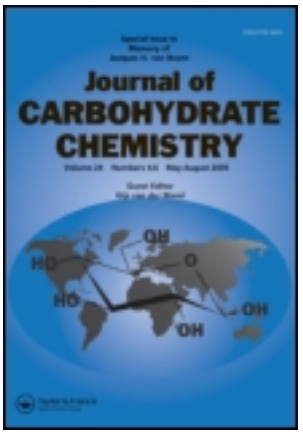

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Synthesis of 2,3-UNSATURATED 4-Amino Sugars and Cyclohexyl 2,3-Di-O-Acetyl-4,6-Di-O-Methyl-α-D-Manno-Pyranoside from Cyclohexyl 4,6-Di-O-Acetyl-2,3-Dideoxy-α-D-erythro-Hex-2-Enopyranoside

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SYNTHESIS OF 2,3-UNSATURATED 4-AMINO SUGARS AND CYCLOHEXYL 2,3-DI-*O*-ACETYL-4,6-DI-*O*-METHYL-α-D-MANNO-PYRANOSIDE FROM CYCLOHEXYL 4,6-DI-*O*-ACETYL-2,3-DIDEOXY-α-D-*erythro*-HEX-2-ENOPYRANOSIDE

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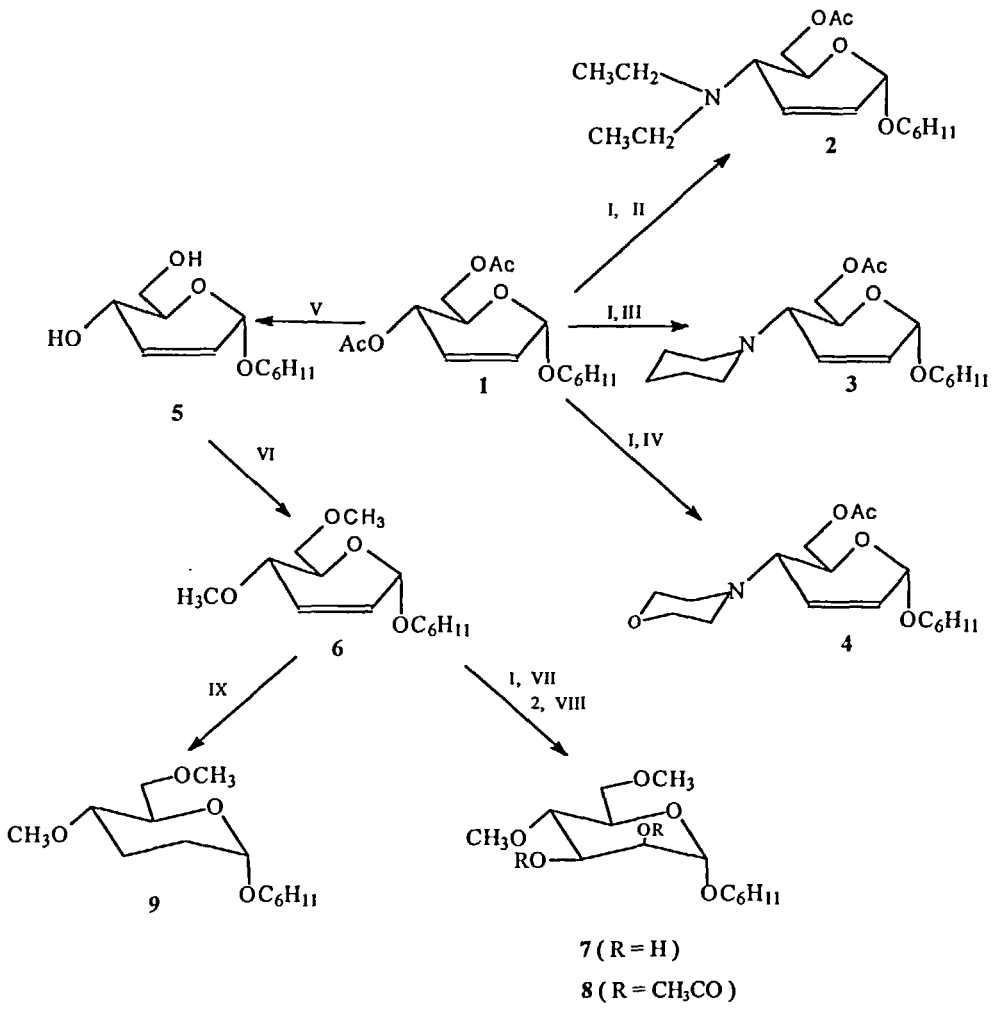
ABSTRACT

