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Synthesis of Adenosine Diphosphate Ribose Histidine

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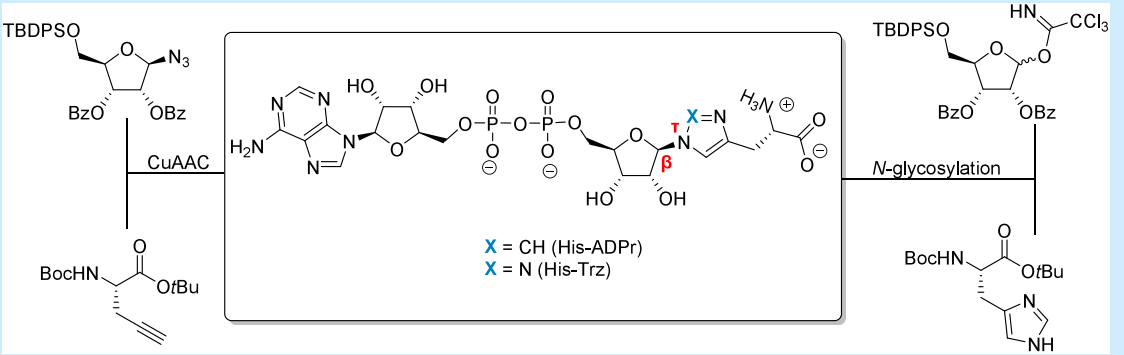
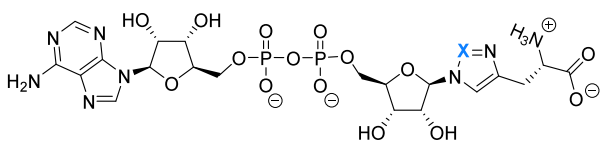


ABSTRACT: Adenosine diphosphate ribosylated histidine (His-ADPr) is a vital signaling molecule for the bacterial immune system, the antiphage system in particular. In this unique second messenger molecule, the distal nitrogen of the histidine side chain is ribosylated in a β fashion. Here, we describe the synthesis of this bacterial metabolite and its triazole isostere and evaluate the stability of His-ADPr to relevant ribosyl hydrolases.

The mechanism of bacterial immunity has attracted much interest over the past decades, particularly the CRISPR-Cas and antiphage systems, which have been extensively investigated.[1,2] The antiphage defense in bacteria involves multiple pathways that work together to prevent phage infection.[3] One example is the Thoeris defense system, in which Toll-interleukin receptor (TIR) domains recognize phage invasion and then produce immune signaling molecules to start the interruption of the infection process.[4−6] The most studied class of these messenger molecules emerge from the transformation of nicotinamide adenine dinucleotide (NAD^+) into different cyclic adenosine diphosphate ribosides (cADPr), which activate the Thoeris-associated protein ThsA.[6,7] Recently, another unique NAD^+-derived signaling molecule was discovered to activate the Thoeris system by binding to the ThsA, namely, adenosine diphosphate ribosylated histidine (His-ADPr, structure **1** in Figure 1).[8] His-ADPr induces the oligomerization of ThsA, which destabilizes the cell membrane and causes cell death, leading to efficient antiphage defense. It proved to be possible to isolate small quantities of His-ADPr (**1**) from lysates of phage-infected cells using the phage protein ModTad2 to capture this ADPr-metabolite.[8] The structure of this His-ADPr was elucidated using mass spectrometry and X-ray crystallography, showing the histidine to be linked to the ribose through a β-ribosyl linkage to the distal N of the imidazole ring (i.e., the τ-position).

This is highly unusual as all known ADP-ribosyltransferase enzymes modify proteins, nucleic acids and small molecules via α-ribosyl linkage.[9,10] To enable further studies into the mode of action of His-ADPr and enzymes that may process this molecule, a scalable route of synthesis would be desirable to generate sufficient amounts of this intriguing messenger molecule. We here report the synthesis of His-ADPr (**1**) based on the stereo- and regioselective glycosylation of the histidine imidazole ring, for which little precedent exists. The pyrophosphate linkage was forged in a convergent manner, using the P(III)-P(V) coupling chemistry we previously



1 X = CH
2 X = N

Figure 1. His-ADPr (**1**) and Trz-ADPr (**2**).

