Oligonucleotide Analogues with Integrated Bases and Backbone

Part 16[1])

Synthesis and Association of Ethylene-Linked Self-Complementary Dimers

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The self-complementary, ethylene-linked U*[c_a]A$^{(*)}$ dinucleotide analogues **8**, **10**, **12**, **14**, **16**, and **18**, and the sequence-isomeric A*[c_a]U$^{(*)}$ analogues **20**, **22**, **24**, **26**, **28**, and **30** were obtained by Pd/C-catalyzed hydrogenation of the corresponding, known ethynylene-linked dimers. The association of the ethylene-linked dimers was investigated by NMR and CD spectroscopy. The U*[c_a]A$^{(*)}$ dimers form linear duplexes and higher associates (K between 29 and 114M^{-1}). The A*[c_a]U$^{(*)}$ dimers, while associating more strongly (K between 88 and 345M^{-1}), lead mostly to linear duplexes and higher associates; they form only minor amounts of cyclic duplexes. The enthalpy–entropy compensation characterizing the association of the U*[c_x]A$^{(*)}$ and A*[c_x]U$^{(*)}$ dimers (x = y, e, and a) is discussed.

Introduction. – In oligonucleotide analogues with integrated backbone and bases (ONIBs), the contiguous backbone of oligonucleotides is replaced by linking elements between the nucleobases. We have synthesized ONIBs featuring a C_2 linker between C(5′) and either C(6) of an adjacent uridine unit, or C(8) of an adjacent adenine unit, and we have analyzed in some detail the association of 2′,3′-*O*-isopropylidene-protected, self-complementary dimers and tetramers linked by either an ethenylene [1] or an ethynylene unit [2][3]. These ONIBs associate in $CHCl_3$ solution to form cyclic and/or linear duplexes and linear higher associates. Formation of cyclic duplexes requires in all cases a *syn*-conformation of the nucleobase of unit I (compare **1**–**6**). It also requires a *gg*-type orientation of the ethynyl substituent at C(5′) of **1** and **2**, and a *gt*-type orientation of the ethenyl substituent at C(5′) of **3** and **4**. The *gg*-orientation is prevented, in U*[c_y]A$^{(*)}$ dimers **1** with X = OH[2]), by formation of a persistent intramolecular H-bond from the C(5′/I)–OH group to N(3/I) of the adenosine unit[3]).

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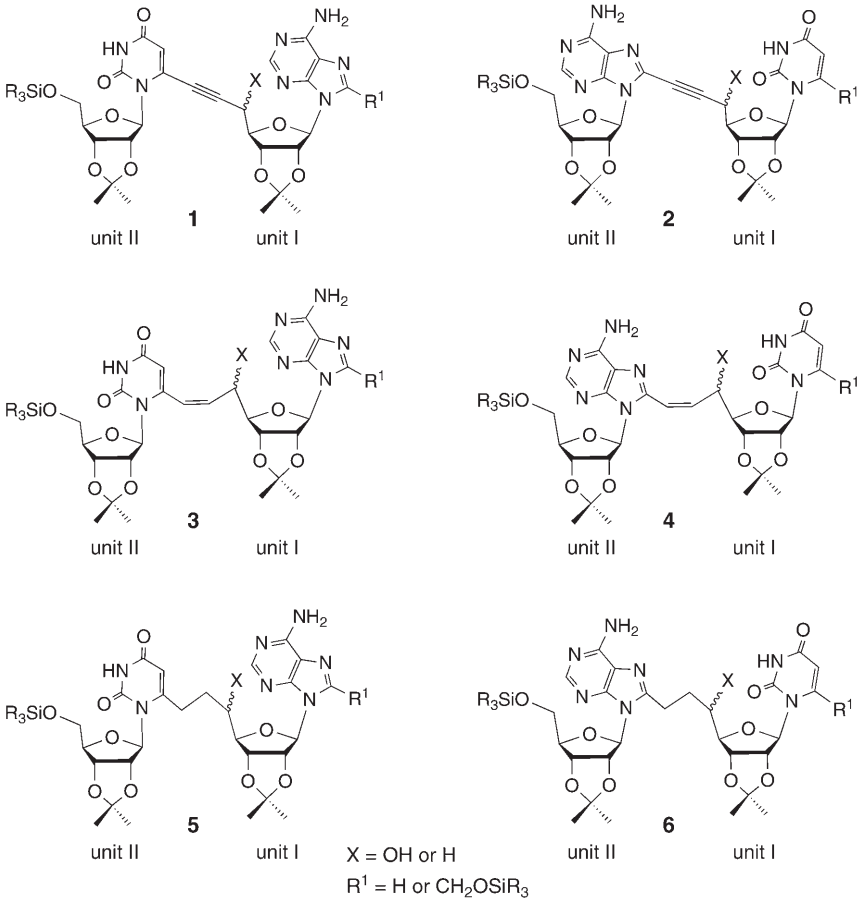
1) Part 15: [1].

2) *Conventions for abbreviated notation:* The substitution at C(6) of pyrimidines and C(8) of purines is denoted by an asterisk (*); for example U* and A* for methylated uridine and adenosine derivatives, respectively. U$^{(*)}$ and A$^{(*)}$ represents both unsubstituted and methylated nucleobases. The moiety linking C(6)–CH_2 or C(8)–CH_2 and C(5′) of the previous unit is indicated in square brackets, such as [c] for a C-atom. The indices y, e, and a indicate a triple, double, or single bond, respectively.

3) The propargylic HO–C(5′/I) group of the analogous A*[c_y]U$^{(*)}$ dimers **2** forms only a weakly persistent intramolecular H-bond to O=C(2/I) of the uracil moiety, and may form an intermolecular H-bond in cyclic duplexes.



In the U*[c_e]A$^{(*)}$ dimers **3** with X = OH, the allylic C(5′/I)–OH group forms a less persistent intramolecular H-bond, and impairs the formation of cyclic duplexes without, however, preventing it.

All di- and tetrameric ONIBs that we analyzed so far possess a rigid diatomic linker (a 1,2-disubstituted alkyne or alkene moiety). Considering the entropic contribution to the simplex/duplex equilibria, we wondered about the association of self-complementary dimeric ONIBs linked by the flexible ethylene (ethane-1,2-diyl) unit. Their association should provide further information about the effect of the structure of the linker and, if strong enough, allow to determine the preferred conformation of the linker in the duplex. One expects the secondary OH group of the ethylene-linked U*[c_a]A$^{(*)}$ dimers **5** (X = OH) to form a less persistent C(5′)–OH···N(3/I) H-bond than the allylic OH group of **3** (X = OH) and the propargylic OH group of **1** (X = OH), as suggested by the p*K* values of propan-1-ol (16.1 [4]), prop-2-en-1-ol (15.1–15.5 [4][5]), and prop-2-yn-1-ol (13.2–13.6 [4][5]). A more readily broken H-bond of **5** may facilitate the formation of cyclic duplexes.

The desired self-complementary ethylene-linked dimers **5** and **6** (X = OH or H) should be readily prepared by hydrogenation of the alkynes **1** and **2**. We report their synthesis and the analysis of their association.

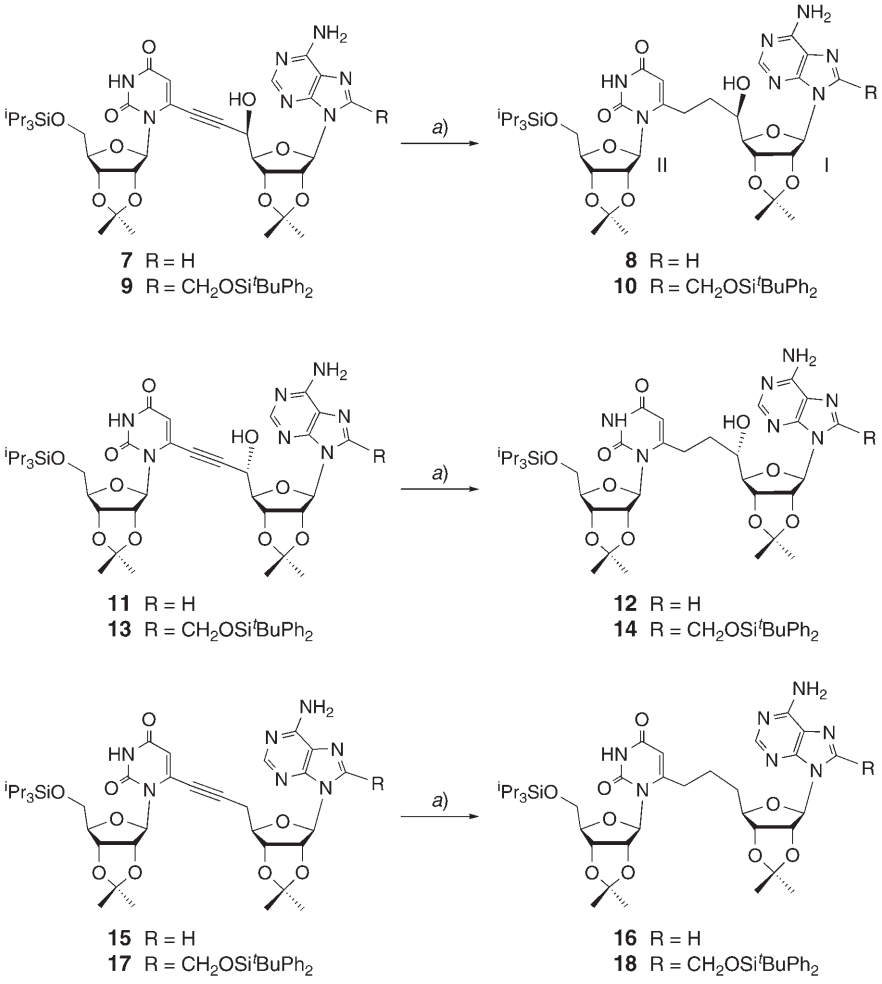
Results and Discussion. – 1. *Synthesis.* The Pd/C-catalyzed hydrogenation of the ethynylene-linked U*[c_y]A$^{(*)}$ dinucleosides **7**, **9**, **11**, **13**, **15**, and **17** [2] to the desired U*[c_a]A$^{(*)}$ dimers required harsh conditions, *viz.* 5.5–6.0 bar H_2 and HCOOH in MeOH as the solvent, and yielded 70–83% of the corresponding ethylene-linked dimers **8**, **10**, **12**, **14**, **16**, and **18**, respectively (*Scheme 1*).

