Oligonucleosides with a Nucleobase-Including Backbone

Part 1

Concept, Force-Field Calculations, and Synthesis of Uridine-Derived Monomers and Dimers

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A new type of oligonucleosides has been devised to investigate the potential of oligonucleosides with a nucleobase-including backbone to form homo- and/or heteroduplexes (*cf. Fig. 2*). It is characterised by ethynyl-linkages between C(5′) and C(6) of uridine, and between C(5′) and C(8) of adenosine. Force-field calculations and *Maruzen* model studies suggest that such oligonucleosides form autonomous pairing systems and hybridize with RNA. We describe the syntheses of uridine-derived monomers, suitable for the construction of oligomers, and of a dimer. Treatment of uridine-5′-carbaldehyde (**2**) with triethylsilyl acetylide gave the diastereoisomeric propargylic alcohols **6** and **7** (1:2, 80%; *Scheme 1*). Their configuration at C(5′) was determined on the basis of NOE experiments and X-ray crystal-structure analysis. Iodination at C(6) of the (*R*)-configured alcohol **7** by treatment with lithium diisopropylamide (LDA) and *N*-iodosuccinimide (NIS) gave the iodide **17** (62%), which was silylated at O–C(5′) to yield **18** (89%; *Scheme 2*). *C*-Desilylation of **7** with NaOH in MeOH/H_2O led to the alkyne **10** (98%); *O*-silylation of **10** at O–C(5′) gave **16** (84%). Cross-coupling of **18** and **16** yielded 63% of the dimer **19**, which was *C*-desilylated to **20** in 63% yield. Cross-coupling of **10** and the 6-iodouridine **13** (70%), followed by treatment of the resulting dimer **14** with HF and HCl in MeCN/H_2O, gave the deprotected dimer **15** (73%).

Introduction and Concept. – Pairing studies of DNA/RNA-analogues[1]) [6–10] with modified carbohydrate, nucleobase, and backbone moieties form the basis of current insight into the structural requirements for the formation of stable duplexes. All backbone-modified analogues that have so far been investigated maintain a separation between nucleobase and backbone, irrespective of whether the backbone is derived from a carbohydrate or a peptide (PNA [11][12]). This leads to the question of whether this structural invariant, which implies a functional differentiation of nucleobases and backbone is indeed required for the formation of homo- and/or heteroduplexes. To answer this question, we have conceived a new type of oligonucleoside analogues that possess a nucleobase-including backbone (*Fig. 1*). In these analogues, the 3′,5′-phosphodiester linkage of RNA is replaced by a link **L** between C(5′) and C(6) or C(5) of uridine, and between C(5′) and C(8) or C(2) of adenosine, respectively (structures **I**–**IV** in *Fig. 2*). From among the conceivable charged or uncharged links **L**, we have chosen the ethynediyl group as the sterically least demanding with the potential for a convergent, ideally binomial, synthesis of oligomers [13] and a reactivity that should

[1]) Most DNA and RNA analogues have been prepared in search of antisense compounds [1][2], to investigate autonomous pairing systems, protein/DNA interactions [3], electron transfer in DNA [4], and DNA damage [5].

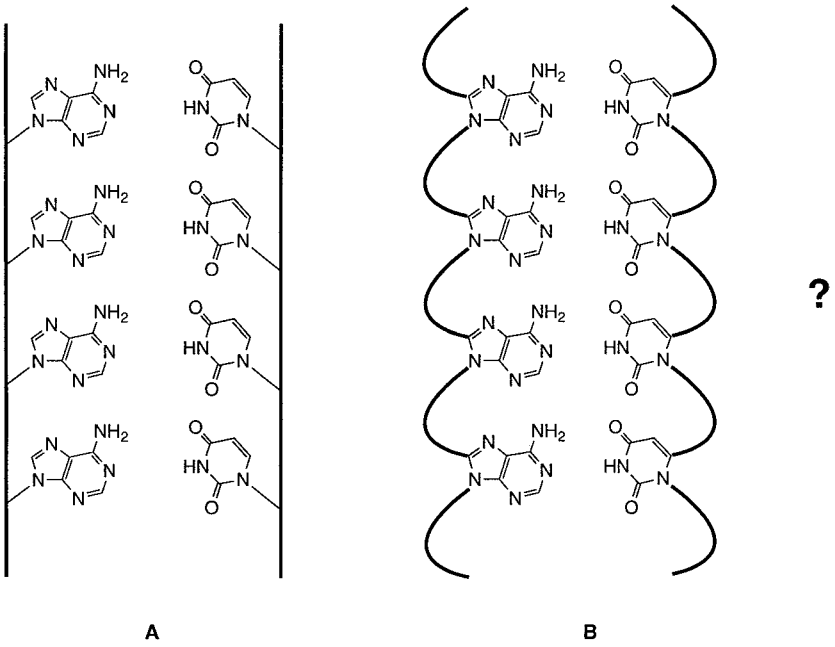


Fig. 1. *Conventional oligonucleotides with structural separation of the nucleobases and the backbone* (**A**) *and oligonucleosides with a nucelobase-including backbone* (**B**)

allow for facile derivatisations. The 5′-OH groups should be retained to favour water-solubility, to allow for derivatisations, and to simplify the synthesis. Before undertaking the synthesis, we decided to evaluate the potential of the 5′,6-linked pyrimidine analogues **I-A**, the 5′,8-linked purine analogues **III-A**, and their 5′,5- and 5′,2-linked regioisomers corresponding to **II** and **IV** (*Fig. 2*) to form homo- and/or heteroduplexes, using both force-field calculations and *Maruzen* models. We report the results of the calculation and model-studies, the syntheses of uridine-derived monomers, suitable for the construction of oligomers, and the synthesis of a deprotected dimer.

Results and Discussion. – 1. *Nomenclature.* The names for the nucleosides bearing ethynyl groups are abbreviated by a combination of a single letter for the base (U and A), three letters for the carbohydrate chain (Hep for 6,7-dideoxyhex-6-ynofuranosyl), and a single letter for the configurational prefix (r for D-*ribo*, a for D-*allo*, and t for L-*talo*). The linking mode in oligomers is indicated by two numerals in parenthesis. A dash, as in (3′-5′), indicates a phosphinato group between O(3′) and O(5′) (natural nucleotides) and determines the (3 → 5′) direction of the linkage. The en dash, as in (5–7′), indicates a single bond between the two specified centers (acetyleno analogues) and the (5 → 7′) direction of the linkage. The chain direction in heteroduplexes is assigned by correlating the connecting site at the base and the 3′ connecting site, and the connecting site at the terminal acetylenic atom and the 5′ connecting site. Thus, in the heteroduplex (7′–5)rHepU_6 · (5′-3′)A_6, the strands are parallel. As proposed in the

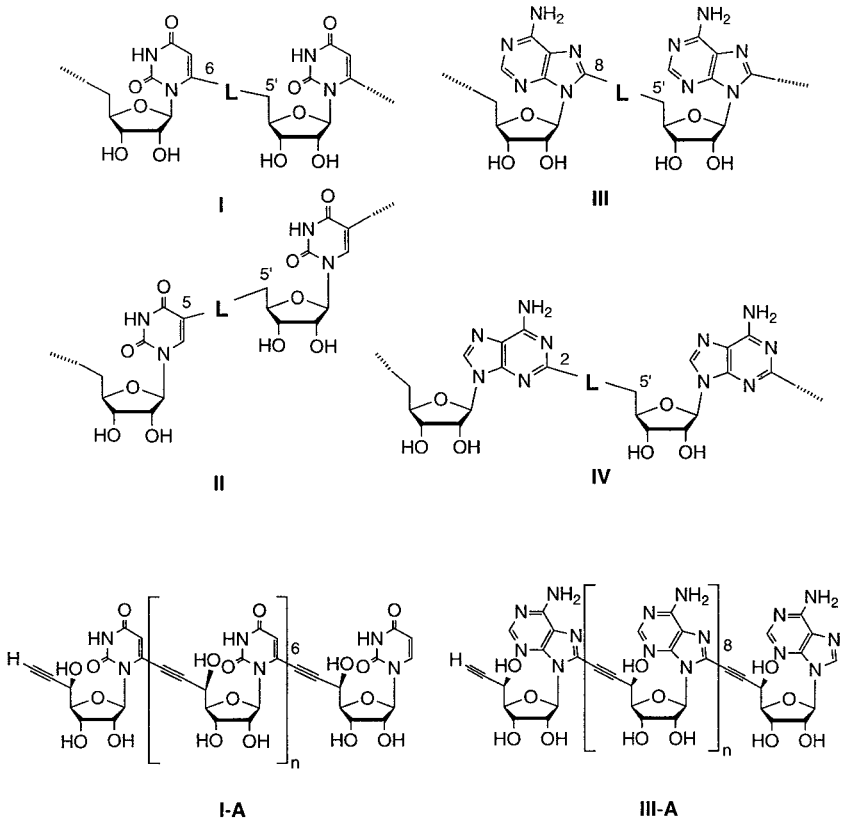


Fig. 2. *Oligonucleosides* **I**–**IV** *varying in the connecting points of the link* **L** *on the sugar and the nucleobase moiety and proposed uridine and adenosine oligomers* **I-A** *and* **III-A**

1996 recommendations for the nomenclature of carbohydrates [14], 'downstream and upstream end' are the expressions used to name the ends at the start (opposite to the arrow direction) and at the end of the strand. Starting from the downstream end, the nucleosides are numbered by roman numerals (*e.g.*, H–C(6/II) = H–C(6) of the second nucleobase, H–C(1′/III) = H–C(1′) of the third furanosyl unit).

2. *Force-Field Calculations of Acetyleno Analogues of RNA Oligonucleotides.* Force-field calculations were performed to evaluate the potential of oligonucleosides possessing acetyleno bridges between the carbohydrate moiety and the nucleobase to form homo- and heteroduplexes similar to the homoduplexes of natural RNA, and to evaluate the appropriate chain length of the carbohydrate unit and the appropriate attachment points between the carbohydrate unit and the nucleobase. Force-field calculations were, however, not intended to find other possible helical or non-helical tertiary structures of such hetero- and homoduplexes possessing a modified backbone.

Calculations were performed with *Macromodel V. 4.5* (Amber* force field, gas phase) [15]. To obtain hetero- and homoduplexes possessing a modified backbone, the A helix of a RNA oligomer was built with the grow tool of *Macromodel*, energy-minimised, and modified. First, evaluation of the chain length of the link showed that

an acetyleno group between C(5′) and the base is better than a buta-1,3-diyne group between C(5′) and the base, and much better than an acetyleno group between C(4′) and the base. A C(5′)–OH group has a negligible influence upon the tertiary structure, independent of the configuration at C(5′); modified strands containing rHepU, aHepU, tHepU, rHepA, aHepA, and tHepA residues lead to similar RNA hetero- and homoduplexes. Next, the attachment point at the base was evaluated. For uridine, C(6) is superior to C(5), whereas both C(2) and C(8) of adenosine are appropriate attachment points. *Fig. 3* shows the calculated helical structures of the homoduplex (7′–6)aHep-

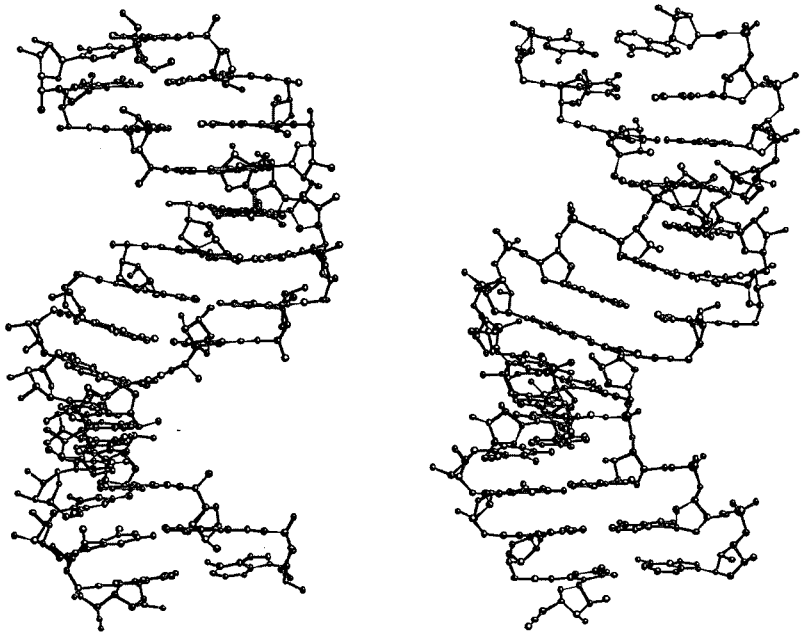


Fig. 3. *Amber*-calculated structures of the fully- and the semi-modified duplex (7′-6)aHepU_{14}·(8–7′)aHepA_{14} and (7′–6)aHepU_{14}·(5′-3′)A_{14}*

U_{14}·(8–7′)aHepA_{14} and the heteroduplex (7′–6)aHepU_{14}·(5′-3′)A_{14}. There are A helices (11 residues per turn), showing slightly enhanced axial rises (*ca.* 2.9 Å instead of 2.74 Å), but similar propeller- and buckle-twist angles as the unmodified (3′-5′)U_{14}·(5′-3′)A_{14}. The ring pucker is changed from ^3E for (3′-5′)U_{14} and $^3T_2$ for (5′-3′)A_{14} to ^4E for both (7′–6)aHepU_{14} and (8–7′)aHepA_{14}. Finally, the compatibility of these acetyleno nucleosides with natural nucleotides in the same strand was evaluated. Replacing a (3′-5′)U unit by a (7′–5)-linked aHepU or a (7′–6)-linked aHepU unit and replacing a (5′-3′)A unit by a (8–7′)-linked aHepA led to severely propeller- and buckle-twisted base pairs. However, a (7′–2)-linked aHepA is tolerated in a strand of natural nucleotides.

