Synthesis of 2-Chloro-2′-5′-dideoxy-5′-difluoromethylphosphinyladenosine: A Nonhydrolyzable Isosteric, Isopolar Analog of 2-Chlorodeoxyadenosine Monophosphate

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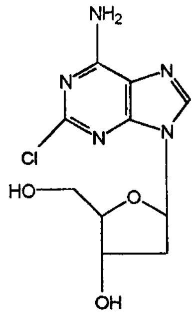
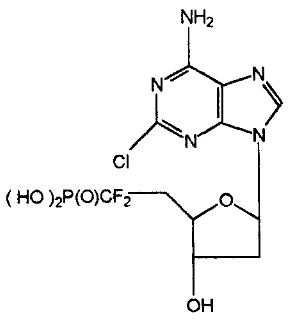
2-Chloro-2′-5′-dideoxy-5′-difluoromethylphosphinyladenosine (**5**) was synthesized in thirteen steps from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranoside (**1**), a carbohydrate which is substituted differently at the 2- and 3-positions, making possible selective deprotection and reductive deoxygenation at the 2′-position of a nucleoside subsequent to glycosylation. Purine nucleoside phosphonate **5** is an analog of the monophosphate ester of the potent, clinically effective immunomodulatory agent 2-chlorodeoxyadenosine (2-CdA), and was synthesized to present a potential means of circumventing drug resistance in target immune cells.

2-Chlorodeoxyadenosine (2-CdA) has been shown to be an effective chemotherapeutic agent in the treatment of refractory chronic lymphocytic leukemia (CLL)[3-6] and in hairy cell leukemia (HCL).[2,4,6] However, the biochemical basis for the clinical efficacy of 2-CdA has not been clearly established. It is known that, in vitro, 2-CdA is toxic only as a nucleotide, that 2-CdA is phosphorylated by deoxycytidine kinase (dCK), and that mutant lymphoblastoid cells lacking dCK are not susceptible to 2-CdA chemotherapy.[7-9] The cellular levels of 5′-nucleotidase (5′-NT), the enzyme responsible for the dephosphorylation of 2-CdA-5′-monophosphate (2-CdAMP), relative to those of dCK, are putative determinants of response to 2-CdA chemotherapy.[8,9] There are significant populations of CLL and HCL patients who are not responsive to 2-CdA, due to either elevated levels of 5′-NT and/or lack of dCK.[8]

These nonresponders, with mutant lymphoblast phenotypes having either severe diminution or complete lack of dCK expression, would benefit from a 2-CdA chemotherapy regimen in which 2-CdA were delivered as the nucleotide. One potentially useful approach to this problem is the synthesis of nonhydrolyzable nucleotide analogs,[10] which bypass the requirement for nucleoside kinase activation, and cannot be dephosphorylated to the nucleosides by 5′-NT.



