to a procedure recommended for relatively unreactive allyl acetate.[7] A mixture of 1.36 g (5 mmol) of **2**, 0.76 mL (5 mmol) of dimethyl malonate, 0.40 mL (2.6 mmol) of DBU, and 0.490 g (0.42 mmol) of $Pd(Ph_3P)_4$ in 13 mL of toluene was stirred at room temperature for 18 h and was further maintained at 100 °C for 7 h. High-resolution NMR spectrum of the crude product and TLC revealed no incorporation of malonate into the sugar residue. Unconverted starting material was recovered mostly intact.

The reaction was repeated under modified conditions reported in this paper as follows: to 1.2 g (4.41 mmol) of triacetylglucal, 0.0376 g (0.065 mmol) of $Pd(dba)_2$, and 0.026 g of DIPHOS in 5 mL of THF was added 0.83 g (4.88 mmol) of potassium dimethyl malonate in 10 mL of THF. The mixture was stirred at room temperature for 3 days and further refluxed for 12 h. TLC revealed only unconverted starting material.

3-Acetyl-1,2-dideoxy-4,6-*O*-isopropylidene-D-*arabino*-hex-1-enopyranose (3b). The acetoxy derivative **3b** was prepared according to the procedure reported above for **3c** except substituting acetic anhydride for trifluoroacetic anhydride. Chromatography on silica gave the pure compound: ^1H NMR (80 MHz) δ 1.40 (s, 3 H), 1.50 (s, 3 H), 2.07 (s, 3 H), 3.87 (m, 4 H), 4.73 (dd, J = 6, 2 Hz, 1 H), 5.33 (d, J = 7 Hz, 1 H), 6.33 (dd, J = 6, 2 Hz, 1 H); HRMS, 228.0981 (M^+·; calcd for $C_{11}H_{16}O_5$ 228.0997).

Attempted Alkylation of 3b. Potassium salt of dimethyl malonate was prepared from 0.20 g (4.98 mmol) of potassium hydride and 0.65 mL (12.7 mmol) of dimethyl malonate in 10 mL of anhydrous THF, and this solution was added to 0.628 g (2.71 mmol) of **3b** dissolved in 5 mL of THF. To this were added 0.0376 g of $Pd(dba)_2$ and 0.026 g of DIPHOS. The mixture was stirred for 3 days at room temperature and subsequently was refluxed for 12 h. The reaction was worked up, and the product was analyzed by TLC and high-resolution ^1H NMR. No trace of coupling product **4** was detected.

Preparation and Attempted Pd(0)-Catalyzed Alkylation of the Phosphate 3d. The diethyl phosphate **3d** was prepared by treating the alcohol **2** with diethyl chlorophosphate in the presence of triethylamine and (dimethylamino)pyridine in methylene chloride. A mixture of 0.464 g (1.44 mmol) of **3d**, 0.166 g (0.144 mmol) of $Pd(Ph_3P)_4$, and 0.244 g (1.43 mmol) of potassium dimethyl malonate in 10 mL of THF was stirred at room temperature for 2 days. No alkylation products were detected by comparison of TLC's of this reaction mixture with those of an authentic sample of **4**.

Hydrolysis of 4 and 5. A solution of 0.73 g of **4** in 2 mL of THF and 1 mL of methanol was stirred with 1 mL of 2 N HCl for 3 h. Methylene chloride (30 mL) and 10 mL of saturated sodium bicarbonate were added, and the organic layer was separated. Further extraction with methylene chloride, drying, and concentration yielded an oil, which was purified by column chromatography (3% methanol/CH_2Cl_2, silica) to get 0.55 g (88%) of **6**: $[\alpha]_D$ 50.1 ± 0.4° (*c* 2 $CDCl_3$); IR (neat) 3200–3550 (br), 1730 cm^{-1}; ^1H NMR (360 MHz) δ 3.39 (m br, H_5 and OH, 2 H), 3.55 (d, $J_{1,7}$ = 8 Hz, $HC(CO_2Me)_2$, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.70–3.80 (m br, $H_{6,6}$ and OH, 3 H), 4.15 (d br, $J_{4,5}$ = 7 Hz, H_4, 1 H), 4.77 (dm, $J_{1,7}$ = 8 Hz, H_1, 1 H), 5.78–5.95 (m, $H_{2,3}$, 2 H); ^{13}C NMR δ 52.69, 52.73, 56.49, 62.60, 63.38, 72.76, 78.82, 127.30, 131.30, 166.94, 167.33; HRMS, 211.0596 (M^+· – (CH_3O + H_2O); calcd for $C_{10}H_{11}O_5$ 211.0607).

