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Synthesis of an Oxidation-Stable Analogue of Cyclic Pyranopterin Monophosphate (cPMP)

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Molybdenum cofactor (Moco) deficiency is a lethal hereditary metabolic disease. A recently developed therapy requires continuous intravenous supplementation of the biosynthetic Moco precursor cyclic pyranopterin monophosphate (cPMP). The limited stability of the latter natural product, mostly due to oxidative degradation, is problematic for oral administration. Therefore, the synthesis of more stable cPMP analogues is of great interest. In this context and for the first time, the synthesis of a cPMP analogue, in which the oxidation-labile reduced pterin unit is replaced by a pyrazine moiety, was achieved starting from the chiral pool materials D-galactose or D-arabitol. Our synthesis, 13 steps in total, includes the following key transformations: i) pyrazine lithiation, followed by acylation; ii) closure of the pyrane ring by nucleophilic aromatic substitution; and iii) introduction of phosphate.

Introduction

Molybdenum is essential for approximately two thirds of all genetically investigated organisms.[1] Its catalytic activity in the biological setting hinges on complexation to a specific ligand.[1b,2] With the exception of the enzyme nitrogenase, molybdenum is typically bound to a pterin molecule (MPT, **3**; Scheme 1), thus forming the molybdenum cofactor (Moco, **5**; Scheme 1), which is located at the enzymes's active site. Molybdenum enzymes catalyse a variety of redox processes in carbon, nitrogen, and sulfur metabolism.[3] In mammals, four different molybdenum enzymes have been identified: i) sulfite oxidase; ii) aldehyde oxidase; iii) xanthine oxidoreductase; and iv) mitochondrial benzoamidoxime reductase.[4] The synthesis of Moco (**5**) follows, in all organisms studied to date, a conserved biosynthetic pathway (Scheme 1).[5] Starting from GTP (**1**), the biosynthesis proceeds in four steps with the involvement of at least six enzymes.[1a,5] In the first step, cPMP (**2**) is formed by a complex reaction sequence − and by a mechanism that is not yet fully understood − from GTP (**1**).[1a] cPMP (**2**) contains a reduced pyranopterin moiety and a cyclic phosphate. In addition, the geminal diol is a characteristic structural feature. Presumably, this hydrate form of the parent ketone is favoured by the strongly electron-withdrawing substitution pattern, i.e., O- and N-substitution of the ketone's α-positions.[1a,4b,5,6]

Subsequently, two sulfur atoms are incorporated into cPMP (**2**) to give MPT (**3**). Complexation to molybdenum occurs after activation of the intermediate pterin MPT (**3**) to give adenylated MPT (MPT-AMP, **4**).[8] Compared to Moco (**5**) itself, or to its other biosynthetic precursors, cPMP (**2**) is the most oxygen-stable intermediate. Nevertheless, cPMP (**2**) is oxidized under aerobic conditions, with a half-life of only a few hours, to give the biologically inactive, ring-opened "compound Z" (**6**; Scheme 1).[1a,2,4b,7]

Any kind of blockage of the Moco biosynthesis causes deactivation of all molybdenum-containing enzymes.[5b] Human Moco deficiency is an autosomal recessive hereditary metabolic disorder, with symptoms resulting mainly from the lack of sulfite oxidase activity. This, in turn, leads to elevated levels of toxic sulfite and tissue-specific lack of sulfate.[9] Moco deficiency affects newborns immediately after birth. The symptoms are progressive neurologic damage, usually resulting in early childhood death.[10] The frequency of occurrence of Moco deficiency is assumed to be 1 in 100000 or less.[1a] Nevertheless, to date, over 100 cases have been reported. Higher numbers can be assumed, however, as many cases probably escape diagnosis.[5b,11] Based on the location of the mutational blockage in the biosynthetic sequence, patients are classified into three groups. About two thirds belong to group A, for whom the production of cPMP (**2**) from GTP (**1**) is impeded. In type B and C patients, the further conversion of cPMP (**2**) into MPT (**3**), or the metal insertion are affected, respectively.[4b,11,12]

On the basis of promising results in a mouse model,[13] five Moco-deficiency type A patients have been successfully treated in replacement therapy, by permanent intravenous supplementation of cPMP (**2**).[4b,11b] The cPMP (**2**) necessary is currently being produced biotechnologically, using

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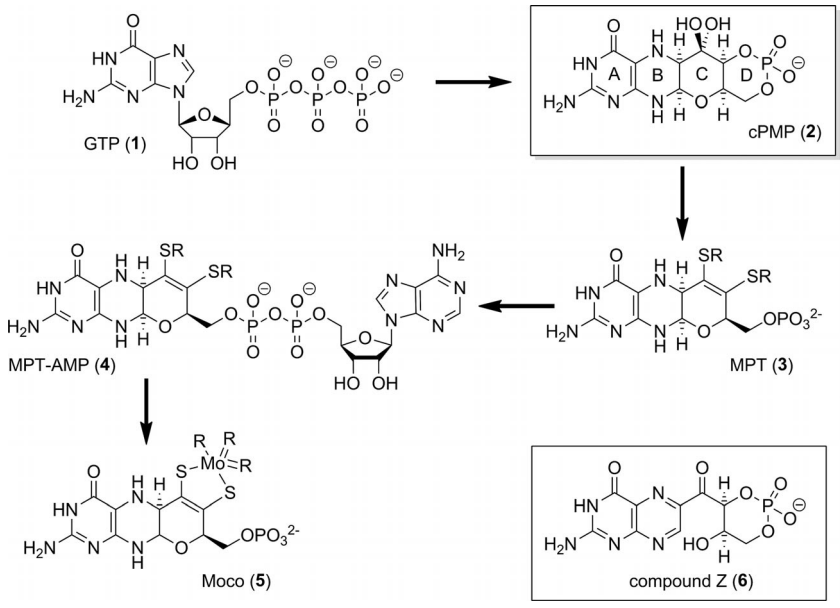


Scheme 1. Biosynthesis of Moco and structure of compound Z.[1a]

genetically modified *E. coli* developed by Schwarz et al.,[6,11b,13b,14a] followed by HPLC purification, and storage at –80 °C.[11b] Recently, the organic synthesis of labile cPMP (**2**) using the Viscontini reaction as the key step was reported.[14b,14c]

Even though a biotechnological source exists, and an organic synthesis has been reported, the lability of cPMP (**2**) still remains a major roadblock en route to the highly desirable oral administration of cPMP supplements. The sensitivity of hydrogenated pterins to oxygen, and their poor solubility in most solvents, are well known.[4b,15] Based on work of Viscontini et al., the first chemical synthesis of the pyranopterin skeleton was accomplished by Pfleiderer et al. in 1990.[16] As regards synthetic approaches to Moco (**5**) or Moco analogues, the work of the groups of Joule and Garner,[17] Basu,[18] Burgmayer,[19] Goswami,[20] and Holm[21] in particular should be mentioned.[15] All of these investigations confirm that the hydropterin moiety lies at the heart of the molecules' susceptibility to oxidation and concomitant ring cleavage (cf. formation of "compound Z" from cPMP, Scheme 1). Therefore, the organic synthesis of simplified and more stable analogues of cPMP (**2**) appears to be the logical consequence.

Results and Discussion

Structural Design of a Simplified and Oxygen Resistant cPMP Analogue

Bearing in mind the biosynthetic conversion of cPMP (**2**) into Moco (**5**), conservation of the "eastern part" (black in Figure 1), consisting of the hydropyran ring and the cyclic phosphate, was considered to be crucial for biological activity. With regard to the "western part" of cPMP (**2**; Scheme 1), the exact role of the pterin moiety for substrate/cofactor binding in the enzyme(s) is still in need of clarification.[1a,15] We felt that modification of this part of the molecule may be the best way to overcome cPMP's oxygen lability. As this lability can be assumed to be due to the presence of the hydropterin moiety, and the *N*,*O*-acetal substructure,[22] the logical move was to replace cPMP's piperazine B-ring by a pyrazine moiety (grey in Figure 1). In summary, we planned to synthesize compounds of type **A** as cPMP analogues (Figure 1).

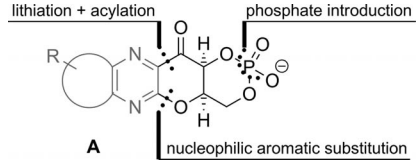
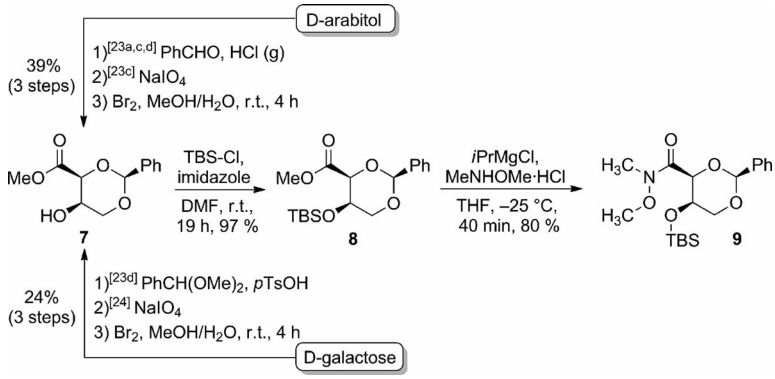


Figure 1. Retrosynthetic analysis of target cPMP analogue **A** ("eastern" building block in black, "western" building block in grey).

