developed for predicting structures of chemically bonded molecules can be useful for discussing complexes like ArClF. Applying the Walsh rules for triatomic molecules, ArClF is predicted to be linear, with Cl the central atom, as is observed. The molecular quadrupole moment of CO_2 is large. The difference in electrostatic quadrupole–quadrupole interaction in $(CO_2)_2$ at 4.1 Å between linear (repulsive) and T (attractive) configurations is 8 kJ/mol.[42] It is not surprising, then, that the equilibrium structure is T-shaped, with a relatively short intermolecular bond.

For H_2–Ar and $(H_2)_2$ the intermolecular bond is significantly greater than the sum of van der Waals radii. For these hydrogen-containing molecules this discrepancy may reside in the way the structures have been represented. The values of bond length R_0 are much longer than, e.g., R_e (for $(H_2)_2$ $R_e \sim 3.0$ Å, $R_0 \sim 4.4$ Å) because of the unusually large amplitude vibration of the light H_2 molecule against the weak intermolecular bond. Had a value nearer R_e been presented in Figure 3, the van der Waals structures would have been more consistent with the van der Waals radii. These near-free-rotor structures are represented by the arrows in Figure 3.

The discrepancy between intermolecular bond lengths and van der Waals radii for the remaining molecules N_2–Ar, $(N_2)_2$, and $(O_2)_2$ may be due in part to errors in determining the bond lengths. The structures can be rationalized by discussing the delicate balance among anisotropic dispersion, quadrupole, and repulsive forces. In the case of $(O_2)_2$, as discussed earlier, the anisotropic dispersion forces stabilize the rectangular geometry. For $(N_2)_2$, quadrupole–quadrupole interactions favor the T configuration as in the case of $(CO_2)_2$. (The quadrupole moment of N_2 is smaller than that of CO_2 but larger than O_2.) It has been argued[19] that the T configuration of N_2–Ar, rather than the linear arrangement, is favored because repulsive interactions are minimized while dispersion interactions operate effectively.

In all cases where crystal structure can be compared to the polyatomic van der Waals molecule structure the general molecular arrangements are in agreement. Evidence for the zig-zag hydrogen bond is found in ice[43] and solid HF.[44] Rectangular or near-rectangular structures are reported for solid nitric oxide[45] and oxygen.[46] A near-T configuration is found in solid nitrogen[47] and carbon dioxide.[48] Evidence for nearly free rotation is found in solid hydrogen.[49] However, in many of these cases significant discrepancies exist for the bond lengths.

Summary

Studies of van der Waals molecules provide a new source of information to map intermolecular interactions, augmenting that available from molecular beam scattering and macroscopic measurements. It is apparent that arguments used to discuss bonding in most van der Waals molecules are made with more confidence when the structures and properties are known beforehand. With the present excitement and interest in van der Waals molecules, it may not be long before our knowledge of intermolecular interactions will allow a more substantial understanding of this new class of molecules.

This work was supported by the National Science Foundation under Grant GP-37043X1.

(41) A. D. Walsh, *J. Chem. Soc.*, 2266 (1953).
(42) Using the coupling constant $3\Theta/4R_0^5 = 0.7$ kJ/mol from ref 32 and orientational factors from A. Buckingham, *Q. Rev., Chem. Soc.*, 13, 183 (1959).
(43) For example, see discussion in ref 38, p 464 ff.
(44) M. Atoji and W. N. Lipscomb, *Acta Crystallogr.*, 7, 173 (1954).
(45) W. Lipscomb, F. Wang, W. May, and E. Lippert, Jr., *Acta Crystallogr.*, 14, 1100 (1961).
(46) C. Barrett, L. Meyer, and J. Wasserman, *J. Chem. Phys.*, 47, 592 (1967).
(47) T. Jordon, H. Smith, W. Streib, and W. Lipscomb, *J. Chem. Phys.*, 41, 756 (1964).
(48) W. Keesom and J. Köhler, *Physica*, 1, 167, 655 (1934).
(49) J. van Kranendonk and H. P. Gush, *Phys. Lett.*, 1, 22 (1962).

Some Progeny of 2,3-Unsaturated Sugars—They Little Resemble Grandfather Glucose

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The author has been both praised and abused for using carbohydrate derivatives "to do organic chemistry". One friend allowed that there are aspects of sugar chemistry which deserve the attention of competent chemists, while another expressed amazement that we know how to use a drybox since sugars are water soluble. A Nobel Laureate known to the author declared that the stabilization of the anomeric cation by the ring oxygen constitutes half of sugar chemistry. A graduate student (from another area) was amazed to find that many of the fabled mysteries of the hexoses garnered during that fateful 2 weeks of Org. Chem. II disappeared once he drew the

Bert Fraser-Reid was born in Jamaica, received his primary and secondary education there, and then worked for 5 years during which time he made his first acquaintance with chemistry. He emigrated to Canada and obtained his B.Sc. and M.Sc. (with J. K. N. Jones) at Queen's University, Kingston, Ontario, and his Ph.D. in 1964 at the University of Alberta (Edmonton) under R. U. Lemieux. After 2 years of postdoctoral study with Sir Derek Barton at Imperial College, London, he joined the fledgling University at Waterloo in 1966 where he is currently an Associate Professor. He is an accomplished musician on the pipe organ and piano.

structures properly. An eminent chemist wants to use sugars; but he finds the names annoying.

Fortunately there is another side of the coin. After a brief affair with "natural products", an associate complained that steroids were a nuisance, because they kept crystallizing, even when impure.

The foregoing notwithstanding, there is a growing willingness for "organic chemists" to come into contact with sugars voluntarily. A leading synthetic chemist is trying to use one in his prostaglandin synthesis, and in the office of another, I spied all recent issues of *Specialist Reports* on carbohydrate chemistry. Yet another discovered them while studying the ozonolysis of acetals. These few cracks in the insulation suggest that the mainstream of organic chemistry is no longer innocent of these non-"natural products".

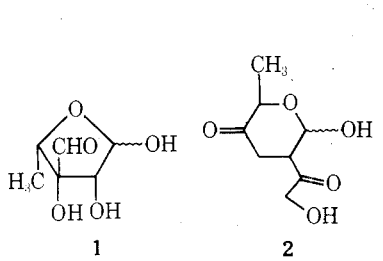
This innocence is odd because many principles, so germane to the chemical fabric that they are currently presented in elementary organic chemistry courses, were hatched from carbohydrates. Three outstanding examples are the concept of conformational influence upon chemical reactivity (Haworth, 1929), neighboring-group participation (Isbell, 1931), and the applicability of coupling constants to structure elucidation (Lemieux, 1954).

Apropos the last observation, carbohydrates find great favor in spectroscopic studies. However, many modified sugars have recently become available which could be used with advantage in syntheses and mechanistic investigations, were their existence widely known. Hopefully this Account will make one small step in that direction.

True, the names are a pain in the abstracts and the wretched things just will not crystallize. But working with syrups is a state of mind very much like eating green eggs and ham.[1]

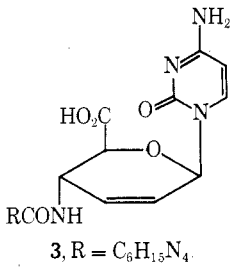
The discovery in 1944 of streptomycin,[2] a chemotherapeutic agent effective against some penicillin-resistant infections, and yet of comparatively low toxicity,[3] was understandably of immediate interest. In the succeeding 10 years, this interest was sustained, for it required that long to decipher the molecule, bringing to a conclusion one of the most impressive chapters in the annals of classical structure elucidation.[4]

The primary obstacle was the sugar component whose formula, $C_6H_{10}O_5$, was consonant with a simple hexose ($C_6H_{12}O_6$) anhydride. But it was nothing so prosaic. Thus streptose, **1**, whose unusual structure[5] was secured by synthesis only recently, was the first branched-chain sugar to be obtained from a microorganism. This source has since proved to be prolific, providing more than a dozen of these "rare" sugars,[6] and to judge from the recent addition to the list of pillarose (**2**)[7] from the antibiotic pillaromycin A15,[8] it would appear that the sugars get more rare every day.



