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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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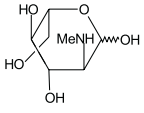
A reação de tri-*O*-acetil-D-glucal (**1**) com cicloexanol (**2**) usando o método de Ferrier forneceu o glicosídeo cicloexílico insaturado **3**, que por sua vez produziu o composto **12** através da seqüência envolvendo hidrólise, tritilação seletiva no oxigênio do C-6, oxidação alílica e cicloadição 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, $^3J_{3\text{-}2}$ 10.1 Hz, $^4J_{3\text{-}1}$ 1,3 Hz, $^3J_{3\text{-}4}$ 1.7 Hz, 1 H, H-3), 5.72 (ddd, $^3J_{2\text{-}3}$ 10.1 Hz, $^3J_{2\text{-}1}$ 2.7 Hz, $^4J_{2\text{-}4}$ 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, $^3J_{5\text{-}6}$ 5.5Hz, $^3J_{5\text{-}6'}$ 5.1 Hz, $^3J_{5\text{-}4}$ 9.0 Hz, 1 H, H-5), 3.67 (m, 1 H, O-CH), 3.42 (dd, $^2J_{6'\text{-}6}$ 9.7 Hz, $^3J_{6'\text{-}5}$ 5.1Hz, 1H, H-6'), 3.34 (dd, $^2J_{6\text{-}6'}$ 9.7 Hz, $^3J_{6\text{-}5}$ 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 $C_{31}H_{34}O_4 \cdot 1/2H_2O$: 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, $^3J_{2\text{-}3}$ 10.2 Hz, $^3J_{2\text{-}1}$ 3.6 Hz, 1 H, H-2), 6.11 (d, $^3J_{3\text{-}2}$ 10.2 Hz, 1 H, H-3), 5.17 (d, $^3J_{1\text{-}2}$ 3.6 Hz, 1 H, H-1), 4.53 (t, $^3J_{5\text{-}6}$ 4.2 Hz, 1 H, H-5), 3.92 (dd, $^2J_{6\text{-}6'}$ 11.8 Hz, $^3J_{6\text{-}5}$ 4.2 Hz, 1 H, H-6), 4.02 (dd, $^2J_{6'\text{-}6}$ 11.8 Hz, $^3J_{6'\text{-}5}$ 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, $^3J_{2\text{-}3}$ 10.2 Hz, $^3J_{1\text{-}2}$ 3.4 Hz, 1 H, H-2), 6.07 (d, $^3J_{3\text{-}2}$ 10.2 Hz,1 H, H-3), 5.49 (d, $^3J_{1\text{-}2}$ 3.4 Hz, 1 H, H-1), 4,70 (dd, $^3J_{5\text{-}6}$ 7.2 Hz, $^3J_{5\text{-}6'}$ 2.4 Hz, 1 H, H-5), 3.86 (m, 1 H, O-CH), 3.63 (dd, $^2J_{6'\text{-}6}$ 10.2 Hz, $^3J_{6'\text{-}5}$ 2.4 Hz, 1 H, H-6'), 3.44 (dd, $^2J_{6\text{-}6'}$ 10.2 Hz, $^3J_{6\text{-}5}$ 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, $^3J_{1\text{-}2}$ 4.2 Hz, 1 H, H-1), 4.91 (t, $^3J_{5\text{-}6}$ $^3J_{5\text{-}6'}$ 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, $^3J_{6\text{-}5}$ $^3J_{6'\text{-}5}$ 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 $C_{32}H_{34}N_2O_4 \cdot {}^1/_4H_2O$: C, 74.61; H, 6.75; N, 5.43.

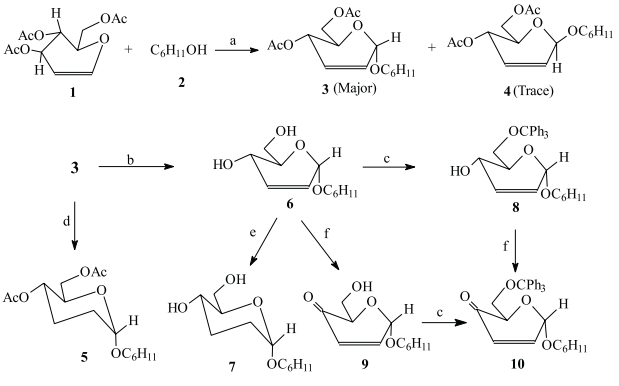
*Cyclohexyl 1'-N-acetyl-4,6-di-O-acetyl-α-D-*lyxo-*hexo-pyranoside-(2,3:3',4')-2-pyrazoline (**17**)*

