REACTIVITY OF DIMETHYLPHENYLSILYLLITHIUM TOWARD 5- AND 6-SUBSTITUTED 1,3-DIMETHYLURACIL DERIVATIVES

Raffaele Saladino,[a*] Luigi Stasi,[b] Gabriele Volpe,[b] Rosario Nicoletti,[b] and Maurizio Botta[c*]

[a]Dipartimento Agrochimico Agrobiologico, Università degli studi di Viterbo "La Tuscia", via San Camillo de Lellis, 01100 Viterbo, Italy, [b]Dipartimento di Chimica, Università "La Sapienza", ple. Aldo Moro 5, 00185 Roma, Italy, [c]Dipartimento Farmaco Chimico Tecnologico, Banchi di Sotto 55, Università degli Studi di Siena, 53100 Siena, Italy

Abstract- Dimethylphenylsilyllithium ($PhMe_2SiLi$) reacts with 5-substituted 1,3-dimethyluracils by selective addition at the electrophilic C-6 position of the uracil ring to give the corresponding 6-dimethylphenylsilyl-5,6-dihydrouracil derivatives. The reaction of $PhMe_2SiLi$ with 6-substituted 1,3-dimethyluracils showed a different selectivity, and an unusual addition at the C-5 position was observed. This synthetic procedure appears to be an efficient entry to a new class of highly functionalized 5,6-dihydro-1,3-dimethyluracils characterized by the presence of a silicon substituent selectively introduced at the C-5 and C-6 positions of the uracil ring.

Model addition reactions of nucleophiles to C-5 and C-6 positions of uracil derivatives are important transformations because of their biological significance,[1] as for example the thymidylate synthase-catalysed conversion of urydylate (dUMP) into thymidylate (dTMP).[2] Carbon,[3] sulphur,[4] oxygen, selenium, and nitrogen[5] nucleophiles have all been used for the nucleophile induced ring transformations of uracil derivatives with varying degree of success as well as limitations due to side reactions. Additions of nucleophiles on the uracil ring are known to occur *via* initial attack on the C-6 position, giving rise to a 5,6-dihydrouracil intermediate from which the respective product is formed. Unprotected uracil derivatives are usually not reactive because of the anion formation in basic media which makes attack by nucleophiles more difficult. For this reason, 1,3-dialkylated uracils, such as 1,3-dimethyluracil derivatives, are more susceptible to nucleophilic attack and are extensively used as model substrates.

Dimethylphenylsilyllithium ($PhMe_2SiLi$) is a versatile silylating reagent prepared from both Si-Si bond fission of the corresponding organodisilane[6, 7] and from easily available chlorodimethylphenylsilane and lithium in solvent like tetrahydrofuran and tetrahydropyran.[8] Compounds with silicon-alkali metal bond are nucleophilic

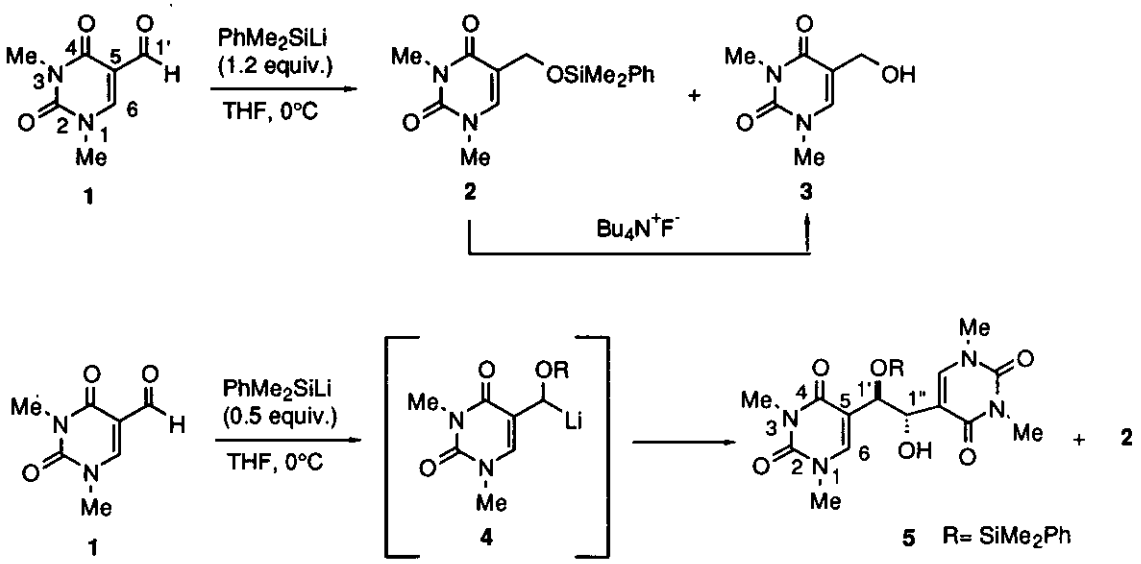
silicon reagents and react with a wide range of electrophiles.[9] In particular, the reaction of $PhMe_2SiLi$ with CO_2 is a versatile route to silylcarboxylic acids, while silyl alcohols are obtained by reaction with aliphatic aldehydes or ketones.[10] With aromatic carbonyl compounds a different reaction pattern is usually observed and the initial adducts undergo Brook rearrangement to give silyl ethers.[11] α,β-Unsaturated ketones react with alkylsilyllithium reagents at low temperature in THF/HMPA (5:1) by conjugate addition.[12] The solvent system and the presence of substituents on the α,β-unsaturated moiety control the regioselectivity of the reaction.[13,14]