The synthesis of three 2,3-unsaturated 4-amino sugars **2-4** and cyclohexyl 2,3-di-*O*-acetyl-4,6-di-*O*-methyl-α-D-mannopyranoside **8** starting from cyclohexyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **1** is described. The amino sugars were prepared by allylic substitution using a palladium catalyst.

INTRODUCTION

During the course of our studies on the synthesis of novel amino sugar derivatives, we chose to investigate a route to cyclohexyl amino glycosides using a palladium-based allylic substitution reaction. Baer and Hanna[4] reported the synthesis of unsaturated amino sugars from ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside with secondary amines in the presence of tetrakis(triphenylphosphine) palladium (0). We decided to attempt

this reaction on substrates with a larger cyclohexyl group as the aglycone. The resulting cyclohexyl amino glycosides with different amino substitution at C-4 were of interest to us as models of amino sugar-containing disaccharides such as those found in aminoglycoside antibiotics.[5] This communication reports the preparation of three new 2,3-unsaturated 4-amino sugars **2-4** and cyclohexyl 2,3-di-*O*-acetyl-4,6-di-*O*-methyl-α-D-mannopyranoside **8** from cyclohexyl glucoside **1** (Scheme).[6,7]



I) $[(Ph)_3P]_4Pd$ (0), THF; II) Et_2NH; III) Piperidine; IV) Morpholine; V) CH_3OH, H_2O, Et_3N, R.T.; VI) DME, NaH, CH_3I; VII) Aq. $KMnO_4$; VIII) Ac_2O, Py; IX) Pd/H_2

Scheme

RESULTS AND DISCUSSION

Reaction of cyclohexyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[6] **1** with diethylamine, piperidine and morpholine in the presence of tetrakis(triphenylphosphine) palladium (0) provided the desired unsaturated amino glucosides **2-4** with a 40 to 58% yield (Scheme). The reaction of **1** with palladium catalyst generates a π-complex from which acetate ion is lost to form the π-allyl palladium complex. Attack of the nucleophile (a secondary amine) may take place either at C-2 or C-4. However, the anomeric carbon possesses a bulky cyclohexyl group in the pseudo axial position which restricts the approach of nucleophile at C-2 from the same side. The only position then left is C-4, where the nucleophile attacks from the same side which was previously occupied by the acetyl group, thus retaining the configuration at this position. The structures of the products were assigned on the basis of their NMR spectra. The 300 MHz ^{1}H NMR spectrum of **2** showed a narrow multiplet at δ 5.11 ppm (W/2 = 5.4 Hz) for H-1. Irradiation of H-1 established its coupling with H-2, H-3, and H-4 at δ5.82, 6.03 and 3.30 ppm respectively. Two-dimensional ^{1}H-^{1}H NMR spectrum confirmed this proposition. The large coupling constant (10.0Hz) between H-4 and H-5 leaves no doubt about the configuration of H-4. Compounds **3** and **4** had ^{1}H NMR spectra compatible with their structures.

