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Rapid and practical synthesis of (−)-1-deoxyaltronojirimycin†

Oskari K. Karjalainen and Ari M. P. Koskinen*

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Herein a practical and scalable route to 1-deoxyaltronojirimycin is presented. The target is achieved in 9 steps and 43% yield featuring only two chromatographic purifications.

Introduction

The story of the nojirimycins begins with the isolation of nojirimycin (1, Fig. 1) in 1966 by Inuoye et al. from several strains of Streptomyces. This highly polar “heterosugar” was first identified as an antibiotic and later recognized as a glucosidase inhibitor. In 1976, Bayer chemists discovered that the stable, naturally occurring 1-deoxynojirimycin (2, originally synthesized in 1966 by Paulsen et al.) is a potent α-glucosidase inhibitor. Since these seminal discoveries nojirimycins have attracted a great deal of attention both from the academia as well as the pharma industry. Two derivatives of 2 are currently in the market for the treatment of two different human conditions. The inhibitory power of 2 is being realized in miglitol (Glyset®, 3), a drug for treating type II diabetes mellitus. The drug effectively lowers blood sugar levels by inhibiting the break down of dietary sugars. On the other hand, N-butyl-DNJ (Zavesca®, 4) is being used for the treatment of Gaucher disease, a serious lysosomal storage disorder previously only treatable through enzyme replacement therapy. Zavesca® inhibits the biosynthesis of glycosphingolipids, thereby decreasing their accumulation in the body. Besides these two targets, inhibition of several other enzymes have been or are being investigated, including glycosyl transferases, glycogen phosphorylase, sugar nucleoside mutase and metalloproteinases. Zavesca® has also shown some promise as a male contraceptive. Iminosugar derivatives have been reported to be active against the Flaviviridae viral family, cytotoxic against several cancer cell lines and to inhibit angiogenesis. Hence the need to be able to produce practical amounts of nojirimycin analogues with varying stereochemical configurations is apparent. Herein we wish to describe a practical route to (−)-1-deoxyaltronojirimycin (5); a nojirimycin analogue having altrose stereochemistry.

Results and discussion

Due to the high interest the synthetic community has had in these so called azasugars, many imaginative synthetic routes have been devised. Nojirimycins and derivatives thereof have been accessed for example from carbohydrates, amino acids and tartaric acid. Our laboratory has had a long term interest in diastereoselective synthesis of enantiopure (vicinal) amino alcohols from amino acids. Previously we described the diastereoselective synthesis of (−)-1-deoxygalactonojirimycin (DGJ, 6) using the general strategy outlined in Scheme 1. Disconnection along the C1–N bond gives rise to an open-chain compound 8 with a leaving group at C1. This can be thought to be derived from the differentially protected bis-alllylic alcohol 9. This is in turn accesible from Garner’s aldehyde (10) and a protected propargyl alcohol 11 via formal reductive coupling. We have successfully accessed...
allylic alcohols such as 9 through Horner–Wadsworth–Emmons reaction between an amino acid derived β-keto phosphonate and the corresponding aldehyde followed by diastereoselective reduction. However, we noted that the diastereoselectivity of the reduction is highly sensitive to the actual substrate, and more importantly partial racemization of the phosphonate becomes a problem in large scale synthesis. To overcome this problem, we have used a zinc nucleophile generated by hydrozirconation–transmetallation sequence to couple (−)-10 and 12 with exceptional syn preference.21 Instead, we turned our attention to lithiated nucleophiles, as it is known that their coupling step. Despite a promising literature precedent, we were not able to reverse the diastereoselectivity.21 Instead, we turned our attention to lithiated nucleophiles, as it is known that their addition to 10 proceeds with anti preference.

Scheme 2 Key reductive coupling.

The synthesis commenced with the addition of lithiated 12 to the (−)-Garner aldehyde (Scheme 3).22 We found out that if performed in THF, the addition proceeded smoothly and in useful diastereomeric ratio (>15 : 1). No difference in diastereomeric ratio was detected in the presence of HMPA. We then envisioned that reduction of the triple bond with Red-Al would deliver the anti congener of 13. Instead a mixture of 15 and the allene 16 was produced as evidenced by the high carbon shift at δ = 207.9 ppm.23 Under no conditions could the undesired elimination of TBSO be suppressed.

Scheme 3 Alkynylation of 10 and attempted reduction.

