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1,4-Disila[6]radialene: Aktivierungsparameter der Sessel-Twist-Inversion und analytische Enantiomerentrennung der Twist-Konformeren

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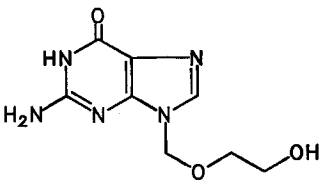
The reaction of 2,4-bis-*O*-trimethylsilyluracil (**2**) and 5-fluoro-2,4-bis-*O*-trimethylsilyluracil (**3**), respectively, with acetals **4a – m** of various aliphatic and aromatic aldehydes in the presence of trimethylsilyl trifluoromethanesulfonate (**5**) at −30°C gives the 1-(1′-alkoxyalkyl)- and 1-(1′-alkoxy-1′-phenylmethyl)-pyrimidines **6a – m** and the corresponding 5-fluorouracil derivatives **7a – f** in 40 – 91% yield.

The interest in the synthesis [2] and biological activity [3] of nucleoside derivatives has considerably increased in the last decade. These compounds may be used in the chemotherapy of cancer and especially in the treatment of virus infections. Indeed, the widely used virustatic agent acyclovir (**1**), which is employed against herpes infection, is a nucleoside analogue with a purine and a modified ribose moiety. The antiviral action of these substances or their metabolites is generally due to an inhibition of DNA polymerases. Thus, acyclovir is phosphorylated by thymidine kinases to give a triphosphate with an exceptionally enhanced affinity to viral DNA polymerases.



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In contrast, pyrimidine-derived acyclonucleosides have not yet been found to show a significant activity against virus diseases [2,4]. Kelley[5] explained this fact by the lower substrate affinity and inhibition properties of these compounds. However, a structure-activity relationship so far cannot be given for new antiviral agents. Therefore, new pyrimidine acyclonucleosides are still of great interest, also with regard to their anticancer activity, since it has been shown that various 5-fluorouracil derivatives are active against some malignant cell lines due to an inhibition of thymidylate synthetase by the formation of 5-fluorodeoxyuridine monophosphate or by incorporation of 5-fluorouridine monophosphate into RNA. In some malignant tumors the activity of uridine phosphates is enhanced[7]; therefore, 5-fluoro acylonucleosides may even exhibit a higher antitumor activity with simultaneously lower toxicity than 5-fluorouracil itself[7].

Acyclonucleosides are commonly synthesized by reaction of nucleic bases with α-chloromethyl ethers in the presence of strong bases or by reaction of persilylated purines or pyrimidines with α-halo or α-acetoxymethyl ethers catalyzed by various Lewis acids or bases[8]. 1′-Alkyl-acyclopyrimidines cannot be prepared by this method, but there are a few examples for the synthesis of 1′-alkyl-substituted acyclonucleosides, e. g. by the oxidative cleavage of the pentose moiety in cyclic nucleosides[9], a Michael-type reaction of α,β-unsaturated carbonyl compounds with uracil[10] or the $SnCl_4$-catalyzed reaction of acetales and acylales with persilylated purine and pyrimidines[11]. These procedures, however, have only a limited scope of application.

In this paper we describe a new and highly efficient procedure for the synthesis of 1-(1′-alkoxyalkyl)- and 1-(1′-alkoxy-1′-phenylmethyl)uracil derivatives **6a – m** and the corresponding 5-fluorouracil derivatives **7a – f**, which can be carried out also on a large scale. The reaction of 2,4-bis-*O*-trimethylsilyluracil (**2**) and its 5-fluoro derivative **3**[12] with acetals **4a – m** of various aliphatic and aromatic aldehydes in dichloromethane at −30°C affords the desired products **6a – m** and **7a – f**, respectively, after addition of 1.1 equivalents of trimethylsilyl trifluoromethanesulfonate (TMS triflate) (**5**) in 40 – 91% yield (Table 1). It is essential to maintain anhydrous conditions during the transformations; to obtain good yields, it is also advisable to work under argon or nitrogen.

The reaction is complete within 2 – 12 hours and then quenched by the addition of a 1:1 mixture of triethylamine and methanol. The products are purified by column chromatography or crystallization. The described transformations may also be carried out with catalytic amounts of TMS triflate (20 mol-%) if the reaction is performed at higher temperature (CH_2Cl_2, reflux), but the yields are usually lower.

There is some limitation with respect to the used acetals **4**. Thus, acetals of aliphatic and aromatic aldehydes can be employed. Even cyclic acetals such as 2-phenyl-1,3-dioxane react at −20 to 0°C to give **6m** after hydrolysis of the intermediately formed trimethylsilyl ether in 51% yield. Acyclopyrimidines of type **6m** are especially interesting because of the hydroxy group in the side chain. In nearly all transformations the yields of the 5-fluorouracil derivatives **7** are higher compared to those of the uracil derivatives **6**.

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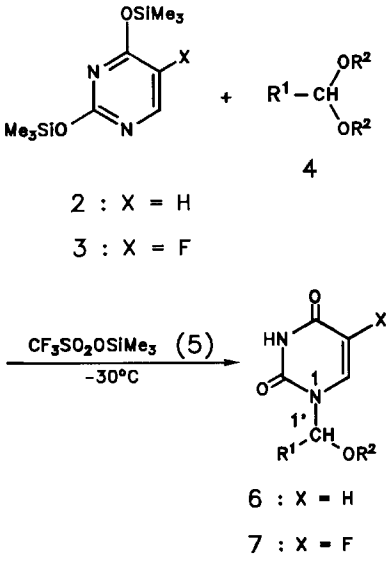
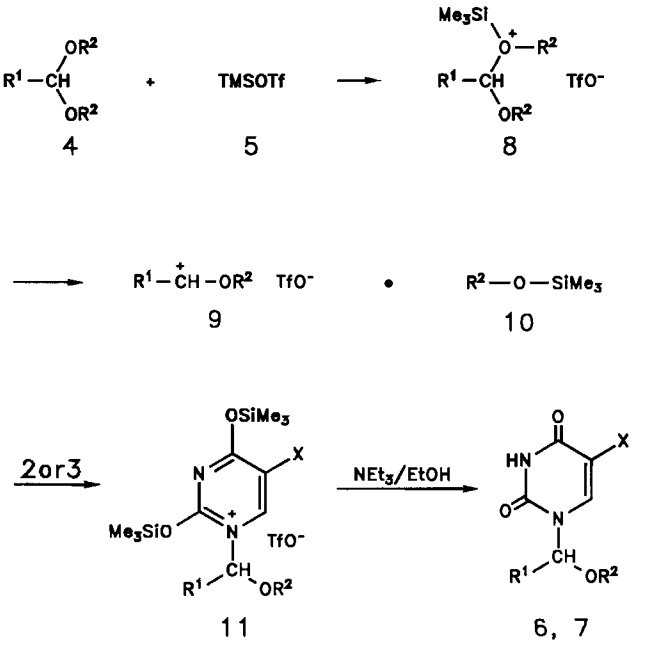