Next, we concentrated our attention on the preparation of **8** from **1.** Deacetylation (Et_3N-H_2O-MeOH) of **1** provided **5,** which in turn was dimethylated to furnish **6.** Further confirmation of the structure of **6** was obtained by its conversion to **9.** The anomeric proton of **9** appeared at δ 4.97 ppm (J = 2.1 Hz) as a broad doublet. Irradiation of H-1 gave a NOE difference spectrum which clearly showed an intensity enhancement for H-4 (4.27%), but not for H-5, H-6 and H-6' supporting the equatorial disposition of H-1 and axial orientation of H-4. Similar H-1 and H-4 interactions have been observed before in unsaturated C-glycopyranosides where nuclear Overhauser difference spectroscopy[8] was used to establish the configuration of H-1 and H-4 protons. More recently, NOESY helped to determine the configurations of such protons in β-cyclodextrin.[9]

Treatment of **6** with an aqueous potassium permanganate solution yielded **7** as a syrup. For further characterization of this product, it was transformed into its di-*O*-acetyl derivative **8.** The ^{1}H NMR spectrum of **8,** with the aid of double resonance work, established the *manno* configuration of this product.

CONCLUSION

In this paper, we have described the synthesis of three new 2,3-unsaturated 4-amino sugars with a cyclohexyl group as the aglycone using a palladium-based substitution reaction. The reaction was highly regioselective giving only the 4-amino sugars as products, and analysis of NMR spectral data corroborated the assignments of stereochemistry at C-1 and C-4.

EXPERIMENTAL

General Methods. Melting points were determined with a Digital Melting Point Apparatus, series IA-9100, Electrothermal Engineering Ltd., England. ^{1}H NMR spectra were recorded with either a Bruker model AC 300P in "Instituto de Química, Universidade de Campinas (UNICAMP)" or with a Varian 300 MHz Unity Plus instrument. Thin-layer chromatography (TLC) was carried out on plates coated with silica gel 60 followed by the exposure of the plates in a chamber containing iodine vapors which revealed the spots. For compounds 2-4, the solvent system used for developing the TLC plates was a mixture of 1:1 ethyl acetate and petroleum ether (bp 35-60 °C).

Unsaturated Amino Sugars 2-4. A mixture of cyclohexyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **1** (0.40 g, 1.28 mmol), triphenylphosphine (0.286 g, 1.096 mmol) and tetrakis(triphenylphosphine) palladium (0) (0.126 g, 0.1095 mmol) in dry tetrahydrofuran (15 mL) in a 50 mL round-bottom flask which was equipped with a condenser, was stirred for 30 min. at room temperature under a nitrogen atmosphere. The appropriate amine (2 mL), previously dried over potassium hydroxide pellets, was then added and the reaction mixture placed in an oil bath maintained at 75 °C and stirred for an additional 22 h at this temperature. TLC (petroleum ether (30-60 °C)/diethyl ether, 1:1) showed the disappearance of the starting material **1**. Product purification was achieved by column chromatography using silica gel eluting either with *n*-hexane or with a mixture of *n*-hexane-chloroform (9:1).

Cyclohexyl 6-*O*-acetyl-4-*N,N*-diethylamino-2,3,4-trideoxy-α-D-*erythro*-hex-2-eno pyranoside (2). Compound **2** with R_f value ≈ 0.70 (R_f value of **1** ≈ 0.61) was obtained as a syrup with a 58% yield after chromatography. Attempts to crystallize this compound failed.

