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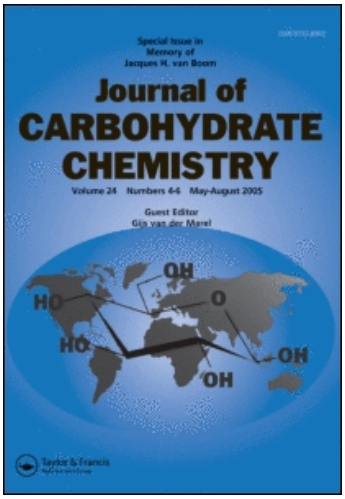

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Synthesis of the Dimethyl Ester of 1-Deoxy-l-Idonojirimycin-1-Methylenphosphonate: A New Approach to Iminosugar Phosphonates

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Synthesis of the Dimethyl Ester of 1-Deoxy-L-Idonojirimycin-1-Methylenphosphonate: A New Approach to Iminosugar Phosphonates

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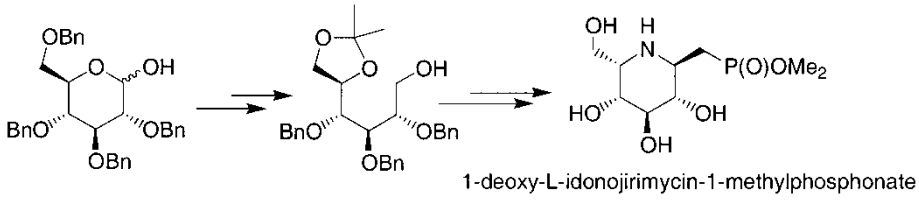
1-Methylenphosphonate-1-deoxy-L-idonojirimycin (**1**) has been synthesized starting from commercially available tetrabenzyl glucose, the key steps being substitution of the hydroxyl group at C-5 of compound **7** with an azido group, stereoselective reaction of the aldehyde at C-1 of compound **10** with dimethyl methylenephosphonate anion, conversion of the azide into an amino group, and finally cyclization of the aminoalcohol **12**.



1-deoxy-L-idonojirimycin-1-methylphosphonate

Keywords Carbohydrate analogs, Iminosugars, Phosphonates, Inhibitors

Received October 6, 2005; accepted November 10, 2005.
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INTRODUCTION

Naturally occurring iminosugars are known to be potent inhibitors of carbohydrate processing enzymes such as glycosidases and glycosyltransferases,[1] which are involved in many biological and pathological process. This has suggested their used in a wide range of potential therapeutic applications,[2–6] and has stimulated synthetic chemists to develop new and more efficient synthetic strategies for the preparation of new, more potent and selective iminosugar derivatives. Due to the great interest in these compounds, a great number of novel structures have been synthesized so far, nonetheless, there are only very few examples of iminosugar phosphonates.[7] In this work we report the synthesis of a new compound 1-deoxy-L-idonojirimycin-1-methylenphosphonate using a novel approach to iminosugar phosphonates.

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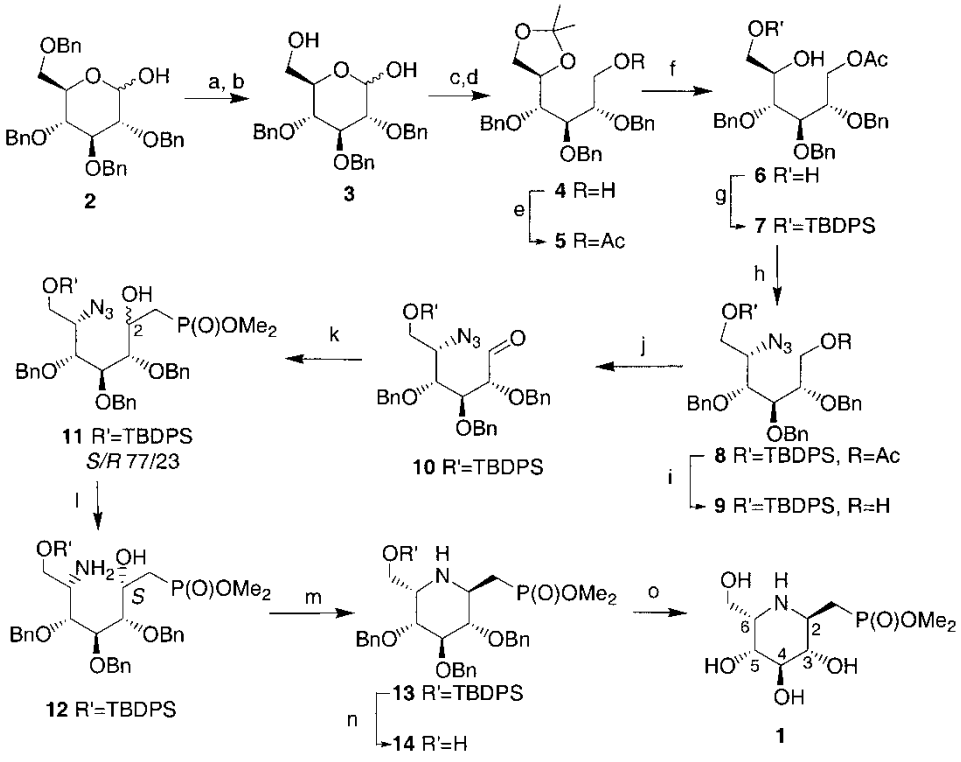
RESULTS AND DISCUSSION

