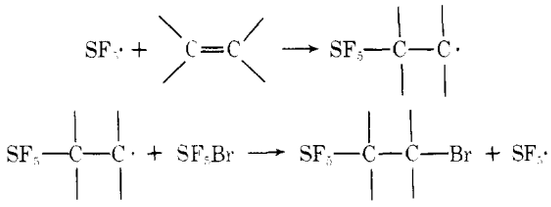
Scheme I

Initiation

$$SF_5Br \longrightarrow SF_5 + Br\cdot$$

Propagation



more likely to occur at the bromine atom than at the sulfur, which is highly protected by fluorine atoms.

Experimental Section

All reactant manipulations were conducted in a Pyrex system equipped with greaseless Kontes glass/Teflon valves. Infrared spectra were recorded on a Perkin-Elmer Model 567 spectrophotometer using a 10-cm cell equipped with KBr windows. NMR spectra were recorded on a JEOL PS-100 spectrometer operating at 100 MHz for proton and 94.1 MHz for fluorine resonances. Chromatographic separations were carried out using a Gow-Mac Model 69-550 gas chromatograph equipped with an 8 ft × ¼ in. SS column packed with 20% DC-QF-1 45/60 Chromosorb P, operating at 90 °C for the addition products and ambient temperatures for the olefins with a flow rate of 40 cm^3/min. Liquid injections were made at an injection port temperature of 120 °C. Analyses were performed by PCR, Inc., Gainesville, Fla.

2-Bromo-1,2-difluoroethylsulfur Pentafluoride. In a typical reaction, SF_5Br (0.207 g, 1 mmol) and $C_2F_2H_2$ (0.0649 g, 1 mmol) were condensed into a 3-mL Pyrex cell equipped with a glass/Teflon valve. Depending upon the nature of the experiment to be conducted, the reaction mixture was stored either in the dark or left under ambient lighting conditions for 1 week. The volatile materials were then transferred to a vacuum system, and a preliminary separation was made by fractional condensation through a series of traps at −78, −116, and −196 °C. Any unreacted difluoroethylene was collected at −196 °C, with the SF_5Br and small amounts of S_2F_{10} being isolated at −116 °C. The material that was not volatile at −78 °C was separated by GLC. No attempt was made to identify minor products that were formed.

***erythro*-$SF_5CHFCHFBr$:** IR 3030 (vw), 3000 (sh), 1480 (vw), 1360 (vw), 1310 (vw), 1285 (vw), 1240 (vw), 1210 (w), 1175 (w), 1150 (m), 1105 (m), 1085 (w), 1060 (w), 910 (s), 885 (vs), 770 (w), 695 (w), 665 (m), 615 (m), 575 (w), 520 (vw) cm^{-1}.

Anal. Calcd for $C_2H_2F_7SBr$: C, 8.86; H, 0.74; F, 49.07; S, 11.8. Found: C, 9.01; H, 0.90; F, 49.54; S, 12.41.

***threo*-$SF_5CHFCHFBr$:** IR 3025 (vw), 3010 (vw), 1480 (vw), 1365 (vw), 1295 (vw), 1235 (vw), 1180 (m), 1135 (w), 1095 (m), 1055 (vw), 945 (m), 885 (vs), 785 (w), 745 (w), 695 (w), 660 (m), 610 (m), 575 (w) cm^{-1}.

Anal. Found: C, 9.03; H, 0.90; F, 42.91; S, 12.58.

1-Pentafluorosulfur-1,2-difluoroethylene. *threo*-$SF_5CHFCFHBr$ (0.147 g, 0.541 mmol) was condensed into a Pyrex reactor containing powdered KOH (0.168 g, 2.98 mmol) and left at ambient temperature for 5 min. The volatile material (0.539 mmol) was dried over P_2O_5 and separated by GLC using gas injections.

***cis*-$SF_5CF{=}CFH$:** mol wt 189.6 (calcd, 190.08); IR 3150 (vw), 2900 (vvw), 1715 (w), 1355 (w), 1190 (m), 1140 (w), 900 (vs), 810 (m), 695 (w), 625 (w), 585 (vw), 550 (vw) cm^{-1}.

