Route Efficiency Assessment and Review of the Synthesis of β-Nucleosides via *N*-Glycosylation of Nucleobases

This document contains the experimental details and calculations for all synthesis. Glycosylation reactions for the synthesis of nucleosides are numbered **N1**–**N80** and reactions/routes to sugar synthons are numbered **S1**–**S26**. The nucleoside syntheses are sorted according to the sugar synthon they employ for *N*-glycosylation.

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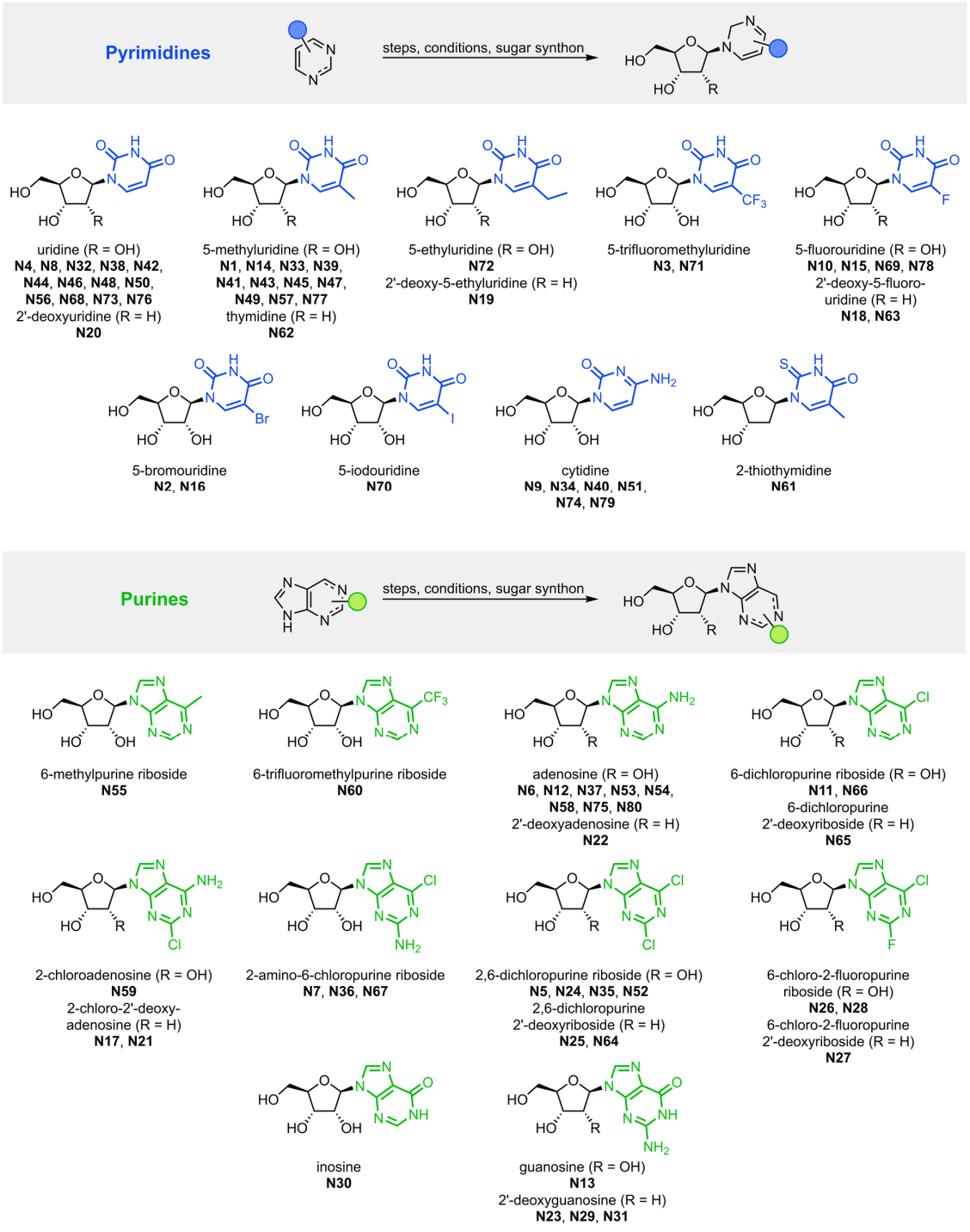
Chart S1. All nucleobases and nucleosides in this article



Author contributions (with definitions as recommended by Brand *et al.*[1])

Conceptualization, F.K.; Data curation, F.K.; Formal analysis, F.K.; Funding acquisition, P.N. and A.W.; Investigation, F.K. and M.R.L.S.; Methodology, F.K.; Project administration, F.K.; Resources, P.N. and A.W.; Software, - ; Supervision, A.W.; Validation, - ; Visualization, F.K.; Writing—original draft, F.K.; Writing—review & editing, F.K., M.R.L.S., P.N. and A.W.

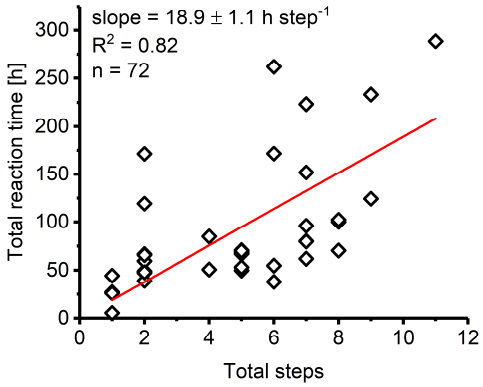


Figure S1. Reaction time per step. A step was considered as every transformation followed by some form of workup or purification. Route time was calculated as described below.

General Information

For each procedure, the following experimental details were extracted from the original report: quantities (g, mol) of all starting materials, reaction solvents (L, g), quenching solutions (L, g; including content of salts) and extraction solvents (L, g), reaction time (h) and amount of product (yield, g, mol).

From these raw data, the following quantities were calculated as detailed below and in the analysis of the respective procedure:
Simple E-factor (sEF), complete E-factor (cEF), total reaction time, total reaction solvent use and product generated.

In multistep processes, the sEF and cEF were calculated as follows:

$$\mathrm{EF} = \frac{\sum \mathrm{M} - \mathrm{P}}{\mathrm{P}} = \frac{\mathrm{M_1} + \mathrm{M_2} + \cdots + \mathrm{M_{n-1}} + \mathrm{M_n} - \mathrm{P}}{\mathrm{P}} = \frac{\mathrm{M_1} + \mathrm{M_1} * \mathrm{EF_1} + \mathrm{M_2} + \cdots + \mathrm{M_{n-1}} + \mathrm{M_n} - \mathrm{P}}{\mathrm{P}} = \ldots$$

Here, $\sum \mathrm{M}$ is the total mass of all (n) materials used with M_i being masses of the individual materials i (i = 1, 2, … n−1, n) and P the mass of the generated product. If any of the materials i had to be synthesized beforehand (and therefore had an E-factor for that prior step already associated to it), M_i was extended by the E-factor of that prior step, EF_1, multiplied with M_i. sEF and cEF were calculated according to this equation under consideration of the respective materials (see below).

Please note, we herein adhered to the compound naming provided by the authors of the respective manuscripts. We assume that all quantities reported in the literature are correct and included them in our calculations at face value (even if, in some cases, quantities reported throughout the manuscript(s) may have been inconsistent). We assume that all quantities provided in the literature are correct to the valid digit reported. Calculated values are rounded to the nearest milligram.

If any quantities were not explicitly provided, we transformed them from reported quantities and listed the conversion metric (generally molecular weight or density) whenever possible. If any quantities were not reported in any form, we explicitly stated this is in the respective procedure and used the following assumptions (following recommendations by Hollmann and colleagues[2]):

- Reactions were performed at a concentration of 0.2 M
- Solvents for extraction were used in equal volume to the initial solution
- Aqueous solutions for washing organic extracts were used in equal volume to the extract volume (except brine, where we assumed 50% extract volume)
- Anhydrous salts for drying of extracts were used as 20 mg per mL of extract volume
- Solvents for dilution were used as two times the volume of the initial solution

- Solvents for extraction of solids were used as 5 mL per gram of crude material
- Solvents for chromatography were used as 500 mL per gram of crude product (the crude product being composed of the entire weight of all reagents used for synthesis)
- Solvents for recrystallization were used as 10 mL per gram of crude product
- Silica gel for chromatography was used as 20 g per g of crude product

All estimated quantities are typeset in italics. Whenever we estimated any quantity, we explicitly stated that this is an assumption.

Waste weights from solvent mixtures (for extraction, chromatography, recrystallization and otherwise) were calculated via their volumetric ratios and their respective individual densities (assuming no volume loss upon mixing). Aqueous solutions for washing of extracts were treated as saturated solutions at room temperature. Their solid components (generally inorganic salts) were treated separately from their water content and calculated from the solid weight percentage assuming the rest of the weight being water with ρ = 1.00 g·cm^{-3}. Aqueous hydrochloric acid was treated as water with a concentration-dependent density. Buffer components were calculated based on their concentration assuming no contribution to the solution volume, which we assumed to be exclusively water. Again, estimated quantities are clearly stated as such and all conversions are detailed with conversion metrics (generally density, molecular weight or solubility; with references provided as appropriate).

We assumed that all routes need to start from unprotected starting materials (generally either ribose or a natural nucleoside) and end with an unprotected product. Therefore, we refer to all E-factors reported in the main text as *route E-factors*. Thus, if protecting groups were applied along the way, we included their installation and removal into the E-factor of that route. If the authors of a given synthesis reported the preparation of any synthon they used (generally protected glycosides), we used their procedure to calculate the E-factor for that synthon. If the authors did not report the synthesis of a protected synthon they used as a starting material, we either consulted the report which they cited for its synthesis or − in lieu of that − assumed they used a known method for its preparation. In the latter case we selected a common literature method for its synthesis and used that procedure as a basis for the E-factor calculation of that synthon. In any case, the route to a specific synthon (and possible E-factor contributions arising from that) is outlined at the bottom of each reaction described.

Quantities are listed for every procedure extracted from the literature and marked according to several categories. Reagents and organic compounds are green, inorganics and salts are orange,

solvents are red, water is blue, and **products** are bold black. Cumulative E-factor contributions from these categories were calculated using the contributions of the respective step and including the product of the weight of the previously synthesized starting material and its E-factor contribution of that category. For example, if A and B were reacted to C with B being a product from a previous step, the reagent contribution to the synthesis of C (X_C) was calculated as

$$X_C = M_A + M_B + M_B * X_B$$

where M_A is the mass of reagent A, M_B is the applied mass of the previously prepared reagent B and X_B is the reagent contribution to the E-factor from the prior synthesis of B.

The simple E-factor (sEF) contains only the reagents and starting materials used for synthesis, which includes solely the reagents used throughout the synthesis/route. The complete E-factor (cEF) contains all material used for the synthesis, which includes all reagents, inorganics, organic solvents and water. The individual contributions to the cEF (reagents, inorganic, organic solvents and water) were calculated by adding up all material from this category and dividing this quantity by the amount of product generated.

For the calculation of synthesis duration and solvent use in multistep processes, the reaction time was treated additively and the reaction volume was summed over all steps with the contribution of prior steps being normalized to the amount of material used in the prior steps (analogous to the cEF calculation). Unless stated otherwise in the original report, the following time assumptions were made for synthetic procedures:

- Overnight reactions were run for 18 h
- Every operation (reaction setup, addition of material, extraction, filtration, washing, drying over anhydrous salt) took 5 min
- Drying of material under vacuum took 30 min
- Material purified by HPLC was lyophilized, which took overnight (18 h)
- Purification on silica gel (manual or HPLC, normal or reverse phase) took 2 h
- Recrystallization took 2 h

Many of the routes discussed in this manuscript necessitated the preparation of protected sugar synthons that were used directly or indirectly for *N*-glycosylation. For the sake of this analysis, we assumed that these synthons were prepared via the following literature routes (**S1**–**S26**).

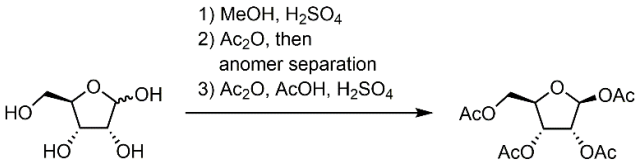
Sugar Synthons

1,2,3,5-Tetra-*O*-acetyl-β-D-ribose

Reaction S1

Andreeva *et al. Tet. Lett*. **2019**, *60*, 151267, doi: 10.1016/j.tetlet.2019.151276

Reaction from their Supplementary Information, compound **9b**



The experimental details for this synthesis were provided in the Supplementary Information (page 7, compound **9b**). D-ribose (33.3 mmol, 5 g) in MeOH (100 mL, 79 g with ρ = 0.79 g·cm^{-3}) was treated with sulfuric acid (0.5 mL, 0.915 g with ρ = 1.83 g·cm^{-3}). Following 6 h of stirring the mixture was neutralized with sodium bicarbonate (8 g), filtered and evaporated to provide the methylated ribofuranosides as a crude product. The crude product was then dissolved in pyridine (10 mL, 9.8 g with ρ = 0.98 g·cm^{-3}) and reacted with acetic anhydride (5 mL, 5.4 g with ρ = 1.08 g·cm^{-3}). After stirring for 24 h the mixture was poured into crushed ice (amount not stated, we assumed the ice equivalent of 15 mL of water, *15 g* with ρ = 1.00 g·cm^{-3}), extracted with CH_2Cl_2 (150 mL, 199.5 g with ρ = 1.33 g·cm^{-3}) and saturated aqueous sodium sulfate (300 mL, 345 g with ρ = 1.15 g·cm^{-3} according to Okorafor *J. Chem. Eng. Data* **1999**, *44*, 488–490, doi: 10.1021/je980243v; with *54.855 g* of salt with a solubility of 159 g·L^{-1} and *290.145 g* of water), dried over magnesium sulfate (*3 g* for 150 mL of extract) and evaporated to yield the triacetylated methyl ribofuranosides as a crude product (5.9 g) which was subjected to chromatography on silica gel (using *118 g* of silica gel and 2.95 L of petroleum ether/ethyl acetate 3:1 for 5.9 g of crude product, which corresponds to 2.213 L of petroleum ether, *1438.45 g* with ρ = 0.65 g·cm^{-3} and 737.5 mL of ethyl acetate, *663.75 g* with ρ = 0.90 g·cm^{-3}). The pure β-anomer (4 g) was reacted with acetic anhydride (14 mL, 15.12 g with ρ = 1.08 g·cm^{-3}) in acetic acid (10.5 mL, 11.025 g with ρ = 1.05 g·cm^{-3}) and sulfuric acid (0.4 mL, 0.732 g with ρ = 1.83 g·cm^{-3}). After stirring for 3 h the reaction was neutralized with sodium bicarbonate (we assumed 191 mmol sodium bicarbonate for the neutralization of 184 mmol acetic acid and 7 mmol sulfuric acid, which corresponds to *20.246 g* calculated with a molecular weight of 106.0 g·mol^{-1}). The reaction mixture was evaporated and redissolved in $CHCl_3$ (50 mL, 74.5 g with ρ = 1.49 g·cm^{-3}), washed with water (150 mL, 150 g with ρ = 1.00 g·cm^{-3}), dried over magnesium sulfate (*1 g* for 50 mL of extract) and evaporated to dryness. Recrystallization from EtOH (40 mL for 4 g of crude product, *31.6 g* with ρ = 0.79 g·cm^{-3}) afforded pure 1,2,3,5-Tetra-*O*-acetyl-β-D-ribose in 43% yield (**3.3 g**).

The reaction took 41.33 h (10 min reaction setup + 6 h methylation + 10 min workup + 30 min drying + 10 min reaction setup + 24 h acetylation + 20 min workup + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 3 h acetylation + 5 min workup + 30 min drying + 15 min workup + 30 min drying + 2 h recrystallization + 30 min drying) and consumed 120.5 mL of reaction solvent (100 mL MeOH + 10 mL pyridine + 10.5 mL acetic acid), corresponding to 36.52 mL per gram of product.

Thus, the preparation of 1,2,3,5-tetra-*O*-acetyl-β-D-ribose had a sEF of 7.2, calculated as

$$\mathrm{sEF} = \frac{5 + 0.915 + 5.4 + 15.12 + 0.732 - \mathbf{3.3}}{\mathbf{3.3}}$$

and a cEF of 967, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}5 + 0.915 + 5.4 + 15.12 + 0.732 + 8 + 54.855 + 3 + 118 + 20.246 + 1 \\ +79 + 9.8 + 199.5 + 1438.5 + 663.75 + 11.025 + 74.5 + 31.6 + 15 + 290.145 + 150 - \mathbf{3.3}\end{array}}{\mathbf{3.3}}$$

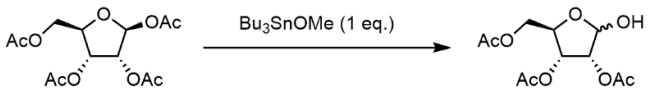
with contributions from reagents (8), inorganics (62), organic solvents (760) and water (138).

2,3,5-Tri-*O*-acetyl-ribose

Reaction S2

Nudelman *et al. Carbohydr. Res.* **1987**, *162*, 145−152, doi: 10.1016/0008-6215(87)80209-4

Reaction from their Table 1, compound **6h**



The experimental details for this synthesis were provided in the main text (page 5, Table 1, compound **6h**) and the Experimental section of the main text (page 7). 1,2,3,5-Tetra-*O*-acetyl-β-D-ribose (1 mmol, 318 mg calculated with a molecular weight of 318.3 g·mol^{-1}) was reacted with tributyltin methoxide (1 mmol, 321 mg calculated with a molecular weight of 321.1 g·mol^{-1}) in dichloroethane (amount not stated, we assumed 5 mL for 0.2 M, *6.25 g* with ρ = 1.49 g·cm^{-3}) for 1.5 h. Removal of the solvent under reduced pressure and chromatography of the crude product on silica gel (*12.780 g* of silica gel and 319.5 mL of solvent for 639 mg of crude product; solvent ratio was not stated, we assumed petroleum ether/ethyl acetate 3:1 as for reaction S1, which corresponds to 239.625 mL of petroleum ether, *155.756 g* with ρ = 0.65 g·cm^{-3} and 59.875 mL of ethyl acetate, *53.888 g* with ρ = 0.90 g·cm^{-3}) provided 2,3,5-tri-*O*-acetyl-ribose in 80% yield (0.8 mmol, **221 mg** calculated with a molecular weight of 276.2 g·mol^{-1}).

The reaction took a total of 4.16 h (10 min reaction setup + 1.5 h deprotection + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 5 mL of reaction solvent (5 mL dichloroethane), corresponding to 34.24 mL per gram of product, considering the contribution of the starting material 1,2,3,5-Tetra-*O*-acetyl-β-D-ribose from Reaction S1, calculated as

$$\frac{5\ \mathrm{mL}}{0.221\ \mathrm{g}} + 0.318 * \frac{36.52\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 1,2,3,5-tetra-*O*-acetyl-ribose of 7.2 (Reaction S1), the preparation of 2,3,5-tri-*O*-acetyl-ribose had a sEF of 12.3, calculated as

$$\mathrm{sEF} = \frac{0.318 + 0.318 * 7.2 + 0.321 - \mathbf{0.221}}{\mathbf{0.221}}$$

and (considering the cEF of the starting material of 967) a cEF of 2428, calculated as

$$\mathrm{cEF} = \frac{0.318 + 0.318 * 967 + 0.321 + 12.78 + 6.25 + 155.756 + 53.888 - \mathbf{0.221}}{\mathbf{0.221}}$$

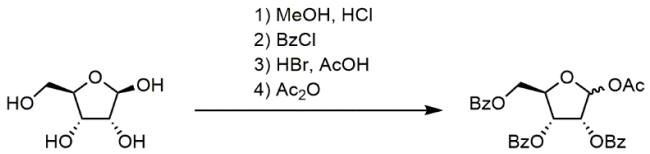
with combined contributions from reagents (14), inorganics (147), organic solvents (2070) and water (199), considering the contributions from the starting material 1,2,3,5-tetra-*O*-acetyl-ribose.

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose

Reaction S3

Kissman *et al. J. Am. Chem. Soc*. **1955**, *77*, 18–24, doi: 10.1021/ja01606a005

Reaction from their first chart, compound **X**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 4, compound **X**). D-ribose (250 mmol, 37.5 g) was reacted in MeOH (825 mL, 651.75 g with ρ = 0.79 g·cm^{-3}) and methanolic hydrochloric acid (11 mL containing 3.3 g of the gas, which corresponds to 3.3 g of HCl and 6.6 mL, 5.95 g of MeOH assuming ρ = 0.90 g·cm^{-3} of methanolic HCl). The reaction was stirred for 90 min, quenched with pyridine (75 mL, 73.5 g with ρ = 0.98 g·cm^{-3}), dried in vacuo, redissolved in pyridine (75 mL, 73.5 g with ρ = 0.98 g·cm^{-3}) and dried in vacuo. The crude product was dissolved in CH_2Cl_2 (200 mL, 266 g with ρ = 1.33 g·cm^{-3}) and pyridine (440 mL, 431.2 g with ρ = 0.98 g·cm^{-3}) and reacted with benzoyl chloride (146 mL, 1.25 mol, 175.75 g calculated with a molecular weight of 140.6 g·mol^{-1}). After 48 h the reaction was quenched with water (1000 mL, 1000 g with ρ = 1.00 g·cm^{-3}) and the aqueous phase extracted with $CHCl_3$ (300 mL, 447 g with ρ = 1.49 g·cm^{-3}), washed with saturated aqueous sodium bicarbonate (200 mL, 220 g with ρ = 1.10 g·cm^{-3}; with *4.4 g* of salt with a solubility of 20 g·L^{-1} and *216 g* of water) and water (100 mL, 100 g with ρ = 1.00 g·cm^{-3}). The organic phase was dried over magnesium sulfate (*6 g* for 300 mL of extract) and dried. Residual pyridine was removed by codistillation with toluene (amount not stated, we assumed 100 mL, *87 g* with ρ = 0.87 g·cm^{-3}). The crude product (166 g) was dissolved in hydrogen bromide in acetic acid (500 mL with 30 w% HBr, 675 g assuming ρ = 1.35 g·cm^{-3}; with *202.5 g* of HBr and *472.5 g* of acetic acid) and reacted for 1 h. The reaction was quenched with water (4 L, 4000 g with ρ = 1.00 g·cm^{-3}) and extracted with $CHCl_3$ (1200 mL, 1788 g with ρ = 1.49 g·cm^{-3}). The extracts were washed with saturated aqueous sodium bicarbonate (1000 mL, 1100 g with ρ = 1.10 g·cm^{-3}; with *22 g* of salt with a solubility of 20 g·L^{-1} and *1078 g* of water), dried over magnesium sulfate (*24 g* for 1200 mL of extract), filtered and reduced to a volume of 300 mL. Pyridine (70 mL, 68.6 g with ρ = 0.98 g·cm^{-3}) and acetic anhydride (70 mL, 75.6 g with ρ = 1.08 g·cm^{-3}) were added, the mixture was stirred for 48 h, reduced to 150 mL, quenched with water (500 mL, 500 g with ρ = 1.00 g·cm^{-3}), extracted with $CHCl_3$ (450 mL, 670.5 g with ρ = 1.49 g·cm^{-3}). Washing with saturated aqueous sodium bicarbonate (150 mL, 165 g with ρ = 1.10 g·cm^{-3}; with *3.3 g* of salt with a solubility of 20 g·L^{-1} and *161.7 g* of water), drying over magnesium sulfate (*9 g* for 450 mL of extract), filtration, evaporation, codistillation with toluene (amount not

stated, we again assumed 100 mL, *87 g* with ρ = 0.87 g·cm^{-3}), trituration with ethanol (300 mL, *237 g* with ρ = 0.79 g·cm^{-3}) overnight, filtration and recrystallization from ethanol/ethyl acetate 5:2 (808 mL for 80.8 g of crude product, corresponding to 577.143 mL of ethanol, *455.943 g* with ρ = 0.79 g·cm^{-3} and 230.857 mL of ethyl acetate, *207.771 g* with ρ = 0.90 g·cm^{-3}) provided 1-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose in 57% yield (**71.8 g**).

The reaction took a total of 142.16 h (10 min reaction setup + 1.5 h methylation + 5 min quenching + 30 min drying + 5 min dissolving + 30 min drying + 15 min reaction setup + 48 h benzoylation + 25 min workup + 30 min drying + 1 h distillation + 10 min reaction setup + 1 h deprotection + 25 min workup + 30 min drying + 10 min reaction setup + 48 h acetylation + 30 min drying + 25 min workup + 30 min drying + 1 h distillation + 18 h trituration + 18 h recrystallization + 30 min drying) and consumed a total of 2335 mL of reaction solvent (825 mL MeOH + 200 mL CH_2Cl_2 + 440 mL pyridine + 500 mL HBr in acetic acid + 300 mL CH_2Cl_2 + 70 mL pyridine), corresponding to 32.52 mL per gram of product.

Thus, the preparation of 1-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose had a sEF of 5.9, calculated as

$$\mathrm{sEF} = \frac{37.5 + 3.3 + 175.75 + 202.5 + 75.6 - \mathbf{71.8}}{\mathbf{71.8}}$$

and a cEF of 174, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}37.5 + 3.3 + 175.75 + 202.5 + 75.6 + 4.4 + 6 + 22 + 24 + 3.3 + 9 \\ +651.75 + 5.95 + 73.5 + 73.5 + 266 + 431.2 + 447 + 87 + 472.5 + 1788 + 68.6 + 670.5 + 87 \\ +237 + 455.943 + 207.771 + 1000 + 216 + 100 + 4000 + 500 + 161.7 - \mathbf{71.8}\end{array}}{\mathbf{71.8}}$$

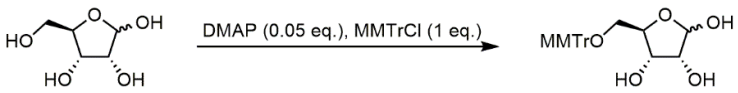
with contributions from reagents (7), inorganics (1), organic solvents (84) and water (83).

5-*O*-Monomethoxytrityl-D-ribose

Reaction S4

Downey *et al. Org. Lett.* **2015**, *17*, 4604−4607, doi: 10.1021/acs.orglett.5b02332

Reaction from their Supporting Information, compound 4



The experimental details for this synthesis were provided in the Supporting Information (compound **4**, page 17). D-ribose (2 g, 13.34 mmol), DMAP (45 mg, 0.37 mmol), NEt_3 (3 mL, 2.19 g ρ = 0.73 g·cm^{-3}), and 4-methoxytrityl chloride (2.05 g, 6.66 mmol) were reacted in DMF (15 mL, 14.25 g with ρ = 0.95 g·cm^{-3}). After 24 h the reaction was quenched in ice water (100 mL, 100 g with ρ = 1.00 g·cm^{-3}), extracted with CH_2Cl_2 (100 mL, 133 g with ρ = 1.33 g·cm^{-3}) and the organic layer was washed with concentrated aqueous NH_4Cl (100 mL, 107 g with ρ = 1.07 g·cm^{-3} according to Stefan-Kharicha *et al. J. Chem. Eng. Data* **2018**, *63*, 3170−3183, doi: 10.1021/acs.jced.7b01062; with *26.75 g* of salt with a solubility of 250 g·L^{-1} and *80.25 g* of water) to give a crude product upon drying over sodium sulfate (*2 g* for 100 mL of extract), filtration and concentration *in vacuo*. Flash chromatography on silica gel (using *125.8 g* of silica gel and 3.145 L of solvent for 6.29 g of crude product, with the solvents being i) petroleum ether/ethyl acetate 1:1 and ii) CH_2Cl_2/MeOH 19:1, which − assuming equal amounts of both solvent combination − corresponds to 786 mL of petroleum ether, *511.063 g* with ρ = 0.65 g·cm^{-3}, 786 mL of ethyl acetate, *707.625 g* with ρ = 0.90 g·cm^{-3}, 1.494 L CH_2Cl_2, *1986.854 g* with ρ = 1.33 g·cm^{-3} and 78.625 mL MeOH, *62.114 g* with ρ = 0.79 g·cm^{-3}) provided the protected ribose in 62% yield (**1.74 g**).

The reaction took a total of 30.25 h (20 min reaction setup + 12 h of reaction time at 0 °C + 12 h reaction time at room temperature + 25 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed 15 mL of reaction solvent (15 mL DMF), corresponding to 8.62 mL of per gram of product.

Thus, the preparation of 5-*O*-monomethoxytrityl-D-ribose had a sEF of 2.6, calculated as

$$\mathrm{sEF} = \frac{2 + 0.045 + 2.19 + 2.05 - \mathbf{1.74}}{\mathbf{1.74}}$$

and a cEF of 2158, calculated as

$$\mathrm{cEF} = \frac{2 + 0.045 + 2.19 + 2.05 + 26.75 + 2 + 125.8 + 14.25 + 133 + 511.063 + 707.625 + 1986.854 + 62 + 100 + 80.25 - \mathbf{1.74}}{\mathbf{1.74}}$$

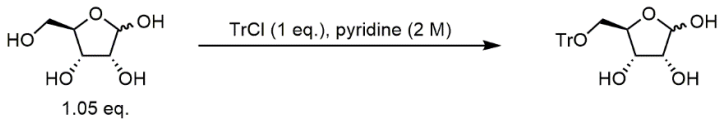
with contributions from reagents (4), inorganics (89), organic solvents (1963) and water (104).

5-*O*-trityl-D-ribose

Reaction S5

Downey *et al. Chem. Eur. J.* **2017**, *23*, 3910 – 3917, doi: 10.1002/chem.201604955

Reaction from their Supporting Information, compound 1



The experimental details for this synthesis were provided in the Supporting Information (compound **1**, page 63). D-ribose (155 g, 1.05 mol) and trityl chloride (278 g, 1 mol) were reacted in pyridine (500 mL, 490 g with ρ = 0.98 g·cm^{-3}). After 6 h the mixture was dried in vacuo and redissolved in CH_2Cl_2 (1.5 L, 1995 g with ρ = 1.33 g·cm^{-3}) and washed with water (600 mL, 600 g with ρ = 1.00 g·cm^{-3}). The aqueous layer was extracted with CH_2Cl_2 (1.2 L, 1596 g with ρ = 1.33 g·cm^{-3}) which provided a crude product upon drying over sodium sulfate (*54 g* for 2.7 L of extract). The crude product was redissolved in CH_2Cl_2 (300 mL, 399 g with ρ = 1.33 g·cm^{-3}) and added dropwise to a mixture of cyclohexane (1 L, 780 g with ρ = 0.78 g·cm^{-3}) and CH_2Cl_2 (100 mL, 133 g with ρ = 1.33 g·cm^{-3}) which effected precipitation of a solid upon rigorous stirring. After 1 h of stirring the solid was filtered off, washed with hexane (500 mL, 330 g with ρ = 0.66 g·cm^{-3}) and water (500 mL, 500 g with ρ = 1.00 g·cm^{-3}) to provide pure 5-*O*-trityl-D-ribose in 52% yield (**203.9 g**).

The reaction took a total of 8.92 h (10 min reaction setup + 6 h reaction time + 30 min drying + 20 min workup + 30 min drying + 10 min workup + 1 h precipitation + 15 min workup) and consumed a total of 0.5 L of reaction solvent (0.5 L pyridine), corresponding to 2.45 mL per gram of product.

Thus, the preparation of 5-*O*-trityl-D-ribose had a sEF of 1.1, calculated as

$$\mathrm{sEF} = \frac{155 + 278 - \mathbf{203.9}}{\mathbf{203.9}}$$

and a cEF of 35, calculated as

$$\mathrm{cEF} = \frac{155 + 278 + 54 + 490 + 1995 + 1596 + 399 + 780 + 133 + 330 + 600 + 500 - \mathbf{203.9}}{\mathbf{203.9}}$$

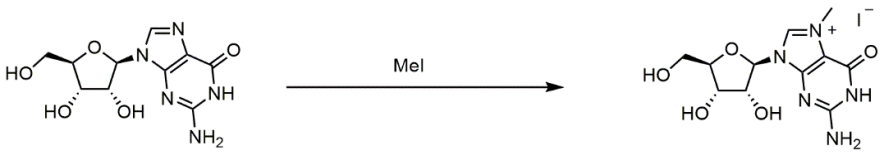
with contributions from reagents (2), inorganics (0), organic solvents (28) and water (104).

7-methylguanosine hydroiodide

Reaction S6

Alexeev *et al. BBA-PROTEINS PROTEOM* **2020**, 140292, doi: 10.1016/j.bbapap.2019.140292

Reaction from their Scheme 2, compound **1**



The experimental details for this synthesis were provided in the Materials and Methods section in the main text (page 2, compound **1**). Guanosine dihydrate (5 g, 15.6 mmol) was reacted with iodomethane (4.4 mL, 10.03 g with ρ = 2.28 g·cm^{-3}, 70.5 mmol) in DMF (100 mL, 95 g with ρ = 0.95 g·cm^{-3}) for 25 h. The mixture was filtered and added to CH_2Cl_2 (1 L, 1330 g with ρ = 1.33 g·cm^{-3}) to precipitate the methylated nucleoside over 16 h. The precipitate was filtered off, washed with diethyl ether (100 mL, 71 g with ρ = 0.71 g·cm^{-3}) and CH_2Cl_2 (100 mL, 133 g with ρ = 1.33 g·cm^{-3}) and dried for 1 h to provide pure 7-methylguanosine hydroiodide in 84% yield (**5.6 g**).

The reaction took a total of 42.33 h (10 min reaction setup + 25 h methylation + 16 h of precipitation + 10 min workup + 1 h drying) and consumed a total of 100 mL of reaction solvent (100 mL DMF), corresponding to 17.86 mL solvent per gram of product.

Thus, the preparation of 7-methylguanosine had a sEF of 1.7, calculated as

$$\mathrm{sEF} = \frac{5 + 10.03 - \mathbf{5.6}}{\mathbf{5.6}}$$

and a cEF of 293, calculated as

$$\mathrm{cEF} = \frac{5 + 10.03 + 95 + 1330 + 71 + 133 - \mathbf{5.6}}{\mathbf{5.6}}$$

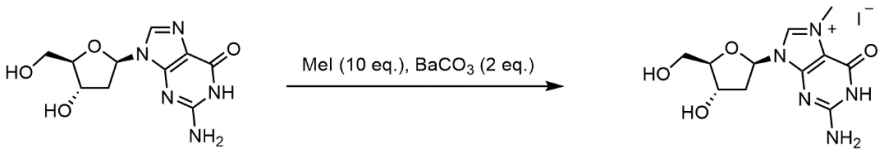
with contributions from reagents (3), inorganics (0), organic solvents (291) and water (0).

2'-deoxy-7-methylguanosine hydroiodide

Reaction S7

Drenichev *et al. Adv. Synth. Catal.* **2018**, *360*, 305–312, doi: 10.1002/adsc.201701005

Reaction from their Scheme 2, compound 1



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 6, compound **1**). 2'-guanosine monohydrate (5 g, 17.5 mmol) was reacted with barium carbonate (6.9 g, 35 mmol) and iodomethane (10.9 mL, 24.85 g with ρ = 2.28 g·cm^{-3}, 175 mmol) in DMF (100 mL, 95 g with ρ = 0.95 g·cm^{-3}). After 6 h the mixture was filtered and the filtrate was washed with DMF (50 mL, 47.5 g with ρ = 0.95 g·cm^{-3}) and the resulting solution diluted with $CHCl_3$ (0.5 L, 745 g with ρ = 1.49 g·cm^{-3}) to precipitate the methylated nucleoside over 16 h. The crude product was filtered off and further purified by washing it with ethanol (100 mL, 79 g with ρ = 0.79 g·cm^{-3}) and $CHCl_3$ (100 mL, 149 g with ρ = 1.49 g·cm^{-3}) to afford pure 7-methyl-2'-deoxyguanosine hydroiodide upon drying for 1 h in 65% yield (**4.6 g**).

The reaction took a total of 23.75 h (15 min reaction setup + 6 h reaction time + 15 min workup + 16 h precipitation + 15 min workup + 1 h drying) and consumed a total of 100 mL of reaction solvent (100 mL DMF), corresponding to 21.74 mL per gram of product.

Thus, the preparation of 7-methyl-2'-deoxyguanosine had a sEF of 7.0, calculated as

$$\mathrm{sEF} = \frac{5 + 6.9 + 24.85 - \mathbf{4.6}}{\mathbf{4.6}}$$

and a cEF of 249, calculated as

$$\mathrm{cEF} = \frac{5 + 6.9 + 24.85 + 95 + 47.5 + 745 + 79 + 149 - \mathbf{4.6}}{\mathbf{4.6}}$$

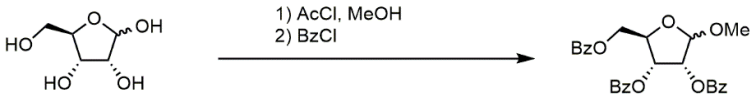
with contributions from reagents (8), inorganics (0), organic solvents (243) and water (0).

2,3,5-Tri-*O*-benzoyl-1-*O*-methyl-D-ribose

Reaction S8

Ramamurty *et al. J. Org. Chem*. **2011**, *76*, 2245–2247, doi: 10.1021/jo1021376

Reaction from their Scheme 1, compound **7a**



The experimental details for this synthesis were provided in the Supplementary Material (page 2 and 3, "steps 1&2" and compound **7a**). Ribose (5 g, 33 mmol) was reacted with acetyl chloride (2.1 mL, 2.31 g with ρ = 1.10 g·cm^{-3}) in methanol (120 mL, 94.8 g with ρ = 0.79 g·cm^{-3}) for 1 h. The reaction was quenched with pyridine (amount not stated, we assumed 3 mL to quench residual acetyl chloride, *2.94 g* with ρ = 0.98 g·cm^{-3}). Drying of the mixture gave a crude product which was subjected to the next step immediately by adding benzoyl chloride (132 mmol, 18.559 g calculated with a molecular weight of 140.6 g·mol^{-1}) and pyridine (amount not stated, we assumed 165 mL for a concentration of 0.2 M of the sugar, *161.7 g* with ρ = 0.98 g·cm^{-3}). Following an overnight reaction, the mixture was quenched by the addition of water (amount not stated, we assumed an equal volume to the reaction mixture of 165 mL, *165 g* with ρ = 1.00 g·cm^{-3}). Extraction with CH_2Cl_2 (amount not stated, we assumed an equal volume to the aqueous phase of 165 mL, *219.45 g* with ρ = 1.33 g·cm^{-3}) and washing with water (amount not stated, we assumed an equal volume to the organic extract of 165 mL, *165 g* with ρ = 1.00 g·cm^{-3}), 3 N sulfuric acid (amount not stated, we assumed an equal volume to the organic extract of 165 mL, *181.5 g* assuming ρ = 1.10 g·cm^{-3}), saturated $NaHCO_3$ (amount not stated, we assumed an equal volume to the organic extract of 165 mL, 181.5 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *39.386 g* of salt with a solubility of 217 g·L^{-1} and *142.112 g* of water) and brine (amount not stated, we assumed half the volume of the organic extract, corresponding to 82.5 mL, 98.175 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *35.343 g* of salt with a solubility of 360 g·L^{-1} and *62.832 g* of water) gave a crude product upon drying which was purified by column chromatography on silica gel (using *517.37 g* of silica gel and 12.935 L of hexanes/ethyl acetate 4:1 for 25.869 g of crude product, which corresponds to 10.348 L of hexanes, *6829.8 g* with ρ = 0.66 g·cm^{-3} and 2.587 L of ethyl acetate, *2328.3 g* with ρ = 0.90 g·cm^{-3}) to afford 2,3,5-Tri-*O*-benzoyl-1-*O*-methyl-D-ribose in 72.5% yield (**11.5 g**).

The reaction took a total of 23.42 h (10 min reaction setup + 1 h methylation + 5 min workup + 30 min drying + 10 min addition of material + 18 h benzoylation + 30 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 285 mL of reaction solvent (120 mL methanol + 165 mL pyridine), corresponding to 24.78 mL per gram of product.

Thus, the preparation of 2,3,5-Tri-*O*-benzoyl-1-*O*-methyl-D-ribose had a sEF of 1.2, calculated as

$$\mathrm{sEF} = \frac{5 + 2.31 + 18.559 - \mathbf{11.5}}{\mathbf{11.5}}$$

and a cEF of 953, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}5 + 2.31 + 18.559 + 39.386 + 35.343 + 517.37 \\ +94.8 + 2.94 + 161.7 + 219.45 + 181.5 + 6829.8 + 2328.3 \\ +165 + 165 + 142.112 + 62.832 - \mathbf{11.5}\end{array}}{\mathbf{11.5}}$$

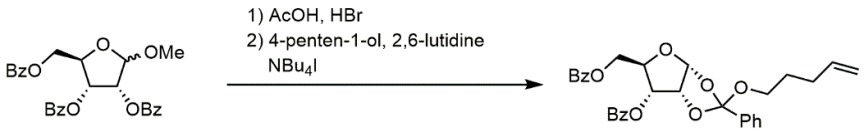
with contributions from reagents (2), inorganics (51), organic solvents (854) and water (46).

3,5-Di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate)

Reaction S9

Ramamurty *et al. J. Org. Chem*. **2011**, *76*, 2245–2247, doi: 10.1021/jo1021376

Reaction from their Scheme 1, compound 11



The experimental details for this synthesis were provided in the Supplementary Material (page 3 and 5, "steps 3&4" and compound **11**). 2,3,5-Tri-*O*-benzoyl-1-*O*-methyl-D-ribose (5 g, 10.5 mmol) was reacted with HBr (18 mL, 45% we assume (w/v), in acetic acid, 24.3 g assuming ρ = 1.35 g·cm^{-3}; with *8.019 g* of HBr and *16.281 g* of acetic acid) in acetic acid (25 mL, 26.25 g with ρ = 1.05 g·cm^{-3}) for 10 min. After completion, the reaction was diluted with CH_2Cl_2 (100 mL, 133 g with ρ = 1.33 g·cm^{-3}), washed with water (500 mL, 500 g with ρ = 1.00 g·cm^{-3}), aqueous $NaHCO_3$ (150 mL, 165 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *35.805 g* of salt with a solubility of 217 g·L^{-1} and *129.195 g* of water) and brine (25 mL, 29.75 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *10.71 g* of salt with a solubility of 360 g·L^{-1} and *19.04 g* of water) to give a crude product (5.1 g) upon drying over sodium sulfate (*2 g* for 100 mL of extract), filtration and evaporation. The crude product was submitted to the next step immediately and reacted with 4-penten-1-ol (2 mL, 19.4 mmol, 1.66 g with ρ = 0.83 g·cm^{-3}), 2,6-lutidine (2.48 mL, 21.3 mmol, 2.29 g with ρ = 0.92 g·cm^{-3}), tetrabutylammonium iodide (358 mg, 0.97 mmol) in CH_2Cl_2 (75 mL, 99.75 g with ρ = 1.33 g·cm^{-3}) overnight. After reaction completion, the mixture was washed with water (300 mL, 300 g with ρ = 1.00 g·cm^{-3}) and brine (25 mL, 14.875 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *5.335 g* of salt with a solubility of 360 g·L^{-1} and *9.52 g* of water) to give a crude product upon drying over sodium sulfate (*1.5 g* for 75 mL of extract), filtration and evaporation. The protected orthoester was obtained by purification on silica gel (using *188.16 g* of silica gel and 4.704 L of hexanes/ethyl acetate 9:1 for 9.408 g of crude product, which corresponds to 4.234 L of hexanes, *2794.44 g* with ρ = 0.66 g·cm^{-3} and 0.47 L of ethyl acetate, *423 g* with ρ = 0.90 g·cm^{-3}) in 71% yield (**3.95 g**).

The reaction took a total of 23.17 h (10 min reaction setup + 10 min for the first step + 30 min workup + 30 min drying + 30 min addition of reagents + 18 h reaction time for the second step + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 100 mL of reaction solvent (25 mL acetic acid + 75 mL CH_2Cl_2), corresponding to 149.22 mL per gram of product, considering the

contribution of the starting material 2,3,5-tri-*O*-benzoyl-1-*O*-methyl-D-ribose from Reaction S8, calculated as

$$\frac{100\ \text{mL}}{3.95\ \text{g}} + 5 * \frac{24.78\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-Tri-*O*-benzoyl-1-*O*-methyl-D-ribose of 1.2 (Reaction S8), the preparation of 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) had a sEF of 4.9, calculated as

$$\text{sEF} = \frac{5 + 5 * 1.2 + 8.019 + 1.66 + 2.29 + 0.358 - \mathbf{3.95}}{\mathbf{3.95}}$$

and (considering the cEF of the starting material of 953) a cEF of 2398, calculated as

$$\text{cEF} = \frac{\begin{array}{c}5 + 5 * 953 + 8.019 + 1.66 + 2.29 + 0.358 + 35.805 + 10.71 + 2 + 5.335 + 1.5 + 188.16 \\ +16.281 + 26.25 + 133 + 99.75 + 2794.44 + 423 \\ +500 + 129.195 + 19.04 + 300 + 9.52 - \mathbf{3.95}\end{array}}{\mathbf{3.95}}$$

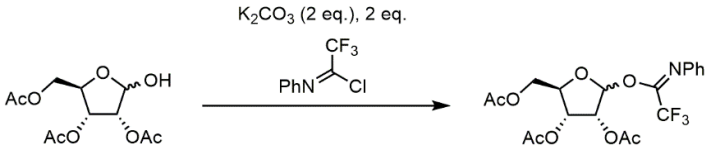
with combined contributions from reagents (7), inorganics (126), organic solvents (1965) and water (301), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-1-*O*-methyl-D-ribose.

2,3,5-Tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate

Reaction S10

Thomas *et al. J. Org. Chem*. **2007**, *72*, 11, 4262−4264, doi: 10.1021/jo0701839

Reaction from their Supplementary Information, compound **9e**



The experimental details for this synthesis was provided in the Supporting Information (page 7, compound **9e**). 2,3,5-Tri-*O*-acetyl-D-ribose (3.16 mmol, 872 mg) was reacted with *N*-phenyl trifluoroacetimidoyl chloride (6.3 mmol, 1.32 g) and K_2CO_3 (6.3 mmol, 872 mg) in CH_2Cl_2 (15 mL, 19.95 g with ρ = 1.33 g·cm^{-3}) overnight. The reaction mixture was then evaporated and subjected to chromatography on silica gel (using *61.28 g* of silica gel and 1.532 L of petroleum ether/ethyl acetate 7:3 for 3.062 g of crude product, which corresponds to 1.072 L of petroleum ether, *697.06 g* with ρ = 0.65 g·cm^{-3} and 0.46 L of ethyl acetate, *414 g* with ρ = 0.90 g·cm^{-3}) to afford 2,3,5-tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate in 87% yield (**1.24 g**).

The reaction took a total of 21.25 h (15 min reaction setup + 18 h reaction time + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 15 mL reaction solvent (15 mL CH_2Cl_2), corresponding to 41.95 mL of solvent per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-acetyl-D-ribose from Reaction S2, calculated as

$$\frac{15\ \text{mL}}{1.24\ \text{g}} + 0.872 * \frac{34.24\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-acetyl-D-ribose of 12.3 (Reaction S2), the preparation of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate had a sEF of 10.1, calculated as

$$\text{sEF} = \frac{0.872 + 0.872 * 12.3 + 1.32 + 0.872 - \mathbf{1.24}}{\mathbf{1.24}}$$

and (considering the cEF of the starting material of 2428) a cEF of 2670, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.872 + 0.872 * 2428 + 1.32 + 0.872 + 61.28 \\ +19.95 + 697.06 + 414\end{array} \mathbf{-1.24}}{\mathbf{1.24}}$$

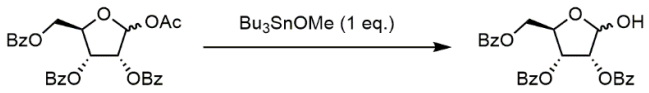
with combined contributions from reagents (12), inorganics (153), organic solvents (2368) and water (140), considering the contribution from the starting material 2,3,5-tri-*O*-acetyl-D-ribose.

2,3,5-Tri-*O*-benzoyl-D-ribose

Reaction S11

Nudelman *et al. Carbohydr. Res.* **1987**, *162*, 145−152, doi: 10.1016/0008-6215(87)80209-4

Reaction from their Table 1, compound **6i**



The experimental details for this synthesis were provided in the main text (page 5, Table 1, compound **6i**) and the Experimental section of the main text (page 7). 1-Acetyl-2,3,5-tri-*O*-benzoyl-D-ribose (1 mmol, 505 mg calculated with a molecular weight of 504.5 g·mol^{-1}) was reacted with tributyltin methoxide (1 mmol, 321 mg calculated with a molecular weight of 321.1 g·mol^{-1}) in dichloroethane (5 mL for 0.2 M, *6.25 g* with ρ = 1.49 g·cm^{-3}) for 2.5 h. Removal of the solvent under reduced pressure and chromatography of the crude product on silica gel (*16.52 g* of silica gel and 413 mL of solvent for 826 mg of crude product; solvent ratio was not stated, we assumed petroleum ether/ethyl acetate 3:1 as for reaction S1, which corresponds to 309.75 mL of petroleum ether, *201.338 g* with ρ = 0.65 g·cm^{-3} and 103.25 mL of ethyl acetate, *92.925 g* with ρ = 0.90 g·cm^{-3}) provided 2,3,5-tri-*O*-benzoyl-D-ribose in 75% yield (0.75 mmol, **347 mg** calculated with a molecular weight of 462.5 g·mol^{-1}).

The reaction took a total of 5.16 h (10 min reaction setup + 2.5 h deprotection + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 5 mL of reaction solvent (5 mL dichloroethane), corresponding to 30.83 mL per gram of product, considering the contribution of the starting material 1-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose from Reaction S3, calculated as

$$\frac{5\ \text{mL}}{0.347\ \text{g}} + 0.505 * \frac{32.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose of 5.9 (Reaction S3), the preparation of 2,3,5-tri-*O*-benzoyl-D-ribose had a sEF of 10.0, calculated as

$$\text{sEF} = \frac{0.505 + 0.505 * 5.9 + 0.321 - \mathbf{0.347}}{\mathbf{0.347}}$$

and (considering the cEF of the starting material of 174) a cEF of 1168, calculated as

$$\text{cEF} = \frac{0.505 + 0.505 * 174 + 16.52 + 6.25 + 201.338 + 92.925 - \mathbf{0.347}}{\mathbf{0.347}}$$

with combined contributions from reagents (13), inorganics (49), organic solvents (988) and water (121), considering the contributions from the starting material 1-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose.

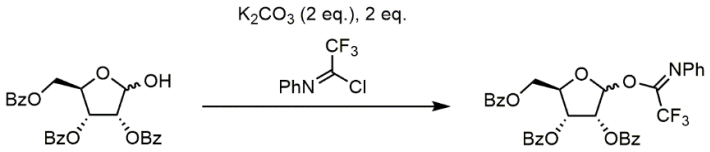
2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate

Reaction S12

We assume that this compound could be prepared analogously to the acetylated compound from Reaction S10 using the method from

Thomas *et al. J. Org. Chem*. **2007**, *72*, 11, 4262–4264, doi: 10.1021/jo0701839

Reaction from their Supplementary Information, compound **9e**



The experimental details for this synthesis was provided in the Supporting Information (page 7, compound **9e**). 2,3,5-Tri-*O*-benzoyl-D-ribose (3.16 mmol, 1.462 g calculated with a molecular weight of 462.5 g·mol^{-1}) was reacted with *N*-phenyl trifluoroacetimidoyl chloride (6.3 mmol, 1.32 g) and K_2CO_3 (6.3 mmol, 872 mg) in CH_2Cl_2 (15 mL, 19.95 g with ρ = 1.33 g·cm^{-3}) overnight. The reaction mixture was then evaporated and subjected to chromatography on silica gel (using *73.08 g* of silica gel and 1.872 L of petroleum ether/ethyl acetate 7:3 for 3.654 g of crude product, which corresponds to 1.279 L of petroleum ether, *831.35 g* with ρ = 0.65 g·cm^{-3} and 0.593 L of ethyl acetate, *533.7 g* with ρ = 0.90 g·cm^{-3}) to afford 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate in what we assume would (analogously to reaction S10) be 87% yield (2.75 mmol, **1.742 g** calculated with a molecular weight of 633.6 g·mol^{-1}).

The reaction took a total of 21.25 h (15 min reaction setup + 18 h reaction time + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 15 mL reaction solvent (15 mL CH_2Cl_2), corresponding to 53.68 mL of solvent per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-benzoyl-D-ribose from Reaction S11, calculated as

$$\frac{15\ \text{mL}}{1.742\ \text{g}} + 1.462 * \frac{30.83\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-benzoyl-D-ribose of 10.0 (Reaction S11), the preparation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate had a sEF of 9.5, calculated as

$$\text{sEF} = \frac{1.462 + 1.462 * 10 + 1.32 + 0.872 - \mathbf{1.742}}{\mathbf{1.742}}$$

and (considering the cEF of the starting material of 1168) a cEF of 1818, calculated as

$$\text{cEF} = \frac{\begin{array}{c}1.462 + 1.462 * 1168 + 1.32 + 0.872 + 73.08 \\ +19.95 + 831.35 + 533.7\end{array} \mathbf{-1.742}}{\mathbf{1.742}}$$

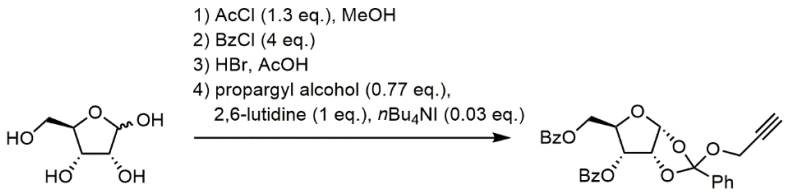
with combined contributions from reagents (13), inorganics (83), organic solvents (1624) and water (102), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-D-ribose.

3,5-Di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate

Reaction S13

Thadke *et al. J. Org. Chem*. **2014**, *79*, 7358−7371, doi: 10.1021/jo501052y

Reaction from their Scheme 1, compound **7a**



The experimental details for this synthesis were provided in the Experimental Section of the main text of the article of Thadke and colleagues (page 4 and 5, compound **7a**). Exact quantities for this synthesis were not provided (which also holds true for the report by Rao, who used this compound and only cited Thadke and colleagues), but it was stated that this compound was prepared by the same procedure detailed for a similar carbohydrate (arabinose). Therefore, we proportionally adjusted all quantities provided for the arabinose method to the scale of this synthesis. D-ribose (52.5 mmol, 7.88 g calculated with a molecular weight of 150.1 g·mol^{-1}) was reacted with acetyl chloride (68.25 mmol, 5.392 g calculated with a molecular weight of 79 g·mol^{-1}) in methanol (55 mL, 43.45 g with ρ = 0.79 g·cm^{-3}) for 7 h. The reaction was quenched in pyridine (16 mL, 15.68 g with ρ = 0.98 g·cm^{-3}), concentrated, redissolved in pyridine (80 mL, 78.4 g with ρ = 0.98 g·cm^{-3}) and treated with benzoyl chloride (24 mL, 29.02 g with ρ = 1.21 g·cm^{-3}) for 12 h. Quenching with water (amount stated as "a few pieces of ice", we assume *15 g*), stirring for 30 min, extraction with CH_2Cl_2 (400 mL, 532 g with ρ = 1.33 g·cm^{-3}) and washing with 3 N sulfuric acid (amount not stated, we assumed an equal volume to the organic extract of 400 mL, 440 g assuming ρ = 1.10 g·cm^{-3}) provided the crude product upon drying over sodium sulfate (*8 g* for 400 mL of extract) and concentration. The material was further treated with HBr in acetic acid (100 mL with 30 w% HBr, 135 g assuming ρ = 1.35 g·cm^{-3}; with *40.5 g* of HBr and *94.5 g* of acetic acid) for 10 min, concentrated and redissolved in CH_2Cl_2 (81 mL, 107.73 g with ρ = 1.33 g·cm^{-3}) to be reacted with propargyl alcohol (40.4 mmol, 2.266 g calculated with a molecular weight of 56.1 g·mol^{-1}), 2,6-lutidine (52.5 mmol, 5.628 g calculated with a molecular weight of 107.2 g·mol^{-1}) and tetra-*n*-butyl ammonium iodide (1.6 mmol, 591 mg calculated with a molecular weight of 369.4 g·mol^{-1}) for 4 h. Dilution with CH_2Cl_2 (100 mL, 133 g with ρ = 1.33 g·cm^{-3}) and water (200 mL, 200 g with ρ = 1.00 g·cm^{-3}), extraction with CH_2Cl_2 (400 mL, 532 g with ρ = 1.33 g·cm^{-3}), washing with saturated aqueous oxalic acid (amount not stated, we assume an equal quantity to the organic extract of 500 mL, 525 g assuming ρ = 1.05 g·cm^{-3}, with *47.25 g* of solids with a solubility of 90 g·L^{-1} and *498.75 g* of water) and saturated aqueous sodium bicarbonate (amount not stated, we assume an equal quantity to the organic extract of 500 mL, 550 g with ρ = 1.10 g·cm^{-3}; with

11 g of salt with a solubility of 20 g·L^{-1} and *539 g* of water), drying over sodium sulfate (*10 g* for 500 mL of extract), concentration and purification on silica gel (using *1000 g* of silica gel and 25 L of petroleum ether/ethyl acetate 4:1 for an assumed weight of 50 g of crude product, which corresponds to 20 L of petroleum ether, *13000 g* with ρ = 0.65 g·cm^{-3} and 5 L of ethyl acetate, *4000 g* with ρ = 0.90 g·cm^{-3}) provided 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate in 55% yield over 4 steps (**18.3 g**).

The reaction took a total of 28 h (15 min reaction setup + 7.5 h methylation + 5 min workup + 30 min drying + 10 min addition of material + 12.5 h benzoylation + 25 min workup + 10 min bromination + 30 min drying + 20 min addition of material + 4 h propargylation + 35 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 316 mL of reaction solvent (55 mL methanol + 80 mL pyridine + 100 mL acetic acid + 81 mL CH_2Cl_2), corresponding to 17.27 mL per gram of product.

Thus, the preparation of 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate had a sEF of 4.0, calculated as

$$\mathrm{sEF} = \frac{7.88 + 5.392 + 29.02 + 40.5 + 2.266 + 5.628 + 0.591 - \mathbf{18.3}}{\mathbf{18.3}}$$

and a cEF of 1168, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}7.88 + 5.392 + 29.02 + 40.5 + 2.266 + 5.628 + 0.591 + 8 + 47.25 + 11 + 10 + 1000 \\ +42.45 + 15.68 + 78.4 + 532 + 440 + 94.5 + 107.73 + 133 + 532 + 13000 + 4000 \\ +15 + 200 + 498.75 + 539 - \mathbf{18.3}\end{array}}{\mathbf{18.3}}$$

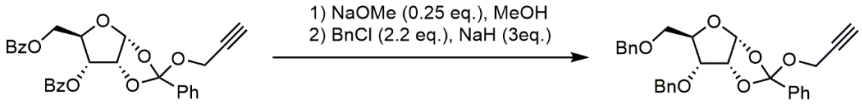
with contributions from reagents (5), inorganics (59), organic solvents (1037) and water (68).

