Synthesis of Spacer-Linked Tail to Tail Dimers Derived from a Conformationally Rigid Aminodeoxysugar by Olefin Metathesis

Andreas Kirschning,* Guang-Wu Chen

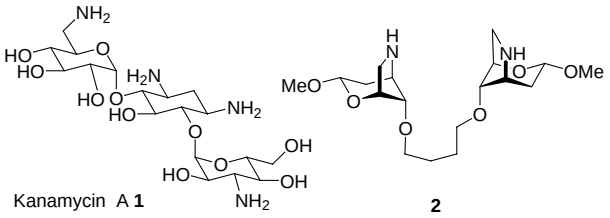
Institut für Organische Chemie der Technischen Universität Clausthal, Leibnizstraße 6, D-38678 Clausthal-Zellerfeld, Germany
Fax (+)(0)5323722858; E-mail: andreas.kirschning@tu-clausthal.de

Received 14 February 2000; revised 21 March 2000

Abstract: The preparation of new tail to tail dimers of bridged aminodeoxysugars **2** and **11** is described. The first key step in the synthesis is the formation of the aminomethyl bridge in the carbohydrate-derived monomer **7** which is achieved by silver promoted ring closure of methyl 3-acetamido-6-bromo-2,3,6-trideoxy α-D-glucoside **6**. Secondly, olefin metathesis of the corresponding 4-*O*-allyl glycoside **9** constitutes a powerful tool for dimerization, which allows synthesis of 1,4-butanediol-linked tail to tail neooligosaccharides **2** and **11**.

Key words: neooligosaccharide, metathesis, aminodeoxysugar, conformational restriction

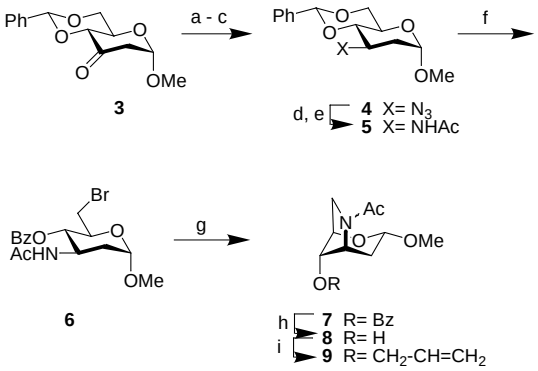
Oligocationic compounds, namely protonable polyamines, have recently seen considerable attention because of their key role in biological processes. This increased interest is particularly associated with their ability to specifically bind to polynucleotides connected with the possibility of inhibiting DNA duplication or RNA catalysis, or the forcing of RNA into an alternate conformation.[1,2] For example, nature has utilized aminodeoxy sugars present in glycoconjugates like the anthracycline antibiotic daunomycin as well as amino glycoside antibiotics like kanamycin A (**1**) to target polynucleotides. These structures are ideally suited for binding as the rigid character of the pyran ring along with the flexibility associated with the glycosidic linkage give them the ability of preorganization. In an elegant study, Tor and coworkers showed that multivalent linker-modified dimers derived from **1** also recognize RNA with enhanced binding along with improved ribozyme inhibitory activity.[1b,3] Recently, we initiated a project on the preparation of new 1,4-butanediol-linked oligomeric aminodeoxysugars[4] in order to search for specific RNA-binders with new therapeutic properties.



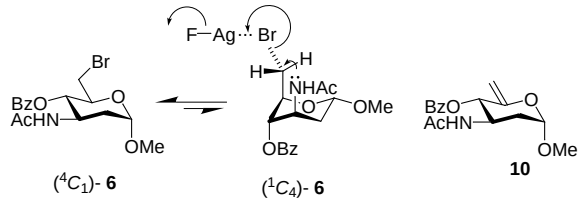
In this paper, we describe the first synthesis of C_2-symmetric 1,4-butanediol-linked neooligosaccharides **2** and **11** derived from a bridged aminodeoxysugar derivative. By bridging[5] the amino group-containing unit a conformationally rigid structure is achieved while the linker serves as a flexible spacer, helping to appropriately orientate the rigidified amino groups in space. Based on our previous results[4] and recent work published by the groups of Roy and Stütz,[6] we envisaged olefin metathesis[7] as a powerful method to dimerize allyl protected glycosides. While it was known from earlier publications[4,6] that allyl glycosides are very well suited for this purpose, it is also demonstrated in this paper that tail to tail dimerization can be achieved by using a 4-*O*-allylated sugar monomer **9**.

