Synthesis of a Dihydropyranonucleoside Using an Oxidative Glycosylation Reaction Mediated by Hypervalent Iodine

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Abstract: As a part of our ongoing studies of structure–activity relationships regarding cyclohexenyl nucleosides, we were prompted to synthesize a dihydropyranonucleoside as a potential anti-HIV agent. The synthesis of a glycal moiety started from but-2-enediol, which was converted into a di-PMB derivative in several steps. The introduction of an allyl group followed by ring-closing metathesis gave a dihydropyran derivative. After isomerization of the double bond catalyzed by Wilkinson's catalyst, the resulting glycal, 2,3-bis[(4-methoxybenzyloxy)methyl]-3,4-dihydro-2*H*-pyran, was subjected to an oxidative glycosylation reaction mediated by hypervalent iodine. Treatment of 2,3-bis[(4-methoxybenzyloxy)methyl]-3,4-dihydro-2*H*-pyran with $(PhSe)_2$/$PhI(OAc)_2$/TMSOTf (cat.) gave the desired pyranyluracils as a mixture of anomers that were converted into the final target, dihydropyranocytidine, after several manipulations and separation of the anomers.

Key words: glycosylation, nucleoside, oxidation, iodine, antiviral

Since the discovery of AZT,[1] nucleoside derivatives have been recognized as promising targets for the development of novel therapeutics that are effective in treating HIV, a causative agent of AIDS, because the triphosphate forms of AZT and other anti-HIV nucleosides can efficiently inhibit the reverse transcriptase that is encoded by HIV.[2] To date, many anti-HIV drugs designed based on nucleosides have been approved and extensively used in the clinical field.[2] Considerable interest continues to exist in the search for new anti-HIV nucleosides via the design and synthesis of nucleosides that contain a modified sugar portion.[2,3] One such early example is stavudine (D4T), a dideoxydidehydro analogue of thymidine (Figure 1).[4] Since the vast majority of naturally occurring nucleosides are 'D-nucleosides', the biologically active nucleosides often contain a skeleton constructed from a D-sugar, as exemplified by stavudine.[2,3] On the other hand, several 'L-nucleosides' have proved to have antiviral and antitumor activity because deoxynucleoside kinase, a key enzyme in the formation of active triphosphate forms of anti-HIV nucleosides, is capable of recognizing several L-nucleoside analogues as well as D-nucleosides and it converts them into their monophosphates.[2,5] The HIV drug lamivudine (Figure 1) is an example where the L-isomer of 3′-deoxy-3′-thiacytidine is more active against HIV and less toxic.[6] These results clearly suggest that the both D- and L-isomers of nucleosides can possess anti-HIV activity.

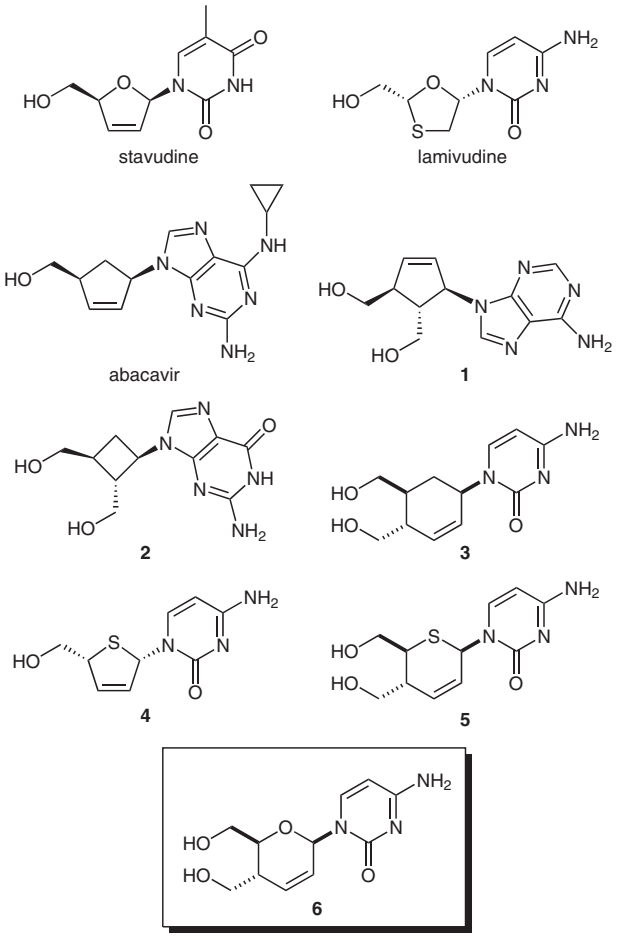

Figure 1 Structures of anti-HIV nucleosides

Based on these considerations, the focus of our recent studies has been on the synthesis of racemic nucleoside derivatives constructed on a novel sugar skeleton.[7] Carbocyclic nucleosides are a class of interesting compounds that have anti-HIV activity: Abacabir was approved as an anti-HIV drug (Figure 1).[2,8] Its analogue **1**[9] and the cyclobutane nucleoside **2**,[10] which is a carbocyclic analogue of oxetanosine, were also reported to have anti-HIV activity. As a new carbocyclic nucleoside, we designed and synthesized the racemic cyclohexenylcytosine **3**, which

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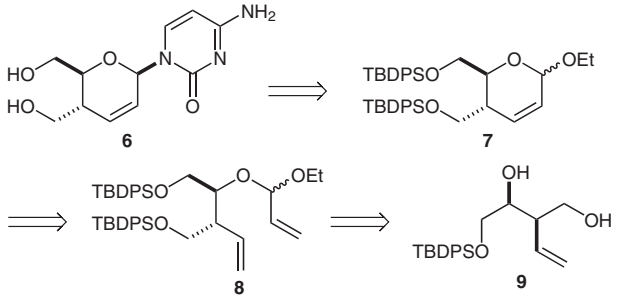
showed weak activity against HIV.[7c] To improve the anti-HIV activity of **3**, we next designed the dihydrothiopyranonucleoside **5**, since L-4′-thioD4C **4** was proved to possess potent anti-HIV activity.[7f] The synthesis of **5** was achieved by ring-closing metathesis and Pummerer-type thioglycosylation as key reactions; **5** showed significant anti-HIV activity.[7f]

As a part of our ongoing structure–activity relationship studies of the cyclohexenyl nucleosides described above, we herein report the synthesis of dihydropyranonucleoside **6** as a potential anti-HIV agent (Figure 1).

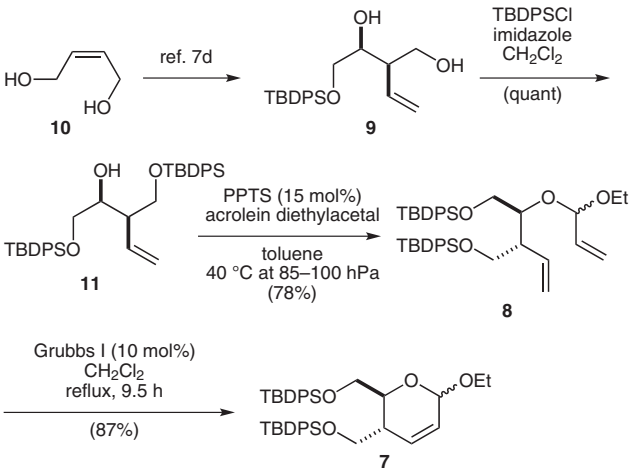
Our initial attempt to synthesize dihydropyranonucleoside **6** involved a series of reactions shown in Scheme 1. A sugar donor **7** for the glycosylation reaction could be prepared by ring-closing metathesis of **8** (Scheme 1).



