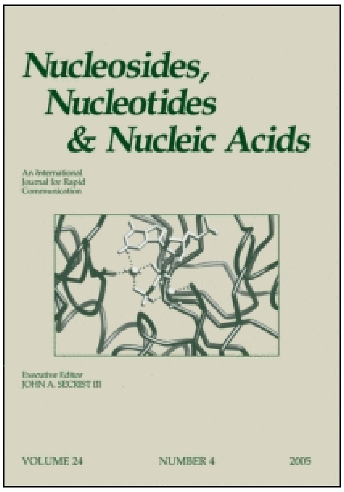

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An Efficient Synthesis Of Acyclic N^7- and N^9-Adenine Nucleosides Via Alkylation With Secondary Carbon Electrophiles to Introduce Versatile Functional Groups At the C-1 Position of Acyclic Moiety

Pravin L. Kotian[a]; V. Satish Kumar[a]; Tsu-Hsing Lin[a]; Yahya El-Kattan[a]; Ajit Ghosh[a]; Minwan Wu[a]; Xiaogang Cheng[a]; Shanta Bantia[a]; Yarlagadda S. Babu[a]; Pooran Chand[a]
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AN EFFICIENT SYNTHESIS OF ACYCLIC N^7- AND N^9-ADENINE NUCLEOSIDES VIA ALKYLATION WITH SECONDARY CARBON ELECTROPHILES TO INTRODUCE VERSATILE FUNCTIONAL GROUPS AT THE C-1 POSITION OF ACYCLIC MOIETY

Pravin L. Kotian, V. Satish Kumar, Tsu-Hsing Lin, Yahya El-Kattan, Ajit Ghosh, Minwan Wu, Xiaogang Cheng, Shanta Bantia, Yarlagadda S. Babu, and Pooran Chand □ *BioCryst Pharmaceuticals, Inc., Birmingham, Alabama, USA*

□ *The introduction of versatile functional groups, allyl and ester, at the C-1 position of the acyclic chain in acyclic adenine nucleosides was achieved for the first time directly by alkylation of adenine and N^6-protected adenine. Thus, the C-1′-substituted N^9-adenine acyclic nucleoside, adenine-9-yl-pent-4-enoic acid ethyl ester (**11**), was prepared by direct alkylation of adenine with 2-bromopent-4-enoic acid ethyl ester (**6**), while the corresponding N^7-regioisomer, 2-[6-(dimethylaminomethyleneamino)-purin-7-yl]-pent-4-enoic acid ethyl ester (**10**), was obtained in one step by the coupling of N, N-dimethyl-N′- (9H-purin-6-yl)-formamidine (**9**) with 2-bromopent-4-enoic acid ethyl ester (**6**). The functional groups, ester and allyl, were converted to the desired hydroxymethyl and hydroxyethyl groups, and subsequently to phosphonomethyl derivatives and corresponding pyrophosphorylphosphonates.*

Keywords N^7- and N^9-Adenine nucleosides; N-Alkylation of adenine

INTRODUCTION

Acyclovir (**1a**) and ganciclovir (**1b**) are well-known purine-based acyclic nucleoside drugs.[1–4] Extensive work has been done on phosphonomethyl ether derivatives of purine acyclic nucleosides, such as PMEA (**2a**), PMPA (**2c**), HPMPA (**2e**), FPMPA (**2f**), PMEDAP (**2g**), HPMPDAP (**2h**), PMEG (**3a**), PMPG (**3b**), and HPMPG (**3c**).[5–11] This work resulted in two

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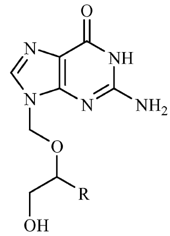
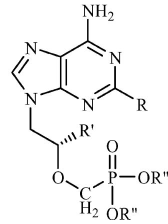
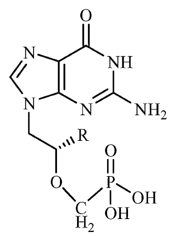


1a, R=H (Acyclovir)
1b, R=CH_2OH (Ganciclovir)



2a, R=H, R'=H, R"=H (PMEA)
2b, R=H, R'=H, R"=$CH_2OC(O)C(CH_3)_3$ (Adefovir dipivoxil)
2c, R=H, R'=CH_3, R"=H (PMPA)
2d, R=H, R'=CH_3, R"=$CH_2OC(O)OCH(CH_3)_2$ (Tenofovir disoproxil)
2e, R=H, R'=CH_2OH, R"=H (HPMPA)
2f, R=H, R'=CH_2F, R"=H (FPMPA)
2g, R=NH_2, R'=H, R"=H (PMEDAP)
2h, R=NH_2, R'=CH_2OH, R"=H (HPMPDAP)



3a, R=H (PMEG)
3b, R=CH_3 (PMPG)
3c, R=CH_2OH (HPMPG)

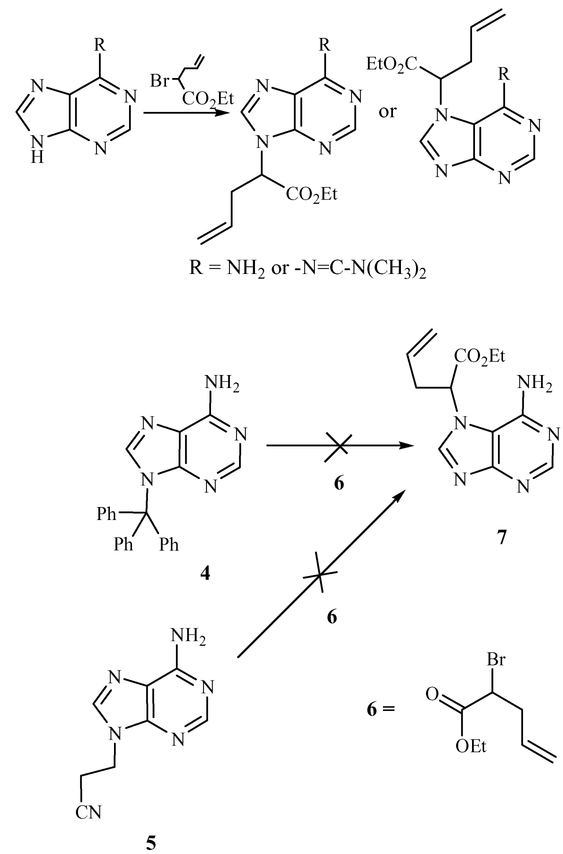
Chart 1

FDA-approved drugs, adefovir dipivoxil (**2b**) for HBV and tenofovir disoproxil (**2d**) for HIV infections. The structure of compounds **1–3** are given in Chart 1. The introduction of phosphonomethyl ether functionality in place of phosphoric acid ester may be important because: a) it is expected to be chemically and metabolically stable; b) the β-oxygen atom in phosphonomethyl ether functionality enhances the acidity of phosphonate and brings its second pKa closer to that of phosphate ester; and c) the oxygen atom in the immediate vicinity of phosphorus has been demonstrated to play a critical role for the enzymatic phosphorylation and thus for antiviral activity.[12,13] All these nucleosides are N^9-substituted and either have no substituent or have the substitution from the C-2′ position in the acyclic part of the molecule. In spite of the strong similarity in the structures of these compounds, different modes of action and profiles of antiviral activity have been reported for variously substituted acyclic structures. There are limited numbers of reports in the literature on N^7-acyclic nucleosides. The 6-deoxy derivative of the N^7-regioisomer of ganciclovir has been found to display excellent antiherpes action.[14] Regarding the C-1′ substitutions on N^7- and N^9-derivatives, there are only a few literature references.[15–18] Therefore, we were interested in exploring N^7- and N^9-substituted acyclic nucleosides branching particularly from the C-1′ position as possible antiviral agents.

