Development of Diversified Methods for Chemical Modification of the 5,6-Double Bond of Uracil Derivatives Depending on Active Methylene Compounds

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Abstract: The reaction of 5-halogenouracil and uridine derivatives 1 and 7 with active methylene compounds under basic conditions produced diverse and selective C-C bond formation products by virtue of the nature of the carbanions. Three different types of reactions such as the regioselective C-C bond formation at the 5- and 6-positions of uracil and uridine derivatives (products 2, 5, 8, 17, 20 and 21), and the formation of fused heterocycle derivatives 2,4-diazabicyclo[4.1.0]heptane (15) and 2,4-diazabicyclo-[4.1.0]nonane (16) via dual C-C bond formations at both the 5- and 6-positions were due to the different active methylene compounds used as reagents.
1. Introduction

Many 5-substituted pyrimidine nucleoside derivatives and their base moieties possess antimicrobial, antifungus, antiviral, and anticancer activities due mainly to antimetabolic effects (Table 1) [1–6]. Specifically, 5-fluorouracil (5-Fu) is a widely-used anticancer drug [1–5] and 5-fluoro-2’-deoxyuridine (floxuridine) and 5’-deoxy-5-fluorouridine (doxifluidine) are also well known as cancer drugs especially effective in the treatment of kidney carcinoma [1–6] and digestive system cancer, respectively. 5-Iodo-2’-deoxyuridine (idoxuridine) is an effective drug for herpes simplex virus mainly used as eye-drops [7], and 5-bromo-2’-deoxyuridine (bioxuridine) is used as a radiation enhancer. Furthermore, zidovudine and sanilvudine exhibit reverse transcriptase inhibitory activity and are in widespread clinical use as anti-HIV drugs. Since most of the biologically-active chemically modified pyrimidine derivatives are functionalized on the 5,6-double bond (especially the 5-position), the development of easy-to-use and specific chemical modification methods at the 5 and 6-positions of the pyrimidine nuclei is still quite important as related to the creation of novel antimetabolites.

Table 1. Selected biologically active 5-substituted pyrimidine nucleoside derivatives.

| R | X | Generic name          |
|---|---|-----------------------|
| H | F  | Fluorouracil (5-Fu)   |
| F  |    | Floxuridine           |
| I  |    | Idoxuridine           |
| Br |    | Broxuridine           |
|    | F  | Doxifluridine         |
|    | Me | Zidovuridine          |
|    | Me | Sanilvudine           |

A number of chemical modification methods at the 5-position of the uracil derivatives have been reported in the literature [8], although the functionalization methods for the 6-position have rarely been reported. Pd-catalyzed C–C bond formation reactions at the 5-position of the uracil ring, such as the Heck [9], Stille [10], and Sonogashira reactions [11,12], etc. [13,14] have been investigated in detail as widely applicable methods. The Mannich reaction [15–18], hydroxymethylation [19,20], the Morita-Baylis-Hillman reaction [21,22] and Wittig reaction using 5-hydroxyuridine [23] are also useful methods to synthesize chemically-modified uracil derivatives possessing a carbon functional group at the 5-position. Furthermore, it is well known that 5-bromouracils react easily with several nucleophiles [24] (Scheme 1).
Simple debromination smoothly occurred by the use of sulfite or thiolate anion (\(-\text{SO}_3\text{H}\) or \(-\text{SR}\)) \([24–29]\), and the cyanide anion (\(-\text{CN}\)) induced the cine-substitution reaction to produce 6-cyanouracil derivatives \([28,30–32]\). The reaction with amines produced 5-substituted uracil derivatives \([28]\). It is well known that all these reactions occurred via the 5,6-dihydro adducts as intermediates. On the other hand, only few carbanion-mediated nucleophilic reactions of the 5-bromo-uracil derivatives have been reported. Among them, Inoue et al. pioneeringly reported the formation of the 5-bis(ethoxycarbonyl)methyl-substituted uridine derivative by the reaction of 5-bromo-5',N3-dibenzoyl-2',3'-O-isopropylideneuridine and the carbanion generated from dimethylmalonate and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) \([33]\). It has been proven that the 5-bis(ethoxycarbonyl)methyl-substituted uridine derivative was generated via the 5,6-di-bis(ethoxycarbonyl)methyl-substituted 5,6-dihydrouridine intermediate in our preliminary research as a collaboration project with Inoue et al. \([34]\). We now provide detailed results for the formation of the 5-substituted-uracil derivatives starting from the 5-halogenouracil derivatives using the carbanion generated from active methylene compounds and bases. The diversity of the reaction of the 5-bromouracil derivatives with carbanions exclusively based on the kind of active methylene compounds as carbanion sources.

2. Results and Discussion

Our initial studies focused on the formation of the 5-substituted uracils. 5-Bis(ethoxycarbonyl)methyl-1,3-dimethyluracil (2) was obtained by the reaction of 1,3-dimethyl-5-halogenouracils (1) and diethyl malonate (3.3 equiv.) together with sodium ethoxide (3.0 equiv., generated \textit{in situ} from sodium metal and anhydrous EtOH) in anhydrous EtOH at rt in 60–67% isolated yields (Table 2).

While 2 gave satisfactory spectral and microanalytical results consistent with the chemical structure, it was transformed into the known compound 1,3-dimethyluracil-5-acetic acid (3) \([23]\), in a refluxing
47% HBr aqueous solution for 1 h in 95% yield to further confirm the structure. The results in Table 2 show that the rate of the reaction can be significantly affected by the type of halogens (Br, Cl and F). It is noteworthy that the reaction smoothly proceeded by the use of even 5-fluoro-1,3-dimethyluracil (1c) as the substrate although a prolonged reaction time was necessary (Entry 3).

**Table 2.** Formation of 5-bis(ethoxycarbonyl)methyl-1,3-dimethyluracil (2).

| Entry | Starting Compd. | X   | Reaction time (h) | Yield (%) |
|-------|-----------------|-----|-------------------|-----------|
| 1     | 1a              | Br  | 8                 | 60        |
| 2     | 1b              | Cl  | 16                | 67        |
| 3     | 1c              | F   | 24                | 65        |

Although the highly stable C-F bond at the 5-position of the uracil ring severely retards the substitution between the F atom and malonate carbanion, there is a significant acceleration effect by the strongly electron-withdrawing nature of the F atom to reduce the electron density at the conjugated 6-position of the uracil ring, which suggests that the carbon at the 6-position undergoes a decrease in electron density compared to Br and Cl. A balance of these opposite properties seems to influence the reactivity of the 5-fluoro-1,3-dimethyluracil (1c) in a subtle way.

In relation to these results, we detected the presence of an intermediate 4 during the reaction of 1a and diethyl malonate carbanion by TLC analysis (invisible under a UV-lamp, but the spot was directly stained by iodine absorption). The intermediate 4 was isolated in 41% yield along with 33% of unchanged 1a by interruption of the reaction after a short time (2 h). The structure of the intermediate 4 was assigned by spectral and microanalytical results to 5,6-di-[bis(ethoxycarbonyl)methyl]-5,6-dihydro-1,3-dimethyluracil with a *trans*-configuration based on the $^1$H-NMR spectral data. The isolated intermediate 4 could be transformed by only stirring with sodium ethoxide in anhydrous EtOH at rt for 8 h to give the corresponding 5-bis(ethoxycarbonyl)methyl-1,3-dimethyluracil (2) in 67% yield (Scheme 2).

**Scheme 2.** Formation of 5,6-di-[bis(ethoxycarbonyl)methyl]-5,6-dihydro-1,3-dimethyluracil (4) and its reactivity.

Based on these results, the plausible reaction mechanism for the formation of 2 involving a Michael 1,4-addition is indicated in Scheme 3. The intermediate 4 could be obtained via the generation of the
C-6 malonate adduct (A) by the nucleophilic attack of a diethyl malonate carbanion on the 6-position of the uracil ring and nucleophilic substitution between the bromine atom at the 5-position \((sp^3\)-carbon) of A and the remaining malonate carbanion (SN\(_2\) reaction). Subsequent C–C bond cleavage at the 6-position of 4 under basic conditions (E\(_2\) reaction) is a key and rate-determining step for the formation of 2, and this is why the 5,6-di-[bis(ethoxycarbonyl)methyl]-5,6-dihydro-1,3-dimethyluracil (4) could be isolated (Scheme 3) [24].

**Scheme 3.** Plausible reaction mechanism.

![Scheme 3](image)

The C–C bond formation reaction at the 5-position of 1a was also achieved using benzylphenylketone as a carbanion source, and 5-(\(\alpha\)-benzoyl)benzyl-1,3-dimethyluracil (5) was obtained in 96% yield after only a 1 h reaction at rt (Scheme 4).

**Scheme 4.** Formation of 5-(\(\alpha\)-benzoyl)benzyl-1,3-dimethyluracil (5).

![Scheme 4](image)

Since these reactions using active methylene compounds as nucleophile sources were essential to perform under strong basic conditions due to the generation of carbanions, the use of the unprotected 5-bromouridine (6a) or 5-bromo-2'-deoxyuridine (6b) at the 3-position as a substrate were not suitable due to the formation of the inactive uracil-anion (Scheme 5).
Hence, we next investigated the adding of a protective group to the 3-position of the uridine derivatives. 5-Bromo-3-\(\beta\)-methoxybenzyluridine (7a) was smoothly reacted with dimethyl malonate and benzylphenylketone at rt and the corresponding 5-substituted products 8a–c were obtained in moderate yields (Table 3, Entries 1–3). These products were easily deprotected to give 9a–c by stirring with AlCl\(_3\) (8.0 equiv.) in anisole at rt [35]. Since this deprotection method was unfortunately not applicable to the deprotection of the 3-\(\beta\)-methoxybenzyl-2'-deoxyuridine derivatives due to the instability of the \(\text{N}\)-glycosidic bond, we next investigated the introduction of the benzylxymethyl (BOM) functionality as an \(\text{N}_3\)-protective group [36,37]. The C–C bond formation reaction at the 5-position of the both 5-bromo-\(\text{N}_3\)-BOM protected uridine (7b) and deoxyuridine (7c) easily proceeded by the use of diethyl and dimethyl malonates and benzylphenylketone, respectively, to give the 5-substituted uridine derivatives 8d–i in 42–52% yields (Entries 4–9). Furthermore, the \(\text{N}_3\)-BOM protective group of the 5-bis(ethoxycarbonyl)methyl-substituted uridines (compounds 8d, e, g, h) was deprotected under Pd/C-catalyzed hydrogenation conditions in MeOH at rt in good to moderate yields (Entries 4, 5, 7 and 8). Although the deprotection took a prolonged reaction time (72 h), it was fortunately revealed that the addition of ammonium acetate (NH\(_4\)OAc, 1.0 equiv.) could efficiently enhance the deprotection of 8g and 8h, and the deprotected products 9d and 9e were obtained in better yields (72 and 86%, respectively) within shorter reaction periods (20 and 24 h, respectively, Entries 7 and 8). While the deprotection intricately proceeded in the case of the 5-(\(\alpha\)-benzoyl)benzyl-3-benzylxymethyluridine derivatives 8f, i due to the existence of an additional reducible functionality (aromatic ketone, Entries 6 and 9, Scheme 6), 5-(2-hydroxy-1,2-diphenylethyl)-2'-deoxyuridine (13, 20% yield) and 5-(1,2-diphenylethyl)-2'-deoxyuridine (14, 27%) could be isolated by careful preparative TLC (eluent: 5:1 CHCl\(_3\)--MeOH). Inspired by these results, we attempted the functional group transformation under Pd/C-catalyzed hydrogenation conditions using 5-(\(\alpha\)-benzoyl)benzyl-3-methoxybenzyluridine (8c) as a substrate. Consequently, a mixture of 3-\(\beta\)-methoxybenzyl-5-(1,2-diphenylethyl)uridine (10, 45% yield) and 3-\(\beta\)-methoxybenzyl-5-(2-hydroxy-1,2-diphenylethyl)uridine (11, 34% yield) was obtained and 10 was smoothly deprotected by the treatment with AlCl\(_3\) at rt for 24 h to give the corresponding 5-(1,2-diphenylethyl)uridine (12) in 79% yield. On the other hand, when the Pd/C-ethylenediamine complex [Pd/C(en)]\([38–46]\] was used as a catalyst, the chemoselective hydrogenation occurred and 11 was isolated as the sole product (Scheme 7).