The specific rotation of the pure material is $[\alpha]_D^{20}$ +157.4° (*c* 0.005, dichloromethane). IR (liq. film) 1744 (ν-COO-) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, 6H, $2CH_3$), 1.15-1.50 (m, 10H, $5CH_2$), 2.09 (s, 3H, OAc), 2.37-2.64 (m, 4H, $2CH_2N$), 3.30 (dddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{3,4}$ =1.95 Hz, $J_{2,4}$ = 1.71 Hz, and $J_{1,4} \approx$ 1.0 Hz, H-4), 3.62 (m, 1H, CHO-), 3.98 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6}$ = 6.1 Hz and $J_{5,6'}$ = 2.1 Hz, H-5), 4.30 (dd, 1H, J = 11.6 Hz, J = 6.1 Hz, H-6), 4.4 (dd, 1H, J = 11.6 Hz, 2.2 Hz, H-6'), 5.1 (nm, 1H, $J_{1,2}$ = 2.7 Hz, $J_{1,3} \approx$1.0 Hz, $J_{1,4}$ = 1.0 Hz, H-1), 5.8 (ddd, 1H, $J_{2,3}$ = 10.3 Hz, $J_{1,2}$ = 2.7 Hz, and $J_{2,4}$ = 1.95 Hz, H-2), 6.0 (ddd, 1H, $J_{2,3}$ = 10,3 Hz, $J_{1,3} \approx$ 1.0 Hz and $J_{3,4}$ = 1.95 Hz, H-3).

Anal. Calcd for $C_{18}H_{33}O_4N$ (325.43): C, 66.45; H, 9.60. Found: C, 66.85; H, 9.88.

Cyclohexyl 6-*O*-acetyl-2,3,4-trideoxy-4-piperidino-α-D-*erythro*-hex-2-enopyranoside (3). The reaction product showed an R_f value of 0.72. Chromatography on a silica gel column eluting first with *n*-hexane eliminated a non-polar impurity. Compound **3** eluted when the column was flushed with *n*-hexane-chloroform (9:1). Combining the fractions with R_f value 0.72 followed by solvent evaporation left a viscous mass. After drying, the yield of chromatographically pure **3** was 40%. $[\alpha]_D^{20}$ +142.5° (*c* 0.006, dichloromethane). IR (liq. film) 1747.5 (ν -COO-) cm^{-1}); ^1H NMR ($CDCl_3$) δ 1.12-2.02 (m, 16H, CH_2), 2.09 (s, 3H, OAc), 2.40 (m, 2H, CH_2N) 2.65 (m, 2H, CH_2N), 3.05 (dddd, 1H, $J_{4,5}$ = 9.90 Hz, $J_{3,4} \leq$ 1.90 Hz, $J_{2,4} \leq$ 1.70 Hz & $J_{1,4} \leq$ 1.0 Hz, H-4), 3.63 (m, 1H, CHO-), 4.12 (ddd, 1H, $J_{4,5}$ = 9.90 Hz, $J_{5,6}$ = 7.5 Hz, $J_{5,6'}$ = 2.1 Hz, H-5), 4.23 (dd, 1H, $J_{6,6'}$ = 11.7 Hz, $J_{5,6}$ = 6.9 Hz, H-6), 4.45 (dd, 1H, $J_{6,6'}$ = 11.5 Hz, $J_{5,6'}$ = 2.25 Hz, H-6'), 5.09 (nm, 1H, H-1), 5.81 (ddd, 1H, $J_{2,3}$ = 10.20 Hz, $J_{1,2}$ = 2.4 Hz and $J_{2,4}$ = 2.7 Hz, H-2), 6.1 (dnm, 1H, $J_{2,3}$ = 10.20 Hz, $J_{3,4}$ = 1.90 Hz, $J_{1,3} \leq$ 1.00 Hz, H-3).

Anal. Calcd for $C_{19}H_{31}NO_4$ (337.44): C, 67.62; H, 9.26; N, 4.15. Found: C, 67.68; H, 9.14; N, 4.15.

Cyclohexyl-6-*O*-acetyl-4-morpholino-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (4). The product was obtained by column chromatography by eluting with *n*-hexane-$CHCl_3$ (9:1); yield, 45%; $R_f \approx$ 0.52; $[\alpha]_D^{20}$ +134.6° (*c* 0.008, dichloromethane). IR (liq film) 1733.1 (ν -COO-) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1,10-2.05 (m, 10H, $5CH_2$), 2.09 (s, 3H, OAc), 2.55 (m, 2H, CH_2N), 2.72 (m, 2H, CH_2N), 3.07 (dddd, 1H, $J_{4,5}$ = 10.2, $J_{3,4} \approx$ 1.80 Hz, $J_{2,4} \approx$ 1.60 Hz, $J_{1,4} \approx$ 1.0 Hz, H-4), 3.63 (nm, 4H, $2CH_2O$), 3.66 (m, 1H, CHO-), 4.12 (ddd, 1H,

