Diastereoselective synthesis of (±)-1′,4′-dimethyluridine†

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The *de novo* synthesis of racemic 1′,4′-dimethyluridine was accomplished in 12 steps starting from 2,5-dimethylfuran and vinylene carbonate. Key steps of the sequence include the stereoconvergent preparation of a *meso* diacid, and a stereoselective glycosylation without neighboring group participation. Such 1′,4′-disubstituted ribonucleoside analogues are undisclosed compounds, which may present interesting biological activities.

Introduction

Nucleoside analogues constitute an interesting class of therapeutic molecules, and their antiviral or anticancer properties are well demonstrated. These prodrugs, after intracellular conversion to their phosphorylated forms, are able to mimic the structural and functional features of natural nucleosides, and interact with viral or cellular enzymatic systems involved in nucleic acid biosynthesis. During previous decades, intense research has been dedicated to the discovery of new nucleoside analogues with chemical modifications on the heterocyclic base and/or the sugar moiety of natural nucleosides. To date, several have been marketed for the treatment of viral infections[1] or cancers,[2] but public health challenges remain, especially for the treatment of RNA viral infections, such as hepatitis C. The latter disease is highly prevalent, and progresses in most cases to chronic hepatitis, increasing the risk of developing liver cirrhosis and eventually hepatocellular carcinoma. No vaccine is currently available, and the sole treatment consists of a combination of ribavirin, a nucleoside analogue, and pegylated interferon. This treatment has, however, limited efficacy, and major side effects.[3]

Thus, we think that the discovery of new and original ribonucleoside analogues is a field of interest for medicinal chemists, and we became interested in the study of 1′,4′-disubstituted compounds. Various 1′- or 4′-substituted nucleoside analogues are already described in the literature, and their biological activity was evaluated.[4] Several substituents were introduced, such as alkyl groups, halogen, ether or cyano moieties, but to our knowledge, only one publication reports the preparation of a 1′,4′-disubstitued nucleoside analogue[5] with an ether link between both positions. This is not surprising, as the proposed molecules represent a synthetic challenge: modifications on natural nucleosides require long reaction sequences, and are limited to specific substituents. Indeed, incorporation of a methyl group in this way would be tedious, but such a small substituent could also lead to interesting biological activity, as already seen with other nucleoside analogues.[6]

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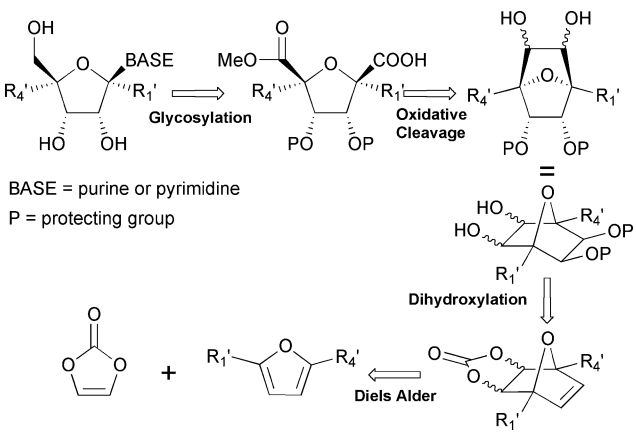
In view of these facts, we decided to explore a synthetic pathway, based on a Diels–Alder reaction between a 2,5-disubstituted furan and vinylene carbonate (Scheme 1). This route proceeds through a 7-oxabicyclo[2.2.1]heptane derivative, which can be regio- and stereoselectively modified. This chemistry is well documented, as well as its application to the synthesis of sugar derivatives,[7] but to our knowledge, it was never applied to the synthesis of nucleoside analogues. This approach was only envisioned thirty years ago by Schmidt, and never carried through to completion.[8] We think it has the potential to enable efficient access to various ribonucleoside analogues, especially modified at the 1′ and 4′ centers simultaneously.



