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Note

Carbohydrate *N*-phosphinyl imine derivatives: synthesis and conversion to amino sugars

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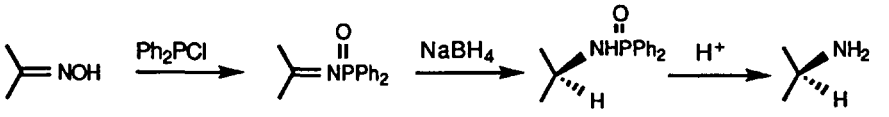
In 1978, Stec and Krzyzanowska described a new route to primary amines based on the chemistry of *N*-diphenylphosphinyl imines [1,2]. These novel imine derivatives were prepared from the corresponding oximes by treatment with cholorodiphenylphosphine and triethylamine (Scheme 1). Unlike the oximes from which they are derived, the phosphinyl imines possess an electrophilic imine carbon and undergo facile reduction with sodium borohydride. The overall sequence is complementary to the reductive amination of the parent carbonyl compounds. Other nucleophiles such as cyanide ion and Grignard reagents were shown to add to *N*-phosphinyl imines [1], and both diastereoselective and enantioselective reductions with hydride reagents have been described by Hutchins and co-workers [3,4]. We became interested in the potential synthetic applications of carbohydrate-derived *N*-phosphinyl imines during the course of our studies of amino and nitro sugar synthesis. Herein we describe the preparation and



Scheme 1.

reduction of carbohydrate *N*-phosphinyl imines of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-3-ulose oxime (**1**) and methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranosid-3-ulose oxime (**2**).

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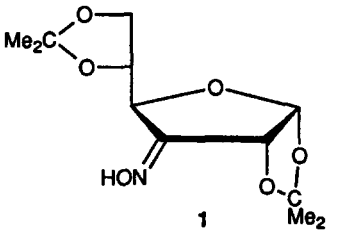
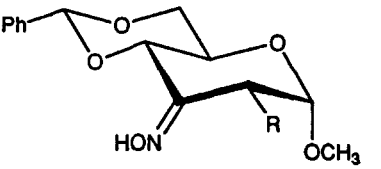
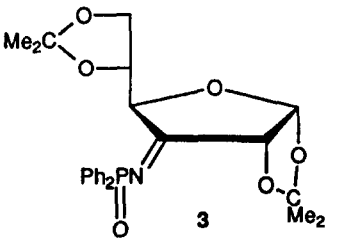
Oximes **1** [5] and **2** [6,7] were prepared by treatment of the corresponding ketones with hydroxylamine hydrochloride and sodium hydroxide in ethanol. Conversion of the oximes to their *N*-phosphinyl imine derivatives **3** and **4** was carried out with chlorodiphenylphosphine and triethylamine in dichloromethane–petroleum ether at −40°C.



1



2: R = H
11: R = OBz



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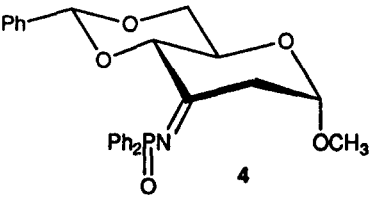

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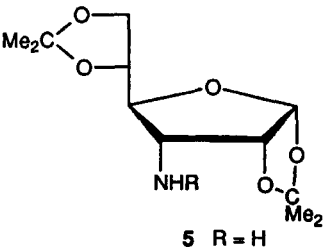
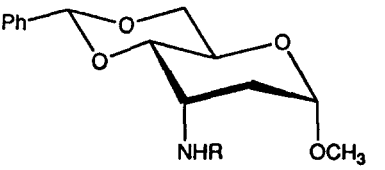
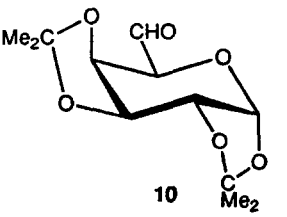


5 R = H
7 R = Ac



6 R = $Ph_2P(O)$
8 R = H

9



10

The procedure described by Stec and co-workers was followed closely, except that the filtration of the amine hydrochloride salt was omitted during the preparation of **4**. Both *N*-phosphinyl imines were obtained as white solids. Instability toward moisture was evidenced by decomposition on prolonged standing, accompanied by the formation of diphenylphosphinamide **9** [1]. Purification of **3** was effected by column chromatography on basic alumina, which removed traces of amine hydrochloride salt. Amine hydrochloride salts were separated from **4** by aqueous extraction.