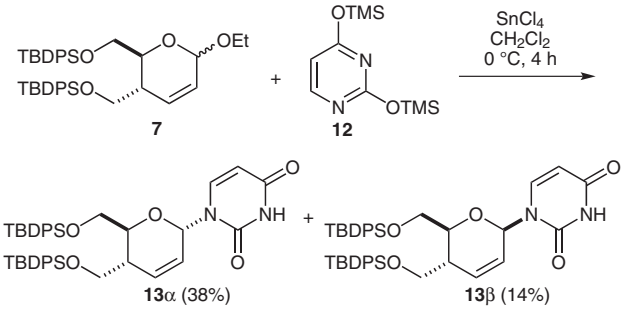
Scheme 1 Retrosynthesis of dihydropyranonucleoside **6**

cis-But-2-ene-1,4-diol (**10**) was converted into the homoallyl alcohol derivative **9**,[7d] the primary hydroxyl group of which was selectively protected by a TBDPS group to give **11**. Introduction of a mixed acetal unit into **11** was achieved by treatment with acrolein diethyl acetal in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS)[11] to give diene **8** in 78% yield. Ring-closing metathesis of **8** using Grubbs first-generation catalyst gave the dihydropyran derivative **7** in good yield (Scheme 2). The dihydropyran derivative **7** thus obtained was subjected to glycosylation reaction under Vorbrüggen conditions.[12] Treatment of **7** with *O*,*O*′-bis(trimethylsilyl)uracil (**12**) in the presence of tin(IV) chloride gave a mixture of α- and β-anomers **13** in 38% and 14% yield, respectively (Scheme 3). Although the dihydropyranonucleosides were obtained, the reaction lacks reproducibility. In addition, there was a fatal drawback associated with this reaction: the undesired α-anomer **13α** was the predominant reaction product.

To overcome this problem, we employed an alternative strategy, namely, glycosylation to produce a glycal and subsequent elimination. We previously reported on a novel glycosylation reaction using a glycal derivative as a sugar donor, which proceeded under oxidative conditions using the diphenyl diselenide/(diacetoxyiodo)benzene/trimethylsilyl triflate system.[13] By analogy, the desired **6** would be obtained from a 2′-seleno derivative **14** that could be synthesized by oxidative coupling between glycal derivative **15** and a silylated nucleobase. The glycal **15**

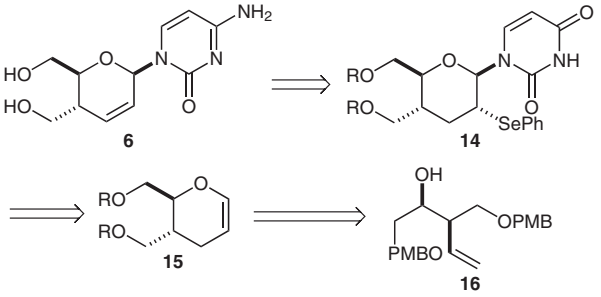


Scheme 2 Synthesis of the dihydropyran derivative **7**



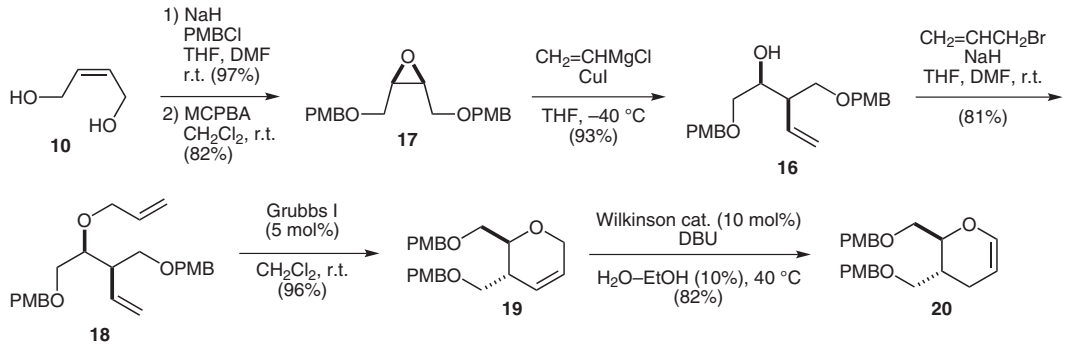
Scheme 3 Glycosylation reaction of **7**

should be obtainable from a homoallyl alcohol derivative **16** using a reaction scheme similar to that described above (Scheme 4).



Scheme 4 Revised retrosynthesis of dihydropyranonucleoside **6**

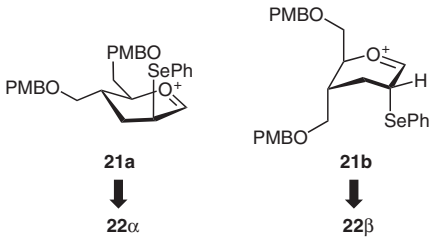
Protection of *cis*-but-2-ene-1,4-diol (**10**) with as its 4-methoxybenzyl (PMB) ether followed by epoxidation using 3-chloroperoxybenzoic acid permitted **10** to be converted into the epoxide **17** in 82% yield. The epoxide ring of **17** was cleaved by treatment with vinylmagnesium chloride to give the homoallyl alcohol derivative **16**, the hydroxyl group of which was then allylated to give a diene **18** in good yield. To construct a dihydropyran ring, the ring-closing metathesis of **18** catalyzed by Grubbs first-generation catalyst was performed to give the dihydropyran de-



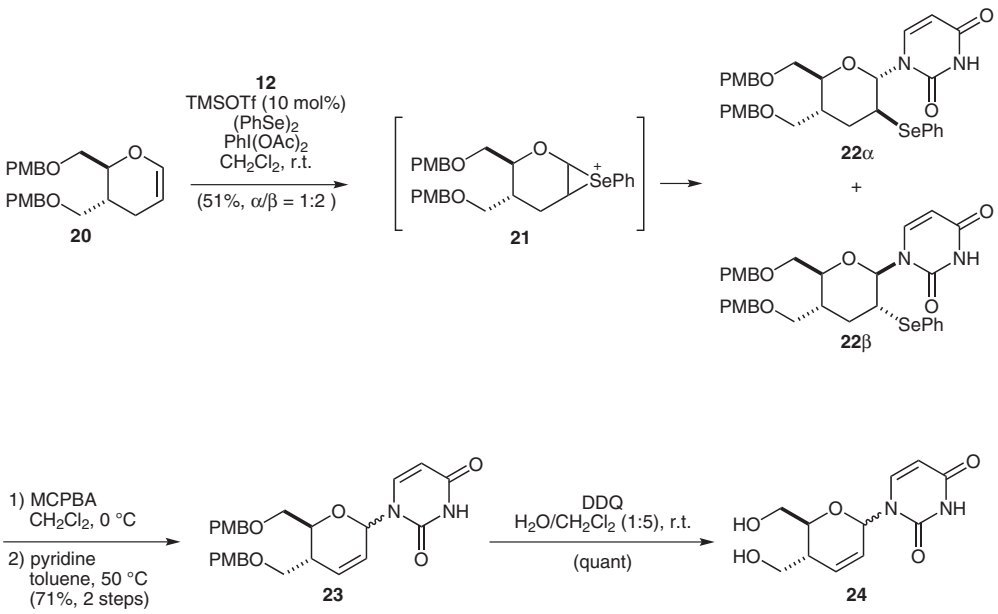
Scheme 5 Synthesis of glycal **21**

rivative **19** in excellent yield. Isomerization of the double bond in **19** was achieved by treatment with Wilkinson's catalyst under basic conditions[14] to afford the glycal **20** in 82% yield (Scheme 5).

