VOLUME 29 NUMBER 2

ACCOUNTS of CHEMICAL RESEARCH®

FEBRUARY 1996

Some Progeny of 2,3-Unsaturated Sugars—They Little Resemble Grandfather Glucose: Twenty Years Later[†,1]

BERT FRASER-REID

Department of Chemistry, Duke University, Durham, North Carolina 27708

Received June 27, 1995

Introduction

Twenty-years ago in an article with a similar caption,[1a] the author urged organic chemists "to come into contact with sugars voluntarily", and from Figure 1 it might be concluded that the entire chemistry community read the article. However, reality suggests that the steep incline in the curve was due to the explosion of interest in the synthesis of macrolides, with sugars serving as chiral synthons or "chirons" [2] for many of these endeavors. Chirality aside, our wish was to explore an approach that was uniquely "carbohydrate" in content and form, and therefore not applicable to other members of the chiral pool.

The notion of macrolides as "long chain" sugars had been advanced in the early scholarly writings of Celmer,[3] and the *ansa* chain of streptovaricin A, **1**, with its imposing array of nine contiguous chiral centers, could therefore be regarded as a long, dialdehydo sugar (Scheme 1). Each set of pendant 1,4-related "C" and "O" functionalities constitutes, retrosynthetically, a pyranose residue,[4] and thus the coiled pattern **1′** led to tripyranoside **2**, which is held together at both ends by axial glycosidic linkages in keeping with the anomeric effect.[5] Compound **2** might therefore be considered to be a long, branched-chain sugar, and ever since the discovery of streptomycin,[6] branched-chain sugars have been deemed to be "biologically important". Indeed they were the *raison d'etre* for our initial foray into the chemistry of unsaturated sugars,[1a] and accordingly, further retroanalysis of compound **2** led inexorably to the bis-2,3-unsaturated tripyranoside **3**.

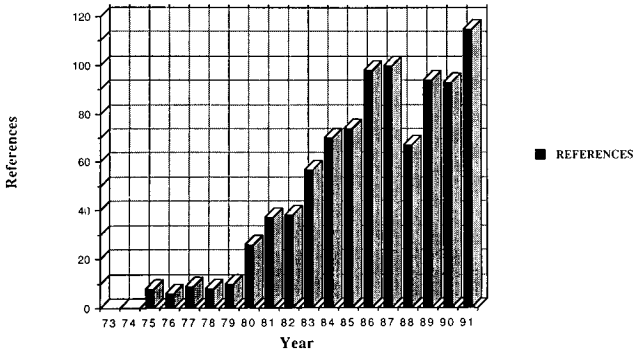


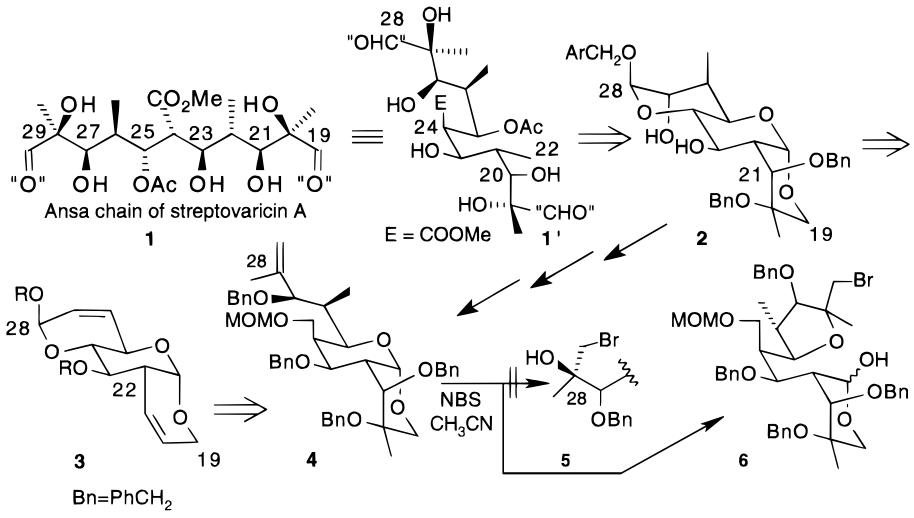
Figure 1. Synthesis of enantiomerically pure non-carbohydrate compounds from carbohydrate precursors. Based on data from specialist reports of the Royal Society of Chemistry.

A Contemporary Case of Serendipity: Discovery of *n*-Pentenyl Glycosides (NPGs). Compound **2** was readily prepared[7] and processed to give the dipyranoside **4**, which presented two challenges: (a) hydrolysis of the remaining acetal and (b) hydration of the alkene moiety of **4** to give the C28 tertiary alcohol as in **5**. Attempts at task a using a variety of acid-catalyzed prescriptions were unavailing, but in the reckless hope that postponement would foster good luck, attention was focused on task b, bromohydration followed by reductive debromination being the procedure which Mootoo chose. The product from treating **4** with *N*-bromosuccinimide/water did indeed contain Br and OH; but instead of the desired vicinal bromohydrin **5**, the (bromomethyl)furan **6** was obtained. Thus the second "problem" had solved the first, in that

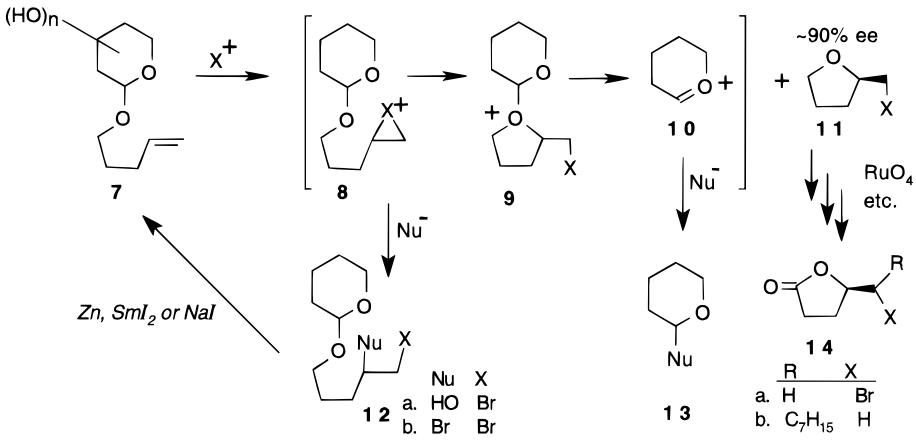
Bert Fraser-Reid was born in Jamaica in 1934. After finishing high school and working for five years, he moved to Canada to attend universities (Queen's, B.Sc. 1959, MSc. 1961; Alberta, Ph.D. 1964) and then went to England for postdoctoral studies (Imperial College, 1964–1966). He returned to Canada to join the fledgling University of Waterloo in 1966 and then moved to the University of Maryland in 1980 and to Duke in 1983. Music, which was nearly his vocation, is today an avocation, and recitals on the pipe organ and piano have been performed at several scientific fora.

