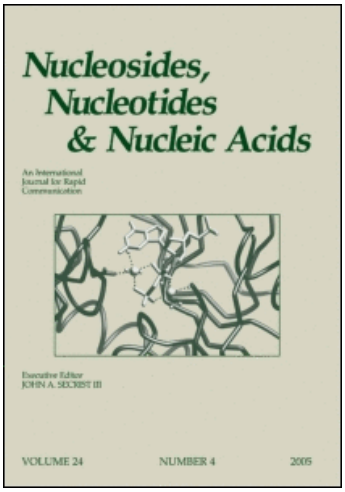

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Synthesis of Modified Nucleosides. Palladium-Catalysed Couplings of Organostannanes or Organoboranes with Pyrimidine Nucleosides

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SYNTHESIS OF MODIFIED NUCLEOSIDES. PALLADIUM-CATALYSED COUPLINGS OF ORGANOSTANNANES OR ORGANOBORANES WITH PYRIMIDINE NUCLEOSIDES.

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Abstract. Coupling of suitably protected 5-iodouridine or 5-iodo-2'-deoxyuridine with either arylboronic acids or aryltrimethylstannanes in the presence of a palladium catalyst gave moderate yields of the corresponding 5-aryluridines and 5-aryl-2'-deoxyuridines. 5-Hydroxyuridine was converted into 5-(trifluoromethanesulphonyl)uridine in good yield and the triacetate of this modified nucleoside also underwent palladium-catalysed couplings with a variety of organostannanes to produce the 5-substituted uridine in excellent yield.

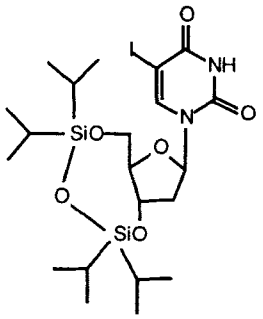
The design of new nucleoside based drugs which possess high levels of antiviral activity with minimum levels of cell toxicity requires methodologies which offer a large variety of chemically modified nucleosides for *in vitro* and *in vivo* studies. Pyrimidine nucleosides substituted at the 5-position represent an important class of biologically active molecules. Nucleosides incorporating such modifications have been shown to possess potent antiviral activity against the Herpes Simplex Virus[1] and the Human Immunodefeciency Virus (AIDS).[2] In addition to the synthesis of biologically active compounds considerable interest has been shown in developing modified pyrimidine nucleosides as probes for histological studies. The incorporation of a fluorescent label in the 5-position of modified 2'-deoxyuridine compounds has demonstrated the feasibility of this approach.[3]

Pyrimidine nucleosides modified at the 5-position have been previously prepared by a number of routes. These have included (i) the synthesis of 5-aryl-2'-deoxyuridines by the photochemically induced coupling of a 5-iodo-2'-deoxyuridine with an electron rich aromatic ring,[4] (ii) the palladium-catalysed coupling of aryl or vinyl halides with 5-mercurated-2'-deoxyuridines,[5] (iii) the Heck reaction of activated alkenes with 5-iodopyrimidine nucleosides,[6] (iv) palladium-catalysed coupling of alkenyl- and alkynylzirconium compounds with suitably protected 5-iodo-2'-deoxyuridine[7] and (v) the palladium-catalysed coupling of terminal alkynes with iodopyrimidine nucleosides.[8]

Many of these routes are specific to the particular type of group which has to be transferred to the 5-position of the pyrimidine ring. Vinylstannanes have been reported to couple with 5-halopyrimidines in the presence of a palladium catalyst.[9] In addition, organostannanes have been shown to couple with 2-iodoadenosine derivatives under similar conditions.[10] We wished to explore the versatility of organoboranes and organostannanes as coupling partners with suitably protected uridine nucleosides as a general route to the important 5-substituted uridine class of compounds. A preliminary account of part of this work has appeared recently.[11]

Results and Discussion

The addition of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane to 5-iodo-2'-deoxyuridine gave the 3',5'-cyclic disiloxanyl derivative **1** which was soluble in organic solvents in 70% isolated yield. Similarly, addition of an excess thexyldimethylsilyl chloride to 5-iodouridine gave the trisiloxy derivative **2** as a waxy solid in 75% isolated yield. Compounds **1** and **2** served as useful precursors for the preparation of 5-aryl pyrimidine nucleosides.



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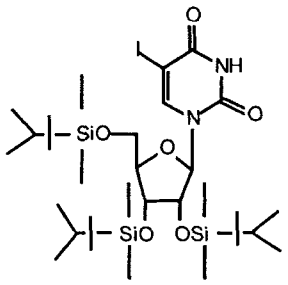


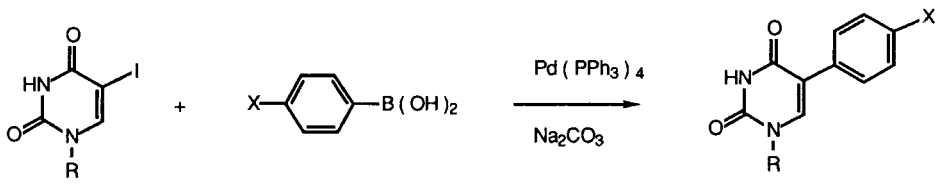
2

Aryl boronic acids have been shown to undergo a palladium-catalysed coupling with aryl and vinyl halides.[12] The aryl boronic acids were conveniently prepared by reacting the appropriate aryl lithium or aryl Grignard reagent with tri-n-butylborate followed by mild acid hydrolysis. The aryl boronic acids used in this work were crystalline solids and were insensitive to air and moisture.

Coupling of either **1** or **2** with phenyl boronic acid under the standard conditions as described by Suzuki[12] gave the expected 5-phenyl derivatives **3a** and **4a**. For example, heating a toluene solution of **1** or **2** with phenyl boronic acid in the presence of aqueous sodium carbonate and a catalytic quantity of $Pd(PPh_3)_4$ gave **3a** in 55% yield and **4a** in 49% yield (**Scheme 1**). A small quantity of biphenyl was also isolated from these reaction mixtures.

The reaction was also extended to 4-methoxyphenyl boronic acid for **1** and **2** and to 4-dimethyl aminophenyl boronic acid for **1** (**Scheme 1**). The yields for these reactions were

all moderate and minor variations in the experimental conditions did not improve the isolated yields. No starting material was recovered from the reaction mixtures and it is not clear where the remaining material has gone, although on column chromatography there is considerable baseline material. The work up for the reactions involved a simple aqueous washing and flash chromatography.



