# Oligonucleotide Analogues with Integrated Bases and Backbones

Part 23

## Conformational Analysis and Association of Sulfonyl- and Sulfinylmethylene Adenosine and Uridine Dinucleosides

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The sulfone **2**, and the sulfoxides (*S*)-**3** and (*R*)-**3** were obtained by oxidation of the thiomethylene-linked A*[s]U dinucleoside **1**. Conformational analysis and association studies of **2**, (*S*)-**3**, and (*R*)-**3** reveal a strong influence of the configuration on the conformation of the linking unit and on the self-association of the dinucleosides.

**Introduction.** – Oligoribonucleotide analogues integrating backbone and bases (ONIBs) are characterized by replacing the backbone of the parent oligonucleotide by a linker between the nucleobases. They form linear and/or cyclic duplexes, depending on the nature of the linking unit, the sequence of the nucleobases, and the substitution of C(6) of terminal U and C(8) of terminal A units [1–8]. The thiomethylene-linked self-complementary A*[s]U[1]) dinucleoside **1** (*Scheme*) forms mainly linear associates in $CHCl_3$ solution [6]. Wondering about the influence of the oxidation state of the S-atom on the conformation of the linker and on the association of the resulting species, we decided to synthesise sulfone **2**, and the sulfoxides **3** and **4**.

**Results and Discussion.** – *Synthesis of the Sulfone* **2** *and the Sulfoxides* **3** *and* **4**. Catalytic oxidation of the sulfide **1** [6] in $CH_2Cl_2$ with aqueous $H_2O_2$ and $Na_2WO_4$ in the presence of $NMe(C_8H_{17})_3(HSO_4)$ [9] led, in a yield of 84%, to sulfone **2** (*Scheme*). Oxidation of **1** with $NaIO_4$ and separation of the products by flash chromatography gave the diastereoisomeric sulfoxides (*S*)-**3** (45%) and (*R*)-**3** (30%). Desilylation of (*S*)-**3** and (*R*)-**3** with $(HF)_3 \cdot Et_3N$ yielded 78% of the alcohol (*S*)-**4** and 56% of the diastereoisomer (*R*)-**4**. Screening a number of solvents [10] failed to provide crystals of (*S*)-**4** and (*R*)-**4**, with (*S*)-**4** leading to a fibrous solid from MeOH, and gels or partial gels with acetone, butan-2-one, MeCN, AcOEt, and linear or branched alcohols (*Table 1*). Alcohol (*R*)-**4** was only soluble in DMF, DMSO, and 2,2,2-trifluoroethanol. It formed a partial gel in MeOH and proved insoluble in all other tested solvents.

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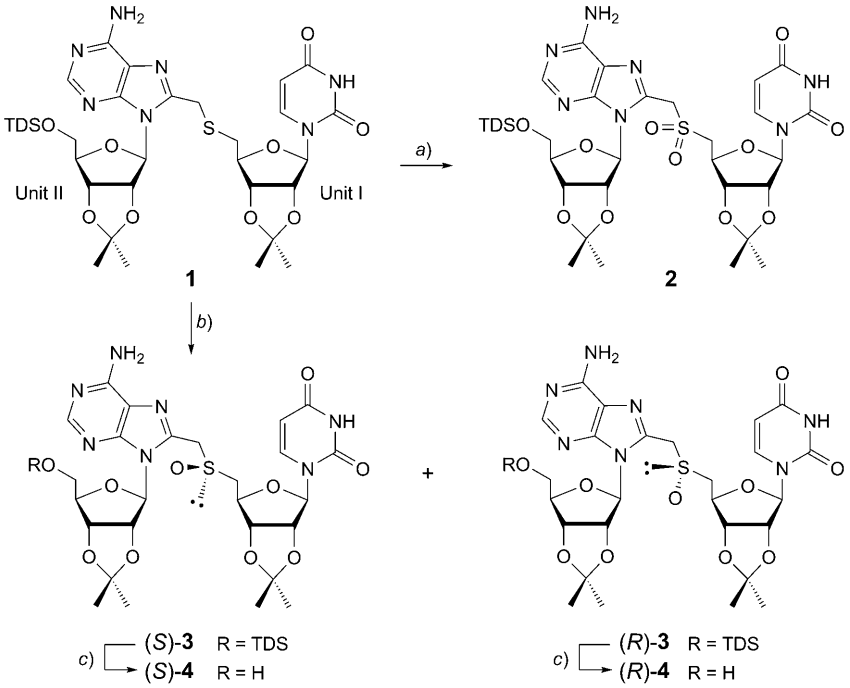
[1]) *Conventions for abbreviated notation:* The substitution at C(6) of pyrimidines is denoted by an asterisk (*); for example, A* for hydroxymethylated adenosine. The moiety x linking C(8)–$CH_2$ of unit II and C(5′) of unit I is indicated in square brackets, *i.e.*, [s] for a S-atom.

*Scheme*




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

*a*) $Na_2WO_4 \cdot (H_2O)_2$, $MeN(C_8H_{17})_3(HSO_4)$, $PhPO(OH)_2$, 30% aq. $H_2O_2/CH_2Cl_2$; 84%. *b*) $NaIO_4$, $MeOH/H_2O/MeCN$; 45% of (*S*)-**3**, 30% of (*R*)-**3**. *c*) $(HF)_3 \cdot Et_3N$, THF; 78% of (*S*)-**4**; 56% of (*R*)-**4**.