Scheme 1 Retrosynthesis

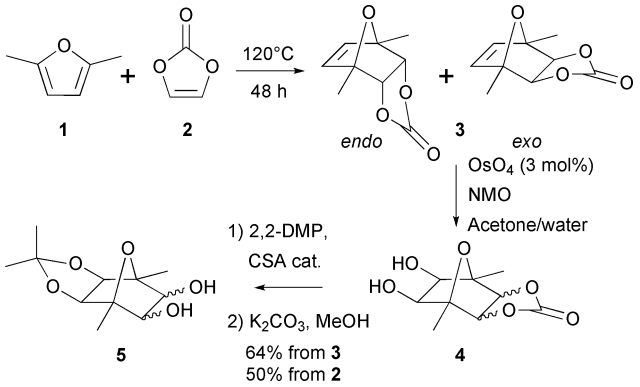
In this paper, we want to report our first results regarding the preparation of racemic 1′,4′-dimethyluridine. Our strategy is based on: a selective dihydroxylation of the Diels–Alder adduct, the oxidative cleavage of the 1,2-diol to reveal the nucleoside skeleton, and the selective introduction of the heterocyclic base from a carboxylic acid moiety (Scheme 1). In this approach, we make use of both isomers of the Diels–Alder reaction, as they both conduct to a *cis*-1,2-diol suitable for the oxidative cleavage.

Results and discussion

Preparation of the 7-oxabicyclo[2.2.1]heptane synthon

The Diels–Alder condensation between 2,5-dimethylfuran **1** and vinylene carbonate **2** gives adducts **3** after 2 d at 120 °C, as a

mixture of *endo* and *exo* diastereomers in a 2 : 1 ratio[9] (Scheme 2). Although both isomers can be separated, we did not focus on such a separation, as our strategy relies on a stereoconvergent approach (*vide supra*).



Scheme 2 Synthesis of diols **4**

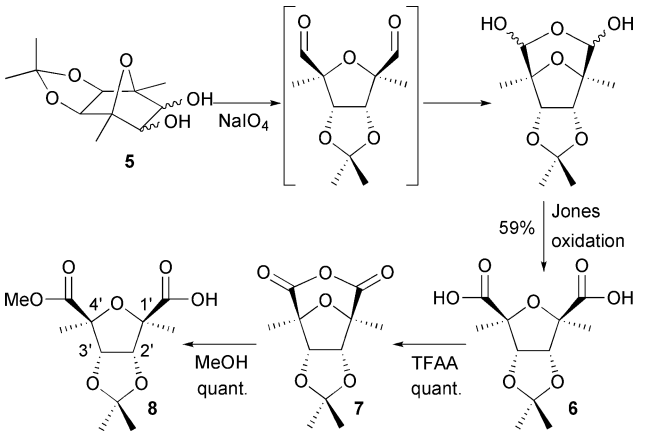
From the crude mixture, we could isolate a 1 : 1 *endo* : *exo* mixture after crystallization in diethyl ether with 36% yield, and we carried on the synthesis with this mixture: dihydroxylation catalyzed by osmium tetroxide occurs *via* an *exo* attack only, and again leads to a 1 : 1 mixture of diols **4** (Scheme 2). This selectivity is well described on such 7-oxabicyclo[2.2.1]heptane substrates,[10] and we could not detect in the crude reaction mixture the other diastereomers corresponding to an *endo* dihydroxylation with ^{1}H NMR.

The crude mixture of diols **4** could be directly engaged for protection of the diol moiety as an acetonide, followed by hydrolysis of the carbonate with potassium carbonate in methanol (Scheme 2). At this stage, the product was purified by crystallization, without modification of the diastereomeric ratio of both isomers. Thus, diols **5** were obtained with 64% yield for the three steps, still as a 1 : 1 mixture.

The mother liquors obtained after crystallization of the Diels–Alder adducts **3** contained a 3 : 1 mixture of both *endo* and *exo* isomers (major isomer not identified), and could also be used without further treatment for dihydroxylation, albeit with 4 mol% OsO_4. We thus obtained a 3 : 1 mixture of diols **4**, which we were able to purify by crystallization, with a yield of 33% (with respect to **2**). During this process, we isolated a small amount (3%) of each pure isomer for characterisation (see the experimental part for details). All this material, as a mixture of isomers, was transformed into diols **5**, according to the previous sequence, with 82% yield. Thus, the global yield of the first four steps of our reaction sequence was 50%, without any purification by silica gel chromatography.

