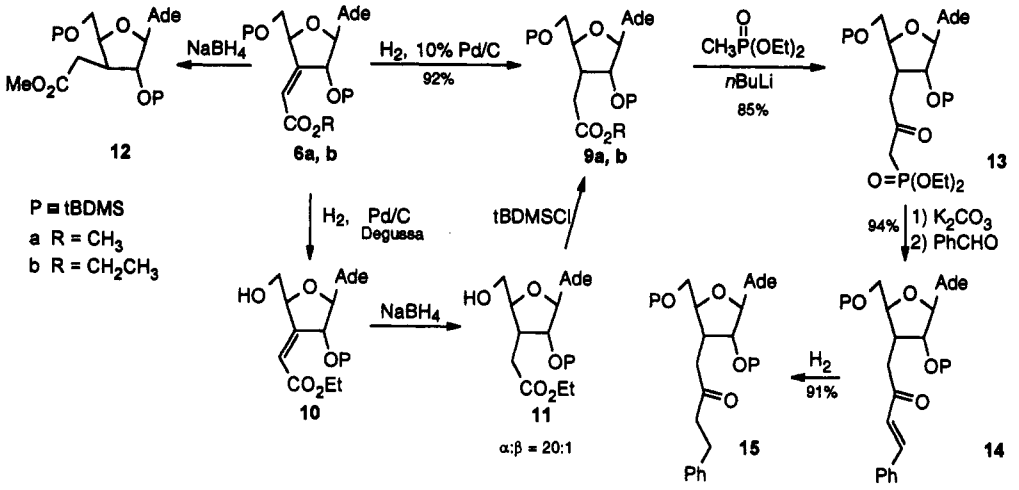
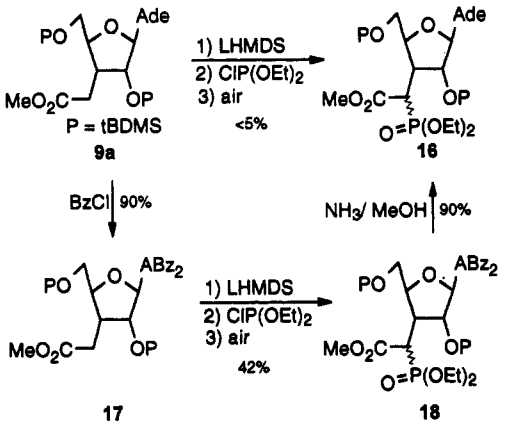
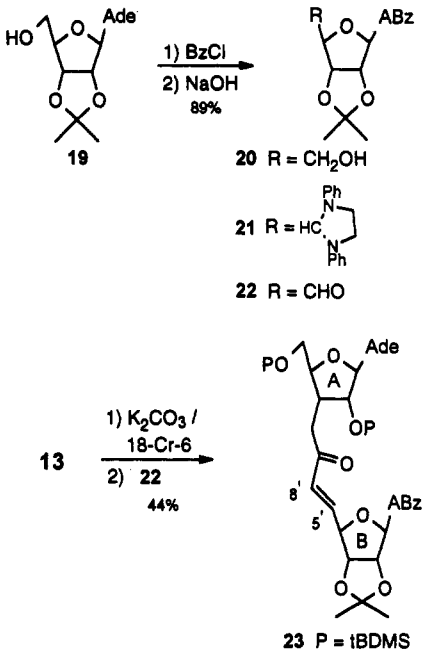
Scheme II



Scheme III



Scheme IV



has been prepared in situ from the parent 5′-alcohol **19**,[18] we chose to use aldehyde derived from 5′-imidazolidine **21**.[19] The N^6-benzoyl compound **20** was prepared from 2′,3′-*O*-isopropylideneadenosine (**19**) based on the method of Chládek and Smrt.[20] Conversion of compound **20** to the 5′-aldehyde **22** was achieved by a straightforward route involving oxidation, reaction with *N*,*N*′-diphenylethylenediamine, purification of this intermediate, and hydrolysis of protected aldehyde **21**, as described by Jones *et al.*[19]

The targeted dinucleotide analogue **23** was obtained through an HWE condensation of phosphonate **13** with aldehyde **22** (Scheme IV). Treatment of phosphonate **13** with K_2CO_3 in the presence of 18-crown-6, followed by addition of aldehyde **22** generated from diamine **21** and used without further purification, gave the desired enone **23**. This product was obtained as a single stereoisomer, assigned a trans configuration on the basis of ^{1}H NMR data (J = 15.9 Hz). Although the yield for this final step was only 44%, this probably reflects the difficulty of working with nucleoside 5′-aldehydes because it has been shown that condensation with simple aldehydes proceeds in good yield (vide infra).

In this report we have described the synthesis of some new nucleoside phosphonates, compounds **13** and **16**, as well as a new type of dinucleotide analogue, the enone **23**. Compounds such as **23** should be of interest for the potential stability they could contribute to oligonucleotides if incorporated as 3′-terminal residues, as well as for their potential to react with nucleases through Michael addition. Furthermore, intermediates reported here can themselves be considered to be nucleotide analogues, including the 3′-methylene carboxylate **9** that can be viewed as an analogue of a 3′-nucleotide and the 3′-keto phosphonate **13** that could be viewed as an analogue of a 3′-diphosphate. Studies on the biological activity of these compounds, and synthesis of related nucleoside phosphonates, will be reported in due course.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone and pyridine was distilled from calcium hydride immediately prior to use. All reactions in these solvents were conducted under a positive pressure of an inert gas. Column chromatography was done on Merck grade 62A silica gel (100–200 mesh), while radial chromatography was performed with a Chromatotron apparatus

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(19) Ranganathan, R. S.; Jones, G. H.; Moffat, J. G. *J. Org. Chem.* **1974**, *39*, 290.

(20) Chladek, S.; Smrt, J. *Collect. Czech. Chem. Commun.* **1964**, *29*, 214. Koster, H.; Kulikowski, K.; Liese, T.; Heikens, W.; Kohli, V. *Tetrahedron* **1981**, *37*, 363.

and Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. NMR spectra (^1H and ^{13}C) were recorded with $CDCl_3$ as solvent and residual $CHCl_3$ as internal standard; ^{31}P chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). Elemental analyses were performed by Atlantic Microlab, Inc.