2-CdA



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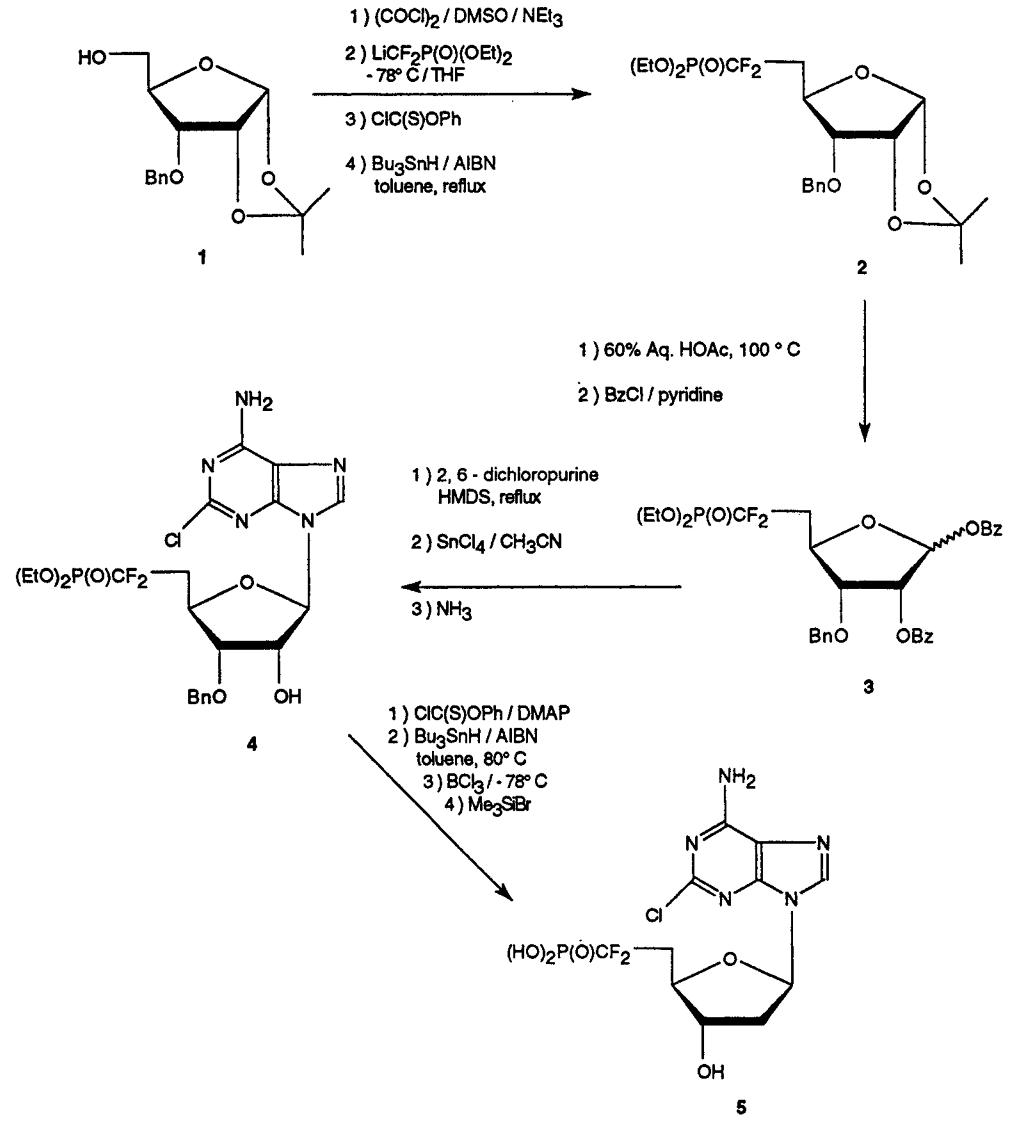
The target we chose as a nonhydrolyzable 2-CdA-5′-monophosphate (2-CdAMP) analog was **5**. A feature of **5** which provided an impetus for its synthesis was the use of a difluoromethylene group as the isosteric bridge between the ribose and phosphate moieties. The difluoromethylene substituent could be considered to be an isopolar as well as an isosteric replacement of the bridging phosphate oxygen, and has been shown and claimed to result in phosphate analogs which resemble phosphate ester linkages more closely than analogs having an unsubstituted methylene group as the replacement for oxygen.[11-14] We[15] and another group[16] have reported the synthesis of purine ribonucleotide analogs having a structure analogous to **5**. The work we report here concerns the synthesis of a carbohydrate which is adequately substituted for synthesis of either ribo- or deoxyribonucleotide analogs, and initial studies on the purine glycosylation chemistry of carbohydrate **3** (Scheme), leading to an isosteric, isopolar analog of 2-CdAMP.