3,5-Di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate

Reaction S14

Thadke *et al. J. Org. Chem*. **2014**, *79*, 7358−7371, doi: 10.1021/jo501052y

Reaction from their Scheme 2, compound **7b**



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 5, compound **7b** and general procedure c)). 3,5-Di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate (5 g, 10 mmol) was reacted with sodium methoxide (150 mg, 2.5 mmol) in CH_2Cl_2:MeOH (ratio not stated, we assumed 1:1, amount not stated, we assumed 50 mL for 0.2 M of the sugar, *53 g* assuming ρ = 1.06 g·cm^{-3} for 1:1 CH_2Cl_2:MeOH) for 2 h. Concentration of the reaction mixture, redissolution in water (amount not stated, we assume 50 mL for 0.2 M, 50 g with ρ = 1.00 g·cm^{-3}) and ethyl acetate (amount not stated, we assume an equal volume to the aqueous phase of 50 mL, 45 g with ρ = 0.90 g·cm^{-3}), extraction with ethyl acetate (100 mL, 90 g with ρ = 0.90 g·cm^{-3}) and stirring in petroleum ether (amount not stated, we assume 50 mL for 0.2 M, 32.5 g with ρ = 0.65 g·cm^{-3}) for 10 min afforded a deprotected crude product (2.8 g) upon concentration. This product was directly used in the subsequent step by reacting it with sodium hydride (30 mmol, 1.25 g) and benzyl bromide (22 mmol, 3.762 g calculated with a molecular weight of 171.0 g·mol^{-1}) in DMF (20 mL, 15.8 g with ρ = 0.79 g·cm^{-3}) for 2 h. Addition of methanol (1 mL, 0.79 g with ρ = 0.79 g·cm^{-3}) with water (100 mL, 100 g with ρ = 1.00 g·cm^{-3}), extraction with ethyl acetate (200 mL, 180 g with ρ = 0.90 g·cm^{-3}) and washing with brine (amount not stated, we assume half the volume of the organic phase which corresponds to 100 mL, 119 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *42.84 g* of salt with a solubility of 360 g·L^{-1} and *76.16 g* of water) afforded a crude product upon drying over sodium sulfate (*4 g* for 200 mL of extract) and concentration. Purification on silica gel (using *150.24 g* of silica gel and 3.756 L of petroleum ether/ethyl acetate 85:15 for an assumed weight of 7.512 g of crude product, which corresponds to 3.198 L of petroleum ether, *2078.5 g* with ρ = 0.65 g·cm^{-3} and 0.564 L of ethyl acetate, *507.6 g* with ρ = 0.90 g·cm^{-3}) provided 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate in 82% yield (**3.87 g**).

The reaction took a total of 9.25 h (10 min reaction setup + 2 h deprotection + 30 min drying + 20 min workup + 10 m stirring in petroleum ether + 30 min drying + 10 min addition of material + 2 h benzylation + 25 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 70 mL of reaction solvent (50 mL CH_2Cl_2:MeOH + 20 mL DMF), corresponding to 104.44 mL of solvent

per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate from Reaction S13, calculated as

$$\frac{70\ \mathrm{mL}}{3.87\ \mathrm{g}} + 5 * \frac{17.27\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate of 4.0 (Reaction S13), the preparation of 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate had a sEF of 6.8, calculated as

$$\mathrm{sEF} = \frac{5 + 5 * 4 + 0.15 + 1.25 + 3.762 - \mathbf{3.87}}{\mathbf{3.87}}$$

and (considering the cEF of the starting material of 1168) a cEF of 2396, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c} 5 + 5 * 1168 + 0.15 + 1.25 + 3.762 + 42.84 + 4 + 150.24 \\ +53 + 45 + 90 + 32.5 + 15.8 + 0.79 + 180 + 2078.5 + 507.6 + 50 + 100 + 76.16 \\ -\mathbf{3.87} \end{array}}{\mathbf{3.87}}$$

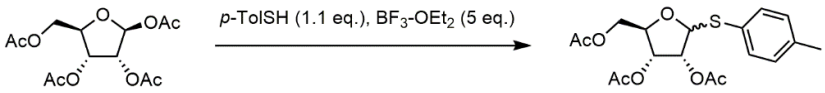
with combined contributions from reagents (9), inorganics (127), organic solvents (2116) and water (146), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate.

p-Tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose

Reaction S15

Kurosu and Li *J. Org. Chem.* **2008**, *73*, 9767–9770, doi: 10.1021/jo801408x

Reaction from their Supplementary Material, compound **1b**



The experimental details for this synthesis were provided in the Supplementary Material (page 2, compound **1b**). 1,2,3,5-Tetra-*O*-acetyl-β-D-ribose (7.86 mmol, 2.5 g) was reacted with *p*-toluene thiol (8.64 mmol, 1.07 g) and boron trifluoride etherate (39.3 mmol, 5.5 g) in CH_2Cl_2 (30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}) for 1 h. Upon completion, the reaction was quenched with aqueous $NaHCO_3$ (amount not stated, we assume an equal concentration to the organic phase of 30 mL, 33 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *7.161 g* of salt with a solubility of 217 g·L^{-1} and *25.839 g* of water) and the aqueous phase was extracted with CH_2Cl_2 (amount not stated, we assume an equal volume to the aqueous phase of 30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}). Washing with brine (amount not stated, we assumed half the volume to the organic phase, which corresponds to 30 mL, 35.7 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *12.852 g* of salt with a solubility of 360 g·L^{-1} and *22.848 g* of water), drying over sodium sulfate (*1.2 g* for 60 mL of extract) and concentration provided a crude product that was subjected to chromatography on silica gel (using *181.4 g* of silica gel and 4.535 L of hexane/ethyl acetate 2:1, as the average of a linear gradient from 3:1 to 1:1, for an assumed weight of 9.07 g of crude product, which corresponds to 2.993 L of hexane, *1975.446 g* with ρ = 0.66 g·cm^{-3} and 1.497 L of ethyl acetate, *1346.895 g* with ρ = 0.90 g·cm^{-3}) to afford p-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose in 80% yield (**2.4 g**).

The reaction took a total of 4.58 h (15 min reaction setup + 1 h thiolation + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 30 mL of reaction solvent (30 mL CH_2Cl_2), corresponding to 103.8 mL per gram of product, considering the contribution of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose from Reaction S1, calculated as

$$\frac{30\ \text{mL}}{2.4\ \text{g}} + 2.5 * \frac{36.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose of 7.2 (Reaction S1), the preparation of p-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose had a sEF of 10.3, calculated as

$$\text{sEF} = \frac{2.5 + 5 * 7.2 + 1.07 + 5.5 - \mathbf{2.4}}{\mathbf{2.4}}$$

and (considering the cEF of the starting material of 967) a cEF of 2532, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}2.5 + 2.5 * 967 + 1.07 + 5.5 + 7.161 + 12.852 + 1.2 + 181.4 \\ +39.9 + 39.9 + 1975.446 + 1346.895 + 25.839 + 22.848\end{array}}{\mathbf{2.4}} - \mathbf{2.4}$$

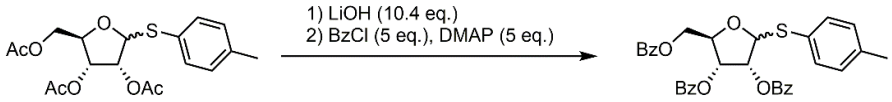
with combined contributions from reagents (12), inorganics (152), organic solvents (2209) and water (164), considering the contribution from the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose.

p-Tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose

Reaction S16

Kurosu and Li *J. Org. Chem.* **2008**, *73*, 9767–9770, doi: 10.1021/jo801408x

Reaction from their Supplementary Material, compound **1a**



The experimental details for this synthesis were provided in the Supplementary Material (page 2, compound **1a**). *p*-Tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose (2.88 mmol, 1.1 g) was reacted with lithium hydroxide (23 mmol, 522 mg) in MeOH/water (10:1, 20 mL, corresponding to 18.18 mL MeOH, 14.36 g with ρ = 0.79 g·cm^{-3} and 1.82 mL of water, 1.82 g with ρ = 1.00 g·cm^{-3}) for 12 h. Afterward that the mixture was neutralized with 1M HCl (amount not stated, we assumed 23 mmol HCl, 23 mL, 23.46 g with ρ = 1.02 g·cm^{-3}) and extracted with $CHCl_3$ (amount not stated, we assumed an equal volume of 43 mL, *64.07 g* with ρ = 1.49 g·cm^{-3}). The extract was washed with brine (amount not stated, we assumed half the extract volume, corresponding to 21.5 mL, 25.585 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *9.21 g* of salt with a solubility of 360 g·L^{-1} and *16.374 g* of water), dried over sodium sulfate (*0.86 g* for 43 mL of extract) and concentrated *in vacuo* to provide a crude product. The crude product was then reacted with benzoyl chloride (14.4 mmol, 2.025 g calculated with a molecular weight of 140.6 g·mol^{-1}), 4-dimethylaminopyridine (14.4 mmol, 1.760 g calculated with a molecular weight of 122.2 g·mol^{-1}) in CH_2Cl_2 (30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}) for an unreported time (reaction time not stated, we assumed 6 h). The mixture was quenched with aqueous saturated $NaHCO_3$ (amount not stated, we assumed an equal volume to the organic phase of 30 mL, 33 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *7.161 g* of salt with a solubility of 217 g·L^{-1} and *25.839 g* of water), extracted with CH_2Cl_2 (amount not stated, we assumed an equal volume to the original solution of 60 mL, *79.8 g* with ρ = 1.33 g·cm^{-3}). The organic phase was washed with brine (amount not stated, we assumed half the extract volume, corresponding to 30 mL, 35.7 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *12.852 g* of salt with a solubility of 360 g·L^{-1} and *22.848 g* of water), dried over anhydrous sodium sulfate (*1.2 g* for 60 mL of extract), concentrated *in vacuo* and subjected to purification on silica gel (using *108.14 g* of silica gel and 2.704 L of hexane/ethyl acetate 3:1 for an assumed weight of 5.407 g of crude product, which corresponds to 1.556 L of hexane, *1026.96 g* with ρ = 0.66 g·cm^{-3} and 1.148 L of ethyl acetate, *1033.2 g* with ρ = 0.90 g·cm^{-3}) to afford p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose in quantitative yield (2.88 mmol, **1.63 g**).

The reaction took a total of 22.58 h (15 min reaction setup + 12 h deprotection + 15 min workup + 30 min drying + 15 min reaction setup + 6 h benzoylation + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 50 mL reaction solvent (20 mL MeOH/water + 30 mL CH_2Cl_2), corresponding to 144.9 mL per gram of product, considering the contribution of the starting material *p*-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose from Reaction S15, calculated as

$$\frac{50\ \text{mL}}{1.63\ \text{g}} + 1.1 * \frac{103.8\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material *p*-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose of 10.3 (Reaction S15), the preparation of *p*-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose had a sEF of 9.4, calculated as

$$\text{sEF} = \frac{1.1 + 1.1 * 10.3 + 0.522 + 2.205 + 1.76 - \mathbf{1.63}}{\mathbf{1.63}}$$

and (considering the cEF of the starting material of 2532) a cEF of 3238, calculated as

$$\text{cEF} = \frac{\begin{array}{c}1.1 + 1.1 * 2532 + 0.522 + 2.205 + 1.76 + 9.21 + 0.86 + 7.161 + 12.852 + 1.2 + 108.14 \\ +14.36 + 64.07 + 39.9 + 79.8 + 1026.96 + 1033.2 + 1.82 + 23.46 + 16.374 + 25.839 + 22.848 \\ -\mathbf{1.63}\end{array}}{\mathbf{1.63}}$$

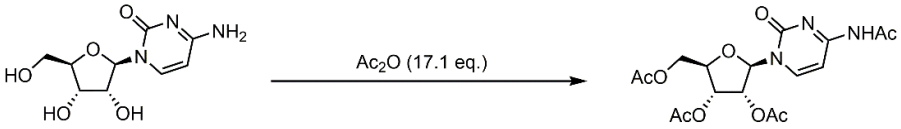
with combined contributions from reagents (12), inorganics (188), organic solvents (2876) and water (166), considering the contribution from the starting material *p*-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose.

4*N*-2',3',5'-Tri-*O*-tetraacetylcytidine

Reaction S17

Nowak et al. *J. Org. Chem.* **2005**, *70*, 7455–7458, doi: 10.1021/jo051256w

Reaction from their Supplementary Material, compound **11a**



The experimental details for this synthesis were provided in the Supplementary Material (page 9, compound **11a**). Cytidine (0.62 mmol, 150 mg) was reacted with acetic anhydride (10.6 mmol, 1.08 g) in pyridine (3 mL, 2.94 g with ρ = 0.98 g·cm^{-3}) for 1 h. After the reaction, the mixture was dried *in vacuo* to yield the acetylated nucleoside in quantitative yield (**250 mg**).

The reaction took a total of 1.67 h (10 min reaction setup + 1 h acetylation + 30 min drying) and consumed a total of 3 mL of reaction solvent (3 mL pyridine), corresponding to 12 mL per gram of product.

Thus, the preparation of 4-*N*-2',3',5'-tri-*O*-tetraacetylcytidine had a sEF of 3.9, calculated as

$$\mathrm{sEF} = \frac{0.15 + 1.08 - \mathbf{0.25}}{\mathbf{0.25}}$$

and a cEF of 16, calculated as

$$\mathrm{cEF} = \frac{0.15 + 1.08 + 2.94 - \mathbf{0.25}}{\mathbf{0.25}}$$

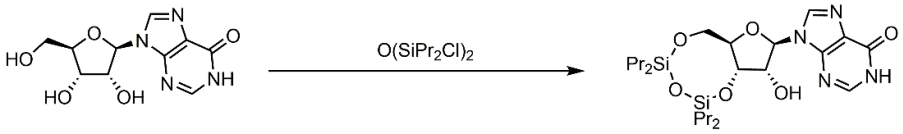
with contributions from reagents (5), inorganics (0), organic solvents (12) and water (0).

3’-5’-*O*-(Tetraisopropyldisiloxan-1,3-diyl)-inosine

Reaction S18

Kawase *et al. Chem. Pharm. Bull.* **1989**, *37*, 2313–2317, doi: 10.1248/cpb.37.2313

Reaction from their Materials and Methods section, compound **1**



The experimental details for this synthesis were provided in the Materials and Methods section (page 1, compound **1**). Inosine (30 mmol, 8.05 g) was reacted neat with 1,3-dichloro-1,1,3,3-tetraiso-propyldisiloxane (36 mmol, 11.4 mL, 11.286 g with ρ = 0.99 g·cm^{-3}) for 3 h. The reaction was quenched with water (20 mL, 20 g with ρ = 1.00 g·cm^{-3}) and extracted with $CHCl_3$ (amount not stated, we assumed an equal volume to the aqueous phase of 20 mL, 29.8 g with ρ = 1.49 g·cm^{-3}). The organic phase was washed with water (amount not stated, we assumed an equal volume to the organic phase of 20 mL, 20 g with ρ = 1.00 g·cm^{-3}), dried over sodium sulfate (400 mg for 20 mL) and concentrated *in vacuo*. Column chromatography on silica gel (using 270 g of silica gel and 9668 mL of $CHCl_3$/methanol 96:4 for an assumed weight of 19.336 g of crude product, which corresponds to 9281.28 mL of $CHCl_3$, *13829.1 g* with ρ = 1.49 g·cm^{-3} and 386.72 mL of methanol, *305.809 g* with ρ = 0.79 g·cm^{-3}) provided the protected nucleoside in 81% yield (**12.5 g**).

The reaction took a total of 6.5 h (10 min reaction setup + 3 h protection + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed no reaction solvent, corresponding to 0 mL per gram of product.

Thus, the preparation of 3’-5’-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine had a sEF of 0.5, calculated as

$$\mathrm{sEF} = \frac{8.05 + 11.286 - \mathbf{12.5}}{\mathbf{12.5}}$$

and a cEF of 1159, calculated as

$$\mathrm{cEF} = \frac{8.05 + 11.286 + 0.4 + 270 + 29.8 + 13829.1 + 305.809 + 20 + 20 - \mathbf{12.5}}{\mathbf{12.5}}$$

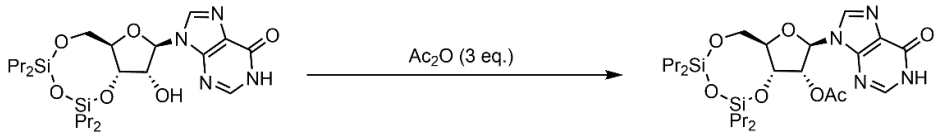
with contributions from reagents (2), inorganics (22), organic solvents (1133) and water (3).

2'-*O*-Acetyl-3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine

Reaction S19

Boryski *Nucleo. & Nucleo.* **1998**, *17*, 1547–1556, doi: 10.1080/07328319808004685

Reaction from his Scheme 2, compound **7**



The experimental details for this synthesis were provided in the Materials and Methods section (page 8, compound **7**). 3'-5'-*O*-(Tetraisopropyldisiloxan-1,3-diyl)-inosine (6.265 mmol, 3.2 g) was reacted with acetic anhydride (18.8 mmol, 1.92 g) in pyridine (50 mL, 49 g with ρ = 0.98 g·cm^{-3}) for 8 h. The reaction was quenched with methanol (20 mL, 15.8 g with ρ = 0.79 g·cm^{-3}) for 20 min. The solvents were evaporated *in vacuo* and residual solvent was coevaporated with toluene/$CHCl_3$ (2:1, 100 mL, corresponding to 66.67 mL of toluene, 58.67 g with ρ = 0.88 g·cm^{-3} and 33.33 g of $CHCl_3$, 49.662 g with ρ = 1.49 g·cm^{-3}) and methanol (60 mL, 47.4 g with ρ = 0.79 g·cm^{-3}) to provide the protected nucleoside in quantitative yield (3.47 g).

The reaction took a total of 10.17 h (10 min reaction setup + 8 h acetylation + 20 min workup + 30 min drying + 5 min workup + 30 min drying + 5 min workup + 30 min drying) and consumed a total of 50 mL reaction solvent (50 mL pyridine), corresponding to 14.4 mL per gram of product, considering the contribution of the starting material 3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine from Reaction S18, calculated as

$$\frac{50\ \text{mL}}{3.47\ \text{g}} + 3.2 * \frac{0\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine of 0.5 (Reaction S18), the preparation of 2'-*O*-acetyl-3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine had a sEF of 0.9, calculated as

$$\text{sEF} = \frac{3.2 + 3.2 * 0.5 + 1.92 - \mathbf{3.47}}{\mathbf{3.47}}$$

and (considering the cEF of the starting material of 1159) a cEF of 1133, calculated as

$$\text{cEF} = \frac{\begin{matrix}3.2 + 3.2 * 1159 + 1.92 \\ +49 + 15.8 + 58.67 + 49.662 + 47.4\end{matrix} \\ \mathbf{-3.47}}{\mathbf{3.47}}$$

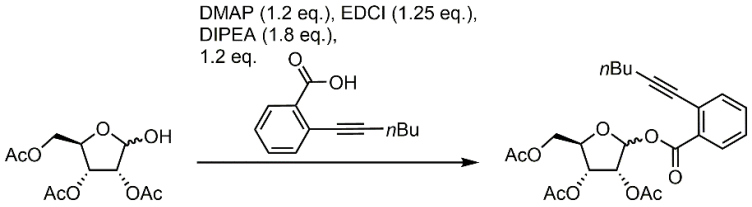
with combined contributions from reagents (3), inorganics (20), organic solvents (1108) and water (3), considering the contribution from the starting material 3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine.

2,3,5-Tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate

Reaction S20

Zhang *et al. Angew. Chem. Int. Ed*. **2011**, *50*, 4933–4936, doi: 10.1002/anie.201100514

Reaction from their Supplementary Material, compound **1b**



The experimental details for this synthesis were provided in the Supplementary Material (page 3, compound **1b**). 2,3,5-Tri-*O*-acetyl-β-D-ribofuranose (16 mmol, 4.42 g) was reacted with *ortho*-hexynylbenzoic acid (19.2 mmol, 3.24 g), 4-(dimethylamino)-pyridine (19.2 mmol, 2.34 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (20 mmol, 3.83 g) and *N*,*N*-diisopropylethylamine (28.8 mmol, 5.03 g) in CH_2Cl_2 (20 mL, 26.6 g with ρ = 1.33 g·cm^{-3}) for 3 h. The mixture was then diluted with CH_2Cl_2 (amount not stated, we assumed twice the volume of the original solution, corresponding to 40 mL, 53.2 g with ρ = 1.33 g·cm^{-3}), washed with saturated aqueous $NaHCO_3$ (amount not stated, we assumed an equal volume to the organic phase of 60 mL, 66 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *14.322 g* of salt with a solubility of 217 g·L^{-1} and *51.678 g* of water), brine (amount not stated, we assumed half the volume of the organic phase, corresponding to 30 mL, 35.7 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *12.852 g* of salt with a solubility of 360 g·L^{-1} and *22.848 g* of water), dried over anhydrous sodium sulfate (*1.2 g* for 60 mL of extract) and concentrated *in vacuo*. Column chromatography on silica gel (using *377.2 g* of silica gel and 9.43 L of petroleum ether/ethyl acetate 2:1 for an assumed weight of 18.86 g of crude product, which corresponds to 6.286 L of petroleum ether, *4086.292 g* with ρ = 0.65 g·cm^{-3} and 3.143 L of ethyl acetate, *2828.972 g* with ρ = 0.90 g·cm^{-3}) to provide 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate in 93% yield (**6.8 g**).

The reaction took a total of 6.75 h (25 min reaction setup + 3 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 20 mL of reaction solvent (20 mL CH_2Cl_2), corresponding to 154.3 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-acetyl-ribose from Reaction S2, calculated as

$$\frac{20\ \text{mL}}{6.8\ \text{g}} + 4.42 * \frac{34.24\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-acetyl-ribose of 12.3 (Reaction S2), the preparation of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate had a sEF of 9.8, calculated as

$$\mathrm{sEF} = \frac{4.42 + 4.42 * 12.3 + 3.24 + 2.34 + 3.83 + 5.03 - \mathbf{6.8}}{\mathbf{6.8}}$$

and (considering the cEF of the starting material of 2428) a cEF of 2679, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}4.42 + 4.42 * 2428 + 3.24 + 2.34 + 3.83 + 5.03 + 14.322 + 12.852 + 1.2 + 377.2 \\ +26.6 + 53.2 + 4086.292 + 2828.972 + 51.678 + 22.848 \\ \mathbf{-6.8}\end{array}}{\mathbf{6.8}}$$

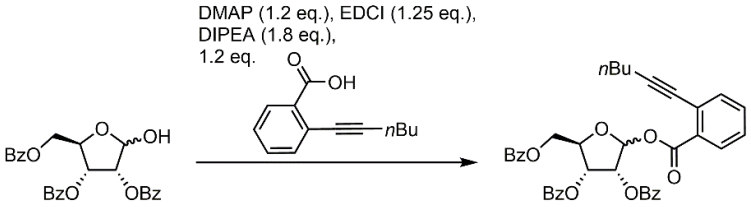
with combined contributions from reagents (12), inorganics (155), organic solvents (2374) and water (140), considering the contribution from the starting material 2,3,5-tri-*O*-acetyl-ribose.

2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate

Reaction S21

Zhang *et al. Angew. Chem. Int. Ed*. **2011**, *50*, 4933–4936, doi: 10.1002/anie.201100514

Reaction from their Supplementary Material, compound **1a**



The experimental details for this synthesis were provided in the Supplementary Material (page 3, general procedure). The exact details for this compound were not provided, so we assumed that it was prepared in the same way as the acetylated analog following the general procedure described in the article. 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranose (16 mmol, 7.4 g calculated with a molecular weight of 462.5 g·mol^{-1}) was reacted with *ortho*-hexynylbenzoic acid (19.2 mmol, 3.24 g), 4-(dimethylamino)-pyridine (19.2 mmol, 2.34 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (20 mmol, 3.83 g) and *N*,*N*-diisopropylethylamine (28.8 mmol, 5.03 g) in CH_2Cl_2 (20 mL, 26.6 g with ρ = 1.33 g·cm^{-3}) for 3 h. The mixture was then diluted with CH_2Cl_2 (amount not stated, we assumed twice the volume of the original solution, corresponding to 40 mL, 53.2 g with ρ = 1.33 g·cm^{-3}), washed with saturated aqueous $NaHCO_3$ (amount not stated, we assumed an equal volume to the organic phase of 60 mL, 66 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *14.322 g* of salt with a solubility of 217 g·L^{-1} and *51.678 g* of water), brine (amount not stated, we assumed half the volume of the organic phase, corresponding to 30 mL, 35.7 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *12.852 g* of salt with a solubility of 360 g·L^{-1} and *22.848 g* of water), dried over anhydrous sodium sulfate (*1.2 g* for 60 mL of extract) and concentrated *in vacuo*. Column chromatography on silica gel (using *436.8 g* of silica gel and 10.92 L of petroleum ether/ethyl acetate 2:1 for an assumed weight of 21.84 g of crude product, which corresponds to 7.279 L of petroleum ether, *4731.953 g* with ρ = 0.65 g·cm^{-3} and 3.64 L of ethyl acetate, *3276.066 g* with ρ = 0.90 g·cm^{-3}) to provide 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate in 93% yield (14.88 mmol, **9.623 g**, calculated with a molecular weight of 646.7 g·mol^{-1}).

The reaction took a total of 6.75 h (25 min reaction setup + 3 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 20 mL of reaction solvent (20 mL CH_2Cl_2), corresponding to 230.2 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-benzoyl-ribose from Reaction S11, calculated as

$$\frac{20\ \text{mL}}{9.623\ \text{g}} + 7.4 * \frac{30.83\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-benzoyl-ribose of 10.0 (Reaction S11), the preparation of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate had a sEF of 9.0, calculated as

$$\text{sEF} = \frac{7.4 + 7.4 * 10 + 3.24 + 2.34 + 3.83 + 5.03 - \mathbf{9.623}}{\mathbf{9.623}}$$

and (considering the cEF of the starting material of 1168) a cEF of 1790, calculated as

$$\text{cEF} = \frac{\begin{array}{c}7.4 + 7.4 * 1168 + 3.24 + 2.34 + 3.83 + 5.03 + 14.322 + 12.852 + 1.2 + 436.8 \\ +26.6 + 53.2 + 4731.953 + 3276.066 + 51.678 + 22.848 \\ -\mathbf{9.623}\end{array}}{\mathbf{9.623}}$$

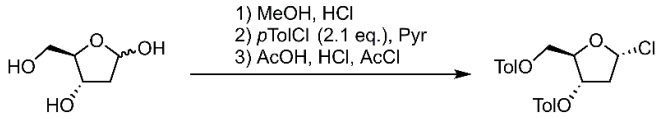
with combined contributions from reagents (13), inorganics (80), organic solvents (1600) and water (101), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-ribose.

1-Chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose

Reaction S22

Rolland *et al. Synth. Comm*. **1997**, *27*, 3505–3511, doi: 10.1080/00397919708007071

Reaction from their main text, compound **4a**



The experimental details for this synthesis were provided in the Experimental section (page 5, compound **4a**). 2-Deoxyribose (74.5 mmol, 10 g) was reacted in MeOH (120 mL, 94.8 g with ρ = 0.79 g·cm^{-3}) and methanolic HCl (20 mL, prepared by adding 0.34 mL acetyl chloride to 20 mL MeOH, corresponding to 15.8 g MeOH with ρ = 0.79 g·cm^{-3} and 0.374 g acetyl chloride with ρ = 1.10 g·cm^{-3}) for 25 min. The solution was then neutralized with sodium bicarbonate (4 g), filtered and dried *in vacuo* by coevaporation with pyridine (100 mL, 98 g with ρ = 0.98 g·cm^{-3}). The residue was dissolved in pyridine (60 mL, 58.8 g with ρ = 0.98 g·cm^{-3}) and reacted with *p*-toluoyl chloride (160 mmol, 24.736 g, calculated with a molecular weight of 154.6 g·mol^{-1}) for 18 h. The mixture was then diluted with water (150 mL, 150 g with ρ = 1.00 g·cm^{-3}) and extracted three times with CH_2Cl_2 (amount not stated, we assumed an equal volume to the initial volume of 210 mL per extraction, corresponding to 630 mL, 836.9 g with ρ = 1.33 g·cm^{-3}). The combined organic layer was washed twice with $NaHCO_3$ (amount not stated, we assume an equal volume to organic phase of 630 mL per washing, corresponding to 1260 mL, 1386 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128–132, doi: 10.1021/je970197j; with *300.762 g* of salt with a solubility of 217 g·L^{-1} and *1085.238 g* of water), 2 M aqueous HCl (amount not stated, we assumed an equal amount to the organic phase of 630 mL, *655.2 g* with ρ = 1.04 g·cm^{-3}) and water (amount not stated, we assumed an equal volume to the organic phase of 630 mL, 630 g with ρ = 1.00 g·cm^{-3}), dried over anhydrous $NaHCO_3$ (*12.6 g* for 630 mL of extract) and evaporated *in vacuo*. The residue was dissolved in acetic acid (40 mL, 42 g with ρ = 1.05 g·cm^{-3}) and saturated HCl in acetic acid (63 mL, prepared by adding 10.137 mL acetyl chloride to 50.375 mL acetic acid and 2.488 mL water, corresponding to 11.151 g acetyl chloride with ρ = 1.10 g·cm^{-3}, 52.894 g acetic acid with ρ = 1.05 g·cm^{-3} and 2.488 g water with ρ = 1.00 g·cm^{-3}) and reacted with acetyl chloride (5 mL, 5.5 g with ρ = 1.10 g·cm^{-3}) which caused immediate precipitation of the product which was obtained by filtration, washing with cold ether (we assumed methyl-*tert*-butylether; amount not stated, we assumed 20 mL, *14.8 g* with ρ = 0.74 g·cm^{-3}) and drying in a vacuum dessicator in 58% yield (**16.8 g**).

The reaction took a total of 21.58 h (10 min reaction setup + 25 min methoxylation + 10 min workup + 30 min drying + 10 min reaction setup + 18 h protection + 45 min workup + 30 min drying + 15 min reaction setup + 10 min workup + 30 min drying) and consumed a total of 303 mL of reaction solvent (140 mL MeOH + 60 mL pyridine + 103 mL acetic acid), corresponding to 18.0 mL per gram of product.

Thus, the preparation of 1-Chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose had a sEF of 1.8, calculated as

$$\mathrm{sEF} = \frac{10 + 0.374 + 24.736 + 11.151 - \mathbf{16.8}}{\mathbf{16.8}}$$

and a cEF of 234, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}10 + 0.374 + 24.736 + 11.151 + 4 + 300.762 + 12.6 + \\ +94.8 + 15.8 + 98 + 836.9 + 42 + 52.894 + 5.5 + 14.8 + 150 + 1085.238 + 655.2 + 630 + 2.488 - \mathbf{16.8}\end{array}}{\mathbf{16.8}}$$

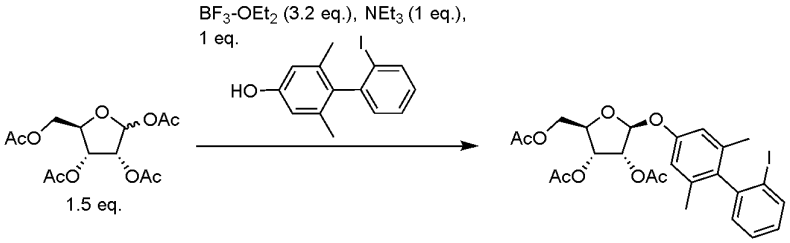
with contributions from reagents (3), inorganics (19), organic solvents (63) and water (150).

3,5-Dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-*O*-acetyl-β-D-ribofuranoside

Reaction S23

Hu *et al. J. Am. Chem. Soc.* **2019**, *141*, 4806–4810, doi: 10.1021/jacs.9b00210

Reaction from their Supplementary Information, compound **8d**



The experimental details for this synthesis were provided in the Supplementary Information (page 12, compound **8d**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a similar procedure from the same manuscript. Therefore, we assumed that the exact same procedure was used and adjusted all quantities to the scale of this synthesis. 1,2,3,5-Tetra-*O*-acetyl-β-D-ribose (1.29 mmol, 410 mg) was reacted with 2,6-dimethyl-2'-iodobiphenol (0.86 mmol, 278 mg), triethylamine (0.821 mmol, 0.114 mL, 83 mg with ρ = 0.73 g·cm^{-3}) and boron trifluoride etherate (2.71 mmol, 385 mg calculated with a molecular weight of 142.0 g·mol^{-1}) in CH_2Cl_2 (6.88 mL, 9.15 g with ρ = 1.33 g·cm^{-3}) for 20 h. The reaction was quenched with triethylamine (amount not stated, we assumed 1 mL, 730 mg with ρ = 0.73 g·cm^{-3}) and the solvent was removed *in vacuo*. Column chromatography on silica gel (using *21.46 g* of silica gel and 536.5 mL of petroleum ether/ethyl acetate 10:1 for an assumed weight of 1.073 g of crude product, which corresponds to 487.727 mL of petroleum ether, *317.023 g* with ρ = 0.65 g·cm^{-3} and 48.773 mL of ethyl acetate, *38.53 g* with ρ = 0.79 g·cm^{-3}) provided the glycoside in 84% yield (**420 mg**).

The reaction took a total of 23.42 h (20 min reaction setup + 20 h reaction time + 5 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 6.88 mL of reaction solvent (6.88 mL CH_2Cl_2), corresponding to 31.2 mL per gram of product, considering the contribution of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose from Reaction S1, calculated as

$$\frac{6.88\ \text{mL}}{0.42\ \text{g}} + 0.41 * \frac{36.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose of 7.2 (Reaction S1), the preparation of 3,5-dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-acetyl-β-D-ribofuranosidehad a sEF of 8.6, calculated as

$$\text{sEF} = \frac{0.41 + 0.41 * 7.2 + 0.278 + 0.385 - \mathbf{0.42}}{\mathbf{0.42}}$$

and (considering the cEF of the starting material of 967) a cEF of 1867, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}0.41 + 0.41 * 967 + 0.278 + 0.385 + 21.46 \\ +0.083 + 9.15 + 0.73 + 317.023 + 38.53\end{array}}{\mathbf{0.42}} \mathbf{- 0.42}$$

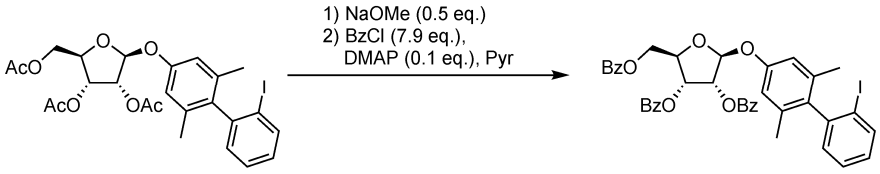
with combined contributions from reagents (10), inorganics (112), organic solvents (1612) and water (135), considering the contribution from the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose.

3,5-Dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside

Reaction S24

Hu *et al. J. Am. Chem. Soc.* **2019**, *141*, 4806–4810, doi: 10.1021/jacs.9b00210

Reaction from their Supplementary Information, compound **S16**



The experimental details for this synthesis were provided in the Supplementary Information (page 16, compound **S16**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a similar procedure from the same manuscript. Therefore, we assumed that the exact same procedure was used and adjusted all quantities to the scale of this synthesis. 3,5-Dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-acetyl-β-D-ribofuranoside (0.72 mmol, 420 mg) was reacted with sodium methoxide (0.36 mmol, 19 mg) in MeOH (12 mL, 9.48 g with ρ = 0.79 g·cm^{-3}) and CH_2Cl_2 (2.4 mL, 3.192 g with ρ = 1.33 g·cm^{-3}) for 2 h. The mixture was neutralized with H^+ resin and filtered. The filtrate was concentrated *in vacuo* to afford a solid, which was co-evaporated with toluene (amount not stated, we assumed 20 mL, *17.4 g* with ρ = 0.87 g·cm^{-3}). The crude product was then reacted with dimethylaminopyridine (0.072 mmol, 9 mg) and benzoyl chloride (1.1 mL, 5.7 mmol, 801 mg calculated with a molecular weight of 140.6 g·mol^{-1}) in pyridine (6 mL, 5.88 g with ρ = 0.98 g·cm^{-3}) for 5 h. The reaction was quenched with MeOH (1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}), concentrated *in vacuo*, diluted with ethyl acetate (amount not stated, we assumed 5 mL, 4.5 g with ρ = 0.90 g·cm^{-3}), washed with 1 M HCl (amount not stated, we assumed 5 mL, *5.1 g* with ρ = 1.02 g·cm^{-3}) and saturated aqueous $NaHCO_3$ (amount not stated, we assumed 5 mL, 5.5 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *1.194 g* of salt with a solubility of 217 g·L^{-1} and *4.307 g* of water), dried over sodium sulfate (*100 mg* for 5 mL) and concentrated *in vacuo*. Column chromatography on silica gel (using *24.98 g* of silica gel and 624.5 mL of petroleum ether/ethyl acetate 10:1 for an assumed weight of 1.249 g of crude product, which corresponds to 567.727 mL of petroleum ether, *369.023 g* with ρ = 0.65 g·cm^{-3} and 56.772 mL of ethyl acetate, *51.095 g* with ρ = 0.79 g·cm^{-3}) provided the glycoside in 92% yield (**510 mg**).

The reaction took a total of 12.58 h (15 min reaction setup + 2 h reaction time + 10 min workup + 30 min drying + 30 min drying + 15 min reaction setup + 5 h reaction time + 5 min quenching + 30 min drying + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of

20.4 mL of reaction solvent (12 mL MeOH + 2.4 mL CH_2Cl_2 + 6 mL pyridine), corresponding to 52.1 mL per gram of product, considering the contribution of the starting material 3,5-dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-acetyl-β-D-ribofuranoside from Reaction S23, calculated as

$$\frac{20.4\ \text{mL}}{0.51\ \text{g}} + 0.42 * \frac{31.16\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-acetyl-β-D-ribofuranoside of 8.6 (Reaction S23), the preparation of 3,5-dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside had a sEF of 8.3, calculated as

$$\text{sEF} = \frac{0.42 + 0.42 * 8.6 + 0.019 + 0.009 + 0.801 - \mathbf{0.51}}{\mathbf{0.51}}$$

and (considering the cEF of the starting material of 1867) a cEF of 2439, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.42 + 0.42 * 1867 + 0.019 + 0.009 + 0.801 + 1.194 + 0.1 + 24.98 \\ +17.4 + 5.88 + 4.5 + 369.023 + 51.095 + 5.1 + 4.307\end{array} \mathbf{-0.42}}{\mathbf{0.42}}$$

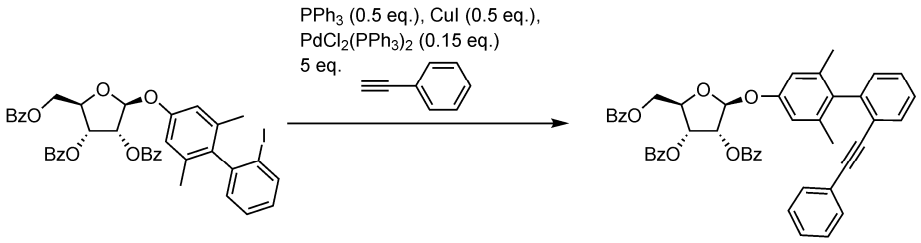
with combined contributions from reagents (10), inorganics (141), organic solvents (2163) and water (127), considering the contribution from the starting material 3,5-dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-acetyl-β-D-ribofuranoside.

3,5-Dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside

Reaction S25

Hu *et al. J. Am. Chem. Soc.* **2019**, *141*, 4806–4810, doi: 10.1021/jacs.9b00210

Reaction from their Supplementary Information, compound **9h**



The experimental details for this synthesis were provided in the Supplementary Information (page 22, compound **9h**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a similar procedure from the same manuscript. Therefore, we assumed that the exact same procedure was used and adjusted all quantities to the scale of this synthesis. 3,5-Dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside (0.65 mmol, 498 mg) was reacted with triphenylphosphine (0.33 mmol, 86 mg), bis(triphenylphosphine)palladium(II) dichloride (0.098 mmol, 68 mg), copper iodide (0.33 mmol, 63 mg) and phenylacetylene (3.25 mmol, 378 mg calculated with a molecular weight of 102.1 g·mol^{-1}) in DMF (5.7 mL, 5.417 g with ρ = 0.95 g·cm^{-3}) and diisopropylamine (12.544 mL, 9.032 g with ρ = 0.72 g·cm^{-3}) for 10 h. The reaction was quenched with NH_4Cl (amount not stated, we assumed it was 2 mL of an aqueous saturated solution, 2.14 g with ρ = 1.07 g·cm^{-3} according to Stefan-Kharicha *et al. J. Chem. Eng. Data* **2018**, *63*, 3170−3183, doi: 10.1021/acs.jced.7b01062; with *0.535 g* of salt with a solubility of 250 g·L^{-1} and *1.605 g* of water) and the resulting mixture extracted three times with ethyl acetate (amount not stated, we assumed 60.732 mL for 20.244 mL of solution to be extracted, corresponding to *54.659 g* with ρ = 0.90 g·cm^{-3}). The organic phase was washed with brine (amount not stated, we assumed half the volume of the solution, corresponding to 30.366 mL, 36.136 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *13.009 g* of salt with a solubility of 360 g·L^{-1} and *23.127 g* of water), dried over anhydrous sodium sulfate (*1.215 g* for 60.732 mL) and concentrated *in vacuo*. Column chromatography on silica gel (using *21.86 g* of silica gel and 546.5 mL of petroleum ether/ethyl acetate 10:1 for an assumed weight of 1.093 g of crude product, which corresponds to 496.818 mL of petroleum ether, *322.932 g* with ρ = 0.65 g·cm^{-3} and 49.682 mL of ethyl acetate, *44.714 g* with ρ = 0.90 g·cm^{-3}) provided the glycoside in 91% yield (**436 mg**).

The reaction took a total of 13.92 h (25 min reaction setup + 10 h reaction time + 30 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 18.244 mL of reaction solvent

(5.7 mL DMF + 12.544 mL diisopropylamine), corresponding to 68.3 mL per gram of product, considering the contribution of the starting material 3,5-dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside from Reaction S24, calculated as

$$\frac{18.244\ \text{mL}}{0.436\ \text{g}} + 0.498 * \frac{53.09\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside of 8.3 (Reaction S24), the preparation of 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside had a sEF of 11.0, calculated as

$$\text{sEF} = \frac{0.498 + 0.498 * 8.3 + 0.086 + 0.068 + 0.063 + 0.378 - \mathbf{0.436}}{\mathbf{0.436}}$$

and (considering the cEF of the starting material of 2439) a cEF of 3926, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.498 + 0.498 * 2439 + 0.086 + 0.068 + 0.063 + 0.378 + 0.535 + 13.009 + 1.215 + 21.86 \\ +5.417 + 9.032 + 54.659 + 322.932 + 44.714 + 1.605 + 23.127 \\ -\mathbf{0.436}\end{array}}{\mathbf{0.436}}$$

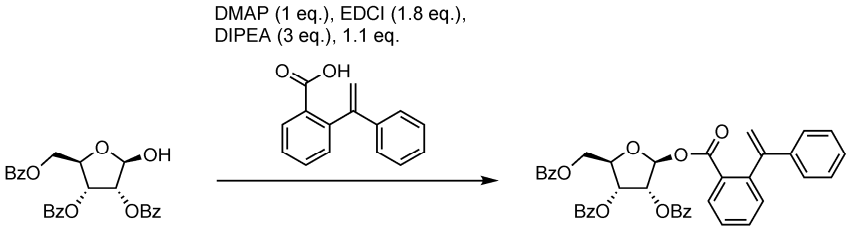
with combined contributions from reagents (14), inorganics (245), organic solvents (3472) and water (202), considering the contribution from the starting material 3,5-dimethyl-4-(2'-iodophenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside.

2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate

Reaction S26

Li *et al. Nat. Comm.* **2020**, *11*, 405–414, doi: 10.1038/s41467-020-14295-z

Reaction from their Supplementary Information, compound **1l**



The experimental details for this synthesis were provided in the Supplementary Information (page 10, compound **1l**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure from the same manuscript (General Procedure A, page 2). Therefore, we assumed that the exact same procedure was used and adjusted all quantities to the scale of this synthesis. 2,3,5-Tri-O-benzoyl-D-ribose (0.87 mmol, 402 mg) was reacted with 2-(1-phenylvinyl)benzoic acid (0.957 mmol, 215 mg calculated with a molecular weight of 224.3 g·mol^{-1}), 4-dimethylaminopyridine (0.87 mmol, 106 mg calculated with a molecular weight of 122.2 g·mol^{-1}), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (1.566 mmol, 300 mg calculated with a molecular weight of 191.7 g·mol^{-1}) and *N*,*N*-diisopropylethylamine (2.61 mmol, 337 mg calculated with a molecular weight of 129.3 g·mol^{-1}) in CH_2Cl_2 (amount stated as 0.1 M, corresponding to 8.7 mL, 11.571 g with ρ = 1.33 g·cm^{-3}, assuming that the sugar component was the determining component for the concentration) for 3 h. The mixture was then diluted with CH_2Cl_2 (amount not stated, we assumed a twofold volume of solvent compared to the initial solution, corresponding to 17.4 mL, 23.142 g with ρ = 1.33 g·cm^{-3}), washed with water (amount not stated, we assumed an equal volume to the organic phase of 26.1 mL, 26.1 g with ρ = 1.00 g·cm^{-3}) and brine (amount not stated, we assumed half the volume of the organic phase, corresponding to 13.05 mL, 15.53 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *5.591 g* of salt with a solubility of 360 g·L^{-1} and *9.939 g* of water), dried over anhydrous sodium sulfate (*522 mg* for 26.1 mL) and concentrated *in vacuo*. Column chromatography on silica gel (using *27.2 g* of silica gel and 680 mL of petroleum ether/ethyl acetate 5:1 for an assumed weight of 1.36 g of crude product, which corresponds to 566.667 mL of petroleum ether, *368.333 g* with ρ = 0.65 g·cm^{-3} and 113.333 mL of ethyl acetate, *102 g* with ρ = 0.90 g·cm^{-3}) provided the glycoside in 96% yield (**560 mg**).

The reaction took a total of 6.75 h (25 min reaction setup + 3 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 8.7 mL of reaction solvent (8.7 mL

CH_2Cl_2), corresponding to 27.9 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-O-benzoyl-D-ribose from Reaction S11, calculated as

$$\frac{8.7\ \text{mL}}{0.56\ \text{g}} + 0.402 * \frac{30.83\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-O-benzoyl-D-ribose of 10.0 (Reaction S11), the preparation of 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate had a sEF of 8.6, calculated as

$$\text{sEF} = \frac{0.402 + 0.402 * 10.0 + 0.215 + 0.106 + 0.3 + 0.337 - \mathbf{0.56}}{\mathbf{0.56}}$$

and (considering the cEF of the starting material of 1168) a cEF of 1866, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.402 + 0.402 * 1168 + 0.215 + 0.106 + 0.3 + 0.337 + 5.591 + 0.522 + 27.2 \\ +11.571 + 23.142 + 368.333 + 102 + 26.1 + 9.939 \\ \mathbf{-0.56}\end{array}}{\mathbf{0.56}}$$

with combined contributions from reagents (12), inorganics (95), organic solvents (1611) and water (151), considering the contribution from the starting material 2,3,5-tri-O-benzoyl-D-ribose.

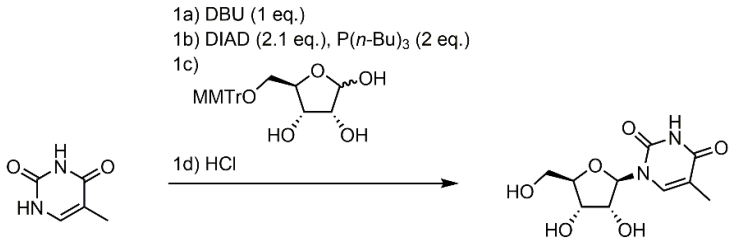
Nucleosides

Anhydroses

Reaction N1

Downey *et al. Org. Lett.* **2015**, *17*, 4604−4607, doi: 10.1021/acs.orglett.5b02332

Reaction from their Scheme 4, compound **3h**



The experimental details for this synthesis were provided in the Supporting Information (compound **3h**, page 20 and 28). Thymine (126 mg, 1 mmol), DBU (150 µL, 153 mg with ρ = 1.02 g·cm^{-3}, 1 mmol), DIAD (420 µL, 433 mg with ρ = 1.03 g·cm^{-3}, 2.1 mmol), P(*n*-Bu)$_3$ (530 µL, 424 mg with ρ = 0.80 g·cm^{-3}, 2.0 mmol) and 5-*O*-monomethoxytrityl-D-ribose (845 mg, 1.5 mmol) were reacted in MeCN (10 mL, 7.9 g with ρ = 0.79 g·cm^{-3}) for 12 h. For deprotection, the reaction was acidified with 1 M HCl (amount not stated, we assumed 1 mL, *1.02 g* with ρ = 1.02 g·cm^{-3}) for 1 h and neutralized with 1 M NaOH (amount not stated, we assumed 1 mL, 1.08 g with ρ = 1.08 g·cm^{-3}, corresponding to *40 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *1.04 g* of water). The mixture was concentrated *in vacuo* to yield a crude product. Trituration in MeOH/CH_2Cl_2 (120 mL, 6:1, corresponding to 102.857 mL MeOH, 81.257 g with ρ = 0.79 g·cm^{-3} and 17.143 mL CH_2Cl_2, 22.8 g with ρ = 1.33 g·cm^{-3}) for 20 min, filtration and purification on silica gel (using *39.62 g* of silica gel and 0.99 L of MeOH/ CH_2Cl_2 12.5:87.5, as the average of a linear gradient from 10:90 to 15:85, for an assumed weight of 1.98 g of crude product, which corresponds to 123 mL of MeOH, *97.763 g* with ρ = 0.79 g·cm^{-3} and 867 mL of CH_2Cl_2, *1153.11 g* with ρ = 1.33 g·cm^{-3}) provided the nucleoside in 39% yield (**101 mg**).

The reaction took a total of 17.25 h (25 min reaction setup + 15 min addition of material + 12 h reaction time + 1 h for deprotection + 15 min workup + 20 min trituration + 30 min drying + 2 h purification + 30 min drying) and consumed 10 mL of reaction solvent (10 mL MeCN), corresponding to 106.3 mL per gram of product, considering the contribution of the starting material 5-*O*-monomethoxytrityl-D-ribose from Reaction S4, calculated as

$$\frac{10\ \text{mL}}{0.101\ \text{g}} + 0.845 * \frac{8.62\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-monomethoxytrityl-D-ribose of 2.6 (Reaction S4), the preparation of **3h** had a sEF of 40.4, calculated as

$$\text{sEF} = \frac{0.126 + 0.153 + 0.433 + 0.424 + 0.845 + 0.854 * 2.6 - \mathbf{0.101}}{\mathbf{0.101}}$$

and (considering the cEF of the starting material of 2158) a cEF of 31980, calculated as

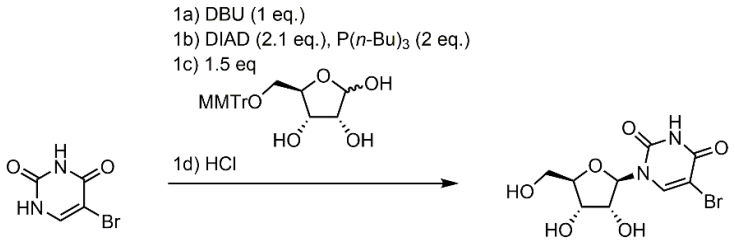
$$\mathrm{cEF} = \frac{0.126 + 0.153 + 0.433 + 0.424 + 0.845 + 0.854 * 2158 + 0.04 + 39.62 \\ +7.9 + 81.257 + 22.8 + 97.763 + 1153.11 + 1.02 + 1.04 \\ \mathbf{-0.101}}{\mathbf{0.101}}$$

with combined contributions from reagents (53), inorganics (1137), organic solvents (29916) and water (890), considering the contribution from the starting material 5-*O*-monomethoxytrityl-D-ribose.

Reaction N2

Downey *et al. Org. Lett.* **2015**, *17*, 4604−4607, doi: 10.1021/acs.orglett.5b02332

Reaction from their Scheme 4, compound **3l**



The experimental details for this synthesis were provided in the Supporting Information (compound **3l**, page 20 and 31). 5-Bromouracil (191 mg, 1 mmol), DBU (150 µL, 153 mg with ρ = 1.02 g·cm^{-3}, 1 mmol), DIAD (420 µL, 433 mg with ρ = 1.03 g·cm^{-3}, 2.1 mmol), P(*n*-Bu)$_3$ (530 µL, 424 mg with ρ = 0.80 g·cm^{-3}, 2.0 mmol) and 5-*O*-monomethoxytrityl-D-ribose (845 mg, 1.5 mmol) were reacted in MeCN (10 mL, 7.9 g with ρ = 0.79 g·cm^{-3}). For deprotection, the reaction was acidified with 1 M HCl (amount not stated, we assumed 1 mL, *1.02 g* with ρ = 1.02 g·cm^{-3}) for 1 h and neutralized with 1 M NaOH (amount not stated, we assumed 1 mL, 1.08 g with ρ = 1.08 g·cm^{-3}, corresponding to *40 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *1.04 g* of water). The mixture was concentrated *in vacuo* to yield a crude product. Trituration in MeOH/CH_2Cl_2 (120 mL, 6:1, corresponding to 102.857 mL MeOH, 81.257 g with ρ = 0.79 g·cm^{-3} and 17.143 mL CH_2Cl_2, 22.8 g with ρ = 1.33 g·cm^{-3}) for 20 min, filtration and purification on silica gel (using *39.62 g* of silica gel and 0.99 L of MeOH/CH_2Cl_2 12.5:87.5, as the average of a linear gradient from 10:90 to 15:85, for an assumed weight of 1.98 g of crude product, which corresponds to 123 mL of MeOH, *97.763 g* with ρ = 0.79 g·cm^{-3} and 867 mL of CH_2Cl_2, *1153.11 g* with ρ = 1.33 g·cm^{-3}) provided the nucleoside in 28% yield (**90 mg**).

The reaction took a total of 17.25 h (25 min reaction setup + 15 min addition of material + 12 h reaction time + 1 h for deprotection + 15 min workup + 20 min trituration + 30 min drying + 2 h purification + 30 min drying) and consumed 10 mL of reaction solvent (10 mL MeCN), corresponding to 118.4 mL per gram of product, considering the contribution of the starting material 5-*O*-monomethoxytrityl-D-ribose from Reaction S4, calculated as

$$\frac{10\ \text{mL}}{0.09\ \text{g}} + 0.845 * \frac{8.62\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-monomethoxytrityl-D-ribose of 2.6 (Reaction S4), the preparation of **3l** had a sEF of 46.1, calculated as

$$\text{sEF} = \frac{0.191 + 0.153 + 0.433 + 0.424 + 0.845 + 0.854 * 2.6 - \mathbf{0.09}}{\mathbf{0.09}}$$

and (considering the cEF of the starting material of 2158) a cEF of 35889, calculated as

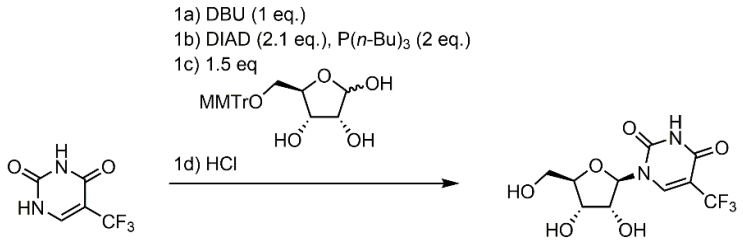
$$\mathrm{cEF} = \frac{\begin{array}{c}0.191 + 0.153 + 0.433 + 0.424 + 0.845 + 0.854 * 2158 + 0.04 + 39.62 \\ +7.9 + 81.257 + 22.8 + 97.763 + 1153.11 + 1.02 + 1.04\end{array}}{\mathbf{0.09}} - \mathbf{0.09}$$

with combined contributions from reagents (60), inorganics (1276), organic solvents (33573) and water (999), considering the contribution from the starting material 5-*O*-monomethoxytrityl-D-ribose.

Reaction N3

Downey *et al. Org. Lett.* **2015**, *17*, 4604−4607, doi: 10.1021/acs.orglett.5b02332

Reaction from their Scheme 4, compound **3j**



The experimental details for this synthesis were provided in the Supporting Information (compound **3j**, page 20 and 29). 5-trifluoromethyluracil (181 mg, 1 mmol), DBU (150 µL, 153 mg with ρ = 1.02 g·cm^{-3}, 1 mmol), DIAD (420 µL, 433 mg with ρ = 1.03 g·cm^{-3}, 2.1 mmol), P(*n*-Bu)$_3$ (530 µL, 424 mg with ρ = 0.80 g·cm^{-3}, 2.0 mmol) and 5-*O*-monomethoxytrityl-D-ribose (845 mg, 1.5 mmol) were reacted in MeCN (10 mL, 7.9 g with ρ = 0.79 g·cm^{-3}). For deprotection, the reaction was acidified with 1 M HCl (amount not stated, we assumed 1 mL, *1.02 g* with ρ = 1.02 g·cm^{-3}) for 1 h and neutralized with 1 M NaOH (amount not stated, we assumed 1 mL, 1.08 g with ρ = 1.08 g·cm^{-3}, corresponding to *40 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *1.04 g* of water). The mixture was concentrated *in vacuo* to yield a crude product. Trituration in MeOH/CH_2Cl_2 (120 mL, 6:1, corresponding to 102.857 mL MeOH, 81.257 g with ρ = 0.79 g·cm^{-3} and 17.143 mL CH_2Cl_2, 22.8 g with ρ = 1.33 g·cm^{-3}) for 20 min, filtration and purification on silica gel (using *39.62 g* of silica gel and 0.99 L of MeOH/CH_2Cl_2 12.5:87.5, as the average of a linear gradient from 10:90 to 15:85, for an assumed weight of 1.98 g of crude product, which corresponds to 123 mL of MeOH, *97.763 g* with ρ = 0.79 g·cm^{-3} and 867 mL of CH_2Cl_2, *1153.11 g* with ρ = 1.33 g·cm^{-3}) provided the nucleoside in 31% yield (**97 mg**).

The reaction took a total of 17.25 h (25 min reaction setup + 15 min addition of material + 12 h reaction time + 1 h for deprotection + 15 min workup + 20 min trituration + 30 min drying + 2 h purification + 30 min drying) and consumed 10 mL of reaction solvent (10 mL MeCN), corresponding to 110.4 mL per gram of product, considering the contribution of the starting material 5-*O*-monomethoxytrityl-D-ribose from Reaction S4, calculated as

$$\frac{10\ \mathrm{mL}}{0.097\ \mathrm{g}} + 0.845 * \frac{8.62\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 5-*O*-monomethoxytrityl-D-ribose of 2.6 (Reaction S4), the preparation of **3j** had a sEF of 42.7, calculated as

$$\mathrm{sEF} = \frac{0.181 + 0.153 + 0.433 + 0.424 + 0.845 + 0.854 * 2.6 - \mathbf{0.097}}{\mathbf{0.097}}$$

and (considering the cEF of the starting material of 2158) a cEF of 33299, calculated as

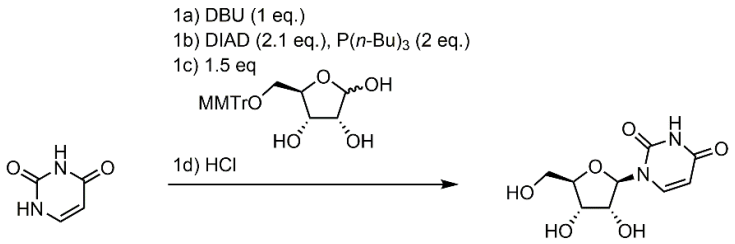
$$\mathrm{cEF} = \frac{\begin{array}{c}0.181 + 0.153 + 0.433 + 0.424 + 0.845 + 0.854 * 2158 + 0.04 + 39.62 \\ +7.9 + 81.257 + 22.8 + 97.763 + 1153.11 + 1.02 + 1.04\end{array}}{\mathbf{0.097}} \mathbf{-0.097}$$

with combined contributions from reagents (56), inorganics (1184), organic solvents (31150) and water (927), considering the contribution from the starting material 5-*O*-monomethoxytrityl-D-ribose.