Different approaches have been followed for the synthesis of N^7 derivatives of nucleosides. The N^7 isomer of purine, 7-(α-D-ribofuranosyl)adenine, isolated from pseudo-vitamin B_{12} was the first literature example of N^7-purine.[19a] The main problem for synthesis of N^7 nucleosides is the preferential alkylation at the N^9 position of the purines and N^7 is the minor isomer.[19b] The N^7-alkylated product has been reported to be obtained by N^7-/N^9-glycosyl transfer.[20] Detailed studies on N^7 and N^9 alkylation of guanine have been conducted by Kjellberg and Johansson.[21] They have reported the influence of the base, the alkylating agent, and the type of derivatization of the purine moiety on relative formation of N^7 and N^9 isomers. Montgomery and Thomas demonstrated the utility of removable blocking groups at N^3 of the adenine in the exclusive formation of 7-glycosyladenine in glycosylation and transglycosylation reactions.[22] Hakimelahi has reported regioselective alkylations at the N^7 position in high yield by first tritylating adenine at the N^9 position and then alkylating the N^7 position with concomitant self-detritylation, which resulted in the desired N^7-alkylated products.[23] Holy and Okumura have demonstrated alkylation of *N,N*-dimethyl-*N′*-(9*H*-purin-6-yl)-formamidine (**9**) with certain halogeno derivatives having electron-withdrawing groups that lead selectively to N^7-substituted nucleosides.[24–26] Holy has reported that the preparation of C-1′-substituted analogues (N^7 or N^9) with various electron-withdrawing functional groups in the C-1′ position is particularly difficult, since the elimination process during alkylation of the heterocyclic base is strongly preferred.[24,26] The compounds with electron-withdrawing groups at the C-1′ position were prepared by Holy but in three steps, which resulted in poor yield.[24,26] Since our main interest is in the preparation of C-1′-substituted acyclic nucleosides (N^7 and N^9) having ester and allyl functionalities suitable for transformation to hydroxymethyl and hydroxyethyl groups, we were interested in developing an easy method for direct alkylation of adenine; therefore, we reinvestigated the alkylation with electron-withdrawing groups. The results of investigation of the alkylation of adenine and *N,N*-dimethyl-*N′*-(9*H*-purin-6-yl)-formamidine with electron-withdrawing substituent at the C-1′ position using 2-bromopent-4-enoic acid ethyl ester[27] (**6**) as our alkylating agent will be discussed in this article. The conversion of allyl and ester functionalities to the desired hydroxyethyl and hydroxymethyl functionalities and subsequently to phosphonomethyl derivatives and corresponding pyrophosphorylphosphonates will also be discussed.

RESULTS AND DISCUSSION

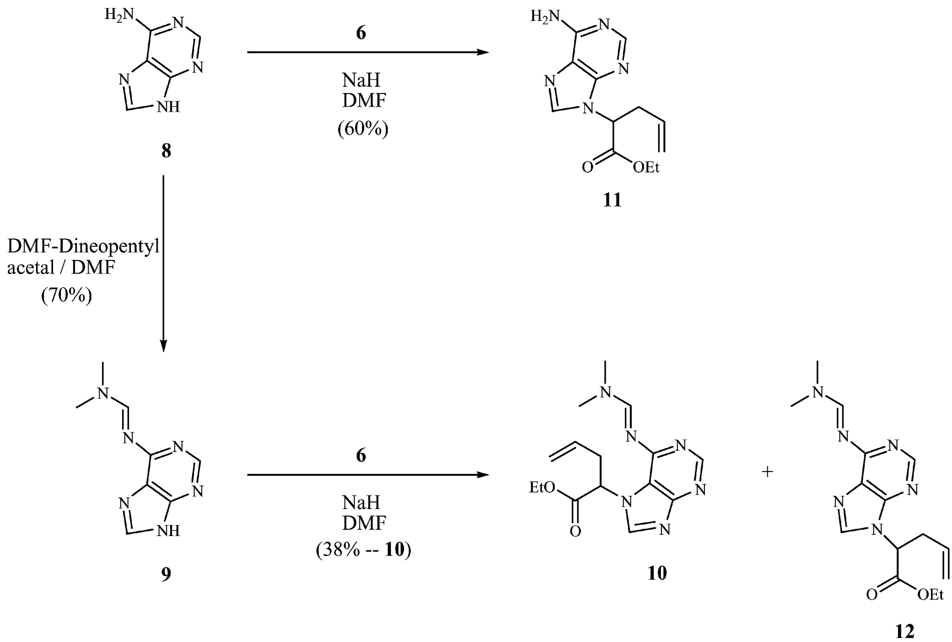
Our objective is to have ester and allyl functionalities in the acyclic part of the nucleoside at the C-1′ position; therefore, we chose to use 2-bromopent-4-enoic acid ethyl ester (**6**) as the alkylating agent so that both functionalities can be introduced at the same time. These functional groups would be further modified to the desired hydroxymethyl and hydroxyethyl groups. We first attempted the synthesis of compound **7** (Scheme 1) using Hakimelahi's



SCHEME 1

approach towards N^7 alkylation from 9-trityl-9*H*-purin-6-ylamine (**4**) with **6** using lithium 2,2,6,6-tetramethyl piperidine as a base, which resulted in no reaction. Our attempt to alkylate 3-(6-amino-purin-9-yl)-propionitrile (**5**) under similar conditions also failed.

Holy has prepared the methyl ester of **10** from **9**[28] in three steps: a) alkylation with chloroacetonitrile; b) alkylation of the active methylene group with allyl bromide; and c) basic hydrolysis of the nitrile to the ester with sodium methoxide in methanol.[24,26] We have followed the same concept of alkylation, but we attempted to introduce allyl and ester functionalities at the same time using **6** as the alkylating agent on **9** (Scheme 2). Various reaction conditions, such as different bases (NaH and DBU), solvents (THF and DMF), and the temperature, were examined for the alkylation of compound **9** with **6**. The best results were obtained when NaH and **9** were heated at 100°C in DMF for 1 h, followed by the addition of the electrophile **6** to the anion at room temperature and stirring at room temperature for 16 h. This reaction resulted in a mixture of N^7 (**10**) and N^9 (**12**) isomers in the ratio of 4



SCHEME 2

to 1 and the N^7-alkylated product **10** was isolated as a white solid by the filtration of the cold reaction mixture in 21% yield. The filtrate containing both N^9 and N^7 isomers was concentrated and chromatography of the residue gave the product, which on recrystallization further yielded 17% of the N^7 derivative. The structure of N^7 isomer was confirmed by X-ray crystallography (Chart 2) and comparison of the NMR spectrum with the corresponding methyl ester reported by Holy.[26] This method is much superior in terms of number of steps, isolation of the product, and yield.

