Convergent or Linear? A Challenging Question in Carbocyclic Nucleoside Chemistry

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Abstract: North-methanocarbathymidine (N-MCT) is a carbocyclic nucleoside analogue with potent anti-HSV and KSHV activity. The critical step in the synthesis of N-MCT and other carbocyclic nucleoside analogues is the introduction of the nucleobase into the carbocyclic moiety. For this, convergent and linear strategies were compared side by side. In the convergent approach, the base was coupled to the carbocyclic moiety by either a Mitsunobu reaction or by displacement of a mesylate. This strategy leads to the formation of various amounts of the O^2-regioisomer, depending on the applied procedure. Additionally, by-products of the Mitsunobu reaction have to be separated from the coupling products. Although lengthier, the linear strategy leads selectively to the target compound N-MCT with overall yields comparable to the convergent approaches, making this strategy more compatible for future large-scale syntheses.

Key words: medicinal chemistry, nucleosides, carbocycles, Mitsunobu reaction, regioselectivity

The key synthetic step in carbocyclic nucleoside chemistry is the condensation of the pseudosugar moiety with the heterocyclic nucleobase (Figure 1). Over the last decades, a number of strategies to achieve this goal, which can be classified into two major categories as convergent and linear, have been developed.[1] In the convergent approach, the complete nucleobase is coupled directly to an activated carbocycle, opening the opportunity for the rapid synthesis of a variety of carbocyclic nucleosides. This is especially desired if nucleosides built on a specific carbocycle are to be screened for biological activity.[2] Unfortunately, nucleobases can react as ambident nucleophiles, leading to mixtures of isomers (N^1- and O^2-regioisomers for pyrimidines and N^7- and N^9-regioisomers for purines) and their separation can be a challenging and time-consuming task. In the linear approach, a pre-functionalized carbocyclic amine is prepared and then subsequently modified by the step-wise build-up of the heterocyclic base. By applying this strategy, only one of the possible regioisomers is obtained; however, each nucleoside analogue requires a separate multistep synthesis. In this paper, we report on the direct comparison of both approaches and focus on their discrete advantages and disadvantages with respect to both lab-scale and larger-scale reactions.

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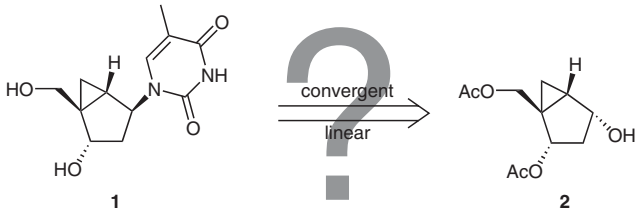


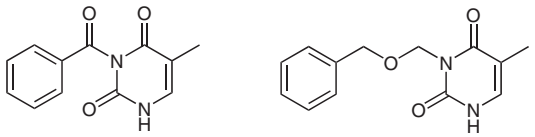
Figure 1 Strategies for carbocyclic nucleoside synthesis

The starting point of this investigation was the necessity for a high-yielding and convenient synthesis for the carbocyclic nucleoside north-methanocarbathymidine (**1**, N-MCT).[3] N-MCT (**1**) is a thymidine analogue, based on a bicyclo[3.1.0]hexane template[4] locked in the northern conformation as defined in the pseudorotational cycle.[5] The concept of locked nucleosides with this scaffold was originally introduced to investigate the conformational preferences of various enzymes, particularly kinases and polymerases.[6] However, besides their role as molecular probes, some conformationally restricted nucleosides showed interesting antiviral properties.[7] Among these, N-MCT (**1**) was found to exhibit greater antiherpetic activity against herpes virus types 1 (HSV-1), 2 (HSV-2),[8] and Kaposi's sarcoma-associated herpesvirus (KSHV)[9] than the reference compounds acyclovir, gancyclovir, and cidofovir. Additionally, the nucleoside triphosphate (N-MCT-TP) is a potent inhibitor of HIV replication by acting as a delayed chain terminator.[10] These outstanding antiviral properties make N-MCT (**1**) an interesting molecule for clinical studies. Therefore, a high-yielding and selective synthetic route is highly desirable.

Convergent Strategy: Introduction of the Nucleobase by Mitsunobu Chemistry

As starting material for our investigations, we chose the bicyclic hexanol **2**, which can be obtained in high optical purity by the previously reported procedure.[11] For the convergent approach, **2** was coupled directly with the N^3-protected thymines **3**[12] and **4**[13] under Mitsunobu conditions[14] (Figure 2).

As mentioned before, pyrimidine bases can react as ambident nucleophiles and mixtures of N^1- and O^2-alkylated products are generally obtained under Mitsunobu conditions. The product ratio seems to be dependent upon the



3 4

Figure 2 N^3-Protected thymines for use in Mitsunobu couplings

reaction temperature,[15] solvent,[16] protected nucleobase,[17] the alcohol itself,[18] and the order in which the components are added to each other.[19] In this study, we followed a reliable Mitsunobu-protocol developed for the synthesis of carbocyclic nucleosides with the natural *deoxyribo*-configuration, which predominantly leads to the desired N^1-alkylated regioisomers.[20] Recent studies on the influence of the protecting group on the heterocycle have shown that the benzyloxymethyl group (BOM) on N^3 of pyrimidines leads to an improved product N^1/O^2 ratio[17b] compared to the standard benzoyl protected derivative **3**. In this study, both nucleophiles were evaluated for their coupling behavior. For this, the pre-formed complex from triphenylphosphine and diisopropylazodicarboxylate (DIAD) was added slowly to a mixture of the starting material **2** and the protected nucleobase in acetonitrile, since polar solvents seem to favor N^1-alkylation[16b] (Scheme 1). Overall, coupling yields for both procedures were comparable: 79% of **1** and **5** (for **3**) and 76% of **6** and **7** (for **4**). As expected, the BOM-protected base **4** yielded 10% more of the desired N^1-product than that obtained from the classic N^3-benzoyl derivative **3**. However, the extra hydrogenation step to remove the BOM group lowered the overall yield somewhat giving 56% of **1** compared to 60% obtained from using **3**. In both cases, the N^1- and O^2-regioisomers were easily separated by regular column chromatography on silica gel. The product distributions were determined from the crude reaction mixtures after evaporation of the solvent. A small sample was dissolved in $CDCl_3$ and the solutions were analyzed by ^1H NMR spectroscopy. The ratios were obtained after integration of the respective signals of the H-4′ protons, which appear as distinctive doublets at 4.96 (N^1) and 5.29 (O^2) ppm (Figure 3).