Table 1. Synthesis of acyclonucleosides **6** and **7**

Reaction of	Products	X	R^1	R^2	Yield %
2 with **4a**	**6a**	H	H	CH_3	74
4b	**6b**	H	CH_2OCH_3	CH_3	81
4c	**6c**	H	CH_2OBzl	CH_3	66
4d	**6d**	H	CH_2CH_2OBzl	CH_3	80
4e	**6e**	H	$[CH_2]_3OBzl$	CH_3	70
4f	**6f**	H	$CH_2CH_2CH_3$	CH_2CH_3	77
4g	**6g**	H	CH_2Br	CH_3	40
4h	**6h**	H	C_6H_5	CH_3	91
4i	**6i**	H	C_6H_4Br-*o*	CH_3	74
4k	**6k**	H	$CH_2CO_2CH_3$	CH_3	56
4l	**6l**	H	CH_2CH_2Cl	CH_2CH_3	56
4m	**6m**	H	C_6H_5	$[CH_2]_3OH$	51
3 with **4b**	**7a**	F	CH_2OCH_3	CH_3	83
4d	**7b**	F	CH_2CH_2OBzl	CH_3	71
4g	**7c**	F	CH_2Br	CH_2CH_3	71
4k	**7d**	F	$CH_2CO_2CH_3$	CH_3	81
4l	**7e**	F	CH_2CH_2Cl	CH_2CH_3	91
4n	**7f**	F	CH_2CH_2OBzl	$[CH_2]_3CO_2CH_3$	62

The acyclopyrimidine derivatives **7**, e.g. **7c** and **7f**, constitute a new class of potential antitumor agents, since 5-fluorouracil, a widely used antitumor drug [13], is bound to a cytostatic aldehyde. Thus, two active substances are combined here in one drug.

Studies on the mechanism of the reaction have not been made so far, but we assume that first an oxonium ion **8** is formed which can collapse to the carbenium ion **9** and the alkyl trimethylsilyl ether **10**. Nucleophilic addition of N-1 of **2** or **3** to **9** would provide **11**, which is stable at low temperature and transformed into **6** and **7**, respectively, by hydrolysis. Therefore, 1.2 equivalents of TMS triflate (**5**) are needed if the reaction is performed at −30°C. At higher temperature (40°C), the reaction of **2** and **3**, respectively, with **9** leads directly to **6** and **7** with regeneration of the catalyst **5**. Therefore, under these conditions only 20 mol-% of **5** must be added.



The structures of **6** and **7** have been determined mainly by ^{1}H- and ^{13}C-NMR spectroscopy. The resonance lines for 1′-H in the 1′-alkyl-substituted compounds **6a**–**6g**, **k**, **l** and **7a**–**f** are observed at $\delta = 5.6-5.8$ and for 1′-H in the 1′-phenyl-substituted analogues **6h**, **i**, **m** at $\delta = 6.9-7.0$. Noteworthy, the signals for 1′-H in the 5-fluoroacyclonucleosides **7a**–**f** appear as a doublet with $J \approx 2$ Hz, due to coupling with the fluoro atom. The signals for C-1′ in **6a**–**m** and **7a**–**f** are found at $\delta = 77-87$. The chemical shifts of the other ^{13}C-NMR signals for the pyrimidine moiety are in agreement with those described by Ogilvie[14] for related compounds.

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Experimental

Melting points: Mettler FP 61 (uncorrected values). – IR: Bruker IFS 25,– UV: Varian Cary 219, Perkin-Elmer Lambda 2, Perkin-Elmer Lambda 9. – ^{1}H and ^{13}C NMR: Varian FT-80 A, XL 200, VXR 200, VXR 500 (internal TMS); multiplicities were determined with the APT pulse sequence. – MS: Varian MAT 311A; high resolution: Varian MAT 731. – Elemental analyses were carried out at the analytical laboratory of Göttingen university. – The progress of all reactions was monitored by TLC (Macherey, Nagel & Co., DC-Fertigfolien SIL G/UV_{254}, 0.25 mm). Flash chromatography and column chromatography were performed with Kieselgel of Fa. Woelm Pharma (0.032–0.063 mm). – Solvents used for TLC and column chromatography were ethyl acetate/petroleum ether/methanol (5:5:0.6) (A), *tert*-butyl methyl ether/petroleum ether (2:1) (B), dichloromethane/petroleum ether/ethanol (10:3:1) (C), dichloromethane/petroleum ether/ethanol (20:5:1) (D). – It is essential to use pure substrates, otherwise decomposition and a considerable decrease in yield was observed.

Synthesis of Acyclonucleosides of Uracil and 5-Fluorouracil. – General Procedure: To a solution of bistrimethylsilyluracil **2** (512

mg, 2.00 mmol) and 5-fluorobistrimethylsilyluracil **3** (548 mg, 2.00 mmol), respectively, and 1.2 equivalents of the acetal **4** in 5 ml of anhydrous dichloromethane under argon at −30°C was added dropwise with stirring trimethylsilyl trifluoromethanesulfonate (**8**) (0.40 ml, 2.20 mmol). After 2−12 h of stirring at −30°C, the reaction was quenched by addition of 1 ml of a mixture of triethylamine/methanol (1:1). The reaction mixture was then filtered, if necessary, the solution concentrated and the residue purified by chromatography or crystallisation to give **6** and **7**, respectively.