As mentioned above, the oxidative glycosylation of *O*,*O*′-bis(trimethylsilyl)uracil using the glycal **20** as a sugar donor was attempted. The reaction of **20** with *O*,*O*′-bis(trimethylsilyl)uracil (**12**) in the presence of diphenyl diselenide, (diacetoxyiodo)benzene, and a catalytic amount of trimethylsilyl triflate gave an inseparable mixture of α- and β-anomers **22α**,**β** (α/β = 1:2) in 51% yield (Scheme 6). Analogous to the reaction mediated by benzeneselenenyl chloride,[15] it is obvious that the reaction proceeded through the generation of the episelenium ion **21**, resulting in the selective formation of 1′,2′-*trans* adducts. To form the episelenium ion **21**, it is necessary that the phenylseleno group should occupy an axial position in the carbocation intermediate. Thus, we should consider the two carbocation intermediates **21a** and **21b**. The former could give 2′-selenonucleoside **22α** and the latter could give **21β** (Scheme 7). The steric repulsion between two benzyloxymethyl substituents should favor the formation of the all axial-substituted carbocation intermediate **21b**. In addition, the carbocation **21b** is thought to be more stable than **21a** due to its reduction of unfavorable dipole interaction and have a structure similar to the carbocation generated from conformationally 'super armed glycosyl donor'.[16] As a result, the β-anomer **22β** should be predominantly formed.



Scheme 7 Speculated carbocation intermediates **21a** and **21b**

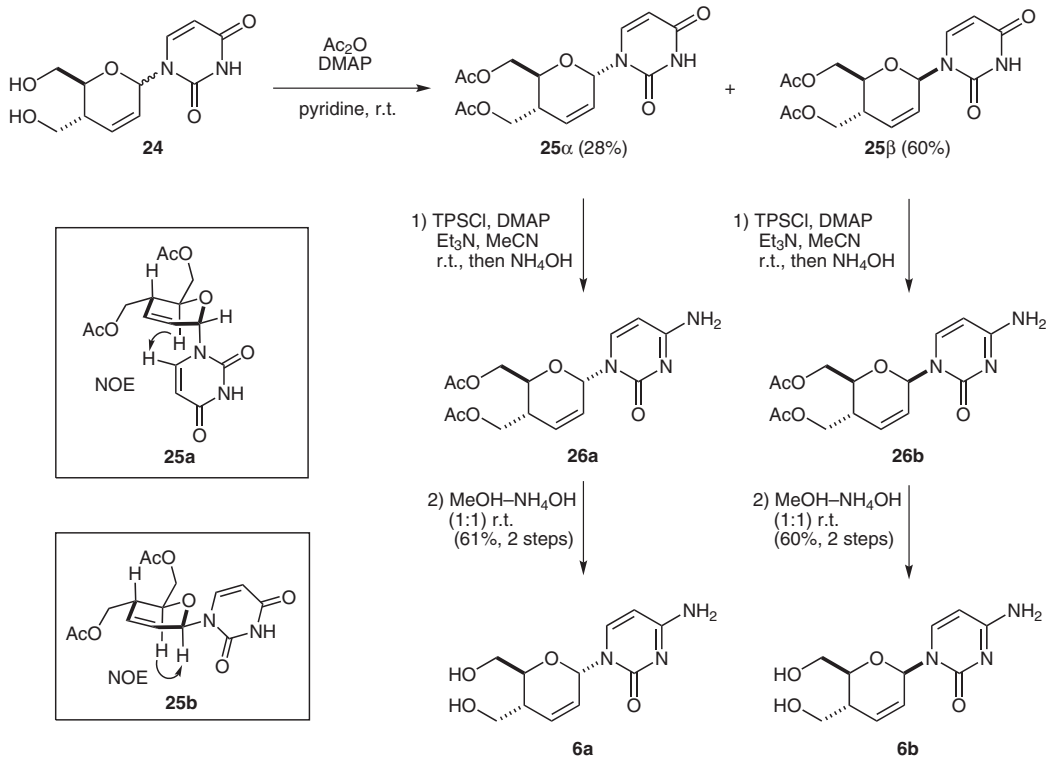


Scheme 6 Oxidative glycosylation using the glycal **21** mediated by hypervalent iodine

Compounds **22α** and **22β** were oxidized by treatment with 3-chloroperoxybenzoic acid to give the corresponding selenoxides. An elimination reaction of the resulting selenoxides without purification gave **23** in 71% from **22**. However, it was not possible to separate the anomers of **23**, even at this step. We then decided to convert the protecting group of **23** into one that would be more amenable to further transformation and might result in a more feasible separation. Thus, the PMB group of **23** was deprotected by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to give a mixture of free nucleosides **24** (Scheme 6).

Since the free nucleosides **24** needed further purification, we decided to purify **24** after conversion into the corresponding acetates. Fortunately, acetylation of **24** gave a mixture of diacetates **25α** and **25β** that could be separated in 28% and 60% yields, respectively, by simple silica gel column chromatography. At this point, we performed NOE experiments on **25α** and **25β** and the data clearly show that the major product is the desired β-anomer as depicted in Scheme 8.[17] The major β-anomer **25β** was converted into a cytosine derivative **26β** by treatment with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl), triethylamine, and 4-(dimethylamino)pyridine, followed by concentrated ammonium hydroxide.[18] The crude reaction mixture was further treated with concentrated ammonium hydroxide in methanol to deprotect the acetyl group, giving the desired dihydropyranylcytosine derivative **6β** in 60% from **25β**. The α-anomer of the dihydropyranylcytosine derivative **6α** was synthesized from **25α** in 61% yield in a similar manner (Scheme 8).

In conclusion, we report on the design and synthesis of a dihydropyranonucleoside as a potential anti-HIV agent. The synthesis of a glycal derivative, the sugar donor unit for the oxidative glycosylation reaction, was achieved by ring-closing metathesis and isomerization of the double bond catalyzed by Wilkinson's catalyst as key reactions. The reaction of the glycal and persilylated uracil with diphenyl diselenide/(diacetoxyiodo)benzene/trimethylsilyl triflate (cat.) gave the desired 2-(phenylseleno)pyranyluracils as a mixture of anomers that were converted into the final target dihydropyranocytidines. To our surprise, antiviral evaluations of the final compounds revealed that neither **6α** nor **6β** showed activity against HIV.[19] As a consequence, the potency of anti-HIV activities of these cytosine derivatives was summarized as follows: dihydrothiopyranyl > cyclohexenyl > dihydropyranyl. The results suggest that the mode of recognition around the sugar part of the cyclohexenyl and dihydrothiopyranyl derivatives by target enzymes of anti-HIV drugs, e.g. deoxynucleoside kinase and reverse transcriptase, may be different in the case of a normal nucleoside bearing an *N*,*O*-acetal unit. Although active compounds were not obtained, there is no doubt that the accumulation of SAR studies, including these studies, may provide new insights in the design of novel anti-HIV nucleosides.



Scheme 8 Synthesis of dihydropyranylcytosine derivatives **6**

Melting points are uncorrected. NMR spectra were recorded at 400 MHz (^{1}H), 100 MHz (^{13}C) using $CDCl_3$ as a solvent. As an internal standard, TMS was used for $CDCl_3$. Mass spectra were obtained by EI mode. In CI mass spectra, isobutane was used. Silica gel for chromatography was Silica Gel 60N (spherical, neutral, 100–210 μm, Kanto Chemical Co. Inc.). Reactions involving reagents that are sensitive to moisture were performed under an argon atmosphere.

