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Preliminary communication

Novel aminocyclitol antibiotics derived from natural carbohydrates

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Recently considerable effort has been devoted to synthesize amino-monocarba-disaccharides [1], since numerous pseudodisaccharide-type aminocyclitol antibiotics (e.g., fortimycins, sporaricins, sannamycins, etc.), carrying one or more amino groups in either the cyclitol or the sugar portion, have been shown [2] to possess significant antibacterial activity. In addition, structurally similar compounds act as glycosidase enzyme inhibitors [1] and certain aminoglycosyl-inositol phosphates are considered [3] as insulin mimetics. The present communication reports the preparation of novel pseudodisaccharide-type aminocyclitol antibiotics from natural sugars, including D-arabinose, D-glucosamine, and 3-amino-2,3,6-trideoxy-L-hexoses [4], by the direct glycosylation of a functionalized cyclitol, or by means of the Ferrier carbocyclic ring-transformation [5] of a reducing disaccharide.

The aglycons (2*S*,3*R*,5*R*)-2,3-dibenzoyloxy-5-hydroxycyclohexanone (**1**) and the corresponding 3-azido analogue **2**, employed for the glycosylations, were prepared by means of the mercury salt-mediated Ferrier carbocyclization of the respective methyl hex-5-enopyranosides [6,7]. Since glycosylation of inososes **1** and **2** with different donors and under various conditions led to extensive β-elimination of the C-5 hydroxyl group, their carbonyl function was protected by treatment with 1,2-ethanedithiol (CH_2Cl_2–$BF_3 \cdot Et_2O$) to afford the dithiolane derivatives **3** (82%; mp 131–132°C, $[\alpha]_D$ −43.3°) and **4** (86%; $[\alpha]_D$ +21.6°). From the azidocyclohexanone **2**, the *O*-benzyloxime **5** (mp 89–90°C, $[\alpha]_D$ −81°) was also prepared in 76% yield.

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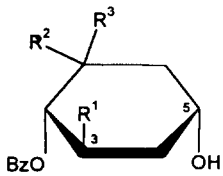
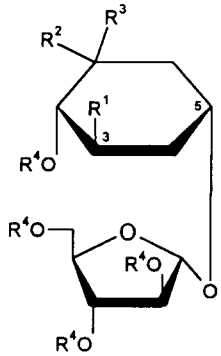
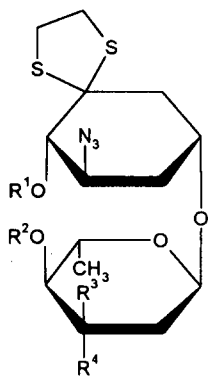
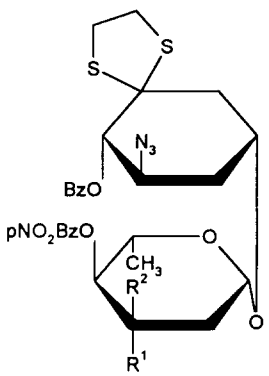




1 R^1=OBz; R^2,R^3=O
2 R^1=N_3; R^2,R^3=O
3 R^1=OBz; R^2,R^3=$S(CH_2)_2S$
4 R^1=N_3; R^2,R^3=$S(CH_2)_2S$
5 R^1=N_3; R^2,R^3=NOBn

6 R^1=OBz; R^2,R^3=$S(CH_2)_2S$; R^4=Bz
7 R^1=N_3; R^2,R^3=$S(CH_2)_2S$; R^4=Bz
8 R^1=N_3; R^2,R^3=$S(CH_2)_2S$; R^4=H
9 R^1=N_3; R^2,R^3=NOBn; R^4=Bz
10 R^1=N_3; R^2,R^3=NOBn; R^4=H
11 R^1=NH_2; R^2=R^3=R^4=H
12 R^1=OH; R^2=R^3=R^4=H





13 R^1=Bz; R^2=pNO_2Bz; R^3=H; R^4=N_3
14 R^1=Bz; R^2=pNO_2Bz; R^3=N_3; R^4=H
15 R^1=R^2=R^3=H; R^4=N_3
16 R^1=R^2=R^4=H; R^3=N_3