(1'RS)-1-(1'-Methoxymethyl)uracil (**6a**): Reaction of **2** (512 mg, 2.00 mmol) with dimethoxymethane (**4a**) (183 mg, 2.40 mmol) according to the general procedure yielded 231 mg (74%) of **6a** as colourless crystals. – R_f = 0.13 (solvent A). – M.p. 159°C (ethyl acetate/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3170 cm^{-1}, 3110 (NH), 3058 (C=CH), 2976, 2950, 2882 (CH), 1734, 1682 (CO), 1630 (C=C), 1458, 1370 (CH). – UV (acetonitrile): λ_{max} (lg ε) = 257 nm (3.981). – ^{1}H NMR ([D$_6$]DMSO):δ = 3.25 (s, 3H, OCH_3), 4.98 (s, 2H, 1'-H_2), 5.56 (d, J = 8 Hz, 1H, 5-H), 7.64 (d, J = 8 Hz, 1H, 6-H), 11.20 (s, 1H, NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 55.9 (OCH_3), 77.5 (C-1'), 101.5 (C-5), 144.9 (C-6), 151.0 (C-2), 163.5 (C-4). – MS (70 eV): m/z (%) = 156 (7) [M^+], 141 (27) [$M^+ - CH_3$], 125 (2) [$M^+ - OCH_3$], 45 (100) [$M^+ - C_4H_3O_2N$].

$C_6H_8N_2O_3$ (156.1) Calcd. C 46.15 H 5.15
Found C 46.23 H 5.30

(1'RS)-1-(1',2'-Dimethoxyethyl)uracil (**6b**): Reaction of **2** (512 mg, 2.00 mmol) with 1,1,2-trimethoxyethane (**4b**) (288 mg, 2.40 mmol) according to the general procedure yielded 324 mg (81%) of **6b** as colourless crystals. – R_f = 0.44 (solvent A). – M.p. 93°C (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3182 cm^{-1}, 3066 (NH), 2996 (C=CH), 2956, 2932, 2890 (CH), 1704, 1694 (CO), 1628 (C=C), 1462, 1388 (CH). – UV (acetonitrile): λ_{max} (lg ε) = 259 nm (3.998). – ^{1}H NMR ($CDCl_3$): δ = 3.38 (2s, 6H, $2OCH_3$), 4.57 (d, J = 7 Hz, 2H, 2'-H_2), 5.72 (t, J = 7 Hz, 1H, 1'-H), 5.75 (d, J = 8 Hz, 1H, 5-H), 7.36 (d, J = 8 Hz, 1H, 6-H), 9.05 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 57.0, 59.6 (OCH_3), 72.4 (C-2'), 84.3 (C-1'), 102.8 (C-5), 139.9 (C-6), 151.5 (C-2), 163.9 (C-4). – MS (70 eV): m/z (%) = 200 (11) [M^+], 169 (4) [$M^+ - OCH_3$], 155 (100) [$M^+ - C_2H_5O$], 112 (87) [$C_4H_4O_2N^+$], 89 (14) [$M^+ - C_4H_3O_2N$].

$C_8H_{12}N_2O_4$ (200.2) Calcd. C 48.00 H 6.04 N 13.99
Found C 48.10 H 6.17 N 13.83

(1'RS)-1-(2'-Benzyloxy-1'-methoxyethyl)uracil (**6c**): Reaction of **2** (512 mg, 2.00 mmol) with 2-benzyloxy-1,1-dimethoxyethane (**4c**) (70 mg, 2.40 mmol) according to the general procedure yielded 365 mg (66%) of **6c** as colourless crystals. – R_f = 0.65 (solvent A). – M.p. 105°C (ethyl acetate/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3192 cm^{-1}, 3108 (NH), 3062 (C=CH), 2930, 2878 (CH), 1704, 1684 (CO), 1624 (C=C), 1418, 1392 (CH), 744, 700 (CH, Ar). – UV (acetonitrile): λ_{max} (lg ε) = 258 nm (4.010). – ^{1}H NMR ($CDCl_3$): δ = 3.12 (d, J = 7 Hz, 2H, 2'-H_2), 3.35 (s, 3H, OCH_3), 5.03 (s, 2H, Ph-CH_2), 5.60−5.78 (m, 2H, 5-H, 1'-H), 7.10−7.35 (m, 6H, C_6H_5, 6-H), 8.10 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 57.0 (OCH_3), 69.7 (C-2'), 73.6 (CH_2-Ph), 84.6 (C-1'), 102.6 (C-5), 127.7, 128.0, 128.5 (C-*o*, C-*m*, C-*p*), 137.2 (C-*i*), 139.9 (C-6), 151.4 (C-4), 163.8 (C-2). – MS (70 eV): m/z (%) = 276 (3) [M^+], 112 (84) [$C_4H_4NO_2^+$], 91 (100) [$C_7H_7^+$].

$C_{14}H_{16}N_2O_4$ (276.3) Calcd. C 60.86 H 5.84 N 10.14
Found C 60.72 H 6.02 N 10.21

(1'RS)-1-(3'-Benzyloxy-1'-methoxypropyl)uracil (**6d**): Reaction of **2** (512 mg, 2.00 mmol) with 3-benzyloxy-1,1-dimethoxypropane (**4d**) (500 mg, 2.40 mmol) according to the general procedure yielded 464 mg (80%) of **6d** as a colourless oil. – R_f = 0.18 (solvent E). – IR (film): $\tilde{\nu}$ = 3194 cm^{-1}, 3088 (NH), 3036 (C=CH), 2938, 2868 (CH), 1688, 1678 (CO), 1630 (C=C), 1422, 1380 (CH), 742, 700 (CH, Ar). – UV (acetonitrile): λ_{max} (lg ε) = 259 nm (4.073). – ^{1}H NMR ($CDCl_3$): δ = 2.05 (q, J = 7 Hz, 2H, 2'-H_2), 3.30 (s, 3H, CH_3), 3.55 (t, J = 7 Hz, 2H, 3'-H_2), 4.44 (s, 2H, Ph-CH_2), 5.72 (d, J = 6 Hz, 1H, 5-H), 5.80 (t, J = 7 Hz, 1H, 1'-H), 7.26 (s, 5H, C_6H_5), 7.26 (d, J = 6 Hz, 1H, 6-H), 9.25 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 35.4 (C-2'), 56.5 (OCH_3), 65.3 (C-3'), 73.1 (CH_2-Ph), 84.8 (C-1'), 103.1 (C-5), 127.7, 127.7, 128.4, 137.9 (C-*o*, C-*m*, C-*p*, C-*i*), 139.2 (C-6), 151.4 (C-2), 163.8 (C-4). – MS (70 eV): m/z (%) = 290 (1) [M^+], 179 (5) [$M^+ - C_4H_3O_2N$], 113 (5) [$C_4H_5O_2N^+$], 106 (14) [$C_7H_8O^+$], 91 (85) [$C_7H_7^+$], 69 (12) [$C_3H_3ON^+$], 43 (100) [CHON$^+$].

