Two Convergent Approaches toward Novel Carbocyclic C-Nucleosides

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Abstract: Two convergent methodologies for construction of novel carbocyclic C-nucleosides allowing the syntheses of derivatives with uracil heterobase substituted at the position C-5 as well as C-6 were developed. The crucial step of the first methodology was the reaction of (6-chloro-2,4-dimethoxypyrimidin-5-yl)lithium, the nucleobase precursor, with suitable ketones, the carbocyclic pseudosugar precursors. The second approach was based on the copper-catalyzed cross-coupling between magnesiated pyrimidine and appropriate allyl chlorides. These methodologies were applied for the synthesis of novel carbocyclic C-nucleosides bearing cyclohexene or cyclohexane as a pseudosugar.

Key words: carbocyclic C-nucleosides, convergent approach, uracil, pyrimidines, cross-coupling reaction

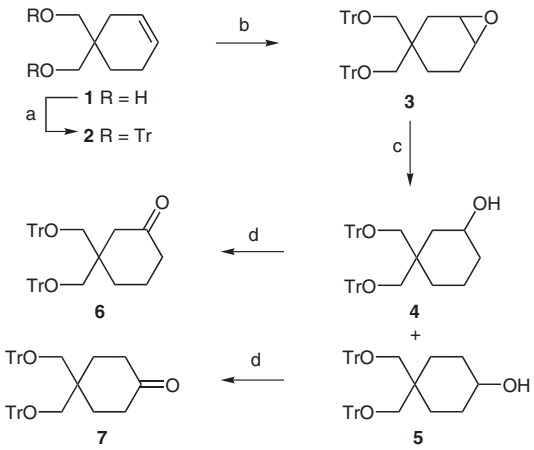
Carbocyclic nucleosides[1,2] and C-nucleosides[2,3] belong to the very important concepts in the development of novel substances for biomedical applications. Carbocyclic C-nucleosides originated from the combination of these two approaches. The characteristic feature of all forenamed nucleoside analogues is the enhanced hydrolytic stability of the bond between nucleobase and sugar (pseudosugar) moiety. Although the first attempts to synthesize carbocyclic C-nucleosides dates back to the 1960s,[4] only few examples of such compounds have been prepared and tested for biological activity since then.[5] Rao and co-workers[6] showed that 9-deazaneplanocin A exerts moderate anti-HIV activity and found that several pyrimidine bases bearing cyclopentenyl analogues of C-nucleosides are antivirally active. Furthermore, several other variously modified derivatives with carbocyclic pseudosugar bonded to the heterocyclic base by carbon–carbon bond were identified to possess interesting biological properties.[7]

The crucial drawback of all the mentioned carbocyclic C-nucleoside syntheses is the traditional linear approach. In most cases the nucleobase was built up in several steps on the carbocyclic pseudosugar. Therefore, novel straightforward synthetic pathways towards carbocyclic C-nucleosides are still necessary.

In this paper, we continue our investigation in the field of carbanucleosides[8] by the synthesis of novel cyclohexyl and cylohexenyl C-nucleosides with pyrimidine nucleobases. Cyclohexane used in this study seems to be a suitable model for further investigation of novel, more direct routes toward this type of compounds.

We decided to explore the possibilities of direct connection of a pyrimidine base and a cyclohexane ring to avoid the difficulties caused by the base building. As a result of this effort, we have developed two convergent synthetic methods for the preparation of carbocyclic C-nucleosides. One of them led to the uracil derivatives with the cyclohexane (or cyclohexene) ring attached at the C-5 position and the other at the C-6 position.

The former synthetic route started from cyclohex-3-ene-1,1-diyldimethanol (**1**) by a slightly modified procedure of tritylation and subsequent epoxidation as described by Mikhailov and co-workers.[9] The cyclohexanols **4** and **5** were synthesized by reduction of epoxide **3** with lithium aluminum hydride in diethyl ether. The reduction proceeded smoothly in good yield and the resolution of isomers **4** and **5** was performed by simple column chromatography. Further oxidation to ketones **6** and **7** was performed by pyridinium dichromate (PDC) in *N*,*N*-dimethylformamide (Scheme 1).



Scheme 1 *Reagents and conditions*: a) TrCl, pyridine, 100 °C, 86%; b) MCPBA, CH_2Cl_2, 0 °C, 75%; c) $LiAlH_4$, Et_2O, 40% of **4**, 37% of **5**; d) PDC, DMF, 88% of **6**, 86% of **7**.

The key step of this pathway was the reaction of these ketones with (6-chloro-2,4-dimethoxypyrimidin-5-yl)lithium (**9**) prepared form 6-chloro-2,4-dimethoxypyrimidine (**8**) and *n*-BuLi.[10] Thermal stability of the organolithium compound **9** was demonstrated on a simple study performed as a yield comparison of its reaction with benzaldehyde after stirring the lithiated species for appropriate

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time at defined temperature. As depicted in Table 1 and Figure 1, the stability showed an extreme loop between 0 and –25 °C.

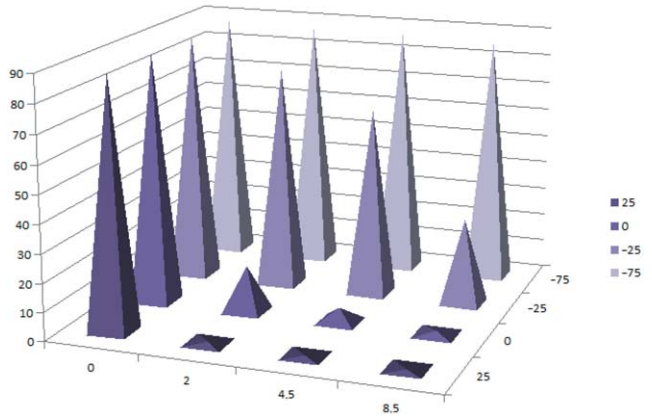


Figure 1 Time-dependence of thermal stability of (4-chloro-2,6-dimethoxypyrimidin-5-yl)lithium (**9**) in THF; x-axis refers to the reaction temperature (°C), y-axis refers to the time of stirring (h), z-axis refers to the yields obtained from the reaction with benzaldehyde (%)

Table 1 Time-Dependence of Thermal Stability of the Organolithium **9** in THF[a]

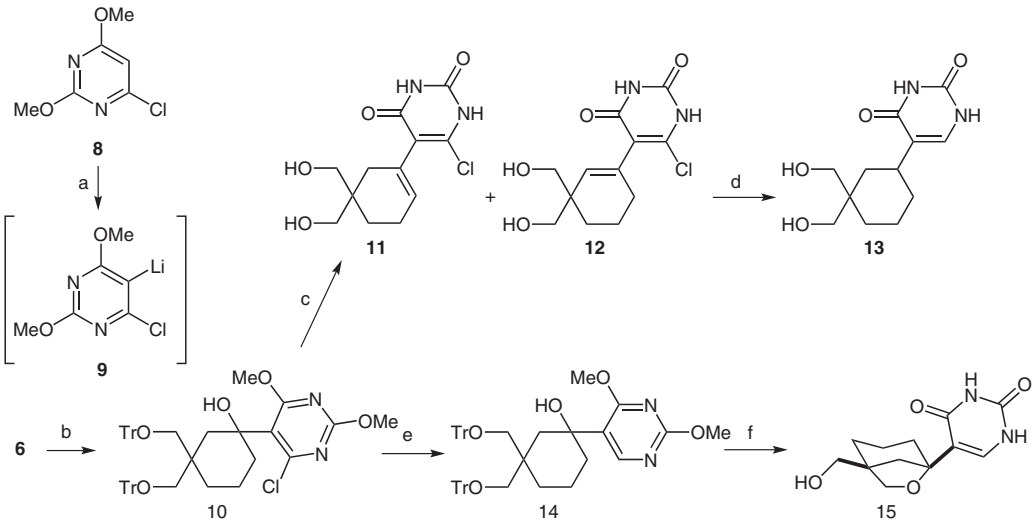
Time of stirring (h)	Temperature of stirring (°C)			
	–75	–25	0	25
2	87%	78%	16%	0.5%
4.5	86%	70%	0.1%	0%
8.5	84%	43%	0%	0%

[a] A solution of **9** was prepared by treatment of **8** in THF with *n*-BuLi for 30 min at –75 °C and transferred to the vessels kept at the appropriate temperatures and also to the reference vessel containing 3 equiv of benzaldehyde in THF and stirred for additional 1 h at –75 °C; yield 88%. The samples, took at the defined intervals, were treated with 3 equiv of benzaldehyde in THF for 1 h at –75 °C as well. Yields were determined by GC-MS after usual workup.

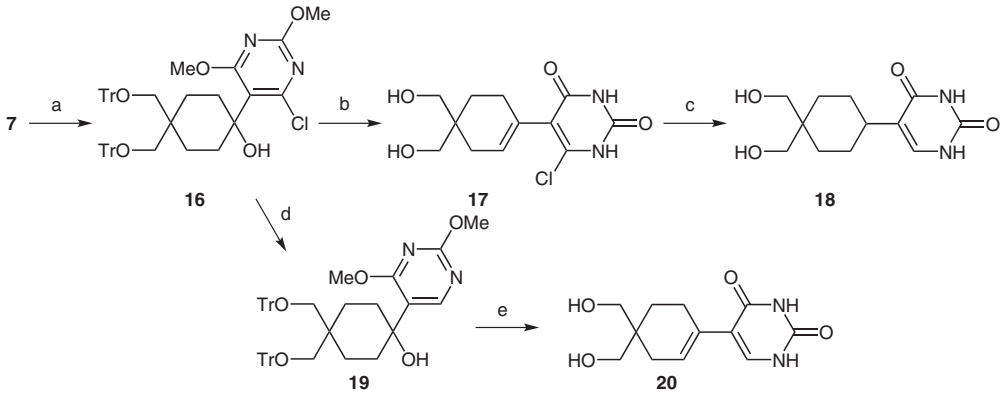
Treatment of the ketone **6** with organolithium species **9** resulted in the formation of expected adduct **10** in very good yield when the reaction temperature was kept around –30 °C. On heating the intermediate **10** with aqueous hydrochloric acid in a mixture of tetrahydrofuran and 1,4-dioxane, removal of protecting groups as well as elimination of tertiary hydroxy group occurred, forming products **11** and **12** in approximately 6:1 ratio. The prevailing isomer **11** was partially separated by crystallization and the other isomer **12** and a further portion of **11** was isolated by preparative HPLC. The mixture of isomers **11/12**, isolated by standard column chromatography, was utilized in the next step where the double bond and the chlorine atom were removed by catalytic hydrogenation to yield the pseudouridine derivative **13**.