0001-4842/96/0129-0057$12.00/0

Scheme 1



Scheme 2



the internal acetal of **4** had been opened, thereby clearing the path to Mootoo's objective.[8]

But in this exercise, serendipity had taught us that an acetal could be readily hydrolyzed under neutral conditions by oxidation of a remote double bond: thus arose the chemistry of *n*-pentenyl glycosides (NPGs) **7**.[9] The process could be envisaged in terms of the cascade of cationic intermediates **8** → **9** → **10** culminating in the substituted product, **13** (Scheme 2).

Armed/Disarmed Strategy for Complex Oligosaccharides. An early contribution of NPGs to synthetic methodology was the concept of *armed/disarmed* coupling for oligosaccharide assembly.[10] That esterified sugars display lower anomeric reactivity relative to their etherified counterparts was "well known";[11] however it was with NPGs that the synthetic potential of this phenomenon was first reduced to practice. Thus we showed that if the "disarmed" reactant, e.g., **16**, carried a free OH, cross-coupling with the "armed" partner, ether **15**, occurred to give the cross-coupled product **17a**, rather than the self-coupled (**16** + **16**) alternative (Scheme 3). Compound **17a** is itself disarmed, and thus further coupling is disfavored. However, deacetylation followed by etherification would give **17b**, which, being armed, is primed for further coupling to give trisaccharide **18**.

The armed/disarmed strategy has been extended to other glycosyl donors, and several permutations[12] of the basic principle, such as semi-disarmed and latent, have been developed which enhance the versatility and value of the concept.

These serendipitous developments prompted us to embark upon a program of oligosaccharide synthesis designed to explore, exploit, and develop NPG chemistry. Our timing could not have been more propitious

† This Account was written during a month-long lecture tour of Japan sponsored by the Japan Society for the Promotion of Science. I thank them for the wonderful opportunity, and I am grateful to my host, Professor Keisuke Suzuki, for much generosity and kindness.

(1) (a) Fraser-Reid, B. *Acc. Chem. Res.* **1975**, *8*, 192. (b) Fraser-Reid, B. *Acc. Chem. Res.* **1985**, *18*, 347.

(2) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983.

(3) Celmer, W. *Pure Appl. Chem.* **1971**, *28*, 413.

(4) Fraser-Reid, B.; Magdzinski, L.; Molino, B. *J. Am. Chem. Soc.* **1984**, *106*, 731.

(5) Lemieux, R. U. In *Molecular Rearrangement*; DeMayo, P., Ed.; Interscience: New York, 1964; Vol. 2, p 709. *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983.

(6) For a review, see: Lemieux, R. U.; Wolfrom, M. L. *Adv. Carbohydr. Chem.* **1948**, *3*, 337.

(7) Fraser-Reid, B.; Molino, B. F.; Magdzinski, L.; Mootoo, D. R. *J. Org. Chem.* **1987**, *52*, 4505.

(8) Mootoo, D. R.; Fraser-Reid, B. *J Org. Chem.* **1989**, *54*, 5548. Mootoo, D. R.; Fraser-Reid, B. *Tetrahedron* **1990**, *46*, 185.

(9) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662.

(10) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.

(11) See, for example: Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.

(12) See, for example: Roy, R.; Anderson, F. O.; Letellier, M. *Tetrahedron Lett.* **1992**, *33*, 6053. Sliedregt, L. A. J. M.; Zegelaar-Jaarsvald, K.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1993**, 335.

because 1988, the year of our first report,[9] also saw the first assignment of covalent structure to a glycosylphosphatidyl inositol (GPI) membrane anchor,[13] and so our interest was triggered.

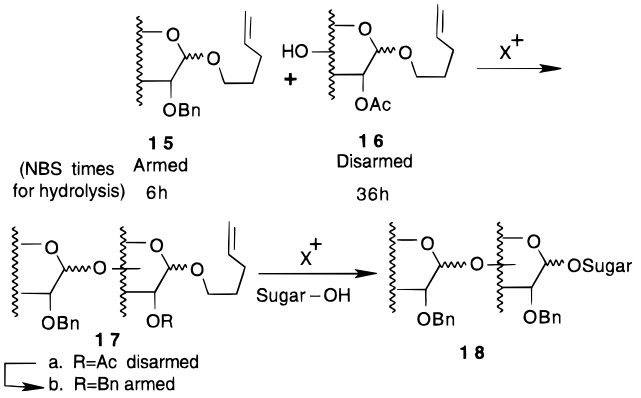
A remarkable feature of GPI anchors, about which a corpus of structural information has accumulated rapidly,[14] is that a pentasaccharide core, highlighted in **19**, has been conserved throughout evolution from bacteria to humans, species-specificity being conferred by the attachment of sundry sugars here and there. For example, in the case of the rat brain Thy-1 anchor **19**, the core bears extra galactosamine, mannose, and ethanolamine phosphate residues. As the first GPI anchor from a mammalian source to be characterized, **19** earned the attention of a multiracial, multinational, multiethnic task force, who achieved the first synthesis of a fully phosphorylated anchor.[15]

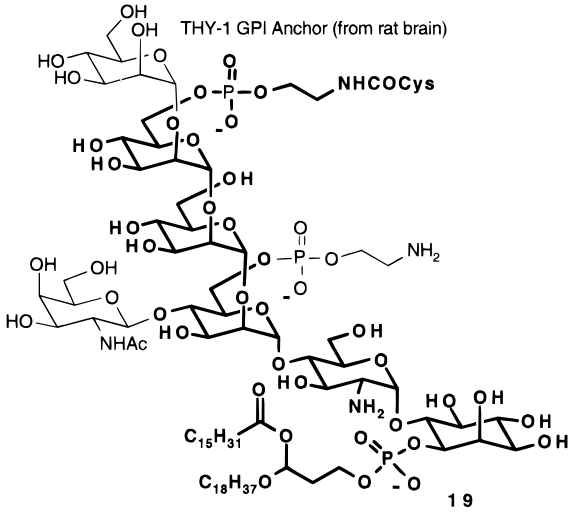
The ability to "sidetrack" NPG activity by 1,2-dibromination **7** → **8** → **12b** → **7**, was a device which emanated from mechanistic studies on how to suppress the intramolecular reaction **8** → **9**.[16] This sidetracking ploy allows the option of using a given NPG either as a glycosyl donor, *via* **10**, or as a glycosyl acceptor, *via* **12**. For the latter case, the double bond can be restored by the use of Zn, samarium(II) iodide, or NaI.[17] The number of NPG precursors needed for a given synthesis can therefore be reduced, as was ably demonstrated by Merritt *et. al.* in our synthesis of the nonasaccharide component from a high-mannose glycoprotein, for which only two starting materials were required.[18]

