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Supported Synthesis of Adenosine Nucleotides and Derivatives on a Benzene-Centered Tripodal Soluble Support

Lucie Appy,^[a] Suzanne Peyrottes,^[a] and Béatrice Roy*^[a]

The first soluble-phase synthesis of adenosine nucleotides including α,β and β,γ -methylene bisphosphonate analogues on a multi-pod support is reported. Anchoring of a 2',3'-protected purine nucleoside to the tripodal support via the nucleobase was successfully achieved using a microwave assisted Cu(I)-catalyzed azide-alkyne cycloaddition. Then, phosphorylation was performed, followed by cleavage with aqueous ammonia

to provide adenine derivatives, and finally deprotection. When using benzylamine instead of ammonia, a derivative with N⁶-benzylamine adenine as nucleobase was obtained. This methodology allows to access adenosine 5'-mono, di and triphosphates, as well as various analogues of pharmacological interest in modest to good yields.

Introduction

Nucleotides and their conjugates represent a valuable class of biomolecules involved in key functional and structural roles in cells. Their analogues have also found applications as therapeutic^[1] and diagnostic agents,^[2] as well as tools for the study of biochemical and pharmacological processes.^[3,4] Several chemical methods for their preparation have been developed,^[5] implying classical solution synthesis, solid-phase synthesis,^[6] and liquid-phase synthesis using a polymer as support^[7,8] or ionic liquids.^[9] New reagents and strategies have also emerged recently.^[10] Still, solution phase dominates the field. The use of soluble supports has been regarded as an approach that could combine the advantageous features of both solution and solid-phase syntheses. In this regard, we previously reported strategies using polyethyleneglycol (PEG) support to gain access to 5'-polyphosphorylated derivatives of cytidine and analogues. This last was based on the anchoring of the exocyclic amino group of the pyrimidine to basolabile succinyl or traceless carboxylethoxy linkers, followed by regioselective 5'-phosphorylation and release from the support.^[7,8] However, its application to purine derivatives failed.^[8] Therefore, we turned our attention to an alternative soluble-supported approach to anchor purines. So far, a single and short report on ionic-tag-assisted synthesis of 2'-deoxyadenosine-5'-triphosphate (dATP) has been reported.^[9] Thus, a soluble-phase methodology affording purine-containing nucleotides remains an appealing area of research. Soluble-supported synthesis has received continuous

interest in the field of oligonucleotides as an alternative approach to solid-phase synthesis.^[11] Several protocols reported the preparation of both DNA and RNA oligomers of limited length in gram scale without any special equipment. The 3'-terminal protected nucleoside is attached through its 2' or 3' hydroxyl via a linker to the soluble support and elongation is carried out in the 3'→5' direction. Interestingly, this synthetic strategy in solution involves a smaller excess of building blocks, the scale up procedure is straightforward and expensive solid support materials is not required.

To formulate our work plan, we considered (i) anchoring of the nucleoside to the support through the nucleobase, (ii) synthesis of the supported nucleoside and phosphorylation steps, and (iii) suitable cleavage conditions considering the stability of the final products. In this regard, the Huisgen 1,3-dipolar cycloaddition of azides (1,3-dipolar partner) and alkynes (dipolarophile) to form 1,2,3-triazoles has become an invaluable tool for biorthogonal conjugation,^[12] with many applications in the field of nucleoside, nucleotide, and oligonucleotide chemistry.^[13] In 2010, Mathew and co-workers reported the synthesis of new C(6) 1,2,3-triazole adenosine derivatives via a Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC).^[14] Noteworthy, whatever the conditions used to perform the 1,3-dipolar cycloaddition of 6-azido-9-(β -D-ribofuranosyl)purine and phenylacetylene, the main product of the reaction was adenosine, originating from the reduction of the azide moiety. However, the "click reaction" could be accomplished using a C(6) acetylene nucleoside as dipolarophile in the presence of azides under microwave activation.^[14] The same year, Lakshman and co-workers reported successful CuAAC reaction of sugar-protected C(6) azidopurine nucleosides with alkynes affording the corresponding 1,4-disubstituted triazolyl products.^[15] Several reports from Turk's group have also focused on CuAAC reactions between 2,6-diazidopurine nucleosides and terminal alkynes.^[16,17] They showed that 2,6-bis-triazolylpurine nucleosides could undergo regioselective nucleophilic aromatic substitution with S- and N-nucleophiles at the C(6) position.^[16]

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Similarly, S_NAr -Arbuzov reactions using trialkylphosphites afforded C(6) phosphonate purine derivatives.^[18]

Based on these data from the literature, we envisaged to anchor a C-6 azidopurine nucleoside to a soluble support possessing terminal alkynes via a copper-catalyzed azide-alkyne cycloaddition. Cleavage from the support using an ammonia solution would allow introduction of an amino function in place of the triazole, and therefore release adenine as a nucleobase in the final product (Scheme 1). In addition, substitution of the triazole by various nucleophiles would enable access to structural diversity. Finally, one major advantage of using a soluble support is the opportunity to run purifications by size-exclusion chromatography or precipitation.^[11]

Herein, we report an original soluble-phase synthesis of adenosine 5'-mono and polyphosphates using a tripod support. Synthetic methylene bisphosphonates of therapeutic interest were also obtained. These include α,β -methylene ADP and its N^6 -benzyl derivative, as well as β,γ -methylene ATP. The advantage of methylene bisphosphonates is the extreme stability of the P-C bonds, which precludes any enzymatic cleavage. Hence, such compounds can serve as chemical probes to investigate the mechanism of phosphoryl transfer processes, as well as enzyme inhibitors (e.g. *ecto*-5'-nucleotidase) with great potential as immune-oncology agents.^[19-21]

Results and Discussion

As the CuAAC is not achievable with unprotected 6-azido-9- β -D-ribofuranosylpurine^[14] but works well on the protected glycosyl derivatives,^[15] we decided to install a protecting group on the 2',3'-hydroxyl positions of the nucleoside, thus allowing to introduce (poly)phosphate or bisphosphonate moieties into the 5'-position. Our first attempts to link 2',3'-isopropylidene 6-

azido-9- β -D-ribofuranosylpurine **1** (Scheme 1) to tetrapodal pentaerythritol-based supports such as (2-propynyloxymethyl) methane^[22] or pentaerythrityltetrakis(3-ethynylphenyl)ether^[23] via Cu(I)-mediated azide-alkyne ligation were unsuccessful. Indeed, we faced several issues such as very low yields together with difficult isolation and characterization of the supported products (data not shown). We then considered the supports having a 1,3,5-trisubstituted benzene core decorated with terminal alkynes. Gratefully, 1,3,5-tris(prop-2-yn-1-yloxy) benzene **2** allowed us to achieve our goals. As outlined in Scheme 1, the supported nucleoside can readily be obtained by "click chemistry" between azidonucleoside **1** (1,3-dipolar partner) and derivative **2** (dipolarophile).

