# Preface

Issue Number 8 of the 1975 *Journal Accounts of Chemical Research* included an article captioned "Some Progeny of 2,3-Unsaturated Sugars – They Little Resemble Grandfather Glucose," in which the early work of our research group (Fraser-Reid's Rowdies as they called themselves) was reviewed. In the introduction, I noted that "the mainstream of organic chemistry—[was]—innocent of these non-'natural products'," and that "[a] Nobel Laureate known to the author declared that—[stabilization at the anomeric center]—constitutes half of sugar chemistry" (see also David Crich's chapter). Nevertheless, there was "a growing willingness for 'organic chemists' to come into contact with sugars voluntarily." By way of recommendation, I expressed the hope that although "the names are a pain in the abstracts—and the wretched things just will not crystallize—working with syrups is a state of mind very much like eating green eggs and ham."

Carbohydrate chemistry was at that time foreign territory except to the few who encountered it during the fateful 2 weeks of stereochemistry in the sophomore organic course. Admittedly, carbohydrates are ideal for demonstrating the differences between enantiomers and diastereomers, *R* and *S*, D and L, d and l, (+) and (−), etc.; but with such arid fare, it is not surprising that sophomores have been known to say that "studying organic chemistry is like beating your head against the wall, because it feels so good when you stop."

One wonders whether that sentiment may have been different if text books expressly noted that Emil Fischer's synthesis of glucose provided the first experimental validation for van't Hoff's then spurned concept of tetrahedral carbon. Fischer therefore confirmed the three-dimensional parameters, decades before the advent of $sp^3$ hybridization that is on the high school curriculum. Indeed, the clumsy attempts at drawing tetrahedral carbon skeleta undoubtedly inspired the 1875 development of the Fischer projection, so despised by sophomores.

The connection between chirality and glucose, begun by Fischer, resurfaced in the 1970s, when a frisson of "chiral syntheses" rippled through organic chemistry. The prostaglandins were then of major scientific interest, and so Gilbert Stork's report of rapid enantiopure syntheses of three members of the family, $PGA_2$ from erythrose (1976), $PGE_1$ from glyceraldehyde (1977), and $PGF_{2\alpha}$ from glucose

(1978), was seminal, because an eminent organic chemist had ventured into the minefield of "sugar" chemistry. To some, this achievement may have seemed an apostasy, especially for those who did not know of Stork's early attempts to synthesize sucrose.

By breaking the ice, Stork facilitated the fledging efforts of enthusiasts, including me and a brilliant group of undergraduate collaborators at Canada's University of Waterloo, who accomplished enantiodivergent syntheses of (+) and (−) chrysanthemic acid, (+) and (−) frontalin, and also established, by synthesis, the chirality of avenaciolide and, hence, its congeners.

A decade later, *Accounts of Chemical Research* carried a 10 years later update of our "Grandfather Glucose" experiments, accompanied by my editorial, entitled "The Malaise Reaction." The editorial extolled the merits of serendipity in organic synthesis noting that "I am green with envy (although those who know me will find this hard to visualize)," of those who have the creativity to transform a fortuitous encounter into an advantage. I did not anticipate that within 5 years, Fraser-Reid Rowdies would also be visited by "the three Princes of Serendip."

In light of the above-mentioned "chiral synthesis" ripple, our sugar chemistry inspired us to undertake enantiopure syntheses of "natural products." However, Chap. 1 of this book shows that this exploration had the reverse effect, in which our enantiopure syntheses inspired us to undertake sugar syntheses – or more precisely to embark on oligosaccharide syntheses.

Thus, in synthesizing a molecule with nine contiguous chiral centers from D-glucose (see Chap. 1), David Mootoo, then one of the Rowdies, made a tangential observation. A seemingly well-planned reaction had given him an excellent yield – alas of the wrong product. He nevertheless took the time to do a structure determination. Insight into how this "wrong" product had been formed led to the development of *n*-pentenyl glycosides (NPGs).

Aggressive prosecution continued, and Mootoo made a further serendipitous observation. Benzylated NPGs had undergone oxidative hydrolysis in 6 h, and the same was expected for acetylated NPGs. However, for the sake of completeness, I asked another graduate student to verify that which "was expected." After 6 h, the student reported that the acetylated NPG was not responding to oxidative hydrolysis.

I discussed the potential of this interesting anomaly with Mootoo, but "to make assurances doubly sure," he volunteered to verify the results. In short, he found that the reaction of the acetylated NPG's required 36 h – not 6 h. And within days of uncovering this disparity, the electronic armed/disarmed strategy for oligosaccharide assembly had been promulgated.

That acyl-protecting groups deactivate glycosyl donors in comparison to other counterparts had been known. Why the disparity had not been earlier exploited for synthetic advantage is open to speculation. However, experiments in our laboratory suggest that if the "disarmed" partner is too reactive, chemoselectivity will be poor – a condition that would apply to glycosyl bromides, the major donors then in use.

It is truly gratifying for Fraser-Reid's Rowdies and the writer to witness the remarkable advances that are now possible in oligosaccharide synthesis. Our furtive efforts at chemoselectivity 25 years ago did not anticipate that regio- and

stereo-selectivities would join chemoselectivity in being protecting group-dependent phenomena.

The very terms "armed and disarmed" drew rebuke for sounding too warlike. Why not active and inactive? My answer at that time was contrived – for I could not have foreseen that the latter terms would find their way into the lexicon as in "active-latent or disarmed-latent donors," invoking a totally different meaning from "armed." So would super-armed, super-disarmed, and semi-disarmed.

All of these, and more, are featured in this book's chapters, confirming that "protecting groups do more than protect." Indeed they are shown to be implements for saccharide tuning whereby chemo-, regio-, and stereo-selectivity can be specifically designed. What about Trost's fourth, and remaining, factor, enantioselectivity? This question may not be as irrelevant as the writer once thought. Boon's intriguing double-stereo differentiation strategy for anomeric stereocontrol is an elegant example of the synergy between regio- and stereo-selectivities. Whether these effects can be "tuned" by protecting groups remains to be seen.

I cannot conclude this Preface without recalling the 1988 event that really launched NPG investigations. An international group of Fraser-Reid's Rowdies comprised of C. Webster Andrews (USA), Peter Konradsson (Sweden), Jose Manuel Llera (Spain), David Mootoo (Trinidad and Tobago), Andrew Ratcliffe (England), Uko Udodong (Nigeria), Zufan Wu (China), and I (Jamaica) traveled by station wagon from Durham, North Carolina to Pittsburgh, Pennsylvania to attend a conference. Throughout the 16 h going and 16 h returning, these colleagues engaged in an endless stream of ideas about how NPGs could be used to address synthetic, mechanistic, and theoretical issues. All that remained was for me to secure the funding to enable them to pursue their enthusiasms, and in this regard we are specifically indebted to the then independent Burroughs Wellcome and Glaxo, whose early funding enabled us to establish that NPGs were not merely "a new version of the Koenig's Knorr reaction" as one reviewer had proclaimed. The National Science Foundation gave support from the earliest days and continues to the present. For our major programs not reviewed in this book, we are indebted to the National Institutes of Health and the Mitzutani Foundation for generous support.

I must also express my gratitude to two other Rowdies, J. Cristobal Lopez and Ana Gomez, who are not only exploring new frontiers to NPG chemistry, but also relentlessly trying to keep me alert about what is happening "out there" – and even helping to edit this book.

Finally, I must thank my wife Lillian for constant support and patience for all 47 years of our marriage, and my two children, Andrea and Terry. All three of them make me realize that how very fortunate and blessed I am, to have experienced the true meaning of family.

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