For the synthesis of cPMP analogue **A**, we envisaged the following three key steps: i) C–C coupling by *ortho*-lithiation of the 1,4-diazine, followed by acylation with a Weinreb amide; ii) C–O coupling by nucleophilic aromatic substitution of a halide; and iii) introduction of the phosphate. We expected the carbonyl group of analogue **A** to exist in equilibrium with its hydrate, as is seen for the natural product, cPMP (**2**).

Synthesis of the Eastern Building Block (as a Weinreb Amide)

Weinreb amide **9** could be synthesized in five steps starting from D-arabitol or D-galactose (Scheme 2). To this end, the known benzylidene protection[23] and periodate cleavage[23c,24] of the starting carbohydrates was followed by oxi-



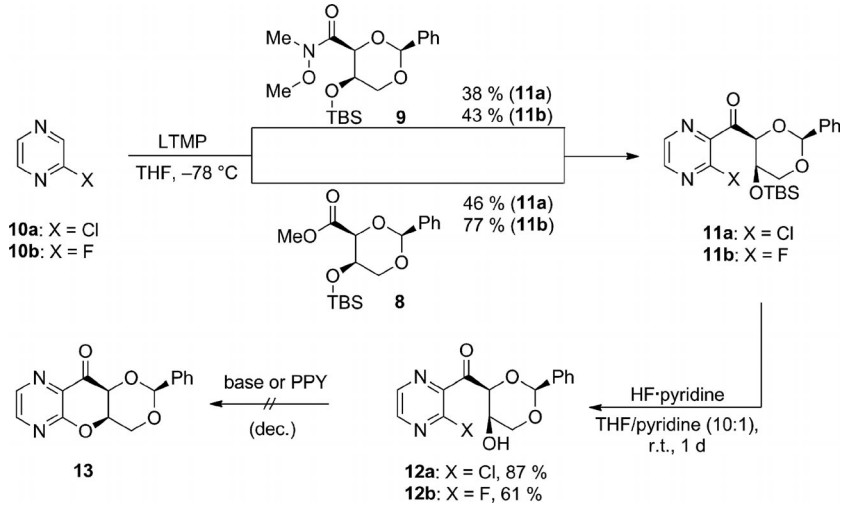
Scheme 2. Synthesis of the eastern building block, i.e., Weinreb amide **9**.

dation of the intermediate aldehyde to give methyl ester **7**,[25] by treatment with bromine in methanol/water (9:1), in analogy to a procedure reported by Williams et al.[26] The free hydroxy group of methyl ester **7** was smoothly protected as its TBS (*tert*-butyldimethylsilyl) ether, and the resulting methyl ester (i.e., **8**) was converted into Weinreb amide **9** in 80% yield following a procedure by Williams et al.[27] (Scheme 2).

ortho-Acylation of 2-Halopyrazines, and Attempted Cyclization by Nucleophilic Aromatic Substitution

The *ortho*-lithiation of 2-chloro- and 2-fluoropyrazines **10a** and **10b** with lithium tetramethylpiperidide (LTMP) according to Quéguiner et al.,[28] and reaction with Weinreb amide **9** gave acylated pyrazines **11a** and **11b** in yields of 38 and 43%, respectively (Scheme 3). In our hands, the generation of the lithiated halopyrazines in the presence of the Weinreb amide ("in situ quench" conditions) proved superior to the addition of the electrophile *after* lithiation of the pyrazine. In contrast to pyrazines **10a** and **10b**, the corresponding quinoxalines turned out to be poor substrates for this coupling approach by *ortho*-lithiation/acylation. Interestingly, using methyl ester **8** instead of the Weinreb amide resulted in an even better yield of up to 77%. Cleavage of the TBS group was effected with hydrogen fluoride in pyridine to give ketones **12a** and **12b** (Scheme 3).

For the planned ring-closing nucleophilic aromatic substitution, various bases (NaH, KO*t*Bu, Ag_2O, tetramethylguanidine, NEt_3, K_2CO_3) as well as acyl-transfer catalysts (such as 4-pyrrolidinopyridine, PPY) were explored. In model studies, the latter gave quite satisfactory results in *intermolecular* substitutions of fluoro-substituted 1,4-diazines with alcohols. Unfortunately, in the case of the desired *intramolecular* substitution, decomposition of the β-hydroxy ketones (i.e., **12a** and **12b**) was observed exclusively with PPY and with all of the bases listed above. Simple heating of the starting material, without added reagents, led to the same result. A possible explanation for this unexpected failure of the ring closure was revealed by the X-ray crystal structures of β-hydroxy ketone **12a** (Figure 2) and of TBS-protected β-hydroxy ketone **11b** (see Supporting Information). For example, the diffraction analysis of **12a** revealed that in the conformer present in the crystal, the hydroxy group and the pyrazine C–F bond are not in close proximity, but are pointing away from one another. DFT



Scheme 3. C–C coupling by *ortho*-acylation of 2-halopyrazines **10a** and **10b** [LTMP = lithium-2,2,6,6-tetramethylpiperidide, PPY = 4-(1-pyrrolidinyl)pyridine].

calculations (see Supporting Information) indicated that rotation around the $C_{pyrazine}$–$C_{carbonyl}$ bond is possible, but that the unreactive conformation as found in the crystal is energetically strongly favoured. The X-ray crystal structure shown in Figure 2 furthermore shows that the hydroxy group and the acidic proton in the ketone's α-position have an almost perfectly antiperiplanar diaxial orientation. Under the basic reaction conditions, ketones **12a** and **12b** may therefore easily undergo undesired alternative transformations e.g., retro-aldol reaction, or elimination.

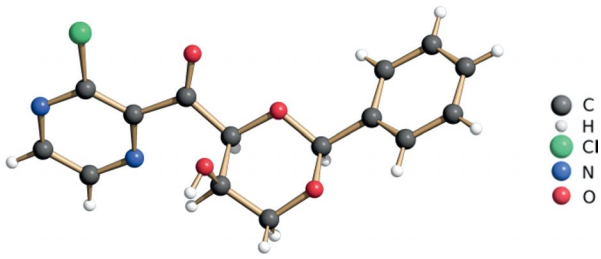


Figure 2. X-ray crystal structure of β-hydroxy ketone **12a**.

As a consequence of the above analysis, we decided to temporarily deactivate the keto functionality by protection. Acetalization required unacceptably harsh reaction conditions (e.g., TfOH in neopentyl glycol, 140 °C, 4 Å MS), and so we considered reducing the carbonyl group to a secondary alcohol. As shown in Scheme 4, treatment of β-hydroxy ketones **12a** and **12b** with sodium borohydride gave epimeric diols **14a** and **15a**, and **14b** and **15b**, respectively, in good yields and with diastereomeric ratios of ca. 1:1. The epimeric pairs of diols could be separated chromatographically, and the configurations of the newly formed stereocentres were assigned by X-ray crystallography (see Figure 3 for the X-ray crystal structures of **14a** and **15a**). To our delight, treatment of diols **14a** and **14b** with base effected the desired ring-closing nucleophilic aromatic substitution to give compound **16**, and similar treatment of **15a** and **15b** resulted in the analogous formation of compound **17** (Scheme 4). Despite extensive testing of various bases, acyl-transfer catalysts, and temperatures, the cyclization yields for either epimer could not be raised above the ones given in Scheme 4. The best results were obtained using potassium *tert*-butoxide. High-dilution conditions led to only slightly improved yields.

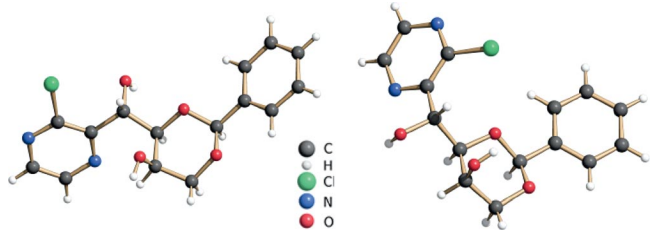


Figure 3. X-ray crystal structures of epimeric diols **14a** (left) and **15a** (right).