The synthesis of compound **2** started from inexpensive phloroglucinol and was performed according to a procedure adapted from the literature.^[24] Reaction of phloroglucinol with an excess of propargyl bromide and potassium carbonate in dry *N,N*-dimethylformamide (DMF) for 12 h at room temperature afforded the trialkyne **2** in 96% yield. On the other hand, 6-azido-9- β -D-ribofuranosylpurine **3** was synthesized in two steps from 6-chloro-9- β -D-ribofuranosylpurine (Scheme 2a) by reaction with hydrazine hydrate, followed by treatment with sodium nitrite in aqueous acetic acid at 0 °C (70% overall yield).^[25] Then, the 2',3'-*O*-isopropylidene protecting group was introduced by treatment with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluene sulfonic acid (PTSA) to afford **1** in 92% yield.^[26] Both 6-azidopurine and their nucleoside derivatives can exist in the alternate tetrazolyl forms.^[15,25,27] As shown in Scheme 2b, only the tetrazole form of **1** is observed in DMF-d₇ while both forms coexist in CDCl₃ (see the Supporting Information). Despite this equilibrium, it has been shown that azide-tetrazole mixtures can undergo successful CuAAC reactions to afford 1,4-disubstituted triazoles.^[15]



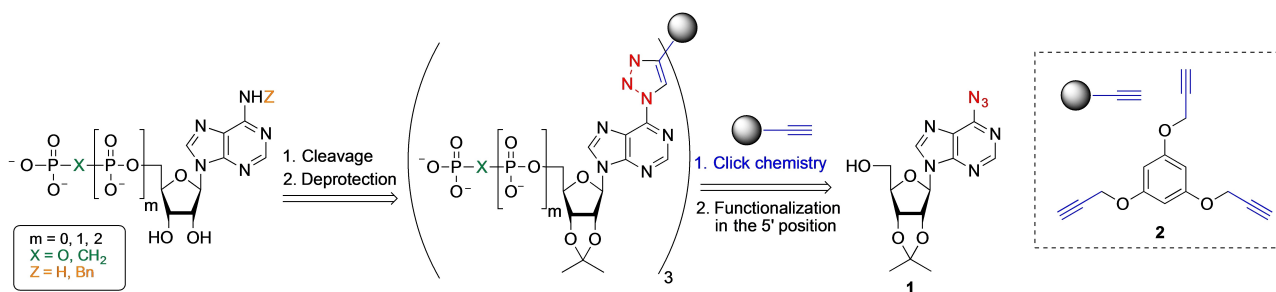
Béatrice Roy is Associate Professor at the University of Montpellier, France. She completed her PhD in 1993 at the University of Grenoble, where she worked under the supervision of Prof. M. Fontecave on the design of new inhibitors of the ribonucleotide reductase. She later held a postdoctoral position at the University of Paris Sud, where she was appointed as Lecturer in 1997. In 2002, she moved to the University of Montpellier in the research group of Dr G. Gosselin. She is currently working in the team "Nucleosides & Phosphorylated Effectors". Her research interests focus on the development of new synthetic methodologies for nucleotides and their derivatives for biomedical applications.



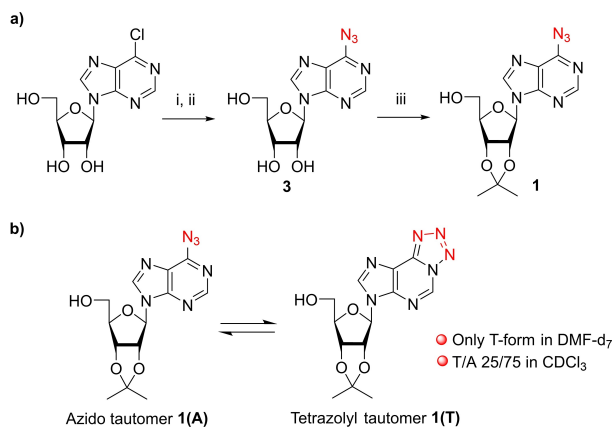
Lucie Appy obtained her master's degree in "Research and Innovation" at Montpellier University, France. She received her PhD in 2020 from the University of Montpellier, under the guidance of Dr. Béatrice Roy and Dr. Suzanne Peyrottes in the "Nucleosides & Phosphorylated Effectors" team. Her PhD project aimed at developing new synthetic methodologies that offer easy handling, short reaction time and simplified purification steps to obtain nucleotides and their conjugates.



Suzanne Peyrottes graduated in Chemistry from Montpellier University (France) and completed her postdoctoral study at the MRC (Cambridge, UK). She is currently Research Director at CNRS, working on the design of potential therapeutic agents to treat infections and cancers, while developing new synthetic methodologies related to nucleic acid components. She heads the team "Nucleosides & Phosphorylated Effectors" belonging to the Institute of Biomolecules Max Mousseron (IBMM, Montpellier, France).



Scheme 1. Retrosynthetic strategy for the synthesis of nucleotides and derivatives.



Scheme 2. a) Preparation of the azidonucleoside **1**. Reaction conditions and yields. (i) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, 0°C , 2 h; (ii) NaNO_2 , AcOH , 0°C , 2 h, 70% (2 steps); (iii) dimethoxypropane, PTSA, DMF, 40°C , 2 h, 92%. b) Azide-tetrazole equilibrium of **1**.

At the outset, the best conditions described for the CuAAC reaction of sugar-protected C-6 azidopurine nucleosides with phenylacetylene were considered.^[15] However, only reduction of **1** into 2',3'-*O*-isopropylidene adenosine was observed in the presence of CuSO_4/Na ascorbate in a biphasic $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ system (data not shown). Indeed, reduction of the azide moiety to the corresponding amine is a competing process in Cu-mediated azide-alkyne ligation.^[14–15]

Thus, optimization was carried out in DMF in the presence of 4 equiv. of azidonucleoside per support, Cu(I) as catalyst and *N,N*-diisopropylethylamine (DIPEA) as additive.^[28] While no cycloaddition was observed at room temperature (Table 1, entry 1), heating the reaction mixture at 80°C afforded the 1,4-triazole **4** in 30 min (Table 1, entry 2). The reaction was easily monitored by TLC since **4** shows fluorescence extinction at 254 nm as well as a blue spot upon irradiation at 365 nm. To our delight, the conversion was improved when microwave (MW) activation was applied,^[28] allowing to reduce both reaction time and temperature. The best conditions involved the use of CuI for 10 min at 40°C under microwave irradiations, giving rise to the supported nucleoside **4** in 97% yield, after precipitation from iced water (Table 1, entry 3). Therefore, in agreement with previous reports on click reactions with C-6 azidonucleosides,^[14,15] we found that the copper-catalyzed

Table 1. Optimization of reaction conditions for the click reaction.

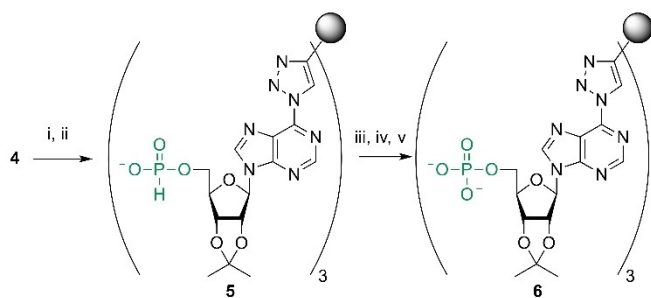
Entry ^a	Conditions	4 , Yield [%] ^b
1	rt, 24 h	–
2	80°C , 30 min	71
3	MW, 40°C , 850 W, 10 min	97

[a] Reaction conditions: **2** (0.2 mmol), **1** (0.8 mmol, 4.0 equiv), CuI (0.06 mmol, 0.3 equiv), DIPEA (1.2 mmol, 6.0 equiv), DMF (2.0 mL). [b] Isolated yield after precipitation.

cycloaddition of azide **1** and trialkyne **2** can be performed in excellent yields. Before carrying on the phosphorylation steps, we assessed the feasibility of cleavage of the supported nucleoside. Pleasingly, treatment of **4** with $\text{NH}_4\text{OH}/N$ -methylpyrrolidone (4:1) at 50°C for 24 h afforded quantitatively 2',3'-isopropylidene adenosine (data not shown). We thus moved forward with the next steps.

