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Totally Chemical Synthesis of Azasugars via Thiazole Intermediates.[1] Stereodivergent Routes to (-)-Nojirimycin, (-)-Mannojirimycin and Their 3-Deoxy Derivatives from Serine

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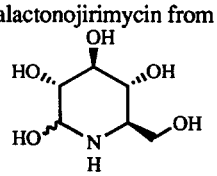
Key Words: thiazole, azasugars, nojirimycin, mannojirimycin, glycosidase inhibitors

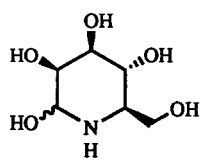
***Abstract**: The synthesis of the (-)-antipodes of the natural products nojirimycin (+)-1 and mannojirimycin (+)-2 has been carried out by stereocontrolled reduction of the thiazole ketone 7 as a common key intermediate. This ketone was in turn obtained from the L-serine derived aldehyde 3 by two convergent routes involving carbonylolefination and dihydroxylation processes. Moreover, 3-deoxy derivatives of (-)-1 and (-)-2 have been prepared from 3 and the lithium enolate of 2-acetylthiazole followed by stereocontrolled reduction of the resultant aldol.*

Introduction

Naturally occurring and synthetic polyhydroxylated piperidines (azahexoses) and pyrrolidines (azafuranoses) and their derivatives have emerged as potent and specific inhibitors of glycosidase enzymes.[3] For example, nojirimycin (+)-**1**, related to glucose by replacing the ring oxygen by the NH group is a powerful glucosidase inhibitor,[4] and mannojirimycin (+)-**2**, related similarly to mannose, is a mannosidase inhibitor.[5] Among the various biological activities of azasugars, much recent interest has been centered on their antiviral properties arising from the inhibition of glycoprotein processing necessary for virus replication,[6] including HIV-1, the virus responsible for AIDS. The worldwide intense search for potential drugs against AIDS has provided a great impetus for the synthesis of numerous azasugars by chemical and combined chemical and enzymatic approaches mainly from sugar-based starting materials.[7] Quite surprisingly, none of these methods employ natural amino acids as starting materials. We have recently reported a totally chemical synthesis of the galactosidase inhibitor, galactonojirimycin from serine.[8]



(+)-1

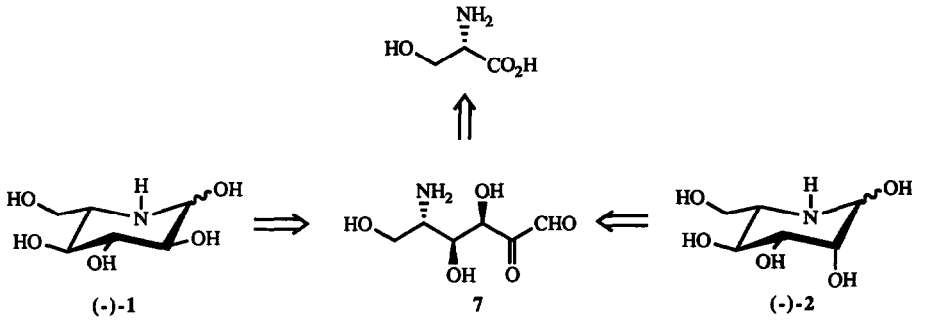


(+)-2

Our main objective was to develop a divergent synthetic route to both nojirimycin **1** and mannojirimycin **2** via a common advanced intermediate obtained from an α-amino acid. The *S*- or *R*-configuration of this starting material would establish the antipodal form of **1** and **2**. Retrosynthetic analysis indicates the α-keto aldehyde **7** as such an intermediate (Scheme 1, L-series is shown) which should lead to either **1** or **2** by

stereocontrolled reduction of the ketone carbonyl. We describe here the implementation of this strategy starting from L-serine by two complementary routes based on the thiazole-aldehyde synthesis.[9] We also report in full[10] the synthesis of 3-deoxy derivatives of (-)-1 and (-)-2 from the same amino acid via thiazole intermediates.

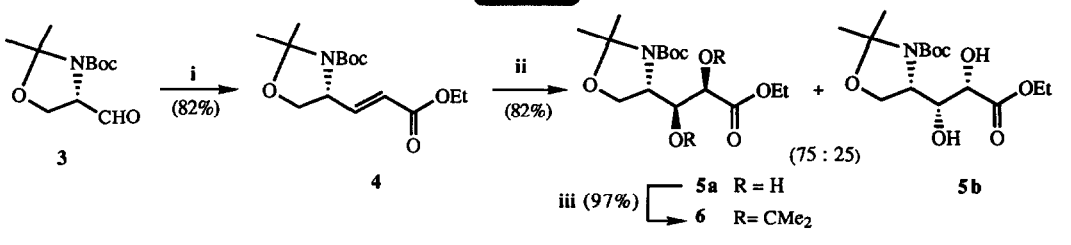
Scheme 1



Results and Discussion

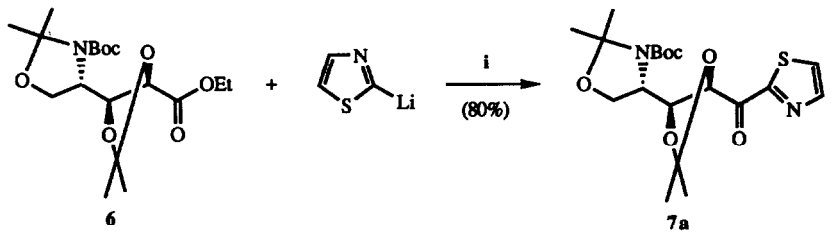
Having demonstrated the effective synthetic equivalence of 2-substituted thiazoles to aldehydes,[1] we planned the synthesis of a thiazole masked precursor to the α-keto aldehyde **7** via the L-serinal derivative **3** that combines configurational stability with ease of preparation on a large scale from L-serine.[11] The enantiomer of the amino aldehyde **3** is equally available from D-serine.[11,12] Thus, the Wittig olefination of **3** (Scheme 2) with the commercially available ethyl (triphenylphosphoranylidene) acetate in benzene as a solvent provided the *E*-alkene **4** as a single isomer whose configuration is supported by the large coupling constant (J = 16.0 Hz) of the vinylic protons.[13] The *cis* dihydroxylation of this enoate using catalytic osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide as a reoxidant (OsO_4/NMO), afforded a 75:25 mixture of diols *anti*-**5a** and *syn*-**5b** in 82% total yield. The major isomer *anti*-**5a** whose configuration was assigned from literature precedents,[7b,14] was isolated by silica gel chromatography in 61% yield. This diol was protected as the acetonide derivative **6** by treatment with 2,2-dimethoxypropane in refluxing benzene in the presence of a catalytic amount of *p*-toluensulfonic acid. The high yield substitution[15] on the ethyl ester **6** with 2-lithiothiazole generated *in situ* from 2-bromothiazole and *n*-butyllithium (Scheme 3) produced the 2-thiazolyl ketone **7a** in 80% yield (38.8 % from **3**).

Scheme 2



i: Ph_3P=CH-COOEt / C_6H_6 / r.t. / 36 h. ii: OsO_4 / NMO / ^tBuOH / H_2O /r.t. / 24 h. iii: C_6H_6 / DMP / TosOH / refl./ 10 min.

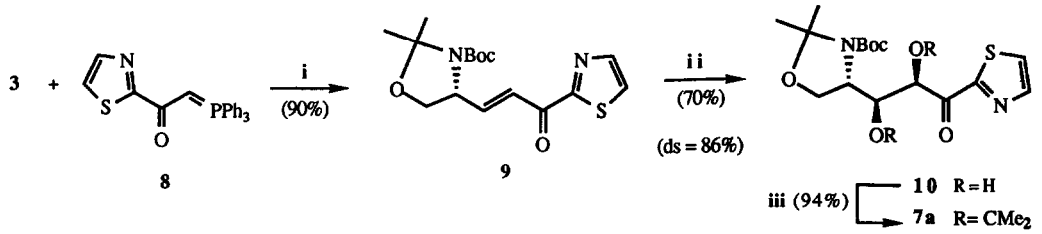
Scheme 3



i: 2-lithiothiazole (from 2-bromothiazole and n-BuLi / Et_2O / -78°C), -45 °C / 6 h.

