The Chemistry of Hexenuloses

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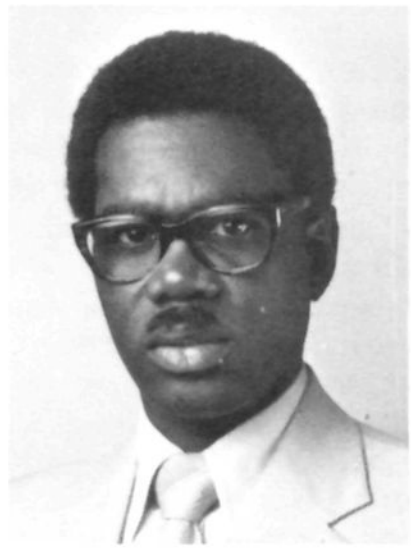
Contents



Neville L. Holder was born in Barbados, West Indies, where he received his elementary and high school education. In 1965, he graduated with a B.Sc. (Gen) Hons. degree from the University of the West Indies and in 1968 was awarded his M.Sc. degree. He obtained his Ph.D. in 1972 from the University of Waterloo for his work on α,β-unsaturated keto sugars with Professor B. O. Fraser-Reid. He was a Research Chemist at the Gillette Research Institute, Rockville, Maryland prior to joining the Process Chemistry Department, Pre-Clinical Research and Development at Smith Kline and French Laboratories, where he is currently an Associate Senior Investigator. His research interests include process research and development of ethical pharmaceuticals, isolation and structure elucidation of organic compounds, and synthesis and photochemistry of α,β-unsaturated keto sugars. He is a member of AAAS, ACS, Royal Institute/Chemical Society and the New York Academy of Science.

I. Introduction

Hexenuloses have played a major role in carbohydrate research and are some of the most attractive molecules for synthetic manipulations. Past trends emphasized the use of pyranosuloses as starting materials in the syntheses of rare sugars,[1] antibiotic sugars,[2] and branched-chain sugars.[3] However, recent efforts focused on the incorporation of conjugated ketonic and olefinic functionalities in carbohydrate molecules. The tremendous flexibility offered by the α,β-unsaturated-keto chromophore in its chemical reactions[4–8] provides an almost unique opportunity in devising new synthetic routes to aminodeoxy and branched-chain sugars. The novel sugars isolated from natural sources[9–13] over the past 20 years have provided carbohydrate chemists with new and challenging problems of structural determination and synthesis.

Generally, two approaches have been applied to the syntheses of modified sugars. One of them uses fairly simple noncarbohydrate precursors as starting materials,[14] whereas the other involves transformations of carbohydrate precursors.[15,16] The potential complexity of synthetic transformations on carbohydrate precursors had deterred many chemists from exploiting the attributes which these precursors possess. With advances in spectroscopic and chromatographic techniques and emergence of many gentle reagents, chemists have approached such tasks with greater confidence. Recently, there has been an increase in the use of carbohydrates as chiral synthons in asymmetric synthesis of natural products.[17]

The α,β-unsaturated-keto chromophore is arranged in a number of ways: (a) in the form of a hex-2-enopyranosid-4-ulose (**1**, R = OH, *O*-acyl, *O*-trityl, or H; R^1 = CH_3 or C_2H_5; R^2 = H or CH_3; R^3 = CH_3 or H), (b) as a hex-3-enopyranosidulose (**2**, R = H, OH, *O*-acyl, or *O*-trityl), (c) as a 1,5-anhydro-2-deoxyhex-1-en-3-ulose (**3**, R = H, acyl, trityl; R^1 = H or acyl), or (d) as

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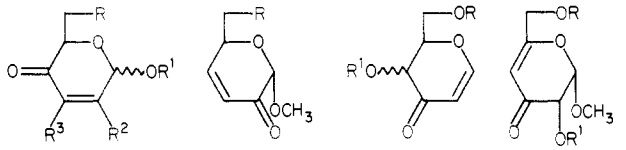
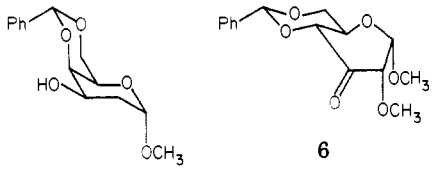
a hex-4-enopyranosid-3-ulose (4, R = H or trityl; R^1 = H or acyl). Classes 3 and 4 are vinylogous ethers, and



1 2 3 4

may also be considered as dihydro-γ-pyrones. On the other hand, 1 and 2 are 3,6-dihydro-2*H*-pyran-3-ones.