$C_{15}H_{18}N_2O_4$ (290.3) Calcd. C 62.06 H 6.25 N 9.65
Found C 61.99 H 6.34 N 9.62

(1'RS)-1-(4'-Benzyloxy-1'-methoxybutyl)uracil (**6e**): Reaction of **2** (512 mg, 2.00 mmol) with 4-benzyloxy-1,1-dimethoxybutane (**4e**) (540 mg, 2.40 mmol) according to the general procedure yielded 426 mg (70%) of **6e** as colourless crystals. – R_f = 0.64 (solvent A). – M.p. 65°C (ethyl acetate/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3520 cm^{-1}, 3194 (NH), 3962, 3034 (C=CH), 2938, 2862 (CH), 1690 (CO), 1630 (CO), 1630 (C=C), 1420, 1382 (CH), 740, 700 (CH, Ar). – UV (acetonitrile): λ_{max} (lg ε) = 260 nm (3.983). – ^{1}H NMR ($CDCl_3$): δ = 1.40−2.00 (m, 4H, 2'-H_2, 3'-H_2), 3.27 (s, 3H, OCH_3), 3.45 (t, J = 7 Hz, 2H, 4'-H_2), 4.45 (s, 2H, Ph-CH_2), 5.58 (t, J = 7 Hz, 1H, 1'-H), 5.80 (d, J = 8 Hz, 1H, 5-H), 7.25 (s, 5H, C_6H_5), 7.25 (d, J = 8 Hz, 1H, 6-H), 9.50 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 24.8 (C-2'), 31.9 (C-3'), 56.5 (OCH_3), 69.2 (C-4'), 72.8 (CH_2-Ph), 86.5 (C-1'), 103.2 (C-5), 127.5, 127.6, 128.3, 138.3 (C-*o*, C-*m*, C-*p*, C-*i*), 139.0 (C-6), 151.9 (C-2), 163.9 (C-4). – MS (70 eV): m/z (%) = 304 (0.4) [M^+], 273 (0.05) [$M^+ - OCH_3$], 193 (12) [$M^+ - C_4H_3NO_2$], 91 (100) [$C_7H_7^+$], 43 (7) [CHNO$^+$].

$C_{16}H_{20}N_2O_4$ (304.3) Calcd. C 63.14 H 6.62 N 9.20
Found C 63.00 H 6.54 N 9.20

(1'RS)-1-(1'-Ethoxybutyl)uracil (**6f**): Reaction of **2** (512 mg, 2.00 mmol) with 1,1-diethoxybutane (**4f**) (350 mg, 2.40 mmol) according to the general procedure yielded 313 mg (74%) of **6f** as colourless crystals. – R_f = 0.62 (solvent A). – M.p. 75°C (ethyl acetate/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3160 cm^{-1}, 3094 (NH), 3052 (C=CH), 2970, 2934, 2876 (CH), 1704, 1676 (CO), 1620 (C=C), 1468, 1386 (CH). – UV (acetonitrile): λ_{max} (lg ε) = 260 nm (4.064). – ^{1}H NMR ($CDCl_3$): δ = 0.95 (t, J = 7 Hz, 3H, 4'-H_3), 1.20 (t, J = 7 Hz, 3H, 2''-H_3), 1.25 (m, 4H, 2'-H_2, 3'-H_2), 3.50 (q, J = 7 Hz, 2H, OCH_2), 5.72 (t, J = 7 Hz, 1H, 1'-H), 5.73 (d, J = 8 Hz, 1H, 5-H), 7.35 (d, J = 8 Hz, 1H, 6-H), 9.40 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 13.6 (C-4'), 14.8 (CH_3CH_2O), 17.8 (C-3'), 37.2 (C-2'), 64.7 (OCH_3CH_2), 84.9 (C-1'), 103.1 (C-5), 139.3 (C-6), 151.6 (C-2), 164.4 (C-4). – MS (70 eV): m/z (%) = 212 (14) [M^+], 169 (2) [$M^+ - C_3H_7$], 167 (2) [$M^+ - C_2H_5O$], 112 (1) [$C_4H_4NO_2^+$], 101 (100) [$M^+ - C_4H_3NO_2$], 69 (4) [$C_3H_3NO^+$], 55 (54) [$C_4H_7^+$], 43 (14) [CHNO$^+$].

$C_{10}H_{16}N_2O_3$ (212.2) Calcd. C 56.59 H 7.60 N 13.20
Found C 56.38 H 7.66 N 13.18

(1'RS)-1-(2'-Bromo-1'-methoxyethyl)uracil (**6g**): Reaction of **2** (512 mg, 2.00 mmol) with 2-bromo-1,1-dimethoxyethane (**4g**) (284 µl, 2.40 mmol) for 12 h according to the general procedure yielded 199 mg (40%) of **6g** as colourless crystals. – R_f = 0.19 (solvent B). – M.p. 154 °C (dichloromethane/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3444 cm^{-1}, 3166 (NH), 2976, 2940 (CH), 1706, 1680, 1624 (NC=O), 1228, 1164, 1118, 1034 (C−O), 642 (C−Br). – UV (methanol): λ_{max} (lg ε) = 205 nm (3.928), 257 (3.987). – ^{1}H NMR ($CDCl_3$): δ = 3.45 (s, 3H, OCH_3), 3.54 (d, J = 5 Hz, 2H, CH_2Br), 5.75 (t, J = 5 Hz, 1H, 1'-H), 5.80 (d, J = 8 Hz, 1H, 5-H), 7.36 (d,

J = 8 Hz, 1H, 6-H), 9.75 (br.s, 1H, NH). – ^{13}C NMR (CD_3OD/$CDCl_3$): δ = 31.66 (CH_2Br), 57.64 (CH_3O), 85.46 (C-1′), 103.1 (C-5), 139.5 (C-6), 151.5 (C-2), 164.8 (C-4). – MS (70 eV): *m/z* (%) = 250, 248 (3, 3) [M^+], 219, 217 (1, 1) [$M^+ - OCH_3$], 169 (3) [M^+ – Br], 139 (88) [$M^+ - CH_3O$ – Br], 138 (30) [$C_3H_6BrO^+$], 137 (100) [$M^+ - CH_3OH$ – HBr].