Given the central role of the ketone **7a** as a key intermediate in the planned synthetic route, we explored an alternative approach using a newcomer to the family of thiazole armed reagents,[1,16] i.e. the stabilized carbonylphosphorane **8** (2-TCMP) (Scheme 4). This masked equivalent of the formyl phosphorane Ph_3P=CH-CO-CHO, can be readily prepared on a large scale from commercially available reagents and stored at room temperature without any appreciable decomposition.[17] The reaction of **8** with L-serinal **3** in benzene was stereoselective in favor of the *E*-enone **9** (vinylic protons, J = 15.8 Hz).[13] The *cis* dihydroxylation of **9** with OsO_4/NMO proceeded with good asymmetric induction giving rise to an 86:14 mixture of *anti*-**10** and its *syn*-diastereomer (not shown). Silica gel chromatography of this mixture gave pure *anti*-**10** (60 %) which by protection of the 1,2-diol fragment as the acetonide derivative afforded the target thiazolyl ketone **7a** in 94% yield (51 % from **3**). Thus, this route appeared to produce **7a** in higher yield than the procedure of Schemes 2 and 3.

Scheme 4

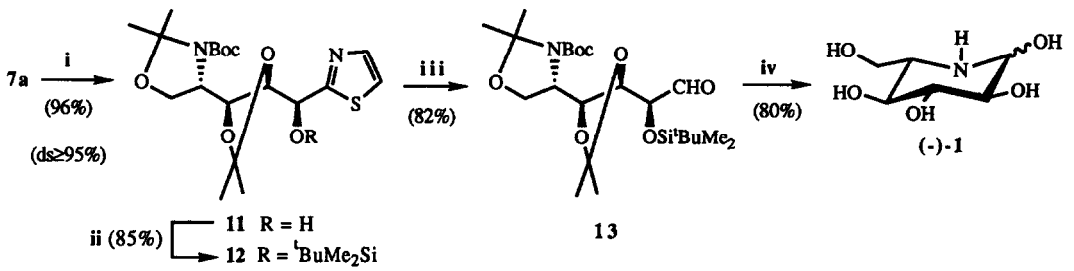


i: Toluene, reflux, 18 h. ii: OsO_4 / NMO / ^tBuOH / H_2O / r.t. / 24 h. iii: C_6H_6 / DMP / TosOH / reflux / 10 min.

L-(-)-Nojirimicyn.[18] The synthesis of either nojirimycin (-)-**1** and mannonojirimycin (-)-**2** from the masked α-keto aldehyde **7a** requires the stereocontrolled reduction of the carbonyl to an alcohol of either *R* and *S* configuration. Thus, treatment of **7a** with sodium borohydride in methanol (Scheme 5) gave the alcohol **11** as a single diastereomer (ds ≥ 95 % by ^1H NMR) in almost quantitative yield. The *S*-configuration at the newly formed stereocenter of **11** was tentatively assigned on the basis of the literature precedents on the reduction of α,β-dialkoxy ketones with sodium borohydride.[19] This stereochemical outcome was consistent the Felkin-Anh

model of asymmetric induction.[20] Silylation of the hydroxyl group with *tert*-butyldimethylsilyl chloride afforded **12** (85%). The application of the one-pot thiazolyl-to-formyl unmasking protocol[9] to **12** (*N*-methylation, reduction, and hydrolysis) furnished the aldehyde **13** in 82% isolated yield after chromatographic purification. The removal of all protecting groups in **13** by treatment with trifluoroacetic acid-water gave the target compound nojirimycin (-)-**1**. This compound was isolated as the free base by ion exchange chromatography (Amberlyst A-26) in the form of an amorphous solid showing m.p. and optical rotation in excellent agreement with literature values of natural and synthetic nojirimycin (see experimental). This final observation confirmed the stereochemical assignments to all chiral intermediate precursors to the aldehyde **13**.

Scheme 5

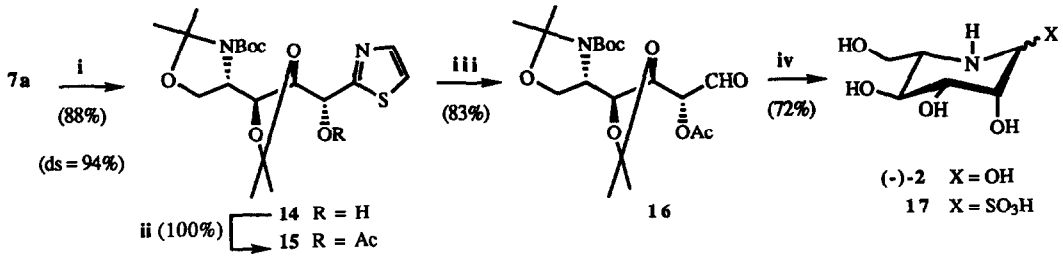


i: $NaBH_4$ / MeOH / -60°C / 1 h. ii: ^{t}BuMe$_2$SiCl / Imidazole / DMF / 80°C /12 h. iii: a) MeI / CH_3CN / reflux / 16 h; b) $NaBH_4$ / MeOH / r.t. / 30 min; c) $HgCl_2$ /CH_3CN / H_2O / r.t. / 15 min. iv: TFA / H_2O / r.t. / 30 min.

L-(-)-Mannojirimycin.[21] We next turned to the reduction of the carbonyl **7a** in the opposite sense to obtain the alcohol with the *R*-configuration corresponding to that at C-2 of mannojirimycin (-)-**2**. Guided by previous studies on the stereoselective reduction of chiral α,β-dialkoxy thiazolyl ketones,[19b] the reduction of **7a** with Red-Al [$NaAlH_2$-(OCH_2CH_2OMe)] in toluene at -78 °C gave the *R*-alcohol **14** (ds 94% by ^{1}H NMR) in 83% isolated yield after chromatography (Scheme 6). The observed diastereofacial selectivity associated with the use of Red-Al can be explained by an α-chelate model resulting from the coordination of aluminum to alkoxy and carbonyl oxygens.[22] The alcohol **14** was protected as the *O*-acetyl derivative **15** which by the usual formyl deblocking protocol[9] afforded the chiral aldehyde **16** in good yield. Mannojirimycin(-)-**2** was obtained from **16** by removal of all protecting groups with trifluoroacetic acid-water and isolated as the crystalline bisulfite derivative **17** (72% yield). Compound **17**, existing as a mixture of α and β anomers in the pyranose form, showed physical data, i.e. m.p.and optical rotation, in good agreement with literature values of natural and synthetic mannojirimycin (see experimental).

An alternative route to the alcohol **14** was also developed. In this approach (Schemes 7 and 8) the two-carbon chain elongation of L-serinal **3** was carried out using the semistabilized 2-thiazolylmethylenetriphenylphosphorane (2-TMP, **18**) generated in benzene as described.[23] The olefination of **3** with **18** was quite stereoselective in favor of the *E*-alkenylthiazole **19** (92%) as shown by the coupling constant (J = 16.1 Hz) of the vinylic protons.[13] The *cis*-dihydroxylation of **19** with OsO_4 / NMO furnished the 1,2-diol **20** as a 73:27 mixture of diastereomers (86% combined yield) from which the major isomer **20a** was obtained in

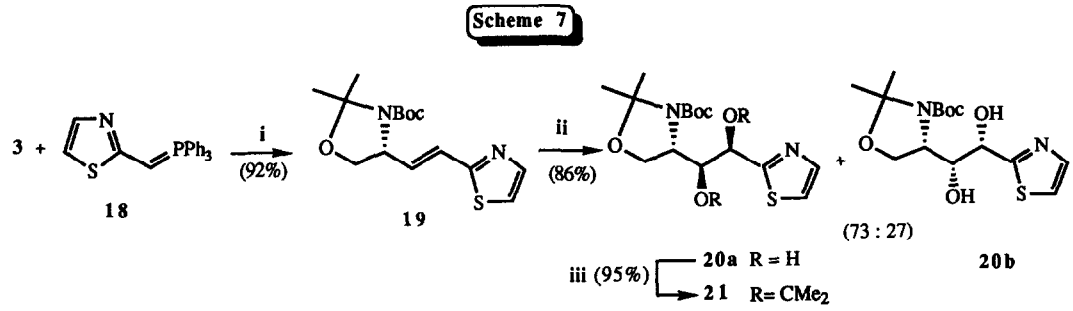
Scheme 6



i: Red-Al / toluene / -78°C / 2 h. ii: Ac_2O / pyridine / DMAP / r.t. / 16 h. iii: a) MeI / CH_3CN / reflux / 16 h; b) $NaBH_4$ / MeOH / r.t. / 30 min; c) $HgCl_2$ /CH_3CN / H_2O / r.t. / 15 min. iv: a) TFA / H_2O / r.t. / 30 min; b) SO_2 / H_2O.