The addition of the $PhMe_2Si$ group to α,β-unsaturated carbonyl compounds has been applied as a key step in the synthesis and selective functionalization of analogs of mevinic acids,[15] β-lactam derivatives,[16] hydroxylate steroid hormones,[17] alkaloids,[18] and sesquiterpenes.[19] Moreover, several compounds characterized by important biological activity retain their pharmacological properties when the substitution of a carbon atom with a silicon moiety is performed.[20]

Despite several examples reported in the literature,[13,14, 21] to the best of our knowledge, there are not reports dealing with the reactivity of $PhMe_2SiLi$ with the α,β-unsaturated carbonyl moiety present on the uracil ring. With the aim to develop new and selective procedures for the functionalization of nucleic acids and their components,[22] and as a part of a project based on the study of the reactivity of organolithium containing silicon reagents with uracil derivatives and pyrimidine nucleosides,[23] we report here the reaction of $PhMe_2SiLi$ with several 5- and 6-substituted 1,3-dimetyhluracil derivatives. As a general reaction pattern $PhMe_2SiLi$ reacts with 5-substituted uracils by selective addition at the electrophilic C-6 position of the uracil ring to give the corresponding 6-dimethylphenylsilyl-5,6-dihydrouracil derivatives. The reaction of $PhMe_2SiLi$ with 6-substituted uracils showed a different selectivity and an unusual addition at the C-5 position was the main observed process. This synthetic procedure appears to be an efficient entry to a new class of highly functionalized 5,6-dihydro-1,3-dimethyluracils characterized by the presence of a silicon substituent selectively introduced at the C-5 and C-6 positions of the uracil ring.

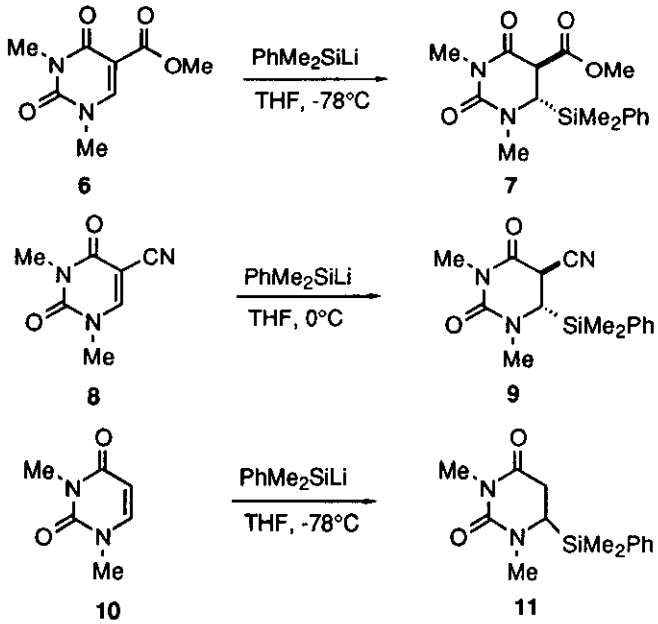
1,3-Dimethyl-5-formyluracil (**1**) (1 mmol, 168 mg) treated with freshly prepared $PhMe_2SiLi$ (0.5 N solution in dry THF; 1.2 equiv) in THF at 0 °C gave 1,3-dimethyl-5-[(dimethylphenylsilyloxy)methan-1'-yl)]uracil (**2**), and 1,3-dimethyl-5-hydroxymethyluracil (**3**) in 28 and 43% yield, respectively (Scheme 1). Moreover, compound **2** treated with tetrabutylammonium fluoride (TBAF), under usual experimental conditions,[24] gave **3** in quantitative yield. The formation of products (**2**) and (**3**) is probably due to selective addition of $PhMe_2SiLi$ on the formyl moiety followed by Brook rearrangement. The same reaction performed with a substoichiometric amount of $PhMe_2SiLi$ (0.5 equiv) gave the threo bis-uracil diol derivative (**5**) as the main product in 83% yield, besides (**2**), as by-product, in 12% yield (Scheme 1). The stereochemistry of the 1- and 1'-positions for (**5**) was assigned to be threo on the basis of the coupling constant value ($J_{1',1''}$= 3.6 Hz) according to data reported in the literature.[25] It is reasonable to suggest that compound (**5**) may be formed by selective addition of the hypothesized Brook intermediate (**4**) (Scheme 1) on the formyl group of a second molecule of the substrate present in large excess in the reaction mixture. This procedure appears to be a new synthetic pathway to obtain bipyrimidine derivatives which, due to their biological importance, keep on attracting much interest .[26] 1,3-Dimethyl-5-carboxymethyluracil (**6**) (1 mmol, 198 mg) treated with 1.5 equiv

of $PhMe_2SiLi$ in THF at -78 °C gave 1,3-dimethyl-5,6-dihydro-5-carboxymethyl-6-dimethylphenylsilyluracil (**7**), as the sole product in 87% yield (Scheme 2).



