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N-Functionalization of uracil derivatives: synthesis of chiral 2-(3-methyl-5-nitro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)alkanoic acids and their methyl esters

Andrzej Gondela and Krzysztof Walczak*

Department of Organic Chemistry, Biochemistry and Biotechnology, Silesian University of Technology, Krzywoustego 4, 44-100 Gliwice, Poland

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Abstract—3-Methyl-5-nitro-1-(4-nitrophenyl)uracil has been obtained by regioselective arylation of uracil using 4-nitrofluorobenzene, followed by methylation at the nitrogen atom N-3 and subsequent nitration of the uracil ring. 3-Methyl-5-nitro-1-(4-nitrophenyl)uracil, which was treated with either certain amino acids methyl ester or free amino acids underwent an *ANRORC* type substitution reaction. Appropriate methyl 2-substituted alkanoates or alkanoic acids containing 3-methyl-5-nitrouracil parts were obtained in satisfactory yields. A similar reaction can be carried out using 5-cyano-3-methyl-1-(4-nitrophenyl)uracil as a substrate.
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1. Introduction

Synthetic analogues of natural biopolymers, such as nucleic acids and peptides, are promising candidates as both antisense and antigene drugs, as diagnostic and biological tools. The improved hybridization properties exhibited by oligonucleotides containing LNA (locked nucleic acids)[1] and peptide nucleic acids (PNAs)[2] are particularly interesting for such purposes. In particular, PNAs have become an important class of DNA-analogues as they show a strong binding affinity to complementary DNA or RNA by Watson–Crick base-paring.[3,4] However, they are not suitable substrates for enzymatic degradation due to the lack of a sugar-phosphate backbone replaced by a polyamide backbone. When DNA analogues are used as drugs, a number of issues have to be taken into consideration, for example, their cellular uptake, biological stability and the cellular enzyme susceptibility of their hybrids with nucleic acids.

The simple and easy synthetic methodologies are also important for their usefulness. This has led to the design and synthesis of a wide variety of oligonucleotides analogues.[5,6] The pyrimidine nucleosides and their analogues exhibited extremely diverse physiological activity. 5-Fluorouracil is an important anticancer agent widely used in oncology.[7] 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) is applied as a non-nucleoside reverse transcriptase inhibitor in HIV-infection therapy.[8] 5-Nitro-1-[3-(5-nitro-2-furan-2-yl)acryloyl]-uracil exhibits antitumour activity on leukaemia P388 cells.[9] An inhibition effect on macrophage RAW 264.7 of 1-(2-hydroxy-3-methoxypropyl)-5-nitrouracil was also reported.[10] The most common strategies for the alkylation of uracil are based on the nucleophilic substitution of a suitable alkylating agent by activated uracil (either in the form of anion or persilylated derivative).[11,12] Another approach is based on the Michael-type addition of uracil derivatives with an appropriate acceptor, for example, methyl acrylate or acrylonitrile.[13–15] It is known that 1,3-disubstituted uracil derivatives which possess an electron-withdrawing group such as a nitro or cyano at the 5-position are susceptible to the attack of *N*-centred nucleophiles according to the *ANRORC* mechanism (addition of nucleophile, ring opening, ring closure).[16–18]

2. Results and discussion

We herein report a simple method for the synthesis of chiral alkanoates and alkanoic acids possessing at the α-carbon atom a 5-substituted uracil moiety. As a source of chirality, we applied both α-amino acids and

* Corresponding author. Tel.: +48 32 237 17 92; fax: +48 32 237 20 94; e-mail: krzysztof.walczak@polsl.pl

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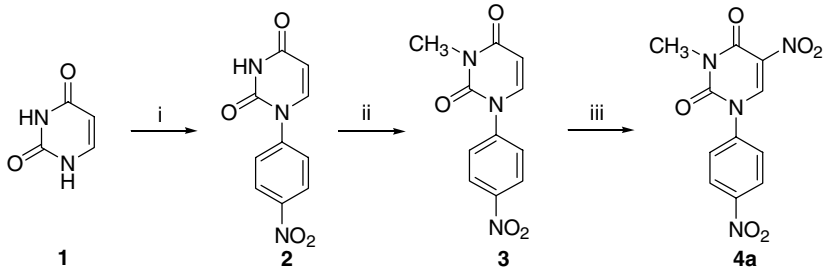
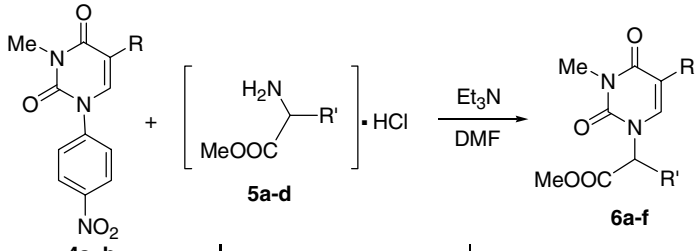


