Palladium-Catalyzed Coupling of Terminal Alkynes with 5-(Trifluoromethanesulfonyloxy)pyrimidine Nucleosides

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The palladium-catalyzed couplings of terminal alkynes with 2',3',5'-tri-*O*-acetyl-5-(triflouromethanesulfonyloxy)uridine, 3',5'-di-*O*-acetyl-5-(triflouromethanesulfonyloxy)-2'-deoxyuridine, and 5-(triflouromethanesulfonyloxy)-2'-deoxyuridine have been investigated under a variety of conditions.

The C5 substitution of 2'-deoxyuridine has been exploited for some time now in the development of antiviral and anticancer agents.[1] For example, (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)[2] and 5-iodo-2'-deoxyuridine (IDU)[3] are two potent antiherpetics that have found clinical applications. Structure–activity relationship studies seem to indicate that the types of C5 substituents likely to confer activity are those which are electron-withdrawing and conjugated to the base ring, as well as being lipophilic and not too sterically demanding (≤4 bonds).[1d]

In particular, pyrimidine nucleosides containing a C5 alkynyl group have been shown to express significant anticancer and/or antiviral properties.[1e,4] This has been, in part, attributed to their ability to act as mechanism-based inhibitors of thymidylate synthase.[5] Also the C5 alkynyl group has been extensively employed as a linker arm for the attachment of fluorescent labels on 2',3'-dideoxynucleotides which are used in modern DNA sequencing techniques.[6] The first reports on the preparation of alkynyl nucleosides involved initial construction of the substituted heterocycle, followed by coupling to the sugar moiety and separation of the resultant anomeric mixture.[7] Heck developed a technique whereby terminal alkynes could be coupled to simple alkenyl or aryl halides.[8] When this method was initially used to couple phenylacetylene with 5-(chloromercurio)- or 5-iodouridine, only starting material or complex mixtures were obtained.[9] A modification to this original procedure involved the use of copper acetylides generated *in situ* and coupling with 5-iodopyrimidine nucleosides.[10] This allowed for ready access to 5-alkynyl-2'-deoxyuridines, several of which expressed appreciable antiviral activity and the corresponding 5'-monophosphates were shown to be mechanism based inhibitors of thymidylate synthase.

The 5-alkynyl-2'-deoxyuridines prepared previously bore only simple alkyl chains or an unsubstituted phenyl ring.[4a,10,11] A subsequent structure–activity relationship study on 5-alkenyl-2'-deoxyuridines revealed that electron-withdrawing, lipophilic groups in the *E*-2 position of the alkenyl substituent enhanced antiviral activity.[1d] The effects of lipophilic electron-withdrawing groups on an acetylenic linkage with regards to antiviral activity for these types of compounds have not been formally investigated to our knowledge.

We have previously reported on the synthesis and palladium-catalyzed couplings of a suitably protected 5-(trifluoromethanesulfonyloxy)uridine with organostannanes.[12] In view of the importance of C5 alkynyl uridine nucleosides and nucleotides, the coupling of terminal alkynes to the 5-trifloxyuridines was considered worthy of investigation. We report here on the synthesis of a series of 5-alkynyluridine and 2'-deoxyuridine derivatives containing fluorine atoms or groups in order to investigate their potential as antiviral/anticancer agents.

Table I. Coupling of Terminal Alkynes with 1 As Described in Figure 1

entry	R^3	reaction conditions: time (h)	reaction conditions: temp (°C)	product 2	isolated yield, %
1	Me_3Si	2.5	50	a	85[a]
2	$HOMe_2C$	0.5	55	b	90[a]
3	Ph	2.0	4.5	c	93
				c'	5
4	4-$MeOC_6H_4$	0.5	55	d	97

[a] Minor amounts of fluorescent material observed by TLC.

Results and Discussion

The acetylated uridine triflate 1[12b] was coupled with a range of terminal alkynes as described in Figure 1. The results of the coupling reactions have been summarized in Table I. Reactions were monitored by TLC and were terminated when complete consumption of 1 was apparent.

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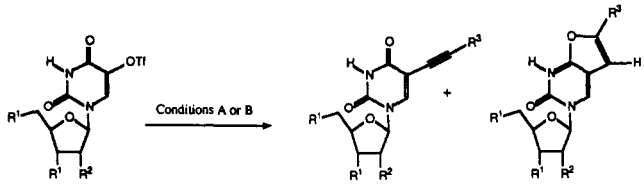
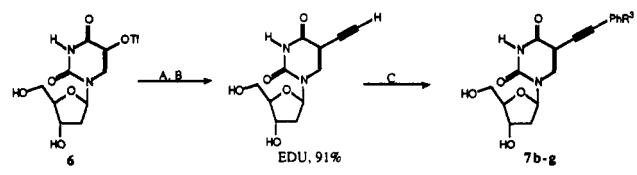


1 R^1 = OAc, R^2 = OAc	Condition A	2a-d	2a'-c'
3 R^1 = OAc, R^2 = H	Conditions A and B	4a-f	4b'-e'
6 R^1 = OH, R^2 = H	Conditions A and B	7a-h	7b'-e', g'

A: R^3-C≡C-H, 1.5equiv; $Pd(PPh_3)_4$, 5%; CuI, 10%; Et_3N, 1.5equiv; DMF
B: R^3-C≡C-H, 2.0-2.5equiv; $Pd(PPh_3)_4$, 10%; CuI, 20%; Et_3N, 1.2equiv; DMF

Figure 1.



A. Me_3Si-≡-H, 1.5 equiv; $Pd(PPh_3)_4$, 5%; CuI, 10%; Et_3N, 1.5 equiv; DMF.
B. TBAF 1 equiv, MeOH
C. R^3PhBr, 1.1equiv; $Pd(PPh_3)_4$, 5%; CuI, 10%; Et_3N, 1.5equiv; DMF.

Figure 2.