The strategy we used for incorporation of a difluoromethyl phosphonate functionality at the 5′-position of ribose (Scheme) was based on methodology developed by Martin et al.[17] An alternate method based on direct displacement of primary triflate esters by diethyl difluoromethylphosphinyllithium has been reported by Berkowitz et al.[18] This method was successfully implemented in a previously reported synthesis of intermediate **2**,[16] giving the product in 96 % yield on a one gram scale. However, our attempts to synthesize **2** using this method were not successful, even on a moderate scale, and we therefore chose Martin's two-step method as a means of preparing **3** on a large scale. Swern oxidation[19] of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranoside (**1**)[18,20] gave the corresponding 5-aldehyde in 83 % yield. Addition of this aldehyde to a THF solution of diethyl difluoromethylphosphinyllithium, at −78 °C, followed by trapping of the adduct with phenyl chlorothionocarbonate and then reductive deoxygenation of the resulting thionocarbonate ester with tributyltin hydride gave the previously reported[16,18] 3-*O*-benzyl-5-deoxy-5-difluoromethylphosphinyl-1,2-*O*-isopropylidene-D-ribofuranoside (**2**) in 48 % yield. The isopropylidene group was then cleaved by heating in 60 % aqueous acetic acid, and treatment of the deprotected compound with benzoyl chloride in pyridine afforded **3** in 57 % yield. Carbohydrate **3** was then used in purine glycosylation studies.

Earlier investigations involving glycosylation of pyrimidine bases with ribose-5-phosphonate substrates,[21] in addition to previous work done by us[15] and others[16] with purine bases had determined that Vorbruggen glycosylation[22] of substrates containing the difluoromethylphosphonate moiety required three equivalents of tin(IV) chloride in order for the glycosylation to go to completion. Other Lewis acids tried, boron trifluoride–diethyl ether complex and trimethylsilyl trifluoromethanesulfonate, resulted mainly in decomposition of starting mate-



Scheme

rial. Treatment of **3** with three equivalents of tin(IV) chloride in the presence of silylated 2,6-dichloropurine at room temperature gave a nucleoside as the major product in 23% yield.

Concomitant 2′-deblocking and amination of the 6-position of the purine ring using liquid ammonia gave selectively 3′-protected ribonucleotide analog **4** having a UV $\lambda_{max} = 265$ nm, characteristic of a glycosidic linkage between N-9 of 2-chloroadenine and the ribose ring,[23] in 58% yield. Compound **4** was then converted to the corresponding 2′-phenylthionocarbonate ester and reductively deoxygenated according to the method of Robins et al.[24] in 55% isolated yield. Treatment of this 2′-deoxygenated product with boron trichloride in dichloromethane at −78 °C,[25] followed by reaction with bromotrimethylsilane cleaved the sugar benzyl and phosphonate ethyl groups, respectively. The product was desilylated to give crude **5**, which was purified using HPLC and isolated as its disodium salt in 53% yield.

Compound **5** was tested for cytotoxicity in both wild-type and deoxycytidine kinase-deficient T cells, and was found not be appreciably cytotoxic in either cell type. A subsequent HPLC study indicated that compound **5** was distributed equally between the extracellular and intracellular spaces. No peaks corresponding to the diphosphate or triphosphate analogs of **5** were detected in this study, indicating that the phosphorylation of **5** proceeds, if at all, with difficulty inside T cells.

In summary, a nonhydrolyzable, isosteric, isopolar analog of 2-chloroadenosine monophosphate **5** was synthesized from the appropriately functionalized ribose intermediate **1** in thirteen steps. Nucleotide analog **5** represents a possible chemotherapeutic treatment of T cell malignancies for patients who do not respond to 2-CdA chemotherapy. In addition, the route developed to this deoxyribonucleotide analog can be considered to be a model procedure, on which the syntheses of other nonhydrolyzable 2′-deoxynucleotide analogs may be based.

All chemicals were of reagent grade. CH_2Cl_2 was dried by distillation from CaH_2 and stored in an Ar atmosphere over 4 Å molecular sieves. THF was dried by distillation from potassium benzophenone ketyl in an Ar atmosphere and used immediately after distillation. DMSO was dried by low vacuum distillation from CaH_2 and was stored in an Ar atmosphere over 4 Å molecular sieves. Drying of organic phases was done using anhyd $MgSO_4$. Unless otherwise specified, chromatographic purification of products was accomplished by adsorption to coarse (60–200 mesh) silica gel, application to a column of flash silica gel, and elution under an air pressure of 15 psi. Diethyl difluoromethylphosphonate was synthesized by a previously described procedure.[26]

Ultraviolet spectra were measured on a Kontron Uvikon 930 spectrophotometer. NMR spectra were recorded on a Varian Unity 500 spectrometer. Mass Spectra were recorded at the Southern California Mass Specroscopy Facility at the Department of Chemistry of the University of California, Riverside. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ.

