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Base-modified Pyrimidine Nucleosides. Efficient Entry to 6-derivatized Uridines by Sn-Pd Transmetallation-coupling Process

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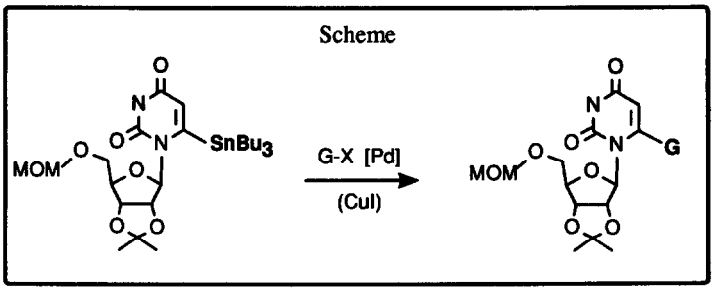
Abstract The palladium-catalyzed reaction of 6-tributylstannyluridine derivative **5** with a variety of aryl, vinyl, alkynyl, and allyl halides provides an efficient method for the synthesis of the corresponding cross-coupled products In all cases, an enhancement on the rate and isolated yields was attained by using CuI as co-catalyst

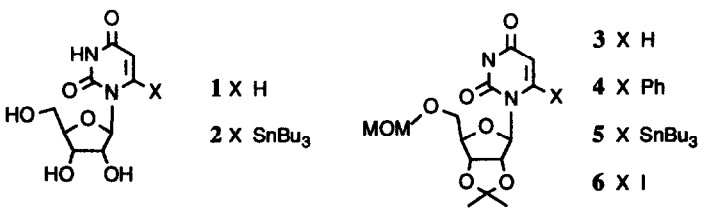
Since the discovery (in the middle 1980s) of 3'-azido-3'-deoxythymidine (zidovudine,AZT)[1]as an antiretroviral agent for prophylaxis or therapy of acquired immunodeficiency syndrome (AIDS), there was a flurry of interest in the synthesis and biological evaluation of modified nucleosides [2] Furthermore, the potent and selective antiherpetic action of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)[3] and 5-(2-chloroethyl)-2'-deoxyuridine (CEDU)[4] has led to continue efforts to develop new nucleoside antiviral agents Base-modified pyrimidine nucleosides, so far synthesized in this context, have generally been substituted at the 5-position, presumably because of the ease of functionalization at this site [5] The synthesis of 5-derivatized nucleosides has been achieved either by elaboration of the easily accessible 5-halo compounds[6] (*via* Heck coupling protocol) or by *de novo* synthesis (*e g* ,direct glycosylation of the preformed pyrimidine base analogues by the procedure of Vorbruggen) [7] Thus, while the methods for the preparation of 5-substituted nucleosides are well established, there is a need for yet easier access to 6-derivatized analogues [8] Recently, Miyasaka and co-workers[9] have reported an interesting anti-HIV-1 activity of various 6-substituted uridines These compounds were synthesized by quenching of 6-lithio species with electrophiles, however, there are several limitations to this route To circumvent these problems we have devised an alternative (and complementary) procedure for the access to bulky and higher homologues and in this paper we will highlight the ability of the protected 6-tributylstannane **5** to act as a uridin-6-yl anion equivalent (Scheme) Accordingly, incorporation of tin into nucleosides would provide the opportunity for cross-coupling reactions thereby extending the range of available derivatives yet further and most of these synthetically useful transformations rely on the transmetallation from Sn to Pd as a key step [10,11]

In all such coupling reactions the initial step appears to be the oxidative addition of the halide on a palladium zerovalent complex 'PdL_2' The subsequent steps are transmetallation (*i e* ,transfer of a group from stannane to 'PdL_2') and reductive elimination which can compete with β-elimination when alkylstannanes

with β-hydrogen atoms are employed



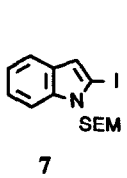
In principle, the unprotected 6-stannylated uridine **2** [12] could be prepared by metallation of uridine **1** *per se* and quenching the lithio derivative with trialkyltin halides In order to avoid complications, the hydroxy functions in **1** were protected as 2',3'-isopropylidene-5'-*O*-methoxymethyl derivative **3** [13] It was well established that both protecting groups in **3** can be easily removed under acidic conditions such as 50% TFA in water [13] This intermediate lithiated (LDA, THF, -78°C) regioselectively at C-6 (stabilization by intramolecular complexation) and the stannylated product **5** was isolated, after quenching with n-Bu_3SnCl, in virtually quantitative yield The stannane obtained not only withstood silica gel chromatography but could be kept at 0°C for prolonged periods of time without significant decomposition [as judged by $^{119}Sn\{^1H\}$ spectroscopy] [14]



