# Synthesis of 2′-deoxy-2′-spirocyclopropyl cytidine as potential inhibitor of ribonucleotide diphosphate reductase

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Based on the mechanism of action of ribonucleoside diphosphate reductase (RDPR), a new class of nucleosides that may act as inhibitors of this enzyme was designed. Starting from uridine, a 2′-deoxy-2′-spirocyclopropyl derivative of cytosine was prepared. The key step of the synthesis is the condensation of diazomethane with a suitably protected 2′-methylene nucleoside. Light-induced nitrogen extrusion affords the cyclopropane ring.

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En se basant sur le mécanisme d'action de la réductase du diphosphate de ribonucléoside (RDPR), on a mis au point une nouvelle classe de nucléosides qui peuvent agir comme inhibiteurs de cet enzyme. Utilisant l'uridine comme produit de départ, on a préparé un dérivé 2′-désoxy-2′-spirocyclopropylé de la cytosine. L'étape clé de la synthèse est la condensation du diazométhane avec un 2′-méthylène nucléoside protégé d'une façon appropriée. Sous l'influence de la lumière, il y a extrusion d'azote et formation du noyau cyclopropane.

[Traduit par la rédaction]

Ribonucleoside diphosphate reductase (RDPR) is a key enzyme in the *de novo* production of deoxynucleoside precursors for DNA synthesis and is tightly linked to neoplastic transformation and progression (1). Accordingly, RDPR appears as a very attractive target for new anticancer agents and much research has been aimed at better understanding its mechanism of action (2) and at devising selective inhibitors (3). Among them, 2′-deoxy-2′-halogenated cytidine derivatives such as 2′-deoxy-2′,2′-difluorocytidine (4) and 2′-deoxy-2′-methylidenecytidine (5) are the more promising.

Since the extensive study of the molecular mechanism of this enzyme by Stubbe *et al.* (2*a*), a tyrosinyl radical is suspected to be the initiator of the enzymatic reaction by abstraction of H-3′. The resulting radical then undergoes a series of transformations to afford the 2′-deoxynucleotide with concomitant regeneration of the tyrosinyl radical.

We thought that it could be possible to design inhibitors utilizing this radical processing.[2] Since radical rearrangements involving β-scission of a cyclopropylmethyl moiety are known to be extremely rapid, they were used as mechanistic probes in reaction pathways implicating radical intermediates (7). Consequently, we decided to prepare a nucleoside derivative bearing a cyclopropyl ring at C-2′ that may act as an in vivo irreversible inhibitor of RDPR. Since the more active inhibitors are found in the cytidine series, 2′-deoxy-2′-spirocyclopropyl cytidine was chosen as target molecule.

The 3′,5′-*O*-protected derivative **1** (8) was smoothly oxidized by the pyridinium dichromate (PDC) – acetic acid reagent (9). This system, which requires only 1.5 molar equivalent of chromium species, was found to be superior to other reagents widely used for the oxidation of nucleosides (10). Further Wittig reaction on the 2′-keto nucleoside **2** was conducted with triphenylmethylene phosphorane generated from methyltriphenyl phosphonium iodide and *sec*-butyllithium in THF at −78°C to −30°C. This technique avoids the use of DMSO as in the procedure of Sano *et al.* (11) and compares favorably with the "salt-free" conditions successfully employed by Samano and Robins (10). Thus we were able to obtain the 2′-deoxy-2′-methylene uridine derivative **3***a* in 70% yield from uridine.

Despite numerous attempts, the samarium-promoted cyclopropanation reaction failed both on the free and on the protected methylene nucleoside although this method had been claimed to work well on various allylic alcohols (12). Deoxyspirocyclopropyl pentoses have previously been prepared by cycloaddition of diazomethane followed by photoinduced nitrogen extrusion from the resulting isomeric spiropyrazolines (13).

