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Bicyclic nucleoside analogues from D-glucose: synthesis of chiral as well as racemic 1,4-dioxepane ring-fused derivatives

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Abstract—The dioxepanofuranose derivatives **4** and **12**, obtained through the cyclization of the 3-(2-hydroxyethyl) ether of a D-*xylo*-pentodialdose derivative, were appropriately functionalized and elaborated to the first examples of the new class of 3′-*O*, and 5′-*O*-bicyclic nucleoside analogues **9**, **10**, and **14** with a fused seven-membered ring. Reactions carried out through the intermediacy of the D-*xylo*-pentodialdose derivative **5** yielded racemic products, while prior protection of the 4-formyl group (as in **7**) before deprotection of the 1,2-hydroxyl groups led to optically active analogues.

Keywords: Bicyclic nucleosides; Synthesis; Chiral; Racemic; 1,4-Dioxepane

1. Introduction

The recent decades have witnessed an increased quest for unnatural nucleoside analogues in search of effective inhibitors of HIV, HSV, and tumor cells. The desire to achieve structural alterations in the heterocyclic ring, in the sugar moiety or in both has culminated in feverish synthetic activity in the generation of C-branched sugar nucleosides,[1] bicyclic sugar nucleosides[2] (2′,4′-linked,[3] 1′,3′-linked,[4] 2′,3′-linked,[5] 3′,4′-linked,[6] 3′,5′-linked[7]), acyclic sugar nucleosides,[8] carbocyclic nucleosides,[9] and dideoxy nucleosides.[10] Later on, dideoxy nucleoside prototypes such as dioxolane-T[11] and BCH-189[12] having two heteroatoms within the carbohydrate framework, and dioxepanyl nucleoside analogues[13] have also been added to the list. The fact that the presence of one more heteroatom in the ribose ring of a nucleoside[11,12] imparts anti-HIV/anti-neoplastic activities to it prompted us to take up a programme on the synthesis of bicyclic nucleosides having dioxygenated heterocycles of varied ring sizes fused to the ribose ring, on which no work appears to have been reported so far. In this communication we wish to report a simple convergent approach for the synthesis of bicyclic nucleosides with a fused dioxepane ring.

2. Results and discussion

Compound **1**, prepared via etherification[14] of the 3-OH group of the commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with methyl bromoacetate, was conveniently reduced with $NaBH_4$–*tert*-BuOH–MeOH[15] to furnish **2**. Selective removal of the 5,6-*O*-isopropylidene group by dil HOAc treatment provided **3**, the vicinal diol group of which was cleaved by sodium periodate in aq EtOH to yield **4**; the product was found to exist in the hemi-acetal form as determined by NMR spectroscopy. Treatment of **4** with dil H_2SO_4 in 3:1 CH_3CN–H_2O released the 1,2-*O*-isopropylidene group, furnishing an optically inactive triol mixture through the intermediacy of the open-chain meso dialdose **5** (Scheme 1). The central carbon atom (C-3) of **5** is achirotopic but stereogenic, having a σ-plane of symmetry. The residues around C-3 are structurally identical but have opposite configurations (*S* and *R*), giving rise to