Before the introduction of the phosphate, for which benzylidene cleavage was required, the reoxidation of the secondary hydroxy groups of cyclized epimers **16** and **17** was performed. This transformation could be achieved smoothly using Dess–Martin periodinane in yields of 95 and 74%, respectively (Scheme 4). In the resulting tricyclic ketone (i.e., **13**), the carbon skeleton of cPMP analogue **A**

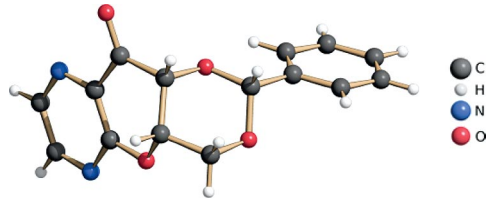
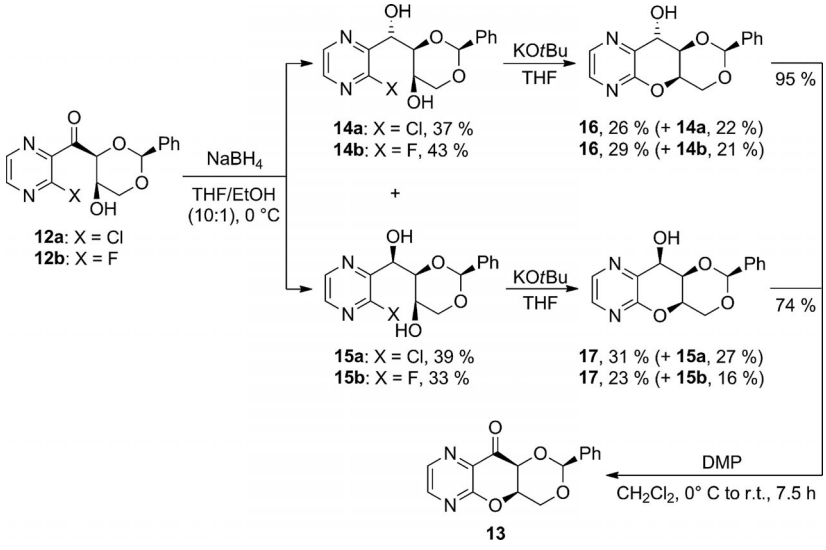
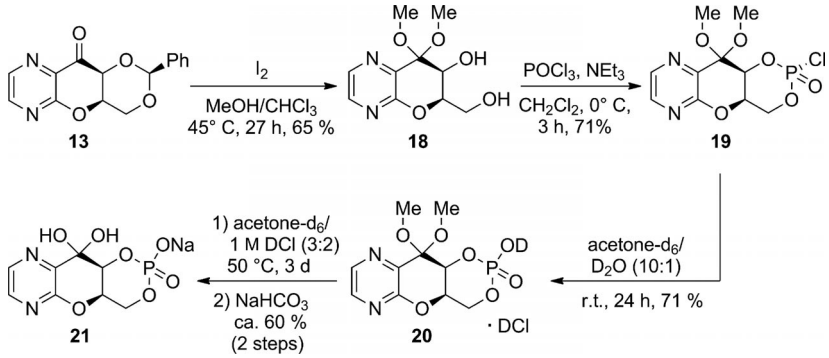


Figure 4. X-ray crystal structure of tricyclic ketone **13**.



Scheme 4. Ring-closing C–O coupling by nucleophilic aromatic substitution (DMP = Dess–Martin periodinane).



Scheme 5. Synthesis of cPMP analogue **21** by phosphate introduction.

is fully assembled. This central intermediate of our synthesis could also be crystallized, and its X-ray structure is shown in Figure 4. The crystal structure nicely demonstrates the bent, non-planar shape of the tricyclic core, resulting from the *cis* junction of the dihydropyranone and 1,3-dioxane rings.

Introduction of the Phosphate

The removal of the benzylidene protecting group from ketone **13** was effected under iodine catalysis[29] in a mixture of methanol and chloroform. These conditions, which resulted from extensive optimization, at the same time effected the conversion of the carbonyl group into its dimethyl acetal to give **18** (Scheme 5). In view of the difficulties encountered in the acetalization of TBS-protected hydroxy ketones **11a** and **11b** (see above), this result was surprising, and was attributed to a reduced steric crowding after removal of the benzylidene group, together with a potential electrophilic activation of the ketone by intramolecular hydrogen bonding.[30] Treatment of diol **18** with phosphorus oxychloride gave, after flash chromatography, phosphoryl chloride **19** as a single diastereomer in 71% yield. The hydrolysis of the latter compound was accomplished in a mixture of D_2O and [D_6]acetone (to enable monitoring by NMR spectroscopy) to give phosphoric acid **20** in 71% yield (Scheme 5). The synthesis of cPMP analogue **A** was completed by cleaving the dimethyl acetal of compound **20** by heating in the presence of an excess of deuterium chloride solution. Due to slow accompanying phosphate hydrolysis, purification was carried out by preparative reverse-phase HPLC after treatment with sodium hydrogen carbonate. According to its NMR spectroscopic data, the product was obtained as its ketone hydrate (i.e., **21**), and ^{31}P NMR spectroscopy indicated the presence of small amounts of inorganic phosphate. Both the relative and the absolute configuration of the cPMP analogue were confirmed by the X-ray crystal structure of the sodium salt of dimethyl acetal **20**, as shown in Figure 5. Upon exposure to air, cPMP analogue **21** and its precursors did not show any tendency towards oxidative degradation.

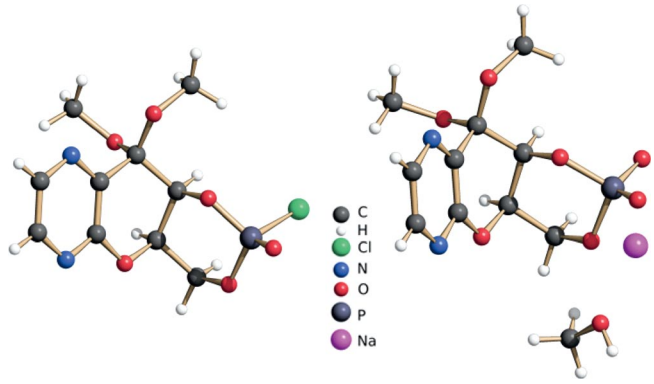


Figure 5. X-ray crystal structures of phosphoryl chloride **19** (left), the sodium salt of dimethyl acetal **20** (right), and cPMP analogue **21** (the sodium salt crystallizes with one equivalent of methanol).

Conclusions

We report the first synthesis and structural characterization of an analogue of cyclic pyranopterin monophosphate (cPMP, **2**), namely cyclic phosphate **21**. As a key feature, the reduced pterin moiety of the natural product (i.e., **2**) is replaced by a pyrazine in **21**. Unlike the natural product (i.e., **2**), its analogue **21** does not show any tendency towards oxidative degradation. Key steps of the synthesis of **21** are: i) C–C coupling of the eastern and western building blocks by *ortho*-lithiation/acylation of a 2-halopyrazine; ii) ring-closing C–O bond formation by nucleophilic aromatic substitution, requiring temporary reduction of the eastern building block's keto functionality to an alcohol; and iii) introduction of the phosphoric diester. Tests for biological activity are underway.

Experimental Section

General Remarks: 2,2,6,6-Tetramethylpiperidine, 2-chloropyrazine (**10a**), 2-fluoropyrazine (**10b**), and phosphorus oxychloride were distilled before use and stored over molecular sieves. 1,3-*O*-Benzylidene-D-arabitol was prepared according to a literature procedure.[23a,23c,23d] The concentration of *n*BuLi solutions was determined by titration against *N*-benzylbenzamide.[31] All other chemicals were purchased from commercial suppliers, and were used

without further purification. *N*,*N*-Dimethylformamide was purchased from Acros (99.8%, extra dry, over MS). Solvents were dried before use according to standard procedures. Aluminium-backed TLC plates coated with 0.2 mm silica containing a fluorescent indicator (ALUGRAM® SIL G/UV$_{254}$) were purchased from Macherey–Nagel. Flash chromatography was carried out on silica gel (Acros, 0.035–0.070 mm, 60 Å). NMR spectra were recorded with Bruker DPX 200, DPX 300, AV 300, DRX 500, and AV 600 spectrometers at room temperature, unless otherwise noted, and were referenced to the solvent used. Melting points were measured with a B-545 Büchi apparatus. Optical rotations were measured with a Perkin–Elmer 343plus polarimeter. HRMS data were recorded with a Finnigan MAT 900 S instrument. Infrared (IR) spectra were recorded with a Shimadzu IR-Affinity-1 spectrometer. CHN analysis was carried out with an Elementar Analysensysteme GmbH Vario EL instrument. Preparative reverse-phase HPLC was performed using an EC-Nucleodur 100–16 C-18 column (50 mm × 250 mm, Macherey–Nagel) with a NovaPrep 200 pump, a LaChrom L-7400 (Merck Hitachi) UV detector, and a K-2401 (Knauer) refractive index detector. X-ray structural data were collected with a Nonius Kappa CCD diffractometer at the temperatures stated. Structures were solved using SHELXS97 and refined with SHELXL97 using the full-matrix least-squares method on $|F^2|$.

Methyl (2*S*,4*S*,5*R*)-5-Hydroxy-2-phenyl-1,3-dioxane-4-carboxylate (7): 1,3-*O*-Benzylidene-D-arabitol (6.35 g, 26.4 mmol) was dissolved in CH_2Cl_2 (70 mL), and saturated aqueous $NaHCO_3$ (13 mL) was added. Sodium periodate (11.3 g, 52.8 mmol) was added to the stirred mixture at 0 °C over 10 min. The mixture was stirred for 2 h at room temperature, then it was filtered, and the insoluble residue was washed with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried with $MgSO_4$, and evaporated under reduced pressure to give the intermediate aldehyde (5.55 g) as a colourless foam that was used in the next step without further purification.