First, we considered phosphorylation with POCl_3 in triethylphosphate according to a protocol optimized for PEG-supported synthesis.^[7,8] However, these conditions led to degradation and low yields (data not shown). We then used P(III) chemistry involving a *H*-phosphonate intermediate (Scheme 3).^[7,29] Accordingly, the nucleoside 5'-*H*-phosphonate monoester **5** was prepared through transesterification of diphenylphosphite with **4** in pyridine.

Addition of water/ NEt_3 to the reaction mixture resulted in rapid hydrolysis of the nucleoside phenyl *H*-phosphonate diester intermediate (not isolated) to **5**, which was easily purified by size-exclusion chromatography. Silylation of **5** with *N,O*-bis(trimethylsilyl)acetamide (BSA) allowed the quantitative formation of the bis(trimethylsilyl)-phosphite, as shown by ^{31}P NMR (Figure 1). Then, oxidation with (–)-(8,8-dichlorocamphoryl-sulfonyl)oxaziridine (DCSO) to the corresponding bis(trimethylsilyl)phosphate, followed by hydrolysis gave rise to the supported nucleotide **6** in 60% overall yield (Scheme 3).



Scheme 3. Preparation of supported compound **6**. Reaction conditions and yields: (i) diphenylphosphite (20 equiv.), anhydrous pyridine, rt, 20 min; (ii) triethylamine/water 1:1, rt, 1 h, 82%; (iii) bis(trimethylsilyl)acetamide (20 equiv.), DMF, 50 °C, 2 h; (iv) DCSO (10 equiv.), rt, 2 h; (v) triethylamine/water 1:1, rt, 1 h, 60%.

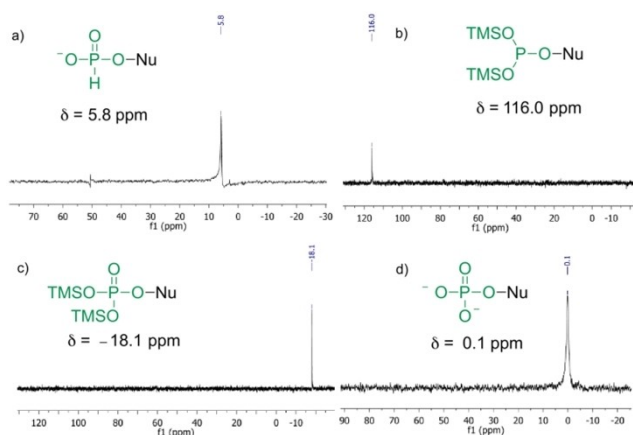


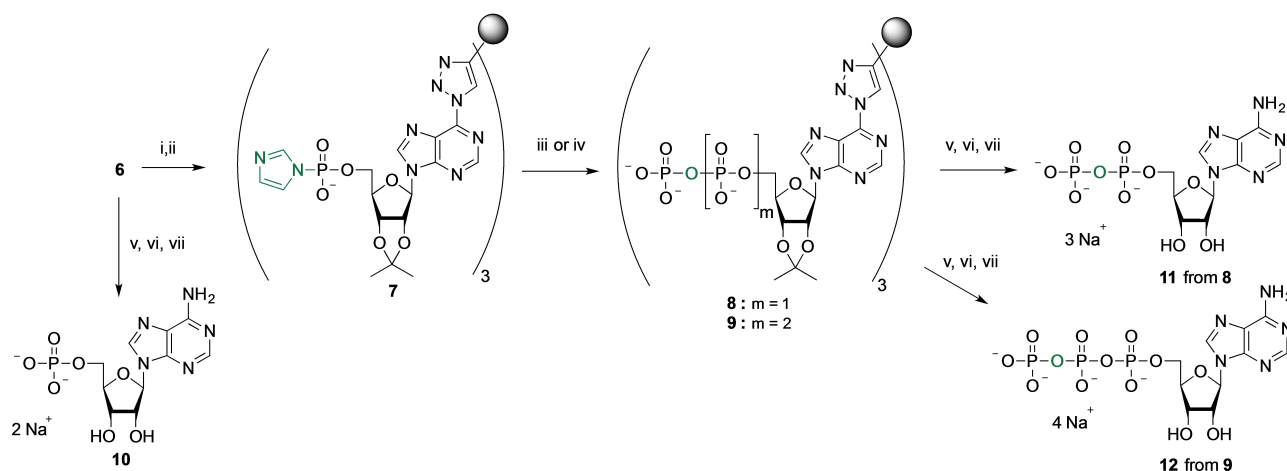
Figure 1. Stepwise conversion of **5** to **6** monitored by ^{31}P NMR. Aliquots of the reaction medium were taken at time intervals and diluted in a deuterated solvent for analysis. a) Before addition of BSA (D_2O), b) 2 h after addition of BSA (CDCl_3), c) 2 h after addition of DCSO (CDCl_3), d) 1 h after addition of $\text{NEt}_3/\text{H}_2\text{O}$ ($\text{DMSO}-d_6$).

A widely used P(V) method to prepare 5'-polyphosphorylated derivatives involves phosphorimidazolide intermediates.^[5a,c] Thus, activation of tri- or tetra-alkylammonium salts of a 5'-nucleotide with N,N' -carbonyldiimidazole (CDI) in dry DMF, followed by addition of the selected phosphoryl reagent affords a wide range of nucleotide derivatives. Accordingly, activation of supported nucleoside monophosphate **6** by an excess of CDI allowed to obtain quantitatively phosphorimidazolide **7** (Scheme 4), as shown by ^{31}P NMR (singlet at -10.6 ppm). After completion, the reaction mixture was treated with phosphate or pyrophosphate to afford the supported nucleoside 5'-diphosphate **8** or 5'-triphosphate **9**, respectively (Scheme 4). Isolation was easily performed by size-exclusion chromatography since the final compounds elute rapidly due to their high size compared to the P -reagents. Yields ranged from 68 to 78% over 3 steps.