3-*O*-Benzyl-5-deoxy-5-difluoromethylphosphinyl-D-ribofuranoside (2):

A solution of anhyd DMSO (40 mL, 0.563 mol) in anhyd CH_2Cl_2 (100 mL) was added to a solution of oxalyl chloride (17.2 mL, 0.197 mol) in anhyd CH_2Cl_2 (150 mL) at $-78\,^{\circ}C$ and the mixture was stirred 10 min at $-78\,^{\circ}C$. Then a solution of **1**[20] (48.2 g, 0.172 mol) in CH_2Cl_2 (250 mL) was added dropwise, and the mixture stirred 15 min at $-78\,^{\circ}C$. Et_3N (150 mL, 1.07 mol) was then added, the mixture warmed to r.t. To this mixture water (300 mL) was added, the organic phase separated, dried, concentrated and chromatographed (50 % EtOAc/hexanes) to give the intermediate aldehyde as a viscous syrup (40.3 g, 84 %).

^1H NMR ($CDCl_3$): $\delta = 9.62$ (s, 1 H, H-5), 7.38–7.26 (m, 5 H, aromatic), 5.75 (d, 1 H, $J = 3$ Hz, H-1), 5.67 (d, 1 H, $J = 3$ Hz, H-2), 4.73 (d, 1 H, benzylic), 4.56 (d, 1 H, benzylic), 4.22 (dd, 1 H, $J = 4$, 9 Hz, H-3), 3.95 (dd, 1 H, $J = 4$, 9 Hz, H-4), 1.50 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3).

A $-78\,^{\circ}C$ solution of diethyl difluoromethylphosphonate (21.8 g, 0.116 mol) in anhyd THF (100 mL) was added via cannula under a positive pressure or Ar to a solution of lithium diisopropylamide (2.0 M, 75 mL, 150 mmol) at $-78\,^{\circ}C$, and the mixture stirred for 45 min at $-78\,^{\circ}C$. A precooled ($-78\,^{\circ}C$) solution of the above aldehyde (38 g, 0.137 mol) in anhyd THF (400 mL) was added to this mixture via cannula, and the resulting mixture stirred for 6 h at $-78\,^{\circ}C$, then quenched by the addition of phenyl chlorothionoformate (35 mL, 0.253 mol) in one portion, and stirred an additional 45 min at $-78\,^{\circ}C$. The mixture was then warmed to r.t. and poured into Et_2O (750 mL). The Et_2O was washed with sat. NH_4Cl solution (3 × 500 mL), dried, concentrated and chromatographed (hexanes – 50 % EtOAc/hexanes) to give the intermediate β-phosphonothionocarbonate ester as a tan oil (47.2 g, 68 %).

This oil (47.2 g, 78.4 mmol) and azobisisobutyronitrile (AIBN, 3.5 g, 21.3 mmol) were dissolved in anhyd toluene (500 mL), Bu_3SnH (32.3 mL, 0.120 mol) added and the mixture heated at reflux for 2.5 h. The mixture was then concentrated in vacuo to a residue, and the residue partitioned between hexanes and MeCN (750 mL each), and the MeCN layer was concentrated and chromatographed (hexanes – 60 % EtOAc/hexanes) to give **2**[16,18] as a tan oil (25.0 g, 71 %).

^1H NMR ($CDCl_3$): $\delta = 7.30$ (m, 5 H, aromatic), 5.78 (dd, 1 H, H-1), 4.80, 4.58 (2 d, 2 H, benzylic), 4.40 (app t, 1 H, H-3), 4.25 (q, 4 H, $2 \times OCH_2CH_3$), 3.42 (dd, 1 H, $J = 4$, 9 Hz, H-4), 2.50–2.05 (m, 2 H, H-5), 1.60 (s, 6 H, $2 \times CH_3$), 1.36 (t, 6 H, $2 \times OCH_2CH_3$).