Methyl uloside **3,** which was prepared in two steps from D-mannose,[8] was the starting point for the synthesis of spacer-linked homodimers **2** and **11** (Scheme 1). The sequence was initiated by stereoselective reduction of the keto group (*ribo*/*arabino* = >15:1) followed by activation of the alcohol group as a triflate[9] and terminated by nucleophilic attack of the azide anion to furnish *arabino*-configured 3-azido methyl glycoside **4**.[10] Functional group manipulations using two well established reactions[11] afforded the corresponding acetamido derivative **5**[12] which paved the way for the oxidative opening of the benzylidene group resulting in the formation of methyl 3-acetamido-6-bromo-2,3,6-trideoxy-α-D-glucoside **6**. Treatment of this bromide with anhydrous silver fluoride led to activation of C-6, and intramolecular attack of the acetamido group onto the highly electrophilic carbon affording bridged deoxysugar **7**. Prior to the ring closure, a switch from the ($^4C_1$)- to ($^1C_4$)-conformation in **6** has to be assumed (Scheme 2).[13] Remarkably, formation of the expected elimination product **10** was not detected, which in part has to be ascribed to the 3,5-*cis* substitution pattern on the pyran ring.[13] Benzoate **7** was hydrolyzed under basic conditions and the resulting alcohol **8** was finally allylated under standard conditions to afford the targeted 4-*O*-allyl protected monomer **9**.

At this point, allyl ether **9** was dimerized, using Grubbs catalyst **12**, the most insensitive metathesis catalyst towards polar functionalities like the acetamido group. As expected, the ^{1}H NMR and ^{13}C NMR spectra of the C_2-symmetric homodimeric reaction product **11** (*E*/*Z* = 6:1) showed only half the set of signals for all protons as well as carbon atoms.[14] Further structural support was gained from proton integration and mass spectrometry. Stütz and coworkers recently demonstrated that the stereoselectivity of the intermolecular metathesis reaction is

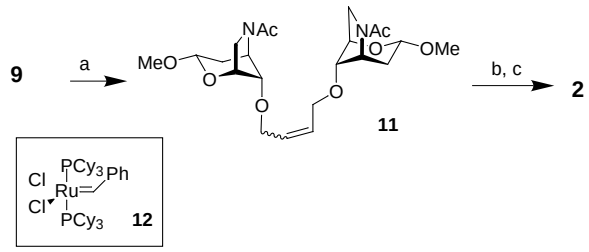


Scheme 1 Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to r.t., 2 h; (b) Tf_2O, pyridine, CH_2Cl_2, r.t., 45 min; (c) NaN_3, DMF, r.t., 1.5 h (87% for three steps); (d) $LiAlH_4$, THF, 0 °C, 1 h; (e) Ac_2O, pyridine, r.t., 2 h (91% for two steps); (f) CCl_4, NBS, $BaCO_3$, Δ, 6 h (76%); (g) AgF, pyridine, r.t., 14 h (95%); (h) NaOMe, MeOH, r.t., 3 h; (i) NaH, allyl bromide, r.t., 12 h (95% for two steps).



Scheme 2

highly dependent on the configuration and the nature of protecting groups present in carbohydrate derived terminal olefins.[6c] Our synthesis was completed by catalytic hydrogenation of the double bond followed by deacetylation under standard conditions furnishing the desired spacer-linked dimer **2**.



Scheme 3 Reagents and conditions: (a) 12 (8 mol%), C_6H_6, 50 °C, 18 h (88%); (b) H_2, PtO_2, CH_2Cl_2/MeOH (3: 1), r.t., 16 h (99%); (c) $Ba(OH)_2$ 8 H_2O, Δ, 24 h (84%).

