A mild and efficient methodology for the synthesis of 5-halogeno uracil nucleosides that occurs via a 5-halogeno-6-azido-5,6-dihydro intermediate

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A mild and efficient methodology for the synthesis of 5-halogeno (iodo, bromo, or chloro) uracil nucleosides has been developed. 5-Halo-2′-deoxyuridines **4***a–c* (84–95%), 5-halouridines **7***a–c* (45–95%), and 5-haloarabinouridines **8***a–c* (65–95%) were synthesized in good to excellent yields by the reaction of 2′-deoxyuridine (**2**), uridine (**5**), and arabinouridine (**6**), respectively, with iodine monochloride, or *N*-bromo (or chloro)succinimide, and sodium azide at 25–45°C. These C-5 halogenation reactions proceed via a 5-halo-6-azido-5,6-dihydro intermediate (**3**), from which HN_3 is eliminated, to yield the 5-halogeno uracil nucleoside. The 5-halo-6-azido-5,6-dihydro intermediate products (**10***a*, **10***b*) could be isolated from the reaction of 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**9**) with iodine monochloride or *N*-bromosuccinimide and sodium azide at 0°C. The isolation of **10***a*, **10***b* indicates that the C-5 halogenation reaction proceeds via a 5-halo-6-azido-5,6-dihydro intermediate.

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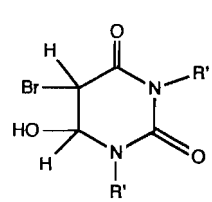
On a mis au point une méthodologie douce et efficace de synthèse des nucléosides des 5-halogéno (iodo, bromo ou chloro) uraciles. On a synthétisé les 5-halo-2′-désoxyuridines (**4***a–c*, 84–95%), 5-halouridines (**7***a–c*, 45–95%) et 5-halorarabinouridines (**8***a–c*, 65–95%) par réactions respectivement de la 2′-désoxyuridine (**2**), de l'uridine (**5**) et de l'arabinouridine (**6**) avec du monochlorure d'iode ou de *N*-bromo(ou chloro)succinimide et de l'azoture de sodium à des températures allant de 25 à 45°C. Ces réactions d'halogénation en C-5 se produisent par le biais d'un intermédiaire 5-halo-6-azido-5,6-dihydro (**3**) à partir duquel il y a élimination de HN_3 et formation du nucléoside du 5-halogénouracile. On a pu isoler les intermédiaires 5-halo-6-azido-5,6-dihydro (**10***a*, **10***b*) lors de la réaction du 3′,5′-di-*O*-acétyl-2′-désoxyuridine (**9**) avec le monochlorure d'iode ou le *N*-bromosuccinimide et l'azoture de sodium à 0°C. En isolant les intermédiaires **10***a*, **10***b*, on confirme que la réaction d'halogénation en C-5 se produit par le biais d'un intermédiaire 5-halo-6-azido-5,6-dihydro.

[Traduit par la rédaction]

Analogs of 5-halouracils constitute a biologically important class of compounds, which possess interesting biochemical and biophysical properties (1), and which have been investigated extensively as antineoplastic and antiviral agents (2). In addition, some 5-chlorouracil nucleoside analogs, which are less cytotoxic, exhibit selective anti-HIV activity (3). Studies utilizing 5-halouracil derivatives have also provided important biochemical information pertaining to their cellular biochemistry, affinity for a nucleoside transporter, enzyme–substrate specificity, and the nature of enzyme–substrate interaction(s). Radiohalogenated uracil nucleosides are useful mechanistic probes to study DNA metabolism (4). Halogenated nucleosides have also been used as synthons for the synthesis of biologically active nucleoside analogs (5–10). Therefore, new methods for the efficient synthesis of 5-halouracil nucleoside derivatives, using mild reaction conditions, are of great interest in medicinal chemistry.

