

33. Highly Stereoselective Total Syntheses of 2,5-Anhydro-4-deoxy-D-ribo-hexonic Acid and of (1*S*)-1-*C*-(6-Amino-7*H*-purin-8-yl)-1,4-anhydro-3-deoxy-D-erythro-pentitol (= Cordycepin C)¹⁾²⁾

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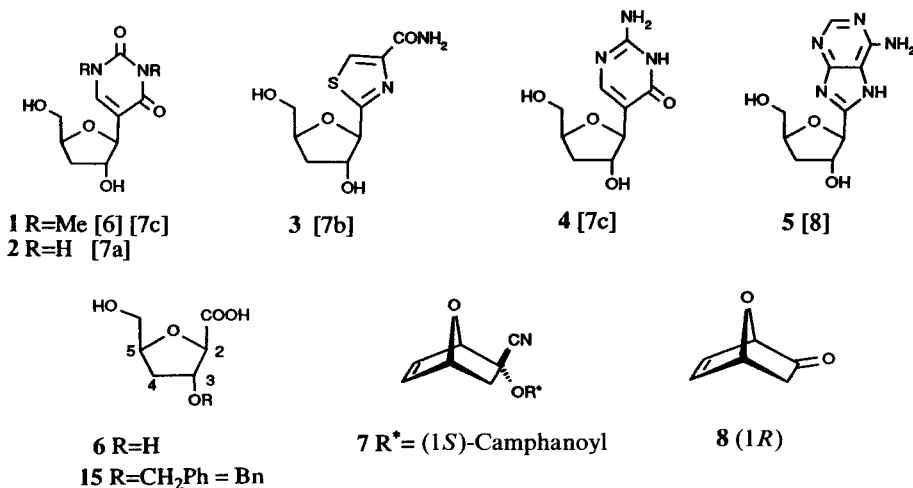
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Dedicated to Prof. Hans Dahn on the occasion of his 70th birthday

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Highly regio- and stereoselective monohydroxylation of the C=C bond of (+)-7-oxabicyclo[2.2.1]hept-5-en-2-one (**8**) was achieved *via* LiAlH₄ reduction of the corresponding 5,6-*exo*-epoxy dimethyl acetal **9**. The reaction gave exclusively (–)-(1*R*,2*R*,4*S*)-6,6-dimethoxy-7-oxabicyclo[2.2.1]heptan-2-*exo*-ol (**10**) which was transformed into 2,5-anhydro-3-*O*-benzyl-4-deoxy-D-ribo-hexonic acid (**15**) and 2,5-anhydro-4-deoxy-D-ribo-hexonic acid (**6**) *via* ozonolysis of (–)-(1*R*,4*S*,6*R*)-6-*exo*-benzyloxy-2-[[*tert*-butyl]dimethylsilyl]oxy}-7-oxabicyclo[2.2.1]hept-2-ene (**14**). Cordycepin C (**5**) was derived from **6** and 4,5,6-triaminopyrimidine using CsF/DMF to generate the adenine heterocycle.

Introduction. – *C*-Nucleosides have attracted a wide interest because of their biological activity; some members possess antitumor and/or antiviral properties [3] [4]. In general, they are β-*C*-glycosides derived from D-ribose [3] [5]. The need for new antiviral agents for human immunodeficiency virus has stimulated a regain of interest in the



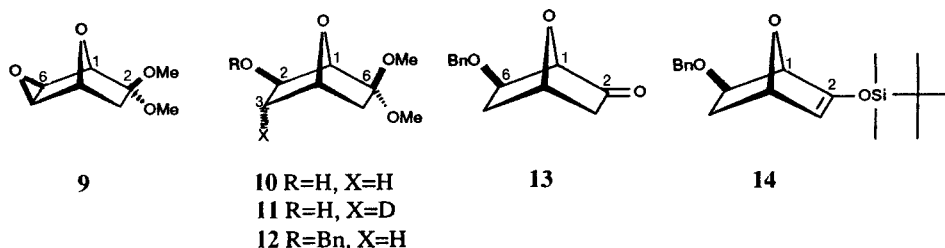
¹⁾ Enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives ('naked sugars') as synthetic intermediates, Part V. Part III: [1]. Part IV: [2].

²⁾ Part of the planned Ph.D. thesis of F. G., University of Lausanne.

synthesis of new nucleosides and *C*-nucleosides [6]. *C*-Nucleosides **1–5** are rare examples of 3'-deoxy- β -D-*erythro*-pentofuranosyl derivatives [3] [4] [6–8]. Compounds **1–4** were prepared by reduction of the corresponding *C*-(β -D-*ribo*-pentofuranosyl) derivatives or analogues. The *C*-nucleoside analogue of cordycepin, cordycepin C (= (1*S*)-1-*C*-(6-amino-7*H*-purin-8-yl)-1,4-anhydro-3-deoxy- β -D-*erythro*-pentitol; **5**) whose synthesis was first reported by *El Khadem* and *El Ashry* [8] was obtained by condensation of 4,5,6-triaminopyrimidine with 2,5-anhydro-4-deoxy- β -D-*ribo*-hexonic acid (**6**). Acid **6** was derived from D-xylose in 13 steps in less than 16% yield [8].

