Oligonucleotide Analogues with Integrated Bases and Backbone

Part 21

Influence of the Hydrogen-Bonding Motif on the Gelation of Self-Complementary A*[s]U(*) Dinucleosides

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Gelation of organic solvents by the A*[s]U(*) dinucleosides **1** and **2** requires the formation of linear associates cross-linked by H-bonding involving either the nucleobase or $HOCH_2-C(6/I)$. This is evidenced by the absence of gel formation of the N^6-methyladenosine analogue **5** of **1** and the dehydroxy analogue **4** of **2**.

Introduction. – The A*[s]U(*[1]) dinucleosides **1** and **2** were synthesised to analyse the self- and hetero-association of thiomethylene linked oligonucleotide analogues (ONIBs), and found to form thermoreversible gels in organic solvents [1][2]. The gelation involves a network of dinucleosides, associated by H-bonds between the nucleobases, as shown by correlating solvent polarity and properties of the gels, and by the absence of gel formation of the *C(6)*-deaminated analogue **3** of **1** [3].

To generate a network, these dinucleosides must preferentially associate to form linear rather than cyclic duplexes, as only linear duplexes can lead to higher associates [1][2][4–6]. Moreover, the linear associates must be cross-linked to form a three-dimensional network that cannot result from a mere linear sequence of dinucleosides $A^*[s]U^{(*)}\cdots(A^*[s]U^{(*)}\cdots)_nA^*[s]U^{(*)}$. We assumed that cross-linking the linear oligoplexes involves the adenosine moiety that can simultaneously form *Watson–Crick* and *Hoogsteen*-type H-bonds, as in the fundamental motif for triple helixes [7]. Analysis of the gel formation by the A*[s]U* dimer **2** must also take into account that substitution at C(6/I) results in a predominant *syn*-conformation of the nucleobase, and that this conformation favours the formation of cyclic duplexes (*cf.* [1]). We thus wondered if the CH_2OH group at C(6/I) has the function of bridging linear oligoplexes, as it was observed in the crystal structure of a U*[s]A* dinucleoside [1].

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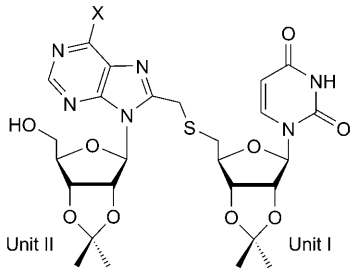
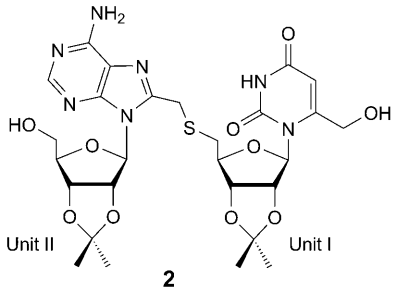
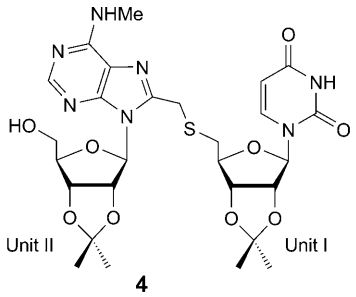
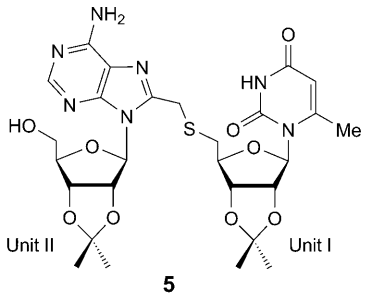
[1]) *Conventions for abbreviated notation:* The substitution at C(6) of pyrimidines and C(8) of purines is denoted by an asterisk (*); for example, A* and U* for hydroxymethylated adenosine and uridine derivatives, respectively. $U^{(*)}$ represents both unsubstituted and hydroxymethylated uridine derivative. The replacement of the amino group at C(6) of adenosine by a methylamino group and the replacement of the hydroxymethyl group of uridine by an H-atom are denoted by 'Me' in superscript (^{Me}) and 'H' in superscript (^{H}), resp.; for example, ^{Me}A and ^{H}U represent N^6-methyladenosine and *C(6)*-methyluridine derivatives, resp. The moiety x linking $C(8)-CH_2$ of unit II and C(5′) of unit I is indicated in square brackets, *i.e.*, [s] for a S-atom.







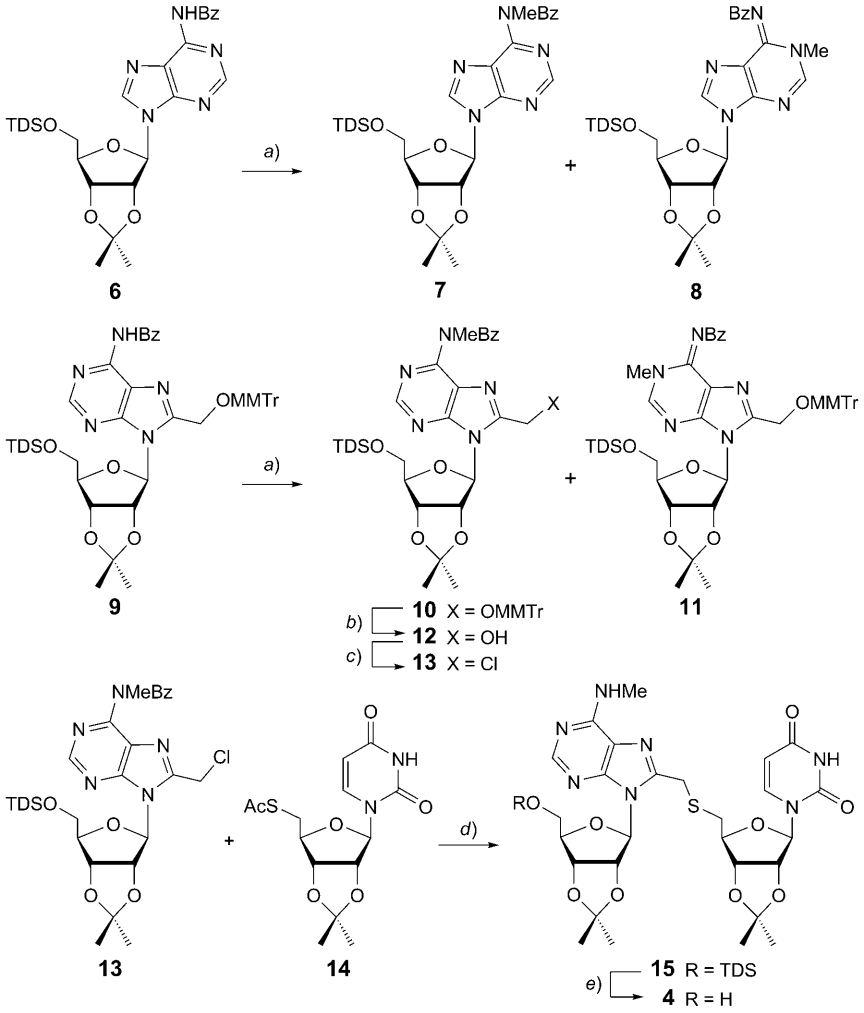


To test this hypothesis, we planned to synthesise the N^6-methyladenosine analogue **4**, and the deoxy analogue **5**, and to evaluate their ability to gelate solvents.

Results and Discussion. – *Synthesis of the* $^{Me}A*[s]U$ *Dinucleoside* **4**. To synthesize the dinucleoside **4**, we substituted the chloromethylated N^6-methyladenosine derivative **13** by the thiolate resulting from deacetylation of the known thioacetate **14** [1] (*Scheme 1*). In view of obtaining **13**, we treated the protected adenosine **6** [1] with MeI in a biphasic CH_2Cl_2/1M aq. NaOH mixture under phase-transfer conditions [8], and obtained the desired N^6-methyladenosine **7** in 68% and the 1-methyladenosine **8** in 21% yield. Attempts at introducing a CH_2OH group at C(8) of N^6-methyladenosine **7** by deprotonation with lithium diisopropylamide (LDA) [9], formylation with DMF, hydrolysis, and reduction of the resulting aldehyde with $NaBH_4$ [10] failed. We, therefore, started from the hydroxymethylated adenosine derivative **9** [1]. Methylation under phase-transfer conditions afforded the regioisomeric monomethyl adenosines **10** (73%) and **11** (21%). Detritylation of **10** gave the alcohol **12** that was transformed into the chloro derivative **13** by mesylation, followed by *in-situ* substitution with LiCl. Treating a mixture of **13** and **14** with MeONa in dry, O_2-free MeOH yielded 96% of the dinucleoside **15** that was desilylated with $(HF)_3 \cdot Et_3N$ to provide **4** in 98% yield.