(2*R,3*S**)-1-(*tert*-Butyldiphenylsiloxy)-3-[(*tert*-butyldiphenylsiloxy)methyl]pent-4-en-2-ol (11)**

To a solution of **9**[7d] (1.62 g, 4.39 mmol) in CH_2Cl_2 (70 mL) were added imidazole (0.45 g, 6.58 mmol) and TBDPSCl (1.35 mL, 5.27 mmol) at r.t. The mixture was stirred at r.t. for 6 h, and then it was diluted with CH_2Cl_2 and washed with H_2O and sat. NaCl. The organic layer was dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 10% EtOAc–hexane) to give **11** (2.64 g, 99%) as a colorless oil.

IR (neat): 3584, 3508, 3071, 2930, 2857, 1471, 1427, 1112, 823, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9 H), 1.05 (s, 9 H), 2.39–2.45 (m, 1 H), 2.67 (br s, 1 H), 3.65 (d, *J* = 6.3 Hz, 2 H), 3.70 (dd, *J* = 4.9, 10.1 Hz, 1 H), 3.82 (dd, *J* = 7.0, 9.9 Hz, 1 H), 4.09 (br s, 1 H), 5.02 (dd, *J* = 1.5, 17. 6 Hz, 1 H), 5.10 (dd, *J* = 1.9, 10.6 Hz, 1 H), 5.81–5.91 (m, 1 H), 7.35–7.44 (m, 12 H), 7.62–7.70 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.2, 26.8, 48.0, 65.5, 66.1, 71.7, 118.1, 127.6, 127.7, 127.7, 129.7, 129.7, 129.7, 133.3, 133.3, 133.4, 134.9, 135.5, 135.5, 135.6.

MS (FAB): *m*/*z* = 609 [M$^+$ + 1].

HRMS: *m*/*z* [M$^+$] calcd for $C_{38}H_{48}O_3Si_2$: 608.3142; found: 609.3198.

(5*R,6*S**)-5,6-Bis[(*tert*-butyldiphenylsiloxy)methyl]-3-ethoxy-4-oxaocta-1,7-diene (8)**

To a solution of **11** (1.05 g, 1.73 mmol) in toluene (40 mL) were added acrolein diethyl acetal (2 mL, 13.5 mmol) and PPTS (65 mg, 0.26 mmol) at r.t. The mixture was rotated on a rotary evaporator at 85 hPa with keeping the temperature at 40 °C to remove the liberated EtOH. After 3.5 h, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with sat. $NaHCO_3$ and sat. NaCl. The organic layer was dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, hexane–EtOAc–Et_3N, 100:1:0.25) to give **8** (941 mg, 78%) as a colorless oil.

IR (neat): 3071, 2959, 2931, 2858, 1472, 1427, 1111, 824, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.0 Hz, 3 H), 1.04–1.10 (m, 18 H), 2.69–2.75 (m, 0.5 H), 2.82–2.88 (m, 0.5 H), 3.28–3.44, (m, 1.5 H), 3.56–3.75 (m, 2.5 H), 3.77–3.90 (m, 1 H), 4.10–4.18 (m, 1 H), 4.94 (dd, *J* = 5.3, 8.8 Hz, 1 H), 5.00–5.27 (m, 4 H), 5.68–5.75 (m, 2 H), 7.34–7.43 (m, 12 H), 7.65–7.70 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 15.2, 19.2, 19.2, 19.3, 26.8, 26.8, 26.9, 47.9, 48.3, 60.7, 61.7, 63.7, 63.8, 64.0, 64.1, 74.7, 76.2, 102.4, 103.4, 117.7, 117.7, 118.3, 118.6, 127.6, 127.6, 129.6, 129.6, 133.5, 133.5, 133.6, 133.7, 133.7, 133.9, 133.9, 134.5, 135.5, 135.5, 135.5, 135.6, 136.1.

MS (EI): *m*/*z* = 647 [M$^+$ – 45], 635 [M$^+$ – 57].

(2*S,3*R**)-2,3-Bis[(*tert*-butyldiphenylsiloxy)methyl]-6-ethoxy-3,6-dihydro-2*H*-pyran (7)**

To a solution of **11** (726 mg, 1.05 mmol) in CH_2Cl_2 (130 mL) was added Grubbs I catalyst (43 mg, 5 mol%). The mixture was kept under reflux for 9.5 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 4% EtOAc–hexane) to give **7** (603 mg, 87%) as a colorless oil.

IR (neat): 3071, 3048, 2931, 2858, 1471, 1428, 1112, 823, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99–1.05 (m, 18 H), 1.11 (t, *J* = 7.3 Hz, 1.5 H), 1.21 (t, *J* = 7.0 Hz, 1.5 H), 2.35–2.41 (m, 0.5 H), 2.51–2.56 (m, 0.5 H), 3.36–3.93 (m, 6 H), 4.08–4.12 (m, 1 H), 4.91 (s, 0.5 H), 5.01 (s, 0.5 H), 5.70 (d, *J* = 10.1 Hz, 0.5 H), 5.80–5.83 (m, 1 H), 6.07 (d, *J* = 10.1 Hz, 0.5 H), 7.25–7.40 (m, 12 H), 7.57–7.68 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 15.3, 19.1, 19.2, 26.7, 26.8, 37.9, 39.0, 63.0, 63.1, 64.1, 64.2, 64.9, 65.4, 69.8, 73.0, 93.6, 94.3, 125.8, 127.3, 127.5, 127.6, 127.6, 128.7, 129.5, 129.6, 131.1, 133.3, 133.5, 133.6, 133.7, 135.5, 135.6, 135.6.

MS (EI): *m*/*z* = 664 [M$^+$].

HRMS: *m*/*z* [M$^+$] calcd for $C_{41}H_{52}O_4Si_2$: 664.3404; found: 664.3408.

1-{(2*S,5*R**,6*S**)-5,6-Bis[(*tert*-butyldiphenylsiloxy)methyl]-5,6-dihydro-2*H*-pyran-2-yl}pyrimidine-2,4(1*H*,3*H*)-dione (13α) and 1-{(2*R**,5*R**,6*S**)-5,6-Bis[(*tert*-butyldiphenylsiloxy)methyl]-5,6-dihydro-2*H*-pyran-2-yl}pyrimidine-2,4(1*H*,3*H*)-dione (13β)**

To a solution of **7** (464 mg, 0.70 mmol) in CH_2Cl_2 (40 mL) were added *O*,*O*′-bis(trimethylsilyl)uracil (365 μL, 1.4 mmol) and 1 M $SnCl_4$ in CH_2Cl_2 (1.4 mmol, 1.4 mL) at 0 °C. The mixture was stirred at this temperature for 4 h, and then it was quenched with sat. $NaHCO_3$. Insoluble materials were removed by Celite filtration. The filtrate was extracted with CH_2Cl_2. The separated organic layer was washed with sat. NaCl and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 33% EtOAc–hexane) to give **13β** (less polar, 75 mg, 14%) and **13α** (more polar, 196 mg, 38%), both as amorphous foams.

13α

IR (KBr): 3178, 3071, 2931, 2858, 1693, 1428, 1246, 1113, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 9 H), 1.04 (s, 9 H), 2.54 (br s, 1 H), 3.58 (dd, *J* = 4.6, 10.4 Hz, 1 H), 3.64 (dd, *J* = 4.8, 11.6 Hz, 1 H), 3.71–3.81 (m, 3 H), 5.39 (dd, *J* = 2.2, 8.0 Hz, 1 H), 5.73, (dt, *J* = 2.7, 10.1 Hz, 1 H), 6.27–6.30 (m, 1 H), 6.41 (s, 1 H), 7.31–7.48 (m, 13 H), 7.57–7.63 (m, 8 H), 8.85 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.3, 26.7, 26.9, 37.4, 63.7, 64.1, 70.9, 76.6, 77.2, 101.2, 122.9, 127.7, 127.7, 127.8, 127.9, 129.7, 130.0, 130.0, 132.8, 132.9, 133.1, 133.2, 135.5, 135.5, 135.6, 135.6, 135.6, 141.3, 150.6, 163.1.