Our synthetic route started from tetrabenzyl glucose **2**. In order to introduce a nitrogen atom at C-5, which was required for the generation of the iminosugars, the following synthetic scheme was elaborated (Sch. 1): acetolysis and basic hydrolysis of the acetate afforded compound **3**, which in turn was reduced to the corresponding alditol, which was protected as isopropylidene derivative **4**. Protection of the primary hydroxyl group at C-1 as acetate (**5**) and cleavage of the isopropylidene group followed by protection of the primary hydroxyl group at C-6 as t-butyldiphenylsilyl ether afforded compound **7** with a free hydroxyl group at C-5. The free hydroxyl group of **7** was exploited for the introduction of the nitrogen atom; its substitution with an azide through a Mitsunobu reaction afforded compound **8** with inversion of configuration at C-5. In order to introduce the methylenephosphonate moiety, the acetylated primary hydroxyl group at C-1 was selectively deprotected and oxidized to the corresponding aldehyde **10**, and then subjected to a nucleophilic attack using lithium methylenedimethyl phosphonate. The reaction afforded compound **11** as an inseparable mixture of diastereoisomers in a ratio of $R/S = 23{:}77$, determined by ^{1}H NMR spectroscopy. Only after reduction with thiphenylphosphine in water/THF the corresponding major amine **12** was obtained as pure product in 51% yield over the two steps.

The absolute configuration of the newly formed stereocenter was attributed to the cyclized product and is discussed later on. Compound **12** was then cyclized through an intramolecular Mitsunobu reaction, affording, after removal of the silyl protection, pure compound **14** in 58% yield over the two steps. Final debenzylation afforded the dimethyl ester of 1-deoxy-L-idonojirimycin-1-methylenphosphonate (**1**). ^{1}H NMR spectroscopic analysis of compound **14** allowed us to determine the absolute configuration of the C(2) stereocenter formed during the additon of the phosphonate group. The



Scheme 1: *Reagents and conditions.* a) Ac_2O/TFA 4/1 then NaOH 4M; b) Na, MeOH; c) $NaBH_4$, EtOH; d) 2,2-dimethoxypropane, camphor-10-sulfonic acid, CH_3CN (91% over four steps); e) Ac_2O, pyridine, DMAP, CH_2Cl_2 (96%); f) H_2O, CSA, CH_3CN, 60°C (96%); g) TBDPSCl, imidazole, CH_2Cl_2 (95%); h) $(PhO)_2PON_3$, PPh_3, DIAD, THF (71%); i) MeONa, MeOH (91%); j) Dess-Martin periodinane, CH_2Cl_2; k) $CH_3PO(OMe)_2$, BuLi, THF, −78°C (62% over two steps); l) PPh_3, H_2O, THF, 60°C (51%); m) PPh_3, DIAD, THF; n) TBAF, THF (58% over two steps); o) $Pd(OH)_2/C$, H_2, MeOH/AcOH 98%.

values of the coupling constants ($J_{3,2} = 8.5$ Hz, $J_{4,3} = 8.0$ Hz, and $J_{5,4} = 9.0$ Hz) (Fig. 1) were indicative of a *trans*-diaxial disposition of the protons, thus indicating a $^4C_1$ conformation; moreover, the diaxial disposition of C(2)-H/C(3)-H allowed to determine the absolute configuration (R) of C(2).

Biological evaluation of compound **1** in a variety of glycosidase inhibition assay is in due course.

EXPERIMENTAL

General Remarks

All solvents were dried with molecular sieves for at least 24 h prior to use. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates

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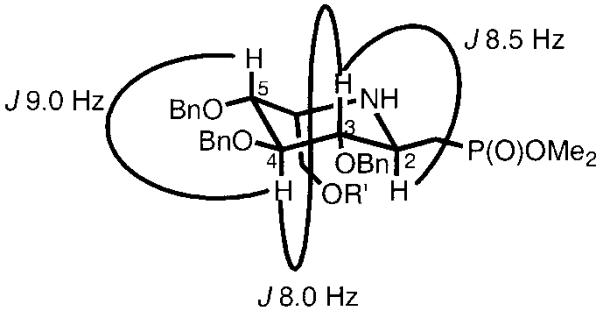

Figure 1: Conformation and coupling constants values of compound **13**.

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(Merck) with detection using UV light when possible, or by charring with a solution of concd. H_2SO_4/EtOH/H_2O (5:45:45) or a solution of $(NH_4)_6Mo_7O_{24}$ (21 g), $Ce(SO_4)_2$ (1 g), concd. H_2SO_4 (31 mL) in water (500 mL). Flash column chromatography was performed on silica gel 230–400 mesh (Merck). ^1H, ^{13}C NMR, and ^{31}P spectra were recorded at 25°C with a Varian Mercury 400 MHz instrument using $CDCl_3$ as the solvent unless otherwise stated. Chemical shift assignments, reported in ppm, are referenced to the corresponding solvent peaks. Mass spectra were recorded with a MALDI2 Kompakt Kratos instrument, using gentisic acid (DHB) as the matrix. Optical rotations were measured at rt using a Krüss P3002 electronic polarimeter and are reported in units of $10^{-1}\,deg \cdot cm^2 \cdot g^{-1}$. Elemental analyses were performed using a Perkin-Elmer Series II Analyzer 2400.

2,3,4-Tri-*O*-benzyl-D-glucopyranose (3). Compound **2** (2.5 g, 4.62 mmol), was cooled to 0°C under an inert atmosphere, and a solution of Ac_2O/TFA 4/1 (30 mL) was slowly added. The reaction was left stirring at 0°C. After 3 h ice-cold water was added (50 mL), and after 15 min the reaction mixture was neutralized by a slow addition at 0°C of NaOH 4M. The mixture was then extracted with AcOEt (3 × 100 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was eliminated under reduced pressure. The crude was dissolved in dry MeOH (10 mL) and a catalytic amount of Na was added. After 15 min the reaction mixture was neutralized with amberlite IR 120-H^+, filtered, and evaporated, affording known compound **3**[8] as mixture of diastereoisomers. Crude **3** was directly used for the following step.