1

2



3, R = $C_6H_{15}N_4$

While it is true that many substances with biological activity contain modified sugars, it does not follow logically[9] that all modified sugars confer biological activity. However, the circumstance that rare sugars frequently have biological activity prompts speculation about structure–activity relationships. If only for heuristic purposes, it is well to have a wide assortment of modified sugars about which to speculate. Since structure modifications of organic molecules proceed most adeptly from centers of unsaturation, interest in unsaturated sugars is a logical outgrowth.

However, the importance of unsaturated sugars was established independently, with the advent in 1958 of blasticidin S, **3**, the powerful inhibitor of the blast rust disease in rice plants.[10] Furthermore, a biogenetic proposal,[11] since disproved,[12] once invoked olefinic sugars as intermediates in RNA → DNA conversion.

The specific introduction of carbonyl and olefinic unsaturation in a sugar molecule is fraught with difficulty in view of the abundance of hydroxyl functions. Fortunately, the deployment of blocking groups of various ilk, design, and purpose has been raised to a veritable art by earlier generations of carbohydrate chemists. This legacy, combined with the emergence of modern reagents, gentle enough for use with frail sugars, has allowed a harvest rich in exciting unsaturated sugars. The activity has been intense and varied; hence this Account will concentrate primarily upon researches in which 2,3-unsaturated sugars are featured, not only because of the author's bent, but because these species are available, readily and in great variety, from commonplace carbohydrate precursors.[13]

Olefin-Based Transformations

The first reported 2,3-unsaturated sugar was pseudoglucal diacetate (**5**),[14] obtained by hydrolytic rearrangement of that venerable unsaturated sugar, triacetylglucal (**4**).[15] It is therefore interesting to note that the latter, **4**, was synthesized by accident and is

(1) Dr. Seuss, "Green Eggs and Ham", Beginner Books, Random House, 1960.

(2) S. A. Waksman and B. B. Woodruff, *J. Bacteriol.*, **40**, 581 (1940).

(3) H. J. Robinson, D. G. Smith, and O. E. Graessle, *Proc. Soc. Exp. Biol. Med.*, **57**, 226 (1944).

(4) For a condensed review see R. U. Lemieux and M. L. Wolfrom, *Adv. Carbohyd. Chem.*, **3**, 337 (1948).

(5) M. L. Wolfrom and C. W. Dewalt, *J. Am. Chem. Soc.*, **70**, 3148 (1948).

(6) H. Grisebach and R. Schmid, *Angew. Chem., Int. Ed. Engl.*, **11**, 159 (1972); S. Hanessian and T. H. Haskell in "The Carbohydrates", Vol. 11A, W. Pigman and D. Horton, Ed., 2nd ed, Academic Press, N.Y., 1970, p 14.

(7) At the time of writing this article, it appears that structure **2** is not correct for pillarose, the sugar component of pillaromycin A. See future publications by D. L. Walker and B. Fraser-Reid for further details.

(8) M. Asai, *Chem. Pharm. Bull.*, **18**, 1699, 1706, 1713 (1970).

(9) L. S. Stebbing, "A Modern Elementary Logic", Methuen & Co. Ltd., London, 1957, Chapter 4.

(10) S. Takeuchi, K. Hurayana, K. Ueda, H. Sakai, and H. Yonehara, *J. Antibiot., Ser. A*, **11**, 1 (1958); H. Yonehara and N. Otake, *Tetrahedron Lett.*, 3758 (1966); J. J. Fox and K. A. Watanabe, *ibid.*, 897 (1966).

(11) A. Larsson, *Biochemistry*, **4**, 1984 (1965).

(12) R. L. Blakley, R. K. Ghambeer, T. J. Batterham, and C. Brownson, *Biochem. Biophys. Res. Commun.*, **24**, 418 (1966); M. M. Gottesman and W. S. Beck, *ibid.*, **24**, 353 (1966).

(13) For recent comprehensive surveys, see: R. J. Ferrier, *Adv. Carbohydr. Chem.*, **24**, 199 (1969); **20**, 67 (1965).

(14) M. Bergmann, *Justus Liebigs Ann. Chem.*, **443**, 223 (1925).

(15) E. Fischer, M. Bergmann, and H. Schotte, *Justus Liebigs Ann. Chem.*, **53**, 509 (1920).

Chart I

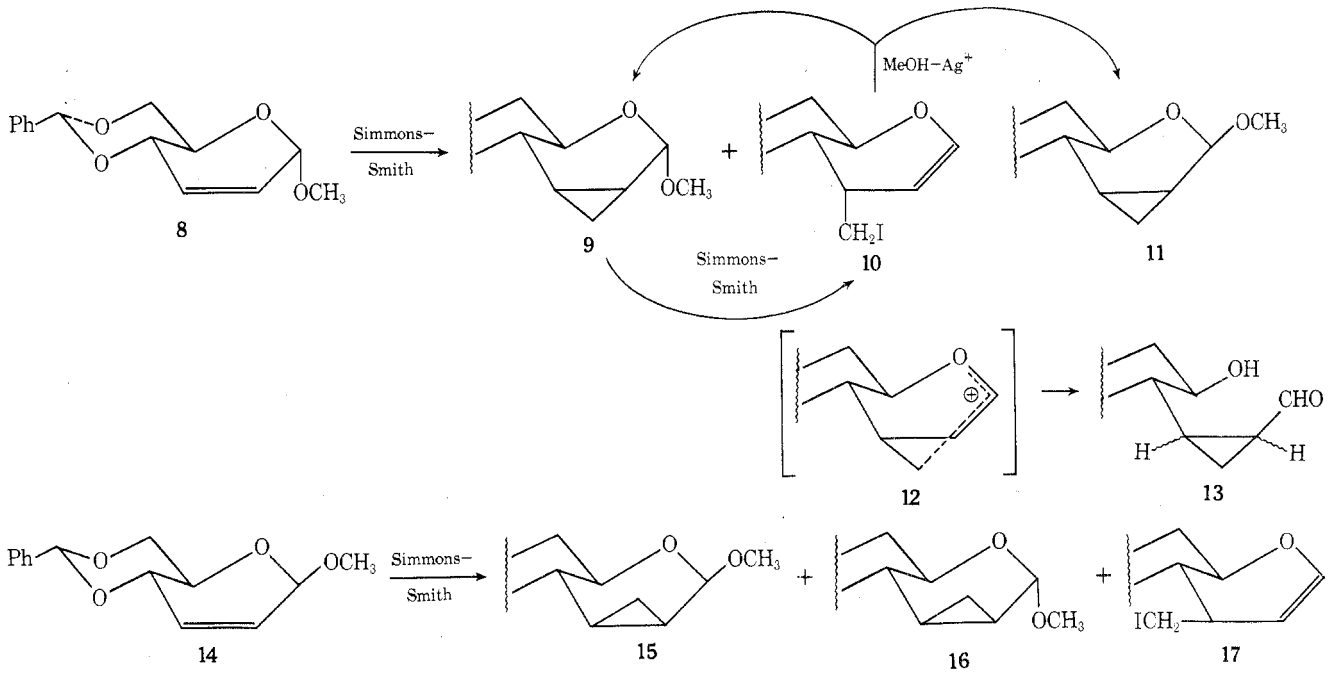
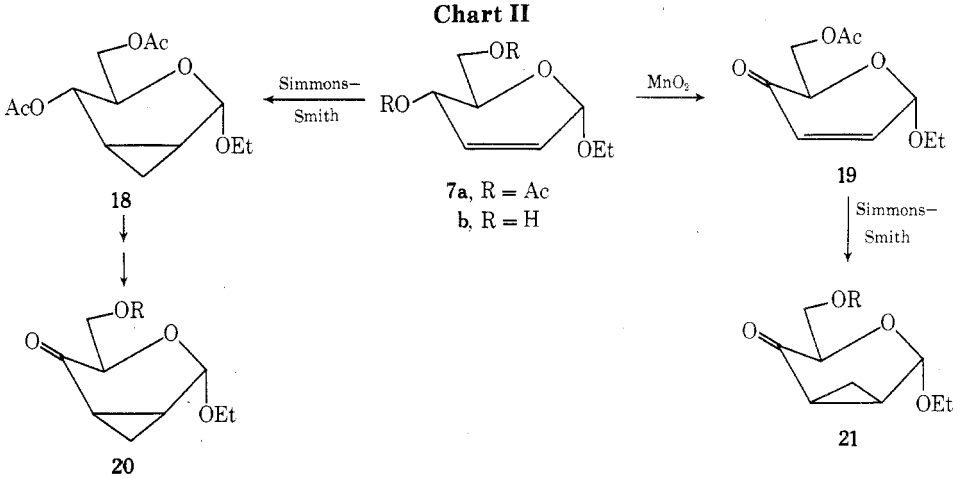
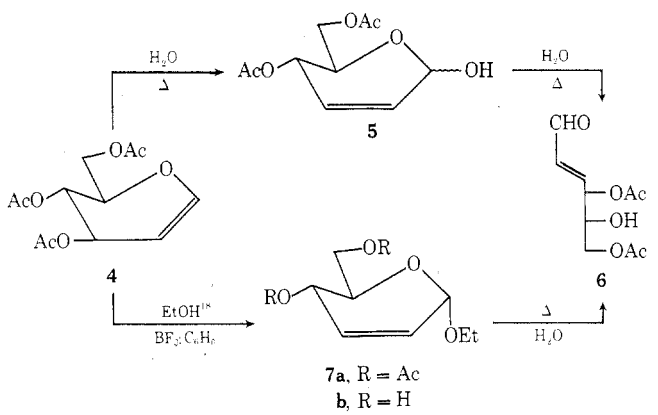