The question of whether such acetyleno-oligonucleosides may form other helical or non-helical tertiary structures was investigated with the help of *Maruzen* models.

3. Maruzen *Model Studies*. *Maruzen*-model studies have been performed on the homoduplex (7′−6)aHepU · (8−7′)aHepA and the heteroduplexes (7′−6)aHepU · (5′-3′)A and (3′-5′)U · (8−7′)aHepA. Since *Maruzen* models fix the bond angles of sp^2 and sp centers at 120° and 180°, respectively, the repeating unit of a HepU and aHepA in all structures is characterised by three torsion angles χ, ν, μ, and the sugar-pucker. Based on the results of the force-field calculations, a ^4E sugar pucker of these acetyleno-oligonucleosides was used. For heteroduplexes, all torsion angles of the RNA strands with the exception of χ were chosen as described for RNA strands in RNA duplexes [16]. *Table 1* shows all so far constructed types of helix or ladder structures of homo-

Table 1. *Tertiary Structure, Orientation of Strands, and Torsion-Angle Ranges for* χ, ν, *and* μ[a]) *of Homo- and Heteroduplexes Containing Acetyleno-Nucleoside Strands Derived from* Maruzen *Models*

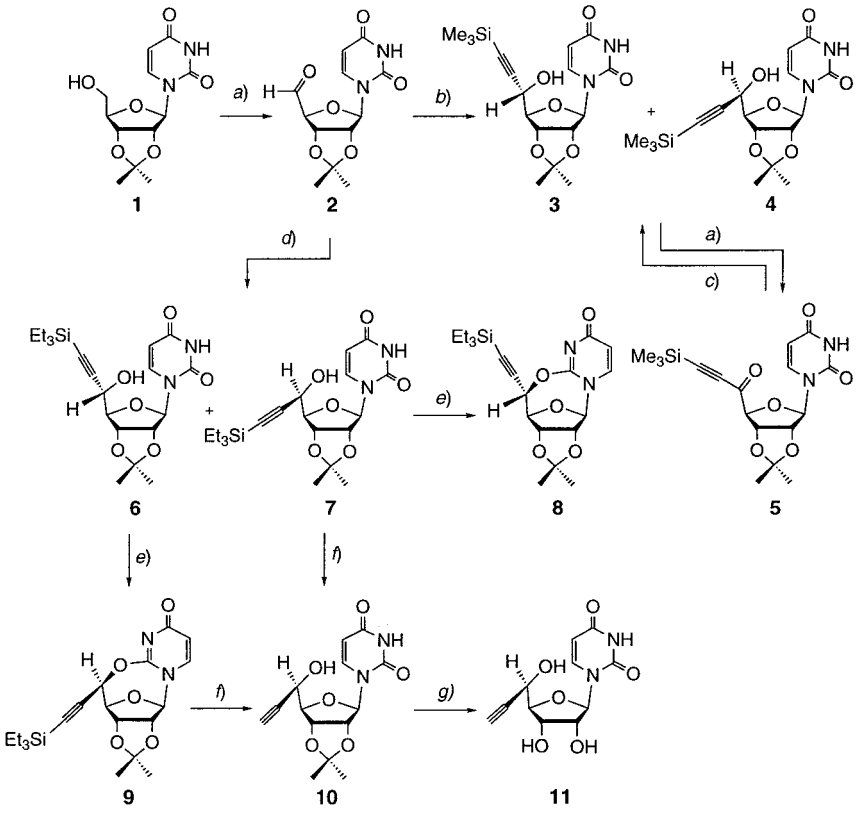
Duplex	Tertiary structure, orientation of strands	χ(aHepU) or χ(U)	ν(aHepU)	μ(aHepU)	χ(aHepA) or χ(A)	ν(aHepA)	μ(aHepA)
$aHepU_n \cdot aHepA_n$	right-handed helix, antiparallel	*ac*, *ap*	*sc*	− *sc*	*ac*	*sc*	− *sc*
$aHepU_n \cdot aHepA_n$	left-handed helix, antiparallel	− *sc*	*ac*	*sc*	− *sc*	*ac*	*sc*
$aHepU_n \cdot A_n$	right-handed helix, parallel	*ac*, *ap*	*sc*	− *sc*	− *ac*, − *ap*		
$aHepU_n \cdot A_n$	ladder structure, antiparallel	*ac*	*sc*	− *sc*	*sc*		
$aHepU_n \cdot A_n$	ladder structure, antiparallel	− *sc*	*ac*	*sc*	− *sc*		
$aHepU_n \cdot A_n$	left-handed helix, parallel	− *sc*	*sc*	*sc*	*ac*		
$U_n \cdot aHepA_n$	right-handed helix, parallel	− *ac*, − *ap*			*sc*, *ac*	*sc*	− *sc*
$U_n \cdot aHepA_n$	ladder structure, antiparallel	*sc*			*sc*, *ac*	*sc*, − *sc*	
$U_n \cdot aHepA_n$	ladder structure, antiparallel	− *sc*			− *sc*	*ap*	*sc*
$U_n \cdot aHepA_n$	left-handed helix, parallel	*ac*, *ap*			− *sc*	*ac*	*sc*

[a]) χ(aHepU) and χ(U): torsion angle O(4′)−C(1′)−N(1)−C(2), χ(aHepA) and χ(A): torsion angle O(4′)−C(1′)−N(9)−C(4), ν(aHepU) and ν(aHepA): torsion angle C(3′)−C(4′)−C(5′)−C(6′), μ(aHepU): torsion angle C(4′)−C(5′)−C(6)−N(1), μ(aHepA): torsion angle C(4′)−C(5′)−C(8)−N(9).

and heteroduplexes of acetyleno-oligonucleosides. All these models maintain a parallel orientation of *Watson-Crick* base pairs at a distance of *ca.* 3 Å, comparable to the distance between base pairs in RNA duplexes (2.6–3.3 Å [17]). The homoduplex of (7′−6)aHepU · (8−7′)aHepA can form a right- and a left-handed helix with antiparallel strand orientation. For heteroduplexes, we find a left- and a right-handed helix and two ladder structures. Rotation of all χ angles in the RNA strand by 180° or the rotation of all χ angles and μ angles in the modified strand by 180° causes a change from a helix to a ladder structure, while rotation of all χ angles by 180° in both single strands causes a change from a right-handed helix to a left-handed helix.

4. *Synthesis of Uridine-Derived Monomers and Dimers.* A binomial synthesis of the desired uridine-derived oligomers based on the *Sonogashira* coupling [18] requires a regioselective cross coupling of two doubly functionalised and selectively protected monomers. One kind of these monomers is represented by the iodo-uridines **17** and **18** that possess a protected alkynyl group, while C(6) is activated by the I substituent (*cf. Scheme 2*). The alkynes **10** and **16** possessing a monosubstituted alkynyl group correspond to the second kind of monomers if one implies activation of H–C(6) subsequent to the cross coupling, *e.g.*, by regioselective iodination. These monomers **10**, **16**, and **17** were prepared from the (5′*R*) (=D-*allo*) configured propargylic alcohol **7**, which was synthesized from uridine in three steps (*Scheme 1*). Repetition of the oxidation of 2′,3′-*O*-isopropylideneuridine (**1**) with CrO_3 [19], or DCC/DMSO [20] on a scale of 0.3 to 1 g gave the carbaldehyde **2** in high yields. Unfortunately, these methods proved unsatisfactory when the scale was increased to 10 g. Oxidation with CrO_3 and pyridine in a mixture of CH_2Cl_2 and DMF yielded only 40% of **2**, while oxidation with pyridinium chlorochromate (PCC) was difficult to reproduce. *Pfitzner-*

Scheme 1



a) Periodinane, CH_2Cl_2; 81% (**2**); 93% (**5**). *b*) $BrMgC{\equiv}C{-}SiMe_3$, THF; 80% of **3**/**4** 1:2. *c*) $NaBH_4$, EtOH; 99% of **3**/**4** 1:1. *d*) $BrMgC{\equiv}C{-}SiEt_3$, THF; 80% of **6**/**7** 1:2. *e*) DEAD, Ph_3P, THF; 94% (**8**); 94% (**9**). *f*) NaOH, MeOH/H_2O 1:1; 98% from **7**; 95% from **9**. *g*) H_2O/MeCN/37% HCl/40% HF 100:50:2:2; quant.

Moffatt oxidation followed by treatment of the crude aldehyde with *N*,*N*′-diphenylethylenediamine [21] gave the *N*,*N*′-diphenylimidazolidine in high yield, but its cleavage with *Dowex 50WX8* (H^+ form) in aqueous THF led to the highly water-soluble hydrate of **2**, which was degraded during attempted alkynylation. However, oxidation of **1** with periodinane [22] on a 50-g scale gave **2** in 95% yield as *ca*. 85% pure material. Treatment of crude **2** with 2.5 equiv. of $Me_3SiC{\equiv}CMgBr$ led in 80% to a 1:2 mixture of the diastereoisomeric propargylic alcohols **3** and **4**, which were, at best, partially separated by flash chromatography (FC) and crystallization[2]). Substitution of $Me_3SiC{\equiv}CMgBr$ by bis[(trimethylsilyl)ethinyl]zinc or addition of $CeCl_3$ [23] had no significant influence on yield and ratio of the products. Oxidation of **3**/**4** (1:1) with periodinane yielded 93% of a single ketone **5**, establishing that **3** and **4** are diastereoisomers. This ketone could not be reduced with a sufficiently high degree of diastereoselectivity (<2:1) by either $NaBH_4$, Alpine Borane [24], or BH_3 in the presence of *Corey*'s oxazaborolidine [25]. Addition of $Et_3SiC{\equiv}CMgBr$ to **2** yielded 80% of a 1:2 mixture **6**/**7**. In contradistinction to the trimethylsilyl derivatives **3** and **4**, the triethylsilyl derivatives **6** and **7** were easily separated by a combination of FC and crystallization. Treatment of 2′,3′-*O*-isopropylidene-uridines with PPh_3 and diethyl azodicarboxylate (DEAD) yields the corresponding 2,5′-anhydro-uridines [26] which are hydrolysed under basic conditions [27]. This sequence should allow inversion of the configuration at C(5′) of **6** and **7**. Indeed, treatment of the D-*allo*-isomer **7** with PPh_3 and DEAD gave 94% of the L-*talo* 2,5′-anhydride **8**; similarly, the L-*talo* **6** gave 94% of the D-*allo* anhydride **9**[3]). The rigid skeleton of **8** and **9** allowed assignment of the absolute configuration at C(5′) by ^{1}H-NMR spectroscopy (see below). *C*-Desilylation of the major isomer **7** with NaOH in $MeOH/H_2O$ proceeded quantitatively to the crystalline alcohol **10**. This alcohol was also prepared in an overall yield of 89% by hydrolysis with NaOH in $MeOH/H_2O$[4]) of the anhydride **9** obtained from the minor isomer **6**. Hydrolysis of **9** gave **10**. Deisopropylidenation of **10** in a mixture of 0.16N HCl and 0.3N HF in $MeCN/H_2O$ 1:2 [28] at 23° gave quantitatively the crystalline triol **11**.

MM3* Molecular modelling showed that the anhydrides **8** and **9** possess a rigid skeleton. The furanose ring adopts a E_O conformation, as evidenced by $J(1',2') = J(3',4') = 0$ Hz. The 1,5,3-dioxazepane ring adopts a chair-like conformation. As expected, the pseudoequatorial H–C(5′) of **8** resonates at lower field (5.15 ppm) than the pseudoaxial H–C(5′) of **9** (4.86 ppm); both H–C(5′) show a small $J(4',5')$ value (**8**: 1.6, **9**: 1.2 Hz), demonstrating the *gauche* orientation of H–C(4′) and H–C(5′). The configuration at C(5′) was determined by NOE experiments. Irradiation of H–C(5′) of **8** led to a NOE of 8% for H–C(3′) at 4.95 ppm, and of 12% for H–C(4′) at 4.63 ppm, evidencing the (5′*S*)-configuration of **8**. Irradiation of H–C(5′) of **9** led only to a NOE

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[2]) Protection of HO–C(5′) of **3**/**4** 1:2 by an Ac, (substituted) benzoyl, 1-naphthoyl, 2-naphthoyl (allyloxy)carbonyl, (benzyloxy)carbonyl, imidazolylcarbonyl, or imidazolylthiocarbonyl group gave, in each case, an inseparable mixture of diastereoisomers.

