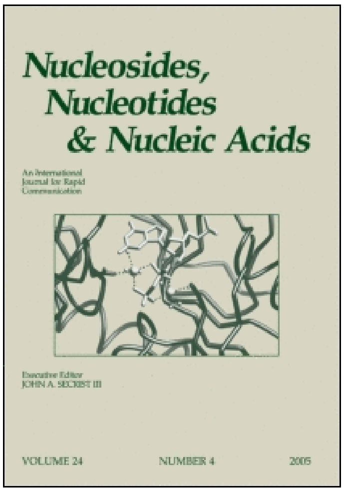


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Palladium-Mediated Coupling Reactions of an Aminosubstituted Heterocycle. Direct Synthesis of C-Nucleosides Related to Adenosine

Han-Cheng Zhang[a]; Mohamed Brakta[a]; G. Doyle Daves Jr.[a]
[a] Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York

To cite this Article Zhang, Han-Cheng , Brakta, Mohamed and Daves Jr., G. Doyle(1995) 'Palladium-Mediated Coupling Reactions of an Aminosubstituted Heterocycle. Direct Synthesis of C-Nucleosides Related to Adenosine', Nucleosides, Nucleotides and Nucleic Acids, 14: 1, 105 — 116

To link to this Article: DOI: 10.1080/15257779508014656

URL: http://dx.doi.org/10.1080/15257779508014656

NUCLEOSIDES & NUCLEOTIDES, 14(1&2), 105-116 (1995)

PALLADIUM-MEDIATED COUPLING REACTIONS OF AN AMINO-SUBSTITUTED HETEROCYCLE. DIRECT SYNTHESIS OF C-NUCLEOSIDES RELATED TO ADENOSINE

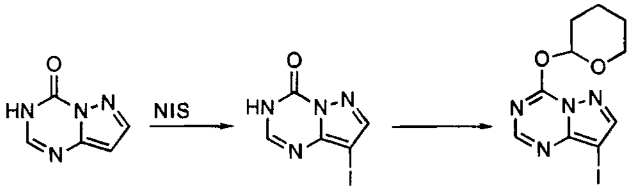
Han-Cheng Zhang, Mohamed Brakta and G. Doyle Daves, Jr.*
Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180

Abstract

C-Nucleosides of the pyrazolo[1,5-a]-1,3,5-triazine aglycon system have been prepared by palladium-mediated coupling of 8-iodopyrazolo[1,5-a]-1,3,5-triazines. 4-(*N,N'*-Diisobutyloxycarbonyl)amino-8-iodopyrazolo[1,5-a]-1,3,5-triazine and the furanoid glycal 1,4-anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol coupled in the presence of catalytic palladium(0) to yield, after desilylation of the intermediate silyl enol ether, a C-glycoside analog of adenosine.

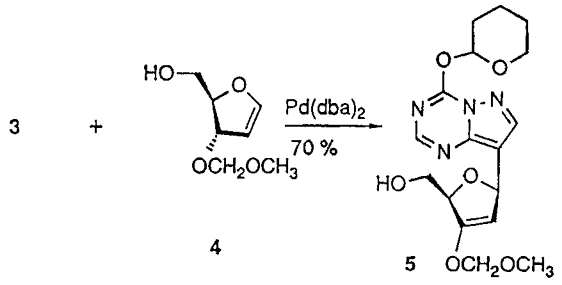
In connection with our ongoing interest in efficient methods for preparation of C-nucleosides and C-glycosides,[1-4] we have extended the study of palladium-mediated coupling reactions of nitrogen heterocycles, initiated in a study of the pyrazolo[4,3-d]pyrimidine system[5] (aglycon of the important antibiotic, formycins[6]) to reactions of iodo derivatives of pyrazolo[1,5-a]-1,3,5-triazine.[7] We now report the first successful palladium-mediated coupling reaction of an amino substituted aglycon with a glycal (1,2-unsaturated carbohydrate) to form directly a C-nucleoside analog of adenosine. This work complements and extends pyrazolo[1,5-a]-1,3,5-triazine C-nucleoside chemistry.[7,8]