***trans*-$SF_5CF{=}CFH$:** mol wt 189.8 (calcd, 190.08); IR 3110 (vw), 1705 (w), 1230 (m), 1200 (m), 900 (vs), 890 (s), 835 (w), 710 (vw), 630 (w), 575 (vw), 540 (w) cm^{-1}.

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Acetylenic Nucleosides. 1. Synthesis of 1-(5,6-Dideoxy-β-D-*ribo*-hex-5-ynofuranosyl)uracil and 1-(2,5,6-Trideoxy-β-D-*erythro*-hex-5-ynofuranosyl)-5-methyluracil

Ram A. Sharma and Miroslav Bobek*

Department of Experimental Therapeutics and Grace Cancer Drug Center, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, New York 14263

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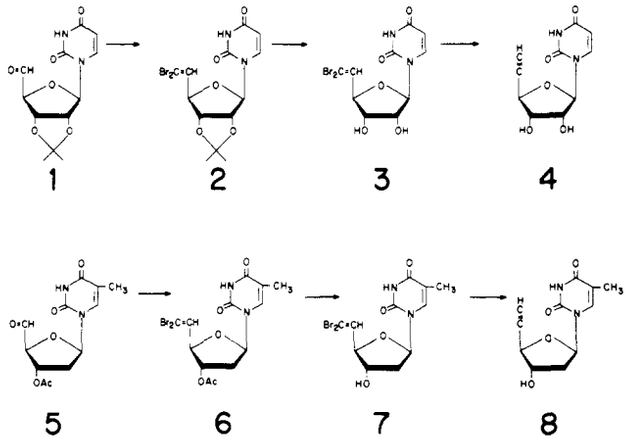
We have recently synthesized 5-ethynyluridine[1] and 5-ethynyl-2′-deoxyuridine,[2] which showed significant (50% at 2×10^{-8} M) growth inhibitory activity against L-1210 cells in vitro. This finding, and the fact that various drugs incorporating the acetylenic function can behave as specific inhibitors[3] for certain enzymatic systems, suggested that nucleosides bearing the acetylenic function at various positions in the carbohydrate moiety of pyrimidines and purines are of interest as potential antimetabolites. In this paper, we describe the synthesis of 1-(5,6-dideoxy-β-D-*ribo*-hex-5-ynofuranosyl)uracil (**4**) and 1-(2,5,6-trideoxy-β-D-*erythro*-hex-5-ynofuranosyl)-5-methyluracil (**8**).

Introduction of unsaturated groups in the sugar moiety of the pyrimidine nucleosides using the Wittig reaction has not been very useful, presumably due to the instability of the aldehyde or the product under the experimental conditions used.[4] Recently, a modified Wittig-type method for the transformation of aldehydes to dibromo olefins and their subsequent conversion to acetylenes has been developed.[5-7] We have used this procedure effectively in our previous[2] work and now explored its potential for the preparation of nucleosides modified in the carbohydrate portion.

The crude 2′,3′-*O*-isopropylideneuridine-5′-aldehyde[4] (**1**) was condensed with (dibromomethylene)triphenylphosphorane,[7] yielding 1-(5,6-dideoxy-6,6-dibromo-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)uracil (**2**). Treatment of



2 with formic acid at room temperature removed the isopropylidene group and provided 1-(5,6-dideoxy-6,6-dibromo-β-D-*ribo*-hex-5-enofuranosyl)uracil (**3**) in excellent yield. The transformation of **3** to acetylenic derivative **4** was achieved by stirring with *n*-butyllithium in tetrahydrofuran in a dry ice–acetone bath, followed by neutralization with acetic acid.

Utilizing similar experimental conditions, 3′-*O*-acetylthymidine-5′-aldehyde[8] (**5**) was condensed with (dibromomethylene)triphenylphosphorane in methylene chloride to afford 1-(2,5,6-trideoxy-6,6-dibromo-3-*O*-acetyl-β-D-*erythro*-hex-5-enofuranosyl)-5-methyluracil (**6**).