Synthesis of sugar skeleton

Continuation of the synthesis implies oxidative cleavage of the *cis*-1,2-diol. To our surprise, treatment of diols **5** with $NaIO_4$ in acetone–water led to an intractable mixture of at least three different compounds. Furthermore, no signal for an aldehyde proton could be detected in the crude ^{1}H NMR spectrum. However, Jones oxidation of this mixture gave the desired diacid, and we therefore assume that the dialdehyde spontaneously cyclizes into a hydrate form under the reaction conditions (Scheme 3). This



Scheme 3 Stereoconvergent synthesis of diacid **6** and its further desymetrization *via* the corresponding anhydride

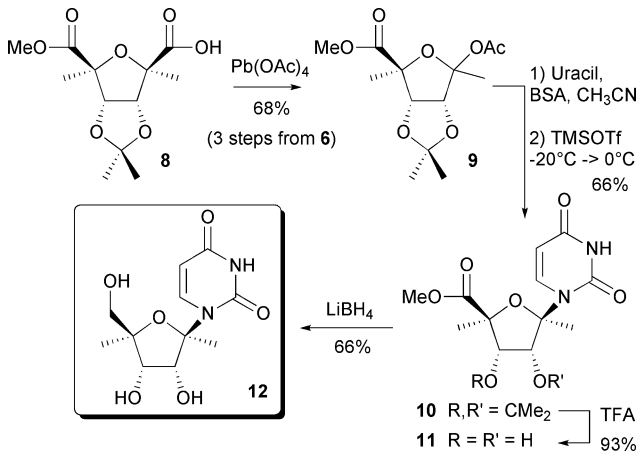
hydrate can exist under three different diastereomers, and they are not separable; detection with mass spectrometry (ESI) of ions corresponding to the protonated dialdehyde ($MH^+ = 229$) and the corresponding hydrates ($MNa^+ = 269$ and $MNa^+ = 287$) clearly supports this hypothesis.

Under these conditions, treatment with $NaIO_4$ directly followed by Jones oxidation, the diacid **6** was obtained as desired, and as a sole isomer. Also, this solid product was efficiently purified by trituration, with a reproducible yield of 59% from diols **5**. We think that this rather modest yield is due to partial deprotection of the acetonide during Jones oxidation, and concomitant loss of the corresponding diol in the aqueous layer. Neither milder oxidants ($NaClO_2$, PCC, PDC) nor direct cleavage of the vicinal diol into the diacid were successful ($NaIO_4$ with cat. $KMnO_4$). We interpret these results in terms of stability of the cyclic hydrates, which then require a strong acidic medium to be hydrolysed before oxidation occurs. Nevertheless, the beginning of our synthesis is very robust, requires no other purification than crystallization, and can be performed on a gram scale.

Diacid **6** then gives the anhydride **7** upon treatment with trifluoroacetic anhydride at room temperature. This anhydride can be isolated and characterized by ^{1}H and ^{13}C NMR, and stored in the freezer for several days without noticeable hydrolysis. This *meso* compound can be used for an enantioselective desymmetrization,[11] but in a first approach, we decided to carry out the synthesis on racemic matter, in order to validate the possibility of obtaining the final nucleoside analogue. Thus, treatment of anhydride **7** with dry methanol led to monoacid **8** as a unique diastereomer. This monoacid possesses all the moieties required to lead to the nucleoside skeleton, with correct relative configurations on the sugar ring (Scheme 3, nucleoside numbering).

Introduction of the heterocyclic base by glycosylation

Treatment of monoacid **8** with lead(IV) tetraacetate in acetonitrile[12] led smoothly to the corresponding acetate **9** (Scheme 4), interestingly as a unique isomer. This selectivity is remarkable, as the reaction is supposed to proceed *via* a radical intermediate, which can equilibrate before trapping by the acetate. The yield of the transformation is also very good, as on large scale the acetate **9** is obtained form the diacid **6** with a 68% overall yield, without any intermediate purification.



Scheme 4 Completion of the synthesis

We were not able to assign with certainty the configuration of the anomeric center in **9**. The chirality is lost during the following glycosylation: introduction of uracil under Vorbrüggen conditions[13] proceeds through an intermediate oxonium, with the carbon atom under an sp^2 hybridisation state. The conditions of the glycosylation were difficult to set up: standard procedures suppose addition of TMSOTf to a mixture of the sugar and silylated uracil at 0 °C, then either heating at 80 °C for 3–4 h, or standing at room temperature overnight, and were already successfully applied to such activated ketose derivatives.[14] However, none of these conditions applied to **9** enabled the isolation of a product bearing the desired uracil moiety.

However, we found that addition of TMSOTf at −20 °C, followed by stirring for 1 h at this temperature, and quenching with aqueous sodium bicarbonate at 0 °C leads to clean formation of the desired condensation product **10**, with a reproducible 60–65% yield. Also, most surprising was the excellent stereocontrol of the reaction: the β-anomer was obtained with a 9 : 1 selectivity (see below for stereochemical justification). Although we were unable to separate the diastereomers of the reaction with column chromatography, we could purify the major compound after crystallization from AcOEt–pet. ether.