Chart II



improperly named, the suffix "al" having been appended by Emil Fischer who was misled by a positive Fuchsin SO_2 test on his crude material into thinking that he had prepared an aldehyde.[16] We recently suggested **6** as the culpable aldehyde since, upon prolonged hydrolysis of **4**, compound **6** is produced.[17]



That pioneering transformation **4** → **5** has been capitalized by Ferrier[18] into a direct synthesis of **7** which, given the ready availability of **4**,[19] makes **7** the most accessible hex-2-enopyranoside. The next most accessible are the benzylidenated analogs, **8** and **14**, several routes to which have been developed.[20]

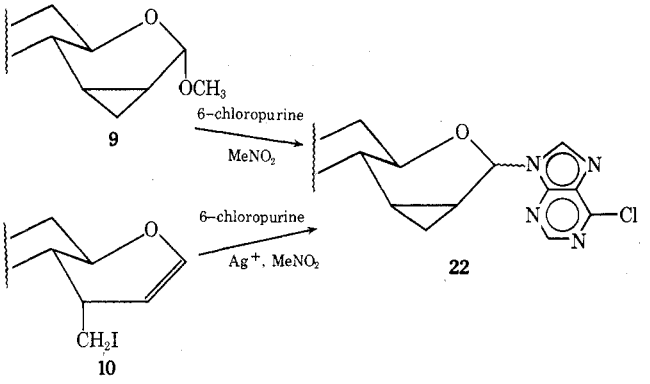
Cyclopropanation would produce an unusual dideoxy branched-chain sugar, a trail which had been blazed by Brimacombe[21] using a different olefinic sugar. For the 2,3-olefins, Horton achieved the first synthesis of **9**.[22] The series **11**, **15** and **16** was completed by us (Chart I)[23] and extended to Ferrier's olefin **7** for the preparation of the isomeric cyclopropyl ketones **20** and **21** (Chart II).[24] These provide an

(16) E. Fischer and C. Z. Sitzungsber, *K. Preuss. Akad. Wiss.*, **16**, 311 (1913). E. Fischer, *Chem. Ber.*, **47**, 196 (1914).
(17) B. Fraser-Reid and B. Radatus, *J. Am. Chem. Soc.*, **92**, 5288 (1970).
(18) R. J. Ferrier and N. Prasad, *J. Chem. Soc. C*, 570, 575 (1969).
(19) W. Roth and W. Pigman, *Methods Carbohydr. Chem.*, **2**, 405 (1963).
(20) The procedure currently preferred in this laboratory is that of R. D. Guthrie, R. D. Wells, and G. J. Williams, *Carbohydr. Res.*, **10**, 172 (1969).
(21) J. S. Brimacombe, P. A. Gent, and T. A. Hamor, *Chem. Commun.*, 1305 (1967).
(22) E. L. Albano, D. Horton, and J. H. Lauterbach, *Carbohydr. Res.*, **9**, 149 (1969).
(23) B. Radatus and B. Fraser-Reid, *Can. J. Ch.*, **50**, 2909 (1972).
(24) B. Fraser-Reid and B. J. Carthy, *Can. J. Chem.*, **50**, 2928 (1972).

interesting contrast. The formation of **18** from **7a** follows the traditional stereochemical course[25] with the cyclopropane ring syn to the ethoxy group. However with ketone **19**, the anti isomer (**21**) is given. This is presumably because the 6-*O*-acetyl group triumphs over the ethoxy aglycon for complexation with the organozinc intermediate, thereby delivering the methylene addendum from above.[24]

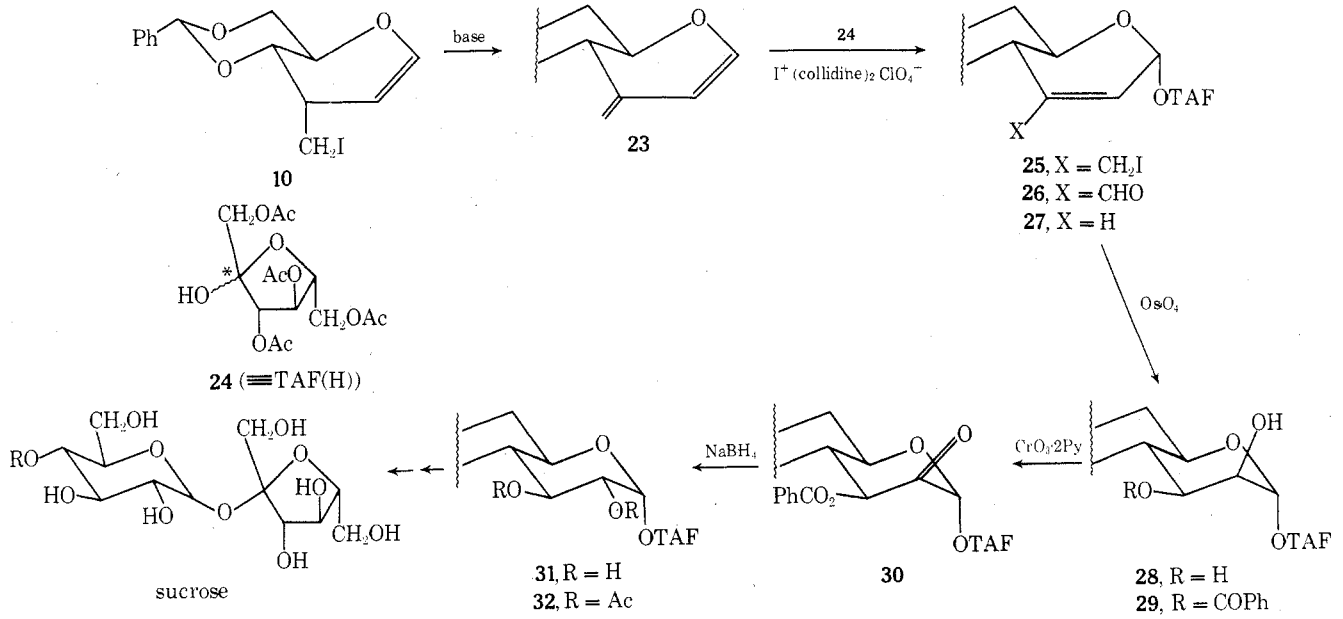
The homoallyl iodide **10** was an unexpected by-product of the Simmons–Smith reaction of **8**, and it is obtainable alternatively by resubjecting the cyclopropane **9** to the Simmons–Smith medium.[23] This interesting iodide, **10**, provided us with an early opportunity to examine the ion **12**, named a *cyclopropylcarbinyloxocarbonium ion* in recognition of the two stabilizing contributors, riding tandem therein.[26] The remarkable stability of ion **12** is reflected in the fact that, upon treatment of the glycoside **9** or **11** with boiling water, the methoxyl group is readily lost, the product being the carboxaldehyde **13**.[27] Appropriately, ion **12** also intervenes in the reactions of **10** so that hydrolysis of the latter also produces **13** in quantitative yield.[27] There are in fact two possible diastereomeric forms of the ion **12**, one arising from **9, 10, 11**, and another from **15, 16, 17**, and both ions could exhibit different stabilization depending on whether the orientation of the cyclopropyl ring and the carbonium ion is bisected or perpendicular.[28] However, a study of solvolyses of the cyclopropyl compounds **9, 11** vs. **15, 16** indicates that orientational effects are not important. This would seem to indicate that the stabilization of the anomeric cation by the ring oxygen completely overwhelms that from the cyclopropyl ring.[29] On the other hand, with the related homoallyl iodides **10** and **17** there is a pronounced difference in the relative rates as well as in the products obtained from their solvolyses.[29]