In a different approach, the precursor **10** can be hydrogenated first to afford the derivative **14**, and then deprotected and eliminated. Surprisingly, the main product of this deprotection/elimination procedure was the bicyclic compound (±)-**15** resulting from the acid-catalyzed intramolecular etherification rather than the product of elimination (Scheme 2). This empirical observation can be explained by significantly higher sterical hindrance of the reaction center in the carbocationic transition state in the presence of the chlorine atom on the pyrimidine moiety.

The ketone **7** underwent similar procedure as its counterpart. The deprotection/elimination step afforded only one product **17** due to the symmetry of the starting material; the transformation proceeded with an excellent yield. Hydrogenation of this intermediate gave the final compound **18**. Also, the removal of the chlorine atom from the substrate **16** was similarly successful (Scheme 3). In contrast to the other isomer, the treatment of substrate **19** with hydrochloric acid in tetrahydrofuran–1,4-dioxane gave the elimination product **20**. The building blocks for the later methodology of derivatization of uracils and their analogues at position C-6 were also obtained from compound



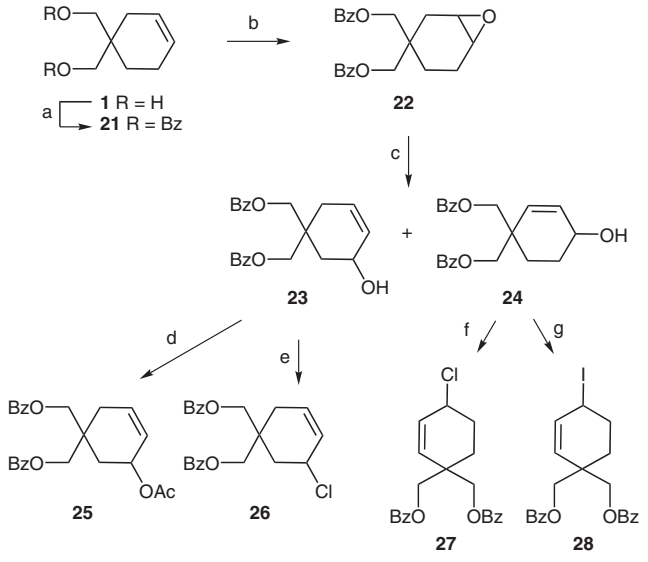
Scheme 2 *Reagents and conditions*: a) *n*-BuLi, THF, –75 °C; b) **9**, THF, < –20 °C, 82%; c) HCl, THF, 1,4-dioxane, 56% of **11**, 11% of **12**; d) H_2, $Pd(OH)_2$/C, MeOH, 87%; e) H_2, $Pd(OH)_2$/C, Et_3N, EtOH, 94%; f) HCl, THF, 1,4-dioxane, 58%.



Scheme 3 *Reagents and conditions*: a) 9, THF, < –20 °C, 89%; b) HCl, THF, 1,4-dioxane, 70%; c) H_2, $Pd(OH)_2$/C, MeOH, 89%; d) H_2, $Pd(OH)_2$/C, Et_3N, EtOH, 98%; e) HCl, THF, 1,4-dioxane, 49%.

1. The crucial allylic intermediates **23** and **24** were prepared from the epoxide **22**, obtained from **1** by simple benzoylation[19] and epoxidation, by Lewis acid induced rearrangement[11] on treatment with TMSOTf and DBU, and subsequent hydrolysis of the formed trimethylsilyl ether by dilute hydrochloric acid.

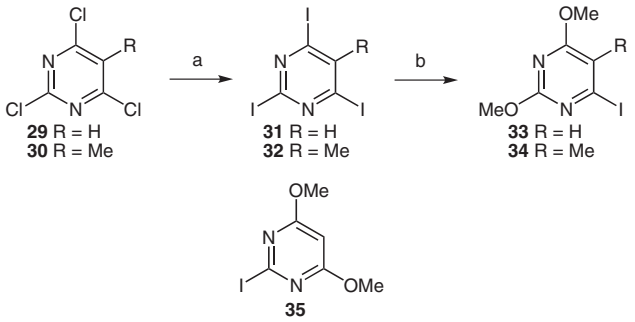
The allylic alcohols **23** and **24** were easily separated by column chromatography and obtained in good yields in almost 1:1 ratio (Scheme 4). Since the hydroxy group is a very poor leaving group, the obtained alcohols were transformed into various allylic substrates traditionally used in the coupling reactions with organometallic compounds.



Scheme 4 *Reagents and conditions*: a) BzCl, pyridine, 78%; b) MCPBA, CH_2Cl_2, 77%; c) i.TMSOTf, DBU, toluene, ii. aq HCl, MeOH, 34% of **23**, 31% of **24**; d) Ac_2O, DMAP, MeCN, 92%; e) NCS, PPh_3, THF, 87%; f) NCS, PPh_3, THF, 88%; g) NaI, TMSCl, H_2O, MeCN, 98%.

Thus, substrate **25** was prepared by simple acetylation of alcohol **23** with acetic anhydride in the presence of DMAP as a catalyst. Both alcohols were converted to appropriate allyl chlorides **26** and **27** on treatment with in situ prepared complex triphenylphosphine–*N*-chlorosuccinimide.[12] This method proved very effective for formation of such allylic substrates and afforded excellent yields of desired products. In contrast to comparable allyl bromides and allyl iodides, these products can be chromatographed on silica gel and stored for several weeks without significant loss of quality. The allyl iodide **28**, prepared by the reaction of allyl alcohol with in situ generated anhydrous hydroiodic acid,[13] was obtained in excellent yield. However, this compound decomposes rapidly and cannot be stored and hence was used in the next step immediately after preparation (Scheme 4). Also, the mixtures of isomeric allyl bromides was prepared directly by reaction of cyclohexane derivative **2** or **21** with *N*-bromosuccinimide in CCl_4 in the presence of AIBN. The reactions proceeded smoothly in very good yield. Unfortunately, these mixtures could not be separated (or even purified) by chromatography and their further reactions resulted in the hardly separable mixtures of coupling products.

The starting pyrimidine iodides, 4-iodo-2,6-dimethoxypyrimidine (**33**)[14] and 4-iodo-2,6-dimethoxy-5-methylpyrimidine (**34**), were prepared in two steps from appropriate trichloropyrimidines (Scheme 5). The chlorine atoms were substituted by iodine on treatment with aqueous hydroiodic acid. This reaction proceeds in good yields but the workup is somewhat tricky. The product should be collected only by filtration, washed with water

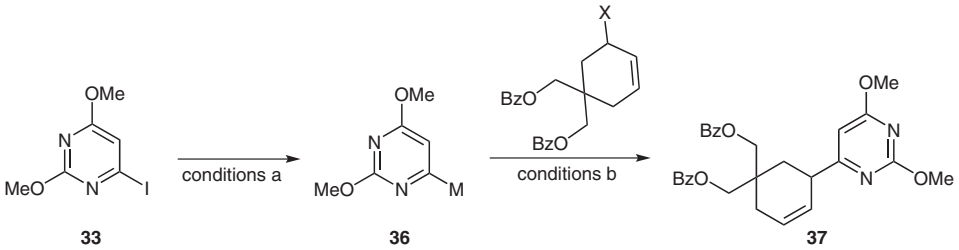


Scheme 5 *Reagents and conditions*: a) 57% HI; b) NaOMe, MeOH, THF, 50% for **33** (two steps, 11% of byproduct **35**), 56% for **34** (two steps).

and dried in dessicator over P_2O_5, because any other handling (such as co-evaporation with a solvent), resulted in rapid darkening and decomposition of the product. Further reaction of triiodopyrimidines with sodium methoxide afforded the desired protected iodo derivatives. The usual by-product of this transformation was the alternative regioisomer **35**. As shown in Table 2, all attempts to metalate the pyrimidine derivative and use the metalated species for cross-coupling reactions with allylic substrates started with the preparation of organozinc intermediate by iodine–lithium exchange followed by transmetalation of lithium with zinc chloride. The organozinc species prepared was reacted under palladium catalysis with allyl acetate **25** as well as with allyl chloride **26**.

Unfortunately, regardless of the catalyst used, allyl acetate gave no reaction at all and reaction with allyl chlorides afforded only degradation products. The application of lithium–tin exchange was unsuccessful as well. This behavior is surprising since similar reactions with either organozinc species or stannanes are routinely performed and were studied in detail.[15] The results did not suggest whether the weak point is the lithiation procedure or the cross-coupling reaction. Although the same lithiated pyrimidine was successively used in a different synthesis,[16] fast darkening of the freshly lithiated intermediate indicates rapid decomposition of this species. Therefore, we decided to switch to the preparation of Grignard reagent of this pyrimidine derivative according to the well estab-

Table 2 Cross-Coupling Reactions with Allyl Acetates and Chlorides



33 **36** **37**

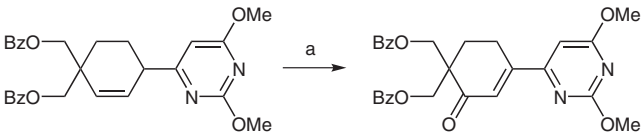
Entry	X	Conditions a	M	Conditions b	Solvent	Yield (%)
1	OAc	1. BuLi, –78 °C 2. $ZnCl_2$, r.t.	ZnCl	5 mol% $Pd(PPh_3)_4$, 60 °C	THF	nr[a]
2	OAc	1. BuLi, –78 °C 2. $ZnCl_2$, r.t.	ZnCl	3 mol% $Pd(AcO)_2$, 6 mol% DPEPhos, 60 °C	THF	nr[a]
3	OAc	1. BuLi, –78 °C 2. $ZnCl_2$, r.t.	ZnCl	3 mol% $Pd(AcO)_2$, 6 mol% XantPhos, 60 °C	THF	nr[a]
4	OAc	1. BuLi, –78 °C 2. $ZnCl_2$ r.t.	ZnCl	3 mol% $Pd(AcO)_2$, 6 mol% dppp, 60 °C	THF	nr[a]
5	OAc	1. BuLi, –78 °C 2. $ZnCl_2$, r.t.	ZnCl	5 mol% $Pd(dppf)_2Cl_2$, 60 °C	THF	nr[a]
6	Cl	1. BuLi, –78 °C 2. $ZnCl_2$, r.t.	ZnCl	5 mol% $Pd(PPh_3)_4$, 60 °C	THF	dec.[b]
7	Cl	1. BuLi, –78 °C 2. $ZnCl_2$, r.t.	ZnCl	5 mol% $Pd(dppf)_2Cl_2$, 60 °C	THF	dec.[b]
8	Cl	1. BuLi, –78 °C 2. Bu_3SnCl, r.t.	Bu_3Sn	5 mol% $Pd(dppf)_2Cl_2$, 60 °C	THF	dec.[b]
9	Cl	1. BuLi, –78 °C 2. $ZnCl_2$, r.t.	ZnCl	5 mol% $Pd(PPh_3)_4$, 60 °C	Et_2O	dec.[b]
10	Cl	*i*-PrMgCl·LiCl, –25 °C	MgCl·LiCl	$Pd_2(dba)_3$, XPhos, –25 to 0 °C, 16 h, r.t.	THF	trace
11	Cl	*i*-PrMgCl·LiCl, –25 °C	MgCl·LiCl	5 mol% $Pd(dppf)_2Cl_2$, –25 to 0 °C, 16 h, r.t.	THF	trace
12	Cl	*i*-PrMgCl·LiCl, –25 °C	MgCl·LiCl	CuI·2LiCl, –25 to 0 °C, 16 h, 0 °C	THF	26
13	Cl	*i*-PrMgCl·LiCl, –25 °C	MgCl·LiCl	$Ni(dppp)_2Cl_2$, –25 to 0 °C, 16 h, r.t.	THF	8
14	Cl	*i*-PrMgCl·LiCl, –25 °C	MgCl·LiCl	CuI·2LiCl, –25 °C, 36 h	THF	77

[a] The starting allylic substrate remained unchanged; nr = no reaction.
[b] The starting allylic substrate decomposed.

lished Knochel's procedure[17] using the reaction of pyrimidinyl iodide with *i*-PrMgCl·LiCl.

