.28301852 | -1.14003904 | 4.09868077 |
| O | 1.61182763 | -1.21724875 | 1.60207106 |
| C | -3.31867286 | 0.80812708 | 4.80174345 |

| | | | |
|---|---|---|---|
| H | -4.31580707 | 1.10473530 | 4.44435847 |
| H | -3.43526217 | 0.16012423 | 5.67139698 |
| H | -2.77552385 | 1.71438059 | 5.10691258 |
| C | -4.84109173 | -1.66851987 | 1.36981153 |
| H | -5.74838147 | -1.31165850 | 0.87938241 |
| H | -4.75840152 | -2.75140806 | 1.22796076 |
| H | -4.90879845 | -1.44951152 | 2.44387192 |
| C | -2.49817056 | -3.96219970 | -1.05899954 |
| H | -1.52850189 | -4.08534130 | -1.55216144 |
| H | -2.98038864 | -4.93701346 | -0.96722420 |
| H | -3.13540262 | -3.31145717 | -1.67278641 |
| C | 1.35325271 | -3.96050277 | 0.05599125 |
| H | 2.11472154 | -3.57520245 | 0.74203067 |
| H | 0.83811751 | -4.80851822 | 0.52640015 |
| H | 1.84019723 | -4.30685266 | -0.85661547 |

**TS-d**

50

E: -1021.96570671 ; H: -1021.516484 ; G: -1021.600782

| | | | |
|---|---|---|---|
| C | -1.99010323 | -2.13006763 | 0.30894089 |
| C | -0.55241563 | -2.32847379 | 0.77678657 |
| C | 0.05021815 | -0.97408751 | 1.25684932 |
| C | -2.08036968 | -0.04987500 | 1.72258994 |
| C | -2.80370250 | -1.33821226 | 1.32398173 |
| H | -0.55401721 | -3.00639271 | 1.64158860 |
| H | -1.97624799 | -1.56452539 | -0.63379320 |
| H | -2.00013636 | 0.59940265 | 0.83656801 |
| H | -2.93362751 | -1.94659029 | 2.22546500 |
| H | -0.03003190 | -0.29132898 | 0.24715729 |
| O | -0.78409689 | -0.35517873 | 2.21071598 |
| C | -2.82931484 | 0.72956475 | 2.78040123 |
| H | -2.20219770 | 1.57065519 | 3.11100381 |
| H | -3.74230546 | 1.14082767 | 2.32678460 |

| | | | |
|---|---|---|---|
| O | -3.15179091 | -0.10652962 | 3.86267592 |
| O | -4.05423683 | -0.99295986 | 0.76849894 |
| O | -2.62192605 | -3.37777069 | 0.11729274 |
| O | 0.19109626 | -2.86283639 | -0.27828441 |
| S | 0.88734652 | 0.95030785 | -0.75853040 |
| S | 2.39415912 | 0.54721636 | 0.40478165 |
| C | 2.51617829 | 1.84908147 | 1.77011454 |
| C | 3.33779795 | 2.99915552 | 1.18965334 |
| H | 2.81181544 | 3.49452016 | 0.36967417 |
| H | 3.51311331 | 3.74068737 | 1.97578785 |
| H | 4.31196865 | 2.66268314 | 0.82412257 |
| C | 1.14746615 | 2.31375710 | 2.23386397 |
| H | 0.55233419 | 1.48303565 | 2.61580700 |
| H | 1.28666106 | 3.04657291 | 3.03524395 |
| H | 0.59354248 | 2.80162343 | 1.42871521 |
| C | 3.27481575 | 1.12886608 | 2.88395839 |
| H | 3.47418692 | 1.84205199 | 3.68925470 |
| H | 2.68803946 | 0.30193113 | 3.28542487 |
| H | 4.23867333 | 0.74278831 | 2.53781144 |
| O | 1.28641568 | -0.99813305 | 1.59818692 |
| C | -3.88720668 | 0.56458621 | 4.85150234 |
| H | -4.83632880 | 0.95545957 | 4.45523575 |
| H | -4.10542576 | -0.15322923 | 5.64334066 |
| H | -3.31935923 | 1.40261302 | 5.28103040 |
| C | -5.14487471 | -1.68756375 | 1.33422218 |
| H | -6.04551110 | -1.33321166 | 0.82962704 |
| H | -5.05013476 | -2.76809778 | 1.18075434 |
| H | -5.23413746 | -1.48099769 | 2.40885322 |
| C | -2.70366640 | -3.79103731 | -1.22943552 |
| H | -1.71263859 | -3.88483524 | -1.68504346 |
| H | -3.19211789 | -4.76701416 | -1.23240142 |
| H | -3.31059469 | -3.09467827 | -1.82378414 |
| C | 1.24405616 | -3.71946724 | 0.11900204 |
| H | 1.95657791 | -3.20313244 | 0.76826313 |

