Some Progeny of 2,3-Unsaturated Sugars—They Little Resemble Grandfather Glucose: Ten Years Later

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It is hard to believe that 10 years have elapsed since I made observations such as "there is a growing willingness for 'organic chemists' to come into contact with sugars voluntarily"; or "many modified sugars—could be used with advantage in synthesis—were their existence widely known"; or "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] [Dr. Suess, "Green Eggs and Ham", Beginner Books, Random House, 1960]."

The pace and character of the changes have been mind boggling. Mainstream organic students who had not entered puberty in 1975 now know more about the anomeric effect than me. Carbohydrate-related papers at national meetings are so numerous and diffuse that it is impossible to catch them all. This ferment, however, is not universally acclaimed, because, not surprisingly, there is frequent, if unwitting, disregard for the "old" carbohydrate literature. And a respected German chemist recently introduced the author as "a former carbohydrate chemist".

Nevertheless, these ten years have been rewarding for our laboratory, and 2,3-unsaturated sugars have continued to serve us well. In this Account, we describe some of these developments.

Some Recent Chemistry of 2,3-Unsaturated Sugars

At the outset it is appropriate to survey some aspects of the chemistry of the 2,3-unsaturated sugars that have a bearing upon the syntheses to be discussed.

The Ferrier rearrangement[2] (Scheme Ia) continues to be the fountainhead of most of our needs, and the fact that triacetyl glucal,[3] **1**, can now be purchased adds even more to its attractiveness. In the initial version,[2] the delocalized allyloxocarbenium ion, **2**, was trapped with an alcohol; ethanol is our favorite, simply because the α-D product **3a** crystallizes readily from the crude reaction mixture. In the course of our synthetic studies, we have quenched the ion **2** with triethylsilane to give **5** and with a variety of enol silanes to give, for example, **6a**.[4] The concurrent studies of Grynkiewicz and BeMiller with enol acetates, to give **6b** for example,[5] were also timely developments.

The structure of the major anomers of *C*-glycosides such as **6** follows independently from comparison of their ^{13}C NMR data with those of their cis (or β-D) counterparts.[6] However, independent proof comes from the Eschenmoser–Claisen rearrangement[7] on the axial alcohol **7** which must necessarily give the α-D amide **6c**.[8]

An alternative chemical proof, summarized in Scheme Ic, is significant because it launched us into a major synthetic venture on the trichothecanes (vide infra). Chain elongation of carbohydrates via Wittig type rearrangements had been pioneered by Zhdanov,[9] with significant subsequent contributions by Moffatt[10] and Hanessian.[11] Ring closure of **8** seemed to give only one product on the basis of TLC evidence;[4] however, our carbohydrate training prompted us to consult a more discriminating, but sadly neglected monitor, viz., optical rotation. Interestingly, we found that after 1 h the optical rotation was a maximum and a 1:1 mixture of **9** and **10** existed. Equilibrium, attained after 7 h, gave **9** exclusively, and it is presumed that the oxyanion **11** is an intermediate in that process[4].

Proof of the structure of **10** followed from the ready formation of lactone **12** and from comparison with **6d** prepared from the aforementioned Claisen rearrangement product **6c**.

Finally, the advent of pyridinium chlorochromate,[12] was propitious since this reagent oxidizes diols such as **3b** selectively to **4a**, thereby dispensing with the need for previously used magnanese dioxide, which was effective only if homemade and used in extremely dilute solutions.[13]

Some Simple Pyranoid Systems

A connection between insect pheromones and Masamune's landmark synthesis of methymycin[14] would seem tenuous except for the fact that α-multristriatin,[15] **15**, and Prelog–Djerassi lactone, **20**, may both be viewed as 2,4-dideoxy-di-*C*-methylhexopyranoses. The methyl groups are diequatorial in both since the molecules are in the $^4C_1$ and $^1C_4$ conformations,[16] respectively. The

To the data "ten years ago" must be added the southward trek from Canada toward the author's native land, Jamaica. He left Waterloo in 1980 for Maryland and in 1983 moved to Duke where he is currently James B. Duke Professor of Chemistry. Further movement away from the snow will depend on whether an institution is able to provide access to a pipe organ more magnificent than Duke's Flentrop.

(1) Fraser-Reid, B. *Acc. Chem. Res.* **1975**, *8*, 192.
(2) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, *570*, 575.
(3) For the purists: 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol.
(4) Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522.
(5) Grynkiewicz, G.; BeMiller, J. N. *J. Carbohydr. Res.* **1982**, *1*, 121.
(6) Achmatowicz, O.; Burkowski, P. *Rocz. Chem.* **1973**, *47*, 99.
(7) Wick, A. E.; Feliex, D.; Steen, K.; Eschenmoser, A. *Helv. Chim Acta* **1964**, *47*, 2425.
(8) Tulshian, D. B.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 518.
(9) Zhdanov, Y. A.; Alexeev, Y. E.; Alexeeva, V. G. *Adv. Carbohydr. Chem. Biochem.* **1972**, *27*, 227.
(10) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Madox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.
(11) Hanessian, S.; Ogawa, T.; Guindon, Y. *Carbohydr. Res.* **1974**, *38*, C-12.
(12) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(13) Fraser-Reid, B.; McLean, A.; Usherwood, E. W.; Yunker, M. B. *Can. J. Chem.* **1970**, *48*, 2877.
(14) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *Ibid.* **1975**, *97*, 3513.
(15) Gore, W. E.; Pearce, G. T.; Silverstein, R. M. *J. Org. Chem.* **1976**, *41*, 2979.
(16) Schwarz, J. C. P. *J. Chem. Soc., Chem. Commun.* **1973**, 505.