9-(2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-((methoxycarbonyl)methylidene)-β-D-ribofuranosyl)adenine (6a). Procedure A. A solution of ketone **1**[10] (493 mg, 1 mmol) and (carbomethoxymethylene)triphenylphosphorane (401 mg, 1.2 mmol) in THF (15 mL) was heated at reflux for 7 h. The solvent was removed in vacuo and the brown oily residue was suspended in a 1:1 mixture of EtOAc and hexane. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate was concentrated. Purification by flash chromatography (silica gel, 39:1 $CHCl_3$ and CH_3OH) gave pure compound **6a** (485 mg, 88%): ^1H NMR δ 8.33 (s, 1H), 8.31 (s, 1H), 5.96 –5.93 (m, 2H), 5.90 (br s, 2H), 5.43 (m, 1H), 5.13 (dm, 1H, $J_{1',2'}$ = 7.6 Hz), 4.20 (dd, 1H, $J_{5'a,5'b}$ = 11.0 Hz, $J_{5'b,4'}$ = 1.9 Hz), 3.97 (dd, 1H, $J_{5'a,5'b}$ = 11.0 Hz, $J_{5'b,4'}$ = 2.0 Hz), 3.76 (s, 3H), 0.92 and 0.76 (2s, 18H), 0.10, 0.06, –0.13, and 0.55 (4s, 12H); ^{13}C NMR δ 165.6, 160.0, 155.8, 153.1, 150.4, 138.3, 119.3, 113.0, 85.4, 80.3, 78.5, 64.4, 51.5, 25.9 (3C), 25.3 (3C), 18.3, 17.7, –5.2, –5.5, –5.61, –5.69. Anal Calcd for $C_{25}H_{43}N_5O_5Si_2$: C, 54.61; H, 7.88; N, 12.74. Found: C, 54.42; H, 7.89; N, 12.66.

Procedure B. Sodium hydride (60% dispersion in mineral oil; 13.2 mg, 0.33 mmol) was washed with pentane and then suspended in THF (3 mL) at 0 °C. A solution of trimethyl phosphonoacetate (60.1 mg, 0.33 mmol) in THF (2 mL) was added, and the mixture was stirred for 30 min at rt. The resulting solution was cooled to 0 °C, and a solution of ketone **1** (147.9 mg, 0.3 mmol) in THF (2 mL) was added dropwise. After the mixture was stirred overnight at rt, the reaction was quenched by addition of water (1 mL). The organic layer was separated, and the aqueous layer was extracted with ether (5 mL). The combined organic extract was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (9:1 $CHCl_3$ and CH_3OH) gave a 5:1 mixture (102 mg, 62%) of **6a** and the isomeric **7a** as a single spot on TLC. Selected ^1H NMR for **7a**: δ 8.30 (s, 1H), 7.96 (s, 1H), 6.24 (br s, 2H), 6.13 (br s, 1H), 6.03 (m, 1H), 5.80 (br s, 1H), 4.93 (m, 1H), 3.69 (s, 3H).

9-(2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-((methoxycarbonyl)methylene)-β-D-ribofuranosyl)adenine (9). A mixture of **6a** (549 mg, 1 mmol) and 10% Pd–C (825 mg) in CH_3OH (10 mL) was stirred for 3 days under H_2. After completion of the reaction, the solution was filtered through Celite and the pad was rinsed with CH_3OH. The filtrate was concentrated in vacuo and the residue was suspended in CH_2Cl_2 (20 mL) with vigorous stirring. The insoluble solid was removed by filtration and the filtrate was concentrated in vacuo to give compound **9a** as a white solid (484 mg, 88%): ^1H NMR δ 8.34 (s, 1H), 8.31 (s, 1H), 6.02 (d, 1H, $J_{1',2'}$ = 1.0 Hz), 5.83 (br s, 2H), 4.64 (dd, 1H, $J_{1',2'}$ = 1.0 Hz, $J_{2',3'}$ = 4.9 Hz), 4.08 (d, 1H, $J_{3',4'}$ = 9.6 Hz), 4.08 (dd, 1H), 3.77 (dd, 1H, $J_{5'a,5'b}$ = 12.2 Hz, $J_{5'b,4'}$ = 3.3 Hz), 3.63 (s, 3H), 2.82–2.74 (m, 1H), 2.69 (dd, 1H, $J_{6'a,6'b}$ = 16.4 Hz, $J_{6'a,3'a}$ = 9.6 Hz), 2.37 (dd, 1H, $J_{6'a,6'b}$ = 16.4 Hz, $J_{6'b,3'a}$ = 4.3 Hz), 0.93 and 0.90 (2s, 18H), 0.03, 0.21, 0.11, and 0.12 (4s, 12H); ^{13}C NMR δ 172.2, 155.2, 152.7, 149.4, 138.8, 120.0, 90.6, 84.2, 77.8, 62.5, 51.7, 38.1, 29.5, 26.0 (3C), 25.7 (3C), 18.5, 18.0, –4.4, –5.3, –5.5, –5.6. Anal Calcd for $C_{25}H_{45}N_5O_5Si_2$: C, 54.41; H, 8.22; N, 12.69. Found: C, 54.38; H, 8.00; N, 12.63.

The ethyl derivative **9b** was prepared from **6b**[12] in the same manner as above: selected ^1H NMR δ 4.13–4.06 (m, 4H, H-4', H-5'a, $-CO_2CH_2-$), 1.22 (t, 3H, $-CO_2CH_2CH_3$, J = 7.2 Hz).

