Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1215–1220

BIOORGANIC &
MEDICINAL CHEMISTRY
LETTERS

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

Yili Ding* and Ole Hindsgaul

The Burnham Institute, La Jolla Cancer Research Center, 10901 North Torrey Pines Road, La Jolla, CA 92037
U.S.A.

Chemsitry Department, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada

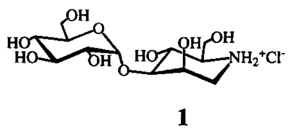
Received 10 February 1998; accepted 8 April 1998

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.

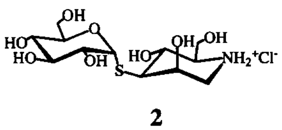
Glycosidase inhibitors are useful tools in the study of *N*-linked glycoprotein biosynthesis.[1] The aza-disaccharide 1-deoxy-3-*O*-(α-D-glucopyranosyl)-mannojirimycin (**1**) is an effective inhibitor of *endo*-α-D-mannosidase, the enzyme responsible for the cleavage of α-D-Glc-(1→3)-D-man from the $GlcMan_9GlcNAc_2$ 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]

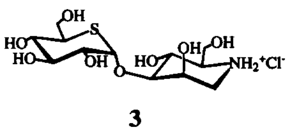
We report here the syntheses of 1-deoxy-3-*S*-(1-thio-α-D-glucopyranosyl)-mannojirimycin (**2**) and 1-deoxy-3-*O*-(5-thio-α-D-glucopyranosyl)-mannojirimycin (**3**), the thio analogs of **1**.



1



2

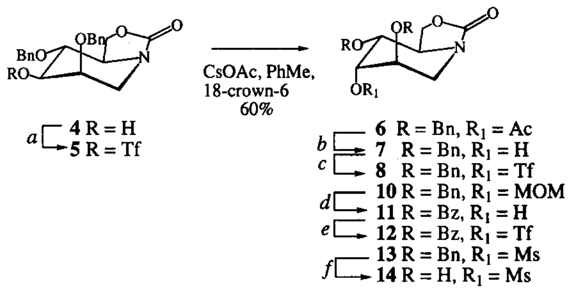


3

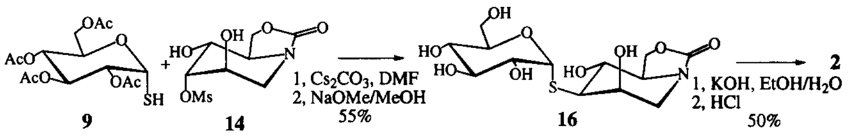
PII: S0960-894X(98)00198-X

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

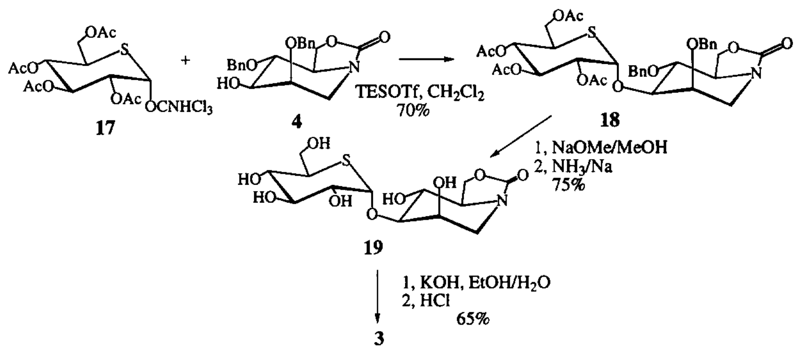
The 1-deoxy mannojirimycin derivative **4**[7] was selected as the starting material and was converted to the triflate **5** (80% yield), which was then treated with CsOAc to afford acetate **6** in 60% yield. Subsequent deacetylation and triflation provided altrojirimycin derivative **8** in 75% yield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

This work was funded in part by the National Sciences and Engineering Research Council of Canada.

References and Notes

1. (a) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acda. Sci. U. S. A.* **1988**, *85* 9229. (b) Tsukamoto, K.; Uno, A.; Shimada, S.; Imokow, G. *Clin. Res.* **1989**, *37*, 722A.

2. Hiraizumi, S.; Spohr, U.; Spiro, R. G. *J. Bio. Chem.* **1993**, *268*, 9927.

3. Spiro, R. G. Unpublished results.

4. (a) Yuasa, H.; Hindsgaul, O.; Palcic, M. M. *J. Amer. Chem. Soc.* **1992**, *114*, 5891. (b) Hoffman, D. J.; Whistler, R. L. *Biochemistry.* **1968**, *7*, 4479. (c) Chen, M, Whistler, R. L. *Arch. Biochem. Biophs.* **1975**, *169*, 392. (d) Critchley, D. R, Eichholz, A.; Crane, R. K. *Biochem. Biophys. Acta.* **1970**, *211*, 244.

5. Defaye, J.; Gelas, J. In: atta-ur-Rohman, editor. *Studies in Natural Product Chemistry.* Vol 8. Stereoselective Synthesis (Part E). Amsterdam: Elsevier. **1991**, 315.

6. Spiro, R. G. Personal communication.

7. Spohr, U.; Bach, M.; Spiro, R. G. *Can. J. Chem.* **1993**, *71*, 1928.

8. Defaye, J.; Guillot, J. M. *Carbohydr, Res.* **1994**, *253*, 185.

9. Due to the lability of compound **12**, its NMR spectra were not recorded.

10. Mehta, S.; Pinto, B. M. *Tetrahedron Lett.* **1992**, *33*, 7675.

11. Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212.

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 (CO), 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 *C*H_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 CO*C*H_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]$^+$.