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SYNTHESES OF 1-DEOXY-3-*S*-(1-THIO-α-D-GLUCOPYRANOSYL)-MANNOJIRIMYCIN AND 1-DEOXY-3-*O*-(5-THIO-α-D-GLUCOPYRANOSYL)-MANNOJIRIMYCIN AS POTENTIAL INHIBITORS OF *endo*-α-D-MANNOSIDASE

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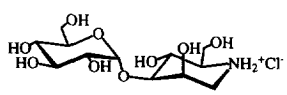
Abstract: 1-Deoxy-3-*S*-(1-thio-α-D-glucopyranosyl)-mannojirimycin and 1-deoxy-3-*O*-(5-thio-α-D-glucopyranosyl) mannojirimycin were chemically synthesized as potential inhibitors of *endo*-α-D-mannosidase.

Glycosidase inhibitors are useful tools in the study of *N*-linked glycoprotein biosynthesis.[1] The aza-disaccharide 1-deoxy-3-*O*-(α-D-glucopyranosyl)-mannojirimycin (**1**) is an effective inhibitor of *endo*-α-D-mannosidase, the enzyme responsible for the cleavage of α-D-Glc-(1→3)-D-man from the $GlcMan_9GlcNAc_2$ oligosaccharide present in immature *N*-linked glycoproteins.[2] However, this disaccharide can be cleaved by intracellular glucosidases.[3]

1-Thioglycosides and 5-thioglycosides have been shown to exhibit excellent glycosidase inhibitory activities, both as monosaccharides and as disaccharides.[4,5] The replacement of the glucosyl unit in disaccharide **1** with 1-thioglucose or 5-thioglucose might therefore result in more metabolically-stable inhibitors for *endo*-α-mannosidase which could be resistant to cleavage by cellular glucosidases.[6]

We report here the syntheses of 1-deoxy-3-*S*-(1-thio-α-D-glucopyranosyl)-mannojirimycin (**2**) and 1-deoxy-3-*O*-(5-thio-α-D-glucopyranosyl)-mannojirimycin (**3**), the thio analogs of **1**.



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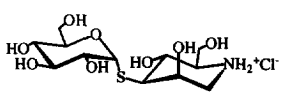

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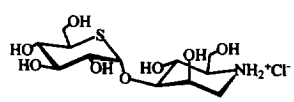
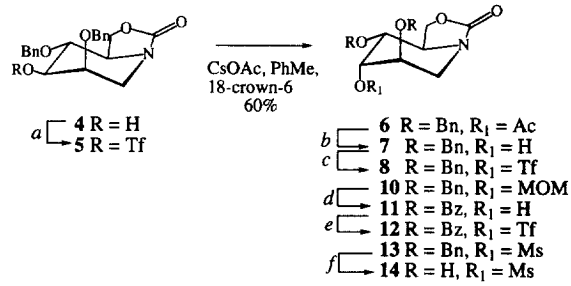


3

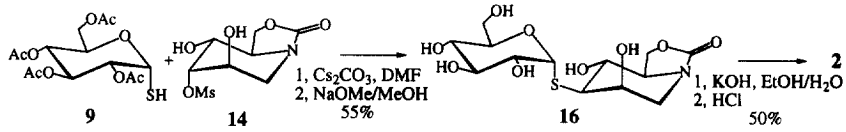
0960-894X/98/$19.00
PII: S0960-894X(98)00198-X

