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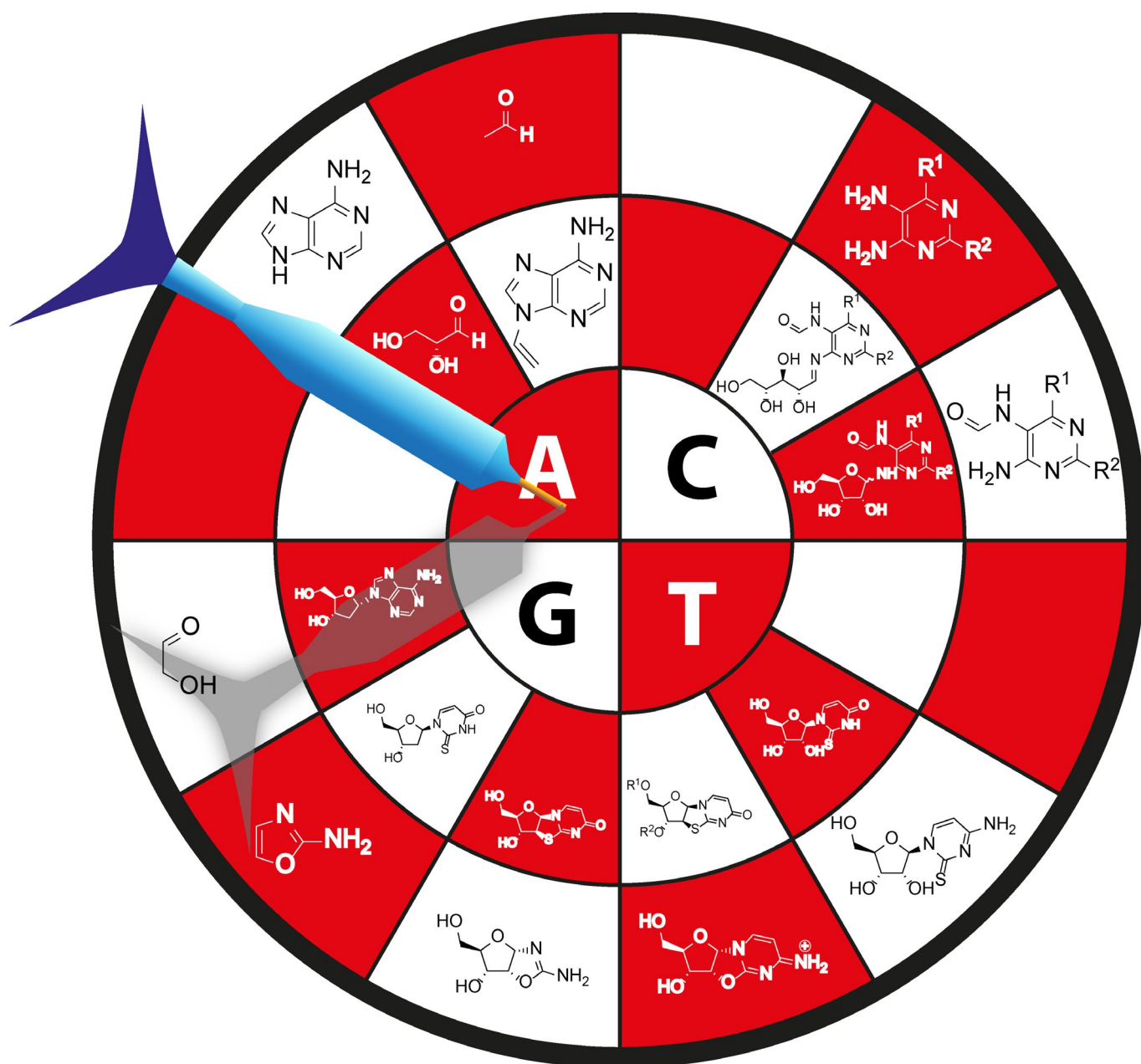


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Prebiotic Chemistry | *Reviews Showcase*

# Prebiotic Nucleoside Synthesis: The Selectivity of Simplicity

 Florian M. Kruse,<sup>[a]</sup> Jennifer S. Teichert,<sup>[a, b]</sup> and Oliver Trapp\*<sup>[a, b]</sup>


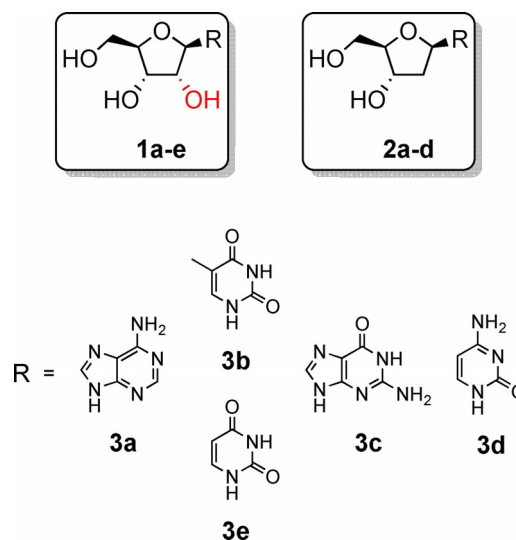
**Abstract:** Ever since the discovery of nucleic acids 150 years ago,<sup>[1]</sup> major achievements have been made in understanding and decrypting the fascinating scientific questions of the genetic code.<sup>[2]</sup> However, the most fundamental question about the origin and the evolution of the genetic code remains a mystery. How did nature manage to build up such intriguingly complex molecules able to encode structure

and function from simple building blocks? What conditions were required? How could the precursors survive the hostile environment of early Earth? Over the past decades, promising synthetic concepts were proposed providing clarity in the field of prebiotic nucleic acid research. In this Minireview, we show the current status and various approaches to answer these fascinating questions.

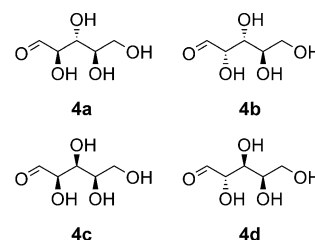
## Introduction

Nucleic acid research started 1871, with a small sentence in the essay “Über die chemische Zusammensetzung der Eiterzellen” (“About the chemical composition of pus cells”) by Miescher, stating the discovery of “nuclein” from white blood cells.<sup>[1]</sup> He characterized this substance as nitrogen containing and being very rich in phosphorous. The following decades were marked by resolving the molecular structure of the “nuclein”. Levene made a major contribution at the end of the 19<sup>th</sup> century,<sup>[3]</sup> when he was able to show that the “nuclein” consists of a heterocyclic unit connected to a sugar, the nucleoside (see Figure 1). In case of a phosphorylated sugar he coined the term nucleotide. Considering the limited analytical possibilities, strikingly precise structures of the nucleosides and nucleotides were postulated. The sugar unit was identified as a pentose structure in 1909; however, it was unclear if it is a D-ribose **4a** or a D-arabinose **4b** unit, merely D-lyxose **4c** could be excluded (see Figure 2).<sup>[4]</sup>

The beginning of nucleic acid research focused on the structure elucidation of the RNA and DNA nucleosides.<sup>[2a]</sup> As early as the 1950's the prebiotic synthesis, in the context of the Origins of Life, has been subject of increasing interest, aiming on the synthesis of the canonical ribonucleosides under prebiotic conditions.<sup>[5–12]</sup>



**Figure 1.** Comparison of RNA-nucleosides **1a–e** with DNA-nucleosides **2a–d** which lack of the 2'-hydroxy group. In RNA mostly the bases **3a, 3e, 3c** and **3d** are implemented, whereas in DNA **3a–d** are the only occurring nucleobases.



**Figure 2.** Structures of D-ribose **4a**, D-arabinose **4b**, D-lyxose **4c** and D-xylose **4d**.

## Definition of Plausible Prebiotic Conditions

The possible reaction conditions on early Earth that led to the emergence of Life are subject to intense debate among scientists of various fields. Consequently, the assumed reaction conditions change depending on the angle of view. The current, cross-disciplinary opinion is that early Earth's atmosphere was lacking oxygen.<sup>[13–16]</sup> Depending on the exerted geological scenario, the constituents of the atmosphere vary accordingly. As of today, most scientists agree that the main constituents of the early atmosphere of the earth are N<sub>2</sub>, H<sub>2</sub>O and CO<sub>2</sub>.<sup>[17,18]</sup> Determined by the reduction state, little H<sub>2</sub> and CO was pres-

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ent.<sup>[17,19–21]</sup> NH<sub>3</sub> and CH<sub>4</sub> were unlikely to be present, as it is proven by photochemical studies that they would decompose quickly under UV irradiation.<sup>[22]</sup> Further, it is assumed that a reasonably high amount of liquid H<sub>2</sub>O was present on early Earth.<sup>[23–25]</sup> A detailed view on the conditions and possible scenarios is provided by Kitadai et al.<sup>[26]</sup> The presence of liquid water, brings up a main question of paleoclimatology, why was the young Earth fairly warm, although the sun's activity must have been 25% lower than today's sun?<sup>[27]</sup> It is believed that the early Earth provided warm ponds in which Life could develop. The hypothesis favored by many scientists is that insulating greenhouse gases kept the early Earth warm.<sup>[28]</sup>

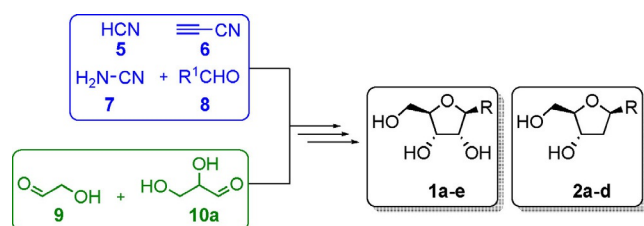
Apart from CO<sub>2</sub>, another greenhouse gas might have been nitrous oxide N<sub>2</sub>O, which is 300 times more potent than its carbon analogue. The N<sub>2</sub>O might have formed during bombardments by solar wind.<sup>[29,30]</sup> Additional, by-products of the intense radiation might have been HCN **5** and substituted acetylenes **6**.