The A*[c_y]U$^{(*)}$ dimers proved more reactive and were hydrogenated in the absence of HCOOH. Hydrogenation of the propargyl alcohols **19**, **21**, **23**, and **25** [2] under H_2 (5 bar) in AcOEt yielded the desired A*[c_a]U$^{(*)}$ alcohols **20**, **22**, **24**, and **26** in a yield of 98, 66, 64, and 61%, respectively (*Scheme 2*). The *C(5′/I)*-deoxygenated dimers **27** and **29** proved less reactive and were hydrogenated in MeOH under a slightly higher pressure of H_2 (5.5 bar) to yield 90% of **28** and 78% of **30**.

2. *Association of the U*[c_a]A$^{(*)}$ and A*[c_a]U$^{(*)}$ Dimers in $CHCl_3$ Solution.* Similarly to the analogous ethynylene- and ethenylene-linked dinucleosides **1**–**4** [1][2], the saturated U*[c_a]A$^{(*)}$ and A*[c_a]U$^{(*)}$ analogues **5** and **6** should associate in $CHCl_3$ to form cyclic and/or linear duplexes and higher associates. The formation of cyclic duplexes is mainly influenced by structural parameters of unit I, *viz.* the orientation of the nucleobase, as specified by the χ angle and affected by substitution at C(6/I) or C(8/I), the furanose ring conformation, the orientation of the linking ethylene moiety, as described by the torsional angle ϕ_{CO} (C(6′/I)–C(5′/I)–C(4′/I)–O(4′/I)), the nature of the substituent (OH or H) at C(5′/I), and the configuration at C(5′/I) of the alcohols. Destabilizing steric interactions between the ribosyl units must also be taken into consideration.

The association of the U*[c_a]A$^{(*)}$ and A*[c_a]U$^{(*)}$ dinucleosides **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **26**, **28**, and **30** in $CHCl_3$ solution was investigated by NMR and circular dichroism (CD) spectroscopy, similarly as described for the ethynylene- and ethenylene-linked dinucleosides [1][2]. Association is revealed by the concentration dependence of ^{1}H-NMR signals, and best analysed on the basis of the concentration dependence of δ(HN(3)) of the uracil moiety (readily assigned, large δ range, no overlap with other signals). A large $\Delta\delta$ value between simplex (extrapolation to c = 0 mM) and duplex(es) ($c > 20$ mM), a strong bending of the curve at low concentration, and a plateau at high concentration evidence the formation of cyclic duplexes, whereas a distinctly smaller $\Delta\delta$ value between simplex and duplex, a moderate bending of the curve at low concentration, and a continued increase of the downfield shift with increasing concentration evidence linear duplexes and higher associates. Graphical analysis [6] or analysis by linear least-squares fitting [7] of these curves leads to the association constant K, and to the calculated chemical shift for HN(3) of the simplex and of the duplex. The thermodynamic parameters were calculated on the basis of the temperature dependence of δ(HN(3)) for 8–10 mM solutions from 0 to 50° in 10° intervals (*van't Hoff* plot). A thorough analysis of the ^{1}H- and ^{13}C-NMR spectra (recorded at a concentration where *ca.* 80% of the dinucleosides are in the form of duplexes) and the concentration dependence of additional ^{1}H-NMR parameters (such as δ(H–C(2′/I)) and J(4′,5′/I)) allow a more precise determination of the conformation

Scheme 1



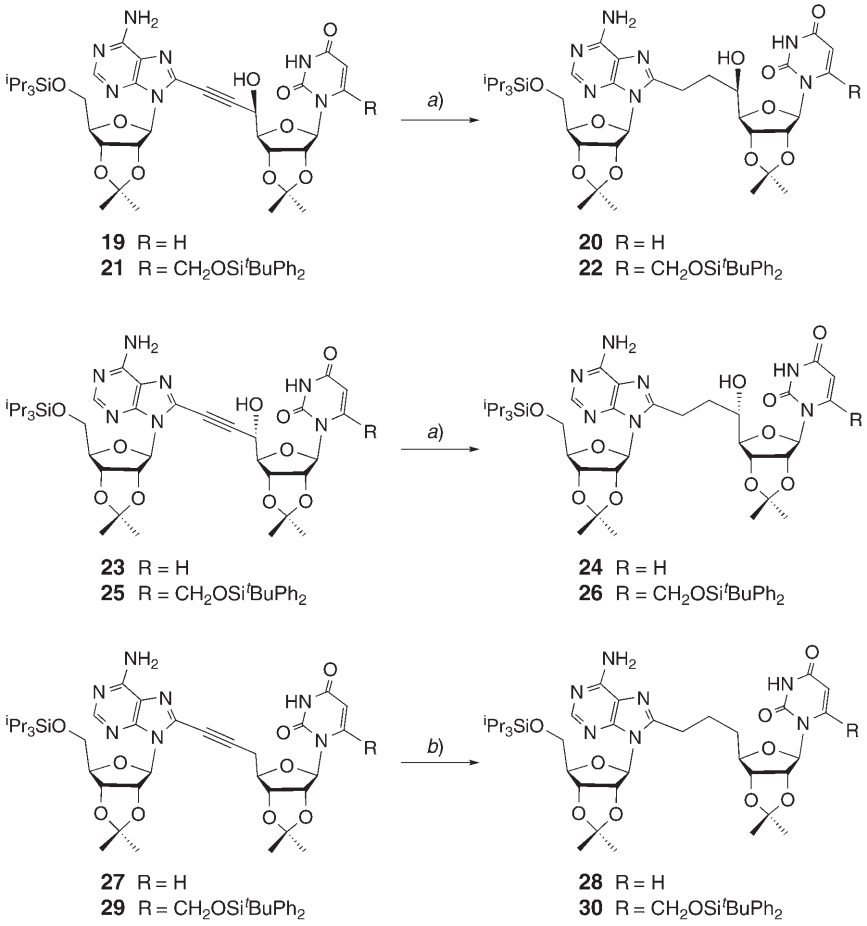
a) 10% Pd/C, HCO_2H, 5.5–6.0 bar of H_2, MeOH; 83% of **8**; 74% of **10**; 72% of **12**; 70% of **14**; 77% of **16**; 80% of **18**.

of the duplexes. π-Stacking in cyclic duplexes is evidenced by a temperature-dependent strong decrease of the ellipticity in the CD spectra.

In the following, observations valid for all U*[c_a]A$^{(*)}$ and A*[c_a]U$^{(*)}$ dimers are discussed first, followed by an analysis of the association of the U*[c_a]A$^{(*)}$ and A*[c_a]U$^{(*)}$ dinucleosides, as described in the preceding paragraph.

2.1. *Discussion of NMR Parameters Relevant to Both U*[c_a]A$^{(*)}$ and A*[c_a]U$^{(*)}$ Dimers.* ^{1}H-NMR spectra were recorded of 30 mM solutions in $CDCl_3$ of the dimers **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **26**, and **30**, and of a 20 mM solution of **8** (*Tables 4* and *6* in the *Exper. Part*). The assignments are based on selective homodecoupling experiments, and

Scheme 2



a) 10% Pd/C, 5.0 bar of H_2, AcOEt; 98% of **20**; 66% of **22**; 64% of **24**; 61% of **26**. *b*) 10% Pd/C, 5.5 bar of H_2, MeOH; 90% of **28**; 78% of **30**.

corroborated by DQFCOSY and HSQC spectra of **8**, **18**, and **28**, and by a HMBC spectrum of **28**. The C(7′/I)H_2 signals of the U*[c_a]A$^{(*)}$ dimers appear upfield to the C(7′/I)H_2 signals of the A*[c_a]U$^{(*)}$ sequence isomers ($\Delta\delta = 0.28-0.42$ ppm for the alcohols, and 0.43–0.53 ppm for the *C(5′/I)*-deoxy compounds). Similarly, the C(6′/I)H_2 signals of the U*[c_a]A$^{(*)}$ alcohols **8**, **10**, **12**, and **14** appear upfield to the C(6′/I)H_2 signals of the A*[c_a]U$^{(*)}$ alcohols **20**, **22**, **24**, and **26** (2.00–1.75 *vs.* 2.20–1.90 ppm). H–C(5′/I) of the U*[c_a]A$^{(*)}$ and A*[c_a]U$^{(*)}$ alcohols resonates at 4.04–3.98 ppm. The signals of C(5′/I)H_2 and C(6′/I)H_2 of the deoxy analogues **16** and **18** appear upfield to those of C(5′/I)H_2 and C(6′/I)H_2 of **28** and **30** (1.86–1.65 *vs.* 2.03–1.70 ppm).

The *syn*-conformation of unit II is evidenced by the characteristic downfield shift of H–C(2′/II) of the U*[c_a]A$^{(*)}$ dimers **8**, **10**, **12**, **14**, **16**, and **18** (5.17–5.26 ppm), and the

A*[c_a]U$^{(*)}$ analogues **20**, **22**, **24**, **26**, **28**, and **30** (5.84–5.88 ppm; *Tables 4* and *6* in the *Exper. Part*). The uridine unit of the U*[c_a]A$^{(*)}$ dimers shows a stronger preference for the (*N*)-conformation than the adenine unit of the A*[c_a]U$^{(*)}$ dimers ($J(1',2')/J(3',4') \leq 0.3$ and 0.5–0.66, resp.).

C(7′/I) of the U*[c_a]A$^{(*)}$ alcohols **8**, **10**, **12**, and **14** resonates downfield to C(7′/I) of the A*[c_a]U$^{(*)}$ alcohols **20**, **22**, **24**, and **26** (29.2–29.7 *vs.* 24.1–24.5 ppm; *Tables 5* and *7* in the *Exper. Part*). Deoxygenation at C(5′/I) led to a downfield shift of *ca.* 3 ppm for C(7′/I) of **16**, **18**, **28**, and **30**. C(5′/I) and C(6′/I) of the alcohols **8**, **10**, **12**, **14**, **20**, **22**, **24**, and **26** resonate at 69.7–71.3 and 30.2–32.0 ppm, respectively. Deoxygenation at C(5′/I) led to the expected upfield shifts for C(5′/I) and C(6′/I) of **16**, **18**, **28**, and **30**, resonating at 32.4–33.2 and 23.5–24.7 ppm, respectively.