H 0.85279778 -4.60581967 0.63564271

H 1.75163007 -4.03812894 -0.79242066

**11**

34

E: -843.160478373 ; H: -842.853726 ; G: -842.918710

C -1.87967713 -2.11559105 0.14623597

C -0.42221583 -2.16374829 0.58605109

C 0.14381549 -0.80623972 1.02760774

C -2.11078907 0.07842084 1.31666883

C -2.68586946 -1.32656213 1.16248537

H -0.38631317 -2.79742305 1.48693511

H -1.95104870 -1.61675785 -0.83009971

H -2.26750551 0.62201705 0.37786727

H -2.64100135 -1.83637708 2.13133732

O -0.69791476 0.07773299 1.58877543

C -2.78351843 0.85661322 2.42506880

H -2.26394914 1.81622050 2.55505326

H -3.81842744 1.06416462 2.11878552

O -2.75465337 0.10610652 3.61089625

O -4.01848483 -1.17853273 0.73530185

O -2.40623841 -3.41867460 0.07376017

O 0.34713931 -2.71772367 -0.43933865

C -3.38554117 0.76802953 4.67766287

H -4.44653849 0.96149546 4.46234267

H -3.31536025 0.12073201 5.55255010

H -2.89546240 1.72503573 4.90524599

C -4.94574096 -1.96715226 1.45391227

H -5.92920010 -1.76713485 1.02607889

H -4.72235695 -3.03413451 1.35342810

H -4.95643797 -1.69653951 2.51779838

C -2.49750591 -3.94937901 -1.23224416

H -1.51391031 -4.02797210 -1.70600884

H -2.93042043 -4.94634753 -1.13678987
H -3.15676427 -3.33865213 -1.86300207
C 1.43273577 -3.51114632 0.00071275
H 2.13136621 -2.93467290 0.61300467
H 1.07496844 -4.38199984 0.56674293
O 1.31255596 -0.55185141 0.96982389
H 1.94883536 -3.86025983 -0.89415837

***tert*-Butyl thiosulfenic acid (*tert*-BuSSH)**

16

E: -178.867834454 ; H: -178.725424 ; G: -178.768935

S 2.26054604 4.99610457 0.71368171
C 3.26851712 4.55787641 -0.80275231
C 4.44479347 3.77349788 -0.21620879
H 4.10956238 2.87307378 0.30596742
H 5.10749159 3.46103526 -1.02920478
H 5.03246329 4.38141854 0.47740190
C 2.45694252 3.68423225 -1.75264941
H 1.57856631 4.21370746 -2.12960843
H 3.07428955 3.40861090 -2.61455502
H 2.12346944 2.76664323 -1.26213198
C 3.75744872 5.82177833 -1.50134837
H 4.39282364 5.54901205 -2.35078321
H 2.92308298 6.41008742 -1.89205711
H 4.34319920 6.45161694 -0.82685574
S 0.61454744 6.03657847 -0.01215124
H 1.15214333 7.28061089 -0.02839948