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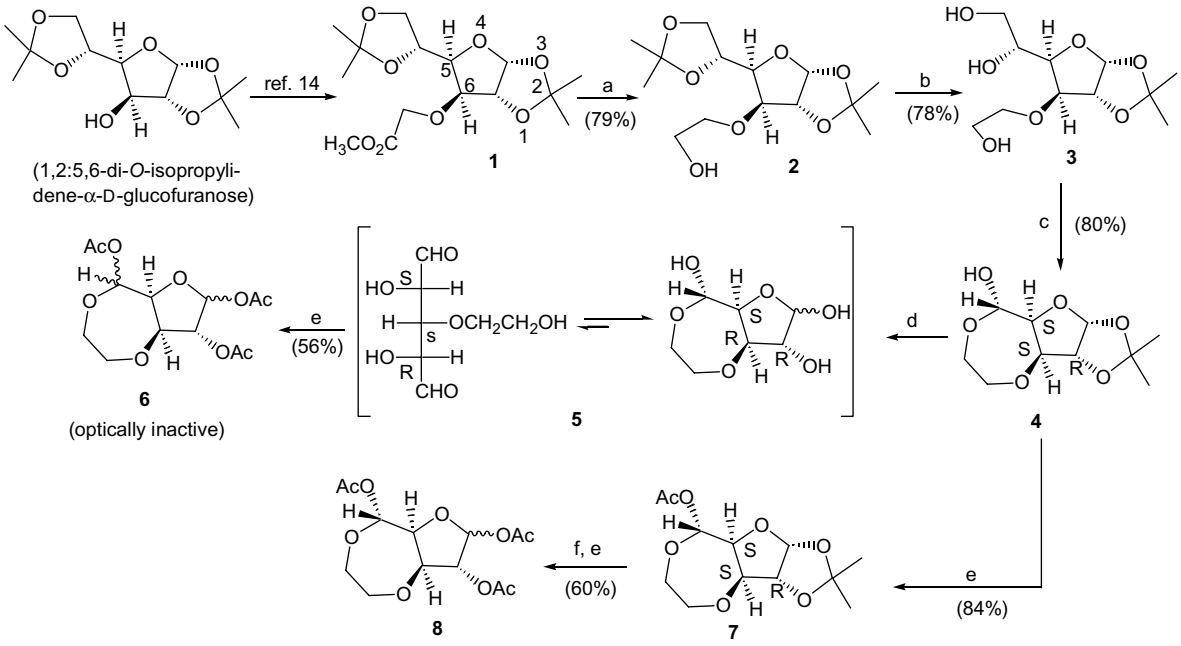
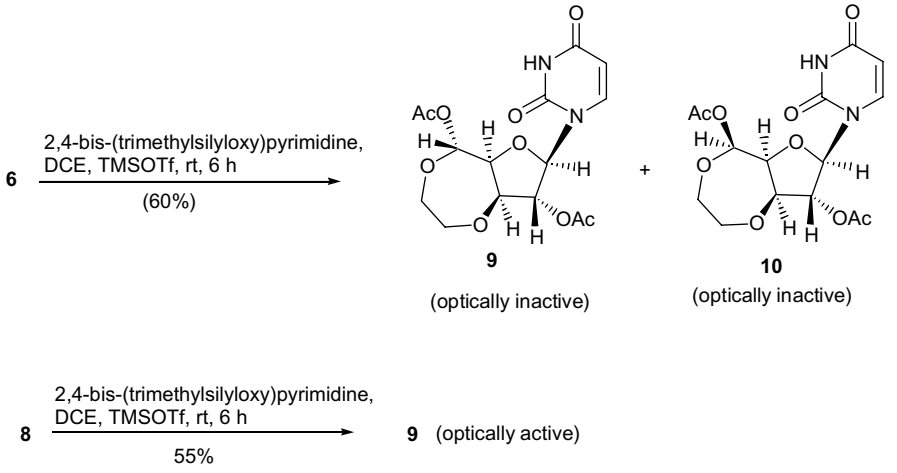


Scheme 1. Construction of D-glucose-based chiral dioxepane **4** and its conversion to furodioxepanes **6**, **7** and **8**. Reagents and conditions: (a) $NaBH_4$, *tert*-BuOH, MeOH, reflux, 1 h; (b) 4:1 HOAc–H_2O, rt, 12 h; (c) $NaIO_4$ (1.2 equiv), 1:1 EtOH–H_2O, 5–10 °C, 45 min; (d) H_2SO_4 (4%), 3:1 CH_3CN–H_2O, rt, 12 h; (e) Ac_2O/Py, rt, 12 h; (f) aq HOAc (75%), reflux, 5 h.

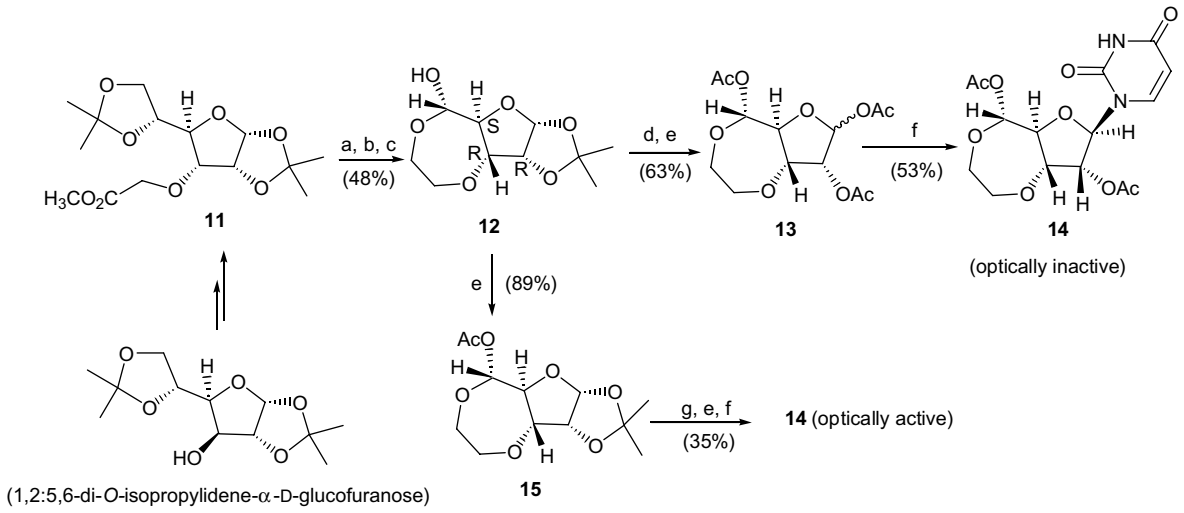
an optically inactive mixture. Acetylation of the triol mixture using Ac_2O–pyridine afforded a mixture of triacetates **6** lacking optical activity. Chirality of the product could, however, be secured by initial protection of the 5-hydroxyl group of **4** through acetylation (Ac_2O–pyridine) to furnish **7**, which after removal of the *O*-isopropylidene group, followed by acetylation, afforded a mixture of optically active anomers **8**.

