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Note

Synthesis and hypolipidemic activity of *N*-phthalimidomethyl tetra-*O*-acyl-α-D-mannopyranosides

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Abstract

A facile synthesis of anomerically pure phthalimidomethyl 2,3,4,6-tetra-*O*-acetyl- and phthalimidomethyl 2,3-di-*O*-acetyl-4,6-di-*O*-benzoyl-α-D-mannopyranosides (**6** and **9b**) starting from *N*-hydroxymethylphthalimide and tri-*O*-acetyl-D-glucal is described. Compounds **3**, **6**, **8**, **9a** and **9b** have been tested for their hypolipidemic activity in mice. All these compound showed significant reduction of plasma cholesterol and triglyceride levels. Compound **9b** has been found to possess the highest activity. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: α-D-Mannopyranoside; *N*-Hydroxymethylphthalimide; Tri-*O*-acetyl-D-glucal

Phthalimide derivatives are known to display antitumor,[1] anticonvulsant,[2] and hypolipidemic[3,4] activities. Our own group has been interested in N-substituted phthalimides and found that *N*-[3-phenyl-1,2,4-oxadiazol-5-yl]methylphthalimide possesses enhanced analgesic activity.[5] A recent report describes the synthesis of methyl 2,6-anhydro-3-deoxy-3-phthalimido-α-D-mannopyranoside and its ^{15}N-labeled analog, for which the spectroscopic and stereochemical studies were carried out,[6] but no biological activity tests have been reported. The literature does not record a phthalimidoylalkyl moiety as an aglycone in mannopyranoside derivative. If such glycoside is prepared, the carbohydrate moiety might play an important role as a carrier of this group to an appropriate site suited for the pharmacological activity. With this objective in mind, the synthesis of phthalimidoylmethyl mannopyranoside was planned and, indeed, compounds **3**, **6**, **8**, **9a** and **9b** exhibited significant hypolipidemic activity. The results are described below.

The synthesis of *N*-phthalimidomethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**3**) was achieved in high yield by the reaction of *N*-hydroxymethylphthal-

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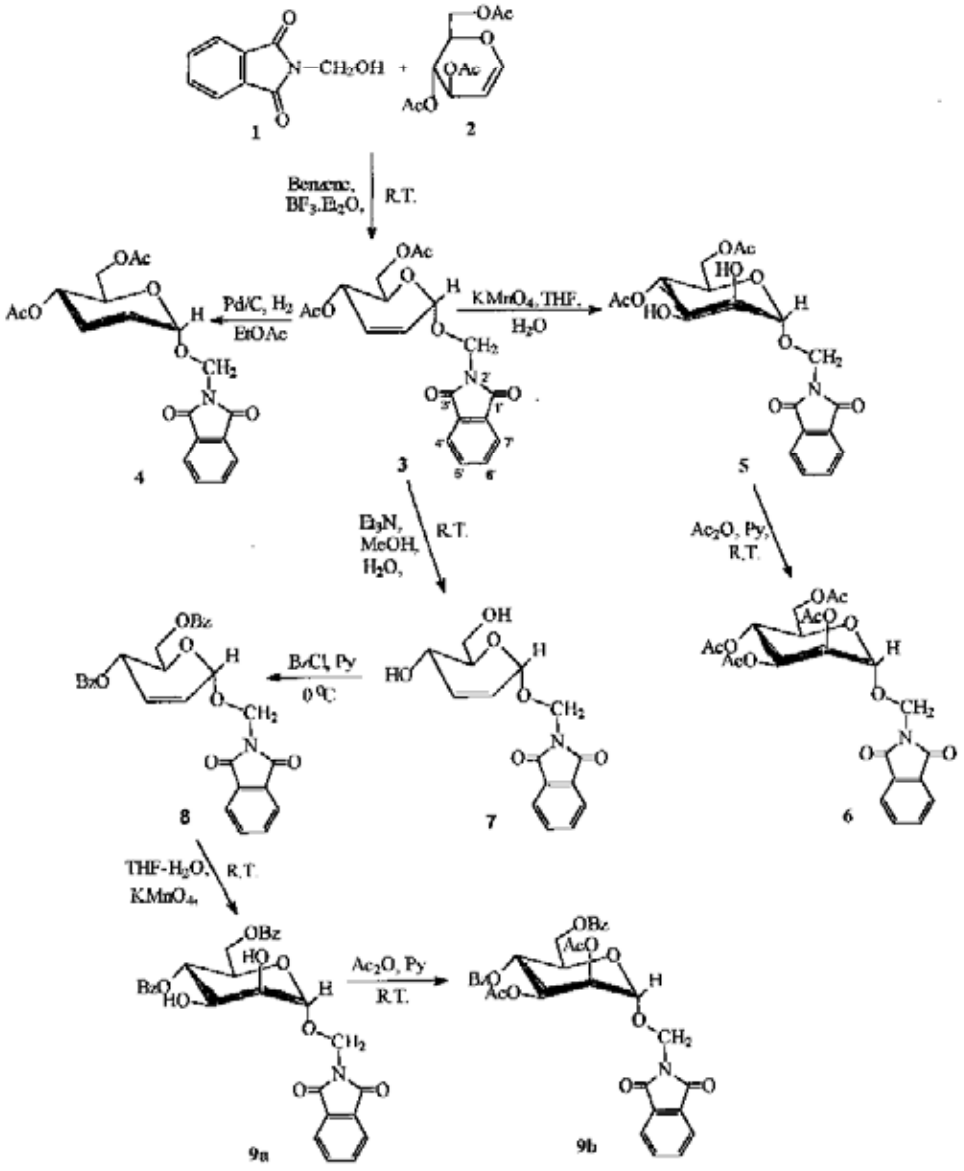
imide (**1**) with 3,4,6-tri-*O*-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (tri-*O*-acetyl-D-glucal) (**2**) using Ferrier's method[7] (Scheme 1). Although, it is known[7] that the unsaturated sugars formed by Ferrier's method contain more than 90% of α anomer, in the present work, only one product was isolated. In order to confirm the anomeric configuration of **3**, we hydrogenated it. The product **4** gave an anomeric proton at δ 5.07 ppm as a broad singlet ($W/2 \approx 4.08$ Hz) indicating the axial configuration of the phthalimidomethyloxy group. Hence, it is concluded that compound **3** is exclusively the α anomer. Once the anomeric configuration of **3** has been established, we proceeded to treat it with potassium permanganate. The reaction furnished presumably a diol **5**, but it was difficult to establish the configuration of the hydroxyl groups at C-2 and C-3 by ^{1}H NMR. We acetylated **5** and got the tetra-*O*-acetyl derivative **6**. The ^{1}H NMR spectrum of this compound showed four signals between δ 2.07 and 2.13 ppm due to acetyl groups. However, the ^{1}H NMR spectrum turned out to be more complicated because H-2, H-3, H-4 and –N–CH_2–O– protons appeared between δ 5.20 and 5.40 ppm. All attempts to determine the configurations at C-2 and C-3 by NMR spectroscopy failed. Even the shift reagent did not help to



Scheme 1.

Table 1
Effect of compounds **3**, **6**, **8**, **9a** and **9b** on mice plasma cholesterol and triglyceride levels of mice [a]

Compound	Cholesterol (mmol/L)		Triglycerides (mmol/L)	
	Before	After	Before	After
3 [b]	3.43 ± 0.29	2.71 ± 0.37 [e]	1.94 ± 0.23	1.44 ± 0.24 [d]
6 [b]	2.98 ± 0.26	2.42 ± 0.22 [f]	1.65 ± 0.08	1.35 ± 0.08 [e]
8 [c]	3.07 ± 0.34	2.54 ± 0.26 [f]	1.63 ± 0.15	1.28 ± 0.12 [f]
9a [c]	3.40 ± 0.46	2.91 ± 0.51 [e]	1.92 ± 0.18	1.48 ± 0.13 [d]
9b [c]	3.43 ± 0.26	2.93 ± 0.28 [d]	1.83 ± 0.25	1.33 ± 0.20 [e]
1% CMC	2.68 ± 0.16	2.66 ± 0.17	1.09 ± 0.04	1.09 ± 0.04

[a] Number of mice for each test group = 6. Results are shown as the mean ± S.D.
[b] Results for treatment with 20 mg/kg per day.
[c] Results for treatment with 10 mg/kg per day.
[d] $P < 0.01$.
[e] $P < 0.001$.
[f] $P < 0.0001$.

separate the peaks sufficiently for configurational analysis. Frustrated with the tetra-*O*-acetyl compound **6**, we turned our attention to the 4,6-di-*O*-benzoyl derivative with the hope to get separation of the H-2, H-3 and H-4 protons for determining their correct configurations. To achieve this goal, compound **3** was hydrolyzed to **7** using a mixture of triethylamine, methanol and water. Benzoylation of **7** and usual work-up afforded a crystalline compound **8** which showed a single spot on TLC (R_f 0.70). The 300 MHz ^{1}H NMR spectrum of this derivative showed a broad signal for H-1 at δ 5.38 ppm with a narrow splitting at the top of the peak. It was therefore not possible to determine the anomeric configuration with certainty. However, the COSY (^{1}H–^{1}H) spectrum clearly showed that H-1 is coupled with H-2 at δ 5.88 and H-4 at δ 5.72. The latter coupling between H-1 and H-4 can only take place if H-1 and H-4 are on the same side, i.e., the anomeric proton at C-1 is oriented equatorially and H-4 is oriented axially. cis-Hydroylation of **8** gave **9a**, which was acetylated. The structure of the resulting di-*O*-acetyl derivative **9b** was deduced from its ^{1}H NMR spectrum. The anomeric proton appeared as a doublet (J 2.1 Hz), H-2 as a doublet of doublets at 5.28 (J 1.8 and 3.3 Hz), H-4 as a triplet (J 10.1 Hz) and H-3 as a doublet of doublets (J 10.2 and 3.3 Hz). With this information, it is obvious that **3** is a mannopyranoside with the aglycone portion oriented axially at C-1.

Compounds **3**, **6**, **8**, **9a**,**b** have been tested for their hypolipidemic activity. Phthalimidomethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**3**) reduced the total plasma cholesterol and triglycerides levels by 21 and 25% in normolipidemic Swiss white male mice (Table 1) after 16 days of treatment with 20 mg/kg per day. A smaller reduction was found when the animals were treated with phthalimidomethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**6**), where the cholesterol and triglycerides levels decreased by 17–18%. An improvement in hypotriglyceridemic activity in vivo, but not in the hypocholesterolemic activity, was observed in compounds **8**, **9a** and **9b**, respectively. As shown in Table 1, the animals treated with phthalimidoylmethyl 4,6-di-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**8**), phthalimidoylmethyl 4,6-di-*O*-benzoyl-α-D-mannopyranoside (**9a**) and phthalimidoylmethyl 2,3-di-*O*-acetyl-4,6-di-*O*-benzoyl-α-D-mannopyranoside (**9b**), at 10/mg/kg per day, exhibited significant reduction of the plasma triglyceride concentrations (21, 23 and 27%, respectively). Therefore, although all compounds showed strong hypolipidemic activity for reducing triglycerides, compound **9b** has been found to possess the highest activity. Finally, it was found that administration of 1% carboxymethyl cellulose (CMC) to the animals had no significant changes in mice plasma cholesterol and triglycerides (2%).

In conclusion, the results show that these drugs are able to reduce the plasma lipid levels in normolipidemic mice and that they offer excellent promise as new hypolipidemic agents.

1. Experimental

General methods.—Melting points were determined on an Electrothermal digital melting point apparatus (model 9100) and are uncorrected. Infrared spectra were measured with a

Bruker model IFS66 FT-IR spectrophotomer using potassium bromide discs. NMR spectra were recorded with a Varian Unity Plus 300 MHz instrument using $CDCl_3$ as solvent, unless otherwise stated, and Me_4Si as internal standard. The specific rotation of compound **8** was obtained on a Perkin–Elmer, model 241 polarimeter and the sp rotations of other compounds were measured on JASCO, model DIP-370 polarimeter. Silica gel coated plates with fluorescent indicator (PF_{254}) were used for thin-layer chromatography (TLC) and the spots were revealed under ultraviolet light. The solvent system for running the TLC plates was a mixture of 1:9 EtOAc–CH_2Cl_2.

Phthalimidomethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**3**).—*N*-(Hydroxymethyl)phthalimide (**1**) (0.23 g, 1.30 mmol), and tri-*O*-acetyl-D-glucal (**2**) (0.33 g, 1.21 mmol) in dry benzene (40 mL), were stirred in a 150 mL round-bottom flask under nitrogen atmosphere. Borontrifluoride etherate (0.5 mL) was added to it and the stirring continued for 75 min at rt. Thin-layer chromatography showed a fast moving spot of R_f 0.62 (alcohol **1** had R_f 0.34). Neutralization of this solution with solid $NaHCO_3$, drying with anhyd Na_2SO_4 followed by solvent evaporation left a crystalline solid which, after chromatography over silica gel, provided crystals (0.36 g, 76.3% based on **2**), which after recrystallization from EtOH melted at 120–120.8 °C; $[\alpha]_D^{25}$ +46° ± 2 (*c* 0.9, $CHCl_3$); R_f 0.62; IR (KBr): 3055 (C–H, ar), 2938 (C–H, aliph.), 1760 (ν_{as} CO, of phthalimide part) and 1726 (ν_s CO of phthalimide group and CO of acetyl groups), 1609 cm^{-1} (C=C, ar). ^1H NMR ($CDCl_3$): δ 2.08 (s, 3 H, CH_3CO–), 2.09 (s, 3 H, CH_3CO–), 4.10–4.26 (m, 3 H, H-5, H-6, H-6′), 5.27 and 5.35 (2d, 2 H, *J* 10.20 Hz, –N–CH_2–O–), 5.38 (m, 2 H, H-1 and H-4), 5.80 (ddd, $J_{2,3}$ 10.20, $J_{1,2}$ 2.70, $J_{2,4}$ 1.5 Hz, H-2), 5.90 (d, $J_{3,2}$ 10.2 Hz, H-3), 7.78 (dd, 2 H, *J* 5.40, *J* 3.0 Hz, AA′ BB′ system, H-5′ and H-6′), 7.92 (dd, 2 H, *J* 5.40, *J* 3.00 Hz, AA′BB′ system, H-4′ and H-7′). Anal. Calcd for $C_{19}H_{19}NO_8$ (389.34): C, 58.61; H, 4.92; N, 3.60. Found. C, 58.34; H, 4.68; N, 3.58.

Phthalimidomethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hexopyranoside (**4**).—Compound **3** (0.1g, 0.26 mmol) in EtOAc (5.0 mL) was hydrogenated at rt in the presence of 5% palladium on charcoal (15 mg) for 4 h at 101 KPa. Removal of the catalyst by filtration left a clear solution which showed one spot on TLC with R_f 0.50; the R_f of the starting material in this system was 0.39. Solvent evaporation left a solid which weighed 75 mg (74.6%). Crystallization and recrystallization of **4** from EtOH gave crystals with mp 97.2–97.7 °C; $[\alpha]_D^{25}$ +79.9° ± 0.4 (*c* 2.0, $CHCl_3$); R_f 0.50; IR (KBr): 3052 (C–H, Ar), 2984 (νCH_3), 2925 (ν_{as}-CH_2–), 2993 (ν_s-CH_2–), 1778 (ν_{as}, CO of phthalimide function), 1733 (ν_s, CO of phthalimide and acetyl groups), 1615 (νC=C, Ar). ^1H NMR ($CDCl_3$): δ 1.68–1.88 (m, 4 H, $2CH_2$), 1.96 (s, 3 H, CH_3CO–), 2.00 (s, 3 H, CH_3CO–), 3.92–4.1 (m, 2 H, H-6, H-6′), 4.20 (m, 1 H, H-5), 4.60 (m, 1 H, H-4), 5.07 (bs, 1 H, H-1), 5.12 and 5.22 (2d, 2 H, *J* 10.20 Hz, N–CH_2–O–), 7.72 (dd, 2 H, *J* 5.7, *J* 3.3 Hz, H-5′ and H-6′), 7.85 (dd, 2 H, *J* 5.7, *J* 3.3 Hz, H-4′ and H-7′). Anal. Calcd For $C_{19}H_{21}NO_8$ (391.36): C, 58.31; H, 5.37; N, 3.58. Found: C, 58.01; H, 5.25; N, 3.45.

Phthalimidomethyl 4,6-di-O-acetyl-α-D-mannopyranoside (**5**).—Compound **3** (0.30 g, 0.77 mmol) in THF (18 mL) was treated with a solution of $KMnO_4$ (0.14 g, 0.89 mmol in 10 mL of water) and the contents were stirred at rt for 5 h. TLC showed the disappearance of the starting material and appearance of a new product with R_f 0.30. Filtration over celite followed by solvent removal under reduced pressure gave a crude product which was chromatographed over a column containing silica gel. Pure **5** was eluted from 4:1 $CHCl_3$–EtOAc. Fractions containing **5** were combined, and the solvent evaporated to give 0.235 g of chromatographically pure product which, after crystallization from EtOH, yielded 0.21 g (64.4%) of pure **5**, mp 115.2–115.5 °C; $[\alpha]_D^{25}$ +26° ± 2 (*c* 0.7, $CHCl_3$); R_f 0.30; IR (KBr): 3100–3661 (broad, OH), 1781 (ν_{as}-CON–), 1725 (ν_sCO of phthalimide group and νCO of acetyl groups), 1611 cm^{-1}(ν-C=C–, ar). ^1H NMR ($CDCl_3$): δ 2.07–2.13 (2s, 6 H, $2CH_3CO$–), 2.9–3.5 (b, 2 H, OH), 3.80–4.10 (m, 4 H, H-2, H-3, H-6, H-6′), 4.20–4.36 (m, 1 H, H-5), 5.01–5.18 (dd, 1 H, *J* 10.2, *J* 9.6 Hz, H-4,), 5.2 (bs, 1 H, H-1), 5.26 and 5.29 (2d, 2 H, *J* 10.20 Hz, –N–CH_2–O–) 7.80 (m, 2 H, *J* 5.40, *J* 3.0 Hz, H-5′ and H-6′), 7.94 (m, 2 H, *J* 5.40, *J* 3.0 Hz, H-4′ and H-7′).

Phthalimidomethyl 2,3,4,6-tetra-O-*acetyl*-α-D-*mannopyranoside* (**6**).—Compound **5** (0.14 g, 0.33 mmol) was dissolved in dry pyridine (2.0 mL), cooled to 0 °C under N_2 atmosphere followed by the addition of Ac_2O (1.39 g, 1.5 mL, 13.6 mmol). The contents were left under stirring overnight at rt. Solvent evaporation left a viscous mass with R_f 0.5. Liquid chromatography over silica gel using 1:9 hexane–$CHCl_3$ provided 0.135 g (80.4%) of pure **6**; $[\alpha]_D^{25}$ +31° ± 1 (*c* 1.2, $CHCl_3$); R_f 0.5; IR (KBr): 2961 (νC–H), 1778 (ν_{as}CO of phthalimide group), 1752 (ν_sCO of phthalimide groups), 1726 (νCO of acetyl groups), 1610 cm^{-1} (ν-C=C–, ar). ^1H MNR ($CDCl_3$): δ 1.97 (s, 3 H, CH_3CO–), 2.03 (s, 3 H, CH_3CO–), 2.06 (s, 3 H, CH_3CO–), 2.16 (s, 3 H, CH_3CO–), 4.00 (dd, 1 H, *J* 12.30, *J* 2.10, H-6 or H-6′), 4.12 (m, 1 H, H-5), 4.27 (dd, 1 H, *J* 12.30, *J* 4.50 Hz, H-6 or H-6′), 5.15 (d, 1 H, *J* 2.10 Hz, H-1), 5.22–5.40 (m, 5 H, H-2, H-3, H-4 and –N–CH_2–O–), 7.81 (dd, 2 H, *J* 5.70, *J* 3.30 Hz AA′BB′, H-5′ and H-6′), 7.94 (dd, 2 H, *J* 5.7, *J* 3.20 Hz, AA′BB′, H-4′ and H-7′). Anal. Calcd. for $C_{23}H_{25}NO_{12}$ (507.43): C, 54.43; H, 4.93; N, 2.76. Found: C, 54.32; H,5.16; N, 2.59.

Phthalimidomethyl 2,3-dideoxy-α-D-erythro-*hex*-2-*enopyranoside* (**7**).—Compound **3** (2.75 g, 7.06 mmol) was dissolved in a 9:6:1 mixture of MeOH (27.0 mL), water (18.0 mL) and Et_3N (3.0 mL) and stirred at rt for 5 h. TLC plate revealed the disappearance of the starting material and appearance of a new spot (R_f 0.05). Solvent evaporation left 2.42 g of crude **7** which, after column chromatography over silica gel provided 1.84 g (86%) of pure **7** as a semi-solid mass; IR (KBr): 3311 (b, νOH), 2944 (νCH_2), 2914 (νCH), 1779 (ν_{as}CO of phthalimide group), 1734 (ν_sCO of phthalimide group), 1610 cm^{-1} (νC=C, ar). ^1H NMR ($CDCl_3$): δ 1.4–2.4 (b, 2 H, OH), 3.70–3.81 (m, 3 H, H-5, H-6, H-6′), 4.20 (dd, *J* 9.0 Hz, 1.8 Hz, H-4), 5.27 (narrow multiplet, 1 H, *J* 2.1 Hz, H-1), 5.31 (s, 2 H, N–CH_2–O), 5.72 (ddd, 1 H, *J* 10.5, *J* 2.7, *J* 2.1 Hz, H-2), 5.98 (dt, 1 H, *J* 10.5, *J* 1.2 Hz, H-3), 7.78 (dd, 2 H, *J* 5.4, *J* 3.0 Hz, H-5′ and H-6′), 7.92 (dd, 2 H, *J* 5.7, *J* 3.0 Hz, H-4′, and H-7′). Anal. Calcd for $C_{15}H_{15}NO_6$ (305.28): C, 59.01; H, 4.95; N, 4.58. Found: C, 59.48; H, 5.69, N, 4.26.

Phthalimidomethyl 4,6-di-O-*benzoyl-2,3-dideoxy*-α-D-erythro-*hex*-2-*enopyranoside* (**8**).—To compound **7** (2.15 g, 7.04 mmol) in dry pyridine (3.0 mL) at 0 °C and under N_2 atmosphere was added BzCl (2.47 g, 2.04 mL, 17.6 mmol). The contents were maintained at this temperature for 3 h under stirring. At this point, completion of the reaction was checked by TCL (R_f 0.7; starting compound **7** had R_f 0.05). Neutralization of the contents with $NaHCO_3$ and extraction with CH_2Cl_2, drying ($NaSO_4$) and solvent evaporation afforded 2.53 g of the crude product. Liquid chromatography over silica gel using 4:1 hexane–EtOAc gave 2.42g (66.9%) of chromatographically pure **8**. Crystallization and recrystallization from EtOH furnished crystals, mp 125.7–126.4 °C; $[\alpha]_D^{20}$ +91.65° (*c* 2, $CHCl_3$); R_f 0.7; IR (KBr): 3033 (νC=C, ar), 3070 (νC=C, ar), 1785 (ν_{as}CO of phthalimide group), 1723 (ν_s CO of phthalimide part and νCO of benzoyl groups), 1600 (νC=C, ar). ^1H NMR ($CDCl_3$): δ 3.8–4.58 (m, 3 H, H-5, H-6, and H-6′), 5.31 and 5.39 (2d, 2 H, *J* 10.2 Hz, O–CH_2–N), 5.44 (nm, 1 H, H-1), 5.72 (d, 1 H, *J* 7.8 Hz, H-4), 5.87 (dt, 1 H, *J* 10.5, *J* 2.7, *J* 2.1 Hz, H-2), 6.05 (d, 1 H, *J* 10.5 Hz, H-3), 7.39 (t, 2 H, *J* 7.5 Hz, meta protons of one benzoyl group), 7.42 (t, 2 H, *J* 7.5 Hz, meta protons of the other benzoyl group), 7.49–7.60 (m, 2 H, para protons of the benzoyl groups), 7.76 (dd, 2 H, *J* 5.55, *J* 3.30 Hz, H-5′, H-6′), 7.90 (dd, 2 H, *J* 5.40, *J* 3.00 Hz, H-4′ and H-7′), 8.0 (dd, 2 H, *J* 8.40, *J* 1.65 Hz, ortho protons of one benzoyl group), 8.04 (dd, 2 H, *J* 8.40, *J* 1.20 Hz, ortho protons of other benzoyl group). Anal. Calcd for $C_{29}H_{23}NO_8$ (513.47): C, 67.83; H, 4.51; N, 2.73. Found: C, 67.81; H, 4.54; N, 2.90.

