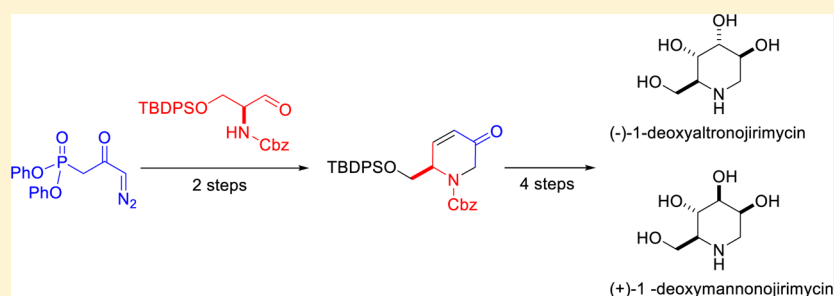


Six-Step Syntheses of (–)-1-Deoxyaltronojirimycin and (+)-1-Deoxymannonojirimycin from *N*-*Z*-*O*-TBDPS-L-serinal

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S Supporting Information



ABSTRACT: Highly stereoselective six-step syntheses of (–)-1-deoxyaltronojirimycin (*alatro*-DNJ) and (+)-1-deoxymannonojirimycin (*manno*-DNJ) from *N*-Cbz-*O*-TBDPS-*L*-serinal are described. Key transformations involve a two-step preparation of a functionalized dihydropyridin-3-one as a common intermediate followed by Luche reduction and dihydroxylation (for *alatro*-DNJ). The same sequence employing an epoxidation/epoxide opening in place of dihydroxylation furnishes *manno*-DNJ.

Piperidines make up a well-known class of nitrogen heterocycles with a vast distribution in nature.¹ Because they have interesting and diverse properties, piperidines have been the target of many research groups.² The synthesis of fully substituted or polysubstituted piperidines is one of the most challenging tasks in the chemistry of nitrogen heterocycles, especially with respect to controlling the relative stereochemistry of up to five stereogenic centers in the ring (32 stereoisomers for fully substituted piperidines). Examples are the syntheses of aza sugars, such as the well-known nojirimycin. Nojirimycin was isolated in 1966 by Inuoye from strains of *Streptomyces*, and they were shown to act as potent glucosidase inhibitors.³ Its natural analogue, 1-deoxynojirimycin (DNJ), has similar biological activities.⁴ Moreover, two derivatives of DNJ, Glyset and Zavesca, are marketed for the treatment of diabetes and Gaucher disease, respectively.⁵ In view of this, the synthesis of natural or synthetic DNJ analogues has attracted much attention, especially for short and divergent approaches. Antidiabetic,⁶ anti-HIV,⁷ antiobesity,⁸ and anticancer activities⁹ are some of the biological properties of these compounds (Figure 1).

In 2013, we developed a one-step method for preparing α,β -unsaturated diazoketones with *Z* geometry from aldehydes and a new Horner–Wadsworth–Emmons reagent.¹⁰ Using *N*-tosyl-protected amino aldehydes, we prepared γ -amino unsaturated diazoketones, which in turn were directly converted to chiral dihydropyridin-3-ones after an intramolecular N–H insertion reaction.¹¹ Dihydropyridin-3-ones are powerful multifunctional intermediates that can be converted to polysubstituted piperidines¹² after a few manipulations. We envisaged that

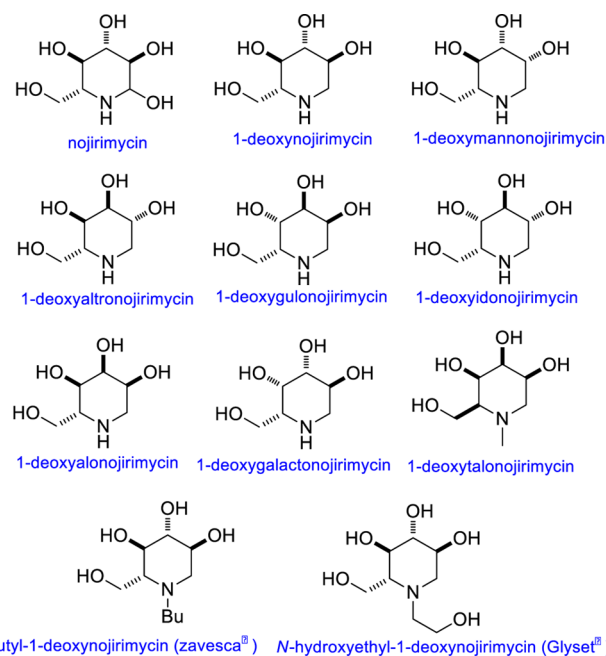


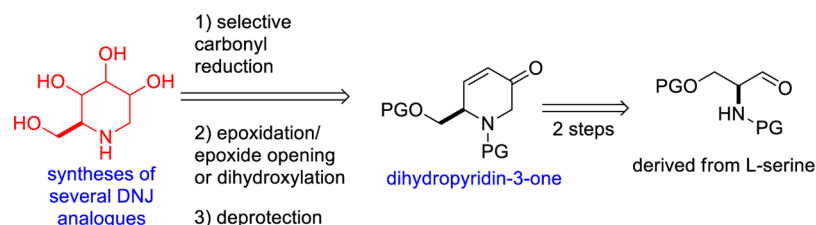
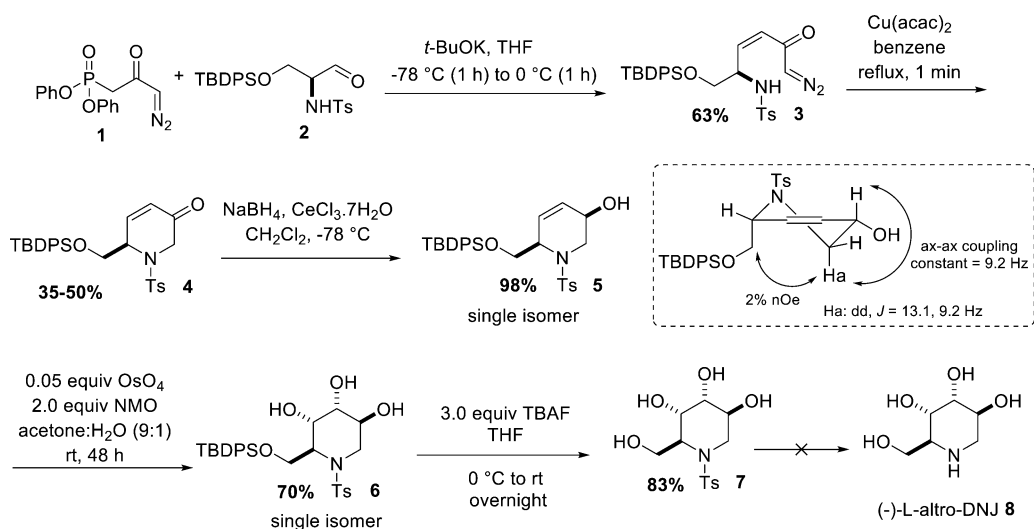
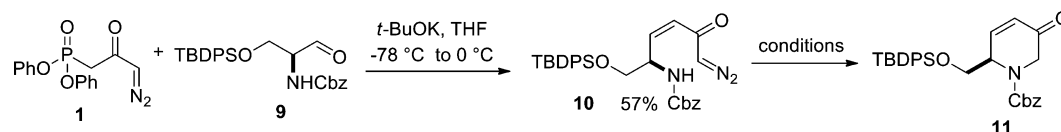
Figure 1. Nojirimycin, deoxynojirimycin, and their analogues and derivatives.