Synthesis of 1-deoxy-3-*S*-(1-thio-α-D-glucopyranosyl)-mannojirimycin

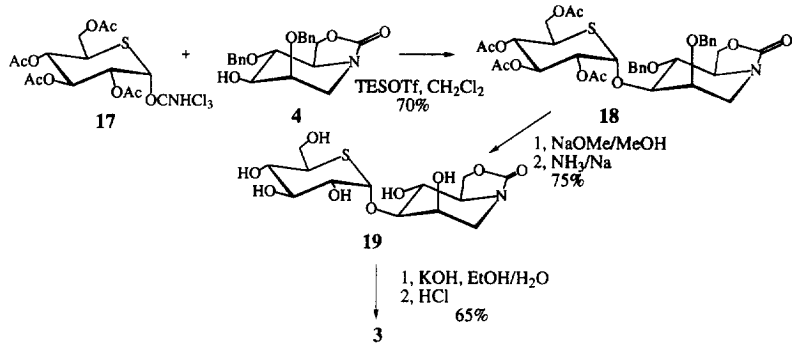
The 1-deoxy mannojirimycin derivative **4**[7] was selected as the starting material and was converted to the triflate **5** (80% yield), which was then treated with CsOAc to afford acetate **6** in 60% yield. Subsequent deacetylation and triflation provided altrojirimycin derivative **8** in 75% yield (two steps).



Scheme 1: *a*: $(Tf)_2O$, Pyridine/CH_2Cl_2, 80%; *b*: NaOMe/MeOH, 100%; *c*: $(Tf)_2O$, Pyridine/CH_2Cl_2, 75%; **7**→**10**: $CH_2(OMe)_2$, P_2O_5, 78%; *d*: 1, Pd/C, H_2, 2, BzCl/pyridine, 3, Me_3SiBr, 50%; *e*: $(Tf)_2O$, Pyridine; **7**→**13**: MsCl/pyridine, 85%; *f*: Pd/C, H_2, 75%.



Scheme 2



Scheme 3

Our initial attempt to prepare **2** involved the reaction of triflate **8** with the sodium salt of 2,3,4,6-tetra-*O*-acetyl 1-thio α-D-glucopyranose (**9**).[8] However, none of the desired disaccharide was isolated under a variety of reaction conditions; only the elimination product was observed. The reaction of triflate **8** with KSAc or CsSAc gave similar results. Presumably the two benzyl ethers at C-2 and C-4 in **8** hindered S_N2 attack at a hindered C-3 position.

Alcohol **7** was converted to the methoxymethyl (MOM) ether derivative **10** in 78% yield by reaction with $CH_2(OMe)_2$ in the presence of P_2O_5. Hydrogenation, acetylation and removal of the MOM group afforded alcohol **11** in 50% yield (three steps). Triflation of **11** gave **12**[9] which failed to couple with per-*O*-acetyl-1-thio-α-D-glucose (**9**).

Alcohol **5** was then converted to the less-labile mesylate **13** (85%). Hydrogenation of the benzyl ethers (AcOH, Pd/C, H_2, 50 °C, 2 days) afforded **14** in 75% yield. The coupling reaction of the unprotected mesylate **14** with **9** in DMF in the presence of Cs_2CO_3 afforded the desired thio-linked disaccharide **15.** Deacetylation of crude **15** provided the disaccharide **16** in 55% yield (two steps). The final disaccharide **2** was obtained in 50% yield by opening of the cyclic carbamate.

Synthesis of 1-deoxy-3-O-(5-thio-α-D-glucopyranosyl)-mannojirimycin

Using the method of Schmidt,[10] 5-thioglucopyranosyl trichloroacetimidate (**17**)[11] was glycosylated with **4**. The glycosylation reaction was catalyzed with 0.3 equivalents of triethylsilyl triflate and afforded exclusively the α-disaccharide **18** in 70% yield. The ^{1}H NMR spectrum of **18** contained a signal at 5.06 ppm (d, 1H, $J_{1,2}$=2.7 Hz) confirming the α-configuration. Signals at 2.03, 1.97, 1.93, and 1.72 ppm (^{1}H NMR), in addition to those at 170.4, 170.0, 169.6, and 169.3 ppm in the ^{13}C NMR spectrum, confirmed that the structure contained a 1,2-*cis* glycoside and not a 1,2-orthoester.[10] Deacetylation of **18** with NaOMe in methanol, followed by debenzylation with NH_3/Na, provided disaccharide **19** in 75% yield (two steps). The cyclic carbamate of **19** was readily saponified with ethanol/H_2O/KOH, then reacted with hydrochloric acid, to give the final 5-thio disaccharide **3** in 65% yield.