2,3,4-Tri-*O*-benzyl-5,6-*O*–isopropylidene-D-glucitol (4). Crude compound **3** was dissolved in EtOH (30 mL) and $NaBH_4$ (1.17 g, 31 mmol) was added in five portions. After 3 h the solvent was removed under reduced pressure and the solid residue was suspended in a saturated solution of Na_2CO_3 (30 mL). The suspension was stirred for 20 min and then extracted with EtOAc

(3×30 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was eliminated under reduced pressure. The crude was dissolved in dry CH_3CN (10 mL) under inert atmosphere, and 2,2-dimethoxypropane (1.2 mL, 10.07 mmol) and a catalytic amount of camphor-10-sulfonic acid were added. After 1 h the reaction was neutralized with triethylamine and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate v/v 7/3), yielding **4** (3.48 g, 91% from **2**) as a colorless oil. $[\alpha]_D^{20}$ +1.2 (*c* 0.4 $CHCl_3$); ^{1}H NMR: $\delta = 1.33$ (s, 3 H, C*H*$_3$iPr), 1.42 (s, 3 H, C*H*$_3$iPr), 3.50 [m, 1 H, C(1a)-H], 3.70–3.78 [m, 3 H, C(2)-H, C(3)-H, C(1b)-H], 3.93–3.97 [m, 2 H, C(4)-H, C(6a)-H], 4.03 [dd, 1 H, $J = 8.0$ Hz, $J = 7.2$ Hz, C(6b)-H], 4.22 [bdt, 1 H, $J = 7.2$ Hz, $J = 4.0$ Hz, C(5)-H], 4.61–4.68 (m, 4 H, 4C*H*Ph), 4.75 (d, 1 H, $J = 11.2$ Hz, C*H*Ph), 4.83 (d, 1 H, $J = 11.6$ Hz, C*H*Ph), 7.19–7.34 (m, 15 H, C*H*Ar) ppm. ^{13}C NMR: $\delta = 25.38$, 26.97 (2 *C*H$_3$iPr), 61.87, 66.20 [C(1), C(6)], 73.30, 74.33, 75.05 (3*C*H$_2$Ph), 77.44, 78.33, 78.83, 79.88 [C(2), C(3), C(4), C(5)], 108.5 (*C*qiPr), 127.9–128.7 (*C*HAr), 138.1, 138.2, 138.3 (*C*qAr) ppm. MS (MALDI-TOF): m/z 515 $[M + Na]^+$, 531 $[M + K]^+$; $C_{30}H_{36}O_6$ (492.25): Calcd.; C, 73.15; H, 7.37. found; C, 72.95; H, 7.21.

1-*O*-Acetyl-2,3,4-tri-*O*-benzyl-5,6-*O*–isopropylidene-D-glucitol (5). Compound **4** (183 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (2 mL) and pyridine (6 equiv., 2.22 mmol, 176 mg, 179 μL), DMAP (0.1 equiv., 0.04 mmol, 5 mg), and acetic anhydride (3 equiv., 1.11 mmol, 114 mg, 105 μL) were added. The solution was stirred at rt for 1 h, and then HCl (5%, 2 mL) was added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4. The solvent was eliminated under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate v/v 10/1), yielding **5** (189 mg, 96%) as colorless oil. $[\alpha]_D^{20} + 7.0$ (*c* 1.0 $CHCl_3$); ^{1}H NMR: $\delta = 1.23$ (s, 3 H, C*H*$_3$iPr), 1.33 (s, 3 H, C*H*$_3$iPr), 1.93 (s, 3H, C*H*$_3$Ac), 3.58 [dd, 1 H, $J = 6.1$ Hz, $J = 4.1$ Hz, C(4)-H], 3.79 [ddd, 1 H, $J = 9.4$ Hz, $J = 5.9$ Hz, $J = 3.3$ Hz, C(2)-H], 3.83–3.87 [m, 2 H, C(3)-H, C(6a)-H], 3.92 [bt, 1 H, $J = 7.6$ Hz, C(6b)-H], 4.00 [dd, 1 H, $J = 12.0$ Hz, $J = 5.9$ Hz, C(1a)-H], 4.12 [ddd, 1 H, $J = 11.3$ Hz, $J = 6.8$ Hz, $J = 4.2$ Hz, C(5)-H], 4.25 [dd, 1 H, $J = 12.0$ Hz, $J = 3.4$ Hz, C(1b)-H], 4.51 (d, 1 H, $J = 11.6$ Hz, C*H*Ph), 4.55 (d, 1 H, $J = 11.3$ Hz, C*H*Ph), 4.57 (d, 1 H, $J = 11.3$ Hz, C*H*Ph), 4.58 (d, 1 H, $J = 11.6$ Hz, C*H*Ph), 4.64 (d, 1 H, $J = 11.3$ Hz, C*H*Ph), 4.73 (d, 1 H, $J = 11.3$ Hz, C*H*Ph), 7.19–7.24 (m, 15 H, C*H*Ar) ppm. ^{13}C NMR: $\delta = 21.43$(*C*H$_3$Ac), 25.43, 26.97 (2 *C*H$_3$iPr), 64.23, 66.21 [C(1), C(6)], 73.35, 74.47, 74.95 (3*C*H$_2$Ph), 77.36, 77.54, 78.53, 79.33 [C(2), C(3), C(4), C(5)], 108.5 (*C*qiPr), 127.9–132.4 (*C*HAr), 138.2, 138.4, 138.4 (*C*qAr), 170.9 (*C*=O) ppm. MS (MALDI-TOF): m/z 557 $[M + Na]^+$, 573 $[M + K]^+$; $C_{32}H_{38}O_7$ (534.26): Calcd; C, 71.89; H, 7.16. Found; C, 71.95; H 7.20.