In summary, we have described an efficient synthetic route towards 1,4-butanediol linked tail to tail dimers derived from a conformationally rigidified, bridged aminodeoxy sugar derivative. Studies on the biological properties of these new neooligosaccharides are underway.

All temperatures quoted are uncorrected. Optical rotations were recorded on a Perkin−Elmer 141 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR, ^{13}C NMR, ^{1}H, ^{1}H- and ^{1}H, ^{13}C-COSY as well as NOESY spectra were recorded on a Bruker DPX 200-NMR and a ARX 400-NMR spectrometer for solutions in $CDCl_3$ using residual $CHCl_3$ as internal standard (δ = 7.26 ppm), unless otherwise stated. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shift values of ^{13}C NMR spectra are reported as values in ppm relative to residual $CHCl_3$ (δ = 77 ppm) as internal standard. The multiplicities refer to the resonances in the off-resonance spectra and were elucidated using the distortionless enhancement by polarisation transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are reported using the following abbreviations: s = singlet (due to quaternary carbon), d = doublet (methine), q = quartet (methyl), t = triplet (methylene). Mass spectra were obtained using a LCQ Finnigan (ESI) instrument. Ion mass (*m/z*) signals are reported as values in atomic mass units followed, in parentheses, by the peak intensities relative to the base peak (100%). Combustion analyses were performed by the Institut für Pharmazeutische Chemie, Technische Universität Braunschweig and Institut für Chemie, Humboldt Universität zu Berlin. All solvents used were of reagent grade and were further dried. Reactions were monitored by TLC on silica gel 60 F^{254} (E. Merck, Darmstadt) and spots were detected either by UV-absorption or by charring with H_2SO_4/4-methoxybenzaldehyde in MeOH. Preparative column chromatography was performed on silica gel 60 (E. Merck, Darmstadt). Ulose 3 was synthesized according to the literature.[8]

Methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside (4)

To a solution of ulose **3** (11.4 g, 43.1 mmol) in dry MeOH (400 mL) was added $NaBH_4$ (3.3 g, mmol) at 0 °C in one portion and the suspension was stirred at r.t. for 2 h. After addition of a mixture of H_2O/CH_2Cl_2 (1:1; 440 mL), the layers were separated and the organic phase was washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product (11.4 g) was dissolved in CH_2Cl_2 (200 mL) and added dropwise to a solution prepared by dissolving $(CF_3SO_2)_2O$ (16.8 g, 10 mL, 59.6 mmol) in CH_2Cl_2 (200 mL) at −5 °C to which a mixture of dry pyridine (13.4 g, 170 mmol) in CH_2Cl_2 (200 mL) had been added. The reaction mixture was stirred for 45 min at r.t. and poured into an ice cold aq bicarbonate solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a red oil. After co-distillation with toluene a crystalline material was obtained which was recrystallized in Et_2O/hexane (2:1) to give colorless crystals (mp 65−70 °C dec.). However, the red oil can directly be used for the next step by dissolving it at r.t. in dry DMF (260 mL) and treating it with NaN_3 (10.9 g, 167.7 mmol) in one portion. The solution was stirred at at r.t. for 1.5 h, cooled to ambient temperature and hydrolyzed by adding a mixture of H_2O/Et_2O (1:1, 300 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated in vacuo. DMF was removed by Kugelrohr distillation to afford a yellow oil. This was further purified by flash column chromatography (Et_2O/hexane, 2: 1) to afford colorless needles (10.9 g, 37.4 mmol; 87%): mp 114−115 °C (EtOH/hexane, 10:1). $[\alpha]_D^{21}$ +108.9 (*c* 1.5, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 7.35−7.52 (m, 5H, ArH), 5.62 (s, 1H, PhCH), 4.78 (dd, 1H, *J* = 1.0, 4.0, Hz, 1-H), 4.28 (dd, 1H, *J* = 4.6, 9.6 Hz, 6-H_{eq}), 4.05 (ddd, 1H, *J* = 5.0, 9.6, 12.0 Hz, 3-H), 3.85 (ddd, 1H, *J* = 4.6, 9.6, 12.0 Hz, 5-H), 3.76 (dd, 1H, *J* = 9.6, 12.0 Hz, 6-H_{ax}), 3.58 (t, 1H, *J* = 9.6 Hz, 4-H), 3.35 (s, 3H, OCH_3), 2.17 (ddd, 1H, *J* = 1.0, 5.0, 13.4 Hz, 1H, 2-H_{eq}), 1.72 (ddd, 1H, *J* = 4.0, 12.0, 13.4 Hz, 2-H_{ax}).