Scheme 1

The stereochemistry of the 5- and 6-positions for **7** was assigned to be <u>trans</u> on the basis of the coupling constant value (J= 1.2 Hz) between protons H-5 and H-6.

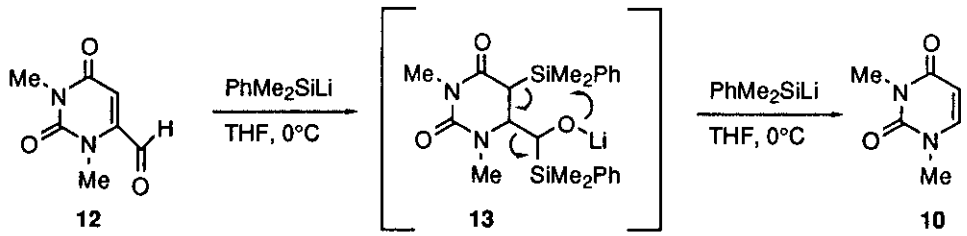


Scheme 2

In the latter case, the less electrophilic character of the carboxylate moiety[27] compared with that of the aldehyde moiety, is probably responsible for the selective attack at the C-6 position of the uracil ring. In a similar way, the reaction of 1,3-dimethyl-5-cyanouracil (**8**) (1 mmol, 165 mg) with 1.5 equiv of $PhMe_2SiLi$ in THF at 0 °C gave 1,3-dimethyl-5,6-dihydro-5-cyano-6-dimethylphenylsilyluracil (**9**), in 91% yield (Scheme 2). The stereochemistry of the 5- and 6-positions for **9** was assigned to be trans on the basis of the coupling constant value (J= 1.4 Hz) between protons H-5 and H-6. The selective addition at the 6-position of the uracil ring was also observed, under similar experimental conditions, in the reaction of $PhMe_2SiLi$ with 1,3-dimethyluracil (**10**) to give 1,3-dimethyl-5,6-dihydro-6-dimethylphenylsilyl uracil (**11**) in 77% yield (Scheme 2).

It is well known that the reactivity of nucleophiles toward 5- and 6-substituted uracils is quite different, depending on the nature and position of the substituents on the C-5,6 double bond.[28] For example, diazomethane reacts with 1,3-dimethyl-6-formyluracil to give the corresponding 1,3-dimethyl-6-oxiranyl derivative,[29] while the same reaction performed on 1,3-dimethyl-5-formyluracil gave a complex mixture of products in which a 1,3,4-oxadiazole derivative was obtained as the main product.[23] For this reason, and to further generalize the reactivity of $PhMe_2SiLi$ with uracil derivatives, we examined the addition of $PhMe_2SiLi$ toward compounds (**12**), (**15**), and (**17**), that are the C-6 isomers of substrates (**1**), (**6**), and (**8**).

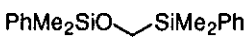
The reaction of 1,3-dimethyl-6-formyluracil (**12**) (1 mmol, 168 mg) with $PhMe_2SiLi$ (2.0 equiv) in THF at 0 °C gave 1,3-dimethyluracil (**10**) as the sole product in 65% yield (Scheme 3).[30]



12 **13** **10**

Scheme 3

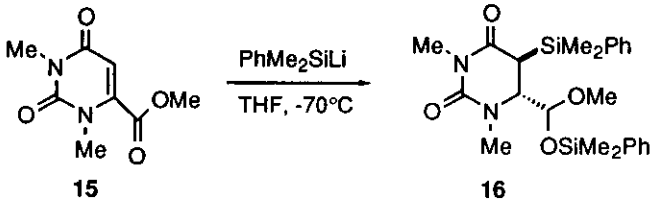
A reasonable pathway for the unexpected formation of **10** is depicted in Scheme 3. Probably, the reaction proceeds through the initial addition of $PhMe_2SiLi$ both at the 5-position of the uracil ring and at the formyl moiety to give the intermediate (**13**) (not isolated in our case even when the reaction was performed at -78 °C) which might undergo spontaneous deformylation. This pathway is in accord with the previously reported reductive decyanation of 6-cyanouracil with thiolates,[31] and with the bisulfite-catalyzed decarboxylation reaction of carboxyuracil derivatives,[32] and further confirmed by the presence of the silylether derivative **14** in the reaction mixture (as shown by GC-MS measurements).[33]



14

The addition of $PhMe_2SiLi$ at the C-5 position of the uracil ring was further confirmed by the reaction of $PhMe_2SiLi$ with 1,3-dimethyl-6-carboxymethyluracil (1,3-dimethylorotic acid methyl ester) (**15**). The reaction

