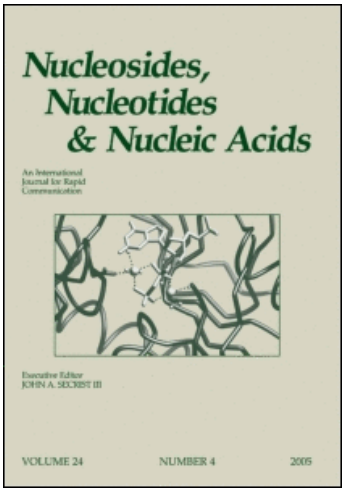

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Regio-and Stereoselective Functionalization of Pyrimidinediones by Cohalogenation with Oxygen Nucleophiles

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REGIO- AND STEREOSELECTIVE FUNCTIONALIZATION OF PYRIMIDINEDIONES BY COHALOGENATION WITH OXYGEN NUCLEOPHILES

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Abstract. A detailed study of the regio- and stereoselective electrophilic functionalization of the C5-C6 double bond in the uracil and thymine series using the cohalogenation with various oxygen nucleophiles is described.

Pyrimidinediones and more particularly uracil derivatives exhibit extremely diverse physiological activities and are found in a multitude of bioactives important molecules including nucleic acids.[1] Selective chemical modification of this heterocyclic nucleus, especially at the C5 or the C6 position[2] plays an important role for the development of new medicinal agents used for the treatment of cancer and viral infections such as herpes and AIDS.[3] In this effort and owing to our continuing interest for the cohalogenation of olefins[4] we have studied the reactivity of the C5-C6 double bond of pyrimidinediones towards various oxygen nucleophiles.[5]

While important work has been devoted to the utilization of the 5,6-double bond in cycloaddition processes,[6] exploitation of electrophilic additions of halogens have found little attention from a synthetic point of view.

The first example was published in 1912[7] with the bromination of uridine in water, which gave the C5-bromo derivative by an addition/elimination sequence.[8] More than fifty years later Wang[9] reported the isolation of the intermediate bromohydrines in the uracil and thymine series.[10] Similarly, haloalkoxylations of the C5-C6 double bond using either

MeOH[11] or EtOH[12] was shown to be an efficient procedure for the selective functionalization of these heterocyclic nuclei but have found only limited synthetic development.[13] A wider interest has been given to the fluroalkoxylation[14] or fluoroacetoxylation[15] which allowed for the selective introduction of a fluorine atom at C5.

In this article we present full details of the regio- and stereoselective electrophilic functionalization of uracil and thymine derivatives by using the cohalogenation of the C5-C6 double bond with various oxygen nucleophiles such as acetylenic alcohols, unsaturated carboxylic acids and ethylene oxide. The methodology provides an efficient steroselective access to structurally diverse and synthetically valuable[16] nucleosidic bases with biological potentialities.

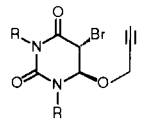
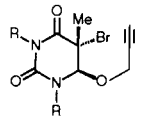
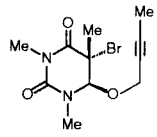
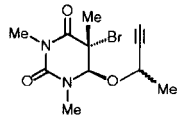
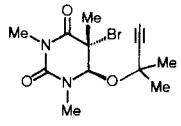
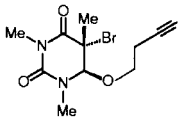
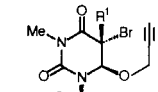
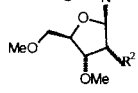
The results of our study on the cohalogenation of pyrimidinediones are reported in Tables 1 and 2. The reactions were performed using *N*-bromosuccinimide (NBS) or bromine as source of electrophilic halogen and various oxygen nucleophiles.

Propargylic alcohols **2** give generally good yields of the expected unsaturated alkoxybromides **7a-j** with a total *trans*-stereocontrol and a complete regioselectivity in favour of 5-bromo 6-alkoxy ethers (Scheme 1).

Interestingly, functionalization of unprotected uracil **1a** and thymine **1c** proceeds smoothly with propargylic alcohol **2a** to give respectively **7a** and **7c** in 59% and 91% isolated yields (entries 1, 3). A ^{15}N NMR of **7c** using the INEPT protocol with $CH_3{}^{15}NO_2$ as internal reference clearly showed the presence of a tautomeric equilibrum between three isomeric forms (Scheme 2).

1*N*,3*N*-Dimethylated derivatives[17] **1b** and **1d** also react very easily under the standard conditions with α,β-acetylenic alcohols **2a** and **2b** to give the corresponding bromoethers with high yields (entries 2, 4, 5). Less reactive secondary and tertiary propargylic alcohols **2c** and **2d** gave satisfactory results (entries 6, 7) with the assistance of a catalytic amount of H_2SO_4, which is known to increase the rate of the cohalogenation in the case of conjugated carbonyl compounds.[18] Under these conditions, **7f** was prepared in almost quantitative yield from alcohol **2c** (entry 6) while **7g** was produced in 40 % yield starting from **2d** (entry 7). The conjugated character of the alcohol is not absolutely necessary as shown by the high yield obtained with 3-butynol **(2e)** (entry 8). Finally, in the nucleoside