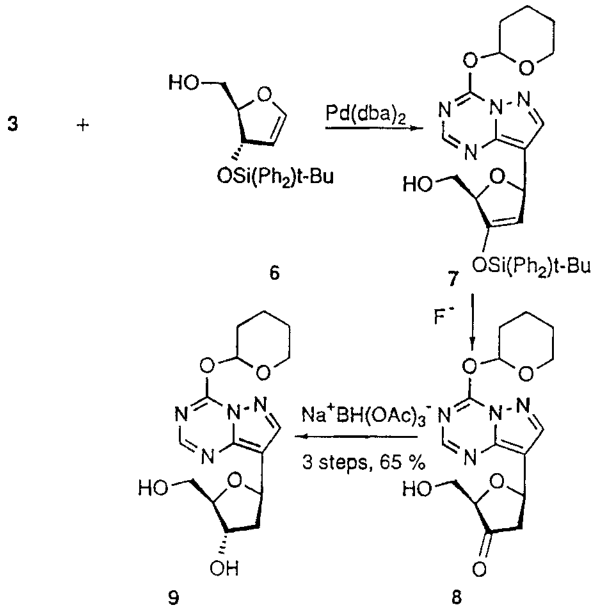
8-Iodopyrazolo[1,5-a]-1,3,5-triazin-4-one (**2**) was prepared from **1**[7] by iodination using *N*-iodosuccinimide. Attempted palladium-mediated coupling of iodo aglycon derivative **2** with 1,4-anhydro-2-deoxy-3-*O*-(methoxymethyl)-D-*erythro*-pent-1-enitol[9] (**4**) using catalytic palladium dibenzylideneacetone, Pd(dba)$_2$, and triphenylarsine [5,10] (2 equiv. per Pd) in acetonitrile (reaction conditions developed in our previous study of the pyrazolo[4,3-d]pyrimidine aglycon system[5]) was unsuccessful.[11]

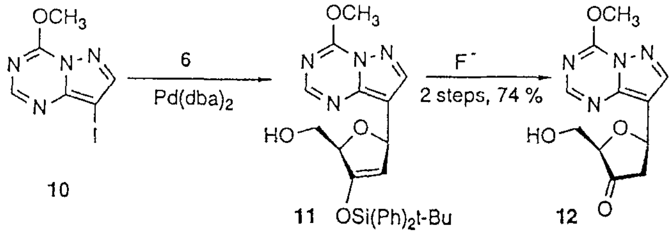


1 2 3

Tetrahydropyranylation of **2** (3,4-dihydropyran, H^+, 78%) produced 8-iodo-4-[(tetrahydropyran-2-yl)oxy]pyrazolo[1,5-a]-1,3,5-triazine (**3**) which underwent regio- and stereospecific coupling with furanoid glycal **4**[9] under the indicated reaction conditions to produce C-nucleoside **5** in good yield along with 15 percent of deiodinated aglycon. In contrast to the corresponding reaction in the pyrazolo[4,3-d]pyrimidine series,[5] no significant aglycon dimerization occurred.

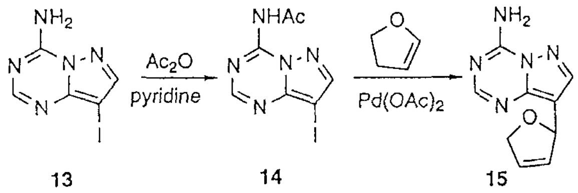




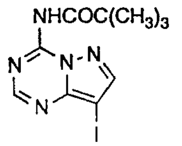


Coupling of iodoaglycon derivative **3** with 3-*O*-silylated furanoid glycal **6**[12] followed by desilylation of the intermediate product, silyl enol ether **7**, with tetrabutylammonium fluoride[12] and stereospecific hydroxy-activated reduction of the 3'-keto group of intermediate **8** using sodium triacetoxyborohydride[5,12,13] yielded the 2'-deoxyribofuranosyl C-nucleoside **9** in 65 percent yield for the three steps.[2,14] The coupling reaction was accompanied by aglycon deiodination (17%); no aglycon dimerization was observed. Similarly, palladium-mediated coupling of 8-iodo-4-methoxypyrazolo[1,5-a]-1,3,5-triazine (**10**) and furanoid glycal **6** efficiently produced C-nucleoside intermediate **11** which was desilylated to form 3'-keto C-nucleoside **12**.

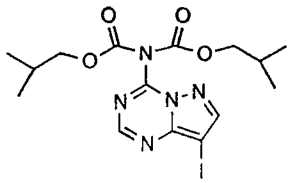
These successful results led us to undertake the more challenging task of coupling a furanoid glycal with an amino-substituted aglycon derivative to form C-nucleoside anologs of adenosine directly. 4-Aminopyrazolo[1,5-a]-1,3,5-triazine[7] was iodinated (*N*-iodosuccinimide) to form **13** which was acetylated using acetic anhydride-pyridine (**13** -> **14**). Palladium-mediated coupling of iodoaglycon **14** with excess 2,3-dihydrofuran occurred at elevated temperature (80-100 °C). It is interesting that the product, **15**, lacked the amino-protecting acetyl group of aglycon precursor **14**.



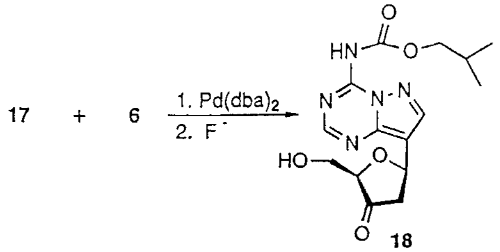
Attempts to achieve coupling of **14** with furanoid glycal **6**[12] under the same conditions were unsuccessful. Reasoning that the acetyl group was too labile and too small to effectively prevent the aglycon amino group of **14** (together with ring nitrogens) from binding and thereby inactivating the palladium catalyst, the bulky pivalylamide **16** was prepared. Unfortunately, aglycon derivative **16** also failed to undergo palladium-mediated coupling with glycal **6**. As a result, the aglycon bis-carbamate derivative **17** was prepared by reaction of **13** with isobutyloxycarbonyl chloride in the presence of pyridine.