Further screening of catalytic systems revealed that the only acceptable results could be obtained under copper catalysis. Although the screening attempt resulted in only 26% yield of the desired product, further optimization of the reaction conditions led to the significant increase of the reaction yield to 77%. Similar conditions were applied also for the coupling of the magnesiated pyrimidine with allyl chloride **27** and allyl iodide **28** (Table 3). The results of the coupling reactions of both substrates are comparable, because the yield of the reaction with allyl iodide includes also the previous step. However, as we stressed above, the use of the iodide **28** should be avoided due to its stability parameters. The only isolated product was the isomer **38**. The steric hinderance most likely prohibits the allylic rearrangement and formation of isomeric product often observed in this type of reactions under copper catalysis.[18]

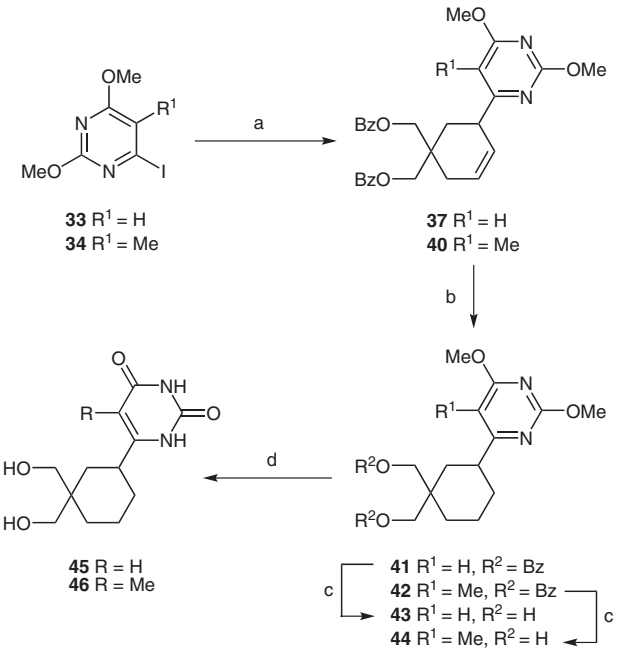
Unfortunately, the product **38** exerted surprising sensitivity towards oxidative degradation and almost completely decomposed in one month (Scheme 6). The main product (~50%) of this degradation was identified as [4-(2,6-dimethoxypyrimidin-4-yl)-2-oxocyclohex-3-ene-1,1-diyl]dimethanediyl dibenzoate (**39**).



38 **39**

Scheme 6 *Reagents and conditions*: a) air, light, 1 month.

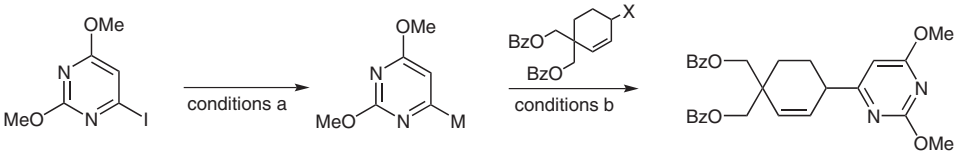
The compounds **37** and **38** were therefore hydrogenated right after their preparation to avoid this decomposition process. Benzoyl groups were then removed by treatment with potassium carbonate in methanol and the final products were released from their methylated precursors on treatment with concentrated hydrochloric acid in a mixture of tetrahydrofuran and 1,4-dioxane. Furthermore, the similar reaction scheme was also used for the preparation of thymine derivatives **46** and **53** starting from pyrimidine derivative **34** and allyl chlorides **26** and **27** (Scheme 7 and Scheme 8).



Scheme 7 *Reagents and conditions*: a) i. *i*-PrMgCl·LiCl, THF, –25 °C; ii. **26**, CuI·2LiCl, THF, –25 °C, 77% for **37**, 71% for **40**; b) H_2, $Pd(OH)_2$, MeOH, 95% for **41**, 93% for **42**; c) K_2CO_3, MeOH, 92% for **43**, 89% for **44**; d) HCl, THF, 1,4-dioxane, 66% for **45**, 72% for **46**.

The crucial disadvantage of linear strategies towards new carbocyclic C-nucleosides is low efficiency of single steps leading to the diminished productivity of the whole process. Herein, we have introduced two novel convergent approaches for suitable synthesis of this class of nucleoside analogues based on the application of organometallic derivatives of 2,4-dimethoxypyrimidines.

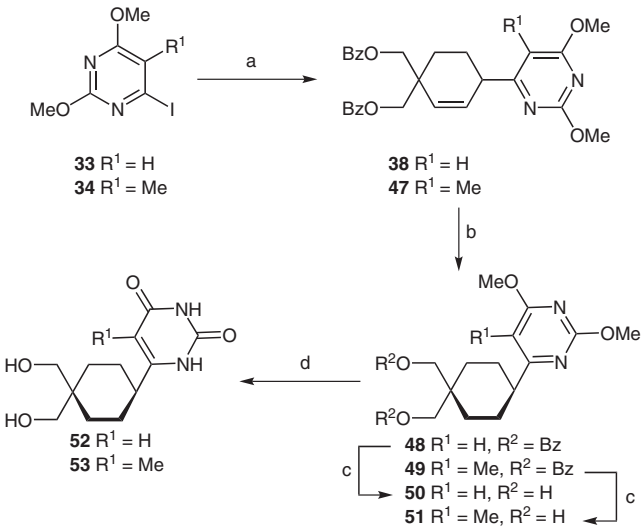
Table 3 Cross-Coupling Reactions with Allyl Chlorides and Iodides



33 **36** **38**

Entry	X	Conditions a	M	Conditions b	Solvent	Yield (%)
1	I	*i*-PrMgCl·LiCl, –25 °C	MgCl·LiCl	CuI·2LiCl; –25 °C, 1 h; 0 °C, 4 h; 12 h, r.t.	THF	33
2	Cl	*i*-PrMgCl·LiCl, –25 °C	MgCl·LiCl	CuI·2LiCl; –25 °C, 1 h; 0 °C, 4 h; 12 h, r.t.	THF	41
3	Cl	*i*-PrMgCl·LiCl, –25 °C	MgCl·LiCl	CuI·2LiCl; –25 °C, 36 h	THF	60

One approach utilized the reaction of (4-chloro-2,6-dimethoxypyrimidin-5-yl)lithium with the proper ketone precursor as the essential step of the pseudouridine analogue synthesis. The second approach employed copper-catalyzed reaction of organomagnesium derivative of 2,4-dimethoxypyrimidine with suitable allyl chloride in order to prepare the derivatives with the carbocyclic ring connected to the pyrimidine base at position C-6. These two approaches open the desired direct way towards the carbocyclic C-nucleosides with the pseudosugar moiety bonded to the uracil heterobase at the both possible positions (C-5 and C-6).



Scheme 8 *Reagents and conditions*: a) i. *i*-PrMgCl·LiCl, THF, –25 °C; ii. **27**, CuI·2LiCl, THF, –25 °C, 60% for **38,** 52% for **47**; b) H_2, $Pd(OH)_2$, MeOH, 89% for **48**, 80% for **49**; c) K_2CO_3, MeOH; 85% for **50**, 66% for **51**; d) HCl, THF, 1,4-dioxane, 75% for **52**, 79% for **53**.

Moreover, the latter method is not limited only to the uracil derivatives but can be also used for the straightforward synthesis of thymine analogues. Although the preliminary biological results of the synthesized nucleoside derivatives hold little hope for further development of the six-membered analogues, we are convinced that the applied procedures can be utilized in the synthesis of various other interesting targets among carbocyclic C-nucleosides.

The chemicals were obtained from commercial sources (Sigma-Aldrich) or prepared according to published procedures. 4-Chloro-2,6-dimethoxypyrimidine was sublimed under reduced pressure (75 °C, ~ 1 mbar) before use. Melting points are uncorrected and were determined on a Kofler block or on a Büchi Melting Point B-540 apparatus. NMR spectra were recorded on Bruker Avance II 600 (^{1}H NMR at 600 MHz, ^{13}C NMR at 151 MHz), Bruker Avance 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 125.8 MHz) and Bruker Avance 400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 100.6 MHz) spectrometers. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix) or EI (electron energy 70 eV) or on LTQ Orbitrap XL (Thermo Fisher Scientific) spectrometer using electrospray ionization (ESI). The GC-MS analyses were performed on an Agilent 5975B MSD. Preparative HPLC separations were performed on a column packed with 10 mm C18 reversed-phase silica gel (Luna), 250 × 21 mm; in ca 300 mg portions of mixtures using linear gradient 0.1 M triethylammonium hydrogen carbonate (TEAB) in H_2O and in 50% MeOH (linear gradient of TEAB in 50% MeOH, 0–100%). IR specra were recorded on an FTIR Bruker Equinox IFS 55 spectrophotometer in KBr pellets or in $CHCl_3$. The elemental analyses were determined on a Perkin-Elmer CHN Analyzer 2400, Series II Sys (Perkin Elmer, Norwolk, CT, USA). Petroleum ether (PE) refers to the fraction boiling in the range 50–70 °C.

1-(4-Chloro-2,6-dimethoxypyrimidin-5-yl)-3,3-Bis(trityloxymethyl)cyclohexanol (10)

n-BuLi (1.6 M, 4.2 mL, 6.7 mmol) was added dropwise to a stirred solution of 6-chloro-2,4-dimethoxypyrimidine (1.06 g, 6.06 mmol) in THF (40 mL) cooled to –75 °C. After 25 min, a solution of ketone **6** (3 g, 4.66 mmol) in THF (35 mL) was added and the mixture was stirred for 35 min at –75 °C, 2 h at –30 °C, and 16 h at 0 °C. The resulting solution was partitioned between Et_2O (2 × 300 mL) and aq NH_4Cl (200 mL) and the combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), evaporated, and the product was purified by chromatography (PE–EtOAc, 4:1). Crystallization from cyclohexane gave white crystals; yield: 3.14 g (82%); mp 196–197.5 °C.

