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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 griseosporeus*[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 peptideglycan 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-Pelletier[12] for the assignment of the stereochemistry.

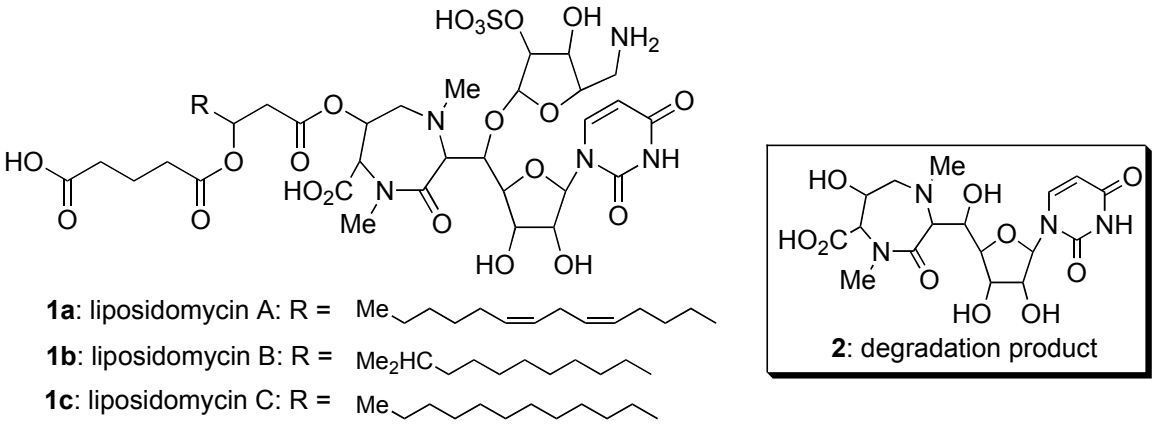


Figure 1. The structure of liposidomycins

Synthesized compound (**8**) by the Knapp group has all functional groups of the diazepanone ring part. From the NMR studies of **8**, the stereochemistry at the diazepanone part was assigned to be 5'(*S*), 6'(*S*), 2'''(*S*) and 3'''(*S*) stereochemistry.[13,14] They also succeeded in the synthesis of compound (**9**) that is one of the degradation products of liposidomycin, the stereochemistry of the sugar part was determined.[15] In 2005, Matsuda *et al*. succeeded in the total synthesis of caprazol (**4**), a core structure of caprazamycin (**Figure 2**).[16]

RESULTS AND DISCUSSION

We previously studied the assignment of liposidomycin stereochemistry, and the synthesis of 1,4-diazepane-3-one analog was reported.[17] In the synthesis of caprazol, uridine was used as the starting material, and the diazepanone ring part was synthesized subsequently. In this study, we examined the uracil group introduction into the triacetyl compound (**20**). In our synthetic approach for degradation product (**2**), a uracil group will be introduced after the construction of the diazepanone ring part.

By the coupling of the amine part (**10**)[18] and the carboxylic acid part (**11**), the precursor of diazepanone compound (**12**) was synthesized. Selective hydrolysis of one acetonide group of **12** under acidic conditions gave 1,2-diol (**13**) in 76% yield. The primary hydroxy group and secondary hydroxyl group were protected with the TBDMS group and Bz group to afford **15** in good yield.[19] The deprotection of the TBDMS group by HF-pyridine gave **16** in 95% yield. The diazepanone ring construction was achieved by a reductive amination method. The aldehyde obtained by Swern oxidation was treated with 10% Pd-C/H_2 in EtOAc to produce 1,4-diazepane-3-one compound (**17**) in 39% yield (2 steps). The methylation of the *N*-1 position at the diazepanone ring part was carried out with HCHO, AcOH and $NaBH_3CN$ in MeCN to give *N*-methyl amine (**18**) in 85% yield (**Scheme 1**).