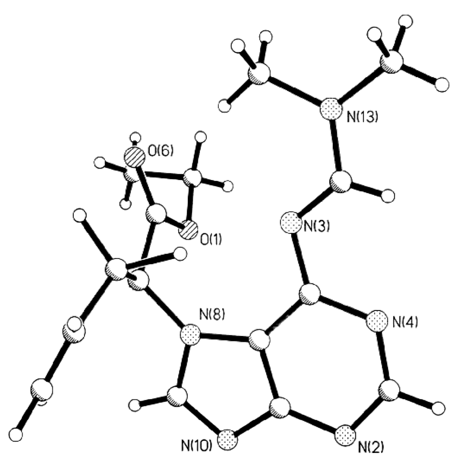


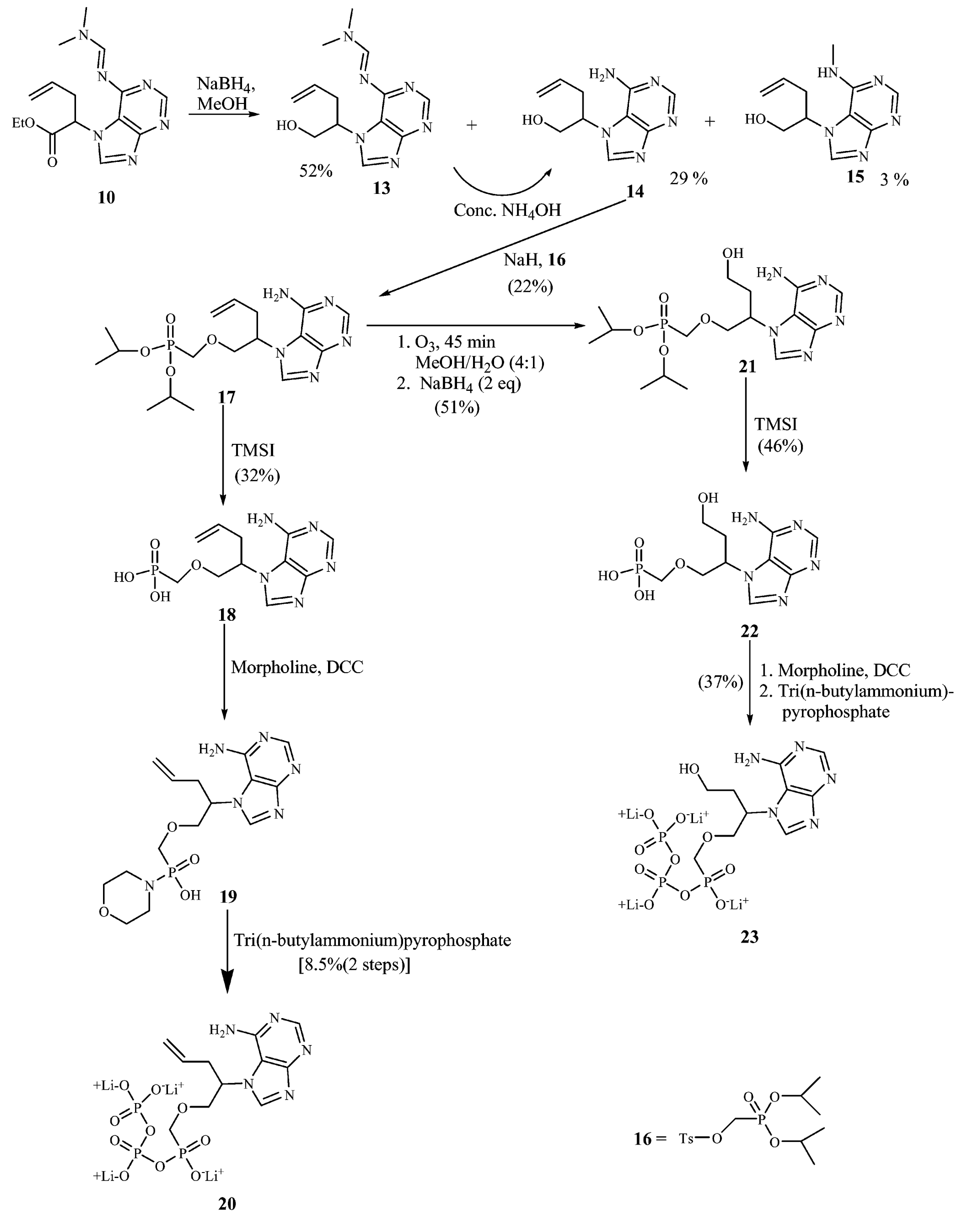
Chart 2

The methods of choice for the synthesis of the C-1′-substituted N^9 nucleosides are through the Mitsunobu reaction and building of the purine base.[29,30] In one case, the acetoxy group was used as the leaving group, which is rather difficult to prepare compared to the bromo compounds.[31] Holy prepared these types of compounds, again taking advantage of the active methylene group of the side chain through condensation of aldehydes. In our approach, direct alkylation of adenine **8** with **6** was achieved to produce compound **11** in DMF using sodium hydride as base, which is an easy method and might become a method of choice for C-1′-substituted acyclic nucleosides. Again, both allyl and ester groups are very useful for conversion to other groups.

Further modifications of the ester to hydroxymethyl and allyl to hydroxyethyl were based upon known literature procedures. Reduction of the ester group in **10** (Scheme 3) with sodium borohydride in MeOH gave the desired hydroxymethyl product **13** in 52% yield, N^6-deprotected **14** in 29% yield, and N-methylated product **15** in 3% isolated yield, which were easily separated by chromatography on a silica gel column. The NMR spectra of compounds **13** and **14** match the NMR spectra of the same compounds reported by Holy.[26] Compound **13** was hydrolyzed to compound **14** under basic conditions.[26] Phosphonomethyl derivative **18** was prepared from **14** by the reaction of sodium hydride and p-toluenesulfonyloxymethylphosphonate[32] (**16**) to give **17** followed by TMSI-mediated hydrolysis. The phosphonic acid **18** thus obtained was converted to **19** using morpholine and DCC as the activating reagent. Reaction of **19** with tri(n-butylammonium)pyrophosphate furnished the pyrophosphorylphosphonate **20**.[33] Ozonolysis of the terminal alkene in compound **17** followed by reduction with $NaBH_4$ gave the desired alcohol **21**, which was converted to the pyrophosphorylphosphonate **23** via the phosphonic acid **22** as described for compound **20**.

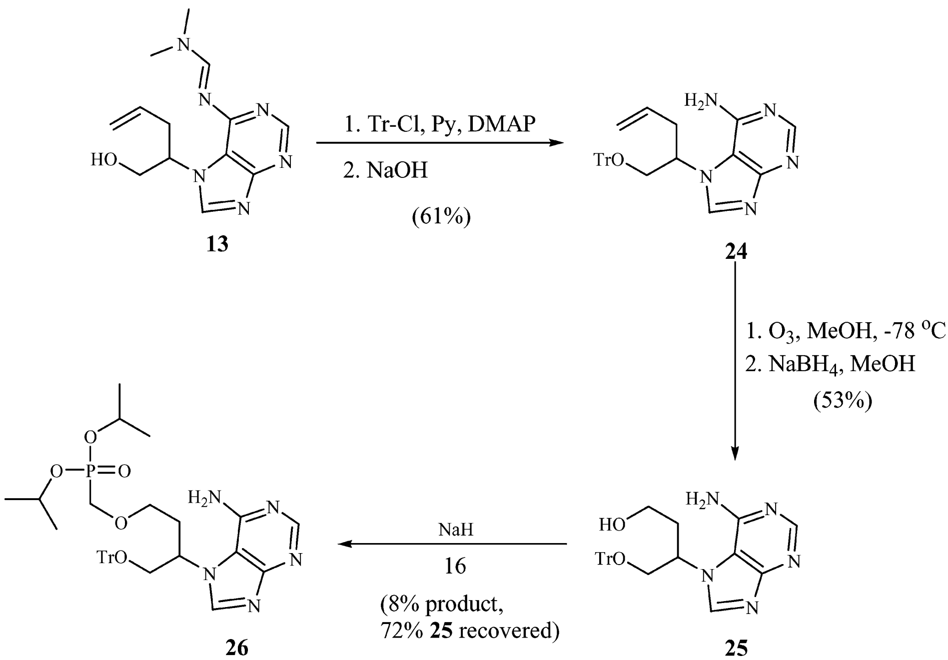
Our next goal was to prepare compound **36** from **13**. Protection of the hydroxyl group in **13** (Scheme 4) with trityl followed by basic hydrolysis of imine gave adenine derivative **24**. The ozonolysis of **24** and the reduction of the resultant ozonide occurred smoothly and **25** was isolated. Phosphonomethylation of **25** under similar conditions as used for **14** resulted in a messy reaction and gave the phosphonate **26** only in 8% yield. We attempted to run the same reaction sequence to improve the yield for compound **26** by modifying the protecting groups on the hydroxyl, such as THP, TBDPS, and MOM with no success.

To circumvent this problem, we decided to take an alternate convergent approach through alkylation of compound **9** with the corresponding phosphonate **31** (Scheme 5). The phosphonate **31** was prepared from known compound **27**.[34] Alkylation of **27** with **16** using NaH as base gave **28**, which upon hydrolysis with 80% aqueous acetic acid gave **29**. The primary hydroxyl group of **29** was selectively protected with trityl to give compound **30**, which on mesylation of the secondary hydroxyl group produced the desired alkylating



SCHEME 3

reagent **31**. Alkylation of compound **9** with phosphonate **31** using NaH as base resulted in slightly improved yield of 18% of the desired N^7 derivative **32**. The majority of alkylation occurred at N^9 position in this case, and 15% of **33** and 18% of **34** were isolated. The decrease in yield for the formation of N^7 compound **32** may be due to several reasons, such as the steric bulk of the alkylating reagent, low reactivity of the secondary carbon since the mesylate