2.2. *Association of the U*[c_a]A$^{(*)}$ Dimers: Formation of Linear Duplexes and Higher Associates.* The curves representing the concentration dependence of the chemical shift of HN(3/II) of **8**, **12**, and **16** show the typical progression of linear duplexes and higher associates, *i.e.*, a moderate chemical-shift difference between simplex and duplex ($\Delta\delta = 2.9–3.6$ ppm for a 30 *vs.* a 1 mM solution), a weak bending of the curve at concentrations of 1 to 10 mM, and a continued constant increase of the downfield shift at concentrations above 30 mM (*Fig. 1*,*a*). The U*[c_a]A* alcohols **10** and **14** ($\Delta\delta = 2.5$ ppm for a 30 *vs.* a 1 mM solution) show a pronounced weaker tendency to form a duplex. This is presumably due to the fact that *Watson–Crick*- and *Hoogsteen*-type base pairing are both disfavoured, either by the intramolecular H-bond to N(3/I) or by the substituent at C(8/I). In contradistinction to the curves for **8**, **12**, and **16** that show no flattening, the curve for **18** shows a weak flattening at higher concentrations, suggesting the formation of small amounts of a cyclic duplex.

Graphical analysis [6] of the curves in *Fig. 1*,*a* led to small *K* values, ranging between 29 M^{-1} for **14** and 114 M^{-1} for **18** (*Table 1*). These values are not accurate, as the graphical determination is based on the assumption of a constant $\delta(NH_{duplex})$ value which is only valid if no higher associates are formed. The moderate quality of the association constants is evidenced by the broad range of the $\delta(NH_{simplex})$ and $\delta(NH_{duplex})$ values, varying between 7.33 and 7.78 ppm for the simplex (the typical value is narrowly centered around *ca.* 7.70 ppm [1]) and between 12.24 and 13.62 ppm for the duplex. Since these values are used in the *van't Hoff* analysis of the association of U*[c_a]A$^{(*)}$ dimers, the thermodynamic values in *Table 1* are also not accurate. The ΔH values characterizing the association of **8**, **10**, **14**, and **18** (−6.2 to −7.9 kcal/mol) agree well with the formation of linear duplexes *via* two H-bonds; typical values are *ca.* 7 kcal/mol for the formation of a base pair [1][2]. The larger ΔH value for the association of **18** (−10.5 kcal/mol) suggests the formation of linear duplexes and of minor amounts of a cyclic duplex. The ΔH value for the association of **12** (−9.1 kcal/mol) is presumably too large, as suggested by the considerable shift difference of 6.3 ppm between $\delta(NH_{simplex})$ and $\delta(NH_{duplex})$.

A persistent intramolecular H-bond of HO–C(5′/I) to N(3/I) of the alcohols **8**, **10**, **12**, and **14** is evidenced by the downfield shift of HO–C(5′/I) (6.36–6.89 ppm; *Table 4* in the *Exper. Part*), the upfield shift of H–C(2′/I) (5.15–5.21 ppm), the small J(5′,OH/I) values (< 1.5 Hz) of the D-*allo*-dimers **8** and **10**, the large J(5′,OH) values (≥ 11.1 Hz) of the L-*talo*-dimers **12** and **14**, the small J(4′,5′/I) values (< 1.0 Hz), and the (*S*)-conformation of the furanose rings ($J(1',2'/I)/J(3',4'/I) \geq 2.5$) of all these alcohols

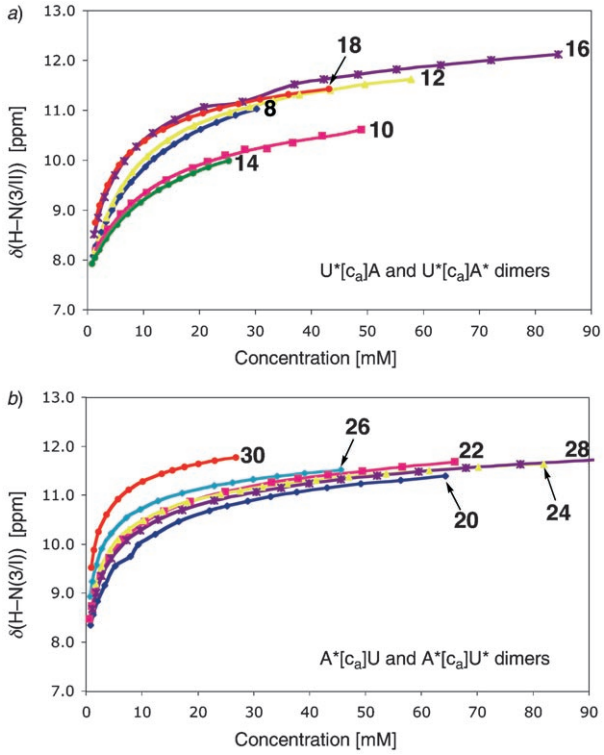


Fig. 1. *Concentration dependence of* a) *δ(HN(3/II)) of the U*[c$_a$]A$^{(*)}$ dimers* **8**, **10**, **12**, **14**, **16**, *and* **18**, *and* b) *δ(HN(3/I)) of the A*[c$_a$]U$^{(*)}$ dimers* **20**, **22**, **24**, **26**, **28**, *and* **30** *for solutions in CDCl$_3$*

[2][8]. These values hardly change upon diluting the solutions from 20–30 to 1 mM (see δ(HO–C(5′/I)) in *Table 2*), as expected for persistent intramolecular H-bonds. The *tg*-orientation of the ethylene linker of **8** and **10**, and the *gt*-orientation of **12** and **14** are determined by the intramolecular H-bond. The conformation of the ethylene linker of the deoxy analogue **18** is described by a *ca.* 1:1 *gt*/*tg*-equilibrium, as evidenced by $J(4',5'a/I) = J(4',5'b/I) = 7.2$ Hz. The smaller $J(4',5'a/I)$ and $J(4',5'b/I)$ values for **16** (6.5 Hz) reveal a 1:1 *gt*/*tg* conformational equilibrium with a minor contribution of the *gg*-conformer. This difference between **16** and **18** is a consequence of the exclusive *syn*-conformation of the *C(8/I)*-substituted **18** and the *ca.* 4:1 *syn*/*anti*-equilibrium adopted by the *C(8/I)*-unsubstituted **16**, as evidenced by δ(H–C(2′/I)) of 5.54 ppm for **16** and of 5.64 ppm for **18**.

The HN(3/II) and H_2N–C(6/I) signals of the U*[c$_a$]A$^{(*)}$ dimers are strongly shifted upfield upon diluting their solutions from 30 to 1 mM ($\Delta\delta = 2.1-2.9$ and 0.3–0.9 ppm, resp.; *Table 2*), whereas the CH signals are hardly affected ($\Delta\delta \leq 0.06$ ppm). $J(4',5'/I)$ remains constant over the whole concentration range. These observations ascertain that all U*[c$_a$]A$^{(*)}$ dimers form linear duplexes and higher associates; in addition, **18** also forms a cyclic duplex, as discussed above.

Table 1. *Association Constants* K, *and δ(NH) of the Simplex and the Duplex as Calculated from the Concentration Dependence of δ(HN(3)) in $CDCl_3$ at 295 K for the Dimers* **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **26**, **28**, *and* **30**, *and Determination of the Thermodynamic Parameters by* van't Hoff *Analysis of the Temperature Dependence of δ(HN(3)) for 8–10 mM Solutions in $CDCl_3$ at 0–50°* (in 10° steps)

Dimer	K [M^{-1}]	$\delta(NH_{simplex})$ [ppm]	$\delta(NH_{duplex})$ [ppm]	ΔG_{298}[a]) [kcal/mol]	ΔH [kcal/mol]	ΔS [cal/mol·K]
U*[c_a]A$^{(*)}$ series:						
8	42	7.65	14.24	−2.2	−6.2	−14.3
10	34	7.78	12.57	−2.1	−6.5	−15.2
12	66	7.33	13.62	−2.5	−9.1	−21.9
14	29	7.70	12.84	−2.0	−7.2	−17.4
16	81	7.66	13.41	−2.6	−7.9	−17.7
18	114	7.72	12.80	−2.8	−10.5	−25.9
A*[c_a]U$^{(*)}$ series:						
20	88	7.92	12.76	−2.7	−8.5	−20.4
22	109	7.98	12.73	−2.8	−8.9	−20.6
24	124	8.19	12.46	−2.8	−9.9	−24.0
26	229	8.08	12.32	−3.2	−11.5	−27.8
28	98	8.00	12.64	−2.7	−10.1	−24.7
30	345	8.17	12.76	−3.5	−14.6	−37.7

[a]) Calculated from K.

Table 2. *Concentration Dependence of the Chemical Shifts* [ppm] *of the Exchangeable H-Atoms of the U*[c_a]A$^{(*)}$ Dimers* **8**, **10**, **12**, **14**, **16**, *and* **18** *in $CDCl_3$*

	Conc. [mM]	**8**	**10**	**12**	**14**	**16**	**18**
HN(3/II)	30 (20 for **8**)	10.61	10.20	11.12	10.14	11.43	11.15
	5	9.31	8.72	9.36	8.65	9.92	9.88
	1	8.27	8.04	8.22	7.98	8.62	8.63
H_2N–C(6/I)	30	6.30	6.15	6.60	6.17	6.38	6.26
	5	5.96	5.72	6.04	5.74	5.98	5.74
	1	5.71	5.55	5.73	5.55	5.67	5.59
HO–C(5′/I)	30	6.89	6.78	6.64	6.36	–	–
	5	6.89	6.82	6.61	6.38	–	–
	1	6.90	6.84	6.60	6.40	–	–

The CD spectra of 2 mM solutions of **8** and **16** show a low ellipticity that decreases only little upon raising the temperature from −10 to 50° (*Fig. 2*). Considering the pronounced π-stacking for cyclic duplexes of the corresponding ethynylene and ethenylene dimers ($\theta > 3 \cdot 10^{-4}$ [1][2]), this observation corroborates the presence of only linear duplexes and higher associates. The larger ellipticity for a 1 mM solution of **18** than the ellipticities for 2 mM solutions of **8** and **16** further evidences a small proportion of a cyclic duplex.