1 **3a-c**

2 **4a-b**

R = 3',5'-cyclic disiloxanyl-2'-deoxyuridine
X = 3a -H (55%), 3b $-OCH_3$ (50%), 3c $-N(CH_3)_2$ (37%)

R = 2',3',5'-tris(thexyldimethylsilyl)uridine
X = 4a -H (49%), 4b $-OCH_3$ (59%).

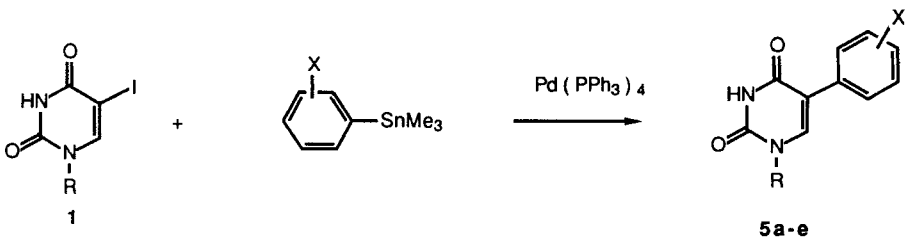
Scheme 1

The coupling of aryl boronic acids bearing electronegative groups was not successful. For example, the reaction between either **1** or **2** and 4-(α,α,α-trifluoromethyl)phenyl boronic acid or 4-(4,4-dimethyl-2-oxazoline)phenyl boronic acid returned only starting material. In separate experiments we have shown that these aryl boronic acids will couple with iodobenzene under identical conditions to those described above to give the expected functionalized biphenyl in good yield. In view of this apparent limitation with the coupling of aryl boronic acids with 5-iodopyrimidine nucleosides an alternative route which was compatible with a variety of functional groups was sought.

Recent work has highlighted the ability of halopyrimidines[9] and 2-iodoadenosine[10] to undergo a palladium-catalysed coulpling with vinylstannanes. We therefore examined the coupling of aryltrimethyl stannanes bearing electron withdrawing groups with 5-iodo pyrimidine nucleosides.

Thus reaction of **1** with 4-fluorophenyltrimethylstannane in dioxane at 75° overnight in the presence of $Pd(PPh_3)_4$ gave the expected 5-aryl-2'-deoxyuridine **5a** in 49% isolated yield. This reaction was extended with equal efficacy to a number of fluoro-substituted aryltrimethylstannanes and gave the expected products in moderate yields (**Scheme 2**). In

contrast to the aryl boronic acids the 4-(4,4-dimethyl-2-oxazoline)phenyl derivative **5c** was prepared in 48% isolated yield.



R = 3',5'- cyclic disiloxanyl-2'-deoxyuridine

X = 5a, 4-fluoro (49%); 5b, 4-α,α,α-trifluoromethyl (40%)
5c, 4-(4,4-dimethyl-2-oxazoline) (48%); 5d, 3,5-difluoro (40%),
5e, 3,5-bis(α,α,α- trifluoromethyl) (43%).

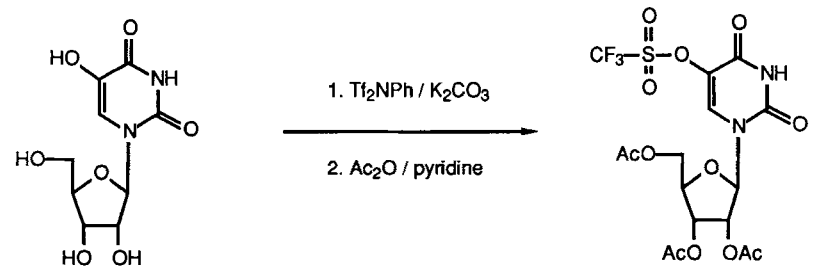
Scheme 2

In spite of numerous attempts we could not improve the yields of the isolated products from these coupling reactions. The starting nucleosides were completely consumed and considerable baseline material was observed on chromatography of the reaction mixtures. We therefore sought a leaving group which might lead to higher yields of coupled product.

Extensive methodology studies have been reported on the use of vinyl- and aryltriflates as coupling partners for organostannanes.[13] In view of this versatility we have examined the preparation of 5-(trifluoromethanesulphonyl)uridine **6** and its subsequent use in coupling reactions.

Initial attempts directed towards the synthesis of **6** from 5-hydroxyuridine concentrated on the selective protection and deprotection of the various hydroxy groups present on the molecule. This route proved inefficient and a simpler procudure was sought which would avoid tedious protection and deprotection steps. *N*-phenyltriflimide has been used as a mild triflating agent[14] and we reasoned that under mildly basic conditions the enolate anion of 5-hydroxyuridine should triflate sufficiently rapidly so as to minimize triflation at the other active sites in the molecule. Gratifyingly, reaction of 5-hydroxyuridine with N-phenyl triflimide in dioxane/water with a slight excess of potassium carbonate gave the desired product **6** in 54% isolated yield. Compound **6** was highly soluble in aqueous solvents and was treated with an excess of acetic anhydride in pyridine and gave the triacetate derivative **7** which was soluble in organic solvents. The moderate yield obtained for the preparation of **6** was attributed to difficulties experienced during the isolation procedure, so a one-pot sequence was attempted by treating the crude uridine triflate **6** with acetic anhydride in pyridine and

this gave the triacetate uridine triflate **7** in 97% isolated yield over the two steps (**Scheme 3**). Compound **7** was a white, crystalline solid which was stable to chromatography and insensitive to air and moisture.



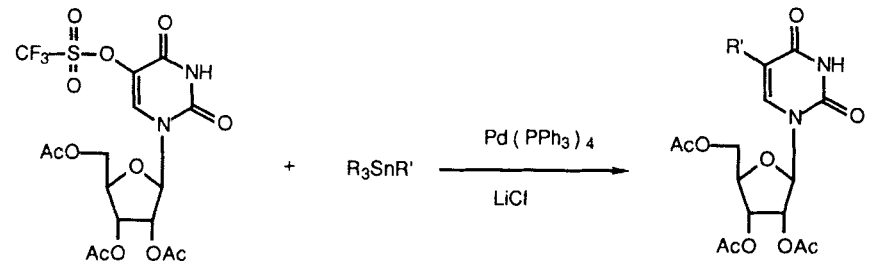
7

Scheme 3

The palladium-catalysed coupling of vinyl and aryltrialkylstannanes with **7** proved to be a general reaction. For example, the addition of a slight excess of tri-*n*-butylethenyl stannane to **7** in the presence of a catalytic quantity of $Pd(PPh_3)_4$, lithium chloride and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol (as a polymerization inhibitor)[15] gave the desired 5-ethenyl uridine derivative **8a** in 87% isolated yield (**Scheme 4**). As previously noted lithium chloride was essential for the coupling reaction with no product being formed in its absence.[15] The polymerization inhibitor was added routinely, although it may not be required in all cases. We found that vinyl-substituted uridines were susceptible to polymerizaion in the absence of inhibitor. The coupling proved to be quite general for vinyl and arylstannanes with a variety of functional groups (**Scheme 4**).