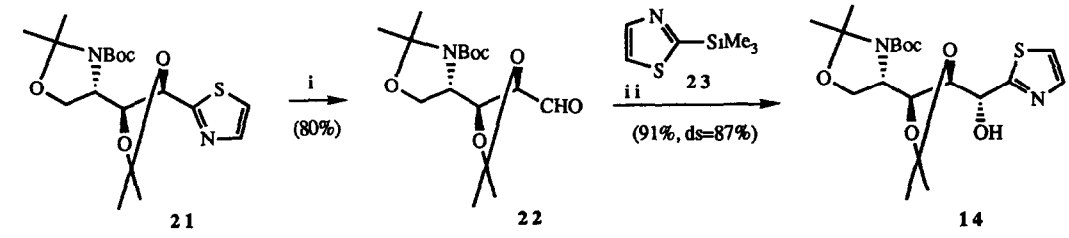
63% isolated yield. After protection of the 1,2-diol **20a** as the acetonide derivative **21**, the aldehyde **22** was revealed (80%) by the usual elaboration of the thiazole ring. The final hydroxymethyl group with *R*-configuration was generated by reaction of **22** with 2-(trimethylsilyl)thiazole (2-TST **23**) in dichloromethane. This reaction afforded the required *anti*-alcohol **14** with good diastereoselectivity (ds 87%) in line with the main stereochemical outcome of addition of **23** to chiral alkoxy aldehydes.[24]

Scheme 7



i: C_6H_6 / r.t. / 20 h. ii: OsO_4 / NMO / ^{t}BuOH / H_2O / r.t. / 24 h. iii: C_6H_6 / DMP / TosOH / reflux / 10 min.

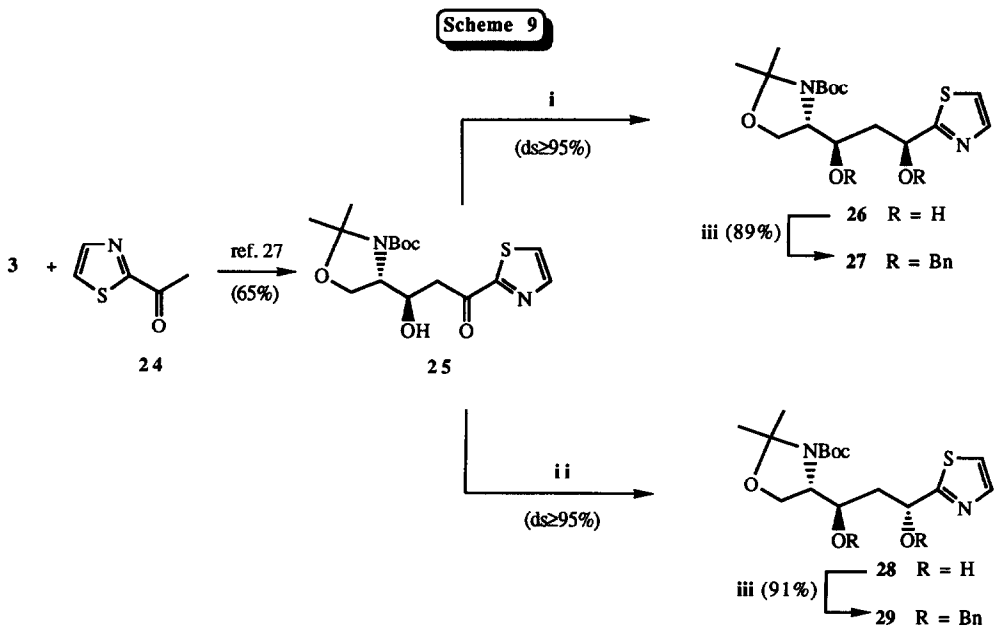
Scheme 8



i: a) MeI / CH_3CN / reflux / 16 h; b) BH_4Na / MeOH / r.t. / 30 min; c) $HgCl_2$ /CH_3CN / H_2O / r.t. / 15 min. ii: a) CH_2Cl_2 / r.t. / 16 h; b) Bu_4NF / THF / r.t. / 2h.

3-Deoxy Derivatives of (-)-1 and (-)-2 1-Deoxy derivatives of nojirimycin (+)-**1** and mannojirimycin (+)-**2** were found to act as powerful competitive inhibitors of glycosidase enzymes as do their parent compounds.[25] Consequently, new azasugars featuring various chemical modifications have been the target of intense synthetic efforts.[7,18,26] The large interest in the structure and enzyme-inhibitory activity relationships provide a further demand for structural variations in these compounds.

Following a preliminary communication,[10] we report here an improved stereodivergent synthesis of 3-deoxy derivatives of both nojirimycin(-)-**1** and mannojirimycin(-)-**2** that relies on the stereocontrolled reduction



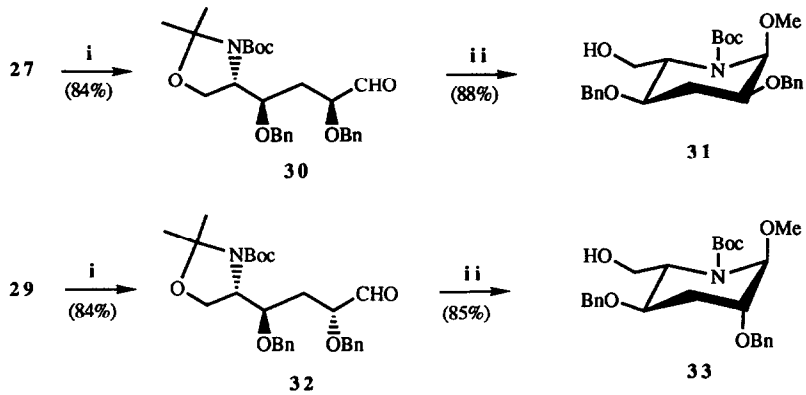
i:$NaBH_4$ - Et_2BOMe / THF / MeOH / -78°C / 6h. ii: $Me_4NBH(OAc)_3$ / CH_3CN / AcOH / -35°C / 36 h. iii: NaH / DMF / $PhCH_2Br$ / r.t. / 12 h.

of the 2-thiazolyl β-hydroxy ketone **25** (Scheme 9). This key intermediate was obtained by the aldol reaction of the protected L-serinal **3** with the lithium enolate of 2-acetylthiazole **24** as described.[27] The reduction of **25** with sodium borohydride in the presence of diethylmethoxyborane,[28] $NaBH_4$-Et_2BOMe, afforded the *syn* 1,3-diol **26** whereas the reaction with tetramethylammonium triacetoxy borohydride,[29] $Me_4NBH(OAc)_3$, gave the *anti*-epimer **28**. In both cases the diastereoselectivity was excellent (ds ≥ 95 % by ^1H NMR) and the chemical yield almost quantitative. The observed stereochemical outcomes leading to *syn* and *anti* 1,3-diols **26** and **28** can be explained by two different models. It has been reported that the reduction of β-hydroxy ketones with $NaBH_4$-Et_2BOMe leads to *syn* 1,3-diols via external hydride delivery on a boron chelate half-chair intermediate,[28] whereas the reduction with $Me_4NBH(OAc)_3$ affords the *anti*-isomer via internal hydride delivery in a six-membered chair-like intermediate.[29] Both diols **26** and **28** were isolated as the corresponding *O*-dibenzyl derivatives **27** and **29** respectively.