**$H_2O$**

3

E: -76.4275279860 ; H: -76.402124 ; G: -76.424194

O -0.67628947 0.17526990 0.00000000
H 0.28093641 0.22261068 0.00000000
H -0.95123014 1.09343607 0.00000000

***tert*-Butyl-2-methyl-propane-2-sulfinothioate**

29

E: -411.295242946 ; H: -411.027881 ; G: -411.084653

| | | | |
|---|---|---|---|
| S | 1.68042553 | 4.01371676 | 0.47343839 |
| C | 3.19635175 | 4.42343002 | -0.56877184 |
| C | 4.31162060 | 3.46274564 | -0.17352232 |
| H | 3.98273215 | 2.41897364 | -0.20875537 |
| H | 5.13826167 | 3.56874879 | -0.88245790 |
| H | 4.70035864 | 3.67456965 | 0.82462900 |
| C | 2.71850998 | 4.15152531 | -1.99695723 |
| H | 1.88136427 | 4.79923358 | -2.26542055 |
| H | 3.54040558 | 4.35366882 | -2.68988347 |
| H | 2.41400758 | 3.10955362 | -2.13537462 |
| C | 3.58028083 | 5.88130103 | -0.38984806 |
| H | 4.38433501 | 6.12961743 | -1.08960317 |
| H | 2.73138540 | 6.53481697 | -0.60197146 |
| H | 3.93550697 | 6.07867078 | 0.62302602 |
| O | 0.67182037 | 5.09584450 | 0.15459531 |
| S | 2.49008574 | 4.31916945 | 2.48222847 |
| C | 1.49592428 | 5.72936509 | 3.21960848 |
| C | 1.72046771 | 7.02945048 | 2.45148996 |
| C | 0.01238739 | 5.37166359 | 3.28930103 |
| C | 2.07782411 | 5.84033704 | 4.63244280 |
| H | 1.33251980 | 6.95360998 | 1.43597501 |
| H | 1.19022312 | 7.84002658 | 2.96418935 |
| H | 2.78096835 | 7.28947189 | 2.41402992 |
| H | -0.14281504 | 4.43944681 | 3.83770839 |
| H | -0.52111162 | 6.17120878 | 3.81562141 |
| H | -0.41984088 | 5.27441723 | 2.29309772 |
| H | 1.55900470 | 6.64828656 | 5.15893247 |
| H | 1.93432286 | 4.91928022 | 5.20354094 |
| H | 3.14430044 | 6.08062740 | 4.61604131 |

**TS-e**

66

E: -1265.83123548 ; H: -1265.234144 ; G: -1265.338414

| | | | |
|---|---|---|---|
| C | 1.14995157 | 0.11866088 | 0.57475386 |
| C | 0.37657468 | -0.35476864 | -0.65344325 |
| C | 0.95356689 | 0.23651636 | -1.95065215 |
| C | 3.09894361 | 0.55153484 | -0.91890870 |
| C | 2.64085540 | -0.09116199 | 0.38752646 |
| H | 0.50187858 | -1.44148937 | -0.73224262 |
| H | 0.97231470 | 1.19211928 | 0.72030346 |
| H | 2.99754049 | 1.63895981 | -0.83520389 |
| H | 2.85693419 | -1.16405034 | 0.34810594 |
| H | 0.11998666 | 1.39947759 | -3.06452278 |
| O | 2.31577138 | 0.09770038 | -2.03019972 |
| C | 4.54957268 | 0.26665032 | -1.23588087 |
| H | 4.75705378 | 0.61111844 | -2.25854579 |
| H | 5.17792109 | 0.84641123 | -0.54420915 |
| O | 4.81049296 | -1.10628809 | -1.10472032 |
| O | 3.36140255 | 0.52286524 | 1.43787947 |
| O | 0.72672404 | -0.59390478 | 1.71781857 |
| O | -0.97106315 | -0.01269150 | -0.48022809 |
| S | 0.13890992 | -0.22499770 | -3.50566564 |
| O | 0.54154716 | 1.69889220 | -2.00276214 |
| C | 6.13020456 | -1.43358050 | -1.45540785 |
| H | 6.85939241 | -0.88823273 | -0.83803996 |
| H | 6.25970762 | -2.50356748 | -1.28860212 |
| H | 6.33329903 | -1.21330908 | -2.51278726 |
| C | 3.85417782 | -0.37890482 | 2.40854921 |
| H | 4.37904225 | 0.21618324 | 3.15788316 |
| H | 3.03864093 | -0.92721183 | 2.89039908 |
| H | 4.55938559 | -1.09154287 | 1.96285445 |
| C | -0.14433268 | 0.12619339 | 2.56242347 |
| H | -1.06623126 | 0.41156213 | 2.04511205 |
| H | -0.39222056 | -0.53222104 | 3.39694668 |