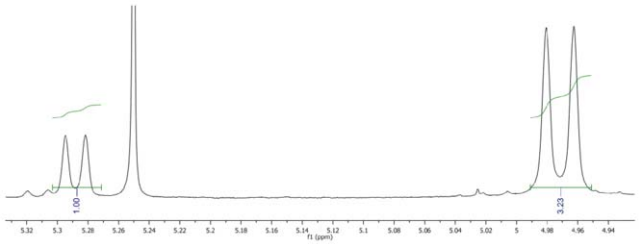
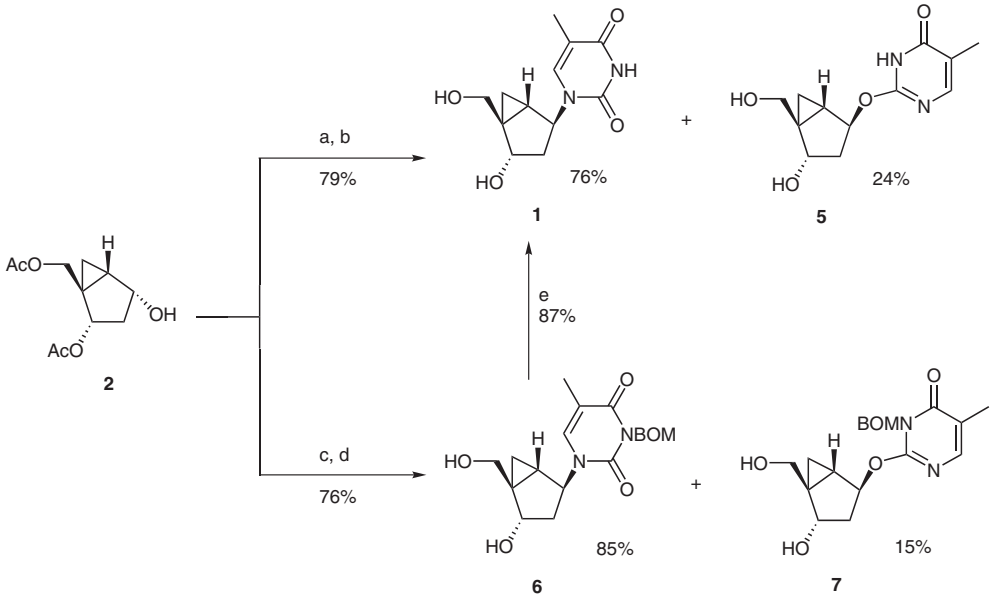


Figure 3 Determination of the product distribution by ^1H NMR spectroscopy from the crude reaction mixture

A major drawback of the Mitsunobu approach is the poor atom economy of the reaction, making it unattractive for larger-scale syntheses.[21] Triphenylphosphine and DIAD are only used to activate the hydroxy group for the subsequent nucleophilic displacement, and inevitably result in the formation of by-products such as triphenylphosphine oxide and diisopropylhydrazine dicarboxylate (DIHD) that have to be separated from the desired compounds. These by-products are insoluble in aqueous media and therefore have to be removed by chromatography.[22]

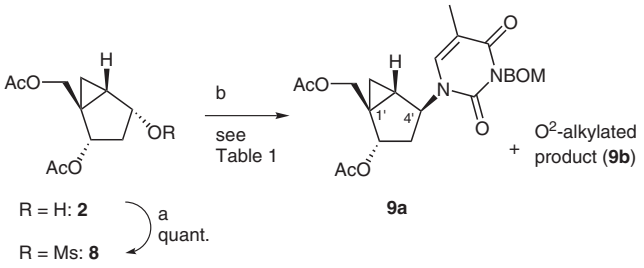
Convergent Strategy: Introduction of the Heterocycle by Displacement of a Mesylate

To overcome the formation of by-products, we decided to investigate the possibility to introduce the base by nucleophilic displacement of a mesylate on the carbocyclic moiety. This approach is not new and a lot of nucleoside analogues have been synthesized by displacing other leav-



Scheme 1 *Reagents and conditions:* (a) Ph_3P, DIAD, **3**, MeCN, –40 °C to r.t., 15 h; (b) 1% NaOH in MeOH, r.t., 15 h; (c) Ph_3P, DIAD, **4**, MeCN, –40 °C to r.t., 15 h; (d) Amberlite OH^-, MeOH, r.t. 5 h; (e) H_2, Pd/C, MeOH, r.t., 15 h.

ing groups such as halides,[23] sulfonates,[24] or opening of epoxides[25] with deprotonated nucleobases. However, the yields are usually low due to side reactions and the low solubility of the nucleobase salts in organic solvents. To increase the solubility and to minimize side reactions, we decided to investigate the behavior of the protected thymine analogues **3** and **4** developed for the coupling with Mitsunobu chemistry in simple displacement reactions. Surprisingly, only very few examples of this straightforward coupling strategy can be found in the literature.[26] Howarth et al. reported on the substitution of brosylates and iodides by N^3-benzoylthymine for the synthesis of α-*cyclo*PNAs in moderate yields. Unfortunately, no comments were made on the formation of O^2-alkylated products and product ratios.[26c] Since we believe that this is the 'Achilles heel' of any convergent approach, it encouraged us to look at this strategy in more detail. In a first attempt, the bicyclic hexanol **2** was converted to its methanesulfonyl ester **8** by reaction with mesyl chloride in dichloromethane in the presence of triethylamine (Scheme 2).



Scheme 2 *Reagents and conditions:* (a) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 1 h; (b) KHMDS, **4**, DMF.

This conversion is quantitative and the crude product obtained from simple extractive workup is sufficiently pure to be used for the following reactions. Attempts to further purify the mesylate **8** by chromatography failed and only products resulting from decomposition on the column were observed. When stored at –20 °C, the activated carbocycle **8** is stable for weeks, but storage at room temperature should be avoided. After deprotonation of 3-*N*-BOM thymine **4** with KHMDS in DMF, the mesylate **8** was added and the clear solution was stirred at different temperatures, until complete consumption of the starting material **8** was observed by TLC (Table 1).

After extractive workup, the crude material was analyzed by ^{1}H NMR and the product ratio was determined by integration of the respective H-4′ and/or 5-methyl protons. Obviously, an increase in temperature results in shorter reaction time, but also in decreased selectivity. At room temperature, this method produced the same product ratio observed for the Mitsunobu coupling with this base. Together with good overall coupling yields, this strategy can be considered as a powerful alternative to Mitsunobu chemistry, especially when removal of triphenylphosphine oxide and DIHD is a problem. Moreover, less waste is created, making this procedure also attractive from an ecological and economical point of view.

Table 1 Condensation of the Mesylate **8** with 3-*N*-BOM-thymine **4** at Different Temperatures[a]

Entry	Temp (°C)	Time (h)	Yield (%) **9a** + **9b**	Ratio (N^1/O^2, %)[b]
1	80	1	79	75:25
2	60	2	81	78:22
3	40	16	77	80:20
4	20	56	79	84:16

[a] All reactions were performed with 3.0 equiv of KHMDS and 3.0 equiv of heterocycle **4**.
[b] Determined by integration of the H-4′ and 5-CH_3 protons of the products from the crude reaction mixture.

