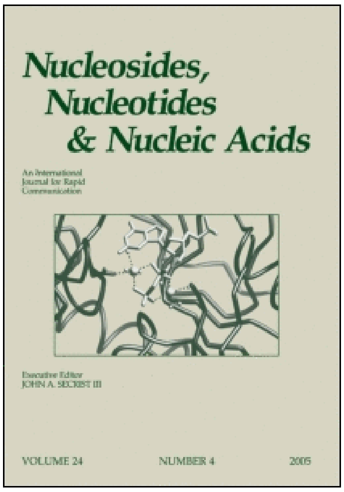

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METHODOLOGY FOR THE SYNTHESIS OF DINUCLEOSIDE MONOPHOSPHATES CONTAINING A 2'-DEOXY-3-ISOADENOSINE UNIT: 3-iso-dApT and Tp(3-iso-dA)

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Abstract. 2'-Deoxy-3-isoadenylyl(3'-5')thymidine and thymidylyl-(3'-5')-2'-deoxy-3-isoadenosine have been synthesized by mild protection/deprotection methodology that circumvents facile N3-C1' hydrolytic cleavage of the 2'-deoxy-3-isoadenosine moiety.

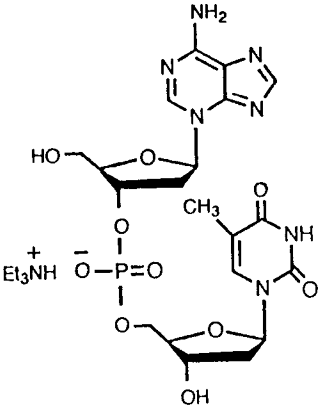
We sought to provide the best conditions for the incorporation of 2'-deoxy-3-isoadenosine units in oligodeoxyribonucleotides of specific length and sequence. Simple versions of dinucleoside monophosphates consisting of 2'-deoxy-3-isoadenosine and thymidine in both possible orders were first selected as models for the synthesis of the oligomers. These two dinucleoside phosphates have the added interest of structural comparison with those containing the normal 2'-deoxyadenosine units.

In a mini-double helix formed by 2'-deoxy-3-isoadenylyl(3'-5')-thymidine (3-iso-dApT, **1** as the Et_3N salt) 3-substitution on adenine confers the property of protonation and alkylation at the 7-position.[1-5] This leads to the proposition, based on the structure and basicity of 3-isoadenosine, 3-ß-D-ribofuranosyladenine (**2**),[6,7] that intermolecular self-association of **1** would involve modified Hoogsteen[8-10] hydrogen bonding.[11] Hydrogen bonding involving the 6-NH_2 and N7 of the adenine moiety is the probable source of the strong interaction in the 1:1 helical complex of poly(3-isoadenylic acid) with poly(U)[12] and the efficient poly(U)-template-directed oligomerization of the imidazolide of 3-isoadenosine 5'-phosphate.[13]

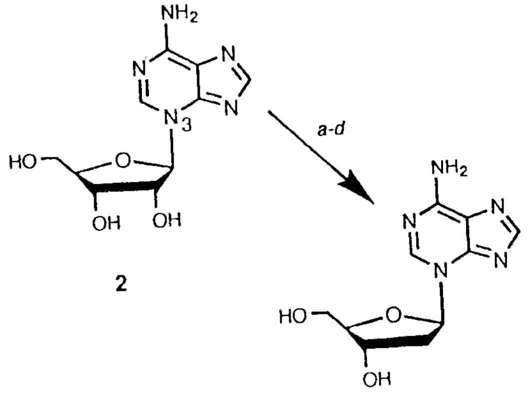
The structure of compound **1**, 3-iso-dApT, should be considered in relation to that of ApU.[14] The crystalline sodium salt hexahydrate of ApU, as shown by X-ray diffraction, consists of two independent molecules that form a small segment of right-handed antiparallel double-helical RNA, with Watson-Crick base-pairing[15] between adenine and uracil. The synthesis of the dinucleoside monophosphate 3-iso-dApT (**1**) represented a challenge because facile hydrolytic cleavage of the 2′-deoxy-3-isoadenosine unit precluded the use of some of the reagents conventionally employed.