SCHEME 4

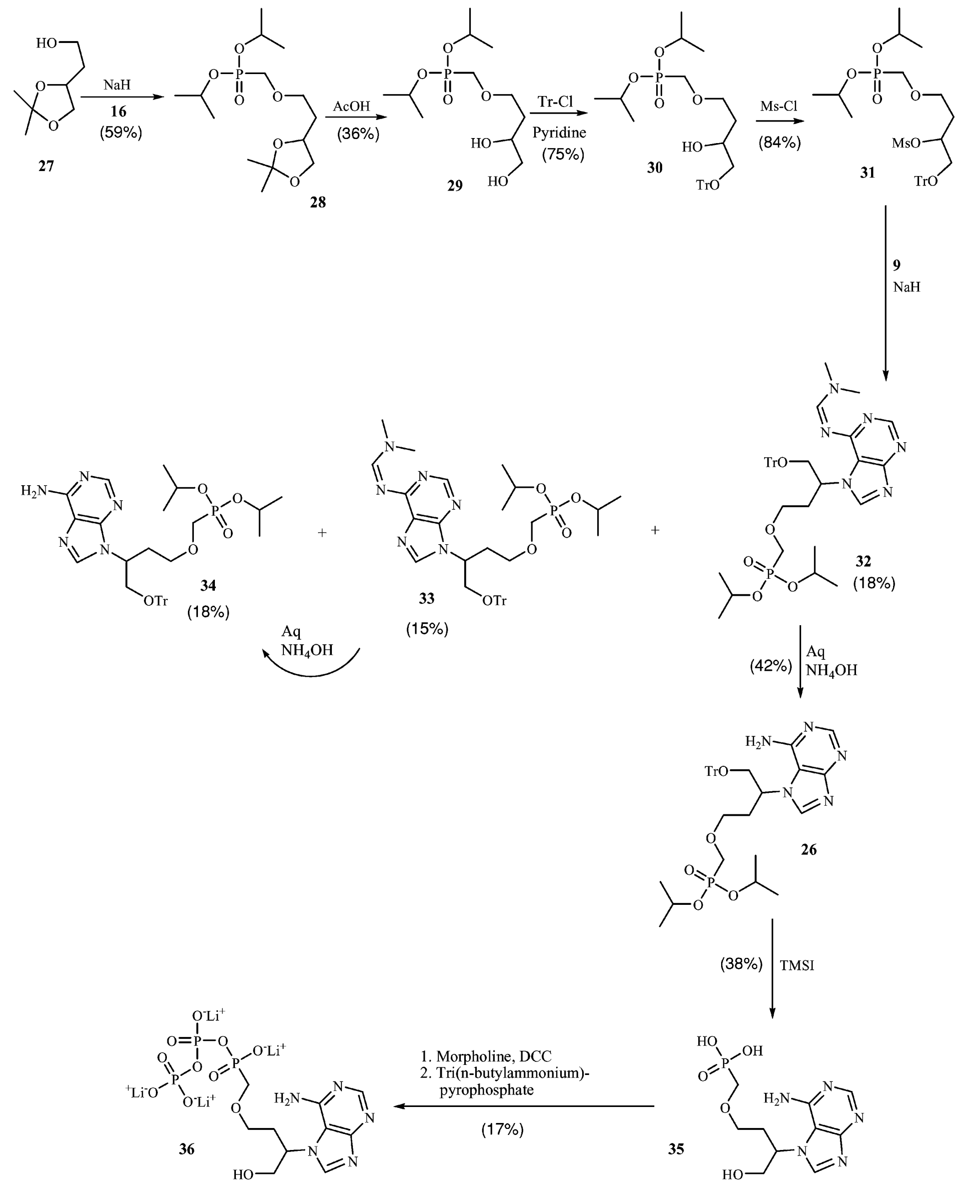
is a poor leaving group compared to bromo, and the absence of the electron-withdrawing group at the C-1′ position. Hydrolysis of compound **32** gave a compound whose NMR and TLC matches with compound **26** prepared in Scheme 4. Compound **26** was converted to pyrophosphorylphosphonate **36** via the phosphonic acid **35** as described for compound **20**.

BIOLOGICAL ACTIVITY

Compounds **18**, **20**, **22**, **23**, **35**, and **36** were evaluated for antiviral activity against HCV in replicon assay but showed poor activity.

EXPERIMENTAL

Unless otherwise stated, all reagents and solvents were purchased from Aldrich and used as received. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS at 0.00 or respective deuterated solvent peak. ^{31}P NMR chemical shifts are reported with respect to D_3PO_4 in D_2O as the external standard. Coupling constants (J) are reported in Hertz. IR spectra were obtained from films on NaCl plates for oils or KBr pellets for solids with a scan range of 4000–500 cm^{-1} on an FT-IR spectrometer (BioRad FTS-3500GX). Mass spectra data were acquired on a Waters ZMD mass spectrometer coupled



SCHEME 5

with a Waters System 2695 for loading of the samples in ES positive or negative mode. UV spectroscopy was carried out on an Agilent 8453 spectrophotometer. For the calculation of the concentration of phosphonates in solution by UV, the reported value of 7-*β*-D-ribofuranosyl-7H-purin-6-amine was taken as reference. The elemental analysis (C, H, and N) were performed by Atlantic Microlab in Norcross, Georgia. The TLC solvent systems CMA-80 and CMA-50 refers to chloroform:methanol:conc. NH_4OH (80:18:2) and chloroform:methanol:conc. NH_4OH (50:40:10), respectively. The non-UV active compounds were visualized by charring the TLC plate sprayed with ammonium molybdate cesium sulfate spray prepared by dissolving conc. H_2SO_4 (22.4 mL), $CeSO_4$ (45 mgs), $(NH_4)_6Mo_7O_{24}$·4 H_2O (7 g) in water in 100 mL volumetric flask. The olefin compounds were visualized by using $KMnO_4$ spray. Ozonolysis was performed using ozone generated by an ozonolyzer from Yanco Industries. Purification by flash column chromatography was performed on a Combiflash Sq16X manufactured by Isco using the appropriate solvent system as described in the experimental procedures.

***N,N*-Dimethyl-*N′*-(9*H*-purin-6-yl)-formamidine (9).** This was prepared by slight modification of the literature procedure.[28] To a mixture of adenine (43.8 g, 0.32 mol) and N,N-dimethylformamide dineopentyl acetal (150 g, 0.65 mol) was added DMF (150 mL) and heated at reflux for 1 h. Additional DMF (75 mL) was added to make the reaction mixture homogeneous and again heated at reflux for 1 h. The reaction mixture was cooled to room temperature and allowed to stand at room temperature for 16 h. The solid obtained was collected by filtration, washed with ethyl acetate (25 mL), and dried under vacuum to furnish 43.22 g (70%) of **9** as a white solid; mp 252–255°C; UV (MeOH) λ_{max} 308 nM; ^{1}H NMR (DMSO-d_6): δ 13.00 (bs, 1H), 8.89 (s, 1H), 8.44 (s, 1H), 8.28 (s, 1H), 3.19 (s, 3H), 3.14 (s, 3H); MS (ES$^+$) 191.59 [100% $(M+1)^+$]. Anal. Calcd for $C_8H_{10}N_6$: C, 50.52; H, 5.30; N, 44.18. Found: C, 50.50; H, 5.23; N, 44.02.

2-[6-(Dimethylamino-methyleneamino)-purin-7-yl]-pent-4-enoic Acid Ethyl Ester (10). To a suspension of NaH (60% suspension in mineral oil, 10.06 g, 0.26 mol) in DMF (700 mL) was slowly added **9** (47.5 g, 0.25 mol) using a solid addition funnel at room temperature. The reaction mixture became homogeneous after stirring for 10 min at room temperature and was then heated at 100°C for 1 h and cooled to room temperature. To this anion, **6** was added (43 mL, 0.29 mol) dropwise at room temperature and stirred for 16 h. The solid precipitated out and was collected by filtration and washed with ether and hexane (100 mL each) to furnish 17 g (21%) of **10** as a white solid. The filtrate was concentrated and purified by flash column chromatography on silica gel, eluting with 0 to 7.5% methanol in chloroform. The appropriate fraction was collected together and concentrated and the residue was recrystallized from ethanol (75 mL) to give 13.65 g (17%) of additional **10** as a white solid; mp 174–175°C; UV (MeOH) λ_{max} 320 nm; ^{1}H NMR (DMSO-d_6): δ 8.89 (s, 1H), 8.43 (s, 2H), 5.91 (m, 1H), 5.77–5.60 (m, 1H), 4.93 (d, $J = 10.0$ Hz, 2H), 4.10 (q, $J = 7.0$ Hz, 2H), 3.20 (s, 3H), 3.19–3.09 (m, 2H), 3.08 (s, 3H), 1.08 (t, $J = 7.0$ Hz, 3H); ^{13}CNMR ($CDCl_3$) : δ 14.16, 35.09, 35.99, 41.11, 59.16, 61.74, 116.97, 118.91, 133.80, 146.76, 152.30, 154.88, 156.96, 161.17, 169.8; IR (KBr) 3452, 3045, 2958, 2903, 2397, 1885, 1735, 1634, 1584, 1545, 1425 cm^{-1}; MS (ES^+) 339.45 [100% (M + Na)]. Anal. Calcd for: $C_{15}H_{20}N_6O_2$: C, 56.95; H, 6.37; N, 26.56. Found: C, 56.99; H, 6.48; N, 26.48. The filtrate was a mixture of **10** and **12**.

