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A. Michael Downey:
Development of New Glycosylation Methods for the Synthesis of Nucleosides

The thesis addresses the most common nuisance of synthetic chemistry - the need to use protecting groups. It is based on 3 papers and the candidate is the first author of all of them. He was responsible for all the experiments, some of which were carried out in collaboration with the Berlin group. The extensive NMR work was done by a specialist but with the candidate substantial experimental involvement. Theoretical calculations were performed by a specialist.

The thesis is split into five chapters: Introduction, Aims, Results and Discussion, Conclusions, and Experimental, followed by literature references. The text reads well and is characterized by logical buildup. The experiments seem to have been done with care and the Experimental part is at the professional level with all the required details. There are minimums typos in the text and the lab slang is also substantially suppressed. The structures and schemes are excellent and the use of color helps the reader considerably.

Chapter 1 – Introduction is concise but informative with key references provided. However, in the overview of glycosylation methods, I would have expected to see the Schmidt methodology mentioned (in addition to Koenigs-Knorr). Also, regarding the Davis method (ref. 80), I feel that its predecessor methodology, ingeniously developed by Fraser-Reid, could have been mentioned as well.
p. 29: Does the pK_a of the anomeric OH represent an average for the α/β mixture?
p. 36, Scheme 1.24: Perhaps the candidate should suggest the mechanism for this gold-catalyzed transglycosylation.
p. 39, Scheme 1.28: In view of the epoxide opening (Path B), would mannose give α-anomer (*trans*)?

Chapter 2 – Specific aims are ambitious and clearly stated

Chapter 3 – Results and Discussion describes the efforts that aim at avoiding and/or minimizing the use of protecting groups and shows the gradual development of the methodology based on the key Mitsunobu-type glycosylation. Particularly refreshing is the mechanistic approach, heavily based on NMR experiments and computational insight, which helped developing the method. The candidate should be particularly praised for all this and for his resilience when the initial results were not much encouraging.
The candidate has found that in order to obtain the desired furanosides, the 5-OH group requires selective protection (with a trityl group). Without that, the system favors the formation of the corresponding pyranosides. The Mitsunobu reaction has been shown by the NMR experiments to proceed with participation of the neighboring 2-OH, generating the unstable 1,2-anhydro intermediate (epoxide). The latter species then undergoes the expected regioselective and stereospecific *trans*-opening at the anomeric center, giving rise to the desired β-anomer. The solubility problems of some of the aglycons were solved, in some instances, by optimizing the solvent but cytosine and guanine turned out to be particularly difficult substrates. The use of the well-behaved 6-chloropurine as an aglycon instead of adenine (p.80-81), followed by a substitution reaction with ammonia to obtain adenosine, all in one pot, is elegant, as it circumvents the rather low regioselectivity attained with adenine itself. Finally, the successful cases were compared with the existing procedures employing the classical protecting groups. In all instances, the new protocol was found to be more efficient in terms of yields of the final products (let alone the atom economy!), which clearly shows the superiority of this approach. The successful synthesis of doxifluridine (a commercial anticancer

drug) in six steps from 5-fluorouracil and ribose is a spectacular demonstration of the power of this methodology.
p.65,66: If 2-OH offers anchimeric assistance, why not the 2-OBz group (known to participate since the Koenigs-Knorr times)? Would another group equipped with a free OH or SR group be more successful (as that in the procedure developed by G.-J. Boons for *O*-glycosides)?
p. 66: the 1,2-anhydro derivative **3.14** was detected by NMR. Since these reactions were carried out in acetonitrile, one is tempted to consider participation of this solvent in the same way as that known from the Schmidt method, where it first acts as a nucleophile at the anomeric center and is then replaced in an S_N2 fashion by the aglycon (with a second inversion).
p. 68, Scheme 3.9: This is an oversimplification of the original protocol (ref 158), which seems to suggest that the R_3P^+O group is replaced by the vicinal alkoxide moiety via a frontal attack.
p. 69-72: The candidate should be praised for the multidisciplinary mechanistic elucidation and varying the Mitsunobu reagents accordingly.
p. 70, the top ^{31}P NMR spectrum: I wonder what are the smaller peaks around the dioxaphospholane signal (at δ 15).
p. 82, Scheme 3.15. The reduction of $-CH_2OH$ to CH_3 might be made more atom-economical by initially forming tosylate, followed by its reduction with Zn/NaI in wet DME. This method is quite reliable and also allows labeling with deuterium or tritium, if need be (*J. Org. Chem.* **1983**, *48*, 2233).
p. 85/86: Why is the 1,2-anhydro derivative **3.30** much less stable than its analogues lacking the CH_2F group?
p.87, 88: Since both NaN_3 and NaCN proved to be unreactive, the candidate turned to tetramethylquanidinium azide and tetraethylammonium cyanide, respectively, which was met with success. Was the use of a crown ether also considered instead?