With the identical procedure, **7** was prepared from **5** in 77% yield: $[\alpha]_D$ –19.2 ± 0.8° (c 1 $CDCl_3$); IR (KBr) 3250–3330 (br), 1724 cm^{-1}; ^1H NMR (360 MHz) δ 1.10 (s, CH_3, 3 H), 2.20–2.40 (s br, OH, 1 H), 2.40–2.60 (s br, OH, 1 H), 3.33 (ddd, $J_{4,5}$ = 8 Hz, $J_{5,6a}$ = 4 Hz, $J_{5,6e}$ = 4 Hz, H_5, 1 H), 3.65–3.80 (m, H_6, 2 H), 4.10 (d, m $J_{4,5}$ = 8 Hz, H_4, 1 H), 4.37 (s br, H_1, 1 H), 5.87–5.97 (m, $H_{2,3}$, 2 H) [assignments and coupling constants established by double irradiation and NOE experiments]; ^{13}C NMR δ 14.58, 36.32, 36.51, 58.41, 62.85, 63.64, 78.96, 79.54, 124.84, 131.98, 214.70, 216.48; HRMS, 240.1007 (M^+·; calcd for $C_{12}H_{16}O_5$ 240.0997).

Benzylation of 4 to 8. To a suspension of 0.017 g (0.45 mmol) of potassium hydride in 2 mL of THF was added 0.136 g (0.45 mmol) of **4** dissolved in 2 mL of THF at 0 °C. The mixture was stirred for 30 min, and 0.072 mL (0.60 mmol) of benzyl bromide was added dropwise from a syringe. The mixture was warmed to room temperature and further stirred for 2 h. Saturated potassium hydrogen phosphate (10 mL) was added, and the product was extracted into methylene chloride. Concentration and isolation by preparative TLC yielded 0.092 g (52%) of **8**: IR (neat) 3080, 3060, 1735, 1605, 1585, 1500, 1200–1100 cm^{-1}; ^1H NMR (360 MHz) δ 1.42 (s, CH_3C, 3 H), 1.52 (s, CH_3C, 3 H), 3.19 (d, J = 14 Hz, PhC*H*, 1 H), 3.43 (ddd, $J_{5,6a}$ = 10 Hz, $J_{4,5}$ = 8 Hz, $J_{5,6e}$ = 5 Hz, H_5, 1 H), 3.60 (d, J = 14 Hz, PhC*H*, 1 H), 3.67 (s, OCH_3, 3 H), 3.70 (s, OCH_3, 3 H), 3.84 (dd, $J_{6a,6e}$ = 10 Hz, $J_{6a,5}$ = 10 Hz, H_{6a}, 1 H), 3.96 (dd, J = 10, 5 Hz, H_{6e}, 1 H), 4.10 (d, m, $J_{4,5}$ = 8 Hz, H_4, 1 H), 4.58 (m, 1 H, H_1), 5.81 (d, $J_{2,3}$ = 10 Hz, H_2, 1 H), 5.96 (ddd, $J_{1,3}$ = $J_{3,4}$ = 2 Hz, H_3, 1 H), 7.12 (m, Ar, 2 H), 7.25 (m, Ar, 3 H); HRMS, 390.1681 (M^+·; calcd for $C_{21}H_{26}O_7$ 390.1678).

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Registry No. **2**, 2873-29-2; **3a**, 51450-36-3; **3b**, 97747-17-6; **3c**, 97689-89-9; **3d**, 97689-91-3; **4**, 97689-95-7; **5**, 97689-90-2; **6**, 97689-92-4; **7**, 97689-93-5; **8**, 97689-94-6; DIPHOS, 1663-45-2; $Pd(dba)_2$, 32005-36-0; $Pd(Ph_3P)_4$, 14221-01-3; dimethyl malonate, 108-59-8; 2-methylcyclopentane-1,3-dione, 765-69-5; diethyl chlorophosphate, 814-49-3; potassium dimethyl malonate, 61111-62-4; benzyl bromide, 100-39-0.

Fluorocarbohydrates in Synthesis. An Efficient Synthesis of 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (β-FIAU) and 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)thymine (β-FMAU)

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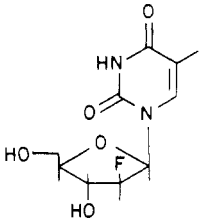
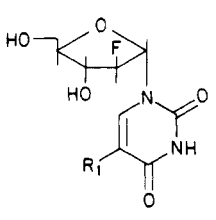
Recent literature[3,4] has indicated an interest in the preparation of nucleosides with antiviral and anticancer properties. The potent antiviral activity of 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (β-FIAU; **1a**, R_1 = I) and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine (β-FMAU; **2a**, R_1 = CH_3) made these compounds candidates for further synthetic development.



