A Divergent Route to Nojirimycin Analogues from L-Serinal and 2-Acetylthiazole

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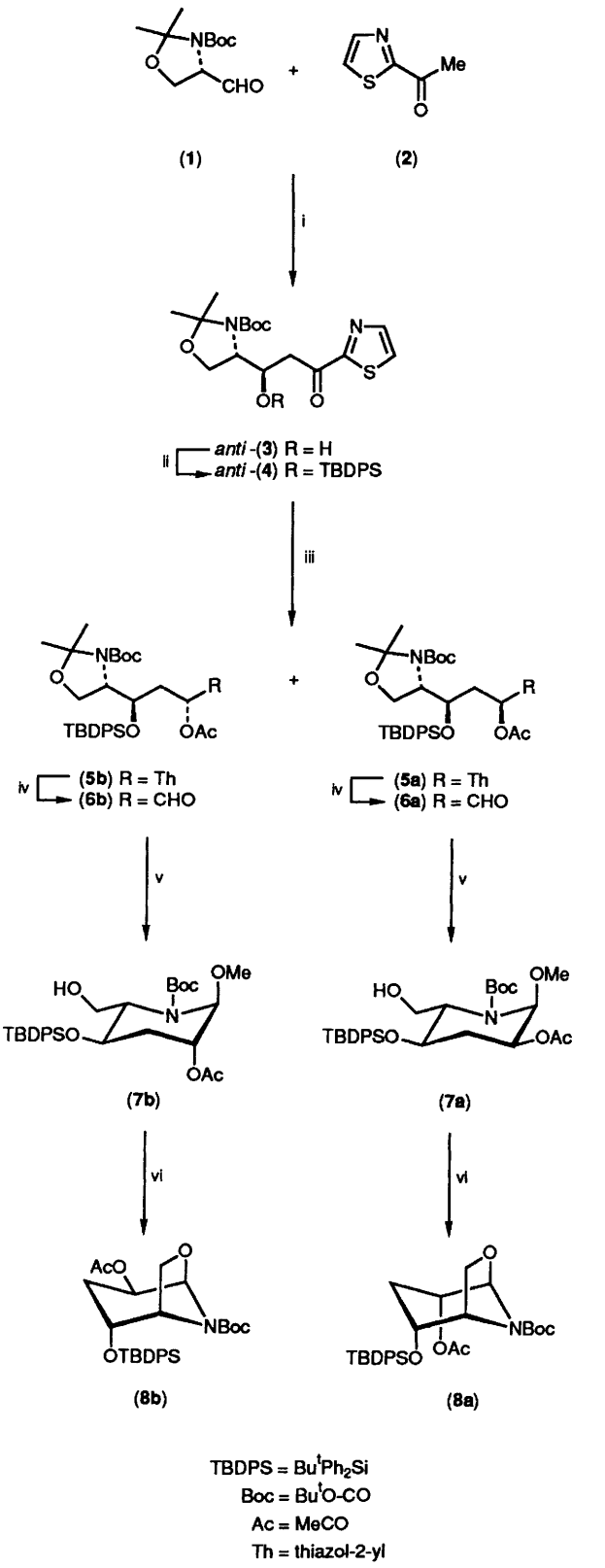
A five-step synthesis of *O,N*-protected (+)-3-deoxynojirimycin (**7a**) and (+)-3-deoxymannojirimycin (**7b**) from *N*-Boc L-serinal acetonide (**1**) employing 2-acetylthiazole (**2**) as a masked α-hydroxypropanal β-anion synthon is described.

There is a growing interest in synthetic methodologies towards polyhydroxylated piperidines since these compounds have been shown to possess potent inhibitory activity against various glucosidases and mannosidases.[1] These compounds (aza sugars) are related to glucosides by substitution of the pyranose oxygen with the amino function and eventually deoxygenation of other positions. Among various 5-deoxy- and 1,5-dideoxy-5-iminohexitols, nojirimycin[2] (5-amino-5-deoxy-D-glucopyranose) and mannojirimycin[3] (5-amino-5-deoxy-D-mannopyranose) as well as their 1-deoxy derivatives, have been the target of several synthetic efforts,[4] most of which involved elaborations of natural sugars. In view of interest in the structure and enzyme-inhibitory activity relationship, the demand for chemical modifications of these compounds has increased. Here we describe a short and facile synthetic sequence for the preparation of (+)-3-deoxynojirimycin (**7a**) and (+)-3-deoxymannojirimycin (**7b**) from the readily available and configurationally stable[5] L-serine derived aldehyde (**1**) *via* thiazole-masked aminohexoses.[6] The main feature of this method is the chain elongation of (**1**) into a three-carbon homologue employing 2-acetylthiazole (**2**) as a very effective equivalent to the α-hydroxypropanal β-anion synthon.[7]