$J_{4,5}$ = 10.2 Hz, $J_{5,6}$ = 7.2 Hz, $J_{5,6'}$ = 2.1 Hz, H-5), 4.24 (dd, 1H, $J_{6,6'}$ = 11.5 Hz, $J_{5,6}$ 7.1 Hz, H-6), 4.48 (dd, 1H, $J_{6,6'}$ =11.5 Hz, $J_{5,6'}$ = 1.8 Hz, H-6'), 5.09 (nm, 1H, $J_{1,2}$ = 2.4 Hz, H-1), 5.87 (ddd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{1,2}$ = 2.4 Hz, $J_{1,4}$ = 2.4 Hz, H-2), 6.1 (dnm, 1H, $J_{2,3}$ = 10,4 Hz $J_{1,3}$ ≤ 1.00 Hz & $J_{3,4}$ ≅ 1.50 Hz, H-3).

Anal. Calcd for $C_{18}H_{29}O_5N$ (339.4): C, 63.69%; H, 8.61%; N, 4.12%. Found: C, 63.90; H, 8.41%; N, 3.90.

Cyclohexyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (5). The hydrolysis of **1** was conducted according to the method of Fraser-Reid.[10] The yield of this product was 88%. The hygroscopic product was crystallized from ethyl acetate and cyclohexane to provide colorless crystals, mp 69-71 °C; lit.[6] mp 67-68 °C. The ^{1}H NMR spectrum of **5** matched that reported.[6]

Cyclohexyl 2,3-dideoxy-4,6-di-*O*-methyl-α-D-*erythro*-hex-2-enopyranoside (6). Sodium hydride (0.125 g, 4.2 mmol; 80% sodium hydride in mineral oil) was washed with hexane to remove mineral oil. To it was added methyl iodide (1.0 mL) under nitrogen followed by the slow addition of a solution of compound **5** (0.32 g, 1.41 mmol) dissolved in DME (5.0 mL), while stirring the contents of the flask at room temperature. After the addition, the contents were stirred for an additional 3 h. TLC (chloroform) showed a faster moving new spot (R_f = 0.4), which after chromatography over silica gel afforded 0.34g (81.5%) of **6.** Crystallization and recrystallization from *n*-pentane gave crystals of **6** with mp 61-62 °C. ^{1}H NMR ($CDCl_3$) δ 1.02-1.94 (m, 10H, 5 CH_2), 3.33 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.55 (dd, 2H, H-6 and H-6'), 3.59 (m, 1H, CH-O-), 3.82 (m, 2H, H-4 and H-5), 5.08 (d, 1H, $J_{1,2}$ = 2.68 Hz, H-1), 5.66 (ddd, 1H, $J_{2,3}$ = 10.25 Hz, $J_{1,2}$ = 2.81 Hz, $J_{2,4}$ = 1.46 Hz, H-2), 5.99 (d, 1H, $J_{2,3}$ = 10.25 Hz, H-3).

Anal. Calcd for $C_{14}H_{24}O_4$ (256.33): C, 65.60; H, 9.44. Found: C, 65.78; H, 9.57.