The preferred route to 2′-deoxy-3-isoadenosine (**3**), which was different from the two routes that had been used previously,[16,17] followed the general sequence:[18-20] (a) reaction of **2** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[21] to give 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-3-isoadenosine, (b) reaction with phenoxythiocarbonyltetrazole as a new preferred reagent for use under neutral conditions, (c) 2′-deoxygenation[22,23] by homolytic cleavage of the 2′-carbon-oxygen bond by tri-*n*-butyltin hydride and AIBN in toluene, and (d) removal of the 3′,5′-*O*-TPDS protecting group in THF with tetra-n-butylammonium fluoride (1.1 M solution).[18,19] The over-all yield from 3-isoadenosine (**2**) to 2′-deoxy-3-isoadenosine (**3**, Scheme I) was 53%. The intermediates and **3** were purified by recrystallization or chromatography.

The synthesis advanced to the desired 3-iso-dApT (**1**) product by the use of allyloxycarbonyl and allyl protection as necessary on hydroxyl, amino, and phosphoramidite groups.[24-27] The intermediates were characterized, after purification by flash chromatography or radial chromatography over silica gel using chloroform-methanol containing a trace of triethylamine, by the known chemical conversions, by NMR, and by FAB mass spectra. The 5′-OH of **3** was protected by reaction with 4,4′-dimethoxytrityl chloride and 4-dimethylaminopyridine in pyridine. The 3′-OH was sequentially protected by reaction with *tert*-butyldimethylsilyl chloride and 4-dimethylaminopyridine in CH_2Cl_2:DMF:Et_3N (3:3:1), and the 6-NH_2, by 1-allyloxycarbonyltetrazole[24] in THF. All reactions were carried out at room temperature, unless otherwise noted, including the final deprotection of the 3′-OH to give N^6-allyloxycarbonyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxy-3-isoadenosine (**4**). The over-all yield from **3** to **4**, which was compromised by the idiosyncrasy of the first step, was 20% (Scheme II).