Treatment of **6** with 2,4-bis-*O*-(trimethylsilyloxy)pyrimidine in dichloroethane in presence of TMSOTf under Vorbrüggen reaction conditions[16] afforded the optically inactive dioxepanonucleosides **9** and **10** in good yields (Scheme 2). Repeating the sequence of the reactions with **8** produced the optically active nucleoside **9**.

On the other hand, the C-3-epimer of **1** (**11**, derived from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose through the oxidation of the 3-OH group, reduction of the generated carbonyl group with $NaBH_4$, and alkylation with methyl bromoacetate) on being subjected to reactions as adopted in Scheme 1 afforded **12**. This was elaborated to the optically inactive isomer of the nucleoside derivative **14** through the triacetoxy intermediate **13** (Scheme 3) using the procedure described in



Scheme 2. Synthesis of bicyclic dioxepanonucleosides **9** and **10**.



Scheme 3. Synthesis of dioxepane **12** and its conversion to bicyclic nucleoside **14**. Reagents and conditions: (a) $NaBH_4$, *tert*-BuOH, MeOH, reflux, 1 h; (b) aq HOAc (80%), rt, 15 h; (c) $NaIO_4$, aq EtOH (50%), 5–10 °C, 45 min; (d) H_2SO_4 (4%), aq CH_3CN (75%), rt, 12 h; (e) Ac_2O/Py, rt, 12 h; (f) 2,4-bis-(trimethylsilyloxy)pyrimidine, DCE, TMSOTf, rt, 6 h; (g) aq HOAc (75%), reflux, 5 h.

Scheme 2. The generation of only one isomer of the second hemiacetal center was observed in this case. However, compound **15** (obtained from **12** by prior protection of the hemiacetal moiety through acetylation) furnished the optically active bicyclic nucleoside **14**.

Regarding the structures and stereochemistry of the nucleosides, introduction of the uracil heterocycle was borne out by the presence of typical signals in the NMR spectra of the products. In the ^{1}H NMR spectrum of **9**, for example, signals for H-5 and H-6 were observed at δ 5.83 (d) and 7.55 (d), while the ^{13}C NMR spectrum contained signals for two olefinic methine carbons (δ 104.1 and 140.1) and two carbonyl carbons (δ 150.4 and 162.9). Mechanistic considerations (participation of the C-2′-OAc group through a dioxolonium intermediate) dictated that the heterocycle must be *trans* to the 2′-OAc group in the product formed. In support, the ^{1}H NMR spectrum of **9** displayed a doublet (δ 6.12, J 3.3 Hz) and a doublet of a doublet (δ 5.08, J 1.2, 3.3 Hz) for the protons H-1′ and H-2′ as observed in related systems.[17] Similar spectral data (^{1}H and ^{13}C NMR) were also obtained for the compounds **10** and **14**. The *trans* disposition of H-4′ and H-5′ in **9** and **14** and the *cis* geometry of these protons in **10** were deduced from the observed coupling constants ($J_{4',5'}$ 7.5 Hz in **9**, 9.0 Hz in **14** and 0 Hz in **10**). The observed J-values (in Hz) were best suited for the indicated structures of the respective nucleosides, based on the calculated dihedral angles for the H–C-4′–C-5′–H unit [$\sim$160° in both **9** and **14** and $\sim$80° in **10** in the energy-minimized structures obtained using ChemOffice, version 6.0].[18] The FABMS of all the bicyclic nucleosides showed pseudo molecular ion peaks at *m*/*z* 371 ($M+H^+$) and 393 ($M+Na^+$) indicating their isomeric nature. The stereochemistries of the precursor molecules **4** and **12** could be similarly settled.

3. Conclusions

In summary, spontaneous cyclization involving the hydroxy group of a C-3 2-hydroxyethyl ether of a C-6 norglucose substrate and the aldehyde function at C-5 is shown to afford, through suitable manipulations of reaction conditions, a new class of bicyclic dioxepane nucleoside analogues in both optically active as well as inactive forms. The latent aldehyde group may serve as a scavenger of many biological nucleophiles and as a handle to yield a variety of derivatives in the laboratory. The method of precursor preparations is straightforward and can be applied to other carbohydrate precursors also, providing a synthetic route to other analogues.