Synthesis of the $A*[s]^HU*$ *Dinucleoside* **5**. Similarly to **15**, the protected dinucleoside **23** was obtained by thioether formation between the chloromethylated adenosine derivative **17** and the thiolate generated from the uridine derived thioacetate **22** (*Scheme 2*). Mesylation of the known *C(8)*-(hydroxymethyl)-adenosine **16** [1] gave

Scheme 1

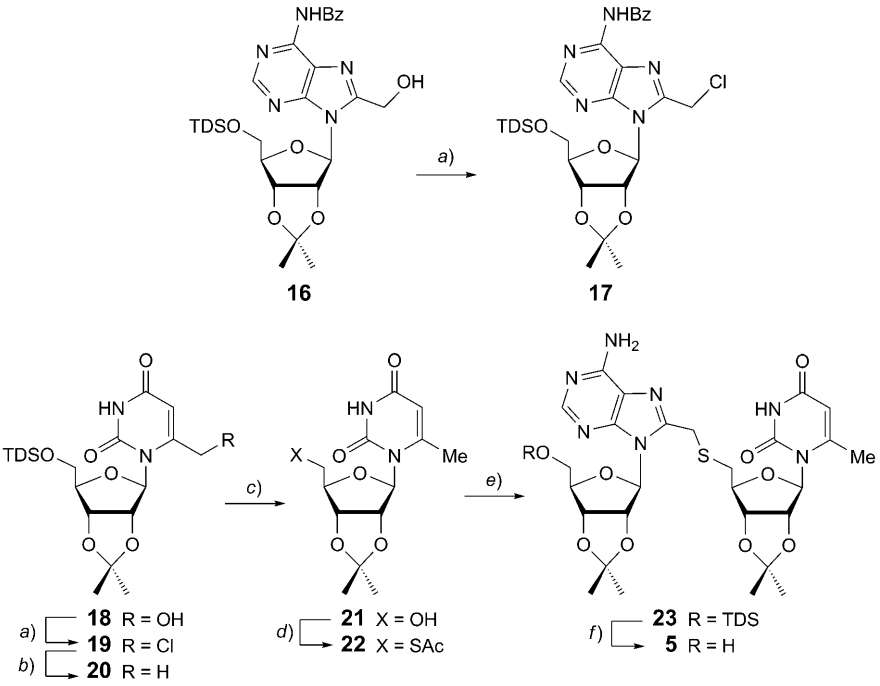


a) MeI, Bu_4NBr, CH_2Cl_2/1M aq. NaOH; 68% of **7** and 21% of **8**; 73% of **10** and 21% of **11**. *b*) Et_3SiH, Cl_2CHCO_2H, CH_2Cl_2; 79%. *c*) MsCl, EtN^iPr_2, CH_2Cl_2, then LiCl; 94%. *d*) MeONa, MeOH; 96%. *e*) $(HF)_3 \cdot Et_3N$, THF; 98%. MMTr = (monomethoxy)trityl (= (4-methoxyphenyl)diphenylmethyl). TDS = dimethyl(thexyl)silyl (thexyl = 1,1,2-trimethylpropyl).

chloride **17**; the intermediated methanesulfonate was not isolated. The uridine thioacetate **22** was synthesized from the known *C(6)*-(hydroxymethyl)-uridine **18** [1]. Mesylation afforded the chloro compound **19** that was reductively dechlorinated in the presence of Pd/C and MgO to yield 89% of the corresponding *C(6)*-methyl derivative **20**. Desilylation afforded the alcohol **21** (96%). Tosylation of **21** and treatment of the resulting crude product with AcSK in DMF yielded 78% of the thioacetate **22**. The A*[s]^{H}U* dinucleoside **23** was initially prepared in 46% yield by exposing **17** and **22** to

MeONa in dry, O_2-free MeOH. Formation of several by-products suggested that deprotonation of the methyl group at C(6) of **22** could compete with *S*-deacetylation. Thus, we treated **22** first with K_2CO_3 in degassed MeOH to obtain the corresponding thiolate, and then added chloro derivative **17**. This indeed resulted in a yield of 78% of **23** that was desilylated to give 92% of the alcohol **5**.

Scheme 2



a) MsCl, EtN^iPr_2, CH_2Cl_2; 81% of **17**; 81% of **19**. *b*) H_2, 10% Pd/C, MgO, AcOEt; 89%. *c*) $Bu_4NF \cdot 3\,H_2O$, THF; 96%. *d*) 1. TsCl, pyridine; 2. AcSK, DMF, 70°; 78%. *e*) K_2CO_3, MeOH, then **17**; 78%. *f*) $(HF)_3 \cdot Et_3N$, THF; 92%. TDS = dimethyl(thexyl)silyl (thexyl = 1,1,2-trimethylpropyl).

Conformation of the Adenosine-Derived Monomers. The N^6-methyladenosine derivative **7** adopts an *anti*-conformation, as revealed by δ(H–C(2′)) of 5.23 ppm (*Table 3* in the *Exper. Part*). H–C(2′) of the 1-methyladenosine derivative **8** resonates at 5.07 ppm. This upfield shift ($\Delta\delta = 0.16$ ppm) could reflect a different *syn*-conformation, a larger proportion of the *anti*-conformer, as previously reported for inosine derivatives [3], or differences in the electronic structure of the nucleobase. A weak predominance of the (*S*)-conformation of **7** and **8** is evidenced by *J*(1′/2′)/*J*(3′/4′) ratios of 1.2 and 1.1, respectively. A large population of the *gg*-conformer (*gg*/*gt*/*tg* 60 : 22 : 18 of **7** and 49 : 24 : 27 of **8**)[2]) is revealed by *J*(4′/5′a) and *J*(4′/5′b) of 3.7–4.4 Hz.

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[2]) See [1] for the calculation of the rotamer distribution.

The *O(5′)*-silylated and 8-substituted adenosines **10**, **13**, and **17** adopt a *syn*-conformation in $CDCl_3$, as revealed by δ(H–C(2′)) of 5.71–5.82 ppm (*Table 3* in the *Exper. Part*). H–C(2′) of the 1-methyladenosine **11** resonates at a higher field (5.50 ppm). A similar upfield shift ($\Delta\delta \approx 0.25$ ppm) as found above for **8** evidences a strong influence of the nature of the nucleobase on δ(H–C(2′)). The upfield shift for H–C(2′) of the alcohol **12** (5.53 ppm), however, reflects a *ca.* 4:1 *syn*/*anti* equilibrium, presumably due to the stabilization of the *anti*-conformer by an intramolecular H-bond between $HOCH_2$–C(8) (*dd* at 3.52 ppm with ^3J(H,OH) = 6.4 and 5.9 Hz) and O–C(5′) (see [1] and [3]). The (*N*)-conformation of **10**–**13** and **17** is indicated by $J(1'/2')/J(3'/4')$ ratios of 0.7–0.8. J(4′,5′a) and J(4′,5′b) values of 5.6–6.4 Hz of **10**, **11**, **13**, and **17** evidence a similar rotameric distribution (*gg*/*gt*/*tg* 12:42:46, 10:39:51, 23:36:41, and 19:36:45, resp.). In agreement with the above mentioned intramolecular H-bond in the *syn*-conformer of **12**, the J(4′,5′a) and J(4′,5′b) values of 4.8 Hz evidence a distinctly larger population of the *gg*-conformation (*gg*/*gt*/*tg* 40:28:32).

Conformation of the Uridine-Derived Monomers. The *C(6)*-substituted uridine derivatives **19**–**22** adopt a *syn*-conformation in solution, as revealed by the downfield shift of H–C(2′) (5.21–5.25 ppm; *Table 7* in the *Exper. Part*). The silyl ethers **19** and **20**, and the thioacetate **22** prefer the (*N*)-conformation, as revealed by a $J(1',2')/J(3',4')$ value of 0.25. They adopt preferentially the *gt*- and *tg*-conformation (*gg*/*gt*/*tg* 8:54:38 of **19** and 5:53:42 of **20**, *gt*/*tg ca.* 1:1 of **22**). The alcohol **21** forms an intramolecular H-bond from HO–C(5′) to O=C(2). This is evidenced by the larger population of the *gg*-rotamer (*gg*/*gt*/*tg* 56:32:12), as deduced from the distinctly smaller J(4′,5′a) and J(4′,5′b) values (3.1 and 4.6 Hz, resp.). A partial persistence of the H-bond is also suggested by the downfield shift of HO–C(5′) resonating at 3.25 ppm.

Crystals of **22** suitable for X-ray analysis were obtained from MeCN[3]). In the crystalline state, **22** adopts a classic *syn*-conformation (O(4′)–C(1′)–N(1)–C(2) = 66.8°), with a planar furanose ring (torsion angles $< 2°$; *Fig. 1,a*). It adopts the *gt*-conformation (O(4′)–C(4′)–C(5′)–S(5′) = 58.3°), as previously observed for other *S*-linked dinucleosides [1]. The molecules are assembled head-to-tail, forming intermolecular N(3)H···O(2′) H-bonds (*Fig. 1,b*).

Association of the $^{Me}A^*[s]U$ and $A^*[s]^HU^*$ Dinucleosides in $CHCl_3$. The self-association of **4**, **5**, **15**, and **23** was investigated by analysing the concentration dependence of the chemical shift for H–N(3/I) and by temperature-dependent circular dichroism, as discussed in detail in [1].

The ^{Me}A*[s]U dimers **15** and **4** associate weakly ($K_{ass} = 76$ and 95 M^{-1}, resp.; *Table 1*) and form linear associates, as shown by the weak curvature of the shift/concentration curves (SCCs; *Fig. 2*), the absence of a plateau at concentrations between 20 and 50 mM, and the numerical analysis of the SCCs according to *Gutowski* and *Saika* [1][11]. The extrapolated chemical-shift values for the duplexes of **15** and **4** (11.44 and 11.42 ppm, resp.; *Table 1*) support the dominant or exclusive formation of

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[3]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-717721. Copies of the data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB21EZ (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

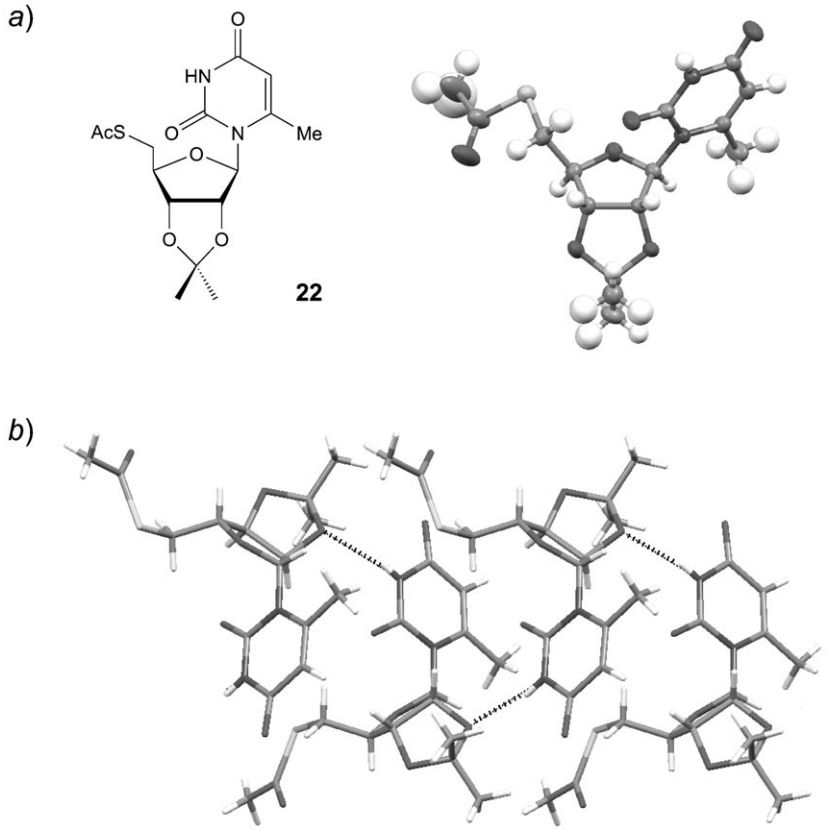

Fig. 1. *Crystal structure of* **22**. *a*) ORTEP Representation. *b*) Molecular packing showing intermolecular N(3)–H···O(2′) H-bonds (hashed bonds).