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developed.[11] We also describe the synthesis of a triazole-based isostere of His-ADPr (Trz-ADPr, **2**) which we generated through a copper-catalyzed cycloaddition, using a suitably protected 1-azido-β-ribose and propargyl glycine.[12,13]

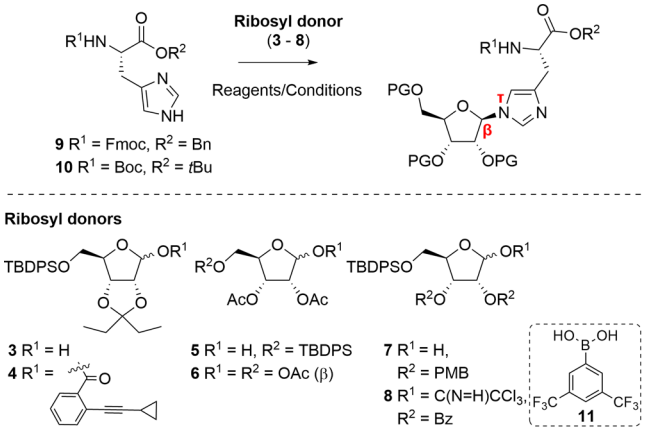
In our earlier work on ADP-ribosylated peptides, we have found that the ribosylation of histidine is challenging due to the difficulties in controlling both the stereo- (α vs β) and regioselectivity (τ vs π). In addition, the imidazole moiety in the histidine was readily overglycosylated, leading to the double-ribosylated histidine products.[14] For example, in our previous efforts to generate α-ribosyl histidine building blocks, we found that the use of powerful ribosyl imidate donors in combination with TMSOTf proved ineffective for ribosylation of the histidine side chain, also after silylation of the imidazole nitrogen prior to glycosylation, in sharp contrast to the successful construction of many other α-ribosylated amino acid side chains.[14,15]

Eventually, we found that basic glycosylation conditions, based on activation of a ribosyl lactol with a phosphonium triflate species, as invented by Mukaiyama and co-workers, proved most effective in producing the target ribosyl histidine, but a mixture of three isomers (α-π, α-τ and β-τ) was formed.[14,16,17] Of note, in these mixtures, the here desired β-τ regio/stereoisomer was the minor product. Based on these earlier attempts, we explored donor **3** (see the SI for the syntheses of all donors depicted in Table 1), in which the bulky isopentylidene group was installed to block the α-face of the ribosyl donors, and acceptor **10** to Mukaiyama conditions (Table 1, entry 1).[18] Next, we probed the use of alkynebenzoate donor **4**, which can be activated under mild gold-catalyzed conditions (entry 2), as this donor type has previously been used in *N*-glycosylation of nucleobases.[19−21] However, this approach also proved unsuccessful and even elevated reaction temperatures failed to promote product formation. Also, ribosyl lactol **5** (entry 3) proved unreactive.

To validate the reactivity of acceptor **10** under the Mukaiyama condensation conditions, we tried to react it with donor **7** (entry 4), which we previously successfully used for ribosylation of histidine.[14] This reaction yielded a mixture of regio- and stereoisomers in an overall adequate yield, indicating that the reactivity of acceptor **10** was not the bottleneck and that the observed lack of reactivity originated from the donors. Next, we explored a Vorbrüggen-type glycosylation with donor **6** and acceptor **9** at reflux temperatures in MeCN (entry 5).[22] This predominantly led to double ribosylated products, as indicated by LC-MS analysis, consistent with previous data on imidazole glycosylation.[23] Based on previously reported glycosylations of histidine using pyranosyl donors, we then turned to ribosyl bromides, which could be formed via an Appel reaction of the corresponding ribosyl lactols.[24−26] When pentylidene protected donor **3** was subjected to Appel conditions (entry 6), TLC analysis revealed the formation of a ribosylated histidine product. Heteronuclear multiple bond correlation (HMBC)-NMR (Figure 2) showed a cross-peak between H1′ and C5 of the imidazole ring, indicating that the desired τ-regioisomer was formed. But NOESY studies of **12** and its desilylated counterpart **13** (generated to allow structural characterization) revealed a NOESY interaction between H1′ and H3′, and the absence of a NOESY-correlation between H1′ and H4′, showing the undesired α-anomer had been formed. The unexpected formation of this anomer likely originates from the intermediate β-ribosyl bromide. Of note, it has previously been reported that the β-anomer of 2,3-isopropylideneribosyl chloride is thermodynamically more stable than its anomeric counterpart.[27]