In all cases the coupled product **2** was obtained in high yield. In most cases coupling was observed at room temperature but it was often very slow; slight elevations in the reaction temperature led to a dramatic increase in the rate of coupling and was, in general, much more convenient. While reactions, generally, proceeded cleanly as evidenced by TLC analysis of the reaction mixtures, in a few cases a fluorescent spot of lower R_f appeared. This byproduct was readily separated from the desired product and was shown in each case to be the rearranged product **2'**. In all cases the formation of **2'** was evidenced by an absence of the NH resonance (δ = 9–11 ppm) in the ^1H NMR spectrum and the appearance of a vinylic resonance (δ = 6–7 ppm) relative to **2**. The formation of this byproduct in the coupling of terminal alkynes to 5-iodouridine derivatives is well precedented.[10] A recent report indicated that the use of DMF as a solvent reduces the amount of cyclized product obtained[13] and it is for this reason that DMF was used in all couplings. It has been demonstrated that the product cyclization is catalyzed by copper(I) iodide.[10b]

Literature reports indicated that (trimethylsilyl)alkynes could be cross coupled with alkenyl and aryl halides (Br or I) or triflates.[14] Since the immediate precursor of the substituted arylacetylenes used in this work was the corresponding aryl(trimethylsilyl)acetylene, direct coupling with the protected 2'-deoxyuridine triflate **3** would have been advantageous. However, no coupling was observed when the rections were attempted under the conditions described in the literature and only the desilylated arylalkyne and **3** could be detected after 24 h by GLC and TLC, respectively. Reactions were then attempted under a variety of conditions with respect to the rates and order of addition of the various reagents but to no avail. Since, in our hands, the (trimethylsilyl)alkynes could not be coupled directly, they were desilylated to give the corresponding arylalkynes in high yield (Experimental Section).

The couplings of terminal alkynes to the protected 5-trifloxy-2'-deoxyuridine **3** were initially carried out under reaction condition A (Figure 1) to give good yields of the expected products **4** and **4'**. The results of these couplings are summarized in Table II, entries 1–5. As expected, the (trimethylsilyl)acetylene coupled as effectively to the protected 5-trifloxy-2'-deoxyuridine **3** as it did to the equivalent uridine **1** (compare entries 1, Tables I and II). The couplings of the arylalkynes containing fluoro substituents, entries 2–5, Table II, were carried out at room temperature, although the consumption of the starting material **3** (as monitored by TLC) was much slower than anticipated for such activated systems. Also, unlike previous couplings, the further addition of alkyne and in some cases catalyst was necessary in order to ensure the complete consumption of the starting material **3**. In the cases of entries 2–4, considerable amounts of cyclized product **4'** was obtained. This was attributed both to the longer reaction times and to the presence of electron-withdrawing groups which appear to promote cyclization. A high R_f (TLC) component in the reaction mixtures was also isolated for entries 3 and 4 and shown to be homocoupled alkyne **5**. The mass balance of homocoupled alkyne plus the expected cross coupled products accounted for all of the terminal alkyne added to the reaction mixture. A similar high-R_f component was detected by TLC for entries 2 and 5 (as an intense and faint spot, respectively) but in these cases the component was not isolated.

5

The reaction conditions described in Figure 2 where chosen to minimize the formation of the homocoupled product **5**. It was found that catalytic amounts of both copper(I) and palladium(0) and base were all required in order to achieve homocoupling of terminal alkynes.[15] Homocoupling was promoted in the presence of electron-withdrawing groups on the phenyl ring of the arylalkynes. Evidently the process of homocoupling competes with cross-coupling not only in the consumption of terminal alkyne but also with regard to access to the catalyst.

In order to increase the overall rate of cross-coupling and so decrease the reaction time and therefore the amount of cyclized product formation, the amounts of both catalysts were increased. An increased amount of terminal alkyne was also used so as to avoid any interruption in the cross-coupling reaction due to premature depletion of arylalkynes through homocoupling (condition B, Figure 1). Only in the case of **4b** did these alterations prove significantly effective (entry 6, Table II). When the amount of catalyst and arylalkynes was doubled in the cases **4c–e**, only a minor benefit was achieved. However, when the reactions were carried out under these new conditions at slightly higher temperatures, a much better

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(15) The experimental procedures for the formation of the homocoupled products **5** are included in the Experimental Section of this paper. A detailed discussion of the mechanism for the homocoupling will be reported elsewhere.

Table II. Coupling of (Trimethylsilyl)acetylene and Arylalkynes with 3 under Conditions A and B As Described in Figure 1

		reaction conditions				
entry	R^3		time (h)	temp (°C)	product 4	isolated yield,[a] %
1	Me_3Si	A	2.5	50	**a**	87
2	3,5-$(CF_3)_2C_6H_4$	A[b]	8.0	20	**b**	51
					b′	21
3	3,5-$F_2C_6H_4$	A[b]	10.0	20	**c**	31
					c′	*
4	4-$CF_3C_6H_5$	A[b]	10.0	20	**d**	43
					d′	*
5	4-FC_6H_5	A[b]	8.0	20	**e**	50
					e′	*
6	3,5-$(CF_3)_2C_6H_4$	B	4.0	20	**b**	80
					b′	7
7	3,5-$F_2C_6H_4$	B	2.0	38	**c**	70
					c′	*
8	4-$CF_3C_6H_5$	B	2.0	37	**d**	82
					d′	*
9	4-FC_6H_5	B	3.0	38	**e**	87
					e′	*
10	C_6F_5	B	5.0	55	**f**	87

[a] Except for those entries denoted by asterisks, where material was detected by TLC but not isolated. [b] Further addition of arylalkyne was required in order to achieve complete consumption of 3.

Table III. Coupling of (Trimethylsilyl)acetylene and Substituted Arylacetylenes with 6 under Conditions A and B As Described in Figure 1

		reaction conditions				
entry	R^3		time (h)	temp (°C)	product 7	isolated yield,[a] %
1	Me_3Si	A	2.0	50	**a**	88
2	3,5-$(CF_3)_2C_6H_4$	B	5.0	30	**b**	*
					b′	*
3	3,5-$F_2C_6H_4$	B	5.0	38	**c**	*
					c′	*
4	4-$CF_3C_6H_5$	B	5.0	38	**d**	*
					d′	*
5	4-FC_6H_5	B	4.0	40	**e**	76
					e′	*
6	C_6F_5	B	3.0	80	**f**	89
7	C_6H_5	A	2.0	50	**g**	88
					g′	*
8	4-$MeOC_6H_5$	A	2.0	65	**h**	95

[a] Except for those entries denoted by asterisks, where material was detected by TLC but not isolated.

result was obtained. Apparently the process of cross-coupling is much more sensitive to minor temperature changes than are either homocoupling or product cyclization. Again, all excess terminal alkyne could be accounted for as homocoupled product for entries 6–8. Formation of **5** also appeared to be occurring in the case of entries 8 and 9 (as observed by TLC), but again this product was not isolated.