16

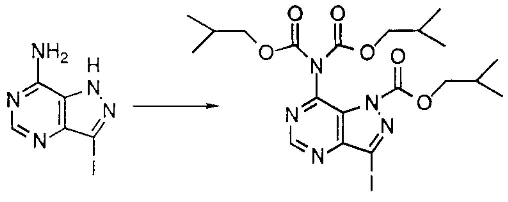


17



18

Aglycon derivative **17**, which possesses bulky groups to shield potential palladium-binding nitrogens, was successfully coupled with glycal **6**[12] in the presence of catalytic palladium dibenzylideneacetone and triphenylarsine to give, after desilylation of the initially formed silyl enol ether with fluoride ion, the 3'-keto C-nucleoside **18** (2 steps, 50%). Again, as in the palladium-mediated reaction of **14**, an acyl group was lost from the amino substituent of the aglycon.



19 **20**

7-Aminopyrazolo[4,3-d]pyrimidine,[15] prepared in two steps from 3-cyano-4-nitropyrazole[16] by reduction and cyclization with formamidine acetate,[17] was iodinated (*N*-iodosuccinimide) to produce 7-amino-3-iodopyrazolo[4,3-d]pyrimidine (**19**) which was converted into the tri-*N*-protected derivative **20** with isobutyloxycarbonyl chloride-pyridine. Attempted palladium-mediated coupling of iodoaglycon derivative **20** with glycal **6** was unsuccessful under a variety of conditions tried. In all cases the protective group on the pyrazole ring nitrogen was lost. Presumably, this lability accounts for the failure to achieve coupling with aglycon derivative **20** since the successful coupling of aglycon derivative **17** attests to the effectiveness of bis-isobutyloxycarbonyl protection of the amino substituent and, in an earlier study,[5] successful coupling reactions of a pyrazolo[4,3-

d]pyrimidine aglycon with a tetrahydropyranyl substituent on the pyrazole ring nitrogen were realized.

Experimental

General Comments. Thin-layer chromatography (TLC) was performed on prescored silica gel GF plates (Analtech). Preparative TLC was carried out on 1 mm thick 20 X 20 cm^2 silica gel GF plates (Analtech). For column chromatography, silica gel 60 (230-400 mesh ASTM, E. Merck) was used. Nuclear magnetic resonance (NMR) spectra were obtained on either a Varian Unity 500 or a Varian Associates XL-200 spectrometer and are referenced to tetramethylsilane. Mass spectra were obtained with a Hewlett Packard 5987A GC/MS system. High resolution mass spectrometry was performed by Dr. Richard Kondrat and Dr. Ron New at the University of California at Riverside. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were carried out by Quantitative Technologies, Whitehouse, NJ.

8-Iodopyrazolo[1,5-a]-1,3,5-triazin-4-one (2). A mixture of pyrazolo[1,5-a]-1,3,5-triazin-4-one[7] (**1**) (2.04 g, 15 mmol) and *N*-iodosuccinimide (4.39 g, 19.5 mmol) in dimethylformamide (DMF) (20 mL) was stirred under nitrogen at 40 °C for 5 h. The solvent was then removed *in vacuo* and CH_2Cl_2 (10 mL) was added. The resulting light yellow solid was collected and suspended in hot water (20 mL) and ammonium hydroxide was added to effect solution. The solution was treated with decolorizing carbon and the resulting hot filtrate was acidified with acetic acid and cooled to give 3.38 g (86 %) of **2** as a light gray solid which was recrystallized from water to give colorless needles: mp 245 °C (dec.); ^1H NMR (DMSO-d_6) δ 8.08 and 8.12 (2s, H-2 and H-7); ^{13}C NMR (DMSO-d_6) δ 54.5 (C-8), 143.5, 146.0, 149.3, 149.5 (C-2, C-4, C-7, C-8a); MS m/z 263 (MH^+).

Anal. Calcd for $C_5H_3IN_4O$: C, 22.9; H, 1.15, N, 21.4. Found: C, 23.2; H, 0.96; N, 21.1.