The latter is one of the most interesting key-compounds in prebiotic chemistry. In combination with other compounds formed under these harsh conditions (Scheme 1: blue box) they open a pathway towards nucleosides. Reflecting the latest cross-disciplinary research, this review will consider the following conditions as prebiotic:

- Aqueous media,<sup>[24]</sup>
- Simple starting materials, gained from high-energy gas phase reaction,<sup>[31]</sup>
- No serious changes of the initial conditions,
- No sequential additions of reagents,
- Moderate temperatures (0 °C < T < 100 °C),<sup>[32,33]</sup>
- Dissolved-metal salts and porous surfaces as additives or catalysts.<sup>[34,35]</sup>

Differing reaction conditions will be explicitly mentioned in this review.

First synthetic approaches by Fischer<sup>[36]</sup> to nucleosides utilized conventional synthetic procedures.



**Scheme 1.** An exemplary pathway towards ribonucleosides ( $R = \mathbf{3a-e}$ ), from simple starting materials derived from gas-phase reactions (blue) and sugar-forming reactions (green).

## Ribonucleoside Synthesis

At the beginning of the 20<sup>th</sup> century D-ribose **4a** and D-deoxyribose **d4a** were identified as structural units in RNA<sup>[37]</sup> and in DNA, respectively.<sup>[38]</sup> Driven by the enormous biological relevance of the nucleic acids, synthetic routes to access the nucleosides were subject of intense investigations.

## The beginning

Taking advantage of Traube's<sup>[39]</sup> first synthesis of purine nucleobases, Fischer synthesized several non-canonical nucleosides.<sup>[39,40]</sup> Fischer's pathway decisively determined future synthetic approaches for the next 90 years by disconnecting the glycosidic bond of the anomeric center in a retrosynthetic approach (cf. Scheme 2), yielding the nucleobase and the sugar moiety.

Restricting the possible points of nucleophilic attack to a minimum, the xanthine derivative theophylline **3f** was employed to optimize the reaction conditions. The heterocycle was successfully coupled to form a glucoside, a rhamnoside and a galactoside, starting from acetobromoglucose **11a**, acetobromogalactose **11b** and acetobromorhamnose **11c**, respec-

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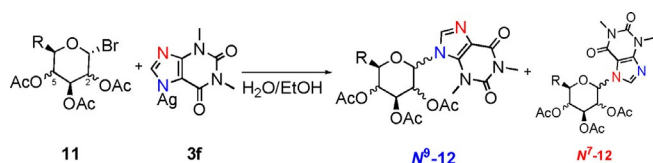


Jennifer S. Teichert successfully completed her studies for a biological and chemical technical assistant in 2009. She graduated from Ludwig-Maximilians-University as B.Sc. in Chemistry & Biochemistry and as M.Sc. in Chemistry in 2016. She is at present investigating prebiotic nucleoside synthesis in the context of her doctoral studies, following Prof. Dr. Oliver Trapp.



Prof. Dr. Oliver Trapp is a full Professor of physical-organic chemistry the Ludwig-Maximilian-University. After studying chemistry at the Eberhard-Karls University Tübingen, he obtained his Ph.D. in 2001 from the University of Tübingen. Following his post-doctoral studies with R.N. Zare at Stanford University (2002–2004) he was Emmy Noether Research Group Leader at the Max-Planck-Institut für Kohlenforschung. In 2009 he was appointed as professor of organic chemistry at the Ruprecht-Karls-University Heidelberg. In 2016 he became Professor at the Ludwig-Maximilians-University in Munich and he is a Max-Planck-Fellow at the Max-Planck-Institute for Astronomy in Heidelberg. His current main research interests are the design and synthesis of self-amplifying enantioselective catalysis, stereochemically flexible ligands and catalyst, stereochemistry, prebiotic chemistry, the Origin of Homochirality, and the Origins of Life.





11a: R = CH<sub>2</sub>OAc, 11b: R = CH<sub>2</sub>OAc (5R), 11c: R = H (2S,5S)

**Scheme 2.** Conventional synthetic approach by Fischer<sup>[36]</sup> to prepare nucleosides, derived from acetobromoglucose **11a**, acetobromogalactose **11b** or acetobromorhamnose **11c**.

tively,<sup>[40]</sup> **3f** was converted to its dry silver salt and was reacted with the corresponding sugar **11a–c** in xylol to give the desired glucoside. Given the analytical tools of the time, it was impossible to determine whether the substitution takes place at N7 or N9 of the purine ring and an assessment of the  $\alpha$ -/ $\beta$ -connectivity at the anomeric center could not be made.<sup>[40]</sup> It was assumed that the attack is taking place at position N7, concluding from the observation that the silver assisted methylation of **3f** results in caffeine. Although successful for purine nucleosides, no synthetic procedure furnishing the corresponding pyrimidine nucleosides could be achieved. However, the canonical nucleosides **1** could not be synthesized.

The synthetic procedure to all purine derivatives was developed by Traube<sup>[39,44]</sup> starting from cyanoacetic acid and urea **17**/guanidine, which gives access to the corresponding amino pyrimidines, convertible into the purine derivatives via the formamidopyrimidines (FaPy) by reaction with formic acid.

The reaction conditions elaborated by Fischer were refined by Todd<sup>[2a,45]</sup> 34 years later. Advances in analytical equipment led to the structural elucidation of the canonical nucleosides. The connectivity was resolved to be a N9-connection of the purine unit to the anomeric center of **4a**. Moreover, it was determined that all canonical purine and pyrimidine nucleosides have  $\beta$ -configuration at the anomeric carbon atom.<sup>[46]</sup> Improvement of the synthesis of 2,8-dichloroadenine and optimization of the synthetic conditions by changing the sugar from **11a** to  $\alpha$ -acetohalogenoxylo pyranose<sup>[47]</sup> introduced an improved synthesis of adenine- and guanine-derived nucleosides.<sup>[46,48]</sup> The first synthesis of cytidine **1d** was reported in 1947,<sup>[49]</sup> finally showing a conventional synthetic pathway towards all canonical nucleosides **1a–e**.

### Early investigations under prebiotic conditions

In the meantime, other scientists pursued the fascinating question of how biological molecules could have formed under the conditions on the early Earth.<sup>[6,7]</sup> Many attempts have been made to discover prebiotically plausible pathways towards the canonical ribonucleosides and deoxyribonucleosides. By studying amino acid formation under conditions of the Miller–Urey experiment<sup>[5]</sup> free nucleobases were identified as one of the components. As expected, heating a solution of **1a** in aqueous ammonia solution, gave the nucleobase **3a** as decomposition product and indicates how sensitive potential prebiotic systems are.<sup>[7]</sup>

Later an entangled reaction network was elucidated (Scheme 3, left side) revealing the formation of the canonical purine nucleobases **3a,c**, via several heterocyclic intermediates, namely AICN **18** and AICA **19**.<sup>[8]</sup> In analogy, the pyrimidine synthesis (Scheme 3, right side) starts from cyanoacetylene **6**, which is a possible product of the discharge reaction between CH<sub>4</sub> and N<sub>2</sub>. Hydrolysis in alkaline media results in the formation of cyanoacetaldehyde **16**, which can in turn react in highly concentrated urea **17**, to give **3d**.<sup>[41]</sup> Uracil **3e** forms subsequently upon hydrolysis. Another route can proceed via cyanovinylurea **15**, which is formed from **6**, isocyanic acid **14** and ammonia, where the latter originates from the thermal composition of **17**.<sup>[42]</sup>

Those pathways provide a possible explanation for the concomitant synthesis of all nucleobases and amino acids. The necessary precursors are descendants from spark discharge reactions of abundant gases.<sup>[50]</sup>