In a final attempt to achieve the desired regio- and stereoselectivity in the histidine ribosylation, we turned to a novel method for *N*-glycosylation of heterocycles that uses boronic acid **11** as a catalyst, as introduced by Taylor and co-workers.[28] Gratifyingly, activation of donor **8** with the boronic acid led to a productive glycosylation reaction, providing the desired β-τ ribosylated histidine (**14**, Figure 2) as the major product, along with the β-π isomer in a 1.8:1 ratio (entry 7). At this stage, the regioisomers were inseparable, but after desilylation with TBAF separation of the regioisomers **15** and **17** by silica gel column chromatography could be achieved. Careful NMR analysis revealed that the anomeric configuration of both isomers was β, as judged from the NOE

Table 1. Ribosylation of the Histidine Side Chain



entry	donor	acceptor	reagents/ conditions	yield
1	**3** (1 equiv)	**10** (2 equiv)	$POBu_3$, Tf_2O, DiPEA	0%[a]
2	**4** (1.3 equiv)	**10** (1 equiv)	PPh_3AuNTf_2 DCM, 50 °C	0%[a]
3	**5** (1 equiv)	**10** (2 equiv)	$POBu_3$, Tf_2O, DiPEA	0%[a]
4	**7** (1 equiv)	**10** (2 equiv)	$POBu_3$, Tf_2O, DiPEA	49%[b]
5	**6** (1 equiv)	**9** (2 equiv)	$HClO_4/SiO_2$, BSTFA MeCN, reflux	over-ribosylation
6	**3** (1 equiv)	**10** (1.5 equiv)	PPh_3, CBr_4, DiPEA, DCM	**12**, 35% (α-τ)
7	**8** (1 equiv)	**10** (1.2 equiv)	**11**, reflux in toluene	**14** + **16**, 61% (1.8:1)

[a]No conversion. [b]Mixture of regio/stereoisomers.

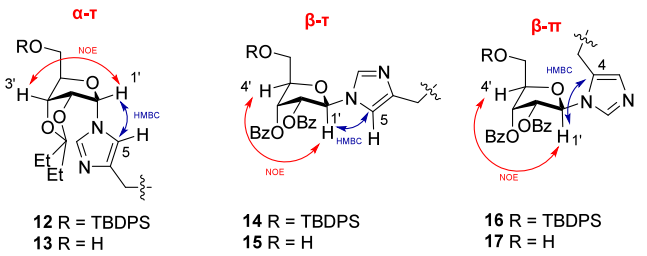


Figure 2. Configuration of His-ADPr by NOESY and HMBC.