Treatment of compound **3***a* by diazomethane in ether at ambient temperature resulted only in the formation of uracil-methylated nucleosides **4** and **5**, together with a very small amount of presumed spiropyrazolines, and this whatever the excess of diazomethane was. Cyclopropanation of allyloxy- and allylamino derivatives was recently carried out with diazomethane in the presence of bisbenzonitrile dichloropalladium (14). Treatment of **3***a* under these conditions afforded **4** and **5** (90:10) together with unreacted starting material.

Nevertheless, we decided to carry out this experiment on the uracil-protected methylene nucleoside **6***b*. The 4-*O*-ethyl protection was chosen because this group could be further replaced by 4-amino, thus leading to cytosine-1-yl derivatives (15). Insufficient stability of the TPDS group during the nucleophilic displacement of the unstable 4-*O*-tosyl derivative (16) required the use of another protective group before activation and transformation at the 4-position of the uracil

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[2]While this paper was in preparation, a similar approach involving 2′-deoxy-2′-spirocyclopropyl derivatives of uridine and adenosine was reported: see ref. 6.

residue (See Scheme 1). Diacetylated 2′-deoxy-2′-methylene derivative **3***b* was efficiently prepared from **3***a* (92%), and transformed into **6***a* (72% yield), which was further acetylated in nearly quantitative yield to get the soluble derivative **6***b*.

Treatment of **6***b* with excess diazomethane in ether for 16 h at ambient temperature gave a separable mixture of isomeric 2′-deoxy-2′-spiropyrazoline derivatives **7** (59%) and **8** (15%). The stereochemistry of the major compound **7** (2′*R*) was deduced from variable temperature $^1$H NMR experiments, which demonstrated restricted rotation of the uracil residue around the glycosidic bond at ambient temperature due to the steric hindrance of the methylene groups of the pyrazoline ring, resulting in low resolution of the signals. At 50°C, a well-resolved spectrum was obtained, indicating the restoration of free rotation of the base. Such a phenomenon was not observed for the minor isomer **8**. Moreover, diazomethane approach from the less-hindered α side of **6***b* seems to be favored, as was previously noticed for the dihydroxylation of the double bond (11).

Exposure of neat **7** and **8** (or their mixture) to daylight during ca. 1 week resulted in the formation of **9***a* by extrusion of nitrogen. The structure of **9***a* was confirmed by mass spectroscopy and the appearance of signals of the cyclopropyl ring between 0.5 and 1 ppm in the $^1$H NMR spectrum.

Treatment of **9***a* by a methanolic solution of ammonia at room temperature afforded the deacetylated 2′-spirocyclopropyl-2′-deoxyuridine derivative **9***b*. The target molecule **9***c* was obtained by treatment of **9***a* with the same solution at 100°C.

The biological evaluation of this compound is in progress (Dr. F. Lavelle, Rhône-Poulenc Rorer).

## Experimental

Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter. The $^1$H NMR spectra were recorded on a Bruker AM-250 spectrometer with TMS as internal standard. Reactions were monitored by analytical TLC using 2×5 cm precoated aluminum plates and silica gel 60 $F_{254}$ (Merck), and detection by UV light and charring with $H_2SO_4$. For column chromatography, Merck silica gel 60 (230–400 mesh) and anhydrous solvents were used. Solvents and reagents were purified and dried by standard procedures.

*2′-Keto-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-*D*-uridine (2)*

To a stirred mixture of **1** (8) (4.86 g, 10 mmol), pyridinium dichromate (5.65 g, 15 mmol), and 4 Å molecular sieves (8 g) in $CH_2Cl_2$ (50 mL), acetic acid (1 mL, 1.75 mmol) is added. Stirring in continued at room temperature for 18 h. Celite (5 g) is added and the mixture is filtered and the solvent evaporated under reduced pressure. To the residue is added a large volume of $Et_2O$ (100 mL) to precipitate most of the chromium salts. The ether solution is dried and slowly filtered through a column containing silica gel and Florisil (1:1). After evaporation pure **2** is obtained (4.11 g, 85%); mp 78–80°C; $[\alpha]_D^{20}$ −25.2 (*c* = 1, $CHCl_3$). Anal. calcd. for $C_{21}H_{36}N_2O_7Si_2$ (484,68): C 52.07, H 7.44, N 5.78; found: C 52.45 H 7.60 N 5.43. The $^1$H NMR data of **2** are identical with the reported values (17).