2.3. *Association of the A*[c_a]U$^{(*)}$ Dimers: Formation Mostly of Linear Duplexes and Higher Associates.* The curves for the concentration dependence of HN(3/I) of **20**, **22**, **24**, **26**, **28**, and **30** show the typical progression of linear duplexes and higher associates

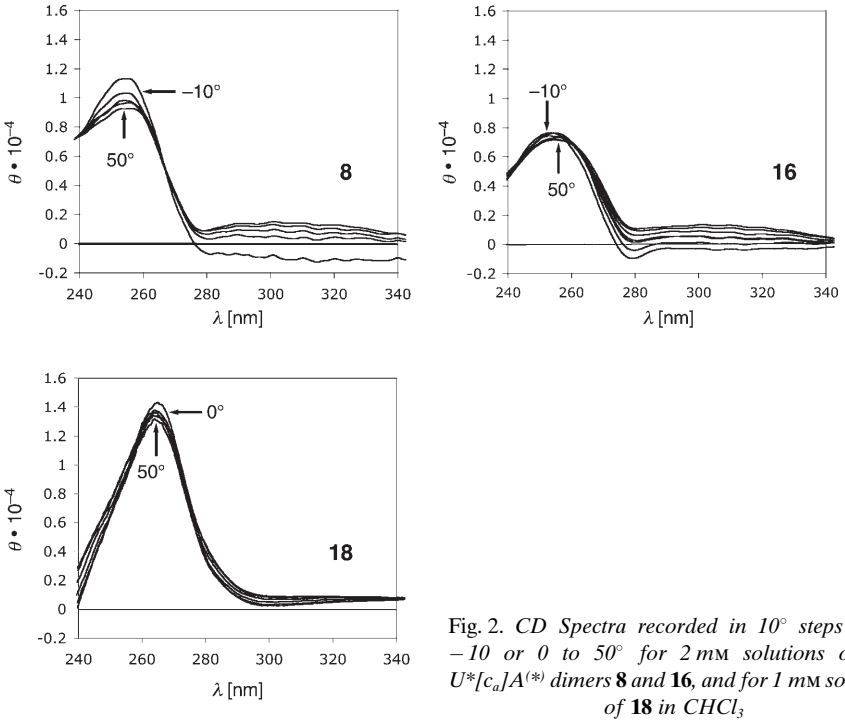


Fig. 2. *CD Spectra recorded in 10° steps from −10 or 0 to 50° for 2 mM solutions of the U*[c$_a$]A$^{(*)}$ dimers* **8** *and* **16**, *and for 1 mM solution of* **18** *in* $CHCl_3$

with a moderate chemical-shift difference between simplex and duplex ($\Delta\delta = 2.9$–3.6 ppm for a 30- *vs.* a 1-mM solution), a weak bending of the curve at concentrations between 1 and 10 mM, and a continued constant increase of the downfield shift at concentrations above 30 mM (*Fig. 1,b*). A slight flattening of the curves at higher concentrations suggests the formation of small amounts of cyclic duplexes. Substitution at C(6/I) leads to a stronger downfield shift for HN(3/I) [2]. The larger difference between the curves for **30** and **28** than between those for **22** and **20**, and for **26** and **24** indicates a slightly larger proportion of a cyclic duplex of **30**. The stronger bending of the curves for all A*[c$_a$]U$^{(*)}$ dimers than of those for the U*[c$_a$]A$^{(*)}$ analogues evidences a higher propensity for duplex formation. In agreement with this interpretation, graphical analysis of the curves resulted in larger K values, ranging from 88 M^{-1} for **20** to 345 M^{-1} for **30** (*Table 1*). These K values are more accurate than those of the U*[c$_a$]A$^{(*)}$ series, as revealed by a smaller variance of $\delta(NH_{simplex})$ and $\delta(NH_{duplex})$.

The thermodynamic parameters characterizing the association of the A*[c$_a$]U$^{(*)}$ dimers were determined by *van't Hoff* analysis of the temperature dependence of δ(HN(3/I)) for 8–10-mM solutions in $CDCl_3$ (*Table 1*). ΔH Values of −8.5 to −11.5 kcal/mol indicate that **20**, **22**, **24**, **26**, and **28** form substantial amounts of higher associates and/or cyclic duplexes. The large ΔH value of **30** (−14.6 kcal/mol) suggests the formation of two base pairs per monomer, *i.e.*, the predominant formation of one or several cyclic duplexes.

HO–C(5′/I) of 30 mM solutions of **20**, **22**, and **24** resonates as very broad *s*s at 5.1–4.9, 4.55–4.35, and 4.7–4.5 ppm, respectively, evidencing an equilibrium of several H-bonded species (*Table 6* in the *Exper. Part*). HO–C(5′/I) of **26**, however, appears as a broad *d* at 4.15 ppm, and $J(5',OH) = 6.3$ Hz is in keeping with a moderately persistent intramolecular H-bond to O=C(2/I), considering that a $J(5',OH)$ value of *ca.* 11.5 Hz is expected for the corresponding, but completely persistent H-bond of a L-*talo*-configured dimer. The uridine unit of the 6-substituted dimers **22**, **26**, and **30** adopts a *syn*-conformation, as evidenced by δ(H–C(2′/I)) of 5.21–5.24 ppm. The upfield shift for H–C(2′/I) of the 6-unsubstituted dimers **24**, **20**, and **28** (4.93, 4.96, and 5.02 ppm, resp.) evidences a preferred *anti*-conformation, decreasing from *ca.* 90% for **24** to *ca.* 60% of **28**[4]). The rather small $J(4',5'/I)$ values for **20**, **22**, and **24** (3.0–4.2 Hz) evidence a preferred *gauche*-orientation of H–C(4′/I) and H–C(5′/I). A preferred *tg*-orientation of the ethylene linker of **20** and **22** is deduced by assuming that a *gg*-orientation is avoided[5]). A similar analysis leads to a preferred *gt*-orientation of **24**. The larger $J(4',5'/I)$ value of 5.1 Hz of **26** suggests a *ca.* 1:1 *gt*/*tg*-orientation of the linker. Similarly as already observed for the U*[c_a]A$^{(*)}$ analogues **16** and **18**, the $J(4',5'/I)$ values of *C(5/I)*-deoxy dimers **28** and **30** (6.3 and 6.9 Hz, resp.) indicate a 1:1 equilibrium of the *gt*- and *tg*-conformers with a minor contribution of the *gg*-conformer of **28**.

The HN(3/I) and H_2N–C(6/II) signals of the A*[c_a]U$^{(*)}$ dimers are shifted upfield upon diluting a 30 mM to a 1 mM solution ($\Delta\delta = 2.0–2.4$ and 0.3–0.9 ppm, resp.; *Table 3*), similarly as observed for HN(3/II) and H_2N–C(6/I) of the U*[c_a]A$^{(*)}$ analogues. Again, the signals for OH and all CH H-atoms do not move much ($\Delta\delta \leq$ 0.04 ppm, with the exception of $\Delta\delta = 0.17$ ppm for HO–C(5/I) of **26**). The $J(4',5'/I)$ values of **20**, **22**, **24**, **28**, and **30** are constant over the whole concentration range, whereas the $J(4',5'/I)$ value of **26** slightly decreases from 5.1 to 4.5 Hz. This decrease and the stronger temperature dependence of δ(HO–C(5/I)) evidence the formation of

Table 3. *Concentration Dependence of the Chemical Shifts* [ppm] *of the Exchangeable H-Atoms of the A*[c_a]U$^{(*)}$ *Dimers* **20**, **22**, **24**, **26**, **28**, *and* **30** *in* $CDCl_3$

	Conc. [mM]	**20**	**22**	**24**	**26**	**28**	**30**
HN(3/I)	30	10.94	11.18	11.14	11.31	11.09	11.84
	5	9.54	9.88	10.01	10.28	9.97	10.92
	1	8.53	8.78	8.99	9.24	8.93	9.69
H_2N–C(6/II)	30	6.22	6.19	6.36	6.40	6.63	7.00
	5	5.80	5.86	6.00	6.10	6.23	6.64
	1	5.52	5.59	5.69	5.78	5.82	6.13
HO–C(5′/I)	30	5.1–4.9	4.55–4.35	4.70–4.50	4.15	–	–
	5	5.0–4.8	4.46–4.32	4.65–4.50	4.05	–	–
	1	5.0–4.8	4.35	4.70–4.55	3.98	–	–

[4]) The *anti*-conformation does not necessarily prevent the formation of cyclic duplexes, since the reverse *Watson–Crick* base-paired duplex of the U*[c_c]A analogue of **16** possesses an *anti*-oriented adenine unit.

[5]) The calculated (Amber* force field [9]) $J(4',5'a/I)$ values of the *tg*- and *gt*-conformers of **20** and **22** are 2.0 and 9.3 Hz, and those of *tg*- and *gt*-conformers of **24** 9.5 and 1.0 Hz, respectively.

small amounts of a cyclic duplex of **26**, in keeping with a stronger flattening at higher concentrations of the curve for **26** (*Fig. 1*, b) as compared to the curves for the other A*[c_a]U(*) dimers.

The CD spectrum of a 2 mM solution of **20** shows a low ellipticity that decreases only little upon raising the temperature from −10 to 50° (*Fig. 3*), evidencing the presence of only linear duplexes and higher associates. The CD spectra of a 2 mM solution of **28**, and of 1 mM solutions of **26** and **30** show a more pronounced ellipticity, evidencing cyclic duplexes that increase in proportion from **28** to **26** and **30**. As expected, the ellipticity in the CD spectrum of **28** decreases with increasing temperature, while the one of the 268 nm band of **26** and **30** increases with increasing temperature. This surprising behaviour is rationalized by an exciton splitting at low temperature that decreases with increasing temperature.

