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Syntheses of Spacer-linked Neodisaccharides Derived from L-Daunosamine

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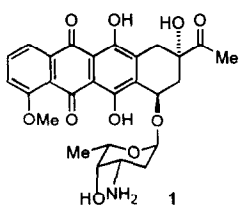
Abstract: The preparation of novel head-to-head spacer-linked bisdaunosamine homodimers **8**, **15** and **18** is described. The synthesis is achieved by double glycosylation of monosilylated 1,4-butanediol **9** using silyl glycoside **5** as glycosyl donor. Alternatively, olefin metathesis of allyl glycosides α-**11** and particularly of α-**12** constitutes a second route toward **8** and its unsaturated derivative **15** while non symmetrical dimer **18** has been obtained by cross metathesis of allyl glycosides **11** and **12**.

Because of their key roles in biological processes, a considerable amount of attention has recently focused on DNA and RNA as a prime target for small molecules and ligands. The binding of small molecules to specific polynucleotide targets can influence the biological activity of DNA or RNA by preventing the binding of biologically relevant macromolecules like regulatory proteins, by inhibiting DNA duplication or RNA catalysis, or by forcing an alternative conformation, particularly in the case of RNA.[1,2] It has been shown that various synthetic polycationic ligands have the ability to selectively interact with RNA by a groove-binding mode. Importantly, many natural products, which contain aminodeoxy sugars as well as chemically designed drugs with antitumor and antibiotic activity target oligonucleotides. Examples are the anthracycline antibiotic daunomycin (**1**) and the amino glycoside kanamycin A (**2**). Recent studies revealed that multivalent linker-modified dimers derived from **2** also recognize RNA with enhanced binding along with improved ribozyme inhibitory activity.[1b,3] Therefore, it is reasonable to assume that the search for specific RNA-binding molecules can lead to new therapeutic agents.



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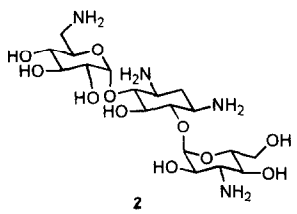

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We reckoned that linear, 1,4-butanediol-linked neooligosaccharides[4] derived from daunosamine, the aminosugar present in **1**, should serve as multivalent probes for studying amino sugar/polynucleotide recognition. In this paper we describe two synthetic routes toward these new neooligosaccharides. The first strategy uses partially protected 1,4-butanediol **9** in a conventional glycosylation reaction whereas the second alternative utilizes olefine metathesis[5] as a method to dimerize allyl protected daunosamine building blocks.

Methyl glycoside **3**[6] was one of the starting monomeric building blocks for the preparation of head-to-head homodimer **8**. The sequence was initiated with the blocking of the 3-amino group by using the 4-nitro-

