Oligonucleotide Analogues with Integrated Bases and Backbones

Part 26

Synthesis, Conformational Analysis, and Association of Aminomethylene-Linked Self-Complementary Adenosine and Uridine Dinucleosides with Enforced *syn*-Conformation

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The self-complementary aminomethylene-linked A*[N]U* dinucleosides **23**–**26** were prepared by reductive coupling of aldehyde **10** and azide **8**. The U*[N]A* sequence isomers **19**–**21** were similarly prepared from aldehyde **14** and azide **3**. The substituents at C(6/I) of **23**–**26** and at C(8/I) of **19**–**21** strongly favour the *syn*-conformation. The A*[N]U* dinucleoside **23** associates more strongly than the sequence-isomeric U*[N]A* dinucleoside **19**. The A*[N]U* dinucleosides **23** and **24** associate more strongly than the analogues devoid of the substituent at C(6/I), while the U*[N]A* dinucleoside **19** associates less strongly than the analogue devoid of the substituent at C(8/I). While **23** and **24** form cyclic duplexes mostly by *Watson–Crick*-type base pairing, **25** only forms linear associates. The U*[N]A* dinucleoside **19** forms mostly linear duplexes and higher associates, and **21** forms cyclic duplexes showing both *Watson–Crick*- and *Hoogsteen*-type base pairing. The cyclic duplexes of the aminomethylene-linked dinucleosides show both the *gg*- and *gt*-orientation of the linker, with the *gg*-orientation being preferred.

Introduction. – Oligonucleotides with integrated bases and backbones (ONIBs) replace the backbone of nucleic acids by linking elements between adjacent nucleobases, and form cyclic duplexes and/or linear associates. This was shown by analysing the association in $CDCl_3$ of partially protected, self-complementary di- and tetranucleosides of the type U*[x]A$^{(*)}$[1]) and A*[x]U$^{(*)}$, possessing a variety of linking elements [1–9]. A conformational analysis of the diastereoisomers of the constitutionally isomeric cyclic duplexes of self-complementary ethylene-, oxymethylene-, thiomethylene-, and aminomethylene-linked dinucleosides rationalized the propensity of pairing, *i.e.*, the formation of cyclic duplexes [7]. Pairing of partially protected, self-complementary dinucleosides in $CDCl_3$ depends on the structure of the linker, the *syn*-orientation of the nucleobases, and the conformation of the ribose unit [7]. The resulting cyclic duplexes form *Watson–Crick* (*WC*), reverse-*Watson–Crick* (r*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 linking C(6)–CH_2 or C(8)–CH_2 of unit II and C(5′) of unit I is indicated in square brackets, *i.e.*, [C] for a C-, [O] for an O-, [N] for a N-, and [S] for a S-atom.

Hoogsteen (*H*), or reverse-*Hoogsteen* (r*H*) H-bonds [10]. Oxymethylene-linked dinucleosides [5][6] form cyclic duplexes that are characterized by a *gg*-conformation about the C(4′)–C(5′) bond. This corresponds to the *ap,ap*-conformation of the 3-oxapentylene fragment of these dinucleosides that agrees with the preferred *ap,ap*-conformation of diethyl ether [11][12]. In contradistinction, thiomethylene-linked dinucleosides form cyclic duplexes with a *gt*-conformation about the C(4′)–C(5′) bond corresponding to the *ap,sc*-conformation of the 3-thiapentylene fragment. The preference for this conformation is in agreement with *ab initio* calculations for Et_2S, suggesting that it prefers the *ap,sc*- over the *ap,ap*-conformation [7][12][13]. Similarly to the oxymethylene-linked U*[O]A$^{(*)}$ dinucleosides, the self-complementary adenosine- and uridine-derived aminomethylene-linked A*[N]U and U*[N]A pair well, and adopt preferentially a *gg*-conformation about the C(4′)–C(5′) bond [9]. These observations and the failure to prepare the sequence-isomeric A*[O]U$^{(*)}$ dinucleosides raised our interest in longer aminomethylene-linked oligonucleosides, not least in view of their solubility in H_2O. Their synthesis requires the introduction of a substituted methylene substituent in unit I, at C(6) of a uridine and at C(8) of an adenosine moiety. We considered it of interest to investigate the introduction and the effect of such a substituent at the dinucleoside stage, expecting it to favour the *syn*-conformation and thereby to improve pairing.

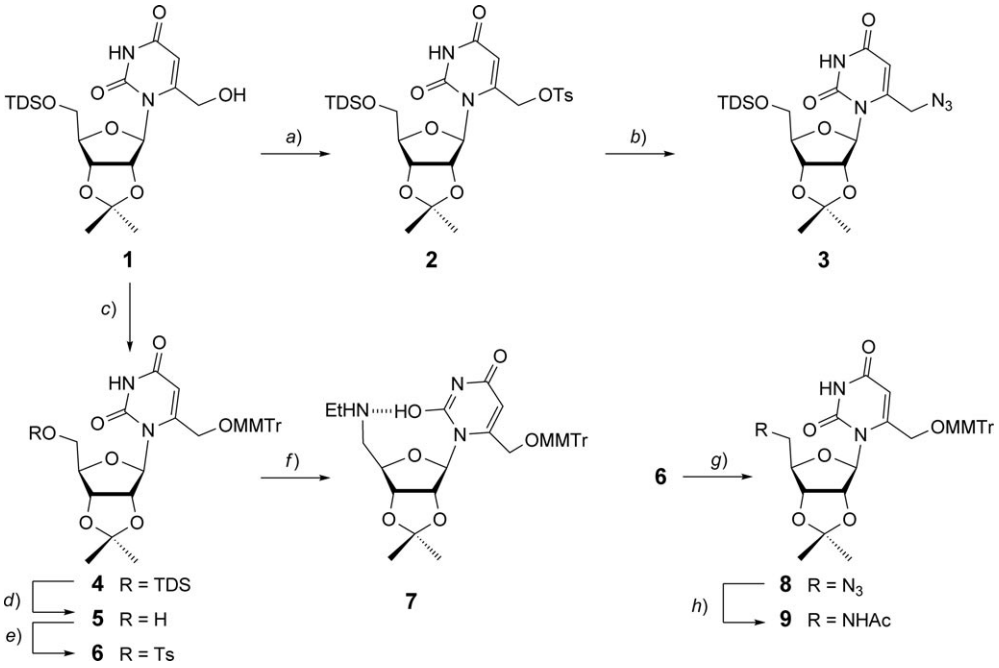
We describe the synthesis of partially protected adenosine- and uridine-derived aminomethylene-linked A*[N]U* and U*[N]A* dinucleosides which possess a substituent at C(6/I) of U and at C(8/I) of A, respectively, their conformational analysis, and their association.

Results and Discussion. – *Synthesis of the U*[N]A* and A*[N]U* Dinucleosides.* We planned to synthesize these dinucleosides by the aza-*Wittig* reaction [14] of a mononucleoside aldehyde with the iminophosphorane derived from a 5′-azido-5′-deoxymononucleoside by treatment with Me_3P [15][16], followed by reduction of the resulting imines [17]. We thus required the azido nucleosides **3** and **8**, and the aldehydes **10** and **14** (*Schemes 1* and *2*). In addition, the ethylamine **7** and the acetamide **9** were of interest as references for the conformational analysis of the dinucleosides. We prepared these compounds from the known protected 6-(hydroxymethyl)uridine **1** [7] (*Scheme 1*) and the protected 8-formyladenosine **10** [7] (*Scheme 2*).

The *C(6)*-substituted *p*-toluenesulfonate **2** was obtained from the hydroxymethyl derivative **1** (87%), and transformed into the *C(6)*-azidomethyl uridine **3** by treatment with NaN_3 in MeCN (82%; *Scheme 1*). THF also proved a suitable solvent for this substitution, while the reaction in DMF, DMSO, or HMPT did not lead to the desired product. The azido derivative **3** proved instable, and the crude product was used for further transformations.

The *C(5′)*-substituted *p*-toluenesulfonate **6** was prepared (86%) from the known monomethoxytrityl ether **5** [7] that was obtained from **1** and MMTrCl in CH_2Cl_2, followed by desilylation [18][19] of the resulting ether **4** (*Scheme 1*). The azide **8** was obtained in a yield of 95% from **6** by substitution with NaN_3 in DMF in the presence of excess NaI. Azide **8** was not formed in the presence of only catalytic amounts of NaI, or by treating **6** with Me_3SiN_3, while the addition of substoechiometric amounts of 18-crown-6 led to **8** in a yield of 82%. The ethylamine **7** was prepared by substitution of

Scheme 1



a) TsCl, 1,4-diazabicyclo[2.2.2]octane (DABCO), CH_2Cl_2; 87%. *b*) NaN_3, MeCN, 80°; 82%. *c*) (MMTrCl), $EtN(i\text{-}Pr)_2$, CH_2Cl_2; 88%. *d*) 1M Bu_4NF in THF; 87%. *e*) TsCl, pyridine; 86%. *f*) 70% $EtNH_2$ in H_2O, DMF, 80°; 88%. *g*) NaN_3, NaI, DMF, 80°; 95%. *h*) H_2, Pd/C, Ac_2O, MeOH; 59%. MMTr = (Monomethoxy)trityl (= (4-methoxyphenyl)diphenylmethyl), TDS = thexyl(dimethyl)silyl (= dimethyl-(1,1,2-trimethylpropyl)silyl).

p-toluenesulfonate **6** with $EtNH_2$ in DMF (88%) [9], and the acetamide **9** (59%) by hydrogenation of **8** in the presence of Pd/C and Ac_2O [9].

Reduction [7][20] of aldehyde **10** gave **11** (93%) that was transformed into the (monomethoxy)trityl ether **12** (85%; *Scheme 2*). Desilylation of **12** with Bu_4NF yielded 91% of the selectively protected alcohol **13** that provided the *p*-toluenesulfonate **15** (75%) under standard conditions [9]. However, a range of conditions failed to transform the *C(8)*-substituted alcohol **13** or the *p*-toluenesulfonate **15** into the desired azidodeoxy-adenosine. Neither a *Mitsunobu* reaction (HN_3) [21] of **13** nor a reaction with diphenylphosphoryl azide (DPPA) [22] afforded the desired product, and treatment of **15** with NaN_3 in DMF in the absence or presence of 18-crown-6 or Bu_4NI led to the N^3,5′-cyclo-nucleoside **16**[2]) and the hydrolysis product **17**. Such hydrolysis products are well precedented [25][26]. The facile intramolecular nucleophilic substitution of N(3) of **15** is not surprising, as even *anti*-configured, 8-unsubstituted analogues of **15** are readily transformed into cycloadenosine derivatives [23–27].

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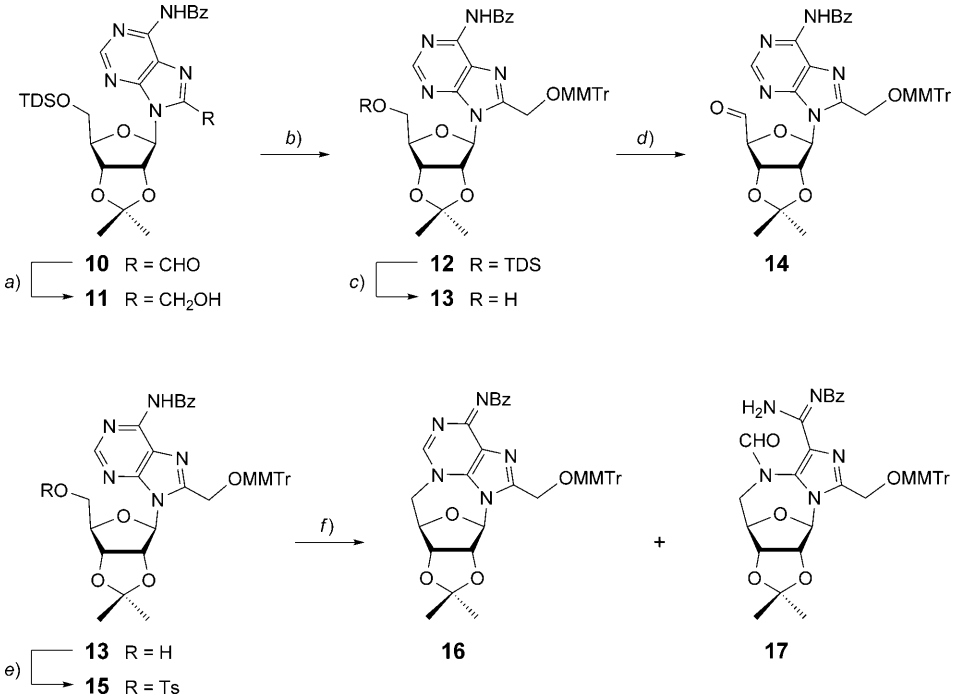
[2]) Compare [23] for the *C(8)*-unsubstituted, and [24] for the *C(8)*-unsubstituted and debenzoylated analogues.