Phthalimidomethyl 4,6-di-O-*benzoyl*-α-D-*mannopyranoside* (**9a**).—To a stirred solution of **8** (0.20 g, 0.039 mmol) in THF (6.0 mL) was added $KMnO_4$ (0.07 g, 0.44 mmol) dropwise in few minutes and the contents were left for 5 h at rt. TLC showed the formation of a new product with a R_f value of 0.17. Removal of MnO_2 by filtration followed by solvent evaporation furnished a semi-solid material, which after chromatography over a short column using 1:1.5 hexane–EtOAc gave 0.13 (61%) of pure **9a**; $[\alpha]_D^{23}$ +52° ± 3 (*c* 0.7, $CHCl_3$); R_f 0.17; IR (KBr): 3494 (b, νOH),

2953 (CH, aliph.), 1779 (ν_{as}CO of phthalimide group), 1723 (ν_{s}CO of phthalimide and benzoyl groups), 1602 (νC=C, ar). Anal. Calcd for $C_{29}H_{25}NO_{10}$ (547.51): C, 63.61; H, 4.60; N, 2.56. Found: C, 63.82; H, 4.77; N, 2.38.

Phthalimidomethyl 2,3-di-O-acetyl-4,6-di-O-benzoyl-α-D-mannopyranoside (**9b**).—To the dihydroxy compound **9a** (0.095 g, 0.17 mmol) in dry pyridine (2.0 mL), in a 10 mL round-bottom flask and cooled to 0 °C. Ac_2O (1.0 mL) was added. Stirring at rt overnight gave the di-*O*-acetyl derivative (TLC, R_f 0.65). Purification was achieved by column chromatography over silica gel. Elution with 1:9 EtOAc–hexane gave pure **9b** (0.10 g, 91%); $[\alpha]_D^{25}$ +35° ± 2 (*c* 1.0, $CHCl_3$); R_f 0.65; IR (KBr): 1781.2 (ν_{as}CO of phthalimide group), 1753.2 (ν_{s}CO of phthalimide part), 1726.1 (νCO of acetyl and benzoyl groups) and 1602.7 cm^{-1} (C=C, Ar); ^1H NMR ($CDCl_3$): δ 1.87 (s, 3 H, CH_3–CO), 2.15 (s, 3 H, CH_3–CO), 4.32–4.52 (m, 3 H, H-5, H-6, H-6′), 5.21 (d, 1 H, *J* 2.10 Hz, H-1), 5.28 and 5.37 (2d, 2 H, *J* 10.2 Hz, O–CH_2–N), 5.28 (dd, 1 H, *J* 3.3, *J* 1.8 Hz, H-2), 5.56 (dd, 1 H, *J* 10.20, *J* 3.30 Hz, H-3), 5.73 (t, 1 H, *J* 10.1 Hz, H-4), 7.34–7.46 (m, 4 H, meta protons of benzoyl group), 7.49–7.60 (m, 2 H, para protons of benzoyl group), 7.79 (dd, 2 H, *J* 5.4, *J* 3.0 Hz, H-5′, H-6′), 7.93 (dd, 2 H, *J* 5.4, *J* 3.0 Hz, H-4′, H-7′), 8.01 (m, 4 H, ortho protons of benzoyl group). Anal. Calcd for $C_{33}H_{29}NO_{12}$ (631.56): C, 62.75; H, 4.63; N, 2.21. Found: C, 62.71; H, 4.91; N, 2.23.

Hypolipidemic activity tests

Drug administration. The compounds were suspended in 1% carboxymethylcellulose and administered orally in the morning[8] at either 10 or 20 mg/kg per day for 2 week periods to normolipidaemic male Swiss White mice (age about 3 months, body weight 30–32 g) by using an intubation needle. Periodic animal body weights were obtained during the experiment and expressed as a percentage of the animal's weight on day 0.

Lipids analysis. Blood was collected by retro-orbital plexus into EDTA-containing tubes (1 mg/mL, disodium salt), on days 0 and 16, and the plasma was separated by centrifugation at 2500*g* for 10 min at 4 °C. Plasma cholesterol was determined by the CHOD-PAP method, an enzymatic assay[9] for photometric determination, using the enzymes cholesterol esterase, cholesterol oxidase and peroxidase contained in E. Merck test 1.14830.0001 Ecoline 25 reagents (Diagnostica–E. Merck KGaA, Darmstadt, Germany), according to the manufacturer's instructions. Plasma triglycerides (E. Merck test 1.19706.0001 System Multi-Test) were also measured enzymatically (GPO-PAP method)[10] by a combination of the reactions catalyzed by lipase, glycerokinase, glycerol phosphate oxidase and peroxidase.

Statistics. All groups had ten animals and each determination was processed before and after the drug treatment. The results are expressed as mean ± S.D. and we used paired Student-'*t*' test. In all cases, $P < 0.05$ was used as the criterion of statistic significance.

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BI-18 PLASMA HDL-CHOLESTEROL ENRICHMENT UPON TREATMENT WITH *N*-PHTHALIMIDOMETHYL α-D-MANNOPYRANOSIDE AND ITS DERIVATIVES

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Introduction

In our research on the synthesis of monosaccharides, we have been interested in the preparation of novel D-mannose derivatives and recently, we wanted to incorporate phthalimide group in mannose. The reason for such a synthesis is that *N*-substituted phthalimides are biologically active. For example, some phthalimide derivatives are antitumor [1], anticonvulsant [2], and hypolipidaemic [3,4]. The literature does not record a phthalimidoylalkyl moiety as an aglycone in monopyranoside.

Several of the extrahepatic manifestations of liver diseases, are exacerbated by abnormal plasma lipoproteins with altered lipid and apolipoprotein compositions. The abnormal circulating lipoproteins have an adverse effect on the process of reverse cholesterol transport, and following interaction with cell membranes, induce cellular dysfunction either indirectly by altering membrane lipid composition, which modulate cellular ion transport, enzymatic and receptor properties, or directly through apolipoprotein-mediated effects [5]. This paper reports the analysis of the cholesterol content in the high density lipoprotein (HDL-cholesterol) from plasma of mice treated with compounds **a**, **b**, **c**, and **d** (Figure 1).

Experimental methods

- ### Materials

An Electrothermal digital melting point apparatus (model 9100) was used to determine the melting points. Infrared spectra were measured with a Bruker model IFS66 FT-IR spectrophotometer using potassium bromide discs. NMR spectra were recorded with a Varian Unity Plus 300 MHz instrument using $CDCl_3$ as solvent, unless otherwise stated, and tetramethylsilane as an internal standard. Silica gel coated plates with fluorescent indicator (PF_{254}) were used for thin-layer chromatography (TLC) and the spots were revealed under ultraviolet light. The solvent system for running the TLC plates was a mixture of 1:9 ethyl acetate-dichloromethane

- ### Synthesis of phthalimidomethyl α-D-mannopyranoside and its derivatives.

Phthalimide (**a**), phthalimidomethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside(**b**), phthalimidomethyl 4,6-di-*O*-benzoyl-α-D-mannopyranoside (**c**) and phthalimidomethyl 2,3-di-O-acetyl-4,6-di-*O*-benzoyl-α-D-mannopyranoside (**d**) (Figure 1) were synthesized following the method described earlier [6], and their structures were deduced by spectroscopic means.

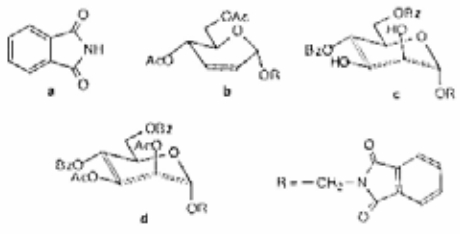

Figure 1: Derivatives of *N*-phthalimidomethyl α-D-mannopyranoside

- **Lipid Analysis**

The compounds were suspended in 1 % carboxymethylcellulose (CMC) and administered orally in the morning [7] at either 10 or 20 mg/kg/day for two-week periods to normolipidaemic male Swiss white mice (body weight 30-32 g). Blood was collected into tubes containing ethylenediaminetetraacetic acid (EDTA 1 mg/mL, disodium salt), on days 0 and 16 and the plasma was separated by centrifugation at 2,500 *x g* for 10 min. Very low density lipoproteins (VLDL) and low density lipoproteins (LDL) in 100 µL of plasma were removed by precipitation with 10 µL of 4% (w/v) natrium phosphotungstate and 2,5 µL of 2M magnesium chloride. The reaction mixture was agitated and centrifuged for 15 min at 3.000 x g and the supernatant, plasma without low density lipoprotein (LDL) and very low density lipoprotein (VLDL), was separated. Plasma cholesterol was determined by the CHOD-PAP method using the enzymes cholesterol esterase, cholesterol oxidase and peroxidase contained in COLESTEROL COD-ANA reagents (enzymatic-trinder), Cat. 60-2/100 (Labtest Diagnostica S.A., Lagoa Santa – MG - Brazil), according to the manufacturer's instructions.

- **Statistics**

All groups had ten animals and each determination was processed before and after the drug treatment. The results are expressed as mean ± S.D. and we used paired Student 't' test. In all cases, $p < 0.05$ was used as the criterion of statistic significance.

Results and discussion

As shown in Figure 2, the plasma HDL-cholesterol for all compounds tested were significantly increased ($p < 0.05$). The groups of mice treated with phthalimide at 20 mg/Kg/day (Figure 2, **a**) increased by 38% the HDL-cholesterol levels. A similar effect was found for phthalimidomethyl 4,6-di-*O*-acetyl-2,3-dideoxy- α-D-erythro-hex-2-enopyranoside (Figure 2, **b**) at 20 mg/Kg/day; plasma HDL-cholesterol was reduced by 39%.. However, phthalimidomethyl 2,3-di-*O*-acetyl-4,6-di-*O*-benzoyl-α-D-mannopyranoside (Figure 2, d) at similar dose (20 mg/Kg/day) increased the plasma HDL-cholesterol only by 27%. Surprisingly, the HDL-cholesterol was increased by 23% in animals treated with phthalimidomethyl 4,6-di-*O*-benzoyl- α-D-mannopyranoside (Figure 2, **c**) at half of the dose (10 mg/Kg/day) used with all the other three drugs. Finally, it is important to report that administration of 1% carboxymethyl-cellulose (Figure 2, CMC) to the animals had no significant changes in mice plasma HDL-cholesterol (3%). There is a growing consensus that elevated levels of HDL-cholesterol have a strong inverse association with the incidence of coronary artery disease [8].

Conclusion

The results show that incorporation of phthalimide group in D-glucal, which resulted in compound **b**, **c** and **d**, was good enough to induce a significantly increased effect in plasma HDL-cholesterol and that might be potential candidate as new hypolipidaemic agents.

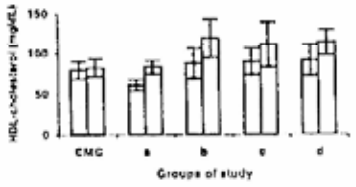

Figure 2 Effect of the compounds CMC, **a**, b, c and **d** on mice plasma HDL-Cholesterol levels. Before ( ) and after ( ) treatment for 16 days.

Acknowledgements

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Article

Synthesis of Cyclohexyl 6-*O*-Trityl-α-D-*Threo*-Hexopyranosid-4-ulo-(2,3:3',4')-2-Pyrazoline

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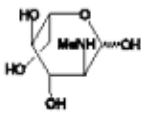
A reação de tri-*O*-acetil-D-glucal (**1**) com cicloexanol (**2**) usando o método de Ferrier forneceu o glicosídeo cicloexílico insaturado **3**, que por sua vez produziu o composto **12** através da seqüência envolvendo hidrólise, tritilação seletiva no oxigênio do C-6, oxidação alílica e cicloadição dipolar 1,3 com diazometano. O produto **17** foi obtido em quatro etapas a partir de **6**. Cálculos semi-empíricos de orbitais moleculares (AM1) para o composto **12** forneceram a conformação estável e também apoiaram a existência do efeito anomérico. Foi feito um esforço para abrir o anel pirazolínico dos compostos **12** e **17**, porém não tivemos sucesso. A carga negativa parcial no C-3 foi responsável pela falta de reatividade deste carbono frente a redução da ligação C=N.