*2′-Deoxy-2′-methylene-3′,5′-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-*D*-uridine (3a)*

Under a pressure of argon, *sec*-butyllithium in hexane (1.4 N, 6.45 mL, 9 mmol) is added to a suspension of triphenylmethyl phosphonium iodide (4.54 g, 11.2 mmol) in THF (20 mL) cooled at −78°C. The homogeneous orange solution is allowed to warm to −30°C and a solution of **2** (2.17 g, 4.5 mmol) in THF (7 mL) is transferred to this mixture under a pressure of argon. After warming to room temperature, stirring is continued for 24 h. THF is evaporated and replaced by $CH_2Cl_2$ (250 mL), water is added (20 mL), and the solution is neutralized with a cooled solution of 2% HCl. The organic layer is washed with $H_2O$ (20 mL), 5% aqueous $NaHCO_3$ (20 mL), $H_2O$ to neutrality, and brine (10 mL). After drying ($Na_2SO_4$), the solvent is evaporated *in vacuo* to give **3***a* (2.0 g), which is chromatographed on a silica gel column. Elution with light petroleum ether – ethyl acetate (7:3) affords pure **3***a* (1.78 g, 82%); mp 174–176°C (lit. (11) mp 130–133°C); $[\alpha]_D^{20}$ +26 (*c* = 1, $CHCl_3$).