IR ($CHCl_3$): 3572, 3088, 3062, 3034, 1595, 1568, 1541, 1490, 1484, 1449, 1389, 1318, 1184, 1160, 1153, 1102, 1075, 1069, 1032, 1002, 948, 899, 708, 700, 647, 633, 617, 534 cm^{-1}.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 1.26–1.37 (m, 3 H, H-4a, H-5), 1.64 (m, 2 H, H-6a and H-4b), 2.02 (dt, *J* = 14.7, 1.9 Hz, 1 H, H-2a), 2.08 (d, *J* = 14.7 Hz, 1 H, H-2b), 2.36 (m, 1 H, H-6b), 2.95 (d, *J* = 8.4 Hz, 1 H, OCH_2), 3.00 (d, *J* = 2.0 Hz, 1 H, OH), 3.37 (d, *J* = 8.4 Hz, 1 H, OCH_2), 3.49 (d, *J* = 8.8 Hz, 1 H, OCH_2), 3.52 (d, *J* = 8.8 Hz, 1 H, OCH_2), 3.88 (s, 3 H, 4′-OCH_3), 3.95 (s, 3 H, 2′-OCH_3), 7.19–7.27 (m, 18 H, C_6H_5), 7.33 (m, 6 H, C_6H_5), 7.45 (m, 6 H, C_6H_5).

^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 17.1, 29.2, 35.6, 38.9, 39.8, 54.9, 55.0, 63.8, 70.0, 74.5, 85.9, 86.1, 118.6, 126.6, 126.7, 127.5, 127.6, 128.7, 128.8, 144.1, 157.3, 161.1, 169.7.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{52}H_{49}ClN_2O_5$: 817.34083; found: 817.34173.

5-[5,5-Bis(hydroxymethyl)cyclohex-1-enyl]-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (11) and 5-[3,3-Bis(hydroxymethyl)cyclohex-1-enyl]-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (12)

A mixture of the substrate **10** (1.3 g, 1.59 mmol), concd HCl (5.3 mL), THF (6.5 mL), and 1,4-dioxane (7.8 mL) was heated to reflux for 2.5 h. The resulting slurry was evaporated to a minimum volume and partitioned between H_2O (100 mL) and PE–toluene (1:5, 40 mL) and the organic phase was once washed with H_2O (100 mL). The combined aqueous portions were evaporated and the residue was either purified by column chromatography (EtOAc–acetone–EtOH–H_2O, 20:3:1:1) to afford a mixture of products **11** and **12** (60%) used in the preparation of **13** or crystallized from H_2O to give the product **11** (156 mg, 34%). The mother liquor was then evaporated and submitted to preparative HPLC, which gave **11** (101 mg, 22%) and **12** (49 mg, 11%).

11

White crystals; mp 247–248.5 °C (H_2O).

IR (KBr): 3400, 3240, 3180, 3068, 3021, 1725, 1653, 1615, 1521, 1429, 1047, 1038, 1030 cm^{-1}.

^{1}H NMR (499.95 MHz, DMSO-d_6): δ = 1.39 (t, *J* = 6.5 Hz, 2 H, H-4′), 1.77 (m, 2 H, H-6′), 2.07 (m, 2 H, H-3′), 3.23 (dd, *J* = 10.6, 5.2

Hz, 2 H, OCH_2), 3.33 (dd, J = 10.6, 5.7 Hz, 2 H, OCH_2), 4.32 (t, J = 5.5 Hz, 2 H, OH), 5.53 (m, 1 H, H-2′), 11.27 (br s, 1 H, NH) 11.86 (br s, 1 H, NH).

^{13}C NMR (125.73 MHz, DMSO-d_6): δ = 22.0, 24.1, 32.5, 38.6, 64.4, 114.00, 128.5, 128.8, 141.3, 149.9, 162.4.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{12}H_{15}ClN_2O_4$ + Na: 309.0613; found: 309.0612.

Anal. Calcd for $C_{12}H_{15}ClN_2O_4$: C, 50.27; H, 5.27; N, 9.77. Found: C, 50.06; H, 5.18; N, 9.52.

12

White crystals; mp 233 °C (H_2O).

IR (KBr): 3433, 3223, 3169, 3046, 1721, 1673, 1613, 1511, 1487, 1429, 1040, 1029 cm^{-1}.

^{1}H NMR (600.13 MHz, DMSO-d_6): δ = 1.34 (m, 2 H, H-4′), 1.58 (m, 2 H, H-5′), 1.98 (dt, J = 6.2, 1.6 Hz, 2 H, H-6′), 3.24 (dd, J = 10.4, 5.3 Hz, 2 H, CH_2O_a), 3.31 (dd, J = 10.4, 5.1 Hz, 2 H, CH_2O_b), 4.41 (t, J = 5.5 Hz, 2 H, OH), 5.43 (t, J = 1.8 Hz, 1 H, H-2′), 11.27 (br s, 1 H, NH), 11.86 (br s, 1 H, NH).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 18.8, 25.8, 28.2, 42.2, 64.4, 113.9, 131.1, 133.2, 141.4, 149.9, 162.3.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{12}H_{15}ClN_2O_4$ + Na: 309.06126; found: 309.06131.

Anal. Calcd for $C_{12}H_{15}ClN_2O_4$: C, 50.27; H, 5.27; N, 9.77. Found: C, 50.01; H, 5.24; N, 9.43.

5-[3,3-Bis(hydroxymethyl)cyclohexyl]pyrimidine-2,4(1*H*,3*H*)-dione (13) and 5-[4,4-Bis(hydroxymethyl)cyclohexyl]pyrimidine-2,4(1*H*,3*H*)-dione (18); General Procedure

$Pd(OH)_2$/C (70 mg) was added to a solution of the substrate (1 mmol) in MeOH (10 mL) and the mixture was stirred under H_2 atmosphere for 48 h. The catalyst was removed by filtration through a Celite pad, washed thoroughly with hot MeOH, and the filtrate was evaporated. Chromatography on a short column of silica gel (EtOAc–acetone–EtOH–H_2O, 36:6:5:3) and crystallization from aq EtOH afforded the products **13** and **18**, respectively.

13

Prepared from a mixture of **11** and **12**; yield: 87%; pale gray crystals; mp 292–293.5 °C.

IR (KBr): 3297, 3230, 3170, 3130, 3082, 3031, 1711, 1672, 1480, 1431, 1234, 1199, 1055, 1049, 774 cm^{-1}.

^{1}H NMR (499.95 MHz, DMSO-d_6): δ = 0.97–1.05 (m, 2 H, H-4′$_{ax}$ and H-6′$_{ax}$), 1.09 (t, J = 13.0 Hz, 1 H, H-2′$_{ax}$), 1.35–1.54 (m, 4 H, H-2′$_{eq}$, H-4′$_{eq}$ and H-5′), 1.70 (dm, J = 13.0 Hz, 1 H, H-6′$_{eq}$), 2.50 (m, 1 H, H-1′), 3.13 (dd, J = 10.4, 5.7 Hz, 1 H, CH_2O), 3.18 (dd, J = 10.4, 5.6 Hz, 1 H, CH_2O), 3.40 (m, 2 H, CH_2O), 4.26 (t, J = 5.3 Hz, 1 H, OH), 4.30 (t, J = 5.6 Hz, 1 H, OH), 7.01 (s, 1 H, H-6), 10.61 (br s, 1 H, NH), 10.96 (br s, 1 H, NH).

^{13}C NMR (125.73 MHz, DMSO-d_6): δ = 21.6, 28.3, 29.5, 32.1, 34.4, 39.9, 61.3, 68.7, 117.6, 136.4, 151.2, 164.4.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{12}H_{18}N_2O_4$ + Na: 277.11588; found: 277.11586.

Anal. Calcd for $C_{12}H_{18}N_2O_4 \cdot H_2O$: C, 55.69; H, 7.21; N, 10.82. Found: C, 54.65; H, 7.20; N, 10.54.

18

Prepared from **17** (see below); yield: 89%; pale gray crystals; mp 329.5–330 °C.

IR (KBr): 3332, 3280, 3219, 3078, 3045, 1712, 1666, 1497, 1435, 1241, 1208, 1043, 775 cm^{-1}.

^{1}H NMR (499.95 MHz, DMSO-d_6): δ = 1.13 (dt, J = 13.5, 4.1 Hz, 2 H, H-3′$_{ax}$ and H-5′$_{ax}$), 1.36 (m, 2 H, H-2′$_{ax}$ and H-6′$_{ax}$), 1.47 (dm, J = 13.2 Hz, 2 H, H-2′$_{eq}$ and H-6′$_{eq}$), 1.53 (dm, 2 H, H-3′$_{eq}$ and H-5′$_{eq}$), 2.25 (tt, J = 12.1, 3.2 Hz, 1 H, H-1′), 3.16 (d, J = 5.5 Hz, 2 H, CH_2O), 3.40 (dd, J = 5.4 Hz, 2 H, CH_2O), 4.22 (t, J = 5.4 Hz, 1 H, OH), 4.30 (t, J = 5.5 Hz, OH), 1 H, OH), 7.07 (s, 1 H, H-6), 10.61 (br s, 1 H, NH), 10.95 (br s, 1 H, NH).

^{13}C NMR (125.73 MHz, DMSO-d_6): δ = 26.7, 29.2, 35.1, 38.5, 61.1, 68.7, 117.3, 136.5, 151.3, 164.4.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{12}H_{18}N_2O_4$ + Na: 277.11588; found: 277.11585.

1-(2,4-Dimethoxypyrimidin-5-yl)-3,3-bis(trityloxymethyl)cyclohexanol (14) and 1-(2,4-Dimethoxypyrimidin-5-yl)-4,4-bis(trityloxymethyl)cyclohexanol (19)

The starting chloro derivative **10** or **16** (1 g, 3.8 mmol) was mixed with toluene (17 mL), abs. EtOH (23 mL), and Et_3N (329 mg). $Pd(OH)_2$ on activated carbon (145 mg) was added and the suspension was kept under H_2 atmosphere for 16 h. Filtration through a Celite pad followed by evaporation and chromatography on silica gel (toluene–EtOAc, 4:1) afforded the products **10** (94%) and **16** (98%) as white foams.

14

IR ($CHCl_3$): 3572, 3088, 3062, 3034, 1595, 1568, 1541, 1490, 1484, 1449, 1389, 1318, 1184, 1160, 1153, 1102, 1075, 1069, 1032, 1002, 948, 899, 708, 700, 647, 633, 617, 534 cm^{-1}.