Reaction N4

Downey *et al. Org. Lett.* **2015**, *17*, 4604−4607, doi: 10.1021/acs.orglett.5b02332

Reaction from their Scheme 4, compound **3i**



The experimental details for this synthesis were provided in the Supporting Information (compound **3i**, page 20 and 28). Uracil (110 mg, 1 mmol), DBU (150 µL, 153 mg with ρ = 1.02 g·cm^{-3}, 1 mmol), DIAD (420 µL, 433 mg with ρ = 1.03 g·cm^{-3}, 2.1 mmol), P(*n*-Bu)$_3$ (530 µL, 424 mg with ρ = 0.80 g·cm^{-3}, 2.0 mmol) and 5-*O*-monomethoxytrityl-D-ribose (845 mg, 1.5 mmol) were reacted in MeCN (10 mL, 7.9 g with ρ = 0.79 g·cm^{-3}). For deprotection, the reaction was acidified with 1 M HCl (amount not stated, we assumed 1 mL, *1.02 g* with ρ = 1.02 g·cm^{-3}) for 1 h and neutralized with 1 M NaOH (amount not stated, we assumed 1 mL, 1.08 g with ρ = 1.08 g·cm^{-3}, corresponding to *40 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *1.04 g* of water). The mixture was concentrated *in vacuo* to yield a crude product. Trituration in MeOH/CH_2Cl_2 (120 mL, 6:1, corresponding to 102.857 mL MeOH, 81.257 g with ρ = 0.79 g·cm^{-3} and 17.143 mL CH_2Cl_2, 22.8 g with ρ = 1.33 g·cm^{-3}) for 20 min, filtration and purification on silica gel (using *39.62 g* of silica gel and 0.99 L of MeOH/CH_2Cl_2 12.5:87.5, as the average of a linear gradient from 10:90 to 15:85, for an assumed weight of 1.98 g of crude product, which corresponds to 123 mL of MeOH, *97.763 g* with ρ = 0.79 g·cm^{-3} and 867 mL of CH_2Cl_2, *1153.11 g* with ρ = 1.33 g·cm^{-3}) provided the nucleoside in 31% yield (**76 mg**).

The reaction took a total of 17.25 h (25 min reaction setup + 15 min addition of material + 12 h reaction time + 1 h for deprotection + 15 min workup + 20 min trituration + 30 min drying + 2 h purification + 30 min drying) and consumed 10 mL of reaction solvent (10 mL MeCN), corresponding to 138.86 mL per gram of product, considering the contribution of the starting material 5-*O*-monomethoxytrityl-D-ribose from Reaction S4, calculated as

$$\frac{10\ \text{mL}}{0.076\ \text{g}} + 0.845 * \frac{8.62\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-monomethoxytrityl-D-ribose of 2.6 (Reaction S4), the preparation of **3i** had a sEF of 53.8, calculated as

$$\text{sEF} = \frac{0.11 + 0.153 + 0.433 + 0.424 + 0.845 + 0.854 * 2.6 - \mathbf{0.076}}{\mathbf{0.076}}$$

and (considering the cEF of the starting material of 2158) a cEF of 42499, calculated as

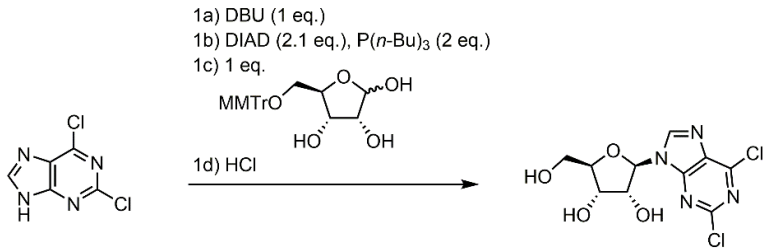
$$\mathrm{cEF} = \frac{\begin{array}{c}0.11 + 0.153 + 0.433 + 0.424 + 0.845 + 0.854 * 2158 + 0.04 + 39.62 \\ +7.9 + 81.257 + 22.8 + 97.763 + 1153.11 + 1.02 + 1.04\end{array}}{\mathbf{0.076}} \mathbf{-0.076}$$

with combined contributions from reagents (70), inorganics (1511), organic solvents (39757) and water (1128), considering the contribution from the starting material 5-*O*-monomethoxytrityl-D-ribose.

Reaction N5

Downey *et al. Org. Lett.* **2015**, *17*, 4604−4607, doi: 10.1021/acs.orglett.5b02332

Reaction from their Scheme 4, compound **3b**



The experimental details for this synthesis were provided in the Supporting Information (compound **3b**, page 20 and 21). 2,6-dichloropurine (197 mg, 1.05 mmol), DBU (157 µL, 160 mg with ρ = 1.02 g·cm^{-3}, 1.05 mmol), DIAD (434 µL, 455 mg with ρ = 1.03 g·cm^{-3}, 2.2 mmol), P(*n*-Bu)$_3$ (560 µL, 448 mg with ρ = 0.80 g·cm^{-3}, 2.0 mmol) and 5-*O*-monomethoxytrityl-D-ribose (444 mg, 1.05 mmol) were reacted in MeCN (11 mL, 8.69 g with ρ = 0.79 g·cm^{-3}). For deprotection, the reaction was acidified with 1 M HCl (amount not stated, we assumed 1 mL, *1.02 g* with ρ = 1.02 g·cm^{-3}) for 15 min and neutralized with 1 M NaOH (amount not stated, we assumed 1 mL, 1.08 g with ρ = 1.08 g·cm^{-3}, corresponding to *40 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *1.04 g* of water). The mixture was concentrated *in vacuo* to yield a crude product. Trituration in MeOH/CH_2Cl_2 (120 mL, 6:1, corresponding to 102.857 mL MeOH, 81.257 g with ρ = 0.79 g·cm^{-3} and 17.143 mL CH_2Cl_2, 22.8 g with ρ = 1.33 g·cm^{-3}) for 20 min, filtration, purification on silica gel (using *25 g* of silica gel and 0.625 L of MeOH/CH_2Cl_2 2.5:97.5, as the average of a linear gradient from 0:100 to 5:95, for an assumed weight of 1.25 g of crude product, which corresponds to 15.625 mL of MeOH, *12.343 g* with ρ = 0.79 g·cm^{-3} and 612.657 mL of CH_2Cl_2, *814.834 g* with ρ = 1.33 g·cm^{-3}) and purification via RP-HPLC (using 56 mL of MeOH/water 1:1, as the average of a linear gradient from 0−100% MeOH, for 112 mg of crude product, which corresponds to 28 mL of MeOH, *22.12 g* with ρ = 0.79 g·cm^{-3} and 28 mL of water, *28 g* with ρ = 1.00 g·cm^{-3}) provided the nucleoside in 28% yield (**94 mg**).

The reaction took a total of 36.5 h (25 min reaction setup + 15 min addition of material + 12 h reaction time + 15 min deprotection + 15 min workup + 20 min trituration + 30 min drying + 2 h purification + 30 min drying + 2 h purification + 18 h lyophilization) and consumed 11 mL of reaction solvent (11 mL MeCN), corresponding to 120.9 mL per gram of product, considering the contribution of the starting material 5-*O*-monomethoxytrityl-D-ribose from Reaction S4, calculated as

$$\frac{11\ \text{mL}}{0.094\ \text{g}} + 0.444 * \frac{8.62\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-monomethoxytrityl-D-ribose of 2.6 (Reaction S4), the preparation of **3b** had a sEF of 29.4, calculated as

$$\mathrm{sEF} = \frac{0.197 + 0.16 + 0.455 + 0.448 + 0.444 + 0.444 * 2.6 - \mathbf{0.094}}{\mathbf{0.094}}$$

and (considering the cEF of the starting material of 2158) a cEF of 21031, calculated as

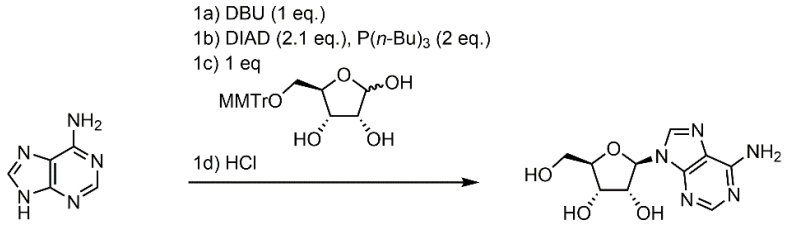
$$\mathrm{cEF} = \frac{\begin{array}{c}0.197 + 0.16 + 0.455 + 0.448 + 0.444 + 0.444 * 2158 + 0.04 + 25 \\ +8.69 + 81.257 + 22.8 + 12.343 + 814.834 + 22.12 + 1.02 + 1.04 + 28 \\ \mathbf{-0.094}\end{array}}{\mathbf{0.094}}$$

with combined contributions from reagents (37), inorganics (687), organic solvents (19498) and water (1003), considering the contribution from the starting material 5-*O*-monomethoxytrityl-D-ribose.

Reaction N6

Downey *et al. Org. Lett.* **2015**, *17*, 4604−4607, doi: 10.1021/acs.orglett.5b02332

Reaction from their Scheme 4, compound **3c**



The experimental details for this synthesis were provided in the Supporting Information (compound **3c**, page 20 and 23). adenine (80 mg, 0.595 mmol), DBU (90 µL, 92 mg with ρ = 1.02 g·cm^{-3}, 0.595 mmol), DIAD (250 µL, 258 mg with ρ = 1.03 g·cm^{-3}, 1.25 mmol), P(*n*-Bu)$_3$ (320 µL, 256 mg with ρ = 0.80 g·cm^{-3}, 1.19 mmol) and 5-*O*-monomethoxytrityl-D-ribose (251 mg, 0.68 mmol) were reacted in MeCN (7 mL, 5.53 g with ρ = 0.79 g·cm^{-3}). For deprotection, the reaction was acidified with 1 M HCl (amount not stated, we assumed 1 mL, *1.02 g* with ρ = 1.02 g·cm^{-3}) and neutralized with 1 M NaOH (amount not stated, we assumed 1 mL, 1.08 g with ρ = 1.08 g·cm^{-3}, corresponding to *40 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *1.04 g* of water). The mixture was concentrated *in vacuo* to yield a crude product. Trituration in MeOH/CH_2Cl_2 (120 mL, 6:1, corresponding to 102.857 mL MeOH, 81.257 g with ρ = 0.79 g·cm^{-3} and 17.143 mL CH_2Cl_2, 22.8 g with ρ = 1.33 g·cm^{-3}) for 20 min, filtration, purification on silica gel (using *18.74 g* of silica gel and 0.469 L of MeOH/CH_2Cl_2 10:90, as the average of a linear gradient from 0–20% MeOH, for an assumed weight of 937 mg of crude product, which corresponds to 46.9 mL of MeOH, *37.051 g* with ρ = 0.79 g·cm^{-3} and 421.1 mL of CH_2Cl_2, *561.393 g* with ρ = 1.33 g·cm^{-3}) and recrystallization from MeOH (1.08 mL for 108 mg of crude product, *853 mg* with ρ = 0.79 g·cm^{-3}) provided the nucleoside in 40% yield (**63 mg**).

The reaction took a total of 19 h (25 min reaction setup + 15 min addition of material + 12 h reaction time + 15 min deprotection + 15 min workup + 20 min trituration + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying) and consumed 7 mL of reaction solvent (7 mL MeCN), corresponding to 113.27 mL per gram of product, considering the contribution of the starting material 5-*O*-monomethoxytrityl-D-ribose from Reaction S4, calculated as

$$\frac{7\ \text{mL}}{0.063\ \text{g}} + 0.251 * \frac{8.62\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-monomethoxytrityl-D-ribose of 2.6 (Reaction S4), the preparation of **3c** had a sEF of 24.2, calculated as

$$\text{sEF} = \frac{0.08 + 0.092 + 0.256 + 0.258 + 0.251 + 0.251 * 2.6 - \mathbf{0.063}}{\mathbf{0.063}}$$

and (considering the cEF of the starting material of 2158) a cEF of 20195, calculated as

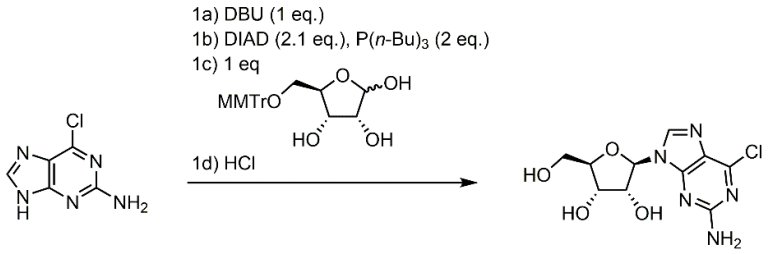
$$\mathrm{cEF} = \frac{\begin{array}{c}0.08 + 0.092 + 0.256 + 0.258 + 0.251 + 0.251 * 2158 + 0.04 + 18.74 \\ +5.53 + 81.257 + 22.8 + 37.051 + 561.393 + 0.853 + 1.02 + 1.04 \\ \mathbf{-0.063}\end{array}}{\mathbf{0.063}}$$

with combined contributions from reagents (31), inorganics (653), organic solvents (19073) and water (447), considering the contribution from the starting material 5-*O*-monomethoxytrityl-D-ribose.

Reaction N7

Downey *et al. Org. Lett.* **2015**, *17*, 4604−4607, doi: 10.1021/acs.orglett.5b02332

Reaction from their Scheme 4, compound **3d**



The experimental details for this synthesis were provided in the Supporting Information (compound **3d**, page 20 and 23). 2-Amino-6-chloropurine (115 mg, 0.68 mmol), DBU (101 µL, 103 mg with ρ = 1.02 g·cm^{-3}, 0.68 mmol), DIAD (280 µL, 288 mg with ρ = 1.03 g·cm^{-3}, 1.43 mmol), P(*n*-Bu)$_3$ (360 µL, 288 mg with ρ = 0.80 g·cm^{-3}, 1.36 mmol) and the protected ribose (287 mg, 0.68 mmol) were reacted in MeCN (7 mL, 5.53 g with ρ = 0.79 g·cm^{-3}). For deprotection, the reaction was acidified with 1 M HCl (amount not stated, we assumed 1 mL, *1.02 g* with ρ = 1.02 g·cm^{-3}) for 15 min and neutralized with 1 M NaOH (amount not stated, we assumed 1 mL, 1.08 g with ρ = 1.08 g·cm^{-3}, corresponding to *40 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *1.04 g* of water). The mixture was concentrated *in vacuo* to yield a crude product. Trituration in MeOH/CH_2Cl_2 (120 mL, 6:1, corresponding to 102.857 mL MeOH, 81.257 g with ρ = 0.79 g·cm^{-3} and 17.143 mL CH_2Cl_2, 22.8 g with ρ = 1.33 g·cm^{-3}) for 20 min, filtration, purification on silica gel (using *21.62 g* of silica gel and 0.541 L of MeOH/CH_2Cl_2 5:95, as the average of a linear gradient from 0−10% MeOH, for an assumed weight of 1.081 g of crude product, which corresponds to 27 mL of MeOH, *21.35 g* with ρ = 0.79 g·cm^{-3} and 513.95 mL of CH_2Cl_2, *683.554 g* with ρ = 1.33 g·cm^{-3}) and recrystallization from water (1.52 mL for 152 mg of crude product, *1.52 g* with ρ = 1.00 g·cm^{-3}) provided the nucleoside in 74% yield (**152 mg**). The reaction took a total of 89 h (25 min reaction setup + 15 min addition of material + 12 h reaction time + 15 min deprotection + 15 min workup + 20 min trituration + 30 min drying + 2 h purification + 30 min drying + 72 h recrystallization + 30 min drying) and consumed 7 mL of reaction solvent (7 mL MeCN), corresponding to 48.5 mL per gram of product, considering the contribution of the starting material 5-*O*-monomethoxytrityl-D-ribose from Reaction S4, calculated as

$$\frac{7\ \text{mL}}{0.152\ \text{g}} + 0.287 * \frac{8.62\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-monomethoxytrityl-D-ribose of 2.6 (Reaction S4), the preparation of **3d** had a sEF of 11.0, calculated as

$$\text{sEF} = \frac{0.115 + 0.103 + 0.288 + 0.288 + 0.287 + 0.287 * 2.6 - \mathbf{0.152}}{\mathbf{0.152}}$$

and (considering the cEF of the starting material of 2158) a cEF of 9605, calculated as

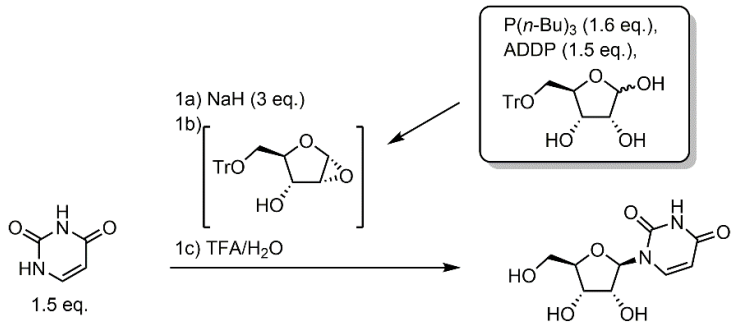
$$\mathrm{cEF} = \frac{\begin{array}{c}0.115 + 0.103 + 0.288 + 0.288 + 0.287 + 0.287 * 2158 + 0.04 + 21.62 \\ +5.53 + 81.257 + 22.8 + 21.35 + 683.554 + 1.02 + 1.04 + 1.52\end{array}}{\mathbf{0.152}} \mathbf{-0.152}$$

with combined contributions from reagents (15), inorganics (311), organic solvents (9065) and water (220), considering the contribution from the starting material 5-*O*-monomethoxytrityl-D-ribose.

Reaction N8

Downey *et al. Chem. Eur. J.* **2017**, *23*, 3910 – 3917, doi: 10.1002/chem.201604955

Reaction from their Scheme 3, compound **5a**



The experimental details for this synthesis were provided in the Supporting Information (compound **5a**, page 8 and 25) and legend of Scheme 3 (page 5). Uracil (426 mg, 3.81 mmol) and NaH (320 mg, 7.62 mmol) were reacted in DMF (10 mL, 9.5 g with ρ = 0.95 g·cm^{-3}) and added to the preformed epoxide which was generated by reacting 5-*O*-trityl-D-ribose (100 mg, 0.254 mmol) with P(*n*-Bu)$_3$ (110 µL, 88 mg with ρ = 0.80 g·cm^{-3}, 0.406 mmol) and 1,1'-azo(dicarbonyl)dipiperidine (96 mg, 0.381 mmol) in MeCN (4 mL, 3.16 g with ρ = 0.79 g·cm^{-3}) for 12.5 h. Deprotection was achieved by adding TFA/water (10 mL, 10.5 g* assuming ρ = 1.05 g·cm^{-3}) for 12 h. Neutralization with Dowex resin, concentration *in vacuo*, purification by chromatography on normal phase silica gel (using *20.6 g* of silica gel and 0.515 L of MeOH/CH_2Cl_2 12.5:87.5, as the average of a linear gradient from 5–20% MeOH, for an assumed weight of 1.03 g of crude product, which corresponds to 64.375 mL of MeOH, *50.856 g* with ρ = 0.79 g·cm^{-3} and 450.625 mL of CH_2Cl_2, *599.331 g* with ρ = 1.33 g·cm^{-3}) and recrystallization from EtOH (1.7 mL for 170 mg of crude product, *1.343 g* with ρ = 0.79 g·cm^{-3}) provided the nucleoside in 28% yield (**170 mg**)

The reaction took a total of 30.16 h (10 min reaction setup + 15 min of deprotonation + 15 min addition of reagents + 12 h for the glycosylation + 15 min workup + 12 h for deprotection + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying; assuming anhydrose formation and nucleobase deprotonation were carried out in parallel) and consumed a total of 24 mL of reaction solvent (10 mL DMF + 4 mL MeCN + 10 mL TFA/water), corresponding to 141.42 mL per gram of product, considering the contribution of the starting material 5-*O*-trityl-D-ribose from Reaction S5, calculated as

$$\frac{24\ \text{mL}}{0.17\ \text{g}} + 0.1 * \frac{2.45\ \text{mL}}{\text{g}}$$

*we argue that (albeit technically an aqueous solution) TFA/water should be considered a solvent in this analysis since it contains halogenated material and demands special waste treatment.

Thus, considering the sEF of the starting material 5-*O*-trityl-D-ribose of 1.1 (Reaction S5), the preparation of **5a** had a sEF of 5.7, calculated as

$$\mathrm{sEF} = \frac{0.426 + 0.32 + 0.1 + 0.1 * 1.1 + 0.096 + 0.088 - \mathbf{0.17}}{\mathbf{0.17}}$$

and (considering the cEF of the starting material of 35) a cEF of 4096, calculated as

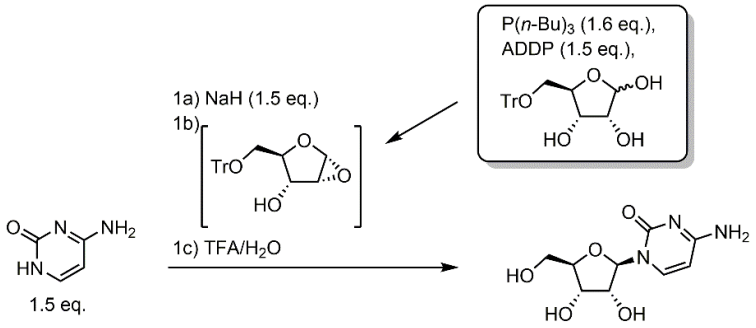
$$\mathrm{cEF} = \frac{\begin{array}{c}0.426 + 0.32 + 0.1 + 0.1 * 35 + 0.096 + 0.088 + 20.6 \\ +9.5 + 3.16 + 10.5 + 50.856 + 599.331 + 1.343 \\ -\mathbf{0.17}\end{array}}{\mathbf{0.17}}$$

with combined contributions from reagents (7), inorganics (121), organic solvents (3985) and water (16), considering the contribution from the starting material 5-*O*-trityl-D-ribose.

Reaction N9

Downey *et al. Chem. Eur. J.* **2017**, *23*, 3910 – 3917, doi: 10.1002/chem.201604955

Reaction from their Scheme 3, compound **5b**



The experimental details for this synthesis were provided in the Supporting Information (compound **5b**, page 8 and 26) and legend of Scheme 3 (page 5). Cytosine (423 mg, 3.81 mmol) and NaH (160 mg, 3.81 mmol) were reacted in DMF (10 mL, 9.5 g with ρ = 0.95 g·cm^{-3}) and added to the preformed epoxide which was generated by reacting 5-*O*-trityl-D-ribose (100 mg, 0.254 mmol) with P(*n*-Bu)$_3$ (110 µL, 88 mg with ρ = 0.80 g·cm^{-3}, 0.406 mmol) and 1,1'-azo(dicaronyl)dipiperidine (96 mg, 0.381 mmol) in MeCN (4 mL, 3.16 g with ρ = 0.79 g·cm^{-3}) for 12.5 h. Deprotection was achieved by adding TFA/water (10 mL, 10.5 g assuming ρ = 1.05 g·cm^{-3}) for 12 h. Neutralization with Dowex resin, concentration *in vacuo*, purification by chromatography on normal phase silica gel (using *17.34 g* of silica gel and 434 mL of MeOH/CH_2Cl_2 14.5:85.5, as the average of a linear gradient from 4–25% MeOH, for an assumed weight of 867 mg of crude product, which corresponds to 62.858 mL of MeOH, *49.657 g* with ρ = 0.79 g·cm^{-3} and 317.07 mL of CH_2Cl_2, *493.523 g* with ρ = 1.33 g·cm^{-3}) and recrystallization from EtOH (2.21 mL for 221 mg of crude product, *1.746 g* with ρ = 0.79 g·cm^{-3}) provided the nucleoside in 36% yield (**221 mg**)

The reaction took a total of 30.16 h (10 min reaction setup + 15 min of deprotonation + 15 min addition of reagents + 12 h for the glycosylation + 15 min workup + 12 h for deprotection + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying; assuming anhydrose formation and nucleobase deprotonation were carried out in parallel) and consumed a total of 24 mL of reaction solvent (10 mL DMF + 4 mL MeCN + 10 mL TFA/water), corresponding to 108.8 mL per gram of product, considering the contribution of the starting material 5-*O*-trityl-D-ribose from Reaction S5, calculated as

$$\frac{24\ \text{mL}}{0.221\ \text{g}} + 0.1 * \frac{2.45\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-trityl-D-ribose of 1.1 (Reaction S5), the preparation of **5b** had a sEF of 3.4, calculated as

$$\mathrm{sEF} = \frac{0.423 + 0.16 + 0.1 + 0.1 * 1.1 + 0.096 + 0.088 - \mathbf{0.221}}{\mathbf{0.221}}$$

and (considering the cEF of the starting material of 35) a cEF of 2668, calculated as

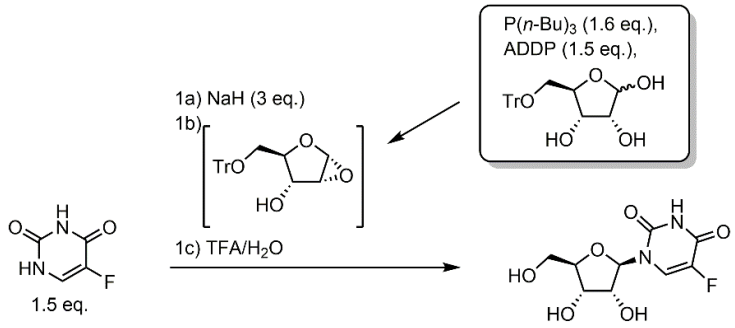
$$\mathrm{cEF} = \frac{\begin{array}{c}0.423 + 0.16 + 0.1 + 0.1 * 35 + 0.096 + 0.088 + 17.34 \\ +9.5 + 3.16 + 10.5 + 49.657 + 493.523 + 1.746 \\ -\mathbf{0.221}\end{array}}{\mathbf{0.221}}$$

with combined contributions from reagents (5), inorganics (79), organic solvents (2583) and water (13), considering the contribution from the starting material 5-*O*-trityl-D-ribose.

Reaction N10

Downey *et al. Chem. Eur. J.* **2017**, *23*, 3910 – 3917, doi: 10.1002/chem.201604955

Reaction from their Scheme 3, compound **5c**



The experimental details for this synthesis were provided in the Supporting Information (compound **5c**, page 8 and 26) and legend of Scheme 3 (page 5). 5-Fluoruracil (500 mg, 3.81 mmol) and NaH (320 mg, 7.62 mmol) were reacted in DMF (10 mL, 9.5 g with ρ = 0.95 g·cm^{-3}) and added to the preformed epoxide which was generated by reacting 5-*O*-trityl-D-ribose (100 mg, 0.254 mmol) with P(*n*-Bu)$_3$ (110 µL, 88 mg with ρ = 0.80 g·cm^{-3}, 0.406 mmol) and 1,1'-azo(dicaronyl)dipiperidine (96 mg, 0.381 mmol) in MeCN (4 mL, 3.16 g with ρ = 0.79 g·cm^{-3}) for 12 h. Deprotection was achieved by adding TFA/water (10 mL, 10.5 g assuming ρ = 1.05 g·cm^{-3}) for 12 h. Neutralization with Dowex resin, concentration *in vacuo*, purification by chromatography on normal phase silica gel (using *22.08 g* of silica gel and 552 mL of MeOH/CH_2Cl_2 12.5:87.5, as the average of a linear gradient from 5–20% MeOH, for an assumed weight of 1.104 g of crude product, which corresponds to 69 mL of MeOH, *54.51 g* with ρ = 0.79 g·cm^{-3} and 483 mL of CH_2Cl_2, *642.39 g* with ρ = 1.33 g·cm^{-3}) and recrystallization from EtOH (2.1 mL for 210 mg of crude product, *1.659 g* with ρ = 0.79 g·cm^{-3}) provided the nucleoside in 31% yield (**210 mg**)

The reaction took a total of 30.16 h (10 min reaction setup + 15 min of deprotonation + 15 min addition of reagents + 12 h for the glycosylation + 15 min workup + 12 h for deprotection + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying; assuming anhydrose formation and nucleobase deprotonation were carried out in parallel) and consumed a total of 24 mL of reaction solvent (10 mL DMF + 4 mL MeCN + 10 mL TFA/water), corresponding to 114.5 mL per gram of product, considering the contribution of the starting material 5-*O*-trityl-D-ribose from Reaction S5, calculated as

$$\frac{24\ \text{mL}}{0.21\ \text{g}} + 0.1 * \frac{2.45\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-trityl-D-ribose of 1.1 (Reaction S5), the preparation of **5c** had a sEF of 4.8, calculated as

$$\mathrm{sEF} = \frac{0.5 + 0.32 + 0.1 + 0.1 * 1.1 + 0.096 + 0.088 - \mathbf{0.21}}{\mathbf{0.21}}$$

and (considering the cEF of the starting material of 35) a cEF of 3563, calculated as

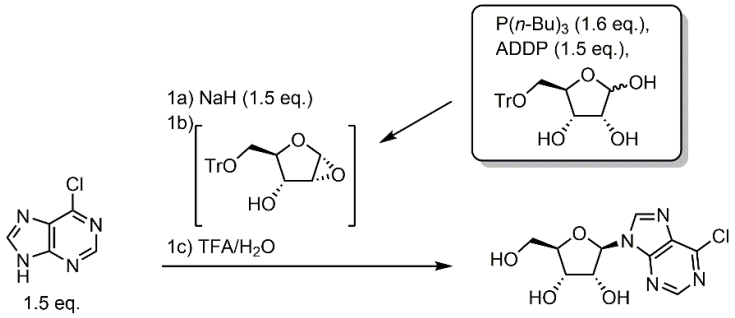
$$\mathrm{cEF} = \frac{\begin{array}{c}0.5 + 0.32 + 0.1 + 0.1 * 35 + 0.096 + 0.088 + 22.08 \\ +9.5 + 3.16 + 10.5 + 54.51 + 642.39 + 1.659\end{array} \\ \mathbf{-0.221}}{\mathbf{0.221}}$$

with combined contributions from reagents (6), inorganics (105), organic solvents (3450) and water (13), considering the contribution from the starting material 5-*O*-trityl-D-ribose.

Reaction N11

Downey *et al. Chem. Eur. J.* **2017**, *23*, 3910 – 3917, doi: 10.1002/chem.201604955

Reaction from their Scheme 3, compound **5d**



The experimental details for this synthesis were provided in the Supporting Information (compound **5d**, page 8 and 27) and legend of Scheme 3 (page 5). 6-chloropurine (587 mg, 3.81 mmol) and NaH (160 mg, 3.81 mmol) were reacted in DMF (10 mL, 9.5 g with ρ = 0.95 g·cm^{-3}) and added to the preformed epoxide which was generated by reacting 5-*O*-trityl-D-ribose (100 mg, 0.254 mmol) with P(*n*-Bu)$_3$ (110 µL, 88 mg with ρ = 0.80 g·cm^{-3}, 0.406 mmol) and 1,1'-azo(dicaronyl)dipiperidine (96 mg, 0.381 mmol) in MeCN (4 mL, 3.16 g with ρ = 0.79 g·cm^{-3}) for 12 h. Deprotection was achieved by adding TFA/water (10 mL, 10.5 g assuming ρ = 1.05 g·cm^{-3}) for 12 h. Neutralization with Dowex resin, concentration *in vacuo*, purification by chromatography on normal phase silica gel gel (using *20.62 g* of silica gel and 515.5 mL of MeOH/CH_2Cl_2 7:93, as the average of a linear gradient from 4–10% MeOH, for an assumed weight of 1.031 g of crude product, which corresponds to 36.085 mL of MeOH, *28.507 g* with ρ = 0.79 g·cm^{-3} and 479.415 mL of CH_2Cl_2, *637.622 g* with ρ = 1.33 g·cm^{-3}) and recrystallization from water (4.08 mL for 408 mg of crude product, *4.08 g* with ρ = 1.00 g·cm^{-3}) provided the nucleoside in 56% yield (**408 mg**)

The reaction took a total of 30.16 h (10 min reaction setup + 15 min of deprotonation + 15 min addition of reagents + 12 h for the glycosylation + 15 min workup + 12 h for deprotection + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying; assuming anhydrose formation and nucleobase deprotonation were carried out in parallel) and consumed a total of 24 mL of reaction solvent (10 mL DMF + 4 mL MeCN + 10 mL TFA/water), corresponding to 59.1 mL per gram of product, considering the contribution of the starting material 5-*O*-trityl-D-ribose from Reaction S5, calculated as

$$\frac{24\ \text{mL}}{0.408\ \text{g}} + 0.1 * \frac{2.45\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-trityl-D-ribose of 1.1 (Reaction S5), the preparation of **5d** had a sEF of 1.8, calculated as

$$\mathrm{sEF} = \frac{0.587 + 0.16 + 0.1 + 0.1 * 1.1 + 0.096 + 0.088 - \mathbf{0.408}}{\mathbf{0.408}}$$

and (considering the cEF of the starting material of 35) a cEF of 1760, calculated as

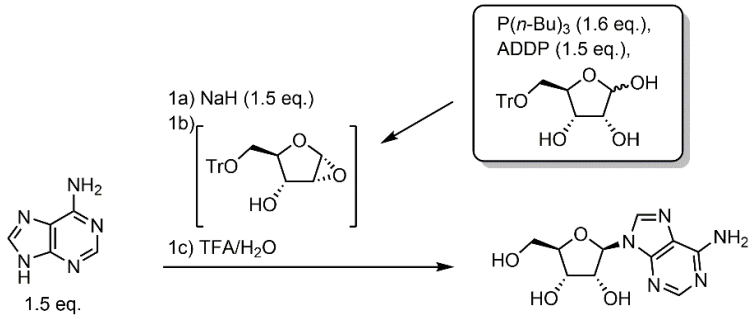
$$\mathrm{cEF} = \frac{\begin{array}{c}0.587 + 0.16 + 0.1 + 0.1 * 35 + 0.096 + 0.088 + 20.62 \\ +9.5 + 3.16 + 10.5 + 28.507 + 637.622 + 4.08\end{array} \\ \mathbf{-0.408}}{\mathbf{0.408}}$$

with combined contributions from reagents (3), inorganics (51), organic solvents (1696) and water (17), considering the contribution from the starting material 5-*O*-trityl-D-ribose.

Reaction N12

Downey *et al. Chem. Eur. J.* **2017**, *23*, 3910 – 3917, doi: 10.1002/chem.201604955

Reaction from their Scheme 3, compound **5e**



The experimental details for this synthesis were provided in the Supporting Information (compound **5e**, page 8 and 27) and legend of Scheme 3 (page 5). Adenine (515 mg, 3.81 mmol) and NaH (160 mg, 3.81 mmol) were reacted in DMF (10 mL, 9.5 g with ρ = 0.95 g·cm^{-3}) and added to the preformed epoxide which was generated by reacting 5-*O*-trityl-D-ribose (100 mg, 0.254 mmol) with P(*n*-Bu)$_3$ (110 µL, 88 mg with ρ = 0.80 g·cm^{-3}, 0.406 mmol) and 1,1'-azo(dicaronyl)dipiperidine (96 mg, 0.381 mmol) in MeCN (4 mL, 3.16 g with ρ = 0.79 g·cm^{-3}) for 12 h. Deprotection was achieved by adding TFA/water (10 mL, 10.5 g assuming ρ = 1.05 g·cm^{-3}) for 12 h. Neutralization with Dowex resin, concentration *in vacuo*, purification by chromatography on normal phase silica gel (using *19.18 g* of silica gel and 479.5 mL of MeOH/CH_2Cl_2 7:93, as the average of a linear gradient from 4–10% MeOH, for an assumed weight of 959 mg of crude product, which corresponds to 33.565 mL of MeOH, *26.516 g* with ρ = 0.79 g·cm^{-3} and 445.935 mL of CH_2Cl_2, *593.094 g* with ρ = 1.33 g·cm^{-3}) and recrystallization from EtOH (4.51 mL for 451 mg of crude product, *3.563 g* with ρ = 0.79 g·cm^{-3}) provided the nucleoside in 33% yield (**220 mg**)

The reaction took a total of 30.16 h (10 min reaction setup + 15 min of deprotonation + 15 min addition of reagents + 12 h for the glycosylation + 15 min workup + 12 h for deprotection + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying; assuming anhydrose formation and nucleobase deprotonation were carried out in parallel) and consumed a total of 24 mL of reaction solvent (10 mL DMF + 4 mL MeCN + 10 mL TFA/water), corresponding to 109.3 mL per gram of product, considering the contribution of the starting material 5-*O*-trityl-D-ribose from Reaction S5, calculated as

$$\frac{24\ \text{mL}}{0.22\ \text{g}} + 0.1 * \frac{2.45\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-trityl-D-ribose of 1.1 (Reaction S5), the preparation of **5e** had a sEF of 3.6, calculated as

$$\mathrm{sEF} = \frac{0.515 + 0.16 + 0.1 + 0.1 * 1.1 + 0.096 + 0.088 - \mathbf{0.22}}{\mathbf{0.22}}$$

and (considering the cEF of the starting material of 35) a cEF of 3051, calculated as

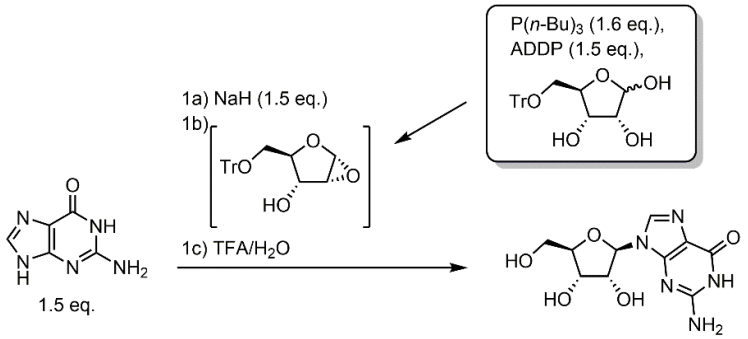
$$\mathrm{cEF} = \frac{\begin{array}{c} 0.515 + 0.16 + 0.1 + 0.1 * 35 + 0.096 + 0.088 + 19.18 \\ +9.5 + 3.16 + 10.5 + 26.516 + 593.094 + 3.563 \end{array} - \mathbf{0.22}}{\mathbf{0.22}}$$

with combined contributions from reagents (5), inorganics (87), organic solvents (2951) and water (13), considering the contribution from the starting material 5-*O*-trityl-D-ribose.

Reaction N13

Downey *et al. Chem. Eur. J.* **2017**, *23*, 3910 – 3917, doi: 10.1002/chem.201604955

Reaction from their Scheme 3, compound **5f**



The experimental details for this synthesis were provided in the Supporting Information (compound **5f**, page 8 and 29) and legend of Scheme 3 (page 5). Guanine (574 mg, 3.81 mmol) and NaH (160 mg, 3.81 mmol) were reacted in DMSO (10 mL, 11 g with ρ = 1.10 g·cm^{-3}) and added to the preformed epoxide which was generated by reacting 5-*O*-trityl-D-ribose (100 mg, 0.254 mmol) with P(*n*-Bu)$_3$ (110 µL, 88 mg with ρ = 0.80 g·cm^{-3}, 0.406 mmol) and 1,1'-azo(dicaronyl)dipiperidine (96 mg, 0.381 mmol) in MeCN (4 mL, 3.16 g with ρ = 0.79 g·cm^{-3}) for 12 h. Deprotection was achieved by adding TFA/water (10 mL, 10.5 g assuming ρ = 1.05 g·cm^{-3}) for 12 h. Concentration *in vacuo*, lyophilization, purification by chromatography on normal phase silica gel (using *20.36 g* of silica gel and 509 mL of MeOH/CH_2Cl_2 14.5:85.5, as the average of a linear gradient from 4–25% MeOH, for an assumed weight of 1.018 g of crude product, which corresponds to 73.805 mL of MeOH, *58.306 g* with ρ = 0.79 g·cm^{-3} and 445.935 mL of CH_2Cl_2, *435.195 g* with ρ = 1.33 g·cm^{-3}), a second purification step over a reverse phase (using *4 g* of reverse phase silica gel and 100 mL of MeOH/water 47.5:52.5, as the average of a linear gradient from 5–100% MeOH, for an assumed weight of 200 mg of crude product, which corresponds to 47.5 mL of MeOH, *37.525 g* with ρ = 0.79 g·cm^{-3} and 52.5 mL of water, *52.5 g* with ρ = 1.00 g·cm^{-3}) and recrystallization from MeOH (1.06 mL for 106 mg of crude product, *0.837 g* with ρ = 0.79 g·cm^{-3}), provided the nucleoside in 15% yield (**106 mg**)

The reaction took a total of 50.66 h (10 min reaction setup + 15 min of deprotonation + 15 min addition of reagents + 12 h for the glycosylation + 15 min workup + 12 h for deprotection + 30 min drying + 18 h lyophilization + 2 h purification + 30 min drying 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying; assuming anhydrose formation and nucleobase deprotonation were carried out in parallel) and consumed a total of 24 mL of reaction solvent (10 mL DMSO + 4 mL MeCN + 10 mL TFA/water), corresponding to 226.7 mL per gram of product, considering the contribution of the starting material 5-*O*-trityl-D-ribose from Reaction S5, calculated as

$$\frac{24\ \text{mL}}{0.106\ \text{g}} + 0.1 * \frac{2.45\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 5-*O*-trityl-D-ribose of 1.1 (Reaction S5), the preparation of **5f** had a sEF of 9.6, calculated as

$$\mathrm{sEF} = \frac{0.574 + 0.16 + 0.1 + 0.1 * 1.1 + 0.096 + 0.088 - \mathbf{0.106}}{\mathbf{0.106}}$$

and (considering the cEF of the starting material of 35) a cEF of 6017, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c} 0.574 + 0.16 + 0.1 + 0.1 * 35 + 0.096 + 0.088 + 20.36 + 4 \\ +11 + 3.16 + 10.5 + 58.306 + 435.195 + 37.525 + 0.837 + 52.5 \\ \mathbf{-0.106} \end{array}}{\mathbf{0.106}}$$

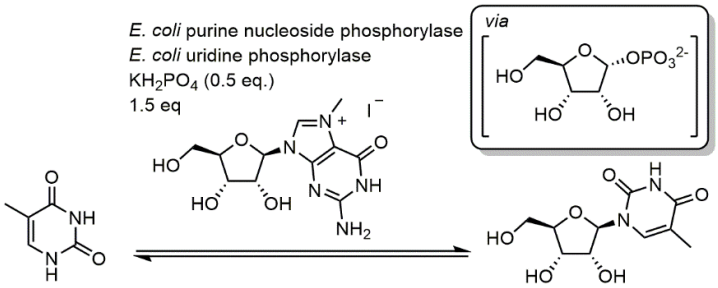
with combined contributions from reagents (11), inorganics (230), organic solvents (5277) and water (522), considering the contribution from the starting material 5-*O*-trityl-D-ribose.

Glycosyl phosphates

Reaction N14

Alexeev *et al. BBA-PROTEINS PROTEOM* **2020**, 140292, doi: 10.1016/j.bbapap.2019.140292

Reaction from their Table 2, compound **2b**



The experimental details for this synthesis were provided in the Materials and Methods section of the main text (page 2, compound **2b**). Thymine (37 mg, 0.3 mmol), 7-methylguanosine hydroiodide (191 mg, 0.45 mmol) and KH_2PO_4 (20 mg, 0.15 mmol) were reacted with *Escherichia coli* purine nucleoside phosphorylase (0.16 mg, including only the enzyme weight of the 32 $g \cdot L^{-1}$ stock solution) and *E. coli* uridine phosphorylase (0.16 mg, amount not stated, we assumed an equal quantity to the purine nucleoside phosphorylase) in 50 mM Tris-HCl buffer (80 mL, 80 g assuming ρ = 1.00 $g \cdot cm^{-3}$; with *630 mg* of salt, calculated with a molecular weight of 157.6 $g \cdot mol^{-1}$, and *79.37 g* of water) for 20 h. After the reaction, the mixture was filtered and the filtrate was washed with water (15 mL, 15 g with ρ = 1.00 $g \cdot cm^{-3}$). Evaporation of the solvent via coevaporation with EtOH (25 mL, 19.75 g with ρ = 0.79 $g \cdot cm^{-3}$) yielded a crude product which was purified by chromatography on silica gel (using 20 mL, 14 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 25 mL of CH_2Cl_2, 33.25 g with ρ = 1.33 $g \cdot cm^{-3}$, 50 mL EtOH/CH_2Cl_2 5:95, which corresponds to 2.5 mL of EtOH, 1.975 g with ρ = 0.79 $g \cdot cm^{-3}$ and 47.5 mL of CH_2Cl_2, 63.175 g with ρ = 1.33 $g \cdot cm^{-3}$, 100 mL EtOH/CH_2Cl_2 10:90, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 90 mL of CH_2Cl_2, 119.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 100 mL EtOH/CH_2Cl_2 20:80, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 80 mL of CH_2Cl_2, 106.4 g with ρ = 1.33 $g \cdot cm^{-3}$) to provide the nucleoside in 75% yield (**58 mg**).

The reaction took a total of 23.58 h (25 min reaction setup + 5 h reaction time with stirring, 15 h reaction time without stirring + 10 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 80 mL of reaction solvent (80 mL Tris-HCl buffer), corresponding to 1386.7 mL per gram of product, considering the contribution of the starting material 7-methylguanosine hydroiodide from Reaction S6, calculated as

$$\frac{80\ \text{mL}}{0.058\ \text{g}} + 0.191 * \frac{17.86\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 7-methylguanosine hydroiodide of 1.7 (Reaction S6), the preparation of **2b** had a sEF of 8.9, calculated as

$$\mathrm{sEF} = \frac{0.037 + 0.191 + 0.191 * 1.7 + 0.02 + 0.00016 + 0.00016 - \mathbf{0.058}}{\mathbf{0.058}}$$

and (considering the cEF of the starting material of 293) a cEF of 8933, calculated as

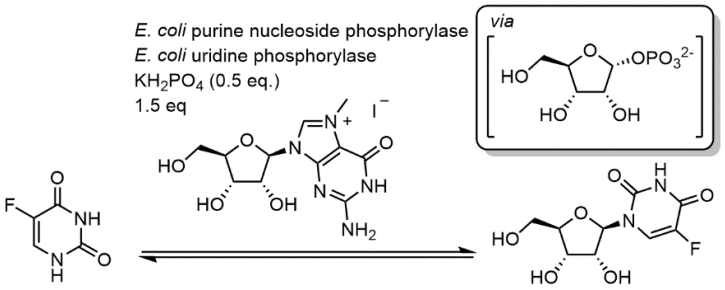
$$\mathrm{cEF} = \frac{\begin{array}{c}0.037 + 0.191 + 0.191 * 293 + 0.02 + 0.00016 + 0.00016 + 0.63 + 14 \\ +19.75 + 33.25 + 1.975 + 63.175 + 7.9 + 119.7 + 15.8 + 106.4 + 79.37 \\ \mathbf{-0.058}\end{array}}{\mathbf{0.058}}$$

with combined contributions from reagents (13), inorganics (252), organic solvents (7302) and water (1368), considering the contribution from the starting material 7-methylguanosine hydroiodide.

Reaction N15

Alexeev *et al. BBA-PROTEINS PROTEOM* **2020**, 140292, doi: 10.1016/j.bbapap.2019.140292

Reaction from their Table 2, compound **2d**



The experimental details for this synthesis were provided in the Materials and Methods section of the main text (page 2, compound **2d**). Exact quantities for this compound were not stated (beyond the starting nucleobase and the yield) by referring to the synthesis having taken place "in a similar way" to **2b**. Thus, we assumed the same ratio of materials and the exact same volumes of solutions used. 5-Fluorouracil (80 mg, 0.57 mmol), 7-methylguanosine hydroiodide (363 mg, 0.855 mmol) and KH_2PO_4 (39 mg, 0.29 mmol) were reacted with *E. coli* purine nucleoside phosphorylase (0.16 mg, including only the enzyme weight of the 32 $g \cdot L^{-1}$ stock solution) and *E. coli* uridine phosphorylase (0.16 mg, amount not stated, we assumed an equal quantity to the purine nucleoside phosphorylase) in 50 mM Tris-HCl buffer (80 mL, 80 g assuming ρ = 1.00 $g \cdot cm^{-3}$; with *630 mg* of salt, calculated with a molecular weight of 157.6 $g \cdot mol^{-1}$, and *79.37 g* of water [3]) for 20 h. After the reaction, the mixture was filtered and the filtrate was washed with water (15 mL, 15 g with ρ = 1.00 $g \cdot cm^{-3}$). Evaporation of the solvent via coevaporation with EtOH (25 mL, 19.75 g with ρ = 0.79 $g \cdot cm^{-3}$) yielded a crude product which was purified by chromatography on silica gel (using 20 mL, 14 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 25 mL of CH_2Cl_2, 33.25 g with ρ = 1.33 $g \cdot cm^{-3}$, 50 mL EtOH/CH_2Cl_2 5:95, which corresponds to 2.5 mL of EtOH, 1.975 g with ρ = 0.79 $g \cdot cm^{-3}$ and 47.5 mL of CH_2Cl_2, 63.175 g with ρ = 1.33 $g \cdot cm^{-3}$, 100 mL EtOH/CH_2Cl_2 10:90, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 90 mL of CH_2Cl_2, 119.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 100 mL EtOH/CH_2Cl_2 20:80, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 80 mL of CH_2Cl_2, 106.4 g with ρ = 1.33 $g \cdot cm^{-3}$) to provide the nucleoside in 76% yield (**122 mg**).

The reaction took a total of 23.58 h (25 min reaction setup + 5 h reaction time with stirring, 15 h reaction time without stirring + 10 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 80 mL of reaction solvent (80 mL Tris-HCl buffer), corresponding to 662.2 mL per gram of product, considering the contribution of the starting material 7-methylguanosine hydroiodide from Reaction S6, calculated as

$$\frac{80\ \text{mL}}{0.122\ \text{g}} + 0.363 * \frac{17.86\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 7-methylguanosine hydroiodide of 1.7 (Reaction S6), the preparation of **2d** had a sEF of 8.0, calculated as

$$\mathrm{sEF} = \frac{0.08 + 0.363 + 0.363 * 1.7 + 0.039 + 0.00016 + 0.00016 - \mathbf{0.122}}{\mathbf{0.122}}$$

and (considering the cEF of the starting material of 293) a cEF of 4661, calculated as

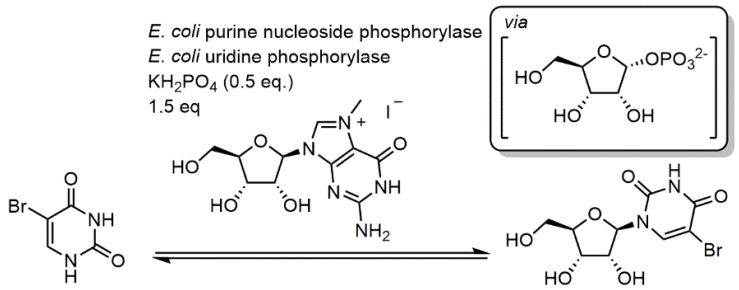
$$\mathrm{cEF} = \frac{\begin{array}{c}0.08 + 0.363 + 0.363 * 293 + 0.039 + 0.00016 + 0.00016 + 0.63 + 14 \\ +19.75 + 33.25 + 1.975 + 63.175 + 7.9 + 119.7 + 15.8 + 106.4 + 79.37 \\ \mathbf{-0.122}\end{array}}{\mathbf{0.122}}$$

with combined contributions from reagents (12), inorganics (120), organic solvents (3882) and water (651), considering the contribution from the starting material 7-methylguanosine hydroiodide.

Reaction N16

Alexeev *et al. BBA-PROTEINS PROTEOM* **2020**, 140292, doi: 10.1016/j.bbapap.2019.140292

Reaction from their Table 2, compound **2f**



The experimental details for this synthesis were provided in the Materials and Methods section of the main text (page 2, compound **2f**). Exact quantities for this compound were not stated (beyond the starting nucleobase and the yield) by referring to the synthesis having taken place "in a similar way" to **2b**. Thus, we assumed the same ratio of materials and the exact same volumes of solutions used. 5-Bromouracil (50 mg, 0.26 mmol), 7-methylguanosine hydroiodide (166 mg, 0.39 mmol) and KH_2PO_4 (18 mg, 0.13 mmol) were reacted with *E. coli* purine nucleoside phosphorylase (0.16 mg, including only the enzyme weight of the 32 $g \cdot L^{-1}$ stock solution) and *E. coli* uridine phosphorylase (0.16 mg, amount not stated, we assumed an equal quantity to the purine nucleoside phosphorylase) in 50 mM Tris-HCl buffer (80 mL, 80 g assuming ρ = 1.00 $g \cdot cm^{-3}$; with *630 mg* of salt, calculated with a molecular weight of 157.6 $g \cdot mol^{-1}$, and *79.37 g* of water [3]) for 20 h. After the reaction, the mixture was filtered and the filtrate was washed with water (15 mL, 15 g with ρ = 1.00 $g \cdot cm^{-3}$). Evaporation of the solvent via coevaporation with EtOH (25 mL, 19.75 g with ρ = 0.79 $g \cdot cm^{-3}$) yielded a crude product which was purified by chromatography on silica gel (using 20 mL, 14 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 25 mL of CH_2Cl_2, 33.25 g with ρ = 1.33 $g \cdot cm^{-3}$, 50 mL EtOH/CH_2Cl_2 5:95, which corresponds to 2.5 mL of EtOH, 1.975 g with ρ = 0.79 $g \cdot cm^{-3}$ and 47.5 mL of CH_2Cl_2, 63.175 g with ρ = 1.33 $g \cdot cm^{-3}$, 100 mL EtOH/CH_2Cl_2 10:90, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 90 mL of CH_2Cl_2, 119.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 100 mL EtOH/CH_2Cl_2 20:80, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 80 mL of CH_2Cl_2, 106.4 g with ρ = 1.33 $g \cdot cm^{-3}$) to provide the nucleoside in 84% yield (**70 mg**).

The reaction took a total of 23.58 h (25 min reaction setup + 5 h reaction time with stirring, 15 h reaction time without stirring + 10 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 80 mL of reaction solvent (80 mL Tris-HCl buffer), corresponding to 1145.8 mL per gram of product, considering the contribution of the starting material 7-methylguanosine hydroiodide from Reaction S6, calculated as

$$\frac{80\ \text{mL}}{0.07\ \text{g}} + 0.166 * \frac{17.86\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 7-methylguanosine hydroiodide of 1.7 (Reaction S6), the preparation of **2f** had a sEF of 6.4, calculated as

$$\mathrm{sEF} = \frac{0.05 + 0.166 + 0.166 * 1.7 + 0.018 + 0.00016 + 0.00016 - \mathbf{0.07}}{\mathbf{0.07}}$$

and (considering the cEF of the starting material of 293) a cEF of 7296, calculated as

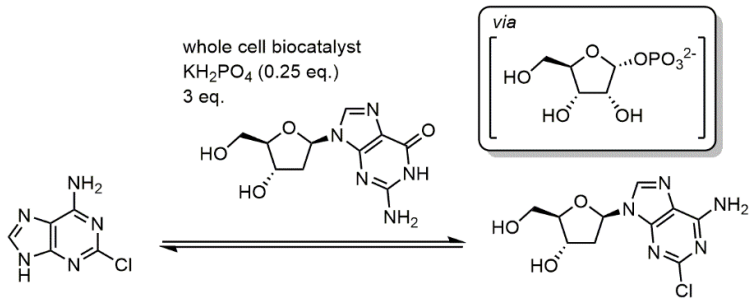
$$\mathrm{cEF} = \frac{\begin{array}{c}0.05 + 0.166 + 0.166 * 293 + 0.018 + 0.00016 + 0.00016 + 0.63 + 14 \\ +19.75 + 33.25 + 1.975 + 63.175 + 7.9 + 119.7 + 15.8 + 106.4 + 79.37 \\ -\mathbf{0.07}\end{array}}{\mathbf{0.07}}$$

with combined contributions from reagents (10), inorganics (209), organic solvents (5947) and water (1134), considering the contribution from the starting material 7-methylguanosine hydroiodide.

Reaction N17

Barai *et al. HCA* **2002**, 1901–1908, doi:10.1002/1522-2675(200207)85:7<1901::AID-HLCA1901>3.0.CO;2-C

Reaction from their Table 1, compound **4**



The experimental details for this synthesis were provided in the Experimental Part of the main text (page 6, compound **4**) and in Table 1. 2-Chloroadenine (1.7 g, 10 mmol), 2'-deoxyguanosine (8.0 g, 30 mmol) and GA-*E. coli* BMT 4D/1A whole cell biocatalyst with nucleoside phosphorylase activity (200 mg) were reacted in as a heterogenous mixture in 10 mM KH_2PO_4 buffer (250 mL, 250 g assuming ρ = 1.00 g·cm^{-3}; with *341 mg* of salt, calculated with a molecular weight of 136.1 g·mol^{-1}, and *249.659 g* of water [3]) for 4 h. Precipitation at 4 °C for 18 h, filtration of the mixture, washing of the filtrate with water (80 mL, 80 g with ρ = 1.00 g·cm^{-3}) provided a crude product upon drying. Purification by chromatography on silica gel (using *198 g* of silica gel and 4.95 L of *MeOH/CH_2Cl_2 5:95*, as the average of a linear gradient from 0–10% MeOH, for an assumed weight of 9.9 g of crude product, which corresponds to 247.5 mL of MeOH, *195.525 g* with ρ = 0.79 g·cm^{-3} and 4.703 L of CH_2Cl_2, *6254.325 g* with ρ = 1.33 g·cm^{-3}) and recrystallization from EtOH (23 mL for 2.3 g of crude product, *18.17 g* with ρ = 0.79 g·cm^{-3}) afforded the nucleoside in 81% yield (**2.3 g**).

The reaction took a total of 27.42 h (15 min reaction setup + 4h reaction time + 18 h precipitation + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying) and consumed of 250 mL of reaction solvent (250 mL of buffer), corresponding to 108.7 mL per gram of product.