17 R^1=N_3; R^2=H
18 R^1=H; R^2=N_3

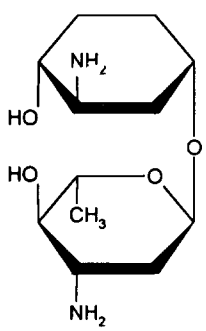
Glycosylation of the protected inososes **3**, **4**, and **5** with 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide [8] under Helferich conditions (CH_2Cl_2, $HgBr_2$, 4 Å molecular sieves) readily furnished the pseudodisaccharides **6** (82%, mp 141–142°C, $[\alpha]_D$ −5.14°), **7** (75%, $[\alpha]_D$ +3.4°), and **9** (78%, $[\alpha]_D$ −55.5°), respectively, as indicated

by the $\Delta\delta$ 10–12 ^{13}C NMR downfield glycosylation shift of the C-5 carbon in the spectra of the products. The α-glycosidic structure of **6**, **7**, and **9** was unequivocally demonstrated by the ^{13}C NMR chemical shift values observed for the anomeric carbon (C-1′) of the arabinofuranosyl moiety (δ 104.62, 104.04, and 104.07, respectively). Formation of the corresponding β anomer could not be detected in any of the three cases.

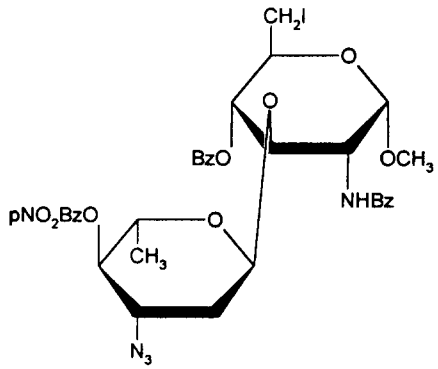
For the synthesis of novel pseudodisaccharide-type antibiotic models carrying 3-azido(amino)-2,3,6-trideoxy-L-hexose sugar portions the 3-azido-dithiolane ester **4** was coupled, separately, with 3-azido-2,3,6-trideoxy-1,4-di-*O*-(*p*-nitrobenzoyl)-L-*arabino*- and -*ribo*-hexopyranose [9] in the presence of trimethylsilyl triflate as promoter (CH_2Cl_2; 4 Å molecular sieves). In both cases a ca. 10:1 mixture of the α- (**13** and **14**) and β-pseudodisaccharides (**17** and **18**) was produced (74% and 68%), and except for **18** all of the glycosides could be readily isolated in pure form by column chromatography. Based on the IR and NMR spectral data, the functional groups of both the glycosyl donors and the aglycon portion remained unchanged during glycosylation, which occurred at the C-5 hydroxyl group of **2** (^{13}C NMR downfield glycosylation shifts: $\Delta\delta$ 1.6, 5.61, and 3.52, respectively, for **13**, **17**, and **14**). In the ^{13}C NMR spectra of the pseudodisaccharides **13** ($[\alpha]_D$ +19.1°) and **14** ($[\alpha]_D$ +92.3°), the C-1′ anomeric carbon of the sugar portion appeared at δ 95.36 and 96.00, respectively, characteristic of an α-interglycosidic linkage. For the β-glycoside **17** ($[\alpha]_D$ +47.4°) C-1′ was assigned at δ 97.84. The α-glycosidic structure of **13** and **14** was further supported by the ^1H NMR data [**13**: $\delta_{H\text{-}1'}$ 5.24 (dd), $J_{1',2'a}$ 3.5, $J_{1',2'e}$ 1.5 Hz; **14**: $\delta_{H\text{-}1'}$ 5.04 (dd), $J_{1',2'a}$ 3.5, $J_{1',2'e}$ 2.0 Hz]. In the ^1H NMR spectrum of **17** the H-1′ proton resonated at δ 4.98 (dd), and the values of the $J_{1',2'a}$ and $J_{1',2'e}$ coupling constants (9.5 and 2.5 Hz, respectively) indicated the β-configuration of the glycosidic linkage.