The application of the thiazolyl-to-formyl deblocking protocol to **27** gave the aldehyde **30** in 84% isolated yield (Scheme 10). Wishing to preserve at this stage the *N*-Boc protection and avoid the formation of

the 1,6-anhydro derivative,[10] the removal of the isopropylidene group of **30** was effected under mild conditions using catalytic TosOH in methanol at 50 °C. This procedure afforded, after column chromatography, the protected azasugar 3-deoxy-nojirimycin **31** in 88% yield. Likewise, the epimer **29** was effectively converted to the protected 3-deoxy-mannojirimycin **33**. The ^{1}H NMR spectra of both **31** and **33** were consistent with the $^1C_4$ pyranose conformation as shown.

Scheme 10



i: a) MeI / CH_3CN / reflux / 16 h; b) $NaBH_4$ / MeOH / r.t. / 30 min; c) $HgCl_2$ /CH_3CN / H_2O / r.t. / 15 min. ii: TosOH (cat.) / MeOH / 50°C / 40 min.

Conclusions

We have presented new synthetic routes to nojirimycin (-)-**1** and mannojirimycin (-)-**2** and their 3-deoxy derivatives **31** and **33** from L-serine using 2-substituted thiazoles as homologating reagents and aldehyde equivalents. The new stereocenters were generated as required in subsequent steps by internal asymmetric induction starting from the 2*S*-configuration of the α-amino acid. Noteworthy are the streocontrolled reductions of ketones **7a** and **25** that furnished the final epimeric products in a stereodivergent fashion. Obviously, this methodology can be applied to the synthesis of the natural products (+)-**1** and (+)-**2** and their 3-deoxy derivatives starting from the commercially available[12] D-serine. This chemistry demonstrates that the thiazole-aldehyde synthesis[9] can be effectively extended to azasugars.

Experimental

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a 80 MHz Bruker WP-80 or on a 300 MHz Varian Unity spectrometer at 55 °C. Chemical shifts are given in parts per million downfield from tetramethylsilane. IR spectra were obtained on a Perkin Elmer Model 297 grating spectrometer. Optical rotations were measured at room temperature (20 °C) using a Perkin Elmer Model 214 polarimeter. Elemental analyses were performed on a 1106 Microanalyzer (Carlo Erba). Thin layer cromatography were carried out on glass-slides precoated with silica gel (Merck Kiesel gel 60 F254) and preparative chromatography

on columns of silica gel (Merck 70-230 mesh).

Ethyl (*4R*)-5-hydroxy-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)-2(*E*)-pentenoate (4). To a well-stirred solution of ethyl (triphenylphosphoranylidene) acetate (2.29 g, 6.59 mmol) in C_6H_6 (30 mL) a solution of *N*-*tert*-butoxycarbonyl L-serinal acetonide[11] **3** (1.50 g, 6.55 mmol) in the same solvent (20 mL) was added. The mixture was stirred at room temperature for 36 h. Filtration through Celite, evaporation of the solvent in vacuo and column chromatography of the residue on silica gel (hexane/diethyl ether, 80:20) gave 1.61 g (82%) of **4**. Oil; $[\alpha]^{20}_D$ = -44.3 (c 1.09, $CHCl_3$); IR ($CHCl_3$) ν 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (dd, 1H, J=16.0, 6.2 Hz), 5.80 (dd, 1H, J=16.0, 1.1 Hz), 4.46 (dddd, 1H, J=6.2, 5.6, 2.8, 1.1 Hz), 4.20 (q, 2H, J=7.1 Hz), 4.09 (dd, 1H, J=8.8, 5.6 Hz), 3.75 (dd, 1H, J=8.8, 2.8 Hz), 1.60 (s, 3H), 1.56 (s, 3H), 1.47 (s, 9H), 1.21 (t, 3H, J=7.1 Hz).

Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.24; H, 8.31; N, 4.60.

Ethyl (*2R,3S,4S*)-2,3,5-trihydroxy-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)pentanoate (5a) and Ethyl (*2S,3R,4S*)-2,3,5-trihydroxy-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)pentanoate (5b). To a solution of *tert*-butyl alcohol (3.3 mL) and water (0.31 mL) in THF (26.5 mL), 4-methylmorpholine *N*-oxide (0.39 g, 3.34 mmol) and OsO_4 (0.15 g, 0.62 mmol, 5 wt. % solution in *tert*-butyl alcohol) were added and the mixture was stirred at room temperature for 1 min. A solution of **4** (1.0 g, 3.34 mmol) in THF (3.5 mL) was added. After 24 h the mixture was treated with Florisil (7.0 g), and $NaHSO_3$ (2.0 g) and stirring continued for 1 h. The reaction mixture was diluted with AcOEt (20 mL), filtered through Celite and the filtrate distilled in vacuo to give a mixture of diols **5a** and **5b** in 75:25 ratio by ^1H NMR. These compounds were separated by column chromatography on silica gel (hexane/diethyl ether, 30:70).
5a (0.68 g, 61%) (R_f: 0.33). Sticky oil; $[\alpha]^{20}_D$ = -21.2 (c 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$+D_2O) δ 4.30 (q, 2H, J=6.6 Hz), 4.20-3.98 (m, 3H), 3.78 (m, 2H), 1.59 (s, 3H), 1.50 (s, 3H), 1.47 (s, 9H), 1.32 (t, 3H, J=6.6 Hz).

Anal. Calcd for $C_{15}H_{27}NO_7$: C, 54.04; H, 8.16; N, 4.20. Found: C, 54.20; H, 8.22; N, 4.41.

5b (0.23 g, 21%) (R_f: 0.19). Sticky oil; $[\alpha]^{20}_D$ = -8.5 (c 0.47, $CHCl_3$); ^1H NMR ($CDCl_3$+D_2O) δ 4.28 (q, 2H, J=6.8 Hz), 4.20 (m, 2H), 4.10-3.85 (m, 3H), 1.62 (s, 3H), 1.54 (s, 3H), 1.49 (s, 9H), 1.25 (t, 3H, J=6.8 Hz).

Anal. Calcd for $C_{15}H_{27}NO_7$: C, 54.04; H, 8.16; N, 4.20. Found: C, 53.96; H, 8.20; N, 4.05.

Ethyl (*2R,3S,4S*)-2,3,5-trihydroxy-2,3-*O*-isopropylidene-4,5-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)pentanoate (6). To a solution of the diol **5a** (0.60 g, 1.80 mmol) in anhydrous C_6H_6 (20 mL), 2,2-dimethoxypropane (6 mL) and *p*-toluensulfonic acid monohydrate (7.6 mg, 0.04 mmol) were added. After refluxing for 10 min, the solution was treated with saturated aqueous $NaHCO_3$. The separated organic layer was dried (Na_2SO_4) and the solvent distilled in vacuo. The residue was chromatographed on silica gel (hexane/diethyl ether, 80:20) to yield 0.65 g (97%) of **6** as a white solid, m.p. 54-56 °C; $[\alpha]^{20}_D$ = -15.4 (c 1.40, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.62 (dd, 1H, J=6.4, 3.2 Hz), 4.50 (d, 1H, J=6.4 Hz), 4.20-3.95 (m, 5H), 1.62 (s, 3H), 1.58 (s, 3H), 1.48 (s, 12H), 1.38 (s, 3H), 1.26 (t, 3H, J=6.6 Hz).

Anal. Calcd for $C_{18}H_{31}NO_7$: C, 57.89; H, 8.37; N, 3.75. Found: C, 57.96; H, 8.50; N, 3.73.