$NaHCO_3$ (44.3 g, 528 mmol) was added to a solution of the crude aldehyde in methanol and water (9:1), and then a solution of Br_2 (16.9 g, 106 mmol) in methanol/water (9:1; 55 mL) was added over 15 min in a dropwise manner. The resulting suspension was stirred for 3 h at room temperature. The mixture was cooled to 0 °C, then solid $Na_2S_2O_3$ was added until it turned colourless. Water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 1:1) to give ester **7** (3.42 g, 14.4 mmol, 55%) as a colourless solid. R_f = 0.28 (cyclohexane/EtOAc, 1:1), m.p. 120–122 °C (ref.[25] 124–125 °C). $[\alpha]_D^{20}$ = –48.5 (c = 1.0, $CHCl_3$); ref.[25] –56.6 (c = 0.22, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.06 (d, J = 11.4 Hz, 1 H, OH), 3.82 (s, 3 H, OCH_3), 4.00 (dd, J = 11.4, 1.4 Hz, 1 H, C*H*OH), 4.11 (dd, J = 12.1, 0.8 Hz, 1 H, CH_2), 4.24 (dd, J = 12.1, 1.7 Hz, 1 H, CH_2), 4.61 (d, J = 1.1 Hz, 1 H), 5.59 (s, 1 H), 7.32–7.44 (m, 3 H, Ar-H), 7.48–7.59 (m, 2 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4 (OCH_3), 64.8 [C(H)OH], 72.1 (CH_2), 78.7 (CH), 101.3 [C(H)Ph], 126.1 (Ar-CH), 128.3 (Ar-CH), 129.2 (Ar-CH), 136.8 (Ar-C), 168.4 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3505, 2874, 1744 (s), 1734 (s), 1441, 1396, 1250 (s), 1223 (s), 1153 (s), 1090 (s), 1015 (s), 935, 822, 750 (s), 689 (s), 658 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{15}O_5$ [M + H]$^+$ 237.076; found 237.076. $C_{12}H_{14}O_5$ (238.24): calcd. C 60.50, H 5.92; found C 60.75, H 6.12. For X-ray data of compound **7**, see Supporting Information.

Methyl (2*S*,4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-phenyl-1,3-dioxane-4-carboxylate (8): *tert*-Butyldimethylsilyl chloride (1.25 g, 8.30 mmol) and imidazole (940 mg, 13.8 mmol) were added to a solution of **7** (1.65 g, 6.90 mmol) in anhydrous DMF (4.4 mL) at 0 °C. The mixture was stirred at room temperature for 19 h, then it was diluted with EtOAc (100 mL), and washed with brine (50 mL) and water (70 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 20:1 to 2:1) to give the TBS-protected alcohol **8** (2.36 g, 6.70 mmol, 97%) as a colourless solid. R_f = 0.20 (cyclohexane/EtOAc, 8:1), m.p. 41–44 °C. $[\alpha]_D^{20}$ = –52.3 (c = 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$), 0.92 [s, 9 H, $SiC(CH_3)_3$], 3.78 (s, 3 H, OCH_3), 4.00–4.22 (m, 3 H), 4.57 (d, J = 1.7 Hz, 1 H), 5.55 (s, 1 H), 7.30–7.42 (m, Ar-H), 7.49–7.59 (m, 2 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1 ($SiCH_3$), –4.4 ($SiCH_3$), 18.0 [s, Si*C*$(CH_3)_3$], 25.6 [SiC(*C*$H_3)_3$], 52.1 (OCH_3), 65.4 [C(H)OTBS], 72.0 (CH_2), 79.3 (CH), 101.3 [C(H)Ph], 126.6 (Ar-CH), 128.3 (Ar-CH), 129.2 (Ar-CH), 137.6 (Ar-C), 168.8 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 2928, 2855, 1767, 1738, 1439, 1362, 1292, 1250, 1210, 1163 (s), 1096 (s), 1016 (s), 935 (s), 833 (s), 808, 775 (s), 758, 694 (s) cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{29}O_5Si$ [M + H]$^+$ 351.163; found 351.163. $C_{18}H_{28}O_5Si$ (352.50): calcd. C 61.33, H 8.01; found C 61.23, H 8.02. For X-ray data of compound **8**, see Supporting Information.

(2*S*,4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-2-phenyl-1,3-dioxane-4-carboxamide (9): *N*,*O*-Dimethylhydroxylamine hydrochloride (304 mg, 3.10 mmol) was added to a stirred solution of ester **8** (705 mg, 2.00 mmol) in anhydrous THF (4 mL) at –25 °C, and then isopropylmagnesium chloride (2.0 M in THF; 3.00 mL, 6.00 mmol) was added dropwise over 20 min. The mixture was stirred for a further 20 min at –25 °C, then it was quenched with saturated aqueous NH_4Cl (1.5 mL) and water (10 mL), and the mixture was extracted with CH_2Cl_2 (2 × 12 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 5:2) to give Weinreb amide **9** (609 mg, 1.60 mmol, 80%) as a colourless solid. R_f = 0.20 (cyclohexane/EtOAc, 5:2), m.p. 134 °C. $[\alpha]_D^{20}$ = –49.7 (c = 1.31, CH_2Cl_2). ^{1}H NMR (200 MHz, [D$_8$]toluene, 75 °C): δ = 0.08 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.95 [s, 9 H, $SiC(CH_3)_3$], 3.07 (s, 3 H, NCH_3), 3.34 (s, 3 H, OCH_3), 3.63 (dd, J = 12.5, 2.0 Hz, 1 H), 3.89–4.05 (m, 2 H), 4.42 (d, J = 1.6 Hz, 1 H), 5.31 (s, 1 H), 7.04–7.19 (m, 3 H, Ar-H), 7.47–7.58 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50 MHz, [D$_8$]toluene, 75 °C): δ = –5.0 ($SiCH_3$), –4.8 ($SiCH_3$), 17.9 [s, Si*C*$(CH_3)_3$], 25.6 [SiC(*C*$H_3)_3$], 33.9 (NCH_3), 60.3 (OCH_3), 65.7 [C(H)OTBS], 72.1 (CH_2), 80.6 (CH), 101.3 [C(H)Ph], 126.4 (Ar-CH), 127.7 (Ar-CH), 128.4 (Ar-CH), 137.0 (Ar-C), 167.2 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 2936, 2859, 1674 (s), 1389, 1317, 1246, 1165, 1099 (s), 1078 (s), 1024 (s), 988, 959, 849, 829 (s), 808 (s), 777 (s), 752 (s), 702 (s), 656 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{31}NO_5Si$-$CH_3^{+\cdot}$ [M + H]$^+$ 366.174; found 366.174. $C_{19}H_{31}NO_5Si$-$CH_3^{+\cdot}$: calcd. C 59.81, H 8.19, N 3.67; found C 59.74, H 8.19, N 3.65. For X-ray data of compound **9**, see Supporting Information.

[(2*S*,4*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl](3-chloropyrazin-2-yl)methanone (11a):

From 9: A solution of 2,2,6,6-tetramethylpiperidine (119 µL, 98.9 mg, 700 µmol) in anhydrous THF (2 mL) was cooled to –30 °C, and *n*BuLi (2.4 M in hexanes; 228 µL, 550 µmol) was added over 5 min. The mixture was stirred at 0 °C for 30 min, then the solution was cooled to –78 °C, and it was added over 8 min to a solution of 2-chloropyrazine (62.5 µL, 80.2 mg, 700 µmol) and Weinreb amide **9** (191 mg, 500 µmol) in anhydrous THF (3 mL) at –78 °C. The mixture was stirred at this temperature for a further

1.5 h, then it was quenched with saturated aqueous NH_4Cl (2 mL), and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3× 3 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 3:1) to give acylated chloropyrazine **11a** (82 mg, 189 μmol, 38%) as a colourless solid.

