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SYNTHETIC STUDIES OF LIPOSIDOMYCIN DEGRADATION PRODUCT: MODEL STUDIES OF URACIL GROUP INTRODUCTION

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Abstract – The model studies of uracil group introduction for liposidomycin degradation product was described. A stereocontrolled synthesis of the liposidomycin diazepanone ring system having a phenyl substituent has been achieved. In the presence of an amino group on the diazepanone ring, the introduction of a uracil group did failed. In the model study with the Ns and formyl protecting group, the *N*-glycosylation proceeded smoothly to obtain the uracil compound in good yield.

INTRODUCTION

Liposidomycins (**1a**, **b**, **c**) found in the culture filtrate and mycelia of *streptomyces griseosporus*¹ as a family of novel lipid-containing nucleoside antibiotics of unusual complexity. They shows highly specific inhibition toward phospho-*N*-acetylmuramylpentapeptide transferase that is the primary stage of a lipid cycle in bacterial peptidoglycan synthesis.² Its inhibition effect is about 30 to 500 times more effective than that of tunicamycin, whereas liposidomycins inhibited mammalian glycoprotein biosynthesis about 30 to 300 times less effectively than tunicamycin.³ Liposidomycin B also inhibits *in vitro* formation of polyprenyl (pyro)phosphate *N*-acetylglucosamine, an intermediate in glycoconjugate biosynthesis.⁴

The structures were proposed on the basis of NMR and mass spectral evidence of degradation compound (**2**)⁵ but the stereogenic centers in the lipid and diazepanone ring parts remained unassigned (**Figure 1**).⁶ In 2004, the stereochemistry of the diazepanone part was revealed by X-ray crystallography analysis of caprazamycin (**3**) that is an analog of liposidomycins.^{7,8} Until the X-ray determination, the synthetic studies of liposidomycins and their model compounds (**5-7**) having a diazepanone ring part have been carried out by Spada and Ubukata,⁹ Kim,^{10,11} and Gravier-Pelletier¹² for the assignment of the stereochemistry.

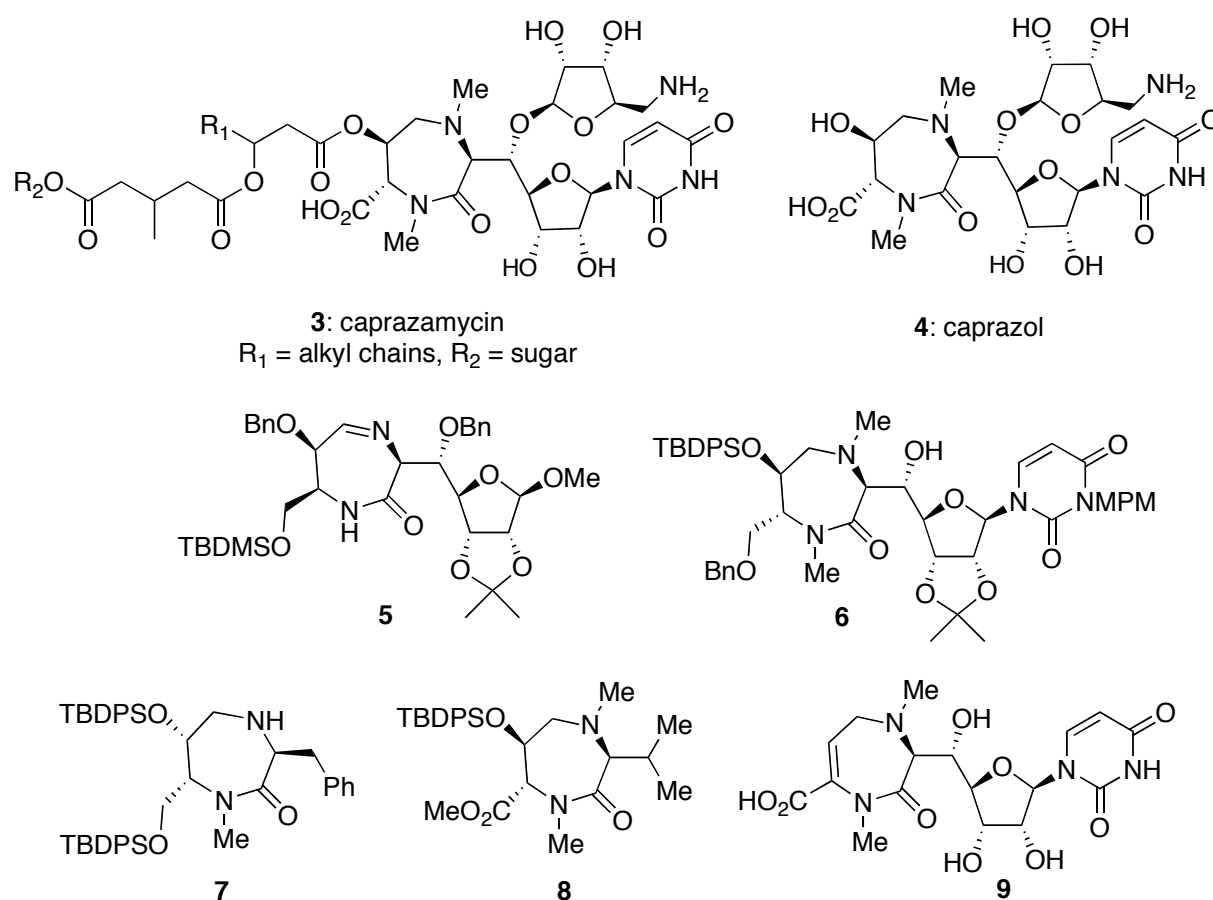
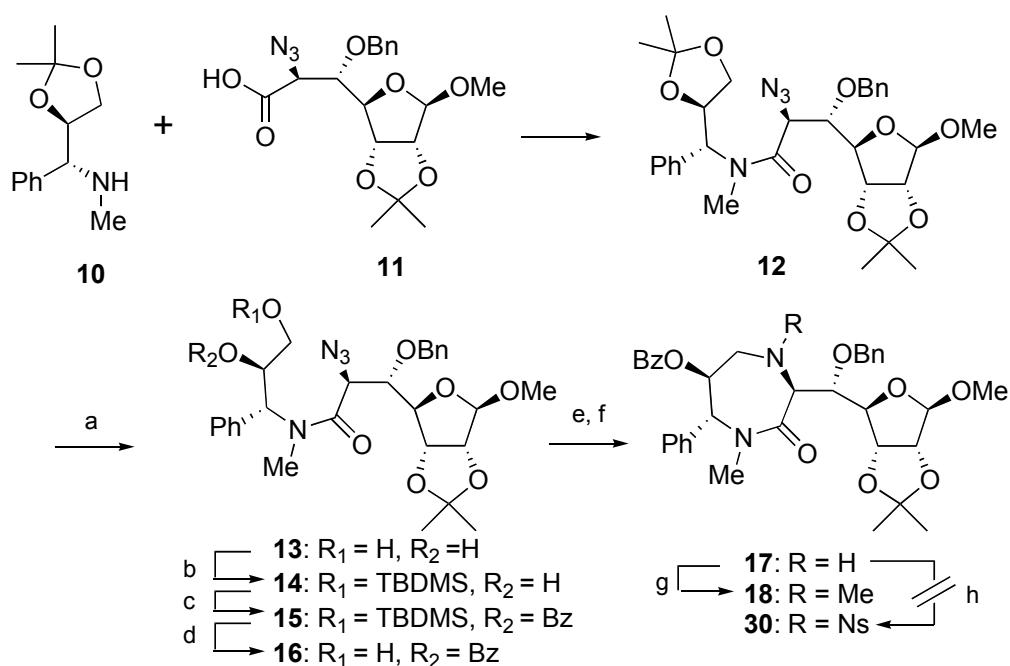