Scheme 2

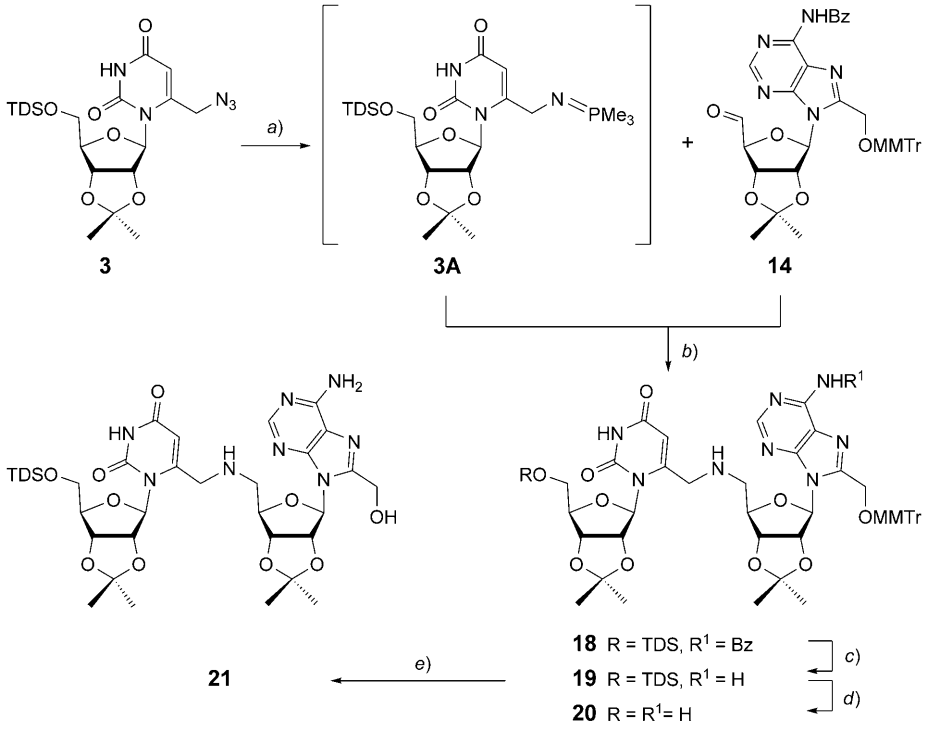


a) $NaBH_4$, MeOH; 93%. *b*) MMTrCl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2; 85%. *c*) 1M Bu_4NF in THF; 91%. *d*) *Dess–Martin*'s periodinane, CH_2Cl_2; 97%. *e*) TsCl, pyridine; 75%. *f*) NaN_3, DMF; 16% of **16** and 30% of **17**.

We, therefore, decided to prepare the desired dinucleoside from the *C(5′)*-aldo-adenosine **14** and the iminophosphorane derived from the azide **3**. Oxidation of **13** with *Dess–Martin*'s periodinane in CH_2Cl_2 [28] yielded 97% of **14**, while oxidation with *o*-iodoxybenzoic acid (IBX) in CH_2Cl_2 or in MeCN [29][30] provided **14** in a yield of only 10%. The aldehyde **14** must be used immediately for the aza-*Wittig* reaction; a sample of **14** epimerized within 24 h by 50% to the corresponding α-L-*lyxo* analogue (*cf.* [31] and refs. cit. therein).

The protected U*[N]A* dinucleoside **18** was synthesized by treating the *C(6)*-(azidomethyl)-uridine **3** with Me_3P, immediately followed by the reaction of the resulting iminophosphorane **3A** with aldehyde **14** and reduction of the resulting imines to **18** (*Scheme 3*). The benzamide **18** was debenzoylated to the amine **19**. The overall reaction proceeded in a mediocre yield (51%), reflecting the poor stability of **3**. The ^{1}H-NMR spectrum of **19** shows two *AB* systems corresponding to the C(8/I)–CH_2 and C(6/II)–CH_2 groups. C(8/I)–CH_2 resonates at 4.48 and 4.40 ppm ($J_{gem} = 12.0$ Hz), while C(6/II)–CH_2 resonates at 3.67 and 3.58 ppm ($J_{gem} = 14.4$ Hz; see *Table 6* in the *Exper. Part*). Dinucleoside **19** was desilylated to the trityl ether **20**, and detritylated by treatment with $Cl_2CHCOOH$ and Et_3SiH [32] to yield 65% of the silyl ether **21**.

Scheme 3

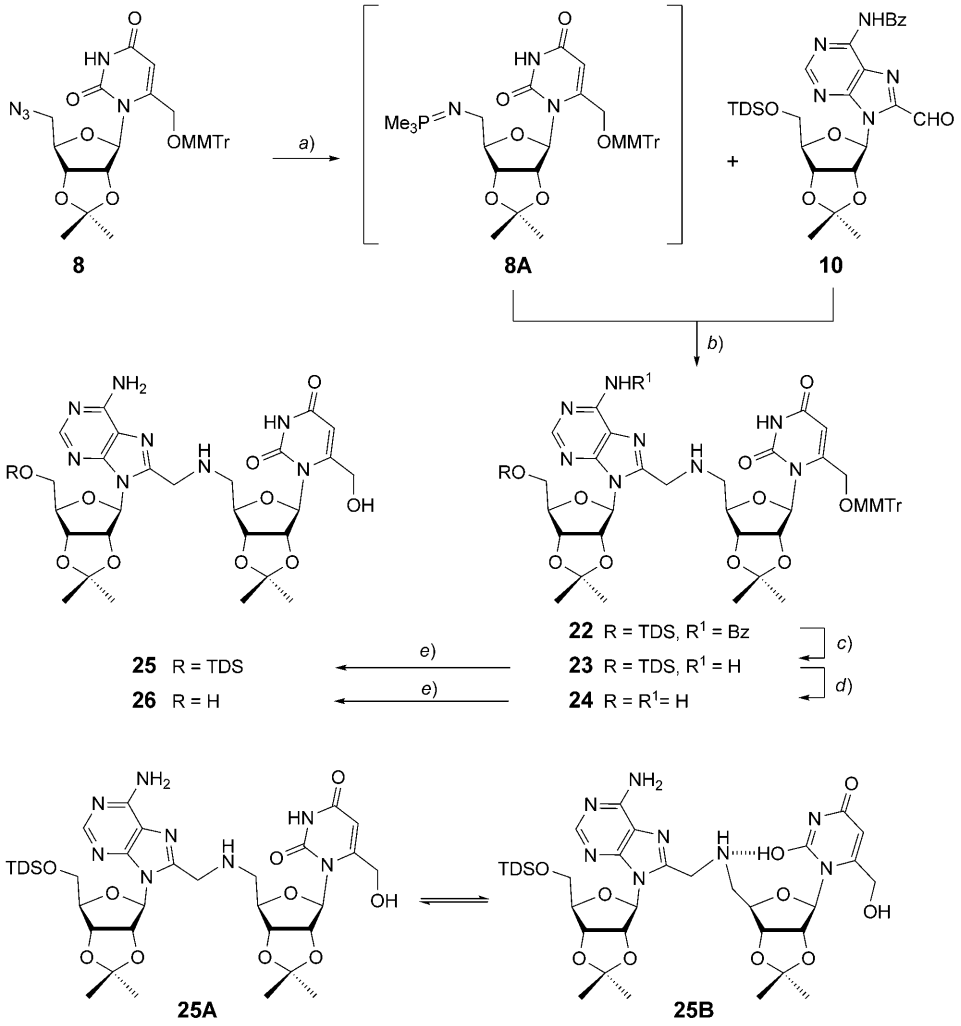


a) Me_3P, THF. *b*) 1. THF; 2. $NaBH_3CN$, AcOH, MeOH. *c*) MeONa, MeOH; 51% from **3**. *d*) HF·pyridine, THF; 73%. *e*) Et_3SiH, Cl_2CHCO_2H, CH_2Cl_2; 65%.

The synthesis of the fully protected A*[N]U* dinucleoside **22** was initiated by treating azide **8** with Me_3P, immediately followed by treatment of the resulting iminophosphorane **8A** with aldehyde **10** (*Scheme 4*). The resulting imines were directly reduced with $NaBH_3CN$ to yield **22** (75% from **8**). Similarly as observed during the synthesis of the *C(6)*-unsubstituted A*[N]U dinucleoside [9], formation of the imines required a high concentration of the mononucleosides. The ^{1}H-NMR spectrum of **22** shows two *AB* systems, one corresponding to the C(6/I)–CH_2 group resonating at 3.99 and 3.92 ppm ($J_{gem} = 12.6$ Hz) and the other corresponding to the C(8/II)–CH_2 group resonating at 4.17 and 4.13 ppm ($J_{gem} = 14.1$ Hz; see *Table 8* in the *Exper. Part*). Debenzoylation [7] of **22** yielded 68% of dinucleoside **23** that was desilylated with $(HF)_3 \cdot Et_3N$ in THF to the alcohol **24** (70%). Detritylation of **23** with $Cl_2CHCOOH$ and Et_3SiH yielded 73% of the silyl ether **25**; similarly, **24** yielded 78% of diol **26**.

Conformation of the Uridine and Adenosine Mononucleosides. The *C(6)*-substituted uridine derivatives **2** and **3** prefer a *syn*-conformation, as revealed by δ(H–C(2′)) of 5.12 and 5.23 ppm, respectively. Their substituents at C(6) do not significantly affect the (*N*)-conformation of the ribose ring. The *gg*/*gt*/*tg*-rotamer distribution for the *p*-toluenesulfonate **2** and the azide **3** shows a preference for the *gt*-rotamers (J(4′,5′a) +

Scheme 4



a) Me_3P, THF. *b*) 1. THF; 2. $NaBH_3CN$, AcOH, MeOH; 75% from **8**. *c*) MeONa, MeOH; 68%. *d*) $(HF)_3 \cdot Et_3N$, THF; 70%. *e*) Et_3SiH, Cl_2CHCO_2H, CH_2Cl_2; 73% of **25**; 78% of **26**.

$J(4',5'b) = 12.0-12.3$ Hz; see *Table 2* in the *Exper. Part*). Similarly to **2** and **3**, the monomethoxytrityl ethers **5**–**9** adopt a *syn*-conformation.

HO–C(5′) of **5** forms a partially persistent H-bond to C(2)=O, leading to a more extensive population of the *gg*-conformer ($J(4',5'a) + J(4',5'b) = 7.9$ Hz) [7] and to a less pronounced (*N*)-conformation of the ribose ring of **5** than for the corresponding azides **3** and **8**, *p*-toluenesulfonates **2** and **6**, and acetamide **9**. The *syn*-conformation is expected on account of the substitution at C(6). Similarly to the C(5′)–OAc and

C(5′)−SAc analogues [7], **6** shows a preference for the *gg*-conformation (*gg*/*gt*/*tg* 51:28:21; calculated according [7][9])[3]), suggesting that these esters are sterically less demanding than silyl ethers.

As for the analogous *C(6)*-unsubstituted *N*-ethylamine [9], there is no signal of the imido NH group of **7**. The OH signal of the tautomeric hydroxyimino structure of **7** in $CDCl_3$ is not visible (it is expected at *ca.* 11 ppm; see compound **25** below), whereas the NH resonates at 7.63 ppm[4]). The hydroxyimino structure of **7** is well-evidenced by the shift of ^{13}C-NMR signals of the uridine C-atoms (see *Table 3* in the *Exper. Part*). A δ(H−C(2′)) of 5.03 ppm and an E_O-conformation of **7** is due to the intramolecular H-bond. The E_O-conformation leads to a larger distance between H−C(2′) and the nucleobase, and is reflected by an upfield shift of the corresponding signal. J(4′,5′a) and J(4′,5′b) of < 1.0 Hz document an exclusive population of the *gg*-conformer.

The preference for the *gg*-rotamer of the acetamide **9** ($J(4',5'_{pro\text{-}S}) = J(4',5'_{pro\text{-}R}) =$ 3.6 Hz; *gg*/*gt*/*tg* 76:19:5) may be due to a partially persistent intramolecular H-bond between the amide N−H and the C(2)=O group. The conformation and, indirectly, the intramolecular H-bond is also evidenced by the CD spectrum of **9** in $CHCl_3$ (1 mM solution at 20°; data not shown), characterized by a negative *Cotton* effect with a minimum at 270 nm [33], similarly as for the *C(6)*-unsubstituted acetamide [9]. The *C(6)*-monomethoxytrityl azide **8** appears to prefer the *gt*-rotamer (*gg*/*gt*/*tg* 7:61:32). For this compound, there is no longer a correlation between chemical shift and coupling constant that formed the basis of the assignment to $H_{pro\text{-}S}$−C(5′) and $H_{pro\text{-}R}$−C(5′)[3]); we based the (tentative) *gt*/*tg*-rotamer ratio on the coupling constant and on the *gauche* effect that favours the *gt*-conformer.