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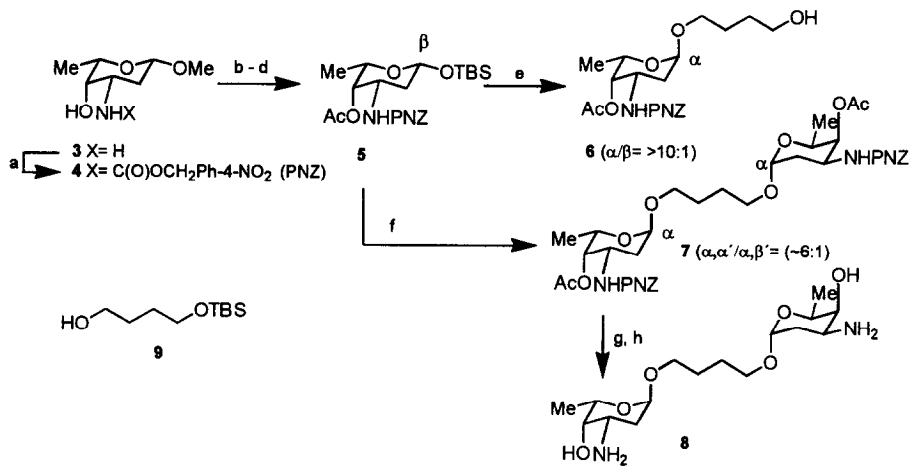
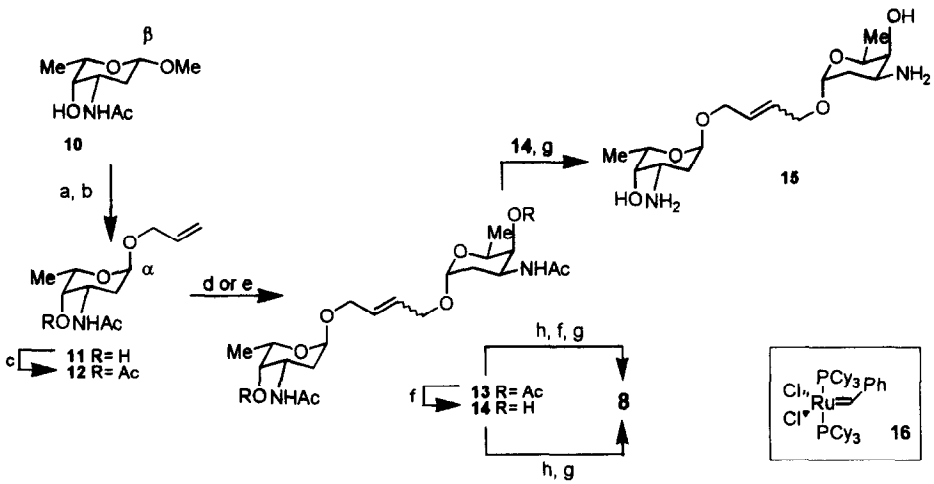
benzyloxycarbonyl group (PNZ), which was first introduced to carbohydrate chemistry by Qian and Hindsgaul.[7] It can reductively be removed under neutral conditions.[8] Functional group manipulations on **4** with three well established reactions[9] afforded silyl glycosides **5** (β/α= >15 : 1), convenient glycosyl donors which were separated by column chromatography.[10] This allowed introduction of the spacer by use of monosilylated 1,4-butanediol **9**.[11] When equimolar amounts of both reactants were coupled with each other, glycoside **6** was isolated as the major product along with traces of homodimers **7** indicating that the spacer-bound silyl group is removed during the course of glycosylation. Therefore, it was reasonable to prepare dimers **7** in one step by changing the molar ratio for **5** and **9**. As expected, for the C_2-symmetric homodimer α,α′-**7**, only half of the set of signals for all protons as well as carbon atoms in the ^{1}H NMR and ^{13}C NMR spectra are visible. Further evidence for a 2 to 1 ratio of sugar and linker was gained from proton integration and mass spectrometry.[12] Deacylation and reductive removal of the PNZ group afforded the target molecule **8**. Efforts to desymmetrize homodimer α,α′-**7** by monodeacylation under basic conditions were only successful in part.



Scheme 1: Reagents and conditons (a) 4-$NO_2PhCH_2OC(O)Cl$ (1 equiv.), NEt_3 (1 equiv.), CH_2Cl_2, 0°C, 2 h (83 %); (b) 5 % HCl, THF/ H_2O (3:2), 75°C, 1 h; (c) ^{t}BuMe$_2$SiCl, imidazole, CH_2Cl_2, 5°C, 15h; (d) Ac_2O, 4-DMAP, CH_2Cl_2, rt, 2 h (78 % for three steps); (e) **5** (1 equiv.), TMSOTf (0.4 equiv.), CH_2Cl_2, -70°C, 15 min, then addition of **9** (2 equiv.), -70 °C→-30°C, 2 h, →5°C, 8 h [44% and **7** (14 %)]; (f) **5** (1 equiv.), TMSOTf (2 equiv.), CH_2Cl_2, -78°C, 15 min, then addition of **9** (1.0 equiv.), -78°C→-15°C, 12 h, [69 % and **6** (19 %)]; (g) NaOMe, MeOH, CH_2Cl_2 (3:1), rt, 17 h; (h) $Na_2S_2O_4$ (8 equiv.), CH_3CN, EtOH, H_2O (3 : 2 : 2), 15 min, 0°C (68 % for two steps).