3. Conclusions. – Based on modeling, we expected that the flexible propylene moiety of the U*[c_a]A(*) and A*[c_a]U(*) dimers should allow, but not favour, the

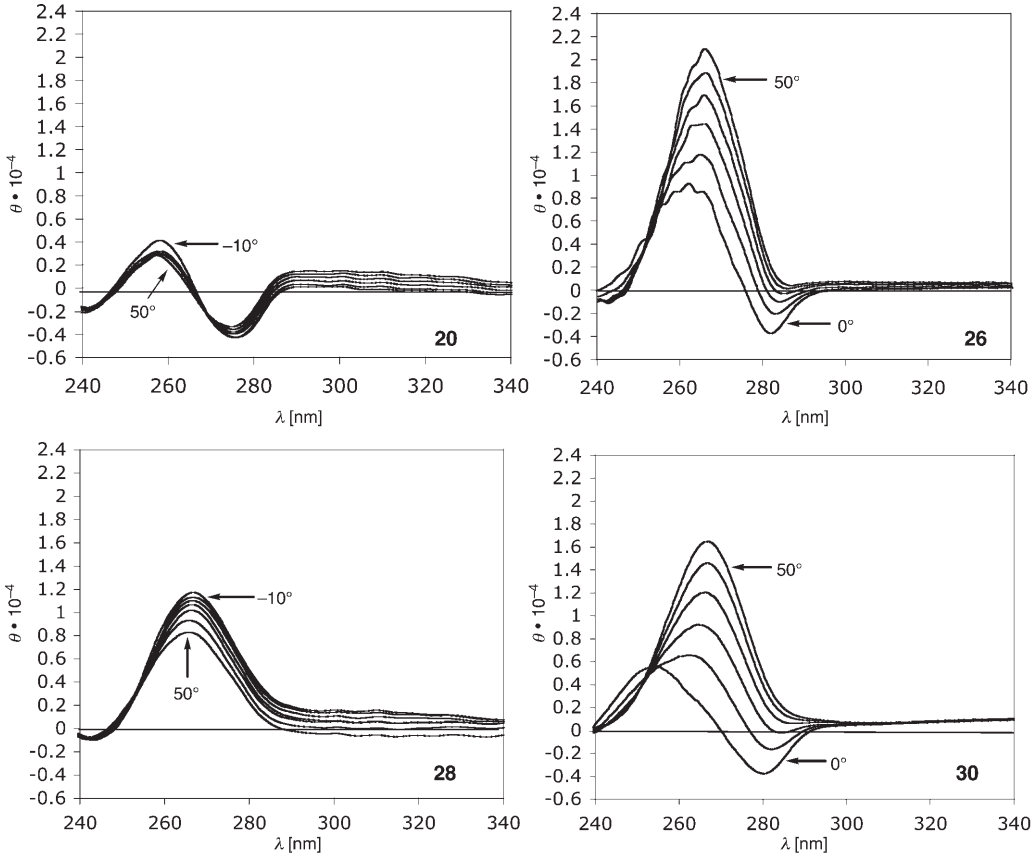


Fig. 3. *CD Spectra recorded in 10° steps from −10 or 0 to 50° for 2 mM solutions of the A*[c_a]U(*) dimers* **20** *and* **28**, *and for 1 mM solutions of* **26** *and* **30** *in* $CHCl_3$

formation of cyclic duplexes. Experimentally, even the *C(5/I)*-deoxy dimers **16**, **18**, **28**, and **30** form only a small amount of cyclic duplexes, a behaviour that is rationalized by the preference of the propylene moiety for the extended *zig-zag* conformation, incompatible with the formation of cyclic duplexes. Unfortunately, an insufficient resolution of the ^{1}H-NMR spectra prevents the determination of the conformation of the propylene unit.

Plotting enthalpies *vs.* entropies of association of the self-complementary U*[c_x]A(*) and A*[c_x]U(*) dimers (x = y, e, and a) results in straight lines, irrespectively of whether linear or cyclic associates are formed (*Fig. 4*). This could be due to an artifact of statistical compensation, considering the relatively narrow experimentally accessible temperature range, or reflect a real (extrathermodynamic) enthalpy–entropy compensation [10–12]. An extrathermodynamic enthalpy–entropy compensation is evidenced by the proposed criteria: a strong deviation of the calculated temperature $T_{calc.}$ (the slope of the enthalpy/entropy plot), varying from 340 K for the A*[c_y]U(*) dimers to 391 K for the A*[c_e]U(*) analogues, from the harmonic mean of the experimental temperature (297 K) and the linear ΔH–ΔG correlations in *Fig. 4* [13].

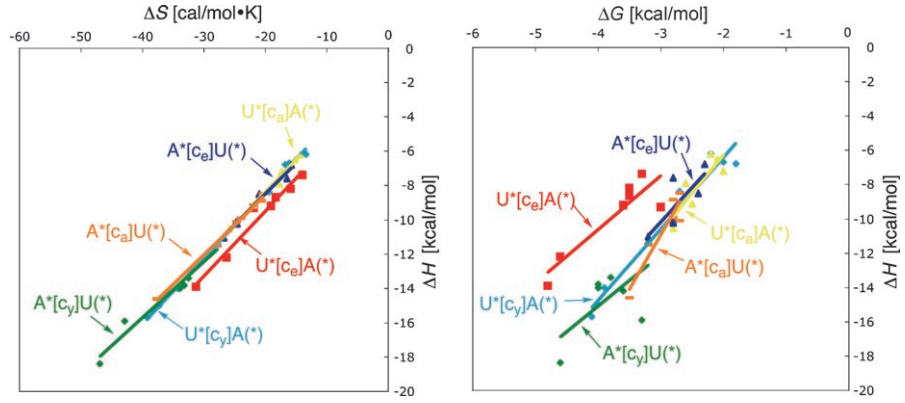


Fig. 4. *Enthalpy–entropy and enthalpy–free energy correlation for the association of the self-complementary U*[c_y]A(*), U*[c_e]A(*), U*[c_a]A(*), A*[c_y]U(*), A*[c_e]U(*), and A*[c_a]U(*) dimers*

We thank the *ETH Zürich*, *F. Hoffmann-La Roche AG*, Basel, and *Givaudan AG*, Dübendorf, for generous support, and Mrs. *B. Brandenberg* for recording the 2D-NMR spectra.

Experimental Part

General. See [14]. For NMR titrations and *van't Hoff* analysis, see [2].

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)uridin-6-yl-(6→7′*-C*)-9-(6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*heptofuranosyl)adenine* (**8**). A suspension of **7** [2] (180 mg, 0.23 mmol), 10% Pd/C (200 mg), and 2 drops of HCO_2H in MeOH (60 ml) was stirred for 36 h under H_2 (5.5 bar) at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 30:1) gave **8** (150 mg, 83%). White solid. R_f ($CHCl_3$/MeOH 20:1) 0.24. M.p. 188–190°. $[\alpha]_D^{25} = -21.3$ (c = 2.0, $CHCl_3$). UV ($CHCl_3$): 259 (22600). IR ($CHCl_3$): 3482*w*, 3411*w* (br.), 3189*w* (br.), 2944*m*, 2867*m*, 1695*s*, 1634*s*, 1473*m*, 1429*w*, 1384*m*, 1334*w*, 1268*w*, 1209*s*, 1156*m*, 1093*s*, 996*w*, 880*m*, 862*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): see *Table 4*, additionally, 3.94 (br. *t*, $J \approx 6.3$, H–C(5′/I)); 3.00 (*dt*, J = 15.3, 7.3, H_a–C(7′/I)); 2.76 (*dt*, J = 15.3, 7.8, H_b–C(7′/I)); 1.89

(br. *q*, $J \approx 6.6$, 2 H–C(6′/I)); 1.63, 1.55, 1.36, 1.35 (4*s*, 2 Me_2C); 1.08–1.01 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (125 MHz, $CDCl_3$): see *Table 5*, additionally, 114.41, 113.69 (2*s*, 2 Me_2C); 27.54, 27.27, 25.45, 25.20 (4*q*, 2 Me_2C); 17.92, 17.88 (2*q*, $(Me_2CH)_3Si$); 11.94 (*d*, $(Me_2CH)_3Si$). MALDI-MS: 796.3 ($[M+Na]^+$, $C_{36}H_{55}N_7NaO_{10}Si^+$). Anal. calc. for $C_{36}H_{55}N_7O_{10}Si$ (773.95): C 55.87, H 7.16, N 12.67; found: C 56.00, H 7.03, N 12.52.

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)uridin-6-yl-(6→7′*-C*)-8-{[(*tert*-*butyl)diphenylsilyloxy]-methyl}-9-(6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*heptofuranosyl)adenine* (**10**). A suspension of **9** [2] (176 mg, 0.23 mmol), 10% Pd/C (80 mg), and 2 drops of HCO_2H in MeOH (40 ml) was stirred under H_2 (5.5 bar) for 36 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 40:1) gave **10** (130 mg, 74%). Light yellow solid. R_f ($CHCl_3$/MeOH 30:1) 0.22. M.p. 149–150°. $[\alpha]_D^{25} = +12.0$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 262 (18500). IR ($CHCl_3$): 3485*w*, 3409*w* (br.), 3187*w* (br.), 2993*m*, 2943*m*, 2866*m*, 1695*s*, 1638*s*, 1453*m*, 1428*m*, 1376*s*, 1156*m*, 1089*s*, 882*m*, 862*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*, additionally, 7.72–7.63 (*m*, 4 arom. H); 7.44–7.30 (*m*, 6 arom. H); 4.02 (br. *dd*, $J = 5.7, 3.9$, H–C(5′/I)); 3.08–2.95 (*m*, H_a–C(7′/I)); 2.83–2.70 (*m*, H_b–C(7′/I)); 1.95–1.85 (*m*, 2 H–C(6′/I)); 1.58, 1.56, 1.36, 1.35 (4*s*, 2 Me_2C); 1.07 (*s*, ^{t}Bu); 1.03–1.00 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*, additionally, 135.49 (4*d*); 132.27, 132.09 (2*s*); 129.85 (2*d*); 127.70 (4*d*); 114.31, 113.58 (2*s*, 2 Me_2C); 27.56, 27.37, 25.56, 25.36 (4*q*, 2 Me_2C); 26.77 (*q*, Me_3C); 19.30 (*s*, Me_3C); 18.02, 17.99 (2*q*, $(Me_2CH)_3Si$); 12.05 (*d*, $(Me_2CH)_3Si$). HR-MALDI-MS: 1064.4970 ($[M+Na]^+$, $C_{53}H_{75}N_7NaO_{11}Si_2^+$; calc. 1064.4961). Anal. calc. for $C_{53}H_{75}N_7O_{11}Si_2$ (1042.37): C 61.07, H 7.25, N 9.41; found: C 60.93, H 7.04, N 9.22.