The alcohol **13** shows an exclusive preference for the *gg*-conformation (J(4′,5′a) = J(4′,5′b) < 1.0 Hz), the (*S*)-conformation of the furanose ring (J(1′,2′)/J(3′,4′) = 2.8), and an upfield shift for H−C(2′)) (5.29 ppm), as it is typical for compounds possessing an intramolecular H-bond from HO−C(5′) to N(3) [7]. The *C(8)*-substituted aldehyde **14** is expected to adopt a *syn*-conformation (δ(H−C(2′)) = 5.53 ppm), and a 1:1 (*S*)/(*N*)-equilibrium may evidence an interaction of N(3) with the CHO group. The *C(8)*-substituted *p*-toluenesulfonate **15** is also expected to adopt a *syn*-conformation, in spite of the somewhat low value for δ(H−C(2′)) of 5.47 ppm. The *gg*/*gt*/*tg* rotamer distribution cannot be assigned due to poorly resolved signals. The N^3,5′-cyclonucleosides **16** and **17** are characterized by δ(H−C(2′)) of 4.88 and 4.70 ppm, respectively, and by an E_O-conformation. The structure of **17** corresponds to a tautomer of the originally proposed structure, as evidenced by the NH_2 group resonating as two *doublet*s at 10.42 and 7.59 ppm ($J = 6$ Hz), a cross-peak between these two signals in the DQF-COSY spectrum, and a downfield shift for the *N*-benzoyl C=O group, resonating at 180.9 ppm, similarly as the corresponding C=O group of **16**. AM1 Calculations suggest a NH···O=C H-bond between the amino and the *N*-CHO group of **17**. The 1,3,5-oxadiazepane ring of **16** adopts an envelope (O below the ring plane) and that of

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[3]) The *gg*/*gt*/*tg* ratio is based on the assignment of the ^{1}H-NMR signals to $H_{pro\text{-}S}$−C(5′) and $H_{pro\text{-}R}$−C(5′). We assumed that the more highly shielded H−C(5′), showing the larger J(4′,5′) coupling, corresponds to $H_{pro\text{-}R}$−C(5′).

[4]) The *triplet* at 6.15 ppm of the corresponding *C(6)*-unsubstituted analogue that we had assigned to the OH group [9] should be assigned to the NH group.

17 a chair conformation (O below and N(5) above the ring plane), similarly as the conformations of closely related cyclo-nucleosides in the solid state [34][35].

*Association and Conformation of the U**[N]*A** *and A**[N]*U** *Dinucleosides in* $CDCl_3$. The self-association of the U*[N]A* dinucleosides **19** and **21**, and of the A*[N]U* sequence isomers **23**–**25** was investigated by analysing conformational aspects and the concentration dependence of the chemical shift of H–N(3/II) of **19** and **21**, and H–N(3/I) of **23**–**25** (shift/concentration curves (SCCs)), as it was described for aminomethylene-linked U*[N]A and A*[N]U analogues [9].

A) *U**[N]*A** *Dinucleosides.* The SCC of the tritylated and silylated U*[N]A* dinucleoside **19** shows a curve progression typical of linear associates and cyclic duplexes, characterized by a weak bending at low concentration and a continued, slower increase at higher concentrations (*Fig. 1*). Unexpectedly, the association is weaker than that of the *C(8)*-unsubstituted **19H** [9]. The SCC of **21** shows a curve progression typical of cyclic duplexes and a minor contribution of linear associates, characterized by a strong bending at low concentrations and an incomplete plateau formation at higher concentrations.

The formation of *Watson–Crick* base-paired cyclic duplexes should lead to a plateau at 13.3 and 12.75 ppm for *C(8/I)*-unsubstituted and -substituted U*[X]A(*) dinucleosides, respectively [1]. The chemical shifts of H–N(3/II) at a 30 mM

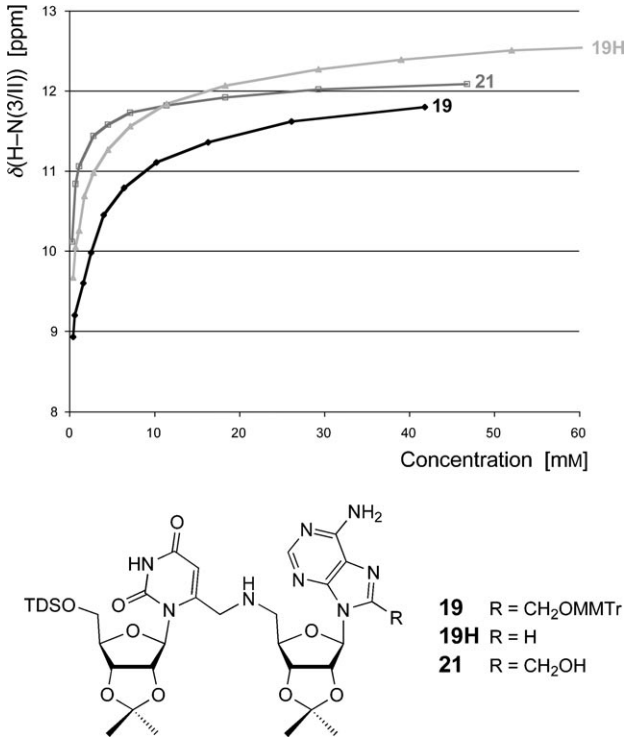

Fig. 1. *Shift/concentration curves* (SCCs) *of the U**[N]*A*(*) *dinucleosides* **19**, **19H**, *and* **21** *in* $CDCl_3$ *solution*

concentration of **19H** (12.27 ppm) and **19** (11.84 ppm) suggest mixtures of linear associates and of cyclic duplexes possessing mostly *Hoogsteen*-type base pairs. The weaker association of **19** than of **19H** is rationalized by an unfavourable steric interaction of the bulky trityl group in the *Hoogsteen*-type base-paired cyclic duplexes of **19**. The (incomplete) plateau at *ca.* 12.1 ppm of **21** suggests a dominant formation of cyclic duplexes and *Hoogsteen*-type base pairing.

The SCCs of **19** and **21** (*Fig. 1*) were analysed numerically by the method proposed by *Gutowsky* and *Saika* [36], including a value of 7.70 ppm for a 0.001 mM solution, corresponding to the chemical shift of the monoplex, as deduced from δ(H–N(3)) of uridine derivatives [7][9]. Inclusion of this value significantly reduced the variance of K_{ass} (*Table 1*). The thermodynamic parameters were determined by *van't Hoff* analysis[5]) of the ^{1}H-NMR spectra [9] recorded of *ca.* 2–5 mM solutions in $CDCl_3$ in intervals of 10° and in the temperature range of 7 to 50°.

Table 1. *Association Constants* K_{ass} *and Extrapolated Chemical Shifts of the Monoplexes* ($c = 0$ mM) *and Duplexes* ($c = \infty$) *as Calculated from the Concentration Dependence of* δ*(HN(3)) in* $CDCl_3$ *at 295 K for the U*[N]A* Dinucleosides* **19** *and* **21**, *and the A*[N]U* Dinucleosides* **23**–**25**, *and Determination of the Thermodynamic Parameters of* **19**, **21**, *and* **23** *by* van't Hoff *Analysis of the Temperature Dependence of* δ*(HN(3)) for* ca. *2–5-mM Solutions in* $CDCl_3$ *at 7–50° K*

Dinucleoside	K_{ass} [M^{-1}]	$\delta_{monoplex}$ [a]) [ppm]	δ_{duplex} [b]) [ppm]	$-\Delta G_{295}$ [c]) [kcal/mol]	$-\Delta H$ [kcal/mol]	$-\Delta S$ [cal/mol·K]
U*[N]A* series						
19 [d])	386 ± 161	7.81 ± 0.19	12.50 ± 0.32	3.5	9.0	19.5
21 [d])	4428 ± 613	7.66 ± 0.10	12.29 ± 0.06	4.9	12.1	26.2
A*[N]U* series						
23 [d])	5662 ± 562	7.63 ± 0.08	13.75 ± 0.04	5.1	15.3	34.8
24 [e])	4768 ± 288	9.97 ± 0.03	13.14 ± 0.20	5.0		
25	not determined					

[a]) Extrapolated for $c = 0$. [b]) Extrapolated for $c = \infty$. [c]) Calculated from K_{ass}. [d]) Including a value of 7.70 ppm for a 0.001-mM solution. [e]) Including a value of 10.00 ppm for a 0.001-mM solution.

The protected U*[N]A* dinucleoside **19** and the corresponding detritylated alcohol **21** associate more weakly ($K_{ass} = 386$ and 4428 M^{-1}, resp.; *Table 1*) than the corresponding U*[O]A* dinucleosides ($K_{ass} = 1611$ and 6822 M^{-1}, resp. [7]), but more strongly than the corresponding U*[S]A* dinucleosides ($K_{ass} = 227$ and 1259 M^{-1}, resp. [7]). In agreement with the SCC, a $-\Delta H$ value of 9.0 kcal/mol for **19** evidences the formation of linear associates and a minor amount only of cyclic duplexes (*Table 1*). The $-\Delta H$ value of 12.1 kcal/mol of **21** is in agreement of the predominant formation of cyclic duplexes. This corresponds to an average strength of an intermolecular H-bond of *ca.* 3.0 kcal/mol, and suggests a strong preference for *Hoogsteen*-type base-pairing, in

[5]) A *caveat* is in order. Neither the condition of an equilibrium exclusively between monoplex and cyclic duplex, nor of the dependence of the chemical shift of H–N(3) exclusively upon H-bonding are fulfilled. We give the $-\Delta H$ and $-\Delta S$ values to facilitate a semiquantitative comparison of their contribution to the association.

agreement with the SCC. In this respect, these dinucleosides behave similarly to the corresponding oxymethylene analogues.

^{1}H-NMR Data characterizing the conformation for 20–30 mM solutions of the U*[N]A* dinucleosides **19**–**21** in $CDCl_3$ are compiled in *Table 6* in the *Exper. Part*. The adenosine moiety (unit I) of **19**–**21** adopts a *syn*-conformation and a *ca.* 1:1 (*S*)/(*N*)-equilibrium. The *J*(4′,5′/I) values indicate a 80:20 *gg*/*gt*-orientation of the linker of **19** and a 65:28:7 *gg*/*gt*/*tg*-orientation of the linker of **21**. This evidences that both the *gg*- and the *gt*-conformers of **21** form cyclic duplexes, while the *tg*-conformers can form only linear associates. The uridine moiety (unit II) of **19**–**21** adopts a (*N*)-conformation. The $HOCH_2$ group of **20** prefers a *gg*/*gt*-orientation (*gg*/*gt*/*tg* 56:36:8), while the silyloxymethyl group of **21** adopts a *gt*/*tg*-orientation (*gg*/*gt*/*tg* 6:57:37).

B) *A**[N]*U** *Dinucleosides*. The SCC*s* of the A*[N]U* dinucleosides **23** and **24** show a curve progression typical of cyclic duplexes and reach a plateau at a concentration of 10 mM (*Fig. 2*). Their association is stronger than that of the *C(6)*-unsubstituted analogues **23H** and **24H** [9] that prefer an *anti*-orientation of the uridine moiety at concentrations where they do not yet associate. The SCC of the silylated (but no longer methoxytritylated) dinucleoside **25** shows a curve progression with a weak bending at low concentrations (< 5 mM) and a steady increase above a concentration of 5 mM: a straight line showing no tendency for the formation of a plateau. This may be rationalized by assuming a weak association of a monoplex to form linear duplexes, and, conceivably, triplexes involving an intermolecular H-bond of the $HOCH_2$ group. The monomer cannot be the imido tautomer **25A**, as this tautomer would require a strong curvature of the SCC at low concentrations, tending towards a chemical shift of *ca.* 7.7 ppm at 0 mM, as it is typical for the monoplex. This observation strongly suggests that the monoplex is the hydroxyimino tautomer **25B**, as it was already observed for the monomeric ethylamino derivative **7**. HO–C(2/I) of the hydroxyimino tautomer **25B** is engaged in a strong intramolecular H-bond to the amino group of the linker and, therefore, expected to resonate at low field (> 10 ppm). Thus, **25** forms an equilibrium between the hydroxyimino tautomer **25B** (dominant at low concentrations) and linear duplexes possessing the imido structure required for base pairing. The weak association (estimated $K_{ass} \leq 100\ M^{-1}$) indicates that the energy gained by forming a base pair (12–15 kcal/mol) is only slightly larger than the energy gained by tautomerisation and formation of the intramolecular OH···N H-bond. The H–N(3/I) signal of the diol **26** is hidden due to coalescence preventing the determination of the SCC. The position of the plateau of **23** (13.5 ppm) and **24** (13.0 ppm) evidences *Watson–Crick*-type base pairs.