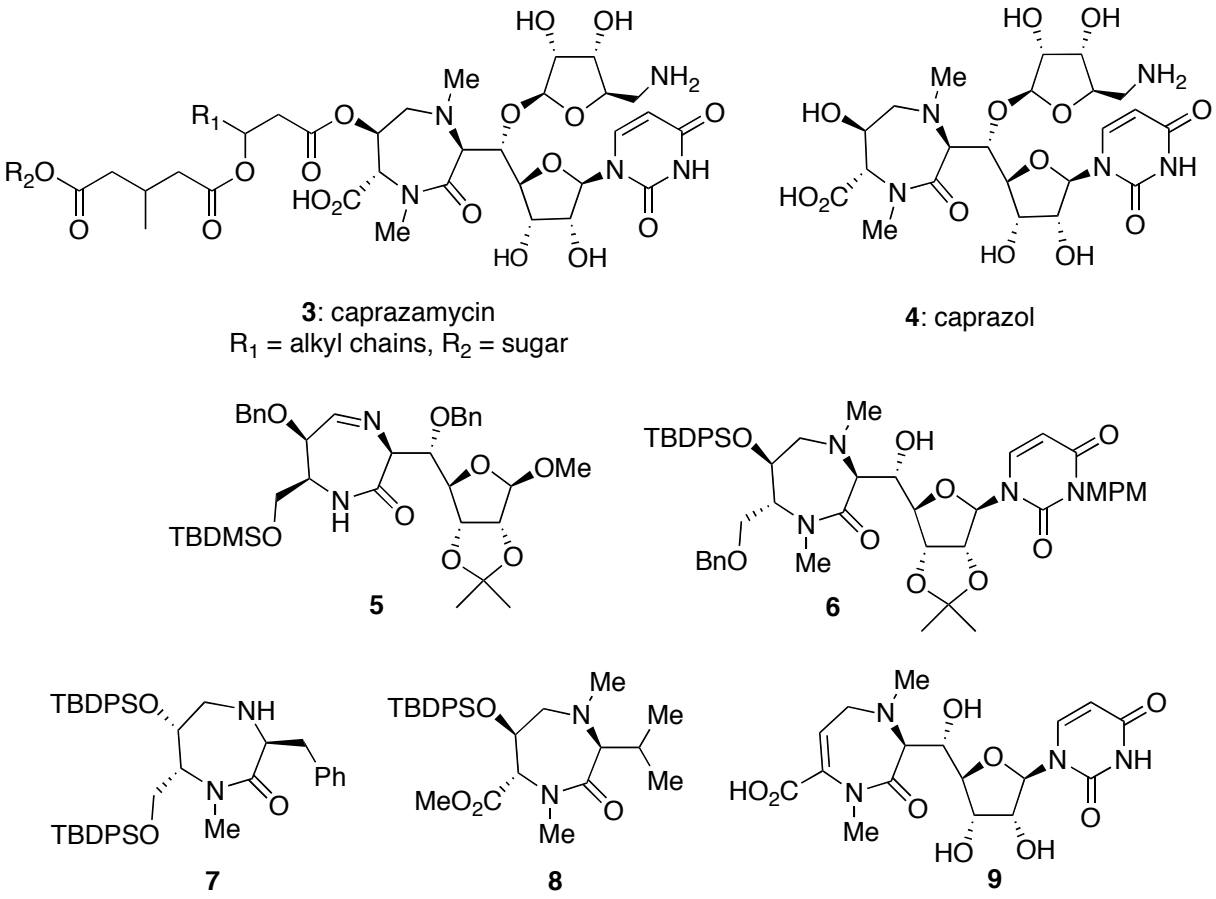
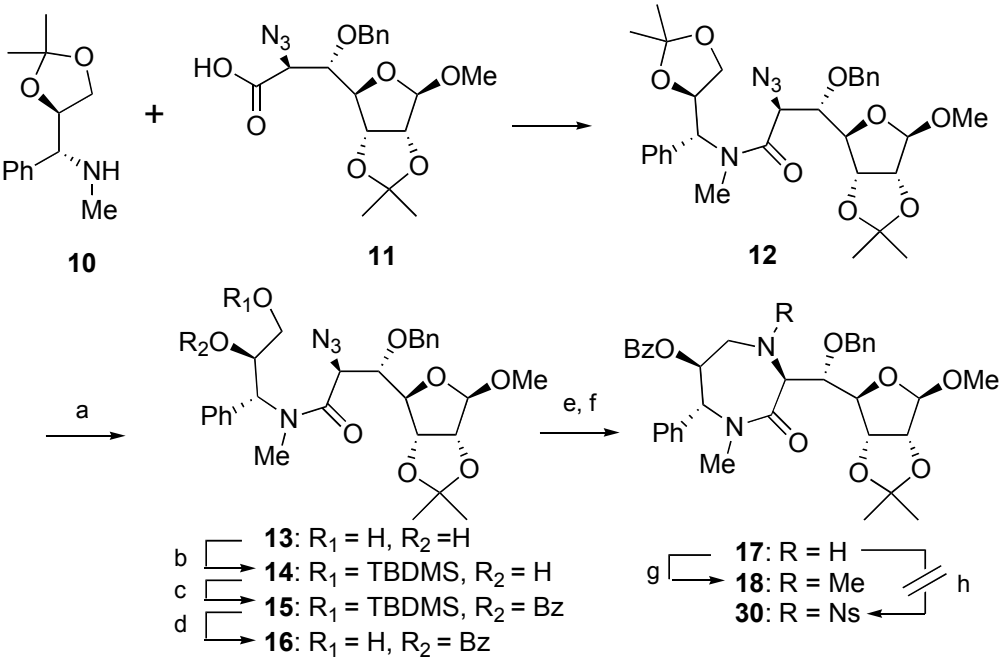