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)uridin-6-yl-(6→7′*-C*)-9-(6,7-dideoxy-2,3*-O-*isopropylidene-α*-L-talo-*heptofuranosyl)adenine* (**12**). A suspension of **11** [2] (50 mg, 0.06 mmol), 10% Pd/C (50 mg), and 2 drops of HCO_2H in MeOH (25 ml) was stirred under H_2 (5.5 bar) for 48 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 25:1) gave **12** (36 mg, 72%). White solid. R_f ($CHCl_3$/MeOH 20:1) 0.24. M.p. 179–181°. $[\alpha]_D^{25} = -27.3$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 260 (28800). IR ($CHCl_3$): 3482*w*, 3411*w* (br.), 3186*w* (br.), 2944*m*, 2867*m*, 1695*s*, 1633*s*, 1454*w*, 1429*w*, 1384*m*, 1335*w*, 1266*w*, 1240*w*, 1156*m*, 1126*m*, 1083*s*, 997*w*, 881*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*, additionally, 3.90–3.78 (*m*, H–C(5′/I)); 2.94–2.80 (*m*, H_a–C(7′/I)); 2.74–2.61 (*m*, H_b–C(7′/I)); 1.92–1.80 (*m*, 2 H–C(6′/I)); 1.64, 1.51, 1.38, 1.33 (4*s*, 2 Me_2C); 1.04–0.97 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*, additionally, 114.10, 113.46 (2*s*, 2 Me_2C); 27.71, 27.30, 25.47, 25.31 (4*q*, 2 Me_2C); 17.99, 17.95 (2*q*, $(Me_2CH)_3Si$); 12.01 (*d*, $(Me_2CH)_3Si$). HR-MALDI-MS: 796.3675 ($[M+Na]^+$, $C_{36}H_{55}N_7NaO_{10}Si^+$; calc. 796.3677).

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)uridin-6-yl-(6→7′*-C*)-8-{[(*tert*-*butyl)diphenylsilyloxy]-methyl}-9-(6,7-dideoxy-2,3*-O-*isopropylidene-α*-L-talo-*heptofuranosyl)adenine* (**14**). A suspension of **13** [2] (65 mg, 0.06 mmol), 10% Pd/C (65 mg), and 3 drops of HCO_2H in MeOH (30 ml) was stirred under H_2 (6.0 bar) for 24 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 40:1) gave **14** (46 mg, 70%). White solid. R_f ($CHCl_3$/MeOH 30:1) 0.26. M.p. 138–140°. $[\alpha]_D^{25} = -19.6$ ($c = 0.5$, $CHCl_3$). UV ($CHCl_3$): 261 (23600). IR ($CHCl_3$): 3410*w* (br.), 3200*w* (br.), 3015*m*, 2943*m*, 2866*m*, 1694*s*, 1637*m*, 1454*m*, 1428*w*, 1376*m*, 1156*w*, 1085*s*, 881*w*, 824*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): see *Table 4*, additionally, 7.70–7.64 (*m*, 4 arom. H); 7.42–7.30 (*m*, 6 arom. H); 3.92–3.80 (*m*, H–C(5′/I)); 2.96–2.82 (*m*, H_a–C(7′/I)); 2.75–2.62 (*m*, H_b–C(7′/I)); 2.00–1.75 (*m*, 2 H–C(6′/I)); 1.58, 1.50, 1.36, 1.31 (4*s*, 2 Me_2C); 1.07 (*s*, ^{t}Bu); 1.04–0.99 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (125 MHz, $CDCl_3$): see *Table 5*, additionally, 135.49 (4*d*); 132.27, 132.06 (2*s*); 129.85 (2*d*); 127.69 (2*d*); 127.65 (2*d*); 114.13, 113.49 (2*s*, 2 Me_2C); 27.64, 27.30, 25.48, 25.42 (4*q*, 2 Me_2C); 26.75 (*q*, Me_3C); 19.33 (*s*, Me_3C); 18.00, 17.97 (2*q*, $(Me_2CH)_3Si$); 12.03 (*d*, $(Me_2CH)_3Si$). HR-MALDI-MS: 1064.4953 ($[M+Na]^+$, $C_{53}H_{75}N_7NaO_{11}Si_2^+$; calc. 1064.4961).

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)uridin-6-yl-(6→7′*-C*)-9-(5,6,7-trideoxy-2,3*-O-*isopropylidene-β*-D-ribo-*heptofuranosyl)adenine* (**16**). A suspension of **15** [2] (65 mg, 0.09 mmol), 10% Pd/C (50 mg), and 3 drops of HCO_2H in MeOH (20 ml) was stirred under H_2 (5.5 bar) for 36 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 30:1) gave **16** (51 mg, 77%). White solid. R_f ($CHCl_3$/MeOH 20:1) 0.20. M.p. 135–136°. $[\alpha]_D^{25} = +28.4$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 259 (21400). IR ($CHCl_3$): 3411*w* (br.), 3190*w* (br.), 3019*m*, 2975*w*, 2868*w*, 1695*m*, 1632*m*, 1597*w*, 1384*m*, 1157*w*, 1088*m*, 878*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*, additionally, 2.62–2.47 (*m*, 2 H–C(7′/I)); 1.86–1.66 (*m*, 2 H–C(5′/I), 2 H–C(6′/I)); 1.61, 1.53, 1.38, 1.34 (4*s*, 2 Me_2C); 1.04–0.98 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*, additionally, 114.48, 113.57 (2*s*, 2 Me_2C); 27.34, 27.28, 25.50

Table 4. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of 30 mM Solutions* (**8**: 20 mM) *of the U*[c$_a$]A$^{(*)}$ Dimers* **8**, **10**, **12**, **14**, **16**, *and* **18** *in CDCl$_3$*[a])

	8[b])	**10**	**12**	**14**	**16**	**18**[b])
Uridine unit (II):						
HN(3)	10.60	10.20	11.12	10.14	11.43	11.15
H–C(5)	5.67	5.66[c])	5.54	5.54	5.43	5.38
H–C(1′)	5.82	5.81	5.72	5.73	5.65	5.63
H–C(2′)	5.26	5.17	5.24	5.18	5.24	5.18
H–C(3′)	4.87	4.84	4.86	4.82	4.85	4.83
H–C(4′)	4.19	4.19	4.13	4.16	4.17	4.125
H$_a$–C(5′)	3.90	3.90	3.87	3.87	3.89	3.87
H$_b$–C(5′)	3.87	3.85	3.82	3.82	3.85	3.83
J(1′,2′)	1.3	< 1.5	0.9	< 1.0	< 1.5	< 1.5
J(2′,3′)	6.4	6.6	6.3	6.3	6.3	6.4
J(3′,4′)	4.2	4.2	4.5	4.5	4.2	4.3
J(4′,5′$_a$)	5.6	6.0	5.7	5.4	6.0	5.6
J(4′,5′$_b$)	7.0	6.6	6.9	6.9	7.2	7.2
J(5′$_a$,5′$_b$)	10.3	10.8	10.2	10.8	10.5	10.5
Adenosine unit (I):						
H$_2$N–C(6)	6.30	6.15	6.60	6.17	6.38	6.26
H–C(2)	8.34	8.34	8.33	8.32	8.38	8.34
H–C(8)	7.93	–	7.90	–	7.94	–
CH$_a$–C(8)	–	5.03	–	5.02	–	5.00
CH$_b$–C(8)	–	4.90	–	4.91	–	4.97
H–C(1′)	5.84	6.45	5.86	6.46	6.03	6.51
H–C(2′)	5.15	5.18	5.19	5.21	5.54	5.64
H–C(3′)	5.05	5.12	5.10	5.15	4.94	5.06
H–C(4′)	4.30	4.27	4.44	4.36	4.23	4.15
HO–C(5′)	6.89	6.78	6.64	6.36	–	–
J(H$_a$,H$_b$)	–	12.9	–	13.2	–	13.1
J(1′,2′)	4.8	4.2	4.8	4.5	2.1	1.7
J(2′,3′)	5.9	6.3	6.0	6.0	6.3	6.5
J(3′,4′)	1.4	1.5	< 1.5	1.8	3.9	4.7
J(4′,5′$_a$)	< 1.0	< 1.0	< 1.0	< 1.0	6.5	7.2
J(4′,5′$_b$)	–	–	–	–	6.5	7.2
J(5′$_a$,OH)	< 1.5	< 1.5	11.4	11.1	–	–

[a]) Assignment based on selective homodecoupling experiments. [b]) Assignment based on a DQFCOSY and a HSQC spectrum. [c]) ^4J(5,NH) = 2.1 Hz.

(2 C) (3*q*, 2 *Me*$_2$C); 18.00, 17.98 (2*q*, (*Me*$_2$CH)$_3$Si); 12.04 (*d*, (Me$_2$*C*H)$_3$Si). HR-MALDI-MS: 780.3637 ([*M* + Na]$^+$, $C_{36}H_{55}N_7NaO_9Si^+$; calc. 780.3735). Anal. calc. for $C_{36}H_{55}N_7O_9Si$ (757.95): C 57.05, H 7.31, N 12.94; found: C 56.85, H 7.13, N 12.82.

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)uridin-6-yl-(6→7′*-C*)-8-[[(*tert-*butyl)diphenylsilyloxy]-methyl]-9-(5,6,7-trideoxy-2,3*-O-*isopropylidene-β*-D-ribo-*heptofuranosyl)adenine* (**18**). A suspension of **17** [2] (40 mg, 0.04 mmol), 10% Pd/C (40 mg), and 3 drops of HCO_2H in MeOH (20 ml) was stirred under H_2 (5.5 bar) for 36 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 40:1) gave **18** (32 mg, 80%). White solid. R_f ($CHCl_3$/MeOH 60:1) 0.11. M.p. 135–137°. $[\alpha]_D^{25} = +8.1$ (*c* = 0.5, $CHCl_3$). UV ($CHCl_3$): 261 (22000). IR ($CHCl_3$): 3410*w*, 3015*m*, 2943*m*, 2866*m*, 1695*s*, 1635*m*, 1447*w*, 1428*w*, 1375*m*, 1329*w*, 1157*w*, 1086*s*, 881*w*, 823*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*, additionally, 7.73–7.64 (*m*, 4 arom. H); 7.45–7.31 (*m*, 6 arom. H); 2.56 (br. *dt*, *J* = 15.6, 7.8, H$_a$–C(7′/I)); 2.46 (br. *dt*,

Table 5. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the U*[c$_a$]A$^{(*)}$ Dimers* **8**, **10**, **12**, **14**, **16**, *and* **18** *in $CDCl_3$*