We report here on the total synthesis of acid **6** which makes use of the readily available, optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives **7** and **8** derived from furane and 1-cyanovinyl (1*S*)-camphanate in 93 and 89% yield, respectively (taking into account the recovered dienophile) [9]. We disclose a method for the stereo- and regioselective monohydroxylation of the double bond in 7-oxatrinorbornenone (**8**³). Since the method of *El Khadem* and *El Ashry* [8] for the conversion of **16** into cordycepin C (**5**) failed in our hands, we have developed an improved technique featuring CsF in DMF as a mean to induce smooth H₂O elimination [10] [11] during the formation of the adenine moiety of **5** without epimerization of the anomeric center [12].

Results and Discussion. – Following the method of *Le Drian* and *Vogel* [13], optically pure 7-oxatrinorbornenone **8** was transformed in two steps into the epoxy acetal **9** (78% overall yield). Heating **9** with an excess of LiAlH₄ in THF (sealed Pyrex tube, 85°, 3 days) gave alcohol **10** (83%). No trace of any isomeric compound could be detected by 360-MHz ¹H-NMR of the crude reaction mixture. The structure of **10** was established unambiguously by its ¹H-NMR spectrum and double-irradiation experiments. Typical were the signals of the bridgehead protons H–C(1) and H–C(4) which resonated at 4.3 (*s*, ³*J*(H–C(1), H_{endo}–C(2)) = 0 Hz [14]) and 4.67 ppm (*t*, ³*J*(H–C(4), H_{exo}–C(3)) $\approx$ ³*J*(H–C(4), H_{exo}–C(5)) = 5 Hz [14]), respectively. The isomeric 6,6-dimethoxy-7-oxabicyclo[2.2.1]heptan-2-*exo*-ol showed two *d* for H–C(1) and H–C(4). The high regioselectivity of reduction **9**→**10** can be attributed to steric hindrance of the *endo* MeO group at C(2) in **9** which impedes the competitive attack of the hydride agent onto the C(5) *endo* position. This hypothesis was consistent with the exclusive formation of the 3-*endo*-deuterio derivative **11**, when the reduction of **9** was carried out with LiAlD₄. The absence of *Wagner-Meerwein* rearrangement products in that reaction is also noteworthy [15].



³) The hydroboration of 5,5-dimethoxy-7-oxabicyclo[2.2.1]hept-2-ene (BH₃·Me₂S, THF; NaOH/H₂O₂) led to a 3:2 mixture of the two regioisomeric 5,5-dimethoxy- and 6,6-dimethoxy-7-oxabicyclo[2.2.1]heptan-2-*exo*-ols in 60% yield.

After benzylation of **10** (NaH/DMF, BnBr; $\rightarrow$ **12**) and hydrolysis (*Nafion*, acetone/ H_2O , reflux, 4 h), the protected 6-*exo*-benzyloxy-7-oxatrinorbornan-2-one **13** was obtained in 81% yield (**10** $\rightarrow$ **13**). The corresponding (*tert*-butyl)dimethylsilyl enol ether **14** was prepared in 93% yield following the technique of *House et al.* [16]. Ozonolysis (3% O_3 in O_2 , MeOH/ CH_2Cl_2 4:1, -78°) followed by treatment with NaBH_4 [17] afforded the hexonic-acid derivative **15** (80%). Hydrogenolysis (H_2 , Pd/C, EtOH) furnished **6** (90%) with physical characteristics (m.p. $83\text{--}85^\circ$, $[\alpha]_D^{25} = -44$ ($c = 1.25$, 95% EtOH))⁴ different from those reported by *El Khadem* and *El Ashry* [8] for that product (oil, $[\alpha]_D^{25} = +24.9$ ($c = 1.16$, 95% EtOH)). The 360-MHz ^1H -NMR spectrum (and other spectral data, see *Exper. Part*) were in agreement with the structure of **6**. In particular, the *trans* relationship between H-C(2) and H-C(3) was established by the value for $J(2,3)$ of 1.5 Hz (*ca.* 0 Hz in **15**; dihedral angle approaching 90°) [18]. The other vicinal coupling constants (application of the *Karplus* rule [19]) suggested the puckered conformation shown in the *Figure* for **6** in CD_3OD . Compounds **15**, **16**, and **5** must have similar conformations for their tetrahydrofuran rings (see *Exper. Part*).