This selectivity is noteworthy, as under standard Vorbrüggen conditions, a poor or even no selectivity is usually obtained[15] unless a participating group is set on the 2′ position, and has very few precedents in the literature.[16] The influence of the C1′-methyl group on the glycosylation reaction is not clear, as few precedents are available in the literature on such a reaction. Direct comparison of two literature precedents[15b,16b] related to analogous substrates suggests, at a first glance, a strong β-directing effect of the C1′ substituent, but another set of results shows no selectivity with a C1′-methyl group.[17] The selectivity of such glycosylation reactions also seems to depend on the 5′ protecting group.[16a,17]

Completion of the synthesis

The completion of the synthesis was not as straightforward as initially planned: the reduction of the ester with $LiAlH_4$ or DiBAl-H at −78 °C led to complex mixtures. With $LiBEt_3H$ at −78 °C, we also obtained a complex mixture of several compounds, which evolved during analysis. Here, we noticed the apparition of a signal in the ^1H NMR spectrum that was characteristic of an aldehyde. Eventually, we found that $LiBH_4$ at 0 °C in THF enables the reduction of the ester **11** into the corresponding alcohol **12**, with a good yield. Some of the desired product **12** had to be discarded because of contamination with an unidentified impurity. Using diethyl ether at room temperature instead led to clean reduction, with 66% yield.

Finally, the deprotection of the acetonide was performed with an acidic treatment (TFA in THF–H_2O). Interestingly, we found that the yield for these last two steps was much higher when we performed deprotection before the reduction, *via* diol **11**. The product **12** tends to decompose under acidic medium, *via* hydrolysis of the carbon–nitrogen bond, with a characteristic precipitation of uracil. Deprotection of the acetonide **10** requires half as much TFA as the corresponding compound bearing an alcohol at C5′.

The relative configurations of the asymmetric centers on the sugar ring of **12** were determined after study of nuclear Overhauser effects (nOes). The product shows the same configuration as natural ribonucleosides, as stated by the strong nOe observed between both H5′ and H6 on one hand, and same H5′ and H3′ or even H2′ on the other hand (Fig. 1).

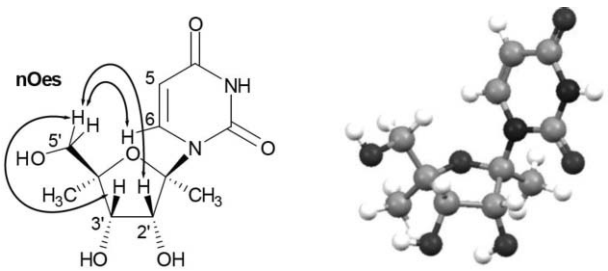


Fig. 1 Observed nuclear Overhauser effects (nOes) and possible envelope-like conformation of the product **12**.

Interestingly, the absence of a nOe between both methyl groups suggests the preference for sugar puckering modes where these groups adopt a *pseudo*-equatorial position. A possible structure obtained with semi-empirical computation (AM1 force field) is depicted in Fig. 1. In this structure, we measured a 4.0 Å distance between H2′ and H5′. Both methyl groups are pointing away from each other and the C–C distance between these groups is 4.3 Å.

Conclusions

In conclusion, we accomplished the synthesis of racemic 1′,4′-dimethyluridine **12** after a 12 step reaction sequence, starting from 2,5-dimethylfuran **1** and vinylene carbonate **2**. We described the significant challenges we met regarding the reactivity of the nucleoside intermediates (Vorbrüggen coupling at low temperature, difficulty of reducing the 5′ ester, sensitivity to hydrolysis), probably induced by the presence of the methyl groups. Working on racemates enables a quicker look at the different possible strategies, and is an essential prerequisite of the enantioselective synthesis. We are currently studying the introduction of other nucleobases, and we noticed that the introduction of purines needs substantial modification of this route. However, we are confident that this approach is valuable for the enantioselective synthesis of diverse analogues bearing such a 1′,4′-disubstitution pattern, even with different substituents. The route is straightforward and

stereoconvergent, and delivers a unique scaffold in the family of nucleoside analogues.

