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# SYNTHESIS OF NON-REDUCING DISACCHARIDES. NEW ANALOGUES OF TREHALOSAMINE CONSTRUCTED FROM ACOSAMINE AND RISTOSAMINE

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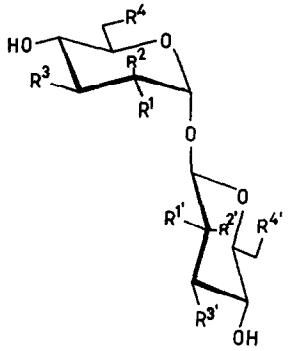
**Abstract** Novel non-reducing disaccharides (**27-31**) synthesized from L-acosamine and L-ristosamine are reported.

In the past decades the syntheses of numerous aminodeoxy analogues[1-7] (**2-6**) of α,α-trehalose (**1**), exhibiting weak antibacterial[2-7] or immunoadjuvant[8] properties, were published. However, the construction of the structurally related, non-reducing disaccharides from L-sugars remained relatively less studied.[9] In view of the demonstrated essential role of oligosaccharides and aminodeoxy sugars in immunological[10] and cell recognition[11] processes and in consideration of their capability of influencing the activity of human natural killer cells[12], the present paper is concerned with syntheses of trehalosamine analogues from the known trideoxyamino sugars, L-acosamine and L-ristosamine.[13]

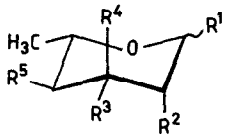
The starting monosaccharides **8** and **9**, prepared[14-16] from L-rhamnose (**7**), were subjected to mild acid hydrolysis to afford **10** and **11**, whose conversions into the glycosyl chlorides **14** and **15** were effected *via* the respective glycosyl esters **12** and **13**.

The symmetric disaccharide **16** with α,α-interglycosidic linkage was first prepared from the L-*arabino* sugar **10** by treatment with the strong Lewis-acid promoter triflic anhydride[17] (in $CH_2Cl_2$, -70 °C → +20 °C, 40 min, yield 54%); surprisingly, the L-*ribo* sugar **11** gave no disaccharide under analogous conditions.

When the glycosyl acceptor **10** was allowed to react with the glycosyl donor **12** in the presence of silver triflate promoter[18] and tetramethylurea ($CH_2Cl_2$, 20 °C, 4 hrs), a 1.5 : 1 : 1.5 mixture of the α,α-**16**, β,β-**17** and α,β-**18** L-*arabino* disaccharides was obtained. On the other hand, the analogous reactions of **11** and **13** (with L-*ribo* configuration) gave rise exclusively to a 1 : 1 mixture (65 %) of β,β-**19** and α,β-**20**; the formation of the protected L-*ribo* disaccharide **21** having α,α-interglycosidic linkage was not detected in either case.



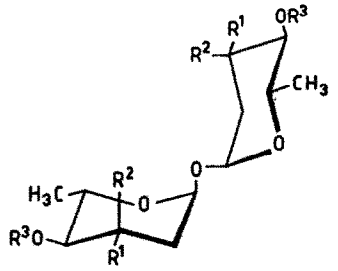
**1** $R^1=R^3=R^4=R^{1'}=R^{4'}=OH$, $R^2=R^{2'}=H$
**2** $R^1=NH_2$, $R^3=R^4=R^{1'}=R^{3'}=R^{4'}=OH$, $R^2=R^{2'}=H$
**3** $R^1=R^{1'}=H$, $R^2=R^{2'}=R^{3'}=R^4=R^{4'}=OH$, $R^3=NH_2$
**4** $R^1=R^3=R^{1'}=R^{3'}=R^{4'}=OH$, $R^4=NH_2$, $R^2=R^{2'}=H$
**5** $R^1=R^3=R^{1'}=R^{3'}=OH$, $R^4=R^{4'}=NH_2$, $R^2=R^{2'}=H$
**6** $R^1=R^{1'}=NHAc$, $R^2=R^{2'}=H$, $R^4=R^{4'}=R^{3'}=OAc$,
$R^3=$ -O-CH(Me)-C(=O)-L-Ala-D-isoGlu-OH



**7** $R^1=R^2=R^3=R^5=OH$, $R^4=H$,
**8** $R^1=OMe$, $R^2=R^4=H$, $R^3=N_3$, $R^5=pNO_2Bz$-
**9** $R^1=OMe$, $R^2=R^3=H$, $R^4=N_3$, $R^5=pNO_2Bz$-
**10** $R^1=OH$, $R^2=R^4=H$, $R^3=N_3$, $R^5=pNO_2Bz$-
**11** $R^1=OH$, $R^2=R^3=H$, $R^4=N_3$, $R^5=pNO_2Bz$-
**12** $R^1=R^5=pNO_2Bz$-, $R^2=R^4=H$, $R^3=N_3$
**13** $R^1=R^5=pNO_2Bz$-, $R^2=R^3=H$, $R^4=N_3$
**14** $R^1=Cl$, $R^2=R^4=H$, $R^3=N_3$, $R^5=pNO_2Bz$-
**15** $R^1=Cl$, $R^2=R^3=H$, $R^4=N_3$, $R^5=pNO_2Bz$-