The *trans* stereochemistry around the double bond of the vinyl-substituted compounds was retained during the coupling reaction as shown by the J_{HH} of approximately 16Hz for the alkene resonances in the ^1H n.m.r. of products **8b,8c,8d,8f**. The reaction of ethyl 2-tri-*n*-butylstannylpropenoate with **7** gave a 46% yield of the expected product **8e** as well as a 40% yield of the *trans* product **8d**. The formation of this unexpected product could be the result of a Heck-type coupling [16] between the terminal carbon of the alkene of the acrylate stannane and **7**. Subsequent palladium-catalysed reduction of the tri-*n*-butyl stannane group would give the observed product. Since Heck reactions are considerably slower for alkenes without electron withdrawing groups[17] the coupling of 2-trimethylstannylpropene with **7** proceeded as expected and gave a good yield of the desired product **8g**.

Arylstannanes possessing both electron donating and electron withdrawing substituents coupled with **7** and showed the expected selective transfer of the aryl group (**Scheme 4**). The presence of an electron withdrawing group on the aromatic ring enhanced the rate of reaction and generally gave a higher isolated yield of the product.



7 **8a-m**

R = Butyl

R' = 8a -CH=CH$_2$ (87%)
8b **E** -CH=CHPh (75%)
8c **E** -CH=CHSi(CH$_3$)$_3$ (73%)
8d **E** -CH=CHCO$_2$CH$_2$CH$_3$ (92%)
8e -C(CO$_2$CH$_2$CH$_3$)=CH$_2$ (46%)
8f **E** -CH=CHOSi(CH$_3$)$_2$C(CH$_3$)$_2$CH(CH$_3$)$_2$ (92%)

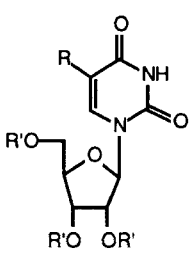
R = Methyl

R' = 8g -C(CH$_3$)=CH$_2$ (86%)
8h -C$_6$H$_5$ (64%)
8i -C$_6$H$_4$(4-OCH$_3$) (55%)
8j -C$_6$H$_4$(4-F) (89%)
8k -C$_6$H$_4$(4-CF$_3$) (91%)
8l -C$_6$H$_3$(3,5-F$_2$) (81%)
8m -C$_6$H$_3$(3,5-(CF$_3$)$_2$) (85%)

Scheme 4

Not all groups could be transferred from the organostannane successfully. For example, addition of either tetramethylstannane, benzyltrimethylstannane, or pentafluorphenyl trimethylstannane to **7** returned only staring material. Alkyl groups are known to transfer slowly[13] and this allows the selective transfer of an aryl or vinyl groups from aryl or vinyltrialkylstannanes. The inability to transfer the pentafluorophenyl group may reflect the stability of the presumed palladium-aryl intermediate.[18]

The biological activities of some pyrimidine nucleosides have been shown to be dependent upon the conformational preference of the base ring with respect to the sugar unit.[19] Uridine nucleosides containing either the ribose or 2'-deoxyribose sugar unit have a preference for the **anti** rather than the **syn** conformation.[7,20] This preference can be altered by the presence of substituents at the 6-position of the pyrmidine base so that the **syn** conformation predominates.[20] Previous n.m.r. methods used to establish the **syn** or **anti** conformational preference of the nucleoside have included (i) the 3-bond proton-carbon coupling constant, $^3J_{C2\text{-}H1'}$,[19] (ii) the relative chemical shift difference between the protons H2a' and H2b' on the carbon C2' of 2'-deoxyribose sugars[20], and (iii) the relative chemical shift difference between the carbons C2' and C3' of ribose nucleosides in the ^{13}C n.m.r. spectrum.[7]



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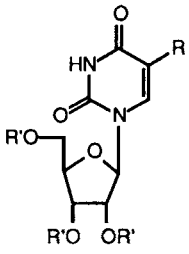

SYN

The ^1H n.m.r. spectra for the triacetate uridine nucleosides containing a 5-aromatic substituent (compounds (**8h-m**) clearly show an upfield shift of one of the acetate methyl signals compared to the 5-vinyl substituted compounds (**8a-g**). This could be readily explained if the uridine nucleoside adopted an **anti** conformation and the aromatic ring in the 5-position was then situated above the C5' acetate group. The acetate methyl would then reside in the shielding region of the aromatic ring and hence the resonance would be shifted upfield with respect to the non-aromatic compounds. All of the aromatic compounds displayed this upfield shift (see Experimental).

Thymidylate synthase is an enzyme which converts 2'-deoxyuridine-5'-phosphate to thymidine-5'-phosphate. The accepted mechanism for this conversion involves a reversible cysteine thiol addition to position 6 of the uridine substrate followed by reaction with 5,10-methylenetetrahydrofolic acid.[4] This reversible addition of cysteine thiol to the 6-position of the uridine base makes the development of mechanism based inhibitors of the enzyme an attractive route. Substituents at the 5-position of the uridine base can influence the electron density at the 6-position and hence the susceptibility of the uridine ring to attack by nucleophilic reagents. Previous studies on *para*-functionalised aryl substituted 2'-deoxyuridine compounds have indicated a close correlation between the Hammett σ_p values and the proton chemical shifts of the N3 hydrogen, the proton chemical shifts of the C6 hydrogen and the carbon chemical shifts of the C6 carbon .[5] This close correlation was taken as indicating that a significant degree of orbital overlap existed between the aryl group and the pyrimidine ring and that the electronic effect of the *para*-substituent was capable of being transmitted to the N3 hydrogen and to the C6 carbon. **Table 1** contains the proton chemical shifts of the C6 hydrogen, the carbon chemical shifts of the C6 carbon and the proton chemical shifts of the N3 hydrogen for the compounds **3a-c** and **5a-e**.