Scheme 1. Synthesis of 3-methyl-5-nitro-1-(4-nitrophenyl)uracil. Reagents and conditions: (i) 1-fluoro-4-nitrobenzene, DMSO, anhydrous K_2CO_3, 80 °C, 3 days, 87%; (ii) NaH, DMF, MeI, rt, 3 h, 87%; (iii) H_2SO_4, HNO_3 (d = 1.5 g/ml), −5 to 0 °C, 0.5 h, then rt, 2 h, 95%.

their methyl esters. The starting 5-nitrouracil derivative **4a** was prepared from uracil by arylation using 4-nitrofluorobenzene, followed by *N*-3 methylation with methyl iodide and *C*-5 nitration of uracil (Scheme 1). 3-Methyl-5-nitro-1-(4-nitrophenyl)uracil **4a** was obtained in 72% total yield, as calculated over three steps. This method gave better results in comparison with the reported synthesis of **4a** involving condensation of phenylurea with methyl 3,3-dimethoxypropanoate and ring closure under acidic conditions resulting in 1-phenyluracil.[19] The condensation step does not exceed 50%. 1-Phenyluracil has been subjected to *N*-3 methylation using methyl iodide and nitration, which occurred on both rings (at *C*-5 of the uracil ring and at C-4 of the benzene ring).[18] When **4a** was mixed with methyl amino acetate hydrochloride **5a** in the presence of equimolar amounts of triethyl amine in anhydrous DMF solution at room temperature, the appearance of the yellow coloured 4-nitroaniline was observed after a few minutes of reaction progress. From the reaction mixture, the desired methyl (3-methyl-5-nitro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetate **6a** was isolated in 58% yield (Scheme 2, Table 1, entry 1). Under the same conditions, **4a** was treated with several methyl esters of chiral amino acids yielding **6b–d** in moderate to good yields.

According to the reaction mechanism and under mild conditions, racemization during synthesis can be prevented. This was confirmed by the identical values of specific rotations when the reaction was repeated with methyl (2*R*)-aminopropanoate (entry 3). Under the same conditions, 5-cyano-3-methyl-1-(4-nitrophenyl)uracil[17] **4b** was treated with either methyl aminoacetate **5a** or methyl (2*S*)-aminopropanoate **5b** and gave the desired products **6e** and **f** in satisfactory yields (entries 5 and 6).



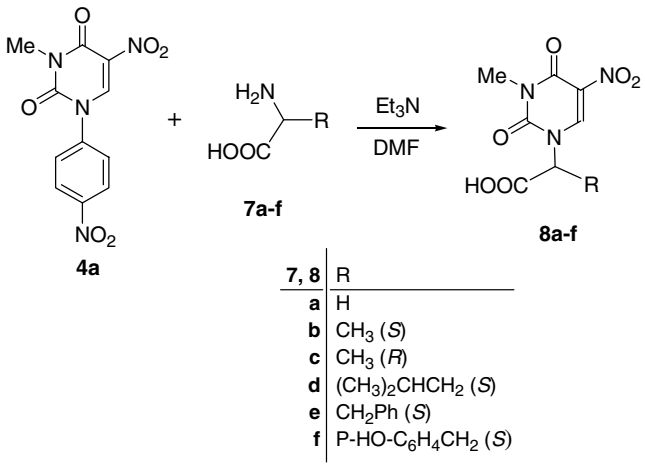
4	R
a	NO_2
b	CN

5, 6	R	R'
a	NO_2	H
b	NO_2	CH_3 (*S*)
c	NO_2	CH_3 (*R*)
d	NO_2	Bn (*S*)
e	CN	H
f	CN	CH_3 (*S*)

Scheme 2. Synthesis of the methyl esters of 2-(3-methyl-5-nitrouracil-1-yl)alkanoic acids and methyl esters of 2-(5-cyano-3-methyluracil-1-yl)alkanoic acids from suitable α-amino acids methyl esters.