4. Experimental

4.1. General

^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ as a solvent using Me_4Si as an internal standard. Fast-atom bombardment mass spectra (FABMS) were obtained using a spectrometer operating at an accelerating voltage of 3 kV and a neutral atom accelerating energy of 6 kV with argon gas and *m*-nitrobenzyl alcohol (*m*-NBA) as the matrix. Specific rotations were measured at 589 nm. TLC was performed on the pre-coated plates (0.25 mm, Silica Gel $60F_{254}$). HPLC was performed on a μ-Bondapak™ C-18 column (7.8 × 300 mm).

4.2. (3a*R*,4*R*,5*R*,6*S*,6a*R*) [5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yloxy]acetic acid methyl ester (1)

Oil-free NaH (obtained from 1.0 g, 60% in oil suspension thoroughly washed with dry petroleum ether) was added portionwise to a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5 g, 19.2 mmol) in THF (50 mL), and the mixture was stirred at rt for 30 min under N_2. Methyl bromoacetate (3 mL) was added dropwise to the refluxing solution, and heating was continued for 3.5 h. The solvent was evaporated in vacuo after destroying excess NaH by adding satd aq NH_4Cl. The resulting brown mass was extracted with $CHCl_3$ (3 × 15 mL). The $CHCl_3$ solution was washed with brine, dried (Na_2SO_4), and concentrated to afford a crude residue. The product from the residue was purified by silica gel (60–120 mesh) column chromatography, eluting with a 1:10 EtOAc–petroleum ether mixture to furnish 5.48 g of **1** (84%) as a solid: $[\alpha]_D^{26}$ −7.7 (*c* 2.3, $CHCl_3$); ^{1}H NMR: δ 1.31 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.49 (s, 3H), 3.77 (s, 3H), 3.96 (d, 1H, *J* 2.6 Hz), 4.00 (dd, 1H, *J* 5.5, 8.5 Hz), 4.10 (m, 2H), 4.27 (s, 2H), 4.33 (m, 1H), 4.72 (d, 1H, *J* 3.6 Hz), 5.91 (d, 1H, 3.6 Hz); ^{13}C NMR: δ 25.1 (*C*H$_3$), 26.0 (*C*H$_3$), 26.6 (2 × *C*H$_3$), 51.7 (*C*H$_3$), 67.0 (*C*H$_2$), 68.0 (*C*H$_2$), 72.4 (*C*H), 80.8 (*C*H), 83.0 (*C*H), 83.4 (*C*H), 105.0 (*C*H), 108.8 (*C*), 111.6 (*C*); 170.4 (*C*); FABMS, *m*/*z*: 333 (M+H$^+$). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28; found: C, 54.07; H, 7.12.

4.3. (3a*R*,4*R*,5*R*,6*S*,6a*R*) 2-[5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yloxy]ethanol (2)

A solution of 1 (1.0 g, 3.0 mmol) in *t*-BuOH (10 mL) containing $NaBH_4$ (340 mg, 10.0 mmol) was heated at reflux for 1 h on a water bath with addition of 2–3 drops of MeOH at an interval of 10 min. The reaction mixture was cooled to rt, water (1 mL) was added to it, and the solvent was evaporated in vacuo. The residue was extracted with $CHCl_3$ (3 × 20 mL). The $CHCl_3$ solution was washed with brine, dried over Na_2SO_4, and concentrated to furnish an oil that was purified by silica gel (60–120 mesh) column chromatography, eluting with 9:1 $CHCl_3$–petroleum ether mixture to afford 722 mg of **2** (79%) as a thick liquid: $[\alpha]_D^{26}$ −43.7 (*c* 2.3, $CHCl_3$); ^{1}H NMR: δ 1.32 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.50 (s, 3H), 3.42 (t, 1H, *J* 6.5 Hz), 3.55–3.61 (m, 1H), 3.64–3.79 (m, 2H), 3.83–3.91 (m, 1H), 4.00–4.18 (m, 4H), 4.32–4.39 (m, 1H), 4.55 (d, 1H, *J* 3.6 Hz), 5.91 (d, 1H, *J* 3.6 Hz); ^{13}C NMR: δ 25.5 (*C*H$_3$), 26.6 (*C*H$_3$), 27.2 (*C*H$_3$), 27.3 (*C*H$_3$), 61.5 (*C*H$_2$), 68.3 (*C*H$_2$), 72.0 (*C*H$_2$), 73.3 (*C*H), 81.7 (*C*H), 82.7 (*C*H), 83.2 (*C*), 106.1 (*C*H), 109.8 (*C*), 112.3 (*C*); FABMS, *m*/*z*: 305 (M+H$^+$). Anal. Calcd for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95; found: C, 55.07; H, 7.80.