This extreme stability of **12** has recently been exploited for the preparation of the nucleosides **22** (α and β). The latter are formed by merely subjecting the cyclopropyl glycoside **9** or its homoallyl relative **10** to boiling nitromethane containing the base.[30]



A second channel of investigation, originating with the iodide **10**, centers upon the diene **23** furnished upon dehydroiodination. Because of its completely flat foreground and the absence of functionalities capable of neighboring-group participation[31] there is nothing to frustrate the approach of a nucleophile to the underside of C-1 of **23**. Consequently, alkoxyhalogenation occurs exclusively in the 1,4 sense giving an abundance of the thermodynamically favored α-D anomer, e.g., **25**.[32,33] Indeed, even with the highly hindered tertiary alcohol of tetracetylfructose (**24**) as nucleophile, the addition was exclusively α-D.

This gratifying result has allowed a contemporary rational approach to the synthesis of that notorious molecule sucrose.[34] Thus silver tetrafluoroborate–dimethyl sulfoxide oxidation[35] of iodide **25** gives alde-



Since **24** consists of α and β anomers, compounds **25** → **32** are actually mixtures containing α and β forms in the fructose moiety.

(25) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **80**, 5323 (1958); W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963); S. Winstein and J. Sonnerberg, *ibid.*, **83**, 3235 (1961).

(26) B. Fraser-Reid and B. Radatus, *Can. J. Chem.*, **47**, 4095 (1969).

(27) B. Fraser-Reid and B. Radatus, *Can. J. Chem.*, **48**, 2146 (1970).

(28) (a) M. Hanack and H. -J. Schneider, *Angew. Chem., Int. Ed. Engl.*, **6**, 666 (1967); (b) H. G. Richey, Jr., in "Carbonium Ions", Vol. 3, G. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N.Y., 1969.

(29) B. K. Radatus, Ph.D. Thesis, University of Waterloo, 1971.

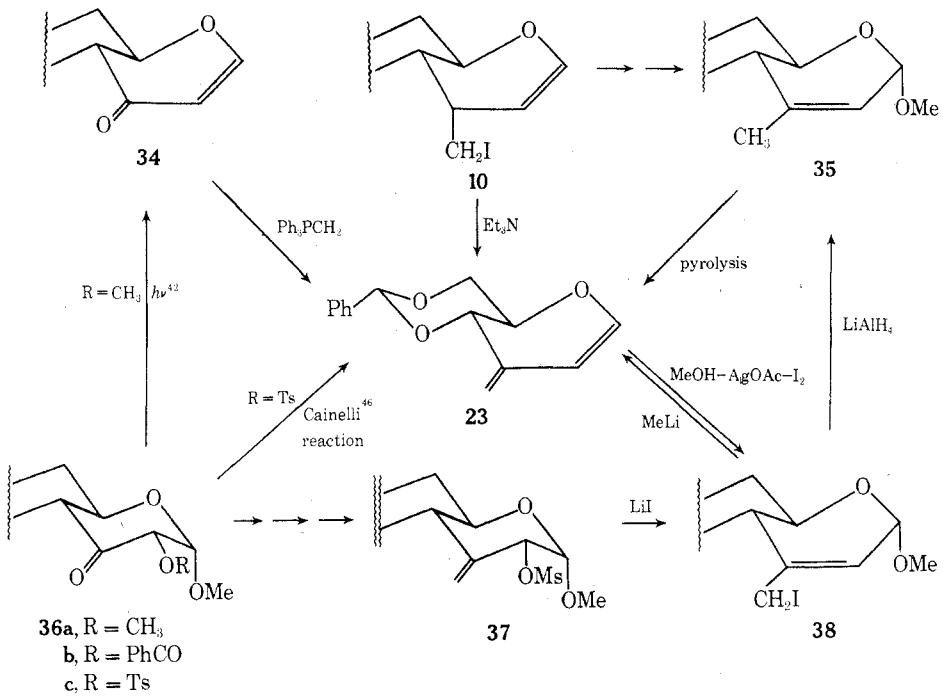
(30) S. Y.-K. Tam and B. Fraser-Reid, VI Central Regional Meeting of the American Chemical Society, Detroit, Mich., April 21–24, 1974, Abstract No. 202.

(31) See, for example, C. Schuerch, *Acc. Chem. Res.*, **6**, 184 (1973).

(32) B. Fraser-Reid and B. Radatus, *Chem. Commun.*, 779 (1970).

(33) The highly delocalized allyloxocarbonium ion, k, is undoubtedly formed first. Addition of thenucleophile, by analogy with the "axial halo

Chart III

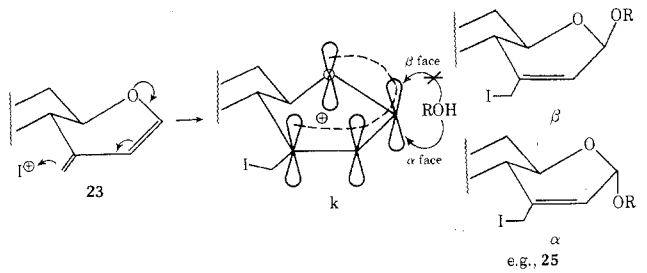


hyde **26** which is decarbonylated[36] in quantitative yield to the olefin **27,** osmylation of which gives **28** exclusively.[37] The problem of inverting the axial alcohol in **28** has been solved by taking advantage of the greater tendency of the equatorial hydroxyl group toward acylation.[38] Thus oxidation of the benzoate **29** followed by borohydride reduction of the 2-ketone **30** furnished the glucose skeleton **31.** The desired compound (**32**) was isolated by seeding the mixture with an authentic sample of benzylidenesucrose hexaacetate obtained from Dr. R. Khan.[39]

The foregoing suggests that diene **23** ought to permit the synthesis of a wide assortment of disaccharides, particularly of the elusive α-D-glucosyl variety.[40] Development of this approach requires better access to the diene than that (7%) provided by the homoallyl iodide **10** (Chart I). Alternative routes to **23** are shown in Chart III.[41] The most direct is, of course, the Wittig reaction upon enone **34,** the latter being available by photolysis of ketone **36,**[42] but the yields are very poor. The loss of methanol upon pyrolysis of **35** proceeds surprisingly well, but this route is vitiated by the demanding road to **35.**[43] A better route to **23** is by methyllithium treatment of iodide **38,** the latter being prepared from the ketobenzoate **36b**[44] via **37.** However, the entire process can be telescoped by using the known keto tosylate **36c,**[45] which upon treatment with the Cainelli reagent[46] for 2 hr afforded **23** in 50% yield.