[3]) Treatment of **6** with PPh_3, DEAD, and 4-nitrobenzoic acid gave a 1:3 mixture of **9** and the 5′-*O*-(4-nitrobenzoyl) derivative of **7**. Similarly, **7** led to a 1:3 mixture of **8** and the 5′-*O*-(4-nitrobenzoyl) derivative of **6**.

[4]) Treatment of **9** with $TsOH \cdot H_2O$ in $MeOH/H_2O$ yielded 90–95% of **7** besides 5–10% of **6**.

(19%) for H–C(4′) at 4.68 ppm, in keeping with the (5′*R*)-configuration of **9** and, hence, also of **10** and **7**.

The (5′*R*)-configuration of **9**, **10**, and **11** was also established by X-ray analyses[5]) (*Fig. 4*). Similarly to force-field calculations and the solid-state structure of 2′,3′-*O*-isopropylidene-2,5′-anhydrouridine [29], the 1,5,3-dioxazepane ring of crystalline **9** adopts a chair-like conformation, the furanose ring a E_O conformation (pseudorotational phase angle [30] $P = 270°$). The propargylic alcohol **10**, in the solid state, possesses an intramolecular O(5′)–H···O(2) H-bond characterized by a H···O distance of 1.74 Å, and a O(5′)–H···O(2) bond angle of 156.9°. This is the first example of an O(5′)–H···O(2′) intramolecular H-bond of a 6-unsubstituted uridine in the solid state (for intramolecular H-bonds in 6-substituted uridines, see [31–33]). The furanose ring of **10** adopts a E_1 conformation, which belongs to the southern puckering family ($P = 165°$). The crystalline triol **11** possesses the ^2E conformation and forms only intermolecular H-bonds: O(5′)H to O(4′), O(3′)H to HO(2′), O(2′)H to HO(3′), and N(3)H to O=C(4). The anhydro bond of **9** (O(4′)–C(1′)–N(1)–C(2) χ angle = 67.0°) and the H-bond of **10** ($\chi = 63.1°$) lead to a similar *syn*-conformation. In the absence of an intramolecular H-bond, **11** adopts an *anti*-conformation ($\chi = -124.3°$).

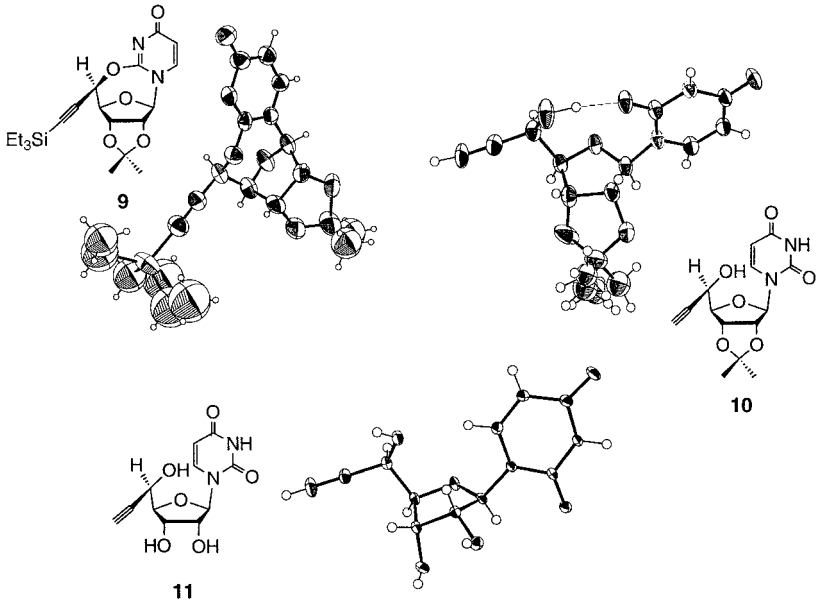

Fig. 4. *X-Ray crystal structures of* **9**, **10**, *and* **11**

We considered it advantageous to use the easily accessible iodide **13** to investigate the conditions of cross-coupling and deprotection of the resulting dimer (*Scheme 2*). 2′,3′-*O*-Isopropylideneuridine (**1**) was silylated and iodinated by treatment with LDA

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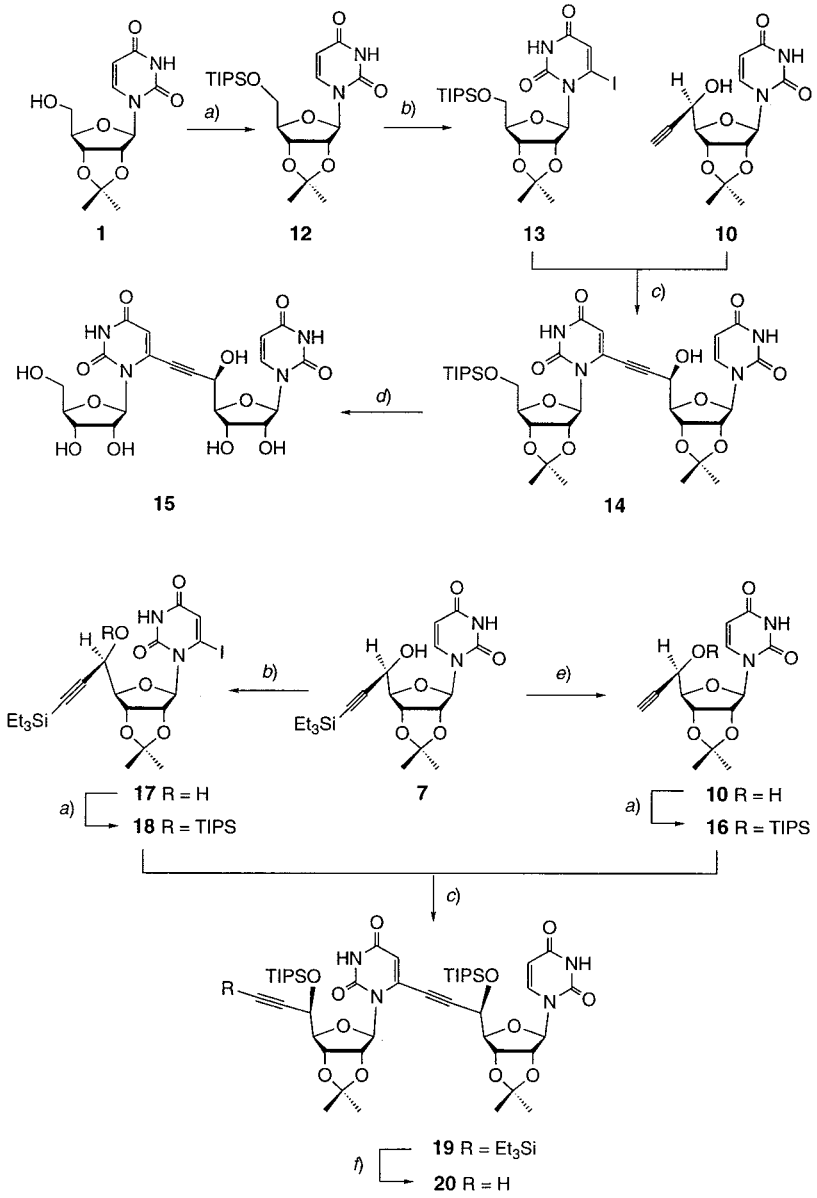
[5]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No CCDC-142232 (**9**), No. CCDC-142233 (**10**), and No. CCDC-142234 (**11**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

Scheme 2



a) TIPSOTf, pyridine, CH_2Cl_2; 94% (**12**); 84% (**16**); 89% (**18**). *b*) LDA, THF, then NIS, then AcOH; 78% (**13**); 62% (**17**). *c*) [$Pd_2(dba)_3$], CuI, P(fur)$_3$, toluene/NEt_3 1:1; 70% (**14**); 63% (**19**). *d*) H_2O/MeCN/37% HCl/40% HF 100:50:2:2; 73%. *e*) NaOH, MeOH/H_2O 1:1; 98%. *f*) $AgNO_3$, MeOH/AcOEt, then KCN; 63%.

and NIS [34] to give 73% of the iodide **13**. Cross-coupling of **10** and **13** in the presence of 5% [$Pd_2(dba)_3$], 7% CuI, and 7% P(fur)$_3$ in toluene/NEt_3 1:1 at 23° [35] resulted in 70% of the dimer **14**, which was purified by FC[6]). Treatment of **14** with dilute aqueous CF_3COOH at room temperature led to partial decomposition. However, applying the same conditions as used for the deisopropylidenation of the monomer **10** (0.16N HCl and 0.3N HF) gave **15** (73%) which is soluble in H_2O and in MeOH and was purified by RP-HPLC.

Iodination of **7** by treatment with LDA and NIS [34] gave 62% of the iodide **17** besides 24% of starting material[7]), which were separated by FC (*Scheme 2*). Silylation of **17** with TIPSOTf yielded 89% of the silyl ether **18**; similarly, **10** yielded 84% of **16**. Cross-coupling of **16** and **18** under the same conditions as used for **10** and **13** gave 63% of the dimer **19**, which was selectively *C*-desilylated with $AgNO_3$ and KCN in MeOH to afford the dimer **20**, a potential partner for a further *Sonogashira* reaction. Coupling constants $J(1',2') = 2.6-3.7$ and $J(3',4') = 2.5-3.7$ Hz show a *ca.* 1:1 equilibrium between the $^3T_2$ and $^2T_3$ conformers for the D-*ribo*- and D-*allo*-configured alcohols **1**, **4**, **7**, **10**, and **17**, the D-*ribo* silyl ether **12**, and the D-*allo* silyl ether **16** (*Table 2*). The small $J(1',2') < 1.0$ Hz and $J(3',4') \leq 2.2$ Hz of the 5-ulofuranosyluridines **2** and **5**, and the L-*talo* alcohols **3** and **6**, however, indicate a preference for the E_O conformer that has already been observed for the 2,5′-anhydrides **8** and **9**. Whereas the 6-iodo-propargylic alcohol **17** still adopts a *ca.* 1:1 equilibrium of $^3T_2$ and $^2T_3$ conformers ($J(1',2') = J(3',4') = 3.7$ Hz), the 6-iodo silyl ethers **13** and **18** prefer the $^3T_2$ conformation, as evidenced by $J(1',2') = 1.2$ and $J(3',4') = 3.6-4.6$ Hz.

The observation of an intramolecular O(5′)–H···O(2) H-bond in the solid state of **10** raises the question of whether such H-bonds are also present in $CDCl_3$ solution. The chemical shift of the OH groups of **3**, **4**, **6**, **7**, and **17** in $CDCl_3$ (3.0–3.8 ppm) does not allow unambigous assignment of an intramolecular H-bond (see [38]). However, a small $J(4',5')$ value may evidence an intramolecular H-bond, as the H–C(4′)–C(5′)–H dihedral angle of −67.4° for the solid-state conformation of **10** corresponds to a $J(4',5') = 1.6$ Hz [39]. The propargylic alcohols **3**, **4**, **6**, **7**, and **10** show $J(4',5') = 3.1-4.7$ Hz, indicating a weak preference for the conformers exhibiting synclinal H–C(4′) and H–C(5′) bonds, which is also observed for the silyl ether **16** ($J(4',5') = 3.7$ Hz). Thus, the similar $J(4',5')$ values of the alcohols and the silyl ether **16** agree with the absence of an intramolecular H-bond. This is corroborated by similar δ(H–C(2′)) values of **3**, **4**, **6**, and **7** (4.87–4.91 ppm) and the silyl ether **16** (4.72 ppm), evidencing a preference for an *anti*-conformation (as already found for uridines; see [40] and refs. cit. there). The downfield shift of H–C(2′) of the iodides **13**, **17**, and **18** (5.20–5.30 ppm, $\Delta\delta = 0.3-0.5$ ppm) evidences a preferred *syn*-conformation. The large $J(4',5')$ values of the silyl ethers **13** (6.7 Hz for both H–C(5)) and **18** (8.4 Hz) indicate a steric interaction between the nucleobase and the side chain at C(4′); the conformer possessing antiperiplanar H–C(4′) and H–C(5′) bonds is favoured. The smaller $J(4',5')$

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6) Preliminary experiments with several acetylenes showed that these conditions were superior to using, *e.g.*, [Pd(PPh_3)$_4$], CuI, and PPh_3 in NEt_3; $PdCl_2(PPh_3)_2$, CuI, and PPh_3 in NEt_3; [$Pd_2(dba)_3$], CuI, and P(fur)$_3$, in TMEDA; $Pd_2(dba)_3$, CuI, and P(fur)$_3$ in NEt_3/DMSO; [$Pd_2(dba)_3$], CuI, and P(fur)$_3$ in NEt_3/DMF; $Pd_2(dba)_3$, CuI, and P(fur)$_3$ in pyridine; $Pd_2(dba)_3$, CuI, and $AsPh_3$ in NEt_3/toluene [36][37].