Next we investigated the reaction of 1a with ethyl phenylacetate and benzyl cyanide in the presence of NaOEt as a base at rt. Surprisingly, and against all expectation, the 2,4-diazabicyclo[4.1.0]heptane
derivatives 15a,b were obtained as the sole product (Scheme 8). The reaction was also found to proceed by the use of DBU instead of NaOEt. The structures of products 15a and 15b were supported by the spectral data and microanalytical results, and the characteristic AB pattern peaks of the bridgehead protons [15a: δ 3.20 (C-6–H), 3.72 (C-1–H), J_{1,6} = 9.0 Hz; 15b: δ 3.03 (C-6–H), 3.58 (C-1–H), J_{1,6} = 8.5 Hz] as a 2,4-diazabicyclo[4.1.0]heptane nucleus were also clearly observed in the ^1H-NMR spectrum [47]. Although the 2,4-diazabicyclo[4.1.0]heptane derivatives were likely the intermediates for the generation of the 5-substituted uracils [33,34], 15a was quite stable under basic conditions (NaOEt), even at the reflux temperature of EtOH.

Table 3. Preparation of 5-substituted uridine derivatives.

| Entry | Starting Compd. (7) | R^1  | R^2  | R^3   | R^4  | Product (8) | Yield (%) | Product (9) | Yield (%) | Time (h) | Yield (%) |
|-------|---------------------|------|------|-------|------|-------------|-----------|-------------|-----------|----------|-----------|
| 1     | 7a PMB OH CO_2Et    | CO_2Et | 8a   | 51    | 9a   | 12          | 46        |             |           |          |           |
| 2     | 7a PMB OH CO_2Me    | CO_2Me | 8b   | 47^a  | 9b   | 24          | 42        |             |           |          |           |
| 3     | 7a PMB OH Ph        | COPh  | 8c   | 60    | 9c   | 4           | 82        |             |           |          |           |
| 4     | 7b BOM OH CO_2Et    | CO_2Et | 8d   | 52    | 9a   | 72          | 69        |             |           |          |           |
| 5     | 7b BOM OH CO_2Me    | CO_2Me | 8e   | 47^a  | 9b   | 72          | 67        |             |           |          |           |
| 6     | 7b BOM OH Ph        | COPh  | 8f   | 47    | 9c   | –           | –^b       |             |           |          |           |
| 7     | 7c BOM H CO_2Et     | CO_2Et | 8g   | 48    | 9d   | 72 (20)^c   | 64 (72)^c |             |           |          |           |
| 8     | 7c BOM H CO_2Me     | CO_2Me | 8h   | 42^a  | 9e   | 72 (24)^c   | 59 (86)^c |             |           |          |           |
| 9     | 7c BOM H Ph         | COPh  | 8i   | 43    | 9f   | –           | –^b,d     |             |           |          |           |

^a^ The reaction was performed using NaOMe in anhydrous MeOH; ^b^ Complex mixture; ^c^ With NH_4OAc; ^d^ See Scheme 7.

Scheme 6. Deprotection of 5-(α-benzoyl)benzyl-3-benzyloxymethyl-2'-deoxyuridine (8i) under Pd/C-catalyzed hydrogenation conditions.
Scheme 7. Pd/C- or Pd/C(en)-catalyzed hydrogenation of 5-(α-benzoyl)benzyl-3-methoxybenzyluridine (8c).

Scheme 8. Formation of 2,4-diazabicyclo[4.1.0]heptane (cyclopropane) and 2,4-diazabicyclo[4.1.0]nonane (cyclopentane) derivatives.

The reaction sequence for the formation of the 2,4-diazabicyclo[4.1.0]heptanes is proposed to occur as shown in Scheme 9. An initial nucleophilic attack at the 6-position of 1a by the carbanion could produce the C-6 adduct (B). The subsequent intramolecular cyclization between the C-5 position and active methine moiety of B accompanied by elimination of the bromide anion from the \( sp^3 \) C-5 position results in the formation of the fused cyclopropane derivatives (15).
Furthermore, 5-bromo-1,3-dimethyluracil (1a) was easily transformed into the corresponding 2,4-diazabicyclo[4.1.0]nonane derivative 16 under similar reaction conditions by the use of dibenzylketone as a 1,3-ambident active methylene compound. While there could be eight diastereoisomers due to the four asymmetric carbons of 16, the $^1$H-NMR analysis suggested that 16 is a single diastereomer possessing a trans-cis-cis configuration.

As noted earlier in the Introduction, not so many chemical modification methods at the 6-position of uracil derivatives are reported in the literature, including the formation of 6-cyanouracil derivatives due to the cine-substitution reaction as shown in Scheme 1 [28,30–32]. In other examples, Tanaka and Miyasaka et al. reported the electrophilic functionalization at the 6-position of 2',3'-isopropylidene-5'-methoxymethyluridine via lithiation at the 6-position of the uracil ring [48], and the photochemically-induced nucleophilic substitution at the 6-position of 6-iodo-2',3'-isopropylidene-5'-methoxymethyluridine [49]. Needless to say, the normal nucleophilic substitution of the 6-halogenouracil derivatives under basic conditions has also been reported in the literature [50].

When 1a was allowed to react with ethyl acetoacetate in the presence of NaOEt in anhydrous EtOH at rt for 72 h, the 1,3-dimethyluracil-6-(α-acetyl)acetic acid ethyl ester (17) was obtained in 62% yield together with 32% of the unchanged 1a [Scheme 10; while the structure of 17 was indicated as the keto-form of the 6-substituent for the purpose of illustration, the actual structure in solution should be the enol-form with intramolecular hydrogen bond (17') based on $^1$H-NMR analytical data]. The reaction also proceeded by the use of NaH as a base in anhydrous DMF. The structure of 17 was supported on the basis of the spectral data and microanalytical results, and confirmed by comparison of the spectral data with those of the product of the alternative synthesis based on the reaction using 6-chloro-1,3-dimethyluracil (19) and ethyl acetoacetate in the presence of NaH in anhydrous DMF at rt. Furthermore, 17 could be quantitatively converted into the well-known 1,3,6-trimethyluracil (18) in 98% yield after a 1 h reflux in a 47% HBr solution.
Scheme 10. Formation of 6-substituted 1,3-dimethyluracils.

The reaction sequence for the formation of 17 is outlined in Scheme 11. Although the Michael adduct (C) can be normally converted to the 6-substituted product 17 accompanied by the elimination of HBr (cine-substitution), it is rather reasonable to suggest that the reaction proceeded via the cyclic intermediate (E) generated by the intramolecular nucleophilic attack of the corresponding enolate anion of D on the 5-position under strong basic conditions [30–32]. We believe that is why the formation of the 6-substituted product 17 occurs when using ethyl acetoacetate.

Scheme 11. Plausible reaction mechanism for the formation of 6-substituted product (17).

The present reaction is applicable for the preparation of the 3-p-methoxybenzyluridine-6-(α-acetyl)acetic acid ethyl ester (20). The treatment of 5-bromo-3-p-methoxybenzyluridine (7a) with ethyl acetoacetate (3.3 equiv.) and t-BuOK (3.0 equiv.) in DMF at rt for 72 h gave 20 in 64% yield (Scheme 12), while the deprotection of 20 using AlCl₃ [35] was unsuccessful due to decomposition. Upon treatment
of 3-benzyloxymethyl-5-bromouridine (7b) and 3-benzyloxymethyl-5-bromodeoxyuridine (7c) with ethyl acetoacetate under analogous conditions, the corresponding 3-benzyloxymethyluridine-6-(α-acetyl)acetic acid ethyl ester derivatives 21a,b were obtained in 48 and 42% yields, respectively. These products 21a,b were easily deprotected to 22a and 22b (while the structures of 21/22a,b were indicated as the keto-forms of the 6-substituent for the purpose of illustration, the actual structure in solution should be the enol-forms with intramolecular hydrogen bond based on centering on the ¹H-NMR data) under neutral Pd/C-catalyzed hydrogenation conditions in MeOH at rt (Scheme 13).

Scheme 12. Preparation of the 3-p-methoxybenzyluridine-6-(α-acetyl)acetic acid ethyl ester (20).

Scheme 13. Preparation of the 3-benzyloxymethyluridine 6-(α-acetyl)acetic acid ethyl ester derivatives 21a and 21b and their efficient deprotection.

These diversified reactivities by virtue of the difference in the active methylene compounds may be controlled by the pKₐ values of the particular active methylene compounds. 5-Substituted products (i.e., compounds 2, 5 and 8) are obtained when using diethyl- and dimethyl malonate and benzylphenylketone possessing moderate acidities (pKₐ in DMSO: 16.4 [51], 15.9 [52] and 17.7 [53], respectively) due to the preference of the intermolecular nucleophilic attack at the 5-position of the adduct (A, Scheme 3) because of the comparatively longer life of the corresponding carbanions. On the other hand, cyclopropane and cyclopentane derivatives 15 and 16 are produced when using the less acidic active methylene compounds, such as ethyl phenylacetate, benzyl cyanide and dibenzylketone (pKₐ in DMSO: 22.7 [54], 21.9 [55] and 18.7 [53], respectively), due to the intramolecular nucleophilic attack at the 5-position of B (Scheme 9) in preference to the intermolecular nucleophilic attack based on excessive amounts of the active methylene compounds due to the unstable nature of the corresponding carbanions. In the case of ethyl acetoacetate (pKₐ in DMSO: 14.2 [56]) capable of forming an enolate (D, Scheme 11) under basic conditions, a special reactivity was observed since the intramolecular cyclization by the enolate-attack at the 5-position preferentially proceeded to give the 6-substituted products 17, 20 and 21. However, an exact rational explanation is difficult because many other active
methylene compounds are not applicable to present reactions by reason of the frequent occurrence of side-reactions such as polymerization and decomposition under basic conditions.

While the synthesized 5- and 6-substituted deoxyuridine derivatives 8g–8i, 9g, 9h, 13, 14, 21b and 22b were evaluated for their antiviral activities against the herpes simplex virus (HSV), human cytomegalovirus (HCMV) and influenza A virus and cytostatic activity, these compounds unfortunately indicated no or minimal activities.

3. Experimental

3.1. General

All reagents were obtained from commercial sources and used without further purification. Analytical thin-layer chromatography (TLC) was carried out on pre-coated Silica gel 60 F-254 plates (32–63 µm particle size) and visualized with UV light (254 nm). The 10% Pd/C was obtained from Merck KGaA or Aldrich. Flash column chromatography was performed with Silica gel 60 (40–63 µm particle size, Merck KGaA) or Silica gel 60N (100–210 µm, Kanto Chemical). The 1H and 13C-NMR spectra were recorded by a JEOL AL 400 spectrometer (Tokyo, Japan), JEOL EX 400 spectrometer (400 MHz for 1H-NMR and 100 MHz for 13C-NMR) or JEOL TNG-GX270 spectrometer (270 MHz for 1H-NMR) with tetramethylsilane or residual protonated solvent used as a reference. Elemental analyses were carried out at the Microanalytical Laboratory of our university (YANACO CHN CORDER MT-5 instrument, Tokyo, Japan). The EI and FAB Mass spectra were obtained using a JEOL JMS-SX102A instrument (Tokyo, Japan). The UV spectra were obtained in ethanol using a Shimadzu UV-260 spectrophotometer (Kyoto, Japan).

