

Oligonucleotide Analogues with Integrated Bases and Backbones

Part 24

Synthesis, Conformational Analysis, and Association of Aminomethylene-Linked Self-Complementary Adenosine and Uridine Dinucleosides

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Inspection of *Maruzen* models and force-field calculations suggest that oligonucleotide analogues integrating backbone and bases (ONIBs) with an aminomethylene linker form similar cyclic duplexes as the analogous oxymethylene linked dinucleosides. The self-complementary adenosine- and uridine-derived aminomethylene-linked A*[N]U dinucleosides **15**–**17** were prepared by an *aza-Wittig* reaction of the aldehyde **10** with an iminophosphorane derived from azide **6**. The sequence-isomeric U*[N]A dinucleosides **18**–**20** were similarly prepared from aldehyde **3** and azide **12**. The *N*-ethylamine **5**, the acetamides **7** and **14**, and the amine **13** were prepared as references for the conformational analysis of the dinucleosides. In contradistinction to the results of calculations, the *N*-ethylamine **5** exists as intramolecularly H-bonded hydroxyimino tautomer. The association in CDCl₃ of these dinucleosides was studied by ¹H-NMR and CD spectroscopy. The A*[N]U dinucleosides **16** and **17** associate more strongly than the sequence isomers **19** and **20**; the cyclic duplexes of **16** form preferentially *Watson–Crick*-type base pairs, while **17**, **19**, and **20** show both *Watson–Crick*- and *Hoogsteen*-type base pairing. The cyclic duplexes of the aminomethylene-linked dinucleosides prefer a *gg*-orientation of the linker. No evidence was found for an intramolecular H-bond of the aminomethylene group. The CD spectra of **16** and **17** show a strong, those of **19** a weak, and those of **20** almost no temperature dependence.

Introduction. – Oligonucleotide analogues integrating backbone and bases (ONIBs) replace the backbone of nucleic acids by linking elements between adjacent nucleobases. ONIBs form cyclic duplexes and/or linear associates, as shown by analysing the association in CDCl₃ of partially protected, self-complementary ethynylene- [1], ethenylene- [2], ethylene- [3], oxymethylene- [4][5], and thiomethylene-linked [6] dinucleosides of the type U*[x]A^(*)1)) and A*[x]U^(*). The formation of cyclic duplexes (*i.e.*, pairing) of partially protected, self-complementary dinucleoside analogues in CDCl₃ depends on the conformation of the linker, the orientation of the nucleobase of unit I, the sequence of nucleobases, and the conformation of the ribofuranose ring. Pairing may occur *via Watson–Crick* (WC),

¹⁾ *Conventions for abbreviated notation:* The substitution at C(6) of pyrimidines and C(8) of purines is denoted by an asterisk (*); for example, A* and U* for thiomethylated adenosine and uridine derivatives, respectively. The moiety x linking C(6)–CH₂ or C(8)–CH₂ of unit II and C(5') of unit I is indicated in square brackets, *i.e.*, [c] for a C-, [o] for a O-, [N] for a N-, and [s] for a S-atom.

reverse *Watson–Crick* (rWC), *Hoogsteen* (H), or reverse *Hoogsteen* (rH) H-bonding [7].

A fully deprotected thiomethylene-linked adenosine and uridine-derived tetranucleoside, and analogous dinucleosides proved insoluble in H₂O. Considering that biological applications of ONIBs will require a modicum of solubility in H₂O, we turned towards designing potentially H₂O-soluble ONIBs. Aminomethylene-linked oligonucleosides appeared promising. They may be sufficiently soluble in H₂O, either as amines, or as ammonium salts, or upon transformation into soluble derivatives by substitution of the amino group of the linking element with an ionisable group. Whereas ammonium groups are excellent H-bond donors, amino groups are weak H-donors [8–10], but good H-bond acceptors, and, in 2-aminoethanols, N–H···O H-bonds cannot successfully compete with O–H···N H-bonds [11–14]. The amino groups should also allow to cross-link such oligonucleosides, thereby considerably increasing the potential of generating novel structures.

We attempted at predicting the propensity of aminomethylene-linked ONIBs to form duplexes, and present the result of modeling studies. We also describe the synthesis of A*[N]U and U*[N]A dinucleosides devoid of a substituent at C(6/I) of U and at C(8/I) of A, respectively. Such substituents favour a *syn*-conformation, as required for the formation of cyclic duplexes. Thus, the envisaged dinucleosides should exhibit a higher tendency to form linear associates than the *C*(6/I)- and *C*(8/I)-substituted analogues, and present a more demanding test of the assumption that aminomethylene-linked ONIBs form cyclic duplexes.

Results and Discussion. – *Conformational Analysis and Molecular Modelling.* The pairing propensity of ethylene- [3], oxymethylene- [4][5], and thiomethylene-linked [6] self-complementary U*[x]A^(*) and A*[x]U^(*) dinucleosides was analysed by evaluating the relative energy of the conformers of the diastereoisomeric constitutional isomers resulting from pairing. The analysis showed that oxymethylene- and thiomethylene-linked dinucleosides undergo pairing, but that the duplexes adopt a different conformation. While the cyclic duplexes of oxymethylene-linked U*[o]A^(*) dinucleosides adopt a *gg*-conformation of the linker [4][5], those of thiomethylene-linked U*[s]A^(*) and A*[s]U^(*) dinucleosides adopt a *gt*-conformation [6]. The greater similarity of N to O rather than to S in terms of electronegativity and bond length suggests that aminomethylene-linked dinucleoside duplexes should adopt a *gg*-conformation.

To analyse the formation of cyclic duplexes of A*[x]U and U*[x]A dinucleosides (x = O, S, and NH) more closely, we modelled *Watson–Crick* H-bonded cyclic duplexes of 2',3'-*O*-isopropylidenated and 5'/II-*O*-methylated derivatives using the programme AMBER* implemented in Macromodel V. 6.0 [15]. We started with U*[o]A^(*) and A*[o]U^(*) dinucleosides obtained by modifying the calculated cyclic duplex of a U*[s]A*[s]U*[s]A* tetranucleoside [16], to avoid complications from H-bonds involving the N–H group. We first set the *tg*-conformation for the MeOC(5')H₂ group of unit II, and then constraints to maintain the *Watson–Crick* base pairing (1.7 Å for the H-bonds) and π -stacking (3.2 Å distance between the base pairs), and to fix either a *gg*- or a *gt*-orientation of the linking unit (torsion angle –60 or +60°). After optimisation, all constraints were released, and the structures for all U*[x]A and

A*[x]U dinucleosides (x = O, S, and NH) were optimized; for x = NH, the two diastereoisomers with the same configuration at the invertomers of both CH₂NHCH₂ groups of the duplex were calculated. To obtain additional duplex structures, different conformations of the linking units were similarly fixed at the start of the calculations, and the constraints were released for the final optimization. Three characteristic properties of the AMBER* force field were observed: 1) In contradistinction to experimental observations, NH of the NHCH₂ linker appears as a powerful H-bond donor; if a H-bond acceptor was within reach, a N–H...X (X = O or N) σ - or π -type H-bond was formed. 2) The base-stacking is maintained (distance of 3.1–3.3 Å between base pairs; concave base pairs were formed instead of flat base pairs with a larger distance). 3) A high-*syn*-conformation is feasible at the cost of an energetic penalty ($\chi \approx 120^\circ$; this features a destabilizing steric interaction of H–C(2') with the nucleobase); experimentally, a weak H-bond of H–C(2') to N(3) of A or to O=C(2) of U is expected to favour a high-*syn* conformation.

The calculations confirmed the preferred *gt*-conformation of the U*[s]A and A*[s]U dinucleosides ($\Delta E = 2.1$ and 0.4 kcal/mol, resp.), and the *gg*-conformation of the U*[o]A dinucleosides ($\Delta E = 2.4$ kcal/mol). They predict a preferred *gg*-conformation also of the A*[o]U sequence isomers ($\Delta E = 0.4$ kcal/mol), for which no experimental data are available.

In the U*[N]A and A*[N]U series, the calculated energy values are strongly influenced by the H-bonds of the NHCH₂ group, meaning that the conformation of the calculated duplexes is far more reliable than the energy values. The *gg*-rotamers of the duplexes are favoured by an intra-residue H-bond to the nucleobase, whereas the *gt*-rotamers can at best form a weak inter-residue H-bond to O(2'/II). The definition of the torsion angles η , θ , ι , and κ characterizing the conformation of the linker, and some structural data of the *gg*-rotamers of the U*[N]A and A*[N]U duplexes are given in Table 1. The most favoured duplexes **UA-1** and **AU-1** (Fig. 1) prefer a *syn*-orientation of the nucleobase and a $g^-g^+tg^-$ orientation of the angles η , θ , ι , and κ . The less favoured duplexes adopt a *tt* orientation of θ and ι (g^-ttg^- for **UA-2**, **UA-3**, and **AU-4**; g^-ttg^+ for **AU-2**, g^-ttt for **AU-3**). This conformation is similar to that of the most stable conformer of Et₂NH [17]. The conformers **UA-2** and **AU-2** may be less disfavoured than calculated, since the calculated conformers possess a high-*syn*-orientation of the nucleobase of unit I. A *gauche* κ angle is expected to be favoured [6], and the energy of 0.71 kcal/mol required for a *gauche* θ angle of **UA-1** and **AU-1** is easily gained by base pairing. Thus, one is led to expect that NHCH₂-linked dinucleosides pair more strongly than the corresponding OCH₂-linked dinucleosides, since the conformation of the duplex resulting from base pairing and base stacking allows the formation of weak intramolecular H-bonds of the NHCH₂ linker.

Synthesis of the A[N]U and U*[N]A Dinucleosides.* We planned to synthesize these dinucleosides by condensing a mononucleoside-derived aldehyde with an iminophosphorane, and reducing the resulting imine. The iminophosphoranes should be obtained by treating 5'-azido-5'-deoxy nucleosides with Me₃P, while the aldehydes were formed, if not isolated, in the course of the synthesis of hydroxymethylated nucleosides [18]. We thus required the 5'-azido-5'-deoxy nucleosides **6** and **12**, and the aldehydes **3** and **10** (Schemes 1 and 2). In addition, the acetamides **7** and **14**, the *N*-ethylamine **5**, and the amine **13** were of interest as references for the conformational analysis of the

Table 1. Some Structural Parameters of the Calculated gg-Configured U*[N]A and A*[N]U Duplexes Possessing Watson–Crick Base Pairing

	U*[N]A Duplexes		
	UA-1	UA-2	UA-3
E_{rel} [kcal/mol]	0	5.4	9.5
$\chi/1$ ($\angle \text{O}-\text{C}(1'/\text{I})-\text{N}(9/\text{I})-\text{C}(5/\text{I})$) [$^{\circ}$]	66	119	88
η ($\angle \text{O}-\text{C}(4'/\text{I})-\text{C}(5'/\text{I})-\text{N}$) [$^{\circ}$]	-47	-54	-52
θ ($\angle \text{C}(4'/\text{I})-\text{C}(5'/\text{I})-\text{N}-\text{CH}_2$) [$^{\circ}$]	104	156	172
ι ($\angle \text{C}(5'/\text{I})-\text{N}-\text{CH}_2-\text{C}(6/\text{II})$) [$^{\circ}$]	-170	-161	154
κ ($\angle \text{N}-\text{CH}_2-\text{C}(6/\text{II})-\text{N}(1/\text{II})$) [$^{\circ}$]	-68	-75	-88
$\chi/2$ ($\angle \text{O}-\text{C}(1'/\text{II})-\text{N}(1/\text{II})-\text{C}(2/\text{II})$) [$^{\circ}$]	55	57	63
NHCH ₂ H-Bond	N-H...N(3/I)	N-H...N(9/I)	N-H...N(3/I)
l [$\text{\AA}$] ($\angle \text{N}-\text{H}\cdots\text{X}$ [$^{\circ}$])	1.86 (168)	2.00 (154)	1.93 (148)
Propeller twist [$^{\circ}$]	12 and 17	43 and 46	small
Buckle twist [$^{\circ}$]	small	small	14 and 15
Roll angle [$^{\circ}$]	small	22 and 24	small

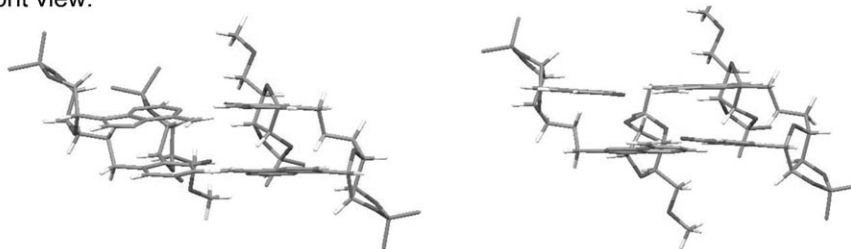
	A*[N]U Duplexes			
	AU-1	AU-2	AU-3	AU-4
E_{rel} [kcal/mol]	0	2.1	11.0	11.1
$\chi/1$ ($\angle \text{O}-\text{C}(1'/\text{I})-\text{N}(1/\text{I})-\text{C}(2/\text{I})$) [$^{\circ}$]	62	125	68	77
η ($\angle \text{O}-\text{C}(4'/\text{I})-\text{C}(5'/\text{I})-\text{N}$) [$^{\circ}$]	-48	-58	-37	-41
θ ($\angle \text{C}(4'/\text{I})-\text{C}(5'/\text{I})-\text{N}-\text{CH}_2$) [$^{\circ}$]	101	161	-153	171
ι ($\angle \text{C}(5'/\text{I})-\text{N}-\text{CH}_2-\text{C}(8/\text{II})$) [$^{\circ}$]	-173	156	-166	144
κ ($\angle \text{N}-\text{CH}_2-\text{C}(8/\text{II})-\text{N}(9/\text{II})$) [$^{\circ}$]	-67	74	-158	-100
$\chi/2$ ($\angle \text{O}-\text{C}(1'/\text{II})-\text{N}(9/\text{II})-\text{C}(6/\text{II})$) [$^{\circ}$]	58	44	39	44
NHCH ₂ H-Bond	N-H...O=C(2/I)	N-H...N(1/I)	N-H...O=C(2/I)	N-H...O=C(2/I)
l [$\text{\AA}$] ($\angle \text{N}-\text{H}\cdots\text{X}$ [$^{\circ}$])	1.73 (171)	1.93 (156)	1.75 (175)	1.73 (168)
Propeller twist [$^{\circ}$]	small	24 and 26	small	twice 30
Buckle twist [$^{\circ}$]	small	small	10 and 11	small
Roll angle [$^{\circ}$]	small	25 and 26	small	30 and 31

dinucleosides. We synthesized these compounds from the known 2',3'-*O*-isopropylidene-uridine (**1**) [19] and -adenosine **8** [20] [21].

