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Tetrahedron
Tetrahedron 61 (2005) 1413–1416

Total synthesis of 1-deoxygulonojirimycin. Revision of the absolute configuration of the natural product

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Received 28 October 2004; revised 2 December 2004; accepted 2 December 2004

Available online 16 December 2004

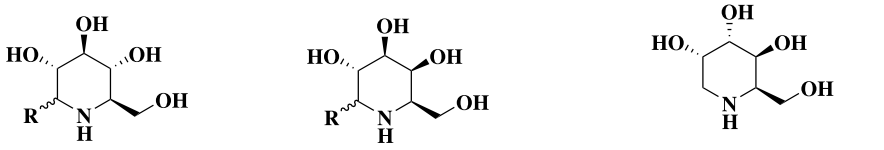
Abstract—A concise, stereoselective synthesis of 1-deoxygulonojirimycin was achieved and the absolute configuration of the natural product was revised. Key features involve diastereoselective oxazoline formation catalyzed by palladium(0), RCM and dihydroxylation.

1. Introduction

Polyhydroxylated piperidines have aroused the widespread attention of organic chemists in recent years due to their very promising biological activity profile and synthetically challenging structural features present in them.[1] Especially, they have been postulated as possible therapeutics including the treatment of viral infections,[2] diabetes,[3] and cancers,[4] and as invaluable tools in the study of enzyme mechanism.[5] These polyhydroxylated piperidines generically termed as iminosugars ('azasugars'), closely resemble monosaccharides in terms of their shape and structure. Nojirimycin(**1**)[6] and 1-deoxynojirimycin(**2**)[7] are analogues of D-glucose and they are glucosidase inhibitors. Similarly, (+)-galactonojirimycin(**3**) and its reduction product (+)-1-deoxygalactonojirimycin(**4**) have been shown to display strong inhibitory activity toward several β-galactosidases[8] and α-galactosidases,[9] and 1-deoxygulonojirimycin(**5**) is a potent and selective inhibitor of fucosidases[10] (Fig. 1).

In our previous report,[11] we showed that the palladium(0)-catalyzed oxazoline formation of homoallyl benzamide coming from protected D-serinol proceeded with high stereoselectivity. And we accomplished the total synthesis of 1-deoxygalactonojirimycin using stereoselective dihydroxylation and piperidine formation by catalytic hydrogenation from chiral oxazoline.[11g]

As part of a program directed at expanding the synthetic utility of oxazoline as a chiral building block for the synthesis of natural products, we report herein a concise and highly stereoselective total synthesis of 1-deoxygulonojirimycin using *trans*-oxazoline **8**, and revise the absolute configuration of natural 1-deoxygulonojirimycin.[12]



1. R=OH (nojirimycin)
2. R=H (1-deoxynojirimycin)
3. R=OH (galactonojirimycin)
4. R=H (1-deoxygalactonojirimycin)
5. 1-deoxygulonojirimycin

Figure 1. Glycosidase inhibitors with the 1-deoxy-azasugar structure.

Keywords: Polyhydroxylated piperidines; Azasugars; Synthesis; Oxazoline.
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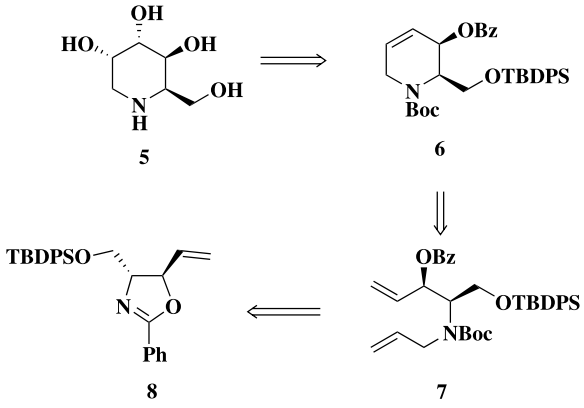
doi:10.1016/j.tet.2004.12.001