Optimization of the Reaction Conditions

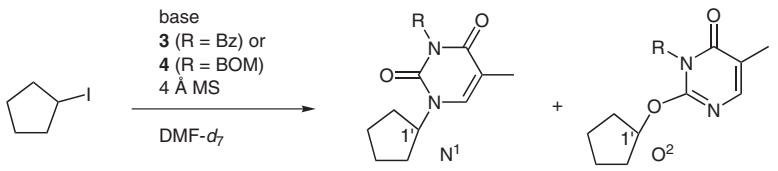
These promising results led us to investigate whether the product ratio could possibly be further fine-tuned to favor the N^1-product by varying the reaction conditions. Therefore, the influence of the counterion and the solvent were examined in simple NMR experiments. For the carbocyclic moiety, cyclopentyl iodide was chosen as a model compound, since it produced comparable product ratios to the mesylate **8** under similar reaction conditions (Table 2). In addition, the observed NMR spectra were significantly simplified, making product-ratio determination a straight forward task.

In polar aprotic solvents, anionic nucleophiles tend to form ion-pair aggregations with their cations, reducing the rate of attack on the electrophile. By varying the cation, the dissociation constants of these ion-pairs change, resulting in different concentrations of free nucleophile and therefore different rate constants can be observed.[27] This phenomenon is especially interesting when ambident nucleophiles are used, since both reaction centers might be influenced differently, possibly resulting in a change of product ratios.

To study the influence of the cation, the protected heterocycles **3** and **4** were deprotonated by various bases in perdeuterated DMF. After addition of cyclopentyl iodide, the mixtures were stirred for the indicated time and product ratios were determined by integration of the H-1′ and/or CH_3 protons of the base. The results of these experiments are summarized in Table 2.

In case of the 3-*N*-benzoyl derivative **3** a slight dependence of the product ratio due to the counterion could be observed (Table 2, entries 1–5), with Cs_2CO_3 being the most effective inorganic base (entry 2). Complexation of the potassium cation with 18-crown-6 (entry 5) led to a marked decrease in the reaction time, possibly due to higher concentrations of 'free' nucleophile in the reaction mixture. Remarkably, all bases examined for deprotonation of the heterocycle **4** resulted in the same product ratio within the experimental error (entries 6–14). Although no change in selectivity was observed, the lipophilic counterions tetramethylammonium and tetrabutylammonium[28]

Table 2 Influence of the Counterion on the Alkylation of Pyrimidine Nucleobases **3** and **4**[a]



Entry	Heterocycle	Base	Temp	Time (h)	Ratio (N^1/O^2, %)[b]
1	**3**	K_2CO_3	r.t.	16	88:12
2	**3**	Cs_2CO_3	r.t.	16	93:7
3	**3**	LiOH	r.t.	16	92:8
4	**3**	$CsOH·H_2O$	r.t.	16	91:9
5	**3**	K_2CO_3 + 18-crown-6	r.t.	2	93:7
6	**4**	KHMDS	60 °C	2	88:12
7	**4**	K_2CO_3	60 °C	2	87:13
8	4	K_2CO_3	r.t.	16	87:13
9	**4**	Cs_2CO_3	r.t.	16	87:13
10	**4**	LiOH	r.t.	16	87:13
11	**4**	$CsOH·H_2O$	r.t.	16	86:14
12	**4**	Me_4NOH	r.t.	2	89:11
13	**4**	Bu_4NOH	r.t.	2	88:12
14	**4**	K_2CO_3 + 18-crown-6	r.t.	2	87:13

[a] All reactions were performed with 3.0 equiv of base and 3.0 equiv of heterocycle.
[b] Determined by integration of the H-1′ and 5-CH_3 protons of the products from the crude reaction mixture in DMF-d_7.

(entries 12 and 13), as well as the complexing agent 18-crown-6 (entry 14) led, as in the case of **3**, to a drastic decrease in reaction times.

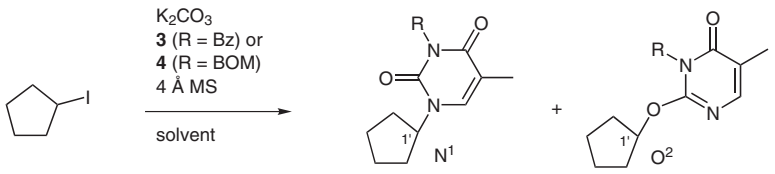
Besides the counterion of the anionic nucleophile, the solvent is a critical factor in nucleophilic substitution reactions.[29] It stabilizes the transition state and forms a cage of solvent molecules around the nucleophile. The influence of the solvent on the regioselectivity in substitution reactions with ambident nucleophiles is based upon the differences in solvation of the reagent in different solvents. Therefore, the relative nucleophilicity of the attacking atoms can also be different, leading to changes in the product ratio. In aprotic solvents, the position with the higher electron density is usually more basic, reacting predominantly with the electrophilic substrate.

To study the influence of the solvent, the protected heterocycles **3** and **4** were treated with potassium carbonate in various aprotic solvents of different polarities. After the addition of cyclopentyl iodide, the mixtures were stirred for the indicated time. The solvents were then evaporated off and the residues were redissolved in $CDCl_3$. The product ratios were again determined by integration of the H-1′ and/or 5-CH_3 protons. The results of these experiments are summarized in Table 3.

As already observed for the coupling under Mitsunobu conditions,[16b] the applied solvent has a major influence on the outcome of the product distribution. The higher the polarity and therefore the ability to solvate cations, the more of the desired N^1-product is formed. Certainly, the N^1-position is the more basic reaction center in the nucleobase derivatives **3** and **4**, since it is the primary site of alkylation by the electrophile when free from interactions with the cation (Table 3, entries 1,2,6 and 7). As the polarity decreases from DMSO to dichloromethane (entries 1–5 and 6–10), the ability of the solvent to solvate cations is also reduced, and the more basic atom becomes increasingly encumbered by the counterion. This leaves the less basic center free for interaction with the electrophile and the product distribution changes in favor of the O^2-product. In addition, the ion-pairing in solvents of low polarity results in very low concentrations of free nucleophile, and only slow or no reactions were observed (entries 4,5, and 8–10).

