Stereoselective Synthesis of L-Deoxyaltronojirimycin from L-Serine

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Received March 25, 2009, Accepted May 14, 2009

(2*S*,3*R*)-3-Hydroxy-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyridine **8**, an important precursor for the synthesis of polyhydroxylated piperidine azasugars, has been prepared from L-serine. Highly stereoselective nucleophilic addition to amino aldehyde **5** gave the corresponding allylic alcohol **6** which proceeded to give dihydro-2*H*-piridine **7a** *via* a Grubbs II catalyzed RCM. Stereoselective H-bond directed epoxidation of allylic alcohol led to the oxiranyl alcohol **9** which was easily converted to L-deoxyaltronojirimycin by regioselective ring opening.

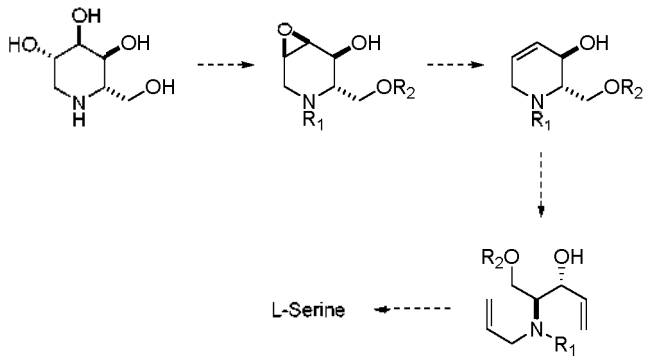
Key Words: Polyhydroxylated piperidine, Azasugars, L-Deoxyaltronojirimycin, Vinyl magnesium bromide, Ring closing metathesis

Introduction

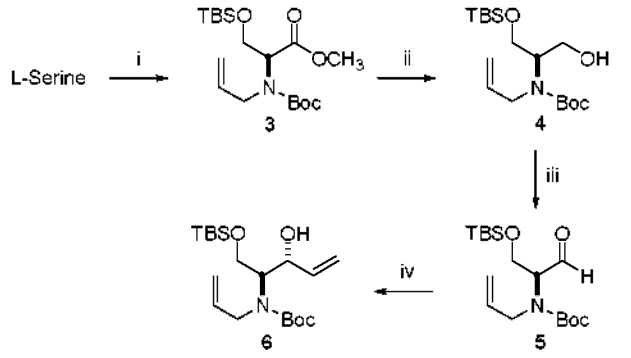
Polyhydroxylated azasugars have become important synthetic targets because of their promising glycosidase inhibitory activity which can be harnessed for the treatment of various diseases such as diabetes, cancer, and viral infections, including AIDS[1]. In particular, enantiopure polyhydroxylated piperidines have been extensively exploited because of their wide-ranging pharmacological properties and their potential as important functional units for further synthetic manipulation.[2] For example, 1-deoxynojirimycin, 1-deoxyaltronojirimycin, 1-deoxymannojirimycin, and castanospermine are well known azasugars which have received considerable research attention.[3]

A number of synthetic strategies have been focused upon the stereoselective synthesis of azasugars from both carbohydrate and non-carbohydrate sources.[4] Carbohydrates are ideally suited to the preparation of single stereoisomers of polyhydroxylated piperidines. However each sugar offers a very limited number of stereoarrays and often requires many tedious protection and deprotection steps to access new diastereomeric series.[5] Obviously, homochiral α-aminoacids are the most suitable starting material for the synthesis of enantiopure polyhydroxylated piperidines. This is because a wide range of methodologies are available for their stereoselective elaboration. However, the stereocontrolled installation of hydroxyl groups on these derivatives has met with considerable difficulty. In a bid to address these issues, we previously reported the development of a new building block for polyhydroxylated piperidines from alanine and its application to *ent*-1,6-dideoxynojirimycin.[6]