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1-*O*-Acetyl-2,3,4-tri-*O*-benzyl-D-glucitol (6). Compound **5** (1.07 g, 2.01 mmol) was dissolved in CH_3CN (10 mL), and then H_2O (500 μL) and CSA (0.1 equiv., 0.2 mmol, 50 mg) were added. The mixture was stirred at 60°C for 20 min, and then $NaHCO_3$ (sat. sol., 5 mL) was added. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4. The solvent was eliminated under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate v/v 8/2), yielding **6** (944 mg, 96%) as colorless oil. $[\alpha]_D^{20}$ +11.2 (*c* 0.9 $CHCl_3$); ^{1}H NMR: $\delta = 1.89$ (s, 3 H, C*H*$_3$Ac), 2.22–2.28 (m, 1 H, O*H*), 3.27 (d, 1 H, $J = 5.6$ Hz, O*H*), 3.55–3.58 [m, 1 H, C(6a)-H], 3.64–3.67 [m, 3 H, C(3)-H, C(4)-H, C(6b)-H], 3.73–3.75 [m, 1 H, C(5)-H], 3.84–3.87 [m, 1 H, C(2)-H], 4.11 [dd, 1 H, $J = 11.5$ Hz, $J = 5.9$ Hz, C(1a)-H], 4.19 [dd, 1 H, $J = 11.5$ Hz, $J = 4.8$ Hz, C(1b)-H], 4.51–4.61 (m, 6 H, 6C*H*Ph), 7.15–7.26 (m, 15 H, C*H*Ar) ppm. ^{13}C-NMR: $\delta = 21.37$ (*C*H$_3$Ac), 63.78, 63.89 [C(1), C(6)], 72.06 [C(5)], 73.61, 74.01, 74.17 (3*C*H$_2$Ph), 76.62, 76.88, 78.20 [C(2), C(3), C(4)], 128.2–128.7 (*C*HAr), 137.6, 137.7, 137.9 (3*C*qAr), 170.8 (*C*=O) ppm. MS (MALDI-TOF): *m/z* 518 $[M + Na]^+$, 534 $[M + K]^+$; $C_{29}H_{34}O_7$ (494.23): Calcd: C, 70.43; H, 6.93. Found: C, 70.29; H, 7.03.

1-*O*-Acetyl-2,3,4-tri-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-D-glucitol (7). Compound **6** (944 mg, 1.93 mmol) was dissolved, under inert atmosphere, in dry CH_2Cl_2 (10 mL), and imidazole (3 equiv., 5.79 mmol, 394 mg) and *tert*-butyldiphenylchlorosilane (1.5 equiv., 2.90 mmol, 741 μL) were added. The solution was stirred at rt overnight, and then CH_3OH (1 mL) and H_2O (10 mL) were added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. The solvent was eliminated under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate v/v 9/1), yielding **7** (1.35 g, 95%) as colorless oil. $[\alpha]_D^{20}$ −1.7 (*c* 1.4 $CHCl_3$); ^{1}H NMR: $\delta = 1.09$ (s, 9 H, C*H*$_3$*t*Bu), 1.98 (s, 3 H, C*H*$_3$Ac), 2.85 (d, 1 H, $J = 5.2$ Hz, O*H*), 3.82–3.88 [m, 4 H, C(3)-H, C(4)-H, C(6a)-H, C(6b)-H], 3.90–3.98 [m, 2 H, C(2)-H, C(5)-H], 4.17 [dd, 1 H, $J = 11.9$ Hz, $J = 6.1$ Hz, C(1a)-H], 4.35 [dd, 1 H, $J = 11.8$ Hz, $J = 3.4$ Hz, C(1b)-H], 4.55 (s, 2 H, C*H*$_2$Ph), 4.61 (d, 1 H, $J = 11.4$ Hz, C*H*Ph), 4.64 (d, 1 H, $J = 10.9$ Hz, C*H*Ph), 4.67 (d, 1 H, $J = 10.9$ Hz, C*H*Ph), 4.69 (d, 1 H, $J = 11.4$ Hz, C*H*Ph), 7.24–7.67 (m, 25 H, C*H*Ar) ppm. ^{13}C-NMR: $\delta = 19.75$ (Cq*t*Bu), 21.39 (*C*H$_3$Ac), 27.36 (*C*H$_3$*t*Bu), 64.53, 65.19 [C(1), C(6)], 72.05 [C(5)], 73.50, 73.54, 74.72 (3*C*H$_2$Ph), 77.33, 77.48, 78.52 [C(2), C(3), (4)], 127.8–130.0 (*C*HAr), 133.2, 133.3 (2CqAr), 135.7, 135.8 (*C*HAr), 138.1, 138.2, 138.2 (3CqAr), 170.8 (*C*=O) ppm. MS (MALDI-TOF): *m/z* 756 $[M + Na]^+$, 772 $[M + K]^+$; $C_{45}H_{52}O_7Si$ (732.35): calcd: C, 73.74; H, 7.15. Found: C, 73.94; H, 7.22.