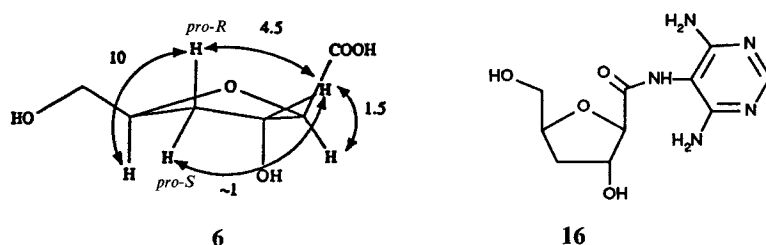


Figure. Coupling constants ($J(\text{H,H})[\text{Hz}]$) and conformation of **6**

Condensation of **6** with 4,5,6-triaminopyrimidine [8] gave the corresponding anhydrous amide **16** (30–45%) whose characteristics ($[\alpha]_D^{25} = +127$ ($c = 0.33$, MeOH)) were similar to those reported by *El Khadem* and *El Ashry* [8] for **16**·1.5 H_2O ($[\alpha]_D^{25} = +94$ ($c = 0.23$, MeOH)). In our hands, pyrolysis [11] ($215\text{--}220^\circ$) of **16** and of **16**·1.5 H_2O failed to afford **5** [8]. Addition of a base or acid catalyst led exclusively to the decomposition of **16**. We found, however, that heating **16** in anhyd. DMF containing CsF to $110\text{--}120^\circ$ (instead of 220°) for 55 h led to the smooth formation of **5**, isolated in 55% yield. Its characteristics (m.p. $222\text{--}225^\circ$ (dec.), $[\alpha]_D^{25} = -6.2$ ($c = 0.32$, H_2O)) differed somewhat from those reported in [8] for this C-nucleoside (m.p. 165° , $[\alpha]_D^{25} = -11.1$ ($c = 0.32$ (H_2O)). All the spectral data recorded for **5**, **6**, and **14** confirmed their structures.

The (2*R*) configuration of **6** was confirmed by its circular dichroism (CD) spectrum which showed a negative Cotton effect (CE) at 215 nm ($\Delta\epsilon_{215} = -0.97$, 95% EtOH) as in the case of 2,5-anhydro-D-*allo*- and 2,5-anhydro-D-*gluco*-hexonic acids [20]. Positive CE's were reported for 2,5-anhydro-4-deoxy-D-*lyxo*- and 2,5-anhydro-D-*manno*-hexonic acids [20]. The (1*S*) configuration of the C-nucleoside **5** was also confirmed by its CD spectrum

⁴) Oxidative anodic decarboxylation of **6** (MeOH, graphite electrodes, 110 mA/cm², 6 F/mol) led to an anomeric mixture of methyl 3-deoxy-D-*erythro*-pentofuranosides in 76% yield. Hydrolysis (0.25M H_2SO_4 in H_2O , 2 h, reflux) of this product afforded cordycepose (= 3-deoxy-D-*erythro*-pentose) in 79% yield whose characteristics were similar to those of the literature [23].

which showed a typical positive CE at 258 nm ($\Delta\epsilon_{258} = +5.8$, MeOH) [12a]⁵). For the related (1*R*)-1-*C*-(6-amino-7*H*-purin-8-yl)-1,4-anhydro-2-deoxy-*D*-erythro-pentitol⁵), a positive CE was recorded near 260 nm, whereas a negative CE was found for its (1*S*) isomer [12a]. The differences in the melting points and $[\alpha]_D$'s between our sample of **5** and that of *El Khadem* and *El Ashry* remain unexplained at this moment.

Conclusion. – *C*-Glycosides and *C*-nucleosides of ribose have already been prepared from furan [21] [22]. With the stereo- and regioselective monohydroxylation of optically pure (+)-7-oxabicyclo[2.2.1]hept-5-en-2-one (**8**) and its further transformation (8 steps, 36% overall yield, or 10 steps, 32% based on 1-cyanovinyl (1*S*)-camphanate) into 2,5-anhydro-4-deoxy-*D*-ribo-hexonic acid (**6**), we have demonstrated the possibility for that route to obtain optically pure 3'-deoxy- β -*D*-erythro-pentofuranosyl derivatives. The partially protected derivative **15** of **6** was also obtained selectively. A smooth technique using CsF in DMF is presented for the transformation of **6** into cordycepin **C** (**5**). Compounds **6** and **15** are potential precursors for the stereoselective synthesis [3–5] [25] of further 3-deoxy- β -*D*-erythro-pentofuranosyl derivatives. The new route presented here for the preparation of **6** and **15** should make the *C*-nucleosides derived from 3-deoxy-ribose better accessible. Starting from (1*S*)-7-oxabicyclo[2.2.1]hept-5-en-2-one (derived from furan and 1-cyanovinyl (1*R*)-camphanate [26]), 2,5-anhydro-4-deoxy-*L*-ribo-hexonic acid (enantiomer of **6**) and the corresponding *C*-nucleosides can be obtained as readily as their *D*-enantiomers.

