Oligonucleotide Analogues with Integrated Bases and Backbones

Part 25

Structural Effects on the Gelation of Self-Complementary A*[s]U Dinucleosides

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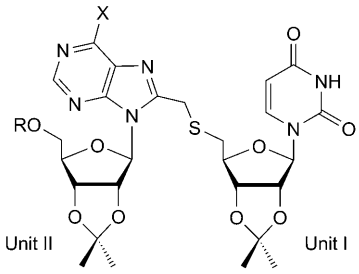
The ability of A*[s]U dinucleosides to gel organic solvents and water is modulated by changing the nature of the substituents at $O-C(2')$ and $O-C(3')$, as evidenced by comparing the gelation of the dinucleosides **7**–**9** and the properties of the gels. A mere extension of the hydrophobic moiety, by replacing the isopropylidene groups of **2** by cyclohexylidene groups, as in **7**, has a small effect, while changing the conformation of the ribose ring and reducing the size of the hydrophobic moiety, as in **8**, has a strong effect on the scope of gelation, the minimum gelation concentration, as low as 0.07% for pentanol and decanol, and the properties of the gel. The fully deprotected dinucleoside **9** gels water at a minimal gelation concentration of 0.6%. A TEM of the corresponding xerogel shows the formation of fibers with a diameter of *ca.* 30 to 90 nm.

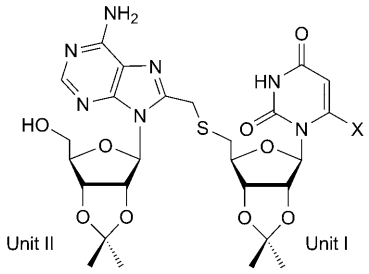
Introduction. – The A*[s]U[1]) silyl ether **1** in $CHCl_3$ solution forms an equilibrium of the monoplex and linear associates [1], whereas the A*[s]U$^{(*)}$ alcohols **2** and **5** form gels with organic solvents involving their self-association to build a network by H-bonding, as evidenced by the absence of gelation by the deaminated ^{H}A*[s]U dinucleoside **3** [2]. Also the corresponding *N*-Me analogue ^{Me}A*[s]U **4** of **2** and the deoxygenated A*[s]^{H}U* analogue **6** of **5** do not form gels, further evidencing that gelation requires the formation of linear associates that are cross-linked by H-bonding involving the nucleobase and/or $HOCH_2-C(6/I)$ [3]. The synthesis and the evaluation of the gelation properties of these dinucleosides identified some of the structural elements involved in the formation of gels. Other structural aspects of these dinucleosides that may affect gelation involve the dimethyl-dioxolane rings, *viz.,* the size of this hydrophobic moiety and the conformational restriction resulting from its annulation. To investigate their effect, we planned to synthesize the cyclohexylidene-

[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 derivatives. The replacement of the amino group at C(6) of adenosine by a N^6-methylamino group and the replacement of the $HOCH_2$ group of uridine by an H-atom are denoted by 'Me' in superscript (^{Me}) and 'H' in superscript (^{H}), respectively; for example, ^{Me}A and ^{H}U represent N^6-methyladenosine and *C(6)*-methyluridine derivatives, respectively. 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.

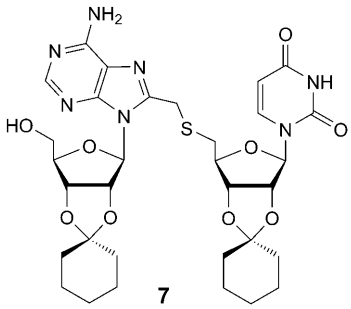
protected A*[s]U dinucleoside **7**, the 2′,3′-di-*O*-methyl ether **8**, and the unprotected dinucleoside **9**, and to evaluate their ability to form gels with different solvents.



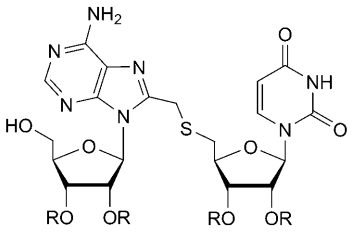
1 X = NH_2, R = TDS
2 X = NH_2, R = H
3 X = R = H
4 X = NHMe, R = H



5 X = CH_2OH
6 X = Me



7

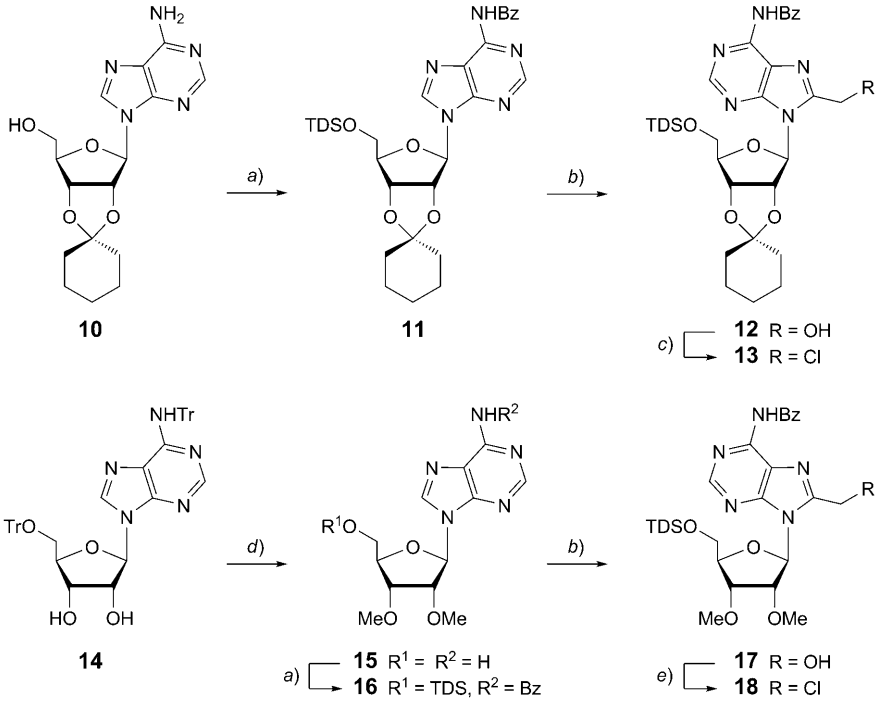


8 R = Me
9 R = H

Results and Discussion. – We envisaged to prepare the dinucleosides **7** and **8** by coupling the 2′,3′-*O*-cyclohexylidene monomers **13** and **20**, and the 2′,3′-di-*O*-methyl monomers **18** and **25**, respectively, according to a previously established procedure [1] (*cf. Scheme 3*). The deprotected pentol **9** should be obtained in one step from the known isopropylidene-protected A*[s]U dinucleoside **28** [1].

Synthesis of the Adenosine Intermediates. A one-pot 5′-*O*-silylation and *N(6)*-benzoylation of the known cyclohexylidene-adenosine **10** [4] provided the fully protected adenosine **11** (80%; *Scheme 1*). It was hydroxymethylated at C(8) by deprotonation with LDA [5], formylation with DMF, hydrolysis, and reduction of the resulting aldehyde [6], to yield 81% of the alcohol **12**. Treatment of this alcohol with MsCl provided the chloromethyl derivative **13** (72%); the initially formed methanesulfonate was not isolated. To synthesize the chloromethylated 2′,3′-di-*O*-methyladenosine **18**, we methylated the OH groups of the ditrityl-protected adenosine **14** [7] with MeI and NaH in THF, and detritylated the crude product by heating in aqueous AcOH to yield 67% of the known 2′,3′-*O*-dimethyladenosine (**15**) which had been obtained by unselective methylation of adenosines [8–10]. Similarly as for the preparation of the cyclohexylidenated chloromethyl-adenosine **13**, the 2′,3′-*O*-dimethyl derivative **15** was silylated and benzoylated to **16** (83%) that was hydroxymethylated to **17** (74%). Mesylation of **17**, followed by addition of LiCl, afforded 95% of the chloride **18**.

Scheme 1



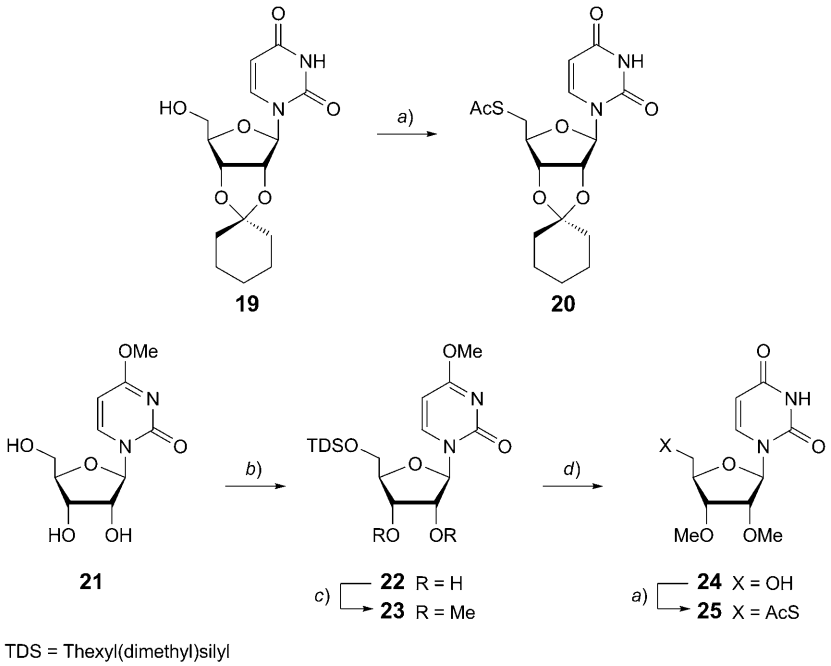
TDS = Thexyl(dimethyl)silyl (= dimethyl(1,1,2-trimethylpropyl)silyl)

a) TDSCl, pyridine, then BzCl; 80% of **11**; 83% of **16**. *b*) 1. LDA (= lithium diisopropylamide), THF, − 78°, then DMF; 2. $NaBH_4$, AcOH, EtOH; 81% of **12**; 95% of **17**. *c*) MsCl, EtN(i-Pr)$_2$, CH_2Cl_2; 72%. *d*) 1. NaH, THF, then MeI; 2. AcOH/H_2O 4 : 1, 100°; 67%. *e*) MsCl, EtN(i-Pr)$_2$, CH_2Cl_2, then LiCl; 95%.

Synthesis of the Uridine Intermediates. Tosylation of 2′,3′-*O*-cyclohexylideneuridine (**19**) [11], followed by substitution with AcSK, afforded the thioacetate **20** (77%; *Scheme 2*). The analogous 2′,3′-*O*-dimethyl derivative **25** was prepared *via* 2′,3′-*O*-dimethyluridine (**24**) [12] that was obtained from the 4-*O*-methyluridine (**21**) [12] by continuous addition over 2 d of excess CH_2N_2, followed by hydrolysis of the methoxyimino group at C(4) [12]. A safer and more convenient access to **24** was realized by silylation of the OH group at C(5′) of **21** with thexyl(dimethyl)silyl chloride (TDSCl) to the silyl ether **22** that was directly *O*-methylated with MeI and Ag_2O to **23**. This 2′,3′-*O*-dimethyl derivative was treated with *Amberlite* resin (H^+ form) in aqueous MeOH to yield 40% (from **21**) of crystalline 2′,3′-di-*O*-methyluridine (**24**). Tosylation, followed by substitution with AcSK, afforded 47% of the thioacetate **25**.