MS (EI): *m*/*z* = 730 [M$^+$].

HRMS: *m*/*z* [M$^+$] calcd for $C_{43}H_{50}N_2O_5Si_2$: 730.3258; found: 730.3278.

13β

IR (KBr): 3196, 3071, 2931, 2858, 1694, 1428, 1252, 1113, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 9 H), 1.03 (s, 9 H), 2.72 (br s, 1 H), 3.50 (dd, *J* = 5.6, 10.6 Hz, 1 H), 3.65 (d, *J* = 4.4 Hz, 1 H), 3.67 (d, *J* = 2.9 Hz, 1 H), 3.79–3.81 (m, 2 H), 5.64–5.70 (m, 2 H), 6.22 (d, *J* = 10.1 Hz, 1 H), 6.39 (s, 1 H), 7.24–7.45 (m, 13 H), 7.56–7.62 (m, 8 H), 8.59 (br, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.3, 26.8, 26.8, 37.3, 63.5, 64.2, 76.6, 78.4, 102.6, 125.2, 127.5, 127.6, 127.7, 127.8, 129.7, 129.8, 133.0, 133.0, 133.3, 133.3, 135.0, 135.5, 135.6, 135.6, 135.7, 140.8, 150.5, 163.3.

MS (EI): *m*/*z* = 730 [M$^+$].

HRMS: *m*/*z* [M$^+$] calcd for $C_{43}H_{50}N_2O_5Si_2$: 730.3258; found: 730.3278.

(2*R,3*S**)-2,3-Bis[(4-methoxybenzyloxy)methyl]oxirane (17)**
To a suspension of NaH (1.8 g, 45 mmol) in THF (30 mL) were added DMF (5 mL) and *cis*-but-2-ene-1,4-diol (1.23 mL, 15 mmol). After stirring at 0 °C for 1 h, 4-methoxybenzyl chloride (6.23 mL, 45 mmol) was added. The mixture was stirred at r.t. for 2 h, and then it was diluted with Et_2O and the entire mixture was washed with 10% K_2CO_3 (15 mL) and sat. NaCl (15 mL). The separated aqueous layer was extracted with Et_2O (30 mL), and the combined organic layers were dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 15–25% EtOAc–hexane) to give di-PMB derivative (4.80 g, 97%) as a light yellow oil.

To a solution of di-PMB derivative (4.8 g, 14.6 mmol) in CH_2Cl_2 (40 mL), was added MCPBA (3.2 g, 18.6 mmol). The mixture was stirred at r.t. for 12 h. The reaction was quenched by the addition of sat. $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2. The separated aqueous layer was washed with 10% $Na_2S_2O_3$ (15 mL) and sat. $NaHCO_3$ (15 mL), then sat. NaCl (15 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 15–25% EtOAc–hexane) to give **17** (4.80 g, 82%) as white crystals; mp 52–53 °C.

IR (KBr): 763, 864, 1052, 1251, 1468, 1616, 2841, 3003 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.25–3.31 (m, 2 H), 3.50 (dd, *J* = 6.5, 11.3 Hz, 2 H), 3.65 (dd, *J* = 3.9, 11.1 Hz, 2 H), 3.81 (s, 6 H), 4.44 (dd, *J* = 5.8, 11.6 Hz, 4 H), 6.87 (d, *J* = 8.7 Hz, 4 H), 7.26 (d, *J* = 8.2 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.4, 55.3, 67.7, 72.9, 113.8, 129.4, 129.8, 159.3.

MS (EI): *m*/*z* = 344 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{20}H_{24}O_5$: 344.1624; found: 344.1628.

(2*S,3*R**)-1-(4-Methoxybenzyloxy)-3-[(4-methoxybenzyloxy)methyl]pent-4-en-2-ol (16)**
To a solution of **17** (6.78 g, 20 mmol) in THF (40 mL) were added vinylmagnesium chloride (18.2 mL, 24 mmol) and CuI (4.6 g, 24 mmol) at –40 °C. The mixture was stirred at this temperature for 18 h, and then it was quenched by the addition of NH_4OH (15 mL) and sat. NH_4Cl (15 mL). The mixture was extracted with Et_2O (50 mL) and the separated organic layer was washed with sat. NaCl (15 mL), then dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 15–25% EtOAc–hexane) to give **16** (6.90 g, 93%) as a light yellow oil.

IR (neat): 820, 1095, 1249, 1514, 1613, 1638, 1885, 2057, 2837, 3001, 3468 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.49–2.55 (m, 1 H), 2.83 (d, *J* = 2.9 Hz, 1 H), 3.45 (dd, *J* = 3.6, 6.0 Hz, 2 H), 3.55 (dd, *J* = 5.3, 9.2 Hz, 1 H), 3.64 (dd, *J* = 6.5, 8.9 Hz, 1 H), 3.81 (s, 6 H), 4.07 (td, *J* = 3.2, 7.2 Hz, 1 H), 4.42–4.45 (m, 4 H), 5.20–5.12 (m, 2 H), 5.91 (ddd, *J* = 8.0, 9.4, 18.1 Hz, 1 H), 6.90 (dd, *J* = 1.9, 8.7 Hz, 4 H), 7.24 (dd, *J* = 2.6, 5.8 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.4, 55.1, 70.4, 71.3, 72.6, 72.3, 72.8, 72.8, 113.6, 117.9, 129.1, 129.2, 129.2, 130.1, 135.0. 159.0, 159.1.

MS (EI): *m*/*z* = 371 [M^+ – 1].

HRMS: *m*/*z* [M^+ –1] calcd for $C_{22}H_{27}O_5$: 371.1867; found: 371.1850.

(2*S,3*R**)-2-(Allyloxy)-1-(4-methoxybenzyloxy)-3-[(4-methoxybenzyloxy)methyl]pent-4-ene (18)**
To a solution of **16** (526 mg, 1.41 mmol) in THF (10 mL) and DMF (2 mL) was added NaH (124 mg, 3.10 mmol) at 0 °C and the mixture was stirred at r.t. for 1 h. After the addition of allyl bromide (183 μL, 2.12 mmol), the mixture was stirred at r.t. for 2 h. The reaction was quenched with sat. NH_4Cl (5 mL) and it was extracted with Et_2O (15 mL). The separated organic layer was washed with sat. NaCl (5 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 5–10% EtOAc–hexane) to give **18** (473 mg, 81%) as a colorless oil.

IR (neat): 820, 1095, 1249, 1514, 1613, 1737, 1882, 2061, 2837, 3074 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.62–2.65 (m, 1 H), 3.39–3.47 (m, 2 H), 3.51 (dd, *J* = 6.5, 9.9 Hz, 1 H), 3.59 (t, *J* = 8.5 Hz, 1 H), 3.79 (s, 7 H), 3.97–4.02 (m, 1 H), 4.19 (dd, *J* = 5.6, 12.8 Hz, 1 H), 4.43 (dd, *J* = 12.1, 16.9 Hz, 4 H), 5.10 (m, 3 H), 5.23 (d, *J* = 1.9 Hz, 1 H), 5.73–5.93 (m, 2 H), 6.87 (d, *J* = 8.7 Hz, 4 H), 7.25 (dd, *J* = 2.2, 8.5 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.4, 55.1, 70.1, 71.4, 72.2, 72.5, 72.8, 76.9, 113.6, 116.1, 117.8, 129.1, 129.2, 130.4, 135.2, 135.4, 159.0.