We are grateful to *F. Hoffmann-La Roche & Co. AG*, Basel, *E.I. du Pont de Nemours & Co.*, Wilmington, Delaware, USA, the *Fonds Herbette*, Lausanne, and the *Swiss National Science Foundation* for financial support.

Experimental Part

General. See [1]. Synthesis of ($\pm$)-**6** and ($\pm$)-**10** to ($\pm$)-**16** follow the same procedures as those given below for the optically pure enantiomers, the starting material being ($\pm$)-**9** [13]. The spectral data were the same as for the optically pure derivatives; for crystalline compounds, the m.p. will be given.

(–)-(1*R*,2*R*,4*S*)-6,6-Dimethoxy-7-oxabicyclo[2.2.1]heptan-2-exo-ol (**10**). LiAlH₄ (595 mg, 15.6 mmol) was added portionwise to a stirred soln. of **9** [13] (1.35 g, 7.84 mmol) in anh. THF (20 ml). The flask was sealed and heated to 80–85° for 3 days (until disappearance of **9**, TLC control). After cooling to 20°, a soln. of 2,2',2''-nitriilotris(ethanol) (2.3 ml, 17.2 mmol) in anh. THF (5 ml) was added dropwise under stirring. After 1 h at 20°, H₂O (0.56 ml, 31.2 mmol) was added and the mixture stirred overnight. The suspension was filtered (*Büchner*) and the precipitate washed with THF (30–40 ml). The solvent was evaporated and the residue filtered through a short column of silica gel (50 × 3 cm, SiO₂ *Merck* 40–63, AcOEt) yielding 1.12 g (83%) of **10** as colourless oil (($\pm$)-**10**: white crystals, m.p. 44–46°). $[\alpha]_{D}^{25} = -10.3$, $[\alpha]_{436}^{25} = -5.2$, $[\alpha]_{546}^{25} = -3.4$, $[\alpha]_{578}^{25} = -2.0$, $[\alpha]_{589}^{25} = -1.8$, ($c = 1.78$, CH₂Cl₂). IR (KBr): 3600, 3400 (br.), 3000, 2960, 2850, 1770, 1720, 1450, 1400, 1335, 1290, 1180, 1130, 1085, 1050, 980, 915, 890, 870. ¹H-NMR (360 MHz, CDCl₃): 4.67 (t, ³*J* = 5, H-C(4)); 4.36 (dd, ³*J* = 6.5, 2, H-C(2)); 4.3 (s, H-C(1)); 3.27, 3.24 (2s, 2 MeO); 2.12 (dd, ²*J* = 13, ³*J* = 7, H_{endo}-C(3)); 1.95 (ddd, ²*J* = 12.5, ³*J* = 5, ⁴*J* = 2.5, H_{exo}-C(5)); 1.9 (br. s, OH); 1.64 (dm, ²*J* = 13, H_{exo}-C(3)); 1.46 (d, ²*J* = 12.5, H_{endo}-C(5)). ¹³C-NMR (90 MHz, CDCl₃): 108.4 (s); 85.8 (d, ¹*J*(C,H) = 157); 76.4 (d, ¹*J*(C,H) = 155); 68.9 (d, ¹*J*(C,H) = 150); 51.2, 48.8 (2q, ¹*J*(C,H) = 140); 42.3, 40.7 (2t, ¹*J*(C,H) = 135). MS (70 eV): 174 (5, *M*⁺), 143 (16), 142 (15), 133 (6), 130 (4), 129 (2), 124 (10), 116 (100), 110 (14). Anal. calc. for C₈H₁₄O₄ (174.20): C 55.16, H 8.10; found: C 55.07, H 8.04.

⁵) We have repeated the synthesis of (1*R*)-1-*C*-(6-amino-7*H*-purin-8-yl)-1,4-anhydro-2-deoxy-*D*-erythro-pentitol using 2,5-anhydro-3-deoxy- β -*D*-ribo-hexonic acid and our method (CsF/DMF, 120°) for the formation of the heterocycle. It did not lead to isomerization at C(1) [24].

(1RS,2RS,3RS,4SR)-6,6-Dimethoxy(3-endo-²H)-7-oxabicyclo[2.2.1]heptan-2-exo-ol ((±)-**11**). Same procedure as for (±)-**10** with LiAlD₄ instead of LiAlH₄. ¹H-NMR (360 MHz, CDCl₃): 4.64 (t, ³J = 5.5, H-C(4)); 4.34 (br. s, H-C(2)); 4.28 (s, H-C(1)); 3.25, 3.22 (2s, 2 MeO); 2.84 (br. s, OH); 1.94 (ddd, ²J = 12.5, ³J = 5.5, ⁴J = 2.5, H_{exo}-C(5)); 1.62 (m, H_{exo}-C(3)); 1.43 (d, ²J = 12.5, H_{endo}-C(5)).