The determination of the configuration of the diastereoisomeric sulfoxides **3** and **4** is based on the observation that solutions of 6-deoxy-6-[(*S*)-methylsulfinyl]glycopyranosides in $CDCl_3$ adopt the *gt*-conformation, whereas the (*R*)-configured diastereoisomers exist as a mixture of *gt*- and *tg*-conformers [11–13].

The *gt*-conformation and thus the (*S*)-configuration of (*S*)-**3** in $CDCl_3$ and of (*S*)-**4** in $CDCl_3/CD_3OD$ 7:1 is evidenced by large *J*(4′,5′a/I) values of 10.3–10.6 Hz with the more deshielded $H_a$–C(5′/I) and small *J*(4′,5′b/I) values of 2.5–2.7 Hz (*Table 3* in the *Exper. Part*). A *ca.* 2:1 *gt*/*tg*-equilibrium of (*R*)-**3** and (*R*)-**4** is deduced from *J*(4′,5′a/I) 7.6–7.7 and *J*(4′,5′b/I) 3.3–4.5 Hz.

2. *Association of the Sulfone* **2**, *and the Sulfoxides* **3** *in* $CHCl_3$. The self-association of the sulfone **2**, and of the sulfoxides (*S*)-**3** and (*R*)-**3** was investigated by analyzing the concentration dependence of the chemical shift for H–N(3/I) (shift–concentration curve, SCC), and by analysing its temperature-dependence by $^1$H-NMR and circular dichroism (CD) spectroscopy. The insolubility of the alcohols (*S*)-**4** and (*R*)-**4** in $CHCl_3$ did not allow investigating their self-association.

The SCCs of **2**, (*S*)-**3**, and (*R*)-**3** show a bending below 20 mM and a flattening above *ca.* 30 mM, but do not reach a plateau (*Fig. 1*). This evidences equilibria between

Table 1. *Solubility of the Dinucleosides* (*S*)-**4** *and* (*R*)-**4** *in Selected Solvents*[a])

| Class | Solvent | (*S*)-**4** | (*R*)-**4** |
|---|---|---|---|
| Aliphatic apolar[b]) | Hexane[c]) | I | I |
| | $CCl_4$ | I | I |
| Aromatic apolar | Toluene | I | I |
| Electron-pair donor | $Et_2O$ | I | I |
| | *t*-BuOMe[b]) | I | I |
| | 1,4-Dioxane | S | I |
| Aprotic dipolar | $CH_2Cl_2$ | I[d]) | I |
| | Acetone | PG | I |
| | Butan-2-one | PG | I |
| | $ClCH_2CH_2Cl$ | S | I |
| | MeCN | PG | I |
| | AcOEt | PG | I |
| Aprotic highly dipolar | DMF | S | S |
| | DMSO | S | S |
| H-Bonding | 2,2,2-Trifluoroethanol | S | S |
| | MeOH | S[e]) | PG |
| | EtOH | PG | I |
| | PrOH | TG | I |
| | BuOH | CG | I |
| | i-PrOH | TG | I |
| | *t*-BuOH | TG | I |
| H-Bonding strongly associated | $H_2O$ | I | I |
| Miscellaneous | $CHCl_3$ | I[d]) | I |
| | $MeOCH_2CH_2OMe$[c]) | S | I |
| | THF[c]) | I[d]) | I |

[a]) [Dinucleoside] = 1% (*w*/*v*), I: insoluble, S: soluble, PG: partial gel, CG: clear gel, TG: turbid gel. [b]) Absent from *Chastrette*'s original classification [10]. [c]) Reclassified solvent. [d]) Soluble at the boiling temperature. [e]) At higher dinucleoside concentration, a fibrous solid was obtained upon cooling.

monoplexes, linear associates, and cyclic duplexes. The sulfoxide (*S*)-**3** shows the largest proportion of cyclic duplexes, as evidenced by the strongest bending below 20 mM and the weakest increase of the downfield shift above 30 mM.

The SCCs of **2**, (*S*)-**3**, and (*R*)-**3** were analysed numerically by the method proposed by *Gutowsky* and *Saika* [14], including a value of 7.70 ppm for a 0.0001-mM solution, corresponding to the chemical shift of the monoplex, as deduced from $\delta$(H–N(3)) of monomeric uridine derivatives (*cf.* [6]). The association constants $K_{ass}$ of the sulfoxides (*S*)-**3** (2556 $M^{-1}$; *Table 2*) and (*R*)-**3** (1965 $M^{-1}$), and of the sulfone **2** (552 $M^{-1}$) are distinctly larger than that of the sulfide **1** (225 $M^{-1}$ [6]). That (*S*)-**3** shows the highest association constant is expected, since already the monoplex adopts completely the required *gt*-orientation of the linker (see above). The calculated chemical-shift values for the cyclic duplexes (11.87 – 12.19 ppm) suggest similar mixtures of *Watson–Crick*- and *Hoogsteen*-type H-bonded cyclic duplexes for all three compounds. The $-\Delta H$ values decreasing from 16.9 for (*S*)-**3** to 14.4 for (*R*)-**3**, and to 10.3 kcal/mol for **2** reflect an increasing contribution of the monoplex rather than an increasing contribution of *Hoogsteen*-type base-paired cyclic duplexes.