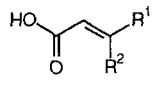
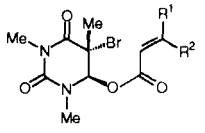
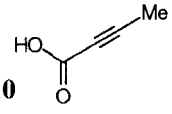
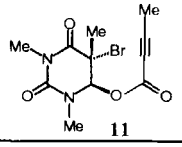
TABLE 1: Cohalogenation of pyrimidinediones **1** with propargylic alcohols **2**.[a]

Entry	1	2 (equiv.)	t (h)	Product	yield (%)[b]
1	**a**	**a** (18)	24	 **7a** (R = H)	59
2	**b**	**a** (20)	3	**7b** (R = Me)	98
3	**c**	**a** (18)	3	 **7c** (R = H)	91
4	**d**	**a** (20)	2	**7d**(R = Me)	90
5	**d**	**b** (7)	24	 **7e**	96
6	**d**	**c** (10)	3	 **7f**[c]	95
7	**d**	**d** (10)	48	 **7g**[c]	40
8	**d**	**e** (30)	15	 **7h**	90
9	**e**	**a** (18)	12	 **7i** (R^1 = H; R^2 = OMe)[d]	51
10	**f**	**a** (18)	12	 **7j** (R^1 = Me; R^2 = H)[d]	70

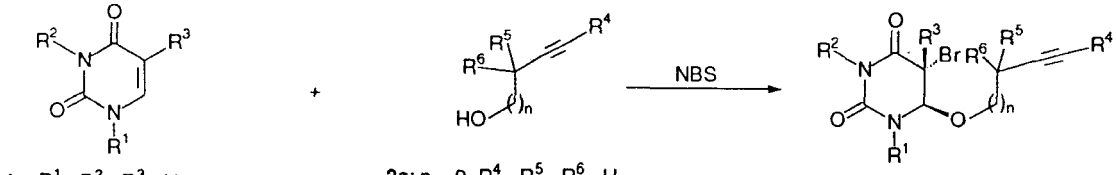
[a]NBS was used as source of Br^+. [b]Isolated. [c]cat. H_2SO_4 was added. [d]Mixture of diastereomers 85:15 determined by NMR (only one shown).

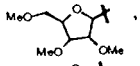
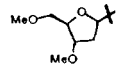
series tetramethyluridine **1e**[19] and trimethylthymidine **1f**[19] are conveniently functionalized by reaction with NBS and propargylic alcohol **1a** leading respectively to **7i** (51 %) and **7j** (70 %) (entries 9, 10). As expected from previous reports related to the stereoselectivity of the functionalization at the C5-C6 double bond,[6a,15a,20] both **7i** and **7j** are obtained as a

TABLE 2. Cohalogenation of **1d** with various unsaturated acids.[a]

Entry	Carboxylic acid	t (h)	Products	yield (%)[b]
				
1	**8a**: $R^1 = R^2 = H$	19	**9a**	61
2	**8b**: $R^1 = Me$; $R^2 = H$	12	**9b**	96
3	**8c**: $R^1 = R^2 = Me$	21	**9c**	66
4	 **10**	19[c]	 **11**	100

[a]NBS was used as source of Br^+. [b]Isolated. [c]Addition of 3Å-MS.

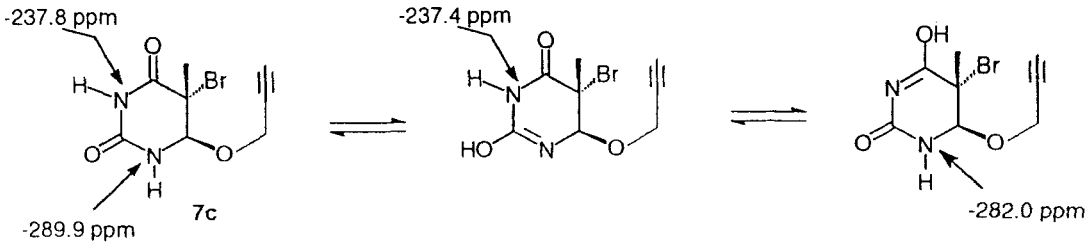


1a: $R^1 = R^2 = R^3 = H$
b: $R^1 = R^2 = Me$, $R^3 = H$
c: $R^1 = R^2 = H$, $R^3 = Me$
d: $R^1 = R^2 = R^3 = Me$
e: R^1 =  , $R^2 = Me$, $R^3 = H$
f: R^2 =  , $R^2 = R^3 = Me$

2a: n = 0, $R^4 = R^5 = R^6 = H$
b: n = 0, $R^4 = Me$, $R^5 = R^6 = H$
c: n = 0, $R^4 = R^5 = H$, $R^6 = Me$
d: n = 0, $R^4 = H$, $R^5 = R^6 = Me$
e: n = 1, $R^4 = R^5 = R^6 = H$

7a-j

Scheme 1



Scheme 2

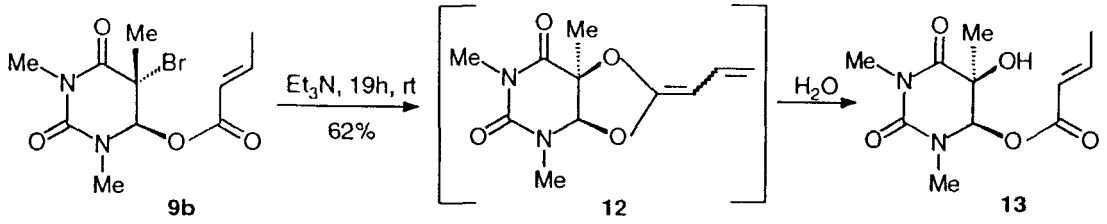
mixture of isomers in a ratio of 85:15 resulting from a diastereofacial differenciation of the C5-C6 double bond due to the presence of the ribose ring at N1.