*3′,5′-Di-*O*-acetyl-2′-deoxy-2′-methylene-β-*D*-uridine (3b)*

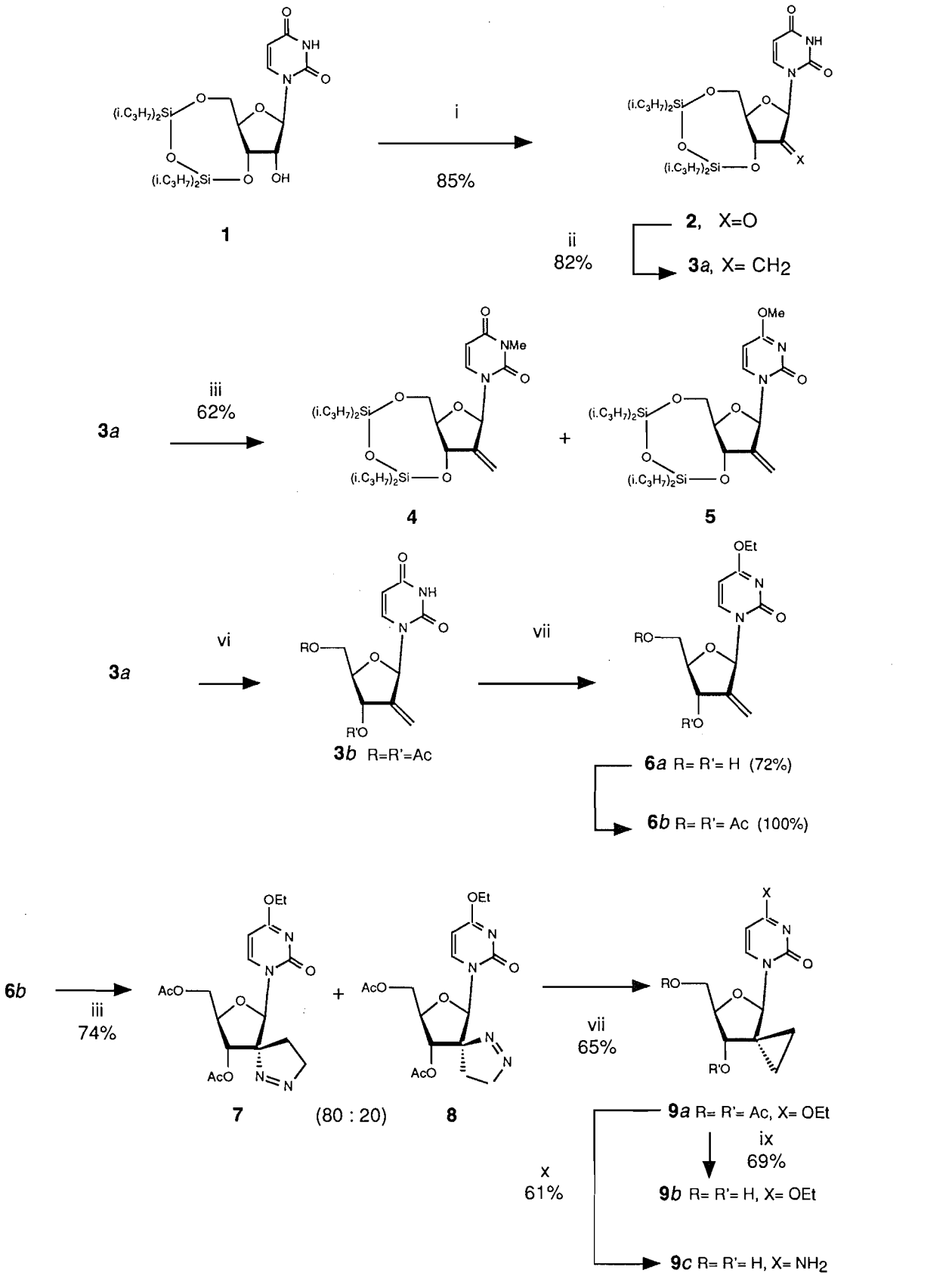
A 1 M solution of $Bu_4N^+$, $F^-$ in THF (11.12 mL, 11.12 mmol) containing **3***a* (2.68 g, 5.56 mmol) is stirred at room temperature for 15 min. THF is evaporated *in vacuo* and acetonitrile (5 mL), $Et_3N$ (7.7 mL, 56 mmol), and, after cooling at 0°C, acetic anhydride (2.62 mL, 55.6 mmol) are added to the reaction mixture. After evaporation to dryness, the residue is partitioned between AcOEt (50 mL) and aqueous $NaHCO_3$ (10 mL), water, and brine (10 mL). After drying ($Na_2SO_4$), the solvent is evaporated and the crude product is chromatographed. Elution with AcOEt – pet. ether (4:6) affords pure **3***b* (1.68 g, 92%); $[\alpha]_D^{20}$ −32.6 (*c* = 0.65, MeOH). $^1$H NMR ($CDCl_3$) δ: 9.48 (br s, 1H, H-3), 7.24 (d, 1H, $J_{5,6}$ = 8.6 Hz, H-6), 6.73 (br s, 1H, H-1′), 5.78 (d, 1H, H-5), 5.64 (br s, 2H, methylene), 5.36 (br s, 1H, H-3′), 4.33 (m, 1H, $J_{5',5''}$ = 12.2 Hz, H-5′,H-5″), 4.2 (m, 1H, $J_{4',5'}$ = 4.2 Hz, $J_{4',5'}$ = 3.9 Hz, H-4′), 2.14 (s, 3H, $CH_3CO$), 2.03 (s, 3H, $CH_3CO$). Anal. calcd. for $C_{14}H_{16}N_2O_7$ (324.28): C 51.85, H 4.94, N 8.64; found: C 51.77, H 5.01, N 8.53.