Treatment of **7**, **9**, **13**, and **14** with $NaOCH_3$ in methanol afforded the *O*-deacylated pseudodisaccharides **8** ($[\alpha]_D$ +95°), **10** ($[\alpha]_D$ +16.8°), **15** ($[\alpha]_D$ +86.2°), and **16** ($[\alpha]_D$ +143.6°) in nearly quantitative yield. Then catalytic hydrogenation of the azido compounds **8** and **15** (Raney nickel in methanol) led to the target; the unique new pseudodisaccharide-type aminocyclitol antibiotic models **11** (51.6%, $[\alpha]_D$ +106.8°) and **19** (62.5%, $[\alpha]_D$ +88.7°). Similar *O*-deacylation and reduction of **6** gave rise to the glycoside **12** ($[\alpha]_D$ +84.5°), isolated in modest yield (40%), probably due to strong adsorption on the catalyst surface.

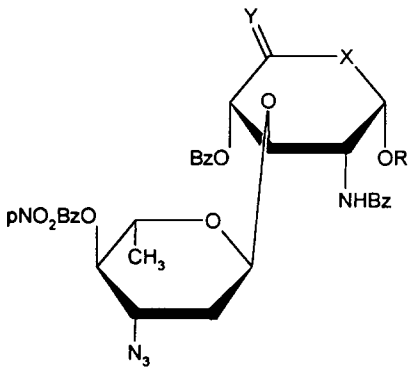
An alternative approach to aminocyclitols structurally related to **19** was based on the Ferrier carbocyclization of the reducing unit of an appropriately functionalized disaccharide. Accordingly, the α-glycoside **20**, composed of D-glucosamine and a 3-azido-trideoxyhexose, was synthesized by glycosylation (CH_2Cl_2, trimethysilyl triflate, 4 Å molecular sieves) of methyl 2-benzamido-4-*O*-benzoyl-2,6-dideoxy-6-iodo-α-D-glucopyranoside with 3-azido-2,3,6-trideoxy-1,4-di-*O*-(*p*-nitrobenzoyl)-L-*arabino*-hexopyranose [9] {**20** had mp 182–184°C, $[\alpha]_D$ −30°, characteristic ^1H NMR data: δ 5.34 (dd, 1 H, $J_{1',2'a}$ 3.5,$J_{1',2'e}$ 1.5 Hz, H-1′), 4.85 (d, 1 H,$J_{1,2}$ 3.5 Hz, H-1), 4.30 (dd, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3)}. Treatment of **20** with silver fluoride in dry pyridine gave 85% of the C-5 *exo*-methylene compound **21** (mp 132–134°C). The $HgCl_2$-mediated carbocyclization of **21** (acetone–water, reflux) readily furnished the new, (1′ → 3)-linked glycosylinososе (2*S*,3*R*,4*S*,5*S*)-3-[3′-azido-2′,3′,6′-trideoxy-4′-*O*-(*p*-nitrobenzoyl)-α-L-



19



20



21 R=CH_3; X=O; Y=CH_2
22 R=H; X=CH_2; Y=O

arabino-hexopyranosyloxy]-4-benzamido-2-benzoyloxy-5-hydroxycyclohexanone (**22**) with 69% yield {mp 233–234°C, $[\alpha]_D$ +42°, ^{13}C NMR data: δ 200.4 (C-1), 166.9, 164.9 and 163.9 (3 ester C = O), 99.7 (C-1′), 80.0 (C-3), 77.5 (C-2), 76.3 (C-4′), 69.9 (C-5), 66.4 (C-5′), 58.7 (C-3′), 54.1 (C-4), 45.0 (C-6), 35.9 (C-2′), 17.4 (CH_3-5′)}. The successful conversion **21** → **22** extends the scope of the Ferrier carbocyclization, proceeding under slightly acidic conditions [7,10], by demonstrating that it can also be readily executed with acid-sensitive saccharides such as the 2-deoxy α-linked disaccharide **21**.

In preliminary in vitro antibacterial tests on the most important Gram-positive and Gram-negative organisms neither of the prepared new cyclitol/aminocyclitol antibiotic models possessed remarkable biological activity.

Acknowledgements

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