Synthesis of the Dinucleosides. The cyclohexylidenated A*[s]U thioether **26** was obtained in 91% yield by nucleophilic substitution of the chloromethylated adenosine **13** by the thiolate that was formed *in situ* by treating the thioacetate **20** with MeONa in degassed dry MeOH [1] (*Scheme 3*). Desilylation of the dinucleoside **26** with $(HF)_3 \cdot Et_3N$ yielded 88% of the alcohol **7**. The methylated A*[s]U dinucleoside **27** was

Scheme 2



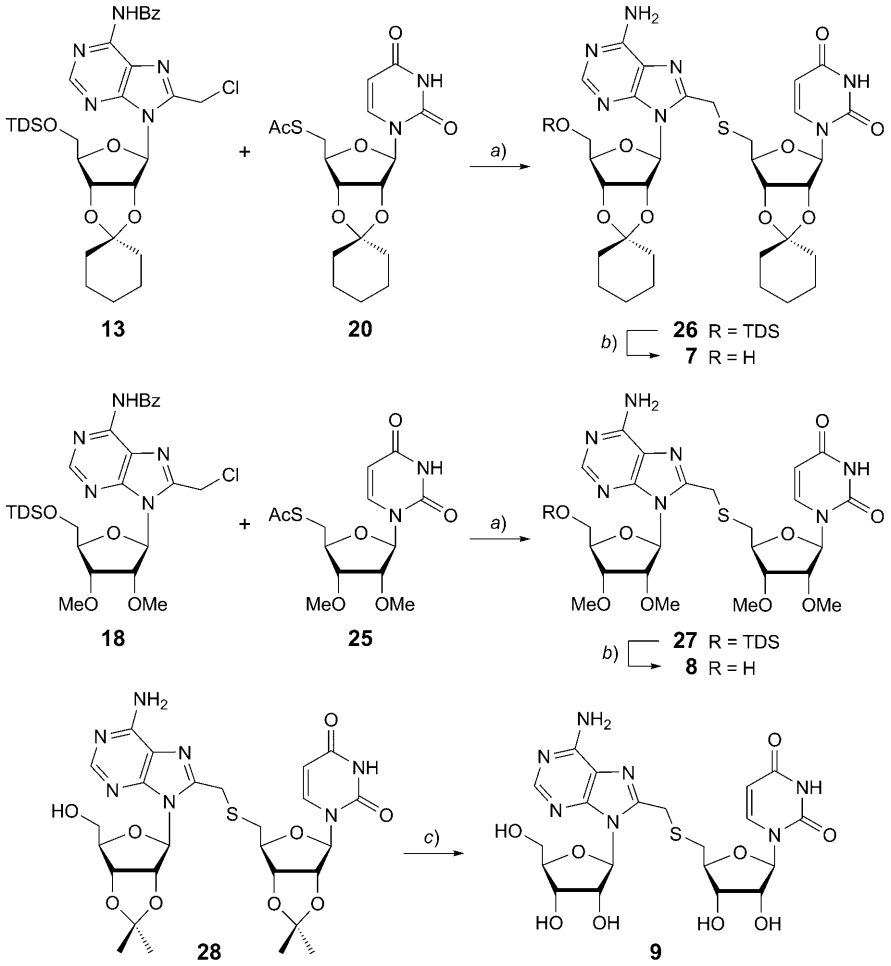
a) 1. TsCl, pyridine; 2. AcSK, DMF, 75°; 77% of **20**; 47% of **25**. *b*) TDSCl, 1*H*-imidazole, DMF. *c*) MeI, Ag_2O, acetone. *d*) *Amberlite IR-120* (H^+ form), MeOH/H_2O 1:5; 40% from **21**.

prepared similarly to **26**, by treating a mixture of the chloromethylated **18** and the thioacetate **25** with MeONa to yield 86% of **27**. This dinucleoside was desilylated to the alcohol **8** (98%). Acid-catalyzed hydrolysis of the isopropylidenated thioether **28** [1] gave the fully deprotected dinucleoside **9** (98%). Of these dinucleosides, only **26** and **27** are soluble in $CHCl_3$, and allowed determining the mode of association in the standard way [1]. The dinucleosides **7**–**9** are not sufficiently soluble in $CHCl_3$. Of these, **7** and **8** form organogels, while **8** and **9** form a hydrogel, as will be discussed after describing the conformation of the mono- and dinucleosides, and the association of **26** and **27**.

Conformation of the Adenosine Mononucleosides. Replacing the isopropylidene by a cyclohexylidene group did not significantly affect the conformation of the adenosine monomers in $CDCl_3$ solution. As previously observed for the corresponding isopropylidene-adenosine derivative [1], the fully protected **11** adopts an *anti*-conformation, as revealed by the chemical shift of 5.31 ppm for H–C(2′) (*Table 5* in the *Exper. Part*). The $J(1',2')/J(3',4')$ ratio of 1.1 reflects a slight preference for the (*S*)-conformation. A *gg*/*tg*/*gt* rotamer distribution of 50:25:25 is evidenced by $J(4',5'a)$ and $J(4',5'b)$ values of 4.2 and 4.4 Hz, respectively[2]). The *C(8)*-chloromethylated

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

Scheme 3



a) MeONa, MeOH; 91% of **26**; 86% of **27**. *b*) $Et_3N \cdot 3$ HF, THF; 88% of **7**; 98% of **8**. *c*) F_3CCOOH (TFA)/H_2O 4 : 1; 98%.

adenosine **13** adopts a *syn*-conformation ($\delta(H-C(2')) = 5.83$ ppm). H–C(2′) of the *C(8)*-hydroxymethylated **12** resonates slightly upfield ($\delta = 5.71$ ppm). An assumed $\delta(H-C(2'))$ of 5.20 ppm for the *anti*-conformer of **12** (*cf.* [1]) suggests a *ca.* 4 : 1 *syn*/*anti*-equilibrium and the stabilization of the *anti*-conformer by an intramolecular H-bond between $HOCH_2-C(8)$ (br. *s* at 5.59 ppm) and O–C(5′) (see [1–3]). Both **12** and **13** show a preference for the (*N*)-conformation ($J(1',2')/J(3',4') = 0.7$) and a similar *gg*/*gt*/*tg* rotamer distribution (17 : 36 : 47 and 17 : 38 : 45, resp.), as deduced from $J(4',5'a)$ and $J(4',5'b)$ values ranging from 5.8 to 6.1 Hz.

The exchange of the isopropylidene and cyclohexylidene protecting group by two Me groups allows a stronger puckering of the furanose ring and leads to an upfield shift of the H–C(2′) and H–C(3′) signals, but is expected to only moderately affect the *syn*/*anti*-equilibrium. The δ values of 5.22 and 5.26 ppm for H–C(2′) of the 8-substituted **17** and **18**, respectively, evidence a similar *syn*-conformation (*Table 5* in the *Exper. Part*). A strong upfield shift for H–C(2′) of the 8-unsubstituted **16** ($\Delta\delta \approx 0.85$ ppm relative to **17** and **18**) evidences a complete *anti*-conformation. These data suggest that chemical shifts of 5.20–5.30 and 4.40 ppm are characteristic for *syn*- and *anti*-configured 2′,3′-di-*O*-methyladenosines in $CDCl_3$, respectively[3]). The orientation of the nucleobase has a strong influence upon the furanose ring conformation and the orientation of the side chain at C(4′). Thus, the *anti*-configured **16** prefers a (*N*)-conformation and *gg*-orientation of the side chain (*gg*/*gt*/*tg* 78 : 8 : 14), whereas the *syn*-configured **17** and **18** adopt an (*S*)-conformation and show a reduced preference for the *gg*-orientation (*gg*/*gt*/*tg* 43 : 15 : 42).

In $CDCl_3$, the alcohol **15** shows a persistent intramolecular H-bond from HO–C(5′) to N(3), resulting in a *syn*-conformation, as revealed by the exclusive population of the *gg*-rotamer ($J(4',5'a) = 1.5$ and $J(4',5'b) = 1.6$ Hz), the strong preference for the (*S*)-conformation ($J(1',2')/J(3',4') > 5.3$), the downfield shift of HO–C(5′) (6.81 ppm), and typical $J(5',OH)$ values of 1.9 and 12.0 Hz (see [1–3][14][15]). As the consequence of the intramolecular H-bond, one observes a characteristic upfield shift of the H–C(2′) signal (($\Delta\delta = 0.5$ ppm, relative to **17** and **18**).

Conformation of the Uridine Mononucleosides. The cyclohexylidenated thioacetate **20** in $CDCl_3$ adopts the same conformation as the isopropylidenated analogue [1], as revealed by similar ^{1}H-NMR chemical shifts ($\Delta\delta \leq 0.07$ ppm) and coupling constants ($\Delta J \leq 0.02$ Hz; *Table 7* in the *Exper. Part*). It forms a *ca.* 3 : 1 *syn*/*anti*-equilibrium, prefers a (*N*)-conformation, and avoids the *gg*-orientation of the $AcSCH_2$ moiety (*gg*/*gt*/*tg* 16 : 42 : 42).

The expectation that the silyl ether **23** prefers an *anti*-conformation, similarly to the corresponding isopropylidene acetal [1], is confirmed by the exclusive *gg*-orientation of the (silyloxy)methyl group of **23** ($J(4',5'a) + J(4',5'b) = 3.1$ Hz (see [16]; *Table 7* in the *Exper. Part*). The *anti*-conformation is confirmed by the shift value for H–C(2′) of 3.90 ppm. The small $J(1',2') < 1.0$ and the large $J(3',4') = 9.2$ Hz of **23** evidence a ^4E-conformation (an extreme (*N*)-type). The downfield shift for H–C(2′) of the thioacetate **25** (4.00 ppm) evidences a *syn*/*anti*-equilibrium, but the proportion of the *syn*-conformer must be distinctly smaller than the 75% found for the isopropylidene and cyclohexylidene acetals (see above), as indicated by a weaker downfield shift for H–C(2′) of the thioacetate **25** ($\Delta\delta = 0.12$ relative to the silyl ether **23** as compared to $\Delta\delta = 0.28$ ppm for the corresponding pair of isopropylidene acetals) and also by a weaker upfield shift for H–C(1′) ($\Delta\delta = 0.16$ *vs.* 0.40 ppm). The smaller proportion of the *syn*-conformer of **25** than of **20** is corroborated by a higher *gg* proportion (*gg*/*gt*/*tg* 32 : 45 : 23 *vs.* 16 : 42 : 42). Both **25** and **20** show a similar preference for the (*N*)-conformation.

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[3]) H–C(2′) of 2′,3′-di-*O*-methyl-5′-*O*-trityladenosines resonates in $CDCl_3$ solution at 4.60–4.63 ppm [13].

The downfield shift for H–C(2′) of the alcohol **24** in D_2O (4.20 ppm) is due to the change of the solvent rather than to a *syn*/*anti*-equilibrium. The (*N*)-conformation and a large proportion of the *gg*-conformer (*gg*/*gt*/*tg* 66:25:9) agree well with an *anti*-oriented uracil moiety.

Conformation of the A[*s*]U Dinucleosides.* The analysis is restricted to the silyl ethers **26** and **27** that are soluble in $CDCl_3$. The NMR data of the dinucleosides **7**–**9** were recorded of solutions in DMSO, *i.e.,* of solvated monoplexes. H–C(2′/I) of **26** and **27** in $CDCl_3$ resonates at 4.99 and 3.90 ppm, respectively (*Table 9* in the *Exper. Part*), suggesting a *ca.* 3:2 *syn*/*anti*-equilibrium for **26** and an *anti*-conformation for **27**. In agreement with this result, a lower proportion of the *gg*-rotamer is found for **26** (*gg*/*gt*/*tg* 26:44:30) than for **27** (*gg*/*gt*/*tg* 53:33:14). Both **26** and **27** show a similar preference for the (*N*)-conformation of unit I. According to these observations, **26** (but not **27**) could form cyclic duplexes.

Association of the A[*s*]U Dinucleosides in $CHCl_3$.* The self-association of the silylated dinucleosides **26** and **27** in $CDCl_3$ was investigated by analyzing the concentration dependence of the chemical shift for H–N(3/I) resulting in shift/concentration curves (SCCs) and by temperature-dependent circular dichroism. The dinucleosides **7**–**9** form gels in several solvents (see below). Their solubility in $CHCl_3$ was too low to analyse their self-association.