9-(2-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-((ethoxycarbonyl)methylidene)-β-D-ribofuranosyl)adenine (10). A mixture of **6b** (140.5 mg, 0.25 mmol) and 5% Degussa-type Pd–C (60 mg) in CH_3OH (1 mL) was stirred overnight under H_2. The resulting solution was filtered, the catalyst was rinsed with CH_3OH, and the filtrate was concentrated in vacuo. Purification by flash chromatography (19:1 $CHCl_3$:CH_3OH) gave unreacted **6b** (56 mg) and deprotected compound **10** (63 mg, 56%, 90% based on recovered starting material): ^1H NMR δ 8.31 (s, 1H), 7.78 (s, 1H), 6.38 (br s, 2H), 5.90 (dd, 1H, J = 2.3, 2.1 Hz), 5.57–5.47 (m, 3H), 4.18 (q, 2H, J = 7.1 Hz), 4.06 (br d, 1H, J = 11.5 Hz), 3.98 (dd, 1H, $J_{5'a,5'b}$ = 11.5 Hz, $J_{5'b,4'}$ = 1.9 Hz), 1.29 (t, 3H, J = 7.1 Hz), 0.78 (s, 9H), –0.12 and –0.60 (2s, 6H). Anal Calcd for $C_{20}H_{33}N_5O_5Si$: C, 53.19; H, 7.37; N, 15.51. Found: C, 53.38; H, 7.34; N, 15.71.

Preparation of 9b from 10. Ester **10** (45 mg, 0.1 mmol) was dissolved in CH_3OH (1 mL), $NaBH_4$ (38 mg, 1.0 mmol) was added, and the mixture was stirred for 3 h at rt. The resulting solution was quenched by addition of a few drops of 50% aqueous acetic acid, diluted with EtOAc (5 mL), and washed with brine (1 mL). After treatment with $MgSO_4$ and concentration in vacuo, the resulting white solid was dissolved in pyridine (0.5 mL) containing tBDMSCl (22.5 mg, 0.15 mmol). The mixture was stirred overnight, and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (3 mL), washed with water (0.5 mL), and purified by flash chromatography (1:2 EtOAc and hexane) to give a mixture of **9** and **12** (21.2 mg, 37%) in a ratio of 12:1 as measured by ^1H NMR. The major component was identical with compound **9b** prepared by direct hydrogenation of **6b**.

9-(2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-((methoxycarbonyl)methylene)-β-D-xylofuranosyl)adenine (12). Ester **9a** (110 mg, 0.2 mmol) was dissolved in CH_3OH (2 mL), $NaBH_4$ (76 mg, 2.0 mmol) was added, and the mixture was stirred for 48 h at rt. The resulting solution was quenched by addition of 1 N acetic acid in ether (0.5 mL) and the solvent was removed in vacuo. The residue was suspended in CH_2Cl_2 (10 mL) with vigorous stirring and the insoluble solid was removed by filtration through Celite. The filtrate was concentrated in vacuo to give a mixture of unreacted **9a**, saturated ester **12**, and alcohol derivatives[12] as observed by ^1H NMR. Purification by flash chromatography (silica gel, 39:1 to 19:1 $CHCl_3$ and CH_3OH) gave pure compound **12** (23 mg, 21%): ^1H NMR δ 8.33 (s, 1H), 8.23 (s, 1H), 5.95 (d, 1H, $J_{1',2'}$ = 6.5 Hz), 5.88 (br s, 2H), 4.58 (dd, 1H, $J_{1',2''}$ = 6.5 Hz, $J_{2',3'}$ = 9.5 Hz), 4.44 (dm, 1H, $J_{3',4'}$ = 8.1 Hz), 3.92 (dd, 1H, $J_{5'a,5'b}$ = 11.8 Hz, $J_{5'b,4'}$ = 3.1 Hz), 3.70 (dd, 1H, $J_{5'b,4'}$ = 2.1 Hz), 3.69 (s, 3H), 3.00–2.89 (m, 1H), 2.74 (dd, 1H, $J_{6'a,6'b}$ = 16.7 Hz, $J_{6'a,3'}$ = 10.6 Hz), 2.37 (dd, 1H, $J_{6'a,6'b}$ = 16.7 Hz, $J_{6'b,3'}$ = 4.9 Hz), 0.96, 0.74 (2s, 18H), 0.15, 0.13, –0.12, –0.59 (4s, 12H); ^{13}C NMR δ 172.5, 155.4, 153.1, 150.5, 138.9, 119.5, 87.5, 79.5, 78.4, 63.7, 51.9, 43.9, 31.7, 26.1 (3C), 25.5 (3C), 18.4, 17.6, –4.8, –5.3, –5.45, –5.48. Anal. Calcd for $C_{25}H_{45}N_5O_5Si_2$: C, 54.41; H, 8.22; N, 12.69. Found: C, 54.59; H, 8.00; N, 12.68.

9-(2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-((((diethoxyphosphinyl)methyl)carbonyl)methylene)-β-D-ribofuranosyl)adenine (13). To a solution of diethyl methylphosphonate (183 mg, 1.2 mmol) in THF (3 mL) was added dropwise a solution of *n*-BuLi in hexane (2.5 N, 5.2 mL) at –78 °C, and the mixture was stirred for a further 40 min. The resulting solution was transferred to a cooled solution of ester **9a** (22.4 mg, 0.4 mmol) via cannula at –78 °C, and the mixture was allowed to warm to rt over 2 h. After the reaction was quenched by addition of 1 N acetic acid in ether (2 mL), the resulting suspension was filtered through Celite. The filtrate was concentrated in vacuo and purified by flash chromatography on silica gel (19:1 $CHCl_3$ and hexane) to yield the desired phosphonate **13** (229 mg, 85%): ^1H NMR δ 8.32 (s, 1H), 8.30 (s, 1H), 6.00 (d, 1H, $J_{1',2'}$ = 1.7 Hz), 5.86 (br s, 2H), 4.67 (dd, 1H, $J_{1',2'}$ = 1.7 Hz, $J_{2',3'}$ = 4.6 Hz), 4.16–4.02 (m, 6H), 3.75 (dd, 1H, $J_{5'a,5'b}$ = 12.3 Hz, $J_{5'b,4'}$ = 3.1 Hz), 3.05 (dd, 1H, $J_{7'a,P}$ = 40.9 Hz, $J_{7'a,7'b}$ = 22.8 Hz), 3.05 (dd, 1H, $J_{7'b,P}$ = 68.1 Hz, $J_{7'a,7'b}$ = 22.8 Hz), 1.30 (td, 6H, J_{HP} = 2.1 Hz, J = 7.1 Hz), 0.92 and 0.86 (2s, 18H), 0.14, 0.11, 0.10, and –0.03 (4s, 12H); ^{13}C NMR δ 200.0 (J_{CP} = 6.1 Hz), 155.3, 152.7, 149.5, 138.8, 119.9, 90.3, 84.4, 77.6, 62.7, 62.6 (d, J_{CP} = 6.9 Hz), 62.5 (J_{CP} = 6.9 Hz), 42.7 (d, J_{CP} = 127.4 Hz), 39.7, 37.0, 26.0 (3C), 25.7 (3C), 18.5, 17.9, 16.4, 16.3, –4.6, –5.4 (3C); ^{31}P NMR ($CDCl_3$) +20.9. Anal. Calcd for $C_{29}H_{54}N_5O_7PSi_2$: C, 51.84; H, 8.10; N, 10.42. Found: C, 51.85; H, 8.14; N, 10.34.