Treatment of *N*-t-butoxycarbonyl L-serinal acetonide (**1**) in



Scheme 1. Only the major isomers *anti*-(**3**) and *anti*-(**4**) are shown for convenience. *Reagents and conditions*: i, Bu^{t}OLi, THF, −40 °C; ii, Bu^{t}Ph$_2$SiCl, imidazole, dimethylformamide, room temp.; iii, $NaBH_4$, MeOH, 0 °C, then Ac_2O–pyridine; iv, MeI, MeCN, reflux, then $NaBH_4$, MeOH, 0 °C, then $HgCl_2$, H_2O–MeCN, room temp.; v, TsOH (Ts = $OSO_2C_6H_4Me$-*p*), MeOH, 50 °C; vi, TsOH, toluene, reflux.

tetrahydrofuran (THF) with the lithium enolate derived from 2-acetylthiazole (**2**) as described,[7] produced the aldol (**3**) as a mixture of *syn* and *anti* diastereoisomers in 70% overall yield (Scheme 1). The protection of the hydroxy group with the t-butyldiphenylsilyl group, by treatment of this mixture with t-butyldiphenylchlorosilane, afforded the *O*-silyl derivatives† *anti*-(**4**) and *syn*-(**4**) (75%) which were separated by flash chromatography (silica, light petroleum–diethyl ether, 75 : 25) in *ca.* 80 : 20 ratio.‡ The reduction ot *anti*-(**4**) in methanol with $NaBH_4$ and successive acetylation of the hydroxy group with acetic anhydride and pyridine afforded the differentially protected *syn*- and *anti*-1,3-diols (**5a**) and (**5b**) in 70 : 30 ratio§ by NMR spectroscopy and 88% overall yield. Stereochemical assignments for (**5a**) and (**5b**) followed their conversion into the corresponding di-*O*-acetates by desilylation and subsequent acetylation and comparison with authentic samples.[7] After separation by flash chromatography (silica, diethyl ether–light petroleum, 60 : 40) the individual isomers (**5a**) and (**5b**) were converted into the aldehydes (**6a**) and (**6b**) (60—65%) by the one-pot thiazolyl-to-formyl deblocking sequence[8] involving *N*-methylation, $NaBH_4$-reduction, and mercury-mediated hydrolysis. The cyclization of (**6a**) to the corresponding azapyranose was first examined. Wishing to preserve at this stage the *N*-Boc protection, the cleavage of the oxazolidine ring was effected by treatment of (**6a**) in methanol with toluene-*p*-sulphonic acid (reflux, 30 min), giving, after silica gel column chromatography (light petroleum–ethyl acetate, 70 : 30), the *O*,*N*-protected (+)-3-deoxynojirimycin (**7a**)¶ (28%) and the 1,6-anhydro derivative (**8a**)¶ (45%). Under milder conditions (50 °C, 40 min), compound (**6a**) gave (**7a**) as a single product (53%) which was successively converted to the 1,6-anhydro sugar (**8a**) (80%) by treatment with toluene-*p*-sulphonic acid in refluxing benzene for 30 min.

† All compounds showed consistent NMR and IR spectral data with the assigned structure and gave satisfactory elemental analyses.

‡ *Syn* and *anti* *O*-silyl derivatives (**4**) are almost quantitatively and more easily separated than *syn* and *anti* aldols (**3**).

§ No substantial change of the level of diastereoselectivity was observed using other reducing agents [$LiAlH_4$, $LiAlH_4$–LiI, di-isobutylaluminium hydride (DIBAL), $Zn(BH_4)_2$].