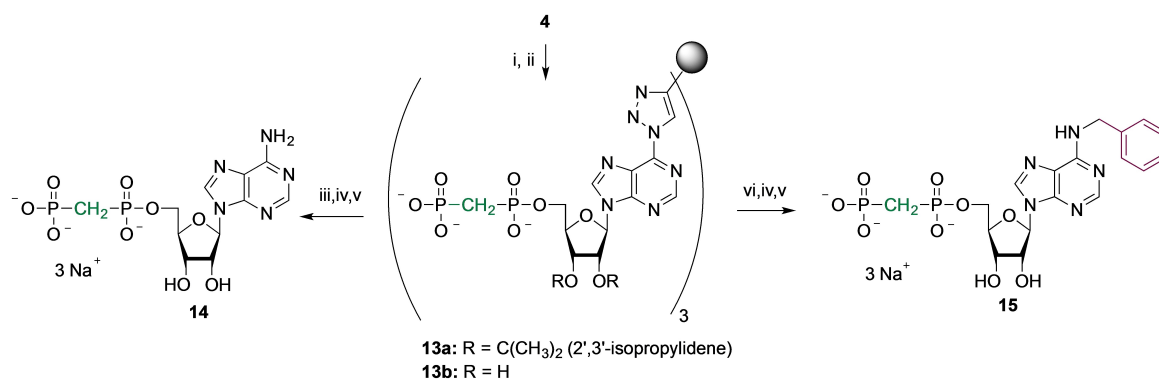
^1H NMR characterization of supported nucleoside and nucleotides was puzzling due to peak broadening that was presumably associated with intermolecular interactions. Nevertheless, ^{31}P NMR and HRMS were consistent with the expected structures.

Supported nucleotides **6** and **8–9** were first treated with concentrated aqueous ammonia (Scheme 4). After completion of the reaction, monitored by HPLC, the adenosine derivatives were purified by RP-18 chromatography, followed by ion exchange on Dowex- Na^+ , and fully characterized (see the Supporting Information). In the second step, removal of the acetonide group was performed using Dowex- H^+ in $\text{H}_2\text{O}/\text{MeOH}$. The resin was filtered off and then cation exchange was performed to provide AMP **10**, ADP **11** and ATP **12** as sodium salts. Pleasingly, we found that the two first steps could be carried out in a single pot, therefore increasing yields. Accordingly, compounds **10–12** were obtained in 40–66% (Scheme 4).

Finally, we expanded the scope of our strategy to relevant bisphosphonates such as α,β -methylene ADP and its N^6 -benzyl derivative which are a potent inhibitors of ecto-5'-nucleotidase



Scheme 4. Access to the supported nucleotides **7–9** and final compounds **10–12**. Reaction conditions and yields: (i) CDI (6 equiv.), DMF, rt, 1 h; (ii) MeOH (20 equiv.), rt, 30 min; (iii) tri- n -butylammonium phosphate (15 equiv.), rt, 20 h, 78% for **8**; (iv) bis(tri- n -butylammonium) pyrophosphate (15 equiv.), rt, 20 h, 68% for **9**; (v) NH_4OH 28%, 50 °C, 1–2 h; (vi) Dowex H^+ , $\text{H}_2\text{O}/\text{MeOH}$ (v/v 1:1), 5 h; (vii) Dowex Na^+ , 40–66% over 3 steps.



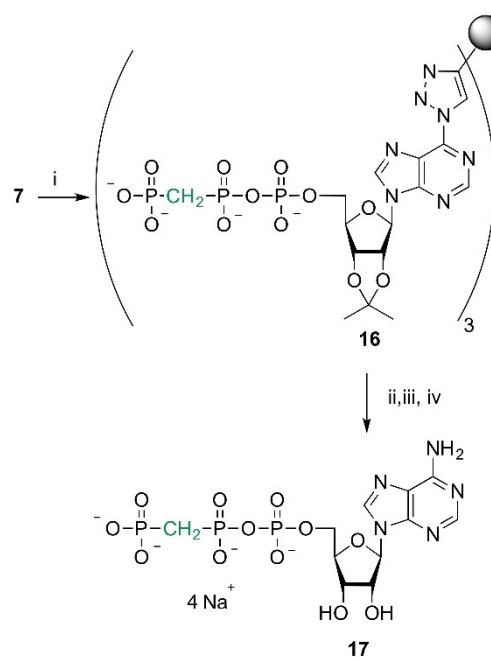
Scheme 5. Phosphorylation, cleavage and deprotection steps to give α,β -bisphosphonates analogues **14** and **15**. Reaction conditions: (i) CH₂(POCl₂)₂ (20 equiv.), trimethyl phosphate, 0 °C, 8 h; (ii) TEAB buffer, 0.5 M pH 7.6, rt, 15 min; (iii) NH₄OH 28%, 50 °C, 1–2 h; (iv) Dowex H⁺, H₂O/MeOH (v/v 1:1), 5 h; (v) Dowex Na⁺; (vi) Benzylamine, H₂O, 50 °C, 1 h. Yields: 30–31% for the last 3 steps.

(CD73) and exhibit pharmacological interest.^[19–21] Supported α,β -methylene bisphosphonates were obtained by 5'-phosphorylation of **4** with methylene bis(phosphonic dichloride) (Scheme 5).^[30] The reaction was carried out at 0 °C, with a 20-fold excess of the P-reagent in trimethylphosphate, and then quenched by addition of aqueous triethylammonium bicarbonate buffer (TEAB). The desired compound **13a** was obtained together with the deprotected side product **13b**, probably due to HCl formation during the reaction. After a straightforward size-exclusion chromatography, a 1:1 mixture of the triethylammonium salts of these two bisphosphonates was obtained in 37% yield. This mixture could be directly used in the next steps, i.e. cleavage with concentrated aqueous ammonia and deprotection, to give rise to adenosine 5'- O - α,β -methylenediphosphate **14** in 31% yield (Scheme 5). In addition, to extend the scope of our methodology, we also performed the cleavage step with benzylamine instead of ammonia. Accordingly, treatment of the mixture of **13a** and **13b** with benzylamine in water, followed by a deprotection step and cation exchange gave rise to compound **15** in 30% yield (Scheme 5).

Finally, supported adenosine β,γ -methylene triphosphate **16** was obtained by conversion of **6** to **7** and then substitution of the imidazole with methylene bis(phosphonate) as shown in Scheme 6. Compound **16** was subjected to cleavage with NH₄OH, removal of the protecting group and ion exchange to afford adenosine β,γ -methylene triphosphate **17** in 38% yield.

Conclusion

We have developed a new synthetic approach of adenosine nucleoside phosphoesters and methylenebisphosphonate derivatives using a tripodal soluble support. Immobilization of the C(6) azidopurine nucleoside to the alkyne trisubstituted benzene core decorated with terminal alkynes was performed efficiently by using the CuAAC reaction. Phosphorylation followed by cleavage from the support and removal of the protecting groups gave the desired products in modest to good yields. Using benzylamine instead of ammonia in the cleavage



Scheme 6. Preparation of β,γ -methylene triphosphate **17**. Reaction conditions: (i) bis(tri-*n*-butylammonium) methylene bisphosphonate (15 equiv), rt, 20 h, 53%; (ii) NH₄OH 28%, 50 °C, 1–2 h; (iii) Dowex H⁺, H₂O/MeOH (v/v 1:1), 5 h; (iv) Dowex Na⁺, 58% over 3 steps.

step allowed formation of a nucleotide with N⁶-benzylamine adenosine as nucleobase. Thus, the use of other nucleophiles could gain access to relevant N⁶-substituted ATP, such as analogues described for the “bump and hole” approach proposed by the Shokat research group.^[31] The opportunity to follow the reactions by HPLC or ³¹P NMR spectroscopy is one of the attractive features of this soluble-supported approach. Interestingly, most of the isolation procedures are based on straightforward precipitation or size-chromatography, which led to minimize the overall process time compared to solution synthesis.

