Synthesis of *(E)*-5-[2-(Tri-n-butylstannyl)vinyl] Substituted 2′-Deoxyuridine Derivatives for Use in Halogenation and Radiohalogenation Reactions

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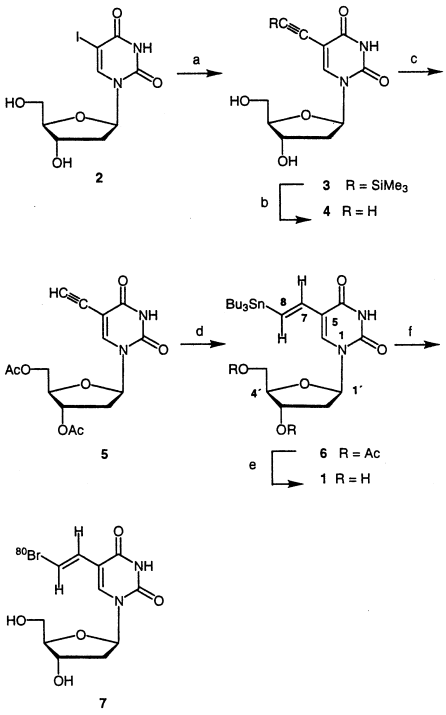
Abstract: A facile synthesis is reported for 5-[2-(tri-*n*-butyl-stannyl)vinyl]-2′-deoxyuridine **1**, starting from commercial 5-iodo-2′-deoxyuridine **2** via the stannylation reaction as the key step. The 3′,5′-di-*O*-acetyl-N(3)-*p*-toluoyl-protected analog of **1**, compound **9**, was then prepared. Electrophilic fluorination of **9** with carrier-added $[^{18}F]F_2$ provided the desired *(E)* and *(Z)* fluorovinyl compounds **10**, but not as the major products. The *E*/*Z* ratio of **10** was 2:1. The main product of the reaction was the proton substituted compound **11**.

Key words: terminal alkyne, stannylation, fluorodestannylation, radiohalogenation

Recently *(E)*-5-(2-[^{125}I]Iodovinyl)-2′-deoxyuridine ([^{125}I]IVDU) and several structural analogs of IVDU were reported[2] as probes for monitoring transfection of tumour cells by viral kinases. Our interest was directed to halovinyldeoxyuridine derivatives which may be used to monitor gene therapy in tumour patients by positron emission tomography (PET). A most promising probe for this purpose would be the fluoro analogue of IVDU, fluorovinyldeoxyuridine, when radiolabelled with the positron emitting isotope of fluorine, ^{18}F ($T_{1/2}$ = 110 min). The ^{80}Br-analogue ($T_{1/2}$ = 17.7 min, 2% β^+, decay by isomeric transition of ^{80m}Br with 4.42 hr), too, may be a suited candidate for PET, at least in animal experiments.

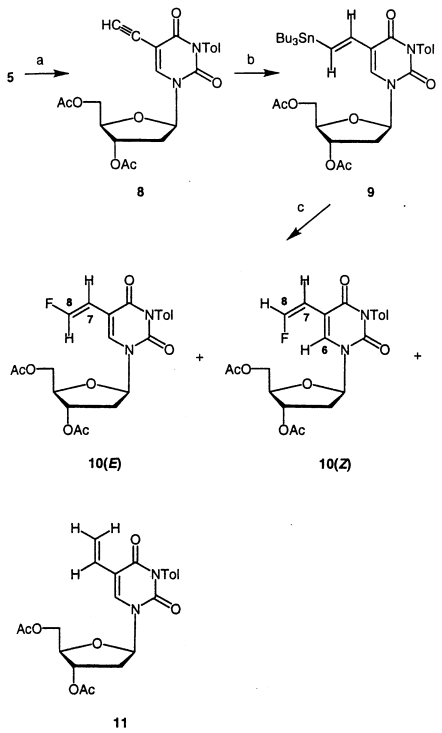
The [^{125}I]IVDU has been synthesized by electrophilic iododesilylation of *(E)*-5-[2-(trimethylsilyl)vinyl]-dUrd using Na^{125}I/ICl.[2] However, the silyl precursor was not suited for a radiofluorination procedure with molecular $[^{18}F]F_2$. For this purpose, the stannyl group has been reported as being the better synthetic equivalent for radiofluorination[3] than the silyl function. Therefore we developed a novel and facile synthesis of 5-[2-(tri-*n*-butylstannyl)vinyl]-dUrd **1** and its toluoyl-protected analog **9**.

