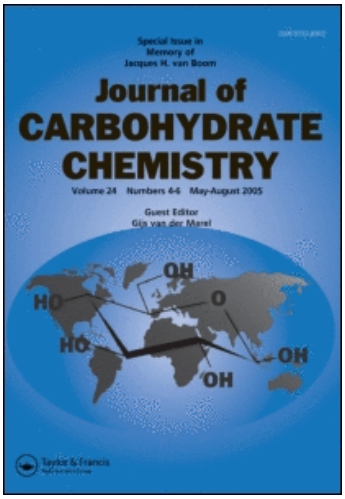

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COMMUNICATION

SYNTHESIS OF 2-CARBAMOYL-2-DEOXY GLYCOSIDES

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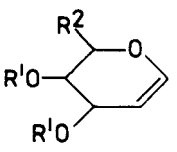
Recently we have reported the addition of trichloracetyl isocyanate to glycals 1.[1,2,3] The reaction led to the highly stereoselective formation of a mixture of unstable [2+2] and [4+2] cycloadducts 2 and 3. The isocyanate adds to the glycal moiety anti to the substituent at C-3. The addition of benzylamine to the reaction mixture led to N-deprotection of 2 and allowed us to isolate stable bicyclic β-lactams 4.[1-3] We have shown also that 2 (a mixture of α-L-gluco and and β-L-manno isomers) obtained from L-rhamnal 1 (R^1=Ac, R^2=CH_3) under high pressure, when treated with methanol, underwent a rapid trans opening of the four-membered ring to give respective glycosides 5 (β-L-gluco and α-L-manno isomers).[4] On the other hand 3 (R^1=Ac, R^2=CH_3) under the same conditions added a molecule of methanol to the C=N double bond affording 6.

Compounds 5 represent a new class of branched monosaccharides which can be utilized in synthesis of selected structures. In addition, the structural relation of 5 to 2-acetamido-2-deoxy sugars offers potential biological activity.

We now report an efficient transformation of the mixture of [2+2] and [4+2] cycloadducts 2 and 3 into carbamoyl glycosides 5.



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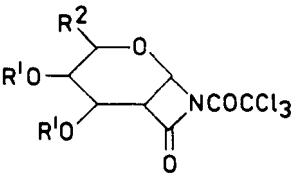

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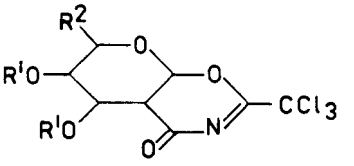

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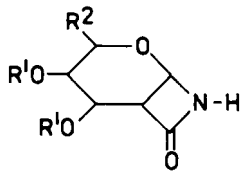

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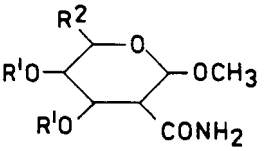

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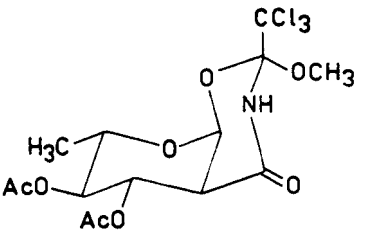

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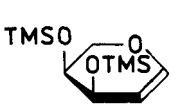
R^1 = Bn , TMS ; R^2 = H , CH_3 , CH_2OR^1

The opening of the β-lactam ring in 2 with alcohol or water proceeded stereospecifically with inversion of configuration of the C-1 carbon atom.[4,5,6] It can be assumed, that the cyclic imidate ring present in 3, when treated with methanol in the presence of an acid catalyst, should also be opened with inversion of configuration at C-1 to produce the same glycoside 5.[7] Hence, cycloaddition of trichloroacetyl isocyanate to glycals 1 followed by methanolysis in the presence of an acid catalyst should give a single product from both intermediates 2 and 3.

As substrates we selected glycals 7, 8 and 9 having labile trimethylsilyl protected hydroxyl groups, and glycals 10 and 11 with benzyl protection. Cycloaddition was performed at room temperature in acetonitrile solution according to the general procedure described before.[1-3] The progress of cycloaddition was monitored with pilot experiments performed in NMR tubes. The mixture of cycloadducts was treated with HCl in methanol to afford methyl glycosides 12, 14, 16, 17, and 18 in 42-74% yield. Glycosides 12, 14, and 18 were contaminated up to 6% with anomers 12, 15, and 19 which were visible in ^{1}H NMR spectra of the crude products. Further purification was achieved by crystallization or chromatographic separation.

Structure of glycosides 12 - 19 were unequivocally proved on the basis of their ^{1}H NMR spectra.