Reaction of tri-*O*-acetyl-D-glucal (**1**) with cyclohexanol (**2**) using Ferrier's method provided the unsaturated cyclohexyl glucoside **3**, which furnished the title compound **12** in a sequence involving hydrolysis, selective tritylation of oxygen at C-6, allylic oxidation with MnO_2 and 1,3-dipolar cycloaddition with diazomethane. Starting from **6**, product **17** was obtained in four steps. Semi-empirical molecular orbital calculations (AM1) were carried out for compound **12** which gave an idea about its stable conformation, and also supported the existence of the anomeric effect. Attempts to open the pyrazoline ring in **12** and **17** failed. Partial negative charge at C-3 was responsible for the lack of reactivity of **12** towards reduction of C=N bond.

Keywords: aminodeoxy sugars, Ferrier's rearrangement, 1,3-dipolar cycloaddition, diazomethane, allylic oxidation

Introduction

The isolation of the antibiotic streptomycin in 1944[1] and the presence of 2-deoxy-2-methylamino-L-glucosamine[2] as one of its components gave an impetus to the study of



amino sugar synthesis. Other antibiotics of this family are kanamycins,[3] neomycins[4] and gentamycins.[5] Many antibiotics composed primarily of carbohydrates have been obtained from microorganisms and are called aminoglycoside antibiotics because they contain amino groups in their glycoside moieties.[6] Prumycin, 4-(D-alanylamino)-2-amino-2,4-dideoxy-L-arabinose, having antitumor activity[7] was synthesized[8] from glycine and L-serine. Another amino sugar derivative has been shown to completely inhibit the derivation of tumor necrosis factor induced by 100 μg/mL *Escherichia coli* endotoxin.[9] 5-Amino-5-deoxy sugars are also known to be glycosidase inhibitors.[10,11]

The importance of amino sugars described above led us to undertake the synthesis of cyclohexyl 3-amino-2-aminomethyl-2,3-dideoxy-α-D-talopyranoside **18** starting from 3,4,6-tri-*O*-acetyl-D-glucal **1**.[12] However, this communication reports the synthesis and characterization of **12** and **17** only.

Experimental

General methods

Melting points were determined with the Thomas Hoover (Unimelt) apparatus and are uncorrected. Elemental

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analyses were carried out at the Instituto de Química, Universidade de São Paulo and in the Department of Fundamental Chemistry of this University. IR spectra were recorded (ν_{max}, cm^{-1}) on a Perkin-Elmer models 467 and 237B spectrophotometers. NMR spectra were measured on a Varian 300 MHz or Bruker 200 MHz instruments in $CDCl_3$ solution unless otherwise stated, and the chemical shifts are reported in parts per million downfield from TMS. Beckmann DB-G or Carl Zeiss-Jena instrument was used for recording the UV spectrum. Specific rotations were obtained on JASCO Model DIP-370 polarimeter. TLC was performed on plates coated with silica gel 60-G (E. Merck). Exposure of the plates to iodine vapors was used to reveal the spots. Silica gel G 70-200 mesh was used for gravitational column chromatography. Anhydrous magnesium sulfate was used to dry the extracts.

Computational method

The semi-empirical molecular orbital calculations (AM1)[13] were carried out using MOPAC 93 program[14,15] on an IBM RISC 6000 computer of this Department. Complete optimization of the geometry was achieved and the gradient norm dropped to 0.02.

*Cyclohexyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-*erythro-*hex-2-enopyranoside (3)*

Tri-*O*-acetyl-D-glucal **1** (5.000 g, 18.38 mmol), cyclohexanol **2** (2.82 g, 28.2 mmol) in dry benzene (50 cm^3) were stirred at room temperature, and boron trifluoride etherate (1 cm^3) was added. The mixture was stirred for 40 min. During this time the solution turned dark brown. TLC ($CHCl_3$-EtOAc 9:1) showed the presence of two spots: R_f = 0.25 (product) and other R_f = 0.18. The latter could either be due to unreacted **1** or to the β-anomer **4**. The mixture was washed with a saturated aqueous solution of sodium bicarbonate (5 x 10 cm^3), water (2 x 10 cm^3), and dried over Na_2SO_4. Filtration and evaporation of the volatiles provided a brown-colored syrup, which was purified by chromatography using hexane-$CHCl_3$ gradient to give **3** as a colorless syrup (3.29 g, 57%); $[\alpha]_D^{25}$ + 111 ± 2° (c 3.3, $CHCl_3$); IR ν_{max}/cm^{-1} 1750 and 1740 (COO) (neat); ^{1}H NMR (200 MHz) δ 5.7-5.9 (m, 2 H, H-2 and H-3), 5.30 (ddd, $^3J_{4,5}$ 9.0 Hz, $^3J_{4,3}$ 1.0 Hz, $^4J_{4,2}$ 1.0 Hz, 1 H, H-4), 5.17 (m, W/2 ≈ 4.5 Hz, 1 H, H-1), 4.1-4.3 (m, 3 H, H-5, H-6 and H-6'), 3.64 (m, 1 H, O-CH), 2.08 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 1.1-2.1 (m, 10 H, 5 CH_2). Elemental analysis: Found: C, 61.66; H, 7.86. Calc. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74.

*Cyclohexyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-*erythro-*hexopyranoside (5)*

Compound **3** (0.05 g, 1.6 mmol) in ethyl acetate (5 cm^3) in the presence of PtO_2 (0.01 g) was hydrogenated at 1 atm. for 12 h at room temperature. Filtration and solvent evaporation yielded **5** as a syrup in almost quantitative yield (one spot on TLC with the same R_f value in $CHCl_3$-EtOAc 9:1 as that of **3**); $[\alpha]_D^{30.5}$ + 100° (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz): δ 4.99 (s,br, W/2 ≈ 4.5 Hz, 1 H, H-1), 4.6-4.8 (m, 1 H, H-4), 4.23 (dd, $^2J_{6,6'}$ 11.7 Hz, $^3J_{6,5}$ 5.6 Hz, 1 H, H-6), 4.10 (dd, $^2J_{6',6}$ 11.7 Hz, $^3J_{6',5}$ 2.3 Hz, 1 H, H-6'), 4.01 (ddd, $^3J_{5,4}$ 10.1 Hz, $^3J_{5,6}$ 5.6 Hz, $^3J_{5,6'}$ 2.3 Hz, 1 H, H-5), 3.56 (m, 1 H, O-CH), 2.08 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 1.2-2.0 (m, 14 H, 7 CH_2). Elemental analysis: Found: C, 61.18; H, 8.42. Calc. for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34.

*Cyclohexyl 2,3-dideoxy-α-D-*erythro-*hex-2-enopyranoside (6)*

A flask containing **3** (3.00 g, 9.62 mmol) in a solution (140 cm^3) of MeOH-H_2O-Et_3N (9:6:1)[16] was kept at room temperature for 1.5h. TLC in $CHCl_3$-AcOEt-CH_3OH (1.0:0.25:0.05) showed the disappearance of the starting material (R_f = 0.75) and the appearance of a new spot with R_f = 0.20. Evaporation and chromatography using $CHCl_3$-hexane (1.0:0.43) gave 1.9g (86.7%) of **6** as hygroscopic crystals: m.p. 67-68°C (from EtOAc-cyclohexane); $[\alpha]_D^{25}$ = + 46.0 ± 0.9° (c 3.4, $CHCl_3$); IR ν_{max}/cm^{-1} 3600-3100 (OH) (Nujol); ^{1}H NMR (300 MHz): δ 5.95 (dt, $^3J_{3,2}$ 10.2 Hz, $^4J_{3,1}$ ≈ 1.3 Hz, $^3J_{3,4}$ ≈ 1.3 Hz, 1 H, H-3), 5.73 (ddd, $^3J_{2,3}$ 10.2 Hz, $^4J_{2,4}$ 2.4 Hz, $^3J_{2,1}$ 2.7 Hz, 1 H, H-2), 5.13 (m, ^3J 1.3 Hz, 1 H, H-1), 4.20 (d,br $^3J_{4,5}$ 9 Hz, 1 H, H-4), 3.85 (d, $^3J_{6,5}$ = $^3J_{6',5}$ 3.9 Hz, 2 H, H-6, H-6'), 3.75 (dt, $^3J_{5,4}$ 9.0 Hz, $^3J_{5,6}$ = $^3J_{5,6'}$ 3.9 Hz, 1 H, H-5), 3.62 (m, 1 H, O-CH), 2.63 and 2.37 (s,br, exchangeable, 2 H, 2 OH), 2.04-1.10 (m, 10 H, 5CH_2). Elemental analysis: Found: C, 61.19; H, 8.57. Calc. for $C_{12}H_{20}O_4$.1/2 H_2O : C, 60.72; H, 8.93.

*Cyclohexyl 2,3-dideoxy-α-D-*erythro-*hexopyranoside (7)*

Compound **6** (0.22 g, 0.93 mmol) in ethanol (20 cm^3) and 5% Pd/C (0.02 g) was hydrogenated at room temperature and at atmospheric pressure for 24 h. TLC in $CHCl_3$-benzene (19.0:1.0) showed a new product with R_f = 0.46. The product was purified by column chromatography using benzene initially followed by benzene-chloroform as gradient. Chloroform-benzene (1:1) eluted product **7** as a viscous liquid (0.10 g, 45% yield): ^{1}H NMR (300 MHz): δ 4.92 (apparent dd, $^3J_{1,2}$ 1.5 Hz, $^3J_{1,2'}$ 3.0 Hz,

1 H, H-1), 3.84-3.71 (m, 2 H), 3.65-3.48 (m, 3 H), 2.69 (bs, s, 2 H, 2 OH), 1.96-1.10 (m, 14 H, 7 CH_2).

*Cyclohexyl 2,3-dideoxy 6-O-trityl-α-D-*erythro-*hex-2-enopyranoside (8)*

Compound **6** (1.00 g, 4.38 mmol) in dry pyridine (5 cm^3) and trityl chloride (1.43 g, 5.13 mmol) were stirred at room temperature under nitrogen for 72 h following the reported procedure.[17] TLC showed only a trace of unreacted **6**. Excess of the trityl chloride was destroyed by putting crushed ice into the flask and letting the contents to warm up to room temperature. The contents of the flask were diluted with $CHCl_3$, transferred to a separatory funnel, washed with a saturated solution of sodium bicarbonate (3 x 5 cm^3), water (2 x 5 cm^3), and finally dried (Na_2SO_4). Solvent removal gave a viscous material which was chromatographed using initially benzene and followed by benzene-$CHCl_3$ (19:1) to give 1.9 g (92.2%) of **8** as a semisolid material; $[\alpha]_D^{25} = +10°$ (c, 1; $CHCl_3$); IR ν_{max}/cm^{-1} 3640-3120 (OH) and 1600 (C = C aromatic) (Nujol); ^{1}H NMR (300 MHz) δ 7.50-7.20 (m, 15 H, Ph-H), 5.89 (ddd, $^3J_{3-2}$ 10.1 Hz, $^4J_{3-1}$ 1,3 Hz, $^3J_{3-4}$ 1.7 Hz, 1 H, H-3), 5.72 (ddd, $^3J_{2-3}$ 10.1 Hz, $^3J_{2-1}$ 2.7 Hz, $^4J_{2-4}$ 2.1 Hz, 1 H, H-2), 5.10 (m, W/2 ≈ 4 Hz, 1 H, H-1), 4.04 (m, 1 H, H-4), 3.90 (ddd, $^3J_{5-6}$ 5.5Hz, $^3J_{5-6'}$ 5.1 Hz, $^3J_{5-4}$ 9.0 Hz, 1 H, H-5), 3.67 (m, 1 H, O-CH), 3.42 (dd, $^2J_{6'-6}$ 9.7 Hz, $^3J_{6'-5}$ 5.1Hz, 1H, H-6'), 3.34 (dd, $^2J_{6-6'}$ 9.7 Hz, $^3J_{6-5}$ 5.5 Hz, 1 H, H-6), 2.30 (s, br,1 H, exchangeable, OH), 2.10-1.00 (m, 10 H, 5 CH_2). Elemental analysis: Found: C, 77,51; H, 7.20. Calc. for $C_{31}H_{34}O_4$ 1/2H_2O: C, 77.63; H, 7.36.