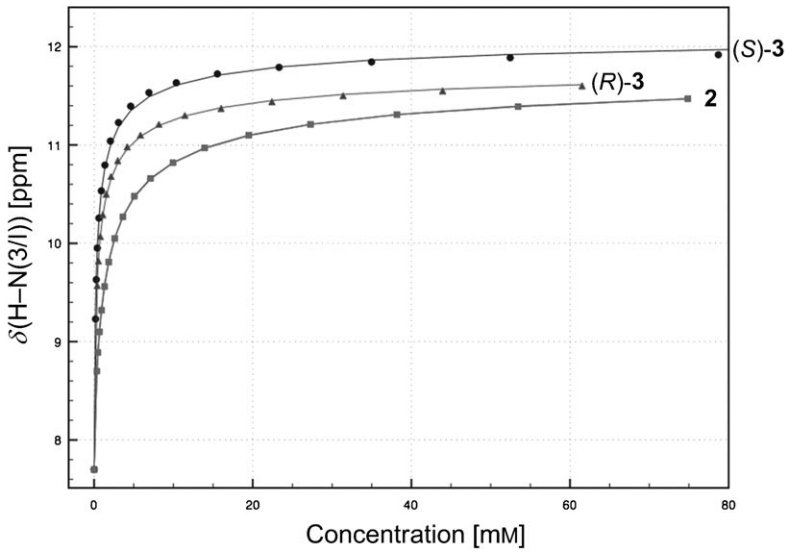



Fig. 1. *Shift–concentration curves* (SCCs) *of the sulfone* **2***, and the sulfoxides* (S)-**3** *and* (R)-**3** *in* $CDCl_3$ *solution* (including a value of 7.70 ppm for a 0.001-mM solution)

Table 2. *Association Constants* $K_{ass}$ *and Extrapolated Chemical Shifts of the Monoplexes and Duplexes from the Concentration Dependence of δ(HN(3)) in* $CDCl_3$ *at 295 K for the A*[s]U(*) Dinucleosides* **2***,* (S)-**3***, and* (R)-**3** (including a value of 7.70 ppm for a 0.0001-mM solution). *Thermodynamic Parameters by* van't Hoff *Analysis of the Temperature Dependence of δ(HN(3)) for 7–10 mM Solutions in* $CDCl_3$ *at 10–50°.*

| Dimer | $K_{ass}$ [$M^{-1}$] | $\delta_{monoplex}$ [a]) [ppm] | $\delta_{duplex}$ [b]) [ppm] | $-\Delta G_{295}$ [c]) [kcal/mol] | $-\Delta H$ [kcal/mol] | $-\Delta S$ [cal/mol K] |
|---|---|---|---|---|---|---|
| **2** | 552 | 7.71 | 11.91 | 3.7 | 10.3 | 22.1 |
| (*S*)-**3** | 2556 | 7.67 | 12.19 | 4.6 | 16.9 | 41.1 |
| (*R*)-**3** | 1965 | 7.69 | 11.87 | 4.4 | 14.4 | 33.2 |

[a]) Extrapolated for 0 mM. [b]) Extrapolated for infinite concentration. [c]) Calculated from $K_{ass}$.

CD Spectra were recorded for 1 mM $CHCl_3$ solutions of **2**, (*S*)-**3**, and (*R*)-**3** in the temperature range from 0 to 50° (*Fig. 2*). The sulfoxide (*S*)-**3** shows both a strong ellipticity and a strong intensity decrease upon raising the temperature. This evidences the presence of a cyclic duplex favouring a fairly effective $\pi$-stacking of the base pairs. In the series of ethynyl-linked dinucleosides, a reverse-*Hoogsteen* base-paired cyclic duplex showed a distinctly stronger CD absorption than *Watson–Crick* base-paired cyclic duplexes [2], suggesting a dominant *Hoogsteen*-type base-paired cyclic duplex also for (*S*)-**3**. The CD spectra of **2**, (*S*)-**3**, and (*R*)-**3** show a stronger positive maximum at 250–270 than at 280–295 nm. This evidences a dominant proportion of cyclic duplexes possessing the same type of base pairing.

3. *Conformation of the Sulfone* **2***, and the Sulfoxides* **3** *and* **4**. The $^1$H-NMR spectra of 36–72-mM solutions of **2** and **3** in $CDCl_3$ reflect the equilibrium between linear