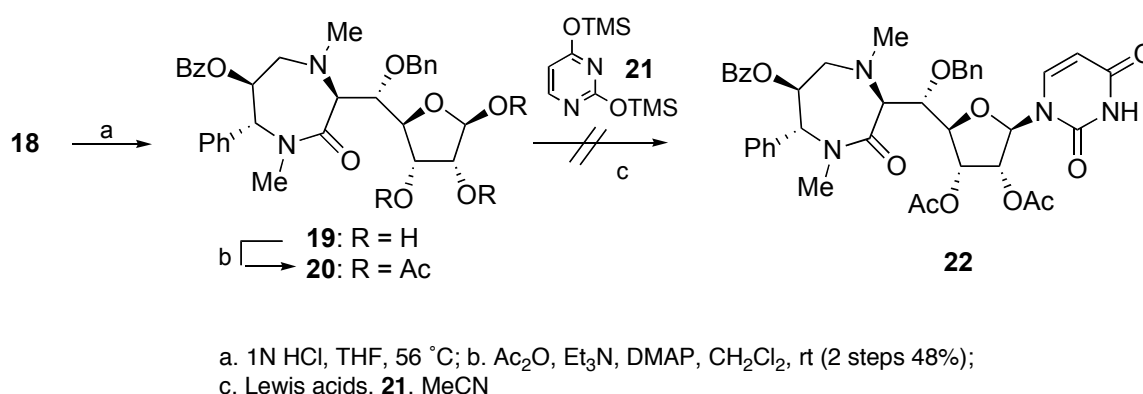
Figure 2. The structure of caprazamycin, caprazol and synthesized liposidomycin model compounds



a. 1N HCl, THF, 45 °C, 76%; b. TBDMSCl, imidazole, CH_2Cl_2 , 89%; c. BzCl, Et_3N , DMAP, CH_2Cl_2 , rt, 95%; d. HF-pyridine, THF, 95%; e. DMSO, $(\text{COCl})_2$, Et_3N , CH_2Cl_2 , 63%; f. 10% Pd-C/ H_2 , EtOAc, AcOH, 63%; g. 37 %-HCHO, NaBH_3CN , AcOH, MeCN, 85%; h. NsCl, Et_3N , CH_2Cl_2 .

Scheme 1. The synthetic scheme for liposidomycin degradation product

The C1-methoxy group and 2,3-acetonide group in the furanose part of **18** were deprotected by 1N HCl to give **19**, and the all hydroxy groups were protected with Ac groups by Ac₂O, TEA, DMAP in CH₂Cl₂ to afford triacetate (**20**) (α/β = 1/4 mixture of the anomeric position) in 48% yield. *N*-glycosylation of **20** with bistrimethylsilyluracil (**21**) and Lewis acids (TMSOTf, SnCl₄, or BF₃ • OEt₂) gave no reaction products. Even with use of excess amounts of the glycosyl donor, due to the presence of an unshared electron pair of *N*-1' nitrogen at the diazepanone ring trapping the Lewis acid,¹⁵ all attempts for the introduction of a uracil group with **21** to **20** were unsuccessful (**Scheme 2**).²⁰

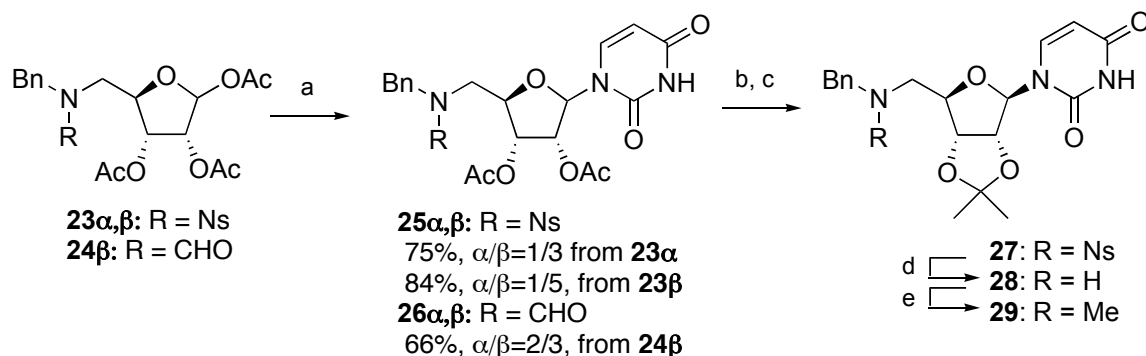


Scheme 2. The synthetic scheme for liposidomycin diazepanone ring part

For the introduction of a uracil group, we prepared the model compound **23** and **24** having an electron-withdrawing Ns^{21,22} group and formyl (CHO) group on the corresponding C-1 nitrogen group (**Scheme 3**). The *N*-glycosylation of **23a** ($J_{1,2}$ = 0 Hz) with **21** in the presence of SnCl₄ as a Lewis acid in MeCN proceeded smoothly to obtain the target compound **25a** ($J_{1,2}$ = 0 Hz) and **25b** ($J_{1,2}$ = 4.4 Hz) in 75% yield with 1/3 selectivity. This selectivity was increased by using **23b** ($J_{1,2}$ = 4.6 Hz) and **21** to α/β = 1/5 selectivity with 84% yield. The *N*-glycosylation of **24b** having formyl group also gave **26a** and **26b** in 66% yield with 2/3 selectivity. After separation of **25a** and **25b**, the Ac group of **25b** was converted to the 2,3-acetonide group *via* 2-step conversion to give **27** in 89 % yield. The Ns group was converted into methyl groups by PhSK treatment and following reductive *N*-methylation of **28** in 63 % and 58% yields, respectively. On these studies, we found the electron-withdrawing group on the amino group played an important role for the introduction of a uracil group. However, any attempt of Ns protection at C1-amino group of **17** were failed (**Scheme 1**). Therefore, the synthesis **30** under another synthetic route is an ongoing project.