We were now in a position to evaluate the Pd-catalyzed cross-coupling of **5** (Stille reaction)[11a] with C-sp (alkynyl), C-sp^2 (aryl and vinyl), and C-sp^3 (alkyl and propargyl) hybridized organic halides To this end, iodobenzene was employed as a model partner and its coupling was attempted using various Pd complexes, such as $Pd(PPh_3)_4$, $Cl_2Pd(PPh_3)_2$, $Cl_2Pd(MeCN)_2$, $Pd_2(dba)_3$ $CHCl_3$, and $Pd(OAc)_2$ as catalysts, in the presence of a ligand, such as PPh_3(TPP) or tris(2-furyl)phosphine (TFP), in various solvents, such as THF, $CHCl_3$, DMF, *N*-methyl-2-pyrrolidinone (NMP) Although the results were condition dependent, low yields (≤35%) in the coupled product **4**, messy reactions and long reaction times were uniformly observed However, a spectacular improvement on the rate of cross-coupling could be achieved by adding purified copper(I) iodide[15] as co-catalyst. For instance, in the presence of Pd catalyst alone and modelling our conditions on those of Farina[16] [$Pd_2(dba)_3$, TFP, NMP], the reaction proceeded very slowly giving 35% of **4** after 6 h (at 120°C), whereas in the presence of 5 mol% $Pd_2(dba)_3$ and 20 mol% CuI (Pd ligand CuI=1 2 2), a good yield (72%) was obtained and the reaction took only 15 min (in THF at 60°C) to reach completion (TLC) (method B,Table). Furthermore, $Pd(TPP)_4$ (10 mol%) in the weakly co-ordinating solvent DMF (at 80°C) in the presence of CuI (20 mol%) (method A) also produced **4** in excellent yield (88%)

As demonstrated by the entries in Table, the cross-coupling of **5** through the agency of Cu(I)[17] was successfully achieved with a variety of organic halides Although there is no consensus concerning the role of CuI, it is generally assumed that it is related to the formation of an organocopper during the transmetallation step from Sn to Pd.[17a]

When 2-iodo-*N*[2-(trimethylsilyl)ethoxymethyl]indole **7**[18] was coupled with **5** the yields of **8** were markedly lower (73%) than those obtained with iodobenzene, suggesting steric hindrance of the hetaryl halide **7** in the oxidative addition step



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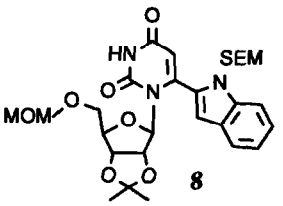

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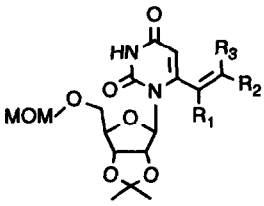


(Z)-**9** R_1, R_2 H R_3 COOMe

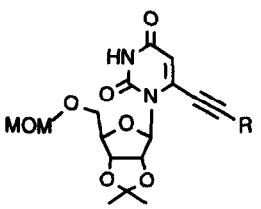
(E)-**9** R_1, R_3 H R_2 COOMe

10 R_1 COOEt R_2, R_3 H

11 R_1, R_3 H R_2 $C(OH)Me_2$

12 R_1, R_2, R_3 H

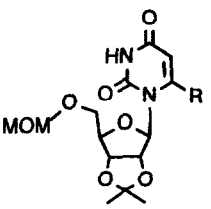
Unexpectedly, in the case of methyl 3-bromopropenoate [19] (entry 4) the transfer of vinyl group was not stereoretentive In fact, starting from a 7 1 mixture of the *Z E* isomers we obtained the product **9** of 3 1 *Z E* purity, while the re-exposure of the starting material or the reaction product to the reaction conditions did not lead to isomerization in either case As yet, the detailed stereomutation mechanism remains unclear but it is likely more complicated than might have been expected, based on Stille's hypothesis [20] In the other case (entry 6) the stereochemical purity of vinylating reagent was completely transferred to the product **11**