^{1}H NMR (499.95 MHz, DMSO-d_6): δ = 0.92 (m, 1 H, H-4a), 1.07–1.20 (m, 3 H, H-6a and H-5), 1.38 (d, J = 14.3 Hz, 1 H, H-2a), 1.69 (dm, J = 13.0 Hz, 1 H, H-4b), 1.87 (m, 1 H, H-6b), 2.04 (d, J = 14.6 Hz, 1 H, H-2b), 2.74 (d, J = 8.2 Hz, 1 H, OCH_2), 3.25 (d, J = 9.2 Hz, 1 H, OCH_2), 3.36 (d, J = 8.3 Hz, 1 H, OCH_2), 3.80 (d, J = 9.1 Hz, 1 H, OCH_2), 3.84 (s, 6 H, OCH_3), 4.56 (s, 1 H, OH), 7.22–7.34 (m, 30 H, 3 × C_6H_5), 8.20 (s, 1 H, H-6′).

^{13}C NMR (125.73 MHz, DMSO-d_6): δ = 16.5, 27.9, 35.0, 39.4, 41.0, 53.9, 54.5, 63.2, 69.6, 70.6, 85.5, 85.7, 122.6, 126.9, 127.1, 127.9, 128.6, 144.2, 144.5, 156.2, 164.0, 167.2.

HRMS-FAB: m/z [M + H]$^+$ calcd for $C_{52}H_{50}N_2O_5$: 783.37980; found: 783.38280.

19

FT-IR ($CHCl_3$): 3576, 3088, 3062, 3034, 1596, 1567, 1490, 1476, 1449, 1386, 1319, 1186, 1160, 1153, 1112, 1090, 1074, 1033, 964, 900, 803, 707, 700, 644, 633, 617, 539 cm^{-1}.

^{1}H NMR (600.13 MHz, DMSO-d_6): δ = 1.19 (dm, J = 13.8 Hz, 2 H, H-3$_{eq}$ and H-5$_{eq}$), 1.43 (td, J = 13.6, 4.3 Hz, 2 H, H-2$_{ax}$ and H-6$_{ax}$), 1.55 (dm, J = 13.4 Hz, 2 H, H-2$_{eq}$ and H-6$_{eq}$), 1.97 (td, J = 13.8, 4.2 Hz, 2 H, H-3$_{ax}$ and H-5$_{ax}$), 3.03 (s, 2 H, OCH_2), 3.31 (s, 2 H, OCH_2), 3.35 (s, 3 H, 4′-OCH_3), 3.83 (s, 3 H, 2′-OCH_3), 7.19–7.39 (m, 30 H, 3 × C_6H_5), 8.25 (s, 1 H, H-6′).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 26.1, 30.0, 37.8, 53.6, 54.5, 62.2, 68.9, 70.0, 85.6, 85.8, 122.5, 127.0, 127.2, 127.9, 128.1, 128.6, 128.6, 144.2, 144.3, 155.8, 164.0, 167.4.

HRMS-FAB: m/z [M + H]$^+$ calcd for $C_{52}H_{50}N_2O_5$: 783.37980; found: 783.38238.

1-(4-Chloro-2,6-dimethoxypyrimidin-5-yl)-4,4-bis(trityloxymethyl)cyclohexanol (16)

n-BuLi (1.6 M in hexanes, 4.2 mL, 6.7 mmol) was added dropwise to a stirred solution of 6-chloro-2,4-dimethoxypyrimidine (**8**; 1.06 g, 6.06 mmol) in THF (40 mL) cooled to –75 °C. After 30 min, the solution of ketone **7** (3 g, 4.66 mmol) in THF (35 mL) was added and the mixture was stirred for 35 min at –75 °C, 4 h at –30 °C, and 16 h at –10 °C. The resulting solution was partitioned between Et_2O

(2 × 300 mL) and aq NH_4Cl (200 mL) and the combined organic portions were washed with brine (200 mL), dried (Na_2SO_4), evaporated and the product was purified by chromatography (PE–EtOAc, 4:1) and crystallization from EtOH to give **16** as white crystals; yield: 3.4 g (89%); mp 131 °C (hydrate) and 165 °C (anhyd).

IR ($CHCl_3$): 3571, 3088, 3062, 3034, 1597, 1570, 1541, 1490, 1483, 1449, 1389, 1316, 1183, 1160, 1153, 1103, 1082, 1071, 1031, 948, 900, 707, 700, 644, 633, 617, 539, 469 cm^{-1}.

^1H NMR (600.13 MHz, DMSO-d_6): δ = 1.45 (m, 6 H, H-2, H-6, H-3a, and H-5a), 1.96 (m, 2 H, H-3b and H-5b), 3.03 (s, 2 H OCH_2), 3.31 (s, 2 H, OCH_2), 3.45 (s, 3 H, 4′-OCH_3), 3.83 (s, 3 H, 2′-OCH_3), 4.59 (s, 1 H, OH), 7.21–7.36 (m, 30 H, 3 × C_6H_5).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 26.1, 30.1, 37.6, 54.6, 55.0, 62.1, 69.1, 72.1, 85.6, 85.8, 127.1, 127.1, 127.9, 128.1, 128.6, 144.2, 144.3, 158.0, 161.1, 169.3.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{52}H_{49}ClN_2O_5$: 817.34083; found: 817.34296.

Deprotection/Elimination Procedure; Preparation of Derivatives 15, 17, and 20; General Procedure

A mixture of substrate (1.22 mmol), concd HCl (4.1 mL), THF (4 mL), 1,4-dioxane (6 mL), and H_2O (0.7 mL) was heated to reflux for 2 h. The resulting slurry was evaporated to a minimum volume and partitioned between H_2O (70 mL) and PE–toluene (1:5, 30 mL). The organic phase was once extracted with H_2O (70 mL). The combined aqueous portions were evaporated and the residue was purified by crystallization to give the products.

***trans*-5-[1-(Hydroxymethyl)-6-oxabicyclo[3.2.1]octan-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione (15)**

This compound was prepared from **14** according to the general procedure, but the crystallization was preceded by a column chromatography (EtOAc–acetone–EtOH– H_2O, 20:3:1:1); yield: 58%; white crystals; mp 264 °C (H_2O).

IR (KBr): 3303, 3237, 3170, 3116, 3032, 1710, 1661, 1496, 1428, 1229, 1203, 1059, 1047, 1035, 763 cm^{-1}.

^1H NMR (600.13 MHz, DMSO-d_6): δ = 1.29–1.36 (m, 2 H, H-4′$_{ax}$ and H-6′$_{eq}$), 1.52 (dt, *J* = 11.1, 2.3 Hz, 1 H, H-2′$_{eq}$), 1.57 (m, 1 H, H-4′$_{eq}$), 1.62–1.71 (m, 2 H, H-5′), 1.97 (d, *J* = 11.1 Hz, 1 H, H-2′$_{ax}$), 2.05 (m, 1 H, H-6′$_{ax}$), 3.27–3.40 (m, 2 H, C*H*$_2$OH), 3.60 (dd, *J* = 7.5, 1.9 Hz, 1 H, CH_2O), 3.70 (d, *J* = 7.5 Hz, 1 H, CH_2O), 4.62 (t, *J* = 5.4 Hz, 1 H, OH), 7.20 (s, 1 H, H-6), 10.65 (br s, 1 H, NH), 11.01 (br s, 1 H, NH).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 19.5, 31.6, 35.9, 44.3, 47.1, 65.6, 74.0, 82.0, 117.5, 136.2, 151.4, 163.2.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{16}N_2O_4$ + Na: 275.10023; found: 275.10027.

Anal. Calcd for $C_{12}H_{16}N_2O_4·H_2O$: C, 56.13; H, 6.48; N, 10.91. Found: C, 56.09; H, 6.18; N, 10.74.

5-[4,4-Bis(hydroxymethyl)cyclohex-1-enyl]-6-chloropyrimidine-2,4(1*H*,3*H*)-dione (17)

Prepared from **16**; yield: 70%; pale yellow crystals; mp 249–250.5 °C (H_2O).

IR (KBr): 3314, 3225, 3152, 3052, 3030, 1735, 1661, 1611, 1518, 1479, 1430, 1035, 825 cm^{-1}.

^1H NMR (499.95 MHz, DMSO-d_6): δ = 1.46 (t, *J* = 6.0 Hz, 2 H, H-5′), 1.83 (m, 2 H, H-3′), 1.99 (m, 2 H, H-6′), 3.26 (dd, *J* = 10.5, 5.1 Hz, 2 H, CH_2O_a), 3.32 (dd, *J* = 10.5, 5.3 Hz, 2 H, CH_2O_b), 4.37 (t, *J* = 5.4 Hz, 2 H, OH), 5.48 (m, 1 H, H-2′), 11.30 (br s, 1 H, NH), 11.88 (br s, 1 H, NH).

^{13}C NMR (125.73 MHz, DMSO-d_6): δ = 24.4, 25.3, 29.5, 37.6, 64.4, 113.9, 128.4, 129.2, 141.0, 149.9, 162.3.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{15}ClN_2O_4$ + Na: 309.06126; found: 309.06101.

Anal. Calcd for $C_{12}H_{15}ClN_2O_4·{}^1/_2H_2O$: C, 48.74; H, 5.45; N, 9.47. Found: C, 48.60; H, 5.46; N, 9.36.

5-[4,4-Bis(hydroxymethyl)cyclohex-1-enyl]pyrimidine-2,4(1*H*,3*H*)-dione (20)

Prepared from **19**; yield: 49%; pale gray crystals; mp >340 °C (H_2O–MeOH).

IR (KBr): 3330, 3210, 3086, 3055, 1722, 1666, 1619, 1488, 1430, 1246, 1219, 1042, 1032, 829, 784 cm^{-1}.

^1H NMR (499.95 MHz, DMSO-d_6): δ = 1.45 (t, *J* = 6.5 Hz, 2 H, H-5′), 1.85 (m, 2 H, H-3′), 2.13 (m, 2 H, H-6′), 3.23 (dd, *J* = 10.5, 5.3 Hz, 2 H, CH_2O_a), 3.27 (dd, *J* = 10.5, 5.4 Hz, 2 H, CH_2O_b), 4.34 (t, *J* = 5.4 Hz, 2 H, OH), 6.19 (m, 1 H, H-2′), 7.17 (s, 1 H, H-6), 10.79 (br s, 1 H, NH), 10.99 (br s, 1 H, NH).

^{13}C NMR (125.73 MHz, DMSO): δ = 23.4, 25.5, 29.7, 37.5, 64.5, 113.9, 124.5, 129.4, 137.1, 150.9, 163.5.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{16}N_2O_4$ + Na: 275.10023; found: 275.10030.