Minimizing the reaction time appeared important in achieving a high ratio of coupled product to cyclized product, the major cause of the extended reaction time has been attributed to a competition for the palladium(0) between the nucleoside triflate and the terminal alkyne. Increasing the competitiveness of the nucleoside substrate for the palladium(0) should increase the rate of reaction and consequently the yield of desired product.

The coupling of the (pentafluorophenyl)alkyne was not attempted until the reaction conditions of the other substituted arylacetylenes had been optimized, as it was anticipated that the powerfully electron-withdrawing perfluoroaryl group would hypersensitize the alkyne toward homocoupling and the cross-coupled product to cyclization. Surprisingly these concerns were quite unfounded; only a small amount of homocoupled material and no cyclized product could be detected in these reactions (TLC). Furthermore, the (pentafluorophenyl)alkyne was the least reactive of all the arylacetylenes, requiring a longer reaction time at the same temperature than even the (*p*-methoxyphenyl)alkyne in order to couple. Nonetheless due to the lack of byproduct formation, the reaction proceeded smoothly at elevated temperatures to give **4f** in high yield (87%, entry 10, Table II). In short, the (pentafluorophenyl)alkyne showed opposite reactivity in all processes (cross-coupling, homocoupling, and cyclization) for which electron-deficient arylalkynes are activated.

The coupling of 5-(trifluoromethanesulfonyloxy)-2′-deoxyuridine (**6**) with alkynes was readily achieved (Figure 1) and the results have been summarized in Table III. The unprotected nucleoside **6** appeared only slightly less reactive than the protected nucleoside. Slightly higher reaction temperatures and/or longer reaction times were required in order to achieve coupling in equivalent reactions (compare Table II, entries 1, 5, 9, and 10, with Table III, entries 1, 5, and 6). The slight reduction in reactivity of the unprotected nucleoside triflate **6** was sufficient in cases sensitive to homocoupling to have this become the favored process. Consequently only small amounts of cross-coupled material could be observed in these cases (entries 2–4, Table III).

The direct coupling of unprotected 5-trifloxy-2′-deoxyuridine **6** with fluoroaromatic alkynes gave directly some compounds which could be sent for testing as anticancer or antiviral agents. Nucleosides which were not accessible from direct coupling of the corresponding arylalkynes with the unprotected nucleoside **6** were readily obtained by deacetylation of the corresponding bisacetate, in particular, **7b–d**. This deprotection was readily achieved by treatment of compounds **4b–d** with methanolic ammonia to give the free hydroxyl products **7b–d** in high yield (80–99%, see Experimental Section).

An alternative to the coupling of terminal acetylenes to 5-trifloxyl-2′-deoxyuridine would be to couple 5-ethynyl-2′-deoxyuridine to either an aryl triflate or halide. This would avoid prior elaboration of the aryl halides or triflates to alkynes in order to achieve coupling to the trifloxy nucleosides. It may also avoid some of the difficulties associated with homocoupling experienced in this work.

5-Ethynyl-2′-deoxyuridine (EDU) is a known compound which exhibits significant antiherpetic activity.[10] If this terminal alkyne could be coupled to the fluorinated aryl bromides used in the preparation of the corresponding arylalkynes, then the modified nucleosides outlined in Table III would be conveniently obtained. EDU was readily prepared by desilylation of the corresponding trimethylsilyl compound **7a**. The best yield was achieved by treatment of the crude product resulting from the coupling of (trimethylsilyl)acetylene with the unprotected nucleoside triflate **6** (entry 1, Table III) with tetrabutylammonium fluoride, giving the desired product (EDU) in high yield (91%, Figure 2). The coupling of EDU with a series of aryl bromides was investigated, reactions were carried out under the conditions depicted in Figure 2, and the results are summarized in Table IV. Only those systems activated toward oxidative addition coupled at all (entries 1–3, Table IV). In the case of bromopentaflu-

Table IV. Coupling of 5-Ethynyl-2′-deoxyuridine to Substituted Aryl Bromides As Described in Figure 2

		reaction conditions			
entry	R^3	time (h)	temp (°C)	product 7	isolated yield, %
1	$3,5\text{-}(CF_3)_2C_6H_4$	4	20	**b**	49
2	$3,5\text{-}F_2C_6H_4$	6	40	**c**	16
3	$4\text{-}CF_3C_6H_5$	6	40	**d**	55
4	$4\text{-}FC_6H_5$	8	50	**e**	0
5	C_6F_5	8	50	**f**	0
6	C_6H_5	18	50	**g**	0

orobenzene, coupling, again, may have been inhibited by the slow rate of reductive elimination.

It was apparent by TLC that the EDU was undergoing competitive decomposition since the UV-active spot corresponding to EDU disappeared after approximately 6 h under the reaction conditions when no coupling took place. Homocoupling of EDU may have been occurring but no new UV-active spot was observed by TLC (254 and 365 nm). The use of aryl iodides in place of the bromides and perhaps the presence of acetate protecting groups on the the sugar ring of EDU may give more efficient couplings, however, these reactions were not investigated.