1

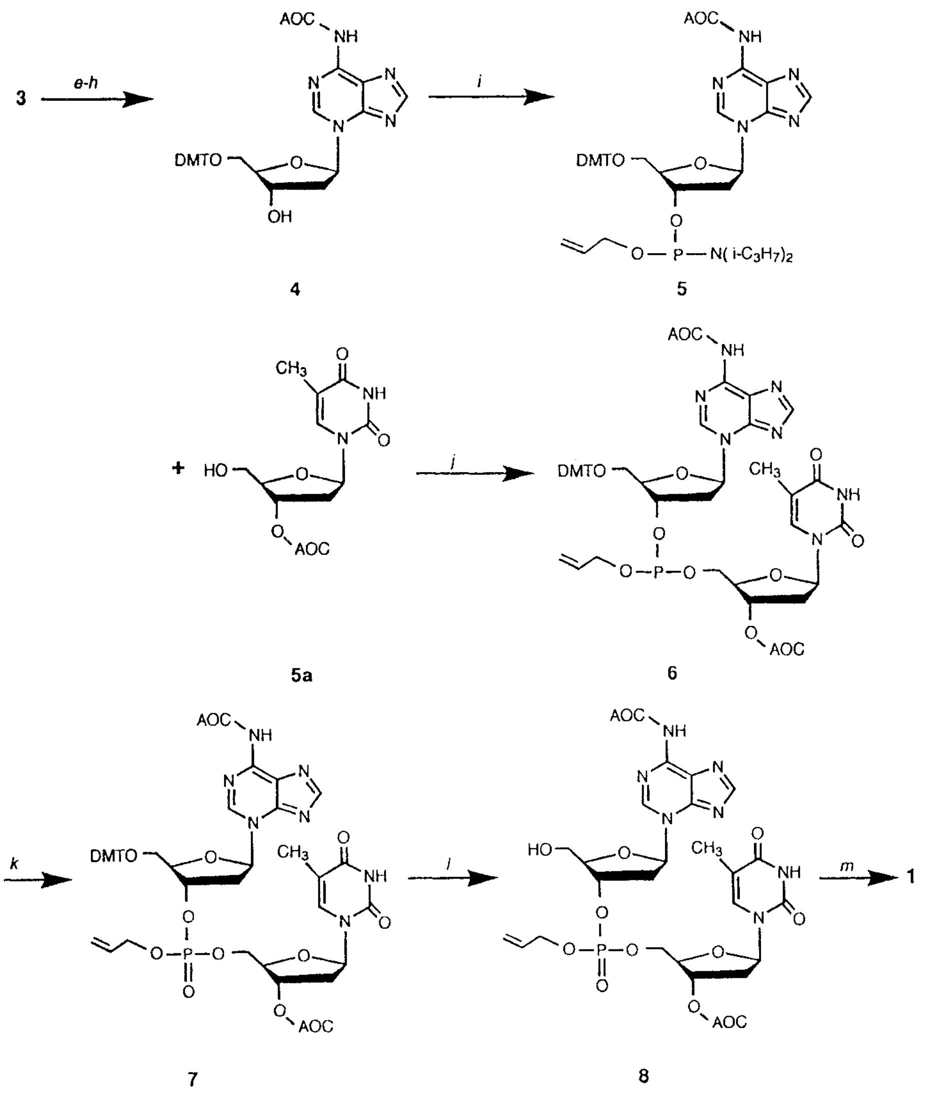


2

3

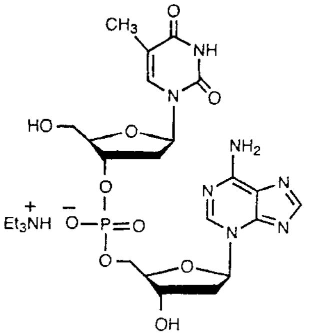
Scheme I, **2** → **3**: a, TPDSCl$_2$, Py, 6 h, 25 °C; b, PTC-tetrazole, THF, 6 h, 25 °C; c, AIBN, $(C_4H_9)_3SnH$, toluene, argon degassing, 6 h, 75 °C; d, $(C_4H_9)_4N^+$ F^-, THF, 4 h, 25 °C.

The phosphorus-containing moiety was introduced into **4** by reaction with allyloxy-bis(diisopropylamino)phosphine, diisopropylamine, and tetrazole in acetonitrile to yield **5** (69%). This, in turn, was coupled with 3′-*O*-allyloxycarbonylthymidine in acetonitrile to give the phosphite ester **6** (47% yield), which was oxidized to the phosphate ester **7** with *tert*-butylhydroperoxide in CH_2Cl_2 at 0 °C (91% yield). The N3-C1′ linkage in the 3-iso series is susceptible to acid hydrolysis *(vide supra)* so that even deblocking of the 5′-OH with dichloroacetic acid in CH_2Cl_2 at room temperature for only 60 sec gave **8** in reduced yield (43% based on unrecovered **7**). Removal of the three allyloxy groups was accomplished with a palladium (0) reagent,[27] and 3-iso-dApT (**1**) was isolated as the triethylammonium salt (55% yield, or 7% over-all yield from **4**).