MS (FAB): *m*/*z* = 413 [M^+ + 1].

HRMS: *m*/*z* [M^+] calcd for $C_{25}H_{33}O_5$: 413.2328; found: 413.2324.

(2*S,3*R**)-2,3-Bis[(4-methoxybenzyloxy)methyl]-3,6-dihydro-2*H*-pyran (19)**
To a solution of **18** (423 mg, 1.03 mmol) in CH_2Cl_2 (10 mL) was added Grubbs I catalyst (42.4 mg, 5 mol%). The mixture was stirred at r.t. for 5 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 10–20% EtOAc–hexane) to give **19** (368 mg, 96%) as a brown oil.

IR (neat): 820, 1090, 1174, 1513, 1612, 1713, 2003, 2858, 3000 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.48 (m, 1 H), 3.35 (ddd, *J* = 5.9, 9.3, 23.4 Hz, 2 H), 3.53 (dd, *J* = 6.3, 10.7 Hz, 1 H), 3.62–3.68 (m, 2 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 4.17–4.18 (m, 2 H), 4.39 (dd, *J* = 11.7, 18.5 Hz, 2 H), 4.50 (dd, *J* = 11.7, 14.6 Hz, 2 H), 5.72 (dd, *J* = 2.2, 10.2 Hz, 1 H), 5.81 (dd, *J* = 2.0, 10.5 Hz, 1 H), 6.86 (d, *J* = 8.3 Hz, 4 H), 7.23 (dd, *J* = 8.3, 23.2 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.6, 55.2, 64.6, 70.6, 70.9, 72.7, 72.9, 75.1, 113.6, 113.7, 125.9, 127.0, 129.1, 129.3, 130.2, 130.3, 159.1.

MS (EI): *m*/*z* = 384 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{23}H_{28}O_5$: 384.1937; found: 384.1940.

(2*S,3*R**)-2,3-Bis[(4-methoxybenzyloxy)methyl]-3,4-dihydro-2*H*-pyran (20)**
To a solution of **19** (510 mg, 1.32 mmol) in H_2O–EtOH (1.5:13.5 mL), was added DBU (195 μL, 1.32 mmol). The mixture was stirred at r.t. for 30 min, and then $RhCl(PPh_3)_3$ (126.5 mg, 10 mol%) was added. The mixture was kept at 40 °C for 4 h. After the addition of H_2O (5 mL), the mixture was allowed to cool to r.t. and then it was extracted with CH_2Cl_2 (15 mL). The separated organic layer was dried (Na_2SO_4) After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 10–20% EtOAc–hexane) to give **20** (409 mg, 82%) as an orange oil.

IR (neat): 820, 1103, 1512, 1614, 1736, 1885, 2060, 2858, 3000 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.97–1.99 (m, 2 H), 2.13 (td, *J* = 6.1, 13.1 Hz, 1 H), 3.39 (m, 2 H), 3.59 (d, *J* = 4.3 Hz, 2 H), 3.80 (s, 6 H), 4.00 (dd, *J* = 4.3, 11.6 Hz, 1 H), 4.37 (dd, *J* = 11.3, 17.6 Hz, 2 H), 4.49 (m, 2 H), 4.65 (m, 1 H), 6.34 (d, *J* = 5.8 Hz, 1 H), 6.86 (d, *J* = 7.2 Hz, 4 H), 7.23 (dd, *J* = 7.7, 19.3 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 33.5, 55.0, 69.6, 70.5, 72.6, 72.8, 75.4, 76.0, 99.3, 113.54, 129.0, 129.2, 130.1, 130.2, 142.6, 159.0.

MS (EI): *m*/*z* = 383 [M$^+$ – 1].

HRMS: *m*/*z* [M$^+$ – 1] calcd for $C_{23}H_{27}O_5$: 383.1867; found: 383.1851.

1-{(2*S,3*S**,5*R**,6*S**)-5,6-Bis[(4-methoxybenzyloxy)methyl]-3-(phenylselanyl)tetrahydro-2*H*-pyran-2-yl}pyrimidine-2,4(1*H*,3*H*)-dione (22α) and 1-{(2*R**,3*R**,5*R**,6*S**)-5,6-Bis[(4-methoxybenzyloxy)methyl]-3-(phenylselanyl)tetrahydro-2*H*-pyran-2-yl}pyrimidine-2,4(1*H*,3*H*)-dione (22β)**

To a solution of **20** (1.36 g, 3.53 mmol) in CH_2Cl_2 (15 mL) were added *O*,*O*′-bis(trimethylsilyl)uracil (905 μL, 3.53 mmol), $(PhSe)_2$ (1.10 g, 3.53 mmol), (diacetoxyiodo)benzene (1.13 g, 3.53 mmol), and TMSOTf (63 μL, 0.35 mmol). The mixture was stirred at r.t. for 2 h, and then it was quenched by the addition of sat. $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (15 mL) and the separated organic layer was washed with sat. NaCl (10 mL) and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 25–50% EtOAc–hexane) to give **22** as a mixture of α- and β-anomers (1.23 g, 51%) as a white foam.

IR (KBr): 819, 1036, 1249, 1677, 1885, 2057, 3056, 3170 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (α,β-mix) = 1.80 (q, *J* = 12.9 Hz, 0.3 H), 2.03–2.10 (m, 1.2 H), 2.29 (dd, *J* = 4.6, 11.8 Hz, 0.3 H), 2.46 (dt, *J* = 4.0, 13.7 Hz, 0.6 H), 3.56–3.62 (m, 1.8 H), 3.56–3.62 (m, 3.0 H), 3.71 (dq, *J* = 2.0, 10.3 Hz, 1 H), 3.81 (s, 5.4 H), 4.11 (t, *J* = 5.6 Hz, 0.3 H), 4.32 (dd, *J* = 4.8, 10.1 Hz, 0.6 H), 4.40–4.52 (m, 3.6 H), 5.26 (d, *J* = 8.2 Hz, 0.6 H), 5.31 (d, *J* = 8.2 Hz, 0.3 H), 5.75 (d, *J* = 9.2 Hz, 0.6 H), 6.05 (d, *J* = 10.6 Hz, 0.3 H), 6.72 (d, *J* = 8.2 Hz, 0.3 H), 6.83–6.90 (m, 3.6 H), 6.98 (d, *J* = 8.2 Hz, 0.6 H), 7.20–7.26 (m, 6.3 H), 7.48–7.50 (m, 1.8 H), 8.25 (br, 0.3 H), 8.35 (br, 0.6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (α,β-mix) = 28.9, 34.3, 35.0, 38.5, 39.4, 55.3, 55.3, 55.3, 69.5, 69.5, 71.0, 72.9, 73.1, 79.6, 81.4, 102.2, 102.2, 113.7, 113.8, 113.9, 128.5, 129.2, 129.4, 129.4, 129.6, 130.0, 135.6, 135.8, 139.6, 150.0, 150.1, 159.2, 159.4, 162.5, 162.5.

MS (EI): *m*/*z* = 653 [M$^+$ + 1].

HRMS: *m*/*z* [M$^+$ + 1] calcd for $C_{33}H_{37}N_2O_7Se$: 653.1758; found: 653.1774.

