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Dess–Martin periodinane-mediated oxidation of the primary alcohol of cytidine into a carboxylic acid†

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Herein the first example of conversion of alcohols into carboxylic acids by use of the Dess–Martin Periodinane (DMP), which is otherwise routinely employed for the conversion to aldehydes, is reported. This methodology will have significant potential utility in the synthesis of cytidine analogues and other related biologically important molecules.

Cytidine is a nucleoside that plays many roles in biological systems. It is a component of DNA, and also commonly features in enzyme substrates, such as cytidine monophosphate-sialic acid.¹ Due to its essential biological importance, multiple analogues have been developed.² In our endeavors to synthesise analogues of cytidine as potential glycosyltransferase inhibitors, we required introduction of an aldehyde at the 5'-alcohol of ribose as a synthetic intermediate. Based on its wide use as a mild and selective reagent to oxidise such alcohols to aldehydes, we selected DMP as a suitable reagent for this purpose. To our surprise, we found that DMP further oxidised the primary alcohol of cytidine to the carboxylic acid, rather than the expected aldehyde.

Dess–Martin Periodinane (DMP) is routinely used for the oxidation of alcohols to aldehydes and ketones.³ Albeit to a lesser extent, DMP has also been used in other synthetically oxidative transformations, such as: oxidative cascade cyclisation of anilidines with double bonds,⁴ synthesis of benzothiazole *via* oxidative cyclisation of thioformanilides,⁵ synthesis of 2-amino-1,4-benzoquinone-4-phenylimides from anilines,⁶ α -organosulfonyloxylation of ketones using DMP and organosulfonic acid,⁷ oxidative allylation of Morita–Baylis–Hillman adducts with allyltrimethylsilane promoted by DMP/BF₃·OEt₂,⁸ oxidation of amides and amines,⁹ oxidation of 2-pyridylseleno

to form terminal alkenes,¹⁰ one-pot synthesis of trichloromethyl carbinols from primary alcohols,¹¹ oxidation of terminal olefins to methyl ketones,¹² oxidative rearrangement for the preparation of α -keto thioesters,¹³ and synthesis of thiazole-5-carbaldehyde *via* oxidative cascade annulation of potassium thiocyanate and tertiary enamines.¹⁴ To the best of our knowledge, no oxidation of a primary alcohol to a carboxylic acid has been reported as within the scope of utility of DMP. Commonly, the carboxyl function is introduced at the 4'-position of cytidine and analogues *via* oxidation with platinum oxide and oxygen¹⁵ or iodobenzene diacetate in combination with TEMPO as catalyst.^{16–18}

To avoid oxidation of the secondary alcohols at the 2'- and 3'-positions of ribose, cytidine was orthogonally protected by initial introduction of the *tert*-butyldimethylsilyl (TBS) group at the primary 5'-O-position, followed by protection of the diol, and subsequent selective hydrolysis of the TBS group. Compound **1a** (Fig. 1) was then reacted with an excess of the recommended 1.1 eq. of DMP (2 eq.). This reaction did not proceed to completion, with conversion of alcohol **1a** reaching a plateau of 80% after 6 h 30 min of the reaction (Table 1, entry 1 and Table S1A, Fig. S1A†). LCMS analysis also revealed some intriguing information. The expected mass of aldehyde **3a** ($[M + H]^+ = 644$) was not observed. Instead, two peaks were observed, both with a mass of 676 amu, which suggested the formation of the stable hemiacetal diastereoisomers **4a** (Scheme 1 and Table S1, Fig. S1†). This could be the result of the reaction of the aldehyde function with the acidic methanol solution used as mobile phase during elution from the LCMS column. The conversion of aldehyde **3a** into hemiacetal **4a** was

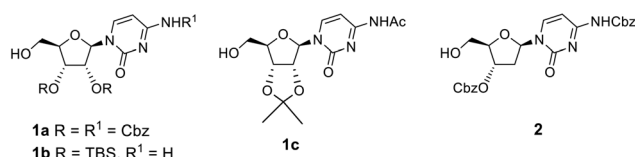


Fig. 1 Chemical structures of synthesised cytidine analogues.