In order to enlarge the scope and the diversity in the functionalization of nucleic bases we have investigated the utilization of various carboxylic acids which, to the best of our knowledge and to the exception of acetic acid, have not been studied to date.[15] Since it is known that halogenation of uracil derivatives in acetic acid gives only 5-halouracils by an addition elimination sequence[21] we have studied the reactivity of the thymine nucleus, which should prevent this drawback.

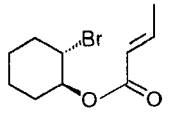
Our results using 1*N*,3*N*-dimethylthymine **1d** are presented in Table 2. Using standard conditions (1.2 equiv. NBS, 5 equiv. unsaturated acid, $CHCl_3$, rt) α,β-unsaturated acids **8a-c** react smoothly to give good yields of the expected *trans*-conjugated esters **9a-c** with total regio- and stereoselectivity (entries 1-3). On the other hand, in the case of tetrolic acid (**10**) the reaction needs the presence of powdered 3Å-molecular sieves to prevent the rapid hydrolysis of the very sensitive acetylenic ester **11**, under the reaction conditions (entry 4).

An example of the reactivity and the synthetic potentiality of these new unsaturated bromo esters is presented by the facile conversion of butenoic derivative **9b**, upon treatment with Et_3N, to the corresponding *cis*-1,2-diol monobutenoic ester **13** (Scheme 3). The transformation evolves through the corresponding ketene acetal **12** generated by Et_3N-promoted proton abstraction from **9b**.[22]

Interestingly, this peculiar reactivity is associated with the heterocyclic nature of **9b** since the corresponding carbocycle **14**[4] remains unchanged under the same conditions even after five days at room temperature.



Scheme 3



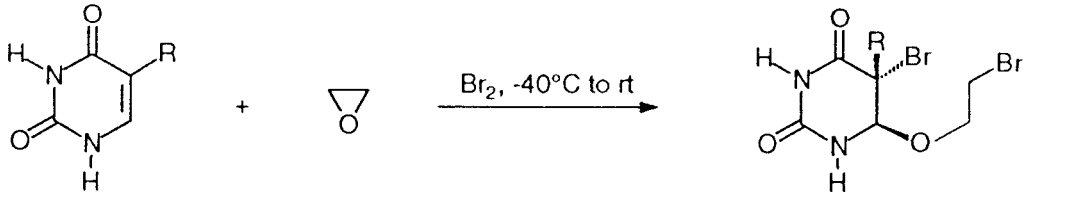
14

Also of interest is the reaction of cohalogenation in ethylene oxide[23] presented in scheme 4. Direct treatment of uracil **1a** and thymine **1c**, in the presence of ethylene oxide, with bromine at low temperature furnished regio- and stereoselectively the respective *trans*-β,β'-dibromo ethers **14a** and **14b** in almost quantitative yields.

In conclusion, the cohalogenation of pyrimidinediones in the presence of various oxygen nucleophiles offers an efficient and general synthesis of highly functionalized heterocycles, which are valuable synthetic intermediates with biological potentialities. The regio- and stereoselectivity of this process allow for the selective functionalization of the C5-C6 double bond of nucleosidic bases in the uracil and thymine series even without protection of the N-H functions. Further work devoted to the synthetic utilization of these functionalized heterocycles especially for radical cyclizations leading to fused furans are under active investigation.

EXPERIMENTAL

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. Reactions, whenever possible, were carried out under N_2 or Ar. IR spectra were obtained neat (NaCl plates) or in solution on a Perkin-Elmer 1600 series FTIR spectrometer. ^1H NMR and ^{13}C NMR spectra were measured on



1a (R = H)
1c (R = Me)

14a (R = H) (98%)
14b (R = Me) (99%)

Scheme 4

a Bruker AC 200 or Bruker AM 400 spectrometers and unless otherwise specified, in $CDCl_3$ using residual $CHCl_3$ as internal reference; chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). Flash chromatograhy[24] was performed using Merck silica gel 60 (250-400 Mesh).

Preparation of β-bromopropargyl ethers 7a-j: To a mixture of pyrimidinediones **1** (0.1 mol) and propargylic alcohols **2** (7-30 equiv., see Table 1) at room temperature under nitrogen was added NBS (0.12 mol) in small portions over 0.5 h. The evolution of the reaction was monitored by TLC and after completion (2-48h) water (30 mL) was added and the mixture was extracted with 3 x 50 mL of CH_2Cl_2. The extracts were washed successively with saturated $NaHSO_3$ solution, aqueous K_2CO_3 and water, dried ($MgSO_4$) and concentrated. The crude products were purified by flash chromatography on silica gel.