From 8: A solution of 2,2,6,6-tetramethylpiperidine (1.79 mL, 1.48 g, 10.5 mmol) in anhydrous THF (30 mL) was cooled to –30 °C, and *n*BuLi (2.4 M in hexanes; 3.42 mL, 8.25 mmol) was added over 5 min. The mixture was stirred at 0 °C for 30 min, then the solution was cooled to –78 °C and added over 20 min to a solution of 2-chloropyrazine (937 μL, 1.20 g, 10.5 mmol) and methyl ester **8** (2.64 g, 7.50 mmol) in anhydrous THF (45 mL) at –78 °C. The mixture was stirred at this temperature for another 60 min, then it was quenched with saturated aqueous NH_4Cl (40 mL), and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with MTBE (methyl *tert*-butyl ether; 3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 8:1 to 4:1) to give acylated chloropyrazine **11a** (1.50 g, 3.45 mmol, 46%) as a colourless solid. R_f = 0.55 (cyclohexane/EtOAc, 2:1), m.p. 147 °C. $[\alpha]_D^{20}$ = –75.1 (*c* = 1.10, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.17 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.86 [s, 9 H, $SiC(CH_3)_3$], 4.15 (dd, *J* = 12.4, 1.3 Hz, 1 H, CH_2), 4.21 (dd, *J* = 12.4, 1.4 Hz, 1 H, CH_2), 4.31–4.38 (m, 1 H, CHOTBS), 5.51 (d, *J* = 1.2 Hz, 1 H), 5.68 (s, 1 H), 7.29–7.39 (m, 3 H, Ar-H), 7.46–7.57 (m, 2 H, Ar-H), 8.51 (d, *J* = 2.3 Hz, 1 H, Pyr-H), 8.54 (d, *J* = 2.3 Hz, 1 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.0 ($SiCH_3$), –4.3 ($SiCH_3$), 18.0 [s, $SiC(CH_3)_3$], 25.7 [$SiC(CH_3)_3$], 66.6 [C(H)OTBS], 71.8 (CH_2), 82.8 (CH), 101.3 [C(H)Ph], 126.4 (Ar-CH), 128.2 (Ar-CH), 129.0 (Ar-CH), 137.7 (Ar-C), 141.1 (Pyr-CH), 145.7 (Pyr-CH), 146.0 (Pyr-C), 147.4 (Pyr-C), 193.0 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 2955, 2930, 2859, 1721, 1539, 1383, 1368, 1250, 1163, 1103, 1084, 1022 (s), 1011, 982, 924, 806, 775 (s), 731 (s), 696 (s), 654 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{27}ClN_2O_4SiNa$ [M + Na]$^+$ 457.133; found 457.132. $C_{21}H_{27}ClN_2O_4Si$ (434.99): calcd. C 57.98, H 6.26, N 6.44; found C 57.87, H 6.23, N 6.35.

[(2*S*,4*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl](3-fluoropyrazin-2-yl)methanone (11b)

From 9: A solution of 2,2,6,6-tetramethylpiperidine (238 μL, 198 mg, 1.40 mmol) in anhydrous THF (4 mL) was cooled to –30 °C and *n*BuLi (2.4 M in hexanes; 456 μL, 1.10 mmol) was added over 5 min. The mixture was stirred at 0 °C for 30 min, then the solution was cooled to –78 °C, and it was added over 8 min to a solution of 2-fluoropyrazine (112 μL, 137 mg, 1.40 mmol) and Weinreb amide **9** (382 mg, 1.00 mmol) in anhydrous THF (6 mL) at –78 °C. The mixture was stirred at this temperature for 1.5 h, then it was quenched with saturated aqueous NH_4Cl (5 mL), and warmed to room temperature. The mixture was extracted with EtOAc (3× 8 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 5:2) to give acylated fluoropyrazine **11b** (178 mg, 426 μmol, 43%) as a pale yellow solid.

From 8: A solution of 2,2,6,6-tetramethylpiperidine (1.79 mL, 1.48 g, 10.5 mmol) in anhydrous THF (30 mL) was cooled to –30 °C, and *n*BuLi (2.4 M in hexanes; 3.42 mL, 8.25 mmol) was added over 5 min. The mixture was stirred at 0 °C for 30 min, then the solution was cooled to –78 °C, and it was added over 20 min to a solution of 2-fluoropyrazine (849 μL, 1.03 g, 10.5 mmol) and methyl ester **8** (2.64 g, 7.50 mmol) in anhydrous THF (45 mL) at –78 °C. The mixture was stirred at this temperature for 60 min, then it was quenched with saturated aqueous NH_4Cl (40 mL), and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with MTBE (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 3:1) to give acylated fluoropyrazine **11b** (2.43 g, 5.81 mmol, 77%) as a pale yellow solid. R_f = 0.30 (cyclohexane/EtOAc, 5:2), m.p. 144 °C. $[\alpha]_D^{20}$ = –95.6 (*c* = 1.28, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.30 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.83 [s, 9 H, $SiC(CH_3)_3$], 4.16–4.23 (m, 2 H, CH_2), 4.35–4.41 (m, 1 H, CHOTBS), 5.64 (d, *J* = 1.6 Hz, 1 H), 5.70 (s, 1 H), 7.32–7.42 (m, 3 H, Ar-H), 7.53–7.63 (m, 2 H, Ar-H), 8.39–8.46 (m, 1 H, Pyr-H), 8.52–8.60 (m, 1 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), –4.2 ($SiCH_3$), 17.9 [s, $SiC(CH_3)_3$], 25.5 [$SiC(CH_3)_3$], 65.7 [C(H)OTBS], 71.7 (CH_2), 82.5 (CH), 101.3 [C(H)Ph], 126.5 (Ar-CH), 128.2 (Ar-CH), 129.1 (Ar-CH), 136.0 ($J_{C,F}$ = 19.3 Hz, Pyr-C), 137.7 (Ar-C), 140.6 ($J_{C,F}$ = 5.3 Hz, Pyr-CH), 145.4 ($J_{C,F}$ = 9.6 Hz, Pyr-CH), 158.2 ($J_{C,F}$ = 268.7 Hz, Pyr-C), 190.7 ($J_{C,F}$ = 6.5 Hz, C=O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –71.1 ppm. IR (ATR): $\tilde{\nu}$ = 2959, 2930, 2855, 1722, 1570, 1389, 1358, 1252, 1155, 1096 (s), 1026 (s), 1016, 982, 932, 845, 826, 775 (s), 750 (s), 702 (s), 606 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{27}FN_2O_4SiNa$ [M + Na]$^+$ 441.162; found 441.162. $C_{21}H_{27}FN_2O_4Si$ (418.54): calcd. C 60.26, H 6.50, N 6.69; found C 60.21, H 6.47, N 6.65. For X-ray data of compound **11b**, see Supporting Information.

(3-Chloro-2-pyrazinyl)[(2*S*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl]methanone (12a): HF·pyridine (ca. 70:30 w/w; 3.55 mL) was added to a solution of TBS-protected alcohol **11a** (1.13 g, 2.59 mmol) in anhydrous THF (70 mL) and anhydrous pyridine (7 mL) at 0 °C. The mixture was stirred for 24 h at room temp., and then saturated aqueous $NaHCO_3$ was added until the evolution of gas had ceased. The mixture was extracted with EtOAc (5× 80 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 3:2) to give alcohol **12a** (726 mg, 2.26 mmol, 87%) as a colourless solid. R_f = 0.30 (cyclohexane/EtOAc, 1:1), m.p. 140–143 °C. $[\alpha]_D^{20}$ = –143.4 (*c* = 0.35, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.24 (br. s, 1 H, OH), 4.08–4.15 (m, 1 H, C*H*OH), 4.19–4.29 (m, 2 H, CH_2), 5.61–5.67 (m, 1 H), 5.72 (s, 1 H), 7.31–7.41 (m, 3 H, Ar-H), 7.45–7.56 (m, 2 H, Ar-H), 8.49–8.57 (m, 2 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.8 [C(H)OH], 72.1 (CH_2), 82.5 (CH), 101.2 [C(H)Ph], 126.0 (Ar-CH), 128.3 (Ar-CH), 129.2 (Ar-CH), 136.9 (Ar-C), 140.9 (Pyr-CH), 145.6 (Pyr-C), 146.1 (Pyr-CH), 147.7 (Pyr-C), 192.7 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3374, 2967, 1726, 1543, 1454, 1377 (s), 1292, 1246, 1152, 1113, 1101, 1076, 1016 (s), 1001 (s), 966 (s), 916, 862, 765, 741 (s), 696 (s), 652, 602 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{13}ClN_2O_4Na$ [M + Na]$^+$ 343.046; found 343.046. $C_{15}H_{13}ClN_2O_4$ (320.73): calcd. C 56.17, H 4.09, N 8.73; found C 56.44, H 4.13, N 8.63. For X-ray data of compound **12a**, see Supporting Information.

(3-Fluoro-2-pyrazinyl)[(2*S*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl]methanone (12b): HF·pyridine (ca. 70:30 w/w; 200 μL) was added to a solution of TBS-protected alcohol **11b** (60.2 mg, 144 μmol) in anhydrous THF (4 mL) and anhydrous pyridine (400 μL) at 0 °C. The mixture was stirred for 18 h at room temp., and then saturated aqueous $NaHCO_3$ (8 mL) was added until the evolution of gas had ceased. The mixture was extracted with EtOAc

(4× 6 mL). The combined extracts were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 1:1) to give alcohol **12b** (26.9 mg, 88.4 μmol, 61%) as an orange oil. R_f = 0.40 (cyclohexane/EtOAc, 1:2), m.p. 41–44 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.23 (br. s, 1 H, OH), 4.19–4.31 (m, 3 H), 5.70–5.81 (m, 2 H), 7.33–7.45 (m, 3 H, Ar-H), 7.49–7.60 (m, 2 H, Ar-H), 8.39–8.49 (m, 1 H, Pyr-H), 8.51–8.59 (m, 1 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.0 [C(H)OH], 72.2 (CH_2), 82.3 (CH), 101.3 [C(H)Ph], 126.1 (Ar-CH), 128.3 (Ar-CH), 129.2 (Ar-CH), 135.5 ($J_{C,F}$ = 18.6 Hz, Pyr-C), 136.9 (Ar-C), 140.6 ($J_{C,F}$ = 5.4 Hz, Pyr-CH), 145.8 ($J_{C,F}$ = 9.9 Hz, Pyr-CH), 158.4 ($J_{C,F}$ = 269.3 Hz, Pyr-C), 190.7 ($J_{C,F}$ = 6.9 Hz, C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3417 (br. s), 2974, 2936, 2876, 1722, 1537, 1450, 1418, 1396, 1260, 1206, 1173, 1094 (s), 1078 (s), 1020 (s), 870, 735 (s), 731 (s), 698 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{13}FN_2O_4Na$ [M + Na]$^+$ 327.0752; found 327.0754.