A Nonacidic Ferrier Rearrangement.[19] The (halomethyl)furan **11** extruded in Scheme 2 is optically active (85−90% ee), and Llera and Lopez demonstrated its value by the synthesis of **14b**,a pheromone from *Bledius spectabilis* (Scheme 2).[20] But the synthesis suffered from poor yields in the RuO_4 oxidation of furan → furanolactone, e.g., **11** → **14a**. Lopez showed that this problem could be obviated by use of a glycosyl pent-4-enoate, e.g., **20**, which underwent a cationic cascade leading to **21** and thence **14a** (Scheme 4a).[21,22]

Lopez was also quick to see a connection to another glycosyl donor, "that venerable unsaturated sugar" [1a] triacetyl glucal **22**. In the classical Ferrier rearrangement, triacetyl glucal **22** is treated with a Lewis acid to generate an allyloxocarbenium **23a**, which is captured by an alcohol to give a glycoside.[23] The 3-*O*-pentenoyl glycal **24** is, like triacetyl glucal, a vinylogous glycosyl ester, and activation by halonium ion, X^+, could conceivably give a similar oxocarbenium ion **23b**, *without the need for acid catalysis*.

Scheme 3





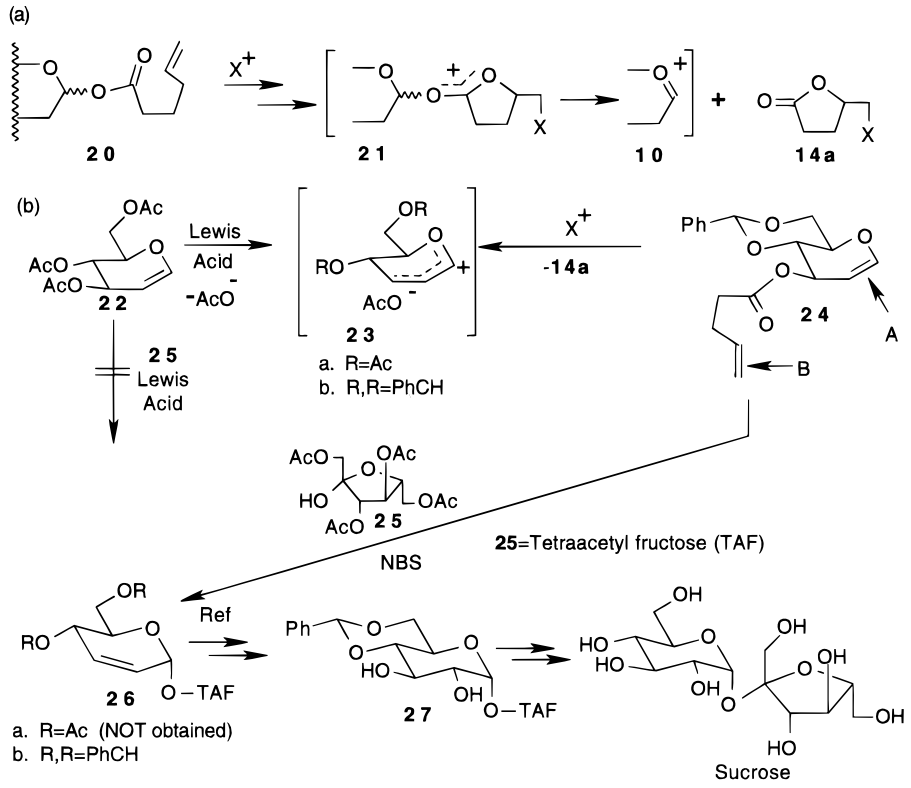
But **24** has two olefinic sites, A and B. Would not the electrophile react preferentially at the electron-rich vinyl ether A? Timely insight came from Danishefsky's laboratory, where it had been shown that esters at C3 disarm glycals toward epoxidation.[24] Accordingly we reasoned that site A of **24** should be similarly deactivated toward I^+. Indeed this proved to be the case.

Sucrose Revisited. This development gave us an opportunity to revisit our sucrose synthesis of 1975.[25] At that time Iley had attempted to couple tetraacetyl fructofuranose **25** with triacetyl glucal **22** under standard Ferrier conditions[23] in the hope of obtaining **26a**. Unfortunately the venture was unsuccessful, and Iley had to resort to a multistep strategy to obtain **26b** and thence **27** before obtaining sucrose.[25]

By contrast, Lopez demonstrated the value of these C3-pentenoylated glycals by showing that **24** could be coupled with fructofuranose **25** in the presence of NBS to give the Iley intermediate **26b** directly. A nonacidic version of the classical Ferrier rearrangement had therefore been developed which allows the use of acid-labile protecting groups as exemplified by the benzylidene ring of **24**.

(13) Ferguson, M. A. J.; Homans, S. W.; Dwek, R. A.; Rademacher, T. W. *Science* **1988**, 753.
(14) For a recent review: McConville, N.; Ferguson, M. A. J. *Biochem. J.* **1993**, *294*, 305.
(15) Roberts, C.; Madsen, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 1546. Madsen, R.; Udodong, U. E.; Roberts, C.; Mootoo, D. R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 1554. Campbell, A. S.; Fraser-Reid, B. *J. Am. Chem. Soc.*, in press. (Respectively: African-American, Danish, Jamaican, Nigerian, Trinidadian, Swedish, Canadian.)
(16) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55* (5), 6068.
(17) Merritt, J. R.; Debenham, J. S.; Fraser-Reid, B. *Carbohydr. Chem.*, in press.
(18) Merritt, J. R.; Naisang, E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4443.
(19) Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1992**, 94.
(20) Llera, J. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 2997.
(21) Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1991**, 159.
(22) Kunz, H.; Werning, P.; Schulz, M. *Synlett* **1990**, 631.
(23) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570, 575.
(24) Friesen, R. W.; Danishefsky, S. *J. Am. Chem. Soc.* **1989**, *111*, 6656.
(25) Iley, D. E.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 2563. Fraser-Reid, B.; Iley, D. E. *Can. J. Chem.* **1979**, *57*, 645.