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Compound 6 is somewhat unstable and decomposes in solid form as well as in solution. One of the products of decomposition was the deblocked nucleoside **7**, as identified by TLC. Since compound **7** is quite stable as compared to **6**, the instability of **6** is presumably due to the interaction of the 3′-acetyl function and 5′-dibromovinyl group.

Treatment of **6** with sodium methoxide in methanol for 30 min, followed by neutralization with Dowex 50 (H^+) resin, gave 1-(2,5,5,-trideoxy-6,6-dibromo-β-D-*erythro*-hex-5-enofuranosyl)-5-methyluracil (**7**) in good yield. Unlike **6**, the deblocked compound **7** was quite stable. Compound **7** on treatment with *n*-butyllithium in tetrahydrofuran gave product **8**.

The structural elucidation for all the compounds was made by mass and NMR spectrometry and by elemental analyses, In the NMR spectra, the C≡CH proton integrated to less than 1 proton. This fact and the downfield shift of the acetylenic proton may be due to the interaction of the ethynyl function with the carbonyl group of the pyrimidine ring. After the completion of this work, a preliminary account of the preparation of some acetylenic nucleosides from nucleoside 5′-aldehydes was given by Moffatt and co-workers.[9]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. UV spectra were measured on a Cary Model 14 spectrophotometer and NMR spectra were measured on a Varian XL-100 spectrometer using Me_4Si as an internal standard. The mass spectra were recorded on a CEC 21-491 double-focusing spectrometer using an ionization voltage of 70 eV. TLC was performed on silica gel N-HR/UV254 precoated plastic sheets (Brinkman), and column chromatography was performed on silica gel (60–200 mesh), J. T. Baker No. 3405. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

1-(5,6-Dideoxy-6,6-dibromo-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)uracil (2). A mixture containing triphenylphosphine (22.14 g, 0.0844 mol), carbon tetrabromide (27.98 g, 0.0844 mol), and zinc dust (5.52 g, 0.0844 mol) in 200 mL of dry methylene chloride was stirred at room temperature for 24 h.[7] To the resulting (dibromomethylene)triphenylphosphorane a solution of aldehyde **1** (prepared from 13.79 g, 0.0485 mol of 2′,3′-*O*-isopropylideneuridine) in 150 mL of anhydrous methylene chloride was added dropwise, and the mixture was stirred for 24 h at room temperature. TLC of the mixture in benzene/ethyl acetate (7:3) showed only one major product containing a sugar moiety. The mixture was evaporated to dryness, suspended in chloroform, and extracted with water. The chloroform layer was dried on anhydrous sodium sulfate, evaporated to a small volume, and poured on a dry silica gel column. The column was washed with 500 mL of benzene and then with benzene/ethyl acetate (7:3). The fractions containing the carbohydrate moiety were combined and passed again through a dry silica gel column using benzene/ethyl acetate (7:3) as eluant. The appropriate fractions were mixed together, evaporated, and triturated with acetone, yielding a colorless crystalline material. The acetone-soluble material was chromatographed again using the above solvent system. The fractions were combined, evaporated, and triturated with acetone. Thus, the yield of TLC-pure **2** was 12.29 g (56%, based on 2′,3′-*O*-isopropylideneuridine used).

Recrystallization from methanol gave an analytically pure sample: mp 230–231 °C; NMR (Me_2SO-d_6) δ 1.30 1.50 (2 s, 6, isopropylidene group), 5.65 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 5.78 (d with small coupling constant, 1, H-1′), 6.85 (d, 1, $J_{4',5'}$ = 8 Hz, 5′-CH=CBr_2), 7.77 (d, 1, $J_{6,5}$ = 8 Hz, H-6), 11.52 (b, 1, NH).

Anal. Calcd for $C_{13}H_{14}N_2Br_2O_5$: C, 35.61; H, 3.19; N, 6.39; Br, 36.53. Found: C, 35.56; H, 3.30; N, 6.24; Br, 36.80.