1a, R_1 = I
2a, R_1 = CH_3



1b, R_1 = I
2b, R_1 = CH_3

Results and Discussion

The most direct synthetic plan to reach **1a** and **2a** required the access to the fluorodeoxy sugar **6**. The latter would be accessible via an appropriately blocked riboside

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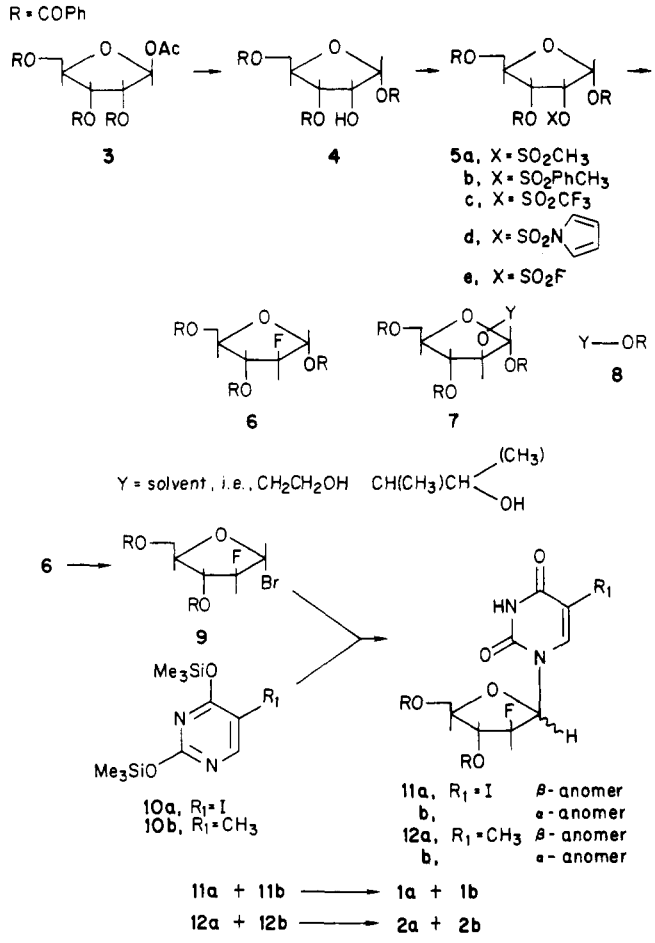
0022-3263/85/1950-3644$01.50/0

Scheme I



such as **4** (see Scheme I). Furthermore, the blocking groups would have to be resistant to the vigorous conditions for the fluorination but easily removed after the sugar was coupled to the nucleoside base.

It was envisioned that an appropriate sulfonate ester at C_2 of riboside **4** would result in the desired 2-deoxy-2-fluoroarabinoside **6** if displacement with fluoride could be accomplished. However, it is known that sulfonates at C_2 of pyranosides do not generally undergo nucleophilic displacement and such reactions are even less common in the furanoside series.[5] It has been suggested that nucleophilic displacement at C_2 creates an unfavorable alignment of dipoles in the transition state particularly when the substituent at C_1 is the α-D-anomer.[6] Although displacement of C_2 sulfonates like **5** appeared to be a particularly difficult case, the results of our recent study[7] on the synthesis of **4** made large amounts available for a comprehensive study of the displacement.

The mesylate **5a** and triflate **5c** were prepared, but the tosylate **5b** resisted our efforts to prepare it. Fluorinations of sulfonates **5a** and **5c** were attempted using TBAF or KHF_2 with a variety of solvents and temperatures. High-field NMR was used to detect the C_2 proton of the desired product **6**, which we anticipated would give an absorption at 5.0–5.5 ppm and show a characteristic geminal fluorine–proton coupling of about 50 Hz. However, in each case the result of the attempted fluorination was either recovery of starting material or elimination product.