Hoogsteen-type H-bonds. The association constants of **15** and **4** are higher than those of their 6-deamino analogues (23 and 20 M^{-1}, resp. [3]), but lower than those of the corresponding A*[s]U dimers (225 and 221 M^{-1}, resp. [1]). These observations are consistent with the crystal structure of N^6-methyladenine derivatives, which revealed a s-*cis*-conformation of the N^6-Me group, preventing *Watson–Crick* pairing [12][13]. *Ab initio* calculations revealed that the s-*trans*-rotamer is less stable by 1.83 kcal/mol than the s-*cis*-isomer [14][15]. An almost exclusive *Hoogsteen*-type H-bonding was also found by association studies of other N^6-methyladenine derivatives in solution, resulting in a lowering of K_{ass} by *ca.* 50%, as compared to adenine [16–18].

The A*[s]^{H}U* dimers **23** and **5** in $CDCl_3$ (K_{ass} = 806 and 720 M^{-1}; *Table 1*) associate more weakly than the *C(6/I)*-hydroxymethyl analogue of **23** (K_{ass} = 3373 M^{-1}; the analogue of **5** forms a gel; see [1]). The SCCs show a flattening above 30 mM, without reaching a plateau, reflecting an equilibrium between monoplex, linear associates, and cyclic duplexes (*Fig. 2*). The chemical shift for H–N(3/I) of **23** at a concentration of 30 mM (12.0 ppm) and similarly of **5** (11.4 ppm) suggests a large proportion of *Watson–Crick*-type base-paired cyclic duplexes of **23**, and a large proportion of *Hoogsteen*-type

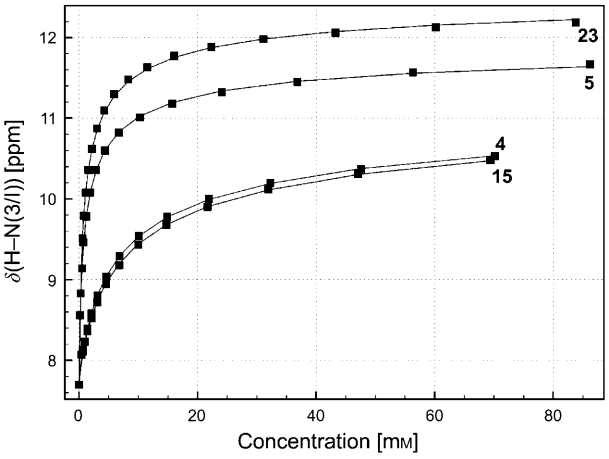

Fig. 2. *Shift/concentration curves* (SCCs) *for the A*[s]U(*) dimers* **4**, **5**, **15**, *and* **23** *in* $CDCl_3$ *solution* (including a value of 7.70 ppm for a 0.0001-mM soln.)

Table 1. *Association Constants* K_{ass} *from the Concentration Dependence of δ(HN(3)) in* $CDCl_3$ *at 295 K for the A*[s]U(*) Dimers* **4**, **5**, **15**, *and* **23** (including a value of 7.70 ppm for a 0.0001 mM soln.), ΔG_{295} *Value, Extrapolated Chemical Shifts of the Monoplexes and Duplexes, and Determination of the Thermodynamic Parameters by* van't Hoff *Analysis of the Temperature Dependence of δ(HN(3)) of* **5** *and* **23** *for 6 mM Solutions in* $CDCl_3$ *at 7–50°*

Dimer	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)]
15	76	7.78	11.44	2.5	[d])	[d])
4	95	7.71	11.42	2.7	[d])	[d])
23	806	7.69	12.63	3.9	14.2	34.8
5	720	7.70	12.01	3.9	10.0	21.0

[a]) Extrapolated for 0 mM. [b]) Extrapolated for infinite concentration. [c]) Calculated from K_{ass}. [d]) Not determined.

base-paired cyclic duplexes of **5** (see [1]), in agreement with the $-\Delta H$ values of 14.2 and 10.0 kcal/mol, as determined by *van't Hoff* analysis of the association of **23** and **5**, respectively.

The temperature-dependent CD spectra recorded for 1 mM solutions of **15** and **4** show a weak variation of the ellipticity, in agreement with the poor stacking expected for linear associates (*Fig. 3*). For **15**, a positive *Cotton* effect was observed with extrema at 265–275 nm (positive) and at 230 nm (negative), whereas the curve of **4** shows a negative *Cotton* effect, with extrema at 230 and 285 nm. This difference may be traced back to the intramolecular H-bond between C(5′)–OH and N(3) of the adenosine moiety of **4**, and the concomitant change of the conformation of the ribofuranosyl ring from *N* (**15**) to *S* (**4**). The CD spectra of the related pair of dinucleosides **23** and **5** show a stronger temperature dependence of the ellipticity that decreases with increasing

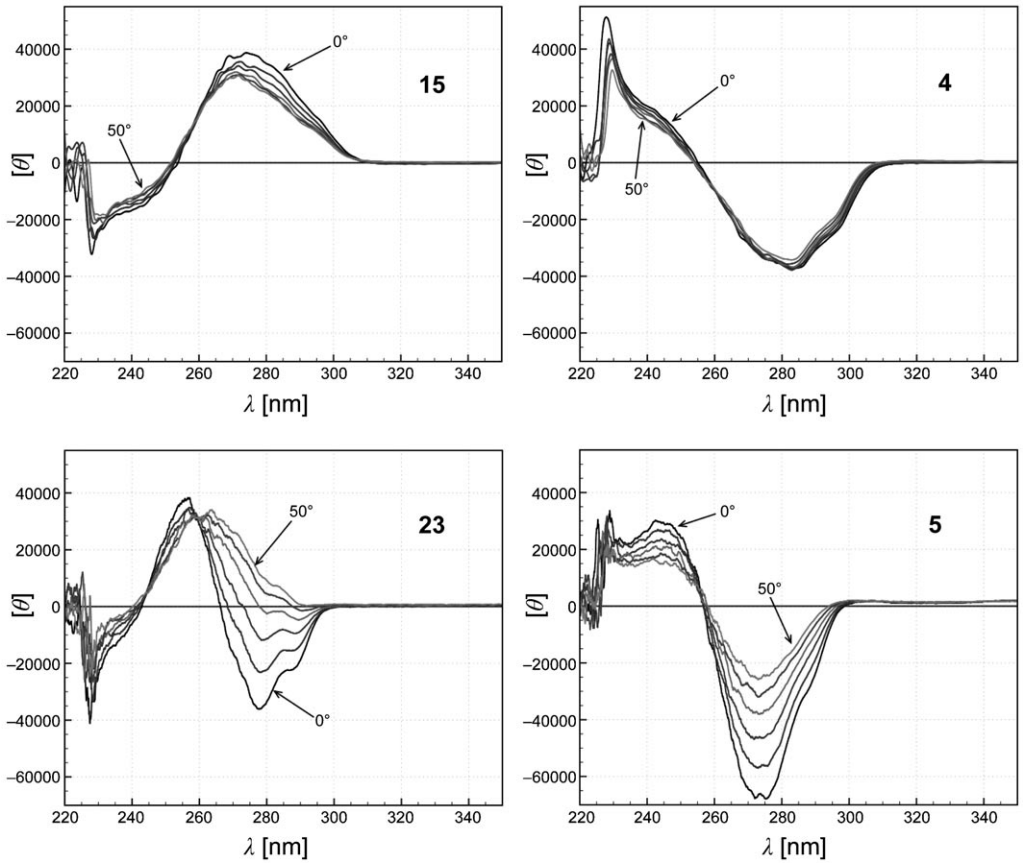

Fig. 3. *Temperature-dependent CD spectra* (solid lines, in 10° steps from 0° to 50°) *of 1-mM solutions of* **4**, **5**, **15**, *and* **23** *in* $CHCl_3$

temperature, evidencing π-stacking of the nucleobases as expected of cyclic duplexes. At 0°, the CD spectra of **23** and **5** are characterised by a negative *Cotton* effect, with extrema at 275–285 nm (both compounds), and at 260 (**23**) and 245 (**5**) nm. Upon increasing the temperature to 50°, the negative *Cotton* effect of **5** decreases, the one of **23** disappears gradually, and only the positive extrema at 260 and 245 nm remain. At 50°, the CD curves of **23** and **5** resemble those of **15** and **4**, respectively. This suggests that the linear associates of the silyl ethers **15** and **23** adopt a similar conformation, and that it differs from that of alcohols **4** and **5**. Hence, the different conformation of the ribofuranosyl ring correlating with the orientation of the C(4′/II) substituent (*gt*/*tg ca.* 1:1 for **15** and **23**; *gg* of **4** and **5**), as determined by the intramolecular H-bond in **4** and **5**, appears to be responsible for the opposite sign of the CD curves at 50°. The molar ellipticity ($[\theta]$) of the four dimers ranges from $-6\cdot10^4$ to $+4\cdot10^4$ deg·cm^2/dmol, and compares well to the one of the corresponding A*[s]U dimers, ranging from *ca.*

$-6\cdot10^4$ to $+2\cdot10^4$ deg·cm²/dmol [1][4]), and of the corresponding ^{H}A*[s]U dimers (deaminated at C(6)), ranging from *ca.* $-5\cdot10^4$ to $+10^4$ deg·cm²/dmol [3].