(1R,4S,6R)-6-exo-(Benzyloxy)-2,2-dimethoxy-7-oxabicyclo[2.2.1]heptane (**12**). A soln. of **10** (540 mg, 3.1 mmol) in anh. DMF (4 ml) was added dropwise to a stirred suspension of NaH (103 mg, 3.4 mmol) in anh. DMF (1.2 ml) cooled to -14°. The temp. was allowed to reach 20° and the mixture stirred until the end of H₂ evolution. After cooling to -14°, a soln. of benzyl bromide (0.4 ml, 3.4 mmol) in anh. DMF (1 ml) was added dropwise. The mixture was then stirred at 25° until disappearance of **10** (TLC control). After 12–14 h, MeOH (2 ml) was added to the homogeneous soln. and the mixture allowed to stand for 1 h at 20°. The solvent was evaporated and the residue dissolved in AcOEt (25 ml). The soln. was washed with H₂O (5 ml) and sat. aq. NaCl soln. (5 ml), the combined aq. phase extracted with AcOEt (5 ml, twice), the combined org. phase dried (MgSO₄) and evaporated, and the residue purified by column chromatography on silica gel (*Lobar B*, Merck 40–60, AcOEt/petroleum ether 2:1) yielding 720 mg (88%) of **12**. Colourless oil. [α]_D²⁵₄₃₆ = -6.5, [α]_D²⁵₅₄₆ = -3.7, [α]_D²⁵₅₇₈ = -3.4, [α]_D²⁵₅₈₉ = -3.1 (c = 1.755, CH₂Cl₂). IR (CHCl₃): 3050, 3000, 2960, 2840, 1490, 1450, 1350, 1330, 1310, 1290, 1240, 1180, 1130, 1090, 1060, 1020. ¹H-NMR (360 MHz, CDCl₃): 7.44–7.31 (m, Ph); 4.72 (t, ³J = 6, H-C(4)); 4.62, 4.57 (2d, ²J = 13, PhCH₂O); 4.5 (s, H-C(1)); 4.24 (dd, ³J = 7, 2.5, H-C(6)); 3.27, 3.23 (2s, 2 MeO); 2.05 (dd, ²J = 12.5, ³J = 7, H_{endo}-C(5)); 2.02 (ddd, ²J = 12.5, ³J = 6, ⁴J = 2.5, H_{exo}-C(3)); 1.88 (dm, ²J = 12.5, H_{exo}-C(5)); 1.48 (d, ²J = 12.5, H_{endo}-C(3)). ¹³C-NMR (90.55 MHz, CDCl₃): 138.1 (s); 128.3, 127.7, 127.5 (3d, ¹J(C,H) = 160); 180.7 (s); 82.7, 76.3 (2d, ¹J(C,H) = 160); 76.7 (d, ¹J(C,H) = 150); 51.0, 48.7 (2q, ¹J(C,H) = 140); 70.9, 40.8, 39.3 (3t, ¹J(C,H) = 140). MS (70 eV): 264 (15, M⁺), 233 (3), 189 (4), 158 (6), 157 (6), 117 (3), 116 (7), 115 (100), 105 (14), 91 (60). Anal. calc. for C₁₅H₂₀O₄ (264.2): C 68.19, H 7.63; found: C 68.21, H 7.55.

(+)-(1R,4S,6R)-6-exo-(Benzyloxy)-7-oxabicyclo[2.2.1]heptan-2-one (**13**). A mixture of **12** (430 mg, 1.62 mmol), acetone (5 ml), H₂O (3 ml) and Nafion (100 mg) was refluxed for 4 h. The mixture was filtered and the solvent evaporated yielding 330 mg (93%) of **13**, colourless oil ((±)-(**13**)): m.p. 35–37°. [α]_D²⁵₃₆₅ = +258, [α]_D²⁵₄₂₆ = +105, [α]_D²⁵₅₄₆ = +50, [α]_D²⁵₅₇₈ = +43, [α]_D²⁵₅₈₉ = +40 (c = 2.17, CH₂Cl₂). IR (CHCl₃): 3020, 3000, 2960, 2900, 2880, 1770, 1490, 1450, 1400, 1350, 1310, 1280, 1240, 1150, 1080, 1040, 1010. ¹H-NMR (360 MHz, CDCl₃): 7.38–7.25 (m, Ph); 5.04 (t, ³J = 6, H-C(4)); 4.6, 4.5 (2d, ²J = 12, PhCH₂O); 4.4 (s, H-C(1)); 4.0 (dd, ³J = 7, 3, H_{endo}-C(6)); 2.43 (ddd, ²J = 17, ³J = 6, ⁴J = 2, H_{exo}-C(3)); 2.11 (dd, ²J = 14, ³J = 7, H_{endo}-C(5)); 2.04 (m, H_{exo}-C(5)); 1.91 (d, ²J = 17, H_{endo}-C(3)). ¹³C-NMR (90.55 MHz, CDCl₃): 221.2, 137.2 (2s); 128.5, 127.9, 127.7 (3d, ¹J(C,H) = 155); 84 (d, ¹J(C,H) = 175); 77, 76.2 (2d, ¹J(C,H) = 150); 71.5 (t, ¹J(C,H) = 145); 43.8, 38.7 (2t, ¹J(C,H) = 125). MS (70 eV): 218 (1, M⁺), 172 (1.4), 146 (1.3), 127 (1.5), 120 (2.5), 105 (4), 92 (10), 91 (100), 77 (13). Anal. calc. for C₁₃H₁₄O₃ (218.25): C 71.54, H 6.46; found: C 71.53, H 6.53.