The best reaction conditions and reagents utilized in these model reactions were applied to the coupling of the protected bases **3** and **4** with the bicyclic mesylate **8**. Because nucleophiles with lipophilic counterions greatly accelerate substitution reactions, **8** was treated with tetramethylammonium or crown-ether potassium salts of the

Table 3 Influence of the Solvent on the Alkylation of Pyrimidine Nucleobases **3** and **4**[a]



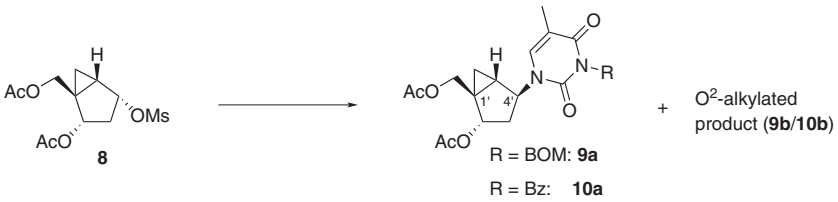
Entry	Heterocycle	Solvent[b]	Time (h)	Ratio (N^1/O^2, %)[c]
1	**3**	DMSO	16	95:5
2	**3**	DMF	16	88:12
3	**3**	MeCN	16	75:25
4	**3**	acetone	16	38:62[d]
5	**3**	CH_2Cl_2	16	only O^2 product[d]
6	**4**	DMSO	16	91:9
7	**4**	DMF	16	87:13
8	**4**	MeCN	24	n.r.[e]
9	**4**	acetone	24	n.r.[e]
10	**4**	CH_2Cl_2	24	n.r.[e]

[a] All reactions were performed with 3.0 equiv of K_2CO_3 and 3.0 equiv of heterocycle.
[b] Decreasing polarity from DMSO to CH_2Cl_2.
[c] Determined by integration of the H-1′ and 5-CH_3 protons of the products from the crude reaction mixture.
[d] Incomplete reaction (TLC).
[e] No reaction (TLC).

nucleobases **3** and **4** in polar solvents (DMF or DMSO) (Table 4). The product ratio was determined by integration of the respective H-4′ and 5-methyl protons in the crude mixtures after extraction with diethyl ether. During extraction, the high-boiling solvents DMSO and DMF remained in the aqueous phase, greatly facilitating the workup. Removal of the protecting groups, performed in the same manner after the coupling under Mitsunobu conditions, led to the target molecule N-MCT (**1**) (results not shown).

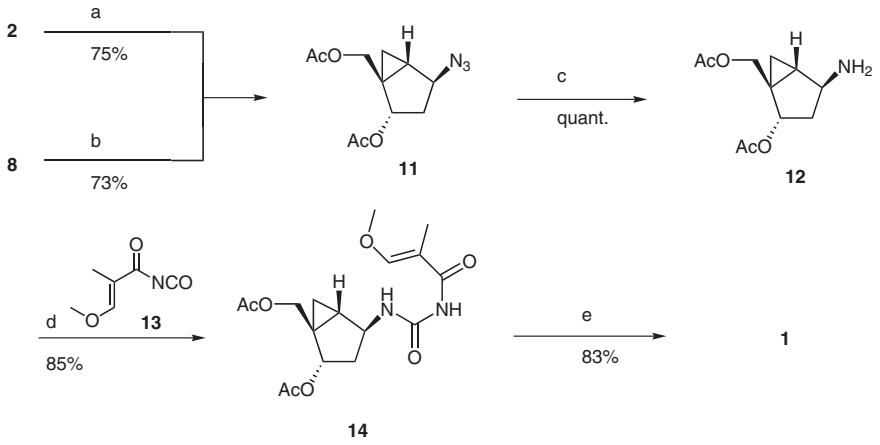
As expected, the reactions were again greatly accelerated by lipophilic counterions. Even when the amount of nucleophile was decreased to 1.5 equivalents (entry 4), the

Table 4 Condensation of the Mesylate **8** with the Protected Thymines **3** and **4** under Optimized Conditions[a]



Entry	Heterocycle	Base	Solvent	Time (h)	Product	Yield (%)[b]	Ratio (N^1/O^2, %)[c]
1	**3**	K_2CO_3 + 18-crown-6	DMF	16	**10a/b**	79	89:11
2	**3**	Cs_2CO_3	DMSO	24	**10a/b**	44	87:13
3	**4**	Me_4NOH	DMF	16	**9a/b**	81	82:18
4[d]	**4**	Me_4NOH	DMF	36	**9a/b**	78	82:18
5	**4**	K_2CO_3 + 18-crown-6	DMSO	16	**9a/b**	79	85:15

[a] All reactions were performed with 3.0 equiv of base and 3.0 equiv of heterocycle at r.t., unless indicated otherwise.
[b] Isolated yield of both regioisomers.
[c] Determined by integration of the H-4′ (carbocycle) and 5-CH_3 (base) protons of the crude products
[d] With 1.5 equiv of base and heterocycle.



Scheme 3 *Reagents and conditions:* (a) DPPA, Et_3N, DMF, 60 °C, 20 h; (b) NaN_3, DMF, 90 °C, 1 h; (c) H_2, Lindlar cat., MeOH–CH_2Cl_2 (1:1), 16 h; (d) DMF–benzene 1:1, 0 °C to r.t., 16 h; (e) 2 N HCl, EtOH, 80 °C, 16 h.

reaction proceeded with sufficient speed with no change in the product ratio. The use of Cs_2CO_3 in DMSO (Table 4, entry 2) in combination with heterocycle **3** resulted in the lowest isolated coupling yields (44%). TLC-analysis of the reaction showed multiple products, probably resulting from elimination and decomposition. The best result in terms of overall yield (79%) and product distribution (89% N^1/11% O^2) was obtained by using heterocycle **3** together with potassium carbonate and 18-crown-6 in DMF (entry 1). The reaction proceeded smoothly and no side products were detected by TLC analysis. Since the experimental procedure is straightforward and leads to excellent product distributions, this method should be considered as alternative to the common Mitsunobu approach.

Formation of the Heterocycle by a Linear Approach

To compare the results obtained from the convergent approaches with the linear strategy, the bicyclic hexanol **2** had to be converted to the bicyclic amine **12** with inverted stereochemistry at C-4. Therefore, the alcohol **2** was reacted with diphenylphosphoryl azide (DPPA) in DMF to yield the azido compound **11** with inversion of configuration (75%) (Scheme 3). Alternatively, the mesylate **8** can be treated with sodium azide in DMF, yielding the azide **11** in 73%. The azide **11** was then quantitatively reduced to the amine **12** by hydrogenation in methanol–dichloromethane (1:1) over Lindlar's catalyst. This amine **12** was subsequently reacted with the acylisocyanate **13** in DMF (85%), prepared freshly from 3-methoxy-2-methylacryloyl chloride[30] and silver isocyanate in benzene. Ring closure of urea **14** under aqueous acidic conditions (83%) also cleaved the acetate protecting groups, yielding the final compound N-MCT (**1**) in 53% overall yield (for DPPA route), starting from the bicyclic hexanol **2**. This overall yield is only slightly lower than the results obtained for the convergent approaches by Mitsunobu chemistry and regular displacement reactions (*vide supra*). Taking into consideration that each step can be purified by simple extraction, all crude materials can be used for the ensuing reactions. This strategy is especially valuable for large-scale syntheses. Furthermore, when separation of the regioisomers is a problem, the classic linear strategy should be the method of choice.