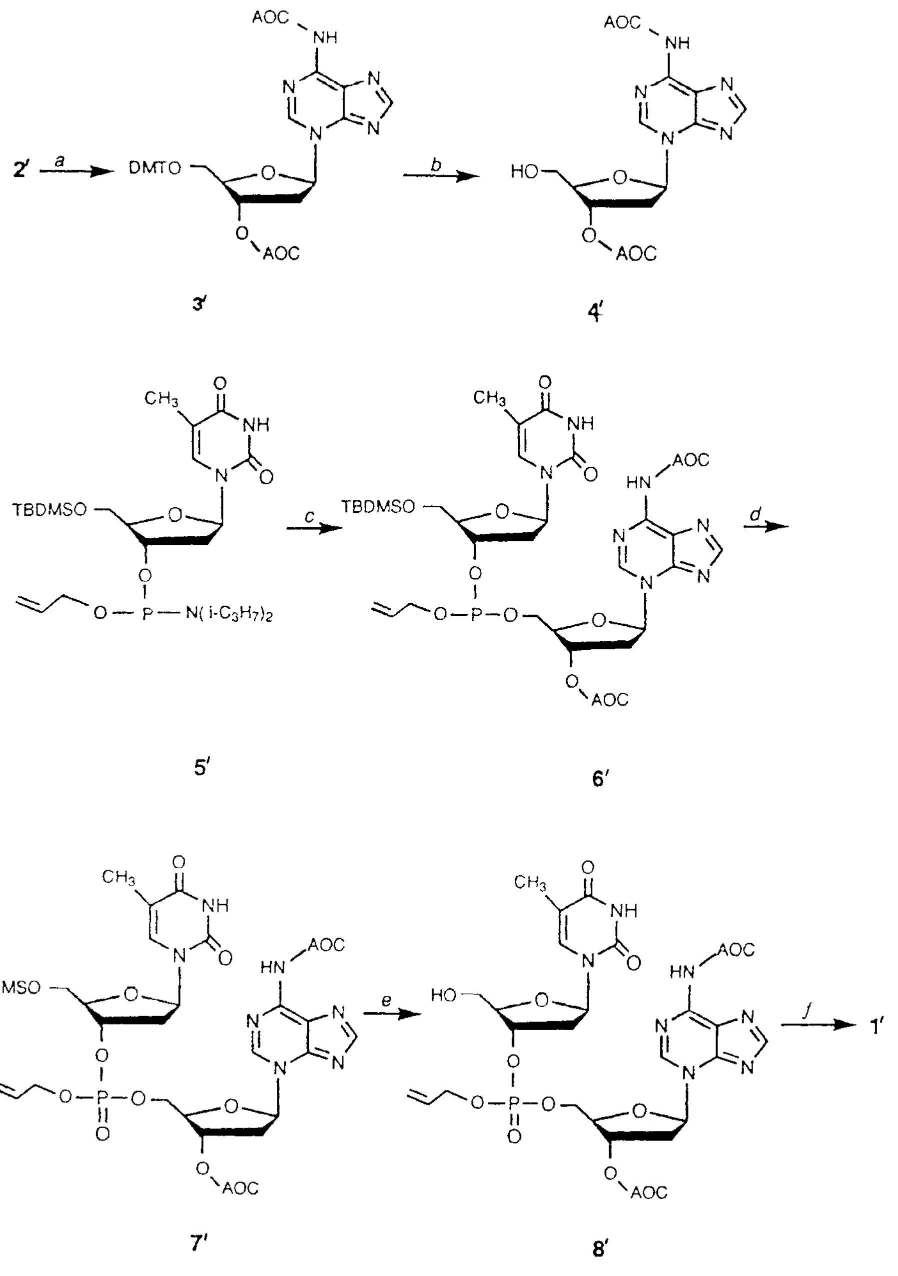
Scheme II, 3 → 8: (at 25 °C unless noted) e, DMTCl, DMAP, Py, 30 min; f, TBDMSCl, DMAP, $(C_2H_5)_3N$, CH_2Cl_2, DMF, 12 h; g, AOC-tetrazole,[28] THF, 30 min; h, $(C_4H_9)_4N^+F^-$ on silica gel, THF, 24 h; i, CH_2=CH-$CH_2OP[N(i\text{-}C_3H_7)_2]_2$, $(i\text{-}C_3H_7)_2NH$, tetrazole, CH_3CN, 2 h; j, tetrazole, CH_3CN, 2.5; k, t-C_4H_9OOH, CH_2Cl_2, 1 h, 0 °C; l, $Cl_2CHCOOH$, CH_2Cl_2, 1 min; m, $(C_6H_5)_3P$, THF, $C_4H_9NH_2$, HCOOH, $Pd_2(dba)_3$•$CHCl_3$, 1 h.