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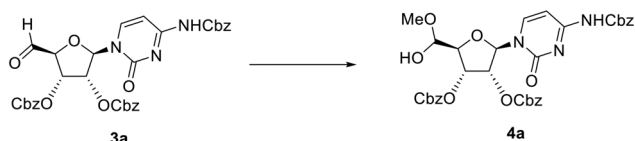
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Table 1 Oxidation of the 5'-hydroxyl of **1a** (6 h 30 min reaction)

Entry	DMP (eq.)	Solvent (mL)	Water ^d (eq.)	Product ^b	
				Aldehyde	Carboxylic acid
1	2 ^c	CH ₂ Cl ₂	—	80%	—
2	4 ^d	CH ₂ Cl ₂	—	66%	31%
3	2	CH ₂ Cl ₂	—	68%	32%
4	4	CH ₂ Cl ₂	—	20%	80%
6	4 ^d	CH ₂ Cl ₂	100 μL (excess) ^e	—	—
7	4 ^d	CH ₂ Cl ₂	10 μL (10 eq.) ^e	80%	10%
8	4 ^d	CH ₂ Cl ₂	1 μL (1 eq.) ^e	47%	53%
9	2 ^d	CH ₂ Cl ₂ ^f	—	80%	—
10	4 ^d	CH ₂ Cl ₂ ^f	—	63%	37%
11	2 ^d	CHCl ₃	—	89%	—
12	4 ^d	CHCl ₃	—	19%	81%
13	2 ^d	CHCl ₃ ^e	—	81%	—
14	4 ^d	CHCl ₃ ^e	—	26%	74%

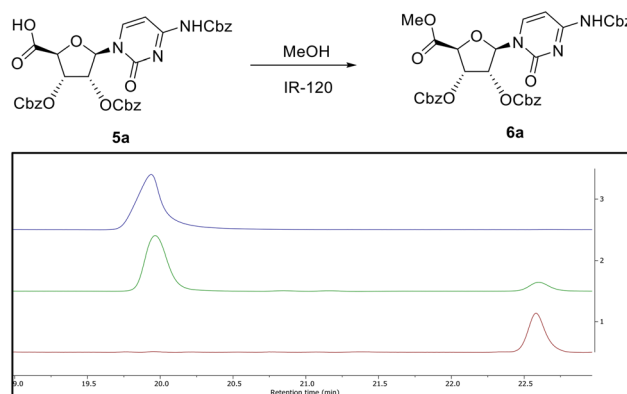
^a All reactions were carried out under an air atmosphere (*i.e.* non-anhydrous). ^b Conversion was calculated based on the area under curve (AUC) of compounds in HPLC chromatograms (see ESI Fig. S4†). ^c Previously opened DMP stored at RT (>3 months). ^d Previously opened DMP stored at -20 °C (>3 months). ^e Water added to solvent before reaction. ^f Anhydrous solvent.

**Scheme 1** Proposed reaction observed during elution of aldehyde **3a** in an LCMS experiment.

complete during the LCMS elution and appeared when the analytical sample was prepared both in methanol and acetonitrile (Table S2 and Fig. S2†).

To improve the conversion of **1a** to the aldehyde, the equivalents of DMP were increased from two to four (Table 1, entry 2). Surprisingly, while the majority of **1a** was converted, the mass of a new peak observed by LCMS was found to be 660 amu (Table S1B and Fig. S1B†). To the best of our knowledge there are no reports using DMP to further oxidise aldehydes to a carboxylic acid. Based on the mass observed, and the increased polarity suggested by LCMS, however, it was hypothesised that the product formed during the oxidation with four eq. of DMP was the respective 5'-carboxylic acid **5a**. NMR analysis of this product confirmed the absence of an aldehyde proton.