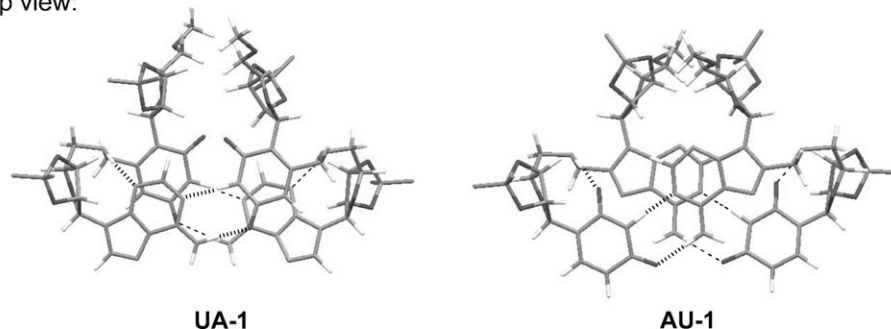
Protecting HO–C(5') of **1** by silylation with *tert*-butyldimethylsilyl chloride (TDS) according to [22] gave **2** that was treated with excess LDA and DMF to yield, upon hydrolysis [18], 98% of aldehyde **3** (*Scheme 1*). The azide **6** was prepared in a yield of 80% from **1** by tosylation to **4**, followed by reaction with NaN₃ [23] [24]. To obtain the acetamide **7**, we hydrogenated **6** in the presence of Pd/C and Ac₂O [24] [25], while treatment of the *p*-toluenesulfonate **4** with EtNH₂ in DMF gave 85% of the crystalline ethylamine **5** (m.p. 191–193°)²). The structure of **5** is evidenced by DQF-COSY, HSQC, and HMBC spectra (see below and *Exper. Part*).

²) *Sayed Ahmed* claimed to have obtained the imido tautomer of **5** by substitution of 2',3'-*O*-isopropylidene-5'-(thiophenyl)uridine with EtNH₂ in boiling MeOH [26]. Although the melting point of 196° is similar to that of **5**, the reported ¹H-NMR data are incompatible with both the hydroxyimino and the imido structure of **5**.

Front view:



Top view:



UA-1

AU-1

Fig. 1. Front and top view of the Amber*-calculated duplexes UA-1 and AU-1

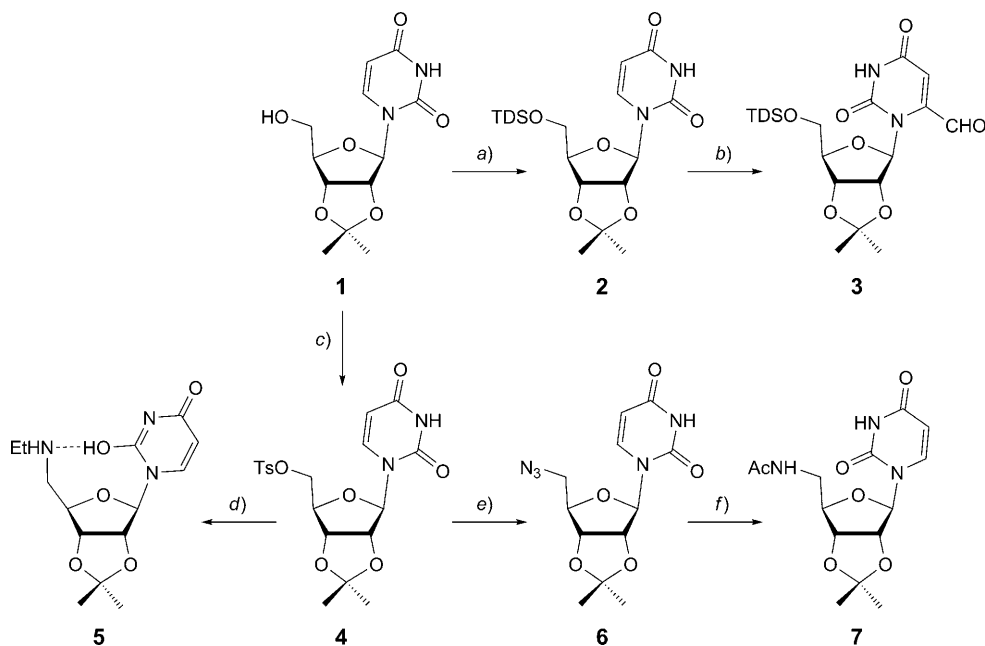
The adenine mononucleosides were prepared by an analogous reaction sequence as the uridine analogues. Silylation of **8** gave the silyl ether **9** (Scheme 2). Deprotonation of **9** with excess LDA, followed by treatment with DMF and hydrolysis, yielded 97% of aldehyde **10**. The azide **12** was obtained in 77% overall yield *via* the known *p*-toluenesulfonate **11** [27–29]. Pd-Catalyzed hydrogenation of **12** in MeOH gave 80% of the known amine **13** [28][29]. In the presence of Ac₂O, the catalytic hydrogenation afforded the acetamide **14** (76%).

With the required aldehydes and azides in hand, we proceeded to prepare the dinucleosides. *Staudinger* reaction of azide **6** with Me₃P in THF [30], followed by treatment of the crude iminophosphorane **6A** with aldehyde **10**, generated an imine [30][31] that was reduced *in situ* with NaBH₃CN [32] to yield 70% of the A*[N]U dinucleoside **15** (Scheme 3). Debzoylation of **15** with MeONa in MeOH gave the silyl ether **16** (90%) that was desilylated by treatment with (HF)₃ · Et₃N in THF [33] to yield 88% of the alcohol **17**. Desilylation with Bu₄NF in THF led in an incomplete reaction to several side-products.

The sequence-isomeric U*[N]A dinucleoside **18** was similarly synthesized by the reaction of azide **12** with Me₃P to the iminophosphorane **12A** and its condensation with aldehyde **3** (Scheme 4). The resulting imine was directly reduced to the protected U*[N]A dinucleoside **18** (84%). Debzoylation of **18** gave the silyl ether **19** (87%) that was desilylated to the alcohol **20** (82%).

Conformation of the Uridine and the Adenosine Monomers. Three main factors, the orientation of the nucleobase (*syn* or *anti*), the pucker of the furanose ring (northern or

Scheme 1



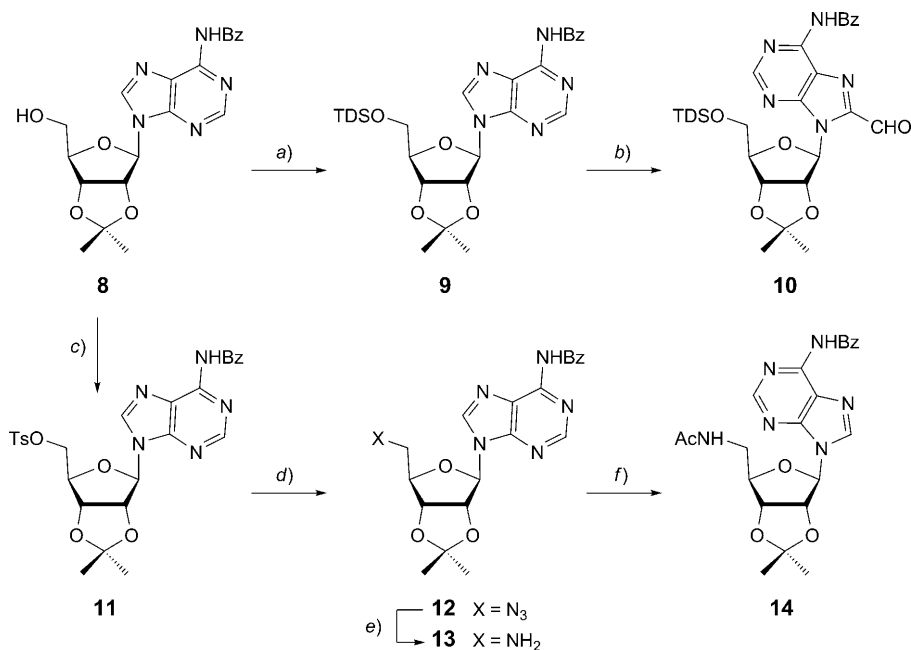
TDS = *tert*-hexyl(dimethyl)silyl (= dimethyl(1,1,2-trimethylpropyl)silyl)

a) TDS-Cl, 1*H*-imidazole, CH₂Cl₂; > 99%. b) LDA (= lithium diisopropylamide), DMF, THF, –76°; 98%. c) TsCl, pyridine; 92%. d) 70% EtNH₂ in H₂O, DMF, 80°; 85%. e) NaN₃, DMF, 80°; 80%. f) H₂, Pd/C, Ac₂O, MeOH; 72%.

southern), and the orientation of the ROCH₂ moiety at C(4') (*gg*, *gt*, or *tg*) influence the conformation of mononucleosides and mononucleotides [34]. These factors can easily be analyzed by ¹H-NMR spectroscopy. The *syn/anti*-orientation of the nucleobase may be deduced from the NOE ratio of H–C(6) of U or H–C(8) of A with H–C(1') and with H–C(2')/H–C(3') [35] rather than from the chemical shift of H–C(2')³. A northern (*N*) ring conformation is evidenced by $J(1'/2')/J(3'/4') \leq 1$ and a southern (*S*) conformation by $J(1',2')/J(3',4') \geq 1$ [34]. The conformation of the RXCH₂ (X = O, S, or NH) group at C(4') is deduced from $J(4',5'a)$ and $J(4',5'b)$. A *gg*-conformer is evidenced by a sum of $J(4',5'a)$ and $J(4',5'b)$ that is smaller than 3 Hz, and a mixture of *gt*- and *tg*-conformers is evidenced by a sum of $J(4',5'a)$ and $J(4',5'b)$ in excess of 12 Hz. Similar $J(4',5'a)$ and $J(4',5'b)$ values indicate a similar population of

³) Typical chemical shifts for 2',3'-*O*-isopropylidened derivatives in CDCl₃ solution: *anti*-configured U: 4.70–4.80 ppm, *syn*-configured U: 5.10–5.20 ppm, *anti*-configured A: 5.20–5.30 ppm, *syn*-configured A: 5.70–5.80 ppm, and *syn*-configured A with an intramolecular H-bond of HO–C(5') to N(3): 5.20–5.30 ppm [6][1].

Scheme 2



a) TDSOCl, 1*H*-imidazole, CH₂Cl₂; 90%. b) LDA, DMF, THF, –76°; 97%. c) TsCl, pyridine; 86%. d) NaN₃, DMF, 80°; 90%. e) H₂, Pd/C, MeOH; 80%. f) **12**, H₂, Pd/C, Ac₂O, MeOH; 76%.

the *gt*- and *tg*-conformations. The *gg/gt/tg* rotamer distribution may be calculated⁴⁾, but this requires an unambiguous assignment of the H–C(5') signals to H_{*pro-R*}–C(5') and H_{*pro-S*}–C(5'). Usually, H_{*pro-S*}–C(5') of ribosides and nucleosides resonates at lower field [34–39], but the relative chemical shift of H_{*pro-R*}–C(5') and H_{*pro-S*}–C(5') may be interchanged by the effect of the surrounding groups, *e.g.*, by AcO–C(3') [40], by a *syn*-oriented nucleobase [6], or by the tertiary structure of RNA [41].