^{13}C NMR (100 MHz): δ = 137.0 (s, Ph), 125.9−129.3 (Ph), 101.5 (d, *C*HPh), 98.1 (d, C-1), 82.1, 69.0 (2d, C-4, C-5), 63.1 (t, C-6), 56.4 (q, OCH_3), 54.8 (d, C-3), 35.5 (t, C-2).

Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.43. Found: C, 57.69; H, 5.94; N, 14.01.

Methyl 3-Acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside (5)

To a solution of compound **4** (5.4 g, 18.5 mmol) in dry THF (300 mL) was added $LiAlH_4$ (3.5 g, 92 mmol) at 0 °C and stirring was continued for 1 h. EtOH was added (25 mL) followed by an aqueous solution of sodium-potassium tartrate (150 mL) and $CHCl_3$ (300 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL) and the combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and evaporated in vacuo. The crude oil was dissolved in dry pyridine (75 mL) and acetic anhydride (30 mL) at 0 °C. After 2 h at r.t., a mixture of H_2O/CH_2Cl_2 (1:1, 50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated in vacuo. Pyridine was removed by co-distillation using toluene to afford colorless crystals (5.16 g, 16.8 mmol, 91%): mp 271−273 °C (subl.). $[\alpha]_D^{22}$ +66 (*c* 1.8, $CHCl_3$). Lit.[12a]: mp 272−274 °C (subl.), $[\alpha]_D^{23}$ +65.

Methyl 3-Acetamido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (6)

To a solution of compound **5** (17.2 g, 56.0 mmol) in dry CCl_4 (430 mL) were added *N*-bromosuccinimide (11.87 g, 66.7 mmol) and barium carbonate (16.0 g, 81.1 mmol). The mixture was refluxed for 6 h (bath temperature 105 °C). After cooling of the faint yellow reaction mixture, the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (250 mL), the clear extract was successively washed with 5% aq sodium hydrogen sulfite, aq sodium bicarbonate, dried ($MgSO_4$) and evaporated in vacuo. The resultant residue (20 g) was purified by column chromatography (silica gel; petroleum ether/EtOAc, 1: 2) to afford the title compound (16.4 g, 42.5 mmol, 75.9%) as colorless crystals: mp 147 °C.

^{1}H NMR (400 MHz): δ = 8.08−7.40 (m, 5H, Ph), 6.05 (d, 1H, *J* = 8.6 Hz, N-H), 5.02 (dd, 1H, *J* = 9.6, 9.6 Hz, 4-H), 4.85 (d, 1H, *J* = 3.2 Hz, 1-H), 4.66 (dddd, 1H, *J* = 4.8, 8.6, 9.6, 13.2 Hz, 3-H), 4.18 (ddd, 1H,*J* = 2.6, 6.2, 9.6 Hz, 5-H), 3.56 (dd, 1H, *J* = 2.6, 9.8 Hz, 6-H), 3.49 (dd, 1H, *J* = 6.2, 9.8 Hz, 6´-H), 3.40 (s, 3H, OCH_3), 2.26 (ddd, 1H, *J* = 0.6, 4.8, 13.2 Hz, 2-H_{eq}), 1.80 (s, 3H, OAc), 1.74 (ddd, 1H, *J* = 3.2, 13.2, 13.2 Hz, 2-H_{ax}).

