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Stereocontrolled Total Synthesis of (+)-1-Deoxynojirimycin

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A highly efficient non-chiral-pool synthesis of (+)-1-deoxynojirimycin has been realized (24 % overall yield, 11 steps, complete stereocontrol). A novel one-pot enol ether metathesis/hydroboration/oxidation sequence is used for the selective formation of the all-*trans* cyclic triol.

Introduction

Iminosugars have been widely studied due primarily to their therapeutic potential as glycosidase inhibitors.[1] A large effort has been devoted to date to the synthesis of both natural and non-natural iminosugars in order to study the influence of substitution and conformational changes on inhibition.[2] Whereas derivatives of (–)-swainsonine and (+)-castanopermine have shown encouraging results against HIV and cancers,[3] those of deoxynojirimycin (**1**) are arguably the most interesting: Miglusat (**2**) is currently used in the treatment of type-II diabetes, and Miglitol (**3**) has recently received FDA authorization for use against Gaucher's disease (Figure 1).[1]

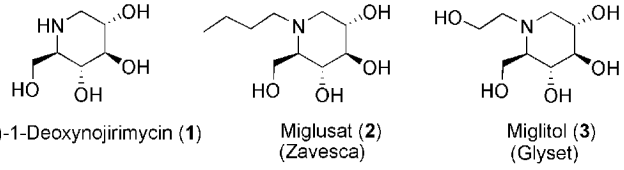

Figure 1. (+)-1-Deoxynojirimycin (**1**) and two drug derivatives, Miglusat (**2**) and Miglitol (**3**).

In a program devoted to the synthesis of polyhydroxylated alkaloids, we became interested in the total synthesis of this piperidine. The first synthesis of (+)-1-deoxynojirimycin was accomplished by Paulsen in 1966,[4] ten years before its earliest isolation from the leaves of mulberry trees (*morus alba*),[5] in the course of preparing nojirimicyn analogs. The vast majority of the ca. 30 subsequent syntheses of (+)-1-deoxynojirimycin have started from monosaccharides, in particular D-glucose.[6] Only four have begun from non-natural material,[7] and of these, only one is fully stereocontrolled.[7b] This is surprising since total synthesis provides opportunities for analog preparation that are unavailable when natural products are used as starting material. This would appear to be particularly true for deoxynojirimycin derivatives.

A metathesis approach to (+)-1-deoxynojirimycin has been realized; however, the synthesis was not selective.[8] The lack of selectivity stemmed from the difficulty in transforming the endocyclic double bond obtained on ring-closing metathesis into the desired *trans*-diol. A method commonly used with dehydropiperidines for obtaining the *trans*-diol involves epoxidation, followed by epoxide opening, but this approach generally lacks selectivity in one, if not both, steps.[8,9] Clean epoxide opening is particularly difficult, being governed by several, often opposing factors.[10]

We have recently demonstrated in a preparation of castanospermine[11] that an effective strategy for overcoming this type of stereocontrol problem, while still using ring-closing metathesis, can be achieved with indolizidines by placing an alkoxyl group on one of the double bonds of the precursor. The enol ether, now generated on metathesis, subsequently undergoes facially selective hydroboration/oxidation to produce the desired *trans*-diol derivative. We felt that this stereocontrol strategy might also be successful for the synthesis of (+)-1-deoxynojirimycin, and if so would suggest a broad scope for the approach and possible use for other piperidines, such as (+)-calystegin B_2, (+)-adenophorine, and (+)-fagomine (Figure 2). Herein, we report a totally

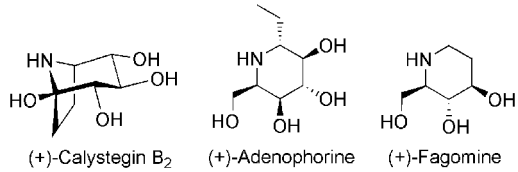

Figure 2. Examples of polyhydroxylated alkaloids with *trans,trans* substitution.