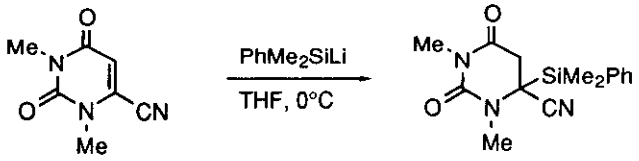
of **15** (1 mmol, 198 mg) with $PhMe_2SiLi$ (1.7 equiv) in THF at -70 °C gave compound (**16**) in 35% yield besides unreacted substrate (Scheme 4). Compound (**16**) was obtained as a mixture of isomers. The stereochemistry of the 5- and 6-positions was assigned to be trans on the basis of the coupling constant value (J= 1.2 Hz) between protons H-5 and H-6. In this case the Brook rearrangement seems to be a very efficient process, and products of decarboxylation were not observed in the reaction mixture.



15 **16**

Scheme 4

Instead, the reaction of 1,3-dimethyl-6-cyanouracil (**17**) (1 mmol, 165 mg) with $PhMe_2SiLi$ (1.7 equiv) in THF at 0 °C gave the product arising from attack at C-6 position of the uracil ring, 1,3-dimethyl-5,6-dihydro-6-cyano-6-dimethyl phenylsilyluracil (**18**) in 58% yield (Scheme 5). Further strengthening for this result came from the reaction of **17** with $PhMe_2SiLi$, performed under similar experimental conditions, using D_2O (>99.8%) for the quenching procedure. In this case, the selective 1,4-addition was confirmed by an incorporation of deuterium at C-5 position in more than 90%. In particular, in the ^1H-NMR spectrum, the intensity of the signal centered at 3.20 ppm decreased and the signal centered at 2.62 ppm with doublet multiplicity partially collapsed into a singlet.



17 **18**

Scheme 5

Thus, the cyano group at C-6 does not effect the reaction regiochemistry and the conjugate addition, previously reported as the main transformation for 1,3-dimethyluracil (**10**) and 5-substituted-1,3-dimethyluracil derivatives (**6**), and (**8**), was the only observed process.

Many natural as well as synthetic uracil derivatives and pyrimidine nucleosides with important biological activities are charactherized by C-5 and C-6 substituents.[34] Recently, we have shown that 1,3-dimethyl-5,6-dihydro-5,6-disubstituted uracil derivatives are characterized by selective antiviral activity.[35] In this context, the efficient addition of dimethylphenylsilyllithium to uracil derivatives appears to be a clean and efficient entry to a new class of highly functionalized 5,6-dihydro-1,3-dimethyluracils with a silicon substituent selectively introduced at the 5- and 6-positions of the uracil ring.

EXPERIMENTAL

NMR spectra were recorded on a Bruker (200) MHz spectrometer and are reported in δ value. IR spectra were recorded on a Perkin Elmer 298 spectrophotometer using NaCl plates. Microanalyses were performed with a C.Erba 1106 analyser. MS spectra were recorded on VG 70/250S spectrometer with an electron beam of 70 eV. Melting points were obtained on Mettler apparatus and are uncorrect. All solvents were ACS reagent grade and when necessary were redistilled and dried according to standard procedures. Chromatographic purifications were performed on columns packed with Merck silica gel, 230-400 mesh for flash-technique. TLC was carried out using Merck platten Kieselgel 60 F254.

Starting Compounds. 1,3-Dimethyluracil (**10**) was synthesized according to the procedure reported by Allen;[36] 1,3-dimethyl-5-formyluracil (**1**) and 1,3-dimethyl-6-formyluracil (**12**) were synthesized according to the procedure reported by Botta;[37] 1,3-dimethyl-5-carboxymethyluracil (**6**) was prepared according to the procedure reported by Curran[38] followed by treatment with diazomethane; 1,3-dimethyl-5-cyanouracil (**8**) was synthesised according to the procedure reported by Liebenow;[39] 1,3-dimethyl-6-carboxymethyluracil (**15**) (orotic acid methyl ester) was prepared following the procedure reported by Botta;[34] 1,3-dimethyl-6-cyanouracil (**17**) was synthesised according to the procedure reported by Senda .[3b]

1,3-Dimethyl-5-[(dimethylphenylsilyloxy)methan-1'-yl]uracil (**2**) and 1,3-dimethyl-5-hydroxymethyluracil (**3**). To a stirred solution of 1,3-dimethyl-5-formyluracil (**1**) (168 mg, 1mmol) in 7 mL of THF was added a solution of $PhMe_2SiLi$ (1.2 mmol, 0.5 N solution in THF) under argon atmosphere at 0°C. The solution was treated with NH_4Cl (5% water solution), the organic layer diluted with EtOAc (100 mL), washed with $NaHCO_3$ (5% water solution) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After silica gel column chromatography (CH_2Cl_2:EtOAc=8:2) the colourless oils (**2**) and (**3**) were obtained in 28 and 43% yields, respectively.