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1-*O*-Acetyl-5-azido-2,3,4-tri-*O*-benzyl-6-*O*–*t*-butyldiphenylsilyl-5-deoxy-D-iditol (8). Compound **7** (189 mg, 0.258 mmol) was dissolved, under inert atmosphere, in dry THF (2 mL). PPh_3 (3 equiv., 0.774 mmol, 203 mg) was added and the mixture was cooled to 0°C. DIAD (3 equiv., 0.774 mmol, 150 μL) and diphenyl phosphoryl azide (3.2 equiv., 0.826 mmol, 180 μL) were slowly added. The mixture was stirred at rt overnight, and then the solvent was evaporated and the crude product was purified by flash chromatography (petroleum ether/ethyl acetate v/v 9/1), yielding **8** (139 mg, 71%) as colorless oil. $[\alpha]_D^{20}$ +12.5 (*c* 0.9 $CHCl_3$); ^{1}H NMR: $\delta = 1.07$ (s, 9 H, C*H*$_3$*t*Bu), 1.98 (s, 3 H, C*H*$_3$Ac), 3.49–3.52 [m, 1 H, C(5)-H], 3.59 [dd, 1 H, $J = 10.3$ Hz, $J = 4.9$ Hz, C(6a)-H], 3.72–3.84 [m, 4 H, C(2)-H, C(3)-H, C(4)-H, C(6b)-H], 4.23–4.26 [m, 2 H, C(1a)-H, C(1b)-H], 4.48 (d, 1 H, $J = 11.5$ Hz, C*H*Ph), 4.55–4.58 (m, 2 H, 2C*H*Ph), 4.65 (d, 1 H, $J = 11.9$ Hz, C*H*Ph), 4.66 (d, 1 H, $J = 11.1$ Hz, C*H*Ph), 4.73 (d, 1 H, $J = 11.5$ Hz, C*H*Ph), 7.18–7.65 (m, 25 H, C*H*Ar) ppm. ^{13}C NMR: $\delta = 19.54$ (Cq*t*Bu), 21.34 (*C*H$_3$Ac), 27.20 (*C*H$_3$*t*Bu), 63.51, 64.38 [C(1), C(6)], 63.88 [C(5)], 72.79, 75.06, 75.06 (3*C*H$_2$Ph), 75.84, 77.69, 78.83 [C(2), C(3), C(4)], 127.9–130.0 (CHAr), 132.9, 133.1 (2CqAr), 135.7, 135.8 (CHAr), 137.7, 137.8, 138.0 (3CqAr), 170.7 (*C*=O) ppm. IR (ν/cm^{-1}): 1739.78 (C=O), 2099.80 (N_3); MS (MALDI-TOF): *m*/*z* 780 $[M + Na]^+$, 796 $[M + K]^+$; $C_{45}H_{51}N_3O_6Si$ (757.35): Calcd: C, 71.30; H, 6.78; N 5.54. Found; C, 71.50; H, 6.62; N, 5.39.

5-Azido-2,3,4-tri-*O*-benzyl-6-*O*–*t*-butyldiphenylsilyl-5-deoxy-D-iditol (9). Compound **8** (130 mg, 0.172 mmol) was dissolved in dry CH_3OH (2 mL) and Na (cat.) was added. The mixture was stirred at rt for 30 min and then was neutralized with amberlite IR 120-H^+. After filtration the solvent was eliminated under reduced pressure and the residue was purified by flash chromatography (petroleum ether/ethyl acetate v/v 8/2), yielding **9** (112 mg, 91%) as colorless oil. $[\alpha]_D^{20}$ +9.3 (*c* 1.3 $CHCl_3$); ^{1}H NMR: $\delta = 1.09$ (s, 9 H, C*H*$_3$*t*Bu), 3.60–3.67 (m, 3 H), 3.72 [dd, 1 H, $J = 10.4$ Hz, $J = 5.2$ Hz], 3.79–3.86 (m, 3 H), 3.92 [dd, 1 H, $J = 7.1$ Hz, $J = 4.2$ Hz], 4.54 (d, 1 H, $J = 11.4$ Hz, C*H*Ph), 4.59 (d, 1 H, $J = 11.7$ Hz, C*H*Ph), 4.62–4.65 (m, 2 H, 2C*H*Ph), 4.68 (d, 1 H, $J = 11.2$ Hz, C*H*Ph), 4.75 (d, 1 H, $J = 11.4$ Hz, C*H*Ph), 7.20–7.67 (m, 25 H, C*H*Ar) ppm. ^{13}C NMR: $\delta = 19.57$ (Cq*t*Bu), 27.22 (*C*H$_3$*t*Bu), 61.68, 64.21 [C(1), C(6)], 63.69 [C(5)], 72.70, 75.00, 75.07 (3*C*H$_2$Ph), 77.80, 78.44, 79.40 [C(2), C(3), C(4)], 128.0–128.8 (CHAr), 130.0, 130.1 (CHAr), 133.0, 133.1 (2CqAr), 135.8–135.9 (CHAr), 137.9, 137.9, 138.0 (3CqAr) ppm. IR: 2100.0, (N_3), 3455.9 (OH); MS (MALDI-TOF): *m*/*z* 739 $[M + Na]^+$, 755 $[M + K]^+$; $C_{43}H_{49}N_3O_5Si$ (715.34): Calcd: C, 72.14; H, 6.90; N, 5.87. Found C, 71.99; H, 6.82; N, 5.50.