This is the first reported synthesis of an aza-disaccharide containing a 5-thiosugar or 1-thiosugar. Biological tests of these disaccharides are in progress.

Acknowledgment

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The spectral data of some selected new compounds:

2, ^{1}H NMR (CD_3OD, 300 MHz): δ 5.43 (d, 1H, $J_{1',2'}$ = 5.7 Hz, H-1), 4.27 (dd, 1H, H-3), 4.25 (m, 1H, H-2); ^{13}C NMR(CD_3OD, 300 MHz): δ 86.73 (C-1'), 75.74, 74.63, 73.18, 71.77, 67.86, 65.29 (C-2, C-4, C-5, C-2', C-3' and C-4'), 62.71, 60.40 (C-6 and C-6'), 59.49 (C-5), 46.06 (C-5'), 39.61 (C-2); ESMS: *m/z* 364 $[M+Na]^+$.

3, ^{1}H NMR (CD_3OD, 300 MHz): δ 5.09 (d, 1H, $J_{1',2'}$ = 1.8 Hz, H-1'), 4.40 (d, 1H, J < 1 Hz, H-2), 4.05 (t, 1H, J = 10.0 Hz, H-4), 3.16 (m, 2H, H-5 and H-1b), 2.90 (d, 1H, $J_{1a,1b}$ = 14.0 Hz, H-1a), 2.68 (m, 1H, H-5'); ^{13}C NMR (CD_3OD, 300 MHz): δ 85.416 (C-1'), 82.02, 77.76, 76.02, 75.81, 67.39, 67.13 (C-3, C-4, C-5, C-2', C-3' and C-4'), 62.54, 62.40 (C-6 and C-6'), 59.59 (C-5), 45.35 (C-1); ESMS: *m/z* 364 $[M+Na]^+$.

5: ^{1}H NMR (CD_3OD, 300 MHz): δ 4.82 (dd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{2,3}$ = 2.6 Hz, H-3), 4.20 (dd, 1H, $J_{1a,1b}$ = 14.7 Hz, H-1a), 4.16 (dd, 1H, H-4), 4.03 (m, 1H, H-2), 4.01 (t, 1H, J = 9.4, H-6), 3.71 (dd, 1H, $J_{6a,6b}$ = 9.3 Hz, $J_{5,6a}$ = 3.3 Hz, H-6a),3.57 (m, 1H, H-5), 2.88 (d, 1H, $J_{1a,1b}$ = 14.8 Hz, H-1a).

6: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.58 (t, 1H, J = 2.7 Hz, H-3), 4.34 (dd, 1H, H-6), 4.07 (d, 1H, J = 14.0 Hz, H-1a), 4.05 (dd, 1H, $J_{4,5}$ = 9.0 Hz, $J_{3,4}$ = 3.3 Hz, H-4), 3.83 (m, 1H, H-5), 3.76 (m, 1H, H-6a), 3.69 (m, 1H, H-2), 3.14 (dd, 1H, $J_{1a,1b}$ = 14.0 Hz, $J_{1a,2}$ = 1.7 Hz, H-1), 2.10 (s, 3H, OAc); ^{13}C NMR (CD_3OD, 300 MHz): δ 73.34, 72.98, 66.47 (C-2, C-3 and C-4), 72.98, 71.29 (two CH_2Ph), 65.79 (C-6), 53.04 (C-5), 38.95 (C-1), 20.87 (OAc).

7: ^{1}H NMR (CD_3OD, 360 MHz): δ 4.30 (t, 1H, J = 9.7 Hz, H-6). 4.15 (t, 1H, J = 3.7 Hz, H-3), 3.96 (dd, 1H, $J_{4,5}$ = 8.9 Hz, $J_{3,4}$ = 3.6 Hz, H-4), 3.91 (dd, 1H, $J_{1a,1b}$ = 14.4 Hz, $J_{1a,2}$ = 1.3 Hz, Ha-1), 3.79 (m, 1H, H-5), 3.69 (m, 1H, H-2), 3.65 (dd, 1H, $J_{6a,6b}$ = 9.7 Hz, $J_{6a,5}$ = 2.5 Hz, H-6a), 3.17 (dd, 1H, $J_{1a,1b}$ = 14.4 Hz, $J_{1b,2}$ = 1.5 Hz, H-1b); ^{13}C NMR (CD_3OD, 300 MHz): δ 75.66, 74.45, 66.43 (C-3, C-4 and C-2), 65.92 (C-6), 52.46 (C-5), 37.92 (C-1).