Scheme 4



Some Tangents to the Circle

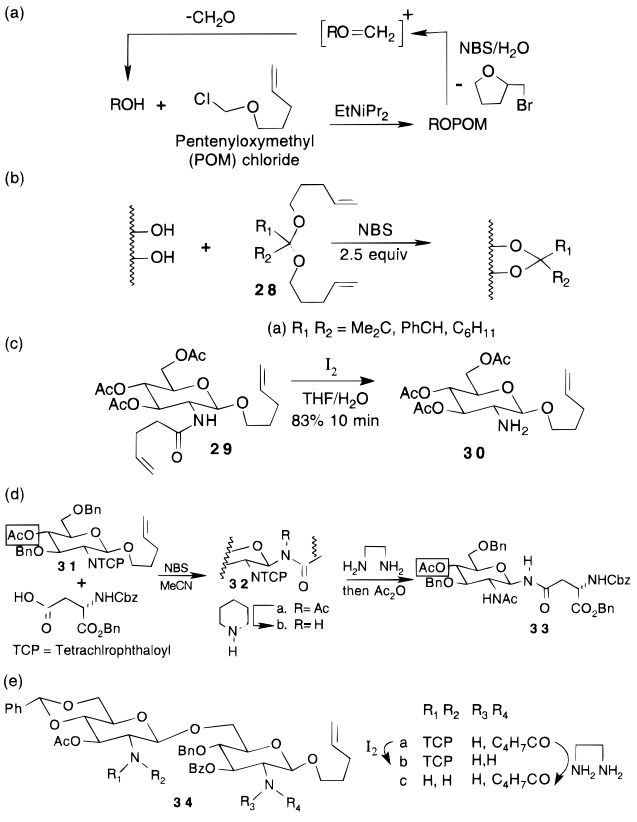
(i) Hydroxyl Protecting Groups. The trail from 2,3-unsaturated sugars to NPGs had gone full circle from sugars to natural products to oligosaccharides, but there were some intriguing tangents along the way. Someone once said (or should have) that the progress of synthetic organic chemistry, particularly in the case of carbohydrates, reflects the development of new protecting groups. In this connection, *n*-pentenyl-based protecting groups for hydroxyls[26] and diols[27] (Scheme 5a,b) are valuable developments that are tangential to our major interests.

Madsen's acetalization reagents, exemplified by **28**,[27] are particularly valuable since they can be used to install one acetal without scrambling other acetals or affecting acid-labile functionalities that are already resident in the substrate.

(ii) Orthogonal Amine Protecting Groups. A tangent of provocative synthetic potential emanated from the challenges that confronted us with the multiple differentiated amino groups of **19**. The difficulties of cleaving carboxamido residues are well-known, but Madsen surmised that pent-4-enamides, such as that in **29**, could be used to obviate those difficulties. Indeed, as illustrated in Scheme 5c, cleavage was effected rapidly and efficiently by treatment with iodine, under conditions that left the glycosidic pentenyl group intact.[28] In addition we found that oxidizable functionalities such as sulfides and electron-rich residues are unaffected.

However, the chemoselectivity displayed in Scheme 5c had a downside in view of the implication that

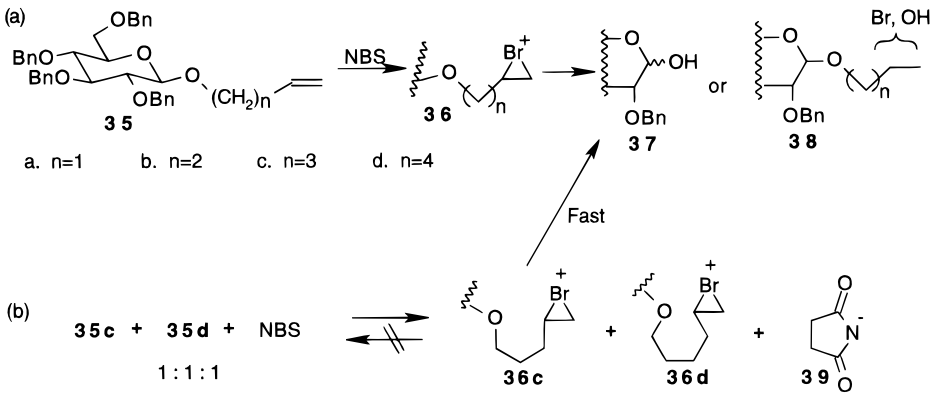
Scheme 5



NPGs such as **29** could not serve as glycosyl donors, because amide deprotection would precede anomeric activation. Since our mission is to develop NPG chemistry, an alternative was clearly required. Upon the premise that electron-withdrawing groups should facilitate phthalimide cleavage, Debenham experimented with the tetrachlorophthaloyl (TCP) group and

(26) Wu, Z.; Mootoo, D. R.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 6549.
(27) Madsen, R.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 772.
(28) Debenham, J. S.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 3303.

Scheme 6



found that compound **31** (Scheme 5d) served as a donor for the *in situ* glycopeptide synthesis developed by Ratcliffe[29] and Handlon[30] to give the *N*-glycosylated product **32a**. The latter, in keeping with Ratcliffe's findings,[29] loses the *N*-Ac group chemospecifically upon treatment with piperidine to give **32b**, the TCP group of which could now be cleaved under conditions so mild that an ester survived in product **33**.

The synthetic potential of these observations arises from the fact that pent-4-enoyl and TCP groups offer orthogonal amine protection, one being removable in the presence of the other under extremely mild conditions as illustrated with **34** in Scheme 5e,[31] and both being removable in the presence of normal phthaloyl group.[28]

(iii) Punctilios[32] about Two Old Reactions. (a) Olefinic Bromination. Serendipity was not yet finished with us. In an attempt to determine whether ω-alkenyl glycosides other than *n*-pentenyl could also be used as glycosyl donors, Rodebaugh looked at the homologous series **35a**−**d**, and found that only pentenyl **35c** suffered oxidative hydrolysis to **37**, all others giving bromohydrins **38a**,**b**,**d** (Scheme 6). The NPG **35c** also reacted the fastest of all four, and Rodebaugh wondered whether this was due to a through-space, ground-state interaction between the glycosidic oxygen and the pentenyl double bond.[33]

To probe this issue and simultaneously avoid the muddying interference of inductive effects, attention was focused on the *n*-pentenyl and *n*-hexenyl analogs **35c** and **35d**. The ratio of the pseudo-first-order rate constants for their disappearance turned out to be ~3.8:1, indicating that there was very little, if any, ground-state activation of **35c**. However, when equimolar amounts of **35c** and **35d** were made to compete for 1 equiv of NBS (Scheme 6b), the ratio of *unreacted* substrates was not ~3.8:1, but 23:1. A steady-state process in which equilibrium was continuously adjusted by the debromination **36d** → **35d** could be discounted, since from the $\Delta H°_f$ values of NBS and succinimide, the anion, **39**, would pick up H^+ much more readily than it would remove Br^+ from **36d**.

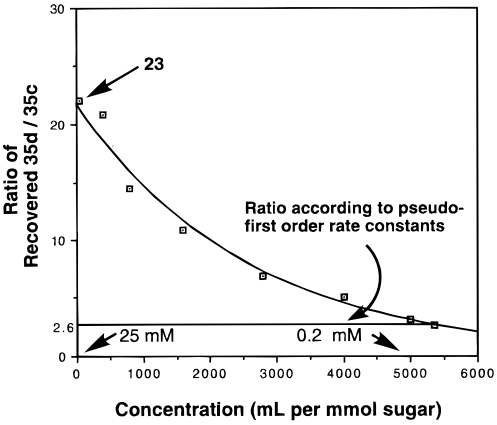


Figure 2. Effect of concentration on the competition of *n*-pentenyl and *n*-hexenyl glucosides for NBS.