The results in **Table 1** show that a strong correlation exists between the proton chemical shifts of the C6 hydrogen of *para*-substituted aryl 3',5'-cyclic disiloxanyl compounds and the Hammett σ_p values . This correlation was not evident with either the proton chemical shifts of the N3 hydrogen or the carbon chemical shifts of the C6 carbon. The results indicate that there is a strong interaction between the aromatic ring and the pyrmidine ring in terms of the electronic influence of the substituent extending to the C6 carbon but that the proton chemical shift of the N3 hydrogen may be influenced by factors other than the substituent at C5.

Table 1. Correlation of ^{1}H n.m.r. and ^{13}C n.m.r. Data for Compounds **3a-c** and **5a-e** with Hammett Parameters[A].

Substituent	σ_p	H6 Hydrogen	N3 Hydrogen	C6 Carbon
$-N(CH_3)_2$	-0.83	7.55	-	134.8
$-OCH_3$	-0.27	7.67	9.19	135.7
- H	0.00	7.74	8.66	136.7
- F	0.06	7.76	8.76	-
-oxazoline	0.33	7.81	9.34	137.2
$-CF_3$	0.54	7.91	9.16	143.9
$-3,5-F_2$	0.68	7.93	9.23	-
$-3,5-(CF_3)_2$	0.86	8.07	9.15	138.4

A. Hammett values taken from Hansch,C.; Leo,A.; Unger,S.H.; Kim,K.H.; Nikaitani,D.; Lien,E.J. *J. Med. Chem.* 1973 , **16**, 1207.

Experimental

Proton and carbon n.m.r. spectra were recorded in deuterochloroform with tetramethylsilane as internal standard on a Brucker CXP-300 spectrometer. Mass spectra were recorded on a AEI-GEC MS 3074 at 70eV or by Fast Atom Bombardment on a VG ZAB 2HF mass spectrometer. Optical rotations were measured on a Perkin Elmer 141 Polarimeter and were measured in chloroform.

1,4-Dioxane was distilled over potassium before use. The drying and purification of other solvents were carried out according to standard literature procedures.[21] All reactions were routinely carried out under an atmosphere of nitrogen. Melting points were obtained on a Reichert hot-stage apparatus and are uncorrected.

The following compounds were prepared according to literature procedures: trimethylstannylpentafluorobenzene[18], trimethylphenylstannane[22], tri-n-butyl ethenylstannane[23], **E**-tri-n-butyl(2-phenyl ethenyl)stannane[24], benzyltrimethyl stannane[25], **E**-1-trimethylsilyl-2-tri-n-butylstannyl ethene[26], ethyl **E**-3-tri-n-butylstannylpropenoate[27], ethyl 2-tri-n-butylstannyl propenoate[27], 2-trimethyl stannylpropene[28], dimethyl-2,3-dimethylbutyl[(3-tri-n-butylstannyl)-2-propenyl) oxy]silane[24],4-(trimethylstannyl)anisole[29], 4-(trimethylstannyl) fluorobenzene[30], 4-(trimethylstannyl)-α,α,α,-trifluoromethyl benzene[31],5-(trimethylstannyl)-1,3-difluoro benzene[30], 5-(trimethylstannyl)1,3-bis-(α,α,α-trifluoromethyl)benzene[30], 4-methoxyphenyl boronic acid[32], 4-dimethylamino phenylboronic acid[33], 2-(4-bromo phenyl)-4,4-dimethyl-2-oxazoline[34], 5-hydroxyuridine [35] , tetrakis(triphenylphosphine)palladium(O)[36], dichlorobis(triphenylphosphine)

palladium(II)[37]. Many of the nucleosides retained solvents when purified and this made it difficult to obtain accurate analytical data on all of the compounds. All compounds were pure by HPLC analysis.

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-iodo-2'-deoxyuridine (1)

To a dimethylformamide (10 ml) solution of 5-iodo-2'-deoxyuridine (2.0 g, 5.60 mmol) was added imidazole (1.7 g, 25.0 mmol) and 1,3-dichloro-1,1',3,3'-tetraisopropyl disiloxane (1.96 g, 6.0 mmol). The reaction mixture was stirred at room temperature for 24 hours after which time t.l.c. analysis indicated the complete consumption of starting material. Water (100 ml) was added and the mixture was extracted with dichloromethane (3x50 ml) and the organic phase was dried with magnesium sulphate. After removal of the solvent the residue was subjected to flash chromatography using 80% petroleum ether and 20% ethyl acetate. Recrystallization from hexane gave a white solid (2.3g, 70 %). m.p. 187°. $[\alpha]_D$ -43.4 (c, 0.50). $C_{21}H_{37}IN_2O_6Si_2$ Calc: C,42.28; H,6.37; N,4.71. Found: C,42.52; H,6.37; N,4.71. ^1H n.m.r. δ 0.9-1.2,m,CH_3; 2.24-2.56, H2'a,H2'b; 3.37,m,H4'; 4.07,m, H5'a,H5'b; 4.46,m,H3'; 6.01,dd,J 1Hz,H1'; 8.03,s,H6. ^{13}C n.m.r. δ 12.4,12.8,13.0, 16.8,16.9,17.0,17.2,17.4,17.5,17.7,CH_3.CH; 39.9,C2'; 60.0,C5'; 67.3,C3'; 68.1,C5; 84.6,C4'; 85.3,C1'; 144.0,C6; 149.9,C2; 160.2,C4.

2',3',5'-Tris-O-[(dimethyl-2-(2,3-dimethylbutyl)silyl]5-iodouridine (2)

To a dimethylformamide (30 ml) solution of 5-iodouridine (5.0 g, 13.5 mmol) was added imidazole (5.5 g, 80.0 mmol) and dimethylthexylsilyl chloride (14.2 g, 80.0 mmol). The reaction mixture was stirred for 24 hours at room temperature after which water (100 ml) was added and the mixture extracted with dichloromethane (3x50 ml). The organic portion was dried over magnesium sulphate and after removal of the solvent the residue was subjected to flash chromatography eluting with 80% petroleum ether and 20% ethyl acetate. A thick, clear oil was obtained (8.0 g, 75%).This oil retained solvent even after prolonged drying under high vacuum. $C_{33}H_{65}IN_2O_6Si_3$ Calc: C,49.8; H,8.2; N,3.5. Found: C,50.7; H, 8.8; N, 3.1. $[\alpha]_D$ -39.8 (c, 0.49). ^1H n.m.r. δ -0.10, 0.30,s, CH_3Si; 0.6-1.0,m,$(CH_3)_2$; 1.60,m,CH; 3.68-4.08,m,H2',3',4',5'; 6.05,d,J 7 Hz, H1'; 7.96,s,H6; 8.91,s,NH. ^{13}C n.m.r. δ -3.2,-3.0,-2.6,-2.5,-2.3,-1.6,18.4,18.5,18.7, 20.1,20.4,20.7, 33.7, 33.9, 34.1,CH_3CH,CH_3Si; 63.1,C5'; 68.7,C5; 72.5,C3'; 75.3,C2'; 86.5,C4'; 87.0,C1'; 144.5,C6; 150.0,C2; 159.9,C4.