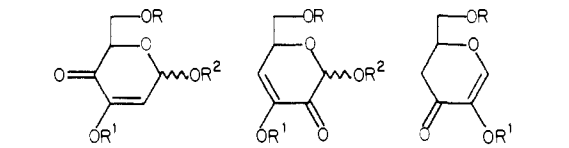
Compounds of class 1 have been utilized most frequently, and the α,β-unsaturated-keto chromophore has been incorporated either by synthetic transformations on simple carbohydrate precursors[15,16] or through molecular rearrangements of simple noncarbohydrate precursors.[18] Hex-3-enopyranosiduloses (2) were reviewed in 1964 by Anet[19] and are theoretically derived from 3-deoxyhexosuloses by loss of water. These hexosuloses have been isolated as intermediates in the conversion of sugars by alkali to metasaccharinic acids[20] and as a 2,4-dinitrophenylosazone in the formation of 5-(hydroxymethyl)-2-furaldehyde under acidic conditions.[21,22] The first synthesis of 1,5-anhydro-2-deoxyhex-1-en-3-uloses 3 was reported by Heyns and Gottschalck[23] and later developed by Tronchet and co-workers.[24] Collins and associates[25-27] obtained the 1,5-anhydro-4,6-*O*-benzylidene-2-deoxyhex-1-en-3-uloses (3, R + R^1 = PhCH) by oxidation of the methyl 2-deoxy-α-D-*lyxo*-hexopyranoside 5[25] and photolysis of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-hexopyranosid-3-ulose 6.[26,27] To date, there is only one



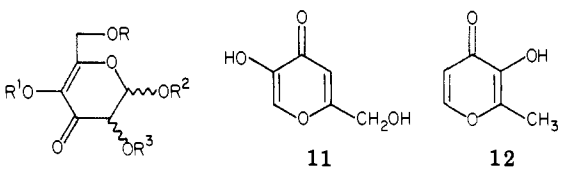
5 6

reported[28] synthesis of hex-4-enopyranosid-3-ulose 4.

Another class of pyranoid sugars containing the α,β-unsaturated-keto chromophore is the enolones (7–10).



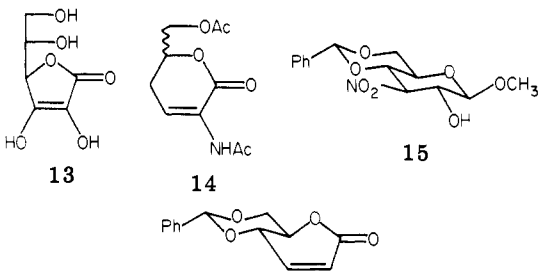
7 8 9



10 11 12

The enolones 7 and 8 have been postulated[29,30] as intermediates in the formation of γ-pyrones from hexose derivatives. In 1978, Lichtenthaler reviewed[31] the chemistry of enolones with emphasis on the synthesis, reactions, and formation of the γ-pyrone system as found in kojic acid (11)[32] and maltol (12).[33]

Ascorbic acid (13) contains another arrangement of the α,β-unsaturated-keto chromophore as an unsaturated furanolactone in which both of the olefinic protons are hydroxylated. Crawford and Crawford[34] recently reviewed synthetic procedures for L-ascorbic acid from readily accessible sugar precursors. Other sugar molecules containing the unsaturated lactone are the hex-2-enono-1,5-lactones. Bergmann and co-workers[35] described the synthesis of 14, while Baer and Rank[36] reported that treatment of the nitro compound 15 with basic aluminum oxide in boiling toluene furnished 4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (16). Zamojski and co-workers[37] described a general synthesis of 2,3-dideoxyhex-2-enono-1,5-lactones from alkyl 2,3-dideoxyhex-2-enopyranosides.