Table I. Fluorination of 5d

entry	solv	reacn temp, °C	reacn time, h	reacn equiv of HF	yield of 6[f], %	other products
1	*a*	160	0.5	0	30	**7**, **8**
2	*a*	80	16.0	0	<10	**5e**
3	*b*	160	1.0	0	35	**5e**, **7**, **8**
4	*c*	160	1.0	0	45	**5e**, **7**, **8**
5	*b*	140	2.5	2	65	**8**
6	*d*	160	3.0	2	25	**5e** (55%), **8**
7	*d*	160	3.0	0	30	**5e** (28%), **7**, **8**
8	*d*	160	18.0	0	60	**7**, **8**
9	*e*	160	3.0	2	<5	dec
10	*b*	135	7.0	2	55	**5e**, **7**, **8**
11	*b*	135	3.5	4	60	**5e**
12	*b*	135	3.5	6	53	**5e**
13	*b*	160	1.0	4	70[g]	**5e**

[a] Ethylene glycol. [b] 2,3-Butanediol. [c] 2,3-Butanediol/acetic acid. [d] Pinacol. [e] Neat. [f] % yield based on HPLC quantitation for **6**. [g] Actual isolated yield from 100 g of **5d**, 63%.

The direct fluorination of **4** with diethylaminosulfur trifluoride (DAST)[8] also failed to give the desired product.

The imidazolylsulfonate **5d**, prepared by Hanessian's procedure,[9] was subjected to fluorination with TBAF and gave only elimination. However, treatment with KHF_2 gave a modest 30% yield of 2-deoxy-2-fluoro-1,3,5-tri-*O*-benzoyl-α-D-arabinofuranose (**6**). As anticipated, the C_2 proton appeared at 5.4 ppm as a doublet with a geminal fluorine coupling of 49 Hz. When the reaction was monitored by HPLC, an intermediate was observed to form rapidly, which was slowly converted to product, and was tentatively identified (NMR) as the sulfonyl fluoride **5e**. Although we did not rigorously identify **5e**, it is closely analogous to the sulfonyl chloride proposed by Hanessian as the intermediate in the preparation of the sulfonylimidazole. Khan[10] and co-workers also reported obtaining a sulfonyl chloride from the reaction of methyl 3-*O*-acetyl-4,6-di-*O*-benzylidene-α-D-glucopyranoside with SO_2Cl_2. By use of HPLC to monitor the conversion of **5d** to **6** the reaction was optimized to give a 63% isolated yield of the desired fluoro sugar **6**. Table I summarizes the experiments that led to this result. The displacement of sulfonate by the reaction solvent results in the production of byproducts **7** and **8**. Using the more hindered 2,3-butanediol results in reduced amounts of **7** and **8**. Additionally, we found that hydrogen fluoride increased the rate of formation of intermediate **5e** and decreased **7** and **8**. The preparation of **5d** and **6** has been successfully scaled up to 1.0 mol.[11]

With the preparation of 2-deoxy-2-fluoro sugar **6**, our major goal was accomplished since Fox[12] had shown the anomeric mixture of 1-bromo-3-*O*-acetyl-2-deoxy-2-fluoro-5-*O*-benzoylarabinose could be coupled with silylated cytosine in 40% yield.

We briefly investigated reaction conditions reported by Vorbruggen[13] to give high yields of nucleosides from acyl sugars. In the case of the 2-deoxy sugar **6**, when we used trifluoromethanesulfonic acid, HMDS, and Me_3SiCl, the

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(11) Scale-up was achieved by Farney, R. F., of Bristol-Myers Pharmaceutical Research and Development, Chemical Process Development Department, Evansville, IN.
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coupling product was not obtained. This may be due to the fact that the alkylating species is the 1,2-acyloxonium ion which cannot be formed from a 2-deoxy sugar. The bromination of **6** with 30% HBr in acetic acid produced a quantitative conversion to 1-α-bromo sugar **9**. The NMR spectrum clearly showed only one anomer which was unambiguously assigned as the α-anomer. The coupling of **9** with bis(*O*-trimethylsilyl)thymine (**10b**) resulted in a nearly quantitative yield of nucleoside **12** as an anomeric mixture (α/β = 1/4). While the thymine coupling in CH_3CN was complete in 1.5 h at reflux, coupling of **9** with silylated 5-iodouracil **10a** required 22 h under the same conditions and resulted in a lower yield of **11** as a mixture of anomers (58%, α/β = 1/9). A 95% yield of **11a,b** was obtained by performing the coupling for 7 days at room temperature (α/β = 1/7). The benzoyl groups were hydrolyzed with methanolic aqueous sodium hydroxide in 90% yield and the desired β-isomers isolated by crystallization from the anomeric mixture.