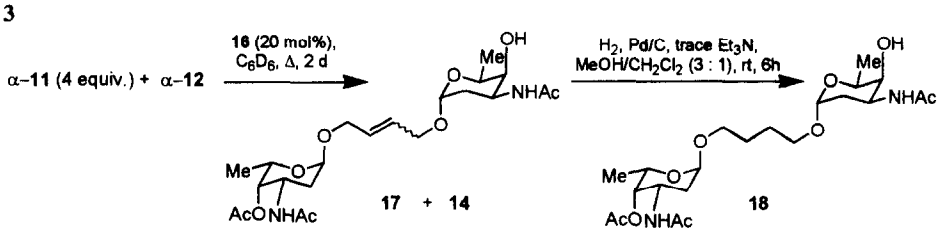
Olefine metathesis of allyl glycosides constitutes a synthetic alternative for preparing head-to-head homodimers based on daunosamine. In fact, this route offers access to both saturated as well as unsaturated spacer-linked dimers. This can be exploited for studying the influence of linker flexibility on the binding properties of the targeted neooligomers with polynucleotides. For this purpose, methyl glycoside **10**[5] was transformed into allyl glycosides **11** (α/β= 6 : 1) in good yield (Scheme 2). At this point, the anomers were



Scheme 2: Reagents and conditons (a) 5 % HCl, THF/ H_2O (3 : 2), 75°C, 2 h; (b) CH_2=CH-CH_2OH, Dowex 50 (H^+- form), 70°C, 1 h, (82 % for two steps); (c) Ac_2O, py, 4-$DMAP_{cat.}$, rt, 1 h, (99 %); (d) **11** and **16** (5 mol %), C_6H_6, 90°C, 6 h (**14**: 47 %); (e) **12** and **16** (11 mol%), C_6H_6, 90°C, 10 h (**13**: 74 %); (f) NaOMe, MeOH, rt, 1 h, (quant.); (g) $Ba(OH)_2$*8 H_2O, Δ, 24 h (**15**: 71 %; **8**: 59 % via route from **13** and 62 % via route from **14**); (h) H_2, Pd/C, trace Et_3N, $MeOH/CH_2Cl_2$ (3 : 1), rt, 8 h (from **13**: 83 %).

separated by column chromatography and the synthesis was continued with the α-glycoside. For estimating the influence of polar functional groups in the metathesis process, **11** was acylated and both alkenes **11** and **12** were dimerized, using Grubb's catalyst **16**.[5] As expected, the amido sugar **11** containing an additional hydroxy group reacted sluggishly to the desired unsaturated homodimer **14** (*E*/*Z*= 3 : 1) so that substantial amounts of starting olefine had to be recovered. The 4-*O*-acyl derivative **12**, however, gave good results under the metathesis reaction conditions to furnish **13** (*E*/*Z*= 3:1)[13] which was further converted into diol **14** and finally spacer-linked bis-daunosamine **15** under basic conditions. Preparation of the saturated analogue **8** *via* this route was achieved by a three step sequence (catalytic hydrogenation, deprotection) starting from **13**. In an analogous fashion, **14** can serve as a precursor for homodimer **8**.

Scheme 3



It should be noted that a mixture of dichloromethane and methanol was necessary for affecting efficient hydrogenation while dichloromethane caused solubility problems and pure methanol led to glycolysis of the amino sugar units. Access to non symmetrical dimers should allow for the preparation of the corresponding spacer-linked trimers and tetramers. Thus, allyl glycoside **12** was treated with 4 equiv. of 4-*O*-unprotected

11 in the presence of the ruthenium catalyst **16** which led to the cross metathesis[14] product **17** (53 % with reference to **12**) along with homodimer **14** (63 % with reference to 3 equiv. of **11**) (Scheme 3). Catalytic hydrogenation of **17** under conditions described for the synthesis **8** afforded 1,4-butanediol-linked bisglycoside **18** (74 %) which paves the way for further homologation.