Previously we have successfully employed the "glycal-procedure" for the synthesis[19] of the L-ristosamine-containing reducing α-interglycosidic heterodisaccharide *avobiose*. Based on these experiences, a related strategy has been utilized for the construction of the target disaccharides from the glycals **32** and **33**, both derived[20] from **7**. Although glycosylation of **10** with **32** in the presence of trimethylsilyl triflate promoter and tetramethylurea ($CH_2Cl_2$, -40 °C → +20 °C, 48 hrs) readily afforded the L-*arabino* α,α-disaccharide **34**, in 51 % yield, the analogous coupling of **11** and **33** in the L-*ribo* series gave exclusively the β,β-interglycosidic compound **35** (42 %).

The experimental fact that all the three formerly used methods failed in synthesizing the non-reducing α,α-L-*ribo*-disaccharides **21** or **36**, certainly calls for an explanation. It is believed that the unfavourable 1,3-*trans-axial* steric effect (due to the presence of the bulky azido and trifluoroacetamido substituents at C-3 in **11**, **15** and **33**), inhibits the formation of an α,α-interglycosidic bond, such as required in **21** and **36**. Moreover, certain intramolecular electronic interactions should also be considered exerting an influence on the formation of the glycosidic linkage[21].

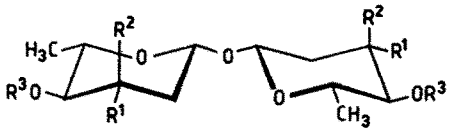


**16** $R^1=N_3$, $R^2=H$, $R^3=pNO_2Bz-$

**21** $R^1=H$, $R^2=N_3$, $R^3=pNO_2Bz-$

**22** $R^1=N_3$, $R^2=R^3=H$

**27** $R^1=NH_2$, $R^2=R^3=H$



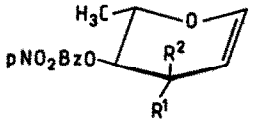
**17** $R^1=N_3$, $R^2=H$, $R^3=pNO_2Bz-$

**19** $R^1=H$, $R^2=N_3$, $R^3=pNO_2Bz-$

**23** $R^1=N_3$, $R^2=R^3=H$

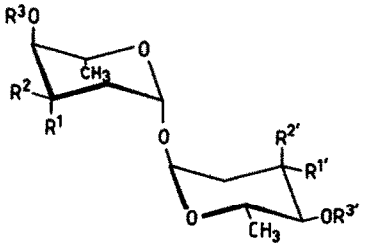
**25** $R^1=R^3=H$, $R^2=N_3$

**28** $R^1=NH_2$, $R^2=R^3=H$

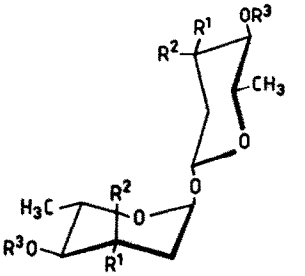


**32** $R^1=NHCOCF_3$, $R^2=H$

**33** $R^1=H$, $R^2=NHCOCF_3$



**35** $R^1=R^{1'}=H$, $R^2=NHCOCF_3$,
$R^3=R^{3'}=pNO_2Bz-$, $R^{2'}=N_3$



**18** $R^1=N_3$, $R^2=H$ $R^3=pNO_2Bz-$

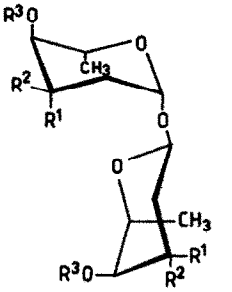
**20** $R^1=H$, $R^2=N_3$, $R^3=pNO_2Bz-$

