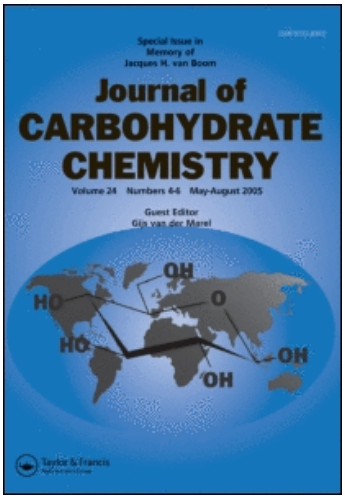

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INTRODUCTION OF 3,4-UNSATURATION IN 2-AMINO-2-DEOXY-D-GLUCOPYRANOSIDES

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ABSTRACT

The triphenylphosphine-iodine-imidazole, and the triphenylphosphine-triiodoimidazole systems have been used to effect 3,4-unsaturation in 2-amino-2-deoxy-D-glucopyranosides. The yields were optimized by variation of solvent, amino protection group and proportions of reagents.

INTRODUCTION

Purpurosamine C (1), 2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranose, is a constituent of the gentamycin C_{1a} aminoglycoside antibiotic, and of 3',4'-dideoxykanamycin B (Dibekacin), a semisynthetic aminoglycoside antibiotic. In order to obtain an easily available synthetic equivalent of this structural element several routes from readily obtainable starting materials were examined.

RESULTS AND DISCUSSION

In the first approach methyl α-D-glucopyranoside was dibenzoylated to give methyl 2,6-di-O-benzoyl-α-D-glucopyranoside[1] (2) in 59 % yield. This was converted into methyl 2,6-di-O-benzoyl-3,4-dideoxy-α-D-*erythro*-hex-3-enopyranoside (3) using the triphenylphosphine-iodine-imidazole reagent[2] in toluene. Extractive work-up followed by chromatography gave 3 in 85 % yield on a ten gram scale, δ_C (25 MHz, $CDCl_3$): 55.8 (OCH_3); 65.4,

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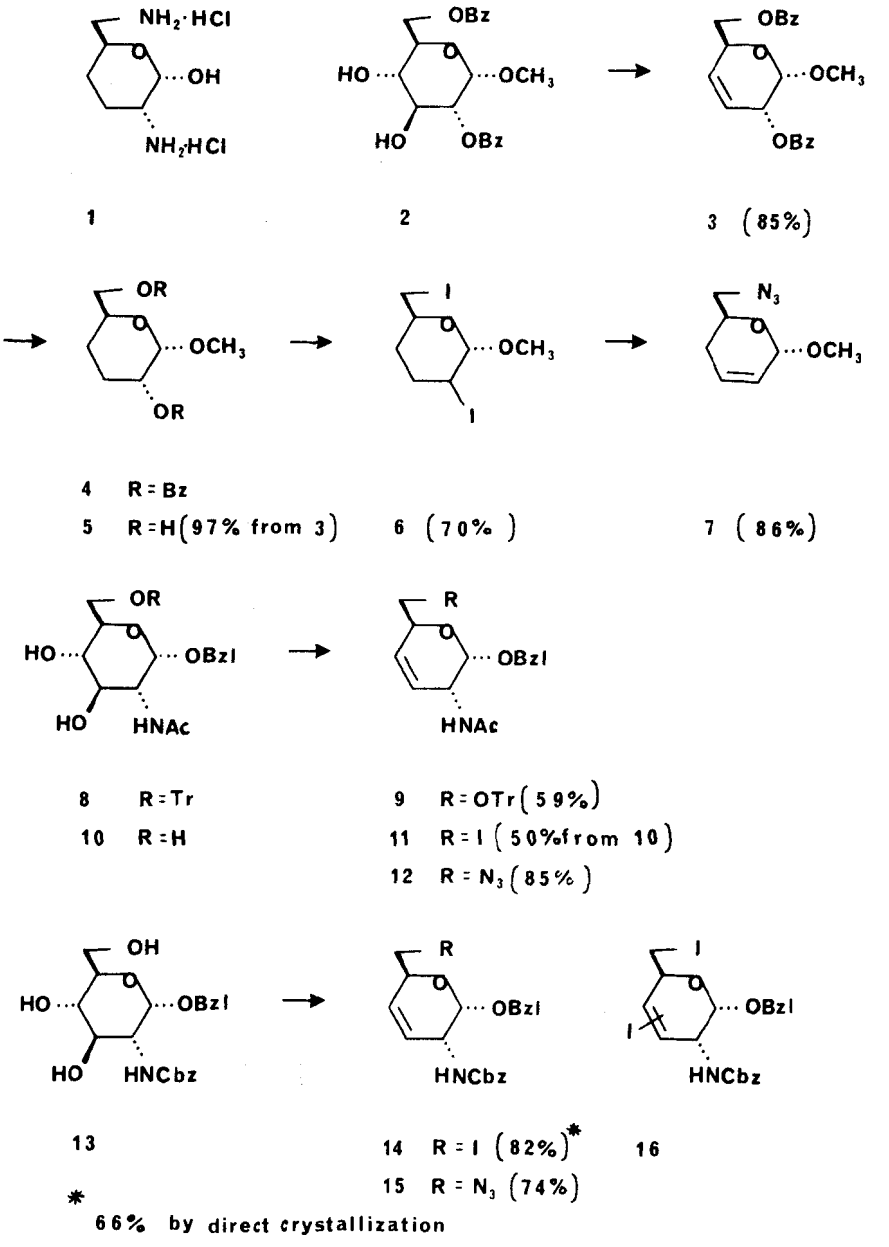