$C_7H_9BrN_2O_3$ (249.1) Calcd. C 33.76 H 3.64 N 11.25
Found C 33.97 H 3.80 N 11.28

(1′RS)-1-(1′-Methoxy-1′-phenylmethyl)uracil (**6h**): Reaction of **2** (512 mg, 2.00 mmol) with benzaldehyde dimethyl acetal (**4h**) (365 mg, 2.40 mmol) according to the general procedure yielded 423 mg (91%) of **6h** as colourless crystals. – R_f = 0.24 (solvent B). – M.p. 142°C (dichloromethane/petroleum ether). – IR (KBr): ṽ = 3434 cm^{-1}, 3148 (NH), 3088, 3012 (CH), 1710, 1682, 1620 (NC=O), 1586 (C=C), 1094, 1074 (C–O), 734, 696 (CH, Ar). – UV (methanol): λ_{max} (lg ε) = 204 nm (4.248, sh), 247 (4.023). – ^{1}H NMR ($CDCl_3$): δ = 3.55 (s, 3H, OCH_3), 5.71 (d, J = 8 Hz, 1H, 5-H), 6.75 (s, 1H, 1′-H), 7.13 (d, J = 8 Hz, 1H, 6-H), 7.39 (s, 5H, C_6H_5), 9.67 (br.s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 56.71 (CH_3O), 85.49 (C-1′), 103.6 (C-5), 126.0 (C-*o*), 128.8 (C-*m*), 129.1 (C-*p*), 136.9 (C-*i*), 139.9 (C-6), 152.1 (C-2), 163.9 (C-4). – MS (70 eV): *m/z* (%) = 232 (11) [M^+], 201 (3) [$M^+ - CH_3O$], 122 (63), 121 (100) [$PhCHOCH_3^+$], 112 (2) [$C_4H_4N_2O_2^+$], 77 (72) [Ph^+].

$C_{12}H_{12}N_2O_3$ (232.2)
Calcd. C 62.06 H 5.21 N 12.06
Found C 61.96 H 5.24 N 12.07
Calcd. 232.0848 Found 232.0848 (MS)

(1′RS)-1-[1′-(2″-Bromophenyl)-1′-methoxymethyl]uracil (**6i**): Reaction of **2** (512 mg, 2.00 mmol) with 2-bromobenzaldehyde dimethyl acetal (**4i**) (554 mg, 2.40 mmol) according to the general procedure yielded after crystallisation 460 mg (74%) of **6i** as colourless crystals. – R_f = 0.38 (solvent C). – M.p. 177°C (dichloromethane/*tert*-butyl methyl ether). – IR (KBr): ṽ = 3434 cm^{-1}, 3154 (NH), 3054, 2938 (CH), 1688 (NC=O), 1570 (C=C, NH), 1248, 1206, 1124, 1086, 1046, 1028 (C–O), 754 (CH, Ar). – UV (methanol): λ_{max} (lg ε) = 258 nm (4.052). – ^{1}H NMR ($CDCl_3$): δ = 3.59 (s, 3H, OCH_3), 5.64 (dd, J = 2, J = 8 Hz, 1H, 5-H), 6.75 (s, 1H, 1′-H), 6.95 (d, J = 8 Hz, 1H, 6-H), 7.12–7.78 (m, 4H, C_6H_4), 9.67 (br.s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 57.03 (CH_3O), 84.95 (C-1′), 103.3 (C-5), 122.3 (C-2″), 127.6 (C-5″), 128.6 (C-6″), 130.9 (C-4″), 133.8 (C-3″) 135.2 (C-1″), 139.9 (C-6), 151.6 (C-2), 163.7 (C-4). – MS (70 eV): *m/z* (%) = 312, 310 (0.2, 0.1) [M^+], 281, 279 (0.4, 0.6) [$M^+ - CH_3O$], 201, 199 (95, 100) [$BrC_6H_4CHOCH_3^+$], 157, 155 (3, 3) [$BrC_6H_4^+$], 119 (4) [$C_6H_4CHOCH_3^+$], 105 (17).

$C_{12}H_{11}BrN_2O_3$ (311.1) Calcd. C 46.32 H 3.56
Found C 47.04 H 4.10

(1′RS)-1-(1′-Methoxy-2′-methoxycarbonylethyl)uracil (**6k**): Reaction of **2** (512 mg, 2.00 mmol) with methyl 3,3-dimethoxypropanoate (**4k**) (355 mg, 2.40 mmol) according to the general procedure yielded after column chromatography [dichloromethane/petroleum ether/ethanol (20:5:1)] 256 mg (56%) of **6k** as colourless crystals. – R_f = 0.17 (solvent D). – M.p. 142 °C (dichloromethane/petroleum ether). – IR (KBr): ṽ = 3434 cm^{-1}, 3170 (NH), 2958 (CH), 1746 (C=O), 1706, 1628 (NC=O), 1386 (CH_3CO), 1258, 1212, 1162, 1116, 1096, 1056 (C–O). – UV (methanol): λ_{max} (lg ε) = 203 nm (3.988), 257 (3.993). – ^{1}H NMR ($CDCl_3$): δ = 2.78 (d, J = 6 Hz, 1H, 2′-H), 2.79 (d, J = 6.5 Hz, 1 H, 2′-H), 3.39 (s, 3H, CH_3O), 3.72 (s, 3H, CO_2CH_3), 5.82 (d, J = 8 Hz, 1H, 5-H), 5.96 (t, J = 6.5 Hz, 1H, 1′-H), 7.33 (d, J = 8 Hz, 1H, 6-H), 0.98 (br.s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 39.75 (C-2′), 52.19 (CO_2CH_3), 57.15 (CH_3O), 83.49 (C-1′), 103.4 (C-5), 138.8 (C-6), 151.0 (C-2), 163.7 (C-4), 168.8 (C=O). – MS (70 eV): *m/z* (%) = 228 (6) [M^+], 197 (3) [$M^+ - CH_3O$], 117 (60) [$C_5H_9O_3^+$], 112 (12) [$C_4H_4N_2O_2^+$], 75 (100), 59 (16) [$CO_2CH_3^+$].