The SCCs of **26** and **27** show a flattening above *ca.* 40 mM without reaching a plateau and a rather low value for δ(H–N(3)) at the lowest practical concentration. They resemble strongly the SCC of corresponding isopropylidene-protected analogue **1** [1] and reflect an equilibrium between monoplexes and linear associates (*Fig. 1*). Somewhat surprising is the rather steep ascent of the SCCs at lower concentrations, suggesting the facile formation of longer linear associates. The SCCs of **26** and **27** were analysed numerically by the method proposed by *Gutowsky* and *Saika* [17] including a value of 7.70 ppm for a 0.0001 mM solution [1]. The extrapolated chemical shift for the

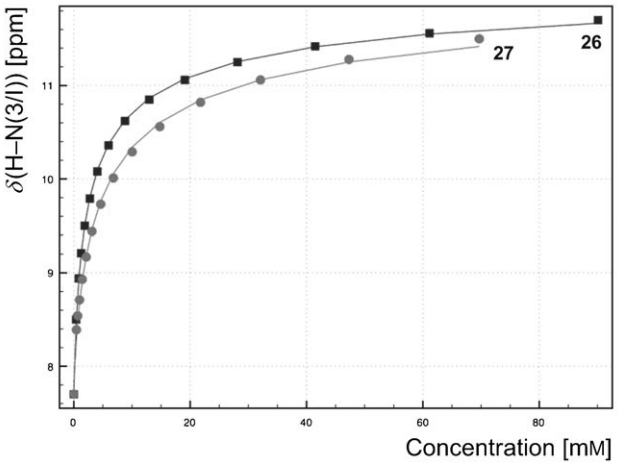

Fig. 1. *Shift/concentration curves* (SCCs) *of the silyl ethers* **26** *and* **27** *in $CDCl_3$ solution* (including a value of 7.70 ppm for a 0.0001 mM soln.).

Table 1. *Association Constants* K_{ass} *from the Concentration Dependence of* δ*(HN(3/I)) in* $CDCl_3$ *at 295 K for the A*[s]U Dinucleotides* **26** *and* **27** (including a value of 7.70 ppm for a 0.0001 mM soln.), *Extrapolated Chemical Shifts of the Monoplexes and Duplexes, and* ΔG_{295} *Values*

Dimer	K_{ass} [M^{-1}]	$\delta_{monoplex}$ [a]) [ppm]	δ_{duplex} [b]) [ppm]	ΔG_{295} [kcal/mol]
26	282	7.73	12.26	– 3.3
27	145	7.82	12.31	– 2.9

[a]) Extrapolated for 0 mM. [b]) Extrapolated for infinite concentration.

duplexes of **26** (12.26 ppm; *Table 1*) and **27** (12.31 ppm) hints at a *ca.* 1:1 mixture of *Watson–Crick*- and *Hoogsteen*-type base-paired associates (*cf.* [14]).

The association constant for the cyclohexenylidenated **26** ($K_{ass} = 282\ M^{-1}$; *Table 1*) is slightly higher than that for its isopropylidene-protected analogue ($K_{ass} = 225\ M^{-1}$ [1]), while the methylated **27** associates more weakly ($K_{ass} = 145\ M^{-1}$), evidencing the influence of the substituent at C(2′) and C(3′) on duplex formation, presumably mostly by affecting the conformation of the ribose ring of unit I (see below). The K_{ass} values agree well with an equilibrium between monoplex and linear associates.

The temperature-dependent CD spectra of 1 mM $CHCl_3$ solutions of **26** and **27** show a stronger variation of the ellipticity (*Fig. 2*) than the spectra of the corresponding isopropylidene acetal **1** (see [1]), evidencing more extensive π-stacking of the nucleobases. Remarkably, the change of the ellipticity of **26** is asymmetric, concerning only the part of the maximum at higher wavelength, while the ellipticity of the complete maximum of **27** is diminished, and the change also affects the minimum at lower wavelength. This may be rationalized by assuming that only the conformation of one of the units of **26** is strongly affected by the temperature change, presumably the (*C(6)*-unsubsituted) uridine moiety. The molar ellipticity ([θ]) of **26** and **27**, between *ca.* $-2\cdot10^4$ and $+3\cdot10^4$ deg·cm²/dmol, compares well with the one of **1** (*ca.* $-1\cdot10^4$ to $+2\cdot10^4$ deg·cm²/dmol [1][4])).

Characterization of the Gels. 1. *Solvents.* We determined the ability of the dinucleosides **7**–**9** to form gels with a selection of 33 solvents, based on classification of *Chastrette et al.* [18], at a concentration of 1% (*w*/*v*), as reported in [2][3]. The monoalcohols **7** and **8** were insoluble in apolar and in most electron-pair donor solvents, and soluble in highly dipolar solvents and in 2,2,2-trifluoroethanol (*Table 2*). Turbid or partial gels[5]) were obtained from aprotic dipolar and H-bonding solvents. Surprisingly, the tetramethyl ether **8** gelates also H_2O ('ambidextrous gelator') and proved largely superior to the other gelators tested (**2** and **5**; see [1]) when considering the scope of gelated solvents. The pentol **9** formed a gel in H_2O. As expected, it is insoluble in all solvents tested, with the exception of the highly dipolar DMF, DMSO, sulfolane, and 2,2,2-trifluoroethanol.

Gel–Sol Transition Temperature and Minimum Gelation Concentration. As previously observed for the A*[s]U(*) gelators **2** and **5** [2], the gel–sol (melting)

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

[5]) See [2] for a definition and evaluation of partial gels.

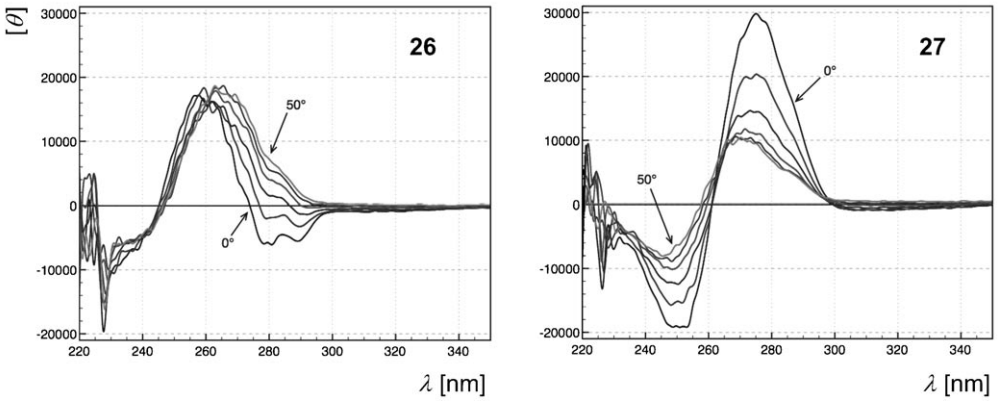

Fig. 2. *Temperature-dependent CD spectra* (in 10° steps from 0 to 50°) *of 1 mM solutions in $CHCl_3$ of the silyl ethers* **26** *and* **27**

temperature (T_m) and minimum gelation concentration (MGC) depend on both the gelator and the solvent. The T_m values for the 1% (*w*/*v*) gels of **7** and **9** are sharp, and range between 56 and 76°, except for gels with MeCN and AcOEt that melt between 57–67° and 64–74°, respectively (*Table 3*). In linear alcohols (MeOH to decan-1-ol), T_m of the gels of **7** increases from 48 to 76° with increasing chain length (decreasing solvent polarity), evidencing the formation of a network of gelator molecules linked by H-bonds [2][3]. Most of the gels formed by the tetra-*O*-methyl derivative **8** show a broad T_m (47 to 80°), and do not clearly reveal the relation between solvent polarity (chain length of linear alcohols) and gel–sol transition temperature. The different behaviour exhibited by **8**, as compared to **7** and **9**, further illustrates the effect of the structure of the gelator on the properties of the gel.

The MGC for the gels of **7** ranges between 0.2% (*w*/*v*) (decan-1-ol) and 0.8% (butan-2-one and *t*-BuOH), while **9** gelates H_2O at a concentration of 0.6% (*Table 4*). The lowest MGC for **8** is obtained with pentan-1-ol and decan-1-ol (0.07%), and the highest one with THF (0.9%). As expected for compounds associating by H-bonds, the MGC observed for **7** and **8** in linear alcohols decreases with decreasing solvent polarity, from 0.5% (EtOH) to 0.2% (decan-1-ol) and from 0.5% (in MeOH) to 0.07% (pentan-1-ol and decan-1-ol), respectively. The efficiency of **7** and **9** is similar to that of other nucleobase-derived gelators, ranging from *ca.* 0.3 to 0.8% [2][19][20]. The remarkable efficiency of **8** in pentan-1-ol and decan-1-ol (MGC 0.07%) allows a comparison with 'supergelators' such as benzylidene acetals of pyranosides [21], or trehalose esters [22] that form gels in cyclohexane and AcOEt, respectively, at a concentration of 0.04%.

Circular Dichroism. The supramolecular structure of the gels of **7**–**9** in different solvents was also studied by temperature-dependent circular dichroism (CD). At 0°, the CD spectrum of the 1% (*w*/*v*) gel of **7** and MeCN shows a minimum and a maximum at *ca.* 285 and 305 nm, respectively (*Fig. 3*). As the temperature increases to 50°, the minimum shifts to *ca.* 280 nm, and its intensity increases significantly, while the maximum shifts to *ca.* 300 nm and becomes slightly more intense. At 60°, the CD spectrum still shows intense signals (minimum and maximum at *ca.* 280 and 300 nm,

Table 2. *Solubility of the Dinucleosides* **7**–**9** *in Selected Solvents and Properties of the Gels*[a])

Class	Solvent	**7**	**8**	**9**
Aliphatic, apolar[b])	Pentane[b])	I[d])	I[d])	–
	Hexane[c])	I	I	I
	Cyclohexane[c])	I	I	–
	CCl_4[c])	I	I	–
Aromatic, apolar	Benzene	I	I	–
	Toluene	I	I	I
Aromatic, relatively polar	Acetophenone	S	**TG**	I
Electron-pair donor	Et_2O	I[d])	I[d])	–
	$(i\text{-}Pr)_2O$	I	I	–
	t-BuOMe[b])	I	I	–
	1,4-Dioxane	S	PG	I
Aprotic, dipolar	CH_2Cl_2	PG	PG[d])	I
	Acetone	PG	**TG**	I
	$ClCH_2CH_2Cl$	**TG**	PG	–
	Butan-2-one	**TG**	TG	–
	MeCN	**TG**	PG	–
	AcOEt	**TG**	PG	I
Aprotic, highly dipolar	DMF	S	S[d])	S[d])
	DMSO	S	S[d])	S[d])
Aprotic, highly dipolar, and highly polarisable H-Bonding	Sulfolane	S	S	S[d])
	2,2,2-Trifluoroethanol	S	S[d])	S
	MeOH	S	**TG**	I[e])
	EtOH	**TG**	**TG**	I
	PrOH	**TG**	**TG**	I
	BuOH	**TG**	**TG**	–
	Pentan-1-ol	**TG**	**TG**	–
	Decan-1-ol[b])	**TG**	**TG**	–
	i-PrOH	**TG**	**TG**	I
	t-BuOH	**TG**	**TG**	–
H-Bonding, strongly associated	H_2O	I	**TG**	**TG**
Miscellaneous	$CHCl_3$	S	**TG**	I
	1,2-Dimethoxyethane[c])	S[d])	**TG**	I
	THF[c])	S[d])	**TG**	–

[a]) [gelator] = 1% (*w*/*v*), I: insoluble, S: soluble, PG: partial gel, TG: turbid gel. [b]) Missing in *Chastrette*'s original classification [18]. [c]) Reclassified solvent. [d]) At 25°. [e]) Soluble at 70°.

resp.) although most gel–sol transitions occur at about this temperature (T_m 57–67°), suggesting that a significant proportion of the gelator is still highly organized. The CD spectra of the gels of **7** in AcOEt, EtOH, and decan-1-ol show similar trends, with a maximum around 290 nm and a broad tail-shaped negative band centered at *ca.* 310 nm. The intensity of both bands decreases with increasing temperature, while a negative band appears around 280 nm. Melting of the gel is associated with a significant loss of band intensity.