Cyclohexyl 4,6-di-*O*-methyl-α-D-mannopyranoside (7). Compoud **6** (0.45 g, 1.7 mmol) in THF (20 mL) was cooled in an ice bath under stirring. Potassium permanganate (0.42 g, 2.66 mmol) was added to it in portions followed by addition of water (10 mL). The contents were stirred briefly and allowed to come to room temperature. After 5 h, the starting material was consumed as verified by TLC. The mixture was filtered over celite and washed with THF. Removal of the solvent gave a syrup which was purified by column chromatography over silica gel first eluting with dichloromethane and later with

CH_2Cl_2/AcOEt (1:1). Syrupy **7** (0.17 g, 37%) gave a single spot with an R_f value of 0.22 (9.8:0.2, dichloromethane/methanol); $[\alpha]_D^{25}$ +68.32° (*c* 3.18, chloroform). ^1H NMR ($CDCl_3$) δ 1.1-2.3 (m, 10 Hz, $5CH_2$), 5.67 (b, 2H, 2OH), 3.42 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.3-3.8 (m, 5H, H-2, H-3, H-4, H-6 and H-6'), 3.82-4.02 (m, 1H, H-5), 4.98 (nm 1H, H-1).

Cyclohexyl 2,3-di-*O*-acetyl-4,6-di-*O*-methyl-α-D-mannopyranoside (8). Compound **7** (0.23 g, 70 mmol) was dissolved in dry pyridine (2.0 mL) and the solution cooled to 0°. Acetic anhydride (1.5 mL) was added and the contents left under stirring overnight. A single spot was observed by TLC (ethyl acetate) having an R_f value of 0.58. Evaporation of the solvents left a syrup which was quickly passed through a silica gel column using chloroform as an eluent. Solvent evaporation provided a colorless syrup weighing 0.19 g (83.6%); $[\alpha]_D^{25}$ +33.45° (*c* 3.88, chloroform). ^1H NMR ($CDCl_3$) δ 1.15-1.98 (m, 10H, $5CH_2$), 2.01 (s, 3H, OAc), 2.14 (s, 3H, OAc), 3.4 (m, 1H, CH-O-), 3.44 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.58 (dd, 1H, $J_{6,6'}$ = 10.5 Hz, $J_{5,6'}$ = 2.4 Hz, H-6'), 3.65 (dd, 1H, $J_{3,4}$ = 9.75 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 3.66 (dd, 1H, $J_{6,6}$ = 10.5 Hz, $J_{5,6}$ = 3.5 Hz, H-6), 3.82 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6}$ = 3.45 Hz, $J_{5,6'}$ = 2.4 Hz, H-5), 4.91 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 5.17 (dd, 1H, $J_{2,3}$ = 3.45 Hz, $J_{1,2}$ = 1.80 Hz, H-2), 5.28 (dd, 1H, $J_{3,4}$ = 9.75 Hz, $J_{2,3}$ = 3.45 Hz, H-3).

Anal. Calcd for $C_{18}H_{30}O_8$: C, 57.73; H, 8.07. Found: C, 57.90; H, 7.97.

Cyclohexyl 2,3-dideoxy-4,6-di-*O*-methyl-α-D-*erythro*-hexopyranoside (9). Compound **6** (0.31 g, 1.21 mmol) in ethyl acetate (10 mL) containing 5% palladium on carbon was hydrogenated at 1 atmosphere pressure for 8 h. Removal of the catalyst by filtration over a layer of celite followed by solvent removal under vacuum left a product which was promptly chromatographed over silica gel to yield 0.20 g (65%) of pure **9**. Its R_f value in chloroform was the same as that of **6**. Its characterization was done with the help of ^1H NMR spectral data. The 300 MHz ^1H NMR spectrum ($CDCl_3$) of this material showed a rather broad anomeric proton signal at δ 4.97 ppm having a width of ca. 4.0 Hz at half height and a splitting of 2.1; $[\alpha]_D^{25}$ +108.9° (*c* 3.98, chloroform). ^1H NMR ($CDCl_3$) δ 1.1-2.2 (m, 14H, $7CH_2$), 3.25 (m, 1H, -CH-O-), 3.36 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.5-

3.69 (m, 3H, H-4, H-6 & H-6'), 3.72 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 3.6 Hz, $J_{5,6'}$ = 2.4 Hz, H-5), 4.97 (bd, 1H, J = 2.1 Hz, H-1).

Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 64.82; H, 9.92.

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