All experiments involving moisture-sensitive compounds were conducted under dry conditions (positive argon pressure) using standard syringe, cannula, and septa apparatus. Solvents: All solvents were purchased anhydrous (Aldrich) and stored over activated molecular sieves. HPLC-grade hexanes, EtOAc, CH_2Cl_2, and MeOH were used in chromatography. Chromatography: Chromatotron (Harrison Research 7924T), Analtech rotors (silica gel GF), UV detection at 254 nm; flash chromatography was performed with Teledyne ISCO CombiFlash Companion. TLC: analytical TLC was performed on Analtech precoated plates (Uniplate, silica gel GHLF, 250 microns) containing a fluorescence indicator; sugar-containing compounds were visualized with the sugar spray reagent [4-methoxybenzaldehyde (5 mL), EtOH (90 mL), concd H_2SO_4 (5 mL), and glacial AcOH (10 mL)] by heating with a heat gun. NMR spectra were recorded using a Varian Inova 400 MHz spectrometer. The coupling constants are reported in Hertz, and the peak shifts are reported in the δ (ppm) scale. Mass spectra (FABMS) were obtained on a VG 7070E mass spectrometer at an accelerating voltage of 6 kV and a resolution of 2000. Glycerol was used as the sample matrix, and ionization was effected by a beam of xenon atoms. Optical rotations were measured on a Jasco P-1010 polarimeter at 589 nm. IR spectra were obtained neat with a Jasco FT-IR/615 spectrometer. Elemental analyses were performed by Atlantic Microlab. Inc., Norcross, Georgia, 30091, USA.

Convergent Strategy: Introduction of the Nucleobase by Mitsunobu Chemistry

1-[(1′*S*,2′*S*,4′*S*,5′*R*)-4′-Hydroxy-5′-(hydroxymethyl)bicyclo[3.1.0]hexan-2′-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (N-MCT, 1)

To a suspension of Ph_3P (344 mg, 1.31 mmol) in anhyd MeCN, 5.0 mL) was added slowly diisopropylazodicarboxylate (DIAD, 238 μL, 1.23 mmol) and the mixture was stirred for 0.5 h at 0 °C. This preformed complex was slowly added to a suspension of the 3-*N*-Bz-thymine **3** (253 mg, 1.10 mmol) and the bicyclic hexanol **2** (100 mg, 0.44 mmol) in anhyd MeCN (3.0 mL) at –40 °C under argon. The reaction was slowly warmed to r.t. (about 4 h) and stirred overnight. The solvent was removed from the mixture and the residue was dissolved in a 1% solution of NaOH in MeOH (10 mL). The mixture was stirred overnight at r.t. The mixture was neutralized by the addition of aq 2 N HCl and the solvent was removed under reduced pressure. The crude product was purified on a Chromatotron

(MeOH in CH_2Cl_2, 5–15%) to yield N-MCT (**1**; 65 mg, 59%) as a colorless foam.

^{1}H NMR (400 MHz, D_2O): δ = 7.68 (q, *J* = 1.0 Hz, 1 H, H-6), 4.71 (d, *J* = 7.2 Hz, 1 H, H-2′), 4.65 (dd, *J* = 8.5, 8.5 Hz, 1 H, H-4′), 4.02 (d, *J* = 12.5 Hz, 1 H, C*H*HOH), 3.22 (d, *J* = 12.5 Hz, 1 H, CH*H*OH), 1.90 (dd, *J* = 15.5, 8.5 Hz, 1 H, H-3′a), 1.71 (d, *J* = 1.0 Hz, 3 H, CH_3), 1.64–1.55 (m, 1 H, H-3′b), 1.35 (dd, *J* = 8.7, 3.8 Hz, 1 H, H-1′), 0.78 (dd, *J* = 6.0, 3.8 Hz, 1 H, H-6′a), 0.65 (dd, *J* = 8.7, 6.0 Hz, 1 H, H-6′b).

^{13}C NMR (100 MHz, D_2O): δ = 166.37 (C-4), 152.13 (C-2), 139.26 (C-6), 110.72 (C-5), 70.57 (C-4′), 62.17 (CH_2OH), 56.75 (C-2′), 36.63 (C-5′), 35.76 (C-3′), 24.76 (C-1′), 11.39 (CH_3), 9.57 (C-6′).

Anal. Calcd for $C_{12}H_{16}N_2O_4 \cdot 0.25\ H_2O$: C, 56.13; H, 6.48; N, 10.91. Found: C, 56.12; H, 6.46; N, 10.73.

All other spectroscopic data were identical to those reported earlier.[7a]

3-(Benzyloxymethyl)-1-[(1′*S*,2′*S*,4′*S*,5′*R*)-4′-hydroxy-5′-(hydroxymethyl)bicyclo[3.1.0]hexan-2′-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (6) and 3-(Benzyloxymethyl)-2-[(1′*S*,2′*S*,4′*S*,5′*R*)-4′-hydroxy-5′-(hydroxymethyl)bicyclo[3.1.0]hexan-2′-yloxy]-5-methylpyrimidin-4(3*H*)-one (7)

To a suspension of Ph_3P (344 mg, 1.31 mmol) in anhyd MeCN (5.0 mL) was added slowly diisopropylazodicarboxylate (DIAD, 238 μL, 1.23 mmol) and the mixture was stirred for 0.5 h at 0 °C. This preformed complex was slowly added to a suspension of the 3-*N*-BOM-thymine **4** (271 mg, 1.10 mmol) and the bicyclic hexanol **2** (100 mg, 0.44 mmol) in anhyd MeCN (3.0 mL) at –40 °C under N_2. The reaction was slowly warmed to r.t. (about 4 h) and stirred overnight. The solvent was removed from the mixture and the residue was dissolved in MeOH (10 mL). To this solution was added Amberlite IRA-400 (OH^-) ion-exchange resin and the mixture was stirred overnight at r.t. The resin was filtered off and the MeOH was removed under reduced pressure. The crude product was purified on a Chromatotron (MeOH in CH_2Cl_2, 0–10%) to yield the title compounds **6** (106 mg, 65%) and **7** (19 mg, 11%) as colorless syrups, with **6** eluting prior to **7**.

N^1-Alkylated Product 6

$[\alpha]_D^{20}$ +17.91 (*c* = 0.875, $CHCl_3$).

IR (neat): 3430, 3075, 2926, 1698, 1632, 1466, 1361, 1286, 1244, 1159, 1069, 927 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (q, *J* = 1.0 Hz, 1 H, H-6), 7.35–7.20 (m, 5 H, CH-arom), 5.47 (s, 2 H, OCH_2N), 4.85 (dd, *J* = 8.2, 8.2 Hz, 1 H, H-4′), 4.85 (d, *J* = 7.3 Hz, 1 H, H-2′), 4.67 (s, 2 H, CH_2-benzyl), 4.18 (d, *J* = 11.3 Hz, 1 H, C*H*HOH), 3.42 (d, *J* = 11.3 Hz, 1 H, CH*H*OH), 1.98 (dd, *J* = 15.2, 8.2 Hz, 1 H, H-3′a), 1.87 (d, *J* = 1.0 Hz, 3 H, CH_3), 1.78–1.68 (m, 1 H, H-3′b), 1.33 (dd, *J* = 8.6, 3.8 Hz, 1 H, H-1′), 0.88 (dd, *J* = 6.0, 3.8 Hz, 1 H, H-6′a), 0.68 (dd, *J* = 8.6, 6.0 Hz, 1 H, H-6′b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163,51 (C-4), 151.50 (C-2), 137.95 (Cq-arom), 136.65 (C-6), 128.25, 127.62 (CH-arom), 109.94 (C-5), 72.27 (CH_2-benzyl), 71.44 (C-4′), 70.34 (OCH_2N), 64.11 (CH_2OH), 57.91 (C-2′), 38.46 (C-5′), 36.61 (C-3′), 25.64 (C-1′), 13.12 (CH_3), 10.21 (C-6′).