Experimental Section

The following compounds were prepared by literature procedures: 5-hydroxy-2′-deoxyuridine,[16] 2′,3′,5′-tri-O-acetyl-5-trifluoromethanesulfonyloxyuridine,[12b] N-phenyltriflimide,[17] tetrakis(triphenylphosphine)palladium(0),[18] dichlorobis(triphenylphosphine)palladium(II).[19]

5-(Trifluoromethanesulfonyloxy)-2′-deoxyuridine (6). Potassium carbonate (0.7 g, 5.0 mmol) was added to a suspension of 5-hydroxy-2′-deoxyuridine (1.12 g, 4.6 mmol) in water (12 mL) to give a clear, orange solution. 1,4-Dioxane (26 mL) followed by a solution of *N*-phenyltriflimide (2.1 g, 5.9 mmol) in 1,4-dioxane (10 mL) was added and the solution left to stir overnight. The reaction mixture was evaporated and the residue purified by flash chromatography (hexanes 60%:ethyl acetate 35%:methanol 5%) to give **6** (1.7 g, 98%) as a white solid: mp 185–6 °C; $[\alpha]$ +27.3° (CH_3OH, c 0.48); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 11.47 (br s, 1 H, NH), 8.54 (s , 1 H, H-6), 6.10 (t, J = 6.10 Hz, 1 H, H-1′), 4.69 (br d, J = 4.11 Hz, 1 H, 3′-OH), 4.47 (br t, J = 4.20 Hz, 1 H, 5′-OH), 4.26 (m, 1 H, H-3′), 3.80 (m, 1 H, H-4′), 3.62 (m, 2 H, H-5′), 2.22 (m, 1 H, H-2′$_\beta$), 2.03 (m, 1 H, H-2′$_\alpha$); FABMS m/z (rel intensity) 377 (M^+ + H, 5), 260, 117 (100); IR (Nujoll mull) ν_{max} 3628 cm^{-1} (m, NH), 3456 (br, OH), 1728 (str br, C=O), 1684 (str, C=O),1239 (m, SO_3); UV (CH_3OH) λ_{max} 269.0 nm (ϵ 1100), 207.5 (1002). Anal. Calcd for $C_{16}H_{11}N_2SO_8F_3$: C, 31.92; H, 2.95; N, 7.44. Found: C, 31.85; H, 2.86; N, 7.32.

3′,5′-Di-*O*-acetyl-5-(trifluoromethanesulfonyloxy)-2′-deoxyuridine (3). Acetic anhydride (4 mL, 40 mmol) was added to a solution of **6** (2.3 g, 6.1 mmol) in pyridine (20 mL), and the resulting solution was allowed to stand overnight. The solution was concentrated and dissolved in ethyl acetate (30 mL), washed with 10% aqueous citric acid (30 mL) and water (2 × 20 mL), and dried over $MgSO_4$. The solution was evaporated onto silica (~2 g) and subjected to flash chromatography (hexanes/ethyl acetate 3:2), giving **3** (2.8g, 100%) as a solid foam: $[\alpha]$ +4.17° (CH_3OH, c 0.48); ^1H NMR δ 10.13 (br s, 1 H, NH), 7.84 (s , 1 H, H-6), 6.17 (dd, J = 8.10 Hz, 5.4 Hz, 1 H, H-1′), 5.15 (m, 1 H, H-3′), 4.40–4.18 (m, 3 H, H-4′,5′), 2.59 (m, 1 H, H-2′$_\beta$), 2.11 (m, 1 H, H-2′$_\alpha$), 2.05 and 2.04 (2 × s, 6H, 2 × CH_3CO_2); ^{13}C NMR δ 170.3 (CH_3CO_2), 156.8 (C4), 148.8 (C2), 133.2 (C6), 126.8 (C5), 116.3 (q, J_{CF} = 322 Hz, CF_3), 86.1 (C1′), 83.0 (C4′), 74.0 (C3′), 63.6 (C5′), 38.1 (C2′), 20.6 & 20.4 (2 × CH_3CO_2); MS m/z (rel intensity) 461 (M^+ + H, <5), 401 (3), 201 (100); IR ($CHCl_3$) ν_{max} 3400 cm^{-1} (m, NH), 3016 (m, CH), 1734 (str br, C=O), 1661 (w, C=O), 1240 (m, SO_3), 1198 (str, SO_3); UV ($CHCl_3$) λ_{max} 268 nm (ϵ 1785); HRMS calcd for $C_{14}H_{16}N_2O_{10}SF_3$ 461.0477, found 461.0491.

2′,3′,5′-Tri-*O*-acetyl-5-[2-(trimethylsilyl)ethynyl]uridine (2a). A stream of nitrogen was passed through a solution of **1** (0.10 g, 0.19 mmol) and $Pd(PPh_3)_4$ (11 mg, 0.01 mmol) in DMF (2.0 mL) for 10 min. To the resultant orange solution were added triethylamine (56 μL, 0.38 mmol), (trimethylsilyl)acetylene (37 mg, 0.38 mmol), and copper(I) iodide (3.30 mg, 0.02 mmol). The solution was heated to 45 °C and the progress of the reaction monitored by TLC (65% hexane, 30% ethyl acetate, 4% methanol, 1% formic acid). After 2.5 h the consumption of starting material was complete and the reaction mixture went from dark orange to black. The solvent was evaporated under vacuum to give a black resin which was dissolved in dichloromethane, and activated charcoal was added. After the solution was stirred for 1 h, the suspension was filtered through Celite, and the tan solution was evaporated onto silica (~200 mg) and chromatographed (65% hexane:35% ethyl acetate). 2′,3′,5′-Tri-*O*-acetyl-5-[2-(trimethylsilyl)ethynyl]uridine (**2a**)(75 mg, 85%) was obtained as a clear solid foam: mp 192–5 °C; $[\alpha]$ −69.52° ($CHCl_3$, c 0.63); ^1H NMR δ 9.53 (br s, 1 H, NH), 8.68 (s , 1 H, H-6), 6.05 (d, J = 4.6 Hz, 1 H, H-1′), 5.25 (m, 2 H, H-2′,3′), 4.29 (m, 2 H, H-4′,5′), 2.12, 2.04, 2.02 (3 × s, 3 × 3 H, 3 × CO_2CH_3), 0.12 (s, 9 H, $Si(CH_3)_3$); MS m/z (rel intensity) 408 (M^+, 8) 451 (25), 446 (27); IR ($CHCl_3$) ν_{max} 3395 cm^{-1} (m, NH), 1752 (str br, C=O), 1722 (br, C=O), 1626 (m, C=C); HRMS calcd for $C_{20}H_{26}N_2O_9$ 466.1408, found 466.1422.

Compounds **2b–e** were prepared in a similar manner as that described for **2a** above, varying only in the reaction time, temperature, and product yield obtained as detailed in Table I. In the cases of **2b–d**, a small amount of byproduct was also isolated (**2b′–d′**, respectively).