Table 3. *Gel–Sol Transition Temperature* (T_m [°]) *of 1% (w/v) Gels of the Dinucleosides* **7**–**9**

Class	Solvent	**7**	**8**	**9**
Aromatic, relatively polar	Acetophenone	–	63	–
Aprotic, dipolar	Acetone	–	60–65	–
	$ClCH_2CH_2Cl$	56	–	–
	Butan-2-one	64	61–63	–
	MeCN	57–67	–	–
	AcOEt	64–74	–	–
H-Bonding	MeOH	–	47–53	–
	EtOH	48	63–65	–
	PrOH	52	63	–
	BuOH	56	62–63	–
	Pentan-1-ol	57	65–67	–
	Decan-1-ol	76	64–80	–
	i-PrOH	55	55–60	–
	t-BuOH	50	49	–
H-bonding, strongly associated	H_2O	–	60–70	42
Miscellaneous	$CHCl_3$	–	55–59	–
	1,2-Dimethoxyethane	–	60–62	–
	THF	–	50–55	–

Table 4. *Minimum Gelation Concentration* (*MGC* [% (*w/v*)]) *of the Gels of the Dinucleosides* **7**–**9**

Class	Solvent	**7**	**8**	**9**
Aromatic, relatively polar	Acetophenone	–	0.2	–
Aprotic, dipolar	Acetone	–	0.4	–
	$ClCH_2CH_2Cl$	0.4	0.5	–
	Butan-2-one	0.8	0.3	–
	MeCN	0.6	–	–
	AcOEt	0.5	–	–
H-Bonding	MeOH	–	0.5	–
	EtOH	0.5	0.4	–
	PrOH	0.4	0.3	–
	BuOH	0.4	0.2	–
	Pentan-1-ol	0.3	0.07	–
	Decan-1-ol	0.2	0.07	–
	i-PrOH	0.3	0.2	–
	t-BuOH	0.8	0.4	–
H-Bonding, strongly associated	H_2O	–	0.5	0.6
Miscellaneous	$CHCl_3$	–	0.4	–
	1,2-Dimethoxyethane	–	0.5	–
	THF	–	0.9	–

The CD spectra recorded for the gel of **7** compare well with those of the analogous isopropylidene A*[s]U gelator **2** in the same solvents [2], suggesting a similar conformation and mode of association in the gel state.

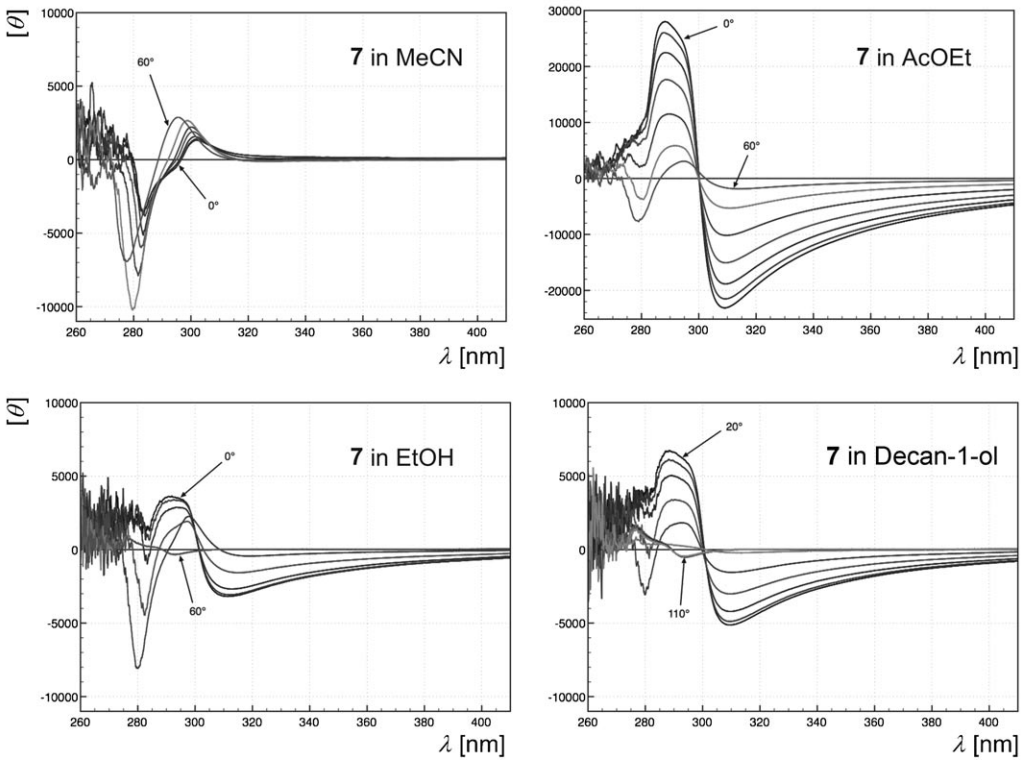

Fig. 3. *Temperature-dependent CD spectra* (in 10° steps from 0 to 60°) *of the cyclohexylidenated alcohol* **7** *for 1% (w/v) gels in MeCN, AcOEt, EtOH, and decan-1-ol*

The 1% (*w*/*v*) gels of **8** in $CHCl_3$ and in decan-1-ol did not lead to satisfactory CD spectra, presumably because of their high turbidity. The problem was avoided by decreasing the amount of gelator. At 0°, the CD curve of the 0.5% (*w*/*v*) gel of **8** in $CHCl_3$ exhibits a minimum and a maximum around 280 and 300 nm, respectively (*Fig. 4*). Their intensity decreases by increasing the temperature up to 50°. The signals disappeared at 60° with melting of the gel. The CD spectra of the 0.1% (*w*/*v*) gel of **8** in decan-1-ol (at 20°) and of the 1% (*w*/*v*) gel of **9** in H_2O (at 10°) show a strong maximum at *ca.* 265 and 285 nm, respectively, and a negative tail-shaped band centered at 310 nm. The intensity of these bands decreased by increasing the temperature to 40 and 60° for **9** and **8**, respectively, where the gel melted. As previously observed and discussed in detail [2], most of the CD spectra of the gels derived from A*[s]U dinucleosides show strong bands with long tails above 300 nm. This feature is ascribed to the formation of a compact network of gelators and a concomitant desolvation of the nucleobases upon gelation.

Scanning Electron Microscopy. The morphology of the 1% (*w*/*v*) hydrogel of **9** was studied by scanning electron microscopy (SEM) of the dried gel, revealing a tertiary and secondary structure formed by a self-assembled network of fibers with a diameter of *ca.* 30 to 90 nm and several μm in length, typical for hydrogels [23] (*Fig. 5*,*a*).

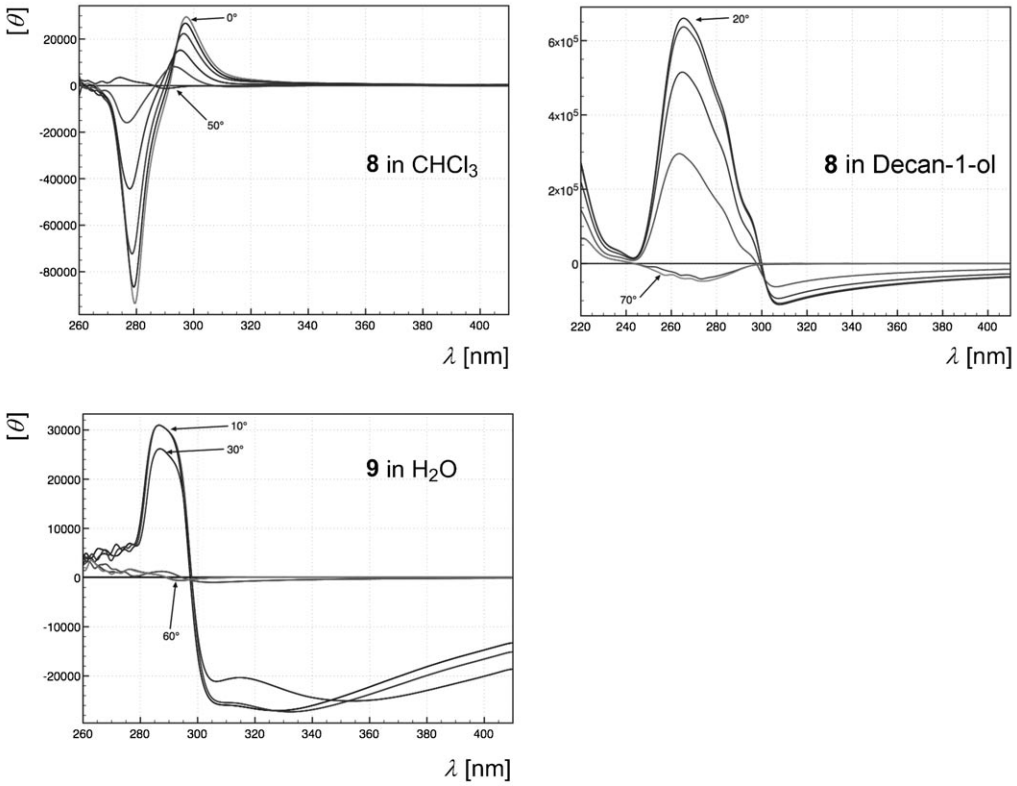

Fig. 4. *Temperature-dependent CD spectra* (in 10° steps from 0 to 50°) *of the tetramethyl ether* **8** *for a 0.5% (w/v) gel in $CHCl_3$ and a 0.1% (w/v) gel in decan-1-ol, and of the pentol* **9** *for a 1% (w/v) gel in H_2O*

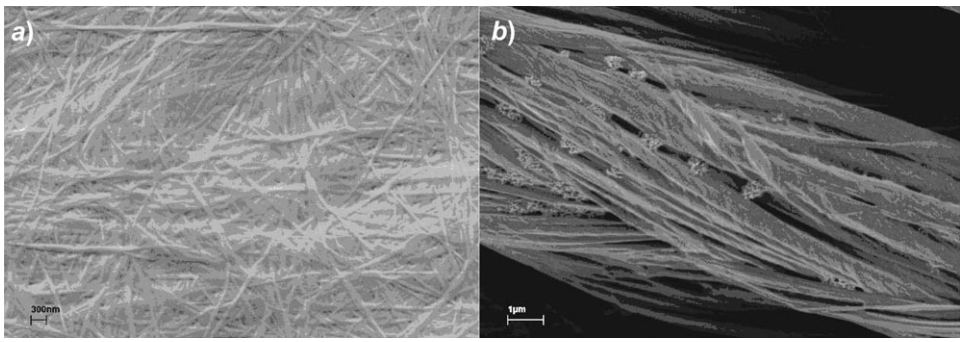

Fig. 5. *Scanning-electron microscopy pictures of the dried* a) *1% (w/v) gel and* b) *0.4% (w/v) solution of the pentan-1-ol* **9** *in H_2O*

Although the primary structure is not directly accessible by this technique, one can reasonably assume that the assembly at the molecular level occurs by reticulation of linear associates by H-bonding involving the nucleobases, as previously evidenced for

A*[s]U dimers [3]. Interestingly, the 0.4% (*w*/*v*) solution of **9** in H_2O (*Fig. 5*, *b*), showed fibrous aggregates with a diameter of several μm, which presumably result from the precipitation of a self-assembled fibrillar network from solution rather than from its entrapment [23].

We thank Dr. *Séverine Hebbe* for exploratory studies of **9**, Dr. *Michael Stalder*, Laboratory of Inorganic Chemistry, ETH Zürich, for recording the SEM pictures, and Dr. *Bruno Bernet* for his contribution to the conformational analysis and for checking the experimental part.

Experimental Part

General. See [2].