8-Iodo-4-[(tetrahydropyran-2-yl)oxy]pyrazolo[1,5-a]-1,3,5-triazine (3). 3,4-Dihydro-2*H*-pyran (2.3 mL, 25 mmol) was added dropwise to a mixture of 8-iodopyrazolo[1,5-a]-1,3,5-triazin-4-one (**2**) (1.31 g, 5.0 mmol) and p-toluenesulfonic acid monohydrate (48 mg, 0.25 mmol) in dry DMF (5 mL) and dry ethyl acetate (15 mL). The reaction mixture was stirred under nitrogen at 65 °C for 30 h. The volatiles were then removed and hexane (20 mL) was added. The resulting light yellow solid was collected and recrystallized from methanol-ethyl acetate to give 1.37 g (79 %) of **3** as a colorless solid: mp 144-144.5 °C; ^1H NMR ($CDCl_3$) δ 1.52-2.06 (m, 6H, tetrahydropyranyl), 3.68 (dt, 1H, J = 2.5, 12.0 Hz, tetrahydropyranyl), 4.16 (m, 1H, tetrahydropyranyl), 5.74 (dd, 1H, J = 2.0 and 10.8 Hz, tetrahydropyranyl), 7.95 and 8.09 (2s, 2H, H-2 and H-7); ^{13}C NMR ($CDCl_3$) δ 54.1 (C-8), 142.5, 143.1, 147.7, 150.4 (C-2, C-4, C-7, C-8a); tetrahydropyranyl residue 22.4, 24.5, 32.0, 69.3, 82.8; MS m/z 347 (MH^+).

Anal. Calcd for $C_{10}H_{11}IN_4O_2$: C, 34.7; H, 3.20; N, 16.2. Found: C, 34.8; H, 3.01; N, 16.1.

(2'*R*)-*Cis*-8-[2',5'-dihydro-5'-(hydroxymethyl)-4'-(methoxymethoxy)-2'-furanyl]-4-[(tetrahydropyran-2-yl)oxy]pyrazolo[1,5-a]-1,3,5-triazine (5). A mixture of bis(dibenzylideneacetone) palladium(0) (14 mg, 0.024 mmol) and triphenylarsine (15 mg, 0.049 mmol) in acetonitrile (3 mL) was stirred under nitrogen at room temperature for 15 min. This complex was then transferred by syringe to a solution of 8-iodo-4-[(tetrahydropyran-2-yl)oxy]pyrazolo[1,5-a]-1,3,5-triazine (**3**) (83 mg, 0.24 mmol), 1,4-anhydro-2-deoxy-3-*O*-(methoxymethyl)-D-*erythro*-pent-1-enitol (**4**)[9] (50 mg, 0.31 mmol) and tri-n-butylamine (86 μL, 0.36 mmol) in acetonitrile (7 mL). The reaction mixture was stirred under nitrogen at 60 °C for 18 h, at which time TLC indicated that the aglyon derivative **3** had been consumed. The dark reaction mixture was then filtered through Celite. The volatiles were removed and the resulting residue was separated by flash column chromatography (ethyl acetate : CH_2Cl_2, 3 :1) to give 63 mg (70 %) of **5** as a colorless solid and 8 mg (15 %) of 4-[(tetrahydropyran-2-yl)oxy]pyrazolo[1,5-a]-1,3,5-triazine as a colorless solid.

For **5** (recrystallized from ethyl acetate-hexane) (a pair of diastereoisomers): mp 142-144.5 °C; ^1H NMR[18] ($CDCl_3$) δ 1.52-2.11 (m, 6H, tetrahydropyranyl), 3.46 (s, 3H, OCH_3), 3.68-3.91 (m, 3H, H-5'a, H-5'b, tetrahydropyranyl), 4.18 (m, 1H, tetrahydropyranyl), 4.77 (m, 1H, H-4'), 4.97-5.04 (m, 3H, H-2', OCH_2O), 5.80 (dd, 1H, J = 1.8 and 10.8 Hz, tetrahydropyranyl), 5.99 (m, 1H, H-1'), 7.94, 8.10 (2s, 2H, H-2 and H-7); ^{13}C NMR ($CDCl_3$) δ 22.4, 24.6, 32.1, 56.3, 62.0, 69.3, 82.6, 83.0, 95.5, 98.4, 115.4, 142.2, 143.0, 144.0, 145.4, 152.1;[19,20] MS m/z 379 (MH^+).

Anal. Calcd for $C_{17}H_{22}N_4O_6$: C, 54.0; H, 5.86; N, 14.8. Found: C, 53.5; H, 5.22; N, 14.6.

For 4-[(tetrahydropyran-2-yl)oxy]pyrazolo[1,5-a]-1,3,5-triazine: ^1H NMR ($CDCl_3$) δ 1.55-2.07 (m, 6H, tetrahydropyranyl), 3.69 (dt, 1H, J = 3.0, 11.5 Hz, tetrahydropyranyl), 4.17 (m, 1H, tetrahydropyranyl), 5.79 (dd, 1H, J = 2.0 and 11.0 Hz, tetrahydropyranyl), 6.43 (d, 1H, J = 2.0 Hz, H-8), 7.95 (d, 1H, H-7), 8.01 (s, H, H-2); ^{13}C NMR ($CDCl_3$) δ 100.2 (C-8), 141.8, 143.3, 146.5, 147.4 (C-2, C-4, C-7, C-8a); tetrahydropyranyl residue 22.5, 24.6, 32.0, 69.3, 82.5; MS m/z 220 ($M^{+\cdot}$); HMRS calcd for $C_{10}H_{12}N_4O_2$: 220.0960, found: 220.0967.