To confirm the presence of the carboxylic acid function *in situ*, a simple esterification of this product was carried out by stirring with acidic ion exchange resin (IR-120) in methanol. LCMS analysis indicated that after 4 h (Fig. 2) this compound

**Fig. 2** Reaction of the product **5a** obtained from the oxidation of **1a** with 4 eq. DMP, with acidic ion exchange resin (IR-120) in methanol. Respective HPLC chromatograms of starting material, potential acid carboxylic **5a** (purple, upper) at RT = 20 min; reaction after 4 h, appearance of a new peak with mass of 674 amu (green, centre) at 22.5 min; reaction after 72 h, with complete disappearance of starting material (red, lower).

had been partially converted into a new product with a mass of 674 amu. This conversion into the corresponding methyl ester **6a**, as confirmed by ¹H NMR, was complete after 72 h (Fig. 2). It is to be noted that the reactions were conducted using DMP reagent stored for several months at room temperature, and that the reaction was carried out using laboratory reagent grade dichloromethane. Concerned that the purity of the DMP material could have led to such reactions, repeats of the oxidation reaction with new batches of DMP – sourced from different suppliers (*i.e.* Aldrich, Fluorochem, Apollo Scientific) were carried out (Table 1, entries 3 and 4). After 6 h, the addition of four eq. DMP resulted in almost quantitative conversion of the alcohol into the carboxylic acid **5a** (Table S1C and Fig. S1C†), whereas two eq. of DMP led to a mixture of aldehyde **3a** and carboxylic acid **5a** (as for entry 2) (Table S1B and Fig. S1B†). Surprisingly, our results showed that rather than being due to potential impurities, carboxylic acid formation seemed proportional to purity of DMP. To confirm this hypothesis, the purity of the batch of DMP used in this oxidation was evaluated by ¹H NMR (Fig. S3†). ¹H NMR analysis revealed degradation of DMP over time, with an apparent shift of the protons associated with the aryl moiety, which is perhaps not surprising since DMP is highly sensitive to moisture. Schreiber *et al.* discussed how the presence of impurities, catalysed by addition of water was sufficient to cause reaction rate acceleration, suggesting that partial hydrolysis of DMP led to a more efficient oxidising agent.¹⁹ The presence of water was therefore investigated in light of our findings. In our case, increasing the quantity of water led to reduced conversion to the carboxylic acid (see below), while a large excess of water (100 eq.) prevented the reaction completely (Table 1, entries 6–8 and Fig. S4†).

Moreover, we found that LCMS analysis of the oxidation of **1a** with a new batch of DMP led to another unexpected peak, albeit in small quantities, with a similar retention time and



mass to the corresponding methyl ester **6a** (Fig. 2). This additional peak was only observed when the LCMS sample was prepared in methanol (Table S2A and Fig. S2A†), while it was absent if the sample was prepared in acetonitrile (Table S2B and Fig. S2B†), showing that a reaction occurred during preparation of the LCMS sample rather than during sample elution. This additional peak was absent when DMP was previously quenched by extractive work-up (Table S3A and Fig. S5A†). These data indicated that **6a** is only formed in the presence of methanol and DMP. Corey and Samuelsson²⁰ demonstrated the one-step conversion of a five-membered carbohydrate furanose (uridine) primary hydroxyl group into carboxylic *tert*-butyl esters *via* the formation of a stable hemiacetal. Herein, we propose that a similar mechanism is involved in the formation of the methyl ester **6a** in the LCMS vial, where the acetic acid that is released during the first alcohol oxidation acts as the catalyst to allow nucleophilic attack of the methanol on the aldehyde to form the respective hemiacetal, which is then further oxidised into the methyl ester by DMP (or derivative) (Scheme 2A). The formation of **6a**, when the LCMS sample contained both DMP and methanol, suggested a similar mechanism for the formation of the 5'-carboxyl cytidine **5a** *via* oxidation by the DMP of a hydrate intermediate (Scheme 2B). It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl group of aldehydes and ketones establishing a reversible equilibrium with an aldehyde hydrate.²¹ In our case, the mass of the respective cytidine hydrate intermediate ($[M + H]^+ = 662$) could be observed in the LCMS analysis of the oxidation of **1a** with two eq. of DMP when the aqueous methanol of the mobile phase was replaced by aqueous acetonitrile (Fig. S6†). In this case, in the absence of methanol, water acts as a nucleophile and the resulting hydrate was stable and visible in the LCMS chromatogram. As stated previously, the reactions were carried out with laboratory reagent grade solvents, and it seemed that to form this stable aldehyde hydrate, water present in the solvent was sufficient.