4.4. (1*R*,3a*R*,5*R*,6*S*,6a*R*) 1-[6-(2-Hydroxyethoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]ethan-1,2-diol (3)

Compound **2** (1.21 g, 3.98 mmol) was dissolved in a mixture of 4:1 HOAc–H_2O (50 mL), and the mixture was stirred at rt for 12 h at the end of which time TLC showed complete disappearance of the starting material. The solvent was evaporated in vacuo to a thick material, which was purified by a silica gel (60–120 mesh) column chromatography eluting with 19:1 $CHCl_3$–MeOH mixture to furnish 820 mg of **3** (78%) as a gum: $[\alpha]_D^{26}$ −37.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 1.32 (s, 3H), 1.49 (s, 3H), 3.30 (br s, 3H), 3.54–3.61 (m, 1H), 3.69 (dd, 1H, *J* 5.7, 11.4 Hz), 3.73–3.76 (m, 2H), 3.86–3.90 (m, 2H), 4.00–4.05 (m, 1H), 4.09–4.15 (m, 2H), 4.55 (d, 1H, *J* 3.6 Hz), 5.92 (d, 1H, *J* 3.6 Hz); ^{13}C NMR: δ 25.9 (*C*H$_3$), 26.5 (*C*H$_3$), 60.8 (*C*H$_2$), 64.1 (*C*H$_2$), 68.9 (*C*H), 71.1 (*C*H$_2$), 79.7 (*C*H), 81.8 (*C*H), 82.4 (*C*H), 105.1 (*C*H), 111.6 (*C*); FABMS, *m*/*z*: 265 (M+H$^+$) and 287 (M+Na$^+$). Anal. Calcd for $C_{11}H_{20}O_7$: C, 49.99; H, 7.63; found: C, 50.07; H, 7.81.

4.5. (3a*R*,3b*S*,8*S*,8a*S*,9a*R*) 2,2-Dimethyl-hexahydro-1,3,4,7,9-pentaoxa-cyclopenta[*a*]azulen-8-ol (4)

To an ice-cooled stirred solution of **3** (790 mg, 3.0 mmol) in 1:1 EtOH–H_2O (20 mL) was added dropwise a solution of $NaIO_4$ (770 mg, 3.35 mmol) in water (2 mL). After 45 min of stirring, the mixture was filtered, the filtrate was evaporated under reduced pressure, and the residue thus obtained was extracted with $CHCl_3$ (3 × 20 mL). The $CHCl_3$ solution was washed with brine, dried (Na_2SO_4) and concentrated to a crude material that was purified by column chromatography using $CHCl_3$ as the eluting solvent to furnish 556 mg of **4** (80%) as a thick gum: $[\alpha]_D^{26}$ +13.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 1.32 (s, 3H), 1.49 (s, 3H), 3.62 (t-like, 1H, *J* 11.0 Hz), 3.81 (t-like, 1H, *J* 11.0 Hz), 3.96 (d, 2H, *J* 12.3 Hz), 4.13 (d, 1H, *J* 3.6 Hz), 4.35 (dd, 1H, *J* 3.9, 6.0 Hz), 4.51 (d, 1H, *J* 3.6 Hz), 4.95 (d, 1H, *J* 6.0 Hz), 5.98 (d, 1H, *J* 3.6 Hz); ^{13}C NMR: δ 26.3 (*C*H$_3$), 26.9 (*C*H$_3$), 70.3 (*C*H$_2$), 74.0 (*C*H$_2$), 84.9 (*C*H), 86.2 (CH), 86.4 (*C*H), 101.3 (*C*H), 105.3 (*C*H), 111.8 (*C*); FABMS, *m*/*z*: 233 (M+H$^+$) and 255 (M+Na$^+$). Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94; found: C, 51.45; H, 6.70.

4.6. (3a*R*,3b*S*,8*S*,8a*S*,9a*R*) Acetic acid 2,2-dimethyl-hexahydro-1,3,4,7,9-pentaoxacyclopent[*a*]azulen-8-yl ester (7)