Experimental

General Procedures

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, acetonitrile and pyridine were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade. Reaction flasks were dried at 100 °C. Air- and moisture-sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with the indicated solvents. Thin layer chromatography was performed using 0.25 mm silica gel plates (Merck). Melting points were determined in open capillary tubes on a Büchi-545 and are uncorrected. UV spectra were recorded on an Uvikon 931 (Kontron). Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 K on a Bruker 300 Avance and DRX 400, on solutions in the indicated solvent. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the residual solvent peak (^{1}H NMR, $CHCl_3$ 7.26, DMSO-d_6 2.50) or the deuterated solvent peaks (^{13}C NMR, $CDCl_3$ 77.16, DMSO-d_6 39.52, CD_3OD 49.00, acetone-d_6 29.84 and 206.26). ^{1}H NMR data are reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz). When possible, hydroxyls were identified by D_2O swap. FAB mass spectra were recorded in the positive-ion or negative-ion mode on a JEOL SX 102. The matrix was a mixture (50 : 50, v/v) of glycerol and thioglycerol (G/T). Electrospray (ES) mass spectra and high resolution mass spectra were obtained on a Waters Q-TOF.

1,7-Dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]dec-8-en-4-one (3). A mixture of 2,5-dimethylfuran **1** (11.17 g, 116.2 mmol) and vinylene carbonate **2** (3.70 g, 58.1 mmol) was heated in a sealed vessel for 48 h at 120 °C. The crude mixture was concentrated *in vacuo*, yielding an orange solid. The solid was triturated in Et_2O, and was filtered on a sintered glass funnel. The white solid thus obtained was washed with Et_2O, and dried, to yield **3** as a 1 : 1 *endo* : *exo* mixture (3.82 g, 36%). The mother liquors were concentrated *in vacuo*, to yield an orange oil (4.38 g, impure material), which was used as it was for the next step (as a *ca.* 3 : 1 mixture of isomers). *1 : 1 mixture of isomers*: IR (neat) ν/cm^{-1} 2981, 2939, 1813, 1785, 1365, 1161, 1142, 1087; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.30 (s, 2H), 6.22 (s, 2H), 4.63 (s, 2H), 4.50 (s, 2H), 1.66 (s, 6H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 155.1, 154.9, 139.4, 137.9, 87.2, 87.2, 81.7, 80.3, 17.3, 13.8; Anal. calcd for $C_9H_{10}O_4$ C 59.34, H 5.53, found C 59.31, H 5.69; MS (ES$^+$) 183 (MH^+), 200 (MNH_4^+).

8,9-Dihydroxy-1,7-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]-decan-4-one (4). To a stirred solution of crude Diels–Alder adduct **3** (4.38 g, 24.0 mmol, 3 : 1 mixture of isomers) in 4 : 1 acetone–water (90 mL) at 0 °C was added *N*-methyl morpholine *N*-oxide (4.35 mL, 25.3 mmol, 60% wt in water) and then dropwise a 4×10^{-2}M solution of OsO_4 in t-BuOH (18.1 mL, 0.72 mmol). The reaction medium turned orange, then brown, and was stirred for 6 h at room temperature. The reaction was quenched by slow addition of a saturated $Na_2S_2O_5$ aqueous solution (23 mL), diluted with CH_2Cl_2 (50 mL), and then filtered on a Celite pad. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried on Na_2SO_4, and concentrated *in vacuo* to yield 4.75 g of a solid compound. This solid was triturated with 70 mL $CHCl_3$ at reflux, and filtered. The resulting solid was washed with $CHCl_3$ and dried, to yield **4** (mixture of isomers) (2.11 g, 26% for both steps with respect to **2**). Crystallization of the mother liquors yielded pure **4** (*minor isomer only*) (300 mg, 3.7%) as a white solid. The mother liquors were concentrated *in vacuo*, and the resulting solid was diluted in 15 mL absolute EtOH and left in the freezer for 60 h. The white solid that precipitated was collected and dried *in vacuo*, to yield **4** (*major isomer only*) (279 mg, 3.5%) as a white solid. Remaining mother liquors were discarded. *Major isomer*: Mp = 240–242 °C (dec.); IR (neat) ν/cm^{-1} 3445, 3367, 2999, 2950, 2913, 1792, 1774, 1376, 1169, 1065, 833; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 4.97 (d, $J = 4.2$, 2H, OH), 4.77 (s, 2H), 3.63 (d, $J = 4.2$, 2H), 1.22 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 154.4, 87.0, 81.6, 70.6, 10.7; Anal. calcd for $C_9H_{12}O_6$ C 50.00, H 5.59, found C 49.90, H 5.87; MS (ES$^+$) 217 (MH^+). *Minor isomer*: Mp = 205-207 °C (dec.); IR (neat) ν/cm^{-1} 3462, 3340, 3006, 2972, 2932, 1812, 1785, 1759, 1448, 1363, 1340, 1183, 1158, 1079, 1015, 865, 836, 769; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 4.98 (m, 2H, OH), 4.73 (s, 2H), 3.77 (m, 2H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 154.4, 86.3, 80.9, 70.0, 14.9; Anal. calcd for $C_9H_{12}O_6$ C 50.00, H 5.59, found C 49.91, H 5.65; MS (ES$^+$) 217 (MH^+), 433 ($2M+H^+$).