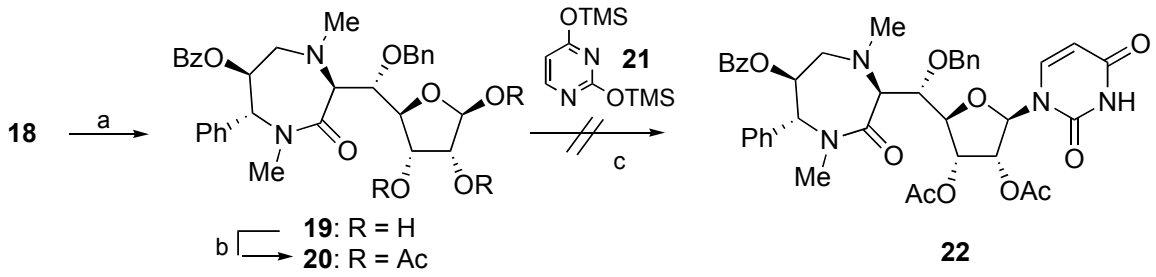
Figure 2. The structure of caprazamycin, caprazol and synthesized liposidomycin model compounds



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, $(COCl)_2$, 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 Ac_2O, TEA, DMAP in CH_2Cl_2 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, $SnCl_4$, or $BF_3 \cdot OEt_2$) 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]



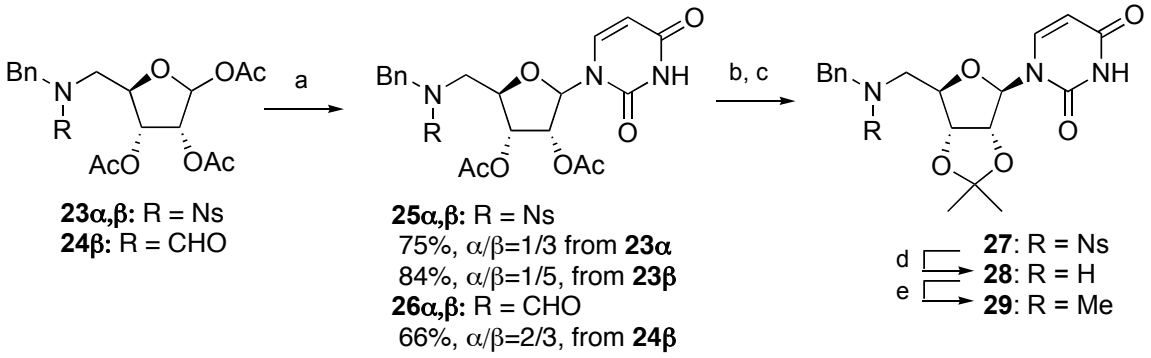
a. 1N HCl, THF, 56 ˚C; b. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (2 steps 48%);
c. Lewis acids, **21**, MeCN

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 **23α** ($J_{1,2}$ = 0 Hz) with **21** in the presence of $SnCl_4$ as a Lewis acid in MeCN proceeded smoothly to obtain the target compound **25α** ($J_{1,2}$ = 0 Hz) and **25β** ($J_{1,2}$ = 4.4 Hz) in 75% yield with 1/3 selectivity. This selectivity was increased by using **23β** ($J_{1,2}$ = 4.6 Hz) and **21** to α/β = 1/5 selectivity with 84% yield. The *N*-glycosylation of **24β** having formyl group also gave **26α** and **26β** in 66% yield with 2/3 selectivity. After separation of **25α** and **25β**, the Ac group of **25β** 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-dimethoxpropane, 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. ^{1}H-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 (Sperical, Neutral) was used for column chromatography.