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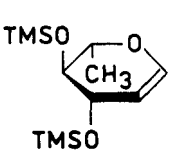

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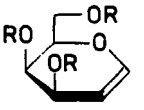
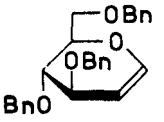


9: R = TMS
10: R = Bn



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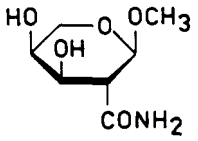

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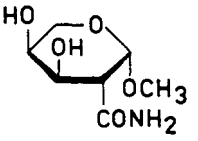

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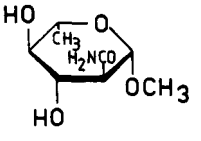

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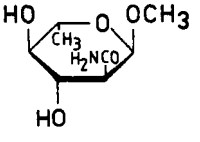

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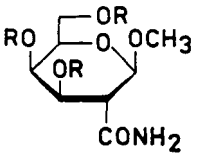
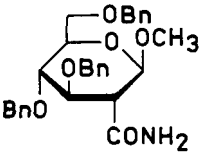


16 : R = H
17 : R = Bn



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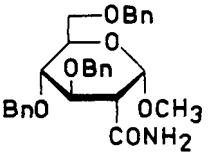

19

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ or D_2O solutions with a Bruker 300 MHz spectrometer (TMS = 0 ppm). IR spectra were obtained on a Unicam SP-200 spectrophotometer. Mass spectra were recorded with a Finnigan Mat 8200 mass spectrometer. Optical rotations were measured with a Perkin-Elmer 141 spectropolarimeter. Melting points are uncorrected. Column chromatography was performed on silica gel Merck (70 - 230 mesh).

General method of preparation of methyl 2-carbamoyl-2-deoxypento- and hexopyranosides. To a solution of glycal (0.01 mol) in dry acetonitrile (8 mL) was added trichloroacetyl isocyanate (0.02 mol) in dry acetonitrile (2 mL). The mixture was left until disappearance of the glycal, the progress of reaction being monitored in an NMR tube according to the procedure described earlier.[1-3] The solvent was evaporated and the residue was dissolved in abs methanol (30 mL). A 1 M solution of HCl in methanol (5 mL) was added, and the reaction mixture

was left overnight at room temperature. The solution was then neutralized with OH^- form ion-exchange resin and concentrated; the glycoside fraction was purified on a silica gel column. Further separation or recrystallization gave pure glycoside.

Methyl 2-Carbamoyl-2-deoxy-α-L-arabinopentopyranoside (12). From 7, 57%: mp 194-196°C; $[\alpha]_D$ +20.7° (c 1, H_2O); IR (KBr) 3400 (OH), 1680 1665, and 1620 cm^{-1} (amide); ^1H NMR (D_2O) δ 2.67(dd, 1H, J_{12} ≈ 8.6, J_{23} ≈ 11.0 Hz, H-2), 3.52 (s, 3H, OCH_3), 3.69 (dd, 1H, J_{45} = 1.2, $J_{5'5'}$ = 13.1 Hz, H-5), 3.90 (m, 1H, H-4), 4.01 (dd, 1H, J_{34} ≈ 3.2 Hz, H-3), 4.02 (dd, 1H, $J_{45'}$ =2.1 Hz, H-5'), 4.99 (d, 1H, H-1). Signals due to β-L-arabino anomer 13 visible in ^1H NMR spectrum of 12 (5%); (D_2O) σ 2.96 (dd, 1H, J_{12} = 3.7, J_{23} = 11.3 Hz, H-2), 3.33 (s, 3H, OCH_3), 3.71 (dd, 1H, J_{45} = 2.0, $J_{5'5'}$ = 12.8 Hz, H-5), 3.89 (d, 1H, H-5'), 3.94 (bs, 1H, H-4), 4.23 (dd, 1H, J_{34} = 3.3 Hz, H-3), 5.02 (d, 1H, H-1).

Anal. (taken for the mixture) Calcd for $C_7H_{13}NO_5$: C, 43.9; H, 6.8 N, 7.3. Found: C, 43.9; H, 7.2; N, 7.1

Methyl 2-Carbamoyl-2,6-dideoxy-β-L-glucohexopyranoside (14). From 8, 60%: mp 180-183°C; $[\alpha]_D$ + 22.2°(c 1, H_2O); IR (KBr) 3400 (OH), 1665, and 1620 cm^{-1} (amide); ^1H NMR (D_2O) σ 1.32 (d, 3H, CH_3), 2.46 (dd, 1H, J_{12} = 8.7, J_{23} = 10.6 Hz, H-2), 3.15 (t, 1H, J_{34} = 9.2 Hz, H-3), 3.50 (s, 3H, OCH_3), 3.52 (m, 1H, H-5), 3.77 (t, 1H, J_{45} = 9.4 Hz, H-4), 4.61 (d, 1H, H-1). Signals due to the α-L-gluco anomer 15 visible in ^1H NMR spectrum of 14 (ca. 6%); (D_2O) δ 1.30 (d, 3H, CH_3), 2.77 (dd, 1H, J_{12} = 3.7, J_{23} = 11.0 Hz, H-2), 3.23 (t, 1H, H-4), 3.35 (s, 3H, OCH_3), 4.02 (t, 1H, J_{34} = 8.8 Hz, H-3); MS m/z (%) 190 (7.8), 173 (2.5), 148 (9.4), 144 (2.7), 130 (5.3), 128 (23.1), 117 (47.8), 116 (14.4), 102 (79.9), 88 (100), 85 (68.5).