1-{(5*R,6*S**)-5,6-Bis[(4-methoxybenzyloxy)methyl]-5,6-dihydro-2*H*-pyran-2-yl}pyrimidine-2,4(1*H*,3*H*)-dione (23)**

To a solution of **22** (α,β-mix, 1.22 g, 1.87 mmol) in CH_2Cl_2 (15 mL) was added MCPBA (605 mg, 2.81 mmol). The mixture was stirred at 0 °C for 30 min, and then it was quenched by the addition of sat. $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (10 mL) and the separated organic layer was washed with sat. NaCl (10 mL) and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was dissolved in toluene (15 mL). To this mixture, pyridine (150 μL, 1.87 mmol) was added. The mixture was kept at 50 °C for 3 h, and it was quenched by the addition of sat. $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (15 mL) and the separated organic layer was washed with sat. NaCl (10 mL) and dried (Na_2SO_4). After concentration, the solvents were removed under reduced pressure and the residue was purified by column chromatography (silica gel, 50–75% EtOAc–hexane) to give **23** as a mixture of α- and β-anomers (613 mg, 71%) as a white foam.

IR (KBr): 761, 1249, 1380, 1515, 1693, 1891, 2057, 2925, 3195 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (α,β-mix) = 2.63–2.66 (m, 0.3 H), 2.70–2.73 (m, 0.6 H), 3.30 (dd, *J* = 5.6, 9.4 Hz, 0.6 H), 3.40 (dd, *J* = 4.8, 9.2 Hz, 0.6 H), 3.49 (dd, *J* = 3.9, 9.7 Hz, 0.3 H), 3.55–3.57 (m, 8 H), 3.80 (s, 6 H), 3.81 (s, 6 H), 4.33–4.53 (m, 8 H), 5.32 (d, *J* = 8.2 Hz, 0.3 H), 5.63 (d *J* = 9.7 Hz, 0.6 H), 5.72 (d, *J* =7.7 Hz, 0.9 H), 6.18 (d, *J* = 10.1 Hz, 0.6 H), 6.27 (d, *J* = 10.1 Hz, 0.3 H), 6.39 (s, 0.3 H), 6.43 (s, 0.6 H), 6.84–6.88 (m, 3.6 H), 7.18–7.22 (m, 3.6 H), 7.28 (d, *J* = 8.2 Hz, 0.6 H), 7.58 (d, *J* = 8.2 Hz, 0.3 H), 8.6 (br, 0.3 H), 8.8 (br, 0.6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (α,β-mix) = 36.1, 36.2, 55.2, 55.3, 69.5, 69.5, 69.8, 70.0, 72.9, 73.0, 73.1, 76.1, 76.4, 77.2, 78.6, 101.0, 102.9, 113.7, 113.8, 113.8, 113.8, 122.6, 125.2, 129.2, 129.3, 129.4, 129.8, 130.0, 134.9, 135.6, 140.7, 141.8, 150.3, 150.7, 159.2, 159.4.

MS (EI): *m*/*z* = 494 [M$^+$].

HRMS: *m*/*z* [M$^+$] calcd for $C_{27}H_{30}N_2O_7$: 494.2053; found: 494.2054.

1-[(5*R,6*S**)-5,6-Bis(hydroxymethyl)-5,6-dihydro-2*H*-pyran-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (24)**

To a solution of **23** (613 mg, 1.24 mmol) in CH_2Cl_2–H_2O (15:3 mL) was added DDQ (1.13 g, 4.96 mmol). The mixture was stirred at r.t. for 30 min, and then it was dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 5–10% MeOH–$CHCl_3$) to give **24** as a mixture of α- and β-anomers (536 mg, quant) as a reddish foam.

IR (KBr): 821, 1253, 1454, 1567, 1691, 2216, 2254, 3372 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ (α,β-mix) = 2.36–2.39 (m, 0.3 H), 2.47–2.49 (m, 0.6 H), 3.53 (dd, *J* = 5.3, 11.1 Hz, 0.9 H), 3.64–3.80 (m, 3.6 H), 5.60 (d, *J* = 8.2 Hz, 0.3 H), 5.67 (d, *J* = 7.7 Hz, 0.6 H), 5.72 (d, *J* = 10.1 Hz, 0.6 H), 5.81 (d, *J* = 10.1 Hz, 0.3 H), 6.21 (d, *J* =10.1 Hz, 0.9 H), 6.28 (s, 0.3 H), 6.33 (s, 0.6 H), 7.48 (d, *J* = 8.2 Hz, 0.6 H), 7.79 (d, *J* = 7.7 Hz, 0.3 H).

^{13}C NMR (100 MHz, CD_3OD): δ (α,β-mix) = 37.7, 37.8, 61.3, 61.7, 62.2, 62.5, 70.9, 76.7, 77.4, 78.5, 100.2, 101.7, 122.5, 125.1, 134.2, 135.3, 141.2, 142.5, 151.0, 151.6, 164.7, 164.9.

MS (EI): *m*/*z* = 254 [M$^+$].

HRMS: *m*/*z* [M$^+$] calcd for $C_{11}H_{14}N_2O_5$: 254.0; found: 254.0891.

1-[(2*S,5*R**,6*S**)-5,6-Bis(acetoxymethyl)-5,6-dihydro-2*H*-pyran-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (25α) and 1-[(2*R**,5*R**,6*S**)-5,6-Bis(acetoxymethyl)-5,6-dihydro-2*H*-pyran-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (25β)**

To a solution of **24** (533 mg, 1.24 mmol) in pyridine (10 mL) were added Ac_2O (351 μL, 3.72 mmol) and DMAP (15.1 mg, 0.12 mmol). The mixture was stirred at r.t. for 3 h, the solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 50 → 75 → 100% EtOAc–hexane) to give **25α** (less polar, 123 mg, 28%) and **25β** (more polar, 265 mg, 60%), both as colorless syrups.

25α

IR (neat): 818, 1075, 1248, 1382, 1457, 1740, 3057, 3207 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 6 H), 2.60–2.62 (m, 1 H), 3.86–3.90 (m, 1 H), 4.15–4.24 (m, 3 H), 4.32 (dd, *J* = 5.9, 12.2 Hz, 1 H), 5.69 (dd, *J* = 1.7, 8.0 Hz, 1 H), 5.82 (dt, *J* = 2.4, 10.2 Hz, 1 H), 6.24 (dt, *J* = 2.1, 10.4 Hz, 1 H), 6.41 (d, *J* = 2.0 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 9.43 (br, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 20.8, 34.9, 63.7, 69.2, 76.2, 102.0, 124.2, 133.0, 140.7, 150.5, 162.9, 170.5, 170.7.

MS (EI): *m*/*z* = 338 [M$^+$].

HRMS: *m*/*z* [M$^+$] calcd for $C_{15}H_{18}N_2O_7$: 338.1114; found: 338.1109.

25β

IR (neat): 822, 1072, 1251, 1387, 1467, 1730, 3055, 3201 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 2.08 (s, 3 H), 2.66–2.69 (m, 1 H), 3.94–3.98 (m, 1 H), 4.08 (dd, *J* = 4.9, 11.7 Hz, 1 H), 4.14 (dd, *J* = 5.4, 11.7 Hz, 1 H), 4.22 (dd, *J* = 5.9, 12.2 Hz, 1 H), 4.33 (dd, *J* = 2.2, 12.4 Hz, 1 H), 5.72–5.76 (m, 2 H), 6.11 (d, *J* = 10.2 Hz, 1 H), 6.47 (d, *J* = 1.5 Hz, 1 H), 7.22 (d, *J* = 8.3 Hz, 1 H), 9.56 (br, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 20.8, 35.2, 63.5, 64.2, 74.5, 78.2, 103.3, 126.5, 132.8, 140.2, 150.6, 163.2, 170.7, 170.8.

MS (EI): m/z = 338 [M^+].

HRMS: m/z [M^+] calcd for $C_{15}H_{18}N_2O_7$: 338.1114; found: 338.1119.