6-Phenyl-3-(2,3,5-tri-*O*-acetyl-β-D-*erythro*-pentofuranosyl)furano[2,3-*d*]pyrimidin-2-one (2c′): 5%; mp 137–9 °C; ^1H NMR δ 8.25 (s , 1 H, H-6), 7.77 (m, 2 H, ArH), 7.47 (m, 3 H, ArH), 6.71 (s, 1H, HC=COPh), 6.27 (d, J = 3.6 Hz, 1 H, H-1′), 5.47 (t, J = 4.5 Hz, 1 H, H-2′), 5.34 (dd, $J_{2',3'}$ = 4.6 Hz, $J_{3',4'}$ = 5.6 Hz, 1 H, H-3′), 4.16 (br s, 3 H, H-4′,5′), 4.39 (m, 3 H, H-4′, 5′), 2.20, 2.17, 2.14 (3 × s, 3 × 3 H, 3 × CH_3CO_2); MS m/z (rel intensity) 470 (M^+, 30), 291 (30), 259 (100); HRMS calcd for $C_{23}H_{22}N_2O_9$ 470.1325, found 470.1307.

3′,5′-Di-*O*-acetyl-5-[2-(trimethylsilyl)ethynyl]-2′-deoxyuridine (4a). Condition A. A stream of nitrogen was passed through a solution of **3** (0.10 g, 0.22 mmol) and $Pd(PPh_3)_4$ (12.5 mg, 0.01 mmol) in DMF (2.0 mL) for 10 min. To the resultant orange solution were added triethylamine (47 μL, 0.33 mmol), (trimethylsilyl)acetylene (33 mg, 0.33 mmol), and copper(I) iodide (3.4 mg, 0.02 mmol). The solution was heated to 50 °C and the progress of the reaction monitored by TLC (70% hexane, 26% ethyl acetate, 3% methanol, 1% formic acid). After 2.5 h the consumption of starting material was complete and the reaction mixture went from dark orange to black. The solvent was evaporated under vacuum to give a black resin which was dissolved in dichloromethane (5 mL). Activated charcoal was added, the slurry was stirred for 1 h, the suspension was filtered through Celite, and the tan solution was evaporated onto silica (~200 mg) and chromatographed (hexane/ethyl acetate 7:3). 3′,5′-Di-*O*-acetyl-5-[2-(trimethylsilyl)ethynyl]-2′-deoxyuridine (**4a**) (78 mg, 87%) was obtained as a clear solid foam: mp 181–2 °C (lit.[10b] mp 178–9 °C); ^1H NMR δ 9.70 (br s, 1 H, NH), 8.10 (s, 1 H, H-6), 5.90 (d, J = 4.60 Hz, 1 H, H-1′), 5.25 (m, 1 H, H-3′), 4.33 (m, 3 H, H-4′, 5′), 2.19, 2.17 (2 × s, 6 H, 2 × CH_3CO_2) 0.22 (s, 9 H, $Si(CH_3)_3$); MS m/z (rel intensity) 408 (M^+, 8), 393 (<1), 279 (100); HRMS calcd for $C_{20}H_{26}N_2O_9$ 408.1321, found, 408.1337.

Compounds **4b–e** were prepared in a similar manner as that described for **4a** above (condition A), varying only in the reaction time, temperature, and product yield obtained as detailed in Table II. In the cases of **4b–e**,considerable amounts of byproduct were also isolated (**4b′–e′**, respectively). In the cases of **4b** and **4c**, 1,4-bis(3,5-difluorophenyl)-1,3-butadiyne (**5**,X = 3,5-F_2) and 1,4-bis[4-(trifluoromethyl)phenyl]-1,3-butadiyne (**35**,X = 4-CF_3) were isolated, respectively, in sufficient quantities as to account

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for the mass balance of all arylalkyne intially added (see below for physical data).

Condition B. Compounds **4b–e** were also prepared in accordance with condition B as was **4f**, varying only in reaction time, temperature, and product yield obtained (Table II), as exemplified for the preparation of **4f** described below.

3′,5′-Di-*O*-acetyl-5-[2-(pentafluorophenyl)ethynyl]-2′-deoxyuridine (4f). A stream of nitrogen was passed through a solution of **3** (0.10 g, 0.22 mmol) and $Pd(PPh_3)_4$ (25 mg, 0.02 mmol) in DMF (2.0 mL) for 10 min. To the resultant orange solution were added triethylamine (34 μL, 0.24 mmol), (pentafluorophenyl)-acetylene (84.5 mg, 0.44 mmol), and copper(I) iodide (7.1mg, 0.05 mmol). The reaction mixture was intially stirred at room temperature for 2.0 h, after which time no product could be detected by TLC (70% hexane, 26% ethyl acetate, 3% methanol, 1% formic acid), and then at 45 °C for 3 h, after which time only a trace of product was detected. The reaction mixture was then heated to 55 °C and the consumption of **3** was complete after 5 h, at which time the orange solution turned black. The solvent was evaporated under vacuum to give a black resin which was dissolved in dichloromethane (5 mL). Activated charcoal was added and the slurry stirred for 1 h. The suspension was filtered through Celite and the tan filtrate was evaporated onto silica (~200 mg) and chromatographed (hexanes/ethyl acetate 7:3). 3′,5′-Di-*O*-acetyl-5-[2-(pentafluorophenyl)ethynyl]-2′-deoxyuridine (**4f**) (95 mg, 87%) was obtained as a white solid: mp 209.0–210.0 °C; [α] −37.88° (CH_3OH, *c* 0.33); ^1H NMR δ 9.84 (br s, 1 H, NH), 8.02 (s, 1 H, H-6), 6.33 (dd, *J* = 7.61 Hz, 5.81 Hz, 1 H, H-1′), 5.26 (m, 1 H, H-3′), 4.35 (m, 3H, H-4′,5′), 2.63 (m, 1 H, H-2′$_\beta$), 2.30 (m, 1 H, H-2′$_\alpha$), 2.16 and 2.13 (2 × s, 6 H, 2 × CH_3CO_2); ^{13}C NMR δ 170.40 and 170.12 (CH_3CO_2), 160.54 (C4), 149.12 (C2), 142.88 (C6), 99.33 (C5), 92.10 (C$_\beta$), 85.73 (C1′), 82.75 (C4′), 73.91 (C3′ and C$_\alpha$), 63.67 (C5′), 38.32 (C2′), 20.77 & 20.55 (CH_3CO_2); MS *m/z* (rel intensity) 502 (M^+, 40), 428 (28), 301 (100); IR ($CHCl_3$) ν_{max} 3388 cm^{-1} (m, NH), 2250 (w, C≡C), 1710 (str br, C=O), 1626 (sh, C=C); UV (CH_3OH) λ_{max} 305 nm (ε 19 489), 217 (13 819); HRMS calcd for $C_{21}H_{15}N_2O_7F_5$ 502.0799, found, 502.0818.