1,2-Dibenzoyl-3-*O*-benzyl-5-deoxy-5-difluoromethylphosphinyl-D-ribofuranoside (3):

Carbohydrate **2** (25.0 g, 0.056 mol) was dissolved in a 60 % solution of aq AcOH (250 mL) and heated at 100 °C for 1 h, then cooled, concentrated in vacuo and chromatographed (50% EtOAc/hexanes – neat EtOAc) to give the deprotected intermediate (12.4 g, 54 %). A portion of this material (6.7 g, 16.3 mmol) was dissolved in pyridine (150 mL), and benzoyl chloride (6.6 mL, 56.8 mmol) was added and the mixture stirred for 45 min at r.t., then concentrated in vacuo, and the residue chromatographed (50 % EtOAc/hexanes) to give **3** as an oil (5.7 g, 57 %).

^1H NMR ($CDCl_3$): $\delta = 8.2$–7.2 (15 H, aromatic), 6.75 (d, 1 H, $J = 4$ Hz, H-1), 6.57 (s, 1 H, H-1), 5.69 (d, 1 H, $J = 4$ Hz, H-2), 5.48 (app t, 1 H, $J = 5$ Hz, H-3), 4.71, 4.62 (2 d, 2 H, benzylic), 4.25 (m, 4 H, $2 \times OCH_2CH_3$), 3.42 (dd, 1 H, $J = 4$, 9 Hz, H-4), 2.45 (m, 2 H, H-5), 1.35 (dt, 6 H, $2 \times OCH_2CH_3$).

HRMS (FAB, DCM/NBA matrix): m/z calc. for $C_{31}H_{33}F_2NaO_9P$ (MNa^+): 641.172798; found: 641.172700.

3′-*O*-Benzyl-2-chloro-5′-deoxy-5′-difluoromethylphosphinyladenosine (4):

2,6-Dichloropurine (978 mg, 5.2 mmol) was suspended in hexamethyldisilazane (HMDS, 25 mL), a crystal of $(NH_4)_2SO_4$ added, and the mixture refluxed 2 h. Excess HMDS was removed in vacuo and a solution of **3** (3.2 g, 5.2 mmol) in anhyd MeCN (25 mL) was added to the residue, followed by $SnCl_4$ (1.82 mL, 15.5 mmol) under an Ar atmosphere. The mixture was stirred for 45 min at r.t., then poured into a vigorously stirring mixture of sat. $NaHCO_3$ solution (125 mL) and EtOAc (125 mL). The two phase mixture was filtered through a Celite plug, and the organic phase separated, dried, concentrated and chromatographed (EtOAc/hexanes, 1:1) to give the glycosylated purine as a glassy foam (762 mg, 23 %). This material (762 mg, 1.21 mmol) was dissolved in a minimal amount of CH_2Cl_2 and transferred to a 100 mL stainless steel bomb, and the solvent evaporated under a stream of Ar. The bomb was cooled to $-78\,^{\circ}C$, and anhyd liquid ammonia (30 mL) was added, and the bomb was sealed, allowed to warm to r.t. and left overnight. The bomb was then recooled to $-78\,^{\circ}C$, opened, and the mixture diluted with MeOH (30 mL), cooled to $-78\,^{\circ}C$, then allowed to warm to r.t. and concentrated in vacuo. The residue was chromatographed (5 % $MeOH/CH_2Cl_2$) to give the 6′-aminated, 2′-debenzoylated nucleoside **4** as a crystalline solid (396 mg, 59 %).

^1H NMR ($CDCl_3$): $\delta = 8.1$ (s, 1 H, purine H-8), 7.8–7.25 (6 H, aromatic), 6.1 (br, 2 H, NH_2), 5.81 (d, 1 H, $J = 5$ Hz, H-1), 4.8, 4.65 (2 d, 2 H, benzylic), 4.6 (m, 1 H, $J = 5.5$ Hz, H-2), 4.45 (app t, 1 H, $J = 4.5$ Hz, H-3), 4.25 (m, 4 H, $2 \times OCH_2CH_3$), 3.42 (dd, 1 H, $J = 4$, 9 Hz, H-4), 2.54 (tt, 2 H, $J_{HF} = 19$ Hz, H-5), 1.4 (m, 6 H, $2 \times OCH_2CH_3$).