Experimental Section

General: All the chemicals and solvents were purchased from commercial suppliers and used without further purification. Anhydrous DMF and pyridine, and Et₂O were commercially available, whereas MeOH and DCM were distilled from CaH₂, trimethyl phosphate over BaO under reduced pressure. Solids were dried over KOH pellets or P₂O₅ under reduced pressure at rt. Moisture sensitive reactions were performed under argon atmosphere using oven-dried glassware. Tri-*n*-butylammonium phosphate,^[32] bis(tri-*n*-butylammonium) pyrophosphate^[33] and bis(tri-*n*-butylammonium) methylenebisphosphonate^[34] were obtained following previously published procedures. Reactions that required heating were performed in a hot plate/heating block apparatus with internal temperature control. Microwave irradiation experiments were carried out in an Anton Paar microwave apparatus with continuous irradiation power of 850 W. Sealed reaction vessels were used and the reaction temperature was monitored with an internal probe. Analytical thin-layer chromatography was performed with commercial plates of silica gel 60, visualized with short-wavelength UV light (254 nm), and stained with a 5% ethanolic sulphuric acid, or using KMnO₄ dip with subsequent heating. Preparative flash chromatography was performed on silica gel 60 (particle size: 0.040–0.063 mm). Size exclusion chromatography was performed using Bio Gel P-2 Gel fine and H₂O as eluant. Ion exchange chromatography was carried out by percolation on a Dowex 50W-X8 (Na⁺ form) resin and H₂O as eluant followed by lyophilization. HPLC-UV analysis was performed using C18 3.5 μm 4.6×100 mm column. The mobile phase consisted of: (A) Trifluoroacetic acid 0.1% in water and (B) ACN applied at a flow rate of 0.3 mL·min⁻¹ in a gradient mode. A linear 15 min gradient from 0% to 100% B, followed by 5 min isocratic 100% B, and then a linear 1 min gradient from 100% to 0% B was used. ¹H NMR (300 or 400 MHz), ¹³C NMR (101, 126 or 151 MHz), and ³¹P NMR (162 MHz) spectra were obtained in CDCl₃ (δ_H 7.26 ppm, δ_C 77.16 ppm) or DMSO-*d*₆ (δ_H 2.50 ppm, δ_C 39.52 ppm) or D₂O (δ_H 4.79 ppm). Data are reported as follow: chemical shift (δ, ppm), multiplicity (s = singlet; d = doublet; dd = double doublet; t = triplet; q, quartet; bs = broad signal; and m = multiplet or not resolved signal). Coupling constants (*J*) are quoted in Hertz. High-resolution mass spectra (HRMS) were recorded on a Q-TOF Synapt-G2-S instrument using electrospray ionization (ESI) in positive or negative ion polarity mode.

6-Azido-9-(2',3'-O-isopropylidene-β-D-ribofuranosyl)purine (1). Compound **3** (2 g, 6.83 mmol, 1 equiv) was dissolved in dry DMF (46 mL), then 2,2-dimethoxypropane (4.2 mL, 34.12 mmol, 5 equiv) and *p*-toluenesulfonic acid (300 mg, 1.74 mmol, 0.25 equiv) were added. The reaction mixture was stirred at 40 °C for 2 h, under an argon atmosphere. The volatiles were evaporated under reduced pressure and the residue was dissolved in water (100 mL). The aqueous layer was extracted with ethyl acetate (4×50 mL) and the combined organic layers were washed with water (3×30 mL), dried on Na₂SO₄ and concentrated under reduced pressure. The desired compound was isolated as a white solid (2.108 g, 92% yield). *R*_f = 0.40 (CH₂Cl₂/MeOH 95:5). In CDCl₃, this compound is present as a mixture of tetrazole and azido forms. Signals of each form are detailed in the following NMR description (A for azide and T for tetrazole, T/A 25/75 in CDCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 9.55 (s, 1H, T), 8.63 (s, 1H×3, A), 8.57 (s, 1H, T), 8.10 (s, 1H×3, A), 6.28 (d, *J* = 3.5 Hz, 1H, T), 5.94 (d, *J* = 4.7 Hz, 1H×3, A), 5.21 (dd, *J* = 6.1, 3.5 Hz, 1H, T), 5.20–5.16 (m, 1H×3, A), 5.14–5.06 (m, 1H+1H×3, A+T), 4.59–4.57 (m, 1H, T), 4.54–4.52 (m, 1H×3, A), 4.05–3.78 (m, 2H+2H×3, A+T), 1.67 (s, 3H, T), 1.64 (s, 3H×3, A), 1.40 (s, 3H, T), 1.37 (s, 3H×3, A); ¹³C NMR (101 MHz, CDCl₃): δ = 154.4, 152.1, 151.0, 143.6, 143.0, 134.2, 125.6, 114.4, 94.4, 93.3, 86.8, 86.4, 84.7, 83.3, 81.7, 81.5,

63.4, 63.1, 29.8, 27.7, 27.4, 25.3; HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₃H₁₆N₇O₄⁺ 334.1264, found 334.1262.

1,3,5-Tris(prop-2-yn-1-yloxy)benzene (2).^[24] Phloroglucinol (1 g, 7.9 mmol, 1 equiv) was dissolved in dry DMF (15 mL), under an inert atmosphere, and K₂CO₃ (5.47 g, 40 mmol, 5 equiv) was added. After 30 min at rt, propargyl bromide (3.54 mL of an 80% w/w solution in toluene, 40 mmol, 5 equiv) was added. The reaction mixture was stirred at rt for 12 h and the solution turned dark. The crude mixture was concentrated in vacuo. The residue was dissolved in CH₂Cl₂ and the organic layer was washed with brine (3×60 mL). The aqueous layer was extracted three times with CH₂Cl₂ (3×50 mL). The organic layers were combined, dried over Na₂SO₄ and evaporated under reduced pressure. The product was isolated by flash chromatography on silica gel (CH₂Cl₂/Cyclohexane 1:1). 1.83 g (7.61 mmol, 96% yield), white solid. *R*_f = 0.56 (CH₂Cl₂/cyclohexane 5:5); ¹H NMR (400 MHz, CDCl₃) δ = 6.27 (s, 3H), 4.65 (d, *J* = 2.4 Hz, 6H), 2.53 (t, *J* = 2.4 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃): δ = 159.5, 95.5, 75.9, 56.1; HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₅H₁₃O₃⁺ 241.0859, found 241.0867.

6-Azido-9-(β-D-ribofuranosyl)purine (3).^[25] 6-Chloro-(β-D-ribofuranosyl)-purine (6 g, 21 mmol, 1 equiv) was added portionwise to hydrazine hydrate solution (57 mL, 50–60% in water) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, concentrated under vacuum and then co-evaporated with isopropanol (4×40 mL). The crude residue (5.92 g) was directly used in the next step and dissolved in a mixture of AcOH (6 mL, 105 mmol, 5 equiv) and water (90 mL). A solution of NaNO₂ (1.74 g, 25 mmol, 1.2 equiv) in water (60 mL) was slowly added to the previous acidic solution and the resulting mixture was stirred at 0 °C for 2 h. The precipitate was filtered-off, washed with cold water, and then recrystallized from water (340 mL). The desired product was isolated as a white powder (4.32 g, 70% yield). *R*_f = 0.55 (CH₂Cl₂/MeOH 8:2); ¹H NMR (300 MHz, DMSO-*d*₆): δ = 10.16 (s, 1H), 8.94 (s, 1H), 6.16 (d, *J* = 5.2 Hz, 1H), 5.64 (d, *J* = 5.9 Hz, 1H), 5.31 (d, *J* = 5.3 Hz, 1H), 5.12 (t, *J* = 5.4 Hz, 1H), 4.58 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.22 (dd, *J* = 9.5, 4.9 Hz, 1H), 4.05–4.01 (m, 1H), 3.79–3.54 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ = 145.4, 142.6, 141.9, 136.1, 120.2, 88.4, 85.7, 74.5, 70.0, 60.9; HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₁₀H₁₂N₇O₄⁺ 294.0951, found 294.0952.