EXPERIMENTAL

General. All melting points (mp) data were measured with Yamato MP-21 melting point apparatus and



a. SnCl_4 , **21**, CH_3CN , 0°C ; b. K_2CO_3 , MeOH, H_2O ; c. CSA, 2,2-dimethoxypropane, CH_2Cl_2 , (2 steps 89%); d. PhSH, KOH, MeCN, 50°C , 63%; e. NaBH_3CN , 37% HCHO, AcOH, MeCN, 58%

Scheme 3. The model study of *N*-glycosylation

are uncorrected. Optical rotation values were measured in CHCl_3 , H_2O or MeOH with a Horiba SEPA-300 high-sensitivity polarimeter. IR spectra were recorded as neat for oils, and as KBr discs for solids, with a Shimadzu OR-8000 spectrometer. ^1H -NMR spectra were recorded in CDCl_3 or CD_3OD by JEOL JNM EX-400 and JEOL JNM LA-400 instruments, while low- and high-resolution mass spectra (MS) were measured with a JEOL JMS AX-500 spectrometer at 70 or 15 eV. Kanto Chemical Co., Ltd. Silica Gel 60N (Spherical, Neutral) was used for column chromatography.

***N*-Methyl-*N*-[(1*R*,2*R*)-2,3-dihydroxy-1-phenyl]propyl-(2*S*,3*S*)-2-azido-3-benzyloxy-3-((2*R*,3*R*,4*R*,5*R*)-3,4-isopropylidenedioxy-5-methoxytetrahydrofuran-2-yl)propionamide (**13**):** To a solution of **12** (155.6 mg, 0.26 mmol) in THF (5 mL) was added 1N HCl (1.5 mL) and stirred for 2.5 h at 45°C . The reaction mixture was quenched with powdered NaHCO_3 and the solvent was removed *in vacuo*. The reaction mixture was dissolved in H_2O and the aqueous solution was extracted with CHCl_3 . The combined organic phases were washed with brine and dried (Na_2SO_4). Filtration, concentration and silica gel column purification (hexane/EtOAc, 1/1) afforded starting material (**12**) (57.5 mg, 0.096 mmol, 37 %) as the first elution and **13** (72.3 mg, 0.13 mmol, 50 %) as a colorless solid: Rf: 0.1 (hexane/EtOAc, 1/1); $[\alpha]_D^{22.0}$ -58.3 (*c* 1.7, CHCl_3); ^1H -NMR (400MHz, CDCl_3): 7.44-7.26 (10H, m), 5.62 (1H, d, $J = 10.2$ Hz), 4.98 (1H, d, $J = 11.6$ Hz), 4.89 (1H, d, $J = 1.2$ Hz), 4.74 (1H, d, $J = 11.6$ Hz), 4.62 (1H, dd, $J = 2.2, 6.1$ Hz), 4.48 (1H, dd, $J = 1.2, 6.1$ Hz), 4.30 (1H, dd, $J = 2.2, 3.7$ Hz), 4.28 (1H, d, $J = 6.7$ Hz), 4.21 (1H, ddd, $J = 10.0, 10.2, 12.4$ Hz), 4.09 (1H, dd, $J = 3.7, 6.7$ Hz), 3.76 (1H, dd, $J = 2.4, 10.0$ Hz), 3.69 (1H, ddd, $J = 2.2, 3.8, 12.4$ Hz), 3.27 (3H, s), 2.72 (3H, m), 1.49 (3H, s), 1.26 (3H, s); ^{13}C -NMR (100MHz, CDCl_3): 170.2, 137.6, 129.3, 128.8, 128.5, 128.2, 127.9, 127.7, 112.8, 110.9, 86.4, 85.2, 80.9, 79.5, 75.0, 68.6,

62.6, 60.5, 58.3, 55.8, 31.6, 26.9, 25.1; IR ν_{max} (neat) cm^{-1} : 3065.3 (w), 3030.5 (w), 2990.0 (w), 2936.0 (m), 2106.5 (s), 1724.6 (w), 1635.8 (s), 1585.7 (w), 1496.9 (w), 1454.5 (w), 1410.1 (w), 1383.1 (w), 1244.2 (w), 1215.3 (w), 1159.4 (w), 1086.1 (m), 937.5 (w), 866.1 (m), 754.3 (s), 702.2 (m), 667.5 (w); FAB-MS m/z (rel. int.): 558 (6), 557 (MH^+ , 16), 525 (18), 391 (30), 149 (100), 91 (100); FAB-HRMS m/z (MH^+): Calcd. for $\text{C}_{28}\text{H}_{37}\text{O}_8\text{N}_4$, 557.2611; found 557.2598.

***N*-Methyl-*N*-[(1*R*,2*R*)-3-*tert*-butyldimethylsilyloxy-2-hydroxy-1-phenyl]propyl-(2*S*,3*S*)-2-azido-3-benzyloxy-3-((2*R*,3*R*,4*R*,5*R*)-3,4-isopropylidenedioxy-5-methoxytetrahydrofuran-2-yl)-**

propionamide (14): To a solution of **13** (110.6 mg, 0.199 mmol) and imidazole (29.8 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) was added slowly a solution of TBDMSCl (32.9 mg, 0.22 mmol) in CH_2Cl_2 (1.5 mL) at rt. After stirring for 12 h at 25°C, the reaction mixture was quenched with saturated aqueous NH_4Cl . The aqueous solution was extracted with CH_2Cl_2 and the combined organic phases were washed with brine and dried (Na_2SO_4). Filtration, concentration and silica gel column purification (hexane/EtOAc, 5/1) afforded **14** (101 mg, 0.15 mmol, 76 %) as a colorless solid: Rf: 0.37 (hexane/EtOAc, 3/1); $[\alpha]_{\text{D}}^{21.4}$ -43.2 (c 3.0, CHCl_3); ^1H -NMR (400MHz, CDCl_3): 7.35-7.16 (10H, m), 5.49 (1H, d, $J = 7.6$ Hz), 4.86 (1H, d, $J = 11.7$ Hz), 4.75 (1H, d, $J = 1.2$ Hz), 4.56 (1H, d, $J = 11.7$ Hz), 4.50 (1H, dd, $J = 1.2, 6.1$ Hz), 4.22 (1H, ddd, $J = 4.6, 6.8, 7.6$ Hz), 4.14 (1H, d, $J = 6.5$ Hz), 4.13 (1H, dd, $J = 2.2, 3.9$ Hz), 3.96 (1H, dd, $J = 3.9, 6.5$ Hz), 3.58 (1H, d, $J = 4.6$ Hz), 3.57 (1H, d, $J = 6.8$ Hz), 3.17 (3H, s), 2.81 (3H, s), 1.35 (3H, s), 1.14 (3H, s), 0.82 (9H, s), 0.00 (6H, s); ^{13}C -NMR (100MHz, CDCl_3): 168.7, 137.8, 136.4, 129.2, 128.5, 128.4, 127.9, 127.8, 127.7, 112.7, 110.8, 86.4, 85.2, 80.9, 79.3, 74.9, 70.4, 64.2, 60.4, 60.2, 59.6, 55.8, 32.5, 26.9, 25.8, 25.2, 18.2, 14.2, -5.42, -5.44; IR ν_{max} (neat) cm^{-1} : 2953.4 (m), 2932.2 (w), 2858.9 (w), 2106.5 (s), 1645.5 (s), 1496.9 (w), 1408.2 (w), 1383.1 (w), 1253.9 (m), 1215.3 (w), 1159.4 (w), 1113.1 (s), 1086.1 (s), 860.4 (m), 837.2 (m), 779.3 (m), 756.2 (s), 702.2 (m), 667.5 (w), 557.5 (w); FAB-MS m/z (rel. int.): 672 (5), 671 (MH^+ , 12), 639 (15), 322 (7), 91 (100), 74 (73); FAB-HRMS m/z (MH^+): Calcd. for $\text{C}_{34}\text{H}_{51}\text{O}_8\text{N}_4\text{Si}$, 671.3476; found 671.3475.