8-(2'-Deoxy-β-D-ribofuranosyl)-4-[(tetrahydropyran-2-yl)oxy] pyrazolo[1,5-a]-1,3,5-triazine (9). To a solution of 8-iodo-4-[(tetrahydropyran-2-

yl)oxy]pyrazolo[1,5-a]-1,3,5-triazine (**3**) (242 mg, 0.70 mmol), 1,4-anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol[12] (**6**) (323 mg, 0.91 mmol) and tri-n-butylamine (250 µL, 1.05 mmol) in acetonitrile (10 mL) was added a complex of bis(dibenzylideneacetone)palladium(0) (40 mg, 0.070 mmol) and triphenylarsine (43 mg, 0.14 mmol) in acetonitrile (5 mL). The reaction mixture was stirred under nitrogen at 60 °C for 15 h, at which time TLC indicated that the aglyon derivative **3** had been consumed. The mixture was then cooled to room temperature and a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.70 mL, 0.70 mmol) was added. The desilylation reaction was complete in 10 min based on TLC. To this reaction mixture sodium triacetoxyborohydride (593 mg, 2.8 mmol) was added and the mixture was stirred at room temperature. After the reduction was complete based on TLC (about 15 min), the mixture was filtered through Celite and the volatiles were removed. The resulting residue was separated by flash column chromatography (methanol : ethyl acetate : hexane, 1: 3 : 3) to give 153 mg (65 %) of **9** as a colorless solid and 26 mg (17 %) of 4-[(tetrahydropyran-2-yl)oxy]pyrazolo[1,5-a]-1,3,5-triazine as a colorless solid.

For **9** (recrystallized from ethanol-benzene-hexane) (a pair of diastereoisomers): mp 153-156 °C; ^{1}H NMR (CDCl$_3$) δ 1.53-2.08 (m, 6H, tetrahydropyranyl), 2.19 (dd, 1H, J = 5.5, 13.0 Hz, H-2'a), 2.35 (m, 1H, H-2'b), 3.69 (m, 2H, H-5'a, tetrahydropyranyl), 3.84 (dd, 1H, $J_{4',5'b}$ = 2.0 Hz, $J_{5'a,5'b}$ = 12.5 Hz, H-5'b), 4.06 (m, 1H, H-4'), 4.17 (m, 1H, tetrahydropyranyl), 4.57 (m, 1H, H-3'), 5.34 (dd, 1H, $J_{1',2'b}$ = 5.5 Hz, $J_{1',2'b}$ = 11.0 Hz, H-1'), 5.78 (dd, 1H, J = 2.5, 10.5 Hz, tetrahydropyranyl), 7.95, 8.08 (2s, 2H, H-2 and H-7); ^{13}C NMR (CDCl$_3$) δ 43.8 (C-2'), 63.4 (C-5'), 72.9, 74.7 (C-1', C-4'), 88.1 (C-3'), 114.5 (C-8), 142.2, 143.0, 144.1, 145.6 (C-2, C-4, C-7, C-8a); tetrahydropyranyl residue 22.5, 24.6, 32.1, 69.4, 82.8.[19]

Anal. Calcd for $C_{15}H_{20}N_4O_5$: C, 53.6; H, 5.99; N, 16.7. Found: C, 53.5; H, 5.65; N, 16.4.

8-Iodo-4-methoxypyrazolo[1,5-a]-1,3,5-triazine (10). 4-Methoxypyrazolo[1,5-a]-1,3,5-triazine (60 mg, 0.40 mmol) in DMF (5 mL) was treated with *N*-iodosuccinimide (117 mg, 0.52 mmol) and the reaction mixture was stirred under nitrogen at 40 °C for 5 h. The solvent was then removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4, evaporated and the resulting residue was purified by preparative TLC (ethyl acetate : hexane, 1 : 2) to afford 92 mg (83 %) of **10** as a light yellow solid: ^{1}H NMR (CDCl$_3$) δ 3.64 (s, 3H, OCH$_3$), 7.86, 8.01 (2s, 2H, H-2 and H-7); MS m/z 276 ($M^{+\cdot}$); HMRS calcd for $C_6H_5IN_4O$: 275.9508, found: 275.9504.

8-(2'-Deoxy-β-D-*glycero*-pentofuran-3'-ulos-1'-yl)-4-methoxypyrazolo[1,5-a]-1,3,5-triazine (12). A complex of bis(dibenzylideneacetone) palladium(0) (11 mg, 0.019 mmol) and triphenylarsine (12 mg, 0.039 mmol) in acetonitrile (3 mL) was added to a solution of 8-iodo-4-methoxypyrazolo[1,5-a]-1,3,5-triazine (**10**) (55 mg, 0.20 mmol), 1,4-anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol[12] (**6**) (92 mg, 0.26 mmol) and tri-n-butylamine (72 μL, 0.30 mmol) in acetonitrile (3 mL) was added. The reaction mixture was stirred under nitrogen at 70 °C for 8 h, at which time TLC indicated that aglyon derivative **10** had been consumed from the dark reaction mixture. Acetic acid (24 μL, 0.4 mmol) was added to the mixture at room temperature followed by a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (200 μL, 0.2 mmol). After the desilylation reaction was complete (monitored by TLC), the reaction mixture was filtered through Celite and the volatiles were removed. The resulting residue was separated by preparative TLC (ethyl acetate : hexane, 1 : 2) to give 39 mg (74 %) of **12** as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 2.84 (m, 2H, H-2'a, H-2'b), 3.66 (s, 3H, OCH_3), 3.92 (m, 2H, H-5'a, H-5'b), 4.05 (m, 1H, H-4'), 5.42 (dd, 1H, $J_{1',2'b}$ = 7.5 Hz, $J_{1',2'b}$ = 9.7 Hz, H-1'), 7.84, 8.03 (2s, 2H, H-2 and H-7); MS m/z 265 (MH^+); HMRS calcd for $C_{11}H_{12}N_4O_4 + H^+$: 265.0937, found: 265.0931.