Conformation of the ^{Me}A[s]U and A*[s]^{H}U* Dinucleosides in $CHCl_3$.* The conformation of unit I is similar for the two ^{Me}A*[s]U dimers **15** and **4**. The chemical shift for H–C(2′/I) of **15** and of **4** (4.88–4.89 ppm; *Table 5* in the *Exper. Part*) reflects a *ca.* 1:1 *syn*/*anti* orientation of the uracil moiety (see [1][3]). The same (*S*)/(*N*) ratio of conformers is indicated by $J(1',2'/I)/J(3',4'/I) = 0.6$, and a *gg*/*gt*/*tg* rotameric distribution of 26:36:38 and 29:43:28, respectively, is deduced from $J(4',5'a/I)$ and $J(4',5'b/I)$ ranging from 5.5 to 6.4 Hz. The *syn*-conformation of the ^{H}U* moiety (unit I) of the A*[s]^{H}U* dinucleosides **23** and **5** is evidenced by δ(H–C(2′/I)) of 5.19 and 5.18 ppm, respectively, while $J(1',2'/I)/J(3',4'/I) = 0.2$ reveals the preference for a (*N*)-conformation, and $J(4',5'a/I)$ and $J(4',5'b/I)$ (5.5–6.4 Hz) suggest a *gg*/*tg*/*gt* rotamer distribution of 6:58:36 and 5:46:49, respectively.

Unit II of the silyl ethers **15** and **23** adopts a *syn*-conformation, as revealed by δ(H–C(2′/II)) = 5.91 and 5.97 ppm, respectively, and shows a slight preference for the (*N*)-conformation ($J(1',2'/II)/J(3',4'/II) = 0.5–0.6$). A *ca.* 1:1 *gt*/*tg* ratio is deduced for **15** and **23** from $J(4',5'a/II)$ and $J(4',5'b/II)$ of 6.2–6.9 Hz. HO–C(5′/II) of the alcohols **4** and **5** forms a persistent intramolecular H-bond to N(3), as evidenced by the exclusive population of the *gg*-rotamer ($J(4',5'a/II) = J(4',5'b/II) < 1.0$ Hz), the strongly preferred (*S*)-conformation ($J(1',2'/II)/J(3',4'/II) > 4.6$), the downfield shift for HO–C(5′/II) (**4**: 6.73 ppm, **5**: 6.63 ppm), the upfield shift for H–C(2′/II) (5.23–5.25 ppm), and the typical small and large $J(5',OH)$ values ($\leq$1.0 and $\geq$10.0 Hz; *cf.* [1][3][19][20]).

Solubility and Gelation Properties of the Dinucleosides **4** *and* **5**. The solubility of **4** and **5**, and their ability to form gels was evaluated with a selection of 16 solvents, based on *Chastrette*'s classification [21], at a concentration of 1% (*w*/*v*), according to the same procedure as reported for **1** and **2** (*Table 2*) [3]. Under these conditions, **4** and **5** were soluble in most of the solvents tested, except in hexane, toluene, $^{i}Pr_2O$, and H_2O. No significant increase of the viscosity of the solution, indicating the formation of gelating associates, was detected.

It thus appears that such dinucleosides may associate to form linear aggregates that are cross-linked by H-bonding involving either the nucleobase or $HOCH_2$–C(6/I) leading to gels, provided that formation of cyclic duplexes is disfavoured. Stacking of the nucleobases appears to contribute to gelation without being a decisive factor.

We thank Dr. *Bruno Bernet* for checking the *Exper. Part* and for helpful suggestions.

Experimental Part

General. See [3]. *van't Hoff* analysis: see [1].

Methylation of **6**. A biphasic mixture of **6** [1] (4.000 g, 7.22 mmol) and Bu_4NBr (2.327 g, 7.22 mmol) in CH_2Cl_2 (18 ml) and 1M aq. NaOH soln. (18 ml) was treated with MeI (1.80 ml, 28.88 mmol), and vigorously stirred for 30 min at 25°. The mixture was extracted three times with CH_2Cl_2. The combined

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[4]) For comparison purposes, the ellipticity (θ, [mdeg]) values reported in [1] were converted to [θ] [deg cm²/dmol].

Table 2. *Solubility of the Dinucleosides* **4** *and* **5** (1% (*w*/*v*)) *in Selected Solvents*

Class	Solvent	**4**[a])	**5**[a])
Aliphatic, apolar[b])	Hexane[c])	I	I
Aromatic, apolar	Toluene	I[d])	I[d])
Electron-pair donor	$^{i}Pr_2O$	I	I
Aprotic, dipolar	CH_2Cl_2	S	S
	Acetone	S	S
	$ClCH_2CH_2Cl$	S	S
	Butan-2-one	S	S
	MeCN	S	S
	AcOEt	S	S
Aprotic, highly dipolar	DMF	S	S
H-Bonding	MeOH	S	S
	EtOH	S	S
	BuOH	S	S
	Decanol[b])	S	I[d])
H-Bonding, strongly associated	H_2O	I	I
Miscellaneous	$CHCl_3$	S	S

[a]) I: insoluble, S: soluble. [b]) Missing in *Chastrette*'s original classification [21]. [c]) Reclassified solvent. [d]) Soluble at 70°.

org. layers were dried (Na_2SO_4) and evaporated. FC (AcOEt/cyclohexane 1:2 → 2:1) gave **7** (2.794 g, 68%) and **8** (873 mg, 21%).

Data of N^6-*Benzoyl-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′*-O-*isopropylidene*-N^6-*methyladenosine* (**7**). Colourless glass. R_f (cyclohexane/AcOEt 1:1) 0.73. $[\alpha]_D^{25} = -51.0$ ($c = 0.95$, $CHCl_3$). UV ($CHCl_3$): 283 (15100). IR (ATR): 3059*w*, 2957*w*, 2867*w*, 1669*m*, 1572*s*, 1457*m*, 1447*m*, 1417*w*, 1374*w*, 1320*s*, 1259*m*, 1207*s*, 1125*m*, 1078*s*, 1039*s*, 1021*s*, 968*w*, 923*w*, 893*w*, 871*m*, 826*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 3*; additionally, 7.47–7.43 (*m*, 2 arom. H); 7.33–7.16 (*m*, 3 arom. H); 3.81 (*s*, MeN); 1.64, 1.41 (2*s*, Me_2C); 1.59 (*sept.*, $J = 6.8$, Me_2CH); 0.85 (*d*, $J = 6.8$, Me_2CH); 0.80, 0.78 (2*s*, Me_2CSi); 0.07, 0.05 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 172.06 (*s*, C=O); 136.11 (*s*); 130.54 (*d*); 128.57 (2*d*); 127.87 (2*d*); 114.23 (*s*, Me_2C); 35.99 (*q*, MeN); 34.11 (*d*, Me_2CH); 27.39, 25.49 (2*q*, Me_2C); 25.43 (*s*, Me_2CSi); 20.42, 20.38 (2*q*, Me_2CSi); 18.61 (*q*, Me_2CH); −3.19, −3.35 (2*q*, Me_2Si). HR-MALDI-MS: 568.2954 ($[M + H]^+$, $C_{29}H_{41}N_5O_5Si^+$; calc. 568.2955).

Data of N^6-*Benzoyl-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′*-O-*isopropylidene-1-methyladenosine* (**8**). Colourless glass. R_f (cyclohexane/AcOEt 1:1) 0.22. $[\alpha]_D^{25} = -76.7$ ($c = 1.2$, $CHCl_3$). UV ($CHCl_3$): 250 (13080), 306 (11800). IR (ATR): 2956*w*, 2867*w*, 1666*m* (sh), 1640*s*, 1577*m*, 1541*s*, 1505*w*, 1463*w*, 1447*w*, 1431*w*, 1376*s*, 1309*m*, 1251*s*, 1211*s*, 1170*w*, 1156*m*, 1127*m*, 1076*s*, 1019*m*, 1003*m*, 969*w*, 925*w*, 873*m*, 828*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 3*; additionally, 8.18–8.14 (*m*, 2 arom. H); 7.51–7.36 (*m*, 3 arom. H); 3.73 (*s*, MeN); 1.60, 1.37 (2*s*, Me_2C); 1.55 (*sept.*, $J = 6.8$, Me_2CH); 0.81 (*d*, $J = 6.8$, Me_2CH); 0.76, 0.75 (2*s*, Me_2CSi); 0.03, −0.01 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 177.09 (*s*, C=O); 135.78 (*s*); 131.84 (*d*); 129.68 (2*d*); 128.00 (2*d*); 114.32 (*s*, Me_2C); 37.08 (*q*, MeN); 34.12 (*d*, Me_2CH); 27.38, 25.55 (2*q*, Me_2C); 25.37 (*s*, Me_2CSi); 20.37 (*q*, Me_2CSi); 18.62, 18.59 (2*q*, Me_2CH); −3.19, −3.32 (2*q*, Me_2Si). HR-MALDI-MS: 568.2955 ($[M + H]^+$, $C_{29}H_{41}N_5O_5Si^+$; calc. 568.2955).