Compound **4** (300 mg, 1.30 mmol) was dissolved in pyridine (10 mL), Ac_2O (1 mL) was added, and the solution was stirred at rt for 12 h. The solvent was evaporated in vacuo, and the crude product was purified by silica gel column chromatography eluting with 3:17 EtOAc–

petroleum ether mixture to afford 297 mg of **7** (84%): $[\alpha]_D^{26}$ +3.6 (*c* 2.0, $CHCl_3$); ^1H NMR: δ 1.32 (s, 3H), 1.50 (s, 3H), 2.13 (s, 3H), 3.57–3.68 (m, 1H), 3.93–4.03 (m, 3H), 4.16 (d, 1H, *J* 3.6 Hz), 4.52–4.55 (m, 2H), 5.68 (d, 1H, *J* 7.3 Hz), 5.97 (d, 1H, *J* 3.6 Hz); ^{13}C NMR: δ 21.1 (CH_3), 26.5 (CH_3), 27.2 (CH_3), 61.5 (CH_2), 71.5 (CH_2), 74.2 (CH_2), 83.7 (*C*H), 84.9 (*C*H), 86.8 (CH), 99.3 (CH), 105.9 (*C*H), 112.1 (*C*), 169.9 (*C*); FABMS, *m*/*z*: 275 ($M+H^+$). Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62; found: C, 52.70; H, 6.48.

4.7. (5*R*,5a*S*,7*R*,8*R*,8a*R*) Acetic acid 8-acetoxy-7-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)hexahydrofuro[3,2-*e*][1,4]dioxepin-5-yl ester (9) and (5*S*,5a*S*,7*R*,8*R*,8a*R*) Acetic acid 8-acetoxy-7-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)hexahydrofuro[3,2-*e*][1,4]dioxepin-5-yl ester (10)

A solution of **4** (340 mg, 1.46 mmol) in a mixture of 1:18:6 H_2SO_4–CH_3CN–H_2O (20 mL) was stirred at rt for 12 h. The acidic solution was neutralized by portion-wise addition of solid $CaCO_3$. The precipitate was filtered off, and the solvent was evaporated in vacuo to a gummy mass, which was dried over P_2O_5 under vacuum. The gummy mass was then treated with pyridine (5 mL) and Ac_2O (1 mL), and the mixture was stirred at rt for 12 h. The solvent was evaporated, and the sticky material was dried in vacuo to furnish a triacetate mixture **6** (260 mg, 56%), which was subsequently used without further purification. Then a mixture of uracil (200 mg, 1.79 mmol) in hexamethyldisilazane (7 mL) and freshly distilled chlorotrimethylsilane (two drops) was heated at reflux under N_2 for 12 h. The solvent was distilled off under vacuum, and a solution of the residue in dichloroethane (5 mL) was added to a stirred solution of the triacetate mixture **6** (200 mg, 0.63 mmol) in dichloroethane (5 mL) containing TMSOTf (0.4 mL). The solution was stirred at rt for 6 h under N_2, when TLC showed complete disappearance of the starting material. The reaction mixture was neutralized with solid $NaHCO_3$, water (2–3 drops) was added to it, and the solvent was evaporated in a rotary evaporator. The residue was extracted with 49:1 $CHCl_3$–MeOH (20 mL). The solution was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was primarily purified by silica gel column chromatography using methanolic $CHCl_3$ (2%) as eluent to afford an anomeric mixture of **9** and **10** (200 mg, 60%), 75 mg of which was separated by reversed-phase HPLC using 3:17 CH_3CN–H_2O as eluent to afford 45 mg of **9** and 18 mg of **10**.

Compound **9** as a foam: ^1H NMR: δ 2.08 (s, 3H), 2.11 (s, 3H), 3.80–3.86 (m, 2H), 3.98–4.06 (m, 2H), 4.58 (d, 1H, *J* 7.3 Hz), 4.76 (t-like, 1H, *J* 6.2, 6.6 Hz), 5.65 (t-like, 1H, *J* 5.1, 5.3 Hz), 5.73 (d, 1H, *J* 8.2 Hz), 5.99 (s, 1H), 6.49 (d, 1H, *J* 4.5 Hz), 7.58 (d, 1H, *J* 8.2 Hz), 9.16 (br s, 1H); ^{13}C NMR: δ 20.8 (CH_3), 21.3 (CH_3), 66.8 (CH_2), 71.9 (*C*H), 72.0 (CH_2), 80.1 (*C*H), 81.1 (*C*H), 83.2 (*C*H), 93.3 (*C*H), 102.5 (*C*H), 142.0 (*C*H), 150.3 (*C*), 163.4 (*C*), 169.5 (*C*), 170.3 (*C*); FABMS, *m*/*z*: 371 ($M+H^+$) and 393 ($M+Na^+$). Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.56; found: C, 48.55; H, 4.72; N, 7.30.