7) Surprisingly, the TIPS–O(5′) protected derivative of **7** decomposed under these conditions.

value of the iodo alcohol **17** (4.2 Hz) is due to a partial intramolecular H-bond favoured by the *syn*-conformation. The ^{13}C-NMR spectra of **1**–**10**, **12**, **13**, and **16**–**18** show the expected shifts for C(2′) (81.4–86.1 ppm), C(3′) (80.0–84.7 ppm), C(4′) (86.9–91.6 ppm, ulofuranosyl derivatives **2** and **5**: 99.5 and 100.3 ppm), and C(5′) (61.6–66.1 ppm, ulofuranosyl derivatives **2** and **5**: 199.6 and 184.4 ppm; *Table 3*). The signals for the C≡CSiR$_3$ groups of **3**, **4**, **6**, **7**, **17**, and **18** appear at characteristic positions (2*s*) at 88.2–92.3 and 101.7–106.5 ppm; *cf.* [35][37], whereas the corresponding C≡CSiR$_3$ groups of the 2,5′-anhydrides **8** and **9** resonate in the narrow range of 95.2–97.4 ppm. The C≡CH groups of **10** and **16** give rise to a *doublet* at 74.7 and 75.8 ppm, and a *singlet* at 81.3 and 81.7 ppm. The introduction of the I substituent at C(6) of **13**, **17**, and **18** leads to an upfield shift of C(6) at 113–114.2 ppm ($\Delta\delta \approx 28$ ppm) and to a downfield shift of C(1′) at 101.6–102.8 ppm ($\Delta\delta \approx 8$ ppm)[8]).

The ^{1}H-NMR assignments of the dimers **14**, **19**, and **20** were corroborated by selective homodecoupling experiments. The values for H–C(2′/II), H–C(3′/II), H–C(4′/II), and H–C(5′/II) of the silyl ethers **14**, **19**, and **20** differ only slightly ($\Delta\delta \leq 0.08$ ppm) from the corresponding values of the silylated iodinated precursors **13** and **18**. Similarly, the *J*(1′,2′/II), *J*(2′,3′/II), *J*(3′,4′/II), and *J*(4′,5′/II) values of **14**, **19**, and **20** differ only slightly ($\Delta J \leq 0.3$ Hz) from the corresponding values of **13** and **18**. This evidences the preferred *syn*-conformation for unit II of **14**, **19**, and **20**. The δ values of H–C(2′/I), H–C(3′/I), H–C(4′/I), H–C(5′/I), *J*(1′,2′/I), *J*(2′,3′/I), *J*(3′,4′/I), and the *J*(4′,5′/I) value of **14**, **19**, and **20** differ more strongly ($\Delta\delta = 0.05$–0.38 ppm, $\Delta J = 0.5$–1.8 Hz) from the corresponding values of the precursors **10** and **16**. Especially the downfield shift of H–C(2′/I) (*ca.* 0.2 ppm) suggests a *ca.* 1:1 equilibrium of the *syn*- and *anti*-conformer for the unit I of the dimers **14**, **19**, and **20**. The ^{13}C-NMR assignments of **14**, **19**, and **20** are based on the ^{1}H,^{13}C-COSY spectrum of **19** (*cf. Table 5*). The δ values for the signals of C(1′) to C(5′) of unit II differ only slightly from the corresponding signals of unit I ($\Delta\delta \leq 2.7$ ppm). In contrast to the I substituent, the acetyleno groups attached at C(6/II) have a negligible influence upon the chemical shift of C(1′/II). The acetylenic C(6′/I) and C(7′/I) of **14**, **19**, and **20** resonate at 100.0–101.0 ppm and 76.6–76.7 ppm [42], respectively, whereas C(6′/II) and C(7′/II) of **19**, and **20** appear at expected positions (Et$_3$Si–C≡C of **19** at 87.8 and 106.3 ppm, HC≡C of **20** at 73.7 and 83.8 ppm). The bridging acetyleno group of **14**, **19**, and **20** leads to a downfield shift of C(5/II) by *ca.* 6 ppm. Deprotection of **14** leads to the expected upfield shifts for C(2′/I), C(3′/I), C(2′/II), and C(3′/II) ($\Delta\delta = 8.2$–9.7 ppm) and to smaller shifts of the other C-atoms ($\Delta\delta = 0.1$–3.8 ppm).

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Experimental Part

General. Solvents were distilled before use: THF from K/benzophenone, CH_2Cl_2 from CaH_2. Reactions were run under Ar. Qual. TLC: precoated silica-gel plates (*Merck* silica gel *60* F_{254}); detection by spraying with 'mostain' (400 ml of 10% aq. H_2SO_4, 20 g of $(NH_4)_6Mo_7O_{24}\cdot H_2O$, 0.4 g of $Ce(SO_4)_2$) and heating. Flash chromatography (FC): silica gel *Merck 60* (0.04–0.063 mm). Optical rotations: 1-dm cell at 25° and 589 nm. FT-

[8]) The downfield shift of C(1′) is surprising. No ^{13}C-NMR data of 6-iodinated uridines are available, but iodination of toluene in *ortho*-position leads to a downfield shift of 7 ppm for the Me group (2-iodotoluene: 28.1 ppm [41], toluene: 21.4 ppm [41]).

IR: 1–2% soln. in the indicated solvent. ^{1}H- and ^{13}C-NMR: at 200, 300, 400, or 500 MHz, and 50, 75, 100, or 125 MHz, resp. MS: Fast-atom-bombardment (FAB; NOBA: 3-nitrobenzyl alcohol), or electron spray ionisation (ESI).

*1-(2,3-*O*-Isopropylidene-β-*D*-ribo-pentodialdo-1,4-furanosyl)uracil* (**2**). At 23°, a soln. of periodinane (89.1 g, 0.21 mol) in CH_2Cl_2 (1 l) was treated with **1** (57 g, 0.2 mol) in 3 portions during 30 min, stirred for 8 h at 23°, and evaporated. The residue was dissolved in AcOEt (500 ml), and filtered. Evaporation gave *ca.* 85% pure **2** (54 g, 81%), which was used without further purification for the next step. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 9.60 (br. *s*, NH); 1.55, 1.38 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*, additionally, 27.3, 25.1 (2*q*, *Me*$_2$C).

Table 2. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of* **1**–**10**, **12**, **13**, **16**, **17**, *and* **18** *in $CDCl_3$ Solution*

	1[a])	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**[a])	**12**	**13**	**16**	**17**	**18**
H–C(5)	5.68	5.79	5.72	5.74	5.80	5.71	5.72	6.07	6.12	5.78	5.67	6.46	5.69	6.51	6.44
H–C(6)	7.82	7.30	7.55	7.53	7.33	7.48	7.55	7.30	7.31	7.87	7.68	–	7.53	–	–
H–C(1′)	5.86	5.52	5.72	5.73	5.57	5.70	5.78	5.37	5.37	5.95	5.99	6.10	5.96	6.04	6.05
H–C(2′)	4.91	5.25	4.91	4.90	5.43	4.94	4.87	4.88	4.91	4.84	4.69	5.20	4.72	5.30	5.27
H–C(3′)	4.82	5.13	4.91	4.98	5.25	4.91	5.00	4.95	5.17	4.98	4.85	4.85	4.94	5.16	5.03
H–C(4′)	4.21	4.57	4.28	4.35	4.66	4.30	4.33	4.63	4.68	4.24	4.27	4.22	4.27	4.28	4.07
H–C(5′)	3.79, 3.70	9.42	4.62	4.64	–	4.63	4.64	5.15	4.86	4.54	4.00, 3.88	3.87	4.76	4.63	4.62
H–C(7′)	–	–	–	–	–	–	–	–	–	2.97	–	–	2.54	–	–
J(5,6)	8.1	7.9	8.1	8.1	8.1	8.1	8.1	7.5	7.5	7.9	8.1	–	8.1	–	–
J(1′,2′)	2.6	0	<1	3.7	<1	1.3	3.7	0	0	3.3	2.8	1.2	3.4	3.7	1.2
J(2′,3′)	6.2	6.2	[b])	6.2	6.2	6.7	6.2	5.3	5.6	6.3	6.2	6.6	6.5	6.3	6.5
J(3′,4′)	3.4	1.3	<1	2.5	<1	2.2	2.8	0	0	2.5	3.4	4.6	3.7	3.7	3.4
J(4′,5′)	3.7, 4.7[c])	0	4.0	3.3	–	4.7	3.1	1.6	1.2	3.7	2.5, 3.4[d])	6.7	3.7	4.2	8.4
J(5′,7′)	–	–	–	–	–	–	–	–	–	2.1	–	–	2.2	–	–

[a]) In CD_3OD. [b]) Not assigned. [c]) $J_{gem} = 12.0$ Hz. [d]) $J_{gem} = 11.2$ Hz.

Table 3. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of* **1**–**13**, **16**, **17**, *and* **18** *in $CDCl_3$ Solution*

	1[a])	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**[a])	**11**[b])	**12**	**13**	**16**	**17**	**18**
C(2)	166.6	163.6	163.1	164.0	163.2	164.1	164.0	171.0	171.2	164.9	169.1	163.7	160.9	163.4	160.5	161.8
C(4)	152.5	150.8	150.1	150.5	150.9	150.3	150.6	155.0	155.6	151.0	155.7	150.4	146.6	150.4	147.8	147.4
C(5)	102.9	103.0	102.3	103.2	103.0	101.8	102.9	110.8	111.2	101.3	106.2	102.5	116.3	102.7	117.6	117.0
C(6)	144.2	144.4	141.7	142.8	144.5	142.6	143.1	141.4	141.5	142.1	145.6	140.9	113.3	141.2	113.6	114.0
C(1′)	94.4	94.2	93.9	95.1	94.9	94.9	96.2	99.0	99.1	92.7	92.4	91.7	101.6	92.0	102.8	102.4
C(2′)	86.1	85.0	82.8	84.1	84.8	84.1	84.4	85.3	85.3	84.2	78.5	85.4	83.4	84.5	81.4	84.2
C(3′)	82.4	83.9	80.0	81.0	84.7	81.1	82.1	82.1	81.5	80.7	74.8	80.0	81.8	80.3	80.4	83.1
C(4′)	88.6	100.3	87.2	88.5	99.5	89.1	88.6	87.3	88.6	88.3	92.1	86.9	89.5	88.6	88.5	91.6
C(5′)	63.3	199.6	62.7	63.1	184.4	63.0	66.1	74.4	75.7	61.6	66.2	63.5	63.7	63.5	63.0	63.9
C(6′)	–	–	101.7	102.4	128.6	104.1	102.9	97.4	96.4	81.3	85.7	–	–	81.7	103.2	106.5
C(7′)	–	–	92.1	91.9	[c])	89.1	92.3	95.2	96.0	74.7	79.1	–	–	75.8	89.3	88.2

[a]) In CD_3OD. [b]) In D_2O. [c]) Not assigned.

*1-[6,7-Dideoxy-2,3-*O*-isopropylidene-7-*C*-(trimethylsilyl)-α-*L*-talo-hept-6-ynofuranosyl]uracil and 1-[6,7-Dideoxy-2,3-*O*-isopropylidene-7-*C*-(trimethylsilyl)-β-*D*-allo-hept-6-ynofuranosyl]uracil* (**3** and **4**, resp.). At 0°, a soln. of (trimethylsilyl)acetylene (36.8 ml, 0.27 mol) in THF (900 ml) was treated dropwise with 3.0M EtMgBr in Et_2O (89 ml, 0.27 mol), stirred at 0° for 15 min and at 23° for 45 min, cooled to −15°, treated dropwise with a soln. of crude **2** (31.6 g, 0.110 mol) in THF (900 ml), stirred at −15° for 1.5 h, treated with sat. aq. NH_4Cl soln. (400 ml), and allowed to warm to 23°. After evaporation, the residue was diluted with AcOEt, washed with sat.

aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:1) and crystallization gave **4** (9.3 g, 21% from **1**) and **3**/**4** 1:1 (18.7 g, 42% from **1**).