5-[2-(Trimethylsilyl)ethynyl]-2′-deoxyuridine (7a). A stream of nitrogen was passed through a solution of **6** (0.20 g, 0.53 mol) and $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) in DMF (4.0 mL) for 10 min. To the resultant orange solution were added triethylamine (115 μL, 0.80 mmol), (trimethylsilyl)acetylene (78 mg, 0.80 mmol), and copper(I) iodide (8.0 mg, 0.05 mmol). The solution was heated to 50 °C and the progress of the reaction monitored by TLC (60% hexane, 35% ethyl acetate, 4% methanol, 1% formic acid). After 2.0 h the consumption of starting material was complete and the reaction mixture went from dark orange to black. The solvent was evaporated under vacuum to give a black resin which was dissolved in methanol (5 mL). Activated charcoal was added, the slurry was stirred for 1 h, the suspension was filtered through Celite, and the tan solution was evaporated onto silica (~400 mg) and chromatographed (65% hexane:35% ethyl acetate). 5-[2-(Trimethylsilyl)-ethynyl]-2′-deoxyuridine (**7a**)(151 mg, 87%) was obtained as a white solid: mp 162–5 °C; [α] +6.32° (CH_3OH, *c* 1.90); ^1H NMR δ 10.70 (br s, 1 H, NH), 8.15 (s , 1 H, H-6), 6.10 (t, *J* = 6.36 Hz, 1 H, H-1′), 4.64 (br s, 1 H, 3′-OH), 4.39 (br s, 1 H, 5′-OH), 4.10 (m, 1 H, H-3′), 3.68 (m, 1 H, H-4′), 3.57 (m, 2 H, H-5′), 2.16 (m, 1 H, H-2′$_\beta$), 1.98 (m, 1 H, H-2′$_\alpha$), 0.24 (s, 9 H, $Si(CH_3)_3$); MS *m/z* (rel intensity) 324 (M^+, <1); UV (CH_3OH) λ_{max} 295 nm (ε 2842), 233.2 (2619), 203.6 (2116). This compound was converted to the known derivative 5-ethynyl-2′-deoxyuridine (EDU). Tetrabutylammonium fluoride (5 mL of 1 M solution, 5.0 mmol) was added. After 30 min all of the crude **7a** was consumed, as shown by TLC (60% hexane, 35% ethyl acetate, 4% methanol, 1% formic acid). Silica (~10 g) was added to the reaction mixture and the slurry evaporated to dryness and subjected to flash chromatograhy (hexanes 65%:ethyl acetate 30%:methanol 5%) to give EDU as a white solid (1.05 g, 91%) (recrystallized from ethyl acetate/hexanes): mp 200–2 °C (lit.[7b] mp 197–9 °C); [α] +25.0° (CH_3OH, *c* 0.70); ^1H NMR δ 10.99 (br s, 1 H, NH), 8.13 (s , 1 H, H-6), 6.00 (t, *J* = 6.33 Hz, 1 H, H-1′), 4.64 (d, *J* = 4.30 Hz, 1 H, 3′-OH), 4.39 (t, *J* = 4.76 Hz, 1 H, 5′-OH), 4.17 (m, 1 H, H-3′), 3.71 (m, 1 H, H-4′), 3.54 (m, 2 H, H-5′), 2.97 (s, 1 H, C≡CH), 2.13 (m, 1 H, H-2′$_\beta$), 1.92 (m, 1 H, H-2′$_\alpha$); UV (CH_3OH) λ_{max} 287.8 nm (ε 12 559), 225.7 (11 953), 204.2 (8064).

An attempt to prepare compounds **7b–h** in a similar manner to that described for **7a** above was successful only for compounds **7e–h**; variations in the reaction conditions and the product yields obtained are detailed in Figure 2 and Table III. For the entries2–4, only trace amounts of product and byproduct (**7b–d, 7b′–d′**, respectively) and considerable amounts of starting material **6** were observed by TLC.

Deacetylation: 5-[2-[3,5-Bis(trifluoromethyl)phenyl]-ethynyl]-2′-deoxyuridine (7b). 4b (87 mg, 0.16 mmol)was added to a saturated solution of methanolic ammonia (5 mL). The resulting solution was stirred for 6 h, at which point TLC analysis revealed the consumption of **4b** to be complete. Silica (~200 mg) was added, and the slurry was evaporated to dryness and subjected to fash chromatography (hexanes 70%:ethyl acetate 25%:methanol 5%), giving **7b** as a white solid (68 mg, 90%). A larger stock of **7b** (135 mg) was recrystallized from 2-isopropanol (~0.5 mL) to give **7b** as a microcrystalline solid (114 mg, 84% recovery): mp 247–250 °C; [α] −8.0° (CH_3OH, *c* 0.50); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 11.25 (br s, 1 H, NH), 8.37 (s , 1 H, H-6), 7.56 (s, 2 H, ArH), 7.40 (s, 1 H, ArH), 5.90 (t, *J* = 7.56 Hz, 1 H, H-1′), 4.70 (m, 1 H, OH), 4.55 (m, 3H, OH), 4.04 (m, 1 H, H-3′), 3.59 (m, 1 H, H-4′), 3.40 (m, 2 H, H-5′), 1.98 (m, 1 H, H-2′$_\beta$), 1.76 (m, 1 H, H-2′$_\alpha$); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 160.80 (C4), 148.51 (C2), 143.97 (C6), 130.39 (q, $^2J_{CF}$ = 34.2, ArC3), 130.22 (ArC2), 124.46 (ArC1), 121.9 (q, J_{CF} = 272.5, CF_3), 119.99 (ArC4), 96.88 (C5), 87.97 (C$_\alpha$), 86.87 (C1′), 84.73 (C$_\beta$), 74.44 (C4′), 69.20 (C3′), 60.12 (C5′), 40.15 (C2′); FABMS *m/z* (rel intensity) (M^+ + H, <5); IR (Nujol mull) ν_{max} 3440 cm^{-1} (m, NH), 3210 (br, OH), 1730 (str , C=O), 1656 (sh, C=C); UV (CH_3OH) λ_{max} 312 nm (ε 24 274), 203 (41 115). Anal. Calcd for $C_{19}H_{14}N_2O_5F_6$: C, 49.14; H, 3.03; N, 6.03. Found: C, 49.22; H, 3.18; N, 6.22.