(-)-(1R,4S,6R)-6-exo-(Benzyloxy)-2-{[(tert-butyl)dimethylsilyl]oxy}-7-oxabicyclo[2.2.1]hept-2-ene (**14**). A mixture of **13** (1.153 g, 5.3 mmol), *N*-[(tert-butyl)dimethylsilyl]-*N*-methyltrifluoroacetamide (10.35 g, 42.9 mmol), and Et₃N (6.8 ml, 48 mmol) in anh. DMF (12 ml) was heated to 60° for 4 days under Ar. The solvent was evaporated (10⁻² Torr) and the residue filtered through a column of silica gel (35 × 3 cm, AcOEt/petroleum ether 1:3) yielding 1.64 g (93%) of **14**, unstable colourless oil which gives white crystals on sublimation. M.p. 51–52°. [α]_D²⁵₃₆₅ = -131, [α]_D²⁵₅₄₆ = -74, [α]_D²⁵₅₇₈ = -40, [α]_D²⁵₅₈₉ = -34.2, [α]_D²⁵₅₈₉ = -33 (c = 1.325, CH₂Cl₂). ¹H-NMR (360 MHz, CDCl₃): 7.32–7.21 (m, Ph); 5.93 (br. d, ³J = 2, H-C(3)); 4.89 (m, H-C(4)); 4.58, 4.53 (2d, ²J = 12, PhCH₂O); 4.45 (d, ²J = 0.8, H-C(1)); 3.94 (dd, ³J = 6.5, 2.5, H-C(6)); 1.91 (dd, ²J = 11.5, ³J = 6.5, H_{endo}-C(5)); 1.77 (ddd, ²J = 11.5, ³J = 4.5, 2.5, H_{exo}-C(5)); 0.87 (s, *t*-Bu); 0.12, 0.08 (2s, 2 Me). ¹³C-NMR (90.55 MHz, CDCl₃): 160.2, 138.2 (2s); 128.4, 127.8, 127.6 (3d, ¹J(C,H) = 160); 107.7 (d, ¹J(C,H) = 170); 82.5 (d, ¹J(C,H) = 165); 78.8 (d, ¹J(C,H) = 160); 78.4 (d, ¹J(C,H) = 150); 71.6 (t, ¹J(C,H) = 145); 37.5 (d, ¹J(C,H) = 135); 25.5 (q, ¹J(C,H) = 125); 18.1 (s); -4.8, -5.0 (2q, ¹J(C,H) = 120).

2,5-Anhydro-3-O-benzyl-4-deoxy-D-ribo-hexonic Acid (**15**). A flux of O₂ containing 3% of O₃ was bubbled through a soln. of **14** (1.6 g, 4.8 mmol) in MeOH/CH₂Cl₂ 4:1 (35 ml) at -78° until persistence of a blue colour. The excess of O₃ was eliminated by purging with N₂, and NaBH₄ (360 mg, 9.6 mmol) was added. After 30 min at -78°, the temp. was allowed to reach 20°, and NaBH₄ (360 mg, 9.6 mmol) was added and the mixture stirred for 3 h. After the addition of Dowex 50W × 8 resin (until pH 1–2), the mixture was filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel (*Lobar C*, Et₂O/MeOH 85:15) yielding 1.064 g (80%) of **15**, colourless oil. [α]_D²⁵₃₆₅ = -64, [α]_D²⁵₅₄₆ = -41, [α]_D²⁵₅₇₈ = -24, [α]_D²⁵₅₈₉ = -21, [α]_D²⁵₅₈₉ = -20 (c = 1.6, CH₂Cl₂). IR (KBr): 3400 (br.), 1730, 1480, 1450, 1350, 1260, 1210, 1080, 1020. ¹H-NMR (360 MHz, CD₃OD): 7.43–7.3 (m, Ph); 5.4 (br. s, 2 OH); 4.84, 4.63 (2d, ²J = 12, PhCH₂O); 4.65 (s, H-C(2)); 4.47 (m, H-C(5)); 4.37 (d, ³J = 5.5, H-C(3)); 3.88 (dd, ²J = 12, ³J = 3.2, H-C(6)); 3.66 (dd, ²J = 12, ³J = 3.8, H-C(6)); 2.14 (dd, ²J = 13.5, ³J(H-C(4), H-C(5)) = 6, ³J(H-C(3), H-C(4)) ≈ 0, H_{pro-S}-C(4)); 1.97 (ddd, ²J = 13.5, ³J(H-C(4), H-C(5))

