Pergamon

Tetrahedron, Vol. 53, No. 32, pp. 11033-11038, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00363-3

Synthesis of Bis-Abasic Cyclic Dinucleotide, Bis-(3→5)-Cyclic Bis(1,4-Anhydro-2-Deoxy-D-*erythro*-Pentitol-3-Phosphate), an Inhibitor of HIV-1 Integrase§

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Abstract: Bis-abasic cyclic dinucleotide, bis-(3→5)-cyclic bis(1,4-anhydro-2-deoxy-D-*erythro*-pentitol-3-phosphate) (**1**), was prepared from 2-deoxy-D-ribose in nine convergent steps, in 18% overall yield. © 1997 Elsevier Science Ltd.

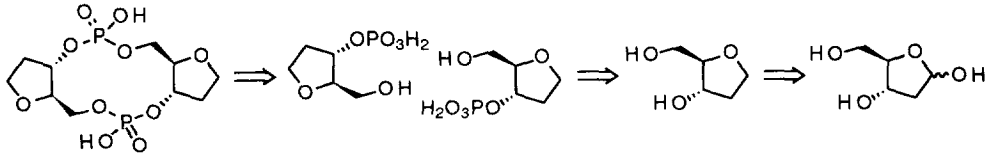
Because the catalytic domain of *Escherichia coli* DNA-dependent RNA polymerase contains two equivalent active sites arranged about a two-fold axis of symmetry, the enzyme translocates itself along the growing RNA polymer in a rotational manner,[1] and bis-(3'→5')-cyclic dinucleotides are sequence-dependent linear competitive inhibitors of the initiation phase of transcription.[2] The possibility that a similar active site topology and mechanism of translocation might be operational in eukaryotic RNA polymerase II or HIV-1 reverse transcriptase is currently being investigated.[3] It has been shown in certain cases, however, that individual nucleotide bases contribute little to the binding of nucleotides to enzyme active sites. In the case of *E. coli* RNA polymerase, for example, ribose 5-diphosphate and ribose 5-triphosphate are competitive inhibitors and have enzyme affinities comparable to those of the natural nucleotide substrates.[4]

We have prepared C_2-symmetric, bis-abasic cyclic bis(deoxyribonucleotide), **1**, as a potential inhibitor of oligonucleotide processing enzymes, including HIV-1 integrase. Our synthesis is quite general and readily adaptable for the preparation of analogs of **1**. Either **1** or derivatives of **1** may be effective inhibitors of the growth of viruses, bacteria, or tumor cells.

RESULTS AND DISCUSSION

Symmetry suggested that dimerization of suitably protected 1,4-anhydro-2-deoxy-D-*erythro*-pentitol 3-phosphate (**2**) would be a logical route to **1** (Scheme 1). Compound **2** was envisioned as proceeding from 1,4-anhydro-2-deoxy-D-*erythro*-pentitol (**3**), which in turn could be derived by reduction of commercially available 2-deoxy-D-ribose (2-deoxy-D-*erythro*-pentose, **4**). We expected that formation of the twelve-

Scheme 1



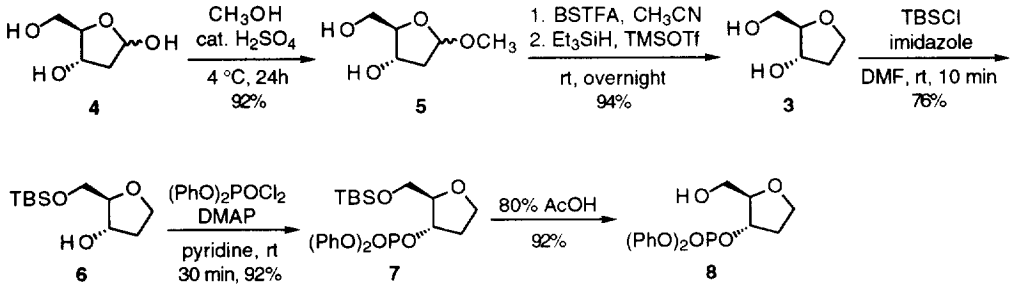
1 **2** **3** **4**

§This paper is dedicated with respect and affection to Professor Samuel J. Danishefsky, in recognition of his enormous contributions as a scientist, scholar, and teacher.

membered macrocycle would be challenging but were confident that methodology used for the preparation of cyclic dinucleotides[5] would be applicable to our work.