8: ^{1}H NMR (CD_3OD, 360 MHz): δ 5.23 (dd, 1H, H-3), 4.31 (t, 1H, J = 7.4 Hz, H-6a), 4.11 (d, 1H, $J_{1a,1b}$ = 14.9 Hz, H-1a), 3.16 (d, 1H, $J_{1a,1b}$ = 14.9 Hz, $J_{1b,2}$ = 1.7 Hz, H-1b).

9: ^{1}H NMR (CD_3OD, 300 MHz): δ 6.30 (d, 1H, $J_{1,2}$ = 5.6 Hz), 5.45 (t, 1H, J = 8.7 Hz, H-3), 5.15 (t, 1H, J = 8.7 Hz, H-2), 4.30 (m, 1H, H-5), 4.10 (m, 2H, H-6); ^{13}C NMR (CD_3OD, 300 MHz): δ 78.2 (C-1), 71.9, 71.4, 69.8, 69.5 (C-2, C-3, C-4 and C-5), 63.0 (C-3).

10: ^{1}H NMR (CD_3OD, 360 MHz): δ 4.40 (t, 2H, J = 12.0 Hz, OCH_2O), 4.33 (t, 1H, J = 8.5 Hz, H-6), 4.18 (dd, 1H, H-3), 4.04 (dd, $J_{4,5}$ = 9.0 Hz, $J_{3,4}$ = 3.5 Hz, H-4), 3.99 (d, J = 15.0 Hz, H-1), 3.95 (m, 1H, H-5), 3.33 (s, 3H, OCH_3), 3.21 (dd, 1H, $J_{1a,1b}$ = 15.0 Hz, $J_{1a,2}$ = 1.6 Hz, H-1); ^{13}C NMR (CD_3OD, 300 MHz): δ 96.70 (OCH_2O), 74.79, 74.24, 71.19 (C-2, C-3 and C-4), 71.19, 70.89 (two CH_2Ph), 65.26 (C-6), 55.69 (OCH_3), 52.84 (C-5), 38.57 (C-1).

11:^{1}H NMR (CD_3OD, 300 MHz): δ 5.39 (dd, 1H, $J_{4,5}$ = 9.7 Hz, $J_{3,4}$ = 2.0 Hz, H-4), 5.29 (m, 1H, H-2), 4.33 (dd, 1H, $J_{6a,6b}$ = 8.4 Hz, $J_{6a,5}$ = 2.6 Hz, H-6), 4.01 (d, 1H, $J_{1a',1b}$ = 14.0 Hz, H-1a), 3.63 (d, 1H, $J_{1a,1b}$ = 14.0 Hz, H-1b).

13: ^{1}H NMR (CD_3OD, 360 MHz): δ 7.2-7.4 (m, 10H, two CH_2Ph), 5.18 (d, 1H, J = 3.9 Hz, H-3), 4.337 (m, 1H, H-2), 4.05 (d, 1H, J = 14.7 Hz, H-1a), 3.99 (dd, 1H, $J_{6a,6b}$ = 7.8 Hz, $J_{6a,5}$ = 3 Hz, H-6a), 3.92 (d, 1H, J = 3.9 Hz, H-4), 3.79 (m, 2H, H-6b and H-5), 3.21(d, 1H, J = 14.7 Hz, H-1b), 3.00(s, 3H, OMs); ^{13}C NMR (CD_3OD, 300 MHz): δ 74.75, 73.84, 72.85, 72.04, 71.62 (two CH_2Ph, C-2, C-3, C-4), 65.30 (C-6), 52.30 (C-5), 38.79, 38.53 (C-1 and OMs).