In order to avoid problems in the reduction step, we protected the secondary alcohol of 14 as the benzyl ether24 (Scheme 4) followed by desilylation of the primary alcohol. NH4F-HF proved to be a far superior desilylation reagent compared to the standard TBAF (tetrabutylammonium fluoride) both in terms of price and practicality, as no hard to remove tetrabutyl ammonium residues are formed in the reaction. In fact, simple silica gel filtration after the desilylation was to provide 17 in more than adequate purity. Treatment of 17 with 2 equivalents of Red-Al produced exclusively the desired trans-allylic alcohol 18 in near quantitative yield, again without any need to resort to chromatography. Osmium catalyzed dihydroxylation under modified Upjohn conditions provided the tetralol 19 in 81% yield (6:1 dr).25 The diastereomeric mixture proved to be extremely difficult to purify. One of the diastereomers is a good ligand for osmium as the black Os(0) was still present even after three chromatographic runs. Nevertheless, adequate amounts of pure 19 could be produced through this route for further experiments.

Attempted mesylation of the primary alcohol only led to decomposition upon isolation. On the other hand, the tosylate 20 was found to be relatively stable. Our first attempt (TsCl, NEt3, CH2Cl2) delivered the tosylate in meager 35% yield. In an effort to improve the yield, we tried numerous bases and conditions (Table 1). Increasing the temperature significantly improved the yield (entry 2). Added secondary base (DMAP) did not improve the yield, on the contrary significant decomposition was evident (entry 3). We also attempted to catalyze the reaction with dibutyl tin oxide as reported.27 However, the substrate proved to be reluctant to such catalysis (entries 4 and 5). We then proceeded to test several other bases, of which N-methyl imidazole proved to be the best, delivering the desired monotosylate 20 in 67–76% yield. It should be noted, that under no conditions we detected any bistosylated products.

With every functionality in place we were now ready for the ring closure. Removal of the N,O-acetal and the BOC-group was accomplished with hydrochloric acid in methanol in quantitative

Table 1 Monotosylation of 19

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additive</th>
<th>T/°C</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3 eq NEt3</td>
<td>—</td>
<td>-10</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>1.3 eq NEt3</td>
<td>—</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>1.3 eq NEt3</td>
<td>0.1 eq DMAP</td>
<td>RT</td>
<td>n. i.</td>
</tr>
<tr>
<td>4</td>
<td>1.0 eq NEt3</td>
<td>2% Bu2SnO</td>
<td>0</td>
<td>n. i.</td>
</tr>
<tr>
<td>5</td>
<td>1.1 eq NEt3</td>
<td>5% Bu2SnO</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>5.0 eq pyr.</td>
<td>—</td>
<td>0–RT</td>
<td>n. r.</td>
</tr>
<tr>
<td>7</td>
<td>2.0 eq DMAP</td>
<td>—</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>5.0 eq 2,4,6-collidine</td>
<td>0.2 eq DMAP</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>9</td>
<td>1.2 eq N-methyl imidazole</td>
<td>—</td>
<td>0</td>
<td>67–76</td>
</tr>
</tbody>
</table>

*Reaction conditions: A flame-dried flask under argon was loaded with 19 (125 mg, 0.30 mmol, 100 mol%) and 3 mL of CH2Cl2. The flask was cooled down to the appropriate temperature, after which base was added followed by TsCl (63 mg, 0.33 mmol, 105 mol%). Stirred until complete consumption of starting material or for 48 h. * Isolated yields after chromatography. * Not isolated. * No reaction took place.
yield. The cyclization was effected by treating the crude salt with calcium carbonate in methanol, yielding the piperidine 21 in 86% yield after chromatography. If the cyclization was effected using triethyl amine or disopropylethyl amine the crude reaction mixture was difficult to purify due to the oily amine salts. Hydrogenolysis of the remaining protecting group under acidic conditions delivered 5·HCl in quantitative yield, thereby completing the synthesis in 32% overall yield over 9 steps.

However, we were not satisfied with the hard-to-purify dihydroxylation production 19, nor with the low yielding tosylation step. To this end another leaving group was envisioned. Allylic chlorination of 18 delivered the chloride 22 in good yield (88%) with no need for chromatographic purification (Scheme 5). Subsequent dihydroxylation delivered 23 in passable yield (81%) and without erosion of the diastereomeric ratio (6 : 1). Moreover, the dihydroxylation was also attempted using KMnO4. Without buffering (CH2Cl2, 1.5 equivalents of primary hydroxyl group. The dihydroxylation was also attempted without erosion of the diastereomeric ratio (6 : 1). Moreover, the dihydroxylation delivered 23 with no need for chromatographic purification (Scheme 5). Subsequent dihydroxylation delivered 23 in passable yield (81%) and without erosion of the diastereomeric ratio (6 : 1). Moreover, the dihydroxylation was also attempted using KMnO4. Without buffering (CH2Cl2, 1.5 equivalents of primary hydroxyl group. The dihydroxylation was also attempted without erosion of the diastereomeric ratio (6 : 1). Moreover, the dihydroxylation delivered 23 with no need for chromatographic purification (Scheme 5).