Our objective herein is to develop a synthetic route to deoxynojirimycin stereoisomers from L-serine. The process we planned is outlined in (Scheme 1). It begins with inexpensive L-serine and proceeds *via* highly stereoselective (> 99:1 *anti:syn* dr) nucleophilic addition to an α-amino aldehyde equivalent.[7] The 4,5-anti diol motif within the target azasugar is installed by regioselective ring opening of an epoxide **9** derived from 3-hydroxy tetrahydropyridine **8**. The latter is a key intermediate in this sequence which should offer broad scope for derivatization. In this instance we showcase its utility by accessing the target L-Deoxyaltronojirimycin (L-*altro*-DNJ) **1** and 2-hydroxymethyl-3-piperidinol **2**. We are aware that two alternative routes to intermediate **8** have been reported (i) *via* Garner's aldehyde, however this did not proceed with such high stereocontrol (5.2:1 *anti:syn* dr) and



Scheme 1. Retrosynthesis of target compound.



Scheme 2. Reagents and conditions: (i) ref. 6.; (ii) $NaBH_4$, THF/MeOH (1:1), reflux, 78%; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C → rt; (iv) vinylMgBr, THF, 0 °C → rt, 15 min, 96%.

even to achieve this selectivity HMPA was required.[8] (ii) Ferreira *et al.* used a chiral auxiliary-based approach however this is obviously much less direct and requires sacrifice of the auxiliary.[9]

Results and Discussion

As our chiral substrate, we choose L-serine which supplies not only the nitrogen atom and the hydroxyl methyl unit of the final L-*altro*-DNJ but also the stereocontrolling asymmetric unit. *N*-Boc-*N*-allyl-*O*-TBS serine methyl ester **3** was synthesized in four easy steps from L-serine as described.[6] The overall yield for this conversion was 47%. Proceeding from the resulting ester **3**, the methyl ester **3** was reduced by $NaBH_4$ producing alcohol **4** in 78% yield (Scheme 2). The primary alcohol group of **4** was converted to amino aldehyde **5** by a Swern oxidation in 92% yield. This aldehyde **5** was used in the next step without further purification because it is unstable to silica gel. Aminoaldeheyde **5** was readily transformed to allylic alcohol **6** *via* nucleophilic addition of vinyl Grignard in 96% yield with 99:1 *anti*:*syn* dr.[7] The diasteroselectivity was assessed by ^{1}H-NMR analysis. The stereochemistry was confirmed by NOESY analysis of compound **1** (*vida infra*). The stereoselectivity can be ascribed to a non-chelated Felkin- Ahn type transition state (Figure 1).[10]

To set up the tetrahydropiperidine ring we used RCM. Thus chiral synthon **6** was treated with Grubbs II catalyst to afford the desired chiral, tetrahydropyridine **7a**.[9] (Scheme 3) This product was obtained as a readily chromatographically separable 85:15 mixture with enamide **7b**.[9,11]

We believe that (2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyridine **7a** should be valuable for the total synthesis of polyhydroxylated piperidines as its allylic alcohol moiety can be readily and stereoselectively derivatized giving novel azasugar derivatives.[8,15] Our end-game to **1** proceeded as follows. The TBS group of tetrahydropyridine **7a** was selectively cleaved with Bu_4NF to give alcohol **8**. Epoxidation of this species proceeded exclusively *syn* to the allylic alcohol to give **9** (Scheme 4). Such high stereoselectivity is not unexpected as the *syn*-facial directing capacity of an alcohol in