Compounds **7c** and **7d** were prepared in a similar manner as that described for **7b** in yields of 99% and 84%, respectively. In each case the yield is for the product isolated by chromatography. High purity samples were obtained from recrystallization in 2-pranol/water (9:1) (~80% recovery).

Reverse Couplings: 5-[2-[3,5-Bis(trifluoromethyl)-phenyl]ethynyl]-2′-deoxyuridine (7b). Copper(I) iodide (6.5 mg, 0.04 mmol) was added to a solution of 3,5-bis(trifluoromethyl)-bromobenzene (0.14 g, 0.48 mmol), 5-ethynyl-2′-deoxyuridine (EDU, 0.10 g, 0.40 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and triethylamine (44 mg, 0.44 mmol) in deoxygenated DMF (2 mL). The solution went very dark within a few minutes. After 30 min of stirring at room temperature, the consumption of EDU was complete. The reaction mixture was evaporated to dryness and the residue dissolved in methanol (10 mL). Decolorizing charcoal was added, and the slurry was stirred for 15 min, filtered through Celite, and evaporated onto silica (~200 mg). The residue was subjected to flash chromatography (hexanes 70%:ethyl acetate 25%:methanol 5%), giving **7b** as a white solid (67 mg, 49%). Spectroscopic data are as described above.

Compounds **7c** and **7d** were prepared in a similar manner as that described for **7b**; variations in reaction times and yields are recorded in Table IV. In each case the yield is for the product isolated by chromatography. As mentioned above, high purity samples were obtained by recrystallization from 2-propanol/water (9:1) (~80% recovery). See above for physical data on compounds **7b–d**. Attempts to prepare compounds **7e–g** by a similar route as that just descibed for **7b–d** were unsuccessful (see Table IV, entries 4–6 for reaction conditions). In each case, the starting material, EDU, was consumed slowly as observed by TLC, although no product was observed.

(4-Fluorophenyl)(trimethylsilyl)acetylene. A stream of nitrogen was passed through a suspension of $Pd(PPh_3)_2Cl_2$ (50 mg, 0.172 mmol) in diisopropylamine (14 mL). To this suspension were added 4-bromofluorobenzene (1.5 g, 8.6 mmol), triphenylphosphine (225 mg, 0.86 mmol), and copper(I) iodide (70 mg, 0.43 mmol), to give an orange suspension. Finally (trimethylsilyl)-acetylene (1.0 g, 10.32 mmol) was added over 30 min; during this addition the solution changed color from orange to brown to black. The reaction was monitored by GLC; after 16 h at room temperature, only a small amount of product and mostly starting material could be observed. The reaction mixture was heated to reflux for 3 h after which time no starting material and only product could be observed. The solution was evaporated under vacuum at room temperature to give a black paste. This residue

was suspended in hexanes (~20 mL) and filtered through Celite to remove catalyst and inorganic salts. The resultant tan solution was again evaporated at room temperature under vacuum to give a tan oil which was distilled using a Kugelrohr apparatus to give (4-fluorophenyl)(trimethylsilyl)acetylene (1.60 g, 97%) as a clear oil: bp 80 °C (0.1 mmHg, block). ^{1}H NMR δ 7.48 (dd, J_{HH} = 8.72 Hz, $^4J_{HF}$ = 5.73 Hz, 2 H, ArH), 6.94 (t, J_{HH} = 8.70, $^3J_{HF}$ = 8.70, 2 H, ArH), 0.24 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C NMR δ 161.79 (d, J_{CF} = 246.6 Hz, C4), 132.95 (C2), 117.20 (d, $^2J_{CF}$ = 22.2 Hz, C3), 116.50 (d, $^4J_{CF}$ = 2.8 Hz, C1), 103.96 (C$_\alpha$), 93.83 (C$_\beta$), -0.10 (Si(CH$_3$)$_3$); ^{29}Si NMR δ -17.62 ppm; MS *m/z* (rel intensity) 192 (M$^+$, 15), 177 (100); IR (film) ν_{max} 2160 (str sh, C≡C), 1600 (str sh, C=C); HRMS calcd for $C_{11}H_{13}SiF$ 192.0771, found 192.0776. The (trimethylsilyl)acetylenes were converted to the known terminal acetylenes using KOH in methanol. (4-Fluorophenyl)(trimethylsilyl)acetylene (1 g, 8.3 mmol) was added to a solution of KOH (0.23 mg, 4.2×10^{-3} mmol, 0.05 mol %) in methanol (10 mL). The reaction was monitored by GLC; no product formation was evident after 3 h. A further 4.5 mg (0.97 mol %) of KOH in methanol (1.1mL) was added to this solution. After the solution stood at room temperature for 1 h, the consumption of starting material and the formation of product were complete. The reaction mixture was diluted with water (20 mL) to give a milky emulsion which was extracted with ether (2 × 15 mL). The ether solution was dried over MgSO$_4$ and the ether removed by distillation at ambient pressure, where the external temperature did not exceed 60 °C. The resultant oil was distilled using a Kugelrohr apparatus to give (4-fluorophenyl)acetylene (896 mg, 90%) as a clear oil: bp 62 °C (28.0 mmHg, block) (lit.[20] 52 °C, 30 mmHg); ^{1}H NMR δ 7.48 (dd, J_{HH} = 8.67 Hz, $^4J_{HF}$ = 5.40 Hz, 2 H, ArH), 6.94 (t, J_{HH} = 8.69, $^3J_{HF}$ = 8.69, 2 H, ArH), 3.03 (s, 1 H, C≡CH); ^{13}C NMR δ 162.88 (d, J_{CF} = 250.3 Hz, C4), 134.15 (C2), 118.29 (C1), 115.66 (d, $^2J_{CF}$ = 23.47 Hz, C3), 82.69 (C$_\alpha$), 77.11 (C$_\beta$); MS *m/z* (rel intensity) 120 (M$^+$, 70), 75 (100); HRMS calcd for C_8H_5F 120.0375, found 120.0375.