1-(5,6-Dideoxy-6,6-dibromo-β-D-*ribo*-hex-5-enofuranosyl)-uracil (3). A solution of 1.1 g of **2** in 200 mL of 90% formic acid was stirred at room temperature for 4 h, when TLC showed no starting material present. The mixture was evaporated and coevaporated with ethanol to afford 1 g (94%) of **3**. The material was recrystallized from methanol, furnishing an analytical sample: mp 197–198 °C; NMR (Me_2SO-d_6) δ 5.68 (d, 1 H, $J_{5,6}$ = 8 Hz, H-5), 5.80 (d, 1 H, $J_{1',2'}$ = 5.5 Hz, H-1′), 7.04 (d, $J_{4',5'}$ = 9 Hz, 5′-CH=CBr_2), 7.74 (d, 1 H, $J_{6,5}$ = 8 Hz, H-6), 11.38 (brd s, 1 H, NH).

Anal. Calcd for $C_{10}H_{10}Br_2N_2O_5$: C, 30.15; H, 2.51; N, 7.04; Br, 40.20. Found: C, 30.29; H, 2.67; N, 7.04; Br, 39.97.

1-(5,6-Dideoxy-β-D-*ribo*-hex-5-ynofuranosyl)uracil (4). A solution of **3** (1.22 g, 0.0030 mol) in 350 mL of anhydrous THF was cooled in a dry ice–acetone bath, and to this solution *n*-BuLi (20 mL, 0.032 mol; 1.6 M solution in hexane) was added. The mixture was stirred for 4 h, neutralized with acetic acid, evaporated, and coevaporated with ethanol. The crude material was dissolved in a small amount of methanol, poured on a dry silica gel column, and eluted with ethyl acetate and then with ethyl acetate/methanol (9:1). The fractions were combined, evaporated, and crystallized from a methanol/ethanol mixture, furnishing an analytically pure sample (0.415 g, 57%) of **4**: mp 209–211 °C; λ_{max}(MeOH) 260 (ε 10 637), λ_{min} 229 nm (1992); mass spectrum, *m/e* 238 (M^+), 112 (B + H), 113 (B + 2H); NMR (Me_2SO-d_6) δ 3.83 (d, 1 H, $J_{4',5'}$ = 2.2 Hz, 5′-C≡CH), 5.78 (d, 1 H, $J_{5,6}$ = 8 Hz, H-5), 5.86 (d, 1 H, $J_{1',2'}$ = 5 Hz, H-1′), 7.60 (d, 1 H, $J_{6,5}$ = 8 Hz, H-6), 11.42 (brd, 1 H, NH).

Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.20 N, 11.76. Found: C, 50.22; H, 4.29; N, 11.68.

1-(2,5,6-Trideoxy-6,6-dibromo-3-*O*-acetyl-β-D-erythro-hex-5-enofuranosyl)-5-methyluracil (6). 3′-*O*-Acetylthymidine-5′-aldehyde[8] (**5**, prepared from 8g, 0.0281 mol of 3′-*O*-acetylthymidine) was reacted with (dibromomethylene)triphenylphosphorane (prepared from 14.76 g (0.0562 mol) of triphenylphosphine, 18.65 g (0.0562 mol) of carbon tetrabromide, and 3.68 g (0.0562 mol) of zinc dust) as described for the preparation of **2**. TLC of the reaction mixture showed one major and another very minor charring spot. The mixture was evaporated to a small volume and chromatographed twice on a dry silica gel column, eluting with benzene/ethyl acetate (7:3) and then with benzene/ethyl acetate (1:1). The combined fractions, after evaporation, were dissolved in methanol, where the product crystallized within 30 min for a 2.4-g yield. The filtrate was chromatographed again on silica gel using the above solvent system, furnishing 4.2 g of the TLC (95%)-pure material. Thus, the total yield of product **6** was 6.6 g (53%). Recrystallization from methanol gave **6** as a colorless, crystalline material: mp 123–125 °C dec; NMR ($CDCl_3$) δ 1.97 (d, 3, $J_{5\text{-}CH_3,6}$ = 1 Hz, 5-CH_3), 2.14 (s, 3, 3′-OAc), 2.45 (m, 2, H-2′), 4.72, 5.27 (m, 2, H-3′, 4′), 6.18 (t, 1, $J_{1',2'}$ = 6.5 Hz, H-1′), 6.62 (d, 1, $J_{5',4'}$ = 8.5 Hz, 5′-CH=CBr_2), 7.14 (d, 1 $J_{6,5\text{-}CH_3}$ = 1 Hz, H-6), 8.96 (brd, 1, NH).