13 R H

14 R Ph

15 R TMS



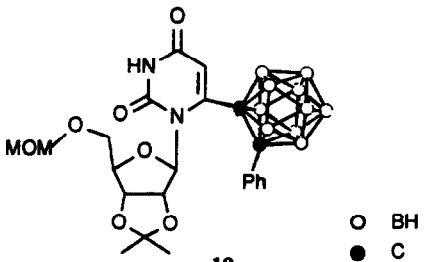
16 R $CH_2CH{=}CMe_2$

17 R CH_2-C≡CH

18 R CH=C=CH_2

The transfer of C-sp hybridized groups (entries 8, 9) deserves some comments In principle, the preparation of the required compounds **14** and **15** would be easily accomplished by Pd-mediated coupling of 6-iodo compound **6**[6] with the corresponding terminal alkynes [21] One limitation is that the reaction seems to require the presence of a base (*e g* , diethylamine, triethylamine, *n*-$BuNH_2$, NaOMe, NaOH under PTC conditions) Although this procedure was successfully applied to prepare 5-alkynyluridines[22] and 6-alkynylthymidines,[23] it was felt that the use of a base could ultimately cause problems when added to 6-iodo compound **6** As anticipated, it is worth noting here that we have so far unable to react **6** with phenyl- and trimethylsilylacetylene under the above conditions Apparently,the increased electron density at C-6 in a 6-iodothymidine (viz , a 5-methyl-6-iodo pyrimidine) in comparison to that of **6** renders the former compound less reactive toward a nucleophilic attack This result indicated that the competitive nucleophilic addition-elimination process [24] between **6** and the base was faster than the oxidative addition of **6** to Pd(0)

complex. Consequently, it became apparent to us that the stannane **5** might serve as efficient partner of 1-haloalkynes (*i.e.*,Ph-C≡Cl[25]and TMS-C≡Cl[25]) in a reversal of the usual cross-coupling methodology. Thus, $Pd(TPP)_4$-catalysed reaction of **5** in the presence of CuI with PhC≡Cl (entry 8) and TMSC≡Cl (entry 9) in warm DMF (80°C) gave the corresponding alkynyl derivatives **14** and **15**[26] in 77 and 69% isolated yields, respectively. Given the accessibility of **5**, the process described herein is the most convenient route to 6-alkynyluridines described to date In addition, these compounds may be of interest for the synthesis of carboranyl nucleosides, a very promising class of[10] B-carriers for boron neutron capture therapy (BNCT) of cancer.[27] Reaction of **14** with bis(acetonitrile)decaborane $[B_{10}H_{12}(MeCN)_2]$[28] in refluxing toluene led to the expected 1,2-dicarba-*closo*-dodecaborane **19** (54%), wherein the icosahedral *o*-carborane cage containing ten boron atoms, is linked to the alkynyl moiety [29]



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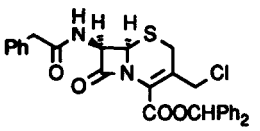
As shown in Table (entries 10-13) allylic halides are also suitable as partners in cross-couplings However, the highest yields were obtained employing a modification of the Farina protocol.[16] The optimized procedure capitalized on a report by Johnson [17a] that employed $Pd_2(dba)_3$ $CHCl_3$ in the presence of TFP as soft ligand and CuI (method B) Once again, by simply adding CuI as co-catalyst a large rate enhancement was obtained (the reaction was 25 times faster than in the absence of CuI) In spite of cephem chloride **20** possesses sensitive functionalities, not compatible with group IA or IIA-type organometallics, it coupled cleanly with **5** (entry 13) leading to **21**(85%), thereby highlighting the mildness of the coupling as well as the versatility of the stannane **5**



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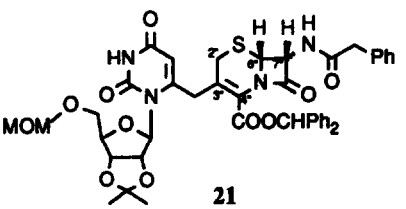

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Finally, coupling of propargylic halides with aryltins is, to best of our knowledge, unprecedented When we used 3-bromopropyne with **5** (entry 14) (method B), the allene **18** was the major product (47%) and the expected 6-propargyl nucleoside **17** was not isolated,but its presence in the crude reaction mixture cannot be ruled out The production of **18** could be explained by assuming that the oxidative addition reaction occurs leading to a (σ-allenyl)palladium(II) species prior to transmetallation and reductive elimination [30]