4-Amino-8-iodopyrazolo[1,5-a]-1,3,5-triazine (13). A mixture of 4-aminopyrazolo[1,5-a]-1,3,5-triazine[7] (1.0 g, 7.4 mmol) and *N*-iodosuccinimide (1.72 g, 7.6 mmol) in 40 mL of DMF was heated at 65 °C for 2 h. The mixture was then evaporated to dryness and $CHCl_3$ was added to the resulting residue. The insoluble crystals were collected by filtration, washed three times with $CHCl_3$ to remove iodine and dried to afford 1.7 g (88 %) of yellow crystals, mp 274-275 °C; ^{1}H NMR (DMSO-d_6) δ 8.10, 8.22 (2s, 2H, H-2 and H-7).

Anal. Calcd. for $C_5H_4N_5I$: C, 23.0; H, 1.55: N, 26.8. Found: C, 23.3; H, 1.40; N, 27.0.

4-Acetamido-8-iodopyrazolo[1,5-a]-1,3,5-triazine (14). A solution of 4-amino-8-iodopyrazolo[1,5-a]-1,3,5-triazine (**13**) (0.60 g, 2.3 mmol) and acetic anhydride (0.86 mL, 9.2 mmol) in 24 mL of pyridine was heated under reflux with exclusion of moisture for 3 h, at which time TLC indicated that reaction was complete. The mixture was cooled and the solvent was removed *in vacuo*. Xylene (3 x 15 mL) was added to the residue and evaporated to remove residual pyridine and acetic anhydride. The insoluble crystals were collected, washed with xylene and dried to yield 0.53 g (80 %) of orange crystals, mp 213-214 °C; ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 8.48, 8.52 (2s, 2H, H-2 and H-7); ^{13}C (DMSO-d_6) δ 25.2 (CH_3), 51.7 (C-8), 146.1, 148.8, 149.3, 153.4 (C-2, C-4, C-7, C-8a), 169.1 (CO).

Anal. Calcd for $C_7H_6N_5OI$: C, 27.7; H, 2.00; N, 23.1. Found: C, 28.0; H, 2.04; N, 23.0.

4-Amino-8-(2',5'-dihydrofuran-2'-yl)pyrazolo[1,5-a]-1,3,5-triazine (15). To a solution of 4-acetamido-8-iodopyrazolo[1,5-a]-1,3,5-triazine (**14**) (150 mg, 0.51 mmol) and tri-n-butylamine (123 µL, 0.51 mmol) in 25 mL of acetonitrile under nitrogen was added by cannula a solution of palladium acetate (11.6 mg, 0.051 mmol) and triphenylphosphine (27.3 mg, 0.10 mmol) in 5 mL of acetonitrile. To this mixture was added 2,3-dihydrofuran (0.78 mL, 10.2 mmol) and tetrabutylammomium chloride (150 mg, 0.51 mmol) in 3 mL of acetonitrile. The reaction mixture was stirred at 80 °C for 12 h. The solvent was then removed and the residue was separated by preparative TLC (EtOAc : MeOH : hexane, 6 : 0.5 : 2) to afford 73 mg (70 %) of **15** as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 4.47-4.80 (m, 2H, H-5's), 5.86-6.04 (m, 2H, H-3', H-4'), 6.14-6.20 (m, 1H, H-2'), 8.01, 8.06 (2s, 2H, H-2 and H-7).

Anal. Calcd for $C_9H_9N_5O$: C, 53.2; H, 4.46; N, 34.5. Found: C, 53,5; H, 4.31; N, 34.3.