The synthesis of β-FIAU (**1a**) and β-FMAU (**2a**) was therefore accomplsihed in four steps from **4** in 45% yield in an especially attractive manner. When compared to the previously published method,[12] which required 12 steps from glucose in overall yield of less than 2%, the present method is clearly superior.

Experimental Section

NMR spectra were recorded on a Bruker WM 360 or Bruker AM 360 spectrometer and are expressed in ppm. IR spectra were recorded on a Beckman 4240 spectrometer and are expressed in cm^{-1}. HPLC analyses were performed on a Hewlett-Packard 1084B instrument using a μ-Bondapak C^{18} reverse-phase column. Elemental analyses were performed by the Analytical Research Department of Bristol-Myers Pharmaceutical Research and Development. Melting points were determined on an Electrothermal melting point apparatus and are not corrected.

2-*O*-(Methylsulfonyl)-1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (5a). A total of 20 g of **4**[7] (0.043 mol) was added portionwise to a solution of pyridine (40 mL, 0.5 mol) and methanesulfonyl chloride (4 mL, 0.052 mol) at 0 °C. After 3 h the reaction was quenched with ice–water and extracted with CH_2Cl_2 (3 × 20 mL). The extract was washed with 1 N HCl, H_2O, and brine before it was dried (Na_2SO_4). The crystalline product was obtained in two crops by addition of Skellysolve B giving 21.8 g of **5a** (94.7%): mp 141–141.5 °C; IR (KBr) 3080, 3040, 3020, 1600, 715 (Ar), 1720, 1275 (COOR), 1370, 1180 (O–SO_2); ^1H NMR (CD_2Cl_2) 8.2–7.3 (m, 15 H, Ar H), 6.83 (d, 1 H, C_1H), 5.79 (dd, 1 H, C_3H), 5.44 (dd, 1 H, C_2H), 4.82–4.65 (m, 3 H, C_4H, C_5H_2), 3.04 (s, 3 H, CH_3). Anal. ($C_{27}H_{24}O_{10}S$) C, H, S.

2-*O*-[(Trifluoromethyl)sulfonyl]-1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (5c). To a solution of 4 (4.62 g, 0.01 mol) in pyridine (20 mL) was added trifluoromethanesulfonyl anhydride (1.7 mL, 2.82 g, 0.01 mol). After 20 h the reaction was quenched in ice–H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, cold 3 N H_2SO_4, and cold saturated $NaHCO_3$. Drying (Na_2SO_4) and concentration gave 5.0 g of **5c** (84%) as a light brown oil: ^1H NMR (CD_2Cl_2) 8.3–7.3 (m, 15 H, Ar H), 6.85 (d, 1 H, C_1H), 5.8 (dd, 1 H, C_3H), 5.55 (dd, 1 H, C_2H), 4.87 (dd, 1 H, C_4H) 4.66 (m, 2 H, C_5H_2).

2-*O*-(Imidazolylsulfonyl)-1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (5d). A mixture of **4** (85 g, 0.184 mol) and 700 mL of CH_2Cl_2 was treated according to the procedure of Hanessian.[9] After 2 h at room temperature, the hazy solution was washed with H_2O and dried over Na_2SO_4. The crystalline product was obtained by dilution with 2.5 volumes of Skellysolve B. The crude product was recrystallized from *i*-PrOH giving 93 g of **5d** (85%): mp 129–130.5 °C; IR (KBr) 3130, 1600, 705 (Ar) 1720, 1225 (COOR), 1425, 1200 (O–SO_2); ^1H NMR (CD_2Cl_2) 8.2–6.9 (m, 18 H, Ar H), 6.67 (d, 1 H, C_1H), 5.63 (dd, 1 H, C_3H), 5.28, (dd, 1 H, C_2H), 4.81 (dd, 1 H, C_4H), 4.65 (m, 2 H, C_5H_2). Anal. ($C_{29}H_{24}N_2O_{10}S$) C, H, N, S.