As the curve of **25** does not show a plateau, it cannot be analysed numerically by the method of *Gutowsky* and *Saika*. The lowest variance was obtained when a value of 7.7 and 10.0 ppm was included for the SCC of **23** and **24**, respectively, at a concentration of 0.001 mM, evidencing that the monomer of **23** adopts completely the imido structure, whereas the monomer of **24** prefers the hydroxyimino tautomer. The precise role of C(6/I)–CH_2OH of **25** and HO–C(5′/II) of **24** in favouring the H-bonded hydroxyimino tautomer is not clear, while it certainly increases the polarity of the dinucleoside. The protected A*[N]U* dinucleoside **23** and the tritylated alcohol **24** associate more strongly (K_{ass} = 5662 and 4768 M^{-1}, resp.; *Table 1*) than the *C(6/I)*-unsubstituted **23H**

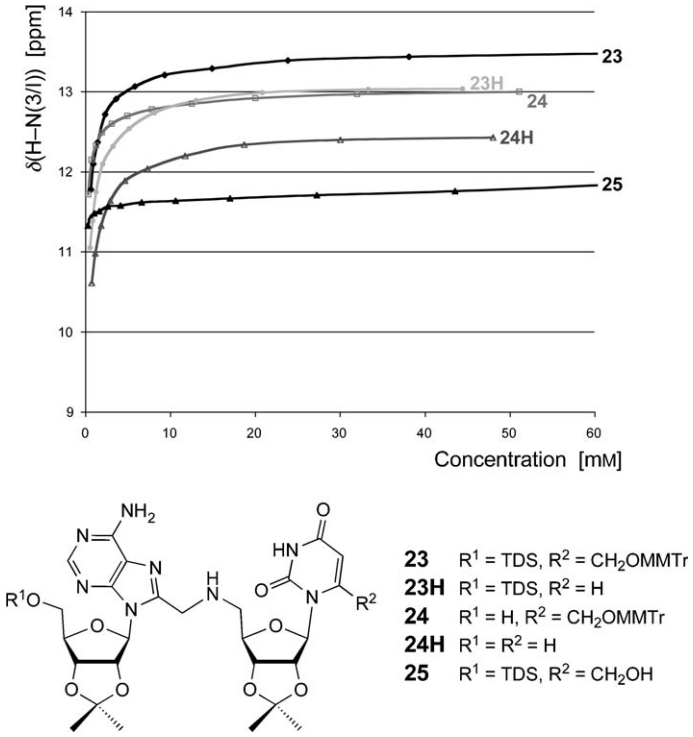

Fig. 2. *Shift/concentration curves* (SCCs) *of the A**[N]*U*(*) *Dinucleosides* **23**–**25**, **23H**, *and* **24H** *in* $CDCl_3$ *solution*

and **24H** ($K_{ass} = 3454$ and 2429 M^{-1}, resp. [9]) and the corresponding A*[s]U* dinucleosides ($K_{ass} = 1334$ and 658 M^{-1}, resp. [7]).

As the chemical shift of H–N(3/I) of monomeric **24** depends strongly on the position of the equilibrium between the tautomers, we could only perform a *van't Hoff* analysis for **23**. The $-\Delta H$ value for **23** (15.3 kcal/mol; *Table 1*) agrees well with the formation of cyclic duplexes by *Watson–Crick*-type H-bonding (*ca.* 4.0 kcal/mol per intermolecular H-bond). A vapour-pressure determination of the apparent molecular weight of **25** in 1, 5, and 20 mM solutions led to a degree of association of 0.92, 1.38, and 1.67, respectively, confirming the formation of linear duplexes only.

^{1}H- and ^{13}C-NMR data characterizing the conformation for 20–30 mM solution of the A*[N]U* dinucleosides **22**–**26** in $CDCl_3$ are compiled in *Tables 8* and *9* in the *Exper. Part*. The chemical shifts for uridine C-atoms reveal the imido structure of all these dinucleosides. The chemical shift of 8.30–8.32 ppm for H–C(2/II) of the adenosine moiety of **23** and **24** is in agreement with *Watson–Crick*-type pairing [7], while values of 8.19 and 8.08 ppm for H–C(2/II) of **25** and **26** hint rather at *Hoogsteen*-type base-pairing. The expected *syn*-conformation of the uridine unit I of **22**–**26** is evidenced by the downfield shift of H–C(2′/I), which is influenced by the (*N*)/(*S*)-equilibrium. Thus, **22**, **25**, and **26** ($\delta = 5.16$–5.17 ppm) strongly prefer the (*N*)-conformation, while **23** and **24** ($\delta = 5.27$ and 5.24 ppm, resp.) adopt a *ca.* 1:1 (*N*)/(*S*)-

equilibrium. For the calculation of the conformational preference of the linker, we assume that $H_{pro\text{-}R}-C(5')$ is the H–C(5′/I) possessing the larger vicinal coupling, *i.e.*, it is the more strongly shielded H–C(5′/I) of **23**, but the more strongly deshielded H–C(5′/I) of **22**, **25**, and **26**. The two H–C(5′/I) of **24** are almost isochronous and show a mean coupling of 4.3 Hz, suggesting similar couplings as observed for **25** (5.5 and 2.8 Hz). The linker of the benzamide **23** adopts a 48:37:14 *gg*/*gt*/*tg*-orientation, whereas the linker of **23**–**26** adopts only *gg*- and *gt*-orientations (*gg*/*gt* 82:18 (**23**), 58:42 (**24** and **25**), and 36:64 (**26**)). Considering that the ^{1}H-NMR spectra were recorded at a concentration between 20 and 30 mM, when the formation of cyclic duplexes is nearly complete, the relatively high proportion of the *gt*-conformer of **23** and **24** must mean that this conformer also forms cyclic duplexes. The linear duplexes of **25** avoid the *tg*-conformation.

The adenosine moiety (unit II) of the silyloxy derivatives **23** and **25** prefers the (*N*)-conformation and is characterized by a *ca*. 1:1 *gt*/*tg*-mixture of conformers. The adenosine moiety of the alcohols **24** and **26** shows the typical (*S*)- and the exclusive *gg*-conformation resulting from the persistent intramolecular C(5′)–OH···N(3) H-bond [1][34].

Conclusions. – As it is typical also for the type and the strength of the association of ONIBs possessing a different linker, the aminomethylene-linked dinucleosides depend on the base sequence, the orientation of the linker relative to the furanose ring, and the orientation of the nucleobases. However, monoplexes of the aminomethylene-linked A*[N]U* dinucleosides may form significant amounts of their intramolecularly H-bonded hydroxyimino tautomer, while their imido tautomers may associate at higher concentrations and lead to either linear and/or cyclic duplexes. The equilibrium of tautomers at lower concentrations is strongly affected by the protection of the OH groups. Although the additional substituent in unit I of the aminomethylene-linked dinucleosides does lead to a higher population of the *syn*-conformer, it will not, for A*[N]U* sequence isomers, automatically favour the formation of cyclic duplexes, as compared to the A*[N]U analogues. For the first time, we obtained evidence that both the *gg*- and the *gt*-conformers of dinucleosides (**21**, **23**, and **24**) form cyclic duplexes.

The U*[N]A(*) dinucleosides pair more strongly than the U*[s]A(*) analogues, but less well than the U*[O]A(*) analogues [7]. This may reflect a conformational aspect in that pairing of U*[O]A(*) dinucleosides involves a *gg*-orientation of the linker, pairing of the U*[N]A(*) analogues *gg*- and *gt*-orientations, and pairing of the U*[s]A(*) analogues a *gt*-orientation.

We thank *Syngenta AG*, Basel, for generous financial support.

Experimental Part

General. See [9].

5′-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-O-isopropylidene-6-{[(4-methylphenylsulfonyl)-oxy]methyl}uridine (**2**). A soln. of **1** [7] (280 mg, 0.61 mmol) in CH_2Cl_2 (2 ml) was cooled to 0°, treated with DABCO (138 mg, 1.23 mmol) and TsCl (174 mg, 0.92 mmol), stirred for 10 min, and diluted with sat. NH_4Cl soln. After extraction with CH_2Cl_2, the combined org. layers were dried ($MgSO_4$) and evaporated. FC (cyclohexane/AcOEt 2:1 → AcOEt) gave **2** (322 mg, 87%). Colourless foam. R_f

(cyclohexane/AcOEt 1:1) 0.52. $[\alpha]_D^{25} = -1.2$ ($c = 0.54$, $CHCl_3$). IR (ATR): 3182*w* (br.), 2965*w*, 2875*w*, 1709*s*, 1636*w*, 1466*w*, 1427*w*, 1385*m*, 1245*s*, 1209*m*, 1187*m*, 1138*w*, 1091*w*, 1065*m*, 1024*m*, 980*w*, 960*w*, 911*w*, 895*w*, 866*m*, 842*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 8.29 (br. *s*, NH); 7.84 (*d*, $J = 8.4$, 2 arom. H); 7.36 (*d*, $J = 8.1$, 2 arom. H); 2.46 (*s*, Me); 1.59 (*sept.*, $J = 6.9$, Me_2CH); 1.56, 1.34 (2*s*, Me_2C); 0.85 (*d*, $J = 6.9$, Me_2CH); 0.83, 0.82 (2*s*, Me_2CSi); 0.07, 0.06 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 145.81, 132.03 (2*s*); 129.96 (2*d*); 128.10 (2*d*); 113.76 (*s*, Me_2C); 34.13 (*d*, Me_2CH); 27.31, 25.42 (2*q*, Me_2C); 25.36 (*s*, Me_2CSi); 21.83 (*q*, Me); 20.38 (*q*, Me_2CSi); 18.53 (*q*, Me_2CH); −3.20 (*q*, Me_2Si). HR-MALDI-MS: 649.2016 (28, $[M+K]^+$, $C_{28}H_{42}KN_2O_9SSi^+$; calc. 649.2017), 633.2272 (100, $[M+Na]^+$, $C_{28}H_{42}N_2NaO_9SSi^+$; calc. 633.2278).

Table 2. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Uridine Monomers* **2**, **3**, *and* **6**–**9** *in $CDCl_3$*

	2	**3**	**6**	**7**	**8**	**9**
H–C(5)	5.72	5.81	5.68	5.82	5.73	5.77
CH_a–C(6)	4.97	4.28	3.97	3.98	4.04	4.03
CH_b–C(6)	4.90	4.28	3.92	3.98	3.97	3.93
H–C(1′)	5.48	5.62	5.61	5.53	5.66	5.51
H–C(2′)	5.12	5.23	5.10	5.03	5.20	5.17
H–C(3′)	4.76	4.81	4.76[a])	4.99	4.84	4.78
H–C(4′)	4.10	4.13	4.23–4.20	4.07	4.08	4.08
H_a–C(5′)	3.75	3.78	4.22	3.99	3.60	3.72
H_b–C(5′)	3.70	3.74	4.19	3.89	3.49	3.41
$J(H_a,H_b)$	13.2	[b])	12.3	[b])	12.6	12.6
J(1′,2′)	< 1.0	1.2	< 1.0	< 1.0	< 1.0	2.1
J(2′,3′)	6.3	6.3	6.6	6.3	6.3	6.6
J(3′,4′)	4.5	4.5	4.2	< 1.0	4.8	4.8
J(4′,5′a)	5.1	5.1	3.9	0	7.8	3.6
J(4′,5′b)	6.9	7.2	5.4	0	4.8	3.6
J(5′a,5′b)	10.8	10.8	10.2	12.6	12.3	14.1

[a]) The signal of H–C(3′) shows an additional splitting due to virtual coupling. [b]) Not assigned.

6-(Azidomethyl)-5′-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′*-O-*isopropylideneuridine* (**3**). A soln. of **2** (500 mg, 0.82 mmol) in dry MeCN (10 ml) was treated with NaN_3 (532 mg, 8.2 mmol) and stirred at 80° for 3 h. The soln. was cooled to 23° and filtered. Evaporation and drying gave **3** (324 mg, 82%). Colourless foam. R_f (AcOEt) 0.85. $[\alpha]_D^{25} = -12.4$ ($c = 1.08$, $CHCl_3$). IR (ATR): 3195*w* (br.), 3054*w* (br.), 2957*w*, 2867*w*, 2110*m*, 1692*s*, 1626*w*, 1460*m*, 1379*m*, 1329*w*, 1251*m*, 1210*m*, 1158*m*, 1132*m*, 1082*s*, 997*w*, 927*w*, 875*m*, 830*s*, 777*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.03 (br. *s*, NH); 1.60 (*sept.*, $J = 6.9$, Me_2CH); 1.54, 1.34 (2*s*, Me_2C); 0.86 (*d*, $J = 6.9$, Me_2CH); 0.85, 0.83 (2*s*, Me_2CSi); 0.08, 0.07 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 113.74 (*s*, Me_2C); 34.15 (*d*, Me_2CH); 27.28, 25.38 (2*q*, Me_2C); 25.38 (*s*, Me_2CSi); 20.42, 20.37 (2*q*, Me_2CSi); 18.53 (*q*, Me_2CH); −3.20 (*q*, Me_2Si). HR-MALDI-MS: 504.2257 (100, $[M+Na]^+$, $C_{21}H_{35}N_5NaO_6Si^+$; calc. 504.2249).