Synthesis of the monomeric species that would eventually be coupled to produce **1** (Scheme 2) began with the acid-catalyzed glycosidation[6] of **4** to give methyl 2-deoxy-D-*erythro*-pentofuranoside (**5**) as a mixture of anomers in 92% yield. Compound **5** was then reduced in a two-step process to give **3** in 94% yield. *In situ* silylation of the two hydroxyl groups by *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) preceded Lewis acid-catalyzed reduction of the methyl acetal by triethylsilane.[7] Selective protection of the primary hydroxyl of **3** as the *tert*-butyldimethylsilyl (TBS) ether[8] produced **6** in 76% yield. Phosphorylation[9] of **6** occurred readily (92% yield) and was followed by desilylation[10] to give 1,4-anhydro-2-deoxy-D-*erythro*-pentitol 3-diphenylphosphate (**8**) in 92% yield (56% overall yield from **4**).

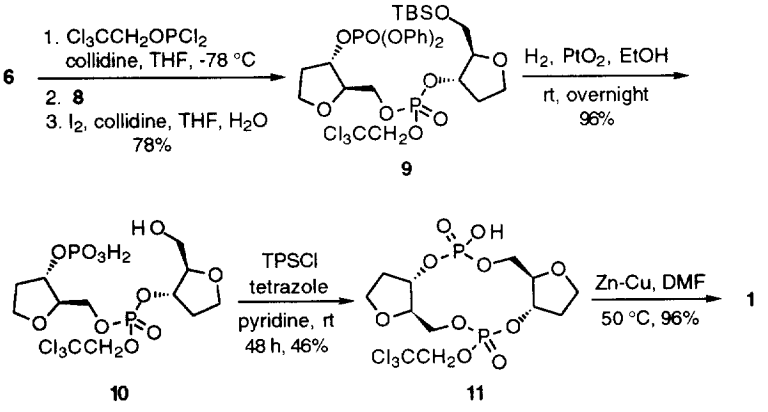
Scheme 2



Formation of the acyclic dinucleotide **9** (Scheme 3) was accomplished by phosphitylation of **6** with 2,2,2-trichloroethyl phosphodichloridite, reaction of the intermediate thus formed with **8**, and subsequent oxidation of the phosphite triester with iodine[11] to give the phosphate triester in 78% yield. Hydrogenolysis of the diphenyl phosphate ester generated the free acid, which promoted concomitant cleavage of the TBS ether, giving **10** in 96% yield. Attempts to couple **6** and **8** as the hydrogen phosphonate diester[12] failed because of hydrolysis of the silyl group prior to attachment of **8**. If successful, the hydrogen phosphonate method would have shortened the synthesis by one step, by obviating the final deprotection step.

Cyclization of **10** using 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl)[13] under dilute conditions[5]

Scheme 3



gave **11** in moderate (46%) yield. The yield is a reflection not so much of the efficiency of cyclization as of the difficulty of isolating and purifying the product. The absence of nonpolar nucleotidyl bases in the product madeseparating **11** from 2,4,6-triisopropylbenzenesulfonic acid difficult. Attempts to cyclize using other dehydrating reagents, such as pivaloyl chloride[12] or dicyclohexylcarbodiimide,[14,15] gave low (< 10%) yields or were completely unsuccessful.