^{13}C NMR (100 MHz): δ = 169.8 (s, O=CN), 166.8 (s, O=CO), 133.7 (s, Ph), 129.9 (d, Ph), 128.9 (s, Ph), 128.6 (d, Ph), 97.9 (d, C-1), 73.1, 69.3 (2d, C-4, C-5), 55.0 (q, OCH_3), 46.7 (d, C-3), 36.2 (t, C-6), 32.6 (t, C-2), 23.3 (q, Ac).

Anal. Calcd for $C_{16}H_{20}BrNO_5$ (386.24): C, 49.75; H, 5.22; Br, 20.69; N, 3.63. Found: C, 49.69; H, 5.30; Br, 20.87; N, 3.31.

Methyl 3-Acetamido-3,6-anhydro-4-*O*-benzoyl-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (7)

To a solution of compound **6** (16.0 g, 41.4 mmol) in dry pyridine (320 mL) was added silver fluoride (16 g, 126.1 mmol). The mixture was stirred at r.t. for 14 h and the dark suspension was poured into Et_2O (800 mL). After filtration over Celite®, the filtrate was washed with CH_2Cl_2 (3 × 300 mL) and the combined extracts were concentrated in vacuo. Addition of toluene (6 × 40 mL) to the residue was used to remove traces of pyridine by co-distillation. Final purification was achieved by column chromatography (silica gel; Et_2O/CH_2Cl_2,1:1) to afford the title compound (11.94 g, 39.1 mmol, 94.5%) as colorless crystals: mp 125 °C (Et_2O).

^{1}H NMR (400 MHz): δ = 8.09−7.42 (m, 5H, Ph), 4.96 and 4.92 (dd, 1H, *J* = 2.8, 5.4 Hz, 4-H), 4.87−4.78 (m, 1H, 1-H), 4.76 (m, 1H, 5-H), 4.69 and 4.44 (2 br t, 1H, 3-H), 3.89−3.55 (m, 2H, 6-H, 6´-H), 3.50 and 3.49 (2s, 3H, OCH_3), 2.35−1.98 (m, 2H, 2-H_{ax}, 2-H_{eq}), 2.15 and 2.09 (2s, 3H, $NCOCH_3$).

Each carbon appeared as a pair of signals due to the presence of two stereoisomers.

^{13}C NMR (100 MHz): δ = 169.0, 168.6 (q), 165.9, 165.8 (q), 133.7, 133.5 (q), 130.0, 129.9 (d), 129.4, 129.2 (q), 128.6, 128.5 (d), 98.3, 97.5 (d), 73.3, 72.2 (d), 70.7, 70.1 (d), 56.9, 56.7 (q), 54.1, 51.6 (d), 50.2, 48.2 (t), 32.1, 30.4 (t), 21.7, 21.6 (q).

Anal. Calcd for $C_{16}H_{19}NO_5$ (305.33): C, 62.94; H, 6.27; N, 4.59. Found: C, 63.05; H, 6.37; N, 4.29.

Methyl 3-Acetamido-4-*O*-allyl-3,6-anhydro-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (9)

To a solution of compound (**7**) (300 mg, 1.02 mmol) in dry MeOH (10 mL) was added sodium methoxide (10.5 mg, 0.19 mmol, 0.2 equiv). The mixture was stirred at r.t. for 3 h (TLC: toluene/acetone, 1:6) and the solvent was removed under reduced pressure. The crude product was directly employed in the next step without any further purification. The residue was dissolved in anhyd THF (10 mL) at r.t. and sodium hydride (55−65% in oil, 0.1 g, 2.5 mmol) was added. After generation of H_2 ceased, the mixture was treated with allyl bromide (0.21 mL, 2.5 mmol, 2.5 equiv). Stirring was continued for 12 h at r.t. After addition of MeOH (5 mL), stirring was continued for 3 h and the solvent was removed in vacuo. The oily residue was dissolved in H_2O (20 mL) and extraction was carried out using CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with H_2O and dried ($MgSO_4$). Concentration under reduced pressure afforded a crude oil (288 mg) which was purified by column chromatography (20 g silica gel; EtOAc with 3% of Et_3N) which afforded the title compound **9** as a 1.2:1 mixture of isomers (226 mg, 0.94 mmol; 95% for two steps).