(2*S*,4*R*,5*R*)-4-[(Ξ)-(3-Chloropyrazin-2-yl)hydroxymethyl]-2-phenyl-1,3-dioxan-5-ol (14a and 15a): A solution of alcohol **12a** (1.70 g, 5.30 mmol) in a mixture of anhydrous THF (40 mL) and anhydrous ethanol (4 mL) was cooled to 0 °C, and sodium borohydride (261 mg, 6.89 mmol) was added with stirring. After 60 min at this temperature, saturated aqueous $NaHCO_3$ (30 mL) was added. The mixture was extracted with CH_2Cl_2 (6× 30 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 2:3 to 0:1) to give alcohol **14a** (633 mg, 1.96 mmol, 37%) and epimeric alcohol **15a** (831 mg, 2.57 mmol, 49%) as colourless solids.

Data for **14a**: R_f = 0.40 (cyclohexane/EtOAc, 1:2), m.p. 109–111 °C. $[\alpha]_D^{20}$ = +80.7 (*c* = 0.83, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.69–3.79 (m, 1 H), 3.93 (d, *J* = 6.1 Hz, 1 H, OH), 4.04 (d, *J* = 12.0 Hz, 1 H), 4.13 (d, *J* = 5.5 Hz, 1 H, OH), 4.22 (d, *J* = 12.0 Hz, 1 H), 4.41–4.49 (m, 1 H), 5.43–5.52 (m, 1 H), 5.56 (s, 1 H), 7.28–7.36 (m, 3 H, Ar-H), 7.36–7.45 (m, 2 H, Ar-H), 8.32 (d, *J* = 2.1 Hz, 1 H, Pyr-H), 8.50 (d, *J* = 2.1 Hz, 1 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.2 [C(H)OH], 70.9 [C(H)OH], 72.4 (CH_2), 78.8 (CH), 101.4 [C(H)Ph], 126.0 (Ar-CH), 128.2 (Ar-CH), 129.1 (Ar-CH), 137.4 (Ar-C), 141.6 (Pyr-CH), 143.6 (Pyr-CH), 148.1 (Pyr-C), 151.5 (Pyr-C) ppm. IR (ATR): $\tilde{\nu}$ = 3381 (br. s), 3279 (br. s), 2968, 2928, 1452, 1389, 1233, 1144, 1098, 1051 (s), 1028 (s), 1001 (s), 866, 760, 700, 656 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{15}ClN_2O_4Na$ [M + Na]$^+$ 345.0613; found 345.0614. For X-ray data of compound **14a**, see Supporting Information.

Data for **15a**: R_f = 0.25 (cyclohexane/EtOAc, 1:2), m.p. 118–120 °C. $[\alpha]_D^{20}$ = +37.4 (*c* = 1.19, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28 (d, *J* = 10.2 Hz, 1 H, OH), 3.81 (d, *J* = 8.6 Hz, 1 H, OH), 3.96–4.14 (m, 3 H), 4.29 (d, *J* = 12.0 Hz, 1 H), 5.41 (s, 1 H), 5.51–5.61 (m, 1 H), 7.27–7.38 (m, 5 H, Ar-H), 8.32 (d, *J* = 2.4 Hz, 1 H, Pyr-H), 8.50 (d, *J* = 2.4 Hz, 1 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.1 [C(H)OH], 67.8 [C(H)OH], 72.5 (CH_2), 82.5 (CH), 101.1 [C(H)Ph], 125.7 (Ar-CH), 128.2 (Ar-CH), 129.0 (Ar-CH), 137.2 (Ar-C), 142.0 (Pyr-CH), 143.2 (Pyr-CH), 149.2 (Pyr-C), 154.1 (Pyr-C) ppm. IR (ATR): $\tilde{\nu}$ = 3364 (br. s), 2957, 2924, 1450, 1379, 1356, 1153, 1086 (s), 1061 (s), 1051 (s), 1001 (s), 962, 760, 746, 704 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{15}ClN_2O_4Na$ [M + Na]$^+$ 345.0613; found 345.0614. $C_{15}H_{15}ClN_2O_4$ (322.75): calcd. C 55.82, H 4.68, N 8.68; found C 55.87, H 4.79, N 8.44. For X-ray data of compound **15a**, see Supporting Information.

(2*S*,4*R*,5*R*)-4-[(Ξ)-(3-Fluoropyrazin-2-yl)hydroxymethyl]-2-phenyl-1,3-dioxan-5-ol (14b and 15b): A solution of alcohol **12b** (960 mg, 3.16 mmol) in a mixture of anhydrous THF (23 mL) and anhydrous ethanol (2.3 mL) was cooled to 0 °C, and sodium borohydride (143 mg, 3.79 mmol) was added with stirring. After 2 h at this temperature, saturated aqueous $NaHCO_3$ (15 mL) and water (10 mL) were added. The mixture was extracted with CH_2Cl_2 (6× 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 1:2) to give alcohol **14b** (417 mg, 1.36 mmol, 43%) and epimeric alcohol **15b** (322 mg, 1.05 mmol, 33%) as colourless solids.

14b: R_f = 0.40 (cyclohexane/EtOAc, 1:3), m.p. 116–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.54–3.71 (m, 2 H), 3.94 (d, *J* = 4.0 Hz, 1 H, OH), 4.04 (d, *J* = 12.1 Hz, 1 H), 4.20 (d, *J* = 12.1 Hz, 1 H), 4.37–4.45 (m, 1 H), 5.33–5.43 (m, 1 H), 5.60 (s, 1 H), 7.29–7.38 (m, 3 H, Ar-H), 7.39–7.49 (m, 2 H, Ar-H), 8.13–8.25 (m, 1 H, Pyr-H), 8.42–8.54 (m, 1 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.6 [C(H)OH], 69.4 [$J_{C,F}$ = 5.6 Hz, C(H)OH], 72.3 (CH_2), 79.8 (CH), 101.5 [C(H)Ph], 125.9 (Ar-CH), 128.2 (Ar-CH), 129.1 (Ar-CH), 137.3 (Ar-C), 141.0 ($J_{C,F}$ = 4.8 Hz, Pyr-CH), 141.3 ($J_{C,F}$ = 8.6 Hz, Pyr-CH), 142.1 ($J_{C,F}$ = 28.5 Hz, Pyr-C), 158.1 ($J_{C,F}$ = 255.4 Hz, Pyr-C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –77.9 ppm. IR (ATR): $\tilde{\nu}$ = 3281 (br. s), 1451, 1400, 1360, 1277, 1242, 1153, 1063 (s), 1028 (s), 853, 820, 745 (s), 702 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{15}FN_2O_4Na$ [M + Na]$^+$ 329.0908; found 329.0909. For X-ray data of compound **14b**, see Supporting Information.

15b: R_f = 0.30 (cyclohexane/EtOAc, 1:3), m.p. 148 °C. $[\alpha]_D^{20}$ = +108.7 (*c* = 0.96, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.32 (d, *J* = 10.9 Hz, 1 H, OH), 3.94 (d, *J* = 7.9 Hz, 1 H, OH), 3.98–4.15 (m, 3 H), 4.29 (d, *J* = 11.9 Hz, 1 H), 5.33–5.48 (m, 2 H), 7.27–7.38 (m, 5 H, Ar-H), 8.08–8.22 (m, 1 H, Pyr-H), 8.40–8.55 (m, 1 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.0 [C(H)OH], 66.1 [$J_{C,F}$ = 5.3 Hz, C(H)OH], 72.4 (CH_2), 82.0 (CH), 100.9 [C(H)Ph], 125.6 (Ar-CH), 128.1 (Ar-CH), 128.9 (Ar-CH), 137.1 (Ar-C), 140.9 ($J_{C,F}$ = 8.8 Hz, Pyr-CH), 141.0 ($J_{C,F}$ = 5.0 Hz, Pyr-CH), 144.7 ($J_{C,F}$ = 30.0 Hz, Pyr-C), 158.4 ($J_{C,F}$ = 255.2 Hz, Pyr-C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –78.0 ppm. IR (ATR): $\tilde{\nu}$ = 3165 (br. s), 2922, 1452, 1416, 1393, 1269, 1233, 1142, 1096 (s), 1020 (s), 980, 854, 754 (s), 700 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{15}FN_2O_4Na$ [M + Na]$^+$ 329.0908; found 329.0909. $C_{15}H_{15}FN_2O_4$ (306.29): calcd. C 58.82, H 4.94, N 9.15; found C 58.86, H 4.97, N 9.15. For X-ray data of compound **15b**, see Supporting Information.