In summary, we have demonstrated that the synthesis of a broad range of uridines having different

functional groups and unusually substituted at C-6 is feasible going the Sn-based Pd-catalysed cross-coupling through the agency of CuI Many of these compounds are not easily available by alternative methods and are of interest for further synthetic elaborations As yet, whether these compounds are active as antiretroviral agents is unknown, but it is expected that the series of 6-substituted uridines generated in this work will function as tools to more fully understand the structural and physicochemical requirements for *in vivo* activity of this important therapeutical class

Table. Pd-CATALYZED COUPLING OF STANNANE 5 WITH HALIDES

Entry	method	halide	products(yield %)	time(min)
1	A	PhI	**5** (88)	15
2	B	PhI	**5** (72)	15
3	A	**7**	**8** (73)	30
4	A	Br-CH=CHCO$_2$Me[a]	**9** (81)[b]	10
5	A	Br-C(CH$_2$)CO$_2$Et	**10** (56)	75
6	A	I-CH=CHC(OH)Me$_2$[c]	**11** (70)[c]	60
7	A	CH$_2$=CH-Br[d]	**12** (80)	100
8	A	Ph-C≡C-I	**14** (77)	30
9	A	TMS-C≡C-I	**15** (69)	20
10	A	Me$_2$C=CH-CH$_2$Br	**16** (62)	60
11	B	Me$_2$C=CH-CH$_2$Br	**16** (84)	30
12	A	**20**	**21** (58)	120
13	B	**20**	**21** (79)	30
14	B	H-C≡C-CH$_2$Br	**18** (47)	120

(A) halide **5**=1 3, Pd(TPP)$_4$ (10% mol), CuI (20% mol), DMF (80°C)
(B) halide **5**=1 3, Pd$_2$(dba)$_3$ (5% mol), TFP (20% mol), CuI (20% mol), THF (60°C)
[a]*Z E=7 1*, [b]*Z E=3 1*, [c]*E>98%*, [d]sealed tube

Acknowledgment. We gratefully appreciate the experimental contribution of Dahlia Nathaniel We wish to thank R Monguzzi for a generous gift of cephem chloride **20** and M Bonfà for the ^{119}Sn spectra Special thanks go to A Cremonesi for the high-resolution mass spectra

EXPERIMENTAL PART

All operations were carried out under dry, oxygen-free nitrogen atmosphere Unless otherwise specified ^{1}H and ^{13}C NMR spectra ($CDCl_3$solutions) were recorded on either a Bruker WP-80 or a CPX-300 and chemical shifts (in ppm) are reported in reference to TMS Coupling constants are expressed in hertz(Hz) For ^{119}Sn NMR ($CDCl_3$) the spectra were recorded on a Varian XL-200 and chemical shifts are referred to tetramethyltin, IR spectra ($CHCl_3$) were recorded on a Perkin Elmer 681 spectrophotometer; EI-MS(70 eV), HR-MS (R=5000) and FAB-MS (positive mode, glycerol matrix) were performed on a VG-7070 EQ-HF

instrument. Starting materials ethyl 2-bromopropenoate [31] and (*E*)-4-iodo-2-methylbuten-3-ol[32] were prepared by adaptation of literature methods Decaborane ($B_{10}H_{14}$) was provided by Aldrich and this highly toxic compound forms impact-sensitive mixture with several materials (CAUTION!).

6-Tributylstannyl-2',3'-isopropylidene-5'-O-methoxymethyluridine 5.