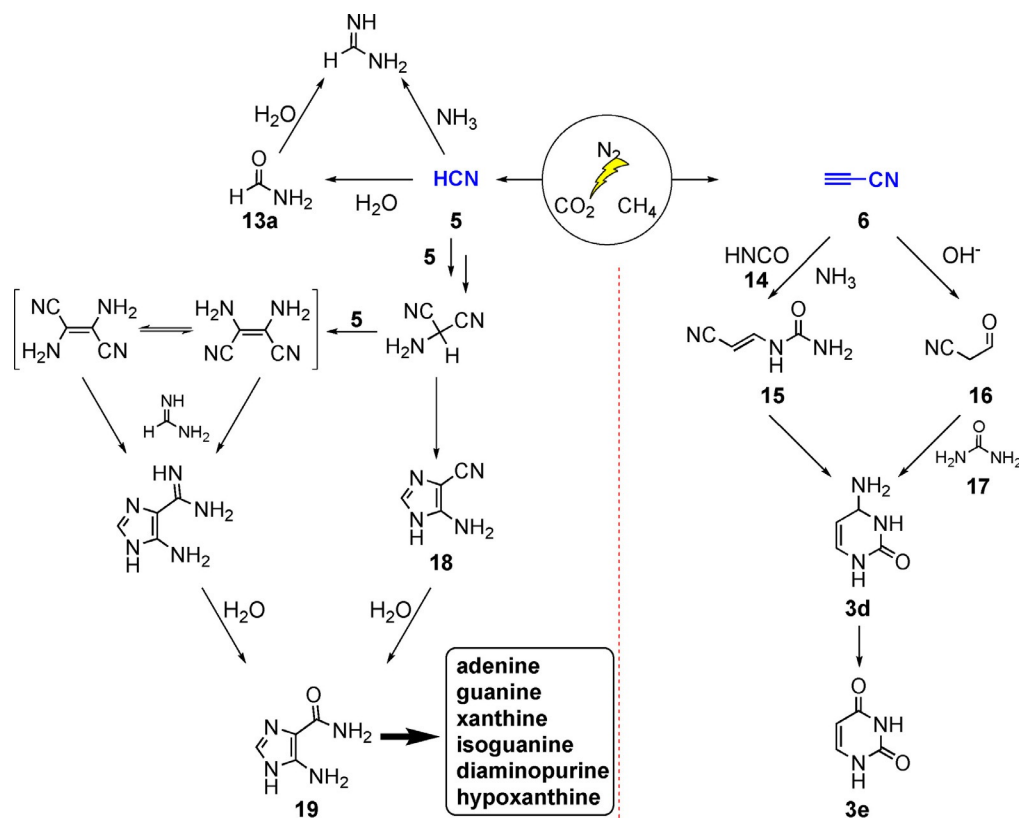
The sugar unit of the nucleoside is believed to originate from the formose reaction.<sup>[52,53]</sup> A base-catalyzed, autocatalytic reaction network, forming complex sugars from formaldehyde **20**, and glycolaldehyde **9** (cf. Scheme 4). Important products of the formose reaction, are for example, glyceraldehyde **10a** and its isomer dihydroacetone **10b**. As the formation of **3** could be realized under prebiotic conditions, various approaches towards pyrimidine and purine nucleosides were investigated.

The retrosynthetic strategy applied was almost exclusively based on the disconnection at the anomeric bond, as developed by Fischer, in 1909.<sup>[40]</sup> First syntheses of purine nucleosides were achieved by UV irradiation of a solution of **3a** and **4a**, in 1963.<sup>[51]</sup>

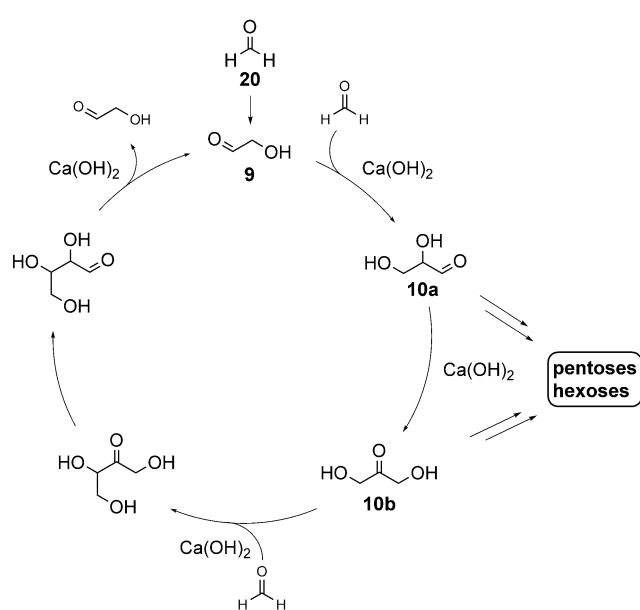
The yields under these conditions and the reproducibility were low.<sup>[9]</sup> Yet, the formation of **1** by heating **3a,c** and **4a** under anhydrous conditions assisted by the addition of inorganic salts could be achieved. Using aminopurines as precursors, the ribosylation of the primary amino group was reported under the same reaction conditions.<sup>[10]</sup>

Conversion to the canonical  $\beta$ -**1** is achieved by hydrolysis in neutral to alkaline aqueous media.<sup>[10]</sup> Reacting free **4a** and **3a,c** in presence of Mg<sup>2+</sup> ions or polyphosphates, directly produces  $\beta$ -**1a,c** in yields below 10%. In addition, the condensation in synthetic as well as natural seawater was studied (cf. Scheme 5). The reactions under the influence of MgCl<sub>2</sub> and (NH<sub>4</sub>)<sub>2</sub>HBO<sub>3</sub> gave high conversions. Surprisingly, evaporating a seawater solution containing **4a** and **3a,c** gave the best results. The reaction does not proceed under assistance of montmorillonite and other clays.<sup>[10]</sup> In presence of free amine groups ribosylation was observed. Disadvantages of these procedures are the depurination of the formed ribonucleoside and the fact that no conversion is detected in reactions with **3b**, **3d** and **3e**. In case of the pyrimidine nucleosides, it is stated that no conversion takes place because pyrimidine nucleosides are not hydrolyzed under acid catalysis, which poses the reversed condensation.<sup>[10,54]</sup>

Two major complications can be identified in the above presented synthesis of **1**: (i) The formation of **1**, by coupling **3** to the pentose sugar **4a** is feasible, but not very efficient. (ii) Interestingly, ribose **4a** is the least stable sugar in this series, it

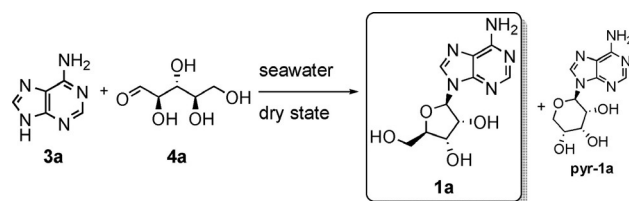


**Scheme 3.** Prebiotically plausible pathways, starting from charge discharge products of carbon dioxide, nitrogen and methane towards the purine nucleobases (left) and pyrimidine nucleobases (right),<sup>[8,41–43]</sup>



**Scheme 4.** The supposed catalytic cycle of the formose reaction.<sup>[52,53]</sup>

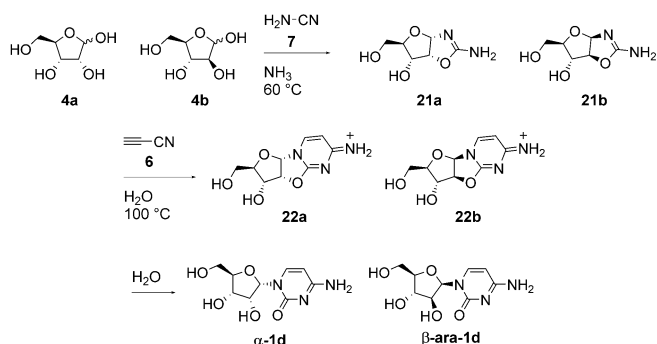
decomposes approximately four times faster than the average pentoses and 16 times faster compared to the hexoses. This marks a significant problem in finding a prebiotically plausible pathway towards **1**, as **4a** decomposes, with a half-life of three hours at pH 10.2 and 55 °C ( $7.0 \times 10^{-5} \text{ s}^{-1}$ ),<sup>[55]</sup> under the formose reaction conditions in which it might be synthesized.



**Scheme 5.** Dry state synthesis of ribonucleosides supported by seawater salts.<sup>[9,56]</sup> Concentration of the major ions in seawater: 0.458 M  $\text{Na}^+$ , 0.056 M  $\text{Mg}^{2+}$ , 0.010 M  $\text{Ca}^{2+}$ , 0.535 M  $\text{Cl}^-$ , 0.028 M  $\text{SO}_4^{2-}$ .

As pointed out, the barrier for the bond-forming reaction between **4** and **3** is intrinsically high. Therefore, a different disconnection rationale was sought after, circumventing the C–N bond formation between **4** and **3** in the last step. This approach presumes that the critical C–N bond formation step is accomplished at the beginning of a pathway (see Scheme 6), employing starting materials with higher nucleophilicity of the nitrogen-containing precursors. A brief overview of the accomplishments in this field is given, using **4a** and cyanamide **7** as the initial compounds of interest.

The synthesis started from either **4a** to gain  $\alpha$ -**1d** or from **4b** to obtain  $\beta$ -**ara-1d**.<sup>[57]</sup> Both sugars were initially transformed to the corresponding ribo-aminooxazoline **21a** or to the arabino-aminooxazoline **21b**. This class of aminooxazolines is proposed to form with a number of sugars, but preferentially with **4a**.<sup>[57]</sup> Additionally, **21a** selectively crystallizes in aqueous