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Scheme 1. Synthetic Approach for the Synthesis of 1-Deoxyojirimycin and Its Analogues

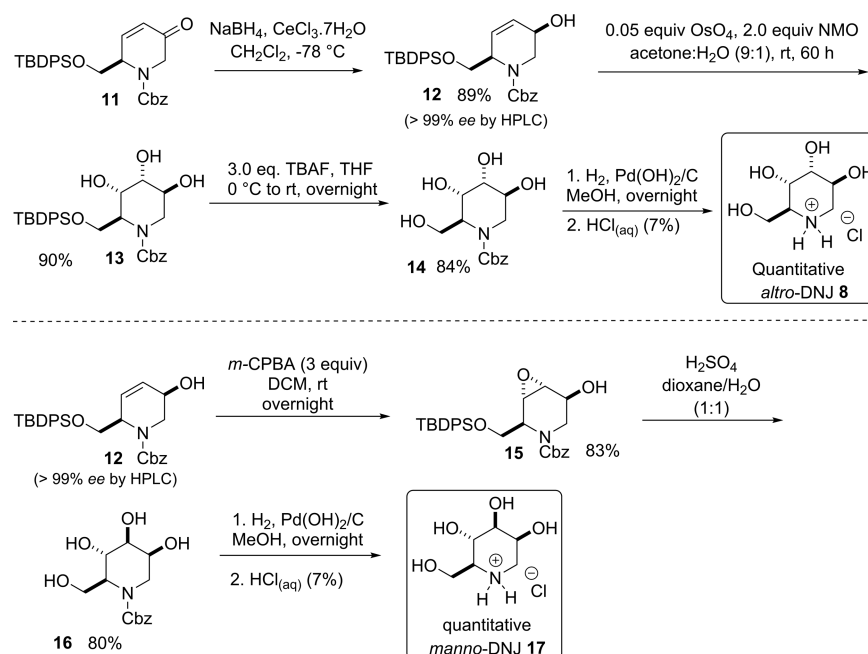
Scheme 2. Attempts To Synthesize *altro*-DNJ from *N*-Tosyl-*O*-TBDPS-serinalTable 1. Metal-Catalyzed N–H Insertion Study from *N*-Cbz-Unsaturated Diazoketone 10

entry ^a	catalyst (mol %)	solvent	<i>T</i> (°C)	<i>t</i> (min)	yield (%)
1 ^b	Cu(acac) ₂ (10%)	benzene	80	1	20–30
2	Rh ₂ (OAc) ₄ (5%)	CH ₂ Cl ₂	25	120	complex mixture
3	Rh ₂ (esp) ₂ (5%)	CH ₂ Cl ₂	25	5	complex mixture
4	Cu(tfacac) ₂ (10%)	CH ₂ Cl ₂	25	120	20
5	Cu(hfacac) ₂ (10%)	benzene	25	40	complex mixture
6 ^c	Cu(acac) ₂ (10%)	CH ₂ Cl ₂	100	1	33
7 ^c	Cu(acac) ₂ (10%)	benzene	100	1	32
8 ^c	Cu(acac) ₂ (10%)	toluene	100	1	41
9 ^c	Cu(acac) ₂ (10%)	DCE	100	1	17
10 ^c	Cu(hfacac) ₂ (10%)	toluene	100	1	8
11 ^c	Cu(acac) ₂ (20%)	toluene	100	1	17
12 ^c	Cu(acac) ₂ (5%)	toluene	100	1	38
13 ^c	Cu(acac) ₂ (10%)	toluene	150	1	37
14 ^c	Cu(OAc) ₂ (10%)	toluene	100	1	36
15 ^c	Cu(acac) ₂ (10%)	toluene	100	2	38

^aOn a 25.0 mg scale. ^bAddition of the catalyst at once to the solution of the diazoketone after reaching reflux. ^cReaction performed under microwave irradiation.

starting from a dihydropyridin-3-one with a hydroxymethyl group at C6, we could perform the synthesis of several DNJs from the same intermediate after carbonyl reduction and double-bond manipulation (Scheme 1). For example, the syntheses of (–)-1-deoxyaltronojirimycin (*altro*-DNJ), deoxymannonojirimycin (*manno*-DNJ), and/or *ido*-DNJ would be the most direct following this strategy. Unlike many

approaches, the use of a single advanced intermediate that can provide several diastereoisomers from deoxyojirimycin is more desirable, especially in medicinal chemistry.¹³ Herein, to demonstrate this, the total syntheses of deoxyaltronojirimycin and deoxymannonojirimycin¹⁴ in six steps are described from known *N*-Cbz-*O*-TBDPS-serinal.

Scheme 3. Total Syntheses of *altro*-DNJ and *manno*-DNJ

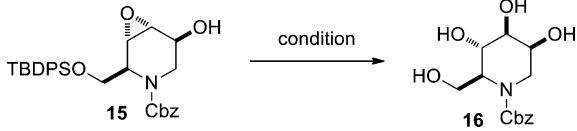
We began our study by employing *N*-tosyl-dihydropyridin-3-one **4** (Scheme 2), previously described by us, aiming to synthesize (–)-1-deoxyaltronojirimycin (*L*-*altro*-DNJ). The Horner–Wadsworth–Emmons reaction of diazophosphonate **1** with *N*-Ts-*O*-TBDPS-serinal **2** furnished *Z*-unsaturated diazoketone **3** in 63% isolated yield (+7% of the *E* isomer; 9:1 dr). A copper-catalyzed intramolecular N–H insertion reaction led to dihydropyridin-3-one **4** in 35–50% yields. Next, the Luche reduction of **4** was expected to provide *cis* allylic alcohol **5** with a high diastereomeric ratio due to the attack of hydride from the opposite face of the bulky CH₂OTBDPS group. In fact, **5** was formed in 98% yield as the only observable isomer (Scheme 2). NMR analysis (NOE effect and H–H coupling constants) confirmed the expected stereochemistry. Dihydroxylation reaction from **5** in the presence of catalytic OsO₄ and NMO furnished **6** in 70% yield as a single isomer, as detected by NMR. Similar to what was observed from the Luche reduction, dihydroxylation probably occurred from the less-hindered α face. Difficulties in proving the expected stereochemistry by NOE compelled us to continue synthesis to the end product (removal of the protecting groups) so that spectroscopic data could be compared with those found in the literature for *altro*-DNJ. Although TBDPS removal in the presence of TBAF gave tetrol **7** in 83% yield, tosyl group removal proved to be problematic. Several attempts to deprotect it using Na/naphthalene and Red-Al failed. Changing the tosyl group to a nosyl group appeared to be an alternative and a solution to the problem. However, during the cyclization step in the preparation of the *N*-Ns dihydropyridin-3-one, a low 8% yield was obtained. We therefore chose to protect the amino function using the alternative benzyloxy carbonyl group (Cbz).