Horner–Wadsworth–Emmons Condensation of Phosphonate 13 with Benzaldehyde. A mixture of compound **13** (67 mg, 0.1 mmol), 18-crown-6 (27 mg, 0.11 mmol), and potassium carbonate (152 mg, 1.1 mmol) in THF (2 mL) was stirred for 1 h at rt. A solution of benzaldehyde (16 mg, 0.15 mmol) in THF (0.3 mL) was added dropwise and the resulting mixture was stirred overnight at rt. After the reaction was quenched by addition of a few drops of saturated aqueous NH_4Cl, the resulting solution was filtered through a $MgSO_4$ pad. Concentration of the filtrate, followed by purification by radial chromatography (39:1 $CHCl_3$ and CH_3OH) gave enone **14** (58.5 mg, 94%): ^1H NMR δ 8.34 (s, 1H), 8.32 (s, 1H), 7.54 (d, 1H, $J_{8',9'}$ = 16.3 Hz), 7.54–7.37 (m, 5H),

6.71 (d, 1H, $J_{8',9'}$ = 16.3 Hz), 6.05 (d, 1H, $J_{1',2'}$ = 1.5 Hz), 6.03 (br s, 2H), 4.74 (dd, 1H, $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 4.8 Hz), 4.13 (dt, 1H, $J_{3',4'}$ = 8.9 Hz, $J_{4',5'}$ = 2.6 Hz), 4.03 (dd, 1H, $J_{5'a,5'b}$ = 11.5 Hz, $J_{5'a,4'}$ = 2.7 Hz), 3.77 (dd, 1H, $J_{5'a,5'b}$ = 11.5 Hz, $J_{5'b,4'}$ = 2.6 Hz), 3.11 (dd, 1H, $J_{6'a,6'b}$ = 17.6 Hz, $J_{6'a,3'}$ = 8.7 Hz), 2.99–2.90 (m, 1H), 2.74 (dd, 1H, $J_{6'a,6'b}$ = 17.6 Hz, $J_{6'b,3'}$ = 4.6 Hz), 0.92 and 0.86 (2s, 18H), 0.16, 0.11, and –0.05 (3s, 12H). Anal. Calcd for $C_{32}H_{49}N_5O_4Si_2$: C, 61.59; H, 7.92; N, 11.22. Found: C, 61.54; H, 8.02; N, 11.14.

Catalytic Hydrogenation of 14. A mixture of compound **14** (58.5 mg) and 10% Pd–C (10 mg) in CH_3OH (1 mL) was stirred for 2 h under H_2. After completion of the reaction, the solution was filtered through Celite and the catalyst was rinsed with CH_3OH. The combined filtrate was concentrated in vacuo and the residue was purified by radial chromatography (19:1 $CHCl_3$ and CH_3OH) to give compound **15** as a white solid (53.4 mg, 91%, 86% overall): ^{1}H NMR δ 8.31 (s, 1H), 8.29 (s, 1H), 7.27–7.12 (m, 5H), 6.08 (br s, 2H), 5.99 (d, 1H, $J_{1',2'}$ = 1.5 Hz), 4.67 (m, 1H), 4.02–3.98 (m, 2H), 3.75 (dd, 1H, $J_{5'a,5'b}$ = 12.4 Hz, $J_{5'b,4'}$ = 3.4 Hz), 2.89–2.40 (m, 7H), 0.91 and 0.86 (2s, 18H), 0.16, 0.09, 0.09, and –0.05 (4s, 12H); ^{13}C NMR δ 207.4, 155.4, 152.7, 149.5, 140.7, 138.7, 128.5 (2C), 128.2 (2C), 126.2, 119.9, 90.4, 84.3, 77.6, 62.9, 44.3, 38.3, 37.4, 29.6, 26.0 (3C), 25.7 (3C), 18.5, 17.9, -4.5, –5.4, –5.5 (2C). Anal. Calcd for $C_{32}H_{51}N_5O_4Si_2$: C, 61.40; H, 8.21; N, 11.19. Found: C, 61.63; H, 8.27; N, 11.16.