HRMS (FAB, DCM/NBA matrix): m/z calc. for $C_{22}H_{27}ClF_2N_5O_6P$ (MH^+): 562.143382; found: 562.142600.

$C_{22}H_{27}ClF_2N_5O_6P$	calc.	C 47.02	H 4.81	N 12.47
(561.5)	found	47.24	5.09	12.15

2-Chloro-2′,5′-dideoxy-5′-difluorometylphosphinyladenine (5):

Nucleoside **4** (209 mg, 0.380 mmol) and 4-dimethylaminopyridine (DMAP, 70 mg, 0.570 mmol) were dissolved in anhyd CH_2Cl_2 (10 mL), and phenyl chlorothionoformate (0.062 mL, 0.450 mmol) was added. The mixture was stirred for 1.5 h, then diluted to a volume of 30 mL with CH_2Cl_2, and washed with water (25 mL), ice-cold 1 N HCl (25 mL), water (25 mL), sat. $NaHCO_3$ (25 mL) and brine (25 mL), then dried, concentrated and dried in vacuo. The resulting residue was dissolved in toluene (5 mL), and AIBN (50 mg, 0.300 mmol) was added, followed by Bu_3SnH (0.200 mL, 0.743 mmol), and the mixture heated at 80 °C for 3 h, then toluene removed in vacuo and the residue partitioned between hexanes and MeCN (25 mL each). The MeCN layer was washed with additional amount of hexanes (25 mL), and then concentrated and chromatographed (neat hexanes – 50 % EtOAc/hexanes) to give the deoxygenated compound as an amorphous solid (113 mg, 55 %). This residue (113 mg, 0.210 mol) was dissolved in CH_2Cl_2 (10 mL), and cooled to $-78\,^{\circ}C$, then BCl_3 (1.0 M in CH_2Cl_2, 2.1 mL, 4.2 mmol) was added under an atmosphere of Ar and the mixture stirred 4 h at $-78\,^{\circ}C$, then anhyd MeOH (10 mL) was added, and the mixture warmed to 0 °C in an ice bath, and sat. NH_4Cl solution (3 mL) added. The mixture was then concentrated in vacuo, coevaporated three times with MeOH (25 mL), and the residue suspended in EtOAc, filtered, and the filtrate concentrated and dried in vacuo. The residue was then suspended in HMDS (10 mL), a crystal of $(NH_4)_2SO_4$ added, and the mixture heated at reflux for 2 h, then excess HMDS removed in vacuo. The silylated nucleoside was dissolved in CH_2Cl_2 (10 mL), bromotrimethylsilane (0.555 mL, 4.2 mmol) was added under an Ar atmosphere, and the mixture was stirred for 48 h at r.t. The mixture was then concentrated in vacuo, and coevaporated with anhyd toluene (2 × 15 mL). The residue was coevaporated with Et_3N (20 mL), and the resulting residue dissolved in a minimal amount of 0.01 M aq triethylammonium hydrogen carbonate (TEAB), and purified by HPLC [Waters RCN 25 × 10 mm C_{18} preparative column, pure TEAB – TEAB/60% aq MeCN (1 : 1) gradient as eluent, monitoring at 265 nm]. The pooled fractions containing the pure product were concentrated by lyophilization, redissolved in water (5 mL), passed over a bed of sodium Dowex ion exchange resin and again lyophilized to give **5** as a white powder (49 mg, 53%).

^{1}H NMR (DMSO-d_6): $\delta = 8.33$ (s, 1 H, purine H-8), 7.80 (br s, 2 H, purine NH_2), 6.21 (s, 1 H, H-1′), 4.36 (br, 1 H, H-3′), 4.12 (br, 1 H, H-4′), 2.70 (br, 1 H, H-2′α), 2.50 (br, 1 H, H-2′β), 2.28 (br, 2 H, H-5′).

HRMS (FAB, MeOH/Gly* matrix): m/z calc. for $C_{11}H_{13}ClF_2N_2O_5P$ ($M^{2-} + H^+$): 398.023266; found: 398.021400.

$C_{11}H_{13}ClF_2N_5O_5P$	calc.	C 33.04	H 3.25	N 17.52
(399.5)	found	33.14	3.28	14.97

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