5-Azido-2,3,4-tri-*O*-benzyl-6-*O*–*t*-butyldiphenylsilyl-5-deoxy-D-idose (10). Compound **9** (826 mg, 1.15 mmol) was dissolved in CH_2Cl_2 (10 mL) and Dess Martin Periodinane (1.5 equiv., 1.73 mmol, 734 mg) was added. The mixture

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was stirred at rt for 30 min, then quenched with a saturated aqueous solution of $NaHCO_3$(5 mL) and a 10% aqueous solution of $Na_2S_2O_3$ (5 mL). The mixture was stirred for 1 h, and then the two layers were separated and the organic layer was washed with a saturated solution of $NaHCO_3$ (2×10 mL) and brine (1×10 mL). The organic layer was dried over Na_2SO_4 and solvent was eliminated under reduced pressure. The crude product was used for the next step without further purification. $[\alpha]_D^{20}$ +20.0 (*c* 1.0 $CHCl_3$); ^{1}H NMR: $\delta = 1.09$ (C*H*$_3$*t*Bu), 3.56–3.61 [m, 1 H, C(5)-H], 3.71 [dd, 1 H, $J = 10.5$ Hz, $J = 7.0$ Hz, C(6a)-H], 3.77 [dd, 1 H, $J = 10.5$ Hz, $J = 4.4$ Hz, C(6b)-H], 3.89 [bt, 1 H, C(4)-H], 3.92–3.96 [m, 2 H, C(2)-H, C(3)-H], 4.48 (s, 2 H, C*H*$_2$Ph), 4.51–4.54 (m, 2 H, 2C*H*Ph), 4.62 (d, 1 H, $J = 11.0$ Hz, C*H*Ph), 4.83 (d, 1 H, $J = 11.9$ Hz, C*H*Ph), 7.26–7.67 (m, 25 H, CHAr), 9.66 [s, 1 H, C(1)-H] ppm. ^{13}C NMR: $\delta = 19.60$ (Cq*t*Bu), 27.22 (*C*H$_3$*t*Bu), 64.09 [C(5)], 64.15 [C(6)], 73.40, 74.42, 74.65 (3*C*H$_2$Ph), 77.12, 79.92, 80.96 [C(2), C(3), C(4)], 127.9–130.1 (CHAr), 132.9, 133.0 (2CqAr), 135.8, 135.9 (CHAr), 137.0, 137.3, 137.5 (3CqAr), 200.6 [C(1)] ppm. IR: 1728.6 (*C*=O), 2100.7, (N_3); MS (MALDI-TOF): *m*/*z* 737 $[M + Na]^+$, 753 $[M + K]^+$; $C_{43}H_{47}N_3O_5Si$ (713.33): Calcd: C, 72.34; H, 6.64; N, 5.89. Found; C, 72.00; H, 6.72; N, 5.55.

(2*R*/*S*,3*R*,4*S*,5*R*,6*S*) Dimethyl 6-Azido-3,4,5-tris-benzyloxy-7-*t*-butyldiphenylsilanyloxy-2-hydroxy-heptylphosphonate (11). In a flame-dried vessel, BuLi (2.30 mmol, 1.6 M in hexane, 1.44 mL) was diluted with dry THF (10 mL), and at −78°C dimethyl methyl phosphonate (2.30 mmol, 254 μL) was slowly added. The mixture was stirred at −78°C for 30 min, and then **10** (1.15 mmol) dissolved in dry THF (8 mL) was added. The mixture was stirred at −78°C for 1 h, then quenched with NH_4Cl (1 M, 4 mL). CH_2Cl_2 (10 mL) was added, and the two layers were separated. The organic layer was washed with NH_4Cl 1M (1×10 mL) and H_2O (2×10 mL). The organic phase was dried over Na_2SO_4, and the solvent was eliminated under reduced pressure. The crude was purified by flash chromatography (petroleum ether/ethyl acetate v/v 4/6), yielding an inseparable mixture of two diasteroisomers (*R*/*S* 23/77, 597 mg, 62% over two steps) as colorless oil.

(2*S*,3*R*,4*S*,5*R*,6*S*) Dimethyl 6-Amino-3,4,5-tris-benzyloxy-7-*t*-butyldiphenylsilanyloxy-2-hydroxy-heptylphosphonate (12). The mixture **11** (381 mg, 0.455 mmol) was dissolved in THF (8 mL). PPh_3 (2 equiv., 0.909 mmol, 239 mg) and H_2O (25 equiv., 11.38 mmol, 205 μL) were added, and the mixture was stirred at 60°C for 18 h. The solvent was evaporated and the crude product was purified by flash chromatography (AcOEt to AcOEt/CH_3OH v/v 15/1), yielding pure **12** (190 mg) (yield 51%) as a colorless oil. $[\alpha]_D^{20}$ +2.7 (*c* 1.0 $CHCl_3$); ^{1}H NMR: $\delta = 1.07$ (s, 9 H, C*H*$_3$*t*Bu), 1.91 [ddd, 1 H, $J = 18.9$ Hz, $J = 15.3$ Hz, $J = 3.3$ Hz, C(1a)-H], 2.10 [ddd, 1 H, $J = 16.0$ Hz,