***N*-Methyl-*N*-[(1*R*,2*R*)-2-benzoyloxy-3-*tert*-butyldimethylsilyloxy-1-phenyl]propyl-(2*S*,3*S*)-2-azido-3-benzyloxy-3-((2*R*,3*R*,4*R*,5*R*)-3,4-isopropylidenedioxy-5-methoxytetrahydrofuran-2-yl)propionamide (15):** Under Ar atmosphere, to a solution of **14** (86.8 mg, 0.129 mmol), Et_3N (216 μL , 1.55 mmol) and DMAP (1.6 mg, 0.013 mmol) in CH_2Cl_2 (5 mL) was added benzoyl chloride (75 μL , 0.65 mmol) at 25°C.

After stirring was continued for 12 h, the reaction mixture was quenched with saturated aqueous. NH_4Cl . The aqueous solution was extracted with CH_2Cl_2 and the combined organic phases were washed with brine and dried (Na_2SO_4). Filtration, concentration and silica gel column purification (hexane/EtOAc, 10/1) afforded **15** (94.4 mg, 0.122 mmol, 94.5 %) as a colorless solid: Rf: 0.53 (benzene/EtOAc, 10/1); $[\alpha]_{\text{D}}^{21.6}$ -79.7 (*c* 2.5, CHCl_3); ^1H -NMR (400MHz, CDCl_3): 7.88 (2H, d, $J = 7.1$ Hz), 7.51-7.22 (13H, m), 6.16 (1H, d, $J = 9.8$ Hz), 6.01 (1H, ddd, $J = 4.2, 6.1, 9.8$ Hz), 4.95 (1H, d, $J = 11.6$ Hz), 4.82 (1H, d, $J = 1.0$ Hz), 4.68 (1H, d, $J = 11.6$ Hz), 4.62 (1H, dd, $J = 2.2, 6.1$ Hz), 4.45 (1H, dd, $J = 1.0, 6.1$ Hz), 4.23 (1H, dd, $J = 2.2, 3.9$ Hz), 4.22 (1H, d, $J = 6.1$ Hz), 4.05 (1H, dd, $J = 3.9, 6.1$ Hz), 3.95 (1H, dd, $J = 4.2, 11.2$ Hz), 3.89 (1H, dd, $J = 6.1, 11.2$ Hz), 3.25 (3H, s), 2.93 (3H, s), 1.44 (3H, s), 1.24 (3H, s), 0.83 (9H, s), 0.00 (3H, s), -0.02 (3H, s); ^{13}C -NMR (100MHz, CDCl_3): 168.6, 165.7, 137.8, 136.1, 133.0, 129.9, 129.6, 128.7, 128.5, 128.4, 128.2, 128.0, 127.7, 127.6, 112.7, 110.8, 86.3, 85.2, 80.9, 79.2, 74.8, 72.0, 63.1, 60.4, 59.9, 57.0, 55.7, 31.7, 26.9, 25.7, 25.2, 18.1, 14.2, -5.58, -5.63; IR ν_{max} (neat) cm^{-1} : 3065.3 (w), 2932.2 (s), 2856.9 (m), 2361.2 (w), 2106.5 (s), 1722.6 (s), 1651.3 (s), 1603.0 (w), 1585.7 (w), 1496.9 (w), 1452.6 (m), 1406.3 (w), 1315.6 (w), 1271.2 (s), 1215.3 (m), 1176.7 (w), 1026.3 (w), 864.2 (m), 839.1 (m), 758.1 (s), 711.8 (s), 667.5 (w); FAB-MS m/z (rel. int.): 775 (MH^+ , 11), 743 (17), 717 (16), 653 (18), 426 (12), 369 (17), 105 (100), 91 (100), 74 (100); FAB-HRMS m/z (MH^+): Calcd. for $\text{C}_{41}\text{H}_{55}\text{O}_9\text{N}_4\text{Si}$, 775.3738; found 775.3754.

***N*-Methyl-*N*-[(1*R*,2*R*)-2-benzoyloxy-3-hydroxy-1-phenyl]-propyl-(2*S*,3*S*)-2-azido-3-benzyloxy-3-((2*R*,3*R*,4*R*,5*R*)-3,4-isopropylidenedioxy-5-methoxytetrahydrofuran-2-yl)propionamide (16):** To a solution of **15** (89.3 mg, 0.115 mmol) in THF (5 mL) was added HF-pyridine (0.2 mL) at 0°C and warmed to 25°C. After stirring was continued for 12 h, powdered NaHCO_3 was added to the reaction mixture to quench the reaction. The reaction mixture was dissolved in H_2O and the aqueous solution was extracted with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). Filtration, concentration and silica gel column purification (hexane/EtOAc, 3/1) afforded **16** (79.5 mg, 0.10 mmol, 95 %) as a colorless solid: Rf: 0.09 (hexane/EtOAc, 3/1); $[\alpha]_{\text{D}}^{23.1}$ -86.5 (*c* 3.1, CHCl_3); ^1H -NMR (400MHz, CDCl_3): 7.84 (1H, d, $J = 7.1$ Hz), 7.51-7.26 (13H, m), 6.26 (1H, d, $J = 11.1$ Hz), 5.72 (1H, ddd, $J = 2.1, 2.4, 11.1$ Hz), 4.98 (1H, d, $J = 11.7$ Hz), 4.86 (1H, d, $J = 1.0$ Hz), 4.74 (1H, d, $J = 11.7$ Hz), 4.65 (1H, dd, $J = 2.2, 6.0$ Hz), 4.48 (1H, dd, $J = 1.0, 6.0$ Hz), 4.31 (1H, d, $J = 6.5$ Hz), 4.30 (1H, dd, $J = 2.2, 3.6$ Hz), 4.10 (1H, dd, $J = 3.6, 6.5$ Hz), 4.00 (1H, dd, $J = 2.4, 13.6$ Hz), 3.81 (1H, dd, $J = 2.1, 13.6$