1,3-Dimethyl-5-[1'-(dimethylphenylsilyl)hydroxymethyl]uracil (**2**): (85 mg, 28%). Anal. Calcd for $C_{15}H_{20}N_2O_3Si$: C, 59.2; H, 6.6; N, 9.2. Found: C, 59.7; H, 6.8; N, 9.1. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.90 (s, 6H, CH_3), 3.37 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 6.41 (s, 1H, CH), 7.35 (m, 5H, Ph-H); IR ($CHCl_3$) ν_{max} 3495 (Ph-H), 2930 (C-H), 1701 (CO), 1666 (CO) and 1640 (C=C) cm^{-1}; MS m/z 304 (M^+, 12%).

1,3-Dimethyl-5-hydroxymethyluracil (**3**): (71 mg, 43%). Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.4; H, 5.9; N, 16.5. Found: C, 49.9; H, 5.7; N, 16.2. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 3.34 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 3.62 (br s, 1H, OH), 4.39 (s, 2H, OCH_2), 7.17 (s, 1H, CH); ^{13}C NMR ($CDCl_3$, MHz) δ_C ppm: 163.64 (C), 161.10 (C), 140.20 (CH), 112.45 (C), 58.99 (CH_2), 37.03 (CH_3), 27.80 (CH_3). I.R. ($CHCl_3$) ν_{max} 3500 (OH), 2890 (C-H), 1710 (CO), 1680 (CO) and 1635 (C=C) cm^{-1}; MS m/z 170 (M^+, 18%).

Bis-uracil diol derivative (**5**). To a stirred solution of 1,3-dimethyl-5-formyluracil (**1**) (168 mg, 1 mmol) in 7 mL of THF was slowly added a solution of $PhMe_2SiLi$ (0.5 mmol, 0.5 N solution in THF) under argon atmosphere at 0°C. The solution was treated with NH_4Cl (5% water solution), the organic layer diluted with

EtOAc (100 mL), washed with $NaHCO_3$ (5% water solution) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After silica gel column chromatography (CH_2Cl_2:EtOAc=7:3) the colourless oil (**5**) was obtained in 83% yield (196 mg): Anal. Calcd for $C_{22}H_{28}N_4O_6Si$: C, 55.8; H, 5.4; N, 11.8. Found: C, 55.9; H, 5.9; N, 11.8. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.29 (s, 6H, CH_3), 2.78 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 3.18 (d, 1H, J = 3.6 Hz), 3.21 (s, 3H, CH_3), 3.31 (d, 1H, CH, J = 3.6 Hz), 3.62 (s, 3H, CH_3), 4.71 (br s, 1H, OH), 6.39 (s, 1H, CH), 6.51 (s, 1H, CH), 7.38 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$, MHz) δ_C ppm: 185.10 (C), 185.01 (C), 184.21 (C), 147.49 (C), 138.12 (C), 133.02 (CH), 128.12 (CH), 127.88 (CH), 51.10 (CH), 37.99 (CH), 29.80 (CH_3), 29.67 (CH_3), 27.87 (CH_3), 0.99 (CH_3). IR ($CHCl_3$) ν_{max} : 3410 (Ph-H), 3000 (C-H), 1717 (CO), 1694 (CO) and 1661 (C=C) cm^{-1}; MS m/z 472 (M^+, 33%).

1,3-Dimethyl-5,6-dihydro-5-carboxymethyl-6-(dimethylphenylsilyl)uracil (**7**). To a stirred solution of 1,3-dimethyl-5-carboxymethyluracil (**6**) (198 mg, 1mmol) in 8 mL of THF was added a solution of $PhMe_2SiLi$ (1.2 mmol, 0.5 N solution in THF) under argon atmosphere at -78°C. The solution was treated with NH_4Cl (5% water solution), the organic layer diluted with EtOAc (100 mL), washed with $NaHCO_3$ (5% water solution) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After silica gel column chromatography (n-hexane:EtOAc=1:1) the colourless oil (**7**) was obtained in 87% yield (290 mg): Anal. Calcd for $C_{16}H_{22}N_2O_4Si$: C, 57.4; H, 6.6; N, 8.4. Found: C, 57.1; H, 6.6; N, 8.3. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.41 (s, 6H, CH_3), 2.86 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.48 (d, 1H, CH, J = 1.2 Hz), 3.70 (d, 1H, CH, J = 1.2 Hz), 7.42 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, MHz) δ_C ppm: 169.04 (C), 165.38 (C), 152.30 (C), 133.70 (CH), 133.50 (C), 130.30 (CH), 128.31 (CH), 53.32 (CH_3), 49.31 (CH), 48.70 (CH), 37.22 (CH_3), 27.53 (CH_3), -4.50 (CH_3). IR ($CHCl_3$) ν_{max}; 3401 (Ph-H), 2980 (CH), 1740 (CO), 1705 (CO) and 1675 (CO) cm^{-1}. MS m/z 334 (M^+ 41%).