4-Amino-1-[(2*S,5*R**,6*S**)-5,6-bis(hydroxymethyl)-5,6-dihydro-2*H*-pyran-2-yl]pyrimidin-2(1*H*)-one (6α)**

To a solution of **25α** (95.1 mg, 0.28 mmol) in MeCN (5 mL) were added TPSCl (170 mg, 0.56 mmol), DMAP (68.4 mg, 0.56 mmol), and Et_3N (77.6 μL, 0.56 mmol). The mixture was stirred at r.t. for 2 h, NH_4OH (1 mL) was added, the mixture was stirred for 2 h, the solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 5–8% MeOH–$CHCl_3$) to give partially purified cytosine derivative (276 mg). The resulting product was dissolved in MeOH–NH_4OH (2.5:2.5 mL). The mixture was stirred at r.t. for 3 h, the solvents were removed under reduced pressure and the residue was purified by column chromatography (silica gel, 5–10% MeOH–$CHCl_3$) to give **6α** (43 mg, 61%) as white crystals; mp 203–207 °C.

IR (KBr): 790, 1062, 1489, 1646, 3351 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 2.28–2.30 (m, 1 H), 3.50–3.65 (m, 5 H), 5.73–5.76 (m, 2 H), 6.24 (m, 1 H), 6.25–6.27 (m, 2 H), 7.71 (d, J = 7.7 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 39.2, 62.8, 63.8, 72.2, 78.7, 95.3, 124.5, 136.2, 144.4, 159.0, 167.8.

MS (EI): m/z = 253 [M^+].

HRMS: m/z [M^+] calcd for $C_{11}H_{15}N_3O_4$: 253.1063; found: 253.1058.

4-Amino-1-[(2*R,5*R**,6*S**)-5,6-bis(hydroxymethyl)-5,6-dihydro-2*H*-pyran-2-yl]pyrimidin-2(1*H*)-one (6β)**

To a solution of **25β** (102 mg, 0.31 mmol) in MeCN (5 mL) were added TPSCl (188 mg, 0.62 mmol), DMAP (75.7 mg, 0.62 mmol), and Et_3N (86.0 μL, 0.62 mmol). The mixture was stirred at r.t. for 2 h, NH_4OH (1 mL) was added, the mixture was stirred for 2 h, the solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 5–8% MeOH–$CHCl_3$) to give partially purified cytosine derivative (102 mg). The resulting product was dissolved in MeOH–NH_4OH (2.5:2.5 mL). The mixture was stirred at r.t. for 3 h, the solvents were removed under reduced pressure, and the residue was purified by reverse-phase column chromatography (ODS, 2–4–8% MeCN–H_2O) to give **6β** (42 mg, 60%) as white crystals; mp 200–205 °C.

IR (KBr): 785, 1051, 1504, 1681, 3381 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 2.50–2.52 (m, 1 H), 3.57 (dd, J = 5.8, 11.1 Hz, 1 H), 3.63–3.71 (m, 2 H), 3.80–3.84 (m, 2 H), 5.74 (m, 1 H), 5.90 (d, J = 7.2 Hz, 1 H), 6.21 (dt, J = 1.9, 10.1 Hz, 1 H), 6.44 (m, 1 H), 7.55 (d, J = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 39.3, 63.2, 64.0, 79.0, 80.9, 96.6, 127.3, 134.9, 143.4, 160.9, 167.8.

MS (EI): m/z = 253 [M^+].

HRMS: m/z [M^+] calcd for $C_{11}H_{15}N_3O_4$: 253.1063; found: 253.1070.

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References

(1) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.

(2) (a) De Clercq, E. *Curr. Opin. Pharmacol.* **2010**, *10*, 507. (b) Broder, S. *Antiviral Res.* **2010**, *85*, 1. (c) Cihlar, T.; Ray, A. S. *Antiviral Res.* **2010**, *85*, 39.

(3) Ichikawa, E.; Kato, K. *Curr. Med. Chem.* **2001**, *8*, 385.

(4) (a) Baba, M.; Pauwels, R.; Herdewijn, P.; De Clercq, E.; Desmyter, J.; Vandeputte, M. *Biochem. Biophys. Res. Commun.* **1987**, *142*, 128. (b) Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N. *Antimicrob. Agents Chemother.* **1987**, *31*, 907.

(5) (a) Gumina, G.; Chong, Y.; Choo, H.; Song, G. Y.; Chu, C. K. *Curr. Top. Med. Chem.* **2002**, *2*, 1065. (b) Sabini, E.; Hazra, S.; Konrad, M.; Lavie, A. *J. Med. Chem.* **2007**, *50*, 3004.

(6) (a) Coates, J. A.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202. (b) Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L. S.; Beach, J. W.; Choi, W. B.; Yeola, S. *Antimicrob. Agents Chemother.* **1992**, *36*, 672.

(7) (a) Yoshimura, Y.; Asami, K.; Matsui, H.; Tanaka, H.; Takahata, H. *Org. Lett.* **2006**, *8*, 6015. (b) Yoshimura, Y.; Yamazaki, Y.; Kawahata, M.; Yamaguchi, K.; Takahata, H. *Tetrahedron Lett.* **2007**, *48*, 4519. (c) Yoshimura, Y.; Ohta, M.; Imahori, T.; Imamichi, T.; Takahata, H. *Org. Lett.* **2008**, *10*, 3449. (d) Yoshimura, Y.; Yamazaki, Y.; Saito, Y.; Takahata, H. *Tetrahedron* **2009**, *65*, 9091. (e) Yoshimura, Y.; Asami, K.; Imamichi, T.; Okuda, T.; Shiraki, K.; Takahata, H. *J. Org. Chem.* **2010**, *75*, 4161. (f) Yoshimura, Y.; Yamazaki, Y.; Saito, Y.; Natori, Y.; Imamichi, T.; Takahata, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3313.

(8) Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; St Clair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.; Reardon, J. E.; Dornsife, R. E.; Averett, D. R.; Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082.

(9) Katagiri, N.; Shiraishi, T.; Sato, H.; Toyota, A.; Kaneko, C.; Yusa, K.; Oh-hara, T.; Tsuruno, T. *Biochem. Biophys. Res. Commun.* **1992**, *184*, 154.

(10) Hayashi, S.; Norbeck, D. W.; Rosenbrook, W.; Fine, R. L.; Matsukura, M.; Plattner, J. J.; Broder, S.; Mitsuya, H. *Antimicrob. Agents Chemother.* **1990**, *34*, 287.

(11) Gollner, A.; Altmann, K.-H.; Gertsch, J.; Mulzer, J. *Chem. Eur. J.* **2009**, *15*, 5979.

(12) (a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234. (b) Ueda, T.; Watanabe, S.-I. *Chem. Pharm. Bull.* **1985**, *33*, 3689.

(13) Yoshimura, Y.; Kan-no, H.; Kiran, Y. B.; Natori, Y.; Saito, Y.; Takahata, H. *Synthesis* **2012**, *44*, 1163.

(14) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672.

(15) Díaz, Y.; El-Laghdach, A.; Matheu, M. I.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501.

(16) (a) Pedersen, C. M.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222. (b) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2103.

(17) Compound **25α** showed 8.8% of NOE at H6 of uracil when irradiated at H5′ and **25β** revealed 6.9% of NOE at H1′ when irradiated at H5′.

(18) Sekine, M.; Matsuzaki, J.; Satoh, M.; Hata, T. *J. Org. Chem.* **1982**, *47*, 571.

(19) Anti-HIV-1 activities of the compounds were evaluated by suppression of HIV replication in PBMCs by p24 antigen capture assay. At any concentrations less than 100 μM, neither **6α** nor **6β** showed anti-HIV activity.