1-(2,5,6-Trideoxy-6,6-dibromo-β-D-*erythro*-hex-5-enofuranosyl)-5-methyluracil (7). A solution of **6** (3 g, 0.0068 mol) in excess of sodium methoxide in methanol was stirred at room temperature for 30 min. It was then neutralized with Dowex 50 (H+) resin and filtered. The resin was washed with methanol, combined, and evaporated to a small volume, where product **7** crystallized for a 2.43-g (90%) yield. An analytical sample was prepared by crystallization from ethanol with mp 203–204 °C; NMR (Me_2SO-d_6) δ 1.82 (s, 3 H, 5-CH_3), 6.20 (t, 1 H, $J_{1',2'}$ = 7 Hz, H-1′), 6.98 (d, 1 H, $J_{4',5'}$ = 8 Hz, 5′-CH=CBr_2), 7.53 (s, 1 H, H-6), 11.33 (s, 1 H, NH).

Anal. Calcd for $C_{11}H_{12}Br_2N_2O_4$: C, 33.33; H, 3.06; N, 7.07; Br, 40.40. Found: C, 33.60; H, 3.16; N, 7.10; Br, 40.12.

1-(2,5,6-Trideoxy-β-D-*erythro*-hex-5-ynofuranosyl)-5-methyluracil (8). A solution of **7** (0.558 g, 0.0014 mol) in dry THF was treated with *n*-BuLi (8 mL, 0.0128 mol; 1.6 M solution in hexane) as described for **4**. The crude material was chromatographed on a dry silica gel column using ethyl acetate as eluent. After evaporation and crystallization from ethanol, the desired product **8** was obtained in a 0.22-g (66%) yield. Recrystallization from ethanol gave an analytical sample: mp 228–230 °C; λ_{max}(MeOH) 265 (ε 12 272), λ_{min} 233 (2265); mass spectrum, *m/e* 236 (M^+), 237 (M^+ + 1), 126 (B + H), 127 (B + 2 H); NMR (Me_2SO-d_6) δ 1.81 (low coupling constant doublet, 3,5-CH_3), 2.14 (m, 2, H-2′), 3.85 (d, 1, $J_{4',5'}$ = 2 Hz, 5′-C≡CH), 4.40 (m, 2, H-3′, 4′), 5.72 (d, 1, 3′-OH), 6.30 (t, 1, $J_{1',2'}$ = 7 Hz, H-1′), 7.54 (d, 1, $J_{6,5\text{-}CH_3}$ = 1,Hz, H-6), 11.35 (s, 1, NH).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.64; H, 5.30; N, 11.69.

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Registry No.—**1**, 27999-65-1; **2**, 64189-19-1; **3**, 64189-20-4; **4**, 64189-21-5; **5**, 5983-15-3; **6**, 64189-22-6; **7**, 64189-23-7; **8**, 64189-24-8; (dibromomethylene)triphenylphosphorane, 42867-45-8; 3′-*O*-acetylthymidine, 21090-30-2.

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Communications

Organic Metals: a General Synthesis of Unsymmetrical Tetrathiafulvalenes

Summary: A number of unsymmetrical tetrathiafulvalenes have been prepared by the use of a new and general synthesis. This synthesis, which involves a phosphorane intermediate, allows the overall specific coupling of two different 1,3-dithiolium salts.