Finally, reductive removal of the trichloroethyl protecting group, using zinc-copper alloy,[16,17] gave **1** in 96% yield (18% overall yield from 2-deoxy-D-ribose). Compound **1** is one of the most potent cyclic dinucleotide or analog inhibitors of HIV-1 integrase (IC_{50} = 130 μM for strand transfer).[18]

EXPERIMENTAL SECTION

All reagents and chemicals were purchased from Sigma or Aldrich. THF was distilled under argon from sodium and benzophenone. Acetonitrile was distilled under argon from calcium hydride. Pyridine was dried over activated 3-Å molecular sieves. Anhydrous DMF was purchased from Aldrich. All reactions were performed in oven-dried glassware under an atmosphere of argon. Unless noted otherwise, NMR spectra were recorded at nominal ^1H, ^{13}C and ^{31}P resonance frequencies of 250, 62.9 and 101 MHz, respectively, using $CDCl_3$ as solvent. All ^{31}P NMR spectra were referenced externally to 85% H_3PO_4. FAB-MS were recorded using Cs^+ (20 eV) as the ionizing beam and either glycerol or *p*-nitrobenzyl alcohol—with or without added NaI—as the matrix. Elemental analysis was performed by Robertson Microlit Laboratories, Inc. TLC was performed on normal phase plates from either Analtech (Silica Gel HL) or Whatman (K6F Silica Gel 60 Å). Compound spots were visualized by dipping plates in either *p*-anisaldehyde or ammonium molybdate-ceric sulfate stain and heating. Column chromatography was performed on Merck grade 9385, 230-400 mesh, 60-Å silica gel. Anion exchange chromatography was performed on Dowex-1×8-100 (HCO_3^-) resin.

Methyl 2-Deoxy-D-*erythro*-pentofuranoside (5). To 3.11 g (22.5 mmol) of 2-deoxy-D-ribose in 30 mL of methanol, at 0 °C, were added 20 mL of methanol containing 313 μL of concentrated sulfuric acid.[6] After the reaction had sat overnight at 4 °C, TLC (95% aqueous acetonitrile) indicated disappearance of starting material (R_f 0.52) and formation of anomeric products (R_f 0.63 and 0.73). The reaction was quenched by stirring with 28 mmol equiv of Amberlite IRA-400 (OH^-) for 30 min. The reaction mixture was then filtered and evaporated under reduced pressure at 35 °C. Purification of the residue by silica gel chromatography (hexanes-ethyl acetate 1:1) yielded 2.91 g (89%) of **5** as a clear oil (4:1 mixture of anomers): ^1H NMR δ 5.13 (m, 0.8H, H-1 major anomer), 4.78 (t, *J* = 2.8 Hz, 0.2H, H-1 minor anomer), 4.54, 4.20-4.06 and 3.87-3.57 (3m, 4H), 3.40 (s, 2.4H, OCH_3 major anomer), 3.35 (s, 0.6H, OCH_3 minor anomer), 2.89-1.82 (m, 4H); IR ($CDCl_3$) 3423, 1216, 756 cm^{-1}; FAB-MS *m/z* 171 ($M + Na^+$), 117. Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.36; H, 8.35.

1,4-Anhydro-2-deoxy-D-*erythro*-pentitol (3). To a 250-mL round-bottom flask were added 1.40 g (9.45 mmol) of **5**, 1.4 mL of acetonitrile, and 19 mmol of BSTFA.[7] The flask was sealed and heated at 78-80 °C. After 3 h, TLC (ethyl acetate-isopropanol 19:1) indicated conversion of **5** (R_f 0.50) to the silylated intermediate (R_f 0.99). The mixture was cooled to rt. Triethylsilane (47 mmol) and trimethylsilyl triflate (47 mmol) were added successively by syringe. After the reaction had stirred overnight, TLC indicated conversion of the intermediate to product (R_f 0.66). The reaction was quenched with 50 mL of water and neutralized by addition of 52.0 mmol equiv of Dowex-1×8-100 (OH^-). After stirring for 30 min, the reaction was filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by silica gel chromatography (ethyl acetate) yielded 1.07 g (96%) of **3** as a clear oil: ^1H NMR δ 4.27 (ddd, *J* = 3.3, 3.5, 6.7 Hz, 1H), 3.96 (dd, *J* = 5.5, 8.4 Hz, 2H), 3.84 (m, 1H), 3.64 (s, 1H), 3.62 (d, *J* = 1.6 Hz, 1H), 3.54 (br s, 2H), 2.11 (m, 1H), 1.91 (m,