5-Bis(ethoxycarbonyl)methyl-1,3-dimethyluracil (2) (Table 2, Entries 1–3). (a) A solution of 5-bromo-1,3-dimethyluracil (1a) (1.85 g, 8.45 mmol) and diethyl malonate (4.48 g, 27.9 mmol) in ethanolic NaOEt [prepared from Na (584 mg, 25.4 mmol) in absolute EtOH (85 mL)] was stirred for 8 h at room temperature. The mixture was evaporated under reduced pressure and the residue was dissolved in H2O (20 mL). The mixture was neutralized with conc. HCl and extracted with CHCl3. The extract was dried over MgSO4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with CHCl3 as the eluant to give compound 2 (1.51 g, 60%) as a colorless oil. 1H-NMR (CDCl3) 7.54 (1H, s, 6-H), 4.87 (s, 1H, CH), 4.21 (q, J = 7.0 Hz, 4H, CH2), 3.42 and 3.31 (each s, each 3H, NMe), 1.25 (t, J = 7.0 Hz, 6H, CMe); 13C-NMR (CDCl3) 167.9, 162.5, 151.2, 142.9, 105.6, 62.3, 48.0, 37.4, 28.3, 14.0; HRMS (EI) calcd. for C13H18N2O6 (M+): m/z 298.1165; found 298.1174; (b) A solution of 5-chloro-1,3-dimethyluracil (1b, 1.75 g, 10.0 mmol) and diethyl malonate (5.29 g, 33.0 mmol) in ethanolic NaOEt [prepared from Na (690 mg, 30.0 mmol) in absolute EtOH (100 mL)] was stirred for 16 h at room temperature and then treated as described above to give 2 (2.00 g, 67%); (c) A solution of 5-fluoro-1,3-dimethyluracil (1c, 474 mg, 3.00 mmol) and diethyl malonate (1.59 g, 9.90 mmol) in ethanolic NaOEt [prepared from Na (207 mg, 9.00 mmol) in absolute EtOH (30 mL)] was stirred for 24 h at room temperature and then treated as described above to give 2 (582 mg, 65%).
1,3-Dimethyluracil-5-acetic acid (3) [23]. A mixture of 5-bis(ethoxycarbonyl)methyl-1,3-dimethyluracil (2) (349 mg, 1.17 mmol) in a 47% HBr solution was refluxed for 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with CHCl₃–MeOH (5:1) as the eluant to give 3 (220 mg, 95%), which was identical to the authentic sample.

5,6-Di-[bis(ethoxycarbonyl)methyl]-5,6-dihydro-1,3-dimethyluracil (4). A solution of 5-bromo-1,3-dimethyluracil (1a) (657 mg, 3.00 mmol) and diethyl malonate (1.59 g, 9.90 mmol) in ethanolic NaOEt [prepared from Na (207 mg, 9.00 mmol) in absolute EtOH (30 mL)] was stirred at room temperature for 2 h. The mixture was neutralized with Amberlite CG-50 (H⁺) and filtered. The ion exchange resin was washed with ethanol, and the combined filtrates were concentrated under reduced pressure. The residue was treated with H₂O (30 mL). The aqueous solution was extracted with CHCl₃ and the extract was dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel with benzene–EtOAc (6:1) as the eluant to give the starting material 1a (217 mg, 33%) and the 5,6-dihydrouracil 4 (564 mg, 41%), which was recrystallized from EtOH. m.p. 85–86 °C; UV λ max. (EtOH) only end absorption; ¹H-NMR (CDCl₃) 4.29 (brd, J = 7.3 Hz, 1H, CH), 4.27–4.15 (m, 8H, CH₂), 3.75 (d, J = 5.6 Hz, 1H, CH), 3.66 (d, J = 7.3 Hz, 1H, CH), 3.50 (brd, J = 5.6 Hz, 1H, CH), 2.96 and 3.16 (each s, each 3H, NMe), 1.35–1.20 (m, 12H, CMe); ¹³C-NMR (CDCl₃) 168.3, 166.8, 166.8, 166.2, 166.1, and 152.4 (each C=O), 62.5, 62.3, 62.3, and 62.2 (each CH₂), 55.6, 54.5, 52.0, and 44.6 (C-5, C-6 and CH × 2), 36.5 and 27.8 (each NMe), 13.9, 13.9, 13.9, and 13.8 (each CMe); MS (EI) m/z 459 (M⁺+H, 3%), 413 (25), 299 (100), 207 (47); Anal calcd. for C₂₀H₃₀N₂O₁₀: C, 52.39; H, 6.60; N, 6.11%; found: C, 52.14; H, 6.65; N, 6.11.

Reaction of 4 with sodium ethoxide: A solution of 4 (101 mg, 0.220 mmol) in ethanolic NaOEt [prepared from Na (14.9 mg, 0.650 mmol) in absolute EtOH (5 mL)] was stirred at room temperature for 8 h. The solvent was removed under reduced pressure and the residue was treated with H₂O (20 mL). The solution was neutralized with c.HCl and the aqueous solution was extracted with CHCl₃. The extract was dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel with benzene–EtOAc (6:1) as the eluant to give 1,3-dimethyluracil-5-malonic acid diethyl ester (2, 44.0 mg, 67%).

5-(α-Benzoyl)benzyl-1,3-dimethyluracil (5). A mixture of 5-bromo-1,3-dimethyluracil (1a) (1.32 g, 6.00 mmol) and benzylphenylketone (3.69 g, 19.8 mmol) in ethanolic NaOEt [prepared from Na (414 mg, 18.0 mmol) in absolute EtOH (60 mL)] was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was treated with H₂O (40 mL). The solution was neutralized with conc. HCl and the aqueous solution was extracted with CHCl₃. The extract was dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl₃ as the eluant to give 5 (1.94 g, 96%), which was recrystallized from CHCl₃. m.p. 128.5–130 °C; UV λ max. (EtOH) 249 nm (ε 16,300 dm³mol⁻¹cm⁻¹); ¹H-NMR (CDCl₃) 8.27–7.88 (m, 2H, COPh), 7.74–7.15 (m, 8H, Ph and COPh), 6.73 (brs, 1H, 6-H), 6.09 (brs, 1H, CH), 3.34 and 3.27 (each s, each 3H, NMe); ¹³C-NMR (CDCl₃) 197.5, 163.2, 151.4, 142.1, 136.1, 135.3, 133.2, 129.5, 129.1, 128.9, 128.6, 128.0, 113.8, 50.8, 37.3, 28.1; MS (EI) m/z 334 (M⁺, 13%), 229 (100), 172 (25),
131 (38), 105 (70); Anal calcd. for C_{20}H_{18}N_{2}O_{3}: C, 71.84; H, 5.43; N, 8.38%; found: C, 71.79; H, 5.47; N, 8.37.

5-Bromo-3-p-methoxybenzyluridine (7a). p-Methoxybenzyl chloride (0.93 mL, 6.80 mmol) was added dropwise to a mixture of 5-bromouridine (2.00 g, 6.20 mmol) and K_{2}CO_{3} (1.11 g, 8.05 mmol) in DMF (10 mL) at room temperature. The mixture was stirred for 24 h and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by recrystallization from MeOH to give 7a (2.42 g, 88%) as a colorless powder. \(^{1}H\)-NMR (DMSO-\(d_{6}\)) 8.60 (s, 1H, 6-H), 7.25 and 7.05 (each d, each \(J = 8.8\) Hz, each 2H, C\(_{6}\)H\(_{4}\)), 5.75 (d, \(J = 4.9\) Hz, 1H, 1'-H), 5.46 (brs, 1H, OH), 5.30 (brs, 1H, OH), 5.05 (brd, \(J = 5.9\) Hz, 1H, OH), 4.93 (s, 2H, CH\(_{2}\)), 4.03–3.99 (m, 2H, 2'-H and 3'-H), 3.87–3.82 (m, 1H, 4'-H), 3.77 (s, 3H, CH\(_{3}\)), 3.62–3.57 (m, 2H, 5'-H); \(^{13}\)C-NMR (DMSO-\(d_{6}\)) 158.5, 158.3, 149.9, 139.1, 129.5, 128.5, 113.7, 94.9, 89.7, 84.5, 73.9, 68.8, 59.7, 55.0, 44.0; MS (EI) \(m/z\) 442 (M\(^{+}\), 8%), 444 (8), 310 (25), 312 (25), 162 (12), 121 (100); HRMS (EI) calcd. for C\(_{17}\)H\(_{19}\)BrN\(_{2}\)O\(_{7}\) (M\(^{+}\)) 442.03756; found: 442.03681; Anal calcd. for C\(_{17}\)H\(_{19}\)BrN\(_{2}\)O\(_{7}\): C, 46.07; H, 4.32; N, 6.32%; found: C, 45.96; H, 4.46; N, 6.33.

5-Bromo-3-benzyloxymethyluridine (7b). Benzyloxymethyl chloride (0.930 mL, 6.80 mmol) was dropwise added to a mixture of 5-bromouridine (2.00 g, 6.20 mmol) and K\(_{2}\)CO\(_{3}\) (1.11 g, 8.05 mmol) in DMF (10 mL) at room temperature. The mixture was stirred for 24 h and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel with CHCl\(_{3}\)-MeOH (50:1) as the eluant to give 7b (1.51 g, 55%) as a colorless powder. \(^{1}H\)-NMR (DMSO-\(d_{6}\)) 8.60 (s, 1H, 6-H), 7.34–7.25 (m, 5H, C\(_{6}\)H\(_{5}\)), 5.72 (d, \(J = 3.7\) Hz, 1H, 1'-H), 5.50–5.47 (m, 1H, OH), 5.37–5.32 (m, 3H, OH and CH\(_{2}\)), 5.09–5.05 (m, 1H, OH), 4.58 (s, 2H, CH\(_{2}\)) 4.09–4.00 (m, 1H, 2'-H), 3.96–3.95 (m, 1H, 3'-H), 3.81–3.74 (m, 1H, 4'-H), 3.61–3.55 (m, 2H, 5'-H); \(^{13}\)C-NMR (DMSO-\(d_{6}\)) 158.6, 150.0, 139.7, 128.1, 127.5, 127.4, 94.8, 89.7, 84.4, 74.0, 71.3, 71.1, 68.6, 59.6; MS (FAB, Gly) \(m/z\) 443 (M\(^{+}\)H, 8%), 445 (8%), 365 (5), 277 (12) 185 (100); HRMS (FAB, Gly) calcd. for C\(_{17}\)H\(_{19}\)BrN\(_{2}\)O\(_{7}\) (M\(^{+}\)) 442.0376; found: 442.0376; Anal calcd. for C\(_{17}\)H\(_{19}\)BrN\(_{2}\)O\(_{7}\): C, 46.07; H, 4.32; N, 6.32%; found: C, 45.96; H, 4.46; N, 6.33.

5-Bromo-3-benzyloxymethyl-2'-deoxyuridine (7c). Benzyloxymethyl chloride (0.460 mL, 2.59 mmol) was dropwise added to a mixture of 5-bromo-2'-deoxyuridine (1.00 g, 2.36 mmol) and K\(_{2}\)CO\(_{3}\) (561 mg, 3.07 mmol) in DMF (10 mL) at room temperature. The mixture was stirred for 24 h and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel with CHCl\(_{3}\)-MeOH (50:1) as the eluant to give 7c (549 mg, 55%) as colorless oil. \(^{1}H\)-NMR (DMSO-\(d_{6}\)) 8.49 (s, 1H, 6-H), 7.34–7.23 (m, 5H, C\(_{6}\)H\(_{5}\)), 6.10 (t, \(J = 6.3\) Hz, 1H, 1'-H), 5.34 (s, 2H, CH\(_{2}\)), 5.25 (brd, \(J = 4.4\) Hz, 1H, OH), 5.21–5.18 (m, 1H, OH), 4.58 (s, 2H, CH\(_{2}\)) 4.25–4.20 (m, 1H, 3'-H), 3.83–3.79 (m, 1H, 4'-H), 3.67–3.54 (m, 2H, 5'-H); MS (FAB, NBA) \(m/z\) 427 (M\(^{+}\)H, 5%), 429 (5), 154 (100), 146 (64); HRMS (FAB, NBA) calcd. for C\(_{17}\)H\(_{19}\)BrN\(_{2}\)O\(_{6}\) (M\(^{+}\)H) 427.04265; found: 427.04935.

5-Bis(ethoxycarbonyl)methyl-3-p-methoxybenzyluridine (8a). A solution of 5-bromo-3-p-methoxybenzyluridine (7a) (500 mg, 1.13 mmol) and diethyl malonate (597 mg, 3.73 mmol) in ethanolic NaOEt [prepared from Na (77.8 mg, 3.38 mmol) in absolute EtOH (10 mL)] was stirred for
24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H2O (30 mL), and the mixture was neutralized with NaHSO4. The solution was extracted with EtOAc and the extract was dried over MgSO4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with CHCl3–MeOH (150:1) as the eluant to give 8a (301 mg, 51%) as a colorless foam. 1H-NMR (DMSO-d6) 8.00 (s, 1H, 6-H), 7.26 and 6.88 (each d, each J = 8.7 Hz, each 2H, C6H4), 5.88 (d, J = 5.1 Hz, 1H, 1'-H), 5.46 (brd, J = 5.9 Hz, 1H, OH), 5.13–5.09 (m, 1H, OH), 4.94 (brd, J = 5.0 Hz, 1H, OH), 4.94 (s, 2H, CH2), 4.16 (q, J = 7.2 Hz, 4H, CH2 × 2), 4.03–3.98 (m, 1H, 2'-H), 3.95–3.90 (m, 1H, 3'-H), 3.90–3.89 (m, 1H, 4'-H), 3.74 (s, 3H, CH3), 3.62–3.45 (m, 2H, 5'-H), 1.19 (t, J = 7.1 Hz, 6H, CH3 × 2); 13C-NMR (DMSO-d6) 166.9, 161.1, 158.6, 150.2, 137.9, 129.5, 128.7, 113.6, 106.9, 88.9, 85.1, 73.8, 69.8, 61.5, 60.8, 55.0, 49.7, 43.3, 13.8; MS (FAB, NBA) m/z 523 (M++H, 29%), 522 (7), 391 (9), 154 (100), 121 (76); HRMS (FAB, NBA) calcd. for C24H31N2O11 (M++H) 523.185; found: 523.1935.