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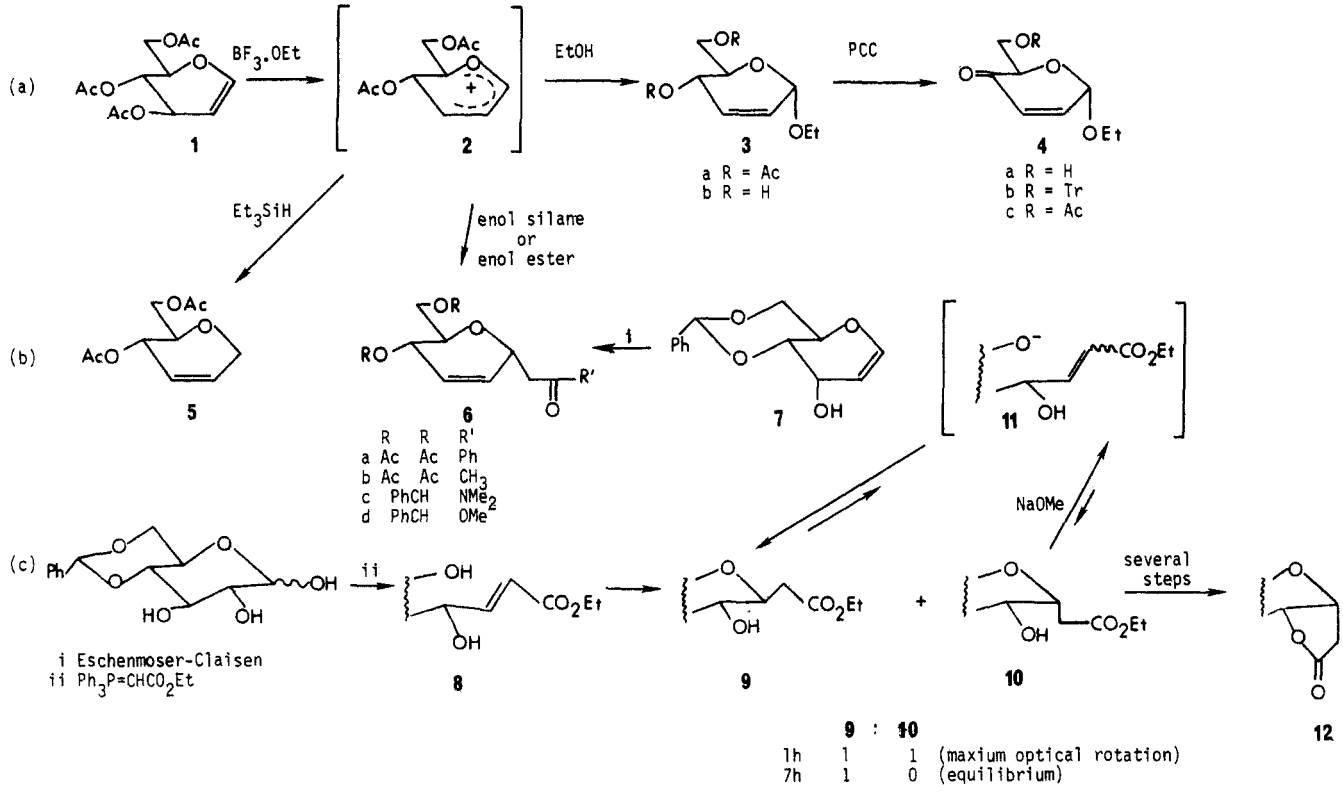
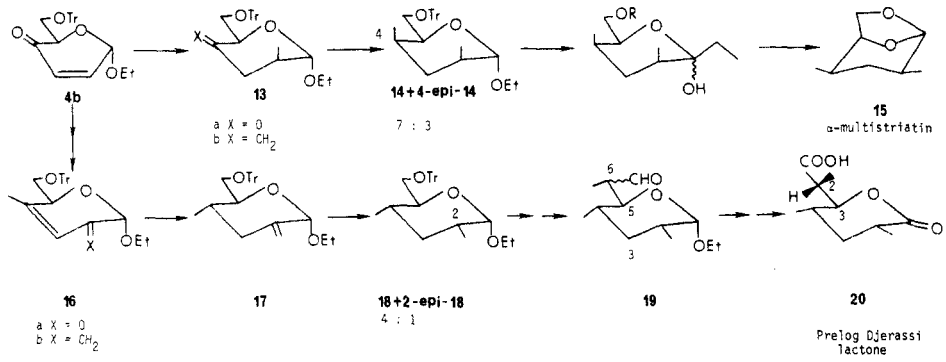
Scheme I



Scheme II



challenge for us was to synthesize both **15**[17] and **20**[18] from the same precursor, and for this objective the α-enone **4b** was a promising candidate (Scheme II). With respect to the α-multistriatin precursor **14**, the axial C2 methyl group was obtained exclusively in **13a** by cuprate addition.[19] High selectivity had been hoped for in the hydrogenation of the exocyclic methylene group in **13b**. However, the best that we could achieve was a 7:3 mixture of **14** and its 4-epimer.

For the diastereomeric diequatorial isomer **18**, enone **4b** was transformed into the 3,4-unsaturated analogue **16a** by addition of methyllithium to give a mixture of tertiary allylic alcohols, followed by oxidative rearrangement. Hydrogenation of the derived diene **16b** led to a 4:1 mixture of **18** and its 2-epimer. Studies in which **17** was prepared independently suggest that the endocyclic double bond was reduced first, and with complete stereoselectivity.[17]

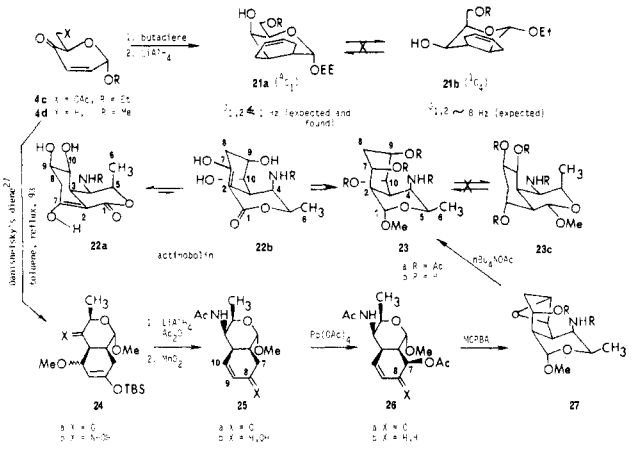
The remaining steps leading to Prelog–Djerassi lactone in Scheme II were less satisfying. Thus, not only was the stereoselectivity at C6 of **19** poor (2:1), but also the structure of the desired epimer could not be assigned unequivocally (as had been the case with **14** and **18**). We will return to this problem of on vs. off template stereocontrol and structure proof later in this Account, but in relation to Prelog–Djerassi lactone, it may be noted that both Ireland[20] and Isobe[21] have designed innovative procedures for creating the off-template (C2) stereocenter of **20** in a controlled, predictable manner.