6-*N*,*N*-Dibenzoyl-9-(2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-((methoxycarbonyl)methylene)-β-D-ribofuranosyl)adenine (17). Benzoyl chloride (211 mg, 1.5 mmol) was added to a stirred solution of compound **9a** (225 mg, 0.5 mmol) in pyridine (3 mL), and the mixture was stirred for a further 5 h at rt. After the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (6 mL) and washed with brine (1 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 39:1 $CHCl_3$ and CH_3OH) gave compound **17** (350 mg, 92%): ^{1}H NMR δ 8.63 (s, 1H), 8.50 (s, 1H), 7.87–7.32 (m, 10H), 6.05 (d, 1H, $J_{1',2'}$ = 1.0 Hz), 4.74 (d, 1H, $J_{2',3'}$ = 3.5 Hz), 4.17–4.02 (m, 1H), 4.03 (dd, 1H, $J_{5'a,5'b}$ = 11.6 Hz, $J_{5'a,4'}$ = 2.9 Hz), 3.78 (dd, 1H, $J_{5'a,5'b}$ = 11.6 Hz, $J_{5'b,4'}$ = 3.0 Hz), 3.66 (s, 3H), 2.81–2.73 (m, 1H), 2.71 (dd, 1H, $J_{6'a,6'b}$ = 15.6 Hz, $J_{6'a,3'a}$ = 9.5 Hz), 2.39 (dd, 1H, $J_{6'a,6'b}$ = 15.6 Hz, $J_{6'b,3'a}$ = 3.6 Hz), 0.90 (s, 18H), 0.16, 0.09, 0.04 (3s, 12H); ^{13}C NMR δ 172.2, 172.0, 152.4, 151.9, 151.5, 143.2, 134.2, 132.7, 129.4, 128.6, 128.1, 90.9, 84.5, 77.6, 62.8, 51.7, 38.7, 29.6, 26.0 (3C), 25.7 (3C), 18.4, 17.9, –4.5, –5.4, –5.5, –5.6. Anal. Calcd for $C_{39}H_{53}N_5O_7Si_2$: C, 61.63; H, 7.03; N, 9.21. Found: C, 62.04; H, 7.25; N, 9.28.

Preparation of Phosphono Ester 18. To a stirred solution of ester **17** (190 mg, 0.25 mmol) in THF (1.5 mL) was added dropwise 1 N lithium hexamethyldisilizide in THF (0.275 mL, 0.275 mmol) at –78 °C. After the solution was stirred for 1.5 h, HMPA (0.047 mL) was added and the mixture was stirred for an additional 30 min. Diethyl phosphorochloridite (0.041 mL, 0.275 mmol) was added dropwise to the resulting enolate, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by addition of acetic acid in ether (1 N, 0.3 mL) and the mixture was filtered through Celite. After concentration to a small volume, the oily residue was stirred overnight in a reaction vessel open to air. Purification by flash chromatography (silica gel, 1:4 to 1:1 EtOAc and hexane) afforded unreacted **17** (52 mg, 27% recovery) and compound **18** (93 mg, 42%) as a mixture of phosphonate diastereomers in a ratio of approximately 4:1 as measured by ^{1}H NMR: ^{1}H NMR major diastereomer, δ 8.60 (s, 1H), 8.44 (s, 1H), 7.83–7.28 (m, 10H), 6.02 (d, 1H, $J_{1',2'}$ = 5.9 Hz), 4.93 (m, 1H), 4.70 (dd, 1H, $J_{1',2'}$ = 5.9 Hz, $J_{2',3'}$ = 8.2 Hz), 4.19–4.08 (m, 4H), 3.97 (dd, 1H, $J_{5'a,5'b}$ = 11.2 Hz, $J_{5'a,4'}$ = 1.5 Hz), 3.81 (s, 3H), 3.77 (dd, 1H, $J_{5'a,5'b}$ = 11.2 Hz, $J_{5'b,4'}$ = 2.4 Hz), 3.43 (dd, 1H, J_{HP} = 24.3 Hz, $J_{6',3'a}$ = 4.1 Hz), 3.07–2.99 (m, 1H), 1.29 (dt, 6H, J_{HP} = 7.1 Hz, J = 7.1 Hz), 0.92 and 0.75 (2s, 18H), –0.03, –0.04, –0.13, and –0.46 (4s, 12H); ^{13}C NMR δ 172.1, 168.9 (d, J_{CP} = 8.6 Hz), 153.2, 152.1, 151.5, 143.1, 134.1, 132.7, 129.3, 128.5, 88.5, 81.6 (d, J_{CP} = 4.0 Hz), 77.8 (d, J_{CP} = 11.6 Hz), 64.7, 62.9 (d, 2C, J_{CP} = 6.7 Hz), 52.5, 41.7 (d, J_{CP} = 133.3 Hz), 40.4, 26.0 (3C), 25.4 (3C), 18.4, 17.7, 16.3 (d, 2C, J_{CP} = 5.1 Hz), –5.3 (2C), –5.49, –5.52; ^{31}P NMR ($CDCl_3$) +22.3; HR FAB MS calcd for $C_{43}H_{63}N_5O_{10}PSi_2$ 896.3854 (M^+ + H), found 896.3859.

Preparation of Phosphono Ester 16. A solution of compound **18** (67.1 mg, 0.075 mmol) in CH_3OH (1 mL) saturated with ammonia was stirred overnight at rt. The solvent was removed in vacuo to give a white foam (69.8 mg, 100%) consisting of 2:1 mixture of benzamide and deprotected phosphonate **16** as observed by ^{1}H NMR. Purification by flash chromatography (4:1 EtOAc and hexane) afforded phosphonate **16** as a mixture of diastereomers (46.2 mg, 90%): ^{1}H NMR major diastereomer, δ 8.28 (s, 1H), 8.27 (s, 1H), 6.07 (br s, 2H), 5.95 (d, 1H, $J_{1',2'}$ = 5.2 Hz), 4.84 (m, 1H), 4.71 (dd, 1H, $J_{1',2'}$ = 5.2 Hz, $J_{2',3'}$ = 7.6 Hz), 4.18–4.06 (m, 4H), 3.87 (dd, 1H, $J_{5'a,5'b}$ = 11.2 Hz, $J_{5'a,4'}$ = 1.6 Hz), 3.79 (s, 3H), 3.71 (dd, 1H, $J_{5'a,5'b}$ = 11.2 Hz, $J_{5'b,4'}$ = 2.2 Hz), 3.44 (dd, 1H, J_{HP} = 23.8 Hz, $J_{6',3'a}$ = 4.6 Hz), 3.05–2.98 (m, 1H), 1.27 (dt, 6H, J_{HP} = 10.2 Hz, J = 7.1 Hz), 0.93 and 0.78 (2s, 18H), 0.12, 0.10, –0.11, and –0.32 (3s, 12H); ^{13}C NMR δ 168.8 (d, J_{CP} = 5.0 Hz), 155.4, 152.9, 150.1, 138.9, 119.5, 88.6, 81.7 (d, J_{CP} = 5.6 Hz), 78.1 (d, J_{CP} = 10.6 Hz), 64.7, 62.9 (d, 2C, J_{CP} = 6.1 Hz), 52.5, 41.d (d, J_{CP} = 133.3), 40.5, 26.0 (3C), 25.5 (3C), 18.4, 17.8, 16.3 (d, 2C, J_{CP} = 5.6 Hz), –5.34, –5.39 (2C), -5.46; ^{31}P NMR ($CDCl_3$) +23.5; HR FAB MS calcd for $C_{29}H_{55}N_5O_8PSi_2$ 688.3327 (M^+ + H), found 688.3316.