| | | | |
|---|---|---|---|
| H | 0.34187372 | 1.02765363 | 2.96034633 |
| C | -1.88701073 | -1.07524567 | -0.64605058 |
| H | -1.81551641 | -1.51232137 | -1.64692767 |
| H | -1.73126334 | -1.85456798 | 0.11161828 |
| H | -2.88407053 | -0.65102779 | -0.51716380 |
| H | 1.23581881 | 2.41482845 | -1.87289782 |
| S | 1.54954261 | 3.95084782 | 0.14292838 |
| C | 3.02794000 | 4.79361633 | 0.94442463 |
| C | 2.72353501 | 4.92035615 | 2.43337799 |
| H | 2.46142784 | 3.95437687 | 2.87457810 |
| H | 3.62280723 | 5.28233022 | 2.94003515 |
| H | 1.91798875 | 5.62899066 | 2.63309053 |
| C | 4.16710035 | 3.80093430 | 0.70426492 |
| H | 4.38307997 | 3.69928666 | -0.36091687 |
| H | 5.06376145 | 4.18629072 | 1.19784973 |
| H | 3.94714912 | 2.81310025 | 1.11961894 |
| C | 3.31500793 | 6.12937853 | 0.27385951 |
| H | 4.27566433 | 6.50511219 | 0.63904417 |
| H | 3.38591592 | 6.01564977 | -0.81012191 |
| H | 2.55565413 | 6.88008151 | 0.50248620 |
| O | 1.95407487 | 3.76692987 | -1.33200969 |
| S | 0.13171613 | 5.50289012 | 0.30602002 |
| C | -1.49115526 | 4.58778340 | 0.02710221 |
| C | -1.70783932 | 4.38445629 | -1.47015962 |
| C | -1.53697380 | 3.25654238 | 0.77115160 |
| C | -2.52425111 | 5.56309736 | 0.59693470 |
| H | -0.95225166 | 3.72550027 | -1.89862531 |
| H | -2.68420265 | 3.91516794 | -1.63054906 |
| H | -1.68897167 | 5.33405406 | -2.00948004 |
| H | -1.26433589 | 3.36851939 | 1.82353241 |
| H | -2.56059179 | 2.87086752 | 0.72433552 |
| H | -0.90348604 | 2.49990357 | 0.30568583 |
| H | -3.52508393 | 5.16234732 | 0.40943911 |
| H | -2.40509195 | 5.69232910 | 1.67557179 |