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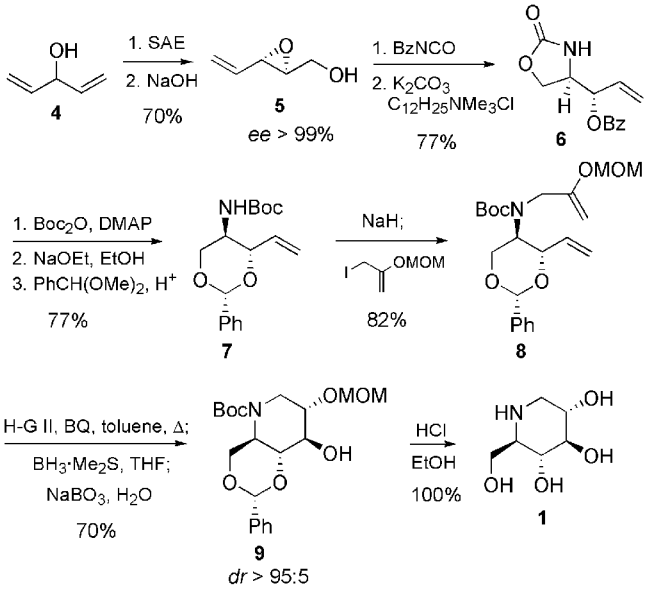
stereoselective, highly efficient synthesis of (+)-1-deoxynojirimycin through the use of this novel enol ether metathesis/hydroboration/oxidation tandem.

Results and Discussion

The synthesis began with the asymmetric epoxidation of penta-1,4-dien-3-ol (**4**, Scheme 1), which was followed by a base-promoted Payne rearrangement to give alcohol **5** (*ee* > 99%).[12] The reaction of alcohol **5** with benzoyl isocyanate set up a base-induced epoxide opening and benzoyl migration to generate oxazolidinone **6** as a single product in 77% yield.[13] *N*-Alkylation of **6** with 3-iodo-2-(methoxymethoxy)prop-1-ene[14] provided what was hoped would be a suitable ring-closing metathesis precursor. However, all attempts to achieve metathesis led to either recovery of starting material or olefin isomerization, even in the presence of a number of ruthenium hydride traps.



Scheme 1. (+)-1-Deoxynojirimycin synthesis.

Fortunately, much more satisfactory results were obtained with benzylidene derivative **7**. This substrate was readily prepared in 77% yield by conversion of oxazolidinone **6** into its *tert*-butyl carbamate, followed by concomitant cleavage of the oxazolidinone and benzoate and protection of the resulting diol.[15] *N*-Alkylation of **7** with 3-iodo-2-(methoxymethoxy)prop-1-ene then provided the desired diene **8**. Pleasingly, the diene in the presence of Grubbs II catalyst and benzoquinone in refluxing toluene was converted into the cyclized enol ether (not shown) in 70% yield. Even better, though, it was found after some experimentation that the Hoveyda–Grubbs II catalyst (10 mol-%), again in combination with benzoquinone in refluxing toluene, gave the same product in 87% yield. The subsequent key hydroboration with borane, followed by oxidation with sodium perborate, afforded alcohol **9** as a single isomer (*dr* > 95:5) in 77% yield. More conveniently, however, these last operations, ring-closing metathesis and hydroboration/oxidation, could also be accomplished in a single reaction vessel, without isolation of the intermediate cyclic enol ether, to afford **9**, once more as a single isomer, but now in 70% overall yield. This simplified, efficient protocol should make this approach to the *trans*,*trans*-triol array even more attractive.

The synthesis was completed by the simultaneous removal of the three protecting groups in **9** through treatment with ethanolic HCl to afford (+)-1-deoxynojirimycin (**1**) in quantitative yield. The synthetically derived (+)-1-deoxynojirimycin (m.p. 198–199 °C, $[\alpha]_D^{20}$ = +39.3) provided spectroscopic data in complete agreement with those in the literature for the naturally derived material (m.p. 199–199.5 °C, $[\alpha]_D^{23}$ = +40.3).[6]

Conclusion

We have developed a totally stereocontrolled synthesis of (+)-1-deoxynojirimycin that proceeds in 11 steps with an overall yield of 24%, which makes it the most efficient of the non-chiral-pool approaches and competitive with those from monosaccharides. The one-pot enol ether metathesis/hydroboration/oxidation sequence, which is the key to this synthesis, should prove useful for the preparation of a number of other biologically active natural products.