A variety of methods have been developed for electrophilic halogenation at the electron-rich C-5 position of uracil nucleosides (for an excellent review, see ref. 11). Prusoff et al. reported the first 5-iodination of uracil using molecular iodine, generated in situ by oxidation of KI with H_2SO_4 and KIO_3 (12). Prusoff also developed methods involving the reaction of I_2, prepared by oxidation of iodide using HNO_3, or molecular iodine in an organic solvent and water to prepare 5-iodo-2′-deoxyuridine (13). However, these harsh reaction conditions and (or) methodologies often afford a moderate yield of the target 5-iodo product due to decomposition and (or) formation of undesirable side product(s). Iodination of 5-mercurouridine derivatives in aqueous alcohol has been described by Dale et al. (14). *N*-Iodosuccinimide and iodine monochloride (ICl) have also been used for the efficient iodination of some uracil nucleosides (15, 16). An effective conversion of protected or unprotected uracil nucleosides to their 5-halo derivatives has been reported using elemental iodine, or a lithium halide, in the presence of ceric ammonium nitrate (CAN) (17). A number of methods have been reported for the synthesis of 5-bromouracil analogs using bromine–water (18, 19), or bromine in either acetic anhydride (20), dimethyl formamide (21), or pyridine (22). The C-5 chlorination of uracil nucleosides has been reported using Cl_2–H_2O under UV irradiation (23) or Cl_2–HOAc (24). Chlorination of uracil analogs has also been effected using elemental chlorine or *N*-chlorosuccinimide in acetic acid at reflux temperatures (25–27), iodobenzene dichloride in warm acetic acid (16), or 3-chloroperoxybenzoic acid in aprotic solvents containing hydrogen chloride (28).

It has been proposed by Wang (29) that the formation of 5-bromouracil analogs upon reaction of uracils with aqueous bromine proceeds via a 5-bromo-6-hydroxy-5,6-dihydro intermediate (**1**) that dehydrates to afford the 5-bromouracil. It was found that 5-bromo-6-hydroxy-5,6-dihydrouracil (**1***a*) dehydrated to 5-bromouracil in less than 10 min at room temperature. In contrast, only 10% dehydration of the 5-bromo-6-



1*a*, R′ = H; **1***b*, R′ = CH_3

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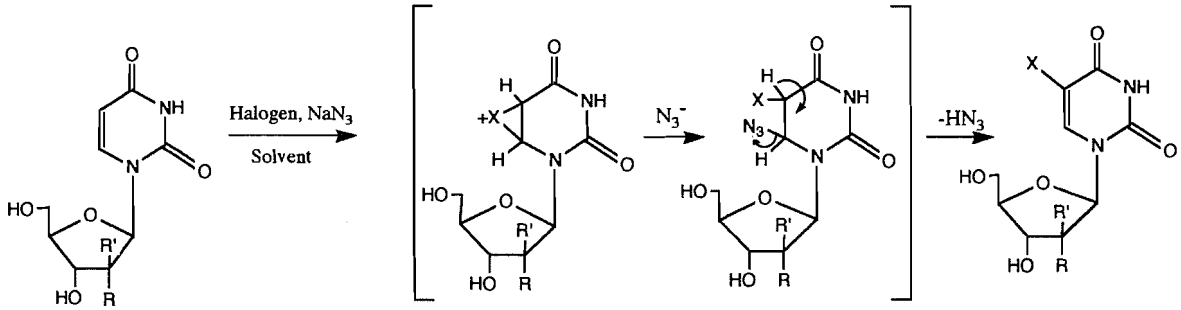


2, R = R' = H
5, R = OH, R' = H
6, R = H, R' = OH

3

4*a*, R = R' = H, X = I
4*b*, R = R' = H, X = Br
4*c*, R = R' = H, X = Cl
7*a*, R = OH, R' = H, X = I
7*b*, R = OH, R' = H, X = Br
7*c*, R = OH, R' = H, X = Cl
8*a*, R = H, R' = OH, X = I
8*b*, R = H, R' = OH, X = Br
8*c*, R = H, R' = OH, X = Cl

SCHEME 1

hydroxy-5,6-dihydro derivative of uridine to give 5-bromouridine was observed in 24 h at room temperature. However, when the 5,6-dihydro derivative of uridine was heated on a steam bath, it was quantitatively dehydrated to yield 5-bromouridine. It was observed by Moore and Anderson (30) that the conversion of 5-bromo-6-hydroxy-5,6-dihydrouracil to 5-bromouracil was accelerated by heating or by acid catalysis. The existence of the 5-bromo-6-hydroxy-5,6-dihydrouracil intermediate (**1***b*) was later confirmed by Tee and Banerjee, using ^{1}H NMR spectroscopy (31). 5-Iodo-6-hydroxy-5,6-dihydrouridine was the major product obtained upon reaction of uridine with iodine monochloride in aqueous DMF, along with the minor product 5-iodouridine (32). A 5-iodo-6-methoxy-5,6-dihydro derivative was formed in appreciable yield during the C-5 iodination of 3′,5′-protected-2′-fluoro-2′-deoxyuridine using iodine monochloride in methanol, and on further heating at reflux temperature was converted to the desired 5-iodo-2′-fluoro-2′-deoxyuridine analog (33). A similar reaction of bromine with a 2′,3′-protected uridine in methanol has also been reported to give 5-bromo-6-methoxy-5,6-dihydrouridine (34). During the C-5 chlorination of 2′-fluoro-2′-deoxyuridine with chlorine in acetic acid, 5-chloro-6-acetoxy-5,6-dihydro-1-(2-fluoro-2-deoxy-β-D-ribofuranosyl)uracil was obtained as the major product, which was subsequently converted to 5-chloro-2′-fluoro-2′-deoxyuridine by treatment with aqueous or methanolic ammonia (24). These studies suggest that the electrophilic halogenation of uracil nucleoside derivatives in the presence of water, alcohol, or acetic acid proceeds via a 5-halo-6-hydroxy (alkoxy or acetoxy)-5,6-dihydro intermediate that requires heating or acid–base catalysis for conversion to the 5-halouracil nucleoside. These results indicate that 5-halo-6-hydroxy (alkoxy or acetoxy)-5,6-dihydro derivatives of uracil nucleosides are relatively stable, and that the stability of the 5,6-dihydro intermediate is dependent upon the C-6 substituent.