Conclusions

Herein we have described a method for producing (-)-altroDNJ hydrochloride in 9 steps with 43% overall yield. Only two chromatographic purifications in the late stages are required, making the route fast and efficient.

Experimental section

Dichloromethane and tetrahydrofuran were obtained from a p.a. quality. Reagents and were obtained from Sigma–Aldrich or from Acros Organics and used as such, unless otherwise stated. TLC monitoring was performed on Merck silica gel 60 F254 (230–400 mesh, aluminium) plates. Stains used to visualize the plates were permanganate (3 g KMnO4, 20 g K2CO3, 5 mL 1 M NaOH, diluted to 300 mL with water), vanillin (3 g vanillin, 2.5 mL conc. H2SO4, 1.5 mL acetic acid, 125 mL EtOH) and UV-light (λ = 254 nm). Flash chromatography was performed on Merck Silica Gel 60 silica. The celite used in filtrations was either Fluka Celite 501 or Sigma–Aldrich Celite 353 Coarse. NMR spectra were recorded on Bruker Avance 400 spectrometer. The spectra were calibrated to either TMS (δ = 0.00 ppm), MeOD (δ = 3.34 ppm, 1H, δ: 49.86 ppm), CDCl3 (δ : 77.00 ppm), Cl-CDCDCl (δ : 6.00 ppm, 13C : 73.8), toluene-d8 (δ : 2.09 ppm, 1H, δ : 20.4) or to D2O (δ : 4.70 ppm, 1H : 49.5 ppm, MeOH as internal standard) depending on the used solvent. Spectra were recorded at 25 °C, unless otherwise stated. Heating of the NMR-samples was performed using a probe heater. IR spectra were recorded on Perkin–Elmer Spectrum One FTIR machine. Optical rotations were measured with Perkin–Elmer 343 polarimeter using sodium D lamp and a 10 cm quartz cuvette. HRMS spectra were recorded on Waters Micromass LCT Premier (ESI/TOF) mass spectrometer.

tert-Butyldimethyl(prop-2-ynloxy)silane (12)

To a solution of propargyl alcohol (1.00 g, 17.8 mmol, 100 mol%) in dry dichloromethane (7 mL) under argon was added tert-butyldimethylsilyl chloride (2.68 g, 17.8 mmol, 100 mol%) followed by imidazole (2.43 g, 35.7 mmol, 200 mol%). The flask was equipped with a condenser after which the solution was heated to reflux. After 2 h the starting material was consumed by TLC and the flask was allowed to cool to room temperature. The reaction was quenched with 10 mL of ice-cold water. The resulting mixture was filtered through a pad of celite. The filtrate was transferred to a separating funnel and the phases were separated. The aqueous phase was extracted 3 × 10 mL CH2Cl2. Combined organic phases were washed with brine (25 mL), dried over Na2SO4 and the bulk of the solvent was evaporated. Distillation under reduced pressure afforded 2.63 g (98%) of clear colorless liquid. Bp = 52 °C (14 torr), Rf 0.68 (1 : 2 EtOAc/Hex, permanganate); 1H-NMR (CDCl3) δ ppm 4.31 (d, 2H, J = 2.4 Hz), 2.39 (t, 1H, J = 2.5 Hz), 0.91 (s, 9H), 0.13 (s, 6H).

(S)-tert-butyl 4-((R)-1(benzloyoxy)-4-hydroxybut-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (17)

A flame-dried flask under argon was charged with 12 (23.7 g, 138.0 mmol, 130 mol%) and 275 mL of dry THF. The solution was cooled to −78 °C and n-BuLi (57.5 mL, 135.0 mmol, 125 mol%, 2.35 M in hexanes) was added over 10 min. The resulting mixture was stirred for an hour. Then 2 (22.7 g, 98.8 mmol, 100 mol%) was added as a THF solution (115 mL + 20 mL for washing, pre-cooled to −78 °C) via cannula over 1 h. The resulting solution was stirred for 1 h and then quenched by adding 100 mL of sat. NH4Cl. The cooling bath was removed and replaced by a warm water bath. After reaching room temperature, the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried over Na2SO4 and concentrated to yield 42.3 g of crude product as slightly yellow oil. Analytical sample was prepared by flash column chromatography (10% ethyl acetate/hexanes).