Experimental Section

[(2*S*,3*S*)-3-Vinyloxiran-2-yl]methyl Benzoylcarbamate (5′):[13] To a solution of alcohol **5** (1.14 g, 11.4 mmol) in Et_2O (70 mL) at 0 °C was added a solution of benzoyl isocyanate (1.84 g, 12.5 mmol) in Et_2O (30 mL). The reaction mixture was stirred at 20 °C for 2 h, whereupon water was added dropwise at 0 °C. The resulting mixture was extracted with Et_2O, and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (SiO_2; pentane/AcOEt, 7:3 to 4:6) gave carbamate **5′** (2.70 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ = –32.2 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3284, 2994, 1766, 1517, 1489, 1196 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1 H, NH), 7.94–7.81 (m, 2 H, Ar-H), 7.61–7.51 (m, 1 H, Ar-H), 7.50–7.41 (m, 2 H, Ar-H), 5.56–5.47 (m, 2 H, 4′-H), 5.34–5.25 (m, 1 H, 3′-H), 4.56 (dd, *J* = 12.2, 3.0 Hz, 1 H, 1a-H), 4.03 (dd, *J* = 12.2, 6.2 Hz, 1 H, 1b-H), 3.34–3.29 (m, 1 H, 3′-H), 3.14 (m, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (C=O), 150.8 (C=O), 134.0 (C-4′), 133.1 (C-Ar), 132.8 (Cq-Ar), 128.8 (C-Ar), 127.8 (C-Ar), 120.7 (C-5′), 65.6 (C-1), 56.8 (C-2′), 56.4 (C3′) ppm. MS (ESI): *m*/*z* = 247.9 $[M + H]^+$, 269.9 $[M + Na]^+$.

(*S*)-1-[(*R*)-2-Oxooxazolidin-4-yl]allyl Benzoate (6):[13] A mixture of carbamate **5′** (2.70 g, 10.9 mmol), K_2CO_3 (1.66 g, 12.0 mmol), and $(C_{12}H_{25})NMe_3Cl$ (cat.) in CH_2Cl_2/H_2O (1:1, 60 mL) was stirred at 20 °C for 16 h. Diethyl ether and water were then added, and the resulting mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (SiO_2; pentane/AcOEt, 7:3 to 5:5) gave oxazolidinone **6** (2.14 g, 80%) as a colorless oil. $[\alpha]_D^{25}$ = –34.3 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3284, 2976, 2916, 1753, 1719, 1267, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08–7.96 (m, 2 H,

Ar-H), 7.61–7.52 (m, 1 H, Ar-H), 7.46–7.39 (m, 2 H, Ar-H), 6.45 (br. s, 1 H, NH), 5.83 (ddd, J = 17.0, 10.6, 6.1 Hz, 1 H, 2-H), 5.58–5.51 (dd, J = 6.0, 4.4 Hz, 1 H, 1-H), 5.46 (td, J = 17.0, 1.1 Hz, 1 H, 3-H), 5.40 (td, J = 10.6, 1.1 Hz, 1 H, 3-H), 4.48 (t, J = 8.9 Hz, 1 H, 5a′-H), 4.38 (dd, J = 8.9, 4.7 Hz, 1 H, 5b′-H), 4.16 (app. dt, J = 8.9, 4.7 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5 (C=O), 159.7 (C=O), 133.5 (C-Ar), 130.7 (C-2), 129.8 (C-Ar), 129.3 (C-Ar), 128.6 (Cq-Ar), 120.8 (C-3), 74.9 (C-1), 65.9 (C-5′), 54.6 (C-4′) ppm. MS (ESI): m/z = 248.0 [M + H]$^+$, 270.0 [M + Na]$^+$.