Availability of diene **23** and access thereby to a variety of hex-2-enopyranosides (e.g., **25–27**) is of significance because of an interesting rearrangement to which these olefins are prone. In 1971 we found that allylic acetals could be reductively rearranged to vinyl ethers by use of *chloride-free* $LiAlH_4$ in ethereal solvents.[47] The complete stereospecificity of the process (eq i and ii, Chart IV) was attributed to intermediacy of the complex "L".[48] However Achmatowicz and Szechner suggested that a C-4 hydroxyl group (free or esterified) is preferred to an alkoxyl group as the site for complexation and that the complex so formed decomposes as shown in "M".[49] Indeed, we have since found that the C-4 complex can decompose in two ways: either via a five- or six-membered state, "M" or "N".[50] Thus while the reaction is always *stereo*specific, it may or may not be *regio*specific. The dilemma resulting from having

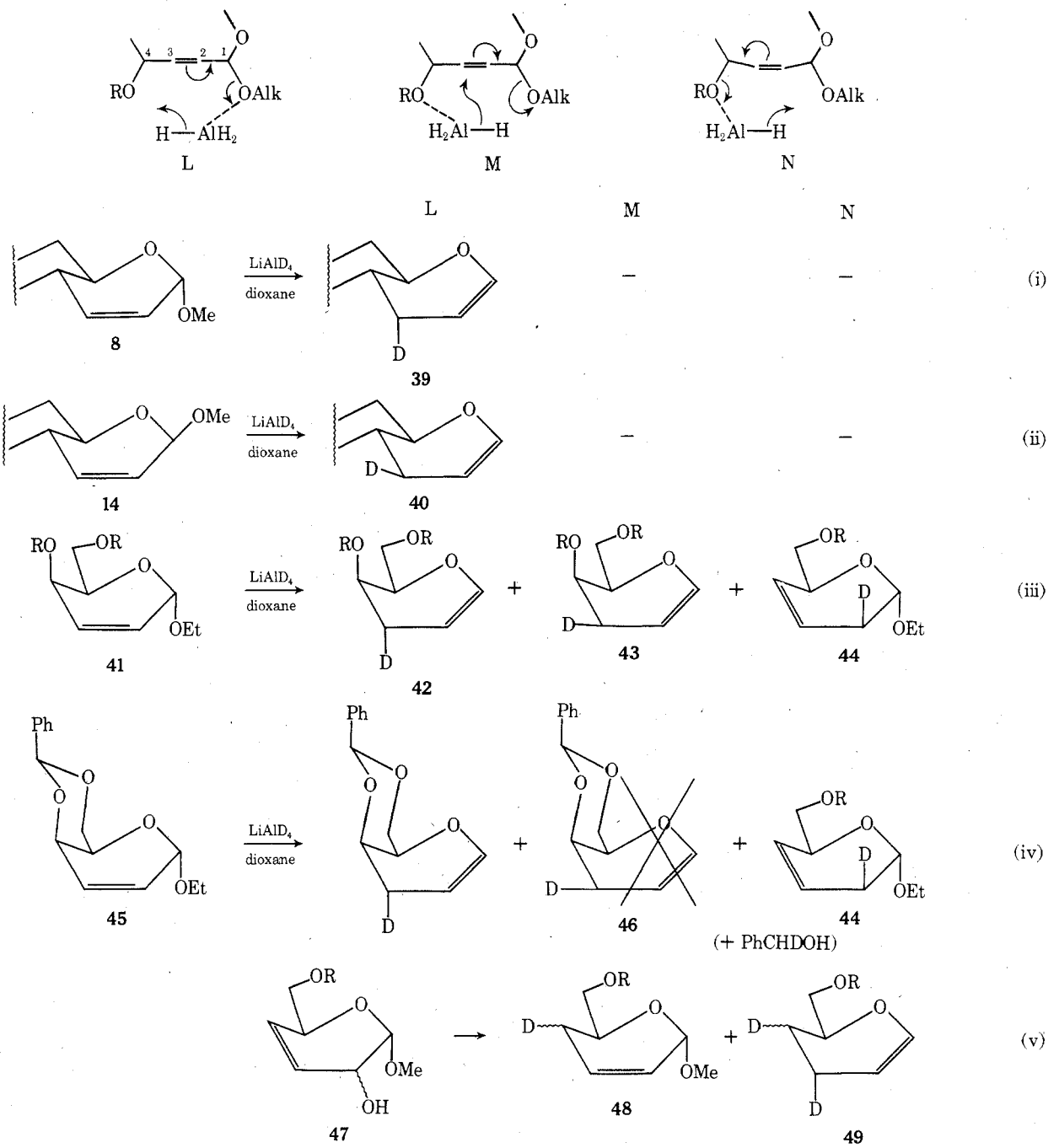
ketone" rationalization of E. J. Corey and R. A. Sneen (*J. Am. Chem. Soc.*, **78,** 6269 (1956)), should occur from the α rather than the β face of k, since the product so formed, **25,** has the best continuous overlap with the inter-



mediate. In the present case, the "kinetic product" is also thermodynamically favored because of the anomeric effect.

(34) D. E. Iley and B. Fraser-Reid, submitted for publication.
(35) B. Ganem and R. K. Boeckman, Jr., *Tetrahedron Lett.*, 917 (1974).
(36) K. Ohno and J. Tsuji, *J. Am. Chem. Soc.*, **90,** 99 (1968); M. Sergent, M. Mongrain, and P. Deslongchamps, *Can. J. Chem.*, **50,** 336 (1971).
(37) S. McNally and W. G. Overend, *J. Chem. Soc.*, 1978 (1966); C. L. Stevens, J. B. Filippi, and K. G. Taylor, *J. Org. Chem.*, **31,** 1292 (1966).
(38) J. M. Williams and A. C. Richardson, *Tetrahedron,* **23,** 1369 (1967).
(39) R. Khan, *Carbohydr. Res.*, **32,** 375 (1974).
(40) For a preliminary discussion of this long-standing problem, see R. U. Lemieux, K. James, and T. L. Nagabhushan, *Can. J. Chem.*, **51,** 42 (1973).
(41) S. Y.-K Tam, D. E. Iley, N. L. Holder, and B. Fraser-Reid, *Can. J. Chem.*, **51,** 350 (1973).
(42) P. J. Benyon, P. M. Collins, P. T. Doganges, and W. G. Overend, *J. Chem. Soc. C,* 1131 (1966).
(43) D. R. Hicks, R. Ambrose, and B. Fraser-Reid, *Tetrahedron Lett.*, 2507 (1973).
(44) F. A. Carey and K. O. Hodgson, *Carbohydr. Res.*, **12,** 463 (1970).
(45) K. Onodera and N. Hashimura, *Methods Carbohydr. Chem.*, **6,** 331 (1966).
(46) F. Bertini, P. Grasselli, G. Zubiani, and G. Cainelli, *Tetrahedron,* **26,** 1281 (1970).
(47) B. Fraser-Reid and B. Radatus, *J. Am. Chem. Soc.*, **92,** 6661 (1970).
(48) Acyclic vinyl ethers are sometimes obtained along with the cyclic compounds in Chart IV; see ref 47.
(49) O. Achmatowicz and B. Szechner, *Tetrahedron Lett.*, 1205 (1972).
(50) S. Y.-K. Tam and B. Fraser-Reid, *Tetrahedron Lett.*, 4897 (1973).

Chart IV[48]



R = H or Ac

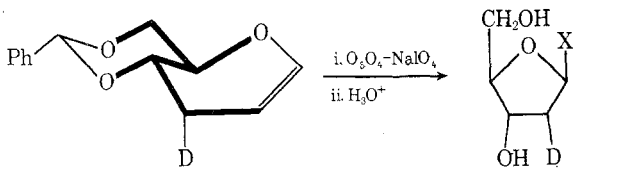
three possible transition states in simultaneous operation is exemplified beautifully in eq iii, where the allylic acetate **41** gives as products **42, 43,** and **44** via "L", "M", and "N", respectively. Comparison of eq iii and iv reveals that etherification of a (potential) hydroxyl group (**41** → **45**) nullifies the propensity toward formation of transition state "M", judging by the absence of **46**.