14: ^{1}H NMR (CD_3OD, 300 MHz): δ 4.69 (t, 1H, J = 3.3 Hz, H-3), 4.36 (t, 1H, J = 8.4 Hz, H-6a), 4.16 (dd, 1H, $J_{6a,6b}$ = 8.4 Hz, $J_{6a,5}$ = 4.8 Hz, H-6b), 3.99 (m, 1H, H-2), 3.88 (dd, 1H, $J_{3,4}$ = 2.4 Hz, $J_{4,5}$ = 9.6 Hz, H-4), 3.73 (m, 1H, H-5), 3.571 (d, 1H, J = 14.0 Hz, H-1a), 3.18 (dd, 1H, $J_{1a,1b}$ = 14.0 Hz, $J_{1a,2}$ = 1.5 Hz, H-1a), 3.06 (s, 3H, OMs); ^{13}C NMR (CD_3OD, 300 MHz): δ 82.08 (C-3), 68.65, 67.47, 67.08 (C-2, C-4 and C-6), 55.72 (C-5), 43.56 (C-1), 38.52 (OMs).

16: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.36 (d, 1H, J = 5.5 Hz, H-1'), 4.49 (t, 1H, J = 8.0 Hz, H-6a), 4.25 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{3,2}$ = 5.0 Hz, H-3); ^{13}C NMR (CD_3OD, 300 MHz): δ 160.41 (*C*O), 86.69 (C-1'), 75.77, 74.49, 73.21, 71.70, 70.31, 67.98, 67.69 (C-2, C-3, C-6, C-2', C-3', C-4' and C-5'), 62.61 (C-6'), 57.10 (C-5), 51.89 (C-3), 43.98 (C-1).

18: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.59 (t, 1H, J = 9.6 Hz, H-3'), 5.23 (t, 1H, J = 9.9 Hz, H-4'), 5.18 (dd, 1H, $J_{2',1'}$ = 2.7 Hz, $J_{2,3}$ = 9.9 Hz, H-2'), 5.06 (d, 1H, $J_{1',2'}$ = 2.7 Hz, H-1'), 4.19 (dd, 1H, $J_{1a,1b}$ = 14.0 Hz,

$J_{1a,2}$ = 3.9 Hz, H-1a), 4.18 (d, 1H, J < 1.0 Hz, H-2), 3.91 (t, 1H, J = 8.7 Hz, H-6a), 3.17 (m, 1H, H-5), 2.86 (d, 1H, J = 14.0 Hz, H-1b), 2.03, 1.93, 1.97, 1.72 (4s, each 3H, 4×OAc); ^{13}C NMR (CD_3OD, 300 MHz): δ 170.41, 169.97, 169.56, 169.35 (4 OAc), 157.71 (*C*ON), 83.94 (C-1'), 81.48, 76.39, 75.03, 74.54, 73.86, 71.88 (C-2, C-3, C-4, C-2', C-3' and C-4'), 70.55, 70.44 (two CH_2Ph), 65.61 (C-6), 60.86 (C-6'), 57.55 (C-5), 40.89 (C-5'), 39.03 (C-1), 20.55, 20.55, 20.55, 20.55 (4 $COCH_3$).

19: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.16 (d, 1H, J < 1.0 Hz, H-1'), 4.51 (t, 1H, J = 6.6 Hz, H-6a), 4.31 (dd, 1H, $J_{1a,1b}$ = 13.0 Hz, $J_{1a,2}$ = 3.0 Hz, H-1a), 4.28 (d, 1H, J < 1.0 Hz, H-2), 3.19 (m, 2H, H-5' and H-1b); ^{13}C NMR (CD_3OD, 300 MHz): δ 162.83 (*C*ON), 85.25 (C-1'), 82.32, 77.71, 75.86, 75.74, 71.02, 69.78 (C-2, C-3, C-4, C-2', C-3' and C-4'), 67.53 (C-6), 62.20 (C-6'), 59.71 (C-5), 46.87, 45.19 (C-5' and C-1); ESMS: *m/z* 390 $[M+Na]^+$.