***Trans*-5-bromo-6-(prop-2-ynyloxy)-dihydropyrimidine-2,4-dione (7a)**. Mixture of tautomers, heavy colorless oil, R_f = 0.42 ($CHCl_3$/MeOH: 9/1); IR (neat) 3300 (ν-C≡C-H), 3020, 2100 (ν-C≡C-), 1710 (ν-C=O), 1680 (ν-C=O), 1220 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 3.07 (1H, t, *J* = 2.4 Hz, -C≡C-H), 4.38 (2H, dd, *J* = 2.4, 1.7 Hz, -O-CH_2-), 4.46 (1H, d, *J* = 2.2 Hz, H5), 5.01 (1H, d, *J* = 2.2 Hz, H6), 8.04 (1H, s broad, >N1-H), 9.61 (1H, s broad, >N3-H); ^{13}C NMR (50 MHz, acetone-d_6) δ 39.3 (C5), 55.7 (CH_2-O-), 77.6 (-C≡C-H), 77.1 (-C≡C-H), 85.8 (C6), 154.2 (C2), 161.1 (C4). Anal. Calcd for $C_7H_7BrN_2O_3$: C, 34.03; H, 2.86; N, 11.34. Found: C, 34.33; H, 2.53; N, 11.46.

***Trans*-5-bromo-1,3-dimethyl-6-(prop-2-ynyloxy)-dihydropyrimidine-2,4-dione (7b).** Heavy colorless oil, R_f = 0.50 ($CHCl_3$/MeOH: 9/1); IR (neat) 3290 (ν-C≡C-H), 2120 (ν-C≡C-), 1720 (ν-C=O), 1680 (ν-C=O), 1140 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) δ 2.58 (1H, t, J = 2.4 Hz, -C≡C-H), 3.19 (3H, s, CH_3 at N1), 3.22 (3H, s, CH_3 at N3), 4.25 (2H, d, J = 2.4 Hz, -O-CH_2-), 4.41 (1H, d, J = 2.27 Hz, H5), 4.91 (1H, d, J = 2.3 Hz, H6); ^{13}C NMR (50 MHz) δ 24.7 (CH_3 at N1), 28.0 (CH_3 at N3), 36.5 (C5), 56.0 (CH_2-O-), 76.9 (-C≡C-H), 77.3 (-C≡C-H), 86.7 (C6), 151.6 (C2), 165.1 (C4). Anal. Calcd for $C_9H_{11}BrN_2O_3$: C, 39.29; H, 4.03; N, 10.18. Found: C, 39.32; H, 4.11; N, 10.23.

***Trans*-5-bromo-5-methyl-6-(prop-2-ynyloxy)-dihydropyrimidine-2,4-dione (7c).** White crystals mp 207-209 °C, R_f = 0.46 ($CHCl_3$/MeOH: 9/1); IR (neat) 3300 (ν-C≡C-H), 3020, 2120 (ν-C≡C-), 1720 (ν-C=O), 1220 (ν-C-O-) cm^{-1}; ^1H NMR (400 MHz, acetone- d_6) δ 1.92 (3H, s, CH_3 at C5), 3.08 (1H, t, J = 2.4 Hz, -C≡C-H), 4.35 (1H, dd, J = 16.0, 2.4 Hz, -O-CH_A-), 4.41 (1H, dd, J = 16.0, 2.4 Hz, -O-CH_B-), 5.03 (1H, s braod, H6), 8.15 (1H, s broad, >N1-H), 9.60 (1H, s broad, >N3-H); ^{13}C NMR (50 MHz, acetone- d_6) δ 22.8 (CH_3 at C5), 52.2 (C5), 55.4 (CH_2-O-), 72.9 (-C≡C-H), 79.3 (-C≡C-H), 83.6 (C6), 152.0 (C2), 177.3 (C4); ^{15}N NMR (100 MHz, $CH_3{}^{15}NO_2$) for the three tautomers δ -237.4, -237.8, -282, -290. Anal. Calcd for $C_8H_9BrN_2O_3$: C, 36.80; H, 3.47; N, 10.73. Found: C, 36.78; H, 3.45; N, 10.74.

***Trans*-5-bromo-1,3,5-trimethyl-6-(prop-2-ynyloxy)-dihydropyrimidine-2,4-dione (7d).** Heavy colorless oil, R_f = 0.80 ($CHCl_3$/MeOH: 9/1); IR (neat) 3270 (ν-C≡C-H), 2120 (ν-C≡C-), 1720 (ν-C=O), 1680 (ν-C=O), 1166 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) δ 1.91 (3H, s, CH_3 at C5), 2.56 (1H, t, J = 2.4 Hz, -C≡C-H), 3.16 (3H, s, CH_3 at N1), 3.24 (3H, s, CH_3 at N3), 4.18 (1H, dd, J =16.4, 2.4 Hz, -O-CH_A-), 4.31 (1H, dd, J = 16.4, 2.4 Hz, -O-CH_B-), 4.85 (1H, s, H6); ^{13}C NMR (50 MHz) δ 23.4 (CH_3 at N1), 28.1 (CH_3 at N3), 37.0 (CH_3 at C5), 53.4 (C5), 56.0 (CH_2-O-), 76.8 (-C≡C-H), 77.5 (-C≡C-H), 89.1 (C6), 151.6 (C2), 166.9 (C4). Anal. Calcd for $C_{10}H_{13}BrN_2O_3$: C, 41.54; H, 4.53; N, 9.69. Found: C, 41.51; H, 4.54; N, 9.65.