Compound **10** as a foam: ^1H NMR: δ 2.14 (s, 6H), 3.69 (m, 1H), 4.00–4.14 (m, 3H), 4.22 (dd, 1H, *J* 1.2, 4.5 Hz), 4.43 (dd, 1H, *J* 4.5, 7.3 Hz), 5.08 (dd, 1H, *J* 1.2, 3.0 Hz), 5.83 (d, 2H, *J* 7.5 Hz), 6.12 (d, 1H, *J* 3.3 Hz), 7.55 (d, 1H, *J* 8.0 Hz), 8.75 (br s, 1H); ^{13}C NMR: δ 21.0 (CH_3), 21.3 (CH_3), 72.0 (CH_2), 74.8 (CH_2), 81.8 (*C*H), 84.2 (*C*H), 86.2 (*C*H), 89.1 (*C*H), 98.6 (*C*H), 104.1 (*C*H), 140.1 (*C*H), 150.4 (*C*), 162.9 (*C*), 169.9 (*C*), 170.1 (*C*); FABMS, *m*/*z*: 371 ($M+H^+$), 393 ($M+Na^+$). Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.56; found: C, 48.62; H, 4.83; N, 7.38.

Optically active form of **9**: Compound **7** (200 mg, 0.73 mmol) was dissolved in 75% aqueous HOAc (20 mL) and heated at reflux for 5 h. The solvent was evaporated; the last traces of pyridine were removed by co-evaporation with toluene, and the residue was acetylated with pyridine (5 mL) and Ac_2O (1 mL) at rt. Usual work-up afforded the mixture of triacetates **8** (232 mg), 75 mg of which was transformed into 48 mg of **9** (55%) as a foamy solid using a procedure similar to that described earlier: $[\alpha]_D^{26}$ +15.6 (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.56; found: C, 48.46; H, 4.80; N, 7.43.

4.8. (3a*R*,4*R*,5*R*,6*R*,6a*R*) [5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yloxy]acetic acid methyl ester (11)

1,2:5,6-Di-*O*-isopropylidene-D-allofuranose (2.5 g, 9.6 mmol) was converted to **11** (2.42 g, 76%) through O-alkylation with methyl bromoacetate according to the procedure as described in the preparation of **1**.

Compound **11** as a thick oil: $[\alpha]_D^{26}$ +71.7 (*c* 1.6, $CHCl_3$); ^1H NMR: δ 1.37 (s, 6H), 1.47 (s, 3H), 1.59 (s, 3H), 3.76 (s, 3H), 3.92 (dd, 1H, *J* 4.5, 8.5 Hz), 3.97–4.12 (m, 3H), 4.25 (d, 1H, *J* 16.8 Hz), 4.31 (dd, 1H, *J* 6.6, 11.0 Hz), 4.40 (d, 1H, *J* 16.8 Hz), 4.77 (t, 1H, *J* 3.9 Hz), 5.75 (d, 1H, *J* 3.6 Hz). ^{13}C NMR: δ 24.9 (CH_3), 26.2 (CH_3), 26.4 (CH_3), 26.7 (CH_3), 51.8 (CH_3), 65.5 (CH_2), 67.6 (CH_2), 75.1 (CH), 78.1 (CH), 78.5 (CH), 79.9 (CH), 103.5 (CH), 109.6 (C), 113.0 (C), 170.6 (C); FABMS, *m*/*z*: 333 ($M+H^+$). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28; found: C, 54.13; H, 7.20.

4.9. (3a*R*,3b*R*,8*S*,8a*S*,9a*R*) 2,2-Dimethylhexahydro-1,3,4,7,9-pentaoxacyclopenta[*a*]azulen-8-ol (12)

The conversion of **11** (100 mg, 0.3 mmol) to **12** (33 mg, 48%) was performed through reduction of the ester

group, selective removal of the 5,6-*O*-isopropylidene group, and vicinal diol cleavage following the procedure as described in the preparation of **4** from **2**.

Compound **12** as a sticky mass: $[\alpha]_D^{26}$ +26.0 (*c* 2.0, $CHCl_3$); ^1H NMR: δ 1.35 (s, 3H), 1.62 (s, 3H), 2.89 (br s, 1H), 3.66 (t-like, 1H, *J* 13.5 Hz), 3.76 (d, 1H, *J* 10.4 Hz), 3.93 (m, 2H), 4.19 (t-like, 1H, *J* 13.5 Hz), 4.27 (dd, 1H, *J* 8.0, 13.5 Hz), 4.64 (s, 1H), 5.06 (d, 1H, *J* 5.0 Hz), 5.79 (s, 1H); ^{13}C NMR: δ 26.2 (CH_3), 26.7 (CH_3), 64.8 (CH_2), 70.9 (CH_2), 78.8 (*C*H), 79.1 (CH), 83.9 (*C*H), 96.9 (*C*H), 104.2 (*C*H), 113.4 (*C*); FABMS, *m*/*z*: 233 ($M+H^+$) and 255 ($M+Na^+$). Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94; found: C, 51.55; H, 6.74.