Hz), 3.25 (3H, s), 2.81 (3H, s), 1.49 (3H, s), 1.27 (3H, s); ^{13}C -NMR (100MHz, CDCl_3): 170.3, 166.2, 137.6, 134.8, 133.2, 129.7, 129.6, 129.5, 128.8, 128.7, 128.5, 128.4, 128.3, 128.25, 127.9, 127.8, 127.6, 112.8, 110.8, 86.4, 85.2, 80.9, 79.4, 74.9, 71.0, 61.2, 60.4, 55.8, 55.7, 31.1, 26.9, 25.1, 21.0, 14.1; IR ν_{max} (neat) cm^{-1} : 3065.3 (w), 3032.5 (w), 2990.0 (w), 2937.9 (m), 2108.5 (s), 1716.9 (s), 1641.6 (s), 1603.0 (w), 1585.7 (w), 1496.9 (w), 1452.6 (m), 1410.1 (w), 1383.1 (w), 1315.6 (w), 1275.1 (s), 1215.3 (m), 1178.6 (w), 1159.4 (w), 1113.1 (s), 1070.6 (s), 1028.2 (m), 866.1 (m), 756.2 (s), 713.7 (s), 667.5 (w), 515.1 (w); FAB-MS m/z (rel. int.): 661 (MH^+ , 13), 629 (18), 539 (12), 391 (17), 105 (100), 91 (100); FAB-HRMS m/z (MNa^+): Calcd. for $\text{C}_{35}\text{H}_{40}\text{O}_9\text{N}_4\text{Na}$, 683.2693; found 683.2666.

(2S,5S,6S)-6-Benzoyloxy-2-[benzyloxy-2-((2R,3R,4R,5R)-3,4-isopropylidenedioxy-5-methoxytetrahydrofuran-2-yl)methyl]-4-methyl-5-phenyl-1,4-diazepan-3-one (17): A solution of DMSO (76.4 μL , 1.08 mmol) in dry CH_2Cl_2 (8 mL) was added to a stirred solution of oxalyl chloride (46.9 μL , 0.538 mmol) in dry CH_2Cl_2 (2 mL) at -78°C . After 15 min, a CH_2Cl_2 (1 mL) solution of **16** (71.1 mg, 0.108 mmol) was added to the reaction mixture. Stirring was continued for 20 min at -78°C , and then Et_3N (450 μL , 3.23 mmol) was added. After 30 min at -78°C , the reaction mixture was warmed to rt and then the reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was diluted with CH_2Cl_2 , and extracted with CH_2Cl_2 (20 mL x 3). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Purification of the residue was accomplished by silica gel column chromatography (hexane/EtOAc, 10/1) to give the aldehyde. A EtOAc solution (6 mL) of the above aldehyde was hydrogenated on 10% $\text{Pd}(\text{OH})_2$ (5 mg) for 18 h at 25°C . Filtration and concentration afforded a crude product, which was purified by silica gel column chromatography (hexane/EtOAc, 5/1) to give pure **17** (25.7 mg, 0.0417 mmol, 2 steps 38.6%) as a colorless solid: Rf: 0.17 (hexane /EtOAc, 3/1); $[\alpha]_{\text{D}}^{20.1}$ -2.0 (*c* 1.2, CHCl_3); ^1H -NMR (400MHz, CDCl_3): 7.96 (2H, d, $J = 7.3$ Hz), 7.55-7.14 (13H, m), 5.74 (1H, ddd, $J = 1.4, 2.7, 5.4$ Hz), 5.12 (1H, d, $J = 5.4$ Hz), 4.89 (1H, d, $J = 11.2$ Hz), 4.81 (1H, s), 4.74 (1H, d, $J = 11.2$ Hz), 4.71 (1H, dd, $J = 1.7, 6.1$ Hz), 4.38 (1H, dd, $J = 1.7, 7.0$ Hz), 4.32 (1H, d, $J = 6.1$ Hz), 4.24 (1H, dd, $J = 2.4, 7.0$ Hz), 3.43 (1H, d, $J = 2.4$ Hz), 3.26 (1H, dd, $J = 2.7, 15.4$ Hz), 3.09 (1H, dd, $J = 1.4, 15.4$ Hz), 3.08 (3H, s), 2.91 (3H, s), 1.36 (3H, s), 1.15 (3H, s); ^{13}C -NMR (100MHz, CDCl_3): 176.0, 165.8, 139.2, 136.3, 133.5, 129.6, 129.4, 128.6, 127.8, 127.3, 125.8, 112.2, 111.1, 87.3, 85.3, 81.3, 79.3, 74.4, 72.1, 68.1, 64.7, 61.6, 55.6, 47.6, 38.7, 33.5, 30.3, 28.9, 26.8, 25.1, 23.7, 14.0, 10.9; IR ν_{max} (neat) cm^{-1} : 3061.4 (w), 3032.5 (w), 2988.1 (w), 2934.1 (m), 1716.9 (s), 1643.6 (s), 1603.0 (w), 1585.7

(w), 1496.9 (w), 1452.6 (m), 1396.6 (w), 1383.1 (w), 1373.5 (w), 1352.3 (w), 1315.6 (w), 1271.2 (s), 1211.4 (w), 1176.7 (w), 1159.4 (w), 1111.1 (s), 1070.6 (w), 1028.2 (w), 1001.2 (w), 976.1 (w), 870.0 (m), 827.6 (w), 790.9 (w), 736.9 (s), 713.7 (w), 700.2 (w); FAB-MS m/z (rel. int.): 617 (MH^+ , 31), 585 (15), 391 (15), 323 (14), 173 (3), 148 (100), 105 (56), 91 (72), 58 (66); FAB-HRMS m/z (MH^+): Calcd. for $C_{35}H_{41}O_8N_2$, 617.2863; found 617.2866.