In summary, we described two synthetic routes toward 1,4-butanediol linked head to head dimers derived from daunosamine which serve as probes for studying aminodeoxy sugar/oligonucleotide affinity.

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References and Notes

1. Reviews: (a) Hermann, T.; Westhof, E., *Curr. Opin. Biotechnol.* **1998**, *9*, 66-73; (b) Michael, K.; Tor, Y., *Chem. Eu. J.* **1998**, *4*, 2091-2098; (c) Pearson, N. D.; Prescott, C. D., *Chem. Biol.* **1997**, *4*, 409-414; (d) Wilson, W. D.; Ratmeyer, L.; Zhao, M.; Ding, D.; McConnaughie, A. W.; Kumar, A.; Boykin, D. W., *J. Mol. Rec.***1996**, *9*, 187-196.
2. (a) Bailly, C.; Hénichart, J.-P., In *Molecular Aspects of Anticancer Drug-DNA Interactions*; (Neidle, S.; Waring, M.; eds.), Macmillan Press Ltd., London **1994**; Vol. 2, 162-196; (b) Nicolaou, K. C., Smith, A. L., In *Modern Acetylene Chemistry*; (Stang, P. J.; Diederich, F.; eds), VCH, Weinheim, **1995**; (c) Nicolaou, K. C.; Schreiner, E. P.; Iwabuchi, Y.; Suzuki, T., *Angew. Chem.* **1992**, *104*, 317-319; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 340-341; (d) Tokuda, M.; Fujiwara, K.; Gomibuchi, T.; Hirama, Uesugi, M.; Sugiura, Y., *Tetrahedron Lett.* **1993**, *34*, 669-672; (e) Depew, K. M.; Zeman, S. M.; Boyer, S. H.; Denhart, D. J.; Ikemoto, N.; Danishefsky, S. J.; Crothers, D. M., *Angew. Chem.* **1996**, *108*, 2972-2975; *Angew. Chem. Int. Ed Engl.* **1996**, *35*, 2797-2801.
3. Wang, H.; Tor, Y., *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1951-1956.
4. For some examples on the preparation of spacer modified disaccharides refer to: (a) Dominique, R.; Das, S. K.; Roy, R., *Chem. Comm.* **1998**, 2437-2438; (b) Patch, R. J.; Chen, H.; Pandit, C. R., *J. Org. Chem.* **1997**, *62*, 1543-1546; (c) Ramza, J.; Descotes, G.; Basset, J.-M.; Mutch, A., *J. Carbohydr. Chem.* **1996**, *15*, 125-136; (d) Descotes, G.; Ramza, J.; Basset, J.-M.; Pagano, S., *Tetrahedron Lett.* **1994**, *35*, 7379-7382; (e) Ats, S.-C.; Lehmann, J.; Petry, S., *Carbohydr. Res.* **1994**, *252*, 325-332; (f) Lehmann, J.; Petry, S., *Carbohydr. Res.* **1990**, *204*, 141-144.
5. (a) Grubbs, R. H.; Chang, S., *Tetrahedron* **1998**, *54*, 4413-4450; (b) Fürstner, A. (ed.) in *Alkene Metathesis in Organic Synthesis*, Springer Verlag, Berlin, Heidelberg **1999**; (c) Schuster, M.; Blechert, S., *Angew. Chem.* **1997**, *108*, 2124-2144; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036-2055; (d) Armstrong, S. K., *J. Chem. Soc., Perkin Trans I* **1998**, 371-388; (e) Fürstner, A., *Topics in Catalysis* **1997**, *4*, 285; (f) Grubbs, R. H.; Miller, S. J.; Fu, G. C., *Acc. Chem. Res.* **1995**, 28, 446-452.