In a separate experiment on 1 mmol scale, the reaction mixture on purification by silica gel chromatography yielded both N^7 (**10**) and N^9 (**12**) isomers in the ratio of 4 to 1 and in 48% overall yield. The structure of **12** was confirmed by the following data **12**, UV (MeOH) λ_{max} 308 nm; ^{1}H NMR (DMSO-d_6): δ 8.9 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 5.74–5.58 (m, 1H), 5.46 (dd, J = 10.5 and 5.0 Hz, 1H), 4.98 (dd, J = 7.5 and 1.5 Hz, 1H), 4.91 (d, J = 10.5 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 3.18 (s, 3H), 3.11 (s, 3H), 3.11–2.93 (m, 2H), 1.13 (t, J = 7.0 Hz, 3H); ^{13}CNMR (DMSO-d_6) : δ 14.26, 34.85, 55.26, 55.92, 61.96, 119.15, 125.24, 133.38, 142.47, 151.92, 152.19, 158.39, 159.44, 169.38; IR (KBr) 3458, 3078, 2982, 2926, 2813, 1443, 1633, 1564, 1418, 1348, 1270, 1205, 1115, 1013 cm^{-1}; MS (ES^+) 317.54 [100% $(M+1)^+$]. Anal. Calcd for: $C_{15}H_{20}N_6O_2 \cdot 0.25\ H_2O$: C, 55.37; H, 6.51; N, 25.83. Found: C, 55.78; H, 6.42; N, 25.77.

2-(6-Amino-purin-9-yl)-pent-4-enoic Acid Ethyl Ester (11). A suspension of NaH (95%, 0.21 g, 8.5 mmol) and adenine (1.13 g, 8.38 mmol) in DMF (20 mL) was sonicated for 10 min and heated at 100°C for 2 h and then cooled to room temperature. To the anion formed was added **6** (2.18 g, 10.5 mmol) in DMF (2.5 mL) dropwise at room temperature and stirred for 16 h and concentrated. The residue on purification by flash column chromatography eluting with 0 to 7.5% methanol in chloroform gave 1.33 g (60%) of **11** as a white solid; mp 130–134°C; UV (MeOH) λ_{max} 260 nm; ^{1}H NMR (DMSO-d_6) : δ8.22 (s, 1H), 8.10 (s, 1H), 7.26 (bs, 2H), 5.75–5.58 (m, 1H), 5.38 (dd, J = 10.5 and 5.0 Hz, 1H), 4.98 (d, J = 17.5, 1H), 4.94 (d, J = 10.5 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 3.18–2.90 (m, 2H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}CNMR (DMSO-d_6) : δ 14.27, 34.82, 55.85, 61.93, 118.72, 119.10, 133.41, 140.55, 149.90, 152.82, 156.31, 169.46; IR (KBr) 3319, 3162, 2982, 2675, 1899, 1744, 1678, 1605, 1576, 1476, 1420, 1198, 1155 cm^{-1}; MS (ES^+) 284.50 [100% $(M + Na)^+$]. Anal. Calcd for: $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 54.93; H, 5.89; N, 26.78.

***N′*-[7-(1-Hydroxymethyl-but-3-enyl)-7*H*-purin-6-yl]-*N*, *N*-dimethyl-formamidine (13), 2-(6-Amino-purin-7-yl)-pent-4-en-1-ol (14), 2-(6-Methylamino-purin-7-yl)-pent-4-en-1-ol (15).** To a solution of **10** (18.96 g, 60 mmol) in methanol (600 mL) was added sodium borohydride (3.42 g, 90 mmol) portionwise at −5°C over a period of 2 h and further stirred for 1 h at −5°C. Additional sodium borohydride (0.43 g, 12 mmol) was added in two installments over a period of 2 h and the mixture stirred at 0°C for an additional 6 h and quenched with glacial acetic acid (18.9 mL, 320 mmol). After stirring for 30 min at room temperature, the reaction mixture was concentrated to dryness and the residue purified by flash column chromatography on silica gel column eluting with 0 to 25% methanol in chloroform to furnish, first **10** (3.11 g, 16%), followed by **13** (8.46 g, 52%), **15** (0.4 g, 3%), and **14** (3.83 g, 29%).

13, White solid; mp 155–156°C; UV (MeOH) λ_{max} 314 nm; ^{1}H NMR (DMSO-d$_6$): δ 8.91 (s, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 5.72 (m, 1H), 5.36 (m, 1H), 5.03 (t, $J = 5.6$ Hz, 1H), 4.96 (d, $J = 16.6$ Hz, 1H), 4.91 (d, $J = 10.0$ Hz, 1H), 3.93 (m, 1H), 3.78 (m, 1H), 3.21 (s, 3H), 3.11 (s, 3H), 2.73 (m, 2H); IR (KBr) 3271, 3090, 2926, 2870, 2356, 1633, 1688, 1547, 1391, 1350 cm^{-1}; MS (ES$^+$) 275.51 [100% $(M+1)^+$]. Anal. Calcd for: $C_{13}H_{18}N_6O$: C, 56.92; H, 6.61; N, 30.64. Found: C, 57.01; H, 6.65; N, 30.48.

14, Off-white solid; mp 186–188°C; UV (MeOH) λ_{max} 271 nm; ^{1}H NMR (DMSO-d$_6$): δ8.38 (s, 1H), 8.17 (s, 1H), 6.90 (s, 2H), 5.72 (m, 1H), 5.29 (bs, 1H), 5.05 (d, $J = 17.0$ Hz, 1H), 4.97 (d, $J = 10.0$ Hz, 1H), 4.83 (m, 1H), 3.73 (bs, 2H), 2.71 (m, 2H); IR (KBr) 3393, 3302, 3145, 2914, 2845, 2762, 1909, 1641, 1603, 1552, 1469, 1392, 1319 cm^{-1}; MS (ES$^+$) 220.56 [100% $(M+1)^+$]. Anal. Calcd for: $C_{10}H_{13}N_5O{\cdot}0.15\ H_2O$: C, 54.09; H, 6.04; N, 31.56. Found: C, 54.28; H, 5.97; N, 31.28.

15, Off-white solid; mp 180–181° C; UV (MeOH) λ_{max} 277 nm; ^{1}H NMR (DMSO-d$_6$): δ 8.34 (s, 1H), 8.26 (s, 1H), 6.94 (bs, 1H), 5.78–5.62 (m, 1H), 5.28 (t, $J = 5.0$ Hz, 1H), 5.04 (d, $J = 17.0$ Hz, 1H), 4.96 (d, $J = 10.0$ Hz, 1H), 4.88–4.77 (m, 1H), 3.72 (t, $J = 5.0$ Hz, 2H), 2.95 (d, $J = 4.5$ Hz, 3H), 2.81–2.62 (m, 2H); IR (KBr) 3380, 3112, 2913, 2862, 1611, 1561, 1471, 1393, 1352, 1227 cm^{-1}; MS (ES$^+$) 234.55 [100% $(M+1)^+$]. Anal. Calcd for: $C_{11}H_{15}N_5O$: C, 56. 64; H, 6.48; N, 30.02. Found: C, 56.67; H, 6.43; N, 30.11.