The arabinosyl derivative of **1** was yet prepared via a palladium-catalyzed coupling reaction of the toluoyl-protected analogue of 1-(β-D-arabinofuranosyl)-5-iodopyrimidin-2,4(3*H*)dione with *trans*-1,2-bis(tri-*n*-butylstannyl)ethene.[4] However, the preparation of the bisorganostannane involved a series of difficult reactions which we wanted to avoid.[5] Seela et al.[6] additionally reported a coupling reaction of an unprotected iodo-substituted adenosine derivative with terminal alkynes under palladium-catalyzed conditions. In this work we examined the unprotected 5-iodo-dUrd (IDU) **2** for a coupling reaction with trimethylsilylethyne (Scheme 1).



Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$ (0.02 eq), CuI (0.08 eq), NEt_3, DMF, Me_3SiCCH (5 eq), rt, 6 h; (b) NaOMe (3eq), MeOH, rt, 30 min, then AG50WX (H^+form), 61% (two steps); (c) Ac_2O, pyridine, rt, 1 h, 97%; (d) $HSnBu_3$ (1.6 eq), AIBN (0.46 eq), toluene, 80 °C, 1 h, 52%; (e) NaOMe (2.5 eq), MeOH, rt, 30 min, then AG50WX (H^+form), 91%; (f) $NH_4[^{80}Br]Br$ (1 eq), chloramine T (CAT, 4 eq), EtOH (aq), rt, 1 min, then aminoethanethiol hydrochloride (AET, 24 eq), 99% (based on $NH_4[^{80}Br]Br$)

Scheme 1



Reagents and conditions: (a) *N*-ethyldiisopropylamine (2 eq), pyridine, *p*-toluoylchloride (2 eq), rt, 2 h, quantitative; (b) $HSnBu_3$ (3.2 eq), AIBN (0.6 eq), toluene, 80 °C, 1 h, 50%; (c) $[^{18}F]F_2$, $CFCl_3$, -70 °C, 7 min, 58%.

Scheme 2

After desilylation of the partly purified product **3** under basic conditions and neutralization with cation exchange resin, 5-ethynyl-dUrd **4** was obtained in 61% yield, based on **2**.[7] Compound **4** was then treated with acetic anhydride as convenient to provide the 3′,5′-di-*O*-acetylated analog **5** in 97% yield. Addition of tri-*n*-butyltin hydride to the terminal alkyne **5** in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) gave the *(E)*-vinylstannane **6** in moderate yield (52%).[8] No *(Z)*-isomer could be observed in the ^1H NMR spectrum. Common deprotection of the 3′,5′-di-*O*-acetyl groups of **6** using NaOMe/MeOH provided **1** in 91% yield. Radiobromination of **1** with $NH_4[^{80}Br]Br$ gave *(E)*-5-(2-[^{80}Br]bromovinyl)-dUrd (BVDU) **7** in good radiochemical yield (99%) within 1 min.[9] The attempted fluorodestannylation of **6** with $[^{18}F]F_2/CFCl_3$ at -70 °C did not provide the expected [^{18}F]fluorovinyl compound, but instead the protonated vinyl derivative was obtained. It was suspected that intermediately a N(3)-[^{18}F]fluorinated compound was formed and that the nitrogen bonded fluorine was lost during workup as usual for *N*-fluoroimides. Thus, the *N*-3 group of **5** was first protected by a toluoyl group[10] and the resulting **8** was stannylated by the same method as that used for **5** to give **9** in 50% overall yield (Scheme 2).