Freshly dried and distilled diisopropylamine (860 µL) was dissolved with stirring under nitrogen in dry THF (10 mL) and the solution cooled to 0° C *n*-BuLi (1 6M, 3 8 mL) was added dropwise over 5 min and the solution stirred for 20 min at 0°C before being cooled to -78°C A solution of **3**[3] (820 mg, 2 44 mmol) in THF(10 mL) was added dropwise via syringe After 90 min, the resulting clear, bright red solution of dianion was treated with *n*-Bu_3SnCl (1 59 g, 4 90 mmol) in dry THF (5 mL) The mixture was allowed to warm to r t and then partitioned between Et_2O (100 mL) and sat NH_4Cl solution (50 mL) The aq layer was extracted with Et_2O (2x25 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated The oily residue was filtered on silica gel column (hexanes-AcOEt, 3 2) affording the stannane **5** (1 40 g, 93%) as a colourless oil, R_f 0 34 HR-MS $C_{26}H_{46}N_2O_7Sn$ (M^+) calcd 618 2327, obsd 618.2305 (the value is given for the most abundant peak in the M^+ ion cluster The shape of the M^+ isotope peaks and their intensities are in full agreement with assigned tin-containing structure) ^{1}H-NMR 0 26 (9H, t, J=6 8, Me), 1 29 (3H, s, Me-exo), 1 49 (3H, s, Me-endo), 1 1-1 7 (18H, m), 3 31 (3H, s, OMe), 3 72 (2H, d, J=6 6, H-5'), 4 19 (1H, dt, J=6 6, 6 6, H-4'), 4 61 (2H, s, OCH_2O), 4 85 (1H, t, J=6 6, H-3'), 5 65 (1H, d, J=6 6, H-2'), 5 25 (1H, s, H-1'), 5 66 (1H, s, H-5), 9 97 (1H, bs, NH).

General Procedure (Method A).

In a typical experiment a 10-mL two-necked round-bottomed flask equipped with a reflux condenser, a septum inlet, and a magnetic stirring bar, was charged with $Pd(TPP)_4$ (0 01 mmol), halide (1 3 mmol) and freshly purified CuI (0 02 mmol) The flask was flushed with nitrogen and filled with dry DMF(5 mL) containing the stannane **5** (1 0 mmol) through the septum inlet with a syringe The mixture was heated at 80°C in an oil bath with stirring At suitable time intervals, a part of reaction mixture was sampled and subjected to TLC analysis After the reaction was complete, the flask was cooled to r.t , and poured into sat NH_4Cl (10 mL) and extracted with Et_2O (2x15 mL) The combined organic layers were washed with sat KF $2H_2O$ solution, water (2x) and brine After drying, the coupled product was isolated by silica gel flash chromatography

General Procedure (Method B).

In a typical experiment a 25-mL flask was charged with $Pd_2(dba)_3$ $CHCl_3$ (0 005 mmol), TFP (0 02 mmol), CuI(0 02 mmol) and halide (1 3 mmol) After flushing with nitrogen, dry THF (10 mL) and the stannane **5** (1 0 mmol) were added and the solution was heated at 60°C (oil bath) After the reaction was complete (TLC), the mixture was evaporated (≥30°C) to dryness under reduced pressure and the black residue, treated as above, was chromatographed over silica gel

2',3'-Isopropylidene-5'-O-methoxymethyl-6-phenyluridine 4

R_f(hexane-EtOAc, 1.1) 0.14; EI-MS 404($C_{20}H_{24}N_2O_7$), IR 1695 cm^{-1}, ^{1}H-NMR. 1 28 & 1 36 (2×s, Me), 3.35 (3H, s; OMe), 3 76 (2H, d, J=6 4, H-5'), 4 13 (1H, dt, J=6 4, 4 4, H-4'), 4 65 (2H, s, OCH_2O), 4 83 (1H,

dd, J=6.6, 4 4, H-3′), 5.19 (1H, dd, J=6 6, 1.0, H-2′), 5 49 (1H, d, J=1; H-1′), 5.62 (1H, s, H-5), 8 72 (1H, bs; NH) Found C, 59.48%, H, 5 87%; N, 6 89% Calcd for $C_{19}H_{21}N_2O_7$ C, 59 40, H, 5 94, N, 6 93

2′,3′-Isopropylidene-5′-O-methoxymethyl-6[1-(2-trimethylsilylethoxymethyl)indol-2-yl]uridine 8.
R_f(AcOEt-hexane, 2 1) 0.36, FAB-MS 825, ^{1}H-NMR 0.11(9H, s, TMS), 0 83 (2H, t, J=8; CH_2Si), 1.24 & 1.32 (2×s, Me), 3 37 (2H, t, J=6 4, OCH_2), 3 74 (2H, d, J=6 4, H-5′), 4 10 (1H, dt, J=6 4, 4.4; H-4′), 4.65 (2H, s, OCH_2O), 4 84 (1H, dd, J=6.4, 4 4, H-3′), 5 19(1H, d, J=6 4, H-2′), 5 45 (1H, s, H-5), 5 50 (2H, s, NCH_2O), 5 87 (1H, s, H-1′), 6 85 (1H, bs, H-3″), 7 22 (1H, t, J=8 2; H-6″), 7 35 (1H, t, J=7.8, H-5″), 7 52 (1H, d, J=8.2, H-7″), 7 68 (1H, d, J=7 8, H-4″), 9 37 (1H, bs, NH) HR-MS $C_{23}H_{26}N_3O_7$ [M^+ - $O(CH_2)_2TMS$] calcd 456 1770, obsd 456 1766