Data of **3**: Colorless solid. R_f(AcOEt/hexane 1:1) 0.25. ^{1}H-NMR (300 MHz, $CDCl_3$ **3**/**4** 1:1): see *Table 2*; additionally, 9.55 (br. *s*, NH); 3.60 (br. *s*, OH); 1.56, 1.34 (2*s*, Me_2C); 0.16 (*s*, Me_3Si). ^{13}C-NMR (50 MHz, $CDCl_3$, **3**/**4** 1:1): see *Table 3*; additionally, 114.7 (*s*, Me_2C); 27.2, 25.3 (2*q*, *Me*$_2$C); −0.3 (*q*, Me_3Si).

Data of **4**: Colourless crystals. R_f(AcOEt/hexane 1:1) 0.26. M.p. 162.5–165.0°. $[\alpha]_D^{25} = -66.9$ ($c = 0.8$, $CHCl_3$). IR ($CHCl_3$): 3390*w* (br.), 3008*w*, 2876*w*, 2176*w*, 1697*s*, 1456*m*, 1385*m*, 1088*m*, 848*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 9.55 (br. *s*, NH); 3.21 (br. *s*, OH); 1.60, 1.38 (2*s*, Me_2C); 0.19 (*s*, Me_3Si). ^{13}C-NMR (50 MHz, $CDCl_3$): see *Table 3*; additionally, 114.0 (*s*, Me_2C); 26.9, 24.9 (2*q*, *Me*$_2$C); −0.7 (*q*, Me_3Si). FAB-MS (NOBA): 761 (19, $[2M+H]^+$), 403 (20, $[M+Na]^+$), 381 (100, $[M+H]^+$), 365 (41, $[M-Me]^+$). Anal. calc. for $C_{17}H_{24}N_2O_6Si$ (380.47): C 53.67, H 6.36, N 7.36; found: C 53.63, H 6.13, N 7.39.

1-[6,7-Dideoxy-2,3-O*-isopropylidene-7*-C*-(trimethylsilyl)-β*-D-ribo*-hept-6-yno-5-ulofuranosyl]uracil* (**5**). At 23°, a soln. of periodinane (0.34 g, 0.8 mmol) in CH_2Cl_2 (10 ml) was treated with **3**/**4** 1:1 (0.26 g, 0.68 mmol), stirred for 30 min at 23°, washed with sat. aq. $NaHCO_3$ (2 × 20 ml), dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:1) and crystallization from AcOEt/hexane gave **5** (0.24 g, 93%). Colourless crystals. R_f(AcOEt/hexane 2:1) 0.52. M.p. 204.5–210.0° (dec.). $[\alpha]_D^{25} = 55.3$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3384*w*, 2960*w*, 2929*w*, 2154*w*, 1716*m*, 1695*s*, 1455*m*, 1377*m*, 1257*m*, 1083*m*, 909*m*, 850*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 8.85 (br. *s*, NH); 1.54, 1.35 (2*s*, Me_2C); 0.25 (*s*,Me_3Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 113.8 (*s*, Me_2C); 26.6, 25.0 (2*q*, *Me*$_2$C); −0.62 (*q*, Me_3Si). FAB-MS (NOBA): 757 (36, $[2M+H]^+$), 379 (100, $[M+H]^+$). Anal. calc. for $C_{17}H_{22}N_2O_6Si$ (378.46): C 53.95, H 5.86, N 7.40; found: C 53.78, H 5.82, N 7.37.

Reduction of **5**. At 23°, a soln. of **5** (30 mg, 0.079 mmol) in EtOH (2 ml) was treated dropwise with a soln. of $NaBH_4$ (3 mg, 0.079 mmol) in EtOH (0.2 ml), stirred for 5 min, treated with sat. aq. NH_4Cl soln. (1 ml), diluted with AcOEt, washed with sat. aq. NH_4Cl soln., sat. aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:1) gave **3**/**4** 1:1 (^{1}H-NMR; 30 mg, 99%).

1-[6,7-Dideoxy-2,3-O*-isopropylidene-7*-C*-(triethylsilyl)-α*-L-talo*-hept-6-ynofuranosyl]uracil and 1-[6,7-Dideoxy-2,3*-O*-isopropylidene-7*-C*-(triethylsilyl)-β*-D-allo*-hept-6-ynofuranosyl]uracil* (**6** and **7**, resp.). At 0°, a soln. of (triethylsilyl)acetylene (58.0 g, 0.44 mol) in THF (900 ml) was treated dropwise with 3.0M EtMgBr in Et_2O (143 ml, 0.44 mol), stirred at 0° for 15 min and at 23° for 45 min, cooled to −15°, treated dropwise with a soln. of crude **2** (50.0 g, 0.187 mol) in THF (900 ml), stirred at −15° for 1.5 h, treated with sat. aq. NH_4Cl soln. (400 ml), and allowed to warm to 23°. After evaporation, the residue was diluted with AcOEt, washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:1) and crystallization gave **6** (15.9 g, 20% from **1**) and **7** (31.9 g, 41% from **1**).

Data of **6**: Colourless crystals. R_f(AcOEt/hexane 1:1) 0.32. M.p. 142.5–144.0°. $[\alpha]_D^{25} = +18.1$ ($c = 6.1$, $CHCl_3$). IR ($CHCl_3$): 3390*w* (br.), 2994*m*, 2913*w*, 2160*w*, 1694*s*, 1457*m*, 1384*m*, 1271*m*, 1087*m*, 909*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 8.9 (br. *s*, NH); 3.0 (br. *s*, OH); 1.60, 1.26 (2*s*, Me_2C); 1.00 (*t*, $J =$ 7.5, (*Me*CH_2)$_3$Si); 0.61 (*q*, $J = 7.5$, (MeCH_2)$_3$Si). ^{13}C-NMR (50 MHz, $CDCl_3$): see *Table 3*; additionally, 114.2 (*s*, Me_2C); 26.9, 24.9 (2*q*, *Me*$_2$C); 6.1 (*q*, (*Me*CH_2)$_3$Si); 3.9 (*t*, (MeCH_2)$_3$Si). FAB-MS (NOBA): 867 (12, $[2M+Na]^+$), 845 (36, $[2M+H]^+$), 445 (89, $[M+Na]^+$), 423 (100, $[M+H]^+$), 407 (43, $[M-Me]^+$). Anal. calc. for $C_{20}H_{30}N_2O_6Si$ (422.55): C 56.85, H 7.16, N 6.63; found: C 56.97, H 7.15, N 6.60.

Data of **7**: Colourless crystals. R_f(AcOEt/hexane 1:1) 0.38. M.p. 167.5–169.0°. $[\alpha]_D^{25} = -67.6$ ($c = 1.1$, $CHCl_3$). IR ($CHCl_3$): 3390*w* (br.), 2958*w*, 2876*w*, 2150*w*, 1697*s*, 1457*m*, 1385*m*, 1272*w*, 1088*m*, 909*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): see *Table 2*; additionally, 9.26 (br. *s*, NH); 3.52 (br. *s*, OH); 1.50, 1.36 (2*s*, Me_2C); 0.99 (*t*, $J =$ 7.5, (*Me*CH_2)$_3$Si); 0.61 (*q*, $J = 7.5$, (MeCH_2)$_3$Si). ^{13}C-NMR (125 MHz, $CDCl_3$): see *Table 3*; additionally, 114.4 (*s*, Me_2C); 27.3, 25.1 (2*q*, *Me*$_2$C); 7.3 (*q*, (*Me*CH_2)$_3$Si); 4.2 (*t*, (MeCH_2)$_3$Si). FAB-MS (NOBA): 868 (7, $[2M+Na]^+$), 845 (13, $[2M+H]^+$), 445 (100, $[M+Na]^+$), 423 (57, $[M+H]^+$), 407 (65, $[M-Me]^+$). Anal. calc. for $C_{20}H_{30}N_2O_6Si$ (422.55): C 56.85, H 7.16, N 6.63; found: C 57.02, H 7.16, N 6.61.

2,5′-Anhydro-1-[6,7-dideoxy-2,3-O*-isopropylidene-7*-C*-(triethylsilyl)-α*-L-talo*-hept-6-ynofuranosyl]uracil* (**8**). A refluxing soln. of **7** (100 mg, 0.24 mmol) and Ph_3P (68 mg, 0.24 mmol) in THF (5 ml) was treated dropwise with diethyl azodicarboxylate (DEAD; 0.045 ml, 0.24 mmol), and stirred for 1 min. After evaporation, FC (AcOEt/hexane 3:1) and crystallisation from AcOEt/hexane gave **8** (90 mg, 94%). Colourless crystals. R_f(AcOEt) 0.31. $[\alpha]_D^{25} = +130$ ($c = 1.3$, $CHCl_3$). IR ($CHCl_3$): 2957*s*, 2927*s*, 2875*m*, 2857*w*, 1644*s*, 1533*s*, 1444*m*, 1378*w*, 1304*w*, 1177*w*, 1076*w*, 1053*m*, 944*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 1.50, 1.36 (2*s*, Me_2C); 0.99 (*t*, $J = 7.5$, (*Me*CH_2)$_3$Si); 0.61 (*q*, $J = 7.5$, (MeCH_2)$_3$Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 113.8 (*s*, Me_2C); 26.1, 24.6 (2*q*, *Me*$_2$C), 7.3 (*q*, (*Me*CH_2)$_3$Si); 3.9 (*t*, (MeCH_2)$_3$Si). FAB-MS

(NOBA): 809 (37 $[2M+H]^+$), 405 (100, M^+). Anal. calc. for $C_{20}H_{28}N_2O_5Si$ (404.54): C 59.38, H 6.98, N 6.92; found: C 59.43, H 7.12, N 6.82.

2,5′-Anhydro-1-[6,7-dideoxy-2,3-O-*isopropylidene-7*-C-*(triethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]uracil* (**9**). A refluxing soln. of **6** (5.1 g, 12.1 mmol) and Ph_3P (3.3 g, 12.7 mmol) in THF (100 ml) was treated dropwise with DEAD (2 ml, 12.7 mmol) and stirred for 1 min. After evaporation, FC (AcOEt/hexane 3:1) and crystallization from AcOEt/hexane gave **9** (4.6 g, 94%). Colourless crystals. R_f(AcOEt) 0.31. M.p. 219–222°. $[\alpha]_D^{25} = -88.7$ ($c = 0.4$, $CHCl_3$). IR ($CHCl_3$): 2999*m*, 2857*w*, 1644*s*, 1531*s*, 1445*m*, 1378*w*, 1061*m*, 867*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 1.50, 1.36 (2*s*, Me_2C); 0.99 (*t*, $J = 7.5$, $(MeCH_2)_3Si$); 0.61 (*q*, $J = 7.5$, $(MeCH_2)_3Si$). ^{13}C-NMR (125 MHz, $CDCl_3$): see *Table 3*; additionally, 113.4 (*s*, Me_2C); 26.0, 24.5 (2*q*, Me_2C); 6.8 (*q*, $(MeCH_2)_3Si$); 4.2 (*t*, $(MeCH_2)_3Si$). FAB-MS (NOBA): 405 (100, $[M+H]^+$). Anal. calc. for $C_{20}H_{28}N_2O_5Si$ (404.54): C 59.38, H 6.98, N 6.92; found: C 59.51, H 6.82, N 6.89.

1-(6,7-Dideoxy-2,3-O-*isopropylidene-β*-D-allo-*hept-6-ynofuranosyl)uracil* (**10**). a) *From* **7**: A soln. of **7** (6.0 g, 14.2 mmol) in MeOH (100 ml) was treated dropwise with a soln. of NaOH (2.84 g, 71.1 mmol) in H_2O (50 ml), stirred at 23° for 2 h, and diluted with sat. aq. NH_4Cl soln. (50 ml). After evaporation, the residue was diluted with AcOEt, washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. The residue was crystallized from AcOEt/hexane 1:2 (300 ml) affording **10** (4.3 g, 98%).

b) *From* **9**: A soln. of **9** (4.0 g, 10.0 mmol) in CH_3OH (50 ml) was treated dropwise with a soln. of NaOH (1.60 g, 50.0 mmol) in H_2O (50 ml), stirred at 23° for 2 h, and diluted with sat. aq. NH_4Cl soln. (50 ml). After evaporation, the residue was diluted with AcOEt, washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. The residue was crystallized from AcOEt/hexane 1:2 (300 ml) affording **10** (2.9 g, 95%). Colourless crystals. R_f(AcOEt/hexane 3:1) 0.37. M.p. 212.5–213.0°. $[\alpha]_D^{25} = -51.3$ ($c = 0.6$, MeOH). IR (KBr): 3333*m* (br.), 3266*m*, 3000*m*, 2811*m*, 2123*w*, 1690*s*, 1467*w*, 1419*m*, 1387*m*, 1301*w*, 1217*w*, 1089*s*, 860*m*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 1.55, 1.35 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 3*; additionally, 113.8 (*s*, Me_2C); 26.1, 24.1 (2*q*, Me_2C). FAB-MS (NOBA): 617 (23, $[2M+H]^+$), 309 (100, $[M+H]^+$), 293 (15, $[M-Me]^+$). Anal. calc. for $C_{14}H_{16}N_2O_6$ (308.29): C 54.54, H 5.23, N 9.09; found: C 54.54, H 5.27, N 9.11.