Diffusion-controlled cyclic bromonium ion transfer had been postulated by Brown and co-workers,[34] and if this was indeed happening in our case, there should be a strong concentration dependence. Indeed, when Rodebaugh decreased the concentration from the original 25 mM to 0.2 mM, he found that the ratio of unreacted substrates, **35d**:**35c**, fell steadily from 23:1 to 2.6:1, the value predicted by the pseudo-first-order rate constants after allowance for the constant change in concentrations[33] (Figure 2).

Thus diffusion-controlled, direct transfer of cyclic bromonium ions as postulated by Brown[34] must therefore be included in mechanistic discussions about one of the oldest organic reactions, viz., the bromination of alkenes.

(b) Glycoside Hydrolysis. As part of his treatise on stereoelectronic effects, Deslongchamps had posited, that cleavage of glycosides is facilitated by an antiperiplanar relationship between the ring-oxygen lone pair and the cleaving bond, a condition which is met in the chair form of axial (**40**) but not equatorial (**41**) glycosides (Scheme 7).[35] The latter would therefore have to become boat-like (**41′**) so that an antiperiplanar lone pair can be presented to the leaving group. This was not a trivial postulate (a) because β glycosides are usually hydrolyzed faster than α and (b) in view of the inherent implication for transition-

(29) Ratcliffe, A. J.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1990**, *112*, 5665. Ratcliffe, A. J.; Konradson, P.; Fraser-Reid, B. *Carbohydr. Res.* **1991**, *216*, 322.

(30) Handlon, A. L.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 3796.

(31) Griffiths, S.; Debenham, J. S. Unpublished results.

(32) See also: Houk, K.; Gonzalez. J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81

(33) Rodebaugh, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1994**, *116*, 3155.

(34) Bennet, A. J.; Brown, R. S.; McClung, R. E. D.; Klobukowski, M.; Aarts, G. H. M.; Santarsiero, B. D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* **1991**, *113*, 8532.

(35) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York **19**83; p 30.

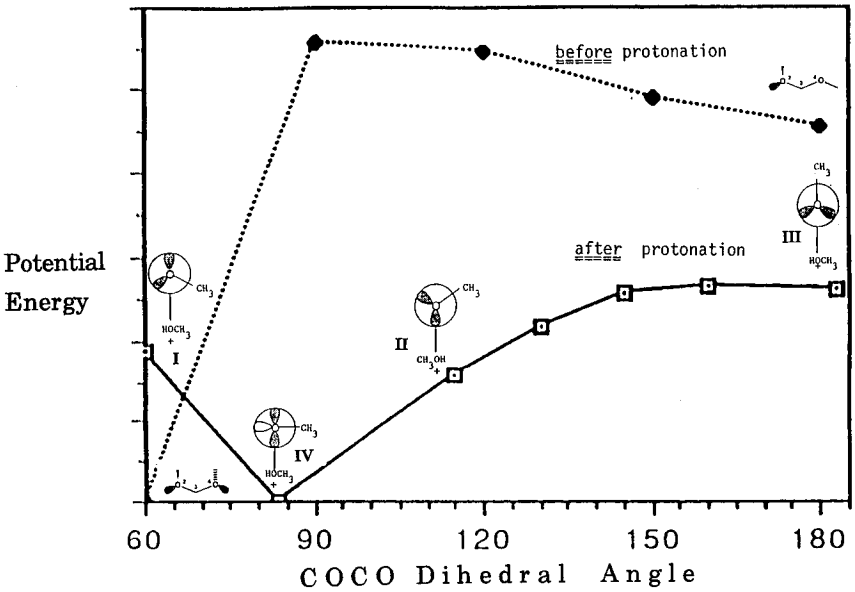
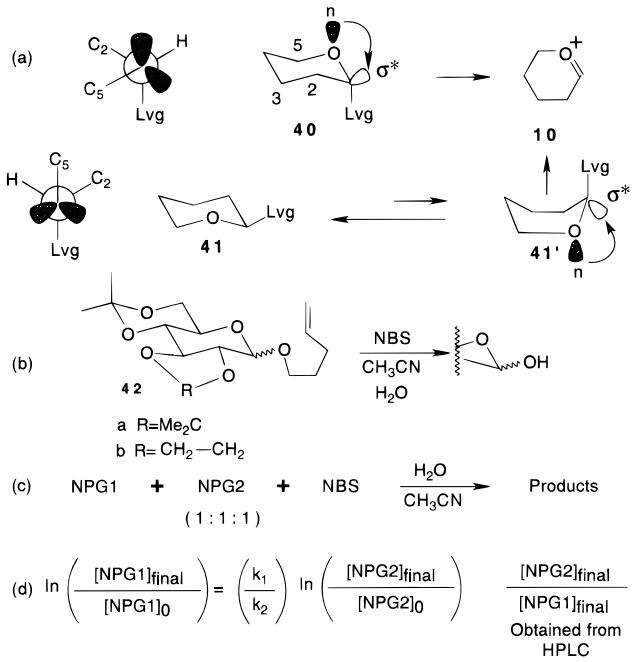


Figure 3. An *ab initio* study of dimethoxymethane protonation model for anti- and synperiplanar lone pair assistance in glycoside hydrolysis.

Scheme 7



state geometries in the enzymic action of glycosidases and glycosyl transferases.[36]

Since NPGs are hydrolyzed under nonacidic conditions, it was possible for us to "tie up" a glycoside with acid-labile acetal rings as shown in **42**, so that chair-to-boat conformational changes were energetically prohibitive (Scheme 7b).[37] Nevertheless, upon treatment with NBS/H_2O, the axially and equatorially oriented analogues, **42a** and **42b** (α and β), were hydrolyzed at comparable rates.[38] At a minimum, these results meant that boat-like structures were not necessary for hydrolysis of β anomers.

In this connection, Wilson has recently developed a facile procedure for determining the relative reactivities of *any* pair of NPGs, α/β anomers or otherwise (Scheme 7c), based on the competition of both for NBS. The key to the method is that the NBS concentration represents the amounts of NPG1 + NPG2 that have reacted. The effects of configurational, conformational, protecting group, torsional, and/or electronic influences upon cleavage of any pair of glycosides can therefore now be determined very simply by plugging the HPLC ratio of the *unreacted* amounts of both NPGs into Wilson's equation, Scheme 7d.[39]

The results with **42a** and **42b** prompted us to undertake an *ab initio* study of lone pair involvement in glycoside hydrolysis using the simplest acetal, dimethoxymethane as a model (Figure 3).[37] The 90° arrangement **IV** shown in Figure 3 corresponds to the glycosyl oxocarbenium ion intermediate. The chair-to-boat change in Scheme 7a, **41** → **41′** → **10,** therefore corresponds to **III** → **I** → **IV**. However, Andrews found that **IV** can be approached with equal ease from the *antiperiplanar* or *synperiplanar* arrangement **I** or **II**, respectively. Indeed the chair-to-boat conversion (i.e., **III** → **I)** would be counterproductive, in that the molecule would have already passed over the desired state, **IV**, *en route*. It is apparent from Figure 3 that there is an energy barrier to bond rotation in the unprotonated acetals, but that this barrier disappears completely upon protonation.