Chapter 4 – Conclusions are succinct and sound. Highlighted is the mechanistic and computational elucidation, which helped to optimize the method and expand its scope, eventually even to cytosine, guanine, and other derivatives. The candidate has emphasized, quite rightly, the fact that the use of protecting groups was minimized (trityl to ensure the formation of furanosides). The successful synthesis of doxifluridine is certainly commendable. However, it is unlikely that the protocol for industrial production would be changed by the company currently producing this drug, simply because every step would require a full approval by drug agencies. Nevertheless, it may serve as an inspiration to generic companies in the future.

Chapter 5 – Experimental Section is professional with only a few occasional points: (1) the amount of silica gel used for chromatography is never mentioned; (2) the concentration of the solution for optical rotation at three decimal points is rather unusual; (3) giving the yields of products after chromatography is OK but when the product was further crystallized, the yield after crystallization should also be given; (4) for known compounds there should be comparison of mp and $[\alpha]_D$ with those published in the literature (pp 109-111, 119, 125, 130, 137, and elsewhere); (5) in compound names the "*H*" and "*d*" should be italicized (it is done only in some cases); (6) there are some widows and orphans, with the compound name at the end of one page and the corresponding text on the following one. Since no data for elemental analyses are given, I assume that copies of NMR spectra will have been available for publications as a proof of purity.
p. 93, last para: It is not entirely clear whether DIAD and Bu_3P were added neat or as solutions.
p. 104, line 10 from the bottom: No amount of MeCN is given.

Minor formal points

p. 19, line 2 from the bottom: "...α-*erythro*-ribofuranose" is obviously an inappropriate name.
p. 26, Scheme 1.14: The last formula, bottom right, is incorrect.
p. 28, 2nd paragraph and elsewhere: "tandem process" should be replaced by "domino process".
p. 41, line 4 from the bottom: "The mechanism is thought to go via..." is a laboratory slang.
p. 42, last para: the candidate uses two ways of spelling for element 16: sulfur and sulphur; the latter form was abandoned even in the UK some 20 years ago.
p. 45, Schemes 1.35 and 1.36: Attempted simplification has resulted in an awkward situation, where from a C_4 compound on the left is obtained C_5 compound on the right. Further: $LiOCl_4$ should probably read $LiClO_4$.

p. 50, line 3 from the bottom and elsewhere: "... to cool the reaction to 0 °C..." should read "to cool the reaction **mixture** to 0 °C". Note that it is the mixture, not the process (i.e., reaction) that is being cooled.
p. 57, lines 6/7 from the bottom: "...the purines being more reactive than the purines..." Apparently, the latter "purines" should read "pyrimidines".
p. 65: "... to elucidate a more thorough mechanism..." should be rephrased.
p. 81, Scheme 3.14: **3.19e** should not contain Tr group. The reagents should read NH_3 (not NH3) and H_2O (not H2O).
p. 81, line 6/7 from the bottom: "the reasons being because..." should be rephrased.
p. 91, 2nd para, line 1/2 should read "...proof of principle..." [not "principal"].
p. 94, line 2 and elsewhere: "The filtrate was filtered off..." requires rephrasing.

Overall: The candidate has clearly demonstrated his ability to carry out high-quality research and to write about it; he should be proud of his achievements. I admire his resilience, especially when the initial phases were less then encouraging. I had the opportunity to monitor the progress of the project by attending the candidate's various presentations, so that I know what I am talking about. The meticulous planning of the experiments, mostly aided by mechanistic and computational studies, can serve as a great example to his colleagues and followers. I have no reservations and recommend that he be awarded a **PhD**. Well done.

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