***Trans*-5-bromo-6-(but-2-ynyloxy)-1,3,5-trimethyl-dihydropyrimidine-2,4-dione (7e).** Heavy colorless oil, R_f = 0.71 ($CHCl_3$/MeOH: 9/1); IR (neat) 2250 (ν-C≡C-), 1720 (ν-C=O), 1680 (ν-C=O), 1166 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) δ 1.80 (3H, t, J = 2.4 Hz, -C≡C-CH_3), 1.84 (3H, s, CH_3 at C5), 3.09 (3H, s, CH_3 at N1), 3.16 (3H, s, CH_3 at N3), 4.08 (1H, dq, J = 15.0, 2.4 Hz, O-CH_A-), 4.18 (1H, dq, J = 15.0, 2.4 Hz, O-CH_B-), 4.78 (1H, s, H6); ^{13}C NMR (50 MHz) δ 13.5 (-C≡C-CH_3), 23.6 (CH_3 at N1), 28.2 (CH_3 at N3), 37.0 (CH_3 at C5), 53.8 (C5), 56.8 (-O-CH_2-), 73.1 (-C≡C-CH_3), 84.9 (-C≡C-CH_3), 89.0 (C6), 151.9 (C2), 167.3 (C4). Anal. Calcd for $C_{11}H_{15}BrN_2O_3$: C, 43.58; H, 4.99; N, 9.24. Found: C, 43.64; H, 5.11; N, 9.19.

***Trans*-5-bromo-1,3,5-trimethyl-6-(1-methyl-prop-2-ynyloxy)-dihydropyrimidine-2,4-dione (7f).** Mixture of two diastereomers (1:1), heavy colorless oil, R_f = 0.63 ($CHCl_3$/MeOH: 9/1); IR (neat) 3290 (ν-C≡C-H), 2110 (ν-C≡C-), 1715 (ν-C=O), 1675 (ν-C=O), 1167 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) δ 1.39 (3H, d, J = 6.7 Hz, -O-CH-CH_3), 1.92 (3H, s, CH_3 at C5), 2.57 (1H, d, J = 1.9 Hz, -C≡C-H), 3.18 (3H, s, CH_3 at N1), 3.23 (3H, s, CH_3 at N3), 4.40 (1H, dq, J = 6.7, 1.9 Hz, -O-CH-), 4.79 (1H, s broad, H6); ^{13}C NMR (50 MHz) δ 21.8 and 22.2 (CH_3 at N1), 23.4 and 23.6 (-O-CH-CH_3), 28.3 (Two signals for CH_3 at N3), 36.1 and 37.4 (CH_3 at C5), 53.7 and 57.7 (C5), 63.3 and 66.0 (-O-CH-CH_3), 74.6 and 77.1 (-C≡C-H), 76.0 and 81.2 (-C≡C-H), 88.5 and 91.0 (C6), 152.0 (Two signals for C2), 167.4 (Tow signals for C4). Anal. Calcd for $C_{11}H_{15}BrN_2O_3$: C, 43.58; H, 4.99; N, 9.24. Found: C, 43.52; H, 4.87; N, 9.32.

***Trans*-5-bromo-6-(1,1-dimethyl-prop-2-ynyloxy)-1,3,5-trimethyl-dihydropyrimidine-2,4-dione (7g).** Heavy colorless oil, R_f = 0.54 ($CHCl_3$/MeOH: 9/1); IR (neat) 3260 (ν-C≡C-H), 2110 (ν-C≡C-), 1720 (ν-C=O), 1680 (ν-C=O), 1164 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) δ 1.44 (3H, s, -O-C-CH_3), 1.45 (3H, s, -O-C-CH_3), 1.91 (3H, s, -CH_3 at C5), 2.69 (1H, s, -C≡C-H), 3.18 (6H, s, broad, CH_3 at N1 and N3), 5.02 (1H, s, H6); ^{13}C NMR (50 MHz) δ 23.9 (CH_3 at N1), 28.1 (CH_3 at N3), 30.0 [Two signals for -O-C-(CH_3)$_2$], 36.9 (CH_3 at C5), 54.8 (C5), 71.7 [-O-C-(CH_3)$_2$], 76.1 (-C≡C-H), 84.1 (-C≡C-H), 87.9 (C6), 152.2 (C2), 167.6 (C4); Anal. Calcd for $C_{12}H_{17}BrN_2O_3$: C, 45.44; H, 5.40; N, 8.83. Found: C, 45.40; H, 5.42; N, 8.85.

***Trans*-5-bromo-6-(but-3-ynyloxy)-1,3,5-trimethyl-dihydropyrimidine-2,4-dione (7h).** Heavy colorless oil, R_f = 0.65 ($CHCl_3$/MeOH: 9/1); IR (neat) 3290 (ν-C≡C-H), 1720 (ν-C=O), 1675 (ν-C=O), 1164 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) δ 1.96 (3H, s, -CH_3 at C5), 2.41 (2H, m, -CH_2-C≡C-), 2.51 (1H, m, -C≡C-H), 3.19 (3H, s, CH_3 at N1), 3.23 (3H, s, CH_3 at N3), 3.57-3.80 (2H, m, -O-CH_2-), 4.62 (1H, s, H6); ^{13}C NMR (50 MHz) δ 19.7 (-CH_2-C≡C-), 23.4 (CH_3 at N1), 28.2 (CH_3 at N3), 37.1 (CH_3 at C5), 53.4 (C5), 67.9 (-O-CH_2-), 70.0 (C≡C-H), 80.1 (-C≡C-H), 91.9 (C6), 151.6 (C2), 167.2 (C4). Anal. Calcd for $C_{11}H_{15}BrN_2O_3$: C, 43.58; H, 4.99; N, 9.24. Found: C, 43.61; H, 5.03; N, 9.29.