^{1}H NMR (400 MHz): δ = 5.98−5.85 (m, 1H, C*H*=), 5.31−5.16 (m, 2H, CH_2=CH-), 4.75−4.67 (m, 1H, 1-H), 4.54 and 4.07 (m, 1H, 3-H), 4.45 and 4.42 (s, 1H, 5-H), 4.20−4.00 (m, 2H, =CHCH_2), 3.73−3.45 (m, 2H, 6-H), 3.60−3.50 (m, 1H, 4-H), 3.43 (s, 3H, OMe), 2.06 and 2.00 (s, 3H, $NCOCH_3$), 2.14−1.97 (m, 2H, 2-H_{ax} and 2-H_{eq}).

Each carbon appeared as a pair of signals due to the presence of two stereoisomers.

^{13}C NMR (100 MHz): δ = 169.0, 168.5 (s, O=CN), 134.0 (d, =CH), 117.9, 117.8 (t, CH_2=), 98.1, 97.4 (d, C-1), 75.3, 74.5 (d, C-4), 73.5, 71.8 (d, C-5), 70.6 (t, =CH-*C*H_2), 56.6, 56.4 (q, OMe), 54.4, 51.3 (d, C-3), 50.0, 48.2 (t, C-6), 31.3, 29.6 (t, C-2), 21.5, 21.3 (q, OC*C*H_3).

Anal. Calcd for $C_{12}H_{19}NO_4$ (241.13): C, 59.73; H, 7.94; N, 5.81. Found: C, 59.81; H, 7.88; N, 5.70.

1,4-Bis[methyl 3´-acetylamido-3´,6´-anhydro-2´,3´,6´-trideoxy-α-D-*arabino*-hexopyranos-4´-yl]-2-butene-1,4-diol (11)

Compound **9** (74 mg, 0.31 mmol) was kept in vacuo (10^{-2} Torr) for 5 h and dissolved in dry benzene (10 mL) under N_2. To this solution was added catalyst **12** (12 mg, 4.8 mol%). The purple solution was stirred at r.t. for 2 h, at which time the starting material had reacted only sluggishly. A second portion of the metathesis catalyst (8 mg, 3.2 mol%, total 8 mol%) was added. After stirring at 50 °C under N_2 for 18 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in Et_2O (30 mL) and Et_3N (1 mL) and stirred for 2 h. Removal of the solvent under reduced pressure afforded an oil, which was purified by column chromatography (CH_2Cl_2/MeOH, 15:1) to afford the title compound **11** (61 mg, 0.134 mmol; 88%) as a mixture of four inseparable stereoisomers (*trans*:*cis* = 6:1). The spectroscopic data for both of the major

trans-isomers are close to identity. Spectroscopic data for the *trans*-isomers:

^{1}H NMR (400 MHz): δ = 5.90−5.84 (m, 2H, 2 × C*H*=), 4.73−4.68 (m, 2H, 2 × 1-H), 4.55 and 4.09 (m, 2H, 2 × 3-H), 4.46 and 4.44 (2s, 2H, 2 × 5-H), 4.20−4.05 (m, 4H, 2 × CH_2CH=), 3.75−3.48 (m, 4H, 2 × 6-H, 6´-H), 3.62−3.53 (m, 2H, 2 × 4-H), 3.44 (s, 6H, 2 × OMe), 2.08 and 2.02 (s, 6H, 2 × NCOCH_3), 2.14−1.84 (m, 4H, 2 × 2-H_{ax}, 2-H_{eq}).

^{13}C NMR (100 MHz): δ = 169.1, 168.6 (s, O = CN), 129.3, 129.2 (d, = *C*H), 98.3, 97.6 (d, C-1), 75.7, 74.7 (d, C-4), 73.5, 71.7 (d, C-5), 69.3 (t, *C*H_2-CH =), 56.8, 56.7, (q, OCH_3), 54.4, 51.3 (d, C-3), 50.1, 48.3 (t, C-6), 31.4, 29.7 (t, C-2), 21.6, 21.4 (q, OC*C*H_3).