We now report a mild and efficient procedure for the C-5 halogenation (iodination, bromination, or chlorination) of 2′-deoxyuridine (**2**), uridine (**5**), and arabinouridine (**6**) that proceeds via a 5-halo-6-azido-5,6-dihydro intermediate (**3**) (Scheme 1). The halogenation of **2**, **5**, and **6** was effected using iodine monochloride, or *N*-bromo (or chloro)succinimide, and sodium azide in acetonitrile or 1,2-dimethoxyethane at 0–45°C. The results are summarized in Table 1.

Reaction of 2′-deoxyuridine (**2**), uridine (**5**), or arabinouridine (**6**) with 2.5 mol equiv. of iodine monochloride (ICl) and 4.0 mol equiv. of sodium azide (NaN_3) in acetonitrile at 25°C afforded the corresponding 5-iodo product **4***a*, **7***a*, or **8***a* in 90–96% isolated yields. The corresponding 5-bromo analogs **4***b*, **7***b*, and **8***b* were synthesized in high yield using *N*-bromosuccinimide (NBS) and NaN_3 in 1,2-dimethoxyethane (DME) at 25°C for 24 h. A similar chlorination reaction of **2**, **5**, and **6** using *N*-chlorosuccinimide (NCS) and NaN_3 in DME at 45°C gave the 5-chloro products **4***c*, **7***c*, and **8***c* in 84, 45, and 65% yields, respectively. The chlorination of **2**, **5**, and **6** using NCS and NaN_3 in DME at 25°C proceeded slowly. The 5-chloro-6-azido-5,6-dihydro intermediates are significantly more stable at 25°C than the corresponding 5-iodo (or bromo)-6-azido-5,6-dihydro intermediates. Increasing the reaction temperature from 25°C to 45°C accelerated the rate of the chlorination reaction and the conversion of the 5-chloro-6-azido-5,6-dihydro intermediate to the 5-chloro product. These results suggest the enhanced stability of the 5-chloro-6-azido-5,6-dihydro intermediate, relative to the bromo and iodo analogs, is dependent upon the steric size of the halogen atom at the C-5 position and (or) the relative configurations at the C-5 and C-6 positions. Iodination or bromination of 2′-deoxyuridine (**2**) with ICl or NBS, in the absence of NaN_3, gave a low yield of the respective products. In contrast, chlorination of **2** using NCS, in the absence of NaN_3, did not occur, which indicates that an azido group at the C-6 position plays an important role in these C-5 halogenation reactions. The azido group at the C-6 position of these 5-halo-6-azido-5,6-dihydro intermediates is an excellent leaving group for regeneration of the 5,6-olefinic bond and it provides an attractive alternative to C-6 OH, OMe, or OAc substituents.

The C-5 halogenation of uracil nucleosides using an electrophilic halogen reagent and sodium azide proceeded efficiently under mild reaction conditions. Halogenation of the uracil nucleosides **2**, **5**, and **6** using this methodology in MeCN or DME was assumed to occur via a 5-halo-6-azido-5,6-dihydro intermediate (**3**) as illustrated in Scheme 1. Subsequent elimination of HN_3 would then afford the 5-halogeno products. The 5-

TABLE 1. C-5 halogenation of 2′-deoxyuridine (**2**), uridine (**5**), arabinouridine (**6**), and 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**9**)[a]