4-(*N*,*N*-Diisobutyloxycarbonyl)amino-8-iodopyrazolo[1,5-a]-1,3,5-triazine (17). Isobutyloxycarbonyl chloride (311 µL, 2.4 mmol) was added dropwise with stirring to a solution of 4-amino-8-iodopyrazolo[1,5-a]-1,3,5-triazine (**13**) (78 mg, 0.30 mmol) in anhydrous pyridine (10 mL) cooled by ice bath. The reaction mixture was stirred under nitrogen at room temperature for 5 h and then the volatiles were evaporated at reduced pressure. After several additions and evaporations of ethanol, the resulting residue was separated by preparative TLC (ethyl acetate : hexane, 1: 5) to give 123 mg (89 %) of **17** as a colorless foam: ^{1}H NMR (CDCl$_3$) δ 0.69 (d, 12H, J = 6.5 Hz, CH$_3$'s), 1.78 (m, 2H, CH's), 3.95 (d, 4H, J = 7.0 Hz, OCH$_2$'s), 8.18, 8.65 (2s, 2H, H-2 and H-7); ^{13}C NMR (CDCl$_3$) δ 18.45 (CH$_3$), 27.33 (CH), 51.25 (C-8), 74.17 (OCH$_2$), 146.73, 149.19, 150.07, 151.38, 152.80 (C-2, C-4, C-7, C-8a and CO); MS m/z 462 (MH$^+$); HMRS calcd for $C_{15}H_{20}IN_5O_4 + H^+$: 462.0638, found: 462.0643.

8-(2'-deoxy-β-D-*glycero*-pentofuran-3'-ulos-1'-yl)-4-(*N*-isobutyloxycarbonyl)aminopyrazolo[1,5-a]-1,3,5-triazine (18). To a solution of 4-(*N*,*N*-diisobutyloxycarbonyl)amino-8-iodopyrazolo[1,5-a]-1,3,5-triazine (**17**) (69 mg, 0.15 mmol), 1,4-anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol[12] (**6**) (71 mg, 0.20 mmol) and tri-n-butylamine (55 µL, 0.23 mmol) in acetonitrile (3 mL) was added a complex of bis(dibenzylideneacetone)palladium(0) (8.6 mg, 0.015 mmol) and triphenylarsine (9.2 mg, 0.030 mmol) in acetonitrile (2 mL). The reaction mixture was stirred under nitrogen at 70 °C for 24 h and then cooled to room temperature and a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (150 µL, 0.15 mmol) was added. After the desilylation reaction was complete (followed by TLC), the reaction mixture was filtered through Celite and the volatiles were removed. The resulting residue was separated by preparative TLC (methanol : ethyl acetate : hexane, 1: 3

:1) to give 26 mg (50 %) of **18** as a light yellow solid: ^{1}H NMR (CDCl$_3$) δ 0.97 (d, 6H, CH$_3$'s), 2.04 (m, 1H, CH), 2.90 (m, 2H, H-2'a, H-2'b), 3.92, 3.96 (dd's, 2H, $J_{4',5'a}$ = 1.5 Hz, $J_{4',5'b}$ < 1 Hz, $J_{5'a,5'b}$ = 12.0 Hz, H-5'a, H-5'b), 4.11 (m, 3H, OCH$_2$, H-4'), 5.52 (dd, 1H, $J_{1',2'b}$ = 7.3 Hz, $J_{1',2'b}$ = 10.3 Hz, H-1'), 8.11, 8.50 (2s, 2H, H-2 and H-7); MS m/z 350 (MH$^+$); HMRS calcd for $C_{15}H_{19}N_5O_5$ + H$^+$: 350.1464, found: 350.1478.

7-Aminopyrazolo[4,3-d]pyrimidine.[15] A mixture of 3-cyano-4-nitropyrazole[16] (2.0 g, 14.5 mmol) and 10% palladium on carbon (0.3 g) in ethanol (20 mL) was shaken under 45 psi of hydrogen at room temperature for 3.5 h. The reduction was complete based on TLC. The mixture was then filtered through Celite and the catalyst was washed with hot ethanol. The combined filtrates were evaporated at reduced pressure and the resulting solid was dried *in vacuo* for 2 h. This crude product was dissolved in ethanol (30 mL) and formamidine acetate (3.02 g, 29 mmol) was added. The mixture was heated under reflux under nitrogen for 4 h and then the solvent was evaporated to dryness *in vacuo*. The resulting residue was separated by flash column chromatography (methanol: ether, 1: 3) to give 1.04 g (53 %) of 7-aminopyrazolo [4,3-d]pyrimidine as a light yellow solid: mp > 300 °C (lit.[15] mp > 300 °C); ^{1}H NMR (DMSO-d$_6$) δ 8.01, 8.14 (2s, H-3 and H-5); MS m/z 136 (MH$^+$).

7-Amino-3-iodopyrazolo[4,3-d]pyrimidine (19). To a solution of 7-aminopyrazolo[4,3-d]pyrimidine (1.00 g, 7.4 mmol) in DMF (15 mL) was added *N*-iodosuccinimide (2.16 g, 9.6 mmol). The reaction mixture was stirred under nitrogen at 40 °C for 4 h. The solvent was concentrated to about 3 mL, and 8 mL of water was added. The resulting light yellow solid was collected and recrystallized from water to give 1.64 g (85 %) of **19** as a colorless solid: ^{1}H NMR (DMSO-d$_6$) δ 8.23 (s, H-3); MS m/z 262 (MH$^+$).