**Scheme 6.** Alternative prebiotic pathway towards pyrimidine ribonucleosides, giving a mixture of the non-canonical stereoisomers  $\alpha$ -1d and  $\beta$ -ara-1d, via the newly described class of sugar aminooxazolines **14**.<sup>[10]</sup>

solution, while the other sugar aminooxazolines do not. Thence **21a** was considered as a “storage form” of the labile **4a** itself, because the former decomposes 70 times slower. Advantageously, the reaction of **7** with free **4a** is more than 200 times faster ( $1.5 \times 10^{-2} \text{ s}^{-1}$ ) compared to its decomposition ( $7.0 \times 10^{-5} \text{ s}^{-1}$ ).<sup>[55]</sup> Another property of **21a** is, that once in crystalline state, it is insoluble in water. The successive reaction<sup>[58]</sup> with **6** leads to the ribo-anhydronucleoside **22a** and to the arabino-anhydronucleoside **22b**. Subsequent hydrolysis of **22** gives  $\alpha$ -1d and  $\beta$ -ara-1d. In case of  $\alpha$ -1d, further hydrolysis leads to  $\alpha$ -uridine **1e**. Unfortunately, this synthesis does not give the same configuration of the nucleosides occurring in natural RNA. Photoisomerization of  $\alpha$ -1d to  $\beta$ -1d under UV light ( $\lambda = 253 \text{ nm}$ ) was found to be feasible to gain the correct configuration at the anomeric center. However, with a rather low yield of only about 5%. It is speculative if the formation of the nucleoside isomers with the unnatural stereochemical configuration can have an enhancing effect in the formation of RNA. The synthesis of the  $\alpha$ - and  $\beta$ -anomers of **1d**, **1e** was comprehensively developed in 1973.<sup>[57]</sup> Beside the optimization of the reaction conditions, leading to higher yields in **21**, it was investigated, whether the newly discovered ribo/arabino aminooxazolines **21** can be formed from different sugars. Indeed, several sugars were successfully tested. In contrast to previous experiments, the reactions of **6** with **21a** and **21b** were carried out in *N,N*-dimethylacetamide, leading to a solution of acrylonitrile isomers. The solution was stable at room temperature and at  $60^\circ\text{C}$  for several hours. The corresponding  $\beta$ -ara-1d and  $\alpha$ -1d were obtained after the addition of water or an aqueous solution of ammonia. Hydrolysis in ammonia was reported to be faster.<sup>[57]</sup> It was realized that an efficient synthesis, an efficient separation or an enrichment mechanism of  $\beta$ -1 is required, otherwise those pathways towards **1** would stand on loose ground. For this reason, it is compulsory to overcome the faux pas of getting the unnatural stereoisomers of the canonical nucleosides. A refined synthesis, concerning the major issues of the pathway, was published 30 years later,<sup>[59]</sup> relying on the basic concepts previously discovered by Sanchez and Orgel.<sup>[10]</sup> So far, solely the synthetic pathways towards the pyrimidine nucleosides have been described. Investigations towards purine nucleosides are ongoing, as adenosine and gua-

nosine are crucial functional units in ATP, ADP, AMP, GMP, NADPH, NADH, FAD and coenzyme A. In contrast to their natural abundance, prebiotic pathways towards purine nucleosides were more difficult to accomplish for a long time. As described above, Orgel showed that adenine can be synthesized from a solution of **5** in water. Therefore, the main procedure towards purine nucleosides was the condensation of free **3a** as its hydrochloride salt and free **4a** in anhydrous molten state.<sup>[9]</sup> This approach, however, produces complex reaction mixtures and very poor yields with respect to **1a**.

## Modern Investigations

The research group of Eschenmoser performed pioneering work in the field of prebiotic chemistry and thus provided many impulses for many other researchers.<sup>[60–62]</sup> A major contribution is their detailed investigation of homo-DNA with respect to the question, why pentose- and not hexoseri- nucleosides were formed?<sup>[63]</sup> The pairing and the strength of the Watson–Crick base pairs,<sup>[64]</sup> in dependence of the variation of the sugar backbone, was intensively studied. This led to insights why ribofuranose was chemically favored over all other sugars, which might have formed under prebiotic conditions. Eschenmoser also focused on the synthesis of heterocycles, respectively **1a–d** and cofactors from small molecules. Distinct, strict rules for these syntheses were defined to explore ubiquitous pathways leading from simple organic molecules to complex heterocycles:

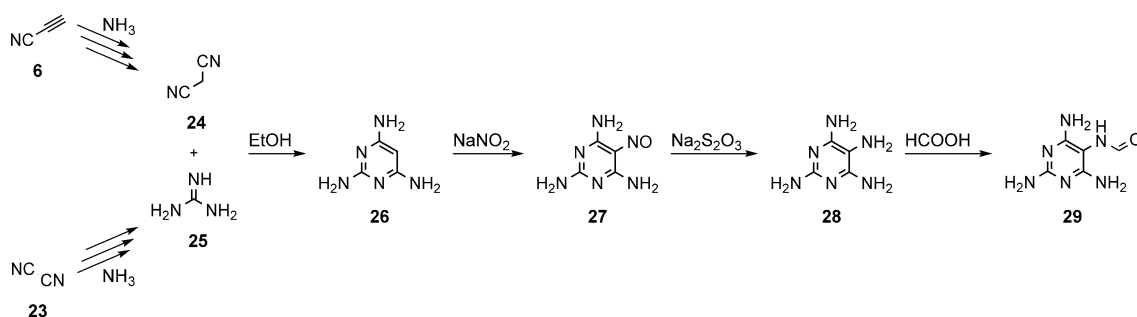
- No molecular oxygen,
- No water,
- Derivatives of cyanogene, cyanoacetylene and ammonia as precursors,
- Heat,
- Monomolecular reactions or bimolecular reactions with one ubiquitous reaction partner.<sup>[62]</sup>

Starting from  $\alpha$ -aminonitrile and **6**, the accompanied formation of amino acids, nucleobases and cofactor precursors could be elucidated.

## Augmenting the pool of precursors and pathways

The synthesis of nucleobase and cofactors leads back to the class of triaminopyrimidines **26**. The condensation of guanidine **25**, derived from cyanogene **23** with malononitrile **24**, derived from **6**, produces **26**. These can be nitrosylated in an acidic environment to gain nitrosopyrimidines **27**, see Scheme 7. Reduction with sodium thiosulfate furnishes the tetraaminopyrimidine **28**, which is stable as its salt but is easily oxidized, to various pteridine derivatives, as its free base. Subsequent heating **28** in formic acid produces formamidopyrimidines **29**. It was discovered that upon melting **29**, variations of canonical and non-canonical nucleobases can be synthesized.<sup>[62]</sup> In 2016, this structural approach was picked up by the Carell group,<sup>[65]</sup> to outline a new pathway towards purine ribonucleosides **1a,c**. Considerations by the Eschenmoser group about the evolution





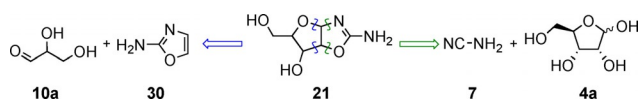
**Scheme 7.** Synthesis of tetraaminopyrimidines starting from HCN-derived precursors.<sup>[62]</sup>

of RNA stated, that the system, which produced RNA, also led to similar structures for example, different sugars, which were ruled out due to chemical selection.<sup>[63b]</sup> A selection for DNA nucleosides, confirming this consideration, was recently proposed by the Trapp group.<sup>[66]</sup> The above presented prebiotic syntheses of **1** do all have the same disconnection approach in common: building a glycosidic bond between **4 a** and **3** in the last possible step. Eschenmoser describes this disconnection as “the notorious nucleosidation problem”.<sup>[67]</sup>

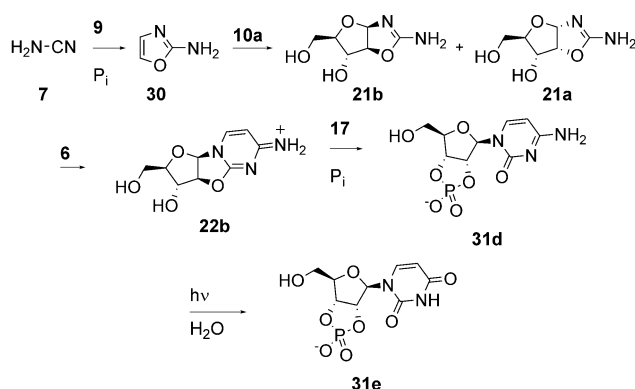
### Orgel refined: The realm of 2-aminooxazole

A previous synthetic procedure by Sanchez and Orgel,<sup>[10]</sup> set the crucial formation of the sugar–nucleoside bond at the beginning of a series of reaction steps. Sutherland<sup>[11]</sup> did pick up this way of approaching this nucleosidation problem, modifying the pathway of Orgel, by introducing inorganic phosphate as a general acid–base catalyst. Further, the previously presented **21** is disconnected in a different retrosynthetic manner to gain **10 a** as a C3-synthon and 2-aminooxazole **30** as a fused heterocycle (cf. Scheme 8). **30** is synthesized from **7** and **9**, in a high yielding condensation reaction. Both, **9** and **10** are products of the base-catalyzed formose reaction.<sup>[52,53]</sup> While **7** is frequently encountered as prebiotic, its origin is not yet resolved. The prebiotic availability is related to its detection in interstellar ices and clouds.<sup>[68–71]</sup> Delivery to primitive Earth could have happened via comets, asteroids and meteorites.

The formation of **30** proceeds quantitatively and the subsequent reaction (see Scheme 9) with **10 a** produces a mixture of **ribo-21 a** (25%), **arabino-21 b** (15%), **lyxo-21 c** (6%) and **xylo-21 d** (4%), additional to hydrolysis products of the former listed species.<sup>[72]</sup> Fortunately, **21 a** crystallizes (60% ee) upon cooling the reaction mixture to 4 °C, however **21 a** possesses the opposite stereochemical configuration to build up the nucleotide in the canonical  $\beta$ -configuration. In a slow, phosphate-



**Scheme 8.** A different disconnection approach of sugar aminooxazolines **21** to overcome the intrinsic problem of nucleosidation.