Moreover, the reaction was repeated with anhydrous dichloromethane under a normal air atmosphere, using either 2

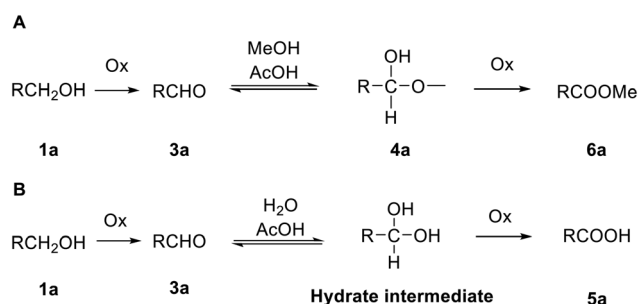
eq. or 4 eq. of DMP (Table 1, entries 9, 10 and Fig. S4†). The results were similar to those observed with reagent grade solvent, confirming that the moisture present in the air is sufficient to catalyse the reaction (Table 1, entries 1 and 2 compared to entries 9 and 10, Fig. S4†); no glove box or drying reagents were used.

To confirm the proposed mechanism and understand the limitations of this reaction, protected cytidine **1a** was reacted with previously opened DMP (4 eq.) with different quantities of water. As discussed earlier, 100 eq. of water prevented any reaction, while 10 eq. of water promoted formation of the aldehyde **3a** (seen as hemiacetal diastereoisomers in LCMS) as the dominant product, and 1 eq. of water rendered an approximately equal proportion of carboxylic acid and aldehyde (Table 1, entries 6–8 and Fig. S4†). This showed that the presence of an excess of water in solution (>1 eq.) prevented further oxidation of aldehyde to the carboxylic acid, possibly due to inactivation of the oxidant, though the addition of a small amount of water promoted carboxylic acid formation. However, as Schreiber *et al.* demonstrated, DMP is most likely converted *in situ* into acetoxyiodinaneoxide.¹⁹ Indeed, in their study 1 μ L of water per mL of dichloromethane was sufficient for hydrolysis.

Finally, reactions were repeated in both anhydrous and reagent grade chloroform (Table 1, entries 11–14 and Fig. S4†). DMP degradation by-products commonly precipitate from chloroform, leaving a larger percentage of DMP in solution. Thus, performing the oxidation in chloroform could be quite different than that observed using dichloromethane, particularly when employing aged batches of DMP. In a similar manner to that observed with dichloromethane, the use of laboratory reagent grade or anhydrous chloroform did not impact the outcome of the reaction. As predicted, however, the use of chloroform clearly drove the reaction towards the carboxylic acid, demonstrating the importance of DMP for the over-oxidation.

Altogether, this evidence seemed to corroborate the proposed mechanism of the reaction, in which DMP (or acetoxyiodinaneoxide) most likely has a dual role: it oxidises the alcohol into the aldehyde and then, when combined with acetic acid and residual water, allows further oxidation of the generated hydrate into the carboxylic acid (Scheme 2B).

To investigate which factors (electronic/steric) might stabilise the nucleoside hydrate and influence this unusual finding, computational chemistry was used. Geometries of compounds **1a** and the hydrate intermediate of **3a**, were optimised in the ground state using density functional theory (DFT) with the M06-2X functional and the 6-31G(d,p) basis set. As shown in Fig. S7,† the low-energy 3D structures of **1a** and the hydrate intermediate of **3a** show significant changes in their geometries after the DFT calculation was finished, as they do not superimpose at all. In particular, the two phenyl rings from the benzyl carbonate (Cbz)-protected diol of cytidine analogue **1a** and the hydrate intermediate of **3a** exhibit π - π stacking interactions (Fig. S7C and D†) that are not observed with their initial coordinates. The notable conformational changes and