(2*S*,5*S*,6*S*)-6-Benzoyloxy-2-[benzyloxy-2-((2*R*,3*R*,4*R*,5*R*)-3,4-isopropylidenedioxy-5-methoxytetrahydrofuran-2-yl)methyl]-1,4-dimethyl-5-phenyl-1,4-diazepan-3-one (18): To a solution of **17** (17.9 mg, 0.029 mmol), 37% HCHO (65.2 μ L, 0.87 mmol) and AcOH (5 μ L, 0.087 mmol) in MeCN (2 mL) was added $NaBH_3CN$ (49.2 mg, 0.78 mmol), at 0°C. After stirring was continued for 12 h, the reaction mixture was quenched with H_2O . The aqueous solution was extracted with CH_2Cl_2 . The combined organic layers were washed with brine and dried (Na_2SO_4). Filtration, concentration and silica gel column purification (hexane/EtOAc, 4/1) afforded **18** (15.6 mg, 0.0247 mmol, 85.3 %) as a colorless solid: Rf: 0.22 (hexane/EtOAc, 3/1); $[\alpha]_D^{25.2} +36.0$ (c 0.7, $CHCl_3$); 1H -NMR (400MHz, $CDCl_3$): 8.09 (2H, m), 7.65-7.19 (13H, m), 5.98 (1H, dt, $J = 4.4, 2.2$ Hz), 5.03 (1H, d, $J = 4.4$ Hz), 4.96 (1H, d, $J = 12.0$ Hz), 4.84 (1H, s), 4.62 (1H, dd, $J = 2.2, 3.3$ Hz), 4.54 (1H, d, $J = 12.0$ Hz), 4.42 (1H, dd, $J = 2.1, 6.1$ Hz), 4.37 (1H, dd, $J = 0.7, 6.1$ Hz), 3.95 (1H, dd, $J = 3.3, 8.1$ Hz), 3.62 (1H, d, $J = 8.1$ Hz), 3.45 (1H, dd, $J = 2.2, 16.0$ Hz), 3.30 (1H, dd, $J = 2.2, 16.0$ Hz), 3.26 (3H, s), 2.77 (3H, s), 2.68 (3H, s), 1.48 (3H, s), 1.21 (3H, s); ^{13}C -NMR (100MHz, $CDCl_3$): 173.0, 165.8, 139.6, 136.0, 133.6, 129.8, 129.5, 129.4, 128.7, 128.1, 127.7, 126.9, 125.5, 112.1, 110.2, 87.0, 85.5, 82.2, 74.4, 73.5, 65.7, 65.0, 56.7, 54.9, 38.6, 38.2, 26.9, 25.1; IR ν_{max} (neat) cm^{-1} : 2936.0 (m), 1716.9 (s), 1645.5 (s), 1496.9 (w), 1450.6 (m), 1352.3 (w), 1313.7 (w), 1273.2 (s), 1211.4 (m), 1159.4 (w), 1111.1 (s), 1070.6 (w), 1028.2 (w), 868.1 (m), 756.2 (m), 713.7 (m), 698.3 (w), 659.7 (w); FAB-MS m/z (rel. int.): 632 (46), 631 (MH^+ , 97), 599 (42), 391 (32), 336 (100), 105 (72), 91 (84); FAB-HRMS m/z (MH^+): Calcd. for $C_{36}H_{43}O_8N_2$, 631.3019; found 631.3026.

(2*S*,5*S*,6*S*)-6-Benzoyloxy-2-[benzyloxy-2-((2*R*,3*R*,4*R*,5*R*)-3,4,5-triacetyltetrahydrofuran-2-yl)-methyl]-1,4-dimethyl-5-phenyl-1,4-diazepan-3-one (20): A solution of **18** (9.7mg, 15 μ mol) in THF (1 mL) was added 1N HCl (2 mL). After stirring was continued for 10 h at 56°C, powdered $NaHCO_3$ was added to the reaction mixture to quench the reaction, extracted with EtOAc, dried over Na_2SO_4 and the solvent was removed. The residue of the triol (**19**) was used in the next reaction. Under Ar, a solution of

crude **19** in CH₂Cl₂ (1 mL) was added acetic anhydride (14.2 μ L, 0.15 mmol), triethylamine (62.7 μ L, 0.45 mmol) and DMAP (0.2 mg, 1.5 μ mol) at 25°C. After stirring was continued for 1 h, the reaction mixture was washed with 1N HCl, H₂O and aqueous NaHCO₃. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was removed. Filtration, concentration and silica gel column purification (hexane/EtOAc, 1/1) gave **20** (5.1 mg, 7.3 μ mol, 2 steps 48.4%) as a colorless solid: Rf: 0.34 (hexane/EtOAc, 1/1); $[\alpha]_D^{23.0} +26.3$ (*c* 0.24, CHCl₃); ¹H-NMR (400MHz, CDCl₃): 8.09 (2H, d, *J* = 7.1 Hz), 7.72-7.22 (13H, m), 6.23 (1H, d, *J* = 4.6 Hz), 5.93 (1H, dt, *J* = 4.4, 2.2 Hz), 5.33 (1H, dd, *J* = 2.0, 6.3 Hz), 5.12 (1H, dd, *J* = 4.6, 6.3 Hz), 5.05 (1H, d, *J* = 4.4 Hz), 4.93 (1H, t, *J* = 2.0 Hz), 4.78 (1H, d, *J* = 10.4 Hz), 4.61 (1H, d, *J* = 10.4 Hz), 4.11 (1H, dd, *J* = 2.0, 9.3 Hz), 3.70 (1H, d, *J* = 9.3 Hz), 3.40 (1H, dd, *J* = 2.2, 15.7 Hz), 3.35 (1H, dd, *J* = 2.2, 15.7 Hz), 3.22 (3H, s), 2.67 (3H, s), 2.16 (3H, s), 2.11 (3H, s), 2.04 (3H, s); ¹³C-NMR (100MHz, CDCl₃): 176.4, 170.3, 170.0, 169.3, 165.9, 137.9, 134.8, 133.6, 130.9, 129.8, 129.5, 129.4, 128.82, 128.77, 128.70, 128.5, 128.1, 127.9, 125.6, 112.7, 93.9, 85.4, 75.9, 74.9, 74.2, 71.0, 70.5, 68.2, 65.7, 56.3, 38.7, 38.4, 30.4, 28.9, 23.0, 21.3, 20.8(Cx2); IR (neat): 2926.4 (m), 2855.0 (w), 1747.7 (s), 1645.5 (m), 1603.0 (w), 1496.9 (w), 1450.6 (w), 1396.6 (w), 1371.6 (w), 1313.7 (w), 1257.7 (s), 1224.9 (s), 1176.7 (w), 1109.2 (m), 1095.7 (m), 1070.6 (m), 1026.3 (m), 1010.8 (m), 939.4 (w), 914.4 (w), 756.2 (s), 713.7 (m), 698.3 (m), 659.7 (w); FAB-MS *m/z* (rel. int.): 703 (MH⁺, 7), 391 (4), 365 (3), 267 (4), 74 (23), 58 (6); FAB-HRMS *m/z* (MH⁺): Calcd. for C₃₈H₄₃O₁₁N₂, 703.2867; found 703.2851.