Of corollary interest to the structure and hydrogen-bonding pattern of 3-iso-dApT (**1**) is a similar analysis for thymidylyl(3',5')-2'-deoxy-3-isoadenosine (Tp(3-iso-dA), **1'** as the Et_3N salt). Because of the preferred locus of protonation and alkylation at N7 for 3-substituted adenines[1-5] this sequential isomer is also a probable candidate for modified[11] Hoogsteen hydrogen bonding in intermolecular self-association.[8-10,11,12] It will be advantageous to compare the structure of Tp(3-iso-dA) (**1'**) directly with that of thymidylyl-(3',5')-2'-deooxyadenosine (TpdA). X-ray diffraction and molecular model building have shown for the triethylammonium salt of the latter, that the adenine of one molecule and the thymine of the next are linked by Hoogsteen-type hydrogen bonds.[28,29] The total structure resembles a macromolecule in which units are linked together by hydrogen bonds, are stabilized by adenine base stacking, and constitute a left-handed helix. Both nucleosides have the anti conformation and both sugar rings have C3'-endo puckers. Comparison of the structure of **1'** with the structure of uridylyl(3'-5')-adenosine, UpA,[30-33] would not be germane to this discussion because the molecules of UpA are zwitterionic, and the adenine is protonated at N1.



1'

The challenge of the synthesis of the dinucleoside monophosphate Tp(3-iso-dA) (**1'**) was met successfully by employing allyl and allyloxycarbonyl protection/deprotection[24,25,27] as necessary on hydroxyl, amino, and phosphoramidite groups, along with more conventional methodology.[26] 2'-Deoxy-3-isoadenosine (**3** = **2'**) was made as described



Scheme III, 2'→ 8': (at 25 °C unless noted) a DMTCl, DMAP Py, 30 min followed by AOC-tetrazole, Et_3N, THF; b, $Cl_2CHCOOH$, CH_2Cl_2, 2 min; c, tetrazole, CH_3CN, 1 h; d, $t\text{-}C_4H_9OOH$, CH_2Cl_2, 0 °C, 1 h; e, TBAF, THF, 24 h; f, $(C_6H_5)_3P$, THF, $C_4H_9NH_2$, HCOOH, $Pd_2(dba)_3 \cdot CHCl_3$, 1 h.

above and converted to **3′** by 4,4′-dimethoxytritylation on the 5′-hydroxyl and reaction at N^6H_2 and 3′-OH with 1-allyloxycarbonyl-tetrazole and triethylamine in THF (**3′**, Scheme III). Removal of the 5′-*O* protection by limited contact (2 min) with dichloroacetic acid in methylene chloride yielded **4′**, followed by combination with **5′**, which yielded the fully protected dinucleoside phosphite **6′**. Oxidation (→ **7′**) and removal of the protecting groups, *t*-butyldimethylsilyl with tetrabutylammonium fluoride adsorbed on silica gel (→ **8′**) and the allyl and allyloxycarbonyl groups by palladium hydrogenolysis, gave Tp(3-iso-dA) as the triethylammonium salt (**1′**) in 14% over-all yield from **3′**. The intermediates in the synthesis were purified by recrystallization or by flash chromatography or radial chromatography over silica gel using chloroform-methanol containing a trace of triethylamine and were characterized by the known chemical conversions and by FAB mass spectrometry.