2′,3′-O-*Isopropylidene-6-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-5′*-O-*(4-methylphenylsulfonyl)uridine* (**6**). A soln. of **5** [7] (3.88 g, 6.62 mmol) in dry pyridine (20 ml) was cooled to 0°, treated with TsCl (1.89 g, 9.93 mmol), and stirred for 6 h at 0–23°. The mixture was diluted with CH_2Cl_2 (80 ml), washed with a 1M H_2SO_4 (2 × 70 ml) and sat. $NaHCO_3$ soln. (70 ml), dried ($MgSO_4$), and evaporated. FC (cyclohexane/AcOEt 3:1) gave **6** (4.2 g, 86%). Colourless foam. R_f (cyclohexane/AcOEt 1:1) 0.34. $[\alpha]_D^{25} = +12.7$ ($c = 0.32$, $CHCl_3$). IR (ATR): 3182*w* (br.), 3054*w*, 3024*w*, 2989*w*, 2930*w*, 2843*w*, 1689*s*, 1625*w*, 1607*w*, 1509*m*, 1492*w*, 1448*m*, 1381*m*, 1371*m*, 1300*w*, 1250*m*, 1211*m*, 1175*s*, 1157*m*, 1095*m*, 1063*s*, 1032*m*, 972*s*, 930*w*, 899*w*, 877*m*, 828*s*, 812*m*, 782*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally,

Table 3. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Uridine Monomers* **2**, **3**, *and* **6**–**9** *in* $CDCl_3$

	2	**3**	**6**	**7**	**8**	**9**
C(2)	149.61	150.01[a])	150.53	148.88	150.60	151.08
C(4)	161.71	162.04	163.25	171.70	163.21	162.68
C(5)	104.58	103.68	102.86	107.03	103.06	103.31
C(6)	147.44	149.47[a])	152.39	154.62	152.27	152.26
CH_2–C(6)	65.35	51.07	62.04	62.69	62.28	62.29
C(1′)	91.75	91.70	92.22	92.90	91.93	91.70
C(2′)	83.94	84.06	84.62	80.22	84.62	83.50
C(3′)	81.80	81.86	81.71	79.71	82.46	80.71
C(4′)	89.42	89.52	86.54	84.21	87.21	84.86
C(5′)	63.71	63.73	70.19	60.46	52.66	40.95

[a]) Assignments may be interchanged.

8.66 (br. *s*, NH); 7.74 (*d*, *J* = 8.1, 2 arom. H); 7.47–7.42 (*m*, 4 arom. H); 7.37–7.23 (*m*, 10 arom. H); 6.86 (*d*, *J* = 8.7, 2 arom. H); 3.81 (*s*, MeO); 2.41 (*s*, Me); 1.40, 1.27 (2*s*, *Me*$_2$C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 158.97, 144.74, 142.99, 142.88, 133.92, 132.69 (6*s*); 130.23 (4*d*); 129.54 (2*d*); 128.11 (2*d*); 128.01 (2*d*); 127.98 (2*d*); 127.43 (4*d*); 113.82 (*s*, Me$_2$*C*); 113.36 (2*d*); 88.23 (*s*, Ph$_2$*C*); 55.19 (*q*, *Me*O); 26.90, 25.13 (2*q*, *Me*$_2$C); 21.56 (*q*, Me). HR-MALDI-MS: 779.2053 (47, $[M+K]^+$, $C_{40}H_{40}KN_2O_{10}Si^+$; calc. 779.2035), 763.2311 (100, $[M+Na]^+$, $C_{40}H_{40}N_2NaO_{10}Si^+$; calc. 763.2296). Anal. calc. for $C_{40}H_{40}N_2O_{10}S$ (740.83): C 64.85, H 5.44, N 3.78; found: C 64.73, H 5.59, N 3.63.

5′-Deoxy-5′-(ethylamino)-2′,3′-O-*isopropylidene-6-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-uridine* (**7**). A soln. of **6** (150 mg, 0.20 mmol) in dry DMF (3 ml) was treated with $EtNH_2$ (70% in H_2O, 13.0 µl, 0.18 mmol), and stirred at 80° for 2 h. The soln. was cooled to 23° and evaporated. FC (AcOEt/MeOH 50:1 → 20:1) gave **7** (108 mg, 88%). Colourless foam. R_f (AcOEt/MeOH 10:1) 0.29. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.68–7.58 (br. *s*, HN–C(5′)); 7.45 (br. *d*, *J* ≈ 8.4, 4 arom. H); 7.31 (*t*, *J* ≈ 8.4, 4 arom. H); 7.27 (*d*, *J* = 8.7, 2 arom. H); 7.22 (br. *t*, *J* ≈ 7.8, 2 arom. H); 6.83 (*d*, *J* = 8.7, 2 arom. H); 3.77 (*s*, MeO); 3.50–3.46 (*m*, CH_2N); 1.23, 1.17 (2*s*, Me$_2$C); 1.14 (*t*, *J* = 7.2, *Me*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 158.73, 143.25, 143.14, 134.22 (4*s*); 130.17–127.26 (several *d*); 114.87 (*s*, Me$_2$*C*); 113.30 (2*d*); 87.77 (*s*, Ph$_2$*C*); 55.26 (*q*, MeO); 36.72 (*t*, CH_2N); 27.15, 25.18 (2*q*, *Me*$_2$C); 14.67 (*q*, *Me*CH_2N). HR-MALDI-MS: 652.2431 (16, $[M+K]^+$, $C_{35}H_{39}KN_3O_7^+$; calc. 652.2420), 636.2696 (34, $[M+Na]^+$, $C_{35}H_{39}N_3NaO_7^+$; calc. 636.2680), 614.2875 (100, $[M+H]^+$, $C_{35}H_{40}N_3O_7^+$; calc. 614.2861).

5′-Azido-5′-deoxy-2′,3′-O-*isopropylidene-6-{[(4-methoxyphenyl)diphenylmethoxy]methyl}uridine* (**8**). A soln. of **6** (1.02 g, 1.38 mmol) in dry DMF (8 ml) was treated with NaN_3 (1.79 g, 27.6 mmol) and NaI (1.03 g, 6.9 mmol) and stirred at 80° for 6 h. The soln. was cooled to 23°, diluted with AcOEt (50 ml), washed with H_2O (5 × 50 ml), dried ($MgSO_4$), and evaporated to give **8** (800 mg, 95%). Colourless foam. R_f (AcOEt) 0.81. $[\alpha]_D^{25} = +12.0$ (*c* = 0.37, $CHCl_3$). IR (ATR): 3195*w* (br.), 3059*w*, 2989*w*, 2934*w*, 2098*m*, 1688*s*, 1607*w*, 1509*m*, 1490*w*, 1447*m*, 1381*m*, 1298*w*, 1251*s*, 1212*m*, 1179*m*, 1157*m*, 1093*m*, 1064*s*, 1033*m*, 978*w*, 905*m*, 876*m*, 831*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 10.00 (br. *s*, NH); 7.49–7.44 (*m*, 4 arom. H); 7.37–7.22 (*m*, 8 arom. H); 6.86 (*d*, *J* = 7.2, 2 arom. H); 3.81 (*s*, MeO); 1.44, 1.30 (2*s*, Me$_2$C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 158.87, 143.05, 142.89, 133.93 (4*s*); 130.26–127.35 (several *d*); 113.91 (*s*, Me$_2$*C*); 113.34 (2*d*); 88.29 (*s*, Ph$_2$*C*); 55.30 (*q*, MeO); 27.20, 25.36 (2*q*, *Me*$_2$C). HR-MALDI-MS: 650.2006 (60, $[M+K]^+$, $C_{33}H_{33}KN_5O_7^+$; calc. 650.2012), 634.2262 (100, $[M+Na]^+$, $C_{33}H_{33}N_5NaO_7^+$; calc. 634.2272).

5′-Acetamido-5′-deoxy-2′,3′-O-*isopropylidene-6-{[(4-methoxyphenyl)diphenylmethoxy]methyl}uridine* (**9**). A suspension of **8** (200 mg, 0.33 mmol), 10% Pd/C (30 mg), and Ac_2O (0.04 ml, 0.66 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 → AcOEt) gave **9** (122 mg, 59%). Colourless foam. R_f (AcOEt/MeOH 10:1) 0.69. $[\alpha]_D^{25} = -26.6$ (*c* = 0.32, $CHCl_3$). IR (ATR): 3318*w* (br.), 3186*w* (br.), 3056*w*, 2986*w*, 2927*w*,

2830*w*, 1692*s*, 1608*m*, 1538*w*, 1509*m*, 1447*m*, 1373*s*, 1299*w*, 1248*s*, 1210*m*, 1178*m*, 1156*m*, 1091*m*, 1062*s*, 978*m*, 901*w*, 876*w*, 830*m*, 796*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 8.82 (br. *s*, NH); 7.48–7.43 (*m*, 4 arom. H); 7.38–7.24 (*m*, 8 arom. H); 6.88–6.83 (*m*, 2 arom. H); 6.56 (*dd*, $J = 6.6$, 3.0, AcN*H*); 3.81 (*s*, MeO); 1.99 (*s*, AcN); 1.37, 1.27 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 170.58 (*s*, Me*C*=O); 158.89, 142.96, 142.84, 133.84 (4*s*); 130.24–127.40 (several *d*); 114.32 (*s*, Me_2C); 113.35 (2*d*); 88.30 (*s*, Ph_2C); 55.31 (*q*, MeO); 27.28, 25.35 (2*q*, Me_2C); 23.15 (*q*, *Me*C=O). HR-MALDI-MS: 666.2205 (32, $[M+K]^+$, $C_{35}H_{37}KN_3O_8^+$; calc. 666.2212), 650.2475 (100, $[M+Na]^+$, $C_{35}H_{37}N_3NaO_8^+$; calc. 650.2473).

N^6-*Benzoyl-9-(2,3*-O-*isopropylidene-β*-D-ribo-*pentodialdo-1,4-furanosyl)-8-{[(4-methoxyphenyl)diphenylmethoxy]methyl}adenine* (**14**). A soln. of **13** [7] (300 mg, 0.42 mmol) in CH_2Cl_2 (3 ml) was treated with *Dess–Martin* periodinane (15 wt.-% in CH_2Cl_2, 0.8 ml, 0.42 mmol), stirred for 15 min, and treated with sat. $Na_2S_2O_3$ soln. After extraction with CH_2Cl_2, the combined org. layers were dried ($MgSO_4$) and evaporated to afford **14** (290 mg, 97%). Upon standing for 1 d, **14** epimerized to a 1:1 mixture of **14** and its α-L-*lyxo*-analogue; the ^{1}H-NMR spectrum showed only signals of **14**, but the ^{13}C-NMR spectrum (recorded 19 h later) a 1:1 mixture of diastereoisomers. Yellow foam. R_f (cyclohexane/AcOEt 1:1) 0.48. IR (ATR): 3229*w* (br.), 3054*w*, 3024*w*, 2989*w*, 2953*w*, 2931*w*, 2830*w*, 1702*w*, 1608*m*, 1583*m*, 1530*w*, 1509*m*, 1487*m*, 1456*m*, 1448*m*, 1430*w*, 1384*w*, 1374*w*, 1341*w*, 1298*w*, 1250*s*, 1212*m*, 1179*m*, 1156*w*, 1092*m*, 1062*s*, 1032*m*, 975*w*, 907*m*, 880*w*, 866*w*, 831*w*, 797*w*, 764*w*, 727*s*, 704*s*, 660*w*, 646*w*, 631*w*, 608*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 8.94 (br. *s*, NH); 8.00 (*d*, $J = 7.5$, 2 arom. H); 7.62–7.22 (*m*, 15 arom. H); 6.85 (*d*, $J = 8.7$, 2 arom. H); 3.78 (*s*, MeO); 1.54, 1.39 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$; 1:1 mixture of diastereoisomers): see *Table 5*; additionally, 164.30 (*s*, NC=O); 158.76, 143.18/143.10 (2*s*), 134.11/133.49 (2*s*); 132.77 (br. *d*); 130.52–127.09 (several *d*); 113.72 (*s*, Me_2C); 113.37/113.20 (2*d*); 88.23 (*s*, Ph_2C); 55.38/55.14 (2*q*, MeO); 26.71, 25.34/25.27 (3*q*, Me_2C). HR-MALDI-MS: 750.2332 (14, $[M+K]^+$, $C_{41}H_{37}KN_5O_7^+$; calc. 750.2325), 734.2590 (100, $[M+Na]^+$, $C_{41}H_{37}N_5NaO_7^+$; calc. 734.2585), 712.2777 (26, $[M+H]^+$, $C_{41}H_{38}N_5O_7^+$; calc. 712.2766).

N^6-*Benzoyl-2′,3′*-O-*isopropylidene-8-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-5′*-O-*(4-methylphenylsulfonyl)adenosine* (**15**). A soln. of **13** (500 mg, 0.7 mmol) in CH_2Cl_2 (3 ml) was cooled to 0°, treated with DABCO (236 mg, 2.10 mmol) and TsCl (267 mg, 1.40 mmol), stirred for 10 min, and treated

Table 4. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Adenosine Monomers* **14**–**17** *in $CDCl_3$*

	14	**15**	**16**	**17**[a])
H–C(2)	8.62	8.62	7.82	8.49
CH_a–C(8)	4.64	4.49	4.56	4.37
CH_b–C(8)	4.54	4.43	4.11	4.16
H–C(1′)	6.53	6.22	5.87	5.98
H–C(2′)	5.53	5.47	4.88	4.70
H–C(3′)	5.32	5.03	4.51	4.68
H–C(4′)	4.48	4.23–4.13	4.75	4.64
H_a–C(5′)	9.32	4.40–4.30	4.50	4.95
H_b–C(5′)	–	4.40–4.30	4.12	3.07
$J(H_a,H_b)$	12.3	12.3	11.7	12.2
J(1′,2′)	< 1.0	1.2	0	0
J(2′,3′)	6.3	6.3	5.7	5.6
J(3′,4′)	< 1.0	3.3	0	0
J(4′,5′a)	0	[b])	2.1	2.4
J(4′,5′b)	–	[b])	2.7	1.6
J(5′a,5′b)	–	[b])	14.4	14.0

[a]) Same numbering as for **14**–**16**. Assignments based on a DQF-COSY and a HSQC spectrum. [b]) Not assigned.