(2*S*,4*R*,10*S*,10a*R*)-2-Phenyl-4,4a,10,10a-tetrahydro-2*H*-[1,3]dioxino[4′,5′:5,6]pyrano[2,3-*b*]pyrazin-10-ol (16)

From 14a: Potassium *tert*-butoxide (192 mg, 1.72 mmol) was added to a solution of diol **14a** (615 mg, 1.91 mmol) in anhydrous THF (220 mL) with stirring at –20 °C. The reaction mixture was warmed to room temperature over 18 h, and then saturated aqueous $NaHCO_3$ (150 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 150 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 1:2 to 0:1) to give cyclized alcohol **16** (129 mg, 451 μmol, 26%) as a colourless oil, together with recovered starting material **14a** (133 mg, 412 μmol, 22%).

From 14b: Potassium *tert*-butoxide (59.0 mg, 526 μmol) was added to a solution of diol **14b** (179 mg, 584 μmol) in anhydrous THF (80 mL) at –20 °C. The reaction mixture was stirred at this temperature for 4 h, and then saturated aqueous $NaHCO_3$ (80 mL) was added. The mixture was extracted with CH_2Cl_2 (3× 80 mL), the

combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 1:2) to give cyclized alcohol **16** (42.9 mg, 150 μmol, 29%) as a colourless oil, together with recovered starting material **14b** (36.8 mg, 120 μmol, 21%). R_f = 0.30 (cyclohexane/EtOAc, 1:3). $[\alpha]_D^{20}$ = +77.6 (c = 0.48, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (dd, J = 12.7, 1.0 Hz, 1 H), 4.45–4.49 (m, 1 H), 4.49–4.54 (m, 1 H, C*H*OH), 4.68 (dd, J = 12.7, 1.4 Hz, 1 H), 4.83–4.93 (m, 1 H), 4.99–5.18 (m, 1 H, OH), 5.70 (s, 1 H), 7.27–7.35 (m, 3 H, Ar-H), 7.35–7.44 (m, 2 H, Ar-H), 8.05 (d, J = 2.5 Hz, 1 H, Pyr-H), 8.23 (d, J = 2.5 Hz, 1 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.0 [C(H)OH], 67.4 (CH), 68.9 (CH_2), 74.3 (CH), 101.2 [C(H)Ph], 126.2 (Ar-CH), 128.2 (Ar-CH), 129.3 (Ar-CH), 137.0 (Ar-C), 137.2 (Pyr-CH), 137.7 (Pyr-C), 143.7 (Pyr-CH), 157.0 (Pyr-C) ppm. IR (ATR): $\tilde{\nu}$ = 3261 (br. s), 2924, 1545, 1418, 1351, 1277, 1165, 1140, 1103 (s), 1045, 995 (s), 966, 910, 806, 731, 698 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{14}N_2O_4$ $[M]^+$ 286.095; found 286.095.

(2*S*,4*R*,10*R*,10a*R*)-2-Phenyl-4,4a,10,10a-tetrahydro-2*H*-[1,3]dioxino[4′,5′:5,6]pyrano[2,3-*b*]pyrazin-10-ol (17)

From 15a: Potassium *tert*-butoxide (357 mg, 3.18 mmol) was added to a solution of diol **15a** (1.14 g, 3.54 mmol) in anhydrous THF (350 mL) with stirring at –20 °C. The reaction mixture was warmed to room temperature over 18 h, and then saturated aqueous $NaHCO_3$ (200 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 200 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 1:3 to 0:1) to give cyclized alcohol **17** (286 mg, 1.00 mmol, 31%) as a pale yellow solid, together with recovered starting material **15a** (311 mg, 946 μmol, 27%).

From 15b: Potassium *tert*-butoxide (83.1 mg, 740 μmol) was added to a solution of diol **15b** (252 mg, 823 μmol) in anhydrous THF (110 mL) at –20 °C. The reaction mixture was stirred at this temperature for 4 h, and then saturated aqueous $NaHCO_3$ (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3× 100 mL), the combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc, 1:3) to give cyclized alcohol **17** (47.9 mg, 167 μmol, 23%) as a colourless solid, together with recovered starting material **15b** (40.0 mg, 131 μmol, 16%). R_f = 0.20 (cyclohexane/EtOAc, 1:3), m.p. 121–125 °C. $[\alpha]_D^{20}$ = +59.6 (c = 0.61, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08–4.17 (m, 1 H, OH), 4.20 (dd, J = 12.6, 1.0 Hz, 1 H), 4.38–4.47 (m, 1 H), 4.60 (dd, J = 12.6, 1.6 Hz, 1 H), 4.64–4.71 (m, 1 H), 4.96–5.09 (m, 1 H, C*H*OH), 5.71 (s, 1 H), 7.24–7.41 (m, 5 H, Ar-H), 7.99–8.14 (m, 2 H, Pyr-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.3 [C(H)OH], 69.1 (CH_2), 69.2 (CH), 72.8 (CH), 101.3 [C(H)Ph], 126.4 (Ar-CH), 128.2 (Ar-CH), 129.3 (Ar-CH), 136.9 (Ar-C), 137.2 (Pyr-CH), 138.4 (Pyr-C), 142.2 (Pyr-CH), 156.3 (Pyr-C) ppm. IR (ATR): $\tilde{\nu}$ = 3273 (br. s), 2914, 1545, 1458, 1416 (s), 1366, 1337, 1281, 1157, 1099 (s), 1038, 1024, 1011, 964, 912, 829, 731 (s), 698 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{14}N_2O_4$ $[M]^+$ 286.095; found 286.095.

(6*R*,7*S*)-7-Hydroxy-6-(hydroxymethyl)-6,7-dihydro-8*H*-pyrano[2,3-*b*]pyrazin-8-one (13)

From 16: Dess–Martin periodinane (189 mg, 444 μmol) was added to a stirred solution of alcohol **16** (106 mg, 370 μmol) in anhydrous CH_2Cl_2 (11 mL) at 0 °C. The reaction mixture was warmed to room temperature over 7.5 h, and then saturated aqueous $NaHCO_3$ (4 mL) and saturated aqueous $Na_2S_2O_3$ (4 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 8 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc) to give ketone **13** (100 mg, 352 μmol, 95%) as a colourless solid.

From 17: Dess–Martin periodinane (457 mg, 1.08 mmol) was added to a stirred solution of alcohol **17** (257 mg, 898 μmol) in anhydrous CH_2Cl_2 (27 mL) at 0 °C. The reaction mixture was warmed to room temperature over 7.5 h, and then saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc) to give ketone **13** (189 mg, 666 μmol, 74%) as a colourless solid. R_f = 0.50 (EtOAc), m.p. >160 °C (decomp.). $[\alpha]_D^{20}$ = –123.0 (c = 0.84, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.31 (dd, J = 13.1, 1.1 Hz, 1 H), 4.53–4.61 (m, 1 H), 4.68 (d, J = 1.1 Hz, 1 H), 4.73 (dd, J = 13.1, 1.5 Hz, 1 H), 5.76 (s, 1 H), 7.28–7.38 (m, 3 H, Ar-H), 7.41–7.52 (m, 2 H, Ar-H), 8.51 (d, J = 2.0 Hz, 1 H, Pyr-H), 8.53 (d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.0 (CH_2), 71.3 (CH), 76.6 (CH), 101.1 [C(H)Ph], 126.1 (Ar-CH), 128.3 (Ar-CH), 129.5 (Ar-CH), 130.4 (Pyr-C), 136.4 (Ar-C), 141.1 (Pyr-CH), 148.9 (Pyr-CH), 163.0 (Py-C), 184.6 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1717 (s), 1558, 1543, 1470, 1321, 1271, 1192, 1134, 1096 (s), 1043, 966, 912, 733, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{12}N_2O_4Na$ $[M + Na]^+$ 307.0689; found 307.0691. For X-ray data of compound **13**, see Supporting Information.