1-(6,7-Dideoxy-β-D-allo-*hept-6-ynofuranosyl)uracil* (**11**). A soln. of **10** (150 mg) in MeCN/H_2O/40% HF/37% HCl 100:50:2:2 (10 ml) was stirred at 23° for 65 h. Evaporation and RP-HPLC (H_2O/MeOH 10:0 → 5:5 → 1:9) gave **11** (130 mg, 99.5%). Colourless crystals. $[\alpha]_D^{25} = -25.4$ ($c = 0.8$, H_2O). IR (KBr): 3433*s* (br.), 3280*s*, 3182*m*, 2125*w*, 1682*s*, 1465*m*, 1386*m*, 1285*m*, 1133*m*, 1110*m*, 1050*m*, 937*m*, 835*m*. ^{1}H-NMR (300 MHz, D_2O): 7.99 (*d*, $J = 8.1$, H–C(6)); 6.03 (*d*, $J = 6.9$, H–C(1′)); 5.71 (*d*, $J = 8.1$, H–C(5)); 4.52 (*dd*, $J = 2.8$, 2.2, H–C(5′)); 4.33 (*dd*, $J = 5.4$, 2.2, H–C(3′)); 4.22 (*dd*, $J = 6.9$, 5.4, H–C(2′)); 4.07 (*dd*, $J = 2.8$, 2.2, H–C(4′)); 2.98 (*d*, $J = 2.2$, H–C(7′)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*. FAB-MS (NOBA): 269 (13, $[M+H]^+$); ESI-MS (pos.-ion mode): 559 (20, $[2M+Na]^+$), 307 (20, $[M+K]^+$), 291 (100, $[M+Na]^+$). ESI-MS (neg.-ion mode): 267 (100, $[M-H]^-$).

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)uridine* (**12**). A soln. of pyridine (30 ml, 370 mmol, distilled from CaH_2) and **1** (20 g, 74 mmol) in CH_2Cl_2 (500 ml) was treated dropwise with TIPSOTf (21 ml, 77 mmol), stirred at 23° for 20 min, washed with brine (3 × 300 ml), dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:1) gave **12** (29.1 g, 94%). Colourless crystals. R_f(AcOEt/hexane 1:1) 0.36. M.p. 119–120°. $[\alpha]_D^{25} = -6.6$ ($c = 9.8$, $CHCl_3$). IR ($CHCl_3$): 3390*w*, 3008*w*, 2945*m*, 2868*m*, 1693*s*, 1458*m*, 1385*m*, 1130*m*, 1086*m*, 969*w*, 883*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.33 (br. *s*, NH); 1.57, 1.34 (2*s*, Me_2C); 1.10–1.05 (*m*, $(Me_2CH)_3$-Si). ^{13}C-NMR (50 MHz, $CDCl_3$): see *Table 3*; additionally, 114.5 (*s*, Me_2C); 27.3, 25.4 (2*q*, Me_2C); 18.0 (*q*, $(Me_2CH)_3Si$), 11.9 (*d*, $(Me_2CH)_3Si$). FAB-MS (NOBA): 441 (54, $[M+H]^+$), 425 (18, $[M-Me]^+$), 397 (100, $[M-Me_2CH]^+$). Anal. calc. for $C_{21}H_{36}N_2O_6Si$ (440.61): C 57.25, H 8.24, N 6.36; found: C 57.42, H 8.41, N 6.35.

6-Iodo-2′,3′-O-*isopropylidene-5′*-O-*(triisopropylsilyl)uridine* (**13**). At −78°, a soln. of (i-Pr)$_2$NH (7.7 ml, 0.054 mol, distilled from CaH_2) in THF (250 ml) was treated dropwise with 1.65M BuLi in hexane (33 ml, 0.054 mol), stirred at −78° for 15 min and at 0° for 15 min, cooled to −78°, treated dropwise with a soln. of **12** (8.0 g, 0.018 mol) in THF (250 ml), stirred for 2.5 h, treated with NIS (12.2 g, 0.159 mol) in THF (250 ml), stirred for 1.5 h, treated with AcOH (6 ml), and allowed to warm to 23°. After evaporation, the residue was diluted with AcOEt, washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 2:3) and crystallization from AcOEt/hexane gave **13** (8.0 g, 78%). Colourless crystals. R_f(AcOEt/hexane 1:2) 0.38. M.p. 152.5–154°. $[\alpha]_D^{25} = +20.1$ ($c = 2.8$, $CHCl_3$). IR ($CHCl_3$): 3384*w*, 2944*s*, 2866*m*, 1721*m*, 1695*s*, 1575*m*, 1384*m*, 1338*m*, 1148*m*, 1088*m*, 1067*m*, 881*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 9.37 (br. *s*, NH); 1.57, 1.38 (2*s*, Me_2C); 1.05–0.95 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (50 MHz, $CDCl_3$): see *Table 3*; additionally, 113.3 (*s*, Me_2C); 26.8, 25.0 (2*q*, Me_2C); 17.5 (*q*, $(Me_2CH)_3Si$); 11.6 (*d*, $(Me_2CH)_3Si$).

FAB-MS (NOBA: 589 (29, $[M+Na]^+$), 567 (38, $[M+H]^+$). Anal. calc. for $C_{21}H_{35}IN_2O_6Si$ (566.51): C 44.52, H 6.23, N 4.94; found: C 44.61, H 6.02, N 5.12.

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)uridin-6-yl-(6→7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*hept-6-ynofuranosyl)uracil* (**14**). A soln. of **10** (1 g, 3.2 mmol), **13** (1.93 g, 3.4 mmol), $[Pd_2(dba)_3]$ (153 mg, 0.16 mmol), CuI (61 mg, 0.32 mmol), and $P(fur_3)$ (79 mg, 0.32 mmol) in degassed Et_3N/toluene 1:1 (60 ml) was stirred for 20 h at 23°. After evaporation, FC (AcOEt/hexane 6:1) gave **14** (1.5 g, 70%). Brown foam. R_f(AcOEt) 0.45. $[\alpha]_D^{25} = +6.5$ ($c = 0.4$, $CHCl_3$). IR ($CHCl_3$): 3386*w* (br.), 3008*w*, 2944*w*, 2225*w*, 1697*s*, 1598*w*, 1456*m*, 1385*m*, 1270*w*, 1088*m*, 882*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 4*; additionally, 1.58, 1.53, 1.37, 1.33 (4*s*, 2 Me_2C); 1.10–1.00 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 5*; additionally, 114.7 (*s*, Me_2C); 113.8 (*s*, Me_2C); 27.22, 27.21, 25.4, 25.3 (4*q*, 2 Me_2C); 17.9 (*q*, $(Me_2CH)_3Si$); 12.0 (*d*, $(Me_2CH)_3Si$). FAB-MS (NOBA): 747 (32, $[M+H]^+$), 731 (26, $[M-Me]^+$), 703 (100, $[M-Me_2CH]^+$). Anal. calc. for $C_{35}H_{50}N_4O_{12}Si$ (746.89): C 56.29, H 6.75, N 7.50; found: C 56.17, H 6.81, N 7.36.

Table 4. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Dimers* **14**, **19**, *and* **20**, *in $CDCl_3$.* Assignments based on selective homodecoupling experiments

	14	**19**	**20**		**14**	**19**	**20**
H–C(5/I)	5.76	5.72	5.72	*J*(5,6/I)	8.1	8.1	8.1
H–C(6/I)	7.45	7.36	7.32	*J*(1′,2′/I)	2.6	2.4	1.9
H–C(1′/I)	5.69	5.83	5.73	*J*(2′,3′/I)	6.5	6.6	6.6
H–C(2′/I)	5.04	4.91	4.97	*J*(3′,4′/I)	3.2	4.3	3.6
H–C(3′/I)	5.09	4.99	4.99	*J*(4′,5′/I)	4.2	4.6	5.5
H–C(4′/I)	4.35	4.22	4.22	*J*(1′,2′/II)	1.4	1.2	1.5
H–C(5′/I)	4.92	5.04	5.03	*J*(2′,3′/II)	6.4	6.5	6.6
H–C(5/II)	6.00	5.97	5.93	*J*(3′,4′/II)	4.3	3.6	3.6
H–C(1′/II)	6.21	6.14	6.21	*J*(4′,5′/II)	6.6	8.1	8.6
H–C(2′/II)	5.20	5.24	5.19	*J*(5′,7′/II)	–	–	2.1
H–C(3′/II)	4.84	5.05	5.04				
H–C(4′/II)	4.18	4.01	4.04				
H–C(5′/II)	3.87	4.64	4.64				
H–C(7′/II)	–	–	2.43				

Table 5. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Dimers* **14**, **19**, *and* **20** *in $CDCl_3$, and of* **15** *in D_2O* Solution

	14	**19**[a])	**20**	**15**[a])		**14**	**19**[a])	**20**	**15**[a])
C(2/I)	163.5	163.3	162.9	168.8	C(2/II)	162.5	162.4	161.9	167.4
C(4/I)	150.5	150.0	149.8	154.4	C(4/II)	149.5	149.4	149.3	153.3
C(5/I)	102.8	102.7	102.8	105.2	C(5/II)	108.4	108.5	108.3	111.1
C(6/I)	142.9	141.6	142.2	144.7	C(6/II)	137.5	137.6	137.5	140.6
C(1′/I)	95.9	93.0	94.2	92.1	C(1′/II)	94.1	94.6	94.7	96.7
C(2′/I)	84.0	84.0	84.0	75.8	C(2′/II)	83.7	83.8	83.9	74.1
C(3′/I)	82.3	80.0	80.7	72.6	C(3′/II)	80.3	82.7	82.7	72.0
C(4′/I)	89.6	88.5	89.0	88.0	C(4′/II)	88.2	91.2	91.3	86.6
C(5′/I)	62.8	63.6	63.7	64.8	C(5′/II)	64.2	63.8	63.3	64.1
C(6′/I)	100.0	100.4	101.0	102.4	C(6′/II)	–	106.3	83.8	–
C(7′/I)	76.6	76.7	76.6	79.1	C(7′/II)	–	87.8	73.7	–

[a]) Assignment based on a HSQC.GRASP spectrum.

Uridin-6-yl-(6→7′-C*)-1-(6,7-dideoxy-β*-D-allo-*hept-6-ynofuranosyl)uracil* (**15**). A soln. of **14** (400 mg, 0.54 mmol) in MeCN/H_2O/40% HF/37% HCl 100:50:2:2 (25 ml) was stirred at 23° for 8 h. Evaporation and RP-HPLC (H_2O/MeOH 10:0→5:5→1:9) gave **15** (200 mg, 73%). White powder. $[\alpha]_D^{25} = -7.1$ ($c = 0.4$, H_2O). IR (KBr): 3412*s* (br.), 2250*w*, 1684*s*, 1459*m*, 1388*m*, 1266*w*, 1114*m*, 1053*m*, 883*w*, 766*w*, 719*w*. ^{1}H-NMR (400 MHz, D_2O): 7.77 (*d*, $J = 8.1$, H–C(6/I)); 6.14 (*s*, H–C(5/II)); 6.05 (*d*, $J = 3.7$, H–C(1′/II)); 5.92 (*d*, $J = 4.7$,

H–C(1′/I)); 5.84 (*d*, *J* = 8.1, H–C(5/I)); 4.97 (*d*, *J* = 4.0, H–C(5′/I)); 4.77 (*dd*, *J* = 6.3, 3.7, H–C(2′/II)); 4.42 (*t*, *J* = 5.5, H–C(2′/I)); 4.39 (*t*, *J* = 5.5, H–C(3′/I)); 4.35 (*t*, *J* = 6.4, H–C(3′/II)); 4.23 (*t*, *J* = 4.0, H–C(4′/I)); 3.91 (*dd*, *J* = 6.4, 3.2, H–C(4′/II)); 3.84 (*dd*, *J* = 12.4, 3.2, H–C(5′/II)); 3.71 (*dd*, *J* = 12.4, 6.1, H–C(5′/II)). ^{13}C-NMR (100 MHz, D_2O): see *Table 4*. ESI-MS (pos.-ion mode): 549 (20, $[M+K]^+$), 533 (100, $[M+Na]^+$); ESI-MS (neg.-ion mode): 509 (100, $[M-H]^-$), 545 (80, $[M+Cl]^-$).