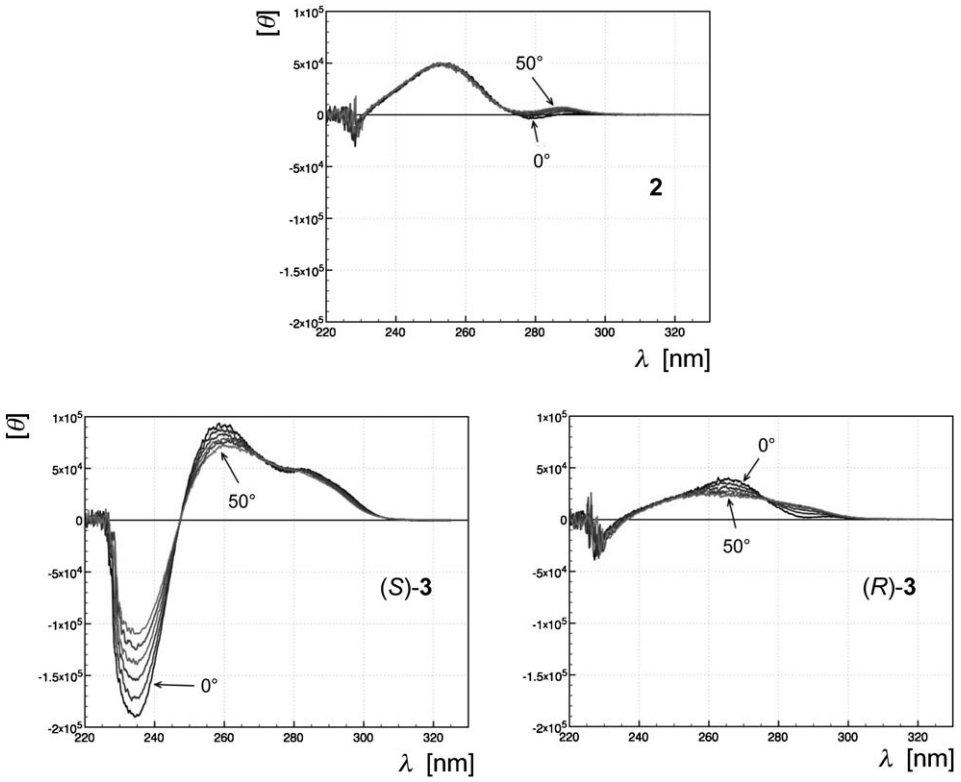



Fig. 2. *Temperature-dependent CD spectra* (in 10° steps from 0° to 50°) *of 7–10-*mM *solutions in* $CHCl_3$ *of the sulfone* **2***, and the sulfoxides (*S*)-***3*** and (*R*)-***3***

associates and cyclic duplexes, whereas the $^1$H-NMR spectrum of **4** in $CDCl_3/CD_3OD$ 7:1 is expected to reflect the conformation of the solvated monoplex[2]) (*Table 3* in the *Exper. Part*).

Unit I of **2** and (*S*)-**3** adopts completely a *syn*-conformation, as revealed by the chemical shifts for H–C(2′/I) (5.08 and 5.11 ppm, resp.). Although a small upfield shift for H–C(2′/I) ($\Delta\delta \approx 0.07$ ppm) of (*S*)-**4** may be taken to suggest a small contribution of the *anti*-conformer, it may also be a consequence of the different solvents. A similar chemical shift for H–C(1′/I) of the diastereoisomers of **3** and **4** ($\Delta\delta \leq 0.02$ ppm) indicates a similar preference for the *syn*-conformation. The upfield shift for H–C(2′/I) of (*R*)-**3** and (*R*)-**4** (4.90 and 4.91 ppm, resp.) must then be an indirect effect of the configurational change of the S-atom, and does not indicate a strong preference for the *anti*-conformer. This conclusion is supported by the observation that (*R*)-**3** shows a stronger preference than **2** for the formation of cyclic duplexes which require a *syn*-orientation of the uracil moiety. All these five compounds prefer a northern

[2]) The addition of 10% of $CD_3OD$ was sufficient to completely break the cyclic duplexes of an ethynyl-linked self-complementary tetranucleoside in $CDCl_3$ solution [15].

conformation of the furanose ring of unit I ($J(1',2'/I)/J(3',4'/I) = 0.3-0.4$). As discussed above, (*S*)-**3** and (*S*)-**4** completely adopt a *gt*-conformation, and **2**, (*R*)-**3**, and (*R*)-**4** a *ca*. 2:1 *gt*/*tg*-equilibrium. Since *tg*-configured dinucleosides can only form linear associates, one expects a larger proportion of the *tg*-conformer for the self-associated **2** and (*R*)-**3** than for the solvated (*R*)-**4**. This is indeed so, as revealed by the $J(4',5'a/I)/J(4',5'b/I)$ ratios of 2.4, 2.3, and 1.7 for **2**, (*R*)-**3**, and (*R*)-**4**, respectively. Since the size of $J(4',5'a/I)$ and $J(4',5'b/I)$ is influenced by the orientation of the O-atoms and the doubly occupied non-bonding orbitals of the S-atom [16], a quantitative determination of the rotameric equilibrium based on the equations given in [6] appears inadequate.

Unit II of the silyl ethers **2** and **3** adopts the expected *syn*-conformation, whereas the *syn*-conformation of unit II of the alcohols **4** is the consequence of the intramolecular O–H···N(3/II) H-bond. This H-bond is evidenced by the upfield shift of H–C(2′/II), the *gg*-orientation of the $HOCH_2$ group, and the southern (*S*) furanose ring conformation (*cf.* [2][6][17][18]). $J(4',5'a/II)$ and $J(4',5'b/II) = 2.0-2.8$ Hz suggest a *ca*. 90% persistence of this H-bond in $CDCl_3/CD_3OD$ 7:1. Surprisingly, the signals of H–C(1′/II) and H–C(2′/II) of (*R*)-**3** are shifted upfield by *ca.* 0.25 ppm as compared to those of **2** and (*S*)-**3**. A similar observation is made for the corresponding signals of (*R*)-**4** as compared to (*S*)-**4** ($\Delta\delta = 0.12$ for H–C(1′/II) and 0.2 ppm for H–C(2′/II)). The silyl ethers **2** and **3** prefer a (*N*)-conformation of the adenosine moiety and a *gt*/*tg*-orientation of the $TDSOCH_2$ group.