(Z)-2′,3′-Isopropylidene-6[2-(methoxycarbonyl)ethenyl]-5′-O-methoxymethyl uridine 9.
R_f (AcOEt-hexane, 5 1) 0 19, IR 3380, 1710, 1695 cm^{-1}, ^{1}H-NMR: 1.30 & 1.50(2×s, Me), 3 35 (3H, s, OMe), 3 73 (3H, s, COOMe), 3 78 (2H, m, H-5′), 4 22 (1H, dt, J=7,4 6; H-4′), 4.65 (2H, s, OCH_2O), 4 86 (1H, dd, J=6 8,4 6; H-3′), 5 18 (1H, d, J=6 8, H-2′), 5 54 (1H, d, J=1, H-5), 5.63 (1H, s; H-1′), 6 28 (1H, d, J=11 4, H-1″), 6 78 (1H, dd, J=11 4, 1, H-2″), 9 45 (1H, bs, NH) **(E)-9** R_f(AcOEt-hexane, 5:1) 0.25, ^{1}H-NMR 1 34 & 1 48 (2×3H, 2×s, Me),3 39 (3H, s, OMe), 3.78 (2H, m, H-5′), 3 85 (3H, s, COOMe), 4 28 (1H, dt,J=6 8, 5, H-4′), 4 67 (2H, s, OCH_2O), 4 86 (1H, dd, J=6 4, 5, H-3′), 5 19(1H, d, J=6 4, H-2′), 5 65 (1H, s, H-5), 5 80 (1H, s; H-1), 6 45 (1H, d,J=15 5, H-1″), 7 54 (1H, d, J=15.5, H-2″), 8 56 (1H, bs, NH) HR MS $C_{18}H_{24}N_2O_9$ (M^+)· calcd 412.1481, obsd 412 1495

6[1-(Ethoxycarbonyl)ethenyl]-2′,3′-isopropylidene-5′-O-methoxymethyluridi ne 10
R_f(EtOAc-hexane, 5 1) 0 26, ^{1}H-NMR 0 93 (3H, t, J=7 2, *Me*-CH_2), 1 34 & 1 50 (6H, 2×s, Me), 3 37 (3H, s; OMe), 3 75 (2H, m, H-5′), 4 18 (2H, dq, J=9 8, 7 2, CH_aH_b), 4 30 (1H, dt, J=7.5, 5 1, H-4′), 4 66 (2H, s, OCH_2O), 4 84 (1H, dd, J=6 8, 5 1, H-3′), 5.14 (1H, dd, J=6 8, 1 7; H-2′), 5 35 (1H, s, H-5), 5 62 (1H, d, J=1.7, H-1′), 6 12 (1H, d, J=0 8, H-2″), 6 71 (1H, d, J=0 8, H-2″), 8 90 (1H, bs, NH) HR-MS $C_{19}H_{26}N_2O_9$ (M^+)· calcd 426 1638; obsd 426 1645

6(3-Hydroxy-3-methyl-1-butenyl)-2′,3′-isopropylidene-5′-O-methoxymethylur idine 11
R_f (AcOEt -hexane, 5 1) 0 21, ^{1}H-NMR 1 31 & 1 53 (6H, 2×s, Me), 1 39 (6H, s, Me), 2 09 (1H, s, OH), 3 35 (3H, s, OMe), 3.75 (2H, m, H-5′), 4 22 (1H, dt, J=7 3, 3 8, H-4′), 4 64 (2H, s; OCH_2O), 4.86 (1H, dd, J=6 8, 4 8, H-3′), 5 16 (1H, dd, J=6 8, 1 8, H-2′), 5 65 (1H, s, H-5), 5 74 (1H, d, J=1.8, H-1′), 6 39 & 6 53 (AB syst, J=15 7, H-1″ & H-2″), 9 10 (1H, bs, NH), ^{13}C-NMR(APT) 23.7 & 25 2(Me), 55 3(OMe), 67 9(C-5′), 71.0(C-3″), 81 9(C-3′), 84 0(C-2′), 87 0(C-4′), 92 3(C-1′), 96 6(OCH_2O), 101 5(C-5), 118.1(C-2″), 149 0 (C-1″), 150 4(C-6), 154 0(C-2), 162 6(C-4) HR-MS $C_{19}H_{26}N_2O_7$ (M^+ - H_2O) calcd 394 1740, obsd 394 1746