6. Prepared in about 15 g scale according to Horton, D.; Weckerle, W., *Carbohydr. Res.* **1975**, *44*, 227-440.
7. Qian, X.; Hindsgaul, O., *Chem. Soc., Chem. Commun.* **1997**, 1059-1060.
8. Guibe-Jampel, E.; Wakselman, M., *Synth. Commun.* **1982**, *12*, 219-223.
9. The sequence can be reversed with reduced overall yield by starting with the 4-*O*-acylation followed by acid promoted acetal hydrolysis and finally with 1-*O*-silylation.
10. Tietze, L.- F.; Fische, R.; Guder, H.-J., *Tetrahedron Lett.* **1982**, *23*, 4661-4664.
11. 1,4-Butanediol was less useful as glycosyl acceptor in the glycosylation of **5**.
12. *trans*-**13**: $[\alpha]_D^{25}$= -150° (*c* 1.46, MeOH/$CHCl_3$= 1:2); ^{1}H NMR ($CDCl_3$, d4-MeOH) δ 6.90 (br d, 2H, 2x N-H), 5.64 (br s, 2H, 2x =CH), 4.93 (br s, 2H, 2x 4-H), 4.85 (d, *J*= 2.1 Hz, 2H, 2x 1-H), 4.28 (m, 2H, 2x 3-H), 3.91 (q, *J*= 6.4 Hz, 2H, 2x 5-H), 3.97-3.75 (2m, 4H, 2x -OCH_2-), 1.99, (s, 6H, 2x OAc), 1.72, (s, 6H, 2x NHAc), 1.77-1.53 (m, 4H, 2x 2-$H_{ax,eq}$), 0.92 (d, *J*= 6.4 Hz, 6H, 2x 6-H); ^{13}C NNR δ 171.1 (s), 170.8 (s), 129.0 (d), 99.3 (d), 70.8 (d), 66.6 (t), 64.9 (t), 43.6 (d), 29.7 (t), 22.2 (q), 20.4 (q), 16.6 (q). LRMS (ES): *m/z* (%):1050.9 (100) [2M+Na^+], 537.4 (39) [M+Na^+], 515.3 (8) [M+H^+].
18: $[\alpha]_D^{25}$= -180° (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, d4-MeOH) δ 4.79 (br, 1H, 4-H), 4.79, 4.72 (2d, *J*= 0.8 and 0.6 Hz, 2H, 1-H, 1′-H), 4.34, 4.15 (2ddd, *J*= 8.0, 2.8, 2.0 and 7.8, 3.2, 2.0 Hz, 2H, 3-H, 3′-H), 3.95, 3.85 (dq and br q, *J*= 6.4, 0.8 and 5.4, Hz, 2H, 5-H, 5′-H), 3.60-3.47 (m, 2H, -OCH_2-), 3.40 (br s, 1H, 4′-H), 3.33-3.20 (m, 4H, CH_2O, 2x N-H), 2.04 (s, 3H, OAc), 1.83, 1.77 (2s, 6H, 2x NHAc), 1.89-1.43 (m, 8H, 2x -OCH_2-CH_2-, 2-H, 2′-H), 1.07, 1.00 (2d, *J*= 6.4 and 5.4 Hz, 6H, 6-H, 6′-H); ^{13}C NMR δ 170.5 (s), 96.7 (d), 68.7 (d), 66.8 (t), 65.8 (d), 45.3 (d), 29.4 (t), 26.2 (t), 22.4 (q), 16.3 (q).
13. The dimerizations commonly furnished small amounts of cross-metathesis products obtained from the initially released styrene.
14. (a) Crowe, W. E.; Goldberg, D. R., *J. Am. Chem. Soc.* **1995**, *117*, 5162-5163; (b) Crowe, W. E.; Zhang, Z. J., *J. Am. Chem. Soc.* **1993**, *115*, 10998-10999.