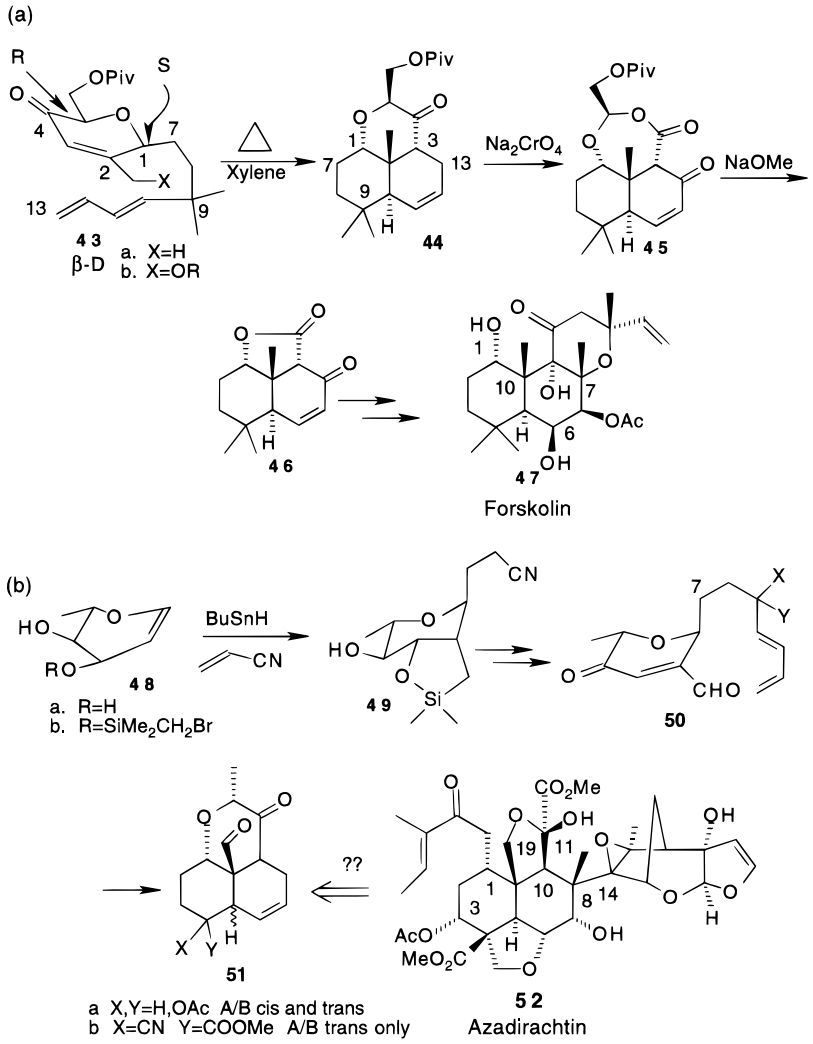
These calculated values are fully consistent with the experimental results for **42a** and **42b (**α and β). In subsequent studies we have addressed the further controversial issue of sp^2 versus sp^3 hybridization of the ring oxygen.[40]

Carbohydrates to Densely Functionalized Carbocycles

Intramolecular Diels–Alder on 2,3-α-Enones. In spite of the "full circle" and "tangents" described

(36) See, for example: Wang, Q.; Withers, S. G. *J. Am. Chem. Soc.* **1995,** *117*, 10137. Sinnott, M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113.
(37) Andrews, C. W.; Fraser-Reid, B.; Bowen, J. P. *J. Chem. Soc., Chem. Commun.* **1989**, 1913.
(38) Ratcliffe, A. J.; Mootoo, D. R.; Andrews, C. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 7661.
(39) Wilson, B. G.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 317.
(40) Andrews, C. W.; Fraser-Reid, B.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 8293.

Scheme 8



above, our research program has never been unmindful of its roots in 2,3-unsaturated sugars. In the first *Accounts* article,[1a] we had already recognized that carbohydrate α-enones usually display high reactivity in cycloadditions and conjugate additions, phenomena that still require convincing rationalization in spite of the valiant efforts of Benko[41] and Underwood and Osterhout.[42] Rahman's successful Diels−Alder strategy for actinobolin[43] emboldened us to explore the fertile ground of intramolecular Diels−Alder chemistry for sugar 2,3-α-enones.

The initial challenge of forskolin, **47,** for us was posed by its densely functionalized B ring, as well the *trans* decalin A/B ring juncture, which is ubiquitous among natural products (Scheme 8). Triene **43a** was prepared by Tsang, and heating in xylene gave tricycle **44** as the only product.[44] The pyranose ring had served its purpose well by ensuring the stereochemistry of **44**, but it was additionally valuable as a source of latent functional groups. Thus treatment with sodium chromate achieved Baeyer−Villiger oxidation at the more electron rich bond and simultaneous allylic oxidation to acetal **45**. Gentle methanolysis then afforded lactone **46**, which had served as a forskolin precursor in syntheses by Zeigler,[45] Rúveda,[46] and their co-workers.

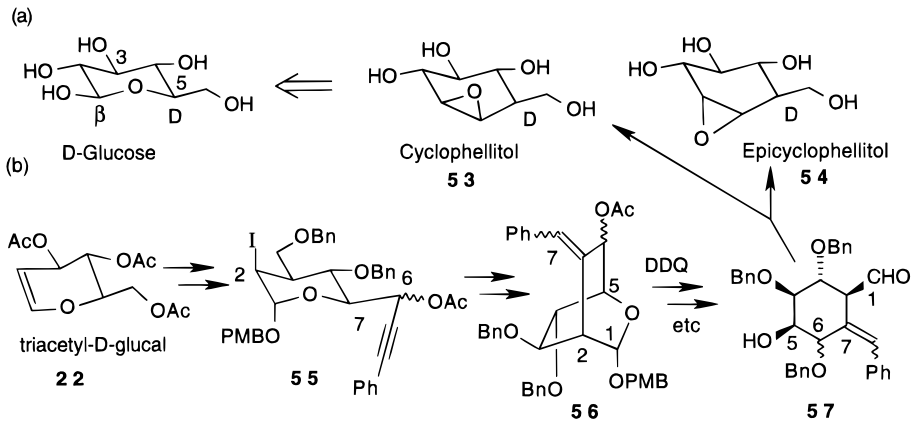
However, the potential of this strategy was undermined by the trojan effort expended by Tsang to establish the vinyl methyl residue of **43a**.[44] Improvements would be clearly necessary, and our *modus operandi* for the future with respect to this aspect took cognizance of the clerodane family of terpenoids in which the C-10 moiety is frequently oxygenated as in azadirachtin, **52**.[47] For such targets, the ideal intramolecular Diels−Alder precursor would carry the predestined CH_2−OR′ synthon at C2 of the enone as in **43b**.