1,4,4,7-Tetramethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]deca-ne-8,9-diol (5). To a stirred solution of Diels–Alder adduct **3** (3.82 g, 21.0 mmol, as a 1 : 1 *endo* : *exo* mixture) in 4 : 1 acetone : water (78 mL) at 0 °C was added *N*-methyl morpholine *N*-oxide (3.80 mL, 22.1 mmol, 60% wt in water) and then dropwise a 4×10^{-2}M solution of OsO_4 in t-BuOH (15.8 mL, 0.63 mmol). The reaction medium turned orange, and was stirred for 6 h at room temperature. The reaction was quenched by slow addition of a saturated $Na_2S_2O_5$ aqueous solution, diluted with CH_2Cl_2 (50 mL), and then filtered on a Celite pad. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried on Na_2SO_4, and concentrated *in vacuo* to yield 4.15 g of diol **4** as a pale yellow solid, which was used crude for the following step. To a solution of above prepared diol **4** (3.26 g, 15.2 mmol) in CH_2Cl_2 (20 mL) and 2,2-dimethoxypropane (20 mL) was added camphor sulfonic acid (108 mg, 0.44 mmol) at room temperature, and the resulting solution was stirred for 4 h. The mixture was diluted with ethyl acetate (100 mL), and quenched with water (20 mL). The layers were separated, and the organic layer was washed with an aqueous saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown oil was placed into methanol (40 mL), and was vigorously stirred with K_2CO_3 (4.2 g, 30.4 mmol) for 2 h. The mixture was diluted with CH_2Cl_2 (50 mL), and quenched by slow addition of water (20 mL) and 1M aqueous HCl (30 mL). The phases were separated, and

the aqueous layer was extracted with CH_2Cl_2 (6 × 30 mL). The combined organic layers were dried on Na_2SO_4, and concentrated *in vacuo* as a solution in a minimum amount of CH_2Cl_2. To this solution was added dropwise petroleum ether until the apparition of a white precipitate. The solid was collected by filtration, rinsed with cold petroleum ether, and dried *in vacuo*. Title compound **5** was obtained as a 1 : 1 *endo* : *exo* mixture, as a white solid (2.42 g, 64% for the three steps). IR (neat) ν/cm^{-1} 3462, 3251, 3002, 2971, 2936, 1448, 1267, 1203, 1057, 867; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.52 (s, 1H), 4.03 (s, 1H), 3.73 (s, 1H), 3.61 (s, 1H), 3.22 (br s, 2H), 1.48 (s, 6H), 1.42 (s, 6H), 1.37 (s, 6H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 112.8, 110.8, 87.0, 85.8, 82.3, 79.7, 72.7, 72.3, 25.9, 25.9, 25.3, 25.2, 14.8, 10.7; Anal. calcd for $C_{11}H_{18}O_5$ C 57.38, H 7.88, found C 57.41, H 7.91; HRMS (ES$^+$) calcd for $C_{11}H_{19}O_5$ (MH$^+$) 231.1232, found 231.1237.