N^6-*Benzoyl-2′,3′*-O-*cyclohexylidene-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]adenosine* (**11**). A soln. of **10** [4] (8.00 g, 23.0 mmol) in dry pyridine at 0° was treated with thexyl(dimethyl)silyl chloride (TDSCl; 6.3 ml, 32.2 mmol), stirred at 25° for 48 h, cooled to 0°, treated with BzCl (13.3 ml, 114.6 mmol), and stirred at 25° for 72 h. The mixture was cooled to 0°, treated with H_2O (26 ml) and 25% $NH_3 \cdot H_2O$ soln. (53 ml), and stirred for 30 min at 0°. After evaporation, a soln. of the residue in toluene was evaporated. A soln. of the residue in AcOEt was washed twice with 0.01M aq. HCl and twice with sat. aq. NH_4Cl soln., dried (Na_2SO_4), and evaporated. FC (cyclohexane/AcOEt 4:1 → 2:1 → 1:1) gave **11** (10.91 g, 80%). White solid. R_f (cyclohexane/AcOEt 1:1) 0.55. M.p. 95° (sintering from 65°). $[\alpha]_D^{25} = -51.0$ ($c = 1.05$, $CHCl_3$). UV ($CHCl_3$): 281 (22000). IR (ATR): 3240*w* (br.), 3200*w* (br.), 2936*m*, 2854*w*, 1696*m*, 1607*m*, 1580*m*, 1510*m*, 1485*m*, 1452*s*, 1407*w*, 1367*w*, 1330*m*, 1287*m*, 1248*s*, 1215*m*, 1162*m*, 1090*s*, 1028*m*, 1000*w*, 968*w*, 939*w*, 927*w*, 909*w*, 875*w*, 827*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 9.12 (br. *s*, NH); 8.02–7.98 (*m*, 2 arom. H); 7.62–7.46 (*m*, 3 arom. H); 1.87–1.82 (*m*, 2 H); 1.71–1.50 (*m*, 6 H); 1.55 (*sept.*, $J = 6.8$, Me_2CH); 1.44–1.38 (*m*, 2 H); 0.82 (*d*, $J = 6.8$, Me_2CH); 0.78 (*s*, Me_2CSi); 0.04 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 164.50 (*s*, C=O); 133.72 (*s*); 132.72 (*d*); 128.84 (2*d*); 127.83 (2*d*); 115.07 (*s*, $(CH_2)_2C$); 37.22, 34.93 (2*t*); 34.17 (*d*, Me_2CH); 25.45 (*s*,

Table 5. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Adenosines* **11**–**13** *and* **15**–**18** *in $CDCl_3$*

	11	**12**	**13**	**15**[a])	**16**	**17**	**18**
H–C(2)	8.80	8.69	8.79	8.33	8.77	8.77	8.77
H–C(8)	8.21	–	–	7.82	8.38	–	–
CH_a–C(8)	–	4.93	4.93	–	–	4.98	4.91
CH_b–C(8)	–	4.93	4.87	–	–	4.94	4.87
H–C(1′)	6.20	6.26	6.30	5.87	6.22	6.07	6.17
H–C(2′)	5.31	5.71	5.83	4.73	4.38	5.22	5.26
H–C(3′)	4.95	5.04	5.10	4.16	4.04	4.20	4.27
H–C(4′)	4.41	4.22	4.29	4.39	4.22	4.16	4.17
H_a–C(5′)	3.84	3.67	3.74	4.02	4.02	3.91	3.92
H_b–C(5′)	3.75	3.58	3.63	3.70	3.81	3.74	3.74
$J(H_a,H_b)$	–	[b])	12.6	–	–	15.7	12.6
J(1′,2′)	2.8	2.4	2.5	8.0	3.7	5.8	5.4
J(2′,3′)	6.2	6.4	6.3	4.9	4.6	5.1	5.1
J(3′,4′)	2.6	3.5	3.4	< 1.5	5.8	4.0	4.4
J(4′,5′a)	4.2	6.1	5.9	1.5	3.4	5.7	5.6
J(4′,5′b)	4.4	5.8	5.9	1.6	2.8	4.1	4.1
J(5′a,5′b)	11.2	10.8	10.8	13.0	11.6	11.2	11.2

[a]) J(5′a,OH) = 1.9, J(5′b,OH) = 12.0 Hz. [b]) Not assigned.

Table 6. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Adenosines* **11**–**13** *and* **15**–**18** *in* $CDCl_3$

	11	**12**	**13**	**15**	**16**	**17**	**18**
C(2)	152.77	152.53	153.05	152.28	152.76	152.54	153.03
C(4)	149.47	149.08	149.61	148.33	149.57	149.25	149.76
C(5)	123.38	121.34	121.97	121.18	123.67	121.97	122.37
C(6)	151.24	152.28	152.17	156.17	151.43	153.00	152.69
C(8)	141.79	154.72	150.04	140.82	141.66	155.16	150.65
CH_2–C(8)	–	57.71	36.72	–	–	57.85	36.73
C(1′)	91.56	90.05	90.44	89.82	87.03	87.45	87.75
C(2′)	84.26	82.77	82.56	81.92	82.08	79.51	79.51
C(3′)	81.18	81.18	81.24	79.54	77.35	78.29	78.21
C(4′)	87.42	87.55	87.68	85.51	82.64	83.04	82.90
C(5′)	63.38	62.80	62.87	63.78	61.97	62.33	62.15

Me_2CSi); 25.15, 24.22, 23.87 (3*t*); 20.47, 20.42 (2*q*, Me_2CSi); 18.64 (*q*, Me_2CH); −3.16, −3.28 (2*q*, Me_2Si). HR-MALDI-MS: 594.3100 ($[M + H]^+$, $C_{31}H_{44}N_5O_5Si^+$; calc. 594.3112).

N^6-*Benzoyl-2′,3′*-O-*cyclohexylidene-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-8-(hydroxymethyl)-adenosine* (**12**). A soln. of $(i\text{-Pr})_2NH$ (9.9 ml, 75.7 mmol) in dry THF (38 ml) at 0° was treated dropwise with 1.6M BuLi in hexane (47.3 ml, 75.7 mmol), stirred for 40 min at 0°, cooled to −78°, treated dropwise with a soln. of **11** (8.989 g, 15.14 mmol) in dry THF (38 ml), stirred for 2 h at −78°, treated dropwise with DMF (29 ml, 375 mmol), stirred for 3 h, treated with AcOH (29 ml), and allowed to warm to 25°. The mixture was diluted with EtOH (38 ml), cooled to 0°, treated portionwise with $NaBH_4$ (1.72 g, 45.4 mmol), stirred for 30 min at 0°, diluted with sat. aq. NH_4Cl soln. (100 ml) and H_2O, and extracted three times with AcOEt. The combined org. layers were washed three times with sat. aq. NH_4Cl soln., dried (Na_2SO_4), and evaporated. FC (cyclohexane/AcOEt 2:1 → 1:1 → AcOEt) gave **12** (7.691 g, 81%). Slightly yellow solid. R_f (cyclohexane/AcOEt 1:1) 0.45. M.p. 115° (sintering from 85°). $[\alpha]_D^{25} = -23.0$ ($c = 0.95$, $CHCl_3$). UV ($CHCl_3$): 283 (21720). IR (ATR): 3407*w* (br.), 3266*w* (br.), 2936*m*, 2864*w*, 1698*m*, 1611*m*, 1584*m*, 1531*w*, 1502*w*, 1484*m*, 1461*m*, 1448*m*, 1430*m*, 1356*m*, 1330*m*, 1249*s*, 1163*m*, 1092*s*, 1047*s*, 1000*m*, 969*m*, 939*m*, 927*m*, 909*m*, 897*m*, 875*m*, 828*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 9.43 (br. *s*, NH); 8.02–7.98 (*m*, 2 arom. H); 7.57–7.42 (*m*, 3 arom. H); 5.59 (br. *s*, OH); 1.83–1.80 (*m*, 2 H); 1.71–1.49 (*m*, 6 H); 1.56 (*sept.*, $J = 6.8$, Me_2CH); 1.46–1.38 (*m*, 2 H); 0.81 (*d*, $J = 6.8$, Me_2CH); 0.77, 0.76 (2*s*, Me_2CSi); −0.04 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 165.03 (*s*, C=O); 133.72 (*s*); 132.80 (*d*); 128.83 (2*d*); 128.00 (2*d*); 115.20 (*s*, $(CH_2)_2C$); 37.07, 34.91 (2*t*); 34.16 (*d*, Me_2CH); 25.34 (*s*, Me_2CSi); 25.11, 24.12, 23.76 (3*t*); 20.37, 20.34 (2*q*, Me_2CSi); 18.55, 18.53 (2*q*, Me_2CH); −3.40 (*q*, Me_2Si). HR-MALDI-MS: 624.3206 ($[M + H]^+$, $C_{32}H_{46}N_5O_6Si^+$; calc. 624.3217).

N^6-*Benzoyl-8-(chloromethyl)-2′,3′*-O-*cyclohexylidene-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-adenosine* (**13**). A soln. of **12** (5.410 g, 8.67 mmol) in dry CH_2Cl_2 (43 ml) at 0° was treated with $EtN(i\text{-Pr})_2$ (2.27 ml, 13.01 mmol) and MsCl (738 µl, 9.54 mmol), stirred at 25° for 20 h, and evaporated. FC (cyclohexane/AcOEt 4:1 → 1:1) gave **13** (4.013 g, 72%). White solid. R_f (cyclohexane/AcOEt 1:4) 0.18. M.p. 90° (sintering from 67°). $[\alpha]_D^{25} = -18.0$ ($c = 0.9$, $CHCl_3$). UV ($CHCl_3$): 285 (22370). IR (ATR): 3249*w* (br.), 2936*m*, 2864*w*, 1697*m*, 1607*m*, 1580*m*, 1525*m*, 1498*m*, 1483*m*, 1463*m*, 1448*m*, 1429*m*, 1357*m*, 1344*m*, 1328*m*, 1248*s*, 1163*m*, 1142*m*, 1091*s*, 1028*m*, 1000*m*, 968*w*, 939*m*, 926*m*, 911*m*, 875*m*, 827*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 9.00 (br. *s*, NH); 8.01–7.98 (*m*, 2 arom. H); 7.63–7.49 (*m*, 3 arom. H); 1.86–1.82 (*m*, 2 H); 1.73–1.52 (*m*, 6 H); 1.56 (*sept.*, $J = 6.8$, Me_2CH); 1.45–1.41 (*m*, 2 H); 0.83 (*d*, $J = 6.8$, Me_2CH); 0.79, 0.78 (2*s*, Me_2CSi); −0.01, −0.03 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 164.36 (*s*, C=O); 133.60 (*s*); 132.86 (*d*); 128.92 (2*d*); 127.81 (2*d*); 115.12 (*s*, $(CH_2)_2C$); 37.25, 35.05 (2*t*); 34.28 (*d*, Me_2CH); 25.45 (*s*, Me_2CSi); 25.22, 24.23, 23.84 (3*t*); 20.51, 20.48 (2*q*, Me_2CSi); 18.70, 18.68 (2*q*, Me_2CH); −3.21 (*q*, Me_2Si). HR-MALDI-MS: 642.2885 ($[M + H]^+$, $C_{32}H_{45}ClN_5O_5Si^+$; calc. 642.2878).