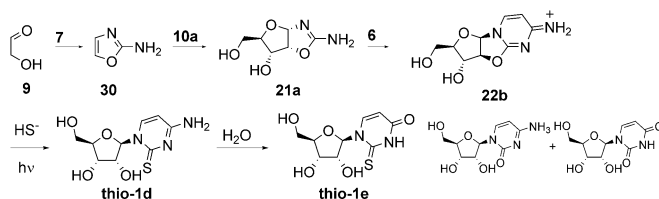
**Scheme 9.** A pathway towards the pyrimidine nucleotides **31 d** and **31 e** via stereochemically enriched arabinose-aminooxazole **21 b**, originating from **7**, **9** and **10 a**.<sup>[73]</sup>

catalyzed, equilibrium **21 a** interconverts to **21 b**, involving a furanose ring opening.<sup>[72]</sup>

The unbuffered reaction of **21 b**, however, leads to the non-canonical arabinose derivative of **1 d**. Succeeding, **22 b** is furnished in a phosphate buffered cyanovinylation step with **6**. Interestingly, a conjugate addition could take place instead of a direct nucleophilic attack of the free amine moiety at the triple bond. From a physical organic perspective, the nucleophilicity of the free exocyclic amine moiety ( $N \approx 13$ )<sup>[73]</sup> is higher than the inner cyclic nitrogen ( $N \approx 9$ ).<sup>[74]</sup> After evaporation of the reaction mixture containing **22**, inorganic phosphate and **17**, the 3'-hydroxy group is selectively phosphorylated.<sup>[75]</sup> An intramolecular attack of the phosphate changes the crucial stereochemistry of the nascent 2'-hydroxy group, forming a cyclic phosphate and releasing the base attached to the sugar unit in the correct stereochemistry. The last step of this reaction series is the loss of the phosphate by partial hydrolysis to yield the desired nucleoside **1**.<sup>[11]</sup> Upon irradiating the reaction mixture in the last reaction step with UV light ( $\lambda = 248$  nm), an equal distribution of **1 d** and **1 e** is formed, whereas all unwanted side products are destroyed. This photoanomerization is just applicable to the 2',3'-cyclic nucleotides. Although elegant, the pathway relies on the water soluble **21 b**, which it is not as easily enrichable as **21 a**. Additionally, it is the minor component of the phosphate catalyzed equilibrium of **21 a** and **21 b**. However, directly starting from **21 a** is not feasible, as the pho-



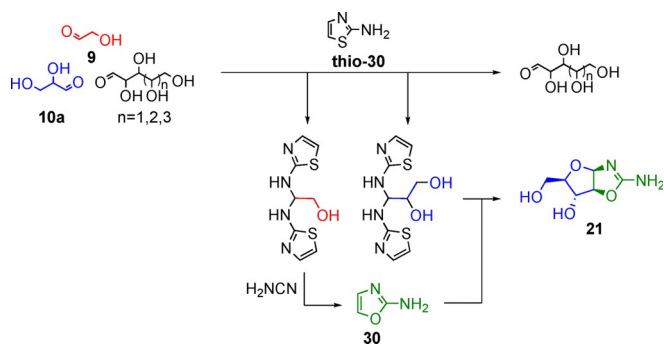
toanomerization of the corresponding  $\alpha$ -riboctidine results in its complete destruction. To overcome these deficiencies a new route (see Scheme 10) based on the thiolysis products of **21a** and **21b** is proposed.<sup>[76]</sup> The thiolysis of **21a** in aqueous formamide yields  $\alpha$ -thio-**1d**. In contrast to  $\alpha$ -**1d**, photoanomerization leads to thio-**1d** in 76% yield, instead of its destruction. From either  $\alpha$ -thio-**1d** or thio-**1d** hydrolysis leads to  $\alpha$ -thio-**1e** and thio-**1e**. Hydrolysis in phosphate buffer (pH 7) of thio-**1d** gives the canonical ribofuranoside **1d**, whereas a slight decrease in pH gives a significant higher amount of thio-**1e**.



**Scheme 10.** An improved pathway towards **1d,e** via  $\alpha$ -thioribocytidine  $\alpha$ -thio-**1d** utilizing **21a** as an enrichable compound.<sup>[77]</sup>

These pathways presented above, constitute very elegant processes towards canonical ribonucleosides from simple organic molecules. A major criticism is that the result of these reaction networks is greatly influenced by external interventions. A sequential addition of the reagents in the described order is essential to guarantee the successful outcome. In Nature, however, such a scenario is unlikely. Bearing the problem of sequential addition in mind, a novel chemical scenario for the consecutive addition of all reagents, was reported. This approach is based on the crystallization of certain intermediate products to avoid accompanying side reactions.<sup>[77]</sup>

This pathway (Scheme 11) is based on 2-aminothiazole thio-**30**, which constitutes stable amins of **9** and **10**. These crystallize selectively, resolving them as enantiopure compounds. The amins of the tetroses, pentoses or hexoses do not precipitate or even form. Both, the **9**-derived amina and the **10**-derived amina react in the above-described way, leading to **31**. This re-



**Scheme 11.** Selective reaction and precipitation of thiazol amins favoring **9** and **10** over C4–6-sugars and enhances the selective formation of glycolaldehyde and glyceraldehyde amins on the way to pyrimidine nucleotides **31**.<sup>[78]</sup>

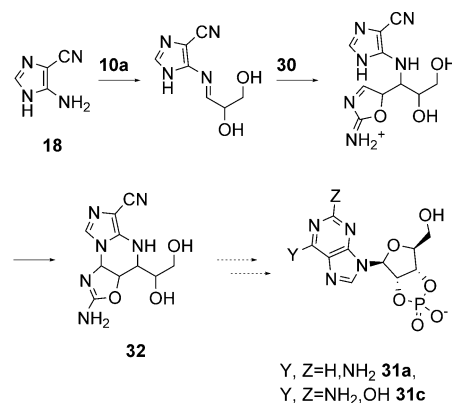
action sequence provides a possible one-pot pathway to solve the criticism of sequential addition of reagents in prebiotic chemistry.<sup>[77]</sup>

A major challenge in explaining the formation of  $\beta$ -**1** is the incompatibility of the reaction conditions leading to purine nucleosides, in contrast to those leading to pyrimidine nucleosides. From a statistical point of view, it is hard to argue that two distinct chemical circumstances lead to the two classes of nucleosides of one informational biopolymer. Regarding this circumstance, it is essential to find uniform reaction conditions leading to both pyrimidine and purine ribonucleosides.

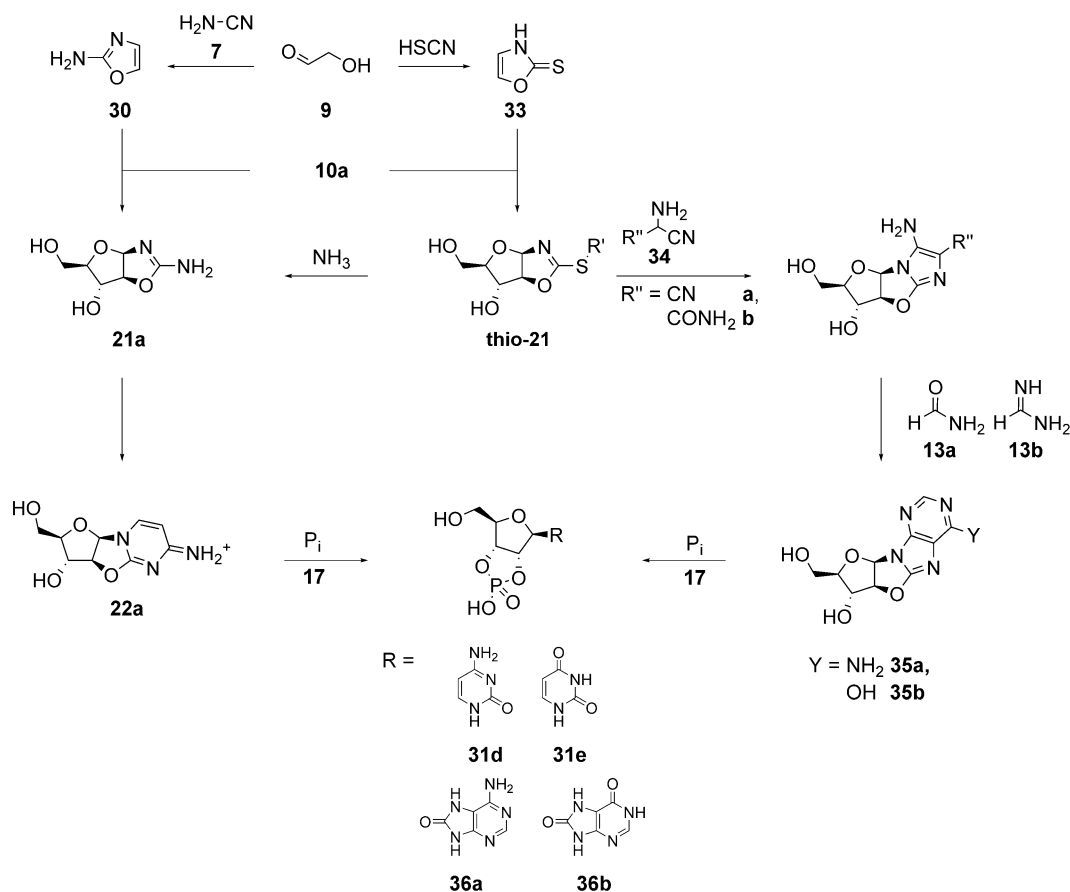
Then again, analyzing the modern biosynthetic procedures towards purine and pyrimidine nucleosides,<sup>[79]</sup> yet these two distinct procedural methods stand out. One attempt to find a uniform pathway to both classes of canonical  $\beta$ -ribonucleosides is based on a multi-component reaction of **30**, a sugar unit and **18** or **19**, both products of the photochemical oligomerization of **5**, described by Orgel (vide supra).<sup>[80]</sup> In this multi-component reaction, see Scheme 12, **32** is obtained from several aldehydes (formaldehyde **20**, acetaldehyde **47**, glycolaldehyde **9** and glyceraldehyde **10a**), via iminium ion formation with **18** or **19** and subsequent cyclization.