2-Deoxy-2-fluoro-1,3,5-tri-*O*-benzoyl-α-D-arabinofuranose (6). A mixture of **5d** (100.8 g, 0.17 mol), KHF_2 (53.1 g, 0.68 mol), and 250 mL of 2,3-butanediol was stirred mechanically under a stream of N_2 with an outlet to a scrubber trap. The flask was immersed in an oil bath at 160 °C, and HF (50% in H_2O, 23.5 mL, 0.68 mol) was added. The reaction was monitored by HPLC.[14a] When the area of **6** was >70% (1 h), the reaction was quenched (150 mL of ice and 100 mL of brine) and extracted with CH_2Cl_2 (4×). The extract was washed with brine, H_2O, and saturated $NaHCO_3$ and then dried over Na_2SO_4 containing Darko-KB (10 g). The drying and decolorizing agents were removed by filtration through a pad of silica gel (240–400 mesh), and the pad was washed with CH_2Cl_2 (2 × 250 mL). The solvent was removed to give an oil, which was crystallized from 250 mL warm 95% EtOH, giving 49.6 g of **6** (62.8%): mp 82 °C; IR (KBr) 3060, 3040, 1600, 710 (Ar), 1725, 1710, 1280, 1090 (COOR); ^1H NMR (CD_2Cl_2) 8.2–7.38 (m, 15 H, Ar H), 6.7 (d, 1 H, C_1H), 5.61 (dd, 1 H, C_3H), 5.4 (d, 1 H, J_{HF} = 49 Hz, C_2H), 4.7 (m, 3 H, C_4H, C_5H_2). Anal. ($C_{26}H_{21}FO_7$) C, H.

2-Deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl Bromide (9). The fluoro sugar **6** (41.3 g, 0.089 mol), 200 mL of CH_2Cl_2, and 49 mL (0.180 mole) of 30% HBr in acetic acid were stirred 16 h at ambient temperature. The solution was evaporated, redissolved in CH_2Cl_2, and then washed with water and saturated $NaHCO_3$. The solution was dried ($MgSO_4$) and concentrated to a viscous syrup, which was further dried under high vacuum 18 h, giving 35 g of **9** (98%): ^1H NMR (CD_2Cl_2) 8.2–7.4 (m, 10 H, Ar H), 6.67 (d, 1 H, C_1H), 5.6 (d, 1 H, J_{HF} = 50 Hz, C_2H), 5.5 (dd, 1 H, C_3H), 4.75 (m, 3 H, C_4H, C_5H_2).

2,4-Bis-*O*-(trimethylsilyl)-5-iodouracil (10a). To a mixture of 5-iodouracil (21.2 g, 0.089 mol), 200 mL of dry CH_3CN, and ammonium sulfate (1.18 g, 0.0089 mol) was added hexamethyldisilazane (16.2 g, 21.2 mL, 0.010 mol) at 40 °C. The resulting mixture was heated at reflux for 24 hr, then cooled, and concentrated under reduced pressure to a syrup, which was used in the subsequent step.

1-(2-Deoxy-2-fluoro-3,5-di-*O*-benzoyl-D-arabinofuranosyl)-5-iodouracil (11a,b). A solution of **9** (17.75 g, 0.0445 mol) in 240 mL of CH_2Cl_2 was stirred with CH_3CN (50 mL) containing **10a** (17.1 g, 0.0445 mol) and NaI (5.34 g, 0.0356 mol) at ambient temperature. After 7 days the reaction was diluted with methyl isobutyl ketone (150 mL) and washed with water. The two-phase mixture was filtered, giving 6.5 g of crude **11a**. The organic layer was separated from the filtrate and washed with 10% sodium thiosulfate solution, water, and brine. After drying (Na_2SO_4), the solvent was evaporated and the residue crystallized from CH_2Cl_2 (50 mL) and Skellysolve B (200 mL), giving 9.4 g of crude **11a,b** (α/β = 1/3).[14b] The crude yield was 15.9 (95.8%). A sample of pure **11a** was obtained by recrystallization of the crude first solid from *i*-PrOH: mp 197 °C; IR (KBr) 3480, 3060 (NH, OH), 3060, 1610, 710 (Ar), 1720, 1665 (COOR, CONHCO), 1265 (COOR); ^1H NMR (Me_2SO-d_6) 8.2–7.5 (m, 12 H, Ar H), 6.35 (d, 1 H, C_1H), 5.73 (dd, 1 H, C_3H), 5.58 (dd, 1 H, J_{HF} = 52 Hz, C_2H), 4.8 (m, 2 H, C_5H_2), 4.68 (dd, 1 H, C_4H). Anal. ($C_{23}H_{18}N_2O_7IF$) C, H, N.