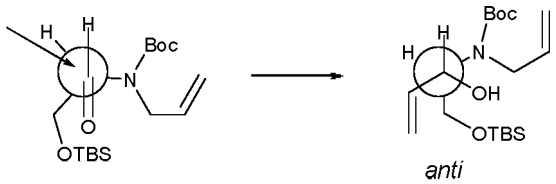
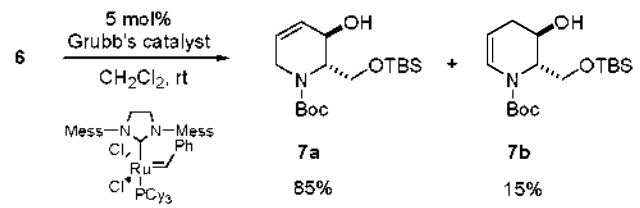
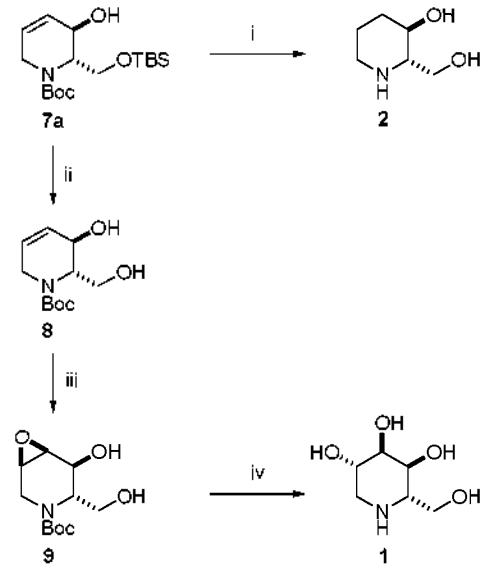


Figure 1. Plausible mechanism of nucleophilic addition.



Scheme 3. Metathesis Reaction.



Scheme 4. Synthesis of target compunds. Reagents and conditions: (i) (a) H_2, Pd/C, MeOH, rt; (b) 6 N HCl, MeOH, 91%; (ii) TBAF, THF, rt, 2 h, 97%; (iii) *m*-CPBA, CH_2Cl_2, rt, 48 h, 67%; (iv) (a) KOH, 1,4-dioxane, H_2O, reflux, 3 h; (b) Dowex 50W-X8 (H^+ form), 83%.

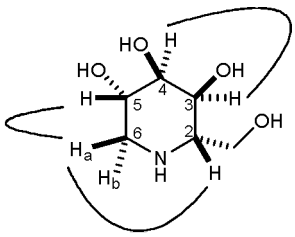


Figure 2. Selected NOESY correlations.

olefinic epoxidation with *m*-CPBA diminishes as the OH group moves further away from the olefin.[12] To minimize a (1,3) strain between the hydroxymethyl group and the *N*-Boc groups, the tetrahydropiperidene is expected to have both substituents (-OH and -CH_2OH) in axial orientation. The high stereoselectivity of the epoxidation step is thus noteworthy because axial hydroxyl functions in cyclohex-2-enol systems usually give low diasteroselectivities in *m*-CPBA epoxidations.[13] However in this case the axial hydroxy methyl substituent probably shields the *anti* face.[14]

When epoxide **9** was exposed to KOH in dioxane and water (1:1), the C-5 position of the oxirane ring was regioselectively opened in excellent yield.[15,16] The reaction mixture was treated with Dowex 50W-X8 to give the free base form of L-*altro*-DNJ **1** without the need for additional ion exchange chromotagraphy. The stereochemistry of the target compound was confirmed by using 2D-NOESY. A strong NOE crosspeak was observed between H6a and H2, indicative of a 1,3-diaxial type arrangement. A strong correlation is also observed between H6a and H5. Given that H6a is axial, this strongly implies H5 is equatorial. Strong correlation between H3 and H4 consistent with a *cis* relationship of these two protons. Furthermore, specific rotation value of $[\alpha]_D^{20}$ -21.8° agrees with that of authentic L-*altro*-DNJ.[16] It is important to note that in the synthesis of **1**

four contiguous stereocenters were set up in four overall steps using three stereoselective transformations, each of which occurred with absolute control. We acknowledge that the previous route to **1** by Takahata has employed epoxidation of a di-oxygen protected analogue of **8**, but this met with low (1:1 dr) stereocontrol. This is presumably because the stereocontrolling element was steric, which is much less reliable in these conditions than H-bonding.