(*4R*)-5-Hydroxy-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)-2(*E*)-penten-1-one (9). To a well-stirred solution of 2-thiazolylcarbonylmethylenetriphenylphosphorane[17] (**8**) (2.55 g, 6.59 mmol) in toluene (30 mL), a solution of *N*-*tert*-butoxycarbonyl L-serinal acetonide[11] **3** (1.50 g, 6.55 mmol) in the same solvent (20 mL) was added and the resultant mixture was refluxed for 18 h. The reaction mixture was filtered through Celite and the solvent removed in vacuo. The residue was chromatographed on silica gel (hexane/diethyl ether, 60:40) to give 2.0 g (90%) of **9**, m.p. 97-99 °C (from hexane); $[\alpha]^{20}_D$ = -67.8 (c 0.61, $CHCl_3$); IR ($CHCl_3$) ν 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (d, 1H, J=3.2 Hz), 7.66 (d, 1H, J=3.2 Hz), 7.38 (d, 1H, J=15.8 Hz), 7.21 (dd, 1H, J=15.8, 9.0 Hz), 4.58 (ddd, 1H, J=9.0, 6.3, 2.9 Hz), 4.14 (dd, 1H, J=9.3, 6.3 Hz), 3.86 (dd, 1H, J=9.3, 2.9 Hz), 1.68 (s, 3H), 1.59 (s, 3H), 1.48 (s, 9H).

Anal. Calcd for $C_{16}H_{22}N_2O_4S$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.65; H, 6.40; N, 8.09.

(*2R,3S,4S*)-2,3,5-Trihydroxy-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)-1-pentanone (10). The osmilation of the enone **9** (1.69 g, 5.0 mmol) was carried out as described above for the enoate **4**. After the usual workup , the diol **10** was obtained in 86% diastereomeric purity by ^1H NMR. Purification by column chromatography on silica gel (hexane/diethyl ether, 40:60) afforded 1.11 g (60%) of pure **10**. Sticky oil; $[\alpha]^{20}_D$ = +41.8 (c 0.98, $CHCl_3$); IR ($CHCl_3$) ν 1705 cm^{-1}; ^1H NMR ($CDCl_3$+D_2O) δ 7.97 (d, 1H, J=3.2 Hz), 7.76 (d, 1H, J=3.2 Hz), 4.32 (m, 1H), 4.12 (d, 1H, J=3.6 Hz), 3.98 (m, 2H), 3.66 (dd, 1H, J=5.2, 3.6 Hz), 1.53 (s, 3H), 1.50 (s, 3H), 1.47 (s, 9H).

Anal. Calcd for $C_{16}H_{24}N_2O_6S$: C, 51.60; H, 6.50; N, 7.52. Found: C, 51.66; H, 6.60; N, 7.48.

(*2R,3S,4S*)-2,3,5-Trihydroxy-2,3-*O*-isopropylidene-4,5-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino-1-(2-thiazolyl)-1-pentanone (7a).

From 6. To a well-stirred solution of BuLi (1.75 mmol, 1.1 mL of a 1.6 M solution in hexanes) in diethyl ether (10 mL), a solution of 2-bromothiazole[1] (0.28 g, 1.70 mmol) in the same solvent (5 mL) was added slowly at -78 °C. After 15 min, a solution of the ester **6** (0.6 g, 1.61 mmol) in diethyl ether (15 mL) was added drop by drop and the mixture was allowed to warm to -45 °C. After stirring at this temperature for 6 h, saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was allowed to warm to room temperature. The organic layer was washed with brine, dried (Na_2SO_4) and distilled in vacuo.The residue was chromatographed on silica gel (hexane /diethyl ether, 70:30) to give 0.53 g (80%) of the ketone **7a**.

From 10. To a solution of the diol **10** (0.75 g, 2 mmol) in anhydrous C_6H_6 (20 mL), 2,2-dimethoxypropane (6 mL) and *p*-toluensulfonic acid monohydrate (7.6 mg, 0.04 mmol) were added. After refluxing for 10 min, saturated aqueous $NaHCO_3$ was added. The organic layer was dried (Na_2SO_4) and distilled in vacuo. The residue was chromatographed on silica gel (hexane/diethyl ether, 70:30) to give 0.78 g (94%) of **7a**.Oil; $[\alpha]^{20}_D$ = -32.1 (c 0.48, $CHCl_3$); IR ($CHCl_3$) ν 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (d, 1H, J=3.2 Hz), 7.60 (d, 1H, J=3.2 Hz), 5.50 (d, 1H, J=6.9 Hz), 5.11 (dd, 1H, J=6.9, 3.7 Hz), 4.29 (m, 1H), 4.06 (m, 2H), 1.51 (s, 3H), 1.46 (s, 9H), 1.43 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H).

Anal. Calcd for $C_{19}H_{28}N_2O_6S$: C, 55.32; H, 6.84; N, 6.80. Found: C, 55.01; H, 7.05; N, 6.98.

(*1S,2R,3S,4S*)-1,2,3,5-Tetrahydroxy-2,3-*O*-isopropylidene-4,5-*N,O*-isopropylidene-4-

(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)pentane (11). To a solution of the ketone **7** (0.5 g, 1.21 mmol) in MeOH (20 mL), $NaBH_4$ (92 mg, 2.42 mmol) was added at -60 °C. After stirring for 1 h, acetone (1 mL) was added an the solvent was evaporated under reduced pressure. The residue was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The combined organic layers were dried (Na_2SO_4), and distilled in vacuo to give the crude alcohol in diastereomeric purity >95% by ^1H NMR. Column chromatography (hexane/diethyl ether, 70:30) of this material gave 0.48 g (96%) of pure **11**. Oil; $[\alpha]^{20}_D$ = -21.4 (c 1.24, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.70 (d, 1H, J=3.2 Hz), 7.31 (d, 1H, J=3.2 Hz), 4.97 (dd, 1H, J=7.5, 2.2 Hz), 4.57 (dd, 1H, J=8.1, 3.2 Hz), 4.46 (dd, 1H, J=8.1, 2.2 Hz), 4.30 (m, 1H), 4.04 (m, 2H), 3.46 (d, 1H, J=7.5 Hz, ex. D_2O), 1.55 (s, 3H), 1.49 (s, 9H), 1.47 (s, 3H), 1.41 (s, 6H).

Anal. Calcd for $C_{19}H_{30}N_2O_6S$: C, 55.05; H, 7.30; N, 6.76. Found: C, 54.73; H, 7.15; N, 6.99.

(*1S,2R,3S,4S*)-2,3,5-Trihydroxy-2,3-*O*-isopropylidene-4,5-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)-1-(2-thiazolyl)pentane (12). A solution of **11** (0.41 g, 1 mmol) in anhydrous DMF (2 mL) was treated with imidazole (0.14 g, 2.1 mmol) and *tert*-butyldimethylsilyl chloride (0.27 g, 1.2 mmol). The solution was heated at 80 °C for 12 h. The crude mixture was poured into water (20 mL) and extracted with n-pentane (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and distilled in vacuo to give the crude product which was purified by column chromatography on silica gel (hexane/diethyl ether, 80:20) to yield 0.45 g (85%) of **12**. Oil; $[\alpha]^{20}_D$ = +16.8 (c 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.70 (d, 1H, J=3.2 Hz), 7.30 (d, 1H, J=3.2 Hz), 5.09 (d, 1H, J=2.9 Hz), 4.48 (dd, 1H, J=6.8, 3.4 Hz), 4.27 (dd, 1H, J=7.1, 2.9 Hz), 4.02-3.86 (m, 3H), 1.48 (s, 9H), 1.46 (s, 6H), 1.40 (s, 3H), 1.28 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), -0.07 (s, 3H).

Anal. Calcd for $C_{25}H_{44}N_2O_6SiS$: C, 60.45; H, 8.93; N, 5.64. Found: C, 60.26; H, 9.24; N, 5.86.