Supported nucleoside (4). Compound **2** (50 mg, 0.2 mmol, 1 equiv) was dissolved in dry DMF (2 mL) in a 10 mL glass vial equipped with magnetic stirring bar. Then compound **1** (277 mg, 0.83 mmol, 4 equiv), CuI (13 mg, 0.066 mmol, 0.3 equiv) and dry DIPEA (0.209 mL, 1.2 mmol, 6 equiv) were added to the solution. The vial was sealed and heated under microwave irradiation at 40 °C for 10 min. The conversion was monitored by TLC (AcOEt/Cyclohexane 6:4, KMnO₄ dip) until starting material disappeared. The formation of the desired product was observed at λ = 365 nm (CH₂Cl₂/MeOH 9:1). The volatiles were removed in vacuo, then the crude product was dissolved in 30 mL CH₂Cl₂ and 30 mL water was added. The aqueous layer was extracted three times with CH₂Cl₂ (3×15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by precipitation in iced water.^[35] 240 mg (0.19 mmol, 97% yield), brown solid. ¹H NMR (400 MHz, CDCl₃): δ = 9.14 (bs, 1H), 8.91 (bs, 1H), 8.44 (bs, 1H), 6.38 (bs, 1H), 6.11 (d, *J* = 4 Hz, 1H), 5.34–5.10 (m, 3H), 4.58 (bs, 2H), 4.03–3.80 (m, 2H), 1.67 (s, 3H), 1.40 (s, 3H); HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₅₄H₅₈N₂₁O₁₅⁺ 1240.4416, found 1240.4423. HPLC: *rt* = 5.05 min (λ_{max} = 286 nm).

Supported 2',3'-O-isopropylidene adenosine H-phosphonate (5). Diphenyl phosphite (0.305 mL, 1.6 mmol, 20 equiv) was added to a solution of compound **4** (100 mg, 0.08 mmol, 1 equiv) in anhydrous pyridine (3.75 mL). The reaction mixture was stirred at rt during 20 min. The conversion was checked by TLC (CH₂Cl₂/MeOH 9:1).

The reaction mixture was treated with a solution of triethylamine and water (1.25 mL, 1:1) and stirred for 1 h at rt, then the volatiles were removed under reduced pressure. The residue was dissolved in water and the aqueous layer was extracted three times with CH_2Cl_2 (3×20 mL). The aqueous layer was freeze-dried. The crude product was purified by Bio Gel P-2 Gel fine.^[35] 93 mg (0.06 mmol, 82% yield), brown solid. ^1H NMR (400 MHz, CH_3OD) δ = 8.75 (bs, 1H), 8.61 (bs, 1H), 7.42 (bs, 1H), 6.62 (d, J_{PH} = 644 Hz, 1H), 6.27 (bs, 1H), 6.07 (bs, 1H), 5.43–5.42 (bs, 2H), 5.19–5.18 (bs, 2H), 4.68–4.65 (bs, 1H), 4.09 (bs, 2H), 3.27 (q, J = 7.3 Hz, 2H), 1.67 (s, 3H), 1.46 (s, 3H), 1.25 (t, J = 7.3 Hz, 3H); ^{31}P NMR (162 MHz, CH_3OD) δ = 5.9 (s); HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{54}\text{H}_{61}\text{N}_{21}\text{O}_{21}\text{P}_3^+$ 1432.3558, found 1432.3556. HPLC: t_r = 3.51 min (λ_{max} = 285 nm).

Supported 2',3'-O-isopropylidene AMP (6). Compound 5 (294 mg, 0.17 mmol, 1 equiv) was dissolved in 10 mL of anhydrous DMF, and bis(trimethylsilyl)acetamide (0.83 mL, 3.3 mmoles, 20 equiv) was added. The reaction mixture was stirred at 50 °C for 2 h affording the silylated phosphite intermediate. The conversion was checked by ^{31}P NMR in CDCl_3 . The mixture was cooled to rt and then oxidation was carried out by addition of (–)-(8,8-dichlorocamphorylsulfonyl)oxaziridine (491 mg, 1.7 mmol, 10 equiv). After 2 h at rt, the conversion was checked by ^{31}P NMR in CDCl_3 and then the reaction was treated by an excess of triethylamine/ H_2O 1:1, for 1 h at rt. The volatiles were evaporated under reduced pressure and the residue was dissolved in water. The aqueous layer was extracted three times with CH_2Cl_2 (3×40 mL). The aqueous layers were combined, lyophilized. The crude product was purified by Bio Gel P-2 Gel, fine.^[35] 152 mg (0.10 mmol, 60% yield), brown solid. ^1H NMR (400 MHz, D_2O) δ = 9.02 (bs, 1H), 8.97 (bs, 1H), 8.90 (bs, 1H), 6.44 (bs, 2H), 5.43 (bs, 2H), 5.19–5.18 (bs, 2H), 4.68 (bs, 1H), 3.95 (bs, 2H), 3.13 (q, J = 7.3 Hz, 2H), 1.64 (s, 3H), 1.41 (s, 3H), 1.21 (t, J = 7.3 Hz, 3H); ^{31}P NMR (162 MHz, D_2O) δ = 2.9; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{54}\text{H}_{55}\text{N}_{21}\text{O}_{24}\text{P}_3^+$ 1474.2591, found 1474.2849. HPLC: t_r = 4.44 min (λ_{max} = 285 nm).

General procedure for the synthesis of 8-9 via phosphorimidazolid 7 (Scheme 4). Compound 6 (1 equiv) was dried by co-evaporation with anhydrous pyridine and the residue was dissolved in anhydrous DMF (6 mL/0.1 mmol). Then CDI (6 equiv) was added, and the reaction mixture was stirred at rt for 1 h. The conversion to the intermediate 7 was monitored by ^{31}P NMR. After completion, the reaction mixture was treated by an excess of dry MeOH (20 equiv) and stirring was pursued for 30 min. Finally, the phosphorylated reagent (15 equiv) was added, and the reaction mixture stirred at rt for 20 h. The solvents were removed under reduced pressure and the residue was dissolved in water. The product was isolated by chromatography on Bio Gel P-2 Gel, fine, followed by freeze-drying.^[36]

Supported phosphorimidazolid intermediate (7). ^{31}P NMR (162 MHz, D_2O) δ = –0.6 (s).