For the synthesis of target compound **2**, key intermediate **7a** was hydrogenated with H_2 and 10% Pd/C in methanol.[17] The remaining protecting groups, *O*-TBS and *N*-Boc, were easily removed in one step with HCl (Scheme 4). The crude product was purified with Dowex 50W-X8 to give the free base (2*S*,3*R*)-2-hydroxymethyl-3-piperidinol **2**.

Conclusion

We have accomplished the asymmetric stereoselective synthesis of L-deoxyaltronojirimycin (L-*altro*-DNJ) from our chiral building block. We utilized this key intermediate to construct the piperidine moiety *via* ring-closing metathesis (RCM). Subsequent epoxidation followed by ring opening installed the remaining contiguous stereogenic centers in the piperidine ring. Continued investigations into the utility of this important synthon are underway.

Experimental Section

General Procedures. All NMR spectra were obtained on a 300 MHz spectrometer. 2D experiments NOSEY were used to assist analysis of 1D spectra obtained on a 500 MHz spectrometer. All NMR experiments were run using standard routines. Flash column chromatography was performed using pre-packed silica gel columns. Thin layer chromatography was performed on commercially available glass-backed silica gel plates. Optical rotations were measured using the Na-D line. All starting materials were dried in a vacuum for one day before use. All non-aqueous reactions were carried out under inert N_2 atmosphere, and reaction solvents were distilled according to standard procedures unless stated otherwise.

(*S*)-Methyl 2-(allyl(*tert*-butoxycarbonyl)amino)-3-(*tert*-butyldimethylsilyloxy)propanoate (3): This was prepared as described.[6] $[\alpha]_D^{20}$ -46.9° (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 1.45 (9H, d, *J* = 7.1 Hz), 3.71 (3H, s), 3.84 (1H, m), 4.11 (3H, m), 4.31 (1H, m), 5.16 (2H, m), 5.87 (1H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ -5.4, 18.1, 25.7, 28.3, 50.1, 51.8, 60.6, 61.8, 80.1, 117.0, 135.5, 155.4, 170.5; EIMS (*m/z*) 373 (M^+); HRMS calcd for $C_{18}H_{35}NO_5Si$ (M^-) 373.2284, found 373.2285.

(*R*)-*tert*-Butyl allyl(1-(*tert*-butyldimethylsilyloxy)-3-hydroxypropan-2-yl)carbamate (4): To a stirred solution of **3** (5.5 g, 14.80 mmol) in THF (90 mL) was added $NaBH_4$. After addition the reaction mixture was then refluxed for 30 min and then (90 mL) of MeOH were added dropwise and refluxed for another 1 hour and then quenched with sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The product was purified by flash column chromatography (hexane: EtOAc = 80:20) to give **4** (4 g, 78%) as colorless oil: $[\alpha]_D^{20}$ -6.4° (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.46 (9H, s), 3.48 (1H, brs), 3.85 (4H, brs), 3.95 (2H, brs), 5.14 (2H, m), 5.85 (1H, brs); ^{13}C NMR (300 MHz; $CDCl_3$) δ -5.5, 18.1, 25.8, 28.3, 5.8, 61.3, 61.8, 63.2, 80.1, 115.9, 135.3, 156.3; EIMS (*m/z*) 345 (M^+); HRMS calcd for $C_{17}H_{35}NO_4Si$ (M^-) 345.2335, found 345.2326.