Thus, the preparation of **4** had a sEF of 3.5, calculated as

$$\mathrm{sEF} = \frac{1.7 + 8 + 0.2 + 0.341 - \mathbf{2.3}}{\mathbf{2.3}}$$

and a cEF of 3045, calculated as

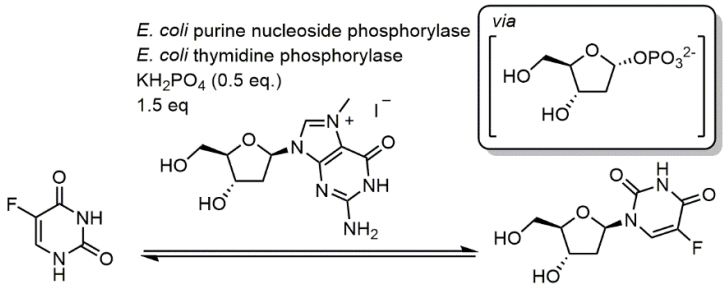
$$\mathrm{cEF} = \frac{1.7 + 8 + 0.2 + 0.341 + 198 + 195.525 + 6254.325 + 18.17 + 249.659 + 80 - \mathbf{2.3}}{\mathbf{2.3}}$$

with contributions from reagents (4), inorganics (86), organic solvents (2812) and water (143).

Reaction N18

Drenichev *et al. Adv. Synth. Catal.* **2018**, *360*, 305–312, doi: 10.1002/adsc.201701005

Reaction from their Table 2, 5-fluoro-2'-deoxyuridine (no compound number given)



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 6, 5-fluoro-2'-deoxyuridine) and Table 2 (page 4). 5-Fluorouracil (227 mg, 1.75 mmol), 7-methyl-2'-deoxyguanosine hydroiodide (1.074 g, 2.62 mmol) and KH_2PO_4 (119 mg, 0.875 mmol) were reacted with *E. coli* purine nucleoside phosphorylase (0.32 mg, including only the enzyme weight of the 32 $g \cdot L^{-1}$ stock solution) and *E. coli* thymidine phosphorylase (0.02 mg, including only the enzyme weight of the 1.7 $g \cdot L^{-1}$ stock solution) in 50 mM Tris-HCl buffer (350 mL, 350 g assuming ρ = 1.00 $g \cdot cm^{-3}$; with *2.758 g* of salt, calculated with a molecular weight of 157.6 $g \cdot mol^{-1}$, and *347.242 g* of water) for 18 h. After the reaction the mixture was filtered repeatedly, concentrated via coevaporation with EtOH (150 mL, 118.5 g with ρ = 0.79 $g \cdot cm^{-3}$) to yield a crude product which was subjected to chromatography on silica gel (using 170 mL, 119 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 15:85, which corresponds to 30 mL of EtOH, 23.7 g with ρ = 0.79 $g \cdot cm^{-3}$ and 170 mL of CH_2Cl_2, 226.1 g with ρ = 1.33 $g \cdot cm^{-3}$) and a second purification step on silica gel (using 50 mL, 35 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$) to provide the nucleoside in 81% yield (**349 mg**).

The reaction took a total of 24.25 h (25 min reaction setup + 18 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 350 mL of reaction solvent (350 mL buffer), corresponding to 1026.2 mL per gram of product, considering the contribution of the starting material 2'-deoxy-7-methylguanosine hydroiodide from Reaction S7, calculated as

$$\frac{350\ \mathrm{mL}}{0.349\ \mathrm{g}} + 1.074 * \frac{21.74\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 2'-deoxy-7-methylguanosine hydroiodide of 7.0 (Reaction S7), the preparation of 5-fluoro-2'-deoxyuridine had a sEF of 24.6, calculated as

$$\mathrm{sEF} = \frac{0.227 + 1.074 + 1.074 * 7 + 0.119 + 0.00032 + 0.00002 - \mathbf{0.349}}{\mathbf{0.349}}$$

and (considering the cEF of the starting material of 249) a cEF of 6225, calculated as

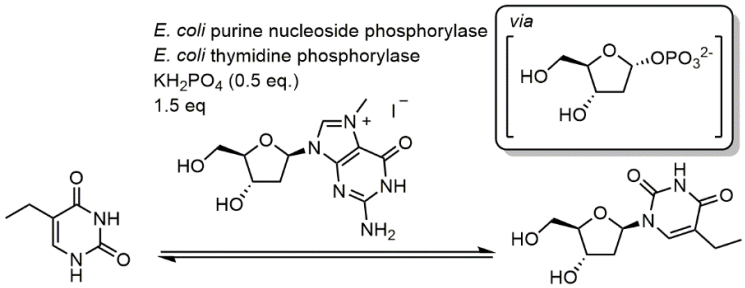
$$\mathrm{cEF} = \frac{\begin{array}{c}0.227 + 1.074 + 1.074 * 249 + 0.119 + 0.00032 + 0.00002 + 2.758 + 119 + 35 \\ +118.5 + 7.9 + 252.7 + 15.8 + 239.4 + 23.7 + 226.1 + 7.9 + 252.7 + 15.8 + 239.4 + 347.242 \\ -\mathbf{0.349}\end{array}}{\mathbf{0.349}}$$

with combined contributions from reagents (29), inorganics (449), organic solvents (4759) and water (995), considering the contribution from the starting material 2'-deoxy-7-methylguanosine hydroiodide.

Reaction N19

Drenichev *et al. Adv. Synth. Catal.* **2018**, *360*, 305–312, doi: 10.1002/adsc.201701005

Reaction from their Table 2, 5-ethyl-2'-deoxyuridine (no compound number given)



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 7, 5-ethyl-2'-deoxyuridine) and Table 2 (page 4). 5-Ethyluracil (245 mg, 1.75 mmol), 7-methyl-2'-deoxyguanosine hydroiodide (1.074 g, 2.62 mmol) and KH_2PO_4 (119 mg, 0.875 mmol) were reacted with *E. coli* purine nucleoside phosphorylase (0.32 mg, including only the enzyme weight of the 32 $g \cdot L^{-1}$ stock solution) and *E. coli* thymidine phosphorylase (0.02 mg, including only the enzyme weight of the 1.7 $g \cdot L^{-1}$ stock solution) in 50 mM Tris-HCl buffer (350 mL, 350 g assuming ρ = 1.00 $g \cdot cm^{-3}$; with *2.758 g* of salt, calculated with a molecular weight of 157.6 $g \cdot mol^{-1}$, and *347.242 g* of water) for 18 h. After the reaction the mixture was filtered repeatedly, concentrated via coevaporation with EtOH (150 mL, 118.5 g with ρ = 0.79 $g \cdot cm^{-3}$) to yield a crude product which was subjected to chromatography on silica gel (using 170 mL, 119 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 15:85, which corresponds to 30 mL of EtOH, 23.7 g with ρ = 0.79 $g \cdot cm^{-3}$ and 170 mL of CH_2Cl_2, 226.1 g with ρ = 1.33 $g \cdot cm^{-3}$) and a second purification step on silica gel (using 50 mL, 35 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$) to provide the nucleoside in 81% yield (**363 mg**).

The reaction took a total of 24.25 h (25 min reaction setup + 18 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 350 mL of reaction solvent (350 mL buffer), corresponding to 987.5 mL per gram of product, considering the contribution of the starting material 2'-deoxy-7-methylguanosine hydroiodide from Reaction S7, calculated as

$$\frac{350\ \mathrm{mL}}{0.363\ \mathrm{g}} + 1.074 * \frac{21.74\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 2'-deoxy-7-methylguanosine hydroiodide of 7.0 (Reaction S7), the preparation of 5-ethyl-2'-deoxyuridine had a sEF of 23.7, calculated as

$$\mathrm{sEF} = \frac{0.245 + 1.074 + 1.074 * 7 + 0.119 + 0.00032 + 0.00002 - \mathbf{0.363}}{\mathbf{0.363}}$$

and (considering the cEF of the starting material of 249) a cEF of 5985, calculated as

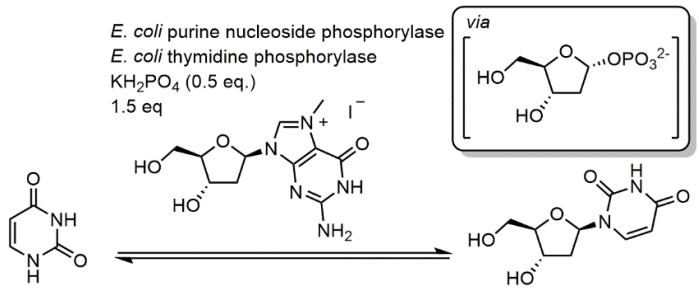
$$\mathrm{cEF} = \frac{\begin{array}{c}0.245 + 1.074 + 1.074 * 249 + 0.119 + 0.00032 + 0.00002 + 2.758 + 119 + 35 \\ +118.5 + 7.9 + 252.7 + 15.8 + 239.4 + 23.7 + 226.1 + 7.9 + 252.7 + 15.8 + 239.4 + 347.242 \\ -\mathbf{0.363}\end{array}}{\mathbf{0.363}}$$

with combined contributions from reagents (28), inorganics (432), organic solvents (4575) and water (957), considering the contribution from the starting material 2'-deoxy-7-methylguanosine hydroiodide.

Reaction N20

Drenichev *et al. Adv. Synth. Catal.* **2018**, *360*, 305–312, doi: 10.1002/adsc.201701005

Reaction from their Table 2, 2'-deoxyuridine (no compound number given)



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 7, 2'-deoxyuridine) and Table 2 (page 4). Uracil (196 mg, 1.75 mmol), 7-methyl-2'-deoxyguanosine hydroiodide (1.074 g, 2.62 mmol) and KH_2PO_4 (119 mg, 0.875 mmol) were reacted with *E. coli* purine nucleoside phosphorylase (0.32 mg, including only the enzyme weight of the 32 $g \cdot L^{-1}$ stock solution) and *E. coli* thymidine phosphorylase (0.02 mg, including only the enzyme weight of the 1.7 $g \cdot L^{-1}$ stock solution) in 50 mM Tris-HCl buffer (350 mL, 350 g assuming ρ = 1.00 $g \cdot cm^{-3}$; with *2.758 g* of salt, calculated with a molecular weight of 157.6 $g \cdot mol^{-1}$, and *347.242 g* of water) for 18 h. After the reaction the mixture was filtered repeatedly, concentrated via coevaporation with EtOH (150 mL, 118.5 g with ρ = 0.79 $g \cdot cm^{-3}$) to yield a crude product which was subjected to chromatography on silica gel (using 170 mL, 119 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 15:85, which corresponds to 30 mL of EtOH, 23.7 g with ρ = 0.79 $g \cdot cm^{-3}$ and 170 mL of CH_2Cl_2, 226.1 g with ρ = 1.33 $g \cdot cm^{-3}$) and a second purification step on silica gel (using 50 mL, 35 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$) to provide the nucleoside in 80% yield (**319 mg**).

The reaction took a total of 24.25 h (25 min reaction setup + 18 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 350 mL of reaction solvent (350 mL buffer), corresponding to 1120.5 mL per gram of product, considering the contribution of the starting material 2'-deoxy-7-methylguanosine hydroiodide from Reaction S7, calculated as

$$\frac{350\ \mathrm{mL}}{0.319\ \mathrm{g}} + 1.074 * \frac{21.74\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 2'-deoxy-7-methylguanosine hydroiodide of 7.0 (Reaction S7), the preparation of 2'-deoxyuridine had a sEF of 26.9, calculated as

$$\mathrm{sEF} = \frac{0.196 + 1.074 + 1.074 * 7 + 0.119 + 0.00032 + 0.00002 - \mathbf{0.319}}{\mathbf{0.319}}$$

and (considering the cEF of the starting material of 249) a cEF of 6810, calculated as

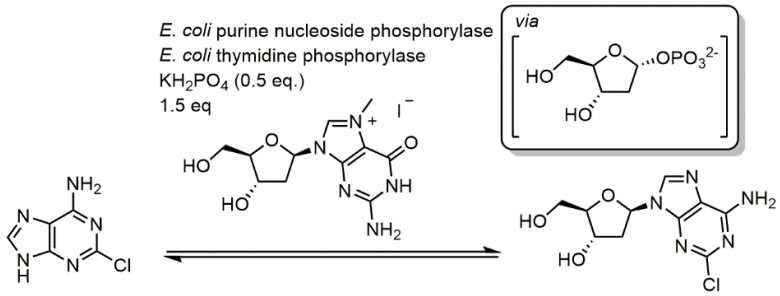
$$\mathrm{cEF} = \frac{\begin{array}{c}0.196 + 1.074 + 1.074 * 249 + 0.119 + 0.00032 + 0.00002 + 2.758 + 119 + 35 \\ +118.5 + 7.9 + 252.7 + 15.8 + 239.4 + 23.7 + 226.1 + 7.9 + 252.7 + 15.8 + 239.4 + 347.242 \\ -\mathbf{0.319}\end{array}}{\mathbf{0.319}}$$

with combined contributions from reagents (31), inorganics (491), organic solvents (5297) and water (1089), considering the contribution from the starting material 2'-deoxy-7-methylguanosine hydroiodide.

Reaction N21

Drenichev *et al. Adv. Synth. Catal.* **2018**, *360*, 305–312, doi: 10.1002/adsc.201701005

Reaction from their Table 2, 2-chloro-2'-deoxyadenosine (no compound number given)



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 7, 2-chloro-2'-deoxyadenosine) and Table 2 (page 4). 2-Chloroadenine (21 mg, 0.124 mmol), 7-methyl-2'-deoxyguanosine hydroiodide (76 mg, 0.186 mmol) and KH_2PO_4 (8 mg, 0.062 mmol) were reacted with *E. coli* purine nucleoside phosphorylase (0.32 mg, including only the enzyme weight of the 32 g·L^{-1} stock solution) in 50 mM Tris-HCl buffer (150 mL, 150 g assuming ρ = 1.00 g·cm^{-3}; with *1.182 g* of salt, calculated with a molecular weight of 157.6 g·mol^{-1}, and *148.818 g* of water) for 144 h. After the reaction the mixture was filtered repeatedly and concentrated via coevaporation with EtOH (30 mL, 23.7 g with ρ = 0.79 g·cm^{-3}) to yield a crude product which was subjected to chromatography on silica gel (using 6.5 mL, 4.55 g of silica gel with ρ = 0.70 g·cm^{-3}, 100 mL EtOH/CH_2Cl_2 5:95, which corresponds to 5 mL of EtOH, 3.95 g with ρ = 0.79 g·cm^{-3} and 95 mL of CH_2Cl_2, 126.35 g with ρ = 1.33 g·cm^{-3}, 100 mL EtOH/CH_2Cl_2 10:90, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 g·cm^{-3} and 90 mL of CH_2Cl_2, 119.7 g with ρ = 1.33 g·cm^{-3}) to provide the nucleoside in 70% yield (**25 mg**).

The reaction took a total of 147.75 h (25 min reaction setup + 144 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 150 mL of reaction solvent (150 mL buffer), corresponding to 6001.7 mL per gram of product, considering the contribution of the starting material 2'-deoxy-7-methylguanosine hydroiodide from Reaction S7, calculated as

$$\frac{150\ \text{mL}}{0.025\ \text{g}} + 0.076 * \frac{21.74\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2'-deoxy-7-methylguanosine hydroiodide of 7.0 (Reaction S7), the preparation of 2-chloro-2'-deoxyadenosine had a sEF of 24.5, calculated as

$$\text{sEF} = \frac{0.021 + 0.076 + 0.076 * 7 + 0.008 + 0.00032 - \mathbf{0.025}}{\mathbf{0.025}}$$

and (considering the cEF of the starting material of 249) a cEF of 18206, calculated as

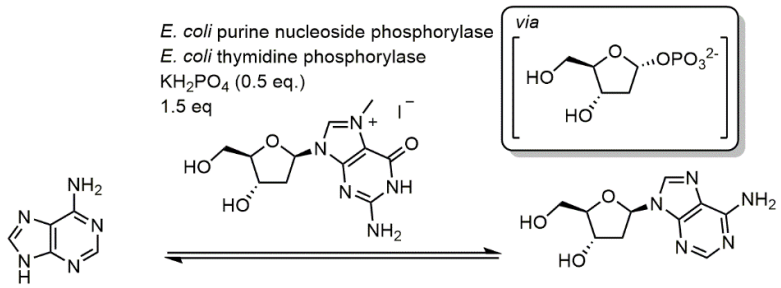
$$\text{cEF} = \frac{\begin{array}{c}0.021 + 0.076 + 0.076 * 249 + 0.008 + 0.00032 + 1.182 + 4.55 \\ +23.7 + 3.95 + 126.35 + 7.9 + 119.7 + 148.818 \\ -\mathbf{0.025}\end{array}}{\mathbf{0.025}}$$

with combined contributions from reagents (29), inorganics (229), organic solvents (12003) and water (5953), considering the contribution from the starting material 2'-deoxy-7-methylguanosine hydroiodide.

Reaction N22

Drenichev *et al. Adv. Synth. Catal.* **2018**, *360*, 305–312, doi: 10.1002/adsc.201701005

Reaction from their Table 2, 2'-deoxyadenosine (no compound number given)



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 7, 2'-deoxyadenosine) and Table 2 (page 4). Adenine (236 mg, 1.75 mmol), 7-methyl-2'-deoxyguanosine hydroiodide (1.074 g, 2.62 mmol) and KH_2PO_4 (119 mg, 0.875 mmol) were reacted with *E. coli* purine nucleoside phosphorylase (0.32 mg, including only the enzyme weight of the 32 $g \cdot L^{-1}$ stock solution) in 50 mM Tris-HCl buffer (350 mL, 350 g assuming ρ = 1.00 $g \cdot cm^{-3}$; with *2.758 g* of salt, calculated with a molecular weight of 157.6 $g \cdot mol^{-1}$, and *347.242 g* of water) for 18 h. After the reaction the mixture was filtered repeatedly, concentrated via coevaporation with EtOH (150 mL, 118.5 g with ρ = 0.79 $g \cdot cm^{-3}$) to yield a crude product which was subjected to chromatography on silica gel (using 170 mL, 119 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 15:85, which corresponds to 30 mL of EtOH, 23.7 g with ρ = 0.79 $g \cdot cm^{-3}$ and 170 mL of CH_2Cl_2, 226.1 g with ρ = 1.33 $g \cdot cm^{-3}$) and a second purification step on silica gel (using 50 mL, 35 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$) to provide the nucleoside in 93% yield (**407 mg**).

The reaction took a total of 24.25 h (25 min reaction setup + 18 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 350 mL of reaction solvent (350 mL buffer), corresponding to 883.3 mL per gram of product, considering the contribution of the starting material 2'-deoxy-7-methylguanosine hydroiodide from Reaction S7, calculated as

$$\frac{350\ \mathrm{mL}}{0.407\ \mathrm{g}} + 1.074 * \frac{21.74\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 2'-deoxy-7-methylguanosine hydroiodide of 7.0 (Reaction S7), the preparation of 2'-deoxyadenosine had a sEF of 21.0, calculated as

$$\mathrm{sEF} = \frac{0.236 + 1.074 + 1.074 * 7 + 0.119 + 0.00032 - \mathbf{0.407}}{\mathbf{0.407}}$$

and (considering the cEF of the starting material of 249) a cEF of 5337, calculated as

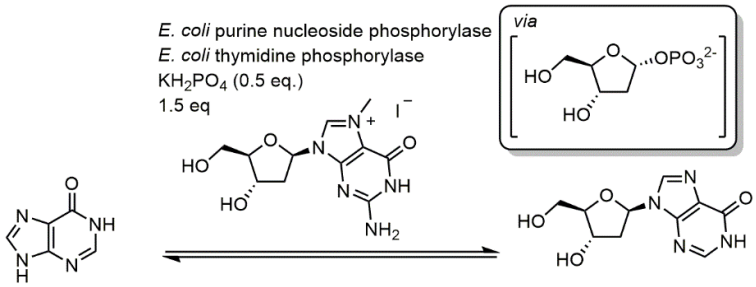
$$\mathrm{cEF} = \frac{\begin{array}{c}0.236 + 1.074 + 1.074 * 249 + 0.119 + 0.00032 + 2.758 + 119 + 35 \\ +118.5 + 7.9 + 252.7 + 15.8 + 239.4 + 23.7 + 226.1 + 7.9 + 252.7 + 15.8 + 239.4 + 347.242 \\ -\mathbf{0.407}\end{array}}{\mathbf{0.407}}$$

with combined contributions from reagents (25), inorganics (385), organic solvents (4081) and water (853), considering the contribution from the starting material 2'-deoxy-7-methylguanosine hydroiodide.

Reaction N23

Drenichev *et al. Adv. Synth. Catal.* **2018**, *360*, 305–312, doi: 10.1002/adsc.201701005

Reaction from their Table 2, 2'-deoxyinosine (no compound number given)



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 8, 2'-deoxyinosine) and Table 2 (page 4). Hypoxanthine (238 mg, 1.75 mmol), 7-methyl-2'-deoxyguanosine hydroiodide (1.074 g, 2.62 mmol) and KH_2PO_4 (119 mg, 0.875 mmol) were reacted with *E. coli* purine nucleoside phosphorylase (0.32 mg, including only the enzyme weight of the 32 $g \cdot L^{-1}$ stock solution) in 50 mM Tris-HCl buffer (350 mL, 350 g assuming ρ = 1.00 $g \cdot cm^{-3}$; with *2.758 g* of salt, calculated with a molecular weight of 157.6 $g \cdot mol^{-1}$, and *347.242 g* of water) for 18 h. After the reaction the mixture was filtered repeatedly, concentrated via coevaporation with EtOH (150 mL, 118.5 g with ρ = 0.79 $g \cdot cm^{-3}$) to yield a crude product which was subjected to chromatography on silica gel (using 170 mL, 119 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 15:85, which corresponds to 30 mL of EtOH, 23.7 g with ρ = 0.79 $g \cdot cm^{-3}$ and 170 mL of CH_2Cl_2, 226.1 g with ρ = 1.33 $g \cdot cm^{-3}$) and a second purification step on silica gel (using 50 mL, 35 g of silica gel with ρ = 0.70 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 5:95, which corresponds to 10 mL of EtOH, 7.9 g with ρ = 0.79 $g \cdot cm^{-3}$ and 190 mL of CH_2Cl_2, 252.7 g with ρ = 1.33 $g \cdot cm^{-3}$, 200 mL EtOH/CH_2Cl_2 10:90, which corresponds to 20 mL of EtOH, 15.8 g with ρ = 0.79 $g \cdot cm^{-3}$ and 180 mL of CH_2Cl_2, 239.4 g with ρ = 1.33 $g \cdot cm^{-3}$) to provide the nucleoside in 95% yield (**419 mg**).

The reaction took a total of 24.25 h (25 min reaction setup + 18 h reaction time + 20 min workup + 30 min drying + 2 h purification + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 350 mL of reaction solvent (350 mL buffer), corresponding to 858.7 mL per gram of product, considering the contribution of the starting material 2'-deoxy-7-methylguanosine hydroiodide from Reaction S7, calculated as

$$\frac{350\ \text{mL}}{0.419\ \text{g}} + 1.074 * \frac{21.74\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2'-deoxy-7-methylguanosine hydroiodide of 7.0 (Reaction S7), the preparation of 2'-deoxyguanosine had a sEF of 20.4, calculated as

$$\mathrm{sEF} = \frac{0.238 + 1.074 + 1.074 * 7 + 0.119 + 0.00032 - \mathbf{0.419}}{\mathbf{0.419}}$$

and (considering the cEF of the starting material of 249) a cEF of 5185, calculated as

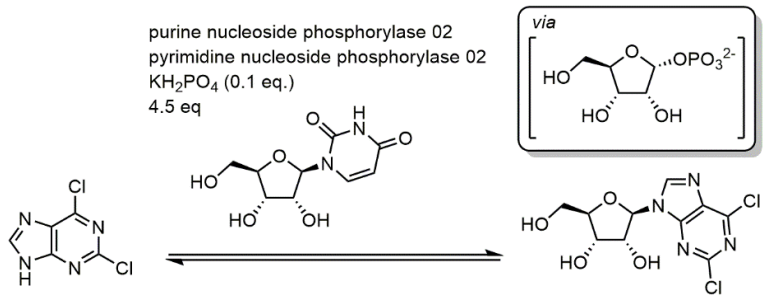
$$\mathrm{cEF} = \frac{\begin{array}{c}0.238 + 1.074 + 1.074 * 249 + 0.119 + 0.00032 + 2.758 + 119 + 35 \\ +118.5 + 7.9 + 252.7 + 15.8 + 239.4 + 23.7 + 226.1 + 7.9 + 252.7 + 15.8 + 239.4 + 347.242 \\ -\mathbf{0.419}\end{array}}{\mathbf{0.419}}$$

with combined contributions from reagents (24), inorganics (374), organic solvents (3964) and water (829), considering the contribution from the starting material 2'-deoxy-7-methylguanosine hydroiodide.

Reaction N24

Yehia *et al. Molecules* **2020**, *25*, 934, doi: 10.3390/molecules25040934

Reaction from their Scheme 1, compound **3a**



The experimental details for this synthesis were provided in the main text (Figure 1, page 4), the Materials and Methods section of the main text (page 7) and the Supplementary Material (page 1 and 3, compound **3a**). 2,6-Dichloropurine (5 mM in 50 mL, corresponding to 0.25 mmol, 47 mg calculated from a molecular weight of 189.0 g·mol^{-1}), uridine (22.5 mM in 50 mL, corresponding to 1.1 mmol, 269 mg calculated from a molecular weight of 244.2 g·mol^{-1}) and phosphate (0.5 mM in 50 mL, corresponding to 0.025 mmol, 4 mg calculated from a molecular weight of 174.2 g·mol^{-1} of K_2HPO_4) were reacted with purine nucleoside phosphorylase 02 (0.1 g·L^{-1} in 50 mL, 5 mg) and pyrimidine nucleoside phosphorylase 02 (0.1 g·L^{-1} in 50 mL, 5 mg) in water (50 mL, 50 g with ρ = 1.00 g·cm^{-3}) for 6h. Upon reaction completion, the enzymes were filtered from the solution and the reaction mixture was subjected to preparative HPLC (using 165 mL of MeCN/water 12.5:87.5, as the average of a linear gradient from 3–22% MeOH, for an assumed weight of 330 mg of crude product, which corresponds to 20.625 mL of MeCN, *16.294 g* with ρ = 0.79 g·cm^{-3} and 144.375 mL of water, *144.375 g* with ρ = 1.00 g·cm^{-3}) to obtain the nucleoside in 49% yield (**34 mg**).

The reaction took a total of 26.5 h (25 min reaction setup + 6h reaction time + 5 min workup + 2 h purification + 18 h lyophilization) and consumed a total of 50 mL of reaction solvent (50 mL of water), corresponding to 1470.6 mL per gram of product.

Thus, the preparation of **3a** had a sEF of 8.7, calculated as

$$\mathrm{sEF} = \frac{0.047 + 0.269 + 0.004 + 0.005 + 0.005 - \mathbf{0.034}}{\mathbf{0.034}}$$

and a cEF of 6205, calculated as

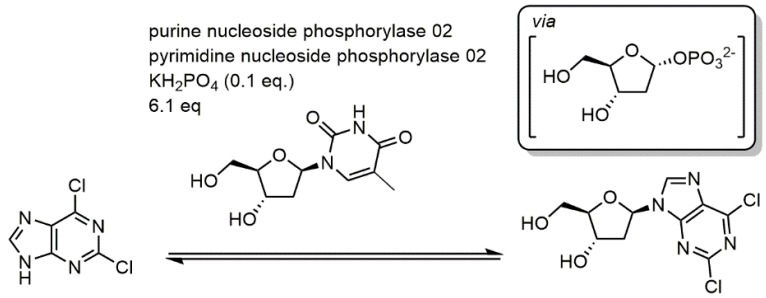
$$\mathrm{cEF} = \frac{0.047 + 0.269 + 0.004 + 0.005 + 0.005 + 16.294 + 50 + 144.375 - \mathbf{0.034}}{\mathbf{0.034}}$$

with contributions from reagents (10), inorganics (0), organic solvents (479) and water (5717).

Reaction N25

Yehia *et al. Molecules* **2020**, *25*, 934, doi: 10.3390/molecules25040934

Reaction from their Scheme 1, compound **3b**



The experimental details for this synthesis were provided in the main text (Figure 1, page 4), the Materials and Methods section of the main text (page 7) and the Supplementary Material (page 1 and 3, compound **3b**). 2,6-Dichloropurine (5 mM in 50 mL, corresponding to 0.25 mmol, 47 mg calculated from a molecular weight of 189 g·mol^{-1}), thymidine (30.5 mM in 50 mL, corresponding to 1.53 mmol, 371 mg calculated from a molecular weight of 242.2 g·mol^{-1}) and phosphate (0.5 mM in 50 mL, corresponding to 0.025 mmol, 4 mg calculated from a molecular weight of 174.2 g·mol^{-1} of K_2HPO_4) were reacted with purine nucleoside phosphorylase 02 (0.1 g·L^{-1} in 50 mL, 5 mg) and pyrimidine nucleoside phosphorylase 02 (0.1 g·L^{-1} in 50 mL, 5 mg) in water (50 mL, 50 g with ρ = 1.00 g·cm^{-3}) for 6 h. Upon reaction completion, the enzymes were filtered from the solution and the reaction mixture was subjected to preparative HPLC (using 216 mL of MeCN/water 14:86, as the average of a linear gradient from 3−25% MeOH, for an assumed weight of 432 mg of crude product, which corresponds to 30.24 mL of MeCN, *23.890 g* with ρ = 0.79 g·cm^{-3} and 185.76 mL of water, *185.76 g* with ρ = 1.00 g·cm^{-3}) to obtain the nucleoside in 45% yield (**36 mg**).

The reaction took a total of 26.5 h (25 min reaction setup + 6h reaction time + 5 min workup + 2 h purification + 18 h lyophilization) and consumed a total of 50 mL of reaction solvent (50 mL of water), corresponding to 1388.9 mL per gram of product.

Thus, the preparation of **3b** had a sEF of 11.0, calculated as

$$\mathrm{sEF} = \frac{0.047 + 0.371 + 0.004 + 0.005 + 0.005 - \mathbf{0.036}}{\mathbf{0.036}}$$

and a cEF of 7224, calculated as

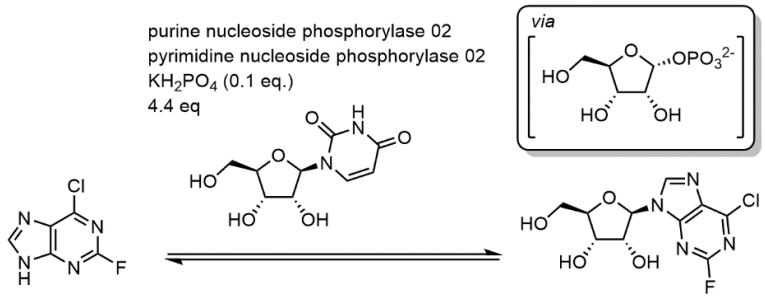
$$\mathrm{cEF} = \frac{0.047 + 0.371 + 0.004 + 0.005 + 0.005 + 23.89 + 50 + 185.76 - \mathbf{0.036}}{\mathbf{0.036}}$$

with contributions from reagents (12), inorganics (0), organic solvents (703) and water (6934).

Reaction N26

Yehia *et al. Molecules* **2020**, *25*, 934, doi: 10.3390/molecules25040934

Reaction from their Scheme 1, compound **3c**



The experimental details for this synthesis were provided in the main text (Figure 1, page 4), the Materials and Methods section of the main text (page 7) and the Supplementary Material (page 1 and 3, compound **3c**). 6-Chloro-2-fluoropurine (5 mM in 50 mL, corresponding to 0.25 mmol, 43 mg calculated from a molecular weight of 172.5 g·mol^{-1}), uridine (22 mM in 50 mL, corresponding to 1.1 mmol, 269 mg calculated from a molecular weight of 244.2 g·mol^{-1}) and phosphate (0.5 mM in 50 mL, corresponding to 0.025 mmol, 4 mg calculated from a molecular weight of 174.2 g·mol^{-1} of K_2HPO_4) were reacted with purine nucleoside phosphorylase 02 (0.1 g·L^{-1} in 50 mL, 5 mg) and pyrimidine nucleoside phosphorylase 02 (0.1 g·L^{-1} in 50 mL, 5 mg) in water (50 mL, 50 g with ρ = 1.00 g·cm^{-3}). Upon reaction completion, the enzymes were filtered from the solution and the reaction mixture was subjected to preparative HPLC (using 163 mL of MeCN/water 12.5:87.5, as the average of a linear gradient from 3–22% MeOH, for an assumed weight of 326 mg of crude product, which corresponds to 20.375 mL of MeCN, *16.096 g* with ρ = 0.79 g·cm^{-3} and 142.625 mL of water, *142.625 g* with ρ = 1.00 g·cm^{-3}) to obtain the nucleoside in 53% yield (**32 mg**).

The reaction took a total of 26.5 h (25 min reaction setup + 6h reaction time + 5 min workup + 2 h purification + 18 h lyophilization) and consumed a total of 50 mL of reaction solvent (50 mL of water), corresponding to 1562.5 mL per gram of product.

Thus, the preparation of **3c** had a sEF of 9.2, calculated as

$$\mathrm{sEF} = \frac{0.043 + 0.269 + 0.004 + 0.005 + 0.005 - \mathbf{0.032}}{\mathbf{0.032}}$$

and a cEF of 6532, calculated as

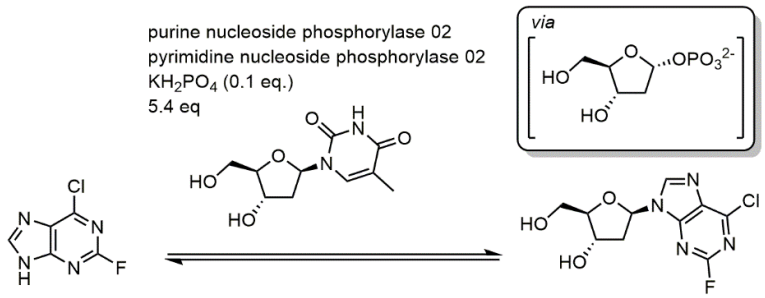
$$\mathrm{cEF} = \frac{0.043 + 0.269 + 0.004 + 0.005 + 0.005 + 16.096 + 50 + 142.625 - \mathbf{0.032}}{\mathbf{0.032}}$$

with contributions from reagents (10), inorganics (0), organic solvents (503) and water (6020).

Reaction N27

Yehia *et al. Molecules* **2020**, *25*, 934, doi: 10.3390/molecules25040934

Reaction from their Scheme 1, compound **3d**



The experimental details for this synthesis were provided in the main text (Figure 1, page 4), the Materials and Methods section of the main text (page 7) and the Supplementary Material (page 1 and 3, compound **3d**). 2,6-Dichloropurine (5 mM in 50 mL, corresponding to 0.25 mmol, 43 mg calculated from a molecular weight of 172.5 g·mol^{-1}), thymidine (27 mM in 50 mL, corresponding to 1.35 mmol, 327 mg calculated from a molecular weight of 242.2 g·mol^{-1}) and phosphate (0.5 mM in 50 mL, corresponding to 0.025 mmol, 4 mg calculated from a molecular weight of 174.2 g·mol^{-1} of K_2HPO_4) were reacted with purine nucleoside phosphorylase 02 (0.1 g·L^{-1} in 50 mL, 5 mg) and pyrimidine nucleoside phosphorylase 02 (0.1 g·L^{-1} in 50 mL, 5 mg) in water (50 mL, 50 g with ρ = 1.00 g·cm^{-3}). Upon reaction completion, the enzymes were filtered from the solution and the reaction mixture was subjected to preparative HPLC (using 192 mL of MeCN/water 14:86, as the average of a linear gradient from 3–25% MeOH, for an assumed weight of 384 mg of crude product, which corresponds to 25.88 mL of MeCN, *21.235 g* with ρ = 0.79 g·cm^{-3} and 165.12 mL of water, *165.12 g* with ρ = 1.00 g·cm^{-3}) to obtain the nucleoside in 54% yield (**32 mg**).

The reaction took a total of 26.5 h (25 min reaction setup + 6h reaction time + 5 min workup + 2 h purification + 18 h lyophilization) and consumed a total of 50 mL of reaction solvent (50 mL of water), corresponding to 1562.5 mL per gram of product.

Thus, the preparation of **3d** had a sEF of 9.5, calculated as

$$\mathrm{sEF} = \frac{0.043 + 0.327 + 0.004 + 0.005 + 0.005 - \mathbf{0.032}}{\mathbf{0.032}}$$

and a cEF of 7397, calculated as

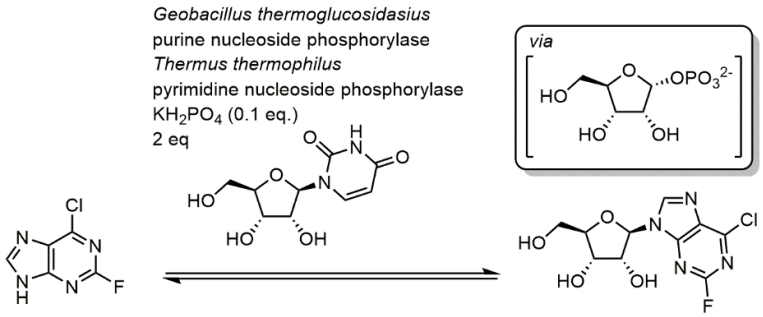
$$\mathrm{cEF} = \frac{0.043 + 0.327 + 0.004 + 0.005 + 0.005 + 21.235 + 50 + 165.12 - \mathbf{0.032}}{\mathbf{0.032}}$$

with contributions from reagents (13), inorganics (0), organic solvents (625) and water (6723).

Reaction N28

Zhou *et al. Adv. Synth. Catal*. **2015**, *357*, 1237–1244, doi: 10.1002/adsc.201400966

Reaction from their Table 4, compound **9**



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 7, compound **9**). 6-Chloro-2-fluoropurine (216 mg, 1.25 mmol) and uridine (610 mg, 2.5 mmol) were reacted with immobilized *Thermus thermophilus* pyrimidine nucleoside phosphorylase (8 mg) and immobilized *Geobacillus thermoglucosidasius* purine nucleoside phosphorylase (15 mg) in 2 mM potassium phosphate buffer (50 mL, 50 g assuming ρ = 1.00 g·cm^{-3}; with 14 mg of salt calculated with a molecular weight of 136.1 g·mol^{-1} and 49.986 g of water) for 20 h. After reaction completion, the immobilized enzymes were removed from the reaction mixture, the nucleoside was obtained upon drying and repeated chromatography on silica gel (using 17.26 g of silica gel and 431.5 mL EtOH/CH_2Cl_2 1:15, for an assumed weight of 863 mg of crude product, which corresponds to 26.969 mL of EtOH, 21.305 g with ρ = 0.79 g·cm^{-3} and 404.531 mL of CH_2Cl_2, 538.027 g with ρ = 1.33 g·cm^{-3}; followed by another chromatography step with 6 g of silica gel and 150 mL ethyl acetate/acetone 7:3, for an assumed weight of 300 mg of crude product, which corresponds to 105 mL of ethyl acetate, 94.5 g with ρ = 0.90 g·cm^{-3} and 45 mL of acetone, 35.1 g with ρ = 0.78 g·cm^{-3}) in 60% yield (**230 mg**).
The reaction took a total of 26 h (25 min reaction setup + 20 h reaction time + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 50 mL of reaction solvent (50 mL buffer), corresponding to 217.4 mL per gram of product.

Thus, the preparation of **9** had a sEF of 2.8, calculated as

$$\mathrm{sEF} = \frac{0.216 + 0.610 + 0.008 + 0.015 + 0.014 - \mathbf{0.230}}{\mathbf{0.230}}$$

and a cEF of 3317, calculated as

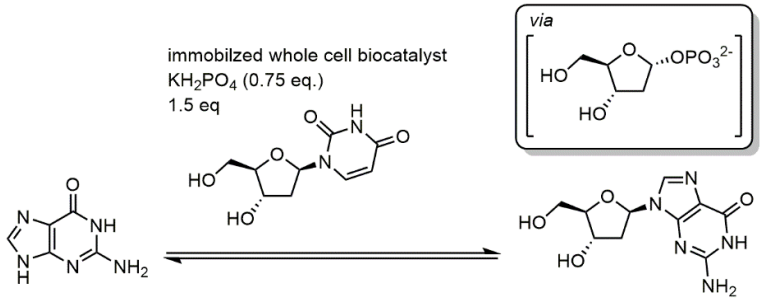
$$\mathrm{cEF} = \frac{0.216 + 0.610 + 0.008 + 0.015 + 0.014 + 17.26 + 6 + 21.305 + 538.027 + 94.5 + 35.1 + 50 - \mathbf{0.230}}{\mathbf{0.230}}$$

with contributions from reagents (4), inorganics (194), organic solvents (2432) and water (217).

Reaction N29

Zuffi *et al. Biocatalysis and Biotransformation* **2004**, *22*, 25–33, doi: 10.1080/10242420310001648551

Reaction from their main text, 2'-deoxyguanosine (no compound number given)



The experimental details for this synthesis were provided in the Materials and Methods section of the main text (page 4, 2'-deoxyguanosine). Guanine (6 g, 40 mmol) in 30% NaOH (50 mL, 65 g assuming ρ = 1.30 g·cm^{-3}, corresponding to 15 g NaOH, 0.2 mol, and 50 g of water) was added to 2'deoxyuridine (12.1 g, 60 mmol) and immobilized biocatalyst (50 g) in 30 mM phosphate buffer (900 mL, 900 g assuming ρ = 1.00 g·cm^{-3}; with 3.675 g of salt calculated with a molecular weight of 136.1 g·mol^{-1} and 896.325 g of water) for 2.5 h. pH control was achieved with 20% HCl (amount not stated, we assumed an equal molar amount of HCl to NaOH, thus 0.2 mol, which corresponds to 30.77 mL assuming a concentration of 6.5 M for 20% HCl and equals 33.847 g 20% HCl with ρ = 1.10 g·cm^{-3}). The mixture was filtered, and the filtrate was collected to recrystallize the nucleoside from water (60 mL, 60 g with ρ = 1.00 g·cm^{-3} for an assume weight of 6 g of crude product). Isolated yield was not stated, so we assumed 50% (**5.66 g** calculated from a molecular weight of 283.2 g·mol^{-1}) based on the bioconversion yield of 72%.

The reaction took a total of 5.5 h (20 min reaction setup + 2.5 h of reaction time + 10 min workup + 2 h recrystallization + 30 min drying) and consumed a total of 980.77 mL of reaction solvent (900 mL buffer + 50 mL NaOH + 30.77 mL HCl), corresponding to 173.3 mL per gram of product.

Thus, the preparation of 2'-deoxyguanosine had a sEF of 11.8, calculated as

$$\mathrm{sEF} = \frac{6 + 12.1 + 50 + 3.675 - \mathbf{5.6}}{\mathbf{5.6}}$$

and a cEF of 200, calculated as

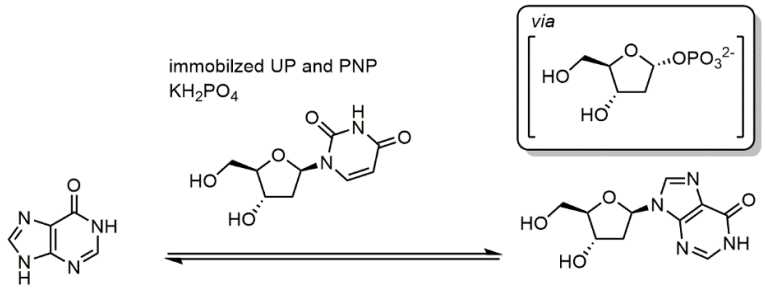
$$\mathrm{cEF} = \frac{6 + 12.1 + 50 + 3.675 + 15 + 50 + 896.325 + 33.847 + 60 - \mathbf{5.6}}{\mathbf{5.6}}$$

with contributions from reagents (13), inorganics (3), organic solvents (0) and water (186).

Reaction N30

Ubiali *et al. Adv. Synth. Catal*. **2004**, *346*, 1361 –1366, doi: 10.1002/adsc.200404019

Reaction from their Scheme 1, 2'-deoxyinosine (no compound number given)



The experimental details for this synthesis were provided in the Materials and Methods section of the main text (page 5, 2'-deoxyinosine). Hypoxanthine (50 mM in 25 mL, 1.25 mmol, 170 mg calculated with a molecular weight of 136.0 g·mol^{-1}) was reacted with 2'-deoxyuridine (570 mg), KH_2PO_4 (68 mg) and immobilized *Bacillus subtilis* uridine phosphorylase and purine nucleoside phosphorylase (amounts not stated, we assumed 5 mg and 5 mg, respectively) in 10 mM K_2CO_3 buffer (50 mL, 50 g assuming ρ = 1.00 g·cm^{-3}; with 66 mg of salt calculated with a molecular weight of 138.2 g·mol^{-1} and 49.933 g of water) for 24 h. The reaction was stopped by filtration of the immobilized enzymes to afford the nucleoside with 85% bioconversion. We assume 90% recovery by preparative HPLC (*using 324 mL MeCN/water 12:88, for an assumed weight of 648 mg of crude product, which corresponds to 38.88 mL of MeCN, 37.715 g with ρ = 0.79 g·cm^{-3} and 293.285 mL of water, 293.285 g with ρ = 1.00 g·cm^{-3}*) which equals a yield of 76% (0.96 mmol, **241 mg** calculated with a molecular weight of 252.2 g·mol^{-1}).

The reaction took a total of 44.5 h (20 min reaction setup + 24 h of reaction time + 10 min workup + 2 h purification + 18 h lyophilization) and consumed a total of 50 mL of reaction solvent (50 mL buffer), corresponding to 207.5 mL per gram of product.

Thus, the preparation of 2'-deoxyinosine had a sEF of 2.8, calculated as

$$\mathrm{sEF} = \frac{0.170 + 0.570 + 0.068 + 0.005 + 0.005 - \mathbf{0.241}}{\mathbf{0.241}}$$

and a cEF of 1584, calculated as

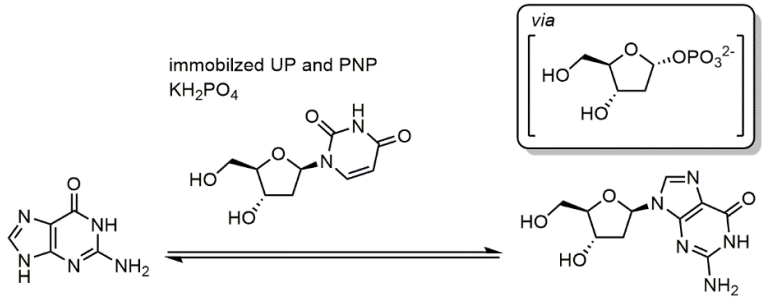
$$\mathrm{cEF} = \frac{0.170 + 0.570 + 0.068 + 0.005 + 0.005 + 0.066 + 37.715 + 49.933 + 293.285 - \mathbf{0.241}}{\mathbf{0.241}}$$

with contributions from reagents (4), inorganics (0), organic solvents (157) and water (1424).

Reaction N31

Ubiali *et al. Adv. Synth. Catal*. **2004**, *346*, 1361 –1366, doi: 10.1002/adsc.200404019

Reaction from their Scheme 1, 2'-deoxyguanosine (no compound number given)



The experimental details for this synthesis were provided in the Materials and Methods section of the main text (page 5, 2'-deoxyinosine). Guanine (50 mM in 25 mL, 1.25 mmol, 189 mg calculated with a molecular weight of 151.1 g·mol^{-1}) was reacted with 2'-deoxyuridine (570 mg), KH_2PO_4 (68 mg) and immobilized *Bacillus subtilis* uridine phosphorylase and purine nucleoside phosphorylase (amounts not stated, we assumed 5 mg and 5 mg, respectively) in 10 mM K_2CO_3 buffer (50 mL, 50 g assuming ρ = 1.00 g·cm^{-3}; with 66 mg of salt calculated with a molecular weight of 138.2 g·mol^{-1} and 49.933 g of water) for 24 h. The reaction was stopped by filtration of the immobilized enzymes to afford the nucleoside upon acidic precipitation in 92% yield (we assume overnight; 1.15 mmol, **307 mg** calculated with a molecular weight of 267.2 g·mol^{-1}).

The reaction took a total of 40.5 h (20 min reaction setup + 24 h of reaction time + 10 min workup + 18 h precipitation) and consumed a total of 50 mL of reaction solvent (50 mL buffer), corresponding to 162.9 mL per gram of product.

Thus, the preparation of 2'-deoxyguanosine had a sEF of 2.0, calculated as

$$\mathrm{sEF} = \frac{0.189 + 0.570 + 0.068 + 0.005 + 0.005 - \mathbf{0.307}}{\mathbf{0.307}}$$

and a cEF of 165, calculated as

$$\mathrm{cEF} = \frac{0.189 + 0.570 + 0.068 + 0.005 + 0.005 + 0.066 + 49.933 - \mathbf{0.307}}{\mathbf{0.307}}$$

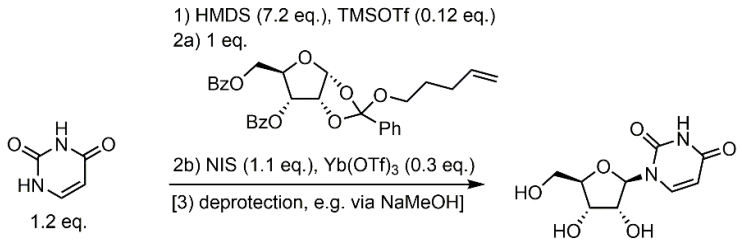
with contributions from reagents (3), inorganics (0), organic solvents (0) and water (163).

***n*-Pentenyl orthoesters**

Reaction N32

Fraser-Reid *et al. Chem. Commun*. **2013**, *49*, 3251–3253, doi: 10.1039/C3CC41036F

Reaction from their Scheme 1, compound **11a**



The experimental details for this synthesis were provided in the main text (Scheme 1, page 2) and in the Supporting Material (page 2 and 3, compound **11a**). Uracil (134 mg, 1.2 mmol) was first silylated neat with bis(trimethylsilyl)amine (7.2 mmol, corresponding to 1.162 g calculated with a molecular weight of 161.4 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.12 mmol, corresponding to 27 mg calculated with a molecular weight of 222.25 g·mol^{-1}) for 2 h. The protected nucleobase was reacted with 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (530 mg, 1 mmol) in MeCN (3 mL, 2.37 g with ρ = 0.79 g·cm^{-3}) for 10 min before adding *N*-iodosuccinimide (1.1 mmol, 248 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and Ytterbium(III) trifluoromethanesulfonate (0.3 mmol, 186 mg calculated with a molecular weight of 620.25 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 4 h. After completion the reaction was quenched with aqueous saturated sodium thiosulfate (5 mL, 6.25 g assuming ρ = 1.25 g·cm^{-3}; with 438 mg of salt with a solubility of 70 g·L^{-1} and 5.813 g of water) and extracted with CH_2Cl_2 (30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}) to provide a crude product upon drying. Column chromatography on silica gel (using *49.84 g* of silica gel and 1.246 L of hexane/ethyl acetate 2:3 for an assumed weight of 2.492 g of crude product, which corresponds to 498.4 mL of hexane, *328.944 g* with ρ = 0.66 g·cm^{-3} and 747.6 L of ethyl acetate, *672.84 g* with ρ = 0.90 g·cm^{-3}) provided the protected nucleoside in 92% yield (511 mg, 0.918 mmol calculated with a molecular weight of 556.5 g·mol^{-1}).

For deprotection we assumed that classic benzoyl deprotection via sodium method was employed. Thus, we assumed the use of the method of Nauš *et al*. (*J. Med. Chem*. **2014**, *57*, 1097–1110, doi: 10.1021/jm4018948) and adjusted the quantities of this method to the above synthesis. The experimental details for this synthesis were provided in the Supplementary Material (page 15, compound **2h**). The protected nucleoside (511 mg, 0.918 mmol) was reacted with sodium methoxide (1 M in MeOH, 4.59 mL, 4.59 mmol, 248 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 3.626 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (6.12 mL, 4.835 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume

4.59 mmol HCl, corresponding to 4.59 mL, *4.682 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 20 mL, *15.8 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 268 mL MeCN/water 12:88, for an assumed weight of 536 mg of crude product, which corresponds to 32.16 mL of MeCN, 25.406 g with ρ = 0.79 g·cm^{-3} and 235.84 mL of water, 235.84 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.817 mmol, **200 mg** calculated with a molecular weight of 244.2 g·mol^{-1}).

The reaction took a total of 33.5 h (15 min reaction setup + 2 h protection + 10 min addition of orthoester + 4 h glycosylation + 15 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 15.71 mL of reaction solvent (3mL MeCN + 2 mL MeCN + 10.71 mL MeOH), corresponding to 157.6 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) from Reaction S9, calculated as

$$\frac{15.71\ \text{mL}}{0.200\ \text{g}} + 0.53 * \frac{149.22\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) of 4.9 (Reaction S9), the preparation of **11a** had a sEF of 24.7, calculated as

$$\text{sEF} = \frac{0.134 + 1.162 + 0.027 + 0.53 + 0.53 * 4.9 + 0.248 + 0.186 + 0.248 - \mathbf{0.2}}{\mathbf{0.2}}$$

and (considering the cEF of the starting material of 2398) a cEF of 13326, calculated as

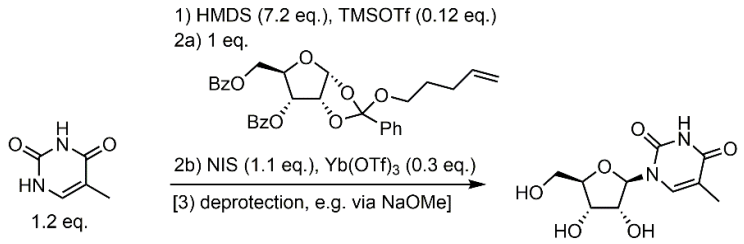
$$\text{cEF} = \frac{\begin{array}{c}0.134 + 1.162 + 0.027 + 0.53 + 0.53 * 2398 + 0.248 + 0.186 + 0.248 + 0.438 + 49.84 \\ +2.37 + 1.58 + 39.9 + 328.944 + 672.84 + 3.626 + 4.835 + 15.8 + 25.406 \\ +5.813 + 4.682 + 235.84 - \mathbf{0.2}\end{array}}{\mathbf{0.2}}$$

with combined contributions from reagents (31), inorganics (585), organic solvents (10684) and water (2029), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate).

Reaction N33

Fraser-Reid *et al. Chem. Commun*. **2013**, *49*, 3251–3253, doi: 10.1039/C3CC41036F

Reaction from their Scheme 1, compound **11b**



The experimental details for this synthesis were provided in the main text (Scheme 1, page 2) and in the Supporting Material (page 2 and 3, compound **11b**). Thymine (76 mg, 0.6 mmol) was first silylated neat with bis(trimethylsilyl)amine (3.6 mmol, corresponding to 581 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.06 mmol, corresponding to 13 mg calculated with a molecular weight of 222.25 g·mol^{-1}) for 2h. The protected nucleobase was reacted with 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (265 mg, 0.5 mmol) in MeCN (3 mL, 2.37 g with ρ = 0.79 g·cm^{-3}) before adding *N*-iodosuccinimide (0.55 mmol, 124 mg calculated with a molecular weight of 224.99 g·mol^{-1}) and Ytterbium(III) trifluoromethanesulfonate (0.15 mmol, 93 mg calculated with a molecular weight of 620.25 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 4 h. After completion the reaction was quenched with aqueous saturated sodium thiosulfate (5 mL, 6.25 g assuming ρ = 1.25 g·cm^{-3}; with 438 mg of salt with a solubility of 70 g·L^{-1} and 5.813 g of water) and extracted with CH_2Cl_2 (30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}) to provide a crude product upon drying. Column chromatography on silica gel (using *22.86 g* of silica gel and 571.5 mL of hexane/ethyl acetate 2:3 for an assumed weight of 1.143 g of crude product, which corresponds to 228.6 mL of hexane, *150.876 g* with ρ = 0.66 g·cm^{-3} and 342.9 mL of ethyl acetate, *308.61 g* with ρ = 0.90 g·cm^{-3}) provided the protected nucleoside in 97% yield (276 mg, 0.482 mmol calculated with a molecular weight of 572.5 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (276 mg, 0.482 mmol) was reacted with sodium methoxide (1 M in MeOH, 2.41 mL, 2.41 mmol, 130 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.904 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (3.213 mL, 2.538 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 2.41 mmol HCl, corresponding to 2.41 mL, *2.458 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 144.5 mL MeCN/water 12:88, for an assumed weight of 289 mg of crude product, which corresponds to 17.34 mL of MeCN, 13.699 g with ρ = 0.79 g·cm^{-3} and 127.16 mL of*

water, 127.16 g with ρ = 1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (0.429 mmol, **111 mg** calculated with a molecular weight of 258.2 g·mol^{-1}).

The reaction took a total of 33.5 h (15 min reaction setup + 2 h protection + 10 min addition of orthoester + 4 h glycosylation + 15 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 10.62 mL of reaction solvent (3mL MeCN + 2 mL MeCN + 5.62 mL MeOH), corresponding to 135.2 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) from Reaction S9, calculated as

$$\frac{10.62\ \text{mL}}{0.111\ \text{g}} + 0.265 * \frac{149.22\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) of 4.9 (Reaction S9), the preparation of **11b** had a sEF of 22.2, calculated as

$$\text{sEF} = \frac{0.076 + 0.581 + 0.013 + 0.265 + 0.265 * 4.9 + 0.124 + 0.093 + 0.130 - \mathbf{0.111}}{\mathbf{0.111}}$$

and (considering the cEF of the starting material of 2398) a cEF of 11935, calculated as

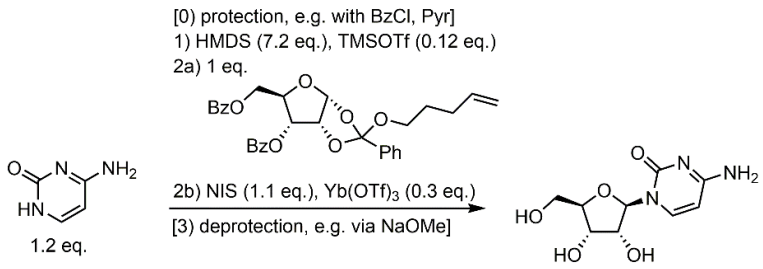
$$\text{cEF} = \frac{\begin{array}{c}0.076 + 0.581 + 0.013 + 0.265 + 0.0265 * 2398 + 0.124 + 0.093 + 0.130 + 0.438 + 22.86 \\ +2.37 + 1.58 + 39.9 + 150.867 + 308.61 + 1.904 + 2.538 + 7.9 + 13.699 \\ +5.813 + 2.458 + 127.16 - \mathbf{0.111}\end{array}}{\mathbf{0.111}}$$

with combined contributions from reagents (28), inorganics (511), organic solvents (9460) and water (1939), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate).

Reaction N34

Fraser-Reid *et al. Chem. Commun*. **2013**, *49*, 3251–3253, doi: 10.1039/C3CC41036F

Reaction from their Scheme 1, compound **12**



The experimental details for this synthesis were provided in the main text (Scheme 1, page 2) and in the Supporting Material (page 2 and 3, compound **12**). For the preparation of *N4*-benzoylcytosine we assume that cytosine could be benzoylated prior to the reaction and used as a crude product without further purification. We assume the conditions used by Mondal and Mugesh (*Chem. Eur. J.* **2019**, 25, 1–9, doi: 10.1002/chem.201805112) and adjusted their quantities to the scale of this synthesis. Cytosine (0.6 mmol, 67 mg calculated with a molecular weight of 111.1 g·mol^{-1}) was reacted with benzoyl chloride (2.5 mmol, 295 mg calculated with a molecular weight of 140.6 g·mol^{-1}) in pyridine (2.2 mL, 2.156 g with ρ = 0.98 g·cm^{-3}) for 6 h. The reaction was quenched with EtOH (1.05 mL, 830 mg with ρ = 0.79 g·cm^{-3}) and 30 min later with water (6.66 mL, 6.66 g with ρ = 1.00 g·cm^{-3}). The solution was stirred for 15 h and the resulting solid isolated by filtration. We assume that this solid could directly be used in the subsequent glycosylation reaction.