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-phenyl-2'-deoxyuridine (3 a)

To a degassed solution of toluene (15ml) was added tetrakis(triphenylphosphine) palladium(O) (0.021 g, 0.018mmol) and 1 (0.10 g, 0.183mmol). To the solution was added sodium carbonate (0.028 g, 0.036mmol in 0.3ml water) and phenylboronic acid (0.025g, 0.20mmol in 1.0ml ethanol). The mixture was heated to reflux for 16 hours. After

the mixture had been cooled it was diluted with diethyl ether (30ml), washed with water (2x20ml) and dried over magnesium sulphate. The residue was purified by chromatography using 80% petroleum ether and 20% ethyl acetate. 55%. $[\alpha]_D$ -49.5 (c, 0.99). ^{1}H n.m.r. δ 0.90-1.20,m,$(CH_3)_2CH$; 2.31-2.60,m, H2'a,H2'b; 3.81,dt,J 3.0 and 7.8 Hz,H4'; 4.52, m,H3'; 4.06,m,H5'a,H5'b; 6.14,dd,J 2.5 and 7.4Hz,H1'; 7.35-7.50,m,Ar; 7.74,s,H6; 8.66,s,NH. ^{13}C n.m.r. δ 12.4,12.9,13.4,16.8, 17.2 , $(CH_3)_2CH$; 39.8,C2', 60.5,C5'; 68.0,C3'; 84.3,C4'; 85.1,C1'; 115.3,C5; 127.9, 128.3, 132.4,136.8,Ar; 136.7,C6; 149.8,C2; 162.1,C4.

Compounds **3b,3c,4a** and **4b** were prepared in an analogous manner.

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-(4-methoxyphenyl)-2'-deoxyuridine (3b)

50%. $[\alpha]_D$ -52.3 (c,0.31). ^{1}H n.m.r. δ 0.90-1.10,m,$(CH_3)_2CH$; 2.30-2.56,m, H2'a,H2'b; 3.78,m,H3'; 3.82,s,OCH_3; 4.06,m,H5'a,H5'b; 4.51,m,H4'; 6.15,dd,J 2.5 and 7.3 Hz, H1'; 6.91,d,J 8.9 Hz, Ar; 7.45,d,J 8.9 Hz,Ar; 7.67,s,H6; 9.19,s,NH. ^{13}C n.m.r. δ 12.3, 13.1, 16,9,$(CH_3)_2CH$; 39.7,C2'; 55.0,OCH_3; 60.5,C5'; 68.6,C3'; 84.0,C4'; 85.0, C1'; 113.7,Ar; 114.8,C5; 130.4,Ar; 135.7,Ar;135.7,C6; 149.9,C2; 159.4,Ar; 162.6,C4.

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-(4-dimethylamino phenyl)-2'-deoxyuridine (3c)

37%. $[\alpha]_D$ -56.6 (c, 0.30). ^{1}H n.m.r. δ 0.90-1.10,m,$(CH_3)_2CH$; 2.29-2.57,m, H2'a,H2'b; 2.96,s,$(CH_3)_2$;3.79,m,H4'; 4.05,m,H5'a,H5'b; 4.54,m,H3'; 6.16,dd J 3.0 and 8.0 Hz,H1'; 6.72,d, J 8.8Hz,Ar; 7.35,d,J 8.8 Hz, Ar; 7.55,s,H6. ^{13}C n.m.r. δ 12.5,13.1, 13.5,16.9, 17.2,17.3,17.5,$(CH_3)_2CH$; 39.9,$(CH_3)_2$; 40.5,C2'; 61.1,C5'; 68.9,C3'; 84.1,C4'; 85.1,C1'; 112.5,Ar; 129.0,Ar; 134.8,C6; 149.5,C2; 162.1,C4.

2',3',5'-Tris-O-[(dimethyl-2-(2,3-dimethylbutyl)silyl]-5-phenyluridine (4a)

49%. $[\alpha]_D$ -60.2 (c, 0.86). ^{13}C n.m.r. δ -3.9,-3.0,-2.8,-1.7,18.3,19.9,20.2, 24.6, 25.1, CH_3 and CH ; 63.0,C5'; 72.3,C3'; 74.7,C2'; 86.1,C4'; 87.1,C1'; 116.1,C5; 127.9, 128.3,128.7,Ar; 135.3,Ar; 137.4,C6; 150.2,C2; 162.2,C4.

2',3',5'-Tris-O-[(dimethyl-2-(2,3-dimethylbutyl)silyl]-5-(4-methoxy phenyl)uridine (4b)

59%. $[\alpha]_D$ -42.0 (c, 0.55). FAB m/z 777 [M+1]. ^{1}H n.m.r. δ -0.05-0.15,s,CH_3Si; 0.68 -0.91,m,CH_3; 1.45-1.60,m,CH; 3.70,m,H2'a,H2'b; 3.79,s,OCH_3; 4.0-4.30,m, H2',H3',H4'; 6.08,d,J 7.3 Hz; 6.88,d J 8.8 Hz, Ar; 7.32,d J 8.8 Hz, Ar; 7.49,s,H6; 8.45,s, NH. ^{13}C n.m.r. δ 18.3,20.0,20.3,24.8,25.3,33.8, CH_3,CH; 55.3,OCH_3; 63.2,C5'; 72.4,C3'; 74.7,C2'; 86.2,C4'; 87.3,C1'; 113.9,Ar; 115.9,C5; 124.9,Ar; 130.1, Ar; 136.9,C6; 150.2 C2; 159.6,Ar; 162.5,C4.