(*2S,3R,4S,5S*)-3,4,6-Trihydroxy-3,4-*O*-isopropylidene-5,6-*N,O*-isopropylidene-5-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldimethylsilyloxy)hexanal (13). A solution of **12** (0.4 g, 0.75 mmol) in freshly distilled CH_3CN (15 mL) was treated with MeI (1.07 g, 7.50 mmol). The solution was refluxed until the starting material disappeared on TLC (ca. 16 h). The solution was concentrated in vacuo, then diethyl ether was added to precipitate the *N*-methyl thiazolium salt, which was collected by filtration. The crude salt was dissolved in MeOH (15 mL) and the solution was treated with $NaBH_4$ (0.05 g, 1.32 mmol) at -10 °C. After 30 min, acetone (1 mL) was added and the solvent was evaporated. Brine (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The extract was dried (Na_2SO_4) and the solvent concentrated in vacuo. The residue, i.e. crude thiazolidine, was dissolved in CH_3CN (3 mL) and the solution was treated with $HgCl_2$ (0.22 g, 0.80 mmol) dissolved in 10 mL of a 4:1 mixture of CH_3CN-H_2O. This solution was stirred at room temperature for 15 min.. The precipitate was removed by filtration and the solvent evaporated in vacuo. The residue was treated with 20 % aqueous KI (15 mL) and then extracted with $CHCl_3$ (3 x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/diethyl ether, 60:40) to give 0.29 g (82%) of **13**. Oil; $[\alpha]^{20}_D$ = -22.2 (c 0.10, $CHCl_3$); IR ($CHCl_3$) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.62 (d, 1H, J=1.4 Hz), 4.40-3.95 (m, 6H), 1.50 (s, 9H), 1.47 (s, 3H), 1.44(s, 3H), 1.40 (s, 3H), 1.27 (s, 3H), 0.95 (s, 9H), 0.10 (s, 6H).

Anal. Calcd for $C_{23}H_{43}NO_7Si$: C, 58.32; H, 9.15; N, 2.96. Found: C, 58.48; H, 8.97; N, 3.27.

Nojirimycin (-)-(1). The aldehyde **13** (0.2 g, 0.42 mmol) was treated with 90% aqueous TFA (5 mL) and the mixture was stirred at room temperature for 30 min. The solvent was distilled under reduced pressure. The residue was dissolved in water (10 mL) and passed through a column of Amberlyst A-26 basic ion exchange resin and eluted with water. The eluant was concentrated in vacuo at room temperature or below and the residue was treated with ethanol to give (-)-**1** as an amorphous powder (60 mg, 80 %), mp 122-124 °C; $[\alpha]^{20}_D$ = -72.1 (c 0.30, H_2O, equilibrium).[lit.[18d] (-)-**1**, $[\alpha]^{20}_D$ -74 (H_2O); lit.[4] (+)-**1**, $[\alpha]^{24}_D$ +71 (H_2O); lit.[18b] (+)-**1**, mp 124-131 °C, $[\alpha]^{24}_D$ +71.2 (H_2O)].

(*1R,2R,3S,4S*)-1,2,3,5-Tetrahydroxy-2,3-*O*-isopropylidene-4,5-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)pentane (14). To a solution of the ketone **7** (0.5 g, 1.21 mmol) in toluene (15 mL), sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (12.1 mmol, 3.46 mL of a 3.5 M solution in toluene) was slowly added at -78 °C. After 1 h stirring at -78 °C, the mixture was allowed to warm to room temperature and stirring was continued for 10 min.. The mixture was quenched with water (15 mL) and extracted with toluene (2 x 15 mL). The combined organic phases were dried (Na_2SO_4) and distilled in vacuo to give the crude alcohol **14** in 94% diastereomeric purity by ^1H NMR. Purification by column chromatography on silica gel (hexane/diethyl ether, 70:30) afforded 0.42 g (83%) of pure **14**. Oil; $[\alpha]^{20}_D$ = -5.9 (c 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.74 (d, 1H, J=3.2 Hz), 7.34 (d, 1H, J=3.2 Hz), 4.99 (d, 1H, J=6.2 Hz), 4.32 (m, 2H), 4.20-4.01 (m, 3H), 3.25 (bs, 1H, ex. with D_2O), 1.53 (s, 3H), 1.49 (s, 9H), 1.46 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H).

Anal. Calcd for $C_{19}H_{30}N_2O_6S$: C, 55.05; H, 7.30; N, 6.76. Found: C, 54.73; H, 7.18; N, 6.97.

(*1R,2R,3S,4S*)-1-Acetoxy-2,3,5-trihydroxy-2,3-*O*-isopropylidene-4,5-*N,O*-isopropylidene--4-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)pentane (15). A solution of **14** (0.38 g, 0.92 mmol) in pyridine (2 mL) was treated with Ac_2O (2 mL) and catalytic dimethylamino pyridine. The mixture was stirred at room temperature for 16 h. The solvent was distilled at low pressure (ca. 1 mmHg) and the residue partitioned between saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated, dried (Na_2SO_4), and distilled in vacuo. The residue was chromatographed on silica gel (hexane/diethyl ether, 60:40) to give 0.42 g (100%) of **15**. Oil; $[\alpha]^{20}_D$ = -22.7 (c 0.66, $CHCl_3$); IR ($CHCl_3$) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, 1H, J=3.2 Hz), 7.31 (d, 1H, J=3.2 Hz), 6.16 (d, 1H, J=1.9 Hz), 4.58 (m, 1H), 4.12 (m, 2H), 3.64 (m, 2H), 2.12 (s, 3H), 1.49 (s, 9H), 1.46 (s, 6H), 1.45 (s, 3H), 1.38 (s, 3H).

Anal. Calcd for $C_{21}H_{32}N_2O_7S$: C, 55.25; H, 7.07; N, 6.14. Found: C, 55.08; H, 7.19; N, 5.94.

(*2R,3R,4S,5S*)-2-Acetoxy-3,4,6-trihydroxy-3,4-*O*-isopropylidene-5,6-*N,O*-isopropylidene-5-(*tert*-butoxycarbonylamino)hexanal (16). The thiazole-to-formyl deblocking of compound **15** (0.38 g, 0.83 mmol) was carried out as described above for the epimer **12**. After purification by column chromatography on silica gel (hexane/diethyl ether, 60:40), 0.28 g (83%) of **16** were obtained. Oil; $[\alpha]^{20}_D$ = -7.5 (c 0.57, $CHCl_3$); IR ($CHCl_3$) ν 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.57 (bs, 1H), 5.12 (d, 1H, J=3.4 Hz), 4.48 (dd, 1H, J=8.5, 3.4 Hz), 4.06 (m, 2H), 3.58 (m, 2H), 2.18 (s, 3H), 1.45 (s, 3H), 1.42 (s, 9H), 1.38 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H).

Anal. Calcd for $C_{19}H_{31}NO_8$: C, 56.84; H, 7.78; N, 3.49. Found: C, 56.69; H, 7.89; N, 3.62.

Mannojirimycin (-)-(2). The aldehyde **16** (0.2 g, 0.49 mmol) was treated with a 90% aqueous solution of TFA (5 mL) and the mixture was stirred at room temperature for 30 min. The solvent was distilled under reduced pressure. The residue was dissolved in water (10 mL) and passed through a column of Amberlyst A-26 basic ion exchange resin and eluted with water. The resulting solution containing mannojirimycin (-)-**2** was saturated with SO_2 and allowed to stand at room temperature for 2 h. The solvent was concentrated at room temperature or below and the resultant crystalline precipitate was filtered, washed with EtOH and dried to give 86 mg (72%) of the bisulfite **17**, mp 162-164 °C; $[\alpha]^{20}_D$ = -4.5 (c 0.31, H_2O, equilibrium). (Lit.[5] (+)-**2**, mp 163-165 °C; $[\alpha]^{20}_D$ = +4.6 (c 0.5,H_2O); Lit.[21] (+)-**2**, mp 163-165 °C; $[\alpha]^{20}_{578}$ = +2 (H_2O)).