$C_9H_{12}N_2O_5$ (228.2)
Calcd. C 47.37 H 5.30 N 12.28
Found C 47.38 H 5.22 N 12.33
Calcd. 228.0746 Found 228.0746 (MS)

(1′RS)-1-(3′-Chloro-1′-ethoxypropyl)uracil (**6l**): Reaction of **2** (512 mg, 2.00 mmol) with 3-chloro-1,1-diethoxypropane (**4l**) (402 µl, 2.40 mmol) according to the general procedure yielded after flash chromatography 261 mg (56%) of **6l** as colourless crystals. – R_f = 0.18 (solvent B). – M.p. 65°C (dichloromethane/petroleum ether). – UV (methanol): λ_{max} (lg ε) = 205 nm (3.899), 259 (3.992). – IR (KBr): ṽ = 3196 cm^{-1} (NH), 2978, 2936 (CH), 1690, 1628 (NC=O), 1238, 1188, 1164, 1108, 1088 (C–O), 814 (C–Cl). – ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, J = 7 Hz, 3H, CH_3), 2.02–2.29 (m, 2H, 2′-H_2). 3.56 (dq, J = 2, J = 7 Hz, 2H, CH_2O), 3.63 (dt, J = 1, J = 6 Hz, 2H, CH_2Cl), 5.82 (d, J = 8 Hz, 1H, 5-H), 5.90 (dd, J = 5, J = 7.5 Hz, 1H, 1′-H), 7.35 (d, J = 8 Hz, 1H, 6-H), 9.11 (br.s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 14.72 (CH_3), 37.73 (C-2′), 39.68 (CH_2Cl), 64.99 (CH_2O), 82.62 (C-1′), 103.3 (C-5), 138.9 (C-6), 151.1 (C-2), 164.0 (C-4). – MS (70 eV): *m/z* (%) = 234, 232 (4, 12) [M^+], 189, 187 (1, 3) [$M^+ - CH_3CH_2O$], 123, 121 (31, 100) [$ClCH_2CH_2$-$CHOCH_2CH_3^+$], 112 (4) [$C_4H_4N_2O_2^+$], 93 (71), 73, (43).

$C_9H_{13}ClN_2O_3$ (232.7)
Calcd. C 46.46 H 5.63 N 12.04
Found C 46.31 H 5.77 N 12.07
Calcd. 232.0615 Found 232.0615 (MS)

(1′RS)-1-[1′-(3″-Hydroxypropyloxy)-1′-phenylmethyl]uracil (**6m**):Reaction of **2** (1.19 g, 4.65 mmol) with 2-phenyl-1,3-dioxan (**4m**) (851 mg, 5.12 mmol) at –20° to 0°C for 12 h according to the general procedure yielded after column chromatography [dichloromethane/petroleum ether/ethanol (10:1:1)] 655 mg (51%) of **6m** as colourless crystals. – R_f = 0.39 (solvent B). – M.p. 132°C (dichloromethane/petroleum ether). – IR (KBr): ṽ = 3390 cm^{-1}, 3146, 3100 (OH, NH), 3042 (Ph-H), 2966, 2944 (CH_2), 1708, 1668, 1618 (NC=O), 1254, 1100, 1078, 1058 (C–O), 744, 700 (CH, Ar). – UV (methanol): λ_{max} (lg ε) = 205 nm (4.368, sh), 257 (4.144). – ^{1}H NMR ($CDCl_3$): δ = 1.91 (br.s, 1H, OH), 1.97 (quint, J = 6 Hz, 2H, 2″-H_2), 3.76–3.98 (m, 4H, 3″-H_2, 1″-H_2) [after D_2O exchange: δ = 3.92, 3.95 (2t, J = 6 Hz)], 5.75 (d, J = 7.5 Hz, 1H, 5-H), 6.91 (s, 1H, 1′-H), 7.21 (d, J = 7.5 Hz, 1H, 6-H), 7.45 (s, 5H, C_6H_5), 9.38 (br.s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 32.23 (C-2″), 57.50 (C-3″), 65.85 (C-1″), 83.61 (C-1′), 102.9 (C-5), 125.9 (C-*o*), 128.6 (C-*m*), 128.7 (C-*p*), 137.6 (C-*i*), 140.0 (C-6), 151.4 (C-2), 163.0 (C-4). – MS (70 eV): *m/z* (%) = 201 (3) [$M^+ - OCH_2CH_2CH_2OH$], 165 (93) [$PhCHOCH_2CH_2CH_2OH^+$], 112 (5) [$C_4H_4N_2O_2^+$], 107 (100) [$PhCHOH^+$], 91 (17) [$PhCH_2^+$], 77 (24) [Ph^+].

$C_{14}H_{16}N_2O_4$ (276.3) Calcd. C 60.86 H 5.84 N 10.14
Found C 61.02 H 5.96 N 10.05

(1′RS)-1-(1′,2′-Dimethoxyethyl)-5-fluorouracil (**7a**): Reaction of **3** (548 mg, 2.00 mmol) with 576 mg of 1,1,2-trimethoxyethane (**4b**) (293 mg, 2.40 mmol) according to the general procedure yielded 362 mg (83%) of **7a** as colourless crystals. – R_f = 0.58 (solvent A). – M.p. 143°C (ethyl acetate/petroleum ether). – IR (KBr): ṽ = 3432 cm^{-1} (OH), 3172, 3078 (NH), 3052 (C=CH), 2960, 2938, 2888 (CH), 1720, 1698 (CO), 1670 (C=C), 1472, 1392 (CH). – UV (acetonitrile): λ_{max} (lg ε) = 265 nm (3.937). – ^{1}H NMR ($CDCl_3$): δ = 3.38 (s, 6H, 2 OCH_3), 3.55 (d, J = 6 Hz, 2H, 2′-H_2), 5.67 (dt, J = 6 Hz, J = 2 Hz, 1H, 1′-H), 7.44 (d, J = 7 Hz, 1H, 6-H), 11.30 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 57.2, 59.7 (OCH_3), 72.3 (C-2′), 84.8 (C-1′), 124.2 (d, J = 33.4 Hz, C-6), 140.8 (d, J = 238 Hz, C-5), 150.1 (C-2), 157.2 (d, J = 26.6 Hz, C-4). – MS (70 eV): *m/z*

(%) = 218 (24) [$M^+ - C_2H_5O$], 130 (74) [$C_4H_3FNO_2^+$], 89 (100) [$M^+ - C_4H_2FNO_2$].