2,2,4,6-Tetramethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4,6-dicarboxylic acid (6). To a solution of $NaIO_4$ (3.18 g, 14.8 mmol) in water (9 mL) was added at 0 °C dropwise a solution of compound **5** (2.0 g, 8.7 mmol) in acetone (25 mL). After 15 min stirring, TLC analysis showed completion of the reaction, and the resulting slurry was diluted with acetone (50 mL) and filtered on a Celite pad. Concentration *in vacuo* yielded a colourless oil, which was diluted with acetone (25 mL) and set at 0 °C. To this solution was added Jones reagent (5.3 mL, *ca.* 21.3 mmol) dropwise at 0 °C. The reaction mixture turned green, and a dark green precipitate appeared. The slurry was stirred for 30 min at room temperature, then quenched with methanol (5 mL). The mixture was diluted with ethyl acetate (200 mL), then water (10 mL) and brine (10 mL) were added. The layers were separated, and the organic layer was washed with water (40 mL) and brine until colourless (2 × 40 mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The resulting solid was triturated with $CHCl_3$–petroleum ether (40 : 60), filtered, washed twice with same solvent, and dried *in vacuo*. Title compound **6** was obtained as a white solid (1.33 g, 59%). Mp = 164-166 °C; IR (neat) ν/cm^{-1} 3542, 2989, 2938, 1714, 1454, 1372, 1274, 1213, 1116, 1071, 975, 868; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.08 (s, 2H), 1.55 (s, 3H), 1.54 (s, 6H), 1.39 (s, 3H); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm) 5.08 (s, 2H), 1.54 (s, 3H), 1.45 (s, 6H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 175.0, 113.5, 87.0, 85.1, 25.9, 24.7, 21.0; Anal. calcd for $C_{11}H_{16}O_7$ C 50.40, H 6.20, found C 50.45, H 6.26; HRMS (ES$^+$) calcd for $C_{11}H_{17}O_7$ (MH$^+$) 261.0974, found 261.0976.

Methyl 6-(acetyloxy)-2,2,4,6-tetramethyltetrahydrofuro [3,4-*d*][1,3]dioxole-4-carboxylate (9). To a solution of compound **6** (600 mg, 2.3 mmol) in CH_2Cl_2 (15 mL) was added trifluoroacetic anhydride (5 mL). The clear solution was stirred for 1 h at room temperature, and concentrated *in vacuo*. The resulting oil was placed into dry methanol (10 mL), and left for 3 h at room temperature. It was then concentrated *in vacuo*. The crude product obtained was diluted in dry acetonitrile (10 mL), and pyridine (340 µL, 4.2 mmol) was added. To this solution, solid $Pb(OAc)_4$ (1.2 g, 2.7 mmol) was added portionwise, and the resulting yellow mixture was stirred for 16 h at room temperature. A white precipitate appeared after 1 h. The resulting slurry was diluted with ethyl acetate (50 mL) and filtered on a Celite pad. The organic layer was then washed with an aqueous saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluting with ethyl acetate–petroleum ether 30 : 70) yielded title compound **9** (450 mg, 68%) as a white foam. IR (neat) ν/cm^{-1} 2962, 2951, 1738, 1448, 1378, 1267, 1242, 1164, 1075, 1014; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.27 (d, J = 5.9, 1H), 4.77 (d, J = 5.9, 1H), 3.76 (s, 3H), 1.92 (s, 3H), 1.77 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.7, 169.3, 113.0, 112.2, 86.9, 85.0, 82.1, 52.6, 26.1, 24.9, 21.9, 19.8, 19.1; HRMS (ES$^+$) calcd for $C_{13}H_{21}O_7$ (MH$^+$) 289.1287, found 289.1292.

The intermediate anhydride **7** can be characterized with NMR and IR. Data for **1,4,4,7-tetramethyl-3,5,9,11-tetraoxatricyclo[5.3.1.0^{2,6}]undecane-8,10-dione (7):** IR (neat) ν/cm^{-1} 2996, 1943, 1790, 1378, 1209, 1140, 1077, 1023, 868, 825; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.69 (s, 2H), 1.64 (s, 6H), 1.54 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.1, 115.4, 85.2, 83.0, 25.9, 25.5, 14.8.

An analytical sample of compound **8** was purified by flash chromatography (CH_2Cl_2–MeOH: 96 : 4). Data for **6-(methoxycarbonyl)-2,2,4,6-tetramethyltetrahydrofuro[3,4-*d*][1,3]-dioxole-4-carboxylic acid (8):** IR (neat) ν/cm^{-1} 3541, 3175, 2993, 2944, 1730, 1449, 1380, 1269, 1213, 1113, 1071, 978, 869; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.06 (d, J = 6.1, 1H), 4.95 (d, J = 6.1, 1H), 3.76 (s, 3H), 1.57 (s, 3H), 1.52 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 176.4, 174.1, 113.4, 86.9, 86.7, 84.2, 83.7, 53.1, 25.7, 24.7, 21.0, 20.1; HRMS (ES$^+$) calcd for $C_{12}H_{19}O_7$ (MH$^+$) 275.1131, found 275.1127.