After radiofluorination[11] of **9** with carrier-added $[^{18}F]F_2$, the obtained product mixture was purified (acetone/*n*-hexane 2:3) and analyzed by electrospray ionization mass spectrometry (ESI-MS) and ^{19}F NMR. Two mass peaks: 474 amu and 456 amu indicated the fluorinated vinyl analogs **10*(E/Z)*** and the protonated vinyl product **11**, respectively. The major product **11** was confirmed by ESI-MS and ^1H NMR. ^{19}F NMR analysis of **10** demonstrated the presence of two isomers, *(E)*-fluorovinyl analog **10*(E)*** and *(Z)*-fluorovinyl analog **10*(Z)*** in a 2:1 ratio.[11] Their structures were confirmed by analysis of the J_{FH} coupling constants within the expected ranges.

References and Notes

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(7) Preparation of 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-ethynylpyrimidin-2,4(3*H*)-dione (**4**): Compound **2** (1.84 g, 5.2 mmol), DMF (13 ml), NEt_3 (26 ml), CuI (81 mg, 0.42 mmol), $(Ph_3P)_2PdCl_2$ (82 mg, 0.12 mmol) and trimethylsilylethyne (2.5 g, 25.7 mmol) were added sequentially to a dried round-bottomed flask (100 ml) with stirring under nitrogen. The reaction was continued at rt for 6 h (TLC control, solvent: MeOH/$CHCl_3$ 1:4). The educt **2** (R_f = 0.56) had been consumed. The product **3** (R_f = 0.65) had been formed. A limited amount of dUrd (R_f = 0.42) had also been formed. After removing the solvent under reduced pressure, the residue was chromatographed (silica gel, MeOH/$CHCl_3$ 1:9) to give the black crude product **3** (ca 2.6 g). Compound **3** was dissolved in MeOH (10 ml) with stirring and NaOMe/MeOH (40 ml, 0.4 N) was added. The reaction was stirred at rt for 30 min. The solution was then neutralized by cation exchange resin AG50W-X8 (H^+form, 200-400 mesh), filtered, concentrated under reduced pressure and chromatographed (silica gel, MeOH/$CHCl_3$ 1:9) to give **4** in 61% yield (798 mg). Yellow crystals, mp: 198 °C (dec.) lit.: 197-199 °C (dec.)[7a]; 200-202 °C[7b], anal. $C_{11}H_{12}N_2O_5 \cdot 0.25\ H_2O$ calcd: C 51.46, H 4.81, N 10.91; found: C 51.76, H 4.94, N 10.75; MW: 252.2, ESI+Q1MS, M = 252 (m/z), $[M+H]^+$ = 253.0, $[M+Na]^+$ = 274.9, $[2M+H]^+$ = 505.1, $[2M+Na]^+$ = 527.1, ESI - Q1MS, M = 252 (m/z), $[M-H]^-$ = 250.9, $[M+^{35}Cl]^-$ = 286.9; $[2M-H]^-$ = 503.1; ^1H NMR (250 MHz, DMSO-d_6): δ 2.07-2.15 (m, 2H, H-2′), 3.29 (s, 2.8 H, H_2O), 3.58 (ddd, 2H, $J_{5'a,5'b}$ = 12.1 Hz, $J_{5',OH}$ = 4.9 Hz, $J_{5',4'}$ = 3.3 Hz, H-5′), 3.79 (q, 1H, J = 3.3 Hz, H-4′), 4.03 (s, 1H, H-8), 4.20-4.25 (m, 1H, H-3′), 5.06 (t, 1H, $J_{OH,5'}$ = 4.9 Hz, 5′-OH), 5.19 (d, 1H, $J_{OH,3'}$ = 4.3 Hz, 3′-OH), 6.09 (t, 1H, $J_{1',2'}$ = 6.6 Hz, H-1′), 8.27 (s, 1H, H-6), 11.55 (s, 1H, NH); ^{13}C NMR (62.90MHz, DMSO-d_6): δ 40.15 (C-2′), 60.81 (C-5′), 69.95 (C-3′), 76.32 (C-8, weak signal), 83.37 (C-7), 84.79(C-1′), 87.56 (C-4′), 97.52 (C-5), 144.40 (C-6), 149.32 (C-2), 161.51 (C-4).