1H); ^{13}C NMR δ 86.3, 72.9, 67.1, 62.8, 35.1; IR ($CDCl_3$) 3387, 1256, 1100, 1031, 756 cm^{-1}; FAB-HRMS calcd for $C_5H_{11}O_3$ (M + H^+) 119.0715, found 119.0708.

1,4-Anhydro-2-deoxy-5-O-(tert-butyldimethylsilyl)-D-*erythro*-pentitol (6). To 380 mg (3.22 mmol) of **3** in 3.25 mL of anhydrous DMF were added 8.04 mmol of imidazole.[8,19] The reaction was stirred for 5 min, and then 4.03 mmol of *tert*-butyldimethylsilyl chloride were added. After 5 min, water was added to quench the reaction. TLC (ethyl acetate) indicated conversion of **3** (R_f 0.26) to monosilylated (R_f 0.65) and disilylated (R_f 0.98) products. The reaction mixture was transferred with chloroform to a separatory funnel and washed with water and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a yellow oil. Purification by silica gel chromatography (hexanes-ethyl acetate 5:1) gave 569 mg (76%) of **6** as a clear oil: ^1H NMR δ 4.24 (m, 1H), 3.89 (m, 2H), 3.71 (m, 1H), 3.65 (ddd, J = 3.0, 4.3, 10.5 Hz, 1H), 3.47 (ddd, J = 1.2, 6.0, 10.5 Hz, 1H), 2.05 (m, 1H), 1.81 (m, 1H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR δ 86.1, 73.8, 67.1, 64.1, 34.7, 25.8, 18.2, -5.5; IR (KBr) 3422, 1472, 1256, 1087, 835 cm^{-1}; FAB-HRMS calcd for $C_{11}H_{25}O_3Si$ (M + H^+) 233.1600, found 233.1573.

1,4-Anhydro-5-O-(*tert*-butyldimethylsilyl)-2-deoxy-D-*erythro*-pentitol 3-(Diphenylphosphate) (7). To 500 mg (2.15 mmol) of **6** in 5 mL of pyridine were added 0.65 mmol of DMAP, followed by 4.30 mmol of diphenyl phosphorochloridate added dropwise.[9] A white precipitate formed immediately. After the reaction had stirred for 30 min, TLC (hexanes-ethyl acetate 3:1) indicated conversion of **6** (R_f 0.45) to **7** (R_f 0.68). The reaction was quenched by addition of 1.5 mL of 1.0 N HCl, followed by 5 mL of 1.0 N $NaHCO_3$. The reaction mixture was transferred with diethyl ether to a separatory funnel, where it was washed successively with 1 M $CuSO_4$, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a slightly yellow oil. Column chromatography (hexanes-ethyl acetate 249:1, followed by 95:5) yielded 924 mg (92%) of **7** as a clear oil: ^1H NMR δ 7.37-7.16 (m, 10H), 5.17 (m, 1H), 4.03 (m, 2H), 3.88 (m, 1H), 3.67 (dd, J = 3.6, 11.0 Hz, 1H), 3.57 (dd, J = 4.5, 11.0 Hz, 1H), 2.13 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 150.4 (d, J_{CP} = 7.6 Hz), 129.7 (d, J_{CP} = 3.2 Hz), 125.3, 120.0 (d, J_{CP} = 3.2 Hz), 85.1 (d, J_{CP} = 6.3 Hz), 81.5 (d, J_{CP} = 6.5 Hz), 67.2, 63.5, 33.8 (d, J_{CP} = 4.0 Hz), 25.7, 18.1, -5.7, -5.6; ^{31}P NMR δ -11.93; IR ($CDCl_3$) 1490, 1215, 771 cm^{-1}; FAB-HRMS calcd for $C_{23}H_{34}O_6PSi$ (M + H^+) 465.1862, found 465.1841.