Methyl 6-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2,4,6-tetramethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxylate (10). To a solution of compound **9** (180 mg, 0.625 mmol) in dry acetonitrile (5 mL) was added uracil (140 mg, 1.25 mmol) and *N*,*O*-bis-trimethylsilyl acetamide (640 µL, 2.60 mmol). The resulting suspension was stirred at 50 °C until clear (1 h). The resulting solution was cooled to –20 °C, and TMSOTf (115 µL, 0.63 mmol) was added dropwise. The temperature was allowed to rise to 0 °C over 1 h, and the reaction mixture was quenched with an aqueous saturated $NaHCO_3$ solution (5 mL), and diluted with CH_2Cl_2 (40 mL). The layers were separated, and the organic layer was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. To the colourless oil thus obtained was added ethyl acetate–petroleum ether 1 : 1, and after 5 min a white precipitated appeared. The solid was filtered, washed twice with the same solvent, and dried *in vacuo*. Title compound **10** was obtained as a white solid (101 mg, 47%), containing less than 3% of the α-anomer. Purification of the mother liquors by flash chromatography on silica gel (eluting with ethyl acetate–petroleum ether 50 : 50) yielded further product as a 3 : 1 β : α mixture of diastereomers (40 mg, overall yield 66%) as a white foam. UV (EtOH) λ_{max} (nm) 262 (ε = 7000); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.69 (s, 1H), 7.83 (d, J = 8.3, 1H), 5.63 (d, J = 8.3, 1H), 5.29 (d, J = 5.8, 1H), 4.92 (d, J = 5.8, 1H), 3.64 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H), 1.54 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.5, 164.2, 150.4, 140.5, 113.1, 101.4, 101.0, 86.7, 85.9, 82.5, 52.7, 25.8, 24.6, 24.1, 19.3; HRMS (ES$^+$) calcd for $C_{15}H_{21}N_2O_7$ (MH$^+$) 341.1349, found 341.1351.

Methyl 5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,4-dihydroxy-2,5-dimethyltetrahydrofuran-2-carboxylate (11). To a solution of compound **10** (90 mg, 0.265 mmol) in THF–water 4 : 1 (1.2 mL) was added at 0 °C trifluoroacetic acid (1.2 mL), and the resulting solution was stirred at room temperature for 6 h, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluting with ethyl acetate–petroleum ether 60 : 40) yielded title compound **11** (74 mg, 93%) as a white solid. UV (EtOH) λ_{max} (nm) 263 ($\varepsilon = 7440$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.31 (s, 1H), 8.14 (d, $J = 8.2$, 1H), 5.79 (d, $J = 8.2$, 1H), 5.01 (s, 1H), 4.45 (d, $J = 4.4$, 1H), 4.35 (d, $J = 4.4$, 1H), 3.68 (s, 3H), 3.37 (br s, 1H), 1.61 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 173.0, 164.6, 152.1, 141.8, 101.2, 100.3, 87.6, 78.0, 75.3, 52.9, 24.0, 18.9; HRMS (ES$^+$) calcd for $C_{12}H_{17}N_2O_7$ (MH^+) 301.1036, found 301.1037.

(±)-1′,4′-Dimethyl-1′,4′-didehydrouridine (12). To a solution of compound **11** (30 mg, 0.10 mmol) in Et_2O (1 mL) was added at 0 °C $LiBH_4$ (7 mg, 0.32 mmol). The resulting suspension was stirred for 24 h at room temperature, then quenched with methanol (1 mL), and stirred for 30 min at room temperature. Acetic acid (80 µL) was then added, and the resulting solution was stirred for 30 min at room temperature, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluting with methanol–CH_2Cl_2 4 : 96) yielded title compound **12** (18 mg, 66%) as a white solid. Mp = 236-238 °C; UV (EtOH) λ_{max} (nm) 263 ($\varepsilon = 7400$); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.20 (br s, 1H), 8.07 (d, $J = 8.2$, 1H), 5.49 (d, $J = 8.2$, 1H), 5.31 (d, $J = 5.4$, 1H, OH), 4.99 (t, $J = 5.4$, 1H, OH), 4.76 (d, $J = 6.2$, 1H, OH), 4.54 (t, $J = 4.8$, 1H), 3.90 (t, $J = 5.6$, 1H), 3.36-3.30 (m, 1H), 3.27 (dd, $J = 11.7$, 5.1, 1H), 1.50 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 166.9, 152.8, 143.0, 101.2, 101.0, 89.6, 78.4, 73.8, 67.3, 23.5, 18.9; HRMS (ES$^+$) calcd for $C_{11}H_{17}N_2O_6$ (MH^+) 273.1087, found 273.1085.

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