Entry	Substrate	Halogenation reagents (mol equiv.)	NaN_3 (mol equiv.)	Solvent	Temp. (°C)	Time (h)	Product (yield, %)[b]
1	**2**	ICl (2.5)	4.0	CH_3CN	25	24.0	**4***a* (96)
2	**2**	ICl (2.0)	0	CH_3CN	25	24.0	**4***a* (20)[c]
3	**5**	ICl (2.5)	4.0	CH_3CN	25	24.0	**7***a* (93)
4	**6**	ICl (2.5)	4.0	CH_3CN	25	36.0	**8***a* (90)
5	**2**	NBS (1.1)	3.0	DME	0	12.0	**4***b* (68)
6	**2**	NBS (1.1)	4.0	DME	25	24.0	**4***b* (90)
7	**2**	NBS (1.1)	0	DME	25	20.0	**4***b* (60)[d]
8	**5**	NBS (1.1)	4.0	DME	25	24.0	**7***b* (95)
9	**6**	NBS (1.3)	4.0	DME	25	24.0	**8***b* (95)
10	**2**	NCS (4.0)	8.0	DME	25	48.0	**4***c* (35)[d]
11	**2**	NCS (4.0)	8.0	DME	45	8.0	**4***c* (84)
12	**5**	NCS (4.0)	8.0	DME	25	48.0	**7***c* (15)[d]
13	**5**	NCS (4.0)	8.0	DME	45	12.0	**7***c* (45)[d]
14	**6**	NCS (4.0)	8.0	DME	25	48.0	**8***c* (25)[d]
15	**6**	NCS (4.0)	8.0	DME	45	12.0	**8***c* (65)
16	**9**	ICl (2.5)	4.0	CH_3CN	25	48.0	**11***a* (94)
17	**9**	ICl (1.5)	3.0	CH_3CN	0	12.0	**11***a* (0)[d]
18	**9**	ICl (2.0)	4.0	CH_3CN	25	24.0	**11***a* (85)
19	**9**	NBS (1.0)	4.0	DME	0	1.0	**11***b* (20)
20	**9**	NBS (1.1)	4.0	DME	25	24.0	**11***b* (95)
21	**9**	NCS (4.0)	8.0	DME	25	48.0	**11***c* (50)[d]
22	**9**	NCS (4.0)	8.0	DME	45	3.0	**11***c* (89)

[a]Halogenation reactions were effected using 0.1 mmol of **2**, **5**, **6**, or **9** at 0–45°C.
[b]Isolated yield of purified product.
[c]Several products were formed (TLC analysis), some starting material and cleavage product (5-iodouracil) were isolated.
[d]Some starting material remained.

bromo (or iodo)-6-azido-5,6-dihydro intermediate product was isolated in 75 and 29% yields, respectively when 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**9**) was allowed to react with ICl, or NBS, and NaN_3 at a reaction temperature of 0 to −5°C (Scheme 2). The addition of halogenoazides to unsymmetrical olefins has been reported to favor an unsymmetrical bridged halonium intermediate (35, 36) of the type illustrated in Scheme 2. The isolation of the 5-halo-6-azido-5,6-dihydro products (**10***a*,*b*), which existed as a mixture of two diastereomers that differ in configuration at the C-5 and (or) C-6 positions, confirmed the reaction mechanism for the formation of the C-5 halogenated pyrimidine nucleosides prepared using the methodology described. The configuration at the C-5 and C-6 positions ($J_{5,6}$ = 3.0 Hz) was not elucidated for **10***a*, **10***b* since these chiral centers are removed upon regeneration of the 5,6-olefinic bond.

Similar halogenations of 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**9**) could also be effected using an electrophilic halogen reagent and sodium azide in MeCN or DME at 25–45°C. Thus, treatment of **9** with 2.5 mol equiv. of ICl and 4.0 mol equiv. of NaN_3 in MeCN at 25°C proceeded well and gave an excellent yield of 3′,5′-di-*O*-acetyl-5-iodo-2′-deoxyuridine (**11***a*, 94% isolated yield). 3′,5′-Di-*O*-acetyl-5-bromo-2′-deoxyuridine (**11***b*) was synthesized in 95% yield using NBS and NaN_3 in DME at 25°C for 24 h. A similar chlorination of **9** using NCS and NaN_3 in DME at 45°C afforded 3′,5′-di-*O*-acetyl-5-chloro-2′-deoxyuridine (**11***c*) in 89% yield.