2′,3′-Di-O-*methyladenosine* (**15**) [8–10]. A suspension of 60% NaH in oil (1.159 g, 28.98 mmol) in THF (20 ml) was cooled to 0°, treated with a soln. of **14** [7] (6.226 g, 8.28 mmol) in THF (20 ml), and stirred at 25° for 2.5 h. The mixture was cooled to 0°, treated with MeI (1.55 ml, 24.8 mmol), stirred at 25° for 3 h, treated with sat. aq. NH_4Cl soln., diluted with H_2O, and extracted three times with AcOEt. The combined org. layers were dried (Na_2SO_4) and evaporated. The residue was treated with AcOH/H_2O 4:1 (50 ml), stirred for 30 min at 100°, and evaporated. FC (AcOEt/MeOH 9:1) and recrystallization in EtOH gave **15** (1.627 g, 67%). White solid. R_f (AcOEt/MeOH 9:1) 0.13. M.p. 181° ([8]: 177°). $[\alpha]_D^{25} = -120.5$ ($c = 0.55$, $CHCl_3$; [8]: −49). UV ($CHCl_3$): 261 (14680). IR (ATR): 3362*m*, 3264*m*, 3230*m*, 3108*m*, 2988*w*, 2921*m*, 2832*w*, 2747*w*, 2692*w*, 1683*s*, 1611*s*, 1567*m*, 1514*w*, 1475*m*, 1422*m*, 1387*m*, 1343*m*, 1325*w*, 1289*s*, 1216*m*, 1186*m*, 1173*w*, 1114*s*, 1095*s*, 1076*s*, 1048*s*, 1021*m*, 977*m*, 952*m*, 911*w*, 879*w*, 815*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 6.81 (*dd*, $J = 12.0$, 1.9, HO–C(5′)); 5.74 (br. *s*, NH_2); 3.54, 3.33 (2*s*, 2 MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 58.60, 58.04 (2*q*, 2 MeO). HR-MALDI-MS: 296.1353 ($[M + H]^+$, $C_{12}H_{18}N_5O_4^+$; calc. 296.1359). Anal. calc. for $C_{12}H_{17}N_5O_4$ (295.30): C 48.81, H 5.80, N 23.72; found: C 48.84, H 5.81, N 23.42.

N^6-*Benzoyl-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-di*-O-*methyladenosine* (**16**). A soln. of **15** (2.879 g, 9.75 mmol) in pyridine (45 ml) at 0° was treated with TDSCl (2.49 ml, 12.68 mmol), stirred at 25° for 7.5 h, and treated with two additional portions of TDSCl (2 × 1.3 ml, 13.2 mmol) over 24 h. The soln. was cooled to 0°, treated with BzCl (5.7 ml, 48.8 mmol), and stirred at 25° for 13 h. The mixture was cooled to 0°, treated with H_2O (20 ml) and 25% $NH_3 \cdot H_2O$ soln. (40 ml), stirred for 30 min at 0°, and evaporated. A soln. of the residue in AcOEt was washed with aq. 0.01M HCl and sat. aq. $NaHCO_3$ soln. The org. layer was dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH 95:5) gave **16** (4.399 g, 83%). White solid. R_f (CH_2Cl_2/MeOH 95:5) 0.38. M.p. 60° (sintering from 45°). $[\alpha]_D^{25} = -13.6$ ($c = 0.9$, $CHCl_3$). UV ($CHCl_3$): 280 (21670). IR (ATR): 3252*w*, 3125*w*, 3059*w*, 2955*m*, 2865*w*, 2830*w*, 1698*m*, 1608*s*, 1580*s*, 1509*m*, 1482*m*, 1451*s*, 1405*w*, 1390*w*, 1377*w*, 1326*m*, 1290*m*, 1248*s*, 1220*s*, 1189*m*, 1124*s*, 1094*s*, 1074*s*, 1048*m*, 1030*m*, 998*m*, 983*m*, 876*m*, 824*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 9.20 (br. *s*, NH); 8.00–7.98 (*m*, 2 arom. H); 7.59–7.46 (*m*, 3 arom. H); 3.57, 3.44 (2*s*, 2 MeO); 1.64 (*sept.*, $J = 6.8$, Me_2CH); 0.88 (*d*, $J = 6.8$, Me_2CH); 0.88 (*s*, Me_2CSi); 0.16, 0.15 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 164.77 (*s*, C=O); 133.89 (*s*); 132.76 (*d*); 128.89 (2*d*); 127.94 (2*d*); 58.70, 58.19 (2*q*, 2 MeO); 34.15 (*d*, Me_2CH); 25.53 (*s*, Me_2CSi); 20.48, 20.40 (2*q*, Me_2CSi); 18.64, 18.56 (2*q*, Me_2CH); −3.24, −3.46 (2*q*, Me_2Si). HR-MALDI-MS: 542.2800 ($[M + H]^+$, $C_{27}H_{40}N_5O_5Si^+$; calc. 542.2799).

N^6-*Benzoyl-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-8-(hydroxymethyl)-2′,3′-di*-O-*methyladenosine* (**17**). A soln. of (i-Pr)$_2$NH (4.85 ml, 37.0 mmol) in THF (25 ml) at 0° was treated dropwise with 1.6M BuLi in hexane (23.1 ml, 37.0 mmol), stirred for 40 min at 0°, cooled to −78°, treated dropwise with a soln. of **16** (4.006 g, 7.40 mmol) in THF (25 ml), stirred for 2 h at −78°, treated dropwise with DMF (14.3 ml, 185 mmol), stirred for 3 h, treated with AcOH (6.4 ml, 111 mmol), and allowed to warm to 25°. The mixture was diluted with EtOH (30 ml), cooled to 0°, treated portionwise with $NaBH_4$ (840 mg, 22.2 mmol), stirred for 30 min at 0°, treated with sat. aq. NH_4Cl soln. and H_2O, and extracted three times with AcOEt. The combined org. layers were washed three times with sat. aq. NH_4Cl soln., dried (Na_2SO_4), and evaporated. FC (CH_2Cl_2/MeOH 95:5) gave **17** (3.134 g, 74%). A sample for analysis was recrystallized in MeCN. White solid. R_f (CH_2Cl_2/MeOH 95:5) 0.23. M.p. 147°. $[\alpha]_D^{25} = -34.9$ ($c = 0.8$, $CHCl_3$). UV ($CHCl_3$): 283 (21380). IR (ATR): 3410*w* (sh.), 3233*w*, 3204*w*, 2955*m*, 2933*m*, 2868*w*, 2831*w*, 1698*s*, 1614*s*, 1583*m*, 1527*m*, 1505*m*, 1488*m*, 1461*m*, 1438*m*, 1344*m* (sh.), 1330*m*, 1301*w*, 1249*s*, 1209*w*, 1121*s*, 1071*s*, 998*m*, 986*m*, 966*w*, 937*w*, 899*w*, 875*w*, 828*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 9.12 (br. *s*, NH); 8.04–8.02 (*m*, 2 arom. H); 7.62–7.50 (*m*, 3 arom. H); 4.24 (*t*, $J = 6.3$, OH); 3.52, 3.43 (2*s*, 2 MeO); 1.59 (*sept.*, $J = 6.9$, Me_2CH); 0.85 (*d*, $J = 6.9$, Me_2CH); 0.81 (*s*, Me_2CSi); 0.08, 0.06 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 164.88 (*s*, C=O); 133.88 (*s*); 132.84 (*d*); 128.96 (2*d*); 128.02 (2*d*); 58.58, 58.14 (2*q*, 2 MeO); 34.23 (*d*, Me_2CH); 25.37 (*s*, Me_2CSi); 20.38, 20.34 (2*q*, Me_2CSi); 18.61 (*q*, Me_2CH); −3.37, −3.42 (2*q*, Me_2Si). HR-MALDI-MS: 572.2904 ($[M + H]^+$, $C_{28}H_{42}N_5O_6Si^+$; calc. 572.2897). Anal. calc. for $C_{28}H_{41}N_5O_6Si$ (571.75): C 58.82, H 7.23, N 12.25; found: C 58.91, H 7.04, N 12.12.

N^6-*Benzoyl-8-(chloromethyl)-5′*-O-*[dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-di*-O-*methyladenosine* (**18**). A soln. of **17** (1.892 g, 3.31 mmol) in CH_2Cl_2 (16 ml) at 0° was treated with EtN(i-Pr)$_2$ (866 µl, 4.97 mmol) and MsCl (256 µl, 3.31 mmol), stirred at 25° for 24 h, treated with LiCl (140 mg, 3.31 mmol),

and stirred for 7 h. The mixture was diluted with H_2O and extracted three times with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (cyclohexane/AcOEt 1:1) gave **18** (1.847 g, 95%). White solid. R_f (cyclohexane/AcOEt 1:1) 0.45. M.p. 65° (sintering from 45°). $[\alpha]_D^{25} = -30.9$ ($c = 0.7$, $CHCl_3$). UV ($CHCl_3$): 286 (22630). IR (ATR): 3411*w*, 3253*w*, 2955*m*, 2929*m*, 2868*w*, 2831*w*, 1697*m*, 1608*s*, 1581*m*, 1525*w*, 1484*m*, 1461*m*, 1422*m*, 1352*m*, 1326*m*, 1247*s*, 1210*w*, 1190*w*, 1172*w*, 1125*w*, 1072*w*, 999*w*, 945*w*, 875*w*, 827*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 9.03 (br. *s*, NH); 8.00–7.98 (*m*, 2 arom. H); 7.60–7.48 (*m*, 3 arom. H); 3.53, 3.45 (2*s*, 2 MeO); 1.56 (*sept.*, $J = 6.9$, Me_2CH); 0.83 (*d*, $J = 6.9$, Me_2CH); 0.79 (*s*, Me_2CSi); 0.08, 0.03 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 6*; additionally, 164.56 (*s*, C=O); 133.78 (*s*); 132.87 (*d*); 128.96 (2*d*); 127.91 (2*d*); 58.59, 58.15 (2*q*, 2 MeO); 34.18 (*d*, Me_2CH); 25.33 (*s*, Me_2CSi); 20.34, 20.30 (2*q*, Me_2CSi); 18.56 (*q*, Me_2CH); −3.40, −3.44 (2*q*, Me_2Si). HR-MALDI-MS: 590.2561 ($[M + H]^+$, $C_{28}H_{41}ClN_5O_5Si^+$; calc. 590.2565).

5′-S-Acetyl-2′,3′-O-cyclohexylidene-5′-thiouridine (**20**). A soln. of **19** [11] (869 mg, 2.68 mmol) in dry pyridine (13 ml) at 0° was treated with TsCl (842 mg, 4.42 mmol), allowed to warm to 25°, stirred for 20 h, and evaporated. A soln. of the residue in dry DMF (4 ml) was treated with AcSK (775 mg, 6.79 mmol) and heated to 75° for 2 h. After evaporating DMF, a soln. of the residue in AcOEt was washed three times with sat. aq. NH_4Cl soln. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (cyclohexane/AcOEt 4:1 → 1:1 → AcOEt) gave **20** (792 mg, 77%). Slightly yellow solid. R_f (cyclohexane/AcOEt 1:1) 0.40. M.p. 95° (sintering from 75°). $[\alpha]_D^{25} = +10.3$ ($c = 0.7$, $CHCl_3$). UV ($CHCl_3$): 259 (10190). IR (ATR): 3188*w* (br.), 3099*w*, 3062*w*, 2935*w*, 2860*w*, 1682*s*, 1631*m*, 1450*m*, 1423*w*, 1376*m*, 1356*w*, 1262*m*, 1229*w*, 1162*m*, 1087*s*, 1048*m*, 1008*m*, 964*w*, 939*m*, 927*m*, 909*m*, 869*w*, 846*m*, 808*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 7*; additionally, 9.67 (br. *s*, NH); 2.37 (*s*, AcS); 1.77–1.72 (*m*, 2 H); 1.69–1.50 (*m*, 6 H); 1.45–1.32 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 8*; additionally, 194.74 (*s*, SC=O); 115.45 (*s*, $(CH_2)_2C$); 37.00, 34.80 (2*t*); 30.71 (*q*, *Me*C=O); 25.00, 24.03, 23.67 (3*t*). HR-MALDI-MS: 405.1080 ($[M + Na]^+$, $C_{17}H_{22}N_2NaO_6S^+$; calc. 405.1096).