Table 1. Yields and properties of 2-(3-methyl-5-substituted uracil-1-yl) alkanoic acids methyl esters

Entry	Product	R	R′	Yield [%]	Reaction time [h]	Mp [°C]	$[\alpha]_D$ (c 1.0, $CHCl_3$)
1	**6a**	NO_2	H	58	24	146–147	
2	**6b**		CH_3 (*S*)	61	48	111–113	+55.8
3	**6c**		CH_3 (*R*)	61	48	111–113	−55.2
4	**6d**		CH_2Ph (*S*)	76	72	Syrup	−22.1
5	**6e**	CN	H	83	24	Syrup	
6	**6f**		CH_3 (*S*)	50	24	138–140	+47



Scheme 3. Synthesis of 2-(3-methyl-5-nitrouracil-1-yl)alkanoic acids from suitable α-amino acids.

These results prompted us to use free amino acids instead of their methyl esters. In contrast to the esters, the amino group of the free amino acids was not reactive as a nucleophile, due to its protonation. The reaction was carried out in aqueous DMF in the presence of one equivalent excess of triethylamine necessary for the shift of betaine-triethylammonium salt equilibrium towards free amine (Scheme 3, Table 2). The reaction occurred rather slowly with the disappearance of the substrate detected after 48–72 h at room temperature, although the preliminary experiments gave the satisfactory results. The obtained yields varied in a range of 46–87%, which can probably be ascribed to the observed partial decomposition of the primary formed ring opened adduct.

3. Conclusion

In conclusion, a new method for preparation of 3-methyl-1-(4-nitrophenyl)-5-nitrouracil has been described. 3-Methyl-1-(4-nitrophenyl)-5-nitrouracil and its 5-cyano derivative treated either with amino acids or their methyl esters underwent the *ANRORC* type reaction to give the appropriate (3-methyl-5-nitro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)alkanoic acids or their methyl esters, respectively. The presence of functional groups in the heterocyclic system (nitro or cyano group) and in the acyclic part (carboxylic or ester group) gave access to their further derivatives. We believe that this method will expand the range of building blocks applied in PNA synthesis.

4. Experimental

Amino acids and the hydrochlorides of their methyl esters were obtained from Fluka and Aldrich. The solvents were dried according to standard procedures and freshly distilled prior to use. Organic solutions were evaporated below 40 °C in vacuo. Analytical samples were recrystallized from methanol and dried in vacuo. ^{1}H NMR spectra were recorded on a 300-MHz Varian Unity Inova spectrometer with tetramethylsilane as an internal standard. Optical rotation measurements were performed on a Perkin–Elmer 141 Polarimeter at the D sodium line at 25 °C. Melting points were determined in open capillary and are uncorrected. Mass spectra were recorded on GCMS Finningan MAT 95 mass spectrometer and HPLC MS Waters Thermabim Mass Detector.

4.1. 1-(4-Nitrophenyl)uracil 2

To a magnetically stirred suspension of uracil **1** (5.5 g, 49 mmol) in dimethyl sulfoxide (70 ml) warmed up to 80 °C, anhydrous potassium carbonate (3.5 g, 25.3 mmol) was added. After 30 min, 4-nitrofluorobenzene (8.4 g, 49.7 mmol) was added. The resulting suspension was stirred in an oily bath at 80 °C until the disappearance of uracil (3 days), after which the reaction mixture was poured onto an ice-water mixture (400 g). The precipitated crude product was filtered off, washed with water (10 ml) and dried on air. Recrystallization from the glacial acetic acid gave pure 1-(4-nitrophenyl)-uracil **2** in 87% yield (10.5 g); mp 306–308 °C. ^{1}H NMR (DMSO-d_6): δ (ppm) = 5.77 (d, 1H, J = 7.9 Hz, H-5), 7.75 (d, 2H, J = 8.9 Hz, H-2′, H-6′), 7.81 (d, 1H, J = 7.9 Hz, H-6), 8.34 (d, 2H, J = 8.9 Hz, H-3′, H-5′), 11.55 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 102.55, 124.28 (2C), 127.97 (2C), 144.11, 144.44, 146.46, 150.00, 163.52. Anal. Calcd for $C_{10}H_7N_3O_4$ (233.18): C, 51.51; H, 3.03; N, 18.02. Found: C, 51.39; H, 2.97; N, 17.89.