As expected, the uridine-6-carbaldehyde **3** adopts a *syn*-conformation. This is evidenced by $\delta(\text{H}–\text{C}(2')) = 5.09$ ppm, and leads to a preferred *gt*- and *tg*-orientation of the silyloxymethyl group ($J(4',5'a) + J(4',5'b) = 10.8$ Hz; Table 3 in the *Exper. Part*). For the 6-unsubstituted uridines, a larger contribution of the *syn*-conformer of azide **6** than of the *p*-toluenesulfonate **4** is evidenced by a stronger downfield shift of H–C(2')

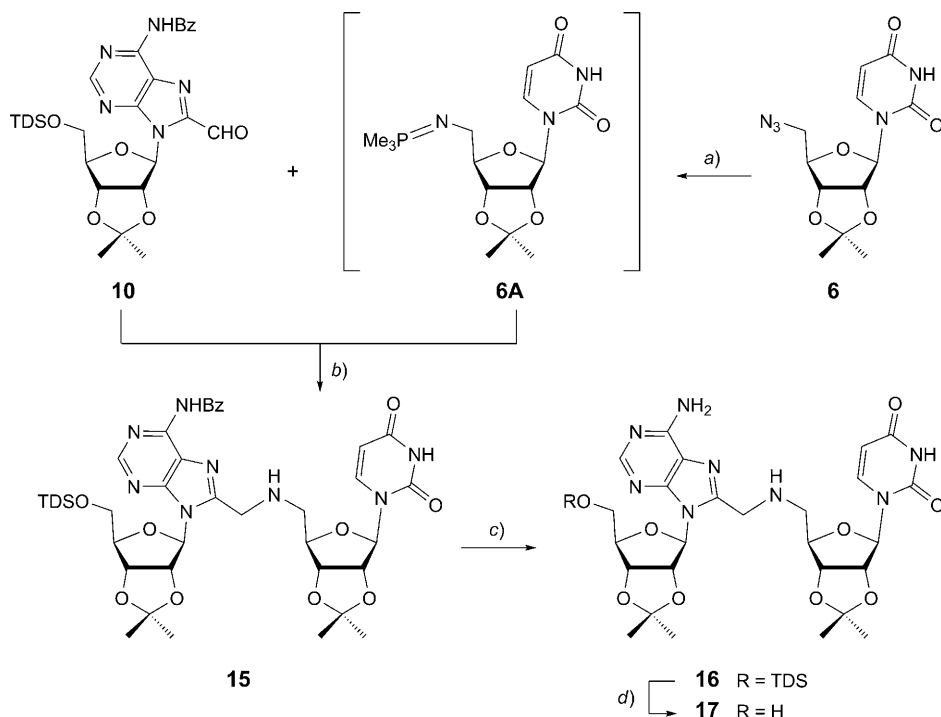
⁴⁾ See [6] for the calculation of the rotamer distribution of 5'-*O* and 5'-*S* nucleosides. The parameters for 5'-amino-5'-deoxy nucleosides were calculated with the force-field programme MM3* [15] leading to the following equations:

$$J(4',5'_{\text{pro-S}}) = 3.6 P_{\text{gg}} + 1.7 P_{\text{gt}} + 10.9 P_{\text{tg}} \quad \text{and}$$

$$J(4',5'_{\text{pro-R}}) = 1.9 P_{\text{gg}} + 10.4 P_{\text{gt}} + 4.2 P_{\text{tg}}$$

We are not aware of any assignment of the H–C(5') signals of 5'-nitrogenated nucleosides to H_{*pro-R*}–C(5') and H_{*pro-S*}–C(5'). Here, we assume that H_{*pro-S*}–C(5') of the 5'-amino and 5'-azido nucleosides resonates at lower field.

Scheme 3

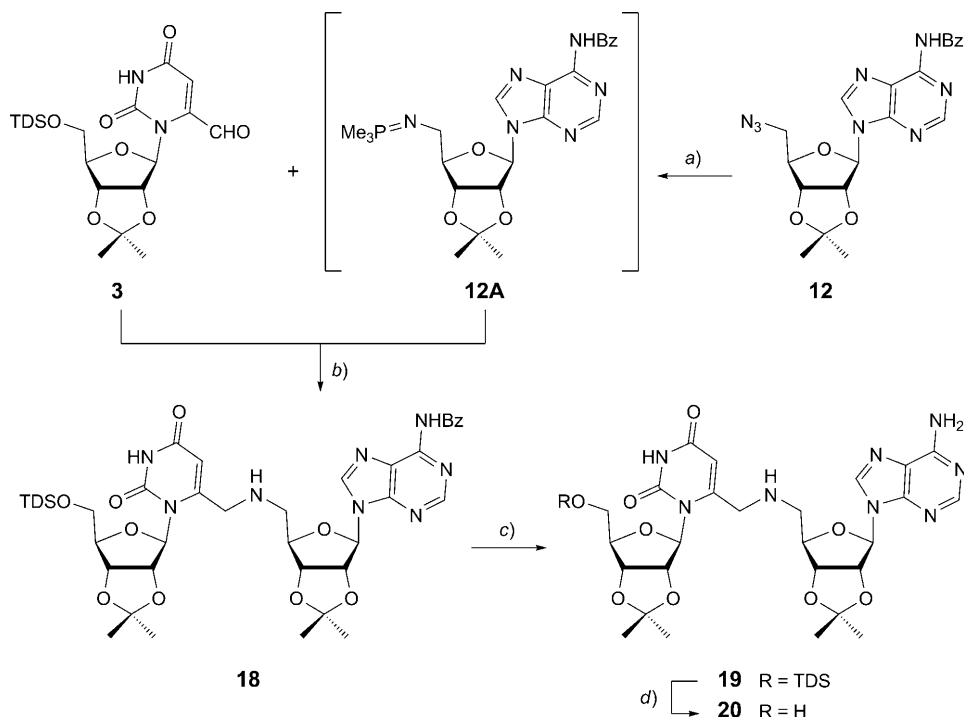


a) Me_3P , THF. b) 1. THF; 2. NaBH_3CN , AcOH, MeOH; 70% from 6. c) MeONa, MeOH; 90%. d) $(\text{HF})_3 \cdot \text{Et}_3\text{N}$, THF; 88%.

(4.99 vs. 4.91 ppm). This is also reflected by a stronger preference of **6** for a *gt/tg* equilibrium ($J(4',5'a) + J(4',5'b) = 10.2$ for **6** and 9.0 Hz for **4**). The amide **7** adopts completely the *syn*-conformation, as evidenced by a NOESY cross peak between H–C(6) and H–C(1'), but not between H–C(6) and H–C(2'), and by the downfield shift of H–C(2') resonating at 5.15 ppm. Thus, **7** prefers the *syn*-conformation more strongly than the corresponding acetate and thioacetate ($\delta(\text{H} - \text{C}(2')) = 5.00$ ppm) which form a *ca.* 3:1 *syn/anti* equilibrium [6]⁵). This is due to a partially persistent intramolecular H-bond of HN–C(5') to O=C(2), as evidenced by a clear preference for the *gg*-rotamer ($J(4',5'_{\text{pro-S}}) = 4.5$ Hz, $J(4',5'_{\text{pro-R}}) = 3.8$ Hz, *gg/gt/tg* = 65:18:17), while there is hardly a downfield shift of the AcNH signal (6.48 vs. 6.45 ppm for methyl 5-deoxy-5-acetamido-2,3-*O*-isopropylidene- β -D-ribofuranoside [43]). The four compounds **3**, **4**, **6**, and **7** adopt a (*N*)-conformation.

⁵) The stronger preference for the *syn*-conformation of 5'-XAc (X = O, S, or NH) and 5'-N₃ derivatives of 6-unsubstituted U and of 8-unsubstituted A mononucleosides than of the corresponding 5'-OSiR₃ or 5'-OTr analogues may be due to a stronger preference of the *gt/tg*-conformers which was already observed in the β -D-ribofuranoside series ($J(4',5'a) + J(4',5'b) = 14.0 - 14.7$ Hz for 5-*O*-acetyl- and 5-azido-5-deoxyribosides; $J(4',5'a) + J(4',5'b) = 8.5 - 10.0$ Hz for 5-*O*-silyl- and 5-*O*-tritylribosides [42]).

Scheme 4



a) Me_3P , THF; b) 1. THF; 2. NaBH_3CN , AcOH, MeOH; 84% from **12**. c) MeONa, MeOH; 87%. d) HF · pyridine, THF; 82%.

The tautomeric hydroxyimino structure of the ethylamine **5** in CDCl_3 is evidenced by the absence of an imido NH signal at low field and by a broad t ($J \approx 4.0$ Hz) at 6.15 ppm assigned to the OH group. However, the EtNH signal is not visible (fast H/D exchange?). The ethylamine **5** adopts a southern and a *gg*-conformation ($J(4',5'a) + J(4',5'b) = 3.2$ Hz; Table 3 in the *Exper. Part*). These structural aspects are characteristic of an intramolecular H-bond, and an $\text{OH} \cdots \text{N}$ H-bond is indeed further evidenced by the downfield shift of the OH signal and its coupling with the MeCH_2 group. Surprising at first view is the absence of a coupling between OH and $\text{H}_2\text{C}(5')$, an observation that is confirmed by the absence of a cross-peak in the DQF-COSY spectrum between the OH and $\text{H}-\text{C}(5')$ signals. AM1 Calculations (programme Spartan 04 for Macintosh [44]) corroborate the hypothesis of an intramolecular H-bond ($\text{OH} \cdots \text{N}$ H-bond: 1.63 Å), but result in a preferred flat (*N*)-conformation (Fig. 2). The $\text{H}-\text{C}(5')-\text{N} \cdots \text{HO}$ torsion angles of 109 and -133° suggest a mean absolute value of 120° for both torsion angles of a flexible molecule, in agreement with the absence of a coupling between OH and $\text{H}_2\text{C}(5')$. The upfield shift for $\text{H}-\text{C}(2')$ resonating at 4.86 ppm may be due to a different structure of the nucleobase, or to the intramolecular H-bond (similarly as observed in the adenosine series; see [1] and refs. cit. therein). The intramolecular $\text{OH} \cdots \text{N}$ H-bond of **5** persists completely in

(D₆)DMSO, with OH resonating as *t* at 7.15 ppm, and presumably also in CD₃OD, as suggested by the *gg*-conformation in both solvents.

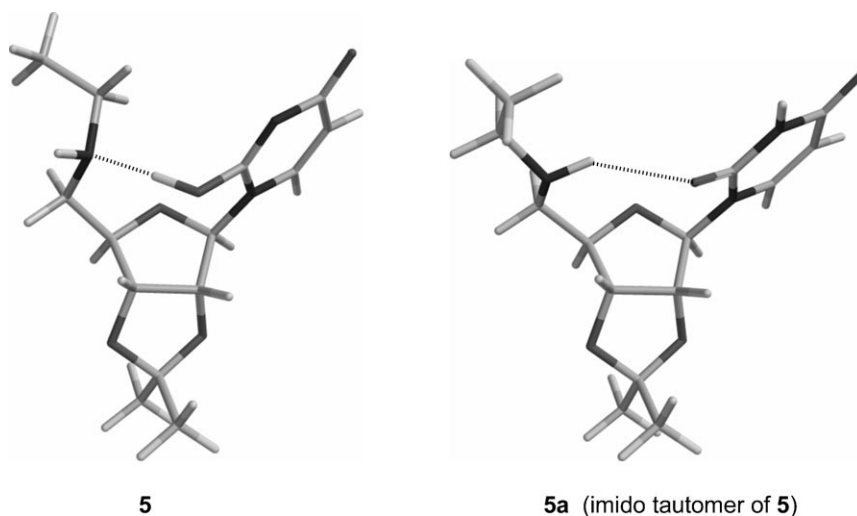


Fig. 2. AM1-Calculated structures of **5** and of its imido tautomer **5a**

However, according to AM1 calculations, the intramolecular H-bonded imido tautomer **5a** (Fig. 2) is more stable than **5** by 20.7 kcal/mol. Although this surprising result agrees well with similar calculations of the tautomers of 1-methyluracil [45], it is incompatible with our observations.

The CD spectrum of a 1-mm solution of **4** in CHCl₃ at 20° shows a positive *Cotton* effect with a maximum at 260 nm, suggesting an *anti*-conformer [46] (Fig. 3). A weak negative *Cotton* effect of **6** (minimum at 290 nm) evidences a substantial amount of the *syn*-conformer, and confirms the conclusion drawn from the NMR data. Finally, **5** and **7** show the typical negative *Cotton* effects (minimum at 270 nm) for *cis*-configured uridines, again in agreement with the results of NMR analysis.

The *C*(8)-formylated adenosine **10** adopts a *syn*-conformation, as evidenced by the downfield shift of H–C(2') (5.62 ppm; Table 5 in the *Exper. Part*), a *gt/tg* equilibrium ($J(4'/5'a) + J(4'/5'b) = 12.9$ Hz), and an (*N*)-conformation. Also the sulfonate **11**, the azide **12**, and the amine **13** adopt (*N*)-conformations. A moderate upfield shift of their H–C(2') signal as compared to the one of **10** ($\Delta\delta = 0.15$ to 0.34 ppm) suggests *syn/anti*-equilibria for these 8-unsubstituted adenosines. This interpretation is supported by a reduced preference for the *gt/tg* relative to the *gg* rotamer population (*gg/gt/tg* ratio of *ca.* 2:2:1, as suggested by $J(4'/5'a) + J(4'/5'b)$ of 10.2–10.4 Hz). The acetamide **14** shows all characteristics of a persistent intramolecular N–H⋯N(3) H-bond, *i.e.*, the downfield shift of AcNH (7.53–7.58 ppm, as compared to 6.48 ppm for **7**), the upfield shift for H–C(2') (5.28 ppm), small $J(4',5'a)$ and $J(4',5'b)$ values (3.6 and 2.7 Hz), a large $J(5'a,OH)$ (8.1 Hz), a small $J(5'b,OH)$ value (*ca.* 3.0 Hz), and a (*S*) ring conformation ($J(1'/2')/J(3'/4') = 1.6$; see [1][6][47][48] for the analogous O–H⋯N(3) H-bond). This intramolecular H-bond is responsible for the slow exchange of AcNH with D₂O; no exchange was observed within one hour at room temperature, when