= 10.5, $^3J(\text{H}-\text{C}(3), \text{H}-\text{C}(4)) = 5.5$, $\text{H}_{\text{pro-R}}-\text{C}(4)$). ^{13}C -NMR (90.55 MHz, CD_3OD): 175.6, 139.2 (2s); 129.4, 128.9, 128.8 (3d, $^1J(\text{C}, \text{H}) = 160$); 84.8 (s, $^1J(\text{C}, \text{H}) = 150$); 83.5 (d, $^1J(\text{C}, \text{H}) = 155$); 82.4 (d, $^1J(\text{C}, \text{H}) = 150$); 72.2, 63.9 (2t, $^1J(\text{C}, \text{H}) = 140$); 33.7 (t, $^1J(\text{C}, \text{H}) = 135$). CI-MS (NH_3): 270 (5, $M^+ + 18$), 253 (13), 252 (94, M^+), 235 (8), 210 (11), 196 (9), 180 (8), 126 (100). Anal. calc. for $\text{C}_{13}\text{H}_{16}\text{O}_5$ (252.26): C 61.89, H 6.39; found: C 61.9, H 6.38.

2,5-Anhydro-4-deoxy-D-ribo-hexonic Acid (6). A mixture of **15** (65 mg, 0.25 mmol), EtOH (1.5 ml), and 10% Pd/C (10 mg) was pressurized with H_2 (1 atm) and stirred for 12 h at 20°. After filtration, the solvent was evaporated yielding 38 mg (90%) of **6**, white crystals. M.p. 83–85° ((±)-(6): m.p. 93–94°). $[\alpha]_{\text{D}}^{25} = -142.2$, $[\alpha]_{\text{D}}^{25} = -90.1$, $[\alpha]_{\text{D}}^{25} = -52.6$, $[\alpha]_{\text{D}}^{25} = -44.7$ ($c = 1.25$, 95% EtOH). IR (KBr): 3350 (br.), 2900, 2600 (br.), 1720, 1450, 1300, 1240, 1120, 1100, 1060, 1030, 970, 940, 870, 860. ^1H -NMR (360 MHz, CD_3OD): 4.66 (ddd, $^3J(\text{H}-\text{C}(3), \text{H}_{\text{pro-R}}-\text{C}(4)) = 4.5$, $^3J(\text{H}-\text{C}(2), \text{H}-\text{C}(3)) = 1.5$, $^3J(\text{H}-\text{C}(3), \text{H}_{\text{pro-S}}-\text{C}(4)) = 1.5$, $\text{H}-\text{C}(3)$); 4.6 (m, $\text{H}-\text{C}(5)$); 4.51 (d, $^3J = 1.5$, $\text{H}-\text{C}(2)$); 3.97 (dd, $^2J = 11.5$, $^3J = 3.2$, $\text{H}-\text{C}(6)$); 3.76 (dd, $^2J = 11.5$, $^3J = 4.0$, $\text{H}-\text{C}(6)$); 2.1 (ddd, $^2J = 13$, $^3J(\text{H}-\text{C}(4), \text{H}-\text{C}(5)) = 10$, $^3J(\text{H}-\text{C}(3), \text{H}-\text{C}(4)) = 4.5$, $\text{H}_{\text{pro-R}}-\text{C}(4)$); 2.05 (ddd, $^2J = 13$, $^3J(\text{H}-\text{C}(4), \text{H}-\text{C}(5)) = 6$, $^3J(\text{H}-\text{C}(3), \text{H}-\text{C}(4)) = 1.5$, $\text{H}_{\text{pro-S}}-\text{C}(4)$). ^{13}C -NMR (90.55 MHz, CD_3OD): 175.9 (s); 86.4, 82.1 (2d, $^1J(\text{C}, \text{H}) = 145$); 77.2 (d, $^1J(\text{C}, \text{H}) = 150$); 64.0 (t, $^1J(\text{C}, \text{H}) = 140$); 35.9 (t, $^1J(\text{C}, \text{H}) = 130$). CI-MS (NH_3): 180 (30, $M^+ + 18$), 162 (100, M^+), 148 (12), 136 (38). Anal. calc. for $\text{C}_6\text{H}_{10}\text{O}_5$ (162.14): C 44.44, H 6.25; found: C 44.53, H 6.15.