Anal. Calcd for $C_6H_{13}NO_7S$: C, 29.63; H, 5.39; N, 5.76. Found: C, 29.41; H, 5.51; N, 5.90.

The free base mannojirimycin (-)-**2** can be obtained from the bisulfite derivative by treatment with Dowex 1 (HO^-) resin as described.[21]

(*3R*)-4-Hydroxy-*N,O*-isopropylidene-3-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)-1(*E*)-butene (19). To a well-stirred suspension of 2-thiazolylmethyltriphenylphosphonium chloride[23] (2.61 g, 6.60 mmol) in C_6H_6 (50 mL), potassium *tert*-butoxide (0.77 g, 6.60 mmol) was added. After 3 h stirring at room temperature, a solution of *N-tert*-butoxycarbonyl L-serinal acetonide[11] **3** (1.50 g, 6.55 mmol) in C_6H_6 (20 mL) was added dropwise and stirring was continued for 20 h at room temperature. The reaction mixture was filtered through Celite, the solvent was removed under vacuum and the residue chromatographed on silica gel (hexane/diethyl ether, 80:20) to give 1.87 g (92%) of **19**. Yellow solid; mp 80-82 °C; $[\alpha]^{20}_D$ = -155.0 (c 0.26, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.73 (d, 1H, J=3.2 Hz), 7.18 (d, 1H, J=3.2 Hz), 6.60 (m, 2H), 4.49 (pseudo dt, 1H, J=5.9, 2.6 Hz), 4.10 (dd, 1H, J=8.7, 5.9 Hz), 3.80 (dd, 1H, J=8.7, 2.7 Hz), 1.53 (s, 3H), 1.47 (s, 3H), 1.42 (s, 9H).

Anal. Calcd for $C_{15}H_{22}N_2O_3S$: C, 58.04; H, 7.14; N, 9.02. Found: C, 58.22; H, 7.32; N, 8.87.

(*1R,2S,3S*)-1,2,4-Trihydroxy-*N,O*-isopropylidene-3-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)butane (20a) and (*1S,2R,3S*)-1,2,4-trihydroxy-*N,O*-isopropylidene-3-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)butane (20b). The osmilation of the alkene **16** (1.5 g, 4.84 mmol) was carried out as described above for the enoate **4**. After the usual workup, a mixture of 1,2-diols **20a** and **20b** was obtained in 73:27 ratio by ^1H NMR. These compounds were separated by column chromatography on silica gel (hexane/diethyl ether 30:70). .

20a (1.05 g, 63%) (R_f: 0.22). Sticky oil; $[\alpha]^{20}_D$ = -55.8 (c 0.26, $CHCl_3$); ^1H NMR ($CDCl_3$+D_2O) δ 7.74 (d, 1H, J=3.2 Hz), 7.25 (d, 1H, J=3.2 Hz), 4.94 (bs, 1H), 4.28 (m, 1H), 4.08-3.98 (m, 3H), 1.54 (s, 3H), 1.50 (s, 9H), 1.42 (s, 3H).

Anal. Calcd for $C_{15}H_{24}N_2O_5S$: C, 52.31; H, 7.02; N, 8.13. Found: C, 52.59; H, 6.70; N, 7.97.

20b (0.38 g, 23%) (R_f: 0.26). Sticky oil; $[\alpha]^{20}_D$ = -8.1 (c 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$+D_2O) δ 7.70 (d, 1H, J=3.2 Hz), 7.26 (d, 1H, J=3.2 Hz), 4.91 (bs, 1H), 4.34 (m, 1H), 4.18-4.06 (m, 3H), 1.57 (s, 3H), 1.50 (s, 3H), 1.48 (s, 9H).

Anal. Calcd for $C_{15}H_{24}N_2O_5S$: C, 52.31; H, 7.02; N, 8.13. Found: C, 52.31; H, 6.77; N, 8.34.

(*1R,2S,3S*)-1,2,4-Trihydroxy-1,2-*O*-isopropylidene-3,4-*N,O*-isopropylidene-3-(*tert*-butoxycarbonylamino-1-(2-thiazolyl)butane (21). The acetonization of compound **20a** (0.9 g, 2.6 mmol) was carried out as described above for **10**. After purification by column chromatography on silica gel (hexane/diethyl ether, 80:20), 0.95 g (95%) of **21** were obtained. Oil; $[\alpha]^{20}_D$ = -27.2 (c 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.72 (d, 1H, J=3.2 Hz), 7.28 (d, 1H, J=3.2 Hz), 5.37 (d, 1H, J=7.2 Hz), 4.82 (dd, 1H, J=7.2, 4.2 Hz), 4.30 (ddd, 1H, J=6.1, 5.0, 4.2 Hz), 4.11 (m, 2H), 1.50 (s, 6H), 1.48 (s, 12H), 1.46 (s, 3H).

Anal. Calcd for $C_{18}H_{28}N_2O_5S$: C, 56.23; H, 7.34; N, 7.28. Found: C, 56.42; H, 7.44; N, 7.46.

(*2R,3S,4S*)-2,3,5-Trihydroxy-2,3-*O*-isopropylidene-4,5-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)pentanal (22). The thiazolyl-to-formyl deblocking of compound **21** (0.8 g, 2.1 mmol) was carried out as described above for **12**. After purification by column chromatography on silica gel (hexane/diethyl ether, 60:40), 0.55 g (80%) of **22** were obtained. Oil; $[\alpha]^{20}_D$ = -30.6 (c 1.10, $CHCl_3$); IR ($CHCl_3$) ν 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.68 (d, 1H, J=1.5 Hz), 4.58 (dd, 1H, J=6.5, 3.5 Hz), 4.42 (dd, 1H, J=6.5, 1.5 Hz), 4.28-3.99 (m, 3H), 1.52 (s, 3H), 1.49 (s, 9H), 1.47 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H).

Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.05; H, 8.18; N, 4.26.

Homologation of the aldehyde 22. To a solution of **22** (0.45 g, 1.37 mmol) in CH_2Cl_2 (30 mL), 2-trimethylsilylthiazole[24,30] **23** (0.22 g, 1.40 mmol) was added. The mixture was stirred at room temperature for 16 h and then the solvent was distilled in vacuo. The residue was dissolved in THF and treated with Bu_4NF (0.37 g, 1.4 mmol). After 2 h stirring at room temperature, the solution was concentrated in vacuo and the residue was partitioned between brine (30 mL) and CH_2Cl_2 (30 mL). The organic layer was dried (Na_2SO_4) and the solvent distilled to yield the crude alcohol **14** in 87% diastereomeric purity by ^1H NMR. Purification by column chromatography (hexane/diethyl ether, 70:30) afforded 0.45 g (79%) of pure **14** which was identical (NMR spectra and optical rotation) to that obtained from the reduction of the ketone **7a** with Red-Al .

(*1S,3R,4S*)-1,3-Dibenzyloxy-5-hydroxy-4,5-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)pentane (27). To a solution of the β-hydroxy ketone[27] **25** (0.7 g, 1.95 mmol) in THF (20 mL) and methanol (4.7 mL) at -78 °C was added diethylmethoxyborane (2.15 mL of a 1.0 M solution in THF, 2.15 mmol). After 15 min, the solution was treated with sodium borohydride (81.5 mg, 2.15 mmol). The suspension was stirred at -78 °C for 6 h, and then quenched with acetic acid (1.5 mL) at -78 °C. The mixture was partitioned between brine (30 mL) and ethyl acetate (30 mL), and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried ($NaHSO_4$), and concentrated in vacuo. The residue was dried again by treatment with anhydrous methanol (20 mL) and removal of the solvent under reduced pressure. This operation was repeated five times to give 0.64 g (92%) of the 1,2-diol **26** which appeared by ^1H NMR ≥ 95% diastereomerically pure. This material was dissolved in anhydrous dimethylformamide (10 mL), cooled to 0 °C and NaH (153 mg of a 60% dispersion in mineral oil, 4.0 mmol) was added. After 15 min at 0 °C the reaction mixture was treated with benzyl bromide (0.68 g, 4.0 mmol) and stirring was continued at room temperature

for 12 h. The mixture was poured into water (50 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Chromatography on silica gel (hexane/diethyl ether, 70:30) of the resultant material afforded 0.93 g (89% from **25**) of pure **27**. Oil; $[\alpha]^{20}_D$ = -29.0 (c 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.73 (d, 1H, J=3.2 Hz), 7.31-7.26 (m, 11H), 4.93 (dd, 1H, J=7.8, 6.1, Hz), 4.60-4.50 (m, 4H), 4.10-4.01 (m, 2H), 3.90 (m, 2H), 2.23 (ddd, 1H, J=14.2, 8.1, 6.1 Hz), 2.05 (ddd, 1H, J=14.2, 7.8, 4.9 Hz), 1.51 (s, 9H), 1.41 (s, 3H), 1.40 (s, 3H).