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, $^3J_{5\text{-}4}$ 5.1 Hz, 1 H, H-4), 4.85 (d, $^3J_{1\text{-}2}$ 6.3 Hz, 1 H, H-1), 4.57 (ddd, $^3J_{5\text{-}4} = {}^3J_{5\text{-}6}$ 4.3 Hz, $^3J_{5\text{-}6'}$ 8.4 Hz, 1 H, H-5), 4.33 (dd, $^3J_{6\text{-}5}$ 7.8 Hz, $^2J_{6\text{-}6'}$ 12.3 Hz, 1 H, H-6), 4.25-4.10 (m, 3 H, H-6', H-7'', OCH), 3.73 (dd, $^3J_{7'\text{-}2}$ 7.5 Hz, $^2J_{7'\text{-}7''}$ 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 $J_{1\text{-}2}$ 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

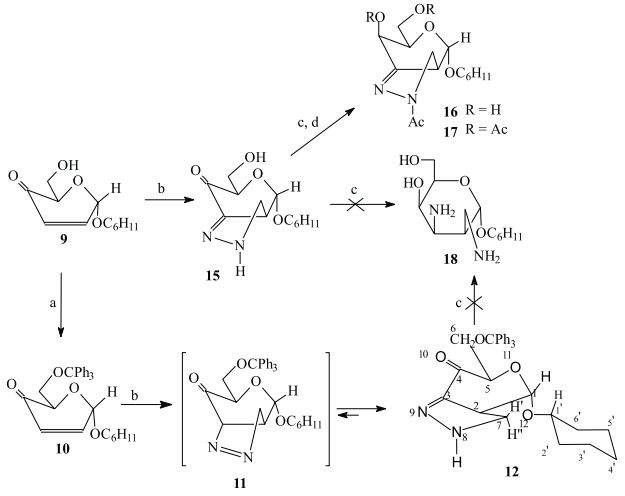


Scheme 1. a) Benzene, $BF_3.Et_2O$, rt (57%); b) Et_3N, MeOH, H_2O, rt (87%); c) Pyridine, Trityl chloride, rt (92%); d) EtOAc, H_2/PtO_2, rt (99%); e) EtOH, H_2/Pt, rt (45%); f) MnO_2, CH_2Cl_2, rt (56% for compound **9** and 72% for compound **10**)

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 $J_{4\text{-}5}$ 10.1 Hz proves that **5** is an α anomer which adopts $^4C_1$ conformation. Observed couplings are incompatible with the β configuration.

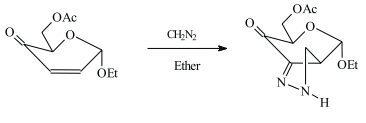
Deacetylation of **3** using triethylamine in methanol[16] gave **6**. Tritylation at the primary OH group[14] furnished **8**, which in turn was subjected to the allylic oxidation at C-4 with activated MnO_2 to give the enone **10**. The same compound was obtained by performing the allylic oxidation 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).

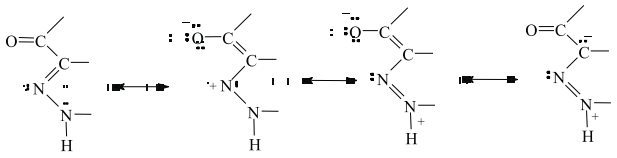


Figure 1. Partial structure of **12** showing the resonance forms of the α,β-unsaturated carbonyl function

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.

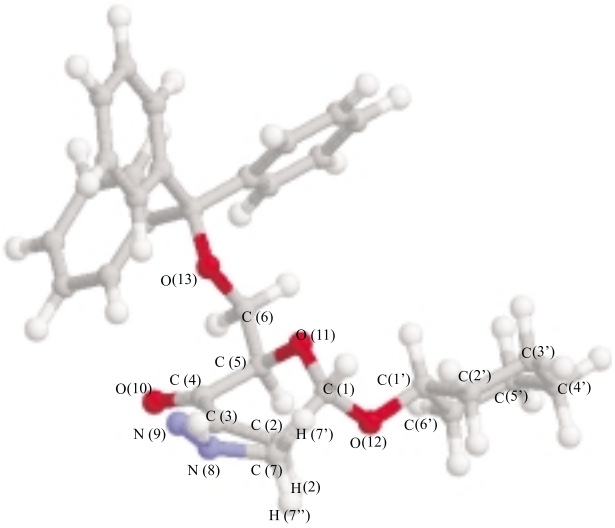


Figure 2. Structure of compound **12** obtained by AM1 calculations

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]

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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_2	**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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