1 α and **1 β** of (2*R*,3*R*,4*R*)-2,3-Diacetyloxy-5-(*N*-benzyl-*N*-nitrobenzenesulfonamide)-1-uracil-D-ribofuranose (**25 α** ,**25 β**): Under Ar, to a solution of **23 β** (161.5 mg, 0.29 mmol) in MeCN (5 mL) was added a solution of bistrimethylsilyluracil (**21**) (226 mg, 0.88 mmol) in MeCN (1.5 mL) and SnCl₄ (103 μ L, 0.88 mmol) at 0°C. After stirring was continued for 3 days at 25°C, the solvent was removed and the reaction was quenched by aqueous NaHCO₃. Filtration on Celite, concentration and silica gel preparative TLC purification (EtOAc) afforded **25 α** (23 mg, 0.038 mmol, 13 %) as a colorless solid and **25 β** (124 mg, 0.20 mmol, 71 %) as a colorless solid: Data for **25 α** ; Rf: 0.50 (EtOAc); $[\alpha]_D^{22.2} +12.1$ (*c* 1.28, CHCl₃); ¹H-NMR (400MHz, CDCl₃): 9.94 (1H, br s), 8.00 (1H, d, *J* = 7.6 Hz), 7.70-7.60 (4H, m), 7.28-7.24 (5H, m), 6.25 (1H, s), 5.74 (1H, dd, *J* = 1.2, 7.6 Hz), 5.66 (1H, dd, *J* = 2.2, 6.6 Hz), 5.55 (1H, t, *J* = 7.1 Hz), 4.74 (1H, d, *J* = 15.5 Hz), 4.54 (1H, d, *J* = 15.5 Hz), 4.20 (1H, dt, *J* = 3.4, 7.1 Hz), 3.69 (1H, dd, *J* = 3.4, 15.6 Hz), 3.59 (1H, dd, *J* = 7.1, 15.6 Hz), 2.08 (3H, s), 2.05 (3H, s); ¹³C-NMR (100MHz, CDCl₃): 169.8,

162.2, 151.8, 147.6, 140.1, 134.9, 133.9, 133.4, 131.6(Cx2), 131.1, 128.8(Cx2), 128.0 (Cx2), 124.2 (Cx2), 101.9, 85.7, 79.1, 73.3, 71.2, 51.9, 47.8, 20.6, 20.4; IR $\nu_{\max}$ (neat) cm^{-1} : 3431.8 (w), 3022.8 (w), 1743.9 (s), 1666.7 (s), 1543.2 (s), 1496.9 (w), 1429.4 (w), 1373.5 (m), 1248.1 (m), 1219.2 (m), 1163.2 (m), 1097.6 (w), 1037.8 (w), 1014.7 (w), 935.6 (w), 852.6 (w), 808.3 (w), 756.2 (s), 700.2 (w), 667.5 (m), 582.6 (w), 536.3 (w); FAB-MS m/z (rel. int.): 625 (MNa^+ , 100), 413 (100), 239 (24), 188 (29), 172 (93), 148 (100), 91 (100); FAB-HRMS m/z (MNa^+): Calcd. for $\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_{11}\text{SNa}$, 625.1216; found 625.1190. Data for **25b**; Rf: 0.57 (EtOAc); $[\alpha]_{\text{D}}^{22.6} +19.8^\circ$ (c 2.35, CHCl_3); $^1\text{H-NMR}$ (400MHz, CDCl_3): 8.75 (1H, br s), 8.00 (1H, d, $J = 8.1$ Hz), 7.72-7.60 (3H, m), 7.27-7.14 (6H, m), 5.75 (1H, dd, $J = 2.2, 8.1$ Hz), 5.69 (1H, d, $J = 4.4$ Hz), 5.27 (1H, dd, $J = 4.4, 6.3$ Hz), 5.08 (1H, t, $J = 6.3$ Hz), 4.66 (1H, d, $J = 15.4$ Hz), 4.53 (1H, d, $J = 15.4$ Hz), 4.16 (1H, ddd, $J = 3.3, 6.3, 8.8$ Hz), 3.71 (1H, dd, $J = 3.3, 15.6$ Hz), 3.55 (1H, dd, $J = 8.8, 15.6$ Hz), 2.08 (3H, s), 2.07 (3H, s); $^{13}\text{C-NMR}$ (100MHz, CDCl_3): 169.7, 169.5, 149.9, 147.8, 141.0, 134.7, 133.7, 133.3, 131.8, 131.3, 128.7 (Cx2), 128.3 (Cx2), 128.1, 124.3, 103.1, 90.1, 79.8, 72.6, 70.9, 52.0, 48.6, 20.4(Cx2); IR $\nu_{\max}$ (neat) cm^{-1} : 3026.7 (m), 1749.6 (s), 1693.7 (s), 1545.2 (s), 1496.9 (w), 1456.4 (m), 1373.5 (s), 1242.3 (s), 1219.2 (m), 1165.1 (s), 1099.6 (m), 1016.6 (m), 933.7 (w), 900.6 (w), 852.6 (w), 812.1 (w), 754.3 (s), 700.2 (w), 667.5 (w), 652.0 (w), 582.6 (m); FAB-MS m/z (rel. int.): 603 (MH^+ , 100), 588 (53), 553 (45), 460 (49), 417 (100), 277 (100), 185 (100), 91 (100), 75 (100); FAB-HRMS m/z (MH^+): Calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_4\text{O}_{11}\text{S}$, 603.1397; found 603.1426.

(1R,2R,3R,4R)-2,3-Isopropylidenedioxy-5-(N-benzyl-N-nitrobenzenesulfonamide)-1-uracil- β -D-ribofuranose (27): To a solution of **25b** (130.5 mg, 0.217 mmol) in MeOH (5 mL) and H_2O (5 mL) was added potassium carbonate (120 mg, 0.87 mmol). After stirring was continued for 120 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous solution was extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and the solvent was removed. The residue of the diol compound was used in the next reaction without further purification. A solution of crude diol compound in CH_2Cl_2 (5 mL) was added 2,2-dimethoxypropane (267 μL , 2.17 mmol) and (+)-camphorsulfonic acid (5.1 mg, 22 μmol) at 25°C . After stirring was continued for 1 h, the reaction mixture was quenched with Et_3N (151 μL , 1.09 mmol) and the solvent was removed. The residue was purified on silica gel preparative-TLC with EtOAc as an eluent to give **27** (184 mg, 0.194 mmol, 89.4%) as a white solid. Rf: 0.72 (EtOAc); $[\alpha]_{\text{D}}^{23.7} +47.0^\circ$ (c 2.68, CHCl_3); $^1\text{H-NMR}$ (400MHz, CDCl_3): 9.53 (1H, br, d, $J = 16.2$ Hz), 7.94 (1H, d, $J = 7.6$ Hz), 7.61-7.46 (3H, m), 7.20-7.07 (6H, m), 5.66 (1H, dd, $J = 2.1,$