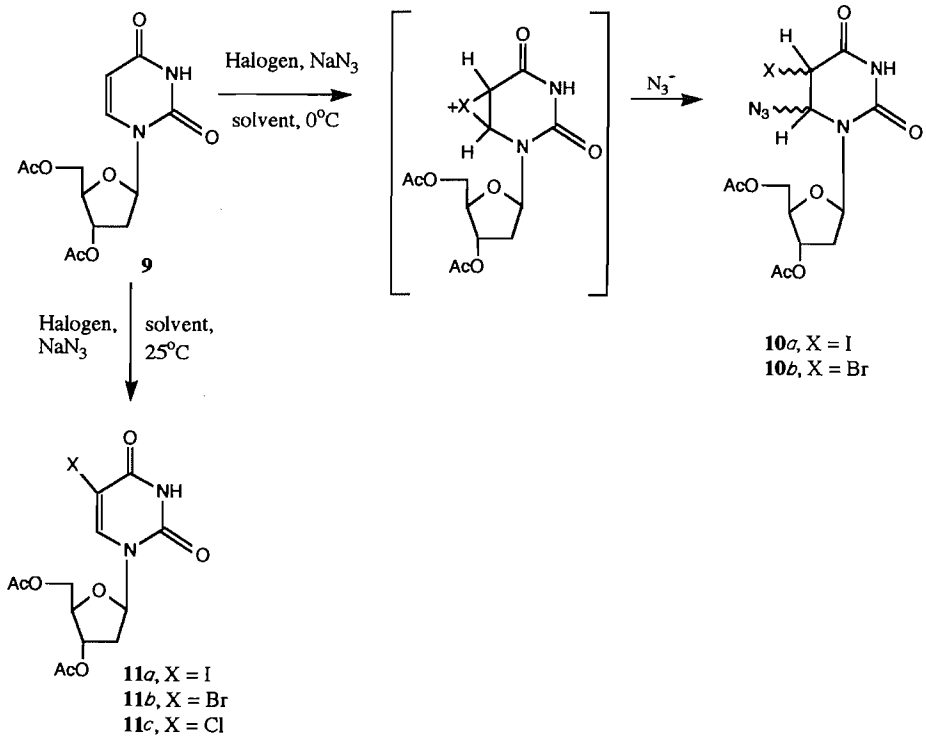
In summary, the new and facile halogenation methods described herein have several advantages over most procedures currently available. These advantages include readily available reagents, mild reaction conditions (25–45°C), facile isolation procedures, and high product yields. This methodology avoids the use of acidic and (or) high reaction temperature conditions, which results in the decomposition of labile substrates. This methodology is applicable to the radioiodination (^{123}I, ^{125}I, ^{131}I) of uracil nucleosides and the potential halogenation of oligonucleosides under mild conditions. Robins et al. (17) developed an efficient method for the synthesis of 3′,5′-di-*O*-acetylated and unprotected 5-halouracil nucleosides using elemental iodine, or a metal halogenide (LiI, LiBr, LiCl) and CAN at 80°C. Our methodology provides marginally higher yields using the unprotected uracil nucleosides, and similar yields using 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**9**). Although the Robins procedure is efficient for the chlorination of **9**, chlorination of 2′-deoxyuridine afforded multiple and (or) decomposition products. Halogenated solvents such as dichloromethane must not be used in this methodology since its reaction with sodium azide may lead to potentially explosive polyazidomethane (37, 38).

Experimental

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR) were determined on a Bruker AM-300 spectrometer using Me_4Si as an internal standard (^1H NMR). The assignment of all exchangeable protons (OH, NH) was confirmed by the addition of D_2O. ^{13}C NMR spectra were acquired using the *J* modulated spin echo technique where methyl and methine carbon resonances appear as positive peaks, and methylene and quaternary carbon resonances appear as negative peaks. Microanalyses were within ±0.4% of theoretical values for all elements listed, unless otherwise indicated. Silica gel column chromatography was carried out using Merck 7734 (60–200 mesh) silica gel. 3′,5′-Di-*O*-acetyl-2′-deoxyuridine (**9**) was prepared according to the reported procedure (39). 2′-Deoxyuridine (**2**), uridine (**5**), and arabinouridine (**6**) were purchased from the Aldrich Chemical Co.

5-Iodo-2′-deoxyuridine (4a)

Iodine monochloride (40 mg, 0.25 mmol) was added slowly during a 5 min period to a suspension of sodium azide (26 mg, 0.4 mmol) in



SCHEME 2

acetonitrile (10 mL) at ice-bath temperature with stirring. This mixture was stirred for a further 5 min, a solution of **2** (22.8 mg, 0.1 mmol) in acetronitrile (10 mL) was added and the reaction was warmed to 25°C and stirred for 24 h. Removal of the solvent in vacuo (bath temperature 50°C) and purification of the residue obtained by elution from a silica gel column using chloroform–methanol (85:15, v/v) as eluent afforded **4***a* (34 mg, 96%) (entry 1, Table 1), mp 170–180°C (dec.) (lit. (13) mp 160–180°C (dec.)). The ^{1}H NMR spectrum for **4***a* was identical to that reported (13).

