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Editorial

Special issue in celebration of the 65th birthday of Professor George Fleet

George Fleet actually published his first paper in 1969 in the journal Nature. Not a bad start to an academic career! This paper detailed Postdoc work that George was doing at Oxford on affinity labeling of antibodies with aryl nitrenes, under the supervision of Jeremy Knowles and Rodney Porter, the latter winning the Nobel Prize for Medicine shortly afterwards in 1972. By way of explanation George once said to me 'Ian was a bit slow in writing things up in those days' ... referring to publications from his earlier Ph.D. at Cambridge with Ian Fleming. In this respect George rather overstated things and his first paper with Ian was also published in 1969. However, having one's first paper be one that is published in Nature remains a remarkable debut to what has turned out to be an outstanding academic and publishing career. At the last count George had over 480 publications, which together have been cited more than 10,000 times, with a H-index of 52. These simple statistics alone give quantitative proof of the extremely extensive contribution that George has made to science during his prolific career.

After working with Knowles and Porter, George crossed the Atlantic to work with EJ Corey, at Harvard, for what was probably the most formative stage in his career. 'EJ' as George still affectionately calls him of course later proved to be George's second Nobel Prize winning supervisor, winning the Chemistry Nobel in 1990. Although he only published two papers jointly with EJ, one of which detailed the 'Corey–Fleet reagent' (chromium trioxide–3,5-dimethylpyrazole), the 'Corey philosophy' became deeply embedded, and immediately upon his return to the UK he set himself up as an independent researcher at Oxford in the Dyson Perrins Laboratory (the DP) on South Parks Road. He also took up a Fellowship at St John's College, where he remains today, though research moved out of the DP in 2004. His continued interest in oxidation and reduction chemistry quickly resulted in the discovery of the 'Fleet reducing reagent'—bis(triphenylphosphine)copper(I) tetrahydroborate—and also manifested itself in George's writing of the annual chapter on oxidation and reduction in '*Organic Reaction Mechanisms*' for many years afterwards. However it was at the beginning of the 1980s that George's interests were to turn to the carbohydrate field, for which he is of course now best known, and for which he was awarded the Haworth Medal by the Royal Society of Chemistry in 1999. The arrival of Tony Shing as a Postdoc in his group, a contributor to this special issue, and Max Gough as a D.Phil student, coincided with the beginning of an extremely productive period. After syntheses of the pseudomonic and shikimic acids the burgeoning 'GWJF group,' based in the beloved Perkin Lab of the DP, was very soon deeply immersed in the synthesis of amino sugar glycosidase inhibitors. Particular milestones included the syntheses of swainsonine, 1,4-dideoxy-1,4-imino-D-mannitol (DIM), deoxymannojirimycin (DMJ), 6-epi-castanospermine, trihydroxy pipecolic acids, and *n*-butyl deoxynojirimycin (DNJ). In particular great excitement surrounded *n*-butyl-DNJ,

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which at one time was thought to have great potential as an anti-HIV agent, and was the subject of a 1989 Patent with the co-inventor Raymond Dwek. Though this anti-viral activity eventually proved not to be clinically useful, *n*-butyl-DNJ did find other uses, and is of course now a commercial product marketed as a treatment for Gaucher's disease under the trade name Zavesca®. During this time George also established major long-term collaborations in iminosugars with Bryan Winchester, Rob Nash, Linda Fellows, Naoki Asano, Atsushi Kato, Terry Butters, and Mark Wormald. Many other iminosugar syntheses followed as outlined in a review in this special issue by Ben Davis. However, besides simply 'completing target syntheses', George has always maintained a keen mechanistic interest in Organic Chemistry, and substantial methodological developments have also been forthcoming from his group; developments which have derived from careful analysis and rationale of sometimes surprising reactions. As we know Carbohydrate Chemistry is far from the most straightforward branch of Organic Chemistry and surprising things may happen when you simply change the sugar under investigation. One of George's favourite phrases, referring to the contrasting reactivity of different carbohydrates, is 'they're all different you know'. They indeed are, and with carbohydrates you can never take anything for granted. Unfortunately sometimes people do, though George has never been one of them, and he has always been quick to correct those who do. His 1990 paper entitled 'Some comments on an allegedly facile synthesis of nojirimycin' illustrates his occasional aggression in this respect!