R, 0.56 (2 : 1 Hex/EtOAc); [α]29 D = −35.0 (c 2.83, DCM) lit. −35.8 (c 1.1 CDCl3); HRMS Found 422.2337 Calculated for 422.2339 C20H37NNaO5Si [M + Na]; 1H-NMR (400 MHz, CDCl3, 60 °C)
A flame-dried flask under argon charged with compound 17 (3.40 g, 9.10 mmol, 100 mol%) and dry THF (45 mL) was placed in an ice/water bath. Then Red-Al was added dropwise (5.55 mL, 18.2 mmol, 65 w-% in toluene). After 15 min of stirring, the reaction was quenched by dropwise addition of MeOH (1 mL, until no further gas evolution occurs). Then 5 g of Rochelle’s Salt was added followed by 5 mL of sat. aq. rochelle’s salt. After 30 min of stirring the mixture was filtered through a pad of celite (filter cake was washed with 3 x 30 mL of methylene chloride) and concentrated. The crude residue was dissolved in methylene chloride and filtered through a pad of silica gel (washed with 50% EtOAc/Hexanes). After concentration 3.43 g (99%) of colorless oil was obtained.

To a solution of 18 (2.28 g, 6.06 mmol, 100 mol%) and citric acid (1.40 g, 7.27 mmol, 120 mol%) in acetone/H2O (8 : 1, 27 ml) was added OsO4 (770 µL [4% in H2O], 0.12 mmol, 2 mol%). To the resulting yellow solution was added N-methylmorpholine N-oxide (0.98 g, 7.27 mmol, 120 mol%) as a single portion. The light green solution was stirred for 6 h, until complete by TLC (color also changes gradually back to yellow). Acetone was evaporated with rotary evaporator, the aqueous residue was acidified with 1 M HCl (3.5 mL) and diluted (20 mL H2O). Extraction (3 x 20 mL EtOAc), brine wash and drying yielded 2.54 g of dark foamy matter.

Separation of the diastereomeric mixture (c. 6 : 1) is extremely difficult. Repeated chromatographic runs (3-4) on MeOH–DCM or EtOAc–DCM gives the product as white foamy matter.

To a stirred solution of 19 (540 mg, 1.33 mmol, 100 mol%) and p-toluenesulfonylchloride (280 mg, 1.46 mmol, 110 mol%) in dry CH2Cl2 (6 mL) under argon was added N-methyl imidazole (250 µL, 2.13 mmol, 150 mol%) at 0 °C. After 4 h of stirring the reaction was quenched with water (10 mL). Aqueous phase
was extracted 3 × 5 mL CH₂Cl₂. Combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. Chromatographic purification (EtOAc–CH₂Cl₂, 0%→30%) gave 510 mg of colorless oil. Decomposes if heated!

\[ R = 0.84 \text{ (65% EtOAc/Hex ~ 1% MeOH)} \ [\alpha]_{D}^{20} = -20.4 \text{ (c = 1.0, DCM)} \]

HRMS Found 588.2244 Calculated for 588.2243 C₂₈H₃₈NNaO₉S [M + Na]+; 1H-NMR (400 MHz, CDCl₃) \( \delta = 7.67-7.74 \) (m, 2 H), 7.20–7.31 (m, 7 H), 4.41–4.82 (m, 2 H), 3.84–4.21 (m, 7 H), 3.34 (br, s, 1 H), 2.36 (s, 3 H), 1.33–1.57 (m, 15 H) ¹³C-NMR: We were unable to obtain a clear spectrum due to the extensive rotamerism and heat sensitivity IR \( \nu_{max}/cm^{-1} = 3392, 1661, 1396, 1366, 1176 \) (neat)

\( (3S,4R,5S,6S)\)-(benzoylloxy)-6-(hydroxymethyl)piperidine-3,4-diol (21) \)

Compound 20 (500 mg, 0.88 mmol, 100-mol%) was dissolved in MeOH (4 mL) and the flask was then cooled to 0 °C. Freshly prepared, saturated HCl(g)/MeOH was added (c. 4 mL) and the cooling bath was removed. After 1 h of stirring, starting material was completely consumed. Solvent was evaporated to give 430 mg of crude as white foam.