***tert*-Butyl-allyl((2*S*,3*R*)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxypent-4-en-2-yl)carbamate (6):** Oxalylchloride (3.68 mL, 29.03 mmol) was dissolved in dry CH_2Cl_2 (110 mL). This was cooled to -78 °C and to it was added DMSO (3.6 mL) and the resulting mixture stirred for 10 min. To this was added a solution of **4** (4 g, 11.60 mmol) in CH_2Cl_2 (10 mL) and the resulting mixture was stirred for 15 min. To this was added Et_3N (8 mL, 58.04 mmol). After 15 min, the mixture was warmed to rt. After 30 min the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude compound was used in the next step without purification.

A precooled solution of vinylmagnesium bromide (3.3 mL, 24.60 mmol) in dry THF was added dropwise under N_2 to a stirred solution of aldehyde (2.8 g, 8.20 mmol) in dry THF at 0 °C. After stirring at this temperature for 10 min (TLC control), a saturated aqueous solution of ammonium chloride (10 mL) was added, and the reaction mixture was allowed to reach rt then extracted with EtOAc. The extracts were washed with brine, dried over Na_2SO_4 and evaporated. The product was purified by flash column chromatography (hexanes: EtOAc = 90:10) to afford compound **6** (2.75 g, 96%) as colorless oil; $[\alpha]_D^{20}$ -10.7° (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.07 (6H, s), 0.90 (9H, s), 1.46 (9H, s), 3.44 (1H, d, *J* = 3.8 Hz), 3.92 (4H, m), 4.50 (1H, m), 5.13 (3H, m), 5.31 (1H, m), 5.85 (1H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ -5.5, 18.1, 25.8, 28.3, 52.6, 60.9, 65.1, 74.8, 80.3, 116.1, 135.1, 138.5, 156.2; EIMS (*m/z*) 371 (M^+); HRMS calcd for $C_{19}H_{37}NO_4Si$ (M^-) 371.2492, found 371.2487.

(5*R*,6*S*)-*tert*-Butyl-6-((*tert*-butyldimethylsilyloxy)methyl)-5-hydroxy-5,6-dihydro-pyridine (2*H*)-carboxylate (7a): To a solution of **6** (2 g, 5.40 mmol) in dry CH_2Cl_2 (108 mL) was added Grubbs II catalyst (240 mg, 0.30 mmol) under N_2. The reaction mixture was stirred at rt overnight. The solution was concentrated. The product was isolated by flash column chromatography (hexane: EtOAc = 65:35) to afford **7a** (1.58 g, 85%) as brown oil. $[\alpha]_D^{20}$ -63.7° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.07 (3H, d, *J* = 7 Hz), 1.49 (9H, s), 3.57 (1H, d, *J* = 19.54 Hz), 3.88 (1H, m), 5.97 (2H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ 14.9, 28.4, 39.8, 60.3, 67.5, 79.9, 124.4, 127.7, 155.6; FAB-MS found 344.2277, calcd 344.2179 [(M + H)$^-$, M = $C_{17}H_{33}NO_4Si$].

(5*R*,6*S*)-*tert*-Butyl-5-hydroxy-6-(hydroxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (8): **7a** (1.3 g, 3.80 mmol) was dissolved in THF (20 mL). To it was added (8 mL, 7.60 mmol) of TBAF (1.0 M in THF). After 3 h, the mixture was quenched with sat. aq. NH_4Cl. The aqueous phase was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The product was isolated by flash column chromatography on silica

gel using (hexane: acetone = 50:50) to give **8** (850 mg, 97%) as colorless oil; $[\alpha]_D^{20}$ -87.8° (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$) δ 1.47 (9H, s), 3.52 (3H, m), 4.27 (2H, brs), 4.46 (1H, m), 5.93 (2H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ 28.3, 41.0, 58.1, 60.9, 63.0, 80.5, 124.6, 127.3, 156.4; FAB-MS found 230.1387, calcd 230.1314 [$(M + H)^-$, $M = C_{11}H_{20}NO_4$].