Supported 2',3'-O-isopropylidene adenosine 5'-diphosphate (8). Compound 8 was prepared from 6 (140 mg, 0.067 mmol) according to the general procedure. 90 mg (0.052 mmol, 78% yield), brown solid. ^1H NMR (400 MHz, D_2O) δ = 8.67 (bs, 2H), 7.44 (bs, 1H), 6.30 (bs, 2H), 5.43–5.21 (m, 4H), 4.22–4.11 (m, 3H), 1.72 (s, 3H), 1.49 (s, 3H); ^{31}P NMR (162 MHz, D_2O) δ = –10.8 (d, J = 20.8 Hz), –11.7 (d, J = 20.8 Hz). HPLC: t_r = 4.16 min (λ_{max} = 284 nm).

Supported 2',3'-O-isopropylidene adenosine 5'-triphosphate (9). Compound 9 was prepared from 6 (140 mg, 0.067 mmol) according to the general procedure. 50 mg (0.025 mmol, 68% yield), brown solid. ^1H NMR (400 MHz, D_2O) δ = 8.71 (br, 2H), 7.43 (s, 1H), 6.28 (s, 2H), 5.50–5.00 (m, 4H), 4.26 (bs, 3H), 1.66 (s, 3H), 1.45 (s, 3H); ^{31}P NMR (162 MHz, D_2O) δ = –10.5 (bs, P_γ), –11.7 (bs, P_α), –22.9 (bs, P_β); HPLC: t_r = 4.24 min (λ_{max} = 284 nm).

General procedure for the one-pot cleavage and removal of the protecting group (Scheme 4): The supported 2',3'-O-isopropylidene adenosine derivative (1 equiv) was dissolved in 1 mL of concentrated aqueous ammonia solution. The reaction mixture was stirred at 50 °C in a sealed tube for 1–2 h. After evaporation under reduced pressure, the crude product was dissolved in $\text{H}_2\text{O}/\text{MeOH}$ (1:1, 2 mL) and Dowex resin (H^+ form, 50 mg) was added. The mixture was heated at 50 °C for 5 h. The conversion was checked by HPLC. The resin was removed by filtration and the filtrate was percolated through a column of Dowex resin 50WX8 (Na^+ form) followed by freeze-drying. The last purification step was performed with either method A or B. Method A: The crude product was applied to a plug of C_{18} -AQ-RP-silica, eluted with a gradient of water to methanol, and the product-containing fractions were combined and concentrated under reduced pressure. Method B: The crude product was purified by DEAE-Sephadex using a linear gradient from 10^{-3} M to 0.6 M TEAB pH 7.5. Pure fractions were combined and concentrated under high vacuum.

Adenosine 5'-monophosphate disodium salt (10).^[37] The general procedure was carried out starting from 6 (236 mg, 0.11 mmol). The crude product was purified according to method A. 17 mg (0.043 mmol, 40% yield), white solid. ^1H NMR (400 MHz, D_2O): δ = 8.55 (s, 1H), 8.17 (s, 1H), 6.07 (d, J = 6.0 Hz, 1H), 4.77–4.73 (m, 1H), 4.45 (dd, J = 5.0, 3.4 Hz, 1H), 4.31–4.30 (m, 1H), 3.94 (t, J = 3.7 Hz, 2H); ^{13}C NMR (126 MHz, D_2O): δ = 155.5, 152.7, 149.0, 140.1, 118.5, 86.6, 84.8 (d, J = 8.8 Hz), 74.4, 70.7, 63.3; ^{31}P NMR (162 MHz, D_2O) δ = 3.6 (s); HRMS (ESI) m/z : calcd for $\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_7\text{P}^-$ $[\text{M} - \text{H}]^-$ 346.0558, found 346.0561. HPLC: t_r = 3.21 min (λ_{max} = 258 nm).

Adenosine 5'-diphosphate trisodium salt (11).^[38] The general procedure was carried out starting from 8 (190 mg, 0.07 mmol). The crude product was purified according to method A. 23 mg (0.047 mmol, 66% yield), white solid. ^1H NMR (400 MHz, D_2O) δ = 8.45 (s, 1H), 8.15 (s, 1H), 6.06 (d, J = 5.6 Hz, 1H), 4.70 (m, 1H), 4.52 (m, 1H), 4.33 (bs, 1H), 4.17 (m, 2H); ^{13}C NMR (126 MHz, D_2O): δ = 155.4, 152.2, 148.9, 139.7, 118.4, 86.8, 83.8 (d, J = 9.0 Hz), 74.2, 70.1, 64.7 (d, J = 4.9 Hz); ^{31}P NMR (202 MHz, D_2O): δ = –9.2 (d, J = 20.7 Hz), –11.1 (d, J = 20.7 Hz); HRMS (ESI) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_5\text{O}_{10}\text{P}_2^+$ 428.0367, found 428.0369. HPLC: t_r = 3.08 min (λ_{max} = 258 nm).

Adenosine 5'-triphosphate tetrasodium salt (12).^[39] The general procedure was carried out starting from 9 (190 mg, 0.09 mmol). The crude product was purified according to method A. 31 mg (0.053 mmol, 58% yield), white solid. ^1H NMR (400 MHz, D_2O) δ = 8.43 (s, 1H), 8.14 (s, 1H), 6.05 (d, J = 6 Hz, 1H), 4.70–4.49 (m, 2H), 4.32–4.31 (m, 2H), 4.15–4.14 (m, 1H); ^{13}C NMR (126 MHz, D_2O): δ = 155.5, 152.6, 149.1, 139.8, 118.5, 86.8 (d, J = 31.2 Hz), 83.9 (dd, J = 17.6 Hz, 9.0 Hz), 74.2 (d, J = 7.9 Hz), 70.3, 65.1 (d, J = 5.2 Hz); ^{31}P NMR (162 MHz, D_2O) δ = –9.2 (bs, P_γ), –11.0 (bs, P_α), –22.6 (bs, P_β); HRMS (ESI) m/z : $[\text{M} - \text{H}]^-$ calcd. for $\text{C}_{10}\text{H}_{17}\text{N}_5\text{O}_{13}\text{P}_3^-$ 508.0030, found 508.0036. HPLC: t_r = 3 min (λ_{max} = 258 nm).

Supported bisphosphonates 13a and 13b. A solution of methylene bis(phosphonic dichloride) (804 mg, 3.22 mmol, 30 equiv) in trimethyl phosphate (1.6 mL) was added to a suspension of 4 (200 mg, 0.16 mmol, 1 equiv) in trimethylphosphate (1.6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 8 h and conversion was monitored by HPLC. The mixture was quenched with 30 mL of a cold 0.5 M aqueous TEAB solution (pH 7.5). Trimethyl phosphate was extracted using tert-butyl methyl ether (3×100 mL) and the aqueous layer was lyophilized. The crude product was dissolved in water and purified by Bio Gel P-2 Gel, fine. A mixture of compounds 13a and 13b (1:1) was isolated in 37% yield.^[36] ^1H NMR (400 MHz, D_2O) δ = 8.74 (bs, 2H), 7.43 (bs, 1H), 6.33 (bs, 2H), 5.36–5.00 (m, 4H), 4.45–3.60 (m, 3H), 2.23 (bs, 2H, PCH_2P), 1.62 (bs, 3H), 1.32 (bs, 3H); ^{31}P NMR (162 MHz, D_2O) δ = 7.8 (s, P_α), 16.5 (s, P_β).