We expected that the enhanced reactivity of the imine carbon in **3** and **4** would lead to synthetically useful transformations such as the conversion to amino sugars and alkylation with organometallic reagents to give branched-chain carbohydrates. The former transformation requires reduction to the *N*-phosphinyl amine followed by deprotection of the nitrogen functionality. To our surprise, treatment of **3** with sodium borohydride directly gave 3-amino-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) [9,10]. It is unlikely that the spontaneous cleavage of the nitrogen–phosphorus bond occurs during quenching of the borohydride reduction since the removal of this blocking group requires much more acidic conditions (12 h treatment with N HCl). Activation of the N–P bond toward cleavage under the reaction conditions may be assisted by metal coordination involving the 1,2-*O*-isopropylidene group. The reduction is completely stereoselective, favoring the formation of the amine with the D-*allo* configuration. The stereochemistry of the amine was further confirmed by conversion to the known *N*-acetyl derivative [11].

Reduction of *N*-phosphinyl imine **4** with sodium borohydride proceeded as expected to give the protected amine **6** stereoselectively. The epimeric D-*arabino* product was not observed. By comparison, reduction of the oxime with lithium aluminum hydride gives an 87:13 ratio of D-*ribo* to D-*arabino* products [6]. The high stereoselectivity observed in the reduction of **4** probably arises from the lower reactivity of the hydride donor and the greater streric hindrance toward α-face addition caused by the bulky diphenylphosphinoyl group. No loss of the protecting group was observed under the reaction conditions. Deprotection of the amino group in **6** was carried out by treatment with HCl in a mixture of diethyl ether–oxolane at room temperature. Recrystallization of the crude product from ether gave methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**8**) [7].

The above results demonstrate that carbohydrate-derived *N*-phosphinyl imines can be converted to amino sugars under mild conditions. Some limitations of the sequence depicted in Scheme 1 were revealed in the present study. The attempted preparation of *N*-phosphinyl imines of dialdose **10** [12] was unsuccessful, presumably due to the instability of the products under the reaction conditions. The 2-*O*-benzoyl analogue (**11**) of oxime **2** failed to give an *N*-phosphinyl imine under the same reaction conditions. Additional experiments are required to further define the scope of *N*-phosphinyl imine synthesis from keto and aldehydo sugars and to explore other transformations of these carbohydrate derivatives [2].

[1] An alternative method for preparing *N*-phosphinyl imines from aldehydes and diphenylphosphinamide has been described [8].

[2] Recently, the addition of organocerium reagents to carbohydrate *O*-benzyl oximes has been reported [13].

1. Experimental

General methods.—^{1}H NMR spectra were recorded at 200.05 MHz, and ^{13}C NMR spectra were recorded at 50.3 MHz on a Varian XL-200 instrument using deuteriochloroform or tetramethylsilane as the internal standard. HRMS measurements were determined at the University of Pennsylvania on a VG 7070-H spectrometer using CI in the positive-ion mode with ammonia as the reagent gas. Thin-layer chromatography was carried out with aluminum-supported plates of Silica Gel 60 (F_{254}, 0.2 mm, E. Merck). Petroleum ether refers to the fraction boiling at 30–60°C. Chloroform and dichloromethane were dried by passing through a column of basic alumina (Woelm, activity 1). Methanol was distilled from calcium hydride. Anhydrous oxolane (tetrahydrofuran, THF) and dimethyl sulfoxide (Me_2SO) were purchased from Aldrich Chemical Co.