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$J = 15.3$ Hz, $J = 9.6$ Hz, C(1b)-H], 3.14–3.16 [m, 1 H, C(6)-H], 3.51 [dd, 1 H, $J = 9.6$ Hz, $J = 7.4$ Hz, C(7a)-H], 3.63–3.72 [m, 2 H, C(3)-H, C(7b)-H], 3.66 (d, 3 H, $J_{H,P} = 5.7$ Hz, OCH_3), 3.69 (d, 3 H, $J_{H,P} = 5.6$ Hz, OCH_3), 3.81 [dd, 1 H, $J = 6.1$ Hz, $J = 3.1$ Hz, C(5)-H], 4.11 [bt, 1 H, C(4)-H], 4.30–4.36 [m, 1 H, C(2)-H], 4.48 (d, 1 H, $J = 11.1$ Hz, C*H*Ph), 4.54 (d, 1 H, $J = 11.2$ Hz, C*H*Ph), 4.70 (s, 2 H, CH_2Ph), 4.76 (d, 1 H, $J = 11.2$ Hz, C*H*Ph), 4.81 (d, 1 H, $J = 11.1$ Hz, C*H*Ph), 7.20–7.65 (m, 25 H, CHAr) ppm. ^{13}C NMR: $\delta = 19.68$ (Cq*t*Bu), 27.37 (CH$_3$*t*Bu), 30.19 [d, $^1J_{C,P} = 139.5$ Hz, C(1)], 52.67, 52.74 (O*C*H$_3$), 53.70 [C(6)], 66.4 [d, $^2J_{C,P} = 4.6$ Hz, C(2)], 66.98 [C(7)], 74.57, 74.78, 74.87 (3*C*H$_2$Ph), 78.97, 81.17, 81.31 [C(3), C(4), C(5)], 127.8–129.9 (CHAr), 133.5, 133.6 (2CqAr), 135.8 (CHAr), 138.3, 138.4, 138.5 (3CqAr) ppm. IR: 3349.6, 3361.7 (NH$_2$, OH); MS (MALDI-TOF): m/z 812 $[M + H]^+$, 834 $[M + Na]^+$, 850 $[M + K]^+$; $C_{46}H_{58}NO_8PSi$ (811.37): calcd. C, 68.04; H, 7.20; N, 1.72. Found C, 67.97; H, 7.03; N, 1.85.

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(2*R*,3*S*,4*S*,5*R*,6*S*) Dimethyl [3,4,5-Tris-benzyloxy-6-(*t*-butyldiphenylsilanyloxymethyl)- piperidin-2-yl]-methylenephosphonate (13). Compound **12** (227 mg, 0.280 mmol) was dissolved under inert atmosphere in dry THF (3 mL), and then PPh$_3$ (2 equiv., 0.559 mmol, 147 mg) was added. The solution was cooled at 0°C, and then DIAD (2 equiv., 0.559 mmol, 108 μL) was slowly added. The mixture was stirred for 18 h at rt, and then the solvent was removed under reduced pressure and the crude was purified by flash chromatography (ethyl acetate), yielding an inseparable mixture of **13** and triphenylphosphine oxide, which was subjected to NMR analysis. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): $\delta = 1.09$ (s, 9 H, CH_3*t*Bu), 1.69 (ddd, 1 H, $J_{H,P} = 15.6$ Hz, $J = 14.9$ Hz, $J = 10.0$ Hz, C*H*P), 2.44 (bdd, 1 H, $J_{H,P} = 20.1$ Hz, $J = 14.6$ Hz, C*H*P), 3.11 [bt, 1 H, $J = 8.8$ Hz, C(3)-H], 3.31 [bt, 1 H, $J = 9.4$ Hz, C(2)-H], 3.38–3.41 [m, 1 H, C(6)-H], 3.62–3.67 [m, 1 H, C(4)-H], 3.68 (d, 3 H, $J_{H,P} = 10.9$ Hz, OCH_3), 3.71 (d, 3 H, $J_{H,P} = 11.1$ Hz, OCH_3), 3.75–3.79 [m, 2 H, C(5)-H, C*H*OH], 4.01 (bt, 1 H, C*H*OH), 4.34 (d, 1 H, $J = 11.5$ Hz, C*H*Ph), 4.38 (d, 1 H, $J = 11.5$ Hz, C*H*Ph), 4.59 (d, 1 H, $J = 11.9$ Hz, C*H*Ph), 4.66 (d, 1 H, $J = 11.7$ Hz, C*H*Ph), 4.82 (d, 1 H, $J = 11.7$ Hz, C*H*Ph), 4.94 (d, 1 H, $J = 11.9$ Hz, C*H*Ph), 7.10–7.71 (m, CHAr) ppm. ^{13}C NMR: $\delta = 19.62$ (Cq*t*Bu), 27.24 (*C*H$_3$*t*Bu), 28.47 (d, $^1J_{C,P} = 139.6$ Hz, *C*H$_2$P), 49.46 [d, $^2J_{C,P} = 5.4$ Hz, C(2)], 52.72 (d, $^3J_{C,P} = 6.1$ Hz, OCH$_3$), 52.94 (d, $^3J_{C,P} = 6.1$ Hz, O*C*H$_3$), 56.40 [C(6)], 60.75 (*C*H$_2$OTBDPS), 75.60, 75.77, 75.79 (3*C*H$_2$Ph), 80.51 [C(5)], 83.52 [d, $^4J_{C,P} = 1.1$ Hz, C(4), 83.77 [d, $^3J_{C,P} = 16.9$ Hz, C(3)], 127.8–128.7 (CHAr), 129.9, 130.0 (CHAr), 132.1–132.3 (CHAr), 132.2, 133.2, 133.5, 133.6 (4CqAr), 135.7, 135.8 (CHAr), 138.1, 138.3, 138.8 (3CqAr).