In conclusion, this model study has shown how the hydrolytically-susceptible 3-isoadenosine unit can be incorporated in an oligodeoxy-nucleotide sequence in either a **3′** or **5′** sense. Compound **5**, N^6-allyloxycarbonyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxy-3-isoadenosyl-3′-*O*-(allyl N,N-diisopropyl)phosphoramidite, is especially useful as a building block for specific sequences that contain the adenosine isomer.[34] The two unnatural dinucleoside monophosphates, 3-iso-dApT and Tp(3-iso-dA), are candidates for structural comparison with their natural counterparts.

EXPERIMENTAL SECTION

This section can be abbreviated because the reaction conditions for the syntheses of all intermediates are given in the legends to Schemes I and II. The susceptibility of the 2′-deoxy-3-isoadenosine moiety to hydrolysis and rearrangement required divergence from the sequence normally employed in the automation of oligonucleotide synthesis.[26] This fact was confirmed for us by another laboratory noted for skill in oligodeoxyribonucleotide synthesis. Accordingly, the desired compounds, **3** and **1** were made by the processes outlined in Schemes I and II, and representative intermediates along the pathway were characterized to monitor the specifically modified procedures.

Scheme I. After a: **3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)-3-isoadenosine**, $C_{22}H_{39}N_5O_5Si_2$. Pyridine was removed under reduced pressure (bath temperature < 40 °C) to 1/10 volume. Water was added, and the solid that precipitated was filtered, washed with hexane, and recrystallized from acetonitrile: yield 96%; low resolution FAB MS *m/z* 510.3 (MH^+).

1-Phenoxythiocarbonyltetrazole (reagent under b). The procedure was similar to that described for 1-allyloxythiocarbonyltetrazole.[27] Phenylthionochloroformate (2.0 g, 11.6 mmol) was added to a mixture of 1*H*-tetrazole (725 mg, 10.3 mmol) and triethylamine (1.54 ml, 11.1 mmol) in THF (15 ml) at 0 °C during 15 min. The reaction mixture was stirred at 0 °C for 30 min, filtered through a pad of Celite, and concentrated to 0.05-0.10 volume. The concentrate was used directly.

After b: **2′-*O*-phenoxythiocarbonyl-3′,5′-*O*-(1,1,3,3,tetraisopropyldisiloxa-1,3-diyl)-3-isoadenosine,** $C_{29}H_{43}N_5O_6SSi_2$. The isolation procedure was similar to that used after a, and purification was effected by flash chromatography: yield 79%: low resolution FAB MS *m/z* 646.3 (MH^+).

After c: **2′-Deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)-3-isoadenosine**, $C_{22}H_{39}N_5O_4Si_2$. The most efficient deoxygenation reaction resulted from the phenoxythiocarbonylation of the 2′-hydroxyl in place of other thiocarbonylations that have been employed.[18,19,22,23] Following the conditions described in c solvent was removed under reduced pressure and purification was effected by flash chromatography: yield, 76%; low resolution FAB MS *m/z* 494.3 (MH^+).

After d: **2′-deoxy-3-isoadenosine (3)**,[16,17] $C_{10}H_{13}N_5O_3$. The solvent was evaporated, the residue was dissolved in water and extracted with ether. The aqueous layer was concentrated to dryness, and the residual solid was recrystallized from ethanol: yield, 91%; low resolution FAB MS *m/z* 252.1 (MH^+).

Scheme II. After e: **5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxy-3-isoadenosine**, $C_{31}H_{31}N_5O_5$. Following removal of pyridine under vacuum and its final traces by codistillation with toluene, the residual solid was purified by flash chromatography: yield, 45%; low resolution FAB MS *m/z* 554.3 (MH^+).

After f: **3′-*O*-*t*-butyldimethylsilyl-5′-*O*-(4,4′dimethoxytrityl)-2′-deoxy-3-isoadenosine**, $C_{37}H_{45}N_5O_5Si$: yield, 81%; low resolution FAB MS *m/z* 668.2 (MH^+) .