The formation of **44** in eq iii and iv indicates that the rearrangement can occur with a simple allylic alcohol. Hence **47** affords a mixture of **48** and **49,** the orientation of the C-4 deuterium being syn to that of the hydroxyl group in **47.** Unfortunately the process was successful only with carbohydrate substrates, steroidal allylic alcohols for example being totally unresponsive.[50,51]

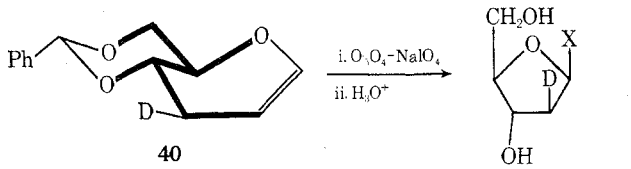
The transformations in eq i and ii enabled us to establish conclusively the stereochemical course in the deoxygenation of ribonucleotides to 2′-deoxyribonucleotides.[52] The 2-deoxyriboses **50** and **52,** present in embryo in **39** and **40** (heavy lines), were released[53] and converted to the deuterated nucleosides **51** and **53.** These, when compared directly with the material obtained from enzymic, in vitro reduction of ribonucleic acids in deuterium oxide,[54] confirmed that the product from the latter route was identical

(51) For related information see W. T. Bordon, *J. Chem. Soc., Chem. Commun.*, 381 (1971); *J. Am. Chem. Soc.*, 92, 4898 (1970).
(52) B. Fraser-Reid and B. Radatus, *J. Am. Chem. Soc.*, 93, 6342 (1971).
(53) B. Radatus, M. Yunker, and B. Fraser-Reid, *J. Am. Chem. Soc.*, 93, 3086 (1971).
(54) L. J. Durham, A. Larsson, and P. Reichard, *Eur. J. Biochem.*, 1, 92 (1967).

to our **51**.[55] Hence the enzymic reduction, like catalytic hydrogenolysis of alcohols, proceeds with retention of configuration.[56]



39 **50**, X = OH; **51**, X = cytosine



40 **52**, X = OH; **53**, X = cytosine

Enone-Based Transformations

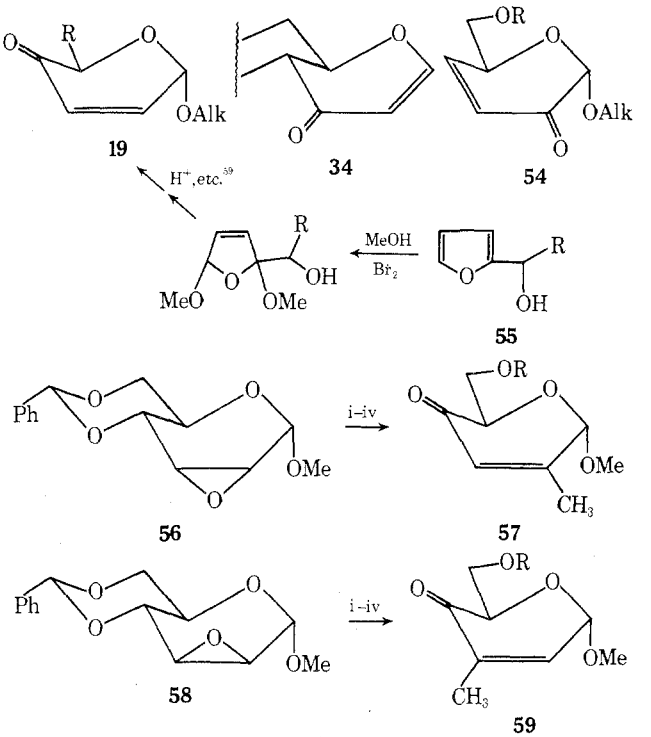
The foregoing has centered upon olefinic unsaturation as the vehicle by which modification is achieved. Isolated ketonic unsaturation offers an alternative which has been duly explored.[57] We therefore undertook to investigate molecules having both types of unsaturation in conjugation because of the vast array of transformations to which enones are susceptible.

At the inception of our studies, congeners of enones **34**[42] and **54**[58] but not of **19** were known. The simplest route to **19** is shown in Chart II; but a valuable alternative, particularly if enantiomeric purity is irrelevant, utilizes a two-step sequence from furan alcohols e.g., **55**, developed by Achmatowicz and coworkers.[59]

The scope of these enones for syntheses of sugars bearing a *C*-methyl branch would be enhanced if the olefinic carbons were furnished with a methyl substituent. To this end the oxiranes **56** and **58** were converted to the 2- and 3-methyl ketones **57** and **59**, respectively, as shown in Chart V.[60] The reactions with lithium dimethylcuprate are particularly significant since, with methyllithium or Grignard reagents, **56** and **58** give a plethora of aberrant compounds,[61] little if any of the expected alcohols being formed.

Alkylations. Alkyl substitution of the saccharide ring may be achieved by reaction of lithium alkylcuprate reagents with the enones.[62] However, conjugate addition of a functionalized carbon, an enter-

Chart V



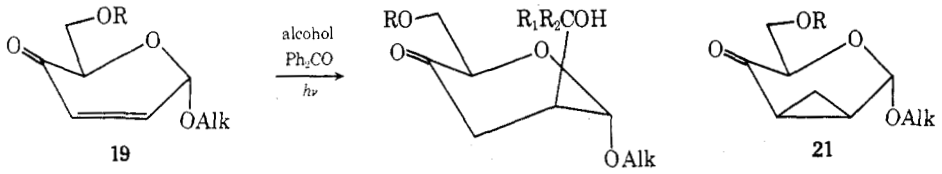
(i) $LiMe_2Cu$; (ii) xanthate pyrolysis; (iii) MeOH-TsOH; (iv) MnO_2

prising adventure at any time, is even more challenging with carbohydrate enones, since these delicate substrates would perish in some of the reaction media used. This problem was overcome by use of the procedure of Schenck[63] and (later) Pfau[64] for photosensitized addition of secondary alcohols to enones. In fact, we found that 2-propanol, ethanol, and even methanol added to enone **19** readily and in high yield, giving **60**, **61**, and **62**, respectively.[62] Fortuitously, these additions give *only* the axial isomers as shown, this being established for the methanol adduct **62** by tosylation and cyclization to the known cyclopropyl ketone **21** (Chart II). However, the additions are not *stereo*specific with all enones, although they are always *regio*specific. This result contrasts with the addition of dioxolane to triacetylglucal (**4**), which occurs at either end of the double bond.[65] In our work sensitized addition of methanol to **34** yields **68** (α and β) as the only adduct(s), thereby opening a ready route to *C*-glycosides.[66]

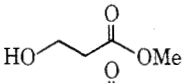
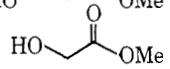
The process can be remarkably selective as in the reactions of **19** with ethylene glycol to give the monomeric product **63** in 80% yield, or with the hydracrylic ester to give **64** exclusively. The failure to obtain any reaction with methyl glycolate indicates the generally deactivating effect of the carboxyl group. With 2-hydroxymethyldioxolane, addition occurs at the tertiary site only, giving **65**. The scope of the process is broadened by noting that cyclohexane and acetonitrile are suitable solvents, thereby extending its applicability to addenda which for one reason or another cannot function as solvents.[67]

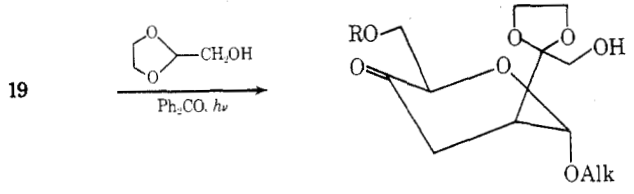
(55) For a different synthesis of 2-deuterio-2-deoxyribose, see S. David and J. Eustache, *Carbohydr. Res.*, **20**, 319 (1971).
(56) E. R. Alexander, *J. Am. Chem. Soc.*, **72**, 3796 (1950).
(57) For some examples see ref 2 in B. Fraser-Reid, A. McLean, E. W. Usherwood, and M. Yunker, *Can. J. Chem.*, **48**, 2877 (1970).
(58) E. F. L. J. Anet, *Carbohydr. Res.*, **1**, 348 (1966); K. Bock and C. Pedersen, *Tetrahedron Lett.*, 2983 (1969).
(59) O. Achmatowicz Jr., P. Bukowski, B. Szechner, Z. Zweizchowska, and A. Zamojski, *Tetrahedron*, **22**, 1973 (1971).
(60) See ref 38 for step i. Steps ii–iv are the unpublished work of D. R. Hicks.
(61) T. D. Inch and G. J. Lewis, *Carbohydr. Res.*, **15**, 1 (1970); G. N. Richards and L. F. Wiggins, *J. Chem. Soc.*, 2442 (1953); R. U. Lemieux, E. Fraga, and K. A. Watanabe, *Can. J. Chem.*, **46**, 61 (1968); M. Sharma and R. K. Brown, *ibid.*, **46**, 757 (1968); W. G. Overend and N. R. Williams, *J. Chem. Soc.*, 7378 (1965).
(62) B. Fraser-Reid, N. L. Holder, and M. B. Yunker, *J. Chem. Soc., Chem. Commun.*, 1286 (1972).
(63) G. O. Schenck, G. Koltzenburg, and H. Grossmann, *Angew. Chem.*, **69**, 177 (1957).
(64) R. Dulou, M. Vilkas, and M. Pfau, *C. R. Acad. Sci.*, **249**, 429 (1959).
(65) K. Ohga and T. Matsuo, *J. Org. Chem.*, **39**, 106 (1974).
(66) D. L. Walker, B. Fraser-Reid, and J. K. Saunders, *J. Chem. Soc., Chem. Commun.*, 319 (1974).