Annulated Pyranosides—Actinobolin

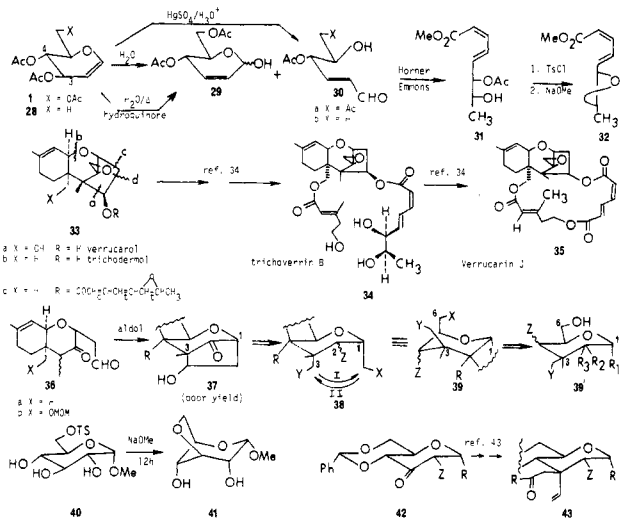
A cynical referee in evaluating one of our adventures wondered ruefully whether there ought not to be a rule for the conservation of asymmetry! This indeed is a troubling aspect. In the preparation of enone **4**, for example, three of the four chiral centers of D-glucose,

(17) Fitzsimmons, B. J.; Plaumann, D. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1979**, 3925. See also: Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1978**, *56*, 2700.
(18) Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.* **1981**, *22*, 2533.
(19) Yunker, M. B.; Plaumann, D. E.; Fraser-Reid, B. *Can. J. Chem.* **1977**, *55*, 4002.
(20) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479.
(21) Isobe, M.; Ichikawa, Y.; Goto, T.; *Tetrahedron Lett.* **1981**, *22*, 4287.

Scheme III



Scheme IV



the ultimate precursor, are destroyed and this might very well appear as a waste of chirality. In the Prelog–Djerassi lactone and α-multistriatin syntheses described above, the benefits accruing to the carbohydrate-based approach, if judged solely on the recovery of chirality, would seem to be marginal at best.

However, a more satisfying exercise comes from the observation that **4** gives single Diels–Alder products, the C4 carbonyl of which can be reduced with complete stereoselectivity, e.g., in **21**.[22] Thus, asymmetry at C2, C3, and C4 can be recovered fully, and a more complex structure achieved. This seems a reasonable quid pro quo.

This observation laid the foundation for a synthesis of actinobolin, **22**, summarized in Scheme III. This densely functionalized, notoriously labile molecule resides in conformation **22a** wherein the C9/C10 hydroxyl groups are trans diequatorial.[23] Were the molecule to exist in conformation **22b**, the synthetic challenge would be facilitated since these hydroxyl groups could now be created by trans diaxial opening of an epoxide, for example, **27**. The prospect of locking this precursor in the conformation shown was suggested by the observation that for **21**, $J_{1,2} \approx 1$ Hz; thus the conformer **21b** is not present even to the extent of 5% in the equilibrium population!![22]

On the assumption[24] that the anomeric[25] effect was responsible for the bias favoring **21a** over **21b**, the α-glycoside **23** surfaced as the logical progenitor of actinobolin.[26]

Danishefsky's diene[27] was the obvious choice for providing the highly functionalized carbocyclic moiety of **24a**. However, the acid-catalyzed hydrolyses normally prescribed for unmasking comparable adducts[27] were precluded by the acid-sensitive glycosidic center of **24a**. Fortunately, it was found that lithium aluminum hydride was an excellent reagent for this purpose.[28] Thus oxime **24b** was treated with lithium aluminum hydride, and in situ acylation afforded the α-enone **25a**. The carbocyclic ring was thereby readied for the prospective C9/C10 epoxidation as well as the C7 oxygenation, and the C4 amine had been created concomitantly with complete stereoselectivity.

Subsequent transformations then led to alkene **26b**, from which the required exo epoxide **27** was obtained. Acetolysis now gave a single product, the structure of which was indeed **23a** in view of the NMR parameters $J_{9,10} = 5$ Hz and $J_{1,2} = 1$ Hz. Thus in spite of the heavy freight of axial substituents, those at C4 and C7 actually being in physical contact, the molecule resides entirely in the conformation **23a** where it enjoys the anomeric effect.[24] Not surprisingly, then, the triol **23b** *fails to give an acetonide under conditions that succeed readily in the case of actinobolin itself*, **22a**.

The successful synthesis of actinobolin **22** relied, ultimately, on the fact that the 2,3-unsaturated sugar **4** gave rise to a Diels–Alder progeny, **24**, which was ideally equipped, functionally and topologically, for the predestined transformations.

Bisannulated Pyranosides—Trichothecanes

The macrocyclic trichothecane verrucarin J, **35**, would seem an unlikely target for synthesis from D-glucose, but this was actually undertaken, albeit in a somewhat indirect manner. Our interests had been triggered by the "incomplete macrocycles", for example, trichoverrin B, **34**, and trichodermadiene, **33c**, in which the intricate concatenation of ether–ester–olefin–alcohol functionalities of the macrocycle is disrupted.[29] The painstaking studies of Jarvis and co-workers had established the gross structural features of the macrocyclic components, but not their relative and absolute stereochemistries.