¶ *Selected spectroscopic data*: (**7a**), oil, $[\alpha]_D^{20}$ +25.6° (*c* 0.39, $CHCl_3$); IR $\nu_{max.}$ ($CHCl_3$) 3400, 1730, 1690 cm^{-1}; ^{1}H NMR (80 MHz, C_6D_6–D_2O, 90 °C), δ 1.20 (s, 9 H), 1.40 (s, 9 H), 1.85 (s, 3 H), 2.05 (t, 2 H, *J* 3.6 Hz), 3.22 (s, 3 H), 3.37 (d, 1 H, *J* 6.0 Hz), 3.41 (d, 1 H, *J* 5.6 Hz), 4.20 (m, 1 H), 4.41 (m, 1 H), 5.05 (dt, 1 H, *J* 3.6, 2.4 Hz), 5.50 (d, 1 H, *J* 2.4 Hz), 7.25 (m, 6 H), 7.80 (m, 4 H).

(**8a**), oil, $[\alpha]_D^{20}$ +4.3° (*c* 0.69, $CHCl_3$); ^{1}H NMR (80 MHz, C_6D_6, 63 °C) δ 1.22 (s, 9 H), 1.40 (s, 9 H), 1.55 (m, 2 H), 1.90 (s, 3 H), 2.80 (dd, 1 H, *J* 14.6, 1.4 Hz), 3.15 (dd, 1 H, *J* 14.6, 10.0 Hz), 3.35 (br, 1 H), 4.42 (br, 1 H), 4.75 (br, 1 H), 6.03 (d, 1 H, *J* 3.6 Hz), 7.22 (m, 6 H), 7.85 (m, 4 H).

(**7b**), oil, $[\alpha]_D^{20}$ +15.0° (*c* 1.02, $CHCl_3$), IR $\nu_{max.}$ ($CHCl_3$) 3400, 1730, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.08 (s, 4.5 H) and 1.10 (s, 4.5 H) (s, 9 H, in C_6D_6–D_2O, 90 °C, 80 MHz), 1.42 (s, 4.5 H) and 1.52 (s, 4.5 H) (s, 9 H, in C_6D_6–D_2O, 90 °C, 80 MHz), 1.92 (m, 1 H), 2.08 (m, 1 H), 2.14 (s, 3 H), 2.40 (dd, 0.5 H, *J* 8.8, 4.0 Hz), 3.2 (m, 1 H), 3.32 (m, 1 H), 3.38 (s, 1.5 H), and 3.45 (s, 1.5 H) (s, 3 H, in C_6D_6–D_2O, 90 °C, 80 MHz), 3.91 (t, 0.5 H, *J* 4.6 Hz), 4.13 (m, 2 H), 5.36 (t, 0.5 H, *J* 4.0 Hz), and 5.40 (t, 0.5 H, *J* 4.0 Hz) (still multiplet in C_6D_6–D_2O, 90 °C, 80 MHz), 5.52 (d, 0.5 H, *J* 3.5 Hz), and 5.68 (d, 0.5 H, *J* 3.5 Hz) (d 1 H, *J* 3.5 Hz in C_6D_6–D_2O, 90 °C, 80 MHz), 7.40 (m, 6 H), 7.68 (m, 4 H).

(**8b**), oil, $[\alpha]_D^{20}$ +20.1° (*c* 4.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.08 (s, 9 H), 1.52 (s, 9 H) 1.60 (ddd, 1 H, *J* 14.5, 10.5, 4.3 Hz), 1.95 (br. dd, 1 H, *J* 14.5, 6.0 Hz), 2.06 (s, 3 H), 3.51 (d, 1 H, *J* 8.7 Hz), 3.58 (dd, 1 H, *J* 8.7, 5.3 Hz), 3.88 (dt, 1 H, *J* 3.7, 1.7 Hz), 4.42 (br. s, 1 H), 5.12 (ddd, 1 H, *J* 10.5, 6.0, 1.6 Hz), 5.70 (br. s, 1 H), 7.42 (m, 6 H), 7.70 (m, 4 H).

This is consistent with the α-anomeric form and $^1C_4$ conformation of the amino-pyranose (**7a**) and its conversion to (**8a**) by inversion to the $^4C_1$ conformation and cyclization by an internal S_N2cA reaction. Similarly, starting from the aldehyde (**6b**), the *O,N*-protected (+)-3-deoxymannojirimycin (**7b**)¶ (57%) was synthesised and transformed into the 1,6-anhydro derivative (**8b**)¶ (95%). This provides a five-step synthesis of aza sugars of the nojirimycin family in which the new asymmetric centres are created in subsequent steps by exploiting the 2*S* configuration of L-serine and the thiazole ring is employed as an effective formyl group equivalent. Application of this technology to the *de novo* synthesis of various aza sugars now becomes of interest.

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