ESI-MS: *m*/*z* = 373 (M + H), 395 (M + Na), 411 (M + K).

Anal. Calcd for $C_{20}H_{24}N_2O_4 \cdot H_2O$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.46; H, 6.41; N, 7.20.

O^2-Alkylated Product 7

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (q, *J* = 1.0 Hz, 1 H, H-6), 7.35–7.20 (m, 5 H, CH-arom), 5.52 (d, *J* = 10.0 Hz, 1 H, OC*H*HN), 5.39 (d, *J* = 10.0 Hz, 1 H, OCH*H*N), 5.33 (d, *J* = 5.5 Hz, 1 H, H-2′), 4.80 (ddd, *J* = 8.2, 8.2, 4.4 Hz, 1 H, H-4′), 4.61 (d, *J* = 12.0 Hz, 1 H, C*H*H-benzyl), 4.57 (d, *J* = 12.0 Hz, 1 H, CH*H*-benzyl), 3.65 (dd, *J* = 11.5, 6.6 Hz, 1 H, C*H*HOH), 3.54 (dd, *J* = 11.5, Hz, 4.0 Hz, 1 H, CH*H*OH), 2.15 (ddd, *J* = 15.2, 8.2, 1.0 Hz, 1 H, H-3′a), 2.13 (d, *J* = 4.4 Hz, 1 H, 4-OH), 2.00 (dd, *J* = 6.6, 4.4 Hz, 1 H, CH_2OH), 1.92 (d, *J* = 1.0 Hz, 3 H, CH_3), 1.53–1.45 (m, 2 H, H-3′b, H-1′), 0.85 (dd, *J* = 5.9, 4.0 Hz, 1 H, H-6′a), 0.62 (dd, *J* = 8.6, 5.9 Hz, 1 H, H-6′b).

APCI-MS: *m*/*z* (%) = 373 (40), 247 (100).

1-[(1′*S*,2′*S*,4′*S*,5′*R*)-4′-Hydroxy-5′-(hydroxymethyl)bicyclo[3.1.0]hexan-2′-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (N-MCT, 1)

The BOM-protected nucleoside **6** (50 mg, 0.135 mmol) was dissolved in MeOH (5.0 mL) and 10% Pd/C (10 mg) was added. The flask was flushed with H_2 and the mixture was stirred overnight under a H_2 atmosphere. The catalyst was filtered off over a short pad of Celite and the filtrate was concentrated under reduced pressure. The crude was purified on a Chromatotron (MeOH in CH_2Cl_2 5–15%) to yield the title compound **1** (30.0 mg, 87%) as a colorless foam. The spectroscopic data were identical to those reported above.

Convergent Strategy: Introduction of the Heterocycle by Displacement of a Mesylate

[(1*R*,2*S*,4*R*,5*S*)-2-Acetoxy-4-(methylsulfonyloxy)bicyclo[3.1.0]hexan-1-yl]methyl Acetate (8)

The bicyclic hexanol **2** (60.0 mg, 0.236 mmol) was dissolved in anhyd CH_2Cl_2 (2 mL) under argon at 0 °C and Et_3N (110 μL, 0.789 mmol) and $MeSO_2Cl$ (MsCl, 30.5 μL, 0.394 mmol) were slowly added. The mixture was stirred for 1 h at 0 °C and then poured into a mixture of ice-cold phosphate buffer (pH, 7.2, 25 mL) and Et_2O (25 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The crude mesylate **2** was used in the next substitution reaction without any further purification (decomposition occurred during chromatography on silica gel).

IR (neat): 3019, 2941, 1733, 1446, 1351, 1237, 1171, 1032, 970, 922, 846 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.20 (dd, *J* = 7.8, 7.8 Hz, 1 H, H-2), 5.17–5.11 (m, 1 H, H-4), 4.20 (d, *J* = 12.0 Hz, 1 H, C*H*HOAc), 3.78 (d, *J* = 12.0 Hz, 1 H, CH*H*OAc), 2.94 (s, 3 H, CH_3SO_3), 2.63 (ddd, *J* = 14.1, 7.8, 7.8 Hz, 1 H, H-3a), 1.99 (s, 3 H, $OCOCH_3$), 1.98 (s, 3 H, $OCOCH_3$), 1.83–1.78 (m, 1 H, H-3b), 1.25 (dd, *J* = 6.0, 4.3 Hz, 1 H, H-6a), 0.81 (dd, *J* = 7.0, 7.0 Hz, 1 H, H-6b).

FAB-MS: *m*/*z* (%) = 307 (5), 247 (24), 211 (100).

Displacement of Mesylates by N^3-Protected Pyrimidines; General Procedures

Method A (for N^3-alkylated or acylated pyrimidines): The N^3-protected pyrimidine (**3** or **4**, 3.0 equiv) was dissolved in anhyd DMF or DMSO (7 mL/mmol) at r.t. under argon. Powdered 4 Å molecular sieves (300 mg/mmol), K_2CO_3 (3.0 equiv) and 18-crown-6 (3.0 equiv) were added and the mixture was stirred for 15 min at r.t. The mesylate **8** (1.0 equiv) was dissolved in anhyd DMF or DMSO (7 mL/mmol) and then added dropwise to the deprotonated nucleobase. The mixture was stirred at r.t. until all the starting material was consumed according to TLC. The mixture was poured into a mixture of phosphate buffer (pH 7.2, 2 mL) and Et_2O (20 mL), and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude materials were purified by flash chromatography yielding the protected nucleoside analogues as colorless syrups.

Method B (for N^3-alkylated pyrimidines): The tetraalkylammonium salt of the BOM-protected nucleobase **4** (3.0 equiv) was dissolved in anhyd DMF or DMSO (7 mL/mmol) at r.t. under an atmosphere

of argon and powdered 4 Å molecular sieves (300 mg/mmol) were added. After the addition of the mesylate **8** (1.0 equiv), dissolved in anhyd DMF or DMSO (7 mL/mmol), the mixture was stirred until all the starting material was consumed as monitored by TLC. The workup procedure was identical to that described in the general method A.