After g: ***N*^{6}-allyloxycarbonyl-3'-*O*-*t*-butyldimethylsilyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxy-3-isoadenosine**, $C_{41}H_{49}N_5O_7Si$: yield, 71%; low resolution FAB MS *m/z* 752.4 (MH^+).

After h: ***N*^{6}-allyloxycarbonyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxy-3-isoadenosine** (**4**), $C_{35}H_{35}N_5O_7$: yield, 79%; low resolution FAB MS *m/z* 638.4 (MH^+) .

After i: ***N*^{6}-allyloxycarbonyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxy-3-isoadenosyl-3′-*O*-(allyl N,N-diisopropyl)phosphoramidite** (**5**), $C_{44}H_{53}N_6O_8P$: yield, 69%; low resolution FAB MS *m/z* 825.2 (MH^+).

3′-*O*-Allyloxycarbonylthymidine^{25} (**5a**), $C_{14}H_{18}N_2O_7$; low resolution FAB MS *m/z* 327.1 (MH^+) .

After j: **allyl 3′-[*N*^{6}-allyloxycarbonyl-5′-*O*-(-4,4′-dimethoxytrityl)-2′-deoxy-3-isoadenosyl] 5′-(3′-*O*-allyloxycarbonyl)thymidyl phosphite** (**6**), $C_{52}H_{56}N_7O_{15}P$: yield (based on unrecovered **5**), 47%.

After k: **allyl[*N*^{6}-allyloxycarbonyl-5′-*O*-(4,4′dimethoxytrityl)-2′-deoxy-3-isoadenylyl](3′-5′)-3′-*O*-allyloxycarbonylthymidine** (**7**), $C_{52}H_{56}N_7O_{16}P$: yield 91%.

After l: **allyl(*N*^{6}-allyloxycarbonyl-2′-deoxy-3-isoadenylyl)-(3′-5′)-3′-*O*-allyloxycarbonylthymidine** (**8**), $C_{31}H_{38}N_7O_{14}P$. After the 60-sec hydrolysis, the solution was quickly basified with saturated $NaHCO_3$ solution. Extraction with ethyl acetate was followed by drying of the ethyl acetate layer over anhydrous Na_2SO_4, filtration, concentration, and purification by flash chromatography to yield **8** (43% based upon unrecovered **7**) as a colorless solid: low resolution FAB MS *m/z* 764 (MH^+).

After m: **2′-deoxy-3-isoadenylyl(3′-5′)thymidine, 3-iso-dApT as the triethyl ammonium salt** (**1**), $C_{20}H_{26}N_7O_{10}P$ (MW 555); Et_3NH^+ salt, $C_{26}H_{41}N_8O_{10}P$ (MW 656). After m, the reaction mixture was diluted with ethyl acetate and extracted with water. The aqueous solution was loaded on a Sephadex A-25 column and fluted with a 0-0.7 M TEAB gradient. Appropriate fractions were combined and lyophilized. The residual solid was treated with acetonitrile, maintained overnight at 0 °C, filtered, and washed with acetonitrile: yield, 55%; low resolution FAB MS *m/z* (-ve ion) 554.2 (M-1); high resolution FAB MS *m/z* (-ve ion) 554.1403 ($C_{20}H_{25}N_7O_{10}P$ requires 554.1401 amu); UV λ_{max} 269 nm.

2'-Deoxy-3-isoadenosine (**3**, also **2'**) and **5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxy-3-isoadenosine** were synthesized according to the methods described. The latter was treated with 1-allyloxycarbonyltetrazole.[26] The intermediate ***N*^{6},3'-*O*-diallyloxycarbonyl-5'-*O*-(4,4'dimethoxytrityl)-2'-deoxy-3-isoadenosine** (**3'** in Scheme III) was not isolated but was treated directly and briefly (2 min) with $Cl_2CHCOOH$ in CH_2Cl_2 to give ***N*^{6},3'-*O*-diallyloxycarbonyl-2'-deoxy-3-isoadenosine** (**4'**), $C_{18}H_{21}N_5O_7$: yield, 37% from **2**; low resolution FAB MS *m/z* 420.1 (MH^+).