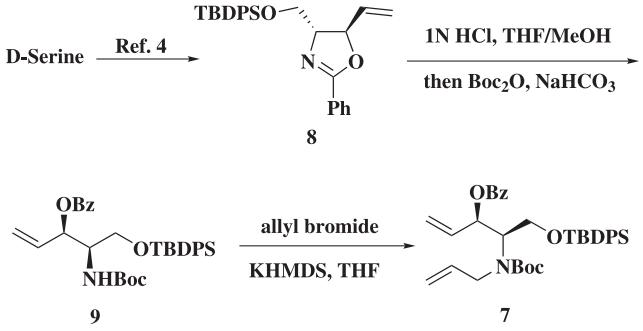
2. Results and discussion

Our retrosynthetic analysis is shown in Scheme 1. Deoxyazasugar **5** may be synthesized by stereoselective dihydroxylation of piperidine compound **6** which would be prepared by ring-closing metathesis (RCM) of *di*-olefin compound **7**. And *di*-olefin compound **7** may be synthesized by hydrolysis and allylation of *trans*-oxazoline **8**. The synthesis of *trans*-oxazoline **8** is made from D-serine according to the known procedure.[11b]



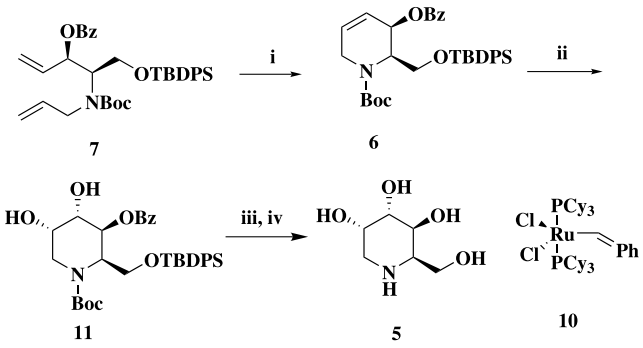
Scheme 1. Retrosynthetic analysis.

Hydrolysis of the TBDPS protected oxazoline **8** under acidic conditions yielded the ammonium hydrochloride benzoate, which, upon neutralization in the presence of di-*tert*-butyl dicarbonate, resulted in the formation of **9** in 89% yield.[13] *N*-Allylation of carbamate **9** using allylbromide and potassium bis(trimethyl)amide gave the desired *di*-olefin compound **7** in 98% yield (Scheme 2).



Scheme 2. Reagents and conditions: (i) 2 N HCl, THF, rt, 16 h, then Boc_2O, $NaHCO_3$, rt, 2 h, 89%; (ii) allyl bromide, KHMDS, THF/DMF (3:1), 0 °C, 30 min, then rt, 5 h, 98%.

Ring-closing metathesis (RCM) of **7** using Grubbs' catalyst,[14,15] $Cl_2(PCy_3)_2Ru{=}CHPh$, (5 mol%) in CH_2Cl_2 for 9 h at room temperature afforded piperidine compound **6** in 96% yields. The stereoselective dihydroxylation[16] of **6** using a catalytic amount of osmium tetroxide with 1.5 equiv of *N*-methylmorpholine *N*-oxide as reoxidant (OsO_4/NMO) in acetone afforded diol **11** as a single isomer in 92% yields. After deprotection of all protecting group with aqueous 6 N HCl in refluxing MeOH, ion-exchange chromatography gave the 1-deoxygulonojirimycin **5** in 75% yields (Scheme 3).



Scheme 3. Reagents and conditions: (i) 10 (5 mol%), CH_2Cl_2, rt, 9 h, 96%; (ii) OsO_4 (5 mol%), NMO, acetone, rt, 12 h, 92%; (iii) 6 N HCl, MeOH, reflux, 24 h; (iv) Dowex-50WX8 H+ resin, 3% NH_4OH, 75% (for 2 steps).