Anal. Calcd for $C_{12}H_{16}N_2O_4·H_2O$: C, 56.13; H, 6.48; N, 10.91. Found: C, 56.15; H, 6.47; N, 10.56.

Coupling of Iodopyrimidines 33 and 34 with Allyl Chlorides 26 and 27; General Procedure

A solution of *i*-PrMgCl·LiCl in THF (1 M, 4.3 mL) was added to a solution of iodopyrimidine **33** or **34** (3.9 mmol) in THF (14 mL) under an argon atmosphere at –25 °C. The reaction mixture was stirred under the same conditions for 1 h before a solution of allyl chloride **26** (2.6 mmol) in THF (27 mL), treated with a solution of CuI (95 mg, 0.5 mmol) and LiCl (42 mg, 1 mmol) in THF (0.84 mL), was added via a syringe. The resulting mixture was stirred at –25 °C for 48 h. Sat. aq NH_4Cl (100 mL) was added to the reaction mixture followed by 5% aq NH_4OH (15 mL) and sat. aq Na_2EDTA (15 mL). The biphasic system was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with H_2O (100 mL), dried (Na_2SO_4), and evaporated. Chromatography on a silica gel column afforded the products.

[5-(2,6-Dimethoxypyrimidin-4-yl)cyclohex-3-ene-1,1-diyl]bismethylene Dibenzoate (37)

Prepared from **26** and **33**. Chromatography: hexanes–EtOAc (6:1); yield: 77%; air-sensitive colorless oil.

^1H NMR (499.95 MHz, $CDCl_3$): δ = 1.87 (dd, *J* = 13.3, 10.9 Hz, 1 H, H-6), 2.17–2.26 (m, 2 H, H-2), 2.28 (m, 1 H, H-6b), 3.51 (m, 1 H, H-5), 3.92 (s, 3 H, 2′-OCH_3), 3.93 (s, 3 H, 6′-OCH_3), 4.33 (m, 2 H CH_2O), 4.47 (s, 2 H, CH_2O), 5.85 (dm, *J* = 10.1 Hz, 1 H, H-4), 5.88 (dm, *J* = 10.1 Hz, 1 H, H-3), 6.26 (s, 1 H, H-5′), 7.39–7.44 (m, 4 H, H-3″), 7.53–7.58 (m, 2 H, H-4″), 7.99 (m, 2 H, H-2″), 8.04 (m, 2 H H-2″).

^{13}C NMR (125.70 MHz, $CDCl_3$): δ = 29.8, 32.9, 37.2, 40.1, 53.8, 54.5, 65.3, 69.3, 96.6, 125.9, 127.3, 128.4, 128.4, 129.6, 129.6, 129.9, 130.0, 133.1, 133.1, 165.3, 166.3, 166.5, 172.2, 174.7.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{28}H_{28}N_2O_6$ + Na: 511.1840; found: 511.1836.

[5-(2,6-Dimethoxy-5-methylpyrimidin-4-yl)cyclohex-3-ene-1,1-diyl]bismethylene Dibenzoate (40)

Prepared from **26** and **34**. Chromatography: hexanes–EtOAc (5:1); yield: 71%; air-sensitive colorless oil.

^1H NMR (499.95 MHz, $CDCl_3$): δ = 1.98 (dd, *J* = 13.2, 11.3 Hz, 1 H, H-6), 1.99 (s, 3 H, 5′-CH_3), 2.06 (m, 1 H, H-6b), 2.17 (dm, 1 H, *J* = 18.2 Hz, H-2), 2.33 (dm, *J* = 18.2 Hz, 1 H, H-2), 3.81 (m, 1 H,

H-5), 3.92 (s, 3 H, 2′-OCH_3), 3.94 (s, 3 H, 6′-OCH_3), 4.35 (d, J = 11.0 Hz, 1 H, CH_2O), 4.38 (d, J = 11.0 Hz, 1 H, CH_2O), 4.44 (d, J = 11.3 Hz, 1 H, CH_2O), 4.60 (d, J = 11.3 Hz, 1 H, CH_2O), 5.73 (dm, J = 10.1 Hz, 1 H, H-4), 5.83 (dm, J = 10.1 Hz, 1 H, H-3), 7.40–7.45 (m, 4 H, H-3″), 7.53–7.58 (m, 2 H, H-4″), 8.00–8.05 (m, 4 H, H-2″).

^{13}C NMR (125.70 MHz, $CDCl_3$): δ = 9.4, 29.8, 31.2, 36.3, 37.1, 53.9, 54.3, 65.1, 69.7, 107.4, 124.6, 127.9, 128.4, 128.4, 129.5, 129.8, 129.9, 133.0, 133.1, 163.0, 166.3, 166.5, 169.8, 170.0.

HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{29}H_{30}N_2O_6$: 503.21766; found: 503.21772.

[4-(2,6-Dimethoxypyrimidin-4-yl)cyclohex-2-ene-1,1-diyl]bismethylene Dibenzoate (38)

Prepared from **27** and **33**. Chromatography: hexanes–EtOAc (4:1); yield: 60%; air-sensitive colorless oil.

^{1}H NMR (600.13 MHz, DMSO-d_6): δ = 1.72 (m, 1 H, H-6′a), 1.89 (m, 2 H, H-5′a and H-6′b), 2.05 (m, 1 H, H-5′b), 3.43 (m, 1 H, H-4′), 3.87 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.29 (d, J = 10.9 Hz, 1 H, OCH_2), 4.32 (d, J = 11.0 Hz, 1 H, OCH_2), 4.38 (d, J = 10.9 Hz, 1 H, OCH_2), 4.42 (d, J = 11.0 Hz, 1 H, OCH_2), 5.88 (dd, J = 10.2, 2.3 Hz, 1 H, H-2′), 6.03 (dd, J = 10.2, 3.1 Hz, 1 H, H-3′), 6.40 (s, 1 H, H-5), 7.51 (m, 4 H, H-3″), 7.66 (m, 2 H, H-4″), 7.95 (m, 2 H, H-2″), 7.99 (m, 2 H, H-2″).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 24.2, 25.4, 39.2, 42.1, 53.9, 54.5, 67.3, 67.8, 99.0, 129.0, 129.1, 129.2, 129.4, 129.4, 129.6, 129.7, 131.8, 133.7, 133.7, 165.1, 165.8, 171.8, 174.6.

HRMS-ESI: m/z $[M + Na]^+$ calcd for $C_{28}H_{28}N_2O_6$ + Na: 511.1840; found: 511.1836.

[4-(2,6-Dimethoxy-5-methylpyrimidin-4-yl)cyclohex-2-ene-1,1-diyl]bismethylene Dibenzoate (47)

Prepared from **27** and **34**. Chromatography: hexanes–EtOAc (11:2); yield: 52%; air-sensitive colorless oil.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 1.75 (ddd, J = 13.6, 11.9 Hz, 3.6 Hz, 1 H, H-6a), 1.96 (m, 1 H, H-5a), 2.02 (m, 1 H, H-5b), 2.10 (s, 3 H, 5′-CH_3), 2.12 (m, 1 H, H-6b), 3.72 (m, 1 H, H-4), 4.33 (d, J = 10.8 Hz, 1 H, CH_2O), 4.40 (d, J = 11.1 Hz, 1 H, CH_2O), 4.45 (d, J = 10.8 Hz, 1 H, CH_2O), 4.54 (d, J = 11.1 Hz, 1 H, CH_2O), 5.85 (ddd, J = 10.2, 2.5, 1.1 Hz, 1 H, H-2), 5.93 (ddd, J = 10.2, 2.5, 0.8 Hz, 1 H, H-3), 7.41–7.46 (m, 4 H, H-3″), 7.54–7.58 (m, 2 H, H-4″), 8.02–8.06 (m, 4 H, H-2″).

^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 9.6, 23.8, 26.7, 38.9, 39.6, 54.0, 54.4, 66.8, 68.3, 107.4, 127.6, 128.4, 128.4, 129.6, 130.0, 132.5, 133.0, 133.1, 162.9, 166.3, 166.4, 169.9, 169.9.

HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{29}H_{30}N_2O_6$: 503.21766; found: 503.21760.

[4-(2,6-Dimethoxypyrimidin-4-yl)-2-oxocyclohex-3-ene-1,1-diyl]bismethylene Dibenzoate (39)

The compound **38** (300 mg, 0.6 mmol) was exposed to sunlight in a glass vessel for 1 month. The mixture of products was chromatographed (hexanes–EtOAc, 3:1) on a silica gel column to afford the product **39** (154 mg, 50%).

^{1}H NMR (600.13 MHz, DMSO-d_6): δ = 2.39 (t, J = 6.3 Hz, 2 H, H-6′), 2.98 (td, J = 6.3, 1.7 Hz, 2 H, H-5′), 3.94 (s, 3 H, 6-OCH_3), 3.94 (s, 3 H, 2-OCH_3), 4.59 (d, J = 11.3 Hz, 2 H, CH_2O), 4.61 (d, J = 11.3 Hz, 2 H, CH_2O), 7.00 (s, 2 H, H-5 and H-3′), 7.50 (m, 4 H, H-3″), 7.66 (m, 2 H, H-4″), 7.93 (m, 4 H, H-2″).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 22.3, 26.8, 48.2, 54.4, 54.8, 64.9, 99.7, 126.5, 129.1, 129.4, 129.4, 133.8, 155.3, 163.6, 164.9, 165.6, 172.7, 199.3.

HRMS-ESI: m/z $[M + Na]^+$ calcd for $C_{28}H_{26}N_2O_7$ + Na: 525.1632; found: 525.1628.

Hydrogenation of the Coupling Products; General Procedure

$Pd(OH)_2$/C (150 mg) was added to a solution of the substrate (1.5 mmol) in MeOH (75 mL) and the mixture was stirred under H_2 atmosphere for 20 h. The catalyst was removed by filtration through a Celite pad and the filtrate was evaporated. Products were purified by column chromatography.

[3-(2,6-Dimethoxypyrimidin-4-yl)cyclohexane-1,1-diyl]bismethylene Dibenzoate (41)

Prepared from **37**. Chromatography: hexanes–EtOAc (5:1); yield: 95%; colorless oil.

IR ($CHCl_3$): 3092, 3065, 3027, 1718, 1596, 1585, 1568, 1494, 1480, 1453, 1386, 1316, 1280, 1269, 1177, 1111, 1070, 1027, 985, 838, 713, 687, 617 cm^{-1}.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 1.43 (td, J = 13.6, 4.4 Hz, 1 H, H-6_{ax}), 1.56 (m, 1 H, H-4_{ax}), 1.67 (qt, J = 13.7, 3.6 Hz, 1 H, H-6_{ax}), 1.68 (dd, J = 13.6, 12.9 Hz, 1 H, H-2_{ax}), 1.82 (dm, J = 14.0 Hz, 1 H, H-5_{eq}), 1.92 (dm, J = 13.7 Hz, 1 H, H-6_{eq}), 1.98 (dm, J = 12.7 Hz, 1 H, H-4_{eq}), 2.06 (dm, J = 13.6 Hz, 1 H, H-2_{eq}), 2.83 (m, 1 H, H-3), 3.93 (s, 3 H, 2′-OCH_3), 3.94 (s, 3 H, 6′-OCH_3), 4.27 (d, J = 10.9 Hz, 1 H, CH_2O), 4.32 (d, J = 10.9 Hz, 1 H, CH_2O), 4.58 (s, 2 H, CH_2O), 6.21 (s, 1 H, H-5′), 7.40–7.44 (m, 4 H, H-3″), 7.53–7.57 (m, 2 H, H-4″), 8.01–8.04 (m, 4 H, H-2″).