1-(2-Deoxy-2-fluoro-β-arabinofuranosyl)-5-iodouracil (β-FIAU; 1a). A mixture of **11a** (4.7 g, 0.0081 mol) in 30 mL of methanol and 30 mL of water was stirred and 3 N NaOH added slowly until a complete solution was obtained at pH 10.5. After 16 h the solution was diluted with water (25 mL) and concentrated (ca. 30 mL) and the base neutralized with 3 N HCl (pH 6.5–7.0). The mixture was cooled at 0 °C (5 h), and the product collected to give 2.7 g of **1a** (90% yield): mp 223–226 °C; IR (KBr) 3400, 3200 (NH, OH), 1725, 1665, (CONHCO), 1050 (C–O); ^1H NMR (CD_3OD) 8.28 (d, 1 H, Ar H), 6.16 (dd, 1 H, C_1H), 5.04 (dd, 1 H, J_{HF} = 45 Hz, C_2H), 4.32 (dd, 1 H, C_3H), 3.95–3.7 (m, 3 H, C_4H, C_5H_2). Anal. ($C_9H_{10}N_2O_5IF$) C, H, N.

2,4-Bis-*O*-(trimethylsilyl)thymine (10b). To a mixture of thymine (6.4 g, 0.051 mol), $(NH_4)_2SO_4$ (0.6 g, 0.0045 mol), and

(14) (a) The HPLC analysis of the fluorination reaction was carried out on a Waters μ-Bondapak reverse-phase column using 70% CH_3CN, 30% H_2O. With UV detection at 254 nm and a flow rate of 2 mL/min, the retention times were 4.8 min for **5d**, 6.7 min for **6**, and 7.3 min for **5e**. (b) The HPLC analysis of the coupling reaction was carried out on a Waters μ-Bondapak reverse-phase column using 60% CH_3CN, 40% H_2O. With UV detection at 254 nm and a flow rate of 2 mL/min, the retention times were 1.8 min for 5-iodouracil, 4.8 min for α-FIAU (**11b**), 5.2 min for β-FIAU (**11a**), and 10.1 min for the bromo sugar **9**.

CH_3CN (180 mL) at 40 °C was added hexamethyldisilazane (12 mL, 0.057 mol). The mixture was refluxed 20 h, and after removal of NH_3 with vacuum (30 mmHg, 30 min) the solution was used for the preparation of **12a,b**.

1-(2-Deoxy-2-fluoro-3,5-di-*O*-benzoyl-D-arabinofuranosyl)thymine (12a,b). The silylation mixture containing **10b** (13.8 g, 0.051 mol) was stirred with a solution of **9** (17.6 g, 0.042 mol) in CH_3CN (30 mL) at reflux 1.5 h. The reaction was quenched in ice–water and extracted with CH_2Cl_2. The extract was washed with water, dried (Mg_2SO_4), and concentrated to give 19.4 g (99% yield) of crude product **12a,b** (α/β = 1/3).[14b] The crude solid was stirred with 50 mL of CH_2Cl_2 and filtered, giving 4.9 g of the β-anomer **12a**: mp 120–122 °C; IR (KBr) 3190 (NH), 1605, 715 (Ar), 1720, 1670 (COOR, CONHCO), 1265 (COOR); ^1H NMR (Me_2SO-d_6) 8.2–7.4 (m, 12 H, Ar H, NH), 6.37 (dd, 1 H, C_1H), 5.68 (dd, 1 H, C_3H), 5.58 (dd, 1 H, J_{HF} = 50 Hz, C_2H), 4.69 (m, 3 H, C_4H, C_5H_2), 1.65 (s, 3 H, CH_3). Anal. ($C_{24}H_{21}N_2O_7F$) C, H, N.

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)thymine (β-FMAU; 2a). A slurry of 50% aqueous methanol (220 mL) and the anomeric mixture of dibenzoyl-FMAU (**12a,b**) (α/β = 2/3, 14.5 g, 0.031 mol) was adjusted to pH 10.5 with 3 N NaOH and maintained at that pH for 16 h. The solvent was evaporated and the residue dissolved in water (150 mL), neutralized (pH 6.5–7.0) with concentrated HCl, and evaporated to dryness. Addition of CH_3CN (50 mL) precipitated the inorganic salts, which were removed by filtration. The filtrate was evaporated to yield 7.3 g (90%) of **2a,b** (α/β = 2/3). A sample of the pure β-anomer was obtained by cooling a solution of the mixture in 10 mL of water for 16 h: mp 187–188 °C IR (KBr) 3460, 3400, 3000 (NH, OH), 1690, 1660 (CONHCO), 1035 (C–O); ^1H NMR (CD_3OD) 7.74 (m, 1 H, Ar H), 6.18 (dd, 1 H, C_1H), 5.0 (m, 1 H, J_{HF} = 50 Hz, C_2H), 4.32 (m, 1 H, C_3H), 4.0–3.8 (m, 3 H, C_4H, C_5H_2), 1.86 (s, 3 H, CH_3). Anal. ($C_{10}H_{13}N_2O_5F$) C, H, N.