Sir: Tetrathiafulvalene (TTF) and its derivatives are heterocycles of great current interest in view of their ability to act as π donors in the preparation of organic charge-transfer salts having metallic properties.[1] Almost all known TTF derivatives are symmetrical about the central double bond, due to the fact that general methods for their synthesis have involved the coupling or condensation of two identical S_2 containing moieties, usually a 1,3-dithiol-2-thione (or selone) or a 1,3-dithiolium ion.[2] With the exception of monoethyl- and monocarboxytetrathiofulvalene (prepared from lithiated TTF),[3] the few known unsymmetrical TTF derivatives have been prepared by random coupling or condensation; their separation from symmetrical co-products was the result of fortuitous crystallization properties in two cases,[4] and sufficient polarity differences to allow chromatographic separation[5] in a third case. We now report the discovery of a fundamentally new TTF synthesis which allows the preparation of a wide range of unsymmetrical TTF derivatives from two different 1,3-dithiolium cations without the concomitant formation of symmetrical byproducts.

A recent report has described the reaction of 1,3-benzodithiolium fluoborate (1) with triphenylphosphine to give the phosphonium salt **2** (Scheme I); deprotonation of the latter with *n*-butyllithium at −78 °C and reaction of the resulting unstable phosphorane **3** with various aldehydes afforded 1,4-benzodithiafulvalenes (**4**) in good yield.[6,7] Our attempts to couple phosphorane **3** with various 1,3-dithiol-2-thiones (or selones) were unsuccessful. However, the red color of **3** was discharged at −78 °C upon addition of the 1,3-dithiolium salts

Scheme I

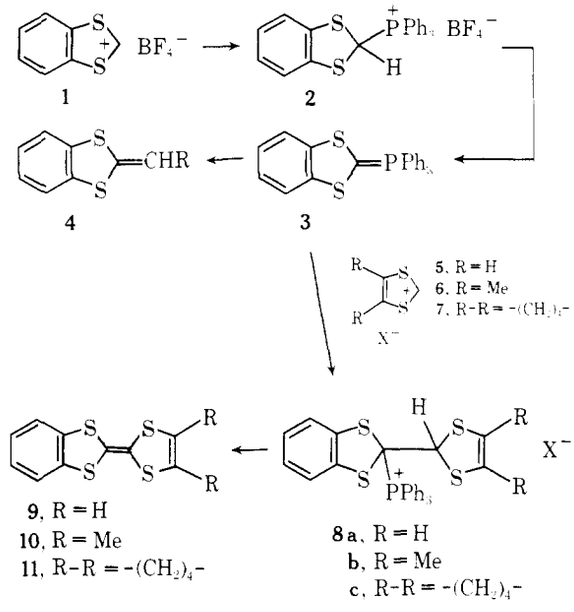

Table I

TTF derivative	Mp, °C (uncorr)	Yield,[a] %	NMR[e] ($CDCl_3$), δ	UV-visible, nm (log ϵ)
9	135–136 (lit.[5] 138.5–140)	40	*d*	
10	190–191	30	1.9 (s, 6 H) 7.1–7.2 (m, 4 H)	247 (3.84), 253 (3.94), 259.5 (4.00), 292 (4.15), 319 (4.11), 454 (2.5)
11	207–208	31	1.7–2.4 (m, 8 H) 7.1–7.3 (m, 4 H)	258 (3.83), 265 (3.89), 271 (3.91), 281 (3.98), 293 (4.04), 307 (4.00), 319 (3.99), 456 (2.28)
14	105–106	18[b] 41[c]	1.6–2.5 (m, 8 H) 6.25 (s, 2 H)	274 (3.84), 299 (4.02), 310 (3.99), 322 (3.98), 364 (3.18), 460 (2.41)
15	174–175	43	1.5–2.4 (m, 8 H) 1.9 (s, 6 H)	286 (4.01), 298 (4.05), 314 (4.02), 323 (3.98), 478 (2.33)

[a] Isolated, crystallized yield, based on phosphonium salt. [b] Based on **13**. [c] Based on **12**. [d] In accord with ref 5. [e] In units downfield from Me_4Si.

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