The synthetic product **5** was found to be identical with the natural 1-deoxygulonojirimycin and those previously reported by NMR spectroscopy but possessing the opposite sign of optical rotation. Hence, the absolute configuration of the naturally occurring aza-sugar 1-deoxygulonojirimycin is (2*S*,3*R*,4*R*,5*R*), as shown in Figure 2.[17]

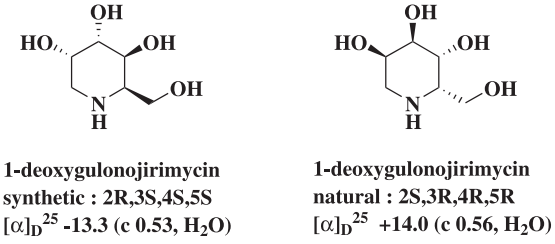


Figure 2.

3. Conclusions

We have accomplished the asymmetric stereoselective synthesis of 1-deoxygulonojirimycin **5** from *trans*-oxazoline **8**. We utilized the diastereoselective oxazoline formation by palladium(0) catalyst, ring-closing metathesis (RCM) of di-olefin compound **7** to construct the piperidine moiety, and subsequent dihydroxylation to install four contiguous stereogenic centers in the piperidine ring.

4. Experimental

4.1. General

Optical rotations were measured on a JASCO DIP 1020 digital polarimeter. ^1H NMR spectra were recorded at Varian inova FT NMR 500 or 300 MHz in $CDCl_3$ unless specified otherwise. ^{13}C NMR spectra were recorded at 125 or 75 MHz in $CDCl_3$ unless specified otherwise. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$. IR spectra were measured on a Bruker FT-IR spectrometer. The high resolution mass spectra (FAB-MS) were taken on a JMS-700 Mstation. Flash chromatography was executed with Merck Kiesegel 60 (230–400 mesh) using mixtures of ethyl acetate and hexane as eluants. Ethyl acetate and hexane were dried and purified by distillation prior to use. Tetrahydrofuran (THF) and diethylether (Et_2O) was distilled over sodium and

benzophenone (indicator). Methylene chloride (CH_2Cl_2) was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification.

4.1.1. (4*R*,5*R*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2-phenyl-5-vinyl-4,5-dihydrooxazole (8). *trans*-Oxazoline **8** was synthesized according to the Ref. 10b; colorless oil; $[\alpha]_D^{25} = +24.9$ (*c* 2.0, $CHCl_3$); IR (neat) 3069, 2930, 2857, 1648 cm^{-1}; ^1H NMR (300 MHz) δ 1.02 (s, 9H), 3.78 (dd, $J=10.5$, 6.5 Hz, 1H), 3.94 (dd, $J=10.5$, 4.0 Hz, 1H), 4.10 (ddd, $J=6.5$, 6.5, 4.0 Hz, 1H), 5.12 (dddd $J=6.5$, 6.5, 1.5, 1.5 Hz, 1H), 5.23 (ddd $J=10.0$, 1.5.1.5 Hz, 1H), 5.33–5.39 (ddd, $J=16.5$, 1.5, 1.5 Hz, 1H), 5.91–6.02 (ddd, $J=16.5$, 10.5, 6.5 Hz, 1H), 7.32–7.48 (m, 9H), 7.65–7.72 (m, 4H), 7.95–7.98 (m, 2H); ^{13}C NMR (75 MHz) δ 19.6, 27.1. 65.6, 74.2, 83.3, 116.9, 127.97, 128.02, 128.6, 129.9, 130.00, 130.04, 131.7, 133.5, 133.7, 135.1, 135.9, 136.0, 136.9, 164.3; HRMS *m*/*z* calcd for $C_{28}H_{32}NO_2Si$ 442.2202, found 442.2207.