5-Bis(methoxycarbonyl)methyl-3-p-methoxybenzyluridine (8b). A solution of 5-bromo-3-p-methoxybenzyluridine (7a) (500 mg, 1.13 mmol) and dimethyl malonate (493 mg, 3.73 mmol) in ethanolic NaOEt [prepared from Na (77.8 mg, 3.38 mmol) in absolute EtOH (10 mL)] was stirred for 24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H2O (30 mL), and the mixture was neutralized with NaHSO4. The solution was extracted with EtOAc and the extract was dried over MgSO4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl3–MeOH (150:1) as the eluant to give 8b (262 mg, 47%) as a colorless foam. 1H-NMR (DMSO-d6) 7.99 (s, 1H, 6-H), 7.24 and 6.86 (each d, each J = 8.5 Hz, each 2H, C6H4), 5.84 (d, J = 3.9 Hz, 1H, 1'-H), 5.45 (brd, J = 5.8 Hz, 1H, OH), 5.05 (brd, J = 4.3 Hz, 1H, OH), 4.85 (s, 2H, CH2), 4.64 (s, 1H, CH), 4.01–3.99 (m, 1H, 2'-H), 3.98–3.97 (m, 1H, 3'-H), 3.92–3.87 (m, 1H, 4'-H), 3.17 (s, 6H, CH3 × 2), 3.66 (s, 3H, CH3), 3.57–3.50 (m, 2H, 5'-H); MS (EI) m/z 494 (M+, 5%), 462 (17), 304 (18), 162 (17), 121 (100); HRMS (EI) calcd. for C22H28N2O11 (M+): 494.15366; found: 494.15423.

5-[(α-Benzoyl)benzyl]-3-p-methoxybenzyluridine (8c). A solution of 5-bromo-3-p-methoxybenzyluridine (7a) (500 mg, 1.13 mmol) and benzylphenylketone (732 mg, 3.73 mmol) in ethanolic NaOEt [prepared from Na (77.8 mg, 3.38 mmol) in absolute ethanol (10 mL)] was stirred for 24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H2O (30 mL), and the mixture was neutralized with NaHSO4. The solution was extracted with EtOAc and the extract was dried over MgSO4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl3–MeOH (150:1) as the eluant to give 8c (379 mg, 60%) as a colorless foam. 1H-NMR (DMSO-d6) 7.99 (d, J = 7.8 Hz, 2H, o-Bz), 7.55 (t, J = 7.3 Hz, 1H, p-Bz), 7.46 (t, J = 6.8 Hz, m-Bz), 7.35–7.31 (m, 5H, C6H5), 7.28 and 6.83 (each d, each J = 6.3 Hz, each 2H, C6H4), 7.01 and 7.04 (each s, total 1H, 6-H), 6.10 (s, 1H, CH), 5.79 (d, J = 5.4 Hz, 1H, 1'-H), 5.41 (brd, J = 5.9 Hz, 1H, OH), 5.33–5.32 (m, J = 5.8 Hz, 1H, OH), 5.10–5.06 (m, 1H, OH), 4.89 (s, 2H, CH2) 4.66–4.63 (m, 1H, 2'-H), 4.59–4.56 (m, 1H, 3'-H), 3.87–3.84 (m, 1H, 4'-H), 3.76 (s, 3H, CH3), 3.68–3.58 (m, 2H, 5'-H); 13C-NMR (DMSO-d6) 196.5, 161.5, 158.2, 150.3, 136.9, 136.8, 136.7, 135.8, 135.0, 134.8, 133.2, 129.4, 129.1, 128.6, 127.7, 114.2, 112.6, 88.7, 84.8, 73.4, 70.2, 61.2, 55.0,
5-Bis(ethoxycarbonylmethyl)-3-benzyloxymethyluridine (8d): A solution of 5-bromo-3-benzyloxy-methyluridine (7b) (500 mg, 1.13 mmol) and diethyl malonate (597 mg, 3.73 mmol) in ethanolic NaOEt [prepared from Na (77.8 mg, 3.38 mmol) in absolute ethanol (10 mL)] was stirred for 24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H2O (30 mL), and the mixture was neutralized with NaHSO4. The solution was extracted with CHCl3 and the extract was dried over MgSO4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl3–MeOH (150:1) as the eluant to give 8d (307 mg, 52%) as a colorless oil. 1H-NMR (DMSO-d6) δ 8.00 (s, 1H, 6-H), 7.34–7.24 (m, 5H, C6H5), 5.83 (d, J = 5.4 Hz, 1H, 1'-H), 5.48 (brd, J = 5.4 Hz, 1H, OH), 5.39–5.26 (m, 2H, CH2), 5.16–5.14 (m, 1H, OH), 5.04 (brd, J = 4.9 Hz, 1H, OH), 4.59 (s, 2H, CH2), 4.20–4.10 (m, 5H, CH2 × 2 and 2'-H), 4.00–3.98 (m, 1H, 3'-H), 3.89–3.82 (m, 1H, 4'-H), 3.65–3.50 (m, 2H, 5'-H), 1.17 (J = 6.9 Hz, 6H, CH3 × 2); MS (FAB, NBA) m/z 523 (M++H, 32%), 416 (8%), 238 (9), 154 (100), 107 (24); HRMS (FAB, NBA) calcd. for C24H30N2O11 (M++H): 523.19343; found: 523.19283.

5-Bis(methoxycarbonylmethyl)-3-benzyloxymethyl-2'-deoxyuridine (8e). A solution of 5-bromo-3-benzyloxymethyluridine (7b) (500 mg, 1.13 mmol) and dimethyl malonate (493 mg, 3.73 mmol) in ethanolic NaOEt [prepared from Na (77.8 mg, 3.38 mmol) in absolute EtOH (10 mL)] was stirred for 24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H2O (30 mL), and the mixture was neutralized with NaHSO4. The solution was extracted with EtOAc and the extract was dried over MgSO4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl3–MeOH (150:1) to give 8e (263 mg, 47%) as a colorless oil. 1H-NMR (DMSO-d6) δ 8.00 (s, 1H, 6-H), 7.35–7.27 (m, 5H, C6H5), 5.83 (d, J = 4.6 Hz, 1H, 1'-H), 5.47 (brd, J = 5.9 Hz, 1H, OH), 5.32 (s, 2H, CH2), 5.14–5.12 (m, 1H, OH), 5.05 (brd, J = 4.8 Hz, 1H, OH), 4.70 (s, 1H, CH), 4.57 (s, 2H, CH2), 4.04–4.02 (m, 1H, 2'-H), 4.01–3.98 (m, 1H, 3'-H), 3.94–3.92 (m, 1H, 4'-H), 3.69 (s, 6H, CH3 × 2), 3.68–3.65 (m, 2H, 5'-H); MS (FAB, NBA) m/z 495 (M++H, 5%), 238 (10), 176 (8), 154 (100), 85 (47); HRMS (FAB, NBA) calcd. for C22H28N2O11 (M++H): 495.15366; found: 494.16221.

5-(α-Benzoyl)benzyl-3-p-methoxybenzyluridine (8f): A solution of 5-bromo-3-benzoyloxy-methyluridine (7b) (500 mg, 1.13 mmol) and benzylphenylketone (732 mg, 3.73 mmol) in ethanolic NaOEt [prepared from Na (77.8 mg, 3.38 mmol) in absolute ethanol (10 mL)] was stirred for 24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H2O (30 mL), and the mixture was neutralized with NaHSO4. The solution was extracted with EtOAc and the extract was dried over MgSO4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl3–MeOH (150:1) as the eluant to give 8f (297 mg, 47%) as a colorless oil. 1H-NMR (DMSO-d6) δ 8.01 (d, J = 7.7 Hz, 2H, o-Bz), 7.57 (t, J = 7.7 Hz, 1H, p-Bz), 7.48 (t, J = 7.2 Hz, m-Bz), 7.49–7.24 (m, 10H, C6H5 × 2), 7.10 and 7.04 (each s, total 1H, 6-H), 6.08 (s, 1H, CH), 5.80 (d, J = 5.8 Hz, 1H, 1'-H), 5.45 (brd, J = 5.8 Hz, 1H, OH), 5.36–5.32 (m, 3H, OH and CH2), 5.08 (brd, J = 4.8 Hz, 1H, OH), 4.55 (s, 2H, CH2), 4.04–3.98 (m, 1H, 2'-H), 3.90–3.88 (m, 5H, C6H5).
1H, 3'-H), 3.76–3.73 (m, 1H, 4'-H), 3.68–3.58 (m, 2H, 5'-H); MS (FAB, NBA) m/z 559 (M^+H, 5%), 238 (21), 176 (6), 154 (100), 85 (67); HRMS (FAB, NBA) calcd. for C_{31}H_{30}N_{2}O_{8} (M^+H): 559.20803; found: 559.20701.

5-Bis(ethoxycarbonyl)methyl-3-benzyloxymethyl-2'-deoxyuridine (8g). A solution of 5-bromo-3-benzyloxymethyl-2'-deoxyuridine (7c) (299 mg, 0.700 mmol) and diethyl malonate (370 mg, 2.31 mmol) in ethanolic NaOEt [prepared from Na (48.3 mg, 2.10 mmol) in absolute EtOH (10 mL)] was stirred for 24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H_{2}O (30 mL), and the mixture was neutralized with NaHSO_{4}. The solution was extracted with EtOAc and the extract was dried over MgSO_{4}. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl_{3}–MeOH (200:1) as the eluant to give 8g (170 mg, 48%) as a colorless oil. ^{1}H-NMR (CDCl_{3}) 8.09 (s, 1H, 6-H), 7.36–7.23 (m, 5H, C_{6}H_{5}), 6.26 (t, J = 6.5 Hz, 1H, 1'-H), 5.47 (s, 2H, CH_{2}), 5.09–5.02 (brs, 1H, OH), 4.99–4.93 (brs, 1H, OH), 4.87 (s, 1H, CH), 4.68 (s, 2H, CH_{2}), 4.53–4.48 (m, 1H, 3'-H), 4.28–4.16 (m, 4H, CH_{2} × 2), 3.81–3.75 (m, 1H, 4'-H), 3.75–3.54 (m, 2H, 5'-H), 2.47–2.25 (m, 2H, 2'-H), 1.28 (t, J = 7.2 Hz, 6H, CH_{3} × 2); MS (FAB, NBA) m/z 507 (M^+H, 36%), 391 (18), 284 (11), 154 (100), 91 (50); HRMS (FAB, NBA) calcd. for C_{24}H_{30}N_{2}O_{10} (M^+H): 507.19783; found: 507.19747.

5-Bis(methoxycarbonyl)methyl-3-benzyloxymethyl-2'-deoxyuridine (8h). A solution of 5-bromo-3-benzyloxy-2' deoxymethyluridine (7c) (299 mg, 0.700 mmol) and dimethyl malonate (305 mg, 2.31 mmol) in ethanolic NaOEt [prepared from Na (48.3 mg, 2.10 mmol) in absolute EtOH (10 mL)] was stirred for 24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H_{2}O (30 mL), and the mixture was neutralized with NaHSO_{4}. The solution was extracted with EtOAc and the extract was dried over MgSO_{4}. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl_{3}–MeOH (200:1) as the eluant to give 8h (141 mg, 42%) as a colorless oil. ^{1}H-NMR (CDCl_{3}) 8.10 (s, 1H, 6-H), 7.36–7.23 (m, 5H, C_{6}H_{5}), 6.26 (t, J = 6.2 Hz, 1H, 1'-H), 5.47 (s, 2H, CH_{2}), 5.10–5.06 (m, 1H, OH), 4.93 (brs, 1H, OH), 4.90 (s, 1H, CH), 4.68 (s, 2H, CH_{2}), 4.03–3.98 (m, 1H, 3'-H), 3.93–3.86 (d, J = 3.6 Hz, 1H, 4'-H), 3.77 (s, 4H, CH_{2} × 2), 3.58–3.46 (m, 2H, 5'-H), 2.44–2.24 (m, 2H, 2'-H); MS (FAB, NBA) m/z 479 (M^+H, 5%), 391 (5%), 176 (10), 154 (100), 89 (64); HRMS (FAB, NBA) calcd. for C_{22}H_{26}N_{2}O_{10} (M^+H): 479.15875; found: 479.16750.