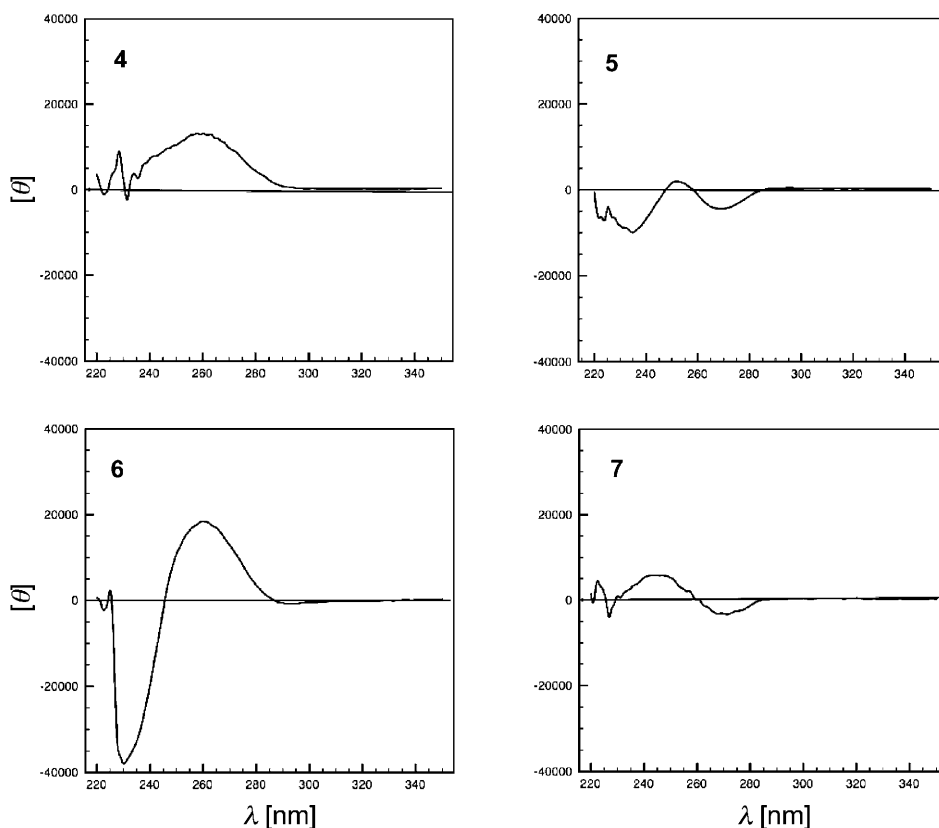


Fig. 3. CD Spectra of 1-mM solutions at 20° of the A*[N]U and U*[N]A dinucleosides **4–7** in CDCl₃

BzNH was completely exchanged. In the NOESY spectrum of **14**, the intramolecular H-bond is corroborated by a cross-peak between Me and H–C(2), a strong cross-peak between NH and H–C(5'b), and a weak cross-peak between NH and H–C(5'a). The *syn*-conformation is revealed by a strong cross-peak between H–C(8) and H–C(1') and a weak cross-peak between H–C(8) and H–C(2'). The presence of an intramolecular H-bond in **14**, but not in **13**, reflects the good H-donating properties of the NH group of amides.

Association and Conformation of the A[N]U and U*[N]A Dinucleosides in CDCl₃.* The self-association of the A*[N]U dinucleosides **16** and **17**, and of the U*[N]A sequence isomers **19** and **20** was investigated by analysing the concentration dependence of the chemical shift of H–N(3/I) of **16** and **17**, and H–N(3/II) of **19** and **20** (shift/concentration curves, SCCs), and the determination of conformational aspects from ¹H-NMR spectra, similarly as it was described for thiomethylene-linked analogues [6]. Base stacking was investigated by CD spectroscopy.

The SCCs of the A*[N]U dinucleosides **16** and **17** show the characteristics denoting the formation of cyclic duplexes, *i.e.*, a strong bending at concentrations below 15 mM and formation of a plateau at concentrations above 15 mM (Fig. 4). The SCC of the

U*[N]A dinucleoside **20** and especially that of **19** show a distinctly weaker bending at low concentrations and a weak, but steady increase at concentrations above 20 mM, revealing equilibria between the monoplex, linear associates, and cyclic duplexes. The downfield shift of the plateau of **16** (13.02 ppm at 30 mM) indicates *Watson–Crick*-type base pairing and the upfield shift of the plateau of **17** (12.40 ppm) *Hoogsteen*-type base pairing (cf. [1][6][49]). Unfortunately, a broad H–N(3/I) signal in the ROESY spectrum of **17** prevents the detection of cross peaks with H–C(2/II) and/or CH₂–C(8/II). The signal of H–C(6/I) shows strong cross-peaks with the signals of H–C(1'/I) and H–C(2'/I), and weak cross-peaks with the signals of H–C(3'/I) and H₂C(5'/I), evidencing a *syn/anti*-equilibrium. Thus, the upfield shift of H–N(3/I) is partially due to minor amounts of linear associates possessing an *anti*-oriented uracil moiety. Although substantial amounts of linear associates of **20** and especially of **19** lead to an upfield shift for H–N(3/I), the chemical shift at 30 mM (12.56 and 12.27 ppm, resp.) suggests mixtures of *Watson–Crick*- and *Hoogsteen*-type base-paired cyclic duplexes, and a 1:1 mixture is evidenced for **19** by cross-peaks of similar intensity in the NOESY spectrum between H–N(3/II) and both H–C(2/I) and H–C(8/I).

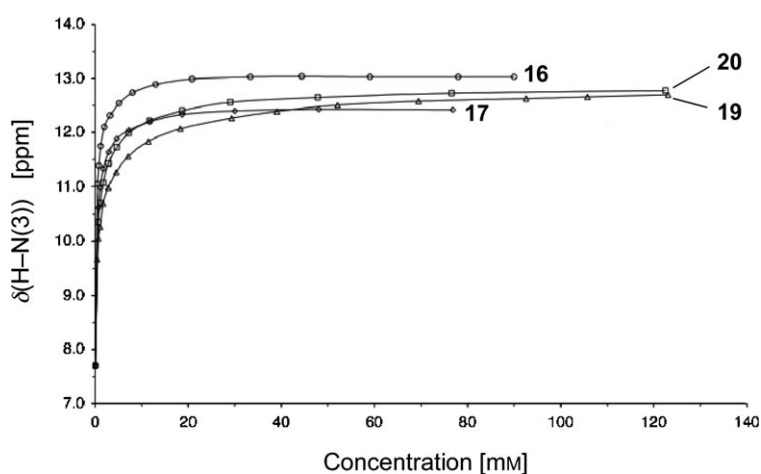


Fig. 4. Shift/concentration curves (SCCs) of the A*[N]U and U*[N]A dinucleosides **16**, **17**, **19**, and **20** in CDCl₃ solution (including a value of 7.70 ppm for a 0.001-mM solution).

A *syn*-conformation of the uridine moiety of the A*[N]U dinucleosides **16** and **17** is evidenced by $\delta(\text{H–C}(2'))$ of 5.18–5.19 ppm (Table 7 in the *Exper. Part*), suggesting only a minor contribution of the *anti*-conformer of **17** detected by NOESY cross peaks. The *gg*-orientation of the linker is more strongly preferred by **16** than by **17** as indicated by smaller $J(4'/5'a)$ and $J(4'/5'b)$ values (3.1/4.4 vs. 3.5/5.4 Hz). Calculations suggest a *gg/gt/tg* equilibrium of 70:29:1 for **16** and of 50:40:10 for **17**. $J(1'/2')/J(3'/4')$ Ratios of 1.3 and 0.8 evidence that **16** prefers a (*S*)- and **17** a (*N*)-conformation. The formation of mainly linear associates of the benzamide **15** is suggested by the preference for the *anti*-conformer ($\delta(\text{H–C}(2')) = 4.94$ ppm), and by a 2:2:1 *gg/gt/tg* ratio. H–N(5'/I) is increasingly deshielded from **17** (1.76 ppm) via **15** (2.13 ppm) to **16** (2.73 ppm), and may indicate an increasing H-donating NH group. A deeper analysis would require

knowledge about the H-bond acceptor (O or N; π - or σ -orbitals as H-acceptors). It is, however, clear that association prevents tautomerisation to a hydroxyimino species and formation of an O–H $\cdots$ N H-bond, as observed for the monomer **5**.

H–C(2'/I) of the U*[N]A dinucleosides **18**–**20** resonates at 5.51–5.52 ppm (Table 9 in the *Exper. Part*), at the same position as the monomeric AcOC(5') and AcSC(5') analogues [6]. This may be interpreted as suggesting a *ca.* 85:15 *syn/anti*-equilibrium for the adenosine unit. In the NOESY spectrum of **19**, cross-peaks of similar intensity between H–C(8/I), and both H–C(1'/I) and H–C(2'/I) suggest even a 1:1 *syn/anti*-equilibrium. Similar $J(1'/2'/I)$ and $J(3'/4'/I)$ values for **18**–**20** show a *ca.* 1:1 (*N*)/(*S*) equilibrium, and similar $J(4'/5'a/I)$ and $J(4'/5'b/I)$ values of 3.1–4.2 Hz denote a dominant *gg*-rotamer (85% for **18** and **19**; 70% for **20**). With HN–C(5'/I) of **18**–**20** resonating at 1.9–2.2 ppm there is no spectroscopic evidence for an intramolecular H-bond.

Unit II of **15**–**20** shows the same conformational properties as the corresponding mononucleosides, *i.e.*, a *syn*-orientation of the nucleobase, the *gt/tg*-equilibrium of the TDSOCH₂ group of **15**, **16**, **18**, and **19**, a completely persistent intramolecular O–H $\cdots$ N(3) H-bond of **17**, and a partially persistent O–H $\cdots$ O=C(2) H-bond of **20**.

These NMR investigations led to the following conclusions. The cyclic duplexes of **16** possess *Watson–Crick*-type base pairing, whereas the cyclic duplexes of **17**, **19**, and **20** possess both *Watson–Crick*- and *Hoogsteen*-type base pairing. The cyclic duplexes of the U*[N]A and A*[N]U dinucleosides prefer a *gg*-orientation of the linker. A minor contribution of cyclic duplexes possessing a *gt*-oriented linker is suggested by a preference of the *gt*- over the *tg*-conformation of the dinucleosides (*gt/tg* 29:1 for **16**, 4:1 for **17**, 14:1 for **19**, and 9:1 for **20**) that is more pronounced than for the closely related mononucleosides (*gt/tg* 1:1 for **6** and 2:1 for **13**). Thus, the conformational preferences of the cyclic duplexes of the NHCH₂-linked dinucleosides are indeed more similar to those of the OCH₂-linked analogues than to those of the SCH₂-linked analogues. No evidence was found for an intramolecular H-bond of the CH₂NH group.

The SCCs of **16**, **17**, **19**, and **20** (Fig. 4) were analysed numerically by the method proposed by Gutowsky and Saika [50], including a value of 7.70 ppm for a 0.001 mM solution, corresponding to the chemical shift of the monoplex, as deduced from $\delta(\text{H–N}(3))$ of monomeric uridine derivatives [6]. Inclusion of this value significantly reduced the variance of K_{ass} . The thermodynamic parameters (Table 2) were determined by *van't Hoff* analysis of the ¹H-NMR spectra recorded of *ca.* 2–5-mM solutions in CDCl₃ in intervals of 10° and in the temperature range of 7 to 50°.

However, the U*[N]A dinucleosides **19** and **20** ($K_{\text{ass}} = 872$ and 1291 M^{-1} , resp.; Table 2) associate distinctly more weakly than the corresponding U*[o]A dinucleosides ($K_{\text{ass}} = 18400$ and 12300 M^{-1} [6]), but about as strongly as the corresponding U*[s]A dinucleosides ($K_{\text{ass}} = 198$ and 1529 M^{-1} [6]). The A*[N]U dinucleosides **16** and **17** ($K_{\text{ass}} = 3454$ and 2429 M^{-1} , resp.) associate 11- and 15-times more strongly than the A*[s]U analogues ($K_{\text{ass}} = 225$ and 221 M^{-1} ; no data are available for A*[o]U analogues). The $-\Delta H$ values for **19** (10.8 kcal/mol) and **20** (9.5 kcal/mol) are typical for equilibria of the monoplex, cyclic duplexes, and substantial amounts of linear associates [3]. The $-\Delta H$ values for **16** (16.6 kcal/mol) and **17** (16.8 kcal/mol) evidence equilibria between monoplex and cyclic duplexes possessing *Watson–Crick*-type base pairing. These values are larger than expected and may comprise a (small) contribution

Table 2. Association Constants K_{ass} and Extrapolated Chemical Shift of the Monplexes ($c = 0$ mM) and Duplexes ($c = \infty$) as Calculated from the Concentration Dependence of $\delta(\text{HN}(3))$ in CDCl_3 at 295 K for the A*[N]U Dinucleosides **16** and **17**, and the U*[N]A Dinucleosides **19** and **20** (including a value of 7.70 ppm for a 0.001-mM solution), and Determination of the Thermodynamic Parameters by van't Hoff Analysis of the Temperature Dependence of $\delta(\text{HN}(3))$ for ca. 2–5-mM Solutions in CDCl_3 at 7–50°

Dinucleoside	K_{ass} [M^{-1}]	$\delta_{\text{monoplex}}^{\text{a)}}$ [ppm]	$\delta_{\text{duplex}}^{\text{b)}}$ [ppm]	$-\Delta G_{295}^{\text{c)}}$ [kcal/mol]	$-\Delta H$ [kcal/mol]	$-\Delta S$ [cal/mol · K]
A*[N]U Series						
16	3454 ± 323	7.66 ± 0.08	13.43 ± 0.06	4.8	16.6	38.7
17	2429 ± 409	7.67 ± 0.14	12.80 ± 0.08	4.6	16.8	41.3
U*[N]A Series						
19	872 ± 183	7.77 ± 0.22	12.97 ± 0.11	3.9	10.8	23.4
20	1291 ± 71	7.69 ± 0.06	13.11 ± 0.04	4.2	9.5	20.3

a) Extrapolated for $c = 0$. b) Extrapolated for $c = \infty$. c) Calculated from K_{ass} .

of a weak intramolecular H-bond of CH_2NH . The similarity of the $-\Delta H$ values for **16** and **17** is surprising, as a smaller $-\Delta H$ value is expected for **17**, considering that it is a mixture of Watson–Crick- and Hoogsteen-type base paired cyclic duplexes.