(22) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1983**, *105*, 5874.

(23) Munk, M. E.; Nelson, D. E.; Antosz, F. J.; Harold, D. L., Jr.; Haskell, T. H. *J. Am. Chem. Soc.* **1968**, *90*, 1087. Munk, M. E.; Sodano, C. S.; McLean, R. L.; Haskell, T. H. *Ibid.* **1967**, *89*, 4158. Nelson, D. B.; Munk, M. E. *J. Org. Chem.* **1970**, *35*, 3832.

(24) Whether this assumption is viable is nevertheless debatable. Destabilizing nonbonded interactions in **2a** and more so in **23a** can be estimated to be at least 10 kcal/mol and therefore cannot be offset by the ~1.5-kcal benefit offered by the anomeric effect.

(25) Lemieux, R. U.; Chu, N. J. *Abstr. Pap.—Am. Chem. Soc.* **1958**, *133rd*, 31*N*. Szarek, W. A.; Horton, D. eds. "The Anomeric Effect"; American Chemical Society: Washington, D.C., 1979; *ACS Symp. Ser. No. 87*. Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: New York, 1983.

(26) Rahman, Md A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576.

(27) See, for example: Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1979**, *101*, 7020. Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *Ibid.* **1981**, *103*, 3460.

(28) Fraser-Reid, B.; Rahman, M. A.; Kelly, D. R.; Srivastava, R. M. *J. Org. Chem.* **1984**, *49*, 1836. Rahman, M. A.; Kelly, D. R.; Srivastave, R. M.; Fraser-Reid, B. *Carbohydr. Res.* **1985**, *136*, 91.

(29) Jarvis, B. B.; Pavanasasivam, G.; Holmlund, C. E.; DeSilva, T.; Stahly, G. P.; Mazzola, E. P. *J. Am. Chem. Soc.* **1981**, *103*, 472. Jarvis, B. B.; Midiwo, J. O.; Stahly, G. P.; Pavanasasivam, G.; Mazzola, E. P. *Tetrahedron Lett.* **1980**, 787.

The intellectual connection between the appendages of trichoverrin B, **34**, and 2,3-unsaturated sugars did not require a monumental leap, since in reexamining the hydrolysis of triacetyl glucal **1** (Scheme IV) we had found that a mixture of *pseudo*-glucal, **29**, and the hydroxy aldehyde **30a** had been produced.[30] Formation of the latter could be suppressed by darkness or free radical scavengers;[30] but more pertinent for the task at hand was the contribution of Perlin for obtaining **30a** exclusively via treatment of **1** with mercuric sulfate.[31]

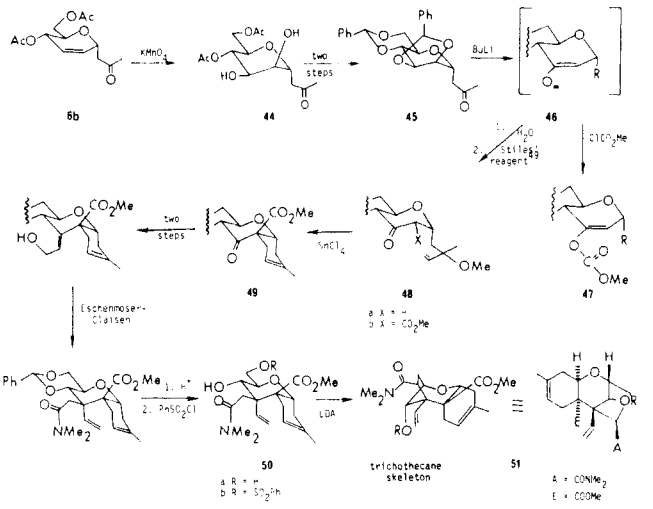
The Perlin procedure was therefore applied to the 6-deoxy glycal **28**, and Peterson olefination of the product **30b**[32] gave a 1:1 mixture of **31** and its *EE* isomer, which though modest, was better than other olefination recipes that were tried.[33] Standard operations on **31** afforded the epoxy ester **32**.

Similar reactions with triacetyl galactal (the 4-epimer of **1**) afforded the *threo* analogue of **31**. The optical rotations of the synthetic erythro and threo compounds were compared with those of Jarvis' samples,[29] and we were thereby able to establish that the natural product had the D-erythro absolute configuration, i.e., **31**.[33] However, the epoxide (see **33c**) was the enantiomer of **32**. Subsequently, **31** was attached to verrucarol, **33a**, paving the way for a synthesis of trichoverrin B, **34**, and thence verrucarin J, **35**, by a novel oxidative ring closure.[34]

The sample of verrucarol used above for our synthesis of trichoverrin B was obtained by deoxygenation of anguidine.[35] Thus, a synthesis of verrucarol is all that stands between us and a claim for a total synthesis of verrucarin J from D-glucose. However, there was a more rational ground for our entry into this phase of trichothecane synthesis. In their seminal, early studies in the field, Colvin and Raphael had designed, as their key step, a ring closure of the keto aldehyde **36a**. The reaction proved to be very troublesome, and an ingenious solution was required to obtain a 10% yield of an aldol product (e.g., **37**) from which trichodermol, **33b**, was then prepared.[36a] However, even this "ingenious solution" failed in the case of the verrucarol precursor **36b**.[36b]

Our attention was caught by the similarity of **36a** to the *C*-glycosides shown in Scheme I. As indicated in Scheme Ic, the α-D-"anomer" **10** is thermodynamically unstable with respect to the β-D from **9**. This easy base-catalyzed $\alpha \rightarrow \beta$ equilibration was undoubtedly responsible for (some of) the problems encountered by Raphael and Colvin.[36,37] These studies therefore suggested that approaches to the trichothecanes, based on a bond "a" disconnection of **33**, were not feasible.[39-41]

Scheme V



Now the mental bridge between Raphael's intermediate **36** and the *C*-glycosides **6** and **10** led, tacitly, to a perspective (**37**) in which the pyran residue of verrucarol is presented in the "usual" $^4C_1$ conformation,[16] the bridging five-membered ring being fused through C1 and C3. That this presentation coincides with the absolute stereochemistry of the natural verrucarol did not escape our notice. As an alternative approach, synthetic studies based on disconnection "c" were attempted,[42] although in this article we will focus only on disconnection of bond "d" which leads to an intermediate such as **38**.