5-(α-Benzoyl)benzyl-3-benzyloxymethyl-2'-deoxyuridine (8i). A solution of 5-bromo-3-benzyloxy-2'-deoxymethyluridine (7c) (299 mg, 0.700 mmol) and dimethyl malonate (305 mg, 2.31 mmol) in ethanolic NaOEt [prepared from Na (48.3 mg, 2.10 mmol) in absolute EtOH (10 mL)] was stirred for 24 h at room temperature. The mixture was evaporated under reduced pressure, the residue was dissolved in H_{2}O (30 mL), and the mixture was neutralized with NaHSO_{4}. The solution was extracted with EtOAc and the extract was dried over MgSO_{4}. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl_{3}–MeOH (200:1) as the eluant to give 8i (163 mg, 43%) as a colorless oil. ^{1}H-NMR (DMSO-d_{6}) 8.02 (d, J = 7.6 Hz, 2H, O-Bz), 7.58 (t, J = 7.3 Hz, 1H, p-Bz), 7.47 (t, J = 7.6 Hz, m-Bz), 7.40–7.26 (m, 10H, C_{6}H_{5} × 2), 7.00 and 6.93 (each s, total 1H, 6-H), 6.12–6.06 (m, 2H, CH and 1'-H), 5.31 (s, 2H, CH_{2}), 5.24–5.20 (m,
5-Bis(ethoxycarbonyl)methyluridine (9a). (a) A solution of 5-bis(ethoxycarbonyl)methyl-3-\(p\)-methoxybenzyluridine (8a) (100 mg, 0.191 mmol) and AlCl\(_3\) (204 mg, 1.53 mmol) in absolute anisole (1.0 mL) was stirred for 12 h at room temperature. The residue was purified by column chromatography on silica gel with CHCl\(_3\)-MeOH (30:1) as the eluant to give 9a (35.4 mg, 46%) as a colorless oil (Table 3, Entry 1).

\(^1\)H-NMR (DMSO-\(d_6\)) 11.58 (s, 1H, 3-NH), 7.87 (s, 1H, 6-H), 5.80 (d, \(J = 5.4\) Hz, 1H, 1'-H), 5.40 (brd, \(J = 5.3\) Hz, 1H, OH), 5.02–4.92 (m, 1H, OH), 4.57 (s, 1H, CH), 4.13 (q, \(J = 7.0\) Hz, 4H, CH\(_2\) × 2), 4.01–3.96 (m, 1H, 2'-H), 3.95–3.90 (m, 1H, 3'-H), 3.88–3.82 (m, 1H, 4'-H), 3.60–3.50 (m, 2H, 5'-H), 1.17 (\(J = 7.0\) Hz, 6H, CH\(_3\) × 2), 1.17 (\(J = 7.0\) Hz, 6H, CH\(_3\) × 2).

(b) A mixture of 8d (136 mg, 0.260 mmol) and Pd/C (40.8 mg) was stirred at room temperature under an H\(_2\) atmosphere. After 72 h, the mixture was filtered using a membrane filter (Millex-LH, 0.45 \(\mu\)m), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl\(_3\)-MeOH (30:1) to give 9a (72.2 mg, 69%) (Table 3, Entry 4).

5-Bis(methoxycarbonyl)methyluridine (9b). (a) A solution of 5-bis(methoxycarbonyl)methyl-3-\(p\)-methoxybenzyluridine (8b) (100 mg, 0.202 mmol) and AlCl\(_3\) (216 mg, 1.62 mmol) in absolute anisole (1.0 mL) was stirred for 24 h at room temperature. To the mixture was MeOH, and the mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with CHCl\(_3\)-MeOH (30:1) as the eluant to give 9b (31.8 mg, 42%) as a colorless oil (Table 3, Entry 2).

\(^1\)H-NMR (DMSO-\(d_6\)) 11.60 (s, 1H, 3-NH), 7.87 (s, 1H, 6-H), 5.79 (d, \(J = 5.6\) Hz, 1H, 1'-H), 5.39 (brs, 1H, OH), 5.01 (brs, 1H, OH), 5.00 (brs, 1H, OH), 4.62 (s, 1H, CH), 4.03–3.96 (m, 1H, 2'-H), 3.95–3.90 (m, 1H, 3'-H), 3.93–3.84 (m, 1H, 4'-H), 3.66 (s, 6H, CH\(_3\) × 2), 3.61–3.49 (m, 2H, 5'-H); MS (FAB, Gly) m/z 375 (M++H, 3%), 307 (20), 289 (15), 238 (16), 154 (100), 136 (65), 107 (19), 85 (56); HRMS (FAB, Gly) calcd. for C\(_{14}\)H\(_{19}\)N\(_2\)O\(_{10}\) (M++H): 375.0961; found: 375.1042; (b) A mixture of 8e (129 mg, 0.26 mmol) and Pd/C (38.7 mg) was stirred at room temperature under an H\(_2\) atmosphere. After 72 h, the mixture was filtered using a membrane filter (Millex-LH, 0.45 \(\mu\)m), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl\(_3\)/MeOH (30:1) to give 9b (65.2 mg, 67%) (Table 3, Entry 5).

5-(\(\alpha\)-Benzoyl)benzyluridine (9c). A solution of 5-(\(\alpha\)-benzoyl)benzyl-3-\(p\)-methoxybenzyluridine (8c) (100 mg, 0.179 mmol) and AlCl\(_3\) (191 mg, 1.43 mmol) in absolute anisole (1.0 mL) was stirred for 4 h at room temperature. To the mixture was added MeOH, and the mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with CHCl\(_3\)-MeOH (30:1) as the eluant to give 9c (64 mg, 82%) as a pale yellow foam.

\(^1\)H-NMR (DMSO-\(d_6\)) 11.50 (s, 1H, 3-NH), 7.97 (d, \(J = 7.8\) Hz, 2H, o-Bz), 7.55 (t, \(J = 7.3\) Hz, 1H, p-Bz), 7.44 (t, \(J = 7.3\) Hz, m-Bz), 7.33–7.27 (m, 5H, C\(_6\)H\(_5\)), 7.01 and 6.95 (each s, total 1H, 6-H), 6.10 (s, 1H, CH), 5.78–5.72 (m, 1H, 1'-H), 5.37 (brs,
1H, OH), 5.28 (brs, 1H, OH), 5.10–5.06 (m, 1H, OH), 4.68–4.63 (m, 2H, CH₂), 3.86–3.78 (m, 1H, 2'-H), 3.66–3.60 (m, 1H, 4'-H), 3.53–3.29 (m, 2H, 5'-H); MS (EI) m/z 438 (M⁺, 6%), 306 (17), 201 (55), 158 (13), 115 (10), 105 (100), 77 (25); HRMS (EI) calcd. for C₂₃H₂₂N₂O₇ (M⁺): 438.1427; found: 438.1418.

5-Bis(ethoxycarbonyl)methyl-2'-deoxyuridine (9d). A mixture of 5-bis(ethoxycarbonyl)methyl-3'-benzoyloxymethyl-2'-deoxyuridine (8g) (50.7 mg 0.100 mmol) and Pd/C (Merck) (15.0 mg) in MeOH (1.0 mL) was stirred under H₂ atmosphere at room temperature. After 24 h, the mixture was filtered using a membrane filter (Millex-LH, 0.45 µm), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl₃–MeOH (30:1) as the eluant to give 9d (24.7 mg, 64%) as a colorless oil. ¹H-NMR (DMSO-d₆) 11.55 (s, 1H, 3-NH), 7.84 (s, 1H, 6-H), 6.16 (t, J = 6.8 Hz, 1H, 1'-H), 5.24 (brd, J = 4.1 Hz, 1H, OH), 4.95–4.91 (m, 1H, OH), 4.58 (s, 1H, CH), 4.22–4.18 (m, 1H, 3'-H), 4.06 (q, J = 7.2 Hz, 4H, CH₂ × 2), 3.80–3.78 (m, 1H, 4'-H), 3.55–3.40 (d, J = 4.6 Hz, 2H, 5'-H), 2.17–1.97 (m, 2H, 2'-H), 1.17 (t, J = 7.1 Hz, 6H, CH₃ × 2); MS (FAB, NBA) m/z 387 (M++H, 9%), 271 (12), 176 (8), 154 (100), 107 (19), 89 (17); HRMS (FAB, NBA) calcd. for C₁₆H₂₂N₂O₉ (M++H): 387.13253; found: 387.14105.

5-Bis(methoxycarbonyl)methyl-2'-deoxyuridine (9e). A mixture of 5-bis(methoxycarbonyl)methyl-3'-benzoyloxymethyl-2'-deoxyuridine (8h) (50 mg 0.105 mmol) and Pd/C (Merck) (15.0 mg) in MeOH (1.0 mL) was stirred under an H₂ atmosphere at room temperature. After 72 h, the mixture was filtered using a membrane filter (Millex-LH, 0.45 µm), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl₃–MeOH (30:1) as the eluant to give 9e (22.2 mg, 59%) as a colorless oil. ¹H-NMR (DMSO-d₆) 11.56 (s, 1H, 3-NH), 7.86 (s, 1H, 6-H), 5.81–5.78 (m, 1H, 1'-H), 5.24 (brd, J = 4.1 Hz, 1H, OH), 4.95–4.90 (m, 1H, OH), 4.64 (s, 1H, CH), 4.09–4.02 (m, 1H, 3'-H), 3.81–3.76 (m, 1H, 4'-H), 3.66 (s, 4H, CH₂ × 2), 3.55–3.49 (m, 2H, 5'-H), 2.17–1.99 (m, 2H, 2'-H); MS (FAB, NBA) m/z 359 (M++H, 32%), 243 (33%), 154 (100), 107 (10), 85 (62); HRMS (FAB, NBA) calcd. for C₁₄H₁₈N₂O₉ (M++H): 359.10123; found: 359.10827.

5-(2-Hydroxy-1,2-diphenylethyl)-2'-deoxyuridine (13) and 5-(1,2-diphenylethyl)-2'-deoxyuridine (14). A mixture of 5-α-benzoylbenzyl-3-benzyloxymethyl-2'-deoxyuridine (8i) (81.4 mg 0.150 mmol) and Pd/C (20.3 mg) in MeOH (1.0 mL) was stirred under H₂ atmosphere at room temperature for 48 h. The mixture was filtered using a membrane filter (Millex-LH, 0.45 µm), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl₃–MeOH (30:1) as the eluant to give 13 (12.7 mg, 20%) as a light brown oil and 14 (16.5 mg, 27%) as a colorless oil.

13: ¹H-NMR (DMSO-d₆) 11.11 (d, J = 10.6 Hz, 1H, 3-NH), 7.97 and 7.90 (each s, 1H, 6-H), 7.25–7.10 (m, 10H, C₆H₅ × 2), 6.11–6.05 (m, 1H, 1'-H), 5.32–5.09 (m, 4H, CH₂ × 2 and OH × 2), 4.53 (s, 1H, OH), 4.30–4.22 (m, 1H, 3'-H), 3.82–3.78 (m, 1H, 4'-H), 3.70–3.59 (m, 2H, 5'-H), 2.11–1.90 (m, 2H, 2'-H); MS (FAB, NBA) m/z 425 (M⁺+H, 19%), 291 (65), 202 (17), 176 (8), 154 (100), 107 (26), 77 (21); HRMS (FAB, NBA) calcd. for C₂₃H₂₄N₂O₉ (M⁺+H): 425.16344; found: 425.17190.