Following the sequence described in Scheme 2, *Z*-unsaturated diazoketone **10** was prepared from diazophosphonate **1** and the known *N*-Cbz-*O*-TBDPS-*L*-serinal **9** in 57% isolated yield (+6% *E* isomer; 9:1 dr). A copper-catalyzed N–H insertion reaction from **10** in refluxing benzene furnished a 20–

30% yield of the *N*-Cbz dihydropyridin-3-one **11**, forcing us to perform an optimization study (Table 1).

Rhodium salts showed the same behavior during cyclization with *N*-Ts diazoketones, in all cases furnishing a complex mixture of products. Use of the more reactive Cu(tfacac)₂ and Cu(hfacac)₂ did not improve the cyclization yield, leading to a no more than 20% yield or a complex mixture. Better yields could be observed when these reactions were performed under microwave irradiation. For example, yields varying from 38 to 41% were obtained after these mixtures had been heated in toluene at 100 °C for 1 min in the presence of 5–10 mol % Cu(acac)₂ or Cu(OAc)₂. Heating the reaction mixture to 150 °C did not change the yield, and using 20 mol % catalysts decreased the yield to 17%. Using the best condition depicted in Table 1 (entry 8), we could prepare dihydropyridinone **11** in good quantities to proceed with the syntheses of *altro*-DNJ, *manno*-DNJ, or *ido*-DNJ (Scheme 3).

For the synthesis of *altro*-DNJ, the same sequence described in Scheme 2 was applied. Luche reduction, dihydroxylation, and TBDPS deprotection led to *N*-Cbz-protected tetrol **14** in 67% overall yield through these three steps. Similar to what was observed in the sequence with *N*-Ts dihydropyridinone **4**, only single isomers were observed by NMR. Removal of the Cbz protecting group was then straightforward, furnishing (–)-*L*-*altro*-DNJ **8** in quantitative yield. Comparison of the NMR spectra of **8** with those described in the literature confirmed the expected stereochemistry. We next turned our attention to preparing epoxide **15** from the same intermediate **11** and studying the regiochemistry of the epoxide ring opening. As seen for the dihydroxylation reaction, *m*-CPBA oxidation of *cis* allylic alcohol **12** afforded epoxide **15** in 83% yield as the only observable isomer from epoxidation of the less-hindered α face. Epoxide opening proved to be very difficult (Table 2); heating **15** carefully with 3 equiv of a 1 M H₂SO₄ solution in a 1:1 dioxane/water mixture was the best option. Employing this condition, epoxide opening from C4 with concomitant TBDPS removal furnished tetrol **16** in 80% yield with high regioselectivity (10:1). Hydrogenolysis of the Cbz carbamate

Table 2. Epoxide Opening Optimization Studies¹⁵


entry	conditions	time	yield (%)
1	1 M H ₂ SO ₄ , dioxane, 95 °C	overnight	complex mixture
2	0.3 M KOH, dioxane, 60 °C	16 h	complex mixture
3	Al ₂ O ₃ , H ₂ O (10 wt %), Et ₂ O	16 h	no reaction
4	BF ₃ ·Et ₂ O (1 equiv), BnOH (15 equiv), DCM	overnight	complex mixture
5	10% HCl/dioxane	1 h (50 °C)	complex mixture
6	1 M H ₂ SO ₄ , dioxane/H ₂ O (1:1)	2 h (rt) → 2 h (80 °C)	80
7	CF ₃ COOH (3 equiv), THF/H ₂ O (3:1), 65 °C	overnight	35
8	CCl ₃ COOH (20 equiv)	36 h	10

in the presence of Pd(OH)₂/C and H₂ gave (+)-*L*-manno-DNJ in quantitative yield.

In summary, we were able to complete the total syntheses of *altro*-DNJ and *manno*-DNJ in six steps from the known *N*-*Z*-*O*-TBDPS-*L*-serinal in a divergent fashion. The use of the same intermediate, dihydropyridin-3-one, not only permitted the short syntheses of these two selected DNJ analogues but also has the potential to be employed in the preparation of other DNJ diastereoisomers after appropriate changes in the synthetic approach. For example, selective reduction of **11** to the *trans* allylic alcohol and further investigation may provide other DNJ isomers.

EXPERIMENTAL SECTION

General Procedures. All solvents were dried and distilled prior to use by standard procedures. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Diazophosphate **1** was prepared according to method developed by our research group.¹⁰ The aldehydes *N*-*Ts*-TBDPS-*L*-serinal **2**^{10b} and *N*-Cbz-TBDPS-*L*-serinal **9**¹⁶ were prepared from *N*-*Ts*-TBDPS-*L*-serinol¹⁷ and *N*-Cbz-TBDPS-*L*-serinol,¹⁸ respectively, after the IBX oxidation reaction. Reactions were monitored by thin layer chromatography (TLC), performed on 0.25 mm silica gel plates using UV light as a visualizing agent and potassium permanganate in aqueous KOH for staining. Column chromatography was performed using silica gel 60 (particle sizes of 0.063–0.210 mm). Unless stated otherwise, all the yields refer to isolated products after flash column chromatography. The solvent mixtures employed in TLC analysis and in flash column chromatography purifications are reported as volume by volume and in percentages. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded using 300, 400, and 500 MHz equipment. For ¹H NMR spectra, chemical shifts (δ) are referenced from TMS (0.00 ppm), DMSO-*d*₆ (2.54 ppm), and D₂O (4.79 ppm). Coupling constants (*J*) are reported in hertz. For multiplicities, the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; bs, broad singlet; dt, double triplet. Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded using a NMR spectrometer at 100 or 125 MHz. For ¹³C NMR spectra, chemical shifts (δ) are given from CDCl₃ (77.0 ppm), DMSO-*d*₆ (40.0 ppm), and D₂O (MeOH as a reference, 49.50 ppm). Infrared spectra were recorded using FT-IR at 4.0 cm⁻¹ resolution and are reported in wavenumbers. Melting points were determined using a digital melting point apparatus and were not corrected. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) (hybrid linear ion trap–orbitrap FT-MS

and QqTOF/MS). Microwave experiments were performed in an Anton Paar Monomode 300 system allowing temperatures from 0 to 300 °C (measured with a Ruby thermometer), powers from 0 to 850 W, and pressures from 0 to 30 bar. Experiments were performed in sealed glass vials (4–30 mL) equipped a snap cap and a silicon septum.