(*R*)-*tert*-Butyl 4-[(*S*)-1-(Benzoyloxy)allyl]-2-oxooxazolidine-3-carboxylate (6′): A solution of oxazolidinone **6** (587 mg, 2.37 mmol), Et_3N (0.840 mL, 6.03 mmol), DMAP (94 mg, 0.77 mmol), and Boc_2O (1.86 g, 8.52 mmol) in CH_2Cl_2 (22 mL) was stirred for 1.5 h and then concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2/2.5% Et_3N; pentane/Et_2O, 7:3 to 4:6) gave Boc derivative **6′** (753 mg, 91%) as white solid. m.p. 72–73 °C. $[\alpha]_D^{20}$ = +101.9 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2981, 2931, 1820, 1727, 1369, 1264, 1070 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–7.98 (m, 2 H, Ar-H), 7.61–7.53 (m, 1 H, Ar-H), 7.49–7.39 (m, 2 H, Ar-H), 6.08 (ddd, J = 4.8, 3.4, 1.6 Hz, 1 H, 1′-H), 5.83 (ddd, J = 17.2, 10.8, 4.8 Hz, 1 H, 2′-H), 5.49–5.44 (m, 2 H, 3′-H), 4.44–4.36 (m, 2 H, 4,5a-H), 4.34 (t, J = 9.5 Hz, 1 H, 5b-H), 1.55 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3 (C=O), 151.8 (C=O), 148.9 (C=O), 133.6 (C-Ar), 131.2 (C-2′), 129.8 (C-Ar), 129.1 (Cq-Ar), 128.6 (C-Ar), 119.4 (C-3′), 84.6 (Cq-*t*Bu), 72.4 (C-1′), 61.9 (C-5), 56.7 (C-4), 27.9 (C-*t*Bu) ppm. MS (ESI): m/z = 370.0 [M + Na]$^+$. HRMS (FT, ESI): calcd. for $C_{18}H_{21}NO_6$ Na 370.12611, found 370.12701.

***tert*-Butyl [(2*R*,3*S*)-1,3-Dihydroxypent-4-en-2-yl]carbamate (6′′):**[15] A solution of Boc derivative **6′** (223 mg, 0.64 mmol) in dry ethanol (14 mL) at 0 °C was treated dropwise with a solution of EtONa in ethanol (0.80 mL, 2.4 M, 1.9 mmol). The reaction mixture was stirred at 0 °C for 1 h and then warmed to 20 °C over 1 h. Solid NH_4Cl was added, and the resulting mixture was filtered through a plug of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (SiO_2/2.5% Et_3N; pentane/AcOEt, 5:5 to 3:7) to give diol **6′′** (130 mg, 93%) as a colorless oil. $[\alpha]_D^{20}$ = –4.2 (c = 0.7, $CHCl_3$) {ref.[13] $[\alpha]_D^{23}$ = –5.4 (c = 1.1, $CHCl_3$)}. IR (neat): $\tilde{\nu}_{max}$ = 3368, 2978, 2932, 1691, 1510, 1170 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.94 (ddd, J = 17.2, 10.6, 5.3 Hz, 1 H, 4-H), 5.39 (td, J = 17.2, 1.5 Hz, 1 H, 5-H), 5.33 (br. s, 1 H, NH), 5.26 (td, J = 10.6, 1.5 Hz, 1 H, 5-H), 4.38 (m, 1 H, 3-H), 3.93 (dd, J = 11.2, 3.6 Hz, 1 H, 1a-H), 3.71 (dd, J = 11.2, 3.6 Hz, 1 H, 1b-H), 3.63 (br. s, 1 H, 2-H), 2.91 (br. d, J = 3.0 Hz, 1 H, OH), 2.64 (br. s, 1 H, OH), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (C=O), 137.4 (C-4), 116.5 (C-5), 79.9 (Cq-*t*Bu), 74.9 (C-3), 62.5 (C-1), 54.9 (C-2), 28.4 (C-*t*Bu) ppm. MS (ESI): m/z = 239.9 [M + Na]$^+$.