[2-(6-Amino-purin-7-yl)-pent-4-enyloxymethyl]-phosphonic Acid Diisopropyl Ester (17). A slurry of NaH (60%, suspension in mineral oil, 0.87 g, 21.68 mmol) and **14** (3.8 g, 17.34 mmol) in DMF (175 mL) was sonicated for 10 min at room temperature and stirred for an additional 30 min. To the anion formed was added **16**[23] (7.89 g, 22.55 mmol) in DMF (25 mL) dropwise at room temperature and stirred for 16 h. The reaction was quenched with glacial acetic acid (1.62 mL, 27 mmol) and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 0 to 25% methanol in chloroform to give 1.48 g (22%) of **17** as a beige solid; mp 120–126°C; UV (MeOH) λ_{max} 272 nm; ^{1}H NMR (DMSO-d$_6$): δ8.40 (s, 1H), 8.16 (s, 1H), 6.89 (bs, 2H), 5.79–5.63 (m, 1H), 5.12–4.94 (m, 3H), 4.54–4.39 (m, 2H), 3.96 (dd, $J = 10.0$ and 7.0 Hz, 1H), 3.85 (dd, $J = 10.0$ and 3.5 Hz, 1H), 3.77 (d, $J = 8.0$ Hz, 2H), 2.79–2.57 (m, 2H), 1.13 (d, $J = 6.2$ Hz, 6H), 1.08 (2 d, $J = 6.2$ Hz, 6H); ^{31}P NMR (DMSO-d$_6$) δ19.87; IR (KBr) 3335, 3158, 2981, 2935, 1655, 1603, 1550, 1584, 1474, 1389, 1256, 1093 cm^{-1}; MS (ES$^+$) 420.42 [100% $(M+Na)^+$]. Anal. Calcd for: $C_{17}H_{28}N_5O_4P$: C, 51.38; H, 7.10; N, 17.62. Found: C, 51.38; H, 7.02; N, 17.67. Unreacted **14** (2.41 g, **64%**) was recovered from the column.

[2-(6-Amino-purin-7-yl)-pent-4-enyloxymethyl]-phosphonic acid (18). To a solution of **17** (0.25 g, 0.63 mmol) in DMF (5 mL) at 0°C was added TMSI (0.89 mL, 6.29 mmol) and allowed to stir at room temperature for 16 h. The reaction was cooled to 0°C and again added TMSI (0.89 mL, 6.29 mmol) and stirred at room temperature for an additional 24 h. The reaction mixture was quenched with methanol (10 mL) and neutralized with triethylamine and concentrated to dryness under vacuum. The residue was purified by flash column chromatography using Combiflash Sq16X on 10 g silica gel, eluting with 0 to 100% methanol in CMA-50 to furnish 63 mg (32%) of **18** (calculated on the basis of UV absorption concentration in water of the purified product); UV (water) λ_{max} 272 nm; ^{1}H NMR (D_2O): δ 8.48 (s, 1H), 8.25 (s, 1H), 5.79–5.62 (m, 1H), 5.08–4.89 (m, 4H), 4.12–3.96 (m, 2H), 3.67 (m, 1H), 2.80 (t, $J = 7.0$ Hz, 2H). ^{31}P NMR (D_2O) δ 16.20; MS (ES^{+}) 314.4 [100% $(M+1)^{+}$].

Pyrophosphorylphosphonate of [2-(6-amino-purin-7-yl)-pent-4-enyloxymethyl]-phosphonic acid (20). A solution of N,N′-dicyclohexylcarbodiimide (0.33 g, 1.61 mmol) in *tert*-butyl alcohol (20 mL) was added to a stirred solution of **18** (63 mg, 0.20 mmol) and morpholine (0.26 g, 3.02 mmol) in aqueous *tert*-butyl alcohol (1:1; 40 mL) over a period of 15 min. The mixture was then heated at reflux for 5 h and morpholine (0.26 g, 3.02 mmol) and N,N′-dicyclohexylcarbodiimide (0.33 g, 1.61 mmol) in *tert*-butyl alcohol (20 mL) were again added and further heated at reflux for 20 h. The reaction mixture was concentrated to dryness to give crude **19** [MS (ES^{+}) 383.0 (100%; $M+1$)], which was used as such for the next step. Crude **19** was dissolved in DMSO (25 mL) and tri-n-butylammonium pyrophosphate (1.6 M tri-n-butylamine/1 M pyrophosphate, 0.67 g, 1.41 mmol) added to it. After stirring at room temperature for 3.5 days, the reaction mixture was triturated twice with ether (100 mL) and the ethereal phase removed by decantation. The residue was washed once more with ether (100 mL) and traces of ether removed under vacuum. The residue obtained was dissolved in water (10 mL) and filtered to remove insoluble material. The filtrate was purified by diethylaminoethyl (DEAE) weak anion with a Sepharose FF column (50 g) using triethylammonium hydrogen carbonate (TEAB) as buffer 0 to 0.1 M in water (700 mL). The product was found contaminated with pyrophosphate and trisodium metaphosphate by ^{31}P NMR spectrum analysis. The crude product obtained was dissolved in water (2 mL) and applied on a column of Dowex 1X2 (Cl-form; 100 mL), elution with linear gradient of 0–0.4 mol L^{-1} lithium chloride in 0.01 mol L^{-1} hydrochloric acid (500 mL). The relevant product fractions were combined, neutralized with 0.5 mol L^{-1} lithium hydroxide to pH 6.7–6.8, and concentrated under vacuum to dryness. The thick suspension was mixed with ethanol (30 mL) and centrifuged. The sediment obtained was washed with ethanol and dried under vacuum at room temperature to furnish desired triphosphate **20** (8.5 mg, 8.5%); UV (water) λ_{max} 271 nm; ^{1}H NMR (D_2O): δ 8.24 (s, 1H), 8.00 (s, 1H), 5.56–5.40 (m, 1H), 4.85–4.71 (m, 3H), 3.92 (dd, $J = 3.7$ and 10.4 Hz, 1H), 3.83 (dd, $J = 7.9$ and 10.4 Hz, 1H), 3.60 (d, $J = 8.1$ Hz, 2H), 2.58 (t, $J = 7.5$ Hz, 2H); 31PNMR (D_2O) δ 9.25 (dt, $J = 8.9$ and 25.2 Hz, 1P), −4.10 (d, $J = 19.3$ Hz, 1P), −19.63 (dd, 19.3 and 25.2 Hz, 1P); MS (ES$^+$) 498.06 [100% (M+1)$^+$]. Anal. Calcd for: $C_{11}H_{14}Li_4N_5O_{10}P_3\cdot 5\ H_2O\cdot LiCl$: C, 20.98; H, 3.85; N, 11.13. Found: C, 21.36; H, 3.88; N, 10.89.

[2-(6-Amino-purin-7-yl)-4-hydroxy-butoxymethyl]-phosphonic acid diisopropyl ester (21). A solution of **17** (0.98 g, 2.46 mmol) in methanol:water (4:1, 25 mL) was cooled to −78° C and oxygen slowly bubbled through it for 5 min. The reaction mixture was then ozonized for 1 h or until all starting material disappeared as evidenced by TLC analysis. To this reaction mixture at −78° C was added sodium borohydride (0.37 g, 9.87 mmol) in three portions over a period of 1 h and then allowed to warm to room temperature for 16 h and quenched with acetic acid (2.9 mL, 49.35 mmol). After stirring for 10 min at room temperature, the mixture was concentrated and the residue obtained was purified by flash column chromatography using Combiflash Sq16X on 40 g silica gel, eluting with 0 to 10% methanol in chloroform to furnish 0.5 g (51%) of **21** as a white solid; mp 138°C; UV (MeOH) λ_{max} 271 nm; ^{1}H NMR (DMSO-d_6): δ 8.42 (s, 1H), 8.17 (s, 1H), 6.86 (bs, 2H), 5.03–4.92 (m, 2H), 4.54–4.36 (m, 2H), 4.01 (dd, $J = 10.0$ and 7.0 Hz, 1H), 3.89 (dd, $J = 10.0$ and 3.0 Hz, 1H), 3.75 (d, $J = 8.0$ Hz, 2H), 3.52–3.40 (m 1H), 3.33–3.22 (m, 1H), 2.14–1.97 (m, 2H), 1.13 (d, $J = 6.0$ Hz, 6H), 1.08 (2d, $J = 6.0$ Hz, 6H); ^{31}P NMR (DMSO-d_6): δ 19.86; MS (ES$^+$) 402.44 [100% $(M+1)^+$]. Anal. Calcd for: $C_{16}H_{28}N_5O_5P$: C, 47.87; H, 7.03; N, 17.44. Found: C, 48.03; H, 7.03; N, 17.17.