The CD spectra of the dinucleosides **16**, **17**, **19**, and **20** were recorded of 1 mM solutions in CHCl_3 in the temperature range from 0° to 50° (Fig. 5). They show a significant dependence of the molar ellipticity ($[\theta]$ [$\text{deg} \cdot \text{cm}^2 \cdot \text{dmol}^{-1}$]) on the temperature for the A*[N]U dinucleosides **16** and **17**, a weaker one for the sequence isomer **19** and almost no temperature dependence for **20**. These values denote a strong base stacking in the cyclic duplexes of **16** and **17**. The low values of the ellipticity, and the poor temperature dependence of the CD spectra of **19** and **20** may be characteristic for duplexes of U*[N]A dinucleosides; this may be relevant for the pairing of NHCH_2 -linked ONIBs in H_2O .

We expect that protonation of CH_2NH moiety of the U*[N]A and A*[N]U dinucleosides will lead to strong intramolecular H-bond of the ammonium group with N(3/I) of the U*[N]A and possibly also with $\text{O}=\text{C}(2/\text{I})$ of the A*[N]U dinucleosides. Such H-bonds lead to a *gg*-conformation and to a *syn*-orientation of unit I, and they prevent the formation of parallel base pairs in a cyclic duplex. Therefore, protonation is expected to lead to linear associates only. The positive Cotton effect of **16** · TFA and **19** · TFA at ca. 260 nm agrees indeed with a *syn*-oriented nucleobase of unit I (Fig. 5).

We thank Syngenta AG, Basel, and F. Hoffmann-La Roche AG, Basel, for generous financial support.

Experimental Part

General. Solvents were distilled: CH_2Cl_2 , MeOH, (i-Pr) $_2\text{NH}$, EtN(i-Pr) $_2$, and pyridine over CaH_2 ; THF over Na/benzophenone. DMF was dried over 4-Å mol. sieves. Reactions were run under N_2 . Qual. TLC: precoated silica-gel glass plates (Merck silica gel 60 F254); detection by spraying with ‘mostain’ (400 ml of 10% H_2SO_4 soln., 20 g of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 6\text{H}_2\text{O}$, 0.4 g of $\text{Ce}(\text{SO}_4)_2$) and heating. Flash chromatography (FC): Merck silica gel 60 (0.063–0.200 mm). Optical rotation: 1-dm cell at 25° and 589 nm; concentration c in g/100 ml. Temp.-dependent CD (10° steps from 0° to 50°): 1-mM soln. in CHCl_3 in a 1-mm Suprasil cell. FT-IR Spectra: solid state (ATR), absorption in cm^{-1} . UV Spectra: 10^{-5} M

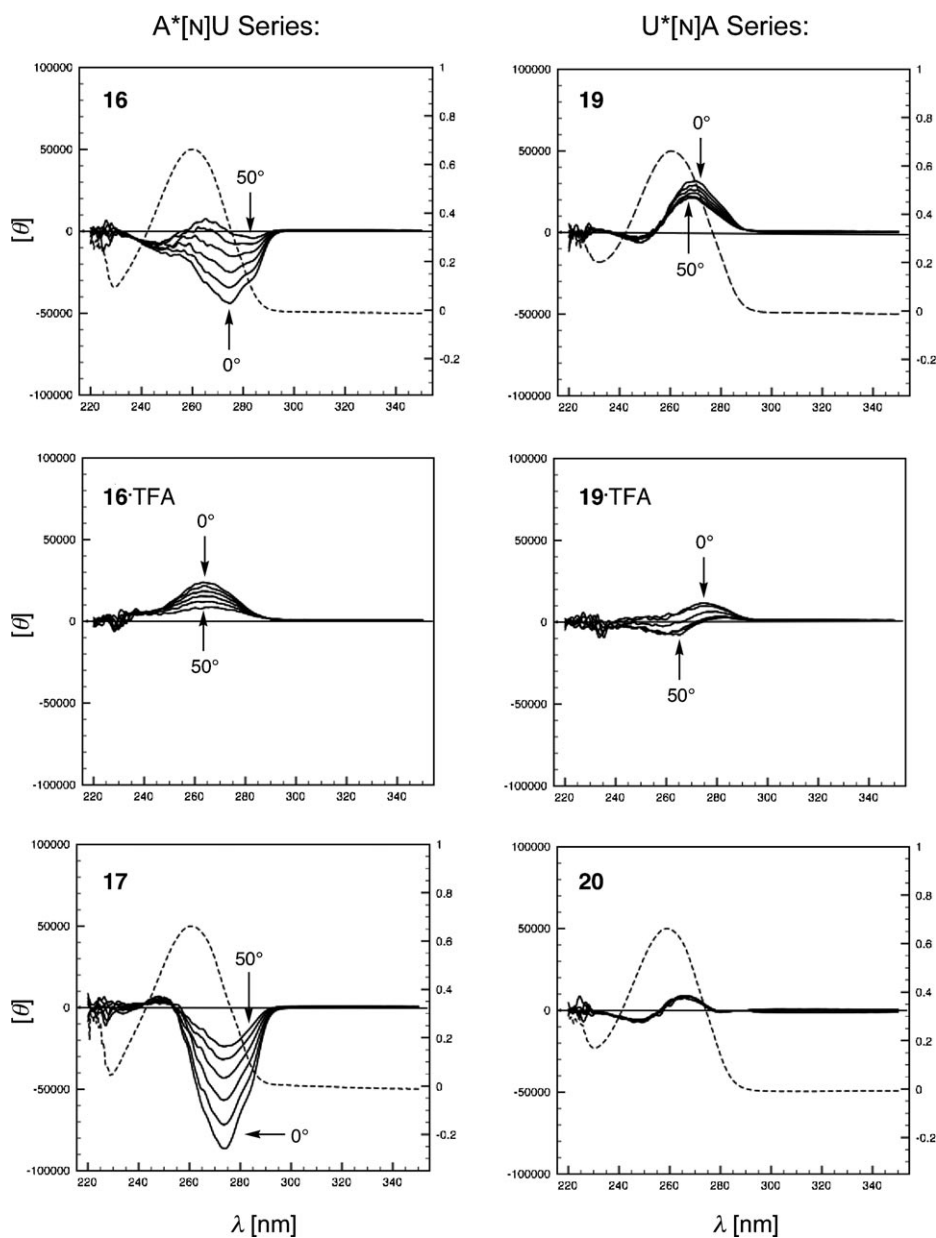


Fig. 5. Temperature-dependent CD spectra (solid lines, in 10° steps from 0° to 50°) and UV spectra (dashed lines) of 1-mM solutions of the A*[N]U and U*[N]A dinucleosides **16**, **17**, **19**, and **20** in CDCl₃

soln. in CHCl₃ at 20° in a 1-cm or 1-mm *Suprasil* cell. ¹H- and ¹³C-NMR spectra: at 300, 400, or 500 MHz, and 75, 100 or 125 MHz, resp. MS: high-resolution matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (HR-MALDI-TOF) with 3-hydroxypicolinic acid (3-HPA) matrix.

General Procedure for NMR Studies. NMR Experiments were performed at 295 K on a *Varian Gemini 300* spectrometer (300 MHz) in CDCl_3 (passed through basic aluminium oxide and dried over 4-Å mol. sieves prior to use). Experiments started at the highest concentration, with stepwise replacement of 0.3 ml of the 0.8 ml soln. with 0.3 ml pure CDCl_3 . The data were analysed by non-linear least-squares fitting using MATLAB (trust-region algorithm); the parameters were K_{ass} , $\delta(\text{H}-\text{N}(3/\text{I or II}))$; $c = 0$ mm), and $\delta(\text{H}-\text{N}(3/\text{I or II}))$; $c \rightarrow \infty$). The thermodynamic parameters were determined by *van't Hoff* analysis. The uracil $\delta(\text{H}-\text{N}(3/\text{I or II}))$ was monitored at 7, 15, 22, 30, 40, and 50° and at a fixed concentration, typically between 2 and 5 mM.

5'-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-6-formyl-2',3'-O-isopropylideneuridine (3). A soln. of (i-Pr)₂NH (11.03 ml, 84.11 mmol) in dry THF (80 ml) was treated dropwise, at –76° under N₂, with 1.6M BuLi in hexane (52.57 ml, 84.11 mmol), stirred for 15 min at –76° and for 15 min at 0°. The mixture was cooled to –76°, treated dropwise with a soln. of **2** [6] (7.17 g, 16.82 mmol) in THF (80 ml) and stirred for 1.5 h, treated dropwise with dry DMF (32.52 ml, 0.42 mol), and stirred for an additional h at –76°. The mixture was allowed to reach 24°, treated with sat. NH₄Cl soln. (100 ml), and neutralized with AcOH to pH 7. After extraction with AcOEt (100 ml), the org. phase was washed with H₂O (5 × 100 ml), dried (MgSO₄), and evaporated, to afford **3** (7.51 g, 98%). Yellow foam. R_f (AcOEt) 0.76. $[\alpha]_{\text{D}}^{25} = +14.5$ ($c = 1.0$, CHCl_3). IR (ATR): 3204w (br.), 3059w, 2957w, 2868w, 1687s, 1462m, 1373m, 1251m, 1211m, 1157w, 1079s, 967w, 874m, 827s. ¹H-NMR (300 MHz, CDCl_3): see Table 3; additionally, 9.69 (s, CH=O); 8.81 (br. s, NH); 1.61 (sept., $J = 6.9$, Me₂CH); 1.57, 1.35 (2s, Me₂C); 0.86 (d, $J = 6.9$, Me₂CH); 0.84 (s, Me₂CSi); 0.09 (s, Me₂Si). ¹³C-NMR (75 MHz, CDCl_3): see Table 4; additionally, 184.62 (d, CH=O); 114.47 (s, Me₂C); 33.94 (d, Me₂CH); 27.09, 25.25 (2q, Me₂C); 25.25 (s, Me₂CSi); 20.22, 20.17 (2q, Me₂CH); 18.37 (q, Me₂CSi); –3.47 (q, Me₂Si). HR-MALDI-MS: 477.2021 (100, $[M + \text{Na}]^+$, C₂₁H₃₄N₂NaO₇Si⁺; calc. 477.2027). Anal. calc. for C₂₁H₃₄N₂O₇Si (454.59): C 55.48, H 7.54, N 6.16; found: C 55.20, H 7.38, N 6.06.

Table 3. Selected ¹H-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] of the Uridine Monomers **3–7** in CDCl_3

	3	4	5 ^{a)}	6	7
H–C(5)	6.22	5.70	5.76	5.76	5.76
H–C(6)	–	7.23	7.35	7.29	7.20
H–C(1')	6.39	5.66	5.26	5.66	5.33
H–C(2')	5.09	4.91	4.86	4.99	5.15
H–C(3')	4.81	4.78	4.97	4.81	4.78
H–C(4')	4.14	4.34	4.42	4.24	4.24
H _a –C(5')	3.81	4.28	4.02	3.62	3.74
H _b –C(5')	3.75	4.24	3.91	3.62	3.47
$J(5,6)$	–	8.1	8.0	8.1	8.0
$J(1',2')$	2.4	2.1	4.0	2.1	2.7
$J(2',3')$	6.6	6.6	6.0	6.6	6.6
$J(3',4')$	4.2	3.6	2.0	4.5	4.3
$J(4',5'a)$	4.5	3.6	2.0	5.1	4.5
$J(4',5'b)$	6.3	5.4	1.2	5.1	3.8
$J(5'a,5'b)$	11.1	10.8	11.6	^{b)}	14.4

^{a)} Assignments based on a DQF-COSY and a HSQC spectrum. ^{b)} Not assigned.

2',3'-O-Isopropylidene-5'-O-(4-toluenesulfonyl)uridine (4). Prepared according to [23]. M.p. 149–150° ([51]: 150°). $[\alpha]_{\text{D}}^{25} = +15.0$ ($c = 0.09$, DMF) ([52]: $[\alpha]_{\text{D}}^{20} = +39.3$ ($c = 0.09$, DMF)). ¹H-NMR (300 MHz, CDCl_3): see Table 3; additionally, 8.40 (br. s, NH); 7.77 (d, $J = 8.4$, 2 arom. H); 7.34 (d, $J = 8.4$, 2 arom. H); 2.45 (s, Me); 1.55, 1.33 (2s, Me₂C). ¹³C-NMR (75 MHz, CDCl_3): see Table 4; additionally, 145.16 (s); 132.34 (s); 129.79 (2d); 127.85 (2d); 114.59 (s, Me₂C); 27.10, 25.27 (2q, Me₂C); 21.77 (q, Me).

Table 4. Selected ^{13}C -NMR Chemical Shifts [ppm] of the Uridine Monomers **3–7** in CDCl_3

	3	4	5^a	6	7
C(2)	149.79	149.81	152.84	149.77	150.36
C(4)	161.76	163.11	169.50	162.96	163.44
C(5)	111.54	102.64	105.92	102.81	102.70
C(6)	147.29	142.15	143.79	142.21	143.73
C(1')	90.86	94.78	97.72	94.65	96.89
C(2')	84.15	84.30	83.25	84.27	83.40
C(3')	81.04	80.79	81.38	81.42	81.02
C(4')	87.94	85.01	85.93	85.71	85.32
C(5')	63.06	69.32	61.42	52.35	41.08

^a) Assignments based on a HSQC spectrum.