1,4-Anhydro-2-deoxy-D-*erythro*-pentitol 3-(Diphenylphosphate) (8). Compound **7** (729 mg, 1.56 mmol) was stirred in 28 mL of 80% aqueous acetic acid overnight.[10] The solution was concentrated *in vacuo* and purified by silica gel chromatography (ethyl acetate) to yield 501 mg (92%) of **8** as a clear oil: ^1H NMR δ 7.52-7.31 (m, 4H), 7.27-7.16 (m, 6H), 5.10 (m, 1H), 4.00 (m, 2H), 3.87 (m, 1H), 3.61 (m, 2H), 2.65 (br s, 1H), 2.13 (m, 2H); ^{13}C NMR δ 150.3, 129.8, 125.5, 120.0 (d, J_{CP} = 3.3 Hz), 85.0 (d, J_{CP} = 5.6 Hz), 80.9 (d, J_{CP} = 6.2 Hz), 67.2, 62.2, 34.1 (d, J_{CP} = 4.4 Hz); ^{31}P NMR δ -11.64; IR (KBr) 3439, 1590, 1489, 1283, 1189, 1024, 959, 756 cm^{-1}; FAB-HRMS calcd for $C_{17}H_{20}O_6P$ (M + H^+) 351.1009, found 351.0998.

1,4-Anhydro-2-deoxy-3-*O*-(diphenoxyphosphoryl)-D-*erythro*-pentitol 5-[1,4-Anhydro-2-deoxy-5-*O*-(*tert*-butyldimethylsilyl)-D-*erythro*-pentit-3-yl 2,2,2-Trichloroethyl Phosphate] (9). To 460 μL (3.4 mmol) of collidine and 120 μL (0.770 mmol) of 2,2,2-trichloroethyl phosphodichloridite[11] in 5.0 mL of THF, at -78 °C, was added dropwise over 2 min a solution of 191 mg (0.856 mmol) of **6** in 2.4 mL of THF. After 3 min, TLC (hexanes-ethyl acetate 1:1) indicated disappearance of **6** (R_f 0.74) and formation of a dialkyl phosphochloridite intermediate (R_f 0.85). Then, 150 mg (0.428 mmol) of **8** (R_f 0.19) in 1.4 mL of THF were added slowly to the reaction. After 15 min, TLC indicated disappearance of the first intermediate and appearance of a phosphite triester (R_f 0.57). The temperature of the reaction was raised

to -10 °C, and a solution of I_2 (195 mg, 0.770 mmol) and collidine (210 μL) in 12.0 mL of THF and 6.0 mL of water was added. The reaction mixture was stirred for an additional 15-20 min, concentrated to dryness *in vacuo*, and partitioned between water and diethyl ether. The combined organic layers were washed twice with 1 M $NaHSO_3$ and once with saturated NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography, using a stepwise gradient of hexanes-ethyl acetate (6:1 to 3:1) gave 258 mg (78%) of **9** as a clear oil that was a 4:1 mixture of diastereomers at phosphorous: ^{1}H NMR δ 7.39-7.18 (m, 10H), 5.12 (m, 1H), 5.04 (m, 1H), 4.64-4.55 (m, 2H), 4.24-4.12 (m, 3H), 4.09-4.01 (m, 3H), 3.90 (m, 2H), 3.73 (m, 1H), 3.60 (m, 1H), 2.15 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 150.4, 129.9, 125.6, 120.1 (d, J_{CP} = 4.6 Hz), 85.4 (d, J_{CP} = 5.3 Hz), 85.3 (d, J_{CP} = 5.6 Hz), 82.9 (m), 81.3 (m), 80.3 (m), 77.6, 76.8 (m), 67.9, 67.5, 63.5, 34.0, 33.9, 25.9, 18.3, -5.4, -5.5; ^{31}P NMR δ -2.35 (0.8P), -3.07 (0.2P), -11.4 (1P); IR ($CDCl_3$) 1591, 1489, 1215, 1025, 963, 769 cm^{-1}; FAB-HRMS calcd for $C_{30}H_{44}Cl_3O_{11}P_2Si$ (M + H$^+$) 775.1197, found 775.1194.