**24** $R^1=N_3$, $R^2=R^3=H$

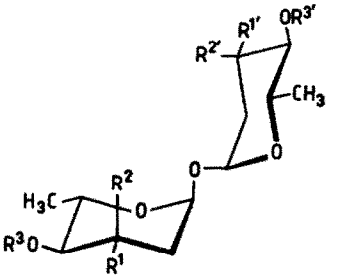
**26** $R^1=R^3=H$, $R^2=N_3$

**29** $R^1=NH_2$, $R^2=R^3=H$

**31** $R^1=R^3=H$ $R^2=NH_2$



**30** $R^1=R^3=H$, $R^2=NH_2$



**34** $R^1=NHCOCF_3$, $R^{1'}=N_3$,
$R^2=R^{2'}=H$, $R^3=R^{3'}=pNO_2Bz-$

**36** $R^2=NHCOCF_3$, $R^{2'}=N_3$,
$R^1=R^{1'}=H$, $R^3=R^{3'}=pNO_2Bz-$

O-Deacylation of **16-20** (NaOMe/MeOH, 40 °C, 1 h) gave rise to the azidodisaccharides **22-26**, which upon catalytic hydrogenation (PdC/MeOH, 20 °C, 1 at.) were transformed into the target aminodisaccharides **27-31**[22] in nearly quantitative yields. Of these compounds the α,α-(**27**) and α,β-L-*arabino* (**29**), and α,β-L-*ribo* (**31**) disaccharides exhibit remarkably high negative specific optical rotation values in aqueous solutions, whereas the L-*arabino* (**28**) and L-*ribo* (**30**) β,β-disaccharides (and the intermediates of their synthesis) had positive rotation values.[23]

For assignments of the $^{1}H$- and $^{13}C$-NMR spectra of the synthesized disaccharides 2D homo[24-26] and heteronuclear[27,28] methods were applied. Based on the relatively large values (~9 Hz) of the $J_{3,4}$ and $J_{4,5}$ coupling constants, most of the target molecules (**27-29** and **31**) were shown[29] to assume the $^{1}C_4$-$^{1}C_4$ conformation in the solvents applied. However, exceptions were observed for the symmetric **30** and asymmetric **35** (both with β,β-linkage) where the 3-5 Hz values of $J_{1,2}$ and $J_{4,5}$ indicate the presence of equilibria shifted towards the $^{4}C_1$-$^{4}C_1$ and $^{4}C_1$-$^{1}C_4$ conformation, respectively.

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21. An interaction between the positively charged glycosyl cation (produced from the glycosyl chloride **15** on the action of silver triflate) and the lone-pair of the nitrogen atom of the C-3 *axial* azido group can be considered. Owing to this effect, attack of the glycosyl acceptor at the opposite side of the pyranosyl ring is possible. Such an effect is excluded in the case of **14** carrying an *equatorially* oriented C-3 azido group.
22. For each new compound satisfactory elemental analyses were obtained.
23. Physical data for the target aminodisaccharides: **27**: mp=212 °C, [α]=-140 (c=0,2 $H_2O$); **28**: mp=222 °C, [α]=+25 (c=0,2 $H_2O$); **29**: mp=196 °C, [α]=-48 (c=0,5 $H_2O$); **30**: mp=186 °C, [α]=+50 (c=1.0 $H_2O$); **31**: mp=199 °C, [α]=-79 (c=0,5 $H_2O$).
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29. Selected $^1$H-NMR data (in $D_2O$, 200 MHz, 298 K): **27**: δ: H-1=5.15, H-2ax=1.66, H-2eq=2.06, H-3=3.08, H-4=2.98, H-5=3.7, H-6=1.24 (ppm), *J*1eq,2ax=2.5, *J*1eq,2eq=0, *J*4ax,5ax=9.0 (Hz); **28**: δ: H-1=5.03, H-2ax=1.40, H-2eq=2.12, H-3=2.81, H-4=2.91, H-5=3.44, H-6=1.26 (ppm), **29**: δ: H-1(α)=5.18, H-1(β)=4.85, H-2ax(α)=1.63, H-2ax(β)=1.44, H-2eq(α)=2.08, H-2eq(β)=2.18, H-3(α)/H-4(α)=2.97-3.05*, H-3(β)/H-4(β)=2.82-2.93*, H-5(α)=3.86, H-5(β)=3.44, H-6(α)=1.23,

H-6(β)=1.28 (ppm), *J*1eq,2ax(α)=3.5, *J*1eq,2eq(α)=0, *J*4ax,5ax(α)=9.5, *J*1eq,2ax(β)=10, *J*1eq,2eq(β)=2.5, *J*4ax,5ax(β)=9.5 (Hz); **30**: δ: H-1=5.35, H-2ax=2.21, H-2eq=1.97, H-3=3.89, H-4=3.81, H-5=4.01, H-6=1.33 (ppm), *J*1eq,2ax=3.0, *J*1eq,2eq=5.0, *J*4eq,5eq=5.0 (Hz); **31**: δ: H-1(α)=5.18, H-1(β)=5.05, H-2ax(α)/H-2eq(α)=2.05-2.15*, H-2ax(β)/H-2eq(β)= 1.81-2.17*, H-3(α)=3.6, H-3(β)=3.57, H-4(α)=3.63, H-4(β)=3.50, H-5(α)=4.04, H-5(β)=3.84, H-6(α)=1.25, H-6(β)=1.29 (ppm), *J*1eq,2ax(α)=3.0, *J*1eq,2eq(α)=3.0, *J*4ax,5ax(α)=9.0, *J*1ax,2ax(β)=9.0, *J*1ax,2eq(β)=2.5, *J*4ax,5ax(β)=9.0 (Hz)

*: Data are interchangeable.