Methylation of **9**. A biphasic mixture of **9** [1] (3.246 g, 3.79 mmol) and Bu_4NBr (1.224 g, 3.79 mmol) in CH_2Cl_2 (19 ml) and 1M aq. NaOH soln. (19 ml) was treated with MeI (944 µl, 15.16 mmol), and vigorously stirred for 30 min at 25°. The mixture was extracted three times with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (AcOEt/cyclohexane 1:4 → 1:1) gave **10** (2.420 g, 73%) and **11** (676 mg, 21%).

Table 3. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Adenosine Monomers* **7**, **8**, **10**–**13**, *and* **17** *in $CDCl_3$*

	7	**8**	**10**	**11**	**12**	**13**	**17**
H–C(2)	8.57	7.98	8.48	7.89	8.53	8.52	8.79
H–C(8)	8.18	7.79	–	–	–	–	–
CH_a–C(8)	–	–	4.44	4.25	4.88	4.84	4.94
CH_b–C(8)	–	–	4.40	4.21	4.84	4.78	4.87
H–C(1′)	6.17	5.99	6.13	6.07	6.24	6.25	6.31
H–C(2′)	5.23	5.07	5.71	5.50	5.53	5.74	5.82
H–C(3′)	4.94	4.86	4.92	4.78	5.02	5.07	5.12
H–C(4′)	4.45	4.33	4.11	4.06	4.23	4.25	4.29
H_a–C(5′)	3.86	3.71	3.70	3.71	3.80	3.72	3.74
H_b–C(5′)	3.76	3.71	3.60	3.59	3.78	3.64	3.63
$J(H_a,H_b)$	–	–	11.9	11.8	14.7	12.5	12.6
J(1′,2′)	2.8	2.9	2.8	2.9	2.9	2.6	2.4
J(2′,3′)	6.2	6.3	6.6	6.7	6.7	6.5	6.4
J(3′,4′)	2.3	2.6	3.7	4.0	3.9	3.6	3.4
J(4′,5′a)	3.7	4.4	6.0	6.4	4.8	5.6	5.9
J(4′,5′b)	4.0	4.4	6.3	6.2	4.8	5.7	5.8
J(5′a,5′b)	11.3	[a])	10.8	10.6	11.1	10.9	10.8

[a]) Not assigned.

Table 4. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Adenosine Monomers* **7**, **8**, **10**–**13**, *and* **17** *in $CDCl_3$*

	7	**8**	**10**	**11**	**12**	**13**	**17**
C(2)	154.73	146.91	153.55	146.35	151.84	152.22	153.08
C(4)	151.83	144.87	151.50	145.89	153.83	150.31	149.64
C(5)	126.44	122.56	125.63	121.58	124.89	125.08	121.95
C(6)	152.08	147.38	154.71[a])	148.43[a])	154.48[a])	155.23	152.16
C(8)	141.95	138.14	152.52[a])	146.76[a])	154.58[a])	153.32	150.01
CH$_2$–C(8)	–	–	59.40	59.53	58.41	36.65	36.74
C(1′)	91.75	91.18	90.14	89.86	89.88	90.15	90.29
C(2′)	84.86	84.93	82.67	83.28	83.73	83.02	83.12
C(3′)	81.54	81.48	81.80	81.74	80.68	81.37	81.55
C(4′)	87.22	86.90	86.87	86.43	86.68	87.31	87.62
C(5′)	63.44	63.16	63.08	63.16	62.69	62.75	62.78

[a]) Assignments may be interchanged.

Data of N^6*-Benzoyl-5′*-O*-[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′*-O*-isopropylidene-8-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-*N^6*-methyladenosine* (**10**). White solid. R_f (cyclohexane/AcOEt 2:1) 0.71. M.p. 68–78°. $[\alpha]_D^{25} = -21.1$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 241 (20270), 285 (18030). IR (ATR): 3059*w*, 3028*w*, 2955*w*, 2931*w*, 2865*w*, 1673*m*, 1590*m*, 1575*s*, 1509*m*, 1491*w*, 1447*m*, 1416*w*, 1370*w*, 1344*m*, 1317*m*, 1307*m*, 1250*s*, 1213*m*, 1179*m*, 1154*m*, 1129*m*, 1062*s*, 1038*s*, 975*m*, 917*m*, 899*m*, 866*m*, 822*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 3*; additionally, 7.51–7.15 (17 arom. H); 6.88–6.85 (2 arom. H); 3.81 (*s*, MeN); 3.79 (*s*, MeO); 1.57 (*sept.*, $J = 6.8$, Me$_2$C*H*); 1.48, 1.35 (2*s*, Me$_2$C); 0.83 (*d*, $J = 6.8$, *Me*$_2$CH); 0.79, 0.78 (2*s*, Me$_2$CSi); −0.04 (*s*, Me$_2$Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 172.29 (*s*, C=O); 159.02, 143.57, 143.50, 136.44, 134.54 (5*s*); 130.63 (2*d*); 130.61 (*d*);

128.72 (2*d*); 128.54 (4*d*); 128.14 (4*d*); 127.99 (2*d*); 127.40 (2*d*); 114.37 (*s*, Me_2C); 113.47 (2*d*); 88.10 (*s*, Ph_2C); 55.37 (*q*, MeO); 35.88 (*q*, MeN); 34.20 (*d*, Me_2CH); 27.37, 25.67 (2*q*, Me_2C); 25.35 (*s*, Me_2CSi); 20.40 (*q*, Me_2CSi); 18.57, 18.53 (2*q*, Me_2CH); −3.30, −3.34 (2*q*, Me_2Si). HR-MALDI-MS: 892.4064 ($[M + Na]^+$, $C_{50}H_{59}N_5NaO_7Si^+$; calc. 892.4081).

Data of N^6*-Benzoyl-5′-*O*-[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-*O*-isopropylidene-8-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-1-methyladenosine* (**11**). Colourless glass. R_f (cyclohexane/AcOEt 2:1) 0.26. $[\alpha]_D^{25} = -25.6$ ($c = 1.3$, $CHCl_3$). UV ($CHCl_3$): 241 (24340), 277 (11920), 305 (12000). IR (ATR): 3058*w*, 3028*w*, 2956*w*, 2867*w*, 1645*s*, 1607*m*, 1578*m*, 1542*m*, 1509*m*, 1489*w*, 1463*w*, 1447*m*, 1416*w*, 1391*m*, 1372*m*, 1346*w*, 1307*m*, 1250*s*, 1213*m*, 1178*m*, 1155*m*, 1060*s*, 1032*s*, 1002*w*, 970*m*, 928*w*, 901*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 3*; additionally, 8.16–8.13 (*m*, 2 arom. H); 7.54–7.20 (*m*, 15 arom. H); 6.78–6.75 (*m*, 2 arom. H); 3.78 (*s*, MeO); 3.71 (*s*, MeN); 1.61 (*sept.*, $J = 6.9$, Me_2CH); 1.46, 1.33 (2*s*, Me_2C); 0.87 (*d*, $J = 6.9$, Me_2CH); 0.83 (*s*, Me_2CSi); 0.05, 0.04 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 177.84 (*s*, C=O); 158.79, 143.71, 143.64, 136.24, 134.85 (5*s*); 131.78 (*d*); 130.48 (2*d*); 129.78 (2*d*); 128.56, 128.54 (4*d*); 128.06 (2*d*); 127.97, 127.96 (4*d*); 127.12 (2*d*); 114.46 (*s*, Me_2C); 113.33 (2*d*); 87.86 (*s*, Ph_2C); 55.34 (*q*, MeO); 36.82 (*q*, MeN); 34.22 (*d*, Me_2CH); 27.38, 25.73 (2*q*, Me_2C); 25.35 (*s*, Me_2CSi); 20.44 (*q*, Me_2CSi); 18.63, 18.61 (2*q*, Me_2CH); −3.18, −3.26 (2*q*, Me_2Si). HR-MALDI-MS: 892.4069 ($[M + Na]^+$, $C_{50}H_{59}N_5NaO_7Si^+$; calc. 892.4081).

N^6*-Benzoyl-5′-*O*-[dimethyl(1,1,2-trimethylpropyl)silyl]-8-(hydroxymethyl)-2′,3′-*O*-isopropylidene-*N^6*-methyladenosine* (**12**). A soln. of **10** (1.637 g, 1.88 mmol) in CH_2Cl_2 (10 ml) was treated with Et_3SiH (2.4 ml, 15.0 mmol) and $Cl_2CHCOOH$ (1.9 ml, 22.6 mmol), and stirred for 15 min at 25°. The mixture was neutralised with sat. aq. $NaHCO_3$ soln., and the aq. layer was extracted with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (cyclohexane/AcOEt 2:1 → 1:1) gave **12** (884 mg, 79%). White solid. R_f (cyclohexane/AcOEt 2:1) 0.24. M.p. 55–60°. $[\alpha]_D^{25} = -24.1$ ($c = 0.75$, $CHCl_3$). UV ($CHCl_3$): 286 (15280). IR (ATR): 3375*w*, 3346*w*, 2956*w*, 2868*w*, 1671*m*, 1590*s*, 1575*s*, 1458*m*, 1447*m*, 1418*w*, 1372*m*, 1344*m*, 1321*s*, 1275*m*, 1251*m*, 1210*m*, 1155*m*, 1130*m*, 1079*s*, 1044*s*, 971*w*, 911*w*, 866*m*, 828*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 3*; additionally, 7.45–7.42 (*m*, 2 arom. H); 7.32–7.27 (*m*, 1 arom. H); 7.20–7.16 (*m*, 2 arom. H); 3.78 (*s*, MeN); 3.52 (*dd*, $J = 6.4, 5.9$, OH); 1.62, 1.38 (2*s*, Me_2C); 1.61 (*sept.*, $J = 6.9$, Me_2CH); 0.86 (*d*, $J = 6.9$, Me_2CH); 0.83 (*s*, Me_2CSi); 0.05 (*s*, Me_2Si). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 4*; additionally, 172.32 (*s*, C=O); 136.34 (*s*); 130.75 (*d*); 128.71 (2*d*); 128.00 (2*d*); 115.00 (*s*, Me_2C); 35.89 (*q*, MeN); 34.17 (*d*, Me_2CH); 27.33, 25.49 (2*q*, Me_2C); 25.56 (*s*, Me_2CSi); 20.44, 20.40 (2*q*, Me_2CSi); 18.54 (*q*, Me_2CH); −3.34 (*q*, Me_2Si). HR-MALDI-MS: 598.3056 ($[M + H]^+$, $C_{30}H_{44}N_5O_6Si^+$; calc. 598.3061).