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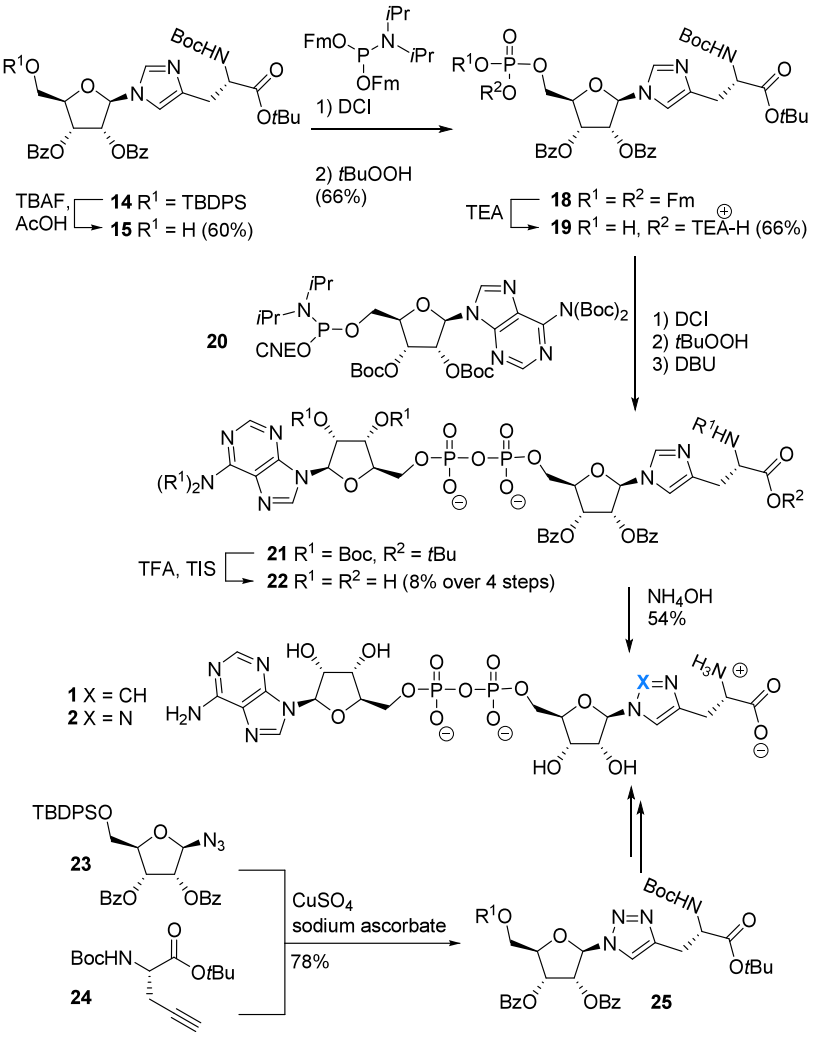
Scheme 1. Synthesis of His-ADPr 1 and Trz-ADPr 2



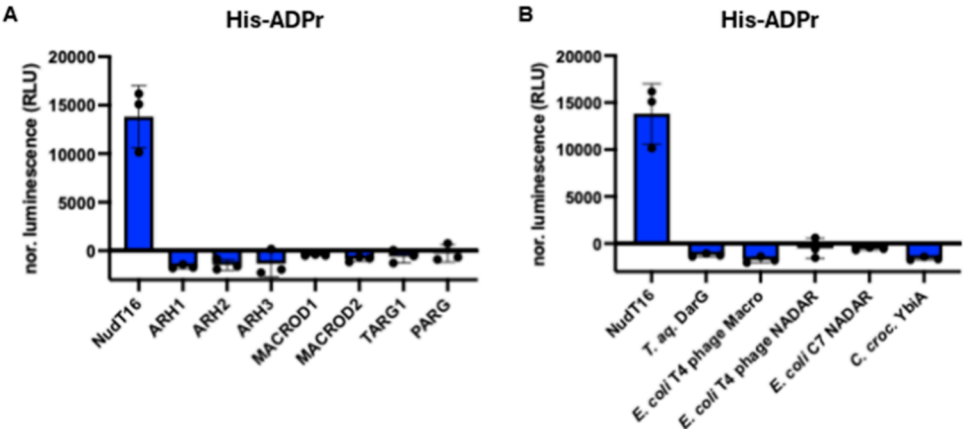


Figure 3. ADP-ribosylhydrolase activity against chemically synthesized His-ADPr, as determined using the AMP-glo assay. Panel A illustrates enzymatic activities across the selected human hydrolase panel, whereas panel B presents activities from the selected bacterial and phage hydrolases. Hydrolase turnover of His-ADPr was monitored as AMP release, generated directly via NudT16 or indirectly through conversion of ADP-ribose to AMP by NudT5, and measured using AMP-Glo assay (Promega). Results were background-corrected and normalized to NudT5, with data shown as mean ± SD from triplicates.

interactions between H1′ and H4′ (Figure 2). These interactions were not present in the α-τ isomers. HMBC measurements showed a coupling between C5 of the imidazole ring and ribosyl H1′ in **15**, pointing to the formation of the desired τ-isomer (Figure 2). For π-isomer **17**, this interaction was absent, but a characteristic cross-peak was detected in the HMBC spectrum between the quaternary carbon of the

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imidazole (C4) and H1', establishing the regiochemistry of **17** (Figure 2).