5'-Deoxy-5'-(ethylamino)-2',3'-O-isopropylideneuridine (5). A soln. of **4** [23] (40 mg, 0.09 mmol) in DMF (3 ml) was treated with 70% aq. EtNH_2 (13 μl , 0.18 mmol) and stirred at 80° for 2 h. The soln. was cooled to 23° and evaporated. FC (AcOEt/MeOH 50:1 $\rightarrow$ 20:1) gave **5** (60 mg, 85%). Colourless foam. R_f (AcOEt/MeOH 10:1) 0.53. M.p. $191\text{--}193^\circ$ ([26]: 196° , but with inconsistent ^1H -NMR data). $[\alpha]_D^{25} = -35.7$ ($c=0.4$, MeOH). UV (MeOH): 227 (13300), 262 (8500). IR (ATR): 3298w (br.), 3072w, 2985w, 2936w, 2861w, 1688w, 1643s, 1612s, 1540s, 1499s, 1456m, 1374m, 1349m, 1333w, 1267w, 1248m, 1213m, 1202m, 1154m, 1116m, 1094s, 1080s, 1035m, 1011m, 968w, 947w, 910m, 884w, 852m, 823m, 787w, 760w, 729s, 683w, 644w, 612w. ^1H -NMR (400 MHz, CDCl_3 ; assignments based on a DQF-COSY and a HSQC spectrum): 6.15 (br. t , $J \approx 4.0$, $\text{HO}-\text{C}(2)$); 3.47–3.33 (m , MeCH_2N); 1.60, 1.38 (2s, Me_2C); 1.17 (t , $J=7.2$, MeCH_2N); signal of $\text{H}-\text{N}(5')$ not visible. ^1H -NMR (300 MHz, $(\text{D}_6)\text{DMSO}$): 7.53 (d , $J=7.5$, $\text{H}-\text{C}(6)$); 7.15 (t , $J=5.4$, $\text{HO}-\text{C}(2)$); 5.63 (d , $J=4.2$, $\text{H}-\text{C}(1')$); 5.56 (d , $J=7.8$, $\text{H}-\text{C}(5)$); 4.92 (dd , $J=6.3$, 4.2, $\text{H}-\text{C}(2')$); 4.82 (dd , $J=6.3$, 3.0, $\text{H}-\text{C}(3')$); 4.13 (q , $J=3.0$, $\text{H}-\text{C}(4')$); 3.64 (br. s , 2 $\text{H}-\text{C}(5')$); 3.22–3.18 (m , MeCH_2N); 1.53, 1.30 (2s, Me_2C); 1.09 (t , $J=7.2$, MeCH_2N). ^1H -NMR (400 MHz, CD_3OD ; assignments based on a DQF-COSY, a HSQC, and a HMBC spectrum): 7.70 (d , $J=7.6$, $\text{H}-\text{C}(6)$); 5.84 (d , $J=7.6$, $\text{H}-\text{C}(5)$); 5.59 (d , $J=3.2$, $\text{H}-\text{C}(1')$); 5.00–4.96 (m , $\text{H}-\text{C}(2')$, $\text{H}-\text{C}(3')$); 4.38 (br. q , $J \approx 2.0$, $\text{H}-\text{C}(4')$); 3.89 (dd , $J=11.8$, 2.4, $\text{H}_a-\text{C}(5')$); 3.85 (dd , $J=11.8$, 2.0, $\text{H}_b-\text{C}(5')$); 3.47 (q , $J=7.2$, MeCH_2N); 1.65, 1.42 (2s, Me_2C); 1.25 (t , $J=7.2$, MeCH_2N). ^{13}C -NMR (100 MHz, CDCl_3 ; assignments based on a HSQC spectrum): 114.87 (s , Me_2C); 36.75 (t , MeCH_2N); 27.40, 25.33 (2 q , Me_2C); 14.50 (q , MeCH_2N). ^{13}C -NMR (100 MHz, CD_3OD ; assignments based on a HSQC and a HMBC spectrum): 174.30 (s , $\text{C}(4)$); 154.54 (s , $\text{C}(2)$); 142.87 (d , $\text{C}(6)$); 116.09 (s , Me_2C); 105.57 (d , $\text{C}(5)$); 98.45 (d , $\text{C}(1')$); 86.65 (d , $\text{C}(4')$); 83.21 (d , $\text{C}(2')$); 81.78 (d , $\text{C}(3')$); 61.88 (t , $\text{C}(5')$); 37.31 (t , MeCH_2N); 27.32, 25.32 (2 q , Me_2C); 14.46 (q , MeCH_2N). HR-MALDI-MS: 334.1370 (38, $[\text{M}+\text{Na}]^+$, $\text{C}_{14}\text{H}_{21}\text{N}_3\text{NaO}_5^+$; calc. 334.1373), 312.1554 (100, $[\text{M}+\text{H}]^+$, $\text{C}_{14}\text{H}_{22}\text{N}_3\text{O}_5^+$; calc. 312.1554).

5'-Azido-5'-deoxy-2',3'-O-isopropylideneuridine (6). Prepared according to [23][24]. $[\alpha]_D^{25} = +149.1$ ($c=0.02$, DMF) ([52]: $[\alpha]_D^{20} = +68.5$ ($c=0.02$, DMF)). ^1H -NMR (300 MHz, CDCl_3): see Table 3; additionally, 9.21 (br. s , NH); 1.57, 1.35 (2s, Me_2C). ^{13}C -NMR (75 MHz, CDCl_3): see Table 4; additionally, 114.74 (s , Me_2C); 27.18, 25.32 (2 q , Me_2C).

5'-Acetamido-5'-deoxy-2',3'-O-isopropylideneuridine (7). A suspension of **6** [23][24] (300 mg, 0.97 mmol), 10% Pd/C (40 mg), and Ac_2O (0.18 ml, 1.94 mmol) in MeOH (5 ml) was stirred under 1 atm of H_2 at 24° for 20 h, and filtered through *Celite*. Evaporation and FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:1 $\rightarrow$ 50:1) gave **7** (226 mg, 72%). Colourless foam. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) 0.62. $[\alpha]_D^{25} = -42.1$ ($c=0.24$, CHCl_3). UV (CHCl_3): 257 (14300). IR (ATR): 3301w, 3059w, 2988w, 2927w, 1667s, 1547m, 1454m, 1426m, 1376s, 1264m, 1211m, 1157m, 1066s, 970w, 907w, 880w, 856m, 809m. ^1H -NMR (500 MHz, CDCl_3): see Table 3; additionally, 8.54 (br. s , $\text{H}-\text{N}(3)$); 6.68 (br. dd , $J=6.8$, 3.8, AcNH); 2.01 (s , AcN); 1.55, 1.34 (2s, Me_2C). ^{13}C -NMR (75 MHz, CDCl_3): see Table 4; additionally, 170.78 (s , $\text{MeC}=\text{O}$); 114.67 (s , Me_2C); 27.25, 25.32 (2 q , Me_2C); 23.08 (q , $\text{MeC}=\text{O}$). HR-MALDI-MS: 348.1165 (83, $[\text{M}+\text{Na}]^+$, $\text{C}_{14}\text{H}_{19}\text{N}_3\text{NaO}_6^+$; calc. 348.1166), 326.1343 (100, $[\text{M}+\text{H}]^+$, $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_6^+$; calc. 326.1347).

N⁶-Benzoyl-5'-O-[dimethyl(1,1,2-trimethylpropyl)silyl]-8-formyl-2',3'-O-isopropylideneadenosine (10). A soln. of (i-Pr)₂NH (16.35 ml, 0.12 mol) in dry THF (100 ml) was treated dropwise at -78° under N₂, with 1.6M BuLi in hexane (77.95 ml, 0.12 mol), and stirred for 15 min at -78° and for 15 min at 0° . The mixture was cooled to -78° , treated dropwise with a soln. of **9** [6] (13.80 g, 24.94 mmol) in THF (100 ml), stirred for 1 h, treated with dry DMF (48.28 ml, 0.62 mol), and stirred for an additional h at -78° . The mixture was allowed to reach 25° , treated with sat. NH₄Cl soln. (100 ml), and neutralized with AcOH to pH 7. After extraction with AcOEt (100 ml), the org. phase was washed with H₂O (4×100 ml), dried (MgSO₄), and evaporated to afford **10** (14.00 g, 97%). Yellow/red foam. *R*_f (AcOEt) 0.83. $[\alpha]_D^{25} = -16.7$ (*c* = 1.0, CHCl₃). IR (ATR): 3252w (br.), 2957w, 2868w, 1703m, 1604m, 1581m, 1509m, 1488m, 1464m, 1373m, 1248s, 1211m, 1157w, 1072s, 929w, 828s. ¹H-NMR (300 MHz, CDCl₃): see Table 5; additionally, 10.04 (s, CH=O); 9.16 (s, NH); 8.04–7.99 (*m*, 2 arom. H); 7.64–7.50 (*m*, 3 arom. H); 1.62, 1.38 (2s, Me₂C); 1.56 (*sept.*, *J* = 6.9, Me₂CH); 0.82 (*d*, *J* = 6.9, Me₂CH); 0.79, 0.78 (2s, Me₂CSi); 0.00, –0.01 (2s, Me₂Si). ¹³C-NMR (75 MHz, CDCl₃): see Table 6; additionally, 183.24 (*d*, CH=O); 164.21 (*s*, NC=O); 133.06 (*s* and *d*); 128.90 (2*d*); 127.79 (2*d*); 114.46 (*s*, Me₂C); 34.11 (*d*, Me₂CH); 27.30, 25.56 (2*q*, Me₂C); 25.31 (*s*, Me₂CSi); 20.34 (*q*, Me₂CSi); 18.53 (*q*, Me₂CH); –3.31 (*q*, Me₂Si). HR-MALDI-MS: 582.2732 (100, [*M* + H]⁺, C₂₉H₄₀N₅O₆Si⁺; calc. 582.2742). Anal. calc. for C₂₉H₃₉N₅O₆Si (581.74): C 59.88, H 6.76, N 12.04; found: C 59.95, H 6.83, N 11.91.

Table 5. Selected ¹H-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] of the Adenosine Monomers **10**–**14** in CDCl₃

	10	11	12	13	14^{a)}
H–C(2)	8.87	8.73	8.84	8.78	8.70
H–C(8)	–	8.08	8.16	8.16	8.04
H–C(1')	6.99	6.15	6.19	6.10	5.89
H–C(2')	5.62	5.38	5.47	5.46	5.28
H–C(3')	5.12	5.06	5.07	5.01	4.84
H–C(4')	4.27	4.52	4.42	4.28	4.42
H _a –C(5')	3.77	4.29	3.61	3.04	3.95
H _b –C(5')	3.67	4.22	3.61	2.95	3.32
<i>J</i> (1',2')	2.7	2.4	2.4	3.0	4.2
<i>J</i> (2',3')	6.6	6.3	6.3	6.3	6.0
<i>J</i> (3',4')	3.9	3.3	3.6	3.3	2.7
<i>J</i> (4',5'a)	6.3	4.5	5.4	4.5	3.6
<i>J</i> (4',5'b)	6.6	5.7	5.4	5.7	2.7
<i>J</i> (5'a,5'b)	10.5	10.5	^{b)}	13.2	14.4

^{a)} *J*(5'a,OH) = 8.1, *J*(5'b,OH) ≈ 3.0 Hz. ^{b)} Not assigned.

N⁶-Benzoyl-2',3'-O-isopropylidene-5'-O-[(4-methylphenyl)sulfonyl]adenosine (11). Prepared according to [28]. $[\alpha]_D^{25} = -17.8$ (*c* = 1.0, CHCl₃). ¹H-NMR (300 MHz, CDCl₃): see Table 5; additionally, 8.95 (br. *s*, NH); 8.04 (*d*, *J* = 7.2, 2 arom. H); 7.67–7.52 (*m*, 5 arom. H); 7.21 (*d*, *J* = 8.4, 2 arom. H); 2.40 (*s*, Me); 1.61, 1.39 (2s, Me₂C). ¹³C-NMR (75 MHz, CDCl₃): see Table 6; additionally, 164.02 (*s*, NC=O); 145.08 (*s*); 133.38 (*s*); 132.75 (*d*); 131.97 (*s*); 129.64 (2*d*); 128.77 (2*d*); 127.78 (2*d*); 127.70 (2*d*); 114.69 (*s*, Me₂C); 27.13, 25.34 (2*q*, Me₂C); 21.72 (*q*, Me).

5'-Azido-N⁶-benzoyl-5'-deoxy-2',3'-O-isopropylideneadenosine (12) [27][29]. A soln. of **11** (1.00 g, 1.66 mmol) in dry DMF (10 ml) was treated with NaN₃ (2.16 g, 33.24 mmol) and stirred at 80° for 5 h. The soln. was cooled to 24° , diluted with AcOEt (50 ml), washed with H₂O (5×50 ml), dried (MgSO₄), and evaporated to give **12** (656 mg, 90%). Colourless foam. *R*_f (AcOEt) 0.66. ¹H-NMR (300 MHz, CDCl₃): see Table 5; additionally, 8.95 (br. *s*, NH); 8.05–7.99 (*m*, 2 arom. H); 7.65–7.50 (*m*, 3 arom. H); 1.64, 1.41

Table 6. Selected ^{13}C -NMR Chemical Shifts [ppm] of the Adenosine Monomers **10**–**14** in CDCl_3

	10	11	12	13	14
C(2)	155.37	152.43	153.09	152.58	152.11
C(4)	151.87	149.56	150.06	149.62	150.20
C(5)	122.83	123.36	123.84	123.63	124.29
C(6)	151.99	150.74	151.37	151.18	150.77
C(8)	145.33	145.08	142.38	142.14	142.72
C(1')	89.79	91.04	90.94	90.81	92.10
C(2')	83.39	84.10	84.29	83.71	82.49
C(3')	81.88	81.38	82.03	81.81	81.38
C(4')	87.37	84.59	85.70	87.74	83.94
C(5')	62.89	68.91	52.49	43.86	41.04

(2s, Me_2C). ^{13}C -NMR (75 MHz, CDCl_3): see Table 6; additionally, 164.86 (s, $\text{NC}=\text{O}$); 133.77 (s); 133.07 (d); 129.09 (2d); 128.12 (2d); 115.22 (s, Me_2C); 27.37, 25.55 (2q, Me_2C).