Table 5. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Adenosine Monomers* **14**–**17** *in* $CDCl_3$

	14[a])	**15**	**16**[b])	**17**[c])
C(2)	152.21, 152.07	152.10	142.93	163.56
C(4)	151.14	151.37	137.31	137.49
C(5)	121.92	122.04	121.37	125.54
C(6)	151.41 (br.)	151.62	149.81	160.99
C(8)	149.13 (br.)	149.12	146.05	142.60
CH_2–C(8)	59.63 (br.)	59.36	58.34	59.01
C(1′)	93.19 (br.)	90.07	91.03	90.97
C(2′)	85.16, 84.94	83.81	85.03	85.60
C(3′)	84.21, 83.97	81.60	80.30	82.26
C(4′)	91.63, 91.53	84.69	86.09	85.80
C(5′)	199.79, 199.67	69.28	55.98	44.83

[a]) 1:1 Mixture of **14** and its α-L-*lyxo*-analogue. [b]) Assignment based on comparison with [38][39]. [c]) Same numbering as for **14**–**16**. Assignments based on a HSQC spectrum and on comparison with data in [40].

with sat. NH_4Cl soln. After extraction with CH_2Cl_2, the combined org. layers were dried ($MgSO_4$) and evaporated. FC (cyclohexane/AcOEt 3:1 → AcOEt) gave **15** (456 mg, 75%). Colourless foam. R_f (cyclohexane/AcOEt 1:1) 0.63. $[\alpha]_D^{25} = -19.4$ ($c = 0.40$, $CHCl_3$). IR (ATR): 3054*w*, 2986*w*, 2927*w*, 1698*w*, 1607*m*, 1579*m*, 1537*w*, 1508*m*, 1488*m*, 1447*m,* 1360*m*, 1338*m*, 1297*w*, 1248*s*, 1188*m*, 1175*s*, 1156*m*, 1094*m*, 1066*s*, 1031*m*, 978*s*, 863*w*, 827*m*, 798*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 9.11 (br. *s*, NH); 8.00 (*d*, *J* = 7.5, 2 arom. H); 7.62–7.47 (*m*, 8 arom. H); 7.39–7.22 (*m*, 9 arom. H); 7.11 (*d*, *J* = 8.4, 2 arom. H); 6.85 (*d*, *J* = 8.7, 2 arom. H); 3.76 (*s*, MeO); 2.34 (*s*, Me); 1.48, 1.33 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*; additionally, 164.35 (*s*, NC=O); 158.77, 144.68 (2*s*); 143.10 (2*s*); 134.09, 133.59 (2*s*); 132.70 (*d*); 132.23 (*s*); 130.40–127.22 (several *d*); 114.46 (*s*, Me_2C); 113.29 (2*d*); 88.07 (*s*, Ph_2C); 55.28 (*q*, MeO); 27.20, 25.53 (2*q*, Me_2C); 21.69 (*q*, Me). HR-MALDI-MS: 906.2573 (24, $[M+K]^+$, $C_{48}H_{45}KN_5O_9S^+$; calc. 906.2570), 890.2814 (100, $[M+Na]^+$, $C_{48}H_{45}N_5NaO_9S^+$; calc. 890.2830), 868.3004 (36, $[M+H]^+$, $C_{48}H_{46}N_5O_9S^+$; calc. 868.3011).

Attempted Azidation of **15**. A soln. of **15** (100 mg, 0.11 mmol) in dry DMF (2 ml) was treated with NaN_3 (63 mg, 1.15 mmol) and stirred for 4 h at 80°. The soln. was cooled to 23°, diluted with AcOEt (5 ml), washed with H_2O (5 × 5 ml), dried ($MgSO_4$), and evaporated. FC (cyclohexane/AcOEt 3:1 → AcOEt) gave **16** (12 mg, 16%) and **17** (23 mg, 30%).

*Data of 3,5′-Anhydro-*N^6*-benzoyl-2′,3′-*O*-isopropylidene-8-{[(4-methoxyphenyl)diphenylmethoxy]-methyl}adenosine* (**16**). R_f (cyclohexane/AcOEt 1:1) 0.73. IR (ATR): 3100–2900*w*, 1640*w* (sh), 1610*m*, 1600*w* (sh), 1509*w*, 1447*w*, 1405*w*, 1381*w*, 1309*w*, 1272*w*, 1250*m*, 1210*w*, 1178*w*, 1159*w*, 1132*w*, 1095*w*, 1052*m*, 975*w*, 905*s*, 874*w*, 859*w*, 834*w*, 725*s*, 712*s*, 677*w*, 646*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 10.42 (br. *d*, *J* = 6.0, NH); 8.16 (*d*, *J* = 6.9, 2 arom. H); 7.50–7.20 (*m*, 15 arom. H); 6.84 (*d*, *J* = 8.6, 2 arom. H); 3.80 (*s*, MeO); 1.47, 1.20 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*; additionally, 180.66 (*s*, Ph*C*=O); 158.96, 143.41, 143.14, 135.37, 133.97 (5*s*); 131.94 (*d*); 130.43 (2*d*); 129.64 (2*d*); 128.16–127.07 (several *d*); 113.58 (*s*, Me_2C); 113.34 (2*d*); 87.92 (*s*, Ph_2C); 55.28 (*q*, MeO); 26.15, 24.73 (2*q*, Me_2C). HR-MALDI-MS: 696.2817 (100, $[M+H]^+$, $C_{41}H_{40}N_5O_6^+$; calc. 696.2822), 273.1267 (33, $CPh_2(C_6H_4OMe)^+$; calc. 273.1274).

Data of N^5*,5′-Anhydro-4-(*N′*-benzoylcarbamimidoyl)-5-formamido-1-(2,3-*O*-isopropylidene-β-*D*-ribofuranosyl)-2-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-1*H*-imidazole* (**17**). Yellow foam. R_f (cyclohexane/AcOEt 1:1) 0.41. ^{1}H-NMR (400 MHz, $CDCl_3$; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 4*; additionally, 10.42 (br. *d*, *J* = 6.0, NH); 8.03 (*d*, *J* = 6.8, 2 arom. H); 7.59 (br. *d*, *J* = 6.0, NH); 7.43–7.15 (*m*, 15 arom. H); 6.78 (*d*, *J* = 8.8, 2 arom. H); 3.72 (*s*, MeO); 1.43, 1.24 (2*s*, Me_2C). ^{13}C-NMR (100 MHz, $CDCl_3$; assignments based on a HSQC spectrum): see *Table 5*; additionally, 180.92 (*s*, Ph*C*=O); 158.96, 143.50, 143.28, 134.44, 132.25 (5*s*); 131.84 (*d*); 130.49 (2*d*); 129.49 (2*d*);

128.41–127.97 (several *d*); 127.30, 127.29 (2*d*); 113.37 (2*d*); 113.06 (*s*, Me_2C); 87.95 (*s*, Ph_2C); 55.25 (*q*, MeO); 26.24, 24.68 (2*q*, Me_2C). HR-MALDI-MS: 714.2913 (100, $[M+H]^+$, $C_{41}H_{40}N_5O_6^+$; calc. 714.7851), 273.1265 (33, $CPh_2(C_6H_4OMe)^+$; calc. 273.1274).

5′-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-O-isopropylideneuridine-6-methyl-(6¹ → 5′-N)-5′-amino-5′-deoxy-2′,3′-O-isopropylidene-8-[[(4-methoxyphenyl)diphenylmethoxy]methyl]adenosine (**19**). A soln. of **3** (200 mg, 0.41 mmol) in THF (1.5 ml) was treated dropwise with 1M Me_3P in THF (0.46 ml, 0.46 mmol), and stirred for 24 h at 23° (TLC: complete conversion of **3**). The mixture was treated with a soln. of **14** (168 mg, 0.41 mmol) in THF (1 ml), stirred for 24 h at 23°, and evaporated. A soln. of the residue in AcOEt (10 ml) was washed with H_2O (3 × 10 ml), dried ($MgSO_4$), and evaporated. A soln. of the residue in MeOH (3 ml) was treated with $NaBH_3CN$ (103 mg, 1.64 mmol) and AcOH (0.1 ml, 1.64 mmol), and stirred for 20 h at 23°. The mixture was diluted with AcOEt, washed with a sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated. A soln. of the residue (crude **18**) in MeOH (1 ml) was treated with a soln. of MeONa (221 mg, 4.10 mmol) in MeOH (2 ml) and stirred for 24 h at 24°. After evaporation, a soln. of the residue in AcOEt (5 ml) was washed with a sat. NH_4Cl soln. and brine, dried ($MgSO_4$), and evaporated. FC (cyclohexane/AcOEt/acetone 4:2:1 → 2:2:1) gave **19** (220 mg, 51%). Colourless foam. R_f (cyclohexane/AcOEt/acetone 1:1:1) 0.32. IR (ATR): 3323*w*, 3191*w*, 2984*w*, 2956*w*, 2931*w*, 2870*w*, 2835*w*, 1689*s*, 1644*m*, 1606*m*, 1579*w*, 1510*w*, 1487*w*, 1463*w*, 1447*m*, 1379*m*, 1329*w*, 1299*w*, 1251*m*, 1212*m*, 1180*w*, 1156*m*, 1129*w*, 1063*s*, 1034*m*, 977*w*, 908*m*, 871*w*, 862*w*, 829*s*, 799*w*, 777*m*, 766*m*, 731*s*, 705*m*, 662*w*, 651*w*, 647*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; assignments based on a DQF-COSY spectrum): see *Table 6*; additionally, 11.20 (*s*, H–N(3/II)); 7.50 (*d*, *J* = 8.0, 4 arom. H); 7.39 (*d*, *J* = 8.8, 2 arom. H); 7.33–7.22 (*m*, 6 arom. H); 6.84 (*d*, *J* = 8.8, 2 arom. H); 6.40 (br. *s*, H_2N–C(6/I)); 3.82–3.75 (br. *s*, HN–C(5′/I)); 3.79 (*s*, MeO); 1.58 (*sept.*, *J* = 6.9, Me_2CH); 1.54, 1.43, 1.36, 1.26 (4*s*, 2 Me_2C); 0.83 (*d*, *J* = 6.9, Me_2CH); 0.80, 0.79 (2*s*, Me_2CSi); 0.04, 0.03 (2*s*, Me_2Si). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 7*; additionally, 158.97, 143.72, 143.64, 134.75 (4*s*); 130.60 (2*d*); 128.59 (2*d*); 128.56 (2*d*); 128.08 (4*d*); 127.30 (2*d*); 114.16, 113.45 (2*s*, 2 Me_2C); 113.35 (2*d*); 89.67 (*s*, Ph_2C); 55.34 (*q*, MeO); 34.21 (*d*, Me_2CH); 27.67, 27.50, 25.91, 25.73 (4*q*, 2 Me_2C); 25.39 (*s*, Me_2CSi); 20.45 (*q*, Me_2CSi); 18.55 (*q*, Me_2CH); −3.18 (*q*, Me_2Si). HR-MALDI-MS: 1085.4553 (50, $[M+K]^+$, $C_{55}H_{70}KN_8O_{11}Si^+$; calc. 1085.4565), 1069.4845 (100, $[M+Na]^+$, $C_{55}H_{70}N_8NaO_{11}Si^+$; calc. 1069.4826).

2′,3′-O-Isopropylideneuridine-6-methyl-(6¹ → 5′-N)-5′-amino-5′-deoxy-2′,3′-O-isopropylidene-8-[[(4-methoxyphenyl)diphenylmethoxy]methyl]adenosine (**20**). In a polyethylene flask, a soln. of **19** (100 mg, 0.1 mmol) in THF (1 ml) was treated with HF · pyridine (86 µl, 1 mmol) and stirred for 10 min at 24°. The mixture was treated with 1M NaOH soln. and extracted with AcOEt. The combined org. phases were washed with brine, dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/MeOH 60:1 → 20:1) gave **20** (66 mg, 73%). Colourless foam. R_f (CH_2Cl_2/MeOH 10:1) 0.70. IR (ATR): 3334*w*, 3192*w*, 2989*w*, 2933*w*, 1693*s*, 1639*m* 1607*m*, 1579*m*, 1512*m*, 1490*w*, 1443*m*, 1379*m*, 1330*m*, 1297*m*, 1251*m*, 1212*m*, 1180*m*, 1155*m*, 1063*s*, 1032*s*, 978*m*, 901*w*, 863*m*, 832*m*, 794*m*, 765*m*, 731*m*, 704*s*. ^{1}H-NMR (400 MHz, $CDCl_3$; assignment based on a DQF-COSY spectrum): see *Table 6*; additionally, 12.16–11.96 (br. *s*, H–N(3/II)); 7.50 (*d*, *J* = 7.6, 4 arom. H); 7.38 (*d*, *J* = 9.2, 2 arom. H); 7.32–7.20 (*m*, 6 arom. H); 6.84 (*d*, *J* = 8.8, 2 arom. H); 6.55 (br. *s*, H_2N–C(6/I)); 3.79 (*s*, MeO); 1.55, 1.44, 1.37, 1.35 (4*s*, 2 Me_2C); signals for HN–C(5′/I) and HO–C(5′/II) not visible. ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 7*; additionally, 158.88, 143.62, 143.57, 134.64 (4*s*); 130.52 (2*d*); 128.48 (4*d*); 127.99 (4*d*); 127.21 (2*d*); 114.17, 113.96 (2*s*, 2 Me_2C); 113.36 (2*d*); 88.08 (*s*, Ph_2C); 55.25 (*q*, OMe); 27.56, 27.45, 25.80, 25.47 (4*q*, 2 Me_2C). HR-MALDI-MS: 943.3387 (60, $[M+K]^+$, $C_{47}H_{52}KN_8O_{11}^+$; calc. 943.3387), 927.3655 (100, $[M+Na]^+$, $C_{47}H_{52}N_8NaO_{11}^+$; calc. 927.3648), 905.3802 (82, $[M+H]^+$, $C_{47}H_{53}N_8O_{11}^+$; calc. 905.3828).