$C_8H_{11}FN_2O_4$ (218.2) Calcd. C 44.04 H 5.08 F 8.71 N 12.84
Found C 43.98 H 5.16 F 8.70 N 12.89

(1'RS)-1-(3'-Benzyloxy-1'-methoxypropyl)-5-fluorouracil (**7b**): Reaction of **3** (548 mg, 2.00 mmol) with 3-benzyloxy-1,1-dimethoxypropane (**4d**) (500 mg, 2.40 mmol) according to the general procedure yielded 420 mg (70%) of **7b** as colourless crystals. – R_f = 0.48 (solvent A). – M.p. 110°C (dichloromethane/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3214 cm^{-1}, 3092 (NH), 3008 (C=CH), 2966, 2934, 2916, 2880 (CH), 1718, 1698 (CO), 1668 (C=C), 1424, 1370 (CH), 746, 700 (CH, Ar). – UV (acetonitrile): λ_{max} (lg ε) = 265 nm (3.946). – ^1H NMR ($CDCl_3$): δ = 1.70 (s, 1H, NH), 1.98 (q, *J* = 7 Hz, 2H, 2'-H_2), 3.30 (s, 3H, OCH_3), 3.52 (t, *J* = 7 Hz, 2H, 3'-H_2), 4.43 (s, 2H, Ph-CH_2), 5.72 (dt, *J* = 7 Hz, *J* = 3 Hz, 1H, 1'-H), 7.30 (s, 5H, C_6H_5), 7.32 (d, *J* = 5 Hz, 1H, 6-H), 8.70 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 35.0 (C-2'), 56.6 (OCH_3), 65.2 (C-3'), 73.1 (CH_2-Ph), 85.4 (C-1'), 122.8 (d, *J* = 32 Hz, C-6), 127.7, 128.4, 137.8 (C-*o*, C-*m*- C-*p*, C-*i*), 141.1 (d, *J* = 237.3 Hz, C-5), 150.0 (C-2), 157.2 (d, *J* = 26.4 Hz, C-4). – MS (70 eV): *m/z* (%) = 308 (3) [M^+], 179 (30) [$M^+ - C_4H_2FNO_2$], 107 (4) [$C_3H_2FNO_2^+$], 91 (100) [$C_7H_7^+$].

$C_{15}H_{17}FN_2O_4$ (308.3) Calcd. C 58.44 H 5.56 F 6.16 N 9.09
Found C 58.48 H 5.60 F 6.40 N 9.19

(1'RS)-1-(2'-Bromo-1'-ethoxyethyl)-5-fluorouracil (**7c**): Reaction of **2** (548 mg, 2.00 mmol) with 2-bromo-1,1-diethoxyethane (**4g**) (361 µl, 2.40 mmol) according to the general procedure yielded after column chromatography [dichloromethane/petroleum ether/ethanol (10:5:1)] 399 mg (71%) of **7c** as colourless crystals. – R_f = 0.34 (solvent D). – M.p. 137°C (dichloromethane/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3426 cm^{-1}, 3061, 2904, 1713, 1660, 1265, 1082. – UV (methanol): λ_{max} (lg ε) = 203 nm (3.973), 264 (3.964). – ^1H NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7 Hz, 3H, CH_3), 3.51, 3.52 (2d, *J* = 5 Hz, 2H, CH_2Br), 3.63 (q, *J* = 7 Hz, 2H, CH_2O), 5.79 (dt, $^5J_{HF}$ = 2 Hz, *J* = 5 Hz, 1H, 1'-H), 7.42 (d, $^3J_{HF}$ = 5.3 Hz, 1H, 6-H), 9.82 (br.s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 14.67 (CH_3), 31.69 (C-2'), 66.27 (CH_2O), 83.58 (C-1'), 122.9 (d, $^2J_{CF}$ = 34 Hz, C-6), 140.9 (d, $^1J_{CF}$ = 242 Hz, C-5), 149.7 (C-2), 157.0 (d, $^2J_{CF}$ = 26 Hz, C-4). – MS (70 eV): *m/z* (%) = 282, 280 (4,4) [M^+], 237, 235 (3, 4) [$M^+ - CH_3CH_2O$], 153, 151 (100, 98) [$C_4H_9BrO^+$], 124, 122 (84, 89).

$C_8H_{10}BrFN_2O_3$ (280.1)
Calcd. C 34.19 H 3.59 N 9.97
Found C 34.62 H 3.42 N 10.02
Calcd. 279.9859 Found 279.9859 (MS)

(1'RS)-5-Fluoro-1-(1'-methoxy-2'-methoxycarbonylethyl)uracil (**7d**): Reaction of **3** (548 mg, 2.00 mmol) with ethyl 3,3-dimethoxypropanoate (**4k**) (355 mg, 2.40 mmol) according to the general procedure yielded 399 mg (81%) of **7d** as colourless crystals. – R_f = 0.41 (solvent C). – M.p. 118°C (dichloromethane/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3456 cm^{-1}, 3434, 3224 (NH), 2978, 2952 (CH), 1728 (C=O), 1704, 1678 (NC=O), 1378 (CH_3CO), 1228, 1216, 1170, 1078. 1052 (C–O, C–F). – UV (methanol): λ (lg ε) = 205 nm (3.922), 265 (3.897). – ^1H NMR ($CDCl_3$): δ = 2.78 (d, *J* = 7 Hz, 1H, 2'-H^a), 2.80 (d, *J* = 5.7 Hz, 1H, 2'-H^b), 3.43 (s, 3H, OCH_3), 3.75 (s, 3H, CH_3OCO), 5.98 (ddd, *J* = 5.7, *J* = 7 Hz, $^5J_{HF}$ = 1.8 Hz, 1H, 1'-H), 7.46 (d, $^3J_{HF}$ = 6 Hz, 1H, 6-H), 9.34–9.58 (m, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 39.52 (C-2'), 52.26 (CH_3OCO), 57.34 (CH_3O), 83.98 (C-1'), 122.9 (d, $^2J_{CF}$ = 33 Hz, C-6), 141.1 (d, $^1J_{CF}$ = 239 Hz, C-5), 149.6 (C-2), 157.2 (d, $^2J_{CF}$ = 26 Hz, C-4), 168.7 (C=O). – MS (70 eV): *m/z* (%) = 246 (10) [M^+], 215 (5) [$M^+ - CH_3O$], 130 (11) [$C_4H_3FN_2O_2^+$], 117 (83) [$C_5H_9O_3^+$], 75 (77), 59 (12) [$CO_2CH_3^+$].