5'-Amino- N^6 -benzoyl-5'-deoxy-2',3'-O-isopropylideneadenosine (13). Prepared according to [28][29]. $[\alpha]_{\text{D}}^{25} = -48.5$ ($c = 1.0$, CHCl_3). ^1H -NMR (300 MHz, CDCl_3): see Table 5; additionally, 8.01 (d, $J = 6.9$, 2 arom. H); 7.59 (t, $J = 6.9$, 1 arom. H); 7.50 (t, $J = 7.2$, 2 arom. H); 1.62, 1.39 (2s, Me_2C); signals of BzNH and NH_2 not visible. ^{13}C -NMR (75 MHz, CDCl_3): see Table 6; additionally, 164.00 (s, $\text{NC}=\text{O}$); 133.47 (s); 132.69 (d); 128.73 (2d); 127.78 (2d); 114.66 (s, Me_2C); 27.34, 25.46 (2q, Me_2C). HR-MALDI-MS: 433.1603 (91, $[M + \text{Na}]^+$, $\text{C}_{20}\text{H}_{22}\text{N}_6\text{NaO}_4^+$; calc. 433.1595), 411.1783 (100, $[M + \text{H}]^+$, $\text{C}_{20}\text{H}_{23}\text{N}_6\text{O}_4^+$; calc. 411.1775).

5'-Acetamido-5'-deoxy- N^6 -benzoyl-2',3'-O-isopropylideneadenosine (14). A suspension of **12** (500 mg, 1.14 mmol), 10% Pd/C (40 mg), and Ac_2O (0.16 ml, 1.71 mmol) in MeOH (5 ml) was stirred under 1 atm of H_2 at 24° for 20 h, and filtered through Celite. Evaporation and FC (cyclohexane/ AcOEt 2:1 $\rightarrow$ AcOEt) gave **14** (394 mg, 76%). Colourless foam. R_f (AcOEt/MeOH 10:1) 0.33. $[\alpha]_{\text{D}}^{25} = -103.1$ ($c = 0.9$, CHCl_3). UV (CHCl_3): 240 (17300), 280 (20800). IR (ATR): 3277w (br.), 3074w (br.), 2987w, 2936w, 1659m, 1608s, 1579s, 1511s, 1486m, 1454s, 1373m, 1329m, 1246s, 1210s, 1156m, 1093s, 1073s, 1028m, 1002w, 969w, 933w, 893w, 866m, 796m, 756w, 707s, 643m. ^1H -NMR (300 MHz, CDCl_3): see Table 5; additionally, 9.39 (br. s, exchange with D_2O , BzNH); 7.98 (d, $J = 7.2$, 2 arom. H); 7.58–7.53 (m, addn. of $\text{D}_2\text{O} \rightarrow$ weak upfield shift, but no exchange, AcNH); 7.55 (t, $J = 7.5$, 1 arom. H); 7.46 (t, $J = 7.5$, 2 arom. H); 2.06 (s, AcN); 1.57, 1.31 (2s, Me_2C). ^{13}C -NMR (75 MHz, CDCl_3): see Table 6; additionally, 170.47 (s, $\text{MeC}=\text{O}$); 164.65 (s, $\text{NC}=\text{O}$); 133.22 (s); 132.77 (d); 128.69 (2d); 127.86 (2d); 114.84 (s, Me_2C); 27.49, 25.36 (2q, Me_2C); 23.23 (q, $\text{MeC}=\text{O}$). HR-MALDI-MS: 491.1443 (30, $[M + \text{K}]^+$, $\text{C}_{22}\text{H}_{24}\text{KN}_6\text{O}_5^+$; calc. 491.1440), 475.1706 (96, $[M + \text{Na}]^+$, $\text{C}_{22}\text{H}_{24}\text{N}_6\text{NaO}_5^+$; calc. 475.1700), 453.1886 (100, $[M + \text{H}]^+$, $\text{C}_{22}\text{H}_{25}\text{N}_6\text{O}_5^+$; calc. 453.1881).

N^6 -Benzoyl-5'-O-[dimethyl(1,1,2-trimethylpropyl)silyl]-2',3'-O-isopropylideneadenosine-8-methyl-(8' $\rightarrow$ 5'-N)-5'-amino-5'-deoxy-2',3'-O-isopropylideneuridine (15). A soln. of **6** (200 mg, 0.65 mmol) in THF (4 ml) was treated dropwise with 1M Me_3P in THF (0.71 ml, 0.71 mmol) and stirred for 6 h at 23° (TLC: complete conversion of **6**). The mixture was treated with a soln. of **10** (378 mg, 0.65 mmol) in THF (3 ml), stirred for 48 h at 23° , and evaporated. A soln. of the residue in AcOEt (15 ml) was washed with H_2O (2 $\times$ 20 ml), dried (MgSO_4), and evaporated. A soln. of the residue in MeOH (6 ml) was treated with NaBH_3CN (163 mg, 2.60 mmol) and AcOH (0.15 ml, 2.60 mmol), stirred for 24 h at 23° , and evaporated. A soln. of the residue in AcOEt (15 ml) was washed with sat. NaHCO_3 soln. and brine, dried (MgSO_4), and evaporated. FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50:1) gave **15** (390 mg, 70%). Yellow solid. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 15:1) 0.43. M.p. 124–126°. $[\alpha]_{\text{D}}^{25} = -16.7$ ($c = 0.46$, CHCl_3). UV (CHCl_3): 260 (14800), 279 (14800). IR (ATR): 3204w, 2956w, 2931w, 2865w, 1690s, 1609m, 1582w, 1482w, 1455m, 1375m, 1249s, 1211m, 1157m, 1072s, 970w, 926w, 828s. ^1H -NMR (300 MHz, CDCl_3): see Table 7; additionally, 9.86 (s, $\text{H}-\text{N}(3/\text{I})$); 9.33 (s, $\text{HN}-\text{C}(6/\text{II})$); 7.99 (d, $J = 6.9$, 2 arom. H); 7.60–7.44 (m, 3 arom. H); 4.18 (s, $\text{CH}_2-\text{C}(8/\text{II})$); 2.13 (br. s, $\text{HN}-\text{C}(5'/\text{I})$); 1.60, 1.53, 1.40, 1.29 (4s, 2 Me_2C); 1.58 (sept., $J = 6.9$, Me_2CH);

0.81 (*d*, *J* = 6.9, Me₂CH); 0.77, 0.76 (2*s*, Me₂CSi); – 0.04, – 0.05 (2*s*, Me₂Si). ¹³C-NMR (75 MHz, CDCl₃): see Table 8; additionally, 164.90 (*s*, PhC=O); 133.54 (*s*); 132.58 (*d*); 128.62 (2*d*); 127.96 (2*d*); 114.55, 113.82 (2*s*, 2 Me₂C); 34.10 (*d*, Me₂CH); 27.27, 25.44 (2*q*, 2 Me₂C); 25.26 (*s*, Me₂CSi); 20.34 (*q*, Me₂CSi); 18.54 (*q*, Me₂CH); – 3.35 (*q*, Me₂Si). HR-MALDI-MS: 871.3715 (55, [*M* + Na]⁺, C₄₁H₅₆N₈NaO₁₀Si⁺; calc. 871.3781), 849.3945 (100, [*M* + H]⁺, C₄₁H₅₇N₈O₁₀Si⁺; calc. 849.3961). Anal. calc. for C₄₁H₅₆N₈O₁₀Si (849.03): C 58.00, H 6.65, N 13.20; found: C 57.80, H 6.69, N 12.96.

Table 7. Selected ¹H-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] of the A*[N]U Dinucleosides **15**–**17** in CDCl₃

	15	16^a	17^a		15	16	17
Uridine unit (I)							
H–C(5/I)	5.62	5.71	5.72				
H–C(6/I)	7.25	7.19	7.20	<i>J</i> (5,6/I)	8.1	8.0	8.1
H–C(1'/I)	5.59	5.30	5.34	<i>J</i> (1',2'/I)	2.4	3.7	2.7
H–C(2'/I)	4.94	5.19	5.18	<i>J</i> (2',3'/I)	6.6	6.4	6.6
H–C(3'/I)	4.82	5.06	5.00	<i>J</i> (3',4'/I)	4.5	2.8	3.5
H–C(4'/I)	4.20	4.36	4.29	<i>J</i> (4',5'a/I)	4.2	3.1	3.5
H _a –C(5'/I)	3.04	3.13	3.01	<i>J</i> (4',5'b/I)	6.0	4.4	5.4
H _b –C(5'/I)	2.97	2.99	2.97	<i>J</i> (5'a,5'b/I)	12.6	12.3	12.3
Adenosine unit (II)							
H–C(2/II)	8.74	8.33	8.30				
CH _a –C(8/II)	4.20	4.20	4.19				
CH _b –C(8/II)	4.20	3.99	4.00	<i>J</i> (H _a ,H _b /II)	^{b)}	14.0	14.6
H–C(1'/II)	6.39	6.42	6.12	<i>J</i> (1',2'/II)	1.8	1.6	5.1
H–C(2'/II)	5.82	5.90	5.30	<i>J</i> (2',3'/II)	6.6	6.3	5.5
H–C(3'/II)	5.15	5.14	5.16	<i>J</i> (3',4'/II)	3.3	2.8	1.0
H–C(4'/II)	4.27	4.29	4.51	<i>J</i> (4',5'a/II)	6.9	6.8	1.2
H _a –C(5'/II)	3.68	3.72	3.97	<i>J</i> (4',5'b/II)	6.6	6.9	<1.0
H _b –C(5'/II)	3.56	3.58	3.79	<i>J</i> (5'a,5'b/II)	10.8	10.6	11.2

^{a)} Assignments based on a DQF-COSY and a HSQC spectrum. ^{b)} Not assigned.

5'-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2',3'-O-isopropylideneadenosine-8-methyl-(8' → 5'-N)-5'-amino-5'-deoxy-2',3'-O-isopropylideneuridine (**16**). A soln. of **15** (470 mg, 0.55 mmol) in MeOH (3 ml) was treated with a soln. of MeONa (299 mg, 5.53 mmol) in MeOH (2 ml), stirred for 48 h at 24°, and evaporated. A soln. of the residue in AcOEt (20 ml) was washed with sat. NH₄Cl soln. and brine, dried (MgSO₄), and evaporated. FC (CH₂Cl₂/MeOH 50:1 → 30:1) gave **16** (370 mg, 90%). Yellow solid. *R*_f (CH₂Cl₂/MeOH 10:1) 0.47. M.p. 129–130°. [*α*]_D²⁵ = –161.0 (*c* = 1.0, CHCl₃). UV (CHCl₃): 260. IR (ATR): 3326*w*, 3192*w*, 2955*w*, 2865*w*, 1693*s*, 1635*m*, 1603*m*, 1574*w*, 1447*m*, 1374*m*, 1329*w*, 1251*m*, 1211*m*, 1157*m*, 1070*s*, 969*w*, 933*w*, 828*s*, 776*m*, 660*w*. ¹H-NMR (400 MHz, CDCl₃; assignments based on a DQF-COSY and a HSQC spectrum): see Table 7; additionally, 12.72 (*s*, H–N(3/I)); 7.26 (br. *s*, H₂N–C(6/II)); 2.63 (br. *s*, HN–C(5'/I)); 1.59, 1.57, 1.39, 1.34 (4*s*, 2 Me₂C); 1.53 (*sept.*, *J* = 6.9, Me₂CH); 0.82 (*d*, *J* = 6.9, Me₂CH); 0.78, 0.76 (2*s*, Me₂CSi); – 0.04, – 0.07 (2*s*, Me₂Si). ¹³C-NMR (100 MHz, CDCl₃; assignments based on a HSQC spectrum): see Table 8; additionally, 114.20, 113.44 (2*s*, 2 Me₂C); 34.11 (*d*, Me₂CH); 27.34, 27.21, 25.43, 25.24 (4*q*, 2 Me₂C); 25.19 (*s*, Me₂CSi); 20.29, 20.26 (2*q*, Me₂CSi); 18.48, 18.44 (2*q*, Me₂CH); – 3.46 (*q*, Me₂Si). HR-MALDI-MS: 767.3502 (19, [*M* + Na]⁺, C₃₄H₅₂N₈NaO₉Si⁺; calc. 767.3519), 745.3686 (100, [*M* + H]⁺, C₃₄H₅₃N₈O₉Si⁺; calc. 745.3699). Anal. calc. for C₃₄H₅₂N₈O₉Si (744.92): C 54.82, H 7.04, N 15.04; found: C 55.09, H 7.00, N 14.90.

2',3'-O-Isopropylideneadenosine-8-methyl-(8' → 5'-N)-5'-amino-5'-deoxy-2',3'-O-isopropylideneuridine (**17**). In a polyethylene flask, a soln. of **16** (200 mg, 0.27 mmol) in THF (2 ml) was treated with

Table 8. Selected ^{13}C -NMR Chemical Shifts [ppm] of the $A^*[N]U$ Dinucleosides **15**–**17** in CDCl_3

	15	16^a	17^a		15	16	17
Uridine unit (I)				Adenosine unit (II)			
C(2/I)	151.79	151.77	151.57	C(2/II)	152.49	152.40	152.21
C(4/I)	163.02	163.50	163.56	C(4/II)	149.90	151.02	150.63
C(5/I)	102.64	103.34	103.22	C(5/II)	122.24	118.12	118.67
C(6/I)	142.20	143.49	143.57	C(6/II)	153.49	155.52	155.94
				C(8/II)	148.87	150.36	149.57
				CH ₂ –C(8/II)	46.75	46.43	46.29
C(1'/I)	93.97	98.25	98.08	C(1'/II)	89.89	90.23	92.54
C(2'/I)	83.08	82.11	82.13	C(2'/II)	83.77	83.24	82.92
C(3'/I)	81.43	81.41	81.77	C(3'/II)	82.12	82.58	81.77
C(4'/I)	85.66	85.28	86.93	C(4'/II)	87.96	88.65	85.85
C(5'/I)	50.57	51.47	51.24	C(5'/II)	62.89	63.21	63.35

^a) Assignments based on a HSQC spectrum.