There are two options depending on whether X is a leaving group with Y an EWG (i.e., option I), or vice-versa, (i.e., option II). However, the precursor for the latter option would be, in fact, an α-*C*-glycoside such as **10** which we have shown to be thermodynamically unstable, vis à vis, the corresponding β (equatorial) anomer.

Option II could therefore be rejected out of hand. Option I would require that a one-carbon entity be installed at C1 of the sugar, and this can indeed be done.[8] However, a new channel was opened, arising from the recognition that **38** possesses a local C2 axis of symmetry which makes it equivalent to **39**. The latter perspective has two outstanding advantages. First, the one-carbon nucleofugal center (X) correlates with the primary hydroxyl of D-glucose as apparent in **39'**. Second, prospects for the EWG partner (Y) were equally promising since our studies on the spiro-Claisen rearrangement as a route to geminal alkylation had shown that the (frequently exclusive) product was the isomer (e.g., **43**) bearing the activated side chain in equatorial orientation.[43]

From the procedural standpoint, the question arose about the order for mounting the carbocyclic rings upon the pyranose. Our analysis took note of the fact that the ring closure desired of **39** is reminiscent of the

(30) Fraser-Reid, B.; Radatus, B. K. *J. Am. Chem. Soc.* **1970**, *92*, 5288. Tam, S. Y.-K.; Fraser-Reid, B. *Carbohydr. Res.* **1975**, *45*, 29.

(31) Gonzalez, F.; Lesage, S.; Perlin, A. S. *Carbohydr. Res.* **1975**, *42*, 267.

(32) There is considerable acetyl migration in **30**.

(33) Tulshian, D. B.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474.

(34) Esmond, R.; Fraser-Reid, B.; Jarvis, B. B. *J. Org. Chem.* **1982**, *47*, 3358.

(35) Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron Lett.* **1980**, 4549.

(36) (a) Colvin, E. W.; Malchenko, S.; Ralphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkins Trans. 1* **1973**, 1989. (b) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *Ibid.* **1978**, 658.

(37) For example reduction of **6c** with DIBAL gives the *equatorial* aldehyde,[8] and Horner Emmons reaction of **6c** gives the olefin of the *epimerized* ketone.[38]

(38) Tsang, R. Ph.D. Thesis, Duke University, 1985.

(39) A number of recent trichothecane syntheses[40] have been based on the biomimetic strategy of: Masuoka, E.; Kamikawa, T. *Tetrahedron Lett.* **1976**, 1691.

(40) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. Trost, B. M.; McDougal, P. G. *Ibid.* **1982**, *104*, 6110. Still, W. C.; Tasi, M. Y. *Ibid.* **1980**, *106*, 3654. Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *Ibid.* **1983**, *105*, 4472.

(41) Attempts at Lewis acid catalyzed intramolecular aldols also failed.[42]

(42) Fraser-Reid, B.; Tsang, R. In "Natural Products Chemistry"; Zalewski, R. I., Skolik, J. J., Eds.; Elsevier: Amsterdam, 1985; p 197.

(43) Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347.

formation of 3,6-anhydro sugars, which, as in the case of **40** → **41**, requires fairly forcing conditions.[44] Considerations based on the anomeric effect[25] suggest that the process should be facilitated when the anomeric substituent (e.g., R_1 in **39′**) is carbon rather than a polar group (e.g., OMe in **40**). Logical extension led to the conclusion that the six-membered ring should be installed between C1 and C2 of the pyranose precursor, as the first order of business.

The evolution of the molecular framework of the trichothecane system is summarized in Scheme V,[51] the chemistry of 2,3-unsaturated sugars being recognizable at two key stages. First, and most obvious, is the starting material **6b**[5] whose preparation was described in Scheme I and in which the desired local C_2 axis of symmetry about the pyran ring is already apparent.

For our second major step, we called upon a unique reaction, discovered, developed, and nurtured in the carbohydrate domain. Rodemeyer reported in 1974 that *O*-benzylidene derivatives of pyranosidic vicinal glycols were readily converted into α-methylene ketones by butyllithium.[45] The process was refined and utilized well by Horton and Weckerle,[46] and it is now known that in systems such as **45**, (i) the 1,3-dioxane ring is unaffected and (ii) deprotonation is exclusively at the axial proton of the 1,3-dioxolane moiety, leading, e.g., to the enolate **46**.

Enolate **46** was the second 2,3-unsaturated system to be utilized. It had been hoped to carboxylate C2 directly; however, only the *O*-acyl derivative **47** was obtained.[47,48] However, when enolate **46** was quenched and the resulting ketone (**48a**) subjected to Stiles' carboxylation,[49] the β-ketoester **48b** was obtained in excellent yield.

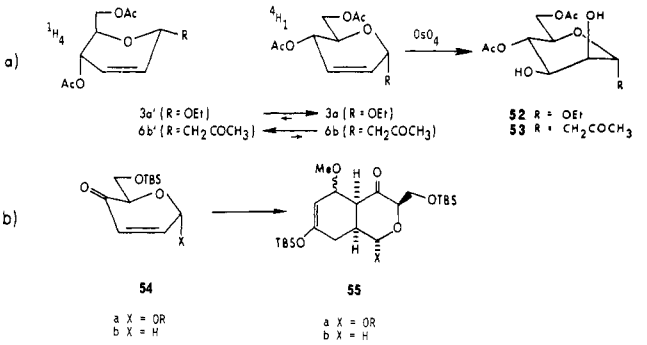
Formation of the cyclohexenyl ring now followed. Cis-ring fusion in **49** is obligatory, and the gratuitous presence of the carbocyclic ester (representing the primary hydroxyl group of verrucarol) and the C-3 carbonyl (the implement for stereocontrolled geminal alkylation[43]) were excellent perquisites.