***Trans*-5-bromo-3-methyl-6-(prop-2-ynyloxy)-1-(1'-β-ribofuranose-2',3',5'-trimethoxy)-dihydropyrimidine-2,4-dione (7i).** Mixture of two diastereomers (6:1), heavy colorless oil, R_f = 0.69 ($CHCl_3$/MeOH: 9/1); IR (neat) 3265 (ν-C≡C-H), 2115 (ν-C≡C-), 1720 (ν-C=O), 1680 (ν-C=O), 1082 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) major isomer δ 2.47 (1H, m, -C≡C-H), 3.18 (3H, s, CH_3 at N3), 3.41 (6H, s, -O-CH_3 at C3' and C5'), 3.45 (2H, m, H5'), 3.61 (3H, s, -O-CH_3 at C2'), 3.87 (1H, m, H4'), 3.98 (1H, m, H2'), 4.15 (1H, m, H3'), 4.19 (1H, dd, J = 16.0, 2.2 Hz, -O-CH_A), 4.33 (1H, dd, J = 16.0, 2.2 Hz, -O-CH_B), 4.56 (1H, d, J = 2.5 Hz, H5), 5.58 (1H, d, J = 2.5 Hz, H6), 5.73 (1H, s, H1'); ^{13}C NMR (50 MHz) δ 27.8 (CH_3 at N3), 39.5 (C5), 56.4 (-O-CH_2), 58.2 (2-OCH_3), 59.1 (-O-CH_3), 70.1 (C5'), 75.0 (-C≡C-H), 76.8 (C2'), 80.2 (-C≡C-H), 80.9 (C3'), 82.1 (C4'), 87.8 (C6), 88.5 (C1'), 151.0 (C2), 165.2 (C4). Anal. Calcd for $C_{16}H_{23}BrN_2O_7$: C, 44.15; H, 5.33; N, 6.44. Found: C, 44.18; H, 5.31; N, 6.47.

***Trans*-5-bromo-1-(1'-β-2'-deoxyribofuranose-3',5'-dimethoxy)-3,5-dimethyl-6-(prop-2-ynyl-oxy)-dihydropyrimidine-2,4-dione (7j).** Mixture of two diastereomers (6:1), heavy colorless oil, R_f = 0.72 ($CHCl_3$/MeOH: 9/1); IR (neat) 3265 (ν-C≡C-H), 2120 (ν-C≡C-), 1725 (ν-C=O), 1685 (ν-C=O), 1157 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) major isomer δ 1.99 (3H, s, CH_3 at C5), 2.22 (2H, m, H2'), 2.44 (1H, t, J = 2.4 Hz, -C≡C-H), 3.17 (3H, s, >N3-CH_3), 3.32 (3H, s, -O-CH_3), 3.38 (3H, s, -O-CH_3), 3.51 (1H, dd, J = 10.4, 3.5 Hz, H5'), 3.62 (1H, dd, J = 10.4, 3.5 Hz, H5'), 3.94 (1H, m, H4'), 4.08 (1H, m, H3'), 4.23 (1H, dd, J = 16.1, 2.3 Hz, -O-CH_A), 4.50 (1H, dd, J = 16.1, 2.3 Hz, -O-CH_B), 5.18 (1H, s, H6), 6.12 (1H, dd, J = 7.6, 6.1 Hz, H1'); characteristic signals of the minor

isomer δ 3.15 (3H, s, >N3-C<u>H</u>$_3$), 5.01 (1H, s, <u>H6</u>), 5.42 (1H, t, J = 7.1Hz, <u>H1'</u>); ^{13}C NMR (50 MHz) major isomer δ 24.4 (>N3-C<u>H</u>$_3$), 28.3 (<u>C2'</u>), 35.7 (<u>C</u>H$_3$ at C5), 53.7 (<u>C5</u>), 56.5 (2-OCH$_3$), 56.8 (-O-<u>C</u>H$_2$), 72.6 (<u>C5'</u>), 74.9 (-<u>C</u>≡C-H), 79.8 (-C≡<u>C</u>-H), 81.0 (<u>C3'</u>), 82.8 (<u>C6</u>), 82.9 (<u>C4'</u>), 85.0 (<u>C1'</u>), 151.4 (<u>C2</u>), 167.3 (<u>C4</u>); minor isomer (distinguishable signals) δ 34.8, 53.5, 56.2, 57.1, 59.2, 73.4, 79.7, 82.8, 83.1, 88.4, 90.9; Anal. Calcd for $C_{16}H_{23}BrN_2O_6$: C, 45.84; H, 5.53; N, 6.68. Found: C, 45.86; H, 5.50; N, 6.71.

Preparation of bromo unsaturated esters 9a-c and 11: NBS (1.1 equiv., 3.3 mmol) was added in small portions, at room temperature under N_2, to a mixture of **(1d)** (1 equiv., 3 mmol), unsaturated acids **8** or **10** (5 equiv, 15 mmol) dissolved in EtOH free $CHCl_3$ (2 mL) and powdered 3Å-MS (0.5 mg) in the case of tetrolic acid **(10)** . The evolution of the reaction was monitored by TLC and after completion (12-19h) water (15 mL) was added and the mixture was extracted with 3 x 20 mL of $CHCl_3$. The extracts were washed successively with saturated $NaHSO_3$ solution, aqueous K_2CO_3 and water, dried ($MgSO_4$) and concentrated. The crude products were purified by flash chromatography on SiO_2 excepted for **11**, which suffered total hydrolysis to give the corresponding bromohydrine.[10] In this case a simple filtration before washing and drying gave, after evaporation of the solvent under reduced pressure, the desired ester **11** in near quantitative yield and with a >95% chemical purety estimated by NMR.