6-Ethenyl-2′,3′-isopropylidene-5′-O-methoxymethyluridine 12
R_f(AcOEt-hexane, 3 2) 0 12, ^{1}H-NMR 1 33 & 1 55 (6H, 2×s, Me), 3 35 (3H, s, OMe), 3.75 (2H, m, H-5′), 4 24 (1H, dt, J=7 5, 4 5, H-4′), 4 64 (2H, s, OCH_2O), 4 86 (1H, dd, J=6 8, 4 5, H-3′), 5.19 (1H, d, J=6 8, H-2′), 5 64 (1H, d, J=12, H-2″), 5 71 (1+1H, 2×s, H-5 plus H-1′), 5 87 (1H, d, J=17 2, H-2″), 6 60 (1H, dd,

J=17 2, 12, H-1″), 9 79 (1H, bs, NH), ^{13}C-NMR 25 2(Me), 27.2(Me), 55 3(OMe), 68.1(C-5′), 82 1(C-3′), 84.2(C-2′), 87.5(C- 4′), 92 3(C-1′), 96 6(OCH_2O), 101 5(C-5), 125.1(C-2″), 128.7(C-1″) HR MS $C_{16}H_{22}N_2O_7$ (M^+) calcd 354 1427, obsd 354 1419

2′,3′-Isopropylidene-5′-O-methoxymethyl-6(2-phenylethynyl)uridine 14

R_f(CH_2Cl_2-EtOAc, 1.1) 0 43, IR 3390, 2210, 1685 cm^{-1}, ^{1}H-NMR 1.34 & 1 55 (6H, 2×s; Me), 3 33 (3H, s; OMe), 3.75 (2H, m; H-5′), 4 29 (1H, dt, J=6.8, 5 2; H-4′), 4 64 (2H, s, OCH_2O), 4 87 (1H, dd, J=6 6, 5 2, H-3′), 5.22 (1H, d, J=6.6, H-2′), 6.00 (1H, s, H-5′), 6 39 (1H, s, H-1′), 7.40 (3H, m; H-3″ and H-4″), 7 55 (2H, d, J=7 8, H-2″), 9 69 (1H, bs; NH) Found C, 61 72%, H, 5 71%, N, 6 58% Calcd for $C_{22}H_{24}N_2O_7$· C, 61 68, H, 5 60, N, 6 51

2′,3′-Isoproylidene-5′-O-methoxymethyl-6(trimethylsilylethynyl)uridine 15

R_f(EtOAc-hexane, 1 1) 0 28; IR 3380, 2240, 1690 cm^{-1}, ^{1}H-NMR 0 26 (9H, s, TMS), 1 33 & 1 52 (6H, 2×s; Me), 3 33 (3H, s, OMe), 3.72 (2H, m, H-5′), 4 27 (1H, dt, J=6 5, 4 4, H-4′), 4 63 (2H, s, OCH_2O), 4 81 (1H, dd, J=6 6,4 4; H-3′), 5 18 (1H, d, J=6 6, H-2′), 5 90 (1H, s, H-5), 6 33 (1H, s, H-1′), 9.37 (1H, bs, NH) HR-MS $C_{18}H_{25}N_2O_7Si$ (M^+ - Me) calcd 409 1431, obsd 409.1419