4.2. 3-Methyl-1-(4-nitrophenyl)uracil 3

To a solution of 1-(4-nitrophenyl)uracil **2** (5.83 g, 25 mmol) in anhydrous *N*,*N*-dimethylformamide (25 ml), sodium hydride (0.83 g, 27 mmol, 80% immersion in a mineral oil) was added in small portions. After 30 min, methyl iodide (1.70 ml, 3.82 g, 27 mmol) was added dropwise. Stirring was continued until decay of the substrate (TLC), after which the reaction mixture was poured onto a 100 g ice-water solution. The resulting precipitate was filtered off, washed with water and

Table 2. Yields and properties of 2-(3-methyl-5-nitrouracil-1-yl)alkanoic acids

Product	R′	Yield [%]	Reaction time [h]	Mp [°C]	$[\alpha]_D$ (c 1.0, MeOH)
8a	H	87	48	158–160	
8b	CH_3 (*S*)	58	48	185–188	+56.1
8c	CH_3 (*R*)	50	48	186–188	−55.8
8d	$(CH_3)_2CHCH_2$ (*S*)	46	48	176–178	+81.1
8e	CH_2Ph (*S*)	50	48	80–82	−90.0
8f	*p*-HO-$C_6H_4CH_2$ (*S*)	57	72	103–105	−13.0

dried in air. Crude product **3** (6.0 g) was recrystallized from methanol. Yield 5.4 g (87%); mp 194–195 °C (lit. mp 193–195 °C).[18] ^{1}H NMR ($CDCl_3$), δ (ppm) = 3.41 (s, 3H, CH_3N), 5.97 (d, 1H, J = 8.0 Hz, H-5), 7.33 (d, 1H, J = 8.0 Hz, H-6), 7.58 (d, 2H, J = 8.9 Hz, H-2′, H-6′), 8.37 (d, 2H, J = 8.9 Hz, H-3′, H-5′). ^{13}C NMR, ($CDCl_3$), δ (ppm) = 28.20, 103.56, 125.06 (2C), 127.33 (2C), 140.83, 144.40, 147.15, 150.56, 162.58.

4.3. 3-Methyl-5-nitro-1-(4-nitrophenyl)uracil 4a

3-Methyl-1-(4-nitrophenyl)uracil **3** (4.0g, 16.2 mmol) was dissolved in concentrated sulfuric acid (15 ml). The reaction mixture was cooled to −5 °C in an ice-bath after which fuming nitric acid (7.5 ml, d = 1.5) was added dropwise over 30 min while stirring. The cooling bath was then removed and stirring continued for 2 h at room temperature. The acidic solution was poured onto ice-water (250 g). The formed precipitate was filtered off and washed with water (100 ml) and methanol (10 ml) to a neutral pH of filtrate. Crude product **4a** was dried on air. Yield 4.5 g (95%); mp 196–198 °C (lit. mp 198–199 °C).[18] ^{1}H NMR (DMSO-d_6), δ (ppm) = 3.27 (s, 3H, CH_3), 7.83 (d, 2H, J = 8.7 Hz, H-2′, H-6′), 8.41 (d, 2H, J = 8.7 Hz, H-3′, H-5′), 9.29 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6), δ (ppm) = 28.36, 124.35 (2C), 126.08 (2C), 128.79, 143.02, 147.17, 147.41, 149.00, 154.42.

4.4. Synthesis of 2-(3-methyl-5-nitrouracil-1-yl)alkanoic methyl esters 6a–d from α-amino acids methyl esters 5a–d (general procedure)

To a solution of the hydrochloride of the α-amino acid methyl ester **5a**–**d** (1.1 mmol) in *N*,*N*-dimethylformamide (5 ml), equimolar amounts of triethylamine were added while stirring. After 30 min, 3-methyl-5-nitro-1-(4-nitrophenyl)uracil **4a** (1.0 mmol) was added to the reaction mixture. The resulting yellow mixture was stirred until the disappearance of the starting uracil (TLC, solvent system A: MeOH/$CHCl_3$ 1:9; B: n-C_6H_{14}/AcOEt 1:1 v/v; 24–73 h). The solvent was evaporated under reduced pressure and the resulting residue purified on the silica gel column using the suitable solvent system (noted below at the adequate compound). After recrystallization from methanol, an analytical sample was obtained.