The benzoylated cytosine (0.6 mmol) was then silylated neat with bis(trimethylsilyl)amine (3.6 mmol, corresponding to 581 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.06 mmol, corresponding to 13 mg calculated with a molecular weight of 222.25 g·mol^{-1}) for 2h. The silyated compound was reacted with 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (265 mg, 0.5 mmol) in MeCN (3 mL, 2.37 g with ρ = 0.79 g·cm^{-3}) before adding *N*-iodosuccinimide (0.55 mmol, 124 mg calculated with a molecular weight of 224.99 g·mol^{-1}) and Ytterbium(III) trifluoromethanesulfonate (0.15 mmol, 93 mg calculated with a molecular weight of 620.25 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}). After completion the reaction was quenched with aqueous saturated sodium thiosulate (5 mL, 6.25 g assuming ρ = 1.25 g·cm^{-3}; with 438 mg of salt with a solubility of 70 g·L^{-1} and 5.813 g of water) and extracted with CH_2Cl_2 (30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}) to provide a crude product upon drying. Column chromatography on silica gel (using *16.88 g* of silica gel and 422 mL of hexane/ethyl acetate 7:3 for an assumed weight of 844 mg of crude product, which corresponds to 295.4 mL of hexane, *194.964 g* with ρ = 0.66 g·cm^{-3} and 126.6 mL of ethyl acetate, *133.94 g* with ρ = 0.90 g·cm^{-3}) provided the protected the protected nucleoside in 82% yield (287 mg, 0.44 mmol calculated with a molecular weight of 659.65 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (287 mg, 0.44 mmol) was reacted with sodium methoxide (1 M in MeOH, 2.2 mL, 2.2 mmol, 119 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.738 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (2.933 mL, 2.317 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 2.2 mmol HCl, corresponding to 2.2 mL, *2.244 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 149.5 mL MeCN/water 12:88, for an assumed weight of 299 mg of crude product, which corresponds to 17.94 mL of MeCN, 14.173 g with ρ = 0.79 g·cm^{-3} and 131.56 mL of water, 131.56 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.392 mmol, **95 mg** calculated with a molecular weight of 243.2 g·mol^{-1}).

The reaction took a total of 53.41 h (10 min reaction setup + 6 h protection + 40 min workup + 15 h precipitation + 5 min filtration + 15 min reaction setup + 2 h silylation + 10 min addition of orthoester + 2 h glycosylation + 15 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 12.33 mL of reaction solvent (2.2 mL pyridine + 3mL MeCN + 2 mL MeCN + 5.13 mL MeOH), corresponding to 176.5 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) from Reaction S9, calculated as

$$\frac{12.33\ \text{mL}}{0.09\ \text{g}} + 0.265 * \frac{149.22\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) of 4.9 (Reaction S9), the preparation of **12** had a sEF of 29.7, calculated as

$$\text{sEF} = \frac{0.067 + 0.295 + 0.581 + 0.013 + 0.265 + 0.265 * 4.9 + 0.124 + 0.093 + 0.119 - \mathbf{0.09}}{\mathbf{0.09}}$$

and (considering the cEF of the starting material of 2398) a cEF of 13359, calculated as

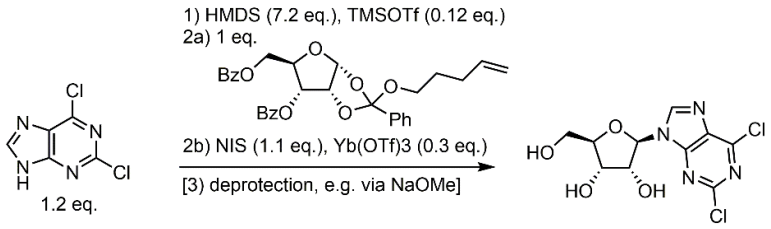
$$\text{cEF} = \frac{\begin{array}{c}0.067 + 0.295 + 0.581 + 0.013 + 0.265 + 0.265 * 2398 + 0.124 + 0.093 + 0.119 + 0.438 + 16.88 \\ +2.156 + 0.83 + 2.37 + 1.58 + 39.9 + 194.964 + 133.94 + 1.738 + 2.317 + 7.9 + 14.173 \\ +6.66 + 5.813 + 2.244 + 131.56 - \mathbf{0.09}\end{array}}{\mathbf{0.09}}$$

with combined contributions from reagents (37), inorganics (563), organic solvents (10251) and water (2512), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate).

Reaction N35

Fraser-Reid *et al. Chem. Commun*. **2013**, *49*, 3251–3253, doi: 10.1039/C3CC41036F

Reaction from their Scheme 1, compound **13a**



The experimental details for this synthesis were provided in the main text (Scheme 1, page 2) and in the Supporting Material (page 2 and 4, compound **13a**). 2,6-Dichloropurine (113 mg, 0.6 mmol) was first silylated neat with bis(trimethylsilyl)amine (3.6 mmol, corresponding to 581 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.06 mmol, corresponding to 13 mg calculated with a molecular weight of 222.25 g·mol^{-1}) for 2h. The protected nucleobase was reacted with 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (265 mg, 0.5 mmol) in MeCN (3 mL, 2.37 g with ρ = 0.79 g·cm^{-3}) before adding *N*-iodosuccinimide (0.55 mmol, 124 mg calculated with a molecular weight of 224.99 g·mol^{-1}) and Ytterbium(III) trifluoromethanesulfonate (0.15 mmol, 93 mg calculated with a molecular weight of 620.25 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 4 h. After completion the reaction was quenched with aqueous saturated sodium thiosulfate (5 mL, 6.25 g assuming ρ = 1.25 g·cm^{-3}; with 438 mg of salt with a solubility of 70 g·L^{-1} and 5.813 g of water) and extracted with CH_2Cl_2 (30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}) to provide a crude product upon drying. Column chromatography on silica gel (using *23.78 g* of silica gel and 594.5 mL of hexane/ethyl acetate 4:1 for an assumed weight of 1.189 g of crude product, which corresponds to 475.6 mL of hexane, *313.896 g* with ρ = 0.66 g·cm^{-3} and 118.9 mL of ethyl acetate, *107.01 g* with ρ = 0.90 g·cm^{-3}) provided the protected the protected nucleoside in 85% yield (269 mg, 0.424 mmol calculated with a molecular weight of 633.44 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (269 mg, 0.424 mmol) was reacted with sodium methoxide (1 M in MeOH, 2.12 mL, 2.12 mmol, 114 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.675 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (2.826 mL, 2.232 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 2.12 mmol HCl, corresponding to 2.12 mL, *2.162 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 140.5 mL MeCN/water 12:88, for an assumed weight of 281 mg of crude product, which corresponds to 16.86 mL of MeCN, 13.319 g with ρ = 0.79 g·cm^{-3} and 123.64 mL of*

water, 123.64 g with ρ = 1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (0.377 mmol, **121 mg** calculated with a molecular weight of 321.1 g·mol^{-1}).

The reaction took a total of 33.5 h (15 min reaction setup + 2 h protection + 10 min addition of orthoester + 4 h glycosylation + 15 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 9.95 mL of reaction solvent (3mL MeCN + 2 mL MeCN + 4.95 mL MeOH), corresponding to 121.8 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) from Reaction S9, calculated as

$$\frac{9.95\ \text{mL}}{0.121\ \text{g}} + 0.265 * \frac{149.22\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) of 4.9 (Reaction S9), the preparation of **13a** had a sEF of 20.5, calculated as

$$\text{sEF} = \frac{0.113 + 0.581 + 0.013 + 0.265 + 0.265 * 4.9 + 0.124 + 0.093 + 0.114 - \mathbf{0.121}}{\mathbf{0.121}}$$

and (considering the cEF of the starting material of 2398) a cEF of 10590, calculated as

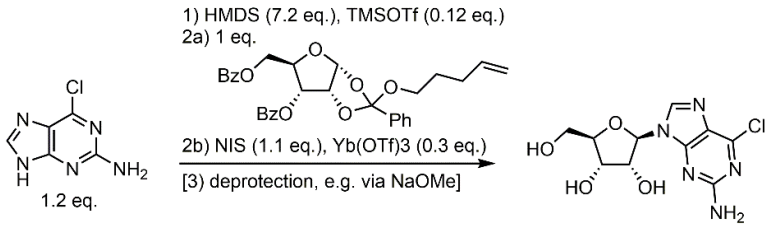
$$\text{cEF} = \frac{\begin{array}{c}0.113 + 0.581 + 0.013 + 0.265 + 0.0265 * 2398 + 0.124 + 0.093 + 0.114 + 0.438 + 23.78 \\ +2.37 + 1.58 + 39.9 + 313.896 + 107.01 + 1.675 + 2.232 + 7.9 + 12.319 \\ +5.813 + 2.162 + 123.64 - \mathbf{0.121}\end{array}}{\mathbf{0.121}}$$

with combined contributions from reagents (26), inorganics (476), organic solvents (8344) and water (1747), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate).

Reaction N36

Fraser-Reid *et al. Chem. Commun*. **2013**, *49*, 3251–3253, doi: 10.1039/C3CC41036F

Reaction from their Scheme 1, compound **13b**



The experimental details for this synthesis were provided in the main text (Scheme 1, page 2) and in the Supporting Material (page 2 and 5, compound **13b**). 2-Amino-6-chloropurine (101 mg, 0.6 mmol) was first silylated neat with bis(trimethylsilyl)amine (3.6 mmol, corresponding to 581 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.06 mmol, corresponding to 13 mg calculated with a molecular weight of 222.25 g·mol^{-1}) for 2h. The protected nucleobase was reacted with material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (265 mg, 0.5 mmol) in MeCN (3 mL, 2.37 g with ρ = 0.79 g·cm^{-3}) before adding *N*-iodosuccinimide (0.55 mmol, 124 mg calculated with a molecular weight of 224.99 g·mol^{-1}) and Ytterbium(III) trifluoromethanesulfonate (0.15 mmol, 93 mg calculated with a molecular weight of 620.25 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}). After completion the reaction was quenched with aqueous saturated sodium thiosulfate (5 mL, 6.25 g assuming ρ = 1.25 g·cm^{-3}; with 438 mg of salt with a solubility of 70 g·L^{-1} and 5.813 g of water) and extracted with CH_2Cl_2 (30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}) to provide a crude product upon drying. Column chromatography on silica gel (using *23.54 g* of silica gel and 588.5 mL of ethyl acetate for an assumed weight of 1.177 g of crude product, which corresponds to *529.65 g* with ρ = 0.90 g·cm^{-3}) provided the protected nucleoside in 70% yield (214 mg, 0.349 mmol calculated with a molecular weight of 614.0 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (214 mg, 0.349 mmol) was reacted with sodium methoxide (1 M in MeOH, 1.755 mL, 1.75 mmol, 95 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.386 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (2.333 mL, 1.843 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 1.75 mmol HCl, corresponding to 1.75 mL, *1.785 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 112.5 mL MeCN/water 12:88, for an assumed weight of 225 mg of crude product, which corresponds to 13.5 mL of MeCN, 10.665 g with ρ = 0.79 g·cm^{-3} and 99 mL of water,*

99 g with ρ = 1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (0.311 mmol, **94 mg** calculated with a molecular weight of 301.7 g·mol^{-1}).

The reaction took a total of 33.5 h (15 min reaction setup + 2 h protection + 10 min addition of orthoester + 4 h glycosylation + 15 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 9.09 mL of reaction solvent (3mL MeCN + 2 mL MeCN + 4.09 mL MeOH), corresponding to 136.2 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) from Reaction S9, calculated as

$$\frac{9.09\ \text{mL}}{0.094\ \text{g}} + 0.265 * \frac{149.22\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) of 4.9 (Reaction S9), the preparation of **13b** had a sEF of 26.3, calculated as

$$\text{sEF} = \frac{0.101 + 0.581 + 0.013 + 0.265 + 0.265 * 4.9 + 0.124 + 0.093 + 0.095 - \mathbf{0.094}}{\mathbf{0.094}}$$

and (considering the cEF of the starting material of 2398) a cEF of 14495, calculated as

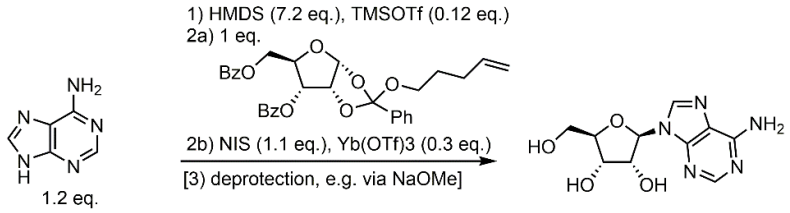
$$\text{cEF} = \frac{\begin{array}{c}0.101 + 0.581 + 0.013 + 0.265 + 0.0265 * 2398 + 0.124 + 0.093 + 0.095 + 0.438 + 23.54 \\ +2.37 + 1.58 + 39.9 + 529.65 + 1.386 + 1.843 + 7.9 + 10.665 \\ +5.813 + 1.785 + 99 - \mathbf{0.094}\end{array}}{\mathbf{0.094}}$$

with combined contributions from reagents (33), inorganics (610), organic solvents (11873) and water (1983), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate).

Reaction N37

Fraser-Reid *et al. Chem. Commun*. **2013**, *49*, 3251–3253, doi: 10.1039/C3CC41036F

Reaction from their Scheme 1, compound **13c**



The experimental details for this synthesis were provided in the main text (Scheme 1, page 2) and in the Supporting Material (page 2 and 5, compound **13b**). Adenine (81 mg, 0.6 mmol) was first silylated neat with bis(trimethylsilyl)amine (3.6 mmol, corresponding to 581 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.06 mmol, corresponding to 13 mg calculated with a molecular weight of 222.25 g·mol^{-1}) for 2h. The protected nucleobase was reacted with material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (265 mg, 0.5 mmol) in MeCN (3 mL, 2.37 g with ρ = 0.79 g·cm^{-3}) before adding *N*-iodosuccinimide (0.55 mmol, 124 mg calculated with a molecular weight of 224.99 g·mol^{-1}) and Ytterbium(III) trifluoromethanesulfonate (0.15 mmol, 93 mg calculated with a molecular weight of 620.25 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}). After completion the reaction was quenched with aqueous saturated sodium thiosulfate (5 mL, 6.25 g assuming ρ = 1.25 g·cm^{-3}; with 438 mg of salt with a solubility of 70 g·L^{-1} and 5.813 g of water) and extracted with CH_2Cl_2 (30 mL, 39.9 g with ρ = 1.33 g·cm^{-3}) to provide a crude product upon drying. Column chromatography on silica gel (using *23.14 g* of silica gel and 578.5 mL of ethyl acetate for an assumed weight of 1.157 g of crude product, which corresponds to *520.65 g* with ρ = 0.90 g·cm^{-3}) provided the protected nucleoside in 30% yield (87 mg, 0.15 mmol calculated with a molecular weight of 579.6 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (87 mg, 0.15 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.75 mL, 0.75 mmol, 41 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.593 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (1.003 mL, 0.792 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.75 mmol HCl, corresponding to 0.75 mL, *0.762 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 5 mL, *3.95 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 46 mL MeCN/water 12:88, for an assumed weight of 92 mg of crude product, which corresponds to 5.52 mL of MeCN, 4.361 g with ρ = 0.79 g·cm^{-3} and 40.48 mL of water, 40.48 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.134 mmol, **36 mg** calculated with a molecular weight of 267.3 g·mol^{-1}).

The reaction took a total of 33.5 h (15 min reaction setup + 2 h protection + 10 min addition of orthoester + 4 h glycosylation + 15 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 6.75 mL of reaction solvent (3mL MeCN + 2 mL MeCN + 1.75 mL MeOH), corresponding to 227.0 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) from Reaction S9, calculated as

$$\frac{6.75\ \mathrm{mL}}{0.036\ \mathrm{g}} + 0.265 * \frac{149.22\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) of 4.9 (Reaction S9), the preparation of **13c** had a sEF of 68.3, calculated as

$$\mathrm{sEF} = \frac{0.081 + 0.581 + 0.013 + 0.265 + 0.265 * 4.9 + 0.124 + 0.093 + 0.041 - \mathbf{0.036}}{\mathbf{0.036}}$$

and (considering the cEF of the starting material of 2398) a cEF of 35596, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}0.081 + 0.581 + 0.013 + 0.265 + 0.0265 * 2398 + 0.124 + 0.093 + 0.041 + 0.438 + 23.14 \\ +2.37 + 1.58 + 39.9 + 520.65 + 0.792 + 0.593 + 3.95 + 4.361 \\ +5.813 + 0.762 + 40.48 - \mathbf{0.036}\end{array}}{\mathbf{0.036}}$$

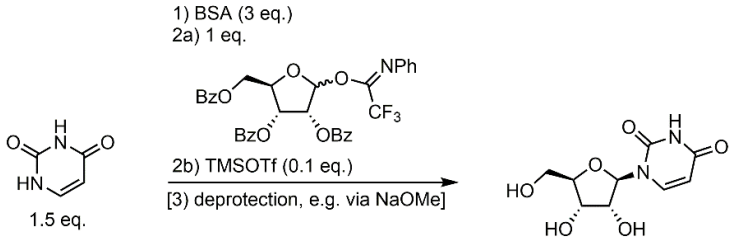
with combined contributions from reagents (85), inorganics (1582), organic solvents (30414) and water (3523), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate).

Trifluoroacetimidates

Reaction N38

Liao *et al. Tetrahedron Letters* **2008**, *49*, 5036–5038, doi: 10.1016/j.tetlet.2008.06.042

Reaction from their Table 1, compound **3aa**



The experimental details for this synthesis were provided in the footnotes of Table 1 (page 2, note a). Additional details were provided by the authors via email upon request (jinxiliao@jxnu.edu.cn and byu@mail.sioc.ac.cn). Uracil (0.45 mmol, 50 mg calculated with a molecular weight of 112.1 g·mol^{-1}) was first silylated by reacting it with bis(trimethylsilyl)acetamide (0.9 mmol, 183 mg calculated with a molecular weight of 203.4 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 30 min. Upon concentration and redissolution in dichloroethane (2 mL, 2.5 g with ρ = 1.25 g·cm^{-3}) it was reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate (0.3 mmol, 190 mg calculated with a molecular weight of 633.6 g·mol^{-1}), 4 Å molecular sieves and trimethylsilyl trifluoromethanesulfonate (0.03 mmol, 7 mg calculated with a molecular weight of 222.2 g·mol^{-1}) in an additional 2 mL of dichloroethane (2.5 g with ρ = 1.25 g·cm^{-3}) for 36 h (time was not stated, so we assumed the mean of all glycosylation times provided in the manuscript). After completion the reaction was quenched with NEt_3 (0.5 mL, 0.365 g with ρ = 0.73 g·cm^{-3}), filtered and concentrated to provide a crude product which afforded the nucleoside upon purification on silica gel (solvents not stated, we assumed the same conditions as Reaction N32 where the same compound was purified using *8.6 g* of silica gel and 215 mL of hexane/ethyl acetate 2:3 for an assumed weight of 430 mg of crude product, which corresponds to 86 mL of hexane, *56.76 g* with ρ = 0.66 g·cm^{-3} and 126 mL of ethyl acetate, *116.1 g* with ρ = 0.90 g·cm^{-3}) in 98% yield (0.3 mmol, 167 mg calculated with a molecular weight of 556.5 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (167 mg, 0.3 mmol) was reacted with sodium methoxide (1 M in MeOH, 1.5 mL, 1.5 mmol, 81 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.185 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 1.5 mmol HCl, corresponding to 1.5 mL, *1.53 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 5 mL, *3.95 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase

HPLC (*using 87.5 mL MeCN/water 12:88, for an assumed weight of 175 mg of crude product, which corresponds to 10.5 mL of MeCN, 8.295 g with ρ = 0.79 g·cm^{-3} and 77 mL of water, 77 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.267 mmol, **65 mg** calculated with a molecular weight of 244.2 g·mol^{-1}).

The reaction took a total of 64.67 h (10 min reaction setup + 30 min silylation + 30 min drying + 30 min addition of glycosyl donor + 36 h glycosylation + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 9.5 mL reaction solvent (2 mL MeCN + 2 mL DCE + 2 mL DCE + 3.5 mL MeOH), corresponding to 156.4 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate from Reaction S12, calculated as

$$\frac{9.5\ \text{mL}}{0.065\ \text{g}} + 0.190 * \frac{53.68\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate of 9.5 (Reaction S12), the preparation of **3aa** had a sEF of 34.6, calculated as

$$\text{sEF} = \frac{0.05 + 0.183 + 0.19 + 0.19 * 9.5 + 0.007 + 0.081 - \mathbf{0.065}}{\mathbf{0.065}}$$

and (considering the cEF of the starting material of 1818) a cEF of 9651, calculated as

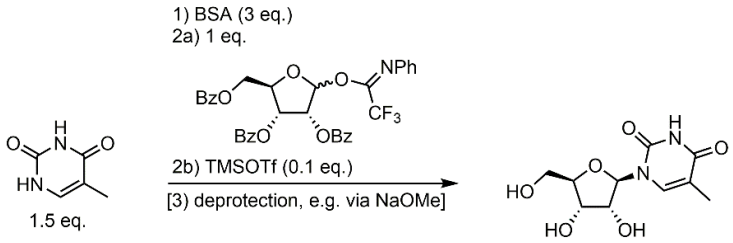
$$\text{cEF} = \frac{\begin{array}{c}0.05 + 0.183 + 0.19 + 0.19 * 1818 + 0.007 + 0.081 + 8.6 \\ +1.58 + 2.5 + 2.5 + 0.365 + 56.76 + 116.1 + 1.158 + 1.58 + 3.9 + 8.295 \\ +1.53 + 77 - \mathbf{0.065}\end{array}}{\mathbf{0.065}}$$

with combined contributions from reagents (46), inorganics (375), organic solvents (7737) and water (1506), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate.

Reaction N39

Liao *et al. Tetrahedron Letters* **2008**, *49*, 5036–5038, doi: 10.1016/j.tetlet.2008.06.042

Reaction from their Table 1, compound **3ab**



The experimental details for this synthesis were provided in the footnotes of Table 1 (page 2, note a). Additional details were provided by the authors via email upon request (jinxiliao@jxnu.edu.cn and byu@mail.sioc.ac.cn). Thymine (0.45 mmol, 57 mg calculated with a molecular weight of 126.1 g·mol^{-1}) was first silylated by reacting it with bis(trimethylsilyl)acetamide (0.9 mmol, 183 mg calculated with a molecular weight of 203.4 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 30 min. Upon concentration and redissolution in dichloroethane (2 mL, 2.5 g with ρ = 1.25 g·cm^{-3}) it was reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate (0.3 mmol, 190 mg calculated with a molecular weight of 633.6 g·mol^{-1}), 4 Å molecular sieves and trimethylsilyl trifluoromethanesulfonate (0.03 mmol, 7 mg calculated with a molecular weight of 222.2 g·mol^{-1}) in an additional 2 mL of dichloroethane (2.5 g with ρ = 1.25 g·cm^{-3}) for 36 h (time was not stated, so we assumed the mean of all glycosylation times provided in the manuscript). After completion the reaction was quenched with NEt_3 (0.5 mL, 0.365 g with ρ = 0.73 g·cm^{-3}), filtered and concentrated to provide a crude product which afforded the nucleoside upon purification on silica gel (solvents not stated, we assumed the same conditions as Reaction N33 where the same compound was purified using *8.74 g* of silica gel and 218.5 mL of hexane/ethyl acetate 2:3 for an assumed weight of 437 mg of crude product, which corresponds to 87.4 mL of hexane, *57.684 g* with ρ = 0.66 g·cm^{-3} and 131.1 mL of ethyl acetate, *117.99 g* with ρ = 0.90 g·cm^{-3}) in 88% yield (0.26 mmol, 149 mg calculated with a molecular weight of 572.5 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (149 mg, 0.26 mmol) was reacted with sodium methoxide (1 M in MeOH, 1.3 mL, 1.3 mmol, 70 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.027 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (1.733 mL, 1.396 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 1.3 mmol HCl, corresponding to 1.3 mL, *1.326 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 5 mL, *3.95 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 78 mL MeCN/water 12:88, for an assumed weight of 156 mg of crude*

product, which corresponds to 9.36 mL of MeCN, 7.394 g with ρ = 0.79 g·cm^{-3} and 68.64 mL of water, 68.64 g with ρ = 1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (0.231 mmol, **60 mg** calculated with a molecular weight of 258.2 g·mol^{-1}).

The reaction took a total of 64.67 h (10 min reaction setup + 30 min silylation + 30 min drying + 30 min addition of glycosyl donor + 36 h glycosylation + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 9 mL reaction solvent (2 mL MeCN + 2 mL DCE + 2 mL DCE + 3 mL MeOH), corresponding to 160.2 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate from Reaction S12, calculated as

$$\frac{9\ \text{mL}}{0.06\ \text{g}} + 0.190 * \frac{53.68\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate of 9.5 (Reaction S12), the preparation of **3ab** had a sEF of 37.6, calculated as

$$\text{sEF} = \frac{0.057 + 0.183 + 0.19 + 0.19 * 9.5 + 0.007 + 0.071 - \mathbf{0.06}}{\mathbf{0.06}}$$

and (considering the cEF of the starting material of 1818) a cEF of 10349, calculated as

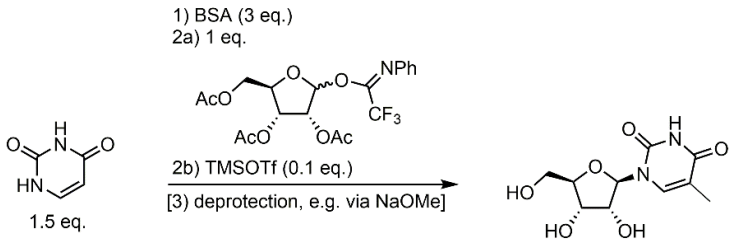
$$\text{cEF} = \frac{\begin{array}{c}0.057 + 0.183 + 0.19 + 0.19 * 1818 + 0.007 + 0.071 + 8.74 \\ +1.58 + 2.5 + 2.5 + 0.365 + 57.684 + 117.99 + 1.027 + 1.396 + 3.95 + 7.394 \\ +1.326 + 68.64 - \mathbf{0.06}\end{array}}{\mathbf{0.06}}$$

with combined contributions from reagents (50), inorganics (409), organic solvents (8416) and water (1489), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate.

Reaction N40

Liao *et al. Tetrahedron Letters* **2008**, *49*, 5036–5038, doi: 10.1016/j.tetlet.2008.06.042

Reaction from their Table 1, compound **3ba**



The experimental details for this synthesis were provided in the footnotes of Table 1 (page 2, note a). Additional details were provided by the authors via email upon request (jinxiliao@jxnu.edu.cn and byu@mail.sioc.ac.cn). Uracil (0.45 mmol, 50 mg calculated with a molecular weight of 126.1 g·mol^{-1}) was first silylated by reacting it with bis(trimethylsilyl)acetamide (0.9 mmol, 183 mg calculated with a molecular weight of 203.4 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 30 min. Upon concentration and redissolution in dichloroethane (2 mL, 2.5 g with ρ = 1.25 g·cm^{-3}) it was reacted with the trifluoroacetimidate donor (0.3 mmol, 134 mg calculated with a molecular weight of 447.4 g·mol^{-1}), 4 Å molecular sieves and trimethylsilyl trifluoromethanesulfonate (0.03 mmol, 7 mg calculated with a molecular weight of 222.2 g·mol^{-1}) in an additional 2 mL of dichloroethane (2.5 g with ρ = 1.25 g·cm^{-3}) for 36 h (time was not stated, so we assumed the mean of all glycosylation times provided in the manuscript). After completion the reaction was quenched with NEt_3 (0.5 mL, 0.365 g with ρ = 0.73 g·cm^{-3}), filtered and concentrated to provide a crude product which afforded the nucleoside upon purification on silica gel (solvents not stated, we assumed the same conditions as Reaction N32 where a similar compound was purified using *7.48 g* of silica gel and 187 mL of hexane/ethyl acetate 2:3 for an assumed weight of 374 mg of crude product, which corresponds to 74.8 mL of hexane, *49.368 g* with ρ = 0.66 g·cm^{-3} and 112.2 mL of ethyl acetate, *100.98 g* with ρ = 0.90 g·cm^{-3}) in 98% yield (0.3 mmol, 111 mg calculated with a molecular weight of 370.3 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (111 mg, 0.3 mmol) was reacted with sodium methoxide (1 M in MeOH, 1.5 mL, 1.5 mmol, 81 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.185 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 1.5 mmol HCl, corresponding to 1.5 mL, *1.53 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 5 mL, *3.95 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 59.5 mL MeCN/water 12:88, for an assumed weight of 119 mg of crude product, which corresponds to 7.14 mL of MeCN, 6.426 g with ρ = 0.79 g·cm^{-3} and 52.36 mL of water, 52.36 g with ρ =*

1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (0.267 mmol, **65 mg** calculated with a molecular weight of 244.2 g·mol^{-1}).

The reaction took a total of 64.67 h (10 min reaction setup + 30 min silylation + 30 min drying + 30 min addition of glycosyl donor + 36 h glycosylation + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 9.5 mL reaction solvent (2 mL MeCN + 2 mL DCE + 2 mL DCE + 3.5 mL MeOH), corresponding to 154.1 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate from Reaction S10, calculated as

$$\frac{9.5\ \text{mL}}{0.065\ \text{g}} + 0.190 * \frac{41.95\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate of 10.1 (Reaction S10), the preparation of **3ba** had a sEF of 36.4, calculated as

$$\text{sEF} = \frac{0.05 + 0.183 + 0.19 + 0.19 * 10.1 + 0.007 + 0.081 - \mathbf{0.065}}{\mathbf{0.065}}$$

and (considering the cEF of the starting material of 2670) a cEF of 11762, calculated as

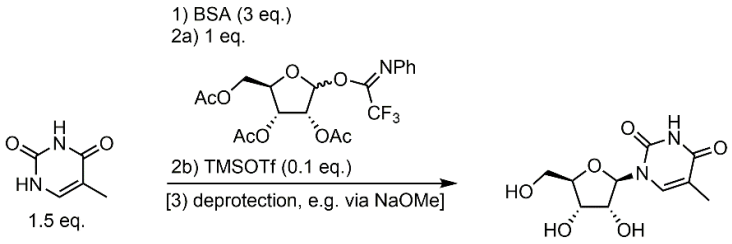
$$\text{cEF} = \frac{\begin{array}{c}0.05 + 0.183 + 0.19 + 0.19 * 2670 + 0.007 + 0.081 + 8.6 \\ +1.58 + 2.5 + 2.5 + 0.365 + 56.76 + 116.1 + 1.158 + 1.58 + 3.9 + 8.295 \\ +1.53 + 52.36 - \mathbf{0.065}\end{array}}{\mathbf{0.065}}$$

with combined contributions from reagents (43), inorganics (580), organic solvents (9911) and water (1238), considering the contribution from the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate.

Reaction N41

Liao *et al. Tetrahedron Letters* **2008**, *49*, 5036–5038, doi: 10.1016/j.tetlet.2008.06.042

Reaction from their Table 1, compound **3bb**



The experimental details for this synthesis were provided in the footnotes of Table 1 (page 2, note a). Additional details were provided by the authors via email upon request (jinxiliao@jxnu.edu.cn and byu@mail.sioc.ac.cn). Thymine (0.45 mmol, 57 mg calculated with a molecular weight of 126.1 g·mol^{-1}) was first silylated by reacting it with bis(trimethylsilyl)acetamide (0.9 mmol, 183 mg calculated with a molecular weight of 203.4 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}). Upon concentration and redissolution in dichloroethane (2 mL, 2.5 g with ρ = 1.25 g·cm^{-3}) it was reacted with the trifluoroacetimidate donor (0.3 mmol, 134 mg calculated with a molecular weight of 447.4 g·mol^{-1}), 4 Å molecular sieves and trimethylsilyl trifluoromethanesulfonate (0.03 mmol, 7 mg calculated with a molecular weight of 222.2 g·mol^{-1}) in an additional 2 mL of dichloroethane (2.5 g with ρ = 1.25 g·cm^{-3}) for 36 h (time was not stated, so we assumed the mean of all glycosylation times provided in the manuscript). After completion the reaction was quenched with NEt_3 (0.5 mL, 0.365 g with ρ = 0.73 g·cm^{-3}), filtered and concentrated to provide a crude product which afforded the nucleoside upon purification on silica gel (solvents not stated, we assumed the same conditions as Reaction N33 where a similar compound was purified using *8.74 g* of silica gel and 190.5 mL of hexane/ethyl acetate 2:3 for an assumed weight of 381 mg of crude product, which corresponds to 76.2 mL of hexane, *50.292 g* with ρ = 0.66 g·cm^{-3} and 114.3 mL of ethyl acetate, *102.87 g* with ρ = 0.90 g·cm^{-3}) in 88% yield (0.26 mmol, 100 mg calculated with a molecular weight of 384.3 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (100 mg, 0.26 mmol) was reacted with sodium methoxide (1 M in MeOH, 1.3 mL, 1.3 mmol, 70 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.027 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (1.733 mL, 1.396 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 1.3 mmol HCl, corresponding to 1.3 mL, *1.326 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 5 mL, *3.95 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 53.5 mL MeCN/water 12:88, for an assumed weight of 107 mg of crude product, which corresponds to 6.42 mL of MeCN, 5.072 g with ρ = 0.79 g·cm^{-3} and 47.08 mL of water,*

47.08 g with ρ = 1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (0.231 mmol, **60 mg** calculated with a molecular weight of 258.2 g·mol^{-1}).

The reaction took a total of 64.67 h (10 min reaction setup + 30 min silylation + 30 min drying + 30 min addition of glycosyl donor + 36 h glycosylation + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 9 mL reaction solvent (2 mL MeCN + 2 mL DCE + 2 mL DCE + 3 mL MeOH), corresponding to 158.0 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate from Reaction S10, calculated as

$$\frac{9\ \text{mL}}{0.06\ \text{g}} + 0.190 * \frac{41.95\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate of 10.1 (Reaction S10), the preparation of **3bb** had a sEF of 39.4, calculated as

$$\text{sEF} = \frac{0.057 + 0.183 + 0.19 + 0.19 * 10.1 + 0.007 + 0.070 - \mathbf{0.06}}{\mathbf{0.06}}$$

and (considering the cEF of the starting material of 2670) a cEF of 12272, calculated as

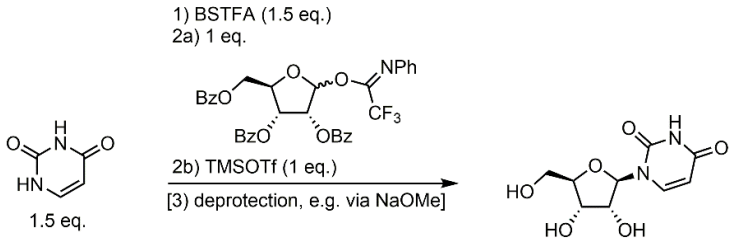
$$\text{cEF} = \frac{\begin{array}{c}0.05 + 0.183 + 0.19 + 0.19 * 2670 + 0.007 + 0.070 + 8.6 \\ +1.58 + 2.5 + 2.5 + 0.365 + 50.292 + 102.87 + 1.027 + 1.396 + 3.95 + 5.072 \\ +1.326 + 47.08 - \mathbf{0.06}\end{array}}{\mathbf{0.06}}$$

with combined contributions from reagents (46), inorganics (630), organic solvents (10358) and water (1250), considering the contribution from the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate.

Reaction N42

Liao *et al. Carbohydrate Research* **2009**, *344*, 1034–1038, doi: 10.1016/j.carres.2009.03.010

Reaction from their Scheme 1 and Table 2, compound **3ea**



The experimental details for this synthesis were provided in Table 2 (page 3). Additional details were provided by the authors via email upon request (jinxiliao@jxnu.edu.cn and byu@mail.sioc.ac.cn). Uracil (0.45 mmol, 50 mg calculated with a molecular weight of 112.1 g·mol^{-1}) was first silylated by reacting it with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (0.45 mmol, 116 mg calculated with a molecular weight of 257.4 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 30 min. Upon concentration and redissolution in CH_2Cl_2 (2 mL, 2.66 g with ρ = 1.33 g·cm^{-3}) it was reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate (0.3 mmol, 190 mg calculated with a molecular weight of 633.6 g·mol^{-1}), 4 Å molecular sieves and trimethylsilyl trifluoromethanesulfonate (0.3 mmol, 67 mg calculated with a molecular weight of 222.2 g·mol^{-1}) in an additional 2 mL of CH_2Cl_2 (2 mL, 2.66 g with ρ = 1.33 g·cm^{-3}) for 36 h (time was not stated, so we assumed the mean of all glycosylation times provided in the manuscript). After completion the reaction was quenched with NEt_3 (0.5 mL, 0.365 g with ρ = 0.73 g·cm^{-3}), filtered and concentrated to provide a crude product which afforded the nucleoside upon purification on silica gel (solvents not stated, we assumed the same conditions as Reaction N32 where the same compound was purified using *8.46 g* of silica gel and 211.5 mL of hexane/ethyl acetate 2:3 for an assumed weight of 423 mg of crude product, which corresponds to 84.6 mL of hexane, *55.836 g* with ρ = 0.66 g·cm^{-3} and 126.9 mL of ethyl acetate, *114.21 g* with ρ = 0.90 g·cm^{-3}) in 88% yield (0.26 mmol, 145 mg calculated with a molecular weight of 556.5 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (145 mg, 0.26 mmol) was reacted with sodium methoxide (1 M in MeOH, 1.3 mL, 1.3 mmol, 70 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.027 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (1.733 mL, 1.396 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 1.3 mmol HCl, corresponding to 1.3 mL, *1.326 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 5 mL, *3.95 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 76 mL MeCN/water 12:88, for an assumed weight of 152 mg of crude*

product, which corresponds to 9.12 mL of MeCN, 8.208 g with ρ = 0.79 g·cm^{-3} and 66.88 mL of water, 66.88 g with ρ = 1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (0.231 mmol, **56 mg** calculated with a molecular weight of 244.2 g·mol^{-1}).

The reaction took a total of 64.67 h (10 min reaction setup + 30 min silylation + 30 min drying + 30 min addition of glycosyl donor + 36 h glycosylation + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 9 mL reaction solvent (2 mL MeCN + 2 mL DCE + 2 mL DCE + 3 mL MeOH), corresponding to 170.9 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate from Reaction S12, calculated as

$$\frac{9\ \text{mL}}{0.056\ \text{g}} + 0.190 * \frac{53.68\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate of 9.5 (Reaction S12), the preparation of **3ea** had a sEF of 40.0, calculated as

$$\text{sEF} = \frac{0.05 + 0.116 + 0.19 + 0.19 * 9.5 + 0.067 + 0.070 - \mathbf{0.056}}{\mathbf{0.056}}$$

and (considering the cEF of the starting material of 1818) a cEF of 10972, calculated as

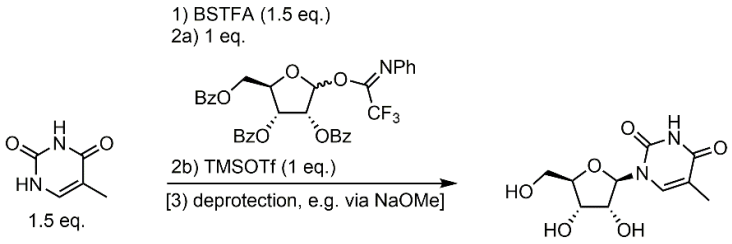
$$\text{cEF} = \frac{\begin{array}{c}0.05 + 0.116 + 0.19 + 0.19 * 1818 + 0.067 + 0.070 + 8.46 \\ +1.58 + 2.66 + 2.66 + 0.365 + 55.836 + 114.21 + 1.027 + 1.396 + 3.95 + 8.208 \\ +1.326 + 66.88 - \mathbf{0.056}\end{array}}{\mathbf{0.056}}$$

with combined contributions from reagents (53), inorganics (433), organic solvents (8937) and water (1564), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate.

Reaction N43

Liao *et al. Carbohydrate Research* **2009**, *344*, 1034–1038, doi: 10.1016/j.carres.2009.03.010

Reaction from their Scheme 1 and Table 2, compound **3eb**



The experimental details for this synthesis were provided in Table 2 (page 3). Additional details were provided by the authors via email upon request (jinxiliao@jxnu.edu.cn and byu@mail.sioc.ac.cn). Thymine (0.45 mmol, 57 mg calculated with a molecular weight of 112.1 g·mol^{-1}) was first silylated by reacting it with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (0.45 mmol, 116 mg calculated with a molecular weight of 257.4 g·mol^{-1}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}). Upon concentration and redissolution in CH_2Cl_2 (2 mL, 2.66 g with ρ = 1.33 g·cm^{-3}) it was reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate (0.3 mmol, 190 mg calculated with a molecular weight of 633.6 g·mol^{-1}), 4 Å molecular sieves and trimethylsilyl trifluoromethanesulfonate (0.3 mmol, 67 mg calculated with a molecular weight of 222.2 g·mol^{-1}) in an additional 2 mL of CH_2Cl_2 (2 mL, 2.66 g with ρ = 1.33 g·cm^{-3}) for 36 h (time was not stated, so we assumed the mean of all glycosylation times provided in the manuscript). After completion the reaction was quenched with NEt_3 (0.5 mL, 0.365 g with ρ = 0.73 g·cm^{-3}), filtered and concentrated to provide a crude product which afforded the nucleoside upon purification on silica gel (solvents not stated, we assumed the same conditions as Reaction N32 where the same compound was purified using *8.6 g* of silica gel and 215 mL of hexane/ethyl acetate 2:3 for an assumed weight of 430 mg of crude product, which corresponds to 86 mL of hexane, *56.76 g* with ρ = 0.66 g·cm^{-3} and 126 mL of ethyl acetate, *116.1 g* with ρ = 0.90 g·cm^{-3}) in 98% yield (172 mg, 0.3 mmol calculated with a molecular weight of 572.5 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (172 mg, 0.3 mmol) was reacted with sodium methoxide (1 M in MeOH, 1.5 mL, 1.5 mmol, 81 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.185 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 1.5 mmol HCl, corresponding to 1.5 mL, *1.53 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 5 mL, *3.95 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 90 mL MeCN/water 12:88, for an assumed weight of 180 mg of crude product, which corresponds to 10.8 mL of MeCN, 8.532 g with ρ = 0.79 g·cm^{-3} and 79.2 mL of water, 79.2 g with ρ =*

1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (0.267 mmol, **67 mg** calculated with a molecular weight of 252.2 g·mol^{-1}).

The reaction took a total of 64.67 h (10 min reaction setup + 30 min silylation + 30 min drying + 30 min addition of glycosyl donor + 36 h glycosylation + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 9.5 mL reaction solvent (2 mL MeCN + 2 mL DCE + 2 mL DCE + 3.5 mL MeOH), corresponding to 152.0 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate from Reaction S12, calculated as

$$\frac{9.5\ \text{mL}}{0.067\ \text{g}} + 0.190 * \frac{53.68\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate of 9.5 (Reaction S12), the preparation of **3ea** had a sEF of 33.6, calculated as

$$\text{sEF} = \frac{0.057 + 0.116 + 0.19 + 0.19 * 9.5 + 0.067 + 0.081 - \mathbf{0.067}}{\mathbf{0.067}}$$

and (considering the cEF of the starting material of 1818) a cEF of 9411, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.057 + 0.116 + 0.19 + 0.19 * 1818 + 0.067 + 0.081 + 8.6 \\ +1.58 + 2.66 + 2.66 + 0.365 + 56.76 + 116.1 + 1.185 + 1.58 + 3.95 + 8.532 \\ +1.53 + 79.2 - \mathbf{0.067}\end{array}}{\mathbf{0.067}}$$

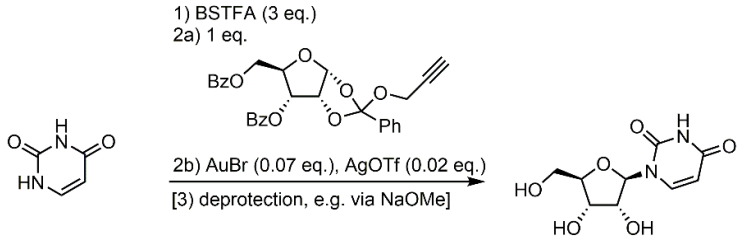
with combined contributions from reagents (44), inorganics (364), organic solvents (7521) and water (1494), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl 1-(*N*-phenyl)-2,2,2-trifluoroacetimidate.

Propargyl-1,2-orthoesters

Reaction N44

Rao *et al. J. Org. Chem.* **2015**, *80*, 1499−1505, doi: 10.1021/jo502413z

Reaction from their Scheme 1, compound **3a**



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 3 and 4, compound **3a**). Uracil (0.89 mmol, 100 mg) was first silylated with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (2.68 mmol, 689 mg) in MeCN (amount not stated, we assumed 4.45 mL for 0.2 M of the nucleobase, 3.516 g with ρ = 0.79 g·cm^{-3}) for 40 min. The silylated base was then reacted with 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate (0.89 mmol, 446 mg), gold(III) bromide (0.06 mmol, 27 mg) and silver trifluoromethanesulfonate (0.02 mmol, 5 mg) in a solvent combination of MeCN/CH_2Cl_2 1:2 which, according to our previous assumption, necessitated addition of CH_2Cl_2 (8.9 mL, 11.837 g with ρ = 1.33 g·cm^{-3}) for 6 h. Concentration *in vacuo* and purification on silica gel (solvent combination not stated, we assumed the same conditions as Reaction N32 where the same compound was purified using *25.88 g* of silica gel and 647 mL of hexane/ethyl acetate 2:3 for an assumed weight of 1.294 g of crude product, which corresponds to 258.8 mL of hexane, *170.808 g* with ρ = 0.66 g·cm^{-3} and 388.2 mL of ethyl acetate, *349.38 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 85% yield (0.76 mmol, 422 mg).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (422 mg, 0.76 mmol) was reacted with sodium methoxide (1 M in MeOH, 3.8 mL, 3.8 mmol, 205 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 3.002 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (5.067 mL, 4.003 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 3.8 mmol HCl, corresponding to 3.8 mL, *3.876 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 221.5 mL MeCN/water 12:88, for an assumed weight of 443 mg of crude product, which corresponds to 26.58 mL of MeCN, 20.998 g with ρ = 0.79 g·cm^{-3} and 194.92 mL of water, 194.92 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.676 mmol, **165 mg** calculated with a molecular weight of 244.2 g·mol^{-1}).

The reaction took a total of 34 h (10 min reaction setup + 40 min silylation + 20 min addition of reagents + 6 h glycosylation + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 22.25 mL of reaction solvent (4.45 mL MeCN + 8.9 mL CH_2Cl_2 + 8.9 mL MeOH), corresponding to 142.6 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate from Reaction S13, calculated as

$$\frac{22.25\ \text{mL}}{0.165\ \text{g}} + 0.446 * \frac{17.27\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate of 4.0 (Reaction S13), the preparation of **3a** had a sEF of 18.7, calculated as

$$\text{sEF} = \frac{0.1 + 0.689 + 0.446 + 0.446 * 4 + 0.027 + 0.005 + 0.205 - \mathbf{0.165}}{\mathbf{0.165}}$$

and (considering the cEF of the starting material of 1168) a cEF of 7990, calculated as

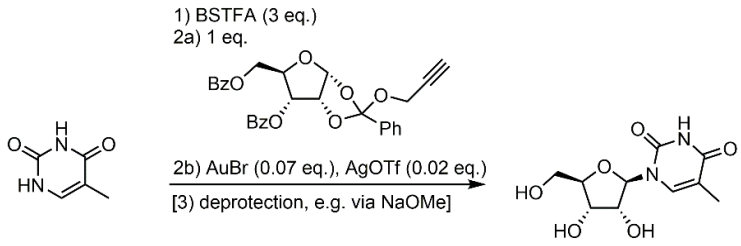
$$\text{cEF} = \frac{\begin{array}{c}0.1 + 0.689 + 0.446 + 0.446 * 1168 + 0.027 + 0.005 + 0.205 + 25.88 \\ +3.516 + 11.837 + 170.808 + 349.38 + 3.002 + 4.003 + 7.9 + 20.998 \\ +3.876 + 194.92 - \mathbf{0.165}\end{array}}{\mathbf{0.165}}$$

with combined contributions from reagents (22), inorganics (316), organic solvents (6266) and water (1389), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate.

Reaction N45

Rao *et al. J. Org. Chem.* **2015**, *80*, 1499−1505, doi: 10.1021/jo502413z

Reaction from their Scheme 1, compound **4a**



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 3 and 4, compound **4a**). Thymine (0.79 mmol, 100 mg) was first silylated with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (2.37 mmol, 612 mg) in MeCN (amount not stated, we assumed 3.95 mL for 0.2 M of the nucleobase, 3.121 g with ρ = 0.79 g·cm^{-3}) for 40 min. The silylated base was then reacted with 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate (0.89 mmol, 396 mg), gold(III) bromide (0.06 mmol, 27 mg) and silver trifluoromethanesulfonate (0.02 mmol, 5 mg) in MeCN/CH_2Cl_2 1:2 which, according to our previous assumption, necessitated addition of CH_2Cl_2 (7.9 mL, 10.507 g with ρ = 1.33 g·cm^{-3}) for 6 h. Concentration *in vacuo* and purification on silica gel (solvent combination not stated, we assumed the same conditions as Reaction N32 where the same compound was purified using *22.8 g* of silica gel and 570 mL of hexane/ethyl acetate 2:3 for an assumed weight of 1.14 g of crude product, which corresponds to 228 mL of hexane, *150.48 g* with ρ = 0.66 g·cm^{-3} and 342 mL of ethyl acetate, *307.8 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 85% yield (0.67 mmol, 422 mg).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (422 mg, 0.67 mmol) was reacted with sodium methoxide (1 M in MeOH, 3.35 mL, 3.35 mmol, 181 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 2.647 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (4.467 mL, 3.529 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 3.35 mmol HCl, corresponding to 3.35 mL, *3.417 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 220 mL MeCN/water 12:88, for an assumed weight of 440 mg of crude product, which corresponds to 26.4 mL of MeCN, 20.856 g with ρ = 0.79 g·cm^{-3} and 193.6 mL of water, 193.6 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.596 mmol, **154 mg** calculated with a molecular weight of 258.2 g·mol^{-1}).

The reaction took a total of 34 h (10 min reaction setup + 40 min silylation + 20 min addition of reagents + 6 h glycosylation + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 19.65 mL of reaction solvent (3.95 mL MeCN + 7.9 mL CH_2Cl_2 + 7.8 mL MeOH), corresponding to 135.3 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate from Reaction S13, calculated as

$$\frac{19.65\ \text{mL}}{0.165\ \text{g}} + 0.395 * \frac{17.27\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate of 4.0 (Reaction S13), the preparation of **4a** had a sEF of 18.0, calculated as

$$\text{sEF} = \frac{0.1 + 0.612 + 0.396 + 0.396 * 4 + 0.027 + 0.005 + 0.181 - \mathbf{0.153}}{\mathbf{0.153}}$$

and (considering the cEF of the starting material of 1168) a cEF of 7780, calculated as

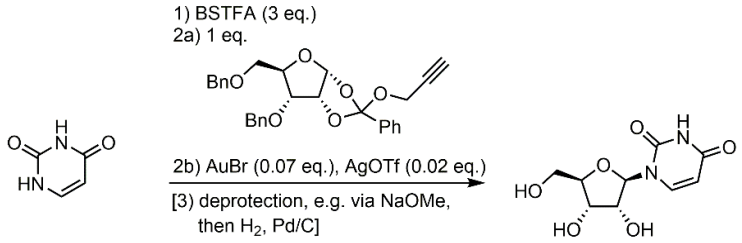
$$\text{cEF} = \frac{\begin{array}{c}0.1 + 0.612 + 0.396 + 0.396 * 1168 + 0.027 + 0.005 + 0.181 + 22.8 \\ +3.121 + 10.507 + 150.48 + 307.8 + 2.647 + 3.529 + 7.9 + 20.856 \\ +3.417 + 193.6 - \mathbf{0.153}\end{array}}{\mathbf{0.153}}$$

with combined contributions from reagents (22), inorganics (302), organic solvents (5997) and water (1464), considering the contribution from the starting material 3,5-di-*O*-benzoyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate.

Reaction N46

Rao *et al. J. Org. Chem.* **2015**, *80*, 1499−1505, doi: 10.1021/jo502413z

Reaction from their Scheme 1, compound **3b**



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 3 and 4, compound **3b**). Uracil (0.89 mmol, 100 mg) was first silylated with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (2.68 mmol, 689 mg) in MeCN (amount not stated, we assumed 4.45 mL for 0.2 M of the nucleobase, 3.516 g with ρ = 0.79 g·cm^{-3}) for 40 min. The silylated base was then reacted with 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate (0.89 mmol, 420 mg calculated with a molecular weight of 472.5 g·mol^{-1}), gold(III) bromide (0.06 mmol, 27 mg) and silver trifluoromethanesulfonate (0.02 mmol, 5 mg) in MeCN/CH_2Cl_2 1:2 which, according to our previous assumption, necessitated addition of CH_2Cl_2 (8.9 mL, 11.837 g with ρ = 1.33 g·cm^{-3}) for 3 h. Concentration *in vacuo* and purification on silica gel (solvent combination not stated, we assumed the same conditions as Reaction N32 where a similar compound was purified using *24.82 g* of silica gel and 620.5 mL of hexane/ethyl acetate 2:3 for an assumed weight of 1.241 g of crude product, which corresponds to 248.2 mL of hexane, *163.812 g* with ρ = 0.66 g·cm^{-3} and 372.3 mL of ethyl acetate, *335.07 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 93% yield (0.83 mmol, 440 mg).

For debenzoylation we assume the same method and conditions described in Reaction N32. The protected nucleoside (440 mg, 0.83 mmol) was reacted with sodium methoxide (1 M in MeOH, 4.15 mL, 4.15 mmol, 224 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 3.279 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (5.534 mL, 4.372 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 4.15 mmol HCl, corresponding to 4.15 mL, *4.233 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo* and coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) to yield a crude product. For removal of the benzyl groups we assume quantitative conversion by catalytic hydrogenation with palladium on charcoal* in methanol using a working concentration of 0.2 M, which equals a solvent amount of 4.15 mL (3.279 g with ρ = 0.9 g·cm^{-3} for methanol), 0.02 equivalents of palladium (0.02 mmol palladium, we assume 20 mg of solids) and hydrogen (we assume 20 eq. of gas, corresponding to 16.6 mmol, 33 mg calculated with a molecular weight of 2 g·mol^{-1}) for 1.5 h to yield

the unprotected nucleoside after drying which was purified by reverse phase HPLC (*using 342 mL MeCN/water 12:88, for an assumed weight of 684 mg of crude product, which corresponds to 41.04 mL of MeCN, 32.422 g with* ρ *= 0.79 g·cm*$^{-3}$ *and 300.96 mL of water, 300.96 g with* ρ *= 1.00 g·cm*$^{-3}$) to provide the unprotected nucleoside in 89% yield (0.739 mmol, **179 mg** calculated with a molecular weight of 242.2 g·mol^{-1}).

*we acknowledge that minor reduction of the pyrimidine base might occur under these conditions but, for the sake of this analysis, we assume that that doesn't happen (also see Johnson *et al. Org. Lett.* **2004**, *25*, 4643−4646, doi: 10.1021/ol048426w).

The reaction took a total of 33.25 h (10 min reaction setup + 40 min silylation + 20 min addition of reagents + 3 h glycosylation + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 15 min reaction setup + 90 min deprotection + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 27.18 mL of reaction solvent (4.45 mL MeCN + 8.9 mL CH_2Cl_2 + 13.83 mL MeOH), corresponding to 195.7 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate from Reaction S14, calculated as

$$\frac{27.18\ \text{mL}}{0.179\ \text{g}} + 0.42 * \frac{104.44\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate of 6.8 (Reaction S14), the preparation of **3b** had a sEF of 23.4, calculated as

$$\text{sEF} = \frac{0.1 + 0.689 + 0.42 + 0.42 * 6.8 + 0.027 + 0.005 + 0.224 + 0.02 + 0.033 - \mathbf{0.179}}{\mathbf{0.179}}$$

and (considering the cEF of the starting material of 2396) a cEF of 10632, calculated as

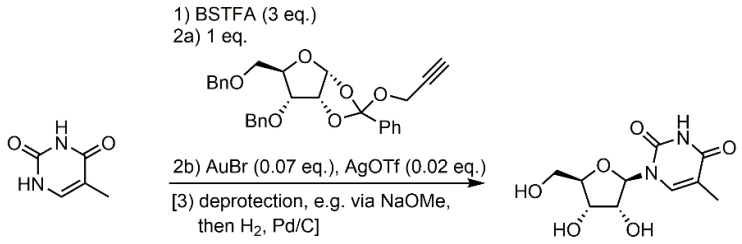
$$\text{cEF} = \frac{\begin{array}{c}0.1 + 0.689 + 0.42 + 0.42 * 2396 + 0.027 + 0.005 + 0.224 + 0.02 + 0.033 + 24.82 \\ +3.516 + 11.837 + 163.812 + 335.07 + 3.279 + 4.372 + 7.9 + 3.279 + 32.422 \\ +4.233 + 300.96 - \mathbf{0.179}\end{array}}{\mathbf{0.179}}$$

with combined contributions from reagents (30), inorganics (437), organic solvents (8124) and water (2048), considering the contribution from the starting material 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate.

Reaction N47

Rao *et al. J. Org. Chem.* **2015**, *80*, 1499−1505, doi: 10.1021/jo502413z

Reaction from their Scheme 1, compound **4b**



The experimental details for this synthesis were provided in the Experimental Section of the main text (page 3 and 5, compound **4b**). Thymine (0.79 mmol, 100 mg) was first silylated with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (2.37 mmol, 612 mg) in MeCN (amount not stated, we assumed 3.95 mL for 0.2 M of the nucleobase, 3.121 g with ρ = 0.79 g·cm^{-3}) for 40 min. The silylated base was then reacted with 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate (0.79 mmol, 373 mg calculated with a molecular weight of 472.5 g·mol^{-1}), gold(III) bromide (0.06 mmol, 27 mg) and silver trifluoromethanesulfonate (0.02 mmol, 5 mg) in 1:2 MeCN/CH_2Cl_2 1:2 which, according to our previous assumption, necessitated addition of CH_2Cl_2 (7.9 mL, 10.507 g with ρ = 1.33 g·cm^{-3}) for 6 h. Concentration *in vacuo* and purification on silica gel (solvent combination not stated, we assumed the same conditions as Reaction N32 where the same compound was purified using *22.34 g* of silica gel and 558.5 mL of hexane/ethyl acetate 2:3 for an assumed weight of 1.117 g of crude product, which corresponds to 223.4 mL of hexane, *147.444 g* with ρ = 0.66 g·cm^{-3} and 335.1 mL of ethyl acetate, *301.59 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 95% yield (0.75 mmol, 410 mg).