[(1*R*,2*S*,4*S*,5*S*)-2-Acetoxy-4-(3-(benzyloxymethyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)bicyclo[3.1.0]hexan-1-yl]methyl Acetate (9a) and ((1*R*,2*S*,4*S*,5*S*)-2-Acetoxy-4-[1-(benzyloxymethyl)-5-methyl-6-oxo-1,6-dihydropyrimidin-2-yloxy)bicyclo[3.1.0]hexan-1-yl]methyl Acetate (9b)

The reaction was carried out according to the general coupling procedure, Method B, with 3-*N*-BOM-thymine tetramethylammonium salt (126 mg, 0.393 mmol), mesylate **8** (40.0 mg, 0.131 mmol), molecular sieves (4 Å, 40 mg), and DMF (2.0 mL). The mixture was stirred overnight at r.t..

N[1]-Alkylated Product 9a

Yield: 39.4 mg (66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 6 H, CH-arom, H-6), 5.53 (dd, *J* = 8.5, 8.5 Hz, 1 H, H-2′), 5.47 (s, 2 H, OCH_2N), 5.04 (d, *J* = 7.7 Hz, 1 H, H-4′), 4.67 (s, 2 H, CH_2-benzyl), 4.60 (d, *J* = 12.0 Hz, 1 H, C*H*HOAc), 3.75 (d, *J* = 12.0 Hz, 1 H, CH*H*OAc), 2.21 (dd, *J* = 15.7, 8.5 Hz, 1 H, H-3′a), 2.10 (s, 3 H, $OCOCH_3$), 2.04 (s, 3 H, $OCOCH_3$), 1.93 (d, *J* = 1.0 Hz, 3 H, CH_3), 1.74 (ddd, *J* = 15.7, 8.5, 8.5 Hz, 1 H, H-3′b), 1.43 (dd, *J* = 8.8, 4.1 Hz, 1 H, H-5′), 0.97 (dd, *J* = 6.1, 4.1 Hz, 1 H, H-6′a), 0.87 (dd, *J* = 8.8, 6.1 Hz, 1 H, H-6′b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.00, 170.53 (2 × O*C*OCH$_3$), 163.16 (C-4), 151.35 (C-2), 138.03 (CH-arom), 135.06 (C-6), 128.22, 127.60, 127.58 (CH-arom), 110.28 (C-5), 73.68 (C-2′), 72.25 (CH_2-benzyl), 70.78 (OCH_2N), 65.20 (*C*H$_2$OAc), 56.55 (C-4′), 35.94 (C-1′), 32.19 (C-3′), 26.16 (C-5′), 20.91 (2 × OCO*C*H$_3$), 13.42 (CH_3), 11.15 (C-6′).

APCI-MS: *m*/*z* (%) = 457 (100), 397 (95).

O[2]-Alkylated Product 9b

Yield: 8.6 mg (15%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (q, *J* = 1.0 Hz, 1 H, H-6), 7.35–7.20 (m, 5 H, CH-arom), 5.60 (dd, *J* = 8.1, 8.1 Hz, 1 H, H-2′), 5.53 (d, *J* = 9.8 Hz, 1 H, OC*H*HN), 5.47 (d, *J* = 9.8 Hz, 1 H, OCH*H*N), 5.35 (d, *J* = 5.1 Hz, 1 H, H-4′), 4.66 (s, 2 H, CH_2-benzyl), 4.25 (d, *J* = 12.0 Hz, 1 H, C*H*HOAc), 3.96 (d, *J* = 12.0 Hz, 1 H, CH*H*OAc), 2.45 (ddd, *J* = 15.4, 8.1, 1.1 Hz, 1 H, H-3′a), 2.04 (s, 3 H, $OCOCH_3$), 1.94 (d, *J* = 1.0 Hz, 3 H, CH_3), 1.92 (s, 3 H, $OCOCH_3$), 1.74 (dd, *J* = 8.8, 4.3 Hz, 1 H, H-5′), 1.57–1.51 (m, 1 H, H-3′b), 0.91 (dd, *J* = 6.2, 4.3 Hz, 1 H, H-6′a), 0.83 (dd, *J* = 8.8, 6.2 Hz, 1 H, H-6′b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.94, 170.87 (2 × O*C*OCH$_3$), 154.18 (C-2), 148.64 (C-4), 137.65, 128.32, 127.71, 127.49 (CH-arom), 117.47 (C-5), 79.72 (C-4′), 74.86 (C-2′), 72.15 (CH_2-benzyl), 70.51 (OCH_2N), 65.19 (*C*H$_2$OAc), 34.52 (C-1′), 30.69 (C-3′), 26.68 (C-5′), 20.98, 20.68 (2 × OCO*C*H$_3$), 13.09 (CH_3), 10.80 (C-6).

APCI-MS: *m*/*z* (%) = 457 (45), 211 (100).

Formation of the Heterocycle by a Linear Approach

[(1*R*,2*S*,4*S*,5*S*)-2-Acetoxy-4-azidobicyclo[3.1.0]hexan-1-yl]methyl Acetate (11)

Method A: To a stirred solution of the alcohol **2** (850 mg, 3.72 mmol) in anhyd DMF (25 mL) was added diphenylphosphoryl azide (DPPA, 2.40 mL, 11.2 mmol) and Et_3N (1.80 mL, 13.0 mmol) under argon at r.t. The mixture was warmed to 60 °C and stirred for 20 h. The solvent was evaporated off and the residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). After phase separation, the aqueous phase was extracted again with CH_2Cl_2 (2 × 50 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography on silica gel (EtOAc in hexanes, 25–45%) to yield the azide **11** (706 mg, 75%) as a colorless oil; $[\alpha]_D^{20}$ –57.71 (*c* = 0.7833, $CHCl_3$).

IR (neat): 3014, 2098, 1733, 1631, 1370, 1230, 1025, 973, 905, 835 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.49 (dd, *J* = 8.4, 8.4 Hz, 1 H, H-2), 4.22 (d, *J* = 12.0 Hz, 1 H, C*H*HOAc), 3.97 (d, *J* = 12.0 Hz, 1 H, CH*H*OAc), 3.81(d, *J* = 6.2 Hz, 1 H, H-4), 2.25 (ddd, *J* = 14.8, 8.1, 1.0 Hz, 1 H, H-3a), 2.09 (s, 3 H, $OCOCH_3$), 1.99 (s, 3 H, $OCOCH_3$), 1.53 (dd, *J* = 8.6, 4.3 Hz, 1 H, H-5), 1.41 (ddd, *J* = 14.8, 8.4, 6.2 Hz, 1 , H-3b), 0.84 (dd, *J* = 6.2, 4.3 Hz, 1 H, H-6a), 0.79–0.75 (m, 1 H, H-6b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.04, 170.83 (2 × O*C*OCH$_3$), 74.73 (C-2), 65.05 (*C*H$_2$OAc), 61.51 (C-4), 34.53 (C-3), 30.78 (C-1), 26.55 (C-5), 20.96, 20.79 (2 × OCO*C*H$_3$), 11.06 (C-6).