***tert*-Butyl [(2*R*,4*S*,5*R*)-2-Phenyl-4-vinyl-1,3-dioxan-5-yl]carbamate (7):**[15] A solution of diol **6′′** (60 mg, 0.28 mmol), benzaldehyde dimethyl acetal (0.084 mL, 0.560 mmol), and camphorsulfonic acid (6 mg, 0.03 mmol) in CH_2Cl_2 (6 mL) was stirred at 20 °C for 6 h. Solid $NaHCO_3$ was then added, the resulting mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2/2.5% Et_3N; pentane/Et_2O, 8:2 to 6:4) gave benzylidene compound **7** (77 mg, 91%) as a white solid. m.p. 124–125 °C. $[\alpha]_D^{25}$ = –31.9 (c = 1.5, $CHCl_3$) {ref.[13] $[\alpha]_D^{23}$ = –29.6 (c = 1.5, $CHCl_3$)}. IR (neat): $\tilde{\nu}_{max}$ = 3349, 2981, 2855, 1680, 1528, 1307 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.45 (m, 2 H, Ar-H), 7.40–7.31 (m, 3 H, Ar-H), 5.96 (ddd, J = 17.3, 10.5, 6.8 Hz, 1 H, 1′-H), 5.52 (s, 1 H, 2-H), 5.42 (d, J = 17.2 Hz, 1 H, 2′-H), 5.31 (d, J = 10.4 Hz, 1 H, 2′-H), 4.37 (dd, J = 10.5, 4.9 Hz, 1 H, 6a-H), 4.29 (br. s, 1 H, NH), 4.03 (br. s, 1 H, 4-H), 3.72 (br. s, 1 H, 5-H), 3.61 (t, J = 10.5 Hz, 1 H, 6b-H), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (C=O), 137.6 (Cq-Ar), 134.5 (C-1′), 129.0 (C-Ar), 128.3 (C-Ar), 126.2 (C-Ar), 119.0 (C-2′), 101.0 (C-2), 82.1 (C-4), 69.9 (C-6), 47.7 (C-5), 28.3 (C-*t*Bu) ppm. MS (ESI): m/z = 306.0 [M + H]$^+$, 328.0 [M + Na]$^+$.

***tert*-Butyl [2-(Methoxymethoxy)allyl][(4*S*,5*R*)-2-phenyl-4-vinyl-1,3-dioxan-5-yl]carbamate (8):** To a stirred mixture of NaH (5.5 mg, 0.14 mmol, 60% in mineral oil) in dry DMF (0.20 mL) at 0 °C was added dropwise a solution of benzylidene compound **7** (28.2 mg, 0.092 mmol) in dry DMF (1.5 mL). After being stirred for 45 min, the mixture was treated dropwise with 3-iodo-2-(methoxymethoxy)prop-1-ene (42.1 mg, 0.185 mmol) and then stirred for an additional 1 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2/2.5% Et_3N; pentane/Et_2O, 9:1 to 7:3) afforded Boc derivative **8** (30.6 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ = –43.4 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2975, 1697, 1155, 1023 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.56–7.44 (m, 2 H, Ar-H), 7.41–7.28 (m, 3 H, Ar-H), 5.93 (ddd, J = 17.3, 10.5, 6.8 Hz, 1 H, 1′-H), 5.64 and 5.55 (2 br. s, 1 H, 2-H), 5.42 and 5.37 (2 d, J = 17.6 Hz, 1 H, 2′-H), 5.28 and 5.26 (2 d, J = 10.5 Hz, 1 H, 2′-H), 5.00–4.95 (m, 1 H), 5.01 and 4.96 (2 s, 2 H, OCH_2O), 4.47 (br. s, 1 H), 4.36 (m, 1 H), 4.29 (d, J = 12.6 Hz, 1 H), 4.16 (m, 2 H), 3.98 (s, 1 H), 3.61–3.41 (m, 1 H), 3.43 (s, 3 H, CH_3O), 1.54 and 1.45 (2 s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 156.8, 156.6, 154.8, 138.0, 135.1,134.7, 128.9, 128.8, 128.2, 126.2, 126.1, 118.4, 118.2, 100.8, 93.9, 93.8, 93.7, 87.6, 86.5, 81.1, 80.2, 79.3, 78.5, 70.3, 68.3, 67.4, 56.3, 56.1, 28.6, 28.3 ppm. MS (ESI): m/z = 428.2 [M + Na]$^+$. HRMS (FT, ESI): calcd. for $C_{22}H_{31}NO_6Na$ 428.20436, found 428.20397.