Other aryl(trimethylsilyl)acetylenes were prepared in a similar manner as that described for (4-fluorophenyl)(trimethylsilyl)-acetylene above, varying only in the reaction time, temperature, and product yield obtained. Other phenylacetylenes were prepared in a similar manner as that described for (4-fluorophenyl)acetylene above, varying only in the reaction time, KOH equivalents, and product yield obtained.

1,4-Bis(3,5-difluorophenyl)-1,3-butadiyne (5, X = 3,5-F$_2$). (3,5-Difluorophenyl)acetylene (100 mg, 0.36 mmol) was added to a solution of Pd(PPh$_3$)$_4$ (17 mg, 0.015 mmol) in deoxygenated DMF (1 mL). The yellow solution was allowed to stir at 38 °C for 2 h, after which time no product formation could be observed by TLC (hexanes). Triethylamine (116 μL, 0.80mmol) was added and a slight color change, yellow to orange was observed. After the solution was stirred at 38 °C for 3 h, a small amount of product could be observed by TLC. The addition of copper(I) iodide (6 mg, 0.037 mmol) gave immediately a deep red/brown solution; significant product formation was evident by TLC after only 30 min. The solution was evaporated and the residue dissolved in hexanes (5 mL), and the resulting slurry was filtered through Celite. Silica (~200 mg) was added to the filtrate, the slurry was evaporated, and the residue was subjected to flash chromatography (hexanes). The product, 1,4-bis(3,5-difluorophenyl)-1,3-butadiyne (5 X = 3,5-F$_2$) was obtained as a colorless solid (98 mg, 99%). This product was unstable at ambient temperature and turned brown overnight: mp 152–3 °C; ^{1}H NMR δ 7.01 (m, 4 H, ArH), 6.66 (m, 2H, ArH); ^{13}C NMR δ 162.3 (dd, J_{CF} = 249.9 Hz, $^3J_{CF}$ = 12.9 Hz, CF), 123.9 (t, $^3J_{CF}$ = 11.6 Hz, ArC), 115.5 (m, ArC), 105.9 (t, $^2J_{CF}$ = 25.4 Hz, ArC), 79.9 (m, ArC≡C—), 74.9 (s, ArC≡C—); MS *m/z* (rel intensity) 274 (M$^+$, 100), 255 (M$^+$ - F, 10), 137 (M$^+$ - $C_8H_3F_2$, 15); IR (film) ν_{max} 1644 (C=C); HRMS calcd for $C_{16}H_8F_4$ 274.0405, found 274.0398.

1,4-Diphenyl-1,3-butadiyne (5, X = H). Copper(I) iodide (16 mg, 0.10 mmol) was added to a solution of phenylacetylene (200 mg, 1.96 mmol), triethylamine (566 μL, 3.92 mmol), and Pd(PPh$_3$)$_4$ (45 mg, 0.04 mmol) in THF (2 mL). The initially orange solution went red/brown after ~5 min. The solution was allowed to stand at room temperature overnight. The reaction mixture was worked up and purified as outlined above. 1,4-Diphenylbutadiyne was obtained as a solid (160 mg, 82%): mp 85–6 °C (lit.[21] mp 86–7 °C); ^{1}H NMR δ 7.58 (m, 4 H, ArH), 7.28 (m, 6 H, ArH); ^{13}C NMR δ 132.5, 129.4, 128.6, 121.8 (ArC), 81.7 (ArC≡C—), 74.1 (ArC≡C—).

1,4-Bis(trimethylsilyl)-1,3-butadiyne. Copper(I) iodide (41 mg, 0.26 mmol) was added to a solution of (trimethylsilyl)-acetylene (800 mg, 5.1mmol) and Pd(PPh$_3$)$_4$ (115 mg, 0.10 mmol) in deoxygenated diisopropylamine (10 mL) to give a black solution. The reaction mixture was stirred at 50 °C for 4 h; no product was observed by TLC (hexanes). The reaction mixture was heated at reflux for 6 h and worked up, and the product was purified as outlined above. Pure 1,4-bis(trimethysilyl)-1,3-butadiyne was obtained as a solid (110 mg, 22%): mp 113–4 °C (lit.[21] 113 °C); ^{13}C NMR δ 88.0 (SiC≡C—), 85.6 (SiC≡C—), -0.5 (Si(CH$_3$)$_3$).

Supplementary Material Available: Spectral data for compounds **2b–d**, **4b**, **4b′**, **4c-e**, **7c–g**, (pentafluorophenyl)-(trimethylsilyl)acetylene, (pentafluorophenyl)acetylene, (3,5-bis-(trifluoromethyl)phenyl)(trimethylsilyl)acetylene, (3,5-bis(trifluoromethyl)phenyl)acetylene, (3,5-difluorophenyl)(trimethylsilyl)acetylene, (3,5-difluorophenyl)acetylene, (4-(trifluoromethyl)phenyl)(trimethylsilyl)acetylene, (4-(trifluoromethyl)-phenyl)acetylene, (4-methoxyphenyl)(trimethylsilyl)acetylene, and (4-methoxyphenyl)acetylene and ^{1}H and/or ^{13}C NMR spectra for compounds **2–c**, **2c′**, **2d**, **3**, **4b**, **4b′**, **4d–f**, **5** (X = 3,5-F$_2$), **7h**, (3,5-difluorophenyl)(trimethylsilyl)acetylene, and (3,5-bis(trifluoromethyl)phenyl)(trimethylsilyl)acetylene (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any curent masthead page for ordering information.

(20) Kodiara, K., Okuhara, K. *Bull. Chem. Soc. Jpn.* 1988, *61*, 1625.

(21) Aldrich Chemical Co. Catalogue (1992), 940 West Saint Paul Avenue, Milwaukee, WI 53233.