Adenosine 5'-O- α,β -methylene diphosphate trisodium salt (14).^[30,40] The general procedure was carried out starting from a 1:1 mixture of **13 a/13 b** (215 mg, 0.081 mmol). The crude product was purified according to method B. 12 mg (0.024 mmol, 31 % yield), white solid. ¹H NMR (400 MHz, D₂O) δ =8.54 (s, 1H), 8.24 (s, 1H), 6.13 (d, J =5.3 Hz, 1H), 4.76 (m, 1H), 4.58 (t, J =4.8 Hz, 1H), 4.37 (d, J =3.1 Hz, 1H), 4.21–4.17 (m, 2H), 2.12 (t, J_{PH} =19.7 Hz, 2H); ¹³C NMR (101 MHz, D₂O): δ =155.6, 152.9, 149.0, 140.0, 118.7, 87.0, 83.0 (d, J =7.8 Hz), 74.2, 70.1, 63.3, 28.1 (t, J =123.3 Hz); ³¹P NMR (162 MHz, D₂O) δ =20.58 (d, J =9.2 Hz), 12.76 (d, J =9.2 Hz); HRMS (ESI) m/z : calcd for C₁₁H₁₈N₅O₉P₂⁺ [M+H]⁺ 426.0574; found 426.0581. HPLC: r_t =2.75 min (λ_{max} =258 nm).

N⁶-benzyladenosine 5'-O- α,β -methylene diphosphate trisodium salt (15).^[19] The general procedure was carried out starting from a 1:1 mixture of **13 a/13 b** (158 mg, 0.06 mmol) except that a solution of benzylamine (200 μ L, 1.80 mmol, 30 equiv) in water (2 mL) was used instead of a concentrated aqueous ammonia solution. The crude product was purified according to method B. 10 mg (0.016 mmol, 30% yield), white solid. ¹H NMR (400 MHz, D₂O) δ =8.48 (s, 1H), 8.17 (s, 1H), 7.38–7.27 (m, 5H), 6.10 (d, J =5.2 Hz, 1H), 4.71 (d, J =5.2 Hz, 2H), 4.55 (t, J =4.6 Hz, 1H), 4.31 (d, J =3.6 Hz, 1H), 4.10–4.10 (m, 2H), 2.02 (t, J_{PH} =19.2 Hz, 2H); ¹³C NMR (151 MHz, D₂O): δ =154.5, 152.8, 139.5, 138.4, 128.7, 127.3, 126.8, 118.9, 86.9, 83.7 (d, J =8.0 Hz), 74.1, 69.8, 63.0 (d, J =4.2 Hz), 58.9, 28.5 (t, J =124.7 Hz), 19.2; ³¹P NMR (162 MHz, D₂O) δ =21.8 (s), 11.7 (s); HRMS (ESI) m/z : [M+H]⁺ calcd. for C₁₈H₂₄N₅O₉P₂⁺ 516.104, found 516.1036. HPLC: r_t =3.28 min (λ_{max} =266 nm).

Supported 2',3'-O-isopropylidene adenosine 5'-O- β,γ -methylene triphosphate (16). Compound **6** (1 equiv) was dried by co-evaporation with anhydrous pyridine and the residue was dissolved in anhydrous DMF (6 mL/0.1 mmol). Then CDI (6 equiv) was added, and the reaction mixture was stirred at rt for 1 h. The conversion to the intermediate **7** was monitored by ³¹P NMR. After completion, the reaction mixture was treated by an excess of dry MeOH (20 equiv) and stirring was pursued for 30 min. Finally, bis(tri-*n*-butylammonium) methylene bisphosphonate (15 equiv) was added and the reaction mixture stirred at rt for 20 h. The solvents were removed under reduced pressure and the residue was dissolved in water. The product was isolated by chromatography on Bio Gel P-2 Gel, fine, followed by freeze-drying.^[36] The reaction was performed starting from **6** (140 mg, 0.067 mmol). 114 mg (0.036 mmol, 53 % yield), brown solid. ¹H NMR (400 MHz, D₂O) δ =8.69 (bs, 2H), 7.43 (bs, 1H), 6.34 (bs, 2H), 5.43–5.28 (m, 4H), 4.23–4.00 (m, 3H), 3.08 (bs, 4H), 2.35 (bs, 2H, PCH₂P), 1.62 (bs, 3H), 1.33 (bs, 3H), 0.88 (bs, 6H); ³¹P NMR (162 MHz, D₂O) δ =15.3 (s, P _{γ}), 8.0 (s, P _{β}), –11.7 (s, P _{α}). HPLC: r_t =4.25 min (λ_{max} =284 nm).

Adenosine 5'-O- β,γ -methylene triphosphate tetrasodium salt (17).^[41] The supported compound **16** (232 mg, 0.073 mmol, 1 equiv) was dissolved in 1 mL of concentrated aqueous ammonia solution. The reaction mixture was stirred at 50 °C in a sealed tube for 1–2 h. After evaporation under reduced pressure, the crude product was dissolved in H₂O/MeOH (1:1, 2 mL) and Dowex resin (H⁺ form, 50 mg) was added. The mixture was heated at 50 °C for 5 h. The conversion was checked by HPLC. The resin was removed by filtration and the filtrate was percolated through a column of Dowex resin 50WX8 (Na⁺ form). The crude product was purified according to method A. 16 mg (0.027 mmol, 38% yield), white solid. ¹H NMR (400 MHz, D₂O) δ =8.47 (s, 1H), 8.20 (s, 1H), 6.08 (d, J =5.8 Hz, 1H), 4.73 (m, 1H), 4.52 (m, 1H), 4.34 (m, 1H), 4.19–4.15 (m, 2H), 2.21 (t, J_{PH} =20.2 Hz, 2H); ¹³C NMR (126 MHz, D₂O): δ =155.6, 152.8, 149.0, 139.7, 118.5, 86.7, 83.9, 74.2, 70.3, 64.8, 29.7 (dd, J =129.9 Hz, J =121.4 Hz); ³¹P NMR (162 MHz, D₂O) δ =13.3 (bs, P _{γ}), 10.9 (m, P _{β}), –10.9 (d, J =26.5 Hz, P _{α}); HRMS (ESI) m/z : [M+H]⁺ calcd. for C₁₁H₁₉N₅O₁₂P₃⁺ 506.0238, found 506.0236. HPLC: r_t =1.86 min (λ_{max} =258 nm).

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Conflict of Interest

The authors declare no conflict of interest.

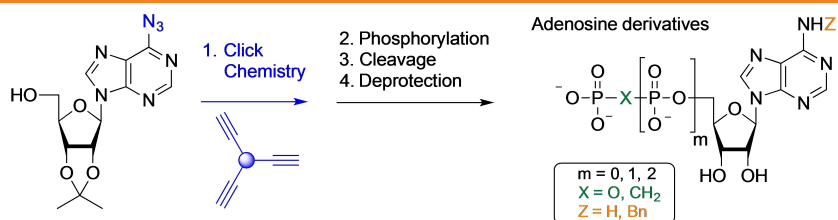
Keywords: Bisphosphonates · Click reaction · Nucleotides · phosphorylation · Soluble-supported synthesis

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FULL PAPERS



A new strategy based on anchoring C(6) azidopurine nucleoside derivative to a tripodal soluble support allows to access the corresponding adenosine

nucleotides. We extended the scope of the method to methylene bisphosphonate analogues and N^6 -benzylamine derivative.

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Supported Synthesis of Adenosine Nucleotides and Derivatives on a Benzene-Centered Tripodal Soluble Support