General Procedure for the HWE Reaction. (*R,Z*)-*N*-[1-[(*tert*-Butyldiphenylsilyl)oxy]-6-diazo-5-oxohex-3-en-2-yl]-4-methylbenzenesulfonamide (**3**).^{10a} To a flame-dried round-bottom flask, under an argon atmosphere, were added *t*-BuOK (88.8 mg, 0.79 mmol, 1.1 equiv) and dry THF (2.60 mL, 0.3 M). The suspension was cooled to 0 °C, and a solution of diphenyl (3-diazo-2-oxopropyl)phosphonate (**1**) (228 mg, 0.72 mmol, 1.0 equiv) in dry THF (14.4 mL, 0.05 M) was added. After 10 min, the solution was cooled to –78 °C, and a solution of (*S*)-*N*-[1-[(*tert*-butyldiphenylsilyl)oxy]-3-oxopropan-2-yl]-4-methylbenzenesulfonamide (**2**) (347 mg, 0.72 mmol, 1.0 equiv) in dry THF (3.60 mL, 0.2 M) was added. After 1 h, the temperature was immediately allowed to increase to 0 °C and the mixture stirred for an additional 1 h, and then a saturated aqueous NH₄Cl solution was added to the reaction vessel. Next, the aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were washed with water and brine, dried over Na₂SO₄, and filtered. The solvent was removed under reduced pressure to furnish the crude product that was purified by flash column chromatography (silica gel, 8:2 diethyl ether/hexanes) to give *Z*- α,β -unsaturated diazoketone (**3**) (248 mg, 63% yield) and the *E* isomer (27.6 mg, 7% yield) as an amorphous yellow solid: mp 90–92; ¹H NMR (300 MHz, CDCl₃) δ 7.65–7.57 (m, 2H), 7.50–7.41 (m, 4H), 7.39–7.29 (m, 4H), 7.26–7.05 (m, 4H), 5.94 (dd, *J* = 11.4, 8.0 Hz, 1H), 5.71 (d, *J* = 11.1 Hz, 1H), 5.41 (d, *J* = 5.2 Hz, 1H), 5.18 (s, 1H), 4.99–4.87 (m, 1H), 3.62 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.56–3.49 (m, 1H), 2.33 (s, 3H), 0.91 (s, 9H).

(*Z*)-Benzyl-1-[(*tert*-butyldiphenylsilyl)oxy]-6-diazo-5-oxohex-3-en-2-yl carbamate (**10**). Amorphous yellow solid: 216 mg, 57% yield; mp 69–72 °C; *R*_f = 0.35 (6:4 Et₂O/petroleum ether); IR ν_{\max} 3071, 2995, 2930, 2856, 2098, 1708, 1645, 1498, 1340, 1216, 1107, 1072, 697 cm⁻¹; ¹H NMR (90 °C, 500 MHz, DMSO-*d*₆) δ 7.68–7.62 (m, 4H), 7.48–7.38 (m, 6H), 7.38–7.27 (m, 5H), 7.11 (bs, 1H), 6.11 (d, *J* = 11.6 Hz, 1H), 6.04 (s, 1H), 5.99 (dd, *J* = 11.6, 8.6 Hz, 1H), 5.44–5.35 (m, 1H), 5.07 (d, *J* = 12.7 Hz, 1H), 5.04 (d, *J* = 12.7 Hz, 1H), 3.80–3.72 (m, 2H), 1.02 (s, 9H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 184.8, 155.5, 142.3, 137.2, 135.1, 133.3, 129.6, 128.2, 127.6, 127.5, 126.3, 120.3, 65.7, 65.4, 56.7, 51.5, 26.7, 18.9; [α]_D²⁵ – 9.4 (*c* = 0.5, MeOH); HRMS (ESI-TOF) calcd for C₃₀H₃₃N₃O₄SiNa [M + Na] 550.2138, found 550.2141.

Procedure for the N–H Insertion Reaction. (*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]methyl-1-tosyl-1,6-dihydropyridin-3(2H)-one (**4**).^{10a} To a flame-dried round-bottom flask were added *Z*- α,β -unsaturated diazoketone (**3**) (250 mg, 0.46 mmol, 1.0 equiv) and distilled benzene (9.2 mL, 0.05 M). The mixture was then warmed to reflux, followed by the addition of copper(II) acetylacetonate (12 mg, 0.049 mmol, 0.1 equiv). After 1 min while being stirred, the reaction mixture was cooled, and the solvent was removed under reduced pressure. Next, the crude product was purified by flash column chromatography (silica gel, 1:1 diethyl ether/hexanes) to furnish the dihydropyridin-3-one (**4**) (84 mg, 35% yield) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.54–7.49 (m, 6H), 7.42–7.27 (m, 6H), 7.18–7.12 (m, 2H), 6.63 (dd, *J* = 10.5, 5.0 Hz, 1H), 5.85 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.57 (ddd, *J* = 9.2, 4.7, 1.7 Hz, 1H), 4.29 (d, *J* = 18.5 Hz, 1H), 4.02 (d, *J* = 18.5 Hz, 1H), 3.97 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.75 (dd, *J* = 10.5, 4.1 Hz, 1H), 2.32 (s, 3H), 0.93 (s, 9H).