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(8) Preparation of 1-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-*(E)*-5-[2-(tri-*n*-butylstannyl)vinyl]pyrimidin-2,4(3*H*)-di-one (**6**): Compound **6** was prepared according to a published method[a] with a slight modification. A round-bottomed flask (250 ml) was charged with toluene (150 ml). Dry N_2 was bubbled through the solvent for 10 min. Compound **5** (300 mg, 0.89 mmol) was added with stirring. It did not immediately dissolve in toluene. Stirring was continued at 80 °C until a clear solution resulted (10 min). The solution was then cooled to 50 °C and bubbling of N_2 was stopped. To this solution tri-*n*-butyltin hydride (414 mg, 1.42 mmol) was added in one portion and AIBN (67 mg, 0.41 mmol) was added sequentially. It was then heated again to 80 °C and stirred for 1 h while the solution changed to pale yellow. TLC (acetone/*n*-hexane 1:1) indicated formation of the product **6** (R_f = 0.64) and consumption of the educt **5** (R_f = 0.38). After evaporation of the solvent at 40 °C under reduced pressure, the residue was chromatographed (silica gel, ethylacetate/*n*-hexane 1:1) giving **6** in 52% yield (291 mg). A white waxy solid was obtained; mp: 114-116 °C. Anal. $C_{27}H_{44}N_2O_7Sn$ calcd: C 51.69, H 7.07, N 4.47; found: C 51.98, H 7.18, N 4.33; MW:627.4, ESI+Q1MS, M = 628 (m/z); $[M+H]^+$ = 629.3, $[M+Na]^+$ = 651.2; isotope clusters in accordance with the presence of Sn; ^1H NMR (250 MHz, $CDCl_3$): δ 0.80-0.97 [m, 15 H, CH_2CH_3 (*n*-Bu_3)], 1.25-1.59 [m, 12 H, CH_2CH_2 (*n*-Bu_3)], 2.10 [s, 3H, CH_3 (Ac)], 2.12 [s, 3H, CH_3 (Ac)], 2.19 (ddd, 1H, $J_{2'a,2'b}$ = 14.2 Hz, $J_{2'a,1'}$ = 8.5 Hz, $J_{2'a,3'}$ = 6.6 Hz, H-2'a), 2.52 (ddd, 1H, $J_{2'b,2'a}$ = 14.2 Hz, $J_{2'b,1'}$ = 5.6 Hz, $J_{2'b,3'}$ = 1.9 Hz, H-2'b), 4.28 (ddd, 1H, $J_{4',5'b}$ = 4.0 Hz, $J_{4',5'a}$ = 3.0 Hz, $J_{4',3'}$ = 2.4 Hz, H-4'), 4.36 (dd, 1H, $J_{5'a,5'b}$ = 12.2 Hz, $J_{5'a,4'}$ = 3.0 Hz, H-5'a), 4.74 (dd, 1H, $J_{5'b,5'a}$ = 12.2 Hz, $J_{5'b,4'}$ = 4.0 Hz, H-5'b), 5.24 (ddd, 1H, $J_{3',2'a}$ = 6.6 Hz, $J_{3',4'}$ = 2.4 Hz, $J_{3',2'b}$ = 1.9 Hz, H-3'), 6.32 (dd, 1H, $J_{1',2'a}$ = 8.5 Hz, $J_{1',2'b}$ = 5.6 Hz, H-1'), 6.63 (dd, 1H, $J_{8,7}$ = 19.7 Hz, $^5J_{8,6}$ = 0.56 Hz, H-8), 6.89 (d, 1H, $J_{7,8}$ = 19.7 Hz, H-7), 7.53 (d, 1H, $^5J_{6,8}$ = 0.56 Hz, H-6), 8.43 (brs, 1H, NH); ^{13}C NMR(62.90 MHz, $CDCl_3$): δ 9.57 (CH_2, *n*-Bu_3), 13.64 (CH_3, *n*-Bu_3), 20.76 (CH_3, Ac), 20.86 (CH_3, Ac), 27.26 (CH_2, J_C 117/119$_{Sn}$ = 54.0 Hz, d, *n*-Bu_3), 29.04 (CH_2, J_C 117/119$_{Sn}$ = 20.2 Hz, d, *n*-Bu_3), 37.92 (C-2'), 63.80 (C-5'), 74.20 (C-3'), 82.47 (C-1'), 85.36 (C-4'), 114.67 (C-5), 132.36 (C-8 or C-7)[b], 134.26 (C-7 or C-8)[b], 135.77 (C-6), 149.32 (C-2), 161.51(C-4), 169.96 (CO, Ac), 170.34 (CO, Ac)
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b) Signals for C-7 and C-8 could not be assigned unequivocally.