**Conclusions.** – The (*S*)-configured sulfinylmethyl-linked A*[s]U dinucleoside (*S*)-**3** adopts completely the *gt*-orientation of the linker required for pairing already as the monoplex, and shows a higher propensity than (*R*)-**3** to form self-complementary cyclic duplexes. Similarly, (*R*)-**3** and the sulfone **2** show both a stronger preference for the *gt*-conformation than the sulfide **1** ($gt/(gg + tg) > 1.5$ *vs.* 0.8) and a higher propensity to form cyclic duplexes. A stereoselective oxidation to the sulfoxides of thiomethylene-linked oligonucleosides is thus of considerable interest.

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## Experimental Part

*General and Evaluation of the Solubility.* See [6] and [7].

*5′-O-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-O-isopropylideneadenosine-8-methyl-(8′ → 5′-S)-5′-deoxy-2′,3′-O-isopropylidene-5′-sulfonyluridine* (**2**). A mixture of **1** [6] (331 mg, 0.43 mmol), $Na_2WO_4 \cdot (H_2O)_2$ (1.4 mg, 4 μmol), $NMe(C_8H_{17})_3(HSO_4)$ [9] (2.0 mg, 4 μmol), $PhPO(OH)_2$ (0.7 mg, 4 μmol) in 30% aq. $H_2O_2$ (1 ml), and $CH_2Cl_2$ (1 ml) was vigorously stirred at 25° for 3 h. The mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$. The combined org. layers were dried ($Na_2SO_4$) and evaporated. FC ($CH_2Cl_2$/MeOH 95:5) gave **2** (291 mg, 84%). White solid. $R_f$ ($CH_2Cl_2$/MeOH 95:5) 0.29. M.p. 155° (dec.). $[\alpha]_D^{25} = -6.1$ ($c = 1.1$, $CHCl_3$). UV ($CHCl_3$): 262 (24170). IR (ATR): 3333*w*, 3193*w*, 2956*w*, 2867*w*, 1692*s*, 1639*m*, 1454*w*, 1375*m*, 1325*m*, 1252*m*, 1212*m*, 1156*m*, 1125*m*, 1080*s*, 971*w*, 935*w*, 829*s*. $^1$H-NMR (300 MHz, $CDCl_3$): see *Table 3*; additionally, 7.25 (*d*, $J = 7.9$, H–C(6/I)); 5.66 (*d*, $J = 7.9$, H–C(5/I)); 1.60, 1.54, 1.40, 1.32 (4*s*, 2 $Me_2C$); 1.54 (*sept.*, $J = 6.8$, $Me_2CH$); 0.81 (*d*, $J = 6.9$, $Me_2CH$); 0.77, 0.76 (2*s*, $Me_2CSi$); −0.01, −0.04 (2*s*, $Me_2Si$). $^{13}$C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 114.81, 114.15 (2*s*, 2 $Me_2C$); 34.16 (*d*, $Me_2CH$); 27.34, 27.16, 25.56, 25.40 (4*q*, 2 $Me_2C$); 25.35 (*s*, $Me_2CSi$); 20.41 (*q*, $Me_2CSi$); 18.57 (*q*, $Me_2CH$); −3.30, −3.33 (2*q*, $Me_2Si$). HR-MALDI-MS: 794.3221 ($[M + H]^+$, $C_{34}H_{52}N_7O_{11}SSi^+$; calc. 794.3215).

Table 3. *Selected $^1$H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the A*[s]U Dinucleosides* **2**, *(*S*)-***3**, *and (*R*)-***3** *in $CDCl_3$, and (*S*)-***4** *and (*R*)-***4** *in $CDCl_3$/$CD_3OD$ 7:1*