5′-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-O-isopropylideneuridine-6-methyl-(6¹ → 5′-N)-5′-amino-5′-deoxy-8-(hydroxymethyl)-2′,3′-O-isopropylideneadenosine (**21**). A soln. of **19** (100 mg, 0.1 mmol) in CH_2Cl_2 (2 ml) was treated with Et_3SiH (0.19 ml, 1.2 mmol) and Cl_2CHCO_2H (66 µl, 0.8 mmol), and stirred for 10 min at 24°. The mixture was treated with *Amberlite IRA-68* (20–50 mesh; free base), stirred for 30 min, filtered, and evaporated. FC (CH_2Cl_2/MeOH 80:1 → 30:1) gave **21** (50 mg, 65%). Colourless solid. R_f (CH_2Cl_2/MeOH 10:1) 0.61. $[\alpha]_D^{25} = -3.5$ (*c* = 0.2, $CHCl_3$). IR (ATR): 3334*w*, 3194*w*, 2953*w*, 2928*w*, 2864*w*, 1690*s*, 1643*m*, 1607*m*, 1579*w*, 1454*m*, 1375*m*, 1329*m*, 1295*m*, 1251*m*, 1211*m*, 1157*m*, 1132*m*, 1073*s*, 986*m*, 935*m*, 860*m*, 829*s*, 798*m*, 776*s*. ^{1}H-NMR (400 MHz, $CDCl_3$; assignments based on a DQF-COSY spectrum): see *Table 6*; additionally, 11.63 (br. *s*, H–N(3/II)); 6.77 (br. *s*,

Table 6. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the U*[N]A* Dinucleosides* **19**–**21** *in $CDCl_3$*

	19[a])	**20**[a])	**21**[a])		**19**[a])	**20**[a])	**21**[a])
Adenosine unit (I)							
H–C(2/I)	8.26	8.27	8.18				
CH_a–C(8/I)	4.48	4.48	4.93				
CH_b–C(8/I)	4.40	4.42	4.81	$J(H_a,H_b/I)$	12.0	11.6	14.8
H–C(1′/I)	6.04	6.06	6.22	J(1′,2′/I)	3.6	3.2	3.2
H–C(2′/I)	5.66	5.65	5.59	J(2′,3′/I)	6.4	6.4	6.4
H–C(3′/I)	5.34	5.28	5.30	J(3′,4′/I)	3.6	*ca.* 3.6	3.6
H–C(4′/I)	4.27	4.29	4.39	J(4′,5′a/I)	3.2	*ca.* 3.6	3.6
H_a–C(5′/I)	3.04	2.98	3.05	J(4′,5′b/I)	3.6	*ca.* 3.6	4.4
H_b–C(5′/I)	2.93	2.98	2.88	J(5′a,5′b/I)	12.0	[b])	12.0
Uridine unit (II)							
H–C(5/II)	5.72	5.70	5.67				
CH_a–C(6/II)	3.67	3.64	3.66				
CH_b–C(6/II)	3.58	3.59	3.59	$J(H_a,H_b/II)$	14.4	14.4	14.4
H–C(1′/II)	6.16	5.97	6.11	J(1′,2′/II)	< 1.0	1.2	< 1.0
H–C(2′/II)	5.32	5.30	5.31	J(2′,3′/II)	6.0	6.0	6.4
H–C(3′/II)	4.86	5.08	4.81	J(3′,4′/II)	4.4	3.6	4.4
H–C(4′/II)	4.13	4.16	4.13	J(4′,5′a/II)	[b])	2.8	5.2
H_a–C(5′/II)	3.82–3.72	3.83	3.78	J(4′,5′b/II)	[b])	4.8	7.2
H_b–C(5′/II)	3.82–3.72	3.76	3.73	J(5′a,5′b/II)	[b])	12.0	10.4

[a]) Assignments based on a DQF-COSY spectrum. [b]) Not assigned.

Table 7. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the U*[N]A* Dinucleosides* **19**–**21** *in $CDCl_3$*

	19	**20**	**21**		**19**	**20**	**21**
Adenosine unit (I)				Uridine unit (II)			
C(2/I)	154.16	153.54	154.08	C(2/II)	151.17	151.89	151.49
C(4/I)	150.78	150.48	151.31	C(4/II)	163.64	163.50	163.75
C(5/I)	119.08	118.89	117.99	C(5/II)	102.92	103.28	103.04
C(6/I)	155.71	155.69	155.47	C(6/II)	152.48	152.37	152.50
C(8/I)	149.05	148.97	150.20	CH_2–C(6/II)	51.08	50.07	50.23
CH_2–C(8/I)	59.43	59.28	56.91				
C(1′/I)	90.18	90.20	89.63	C(1′/I)	91.48	91.43	91.37
C(2′/I)	82.72	82.79	82.83	C(2′/I)	84.41	84.15	84.44
C(3′/I)	81.26	80.67	81.43	C(3′/I)	82.52	81.50	82.28
C(4′/I)	84.68	85.10	84.84	C(4′/I)	88.01	87.91	89.54
C(5′/I)	50.46	50.85	50.77	C(5′/I)	64.28	62.83	64.09

H_2N–C(6/I)); 1.58 (*sept.*, $J = 6.9$, Me_2CH); 1.63, 1.54, 1.39, 1.34 (4*s*, 2 Me_2C); 0.83 (*d*, $J = 6.9$, Me_2CH); 0.81, 0.80 (2*s*, Me_2CSi); 0.06, 0.05 (2*s*, Me_2Si); HN–C(5′/I) and OH not visible. ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 7*; additionally, 114.29, 113.30 (2*s*, 2 Me_2C); 34.11 (*d*, Me_2CH); 27.60, 27.44, 25.85, 25.63 (4*q*, 2 Me_2C); 25.34 (*s*, Me_2CSi); 20.42, 20.38 (2*q*, Me_2CSi); 18.56, 18.52 (2*q*, Me_2CH); −3.17 (*q*, Me_2Si). HR-MALDI-MS: 797.3643 (44, $[M + Na]^+$, $C_{35}H_{54}N_8NaO_{10}Si^+$; calc. 797.3624), 775.3807 (100, $[M + H]^+$, $C_{35}H_{55}N_8O_{10}Si^+$; calc. 775.3805).

N^6-*Benzoyl-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′*-O-*isopropylideneadenosine-8-methyl-(8^1 → 5′*-N*)-5′-amino-5′-deoxy-2′,3′*-O-*isopropylidene-6-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-uridine* (**22**). A soln. of **8** (1.57 g, 2.57 mmol) in THF (15 ml) was treated dropwise with 1M Me_3P in THF (3.08 ml, 3.08 mmol), and stirred for 24 h at 23° (TLC: complete conversion of **8**). The mixture was treated with a soln. of **10** (1.49 g, 2.57 mmol) in THF (10 ml), stirred for 48 h at 23°, and evaporated. A soln. of the residue in AcOEt (20 ml) was washed with H_2O (3 × 20 ml), dried ($MgSO_4$), and evaporated. A soln. of the residue in MeOH (10 ml) was treated with $NaBH_3CN$ (646 mg, 10.28 mmol) and AcOH (0.59 ml, 10.28 mmol), and stirred for 20 h at 23°. The mixture was diluted with AcOEt, washed with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/MeOH 100:1 → 30:1) gave **22** (2.22 g, 75%). Yellow foam. R_f (CH_2Cl_2/MeOH 10:1) 0.43. IR (ATR): 3186*w*, 3050*w*, 2957*w*, 2927*w*, 2857*w*, 1695*s*, 1609*m*, 1583*w*, 1530*w*, 1509*m*, 1488*m*, 1449*m*, 1381*m*, 1324*w*, 1298*w*, 1251*s*, 1212*m*, 1179*m*, 1157*m*, 1083*s*, 1068*s*, 1034*m*, 977*w*, 908*m*, 871*m*, 830*s*, 797*w*, 778*m*, 761*m*, 728*s*, 706*s*, 646*w*, 631*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 8*; additionally, 9.80–9.50 (br. *s*, H–N(3/I)); 9.28 (br. *s*, HN–C(6/II)); 7.98 (*d*, *J* = 7.2, 2 arom. H); 7.55 (*t*, *J* = 7.2, 1 arom. H); 7.48–7.42 (*m*, 6 arom. H); 7.36–7.23 (*m*, 8 arom. H); 6.84 (*d*, *J* = 8.7, 2 arom. H); 3.78 (*s*, MeO); 2.05–1.95 (br. *s*, HN–C(5′/I)); 1.61, 1.42, 1.38, 1.26 (4*s*, 2 Me_2C); 1.54 (*sept.*, *J* = 6.9, Me_2CH); 0.82 (*d*, *J* = 6.9, Me_2CH); 0.77, 0.76 (2*s*, Me_2CSi); −0.04, −0.05 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 9*; additionally, 164.81 (*s*, NC=O); 158.82, 143.04, 142.93, 133.97, 133.63 (5*s*); 132.57 (*d*); 130.32, 130.15 (2*d*); 128.54–127.39 (several *d*); 113.80, 113.74 (2*s*, 2 Me_2C); 113.41 (2*d*); 88.20 (*s*, Ph_2C); 55.15 (*q*, *Me*O); 34.11 (*d*, Me_2CH); 27.29, 27.25, 25.53, 25.48 (4*q*, 2 Me_2C); 25.26 (*s*, Me_2CSi); 20.42, 20.25 (2*q*, Me_2CSi); 18.62, 18.44 (2*q*, Me_2CH); −3.34, −3.37 (2*q*, Me_2Si). HR-MALDI-MS: 1069.4834 (44, $[M+Na]^+$, $C_{55}H_{70}N_8NaO_{11}Si^+$; calc. 1069.4831), 1047.5024 (100, $[M+H]^+$, $C_{55}H_{71}N_8O_{11}Si^+$; calc. 1047.5012).

5′-O-*[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′*-O-*isopropylideneadenosine-8-methyl-(8^1 → 5′*-N*)-5′-amino-5′-deoxy-2′,3′*-O-*isopropylidene-6-{[(4-methoxyphenyl)diphenylmethoxy]methyl}uridine* (**23**). A soln. of **22** (90 mg, 0.08 mmol) in MeOH (1 ml) was treated with a soln. of MeONa (42 mg, 0.80 mmol) in MeOH (2 ml), stirred for 48 h at 24°, and evaporated. A soln. of the residue in AcOEt (5 ml) was washed with a sat. NH_4Cl soln. and brine, dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/MeOH 100:1 → 60:1) gave **23** (55 mg, 68%). Yellow foam. R_f (CH_2Cl_2/MeOH 10:1) 0.47. $[\alpha]_D^{25} = -89.7$ (*c* = 0.36, $CHCl_3$). IR (ATR): 3327*w*, 3182*w*, 2956*w*, 2865*w*, 1695*m*, 1638*m*, 1605*m*, 1576*w*, 1510*w*, 1447*w*, 1373*m*, 1329*w*, 1298*w*, 1251*m*, 1212*m*, 1156*w*, 1067*s*, 869*w*, 828*s*, 799*w*, 766*m*, 703*w*, 630*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 8*; additionally, 13.40 (*s*, H–N(3/I)); 7.53 (br. *s*, H_2N–C(6/II)); 7.45 (*d*, *J* = 7.2, 4 arom. H); 7.37–7.22 (*m*, 8 arom. H); 6.85 (*d*, *J* = 9.0, 2 arom. H); 3.71 (*s*, MeO); 1.90 (br. *s*, HN–C(5′/I)); 1.59, 1.39, 1.29, 1.26 (4*s*, 2 Me_2C); 1.54 (*sept.*, *J* = 6.9, Me_2CH); 0.82 (*d*, *J* = 6.9, Me_2CH); 0.78, 0.77 (2*s*, Me_2CSi); −0.02, −0.06 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 9*; additionally, 158.89, 143.22, 143.11, 134.15 (4*s*); 130.22 (2*d*); 128.12 (8*d*); 127.33 (2*d*); 113.60, 113.24 (2*s*, 2 Me_2C); 113.36 (2*d*); 88.10 (*s*, Ph_2C); 55.14 (*q*, MeO); 33.98 (*d*, Me_2CH); 27.21, 27.11, 25.39, 25.10 (4*q*, 2 Me_2C); 25.10 (*s*, Me_2CSi); 20.17 (*q*, Me_2CSi); 18.37, 18.33 (2*q*, Me_2CH); −3.57 (*q*, Me_2Si). HR-MALDI-MS: 1069.4834 (44, $[M+Na]^+$, $C_{55}H_{70}N_8NaO_{11}Si^+$; calc. 1069.4831), 1047.5024 (100, $[M+H]^+$, $C_{55}H_{71}N_8O_{11}Si^+$; calc. 1047.5012).