Anal. Calcd for $C_{30}H_{38}N_2O_5S$: C, 66.89; H, 7.11; N, 5.20. Found: C, 66.97; H, 7.43; N, 4.86.

(*1R,3R,4S*)-1,3-Dibenzyloxy-5-hydroxy-4,5-*N,O*-isopropylidene-4-(*tert*-butoxycarbonylamino)-1-(2-thiazolyl)pentane (29). To a solution of tetramethylammonium triacetoxyborohydride (3.60 g, 13.7 mmol) in 8 mL of acetonitrile was added 8 mL of anhydrous acetic acid. The mixture was stirred at room temperature for 30 min, cooled to -35 °C and then a solution of the β-hydroxy ketone[27] **25** (0.7 g, 1.95 mmol) in acetonitrile (8 mL) was added. Stirring at -35 °C was continued for 36 h. Then, 10 mL of aqueous 1N solution of sodium potassium tartrate was added. The reaction mixture was allowed to warm to room temperature and partitioned between ethyl acetate (25 mL) and saturated aqueous $NaHCO_3$ (25 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give 0.66 g (94%) of crude 1,2-diol **28** which appeared by ^1H NMR ≥ 95% diastereomerically pure. Benzylation of this material as described above for **26** afforded, after column chromatography on silica gel (hexane/diethyl ether, 70:30) pure **29** as an oil; $[\alpha]^{20}_D$ = +5.2 (c 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.72 (d, 1H, J=3.2 Hz), 7.32-7.26 (m, 11H), 4.94 (dd, 1H, J=8.4, 4.4 Hz), 4.64 (d, 1H, J=11.5 Hz), 4.53 (d, 1H, J=11.8 Hz), 4.41 (d, 1H, J=11.8 Hz), 4.29 (d, 1H, J=11.5 Hz), 4.09 (m, 2H), 3.90 (m, 2H), 2.00 (m, 2H), 1.54 (s, 3H), 1.50 (s, 3H), 1.44 (s, 9H).

Anal. Calcd for $C_{30}H_{38}N_2O_5S$: C, 66.89; H, 7.11; N, 5.20. Found: C, 67.13; H, 7.32; N, 5.40.

(*2S,4R,5S*)-2,4-Dibenzyloxy-6-hydroxy-5,6-*N,O*-isopropylidene-5-(*tert*-butoxycarbonylamino)hexanal (30). The thiazole-to-formyl deblocking of compound **27** (0.50 g, 0.93 mmol) was carried out as described above for compound **12**. After purification by column chromatography on silica gel (hexane/diethyl ether, 60:40), 0.37 g (84%) of the aldehyde **30** were obtained. Oil; $[\alpha]^{20}_D$ = -10.7 (c 0.14, $CHCl_3$); IR ($CHCl_3$) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.55 (bs, 1H), 7.34-7.26 (m, 10H), 4.66 (d, 1H, J=10.7 Hz), 4.62-4.52 (m, 3H), 4.14 (m, 1H), 4.08 (m, 1H), 3.96-3.84 (m, 3H), 1.96 (m, 2H), 1.52 (s, 3H), 1.47 (bs, 12H).

Anal. Calcd for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90. Found: C, 69.75; H, 7.92; N, 2.70.

2,4-Di-*O*-benzyl-3,5-dideoxy-1,5-imino-1-*O*-methyl-*N*-(*tert*-butoxycarbonyl)-*L*-β-glucitol (31). To a solution of the aldehyde **30** (0.35 g, 0.72 mmol) in ahydrous methanol (30 mL), *p*-toluensulfonic acid monohydrate (1.5 mg, 0.0078 mmol) was added and the mixture was heated at 50 °C for 40 min . The reaction mixture was treated with saturated aqueous $NaHCO_3$ (50 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent distilled under reduced pressure. The crude product was chromatographed on silica gel (hexane/diethyl ether, 40:60) to give 0.29 g (88%) of pure **31**. Oil; $[\alpha]^{20}_D$ = -33.3 (c 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.38-7.26 (m, 10H), 4.72 (d, 1H, J=12.5 Hz),

4.60 (m, 2H), 4.40 (d, 1H, J=12.5 Hz), 4.28 (m, 1H), 3.94-3.82 (m, 2H), 3.0-3.64 (m, 3H), 3.42 (s, 1.5H) and 3.41 (s, 1.5H) (s, 3H, in DMSO at 100 °C), 2.80 (bs, 1H, ex. D_2O), 1.96-1.85 (m, 2H), 1.25 (s, 9H).

Anal. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 68.57; H, 7.97; N, 2.85.

(*2R,4R,5S*)-2,4-Dibenzyloxy-6-hydroxy-5,6-*N,O*-isopropylidene-5-(*tert*-butoxycarbonylamino)hexanal (32). The thiazolyl-to-formyl deblocking of compound **29** (0.50 g, 0.93 mmol) was carried out as described above for compound **12**. After purification by column chromatography on silica gel (hexane/diethyl ether, 60:40), 0.38 g (85%) of **32** were obtained. Oil; $[\alpha]^{20}_D$ = +2.6 (c 0.72, $CHCl_3$); IR ($CHCl_3$) ν 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.57 (d, 1H, J=2.0 Hz), 7.30-7.22 (m, 10H), 4.64 (d, 1H, J=11.0 Hz), 4.58 (d, 1H, J=11.7 Hz), 4.37 (d, 1H, J=11.0 Hz), 4.34 (d, 1H, J=11.7 Hz), 4.14 (m, 1H), 4.08 (m, 1H), 3.92-3.84 (m, 3H), 1.84-1.70 (m, 2H), 1.54 (s, 3H), 1.49 (s, 3H), 1.41 (s, 9H).

Anal. Calcd for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90. Found: C, 69.69; H, 7.60; N, 2.75.

2,4-Di-*O*-benzyl-3,5-dideoxy-1,5-imino-1-*O*-methyl-*N*-(*tert*-butoxycarbonyl)-*L*-β-mannitol (33). The cyclization of compound **32** (0.75 g, 0.72 mmol) was carried out as described above for compound **30**. After purification by column chromatography on silica gel (hexane/diethyl ether, 40:60), 0.28 g (85%) of **33** were obtained. Oil; $[\alpha]^{20}_D$ = +4.6 (c 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35-7.26 (m, 10H), 4.60-4.40 (m, 4H), 4.20 (dd, 1H, J=6.0, 4.9 Hz), 3.97 (d, 1H, J=6.0 Hz), 3.83 (ddd, 1H, J=11.8, 5.7, 4.2 Hz), 3.78 (m, 1H), 3.68 (dd, 1H, J=10.9, 5.7 Hz), 3.60 (dd, 1H, J=10.9, 4.2 Hz), 3.42 (s, 1.5H) and 3.39 (s, 1.5H) (s, 3H in DMSO at 100 °C), 2.60 (bs, 1H, ex. D_2O), 2.20-1.94 (m, 2H), 1.38 (s, 9H).

Anal. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 68.11; H, 7.81; N, 3.19

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