*Cyclohexyl 2,3-dideoxy-α-D-*glycero-*hex-2-enopyranoside-4-ulose (9)*

Compound **6** (1.80 g, 7.90 mmol) was dissolved in dry CH_2Cl_2 (450 cm^3) and freshly prepared activated MnO_2[18] was added (18.50 g, 212.8 mmol). The mixture was stirred at room temperature for 4 hours. TLC ($CHCl_3$) showed a new spot with R_f = 0.59 and the presence of some starting alcohol (R_f = 0.38). The mixture was filtered through diatomaceous earth and the clear filtrate was evaporated to give a semi-solid material. Chromatography using hexane initially followed by hexane-chloroform eluted the fast moving compound to furnish 1.0 g (56%) of **9**: m.p. 99°-100 °C (from ether-petroleum ether); IR ν_{max}/cm^{-1}: 3600-3100 (OH, H bonded), 1690 (C = O conjugated) (KBr); ^{1}H NMR (300 MHz): δ 6.87 (dd, $^3J_{2-3}$ 10.2 Hz, $^3J_{2-1}$ 3.6 Hz, 1 H, H-2), 6.11 (d, $^3J_{3-2}$ 10.2 Hz, 1 H, H-3), 5.17 (d, $^3J_{1-2}$ 3.6 Hz, 1 H, H-1), 4.53 (t, $^3J_{5-6}$ 4.2 Hz, 1 H, H-5), 3.92 (dd, $^2J_{6-6'}$ 11.8 Hz, $^3J_{6-5}$ 4.2 Hz, 1 H, H-6), 4.02 (dd, $^2J_{6'-6}$ 11.8 Hz, $^3J_{6'-5}$ 4.2. Hz, 1 H, H-6'), 3.62-3.80 (m, 1 H, O-CH), 2.22 (s,br, exchangeable, 1 H, OH), 2.20-0.80 (m, 10 H, 5-CH_2). Elemental analysis: Found: C, 63.42; H, 8.07. Calc. for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96.

*Cyclohexyl 2,3-dideoxy-6-O-trityl-α-D-*glycero-*hex-2-enopyranosid-4-ulose (10)*

To a solution of **8** (1.00 g, 2.13 mmol) in CH_2Cl_2 (250 cm^3) was added freshly prepared and dried MnO_2[18] (5.00 g, 57.5 mmol). The mixture was stirred for 4 h. TLC ($CHCl_3$) showed the disappearance of **8**. Filtration and evaporation of the solvent left a viscous material which was chromatographed using a mixture of benzene-$CHCl_3$ (1.0:0.43) to give amorphous **10** (0.72 g, 72.4% yield): IR ν_{max}/cm^{-1} 1695 (C=O conjugated) (KBr); ^{1}H NMR (300 MHz): δ 7.50 - 7.20 (m, 15 H, Ph-H), 6.86 (dd, $^3J_{2-3}$ 10.2 Hz, $^3J_{1-2}$ 3.4 Hz, 1 H, H-2), 6.07 (d, $^3J_{3-2}$ 10.2 Hz,1 H, H-3), 5.49 (d, $^3J_{1-2}$ 3.4 Hz, 1 H, H-1), 4,70 (dd, $^3J_{5-6}$ 7.2 Hz, $^3J_{5-6'}$ 2.4 Hz, 1 H, H-5), 3.86 (m, 1 H, O-CH), 3.63 (dd, $^2J_{6'-6}$ 10.2 Hz, $^3J_{6'-5}$ 2.4 Hz, 1 H, H-6'), 3.44 (dd, $^2J_{6-6'}$ 10.2 Hz, $^3J_{6-5}$ 7.2 Hz, 1 H, H-6), 2.20-1.10 (m, 10 H, 5 CH_2). Compound **10** was also prepared by tritylation of **9** in 86% yield.

*Cyclohexyl 6-O-trityl-α-D-*threo-*hexopyranoside-4-ulo-(2,3,:3',4')-2-pyrazoline (12)*

Compound **10** (0.10 g, 0.21 mmol) was dissolved in ether (5.0 cm^3), and the freshly prepared diazomethane[19] in ether was added dropwise at room temperature until the yellow color persisted.[20] The crystals appeared gradually. Decantation of the ethereal layer provided 0.08 g (70.0%) of the crude product. Recrystallization from a large quantity of hot CH_2Cl_2 gave **12** (0.07g , 61.9%): m.p. 184°-186 °C; $[\alpha]_D^{20}$ -200° (c 0.2, pyridine); IR ν_{max}/cm^{-1} 3322 (NH) and 1660 (C=O) (KBr); ^{1}H NMR (300 MHz, pyridine-d_5) δ 9.92 (s,br, 1 H, N-H, exchangeable), 7.8 – 7.1 (m, 15 H, Ph-H), 5.51 (d, $^3J_{1-2}$ 4.2 Hz, 1 H, H-1), 4.91 (t, $^3J_{5-6}$ $^3J_{5-6'}$ 4.8 Hz, 1 H, H-5), 4.24 (d, ^3J 2.1 Hz, 1 H, H-7'), 4.03 (m, 1 H, O-CH), 3.90 (d, $^3J_{6-5}$ $^3J_{6'-5}$ 4.8 Hz, 2 H, H-6 and H-6'), 3.79 (unresolved, 2 H, H-2, H-7''), 2.2-1.1 (m, 10 H, cyclohexyl). Elemental analysis: Found: C, 74.40; H, 6.68; N, 5.25. Calc. for $C_{32}H_{34}N_2O_4$.1/4H_2O: C, 74.61; H, 6.75; N, 5.43.

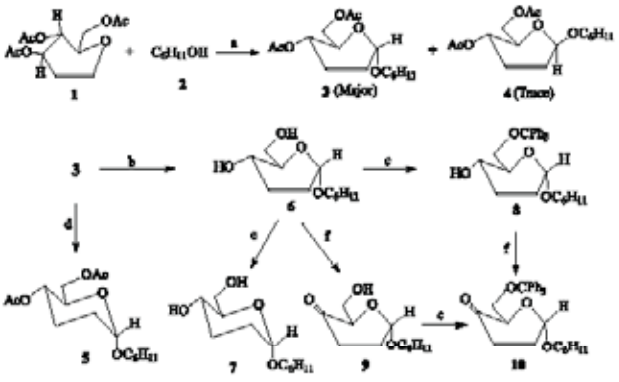
*Cyclohexyl 1'-N-acetyl-4,6-di-O-acetyl-α-D-*lyxo-*hexo-pyranoside-(2,3:3',4')-2-pyrazoline (17)*

Compound **9** (0.27 g, 1.2 mmol) was dissolved in ether (10 cm^3) and to this solution was added diazomethane in ether dropwise at room temperature until the greenish yellow color persisted. TLC (CH_2Cl_2-EtOAc, 9:1) showed

the disappearance of the substrate after 5 min. Solvent evaporation left **15** which was hydrogenated (10 atm) in EtOAc (10 cm^3) at room temperature overnight in the presence of 0.020 g of PtO_2. Filtration and solvent evaporation under vacuum furnished intermediate **16**, which was acetylated and purified by chromatography (hexane-EtOAc 7:3) to give **17** (0.21 g, 45.7%): m.p. 117-118 °C (hexane- ether); ^{1}H NMR (300 MHz): δ 5.85 (d, $^3J_{5,4}$ 5.1 Hz, 1 H, H-4), 4.85 (d, $^3J_{1,2}$ 6.3 Hz, 1 H, H-1), 4.57 (ddd, $^3J_{5,4}$ = $^3J_{5,6}$ 4.3 Hz, $^3J_{5,6'}$ 8.4 Hz, 1 H, H-5), 4.33 (dd, $^3J_{6,5}$ 7.8 Hz, $^2J_{6,6'}$ 12.3 Hz, 1 H, H-6), 4.25-4.10 (m, 3 H, H-6', H-7", OCH), 3.73 (dd, $^3J_{7',2}$ 7.5 Hz, $^2J_{7',7''}$ 12.0 Hz, 1 H, H-7'), 3.28 (quintet, $^3J \approx 6$ Hz, 1 H, H-2), 2.25 and 2.17 (two s, 6 H, OAc), 2.06 (s, 3 H, NAc), 1.90-1.20 (m, 10 H, 5 CH_2). Elemental analysis: Found: C, 57.16; H, 7.37; N, 6.87. Calc. for $C_{19}H_{28}O_7N_2$: C, 57.56; H, 7.12; N, 7.06.

Results and Discussion

Reaction of tri-*O*-acetyl-D-glucal **1** with cyclohexanol **2** and a catalytic quantity of boron trifluoride etherate using the previously reported procedure,[21] provided cyclohexyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **3** as the main product (Scheme 1). The β-anomer which was probably formed as the minor product was inseparable from the unreacted **1** and no effort was made to isolate it. Column chromatography furnished **3** as a thick viscous liquid. Its ^{1}H NMR agreed with the proposed structure but the configuration α became clear only after catalytic reduction of the C-2-C-3 double bond (**3**→**5**). The $J_{1,2}$ coupling constants in the α- and β-2,3-unsaturated hexopyranosyl glycosides are known to be similar.[22] Consequently, evaluation of the anomeric configuration on the basis of these couplings alone is difficult. The 300 MHz ^{1}H NMR spectrum of the reduced

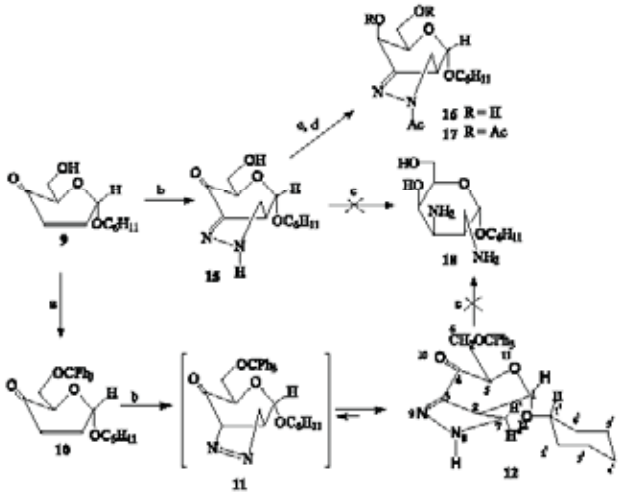


Scheme 1. a) Benzene, BF_3 Et_2O, rt (57%); b) Et_3N, MeOH, H_2O, rt (87%); c) Pyridine, Trityl chloride, rt (92%); d) EtOAc, H_2/PtO_2, rt (99%); e) EtOH, H_2/Pt, rt (45%), f) MnO_2, CH_2Cl_2, rt (56% for compound **9** and 72% for compound **10**)

product **5** showed a signal of the anomeric proton as a broad singlet having a half-width of ca 4.5 Hz. This value together with a coupling constant $J_{4,5}$ 10.1 Hz proves that **5** is an α anomer which adopts $^4C_1$ conformation. Observed couplings are incompatible with the β configuration.

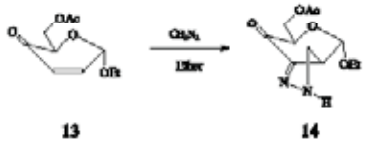
Deacetylation of **3** using triethylamine in methanol[16] gave **6**. Tritylation at the primary OH group[14] furnished **8**, which in turn was subjected to the allylic oxidation at C-4 with activated MnO_2 to give the enone **10**. The same compound was obtained by performing the allylic oxidation first (**6**→**9**) followed by tritylation (**9**→**10**), however the former sequence gave a better yield. Compound **6** was also hydrogenated to give cyclohexyl 2,3-dideoxy-α-D-*erythro*-hexopyranoside **7**.