Procedure for the N–H Insertion Reaction Assisted by Microwave (11**).** A stirred solution of *Z*- α,β -unsaturated diazoketone (**10**) (25.0 mg, 0.05 mmol, 1 equiv) and copper(II) acetylacetonate (1.2 mg, 0.005 mmol, 0.1 equiv) in toluene (0.95 mL, 0.05 M) was heated directly to 100 °C (2 bar pressure) in an Anton Paar microwave (monowave 300) with a ruby sensor and stirred for 1 min. After the mixture had cooled, the solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, 1:9 EtOAc/petroleum ether) to furnish the dihydropyridin-

3-one (**11**) as a yellow oil: 10.3 mg, 41% yield; $R_f = 0.25$ (silica gel, 2:8 EtOAc/petroleum ether); IR ν_{\max} 3071, 3048, 2957, 2930, 2895, 1688, 1426, 1335, 1212, 1100, 991, 822, 697 cm^{-1} ; ^1H NMR (90 °C, 500 MHz, DMSO- d_6) δ 7.76–7.53 (m, 4H), 7.50–7.43 (m, 2H), 7.43–7.28 (m, 9H), 7.18 (dd, $J = 10.4, 5.0$ Hz, 1H), 6.23 (dd, $J = 10.4, 1.4$ Hz, 1H), 5.15 (d, $J = 12.5$ Hz, 1H), 5.11 (d, $J = 12.5$ Hz, 1H), 4.91 (ddd, $J = 10.3, 4.5, 1.4$ Hz, 1H), 4.41 (d, $J = 18.3$ Hz, 1H), 4.01 (dd, $J = 10.4, 4.5$ Hz, 1H), 3.92 (d, $J = 18.3$ Hz, 1H), 3.88 (dd, $J = 10.4, 4.4$ Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (90 °C, 125 MHz, DMSO- d_6) δ 192.9, 154.7, 148.1, 147.1, 136.0, 135.6, 135.4, 132.5, 130.0, 129.9, 128.6, 128.3, 128.0, 127.8, 67.7, 64.2, 53.7, 51.1, 26.7, 19.0; $[\alpha]_{\text{D}}^{25} + 48.6$ ($c = 0.5$, MeOH); HRMS (ESI-TOF) calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_4\text{SiNa}$ [$\text{M} + \text{Na}$] 522.2077, found 522.2083.

General Procedure for the Luche Reduction Reaction. (3*R*,6*R*)-6-[[*tert*-Butyldiphenylsilyloxy]methyl]-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5**). Cerium trichloride heptahydrate (31.4 mg, 0.084 mmol, 1 equiv) was dissolved in dry methanol (0.21 mL, 0.4 M), and this solution was added in a flask containing a solution of dihydropyridin-3-one (**4**) (43.7 mg, 0.084 mmol, 1 equiv) in dichloromethane (1.41 mL, 0.06 M) at -78 °C. After 20 min, sodium borohydride (4.81 mg, 0.126 mmol, 1.5 equiv) was added, and the resulting solution was stirred for 1 h. After this period, the reaction mixture was warmed to 25 °C and the reaction quenched with water. The layers were separated, and the aqueous portion was extracted three times with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to furnish the alcohol (**5**) as a colorless oil: 42.9 mg, 98% yield; $R_f = 0.50$ (8:2 diethyl ether/hexanes); IR ν_{\max} 3474, 3071, 3048, 2955, 2930, 2891, 2858, 1597, 1471, 1428, 1391, 1340, 1307, 1265, 1160, 1103, 1063, 1016, 985, 962, 896, 814, 785, 736, 701, 686, 649, 612 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.66–7.60 (m, 6H), 7.46–7.35 (m, 6H), 7.22–7.18 (m, 2H), 5.81 (d, $J = 11.9$ Hz, 1H), 5.79 (d, $J = 10.9$ Hz, 1H), 4.40–4.34 (m, 1H), 3.95 (dd, $J = 13.1, 6.2$ Hz, 1H), 3.92–3.86 (m, 1H), 3.79–3.73 (m, 2H), 2.97 (dd, $J = 13.1, 9.2$ Hz, 1H), 2.39 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.5, 137.9, 135.8, 135.7, 133.2, 133.1, 131.6, 130.0, 129.9, 129.8, 127.9, 127.8, 127.4, 127.0, 65.9, 62.3, 54.5, 46.5, 26.9, 21.7, 19.4; $[\alpha]_{\text{D}}^{25} + 16.6$ ($c = 0.5$, MeOH); HRMS (ESI-TOF) calcd for $\text{C}_{29}\text{H}_{35}\text{NO}_4\text{SiNa}$ [$\text{M} + \text{Na}$] 544.1954, found 544.1966.

Benzyl-6-[[*tert*-butyldiphenylsilyloxy]methyl]-3-hydroxy-3,6-dihydropyridine-1(2*H*)-carboxylate (**12**). Colorless oil: 625.0 mg, 83% yield (> 99% ee after HPLC analysis; chiralpak AD-H column); $R_f = 0.25$ (silica gel, 1:1 hexane/Et₂O); IR ν_{\max} 3421, 3071, 2995, 2930, 2891, 2858, 1698, 1682, 1214, 1111, 1070, 738, 701 cm^{-1} ; ^1H NMR (90 °C, 500 MHz, DMSO- d_6) δ 7.63–7.57 (m, 4H), 7.47–7.42 (m, 2H), 7.42–7.36 (m, 4H), 7.36–7.25 (m, 5H), 5.87 (d, $J = 10.4$, 1H), 5.75 (ddd, $J = 10.4, 3.4, 2.0$ Hz, 1H), 5.11 (d, $J = 12.5$ Hz, 1H), 5.06 (d, $J = 13.1$ Hz, 1H), 4.90 (s, 1H), 4.52–4.46 (m, 1H), 4.17 (dd, $J = 12.3, 5.9$ Hz, 1H), 4.07–4.00 (m, 1H), 3.78 (dd, $J = 10.0, 5.5$ Hz, 1H), 3.74 (dd, $J = 9.9, 5.9$ Hz, 1H), 2.68 (dd, $J = 11.4, 11.2$, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 155.0, 137.3, 135.5, 135.5, 134.1, 133.7, 133.6, 130.2, 130.2, 128.8, 128.2, 127.9, 125.6, 66.9, 64.8, 62.9, 53.8, 45.5, 27.2, 19.3; $[\alpha]_{\text{D}}^{25} + 32.4$ ($c = 0.5$, MeOH); HRMS (ESI-TOF) calcd for $\text{C}_{30}\text{H}_{35}\text{NO}_4\text{SiNa}$ [$\text{M} + \text{Na}$] 524.2233, found 524.2231.