5-Bromo-2′-deoxyuridine (4b)

N-Bromosuccinimide (NBS, 20 mg, 0.11 mmol) was added at 25°C to a suspension prepared by mixing a solution of **2** (22.8 mg, 0.1 mmol) in 1,2-dimethoxyethane (15 mL) with a solution of sodium azide (26 mg, 0.4 mmol) in water (0.1 mL). After stirring the reaction mixture for 24 h at 25°C, the solvent was removed in vacuo (bath temperature 45°C) and the residue was purified by silica gel column chromatography using chloroform–methanol (90:10, v/v) as eluent to give **4***b* (28 mg, 90%) as a solid (entry 6, Table 1), mp 175–179°C (dec.) (lit. (41) mp 187–189°C (dec.)). The ^{1}H NMR spectrum for **4***b* was identical to that reported (41).

5-Chloro-2′-deoxyuridine (4c)

N-Chlorosuccinimide (NCS, 26.6 mg, 0.2 mmol) was added at 25°C to a suspension prepared by mixing a solution of **2** (22.8 mg, 0.1 mmol) in 1,2-dimethoxyethane (10 mL) with a solution of sodium azide (26 mg, 0.4 mmol) in water (0.1 mL) with a solution of sodium azide (26 mg, 0.4 mmol) in water (0.1 mL). The reaction mixture was stirred for 4 h at 45°C. Additional aliquots of NCS (0.2 mL) and sodium azide (0.4 mmol) were added to the reaction mixture. The reaction was allowed to proceed for 4 h at 45°C with stirring. Removal of the solvent in vacuo (bath temperature 45°C) gave a residue that was purified by silica gel column chromatography using chloroform–methanol (90:10, v/v) as eluent to yield **4***c* (22 mg, 84%) as a solid (entry 11, Table 1), mp 173–176°C (lit. (42) mp 178–179.5°C)). The ^{1}H NMR spectrum for **4***c* was identical to the reported spectral data (42).

Iodination of nucleosides 5 and 6

A mixture of **5** or **6** (0.1 mmol), iodine monochloride (0.25 mmol), sodium azide (0.4 mmol), and acetonitrile (10 mL) was stirred at 25°C. After iodination was complete, the products were isolated by column chromatography as described for **4***a*.

5-Iodouridine (7a)

The white solid product was recrystallized from MeOH to give 35 mg (93%) of **7***a* (entry 3, Table 1), mp 207–209°C (dec.) (lit. (12) mp 205–208°C (dec.)).

5-Iodoarabinouridine (8a)

The white solid was recrystallized from MeOH to give 33 mg (90%) of **8***a* (entry 4, Table 1), mp 190–197°C (dec.) (lit. (43) mp 224–227°C (dec.)); ^{1}H NMR (DMSO-d_6) δ: 3.54–3.68 (m, 2H, H-5′), 3.70–3.78 (m, 1H, H-4′), 3.90–4.06 (m, 2H, H-2′, H-3′), 5.18, (t, $J_{5',OH}$ = 4.0, $J_{5'',OH}$ = 4.0 Hz, 1H, 5′-OH), 5.50 and 5.64 (2 br s, 1H each, 2′-OH, 3′-OH), 5.96 (d, $J_{1',2'}$ = 4.5 Hz, 1H, H-1′), 8.10 (s, 1H, H-6), 11.68 (s, 1H, NH). Anal. calcd. for $C_9H_{11}IN_2O_6$: C 29.20, H 2.99, N 7.57; found: C 29.36, H 2.69, N 7.85.

Bromination of nucleosides 5 and 6

A mixture of **5** or **6** (0.1 mmol), *N*-bromosuccinimide, sodium azide, and 1,2-dimethoxyethane (see Table 1) was stirred at 25°C for 24 h. After the bromination reaction was complete, the products were isolated by column chromatography as described for **4***b*.

5-Bromouridine (7b)

This compound was obtained in 95% yield (entry 8, Table 1), mp 190–198°C (dec. (lit. (18) mp 181–184°C (dec.)).