4.4.1. Methyl 2-(3-methyl-5-nitrouracil-1-yl)acetate 6a. Yield 0.14 g (58%), eluent (n-C_6H_{14}/AcOEt 1:1); R_f = 0.26 (B); MS EI [M^+] = 243 (100). ^{1}H NMR ($CDCl_3$), δ (ppm) = 3.40 (s, 3H, N–CH_3), 3.84 (s, 3H, OCH_3), 4.78 (s, 2H, CH_2), 9.13 (s, 1H, H-6′). ^{13}C NMR ($CDCl_3$), δ (ppm) = 28.44, 50.11, 52.71, 125.03, 147.86, 149.30, 154.05, 167.08. Anal. Calcd for $C_8H_9N_3O_6$ (243.18): C, 39.51; H, 3.73; N, 17.28. Found: C, 39.39; H, 3.92; N, 17.09.

4.4.2. Methyl (*S*)-(+)-2-(3-methyl-5-nitrouracil-1-yl)propionate 6b. Yield 0.16 g (61%), eluent (n-C_6H_{14}/AcOEt 1:1); R_f = 0.55 (B); MS EI [M^+] = 257 (86). ^{1}H NMR ($CDCl_3$), δ (ppm) = 1.77 (d, 3H, J = 7.2 Hz, CH_3), 3.41 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 5.38 (q, 1H, J = 7.2 Hz, CH), 8.77 (s, 1H, H-6′). ^{13}C NMR ($CDCl_3$), δ (ppm) = 16.44, 29.12, 53.61, 55.79, 125.75, 144.25, 149.66, 153.93, 169.78. Anal. Calcd for $C_9H_{11}N_3O_6$ (257.20): C, 42.03; H, 4.31; N, 16.34. Found: C, 42.19; H, 4.43; N, 16.09.

4.4.3. Methyl (*R*)-(−)-2-(3-methyl-5-nitrouracil-1-yl)propionate 6c. Yield 0.16 g (61%), eluent (n-C_6H_{14}/AcOEt); R_f = 0.55 (B); MS EI [M^+] = 257 (27). Anal. Calcd for $C_9H_{11}N_3O_6$ (257.20): C, 42.03; H, 4.31; N, 16.34. Found: C, 42.18; H, 4.20; N, 16.24.

4.4.4. Methyl (*S*)-(−)-3-phenyl-2-(3-methyl-5-nitrouracil-1-yl)propionate 6d. Prepared from methyl L-β-phenylalaninate hydrochloride **5d** (0.43 g, 2.0 mmol), triethylamine (0.20 g, 2.0 mmol) and 3-methyl-5-nitro-1-(4-nitrophenyl)uracil **4a** (0.29 g, 1.0 mmol). Yield 0.25 g (76%) semicrystal material, eluent (MeOH/$CHCl_3$, 1:9) R_f = 0.47 (A); ^{1}H NMR ($CDCl_3$), δ (ppm) = 3.26 (s, 3H, NCH_3), 3.33 (dd, 1H, J = 10.2 Hz, J = 14.7 Hz, CH_{2a}), 3.58 (dd, 1H, J = 5.4 Hz, J = 14.7 Hz, CH_{2b}), 3.86 (s, 3H, OCH_3), 5.51 (dd, 1H, J = 5.4 Hz, J = 10.2 Hz, CH), 7.10–7.13 (m, 2H, Ar), 7.24–7.36 (m, 3H, Ar), 8.48 (s, 1H, H-6′). ^{13}C NMR ($CDCl_3$), δ (ppm) = 29.08, 36.04, 53.65, 61.48, 125.12, 128.24, 128.87 (2C), 129.51 (2C), 134.02, 145.24, 149.59, 153.81, 168.24. Anal. Calcd for $C_{15}H_{15}N_3O_6$ (333.30): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.39; H, 4.40; N, 12.44.

4.5. Synthesis of 2-(5-cyano-3-methyluracil-1-yl)alkanoic acids methyl esters 6e,f from α-amino acids methyl esters 5a and b (general procedure)

The hydrochloride of the α-amino acid methyl ester (2.0 mmol) and an equimolar quantity of triethylamine was magnetically stirred in *N*,*N*-dimethylformamide (2 ml) at room temperature for 30 min, after which 5-cyano-3-methyl-1-(4-nitrophenyl)uracil (1.0 mmol) was added. The resulting yellow mixture was stirred until the decay of the starting uracil (TLC, solvent system A: MeOH/$CHCl_3$ 1:9; B: n-C_6H_{14}/AcOEt 1:1 v/v). The solvent was evaporated under reduced pressure and the resulting residue purified on a silica gel column using the appropriate eluent (indicated at the adequate compound). After recrystallization from methanol, analytical sample was obtained.