Anal. Calcd for $C_5H_4IN_5$: C, 23.0; H, 1.54; N, 26.8. Found: C, 23.2; H, 1.42; N, 26.2.

7-(*N,N*-Diisobutyloxycarbonyl)amino-3-iodo-1-isobutyloxy carbonylpyrazolo[4,3-d]pyrimidine (20). Isobutyloxycarbonyl chloride (778 μL, 6.0 mmol) was added dropwise under nitrogen to a solution of 7-amino-3-iodopyrazolo[4,3-d]pyrimidine (**19**) (131 mg, 0.50 mmol) in anhydrous pyridine (12 mL). The reaction mixture was stirred at room temperature for 5 h and then the volatiles were evaporated at reduced pressure. After several additions and evaporations of ethanol, the resulting residue was separated by flash column chromatography (ethyl acetate : hexane, 1: 7) to give 253 mg (90 %) of **20** as a colorless foam: ^{1}H NMR (CDCl$_3$) δ 0.74 (d, 12H, J = 6.8 Hz, CH$_3$'s), 0.98 (d, 6H, J = 6.8 Hz, CH$_3$'s), 1.75-2.10 (m, 3H, CH's), 3.94 (m, 4H, OCH$_2$'s), 4.25 (d, 2H, J = 7.0 Hz, OCH$_2$), 9.18 (s, 1H, H-3); ^{13}C NMR (CDCl$_3$) δ

18.6, 18.7, 27.4, 27.7, 73.5, 75.3, 103.8, 127.7, 144.9, 148.5, 151.0, 153.0, 153.9; MS m/z 562 (MH^+); HMRS calcd for $C_{20}H_{28}IN_5O_6 + H^+$: 562.1163, found: 562.1156.

Acknowledgment. We thank the National Institute of Allergy and Infectious Diseases for financial support.

REFERENCES

1. Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433-1445.
2. Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201-206.
3. Daves, G. D., Jr. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1991; Vol II, pp 59-99.
4. Daves, G. D. Jr., In *Carbohydrates-Synthetic Methods and Applications in Medicinal Chemistry*: Suami, T., Hasegawa, A., Ogura, H., Eds.; Kodansha, Tokyo, 1992, pp 49-65.
5. Zhang, H.-C.; Daves, G. D., Jr. *J. Org. Chem.* **1992**, *57*, 4690-4696.
6. Hacksell, U.; Daves, G. D., Jr. *Prog. Med Chem.* **1985**, *22*, 1-65.
7. Kobe, J.; Robins, R. K.; O'Brien, D. E. *J. Heterocycl. Chem.* **1974**, *11*, 199-204. Tam, S. Y.-K.; Hwang, J.-S.; De Las Heras, F. G.; Klein, R. S.; Fox, J. J. *J. Heterocycl. Chem.* **1976** *13*, 1305-1308.
8. (a) Gupta, C. M.; Jones, G. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 3000-3009. (b) De Las Heras, F. G.; Chu. C. K.; Tam, S. Y.-K.; Klein, R. S.; Watanabe, K. A.; Fox, J. J. *J. Heterocycl. Chem.* **1976**, *13*, 175-177. (c) Chu, C. K.;Watanabe, K. A.; Fox, J. J. *J. Heterocycl. Chem.* **1980**, *17*, 1435-1449. (d) Chu, C. K. *J. Heterocycl. Chem.* **1984**, *21*, 389-392. (e) Chu, C. K.; Suh, J. J.; Mesbah, M.; Cutler, S. J. *J. Heterocycl. Chem.* **1986**, *23*, 349-352.
9. Cheng, J. C.-Y.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1985**, *50*, 2778-2780.
10. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9595.

11. See, however, results obtained using aqueous conditions for the coupling reaction (Zhang, H.-C.; Daves, G. D., Jr. *Organometallics* **1993**, *12*, 1499-1500).
12. Farr, R. N.; Daves, G. D., Jr. *J. Carbohydr. Chem.* **1990**, *9*, 653-660.
13. Gribble, G. W.; Ferguson, D. C. *J. Chem., Soc. Chem. Commun.* **1975**, 535-536. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.
14. Farr, R. N.; Kwok, D.-I.; Daves, G. D., Jr. *J. Org. Chem.* **1992**, *57*, 2093-2100. Farr, R. N.; Outten, R. A.; Cheng, J. C.-Y.; Daves, G. D., Jr. *Organometallics* **1990**, *9*, 3151-3156.
15. Robins, R. K.; Furcht, F. W.; Grauer, A. N.; Jones, J. W. *J. Am. Chem. Soc.* **1956**, *78*, 2418-2422.
16. Kagan, J.; Melnick, B. *J. Heterocycl. Chem.* **1979**, *16*, 1113-1115.
17. Buchanan, J. G.; Millar, A.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. I* **1985**, 1425-1430.
18. Carbohydrate notation is used for NMR assignments.
19. Some signals appear as two closely spaced singlets owing to the diastereomeric nature of the product.
20. One carbon resonance was obscured by the $CDCl_3$ resonance.

Received June 20, 1994
Accepted September 26, 1994