1,4-Anhydro-2-deoxy-3-O-(dihydroxyphosphoryl)-D-*erythro*-pentitol 5-[1,4-Anhydro-2-deoxy-D-*erythro*-pentit-3-yl 2,2,2-Trichloroethyl Phosphate] (10). A solution of **9** (200 mg, 0.26 mmol) and 15 mL of ethanol containing 23.4 mg of PtO_2 was purged with nitrogen and then placed briefly under a vigorous stream of hydrogen gas. After the reaction had stirred overnight, TLC (hexanes-ethyl acetate 3:1) indicated disappearance of **9** (R_f 0.4). The solution was filtered and adjusted to pH 8 with dilute aqueous sodium hydroxide. The solution was loaded onto a 50-mL column of Dowex-1 (HCO_3^-) and eluted with 200 mM ammonium bicarbonate. The eluant was evaporated under reduced pressure at 30 °C and then dried for 12 h under vacuum to yield 136 mg (96%) of the monoammonium salt of **10** as a clear oil. The product was converted to the monopyridinium salt by treating a solution of **10** in 50% aqueous methanol with Dowex-50W (H$^+$), filtering, and then raising the pH to 4.2 with pyridine: ^{1}H NMR (400 MHz, methanol-d_4) δ 8.77 (br s, 2H), 8.41 (tt, J = 1.3, 7.8 Hz, 1H), 7.91 (dd, J = 6.2, 7.6 Hz, 2H), 6.17 (dt, J = 1.0, 5.3 Hz, 1H), 4.95 (m, 1H), 4.73 (m, 1H), 4.41-4.38 (m, 2H), 4.25-4.09 and 4.04-3.98 (2m, 5H), 3.95-3.84 (m, 2H), 3.59 (ddd, J = 0.5, 4.4, 11.7 Hz, 1H), 3.53 (ddd, J = 1.1, 4.8, 11.9 Hz, 1H), 2.21-2.04 (m, 4H); ^{13}C NMR (101 MHz, methanol-d_4) δ 84.5 (m), 78.7 (m), 72.7 (m), 69.8 (m), 68.4 (2C), 68.2, 68.1, 64.9 (m), 63.1 (m), 34.8, 34.7; ^{31}P NMR (162 MHz, methanol-d_4) δ 0.76 (br s, 1P), -2.38 (m, 0.8P), -2.68 (m, 0.2P); IR (KBr) 3446, 1256, 1096, 1024, 933 cm^{-1}; FAB-HRMS (negative ion) calcd for $C_{12}H_{20}C_{13}O_{11}P_2$ (free acid - H$^+$) 506.9527, found 506.9546.