2′,3′-O-*Isopropylideneadenosine-8-methyl-(8^1 → 5′*-N*)-5′-amino-5′-deoxy-2′,3′*-O-*isopropylidene-6-{[(4-methoxyphenyl)diphenylmethoxy]methyl}uridine* (**24**). In a polyethylene flask, a soln. of **23** (120 mg, 0.11 mmol) in THF (2 ml) was treated with $(HF)_3 \cdot Et_3N$ (0.18 ml, 1.1 mmol), and stirred for 24 h at 24°. The mixture was treated with 1M NaOH and extracted with AcOEt. The combined org. phases were washed with brine, dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/MeOH 60:1 → 20:1) gave **24** (70 mg, 70%). Colourless solid. R_f (CH_2Cl_2/MeOH 10:1) 0.47. M.p. 155–157°. $[\alpha]_D^{25} = -146.4$ (*c* = 0.2, $CHCl_3$). IR (ATR): 3330*w*, 3177*w*, 2984*w*, 2933*w*, 2830*w*, 1695*s*, 1618*m*, 1576*w*, 1509*m*, 1447*m*, 1381*m*, 1334*w*, 1301*w*, 1252*m*, 1214*m*, 1179*w*, 1155*m*, 1066*s*, 1033*m*, 971*w*, 942*w*, 901*w*, 852*m*, 830*m*, 797*w*, 765*w*, 736*w*, 701*m*, 657*w*, 630*w*. ^{1}H-NMR (500 MHz, $CDCl_3$; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 8*; additionally, 12.70 (br. *s*, H–N(3/I)); 7.70–7.50 (br. *s*, H_2N–C(6/II)); 7.48–7.43 (*m*, 4 arom. H); 7.36–7.23 (*m*, 8 arom. H); 6.82 (*d*, *J* = 8.6, 2 arom. H); 3.80 (*s*, MeO); 1.65, 1.39, 1.34, 1.25 (4*s*, 2 Me_2C); signals for HO–C(5′/II) and HN–C(5′/I)) not visible. ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC spectrum): see *Table 9*; additionally, 159.04, 143.32, 143.20, 134.14 (4*s*); 130.39 (2*d*); 128.24 (4*d*); 128.14 (2*d*); 128.11 (2*d*); 127.46 (2*d*); 113.96, 113.63 (2*s*, 2 Me_2C); 113.46 (2*d*);

Table 8. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the A*[N]U* Dinucleosides* **22**–**26** *in $CDCl_3$*

	22	**23**	**24**[a])	**25**[a])	**26**
Uridine unit (I)					
H–C(5/I)	5.67	5.88	5.78	5.38	5.90
CH_a–C(6/I)	3.99	4.03	4.02	4.68	4.58
CH_b–C(6/I)	3.92	3.93	3.95	4.38	4.42
H–C(1′/I)	5.52	5.37	5.51	6.21	5.59
H–C(2′/I)	5.17	5.27	5.24	5.16	5.16
H–C(3′/I)	4.90	5.11	5.04	5.00	4.92
H–C(4′/I)	4.07	4.31	4.15	4.26	4.26
H_a–C(5′/I)	3.01	3.11	2.98	3.14	3.07
H_b–C(5′/I)	2.96	3.02	2.98	2.94	2.95
$J(H_a,H_b$/I)	12.6	12.6	12.7	13.8	14.4
J(1′,2′/I)	< 1.0	3.6	2.7	< 1.0	< 1.0
J(2′,3′/I)	6.3	6.6	6.6	6.3	5.7
J(3′,4′/I)	5.4	3.0	3.6	6.2	4.8
J(4′,5′a/I)	5.4	2.7	[b])	5.5	7.5
J(4′,5′b/I)	3.9	3.6	[b])	2.8	1.8
J(5′a,5′b/I)	12.0	12.3	[c])	12.8	12.6
Adenosine unit (II)					
H–C(2/II)	8.73	8.32	8.30	8.19	8.08
CH_a–C(8/II)	4.17	4.19	4.19	4.09	4.16
CH_b–C(8/II)	4.13	3.95	3.94	3.99	4.04
H–C(1′/II)	6.40	6.46	6.10	6.41	6.23
H–C(2′/II)	5.88	5.96	5.36	5.83	5.33
H–C(3′/II)	5.15	5.14	5.17	5.14	5.16
H–C(4′/II)	4.27	4.26	4.50	4.23	4.46
H_a–C(5′/II)	3.65	3.75	3.97	3.56	3.94
H_b–C(5′/II)	3.55	3.59	3.78	3.49	3.77
$J(H_a,H_b$/II)	14.4	14.1	14.4	13.9	14.0
J(1′,2′/II)	< 1.0	1.8	5.1	1.3	4.8
J(2′,3′/II)	6.3	6.3	5.9	6.2	5.7
J(3′,4′/II)	2.7	2.7	1.1	3.2	< 1.5
J(4′,5′a/II)	6.6	6.6	< 1.5	6.8	< 1.5
J(4′,5′b/II)	6.3	7.2	< 1.5	6.3	< 1.5
J(5′a,5′b/II)	10.5	10.5	[c])	10.5	12.3

[a]) Assignments based on a DQF-COSY and a HSQC spectrum. [b]) H_a–C(5′/I) and H_b–C(5′/I) are nearly isochronous, showing a mean coupling of 4.3 Hz. [c]) Not assigned.

55.27 (*q*, MeO); 27.73, 27.27, 25.37, 25.24 (4*q*, 2 *Me*$_2$C). HR-MALDI-MS: 943.3387 (60, $[M+K]^+$, $C_{47}H_{52}KN_8O_{11}^+$; calc. 943.3387), 927.3655 (100, $[M+Na]^+$, $C_{47}H_{52}N_8NaO_{11}^+$; calc. 927.3653), 905.3802 (82, $[M+H]^+$, $C_{47}H_{53}N_8O_{11}^+$; calc. 905.3828).

5′-O-*[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′*-O-*isopropylideneadenosine-8-methyl-(8^1 → 5′*-N)-*5′-amino-5′-deoxy-6-(hydroxymethyl)-2′,3′*-O-*isopropylideneuridine* (**25**). A soln. of **23** (150 mg, 0.14 mmol) in CH_2Cl_2 (2 ml) was treated with Et_3SiH (0.27 ml, 1.68 mmol) and Cl_2CHCO_2H (93 µl, 1.12 mmol), and stirred for 10 min at 24°. The mixture was treated with *Amberlite IRA-68* (20–50 mesh; free base), stirred for 30 min, filtered, and evaporated. FC (CH_2Cl_2/MeOH 80:1 → 30:1) gave **25** (79 mg, 73%). Colourless foam. R_f (CH_2Cl_2/MeOH 10:1) 0.43. $[\alpha]_D^{25} = -29.4$ ($c = 0.33$, $CHCl_3$). IR (ATR):

Table 9. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the A*[N]U* Dinucleosides* **22**–**26** *in $CDCl_3$*

	22	**23**	**24**[a])	**25**[a])	**26**
Uridine unit (I)					
C(2/I)	151.88	151.69	151.77	151.99	151.21
C(4/I)	162.58	163.13	163.05	165.25	164.08
C(5/I)	103.02	103.61	103.75	102.85	102.30
C(6/I)	152.30	152.77	152.58	154.63	154.23
*C*H$_2$–C(6/I)	62.30	62.16	62.39	62.26	61.46
C(1′/I)	91.71	92.51	88.30	91.27	91.42
C(2′/I)	83.84	82.97	83.17	84.32	83.13
C(3′/I)	81.73	80.94	81.45	80.88	81.47
C(4′/I)	89.84	88.41	86.75	87.63	85.80
C(5′/I)	50.97	51.57	51.44	50.14	50.26
Adenosine unit (II)					
C(2/II)	152.15	152.18	152.19	151.42	151.34
C(4/II)	151.72	150.99	150.83	151.26	150.70
C(5/II)	121.98	117.80	118.56	118.53	118.73
C(6/II)	153.76	155.34	155.94	155.02	155.33
C(8/II)	150.41	150.01	149.51	150.02	149.20
*C*H$_2$–C(8/II)	46.74	46.21	46.33	46.67	46.17
C(1′/II)	91.48	90.26	92.53	89.69	92.06
C(2′/II)	83.13	82.53	82.89	83.33	84.40
C(3′/II)	82.24	81.66	81.77	82.22	82.09
C(4′/II)	87.87	88.10	85.87	88.37	88.95
C(5′/II)	62.91	63.05	63.41	63.00	63.16

[a]) Assignments based on a HSQC spectrum.

3329*w*, 3195*w*, 2956*w*, 2940*w*, 2857*w*, 1698*s*, 1640*m*, 1603*m*, 1576*w*, 1455*m*, 1374*m*, 1330*m*, 1251*m*, 1211*m*, 1157*m*, 1066*s*, 969*w*, 871*m*, 828*s*, 799*m*, 777*m*, 660*w*. ^{1}H-NMR (500 MHz, $CDCl_3$; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 8*; additionally, 11.70–11.50 (br. *s*, H–N(3/I)); 7.70–7.45 (br. *s*, H_2N–C(6/II)); 1.9–1.5 (br. *s*, OH, HN–C(5′/I)); 1.62, 1.57, 1.45, 1.34 (4*s*, 2 Me_2C); 1.52 (*sept.*, *J* = 6.9, Me_2CH); 0.80 (*d*, *J* = 6.9, *Me*$_2$CH); 0.75, 0.74 (2*s*, Me_2CSi); −0.06, −0.07 (2*s*, Me_2Si). ^{13}C-NMR (125 MHz, $CDCl_3$; assignments based on a HSQC spectrum): see *Table 9*; additionally, 114.38, 113.62 (2*s*, 2 Me_2C); 34.08 (*d*, Me_2CH); 27.49, 27.20, 25.51, 25.45 (4*q*, 2 *Me*$_2$C); 25.21 (*s*, Me_2CSi); 20.30, 20.24 (2*q*, *Me*$_2$CSi); 18.46, 18.41 (2*q*, *Me*$_2$CH); −3.48, −3.49 (2*q*, Me_2Si). HR-MALDI-MS: 797.3659 (10, $[M+Na]^+$, $C_{35}H_{54}N_8NaO_{10}Si^+$; calc. 797.3630), 775.3817 (100, $[M+H]^+$, $C_{35}H_{55}N_8O_{10}Si^+$; calc. 775.3810). Anal. calc. for $C_{35}H_{54}N_8O_{11}Si$ (774.94): C 54.25, H 7.02, N 14.46; found: C 53.96, H 7.06, N 14.08.

2′,3′-O-*Isopropylideneadenosine-8-methyl-(8′ → 5′*-N*)-5′-amino-5′-deoxy-6-(hydroxymethyl)-2′,3′*-O-*isopropylideneuridine* (**26**). A soln. of **24** (70 mg, 0.08 mmol) in CH_2Cl_2 (1 ml) was treated with Et_3SiH (0.15 ml, 0.93 mmol) and Cl_2CHCO_2H (0.05 ml, 0.62 mmol), and stirred for 10 min at 24°. The mixture was treated with *Amberlite IRA-68* (20–50 mesh; free base), stirred for 30 min, filtered, and evaporated. FC (CH_2Cl_2/MeOH 50 : 1 → 10 : 1) gave **26** (38 mg, 78%). Colourless foam. R_f (CH_2Cl_2/MeOH 10 : 1) 0.17. IR (ATR): 3318*m* (br.), 3189*m* (br.), 2987*m*, 2933*m*, 2848*w*, 1680*s*, 1647*s*, 1609*m*, 1576*w*, 1454*m*, 1381*s*, 1333*m*, 1303*w*, 1261*w*, 1214*m*, 1158*m*, 1101*s*, 1083*s*, 1068*s*, 1020*w*, 993*w*, 969*w*, 945*w*, 908*w*, 873*w*, 857*w*, 827*w*, 797*w*, 760*w*, 691*w*, 654*w*, 619*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 8*; additionally, 7.19 (br. *s*, H_2N–C(6/II)); 1.67, 1.55, 1.43, 1.32 (4*s*, 2 Me_2C); signals for H–N(3/I) and 2 OH not visible. ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 9*; additionally, 114.00, 113.91 (2*s*, 2 Me_2C); 27.82, 27.43, 25.42 (2 C) (3*q*, 2 *Me*$_2$C). HR-MALDI-MS: 671.2188 (25, $[M+K]^+$, $C_{27}H_{36}KN_8O_{10}^+$; calc. 671.2186), 655.2446 (41, $[M+Na]^+$, $C_{27}H_{36}N_8NaO_{10}^+$; calc. 655.2447), 633.2624 (100, $[M+H]^+$, $C_{27}H_{37}N_8O_{10}^+$; calc. 633.2627).

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