(2*R*,4a*R*,7*S*,8*R*,8a*R*)-*tert*-Butyl 8-Hydroxy-7-(methoxymethoxy)-2-phenyltetrahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine-5(4a*H*)-carboxylate (9): A stirred solution of Boc derivative **8** (69.4 mg, 0.171 mmol), Hoveyda–Grubbs 2nd-generation catalyst (10.7 mg, 0.017 mmol), and benzoquinone (1.9 mg, 0.017 mmol) in degassed toluene (2.0 mL) was refluxed for 4.5 h. The toluene was then removed under reduced pressure, and the residue[16] was dissolved in THF and treated dropwise at 0 °C with BH_3·Me_2S (0.071 mL, 0.748 mmol). After being stirred at 20 °C for 7 h, the reaction mixture was treated with water (2.0 mL), followed by $NaBO_3$·$4H_2O$ (1.15 g, 7.48 mmol). After an additional 18 h at 20 °C, the mixture was extracted with AcOEt. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2/2.5% Et_3N; pentane/Et_2O, 6:4 to 3:7) gave alcohol **9** (45.9 mg, 70%) as a white solid. M.p. 125–126 °C. $[\alpha]_D^{20}$ = +3.6 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3449 (br.), 2972, 2924, 2890, 1697, 1146, 1090, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.46 (m, 2 H, Ar-H), 7.40–7.31 (m, 3 H, Ar-H), 5.57 (s, 1 H, 2-H), 4.76 (m, 3 H, 4-H and OCH_2O), 4.37 (t, J = 10.0 Hz, 1 H, 4-H), 4.23 (dd, J = 13.6, 4.6 Hz, 1 H, 6-H), 3.74–3.58 (m, 2 H, 8,8a-H), 3.53 (ddd, J = 10.0, 7.7, 4.6 Hz, 1 H, 7-H), 3.43 (s, 3 H, CH_3O), 3.24 (app. dt, J = 10.0, 4.6 Hz, 1 H, 4a-H), 2.80 (dd, J = 13.6, 10.0 Hz, 1 H, 6-H), 1.47 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2 (C=O), 137.4 (Cq-Ar), 129.2 (C-Ar), 128.3 (C-Ar), 126.3 (C-Ar), 101.7 (C-2), 96.9 (OCH_2O), 81.2 (Cq-*t*Bu), 80.4 (C-8a), 77.4 (C-7), 75.6 (C-8), 69.8 (C-4), 55.8 (OCH_3), 54.4 (C-4a), 47.8

(C-6), 28.3 (C-*t*Bu) ppm. MS (ESI): *m*/*z* = 418.2 [M + Na]$^+$, 813.3 [2 M + Na]$^+$. HRMS (FT, ESI): calcd. for $C_{20}H_{29}NO_7Na$ 418.18362, found 418.18323.

(+)-1-Deoxynojirimycin (1): A stirred solution of alcohol **9** (45.9 mg, 0.116 mmol) in EtOH/HCl (1%, 3.0 mL) was refluxed for 18 h and then concentrated under reduced pressure. Purification of the residue (DOWEX 50W-X8, H^+ form, water, then 1 N aqueous ammonia) gave **1** (18.9 mg, 100%) as a white solid. M.p. 197–198 °C (ref.[8] m.p. 199–199.5 °C). $[\alpha]_D^{20}$ = +39.3 (*c* = 1.0, H_2O) {ref.[8] $[\alpha]_D^{23}$ = +40.3 (*c* = 1.5, H_2O)}. ^{1}H NMR (400 MHz, D_2O): δ = 3.76 (dd, *J* = 11.7, 2.7 Hz, 1 H, 6a-H), 3.57 (dd, *J* = 11.7, 6.2 Hz, 1 H, 6b-H), 3.44 (ddd, *J* = 10.6, 9.3, 5.1 Hz, 1 H, 2-H), 3.26 (t, *J* = 9.3 Hz, 1 H, 3-H), 3.18 (t, *J* = 9.3 Hz, 1 H, 4-H), 3.07 (dd, *J* = 12.3, 5.1 Hz, 1 H, 1a-H), 2.52 (ddd, *J* = 9.3, 6.0, 2.7 Hz, 1 H, 5-H), 2.43 (t, *J* = 11.7 Hz, 1 H, 1b-H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 78.5, 71.6, 71.0, 61.5, 60.7, 48.8 ppm. MS (ESI): *m*/*z* = 164.0 [M + H]$^+$, 186.0 [M + Na]$^+$.

Supporting Information (see footnote on the first page of this article): Experimental details and spectroscopic data for the metathesis product (**8′**), ^{1}H and ^{13}C NMR spectra of compounds **5′**, **6**, **6′**, **6′′**, **7**, **8**, **8′**, **9**, and **1**.

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[16] For the physical data of the purified enol ether from a separate experiment, see the Supporting Information.

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