Preparation of Enone 23. Dowex 50X8 resin (150 mg) was added to a solution of imidazolidine **21**[19] (100 mg, 0.17 mmol) in 50% aqueous THF (1.5 mL), and the mixture was stirred for 1 h at rt. The resin was removed by filtration and the filtrate was concentrated in vacuo and then dried under high vacuum overnight at 80 °C. The resulting foamy solid **22** was added in one portion to a stirred mixture of phosphonate **13** (33.6 mg, 0.05 mmol), oven-dried K_2CO_3 (11.4 mg), and 18-crown-6 (21.8 mg) in THF (1 mL), and then the mixture was stirred overnight at rt. The resulting solution was diluted with EtOAc (3 mL) and washed with brine (0.5 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to give a yellow gum. Purification by radial chromatography (4:1 EtOAc and hexane, followed by 39:1 $CHCl_3$ and CH_3OH) afforded dinucleotide analogue **23** as a pale yellow solid (20.4 mg, 44%): ^{1}H NMR δ 9.12 (br s, 1H), 8.77 (s, 1H), 8.30 (s, 1H), 8.28 (s, 1H), 8.08 (s, 1H), 8.01–7.48 (m, 5H), 6.87 (dd, 1H, $J_{B5',A8'}$ = 15.9 Hz, $J_{B5',B4'}$ = 5.9 Hz), 6.20 (dd, 1H, $J_{B5',A8'}$ = 15.9 Hz, $J_{A8',B4'}$ = 1.4 Hz), 6.17 (d, 1H, $J_{1',2'}$ = 2.0 Hz), 6.00 (d, 1H, $J_{1',2'}$ = 1.5 Hz), 5.74 (br s, 2H), 5.51 (dd, 1H, $J_{2',3'}$ = 6.3 Hz, $J_{1',2'}$ = 2.0 Hz), 5.10 (dd, 1H, $J_{2',3'}$ = 6.3 Hz, $J_{3',4'}$ = 4.2 Hz), 4.78 (m, 1H), 4.65 (dd, 1H, $J_{2',3'}$ = 4.8 Hz, $J_{1',2'}$ = 1.5 Hz), 4.01 (m, 2H), 3.73 (dd, 1H, $J_{5'a,5'b}$ = 11.2 Hz, $J_{5'b,4'}$ = 3.4 Hz), 2.80–2.95 (m, 2H), 2.47 (dd, 1H, $J_{6'a,6'b}$ = 17.3 Hz, $J_{6'b,3'}$ = 3.6 Hz), 1.64 and 1.40 (2s, 6H), 0.88 and 0.85 (2s, 18H), 0.14, 0.07, 0.06, and –0.09 (4s, 12H). Anal. Calcd for $C_{45}H_{62}N_{10}O_9Si_2 \cdot 2H_2O$: C, 56.11; H, 6.91; N, 14.54. Found: C, 56.29; H, 6.70; N, 14.39.

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Nucleophilic Aromatic Substitution on Ester Derivatives of Carcinogenic *N*-Arylhydroxamic Acids by Aniline and *N,N*-Dimethylaniline

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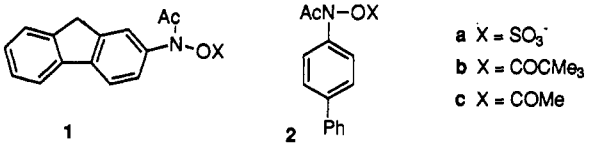
Decomposition of *N*-(pivaloyloxy)-2-(acetylamino)fluorene (**1b**) and *N*-(sulfonatooxy)-4-(acetylamino)-biphenyl (**2a**) in MeOH occurs predominately via N–O bond cleavage to yield oxazoles (**5, 6, 23**), methoxy adducts (**7, 8, 24, 25, 26**), and rearrangement products (**10b, 11b, 28**). Minor ester methanolysis paths lead to the *N*-arylhydroxamic acids (**9, 27**). In the presence of 0.1 M aniline (**3**), **1b** yields a number of adducts (**14–18**) identical to those previously obtained from the reaction of **3** with *N*-(sulfonatooxy)-2-(acetylamino)fluorene (**1a**). This occurs with no change in the rate constant for decomposition of **1b**. At 0.1 M **3** all solvolysis products of **1b**, except the rearrangement products **10b** and **11b**, are reduced below detectable levels. Similar results were obtained for **2a**, which yields the adducts **30–35** in the presence of **3** and **36–38** in the presence of *N,N*-dimethylaniline (**4**). These results are consistent with a mechanism (Scheme V) in which the N–O bond heterolysis leads to a tight ion pair that can undergo internal return to yield the rearrangement products or diffusional separation to yield the free ion. The free nitrenium ion can be trapped by solvent or added nucleophiles. Both the *N*-acetyl-*N*-(4-biphenylyl)nitrenium ion (**45**) and the *N*-acetyl-*N*-(2-fluorenyl)nitrenium ion (**48**) react slowly enough with the solvent to undergo selective reaction with strong nucleophiles. Since **1a**, **1b**, and **2a** span the reactivity range of the ester derivatives of the common *N*-arylhydroxamic acids which undergo N–O bond heterolysis in H_2O, it appears that all of the carcinogenic esters will react with simple aromatic amines via an S_N1 mechanism.