5-Bromoarabinouridine (8b)

This compound was obtained in 95% yield (entry 9, Table 1), mp 182–187°C (dec.) (lit. (43) mp 195–198°C (dec.)); ^{1}H NMR (DMSO-d_6) δ: 3.56–3.66 (m, 2H, H-5′), 3.70–3.80 (m, 1H, H-4′), 3.90–4.08 (m, 2H, H-2′, H-3′), 5.20, 5.52, 5.68 (3 br s, 1H each, 5′-OH, 3′-OH, 2′-OH), 5.96 (d, $J_{1',2'}$ = 4.5 Hz, 1H, H-1′), 8.06 (s, 1H, H-6). Anal. calcd. for $C_9H_{11}BrN_2O_6$: C 33.45, H 3.42, N 8.67; found: C 33.25, H 3.78, N 9.04.

Chlorination of nucleosides 5 and 6

A mixture of **5** or **6** (0.1 mmol), *N*-chlorosuccimide (NCS,

0.2 mmol), sodium azide (0.4 mmol), and 1,2-dimethoxyethane (10 mL) was stirred at 45°C for 6 h. Additional aliquots of NCS (0.2 mmol) and sodium azide (0.4 mmol) were added to the reaction mixture, which was stirred at 45°C for an additional 6 h. The products were purified by silica gel column chromatography as described for **4***c*.

5-Chlorouridine (7c)

Compound **7***c* was obtained in 45% yield (entry 13, Table 1), mp 215–220°C (dec.) (lit. (27) mp 220–223°C (dec.)).

5-Chloroarabinouridine (8c)

Compound **8***c* was obtained in 65% yield (entry 15, Table 1), mp 224–230°C (dec.) (lit. (43) mp 235–237°C (dec.)); ^{1}H NMR (DMSO-d_6) δ: 3.55–3.67 (m, 2H, H-5′), 3.70–3.80 (m, 1H, H-4′), 3.90–4.07 (m, 2H, H-2′, H-3′), 5.20, 5.60, 5.68 (3 br s, 1H each, 5′-OH, 3′-OH, 2′-OH), 5.97 (d, J = 4.5 Hz, 1H, H-1′), 8.06 (s, 1H, H-6), 11.60 (s, 1H, NH). Anal. calcd. for $C_9H_{11}ClN_2O_6$: C 38.78, H 3.97, N 10.05; found: C 38.76, H 3.98, N 10.22.

5-Iodo-6-azido-5,6-dihydro-3′,5′-di-O-acetyl-2′-deoxyuridine (10a)

A mixture of **9** (31.2 mg, 0.1 mmol), sodium azide (20 mg, 0.3 mmol), iodine monochloride (24 mg, 0.15 mmol), and acetonitrile (10 mL) was stirred at −5°C for 12 h. Evaporation of the solvent, work-up and purification of crude product as described for **11***a* yielded **10***a* (14 mg, 29%) as solid and unreacted starting material (**9**). Compound **10***a* was obtained as a mixture of two diastereomers, which could not be separated by silica gel column chromatography; mp 100–105°C (dec.); ^{1}H NMR ($CDCl_3$) (mixture of two diastereomers in a ratio of 2:1) δ: 2.10 and 2.12 (2 s, 3H each, CH_3CO), 2.22–2.3 and 2.32–2.42 (2 m, 1H each, H-2′), 4.16–4.44 (complex m, 3H, H-4′, H-5′), 4.58 and 4.68 (2 d, $J_{5,6}$ = 3.0 Hz, 1H total, H-5), 5.14–5.20 (m, 1H, H-3′), 5.30 and 5.36 (2 d, $J_{5,6}$ = 3.0 Hz, 1H total, H-6), 6.17 and 6.30 (2 t, $J_{1',2'} = J_{1',2''}$ = 6.0 Hz, 1H, H-1′), 8.20 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 13.15 and 15.37 (C-5), 20.89 (CH_3CO), 35.45 and 36.67 (C-2′), 63.87 and 63.96 (C-5′), 69.93 and 71.07 (C-6), 74.09 (C-3′), 81.61 and 81.88 (C-4′), 83.80 and 84.72 (C-1′), 149.45 and 149.63 (C-2), 165.45 and 165.70 (C-4), 170.41 and 170.15 (CH_3CO). Anal. calcd. for $C_{13}H_{16}IN_5O_7$: C 32.44, H 3.35, N 14.55; found: C 32.47, H 3.63, N 14.92.