Chart VI

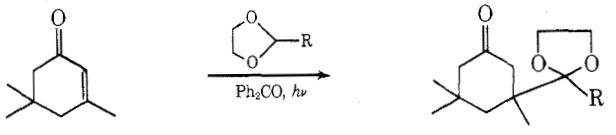


19 21

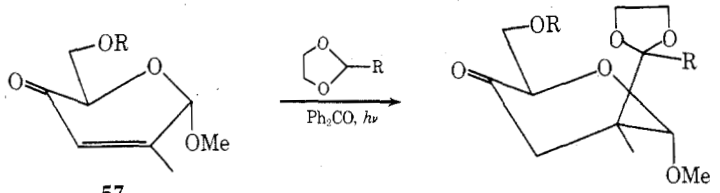
alcohol		R_1	R_2
i-PrOH	**60**	Me	Me
EtOH	**61**	H	Me
MeOH	**62**	H	H
$(CH_2OH)_2$	**63**	H	CH_2OH
	**64**	H	CH_2CO_2Me
		no reaction	



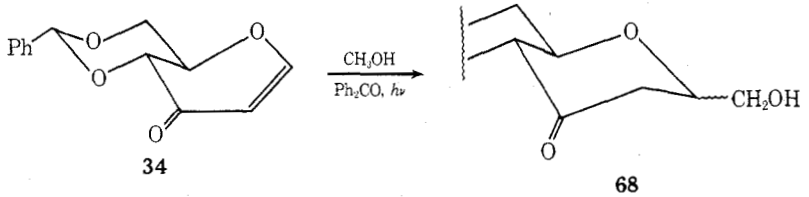
65



66



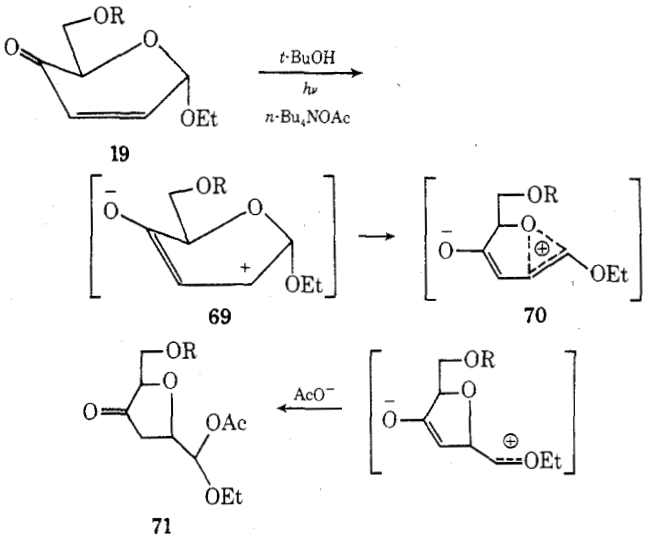
57 67



34 68

It is fortunate for us that carbohydrate substrates rather than carbocyclic enones were used as the testing ground for these photoalkylations, for with the latter the reactions are always slower and usually the yields are poorer owing to accompanying side reactions. However, these disadvantages pale into insignificance when the simplicity of the operation is contrasted with the demands of obtaining these adducts by other reported routes. Indeed, a spectacular triumph is the formation of **66** (~40%), where a maximally hindered single bond has been forged by irradiating isophorone with 2-propyldioxolane[67] and benzophenone in cyclohexane for 72 hr. As might be expected, a comparable carbohydrate enone, **57**, gives a comparable adduct (**67**).

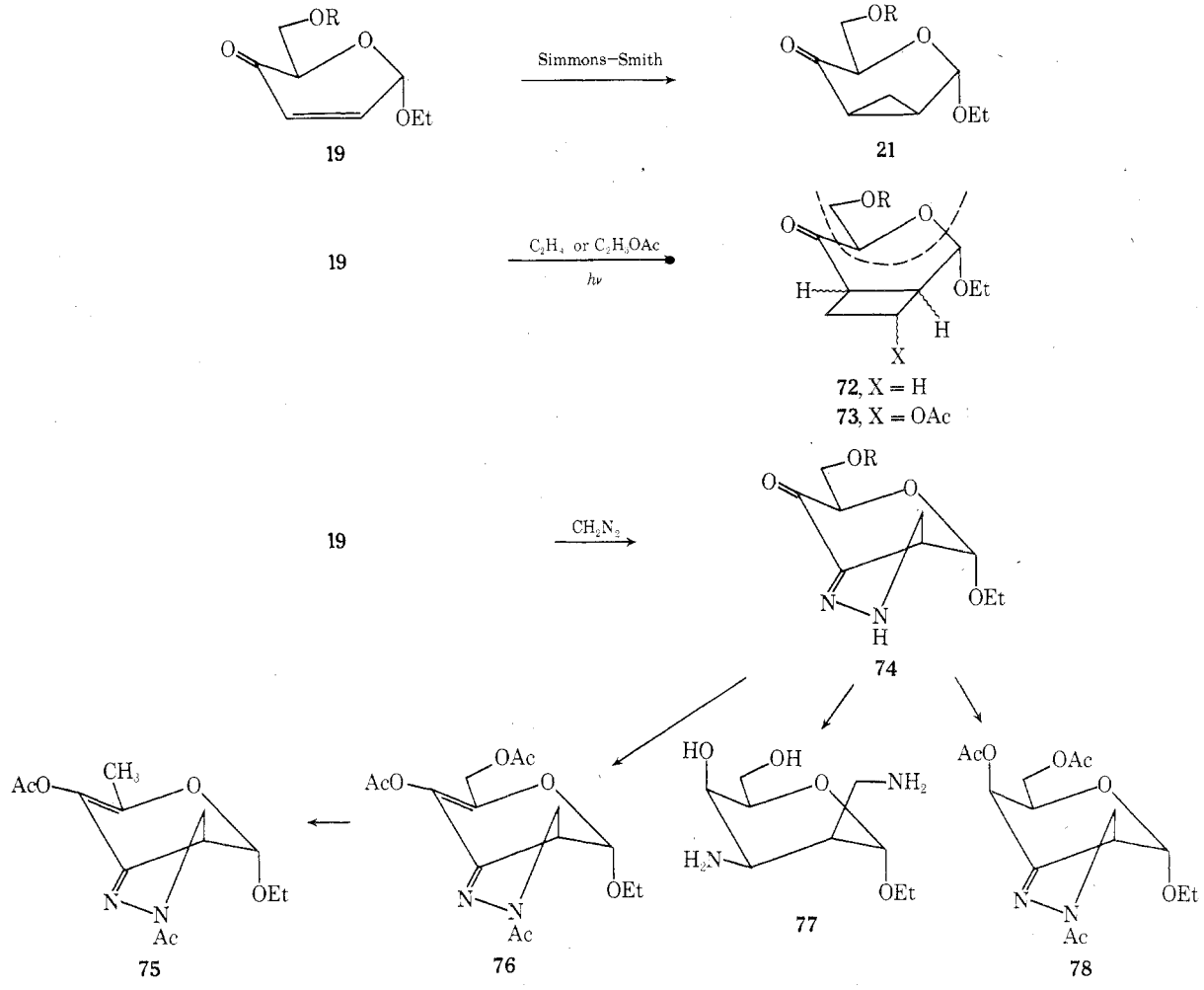
The generally greater reactivity of the carbohydrate enones suggests a role for the ring oxygen. If



19 69 70 71

(67) D. R. Hicks and B. Fraser-Reid, unpublished results.