One of the most remarkable things about George's career thus far has been his ability to re-invent his field of research. In the mid 1990s, when the field of iminosugar glycosidase inhibitors was perhaps becoming something of a more 'mature subject' he jumped into a new area, and began to work on foldamer peptide mimetics. These studies, performed at the inception of the now highly-popular foldamer field, provided seminal insight into hydrogen bonding networks and factors affecting helix formation. In more recent times George has again re-invented his area of research and an extremely successful collaboration with Professor Ken Izumori (Kagawa) on biosynthetic approaches to 'rare sugar' derivatives really has opened up whole new vistas for carbohydrate chemistry by providing ready access of up to kilogram quantities of previously unavailable carbohydrates.

It is extremely pleasing that so many of Georges collaborators and former students have been able to contribute to this issue, together with of course his many academic friends and colleagues. This is surely testament to the fond regard and intellectual respect that we all have for him. George's most prolific collaborator is David Watkin from Chemical Crystallography in Oxford. They have published a remarkable 120+ papers together, and Dave has provided an excellent review on crystallographic methods for determining absolute configuration in this issue. Another extremely long-term collaborator is Bryan Winchester who provides a highly readable and enjoyable perspective on iminosugars, and their evolution from rather 'low-profile' natural products to compounds at the forefront of science as therapeutic agents. Terry Butters, yet another very long-term collaborator, reports on the improvement of intracellular inhibition of glycoprotein processing α-glucosidases by novel alkyl and aryl-substituted DNJ derivatives.

Former Fleet group D.Phil. and Part II students who have been able to contribute include Ben Davis, who has written a typically vibrant and catchily named review of the Fleet group's work on iminosugar synthesis over the years. Martin Smith has written an insightful paper on the Favorskii rearrangement and attempts to induce diastereoselectivity therein. Jonathan Burton, together with Andy Holmes, has contributed a paper on the synthesis of eleutherobin analogies by a tandem Claisen/ring-closing metathesis strategy. Finally our group has provided a paper on stereocontrol of glycosylation via intermediate cyclic thiophenium ions. Remarkably at the time of conception of this Special Issue all four of us were current independent academics in the Sub-Department of Organic Chemistry at Oxford, illustrating the formative influence that George has had there on Organic Chemistry in recent times.

Former Fleet group Postdocs who have contributed include Tony Shing, who reports studies into the asymmetric epoxidation reactions of alkenes by oxone, as catalyzed by a cyclohexane diacetal protected *arabino* ketone. Juan Carlos Estévez, together with his brother Ramón, reports on the synthesis of highly functionalized cyclopentanes from carbohydrate 5-ring lactones. Sigthor Petursson reinforces the utility of the diphenylmethyl (benzhydryl) protecting group, detailing herein a regioselective etherification procedure for diols catalyzed by tin(II) chloride.

Besides those already mentioned other Oxford Chemistry colleagues past and present have also been able to contribute. Current colleagues include Steve Davies who provides a highly topical paper on the asymmetric synthesis of polyhydroxylated pyrrolidines by ring-closing iodoamination. John Simons provides an in-depth review of recent work on conformational studies of hydrated carbohydrates by a combination of vibrational spectroscopy and a variety of computational techniques. David Hodgson reports on tandem catalytic enantioselective carbonyl ylide formation/intramolecular 1,3-dipolar cycloaddition of 2-diazo-3,6-diketo sulfones, mediated by chiral rhodium catalysts. Mark Moloney reports on the synthesis of penta-substituted cyclopropanes by the uncatalyzed reaction of pyroglutamic acid derivatives with diaryl diazo compounds. Veronique Gouverneur details the de novo synthesis of fluorinated hexitols by fluorination of allyl silanes followed by dihydroxylation. Stuart Conway reports on the synthesis of *myo* inositol phosphates via the Ferrier reaction (i.e., the 'type II' Ferrier rearrangement). Michael Willis details studies on catalyzed stereoselective Mannich reactions of α-carbonate functionalized ketones with *N*-tosyl imines, allowing the synthesis of α-hydroxy-β-amino ketones. Former Oxford colleagues include Jim Thomas, who also reports on diastereoselective Mannich reactions; here reaction between a chiral ester and a chiral sulfinimine gives stereocontrolled access to tropiniones as advanced intermediates on the way to a total synthesis of stemofoline. Laurence Harwood also reports on 1,3-dipolar cycloaddition reactions of chiral carbonyl ylides; here the cycloaddition is an intermolecular reaction with an imine, and is mediated by an achiral rhodium catalyst.