Table 7. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Uridines* **20** *and* **22**–**25** *in $CDCl_3$*

	20	**22**	**23**	**24**[a])	**25**
H–C(5)	5.76	5.92	5.81	5.87	5.78
H–C(6)	7.25	8.18	8.34	7.90	7.48
H–C(1′)	5.59	5.82	5.94	5.97	5.78
H–C(2′)	5.02	4.14–4.24	3.88	4.20	4.00
H–C(3′)	4.73	4.14–4.24	3.74	4.02	3.54
H–C(4′)	4.21	4.29	4.13	4.16	4.18
H_a–C(5′)	3.29	3.94	4.09	3.92	3.31
H_b–C(5′)	3.29	3.78	3.78	3.78	3.27
J(5,6)	8.1	7.4	7.4	8.1	8.1
J(5,NH)	2.0	–	–	[b])	[b])
J(1′,2′)	2.0	2.8	< 1.0	3.5	3.0
J(2′,3′)	6.5	[c])	4.7	5.2	5.1
J(3′,4′)	4.0	2.4	9.2	6.3	6.5
J(4′,5′a)	6.5	2.2	1.7	2.9	5.1
J(4′,5′b)	6.5	2.1	1.4	4.0	6.5
J(5′a,5′b)	[b])	11.8	11.8	12.9	14.2

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

*1-{5-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-β-*D*-ribofuranosyl}-4-methoxypyrimidin-2(1*H*)-one* (**22**). A soln. of **21** [12] (3.522 g, 13.64 mmol) and 1*H*-imidazole (1.207 g, 17.73 mmol) in DMF (38 ml) at 0° was treated with TDSCl (2.68 ml, 13.64 mmol), stirred at 25° for 18 h, treated with 1*H*-imidazole

Table 8. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Uridines* **20** *and* **22**–**25** *in $CDCl_3$*

	20	**22**	**23**	**24**[a])	**25**
C(2)	150.10	157.40	155.61	151.07	150.15
C(4)	163.66	172.15	171.83	165.84	163.60
C(5)	102.81	95.66	94.99	101.97	102.68
C(6)	142.92	142.58	142.89	141.34	140.28
C(1′)	95.36	92.82	88.83	87.67	89.72
C(2′)	84.13	77.11	81.41[b])	80.92	80.53
C(3′)	83.05	71.40	75.33	76.81	80.23
C(4′)	86.57	86.89	81.78[b])	82.11	81.27
C(5′)	31.46	62.62	60.53	60.33	31.05

[a]) In D_2O. [b]) Assignments may be interchanged.

(281 mg, 4.13 mmol), cooled to 0°, treated with TDSCl (536 µl, 2.73 mmol), and stirred at 25° for 30 h. After evaporation, a soln. of the residue in AcOEt was washed three times with sat. aq. NH_4Cl soln. and once with sat. aq. $NaHCO_3$ soln. The org. layer was dried (Na_2SO_4) and evaporated to give crude **22** (5.069 g, *ca.* 93%), suitable for the next step without further purification. Colourless paste. R_f (AcOEt/MeOH 9:1) 0.67. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 7*; additionally, 4.75 (br. *s*, exchange with D_2O, OH); 3.95 (*s*, MeO); 3.74 (br. *s*, exchange with D_2O, OH); 1.58 (*sept.*, $J = 6.8$, Me_2CH); 0.84 (*d*, $J = 6.8$, Me_2CH); 0.81 (*s*, Me_2CSi); 0.11 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 8*; additionally, 54.79 (*q*, MeO); 34.10 (*d*, Me_2CH); 25.49 (*s*, Me_2CSi); 20.47, 20.35 (2*q*, Me_2CSi); 18.66, 18.62 (2*q*, Me_2CH); −3.19, −3.29 (2*q*, Me_2Si). HR-MALDI-MS: 423.1919 ($[M + Na]^+$, $C_{18}H_{32}N_2NaO_6Si^+$; calc. 423.1927).

*1-{5-*O*-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2,3-di-*O*-methyl-β-*D*-ribofuranosyl}-4-methoxypyrimidin-2(1*H*)-one* (**23**). A soln. of crude **22** (5.019 g, 12.53 mmol) in acetone (63 ml) was treated with Ag_2O (8.710 g, 37.59 mmol) and MeI (3.12 ml, 50.12 mmol), and stirred at 25° for 72 h. Filtration through *Celite* and evaporation gave crude **23** (5.368 g, *quant.*), suitable for the next step without further purification. Colourless paste. R_f (AcOEt) 0.63. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 7*; additionally, 3.93 (*s*, MeO−C(4)); 3.70, 3.34 (2*s*, 2 MeO); 1.63 (*sept.*, $J = 6.8$, Me_2CH); 0.87 (*d*, $J = 6.8$, Me_2CH); 0.86 (*s*, Me_2CSi); 0.14 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 8*; additionally, 58.67, 58.14 (2*q*, 2 MeO); 54.48 (*q*, MeO−C(4)); 34.11 (*d*, Me_2CH); 25.63 (*s*, Me_2CSi); 20.48, 20.43 (2*q*, Me_2CSi); 18.65 (*q*, Me_2CH); −3.12, −3.35 (2*q*, Me_2Si). HR-MALDI-MS: 429.2419 ($[M + H]^+$, $C_{20}H_{37}N_2O_6Si^+$; calc. 429.2421).

*2′,3′-Di-*O*-methyluridine* (**24**) [12]. A soln. of crude **23** (5.312 g, 12.39 mmol) in MeOH/H_2O 1:5 (68 ml) was treated with *Amberlite* IR-120 (H^+ form, 20 ml), stirred at 25° for 19 h, and filtered. Evaporation, FC (AcOEt/MeOH 9:1), and recrystallization in EtOH gave **24** (1.477 g, 40% from **21**). White solid. R_f (AcOEt/MeOH 9:1) 0.43. M.p. 170–172° ([12]: 176–177°). $[\alpha]_D^{25} = +66.4$ ($c = 1.3$, MeOH) ([12]: $[\alpha]_D^{25} = +74.7$ ($c = 1.3$, MeOH)). ^{1}H-NMR (300 MHz, D_2O): see *Table 7*; additionally, 3.51, 3.44 (2*s*, 2 MeO). ^{13}C-NMR (75 MHz, D_2O): see *Table 8*; additionally, 57.85, 57.51 (2*q*, 2 MeO).

*5′-*S*-Acetyl-2′,3′-di-*O*-methyl-5′-thiouridine* (**25**). A soln. of **24** (1.351 g, 4.96 mmol) in pyridine (25 ml) at 0° was treated with TsCl (1.418 g, 7.44 mmol), stirred at 25° for 4 h, treated with two additional portions of TsCl (2 × 709 mg, 3.72 mmol), added over 3 h, and stirred at 25° for 16 h. The mixture was diluted with CH_2Cl_2, washed with 0.1M H_2SO_4, sat. aq. $NaHCO_3$ soln., and brine. The combined org. layers were dried (Na_2SO_4) and evaporated. A soln. of the residue in DMF (12.4 ml) was treated with AcSK (1.416 g, 12.4 mmol), heated to 75° for 2 h, and evaporated. A soln. of the residue in AcOEt was washed three times with sat. aq. NH_4Cl soln. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (cyclohexane/AcOEt 4:1 → AcOEt → AcOEt/MeOH 9:1) gave **25** (763 mg, 47%). Slightly red solid. R_f (cyclohexane/AcOEt 1:4) 0.24. M.p. 103°. $[\alpha]_D^{25} = +82.6$ ($c = 0.8$, $CHCl_3$). UV ($CHCl_3$): 262 (10010). IR (ATR): 3145*w*, 3004*w*, 2917*w*, 2826*w*, 1770*w*, 1676*s*, 1627*m*, 1461*w*, 1383*m*, 1356*w*, 1319*w*, 1273*m*, 1258*s*, 1217*m*, 1192*w*, 1125*s*, 1106*m*, 1061*s*, 1010*m*, 963*s*, 870*m*, 819*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 7*; additionally, 9.76 (br. *s*, NH); 3.53, 3.41 (2*s*, 2 MeO); 2.38 (*s*, AcS).

^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 8*; additionally, 194.63 (*s*, Me*C*=O); 58.72, 58.36 (2*q*, 2 MeO); 30.69 (*q*, *Me*C=O). HR-MALDI-MS: 353.0778 ($[M + Na]^+$, $C_{13}H_{18}N_2NaO_6S^+$; calc. 353.0783).

*2′,3′-*O*-Cyclohexylidene-5′-*O*-[dimethyl(1,1,2-trimethylpropyl)silyl]adenosine-8-methyl-(8′ → 5′-*S*)-2′,3′-*O*-cyclohexylidene-5′-thiouridine* (**26**). A soln. of **20** (607 mg, 1.59 mmol) and **13** (1.019 g, 1.59 mmol) in dry degassed MeOH (3.2 ml) at 0° was treated with a freshly prepared 1.99M soln. of MeONa in MeOH (3.2 ml, 6.36 mmol), and stirred at 25° for 17 h. The mixture was cooled to 0°, diluted with sat. aq. NH_4Cl soln. and 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 **26** (1.219 g, 91%). White solid. R_f (CH_2Cl_2/MeOH 95:5) 0.28. M.p. 170° (sintering from 140°). $[\alpha]_D^{25} = -79.0$ ($c = 1.0$, $CHCl_3$). UV ($CHCl_3$): 263 (23060). IR (ATR): 3484*w* (sh.), 3330*w* (br.), 3188*w*, 2935*m*, 2863*w*, 1692*s*, 1634*m*, 1603*m*, 1577*w*, 1461*w*, 1446*m*, 1368*m*, 1330*w*, 1251*m*, 1231*w*, 1162*w*, 1144*w*, 1087*s*, 1051*m*, 968*w*, 938*m*, 927*m*, 909*m*, 874*w*, 828*s*. ^{1}H-NMR (300 MHz, $CDCl_3$; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 9*; additionally, 7.28 (*d*, *J* = 8.1, H–C(6/I)); 5.73 (*d*, *J* = 8.1, H–C(5/I)); 1.85–1.81 (*m*, 2 H); 1.74–1.35 (*m*, 18 H); 1.59 (*sept.*, *J* = 6.9, Me_2CH); 0.82 (*d*, *J* = 6.9, Me_2CH); 0.77, 0.76 (2*s*, Me_2CSi); −0.03, −0.06 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 10*; additionally, 115.25, 114.45 (2*s*, 2 $(CH_2)_2C$); 37.18, 37.07, 35.07, 34.83 (4*t*); 34.31 (*d*, Me_2CH); 25.38 (*s*, Me_2CSi); 25.30, 25.11, 24.27, 24.16, 23.90, 23.77 (6*t*); 20.51 (*q*, Me_2CSi); 18.70 (*q*, Me_2CH); −3.19 (*q*, Me_2Si). HR-MALDI-MS: 842.3939 ($[M + H]^+$, $C_{40}H_{60}N_7O_9SSi^+$; calc. 842.3942).

*2′,3′-*O*-Cyclohexylideneadenosine-8-methyl-(8′ → 5′-*S*)-2′,3′-*O*-cyclohexylidene-5′-thiouridine* (**7**). In a polyethylene flask, a soln. of **26** (533 mg, 0.63 mmol) in dry THF (4 ml) at 25° was treated with a soln. of $Et_3N \cdot 3$ HF (1.04 ml, 19 mmol) and stirred at 25° for 49 h. The mixture was cooled to 0°, treated with 1M aq. NaOH soln. until the pH reached *ca.* 9, and extracted once with CH_2Cl_2/MeOH 9:1 and four times with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH 9:1) gave **7** (392 mg, 88%). White solid. R_f (CH_2Cl_2/MeOH 9:1) 0.45. M.p. 165–175°. $[\alpha]_D^{25} = -74.5$ ($c = 0.74$, $CHCl_3$/MeOH 7:1). UV ($CHCl_3$/MeOH 7:1): 264 (25010). IR (ATR): 3331*w*, 3194*w*, 2933*m*, 2859*w*, 1690*s*, 1635*s*, 1603*m*, 1579*m*, 1447*m*, 1369*m*, 1332*m*, 1262*m*, 1230*m*, 1162*m*, 1145*w*, 1089*s*, 1053*s*, 967*m*, 936*s*, 926*s*, 909*m*, 847*m*. ^{1}H-NMR (400 MHz, (D_6)DMSO; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 9*; additionally, 7.69 (*d*, *J* = 8.1, H–C(6/I)); 5.63 (*dd*, *J* = 8.1, 2.1, H–C(5/I)); 5.26 (*dd*, *J* = 6.5, 5.1, HO–C(5′/II); 1.81–1.78 (*m*, 2 H); 1.62–1.29 (*m*, 18 H). ^{13}C-NMR (100 MHz, (D_6)DMSO; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 10*; additionally, 113.90, 113.76 (2*s*, 2 $(CH_2)_2C$); 36.68, 36.42, 34.43, 34.19 (4*t*); 24.48, 24.43, 23.67, 23.56, 23.25, 23.16 (6*t*). HR-MALDI-MS: 700.2760 ($[M + H]^+$, $C_{32}H_{42}N_7O_9S^+$; calc. 700.2765).