*1,2:5,6-Di-*O*-isopropylidene-α-*D*-ribo-hexafuranos-3-ulose diphenylphosphinamide* (**3**).—Oxime **1** [5] (1.00 g, 3.63 mmol) was added to a mixture of triethylamine (5 mL) and 1:1 dichloromethane–petroleum ether (80 mL) with stirring at −40°C (dry ice–acetonitrile bath). A solution of chlorodiphenylphosphine (0.78 mL, 4.36 mmol) in dichloromethane (1.0 mL) was added slowly while maintaining the temperature below −30°C. The mixture was stirred for 1 h and solids were removed by filtration. After concentration of the filtrate, the residue was dissolved in dichloromethane (20 mL) and passed through a column of basic alumina (Woelm, activity 1). Removal of the solvent afforded **3** (1.22 g, 73%) as a white solid: R_f (ethyl acetate) 0.77; mp 144–146°C; $[\alpha]_D$ +32° (*c* 1.0, $CHCl_3$); IR (Nujol) 3023, 2958, 1460, 1376 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.29, 1.30, 1.47, 1.50 (4s, 12 H, CH_3), 3.85–3.65 (m, 2 H, H-6,6′), 4.34 (m, 1 H, H-5), 4.87 (m, 1 H, H-4), 5.30 (dd, 1 H, $J_{2,1}$ 4.38 Hz, $J_{2,4}$ 1.20 Hz, H-2), 6.03 (d, 1 H, H-1), 7.19–8.10 (m, 10 H, PhH); ^{13}C NMR ($CDCl_3$): δ 25.3, 25.7, 27.7, 27.9, 66.6, 69.5, 83.4, 104.4 (C-1), 110.2, 112.6, 114.1, 125.4, 126.4, 127.9, 128.1, 128.4, 128.9, 131.2, 132.5, 133.4, 147.7 (C=N); HRMS: Calcd for $C_{24}H_{29}NO_6P$ (M + H): 458.1732. Found: 458.1741.

*Methyl 4,6-*O*-benzylidene-2-deoxy-α-*D*-erythro-hexopyranosid-3-ulose diphenylphosphinamide* (**4**).—A 250 mL three-necked flask was charged with a solution of oxime **2** [6,7] (0.75 g) in 1:1 dichloromethane–petroleum ether (100 mL) and triethylamine (2.0 mL). The solution was cooled to 0°C and stirred for 10 min after which chlorodiphenylphosphine (0.60 g, 2.70 mmol) in dichloromethane (5 mL) was slowly added. The reaction mixture was then stirred at 0°C for 1 h and concentrated to a residue that was dissolved in dichloromethane. The resulting solution was washed with 10% aq sodium chloride, and the organic layer was dried ($MgSO_4$) and concentrated to give 0.80 g (64%) of *N*-phosphinyl imine **4**: R_f (1:1 ethyl acetate–petroleum ether) 0.59; mp 70–72°C; $[\alpha]_D$ +181° (*c* 1.0, $CHCl_3$); IR (melt) 3060, 2986, 1528, 1458, 1362 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.23 (dd, 1 H, $J_{2,1}$ 4.44 Hz, $J_{2,2'}$ 15.24 Hz, H-2), 3.37 (s, 3 H, OCH_3), 3.57 (d, 1 H, H-2′), 3.81 (m, 1 H, H-6), 4.05 (m, 1 H, H-5), 4.23 (d, 1 H, $J_{6',5}$ 9.3 Hz, H-6′), 4.92 (d, 1 H, $J_{1,2}$ 4.43 Hz, H-1), 5.62 (s, 1 H, PhCH), 7.50 (m, 10 H, PhH); ^{13}C NMR ($CDCl_3$): δ 30.1, 54.7, 64.6, 69.3, 77.5, 98.4, 102.1, 125.8, 126.3, 128.1, 128.4, 129.3, 131.5, 131.7, 132.3, 149.1 (C=N). HRMS: Calcd for $C_{26}H_{27}NO_5P$ (M + H): 465.1705. Found: 465.1790.

3-Amino-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**5**).—Sodium borohydride (0.067 g, 1.76 mmol) was added to a solution of *N*-phosphinyl imine **3** (0.40 g, 0.88 mmol) in oxolane (15 mL), and the mixture was stirred overnight at room temperature. Satd aq ammonium chloride was added, and the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (20 mL) and washed with water (3 × 25 mL). The organic phase was dried ($MgSO_4$) and concentrated to give amine **5** as a white solid (0.24 g, 86%): mp 90°C; lit. [9,10] mp 92–93°C; $[\alpha]_D$ +26.1° (*c* 1.0, $CHCl_3$), lit. [10] $[\alpha]_D$ +32.7° (*c* 2.39); ^1H NMR ($CDCl_3$): δ 1.36, 1.38, 1.45, 1.56 (4s, 12 H, CH_3), 3.15 (m, 1 H, H-3), 3.61 (m, 1 H, H-6/6'), 3.90–4.20 (m, 3 H, H-4,5,6/6'), 4.44 (br 2 H, NH_2), 5.01 (m, 1 H, H-2), 5.81 (d, 1 H, $J_{1,2}$ 3.62 Hz, H-1).