5-(4-methoxyphenyl)uridine , free hydroxy from 4b

To a dry tetrahydrofuran (10 ml) solution of **4b** (0.115g, 0.148 mmol) was added tetrabutylammonium fluoride (0.90 ml, 1M tetrahydrofuran solution, 0.892 mmol) and the solution was stirrted for 3 hours at room temperature. The solvent was removed under reduced pressure and the residue purified by flash chromatography using dichloromethane (90%)/ methanol (10%) as eluent. The white solid (96%) was recrystallised from ethanol/ether. M.p. 188-190°. M/z 350 [M]. $C_{16}H_{18}N_2O_7$ Calc: 350.1114; Found: 350.1103. ^{1}H n.m.r. (DMSO d^6) δ 3.60,m,H5a',H5b'; 3.80,s,OCH_3; 4.04,m,H4'; 4.23,m,H2',H3'; 4.64,d J 4.7 Hz,3' OH; 4.90,t, J 4.7 Hz,5' OH; 5.08,d,4.9 Hz, 2' OH; 5.97,d J 3.8 Hz, H1'; 6.68, d J 8.5 Hz, Ar; 7.51,d J 8.9 Hz,Ar; 8.18,s,H6.

5-phenyluridine, free hydroxy from4a

Prepared as described above. M/z 320 [M]. $C_{15}H_{16}N_2O_6$ Calc: 320.1008; Found: 320.0995.

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-(4-fluorophenyl)-2'-deoxyuridine (5a)

49%. $[\alpha]_D$ -32.3 (c, 0.41). ^{19}F n.m.r. δ -37.5. ^{1}H n.m.r. δ 0.90-1.20,m,$(CH_3)_2CH$; 2.30-2.60,m,H2'a, H2'b; 3.80,m,H4'; 4.08,m, H5'a,H5'b; 4.48,m,H3'; 6.12,d, J 2.0 and 7.3Hz,H1'; 7.07,dd J 8.8 and 8.8 Hz Ar; 7.50,dd J 5.4 and 8.8 Hz,Ar; 7.76,s,H6; 8.76,s,NH.

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-(4-α,α,α-trifluoro methylphenyl)-2'-deoxyuridine (5b)

40%. $[\alpha]_D$ -62.3 (c, 0.39). ^{1}H n.m.r. δ 0.90-1.10,m,$(CH_3)_2CH$; 2.32-2.62,m, H2'a,H2'b; 3.81,m,H4'; 4.08,m,H5'a,H5'b; 4.48,m,H3'; 6.12,d J 7.0 Hz,H1'; 7.62,7.67,AB, J 8.5 Hz,Ar.

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-[4-(2-(4,4-dimethyl-2-oxazoline)phenyl)]-2'-deoxyuridine (5c)

48%. $[\alpha]_D$ -36.1 (c, 0.23). ^{1}H n.m.r. δ 0.90-1.20,m,$(CH_3)_2CH$; 1.39,s,$(CH_3)_2$; 2.2-2.6, m, H2'a,H2'b; 4.05,m,H5'a,H5'b; 4.11,s,CH_2; 4.50,m,H3'; 6.20,dd,J 2.3 and 7.2Hz,H1'; 7.58,d,J 8.4Hz,Ar; 7.81,s,H6; 7.93,d,J 8.4Hz,Ar; 9.34,s,NH. ^{13}C n.m.r. δ 12.6, 13.0,13.5, 17.0,17.2,17.4, 28.4,$(CH_3)_2CH$; 40.0,C2'; 60.6,C5'; 68.1,C3'; 79.1,CH_2; 84.6,C4'; 85.3,C1';114.3,C5; 127.9,128.3,Ar; 135.3,Ar;137.2,C6; 139.6,Ar; 149.6,C2; 161.8,C4.

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-(3,5-difluorophenyl)-2'-deoxyuridine (5d)

40%. $[\alpha]_D$ -39.7 (c, 0.34). ^{19}F n.m.r. δ -33.0. ^{1}H n.m.r. δ 0.90-1.10,m, $(CH_3)_2CH$; 2.30-2.60,m, H2'a,H2'b; 3.82,m,H4'; 4.10,m,H5'a,H5'b; 4.48,m,H3'; 6.09,dd J 1.5 and 7.0 Hz,H1'; 6.76,tt J 2.3 and 8.8 Hz,Ar; 7.16,dd J 2.3 and 8.7 Hz,Ar; 7.93,s,H6; 9.23,s,NH. M/z 583 [M+1].

3',5'-[1,3-(1,1,3,3-tetraisopropyldisiloxanyl)]-5-[3,5-bis(α,α,α-trifluoromethyl)phenyl]-2'-deoxyuridine (5e)

43%. $[\alpha]_D$ -61.8 (c, 0.56). ^{19}F n.m.r. δ 13.8. ^1H n.m.r. δ 0.90-1.20,m,$(CH_3)_2CH$; 2.30-2.62,m,H2'a,H2'b; 3.84,m,H4'; 4.11,m,H5'a,H5'b; 6.09,dd,J 1.1 and 6.8 Hz, H1'; 7.82,s,Ar; 8.03,s,Ar; 8.07,s,H6; 9.15,s,NH. M/z 682 [M]. $C_{26}H_{34}F_6N_2O_6Si_2$ [M-C_3H_6]. Calc: 640.1860; Found: 640.1823.

5-(4-α,α,α-trifluoromethylphenyl)-2'-deoxyuridine, free hydroxy from 5b

Prepared as described above. M/z 372 [M]. $C_{16}H_{15}F_3N_2O_5$ Calc: 372.0933; Found: 372.0941.

2',3',5'-Tri-O-Acetyl-5-trifluoromethanesulphonyluridine (7).

To a dioxane/water (4/1, 10ml) solution was added 5-hydroxyuridine (0.84g, 3.23 mmol), potassium carbonate (0.43g, 3.2mmol), and N-phenyltriflimide (0.94g, 3.0mmol). The mixture was stirred at room temperature for 14 hours. The solvent was removed under vacuum and the residue was dissolved in pyridine (20 ml), and acetic anhydride (2.2 ml, mol) added. The mixture was stirred for 20 hours at room temperature. The solvent was removed under vacuum and the residue dissolved in ethyl acetate (20 ml). The organic solution was washed with aqueous citric acid (30%, 2x 20ml), brine and dried over magnesium sulphate. After the solvent was removed the residue was subjected to flash chromatography using chloroform/methanol (4/1) as eluent. The product was obtained as a white solid (1.63g, 97%). m.p. 63-64°. $[\alpha]_D$-12.1 (c, 1.04). UV 265.5nm, ε7402. ^1H n.m.r. δ 2.04,s,CH_3; 2.07,s,CH_3; 2.09,s,CH_3; 4.21-4.41,m,H5a',H5b'; 5.22-5.29, m, H2',H3',H4'; 5.98,d J 4.9Hz,H1'; 7.76,s,H6. ^{13}C n.m.r. δ 20.0, CH_3;62.9,C5'; 69.8,C3'; 73.0,C2'; 80.2,C4'; 87.9,C1';118.6,q J 322 Hz, CF_3; 127.2; 133.6;149.2,C6; 156.9,C2; 169.9,CH_3CO;170.5,C4. FAB m/z 519 (M+H) $C_{16}H_{17}CF_3N_2O_{12}S$ Calc. C 37.07; H 3.31; N 5.40. Found C 36.97; H 3.31; N 5.29.