H -2.46611224 6.54493017 0.11795483

**$H_2S$**

3

E: -11.4074105353 ; H: -11.388566 ; G: -11.412585

S -2.67249646 -1.32174719 0.00000000

H -1.33661789 -1.12688571 0.00000000

H -2.93479542 0.00275452 0.00000000

**TS-f**

63

E: -1189.36751830 ; H: -1188.795816 ; G: -1188.896927

C 0.88516367 0.42030726 0.42656615

C 0.37845583 0.27502316 -1.00719974

C 1.34232334 0.99332929 -1.99571423

C 3.18504644 0.73205855 -0.50872058

C 2.34519842 0.01449205 0.54659082

H 0.36948197 -0.79173892 -1.25743686

H 0.79185498 1.47351659 0.72169786

H 3.17769701 1.80856884 -0.29386022

H 2.43178540 -1.06507015 0.38104489

O 2.64931961 0.50234140 -1.80689368

C 4.62696215 0.27622726 -0.51096891

H 5.14047667 0.74282181 -1.36404072

H 5.10622923 0.62692846 0.41435104

O 4.69299423 -1.12525151 -0.59856928

O 2.84841750 0.36493713 1.82038249

O 0.12132268 -0.39918263 1.29204646

O -0.91452167 0.81634994 -1.07179509

S 0.90475336 0.79429910 -3.72979184

C 6.01190525 -1.59629148 -0.66839141

H 6.59474643 -1.31048928 0.22040260

H 5.96889012 -2.68509664 -0.72466725

H 6.53020797 -1.21697264 -1.56105025

| | | | |
|---|---|---|---|
| C | 2.98547675 | -0.72541707 | 2.70514458 |
| H | 3.35636583 | -0.32345703 | 3.65012132 |
| H | 2.02564969 | -1.22356449 | 2.87791550 |
| H | 3.70965773 | -1.45823454 | 2.32444051 |
| C | -0.87023367 | 0.28695363 | 2.02193652 |
| H | -1.59552990 | 0.77410189 | 1.36143347 |
| H | -1.38695534 | -0.45544339 | 2.63347857 |
| H | -0.42713583 | 1.04056150 | 2.68751444 |
| C | -1.88236192 | -0.01571742 | -1.66913221 |
| H | -1.62474993 | -0.25592220 | -2.70634769 |
| H | -2.01433625 | -0.94503583 | -1.09926126 |
| H | -2.82307053 | 0.53860376 | -1.66260922 |
| S | 1.01430660 | 3.35620327 | -3.25115230 |
| C | 1.65997206 | 3.64985148 | -5.08878401 |
| C | 1.51629704 | 5.16027435 | -5.22644006 |
| H | 2.01730701 | 5.69457026 | -4.41520704 |
| H | 1.99079371 | 5.46489672 | -6.16516541 |
| H | 0.46990904 | 5.46954582 | -5.26284072 |
| C | 3.11753477 | 3.22657553 | -5.00788282 |
| H | 3.20942902 | 2.15571759 | -4.81392610 |
| H | 3.60388480 | 3.44369133 | -5.96405531 |
| H | 3.65623926 | 3.77283924 | -4.22762779 |
| C | 0.89183931 | 2.89187677 | -6.14094519 |
| H | 1.36911236 | 3.06663794 | -7.11151927 |
| H | 0.92148193 | 1.81331987 | -5.96824149 |
| H | -0.14833990 | 3.21590421 | -6.20872776 |
| O | 1.29019378 | 2.36409058 | -1.74500264 |
| S | -1.03433152 | 3.52822680 | -3.45897967 |
| C | -1.47027273 | 4.81812736 | -2.17335139 |
| C | -1.12144771 | 4.31210496 | -0.77624195 |
| C | -0.79703977 | 6.15354168 | -2.46787380 |
| C | -2.98884750 | 4.92951967 | -2.34114041 |
| H | -0.04212473 | 4.25619716 | -0.62628436 |
| H | -1.53337674 | 5.00602435 | -0.03523094 |

| | | | |
|---|---|---|---|
| H | -1.52757817 | 3.31424595 | -0.60200860 |
| H | -1.06552665 | 6.53221338 | -3.45722277 |
| H | -1.11956003 | 6.88888315 | -1.72322813 |
| H | 0.29047273 | 6.07347930 | -2.40559929 |
| H | -3.36684478 | 5.66823518 | -1.62811331 |
| H | -3.26689968 | 5.26148701 | -3.34570457 |
| H | -3.48887073 | 3.97918272 | -2.13521972 |

**_tert_-Butyl-2-methylpropane-2-sulfinodithioate**

29

E: -346.299001374 ; H: -346.032660 ; G: -346.090169

| | | | |
|---|---|---|---|
| S | 1.63633598 | 3.88963578 | 0.39961660 |
| C | 3.17412231 | 4.44158471 | -0.59697435 |
| C | 4.31795617 | 3.55109037 | -0.12381788 |
| H | 4.08886833 | 2.48957752 | -0.25245125 |
| H | 5.20272968 | 3.77658472 | -0.72665992 |
| H | 4.57326715 | 3.73475342 | 0.92139816 |
| C | 2.81033219 | 4.13306543 | -2.04735290 |
| H | 1.99800987 | 4.76785922 | -2.40380530 |
| H | 3.69211508 | 4.32367464 | -2.66640346 |
| H | 2.52491087 | 3.08631343 | -2.18535390 |
| C | 3.47383489 | 5.91361569 | -0.39683214 |
| H | 4.27603997 | 6.20390819 | -1.08225948 |
| H | 2.60120460 | 6.53184093 | -0.61986532 |
| H | 3.81076383 | 6.11627989 | 0.62072003 |
| S | 2.24328743 | 4.18578972 | 2.44966058 |
| C | 1.47483427 | 5.71786577 | 3.22414576 |
| C | 1.77499699 | 6.99162534 | 2.44378623 |
| C | -0.02440736 | 5.51154954 | 3.42602703 |
| C | 2.18831392 | 5.74817476 | 4.58129443 |