For debenzoylation we assume the same method and conditions described in Reaction N32. The protected nucleoside (410 mg, 0.75 mmol) was reacted with sodium methoxide (1 M in MeOH, 3.75 mL, 3.75 mmol, 203 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 2.963 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (5 mL, 3.95 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 3.75 mmol HCl, corresponding to 3.75 mL, *3.825 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo* and coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) to yield a crude product. For removal of the benzyl groups we assume quantitative conversion by catalytic hydrogenation with palladium on charcoal* in methanol using a working concentration of 0.2 M, which equals a solvent amount of 3.75 mL (2.963 g with ρ = 0.9 g·cm^{-3} for methanol), 0.02 equivalents of palladium (0.02 mmol palladium, we assume 20 mg of solids) and hydrogen (we assume 20 eq. of gas, corresponding to 15 mmol, 30 mg calculated with a molecular weight of 2 g·mol^{-1}) for 1.5 h to yield

the unprotected nucleoside after drying which was purified by reverse phase HPLC (*using 316.5 mL MeCN/water 12:88, for an assumed weight of 633 mg of crude product, which corresponds to 37.98 mL of MeCN, 30.004 g with* ρ *= 0.79 g·cm*$^{-3}$ *and 278.52 mL of water, 278.52 g with* ρ *= 1.00 g·cm*$^{-3}$) to provide the unprotected nucleoside in 89% yield (0.668 mmol, **172 mg** calculated with a molecular weight of 258.2 g·mol^{-1}).

*we acknowledge that minor reduction of the pyrimidine base might occur under these conditions but, for the sake of this analysis, we assume that that doesn't happen (also see Johnson *et al. Org. Lett.* **2004**, *25*, 4643−4646, doi: 10.1021/ol048426w).

The reaction took a total of 33.25 h (10 min reaction setup + 40 min silylation + 20 min addition of reagents + 3 h glycosylation + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 15 min reaction setup + 90 min deprotection + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 25.85 mL of reaction solvent (4.45 mL MeCN + 8.9 mL CH_2Cl_2 + 12.5 mL MeOH), corresponding to 189.2 mL per gram of product, considering the contribution of the starting material 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate from Reaction S14, calculated as

$$\frac{25.85\ \text{mL}}{0.172\ \text{g}} + 0.373 * \frac{104.44\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate of 6.8 (Reaction S14), the preparation of **4b** had a sEF of 21.7, calculated as

$$\text{sEF} = \frac{0.1 + 0.612 + 0.373 + 0.373 * 6.8 + 0.027 + 0.005 + 0.202 + 0.02 + 0.03 - \mathbf{0.172}}{\mathbf{0.172}}$$

and (considering the cEF of the starting material of 2396) a cEF of 9942, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.1 + 0.612 + 0.373 + 0.373 * 2396 + 0.027 + 0.005 + 0.203 + 0.02 + 0.03 + 22.34 \\ +3.121 + 10.507 + 147.444 + 301.59 + 2.963 + 3.95 + 7.9 + 2.963 + 30.004 \\ +3.825 + 278.52 - \mathbf{0.172}\end{array}}{\mathbf{0.172}}$$

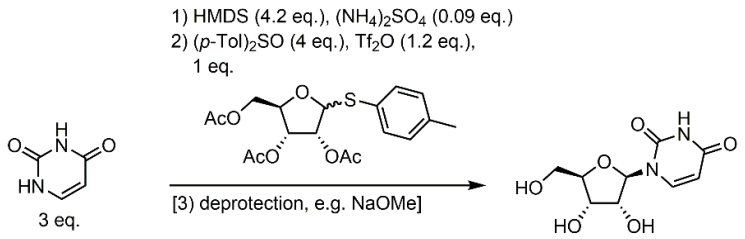
with combined contributions from reagents (27), inorganics (405), organic solvents (7556) and water (1958), considering the contribution from the starting material 3,5-di-*O*-benzyl-α-D-ribofuranoside (prop-2-yn-1-yl)-1,2-orthobenzoate.

Thioglycosides

Reaction N48

Liu *et al. Chem. Commun*. **2015**, *51*, 12803−12806, doi: 10.1039/c5cc03617h

Reaction from their Scheme 1, compound **9**



The experimental details for this synthesis were provided in the Supplementary Material (page 6, General procedure 1) and in Scheme 1 (page 2, compound **9**). This synthesis used silylated uracil, which was prepared by the authors beforehand and described in the same manuscript (Supplementary Material, page 5). We herein assume that silylation was carried out in the same pot prior to glycosylation and afforded a crude product which was used without further purification. Uracil (0.207 mmol, 23 mg calculated with a molecular weight of 112.1 g·mol^{-1}) was reacted with hexamethyldisilazane (0.29 mmol, 47 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and ammonium sulfate (0.006 mmol, 1 mg calculated with a molecular weight of 132.1 g·mol^{-1}) for 5 h. p-Tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose (0.069 mmol, 26 mg calculated with a molecular weight of 382.4 g·mol^{-1}) was first activated with 3 Å molecular sieves, *p*-tolyl sulfoxide (0.276 mmol, 91 mg calculated with a molecular weight of 330.3 g·mol^{-1}) and trifluoromethanesulfonic anhydride (0.083 mmol, 23 mg calculated with a molecular weight of 282.2 g·mol^{-1}) in CH_2Cl_2 (2.5 mL, 3.325 g with ρ = 1.33 g·cm^{-3}) for 50 min. The silylated nucleobase was then added as a solution in MeCN (0.7 mL, 553 mg with ρ = 0.79 g·cm^{-3}). After 4 h, the reaction was quenched with aqueous $NaHCO_3$ (1 mL, 1.1 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *0.239 g* of salt with a solubility of 217 g·L^{-1} and *0.861 g* of water), diluted with CH_2Cl_2 (amount not stated, we assumed twice the volume of the initial solution, corresponding to 7 mL, 9.31 g with ρ = 1.33 g·cm^{-3}), filtered, washed with brine (amount not stated, we assumed half the volume of the solution, corresponding to 5.1 mL, 6.069 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *2.185 g* of salt with a solubility of 360 g·L^{-1} and *3.884 g* of water), dried (we assume sodium sulfate was used, *0.204 g* for 10.2 mL of extract) and concentrated *in vacuo* to afford a crude product which was subjected to chromatography on silica gel (using *4.22 g* of silica gel and 131.875 mL of petroleum ether/ethyl acetate 1:3 for an assumed weight of 211 mg of crude product, which corresponds to 32.969 mL of petroleum ether,

21.430 g with ρ = 0.65 g·cm^{-3} and 98.906 mL of ethyl acetate, *89.016 g* with ρ = 0.90 g·cm^{-3}) to provide the nucleoside in 81% yield (0.056 mmol, 21 mg calculated with a molecular weight of 370.1 g·mol^{-1}). For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (21 mg, 0.056 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.28 mL, 0.28 mmol, 15 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.221 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.373 mL, 0.295 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.28 mmol HCl, corresponding to 0.28 mL, *0.286 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 18 mL MeCN/water 12:88, for an assumed weight of 36 mg of crude product, which corresponds to 2.16 mL of MeCN, 1.706 g with ρ = 0.79 g·cm^{-3} and 15.84 mL of water, 15.84 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.050 mmol, **12 mg** calculated with a molecular weight of 242.2 g·mol^{-1}).

The reaction took a total of 33.83 h (15 min reaction setup + 5h silylation + 50 min donor activation + 5 min addition of material + 4 h glycosylation + 25 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 90 min deprotection + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 3.85 mL of reaction solvent (2.5 mL CH_2Cl_2 + 0.7 mL MeCN + 0.65 mL MeOH), corresponding to 323.5 mL per gram of product, considering the contribution of the starting material p-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose from Reaction S15, calculated as

$$\frac{3.85\ \text{mL}}{0.012\ \text{g}} + 0.026 * \frac{103.8\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material p-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose of 10.3 (Reaction S15), the preparation of **9** had a sEF of 40.2, calculated as

$$\text{sEF} = \frac{0.023 + 0.047 + 0.001 + 0.026 + 0.026 * 10.3 + 0.091 + 0.023 + 0.015 - \mathbf{0.012}}{\mathbf{0.012}}$$

and (considering the cEF of the starting material of 2532) a cEF of 18433, calculated as

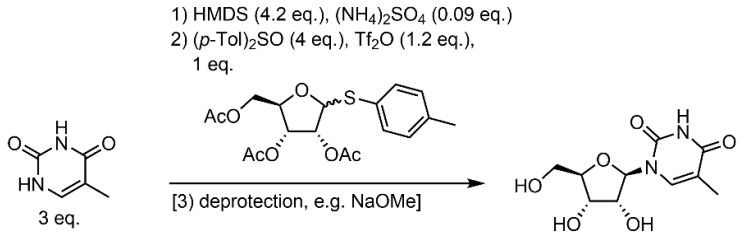
$$\text{cEF} = \frac{\begin{array}{c}0.023 + 0.047 + 0.001 + 0.026 + 0.026 * 2532 + 0.091 + 0.023 + 0.015 + 0.239 + 2.185 + 0.204 + 4.22 \\ +3.325 + 0.553 + 9.31 + 21.43 + 89.016 + 0.221 + 0.295 + 1.58 + 1.706 \\ +0.861 + 3.884 + 0.286 + 15.84 - \mathbf{0.012}\end{array}}{\mathbf{0.012}}$$

with combined contributions from reagents (45), inorganics (900), organic solvents (15406) and water (2095), considering the contribution from the starting material p-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose.

Reaction N49

Liu *et al. Chem. Commun*. **2015**, *51*, 12803−12806, doi: 10.1039/c5cc03617h

Reaction from their Scheme 1, compound **10**



The experimental details for this synthesis were provided in the Supplementary Material (page 6, General procedure 1) and in Scheme 1 (page 2, compound **10**). This synthesis used silylated thymine, which was prepared by the authors beforehand and described in the same manuscript (Supplementary Material, page 5). We herein assume that silylation was carried out in the same pot prior to glycosylation and afforded a crude product which was used without further purification. Thymine (0.207 mmol, 26 mg calculated with a molecular weight of 126.1 g·mol^{-1}) was reacted with hexamethyldisilazane (0.29 mmol, 47 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and ammonium sulfate (0.006 mmol, 1 mg calculated with a molecular weight of 132.1 g·mol^{-1}) for 5 h. p-Tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose (0.069 mmol, 26 mg calculated with a molecular weight of 382.4 g·mol^{-1}) was first activated with 3 Å molecular sieves, *p*-tolyl sulfoxide (0.276 mmol, 91 mg calculated with a molecular weight of 330.3 g·mol^{-1}) and trifluoromethanesulfonic anhydride (0.083 mmol, 23 mg calculated with a molecular weight of 282.2 g·mol^{-1}) in CH_2Cl_2 (2.5 mL, 3.325 g with ρ = 1.33 g·cm^{-3}) for 50 min. The silylated nucleobase was then added as a solution in MeCN (0.7 mL, 553 mg with ρ = 0.79 g·cm^{-3}). After 4 h, the reaction was quenched with aqueous $NaHCO_3$ (1 mL, 1.1 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *0.239 g* of salt with a solubility of 217 g·L^{-1} and *0.861 g* of water), diluted with CH_2Cl_2 (amount not stated, we assumed twice the volume of the initial solution, corresponding to 7 mL, 9.31 g with ρ = 1.33 g·cm^{-3}), filtered, washed with brine (amount not stated, we assumed half the volume of the solution, corresponding to 5.1 mL, 6.069 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *2.185 g* of salt with a solubility of 360 g·L^{-1} and *3.884 g* of water), dried (we assume sodium sulfate was used, *0.204 g* for 10.2 mL of extract) and concentrated *in vacuo* to afford a crude product which was subjected to chromatography on silica gel (using *4.28 g* of silica gel and 107 mL of petroleum ether/ethyl acetate 2:5 for an assumed weight of 214 mg of crude product, which corresponds to 42.8 mL of petroleum ether, *27.82 g* with ρ = 0.65 g·cm^{-3} and 64.2 mL of ethyl acetate, *57.78 g* with ρ = 0.90 g·cm^{-3}) to provide the nucleoside in 81% yield (0.056 mmol, 21 mg calculated with a molecular weight of 384.1 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (21 mg, 0.056 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.28 mL, 0.28 mmol, 15 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.221 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.373 mL, 0.295 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.28 mmol HCl, corresponding to 0.28 mL, *0.286 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 18 mL MeCN/water 12:88, for an assumed weight of 36 mg of crude product, which corresponds to 2.16 mL of MeCN, 1.706 g with ρ = 0.79 g·cm^{-3} and 15.84 mL of water, 15.84 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.050 mmol, **13 mg** calculated with a molecular weight of 258.2 g·mol^{-1}).

The reaction took a total of 33.83 h (15 min reaction setup + 5h silylation + 50 min donor activation + 5 min addition of material + 4 h glycosylation + 25 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 90 min deprotection + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 3.85 mL of reaction solvent (2.5 mL CH_2Cl_2 + 0.7 mL MeCN + 0.65 mL MeOH), corresponding to 298.9 mL per gram of product, considering the contribution of the starting material p-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose from Reaction S15, calculated as

$$\frac{3.85\ \text{mL}}{0.013\ \text{g}} + 0.026 * \frac{103.8\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material p-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose of 10.3 (Reaction S15), the preparation of **10** had a sEF of 37.2, calculated as

$$\text{sEF} = \frac{0.026 + 0.047 + 0.001 + 0.026 + 0.026 * 10.3 + 0.091 + 0.023 + 0.015 - \mathbf{0.013}}{\mathbf{0.013}}$$

and (considering the cEF of the starting material of 2532) a cEF of 15109, calculated as

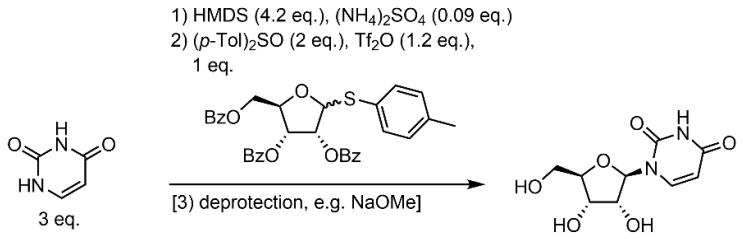
$$\text{cEF} = \frac{\begin{array}{c}0.026 + 0.047 + 0.001 + 0.026 + 0.026 * 2532 + 0.091 + 0.023 + 0.015 + 0.239 + 2.185 + 0.204 + 4.28 \\ +3.325 + 0.553 + 9.31 + 27.82 + 57.78 + 0.221 + 0.295 + 1.58 + 1.706 \\ +0.861 + 3.884 + 0.286 + 15.84 - \mathbf{0.013}\end{array}}{\mathbf{0.013}}$$

with combined contributions from reagents (42), inorganics (835), organic solvents (12309) and water (1933), considering the contribution from the starting material p-tolyl-2,3,5-tri-*O*-acetyl-1-thio-D-ribose.

Reaction N50

Liu *et al. Chem. Commun*. **2015**, *51*, 12803−12806, doi: 10.1039/c5cc03617h

Reaction from their Scheme 1, compound **18**



The experimental details for this synthesis were provided in the Supplementary Material (page 6, General procedure 1) and in Scheme 1 (page 2, compound **18**). This synthesis used silylated uracil, which was prepared by the authors beforehand and described in the same manuscript (Supplementary Material, page 5). We herein assume that silylation was carried out in the same pot prior to glycosylation and afforded a crude product which was used without further purification. Uracil (0.207 mmol, 23 mg calculated with a molecular weight of 112.1 g·mol^{-1}) was reacted with hexamethyldisilazane (0.29 mmol, 47 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and ammonium sulfate (0.006 mmol, 1 mg calculated with a molecular weight of 132.1 g·mol^{-1}) for 5 h. p-Tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose (0.069 mmol, 39 mg calculated with a molecular weight of 568.6 g·mol^{-1}) was first activated with 3 Å molecular sieves, *p*-tolyl sulfoxide (0.138 mmol, 46 mg calculated with a molecular weight of 330.3 g·mol^{-1}) and trifluoromethanesulfonic anhydride (0.083 mmol, 23 mg calculated with a molecular weight of 282.2 g·mol^{-1}) in CH_2Cl_2 (2.5 mL, 3.325 g with ρ = 1.33 g·cm^{-3}) for 50 min. The silylated nucleobase was then added as a solution in MeCN (0.7 mL, 553 mg with ρ = 0.79 g·cm^{-3}). After 4 h, the reaction was quenched with aqueous $NaHCO_3$ (1 mL, 1.1 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *0.239 g* of salt with a solubility of 217 g·L^{-1} and *0.861 g* of water), diluted with CH_2Cl_2 (amount not stated, we assumed twice the volume of the initial solution, corresponding to 7 mL, 9.31 g with ρ = 1.33 g·cm^{-3}), filtered, washed with brine (amount not stated, we assumed half the volume of the solution, corresponding to 5.1 mL, 6.069 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *2.185 g* of salt with a solubility of 360 g·L^{-1} and *3.884 g* of water), dried (we assume sodium sulfate was used, *0.204 g* for 10.2 mL of extract) and concentrated *in vacuo* to afford a crude product which was subjected to chromatography on silica gel (using *3.58 g* of silica gel and 89.5 mL of petroleum ether/ethyl acetate 2:3 for an assumed weight of 179 mg of crude product, which corresponds to 35.8 mL of petroleum ether, *23.27 g* with ρ = 0.65 g·cm^{-3} and 53.7 mL of ethyl acetate, *48.33 g* with ρ = 0.90 g·cm^{-3}) to provide the nucleoside in 85% yield (0.059 mmol, 33 mg calculated with a molecular weight of 556.5 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (33 mg, 0.059 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.295 mL, 0.295 mmol, 16 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.233 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.393 mL, 0.31 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.295 mmol HCl, corresponding to 0.295 mL, *0.301 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 24.5 mL MeCN/water 12:88, for an assumed weight of 49 mg of crude product, which corresponds to 2.94 mL of MeCN, 2.323 g with ρ = 0.79 g·cm^{-3} and 21.56 mL of water, 21.56 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.053 mmol, **13 mg** calculated with a molecular weight of 242.2 g·mol^{-1}).

The reaction took a total of 33.83 h (15 min reaction setup + 5h silylation + 50 min donor activation + 5 min addition of material + 4 h glycosylation + 25 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 90 min deprotection + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 3.89 mL of reaction solvent (2.5 mL CH_2Cl_2 + 0.7 mL MeCN + 0.69 mL MeOH), corresponding to 355.7 mL per gram of product, considering the contribution of the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose from Reaction S16, calculated as

$$\frac{3.89\ \text{mL}}{0.013\ \text{g}} + 0.039 * \frac{144.9\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose of 9.4 (Reaction S16), the preparation of **18** had a sEF of 42.2, calculated as

$$\text{sEF} = \frac{0.023 + 0.047 + 0.001 + 0.039 + 0.039 * 9.4 + 0.046 + 0.023 + 0.016 - \mathbf{0.013}}{\mathbf{0.013}}$$

and (considering the cEF of the starting material of 3238) a cEF of 19149, calculated as

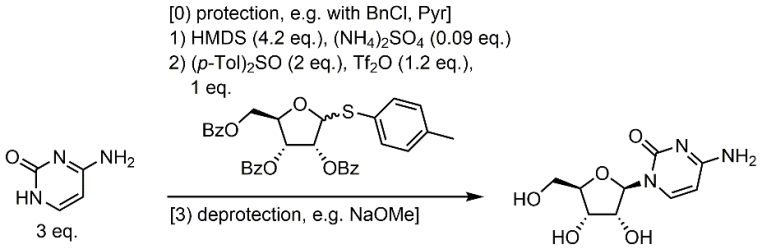
$$\text{cEF} = \frac{\begin{array}{c}0.023 + 0.047 + 0.001 + 0.039 + 0.039 * 3238 + 0.046 + 0.023 + 0.016 + 0.239 + 2.185 + 0.204 + 3.58 \\ +3.325 + 0.553 + 9.31 + 23.7 + 48.33 + 0.233 + 0.31 + 1.58 + 2.323 \\ +0.861 + 3.884 + 0.301 + 21.56 - \mathbf{0.013}\end{array}}{\mathbf{0.013}}$$

with combined contributions from reagents (51), inorganics (1042), organic solvents (15525) and water (2545), considering the contribution from the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose.

Reaction N51

Liu *et al. Chem. Commun*. **2015**, *51*, 12803−12806, doi: 10.1039/c5cc03617h

Reaction from their Scheme 1, compound **20**



The experimental details for this synthesis were provided in the Supplementary Material (page 6, General procedure 1) and in Scheme 1 (page 2, compound **20**). For the preparation of *N4*-benzoylcytosine we assume that cytosine could be benzoylated prior to the reaction and used as a crude product without further purification. We assume the conditions used by Mondal and Mugesh (*Chem. Eur. J.* **2019**, 25, 1–9, doi: 10.1002/chem.201805112) and adjusted their quantities to the scale of this synthesis. Cytosine (0.207 mmol, 23 mg calculated with a molecular weight of 111.1 g·mol^{-1}) was reacted with benzoyl chloride (0.863 mmol, 121 mg calculated with a molecular weight of 140.6 g·mol^{-1}) in pyridine (0.759 mL, 0.744 g with ρ = 0.98 g·cm^{-3}) for 6 h. The reaction was quenched with EtOH (0.362 mL, 286 mg with ρ = 0.79 g·cm^{-3}) and 30 min later with water (2.296 mL, 2.296 g with ρ = 1.00 g·cm^{-3}). The solution was stirred for 15 h and the resulting solid isolated by filtration. We assume that this solid could directly be used in the subsequent glycosylation reaction.

The benzoylated base was then silylated (Supplementary Material, page 5). We herein assume that silylation was carried out in the same pot prior to glycosylation and afforded a crude product which was used without further purification. *N*4-benzoylcytosine (0.207 mmol, 45 mg calculated with a molecular weight of 217.2 g·mol^{-1}) was reacted with hexamethyldisilazane (0.29 mmol, 47 mg calculated with a molecular weight of 161.4 g·mol^{-1}) and ammonium sulfate (0.006 mmol, 1 mg calculated with a molecular weight of 132.1 g·mol^{-1}) for 5 h. p-Tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose (0.069 mmol, 39 mg calculated with a molecular weight of 568.6 g·mol^{-1}) was first activated with 3 Å molecular sieves, *p*-tolyl sulfoxide (0.138 mmol, 46 mg calculated with a molecular weight of 330.3 g·mol^{-1}) and trifluoromethanesulfonic anhydride (0.083 mmol, 23 mg calculated with a molecular weight of 282.2 g·mol^{-1}) in CH_2Cl_2 (2.5 mL, 3.325 g with ρ = 1.33 g·cm^{-3}) for 50 min. The silylated nucleobase was then added as a solution in MeCN (0.7 mL, 553 mg with ρ = 0.79 g·cm^{-3}). After 4 h, the reaction was quenched with aqueous $NaHCO_3$ (1 mL, 1.1 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *0.239 g* of salt with a solubility of 217 g·L^{-1} and *0.861 g* of water), diluted with CH_2Cl_2 (amount not stated, we assumed twice the volume of the initial solution, corresponding to 7 mL, 9.31 g with ρ = 1.33 g·cm^{-3}), filtered,

washed with brine (amount not stated, we assumed half the volume of the solution, corresponding to 5.1 mL, 6.069 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *2.185 g* of salt with a solubility of 360 g·L^{-1} and *3.884 g* of water), dried (we assume sodium sulfate was used, *0.204 g* for 10.2 mL of extract) and concentrated *in vacuo* to afford a crude product which was subjected to chromatography on silica gel (using *4.02 g* of silica gel and 100.5 mL of petroleum ether/ethyl acetate 2:3 for an assumed weight of 201 mg of crude product, which corresponds to 40.2 mL of petroleum ether, *26.13 g* with ρ = 0.65 g·cm^{-3} and 60.3 mL of ethyl acetate, *54.27 g* with ρ = 0.90 g·cm^{-3}) to provide the nucleoside in quantitative yield (0.069 mmol, 46 mg calculated with a molecular weight of 661.2 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (46 mg, 0.069 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.345 mL, 0.345 mmol, 19 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.273 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.46 mL, 0.363 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.345 mmol HCl, corresponding to 0.345 mL, *0.352 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 32.5 mL MeCN/water 12:88, for an assumed weight of 65 mg of crude product, which corresponds to 3.9 mL of MeCN, 3.081 g with ρ = 0.79 g·cm^{-3} and 28.6 mL of water, 28.6 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.061 mmol, **15 mg** calculated with a molecular weight of 245.1 g·mol^{-1}).

The reaction took a total of 55.75 h (15 min reaction setup + 6 h benzoylation + 35 min workup + 15 h precipitation + 5 min filtration + 15 min reaction setup + 5h silylation + 50 min donor activation + 5 min addition of material + 4 h glycosylation + 25 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 90 min deprotection + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 4.76 mL of reaction solvent (0.76 mL pyridine + 2.5 mL CH_2Cl_2 + 0.7 mL MeCN + 0.8 mL MeOH), corresponding to 373.8 mL per gram of product, considering the contribution of the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose from Reaction S16, calculated as

$$\frac{4.76\ \text{mL}}{0.015\ \text{g}} + 0.039 * \frac{144.9\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose of 9.4 (Reaction S16), the preparation of **20** had a sEF of 44.7, calculated as

$$\text{sEF} = \frac{0.023 + 0.121 + 0.047 + 0.001 + 0.039 + 0.039 * 9.4 + 0.046 + 0.023 + 0.019 - \mathbf{0.015}}{\mathbf{0.015}}$$

and (considering the cEF of the starting material of 3238) a cEF of 17943 calculated as

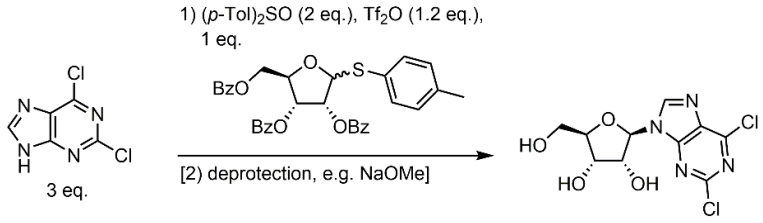
$$\mathrm{cEF} = \frac{\begin{array}{c}0.023 + 0.121 + 0.047 + 0.001 + 0.039 + 0.039 * 3238 + 0.046 + 0.023 + 0.019 \\ +0.239 + 2.185 + 0.204 + 4.02 \\ +0.744 + 0.286 + 3.325 + 0.553 + 9.31 + 26.13 + 54.27 + 0.273 + 0.363 + 1.58 + 3.081 \\ +2.296 + 0.861 + 3.884 + 0.352 + 28.6 - \mathbf{0.015}\end{array}}{\mathbf{0.015}}$$

with combined contributions from reagents (52), inorganics (932), organic solvents (14139) and water (2831), considering the contribution from the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose.

Reaction N52

Liu *et al. Chem. Commun*. **2015**, *51*, 12803−12806, doi: 10.1039/c5cc03617h

Reaction from their Scheme 1, compound **21**



The experimental details for this synthesis were provided in the Supplementary Material (page 6, General procedure 1) and in Scheme 1 (page 2, compound **21**). *p*-Tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose (0.069 mmol, 39 mg calculated with a molecular weight of 568.6 g·mol^{-1}) was first activated with 3 Å molecular sieves, *p*-tolyl sulfoxide (0.138 mmol, 46 mg calculated with a molecular weight of 330.3 g·mol^{-1}) and trifluoromethanesulfonic anhydride (0.083 mmol, 23 mg calculated with a molecular weight of 282.2 g·mol^{-1}) in CH_2Cl_2 (2.5 mL, 3.325 g with ρ = 1.33 g·cm^{-3}) for 50 min. 2,6-Dichloropurine (0.207 mmol, 39 mg calculated with a molecular weight of 189 g·mol^{-1}) was then added as a solution in MeCN (0.7 mL, 553 mg with ρ = 0.79 g·cm^{-3}). Reaction time was not stated, we assumed that "warming to rt [from −40 °C] gradually" took 30 min. The reaction was the quenched with triethylamine (0.1 mL, 0.73 g with ρ = 0.73 g·cm^{-3}), diluted with CH_2Cl_2 (amount not stated, we assumed twice the volume of the initial solution, corresponding to 6.6 mL, 8.778 g with ρ = 1.33 g·cm^{-3}), filtered, washed with brine (amount not stated, we assumed half the volume of the solution, corresponding to 4.95 mL, 5.891 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *2.153 g* of salt with a solubility of 360 g·L^{-1} and *3.738 g* of water), dried (we assume sodium sulfate was used, *0.198 g* for 9.9 mL of extract) and concentrated *in vacuo* to afford a crude product which was subjected to chromatography on silica gel (using *2.94 g* of silica gel and 73.5 mL of petroleum ether/ethyl acetate 2:1 for an assumed weight of 147 mg of crude product, which corresponds to 49 mL of petroleum ether, *31.85 g* with ρ = 0.65 g·cm^{-3} and 24.5 mL of ethyl acetate, *22.05 g* with ρ = 0.90 g·cm^{-3}) to provide the nucleoside in quantitative yield (0.069 mmol, 44 mg calculated with a molecular weight of 633.4 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (44 mg, 0.069 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.345 mL, 0.345 mmol, 19 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.273 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.46 mL, 0.363 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.345 mmol HCl, corresponding to 0.345 mL, *0.352 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification

by reverse phase HPLC (*using 31.5 mL MeCN/water 12:88, for an assumed weight of 63 mg of crude product, which corresponds to 3.78 mL of MeCN, 2.986 g with* ρ *= 0.79 g·cm*$^{-3}$ *and 27.72 mL of water, 27.72 g with* ρ *= 1.00 g·cm*$^{-3}$) to provide the unprotected nucleoside in 89% yield (0.061 mmol, **20 mg** calculated with a molecular weight of 321.1 g·mol^{-1}).

The reaction took a total of 27.42 h (20 min reaction setup + 50 min donor activation + 5 min addition of material + 30 min glycosylation + 25 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 90 min deprotection + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 4 mL of reaction solvent (2.5 mL CH_2Cl_2 + 0.7 mL MeCN + 0.8 mL MeOH), corresponding to 205.7 mL per gram of product, considering the contribution of the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose from Reaction S16, calculated as

$$\frac{4\ \text{mL}}{0.02\ \text{g}} + 0.039 * \frac{144.9\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose of 9.4 (Reaction S16), the preparation of **21** had a sEF of 25.6, calculated as

$$\text{sEF} = \frac{0.039 + 0.039 * 9.4 + 0.046 + 0.023 + 0.039 + 0.019 - \mathbf{0.02}}{\mathbf{0.02}}$$

and (considering the cEF of the starting material of 3238) a cEF of 11801, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.039 + 0.039 * 3238 + 0.046 + 0.023 + 0.039 + 0.019 \\ +2.153 + 0.198 + 2.94 \\ +3.325 + 0.553 + 0.73 + 8.778 + 31.85 + 22.05 + 0.273 + 0.363 + 1.58 + 2.986 \\ +3.738 + 0.352 + 27.72 - \mathbf{0.02}\end{array}}{\mathbf{0.02}}$$

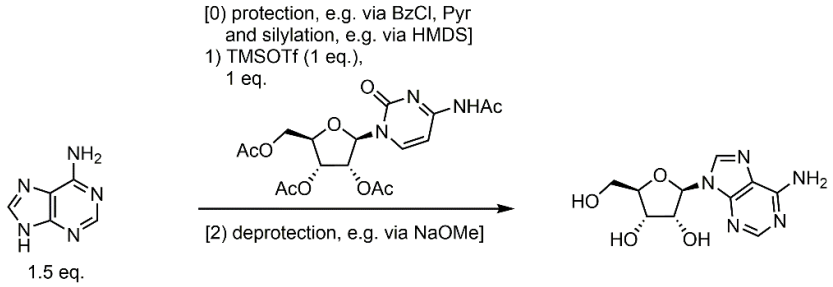
with combined contributions from reagents (32), inorganics (631), organic solvents (9233) and water (1914), considering the contribution from the starting material p-tolyl-2,3,5-tri-*O*-benzoyl-1-thio-D-ribose.

Protected nucleosides

Reaction N53

Azuma and Isono *Chem. Pharm. Bull*. **1977**, *25*, 3347−3353, doi: 10.1248/cpb.25.3347

Reaction from their Chart 1, compound **5**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 6, experiment 8). This synthesis used bis-trimethylsilyl-*N*6-benzoyl-adenine, which we assume was prepared beforehand following the procedures of Liu *et al.* (*Bioorg. Med. Chem*. **2017**, *25*, 4579−4594, doi: 10.1016/j.bmc.2017.06.032; Experimental section, page 9, compound **7**) and Li and Piccirilli (*Synthesis* **2005**, *17*, 2865–2870, doi: 10.1055/s-2005-872204; Experimental section, page 4, synthesis toward compound **2b**). For the sake of this analysis, we assume that those syntheses provided quantitative yield. Quantities were scaled proportionally to this synthesis. Adenine (0.5 mmol, 68 mg) was reacted with benzoyl chloride (1 mmol, 141 mg calculated with a molecular weight of 140.6 g·mol^{-1}) in pyridine (0.845 mL, 828 mg with ρ = 0.98 g·cm^{-3}) for 18 h. The mixture was dried *in vacuo*, redissolved in methanol (1.014 mL, 801 mg with ρ = 0.79 g·cm^{-3}), adjusted to pH 9−10 with 2 M aqueous NaOH (amount not stated, we assumed 1 mL, 1.08 g with ρ = 1.08 g·cm^{-3}, corresponding to *80 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *1 g* of water) and neutralized with 20% aqueous HCl (amount not stated, we assumed 1 mL, 1.02 g with ρ = 1.02 g·cm^{-3}). Drying *in vacuo* yielded a crude product which was used in the subsequent step. The benzoylated nucleobase was reacted with hexamethyldisilazane (1.25 mL, 963 mg with ρ = 0.77 g·cm^{-3}) in pyridine (0.625 mL, 613 mg with ρ = 0.98 g·cm^{-3}) for 3 h. Drying *in vacuo* for 18 h yielded a crude product that could be used without purification. The silylated nucleobase was dissolved in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) and reacted with 4*N*-2',3',5'-tri-*O*-tetraacetylcytidine (0.75 mmol, 288 mg) in dichloroethane (1.7 mL, 2.125 g with ρ = 1.25 g·cm^{-3}) and trimethylsilyl trifluoromethanesulfonate (0.5 mmol, 111 mg) in dichloroethane (0.5 mL, 625 mg with ρ = 1.25 g·cm^{-3}) for 15 h. Workup was not explicitly stated, so we assumed it was the same as in experiment 3 from the same paper. The reaction mixture was diluted with CH_2Cl_2 (10 mL, 13.3 g with ρ = 1.33 g·cm^{-3}), filtered and washed with saturated aqueous $NaHCO_3$ (amount not stated, we assumed an equal volume to the organic extract of 17.5 mL, 19.25 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*,

128–132, doi: 10.1021/je970197j; with *4.177 g* of salt with a solubility of 217 g·L^{-1} and *15.073 g* of water) and water (amount not stated, we assumed an equal volume to the organic extract of 17.5 mL, 17.5 g with ρ = 1.00 g·cm^{-3}), dried over sodium sulfate (350 mg for 17.5 mL of extract), and concentrated *in vacuo*. Column chromatography on silica gel (using 10 g of silica gel and 730 mL of $CHCl_3$/methanol 100:1 for an assumed weight of 1.46 g of crude product, which corresponds to 722.772 mL of $CHCl_3$, *1076.93 g* with ρ = 1.49 g·cm^{-3} and 7.228 mL of methanol, *5.71 g* with ρ = 0.79 g·cm^{-3}) to provide the nucleoside in 81% yield (0.405 mmol, 202 mg).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (202 mg, 0.405 mmol) was reacted with sodium methoxide (1 M in MeOH, 2.025 mL, 2.025 mmol, 109 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.6 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (2.7 mL, 2.133 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 2.025 mmol HCl, corresponding to 2.025 mL, *2.066 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 10 mL, *7.9 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 155.5 mL MeCN/water 12:88, for an assumed weight of 311 mg of crude product, which corresponds to 18.66 mL of MeCN, 14.741 g with ρ = 0.79 g·cm^{-3} and 136.84 mL of water, 136.84 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.361 mmol, **96 mg** calculated with a molecular weight of 267.2 g·mol^{-1}).

The reaction took a total of 83.17 h (10 min reaction setup + 18 h benzoylation + 30 min drying + 15 min workup + 30 min drying + 10 min reaction setup + 3 h silylation + 18 h drying + 25 min reaction setup + 15 h glycosylation + 25 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 10.41 mL of reaction solvent (0.85 mL pyridine + 0.63 mL pyridine + 2 mL MeCN + 2.2 mL dichloroethane + 4.73 mL MeOH), corresponding to 111.9 mL per gram of product, considering the contribution of the starting material 4*N*-2',3',5'-tri-*O*-tetraacetylcytidine from Reaction S17, calculated as

$$\frac{10.41\ \text{mL}}{0.096\ \text{g}} + 0.288 * \frac{12\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 4*N*-2',3',5'-tri-*O*-tetraacetylcytidine of 3.9 (Reaction S17), the preparation of **5** had a sEF of 28.2, calculated as

$$\text{sEF} = \frac{0.068 + 0.141 + 0.963 + 0.288 + 0.288 * 3.9 + 0.111 + 0.109 - \mathbf{0.096}}{\mathbf{0.096}}$$

and (considering the cEF of the starting material of 16) a cEF of 13783, calculated as

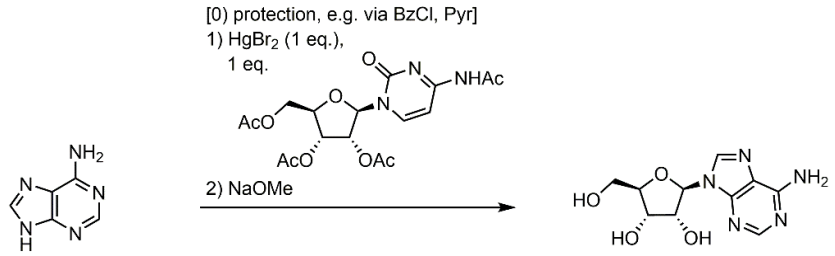
$$\mathrm{cEF} = \frac{\begin{array}{c} 0.068 + 0.141 + 0.963 + 0.288 + 0.111 + 0.109 \\ +0.08 + 4.177 + 0.35 + 10 \\ +0.828 + 0.801 + 0.613 + 1.58 + 2.125 + 0.625 + 13.3 + 1076.93 + 5.71 + 1.6 + 2.133 + 7.9 + 14.741 \\ +1 + 1.02 + 15.073 + 17.5 + 2.066 + 136.84 - \mathbf{0.096} \end{array}}{\mathbf{0.096}}$$

with combined contributions from reagents (33), inorganics (152), organic solvents (11795) and water (1807), considering the contribution from the starting material 4*N*-2',3',5'-tri-*O*-tetraacetylcytidine.

Reaction N54

Miyaki *et al. Chem. Pharm. Bull*. **1970**, *18*, 2459–2468, doi: 10.1248/cpb.18.2459

Reaction from their Chart 1, compound **IIIa**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 6). This synthesis used N6-benzoyladenine, which we assume was prepared in the same pot beforehand following the procedure of Liu *et al.* (*Bioorg. Med. Chem*. **2017**, *25*, 4579–4594, doi: 10.1016/j.bmc.2017.06.032; Experimental section, page 9, compound **7**). For the sake of this analysis, we assume that those syntheses provided quantitative yield. Quantities were scaled proportionally to this synthesis. Adenine (2.144 mmol, 292 mg) was reacted with benzoyl chloride (4.288 mmol, 605 mg calculated with a molecular weight of 140.6 g·mol^{-1}) in pyridine (3.623 mL, 3.551 g with ρ = 0.98 g·cm^{-3}) for 18 h. The mixture was dried *in vacuo*, redissolved in methanol (4.348 mL, 3.435 g with ρ = 0.79 g·cm^{-3}), adjusted to pH 9–10 with 2 M aqueous NaOH (amount not stated, we assumed 4 mL, 4.32 g with ρ = 1.08 g·cm^{-3}, corresponding to *320 mg* NaOH, calculated with a molecular weight of 40 g·mol^{-1}, and *4 g* of water) and neutralized with 20% aqueous HCl (amount not stated, we assumed 4 mL, 4.08 g with ρ = 1.02 g·cm^{-3}). Drying *in vacuo* yielded a crude product which was used in the subsequent step. The benzoylated nucleobase was reacted with 4*N*-2',3',5'-tri-*O*-tetraacetylcytidine (956 mg) and mercury bromide (720 mg) in xylene (4 mL, 3.44 g assuming ρ = 0.86 g·cm^{-3}) for 20 h. The mixture was dried *in vacuo* and extracted with $CHCl_3$ (amount not stated, we assumed 12.865 mL for 2.573 g of material, 19.169 g with ρ = 1.49 g·cm^{-3}). The resulting solution was washed with 30% potassium iodide (amount not stated, we assumed an equal volume to the organic phase of 12.865 mL, 16.725 g assuming ρ = 1.30 g·cm^{-3}, corresponding to 5.017 g of salt and 11.708 g of water) and water (amount not stated, we assumed an equal volume to the organic phase of 12.865 mL, 12.865 g with ρ = 1.00 g·cm^{-3}) and dried (we assumed sodium sulfate was used, 257 mg for 12.865 mL of extract). Column chromatography on silica gel (using 20 g of silica gel and 1287 mL of $CHCl_3$/methanol 99:1 for an assumed weight of 2.573 g of crude product, which corresponds to 1274.13 mL of $CHCl_3$, *1898.454 g* with ρ = 1.49 g·cm^{-3} and 12.87 mL of methanol, *10.167 g* with ρ = 0.79 g·cm^{-3}) to provide the protected nucleoside (770 mg). Deprotection was achieved in 0.1 M NaOMe in MeOH (71 mL, 383 mg NaOMe calculated with a molecular weight of 54 g·mol^{-1} and 56.09 g MeOH). Reaction time was not stated, we assumed 3 h. The mixture was applied to Dowex resin (OH^-)

and elution was performed with water/MeOH (4:1; 576.5 mL for an assumed weight of 1.153 g of crude product, which corresponds to 461.2 mL of water, *461.2 g* with ρ = 1.00 g·cm^{-3} and 115.3 mL of methanol, *91.087 g* with ρ = 0.79 g·cm^{-3}) to afford the β-nucleoside in 39% yield (**90 mg**).

The reaction took a total of 49.17 h (15 min reaction setup + 18 h benzoylation + 30 min drying + 15 min workup + 30 min drying + 15 min reaction setup + 20 h transglycosylation + 30 min drying + 15 min workup + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 3 h deprotection + 2 h purification + 30 min drying) and consumed a total of 78.62 mL of reaction solvent (3.62 mL pyridine + 4 mL xylene + 71 mL MeOH), , corresponding to 885.0 mL per gram of product, considering the contribution of the starting material 4*N*-2',3',5'-tri-*O*-tetraacetylcytidine from Reaction S17, calculated as

$$\frac{78.62\ \text{mL}}{0.09\ \text{g}} + 0.956 * \frac{12\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 4*N*-2',3',5'-tri-*O*-tetraacetylcytidine of 3.9 (Reaction S17), the preparation of **IIIa** had a sEF of 73.3, calculated as

$$\text{sEF} = \frac{0.292 + 0.605 + 0.956 + 0.956 * 3.9 + 0.72 + 0.383 - \mathbf{0.09}}{\mathbf{0.09}}$$

and (considering the cEF of the starting material of 16) a cEF of 29106, calculated as

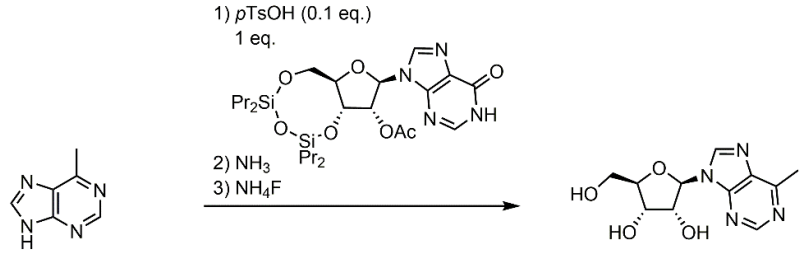
$$\text{cEF} = \frac{\begin{array}{c} 0.292 + 0.605 + 0.956 + 0.956 * 16 + 0.72 + 0.383 \\ +0.32 + 5.017 + 0.257 + 20 \\ +3.551 + 3.435 + 19.169 + 1898.454 + 10.167 + 56.09 + 91.087 \\ +4 + 4.08 + 11.708 + 12.865 + 461.2 - \mathbf{0.09} \end{array}}{\mathbf{0.09}}$$

with combined contributions from reagents (86), inorganics (284), organic solvents (23260) and water (5487), considering the contribution from the starting material 4*N*-2',3',5'-tri-*O*-tetraacetylcytidine.

Reaction N55

Boryski *Nucleo. & Nucleo.* **1998**, *17*, 1547–1556, doi: 10.1080/07328319808004685

Reaction from his Scheme 2, compound **9***



The experimental details for this synthesis were provided in the Materials and Methods section (page 8, compound **9***). 6-Methylpurine (1.5 mmol, 201 mg) was reacted with 2'-*O*-acetyl-3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine (1.5 mmol, 830 mg) and *p*-toluenesulfonic acid monohydrate (0.15 mmol, 29 mg) in chlorobenzene (25 mL, 27.75 g with ρ = 1.11 g·cm^{-3}) for 6 h. The solvent was evaporated *in vacuo* and the crude residue redissolved in CH_2Cl_2/EtOH (98:2, amount not stated, we assumed 5.3 mL for 1.06 g of material, corresponding to 5.194 mL of CH_2Cl_2, 6.908 g with ρ = 1.33 g·cm^{-3}) and 0.106 mL of EtOH, 84 mg with ρ = 0.79 g·cm^{-3}). The mixture was filtered, concentrated and the crude product purified by column chromatography on silica gel (using *21.2 g* of silica gel and 530 mL of CH_2Cl_2/EtOH 97:3, as the average of a linear gradient from 98:2 to 96:4, for an assumed weight of 1.06 g of crude product, which corresponds to 514.1 mL of CH_2Cl_2, *683.753 g* with ρ = 1.33 g·cm^{-3} and 15.9 mL of ethanol, *12.561 g* with ρ = 0.79 g·cm^{-3}) to provide the protected nucleoside in 91% yield (752 mg). For deactylation, the nucleoside was then dissolved in MeOH (30 mL, 23.7 g with ρ = 0.79 g·cm^{-3}) and added to methanolic ammonia (saturated at 0 °C, 6 mL, 4.68 g with ρ = 0.78 g·cm^{-3} we assume that the solution was 5 M, based on the data from Schäfer *et al. Chem. Eng. Data* **2007**, *52*, 1653–1659, doi: 10.1021/je700033y, which corresponds to 510 mg of ammonia and 4.17 g of MeOH) for 3.5 h. Concentration of the solution afforded the deacetylated nucleoside in quantitative yield (1.365 mmol, 665 mg). The following desilylation was described in the same manuscript (page 10, compound **5**) and quantities were scaled to this synthesis. The silylated nucleoside was reacted with ammonium fluoride (17.74 mmol, 658 mg) in MeOH (36.842 mL, 29.105 g with ρ = 0.79 g·cm^{-3}) for 16 h. The mixture was loaded onto silica gel (8 g) by evaporation of the solvent and column chromatography (using 661.5 mL of $CHCl_3$/MeOH 9:1 for an assumed weight of 1.323 g of crude product, which corresponds to 595.35 mL of $CHCl_3$, *887.072 g* with ρ = 1.49 g·cm^{-3} and 66.15 mL of MeOH, *52.289 g* with ρ = 0.79 g·cm^{-3}) afforded the deprotected nucleoside in 98% yield (1.338 mmol, **356 mg** calculated with a molecular weight of 266.3 g·mol^{-1})

***Compound **9** from Boryski still had the silyl protecting groups and was further dehydroxylated before deprotection. We assume that dehydrolyation was skipped and the resulting nucleoside was deprotected directly.

The reaction took a total of 33.17 h (15 min reaction setup + 6 h transglycosylation + 30 min drying + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 5 min reaction setup + 3.5 h deacetylation + 30 min drying + 10 min reaction setup + 16 h desilylation + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 97.84 mL of reaction solvent (25 mL chlorobenzene + 36 mL MeOH + 36.84 mL MeOH), corresponding to 286.8 mL per gram of product, considering the contribution of the starting material 2'-*O*-acetyl-3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine from Reaction S19, calculated as

$$\frac{97.84\ \mathrm{mL}}{0.356\ \mathrm{g}} + 0.83 * \frac{14.4\ \mathrm{mL}}{\mathrm{g}}$$

Thus, considering the sEF of the starting material 2'-*O*-acetyl-3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine of 0.9 (Reaction S19), the preparation of **9*** had a sEF of 7.3, calculated as

$$\mathrm{sEF} = \frac{0.201 + 0.83 + 0.83 * 0.9 + 0.51 + 0.658 - \mathbf{0.356}}{\mathbf{0.356}}$$

and (considering the cEF of the starting material of 1133) a cEF of 7581, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}0.201 + 0.83 + 0.83 * 1133 + 0.51 + 0.658 + 21.2 + 8 \\ +27.75 + 6.908 + 0.084 + 683.753 + 12.561 + 23.7 + 4.17 + 29.105 + 887.072 + 52.389 \\ \mathbf{-0.356}\end{array}}{\mathbf{0.356}}$$

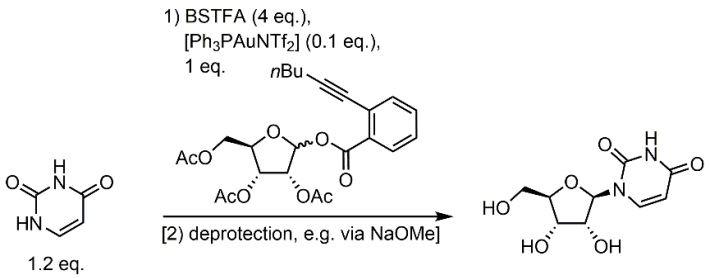
with combined contributions from reagents (13), inorganics (129), organic solvents (7436) and water (7), considering the contribution from the starting material 2'-*O*-acetyl-3'-5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-inosine.

***o*-Hexynylbenzoates**

Reaction N56

Zhang *et al. Angew. Chem. Int. Ed*. **2011**, *50*, 4933–4936, doi: 10.1002/anie.201100514

Reaction from their Scheme 2, compound **6**



The experimental details for this synthesis were provided in the Supplementary Material (page 6, general procedure). The exact details for this compound were not provided, so we assumed it was prepared according to the general procedure using the same quantities and materials as for single described compound (compound **3** in the same manuscript). Uracil (2.4 mmol, 269 mg) was reacted with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate (2 mmol, 921 mg calculated with a molecular weight of 460.5 g·mol^{-1}) and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (9.6 mmol, 2.515 g with ρ = 0.96 g·cm^{-3}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 30 min. After that, [$Ph_3PAuNTf_2$] (0.2 mmol, 148 mg) was added and the solution was stirred for 72 h. The mixture was dried *in vacuo* and subjected to purification on silica gel (using 77.06 g of silica gel and 1.926 L of hexane/ethyl acetate 2:1 for an assumed weight of 3.853 g of crude product, which corresponds to 1283.987 mL of hexane, *847.432 g* with ρ = 0.66 g·cm^{-3} and 642.013 mL of ethyl acetate, *577.812 g* with ρ = 0.90 g·cm^{-3}) to afford the protected nucleoside in 93% yield (1.86 mmol, 689 mg, calculated with a molecular weight of 370.3 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (689 mg, 1.86 mmol) was reacted with sodium methoxide (1 M in MeOH, 9.3 mL, 9.3 mmol, 502 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 7.347 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (12.4 mL, 9.796 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 9.3 mmol HCl, corresponding to 9.3 mL, *9.486 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 40 mL, *31.6 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 595.5 mL MeCN/water 12:88, for an assumed weight of 1.191 g of crude product, which corresponds to 71.46 mL of MeCN, 56.453 g with ρ = 0.79 g·cm^{-3} and 524.04 mL of water, 524.04 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (1.655 mmol, **401 mg** calculated with a molecular weight of 242.2 g·mol^{-1}).

The reaction took a total of 99.67 h (20 min reaction setup + 30 min silylation + 72 h glycosylation + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 23.7 mL of reaction solvent (2 mL MeCN + 21.7 mL MeOH), corresponding to 201.2 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate from Reaction S20, calculated as

$$\frac{23.7\ \text{mL}}{0.401\ \text{g}} + 0.921 * \frac{154.3\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate of 9.8 (Reaction S20), the preparation of **6** had a sEF of 31.1, calculated as

$$\text{sEF} = \frac{0.269 + 0.921 + 0.921 * 9.8 + 2.515 + 0.148 - \mathbf{0.401}}{\mathbf{0.401}}$$

and (considering the cEF of the starting material of 2679) a cEF of 11505, calculated as

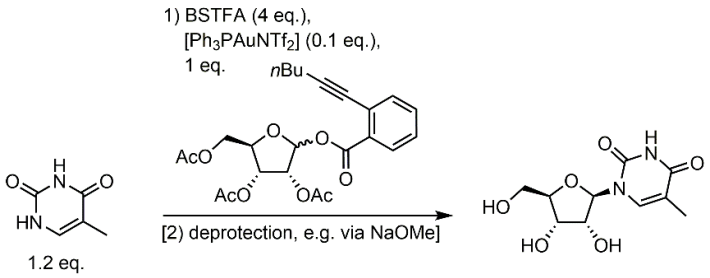
$$\text{cEF} = \frac{\begin{array}{c}0.269 + 0.921 + 0.921 * 2679 + 2.515 + 0.148 + 77.06 \\ +1.58 + 847.432 + 577.812 + 7.347 + 9.796 + 31.6 + 56.453 + 9.486 + 524.04 \\ \mathbf{-0.401}\end{array}}{\mathbf{0.401}}$$

with combined contributions from reagents (37), inorganics (548), organic solvents (9273) and water (1652), considering the contribution from the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate.

Reaction N57

Zhang *et al. Angew. Chem. Int. Ed*. **2011**, *50*, 4933–4936, doi: 10.1002/anie.201100514

Reaction from their Scheme 2, compound **7**



The experimental details for this synthesis were provided in the Supplementary Material (page 6, general procedure). The exact details for this compound were not provided, so we assumed it was prepared according to the general procedure using the same quantities and materials as for single described compound (compound **3** in the same manuscript). Thymine (2.4 mmol, 303 mg calculated with a molecular weight of 126.1 g·mol^{-1}) was reacted with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate (2 mmol, 921 mg calculated with a molecular weight of 460.5 g·mol^{-1}) and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (9.6 mmol, 2.515 g with ρ = 0.96 g·cm^{-3}) in MeCN (2 mL, 1.58 g with ρ = 0.79 g·cm^{-3}) for 30 min. After that, [$Ph_3PAuNTf_2$] (0.2 mmol, 148 mg) was added and the solution was stirred for 72 h. The mixture was dried *in vacuo* and subjected to purification on silica gel (using 77.74 g of silica gel and 1.944 L of hexane/ethyl acetate 2:1 for an assumed weight of 3.887 g of crude product, which corresponds to 1295.87 mL of hexane, *855.274 g* with ρ = 0.66 g·cm^{-3} and 648.13 mL of ethyl acetate, *583.317 g* with ρ = 0.90 g·cm^{-3}) to afford the protected nucleoside in 96% yield (1.92 mmol, 738 mg, calculated with a molecular weight of 384.3 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (738 mg, 1.92 mmol) was reacted with sodium methoxide (1 M in MeOH, 9.6 mL, 9.6 mmol, 518 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 7.584 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (12.8 mL, 10.112 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 9.6 mmol HCl, corresponding to 9.6 mL, *9.792 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 40 mL, *31.6 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 628 mL MeCN/water 12:88, for an assumed weight of 1.256 g of crude product, which corresponds to 75.36 mL of MeCN, 59.534 g with ρ = 0.79 g·cm^{-3} and 552.64 mL of water, 552.64 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (1.709 mmol, **441 mg** calculated with a molecular weight of 258.2 g·mol^{-1}).

The reaction took a total of 99.67 h (20 min reaction setup + 30 min silylation + 72 h glycosylation + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 24.4 mL of reaction solvent (2 mL MeCN + 22.4 mL MeOH), corresponding to 197.4 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate from Reaction S20, calculated as

$$\frac{24.4\ \text{mL}}{0.441\ \text{g}} + 0.921 * \frac{154.3\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate of 9.8 (Reaction S20), the preparation of **7** had a sEF of 28.3 calculated as

$$\text{sEF} = \frac{0.303 + 0.921 + 0.921 * 9.8 + 2.515 + 0.148 - \mathbf{0.441}}{\mathbf{0.441}}$$

and (considering the cEF of the starting material of 2679) a cEF of 10567, calculated as

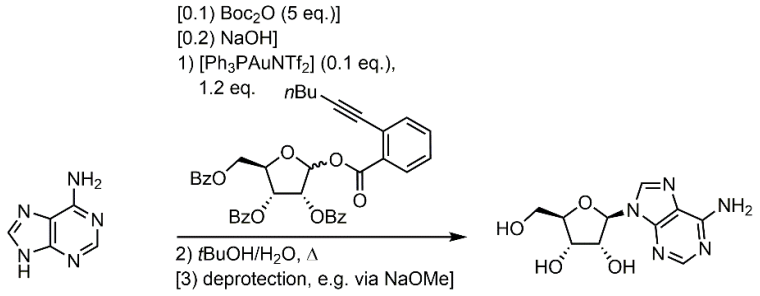
$$\text{cEF} = \frac{\begin{array}{c}0.303 + 0.921 + 0.921 * 2679 + 2.515 + 0.148 + 77.74 \\ +1.58 + 855.274 + 583.317 + 7.584 + 10.112 + 31.6 + 59.534 + 9.792 + 552.64 \\ -\mathbf{0.441}\end{array}}{\mathbf{0.441}}$$

with combined contributions from reagents (34), inorganics (500), organic solvents (8470) and water (1568), considering the contribution from the starting material 2,3,5-tri-*O*-acetyl-D-ribofuranosyl *ortho*-hexynylbenzoate.