$C_9H_{11}FN_2O_5$ (246.2)
Calcd. C 43.91 H 4.50 N 11.38
Found C 43.88 H 4.63 N 11.30
Calcd. 246.0652 Found 246.0652

(1'RS)-1-(3'-Chloro-1'-ethoxypropyl)-5-fluorouracil (**7e**): Reaction of **3** (548 mg, 2.00 mmol) with 3-chloro-1,1-diethoxypropane (**4e**) (402 µl, 2.40 mmol) according to the general procedure yielded after chromatography [dichloromethane/petroleum ether/ethanol (20:5:1)] 456 mg (91%) of **7e** as colourless crystals. – R_f = 0.47 (solvent C). – M.p. 104°C. – IR (KBr): $\tilde{\nu}$ = 3423 cm^{-1}, 3182 (NH), 2980, 2932 (CH), 1710, 1664 (NC=O), 1240, 1200, 1186, 1160, 1120, 1066 (C–O, C–F), 826 (C–Cl). – UV (methanol): λ_{max} (lg ε) = 206 nm (3.995), 267 (3.912). – ^1H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7 Hz, 3H, CH_3). 2.13 (quint, *J* = 6.5 Hz, 2H, 2'-H_2), 3.25–3.75 (m, 4H, CH_2O, CH_2Cl), 5.85 (dt, ^5J = 2 Hz, *J* = 6.5 Hz, 1H, 1'-H), 7.37 (d, $^3J_{HF}$ = 5.3 Hz, 1H, 6-H), 8.30–9.00 (m, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 14.69 (CH_3CH_2O), 37.57, 39.49 (C-3', C-2'), 65.31 (CH_3CH_2O), 83.27 (C-1'), 122.9 (d, $^2J_{CF}$ = 33 Hz, C-6), 141.2 (d, $^1J_{CF}$ = 239 Hz, C-5), 149.7 (C-2), 157.2 (d, $^2J_{CF}$ = 26 Hz, C-4). – MS (70 eV): *m/z* (%) = 252, 250 (1, 4) [M^+], 207, 205 (1, 4) [$M^+ - CH_3CH_2O$], 123, 121 (28, 92) [$ClCH_2CH_2CHO$-$CH_2CH_3^+$], 87 (84), 45 (17) [$CH_3CH_2O^+$]. – Because of the compound's sensitivity no correct combustion analysis was obtained.

$C_9H_{12}ClFN_2O_3$ (250.7) Calcd. 250.0520
Found 250.0520 (MS)

(1'RS)-1-[3'-Benzyloxy-1'-(3''-methoxycarbonylpropyloxy)propyl]-5-fluorouracil (**7f**): Reaction of **3** (548 mg, 2.00 mmol) with 3-benzyloxy-1,1-bis(3-methoxycarbonylpropoxy)propane (**4n**) (918 mg, 2.40 mmol) according to the general procedure yielded after column chromatography [dichloromethane/petroleum ether/ethanol (20:3:1)] 489 mg (62%) of **7f** as colourless crystals. – R_f = 0.21 (solvent C). – M.p. 67°C (dichloromethane/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3434 cm^{-1}, 3202 (NH), 2960, 2924 (CH), 1736 (C=O), 1708, 1672 (NC=O), 1370 (CH_3CO), 1238, 1218, 1126, 1082, 1062 (C–O). – UV (methanol): λ_{max} (lg ε) = 206 nm (4.203), 266 (3.936). – ^1H NMR ($CDCl_3$): δ = 1.80–2.07 (m, 4H, 2''-H_2, 2'-H_2), 2.37 (2t, *J* = 7, *J* = 7.5 Hz, 2H, 3''-H_2), 3.38–3.63 (m, 4H, 3'-H_2, 1''-H_2), 3.66 (s, 3H, CH_3O), 4.38–4.53 (m, 2H, Ph-CH_2), 5.85 (dt, *J* = 6.5 Hz, $^5J_{HF}$ = 2 Hz, 1H, 1'-H), 7.22–7.40 (m, 5H, C_6H_5), 7.34 (d, $^3J_{HF}$ = 5.8 Hz, 1H, 6-H), 9.09 (br.s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 24.55, 30.49 (C-2'', C-3''), 34.98 (C-2'). 51.65 (CO_2CH_3), 65.14, 68.01 (C-3', C-1''), 73.05 (CH_2-Ph), 83.73 (C-1'), 123.2 (d, $^2J_{CF}$ = 33 Hz, C-6), 127.7, 127.8, 128.4, 137.8 (C-*o*, C-*m*, C-*p*, C-*i*), 141.0 (d, $^1J_{CF}$ = 238 Hz, C-5), 149.9 (C-2), 157.2 (d, $^2J_{CF}$ = 26 Hz, C-4), 173.4 (C=O). – MS (70 eV): *m/z* (%) = 265 (13) [M^+ – uracil], 101 (100) [$CH_2CH_2CH_2CO_2CH_3^+$], 91 (76) [$PhCH_2^+$], 59 (54) [$CO_2CH_3^+$].

$C_{19}H_{33}FN_2O_6$ (394.4) Calcd. C 57.86 H 5.88 N 7.10
Found C 57.80 H 5.93 N 6.97

CAS Registry Numbers

2: 10457-14-4 / **3**: 17242-85-2 / **4a**: 109-87-5 / **4b**: 24332-20-5 / **4c**: 127657-97-0 / **4d**: 34591-97-4 / **4e**: 133625-41-9 / **4f**: 3658-95-5 / **4g**: 7252-83-7 / **4h**: 1125-88-8 / **4i**: 35849-09-3 / **4k**: 7424-91-1 / **4l**: 35573-93-4 / **4m**: 772-01-0 / **4n**: 113249-91-5 / **6a**: 133625-42-0 / **6b**: 133625-43-1 / **6c**: 133625-44-2 / **6d**: 133625-45-3 / **6e**: 133625-46-4 / **6f**: 133625-47-5 / **6g**: 133625-48-6 / **6h**: 133625-49-7 / **6i**: 133625-50-0 / **6k**: 133625-51-1 / **6l**: 133625-52-2 / **6m**: 133625-53-3 / **7a**: 133625-54-4 / **7b**: 133625-55-5 / **7c**: 133625-56-6 / **7d**: 133625-57-7 / **7e**: 133625-58-8 / **7f**: 133625-59-9

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