Unfortunately, utilization of the carbonyl of **49** for the planned geminal alkylation could not be carried out as in our model studies;[43] however, the key intermediate **50** which corresponds to synthon **39**/**39′** (Scheme IV) was realized by retooling, and the bridging five-membered ring was then achieved smoothly. Comparison of the resulting tricycle **51** with verrucarol, **33a**, indicates that some functional group adjustments are required. These are currently underway in our laboratory.

It was stated above that the deconvolution of the dioxolane ring of **45** was "our second major step", a categorization that relegates the preceding hydroxylation of **6b** to lower status. However, had the hydroxylation occurred from the α-face of **6b**, the subsequent Rodemeyer reaction would have led to a 2-keto sugar instead of **48a** (since the axial hydrogen would have been at C2).

This result, favorable though it was, warrants closer scrutiny. *O*-Glycosides exist predominantly in the $^4H_1$ conformation such as **3a**; however, Achmatowicz and

Scheme VI



Burkowski have shown that with *C*-glycosides, $^1H_4$ conformers such as **6b′** predominate,[9] an observation which is in keeping with the fact that the anomeric effect of carbon is less than that of oxygen.[25]

On the basis of steric interactions in the major conformers, hydroxylation should occur from the β-face of **3a** (because of the α-OEt group) but from the α-face of **6b′** (because of the β-acetoxymethyl substituent). That this analysis violates an early postulate of Barton[50a] known more familiarly as the Curtin–Hammet principle[50b] should not detract from the experimental findings that the β-diols **52** and **53** (Scheme VIa) are the only products of hydroxylation of **3a** and **6b**, respectively.

There are other anomalies. Thus the stereochemical course of the Diels–Alder reactions of **4c** and **4d** in Scheme III had been attributed to steric hindrance of the anomeric alkoxyl substituent. However, some recent studies (Scheme VIb) have shown that with or without this α-alkoxyl group, addition still occurs from the β-face exclusively. Thus **54a** and **54b** give exclusively the β-adducts **55a** and **55b**, respectively.

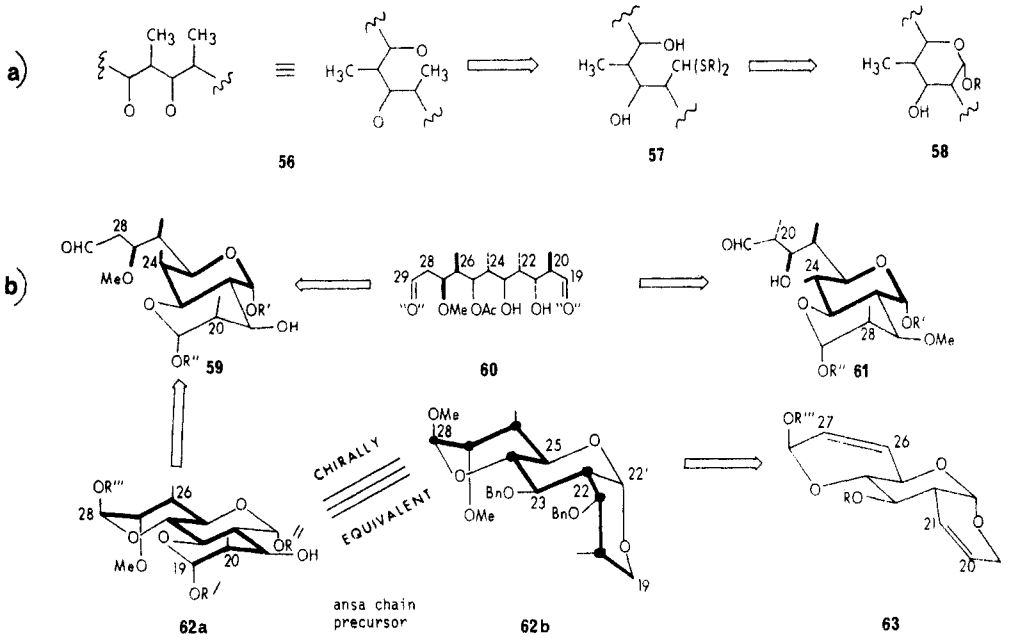
Just as patriotism is the last refuge of a scoundrel,[52] steric hindrance might very well be the last resort of an organic chemist, and in the face of this possibility, it is encouraging to note that help may be at hand. The recent literature contains an interesting blend of theoretical[53] and experimental[54] investigations relating to the effect of an allylic oxygen on the stereochemical outcome of addition to the double bond. In addition our own work has postulated a role for the ring oxygen in some reactions of unsaturated sugars.[55] We are currently trying to see whether these concepts[53–55] can be utilized to account for the apparent anomalies noted above in relation to Scheme VI.

Multiple Contiguous Chiral Centers—Pyranosidic Homologation

These concepts concerning the oxygenation of unsaturated sugars are germane to a new strategy being

(44) Haworth, W. N.; Owen, L. N.; Smith, F. *J. Chem. Soc.* **1941**, 88.
(45) Klemer, A.; Rodemeyer, G. *Chem. Ber.* **1974**, *107*, 2612.
(46) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227.
(47) Tsang, R.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 60. See, however, ref 48.
(48) Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 141.
(49) Finkheimer, H. L.; Stiles, M. *J. Am. Chem. Soc.* **1963**, *85*, 616.
(50) (a) Barton, D. H. R. *Experientia* **1950**, *6*, 316. (b) Seeman, J. *Chem. Rev.* **1983**, *83*, 86.
(51) Tsang, R.; Fraser-Reid, B. *J. Org. Chem.*, in press.
(52) Boswell, J. Esq. "Life of Samuel Johnson Johnson Ll.D."; Barnes and Burr: New York, 1860; p 247.
(53) Caramella, P.; Rondan, N. G.; Paddon-Row, N. M.; Houk, K. E. *J. Am. Chem. Soc.* **1981**, *103*, 2348. Paddon-Row, N. M.; Rondan, N. G.; Houk, K. N. *Ibid.* **1982**, *104*, 7162. Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(54) Cha, J. K.; Christ, W. J.; Kiski, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. Christ, W. J.; Cha, J. K.; Kishi, Y. *Ibid.* **1983**, *24*, 3947. Franck, R. W.; Argade, S.; Subramaniam, C. S.; Frechet, D. M. *Ibid.* **1985**, *26*, 3187. Franck, R. W.; John, T. V.; Olejniczak, K.; Blount, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 1106. McGarvey, G. J.; Williams, J. M. *Ibid.* **1985**, *107*, 1435.
(55) Fraser-Reid, B.; Tsang, R.; Lowe, D. *Chem. Scr.* **1985**, *25*, 117.