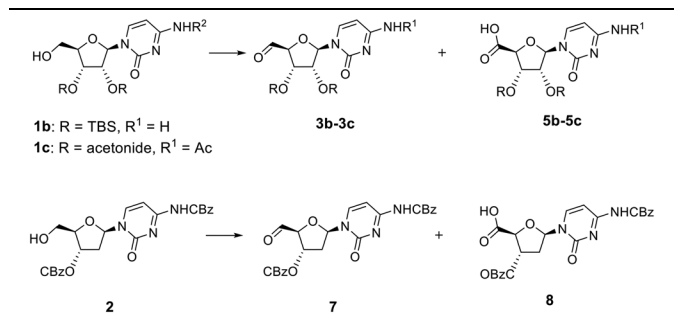
Scheme 2 (A) Proposed mechanism for esterification observed (DMP or derivatives oxidise the primary alcohol **1a** to form aldehyde **3a**, which is in equilibrium with hemiacetal **4a**, as observed by LCMS, which can subsequently be oxidised to form **6a**); (B) proposed mechanism for formation of carboxylic acid **5a**, *via* oxidation of hydrate intermediate.



the maintenance of π - π stacking in **1a** could correspond to further oxidation of aldehyde to carboxylic acid by the virtue of its hydrate intermediate formation. The presence of conformational changes/ π - π stacking within **1a** and the hydrate intermediate of **3a** are thus hypothesised to drive the oxidation of aldehyde to carboxylic acid. The DFT-optimised coordinates of each of the aforementioned structures were subjected to 200 ns molecular dynamics (MD) simulations, with the purpose of further verifying their conformational dynamics and obtaining useful insights into aldehyde/carboxylic acid product formation. Root mean square deviation (RMSD) was also calculated during the course of the simulation, to measure ligand mobility, starting from the DFT-optimised structures. The Cbz-protected cytidine analogue **1a** demonstrated an average RMSD of 2.8 Å, which was in good correlation with the aforementioned conformational changes (Fig. S8†). MD analysis of **1a** confirmed the conformational changes identified in the DFT calculations, in particular, the π - π stacking interactions were abundantly observed between the cytidine ring and one of the Cbz-phenyl rings, and between the two phenyl rings of Cbz throughout the simulation (Fig. S9†). Similarly, the hydrate intermediate of **3a** showed an average RMSD of 2.8 Å (Fig. S8†) and exhibited conformational changes within the phenyl rings of Cbz, establishing π - π stacking interactions, notably present over the course of simulation (Fig. S10†).

To confirm that the π - π stacking interaction could be responsible for stabilizing the aldehyde hydrate formed, three model compounds **1b**, **1c** and **2** that lack this interaction were used (Fig. 1). First, we attempted to oxidise the primary alcohol of deoxycytidine analogue **2** (Fig. 1), in which the 3'-hydroxyl was also protected as benzyl carbonate group, but it represented a less hindered analogue with more conformational flexibility. Oxidation of **2** (Table 2, entries 1 and 2) followed the same trend as for compound **1a**, and a mixture of the respective aldehyde **7** (detected as methyl hemiacetal **10**) and carboxylic acid **8** was obtained with two eq. of DMP (Table S4A and Fig. S11A†). Full conversion into carboxylic acid **8** was observed with four eq. of DMP (Table S4B and Fig. S11B†). We also studied the reactivity of other cytidine analogues in which the diol was protected either as silyloxy (**1b**) or acetonide (**1c**) derivatives (Fig. 1). Protection as the acetonide was expected to also induce conformational rigidity in the ribose ring, which would ultimately restrict the flexibility of the primary alcohol of **1c**, and its reactivity. Indeed, and contrary to the oxidation of the cytidine **1a**, the protection of the diol as an acetonide rendered the analogue less prone to further oxidation; the primary alcohol was completely converted into aldehyde **3b**, using two eq. of DMP within the same reaction time (Table 2, entry 3), and no carboxylic acid analogue was identified in the LCMS analysis (Table S5A and Fig. S12A†). The acetonide protecting group also rendered the aldehyde more stable under purification conditions and long-term storage. We observed that although we could see the aldehyde proton in the ^1H NMR spectrum of the crude of product **3a**, attempts to purify it by column chromatography led to several unidentified decomposition by-products. Aldehyde **3b** was successfully puri-