N^6*-Benzoyl-8-(chloromethyl)-5′-*O*-[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-*O*-isopropylidene-*N^6*-methyladenosine* (**13**). A soln. of **12** (785 mg, 1.31 mmol) in CH_2Cl_2 (6.5 ml) was cooled to 0°, treated with EtN^iPr_2 (342 µl, 1.97 mmol) and MsCl (101 µl, 1.31 mmol), stirred at 25° for 18 h, treated with LiCl (56 mg, 1.31 mmol), and stirred for 3 h. The mixture was diluted with CH_2Cl_2 and washed with H_2O. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (cyclohexane/AcOEt 4:1) gave **13** (755 mg, 94%). White solid. R_f (cyclohexane/AcOEt 4:1) 0.36. M.p. 45–55°. $[\alpha]_D^{25} = -23.0$ ($c = 0.7$, $CHCl_3$). UV ($CHCl_3$): 293 (15390). IR (ATR): 2957*w*, 2868*w*, 1673*m*, 1575*s*, 1461*m*, 1447*m*, 1417*w*, 1374*m*, 1350*m*, 1317*s*, 1277*m*, 1251*m*, 1211*m*, 1177*w*, 1154*m*, 1130*m*, 1080*s*, 1059*s*, 1043*s*, 1024*m*, 971*w*, 913*w*, 866*m*, 825*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 3*; additionally, 7.46–7.43 (*m*, 2 arom. H); 7.32–7.28 (*m*, 1 arom. H); 7.22–7.17 (*m*, 2 arom. H); 3.80 (*s*, MeN); 1.63, 1.40 (2*s*, Me_2C); 1.58 (*sept.*, $J = 6.9$, Me_2CH); 0.84 (*d*, $J = 6.9$, Me_2CH); 0.80, 0.79 (2*s*, Me_2CSi); −0.01, −0.02 (2*s*, Me_2Si). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 4*; additionally, 172.42 (*s*, C=O); 136.27 (*s*); 130.80 (*d*); 128.76 (2*d*); 128.01 (2*d*); 114.62 (*s*, Me_2C); 35.87 (*q*, MeN); 34.22 (*d*, Me_2CH); 27.38, 25.57 (2*q*, Me_2C); 25.43 (*s*, Me_2CSi); 20.43, 20.40 (2*q*, Me_2CSi); 18.58, 18.57 (2*q*, Me_2CH); −3.35 (*q*, Me_2Si). HR-MALDI-MS: 616.2706 ($[M + H]^+$, $C_{30}H_{43}ClN_5O_5Si^+$; calc. 616.2722).

*5′-*O*-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-*O*-isopropylidene-*N^6*-methyladenosine-8-methyl-(8^l → 5′-*S*)-2′,3′-*O*-isopropylidene-5′-thiouridine* (**15**). A soln. of **13** (684 mg, 1.11 mmol) and **14** [1] (380 mg, 1.11 mmol) in dry degassed MeOH (3.5 ml) was cooled to 0°, treated with a freshly prepared 1.27M soln. of MeONa in MeOH (3.5 ml, 4.44 mmol), and stirred at 25° for 19 h. The mixture was diluted with sat. aq. NH_4Cl soln. and H_2O, and extracted four times with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH 95:5) gave **15** (827 mg, 96%). White solid. R_f

(CH_2Cl_2/MeOH 95:5) 0.34. M.p. 192–195°. $[\alpha]_D^{25} = -20.9$ ($c = 0.7$, $CHCl_3$). UV ($CHCl_3$): 266 (22080). IR (ATR): 3314*w*, 2956*w*, 2865*w*, 1692*s*, 1621*s*, 1582*w*, 1535*w*, 1498*w*, 1456*w*, 1421*w*, 1373*s*, 1329*w*, 1296*w*, 1274*m*, 1259*m*, 1210*m*, 1156*w*, 1076*s*, 972*w*, 921*w*, 828*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 5*; additionally, 7.30 (*d*, $J = 8.1$, H–C(6/I)); 5.71 (*d*, $J = 8.1$, H–C(5/I)); 3.14 (*d*, $J = 4.7$, *Me*NH–C(6/II)); 1.54 (*sept.*, $J = 6.9$, Me_2CH); 1.60, 1.51, 1.40, 1.27 (4*s*, 2 *Me*$_2$C); 0.82 (*d*, $J = 6.9$, *Me*$_2$CH); 0.77, 0.76 (2*s*, Me_2CSi); −0.04, −0.06 (2*s*, Me_2Si). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 6*; additionally, 114.87, 113.83 (2*s*, 2 Me_2C); 34.23 (*d*, Me_2CH); 27.65 (*q*, *Me*NH–C(6/II)); 27.31, 27.20, 25.54, 25.38 (4*q*, 2 *Me*$_2$C); 25.35 (*s*, Me_2CSi); 20.42, 20.40 (2*q*, *Me*$_2$CSi); 18.59, 18.56 (2*q*, *Me*$_2$CH); −3.34, −3.36 (2*q*, Me_2Si). HR-MALDI-MS: 776.3454 ($[M + H]^+$, $C_{35}H_{54}N_7O_9SSi^+$; calc. 776.3473).

Table 5. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the A*[s]U$^{(*)}$ Dimers* **4**, **5**, **15**, *and* **23** *in $CDCl_3$*

	15 (96 mM)	**4** (113 mM)	**23** (96 mM)	**5** (123 mM)		**15**	**4**	**23**	**5**
Uridine unit (I)									
H–N(3/I)	10.49	10.58	12.14	11.72					
Me–C(6/I)	–	–	2.31	2.27					
H–C(1′/I)	5.64	5.63	5.70	5.62[a])	*J*(1′,2′/I)	2.4	2.4	0.8	0.8
H–C(2′/I)	4.89	4.88	5.19	5.18	*J*(2′,3′/I)	6.5	6.6	6.4	6.3
H–C(3′/I)	4.65	4.58	4.88	4.93	*J*(3′,4′/I)	4.1	4.1	3.9	4.0
H–C(4′/I)	4.27–4.22	4.23–4.19	4.18	4.13	*J*(4′,5′a/I)	5.8	6.4	7.9	6.9
H_a–C(5′/I)	2.96	3.01	2.99	2.95	*J*(4′,5′b/I)	6.4	5.5	5.7	6.9
H_b–C(5′/I)	2.91	2.90	2.90	2.95	*J*(5′a,5′b/I)	14.0	13.8	12.8	[b])
Adenosine unit (II)									
MeN*H*–*C*(6/II)	6.74	6.90	–	–					
H_2N–C(6/II)	–	–	7.20	7.16					
H–C(2/II)	8.32	8.29	8.34	8.23					
CH_a–C(8/II)	4.28	4.23–4.19	4.10	4.25	*J*(H_a,H_b/II)	14.5	14.7	[b])	14.8
CH_b–C(8/II)	4.08	4.04	4.10	3.98					
H–C(1′/II)	6.24	6.08	6.39	6.18	*J*(1′,2′/II)	1.9	5.1	1.6	5.0
H–C(2′/II)	5.91	5.25	5.97	5.23	*J*(2′,3′/II)	6.3	5.8	6.2	5.9
H–C(3′/II)	5.11	5.09	5.11	5.08	*J*(3′,4′/II)	3.0	1.1	3.0	0.9
H–C(4′/II)	4.27–4.22	4.50	4.23	4.51	*J*(4′,5′a/II)	6.8	< 1.0	6.9	< 1.0
H_a–C(5′/II)	3.67	3.95	3.59	3.95	*J*(4′,5′b/II)	6.2	< 1.0	6.4	< 1.0
H_b–C(5′/II)	3.54	3.77	3.48	3.76	*J*(5′a,5′b/II)	10.5	12.5	10.5	10.5

[a]) Assignment may be interchanged with H–C(5/I). [b]) Not assigned.

*2′,3′-*O*-Isopropylidene-*N^6*-methyladenosine-8-methyl-(8^1 → 5′-*S*)-2′,3′-*O*-isopropylidene-5′-thiouridine* (**4**). In a polyethylene flask, a soln. of **15** (502 mg, 0.65 mmol) in THF (3.2 ml) was treated with $(HF)_3 \cdot Et_3N$ (1.1 ml, 19.4 mmol) and stirred at 25° for 24 h. The mixture was treated with 1M aq. NaOH soln. until the pH reached *ca.* 8, diluted with H_2O, and extracted four times with AcOEt. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH 95:5) gave **4** (400 mg, 98%). White solid. R_f (CH_2Cl_2/MeOH 95:5) 0.27. M.p. 180° (sintering from 150°). $[\alpha]_D^{25} = -72.3$ ($c = 0.6$, $CHCl_3$). UV ($CHCl_3$): 267 (21800). IR (ATR): 3305*w*, 3204*w*, 2986*w*, 2936*w*, 1690*s*, 1622*s*, 1583*w*, 1539*w*, 1499*w*, 1454*w*, 1373*s*, 1331*m*, 1299*w*, 1258*m*, 1212*s*, 1077*s*, 1011*m*, 851*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 5*; additionally, 7.28 (*d*, $J = 8.1$, H–C(6/I)); 6.73 (br. *d*, $J = 11.1$, HO–C(5′/II)); 5.70 (*d*, $J = 8.1$, H–C(5/I)); 3.13 (br. *s*, *Me*NH–C(6/II)); 1.63, 1.47, 1.36, 1.23 (4*s*, 2 Me_2C). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 6*; additionally, 114.86, 114.03 (2*s*, 2 Me_2C); 28.25 (*q*, *Me*NH–C(6/II)); 27.92, 27.12, 25.50, 25.28 (4*q*, 2 *Me*$_2$C). HR-MALDI-MS: 634.2281 ($[M + H]^+$, $C_{27}H_{36}N_7O_9S^+$; calc. 634.2295).