General Procedure for the Dihydroxylation Reaction. (2*S*,3*S*,4*R*,5*S*)-2-[[*tert*-Butyldiphenylsilyloxy]methyl]-1-tosylpiperidine-3,4,5-triol (**6**). In a round-bottom flask, a solution of olefin (**5**) (30.8 mg, 0.059 mmol, 1.0 equiv) was prepared in a 9:1 acetone/water solvent (1.96 mL, 0.03 M). *N*-Methylmorpholine *N*-oxide (13.9 mg, 0.118 mmol, 2.0 equiv) was then added, followed by the addition of a solution of osmium tetroxide (19.8 μL , 0.15 M, 0.05 equiv). The reaction solution was allowed to stir at 25 °C for 60 h, and afterward, water was added and the crude product extracted six times with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Next, the crude product was purified by flash column chromatography (silica gel, 100% ethyl acetate) to furnish the dihydroxylated product (**14**) as a colorless oil: 22.9 mg, 0.040 mmol, 70% yield; $R_f = 0.10$ (8:2 diethyl ether/hexanes); IR ν_{\max} 3421, 3071, 3050, 2953, 2930, 2889, 2858, 1593,

1471, 1428, 1393, 1331, 1307, 1265, 1156, 1109, 1086, 1028, 997, 938, 919, 820, 777, 736, 701, 688, 644, 614 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.65 (d, $J = 8.3$ Hz, 2H), 7.60–7.54 (m, 4H), 7.47–7.35 (m, 6H), 7.14 (d, $J = 8.0$ Hz, 2H), 4.32 (dd, $J = 8.3, 6.4$ Hz, 1H), 4.21 (s, 1H), 3.84 (dd, $J = 13.3, 5.3$ Hz, 1H), 3.80–3.71 (m, 1H), 3.56 (dd, $J = 10.7, 5.6$ Hz, 1H), 3.60 (dd, $J = 10.7, 5.6$ Hz, 1H), 3.54–3.44 (m, 1H), 2.97–2.56 (m, 4H), 2.36 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.3, 137.2, 135.5, 135.5, 132.6, 132.5, 130.0, 130.0, 129.6, 127.9, 127.8, 127.2, 72.7, 68.8, 66.9, 61.7, 60.1, 45.7, 26.9, 21.5, 19.1; $[\alpha]_{\text{D}}^{25} + 7.2$ ($c = 0.5$, MeOH); HRMS (ESI-TOF) calcd for $\text{C}_{29}\text{H}_{38}\text{NO}_6\text{Si}$ [$\text{M} + \text{H}$] 556.2189, found 556.2211.

Benzyl-2-[[*tert*-butyldiphenylsilyloxy]methyl]-3,4,5-trihydroxypiperidine-1-carboxylate (**13**). Amorphous white solid: 279.0 mg, 90% yield; mp 60–65 °C; $R_f = 0.15$ (silica gel, 9:1 AcOEt/MeOH); IR ν_{\max} 3396, 2953, 2930, 2889, 2856, 1671, 1428, 1344, 1191, 1105, 1074, 822, 738 cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6) δ 7.64–7.55 (m, 4H), 7.48–7.35 (m, 6H), 7.35–7.23 (m, 4H), 5.09 (d, $J = 12.7$ Hz, 1H), 5.03 (d, $J = 12.8$ Hz, 1H), 4.57–4.50 (m, 1H), 4.44–4.34 (m, 2H), 4.33–4.26 (m, 1H), 4.05 (dd, $J = 13.2$ Hz, 1H), 3.97–3.94 (m, 1H), 3.80 (dd, $J = 10.6, 6.6$ Hz, 1H), 3.74 (dd, $J = 10.4, 6.9$ Hz, 1H), 3.68–3.57 (m, 1H), 3.37 (ddd, $J = 8.6, 5.4, 3.2$ Hz, 2H), 2.58 (dd, $J = 13.3, 10.7$ Hz, 1H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 155.9, 137.5, 135.5, 135.5, 133.6, 133.5, 130.2, 130.2, 128.7, 128.2, 128.0, 127.7, 72.2, 68.8, 66.9, 66.8, 61.9, 59.8, 45.7, 27.2, 19.2; $[\alpha]_{\text{D}}^{25} + 8.0$ ($c = 0.5$, MeOH); HRMS (ESI-TOF) calcd for $\text{C}_{30}\text{H}_{37}\text{NO}_6\text{SiNa}$ [$\text{M} + \text{Na}$] 558.2288, found 558.2294.

General Procedure for the TBDPS Deprotection Reaction. (2*S*,3*S*,4*R*,5*S*)-2-(Hydroxymethyl)-1-tosylpiperidine-3,4,5-triol (**7**). To a round-bottom flask were added the product of dihydroxylation (**6**) (28.7 mg, 0.052 mmol, 1 equiv) and dry THF (2.58 mL, 0.02 M). To this solution was added a solution of tetrabutylammonium fluoride in THF (156 μL , 1.0 M, 3 equiv) at 0 °C, and the reaction mixture was allowed to reach room temperature and then was stirred for 16 h. After this time, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, 100% ethyl acetate \rightarrow 9:1 AcOEt/MeOH) to provide the deprotected product (**7**) as a colorless oil: 13.7 mg, 86% yield; $R_f = 0.10$ (acetyl acetate); IR ν_{\max} 3382, 3071, 3050, 2955, 2924, 2854, 1731, 1700, 1669, 1599, 1457, 1428, 1379, 1333, 1304, 1259, 1216, 1156, 1111, 1088, 1074, 1028, 1074, 1028, 997, 969, 940, 917, 818, 742, 702, 655, 612 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD with D_2O drop) δ 7.87–7.83 (m, 2H), 7.38–7.34 (m, 2H), 4.24–4.19 (m, 1H), 4.09–4.06 (m, 1H), 3.72–3.51 (m, 5H), 2.86 (dd, $J = 13.4, 10.4$ Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 144.6, 139.4, 130.5, 128.7, 73.4, 70.0, 67.2, 62.8, 60.8, 47.1, 21.4; $[\alpha]_{\text{D}}^{25} + 12.4$ ($c = 0.5$, MeOH); HRMS (ESI-TOF) calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_6$ [$\text{M} + \text{H}$] 318.1011, found 318.1013.

Benzyl (2*S*,3*S*,4*R*,5*S*)-3,4,5-Trihydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (**14**). White semisolid: 70.0 mg, 84% yield; $R_f = 0.20$ [silica gel, 9:1 AcOEt/MeOH (run twice)]; IR ν_{\max} 3363, 2955, 2916, 2850, 669, 1434, 1218, 1070, 1022 cm^{-1} ; ^1H NMR (90 °C, 500 MHz, DMSO- d_6) δ 7.44–7.37 (m, 4H), 7.37–7.30 (m, 1H), 5.16–5.08 (m, 2H), 4.61 (s, 1H), 4.55 (s, 1H), 4.31–4.22 (m, 3H), 4.07 (dd, $J = 13.1, 5.7$ Hz, 1H), 3.97–3.92 (m, 1H), 3.71–3.50 (m, 3H), 3.49–3.42 (m, 1H), 2.69 (dd, $J = 12.8, 11.2$ Hz, 1H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 156.0, 137.7, 128.7, 128.0, 127.7, 73.0, 68.9, 67.0, 66.6, 60.2, 59.5, 45.8; $[\alpha]_{\text{D}}^{25} + 8.2$ ($c = 0.5$, MeOH); HRMS (ESI-TOF) calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_6\text{Na}$ [$\text{M} + \text{Na}$] 320.1110, found 320.1105.