1-[6,7-Dideoxy-2,3-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]uracil* (**16**). A soln. of pyridine (5.0 ml, 62 mmol, distilled from CaH_2) and **10** (2.4 g, 7.8 mmol) in CH_2Cl_2 (100 ml) was treated dropwise with TIPSOTf (4.8 ml, 16 mmol), stirred at 23° for 7 h, washed with brine (3 × 100 ml), dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:3) and crystallization from AcOEt/hexane gave **16** (3.2 g, 84%). Colourless crystals. R_f(AcOEt/hexane 1:1) 0.50. M.p. 136.5–137.5°. $[\alpha]_D^{25} = -32.8$ (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): 3390*w*, 3304*w*, 2947*m*, 2869*m*, 2120*w*, 1695*s*, 1459*m*, 1385*m*, 1262*m*, 1091*m*, 883*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 8.90 (br. *s*, NH); 1.54, 1.35 (2*s*, Me_2C); 1.10–1.05 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 115.1 (*s*, Me_2C); 27.4, 25.5 (2*q*, Me_2C); 18.2, 18.1 (2*q*, $(Me_2CH)_3Si$); 12.6 (*d*, $(Me_2CH)_3Si$). FAB-MS (NOBA): 929 (7, $[2M+H]^+$), 487 (11, $[M+Na]^+$), 465 (80, $[M+H]^+$), 421 (100, $[M-Me_2CH]^+$). Anal. calc. for $C_{23}H_{36}N_2O_6Si$ (464.63): C 59.46, H 7.81, N 6.03; found: C 59.69, H 7.78, N 6.08.

1-[6,7-Dideoxy-2,3-O-*isopropylidene-7*-C-*(triethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]-6-iodouracil* (**17**). At −78°, a soln. of $(i\text{-}Pr)_2NH$ (22.5 ml, 0.159 mol, distilled from CaH_2) in THF (600 ml) was treated dropwise with 1.65M BuLi in hexane (97 ml, 0.159 mol), stirred at −78° for 15 min and at 0° for 15 min, cooled to −78°, treated dropwise with a soln. of **7** (14.6 g, 0.035 mol) in THF (400 ml), stirred for 2.5 h, treated dropwise with NIS (36 g, 0.159 mol) in THF (400 ml), stirred for 1.5 h, treated with AcOH (30 ml), and allowed to warm to 23°. After evaporation, the residue was dissolved in AcOEt, washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 2:3) gave **17** (13.2 g, 62%) and **7** (3.5 g, 24%). Colourless crystals. R_f (AcOEt/hexane 1:1) 0.58. M.p. 177.5–178.0°. $[\alpha]_D^{25} = -13.4$ (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): 3425*w* (sh), 3382*w* (br), 2993*w*, 2962*w*, 2180*w*, 1697*s*, 1574*m*, 1385*m*, 1338*w*, 1087*m*, 848*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.16 (br. *s*, NH); 3.81 (br. *s*, OH); 1.63, 1.37 (2*s*, Me_2C); 0.99 (*t*, *J* = 7.5, $(MeCH_2)_3Si$); 0.62 (*q*, *J* = 7.5, $(MeCH_2)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 114.4 (*s*, Me_2C); 27.4, 25.2 (2*q*, Me_2C); 7.4 (*q*, $(MeCH_2)_3Si$); 4.2 (*t*, $(MeCH_2)_3Si$). FAB-MS (NOBA): 571 (5, $[M+Na]^+$), 549 (6, $[M+H]^+$), 533 (45, $[M-Me]^+$). Anal. calc. for $C_{20}H_{29}IN_2O_6Si$ (548.45): C 43.80, H 5.33, N 5.11; found: C 43.95, H 5.37, N 5.11.

1-[6,7-Dideoxy-2,3-O-*isopropylidene-7*-C-*(triethylsilyl)-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]-6-iodouracil* (**18**). A soln. of pyridine (5.4 ml, 67 mmol, distilled from CaH_2) and **17** (5.0 g, 3.92 mmol) in CH_2Cl_2 (150 ml) was treated dropwise with TIPSOTf (5.4 ml, 20 mmol), stirred at 23° for 20 min, washed with brine (3 × 100 ml), dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:2) gave **18** (5.7 g, 89%). Colourless powder. R_f(AcOEt/hexane 1:1) 0.88. $[\alpha]_D^{25} = +14.2$ (*c* = 6.1, $CHCl_3$). IR ($CHCl_3$): 3384*m*, 2955*s*, 2868*m*, 2172*w*, 1721*s*, 1696*s*, 1572*m*, 1463*m*, 1417*m*, 1384*m*, 1338*m*, 1266*m*, 1148*m*, 1096*m*, 881*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.50 (br. *s*, NH); 1.55, 1.35 (2*s*, Me_2C); 1.10–1.05 (*m*, $(Me_2CH)_3Si$); 0.99 (*t*, *J* = 7.5, $(MeCH_2)_3Si$); 0.62 (*q*, *J* = 7.5, $(MeCH_2)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 113.7 (*s*, Me_2C); 27.1, 25.1 (2*q*, Me_2C); 18.1 (*q*, $(Me_2CH)_3Si$); 12.4 (*d*, $Me_2CH)_3Si$); 7.4 (*q*, $(MeCH_2)_3Si$); 4.2 (*t*, $(MeCH_2)_3Si$). FAB-MS (NOBA): 705 (8, $[M+H]^+$), 689 (15, $[M-Me]^+$). Anal. calc. for $C_{29}H_{49}IN_2O_6Si$ (704.79): C 49.42, H 7.01, N 3.97; found: C 49.50, H 7.01, N 3.91.

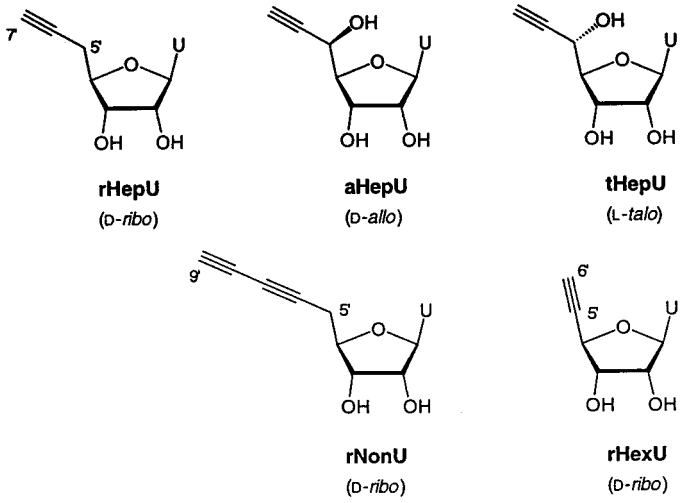
1-[6,7-Dideoxy-2,3-O-*isopropylidene-7*-C-*(triethylsilyl)-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]uracil-6-yl-(6→7′*-C*)-1-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]uracil* (**19**). A soln. of **18** (4.0 g, 5.7 mmol), **16** (2.5 g, 5.4 mmol), $Pd_2(dba)_3$ (256 mg, 0.27 mmol), CuI (72 mg, 0.38 mmol) and P(fur)$_3$ (87 mg, 0.38 mmol) in degassed Et_3N/toluene 1:1 (350 ml) was stirred for 80 h at 23°. After evaporation, FC (AcOEt/hexane 1:3) gave **19** (4.2 g, 63%). Brown foam. R_f(AcOEt/hexane 1:1) 0.36. $[\alpha]_D^{25} = +10.2$ (*c* = 1.7, $CHCl_3$). IR ($CHCl_3$): 3387*w*, 2947*m*, 2868*m*, 2230*w*, 2180*w*, 1697*s*, 1596*w*, 1456*m*, 1384*m*, 1093*m*, 882*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 4*; additionally, 9.50 (br. *s*, NH); 9.38 (br. *s*, NH); 1.59, 1.52, 1.37, 1.31 (4*s*, 2 Me_2C); 1.15–1.05 (*m*, 2 $(Me_2CH)_3Si$); 0.94 (*t*, $(MeCH_2)_3Si$); 0.56 (*q*, $(MeCH_2)_3Si$). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 5*; additionally, 115.0 (*s*, Me_2C); 113.4 (*s*, Me_2C); 27.2, 27.1, 25.4, 24.9 (4*q*, 2 Me_2C); 18.08, 18.06, 18.0, 17.9 (4*q*, 2 $(Me_2CH)_3Si$); 12.5, 12.4 (2*d*, 2 $(Me_2CH)_3Si$); 7.3 (*q*, $(MeCH_2)_3Si$); 4.2 (*t*, $(MeCH_2)_3Si$). FAB-MS (NOBA): 1064 (7, $[M+Na]^+$), 998 (21, $[M-Me_2CH]^+$). Anal. calc. for $C_{52}H_{84}N_4O_{12}Si_3$ (1041.51): C 59.97, H 8.13, N 5.38; found: C 59.92, H 7.94, N 5.38.

1-[6,7-Dideoxy-2,3-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]uracil-6-yl-(6→7′*-C*)-1-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]uracil* (**20**). A soln. of **19** (4.3 g, 4.1 mmol) in MeOH/AcOEt 1:1 (200 ml) was treated dropwise with a soln. of $AgNO_3$

(8.4 g, 49.5 mmol) in H_2O/MeOH 1:1 (30 ml), stirred at 23° under exclusion of light for 4 h, treated with a soln. of KCN (8.4 g) in H_2O (20 ml), and stirred for 1 h. After evaporation, the residue was diluted with AcOEt, washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:2) gave **20** (2.4 g, 63%). Colourless foam. R_f(AcOEt/hexane 1:1) 0.33. $[\alpha]_D^{25} = +8.0$ ($c = 2.4$, $CHCl_3$). IR ($CHCl_3$): 3387*w*, 3306*w*, 2945*m*, 2867*w*, 2260*w*, 2150*w*, 1697*s*, 1596*w*, 1456*m*, 1384*m*, 1094*s*, 1068*m*, 882*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 4*; additionally, 8.90 (br. *s*, NH); 8.75 (br. *s*, NH); 1.58, 1.53, 1.37, 1.33 (4*s*, 2 Me_2C); 1.25–1.15 (*m*, 2 $(Me_2CH)_3Si$); 1.15–1.09 (*m*, 2 $(Me_2CH)_3Si$). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 5*; additionally, 114.8 (*s*, Me_2C); 113.5 (*s*, Me_2C); 27.14, 27.09, 25.3, 25.0 (4*q*, 2 Me_2C); 18.0, 17.9 (2*q*, $(Me_2CH)_3Si$); 12.44, 12.40 (2*d*, 2 $(Me_2CH)_3Si$). FAB-MS (NOBA): 928 (23, $[M+H]^+$), 912 (13, $[M-Me]^+$), 884 (85, $[M-Me_2CH]^+$). MALDI-MS (Indole-3-acetic acid): 949 ($[M+Na]^+$), 965 ($[M+K]^+$). Anal. calc. for $C_{46}H_{70}N_4O_{12}Si_2$ (927.31): C 59.58, H 7.61, N 6.04; found: C 59.59, H 8.04, N 6.00.

Appendix. – *Calculation of Acetyleno Analogues of RNA Oligonucleotides.* Calculations were performed with *Macromodel V.4.5* (Amber* force field, gas phase) [15]). To obtain hetero- and homoduplexes possessing a modified backbone, the A helix of an RNA oligomer was built with the grow tool of *Macromodel*, energy-minimised, and modified. *A priori*, there are two possibilities to bridge the base and the furanosyl unit, with the neighbouring unit either towards the upstream or towards the downstream end, leading either to retention or to inversion of the direction of the strand, respectively. If the neighbouring ribofuranosyl group is on the same side as the attachment point at the base, the desired modified backbone appears feasible, requiring only a different orientation of the ribofuranosyl moiety. If, however, the neighbouring ribofuranosyl group is on the side opposite to the attachment point at the base, then the new backbone requires both a different orientation of the ribofuranosyl moiety and a rotation of the base ($\chi \rightarrow \chi + 180°$). This implies that base pairing must be interrupted and reestablished after rotation, and it is uncertain if a corresponding helix can be formed. The new backbone was built by connecting the base with the ribofuranosyl unit located at the same side of the base as the attachment point. If the attachment point of the base is in the major groove (for C(5) and C(6) of uridine, and for C(8) of adenine), this means a connection with the neighbouring ribofuranosyl unit towards the downstream end, and if the attachment point of the base is in the minor groove (C(2) of adenine), it means connection with the neighbouring ribofuranosyl unit towards the upstream end.

To evaluate the appropriate length of the unsaturated furanosyl unit, in a first set of calculations, we modified the minimised A helix of the hexamer (3′-5′)$U_6 \cdot$(5′-3′)A_6 (see *Fig. 5*). The phosphinato groups and O(5′) of the uridine strand were replaced by *a*) C≡C bridges between C(5) of uracil and C(5′) of the neighbouring nucleoside towards the downstream end ($\rightarrow$heteroduplex (7′–5)rHep$U_6 \cdot$(5′-3′)A_6), *b*) by C≡C–C≡C bridges between C(5) of uracil and C(5′) of the neighbouring nucleoside towards the downstream end ($\rightarrow$heteroduplex (9′–5)rNon$U_6 \cdot$(5′-3′)A_6), and *c*) C≡C bridges between C(5) of uracil and C(4′) of the next nucleoside (replacing C(5′) with retention of configuration ($\rightarrow$heteroduplex (6′–5)rHex$U_6 \cdot$(5′-3′)A_6).