Table 6. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the A*[s]U$^{(*)}$ Dimers* **4**, **5**, **15**, *and* **23** *in $CDCl_3$*

	15	**4**	**23**	**5**		**15**	**4**	**23**	**5**
Uridine unit (I)					Adenosine unit (II)				
C(2/I)	150.44	150.46	152.26[a])	152.47[a])	C(2/II)	153.10	152.80	152.52	152.23
C(4/I)	163.78	163.76	163.03	163.27	C(4/II)	149.48[b])	[c])	150.55	149.71
C(5/I)	102.98	103.02	103.79	103.56	C(5/II)	118.90	119.31	118.38	118.67
C(6/I)	142.19	142.11	151.94[a])	151.41[a])	C(6/II)	155.13	155.37	155.48	155.75
					C(8/II)	148.58	147.75	149.46	148.63
Me–C(6/I)	–	–	20.57	20.55	CH_2–C(8/II)	28.14	28.25	29.14	28.74
C(1′/I)	94.01	93.80	92.21	92.24	C(1′/II)	90.25	92.41	88.58	88.47
C(2′/I)	84.41	84.35	85.07	84.79	C(2′/II)	83.18	82.84	83.09	82.89
C(3′/I)	83.25	83.06	84.81	84.47	C(3′/II)	82.39	81.81	82.32	81.76
C(4′/I)	88.12[a])	85.98	90.10	91.89	C(4′/II)	86.23[a])	85.84	88.22	85.72
C(5′/I)	33.88	33.93	35.15	34.63	C(5′/II)	63.01	63.45	63.03	63.40

[a]) Assignments may be interchanged. [b]) Broad signal. [c]) Not visible.

N^6-*Benzoyl-8-(chloromethyl)-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′*-O-*isopropylideneadenosine* (**17**). A soln. of **16** [1] (5.085 g, 8.71 mmol) in CH_2Cl_2 (29 ml) was cooled to 0°, treated with Et_2N^iPr (1.97 ml, 11.3 mmol) and MsCl (809 µl, 10.45 mmol), allowed to warm to 25°, and stirred for 19 h. Evaporation and FC (cyclohexane/AcOEt 3:7 → 1:1) gave **17** (4.249 g, 81%). White solid. R_f (cyclohexane/AcOEt 1:1) 0.64. M.p. 75–85°. $[\alpha]_D^{25} = -10.5$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 287 (21110). IR (ATR): 3104*w*, 2957*w*, 2867*w*, 1698*m*, 1609*s*, 1583*m*, 1526*w*, 1485*m*, 1460*m*, 1429*m*, 1373*m*, 1357*m*, 1248*s*, 1212*m*, 1156*m*, 1074*s*, 1001*w*, 970*w*, 925*w*, 828*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 3*; additionally, 9.03 (br. *s*, NH); 8.01–7.98 (*m*, 2 arom. H); 7.63–7.48 (*m*, 3 arom. H); 1.63, 1.41 (2*s*, Me_2C); 1.56 (*sept.*, $J = 6.9$, Me_2CH); 0.83 (*d*, $J = 6.9$, Me_2CH); 0.79, 0.78 (2*s*, Me_2CSi); −0.01, −0.02 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 164.39 (*s*, C=O); 133.58 (*s*); 132.86 (*d*); 128.91 (2*d*); 127.83 (2*d*); 114.42 (*s*, Me_2C); 34.24 (*d*, Me_2CH); 27.43, 25.63 (2*q*, Me_2C); 25.47 (*s*, Me_2CSi); 20.50, 20.47 (2*q*, Me_2CSi); 18.66 (*q*, Me_2CH); −3.22 (*q*, Me_2Si). HR-MALDI-MS: 602.2549 ($[M + H]^+$, $C_{29}H_{41}ClN_5O_5Si^+$; calc. 602.2565).

6-(Chloromethyl)-5′-O-[dimethyl(1,1,2-trimethylpropyl)silyl]-2′-3′-O-*isopropylideneuridine* (**19**). A soln. of **18** (3.377 g, 7.40 mmol) in CH_2Cl_2 (37 ml) was cooled to 0°, treated with EtN^iPr_2 (1.98 ml, 11.1 mmol) and MsCl (687 µl, 8.87 mmol), allowed to warm to 25°, and stirred for 18 h. Evaporation and FC (cyclohexane/AcOEt 2:1) gave **19** (2.834 g, 81%). White solid. R_f (cyclohexane/AcOEt 2:1) 0.32. M.p. 78–88°. $[\alpha]_D^{25} = -3.8$ ($c = 0.9$, $CHCl_3$). UV ($CHCl_3$): 268 (17270). IR (ATR): 3196*w* (br.), 3095*w*, 3066*w*, 2957*w*, 2868*w*, 1690*s*, 1625*w*, 1459*m*, 1378*s*, 1250*m*, 1209*m*, 1185*w*, 1157*m*, 1131*m*, 1079*s*, 1060*s*, 980*m*, 936*w*, 874*s*, 827*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 7*; additionally, 10.05 (br. *s*, NH); 1.58 (*sept.*, $J = 6.9$, Me_2CH); 1.53, 1.33 (2*s*, Me_2C); 0.84 (*d*, $J = 6.9$, Me_2CH); 0.81 (*s*, Me_2CSi); 0.06, 0.05 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 8*; additionally, 113.88 (*s*, Me_2C); 34.18 (*d*, Me_2CH); 27.33, 25.43 (2*q*, Me_2C); 25.37 (*s*, Me_2CSi); 20.45, 20.39 (2*q*, Me_2CSi); 18.55 (*q*, Me_2CH); −3.21 (*q*, Me_2Si). HR-MALDI-MS: 497.1849 ($[M + Na]^+$, $C_{21}H_{35}ClN_2NaO_6Si^+$; calc. 497.1851).

5′-O-*[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′-3′*-O-*isopropylidene-6-methyluridine* (**20**). A suspension of **19** (2.838 g, 5.97 mmol), MgO (2.420 g, 60.05 mmol) and 10% Pd/C (640 mg, 0.6 mmol) in AcOEt (60 ml) was stirred under H_2 (1 atm) for 4 h at 25°. Filtration through *Celite*, evaporation, and FC (cyclohexane/AcOEt 2:1 → 1:1) gave **20** (2.338 g, 89%). White solid. R_f (AcOEt) 0.50. M.p. 115.8–116.2°. $[\alpha]_D^{25} = +17.2$ ($c = 1.3$, $CHCl_3$). UV ($CHCl_3$): 261 (11720). IR (ATR): 3193*w* (br.), 3058*w*, 2957*w*, 2937*w*, 2867*w*, 1686*s*, 1626*w*, 1447*m*, 1372*s*, 1327*w*, 1310*w*, 1250*m*, 1209*m*, 1185*w*, 1158*m*, 1131*m*, 1080*s*, 1062*s*, 1006*w*, 974*w*, 935*w*, 875*m*, 826*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 7*; additionally, 10.04 (br. *d*, $J = 1.6$, NH); 1.58 (*sept.*, $J = 6.9$, Me_2CH); 1.52, 1.32 (2*s*, Me_2C); 0.84 (*d*, $J = 6.9$, Me_2CH); 0.81 (*s*, Me_2CSi); 0.06, 0.05 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 8*; additionally, 113.68 (*s*, Me_2C);

Table 7. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Uridine Monomers* **19**–**22** *in $CDCl_3$*

	19	**20**	**21**	**22**		**19**	**20**	**21**	**22**
H–C(5)	5.83	5.55	5.58	5.57					
CH_a–C(6)	4.43	–	–	–	$J(H_a,H_b)$	13.1	–	–	–
CH_b–C(6)	4.32	–	–	–					
Me–C(6)	–	2.32	2.32	2.31					
H–C(1′)	5.81	5.69	5.65	5.65	J(1′,2′)	1.1	1.1	2.4	1.0
H–C(2′)	5.25	5.21	5.25	5.23	J(2′,3′)	6.4	6.4	6.5	6.4
H–C(3′)	4.82	4.81	5.02	4.86	J(3′,4′)	4.4	4.3	4.1	3.8
H–C(4′)	4.15	4.12	4.22	4.12	J(4′,5′a)	5.3	5.6	3.1	7.2
H_a–C(5′)	3.80	3.78	3.86	3.23	J(4′,5′b)	7.0	7.0	4.6	7.2
H_b–C(5′)	3.76	3.74	3.79	3.23	J(5′a,5′b)	11.0	11.1	12.1	[a])

[a]) Not assigned.

Table 8. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Uridine Monomers* **19**–**22** *in $CDCl_3$*

	19	**20**	**21**	**22**		**19**	**20**	**21**	**22**
C(2)	150.51	150.77	151.39[a])	150.92	C(1′)	91.88	91.84	92.30	92.12
C(4)	162.94	163.43	162.76	163.41	C(2′)	84.33	84.35	83.57	85.02
C(5)	104.82	103.09	103.63	103.28	C(3′)	82.01	82.22	80.71	84.49
C(6)	150.86	153.38	152.98[a])	153.16	C(4′)	89.77	89.71	87.97	88.35
CH_2–C(6)	41.15	–	–	–	C(5′)	63.94	64.06	62.90	31.54
Me–C(6)	–	20.51	20.57	20.47					

[a]) Assignments may be interchanged.