(2*R*,3*S*,4*S*,5*R*,6*S*) Dimethyl (3,4,5-Tris-benzyloxy-6-hydroxymethyl-piperidin-2-yl)-methylenephosphonate (14). Compound **13** was dissolved

in dry THF (3 mL), and then TBAF (0.560 mmol, 1 M in THF, 560 μL) was added. The mixture was stirred at rt overnight and then quenched with buffer phosphate (3 mL). The two layers were separated, and the aqueous layer was extracted with AcOEt (3 × 5 mL). The combined organic layers were dried over Na_2SO_4. The solvent was eliminated under reduced pressure, and the residue was purified by flash chromatography (ethyl acetate to ethyl acetate/methanol v/v 9/1), yielding **14** (90 mg, 58% over two steps) as colorless oil. $[\alpha]_D^{20}$ +10.1 (*c* 1.3 $CHCl_3$); ^{1}H NMR: $\delta = 1.62$ (ddd, 1 H, $J = 15.5$ Hz, $J = 15.3$ Hz, $J = 10.3$ Hz, C*H*P), 2.30 (ddd, 1 H, $J = 18.2$ Hz, $J = 15.1$ Hz, $J = 2.1$ Hz, C*H*P), 3.02–3.10 [m, 1 H, C(2)-H], 3.14 [bt, 1 H, $J = 8.5$ Hz, C(3)-H], 3.39 [bdt, 1 H, $J = 10.5$ Hz, $J = 5.4$ Hz, $J = 5.4$ Hz, C(6)-H], 3.70 [dd, 1 H, $J = 9.0$ Hz, $J = 8.0$ Hz, C(4)-H], 3.71 (d, 3 H, $J = 10.9$ Hz, O*C*H_3), 3.72 (d, 3 H, $J = 10.9$ Hz, O*C*H_3), 3.77 [dd, 1 H, $J = 9.0$ Hz, $J = 5.6$ Hz, C(5)-H], 3.77–3.80 (m, 1 H, C*H*OH), 3.86 (bt, 1 H, $J = 10.5$ Hz, C*H*OH), 4.59 (d, 1 H, $J = 11.2$ Hz, C*H*Ph), 4.66 (s, 2 H, CH_2Ph), 4.76 (d, 1 H, $J = 10.9$ Hz, C*H*Ph), 4.90 (d, 1 H, $J = 10.9$ Hz, C*H*Ph), 4.91 (d, 1 H, $J = 11.2$ Hz, C*H*Ph), 7.28–7.33 (m, 15 H, CHAr) ppm. ^{13}C NMR: $\delta = 27.27$ (d, $^1J_{C,P} = 140.3$ Hz, *C*H_2P), 48.90 [d, $^2J_{C,P} = 4.6$ Hz, C(2)], 52.85 (d, $^3J_{C,P} = 6.1$ Hz, O*C*H_3), 52.97 (d, $^3J_{C,P} = 6.1$ Hz, O*C*H_3), 54.99 [C(6)], 58.58 (*C*H_2OH), 73.09, 75.29, 75.90 (3*C*H_2Ph), 81.31 [C(5)], 83.19 [d, $^3J_{C,P} = 16.1$ Hz, C(3)], 83.61 [d, $^4J_{C,P} = 2.3$ Hz, C(4)], 127.9–128.7 (CHAr), 138.1, 138.3, 138.7 (3CqAr) ppm. MS (MALDI-TOF): *m/z* 556 $[M + H]^+$, 578 $[M + Na]^+$, 594 $[M + K]^+$; $C_{30}H_{38}NO_7P$ (555.24): Calcd: C; 64.85; H, 6.89; N, 2.52. Found; C, 64.69; H, 6.77; N, 2.61.

1-Deoxy-L-idonojirimycin-1-methylenphosphonate (1). Compound **14** (50 mg, 0.09 mmol) was dissolved in MeOH (3 mL); a catalytic amount of $Pd(OH)_2$ and acetic acid (1 mL) were added and then the reaction mixture was stirred under H_2 overnight. The catalyst was filtered through a pad of Celite (eluting with MeOH) and then the solvent was evaporated under reduced pressure to afford pure compound **1** (26 mg, 98% yield) as an amorphous solid. $[\alpha]_D^{20}$ −22.4 (*c* 1.0 MeOH); ^{1}H NMR (D_2O): $\delta = 2.32$ (ddd, 1 H, $J = 19.4$ Hz, $J = 16.3$ Hz, $J = 6.6$ Hz, C*H*P), 2.61 (ddd, 1 H, $J = 20.4$ Hz, $J = 16.3$ Hz, $J = 5.8$ Hz, C*H*P), 3.16–3.28 [m, 2 H, C(2)-H, C(6)-H], 3.44–3.51 [m, 2 H, C(3)-H, C(4)-H], 3.66 (d, 3 H, $J = 11.1$ Hz, O*C*H_3), 3.67 (d, 3 H, $J = 11.1$ Hz, O*C*H_3), 3.74–3.79 (m, 2 H, *C*H_2OH), 3.84–3.90 [m, 1 H, C(5)-H] ppm. ^{13}C NMR (D_2O): $\delta = 25.10$ (d, $^1J_{C,P} = 141.8$ Hz, *C*H_2P), 54.33 [d, $^2J_{C,P} = 6.0$ Hz, C(2)], 56.11 (d, $^3J_{C,P} = 6.9$ Hz, PO*C*H_3), 56.18 (d, $^3J_{C,P} = 6.9$ Hz, PO*C*H_3), 56.53 [C(6)], 58.67 (*C*H_2OH), 70.88 [C(5)], 73.09 [d, $^3J_{C,P} = 11.3$ Hz, C(3)], 76.20 [C(4)] ppm. ^{31}P NMR (D_2O): $\delta = 39.11$ ppm; MS (MALDI-TOF): *m/z* 286 $[M + H]^+$; $C_9H_{20}NO_7P$ (285.10): calcd: C, 37.90; H, 7.07, N, 4.91. Found; C, 38.01; H, 6.84; N, 5.03.

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