With pure ribosyl histidine **14** in hand, we next set out to introduce the pyrophosphate moiety, and to this end we first generated the phosphotriester **18** by using di(9-fluorenylmethyl-*N*,*N*-diisopropylphosphoramidite with DCI as activator to deliver the intermediate phosphite triester, which was subsequently oxidized to provide the fully protected **18** (Scheme 1).[11,29] The Fm protecting groups were removed under basic conditions to yield histidine ribosyl phosphate **19**. Next, the DCI-assisted coupling of ribosyl phosphate **19** with adenosine phosphoramidite **20** (for the synthesis of **20**, see SI), followed by oxidation and acidic deprotection, delivered pyrophosphate **21** in an 8% yield over 4 steps upon reversed-phase column chromatography and subsequent HPLC purification. These extra purification steps may explain the relatively lower yield, but are in line with the method published earlier.[29] Finally, saponification of the benzoyl esters with ammonia and subsequent gel filtration provided the target compound **1** in a 54% yield and excellent purity. Using very similar chemistry, we generated the triazole analogue **2** from **25**, which was assembled from 1-azido-β-ribose **23** and propargylalanine **24** (see SI for full details).

As His-ADPr **1** is emerging as an important signaling molecule, we asked whether ADP-ribosylation on histidine can be reversed through enzymatic hydrolysis.[8] Plausible enzyme candidates for such activity are ADP-ribosylhydrolase enzymes.[30] This family of enzymes control many essential processes in organisms across all kingdoms of life by the timely removal of ADP-ribosyl signals mediated by different ADP-ribosyltransferases such as PARPs.[31] First, we analyzed the panel of selected characterized recombinant human ADP-ribosyl hydrolases together with ARH2, whose enzymatic activity has not yet been identified, for their ability to cleave chemically synthesized His-ADPr **1**.[32] To test the cleavage, we used our previously established AMP-Glo biochemical assay.[32−34] As a result, we observed no hydrolytic activity against His-ADPr **1** by any of the selected human ADP-ribosyl hydrolases (Figure 3). This result is consistent with the established substrate specificity of human ADP-ribosylhydrolases, which preferentially hydrolyze α-ADP-ribosyl linkages generated by the PARP family members, as experimentally demonstrated for the DNA damage response hydrolase ARH3.[31,34,35] As a positive control for the assay, we used the Nudix hydrolase member NUDT16, whose activity is independent of the ADP-ribosyl linkage, since it cleaves ADP-ribosylated substrates at the pyrophosphate bond, releasing the AMP moiety that gives a positive signal in this assay.[36] Consistent with expectations, NUDT16 exhibited activity in the assay, as shown in Figure 3A,B. Given the relevance of His-ADPr **1** in bacteria and phages, we next tested several bacterial and phage hydrolases (Figure 3B). Specifically, we tested the well characterized bacterial DarG macrodomain hydrolase from *Thermus aquaticus* (*T. aq.*), which acts on *N*-glycosidic bonds of ADP-ribosylated DNA substrates[37]), as well as one previously uncharacterized, divergent member of the same macrodomain family as DarG (UniProt: E5FIW0), coming from *Escherichia coli* phage (Figure 3B). Finally, we examined several bacterial and phage hydrolases from the poorly characterized NADAR family of ADP-ribosylhydrolases.[38,39] Yet, none of these enzymes tested were able to de-ADP-ribosylate His-ADPr **1** (Figure 3B).

With Trz-ADPr **2**, the results suggested potential low activities of TARG1 and PARG against this nonphysiological substrate (Supporting Information, Figure S1).

In conclusion, we have described the synthesis of the β-τ-isomer of His-ADPr **1**. The synthesis of the desired ribosylated histidine building block was realized through a novel boronic acid-catalyzed glycosylation. NOESY and HMBC measurements revealed the structure of the glycosylation products. Metabolite **1** was screened as substrate for several human, bacterial and phage ADPr hydrolases, but none of the explored ribosylases could turn over this substrate. While this work did not reveal enzymes that can act on His-ADPr, the introduced molecular tools will encourage future efforts to characterize His-ADPr dependent signaling pathways.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c04626.

Detailed experimental procedures and the copies of NMR spectra of the synthesized compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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