4.5.1. Methyl 2-(5-cyano-3-methyluracil-1-yl)acetate 6e. Yield 0.2 g (83%) semicrystal, eluent (n-C_6H_{14}/AcOEt, 1:1); R_f = 0.28 (B). ^{1}H NMR ($CDCl_3$), δ (ppm) = 3.36 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 4.63 (s, 2H, CH_2), 7.99 (s, 1H, H-6′). ^{13}C NMR ($CDCl_3$), δ (ppm) = 28.73, 50.45, 53.34, 89.88, 113.09, 149.90, 150.79, 159.30, 167.20. Anal. Calcd for $C_9H_9N_3O_4$ (223.19): C, 48.43; H, 4.07; N, 18.83. Found: C, 48.22; H, 3.96; N, 18.64.

4.5.2. Methyl (*S*)-(+)-2-(5-cyano-3-methyluracil-1-yl)propionate 6f. Yield 0.12 g (50%), eluent (n-C_6H_{14}/AcOEt, 1:1); R_f = 0.56 (B); MS CI [M+1]$^+$ = 238 (100). ^{1}H NMR ($CDCl_3$), δ (ppm) = 1.70 (d, 3H, J = 7.5 Hz, CH_3) 3.38 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 5.33 (q, 1H, J = 7.5 Hz, CH), 7.95 (s, 1H, H-6′). ^{13}C NMR

($CDCl_3$), δ (ppm) = 16.65, 28.99, 53.64, 55.39, 90.26, 113.26, 148.02, 150.15, 158.89, 170.12. Anal. Calcd for $C_{10}H_{11}N_3O_4$ (237.22): C, 50.63; H, 4.67; N, 17.71. Found: C, 50.38; H, 4.47; N, 17.57.

4.6. Synthesis of 2-(3-methyl-5-nitrouracil-1-yl)alkanoic acids 8a–f from α-amino acids 7a–f (general procedure)

The suitable α-amino acid **7a**–**f** (2.0 mmol) was dissolved in water (1.0 ml) and an equimolar amount of triethylamine added (2 mmol). The mixture was stirred at ambient temperature for 30 min and then 3-methyl-5-nitro-1-(4-nitrophenyl)uracil **4a** (1.0 mmol) and DMF (3.0 ml) were added. During the reaction, triethylamine (1.0 mmol), which was necessary for the shift of betaine-triethylammonium salt equilibrium towards the free amine, was periodically added via syringe. The resulting yellowish-brown mixture was stirred until the decay of the substrate (48–72 h, TLC, MeOH/$CHCl_3$, 20:80). The solvents were evaporated under reduced pressure, and the resulting residue diluted in water (10 ml), acidified with 5% aq HCl and decolourized with charcoal. Water was evaporated under reduced pressure and the yellow residue purified on a silica gel column using the mixture of MeOH and $CHCl_3$ (1:1) as eluent (System A). After recrystallization from methanol, an analytical sample was obtained.

4.6.1. 2-(3-Methyl-5-nitrouracil-1-yl)acetic acid 8a. Yield 0.2 g (87%); R_f = 0.38 (A). ^{1}H NMR (DMSO-d_6), δ (ppm) = 3.22 (s, 3H, NCH_3), 4.36 (s, 2H, CH_2), 9.21 (s, 1H, H-6′), OH—not observed. ^{13}C NMR (DMSO-d_6), δ (ppm) = 28.20, 52.61, 123.76, 149.70, 149.78, 154.37, 169.08. Anal. Calcd for $C_7H_7N_3O_6$ (229.15): C, 36.69; H, 3.08; N, 18.34. Found: C, 36.97; H, 3.06; N, 18.67.