Registry No. **1a**, 69123-98-4; **2a**, 69256-17-3; **2b**, 97672-34-9; **4**, 22224-41-5; **5a**, 7702-26-3; **5c**, 97614-41-0; **5d**, 97614-42-1; **5e**, 97614-50-1; **6**, 97614-43-2; **7** (Y = CH_2CH_2OH), 97614-49-8; **7** (Y = $CH(CH_3)CH(CH_3)OH$), 97614-51-2; **7** (Y = $C(CH_3)_2C(CH_3)_2OH$), 97614-52-3; **8** (Y = CH_2CH_2OH), 94-33-7; **8** (Y = $CH(CH_3)CH(CH[3)OH$), 59517-16-7; **8** (Y = $C(CH_3)_2C(CH_3)_2OH$), 71380-60-4; **9**, 97614-44-3; **10a**, 38953-72-9; **10b**, 7288-28-0; **11a**, 97614-45-4; **11b**, 97614-46-5; **12a**, 97614-47-6; **12b**, 97614-48-7; 5-iodouracil, 696-07-1; thymine, 65-71-4; 2,3-butanediol, 513-85-9; pinacol, 76-09-5; ethylene glycol, 107-21-1.

Conversion of Alkenes to 1,2-Diazides and 1,2-Diamines

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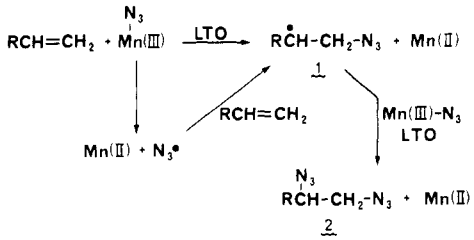
In this paper we wish to report the direct conversion of alkenes into 1,2-diazides as shown in eq 1. This manganese(III) method of vicinal difunctionalization is similar to a method of alkene chlorination reported previously by us[2] and represents one of the very few methods of introducing vicinal diazide functionality. Previously, Fe(III)[3] and Pb(IV)[4a] have been used to convert alkenes to 1,2-diazides, and Pb(IV) has converted 1,3-dienes to 1,4-diazides.[4b] Electrochemical oxidation of the azide anion can also be conducted in the presence of an excess of alkene to generate mono- and diazides in addition to dinitrogen.[5] However, the most common method of introducing vicinal diazides has been via a series of standard S_N2 displacements utilizing the highly nucleophilic azide anion.[6]

$$RCH{=}CH_2 + 2Mn(III) + 2N_3^- + RC(N_3)HCH_2N_3 + 2Mn(II) \quad (1)$$

Scheme I. Proposed Mechanism for Double Azide Addition



We had already demonstrated that manganese(III) acetate hydrate, $Mn_3O(OAc)_7(HOAc)\cdot 5H_2O$, and a chloride salt produced a Mn(III)–Cl species which was capable of oxidatively transferring a Cl ligand directly to an alkene without the intermediacy of free chlorine radicals.[2,7] Because N_3^- has a low E_0 value (variously described as 0.88,[5b] 0.78,[5c] and 0.6[8] V vs. SCE), we felt that it should be easily oxidized and that it may undergo the same type of ligand-transfer oxidation as chlorine or simply add to the alkene as a free $N_3\cdot$ radical. Thus the initial step in the mechanism of double azide addition may be either production of azide radicals or a direct ligand-transfer addition to generate the β-azidoalkyl radical **1** (Scheme I). While we did not determine whether free azido radicals were formed by Mn(III) oxidation, several reaction features were noted. If $N_3\cdot$ radicals were formed, they were trapped very efficiently by the alkene and did not lead to large amounts of molecular nitrogen. More importantly, Mn(III) oxidation of N_3^- in a control experiment conducted in the absence of alkene required 80 min to go to completion, whereas the identical reaction with stoichiometric 1-octene was complete in 10 min. This rate enhancement necessitates that the alkene be intimately involved in Mn(III) reduction and strongly argues for the ligand-transfer oxidation rather than the intermediacy of free azide radicals. The β-azidoalkyl radical **1** apparently reacts with a second Mn(III)–N_3 species in a typical ligand-transfer[9] fashion to complete the double addition.

Other oxidized metal–azide complexes have previously been shown to thermally[10] or photochemically[11] generate $N_3\cdot$ which could be trapped or allowed to dimerize and produce molecular nitrogen. It was anticipated that any Mn(III)–N_3 complex would be very unstable, and therefore

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