Scheme VII



developed in our laboratory for molecules with multiple contiguous chiral centers. The ansa chain of rifamycin[56] which contains eight contiguous chiral centers in an 11-carbon array, **60**, exemplifies the problem. One strategy involving the connection of two sugar-derived subsections follows Hanessian's landmark approach to erythronolide[57] and has been explored by him[58] and Tatsuta.[59]

The strategy being developed by us[60] began by noting that the module **56** which is represented throughout the ansa chain **60** of rifamycin (and indeed, throughout most propionate derived structures) can be equated with a pyranose such as **58** (Scheme VIIa). By invoking the dithioacetal **57**, a type of derivated first prepared by Emil Fisher,[61] and hydrogenolyzed by Wolfrom,[62] we pay homage to our carbohydrate roots!!

There are five 1,4-related CH_3/OH groups in **60**, and therefore five options for the idea expressed in Scheme VIIa. Ground rules for making a rational choice between these various options have been detailed elsewhere,[60] but we discuss here only the bipyranoses which come about by folding from one end to give **59** or from the other to give **61** (Scheme VIIb). Both are plausible synthons but a basis for choosing between them becomes clear when further *pyranosidic homologation* to obtain tripyranoses was contemplated.

For this intriguing prospect to be pursued retrosynthetically, the C24–CH_3 group of each would have to be replaced by an oxygen in order to form the "upper" pyranoside. This oxygen, in the case of **59**, would engage an *achiral* center, i.e., C28, leading to **62a** as shown. On the other hand, with **61** the third ring would have to engage C20—which is a *chiral* center. The outcome is that the tripyranose **62a** possesses a 10-carbon chain (heavy lines) which can accommodate all of the eight chiral centers of rifamycin, whereas the alternative tripyranose (not shown) which could be obtained from **61** would be able to accommodate only seven chiral centers, as a result of having wasted a potentially chiral site by including C28 on the template.

There are several facets of the chemistry of **62** which warrant discussion.[60] For example **62a** and **62b** are chirally equivalent[63] but stereochemically different. Thus whereas the lower ring in the former is *trans*-decalin-like, it is *cis*-decalin-like in the latter.

However, in view of the tenor of this Account, we focus on the relevance of 2,3-unsaturated sugars to this project. The adjacent CH_3 and OH groups on the satellite pyranoside rings of **62** could evidently arise from a 2,3-unsaturated sugar by opening of an epoxide (vide infra). Hence **62b** leads to **63**, which comprises two 2,3-unsaturated sugars. Of course the double bonds would be created and exploited at different stages of the synthesis.

One of our routes to the tripyranose **62b** is summarized is Scheme VIII. The lower 2,3-unsaturated pyranose arises by the intramolecular glycosylation of **64**, which, under the most favorable conditions, gave an 18:1 mixture of **65**α and **65**β.[65] The topological properties of 65β were then exploited twice in succession—first to fix the C20 center in **66** and second to adjust the C21 site in **67**.

Development of the "upper" 2,3-unsaturated pyranose ring was a more eventful exercise. Obviously, ring formation can occur only with a cis double bond; but since trans geometry is easier to secure, a colleague had

(56) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. Iio, H.; Nagaoka, H.; Kishi, Y. *Ibid.* **1980**, *102*, 7965.

(57) Hanessian, S.; Rancourt, G. *Can. J. Chem.* **1977**, *55*, 111. Hanessian, S.; Rancourt, G.; Guidon, Y. *Ibid.* **1978**, *55*, 1843.

(58) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *J. Am. Chem. Soc.* **1982**, *104*, 6164.

(59) Nakata, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749.

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

(61) Fischer, E. *Chem. Ber.* **1894**, *27*, 674.

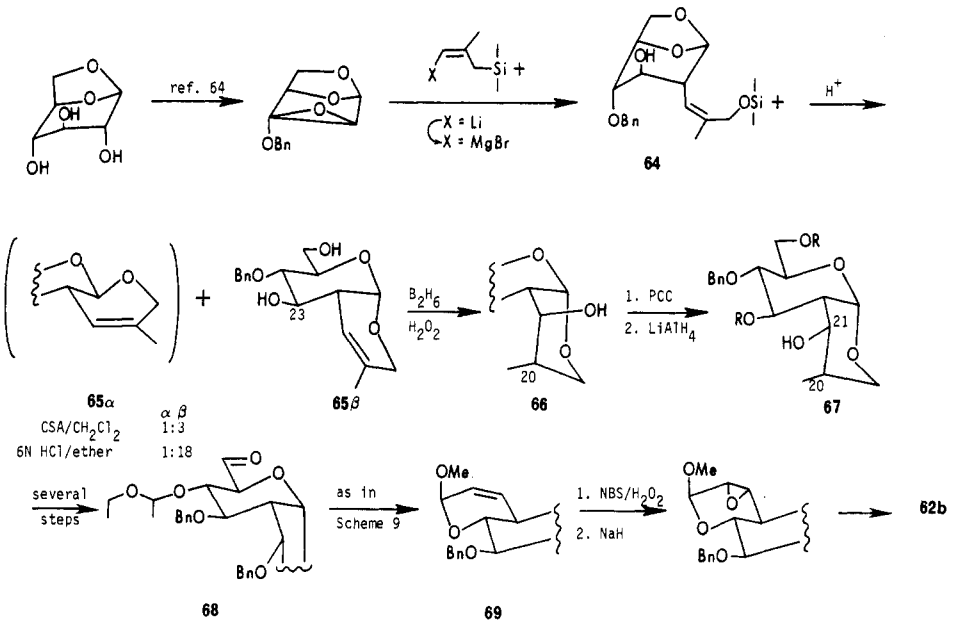
(62) Wolfrom, M. L.; Lemieux, R. U.; Olin, S. M. *J. Am. Chem. Soc.* **1949**, *71*, 2780.