*1-(2-Deoxy-2-methylene-*erythro*-β-*D*-pentofuranosyl)-4-*O*-ethyluracil (6a)*

A suspension of $K_2CO_3$ (590 mg, 5.9 mmol) in a solution of **3***b* (1.29 g, 3.93 mmol) and *p*-toluenesulfonyl chloride (900 mg, 4.72 mmol) in $CH_3CN$ (15 mL) is heated at 85°C for 2 h. After cooling, the solvent is evaporated *in vacuo* and the residue is treated with NaOEt (1.5 M, 26 mL, 40 mmol) in EtOH (20 mL). The solid is filtered off and washed with EtOH. The ethanolic solution is neutralized with Amberlite IRN-77 ($H^+$ form). After filtration and evaporation of the solvent, the solid obtained is chromatographed. Elution with $CHCl_3$–methanol (9:1) affords pure **6***a*; yield: 640 mg (60%); mp 115–116°C; $[\alpha]_D^{20}$ +24.7 (*c* = 0.7, $CH_3OH$). $^1$H NMR (DMSO-*d*6) δ: 7.9 (d, 1H, $J_{5,6}$ = 7.6 Hz, H-6), 651 (s, 1H, H-1′), 6.02 (d, 1H, H-5), 5.68 (d, 1H, $J_{3',OH}$ = 6.4 Hz, 3′-OH), 5.35 (s, 1H, H-2′), 5.24 (s, 1H, H-2″), 5.06 (t, 1H, $J_{6',OH}$ = $J_{6'',OH}$ = 5.1 Hz, 5′-OH), 4.52 (dd, 1H, $J_{3',4'}$ = 6.8 Hz, H-3′), 4.27 (9, 2H, *J* = 7 Hz, O-$CH_2$), 3.67 (m, 1H, H-4′), 3.71 (d, 1H, $J_{5',5''}$ = 12.4 Hz, H-5′), 3.57 (d, 1H, H-5″), 1.25 (t, 3H, $CH_3$).

*1-(3′,5′-Di-*O*-acetyl-2′-deoxy-2′-methylene-*erythro*-β-*D*-pentofuranosyl)-4-*O*-ethyl-uracil (6b)*

A solution of **6***a* (269 mg, 1 mmol) and acetic anhydride (570 mL, 6 mmol) in anhydrous pyridine (5 mL) is stirred at room temperature for 16 h. Solvent is evaporated and the residue is partitioned between $CHCl_3$ (50 mL) and water (10 mL). The organic layer is washed successively with 5% HCl (5 mL) and water, dried ($Na_2SO_4$), filtered, and evaporated. Compound **6***b* (360 mg, 100%) is homogeneous in TLC ($R_f$ 0.62, $CHCl_3$–MeOH, 95:5; $R_f$ 0.51, AcOEt – pet. ether, 7:3) and is characterized as follows. $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.5 (d, 1H, $J_{5,6}$ = 8 Hz, H-6), 6.9 (br s, 1H, H-1′), 5.92 (d, 1H, $J_{5,6}$ = 8 Hz, H-5), 5.68 (m, 1H, $J_{3',4'}$ = 5 Hz, H-3′), 5.6 (br s, 1H, H-2″a), 5.38 (br s, 1H, H-2″b), 4.48 (q, 2H, $CH_2O$ ethyl), 4.38 (d, 2H, H-5′, H-5″), 4.24 (dd, 1H, $J_{4',5'}$ = 5 Hz, H-4′), 2.18 (s, 3H, $CH_3CO$-), 2.10 (s, 3H, $CH_3CO$-), 1.38 (t, 3H, $CH_3$ ethyl). MS (EI) *m/z*: 352 ($M^{+\cdot}$), 293 ($M^{+\cdot}$ −OAc), 227. ($M^{+\cdot}$ −$BH^+$). Anal. calcd. for $C_{16}H_{20}N_2O_7$ (352.34): C 54.54, H 5.72, N 7.94; found: C 54.71, H 5.65, N 7.80.