8.0 Hz), 5.35 (1H, d, $J = 1.4$ Hz), 4.89 (1H, dd, $J = 1.4, 6.4$ Hz), 4.58 (1H, d, $J = 15.7$ Hz), 4.55 (1H, dd, $J = 4.4, 6.4$ Hz), 4.49 (1H, d, $J = 15.7$ Hz), 4.08 (1H, ddd, $J = 4.3, 4.4, 8.4$ Hz), 3.55 (1H, dd, $J = 8.4, 15.4$ Hz), 3.49 (1H, dd, $J = 4.3, 15.4$ Hz), 1.38 (3H, s), 1.20 (3H, s); ^{13}C -NMR (100MHz, CDCl_3): 163.5, 149.8, 147.7, 143.4, 135.1, 133.8, 133.4, 131.8, 131.3, 128.6(Cx2), 128.1, 127.9, 124.3, 114.3, 102.6, 96.1, 86.3, 84.1, 82.4, 60.4, 51.6, 48.6, 27.0, 25.2; IR ν_{max} (neat) cm^{-1} : 3453.2 (w), 3218.1 (w), 3025.8 (w), 1693.7 (s), 1545.2 (s), 1496.9 (w), 1456.4 (m), 1375.4 (m), 1271.2 (m), 1215.3 (m), 1163.2 (s), 1126.6 (w), 1091.8 (m), 1066.8 (m), 1007.0 (w), 941.4 (w), 883.5 (w), 852.6 (w), 756.2 (s), 698.3 (w), 677.5 (w), 652.0 (w), 580.6 (m); FAB-MS m/z (rel. int.): 559 (MH^+ , 100), 413 (81), 391 (100), 329 (93), 307 (100), 257 (76), 175 (100), 153 (100), 136 (100), 91 (100); FAB-HRMS m/z (MH^+): Calcd. for $\text{C}_{25}\text{H}_{27}\text{O}_9\text{N}_4\text{S}$, 559.1499; found 559.1471.

(1R,2R,3R,4R)-2,3-Isopropylidenedioxy-5-(N-benzylamino)-1-uracil- β -D-ribofuranose (28): To a solution of PhSH (45 μL , 0.44 mmol) and KOH (24.7 mg, 0.44 mmol) in MeCN (5 mL) was added a solution of **27** (98.4 mg, 0.18 mmol) in MeCN (5 mL). The reaction mixture was stirred for 12 h at 50°C and then the reaction was quenched with H_2O . The aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried (Na_2SO_4). Filtration, concentration and silica gel preparative-TLC purification (EtOAc) afforded **28** (41.7 mg, 0.112 mmol, 63 %) as a white solid. Rf: 0.25 (EtOAc). $[\alpha]_{\text{D}}^{23.6} +13.5^\circ$ (c 1.96, CHCl_3); ^1H -NMR (400MHz, CDCl_3): 7.29-7.15 (6H, m), 5.61 (1H, d, $J = 2.2$ Hz), 5.60 (1H, d, $J = 8.3$ Hz), 4.87 (1H, dd, $J = 2.2, 6.6$ Hz), 4.67 (1H, dd, $J = 4.5, 6.6$ Hz), 4.15 (1H, ddd, $J = 4.4, 4.5, 6.8$ Hz), 3.79 (1H, d, $J = 13.3$ Hz), 3.75 (1H, d, $J = 13.3$ Hz), 2.89 (1H, dd, $J = 4.4, 12.7$ Hz), 2.83 (1H, dd, $J = 6.8, 12.7$ Hz), 1.50 (3H, s), 1.27 (3H, s); ^{13}C -NMR (100MHz, CDCl_3): 163.2, 149.9, 142.1, 139.7, 128.5(Cx2), 128.1(Cx2), 127.1, 114.6, 102.6, 93.8, 86.1, 84.2, 81.8, 53.7, 50.4, 27.2, 25.3; IR ν_{max} (neat) cm^{-1} : 3538.7 (w), 3218.1 (w), 2990.0 (w), 2936.0 (w), 2831.8 (w), 1693.7 (s), 1496.9 (w), 1456.4 (m), 1383.1 (m), 1271.2 (m), 1215.3 (m), 1159.4 (w), 1088.0 (s), 970.3 (w), 883.5 (w), 862.3 (w), 810.2 (w), 754.3 (s), 700.2 (w), 667.5 (w), 571.0 (w), 547.8 (w), 511.2 (w); FAB-MS m/z (rel. int.): 374 (MH^+ , 100), 262 (23), 184 (20), 133 (13), 119 (24), 91 (98); FAB-HRMS m/z (MH^+): Calcd. for $\text{C}_{19}\text{H}_{24}\text{O}_5\text{N}_3$, 374.1716; found 374.1688.

(1R,2R,3R,4R)-2,3-Isopropylidenedioxy-5-(N-benzyl-N-methylamino)-1-uracil- β -D-ribofuranose (29): To a solution of **28** (39.6 mg, 0.11 mmol), 37wt%-HCHO (238 μL , 3.18 mmol) and acetic acid (18 μL , 0.32 mmol) in MeCN (5 mL) was added NaBH_3CN (200 mg, 2.86 mmol) at 0°C. After stirring was

continued for 12 h at 25°C, the reaction mixture was quenched with H₂O. The aqueous solution was extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried (Na₂SO₄). Filtration, concentration and silica gel preparative-TLC purification (EtOAc) afforded **29** (23.9mg, 0.062 mmol, 58 %) as a white solid. Rf: 0.49 (EtOAc); $[\alpha]_{\text{D}}^{23.2} +22.9^{\circ}$ (c 0.36, CHCl₃); ¹H-NMR (400MHz, CDCl₃): 7.30-7.18 (6H, m), 5.60 (1H, d, *J* = 2.1 Hz), 5.59 (1H, d, *J* = 8.1 Hz), 4.81 (1H, dd, *J* = 2.1, 6.6 Hz), 4.56 (1H, dd, *J* = 4.1, 6.6 Hz), 4.27 (1H, ddd, *J* = 4.1, 4.6, 6.8 Hz), 3.58 (1H, d, *J* = 13.2 Hz), 3.49 (1H, d, *J* = 13.2 Hz), 2.65 (1H, dd, *J* = 8.3, 13.2 Hz), 2.54 (1H, dd, *J* = 4.6, 13.2 Hz), 2.27 (3H, s), 1.51 (3H, s), 1.28 (3H, s); ¹³C-NMR (100MHz, CDCl₃): 164.0, 150.1, 142.3, 137.3, 129.2 (Cx2), 128.3 (Cx2), 127.4, 114.5, 102.2, 94.1, 84.7, 84.5, 82.6, 62.3, 58.6, 42.4, 27.0, 25.2; IR ν_{max} (neat) cm⁻¹: 3453.2 (s), 2928.3 (w), 2853.1 (w), 2406.0 (w), 1674.4 (s), 1456.4 (m), 1383.1 (m), 1271.2 (m), 1217.2 (m), 1159.4 (w), 1113.1 (m), 1076.4 (m), 860.4 (w), 812.1 (w), 748.5 (m), 700.2 (w); FAB-MS *m/z* (rel. int.): 388 (MH⁺, 100), 276 (40), 242 (7), 186 (8), 133 (100), 91 (100); FAB-HRMS *m/z* (MH⁺): Calcd. for C₂₀H₂₆O₅N₃, 388.1872; found 388.1856.

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