5-Bromo-6-azido-5,6-dihydro-3′,5′-di-O-acetyl-2′-deoxyuridine (10b)

A mixture of **9** (31.2 mg, 0.1 mmol), *N*-bromosuccinimide (18 mg, 0.1 mmol), sodium azide (26 mg, 0.4 mmol) in water (0.1 mL), and 1,2-dimethoxyethane (10 mL) was stirred at 0°C for 1 h. Removal of the solvent in vacuo and purification of crude product by silica gel column chromatography with chloroform–methanol (98:2, v/v) as eluent afforded **10***b* (32 mg, 75%) as a solid. The compound **10***b* was obtained as a mixture of two diastereomers, which could not be separated by silica gel column chromatography; mp 140–142°C (dec.); ^{1}H NMR ($CDCl_3$) (mixture of two diastereomers in a ratio of 3:1) δ: 2.13 and 2.15 (2 s, 3H, each, CH_3CO), 2.16–2.26 and 2.32–2.46 (2 m, 1H each, H-2′), 4.20–4.48 (complex m, 4H, H-5, H-4′, H-5′), 5.17–5.22 (m, 1H, H-3′), 5.37 and 5.42 (2 d, $J_{5,6}$ = 3.0 Hz, 1H total, H-6), 6.18 and 5.34 (2 t, $J_{1',2'} = J_{1',2''}$ = 6.0 Hz, 1H total, H-1′), 7.54 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.80 (CH_3CO), 35.64 and 36.47 (C-2′), 37.61 and 38.91 (C-5), 63.82 and 63.91 (C-5′), 68.76 and 69.51 (C-6), 74.06 (C-3′), 81.52 and 81.91 (C-4′), 83.86 and 84.70 (C-1′), 149.52 (C-2), 163.71 (C-4), 170.14 and 170.36 (CH_3CO). Anal. calcd. for $C_{13}H_{16}BrN_5O_7$: C 36.21, H 3.03, N 16.24; found: C 36.51, H 3.24, N 15.98.

5-Iodo-3′,5′-di-O-acetyl-2′-deoxyuridine (11a)

This compound was synthesized by the reaction of **9**, according to the iodination procedure reported for **4***a*. Purification of the residue obtained by elution from a silica gel column using chloroform–methanol (95:5, v/v) as eluent afforded **11***a* (41 mg, 94%) (entry 16, Table 1), mp 157–158°C (lit. (40) mp 158–160°C).

5-Bromo-3′,5′-di-O-acetyl-2′-deoxyuridine (11b)

Compound **11***b* was synthesized by the reaction of **9**, according to the bromination procedure reported for **4***b*. Purification of the residue obtained by silica gel column chromatography using chloroform–methanol (95:5, v/v) as eluent afforded **11***b* (37 mg, 95%) as a viscous oil that did not crystallize (entry 20, Table 1) (lit. (17) mp 152.5–153°C); ^{1}H NMR ($CDCl_3$) δ: 2.10–2.24 (m, 7H, H-2′, CH_3CO), 2.50–2.60 (m, 1H, H-2″), 4.26–4.44 (complex m, 3H, H-4′, H-5′), 5.20–5.26 (m, 1H, H-3′), 6.28 (t, $J_{1',2'} = J_{1',2''}$ = 6.0 Hz, 1H total, 1H, H-1′), 7.90 (s, 1H, H-6), 8.78 (s, 1H, NH). ^{13}C NMR δ: 20.73 (CH_3CO), 38.05 (C-2′), 63.66 (C-5′), 73.88 (C-3′), 82.55 (C-4′), 85.53 (C-1′), 97.29 (C-5), 138.59 (C-6), 149.66 (C-2), 158.89 (C-4), 170.09 (CH_3CO) and 170.30 (CH_3CO). Anal. calcd. for $C_{13}H_{15}BrN_2O_7$: C 39.91, H 3.86, N 7.16; found: C 39.84, H 3.83, N 7.08.

5-Chloro-3′,5′-di-O-acetyl-2′-deoxyuridine (11c)

Compound **11***c* was synthesized by the reaction of **9**, according to the chlorination procedure reported for **4***c*. Purification of the product as described for **11***b* yielded **11***c* (31 mg, 89%) as a viscous oil that did not crystallize (entry 22, Table 1) (lit. (17) mp 174.5–175°C); ^{1}H NMR ($CDCl_3$) δ: 2.10–2.26 (m, 7H, H-2′, CH_3CO), 2.50–2.62 (m, 1H, H-2″), 4.28–4.40 (complex m, 3H, H-4′, H-5′), 5.20–5.25 (m, 1H, H-3′), 6.30 (t, $J_{1',2'} = J_{1',2''}$ = 6.0 Hz, 1H total, H-1′), 7.88 (s, 1H, H-6), 8.80 (s, 1H, NH). Anal. calcd. for $C_{13}H_{15}ClN_2O_7$: C 45.03, H 4.36, N 8.08; found: C 45.08, H 4.70, N 8.08.

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