FAB-MS: *m*/*z* (%) = 254 (45), 194 (100).

Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.26; H, 6.01; N, 16.35.

Method B: The mesylate **8** (81.0 mg, 0.236 mmol) was dissolved in anhyd DMF (2.0 mL) and NaN_3 (170 mg, 2.36 mmol) was added in one portion under argon at r.t. The mixture was heated to 90 °C for 1 h and allowed to cool to r.t. The mixture was poured into a mixture of phosphate buffer (pH 7.2, 25 mL) and Et_2O (25 mL) and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (EtOAc in hexanes, 25–45%) yielded the azide **11** (43.6 mg, 73%) as a colorless oil. The spectroscopic data were identical to those reported above.

[(1*R*,2*S*,4*S*,5*S*)-2-Acetoxy-4-aminobicyclo[3.1.0]hexan-1-yl]methyl Acetate (12)

The azide **11** (690 mg, 2.72 mmol) was dissolved in MeOH (25 mL) and CH_2Cl_2 (25 mL) under argon at r.t. and Lindlar's catalyst (100 mg) was added. The mixture was stirred overnight at r.t., until all the starting material was consumed. The mixture was filtered over a short pad of Celite and the solvent was evaporated off. The crude amine **12** (618 mg, 100%) was sufficiently pure to be used in the next step without any further purification. An analytical sample was prepared by flash chromatography on silica gel (MeOH in EtOAc, 10–40%): $[\alpha]_D^{20}$ –19.21 (*c* = 0.358, $CHCl_3$).

IR (neat): 3332, 2947, 1729, 1654, 1548, 1370, 1238, 1025, 733 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.45 (dd, *J* = 8.4, 8.4 Hz, 1 H, H-2), 4.17 (d, *J* = 11.6 Hz, 1 H, C*H*HOAc), 3.92 (d, *J* = 11.6 Hz, 1 H, CH*H*OAc), 3.15 (d, *J* = 6.0 Hz, 1 H, H-4), 2.40–2.10 (br s, 2 H, NH_2), 1.94 (s, 3 H, $OCOCH_3$), 1.92 (s, 3 H, $OCOCH_3$), 1.74 (dd, *J* = 13.5, 8.0 Hz, 1 H, H-3a), 1.30–1.22 (m, 2 H, H-3b, H-5), 0.72 (dd, *J* = 4.9, 4.9 Hz, 1 H, H-6a), 0.62 (dd, *J* = 8.2, 5.5 Hz, 1 H, H-6b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.46, 171.45 (O*C*OCH$_3$), 75.97 (C-2), 66.39 (*C*H$_2$OAc), 51.15 (C-4), 36.24 (C-3), 30.18 (C-1), 29.53 (C-5), 19.53, 1936 (OCO*C*H$_3$), 10.38 (C-6).

FAB-MS: *m*/*z* (%) = 228 (100), 186 (38).

Anal. Calcd for $C_{11}H_{17}NO_4 \cdot 0.2\ H_2O$: C, 57.23; H, 7.60; N, 6.07. Found: C, 57.08; H, 7.59; N, 5.86.

((1′*R*,2′*S*,4′*S*,5′*S*)-2′-Acetoxy-4′-{3-[(*E*)-3-methoxy-2-methylacryloyl]ureido}bicyclo[3.1.0]hexan-1′-yl)methyl Acetate (14)

To a solution of dried AgNCO (198 mg, 1.32 mmol) in anhyd benzene (5.0 mL) under argon was added 3-methoxy-2-methylacryloyl

chloride dropwise at r.t. The mixture was heated to reflux for 1 h and then cooled to r.t. again. The supernatant was added via syringe to a stirred solution of the amine **12** (50 mg, 0.22 mmol) in anhyd DMF (2.0 mL) at 0 °C under argon. The solution was allowed to warm to r.t. and stirred for 3 h. The solvent was evaporated off and the residue was purified by flash chromatography on silica gel (EtOAc in hexanes, 50–75%) to yield the title compound **14** (68.9 mg, 85%) as a colorless foam; $[\alpha]_D^{20}$ –21.6 (*c* = 0.25, $CHCl_3$).

IR (neat): 3253, 2944, 1735, 1680, 1542, 1476, 1372, 1294, 1237, 1149, 1025, 986 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.87 – 8.80 (m, 1 H, NH), 7.90–7.69 (m, 1 H, NH), 7.24–7.21 (m, 1 H, H-3), 5.49 (dd, *J* = 8.4, 8.4 Hz, 1 H, H-2′), 4.28 (d, *J* = 11.8 Hz, 1 H, C*H*HOAc), 4.21 (dd, *J* = 6.6, 6.6 Hz, 1 H, H-4′), 3.87 (d, *J* = 11.8 Hz, 1 H, CH*H*OAc), 3.79 (d, *J* = 0.8 Hz, 3 H, 3-OCH_3), 2.19 (dd, *J* = 14.4, 8.0 Hz, 1 H, H-3′a), 2.08 (s, 3 H, $OCOCH_3$), 1.98 (s, 3 H, $OCOCH_3$), 1.70 (d, *J* = 1.0 Hz, 3 H, CH_3), 1.43 (dd, *J* = 8.5, 4.8 Hz, 1 H, H-5′), 1.43–1.40 (m, 1 H, H-3′b), 0.90 (dd, *J* = 6.0, 4.8 Hz, 1 H, H-6′a), 0.73 (dd, *J* = 8.5, 6.0 Hz, 1 H, H-6′b).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.32, 169.99 (2 × O*C*OCH$_3$), 167.96 (C-1), 157.38 (C-3), 152.20 (C=O, urea), 105.96 (C-2), 73.75 (C-2′), 64.36 (*C*H$_2$OAc), 60.52 (3-OCH$_3$), 49.41 (C-4′), 34.10 (C-3′), 29.65 (C-1′), 26.27 (C-5′), 20.06, 19.82 (2 × OCO*C*H$_3$), 10.09 (2-CH$_3$), 7.78 (C-6′).

FAB-MS: *m*/*z* (%) = 369 (27), 309 (45), 99 (100).

Anal. Calcd for $C_{17}H_{24}N_2O_7 \cdot 0.1\ H_2O$: C, 55.16; H, 6.59; N, 7.57. Found: C, 54.80; H, 6.51; N, 7.49.

1-[(1′*S*,2′*S*,4′*S*,5′*R*)-4′-Hydroxy-5′-(hydroxymethyl)bicyclo[3.1.0]hexan-2′-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (N-MCT, 1)

The urea **14** (50 mg, 0.136 mmol) was dissolved in EtOH (3.0 mL) and aq 2 N HCl (0.3 mL) was added. The mixture was heated to reflux and stirred overnight. The solvent was removed under reduced pressure and the residue was purified by chromatography on a Chromatotron (MeOH in CH_2Cl_2, 5–15%) to yield N-MCT (**1**; 30.5 mg, 89%) as a colorless foam. The spectroscopic data were identical to those reported above.

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