^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 21.0, 29.3, 31.2, 34.9, 38.2, 40.1, 53.7, 54.5, 64.0, 70.8, 98.4, 128.3, 128.4, 129.6, 129.6, 129.1, 130.0, 133.0, 133.1, 165.2, 166.4, 166.4, 172.0, 175.6.

HRMS-FAB: m/z $[M + Na]^+$ calcd for $C_{28}H_{30}N_2O_6$ + Na: 513.19961; found: 513.19922.

[3-(2,6-Dimethoxy-5-methylpyrimidin-4-yl)cyclohexane-1,1-diyl]bismethylene Dibenzoate (42)

Prepared from **40**. Chromatography: hexanes–EtOAc (5:1); yield: 93%; colorless oil.

IR ($CHCl_3$): 3065, 3029, 3027, 1718, 1602, 1584, 1575, 1492, 1475, 1391, 1380, 1371, 1316, 1284, 1269, 1177, 1113, 1082, 1071, 1027, 1009, 978, 937, 713, 687, 617, 532 cm^{-1}.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 1.50 (td, J = 13.5, 4.5 Hz, 1 H, H-6_{ax}), 1.68 (m, 1 H, H-4_{ax}), 1.70–1.86 (m, 5 H, H-2, H-5 and H-4_{eq}), 1.92 (dm, J = 14.0 Hz, 1 H, H-6_{eq}), 2.01 (s, 3 H, 5′-CH_3), 3.14 (m, 1 H, H-3), 3.94 (s, 3 H, 2′-OCH_3), 3.94 (s, 3 H, 6′-OCH_3), 4.28 (d, J = 10.9 Hz, 1 H, CH_2O), 4.32 (d, J = 10.9 Hz, 1 H, CH_2O), 4.54 (d, J = 11.4 Hz, 1 H, CH_2O), 4.70 (d J = 11.4 Hz, 1 H, CH_2O), 7.39–7.43 (m, 4 H, H-3″), 7.53–7.57 (m, 2 H, H-4″), 8.01–8.04 (m, 4 H, H-2″).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 9.2, 21.1, 29.5, 30.4, 33.9, 35.5, 38.2, 53.9, 54.2, 64.0, 70.9, 106.8, 128.3, 128.4, 129.5, 129.5, 129.8, 130.0, 133.0, 133.1, 165.9, 166.3, 166.4, 169.7, 171.1.

HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{29}H_{32}N_2O_6$: 505.23331; found: 505.23339.

[4-(2,6-Dimethoxypyrimidin-4-yl)cyclohexane-1,1-diyl]bismethylene Dibenzoate (48)

Prepared from **38**. Chromatography: hexanes–EtOAc (4:1); yield: 89%; colorless oil.

IR ($CHCl_3$): 3092, 3072, 3065, 1718, 1596, 1585, 1567, 1494, 1480, 1452, 1386, 1315, 1287, 1272, 1177, 1108, 1071, 1027, 964, 839, 712, 687, 618 cm^{-1}.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 1.57 (td, J = 13.6, 4.1 Hz, 2 H, H-$2'_{ax}$), 1.80 (dm, J = 3.2 Hz, 2 H, H-$3'_{ax}$), 1.92 (dm, J = 13.9 Hz, 2 H, H-$3'_{eq}$), 2.01 (dm, J = 14.1 Hz, 2 H, H-$2'_{eq}$), 2.58 (tt, J = 11.9, 3.7

Hz, 1 H, H-4′), 3.95 (s, 3 H, 6′-OCH_3), 3.98 (s, 3 H, 2′-OCH_3), 4.30 (s, 2 H, CH_2O), 4.54 (s, 2 H, CH_2O), 6.24 (s, 1 H, H-5), 7.41–7.45 (m, 4 H, H-3″), 7.54–7.58 (m, 2 H, H-4″), 8.02–8.05 (m, 4 H, H-2″).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 26.3, 29.6, 37.2, 44.9, 53.7, 54.6, 64.1, 70.5, 98.1, 128.4, 129.6, 130.0, 130.0, 133.1, 165.2, 166.4, 166.4, 172.0, 175.7.

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{28}H_{30}N_2O_6$: 513.19961; found: 513.19922.

[4-(2,6-Dimethoxy-5-methylpyrimidin-4-yl)cyclohexane-1,1-diyl]bismethylene Dibenzoate (49)

Prepared from **47**. Chromatography: hexanes–EtOAc (5:1); yield: 80%; colorless oil.

IR ($CHCl_3$): 3092, 3072, 3065, 3027, 1718, 1602, 1585, 1491, 1476, 1453, 1391, 1381 1370, 1315, 1273, 1177, 1110, 1083, 1071, 1027, 1010, 960, 938, 713, 687, 617, 532 cm^{-1}.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 1.55 (td, *J* = 13.6, 4.2 Hz, 2 H, H-2′, 6′$_{ax}$), 1.68 (dm, *J* = 13.9 Hz, 2 H, H-3′, 5′$_{eq}$), 1.99 (m, 2 H, H-3′, 5′$_{ax}$), 2.04 (m, 2 H, H-2′, 6′$_{eq}$), 2.07 (s, 3 H, 5-CH_3), 2.85 (tt, *J* = 11.7, 3.7 Hz, 1 H, H-4′), 3.96 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.30 (s, 2 H, CH_2O), 4.60 (s, 2 H, CH_2O), 7.41–7.45 (m, 4 H, H-3″), 7.54–7.58 (m, 2 H, H-4″), 8.02–8.05 (m, 4 H, H-2″).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 9.4, 25.6, 29.9, 37.1, 40.9, 53.9, 54.4, 64.1, 70.7, 106.7, 128.4, 129.6, 130.0, 133.0, 133.0, 162.9, 166.4, 166.5, 169.6, 171.3.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{29}H_{32}N_2O_6$: 505.23331; found: 505.23338.

Removal of Benzoyl Protecting Groups; General Procedure

Finely powdered K_2CO_3 (0.746 g, 5.4 mmol) was added to a solution of the respective benzoyl derivative (1.2 mmol) in MeOH (22 mL). The resulting suspension was sonicated in ultrasound bath for 10 min and then stirred at r.t. for 20 h. The solvent was evaporated and the residue was partitioned between EtOAc (3 × 75 mL) and H_2O (25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The products were purified by chromatography.

[3-(2,6-Dimethoxypyrimidin-4-yl)cyclohexane-1,1-diyl]dimethanol (43)

Prepared from **41**. Chromatography: EtOAc–acetone–EtOH–H_2O (20:3:1:1); yield: 92%; colorless oil.

IR ($CHCl_3$): 3628, 3360, 1596, 1567, 1482, 1385, 1100, 1083, 1046, 839 cm^{-1}.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 1.08 (dt, *J* = 13.2, 4.5 Hz, 1 H, H-6$_{ax}$), 1.29 (t, *J* = 13.0 Hz, 1 H, H-2$_{ax}$), 1.32 (m, 1 H, H-4$_{ax}$), 1.46 (m, 1 H, H-5$_{ax}$), 1.49 (m, 1 H, H-6$_{eq}$), 1.55–1.62 (m, 2 H, H-2$_{eq}$ and H-5$_{eq}$), 1.77 (dm, *J* = 12.5 Hz, 1 H, H-4$_{eq}$), 2.65 (tt, *J* = 12.5, 3.5 Hz, 1 H, H-3), 3.17 (m, 2 H, CH_2O), 3.44 (m, 2 H, CH_2O), 3.85 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.34–4.37 (m, 2 H, OH), 6.36 (s, 1 H, H-5).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 21.1, 28.4, 31.5, 34.3, 39.7, 40.0, 53.8, 54.4, 61.3, 68.6, 98.0, 165.0, 171.7, 177.4.

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{22}N_2O_4$ + Na: 305.14718; found: 305.14690.

[3-(2,6-Dimethoxy-5-methylpyrimidin-4-yl)cyclohexane-1,1-diyl]dimethanol (44)

Prepared from **42**. Chromatography: EtOAc–acetone–EtOH–H_2O (20:3:1:1); yield: 89%; white crystals; mp 81–82.5 °C (EtOAc–toluene).

IR ($CHCl_3$): 3629, 3401, 1585, 1572, 1476, 1391, 1380, 1370, 1109, 1082, 1048, 532 cm^{-1}.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 1.09 (m, 1 H, H-6$_{ax}$), 1.30 (t, *J* = 12.9 Hz, 1 H, H-2$_{ax}$), 1.45–1.60 (m, 6 H, H-4, 5, 2$_{eq}$ and 6$_{eq}$), 2.00 (s, 3 H, 5′-CH_3), 2.97 (m, 1 H, H-3), 3.16 (m, 2 H, CH_2O), 3.43 (m, 2 H, CH_2O), 3.84 (s, 3 H, 2′-OCH_3), 3.87 (s, 3 H, 4′-OCH_3), 4.35 (t, *J* = 5.3 Hz, 1 H, OH) 4.35 (t, *J* = 5.5 Hz, 1 H, OH).

^{13}C NMR (150.92 MHz, DMSO): δ = 9.2, 21.2, 28.6, 30.3, 34.0, 35.7, 39.6, 54.0, 54.1, 61.4, 68.7, 106.3, 162.7, 169.2, 172.7.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{15}H_{24}N_2O_4$: 297.18088; found: 297.18096.

Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.71; H, 8.33; N, 9.40.

[4-(2,6-Dimethoxypyrimidin-4-yl)cyclohexane-1,1-diyl]dimethanol (50)

Prepared from **48**. Chromatography: EtOAc–acetone–EtOH–H_2O (20:3:1:1); yield: 85%; white crystals; mp 123–123.5 °C (EtOAc–toluene).

IR ($CHCl_3$): 3629, 3392, 1596, 1566, 1480, 1386, 1100, 1060, 1046, 840 cm^{-1}.