34.19 (*d*, Me_2CH); 27.31, 25.40 (2*q*, Me_2C); 25.37 (*s*, Me_2CSi); 20.45, 20.39 (2*q*, Me_2CSi); 18.59, 18.54 (2*q*, Me_2CH); −3.22 (*q*, Me_2Si). HR-MALDI-MS: 463.2229 ($[M + Na]^+$, $C_{21}H_{36}N_2NaO_6Si^+$; calc. 463.2240).

*2′,3′-*O*-Isopropylidene-6-methyluridine* (**21**). A soln. of **20** (2.189 g, 4.97 mmol) in THF (50 ml) was treated with $Bu_4F \cdot 3\,H_2O$ (4.704 g, 14.9 mmol) and stirred for 19 h. Evaporation and FC (AcOEt) gave **21** (1.425 g, 96%). A sample for analysis was recrystallized from AcOEt. White solid. R_f (AcOEt) 0.43. M.p. 149.0–150.6°. $[\alpha]_D^{25} = -32.7$ ($c = 1.25$, $CHCl_3$). UV ($CHCl_3$): 257 (10050). IR (ATR): 3349*w* (br.), 3164*w* (br.), 3091*w*, 3050*w*, 2989*w*, 2937*w*, 2858*w*, 2808*w*, 1719*m*, 1674*s*, 1619*w*, 1466*m*, 1448*m*, 1380*s*, 1369*s*, 1333*w*, 1309*w*, 1290*w*, 1274*w*, 1232*w*, 1205*m*, 1157*m*, 1113*m*, 1083*m*, 1052*s*, 1030*s*, 1012*s*, 980*m*, 928*w*, 916*w*, 868*s*, 853*m*, 839*m*, 816*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 7*; additionally, 9.76 (br. *s*, NH); 3.25 (br. *s*, OH); 1.55, 1.34 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 8*; additionally, 114.30 (*s*, Me_2C); 27.43, 25.36 (2*q*, Me_2C). HR-EI-MS: 283.0925 ($[M - Me]^+$, $C_{12}H_{15}N_2O_6^+$; calc. 283.0925). Anal. calc. for $C_{13}H_{18}N_2O_6$ (298.29): C 52.35, H 6.08, N 9.39; found: C 52.37, H 5.94, N 9.37.

*5′-*S*-Acetyl-2′-3′-*O*-isopropylidene-6-methyl-5′-thiouridine* (**22**). A soln. of **21** (1.198 g, 4.02 mmol) in dry CH_2Cl_2 (40 ml) was cooled to 0°, treated with 4-(dimethylamino)pyridine (DMAP; 737 mg, 6.03 mmol) and TsCl (843 mg, 4.42 mmol), allowed to warm to 25°, and stirred for 4 h. After dilution with sat. NH_4Cl soln., the mixture was extracted three times with AcOEt. The combined org. layers were dried (Na_2SO_4) and evaporated. A soln. of the residue in dry DMF (25 ml) was treated with AcSK (1.153 g, 10.1 mmol) and heated to 70° for 1 h. The soln. was diluted with AcOEt and washed three times with sat. aq. NH_4Cl soln. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (cyclohexane/AcOEt 1:1 → 1:2) gave **22** (1.116 g, 78%). Recrystallisation of a sample from MeCN gave slightly red crystals suitable for X-ray analysis. R_f (cyclohexane/AcOEt 1:1) 0.19. M.p. 197.5–198.8°.

$[\alpha]_D^{25} = +29.4$ ($c = 1.1$, $CHCl_3$). UV ($CHCl_3$): 258 (12663). IR (ATR): 3201*w* (br.), 3084*w*, 2990*w*, 2935*w*, 2819*w*, 1680*s*, 1626*m*, 1450*w*, 1443*m*, 1414*w*, 1383*s*, 1368*s*, 1309*w*, 1276*m*, 1239*w*, 1207*m*, 1175*w*, 1157*m*, 1136*m*, 1094*s*, 1079*m*, 1052*s*, 1034*m*, 1025*m*, 1015*m*, 997*m*, 983*m*, 971*m*, 953*m*, 911*w*, 868*m*, 842*m*, 829*m*, 809*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 7*; additionally, 10.16 (br. *s*, NH); 2.32 (*s*, AcS); 1.50, 1.31 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 8*; additionally, 194.89 (*s*, Me*C*=O); 113.86 (*s*, Me_2C); 30.67 (*q*, *Me*C=O); 27.15, 25.21 (2*q*, Me_2C). HR-MALDI-MS: 379.0934 ($[M + Na]^+$, $C_{15}H_{20}N_2NaO_6S^+$; calc. 379.0940). Anal. calc. for $C_{15}H_{20}N_2O_6S$ (356.40): C 50.55, H 5.66, N 7.86; found: C 50.77, H 5.71, N 7.96.

X-Ray Analysis of **22**. Dimensions of the analyzed crystal: cube $0.6 \times 0.42 \times 0.4$ mm. $C_{15}H_{20}N_2O_6S$, M_r 356.40, orthorhombic $P2_12_12_1$; $a = 9.1667(2)$, $b = 12.6749(3)$, $c = 14.8909(4)$ Å, $V = 1730.13(7)$ Å^3, $Z = 4$, $D_x = 1.368$ Mg/m^3. The reflections were measured on a *Bruker-Nonius-KappaCCD* diffractometer (graphite monochromator, MoK_α radiation, $\lambda = 0.71073$) at 250 K. All the calculations were performed using maXus (*Bruker Nonius*, Delft, and *MacScience*, Japan). The structure was solved by direct methods and refined by full-matrix least-squares analysis (SHELXL-97) including an isotropic extinction correction. All non-H-atoms were refined anisotropically (H-atoms isotropic, whereby H-positions are based on stereochemical considerations).

2′,3′-O-*Isopropylidene-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]adenosine-8-methyl-(8′ → 5′*-S)-*2′,3′*-O-*isopropylidene-6-methyl-5′-thiouridine* (**23**). A suspension of **22** (952 mg, 2.67 mmol) in dry MeOH (26 ml) was heated to reflux until complete dissolution, cooled to 25°, treated with K_2CO_3 (1.107 g, 8.01 mmol), stirred for 40 min, treated with **17** (1.608 g, 2.67 mmol), and stirred for 15 h at 25°. The mixture was treated with sat. aq. NH_4Cl soln. and diluted with H_2O. After evaporation of MeOH, the residue was extracted four times with AcOEt. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH 95:5) gave **23** (1.626 g, 78%). R_f (CH_2Cl_2/MeOH 90:10) 0.54. M.p. 139–142°. $[\alpha]_D^{25} = -117.3$ ($c = 0.8$, $CHCl_3$). UV ($CHCl_3$): 263 (24730). IR (ATR): 3436*w*, 3346*w*, 3260*w*, 3220*w*, 2959*w*, 2866*w*, 2815*w*, 1687*s*, 1642*s*, 1594*m*, 1574*w*, 1458*w*, 1433*m*, 1417*w*, 1372*s*, 1331*m*, 1291*m*, 1251*m*, 1233*m*, 1216*m*, 1206*m*, 1154*m*, 1141*m*, 1085*s*, 1068*s*, 1056*s*, 977*m*, 966*m*, 934*m*, 896*w*, 872*s*, 853*m*, 828*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 5.58 (*s*, H–C(5/I)); 1.60, 1.49, 1.41, 1.29 (4*s*, 2 Me_2C); 1.52 (*sept.*, $J = 6.9$, Me_2CH); 0.80 (*d*, $J = 6.9$, Me_2CH); 0.75, 0.74 (2*s*, Me_2CSi); −0.05, −0.07 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 113.83, 113.64 (2*s*, 2 Me_2C); 34.25 (*d*, Me_2CH); 27.38, 27.25, 25.64, 25.35 (4*q*, 2 Me_2C); 25.38 (*s*, Me_2CSi); 20.48 (*q*, Me_2CSi); 18.68, 18.66 (2*q*, Me_2CH); −3.21 (*q*, Me_2Si). HR-MALDI-MS: 798.3473 ($[M + H]^+$, $C_{35}H_{53}N_7NaO_9SSi^+$; calc. 798.3292).

2′,3′-O-*Isopropylideneadenosine-8-methyl-(8′ → 5′*-S*)-2′,3′*-O-*isopropylidene-6-methyl-5′-thiouridine* (**5**). In a polyethylene flask, a soln. of **23** (1.008 g, 1.30 mmol) in dry THF (4.5 ml) was treated with $(HF)_3 \cdot Et_3N$ (3.5 ml, 65 mmol) and stirred at 25° for 14 h. The mixture was cooled to 0°, treated with 1M aq. NaOH soln. until the pH reached *ca.* 10 and extracted four times with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH 95:5 → 90:10) gave **5** (754 mg, 92%). White solid. R_f (CH_2Cl_2/MeOH 90:10) 0.42. M.p. 160–164°. $[\alpha]_D^{25} = -105.8$ ($c = 1.1$, $CHCl_3$). UV ($CHCl_3$): 263 (25140). IR (ATR): 3326*w* (br.), 3190*w* (br.), 2986*w*, 2936*w*, 2868*w*, 2823*w*, 1688*s*, 1635*s*, 1604*m*, 1579*m*, 1444*m*, 1371*s*, 1332*m*, 1301*m*, 1266*m*, 1210*s*, 1156*m*, 1069*s*, 969*m*, 946*m*, 869*s*, 850*s*, 823*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 6.63 (*dd*, $J = 10.0$, 1.0, HO–C(5′/II)); 5.52 (*s*, H–C(5/I)); 1.63, 1.48, 1.36, 1.30 (4*s*, 2 Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 113.95, 113.85 (2*s*, 2 Me_2C); 27.96, 27.27 25.61, 25.42 (4*q*, 2 Me_2C). HR-MALDI-MS: 656.2110 ($[M + Na]^+$, $C_{27}H_{35}N_6NaO_9S^+$; calc. 656.2115).

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