These three heteroduplexes were minimised, and their base pairing was compared with that of (3′-5′)U_6·(5′-3′)A_6. All three modified structures retain the double-helix. Characteristic is the change of the furanose ring conformation from ^3E to ^4E. The heptynofuranose derivative (7′−5)rHepU_6·(5′-3′)A_6 is a good mimic as it shows similar buckle and propeller twists as (3′-5′)U_6·(5′-3′)A_6. The nonadiynofuranose derivative (9′−5)rNon-U_6·(5′-3′)A_6 is a less appropriate mimic as it shows similar buckle and propeller twists as (3′-5′)U_6·(5′-3′)A_6, but C≡C−C≡C angles of *ca.* 150°. The strongly buckle- and propeller-twisted base pairs of (6′–5)rHexU_6·(5′-3′)A_6 suggest that hex-5-ynofuranose derivatives are inappropriate mimics. Hept-6-ynofuranose derivatives appear to be valuable mimics for (3′-5′)polyU. Further calculations to evaluate the best connection point at the nucleobase were performed only with hept-6-ynofuranose derivatives.

Calculation of 14-meric duplexes allows the analysis of a complete turn of 11 units, even if the terminal units deviate from regularity. The A helix of (3′-5′)U_{14}·(5′-3′)A_{14} was built and minimised. The tertiary structure of minimised (3′-5′)U_{14}·(5′-3′)A_{14} shows the characteristic properties of an A helix; *i.e.*, the regular pattern (11 units per turn, axial rise $h = 2.74$ Å) with a large central hole and inclined base pairs. The uridine and the adenosine strand of minimised (3′-5′)U_{14}·(5′-3′)A_{14} were modified to afford the heteroduplexes (7′−5)rHe-pU_{14}·(5′-3′)A_{14}, (7′−6)rHepU_{14}·(5′-3′)A_{14}, (3′-5′)U_{14}·(7′−2)rHepA_{14}, and (3′-5′)U_{14}·(8−7′)rHepA_{14}. Minimisation of these heteroduplexes was performed in two steps: first, with constrained interhelix C=O···H−N distances to keep the base pairs together during the strong changes of the backbone followed by a minimisation without any constraint. The rather small energy gain (100–200 kJ/mol) observed for the second minimisation indicates only minor geometrical changes. The natural strand of the heteroduplexes (7′−5)rHepU_{14}·(5′-3′)A_{14} and (7′−6)rHepU_{14}·(5′-3′)A_{14} was modified to afford the homoduplexes (7′−5)rHepU_{14}·(7′−2)rHepA_{14}, (7′−5)rHepU_{14}·(8−7′)rHepA_{14}, and (7′−6)rHepU_{14}·(8−7′)rHepA_{14}. Analogous minimisations as performed for the heteroduplexes gave the minimised structure of the homoduplexes.

The minimised, modified hetero- and homoduplexes were analysed and compared with the natural homoduplex (3′-5′)U_{14}·(5′-3′)A_{14}. Some structural parameters of these calculated duplexes are listed in the *Table 6*. All hetero- and homoduplexes of acetyleno-oligonucleosides retain more or less the starting helix, although some lengthening of the helices is indicated by increased values for the axial rise. In the heteroduplex series, the best results are obtained for (7′−6)rHepU_{14}·(5′-3′)A_{14} and (3′-5′)U_{14}·(8−7′)rHepA_{14}. Both have 11 residues per turn and retain the large central hole. The less distorted A helix and the smaller axial rise clearly indicate that the 6-linked (7′−6)rHepU_{14}·(5′-3′)A_{14} is a better mimic than the 5-linked (7′−5)rHepU_{14}·(5′-3′)A_{14}, whereas the 8-linked (3′-5′)U_{14}·(8−7′)rHepA_{14} is only a slightly better mimic than the 2-linked (3′-5′)U_{14}·(7′−2)rHepA_{14}. In the homoduplex series, the similarity to an A helix decreases from the 6- and 8-linked (7′−6)rHepU_{14}·(8−7′)rHepA_{14} *via* the 5- and 8-linked (7′−5)rHepU_{14}·(8−7′)rHepA_{14} to the 5- and 2-linked (7′−5)rHepU_{14}·(7′−2)rHepA_{14}. These calculations suggest that C(6) of uridine and both C(2) and C(8) of adenosine may act as attachment points for the heptynose. Similar calculations were performed in the DNA series starting from the B helix of (3′-5′)dT_{14}·(5′-3′)dA_{14} and led exactly to the same result as in the RNA series.

Table 6. *Chain Direction, Helix Type, Number of Residues per Turn, Axial Rise, and Furanose Ring Conformations of the Calculated 14meric* ribo-*Configured Hetero- and Homoduplexes*

RNA	Chain Direction	Helix	n	h [Å]	Furanose ring conformation	
					U strand	A strand
(3′-5′)U_{14}·(5′-3′)A_{14}	antiparallel	A	11	2.74	^3E	$^3T_2$
(7′−5)rHepU_{14}·(5′-3′)A_{14}	parallel	A to B	10	3.01	^4E	$^3T_2$
(7′−6)rHepU_{14}·(5′-3′)A_{14}	parallel	A	11	2.89	^4E	$^3T_2$
(3′-5′)U_{14}·(7′−2)rHepA_{14}	antiparallel	A	11	2.87	$^3T_2$	^4E
(3′-5′)U_{14}·(8−7′)rHepA_{14}	parallel	A	11	2.85	$^3T_2$	^4E
(7′−5)rHepU_{14}·(7′−2)rHepA_{14}	parallel	A	10	3.08	^4E	E_2
(7′−5)rHepU_{14}·(8−7′)rHepA_{14}	antiparallel	A	10	3.03	^4E	^4E to E_2
(7′-6)rHepU_{14}·(8−7′)rHepA_{14}	antiparallel	A	11	2.90	^4E	^4E

To evaluate the influence of an OH group at C(5′) on the tertiary structure, $H_{pro\text{-}R}$−C(5′) of the homoduplexes (7′−5)rHepU_{14}·(8−7′)rHepA_{14} and (7′−6)rHepU_{14}·(8−7′)rHepA_{14} were replaced by OH groups affording (7′−5)aHepU_{14}·(8−7′)aHepA_{14} and (7′−6)aHepU_{14}·(8−7′)aHepA_{14}. Intraresidue H-bonds O(5′)−H···O(4′) set by adjusting the dihedral angles C(4′)−C(5′)−O−H were kept during the minimisation.

The configuration at each C(5′) of these homoduplexes was inverted affording (7′−5)tHepU$_{14}$·(8−7′)tHepA$_{14}$ and (7′−6)tHepU$_{14}$·(8−7′)tHepA$_{14}$ that were energy minimised (no intramolecular H-bonds for O(5′)H). The result shows that the additional OH group and the configuration at C(5′) have only a weak influence upon the tertiary structure of the homoduplexes (only small changes of the axial rises; $\Delta h \leq 0.03$ Å) although HO−C(5′) of the D-*allo*-configured duplexes are directed towards the major groove and HO−C(5′) of the L-*talo*-configured duplexes towards the minor groove.

To evaluate the compatibility of a single acetyleno-nucleoside unit in a natural duplex, the fourth nucleoside of one strand of the natural duplex (3′-5′)U$_{14}$·(5′-3′)A$_{14}$ was replaced by a (7′−5)-linked aHepU, a (7′−6)-linked aHepU, a (7′−2)-linked aHepA, and a (8−7′)-linked aHepA unit, resp., and minimised (500 iterations). Strong propeller twists (60–90°) and medium-to-strong buckle twists (30–60°) clearly indicate that the presence of a (7′−5)aHepU, a (7′−6)aHepU, and (8−7′)aHepA unit leads to complete interruption of the base-pairing. However, the presence of a (7′−2)aHepA unit may be tolerated in a natural strand as indicated by similar propeller and buckle twists as in (3′-5′)U$_{14}$·(5′-3′)A$_{14}$.

These force-field calculations show that acetyleno-oligonucleosides may form similar hetero- and homoduplexes as natural oligonucleotides. The hept-6-ynofuranosyl unit may either be attached at C(2) or C(8) of the neighbouring adenine but should be attached at C(6) of the neighbouring uracil. The presence or absence of the HO−C(5′) groups has only a weak influence upon the tertiary structure.

Experimental. – *Force-Field Calculations.* Calculations were performed with *Macromodel V. 4.5* (Amber* force field, gas phase) [15]. To evaluate the length of the unsaturated furanosyl unit, the A helix of the RNA hexamer (3′-5′)U$_6$·(5′-3′)A$_6$ was built with the grow tool of *Macromodel*, minimised (500 iterations), and modified to afford the heteroduplexes (7′−5)rHepU$_6$·(5′-3′)A$_6$, (9′−5)rNonU$_6$·(5′-3′)A$_6$, and (6′−5)rHexU$_6$·(5′-3′)A$_6$. These three heteroduplexes were minimised (500 iterations) and then their base pairing compared with that of (3′-5′)U$_6$·(5′-3′)A$_6$.

To evaluate the connection points between the base and heptynofuranose, the A helix of the RNA 14-mer (3′-5′)U$_{14}$·(5′-3′)A$_{14}$ was built with the grow tool of *Macromodel*, minimised (500 iterations), and modified. The phosphinato bridges and O(5′) of the uridine strand of (3′-5′)U$_{14}$·(5′-3′)A$_{14}$ were deleted and replaced with C≡C bridges either between C(5) and C(5′) of the neighbouring nucleoside towards the downstream end (→ heteroduplex (7′−5)rHepU$_{14}$·(5′-3′)A$_{14}$) and between C(6) and C(5′) of the neighbouring nucleoside towards the downstream end (→ heteroduplex (7′−6)rHepU$_{14}$·(5′-3′)A$_{14}$). The phosphinato bridges and O(5′) of the adenine strand of (3′-5′)U$_{14}$·(5′-3′)A$_{14}$ were deleted and replaced either with C≡C bridges between C(2) and C(5′) of the neighbouring nucleoside towards the upstream end (→ heteroduplex (3′-5′)U$_{14}$·(7′−2)rHepA$_{14}$) or with C≡C bridges between C(8) and C(5′) of the neighbouring nucleoside towards the downstream end (→ heteroduplex (3′-5′)U$_{14}$·(8−7′)rHepA$_{14}$), resp. Minimisations of these heteroduplexes were performed in two steps: 1000 iterations with constrained interhelix C=O···H−N distances (1.73 ± 0.03 Å) to keep the base pairs together during the strong changes of the backbone followed by 1000 iterations without any constraint. The rather small energy gains (100–200 kJ/mol) observed for the second minimisations evidence only minor geometrical changes. To get homoduplexes of acetyleno-oligonucleotides, the phosphinato bridges and O(5′) of the (5′-3′)A$_{14}$ strands of the heteroduplexes (7′−5)rHepU$_{14}$·(5′-3′)A$_{14}$ were replaced by C≡C bridges between C(2) and C(5′) (→ homoduplex (7′−5)rHepU$_{14}$·(7′−2)rHepA$_{14}$) or between C(8) and C(5′) (→ homoduplex (7′−5)rHepU$_{14}$·(8−7′)rHepA$_{14}$), and the phosphinato bridges and O(5′) of the (5′-3′)A$_{14}$ strands of the heteroduplex (7′−6)rHepU$_{14}$·(5′-3′)A$_{14}$ were replaced by C≡C bridges between C(8) and C(5′) (→ homoduplex (7′−6)rHepU$_{14}$·(8−7′)rHepA$_{14}$). Analogous minimisations as performed for the heteroduplexes gave the minimised structures of the homoduplexes.

To evaluate the influence of an OH group at C(5′) on the tertiary structure, H$_{pro\text{-}R}$−C(5′) of the homoduplexes (7′−5)rHepU$_{14}$·(8−7′)rHepA$_{14}$ and (7′−6)rHepU$_{14}$·(8−7′)rHepA$_{14}$ were replaced by OH groups affording (7′−5)aHepU$_{14}$·(8−7′)aHepA$_{14}$ and (7′−6)aHepU$_{14}$·(8−7′)aHepA$_{14}$). Intraresidue H-bonds O(5′)−H···O(4′) were set by adjusting the dihedral angles C(4′)−C(5′)−O−H. These weak intraresidue H-bonds were kept during the minimisations (1000 iterations). The configurations at C(5′) of these homoduplexes were inverted (no intramolecular H-bonds), affording the L-*talo*-configured (7′−5)tHepU$_{14}$·(8−7′)tHepA$_{14}$ and (7′−6)tHepU$_{14}$·(8−7′)tHepA$_{14}$, and minimised (1000 iterations).

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