Reaction N58

Zhang *et al. Angew. Chem. Int. Ed*. **2011**, *50*, 4933–4936, doi: 10.1002/anie.201100514

Reaction from their Scheme 2, compound **20**



The experimental details for this synthesis were provided in the Supplementary Material (pages 5, 10 and 15, general procedures). The exact details for this compound were not provided, so we assumed it was prepared according to the general procedures using the same quantities and materials as for described compounds. For the sake of simplicity, we assumed that Boc-protection of the nucleobases afforded the product in quantitative yield. Adenine (0.2 mmol, 27 mg, calculated with a molecular weight of 135.1 $gmol^{-1}$) was reacted with di-*tert*-butyl decarbonate (1 mmol, 218 mg) and 4-dimethylaminopyridine (0.02 mmol, 2 mg) in THF (1 mL, 890 mg with ρ = 0.89 $g \cdot cm^{-3}$) for 8 h. The mixture was then dried *in vacuo* and subjected to purification on silica gel (using 4.94 g of silica gel and 123.5 mL of petroleum ether/ethyl acetate 4:1 for an assumed weight of 247 mg of crude product, which corresponds to 98.8 mL of petroleum ether, *64.22 g* with ρ = 0.65 $g \cdot cm^{-3}$ and 24.7 mL of ethyl acetate, *22.23 g* with ρ = 0.90 $g \cdot cm^{-3}$) to afford the tris-Boc-nucleobase which was then dissolved in EtOH (2 mL, 1.58 g with ρ = 0.79 $g \cdot cm^{-3}$) and 1 M NaOH (1.73 mL, 1.803 g with ρ = 1.04 $g \cdot cm^{-3}$, corresponding to *69 mg* NaOH, calculated with a molecular weight of 40 $g \cdot mol^{-1}$, and *1.734 g* of water) for 80 h. The mixture was concentrated via coevaporation with water (10 mL, 10 g with ρ = 1.00 $g \cdot cm^{-3}$), acidified with acetic acid (amount not stated, we assumed 1.73 mmol, 104 mg calculated with a molecular weight of 60.1 $gmol^{-1}$) and filtered. The filtrate was collected, washed with water (amount not stated, we assumed 5 mL, 5 g with ρ = 1.00 $g \cdot cm^{-3}$) and dried *in vacuo* to yield the Boc-protected nucleobase (0.2 mmol, 67 mg calculated with a molecular weight of 335.4 $g \cdot mol^{-1}$). The nucleobase was then reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate (0.24 mmol, 155 mg) and 4 Å molecular sieves in CH_2Cl_2 (2 mL, 2.66 g with ρ = 1.33 $g \cdot cm^{-3}$) for 30 min before adding [$Ph_3PAuNTf_2$] (0.024 mmol, 18 mg) and stirring for 3 h. The mixture was filtered, concentrated *in vacuo* and subjected to purification on silica gel (using 4.8 g of silica gel and 120 mL of hexane/ethyl acetate 4:1 for an assumed weight of 240 mg of crude product, which corresponds to 96 mL of hexane, *63.36 g* with ρ = 0.66 $g \cdot cm^{-3}$ and 24 mL of ethyl acetate, *21.6 g* with ρ = 0.90 $g \cdot cm^{-3}$) to afford the protected nucleoside in 77% yield (0.154 mmol, 120 mg, calculated with a molecular

weight of 779.8 g·mol^{-1}). To remove the Boc groups according to the general procedure, the protected nucleoside (0.154 mmol, 120 mg) was heated under reflux for 8 h in *t*BuOH (3.08 mL, 2.402 g with ρ = 0.78 g·cm^{-3}) and water (3.08 mL, 3.08 g with ρ = 1.00 g·cm^{-3}). The mixture was then dried *in vacuo* and subjected to purification on silica gel (using 2.4 g of silica gel and 60 mL of hexane/ethyl acetate 1:2 for an assumed weight of 120 mg of crude product, which corresponds to 20 mL of hexane, *13.2 g* with ρ = 0.66 g·cm^{-3} and 40 mL of ethyl acetate, *36 g* with ρ = 0.90 g·cm^{-3}) to provide the benzoylated nucleoside in 93% yield (0.143 mmol, 83 mg, calculated with a molecular weight of 579.6 g·mol^{-1}).

For debenzoylation we assume the same method and conditions described in Reaction N32. The protected nucleoside (83 mg, 0.143 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.715 mL, 0.715 mmol, 39 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.565 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.954 mL, 0.754 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.715 mmol HCl, corresponding to 0.715 mL, *0.729 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 61 mL MeCN/water 12:88, for an assumed weight of 122 mg of crude product, which corresponds to 7.32 mL of MeCN, 5.783 g with ρ = 0.79 g·cm^{-3} and 53.68 mL of water, 53.68 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.127 mmol, **34 mg** calculated with a molecular weight of 267.2 g·mol^{-1}).

The reaction took a total of 134.5 h (15 min reaction setup + 8 h Boc-protection + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 80 h reaction time + 30 min drying + 15 min workup + 30 min drying + 15 min reaction setup + 3.5 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 8 h deprotection + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 8.4 mL of reaction solvent (1 mL THF + 2 mL EtOH + 1.73 mL NaOH + 2 mL CH_2Cl_2 + 1.67 mL MeOH), corresponding to 282.7 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate from Reaction S21, calculated as

$$\frac{8.4\ \text{mL}}{0.034\ \text{g}} + 0.155 * \frac{230.2\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate of 9.0 (Reaction S21), the preparation of **20** had a sEF of 53.5 calculated as

$$\text{sEF} = \frac{0.027 + 0.218 + 0.155 + 0.155 * 9 + 0.018 + 0.039 - \mathbf{0.034}}{\mathbf{0.034}}$$

and (considering the cEF of the starting material of 1790) a cEF of 17680, calculated as

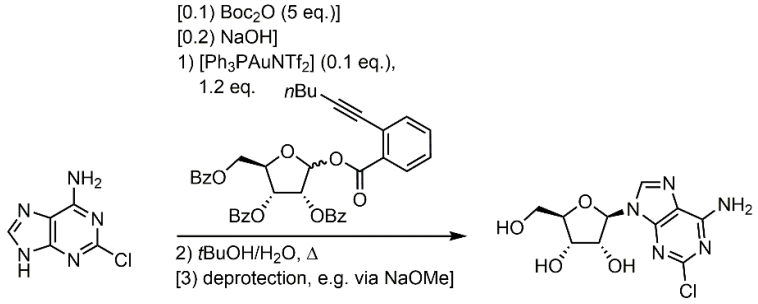
$$\mathrm{cEF} = \frac{\begin{array}{c}0.027 + 0.218 + 0.155 + 0.155 * 1790 + 0.018 + 0.039 + 4.94 + 0.069 + 4.8 + 2.4 + \\ +0.89 + 64.22 + 22.23 + 1.58 + 2.66 + 63.36 + 21.6 + 2.402 + 13.2 + 36 + 0.565 + 0.754 + 1.58 + 5.783 \\ +1.734 + 10 + 5 + 3.08 + 0.729 + 53.68\end{array}}{\mathbf{0.034}} \mathbf{-0.034}$$

with combined contributions from reagents (68), inorganics (724), organic solvents (14260) and water (2643), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate.

Reaction N59

Zhang *et al. Angew. Chem. Int. Ed*. **2011**, *50*, 4933–4936, doi: 10.1002/anie.201100514

Reaction from their Scheme 2, compound **21**



The experimental details for this synthesis were provided in the Supplementary Material (pages 5, 10 and 15, general procedures). The exact details for this compound were not provided, so we assumed it was prepared according to the general procedures using the same quantities and materials as for described compounds. For the sake of simplicity, we assumed that Boc-protection of the nucleobases afforded the product in quantitative yield. 2-chloroadenine (0.2 mmol, 34 mg, calculated with a molecular weight of 169.6 $g mol^{-1}$) was reacted with di-*tert*-butyl decarbonate (1 mmol, 218 mg) and 4-dimethylaminopyridine (0.02 mmol, 2 mg) in THF (1 mL, 890 mg with ρ = 0.89 $g \cdot cm^{-3}$) for 8 h. The mixture was then dried *in vacuo* and subjected to purification on silica gel (using 5.08 g of silica gel and 127 mL of petroleum ether/ethyl acetate 4:1 for an assumed weight of 254 mg of crude product, which corresponds to 101.6 mL of petroleum ether, *66.04 g* with ρ = 0.65 $g \cdot cm^{-3}$ and 25.4 mL of ethyl acetate, *22.86 g* with ρ = 0.90 $g \cdot cm^{-3}$) to afford the tris-Boc-nucleobase which was then dissolved in EtOH (2 mL, 1.58 g with ρ = 0.79 $g \cdot cm^{-3}$) and 1 M NaOH (1.73 mL, 1.803 g with ρ = 1.04 $g \cdot cm^{-3}$, corresponding to *69 mg* NaOH, calculated with a molecular weight of 40 $g \cdot mol^{-1}$, and *1.734 g* of water) for 80 h. The mixture was concentrated via coevaporation with water (10 mL, 10 g with ρ = 1.00 $g \cdot cm^{-3}$), acidified with acetic acid (amount not stated, we assumed 1.73 mmol, 104 mg calculated with a molecular weight of 60.1 $g mol^{-1}$) and filtered. The filtrate was collected, washed with water (amount not stated, we assumed 5 mL, 5 g with ρ = 1.00 $g \cdot cm^{-3}$) and dried *in vacuo* to yield the Boc-protected nucleobase (0.2 mmol, 54 mg calculated with a molecular weight of 269.7 $g \cdot mol^{-1}$). The nucleobase was then reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate (0.24 mmol, 155 mg) and 4 Å molecular sieves in CH_2Cl_2 (2 mL, 2.66 g with ρ = 1.33 $g \cdot cm^{-3}$) for 30 min before adding [$Ph_3PAuNTf_2$] (0.024 mmol, 18 mg) and stirring for 3 h. The mixture was filtered, concentrated *in vacuo* and subjected to purification on silica gel (using 4.54 g of silica gel and 113.5 mL of hexane/ethyl acetate 4:1 for an assumed weight of 227 mg of crude product, which corresponds to 90.8 mL of hexane, *59.928 g* with ρ = 0.66 $g \cdot cm^{-3}$ and 22.7 mL of ethyl acetate, *20.43 g* with ρ = 0.90 $g \cdot cm^{-3}$) to afford the protected nucleoside in 85% yield (0.17 mmol, 121 mg, calculated with a

molecular weight of 714.1 g·mol^{-1}). To remove the Boc groups according to the general procedure, the protected nucleoside (0.17 mmol, 121 mg) was heated under reflux for 8 h in *t*BuOH (3.4 mL, 2.652 g with ρ = 0.78 g·cm^{-3}) and water (3.4 mL, 3.4 g with ρ = 1.00 g·cm^{-3}). The mixture was then dried *in vacuo* and subjected to purification on silica gel (using 2.42 g of silica gel and 60.5 mL of hexane/ethyl acetate 1:2 for an assumed weight of 121 mg of crude product, which corresponds to 20.167 mL of hexane, *13.31 g* with ρ = 0.66 g·cm^{-3} and 40.333 mL of ethyl acetate, *36.3 g* with ρ = 0.90 g·cm^{-3}) to provide the benzoylated nucleoside in 93% yield (0.158 mmol, 97 mg, calculated with a molecular weight of 614.0 g·mol^{-1}).

For debenzoylation we assume the same method and conditions described in Reaction N32. The protected nucleoside (97 mg, 0.158 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.79 mL, 0.79 mmol, 43 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.624 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (1.056 mL, 0.834 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.79 mmol HCl, corresponding to 0.79 mL, *0.806 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 70 mL MeCN/water 12:88, for an assumed weight of 140 mg of crude product, which corresponds to 8.4 mL of MeCN, 6.636 g with ρ = 0.79 g·cm^{-3} and 61.6 mL of water, 61.6 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.141 mmol, **43 mg** calculated with a molecular weight of 301.7 g·mol^{-1}).

The reaction took a total of 134.5 h (15 min reaction setup + 8 h Boc-protection + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 80 h reaction time + 30 min drying + 15 min workup + 30 min drying + 15 min reaction setup + 3.5 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 8 h deprotection + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 8.58 mL of reaction solvent (1 mL THF + 2 mL EtOH + 1.73 mL NaOH + 2 mL CH_2Cl_2 + 1.85 mL MeOH), corresponding to 235.2 mL per gram of product, considering the contribution of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate from Reaction S21, calculated as

$$\frac{8.58\ \text{mL}}{0.043\ \text{g}} + 0.155 * \frac{230.2\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate of 9.0 (Reaction S21), the preparation of **21** had a sEF of 42.3 calculated as

$$\text{sEF} = \frac{0.034 + 0.218 + 0.155 + 0.155 * 9 + 0.018 + 0.043 - \mathbf{0.043}}{\mathbf{0.043}}$$

and (considering the cEF of the starting material of 1790) a cEF of 14102, calculated as

$$\mathrm{cEF} = \frac{\begin{array}{c}0.034 + 0.218 + 0.155 + 0.155 * 1790 + 0.018 + 0.043 + 5.08 + 0.069 + 4.54 + 2.42 \\ +0.89 + 64.22 + 22.23 + 1.58 + 2.66 + 59.928 + 20.43 + 2.652 + 13.31 \\ +36.3 + 0.624 + 0.834 + 1.58 + 6.636 \\ +1.734 + 10 + 5 + 3.4 + 0.806 + 61.6 \\ \mathbf{-0.043}\end{array}}{\mathbf{0.043}}$$

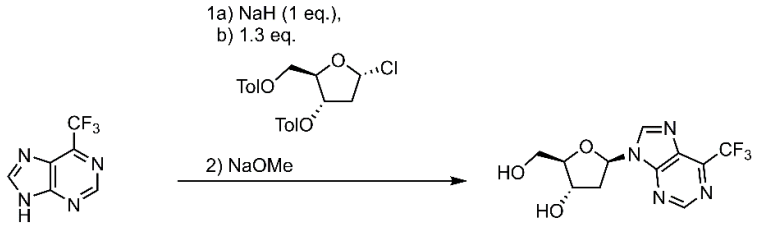
with combined contributions from reagents (54), inorganics (570), organic solvents (11206) and water (2284), considering the contribution from the starting material 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate.

Halogenoses

Reaction N60

Hockova *et al. Tetrahedron* **1999**, *55*, 11109–11118, doi: 10.1016/S0040-4020(99)00615-8

Reaction from their Scheme 1, compound **14**



The experimental details for this synthesis were provided in the Experimental section of the main text (pages 5 and 7, general procedures). We assumed that this compound was prepared according to the general procedure without alterations. 6-(Trifluoromethyl)purine (1.6 mmol, 300 mg) was reacted wit sodium hydride (1.6 mmol, 61 mg) in MeCN (15 mL, 11.85 g with ρ = 0.79 g·cm^{-3}) for 40 min. Then, 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose (2.1 mmol, 699 mg calculated with a molecular weight of 332.8 g·mol^{-1}) was added and the mixture was stirred for 4 h. The solvent was evaporated *in vacuo* and the protected nucleoside was obtained after purification on silica gel (using *21.2 g* of silica gel and 530 mL of petroleum ether/ethyl acetate for an assumed weight of 1.06 g of crude product; solvent mixture was not stated, so we assumed 2:1, which corresponds to 353.33 mL of petroleum ether, *229.664 g* with ρ = 0.65 g·cm^{-3} and 176.67 mL of ethyl acetate, *159.003 g* with ρ = 0.90 g·cm^{-3}) and recrystallization from EtOH (amount not stated, we assumed 10.6 mL for 1.06 g of crude product, 8.374 g with ρ = 0.79 g·cm^{-3}) in 81% yield (1.296 mmol, 700 mg). We assume that the general procedure provided in the same manuscript was applied for deprotection. We adjusted the quantities provided to the scale of this synthesis. The protected nucleoside (1.296 mmol, 700 mg) was dissolved in methanol (25.92 mL, 20.477 g with ρ = 0.79 g·cm^{-3}) and reacted with sodium methoxide (0.13 mL of a 1 M solution in MeOH, corresponding to 0.13 mmol NaOMe, 7 mg calculated with a molecular weight of 54 g·mol^{-1} and 103 mg MeOH) for 18 h. The mixture was concentrated and subjected to purification on silica gel (using *14.14 g* of silica gel and 353.5 mL of ethyl acetate for an assumed weight of 707 mg of crude product, which corresponds to 353.5 mL of ethyl acetate, *318.15 g* with ρ = 0.90 g·cm^{-3}) to afford the unprotected nucleoside in 37% yield (0.48 mmol, **146 mg** calculated with a molecular weight of 304.2 g·mol^{-1}).

The reaction took a total of 31.58 h (10 min reaction setup + 40 min deprotonation + 5 min addition of material + 4 h glycosylation + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying + 10 min reaction setup + 18 h deprotection + 30 min drying + 2 h purification + 30 min drying) and consumed a total of 40.9 mL of reaction solvent (15 mL MeCN + 25.9 mL MeOH),

corresponding to 292.7 mL per gram of product, considering the contribution of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose from Reaction S22, calculated as

$$\frac{40.9\ \text{mL}}{0.146\ \text{g}} + 0.699 * \frac{18\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose of 1.8 (Reaction S22), the preparation of **21** had a sEF of 14.9 calculated as

$$\text{sEF} = \frac{0.3 + 0.061 + 0.699 + 0.699 * 1.8 + 0.007 - \mathbf{0.146}}{\mathbf{0.146}}$$

and (considering the cEF of the starting material of 234) a cEF of 6489, calculated as

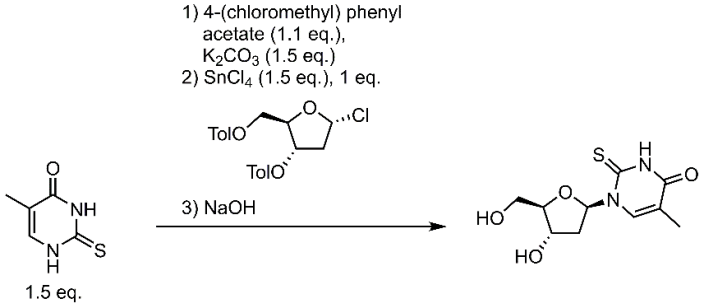
$$\text{cEF} = \frac{\begin{array}{c}0.3 + 0.061 + 0.699 + 0.699 * 234 + 0.007 + 21.2 + 14.14 \\ +11.85 + 229.664 + 159.003 + 8.374 + 20.477 + 0.103 + 318.15 \\ \mathbf{-0.146}\end{array}}{\mathbf{0.146}}$$

with combined contributions from reagents (22), inorganics (333), organic solvents (5422) and water (718), considering the contribution from the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose.

Reaction N61

Ackermann *et al. Nucleic Acids Research* **2013**, *41*, 4729–4739, doi: 10.1093/nar/gkt121

Reaction from their Experimental section, compound **10**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 4, compounds **9** and **10**). We assumed that the modification of the pyrimidine base was carried out beforehand and adjusted the quantities of that synthesis to the scale of the following glycosylation. 2-Thiothymine (19.532 mmol, 2.779 g) was reacted with 4-(chloromethyl)phenyl acetate (21.438 mmol, 3.97 g) and potassium carbonate (29.219 mmol, 4.049 g) in acetone (50 mL, 39 g with ρ = 0.78 g·cm^{-3}) for 3 h. The mixture was dried *in vacuo* and the residue was partitioned between CH_2Cl_2 (amount not stated, we assumed 53.99 mL for 10.798 g of material, *71.807 g* with ρ = 1.33 g·cm^{-3}) and 10% aqueous citric acid (amount not stated, we assumed 53.99 mL for 10.798 g of material, corresponding to *5.399 g* of citric acid and *48.591 g* of water assuming ρ = 1.00 g·cm^{-3}). The organic phase was dried over magnesium sulfate (*1.08 g* for 53.99 mL) and evaporated *in vacuo*. The product was obtained after recrystallization from CH_2Cl_2/CCl_4 (1:2, 80 mL, corresponding to 26.667 mL, 35.467 g of CH_2Cl_2 with ρ = 1.33 g·cm^{-3} and 53.333 mL, 84.799 g of CCl_4 with ρ = 1.59 g·cm^{-3}). The resulting product (11 mmol, 3.2 g) was reacted with bis(trimethylsilyl) acetamide (14.6 mmol, 2.97 g) in CH_2Cl_2 (50 mL, 66.5 g with ρ = 1.33 g·cm^{-3}). Reaction time was not stated, we assumed 30 min. After that, 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose (7.3 mmol, 2.84 g) and tin tetrachloride (11 mmol, 2.865 g calculated with a molecular weight of 260.5 g·mol^{-1}) were added and the mixture stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL, 110 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *23.87 g* of salt with a solubility of 217 g·L^{-1} and *86.13 g* of water), diluted with CH_2Cl_2 (100 mL, 133 g with ρ = 1.33 g·cm^{-3}), dried over magnesium sulfate (*3 g* for 150 mL) and evaporated *in vacuo*. The crude material was dissolved in MeOH (100 mL, 79 g with ρ = 0.79 g·cm^{-3}) and THF (100 mL, 89 g with ρ = 0.89 g·cm^{-3}). 1 M aqueous NaOH (40 mL, corresponding to 40 mmol NaOH, 1.6 g calculated with a molecular weight of 40.0 g·mol^{-1} and 38.4 g of water) was added, the mixture was stirred for 30 min, neutralized with aqueous citric acid (4 g of citric acid and 20 mL, 20 g of water with ρ = 1.00 g·cm^{-3}) and dried *in vacuo*. The resulting material was dissolved in MeOH (*44.525 mL* for 8.905 g

of material), dried over magnesium sulfate (*891 mg* for 44.525 mL) and adsorbed in silica (10 g). Purification on silica gel (using 50 g of silica gel and 4452.5 mL of hexane/ethyl acetate 1:3, as the average of a linear gradient from 1:1 hexane/ethyl acetate to 100% ethyl acetate, for an assumed weight of 8.905 g of crude product, which corresponds to 1113.125 mL of hexane, *734.663 g* with ρ = 0.66 g·cm^{-3} and 3339.375 mL of ethyl acetate, *3005.438 g* with ρ = 0.90 g·cm^{-3}) afforded the nucleoside as an anomeric mixture (1.35 g). The β-anomer was obtained after recrystallization from a mixture of EtOH (40 mL, 31.6 g with ρ = 0.79 g·cm^{-3}) and CH_2Cl_2 (40 mL, 53.2 g with ρ = 1.33 g·cm^{-3}) in 40% glycosylation yield (**750 mg**).

The reaction took a total of 16.5 h (15 min reaction setup + 3 h reaction time + 30 min drying + 15 min workup + 30 min drying + 2 h recrystallization + 30 min drying + 10 min reaction setup + 30 min silylation + 10 min reaction time + 1 h glycosylation + 15 min workup + 30 min drying + 10 min workup + 30 min stirring + 5 min workup + 30 min drying + 10 min workup + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying) and consumed a total of 220 mL of reaction solvent (50 mL acetone + 50 mL CH_2Cl_2 + 40 mL MeOH + 40 mL THF + 40 mL aqueous NaOH), corresponding to 344.5 mL per gram of product, considering the contribution of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose from Reaction S22, calculated as

$$\frac{220\ \text{mL}}{0.75\ \text{g}} + 2.84 * \frac{18\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose of 1.8 (Reaction S22), the preparation of **10** had a sEF of 35.0 calculated as

$$\text{sEF} = \frac{2.779 + 3.97 + 4.049 + 5.399 + 2.84 + 2.84 * 1.8 + 2.865 - \mathbf{0.75}}{\mathbf{0.75}}$$

and (considering the cEF of the starting material of 234) a cEF of 7255, calculated as

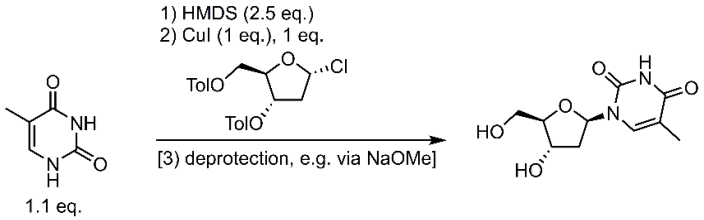
$$\text{cEF} = \frac{\begin{array}{c}2.779 + 3.97 + 4.049 + 5.399 + 2.84 + 2.84 * 234 + 2.865 + 1.08 + 23.87 + 3 + 1.6 + 4 + 0.891 + 10 + 50 \\ +39 + 71.807 + 35.467 + 84.799 + 66.5 + 133 + 79 + 89 + 44.525 + 734.663 + 3005.438 + 31.6 + 53.2 \\ +48.591 + 86.13 + 38.4 + 20 \\ -\mathbf{0.75}\end{array}}{\mathbf{0.75}}$$

with combined contributions from reagents (41), inorganics (198), organic solvents (6196) and water (825), considering the contribution from the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose.

Reaction N62

Freskos *et al. Nucleosides & Nucleotides* **1989**, *8*, 549–555, doi: 10.1080/07328318908054197

Reaction from their Table 2, compound **3b**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 6, compound **3b**). Since this synthesis employed a silylated nucleobase, we assumed that silylation was carried out in the same pot before the glycosylation. The silylation procedure was not described in this paper (cited as "according to standard methods" with a reference to a preceding paper from Niedballa and Vorbrüggen who themselves also described the procedure as "performed according to standard methods" without further reference), thus we assumed the same conditions as in reaction N48 (neat hexamethyldisilazane for 5 h) with 2.5 equivalents of silylation agent to obtain the bis-TMS nucleobase. Thymine (3.4 mmol, 429 mg calculated with a molecular weight of 126.1 g·mol^{-1}) was reacted with hexamethyldisilazane (8.5 mmol, 1.372 g calculated with a molecular weight of 161.4 g·mol^{-1}) for 5 h. The mixture was dried *in vacuo* and used in the following reaction without further purification. The silylated nucleobase was reacted with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose (3.1 mmol, 1.2 g) and copper iodide (3.1 mmol, 600 mg) in $CHCl_3$ (80 mL, 119.2 g with ρ = 1.49 g·cm^{-3}) for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (60 mL, 66 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128–132, doi: 10.1021/je970197j; with *14.322 g* of salt with a solubility of 217 g·L^{-1} and *51.678 g* of water), filtered and extracted with CH_2Cl_2 (50 mL, 66.5 g with 1.33 g·cm^{-3}). The organic phase was washed with brine (60 mL, 71.4 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *25.704 g* of salt with a solubility of 360 g·L^{-1} and *45.696 g* of water), dried over sodium sulfate (*1 g* for 50 mL of extract) and concentrated *in vacuo* to yield a crude product. The material was slurried in EtOH (40 mL, 31.6 g with ρ = 0.79 g·cm^{-3}), filtered and washed with EtOH (30 mL, 23.7 g with ρ = 0.79 g·cm^{-3}) to afford the pure β-anomer in 71% yield (1.1 g).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (1.1 g, 2.2 mmol) was reacted with sodium methoxide (1 M in MeOH, 11 mL, 11 mmol, 594 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 8.69 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (14.667 mL, 11.587 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 11 mmol HCl,

corresponding to 11 mL, *11.22 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 50 mL, *39.5 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 847 mL MeCN/water 12:88, for an assumed weight of 1.694 g of crude product, which corresponds to 101.64 mL of MeCN, 80.296 g with* ρ *= 0.79 g·cm^{-3} and 745.36 mL of water, 745.36 g with* ρ *= 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (1.958 mmol, **474 mg** calculated with a molecular weight of 242.2 g·mol^{-1}).

The reaction took a total of 33.33 h (10 min reaction setup + 5 h silylation + 30 min drying + 15 min reaction setup + 2 h glycosylation + 20 min workup + 30 min drying + 15 min workup + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 105.67 mL of reaction solvent (80 mL CH_2Cl_2 + 25.67 mL MeOH), corresponding to 244.5 mL per gram of product, considering the contribution of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose from Reaction S22, calculated as

$$\frac{105.67\ \text{mL}}{0.474\ \text{g}} + 1.2 * \frac{18\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose of 1.8 (Reaction S22), the preparation of **3b** had a sEF of 12.4 calculated as

$$\text{sEF} = \frac{0.429 + 1.372 + 1.2 + 1.2 * 1.8 + 0.6 + 0.594 - \mathbf{0.474}}{\mathbf{0.474}}$$

and (considering the cEF of the starting material of 234) a cEF of 3152, calculated as

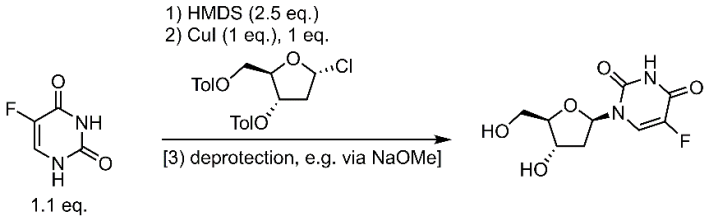
$$\text{cEF} = \frac{\begin{array}{c}0.429 + 1.372 + 1.2 + 1.2 * 234 + 0.6 + 0.594 + 14.322 + 25.704 + 1 \\ +119.2 + 31.6 + 23.7 + 8.69 + 11.587 + 39.5 + 80.296 \\ +51.678 + 45.696 + 11.22 + 745.36 \\ -\mathbf{0.474}\end{array}}{\mathbf{0.474}}$$

with combined contributions from reagents (16), inorganics (135), organic solvents (823) and water (2181), considering the contribution from the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose.

Reaction N63

Freskos *et al. Nucleosides & Nucleotides* **1989**, *8*, 549–555, doi: 10.1080/07328318908054197

Reaction from their Table 2, compound **3e**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 5, Table 2 and page 6, general procedure for compound **3b**). Exact quantities for this compound were not provided, therefore we assumed that this synthesis was carried out with the same quantities as reported in the general procedure. Since this synthesis employed a silylated nucleobase, we assumed that silylation was carried out in the same pot before the glycosylation. The silylation procedure was not described in this paper (cited as "according to standard methods" with a reference to a preceding paper from Niedballa and Vorbrüggen who themselves also described the procedure as "performed according to standard methods" without further reference), thus we assumed the same conditions as in reaction N48 (neat hexamethyldisilazane for 5 h) with 2.5 equivalents of silylation agent to obtain the bis-TMS nucleobase. 5-Fluorouracil (3.4 mmol, 442 mg calculated with a molecular weight of 130.1 g·mol^{-1}) was reacted with hexamethyldisilazane (8.5 mmol, 1.372 g calculated with a molecular weight of 161.4 g·mol^{-1}) for 5 h. The mixture was dried *in vacuo* and used in the following reaction without further purification. The silylated nucleobase was reacted with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose (3.1 mmol, 1.2 g) and copper iodide (3.1 mmol, 600 mg) in $CHCl_3$ (80 mL, 119.2 g with ρ = 1.49 g·cm^{-3}) for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (60 mL, 66 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128–132, doi: 10.1021/je970197j; with *14.322 g* of salt with a solubility of 217 g·L^{-1} and *51.678 g* of water), filtered and extracted with CH_2Cl_2 (50 mL, 66.5 g with 1.33 g·cm^{-3}). The organic phase was washed with brine (60 mL, 71.4 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *25.704 g* of salt with a solubility of 360 g·L^{-1} and *45.696 g* of water), dried over sodium sulfate (*1 g* for 50 mL of extract) and concentrated *in vacuo* to yield a crude product. The material was slurried in EtOH (40 mL, 31.6 g with ρ = 0.79 g·cm^{-3}), filtered and washed with EtOH (30 mL, 23.7 g with ρ = 0.79 g·cm^{-3}) to afford the pure β-anomer. Since yield was not provided for this nucleoside, we assumed that the yield of 3e was the same as for 3b, proportionally adjusted for the lower β:α ratio (73:27 vs 93:7), which corresponds to to 56% yield (1.736 mmol, 838 mg, calculated with a molecular weight of 482.5 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (838 mg, 1.736 mmol) was reacted with sodium methoxide (1 M in MeOH, 8.68 mL, 8.68 mmol, 469 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 6.857 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (11.574 mL, 9.143 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 8.68 mmol HCl, corresponding to 8.68 mL, *8.854 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 40 mL, *31.6 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 653.5 mL MeCN/water 12:88, for an assumed weight of 1.307 g of crude product, which corresponds to 78.42 mL of MeCN, 61.952 g with ρ = 0.79 g·cm^{-3} and 575.08 mL of water, 575.08 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (1.545 mmol, **380 mg** calculated with a molecular weight of 246.2 g·mol^{-1}).

The reaction took a total of 33.33 h (10 min reaction setup + 5 h silylation + 30 min drying + 15 min reaction setup + 2 h glycosylation + 20 min workup + 30 min drying + 15 min workup + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 100.25 mL of reaction solvent (80 mL CH_2Cl_2 + 20.25 mL MeOH), corresponding to 285.4 mL per gram of product, considering the contribution of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose from Reaction S22, calculated as

$$\frac{100.25\ \text{mL}}{0.38\ \text{g}} + 1.2 * \frac{18\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose of 1.8 (Reaction S22), the preparation of **3e** had a sEF of 15.4 calculated as

$$\text{sEF} = \frac{0.442 + 1.372 + 1.2 + 1.2 * 1.8 + 0.6 + 0.469 - \mathbf{0.38}}{\mathbf{0.38}}$$

and (considering the cEF of the starting material of 234) a cEF of 3314, calculated as

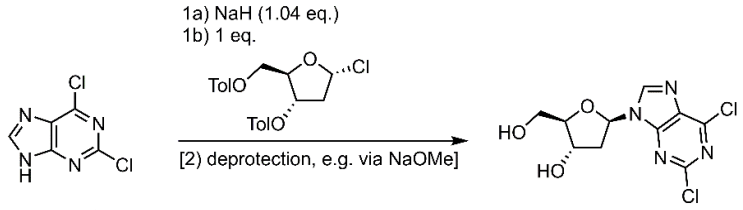
$$\text{cEF} = \frac{\begin{array}{c}0.442 + 1.372 + 1.2 + 1.2 * 234 + 0.6 + 0.469 + 14.322 + 25.704 + 1 \\ +119.2 + 31.6 + 23.7 + 6.857 + 9.143 + 31.6 + 61.952 \\ +51.678 + 45.696 + 8.854 + 575.08 \\ -\mathbf{0.38}\end{array}}{\mathbf{0.38}}$$

with combined contributions from reagents (20), inorganics (168), organic solvents (863) and water (2267), considering the contribution from the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose.

Reaction N64

Kazimierczuk *et al. J. Am. Chem. Soc.* **1984**, *106*, 6379–6382, doi: 10.1021/ja00333a046

Reaction from their Table 1, compound **14**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 4, compound **14**). 2,6-Dichloropurine (5 mmol, 950 mg) was reacted with sodium hydride (5.2 mmol, 250 mg) in MeCN (35 mL, 27.65 g with ρ = 0.79 g·cm^{-3}) for 30 min. Then, 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose (5 mmol, 1.95 g) was added over 20 min and the reaction stirred for 15 h. The mixture was filtered, concentrated in vacuo and subjected to column chromatography on silica gel (using *63 g* of silica gel and 1.575 L of toluene/acetone 9:1 for an assumed weight of 3.15 g of crude product, which corresponds to 1417.5 mL of toluene, *1233.225 g* with ρ = 0.87 g·cm^{-3} and 157.5 mL of acetone, *122.85 g* with ρ = 0.78 g·cm^{-3}) and recrystallization from EtOH (we assumed 16 mL for 1.6 g of product, corresponding to *12.64 g* with ρ = 0.79 g·cm^{-3}) to provide the protected nucleoside in 59% yield (2.95 mmol, 1.6 g).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (1.6 g, 2.95 mmol) was reacted with sodium methoxide (1 M in MeOH, 14.75 mL, 14.75 mmol, 797 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 11.653 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (19.668 mL, 15.538 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 14.75 mmol HCl, corresponding to 14.75 mL, *15.045 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 60 mL, *47.4 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 1198.5 mL MeCN/water 12:88, for an assumed weight of 2.397 g of crude product, which corresponds to 143.82 mL of MeCN, 113.618 g with ρ = 0.79 g·cm^{-3} and 1054.68 mL of water, 1054.68 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (2.626 mmol, **801 mg** calculated with a molecular weight of 305.1 g·mol^{-1}).

The reaction took a total of 45.42 h (10 min reaction setup + 30 min deprotonation + 20 min addition of material + 15 h glycosylation + 5 min filtration + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 69.42 mL of reaction solvent (35 mL MeCN + 34.42 mL MeOH) , corresponding to 121.8 mL per gram of product, considering the

contribution of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose from Reaction S22, calculated as

$$\frac{69.42\ \text{mL}}{0.801\ \text{g}} + 1.95 * \frac{18\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose of 1.8 (Reaction S22), the preparation of **14** had a sEF of 8.3 calculated as

$$\text{sEF} = \frac{0.95 + 0.25 + 1.95 + 1.95 * 1.8 + 0.797 - \mathbf{0.801}}{\mathbf{0.801}}$$

and (considering the cEF of the starting material of 234) a cEF of 3966, calculated as

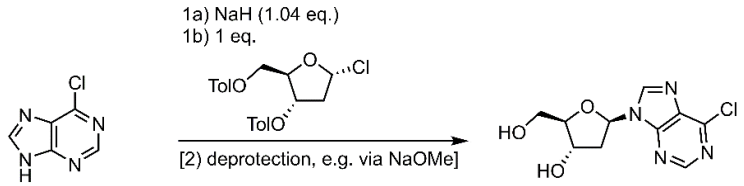
$$\text{cEF} = \frac{\begin{array}{c}0.95 + 0.25 + 1.95 + 1.95 * 234 + 0.797 + 63 \\ +27.65 + 1233.225 + 122.85 + 12.64 + 11.653 + 15.538 + 47.4 + 113.618 \\ +15.045 + 1054.68 \\ -\mathbf{0.801}\end{array}}{\mathbf{0.801}}$$

with combined contributions from reagents (12), inorganics (125), organic solvents (2132) and water (1701), considering the contribution from the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose.

Reaction N65

Kazimierczuk *et al. J. Am. Chem. Soc.* **1984**, *106*, 6379–6382, doi: 10.1021/ja00333a046

Reaction from their Table 1, compound **17**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 4, compound **17**). 6-Chloropurine (5 mmol, 770 mg) was reacted with sodium hydride (5.2 mmol, 250 mg) in MeCN (50 mL, 39.5 g with ρ = 0.79 g·cm^{-3}) for 30 min. Then, 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose (5.15 mmol, 2 g) was added over 20 min and the reaction stirred for 15 h. The mixture was filtered, concentrated in vacuo and subjected to column chromatography on silica gel (using *60.4 g* of silica gel and 1.51 L of toluene/acetone 9:1 for an assumed weight of 3.02 g of crude product, which corresponds to 1359 mL of toluene, *1182.33 g* with ρ = 0.87 g·cm^{-3} and 151 mL of acetone, *117.78 g* with ρ = 0.78 g·cm^{-3}) and recrystallization from EtOH (we assumed 15.1 mL for 1.51 g of product, corresponding to *11.929 g* with ρ = 0.79 g·cm^{-3}) to provide the protected nucleoside in 59% yield (2.95 mmol, 1.51 g).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (1.51 g, 2.95 mmol) was reacted with sodium methoxide (1 M in MeOH, 14.75 mL, 14.75 mmol, 797 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 11.653 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (19.668 mL, 15.538 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 14.75 mmol HCl, corresponding to 14.75 mL, *15.045 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 60 mL, *47.4 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 1153.5 mL MeCN/water 12:88, for an assumed weight of 2.307 g of crude product, which corresponds to 138.42 mL of MeCN, 109.352 g with ρ = 0.79 g·cm^{-3} and 1015.08 mL of water, 1015.08 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (2.626 mmol, **711 mg** calculated with a molecular weight of 270.7 g·mol^{-1}).

The reaction took a total of 45.42 h (10 min reaction setup + 30 min deprotonation + 20 min addition of material + 15 h glycosylation + 5 min filtration + 30 min drying + 2 h purification + 30 min drying + 2 h recrystallization + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 69.42 mL of reaction solvent (35 mL MeCN + 34.42 mL MeOH), corresponding to 133.6 mL per gram of product, considering the

contribution of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose from Reaction S22, calculated as

$$\frac{69.42\ \text{mL}}{0.711\ \text{g}} + 2 * \frac{18\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose of 1.8 (Reaction S22), the preparation of **17** had a sEF of 9.4 calculated as

$$\text{sEF} = \frac{0.77 + 0.25 + 2 + 2 * 1.8 + 0.797 - \mathbf{0.711}}{\mathbf{0.711}}$$

and (considering the cEF of the starting material of 234) a cEF of 4357, calculated as

$$\text{cEF} = \frac{\begin{array}{c} 0.77 + 0.25 + 2 + 2 * 234 + 0.797 + 60.4 \\ +39.5 + 1182.33 + 117.78 + 11.929 + 11.653 + 15.538 + 47.4 + 109.352 \\ +15.045 + 1015.68 \\ -\mathbf{0.711} \end{array}}{\mathbf{0.711}}$$

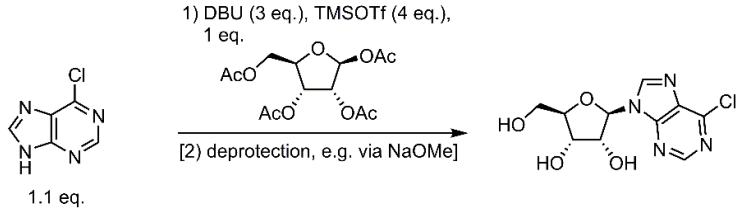
with combined contributions from reagents (14), inorganics (138), organic solvents (2337) and water (1872), considering the contribution from the starting material 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-ribose.

Glycosyl acetates

Reaction N66

Moreau *et al. J. Med. Chem.* **2013**, *56*, 10079–10102, doi: 10.1021/jm401497a

Reaction from their Scheme 4, compound **19**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 16, compound **19**). 6-Chloropurine (16.17 mmol, 2.5 g) was reacted with 1,2,3,5-tetra-*O*-acetyl-β-D-ribose (14.7 mmol, 4.7 g), 1,8-diazabicyclo[5.4.0]undec-7-ene (44.1 mmol, 6.712 g calculated with a molecular weight of 152.2 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (58.8 mmol, 13.071 g calculated with a molecular weight of 222.3 g·mol^{-1}) in MeCN (100 mL, 79 g with ρ = 0.79 g·cm^{-3}) for 2 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (400 mL, 440 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *95.48 g* of salt with a solubility of 217 g·L^{-1} and *344.52 g* of water) and extracted with CH_2Cl_2 (900 mL, 1197 g with ρ = 1.33 g·cm^{-3}). The organic phase was dried over sodium sulfate (*18 g* for 900 mL of extract) and concentrated *in vacuo*. The resulting crude product was subjected to column chromatography on silica gel (using *539.66 g* of silica gel and 13491.5 mL of CH_2Cl_2/acetone 9:1 for an assumed weight of 26.983 g of crude product, which corresponds to 12142.35 mL of CH_2Cl_2, *16149.326 g* with ρ = 1.33 g·cm^{-3} and 1349.15 mL of acetone, *1052.337 g* with ρ = 0.78 g·cm^{-3}) to afford the protected nucleoside in 91% yield (13.377 mmol, 4.9 g).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (4.9 g, 13.377 mmol) was reacted with sodium methoxide (1 M in MeOH, 66.885 mL, 66.885 mmol, 3.612 g NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 52.839 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (89.186 mL, 70.457 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 66.885 mmol HCl, corresponding to 66.885 mL, *68.223 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 250 mL, *197.5 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 4256 mL MeCN/water 12:88, for an assumed weight of 8.512 g of crude product, which corresponds to 510.72 mL of MeCN, 403.469 g with ρ = 0.79 g·cm^{-3} and 3745.28 mL of water, 3745.28 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (11.906 mmol, **3.413 g** calculated with a molecular weight of 286.7 g·mol^{-1}).

The reaction took a total of 29.42 h (20 min reaction setup + 2 h glycosylation + 15 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 256.07 mL of reaction solvent (100 mL MeCN + 156.07 mL MeOH), corresponding to 246.7 mL per gram of product, considering the contribution of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose from Reaction S1, calculated as

$$\frac{256.07\ \text{mL}}{3.413\ \text{g}} + 4.7 * \frac{36.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose of 7.2 (Reaction S1), the preparation of **19** had a sEF of 17.9 calculated as

$$\text{sEF} = \frac{2.5 + 4.7 + 4.7 * 7.2 + 6.712 + 13.071 + 3.612 - \mathbf{3.413}}{\mathbf{3.413}}$$

and (considering the cEF of the starting material of 967) a cEF of 8375, calculated as

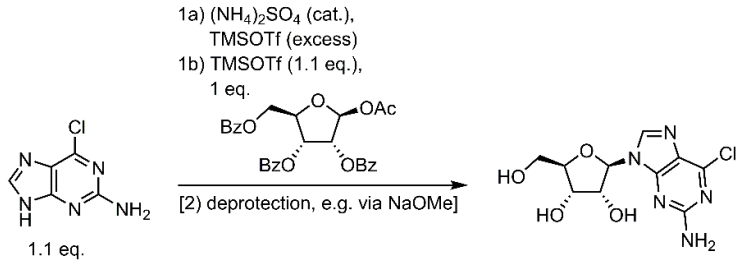
$$\text{cEF} = \frac{\begin{array}{c}2.5 + 4.7 + 4.7 * 967 + 6.712 + 13.071 + 3.612 + 95.48 + 18 + 539.66 \\ +79 + 1197 + 16149.326 + 1052.337 + 52.839 + 70.457 + 197.5 + 403.469 \\ +344.52 + 68.223 + 3745.28 \\ \mathbf{-3.413}\end{array}}{\mathbf{3.413}}$$

with combined contributions from reagents (20), inorganics (277), organic solvents (6673) and water (1408), considering the contribution from the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose.

Reaction N67

Kim *Arch. Pharm. Res.* **2001**, *24*, 508–513, doi: 10.1007/BF02975154

Reaction from their Scheme 1, compound **7**



The experimental details for this synthesis were provided in the Materials and Methods section of the main text (page 2, compound **7**). 2-Amino-6-chloropurine (13.9 mmol, 2.362 g) was reacted with ammonium sulfate (stated as "catalytic amount", we assumed 2 mol%, corresponding to 0.278 mmol, 37 mg calculated with a molecular weight of 132.2 g·mol^{-1}) in neat hexamethyldisilazane (90 mL, 69.3 g with ρ = 0.77 g·cm^{-3}) for 24 h. The mixture was concentrated *in vacuo* and dissolved in dichloroethane (60 mL, 75 g with ρ = 1.25 g·cm^{-3}) and reacted with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (13.9 mmol, 7.03 g) and trimethylsilyl trifluoromethanesulfonate (14.9 mmol, 3.312 g calculated with a molecular weight of 222.3 g·mol^{-1}) for 68 h. The reaction was then quenched with aqueous saturated $NaHCO_3$ (100 mL, 110 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *23.87 g* of salt with a solubility of 217 g·L^{-1} and *86.13 g* of water) and extracted with CH_2Cl_2 (150 mL, 199.5 g with ρ = 1.33 g·cm^{-3}). The organic phase was washed with brine (amount not stated, we assumed half the volume to the organic phase, which corresponds to 75 mL, 89.25 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *32.13 g* of salt with a solubility of 360 g·L^{-1} and *57.12 g* of water), dried over sodium sulfate (*3 g* for 150 mL of extract), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (using *254.82 g* of silica gel and 6370.5 mL of hexane/ethyl acetate 1:1, as the average of a linear gradient from 2:1 hexane/ethyl acetate to 1:2 hexane/ethyl acetate, for an assumed weight of 12.741 g of crude product, which corresponds to 3185.25 mL of hexane, *2102.265 g* with ρ = 0.66 g·cm^{-3} and 3185.75 mL of ethyl acetate, *2866.725 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 91% yield (12.649 mmol, 7.75 g).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (7.75 g, 12.649 mmol) was reacted with sodium methoxide (1 M in MeOH, 63.245 mL, 63.245 mmol, 3.415 g NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 49.964 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (84.332 mL, 66.623 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 63.245 mmol HCl, corresponding to 63.245 mL, *64.51 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*,

coevaporated with MeOH (amount not stated, we assume 220 mL, *173.8 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 5582.5 mL MeCN/water 12:88, for an assumed weight of 11.165 g of crude product, which corresponds to 669.9 mL of MeCN, 529.221 g with ρ = 0.79 g·cm^{-3} and 4912.6 mL of water, 4912.6 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (11.258 mmol, **3.397 g** calculated with a molecular weight of 301.7 g·mol^{-1}). The reaction took a total of 119.67 h (10 min reaction setup + 24 h silylation + 15 min reaction setup + 68 h glycosylation + 25 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 207.57 mL of reaction solvent (60 mL dichloroethane + 147.57 mL MeOH), corresponding to 289.7 mL per gram of product, considering the contribution of the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose from Reaction S3, calculated as

$$\frac{207.57\ \text{mL}}{3.397\ \text{g}} + 7.03 * \frac{32.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose of 5.9 (Reaction S3), the preparation of **7** had a sEF of 36.4 calculated as

$$\text{sEF} = \frac{2.362 + 0.037 + 69.3 + 7.03 + 7.03 * 5.9 + 3.312 + 3.415 - \mathbf{3.397}}{\mathbf{3.397}}$$

and (considering the cEF of the starting material of 174) a cEF of 3769, calculated as

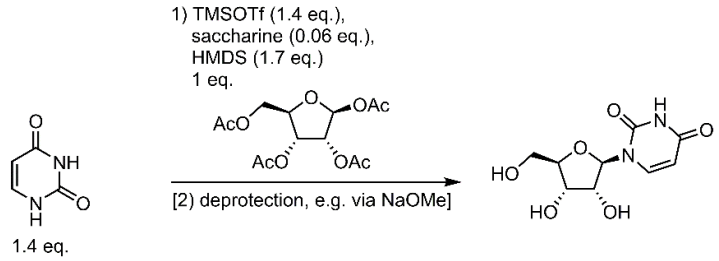
$$\text{cEF} = \frac{\begin{array}{c}2.362 + 0.037 + 69.3 + 7.03 + 3.312 + 3.412 + 23.87 + 32.13 + 3 + 254.82 \\ +75 + 199.5 + 2102.265 + 2866.725 + 49.964 + 66.623 + 173.8 + 529.221 \\ +86.13 + 57.12 + 64.51 + 4912.6 \\ -\mathbf{3.397}\end{array}}{\mathbf{3.397}}$$

with combined contributions from reagents (40), inorganics (94), organic solvents (1959) and water (1679), considering the contribution from the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose.

Reaction N68

Parmenopoulou *et al. Bioorg. Med. Chem.* **2012**, *20*, 7184–7193, doi: 10.1016/j.bmc.2012.09.067

Reaction from their Experimental Section, compound **6a**



The experimental details for this synthesis were provided in the Materials and Methods section of the main text (page 8, compound **6a**). Uracil (8.8 mmol, 986 mg calculated with a molecular weight of 112.1 g·mol^{-1}) was reacted with hexamethyldisilazane (10.9 mmol, 1.759 g calculated with a molecular weight of 161.4 g·mol^{-1}), 1,2,3,5-tetra-*O*-acetyl-β-D-ribose (6.28 mmol, 1.999 g calculated with a molecular weight of 318.3 g·mol^{-1}), saccharine (0.4 mmol, 73 mg calculated with a molecular weight of 183.2 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (8.8 mmol, 1.956 g calculated with a molecular weight of 222.3 g·mol^{-1}) in MeCN (30.8 mL, 24.332 g with ρ = 0.79 g·cm^{-3}) in a microwave oven for 3 min. The mixture was neutralized with aqueous $NaHCO_3$ (amount not stated, we assumed 8.8 mmol $NaHCO_3$ and a saturated solution with a concentration of 2.58 M, based on the solubility limit of 217 g·L^{-1}, which corresponds to 3.411 mL and 3.75 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128–132, doi: 10.1021/je970197j; with *0.814 g* of salt with a solubility of 217 g·L^{-1} and *2.936 g* of water) and extracted with CH_2Cl_2 (amount not stated, we assumed an equal volume compared to the initial solution, corresponding to 34.2 mL, *45.486 g* with ρ = 0.79 g·cm^{-3}). The organic phase was dried over anhydrous sodium sulfate (*684 mg* for 34.2 mL of extract), filtered, evaporated and subjected to purification on silica gel (using *135.46 g* of silica gel and 3386.5 mL of hexane/ethyl acetate 3:7, for an assumed weight of 6.773 g of crude product, which corresponds to 1015.95 mL of hexane, *670.527 g* with ρ = 0.66 g·cm^{-3} and 2370.55 mL of ethyl acetate, *2133.495 g* with ρ = 0.90 g·cm^{-3}) to afford the protected nucleoside. Isolated yield was reported to be between 75 and 82%, so we assumed the rounded mean of these values, 79% (4.961 mmol, 1.837 g calculated with a molecular weight of 370.3 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (1.837 g, 4.961 mmol) was reacted with sodium methoxide (1 M in MeOH, 24.805 mL, 24.805 mmol, 1.339 g NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 19.596 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (33.076 mL, 26.13 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 24.805 mmol HCl, corresponding to 24.805 mL, *25.301 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*,

coevaporated with MeOH (amount not stated, we assume 90 mL, *71.1 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 1588 mL MeCN/water 12:88, for an assumed weight of 3.176 g of crude product, which corresponds to 190.56 mL of MeCN, 150.542 g with* ρ *= 0.79 g·cm^{-3} and 1367.44 mL of water, 1367.44 g with* ρ *= 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (4.415 mmol, **1.078 g** calculated with a molecular weight of 244.2 g·mol^{-1}).

The reaction took a total of 27.55 h (20 min reaction setup + 3 min glycosylation + 20 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 88.68 mL of reaction solvent (30.8 mL MeCN + 57.88 mL MeOH), corresponding to 155.3 mL per gram of product, considering the contribution of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose from Reaction S1, calculated as

$$\frac{88.68\ \text{mL}}{1.078\ \text{g}} + 1.999 * \frac{36.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose of 7.2 (Reaction S1), the preparation of **6a** had a sEF of 19.9 calculated as

$$\text{sEF} = \frac{0.986 + 1.759 + 1.999 + 1.999 * 7.2 + 0.073 + 1.956 + 1.339 - \mathbf{1.078}}{\mathbf{1.078}}$$

and (considering the cEF of the starting material of 967) a cEF of 6135, calculated as

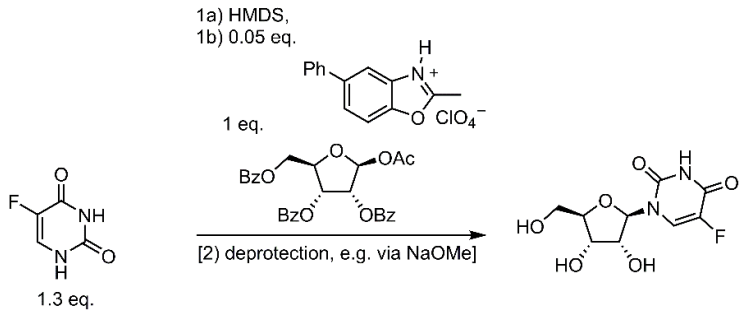
$$\text{cEF} = \frac{\begin{array}{c}0.986 + 1.759 + 1.999 + 1.999 * 967 + 0.073 + 1.956 + 1.339 + 0.814 + 0.684 + 135.46 \\ +24.332 + 45.486 + 670.527 + 2133.495 + 19.596 + 26.13 + 71.1 + 150.542 \\ +2.936 + 25.301 + 1367.44 \\ -\mathbf{1.078}\end{array}}{\mathbf{1.078}}$$

with combined contributions from reagents (22), inorganics (242), organic solvents (4323) and water (1551), considering the contribution from the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose.

Reaction N69

Shirouzu *et al. Tetrahedron* **2014**, *70*, 3635–3639, doi: 10.1016/j.tet.2014.03.013

Reaction from their Table 2, compound **3a**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 4, compound **3a**). 5-Fluorouracil (2.6 mmol, 339 mg) was reacted with hexamethyldisilazane (4 mL, 3.08 g with ρ = 0.77 g·cm^{-3}) in pyridine (2 mL, 1.96 g with ρ = 0.98 g·cm^{-3}) for 30 min. The mixture was then concentrated *in vacuo* and the residue was redissolved in acetone (20 mL, 15.6 g with ρ = 0.78 g·cm^{-3}). 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (2 mmol, 1.02 g) and 2-methyl-5-phenylbenzoxazolium perchlorate (0.1 mmol, 31 mg) were added and the mixture was stirred for 15 min. The solvent was reduced to 10 mL *in vacuo* and the residue was diluted with ethyl acetate (300 mL, 270 g with ρ = 0.90 g·cm^{-3}) and washed with saturated aqueous $NaHCO_3$ (100 mL, 110 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128–132, doi: 10.1021/je970197j; with *23.87 g* of salt with a solubility of 217 g·L^{-1} and *86.13 g* of water). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (200 mL, 220 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128–132, doi: 10.1021/je970197j; with *47.74 g* of salt with a solubility of 217 g·L^{-1} and *172.26 g* of water) and brine (100 mL, 119 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *42.84 g* of salt with a solubility of 360 g·L^{-1} and *76.16 g* of water), dried over anhydrous sodium sulfate (*6 g* for 300 mL of extract) and concentrated *in vacuo*. Recrystallization from ethyl acetate (31 mL, 27.9 g with ρ = 0.90 g·cm^{-3}) and hexane (30 mL, 19.8 g with ρ = 0.66 g·cm^{-3}) afforded the protected nucleoside in 91% yield (1.82 mmol, 1.05 g).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (1.05 g, 1.82 mmol) was reacted with sodium methoxide (1 M in MeOH, 9.1 mL, 9.1 mmol, 491 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 7.189 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (12.134 mL, 9.586 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 9.1 mmol HCl, corresponding to 9.1 mL, *9.282 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 30 mL, *23.7 g* with ρ = 0.79 g·cm^{-3}) and subjected to

purification by reverse phase HPLC (*using 770.5 mL MeCN/water 12:88, for an assumed weight of 1.541 g of crude product, which corresponds to 92.46 mL of MeCN, 73.043 g with* ρ *= 0.79 g·cm*$^{-3}$ *and 678.04 mL of water, 678.04 g with* ρ *= 1.00 g·cm*$^{-3}$) to provide the unprotected nucleoside in 89% yield (1.62 mmol, **425 mg** calculated with a molecular weight of 262.2 g·mol^{-1}).

The reaction took a total of 29.5 h (10 min reaction setup + 30 min silylation + 30 min drying + 15 min reaction setup + 15 min glycosylation + 30 min drying + 30 min workup + 30 min drying + 2 h recrystallization + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 43.23 mL of reaction solvent (2 mL pyridine + 20 mL acetone + 21.23 mL MeOH), corresponding to 132.5 mL per gram of product, considering the contribution of the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose from Reaction S3, calculated as

$$\frac{43.23\ \text{mL}}{0.425\ \text{g}} + 1.02 * \frac{32.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose of 5.9 (Reaction S3), the preparation of **3a** had a sEF of 24.8 calculated as

$$\text{sEF} = \frac{0.339 + 3.08 + 1.02 + 1.02 * 5.9 + 0.031 + 0.491 - \mathbf{0.425}}{\mathbf{0.425}}$$

and (considering the cEF of the starting material of 174) a cEF of 4135, calculated as

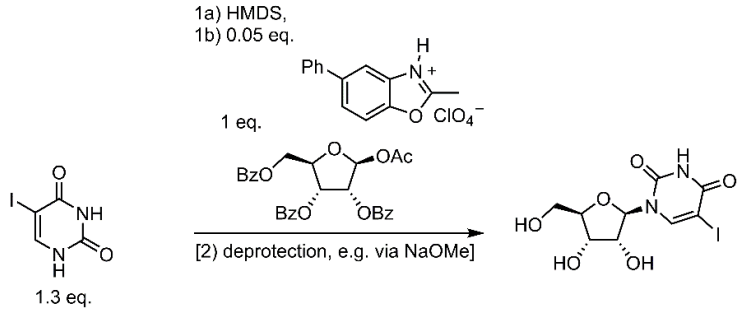
$$\text{cEF} = \frac{\begin{array}{c}0.339 + 3.08 + 1.02 + 1.02 * 174 + 0.031 + 0.491 + 23.87 + 47.74 + 42.84 + 6 \\ +1.96 + 270 + 27.9 + 19.8 + 7.189 + 9.586 + 23.7 + 73.043 \\ +86.13 + 172.26 + 76.16 + 9.282 + 678.04 \\ -\mathbf{0.425}\end{array}}{\mathbf{0.425}}$$

with combined contributions from reagents (28), inorganics (286), organic solvents (1221) and water (2604), considering the contribution from the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose.