LRMS (ES): *m/z* (%) = 477.1 (22) [M+Na^+], 455.4 (100) [M+H^+].

NMR data of alkenic double bond of *cis*-isomers:

^{1}H NMR (400 MHz): δ = 5.80−5.74 (m, 2H, CH =), 4.65−4.61 (m, 2H, 2 × 1-H).

^{13}C NMR (100 MHz): δ = 129.1 (d, = CH).

1,4-Bis[methyl 3´-amino-3´,6´-anhydro-2´,3´,6´-trideoxy-α-D-*arabino*-hexopyranos-4´-yl]-1,4-butanediol (2)

Homodimer (**11**) (61 mg, 0.134 mmol) was dissolved in CH_2Cl_2/MeOH (3:1, 8 mL) and to the solution, PtO_2 was added (3 mg). The suspension was stirred under H_2 atm at r.t. for 16 h, after which time the reduction was complete (TLC: CH_2Cl_2/MeOH, 10:1). After filtration, the reaction mixture was concentrated under reduced pressure to afford an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH, 20:1). The hydrogenated intermediate (61 mg, 0.134 mmol) was dissolved in H_2O (20 mL) at r.t. and treated with barium hydroxide octahydrate (3.0 g, 9.5 mmol). The solution was heated under reflux (130−140 °C) for 24 h. After cooling to r.t., dry ice was added and the suspension was filtered. The filtrate was treated with Amberlite IRA-904 (OH^--form, 20 mL) for 30 min. The solution was filtered again and concentrated in vacuo. The residue still contained some traces of barium salts and was taken up in $CHCl_3$. Filtration and removal of the solvent afforded the title compound **2** (42 mg, 0.113 mmol; 84.3%).

$[\alpha]_D^{23.5}$ +16.9 (*c* 0.64, $CHCl_3$/MeOH, 5:1).

^{1}H NMR (400 MHz): δ = 4.85 (dd, 2H, *J* = 9.2, 3.8 Hz, 2 × 1-H), 4.27 (t, 2H, *J* = 3.2 Hz, 2 × 5-H), 3.60−3.40 (m, 6H, 2 × OCH_2 and 2 × 4-H), 3.42 (s, 6H, 2 × OMe), 3.42−3.32 (m, 2H, 2 × 3-H), 3.16 (d, 2H, *J* = 12.8 Hz, 2 × 6-H), 3.08 (dd, 2H, *J* = 12.8, 4.0 Hz, 2 × 6´-H'), 2.12−2.07 (m, 2H, 2 × NH), 1.92 (ddd, 2H, *J* = 12.8, 9.4, 1.4 Hz, 2 × 2-H_{ax}), 1.69 (m, 4H, CH_2CH_2), 1.64 (dt, 2H, *J* = 12.8, 3.8 Hz, 2 × 2´-H).

^{13}C NMR (100 MHz): δ = 98.1 (d, 2 × C-1), 78.8 (d, 2 × C-4), 73.4 (d, 2 × C-5), 69.3 (t, 2 × OCH_2), 56.3 (q, 2 × OMe), 52.4 (d, 2 × C-3), 47.5 (t, 2 × C-6), 32.6 (t, 2 × C-2), 26.3 (t, *C*H_2-CH_2O).

LRMS (ES): *m/z* (%) = 395.5 (52) [M+Na^+], 373.4 (100) [M+H^+].

Acknowledgement

We thank the Deutsche Forschungsgemeinschaft (SFB 416) as well as the Fonds der Chemischen Industrie for financial support. Preparative assistance by S. Domann, M.-R. Fischer, and S. Pollmann is gratefulley acknowledged.

References

(1) For reviews see:
(a) Hermann, T.; Westhof, E. *Curr. Opin. Biotechnol.* **1998**, *9*, 66.
(b) Michael, K.; Tor, Y. *Chem. Eur. J.* **1998**, *4*, 2091.
(c) Pearson, N. D.; Prescott, C. D. *Chem. Biol.* **1997**, *4*, 409.
(d) Wilson, W. D.; Ratmeyer, L.; Zhao, M.; Ding, D.; McConnaughie, A. W.; Kumar, A.; Boykin, D. W. *J. Mol. Rec.***1996**, *9*, 187.