(9) Preparation of *(E)*-5-(2-[^{80}Br]bromovinyl)-dUrd (BVDU) (**7**) is similar to a known method.[4] *(1) Labelled precursor:* Enriched $NH_4{}^{79}Br$ (1 mg, 0.01 mmol, 91%) was introduced into a capsule of a volume of 1 ml. EtOH (400 µl) and H_2O (50 µl) were added. The mixture was then treated by a supersonic vibrator until a clear solution was obtained. This solution was used as a liquid target. It was irradiated for 4 h with thermal neutrons. $NH_4[^{80}Br]Br$ ($3.7•10^8$ Bq) was obtained according to the $^{79}Br(n,\gamma)^{80}Br$ nuclear reaction. *(2) Radioactive synthesis:* Educt **1** (6 mg, 0.01 mmol) was dissolved in ethanol (100 µl) by ultrasonic vibration at rt. The $NH_4[^{80}Br]Br$ solution and subsequently CAT (9 mg, 0.04 mmol) were added and ultrasonic vibration was continued for 1 min. Then AET (27 mg, 0.24 mmol) was added. In radio-TLC ($MeOH/CHCl_3$ 1:4), only one product (R_f = 0.59) was formed. The R_f value of this compound was the same as that of the reference compound BVDU **7** obtained from a similar reaction described in literature.[9a] The radiochemical yield of [^{80}Br]BVDU **7** was 99%.