4.6.2. (*S*)-(+)-2-(3-Methyl-5-nitrouracil-1-yl)propionic acid 8b. Yield 0.14 g (58%); R_f = 0.58 (A); MS ESI $[M+1]^+$ = 244 (14). ^{1}H NMR (DMSO-d_6), δ (ppm) = 1.54 (d, 3H, J = 7.2 Hz, CH_3), 3.22 (s, 3H, N–CH_3), 5.03 (q, 1H, J = 7.2 Hz, CH), 9.07 (s, 1H, H-6′), OH—not observed. ^{13}C NMR (DMSO-d_6), δ (ppm) = 17.10, 28.38, 45.11, 57.65, 124.20, 147.52, 149.69, 154.18, 171.57. Anal. Calcd for $C_8H_9N_3O_6$ (243.18): C, 39.51; H, 3.73; N, 17.28. Found: C, 39.37; H, 3.46; N, 17.07.

4.6.3. (*R*)-(−)-2-(3-Methyl-5-nitrouracil-1-yl)propionic acid 8c. Yield 0.12 g (50%); R_f = 0.58 (A). Anal. Calcd for $C_8H_9N_3O_6$ (243.18): C, 39.51; H, 3.73; N, 17.28. Found: C, 39.17; H, 3.44; N, 16.97.

4.6.4. (*S*)-(+)-4-Methyl-2-(3-methyl-5-nitrouracil-1-yl)pentanoic acid 8d. Yield 0.13 g (46%); R_f = 0.16 (MeOH/$CHCl_3$, 2:8). ^{1}H NMR (DMSO-d_6), δ (ppm) = 0.88 (d, 3H, J = 6.6 Hz, CH_3), 0.89 (d, 3H, J = 6.6 Hz, CH_3), 1.44–1.58 (m, 1H, CH), 1.76–2.00 (m, 2H, CH_2), 3.22 (s, 3H, N–CH_3), 5.03 (dd, 1H, J = 4.5 Hz, J = 10.5 Hz, CH), 9.01 (s, 1H, H-6′), OH—not observed. ^{13}C NMR (DMSO-d_6), δ (ppm) = 21.30, 22.99, 24.43, 28.47, 48.62, 59.88, 124.25, 147.41, 150.10, 154.04, 171.50. Anal. Calcd for $C_{11}H_{15}N_3O_6$ (285.26): C, 46.32; H, 5.30; N, 14.73. Found: C, 46.55; H, 5.61; N, 14.45.

4.6.5. (*S*)-(−)-3-Phenyl-2-(3-methyl-5-nitrouracil-1-yl)propionic acid 8e. Yield 0.15 g (50%); R_f = 0.81 (A). ^{1}H NMR (DMSO-d_6), δ (ppm) = 3.17 (s, 3H, N–CH_3), 3.37 (dd, 1H, J = 9.9 Hz, J = 14.1 Hz, CH_{2a}), 3.47 (dd, 1H, J = 5.7 Hz, J = 14.1 Hz, CH_{2b}), 5.41 (dd, 1H, J = 5.7 Hz, J = 9.9 Hz, CH), 7.16–7.32 (m, 5H, Ar), 9.06 (s, 1H, H-6′), 13.4 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6), δ (ppm) = 28.38, 34.93, 63.21, 124.36, 126.92, 128.59 (2C), 129.07 (2C), 136.47, 147.71, 149.18, 153.66, 169.26. Anal. Calcd for $C_{14}H_{13}N_3O_6$ (319.27): C, 52.67; H, 4.10; N, 13.16. Found: C, 52.95; H, 4.50; N, 12.88.

4.6.6. (*S*)-(−)-3-(4-Hydroxyphenyl)-2-(3-methyl-5-nitrouracil-1-yl)propionic acid 8f. Yield 0.19 g (57%); R_f = 0.81 (A). ^{1}H NMR (DMSO-d_6), δ (ppm) = 3.14 (s, 3H, N–CH_3), 3.24 (d, 1H, J = 5.4 Hz, CH_2), 5.23 (d, 1H, J = 5.4 Hz, CH), 6.62 (d, 2H, J = 8.7 Hz, H-2′, H-6′), 6.96 (d, 2H, J = 8.7 Hz, H-3′, H-5′), 8.82 (s, 1H, H-6″), 9.43 (br s, 1H, OH–Ar), COOH—not observed. ^{13}C NMR (DMSO-d_6), δ (ppm) = 28.33, 35.81, 62.93, 115.26 (2C), 123.25, 127.15, 130.18 (2C), 148.25, 149.82, 153.89, 156.11, 169.99. Anal. Calcd for $C_{14}H_{13}N_3O_7$ (335.27): C, 50.16; H, 3.91; N, 12.53. Found: C, 49.85; H, 4.25; N, 12.17.

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