Elemental analysis of compound 14 was not consistent. However, acetylation of 14 with acetic anhydride and pyridine afforded the known 3,4-di-O-acetyl derivative.[4]

Methyl 2-Carbamoyl-2-deoxy-β-L-galactohexopyranoside (16). From 9, 58%: mp 201-203°C; $[\alpha]_D$ + 3.0° (c 1, H_2O); IR (KBr) 3420(OH), 1670, and 1625cm^{-1} (amide); ^1H NMR (D_2O) δ 2.64 (dd, 1H, J_{12} = 8.7, J_{23} = 11.1 Hz, H-2), 3.54 (s, 3H, OCH_3), 3.69 (dd, 1H, J_{56} = 4.5, $J_{66'}$ = 7.7 Hz, H-6), 3.75-3.94 (m, 3H, H-4,5,6'), 3.99 (dd, J_{34} = 3.2 Hz, H-3), 4.56 (d, 1H, H-1).

Anal. Calcd for $C_8H_{15}NO_6$: C, 43.4; H, 6.8; N, 6.3. Found: C, 43.5, H, 7.1; N, 6.4.

Methyl 3,4,6-Tri-O-benzyl-2-carbamoyl-2-deoxy-β-L-galactohexopyranoside (17). From 10, 42%: mp 175-180°C; $[\alpha]_D$ -17.5° (c 1, $CHCl_3$); IR (KBr) 3400, 3200 (NH_2), 1690, 1675, and 1650 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 2.76 (dd, 1H, J_{12} ▫ 8.5, J_{23} ▫ 10.6 Hz, H-2), 3.42 (s, 3H, OCH_3), 3.45-3.65 (m, 3H, H-5,6,6'), 3.75-3.95 (m, 2H, H-3,4), 4.3-4.9 (m, 6H, benzyl), 4.44 (d, 1H, H-1), 5.42, 5.65 (2bs, 2H, NH_2), 7.1-7.4 (m, 15H, benzyl).

Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.8; H, 6.7; N, 2.8. Found: C,70.3; H, 6.6; N, 3.0.

Methyl 3,4,6-Tri-O-benzyl-2-carbamoyl-2-deoxy-β-L-glucohexopyranoside (18). From 11, 74%: mp 164-166°C; $[\alpha]_D$ -21.0° (c 1, $CHCl_3$); IR (KBr) 3400, 3200 (NH_2), 1660, and 1640 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 2.46 (dd, 1H, J_{12} = 8.4, J_{23} = 10.6 Hz, H-2), 3.51 (m, 1H, H-5), 3.52 (s, 3H, OCH_3), 3.64 (t, 1H, J_{34} = 8.9, J_{45} = 9.7 Hz, H-4), 4.06 (dd, 1H, H-3), 4.53 (d, 1H, H-1), 4.5-4.9(m, 6H, benzyl), 5.48, 5.70 (2bs, 2H, NH_2), 7.1-7.5 (m, 15H, benzyl).

Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.8; H, 6.7; N, 2.8. Found: C, 71.0; H, 6.7; N, 2.9.

The α-L-anomer 19 was isolated by chromatography using hexane-ethyl ether-methanol 1:1:0.04 as solvent, 6%: mp 191-193°C; $[\alpha]_D$ + 94.0° (c 1, $CHCl_3$); IR (KBr) 3400, 3200 (NH_2), 1675, and 1620 cm^{-1} (amide): ^1H NMR ($CDCl_3$) δ 2.78 (dd, 1H, J_{12} = 3.0, J_{23} ▫ 11.1 Hz, H-2), 3.40 (s, 3H, OCH_3), 3.64-3.88 (m, 4H, H-4,5,6,6'), 4.19 (dd, 1H, J_{34} = 8.9 Hz, H-3), 4.48-4.90 (m, 6H, benzyl), 5.00 (d, 1H, H-1), 7.1-7.4 (m, 15H, benzyl).

Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.8; H, 6.7; N, 2.8. Found: 70.8; H, 6.7; N, 3.0.

ACKNOWLEDGMENT

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