	8[a])	**10**	**12**	**14**	**16**	**18**[a])
Uridine unit (II):						
C(2)	151.27	150.63	151.07	150.61	150.91	150.90
C(4)	163.58	162.93	163.50	162.72	163.08	163.47
C(5)	102.68	102.29	101.95	101.85	102.15	102.08
C(6)	156.21[b])	155.19[b])	156.20[b])	155.68[b])	155.64	155.59[b])
C(1′)	91.78	91.67[c])	91.41	91.42	91.49	91.54
C(2′)	84.18	84.07	84.16	84.11	84.21	84.25
C(3′)	82.45	82.35	82.52	82.27[c])	82.33	83.38
C(4′)	89.37	89.29	89.37	89.43	86.61	86.58
C(5′)	64.31	64.30	64.27	64.33	64.33	64.35
Adenosine unit (I):						
C(2)	152.80	152.32	152.38	152.16	152.88	152.51
C(4)	148.24	149.39[d])	147.90	149.39[d])	149.05	149.84
C(5)	120.58	118.92	120.42	118.90	119.91	118.58
C(6)	156.24[b])	155.68[b])	156.41[b])	156.45[b])	155.64	156.00[b])
C(8)	140.21	149.62[d])	140.04	149.57[d])	139.97	150.51
*C*H$_2$–C(8)	–	59.65	–	59.70	–	59.78
C(1′)	93.66	91.58[c])	94.13	91.97	90.25	89.10
C(2′)	83.19	83.43	82.52	82.77	83.98[b])	84.08
C(3′)	79.66	79.20	82.27	82.21[c])	83.94[b])	83.93
C(4′)	88.93	88.55	87.21	87.09	89.42	89.45
C(5′)	69.70	69.66	71.09	70.92	32.42	32.45
C(6′)	30.20	30.36	31.74	31.97	23.65	23.54
C(7′)	29.70	29.22	29.29	29.27	32.25	32.01

[a]) Assignments based on a HSQC spectrum. [b]) [c]) [d]) Assignments may be interchanged.

$J = 15.7, 7.4$, H$_b$–C(7′/I)); 1.80 (q, $J \approx 7.2$, 2 H–C(5′/I)); 1.75–1.65 (m, 2 H–C(6′/I)); 1.61, 1.53, 1.39, 1.35 (4*s*, 2 Me$_2$C); 1.08 (*s*, ^{t}Bu); 1.04–0.98 (m, (Me$_2$CH)$_3$Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*, additionally, 135.70 (2*d*); 135.68 (2*d*); 132.42, 132.40 (2*s*); 130.02, 129.90 (2*d*); 127.87 (2*d*); 127.74 (2*d*); 114.22, 113.62 (2*s*, 2 Me$_2$*C*); 27.36, 27.30, 25.54, 25.49 (4*q*, 2 *Me*$_2$C); 26.72 (q, *Me*$_3$C); 19.22 (*s*, Me$_3$*C*); 17.91, 17.88 (2*q*, (*Me*$_2$CH)$_3$Si); 11.94 (*d*, (Me$_2$CH)$_3$Si). MALDI-MS: 1048.5030 ([M + Na]$^+$, $C_{53}H_{75}N_7NaO_{10}Si_2^+$; calc. 1048.5012).

2′,3′-O-*Isopropylidene*-5′-O-*(triisopropylsilyl)adenosin-8-yl-(8→7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*heptofuranosyl)uracil* (**20**). A suspension of **19** [2] (51 mg, 0.066 mmol) and 10% Pd/C (50 mg) in AcOEt (40 ml) was stirred under H_2 (5.0 bar) for 5 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 15:1) gave **20** (50 mg, 98%). White solid. R_f ($CHCl_3$/MeOH 10:1) 0.28. M.p. 144–146°. $[\alpha]_D^{25} = -12.1$ ($c = 0.5$, $CHCl_3$). UV ($CHCl_3$): 261 (32300). IR ($CHCl_3$): 3411*w* (br.), 3200*w* (br.), 3015*m*, 2944*m*, 2867*m*, 1696*s*, 1635*m*, 1456*w*, 1384*m*, 1331*w*, 1157*w*, 1090*s*, 881*w*, 808*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 6*, additionally, 3.99 (br. *dt*, $J \approx 9.3, 3.6$, H–C(5′/I)); 3.25 (br. *dt*, $J = 15.6, 6.9$, H$_a$–C(7′/I)); 3.16 (br. *dt*, $J = 15.6, 6.9$, H$_b$–C(7′/I)); 2.20–1.98 (m, 2 H–C(6′/I)); 1.61, 1.58, 1.41, 1.35 (4*s*, 2 Me$_2$C); 0.96 (br. *s*, (Me$_2$CH)$_3$Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 7*, additionally, 114.35, 113.70 (2*s*, 2 Me$_2$*C*); 27.31, 27.24, 25.43, 25.34 (4*q*, 2 *Me*$_2$C); 17.94, 17.92 (2*q*, (*Me*$_2$CH)$_3$Si); 11.94 (*d*, (Me$_2$*C*H)$_3$Si). HR-MALDI-MS: 796.3681 ([M + Na]$^+$, $C_{36}H_{55}N_7NaO_{10}Si^+$; calc. 796.3677). Anal. calc. for $C_{36}H_{55}N_7O_{10}Si$ (773.95): C 55.87, H 7.16, N 12.67; found: C 55.98, H 7.07, N 12.31.

2′,3′-O-*Isopropylidene*-5′-O-*(triisopropylsilyl)adenosin-8-yl-(8→7′*-C*)-6-{[(*tert-*butyl)diphenylsilyloxy]methyl}-1-(6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*heptofuranosyl)uracil* (**22**). A suspension of

21 [2] (60 mg, 0.06 mmol) and 10% Pd/C (60 mg) in AcOEt (30 ml) was stirred under H_2 (5.0 bar) for 5.5 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 50:1) gave **22** (40 mg, 66%). White solid. R_f ($CHCl_3$/MeOH 20:1) 0.22. M.p. 112–114°. $[\alpha]_D^{25} = -18.9$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 261 (22500). IR ($CHCl_3$): 3485*w*, 3411*w* (br.), 3200*w* (br.), 3014*m*, 2944*m*, 2866*m*, 1698*s*, 1635*m*, 1462*w*, 1383*m*, 1157*m*, 1092*s*, 881*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 6*, additionally, 7.69–7.64 (*m*, 4 arom. H); 7.49–7.38 (*m*, 6 arom. H); 4.00–3.92 (*m*, $J \approx 6.3$, H–C(5′/I)); 3.26–3.11 (*m*, 2 H–C(7′/I)); 2.20–1.95 (*m*, 2 H–C(6′/I)); 1.60, 1.46, 1.41, 1.32 (4*s*, 2 Me_2C); 1.09 (*s*, ^{t}Bu); 1.00–0.90 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 7*, additionally, 135.40 (4*d*); 131.72 (2*s*); 130.23 (2*d*); 127.95 (4*d*); 113.93, 113.59 (2*s*, 2 Me_2C); 27.34, 27.24, 25.47, 25.30 (4*q*, 2 Me_2C); 26.69 (*q*, Me_3C); 19.31 (*s*, Me_3C); 17.95, 17.92 (2*q*, $(Me_2CH)_3Si$); 11.95 (*d*, $(Me_2CH)_3Si$). HR-MALDI-MS: 1064.4980 ($[M+Na]^+$, $C_{53}H_{75}N_7NaO_{11}Si_2^+$; calc. 1064.4961).

Table 6. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of 30 mM solutions of the A*[c$_a$]U$^{(*)}$ Dimers* **20**, **22**, **24**, **26**, **28**, *and* **30** *in $CDCl_3$*[a])

	20	**22**	**24**	**26**	**28**[b])	**30**
Adenosine unit (II):						
H_2N–C(6)	6.22	6.19	6.36	6.40	6.63	7.00
H–C(2)	8.24	8.21	8.26	8.24	8.26	8.28
H–C(1′)	6.07	6.10	6.05	6.03	6.00	6.01
H–C(2′)	5.85	5.84	5.88	5.87	5.84	5.86
H–C(3′)	5.17	5.18	5.18	5.19	5.18	5.20
H–C(4′)	4.29	4.28	4.30	4.28	4.29	4.29
H_a–C(5′)	3.80	3.80	3.79	3.79	3.80	3.81
H_b–C(5′)	3.66	3.66	3.64	3.64	3.65	3.64
J(1′,2′)	1.5	1.8	1.8	1.8	1.5	1.8
J(2′,3′)	6.3	6.3	6.3	6.3	6.6	6.3
J(3′,4′)	3.0	3.0	3.0	3.0	3.0	2.7
J(4′,5′$_a$)	6.9	6.9	6.9	7.2	7.2	7.2
J(4′,5′$_b$)	6.3	6.3	6.6	6.0	6.6	6.6
J(5′$_a$,5′$_b$)	10.2	10.2	10.2	10.2	10.2	10.2
Uridine unit (I):						
HN(3)	10.94	11.18	11.14	11.31	11.09	11.84
H–C(5)	5.69	5.68	5.69	5.62	5.72	5.85
H–C(6)	7.47	–	7.53	–	7.22	–
CH_a–C(6)	–	4.53	–	4.53	–	4.58
CH_b–C(6)	–	4.42	–	4.38	–	4.39
H–C(1′)	5.69	5.73	5.77	5.77	5.56	5.65
H–C(2′)	4.96	5.21	4.93	5.21	5.02	5.24
H–C(3′)	5.01	5.12	4.96	5.06	4.68	4.83
H–C(4′)	4.11	3.99	4.13	4.06	4.11	4.08
HO–C(5′)	5.1–4.9[c])	4.55–4.35[c])	4.7–4.5[c])	4.15[d])	–	–
J(5,6)	8.1	–	8.1	–	8.1	–
J(H_a,H_b)	–	14.1	–	14.1	–	14.1
J(1′,2′)	2.4	2.1	2.4	2.1	1.8	1.5
J(2′,3′)	6.3	6.3	6.3	6.3	6.6	6.3
J(3′,4′)	3.3	3.3	3.0	4.2	4.5	4.2
J(4′,5′$_a$)	3.9	4.2	3.0	5.1	6.3	6.9
J(4′,5′$_b$)	–	–	–	–	6.3	6.9

[a]) Assignments based on selective homodecoupling experiments. [b]) Assignments based on DQFCOSY, HSQC, and HMBC spectra. [c]) *J*(5′,OH) could not be determined. [d]) *J*(5′,OH) = 6.3 Hz.