Procedure for Epoxidation. *Benzyl* (1*S*,2*S*,5*S*,6*R*)-2-[[*tert*-Butyldiphenylsilyloxy]methyl]-5-hydroxy-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (**15**). In a round-bottom flask (10 mL), a solution of olefin (**12**) (200.0 mg, 0.40 mmol, 1.0 equiv) in dichloromethane (5.0 mL, 0.08 M) was prepared. Next, 77% *m*-CPBA (268.0 mg, 1.20 mmol, 3.0 equiv) was added in one portion. After being stirred at room temperature for 12 h, the reaction mixture was diluted with dichloromethane and washed with a saturated NaHCO_3 aqueous solution and brine. The aqueous portion was extracted three times with dichloromethane, and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Next, the crude product was purified by flash column chromatography (silica gel, 1:1 *n*-hexanes/Et₂O) to furnish the epoxide (**15**) as a colorless oil:

171.0 mg, 83% yield; $R_f = 0.21$ (silica gel, 1:1 *n*-hexanes/Et₂O); IR ν_{\max} 3041, 3071, 3031, 2953, 2930, 2856, 1700, 1686, 1426, 1307, 1274, 1257, 1191, 1111, 1068, 740, 699 cm⁻¹; ¹H NMR (90 °C, 500 MHz, DMSO-*d*₆) δ 7.69–7.59 (m, 4H), 7.50–7.36 (m, 6H), 7.35–7.26 (m, 5H), 5.16–5.09 (m, 1H), 5.09–4.98 (m, 2H), 4.54–4.37 (m, 1H), 3.90–3.80 (m, 2H), 3.78–3.68 (m, 2H), 3.63–3.58 (m, 1H), 3.38–3.34 (m, 1H), 1.02 (s, 9H) (OH not observed); ¹³C NMR (90 °C, 125 MHz, DMSO-*d*₆) δ 154.7, 137.2, 135.5 (2C), 133.6, 130.2, 128.8, 128.2, 127.9, 79.6, 67.1, 65.2, 61.8, 55.1, 54.0, 50.7, 27.1, 19.3; [α]_D²⁵ + 8.4 (*c* = 0.5, MeOH); HRMS (ESI-TOF) calcd for C₃₀H₃₅NO₃SiNa [M + Na] 540.2182, found 540.2184.

Epoxide Ring Opening Reaction. *Benzyl (2S,3S,4S,5S)-3,4,5-Trihydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (16)*. In a round-bottom flask (10 mL), a solution of epoxide (**15**) (26.0 mg, 0.05 mmol, 1.0 equiv) in a 1:1 H₂O/dioxane solvent (2.5 mL, 0.02 M) was prepared. After that, a 1.0 M aqueous solution of H₂SO₄ (0.15 mL, 0.15 mmol, 3.0 equiv) was added dropwise. The reaction mixture was allowed to stir 2 h at room temperature and then heated to 80 °C for 2 h. After completion, the reaction mixture was diluted with NaHCO₃ and extracted with AcOEt (six times). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. Next, the crude product was purified by flash column chromatography (silica gel, 100% AcOEt → 9:1 AcOEt/MeOH) to furnish tetrol (**16**) as a colorless oil: 12.0 mg, 80% yield; $R_f = 0.3$ (silica gel, 9:1 AcOEt/MeOH); IR ν_{\max} 3367, 2955, 2922, 2852, 1669, 1457, 1131, 954, 917 cm⁻¹; ¹H NMR (90 °C, 500 MHz, DMSO-*d*₆ with D₂O drop) δ 7.38–7.32 (m, 4H), 7.32–7.26 (m, 1H), 5.09 (d, *J* = 12.9 Hz, 1H), 5.06 (d, *J* = 13.0 Hz, 1H), 4.09 (dd, *J* = 6.8, 6.7 Hz, 1H), 3.86–3.78 (m, 2H), 3.76–3.67 (m, 2H), 3.64 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.61 (dd, *J* = 8.7, 4.4 Hz, 1H), 2.93 (dd, *J* = 12.1, 11.3 Hz, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 156.4, 138.0, 128.9, 128.2, 127.8, 71.3, 69.5, 66.7, 64.6, 60.2, 59.8, 41.3; [α]_D²⁵ + 4.0 (*c* = 0.5, MeOH), HRMS (ESI-TOF) calcd for C₁₄H₁₉NO₆Na [M + Na] 320.1110, found 320.1114.

Removal of the Cbz Protecting Group. *(2S,3S,4R,5S)-3,4,5-Trihydroxy-2-(hydroxymethyl)piperidin-1-ium Chloride (l-altra-1-DNJ hydrochloride) (8)*. To a round-bottom flask (10 mL) were added tetrol (**14**) (21.0 mg, 0.07 mmol, 1 equiv) and dry methanol (1 mL, 0.07 M). To this solution was added in one portion 20 mol % Pd(OH)₂/C (4.5 mg, 0.07 mmol). The reaction mixture was allowed to stir for 24 h under a hydrogen atmosphere. After that, the reaction mixture was filtered with a short pad of Celite and concentrated under reduced pressure. To the crude product was added an aqueous solution of 7% HCl and the solvent removed under reduced pressure to furnish the hydrochloride (**8**) as a yellow oil: 14.0 mg (quantitative yield); ¹H NMR (500 MHz, D₂O) δ 4.19–4.16 (m, 1H), 4.08–4.03 (m, 2H), 3.99 (dd, *J* = 12.6, 3.3 Hz, 1H), 3.86 (dd, *J* = 12.6, 6.8 Hz, 1H), 3.44–3.36 (m, 2H), 3.25 (dd, *J* = 13.5, 2.9 Hz, 1H); ¹³C NMR (125 MHz, D₂O) δ 68.5, 66.2, 63.6, 58.2, 55.9, 43.9; [α]_D²⁵ – 11.4 (*c* = 0.5, MeOH) (lit.^{14c} – 36.7, *c* = 1, MeOH; lit.^{14d} – 7.2, *c* = 0.5, MeOH); HRMS (ESI-TOF) calcd for C₆H₁₄NO₄ [M + H] 164.0917, found 164.0924.