Table 2 Oxidation of the 5'-hydroxy of cytidine analogues **1b**, **1c** and **2** (6 h 30 min reaction)



Entry	Compound	DMP (eq.)	Product ^a	
			Aldehyde	Carboxylic acid
1	2	2	59%	41%
2	2	4	—	>95%
3	1c	2	>95%	—
4	1c	4	58%	42%
5	1b	2	93%	7%
6	1b	4	—	>95%

^a Conversion was calculated based on the area under curve (AUC) of compounds in HPLC chromatograms (cf. ESI†).

fied and characterised, however. Likewise, for aldehydes **3a** and **7**, LCMS analysis of aldehyde **3c** revealed two peaks in the UV chromatogram, both with a mass of 356 amu that corresponded to the respective hemiacetal diastereoisomers, while ^1H NMR analysis of the pure compound showed the aldehyde proton at 9.39 ppm (Fig. S13A†).

Interestingly, the addition of methanol and silica to the crude sample of oxidation of **1c**, followed by solvent concentration at 40 °C and column chromatography led to partial formation of the hemiacetal, which co-eluted with the aldehyde. NMR analysis of this mixture showed that in addition to the aldehyde proton at 9.39 ppm, two more broad peaks were observed at 9.59 and 9.88 ppm, along with two singlets at 3.48 and 3.51 ppm (Fig. S13B†), corresponding to the hydroxyl and methoxy groups of the methyl hemiacetal **4c**, respectively. When the amount of DMP was increased to four eq., LCMS analysis showed that oxidation of cytidine **1c** led to a mixture of the aldehyde **3c**, and the respective carboxylic acid **5b** with a mass of $[\text{M} + \text{H}]^+ = 340$ (Table 2, entry 4 and Table S5B, Fig. S12B†). As shown in Fig. S14,† the initial geometry of cytidine analogue **1c** does not change after the DFT-based optimisation as they demonstrated a perfect superposition, which might correlate with a decreased ability to undergo oxidation to the carboxylic acid under the same conditions as compound **1a**. When the diol was protected by TBS groups, the addition of two eq. of DMP led to formation of the aldehyde **3b** (Table 2, entry 5 and Table S6A, Fig. S15A†), albeit with a slight contamination of the carboxylic acid **5b**. However, oxidation of **1b** with four eq. of DMP completely favoured the formation of the carboxylic acid **5b** (Table 2, entry 6 and Table S6B, Fig. S15B†).



Absence of π - π stacking interactions did not prevent carboxylic acid formation. Computational chemistry also highlighted that unlike the exclusive presence of intramolecular π - π stacking only with **1a** and the hydrate intermediate of **3a**, the H-bond interaction between the primary alcohol and the cytidine carbonyl consistently existed for 74%, 73% and 86% of the simulation time for **1a**, hydrate intermediate of **3a**, and **1c**, respectively (Fig. S16[†]). If one hydroxyl of a hydrate intermediate is involved in an intramolecular hydrogen bonding interaction, the nucleophilicity of the geminal hydroxyl would be expected to increase, thereby making it more reactive toward the electrophilic DMP (or derivative). Therefore, methyl ribosides **11** and **12** were chosen as not containing any type of π - π stacking or H-bond interactions. They were prepared and reacted with two and four eq. of DMP for 6 h 30 min (Table 3). Compound **11** was not easily monitored by UV absorbance, so its oxidation was monitored by ¹H NMR analysis of the crude product (Fig. S17[†]) and compared with reported spectra for compound **13** and **14**.^{22,23} The outcome of the reaction was similar to the oxidation of compound **1c**, with no 5-carboxylic acid methyl ribose obtained when **11** was reacted with 2 eq. of DMP: total conversion to aldehyde **13** was observed (Fig. S15B[†]). Comparatively, with addition of 4 eq. of DMP (Fig. S15C[†]), NMR analysis highlighted the presence of the aldehyde in a 50/50 mixture, similar than the ratio of 42/58 (carboxylic acid/aldehyde) previously reported for oxidation of compound **1c**. Oxidation of riboside **12**, in which the 2,3-diol is protected as benzyl carbonate, promoted carboxylic acid **16** in also similar percentage with two eq. of DMP (Table S7 and Fig. S18A,† 43%) and four eq. (Table S7 and Fig. S18B,† 81%) compared to compound **1** (Table S1 and Fig. S1,† 32% and 80% respectively).