[2-(6-Amino-purin-7-yl)-4-hydroxy-butoxymethyl]-phosphonic acid (22). Prepared from **21** (0.18 g, 0.44 mmol) using the same procedure as described for **18** to give 66.3 mg (46%) of **22** (calculated on the basis of UV absorption concentration in water of the purified product); UV (water) λ_{max} 272 nm; ^{1}H NMR (D_2O): δ 8.24 (s, 1H), 7.99 (s, 1H), 4.78–4.68 (m, 1H), 3.80–3.69 (m, 2H), 3.43–3.29 (m, 3H), 3.20–3.12 (m, 1H), 2.00 (q, $J = 6.78$ Hz, 2H). ^{31}P NMR (D_2O) δ 16.25; MS (ES$^+$) 318.4 [100% $(M+1)^+$].

Pyrophosphorylphosphonate of [2-(6-amino-purin-7-yl)-4-hydroxy-butoxymethyl]-phosphonic acid (23). Prepared from **22** (63 mg, 0.20 mmol) using the same procedure as described for **20** to give **23** (37 mg, 37%); UV (water) λ_{max} 271;^{1}H NMR (D_2O): δ 8.61 (s, 1H), 8.39 (s, 1H), 5.11–5.02 (m, 1H), 4.12–4.09 (m, 1H), 4.04–3.98 (m, 1H), 3.82–3.78 (m, 2H), 3.73–3.66 (m, 1H), 3.51–3.44 (m, 1H), 2.35–2.28 (m, 2H); ^{31}P NMR (D_2O): δ 9.09 (dt, $J = 10.0$ and 24.5 Hz, 1P), −9.56 (d, $J = 20.7$ Hz, 1P), −22.02 (dd, $J = 19.3$

and 24.5 Hz, IP); MS (ES$^+$) 502.17 [100% $(M+1)^+$]. Anal. Calcd for: $C_{10}H_{14}Li_4N_5O_{11}P_3$·4 H_2O·0.25 LiCl: C, 20.56; H, 3.80; N, 12.00. Found: C, 20.85; H, 4.00; N, 11.70.

7-(1-Trityloxymethyl-but-3-enyl)-7H-purin-6-ylamine (24). To a solution of **13** (0.29 g, 1.07 mmol) in pyridine (10 mL) was added trityl chloride (0.75 g, 2.67 mmol) and DMAP (0.012 g, 0.1 mmol) and stirred at room temperature for 2 days. The reaction mixture was concentrated and the residue dissolved in methanol (10 mL) and an aqueous NaOH solution (1N, 5 mL, 5 mmol) added. After stirring for 2 days at room temperature, the mixture was concentrated and the residue purified by flash column chromatography using Combiflash Sq16X (on 10 g silica gel), eluting with 0 to 10% methanol in chloroform to furnish 0.3 g (61%) of **24** as a white solid; mp 210°C (dec); UV (MeOH) λ_{max} 271 nm; ^{1}H NMR (DMSO-d_6): δ 8.50 (s, 1H), 8.21 (s, 1H), 7.23–7.16 (m, 9H), 7.11–7.04 (m, 6H), 6.88 (bs, 2H), 5.76–5.60 (m, 1H), 5.14–5.04 (m, 2H), 4.97 (dd, $J=10.0$ and 2.0 Hz, 1H), 3.22 (dd, $J=10.0$ and 3.0 Hz, 1H), 3.13 (dd, $J=10.0$ and 5.0 Hz, 1H), 3.02–2.89 (m 1H), 2.86–2.74 (m, 1H); MS (ES$^+$) 484.42 [100% (M + Na)]. Anal. Calcd for: $C_{29}H_{27}N_5O$·0.75 H_2O : C, 73.32; H, 6.05; N, 14.74. Found: C, 73.40; H, 5.79; N, 14.81.

3-(6-Amino-purin-7-yl)-4-trityloxy-butan-1-ol (25). Ozonolysis of **24** was accomplished the same way as described for **21** to give **25** in 53% yield as a white solid; ^{1}H NMR (DMSO-d_6): δ 8.50 (s, 1H), 8.21 (s, 1H), 7.23–7.15 (m, 9H), 7.12–7.05 (m, 6H), 6.82 (bs, 2H), 5.02 (bs, 1H), 4.74 (t, $J=5.0$ Hz, 1H), 3.49–3.37 (m, 2H), 3.29–3.15 (m, 2H), 2.40–2.34 (m, 1H), 2.16–2.01 (m, 1H); MS (ES$^+$) 488.38 [100% $(M+Na)^+$].

[3-(6-Amino-purin-7-yl)-4-trityloxy-butoxymethoxymethyl]-phosphonic acid diisopropyl ester (26) from 25. A slurry of NaH (60%, suspension in mineral oil, 0.015 g, 0.38 mmol) and **25** (0.14 g, 0.3 mmol) in DMF (3 mL) was sonicated for 10 min at room temperature and stirred for an additional 30 min at 50°C. To the anion formed was added **16** dropwise at room temperature (0.133 g, 0.38 mmol) in DMF (1 mL). The reaction mixture was stirred at room temperature for 2.5 h and at 50°C for 1 h, then cooled to room temperature and quenched with glacial acetic acid (0.022 mL, 0.38 mmol). The reaction mixture was concentrated to dryness and the residue taken in chloroform (10 mL) and washed with water (2 × 10 mL). The organic layer was separated, dried over $MgSO_4$, concentrated to dryness, and the residue purified by flash column chromatography using Combiflash Sq16X on 10 g silica gel, eluting with 0 to 100% CMA-80 in chloroform to give 0.015 g (8%, 27% based upon recovered starting material) of **26** as oil; ^{1}H NMR (DMSO-d_6): δ 8.57 (s, 1H), 8.21 (s, 1H), 7.23–7.15 (m, 9H), 7.08–7.04 (m, 6H), 6.83 (bs, 2H), 5.02 (bs, 1H), 4.61–4.44 (m, 2H), 3.64 (d, $J = 7.0$ Hz, 1H), 3.50 (t, $J = 5.0$ Hz, 1H), 3.29–3.08 (m, 4H) 2.36–2.09 (m, 2H), 1.21–1.14 (m, 12H); ^{31}P NMR (DMSO-d_6): δ 20.76; ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H), 8.22 (s, 1H), 7.33–7.25 (m, 15H), 5.70 (bs, 2H), 4.99–4.88 (m, 1H), 4.78–4.62 (m, 2H), 3.62 (dd, $J = 9.0$ and 5.0 Hz, 2H), 3.59–3.54 (m, 2H), 3.42 (t, $J = 5.0$ Hz, 2H), 2.44–2.18 (m, 2H), 1.36–1.25 (m, 12H); ^{31}P NMR ($CDCl_3$): δ 19.73; MS (ES$^+$) 644.40 [100% $(M+1)^+$]. Unreacted **25** (0.1 g, 72%) was recovered from the column.

26 from 32. To a solution of **32** (0.075 g, 0.11 mmol) in methanol (2.5 mL) was added conc. NH_4OH (5 mL) and stirred at room temperature for 3 days. Additional conc. NH_4OH (5 mL) and MeOH (0.5 mL) were added and stirred for 24 h and the process was repeated once more. The reaction mixture was concentrated under vacuum to furnish a residue, which was triturated with hexane and filtered to furnish 0.03 g (42%) of **26** as a white solid. All spectral data are the same as given above.

(3,4-Dihydroxy-butoxymethyl)-phosphonic acid diisopropyl ester (29). A suspension of NaH (60%, suspension in mineral oil, 2.52 g, 63 mmol) in DMF (40 mL) was treated at room temperature with 2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethanol[32] (**27**) (3.06 g, 21 mmol) in DMF (10 mL) and the reaction mixture further stirred for 1 h. To the anion formed **16** was added dropwise at room temperature (7.35 g, 21 mmol) in DMF (10 mL) and stirred for 16 h before quenching with glacial acetic acid (3.75 mL, 62.5 mmol). The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (3×75 mL). The organic layers were combined, washed with water (2×75 mL) and brine (75 mL), and dried over $MgSO_4$. After filtration, the filtrate was concentrated to furnish [2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethoxymethyl]-phosphonic acid diisopropyl ester (**28**, 4 g, 59%) as an oil; MS (ES$^+$) 347.39 [100% $(M+Na)^+$]. The product obtained was pure by TLC analysis to be used for the next step. To **28** obtained above was added 80% acetic acid (150 mL) and stirred at room temperature for 16 h and concentrated to give an oily residue, which was purified by flash column chromatography on silica gel, eluting with 0 to 7.5% methanol in chloroform to furnish 1.24 (36%) of **29** as an oil; ^{1}H NMR (DMSO-d_6): δ 4.64–4.55 (m, 2H), 4.49 (dd, $J = 11.5$ and 5.5 Hz, 2H), 3.68 (d, $J = 8.5$ Hz, 2H), 3.57 (dd, $J = 7.5$ and 6.0 Hz, 2H), 3.53–3.43 (m, 1H), 3.32–3.18 (m, 2H), 1.76–1.64 (m, 1H), 1.47–1.36 (m, 1H), 1.23 (dd, $J = 6.0$ and 2.5 Hz, 12H); ^{31}P NMR (DMSO-d_6): δ 21.02.