By changing the aldehydes, either TNA or RNA precursors can be synthesized. **32** (cf. Scheme 12) crystallizes from aqueous solution. It is proposed that the cyanovinylolation of this class of molecules leads to the **19**-riboside, via a UV-light induced loss of pyrimidine. Possibly a ring closing reaction furnishes the anhydro purine nucleoside, which can be converted to the purine nucleoside by urea-mediated phosphorylation. However, none of the speculated steps is reported and once again, the mere number of steps proves to be difficult to control from the point of chemical selectivity and prebiotic plausibility.<sup>[81]</sup>

In extension to the above-described pathways, a reaction series leading to the 8-oxo-purine nucleosides is described by the Powner group, see Scheme 13. In a variation of the approach leading to the pyrimidine nucleosides, **9** is reacted with thiocyanic acid to give an oxazolthione **33**.<sup>[78]</sup> Similarly, **33** is reacted with **10a**, forming an oxazolidinone thione thio-**21**, which acts as a unified precursor for both the pyrimidine- and



**Scheme 12.** Proposal of a concomitant synthesis of purine and pyrimidine nucleotides derived from 2-aminothiazole **30** as a common precursor.<sup>[82]</sup>



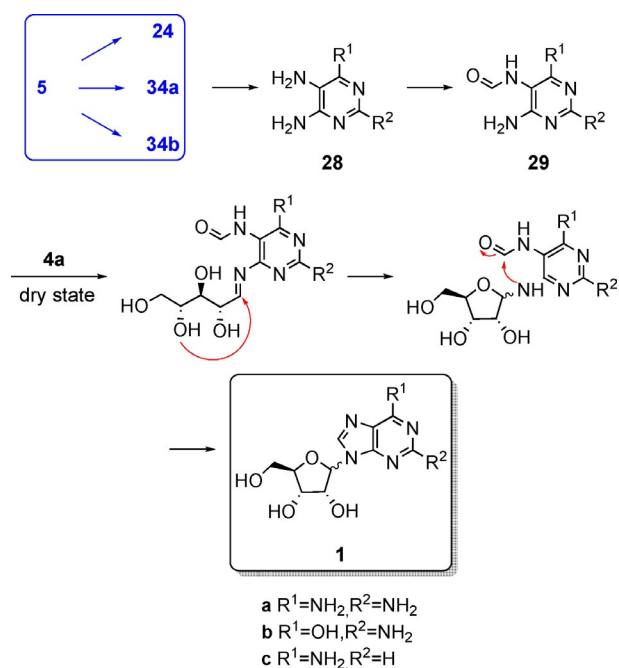
**Scheme 13.** A unified pathway towards pyrimidine nucleotides and 8-oxo-purine nucleotides **31,36** from arabinose-2-aminooxazoline derivatives **thio-21** as common precursor.<sup>[79]</sup>

the purine ribonucleoside formation. The joint precursor circumvents both the nucleosidation step and keeps the instability of the free sugars at bay.

Upon ammonolysis **21a** is generated, reacting in the previously described manner to the pyrimidine nucleotides **31d,e**. Whereas consecutive reaction with 2-aminomalononitrile **34a** and 2-amino-2-cyanoacetamide **34b**, both oligomers of **5**, build up the anhydro purine nucleoside **35** after reaction with formamide **13a** and formamidine **13b**. In a final urea-mediated phosphorylation step the pyrimidine ribonucleotides **31d,e** and the 8-oxo-purine ribonucleotides **36** are obtained. As the 8-oxopurines favour base-pairing in the Hoogsteen<sup>[82]</sup> mode, rather than Watson–Crick base-pairing the prebiotic reduction conditions that would lead to the canonical purine nucleotides remain elusive. Major drawbacks with regards to an actual prebiotic synthesis are the constructed sequential addition of all reagents, resulting from the high reactivity, and thus instability of the reagents thiocyanic acid, **6** and **7**. Furthermore, a sluggish change of pH is needed after each step, as the compounds are not stable under the conditions of the previous formation.

### Eschenmoser refined: The realm of the FaPys

With respect of a prebiotic access towards the canonical  $\beta$ -purine ribonucleoside, the Carell group elaborated the most promising pathway (Scheme 14). This pathway, starts from aminopyrimidines **28**, which are hypothetically easily accessible from **25**, **34a** or **34b**.<sup>[61b,62]</sup> Trinks<sup>[62]</sup> did major work on the formation, reactivity and characterization of various triaminopyrimidines **26**. The precursors themselves are of prebiotic origin, as they are oligomers and condensation products of the **5**-regime.<sup>[61b]</sup> The reactivity of **26** with formic acid and **13b** was studied, resulting in formamidopyrimidines **29**, as purifiable intermediates on the way to the corresponding purine nucleobases. The Carell group<sup>[65]</sup> elegantly refined this pathway by reacting **29**, in dry-state, with **4a** to yield the correlating imine, see Scheme 15. **28** is formylated in an acidic environment. The formylation possesses a high position selectivity towards the amine at C4 or C5. When protonated the nucleophilicity of the inner-cyclic nitrogen is reduced and consequently only the free amino-group N5 remains as nucleophilic moiety. In a dry state reaction, **4a** reacts with one of the amines adjacent to the form-amidine-moiety, to form the **4a**-imine. Selectivity issues during this step are diminished by the mirror symmetry of the molecule. Subsequently, the ribose ring is closed intramolecularly by a nucleophilic attack of the 4'-hydroxy group at the



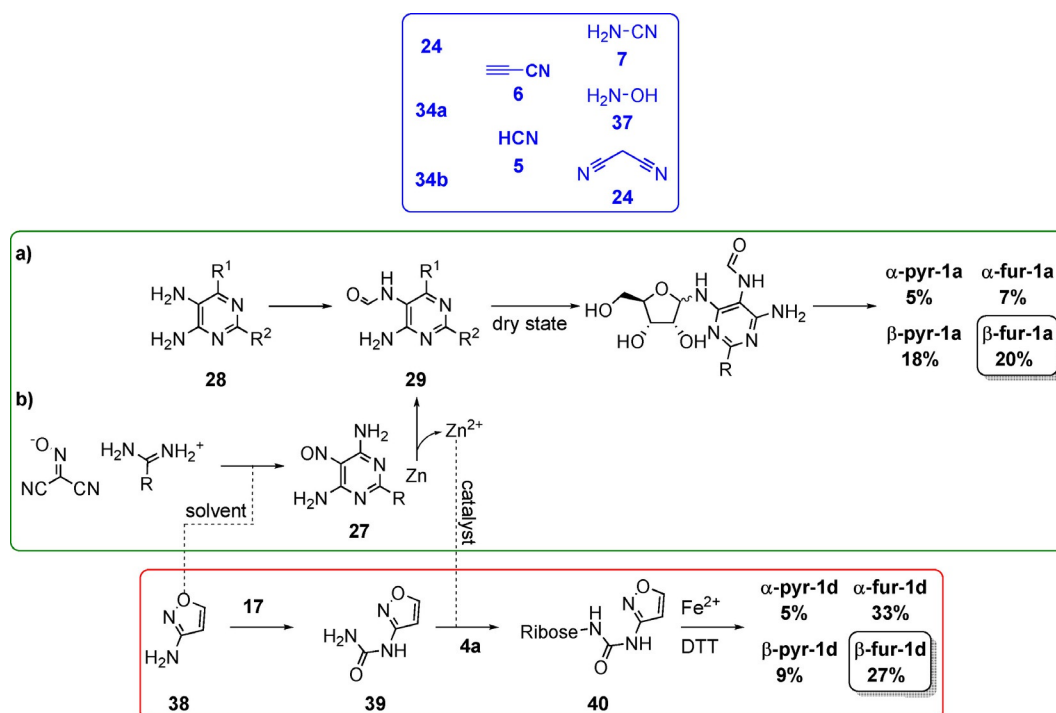
**Scheme 14.** Prebiotically plausible route towards purine nucleosides: Dry state reaction of formamidopyrimidines **29** and D-ribose **4a** supported in alkaline borate media.<sup>[65]</sup>

imine. In a consecutive step, the newly formed amine nucleophilic attacks the formamide, closing the purine base, ending the synthetic pathway towards the furanoside. The ribosylation step performs best under basic conditions, as sodium borate is reported to stabilize the ribose in the desired *cis*-configuration.<sup>[83]</sup>

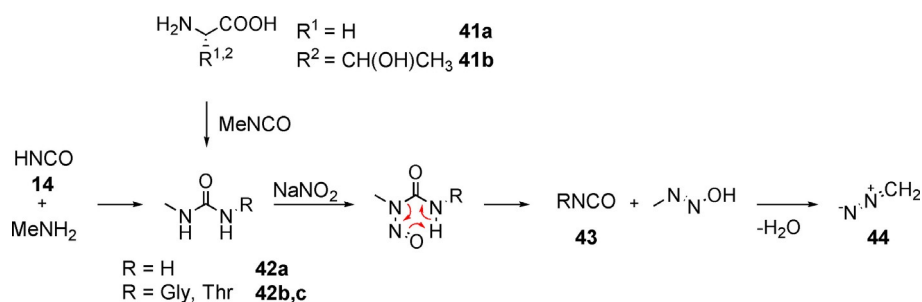
A point of criticism, from a prebiotic synthesis perspective, is the change of media from acidic to alkaline. Communicating adjacent mud pots at different pH values are discussed, however these are very special reaction conditions. Moreover, the respective ribonucleosides are formed in a furanose/pyranose mixture both containing the  $\alpha$ - and  $\beta$ -anomer.