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)adenosin-8-yl-(8 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-α*-L-talo-*heptofuranosyl]uracil* (**24**). A suspension of **23** [2] (79 mg, 0.23 mmol) and 10% Pd/C (60 mg) in AcOEt (30 ml) was stirred under H_2 (5.0 bar) for 2 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 25 : 1) gave **24** (51 mg, 64%). White solid. R_f ($CHCl_3$/MeOH 16 : 1) 0.19. M.p. 148–150°. $[\alpha]_D^{25} = -19.1$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3411*w* (br.), 3200*w* (br.), 3018*m*, 2974*m*, 2868*m*, 1695*s*, 1636*m*, 1456*w*, 1384*m*, 1331*w*, 1256*w*, 1156*w*, 1075*m*, 880*m*, 809*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 6*, additionally, 3.91 (br. *dt*, $J \approx 8.4$, 4.2, H–C(5′/I)); 3.30 (br. *dt*, $J = 15.3$, 7.8, H_a–C(7′/I)); 3.15 (br. *dt*, $J = 15.3$, 7.8, H_b–C(7′/I)); 2.17–2.00 (*m*, 2 H–C(6′/I)); 1.56, 1.54, 1.37, 1.31 (4*s*, 2 Me_2C); 0.97–0.95 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 7*, additionally, 114.33, 113.63 (2*s*, 2 Me_2C); 27.37, 27.22, 25.41 (2 C) (3*q*, 2 Me_2C); 17.92, 17.91 (2*q*, $(Me_2CH)_3Si$); 11.92 (*d*, $(Me_2CH)_3Si$).

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)adenosin-8-yl-(8 → 7′*-C*)-6-{[(*tert-*butyl)diphenylsilyloxy]methyl}-1-(6,7-dideoxy-2,3*-O-*isopropylidene-α*-L-talo-*heptofuranosyl)uracil* (**26**). A suspension of **25** [2] (53 mg, 0.05 mmol) and 10% Pd/C (50 mg) in AcOEt (24 ml) was stirred under H_2 (5.0 bar) for 6 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 40 : 1) gave **26** (32 mg, 61%). White solid. R_f ($CHCl_3$/MeOH 50 : 1) 0.30. M.p. 158–160°. $[\alpha]_D^{25} = -40.5$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 260 (27400). IR ($CHCl_3$): 3411*w*, 3014*m*, 2944*m*, 2866*m*, 1698*s*, 1635*w*, 1462*w*, 1428*w*, 1383*m*, 1331*w*, 1157*m*, 1105*s*, 1072*s*, 880*w*, 840*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 6*, additionally, 7.69–7.64 (*m*, 4 arom. H); 7.49–7.38 (*m*, 6 arom. H); 4.04–3.92 (*m*, H–C(5′/I)); 3.36–3.22 (*m*, H_a–C(7′/I)); 3.19–2.95 (*m*, H_b–C(7′/I)); 2.15–1.90 (*m*, 2 H–C(6′/I)); 1.61, 1.45, 1.41, 1.32 (4*s*, 2 Me_2C); 1.08 (*s*, ^{t}Bu); 0.96 (br. *s*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 7*, additionally, 135.40 (*d*, 4 C); 131.72 (*s*, 2 C);

Table 7. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the U*[c_a]A$^{(*)}$ Dimers* **20**, **22**, **24**, **26**, **28**, *and* **30** *in $CDCl_3$*

	20	**22**	**24**	**26**	**28**[a])	**30**
Adenosine unit (II):						
C(2)	151.98	151.81	152.04	151.85	152.09	151.81
C(4)	150.04	150.04	149.94	150.01	150.28	150.02
C(5)	117.96	118.22	118.00	118.22	118.58	118.43
C(6)	154.48	154.48	154.62	154.64	155.06	155.00
C(8)	152.93	153.33	153.27	153.64	153.03	153.08[b])
C(1′)	90.05	89.99	90.07	90.29	90.22	90.16
C(2′)	82.93	83.05	82.86	82.93	83.06	83.01
C(3′)	82.37	82.50	82.39	82.59	82.63	82.63
C(4′)	88.19	88.16	88.30	88.16	88.35	88.23
C(5′)	63.46	63.50	63.43	63.44	63.61	63.53
Uridine unit (I):						
C(2)	150.53	151.23	150.74	151.45	150.58	151.63
C(4)	163.71	163.10	163.64	162.97	163.57	163.10
C(5)	102.50	102.17	102.77	102.26	102.86	102.38
C(6)	142.34	153.33	142.21	153.09	142.31	153.00[b])
CH_2–C(6)	–	62.17	–	62.20	–	62.29
C(1′)	94.46	91.65	94.01	91.61	94.67	91.28
C(2′)	84.11	83.41	83.73	83.61	84.58	84.92
C(3′)	79.57	80.41	81.14	81.36	83.87	84.24
C(4′)	89.51	89.99	88.99	90.14	87.19	88.79
C(5′)	70.09	70.14	70.91	71.30	32.85	33.16
C(6′)	30.53	30.80	31.73	31.72	24.16	24.67
C(7′)	24.27	24.10	24.49	24.44	27.57	27.98

[a]) Assignments based on a HSQC and a HMBC spectrum. [b]) Assignments may be interchanged.

130.23 (*d*, 2 C); 127.95 (*d*, 2 C); 127.92 (*d*, 2 C); 113.86, 113.52 (2*s*, 2 Me_2C); 27.38, 27.24, 25.47, 25.39 (4*q*, 2 Me_2C); 26.69 (*q*, Me_3C); 19.31 (*s*, Me_3C); 17.95, 17.93 (2*q*, $(Me_2CH)_3Si$); 11.95 (*d*, $(Me_2CH)_3Si$). HR-MALDI-MS: 1064.4916 ($[M+Na]^+$, $C_{53}H_{75}N_7NaO_{11}Si_2^+$; calc. 1064.4961).

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)adenosin-8-yl-(8 → 7′*-C*)-1-(5,6,7-trideoxy-2,3*-O-*isopropylidene-β*-D-ribo-*heptofuranosyl)uracil* (**28**). A suspension of **27** [2] (61 mg, 0.08 mmol) and 10% Pd/C (50 mg) in MeOH (36 ml) was stirred under H_2 (5.5 bar) for 6 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 20 : 1) gave **28** (55 mg, 90%). White solid. R_f ($CHCl_3$/MeOH 20 : 1) 0.20. M.p. 130–132°. $[\alpha]_D^{25} = -18.2$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 260 (21500). IR ($CHCl_3$): 3409*w* (br.), 3200*w* (br.), 3017*s*, 2975*m*, 2867*w*, 1695*s*, 1635*m*, 1454*w*, 1376*m*, 1330*w*, 1262*m*, 1157*w*, 1089*m*, 880*w*, 808*w*. ^{1}H-NMR (500 MHz, $CDCl_3$; assignments based on a HMBC spectrum): see *Table 6*, additionally, 3.14–2.95 (*m*, 2 H–C(7′/I)); 2.03–1.90 (*m*, 2 H–C(6′/I)); 1.90–1.75 (*m*, 2 H–C(5′/I)); 1.61, 1.41 (2*s*, Me_2C/II); 1.55, 1.33 (2*s*, Me_2C/I); 1.01–0.88 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): see *Table 7*, additionally, 114.59 (*s*, Me_2C/I); 113.69 (*s*, Me_2C/II); 27.23, 25.38 (2*q*, 2 Me_2C); 17.89, 17.86 (2*q*, $(Me_2CH)_3Si$); 11.92 (*d*, $(Me_2CH)_3Si$). HR-MALDI-MS: 780.3705 ($[M+Na]^+$, $C_{36}H_{55}N_7NaO_9Si^+$; calc. 780.3728). Anal. calc. for $C_{36}H_{55}N_7O_9Si$ (757.96): C 57.05, H 7.31, N 12.94; found: C 56.90, H 7.24, N 12.77.

2′,3′-O-*Isopropylidene-5′*-O-*(triisopropylsilyl)adenosin-8-yl-(8 → 7′*-C*)-6-{[(*tert-*butyl)diphenylsilyl-oxy]methyl}-1-(5,6,7-trideoxy-2,3*-O-*isopropylidene-β*-D-ribo-*heptofuranosyl)uracil* (**30**). A suspension of **29** [2] (36 mg, 0.035 mmol) and 10% Pd/C (30 mg) in MeOH (15 ml) was stirred under H_2 (5.5 bar) for 7 h at 25°. Filtration through *Celite*, evaporation, and FC ($CHCl_3$/MeOH 80 : 1) gave **30** (28 mg, 78%). White solid. R_f ($CHCl_3$/MeOH 60 : 1) 0.10. M.p. 120–122°. $[\alpha]_D^{25} = -47.6$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 261 (24300). IR ($CHCl_3$): 3408*w*, 3015*m*, 2944*m*, 2866*m*, 1698*s*, 1635*m*, 1462*m*, 1428*w*, 1383*m*, 1330*w*, 1261*w*, 1157*m*, 1096*s*, 1071*s*, 878*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 6*, additionally, 7.71–7.65 (*m*, 4 arom. H); 7.48–7.37 (*m*, 6 arom. H); 3.15–3.04 (*m*, H_a–C(7′/I)); 3.02–2.89 (*m*, H_b–C(7′/I)); 2.02–1.70 (*m*, 2 H–C(5′/I), 2 H–C(6′/I)); 1.62, 1.50, 1.42, 1.31 (4*s*, 2 Me_2C); 1.08 (*s*, ^{t}Bu); 0.96 (br. *s*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 7*, additionally, 135.42 (4*d*); 131.81 (2*s*); 130.19 (2*d*); 127.92 (2*d*); 127.88 (2*d*); 113.52, 113.42 (2*s*, 2 Me_2C); 27.26 (2 C), 25.45, 25.32 (3*q*, 2 Me_2C); 26.67 (*q*, Me_3C); 19.31 (*s*, Me_3C); 17.94 (*q*, $(Me_2CH)_3Si$); 11.95 (*d*, $(Me_2CH)_3Si$). HR-MALDI-MS: 1048.5010 ($[M+Na]^+$, $C_{53}H_{75}N_7NaO_{10}Si_2^+$; calc. 1048.5012). Anal. calc. for $C_{53}H_{75}N_7O_{10}Si_2$ (1026.37): C 62.02, H 7.36, N 9.55; found: C 62.14, H 7.35, N 9.36.

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