(1*R*,4*S*,5*S*,6*S*)-*tert*-Butyl-5-hydroxy-4-(hydroxymethyl)-7-oxa-3-aza-bicyclo[4.1.0]-heptane-3-carboxylate (9): To a stirred suspension of **8** (800 mg, 3.50 mmol) in CH_2Cl_2 (15 mL) was added *m*-CPBA (1.8 g, 60%, 10.50 mmol) at rt. The resulting suspension was stirred for 48 h. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction. The resulting two-phase mixture was stirred vigorously for 15 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel (hexane: EtOAc = 60:40) to give epoxide **9** (580 mg, 68%) as a brown wax; $[\alpha]_D^{20}$ -14.5° (*c* 1, $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$) δ 1.47 (9H, s), 3.41 (2H, m), 3.48 (1H, m), 3.66 (2H, m), 3.96 (1H, d, J = 2.8 Hz), 4.18 (2H, m); ^{13}C NMR (300 MHz; $CDCl_3$) δ 28.3, 51.5, 52.3, 56.9, 60.3, 62.4, 80.9, 127.6, 156.5; EIMS (*m/z*) 245 (M^+); HRMS calcd for $C_{11}H_{19}NO_5$ (M^-) 245.1263, found 245.1263.

L-Deoxyaltronojirimycin (1): A solution of **9** (100 mg, 0.4 mmol) in 1,4-dioxane (5 mL) and 0.3 M KOH (10 mL) was refluxed overnight. After evaporation, Dowex 50W-X8 in water was refluxed for 3 h. The mixture was filtered, and then washed with MeOH. The remaining residue was eluted with 2 mol dm^{-3} NH_4OH. The ammoniacal solution was evaporated, then co-evaporated with toluene to give L-Deoxyaltronojirimycin **1** (55 mg, 84%). $[\alpha]_D^{20}$ -21.8° (*c* 0.6, H_2O); ^1H NMR (300 MHz; D_2O) δ 1.04 (3H, d, J = 6.3 Hz), 2.32 (1H, m), 2.41 (1H, m), 2.89 (2H, m), 3.15 (1H, m), 3.37 (1H, m); ^{13}C NMR (300 MHz; D_2O) δ 16.4, 48.5, 54.9, 70.8, 76.2, 77.9; FAB-MS found 164.0921, calcd 164.0845 [$(M + H)^-$, $M = C_6H_{13}NO_4$].

(2*S*, 3*R*)-2-(Hydroxymethyl)piperidin-3-ol (2): Compound **7a** (100 mg, 0.3 mmol) was dissolved in methanol (3 mL) and 10% palladium carbon was added. Then hydrogen was bubbled into the mixture with stirring at rt for 10 h. The mixture was filtered through celite pad. The filtrate was evaporated and MeOH (1 mL) and 6 N HCl (3 mL) were added to the residue. The mixture was refluxed for 1 h and then evaporated to give **2** as hydrochloride salt. Dowex 50W-X8 in water was added to the compound and stirred for 1 h. The mixture was filtered, and then was washed with MeOH. The remaining residue was eluted with 2 mol dm^{-3} NH_4OH. The ammoniacal solution was evaporated, then co-evaporated with toluene to give **2** (36 mg, 92%) as colorless amorphous solid; $[\alpha]_D^{20}$ -57.2° (*c* 1, H_2O); ^1H NMR (300 MHz; D_2O) δ 1.03 (3H, d, J = 6.3 Hz), 1.22 (1H, m), 1.40 (1H, m), 1.61 (1H, m), 1.87 (1H, m), 2.41 (2H, m), 2.78 (1H, m), 3.10 (1H, m); ^{13}C NMR (300 MHz; D_2O) δ 17.0, 23.9, 32.9, 44.4, 56.9, 72.5; FAB-MS found 132.1025, calcd 132.0946 [$(M + H)^+$, $M = C_6H_{13}NO_2$].

Acknowledgments. This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MEST) (No. 20090081751). Rajesh. R was supported by a grant from the Brain Korea 21 program (BK21).

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