2′,3′-Isopropylidene-5′-O-methoxymethyl-6(3-methyl-2-butenyl)uridine 16

R_f(EtOAc-hexane, 3 1) 0 36, ^{1}H-NMR 1.30 & 1 51 (6H, 2×s, Me), 1 63 (3H, s, Me), 1.74 (3H, s, Me), 3 20 (2H, dd, J=9 4, 8 4, H-1″), 3 32 (3H, s, OMe), 3 73 (2H, m, H-5′), 4 30(1H, dt, J=6 6, 5 2, H-4′), 4 62 (2H, s, MeO*CH*$_2$), 4.83 (1H, dd, J=6 6, H-3″), 5 09(1H, m, H-2″), 5 16 (1H, d, J=6 6, H-2′), 5 58 (1H, s, H-1′), 5 72 (1H, s, H-5), 9 70(1H, bs, NH) Found C, 57 65%, H, 7 18%, N, 6 95% Calcd for $C_{19}H_{28}N_2O_7$· C, 57 57, H, 7 07, N, 7 07

2′,3′-Isopropylidene-5′-O-methoxymethyl-6(1,2-propadiyl)uridine 18

R_f(AcOEt-hexane, 2 1) 0 26, IR 3380, 1955, 1943, 1695 cm^{-1}, ^{1}H-NMR. 1 32 & 1 53 (6H, 2×s, Me), 3 32 (3H, s, OMe), 3 71 (2H, m, H-5′), 4 24 (1H, dt, J=6 2, 5 2, H-4′), 4 62 (2H, s, OCH_2O), 4 86 (1H, dd, J=6.4, 5.2, H-3′), 5 18 (1H, d, J=6 4, H-2′), 5.24 (2H, d, J=6 6, H-2″), 5 73 (1H, s, H-1′), 5 90 (1H, s, H-5), 6 11 (1H, t, J=6 6, H-1″), 9 63 (1H, bs, NH) HR-MS $C_{17}H_{22}N_2O_7$ (M^+) calcd 366 1427; obsd 366.1421

2′,3′-Isopropylidene-5′-O-methoxymethyl-6-(o-carboran-1-yl-phenyl)ethyluridine 19.

A solution of decaborane (122 mg, 1 0 mmol) (CAUTION!) and MeCN (140μL, 2 5 mmol) in dry toluene (5 mL) was heated under reflux for 1 h The solution was cooled to r t , and phenylethynyluridine **14** (428 mg,1 0 mmol) was added The mixture was heated for 20 h at 90°C The progress of the reaction was checked by TLC (AcOEt-hexane,1 1) Following evaporation of the toluene, the remaining residue was taken up in Et_2O (20 mL) and filtered, and the filtrate was evaporated to dryness Purification by column chromatography (AcOEt-hexane,3 2) yielded the carboranyluridine **21** (296 mg, 54%) (R_f0 15) as a colourless glass-like compound FABMS a quasi-molecular ion with the appropriate isotopic distribution was observed at 549 amu, IR(KBr) 3070, 2605, 1680 cm^{-1}

3-[(2',3'-Isopropylidene-5'-O-methoxymethyl)uridin-6-yl]methyl-8-oxo-7[(phenylacetyl)amino]-5-thia -1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid diphenylmethyl ester 21

R_f(AcOEt-hexane, 2 1) 0 16, ^{1}H-NMR 1 25 & 1 30 (6H, 2×s, Me), 3 32 [5H, m, OMe & $CH_2C(3'')$], 3 55 & 3.88 (2H, AB syst, J=17 5, diastereotopic H-2''), 3 58 & 3 65 (2H, AB syst, J=15, CH_2CO), 3 72 (2H, m, H-5'), 4 18 (1H, dt, J=6 7, 5; H-4'), 4 62 (2H, s, OCH_2O), 4 83 (1H, dd, J=6 7, 5, H-3'), 4 98 (1H, d, J=5 2, H-6''), 5.13 (1H, bd, J=6.7, H-2'), 5 39 (1H, s, H-5), 5 66 (1H, bs, H-1'), 5 84 (1H, dd, J=9 2, 5 2, H-7''), 6.87 (1H, s, C*H*Ph_2), 7 65 (1H, bd, J=9 2, NH), 9 40 (1H, bs, NH), ^{13}C-NMR 25 3 & 27 3(Me), 28 6(C-2''), 36 3(*C*H_2C-3''), 43 1(*C*H_2Ph), 67 9(C-5'), 82 2(C-3'), 84 4(C-2'), 87 2(C-4'), 91 1(C-1'), 102 5(C-5), 111 1(*C*HPh_2), 114 2(O-C-O), 134 2(C-4''), 150 1(C-6), 152 5(C-2), 160 4(C-4), 162 9(CO), 165 3(CO), 171 9(CO) (cephem ring numbering)

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