HRMS Found 426.1651 Calculated for 426.1586 C₂₀H₂₉NO₇S [M + H]+; IR \( \nu_{max}/cm^{-1} = 3307, 2925, 2884, 1454, 1074 \) (neat)

To a stirred solution of 2 (2.79 g, 7.39 mmol, 100 mol%) in acetone/H₂O (8 : 1, 40 mL) was added citric acid (2.49 g, 12.93 mmol, 175 mol%) followed by OsO₄ (0.94 mL, 0.15 mmol, 2 mol%, 4 w-% in H₂O). After the addition of osmium, the solution changed to yellow/green in color. Finally N-methyl morpholine N-oxide (1.1 g, 8.13 mmol, 110 mol%) was added and the flask was sealed with a cap. After 18 h of stirring the color had changed to bright yellow. To quench the reaction 470 mg of sodium thiosulfate was added. In 5 min black precipitate had formed. Acetone was evaporated under reduced pressure and the residue was dissolved in 35 mL of water. The aqueous mixture was extracted with EtOAc (3 × 25 mL). Combined organic phases were dried over Na₂SO₄ and concentrated to give 2.84 g of foamy glass-like product. Chromatographic purification (30% → 50% → 60% EtOAc/Hex) yielded 2.08 g (65%) of pure 23 and 390 mg of mixed 23 and 2,3-epi-23. Combined yield 2.47 g (81%), 6 : 1 dr (by NMR).

\[ R = 0.56 \text{ (60% EtOAc/Hex)} \ [\alpha]_{D}^{20} = -35.1 \text{ (c. 1.93, DCM); HRMS Found } 452.1812 \text{ Calculated for } 452.1816 \text{ C}_{20}H_{28}NNaO_{10}Cl [M + Na]+; IR \nu_{max}/cm^{-1} = 7.43–7.31 \text{ (m, 5 H), 4.79} \text{ (d, J = 11.3 Hz, 1 H), 4.65} \text{ (d, J = 11.3 Hz, 1 H), 4.28} \text{ (d, J = 3.4, 10.0 Hz, 1 H), 2.71} \text{ (dd, J = 0.7, 2.2, 13.9 Hz, 1 H), 1H-C-NMR (100 MHz, METHANOL-d₃}, 140.8, 130.2, 129.9, 129.5, 76.1, 72.8, 71.8, 69.7, 62.9, 57.2, 47.5; IR \nu_{max}/cm^{-1} = 3307, 2925, 2884, 1454, 1074 (neat) \]

\( (S)-tert-butyl 4-((1S,2R,3R)-1-(benzoylloxy)-4-chloro-2,3-dihydroxybutyl)-2,2-dimethoxyazolidine-3-carboxylate (23) \)

To a flask charged with 23 (560 mg, 1.3 mmol, 100 mol%) was added iced, freshly prepared HCl(g)/MeOH (10 mL). The solution was stirred at room temperature for 40 min and then heated gently to 50 °C. After further 40 min of stirring the starting material was consumed by TLC, and the previously colorless solution had turned yellow. Solvent was evaporated to yield 430 mg of yellow glass-like gel. The residue was then dissolved in methanol (12 mL) and the ion exchange resin was added (Merck ionenaustauscher II, 500 mg). The mixture was heated to 50 °C and stirred for 16 h. The reaction was not complete by TLC, so 200 mg
more of the resin was added and stirred for further 5 h at reflux. The mixture was filtered through a fritted funnel and concentrated. The crude product was purified by flash chromatography (20% MeOH–CHCl₃ + 1% NH₄OH [25%]) to yield 258 mg of slightly yellow oil (78%) which solidifies into a gummy solid on standing. Spectroscopically identical to one prepared from 20.

(−)-1-Deoxyaltronojirimycin hydrochloride (−)-5 HCl

To a stirred solution of 21 (125 mg, 0.494 mmol, 100 mol%) in MeOH (5 mL) and conc. HCl (10 mL), Pd/C (125 mg, 0.494 mmol, 100 mol%) in MeOH (5 mL) and conc. HCl (10 mL) was added Pd/C (100 mg, 0.05 mmol, 5% in Pd). H₂ was then added at constant temperature and the solution was vigorously stirred for 1 h. The mixture was filtered through a pad of celite and concentrated to yield 106 mg (100%) of the title compound as a white foam.


Notes and references

23 The allene 16 has the following spectorscopic properties: 1H-NMR (400 MHz, CDCl₃) δ = 5.21 (dd, J = 13.0 Hz, 6.6 Hz, 1 H), 4.85 (app. d, J = 5.7 Hz, 2 H), 3.80–4.44 (m, 5 H), 1.58 (bs, 3 H), 1.50 (s, 9H); 13C-NMR (100 MHz, CDCl₃) δ = 70.4, 69.4, 67.1, 64.6, 59.1, 56.8, 49.9, 44.9 and ref. 4.