66.6, 66.7 (C-2, C-5, C-6); 95.8 (C-1). This compound has been prepared, using the same route, by Fraser-Reid and co-workers[3], but was not fully characterized. Hydrogenation of 3 in ethanol containing triethylamine with palladium on carbon (10 %) gave a product 4 having slightly higher TLC mobility than the starting material in toluene-ethyl acetate (6:1), δ_C (25 MHz, $CDCl_3$): 22.9, 26.5 (C-3, C-4); 54.7 (OCH_3); 65.9, 66.4, 70.5 (C-2, C-5, C-6); 96.8 (C-1). Debenzoylation of 4 gave methyl 3,4-dideoxy-α-D-*erythro*-hexopyranoside (5) in 97 % yield from 3. Diiodination using triphenylphosphine-triiodoimidazole[2] in toluene gave methyl 2,3,4,6-tetradeoxy-2,6-diiodo-α-D-*threo*-hexopyranoside (6) in 70 % yield, δ_C (25 MHz, $CDCl_3$): 8.8 (C-6); 27.5, 27.6, 28.0 (C-2, C-3, C-4); 55.1 (OCH_3); 69.1 (C-5); 102.1 (C-1). In the final step, all attempts to convert 6 into the corresponding 2,6-diazido derivative failed. Metal azides and quarternary ammonium- as well as resin-bound azides in various solvents, gave methyl 6-azido-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-2-enopyranoside (7), isolated in 86 % yield using sodium azide in DMF, δ_C (25 MHz, $CDCl_3$): 27.6 (C-4); 54.6, 55.4 (OCH_3, C-6); 66.1 (C-5); 95.8 (C-1); 125.6, 127.8 (C-2, C-3). This approach was thus abandoned.

Substitutions involving a corresponding 3,4-unsaturated derivative were not examined as S_N2' substitutions and sigmatropic rearrangements of the formed allylic azide were expected to complicate any approach along this line.[4]

Next, our attention was turned to glucose derivatives already having a 2-amino-2-deoxy function, and to this end benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside[5] (10) was prepared. Treatment of 10 under standard reaction conditions, i.e. with triphenylphosphine-iodine-imidazole[2] in toluene, failed to give a clean reaction. This was at least in part due to the low solubility of 10. Tritylation of 10 gave benzyl 2-acetamido-2-deoxy-6-O-triphenylmethyl-α-D-glucopyranoside[6] (8) which reacted under the same standard conditions[2] to give benzyl 2-acetamido-2,3,4-trideoxy-6-O-triphenylmethyl-α-D-*erythro*-hex-3-enopyranoside[7] (9) in 59 % yield δ_C (25 MHz, $CDCl_3$): 23.1 ($CO\underline{C}H_3$); 45.5 (C-2); 65.8, 67.7, 69.6 ($\underline{C}H_2\varphi$, C-5, C-6); 86.5 ($\underline{C}\varphi_3$); 94.8 (C-1). The low reactivity of 10 and moderate yield obtained from 8 led to the investigation of a more polar solvent system. Toluene-acetonitrile (2:1), used in similar reactions proved to be convenient.[8] Thus reaction of 10 with triphenylphosphine-triiodoimidazole[2] in toluene-acetonitrile (2:1) at elevated temperatures followed by column