Addition of diazomethane to C-2-C-3 double bond in **10** occurred from the opposite side of the cyclohexyl function to give a transient product **11** which rapidly tautomerized to **12** (Scheme 2).[20] An alternative approach of CH_2N_2 from the same side is unlikely due to the



Scheme 2. a) Pyridine, trityl chloride, rt; b) CH_2N_2, Et_2O, rt (62% for compound **12**); c) H_2/PtO_2, EtOAc, rt or $NaBH_4$, MeOH, rt; d) Pyridine, Ac_2O, rt (46% from **9**)

bulky aglycon. It has already been shown earlier[20] that much smaller ethoxy group in ethyl 6-*O*-acetyl-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranoside-4-ulose **13** controlled the approach of CH_2N_2 in the same way as in our case to furnish **14** exclusively (Scheme 3). The UV spectrum of **12** (λ_{max} = 325 nm) is similar to that of **14** (λ_{max} = 326 nm).[20]



Scheme 3

Following the procedure described above, compound **9** was treated with diazomethane to give **15**. Attempted reduction of **15** with the hope of obtaining a cyclohexyl 3-amino-2-aminometyl-2,3-dideoxy-α-D-talopyranoside **18** unexpectedly didn't go beyond the reduction of the keto function at the C-4 atom. The pyrazoline ring remained unaltered using either sodium borohydride as a reductant or hydrogenation of **15** in the presence of PtO_2 using different conditions (solvent, temperature, pressure). Compound **16** which invariably resulted in all these reactions was isolated and characterized as its triacetate **17**. Similarly, attempted cleavage of the pyrazoline ring in **12** also failed. The inertness of **12** and **15** towards reducing agents to furnish **18** can be rationalized in terms of the partial charges on the carbon atoms 3 and 4 (Table 2). According to the semi-empirical molecular orbital calculations using AM1 method, C-4 in compound **12** has a charge of +0.2885 e.u. whereas C-3 possesses a charge of -0.2087 e.u. For this reason, a nucleophile (base) can attack C-4 easily, but not C-3 due to the partial negative charge present on it.

The 300 MHz ^{1}H NMR spectrum of **12** (in pyridine-d_5) showed the anomeric proton signal at δ 5.51 ppm (J 4.2 Hz) as a doublet. The coupling constant between H-1 and H-2 suggests a torsion angle of -130°. The semi-empirical calculations provided a value of -131.64° for the same dihedral angle. The protons H-2 and H-7'' form a multiplet at δ 3.79 ppm. Irradiation of the H-1 proton simplified this signal to a four-line pattern. Sharpening of this signal indicated a loss of a small long range coupling between H-1 and H-7''. A doublet at 3.90 ppm (J 4.8 Hz) was ascribed to H-6 and H-6' since irradiation of H-5 at δ 4.92 ppm caused its collapse to a singlet. The fact that H-6 and H-6' form a doublet means that the couplings between H-5 and both H-6 and H-6' are similar and implies that the torsion angles between H-5 and H-6, and H-5 and H-6' to be approximately ca. 50° and ca 130°, respectively. We also carried out a variable temperature experiment and found that at 70 °C, H-5 became a doublet of doublet indicating the nonequivalence of H-6 and H6' due to the slow rotation of the C-5 and C-6 bond. In this situation, the coupling constants between H-6 and H-5 and H-6' and H-5 became 6.30 and 2.70 Hz, respectively. Besides this conformational change no other spectral modification was observed during the variable temperature experiment. Irradiation of the protons at δ 3.79 ppm (H-2 and H-7'') simplified two signals: (a) H-1 became a singlet, and (b) the doublet at 4.24 ppm belonging to H-7' collapsed to a singlet. H-7' resonates at lower field due to the weak anisotropic effect produced by the π orbital of C=N bond. COSY spectrum confirmed the suggested connectivities. The chemical shifts of the other protons are given in the experimental section.

The ^{13}C NMR proton decoupled spectrum (in pyridine-d_5) of compound **12** provided all necessary carbon signals and permitted to assign the chemical shifts of all the carbon atoms. The carbonyl carbon and imine carbon atoms showed signals at δ 190.81 and 142.60 ppm respectively. The anomeric carbon is assigned at δ 100.35 ppm. That the oxygen atom of C-1 is attached equatorially to the cyclohexyl ring can be inferred from the chemical shift of ^{13}C-1', which is at δ 74.9 ppm. This is supported by the published values for cyclohexyl derivatives:[23] a carbon atom linked with an equatorial and axial alkoxy group resonate at ca δ 71 ppm and ca 65 ppm respectively. Five carbon signals appeared between δ 24.2 and 34.1 ppm, respectively. This indicates that C-2' and C-6', C-3' and C-5' carbons are diastereotopic.[24] The chemical shifts of the other carbon atoms of the compound **12** are given in Table 1.

Molecular orbital calculations

The semi-empirical molecular orbital calculations (AM1) of compound **12** gave the expected conformation and relative configurations. The torsion angle (H-1)-(C-1)-(C-2)-(H-2) is -131.64° which clearly shows that the anomeric hydrogen is oriented equatorially. The molecular model shows that five carbon atoms of the pyranose ring are somewhat planar and the ring oxygen atom is above the plane. The other conformation where the anomeric hydrogen and CH_2 group are disposed axially gives the enthalpy of formation 1.69 kcal/mole higher than the first one where the anomeric effect dominates.

The calculations showed that the function O=C–C=N behaves like an α,β-unsaturated ketone. The carbon and nitrogen atoms of C=N bond have the atomic charges of - 0.2087 and 0.0394 e.u. respectively. That this is true can

Table 1. ^{13}C NMR shifts[a] of the compound **12**[b]

C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-1'	C-2' or C-6'	C-3' or C-5'	C-4'	C-5' or C-3'	C-6' or C-2'
100.3	48.7	142.6	190.8	77.5	64.4	55.4	74.9	34.1	24.6	26.0	24.2	31.8

a. Recorded in pyridine-d_5 with TMS as an internal standard.
b. Quaternary carbon of CPh_3 group appeared at 87.4 ppm. There are four phenyl signals at 144.5, 129.2, 128.4, 127.5 ppm.

be seen from the resonance forms given below (Figure 1).

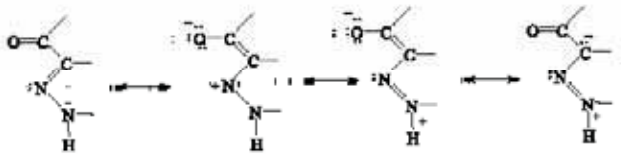


Figure 1. Partial structure of **12** showing the resonance forms of the α,β-unsaturated carbonyl function

The atomic charges, bond lengths, bond angles, and torsion angles of compound **12** are given in Table 2.

The calculations also showed the dihedral angle (H_8)-(N_8)-(C_7)-$(H_{7'})$ as 16.86° and $(H_{7''})$-(C_7)-(N_8)-(H_8) as 103.56°. With this, it is presumed that the inversion of the nitrogen N-8 is slow. The torsion angle (O_{12})-(C_1)-(O_{11})-(C_5) of 75.35° also confirms the pseudoaxial disposition of O-12. The structure of the molecule **12** obtained by the semi-empirical molecular orbital calculations (AM1) is given in Figure 2.

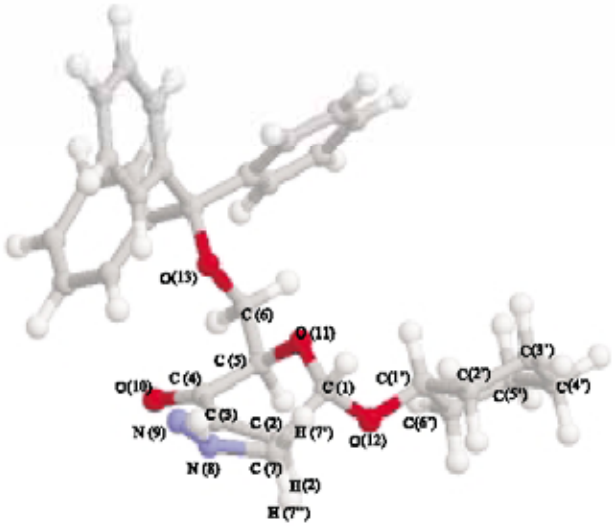


Figure 2. Structure of compound **12** obtained by AM1 calculations

Conclusions

We have achieved the syntheses of **12** (four steps and 32.5% overall yield) and **17** (six steps and 46.0% overall yield) starting from **1**. The structure of **12** has been established with the help of IR and NMR spectroscopies and elemental analyses. Reduction of **12** as well as **15** did not lead to the expected diamino sugar **18**. This difficulty was rationalized in terms of the partial negative charge at C-3, which impedes the approach of the reducing agents. Semi-empirical molecular orbital calculations using AM1 method provided the stable conformation of compound **12** and showed the negative electronic charge at C-3.[25]

Acknowledgements

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Table 2. Atomic charges, bond lengths, bond angles and torsion angles of some selected atoms of compound **12** with cyclohexyloxy group oriented quasiaxially at C-1 obtained by AM1 calculations

Atomic Charge							
C_1	C_2	C_3	C_4	C_7	N_8	N_9	O_{10}
0.1535	-0.1297	-0.2087	0.2885	-0.0998	-0.2415	0.0394	-0.2536
Bond length (Å)							
C_1-O_{12}	C_1-O_{11}	C_2-C_3	C_3=N_9	N_8-C_7	C_4=O_{10}	N_8-N_9	
1.4167	1.4175	1.5282	1.3195	1.4908	1.2294	1.3487	
Bond angles (°)							
C_1 C_2 H_7	C_1 C_2 C_7	C_2 C_3 N_9	C_3 N_9 N_8	C_3 C_4 C_5	C_4 C_3 C_2		
109.34	116.03	113.18	110.4	111.63	117.43		
Torsion angle (°)							
O_{12}-C_1-C_2-H_2	H_2-C_2-C_7-$H_{7'}$	H_2-C_2-C_7-$H_{7''}$	C_2-C_3-C_4-C_5	C_2-C_7-N_8-N_9	H_5-C_5-C_6-H_6	H_5-C_5-C_6-H_6	
-7.11	129.84	7.05	-28.99	-10.24	54.54	125.50	

determining the specific rotations. Our thanks are also due to J. B. P. da Silva, H. C.N. Batista and A. R. de O. Cavalcanti for their assistance in computational work.

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SYNTHESIS OF NEW 2,3-UNSATURATED *O*-GLYCOSIDES THROUGH FERRIER REARRANGEMENT[1]

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ABSTRACT

The synthesis of five new 2,3-unsaturated *O*-glycosides (**3a—e**) employing Ferrier's rearrangement with different catalysts, is reported.

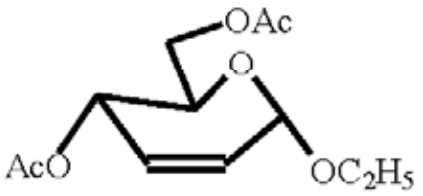
INTRODUCTION

Glycals are key compounds in the synthesis of several groups of natural products[2–4] and 2,3-unsaturated sugars[4,5] and have also been used in electrophilic addition reactions.[6] Similarly 2,3-unsaturated glycosides are very versatile chiral synthetic intermediates,[3] and precursors of 2,3-dideoxy sugars, important structural units in many bioactive natural products such as antibiotics.[7]

The Lewis acid-catalysed rearrangement of glycals in the presence of alcohol, known as the Ferrier reaction,[8] is an important method employed to obtain 2,3-unsaturated glycosides.[9,10] In the present work, the glycosidation reaction of 3,4,6-tri-*O*-acetyl-D-glucal with six alcohols has been examined. The purpose of making these glycosides was twofold: first, these unsaturated glycosides are starting materials for other interesting carbohydrates including aminosugars; second, hydrogenation of the double bond can lead to alkyl 4,6-di-*O*-acetyl-α-D-*erythro*-