We are interested in the mechanisms of nucleophilic aromatic substitution on esters of *N*-arylhydroxylamines because these reactions are relevant to the problems of chemical carcinogenesis by hydroxylamine derivatives.[1,2] The factors which determine whether S_N1 or S_N2 mechanisms are followed in these nitrogen analogues to the well studied benzyl, 1-phenylethyl, or cumyl systems[3] is also of considerable fundamental interest.

The reactions of carcinogens derived from *N*-arylhydroxylamines with aromatic amines in MeOH serve as simple model systems for the interactions of these materials with the DNA bases.[4-6] We first discovered that a number of *N*-aryl-*O*-pivaloylhydroxylamines react efficiently with aniline or *N,N*-dimethylaniline in MeOH to yield diphenylamines or hydrazines by an S_N2 mechanism.[4] The reaction products were formed by direct nucleophilic attack on the nitrogen of the model carcinogen.[4] Subsequently, other workers demonstrated kinetically bimolecular reactions between a number of hydroxylamine derivatives and simple aromatic amines in THF or MeOH.[5] More recently, we found that the hepatacarcinogen *N*-(sulfonatooxy)-2-(acetylamino)fluorene (**1a**) reacts with



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aniline or *N,N*-dimethylaniline to yield a large number of adducts via an S_N1 pathway.[6] Most of the reaction products isolated in this case were formed by nucleophilic substitution on the aromatic ring.[6] The difference in behavior of these materials was attributed to a steric effect of the *N*-acetyl group which hindered the S_N2 attack of the aromatic amines.[6] The *N*-acetyl group also slows down the generation of the nitrenium ion, but once generated, the *N*-acetyl group has remarkably little effect on the subsequent reactions of the nitrenium ion.[7]

In an effort to determine if decreasing the reactivity of **1a** would lead to a change in the mechanism of this reaction, we have examined the reactions of *N*-(pivaloyloxy)-2-(acetylamino)fluorene (**1b**) and *N*-(sulfonatooxy)-4-(acetylamino)biphenyl (**2a**) with aromatic amines in MeOH. Both of these compounds are considerably less

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labile than **1a**.[7-9] Replacement of the SO_4^{2-} leaving group of **1a** with the pivalate leaving group of **1b** leads to a decrease in the rate of hydrolysis of about 400-fold,[8] and **2a** undergoes hydrolysis 95-fold more slowly than **1a** at 20 °C in 5% CH_3CN–H_2O.[7,9]

In spite of the decreased reactivity of **1b** and **2a**, the results reported in this paper show that the mechanism of reaction of these materials with aromatic amines is the same as that of the more reactive **1a**. These three compounds show remarkable similarity in their solvolysis in MeOH and their reactions with aniline or *N,N*-dimethylaniline which provides evidence for a common reaction mechanism under these conditions for all esters of carcinogenic *N*-arylhydroxamic acids. These results also have implications for the *in vivo* reactions of ester derivatives of *N*-arylhydroxamic acids.

Experimental Section

The synthesis of **1a** and **2a**, as their K^+ salts, the purification of the amines **3** and **4**, and the solvent MeOH have been described previously.[4,7,10]

***N*-(Pivaloyloxy)-2-(acetylamino)fluorene (1b).** A solution of 78.9 mg (0.33 mmol) of *N*-hydroxy-2-(acetylamino)fluorene (**9**)[11] and 38.4 μL (0.33 mmol) of *N*-ethylmorpholine in 2 mL of dry CH_2Cl_2 was stirred under a N_2 atmosphere at 0 °C, while a solution of 40.6 μL (0.33 mmol) of pivaloyl chloride in 0.5 mL of CH_2Cl_2 was added in a dropwise fashion. The reaction mixture was stirred for an additional 6 h at room temperature. The reaction mixture was washed with 5% aqueous $NaHCO_3$ (1 × 3 mL) and then with distilled H_2O (2 × 3 mL). The organic material was dried over Na_2SO_4, and the solvent was then removed by rotary evaporation. The gummy residue which remained was subjected to column chromatography on silica gel with a CH_2Cl_2/EtOAc (9/1) eluent. After evaporation of solvent, 85 mg (80%) of material was recovered: mp 96–98 °C; IR (KBr) 1771, 1688 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 7.93 (1H, d, J = 8.2 Hz), 7.89 (1H, d, J = 7.0 Hz), 7.65 (1H, d, J = 1.9 Hz), 7.58 (1H, d, J = 7.5 Hz), 7.44 (1H, dd, J = 8.2, 1.9 Hz), 7.39 (1H, t, J = 7.0 Hz), 7.33 (1H, t, J = 7.4 Hz), 3.92 (2H, s), 2.06 (3H, s), 1.26 (9H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6, 70 °C) δ 174.5, 166.5, 143.5, 143.1, 140.7, 139.7, 137.6, 126.8, 126.5, 124.7, 123.9, 122.0, 119.9, 119.8, 37.4, 36.1, 26.1, 20.9; high-resolution MS *m/e* 323.1558, $C_{20}H_{21}NO_3$ requires 323.1521.

Kinetics. The kinetics of the decomposition of **1b** and **2a** were monitored in MeOD-d_4 (99.8% deuterated) at 50 °C in the presence or absence of **3** or **4** (0.1–0.2 M) by ^1H NMR spectroscopy at 300 MHz as previously described for **1a**.[6] Initial concentrations of **1b** and **2a** were ca. 4 mM. For **1b**, the singlets due to the *tert*-butyl group of the starting material and its decomposition products, which appear in the range from ca. δ 1.5 to 1.2, were used to monitor concentrations. For **2a**, the singlets of the acyl methyl groups of the starting material and its decomposition products, which appear from ca. δ 2.6 to 1.9, were utilized. In one experiment, 4 mM $KHSO_4$ was added to the MeOD-d_4 prior to monitoring the decomposition of **1b**. Kinetic data were handled as described in the earlier paper.[6]

Products. Reaction products were isolated from larger scale reactions (ca. 5 mM in **1b** or **2a**, 50 mL volume) in the presence or absence of 1.0 M **3** or **4** in dry MeOH. The reactions were performed under a N_2 atmosphere at 50 °C. Reactions were allowed to continue for 7–10 half-lives as determined from the kinetics experiments described above. Details of product separations were described in the earlier paper.[6] Characterization of individual reaction products for **1b** and **2a** is described below.