| | **2** 36 mM | (*S*)-**3** 72 mM | (*R*)-**3** 66 mM | (*S*)-**4** 161 mM | (*R*)-**4** 108 mM |
|---|---|---|---|---|---|
| Uridine unit I | | | | | |
| H–N(3/I) | 11.25 | 11.78 | 11.52 | – | – |
| H–C(1′/I) | 5.46 | 5.47 | 5.45 | 5.40 | 5.41 |
| H–C(2′/I) | 5.08 | 5.11 | 4.90 | 5.03 | 4.91 |
| H–C(3′/I) | 5.05 | 4.92 | 5.05 | 4.84 | 4.86 |
| H–C(4′/I) | 4.72 | 4.63 | 4.85 | 4.51 | 4.58 |
| $H_a$–C(5′/I) | 4.07 | 3.37 | 3.80 | 3.40 | 3.41 |
| $H_b$–C(5′/I) | 3.63 | 3.01 | 3.39 | 3.14 | 3.29 |
| *J*(1′,2′/I) | 1.1 | 1.1 | 1.7 | 1.3 | 1.4 |
| *J*(2′,3′/I) | 6.4 | 6.3 | 6.5 | 6.3 | 6.5 |
| *J*(3′,4′/I) | 3.7 | 3.8 | 3.8 | 4.0 | 3.6 |
| *J*(4′,5′$_a$/I) | 8.3 | 10.3 | 7.7 | 10.6 | 7.6 |
| *J*(4′,5′$_b$/I) | 3.4 | 2.5 | 3.3 | 2.7 | 4.5 |
| *J*(5′$_a$,5′$_b$/I) | 14.0 | 13.2 | 14.2 | 13.0 | 14.1 |
| Adenosine unit (II) | | | | | |
| $H_2N$–C(6/II) | 6.86 | 7.23 | 7.12 | – | – |
| H–C(2/II) | 8.29 | 8.32 | 8.22 | 7.94 | 8.04 |
| $CH_a$–C(8/II) | 5.01 | 4.80 | 4.56 | 4.45 | 4.46 |
| $CH_b$–C(8/II) | 4.78 | 4.30 | 4.56 | 4.36 | 4.26 |
| H–C(1′/II) | 6.30 | 6.43 | 6.13 | 5.99 | 5.87 |
| H–C(2′/II) | 5.99 | 5.98 | 5.74 | 5.25 | 5.06 |
| H–C(3′/II) | 5.07 | 5.14 | 5.00 | 5.01 | 4.92 |
| H–C(4′/II) | 4.23 | 4.23 | 4.23 | 4.34 | 4.31 |
| $H_a$–C(5′/II) | 3.66 | 3.58 | 3.77 | 3.78 | 3.78 |
| $H_b$–C(5′/II) | 3.56 | 3.47 | 3.66 | 3.62 | 3.61 |
| *J*($H_a$,$H_b$/II) | 15.3 | 14.4 | [a]) | 14.5 | 14.8 |
| *J*(1′,2′/II) | 1.5 | 1.3 | 2.3 | 4.4 | 4.7 |
| *J*(2′,3′/II) | 6.3 | 6.2 | 6.4 | 5.9 | 6.0 |
| *J*(3′,4′/II) | 3.4 | 3.2 | 3.8 | 2.0 | 2.2 |
| *J*(4′,5′$_a$/II) | 6.0 | 6.7 | 5.3 | 2.0 | 2.0 |
| *J*(4′,5′$_b$/II) | 6.5 | 6.6 | 7.3 | 2.8 | 2.6 |
| *J*(5′$_a$,5′$_b$/II) | 10.8 | 10.5 | 10.9 | 12.6 | 12.6 |

[a]) Not assigned.

*Oxidation of* **1** *with $NaIO_4$.* A soln. of **1** (5.500 g, 6.94 mmol) in MeOH/MeCN/$H_2O$ 1:1:1 (300 ml) was treated with $NaIO_4$ (11.760 g, 55.5 mmol) and stirred for 32 h at 25°. The mixture was treated with sat. aq. $Na_2S_2O_3$ soln. (200 ml). The layers were separated, and the aq. layer was extracted three times with $CH_2Cl_2$ and once with AcOEt. The combined org. layers were dried ($Na_2SO_4$) and evaporated. FC ($CH_2Cl_2$/MeOH 95:5 → 9:1) gave (*S*)-**3** (2.425 g, 45%) and (*R*)-**3** (1.617 g, 30%).

*Data of (*S*)-5′-*O*-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-*O*-isopropylideneadenosine-8-methyl-(8$^1$ → 5′-*S*)-5′-deoxy-2′,3′-*O*-isopropylidene-5′-sulfinyluridine* ((*S*)-**3**). White solid. $R_f$ ($CH_2Cl_2$/MeOH 9:1) 0.33. M.p. 160–170°. $[\alpha]_D^{25} = -5.6$ ($c = 1.3$, $CHCl_3$). UV ($CHCl_3$): 264 (24710). IR (ATR): 3330*w*, 3193*w*, 2956*w*, 2868*w*, 1692*s*, 1634*s*, 1601*w*, 1454*w*, 1373*s*, 1331*w*, 1295*w*, 1253*m*, 1212*m*, 1156*m*, 1068*s*, 972*w*, 934*w*, 828*s*, 800*m*. $^1$H-NMR (400 MHz, $CDCl_3$): see *Table 3*; additionally, 7.25 (*d*, *J* = 8.1, H–C(6/I)); 5.74 (*d*, *J* = 8.1, H–C(5/I)); 1.58, 1.50, 1.40, 1.30 (4*s*, 2 $Me_2C$); 1.52 (*sept.*, *J* = 6.9, $Me_2CH$); 0.80 (*d*,