3-Acetamido-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**7**).—A solution of **5** (0.25 g, 0.97 mmol), acetic anhydride (2.0 mL) and pyridine (2.0 mL) was stirred overnight at room temperature, poured into ice–water (50 mL), and the mixture was extracted with chloroform (3 × 25 mL). The organic phase was washed with N HCl (2 × 20 mL), 10% aq sodium bicarbonate and water, dried ($MgSO_4$) and evaporated to give **7** (0.21 g) as an oil that crystallized: mp 123–125°C, lit. [11] mp 127–128°C; $[\alpha]_D$ +59.2° (*c* 2.0, $CHCl_3$), lit. [11] $[\alpha]_D$ +71.3° (*c* 2.12, $CHCl_3$); IR (Nujol) 3362, 2958, 1680, 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35, 1.40, 1.42 (3s, 12 H, CH_3), 2.03 (s, 3 H, CH_3), 3.85–3.98 (m, 2 H, H-3,4), 4.06–4.26 (m, 3 H, H-5,6,6'), 4.60 (q, 1 H, $J_{2,1}$ 3.81 Hz, $J_{2,3}$ 0.80 Hz, H-2), 5.80 (bs, 1 H, NH), 5.83 (d, 1 H, H-1).

Methyl 4,6-O-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose diphenylphosphinamine (**6**).—Sodium borohydride (0.140 g, 3.38 mmol) was added to a solution of **4** (0.78 g, 3.38 mmol) in oxolane (THF, 25 mL) at 0°C. The mixture was allowed to warm to room temperature and stir for 6 h. Satd aq ammonium chloride (20 mL) was added, and the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with water (2 × 25 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography [14] to give protected amine derivative **6** as a white solid that readily sublimed: $[\alpha]_D$ +162° (*c* 1.25, $CHCl_3$); IR 3285, 3032, 2914, 1446, 1125 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.92–2.00 (m, 1 H, H-2), 2.32–2.41 (m, 2 H, H-2, NH), 3.28 (s, 3 H, OCH_3), 3.51–3.57 (m, 1 H, $J_{4,3}$ 3.33, $J_{4,5}$ 9.60 Hz, H-4), 3.63–3.74 (m, 2 H, H-6,6'), 4.01–4.11 (m, 1 H, H-5), 4.24–4.32 (m, 1 H, H-3), 4.73 (d, 1 H, $J_{1,2}$ 3.26 Hz, H-1), 5.52 (s, 1 H, PhCH), 7.03–7.95 (m, 15 H, PhH); ^{13}C NMR ($CDCl_3$): δ 36.4, 46.1, 55.3, 58.6, 69.3, 78.4, 78.5, 99.2, 101.7, 127.7, 127.9, 128.3, 128.8, 130.7, 131.2, 131.4, 133.6, 137.5; HRMS: Calcd for $C_{26}H_{28}NO_5P$ (M + H): 466.1783. Found: 466.1793.

Methyl 3-amino-4,6-O-benzylidene-2,3-dideoxy-α-D-ribo-hexopyranoside (**8**).—A solution of N HCl in ether (5.1 mL) was added to a stirred solution of **6** (0.81 g, 1.74 mmol) in oxolane (17 mL) at 0°C. The mixture was stirred 12 h at room temperature, treated with satd aq ammonium chloride (15 mL) and concentrated. The residue was dissolved in ethyl acetate (25 mL) and concentrated. The residue was dissolved in ethyl acetate (25 mL), washed with 10% aq sodium carbonate (3 × 25 mL) and water (3 × 25 mL), dried ($MgSO_4$), and concentrated to give **8** as a solid that was washed with hexane and recrystallized from ether to afford 0.194 g (42%) of crystalline amine: mp 117°C, [lit. [7] mp 118–119°C].

Acknowledgements

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