APÊNDICE III

ESPECTROS SELECIONADOS



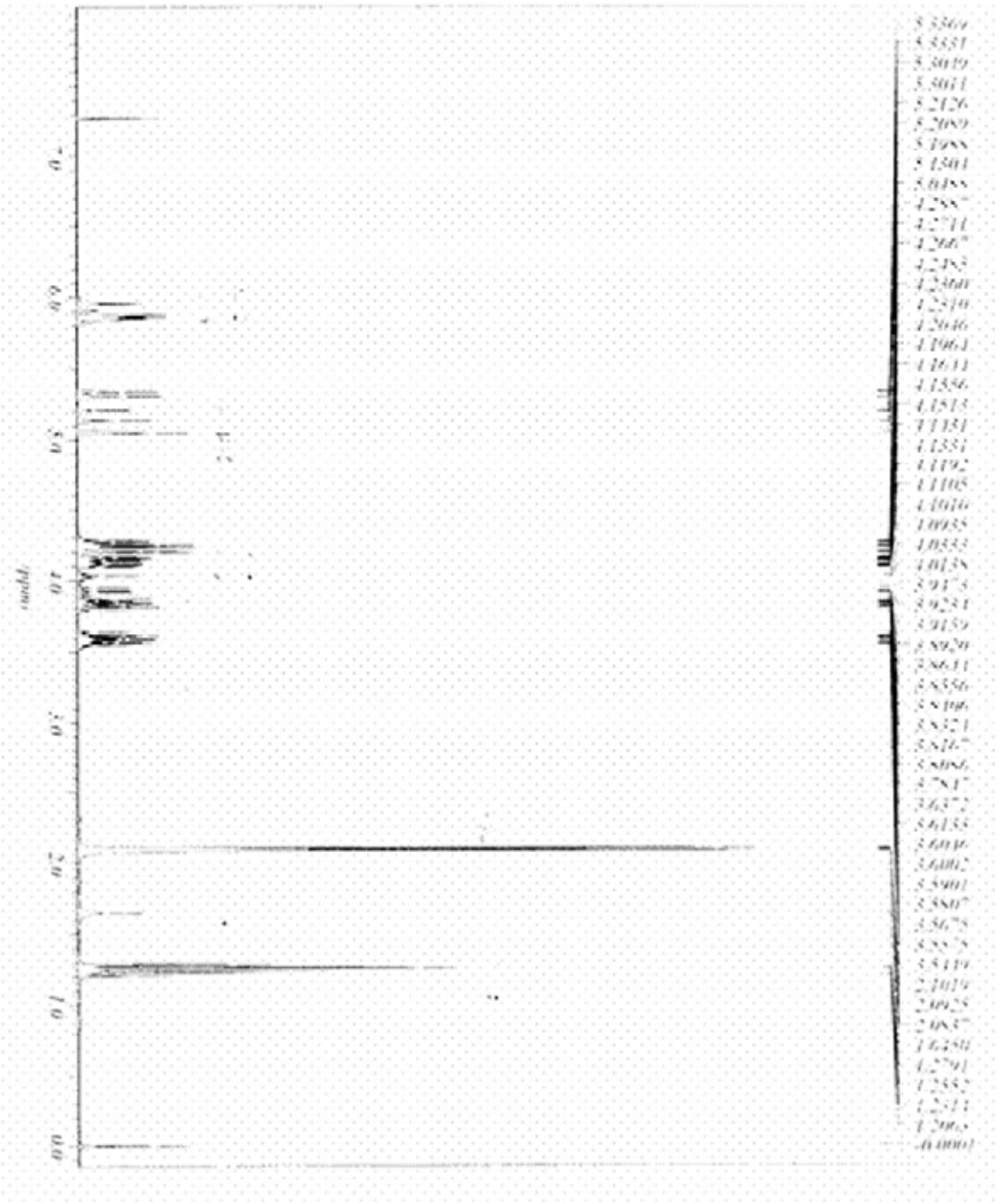
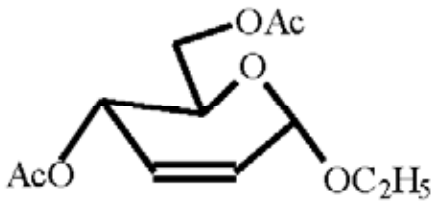


Figura 35: Espectro de RMN ^1H (300 MHz) em $CDCl_3$ do Etil 4,6-di- *O*-Acetil-2,3-didesoxi-α-D-eritro-hex-2-enopiranosídeo (73a)



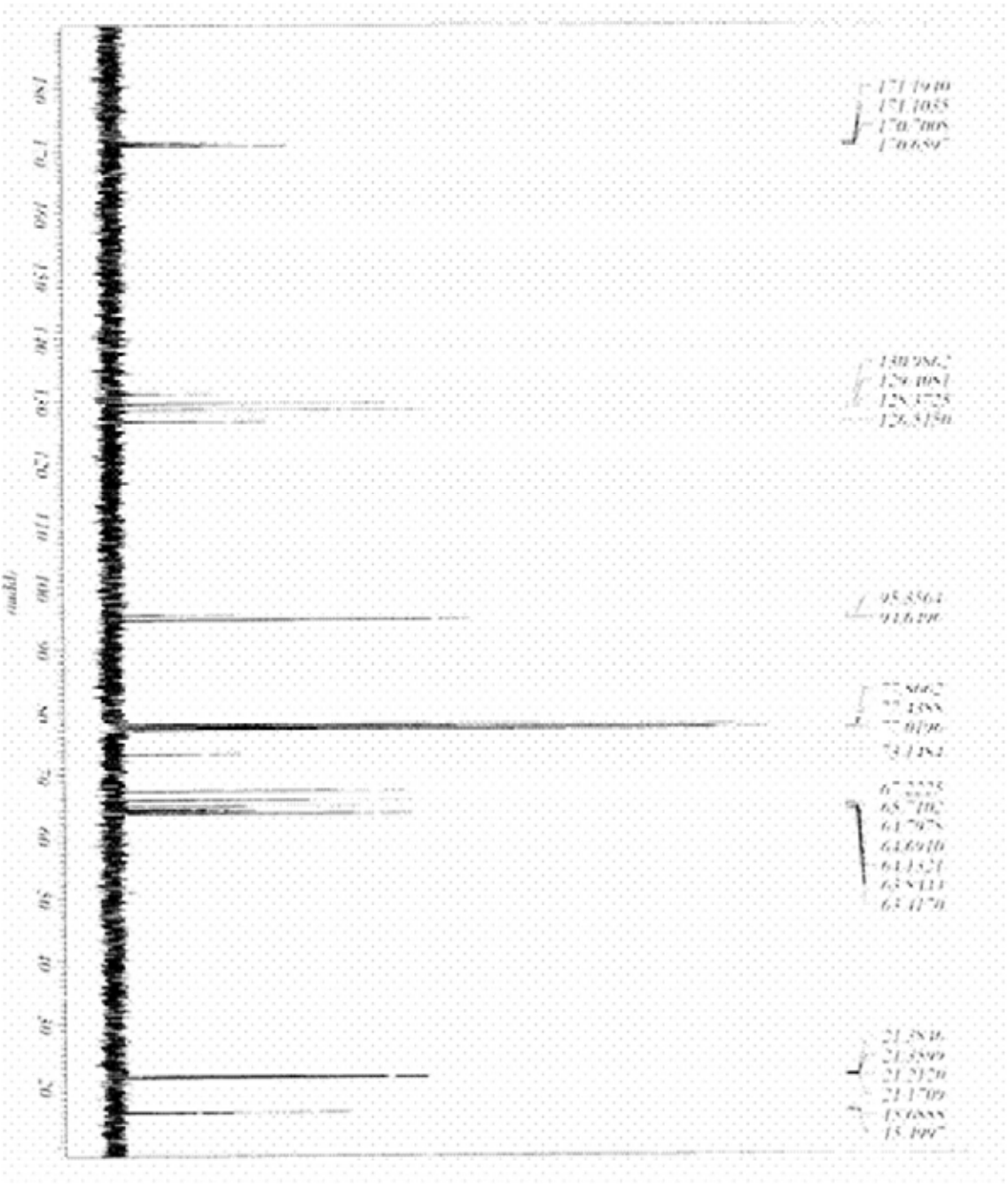
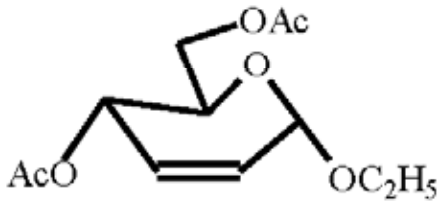


Figura 36: Espectro de RMN ^{13}C (75 MHz) em $CDCl_3$ do Etil 4,6-di- *O*-Acetil-2,3-didesoxi-α-D-eritro-hex-2-enopiranosídeo (73a)



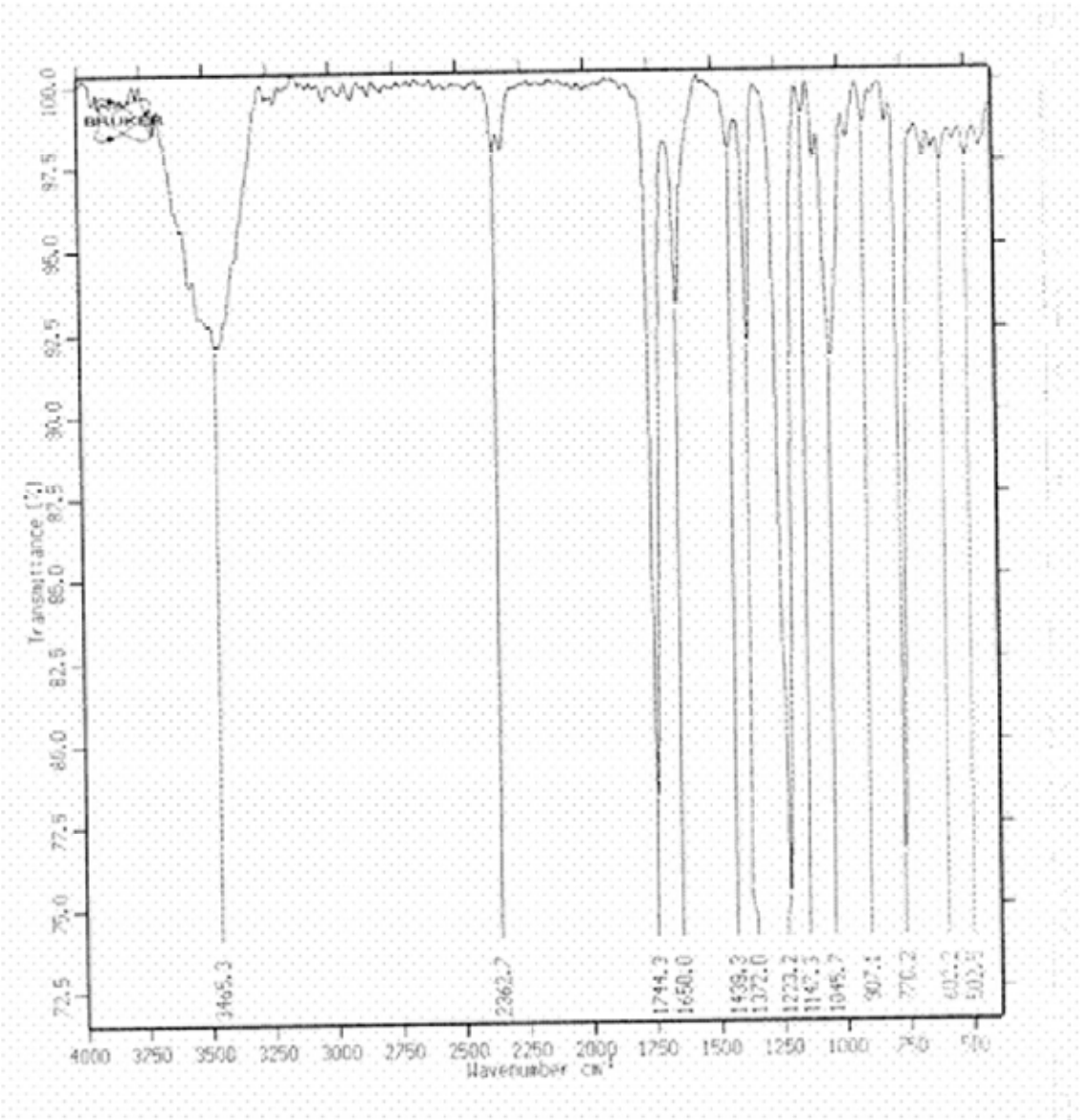
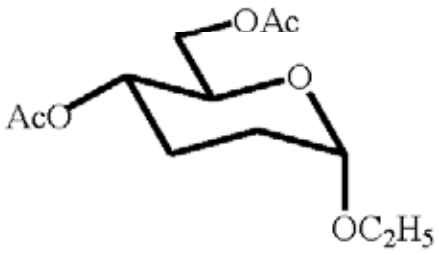


Figura 37: Espectro de Infravermelho do Etil 4,6-di- *O*-Acetil-2,3-didesoxi-α-D-eritro-hex-2-enopiranosídeo (73a)