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(11) Preparation of 1-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-3-*p*-toluoyl-*(E),(Z)*-5-(2-[^{18}F]fluorovinyl)-pyrimidin-2,4-dione (**10**) and 1-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-3-*p*-toluoyl-5-vinylpyrimidin-2,4-dione (**11**):
(1) Production of $[^{18}F]F_2$: A stainless steel target with volume 145 ml was filled with ^{20}Ne containing 3% F_2 (Messer Griesheim). The amount of fluorine in the vessel was setted up to 0.6 mmol. The fluorine was further diluted to 0.6 to 0.7% by pressurizing with the target gas ^{20}Ne to about 15 kg/cm^2. The target was irradiated with ~14 MeV deuterons at a beam current 15 µA for 2 h to generate fluorine-18 according to $^{20}Ne(d,\alpha)^{18}F$. The yield was $2.5•10^8$ Bq/µAh. An amount of 70 ml of the radioactive fluorine containing gas mixture (about 20 µmol of $[^{18}F]F_2$) was used for the subsequent fluorination reaction.
(2) Radiofluorination reaction: An excess of the stannylated precursor **9** (19 mg, 25 µmol) was dissolved in $CFCl_3$ (20 ml) and cooled to -70 °C. The carrier-added $[^{18}F]F_2$ (20 µmol) was bubbled through the cooled solution with a flow rate 10 ml/min for 7 min. A white suspension was formed. The radioactivity of the crude mixture was $3.8•10^8$ Bq as measured by an ionization chamber. About 58% of the radioactivity ($2.2•10^8$ Bq) was found within the peak corresponding to **10** as calculated from radio-TLC (acetone/*n*-hexane 1:1, R_f = 0.56). After decay of **10** the solvent was removed under reduced pressure at 30 °C. The residue obtained was chromatographed (silica gel, acetone/*n*-hexane 2:3, R_f = 0.41) to give a mixture of white products **10** and **11** in 58% yield (7 mg). The ratio of **10** to **11** was nearly 1:7 as evaluated by ESI-MS. **10**: $C_{23}H_{23}FN_2O_8$, MW 474.4. **11**: $C_{23}H_{24}N_2O_8$, MW 456.5. ESI+Q1MS (mixture of **10** and **11**, white solid), M_1 = 474 (m/z), M_2 = 456 (m/z), $[M_1+Na]^+$ = 497.1, $[M_1+M_2+Na]^+$ = 953.2; $[M_2+H]^+$ = 457.1, $[M_2+NH_4]^+$ = 474.1, $[M_2+Na]^+$ = 479.1, $[2M_2+H]^+$ = 913.0, $[2M_2+NH_4]^+$ = 930.3, $[2M_2+Na]^+$ = 935.2; ^1H NMR (250 MHz, $CDCl_3$): δ = 2.09 (s, 3H, CH_3 (Ac)], 2.13 [s, 3H, CH_3 (Ac)], 2.15-2.35 (m, 1H, H-2'a), 2.42 (s, 3H, arom-CH_3), 2.56 (ddd, 1H, $J_{2'b,2'a}$ = 14.3 Hz, $J_{2'b,1'}$ = 5.7 Hz, $J_{2'b,3'}$ = 2.1 Hz, H-2'b), 4.28-4.47 (m, 3H, H-4'+H-5'), 5.22-5.25 (m, 1H, H-3'), 5.29 (dd, 1H, $J_{8a,7}$ = 11.4 Hz, $J_{8a,8b}$ = 1.3 Hz, H-8a), 5.97 (dd, 1H, $J_{8b,7}$ = 17.9 Hz, $J_{8b,8a}$ = 1.3 Hz, H-8b), 6.30 (dd, 1H, $J_{1',2'a}$ = 8.2 Hz, $J_{1',2'b}$ = 5.7 Hz, H-1'), 6.42 (ddd, 1H, $J_{7,8b}$ = 17.9 Hz, $J_{7,8a}$ = 11.4 Hz, $J_{7,6}$ = 0.4 Hz, H-7), 7.26-7.34 (m, 2H, arom), 7.64 (d, 1H, $J_{6,7}$ = 0.4 Hz, H-6), 7.79-7.86 (m, 2H, arom); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.80 (CH_3, Ac), 21.87 (arom-CH_3), 38.06 (C-2'), 63.70 (C-5'), 73.98 (C-3'), 82.67 (C-1'), 85.67 (C-4'), 113.08 (C-5), 116.77 (C-8), 127.47 (C-7), 128.85 (C-CH_3, arom), 129.92 (CH, arom), 130.60 (CH, arom), 134.94 (C-6), 146.56 (C-CO, arom), 148.44 (C-2), 160.86 (C-4), 168.10 (arom-CO), 170.15 (CO, Ac), 170.28 (CO, Ac); ^{19}F NMR (235.34 MHz, $CDCl_3$)/$C_2F_2Cl_4$: δ = -45.60 [dd, $^2J_{F,H-8}$ = 85.1 Hz (expected 70-90), $^3J_{F,H-7}$ = 21.2) Hz (expected 0-20) **10*(E)***], -44.05 [ddd, $^2J_{F,H-8}$ = 82.6 Hz (expected 70-90), $^3J_{F,H-7}$ = 46.0 Hz (expected 10-50), $^5J_{F,H-6}$ = 3.0 Hz, **10*(Z)***].

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