To overcome this problem, an elaborate, multi-step wet-dry-cycle-procedure was developed.<sup>[84]</sup> It increases the overall conversion to **1a,c** as a consequence of precursor enrichment. In an initial step (hydroxyimino)malononitrile is formed from malononitrile **24**, derived from **6**, and sodium nitrite in an acidic environment. Upon cooling, the desired compound crystallizes as its guanidinium salt. When heated, it forms nitrosopyrimidines **27**, which are not soluble in aqueous media, see Scheme 15b. Several derivatization steps are possible to furnish miscellaneous derivatives of **27**. Concluding, **29** is a result of the reduction of **27** in formic acid, in a native iron and nickel-system.<sup>[85]</sup> The reduction thereby results from an in situ formation of hydrogen, from formic acid, oxidizing iron and nickel to their water-soluble salts. The metal salts precipitate under alkaline conditions, while **29** remains soluble and is washed away. A last crystallization step upon drying the supernatant reaction mixture gives **29**. **1a,c** are obtained subsequently from **29** in the way described above.

Beside **1**, a variability of non-canonical RNA nucleosides is present in coding tRNA. These are prebiotically accessible via carbamylation and methylation reactions.<sup>[86]</sup> It is assumed that non-canonical ribonucleosides, which are found in RNA, are ancient hints to an RNA-World.<sup>[87]</sup> The following procedure describes the formation of non-canonical ribonucleosides starting from substituted methylureas **42**, see Scheme 16. **42** is formed by the reaction of its precursor isocyanic acid/isocya-



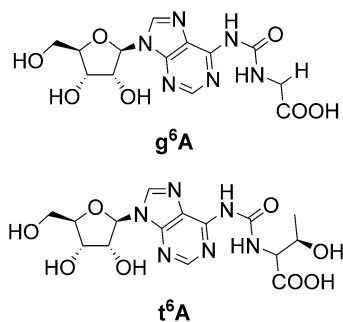
**Scheme 15.** A unified pathway towards ribonucleosides starting from formamidopyrimidines **29** and 3-aminoisoxazole **38**.<sup>[12,65,85]</sup>



**Scheme 16.** Prebiotic formation of diazomethane and a carbamoylation reagent from amino acids to achieve derivatization reagents for canonical RNA nucleosides.<sup>[87]</sup>

nate **14**<sup>[88]</sup> with methylamine and represents a reactive intermediate. Nitrosylation of **42** under borate-alkaline conditions, rearrangement,<sup>[89]</sup> and the elimination of water furnishes diazomethane **44**, which can easily methylate **1**. Complementary, the carbamoylation of the nucleosides is achieved, starting from the amino acid glycine **40a** and threonine **41b** as precursors.<sup>[86]</sup> In analogy, these react with methylisocyanate to lead to the glycine **42b** and threonine **42c** methylurea derivative. The nitrosylation<sup>[90]</sup> yields the isocyanate-derivatives of the amino acids **43b,c**, which can then carbamoylate **1** at N6 to form derivatives of the canonical nucleosides for example, *g*<sup>6</sup>A and *t*<sup>6</sup>A (cf. Figure 3).<sup>[91]</sup> Furthermore, the above presented methylation/carbamoylation is a key step in a proposed synthesis towards the pyrimidine nucleobases.<sup>[92]</sup>

Most recently, a unified pathway towards purine and pyrimidine nucleosides was reported. This pathway starts from one common pool of feedstock molecules, with **6** as the main molecule of interest. The reactions do not proceed in one-pot, but in an interweaved pathway in different environments. The pyrimidine pathway starts by reacting **6** under basic conditions with hydroxylamine **37** to give 3-aminoisoxazole **38**. After subsequent dry down of the reaction mixture, **38** is reacted with **17** in a solid-phase reaction, utilizing zinc(II) or cobalt(II) salts as catalysts. The desired *N*-isoxazolyl-urea **39** is formed with high selectivity, at 95 °C, with only **38** as the remaining impurity. As in previous Carell wet-dry-cycle procedures,<sup>[84]</sup> the metal cations are precipitated as their carbonates, leaving all other compounds in solution. The whole reaction is reported to proceed in a one-pot fashion from **6**, hydroxylamine **37** and **17**.



**Figure 3.** *g*<sup>6</sup>A and *t*<sup>6</sup>A as examples for derivatives of RNA-nucleosides.<sup>[92]</sup>

Subsequently, the mixing of two distinct environments is necessary to provide a solution of pure **4a**. Annealing of **4a** leading to **40** (Scheme 15) takes place in a solid-state reaction, after the drying up of the initial reaction mixture. The reaction is catalyzed by boric acid or other borate containing minerals, such as lüneburgite<sup>[83a]</sup> or borax. Major products are the  $\alpha$ -/ $\beta$ -pyranosides starting from **39**, however heating the mixture under basic conditions shifts the equilibrium towards the  $\alpha$ -/ $\beta$ -furanosides, see Scheme 15.

At the same time the hydrolysis of **40** is observed. The final step of the reaction cascade is a FeS-mediated ring opening of the isoxazole subunit of **40**. A sub-sequent rearrangement furnishes **1d,e** in an  $\alpha$ -/ $\beta$ -mixture, possessing a furanose/pyranose ratio of 17:1.

Even though this pathway provides a unified ancestor for both purine and pyrimidine nucleosides **1a–e**, it possesses a few inconsistencies. Upon evaporating water, **38** functions as a solvent for the formation of **27** from malononitrile and amidines. However, the subsequent transition to **29** does not proceed in this solvent. Therefore, some processes require the removal of the solvent **38** (bp. 228 °C) and later add it to the reaction mixture under prebiotic plausible conditions. The purified **27** are reduced and formylated after incidentally getting in contact with a stream of water containing zinc and formic acid. The formed zinc salts could catalyze the reaction of **38** with **17**, illustrating a possible synergistic effect between two environments. However, this compound is no longer present in the same environment. Not irrelevant, these are minor disturbances regarding the geological setting of the scenario, however a major chemical problem is the need for hydroxylamine **37** under prebiotically plausible conditions. The formation in interstellar ices<sup>[93]</sup> and under ultrasonic radiation<sup>[94]</sup> is hypothesized, however its prebiotic relevance remains dubious. Another potential process could be the Raschig process, where ammonia nitrite is reduced to hydroxylamine by  $\text{SO}_2$ .<sup>[95,96]</sup>

The next step leads to **1d,e** or **1a,c**, whereas **1a** and **1d** are developed with the highest yields. In the case of **1a** the double ribosylation was observed under the conditions applied. The described pathway includes well-designed reactions, however the arrangement and the progression of the reaction cascade and its compulsory succession is rather disputable. The outcome of the pathway is decisively depended on the



precise outside conditions and implies that the formation of Life on Earth is a mere product of coincidence. Continulative investigations are performed in the phosphorylation of ribonucleosides. These provide pathways to form ribonucleotides from **1** under prebiotically plausible conditions. However, these are not directly linked to the synthesis of **1**.<sup>[83, 97, 98]</sup>

The above described pathways<sup>[11, 12, 79, 82, 85]</sup> are attempts to synthesize **1** from common organic feedstock molecules. Different prebiotic scenarios are outlined with the commonality that all molecules must be synthesized under prebiotic circumstances. The prevailing theory is that RNA was the coding polymer at the Origin of Life, as it exhibits catalytic function, information storage ability and the possibility to undergo template-based polymerization. DNA, as the coding polymer of modern Life, however, is said to be developed at a much later stage of chemical evolution, assisted by enzymes, which cleave the decisive 2'-hydroxyl group. Contrary to the instability of the free deoxyribose **d4a**, the corresponding DNA strand is the more stable, of both coding polymers of Life except for acid-catalyzed depurination of adenylates (DNA deadenylates much easier than RNA). This poses the question, why DNA nucleosides, nucleotides or even the DNA polymer should not have played a role in the Origins of Life context. One could argue that maybe DNA is too stable to participate in the chemical evolution. However, the theory is appealing that, at the beginning of Life, there are a flexible, catalytic polymer (RNA) as well as a stable, informational polymer (DNA) working hand-in-hand.

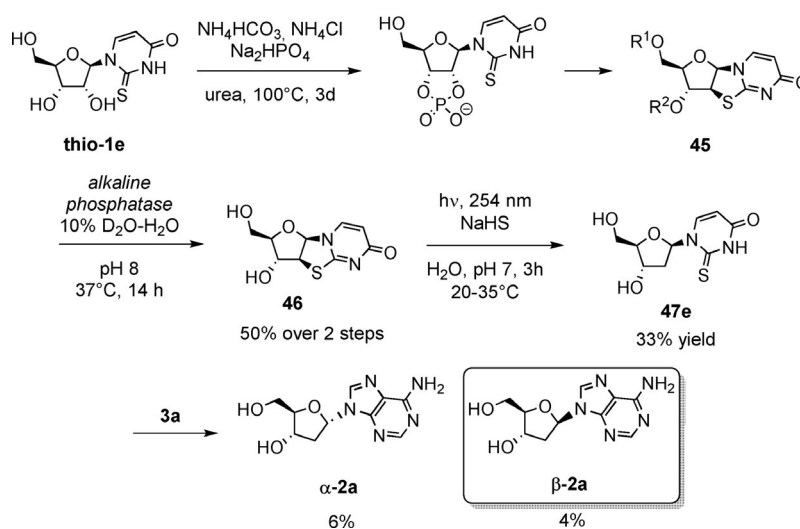
## Chicken or Egg?: Deoxyribonucleoside Synthesis