Chart VII



the zwitterion **69** was an intermediate,[68] the transannular interaction **70** is a concept for which ample precedents exist in carbohydrate reactions.[69] In keeping with these, nucleophilic capture by **70** should be accompanied by ring contraction, giving **71**. However, **71** could not be isolated, not surprisingly, since, being an acetal, it might either add to **19** (Chart VI) or undergo photodecomposition.[70] The reason for the greater reactivity of the carbohydrate enones is therefore still undisclosed.

Cycloadditions. Cycloaddition to these enones suggests itself as an alternative method for modifying the sugar ring, and the examples shown in Chart VII need no comment since they are standard reactions. However, the cycloadducts do have particular appeal in that they present an intensive assembly of functional groups amenable to careful and selective manipulation. Compound **73** for example has (blocked) primary and secondary hydroxyl groups, a ketone, and a masked aldehyde, all four of which can be exploited separately.

Some of these selective exploitations have already been applied to adduct **74** which has furnished the novel dinitrogen compounds **75**–**78**[71] (Chart VII). From a pharmacological standpoint, compounds **74**–**78** are of interest because many antibiotics contain a branched-chain sugar and a nitrogen-containing moiety, both of which are united in this series. Interestingly, compound **76** was in fact found to be a mild antithrombotic agent. The absence of activity in any other member of the series marks this observation as a hapless coincidence or an intriguing structure–activity problem—depending on one's outlook.

Stereochemical considerations reveal added capabilities possessed by these cycloadducts (Chart VII) which are ultimately attributable to the enantiomeric purity of these D sugars. Thus cycloaddition gives either stereochemically pure products, e.g., **21** and **74** or, at the very worst, a mixture of two compounds, e.g., **72** and **73** (ignoring the orientation of X), having the cis-fused ring either "up" or "down". These are diastereomers and therefore should be amenable to simple chromatographic fractionation and their structure, as "up" or "down", should be readily determined by simple ^1H NMR and, if necessary, ^{13}C NMR studies. If these diastereomers are now processed separately and identically, with destruction of the carbohydrate moiety (e.g., by scission along the dotted line in **72**), the resulting products will be *d* and *l* enantiomers. Thus the carbohydrate backbone would have served as a resolving agent, the resolution being a built-in, rather than an extraneous, fea-

(68) For a discussion of this and other possibilities see P. J. Kropp, *Org. Photochem.*, **1**, 1 1967, especially p 67.

(69) R. U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, **42**, 547 1964; B. C. Bera, A. B. Foster, and M. Stacey, *J. Chem. Soc.*, 4531 (1956).

(70) D. Elad and R. D. Youssefyeh, *Tetrahedron Lett.*, 2189 (1963).

(71) R. M. Srivastava, B. J. Carthy, and B. Fraser-Reid, *Tetrahedron Lett.*, 2175, (1974).

ture of the synthesis. In a sense **72** may therefore be termed a "pro-racemic" mixture.[72]

As a bonus to the foregoing, the absolute stereochemistry of each enantiomer will be known a priori from the stereochemistry of the corresponding progenitorial diastereomer as previously determined by the NMR data. X-Ray analysis will therefore be unnecessary.

Case studies designed to explore, among other things, the utility of such "pro-racemic" mixtures for the realization of asymmetric syntheses are under way in the author's laboratory.

Epilog

The transformations described in this Account originate with 2,3-unsaturated hexopyranosides. A subsequent Account might very well focus on different progenitors, since 1,2, 3,4, or 5,6 unsaturation is readily introduced into pyranosides, and the related unsaturated furanosides are growing rapidly.

Although designed primarily as intermediates in the synthesis of modified saccharides, these molecules are often so accessible and so interestingly functionalized that they ought to find additional outlets. Heretofore, sugars have found employment in spectroscopic and, to a lesser extent, mechanistic studies. But by and large, synthetic organic chemistry has remained in splendid isolation from sugars. It is probably for the achievement of asymmetric syntheses that their application augurs best.

However this is virtually virgin territory, and while a prospector or two would be welcome, the urge for self-preservation prays against the eventuality of a sugar-rush.

During 8 years at Waterloo, I have been privileged to receive counsel and guidance in the development of a viable research program from a total of 12 young men. Their skill and ingenuity have been boundless, and their dedication well beyond the call of duty. A special tribute is due to my first Ph.D. collaborator, Dr. Bruno Radatus, who, in those early, uncertain days, refused to let me take an easier, softer path. The pattern he set was continued by Drs. Neville Holder and Steve Tam, and my present graduate students Bob Anderson, Dave Hicks, Dave Iley, Dave Walker, and Mark Yunker continue to be a source of inspiration to me. I am deeply grateful to them all. Generous financial assistance has been received from the National Research Council of Canada, Bristol Laboratories (Syracuse), and the University of Waterloo.

(72) Strictly speaking, **72** would be a "pro-racemic" mixture only if both diastereomers were present in equal amounts. However to our knowledge, there is no word to describe an unequal mixture of enantiomers, and we do not have the classical background to invent one. We have therefore chosen to define as "pro-racemic" that unique mixture (equal or unequal) of two diastereomers which, if separated and processed along identical lines, leads to both enantiomers of a given molecule.

Biosynthesis of Uroporphyrinogens from Porphobilinogen. Mechanism and Nature of the Process

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Porphyrin derivatives play an important part in the biochemistry of all living systems. The sole mention of heme, the chlorophylls, the cytochromes, vitamin B12, and the prosthetic groups of many hemoproteins is sufficient to show the deep involvement of porphyrins in all types of metabolic phenomena.

Porphyrin metabolism is schematically depicted in Figure 1. The polymerization reactions proceed until uroporphyrinogens are formed. Glycine and succinyl-CoA condense to form δ-aminolevulinic acid. The condensation of two units of δ-aminolevulinic acid forms porphobilinogen, and the polymerization of four units of porphobilinogen forms uroporphyrinogens.

Uroporphyrinogen III undergoes a series of structural modifications to afford all the natural porphyrin derivatives[1] and very likely also cobyrinic acid.[2] In higher plants δ-aminolevulinic acid possibly originates via a different pathway.

The superb experimental work of Shemin and his group with the then newly discovered ^{14}C, the contributions of Neuberger, Eriksen, Rimington, Granick, and their associates, as well as the efforts of many other outstanding workers, put the biosynthesis of porphyrins on a firm basis.[3] It was recognized that the polymerization of porphobilinogen (1) affords re-

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Rosalia B. Frydman was born in Poland in 1938, migrated to Argentina in 1947, and in 1962 completed doctoral work at the University of Buenos Aires under C. E. Cardini, working on starch biosynthesis. After postdoctoral work at Berkeley with the late W. Z. Hassid and in Buenos Aires with L. F. Leloir, she joined the faculty of the School of Pharmacy and Biochemistry where she is now Associate Professor. Her research is primarily in enzymology, with special attention to pyrrole metabolism.

(1) J. Lascelles, "Tetrapyrrole Biosynthesis and Its Regulation", W. A. Benjamin, New York, N.Y., 1964, p 38 ff; B. F. Burnham in "Metabolic Pathways", Vol. III. D. M. Greenberg, Ed., 3rd ed, Academic Press, New York, N.Y., 1969, p 403; L. Bogorad in "The Chlorophylls", L. P. Vernon and G. R. Seely, Ed., Academic Press, New York, N.Y., 1966, p 481.

(2) A. Ian Scott, B. Iagen, and E. Lee, *J. Am. Chem. Soc.*, **95**, 5761 (1973), and references therein.