(3-Hydroxy-4-trityloxy-butoxymethyl)-phosphonic acid diisopropyl ester (30). To a solution of **29** (1.24 g, 4.37 mmol) in pyridine (40 mL) was added trityl chloride (1.34 g, 4.8 mmol) and DMAP (0.1 g, 0.44 mmol) and stirred at room temperature for 2 days. The reaction mixture was concentrated and the residue purified by flash column chromatography using Combiflash Sq16X on 40 g silica gel, eluting with 0 to 10% methanol in chloroform to furnish 1.72 g (75%) of **30** as an oil; ^{1}H NMR (DMSO-d_6): δ 7.43–7.18 (m, 15H), 4.77 (d, $J = 5.7$ Hz, 1H), 4.65–4.52 (m, 2H), 3.80–3.70 (m, 1H), 3.66 (d, $J = 8.5$ Hz, 2H), 3.61–348 (m, 2H), 3.00–2.90 (m, 1H), 2.81–2.74 (dd, $J = 8.7$ and 5.7 Hz, 1H), 1.86–1.72 (m 1H), 1.55–1.41 (m, 1H), 1.26–1.19 (m, 12H); MS (ES^+) 549.39 [100% $(M + Na)^+$].

Methanesulfonic acid 3-(diisopropyloxy-phosphorylmethoxy-1-trityloxy-methyl-propyl ester (31). To a solution of **30** (1.72 g, 3.3 mmol), triethylamine (0.7 mL, 4.95 mmol) and DMAP (0.02 g, 0.17 mmol) in dichloromethane (33 mL) at 0°C was added methanesulfonyl chloride (0.32 mL, 8 mmol) and the mixture allowed to warm to room temperature and stirred for 16 h. After quenching the reaction mixture with aqueous HCl (0.2 N, 25 mL), the organic layer was separated and washed with brine (25 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated. The residue obtained was purified by flash column chromatography using Combiflash Sq16X on 40 g silica gel, eluting with 0 to 5% methanol in chloroform to furnish 1.68 g (84%) of **31** as an oil; ^{1}H NMR (DMSO-d_6): δ 7.44–7.23 (m, 15H), 4.85–4.75 (m, 1H), 4.65–4.47 (m, 2H), 3.64 (d, $J = 8.5$ Hz, 2H), 3.59–3.44 (m, 2H), 3.28 (dd, $J = 10.5$ and 3.5 Hz, 1H), 3.16 (s, 3H), 3.13–3.06 (m, 1H), 1.44 (q, $J = 6.0$ Hz, 2H), 1.26–1.17 (m, 12H); ^{31}P NMR (DMSO-d_6): δ 20.70; MS (ES^+) 627.30 [35% $(M + Na)^+$].

{3-[6-(Dimethylamino-methyleneamino)-purin-7-yl]-4-trityloxy-butoxy-methyl}-phosphonic acid diisopropyl ester (32); {3-[6-(dimethylamino-methyleneamino)-purin-9-yl]-4-trityloxy-butoxymethyl}-phosphonic acid diisopropyl ester (33); [3-(6-amino-purin-9-yl)-4-trityloxy-butoxymethyl]-phosphonic acid diisopropyl ester (34). To a suspension of NaH (60%, suspension in mineral oil, 0.044 g, 1.1 mmol) in DMF (5 mL) was added at room temperature **9** (0.19 g, 1.0 mmol) and the reaction mixture heated at 100°C for 1 h. After cooling to room temperature, the anion formed (0.2 N solution in DMF, 3.5 mL, 0.7 mmol) was added to **31** (0.43 g, 0.71 mmol) in DMF (1 mL) and heated at 100°C for **4** h. The reaction mixture was cooled to room temperature and quenched with glacial acetic acid (0.15 mL, 2.5 mmol), diluted with water (10 mL), and extracted with chloroform (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and then dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue obtained was purified very carefully by flash column chromatography using Combiflash Sq16X on 10 g of silica gel, eluting with 0 to 10% methanol in chloroform to give first **33** (0.075 g, 15%) as an oil followed by **34** (0.080 g, 18%) as an oil and **32** (0.090 g, 18%) as an oil.

32, ^{1}H NMR ($CDCl_3$): δ 8.62 (s, 2H), 8.25 (s, 1H), 7.23–7.08 (m, 15H), 4.80–4.63 (m, 3H), 3.56 (d, $J = 8.0$ Hz, 2H), 3.55–3.41 (m, 3H), 3.12 (s, 6H), 3.02–2.79 (m, 2H) 2.42–2.22 (m, 1H), 1.39–1.19 (m, 12H); ^{31}P NMR ($CDCl_3$): δ 20.43; MS (ES^+) 721.36 [100% $(M+Na)^+$].

33, ^{1}H NMR ($CDCl_3$): δ9.00 (s, 1H), 8.41 (s, 1H), 8.07 (s, 1H), 7.25–7.08 (m, 15H), 4.85 (bs, 1H), 4.80–4.64 (m, 2H), 3.72 (t, J = 9.0 Hz, 1H), 3.55 (d, J = 8.0 Hz, 2H), 3.45–3.34 (m, 3H), 3.28 (s, 3H), 3.22 (s, 3H), 2.63–2.45 (m, 1H) 2.33–2.10 (m, 1H), 1.46–1.18 (m, 12H); ^{31}P NMR ($CDCl_3$): δ 20.40; MS (ES^+) 721.34 [100% $(M+Na)^+$].

34, ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H), 7.96 (s, 1H), 7.25–7.14 (m, 15H), 5.57 (bs, 2H), 4.90–4.65 (m, 3H), 3.69 (t, J = 9.0 Hz, 1H), 3.57 (d, J = 8.0 Hz, 2H), 3.54–3.12 (m, 3H), 2.63–2.45 (m, 1H) 2.31–2.11 (m, 1H), 1.47–1.18 (m, 12H); ^{31}P NMR (DMSO-d_6): δ 20.64; MS (ES^+) 666.36 [100% $(M+Na)^+$].

[3-(6-Amino-purin-7-yl)-4-hydroxy-butoxymethyl]-phosphonic acid (35). Prepared from **26** (0.14 g, 0.22 mmol) using the same procedure as described for **18** to give 26.8 mg (38%) of **35** (calculated on the basis of UV absorption concentration in water of the purified product); ^{1}H NMR (D_2O): δ 8.18 (s, 1H), 7.89 (s, 1H), 4.74–4.64 (m, 1H), 3.79 (d, J = 5.1 Hz, 2H), 3.43–3.33 (m, 2H), 3.25–3.18 (m, 2H), 2.12–2.06 (m, 1H), 1.98–1.87 (m, 1H); MS (ES^+) 318.34 [100% $(M+1)^+$].

Pyrophosphorylphosphonate of [3-(6-amino-purin-7-yl)-4-hydroxy-butoxymethyl]-phosphonic acid (36). Prepared from **35** (26.82 mg, 0.084 mmol) as described for **20** to afford **36** (7.5 mg, 17.6%); UV (water) λ_{max} 272 nM; ^{1}H NMR (D_2O): δ 8.37 (s, 1H), 8.13 (s, 1H), 4.87–4.77 (m, 1H), 3.94–3.88 (m, 2H), 3.66–3.54 (m, 2H), 3.45–3.29 (m, 2H), 2.32–2.19 (m, 1H), 2.14–2.03 (m, 1H), ^{31}P NMR (D_2O): δ 9.09 (d, J = 24.5 Hz, 1P), −3.85 (d, J = 19.3 Hz, 1P), −19.21 (t, J = 24.5 Hz, 1P).

CONCLUSION

We have developed an easy method to introduce allyl and ester functionalities at the C-1′ position of acyclic N^7 or N^9 nucleosides. These functional groups are very versatile and may be converted to the desired functional groups. These methods open a new area for the development of C-1′-branched N^7- and N^9-acyclic nucleosides.

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