It had been with 2,3-α-enones of pyranosides that we had stumbled into the area of free radical chemistry in 1972,[48] and free radical chemistry was now tapped for developing an appropriate precursor.

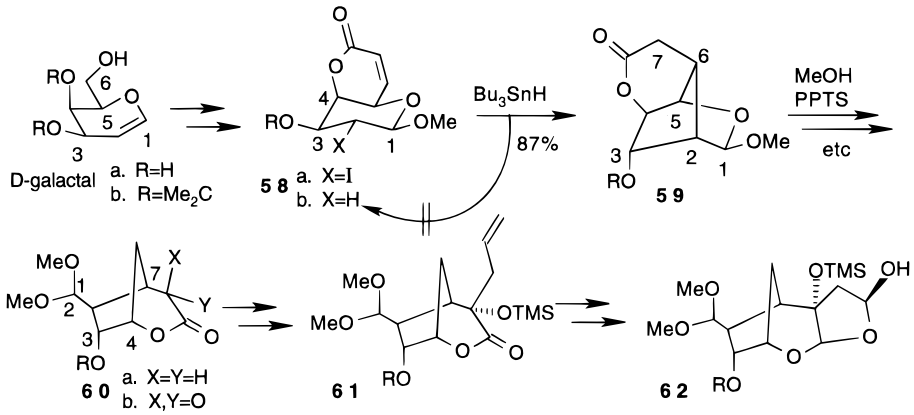
Compound **43** has two chiral centers, *R* and *S*, but

(41) Benko, Z.; Fraser-Reid, B.; Mariano, P. S.; Beckwith, A. L. J. *J. Org. Chem.* **1988**, *53*, 2066.
(42) Fraser-Reid, B.; Underwood, R.; Osterhout, M.; Grossman, J. A.; Liotta, D. *J. Org. Chem.* **1986**, *51*, 2152.
(43) Rahman, Md. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576.
(44) Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065.
(45) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115.
(46) Somoza, C.; Darias, J.; Ruveda, E. A. *J. Org. Chem.* **1989**, *54*, 1593. Colombo, M. I.; Zinczuk, J.; Bacigaluppo, J. A.; Somoza, C.; Ruveda, E. A. *J. Org. Chem.* **1990**, *55*, 5631.
(47) Kraus, W.; Bokel, M.; Klenk, A.; Pohnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435. Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Rep.* **1992**, 109.
(48) Fraser-Reid, B.; Holder, N. L.; Yunker, M. B. *J. Chem. Soc., Chem. Commun.* **1972**, 1286.

Scheme 9



Scheme 10



only the latter survives in **46**. In the parlance of carbohydrate chemistry, the surviving chiral center is found in β-D or α-L *C*-glycosides. The latter, in which the anomeric substituent is (normally) axially oriented, would therefore provide all the *chiral* information which had to be transmitted.

How could an axial carbon branch be appended at the anomeric center? Giese's detailed analysis had taught us that glycosyl radicals exhibit an anomeric effect.[49] Accordingly, Lopez and Gomez[50] applied the Stork/Sher radical cyclization process[51] to the rhamnal derivative **48b** whereby the α-L acrylonitrile adduct **49** was obtained stereoselectivity, with the C1 and C2 carbon branches in place. Notably the C2 substituent of **49** is functionalized, and Fleming/Tamao oxidation[52] paved the way to the intramolecular Diels–Alder precursor **50**, and thence the A/B-*trans* system **51a**, unfortunately contaminated with ~20% of the AB-*cis* product. In Scheme 8a, the absence of a *cis* product to accompany **44** suggests that C9 geminal substitution of the Diels–Alder precursor may be a stereocontrolling entity. Indeed support for this notion came from the stereoselective formation of **51b** by a comparable sequence of reactions.

Inositol, which is biosynthesized from glucose,[53] is a "densely functionalized carbocycle" (or a *carba* sugar),[54] and the achievements of Tsang, Pak, Dickson, and Walton[55] had taught us that such targets could be approached with the help of free radical manipulations. Cyclophellitol, **53**, is a β–D-glucosidase inhibitor, and for proof of structure, Tatsuta had synthesized both **53** and its diastereomer, epicyclophellitol, **54**, from L-glucose and D-galactose, respectively.[56] But given the conformational representations in Scheme 9a, McDevitt surmised that **53** and **54** could both be prepared from D-glucose by taking advantage of exploratory work by Vite and Alonso[57] on radical cyclization of 2-deoxy 2-iodo glycosides for preparing functionalized cyclopentanes and cyclohexanes. Accordingly, McDevitt prepared the iodo alkyne **55**, which cyclized in the key step to yield the bicyclic glycoside **56** in which (a) the desired configuration had been established at the tertiary C2 carbon and (b) the only undefined stereocenters were the two destined to embody the diastereomeric oxirane residues. Oxidative hydrolysis of the glycoside gave a hemiacetal

(49) Dupuis, J.; Giese, B.; Riegge, D.; Fischer, H.; Korth, H.-G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896. Giese, B. *Pure Appl. Chem.* **1988**, *60*, 1655.

(50) Lopez, J. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 3450. Lopez, J. C.; Gomez, A. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1993**, 762.

(51) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *103*, 303, 6384.

(52) Fleming, I.; Kieburn, J. D. *J. Chem. Soc., Chem. Commun.* **1986**, 1198. Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120.

(53) Halliday, J. W.; Anderson, L; *J. Biol. Chem.* **1955**, *217*, 797.