chromatographic purification yielded benzyl 2-acetamido-2,3,4,6-tetradeoxy-6-iodo-α-D-erythro-hex-3-enopyranoside (11) in 50 % yield m.p. 168-170 °C (ethanol), $[\alpha]_D^{22}$ +33° (c 1.05, chloroform), δ_C (25 MHz, $CDCl_3$): 8.8 (C-6); 23.4 ($CO\underline{C}H_3$); 45.4 (C-2); 67.3, 70.0 ($\underline{C}H_2\varphi$, C-5); 95.5 (C-1) . Reacting 11 with tetrabutylammonium azide in toluene at 50 °C for 8 h gave benzyl 2-acetamido-6-azido-2,3,4,6-tetradeoxy-α-D-erythro-hex-3-enopyranoside (12) in 85 % yield m.p. 158-160 °C (acetone), $[\alpha]_D^{22}$ +52° (c 1.0, chloroform), IR (cm^{-1}): 3450 (NH); 2100 (N_3); 1670 (C=O), δ_C (25 MHz, $CDCl_3$): 23.3 ($CO\underline{C}H_3$); 45.3 (C-2); 54.0 (C-6); 67.9, 70.1 ($\underline{C}H_2Ph$, C-5); 95.0 (C-1).

Several factors still made this approach unattractive. The yield was moderate (~50 %), and purification by silica gel column chromatography was necessary. Varying amounts of a by-product were found in the reaction mixture in which H-3 or H-4 had been replaced by iodine (c.f. 16). Similar results have been observed by Barton and co-workers.[9] Reaction of tetra-N-benzyloxycarbonyl-5,6-O-cyclohexylidene-neamine with triphenylphosphine-iodine-imidazole (1:0.6:1) gave tetra-N-benzyloxycarbonyl-3,4-dideoxy-3-ene-5,6-O-cyclohexylidene-neamine in 42 % yield plus a corresponing vinyl iodide in 22 % yield.[9]

We have found that the formation of this vinyl iodide type derivative is promoted by bases (pyridine or excess imidazole). Deprotonation of NH makes the acetamido group participate in the reaction.

To resolve this problem, benzyl 2-(benzyloxycarbonyl)amino-2-deoxy-α-D-glucopyranoside[10] (13), having a less participating N-protecting group, was prepared, and the reaction conditions were adjusted so that the amount of free base was minimized. Reaction of 13 with triphenylphosphine-iodine-imidazole (1:1:1) in toluene-acetonitrile (2:1) produced the desired benzyl 2-(benzyloxycarbonyl)amino-2,3,4,6-tetradeoxy-6-iodo-α-D-erythro-hex-3-enopyranoside (14) in 82 % yield. A small amount of the vinyl iodide 16 could also be isolated and was characterized. (The amount of 16 could be increased to about 50 % by performing the reaction in pyridine solution).

In large-scale preparations, extractive work-up, followed by direct crystallization in ethanol yielded pure 14 in 66 % yield.

Treatment of 14 with freshly prepared tetrabutylammonium azide provided the corresponding 6-azide 15 in 74 % yield. The major side reaction here was elimination of HI giving the conjugated 3,5-diene. Conversion of 15 to pupurosamine C can be accomplished by hydrogenolysis

followed by hydrolysis as described.[4,11] Using a slight excess of triphenylphosphine in methanol, it is also possible to selectively reduce the azide in 15 to the free amine.[12]

The reaction sequence 13-15 thus represents an efficient synthesis of a purpurosamine C precursor, suitable for large-scale preparations. Of the amino protecting groups examined in the reactions, the carbobenzyloxy group is superior to the acetyl group. The phthalimido group does not give any side-reactions at all and is thus superior to both.[12] The rather troublesome introduction and removal of the phthalimido group is, however, a limiting factor in its use.