(HF)₃·Et₃N (0.44 ml, 2.70 mmol) and stirred for 24 h at 24°. The mixture was treated with 1M NaOH and extracted with AcOEt. The org. phase was washed with brine, dried (MgSO₄), and evaporated. FC (CH₂Cl₂/MeOH 80:1 → 20:1) gave **17** (143 mg, 88%). Colourless foam. *R*_f (CH₂Cl₂/MeOH 10:1) 0.23. $[\alpha]_D^{25} = -233.6$ (*c* = 1.0, CHCl₃). UV (CHCl₃): 261 (21400). IR (ATR): 3323w, 3190w, 2986w, 2936w, 2857w, 2817w, 1690s, 1639s, 1605m, 1578w, 1452m, 1374s, 1331w, 1266m 1237m, 1212s, 1156m, 1072s, 968w, 945w, 851m, 799m, 763w, 713w, 620w. ¹H-NMR (500 MHz, CDCl₃; assignments based on a DQF-COSY and a HSQC spectrum): see Table 7; additionally, 12.34 (s, H–N(3/I)); 7.47 (br. s, H₂N–C(6/II)); 6.85–6.30 (br. s, OH); 1.76 (br. s, HN–C(5'/I)); 1.66, 1.55, 1.39, 1.32 (4s, 2 Me₂C). ¹³C-NMR (125 MHz, CDCl₃; assignments based on a HSQC spectrum): see Table 8; additionally, 114.11, 113.96 (2s, 2 Me₂C); 27.71, 27.22, 25.28, 25.23 (4q, 2 Me₂C). HR-MALDI-MS: 641.2060 (20, [M + K]⁺, C₂₆H₃₄KN₈O₇⁺; calc. 641.2080), 625.2329 (52, [M + Na]⁺, C₂₆H₃₄N₈NaO₇⁺; calc. 625.2341), 603.2511 (100, [M + H]⁺, C₂₆H₃₅N₈O₇⁺; calc. 603.2522).

5'-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2',3'-O-isopropylideneuridine-6-methyl-(6' → 5'-N)-5'-amino-N⁶-benzoyl-5'-deoxy-2',3'-O-isopropylideneadenosine (**18**). A soln. of **12** (100 mg, 0.23 mmol) in THF (4 ml) was treated dropwise with 1M Me₃P in THF (0.25 ml, 0.25 mmol), and stirred for 6 h at 23° (TLC: complete conversion of **12**). The mixture was treated with a soln. of **3** (104 mg, 0.23 mmol) in THF (3 ml), stirred for 48 h at 23°, and evaporated. A soln. of the residue in AcOEt (15 ml) was washed with H₂O (2 × 20 ml), dried (MgSO₄), and evaporated. A soln. of the residue in MeOH (4 ml) was treated with NaBH₃CN (58 mg, 0.92 mmol) and AcOH (0.052 ml, 0.92 mmol), stirred for 24 h at 23°, and evaporated. A soln. of the residue in AcOEt (15 ml) was washed with sat. NaHCO₃ soln. and brine, dried (MgSO₄), and evaporated. FC (CH₂Cl₂/MeOH 100:1 → 50:1) gave **18** (165 mg, 84%). Yellow foam. *R*_f (CH₂Cl₂/MeOH 20:1) 0.24. $[\alpha]_D^{25} = -13.4$ (*c* = 0.8, CHCl₃). UV (CHCl₃): 260 (13000), 275 (13700). IR (ATR): 3248w, 3178w, 3090w, 3041w, 2958w, 2927w, 2866w, 1689s, 1608m, 1581w, 1513w, 1484w, 1455m, 1381m, 1331w, 1249m, 1211m, 1156m, 1129w, 1072s, 1029w, 987w, 909m, 873m, 829s, 795m, 777m, 729s, 708s, 687w, 660w, 645m, 619w. ¹H-NMR (500 MHz, CDCl₃; assignments based on a DQF-COSY and a HSQC spectrum): see Table 9; additionally, 10.10 (s, H–N(3/II)); 9.58 (s, HN–C(6/I)); 8.10–8.00 (*m*, 2 arom. H); 7.60–7.40 (*m*, 3 arom. H); 2.18 (br. s, HN–C(5'/I)); 1.64, 1.53, 1.41, 1.31 (4s, 2 Me₂C); 1.57 (*sept.*, *J* = 6.9, Me₂CH); 0.82 (*d*, *J* = 6.9, Me₂CH); 0.80, 0.79 (2s, Me₂CSi); 0.05, 0.04 (2s, Me₂Si). ¹³C-NMR (125 MHz, CDCl₃; assignments based on a HSQC spectrum): see Table 10; additionally, 165.05 (s, PhC=O); 133.32 (s); 132.87 (*d*); 128.75 (2*d*); 128.29 (2*d*); 114.75, 113.42 (2s, 2 Me₂C); 34.01 (*d*, Me₂CH); 27.51, 27.36, 25.67, 25.51 (4q, 2 Me₂C); 25.27 (s, Me₂CSi); 20.35, 20.30 (2q, Me₂CSi); 18.49, 18.45 (2q, Me₂CH); –3.30 (*q*, Me₂Si). HR-MALDI-MS: 887.3484 (22, [M + K]⁺, C₄₁H₅₆KN₈O₁₀Si⁺; calc. 887.3520), 871.3765 (100, [M + Na]⁺, C₄₁H₅₆N₈NaO₁₀Si⁺; calc. 871.3781).

Table 9. Selected ^1H -NMR Chemical Shifts [ppm] and Coupling Constants [Hz] of the $U^*[\text{N}]/A$ Dinucleosides **18–20** in CDCl_3

	18^a	19^a	20		18	19	20
Adenosine unit (I)							
H–C(2/I)	8.77	8.30	8.28				
H–C(8/I)	8.14	7.95	7.95				
H–C(1'/I)	6.03	6.04	6.01	$J(1',2'/\text{I})$	3.5	3.1	3.0
H–C(2'/I)	5.51	5.51	5.52	$J(2',3'/\text{I})$	6.3	6.8	6.3
H–C(3'/I)	5.25	5.31	5.22	$J(3',4'/\text{I})$	3.3	3.4	3.0
H–C(4'/I)	4.42	4.41	4.42	$J(4',5'\text{a}/\text{I})$	3.4	3.4	3.3
H _a –C(5'/I)	3.08	3.06	2.99	$J(4',5'\text{b}/\text{I})$	3.6	3.1	4.2
H _b –C(5'/I)	2.91	2.88	2.90	$J(5'\text{a},5'\text{b}/\text{I})$	12.3	12.3	12.3
Uridine unit (II)							
H–C(5/II)	5.75	5.59	5.63				
CH _a –C(8/II)	3.66	3.63	3.63				
CH _b –C(8/II)	3.66	3.54	3.54	$J(\text{H}_a, \text{H}_b/\text{II})$	^{b)}	13.8	14.1
H–C(1'/II)	6.07	6.17	5.95	$J(1',2'/\text{II})$	< 1.0	< 1.0	1.8
H–C(2'/II)	5.27	5.40	5.32	$J(2',3'/\text{II})$	6.3	6.3	6.3
H–C(3'/II)	4.76	4.87	5.07	$J(3',4'/\text{II})$	4.3	4.4	4.5
H–C(4'/II)	4.12	4.15	4.17	$J(4',5'\text{a}/\text{II})$	5.6	5.5	2.7
H _a –C(5'/II)	3.74	3.78	3.86	$J(4',5'\text{b}/\text{II})$	7.3	7.3	4.5
H _b –C(5'/II)	3.70	3.75	3.80	$J(5'\text{a},5'\text{b}/\text{II})$	10.7	10.7	12.3

^{a)} Assignments based on a DQF-COSY and a HSQC spectrum. ^{b)} Not assigned.Table 10. Selected ^{13}C -NMR Chemical Shifts [ppm] of the $U^*[\text{N}]/A$ Dinucleosides **18–20** in CDCl_3

	18^a	19^a	20		18	19	20
Adenosine unit (I)				Uridine unit (II)			
C(2/I)	152.43	153.58	153.03	C(2/II)	151.06	151.40	151.95
C(4/I)	150.25	149.39	148.87	C(4/II)	162.79	163.82	163.45
C(5/I)	124.24	119.96	119.57	C(5/II)	102.94	103.27	103.38
C(6/I)	153.80	155.97	155.73	C(6/II)	151.63	153.06	152.80
C(8/I)	142.63	139.78	139.90	CH ₂ –C(6/II)	50.75	51.21	50.85
C(1'/I)	91.17	90.84	91.09	C(1'/II)	91.35	91.47	91.31
C(2'/I)	82.99	83.18	83.14	C(2'/II)	84.40	84.61	84.05
C(3'/I)	81.57	81.73	80.57	C(3'/II)	82.28	82.50	81.83
C(4'/I)	84.99	85.44	85.74	C(4'/II)	89.53	89.55	88.06
C(5'/I)	50.30	50.31	50.14	C(5'/II)	64.01	64.15	62.67

^{a)} Assignments based on a HSQC spectrum.

5'-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2',3'-O-isopropylideneuridine-6-methyl-(6' → 5'-N)-5'-amino-5'-deoxy-2',3'-O-isopropylideneadenosine (**19**). A soln. of **18** (165 mg, 0.19 mmol) in MeOH (2 ml) was treated with a soln. of MeONa (105 mg, 1.9 mmol) in MeOH (2 ml), stirred for 48 h at 23°, and evaporated. A soln. of the residue in AcOEt (15 ml) was washed with sat. NH_4Cl soln. and brine, dried (MgSO_4), and evaporated. FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50 : 1 → 20 : 1) gave **19** (123 mg, 87%). Colourless foam. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10 : 1) 0.48. $[\alpha]_D^{25} = -3.4$ ($c = 1.0$, CHCl_3). UV (CHCl_3): 259 (22700). IR (ATR): 3329w, 3192w, 2956w, 2936w, 2865w, 1693s, 1638m, 1602m, 1576w, 1457m, 1374m, 1330w, 1292w, 1251m,

1210m, 1156m, 1127w, 1072s, 991w, 969w, 921w, 862m, 828s, 798m, 777m, 728w, 647w, 623w. ¹H-NMR (500 MHz, CDCl₃; assignments based on a DQF-COSY and a HSQC spectrum): see Table 9; additionally, 11.95 (s, H–N(3/II)); 6.60 (br. s, H₂N–C(6/I)); 2.04 (br. s, HN–C(5'/I)); 1.63, 1.55, 1.41, 1.38 (4s, 2 Me₂C); 1.58 (sept., *J* = 6.9, Me₂CH); 0.82 (*d*, *J* = 6.9, Me₂CH); 0.80, 0.79 (2s, Me₂CSi); 0.04, 0.03 (2s, Me₂Si). ¹³C-NMR (125 MHz, CDCl₃; assignments based on a HSQC spectrum): see Table 10; additionally, 114.37, 113.35 (2s, 2 Me₂C); 34.10 (*d*, Me₂CH); 27.56, 27.46, 25.86, 25.71 (4*q*, 2 Me₂C); 25.57 (s, Me₂CSi); 20.36, 20.32 (2*q*, Me₂CSi); 18.49, 18.45 (2*q*, Me₂CH); –3.27 (*q*, Me₂Si). HR-MALDI-MS: 767.3457 (59, [M + Na]⁺, C₃₄H₅₂N₈NaO₉Si⁺; calc. 767.3519), 745.3685 (100, [M + H]⁺, C₃₄H₅₃N₈O₉Si⁺; calc. 745.3699). Anal. calc. for C₃₄H₅₂N₈O₉Si · MeOH (776.39): C 54.11, H 7.26, N 14.42; found: C 54.29, H 7.02, N 14.51.

2',3'-O-Isopropylideneuridine-6-methyl-(6' → 5'-N)-5'-amino-5'-deoxy-2',3'-O-isopropylideneadenosine (**20**). In a polyethylene flask, a soln. of **19** (90 mg, 0.12 mmol) in THF (2 ml) was treated with HF · pyridine (0.11 ml, 1.20 mmol), and stirred for 1 h at 23°. The mixture was treated with 1M NaOH and extracted with AcOEt. The org. phase was washed with brine, dried (MgSO₄), and evaporated. FC (CH₂Cl₂/MeOH 70 : 1 → 40 : 1) gave **20** (59 mg, 82%). Colourless foam. *R*_f (CH₂Cl₂/MeOH 10 : 1) 0.38. [α]_D²⁵ = +2.2 (*c* = 0.23, CHCl₃). UV (CHCl₃): 259. IR (ATR): 3468w, 3398w, 3323w, 3211w, 2975w, 2933w, 1704s, 1690s, 1649s, 1603m, 1579m, 1500w, 1467m, 1434m, 1422w, 1375m, 1328w, 1300w, 1244m, 1211s, 1156m, 1100s, 1067s, 1049s, 991m, 974m, 940w, 909w, 866m, 844m, 828m, 797m, 769m, 717w, 642w, 617w. ¹H-NMR (300 MHz, CDCl₃): see Table 9; additionally, 12.52 (s, H–N(3/II)); 6.78 (br. s, H₂N–C(6/I)); 2.30–1.80 (HO–C(5'/II), HN–C(5'/I)); 1.61, 1.55, 1.39, 1.36 (4s, 2 Me₂C). ¹³C-NMR (75 MHz, CDCl₃): see Table 10; additionally, 114.16, 113.84 (2s, 2 Me₂C); 27.49, 27.48, 25.76, 25.50 (4*q*, 2 Me₂C). HR-MALDI-MS: 641.2074 (26, [M + K]⁺, C₂₆H₃₄KN₈O₉⁺; calc. 641.2080), 625.2332 (61, [M + Na]⁺, C₂₆H₃₄N₈NaO₉⁺; calc. 625.2341), 603.2512 (100, [M + H]⁺, C₂₆H₃₅N₈O₉⁺; calc. 603.2522).

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