Table 4. *Selected $^{13}$C-NMR Chemical Shifts* [ppm] *of the A*[s]U Dinucleosides* **2**, (S)-**3**, *and* (R)-**3** *in $CDCl_3$, and* (S)-**4** *and* (R)-**4** *in $CDCl_3$/$CD_3OD$ 7:1*

| | **2** | (*S*)-**3** | (*R*)-**3** | (*S*)-**4** | (*R*)-**4** |
|---|---|---|---|---|---|
| Uridine unit I | | | | | |
| C(2/I) | 150.78 | 151.30 | 150.41[a]) | 150.44 | 149.21 |
| C(4/I) | 164.24 | 163.88 | 164.61 | 164.56 | 164.02 |
| C(5/I) | 102.90 | 103.20 | 102.57 | 102.42 | 102.38 |
| C(6/I) | 144.09 | 143.85 | 143.74 | 144.18 | 143.47 |
| C(1′/I) | 97.48 | 97.75 | 96.06 | 97.24 | 96.12 |
| C(2′/I) | 84.26[a]) | 85.08 | 84.41 | 84.54 | 84.12 |
| C(3′/I) | 84.61[a]) | 84.56 | 84.55 | 84.00 | 83.99 |
| C(4′/I) | 83.57 | 83.39[a]) | 81.87[b]) | 83.09[a]) | 81.51[a]) |
| C(5′/I) | 55.65 | 55.70 | 53.10 | 56.29 | 52.56 |
| Adenosine unit II | | | | | |
| C(2/II) | 153.22 | 152.96 | 152.92 | 152.20 | 152.42 |
| C(4/II) | 150.33 | 150.54 | 149.90[a]) | 149.27 | 150.24 |
| C(5/II) | 119.15 | 118.39 | 118.71 | 118.95 | 118.96 |
| C(6/II) | 155.81 | 155.78 | 155.79 | 155.50 | 155.50 |
| C(8/II) | 141.60 | 143.62 | 144.49 | 142.56 | 142.66 |
| $CH_2$–C(8/II) | 53.17 | 48.45 | 49.57 | 49.94 | 48.39 |
| C(1′/II) | 90.38 | 90.81 | 89.93 | 91.84 | 91.93 |
| C(2′/II) | 83.18 | 83.36[a]) | 82.97 | 82.21[a]) | 82.88 |
| C(3′/II) | 81.89 | 82.44 | 81.76[b]) | 81.26 | 81.23[a]) |
| C(4′/II) | 88.14 | 88.68 | 87.79 | 86.12 | 85.82 |
| C(5′/II) | 63.11 | 63.19 | 63.58 | 62.61 | 62.61 |

[a]) [b]) Assignment may be interchanged.

$J$ = 6.9, *Me*$_2$CH); 0.75, 0.74 (2*s*, Me$_2$CSi); −0.05, −0.07 (2*s*, Me$_2$Si). $^{13}$C-NMR (100 MHz, $CDCl_3$): see *Table 4*; additionally 114.65, 113.77 (2*s*, 2 Me$_2$*C*); 34.20 (*d*, Me$_2$*C*H); 27.30, 27.12, 25.56, 25.39 (4*q*, 2 *Me*$_2$C); 25.31 (*s*, Me$_2$*C*Si); 20.40 (*q*, *Me*$_2$CSi); 18.59, 18.57 (2*q*, *Me*$_2$CH); −3.33 (*q*, Me$_2$Si). HR-MALDI-MS: 778.3247 ($[M + H]^+$, $C_{34}H_{52}N_7O_{10}SSi^+$; calc. 778.3266).

*Data of* (R)*-5′-*O*-[Dimethyl(1,1,2-trimethylpropyl)silyl]-2′,3′-*O*-isopropylideneadenosine-8-methyl-(8$^I$ → 5′-*S*)-5′-deoxy-2′,3′-*O*-isopropylidene-5′-sulfinyluridine* ((*R*)-**3**). White solid. $R_f$ ($CH_2Cl_2$/MeOH 9:1) 0.26. M.p. 155–165°. $[\alpha]_D^{25} = +37.0$ ($c$ = 1.3, $CHCl_3$). UV ($CHCl_3$): 262 (25460). IR (ATR): 3329*w*, 3194*w*, 2956*w*, 2868*w*, 1692*s*, 1634*s*, 1601*m*, 1579*w*, 1454*w*, 1374*m*, 1331*w*, 1296*w*, 1252*m*, 1212*m*, 1156*m*, 1068*s*, 972*w*, 934*w*, 828*s*, 800*m*. $^1$H-NMR (400 MHz, $CDCl_3$): see *Table 3*; additionally, 7.24 (*d*, $J$ = 8.1, H–C(6/I)); 5.47 (*d*, $J$ = 8.1, H–C(5/I)); 1.60, 1.54 1.38, 1.29 (4*s*, 2 Me$_2$C); 1.56 (*sept.*, $J$ = 6.9, Me$_2$C*H*); 0.83 (*d*, $J$ = 6.9, *Me*$_2$CH); 0.79, 0.78 (2*s*, Me$_2$CSi); 0.04, 0.01 (2*s*, Me$_2$Si). $^{13}$C-NMR (100 MHz, $CDCl_3$): see *Table 4*; additionally 114.69, 114.43 (2*s*, 2 Me$_2$*C*); 34.19 (*d*, Me$_2$*C*H); 27.41, 27.15, 25.57, 25.37 (4*q*, 2 *Me*$_2$C); 25.32 (*s*, Me$_2$*C*Si); 20.46, 20.43 (2*q*, *Me*$_2$CSi); 18.61, 18.60 (2*q*, *Me*$_2$CH); −3.17, −3.24 (2*q*, *Me*$_2$Si). HR-MALDI-MS: 778.3267 ($[M + H]^+$, $C_{34}H_{52}N_7O_{10}SSi^+$; calc. 778.3266).