Successful oxidation of compounds **11** and **12** suggested that the π - π stacking and H-bond interactions are not the key

factors that stabilise the hydrate, and that some other factors must promote the conversion to a carboxyl group. The particular 5-membered ring conformation would simply allow formation and stabilisation of the hydrate intermediate (which could be observed by LCMS during optimisation of **1a**, Fig. S6[†]), from which the alcohol can further oxidise as classical DMP reaction.

In summary, this methodology affords the 4'-carboxylic acid of cytidine in comparable yields (around 80%) to previously reported methods. However, it poses the advantage that there is no need to use oxygen gas, which is not routinely available in a medicinal chemistry laboratory. Although iodobenzene diacetate has been shown to be an efficient oxidant for the preparation of similar end products, it additionally requires the use of TEMPO as catalyst, whereas in the present study DMP alone as oxidant is sufficient. Also, based on our proposed mechanism we expect that the DMP-mediated oxidation of primary alcohols to carboxylic acids is likely to be more broadly applicable to other nucleosides or compounds in which geminal diols can be stabilised.

To conclude, we observed that DMP fully oxidised the primary alcohol of cytidine into a carboxylic acid depending on 3 factors: (i) the purity of DMP, (ii) the quantity of DMP used in the reaction, and (iii) the protecting group(s) used for the diol of the ribose sugar. This unexpected and not previously reported observation is dependent on the ability of the aldehydes of the carbohydrates to be converted into a stable geminal diol. We have shown the importance of protecting groups that can impact the rate of conversion. We present methodologies to selectively oxidise the primary alcohol of cytidine analogues to either the aldehyde or the carboxylic acid, by careful choice of protecting groups and reaction conditions (see Experimental in ESI[†]). Given the importance of cytidine in biological systems and in potential therapeutically important molecules, these findings are of importance in the synthesis of cytidine analogues. The findings reported herein provide new opportunities to readily synthesise novel 5'-carboxyl derived cytidine analogues, using mild conditions that overcome the problems seen with traditional oxidation methods.

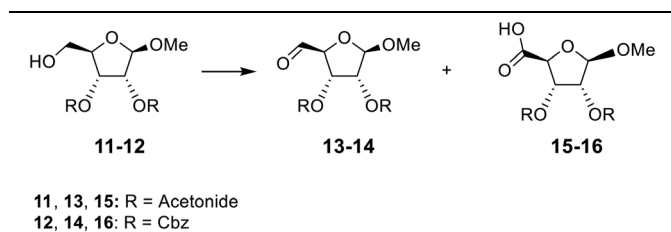
Author contributions

RAF and GRM supervised the research; RAF, AS and GRM conceived the idea; AS performed the research and data analysis (LCMS, NMR), with AR contributing towards data acquisition; VJ performed the computational chemistry studies, under the guidance of LAE; AS prepared the manuscript with contributions from RAF, GRM, VJ and LAE. All authors approved the manuscript.

Conflicts of interest

There are no conflicts to declare.

Table 3 Oxidation of the 5'-hydroxyl of methyl riboside analogues **11** and **12** in dichloromethane and DMP (6 h 30 min reaction)



Entry	Compound	DMP (eq.)	Product ^a	
			Aldehyde	Carboxylic acid
1	9	2	100%	—
2	9	4	50%	50%
3	10	2	57%	43%
4	10	4	19%	81%

^a Conversion was calculated based on aldehyde proton (¹H NMR) for compound **11** and based on the area under curve (AUC) in the HPLC chromatogram for compound **12** (cf. ESI[†]).



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