Many luminaries from the Carbohydrate field have also been able to contribute to this special issue. Jo Thiem reports the synthesis of novel glycosyl amino acids in which sugar and amino acid are linked as an ether of the sugar 2-hydroxyl group; also reported is their elaboration into O-glycopeptide mimetics. Jim Coward reports on the fluoridolysis of 5,6-epoxy sugars for the synthesis of 5-fluoro lactosamine and isolactosamine glycosides as mechanistic probes for fucosyl transferases. Olivier Martin and Phillipe Compain provide an extremely extensive review on the synthesis of iminosugar C-glycosides, encompassing three decades of synthetic endeavor. Del Besra details the synthesis of threitol ceramide as a non-glycosidic analogue of galactosyl ceramide. Antoni Planas reports the stereocontrolled synthesis of a β-*para*nitrophenyl glycoside of a β(1→4) *gluco* tetrasaccharide, which incorporates a 2-deoxy unit at the reducing end, as a mechanistic probe of β-glucanases. Stefan Oscarson details the synthesis of a phosphorylated tetrasaccharide corresponding to a core lipopolysaccharide structure from *Nesseria meningitidis*. Francesco Nicotra reports the synthesis and attachment to a solid support of a C-glycoside of L-fucose as a potential mimic of L-galactose-1-phosphate and therefore also a potential ligand of GDP-L-galactose hydrolase. Rob Field reports the synthesis of a novel Galα(1→4)Gal disaccharide sugar amino acid, which paves the way for the future development of multivalent carbohydrate ligands for *Escherichia coli* verotoxins.

Manuel Martín-Lomas details a practical and efficient synthesis of the core trisaccharide unit of N-glycans. András Lipták reports the synthesis of three regioisomeric pentasaccharides, accessed in order to aid structural elucidation, one of which corresponds to the linear part of the glycan of the Skp1 glycoprotein of *Dictyostelyum discoideum*. Lásló Somsák provides a paper detailing the synthesis of glucosyl amides and triazoles that are investigated as inhibitors of glycogen phosphorylase revealing a new type of amide-triazole bioisosterism. Frieder Lichtenthaler reports on ready synthetic access to 1,5-anhydro derivatives of tagatose, rhamnulose, and xylulose, by controlled hydrolysis of esters of 2-hydroxy glycals. Arnold Stütz provides a report on the synthesis of 2-acetamido-DNJ-lysine hybrids, and their activities as hexosaminidase inhibitors. The Carbohydrate group at Leiden University contributes two papers; Herman Overkleeft reports on the synthesis of monomeric and dimeric lipophilic iminosugars, and their activities as inhibitors of glucosyl ceramide metabolism, whilst Mark Overhand reports the synthesis of sugar amino acids containing a cyclopropane unit as di-peptide isosteres, and their elaboration into oligomers. Bruno Linclau reports on the synthesis of highly functionalized cyclopentanes, or carbafuranoses, via dithiane 'double-opening' of 1,4-bis epoxides. Gurdial Singh reports studies aimed at accessing the dengue viron conserved hexasaccharide, and recounts the unexpected synthesis of a *manno* trehalose containing tetrasaccharide. Finally Ian Cumpstey, actually a former undergraduate student of George's at St John's College in Oxford, contributes a paper on the synthesis of valienamine analogues as mannosidase and hexosaminidase inhibitors.

Anyone who has read this far in the Editorial will by now certainly appreciate the extensive efforts made by a large number of contributors to this Special Issue in a celebration both of science and of the happy occasion of George's 65th birthday. I would like to thank them all, most sincerely, for their participation. Such considerable effort from so many different parties befits the extensive contributions that George has made to Organic Chemistry, and particularly to Carbohydrate Chemistry over his career thus far, and of course we all trust that there is much more to come yet!!

By way of conclusion I am minded of an RSC Haworth Memorial lecture that I attended some time ago, which was entitled 'New developments in sugar chemistry—standing on the shoulders of giants'. For future generations of carbohydrate chemists George Fleet surely is another one of those giants.

Happy Birthday George!

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