***N*-Methyl-*N*-[(1R,2R)-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, $CHCl_3$); ^{1}H-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 $C_{28}H_{37}O_8N_4$, 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); $[\alpha]_D^{21.4}$ -43.2 (c 3.0, $CHCl_3$); ^{1}H-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 $C_{34}H_{51}O_8N_4Si$, 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); $[\alpha]_D^{21.6}$ -79.7 (*c* 2.5, $CHCl_3$); ^{1}H-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 $C_{41}H_{55}O_9N_4Si$, 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); $[\alpha]_D^{23.1}$ -86.5 (*c* 3.1, $CHCl_3$); ^{1}H-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 $C_{35}H_{40}O_9N_4Na$, 683.2693; found 683.2666.

(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]-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% $Pd(OH)_2$ (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); $[\alpha]_D^{20.1}$ -2.0 (*c* 1.2, $CHCl_3$); ^{1}H-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 μL, 0.87mmol) and AcOH (5 μL, 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, $CHCl_3$); ^{1}H-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 μmol) 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 CH_2Cl_2 (1 mL) was added acetic anhydride (14.2 μL, 0.15 mmol), triethylamine (62.7 μL, 0.45 mmol) and DMAP (0.2 mg, 1.5 μmol) at 25°C. After stirring was continued for 1 h, the reaction mixture was washed with 1N HCl, H_2O and aqueous $NaHCO_3$. The organic phase was washed with brine, dried over Na_2SO_4 and the solvent was removed. Filtration, concentration and silica gel column purification (hexane/EtOAc, 1/1) gave **20** (5.1 mg, 7.3 μmol, 2 steps 48.4%) as a colorless solid: Rf: 0.34 (hexane/EtOAc, 1/1); $[\alpha]_D^{23.0}$ +26.3 (*c* 0.24, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$): 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); ^{13}C-NMR (100MHz, $CDCl_3$):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 $C_{38}H_{43}O_{11}N_2$, 703.2867; found 703.2851.

1α and 1β of (2*R*,3*R*,4*R*)-2,3-Diacetyloxy-5-(*N*-benzyl-*N*-nitrobenzenesulfonamide)-1-uracil-D-ribofuranose (25α,β): Under Ar, to a solution of **23β** (161.5 mg, 0.29 mmol) in MeCN (5 mL) was added a solution of bistrimethylsilyluracil (**21**) (226 mg, 0.88mmol) in MeCN (1.5 mL) and $SnCl_4$ (103 μL, 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 $NaHCO_3$. Filtration on Celite, concentration and silica gel preparative TLC purification (EtOAc) afforded **25α** (23 mg, 0.038 mmol, 13 %) as a colorless solid and **25β** (124 mg, 0.20 mmol, 71 %) as a colorless solid: Data for **25α**; Rf: 0.50 (EtOAc); $[\alpha]_D^{22.2}$ +12.1 (*c* 1.28, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$): 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); ^{13}C-NMR (100MHz, $CDCl_3$): 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 ν_{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 $C_{26}H_{26}N_4O_{11}SNa$, 625.1216; found 625.1190. Data for **25β**; Rf: 0.57 (EtOAc); $[\alpha]_D^{22.6}$ +19.8° (*c* 2.35, $CHCl_3$); ^{1}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}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 ν_{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 $C_{26}H_{27}N_4O_{11}S$, 603.1397; found 603.1426.

(1*R*,2*R*,3*R*,4*R*)-2,3-Isopropylidenedioxy-5-(*N*-benzyl-*N*-nitrobenzenesulfonamide)-1-uracil-β-D-ribofuranose (27): To a solution of **25β** (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); $[\alpha]_D^{23.7}$ +47.0° (*c* 2.68, $CHCl_3$); ^{1}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 $C_{25}H_{27}O_9N_4S$, 559.1499; found 559.1471.

(1*R*,2*R*,3*R*,4*R*)-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). $[\alpha]_D^{23.6}$ +13.5˚ (*c* 1.96, $CHCl_3$); ^{1}H-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 $C_{19}H_{24}O_5N_3$, 374.1716; found 374.1688.

(1*R*,2*R*,3*R*,4*R*)-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 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 preparative-TLC purification (EtOAc) afforded **29** (23.9mg, 0.062 mmol, 58 %) as a white solid. Rf: 0.49 (EtOAc); $[\alpha]_D^{23.2}$ +22.9° (*c* 0.36, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$): 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) ; ^{13}C-NMR (100MHz, $CDCl_3$): 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 $C_{20}H_{26}O_5N_3$, 388.1872; found 388.1856.

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