2',3',5'-Tri-O-Acetyl-5-ethenyluridine (8a)[38]

To a degassed solution of 1,4-dioxane (20ml) was added uridine triflate **7** (0.10g,0.19mmol) tetrakis(triphenylphosphine)palladium (O) (0.012g, 0.01mmol), lithium chloride (0.037g, 0.90mmol), ethenyltri-*n*-butylstannane (0.073g, 0.22mmol) and a few crystals of the radical inhibitor 2,6-di-*tert* butyl-4-methylphenol. The mixture was heated at reflux for 4 hours, cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (10ml) and washed with a saturated solution of potassium fluoride (to remove tin residues). The dried diethyl ether layer was concentrated and the residue was subjected to flash chromatography using ethyl acetate and petroleum ether in a 3 to 4 ratio. 87%. $[\alpha]_D$ -21.7 (c, 0.68). FAB m/z 397 [M+1]. UV 249,278nm, ε 5475 . ^1H n.m.r. δ 2.03,s,CH_3; 2.07,s,CH_3; 2.08,s,CH_3; 4.23-4.38,m,H5a',H5b' ; 5.21,dd,J 1.0 and 11.3 Hz, CH=CH; 5.26-5.32,m,H2',H3',H4' ; 5.88,dd J 1.0 and 17.6 Hz,CH=CH; 6.04,d J 5.0 Hz,H1'; 6.33,dd J 11.3 and 17.5 Hz,CH=CH; 7.39,s,H6; 9.55 s,NH. ^{13}C n.m.r. δ 20.3,20.6,CH_3; 63.2,C5'; 70.2,C3'; 72.3,C2'; 80.0,C4';87.2,C1'; 113.7, ; 116.6,127.7,135.5, 149.9,C6; 161.9,C2; 169.7,CH_3CO; 170.3,C4.

The following compounds were prepared in an analogous manner.

2',3',5'-Tri-O-Acetyl-5-(E-2-phenylethenyl)uridine (8b)

75%. m.p. 79-80°. $[\alpha]_D$ -66.7 (c, 0.51). m/z 472 [M]. $C_{23}H_{24}N_2O_9$ Calc. 472.1480. Found: 472.1482. UV 259.6,314.8nm, ε 9702 . ^{1}H n.m.r. δ 2.06,2.07,s,CH3; 4.29-4.35,m, ; 5.29-5.35,m, ; 6.07,d J 5.2 Hz, H1'; 6.73,d J 16.4 Hz,CH=; 7.15-7.38,m, Ar-CH=; 7.48,s,H6; 9.47,s,NH.

2',3',5'-Tri-O-Acetyl-5-(E-2-trimethylsilylethenyl)uridine (8c)

73%. m.p. 48-50°. $C_{20}H_{28}N_2O_9Si$ m/z 453 [M - CH_3] Calc: 453.1329 ; Found: 453.1346 $[\alpha]_D$ -51.6 (c, 0.66). UV 244,294nm, ε 11,919 . ^{1}H n.m.r. δ 0.12, s,Si(CH_3)$_3$; 2.11,s,CH_3; 2.14,s,CH_3; 2.15,s,CH_3; 4.34-4.44,m,H5a',H5b' ; 5.31-5.38, m,H2',H3',H4' ; 6.13,d J 5.1 Hz, H1'; 6.57,6.65, AB, J 19.2 Hz,CH=CH; 7.49,s,H6; 9.21, s,NH. ^{13}C n.m.r. δ 1.7,SiCH_3; 20.0,20.4, CH_3CO; 63.0,C5'; 70.1,C3'; 72.5,C2'; 79.9,C4'; 87.0, C1'; 114.3,C5; 131.7, ; 133.6, ; 135.3, ; 149.7,C6 ; 162.0,C2; 169.5,CH_3CO; 170.0,C4.

2',3',5'-Tri-O-Acetyl-5-(ethyl-1-E-propenoate)uridine (8d)

92%. m.p. 59-60°. $[\alpha]_D$ -61.5 (c, 0.73). m/z 468 [M] $C_{20}H_{24}N_2O_{11}$ Calc:468.1380; Found: 468.1395. UV 298.7nm, ε 7449 . ^{1}H n.m.r. δ 1.23,t J 7.0 Hz,**CH_3**CH_2; 2.04,s,CH_3; 2.06,s,CH_3; 2.12,s,CH_3; 4.14,q J 7.0 Hz, **CH_2**CH_3; 4.31-4.39, m,H5a',H5b' ; 5.22-5.40,m,H2',H3',H4' ; 5.99,d J 5.0 Hz, H1'; 6.89, d J 15.8 Hz , CH=CH; 7.20,d J 15.8 Hz, CH=CH; 7.68,s,H6; 9.68,s,NH. $C_{20}H_{24}N_2O_{11}$ Calc: 468.1380; Found: 468.1395.

2',3',5'-Tri-O-Acetyl-5-(ethyl-2-propenoate)uridine (8e)

46%. $[\alpha]_D$ -33.1 (c, 0.13). FAB m/z 469 [M +1]. UV 271.1nm, ε 8388 . ^{1}H n.m.r. δ 1.24,t J 7.2 Hz, **CH_3**CH_2; 2.04,s,CH_3; 2.07,s,CH_3; 4.17,q J 7.2 Hz, **CH_2**CH_3; 4.29,m, H5a',H5b' ; 5.30,m,H2',H3',H4'; 6.04,d J 5.3 Hz, H1'; 6.15,d J 1.0 Hz, CH_2=CH; 6.43,d J 1.0 Hz, CH_2=CH; 7.71,s,H6; 8.35,s,NH.