Reaction N70

Shirouzu *et al. Tetrahedron* **2014**, *70*, 3635–3639, doi: 10.1016/j.tet.2014.03.013

Reaction from their Table 2, compound **3d**



The experimental details for this synthesis were provided in the Experimental section of the main text (page 4, general procedure for compound **3a** and page 2, Table 2 and SI page 4). Exact experimental details for this synthesis were not provided, so we assumed that **3d** was prepared in the same way as the other compounds following the general procedure described in the article. 5-Iodouracil (2.6 mmol, 619 mg calculated with a molecular weight of 238.0 g·mol^{-1}) was reacted with hexamethyldisilazane (4 mL, 3.08 g with ρ = 0.77 g·cm^{-3}) in pyridine (2 mL, 1.96 g with ρ = 0.98 g·cm^{-3}) for 30 min. The mixture was then concentrated *in vacuo* and the residue was redissolved in acetone (20 mL, 15.6 g with ρ = 0.78 g·cm^{-3}). 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (2 mmol, 1.02 g) and 2-methyl-5-phenylbenzoxazolium perchlorate (0.1 mmol, 31 mg) were added and the mixture was stirred for 15 min. The solvent was reduced to 10 mL *in vacuo* and the residue was diluted with ethyl acetate (300 mL, 270 g with ρ = 0.90 g·cm^{-3}) and washed with saturated aqueous $NaHCO_3$ (100 mL, 110 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *23.87 g* of salt with a solubility of 217 g·L^{-1} and *86.13 g* of water). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (200 mL, 220 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *47.74 g* of salt with a solubility of 217 g·L^{-1} and *172.26 g* of water) and brine (100 mL, 119 g assuming ρ = 1.19 g·cm^{-3} according to Lide, CRC Handbook of Chemistry and Physics, CRC Press, 2005; with *42.84 g* of salt with a solubility of 360 g·L^{-1} and *76.16 g* of water), dried over anhydrous sodium sulfate (*6 g* for 300 mL of extract) and concentrated *in vacuo*. Recrystallization from toluene (25.62 mL, 22.29 g with ρ = 0.87 g·cm^{-3}; adjusted from the reported reaction scale) and hexane (16 mL, 10.56 g with ρ = 0.66 g·cm^{-3}; adjusted from the reported reaction scale) afforded the protected nucleoside in 94% yield (1.88 mmol, 1.283 g calculated with a molecular weight of 682.4 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (1.283 g, 1.88 mmol) was reacted with sodium methoxide (1 M in MeOH, 9.4 mL, 9.4 mmol, 508 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 7.426 g MeOH with

ρ = 0.79 g·cm^{-3}) in MeOH (12.534 mL, 9.902 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 9.4 mmol HCl, corresponding to 9.4 mL, *9.588 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 30 mL, *23.7 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 895.5 mL MeCN/water 12:88, for an assumed weight of 1.791 g of crude product, which corresponds to 107.46 mL of MeCN, 84.893 g with ρ = 0.79 g·cm^{-3} and 788.04 mL of water, 788.04 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (1.67 mmol, **618 mg** calculated with a molecular weight of 370.1 g·mol^{-1}).

The reaction took a total of 29.5 h (10 min reaction setup + 30 min silylation + 30 min drying + 15 min reaction setup + 15 min glycosylation + 30 min drying + 30 min workup + 30 min drying + 2 h recrystallization + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 43.93 mL of reaction solvent (2 mL pyridine + 20 mL acetone + 21.93 mL MeOH), corresponding to 132.5 mL per gram of product, considering the contribution of the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose from Reaction S3, calculated as

$$\frac{43.93\ \text{mL}}{0.619\ \text{g}} + 1.02 * \frac{32.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose of 5.9 (Reaction S3), the preparation of **3d** had a sEF of 17.2 calculated as

$$\text{sEF} = \frac{0.619 + 3.08 + 1.02 + 1.02 * 5.9 + 0.031 + 0.508 - \mathbf{0.618}}{\mathbf{0.618}}$$

and (considering the cEF of the starting material of 174) a cEF of 3019, calculated as

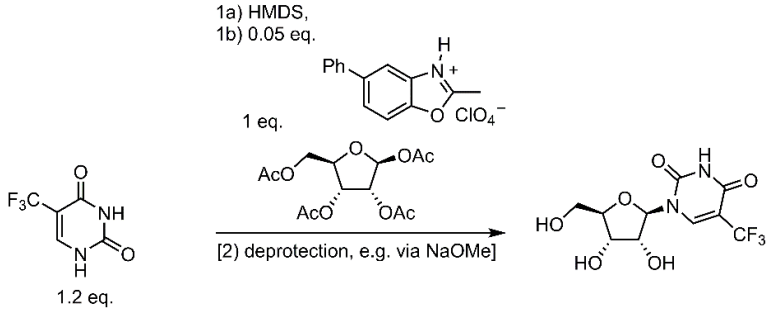
$$\text{cEF} = \frac{\begin{array}{c}0.619 + 3.08 + 1.02 + 1.02 * 174 + 0.031 + 0.508 + 23.87 + 47.74 + 42.84 + 6 \\ +1.96 + 270 + 22.29 + 10.56 + 7.426 + 9.902 + 23.7 + 84.893 \\ +86.13 + 172.26 + 76.16 + 9.588 + 788.04 \\ -\mathbf{0.618}\end{array}}{\mathbf{0.618}}$$

with combined contributions from reagents (20), inorganics (197), organic solvents (836) and water (1969), considering the contribution from the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose.

Reaction N71

Shirouzu *et al. Tetrahedron* **2014**, *70*, 3635–3639, doi: 10.1016/j.tet.2014.03.013

Reaction from their Scheme 2, compound **10e**



The experimental details for this synthesis were provided in the Supporting Information (page 6, compound **10e**). 5-(Trifluoromethyl)uracil (0.36 mmol, 64 mg) was reacted with hexamethyldisilazane (1.2 mL, 924 mg with ρ = 0.77 g·cm^{-3}) in pyridine (0.6 mL, 588 mg with ρ = 0.98 g·cm^{-3}) for 30 min. We assume that the mixture was then dried *in vacuo*. The silylated nucleobase was then reacted with 1,2,3,5-tetra-*O*-acetyl-β-D-ribose (0.3 mmol, 96 mg) and 2-methyl-5-phenylbenzoxazolium perchlorate (0.015 mmol, 5 mg) in MeCN (3 mL, 2.37 g with ρ = 0.77 g·cm^{-3}) for 30 min. We assume that the mixture was then dried in vacuo before being subjected to column purification on silica gel (using *21.78 g* of silica gel and 544.5 mL of CH_2Cl_2/MeOH 98.5:1.5, as the average of a linear gradient from 99:1 to 97:3, for an assumed weight of 1.089 g of crude product, which corresponds to 536.333 mL of CH_2Cl_2, *713.322 g* with ρ = 1.33 g·cm^{-3} and 8.167 mL of MeOH, *6.452 g* with ρ = 0.79 g·cm^{-3}) to afford the protected nucleoside in 96% yield (0.288 mmol, 126 mg).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (126 mg, 0.288 mmol) was reacted with sodium methoxide (1 M in MeOH, 1.44 mL, 1.44 mmol, 78 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 1.138 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (1.92 mL, 1.52 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 1.44 mmol HCl, corresponding to 1.44 mL, *1.469 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 4 mL, *3.16 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 102 mL MeCN/water 12:88, for an assumed weight of 204 mg of crude product, which corresponds to 12.24 mL of MeCN, 9.67 g with ρ = 0.79 g·cm^{-3} and 89.76 mL of water, 89.76 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.256 mmol, **80 mg** calculated with a molecular weight of 312.2 g·mol^{-1}).

The reaction took a total of 28.75 h (10 min reaction setup + 30 min silylation + 30 min drying + 15 min reaction setup + 30 min glycosylation + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h

lyophilization) and consumed a total of 6.96 mL of reaction solvent (0.6 mL pyridine + 3 mL MeCN + 3.36 mL MeOH), corresponding to 90.5 mL per gram of product, considering the contribution of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose from Reaction S1, calculated as

$$\frac{6.96\ \text{mL}}{0.08\ \text{g}} + 0.096 * \frac{36.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose of 7.2 (Reaction S1), the preparation of **10e** had a sEF of 22.2 calculated as

$$\text{sEF} = \frac{0.064 + 0.924 + 0.096 + 0.096 * 7.2 + 0.005 + 0.078 - \mathbf{0.08}}{\mathbf{0.08}}$$

and (considering the cEF of the starting material of 967) a cEF of 11814, calculated as

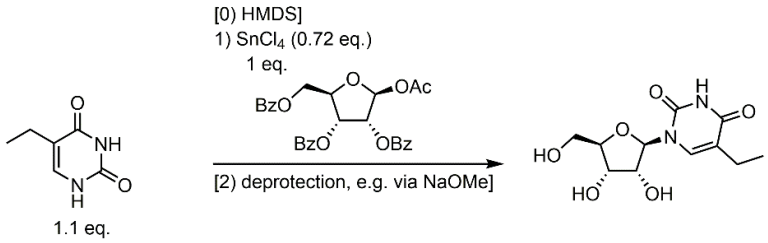
$$\text{cEF} = \frac{\begin{array}{c}0.064 + 0.924 + 0.96 + 0.96 * 7.2 + 0.005 + 0.078 + 21.78 \\ +0.588 + 2.37 + 713.322 + 6.452 + 1.138 + 1.52 + 3.16 + 9.67 \\ +1.469 + 89.76 \\ \mathbf{-0.08}\end{array}}{\mathbf{0.08}}$$

with combined contributions from reagents (24), inorganics (347), organic solvents (10139) and water (1306), considering the contribution from the starting material 1,2,3,5-tetra-*O*-acetyl-β-D-ribose.

Reaction N72

Niedballa *et al. Angew. Chem. Int. Ed.* **1970**, *9*, 461–462, doi: 10.1002/anie.197004612

Reaction from their Table, entry 2 (no compound number given)



The experimental details for this synthesis were provided in the Experimental section of the main text (page 1, general procedure and Table 1). Since this synthesis employed a silylated nucleobase, we assumed that silylation was carried out in the same pot before the glycosylation. The silylation procedure was not described in this paper, thus we assumed the same conditions as in reaction N48 (neat hexamethyldisilazane for 5 h) with 2.5 equivalents of silylation agent to obtain the bis-TMS nucleobase. 5-Ethyluracil (5.53 mmol, 775 mg calculated with a molecular weight of 140.1 g·mol^{-1}) was reacted with hexamethyldisilazane (13.83 mmol, 2.231 g calculated with a molecular weight of 161.4 g·mol^{-1}) for 5 h. The mixture was dried *in vacuo* and used in the following reaction without further purification. The silylated nucleobase was reacted with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (5 mmol, 2.5 g) and tin tetrachloride (3.6 mmol, 938 mg calculated with a molecular weight of 260.5 g·mol^{-1}) in dichloroethane (100 mL, 149 g with ρ = 1.49 g·cm^{-3}) for 48 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (50 mL, 55 g assuming ρ = 1.10 g·cm^{-3} according to Vàzquez *et al. J. Chem. Eng. Data* **1998**, *43*, 128−132, doi: 10.1021/je970197j; with *11.935 g* of salt with a solubility of 217 g·L^{-1} and *43.065 g* of water) and separated. The organic phase was filtered over celite, dried over anhydrous sodium sulfate (*1 g* for 50 mL of extract) and evaporated. Recrystallization from ethanol (42.13 mL for 4.213 g of crude product, *33.283 mg* with ρ = 0.79 g·cm^{-3}) provided the protected nucleoside in 95% yield (4.75 mmol, 2.777 g calculated with a molecular weight of 584.6 g·mol^{-1}).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (2.777 g, 4.75 mmol) was reacted with sodium methoxide (1 M in MeOH, 23.75 mL, 23.75 mmol, 1.283 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 18.763 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (31.668 mL, 25.018 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 23.75 mmol HCl, corresponding to 23.75 mL, *24.225 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 75 mL, *56.25 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 2030 mL MeCN/water 12:88, for an assumed*

weight of 4.06 g of crude product, which corresponds to 243.6 mL of MeCN, 192.444 g with ρ = 0.79 g·cm^{-3} and 1786.4 mL of water, 1786.4 g with ρ = 1.00 g·cm^{-3}) to provide the unprotected nucleoside in 89% yield (4.228 mmol, **1.151 g** calculated with a molecular weight of 272.3 g·mol^{-1}).

The reaction took a total of 81.08 h (10 min reaction setup + 5 h silylation + 30 min drying + 15 min reaction setup + 48 h glycosylation + 20 min workup + 30 min drying + 2 h recrystallization + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 155.42 mL of reaction solvent (100 mL dichloroethane + 55.42 mL MeOH), corresponding to 216.3 mL per gram of product, considering the contribution of the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose from Reaction S3, calculated as

$$\frac{155.42\ \text{mL}}{1.151\ \text{g}} + 2.5 * \frac{32.52\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose of 5.9 (Reaction S3), the preparation of the nucleoside had a sEF of 18.5 calculated as

$$\text{sEF} = \frac{0.775 + 2.231 + 2.5 + 2.5 * 5.9 + 0.938 + 1.283 - \mathbf{1.151}}{\mathbf{1.151}}$$

and (considering the cEF of the starting material of 174) a cEF of 2418, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.775 + 2.231 + 2.5 + 2.5 * 174 + 0.938 + 1.283 + 11.935 + 1 \\ +149 + 33.283 + 18.763 + 25.018 + 56.25 + 192.444 \\ +43.065 + 24.225 + 1786.4 \\ -\mathbf{1.151}\end{array}}{\mathbf{1.151}}$$

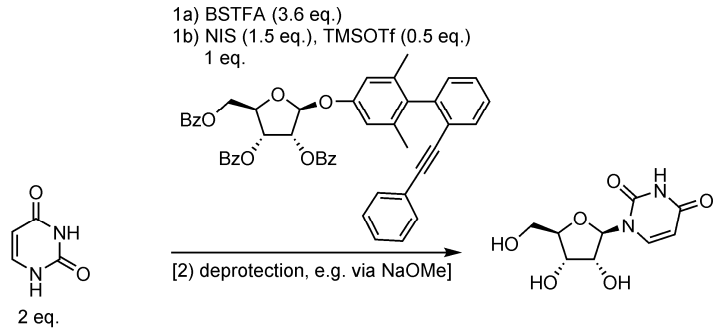
with combined contributions from reagents (22), inorganics (13), organic solvents (595) and water (1791), considering the contribution from the starting material 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose.

(Phenylethynylphenyl)phenyl glycosides

Reaction N73

Hu *et al. J. Am. Chem. Soc.* **2019**, *141*, 4806–4810, doi: 10.1021/jacs.9b00210

Reaction from their Scheme 3, compound **11b**



The experimental details for this synthesis were provided in the Supplementary Information (page 39, compound **11b**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure (General procedure B, described on page 26 of the Supplementary Information). Therefore, we assumed that the exact procedure and quantities described in the General procedure were used. Uracil (0.1 mmol, 11 mg) was reacted with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (0.36 mmol, 93 mg calculated with a molecular weight of 257.4 g·mol^{-1}) in MeCN (amount reported as 0.1 M, which corresponds to 1 mL, 0.79 g with ρ = 0.79 g·cm^{-3}, assuming that the nucleobase was the reference component) for an undisclosed time (we assumed 1 h). Then, 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside (0.05 mmol, 37 mg) was added in MeCN (amount reported as 0.05 M, which corresponds to 1 mL, 0.79 g with ρ = 0.79 g·cm^{-3}) and the mixture was stirred for 10 min. *N*-Iodosuccinimide (0.15 mmol, 34 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.05 mmol, corresponding to 11 mg calculated with a molecular weight of 222.25 g·mol^{-1}) were added and the mixture was stirred for 10 h. The reaction was quenched with triethylamine (amount not stated, we assumed 0.5 mL, 0.365 mg with ρ = 0.73 g·cm^{-3}) and concentrated *in vacuo*. Column chromatography on silica gel (solvents not reported, thus we assumed that the same solvents as in reaction N32 were used where the same product was purified using *3.72 g* of silica gel and 93 mL of hexane/ethyl acetate 2:3 for an assumed weight of 186 mg of crude product, which corresponds to 37.2 mL of hexane, *24.552 g* with ρ = 0.66 g·cm^{-3} and 55.8 L of ethyl acetate, *50.22 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 90% yield (0.045 mmol, **25 mg**).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (25 mg, 0.045 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.225 mL, 0.225 mmol, 12 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.178 g

MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.232 mL, 0.184 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.225 mmol HCl, corresponding to 0.225 mL, *0.3 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 18.5 mL MeCN/water 12:88, for an assumed weight of 37 mg of crude product, which corresponds to 2.22 mL of MeCN, 1.754 g with ρ = 0.79 g·cm^{-3} and 16.28 mL of water, 16.28 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.04 mmol, **10 mg** calculated with a molecular weight of 244.2 g·mol^{-1}).

The reaction took a total of 38.5 h (10 min reaction setup + 1 h silylation + 25 min addition of reagents + 10 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 2.46 mL of reaction solvent (2 mL MeCN + 0.46 mL MeOH), corresponding to 248.5 mL per gram of product, considering the contribution of the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside from Reaction S25, calculated as

$$\frac{2.46\ \text{mL}}{0.01\ \text{g}} + 0.037 * \frac{68.3\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside of 11.0 (Reaction S25), the preparation of the **11b** had a sEF of 59.5 calculated as

$$\text{sEF} = \frac{0.011 + 0.093 + 0.037 + 0.037 * 11 + 0.034 + 0.011 + 0.012 - \mathbf{0.01}}{\mathbf{0.01}}$$

and (considering the cEF of the starting material of 3926) a cEF of 24616, calculated as

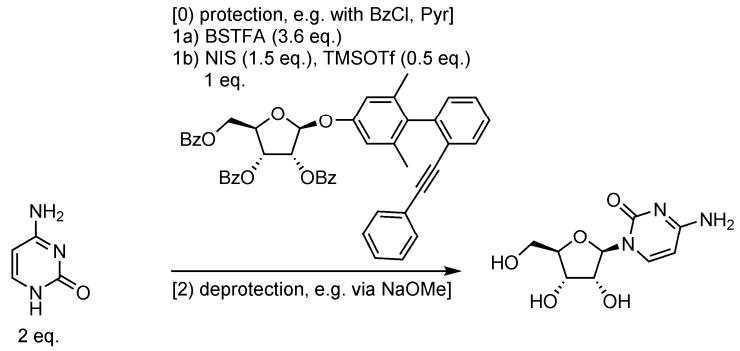
$$\text{cEF} = \frac{\begin{array}{c}0.011 + 0.093 + 0.037 + 0.037 * 3926 + 0.034 + 0.011 + 0.012 + 3.72 \\ +0.79 + 0.79 + 0.365 + 24.552 + 50.22 + 0.178 + 0.184 + 1.58 + 1.754 \\ +0.3 + 16.28 \\ -\mathbf{0.01}\end{array}}{\mathbf{0.01}}$$

with combined contributions from reagents (72), inorganics (1279), organic solvents (20888) and water (2405), considering the contribution from the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside.

Reaction N74

Hu *et al. J. Am. Chem. Soc.* **2019**, *141*, 4806–4810, doi: 10.1021/jacs.9b00210

Reaction from their Scheme 3, compound **11c**



The experimental details for this synthesis were provided in the Supplementary Information (page 39, compound **11c**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure (General procedure B, described on page 26 of the Supplementary Information). Therefore, we assumed that the exact procedure and quantities described in the General procedure were used. For the preparation of *N4*-benzoylcytosine we assume that cytosine could be benzoylated prior to the reaction and used as a crude product without further purification. We assume the conditions used by Mondal and Mugesh (*Chem. Eur. J.* **2019**, 25, 1–9, doi: 10.1002/chem.201805112) and adjusted their quantities to the scale of this synthesis. Cytosine (0.1 mmol, 11 mg calculated with a molecular weight of 111.1 g·mol^{-1}) was reacted with benzoyl chloride (0.417 mmol, 59 mg calculated with a molecular weight of 140.6 g·mol^{-1}) in pyridine (0.367 mL, 0.36 g with ρ = 0.98 g·cm^{-3}) for 6 h. The reaction was quenched with EtOH (0.174 mL, 137 mg with ρ = 0.79 g·cm^{-3}) and 30 min later with water (1.102 mL, 1.102 g with ρ = 1.00 g·cm^{-3}). The solution was stirred for 15 h and the resulting solid isolated by filtration. We assume that this solid could directly be used in the subsequent glycosylation reaction.

N4-benzoylcytosine (0.1 mmol, 22 mg) was reacted with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (0.36 mmol, 93 mg calculated with a molecular weight of 257.4 g·mol^{-1}) in MeCN (amount reported as 0.1 M, which corresponds to 1 mL, 0.79 g with ρ = 0.79 g·cm^{-3}, assuming that the nucleobase was the reference component) for an undisclosed time (we assumed 1 h). Then, 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside (0.05 mmol, 37 mg) was added in MeCN (amount reported as 0.05 M, which corresponds to 1 mL, 0.79 g with ρ = 0.79 g·cm^{-3}) and the mixture was stirred for 10 min. *N*-Iodosuccinimide (0.15 mmol, 34 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.05 mmol, corresponding to 11 mg calculated with a molecular weight of 222.25 g·mol^{-1}) were added and the mixture was stirred for 10 h. The reaction was quenched with triethylamine (amount not stated, we assumed 0.5 mL,

0.365 mg with ρ = 0.73 g·cm^{-3}) and concentrated *in vacuo*. Column chromatography on silica gel (solvents not reported, thus we assumed that the same solvents as in reaction N32 were used where the same product was purified using *3.72 g* of silica gel and 93 mL of hexane/ethyl acetate 2:3 for an assumed weight of 186 mg of crude product, which corresponds to 37.2 mL of hexane, *24.552 g* with ρ = 0.66 g·cm^{-3} and 55.8 L of ethyl acetate, *50.22 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 91% yield (0.045 mmol, **30 mg**).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (30 mg, 0.045 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.225 mL, 0.225 mmol, 12 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.178 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.232 mL, 0.184 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.225 mmol HCl, corresponding to 0.225 mL, *0.3 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 21 mL MeCN/water 12:88, for an assumed weight of 42 mg of crude product, which corresponds to 2.52 mL of MeCN, 1.991 g with ρ = 0.79 g·cm^{-3} and 18.48 mL of water, 18.48 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.04 mmol, **10 mg** calculated with a molecular weight of 243.2 g·mol^{-1}).

The reaction took a total of 60.42 h (10 min reaction setup + 6 h protection + 40 min workup + 15 h precipitation + 5 min filtration + 10 min reaction setup + 1 h silylation + 25 min addition of reagents + 10 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 2.82 mL of reaction solvent (0.36 mL pyridine + 2 mL MeCN + 0.46 mL MeOH), corresponding to 284.5 mL per gram of product, considering the contribution of the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside from Reaction S25, calculated as

$$\frac{2.82\ \text{mL}}{0.01\ \text{g}} + 0.037 * \frac{68.3\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside of 11.0 (Reaction S25), the preparation of the **11c** had a sEF of 65.4 calculated as

$$\text{sEF} = \frac{0.011 + 0.059 + 0.093 + 0.037 + 0.037 * 11 + 0.034 + 0.011 + 0.012 - \mathbf{0.01}}{\mathbf{0.01}}$$

and (considering the cEF of the starting material of 3926) a cEF of 24732, calculated as

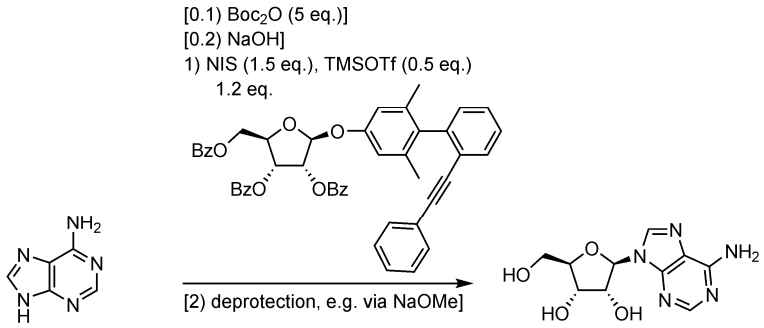
$$\mathrm{cEF} = \frac{\begin{array}{c}0.011 + 0.059 + 0.093 + 0.037 + 0.037 * 3926 + 0.034 + 0.011 + 0.012 + 3.72 \\ +0.36 + 0.137 + 0.79 + 0.79 + 0.365 + 24.552 + 50.22 + 0.178 + 0.184 + 1.58 + 1.754 \\ +1.102 + 0.3 + 16.28\end{array}}{\mathbf{0.01}} \mathbf{-0.01}$$

with combined contributions from reagents (78), inorganics (1279), organic solvents (20937) and water (2516), considering the contribution from the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside.

Reaction N75

Hu *et al. J. Am. Chem. Soc.* **2019**, *141*, 4806–4810, doi: 10.1021/jacs.9b00210

Reaction from their Scheme 3, compound **11e**



The experimental details for this synthesis were provided in the Supplementary Information (page 39, compound **11c**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure (General procedure A, described on page 26 of the Supplementary Information). Therefore, we assumed that the exact procedure and quantities described in the General procedure were used. This synthesis used Boc-protected adenine, whose synthesis was not reported in this report. Therefore, we assumed it was prepared using same the conditions as in reaction N58, where the same nucleobase was synthesized. For the sake of simplicity, we assumed that Boc-protection of the nucleobases afforded the product in quantitative yield. Adenine (0.05 mmol, 7 mg, calculated with a molecular weight of 135.1 $g{\cdot}mol^{-1}$) was reacted with di-*tert*-butyl decarbonate (0.25 mmol, 55 mg) and 4-dimethylaminopyridine (0.005 mmol, 1 mg) in THF (0.25 mL, 222 mg with ρ = 0.89 $g{\cdot}cm^{-3}$) for 8 h. The mixture was then dried *in vacuo* and subjected to purification on silica gel (using 1.26 g of silica gel and 31.5 mL of petroleum ether/ethyl acetate 4:1 for an assumed weight of 63 mg of crude product, which corresponds to 25.2 mL of petroleum ether, *16.38 g* with ρ = 0.65 $g{\cdot}cm^{-3}$ and 6.3 mL of ethyl acetate, *5.67 g* with ρ = 0.90 $g{\cdot}cm^{-3}$) to afford the tris-Boc-nucleobase which was then dissolved in EtOH (0.5 mL, 0.395 g with ρ = 0.79 $g{\cdot}cm^{-3}$) and 1 M NaOH (0.433 mL, 0.450 g with ρ = 1.04 $g{\cdot}cm^{-3}$, corresponding to *17 mg* NaOH, calculated with a molecular weight of 40 $g{\cdot}mol^{-1}$, and *0.433 g* of water) for 80 h. The mixture was concentrated via coevaporation with water (2.5 mL, 2.5 g with ρ = 1.00 $g{\cdot}cm^{-3}$), acidified with acetic acid (amount not stated, we assumed 0.433 mmol, 26 mg calculated with a molecular weight of 60.1 $g{\cdot}mol^{-1}$) and filtered. The filtrate was collected, washed with water (amount not stated, we assumed 1.25 mL, 1.25 g with ρ = 1.00 $g{\cdot}cm^{-3}$) and dried *in vacuo* to yield the Boc-protected nucleobase (0.05 mmol, 17 mg calculated with a molecular weight of 335.4 $g{\cdot}mol^{-1}$). The nucleobase was then reacted with 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside (0.06 mmol, 45 mg) was added in MeCN (amount reported as 0.033 M, which corresponds to 1.8 mL, 1.423 g with ρ = 0.79 $g{\cdot}cm^{-3}$) and

the mixture was stirred for 30 min. *N*-Iodosuccinimide (0.15 mmol, 34 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.015 mmol, corresponding to 3 mg calculated with a molecular weight of 222.25 g·mol^{-1}) were added and the mixture was stirred for 2 h. The reaction was quenched with triethylamine (amount not stated, we assumed 0.5 mL, 0.365 mg with ρ = 0.73 g·cm^{-3}) and concentrated *in vacuo*. Column chromatography on silica gel (solvents not reported, thus we assumed that the same solvents as in reaction N58 were used where the same product was purified using *1.98 g* of silica gel and 49.5 mL of hexane/ethyl acetate 4:1 for an assumed weight of 99 mg of crude product, which corresponds to 39.6 mL of hexane, *26.136 g* with ρ = 0.66 g·cm^{-3} and 9.9 mL of ethyl acetate, *8.91 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 74% yield (0.037 mmol, **29 mg**).

For removal of the Boc groups we assumed the general procedure from N58. The protected nucleoside (0.037 mmol, 29 mg) was heated under reflux for 8 h in *t*BuOH (0.74 mL, 0.577 g with ρ = 0.78 g·cm^{-3}) and water (0.74 mL, 0.74 g with ρ = 1.00 g·cm^{-3}). The mixture was then dried *in vacuo* and we assume it could then be used directly be debenzyolation without any loss of material from the Boc removal. For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (29 mg, 0.037 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.185 mL, 0.185 mmol, 10 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.146 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.191 mL, 0.151 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.185 mmol HCl, corresponding to 0.185 mL, *0.189 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 1 mL, *0.79 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 19.5 mL MeCN/water 12:88, for an assumed weight of 39 mg of crude product, which corresponds to 2.34 mL of MeCN, 1.849 g with ρ = 0.79 g·cm^{-3} and 17.16 mL of water, 17.16 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.033 mmol, **9 mg** calculated with a molecular weight of 267.2 g·mol^{-1}).

The reaction took a total of 131.08 h (15 min reaction setup + 8 h Boc-protection + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 80 h reaction time + 30 min drying + 15 min workup + 30 min drying + 10 min reaction setup + 30 min stirring + 10 min addition of reagents + 2 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 8 h deprotection + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 3.91 mL of reaction solvent (0.25 mL THF + 1.8 mL MeCN + 0.74 mL *t*BuOH + 0.74 mL water + 0.38 mL MeOH), corresponding to 437.5 mL per gram of product, considering the contribution of the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside from Reaction S25, calculated as

$$\frac{3.91\ \text{mL}}{0.009\ \text{g}} + 0.045 * \frac{68.3\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside of 11.0 (Reaction S25), the preparation of the **11e** had a sEF of 71.2 calculated as

$$\text{sEF} = \frac{0.007 + 0.055 + 0.001 + 0.045 + 0.045 * 11 + 0.034 + 0.003 + 0.01 - \mathbf{0.009}}{\mathbf{0.009}}$$

and (considering the cEF of the starting material of 3926) a cEF of 29598, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.007 + 0.055 + 0.001 + 0.045 + 0.045 * 3926 + 0.034 + 0.003 + 0.01 + 1.26 + 0.017 + 1.98 \\ +0.222 + 16.38 + 5.67 + 0.395 + 0.026 + 1.423 + 0.365 + 26.136 + 8.91 + 0.577 + 0.146 + 1.151 \\ 0.79 + 1.849 + 0.433 + 2.5 + 1.25 + 0.74 + 0.189 + 17.16 \\ -\mathbf{0.01}\end{array}}{\mathbf{0.01}}$$

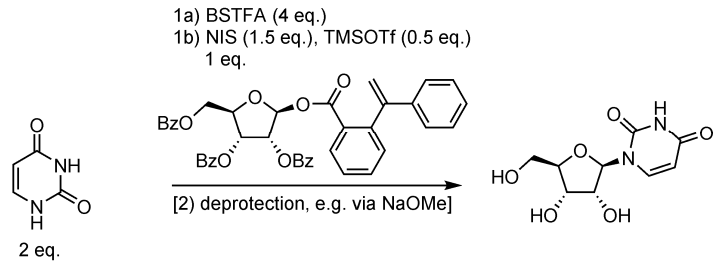
with combined contributions from reagents (87), inorganics (1587), organic solvents (24476) and water (3485), considering the contribution from the starting material 3,5-dimethyl-4-(2'-phenylethylphenyl)phenyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside.

***o*-(1-Phenylvinyl)benzoates**

Reaction N76

Li *et al. Nat. Comm.* **2020**, *11*, 405–414, doi: 10.1038/s41467-020-14295-z

Reaction from their Figure 3, compound **6a**



The experimental details for this synthesis were provided in the Supplementary Information (page 40, compound **6a**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure (General procedure C, described on page 18 of the Supplementary Information). Therefore, we assumed that the exact procedure and quantities described in the General procedure were used. Uracil (0.12 mmol, 14 mg) was first silylated with bis(trimethylsilyl)amine (0.48 mmol, corresponding to 77 mg calculated with a molecular weight of 161.4 g·mol^{-1}) in MeCN (amount reported as 0.1 M, which corresponds to 1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}, assuming that the nucleobase was the reference compound for the concentration) for 30 min. Then, 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate (0.06 mmol, 40 mg) was added in MeCN (amount reported as 0.05 M, which corresponds to 1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}, assuming that the sugar was the reference compound for the concentration) and the solution was stirred for 10 min. Then, *N*-Iodosuccinimide (0.09 mmol, 20 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.03 mmol, corresponding to 7 mg calculated with a molecular weight of 222.25 g·mol^{-1}) were added and the mixture was stirred for 3 h. The reaction was quenched with triethylamine (amount not stated, we assumed 0.5 mL, 0.365 mg with ρ = 0.73 g·cm^{-3}) and concentrated *in vacuo*. Column chromatography on silica gel (solvents not reported, thus we assumed that the same solvents as in reaction N32 were used where the same product was purified using *3.16 g* of silica gel and 79 mL of hexane/ethyl acetate 2:3 for an assumed weight of 158 mg of crude product, which corresponds to 31 mL of hexane, *20.856 g* with ρ = 0.66 g·cm^{-3} and 48 mL of ethyl acetate, *43.2 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 93% yield (0.056 mmol, **31 mg**).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (31 mg, 0.056 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.28 mL, 0.28 mmol, 15 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.222 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.288 mL, 0.227 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction,

the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.28 mmol HCl, corresponding to 0.28 mL, *0.286 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 18 mL MeCN/water 12:88, for an assumed weight of 36 mg of crude product, which corresponds to 2.16 mL of MeCN, 1.706 g with ρ = 0.79 g·cm^{-3} and 15.84 mL of water, 15.84 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.05 mmol, **12 mg** calculated with a molecular weight of 242.2 g·mol^{-1}).

The reaction took a total of 31.08 h (10 min reaction setup + 30 min silylation + 10 min addition of material + 10 min stirring + 10 min addition of reagents + 3 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 2.97 mL of reaction solvent (2.4 mL MeCN + 0.57 mL MeOH), corresponding to 248.6 mL per gram of product, considering the contribution of the starting material 32,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate from Reaction S26, calculated as

$$\frac{2.97\ \text{mL}}{0.012\ \text{g}} + 0.040 * \frac{27.93\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate of 8.6 (Reaction S26), the preparation of the **6a** had a sEF of 42.1 calculated as

$$\text{sEF} = \frac{0.014 + 0.077 + 0.04 + 0.04 * 8.6 + 0.02 + 0.007 + 0.015 - \mathbf{0.012}}{\mathbf{0.012}}$$

and (considering the cEF of the starting material of 1866) a cEF of 13678, calculated as

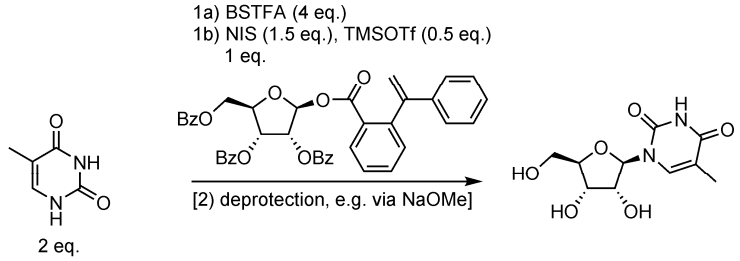
$$\text{cEF} = \frac{\begin{array}{c}0.014 + 0.077 + 0.04 + 0.04 * 8.6 + 0.02 + 0.007 + 0.015 + 3.16 \\ +0.948 + 0.948 + 0.365 + 20.856 + 43.2 + 0.222 + 0.227 + 1.58 + 1.706 \\ +0.286 + 15.84 \\ -\mathbf{0.012}\end{array}}{\mathbf{0.012}}$$

with combined contributions from reagents (54), inorganics (580), organic solvents (11208) and water (1847), considering the contribution from the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate.

Reaction N77

Li *et al. Nat. Comm.* **2020**, *11*, 405–414, doi: 10.1038/s41467-020-14295-z

Reaction from their Figure 3, compound **6b**



The experimental details for this synthesis were provided in the Supplementary Information (page 40, compound **6b**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure (General procedure C, described on page 18 of the Supplementary Information). Therefore, we assumed that the exact procedure and quantities described in the General procedure were used. Thymine (0.12 mmol, 15 mg) was first silylated with bis(trimethylsilyl)amine (0.48 mmol, corresponding to 77 mg calculated with a molecular weight of 161.4 g·mol^{-1}) in MeCN (amount reported as 0.1 M, which corresponds to 1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}, assuming that the nucleobase was the reference compound for the concentration) for 30 min. Then, 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate (0.06 mmol, 40 mg) was added in MeCN (amount reported as 0.05 M, which corresponds to 1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}, assuming that the sugar was the reference compound for the concentration) and the solution was stirred for 10 min. Then, *N*-Iodosuccinimide (0.09 mmol, 20 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.03 mmol, corresponding to 7 mg calculated with a molecular weight of 222.25 g·mol^{-1}) were added and the mixture was stirred for 3 h. The reaction was quenched with triethylamine (amount not stated, we assumed 0.5 mL, 0.365 mg with ρ = 0.73 g·cm^{-3}) and concentrated *in vacuo*. Column chromatography on silica gel (solvents not reported, thus we assumed that the same solvents as in reaction N32 were used where a similar product was purified using *3.16 g* of silica gel and 79 mL of hexane/ethyl acetate 2:3 for an assumed weight of 158 mg of crude product, which corresponds to 31 mL of hexane, *20.856 g* with ρ = 0.66 g·cm^{-3} and 48 mL of ethyl acetate, *43.2 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 85% yield (0.051 mmol, **28 mg**).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (28 mg, 0.051 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.255 mL, 0.255 mmol, 14 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.202 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.262 mL, 0.207 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.255 mmol HCl,

corresponding to 0.255 mL, *0.26 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 16 mL MeCN/water 12:88, for an assumed weight of 32 mg of crude product, which corresponds to 1.92 mL of MeCN, 1.517 g with ρ = 0.79 g·cm^{-3} and 14.08 mL of water, 14.08 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.045 mmol, **12 mg** calculated with a molecular weight of 258.2 g·mol^{-1}).

The reaction took a total of 31.08 h (10 min reaction setup + 30 min silylation + 10 min addition of material + 10 min stirring + 10 min addition of reagents + 3 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 2.92 mL of reaction solvent (2.4 mL MeCN + 0.52 mL MeOH), corresponding to 244.5 mL per gram of product, considering the contribution of the starting material 32,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate from Reaction S26, calculated as

$$\frac{2.92\ \text{mL}}{0.012\ \text{g}} + 0.040 * \frac{27.93\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate of 8.6 (Reaction S26), the preparation of the **6b** had a sEF of 42.1 calculated as

$$\text{sEF} = \frac{0.015 + 0.077 + 0.04 + 0.04 * 8.6 + 0.02 + 0.007 + 0.014 - \mathbf{0.012}}{\mathbf{0.012}}$$

and (considering the cEF of the starting material of 1866) a cEF of 13510, calculated as

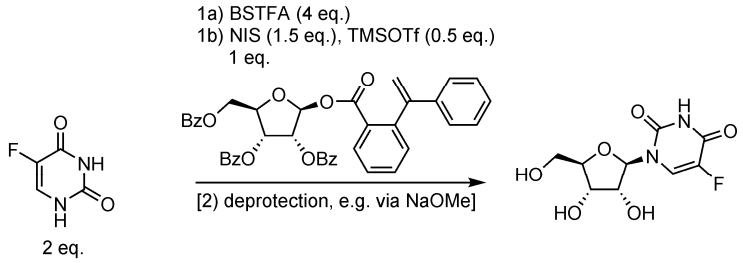
$$\text{cEF} = \frac{\begin{array}{c}0.015 + 0.077 + 0.04 + 0.04 * 8.6 + 0.02 + 0.007 + 0.014 + 3.16 \\ +0.948 + 0.948 + 0.365 + 20.856 + 43.2 + 0.202 + 0.207 + 1.58 + 1.517 \\ +0.26 + 14.08 \\ -\mathbf{0.012}\end{array}}{\mathbf{0.012}}$$

with combined contributions from reagents (54), inorganics (580), organic solvents (11189) and water (1698), considering the contribution from the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate.

Reaction N78

Li *et al. Nat. Comm.* **2020**, *11*, 405–414, doi: 10.1038/s41467-020-14295-z

Reaction from their Figure 3, compound **6d**



The experimental details for this synthesis were provided in the Supplementary Information (page 41, compound **6b**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure (General procedure C, described on page 18 of the Supplementary Information). Therefore, we assumed that the exact procedure and quantities described in the General procedure were used. 5-Fluorouracil (0.12 mmol, 16 mg) was first silylated with bis(trimethylsilyl)amine (0.48 mmol, corresponding to 77 mg calculated with a molecular weight of 161.4 g·mol^{-1}) in MeCN (amount reported as 0.1 M, which corresponds to 1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}, assuming that the nucleobase was the reference compound for the concentration) for 30 min. Then, 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate (0.06 mmol, 40 mg) was added in MeCN (amount reported as 0.05 M, which corresponds to 1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}, assuming that the sugar was the reference compound for the concentration) and the solution was stirred for 10 min. Then, *N*-Iodosuccinimide (0.09 mmol, 20 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.03 mmol, corresponding to 7 mg calculated with a molecular weight of 222.25 g·mol^{-1}) were added and the mixture was stirred for 3 h. The reaction was quenched with triethylamine (amount not stated, we assumed 0.5 mL, 0.365 mg with ρ = 0.73 g·cm^{-3}) and concentrated *in vacuo*. Column chromatography on silica gel (solvents not reported, thus we assumed that the same solvents as in reaction N32 were used where a similar product was purified using *3.16 g* of silica gel and 79 mL of hexane/ethyl acetate 2:3 for an assumed weight of 158 mg of crude product, which corresponds to 31 mL of hexane, *20.856 g* with ρ = 0.66 g·cm^{-3} and 48 mL of ethyl acetate, *43.2 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 96% yield (0.058 mmol, **33 mg**).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (33 mg, 0.058 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.29 mL, 0.29 mmol, 16 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.23 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.298 mL, 0.235 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.255 mmol HCl,

corresponding to 0.29 mL, *0.296 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 24.5 mL MeCN/water 12:88, for an assumed weight of 49 mg of crude product, which corresponds to 2.94 mL of MeCN, 2.323 g with ρ = 0.79 g·cm^{-3} and 21.56 mL of water, 21.56 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.052 mmol, **14 mg** calculated with a molecular weight of 262.2 g·mol^{-1}).

The reaction took a total of 31.08 h (10 min reaction setup + 30 min silylation + 10 min addition of material + 10 min stirring + 10 min addition of reagents + 3 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 2.99 mL of reaction solvent (2.4 mL MeCN + 0.59 mL MeOH), corresponding to 214.7 mL per gram of product, considering the contribution of the starting material 32,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate from Reaction S26, calculated as

$$\frac{2.99\ \text{mL}}{0.014\ \text{g}} + 0.040 * \frac{27.93\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate of 8.6 (Reaction S26), the preparation of the **6d** had a sEF of 36.1 calculated as

$$\text{sEF} = \frac{0.016 + 0.077 + 0.04 + 0.04 * 8.6 + 0.02 + 0.007 + 0.016 - \mathbf{0.014}}{\mathbf{0.014}}$$

and (considering the cEF of the starting material of 1866) a cEF of 12179, calculated as

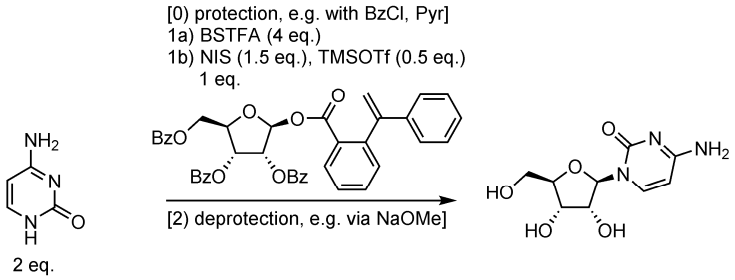
$$\text{cEF} = \frac{\begin{array}{c}0.015 + 0.077 + 0.04 + 0.04 * 8.6 + 0.02 + 0.007 + 0.014 + 3.16 \\ +0.948 + 0.948 + 0.365 + 20.856 + 43.2 + 0.23 + 0.235 + 1.58 + 2.323 \\ +0.296 + 21.56 \\ -\mathbf{0.014}\end{array}}{\mathbf{0.014}}$$

with combined contributions from reagents (47), inorganics (497), organic solvents (9652) and water (1993), considering the contribution from the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate.

Reaction N79

Li *et al. Nat. Comm.* **2020**, *11*, 405–414, doi: 10.1038/s41467-020-14295-z

Reaction from their Figure 3, compound **6c**



The experimental details for this synthesis were provided in the Supplementary Information (page 41, compound **6b**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure (General procedure C, described on page 18 of the Supplementary Information). Therefore, we assumed that the exact procedure and quantities described in the General procedure were used.

For the preparation of *N4*-benzoylcytosine we assume that cytosine could be benzoylated prior to the reaction and used as a crude product without further purification. We assume the conditions used by Mondal and Mugesh (*Chem. Eur. J.* **2019**, 25, 1–9, doi: 10.1002/chem.201805112) and adjusted their quantities to the scale of this synthesis. Cytosine (0.12 mmol, 13 mg calculated with a molecular weight of 111.1 g·mol^{-1}) was reacted with benzoyl chloride (0.5 mmol, 70 mg calculated with a molecular weight of 140.6 g·mol^{-1}) in pyridine (0.44 mL, 0.432 g with ρ = 0.98 g·cm^{-3}) for 6 h. The reaction was quenched with EtOH (0.209 mL, 165 mg with ρ = 0.79 g·cm^{-3}) and 30 min later with water (1.322 mL, 1.322 g with ρ = 1.00 g·cm^{-3}). The solution was stirred for 15 h and the resulting solid isolated by filtration. We assume that this solid could directly be used in the subsequent glycosylation reaction.

N4-benzoylcytosine (0.12 mmol, 26 mg) was first silylated with bis(trimethylsilyl)amine (0.48 mmol, corresponding to 77 mg calculated with a molecular weight of 161.4 g·mol^{-1}) in MeCN (amount reported as 0.1 M, which corresponds to 1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}, assuming that the nucleobase was the reference compound for the concentration) for 30 min. Then, 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate (0.06 mmol, 40 mg) was added in MeCN (amount reported as 0.05 M, which corresponds to 1.2 mL, 948 mg with ρ = 0.79 g·cm^{-3}, assuming that the sugar was the reference compound for the concentration) and the solution was stirred for 10 min. Then, *N*-Iodosuccinimide (0.09 mmol, 20 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.03 mmol, corresponding to 7 mg calculated with a molecular weight of 222.25 g·mol^{-1}) were added and the mixture was stirred for 3 h. The reaction was

quenched with triethylamine (amount not stated, we assumed 0.5 mL, 0.365 mg with ρ = 0.73 g·cm^{-3}) and concentrated *in vacuo*. Column chromatography on silica gel (solvents not reported, thus we assumed that the same solvents as in reaction N34 were used where the same product was purified using *3.4 g* of silica gel and 85 mL of hexane/ethyl acetate 7:3 for an assumed weight of 170 mg of crude product, which corresponds to 59.5 mL of hexane, *39.27 g* with ρ = 0.66 g·cm^{-3} and 25.5 mL of ethyl acetate, *22.95 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 96% yield (0.058 mmol, **38 mg**).

For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (38 mg, 0.058 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.29 mL, 0.29 mmol, 16 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.23 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.298 mL, 0.235 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.255 mmol HCl, corresponding to 0.29 mL, *0.296 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 2 mL, *1.58 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 27 mL MeCN/water 12:88, for an assumed weight of 54 mg of crude product, which corresponds to 3.24 mL of MeCN, 2.56 g with ρ = 0.79 g·cm^{-3} and 23.76 mL of water, 23.76 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.052 mmol, **13 mg** calculated with a molecular weight of 243.2 g·mol^{-1}).

The reaction took a total of 53 h (10 min reaction setup + 6 h protection + 40 min workup + 15 h precipitation + 5 min filtration + 10 min reaction setup + 30 min silylation + 10 min addition of material + 10 min stirring + 10 min addition of reagents + 3 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 3.43 mL of reaction solvent (0.44 mL pyridine + 2.4 mL MeCN + 0.59 mL MeOH), corresponding to 260.0 mL per gram of product, considering the contribution of the starting material 32,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate from Reaction S26, calculated as

$$\frac{3.43\ \text{mL}}{0.013\ \text{g}} + 0.040 * \frac{27.93\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate of 8.6 (Reaction S26), the preparation of the **6c** had a sEF of 44.2 calculated as

$$\text{sEF} = \frac{0.013 + 0.07 + 0.077 + 0.04 + 0.04 * 8.6 + 0.02 + 0.007 + 0.016 - \mathbf{0.013}}{\mathbf{0.013}}$$

and (considering the cEF of the starting material of 1866) a cEF of 13333, calculated as

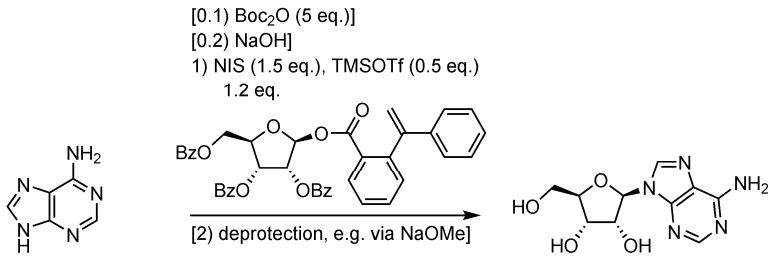
$$\mathrm{cEF} = \frac{\begin{array}{c}0.013 + 0.07 + 0.077 + 0.04 + 0.04 * 8.6 + 0.02 + 0.007 + 0.016 + 3.4 \\ +0.432 + 0.165 + 0.948 + 0.948 + 0.365 + 39.27 + 22.95 + 0.23 + 0.235 + 1.58 + 2.56 \\ +1.322 + 0.296 + 23.76 \\ \mathbf{-0.013}\end{array}}{\mathbf{0.013}}$$

with combined contributions from reagents (56), inorganics (554), organic solvents (10317) and water (2417), considering the contribution from the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate.

Reaction N80

Li *et al. Nat. Comm.* **2020**, *11*, 405–414, doi: 10.1038/s41467-020-14295-z

Reaction from their Figure 3, compound **6o**



The experimental details for this synthesis were provided in the Supplementary Information (page 48, compound **6o**). Exact procedures for this synthesis were not provided, but the synthesis was described to have been carried out using a general procedure (General procedure C, described on page 18 of the Supplementary Information). Therefore, we assumed that the exact procedure and quantities described in the General procedure were used.

This synthesis used Boc-protected adenine, whose synthesis was not reported in this report. Therefore, we assumed it was prepared using same the conditions as in reaction N58, where the same nucleobase was synthesized. For the sake of simplicity, we assumed that Boc-protection of the nucleobases afforded the product in quantitative yield. Adenine (0.05 mmol, 7 mg, calculated with a molecular weight of 135.1 $gmol^{-1}$) was reacted with di-*tert*-butyl decarbonate (0.25 mmol, 55 mg) and 4-dimethylaminopyridine (0.005 mmol, 1 mg) in THF (0.25 mL, 222 mg with ρ = 0.89 $g \cdot cm^{-3}$) for 8 h. The mixture was then dried *in vacuo* and subjected to purification on silica gel (using 1.26 g of silica gel and 31.5 mL of petroleum ether/ethyl acetate 4:1 for an assumed weight of 63 mg of crude product, which corresponds to 25.2 mL of petroleum ether, *16.38 g* with ρ = 0.65 $g \cdot cm^{-3}$ and 6.3 mL of ethyl acetate, *5.67 g* with ρ = 0.90 $g \cdot cm^{-3}$) to afford the tris-Boc-nucleobase which was then dissolved in EtOH (0.5 mL, 0.395 g with ρ = 0.79 $g \cdot cm^{-3}$) and 1 M NaOH (0.433 mL, 0.450 g with ρ = 1.04 $g \cdot cm^{-3}$, corresponding to *17 mg* NaOH, calculated with a molecular weight of 40 $g \cdot mol^{-1}$, and *0.433 g* of water) for 80 h. The mixture was concentrated via coevaporation with water (2.5 mL, 2.5 g with ρ = 1.00 $g \cdot cm^{-3}$), acidified with acetic acid (amount not stated, we assumed 0.433 mmol, 26 mg calculated with a molecular weight of 60.1 $gmol^{-1}$) and filtered. The filtrate was collected, washed with water (amount not stated, we assumed 1.25 mL, 1.25 g with ρ = 1.00 $g \cdot cm^{-3}$) and dried *in vacuo* to yield the Boc-protected nucleobase (0.05 mmol, 17 mg calculated with a molecular weight of 335.4 $g \cdot mol^{-1}$).

The protected nucleobase (0.05 mmol, 17 mg) reacted with 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate (0.06 mmol, 40 mg) in CH_2Cl_2 (amount reported as 0.033 M, which corresponds to 1.515 mL, 2.015 mg with ρ = 1.33 $g \cdot cm^{-3}$, assuming that the nucleobase was the reference

compound for the concentration) for 30 min. Then, *N*-Iodosuccinimide (0.075 mmol, 17 mg calculated with a molecular weight of 225.0 g·mol^{-1}) and trimethylsilyl trifluoromethanesulfonate (0.015 mmol, corresponding to 3 mg calculated with a molecular weight of 222.25 g·mol^{-1}) were added and the mixture was stirred for 2 h. The reaction was quenched with triethylamine (amount not stated, we assumed 0.5 mL, 0.365 mg with ρ = 0.73 g·cm^{-3}) and concentrated *in vacuo*. Column chromatography on silica gel (solvents not reported, thus we assumed that the same solvents as in reaction N58 were used where the same product was purified using *1.54 g* of silica gel and 38.5 mL of hexane/ethyl acetate 4:1 for an assumed weight of 77 mg of crude product, which corresponds to 30.8 mL of hexane, *20.328 g* with ρ = 0.66 g·cm^{-3} and 7.7 mL of ethyl acetate, *6.93 g* with ρ = 0.90 g·cm^{-3}) afforded the protected nucleoside in 84% yield (0.042 mmol, **34 mg**).

For removal of the Boc groups we assumed the general procedure from N58. The protected nucleoside (0.042 mmol, 34 mg) was heated under reflux for 8 h in *t*BuOH (0.877 mL, 0.677 g with ρ = 0.78 g·cm^{-3}) and water (0.877 mL, 0.877 g with ρ = 1.00 g·cm^{-3}). The mixture was then dried *in vacuo* and we assume it could then be used directly be debenzyolation without any loss of material from the Boc removal. For deprotection we assume the same method and conditions described in Reaction N32. The protected nucleoside (34 mg, 0.042 mmol) was reacted with sodium methoxide (1 M in MeOH, 0.21 mL, 0.21 mmol, 11 mg NaOMe calculated with a molecular weight of 54.0 g·mol^{-1} and 0.165 g MeOH with ρ = 0.79 g·cm^{-3}) in MeOH (0.217 mL, 0.171 g with ρ = 0.79 g·cm^{-3}) for 3 h. After the reaction, the mixture was neutralized with aqueous HCl (1 M, amount not stated, we assume 0.21 mmol HCl, corresponding to 0.21 mL, *0.214 g* with ρ = 1.02 g·cm^{-3}), concentrated *in vacuo*, coevaporated with MeOH (amount not stated, we assume 1 mL, *0.79 g* with ρ = 0.79 g·cm^{-3}) and subjected to purification by reverse phase HPLC (*using 22.5 mL MeCN/water 12:88, for an assumed weight of 45 mg of crude product, which corresponds to 2.7 mL of MeCN, 2.133 g with ρ = 0.79 g·cm^{-3} and 19.8 mL of water, 19.8 g with ρ = 1.00 g·cm^{-3}*) to provide the unprotected nucleoside in 89% yield (0.037 mmol, **10 mg** calculated with a molecular weight of 267.2 g·mol^{-1}).

The reaction took a total of 131.08 h (15 min reaction setup + 8 h Boc-protection + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 80 h reaction time + 30 min drying + 15 min workup + 30 min drying + 10 min reaction setup + 30 min stirring + 10 min addition of reagents + 2 h glycosylation + 5 min workup + 30 min drying + 2 h purification + 30 min drying + 10 min reaction setup + 8 h deprotection + 30 min drying + 15 min reaction setup + 3 h deprotection + 5 min workup + 30 min drying + 2 h purification + 18 h lyophilization) and consumed a total of 3.95 mL of reaction solvent (0.25 mL THF + 1.51 mL CH_2Cl_2 + 0.88 mL *t*BuOH + 0.88 mL water + 0.43 mL MeOH), corresponding to 396.1 mL per gram of product, considering the contribution of the starting material 32,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate from Reaction S26, calculated as

$$\frac{3.95\ \text{mL}}{0.010\ \text{g}} + 0.040 * \frac{27.93\ \text{mL}}{\text{g}}$$

Thus, considering the sEF of the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate of 8.6 (Reaction S26), the preparation of the **6o** had a sEF of 46.8 calculated as

$$\text{sEF} = \frac{0.007 + 0.055 + 0.001 + 0.04 + 0.04 * 8.6 + 0.017 + 0.003 + 0.011 - \mathbf{0.01}}{\mathbf{0.01}}$$

and (considering the cEF of the starting material of 1866) a cEF of 15896, calculated as

$$\text{cEF} = \frac{\begin{array}{c}0.007 + 0.055 + 0.001 + 0.04 + 0.04 * 1866 + 0.017 + 0.003 + 0.011 + 1.26 + 0.017 + 1.54 \\ +0.222 + 16.38 + 5.67 + 0.395 + 0.026 + 2.015 + 0.365 + 20.328 + 6.93 + 0.677 + 0.165 \\ +0.171 + 0.79 + 2.133 + 0.433 + 2.5 + 1.25 + 0.877 + 0.214 + 19.8 \\ -\mathbf{0.01}\end{array}}{\mathbf{0.01}}$$

with combined contributions from reagents (61), inorganics (662), organic solvents (12074) and water (3111), considering the contribution from the starting material 2,3,5-tri-O-benzoyl-D-ribofuranosyl 2-(1-phenylvinyl) benzoate.

References

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All other references are listed above the procedure they described or within that procedure if they were consulted for specific metrics (e.g. density or solubility of a compound or mixture).