In the following two major contributions for the synthesis of **2** are presented. The first pathway is proposed by the Sutherland group<sup>[99]</sup> and is in analogy to the dithioreduction of the enzyme ribonucleotide reductase.<sup>[101]</sup> The second approach by

Trapp<sup>[66]</sup> mimics the reaction catalyzed by the enzyme 2-deoxyribose-5-phosphate aldolase.<sup>[101, 102]</sup>

In the first contribution, another variation of the approach<sup>[76]</sup> to **1** via **22**,<sup>[99]</sup> is presented. Initially, the phosphorylation of thio-uridine **thio-1e** in semi-molten urea **17** was investigated. However, not the expected 2',3'-cyclic phosphates, as in the reaction with DAP,<sup>[98]</sup> were detected, but instead a phosphorylated thioanhydro-nucleoside **45** was formed (cf. Scheme 17). **45** is the first example of a C-S connection at the 2'-carbon of the furanose ring. The key step of the ribonucleotide reductase is a stoichiometric radical dithioreduction, the C-S bond of **45** might be susceptible to reduction to form **2**-derivatives. The obtained compound **46** was reacted under UV-irradiation at 254 nm; aqueous H<sub>2</sub>S acted as a reductant. The result was a mixture of 2-thiocytosine **thio-3d**, thiouracil **thio-3e** and 2'-deoxy-2-thiouridine **47e**. However, the reduction is reported to not proceed from the phosphorylated species **45**. Therefore, the free anhydronucleoside **46** was obtained from **45** by treatment with an alkaline phosphatase. Additionally, the thioduction towards the 2'-deoxyribonucleoside just proceeds from the uridineanhydronucleoside **45e** and not from the cytidineanhydronucleoside **45d**.

The analysis of the reaction mixture was executed by NMR spectroscopy with pentaerythrol as an internal standard. Two control reactions were carried out to verify the proposed reaction. First, a reaction in the dark, under the influence of H<sub>2</sub>S and second, irradiation with UV light without the assistance of H<sub>2</sub>S. Both reactions did not lead to **47**. Thus, it is concluded that the reduction starts by light induced, solvated electron from HS<sup>-</sup>, cleaving the C-S bond in a radical process. Although, mimicking the active site reaction of the ribonucleotide reductase in an elegant way, a solution to displace the non-prebiotic alkaline phosphatase needs to be found, disregarding that just the formation of **47e** and not the simultaneous formation of **47d** was observed. As dU **2e** is not a constituent of modern DNA the formation of both **2d** and **2e** via this multistep pathway is highly anticipated. **47** might function as a precursor for



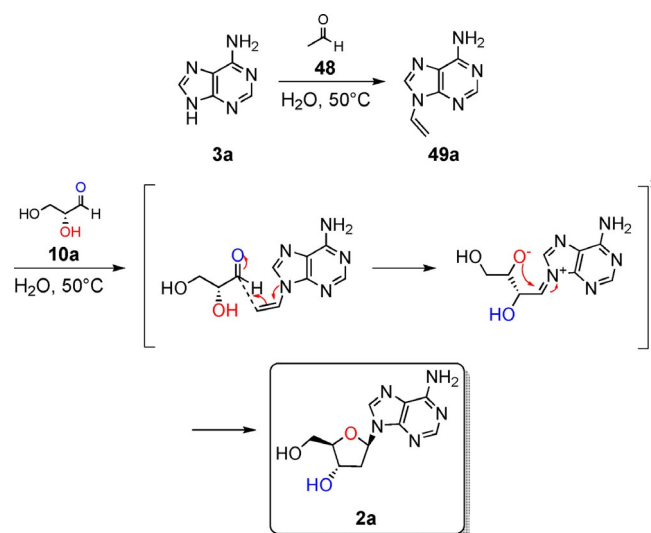
**Scheme 17.** Phosphorylation of **thio-1e** enables the formation of the corresponding thioanhydronucleoside **46** and subsequent formation of deoxythiopyrimidine ribonucleosides.<sup>[100]</sup>

the canonical pyrimidine 2'-deoxynucleosides. However, a direct pathway from **47** towards **2a** is not described. Therefore, it was investigated, if **2a** is accessible via transglycosylation, with **3a** and **47e**. The reaction was solely successful under dry state conditions at 100 °C. However, both the  $\alpha$ - and the  $\beta$ -anomer of **2a** are formed by this process. Again, the classical Fischer disconnection<sup>[40]</sup> at the anomeric carbon is applied to obtain **2**. The substitution of **47e** by **d4a** and application of the reaction conditions of Orgel,<sup>[9]</sup> did not lead to the correct product, but to a vast reaction mixture instead. This again indicates that the reaction barrier for the bond-forming reaction between the sugar and the nucleobase is intrinsically too high and another disconnection rationale, then the one applied for the past 90 years, seems likely. This process solely produces **2d** out of four deoxyribonucleosides, in an overall low selectivity and yield. Complicated by the control of stereochemical selectivity in a radical process, thus concluding that the prebiotic relevance of this scenario is rather questionable.

### The selectivity of simplicity

So far, an ab-initio pathway towards **2** has not been considered. This might result from the often dogmatic discussion that RNA preceded DNA and the chemical fact that **d4a** is unstable under the conditions that are assumed to be prebiotic. Recent advances however show the formation of heterogeneous RNA–DNA chimera.<sup>[103]</sup> These could provide a mechanism for the template, autocatalytic replication and enrichment of informational biopolymers without the need for enzymes. When applying the Fischer approach towards nucleosides, the glycosidations, resulting in **1** are much easier to accomplish than a glycosidation yielding in **2**.

Classifying **3** in two different groups, includes the problem that there is no consistent synthesis of both purine and pyrimidine nucleosides, under the exact same conditions. Until 2019, considering a different disconnection approach towards **2** was disregarded. Trapp<sup>[66]</sup> proposed a uniform pathway towards all four canonical deoxyribonucleosides, via the vinyl nucleobases **49** as a detectable intermediate (Scheme 18). The reaction proceeds under the exact same conditions from all four canonical nucleobases **3**, acetaldehyde **48** and **10a**. In analogy to amino-organocatalysis<sup>[104]</sup> **49** is formed. Stereoselective controlled attack of **49** at the carbonyl group<sup>[105]</sup> of **10a**, builds up **2**, after a 5-*exo-trig* cyclization.<sup>[106]</sup> The reaction proceeds with exclusive  $\beta$ -selectivity. In contrast to the above described syntheses, the reaction proceeds in water at an ambient temperature of 50 °C. No additives, no sequential addition of reagents, no variation of pH and no purification processes are needed. In this case, the statistically more probable C3-sugar **10a** builds up the nucleoside sugar moiety, instead of the precarious C5-sugars **4a** and **d4a**, which are formed to a much lesser extent in a formose reaction mixture. This new modus operandi does not only depict a highly selective pathway towards **2** and addresses the fundamental question “why deoxyribofuranose is favored over all other possible sugars”,<sup>[63a]</sup> but in addition, this pathway mimics the reaction catalyzed by the enzyme 2-

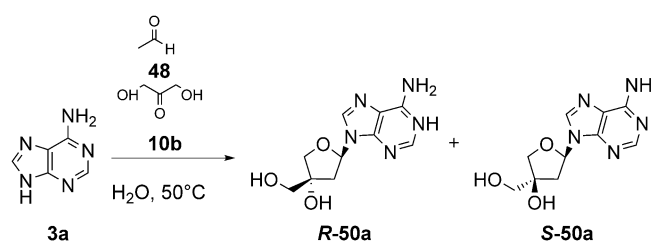


**Scheme 18.** Mechanism of a highly stereo- and furanoselective pathway towards deoxyribonucleosides **2**.<sup>[66]</sup>

deoxyribose-5-phosphate aldolase (DERA, EC 4.1.2.4) from *E. coli*.<sup>[101,102]</sup>

This enzyme catalyzes the reaction of glyceraldehyde-3-phosphate with **49** to obtain the corresponding 5'-deoxyribonucleotides. This biological pathway might be an ancient relic of this reaction at the Origins of Life and thus the proposed prebiotic synthesis is highly plausible.<sup>[101,102]</sup> In a recent article,<sup>[107]</sup> a comment questions the accuracy of the presented analytical data. However, not just highly sensitive extracted ion chromatograms gave proof for the proposed mechanism, but also co-injection with reference samples under UV-analysis verified the correctness of the results. When reacting **49** with formaldehyde **20**, glycolaldehyde **9** or dihydroxyacetone **10b**, several deoxyribonucleoside-derivatives were detected.

However, these are ruled out due to their inability to polymerize or their stereochemical flexibility. The driving force of selection is the reduction of stereochemical flexibility. DAPiNA-nucleosides (cf. Scheme 19) **50**,<sup>[108]</sup> formed from **49** and dihydroxyacetone **10b**, therefore might have been a possible DNA progenitor, but were not selected due to the existence of four epimers and thus too much stereochemical flexibility (cf. Scheme 19). In DNA, the nucleosides just exist in one expected epimer, confining the flexibility to the lowest and simplest pos-



**Scheme 19.** Formation of deoxyribose nucleosides **50** as exemplary, selective pathways elucidating the precedence of deoxyribose over all further possible sugars.

sible. This provides an explanation why deoxyribose is favored over all other sugars. This pathway favors the assumption that DNA evolved much earlier than previously proposed and could have been part of chemical evolution alongside RNA.

The ingenuity of Nature is far beyond human's expectations and thus applying the "selectivity of simplicity" principle to the Origins of Life research is worth the consideration.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** deoxyribonucleoside synthesis · heterocycles · nucleoside synthesis · origins of life · prebiotic chemistry

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