2,2,2-Trichloroethyl [Bis-(3→5)-cyclic Bis(1,4-anhydro-2-deoxy-D-*erythro*-pentitol-3-phosphate)] (11). To a solution of TPSCl (73.5 mg, 0.235 mmol) and tetrazole (49.5 mg, 0.706 mmol) in 7.8 mL of anhydrous pyridine were added dropwise 800 μL of anhydrous pyridine containing 20 mg (0.039 mmol) of **10**.[13] The final concentration of **10** was 5.0 mM.[5] After 16 h, TLC ($CHCl_3$-methanol 1:1) showed conversion of **10** (R_f 0.28) to product (R_f 0.53). After 48 h, water was added to the reaction, and the solvent was removed by rotary evaporation at 35 °C. The residue was transferred to a separatory funnel and partitioned between water and diethyl ether. The aqueous layers were combined and concentrated to yield a white solid. Column chromatography (acetonitrile-methanol, 300 mL of 48:2, followed by 100 mL of 43:7) yielded 8.8 mg (46%) of **11** as a white solid that was a 4:1 mixture of diastereomers. A solution of **11** was adjusted to pH 4.5 with aqueous sodium hydroxide to generate the sodium salt: ^{1}H NMR (free acid, 400 MHz, methanol-d_4) δ 6.22 and 6.17 (2t, J = 5.2 Hz, 1H), 5.18 and 5.12 (2m, 1H), 4.86-4.76 (m, 1H), 4.45-4.39 (m, 2H), 4.24-4.20 and 4.14-4.03 (2m, 2H), 4.00-3.87 (m, 6H), 3.86-3.72 (m, 1H), 2.33-2.09 (m, 4H); ^{13}C NMR (sodium salt, 101 MHz, D_2O) δ 84.0-83.9 (m), 83.6-83.4 (m), 81.5-81.3 (m), 80.5, 78.4-77.9 (m), 72.9-72.7 (m), 70.5-70.3 (m), 68.5-68.0 (m), 67.3-67.2 (m), 64.5, 34.7-34.4 (m), 34.2-34.1 (m); ^{31}P NMR (sodium salt,

162 MHz, D_2O) δ 0.31 (1P), -2.22 (0.8P), -3.23 (0.2P); IR (KBr) 3163, 1404, 1252 cm^{-1}; FAB-HRMS (negative ion) calcd for $C_{12}H_{18}Cl_3O_{10}P_2$ (free acid - H^+) 488.9474, found 488.9441.

Bis-(3→5)-cyclic Bis(1,4-Anhydro-2-deoxy-D-*erythro*-pentitol-3-phosphate) (1). Compound **11** (5.8 mg, 12 μmol) was stirred in 1.5 mL of anhydrous DMF with 33 mg of zinc-copper couple.[16,17] After two days, water was added. The heterogeneous solution was filtered, and the solids were washed with water and methanol. The filtrate and washings were evaporated *in vacuo* , and the residue was dissolved in 5-10 mL of water. The resulting solution was adjusted to pH 9 with aqueous sodium hydroxide, adjusted to a final volume of 40-50 mL with 50% aqueous methanol, and loaded onto a 20-mL column of Dowex-1 (HCO_3^-). The column was rinsed through with 50 mL of 50% aqueous methanol and 50 mL water and then eluted with 150 mL of 65 mM ammonium bicarbonate in 50% aqueous ethanol, followed by 150 mL of 200 mM aqueous ammonium bicarbonate. The fractions containing 200 mM ammonium bicarbonate were concentrated *in vacuo* to yield 4.5 mg (96%) of the diammonium salt of **1** as a white solid: ^1H NMR (400 MHz, D_2O) δ 4.58 (m, 2H), 3.87-3.76 (m, 10H), 2.24 (m, 2H), 1.98 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ 82.2 (m), 74.8 (m), 67.5, 63.2, 33.2; ^{31}P NMR (162 MHz, D_2O) δ 0.35; IR (KBr) 3441, 1645, 1404, 1224, 1071, 923 cm^{-1}; FAB-HRMS (negative ion) calcd for $C_{10}H_{17}O_{10}P_2$ (free acid - H^+) 359.0303, found 359.0297.

ACKNOWLEDGMENTS

We thank Dr. Gordon Nicol for FAB-MS data and Laura Chafin for help in preparing this manuscript. This work was supported, in part, by the University of Delaware Research Foundation.

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(*Received* 23 *August* 1996; *revised* 27 *September* 1996; *accepted* 30 *September* 1996)