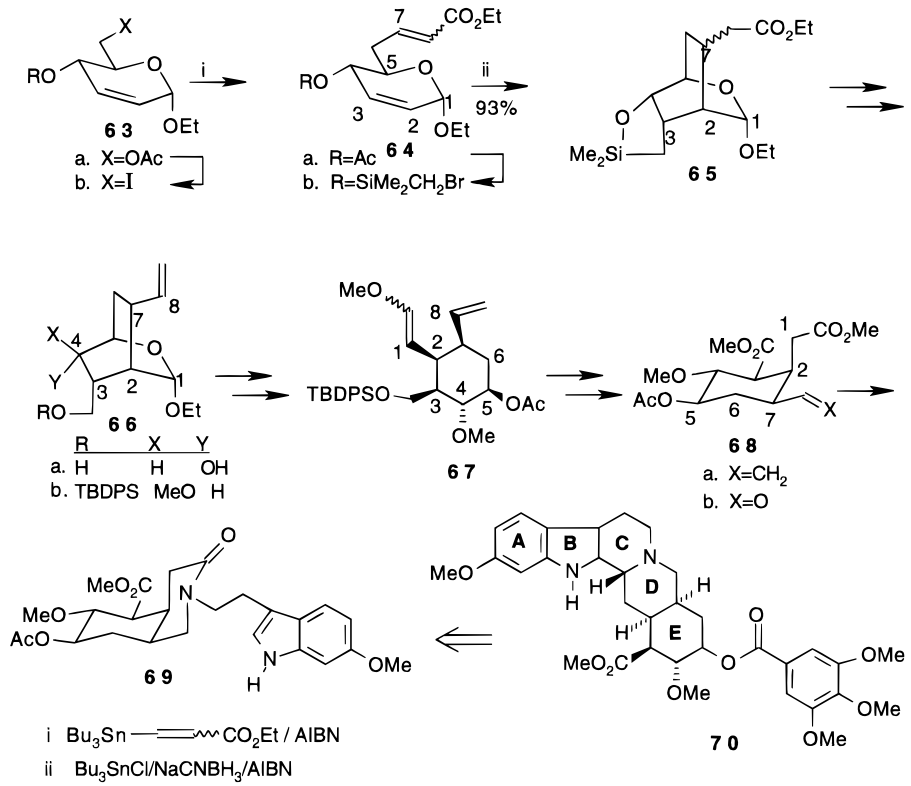
(54) Suami, T.; Ogawa, S. *Adv. Carbohyd. Chem. Biochem.* **1990**, *48*, 21.

(55) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102; Pak, H.; Canalda, I. I.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 3009–3011. Dickson, J. K., Jr.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1440. Walton, R. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791.

(56) Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Carbohydr. Res.* **1991**, *222*, 189.

(57) Vite, G. D.; Alonso, R.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2268. Henry, K. J., Jr.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128.

Scheme 11



that opened spontaneously to aldehyde **57**, from which both **53** and **54** were elaborated.[58]

Intermediate **56** has only one tertiary carbon, but what if more were needed? Henry[59] addressed this problem in his use of D-galactal for obtaining **61**, which is envisaged as a precursor for a dihydrofuran acetal moiety of azadirachtin, **52** (Scheme 10). As is frequently the case, the strategy, seemingly obvious in retrospect, was by no means assured at the outset, specifically whether the C2 radical from **58a** would add conjugately to give to the highly strained tricyclic isomer **59** or, following the path of lesser resistance, be reduced to **59b**. In the event this key reaction proceeded in 87% yield, there being no trace of **58b**.

Henry's use of the C4-OH of **58a** had therefore ensured the C6 configuration in product **59**, and a variation on that theme was explored in a synthesis of reserpine, **70**. In Woodward's legendary synthesis of this material, the densely functionalized carbocyclic entity **68b** had originated in a key Diels–Alder reaction.[60]

Free radical methodology and carbohydrate synthons were not then in vogue, but they are now, and target **68** confronted us with three contiguous tertiary carbon centers. In their exploratory route to cyclohexanes, Alonso, Vite, and McDevitt[61] had shown that a properly oriented C6 substituent would ensure stereoselectivity in the cyclizations of precursors such as **64**. However, for the target at hand, placing a substituent at C6 of **64** would have meant carrying excess baggage, and so Lopez and Gomez designed a subterfuge.[62]

The iodo sugar **63b** was readily prepared from the well-known[23] 2,3-unsaturated sugar **63a**, and the procedure of Russell[63] and Baldwin[64] was applied[65] to obtain diene **64a** as an *E*/*Z* mixture. Notably the C4 configuration of **64** is "wrong", but the α-oriented OH was needed as the pivot for the serial radical cyclization leading to **65** in 93% yield. Having served its purpose well, the C4 center was then inverted, and both C7 diastereomers were processed to give the desired configuration of the vinyl residue in **66**.

With the required three contiguous tertiary carbons now established at C3, C2 and C7, the caged molecule **66b** was opened, providing access to carbocycle **67**. Ozonolysis led to aldehyde **68b** whose "instability" had been noted by Woodward[60] and Pearlman.[66] Nevertheless we were able to establish from NMR spectra that the conformations of **68a**, **68b**, and the reductive amination product **69** were all as shown in Scheme 11.

Epilogue

Evidence for the current interest in the chemistry of carbohydrates ranges from the emergence of several new journals dealing with *GlycoScience*, to the flood of learned meetings too numerous (and expensive) to attend, to entrepreneurial adventures being set up (or

(58) McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 3250.
(59) Henry, K. J., Jr.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128.
(60) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.
(61) Alonso, R. A.; Vite, G. D.; McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 573.
(62) Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.*, in press. Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4048.
(63) Russell, G. A. *Acc. Chem. Res.* **1989**, *22*, 1. Russell, G. A.; Tashtoush, H.; Ngovwatchai, *J. Am. Chem. Soc.* **1984**, *106*, 4622.
(64) Baldwin, J. E.; Kelly, D. R. *J. Chem. Soc., Chem. Commun.* **1985**, 682. Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133.
(65) Gomez, A.; Lopez, J. C.; Fraser-Reid, B. *Synlett* **1993**, 557.
(66) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398.

closed down), all of which attest to the perceived "biological importance" of sugars. This rationale was also the underpinning for our research activities twenty years ago, although our targets then were not oligosaccharides as they are now, but rare and modified sugars such as those found in the (then) new antibiotics. For yesterday's or today's targets, 2,3-unsaturated sugars, more or less embellished, have been the lodestone of our synthetic adventures, whether of saccharides or of "natural products". The force and energy behind these multiple endeavors have been donated by young men and women, known collectively as Fraser-Reid's Rowdies, who have shared their talents as undergraduates, graduates, postdoctoral fellows, or visiting professors. Some of them have been cited by name in this Account, but the unmentioned colleagues are equally in the author's debt, because the willingness of the Rowdies to cooperate with and nurture one another has long been a marvel to the author. It is because of them that working with 2,3-unsaturated sugars has been, and continues to be, such fun for thirty years.

The chemistry described in this Account was executed 100%, and conceived nearly as much, by the young women and men who have spent time in our lab at Duke. Some of them have been identified in the text and footnotes. However, there are many other "Fraser-Reid Rowdies" whose names are found in neither place, simply because their projects did/do not emanate from 2,3-unsaturated sugars. Nevertheless their contributions to the group effort have been constant and invaluable. Their collective enthusiasm, counsel, and camaraderie will inspire, motivate, and linger with the author well into the future. Generous financial assistance from the National Institutes of Health, The National Science Foundation, and Burroughs Wellcome Company is acknowledged, and special thanks are due to Glaxo Inc., who showed early confidence in n-pentenyl glycosides when others did not.

AR950104S