14: ¹H-NMR (DMSO-d₆) 11.19 (s, 1H, 3-NH), 8.04 and 8.00 (each s, 1H, 6-H), 7.25–7.10 (m, 10H, C₆H₅ × 2), 6.16 (t, J = 6.6 Hz, 1H, 1'-H), 5.32–5.20 (m, 4H, CH₂ and OH × 2), 5.24–5.20 (m, 1H, OH),
4.32–4.10 (m, 2H, 3'-H and CH), 3.84–3.80 (m, 1H, 4'-H), 3.68–3.60 (m, 2H, 5'-H), 2.12–2.03 (m, 2H, 2'-H); MS (FAB, NBA) m/z 409 (M++1, 6%), 154 (100), 136 (60), 107 (16), 89 (14); HRMS (FAB, NBA) calcd. for C23H24N2O5 (M++H): 409.16852; found: 409.17779.

Pd/C-catalyzed hydrogenation of 5-(α-benzoyl)benzyl-3-p-methoxybenzyluridine (8c) (Scheme 7). A mixture of 8c (100 mg, 0.179 mmol) and Pd/C (30.0 mg) was stirred at room temperature under an H2 atmosphere. After 48 h, the mixture was filtered using a membrane filter (Millex-LH, 0.45 μm), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl3/MeOH (100:1 to 50:1) to give 3-p-methoxybenzyl-5-(1,2-diphenylethyl)uridine (10, 43.9 mg, 45%) and 3-p-methoxybenzyl-5-(2-hydroxy-1,2-diphenylethyl)uridine (11, 34.1 mg, 34%).

3-p-Methoxybenzyl-5-(1,2-diphenylethyl)uridine (10). A colorless foam. 1H-NMR (DMSO-d6) 8.26 and 8.20 (each s, 1H, 6-H), 7.34–7.18 (m, 12H, C6H5 × 2 and o-PMB), 6.80 (d, J = 6.8 Hz, m-PMB), 5.81 (d, J = 4.1 Hz, 1H, 1'-H), 5.48–5.39 (m, 4H, CH2), 5.12–5.08 (m, 1H, OH), 4.89 (s, 2H, CH2), 4.27–4.21 (m, 1H, 2'-H), 4.09–4.00 (m, 2H and 3'-H), 3.93–3.90 (m, 1H, 4'-H), 3.69 (s, 3H, CH3), 3.40–3.35 (m, 2H, 5'-H); MS (EI) m/z 544 (M+, 2%), 453 (16), 321 (86), 121 (100), 91 (8); HRMS (EI) calcd. for C31H32N2O7 (M+): 544.2210; found: 544.2197.

3-p-Methoxybenzyl-5-(2-hydroxy-1,2-diphenylethyl)uridine (11). Colorless oil. 1H-NMR (DMSO-d6) 8.26 and 8.19 (each s, 1H, 6-H), 7.34–7.04 (m, 12H, C6H5 × 2 and o-PMB), 6.80 (d, J = 6.8 Hz, m-PMB), 5.81 (d, J = 3.9 Hz, 1H, 1'-H), 5.46 (brs, 1H, OH), 5.41 (brs, 1H, OH), 5.14–5.08 (m, 1H, OH), 4.82 (s, 2H, CH2), 4.27–4.21 (m, 1H, 2'-H), 4.09–4.03 (m, 2H, CH and 3'-H), 3.93–3.90 (m, 1H, 4'-H), 3.76–3.60 (m, 5H, CH and OH and CH3), 3.40–3.34 (m, 2H, 5'-H); MS (FAB, Gly) m/z 561 (M++H, 13%), 543 (7), 369 (5), 277 (14), 185 (100), 121 (33); HRMS (FAB, Gly) calcd. for C31H32N2O8 (M++H): 561.2159; found: 561.2228.

Pd/C(en)-catalyzed hydrogenation of 5-(α-benzoyl)benzyl-3-p-methoxybenzyluridine (8c) (Scheme 7). A mixture of 8c (100 mg, 0.179 mmol) and 10% Pd/C(en) (30.0 mg) was stirred at room temperature under an H2 atmosphere. After 48 h, the mixture was filtered using a membrane filter (Millex-LH, 0.45 μm), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl3/MeOH (100:1 to 50:1) to give 11 (63.6 mg, 63%) as a colorless oil.

5-(1,2-Diphenylethyl)uridine (12). According to the procedure for the removal of the PMB group of 5-bis(ethoxycarbonyl)methyluridine (8a), 12 (61 mg, 79%) was obtained as a colorless foam. 1H-NMR (DMSO-d6) 11.23 (s, 1H, 3-NH), 8.14 and 8.10 (each s, 1H, 6-H), 7.34–7.04 (m, 12H, C6H5 × 2 and o-PMB), 6.80 (d, J = 6.8 Hz, m-PMB), 5.81 (d, J = 3.4 Hz, 1H, 1'-H), 5.43 (d, J = 6.2 Hz, 2H, CH2), 5.36 (brs, 1H, OH), 5.36 (brs, 1H, OH), 5.12 (brs, 1H, OH), 4.24–4.10 (m, 3H, 2'-H and 3'-H and CH), 3.72–3.60 (m, 3H, 4'-H and 5'-H); MS (FAB, NBA) m/z 425 (M++H, 21%), 329 (8), 154 (100), 136 (69), 89 (21); HRMS (FAB, NBA) calcd. for C23H24N2O6 (M++H): 425.1634; found: 425.1705.

2,4-Dimethyl-7-ethoxycarbonyl-7-phenyl-2,4-diazabicyclo[4,1,0]heptane-3,5-dione (15a). (a) 5-Bromo-1,3-dimethyluracil (1a, 657 mg, 3.00 mmol) was added to a stirred solution of ethyl
phenylacetate (1.63 g, 9.90 mmol) in ethanolic NaOEt [prepared from Na (207 mg, 9.00 mmol) in absolute EtOH (30 mL)] and the mixture was stirred at room temperature for 10 h. The solvent was removed under reduced pressure, and the residue was dissolved in H2O (20 mL). The solution was neutralized with c. HCl, and the mixture was extracted with CHCl3. The extract was dried over MgSO4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl3 as the eluant and recrystallized from Et2O to give 15a (589 mg, 65%). m.p. 123.5–125 °C; UV λmax (EtOH) only end absorption; 1H-NMR (CDCl3) 7.48–6.98 (m, 5H, Ph), 4.15 (q, J = 7.0 Hz, 2H, CH2), 3.76 and 3.22 (each d, each J = 9.0 Hz, each 1H, 5 and 6-H), 3.25 and 2.76 (each s, each 3H, NMe), 1.18 (t, J = 7 Hz, 3H, CMe); 13C-NMR (CDCl3) 170.5, 165.6, 150.8, 130.7, 129.2, 128.8, 128.8, 62.3, 45.1, 36.3, 30.3, 27.2, 14.0; MS (EI) m/z 302 (M+, 13%), 303 (13), 256 (100), 228 (50), 227 (24), 199 (23) 143 (27); Anal calcd. for C16H18N2O4: C, 63.56; H, 6.00; N, 9.27%; found: C, 63.28; H, 6.00; N, 9.16; (b) 5-Bromo-1,3-dimethyluracil (1a) (657 mg, 3.00 mmol) was dissolved in a solution of ethyl phenylacetate (1.63 g, 9.90 mmol) and DBU (1.37 g, 9.00 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature for 4 days and then the solvent was removed under reduced pressure. The residue was treated as described above to give 15a (635 mg, 70%), which was identical to the product obtained above.

7-Cyano-1,4-dimethyl-7-phenyl-2,4-diazabicyclo[4,1,0]heptane-3,5-dione (15b). 5-Bromo-1,3-dimethyluracil (1a, 657 mg, 3.00 mmol) was added to a stirred solution of benzylcyanide (1.16 g, 9.90 mmol) in ethanolic NaOEt [prepared from Na (207 mg, 9.00 mmol) in absolute EtOH (30 mL)] and the mixture was stirred at room temperature for 10 min. The mixture was neutralized with Amberlite CG-50 (H+) and filtered. The ion exchanger was washed with EtOH. The combined filtrates were concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with chloroform as the eluant to give 15b (720 mg, 94%), which was recrystallized from CHCl3–Et2O. m.p. 134–135 °C; UV λmax (EtOH) only end absorption; νmax 2240 cm⁻¹ (CN); 1H-NMR (CDCl3) 7.68–7.06 (5H, m, Ph), 3.57 (1H, d, J = 8.5 Hz, 6-H), 3.27 and 3.24 (each 3H, each s, NMe), 3.02 (d, J = 8.5 Hz, 1H, 5-H); 13C-NMR (CDCl3) 162.9, 150.7, 131.3, 129.5, 129.1, 125.9, 114.7, 46.5, 35.6, 31.4, 28.0, 25.0; MS (EI), m/z 255 (M⁺, 70%), 198 (36), 170 (100), 169 (85); Anal calcd. for C14H13N3O4: C, 65.87; H, 5.13; N, 16.46%; found: C, 65.88; H, 5.12; N, 16.51.

2,4-Dimethyl-7,9-diphenyl-2,4-diazabicyclo[4,3,0]nonane-3,5,8-trione (16). 5-Bromo-1,3-dimethyluracil (1a) (657 mg, 3.00 mmol) was added to a stirred solution of dibenzylketone (2.08 g, 9.90 mmol) in ethanolic NaOEt [prepared from Na (207 mg, 9.00 mmol) in absolute EtOH (30 mL)] and the mixture was stirred at room temperature for 30 min. The mixture was neutralized with Amberlite CG-50 (H+) and filtered. The ion exchange resin was washed with EtOH. The combined filtrates were concentrated under reduced pressure, and the residue was purified by chromatography on silica gel with CHCl3 as the eluant to give 16 (638 mg, 61%), which was recrystallized from chloroform-ether. m.p. 220–221 °C; UV λmax (EtOH) 266 nm (ε 25,100 dm³mol⁻¹cm⁻¹); m/z 348 (M⁺, 52%), 208 (28), 180 (100); 1H-NMR (CDCl3) 7.70–7.07 (m, 10H, Ph), 5.06 (d, J = 8.0 Hz, 1H, 4a or 7a-H), 4.93 (d, J = 2.0 Hz, 1H, 5 or 7-H), 4.13 (dd, J = 8.5 Hz and 8.0 Hz, 1H, 4a or 7a-H), 3.95 (dd, J = 8.5, 2.0 Hz, 1H, 5 or 7-H), 2.73 and 3.29 (each s, each 3H, NMe); 13C-NMR (CDCl3) 166.4, 155.7, 151.2, 137.5, 134.7,
1,3-Dimethyluracil-6-(α-acetyl)acetic acid ethyl ester (17). (a) A solution of 5-bromo-1,3-dimethyluracil (1a, 2.20 g, 10.0 mmol) and ethyl acetoacetate (4.32 g, 33.0 mmol) in ethanolic NaOEt [prepared from Na (690 mg, 30.0 mmol) in absolute EtOH (100 mL)] was stirred for 3 days at room temperature. The mixture was evaporated under reduced pressure, and the residue was treated with H2O. The resulting precipitate was filtered off, and the mother liquor was extracted with CHCl₃. The extract was dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was treated with Et₂O and the resulting precipitate was filtered off. The combined precipitate was washed with Et₂O to afford the recovered (1a) (700 mg, 32%), which was identical to the authentic sample. The water layer was neutralized with c.HCl, and the mixture was extracted with CHCl₃. The extract was concentrated in vacuo, and the residue was purified by column chromatography on silica gel with CHCl₃ as the eluant to give 17 (1.66 g, 62%). m.p. 100–103 °C; UV λₘₐₓ(EtOH) 268 nm (ε 12,400 dm³ mol⁻¹ cm⁻¹); ¹H-NMR (CDCl₃) 13.10 (s, CH, 1H, deuterium exchangeable), 5.68 (s, 1H, 5-H), 4.32 (q, J = 7.5 Hz, 2H, CH₂), 3.37 and 3.26 (each s, each 3H, NMe), 2.04 (s, 3H, CMe), 1.28 (t, J = 7.5 Hz, 3H, CMe); MS (EI) m/z 268 (M⁺, 74%), 222 (32), 207 (54), 82 (32), 43 (100); Anal. calcd. for C₁₂H₁₆N₂O₅: C, 53.72; H, 6.01; N, 10.44%; found: C, 53.48; H, 6.12; N, 10.52; (b) To a stirred solution of 6-chloro-1,3-dimethyluracil (19) (349 mg, 2.00 mmol) and ethyl acetoacetate (859 mg, 6.60 mmol) in anhydrous DMF (5 mL) was added sodium hydride (60% in mineral oil) (240 mg, 6.00 mmol). The mixture was stirred at room temperature for 5 days, and the solvent was removed under reduced pressure. The residue was dissolved in H₂O (20 mL) and then washed with CHCl₃. The aqueous layer was neutralized with conc. HCl and extracted with CHCl₃. The extract was dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with CHCl₃ as the eluant to give 17 (311 mg, 58%), which was identical to the sample prepared above.