^{1}H NMR (600.13 MHz, DMSO-d_6): δ = 1.19 (m, 2 H, H-2′ and H-6′a), 1.54–1.63 (m, 6 H, H-2′b, 6′b, 3′, and H-5′), 2.42 (m, 1 H, H-4′), 3.18 (d, *J* = 5.4 Hz, 2 H, CH_2OH), 3.41 (d, *J* = 5.3 Hz, 2 H, CH_2OH), 3.85 (s, 3 H, 6-OCH_3), 3.86 (s, 3 H, 2-OCH_3), 4.31 (t, *J* = 5.4 Hz, 1 H, OH), 4.35 (t, *J* = 5.5 Hz, 1 H, OH), 6.39 (s, 1 H, H-5).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 26.6, 28.6, 38.5, 45.0, 53.8, 54.4, 61.0, 68.3, 98.0, 164.9, 171.7, 177.0.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{22}N_2O_4$: 283.16523; found: 283.16527.

Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.55; H, 7.94; N, 9.83.

[4-(2,6-Dimethoxy-5-methylpyrimidin-4-yl)cyclohexane-1,1-diyl]dimethanol (51)

Prepared from **49**. Chromatography: EtOAc–acetone–EtOH–H_2O (20:3:1:1); yield: 66%; white cotton wool like crystals; mp 130.5–131 °C (EtOAc).

IR ($CHCl_3$): 3630, 3402, 1585, 1570, 1476, 1391, 1379, 1370, 1098, 1082, 1042, 532 cm^{-1}.

^{1}H NMR (600.13 MHz, DMSO-d_6): δ = 1.22 (dt, *J* = 13.8, 4.2 Hz, 2 H, H-2′, 6′$_{ax}$), 1.42 (dm, *J* = 13.6 Hz, 2 H, H-3′, 5′$_{eq}$), 1.58 (dm, *J* = 13.8 Hz, 2 H, H-2′, 6′$_{eq}$), 1.70 (m, 2 H, H-3′, 5′$_{ax}$), 2.00 (s, 3 H, 5-CH_3), 2.72 (tt, *J* = 11.8, 3.7 Hz, 1 H, H-4′), 3.19 (d, *J* = 5.5 Hz, 2 H, CH_2O), 3.44 (d, *J* = 5.4 Hz, 2 H, CH_2O), 3.84 (s, 3 H, 2-OCH_3), 3.87 (s, 3 H, 6-OCH_3), 4.33 (t, *J* = 5.4 Hz, 1 H, OH), 4.35 (t, *J* = 5.5 Hz, 1 H, OH).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 7.5, 24.1, 26.8, 36.7, 39.1, 52.2, 52.2, 59.1, 66.7, 104.5, 160.9, 167.4, 170.8.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{15}H_{24}N_2O_4$ + H: 297.18088; found: 297.18103.

Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.73; H, 8.20; N, 9.43.

Removal of Methyl Protecting Groups; General Procedure

A mixture of the protected substrate (0.5 mmol), THF (1 mL), 1,4-dioxane (1 mL), and concd HCl (1.3 mL) was heated to refluxed for 3 h. H_2O (5 mL) was added and after refrigerating the resulting mixture for 30 min, the product was collected by filtration, washed with a mixture of EtOAc and EtOH (2:1, 5 mL) and dried in a vacuum oven to afford the products.

6-[3,3-Bis(hydroxymethyl)cyclohexyl]pyrimidine-2,4(1*H*,3*H*)-dione (45)

Prepared from **43**. Instead of direct collection of crystals by filtration, the mixture was evaporated to a minimum volume and crystallized from H_2O with a drop of EtOH to give the product in 66% yield; white crystals; mp 243–245.5 °C (H_2O–EtOH).

IR (KBr): 3379, 3229, 3168, 3091, 3048, 1709, 1671, 1656, 1630, 1499, 1399, 1047, 1026, 769 cm^{-1}.

^1H NMR (499.95 MHz, DMSO-d_6): δ = 1.07 (dt, *J* = 13.5, 4.6 Hz, 1 H, H-4′$_{ax}$), 1.12 (t, *J* = 13.0 Hz, 1 H, H-2′$_{ax}$), 1.19 (qd, *J* = 12.7, 3.8 Hz, 1 H, H-6′$_{ax}$), 1.38 (qt, *J* = 13.4, 3.6 Hz, 1 H, H-5′$_{ax}$), 1.44 (dm, *J* = 14.7 Hz, 1 H, H-4′$_{eq}$), 1.52–1.60 (m, 2 H, H-2′$_{eq}$ and H-5′$_{eq}$), 1.74 (dm, *J* = 12.8 Hz, 1 H, H-6′$_{eq}$), 2.38 (tt, *J* = 12.5, 3.2 Hz, 1 H, H-1′), 3.14 (dd, *J* = 10.4, 5.7 Hz, 1 H, CH_2O), 3.17 (dd, *J* = 10.4, 5.5 Hz, 1 H, CH_2O), 3.30–3.45 (m, 2 H, CH_2O), 4.29 (t, *J* = 5.7 Hz, 1 H, OH), 4.36 (t, *J* = 5.6 Hz, 1 H, OH), 5.26 (d, *J* = 1.3 Hz, 1 H, H-5), 10.65 (br s, 1 H, NH), 10.89 (br s, 1 H, NH).

^{13}C NMR (125.73 MHz, DMSO-d_6): δ = 21.0, 28.1, 30.1, 33.5, 35.7, 39.8, 61.0, 68.2, 95.9, 151.9, 161.4, 164.6.

HRMS-FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{56}N_6O_{13}$ + Na: 277.11588; found: 277.11591.

Anal. Calcd for $C_{36}H_{56}N_6O_{13}\cdot{}^1/_6\ H_2O$: C, 56.02; H, 7.18; N, 10.89. Found: C, 56.32; H, 7.16; N, 10.62.

6-[3,3-Bis(hydroxymethyl)cyclohexyl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (46)

Prepared from **44**; yield: 72%; white crystals; mp 286 °C (THF–1,4-dioxane–H_2O).

IR (KBr): 3555, 3375, 3225, 3155, 3084, 3026, 1707, 1660, 1500, 1439, 1427, 1376, 1043 cm^{-1}.

^1H NMR (600.13 MHz, DMSO-d_6): δ = 1.07 (dt, *J* = 13.7, 3.7 Hz, 1 H, H-4′$_{ax}$), 1.37 (dm, *J* = 13.0 Hz, 1 H, H-2′$_{eq}$), 1.43 (t, *J* = 12.9 Hz, 1 H, H-2′$_{ax}$), 1.41–1.50 (m, 3 H, H-4′$_{eq}$, H-5′$_{ax}$, and H-6′$_{eq}$), 1.54 (m, 1 H, H-5′$_{eq}$), 1.63 (qd, *J* = 12.5, 3.9 Hz, 1 H, H-6′$_{ax}$), 1.76 (s, 3 H, CH_3), 2.82 (tt, *J* = 12.6, 1.8 Hz, 1 H, H-1′), 3.15 (m, 2 H, CH_2O), 3.43 (m, 2 H, CH_2O), 4.35 (t, *J* = 5.2 Hz, 1 H, OH), 4.38 (t, *J* = 5.5 Hz, 1 H, OH), 10.19 (d, *J* = 1.9 Hz, 1 H, H-3), 10.93 (d, *J* = 1.7 Hz, 1 H, H-1).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 9.4, 21.0, 27.8, 28.0, 31.7, 34.0, 39.5, 60.8, 68.5, 103.1, 151.4, 154.7, 165.2.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{20}N_2O_4$ + Na: 291.13153; found: 291.13167.

Anal. Calcd for $C_{13}H_{20}N_2O_4\cdot H_2O$: C, 57.23; H, 7.57; N, 10.27. Found: C, 57.22; H, 7.62; N, 9.98.

6-[4,4-Bis(hydroxymethyl)cyclohexyl]pyrimidine-2,4(1*H*,3*H*)-dione (52)

Prepared from **50**; yield: 75%; white crystals; mp 331–333 °C (THF–1,4-dioxane–H_2O).

IR (KBr): 3364, 3212, 3131, 3101, 3070, 3019, 1701, 1675, 1628, 1501, 1427, 1405, 1046, 1035, 772 cm^{-1}.

^1H NMR (600.13 MHz, DMSO-d_6): δ = 1.14 (dt, *J* = 13.2, 3.8 Hz, 2 H, H-3′, 5′$_{ax}$), 1.46 (m, 2 H, H-2′, 6′$_{ax}$), 1.50–1.60 (m, 4 H, H-2′, 3′, 5′, 6′$_{eq}$), 2.13 (tt, *J* = 12.0, 3.3 Hz, 1 H, H-1′), 3.15 (s, 2 H, CH_2O), 3.40 (s, 2 H, CH_2O), 4.31 (br s, 2 H, OH), 5.29 (t, *J* = 1.8 Hz, 1 H, H-5), 10.77 (br s, 1 H, H-1), 10.89 (br s, 1 H, H-3).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 25.7, 28.5, 38.6, 41.1, 60.9, 68.3, 96.1, 152.0, 161.1, 164.6.

HRMS-ESI (–): *m*/*z* [M – H]$^-$ calcd for $C_{12}H_{18}N_2O_4$: 253.1183; found: 253.1192.

Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.35; H, 7.14; N, 10.69.

6-[4,4-Bis(hydroxymethyl)cyclohexyl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (53)

Prepared from **51**; yield: 79%; white crystals; mp 320–323.5 °C (THF–1,4-dioxane–H_2O).

IR (KBr): 3430, 3286, 3226, 3170, 3105, 1701, 1664, 1511, 1420, 1371, 1037 cm^{-1}.

^1H NMR (600.13 MHz, DMSO-d_6): δ = 1.18 (dt, *J* = 13.5, 4.2 Hz, 2 H, H-3′, 5′$_{ax}$), 1.34 (dm, *J* = 13.0 Hz, 2 H, H-2′, 6′$_{eq}$), 1.55 (dm, *J* = 13.8 Hz, 2 H, H-3′, 5′$_{eq}$), 1.75 (dq, *J* = 12.9, 3.7 Hz, 2 H, H-2′, 6′$_{ax}$), 1.77 (s, 3 H, 5-CH_3), 2.54 (m, 1 H, H-1′), 3.16 (s, 2 H, CH_2O), 3.52 (s, 2 H, CH_2O), 4.16 (br s, 1 H, OH), 4.34 (br s, 1 H, OH), 10.42 (br d, *J* = 1.9 Hz, 1 H, H-1), 10.93 (br d, *J* = 1.9 Hz, 1 H, H-3).

^{13}C NMR (150.92 MHz, DMSO-d_6): δ = 9.5, 24.2, 28.8, 38.6, 39.6, 60.9, 68.5, 103.1, 151.5, 154.7, 165.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}N_2O_4$: 269.14958; found: 269.14966.

Anal. Calcd for $C_{13}H_{20}N_2O_4\cdot{}^1/_8\ H_2O$: C, 57.71; H, 7.54; N, 10.35. Found: C, 57.73; H, 7.55; N, 10.01.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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