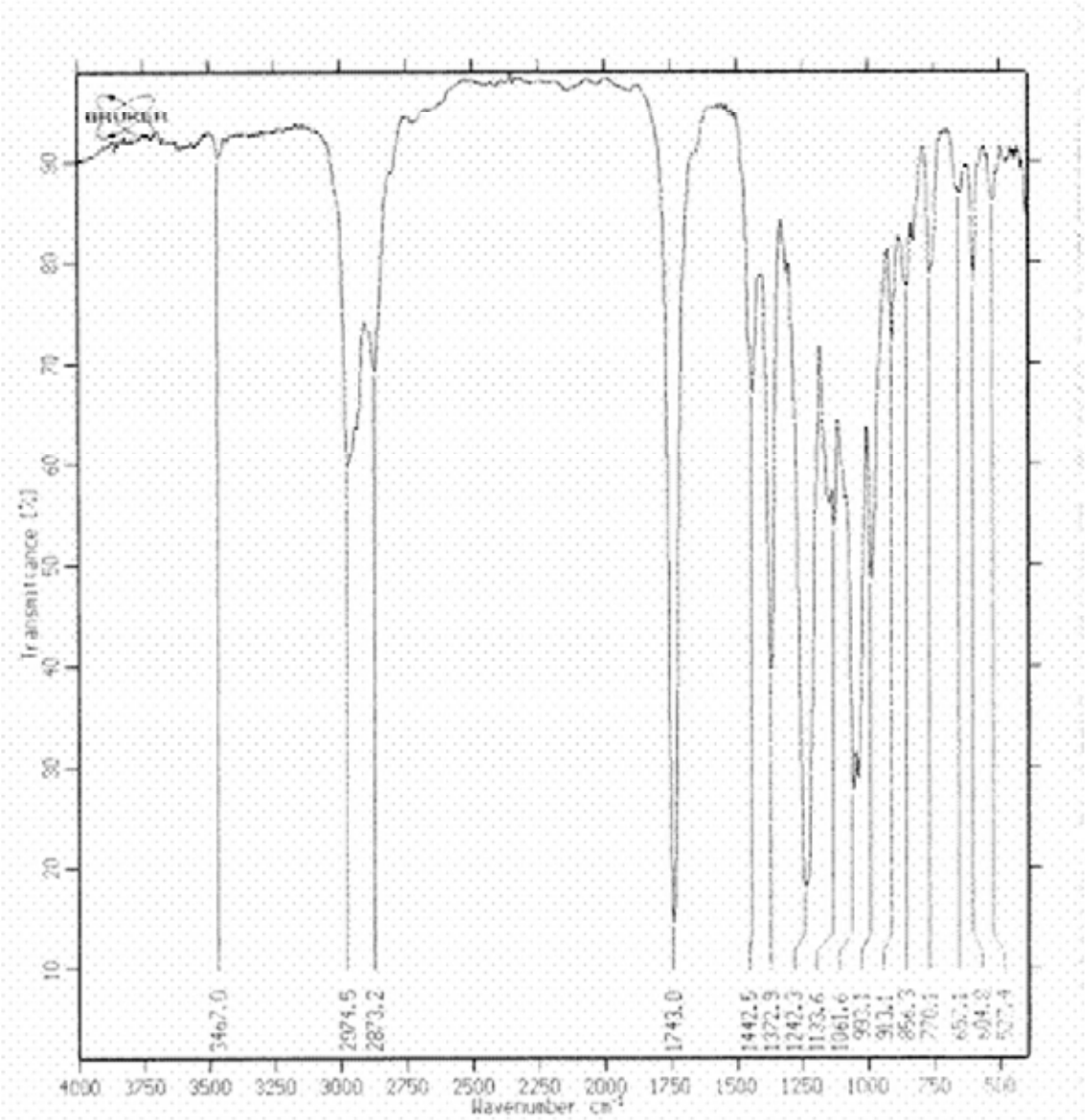
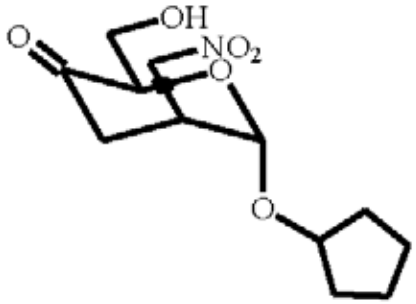


Figura 38: Espectro de Infravermelho do Etil 4,6-di- *O*-Acetil-2,3-didesoxi-α-D-hexopiranosídeo (93a)



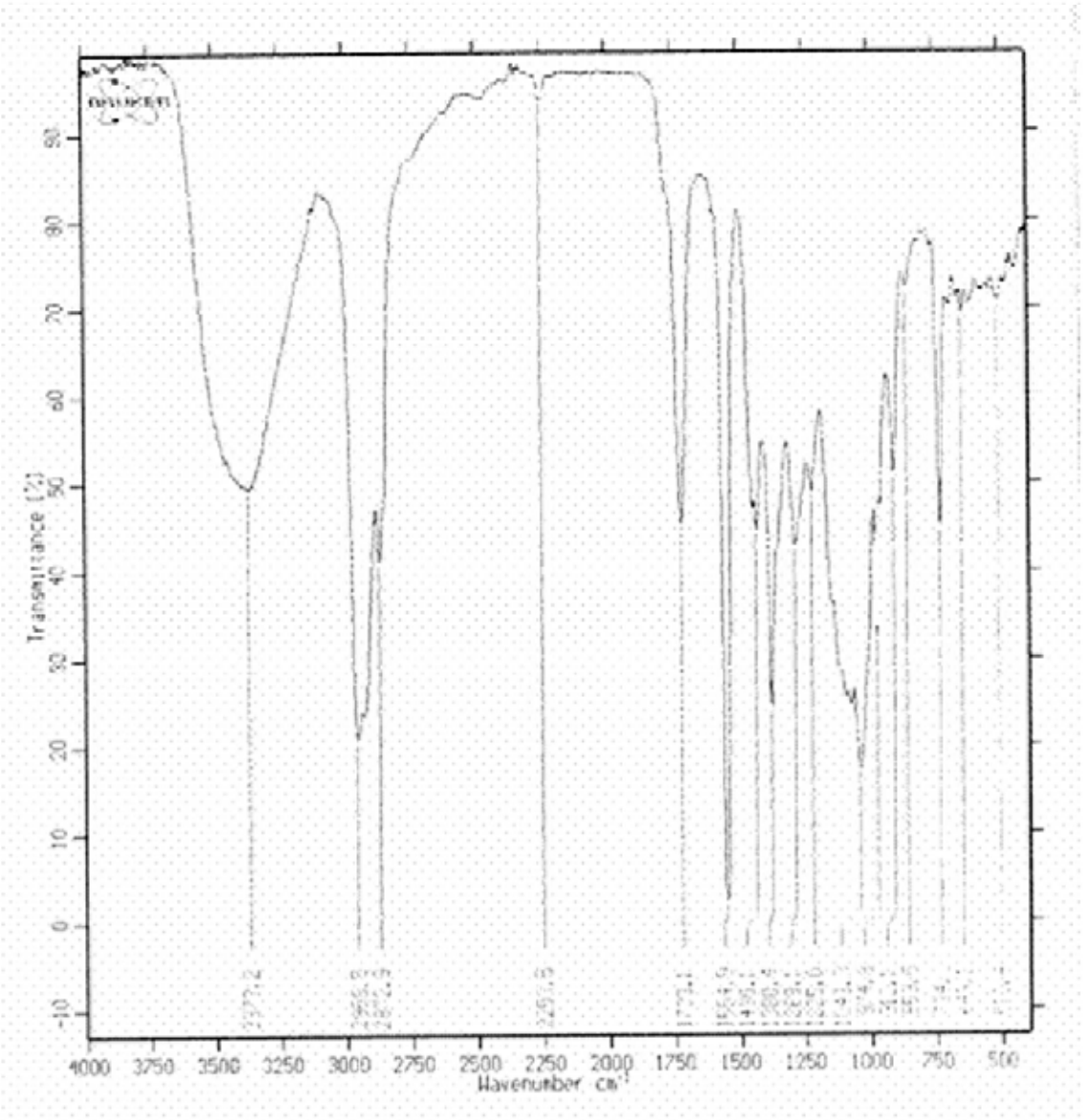
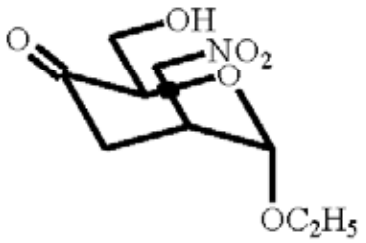


Figura 39: Espectro de Infravermelho do Ciclopentil-2-Nitrometil-2,3-didesoxi-α-D-lixo-hexopiranosid-4-ulose (100d)



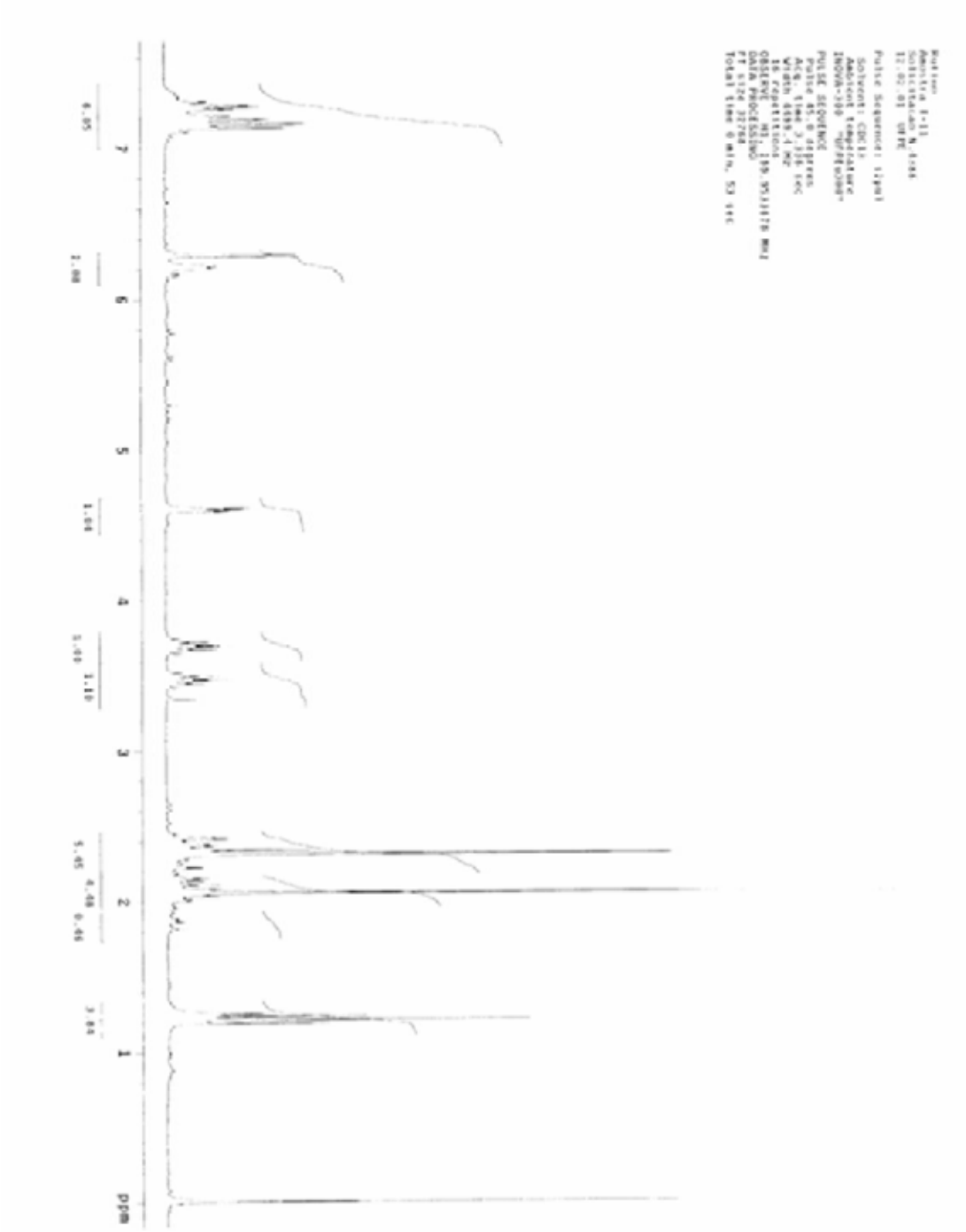


Figura 40: Espectro deRMN ^{1}H (300 MHz) em $CDCl_3$ do Etill-2-Nitrometil-2,3-didesoxi-α-D-*lixo*-hexopiranosid-4-ulose (100a)