1,3-Dimethyl-5,6-dihydro-5-cyano-6-(dimethylphenylsilyl)uracil (**9**). To a stirred solution of 1,3-dimethyl-5-cyanouracil (**8**) (165 mg, 1mmol) in 6 mL of THF was added a solution of $PhMe_2SiLi$ (1.2 mmol, 0.5 N solution in THF) under argon atmosphere at 0°C. The solution was treated with NH_4Cl (5% water solution), the organic layer diluted with EtOAc (100 mL), washed with $NaHCO_3$ (5% water solution) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After silica gel column chromatography (n-hexane:EtOAc=6:4) the colourless oil (**9**) was obtained in 91% yield (273 mg): Anal. Calcd for $C_{15}H_{19}N_3O_2Si$: C, 59.8; H, 6.3; N, 13.9. Found: C, 59.6; H, 6.5; N, 13.9. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.42 (s, 6H, CH_3), 2.83 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 3.24 (d, 1H, CH, J = 1.4 Hz), 3.61 (d, 1H, CH, J = 1.4 Hz), 7.41 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$, MHz) δ_C ppm: 160.88 (C), 150.58 (C), 133.60 (CH), 132.32 (C), 130.78 (CH), 128.54 (CH), 115.71 (CN), 49.92 (CH_3), 35.43 (CH_3), 37.67 (CH), 37.30 (CH), -4.64 (CH_3). IR ($CHCl_3$) ν_{max}; 3315 (Ph-H), 2995 (CH), 2225 (CN), 1710 (CO), 1680 (CO) cm^{-1}. MS m/z 301 (M^+ 31%).

1,3-Dimethyl-5,6-dihydro-6-dimethyl(phenylsilyl)uracil (**11**). To a stirred solution of 1,3-dimethyluracil (**10**) (140 mg, 1 mmol) in 5 mL of THF was added a solution of $PhMe_2SiLi$ (1.2 mmol, 0.5 N solution in THF) under argon atmosphere at -78°C. The solution was treated with NH_4Cl (5% water solution), the organic layer

diluted with EtOAc (100 mL), washed with $NaHCO_3$ (5% water solution) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After silca gel column chromatography (n-hexane:EtOAc=1:1) the colourless oil (**11**) was obtained in 77% yield (212 mg): Anal. Calcd for $C_{14}H_{20}N_2O_2Si$: C, 61.0; H, 6.9; N, 10.7. Found: C, 60.8; H, 7.3; N, 10.1. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.41 (s, 6H, CH_3), 2.65 (m, 1H, CH_2), 2.89 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 3.08 (m, 1H, CH), 7.41 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$, MHz) δ_C ppm: 170.18 (C), 164.10 (C), 133.73 (CH), 130.14 (CH), 128.83 (C), 127.79 (CH), 45.72 (CH), 37.07 (CH_3), 36.51 (CH_2), 27.19 (CH_3), -4.73 (CH_3). IR ($CHCl_3$) ν_{max}; 3440 (Ph-H), 2935 (CH), 1710 (CO) and 1660 (CO) cm^{-1}. MS m/z 276 (M+ 52%).

1,3-Dimethyluracil (**10**) from 6-formyl-1,3-dimethyluracil (**12**). To a stirred solution of 1,3-dimethyl-6-formyluracil (**12**) (168 mg, 1 mmol) in 7 mL of THF was added a solution of $PhMe_2SiLi$ (2.0 mmol, 0.5 N solution in THF) under argon atmosphere at 0°C. The solution was quenched by addition of NH_4Cl (5% water solution), the organic layer diluted with EtOAc (100 mL), washed with $NaHCO_3$ (5% water solution) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After silica gel column chromatography (CH_2Cl_2:EtOAc=7:3) compound (**10**) was obtained in 65% yields (91 mg), mp =120-122°C (lit., 119-122°C).[38] All spectroscopic data were in accord with literature reported data.[38]

1,3-Dimethyl-5,6-dihydro-5-phenyldimethylsilyl-6-[1'-(methoxy-1'-phenyldimethylsilyloxy)methanyl]uracil (**16**). To a stirred solution of 1,3-dimethyl-6-carboxymethyluracil (**15**) (198 mg, 1 mmol) in 8 mL of THF was added a solution of $PhMe_2SiLi$ (2 mmol, 0.5 N solution in THF) under argon atmosphere at -78°C. The solution was quenched by addition of NH_4Cl (5% water solution), the organic layer diluted with EtOAc (100 mL), washed with $NaHCO_3$ (5% water solution) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After silica gel column chromatography (CH_2Cl_2:EtOAc=8:2) the colourless oil (**16**) was obtained in 35 % yield (164 mg). Anal. Calcd for $C_{24}H_{34}N_2O_4Si_2$: C, 70.4; H, 4.7; N, 10.3. Found: C, 69.7; H, 4.9; N, 10.1. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.32 (m, 6H, CH_3), 0.53 (m, 6H, CH_3), 3.22 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 3.33 (d, 1H, CH, J = 1.2 Hz), 3.39 (d, 1H, CH, J = 1.2 Hz), 3.40 (s, 3H, CH_3), 3.99 (m, 1H, CH), 7.53 (m, 10H, Ph-H); ^{13}C NMR ($CDCl_3$, MHz) δ_C ppm: 160.88 (C), 150.58 (C), 134.20 (C), 134.52 (CH), 128.81 (CH), 72.10 (CH), 52.71 (CH_3), 33.07 (CH_3), 33.07 (CH_3), 28.0 (CH), 19.11 (CH), -1.95 (CH_3). IR ($CHCl_3$) ν_{max} 1720 (CO), and 1700 (CO) cm^{-1}. MS m/z 409 (M+ 12%).