(63) Magdzinski, L.; Cweiber, B.; Fraser-Reid, B. *Tetrahedron Lett.* **1983**, *24*, 5823.

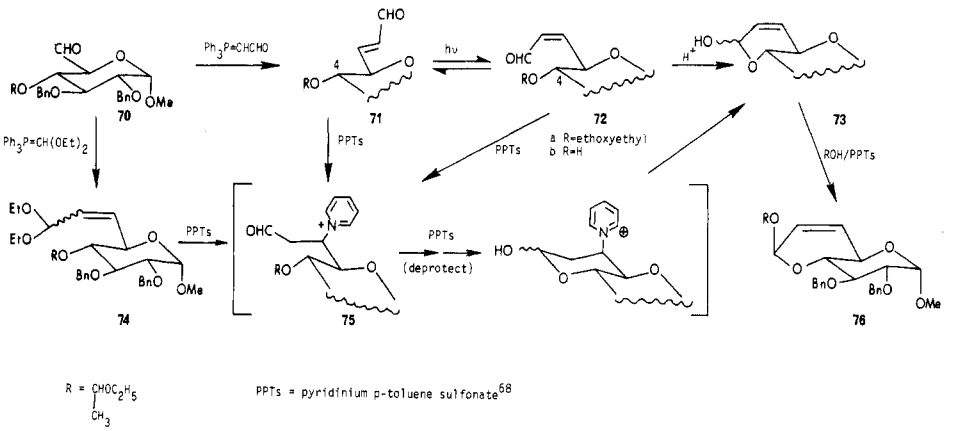
(64) Trnka, T.; Cerny, M. *Collect. Czech. Chem. Commun.* **1971**, *36*, 2216.

(65) The formation of 65α,β is reminiscent of the intramolecular glycosylation carried out by Descotes.[66]

Scheme VIII



Scheme IX



the idea of irradiating the enal **71** in acidic methanol (Scheme IX).[67] In this scenario, four discrete events were projected: (i) olefin isomerization, **71** → **72**, (ii) deprotection of the C_4–OH, **72a** → **72b**, (iii) hemiacetal formation, **72** → **73**, and (iv) glycosylation **73** → **76**—which under the reaction conditions should give the favored axial anomer because of the anomeric effect.[25] Indeed, a 42% yield of **76** was obtained in our first attempt, but it soon became apparent that we had been lucky rather than wise, for on one occasion, after the reaction mixture containing **71** had been allowed to stand around (while waiting for a photoreactor), it was discovered that formation of **76** had progressed equally well in the dark!![66]

Subsequent experimentation with various "acids" made it clear that the use of pyridinium *p*-toluenesulfonate[68] was essential. These data could now be rationalized by the intermediacy of the conjugate addition product **75**, in which case the geometry of the double bond in the 2,3-unsaturated sugar precursor would be irrelevant! Accordingly, aldehyde **70** was treated with the Bestman reagent,[69] and the resulting cis/trans mixture **74** was subjected to the solvolysis conditions. The 2,3-unsaturated pyranoside **76** was indeed obtained in 70–80% yield, *usually as a single anomer*.[60] The foregoing technique was successfully applied to the bipyranose **68** (Scheme VIII) to give **69**, and the target molecule **62b** was then obtained routinely.[60]

There is, in a sense, a common denominator to the strategies for the actinobolin, trichothecane, and ansa targets (Schemes III, V, and VIII, respectively). In all cases, a pyranoid ring provides a stanchion while the peripheral rings are manipulated, with stereocontrolled and easily verifiable precision. In **62b** (Scheme VII), for example, all highlighted centers have been introduced with complete stereoselectivity, and the structure can be assigned by routine study of its 200-MHz ^{1}H NMR spectrum.[63]

Success in these ventures depends on exploitation of the unique features of the pyranoid core, and once the process has been completed, the ring may be destroyed (e.g., **58** → **57**, Scheme VIIa) or lose its integrity (e.g., **23** → **22**, Scheme III). The chemistry of 2,3-unsaturated sugars plays a critical role at least once in each syn-

(66) Descotes, G.; Lissac, M.; Delmau, J.; Duplan, J. *C. R. Acad. Sci. Ser C* **1968**, *267*, 1240.
(67) Molino, B. F.; Magdzinski, L.; Fraser-Reid, B. *Tetrahedron Lett.* **1983**, *24*, 5819.
(68) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(69) Bestmann, H. J.; Roth, K.; Ettlinger, M. *Chem. Ber.* **1982**, *115*, *161*; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 687.

thesis, and this means, in effect, that at least two sites on the pyranoid ring must lose their asymmetry. But in Schemes III, V, and VIII, the recovery of chirality has been excellent if not quantitative, and a much more complex target has been realized. Thus, in our view, the exercise has been justified.

The author's good fortune, already extolled 10 years ago,[1] in attracting a small coterie of inspired collaborators happily continues. The bibliography is in a sense unjust, for it cites only those into whose hands the daily chores have fallen. They, as the author, have benefitted immensely from critical intellectual input from many colleagues. To them all, cited and uncited, the author is grateful, not only for their wise counsel and encouragement, but for their buoyant camaraderie. Financial support from a number of sources is gratefully acknowledged: The National Research Council of Canada, National Institutes of Health (GM 32569 and AI 20117), the National Science Foundation (CHE-83-04283), the donors of the Petroleum Research Fund, administered by the American Chemical Society, Merck, Sharp and Dohme, Burroughs Wellcome, Ciba-Geigy, the University of Maryland, and Duke University.