1,3,6-Trimethyluracil (18) (CAS: 13509-52-9). A mixture of the 1,3-dimethyluracil-6-(α-acetyl)acetic acid ethyl ester (2, 1.32 g, 4.92 mmol) and hydrobromic acid (47%) was refluxed for 1 h. The solvent was removed under reduced pressure, and the residue was treated with H₂O (30 mL). The suspension was extracted with CHCl₃, and the extract was dried over Na₂SO₄. The solvent was removed under reduced pressure to give 18 (743 mg, 98%), which was identical to the authentic sample.

3-p-Methoxybenzyluridine-6-(α-acetyl)acetic acid ethyl ester (20). To a stirred solution of 5-bromo-3-p-methoxybenzyluridine (7a, 1.33 g, 3.00 mmol) and ethyl acetoacetate (1.29 g, 9.90 mmol) in anhydrous DMF (30 mL) was added potassium t-butoxide (1.01 g, 9.00 mmol). The mixture was stirred at room temperature for 3 days, and the solvent was removed under reduced pressure. The residue was dissolved in H₂O (10 mL) and then washed with CHCl₃. The aqueous layer was neutralized with concentrated NaHSO₄ and extracted with CHCl₃. The extract was dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with CHCl₃–MeOH (150:1) as the eluant to give 20 as a light brown foam (946 mg, 64%). ¹H-NMR (CDCl₃) 13.19 (s, 1H, CH), 7.43 and 6.84 (each d, each J = 7.8 Hz,
each 2H, C6H4), 5.67 (d, 1H, J = 3.4 Hz, 5-H), 5.39 (d, J = 5.4 Hz, 1H, 1’-H), 5.37–5.00 (m, 4H, OH x 2, CH2), 4.90 (brd, J = 3.9 Hz, 1H, OH), 4.21–4.16 (m, 3H, 2’-H, CH2), 3.88 (m, 1H, 3’-H), 3.78 (s, 3H, CH3), 3.72 (m, 1H, 4’-H), 3.48 (m, 2H, 5’-H), 2.07 and 2.00 (each s, total 3H, CH3), 1.22 (brt, J = 7.1 Hz, 3H, CH3). MS (EI) m/z 492 (M+, 8%), 360 (32), 314 (18), 162 (15), 121 (100). HRMS (EI) calcd. for C23H28N2O10 (M+): 492.1744; found: 492.1756.

3-Benzylxymethyluridine-6-(α-acetyl)acetic acid ethyl ester (21a). To a stirred solution of 5-bromo-3-benzyloxymethyluridine (7b, 452 mg, 1.02 mmol) and ethyl acetoacetate (586 mg, 4.50 mmol) in anhydrous DMF (30 mL) was added potassium t-butoxide (337 mg 3.00 mmol). The mixture was stirred at room temperature for 3 days and the solvent was removed under reduced pressure. The residue was dissolved in H2O (10 mL) and then washed with CHCl3. The aqueous layer was neutralized with concentrated NaHSO4 and extracted with CHCl3. The extract was dried over Na2SO4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with CHCl3–MeOH (200:1) as the eluant to give 21a (242 mg, 48%) as a colorless oil. 1H-NMR (CDCl3) 12.91 (s, 1H, CH), 7.31 (m, 5H, C6H5), 5.75 (d, 1H, J = 3.1 Hz, 5-H), 5.54 (d, J = 5.9 Hz, 1H, 1’-H), 5.30 (s, 2H, CH2), 5.22 (brd, J = 4.4 Hz, 1H, OH), 5.10–5.07 (m, 1H, OH), 4.99–4.96 (m, 1H, OH), 4.61 (s, 2H, CH2), 4.21–4.15 (m, 3H, 2’-H and CH2), 4.02–3.99 (m, 1H, 3’-H), 3.62–3.58 (m, 1H, 4’-H), 3.49–3.39 (m, 2H, 5’-H), 2.01 and 1.97 (each s, total 3H, CH3), 1.17 (brt, J = 7.1 Hz, 3H, CH3); 13C-NMR (CDCl3) 177.3, 169.7, 161.9, 151.7, 128.4, 127.8, 127.5, 106.5, 106.2, 97.3, 94.7, 93.6, 84.2, 72.6, 72.5, 70.5, 68.9, 62.4, 61.7, 20.18, 14.0; MS (FAB, NBA) m/z 493 (M++H, 12%), 361 (29), 256 (6), 154 (100), 91 (41); HRMS (FAB, NBA) calcd. for C23H28N2O10 (M++H): 493.18218; found: 493.18141.

3-Benzylxymethyl-2’-deoxyuridine-6-(α-acetyl)acetic acid ethyl ester (21b). To a stirred solution of 5-bromo-3-p-methoxybenzyl-2’-deoxyuridine (7c, 297 mg, 0.700 mmol) and ethyl acetoacetate (0.290 mL, 2.32 mmol) in anhydrous DMF (5 mL) was added potassium t-butoxide (237 mg, 2.11 mmol). The mixture was stirred at room temperature for 3 days, and the solvent was removed under reduced pressure. The residue was dissolved in H2O (10 mL) and then washed with CHCl3. The aqueous layer was neutralized with concentrated NaHSO4 and extracted with CHCl3. The extract was dried over Na2SO4 and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel with CHCl3–MeOH (200:1) as the eluant to give 21b (141 mg, 42%) as a colorless oil. 1H-NMR (CDCl3) 13.09 (s, 1H, CH), 7.39–7.29 (m, 5H, C6H5), 5.82–5.76 (m, 1H, 5-H), 5.63–5.60 (m, 1H, 1’-H), 5.43 (s, 2H, CH2), 5.38 (brs, 1H, OH), 4.96 (brs, 1H, OH), 4.74 (s, 2H, CH2), 4.27 (q, J = 7.1 Hz, 2H, CH3), 3.92–3.86 (m, 1H, 3’-H), 3.80–3.74 (m, 1H, 4’-H), 3.62–3.40 (m, 2H, 5’-H), 2.08–1.96 (m, 5H, CH3 and 2’-H), 1.29 (brt, J = 7.0 Hz, 3H, CH3); MS (FAB, NBA) m/z 477 (M++H, 9%), 361 (29), 256 (6), 154 (100), 91 (31); HRMS (FAB, NBA) calcd. for C23H28N2O9 (M++H): 477.18728; found: 477.18841.

Uridine-6-(α-acetyl)acetic acid ethyl ester (22a). A mixture of 3-benzylxymethyluridine-6-(α-acetyl)acetic acid ethyl ester (21a, 100 mg, 0.203 mmol) and Pd/C (30.0 mg) in MeOH (1 mL) was stirred under H2 atmosphere at room temperature for 24 h. The mixture was filtered using a membrane filter (Millex-LH, 0.45 μm), and the filtrate was concentrated in vacuo. The residue was purified by
column chromatography on silica gel with CHCl$_3$–MeOH (40:1) as the eluant to give uridine-6-acetoacetic acid ethyl ester (22a, 59.0 mg, 78%) as a light brown oil. $^1$H-NMR (CDCl$_3$) 12.89 (s, 1H, CH), 11.42 (s, 1H, 3-NH), 5.66 (d, $J = 2.2$ Hz, 1H, 5-H), 5.64 (d, $J = 5.9$ Hz, 1H, 1'-H), 5.24–5.18 (m, 1H, OH), 5.12–5.07 (m, 1H, OH), 5.13–4.97 (m, 1H, OH), 4.17–4.11 (m, 1H, 2'-H), 4.10–3.57 (m, 6H, CH$_2$, 3'-H, 4'-H and 5'-H), 2.02 and 1.98 (each s, total 3H, CH$_3$), 1.18 (brt, $J = 7.1$ Hz, 3H, CH$_3$); $^{13}$C-NMR (CDCl$_3$) 176.5, 175.8, 169.5, 162.5, 105.8, 97.5, 93.8, 92.9, 84.4, 72.2, 70.1, 62.1, 61.2, 19.8, 13.7; MS (FAB, Gly) m/z 373 (M$^+$H, 5%), 277 (10), 270 (33), 184 (100), 115 (57); HRMS (FAB, Gly) calcd. for C$_{15}$H$_{20}$N$_2$O$_9$ (M$^+$H): 373.1169; found: 373.1251.

2'-Deoxyuridine-6-(α-acetyl)acetic acid ethyl ester (22b). A mixture of 3-benzyloxymethyl-2'-deoxyuridine-6-(α-acetyl)acetic acid ethyl ester (21b, 100 mg, 0.210 mmol) and Pd/C (30.0 mg) in MeOH (1 mL) was stirred under H$_2$ atmosphere at room temperature for 48 h. The mixture was filtered using a membrane filter (Millex-LH, 0.45 μm), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel with CHCl$_3$–MeOH (50:1) as the eluant to give 22b (70.3 mg, 94%) as a colorless foam. $^1$H-NMR (CDCl$_3$) 12.83 (s, 1H, CH), 11.35 (s, 1H, 3-NH), 5.73–5.70 (m, 1H, 5-H), 5.58–5.56 (m, 1H, 1'-H), 5.08–4.90 (m, 1H, OH), 4.54–4.48 (m, 1H, OH), 4.23–4.10 (m, 3H, CH$_2$ and 3'-H), 3.61–3.44 (m, 3H, 4'-H and 5'-H), 2.02–1.88 (m, 3H, CH$_3$), 1.23–1.06 (m, 3H, CH$_3$); MS (FAB, NBA) m/z 356 (M$^+$H, 9%), 241 (39), 195 (17), 154 (100); HRMS (FAB, NBA) calcd. for C$_{15}$H$_{20}$N$_2$O$_8$ (M$^+$H): 357.12978; found: 357.13060.

4. Conclusions

We have accounted for the diversity of the C–C bond formation reaction between 5-halogenouracil or 5-halogenouridine derivatives 1 and 7 and carbanions. The reactions of 5-halogenouracil and 5-halogenouridine derivatives 1 and 7 with active methylene compounds under basic conditions selectively gave 5-substituted uracil derivatives 2, 5 and 8 via the isolable 5,6-disubstituted 5,6-dihydrouracil derivatives 4, 4-diazabicyclo[4.1.0]heptane derivatives and 4-diazabicyclo[4.1.0]nonane 15 and 16 and 6-substituted uracil and uridine derivatives 17, 20 and 21, all of which were extremely dependent on the nature of the carbanions.

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References and Notes

1. Rideout, J.L.; Henry, D.W.; Beachen, L.M., III. Nucleotides and Their Biological Applications; Academic Press: New York, NY, USA, 1983.