(i) PDC/AcOH/3 Å mol. sieves/$CH_2Cl_2$; (ii) $Ph_3P^+$, $I^-$/*s*BuLi 2.3 equiv./THF/ −30°C, then room temp.; (iii) $CH_2N_2/Et_2O$/room temp.; (vi) (1): $Bu_4NF$/THF; (2): $Ac_2O/Et_3N/CH_3CN$; (vii) (1): $TsCl/K_2CO_3/CH_3CN$; (2): 1 M NaOEt/EtOH; (viii) *hν*, neat, room temp.; (ix) $NH_3$/MeOH/room temp.; (x) $NH_3$/MeOH/100°C

SCHEME 1

*1-[3',5'-Di-*O*-acetyl-2'-deoxy-2'-(*S*)-spiro-4"-(1"-pyrazoline)-*erythro-*β-*D*-pentofuranosyl]-4-*O*-ethyl-uracil (**7**) and its 2'-(*R*) epimer (**8**)*

Compound **6** (100 mg, 0.28 mmol) is reacted with an excess of a solution of diazomethane in diethyl ether (4 equiv., 5 mL). Completion of the reaction is indicated by TLC ($CHCl_3$–MeOH, 98:2) and the mixture is chromatographed after evaporation *in vacuo*. Elution with $CHCl_3$–MeOH (98:2) affords **7** and **8**; yield: 82 mg (74%). The two epimers can be separated with AcOEt – pet. ether (120:130) as eluent and are characterized as follows:

Compound **7**, 2'-(*S*): $^1$H NMR (400 MHz, $CDCl_3$, 50°C) δ: 7.9 (d, 1H, $J_{5,6}$ = 8 Hz, H-6), 6.04 (br s, 1H, H-1'), 5.96 (d, 1H, H-5), 5.52 (d, 1H, $J_{3',4'}$ = 9 Hz, H-3'), 5.0 (dd, 1H, $J_{4',5'}$ = $J_{4',5'}$ = 3 Hz, H-4'), 4.45–4.7 (m, 6H, $CH_2$-O, $CH_2$-N, H-5', H-5"), 2.20 (s, 3H, $CH_3CO$-), 2.05 ($CH_3CO$-), 1.62 and 1.42 (m, 2H, $CH_2$ pyrazoline), 1.39 (t, 3H, $J$ = 7 Hz, $CH_2$- ethyl).

Compound **8**, 2'-(*R*): $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, 1H, $J_{5,6}$ = 8 Hz, H-6), 6.6 (s, 1H, H-1'), 5.9 (d, 1H, H-5), 5.08 (d, 1H, $J_{3',4'}$ = 4 Hz, H-3'), 4.72 (dd, 1H, $J_{5',5''}$ = 12 Hz, $J_{5',4'}$ = 8 Hz, H-5'), 4.64 (dd, 1H, $J_{4'5''}$ = 4 Hz, H-5"), 4.4–4.52 (m, 5H, $CH_2$-O ethyl, $CH_2$-N, H-4'), 2.22 (m, 1H, H-4"a pyrazoline), 2.20 (s, 3H, $CH_3CO$-), 2.19 (s, 3H, $CH_3CO$-), 1.78 (m, 1H, H-4" pyrazoline). MS (Cl, $NH_3$) *m/z*: 395 (M+1).