*5′-*O*-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-di-*O*-methyladenosine-8-methyl-(8′ → 5′-*S*)-2′,3′-di-*O*-methyl-5′-thiouridine* (**27**). A soln. of **18** (1.152 g, 1.95 mmol) and **25** (645 mg, 1.95 mmol) in degassed MeOH (6 ml) at 0° was treated with a freshly prepared 1.95M soln. of MeONa in MeOH (4.0 ml, 7.8 mmol) and stirred at 25° for 18 h. The mixture was cooled to 0°, treated with sat. aq. NH_4Cl soln. and H_2O, and extracted four times with AcOEt. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH 9:1) gave **27** (1.242 g, 86%). White solid. R_f (CH_2Cl_2/MeOH 9:1) 0.39. M.p. 110–118°. $[\alpha]_D^{25} = -11.6$ ($c = 0.7$, $CHCl_3$). UV ($CHCl_3$): 264 (27090). IR (ATR): 3328*w*, 3194*w*, 2933*m*, 2830*w*, 1690*s*, 1635*s*, 1603*m*, 1576*w*, 1442*m*, 1368*m*, 1329*w*, 1298*w*, 1257*m*, 1207*w*, 1128*s*, 1067*s*, 1018*m*, 990*m*, 875*w*, 828*s*. ^{1}H-NMR (400 MHz, $CDCl_3$; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 9*; additionally, 7.56 (*d*, *J* = 8.1, H–C(6/I)); 5.74 (*d*, *J* = 8.1, H–C(5/I)); 3.52, 3.48, 3.42, 3.33 (4*s*, 4 MeO); 1.56 (*sept.*, *J* = 6.9, Me_2CH); 0.83 (*d*, *J* = 6.9, Me_2CH); 0.78 (*s*, Me_2CSi); 0.04, 0.03 (2*s*, Me_2Si). ^{13}C-NMR (100 MHz, $CDCl_3$; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 10*; additionally, 58.58, 58.52, 58.07, 58.01 (4*q*, 4 MeO); 34.23 (*d*, Me_2CH); 25.27 (*s*, Me_2CSi); 20.36, 20.34 (2*q*, Me_2CSi); 18.60 (*q*, Me_2CH); −3.39, −3.40 (2*q*, Me_2Si). HR-MALDI-MS: 738.3298 ($[M + H]^+$, $C_{32}H_{52}N_7O_9SSi^+$; calc. 738.3316).

*2′,3′-Di-*O*-methyladenosine-8-methyl-(8′ → 5′-*S*)-2′,3′-di-*O*-methyl-5′-thiouridine* (**8**). In a polyethylene flask, a soln. of **27** (683 mg, 0.93 mmol) in THF (6.2 ml) at 25° was treated with a soln. of $(HF)_3 \cdot Et_3N$ (1.52 ml, 27.8 mmol) and stirred at 25° for 48 h. The mixture was diluted with THF, treated with 1M aq. NaOH soln. until the pH reached *ca.* 10, and extracted four times with CH_2Cl_2/MeOH 9:1. The combined org. layers were evaporated. FC (CH_2Cl_2/MeOH 95:5 → 90:10) gave **8** (540 mg, 98%). White

Table 9. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the A*[s]U Dinucleotides:* **26** *and* **27** *in $CDCl_3$, and* **7**–**9** *in (D_6)DMSO Solution*[a])

	26 60 mM	**27** 101 mM	**7** 130 mM	**8** 120 mM	**9** 37 mM
Uridine unit (I)					
H–N(3/I)	11.78	11.59	11.41	11.41	11.34
H–C(1′/I)	5.57	5.87	5.78	5.83	5.78
H–C(2′/I)	4.99	3.90	4.97	4.07–4.09	4.12
H–C(3′/I)	4.73	3.67	4.60	3.73	3.90
H–C(4′/I)	4.22–4.28	4.23–4.28	4.08	4.07–4.09	3.97–4.02
H_a–C(5′/I)	3.00	3.03	2.92	3.00	2.96
H_b–C(5′/I)	2.95	2.96	2.92	2.93	2.87
J(1′,2′/I)	1.8	3.5	2.4	5.4	5.5
J(2′,3′/I)	6.5	5.3	6.5	4.7	5.6
J(3′,4′/I)	4.0	6.2	4.0	4.7	4.7
J(4′,5′a/I)	6.5	5.2	6.7	6.0	5.2
J(4′,5′b/I)	5.6	4.8	6.7	6.3	6.7
J(5′a,5′b/I)	13.3	14.4	[b])	14.1	13.9
Adenosine unit (II)					
H_2N–C(6/II)	6.99	6.51	7.34	7.64	7.37
H–C(2/II)	8.32	8.31	8.12	8.18	8.08
CH_a–C(8/II)	4.18	4.26	4.16	4.13	4.14
CH_b–C(8/II)	4.10	4.11	4.08	4.13	4.03
H–C(1′/II)	6.32	6.05	6.19	6.01	5.92
H–C(2′/II)	5.93	5.45	5.61	4.90	4.81
H–C(3′/II)	5.09	4.23–4.28	5.02	4.16	4.17
H–C(4′/II)	4.22–4.28	4.14	4.17	4.12–4.14	3.97–4.02
H_a–C(5′/II)	3.64	3.93	3.55	3.69	3.69
H_b–C(5′/II)	3.52	3.68	3.47	3.56	3.55
J(H_a,H_b/II)	14.6	14.4	14.4	[b])	14.3
J(1′,2′/II)	1.9	5.8	3.2	7.1	7.2
J(2′,3′/II)	6.2	5.5	6.2	5.1	5.3
J(3′,4′/II)	2.9	3.6	2.9	2.3	2.0
J(4′,5′a/II)	6.9	6.8	4.8	3.8	3.1
J(4′,5′b/II)	6.4	4.5	4.8	3.5	3.1
J(5′a,5′b/II)	10.5	11.0	11.7	12.2	12.4

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

solid. R_f (CH_2Cl_2/MeOH 9:1) 0.36. M.p. 137–148°. $[\alpha]_D^{25} = -56.2$ ($c = 0.9$, DMSO). UV (MeOH): 264 (24220). IR (ATR): 3386*w*, 3327*w*, 3193*m*, 3063*w*, 2988*w*, 2927*w*, 2829*w*, 1704*s*, 1693*s*, 1655*s*, 1633*s*, 1575*w*, 1446*m*, 1372*m*, 1333*m*, 1306*w*, 1275*s*, 1261*s*, 1221*w*, 1200*w*, 1127*m*, 1092*s*, 1065*s*, 1019*m*, 985*m*, 918*w*, 883*w*, 859*w*, 828*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 9*; additionally, 7.65 (*d*, $J = 8.1$, H–C(6/I)); 6.2–5.5 (br. *s*, HO–C(5′/II)); 5.66 (*dd*, $J = 8.1, 2.1$, H–C(5/I)); 3.42, 3.30, 3.27, 3.26 (4*s*, 4 MeO). ^{13}C-NMR (100 MHz, (D_6)DMSO; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 10*; additionally, 57.56, 57.40, 57.26, 57.11 (4*q*, 4 MeO). HR-MALDI-MS: 596.2133 ($[M + H]^+$, $C_{24}H_{34}N_7O_9S^+$; calc. 596.2139).

Adenosine-8-methyl-(8^I → 5′-S)-5′-thiouridine (**9**). A suspension of **28** [1] (426 mg, 0.69 mmol) in H_2O (1.4 ml) at 0° was treated with TFA (5.6 ml), vigorously stirred at 25° for 45 min, and evaporated at 25°. A soln. of the residue in H_2O was treated with *Amberlite* IRA-68 (free base form) until the pH

Table 10. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the A*[s]U Dinucleotides:* **26** *and* **27** *in $CDCl_3$, and* **7**–**9** *in (D_6)DMSO Solution*[a])

	26	**27**	**7**	**8**	**9**
Uridine unit (I)					
C(2/I)	150.97	151.12	150.24	150.43	150.70
C(4/I)	163.75	164.09	163.12	162.88	162.97
C(5/I)	103.14	102.99	102.03	102.31	102.17
C(6/I)	142.72	140.39	142.64	140.45	140.94
C(1′/I)	95.63	89.22	91.74	86.63	88.25
C(2′/I)	84.13	81.42	82.97	80.67	72.49
C(3′/I)	83.35	79.76	82.29	79.29	72.12
C(4′/I)	90.31	81.00	85.22	79.84	82.73
C(5′/I)	34.78	33.67	33.41	33.36	35.51
Adenosine unit (II)					
C(2/II)	152.58	152.66	152.30	151.16	151.85
C(4/II)	150.97	150.77	149.77	149.80	149.66
C(5/II)	118.40	118.82	117.94	118.09	118.24
C(6/II)	155.41	155.46	155.66	154.96	155.79
C(8/II)	149.37	150.04	148.13	148.95	148.48
CH_2–C(8/II)	28.99	28.71	27.73	27.93	27.91
C(1′/II)	88.14	87.53	89.43	86.72	88.70
C(2′/II)	82.51	78.82[b])	81.81	79.95	72.35
C(3′/II)	82.00	78.77[b])	80.95	78.17	70.88
C(4′/II)	87.10	82.84	86.35	83.89	86.79
C(5′/II)	63.09	62.33	61.51	61.86	62.15

[a]) Assignment based on a DQF-COSY and a HSQC spectrum. [b]) Assignment may be interchanged.

reached 7. Filtration (washing with H_2O and MeOH), evaporation, and FC (AcOEt/MeOH/H_2O 7:2:0.5 → 7:2:1) gave **9** (364 mg, 98%). White solid. R_f (AcOEt/MeOH/H_2O 7:2:1) 0.41. M.p. 185° (dec.). $[\alpha]_D^{25} = -40.3$ ($c = 0.5$, DMSO). UV (MeOH): 265 (19280). IR (ATR): 3327*m*, 3195*m*, 2931*w*, 1671*s*, 1645*s*, 1577*m*, 1449*m*, 1378*m*, 1334*m*, 1309*w*, 1261*m*, 1201*m*, 1123*s*, 1080*s*, 1044*s*, 987*m*, 913*w*, 886*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 9*; additionally, 7.64 (*d*, $J = 8.1$, H–C(6/I)); 5.93 (*dd*, $J = 9.4$, 3.1, HO–C(5′/II)); 5.62 (*d*, $J = 8.1$, H–C(5/I)); 5.46 (*d*, $J = 5.7$, HO–C(2′/I)); 5.33 (*d*, $J = 7.6$, HO–C(2′/II)); 5.30 (*d*, $J = 4.3$, HO–C(3′/II)); 5.23 (*d*, $J = 5.5$, HO–C(3′/I)). ^{13}C-NMR (100 MHz, (D_6)DMSO; assignments based on a DQF-COSY and a HSQC spectrum): see *Table 10*. HR-MALDI-MS: 540.1502 ($[M + H]^+$, $C_{20}H_{25}N_7O_9S^+$; calc. 540.1513).

CD Spectra of the Gels. The CD measurements were performed according to [2], except for the gel of **8** in decan-1-ol: 2.0-nm band width, 1-s response, low sensitivity, 0.1 nm data pitch, and 200-nm/min scanning speed.

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