(2) Bailly, C.; Hénichart, J. -P. In *Molecular Aspects of Anticancer Drug-DNA Interactions*, Vol. 2; Neidle, S., Waring, M., Eds.; Macmillan Press: London, 1994; pp 162−196.
Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.
Nicolaou, K. C.; Schreiner, E. P.; Iwabuchi, Y.; Suzuki, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 340.
Tokuda, M.; Fujiwara, K.; Gomibuchi, T.; Hirama, M.; Uesugi, M.; Sugiura, Y. *Tetrahedron Lett.* **1993**, *34*, 669.
Depew, K. M.; Zeman, S. M.; Boyer, S. H.; Denhart, D. J.; Ikemoto, N.; Danishefsky, S. J.; Crothers, D. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2797.

(3) Wang, H.; Tor, Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1951.
Wang, H.; Tor, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 109.

(4) Kirschning, A.; Chen, G. -W. *Tetrahedron Lett.* **1999,** *40*, 4665.

(5) For some recent examples on the preparation of spacer modified oligosaccharides see:
Patch, R. J.; Chen, H.; Pandit, C. R. *J. Org. Chem.* **1997**, *62*, 1543.
Kieburg, C.; Dubber, M.; Lindhorst, Th. K. *Synlett* **1997**, 1447.
Ramza, J.; Descotes, G.; Basset, J. -M.; Mutch, A. *J. Carbohydr. Chem.* **1996**, *15*, 125.
Descotes, G.;Ramza, J.; Basset, J. -M.; Pagano, S. *Tetrahedron Lett.* **1994**, *35*, 7379.
Ats, S. -C.; Lehmann, J.; Petry, S. *Carbohydr. Res.* **1994**, *252*, 325.
Lehmann, J.; Petry, S. *Carbohydr. Res.* **1990**, *204*, 141.

(6) (a) Dominique, R.; Das, S. K.; Roy, R. *Chem. Commun.* **1998**, 2437.
(b) Roy, R.; Dominique, R.; Das, S. K. *J. Org. Chem.* **1999**, *64*, 5408.
(c) Hadwiger, P.; Stütz, A. E. *Synlett* **1999**, 1787.

(7) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer Verlag: Berlin, Heidelberg, 1999.
Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
Ivin, K. J. *J. Mol. Catal. A-Chem.* **1998**, *133*, 1.
Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29.
Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.
Armstrong, S. K. *J. Chem. Soc., Perkin Trans I* **1998**, 371.
Fürstner, A. *Topics in Catalysis* **1997**, *4*, 285.
Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29.
Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, 28, 446.

(8) Klemer, A.; Rodemeyer, D. *Chem. Ber.* **1974**, 2612.

(9) Meyer zu Reckendorf, W.; Spohr, U. *Liebigs Ann. Chem.* **1982**, 137.

(10) Replacement of the corresponding mesylate by azide has been achieved in boiling DMF by Richardson (71%) as well as Guthrie and co-workers (see references 12). We found that under these conditions a substantial amount of the elimination product (22%) was formed.

(11) Greene, T. W. *Protective Groups in Organic synthesis*; Wiley: New York, Chichester, Brisbane, Toronto, Singapore, 1981.

(12) (a) Richardson, A. C. *Carbohydr. Res.* **1967**, *4*, 422.
(b) Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* **1965**, 6956.

(13) Treatment of the *lyxo*-configured 3-epimer of **6** with silver fluoride exclusively affords the corresponding enol ether: Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227.
(14) Assignment of the *trans*- and *cis*- stereoisomers was based on chemical shifts in the ^{13}C NMR spectra: Breitmaier, E.; Voelter, W. *^{13}Carbon NMR Spectroscopy. High Resolution Methods and Applications in Organic Chemistry and Biochemistry*; VCH: New York, 1987; p 192.
Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 5106.

Article Identifier:
1437-210X,E;2000,0,08,1133,1137,ftx,en;Z00700SS.pdf