5'-*O*-t-Butyldimethylsilylthymidyl-3'-*O*-(allyl-N,N-diisopropyl)phosphoramidite (**5'**), is similar to a compound previously described but dimethoxytritylated on the 5'-*O*; ^{31}P-NMR ($CDCl_3$, δ from H_3PO_4): 147.84 and 148.28 ppm (<u>ca</u>. 1:1 diastereomers).

After <u>c</u>: **allyl 3'-(5'-*O*-*t*-Butyldimethylsilylthymidyl) 5'-(*N*^{6},3'-*O*-diallyloxyearbonyl)-2'-deoxy-3-isoadenosyl phosphite** (**6'**), $C_{37}H_{52}N_7O_{13}PSi$: yield, 76%: low resolution FAB MS *m/z* 862.3 (MH+); high resolution FAB MS *m/z* 862.3190 ($C_{37}H_{53}N_7O_{13}PSi$ requires 862.3208 amu).

After <u>d</u>: **allyl 5'-*O*-t-butyldimethylsilylthymidylyl(3'-5')-*N*^{6},3'*O*-diallyloxycarbonyl-2'-deoxy-3-isoadenosine** (**7'**). $C_{37}H_{52}N_7O_{14}PSi$: yield, 89%; low resolution FAB MS *m/z* 878.3 (MH^+); high resolution FAB MS *m/z* 878.3139 ($C_{37}H_{53}N_7O_{14}PSi$ requires 878.3157 amu).

After <u>e</u>: **allyl thymidylyl(3'-5')-*N*^{6},3'-*O*-diallyloxycarbonyl-2'-deoxy-3-isoadenosine** (**8'**), $C_{31}H_{38}N_7O_{14}P$: yield, 85%; low resolution FAB MS *m/z* 764.1 (MH^+); high resolution FAB MS 764.2314 ($C_{31}H_{39}N_7O_{14}P$ requires 764.2293 amu).

After <u>f</u>: **thymidylyl(3'-5')-2'-deoxy-3-isoadenosine, Tp(3-iso-dA) as the triethylammonium salt** (**1'**), $C_{20}H_{26}N_7O_{10}P$ (mw 555): Et_3NH^+ salt, $C_{26}H_{41}N_8O_{10}P$ (mw 656). After <u>f</u>, ethyl acetate was added and the organic layer was washed with water. The aqueous layer and washings were loaded on a Sephadex A-25 column and eluted with a TEAB gradient, 0-0.5 M. Appropriate fractions were pooled and lyophilized. The residual solid was treated with dry $CHCl_3$ to remove excess triethylammonium bicarbonate. The final residue was dissolved in water and relyophilized to give a fluffy, colorless solid: yield, 46%; low resolution FAB MS *m/z* (-ve ion) 554 (M-1); low resolution FAB MS *m/z* 556.1 (MH^+); high resolution FAB MS *m/z* 556.1549 ($C_{20}H_{27}N_7O_{10}P$ requires 556.1557 amu); UV λ_{max} 267 nm.

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Abbreviations: AOC, allyloxycarbonyl; DMAP, 4-dimethylaminopyridine; DMT, 4,4'-dimethoxytrityl; 3-iso-dApT, 2'-deoxy-3-ß-D-ribofuranosyladenylyl(3'-5')thymidine; $Pd_2(dba)_3 \cdot CHCl_3$, tris(dibenzylideneacetone) dipalladium (O) chloroform adduct; PTC, phenoxythiocarbonyl; TBDMS, *t*-butyldimethylsilyl; TPDS, tetraisopropyldisiloxa-1,3-diyl; Tp(3-isodA), thymidylyl(3'-5')-2'deoxy-3-ß-D-ribofuranosyladenine.

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