*1-(3',5'-Di-*O*-acetyl-2'-deoxy-2',2'-spirocyclopropyl-*erythro-β-*D*-pentofuranosyl)-4-*O*-ethyl-uracul (**9**a)*

Compounds **7** and **8** (82 mg, 0.21 mmol) are exposed to sunlight in a round-bottom flask for several days (ca. 1 week). The transformation works better without any solvent, but is also effected in chloroform solution and exposure to a tungsten-filament lamp. Completion of nitrogen extrusion is indicated by TLC ($CHCl_3$–MeOH, 95:5); the resulting product is chromatographed on a silica gel column. Elution with AcOEt – pet. ether (1:1) affords pure **9***a*; yield: 43 mg (65%). $^1$H NMR (400 MHz) $CDCl_3$) δ: 7.76 (d, 1H, $J_{5,6}$ = 8 Hz, H-6), 6.60 (s, 1H, H-1'), 5.95 (d, 1H, H-5), 4.92 (d, 1H, $J_{3',4'}$ = 3 Hz, H-3'), 4.32–4.50 (m, 1H, $CH_2O$, H-4', H-5', and H-5"), 2.17 (s, 3H, $CH_3CO$-), 2.16 (s, 3H, $CH_3CO$-), 1.38 (t, 3H, $CH_3$-$CH_2$), 1.06, 0.78, and 0.56 (3m, 2H, 1H, and 1H, cyclopropane). MS(EI) *m/z*: 366 ($M^+$), 307 ($M^{+\bullet}$ – OAc), 227 ($M^{+\bullet}$ – $BH^+$). Anal. calcd. for $C_{17}H_{20}N_2O_7$ (364.32): C 56.04, H 5.53, N 7.68; found: C 56.12, H 5.50, N 7.59.

*1-(2'-Deoxy-2'-spirocyclopropyl-*erythro-β-*D*-pentofuranosyl)-4-*O*-ethyl-uracil (**9**b)*

Compound **9***a* (50 mg, 0.13 mmol) is dissolved in methanol presaturated with ammonia (5 mL). After 24 h at room temperature, the solvent is evaporated and the residue purified by flash chromatography using chloroform–methanol (19:1) as eluent. Yield: 36 mg (69%) as a colorless syrup. $^1$H NMR (DMSO-$d_6$) δ: 8.24 (d, 1H, $J_{5,6}$ = 7.39 Hz, H-6), 6.04 (d, 1H, H-5), 6.00 (s, 1H, H-1'), 5.19 (d, 1H, $J_{H,OH}$ = 5.84 Hz, 3'-OH), 5.10 (t, 1H, $J_{H,OH}$ = 5.34 Hz, 5'-OH), 4.27 (q, 2H, $J$ = 7.05 Hz, -$OCH_2$), 4.05 ("t", 1H, $J_{3',4'}$ = 6.05 Hz, H-3'), 3.58–3.83 (m, 3H, H-4', H-5', H-5"), 1.27 (t, 3H, $CH_3$), 1.03, 0.58, and 0.47 (3m, 1H, 1H, and 2H, cyclopropane). MS (CI/$NH_3$) *m/z*: 300 (M+18), 283 (M+1).

*2'-Deoxy-2'-spirocyclopropyl cytidine (**9**c)*

Compound **9***a* (180 mg, 0.49 mmol) is dissolved in methanol presaturated with ammonia (40 mL). The mixture is heated in a stainless steel bomb at 100°C for 6 h. The solvent is evaporated and the residue purified as above with chloroform–methanol (2.6:1) as eluent. Yield: 76 mg (61%) as an amorphous solid. $^1$H NMR (DMSO-$d_6$) δ: 7.77 (d, 1H, $J_{5,6}$ = 7.37 Hz, H-6), 6.00 (s, 1H, H-1'), 5.72 (d, 1H, H-5), 5.13 (d, 1H, $J_{H,OH}$ = 5.83 Hz, 3'-OH), 4.99 (t, 1H, $J_{H,OH}$ = 5.24 Hz, 5'-OH), 3.97 ("t", 1H, $J_{3',4'}$ = 5.84 Hz, H-3'), 3.72–3.56 (m, 3H, H-4', H-5', H-5"), 0.98 and 0.46 (2m, 1H and 3H, cyclopropane). MS (CI/$NH_3$) *m/z*: 271 (M+18), 254 (M+1).

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