1,3-Dimethyl-5,6-dihydro-6-cyano-6-(dimethylphenylsilyl)uracil (**18**). To a stirred solution of 1,3-dimethyl-6-cyanouracil (**17**) (165 mg, 1 mmol) in 6 mL of THF was added a solution of $PhMe_2SiLi$ (1.2 mmol, 0.5 N solution in THF) under argon atmosphere at 0°C. The solution was quenched by addition of NH_4Cl (5% water solution), the organic layer diluted with EtOAc (100 mL), washed with $NaHCO_3$ (5% water solution) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After silica gel column chromatography (CH_2Cl_2:EtOAc=7:3) the colourless oil (**18**) was obtained in 58 % yield (174 mg): Anal. Calcd for $C_{15}H_{19}N_3O_2Si$: C, 59.8; H, 6.3; N, 13.9. Found: C, 59.8; H, 6.3; N, 14.0. ^{1}H-NMR ($CDCl_3$,

200 MHz) δH ppm: 0.41 (s, 6H, CH_3), 2.62 (d, 1H, CH, J = 16 Hz), 2.89 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 3.20 (d, 1H, CH, J = 16 Hz), 7.48 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$, MHz) δC ppm: 186.83 (C), 169.43 (C), 135.10 (C), 134.55 (CH), 133.71 (CH), 130.10 (CH), 128.24 (CN), 36.80 (CH_3), 32.87 (CH_2), 26.93 (CH_3), -4,53 (CH_3). IR ($CHCl_3$) ν_{max}; 3450 (Ph-H), 2870 (CH), 2225 (CN), 1710 (CO) and 1680 (CO) cm^{-1}. MS m/z 301 (M+ 13%).

ACKNOWLEDGMENT

Financial support from Italian MURST is acknowledged. One of us (M. Botta) wishes to thank for a grant from the Merck Research Laboratories (Academic Development Program in Chemistry).

REFERENCES

1. A. L. Pogolatti and D. V. Santi, 'Bioorganic Chemistry,' Vol. 1, ed. by E. E. Van Tamelen, Academic Press, New York, 1977, p. 279.
2. C. B. Brouillette, T. C. Chang, and M. P. Mertes, *J. Med. Chem.*, 1979, **12**, 1541.
3. (a) L. Strekowski, R. A. Watson, and M. A. Faunce, *Synthesis*, 1987, 579; (b) S. Senda, K. Hirota, and T. Asao, *J. Org. Chem.*, 1975, **40**, 353.
4. (a) E. Vega, G. A. Rood, E. R. de Ward, and U. K. Pandit, *Tetrahedron*, 1991, **47**, 4361; (b) P. F. C. Varder Meij and U. K. Pandit, *Tetrahedron Lett.*, 1988, **29**, 5445.
5. (a) N. D. P. Cosford and R. F. Schinazi, *J. Org. Chem.*, 1991, **56**, 2161; (b) K. Hirota, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, 1978, **43**, 1193; (c) S. Senda, K. Hirota, and T. Asao, *Chem. Pharm. Bull.*, 1975, **23**, 1708.
6. H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, 1951, **73**, 4030.
7. A. G. Brook and H. Gilman, *J. Am. Chem. Soc.*, 1954, **76**, 278.
8. M. V. George, D. J. Peterson, and H. Gilman, *J. Am. Chem. Soc.*, 1960, **82**, 403.
9. I. Fleming, 'Comprehensive Organic Chemistry,' Chap. 13, ed. by D. N., Pergamen Press, 1979, Oxford, pp.542-686.
10. H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, 1958, **80**, 2680.
11. A. G. Brook, *J. Am. Chem. Soc.*, 1958, **80**, 1886.
12. W. C. Still, *J. Org. Chem.*, 1976, **41**, 3063.
13. W. C. Still and A. Mitra, *Tetrahedron Lett.*, 1978, 2659.
14. M. Koreeda and S. Koo, *Tetrahedron Lett.*, 1990, **31**, 831.
15. D. L. Clive and C. Zhang, *J. Org. Chem.*, 1995, **60**, 1413.
16. C. Palomo, J. M. Aizpurua , M. Iturburu, and R. Urchegui, *J. Org. Chem.*, 1994, **59**, 240.
17. D. Garside, D. N. Kirk, and N. M. Waldron, *Steroids*, 1994, **59**, 702.
18. R. P. Polniaszek and L. W. Dillard, *J. Org. Chem.*, 1992, **57**, 4103.
19. M. K. O'Brien , A. J. Pearson , A. A. Pinkerton, W. Schmidt, and K. Willman, *J. Am. Chem. Soc.*, 1989, **111**, 1499.
20. (a) R. J. Fessenden and R. Rittenhouse, *J. Med. Chem.*, 1968, **11**, 1070; (b) R. J. Fessenden and M. D. Coon, *J. Med. Chem.*, 1964, **7**, 561.