(S)*-2′,3′-*O*-Isopropylideneadenosine-8-methyl-(8$^I$ → 5′-*S*)-5′-deoxy-2′,3′-*O*-isopropylidene-5′-sulfinyluridine* ((*S*)-**4**). In a polyethylene flask, a soln. of (*S*)-**3** (681 mg, 0.88 mmol) in THF (8 ml) was treated with a soln. of $(HF)_3 \cdot Et_3N$ (2.4 ml, 43.8 mmol) and stirred at 25° for 22 h. The mixture was diluted with MeOH/$CH_2Cl_2$ 1:1 (15 ml), treated with aq. 1M NaOH soln. until the pH reached *ca.* 10, and filtered (washing with $H_2O$). FC ($CH_2Cl_2$/MeOH 9:1) of the solid gave (*S*)-**4** (432 mg, 78%). A sample for analysis was recrystallized in MeOH. White fibrous solid. $R_f$ ($CH_2Cl_2$/MeOH 9:1) 0.23. M.p. 207° (dec.). $[\alpha]_D^{25} = +27.2$ ($c$ = 2.4, DMSO). UV ($CHCl_3$/MeOH 7:1): 263 (27180). IR (ATR): 3328*w*, 3192*w*, 2986*w*, 2936*w*, 2815*w*, 1688*s*, 1637*s*, 1603*m*, 1579*m*, 1451*m*, 1374*s*, 1332*m*, 1297*m*, 1263*m*, 1211*s*, 1155*m*, 1062*s*,

1030*s*, 970*m*, 877*m*, 852*s*, 812*m*. $^1$H-NMR (300 MHz, $CDCl_3/CD_3OD$ 7:1): see *Table 3*; additionally, 7.24 (*d*, *J* = 8.1, H–C(6/I)); 5.60 (*d*, *J* = 8.1, H–C(5/I)); 1.53, 1.42 1.29, 1.22 (4*s*, 2 *Me*$_2$C). $^{13}$C-NMR (75 MHz, $CDCl_3/CD_3OD$ 7:1): see *Table 4*; additionally 114.48, 114.28 (2*s*, 2 Me$_2$*C*); 27.28, 26.78, 25.09, 25.06 (4*q*, 2 *Me*$_2$C). HR-MALDI-MS: 658.1913 ($[M + Na]^+$, $C_{26}H_{33}N_7NaO_{10}S^+$; calc. 658.1907). Anal. calc. for $C_{26}H_{33}N_7O_{10}S$ (635.65): C 49.13, H 5.23, N 15.42; found: C 49.25, H 5.26, N 14.93.

*(*R*)-2′,3′*-O-*Isopropylideneadenosine-8-methyl-(8*$^1$ *→ 5′-*S*)-5′-deoxy-2′,3′*-O-*isopropylidene-5′-sulfinyluridine* ((*R*)-**4**). In a polyethylene flask, a soln. of (*R*)-**3** (1.065 g, 1.37 mmol) in THF (8 ml) was treated with a soln. of $(HF)_3 \cdot Et_3N$ (3.7 ml, 68.5 mmol) and stirred at 25° for 22 h. The mixture was diluted with $MeOH/CH_2Cl_2$ 1:1 (15 ml), treated with aq. 5M NaOH soln. until the pH reached *ca*. 11, and filtered (washing with $H_2O$). FC ($CH_2Cl_2$/MeOH 9:1) of the solid gave (*R*)-**4** (489 mg, 56%). White solid. $R_f$ ($CH_2Cl_2$/MeOH 9:1) 0.23. M.p. 211° (dec.). $[\alpha]_D^{25} = -92.5$ (*c* = 0.7, $CHCl_3$/MeOH 7:1). UV ($CHCl_3$/MeOH 7:1): 263 (20040). IR (ATR): 3460*w*, 3331*w*, 3197*w*, 2988*w*, 2932*w*, 1711*s*, 1693*s*, 1648*s*, 1605*m*, 1577*w*, 1484*w*, 1450*m*, 1374*m*, 1339*m*, 1310*m*, 1270*m*, 1253*m*, 1213*s*, 1157*m*, 1068*s*, 1029*s*, 965*m*, 942*m*, 921*m*, 905*m*, 879*m*, 869*m*, 847*m*, 801*m*. $^1$H-NMR (300 MHz, $CDCl_3/CD_3OD$ 7:1): see *Table 3*; additionally, 7.15 (*d*, *J* = 8.1, H–C(6/I)); 5.45 (*d*, *J* = 8.1, H–C(5/I)); 1.50, 1.41, 1.23, 1.19 (4*s*, 2 Me$_2$C). $^{13}$C-NMR (75 MHz, $CDCl_3/CD_3OD$ 7:1): see *Table 4*; additionally, 114.61, 114.35 (2*s*, 2 Me$_2$*C*); 27.25, 26.73, 25.00, 24.92 (4*q*, 2 *Me*$_2$C). HR-MALDI-MS: 658.1919 ($[M + Na]^+$, $C_{26}H_{33}N_7NaO_{10}S^+$; calc. 658.1907).

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