| | | | |
|---|---|---|---|
| H | 1.33193429 | 6.96929238 | 1.44796975 |
| H | 1.34306294 | 7.84068677 | 2.98460529 |
| H | 2.84988866 | 7.16205301 | 2.35680889 |
| H | -0.22212809 | 4.60904196 | 4.00892265 |
| H | -0.43058820 | 6.36961641 | 3.97289393 |
| H | -0.55076687 | 5.43411754 | 2.47490842 |
| H | 1.77773930 | 6.57949429 | 5.16345661 |
| H | 2.02283612 | 4.83006395 | 5.15187905 |
| H | 3.26407605 | 5.90856552 | 4.47368834 |
| S | 0.08147852 | 5.01742447 | -0.18114337 |

## PHARMACOLOGICAL EVALUATIONS

Table S1: Clinical characteristics of the human liver donors

| Liver ID | Age | Sex | Reason for surgery |
|---|---|---|---|
| FT332 | 39 | F | Metastasis from melanoma cancer |
| FT334 | 46 | F | Metastasis from breast tumor |
| FT351 | 75 | M | Metastasis from urothelial carcinoma |

***Rat and human hepatocytes isolation***

Male Wistar rats (160-220 g) were anaesthetized with sodium pentobarbital administered intraperitoneally. Hepatocytes were isolated from rats fed *ad lib* using a two-step perfusion technique (Seglen P.O., 1976). Cell viability, assessed by Trypan Blue exclusion, was consistently greater than 75%. Cells were seeded on collagen-coated 12-well plates in basal medium (William's E containing 11.1 mM glucose, 100 U/mL penicillin, 100 µg/mL streptomycin) supplemented with 6% FCS at a density of 830000 cells/well. After 4 h initial plating, the latter was replaced with a basal medium supplemented with 100 nM dexamethasone (in order to remove dead cells) and cells were cultured for 24 h.

Human hepatocytes were isolated from pieces of liver resection after surgery for medical purpose. Use of this human material was approved by our local and national ethics committee and legal instances (MESR DC-2008-531). List and information on livers used in this study are shown in supplementary data (Table S1). Process for human hepatocyte isolation has been previously described[49-50] and adapted from the two-step perfusion method described for rat hepatocyte isolation.[51] Hepatocytes were seeded at $1.10^6$ hepatocytes/well on collagen type I 12 well plates (BectonDickinson, Pont De Claix, France) in platting medium consisting in short term culture medium[49-50] supplemented with 2% heat inactivate fetal bovine serum (Lonza, Levallois Perret, France). After overnight attachment, platting medium and unattached cells were eliminated and medium changed to glycogen loading medium.

***Pharmacological tests in vitro:***

***1) Rat hepatocyte primary culture***

Hepatocytes were loaded in glycogen by incubation 20 h in loading medium: William's E containing 11.1 mM glucose, 100 U/mL penicillin, 100 µg/mL streptomycin supplemented with 100 nM dexamethasone, 13.9 mM glucose and 100 nM insulin. After loading period, cells were washed three times with PBS and incubated 3 h in buffer (Andersen B. et al., 1999) [117.6 mM NaCl / 5.4 mM KCl / 0.82 mM $MgSO_4$ / 1.5 mM $KH_2PO_4$ / 20.0 mM Hepes / 9.0 mM $NaHCO_3$

/ 0.1% (w/v) BSA / 2.25 mM $CaCl_2$ (pH 7.4)] without or with GP inhibitor at different concentrations in the presence of 100 nM glucagon (stimulating conditions). After 3 h incubation, supernatants were collected and frozen at -20°C until glucose quantification.