21. S. Kusuda, Y. Ueno, T. Hagiwara, and T. Toru, *J. Chem. Soc., Perkin Trans I*, 1993, 1981.
22. (a) R. Saladino, C. Crestini, E. Mincione, G. Costanzo , E. Di Mauro, and R. Negri, *Biorg. & Med. Chem. Lett.*, 1997, **11**, 2041; (b) M. Botta, F. Occhionero, R. Saladino, C. Crestini, and R. Nicoletti, *Tetrahedron Lett.*, 1997, **38**, 8249; (c) M. Botta, R. Saladino, G. Delle Monache, G. Gentile, and R. Nicoletti, *Heterocycles*, 1996, **43**, 1687; (d) R. Saladino, E. Mincione, C. Crestini, R. Negri, E. Di M. Mauro,and G. Costanzo, *J. Am. Chem. Soc.*, 1996, **118**, 5615. (e) R. Saladino, E. Mincione, C. Crestini, and M. Mezzetti, *Tetrahedron*, 1996, **52**, 6759.
23. R. Saladino, L. Stasi, C. Crestini, R. Nicoletti, and M. Botta, *Tetrahedron*, 1997, **53**, 7045.
24. J. W. Gillard, R. Fortin, H. E. Morton, C. Yoakim, C. A. Quesnelle, S. Daignault, and Y. Guindon, *J. Org. Chem.*, 1988, **53**, 2602.
25. C. A. Kingsbury and W. B. Thornton, *J. Org. Chem.*, 1966, **31**, 1000.
26. (a) G. De Munno, T. Poerio, M. Julve, E. Lloret, G. Viau, and A. Caneschi, *J. Chem. Soc., Dalton Trans.*, 1997, 601; (b) R. Ghosh, D. A. Johnston, and D. L. Mutchell, *Nucleic Acid Res.*, 1995, **23**, 4934. (c) M. Botta, R. Saladino, A. Gambacorta, and R. Nicoletti, *Heterocycles*, 1991, **32**, 1537; and references cited therein.
27. J. Carson, K. W. Kraus, and W. M. D. McLeod, *J. Org. Chem.*, 1959, **24**, 392.
28. (a) M. Botta, R. Saladino, G. Gentile, V. Summa, R. Nicoletti, A. Verri, F. Focher, and S. Spadari, *Tetrahedron* , 1994, **50**, 3603; and references cited therein; (b) U. Niedballa and H. Vorbruggen, *J. Org. Chem.*, 1974, **39**, 3660.
29. M. Botta, R. Saladino, A. Gambacorta, and R. Nicoletti, *Tetrahedron Asymmetry*, 1990, **1**, 441.
30. The reaction of **12** with $PhMe_2SiLi$ did not proceed at -78°C.
31. S. Kumar and S. S. Chimni, *J. Chem. Soc., Perkin Trans. I*, 1992, 449.
32. K. Isono and S. Suzuki, *Tetrahedron Lett.*, 1970, 425.
33. Phenyldimethylsilylmethoxy(phenyldimethylsilane) **14** was isolated in a pure form by distillation (168 °C/5 Torr) and further characterized by elemental analysis: Anal. Calcd for $C_{17}H_{24}OSi_2$: C, 67.94; H, 8.05; 18.69. Found: C, 68.10; H, 8.05; Si, 18.45.
34. (a) P. Das, C. P. Spears, A. H. Shahinian, S. K. Dasgupta, and N. G. Kundu, *Biorganic & Medicinal Chem. Lett.*, 1996, **6**, 2477; (b) K. Felczak, A. K. Drabikowska, J. A. Vilpo, T. Kulikowski, and D. Shugar, *J. Med. Chem.*, 1996, **39**, 1720; (c) M. Botta, R. Saladino, D. Lamba, and R. Nicoletti, *Tetrahedron*, 1993, **49**, 6053.
35. R. Saladino, R. Bernini, C. Crestini, E. Mincione, A. Bergamini, S. Marini, and A. T. Palamara, *Tetrahedron*, 1995, **51**, 7561.
36. J. P. Scannal, A. M. Crestfield, and F. W. Allen, *Biochim. Biophys. Acta*, 1958, **32**, 406.
37. M. Botta, F. De Angelis, F. Corelli, M. Menichincheri, R. Nicoletti, M. E. Marongiu, A. Pani, and P. La Colla, *Arch. Pharm.*, 1991, **324**, 203.
38. W. V. Curran and R. P. Anger, *J. Org. Chem.*, 1966, **31**, 201.
39. W. Liebenov and H. Liedtke, *Chem. Ber.*, 1972, **105**, 2095.

Received, 26th June, 1998