2. Chu, C.K. Recent Advances in Nucleosides: Chemistry and Chemotherapy; Elsevier Sciences: Amsterdam, The Netherland, 2002.
3. Blackburn, G.M., Gait, M., Loakes, D., Williams, D.M., Eds. *Nucleic Acids in Chemistry and Biology*, 3rd ed.; RSC Publishing: Cambridge, UK, 2007.
4. Propst, C., Perun, T.J., Eds. *Nucleic Acid Targeted Drug Design*; Dekker: New York, NY, USA, 1992.
5. Zhang, L.-H., Xi, Z., Chattopadhyaya, J., Eds. *Medicinal Chemistry of Nucleic Acids*; Wiley: Hoboken, NJ, USA, 2011.
6. Tanaka, F.; Fukase, T.; Wada, H.; Fukushima, M. The History, Mechanism, and Clinical Use of Oral 5-Fluorouracil Derivatives Chemotherapeutic Agents. *Curr. Pharm. Biotechnol.* **2000**, *1*, 137–164.
7. Whitley, R.J. Antiviral Drug Development: The Road Less Taken. *Ann. Pharmacother.* **1996**, *30*, 967–971.
8. Agrofoglio, A.L.; Gillazeau, I.; Saito, Y. Palladium-Assisted Routes to Nucleosides. *Chem. Rev.* **2003**, *103*, 1875–1916.
9. Bergstrom, D.E. Organometallic Intermediates in the Synthesis of Nucleoside Analogs. *Nucleosides Nucleotides* **1982**, *1*, 1–34.
10. Rahim, S.G.; Trived, N.; Bogunovic-Batkehelor, M.V.; Hardy, G.W.; Mills, G.; Selway, J.W.T.; Snowden, W.; Littler, E.; Coe, P.L.; Basnak, I.; *et al.* Synthesis and Anti-Herpes Virus Activity of 2′-Deoxy-4′-thiopyrimidine Nucleosides. *J. Med. Chem.* **1996**, *39*, 789–795.
11. McGuigan, C.; Yarnold, C.J.; Jones, G.; Velasquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; de Clerc, E.; Balzarini, J. Potent and Selective Inhibition of Varicella-Zoster Virus (VZV) by Nucleoside Analogues with an Unusual Bicyclic Base. *J. Med. Chem.* **1999**, *42*, 4479–4484.
12. McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erischen, J.; Andrei, G.; Snoeck, R.; de Clerc, E.; Balzarini, J. Highly Potent and Selective Inhibition of Varicella-Zoster Virus by Bicyclic Furopyrimidine Nucleosides Bearing an Aryl Side Chain. *J. Med. Chem.* **2000**, *43*, 4993–4997.
13. Hirota, K.; Isobe, Y.; Kitade, Y.; Maki, Y. A Simple Synthesis of 5-(1-Alkenyl)uracil Derivatives by Palladium-Catalyzed Oxidative Coupling of Uracils With Olefins. *Synthesis* **1987**, 495–496.
14. Hirota, K.; Kitade, Y.; Kanbe, Y.; Isobe, Y.; Maki, Y. Facile Synthesis of Thymidine Derivatives by Cross-Coupling of 5-Halogenouridine Derivatives with Trimethylaluminum. *Synthesis* **1993**, 213–216.
15. Jones, S.S.; Reese, C.B.; Ubekawa, A. A Convenient Synthesis of 5-Methyluridine from Uridine. *Synthesis* **1982**, 259–260.
16. Reese, C.B.; Sanghvi, Y.S. Conversion of 2′-Deoxyuridine into Thymidine and Related Studies. *J. Chem. Soc. Chem. Commun.* **1983**, *16*, 877–879.
17. Reese, C.B.; Sanghvi, Y.S. The Synthesis of 5-Carboxymethylaminomethyluridine and 5-Carboxymethylaminomethyl-2-thiouridine. *J. Chem. Soc. Chem. Commun.* **1984**, 62–63.
18. Badman, T.G.; Reese, C.B. Reactions between Methiodides of Nucleoside Mannich Bases and Carbon Nucleophiles. *J. Chem. Soc. Chem. Commun.* **1987**, 1732–1734.
19. Scheit, K.H. Die Synthese der 5′-Diphosphate von 5-Methyl-uridin, 5-Hydroxymethyl-uridin und 3,5-Dimethyl-uridin. *Chem. Ber.* **1966**, *99*, 3884–3891.
20. Cline, R.E.; Fink, R.M.; Fink, K. Synthesis of 5-Substituted Pyrimidines via Formaldehyde Addition. *J. Am. Chem. Soc.* **1959**, *81*, 2521–2527.
21. Sajiki, H.; Yamada, A.; Yasunaga, K.; Tsunoda, T.; Mumen, F.; Hirota, K. A Novel Chemical Modification at the 5-Position of Uridine Derivatives. *Tetrahedron Lett.* **2003**, *44*, 2179–2181.

22. Monguchi, Y.; Yasunaga, K.; Tsunoda, T.; Ando, T.; Maegawa, T.; Hirota, K.; Sajiki, H. C–C Bond Formation on 5-Position of Uridine Ring by Morita-Baylis-Hillman Type Reaction. *Heterocycles* **2010**, *80*, 537–555.

23. Hirota, K.; Suematsu, M.; Kuwabara, Y.; Asao, T.; Senda, S. Novel C–C Bond Formation at the 5-Position of Uracils. Facile Synthesis of 5-Methoxycarbonylmethyluridine and 5-Carbamoylmethyluridine, Minor Component Nucleosides Derived from Transfer Ribonuclease. *J. Chem. Soc. Chem. Commun.* **1981**, *623*–*624*.

24. Bradshaw, T.K.; Huchinson, D.W. 5-Substituted Pyrimidine Nucleosides and Nucleotides. *Chem. Soc. Rev.* **1977**, *6*, 43–62.

25. Wataya, Y.; Negishi, K.; Hayatsu, H. Debromination of 5-Bromo-2'-deoxyuridine by Cysteine. Formation of Deoxouridine and S-[5-(2'-Deoxyuridy1)]cysteine. *Biochemistry* **1973**, *12*, 3992–3998.

26. Rork, G.S.; Pitman, I.H. Kinetic Study of the Dehalogenation of 5-Halo-5,6-dihydropyrimidines in Aqueous Solutions of Sodium Bisulfite. *J. Am. Chem. Soc.* **1975**, *97*, 5566–5572.

27. Sedor, F.A.; Jacobson, D.G.; Sander, E.G. Dehalogenation of 5-Bromouracil by Bisulfite Buffers. Kinetic Evidence for a Multistep Reaction Pathway. *J. Am. Chem. Soc.* **1975**, *97*, 5572–5577.

28. Wataya, Y.; Santi, D.V. A Secondary Isotope Effect in the Cysteine-promoted Dehalogenation of 5-Bromo-2'-deoxyuridine. Evidence for Transient 5,6-Dihydropyrimidine Intermediates. *J. Am. Chem. Soc.* **1977**, *99*, 4534–4536.

29. Pal, B.C. Reaction of 5-Chlorouracil Derivatives with Cysteine. *J. Am. Chem. Soc.* **1978**, *100*, 5170–5174.

30. Inoue, H.; Ueda, T. Synthesis of Orotidine from Uridine. *Chem. Pharm. Bull.* **1971**, *19*, 1743–1744.

31. Senda, S.; Hirota, K.; Asao, T. The Mechanisms of Formation and Reactions of 6-Cyano-1,3-dimethyluracil. *Tetrahedron Lett.* **1973**, *14*, 2647–2650.

32. Senda, S.; Hirota, K.; Asao, T. Pyrimidine Derivatives and Related Compounds. XXV. Synthesis of 6-Cyanouracil Derivatives and the Conversion of 6-Cyano-1,3-dimethyluracil to 5-Cyano Compound. *J. Org. Chem.* **1975**, *40*, 353–356.

33. Inoue, H.; Saito, N.; Ueda, T. Reaction of 5-Bromouridine Derivatives with Dimethyl Malonate Carbanion. A Novel Entry to the Synthesis of Uridine-5-acetic Acids. *Chem. Pharm. Bull.* **1986**, *34*, 4585–4589.

34. Hirota, H.; Sajiki, H.; Maki, Y.; Inoue, H.; Ueda, T. Diversity of the C–C Bond Formation in the Reaction of a 5-Bromouracil Derivative with Carbanions. *J. Chem. Soc. Chem. Commun.* **1989**, *1659*–*1660*.

35. Akiyama, T.; Nishimoto, H.; Ozaki, S. The Selective Protection of Uridine with a p-Methoxybenzyl Chloride: A Synthesis of 2'-O-Methyluridine. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3356–3357.

36. Anderson, H.J.; Groves, J.K. A Protecting Group for the Pyrrole Nitrogen. *Tetrahedron Lett.* **1971**, *34*, 3165–3170.

37. Brown, T.; Jones, J.H.; Richard, J.D. Further Studies on the Protection of Histidine Side Chains in Peptide Synthesis: The Use of the π-Benzyl oxymethyl Group. *J. Chem. Soc. Perkin Trans. 1* **1982**, *1553*–*1558*. 
38. Sajiki, H.; Hattori, K.; Hirota, K. Easy and Partial Hydrogenation of Aromatic Carbonyls to Benzyl Alcohols using Pd/C(en)-Catalyst. *J. Chem. Soc. Perkin Trans. I* 1998, 4043–4044.

39. Sajiki, H.; Hattori, K.; Hirota, K. Pd/C(en)-catalyzed Regioselective Hydrogenolysis of Terminal Epoxides to Secondary Alcohols. *Chem. Commun.* 1999, 1041–1042.

40. Hattori, K.; Sajiki, H.; Hirota, K. Pd/C(en)-Catalyzed Chemoselective Hydrogenation with Retention of the N-Cbz Protective Group and its Scope and Limitations. *Tetrahedron* 2000, 56, 8433–8441.

41. Hattori, K.; Sajiki, H.; Hirota, H. The Undesirable Lability of tert-Butyldimethylsilyl Ethers under Pd/C-Catalyzed Hydrogenation Conditions and Solution of the Problem by Using a Pd/C(en) Catalyst. *Tetrahedron Lett.* 2000, 41, 5711–5714.

42. Sajiki, H.; Hattori, K.; Hirota, K. Highly Chemoselective Hydrogenation with Retention of the Epoxide Function Using a Heterogeneous Pd/C-Ethylenediamine Catalyst and THF. *Chem. Eur. J.* 2000, 6, 2200–2204.

43. Hattori, K.; Sajiki, H.; Hirota, K. Chemoselective Control of Hydrogenation among Aromatic Carbonyl and Benzyl Alcohol Derivatives Using Pd/C(en) Catalyst. *Tetrahedron* 2001, 57, 4817–4824.

44. Hattori, K.; Sajiki, H.; Hirota, K. Undesirable Deprotection of O-TBDMS Groups by Pd/C-Catalyzed Hydrogenation and Chemoselective Hydrogenation Using a Pd/C(en) Catalyst. *Tetrahedron* 2001, 57, 2109–2114.

45. Maegawa, T.; Fujita, Y.; Sakurai, A.; Akashi, A.; Sato, M.; Oono, K.; Sajiki, H. Pd/C(en) Catalyzed Chemoselective Hydrogenation in the Presence of Aryl Nitriles. *Chem. Pharm. Bull.* 2007, 55, 837–839.

46. Sajiki, H.; Hirota, K. Formation of Pd/C-ethylenediamine Complex [Pd/C(en)] and Its application to Selective Hydrogenations. *J. Synth. Org. Chem. Jpn.* 2001, 59, 109–120.

47. Thiellier, H.P.M.; Koomen, G.J.; Pandit, U.K. Unconventional Nucleotide Analogues: Reaction of Carbenes with Uracil and Uridine Derivatives. *Tetrahedron* 1977, 33, 1493–1500.

48. Tanaka, H.; Hayakawa, H.; Haraguchi, K.; Miyasaka, T. Introduction of an Azido Group to the C-6 Position of Uridine by the Use of a 6-Iodouridine Derivative. *Nucleosides Nucleotides* 1985, 6, 461–469.

49. Satoh, K.; Tanaka, H.; Andoh, A.; Miyasaka, T. Photochemical Synthesis of 6-Aryluridines. *Nucleosides Nucleotides* 1986, 6, 461–469.

50. Nagamatsu, T.; Koga, M.; Yoneda, F. Synthesis and Properties of 2,3,4,8-Tetrahydro-2,4-dioxopyrido[2,3-d]pyrimidines (5-Deazalumazines) and Their Bis-compounds. *Chem. Pharm. Bull.* 1984, 32, 1699–1708.

51. Olmstead, W.N.; Bordwell, F.G. Ion-pair Association Constants in Dimethyl Sulfoxide. *J. Org. Chem.* 1980, 45, 3299–3305.

52. Arnett, E.M.; Maroldo, S.G.; Schilling, S.L.; Harrelson, J.A. Ion Pairing and Reactivity of Enolate Anions. 5. Thermodynamics of Ionization of β-Di- and Tricarbonyl Compounds in Dimethyl Sulfoxide Solution and Ion Pairing of Their Alkali Salts. *J. Am. Chem. Soc.* 1984, 106, 6759–6767.

53. Bordwell, F.G.; Harrelson, J.A., Jr. Acidities and Homolytic Bond Dissociation Energies of the α-C–H Bonds in Ketones in DMSO. *Can. J. Chem.* 1990, 68, 1714–1718.
54. Bordwell, F.G.; Fried, H.E. Acidities of the Hydrogen-carbon Protons in Carboxylic Esters, Amides, and Nitriles. *J. Org. Chem.* 1981, 46, 4327–4331.

55. Bordwell, F.G.; Bares, J.E.; Bartmess, J.E.; McCollum, G.J.; van der Puy, M.; Vanier, N.R.; Matthews, W.S. Carbon Acids. 12. Acidifying Effects of Phenyl Substituents. *J. Org. Chem.* 1977, 42, 321–325.

56. Bordwell, F.G. Equilibrium Acidities in Dimethyl Sulfoxide Solution. *Acc. Chem. Res.* 1988, 21, 456–463.

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