***2) Human hepatocyte primary culture***

Hepatocytes were loaded in glycogen by incubation 20 h in loading medium: Ham's F12/William's E medium (1:1) supplemented with bovin serum albumin 15 µg/mL, 66.5 µM ethanolamine, 5 mg/L transferrin, 7.2 µM linoleic acid, 100 nM insulin, 0.1 µM dexamethasone, 4.5 g/L glucose, 0.4 mM sodium pyruvate, 50 mg/L ascorbic acid, 100 U/mL penicillin, 100 µg/mL streptomycin (all products from Sigma-Aldrich, St Quentin Fallavier, France). After loading period, cells were washed three times with PBS and incubated 3 h in DMEM without glucose (Sigma) in the presence of 100 nM glucagon (Novo Nordisk, Puteaux, France) with or without GP inhibitor at different concentrations. After 3 h incubation, supernatants were collected and frozen at -20°C until glucose quantification and plates were washed three times with PBS, dried and frozen at -20°C before intracellular glycogen content measurement.

***Glucose and glycogen quantifications***

Glucose release in nmol/well was measured by using a glucose oxidase kit (Megazyme, Wicklow, Ireland). Results were presented in percentage from glucagon stimulation values. Glucose release quantification was performed in 96 well plates. 10 µL of supernatant was incubated with 150 µL of glucose oxidase solution, 20 min at 40°C. Absorbance at 492 nm was measured and glucose concentration in sample was calculated using a linear regression from standard curve.

Glycogen content was determined as previously described[52] with minor modification and measured as glucose released in nmol/well. Glycogen was hydrolyzed to glucose by amyloglucosidase (exo-α-1,4-glucosidase) digestion. Amyloglucosidase was diluted at 0.75 UI/mL in 0.02 N sodium acetate buffer pH 4.8. 1 mL/well was added and incubated 2 h at 40°C under agitation. After 2 h, glucose released from glycogen hydrolysis was quantified using the same protocol as described above.

***Inhibitory Concentration 50% ($IC_{50}$) calculation***

Glucose in supernatant and intracellular glycogen content were expressed in percentage of glucagon stimulation values for $IC_{50}$ calculation. $IC_{50}$ were determined using GraphPad Prism5 (GraphPad Software, La Jolla, CA, USA). Values are means of three independent experiments.

The compounds displaying no effect up to 1 mM *in vitro* displayed $IC_{50}$ values above 100 µM and were not considered for pharmacological studies *in vivo*.

***Glucagon challenge in vivo***

***Acute test:*** Experiments were performed in male 10-13 week-old Zucker *fa/fa* rats (Harlan Laboratories, Gannat, France) housed in groups of 3 on a 12h/12h light-dark schedule cycle. They were allowed free access to both standard food and fresh water. Institutional guidelines for animal care and use were followed.

After 5 days of stabilization, in each experiment, 6 male Zucker *fa/fa* rats were used. Three rats received a dose of tested compound and three others received the vehicle by oral administration. Twenty minutes later, the glucagon challenge was realized by intra-scapular subcutaneous injection of glucagon (200 µg/kg). Blood samples were collected from the tail vein before and after glucagon administration at 0, 10, 20, 45 min. After centrifugation at 4°C, plasma glucose samples were measured immediately by the glucose oxidase method.[53]

Finally, either vehicle (4-5 mL/kg, *per os*) or GP inhibitors (7.5-90 mg/kg, *per os*) were orally administrated 65 minutes prior to the final blood glucose measurement to assess their ability to reduce the glucagon induced hyperglycemia.[54]

***Subchronic tests:*** After 5 days of stabilization, 6 male Zucker *fa/fa* rats were treated; three of them received a dose of GP inhibitor and three others received the vehicle by oral administration during 4 days. After the fourth administration, animals were submitted to a glucagon challenge test as previously described.

***Data analysis***

All data were expressed as means ± SEM. Multiple group comparisons were performed by analysis of variance (ANOVA) followed by Fisher's protected Least Significant Difference test at * $p<0.05$, ** $p<0.01$ or *** $p<0.001$ using the Stat Graphics software.

For *in vivo* experiments, glycaemia time curves were expressed in mmol/L. Plasma glucose were expressed as variations (delta), meaning that the basal value of glycaemia was subtracted for each individual value and for each rat. The areas under the curve (AUC) for 60 min were established.