2,5-Anhydro-4-deoxy-N-(4',6'-diaminopyrimidin-5'-yl)-D-ribo-hexonamide (16). Same procedure as in [8]. The crude product was purified by chromatography on silica gel (*Lobar B*, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 2:1; removal of the excess of 4,5,6-triaminopyrimidine). Yield 30–45%. Slightly yellow crystals. M.p. 208–210° (dec.). $[\alpha]_{\text{D}}^{25} = +283$, $[\alpha]_{\text{D}}^{25} = +153$, $[\alpha]_{\text{D}}^{25} = +133$, $[\alpha]_{\text{D}}^{25} = +127$ ($c = 0.33$, MeOH). UV (MeOH): 221 (20 200), 260 (50 500). IR (KBr): 3450, 3300 (br.), 3100, 1660, 1640, 1590, 1520, 1480, 1340, 1290, 1240, 1120, 1090, 1060, 1010. ^1H -NMR (250 MHz, CD_3OD): 7.9 (s, $\text{H}-\text{C}(2')$); 4.69 (ddd, $^3J = 5$, 1.5, 1, $\text{H}-\text{C}(3)$); 4.57 (m, $\text{H}-\text{C}(5)$); 4.54 (d, $^3J = 1$, $\text{H}-\text{C}(2)$); 4.07 (dd, $^2J = 12$, $^3J = 2.5$, $\text{H}-\text{C}(6)$); 3.71 (dd, $^2J = 12$, $^3J = 2$, $\text{H}-\text{C}(6)$); 2.23 (ddd, $^2J = 13$, $^3J = 10$, 5, $\text{H}_{\text{pro-R}}-\text{C}(4)$); 1.94 (ddd, $^2J = 13$, $^3J = 5.5$, 1.5, $\text{H}_{\text{pro-S}}-\text{C}(4)$). ^{13}C -NMR (90.55 MHz, D_2O): 173.9, 160.5 (2s); 156.5 (d, $^1J(\text{C}, \text{H}) = 190$); 95.4 (s); 87.9, 82.2, 77.1 (3d, $^1J(\text{C}, \text{H}) = 150$); 62.5 (t, $^1J(\text{C}, \text{H}) = 140$); 35.2 (t, $^1J(\text{C}, \text{H}) = 135$). MS (70 eV): 269 (34, M^+), 251 (4), 220 (10), 164 (15), 152 (51), 125 (100). Anal. calc. for $\text{C}_{10}\text{H}_{15}\text{N}_5\text{O}_4$ (269.26): C 44.65, H 5.61, N 26.0. C 44.46, H 5.68, N 26.12.

(1S)-1-C-(6'-Amino-7'-H-purin-8'-yl)-1,4-anhydro-3-deoxy-D-erythro-pentitol (= Cordycepin C; 5). A mixture of **16** (31 mg, 0.115 mmol), anh. DMF (1 ml), and CsF (87 mg, 0.55 mmol) was heated to 110–120° for 55 h. The mixture was filtered through silica gel rinsing with MeOH, the solvent evaporated, and the residue purified by column chromatography on silica gel (*Lobar B*, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 2:1), yielding 16 mg (55%) of **5**. Colourless crystals. M.p. 223–225° (dec.). $[\alpha]_{\text{D}}^{25} = +12.5$, $[\alpha]_{\text{D}}^{25} = -1.5$, $[\alpha]_{\text{D}}^{25} = -5$, $[\alpha]_{\text{D}}^{25} = -6.8$, $[\alpha]_{\text{D}}^{25} = -6.2$ ($c = 0.32$, H_2O). CD: $\Delta\epsilon_{258} = +5.8$ ($c = 0.095$ g/100 ml, MeOH). UV (MeOH): 211 (13 700), 265 (11 600). IR (KBr): 3400 (br.), 1670, 1610, 1440, 1360, 1340, 1300, 1110, 1080, 1030, 800. ^1H -NMR (250 MHz, CD_3OD): 8.16 (s, $\text{H}-\text{C}(2')$); 5.07 (d, $^3J = 2$, $\text{H}-\text{C}(1)$); 4.6 (m, $\text{H}-\text{C}(2)$); 4.56 (m, $\text{H}-\text{C}(4)$); 4.02 (dd, $^2J = 12$, $^3J = 3$, $\text{H}-\text{C}(5)$); 3.75 (dd, $^2J = 12$, $^3J = 3.5$, $\text{H}-\text{C}(5)$); 2.24 (dd, $^2J = 13.5$, $^3J = 9.5$, 5.5, $\text{H}-\text{C}(3)$); 2.02 (ddd, $^2J = 13.5$, $^3J = 6$, 2, $\text{H}-\text{C}(3)$). ^{13}C -NMR (90.55 MHz, D_6DMSO): 155.5 (s); 152.3 (d, $^1J(\text{C}, \text{H}) = 195$); 151.4 (s); 150.8 (s); 118.6 (s); 82.9, 80.2, 75.9 (3d, $^1J(\text{C}, \text{H}) = 150$); 62.8 (t, $^1J(\text{C}, \text{H}) = 140$); 35.6 (t, $^1J(\text{C}, \text{H}) = 125$). MS (70 eV): 251 (15, M^+), 235 (2.5), 233 (2.3), 220 (3), 203 (22), 178 (41), 164 (100). Anal. calc. for $\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_3$ (251.24): C 47.8, H 5.21, N 27.87; found: C 47.51, H 5.30, N 27.8.

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