(6*R*,7*S*)-6-(Hydroxymethyl)-8,8-dimethoxy-7,8-dihydro-6*H*-pyrano[2,3-*b*]pyrazin-7-ol (18): Ketone **13** (12.6 mg, 44.3 μmol) was dissolved in a mixture of MeOH (800 μL) and $CHCl_3$ (400 μL), and iodine (4.5 mg, 17.7 μmol) was added. The solution was stirred at 45 °C for 27 h with the exclusion of light. Repeated purification by column chromatography (silica gel, $CHCl_3$/MeOH, 20:1) gave dimethyl acetal diol **18** (7.0 mg, 28.9 μmol, 65%) as a colourless oil. R_f = 0.45 ($CHCl_3$/MeOH, 9:1). ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 3.25 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.98–4.07 (m, 2 H, CH_2), 4.32–4.37 (m, 2 H), 4.46 (d, J = 3.9 Hz, 1 H, CHO*H*), 4.51–4.55 (m, 1 H), 8.21 (d, J = 2.4 Hz, 1 H, Pyr-H), 8.25 (d, J = 2.4 Hz, 1 H, Pyr-H) ppm. ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 48.9 (OCH_3), 49.9 (OCH_3), 62.1 (CH_2), 65.5 [C(H)OH], 78.1 (CH), 97.2 [*C*(OMe)$_2$], 137.5 (Pyr-CH), 137.7 (Pyr-C), 143.6 (Pyr-CH), 158.0 (Pyr-C) ppm. IR (ATR): $\tilde{\nu}$ = 3360 (br. s), 2945, 1555, 1418 (s), 1337, 1283, 1211, 1171, 1132, 1101 (s), 1076 (s), 1053 (s), 978, 758 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}N_2O_5Na$ $[M + Na]^+$ 265.0795; found 265.0796.

(2*R*,4a*R*,10a*S*)-2-Chloro-10,10-dimethoxy-4,4a,10,10a-tetrahydro-1,3,2-dioxaphosphinino[4′,5′:5,6]pyrano[2,3-*b*]pyrazine 2-Oxide (19): A solution of anhydrous triethylamine (32.6 μL, 23.7 mg, 234 μmol) and phosphorus oxychloride (10.9 μL, 17.9 mg, 117 μmol) in anhydrous CH_2Cl_2 (4 mL) was added at 0 °C to a solution of dimethyl acetal diol **18** (27.0 mg, 111 μmol) in anhydrous CH_2Cl_2 (4 mL) over 5 min. The mixture was stirred for 3 h, then the volatile components were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc) to give diastereomerically pure chlorophosphate **19** (25.6 mg, 79.3 μmol, 71%) as a colourless solid. R_f = 0.30 (EtOAc), m.p. >130 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.27 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 4.72–4.77 (m, 1 H), 4.78–4.81 (m, 1 H), 4.89–5.00 (m, 1 H), 5.01–5.05 (m, 1 H), 8.33 (d, J = 2.4 Hz, 1 H, Pyr-H), 8.41 (d, J = 2.4 Hz, 1 H, Pyr-H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 49.4 (OCH_3), 50.0 (OCH_3), 68.0 ($J_{C,P}$ = 6.2 Hz, CH), 71.7 ($J_{C,P}$ = 8.8 Hz, CH_2), 73.8 ($J_{C,P}$ = 7.6 Hz, CH), 94.1 [$J_{C,P}$ = 11.4 Hz, *C*(OMe)$_2$], 133.5 (Pyr-C), 138.7 (Pyr-CH), 144.1 (Pyr-CH), 155.4 (Pyr-C) ppm. ^{31}P NMR (203 MHz, $CDCl_3$): δ = –5.6 ppm. IR (ATR): $\tilde{\nu}$ = 2974, 2947, 1555, 1412 (s), 1337, 1315, 1289, 1269, 1171, 1128, 1096, 1061 (s), 988, 874 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{12}ClN_2O_6PNa$ [M + Na]$^+$ 345.0014; found 345.0014. For X-ray data of compound **19**, see Supporting Information.

(4a*R*,10a*S*)-10,10-Dimethoxy-2-oxo-4,4a,10,10a-tetrahydro-1,3,2λ^5-dioxaphosphinino[4′,5′:5,6]pyrano[2,3-*b*]pyrazin-2-(^{2}H)ol Mono(^{2}H)hydrochloride (20): In an NMR tube, chlorophosphate **19** (23.1 mg, 71.6 μmol) was dissolved in [D_6]acetone (500 μL), and then D_2O (50 μL) was added dropwise. After mixing, the solution was kept at room temperature for 24 h. The solution was then transferred to a round-bottomed flask and cooled to –50 °C, and the solvent was evaporated under vacuum (ca. 10^{-3} mbar) with slow warming to room temperature. D_2O (1.5 mL) was added to the resulting residue, the mixture was filtered, and the filtrate was freeze dried to give acid **20** (17.3 mg, 50.5 μmol, 71%) as a pale yellow solid, m.p. >75 °C (decomp.). ^{1}H NMR (300 MHz, D_2O): δ = 3.19 (s, 3 H, OCH_3), 3.50 (s, 3 H, OCH_3), 4.50–4.65 (m, 2 H, CH_2), 4.73–4.78 (m, 1 H), 4.97–5.05 (m, 1 H), 8.32 (d, *J* = 2.6 Hz, 1 H, Pyr-H), 8.34 (d, *J* = 2.6 Hz, 1 H, Pyr-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.7 (OCH_3), 49.6 (OCH_3), 68.2 ($J_{C,P}$ = 5.8 Hz, CH_2), 70.1 ($J_{C,P}$ = 4.0 Hz, CH), 70.6 ($J_{C,P}$ = 4.4 Hz, CH), 94.6 [$J_{C,P}$ = 9.8 Hz, *C*(OMe)$_2$], 133.6 (Pyr-C), 137.3 (Pyr-CH), 144.0 (Pyr-CH), 156.2 (Pyr-C) ppm. ^{31}P NMR (122 MHz, D_2O): δ = –5.2 ppm. IR (ATR): $\tilde{\nu}$ = 2947, 1555, 1458, 1414, 1300, 1269, 1171, 1130, 1098, 1061 (s), 982 (s), 943, 866, 841 (s), 804, 777, 746 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{13}O_7N_2PNa$ [M + Na]$^+$ 327.0353; found 327.0355. For X-ray data of the sodium salt of compound **20**, see Supporting Information.

Sodium (4a*R*,10a*S*)-10,10-Dihydroxy-2-oxo-4,4a,10,10a-tetrahydro-1,3,2λ^5-dioxaphosphinino[4′,5′:5,6]pyrano[2,3-*b*]pyrazin-2-olate (21): In an NMR tube, acid **20** (14.8 mg, 43.3 μmol) was dissolved in a mixture of [D_6]acetone (300 μL) and DCl (1 M in D_2O; 200 μL), and the solution was heated to 50 °C for 3 d. The mixture was transferred to a round-bottomed flask and cooled to –60 °C, and the solvent was evaporated under vacuum (ca. 10^{-3} mbar) with slow warming to room temperature. The resulting brownish residue was dissolved in D_2O (600 μL), and the solution was cooled to 0 °C and neutralized (pH 6–7) with $NaHCO_3$ (1 M in D_2O; 250 μL). Purification by preparative reverse-phase HPLC (Nucleodor C18, H_2O, 50 mL/min, t_R = 5–8 min) followed by freeze drying gave cPMP analogue **21** as a pale yellow solid, containing (according to ^{31}P NMR spectroscopy) minor amounts of inorganic phosphate (δ = 0.1 ppm). Assuming a purity of 70%, a yield of 8.1 mg (27.2 μmol, ca. 60%) was calculated. ^{1}H NMR (600 MHz, D_2O): δ = 4.49–4.58 (m, 2 H, CH_2), 4.62–4.64 (m, 1 H), 4.75–4.77 (m, 1 H), 8.32 (d, *J* = 2.6 Hz, 1 H, Pyr-H), 8.34 (d, *J* = 2.6 Hz, 1 H, Pyr-H) (OH-Protons not detectable) ppm. ^{13}C NMR (150 MHz, D_2O): δ = 68.1 ($J_{C,P}$ = 6.0 Hz, CH_2), 70.1 ($J_{C,P}$ = 4.5 Hz, CH), 75.5 ($J_{C,P}$ = 5.2 Hz, CH), 88.8 [$J_{C,P}$ = 10.0 Hz, *C*(OH)$_2$], 137.2 (Pyr-C), 138.3 (Pyr-CH), 143.8 (Pyr-CH), 155.6 (Pyr-C) ppm. ^{31}P NMR (244 MHz, D_2O): δ = –5.0 ppm (also a signal at 0.1 ppm). HRMS (ESI): calcd. for $C_8H_8N_2O_7P$ [M – Na] 275.0064; found 275.0071; calcd. for $C_8H_6N_2O_6P$ [M – H_2O – Na] 256.9958; found 256.9966.

CCDC-956740 (for **13**), -956741 (for **7**), -956742 (for **11b**), -956743 (for **15b**), -956744 (for **9**), -956745 (for **8**), -956746 (for **12a**), -956747 (for **15a**), -956748 (for **14a**), -956749 (for **21**), and -956750 (for **19a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Supporting Information (see footnote on the first page of this article): DFT calculations on the conformations of compound **12b**; NMR spectra (^{1}H, ^{13}C, ^{31}P) of compounds **12b**, **13**, **14a**, **15a**, **14b**, **15b**, **16**, **17**, **18**, **19**, **20**, and **21**; X-ray data of compounds **7**, **8**, **9**, **11b**, **12a**, **13**, **14a**, **15a**, **15b**, **19**, and **20**.

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