Quantification of reaction products was performed by ^1H NMR of the kinetic reaction mixtures after 10 half-lives, as calculated from the kinetic data. ^1H NMR spectra of each of the reaction products were taken in MeOD-d_4 under the kinetic conditions to provide reliable chemical shift standards. Identification of products in the kinetic mixtures was based on chemical shift coincidences of at least two well resolved peaks for each compound. In all cases agreement between the standard and reaction mixture resonances was ±0.005 ppm. Identities of reaction products were also confirmed by HPLC comparison with authentic samples as described earlier.[6]

Products of 1b. Most of the reaction products observed for **1b** were identical to those previously reported for **1a**.[6] Only the two rearrangement products **10b** and **11b** and the 3-methoxy compound **8** were not previously reported. The isomers **10b** and **11b** were not easily separated by chromatography, so authentic samples of each were prepared from the corresponding hydroxy compounds. An authentic sample of **8** was also prepared.

3-Methoxy-2-(acetylamino)fluorene (8). Treatment of 25 mg of 3-hydroxy-2-(acetylamino)fluorene[9] dissolved in 5 mL of EtOH with a large excess of diazomethane for 24 h led to recovery of 26 mg of crude product after the reaction mixture was quenched with AcOH and evaporation of all solvents. The material was purified by chromatography on silica gel with CH_2Cl_2/EtOAc (3/1) eluent to provide 23 mg (87%) of product: mp 155–156 °C; IR (KBr) 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (1H, s), 7.84 (1H, s, broad), 7.65 (1H, d, J = 7.4 Hz), 7.49 (1H, d, J = 7.3 Hz), 7.33 (1H, t, J = 7.3 Hz), 7.25 (1H, s), 7.23 (1H, t, J = 7.3 Hz), 3.96 (3H, s), 3.82 (2H, s), 2.21 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.1 (C), 147.3 (C), 144.0 (C), 141.7 (C), 136.8 (C), 135.8 (C), 126.8 (C), 126.6 (CH), 126.0 (CH), 124.9 (CH), 119.0 (CH), 116.2 (CH), 101.5 (CH), 55.9 (CH_3), 36.7 (CH_2), 25.0 (CH_3); high-resolution MS *m/e* 253.1107, $C_{16}H_{15}NO_2$ requires 253.1103.

3-(Pivaloyloxy)-2-(acetylamino)fluorene (10b). This compound was synthesized from 3-hydroxy-2-(acetylamino)fluorene[9] as described above for **1b**. The crude product was purified by chromatography on silica gel with EtOAc/hexanes (1/1) eluent: mp 182–184 °C; IR (KBr) 1748, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.65 (1H, d, J = 7.3 Hz), 7.50 (1H, d, J = 7.3 Hz), 7.45 (1H, s), 7.33 (1H, t, J = 7.3 Hz), 7.27 (1H, t, J = 7.3 Hz), 7.16 (1H, s, broad), 3.86 (2H, s), 2.16 (3H, s), 1.43 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.4 (C), 167.9 (C), 143.7 (C), 141.1 (C), 140.8 (C), 140.2 (C), 138.6 (C), 128.3 (C), 126.7 (CH), 126.7 (CH), 125.0 (CH), 119.7 (CH), 119.3 (CH), 113.3 (CH), 39.4 (C), 36.8 (CH_2), 27.2 (CH_3), 24.5 (CH_3); high-resolution MS *m/e* 323.1516, $C_{20}H_{21}NO_3$ requires 323.1521.

1-(Pivaloyloxy)-2-(acetylamino)fluorene (11b). This material was synthesized as described above for **1b** from 1-hydroxy-2-(acetylamino)fluorene.[9] The crude product was purified by chromatography on silica gel with EtOAc/hexanes (1/1) eluent: mp 178–180 °C; IR (KBr) 1750, 1650 cm^{-1}; ^1H NMR (300 MHz), $CDCl_3$) δ 8.03 (1H, d, J = 8.2 Hz), 7.72 (1H, d, J = 7.5 Hz), 7.62 (1H, d, J = 8.2 Hz), 7.47 (1H, d, J = 7.3 Hz), 7.35 (1H, t, J = 7.3 Hz), 7.27 (1H, t, J = 7.4 Hz), 7.08 (1H, s, broad), 3.70 (2H, s), 2.15 (3H, s), 1.46 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.6 (C), 168.0 (C), 142.5 (C), 141.0 (C), 140.2 (C), 138.6 (C), 135.2 (C), 128.4 (C), 126.9 (CH), 126.8 (CH), 124.9 (CH), 122.8 (CH), 120.0 (CH), 117.9 (CH), 39.6 (C), 34.5 (CH_2), 27.2 (CH_3), 24.4 (CH_3); high-resolution MS *m/e* 323.1524, $C_{20}H_{21}NO_3$ requires 323.1521.

Products of 2a. Products of the solvolysis of **2a** included three methoxy adducts **24–26**. An authentic sample of one of these (**24**) was available from an earlier study.[12] Authentic samples of the other two were independently synthesized. Authentic samples of **27–29** were available from previous studies.[7,12] Characterization of **23** and synthesis of **25** and **26** follows.

2-Methyl-6-phenylbenzoxazole (23). After initial recovery from reaction mixtures, this material was purified by recrystallization from MeOH: mp 58–61 °C; IR (KBr) 1611, 1580 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.70 (1H, d, J = 1.7 Hz), 7.67 (1H, d, J = 8.3 Hz), 7.67–7.61 (2H, m), 7.55 (1H, dd, J = 8.3, 1.7 Hz), 7.49–7.43 (2H, m), 7.39–7.33 (1H, m), 2.63 (3H, s); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 164.8 (C), 152.1 (C), 141.5 (C), 141.2 (C), 138.5

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