4.1.2. (3*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyldiphenylsilyloxy)pent-1-en-3-yl benzoate (9). The alcohol **8** (3.50 g, 7.93 mmol) was dissolved in THF (40 mL) and 2 N HCl (27 mL) and stirred for 16 h at rt. The reaction mixture was cooled in an ice bath, and solid $NaHCO_3$ (30 g) was added. Water (130 mL) was added followed by a solution of Boc_2O (3.46 g, 15.9 mmol) in THF (30 mL). After being stirred at room temperature for 2 h, the solution was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (ethyl acetate/hexane = 1/15) to afford **9** (3.96 g, 89%) as a viscous liquid: $[\alpha]_D^{25} = +10.8$ (*c* 2.0 $CHCl_3$); IR (neat) 2931, 2857, 1722, 1503, 1268 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (s, 9H), 1.36 (s, 9H), 3.71 (dd, $J=10.5$, 5.5 Hz, 1H), 3.77 (dd, $J=10.5$, 4.0 Hz, 1H), 4.07 (m, 1H), 4.83 (d, $J=9.5$ Hz, 1H), 5.27 (d, $J=10.0$ Hz, 1H), 5.39 (d, $J=17.0$ Hz, 1H), 5.79 (dd, $J=$ 6.0, 6.0 Hz, 1H), 5.89 (m, 1H), 7.26 (m, 1H), 7.33–7.43 (m, 7H), 7.54–7.59 (m, 3H), 7.64–7.66 (m, 2H), 8.01 (d, $J=$ 7.5 Hz, 2H); ^{13}C NMR (75 MHz) δ 19.3, 26.8, 27.1, 28.5, 54.7, 63.1, 74.5, 79.7, 119.2, 128.01, 128.08, 128.6, 129.9, 130.1, 133.12, 133.19, 133.3, 133.7, 135.1, 135.83, 135.89, 155.7, 165.8;. HRMS *m*/*z* calcd for $C_{33}H_{42}NO_5Si$ 560.2832, found 560.2821

4.1.3. (3*R*,4*R*)-4-(Allyl(*tert*-butoxycarbonyl)amino)-5-(*tert*-butyldiphenylsilyloxy)pent-1-en-3-yl benzoate (7). To a solution of **9** (1.00 g, 1.79 mmol) in 16 mL of THF/DMF (3:1) were added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 3.93 ml, 1.97 mmol), and allyl bromide (0.19 mL, 2.14 mmol) at 0 °C. The mixture was stirred for 30 min and stirring was allowed to continue for 5 h at rt. The reaction was quenched with a saturated aqueous NH_4Cl solution. The organic phase was separated, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue (ethyl acetate/hexane = 1/15) yielded **7** as a colorless oil (1.05 g, 98%); $[\alpha]_D^{25} = +15.9$ (c 1.0, $CHCl_3$); IR (neat) 2931, 2858, 1723, 1695, 1453 cm^{-1}; ^1H NMR (500 MHz): δ 1.05 (s, 9H), 1.39 (s, 9H), 3.81 (m, 2H), 3.87 (m, 1H), 3.98 (m, 1H), 4.64 (m, 1H), 4.93 (m, 1H), 5.04 (m, 1H), 5.17 (m, 1H), 5.33 (d, $J=$ 17.5 Hz, 1H), 5.65–5.89 (m, 3H), 7.31–7.43 (m, 8H), 7.53 (m, 1H), 7.58–7.65 (m, 4H), 7.96–8.03 (m, 2H); ^{13}C NMR (125 MHz): δ 19.3, 27.2, 28.5, 47.5, 59.6, 62.0, 73.4, 79.9, 115.5, 119.2, 127.9, 128.6, 129.8, 129.9, 130.4, 133.2, 133.4, 133.9, 134.2, 135.8, 136.2, 136.3, 156.2, 165.5; HRMS *m*/*z* calcd for $C_{36}H_{46}NO_5Si$ 600.3145, found 600.3150.

4.1.4. (5*R*,6*R*)-*tert*-Butyl 5-(benzoyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (6). Grubbs' catalyst (72 mg, 0.088 mmol, 5 mol%) was added to a mixture of 7 (1.05 g, 1.75 mmol) in CH_2Cl_2 (70 mL). The reaction mixture was stirred at rt for 9 h, the solvent evaporated, and the residue purified by flash chromatography on silica gel (ethyl acetate/hexane = 1/15) to afford 956 mg of **6** as a colorless oil (96%); $[\alpha]_D^{25} = -20.54$ (*c* 1.0, $CHCl_3$); IR (neat) 2931, 1723, 1699, 1411, 1108 cm^{-1}; ^1H NMR (500 MHz): δ 1.04 (s, 9H), 1.52 (s, 9H), 3.51 3.58 (m, 1H), 3.77–3.91 (m, 2H), 4.34–4.42 (m, 1H), 4.57–4.75 (m, 1H), 4.87–4.92 (m, 1H), 5.60–5.77 (m, 2H), 7.31–7.45 (m, 8H), 7.53 (m, 1H), 7.66–7.75 (m, 4H), 7.80–7.83 (m, 2H)); ^{13}C NMR (125 MHz): δ 14.35, 19.42, 27.03, 28.74, 59.81, 67.11, 80.85, 82.16, 124.67, 127.94, 128.49, 128.63, 129.90, 130.06, 130.16, 130.49, 133.37, 133.51, 133.71, 135.84, 136.08, 155.07, 165.79; HRMS *m*/*z* calcd for $C_{34}H_{42}NO_5Si$ 572.2832, found 572.2833.