Acrylic acid *trans*-5-bromo-1,3,5-trimethyl-2,6-dioxo-hexahydropyrimidin-4-yl ester (9a). Colorless oil, R_f = 0.71 ($CHCl_3$/MeOH: 9/1); IR (neat) 2943, 1685 (ν-C=O) cm^{-1}; ^{1}H NMR (200 MHz) δ 1.87 (3H, s, C<u>H</u>$_3$ at C5), 3.16 (3H, s, C<u>H</u>$_3$ at N1),), 3.25 (3H, s, C<u>H</u>$_3$ at N3), 5.95 (1H, dd, J = 10.4, 2.3 Hz, -C=C<u>H</u>, *cis*), 6.04 (1H, m, -C<u>H</u>=CH$_2$, second order); 6.13 (1H, s, <u>H6</u>), 6.45 (1H, dd, J = 16.2, 2.3 Hz, -C=C<u>H</u>, *trans*); ^{13}C NMR (50 MHz) δ 22.9 (<u>C</u>H$_3$ at N1), 28.4 (<u>C</u>H$_3$ at N3), 35.6 (<u>C</u>H$_3$ at C5), 51.3 (<u>C5</u>), 84.2 (<u>C6</u>), 126.3 (-<u>C</u>H=CH$_2$), 133.8 (-CH=<u>C</u>H$_2$), 151.7 (<u>C2</u>), 164.4 (<u>C4</u>), 166.4 (-O-<u>C</u>=O). Anal. Calcd for $C_{10}H_{13}BrN_2O_4$: C, 39.36; H, 4.29; N, 9.18. Found: C, 39.41; H, 4.38; N, 9.25.

***Trans*-but-2-enoic acid *trans*-5-bromo-1,3,5-trimethyl-2,6-dioxohexahydropyrimidin-4-yl ester (9b).** Mixture of *trans* and *cis* double bond isomers (97:3), colorless oil, R_f

= 0.82 ($CHCl_3$/MeOH: 9/1); IR (neat) 2990, 1690 (ν-C=O) cm^{-1}; *trans* isomer: ^1H NMR (200 MHz) δ 1.85 (3H, s, CH_3 at C5), 1.88 (3H, dd, J = 6.9, 1.7 Hz, -CH=CH-CH_3), 3.13 (3H, s, CH_3 at N1), 3.23 (3H, s, , CH_3 at N3), 5.80 (1H, dq, J = 15.0, 1.7 Hz, -CH=CH-CH_3), 6.09 (1H, s, H6), 7.04 (1H, dq, J = 15.0, 6.9 Hz, -C=CH-CH_3); ^{13}C NMR (50 MHz) *trans* isomer: δ 18.1 (-CH=CH-CH_3), 22.8 (CH_3 at N1), 28.3 (CH_3 at N3), 35.4 (CH_3 at C5), 51.5 (C5), 83.7 (C6), 120.5 (O=C-CH=CH-), 148.3 (-C=CH-CH_3), 151.6 (C2), 164.4 (C4), 166.4 (O=C-O) ; *cis* isomer: δ 14.9, 23.4, 27.4, 35.0, 53.7, 91.8, 120.7, 148.0, 151.7, 164.5, 166.8. Anal. Calcd for $C_{11}H_{15}BrN_2O_4$: C, 41.40; H, 4.74; N, 8.78. Found: C, 4.51; H, 4.89; N, 8.83.

3-Methylbut-2-enoic acid *trans*-5-bromo-1,3,5-trimethyl-2,6-dioxo-hexahydropyrimidin-4-yl ester (9c). Colorless oil, R_f = 0.80 (diethyl ether); IR (neat) 2940, 1685 (ν-C=O), 1129 (ν-C-O-) cm^{-1}; ^1H NMR (200 MHz) δ 1.86 (3H, s, CH_3 at C5), 1.91 (3H, d, J = 1.2 Hz, -CH=C-CH_3), 2.16 (3H, d, J = 1.1 Hz, -CH=C-CH_3), 3.15 (3H, s, CH_3 at N1), 3.23 (3H, s, CH_3 at N3), 5.59 [1H, m, -CH=$C(CH_3)_2$], 6.06 (1H, s, H6); ^{13}C NMR (50 MHz) δ 22.9 (-CH=C-CH_3), 23.5 (-CH=C-CH_3), 27.6 (CH_3 at N1), 28.3 (CH_3 at N3), 35.5 (CH_3 at C5), 51.7 (C5), 83.1 (C6), 113.7 (-CH=C<), 151.8 (C2), 161.8 [-CH=C-$(CH_3)_2$], 164.3 (C4), 166.6 (O=C-O). Anal. Calcd for $C_{12}H_{17}BrN_2O_4$: C, 43.26; H, 5.14; N, 8.41. Found: C, 43.32; H, 5.23; N, 8.57.