4.10. (5*R*,5a*S*,7*R*,8*R*,8a*S*) Acetic acid 5-acetoxy-7-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-hexahydrofuro-[3,2-*e*][1,4]dioxepin-8-yl ester (14)

The 1,2-*O*-isopropylidene group of **12** (225 mg, 0.97 mmol) was cleaved by treatment with 4% H_2SO_4 in 1:3 CH_3CN–H_2O (20 mL), followed by acetylation of the product with pyridine (3 mL) and Ac_2O (1 mL) according to the method described above afforded a mixture of crude triacetates **13** (195 mg, 63%). A solution of **13** (105 mg, 0.33 mmol) in dichloroethane (5 mL) was added to a solution of 2,4-bis-(trimethylsilyloxy)pyrimidine [prepared by refluxing a mixture of uracil (1.34 mmol), hexamethyldisilazane (7 mL) and TMSCl (two drops)] in dichloroethane (5 mL) with stirring at rt for 6 h. Usual work-up, followed by reversed-phase HPLC (eluting solvent: 3:17 CH_3CN–H_2O) afforded 65 mg of **14** (53%) as an optically inactive foamy solid: ^1H NMR: δ 2.11 (s, 3H), 2.18 (s, 3H), 3.84–3.92 (m, 1H), 3.98–4.03 (m, 2H), 4.35–4.47 (m, 2H), 4.78 (t, 1H, *J* 9.0 Hz), 5.37 (d, 1H, *J* 4.5 Hz), 5.47 (d, 1H, *J* 9.0 Hz), 5.75 (dd, 1H, *J* 2.0, 8.0 Hz), 6.07 (s, 1H), 7.24 (d, 1H, *J* 8.0 Hz), 8.71 (br s, 1H); ^{13}C NMR: δ 21.1 (CH_3), 21.4 (CH_3), 69.1 (CH_2), 71.5 (CH_2), 75.3 (*C*H), 77.7 (*C*H), 79.2 (*C*H), 89.2 (*C*H), 98.4 (*C*H), 103.3 (*C*H), 141.4 (*C*H), 150.8 (*C*), 162.9 (*C*), 168.9 (*C*), 169.9 (*C*); FABMS, *m*/*z*: 371 ($M+H^+$) and 393 ($M+Na^+$). Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.56; found: C, 48.47; H, 4.81; N, 7.45.

4.11. (3a*R*,3b*R*,8*R*,8a*S*,9a*R*) Acetic acid 2,2-dimethyl-hexahydro-1,3,4,7,9-pentaoxacyclopent[*a*]azulen-8-yl ester (15)

Compound **12** (21 mg, 0.09 mmol) was acetylated in a pyridine (4 mL) and Ac_2O (0.5 mL) mixture. The solvent was evaporated in vacuo, and the crude product was purified by silica gel column chromatography using 1:5 EtOAc–petroleum ether as the eluent to furnish 22 mg of **15** (0.08 mmol, 89%) as a sticky material: $[\alpha]_D^{26}$ +56.7 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 1.36 (s, 3H), 1.64 (s, 3H), 3.71–3.81 (m, 2H), 3.93–3.99 (m, 2H), 4.09 (dd, 1H, *J* 10.6, 13.5 Hz), 4.46 (dd, 1H, *J* 6.6, 9.0 Hz), 4.69 (t, 1H, *J* 3.6 Hz), 5.81 (d, 1H, *J* 3.0 Hz), 5.92 (d, 1H, *J* 6.3 Hz); ^{13}C NMR: δ 21.6 (CH_3), 26.6 (CH_3), 27.2 (CH_3), 67.4 (CH_2), 71.3 (CH_2), 79.3 (*C*H), 79.8 (*C*H), 82.0 (*C*H), 96.6 (*C*H), 104.8 (*C*H), 114.0 (*C*), 170.4 (*C*); FABMS, *m*/*z*: 275 ($M+H^+$) and 297 ($M+Na^+$). Anal. Calcd for $C_{12}H_{18}O_7$: C, 55.55; H, 6.62; found: C, 55.28; H, 6.60.

Preparation of optically active nucleoside **14**: The *O*-isopropylidene group of **15** (15 mg, 0.054 mmol) was cleaved by heating in 75% aq HOAc (5 mL) at reflux for 5 h. The residue after solvent removal was acetylated with a pyridine (2 mL) and Ac_2O (0.5 mL) mixture to give a mixture of triacetates, which was used for the preparation of **14** using the protocol: uracil (20 mg), hexamethyldisilazane (1 mL), TMSCl (one drop), TMSOTf (0.1 mL) and dichloroethane (4 mL). Yield, 7 mg of **14** (35%) as a foamy solid: $[\alpha]_D^{26}$ +8.0 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.56; found: C, 48.38; H, 4.78; N, 7.32.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra of the compounds **1**–**4**, **7**, **9**–**12**, **14**, and **15** can be found in the electronic version of this paper. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2005.02.007.

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