EXPERIMENTAL

General methods were the same as those published elsewhere.[13]

Benzyl 2-(benzyloxycarbonyl)amino-2,3,4,6-tetradeoxy-6-iodo-α-D-erythro-hex-3-enopyranoside (14).

Preparation 1. A mixture of triphenylphosphine (1.57 g, 6.0 mmol) and iodine (1.52 g, 6.0 mmol) in toluene (20 ml) was stirred at room temperature for 30 min. Imidazole (0.41 g, 6.0 mmol) in acetonitrile (10 ml) was added and the mixture was stirred at 50 °C for 10 min. 13[10] (0.40 g, 1.0 mmol) was added and stirring was continued for 1.5 h. The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was purified by silica gel column chromatography using toluene-ethyl acetate (5:1) as eluent giving 393 mg (82 %) of 14, m.p. 139-140 °C (ethanol), $[\alpha]_D^{22}$ -151° (c 1.0, chloroform), δ_C (25 MHz, $CDCl_3$): 8.60 (C-6); 48.32 (C-2); 66.98, 70.20 (2x$\underline{C}H_2\varphi$); 72.69 (C-5); 99.25 (C-1); 125.61, 129.07 (C-3, C-4).

Anal. Calcd for $C_{21}H_{22}NIO_4$: C, 52.6; H, 4.63; N, 2.92; I, 26.4. Found: C, 52.0; H, 4.65; N, 2.85; I,26.9.

A faster-moving component 16 was also isolated (25 mg, 4 %), m.p. 165-167 °C (ethanol), $[\alpha]_D^{22}$ -102° (c 1.4, chloroform).

Anal. Calcd for $C_{21}H_{21}NI_2O_4$: C, 41.7; H, 3.50; N, 2.31; I, 41.9. Found: C, 41.8; H, 3.53; N, 2.46; I, 42.0.

Preparation 2. Iodine (15.2 g, 59.9 mmol) was added in portions to a stirred solution of triphenylphosphine (15.72 g, 59.9 mmol) in toluene (100 ml). The mixture was stirred for 30 min, after which imidazole (4.50 g, 66.1 mmol) in acetonitrile (50 ml) was added. After stirring for 15 min, 13

(4.04 g, 10.0 mmol) was added and stirring was continued for 1.5 h at 50 °C. The mixture was cooled, filtered and concentrated to dryness. The residue was dissolved in toluene (200 ml) and the organic phase was washed with aqueous HCl (1 M, 100 ml), saturated sodium hydrogencarbonate (100 ml), water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was crystallized from warm ethanol (~100 ml) to yield 3.2 g (66 %) of the title compound (14).

Benzyl 6-azido-2-(benzyloxycarbonyl)amino-2,3,4,6-tetradeoxy-α-D-erythro-hex-3-enopyranoside (15). A mixture of 14 (300 mg, 0.63 mmol) and tetrabutylammonium azide (1.2 g, 4.2 mmol) was stirred at 0 °C for 2.5 h and at rt overnight in acetonitrile (50 ml). The reaction mixture was concentrated to almost dryness, and the residue was dissolved in dichloromethane (50 ml). The organic phase was washed with saturated aqueous sodium hydrogencarbonate, water, dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography using toluene-ethyl acetate (7:1) as eluent, yielding 182 mg (74 %) of 15, m.p. 112-113 °C (ethanol), $[\alpha]_D^{22}$ -172° (c 1.0, chloroform), IR (cm^{-1}): 2100 (N_3). δ_C (25 MHz, $CDCl_3$): 49.0 (C-2); 54.3 (C-6); 66.8, 70.0 (2x$CH_2\varphi$); 72.9 (C-5); 99.2 (C-1); 126.8, 127.6 (C-3, C-4).

Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 64.0; H, 5,62; N, 14.2. Found: C, 63.9; H, 5.63; N, 14.0.

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