4.1.5. (2*R*,3*S*,4*S*,5*S*)-*tert*-Butyl 3-(benzoyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)-4,5-dihydroxypiperidine-1-carboxylate (11). To a solution of **6** (833 mg, 1.46 mmol) in acetone (24 mL) were added *N*-methylmorpholine *N*-oxide (50% aqueous solution, 0.68 mL, 2.91 mmol) and the solution of 4 wt/% OsO_4/water (0.46 mL, 0.073 mmol, 5 mol%). The reaction mixture was allowed to stir for 12 h, at which time all staring material had been consumed as judged by TLC. The reaction mixture was poured into a solution of 15% $Na_2S_2O_3$ (120 mL), extracted with CH_2Cl_2 (100 mL×2). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/1) gave *anti*-diol (813 mg, 92%, single isomer) as an oil; $[\alpha]_D^{25} = -6.1$ (c 1.0, $CHCl_3$); IR (neat) 3435, 2931, 1721, 1696, 1425, 1270, 1109 cm^{-1}; ^1H NMR (500 MHz): δ 1.03 (s, 9H), 1.46 (s, 9H), 3.41 (br d, $J=13.0$ Hz), 3.94 (m, 2H), 4.11 (m, 1H), 4.25 (m, 1H), 4.34 (br s, 1H), 4.68 (br s, 1H), 5.45 (dd, $J=10.0$, 6.5 Hz, 1H), 7.29–7.41 (m, 8H), 7.55–7.67 (m, 5H), 7.91 (m, 2H); ^{13}C NMR (125 MHz) 14.4, 19.2, 27.3, 28.6, 45.1, 55.0, 61.5, 68.9, 70.5, 72.1, 80.8, 128.0, 128.6, 129.8, 130.0, 132.8, 132.9, 133.5, 135.7, 135.8, 155.9, 166.9; HRMS *m*/*z* calcd for $C_{34}H_{44}NO_7Si$ 606.2887, found 606.2883.

4.1.6. 1-Deoxygulonojirimycin(5). To a solution of **11** (742 mg, 1.23 mmol) in MeOH (8 mL) was added 6 N HCl (30 mL, 30.64 mmol). The reaction mixture was refluxed for 36 h and evaporated. The residue was treated with Dowex 50WX8-400 ion-exchange resin using a sequence of water and 3% NH_4OH as eluents to yield **5** (149 mg, 75%) as an oil; $[\alpha]_D^{25} = -13.3$ (*c* 0.53, H_2O) [natural product($[\alpha]_D = +14.0$, *c* 0.56, H_2O)]; ^1H NMR (500 MHz, D_2O): δ 2.65 (dd, $J=12.5$, 10.5 Hz, 1H), 2.82 (dd, $J=12.5$, 5.5 Hz, 1H), 2.93 (td, $J=6.5$, 1.5 Hz, 1H), 3.52 (t, $J=$

6.5 Hz, 2H), 3.85–3.91 (m, 3H); ^{13}C NMR (125 MHz, D_2O) 44.2, 54.2, 61.1, 65.6, 69.3, 70.3; HRMS *m*/*z* calcd for $C_6H_{14}NO_4$ 164.0923, found 164.0924.

Acknowledgements

This work was supported by grant No. R01-2001-000-00214-0 from Korea Science & Engineering Foundation.

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