2',3',5'-Tri-O-Acetyl-5-[1-E-(3-(dimethyl-2,3-dimethylbutyl)silyl) oxy)propenyl]uridine (8f)

92%. $[\alpha]_D$ -33.9 (c, 0.91). UV 246nm, ε 8210 . ^{1}H n.m.r. δ 0.67-0.85,m, CH_3Si ; 1.98,s,CH_3; 1.99,s,CH_3; 2.01,s,CH_3; 3.98-4.31,m,H5a',H5b' ; 5.21-5.30,m,H2',H3',H4' ; 5.98,m,H1'; 6.15,d J 15.9 Hz, CH=CH; 6.52,dt J 4.4 and 15.7 Hz, CH=CH; 7.25,s,H6; 9.07,s,NH.

2',3',5'-Tri-O-Acetyl-5-(2-propenyl)uridine (8g)

86%. $[\alpha]_D$ -33.7 (c, 0.61). m/z 410 [M] $C_{18}H_{22}N_2O_9$ Calc: 410.1325; Found: 410.1343. UV 273nm, ε 6,223 . ^{1}H n.m.r. δ 2.03,s,CH_3; 2.09,s,CH_3; 2.11,s,CH_3; 2.13,s,CH_3; 4.31-4.40,m,H5a',H5b' ; 5.15,s,CH_2=CH; 5.36-5.39,m, H2', H3', H4'; 5.60,s,CH_2=CH; 6.12,d J 5.3 Hz,H1'; 7.37,s,H6; 9.28,s,NH.

2',3',5'-Tri-O-Acetyl-5-phenyluridine (8h)

64%. $[\alpha]_D$ -80.8 (c, 0.49). m/z 446 [M]. UV241.9, 282.8nm , ε 9518. $C_{21}H_{22}N_2O_9$ Calc. 446.1331. Found: 446.1325. Calc: C,56.49; H,4.97; N,6.27. Found: C,56.16; H,5.17; N,5.99. ^{1}H n.m.r. δ 1.84,s,CH_3; 2.04,s,CH_3; 2.06,s,CH_3; 4.24-4.33,m,H5a',H5b'; 5.27-5.37,m,H2',H3',H4' ; 6.11,d J 5.6 Hz,H1'; 7.20-7.45,m,Ar; 7.49,s,H6; 9.42,s,NH. ^{13}C n.m.r. δ 20.1, CH_3; 62.9,C5'; 70.0,C3'; 72.5,C2'; 80.0,C4'; 86.9,C1'; 116.2; 128.1; 128.3; 132.0;136.4;150.1,C6; 161.9,C2; 169.6,CH_3CO; 170.0,C4.

2',3',5'-Tri-O-Acetyl-5-(4-methoxyphenyl)uridine (8i)

55%. m.p. 65-67°. $[\alpha]_D$ -66.7 (c, 0.27). UV 243.3nm, ε 11,124 . m/z 476 [M] $C_{22}H_{24}N_2O_{10}$ Calc. 476.1417 Found, 476.1431. ^{1}H n.m.r. δ 1.86,s,CH_3; 2.05,s,CH_3; 2.07,s, CH_3; 3.75,s,OCH_3; 4.24-4.32,m,H5a',H5b'; 5.27-5.36,m,H2',H3',H4' ; 6.10,d J 5.7 Hz,H1'; 6.85,d J 9.0 Hz,Ar; 7.35,d J 9.0 Hz,Ar; 7.42,s, H6; 8.98,s,NH.

2',3',5'-Tri-O-Acetyl-5-(4-fluorophenyl)uridine (8j)

89%. m.p. 69-70°. $[\alpha]_D$ -56.98 (c, 0.70). UV 279 nm, ε 7905 . $C_{21}H_{21}FN_2O_9$ Calc: C,54.31; H, 4.56; N,6.03. Found: C,54.70; H 5.08; N 5.35. m/z 465 [M]. ^{1}H n.m.r. δ 1.92,s,CH_3; 2.21,s,CH_3; 2.14,s,CH_3; 4.36-4.39,m,H5a',H5b' ; 5.30-5.44,m,H2',H3',H4'; 6.15,d J 5.6 Hz, H1'; 7.08,dd J 8.6 Hz,Ar; 7.47,dd J 4.3 and 8.7 Hz , Ar; 7.53,s,H6; 9.49,s,NH.

2',3',5'-Tri-O-Acetyl-5-[4-(α,α,α-trifluoromethyl)phenyl]uridine (8k)

91%. m.p. 78-79°. $[\alpha]_D$ -48.4 (c, 0.69) ^{19}F n.m.r. δ 13.78. UV 278.9 nm, ε 10,181; ^{1}H n.m.r. δ 1.88,s,CH_3; 2.05,s,CH_3; 2.08,s, CH_3; 4.13-4.41,m,H5a',H5b'; 5.22-5.36, m,H2',H3',H4'; 6.06,d J 5.9 Hz,H1'; 7.64,s,Ar; 7.78,s,H6; 7.94,s, Ar; 9.50,s,NH.

2',3',5'-Tri-O-Acetyl-5-(3,5-difluorophenyl)uridine (8l)

81%. m.p. 74-75°. $[\alpha]_D$ -58.35 (c, 0.50). $C_{21}H_{20}F_2N_2O_9$ m/z 482 [M] Calc: 482.1137; Found: 482.1123. UV 281.3nm, ε11,123. ^{19}F n.m.r. δ -32.55. ^{1}H n.m.r. δ 1.94,s,CH_3; 2.05,s,CH_3; 2.07,s, CH_3, 4.18-4.39,m,H5a',H5b'; 5.23-5.36,m,H2',H3',H4'; 6.07,d J 5.5Hz,H1'; 6.73,tt J 2 and 11.7 Hz; 7.03,dd J 2.0 and 8.4 Hz; 7.56,s,H6, 9.34,s,NH.

2',3',5'-Tri-O-Acetyl-5-[3,5-bis(α,α,α-trifluoromethyl)phenyl]uridine (8m)

85%. $[\alpha]_D$ -63.32 (c, 0.58). m.p. 137-139°. UV 279.4 nm, ε 13,362. ^{19}F n.m.r. δ 13.94. FAB m/z (M+1) 583. $C_{23}H_{20}F_6N_2O_9$ Calc. C 47.43; H 3.46; N 4.81. Found C 47.33; H 3.59; N 4.76. ^{1}H n.m.r. δ 1.84,s,CH_3; 2.05,s,CH_3; 2.07,s,CH_3; 4.00-4.34,m, H5a',H5b'; 5.22-5.38,m, H2',H3',H4';6.05,d J 5.5 Hz, H1'; 7.56,s,H6; 9.43,s,NH.

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