(2S,3S,4S,5S)-3,4,5-Trihydroxy-2-(hydroxymethyl)piperidin-1-ium Chloride (l-manno-DNJ hydrochloride) (17). Yellow semisolid: 14.0 mg (quantitative yield); ¹H NMR (500 MHz, D₂O) δ 4.30–4.28 (m, 1H), 4.04 (dd, *J* = 12.6, 3.3 Hz, 1H), 3.94–3.86 (m, *J* = 12.6, 10.7, 8.3 Hz, 2H), 3.73 (dd, *J* = 9.5, 3.1 Hz, 1H), 3.46 (dd, *J* = 13.6, 3.1 Hz, 1H), 3.29 (dd, *J* = 13.6, 1.3 Hz, 1H), 3.23–3.17 (m, 1H); ¹³C NMR (125 MHz, D₂O and MeOH drop) δ 73.0, 66.5, 66.3, 61.0, 58.7, 48.1; [α]_D²⁵ + 8.1 (*c* = 0.3, MeOH) (lit.^{14j} + 11.3, *c* = 0.95, H₂O; lit.¹⁹ + 28, *c* = 1.0, MeOH); HRMS (ESI-TOF) calcd for C₆H₁₄NO₄ [M + H] 164.0917, found 164.0926.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01575.

NMR spectra of all new and final known compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680. (b) Daniel, P. F.; Evans, J. E.; De Gasperi, R.; Winchester, B.; Warren, C. D. *Glycobiology* **1992**, *2*, 327–336.
- (2) (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (b) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 652–671. (c) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.
- (3) Inouye, S.; Tsurouka, T.; Nida, T. *J. Antibiot.* **1966**, *19*, 288–292.
- (4) (a) Nash, R. J.; Kato, A.; Yu, C.; Fleet, G. W. *Future Med. Chem.* **2011**, *3*, 1513–1521. (b) Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219–221.
- (5) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036–2044.
- (6) Aoki, K.; Masuda, K.; Miyazaki, T.; Togashi, Y.; Terauchi, Y. *Endocr. J.* **2010**, *57*, 667–672.
- (7) Taylor, D. L.; Sunkara, P. S.; Liu, P. S.; Kang, M. S.; Bowlin, T. L.; Tymes, A. S. *AIDS* **1991**, *5*, 693–698.
- (8) Kong, W.; Oh, S.; Ahn, Y.; Kim, K.; Kim, J.; Seo, S. *J. Agric. Food Chem.* **2008**, *56*, 2613–2619.
- (9) (a) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265–295. (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477.
- (10) (a) Pinho, V. D.; Burtoloso, A. C. B. *J. Org. Chem.* **2011**, *76*, 289–292. (b) Rosset, I. G.; Burtoloso, A. C. B. *J. Org. Chem.* **2013**, *78*, 9464–9470. (c) Burtoloso, A. C. B.; Dias, R. M. P.; Bernardim, B. Acc. Chem. Res. **2015**, *48*, 921–934.
- (11) For pioneering contributions in the intramolecular N–H insertion reactions, see: (a) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, *19*, 4233–4236. (b) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223–5230. (c) Moody, C. J.; Pearson, C. J.; Lawton, G. *Tetrahedron Lett.* **1985**, *26*, 3167–3170. (d) Ko, K.; Lee, K.; Kim, W. *Tetrahedron Lett.* **1992**, *33*, 6651–6652. (e) Hanessian, S.; Fu, J.; Chiara, J.; Di Fabio, R. *Tetrahedron Lett.* **1993**, *34*, 4157–4160. (f) Podlech, J.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1238–1246. (g) Garcia, C. F.; McKervey, M. A.; Ye, T. *Chem. Commun.* **1996**, 1465–1466.
- (12) (a) O'Doherty, G. A.; Haukaas, M. H. *Org. Lett.* **2001**, *3* (3), 401–404. (b) Harris, J. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 2029–2031. (c) Koulocheri, S. D.; Magiatis, P.; Skaltsounis, A.-L.; Haroutounian, S. A. *Tetrahedron* **2002**, *58*, 6665–6671. (d) Leverett, C. A.; Cassidy, M. P.; Padwa, A. *J. Org. Chem.* **2006**, *71*, 8591–8601. (e) Wong, H.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 7517–7527. (f) Martin, T. J.; Rovis, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 5368–5371.
- (13) Zou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363–1391.

- (14) Recent syntheses for *altro*- and *manno*-DNJ: (a) Chacko, S.; Ramapanicker, R. *J. Org. Chem.* **2015**, *80*, 4776–4782. (b) Singh, P.; Manna, S. K.; Panda, G. *Tetrahedron* **2014**, *70*, 1363–1374. (c) Karjalainen, O.; Koskinen, A. *Org. Biomol. Chem.* **2011**, *9*, 1231–1236. (d) Van den Nieuwendijk, A.; Ruben, M.; Engelsma, S.; Risseeuw, M.; Van den Berg, R.; Boot, R.; Aerts, J.; Brussee, J.; Van der Marel, G.; Overkleef, H. *Org. Lett.* **2010**, *12*, 3957–3959. (e) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 8133–8146. (f) Van Den Nieuwendijk, A. M. C. H.; Van Den Berg, R. J. B. H. N.; Ruben, M.; Witte, M. D.; Brussee, J.; Boot, R. G.; Van Der Marel, G. A.; Aerts, J. M. F. G.; Overkleef, H. S. *Eur. J. Org. Chem.* **2012**, *2012*, 3437–3446. (g) Hoecker, J.; Rudolf, G. C.; Baechle, F.; Fleischer, S.; Lindner, B. D.; Helmchen, G. *Eur. J. Org. Chem.* **2013**, *2013*, 5149–5159. (h) Scarpi, D.; Bartali, L.; Casini, A.; Occhiato, E. G. *Eur. J. Org. Chem.* **2012**, *2012*, 2597–2605. (i) Singh, A.; Kim, B.; Lee, W. K.; Ha, H.-J. *Org. Biomol. Chem.* **2011**, *9*, 1372–1380. (j) Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2042–2045. (k) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136–139.
- (15) Epoxide opening procedures: (a) Rengasamy, R.; Curtis-Long, M. J.; Seo, W. D.; Jung, S. H.; Jeong, I.-Y.; Park, K. H. *J. Org. Chem.* **2008**, *73*, 2898–2901. (b) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270–2274. (c) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136–139. (d) Coleman, R. S.; Fraser, J. R. *J. Org. Chem.* **1993**, *58*, 385–392. (e) Trost, B.; Horne, D.; Woltering, M. *Chem. - Eur. J.* **2006**, *12*, 6607–6620. (f) Sean-Esslinger, C.; Kavanaugh, L. N. U.S. Patent 0056138, 2015.
- (16) Golebiowski, A.; Kozak, J.; Jurczak, J. *J. Org. Chem.* **1991**, *56*, 7344–7347.
- (17) Provoost, O.; Hazelwood, A.; Harrity, J. *Beilstein J. Org. Chem.* **2007**, *3*, 8.
- (18) Brands, K.; Meekel, A.; Pandit, U. *Tetrahedron* **1991**, *47*, 2005–2026.
- (19) Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280–6289.