But-2-ynoic acid *trans*-5-bromo-1,3,5-trimethyl-2,6-dioxo-hexahydropyrimidin-4-yl ester (11). White needles, mp 150-152 °C, R_f = 0.71 (diethyl ether); ^1H NMR (200 MHz) δ 1.88 (3H, s, -C≡C-CH_3), 2.01 (3H, s, CH_3 at C5), 3.14 (3H, s, CH_3 at N1), 3.23 (3H, s, CH_3 at N3), 6.08 (1H, s, H6); ^{13}C NMR (50 MHz) δ 3.9 (-C≡C-CH_3), 22.9 (CH_3 at N1), 28.5 (CH_3 at N3), 34.7 (CH_3 at C5), 50.9 (C5), 70.7 (-C≡C-CH_3), 85.9 (C6), 89.9 (-C≡C-CH_3), 151.7 (C2), 151.9 (O=C-O), 166.3 (C4). Anal. Calcd for $C_{11}H_{13}BrN_2O_4$: C, 41.66; H, 4.13; N, 8.83. Found: C, 41.69; H, 4.15; N, 8.87.

(E)-But-2-enoic acid *cis*-5-hydroxy-1,3,5-trimethyl-2,6-dioxohexahydropyrimidin-4-yl ester (13). A mixture of bromo ester **9b** (0.49 mmol, 150 mg) and Et_3N (18 equiv., 1.3 mL) is stirred at room temperature under argon for 24h. Filtration through a short pad of

celite and evaporation of the volatiles gave a crude oil which was purified by flash chromatography on silica gel to give pure **13** (mixture of 97:3 *trans:cis* isomers; 75 mg, 62%) as a colorless oil, R_f = 0.70 ($CHCl_3$/MeOH: 9/1); IR (neat) 3390 (ν-OH), 2963, 1721 (ν-C=O), 1676 (ν-C=C-), 1160 (ν-C-O-) cm^{-1}; major isomer:^{1}H NMR (200 MHz) δ 1.40 (3H, s, CH_3 at C5), 1.86 (3H, dd, J = 7.0, 1.0 Hz, -CH=CH-CH_3), 3.09 (3H, s, CH_3 at N1), 3.16 (3H, s, CH_3 at N3), 5.77 (1H, dq, J = 15.6, 1.0 Hz, -CH=CH-CH_3), 5.85 (1H, s, H6), 6.98 (1H, dq, J = 15.6, 7.0 Hz, -CH=CH-CH_3); ^{13}C NMR (50 MHz) δ 18.2 (-CH=CH-CH_3), 19.7 (CH_3 at N1), 28.0 (CH_3 at N3), 35.6 (CH_3 at C5), 69.9 (C5), 83.8 (C6), 121.0 (O=C-CH=CH), 148.0 (CH=CH-CH_3), 152.8 (C2), 165.1 (C4), 169.9 (O-C=O). Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.64; H, 6.35; N, 11.04.

Preparation of dibromo ethers 14a,b. Ethylene oxide (40 mL) was condensed at -40 °C in a three-necked round-bottomed flask. The pyrimidinediones **1** (0.02 mol) were then added, followed by a slow addition of a solution of bromine (1 mL) in CH_2Cl_2 (2 mL). Thirty minutes after addition the mixture was allowed to reach room temperature and hydolyzed with ice-cold water (100 mL) and extracted with $CHCl_3$ (3 x 30 mL). The combined organic fractions were washed with aq $Na_2S_2O_3$, water and brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude bromo ethers **14**, which were purified by flash chromatography on SiO_2.

***Trans*-5-bromo-6-(2-bromo ethoxy)-5,6-dihydropyrimidine-2,4-dione 14a.** White crystals, mp 235-237 °C; ^{1}H NMR (200 MHz, acetone-d_6) δ 3.55-3.69 (2H, m, -CH_2-Br), 3.77-4.12 (1H, m, H5), 4.46 (2H, m, O-CH_2), 5.03 (1H, m, H6), 8.04 (1H, s broad, >N1-H), 9.61 (1H, s broad, >N3-H); ^{13}C NMR (50 MHz, acetone-d_6) δ 31.5 (-CH_2-Br), 39.4 (C5), 68.4 (O-CH_2), 82.8 (C6), 152.1 (C2), 167.0 (C4). Anal. Calcd for $C_6H_8Br_2N_2O_3$: C, 22.81; H, 2.55; N, 8.87. Found: C, 22.86; H, 2.59; N, 8.88.

***Trans*-5-bromo-6-(2-bromo ethoxy)-5, methyl-5,6-dihydropyrimidine-2,4-dione 14b.** White crystals, mp 253-255 °C; IR ($CHCl_3$) 3683 (ν-NH), 3619 (ν-NH), 3020, 1720 (ν-C=O), 1102 (ν-C-O-) cm^{-1}; ^{1}H NMR (200 MHz, acetone-d_6) δ 1.96 (3H, s, CH_3 at C5),

3.58-3.73 (2H, m, -C<u>H</u>$_2$-Br), 3.76-4.11 (2H, m, O-C<u>H</u>$_2$), 4.99 (1H, m, <u>H6</u>), 8.13 (1H, s, braod, >N1-<u>H</u>), 9.57 (1H, s, braod, >N3-<u>H</u>); ^{13}C NMR (50 MHz, acetone-d_6) δ 23.3 (<u>C</u>H$_3$ at C5), 30.6 (-CH$_2$-Br), 53.6 (<u>C5</u>), 68.9 (O-<u>C</u>H$_2$), 86.1 (<u>C6</u>), 152.3 (<u>C2</u>), 168.5 (<u>C4</u>). Anal. Calcd for $C_7H_{10}Br_2N_2O_3$: C, 25.48; H, 3.05; N, 8.49. Found: C, 25.56; H, 3.15; N, 8.45.

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