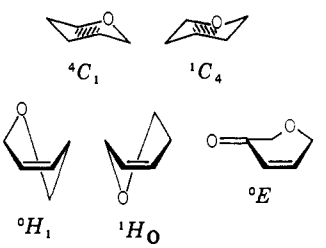
13 14 15 16

II. Scope and Limitations

Some aspects of keto[38] and olefinic[39,40] sugars were reviewed. Except for the review of 3-deoxyglycosuloses,[19] a summary of the work reported by Fraser-Reid and his associates,[40] and annual reports by The Chemical Society,[41] there is no review that discusses the chemistry of hexenuloses. The objective of this article is to document the synthetic methods, give an account of the variety of the chemical reactions of hexenuloses 1, 2, and 3, demonstrate their synthetic potential as educts in asymmetric syntheses, and review the biological activities they have shown in in vitro and in vivo screening studies. Since a number of excellent articles have appeared that reviewed various aspects of enolones[31] and kojic[32] and ascorbic[34] acids, these topics and the chemistry of the hex-2-enono-1,5-lactones will not be treated here.

III. Nomenclature

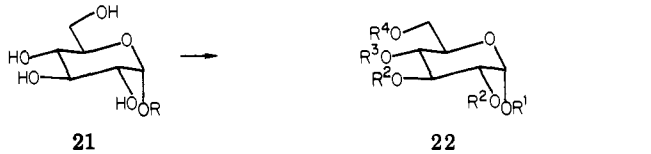
Hexenuloses are also commonly referred to as α,β-unsaturated-keto sugars or carbohydrate enones. Although these latter terms are less specific, they will be used interchangeably with hexenuloses in this review. The nomenclature system used in this review will follow the revised "Rules of Carbohydrate Nomenclature".[42] The convention used in denoting the conformations of the pyranoid compounds is in accord with the rules enunciated by Stoddart.[43] Conformations are designated *C* for chair, *H* for half-chair, and *E* for envelope.



$^4C_1$ $^1C_4$ $^0H_1$ $^1H_0$ ^0E

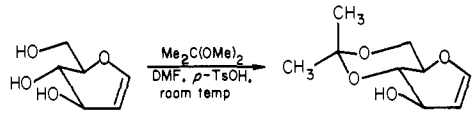
The names of compounds 17 to 20 serve to illustrate some of the principles of carbohydrate nomenclature.

SCHEME I



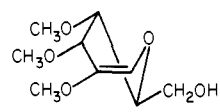
21 22

R	R^1	R^2	$R^3 + R^4$	ref
H or CH_3	H or CH_3	H		52, 53
CH_3	CH_3	H		54-56, 64
CH_3	CH_3	H		57-65
CH_3	CH_3	Ac		66, 67

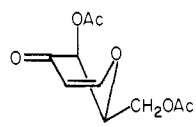


25 26

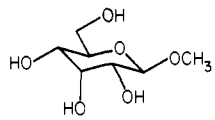
Compounds 17, 18, and 19 are drawn in the $^4H_5$, E_5, and $^4C_1$ conformations respectively.



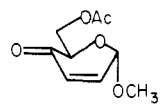
17
1,5-anhydro-2,3,4-tri-*O*-methyl-D-*arabino*-hex-1-enitol



18
1,5-anhydro-4,6-di-*O*-acetyl-2-deoxy-D-*threo*-hex-1-en-3-ulose

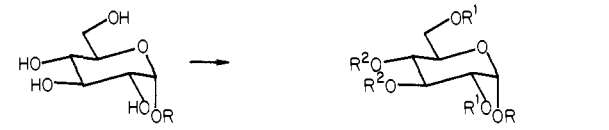


19
methyl β-D-allopyranoside



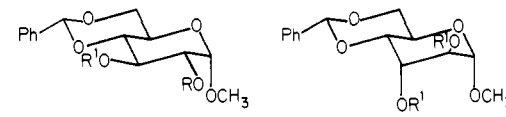
20
methyl 6-*O*-acetyl-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose

SCHEME II



21 27

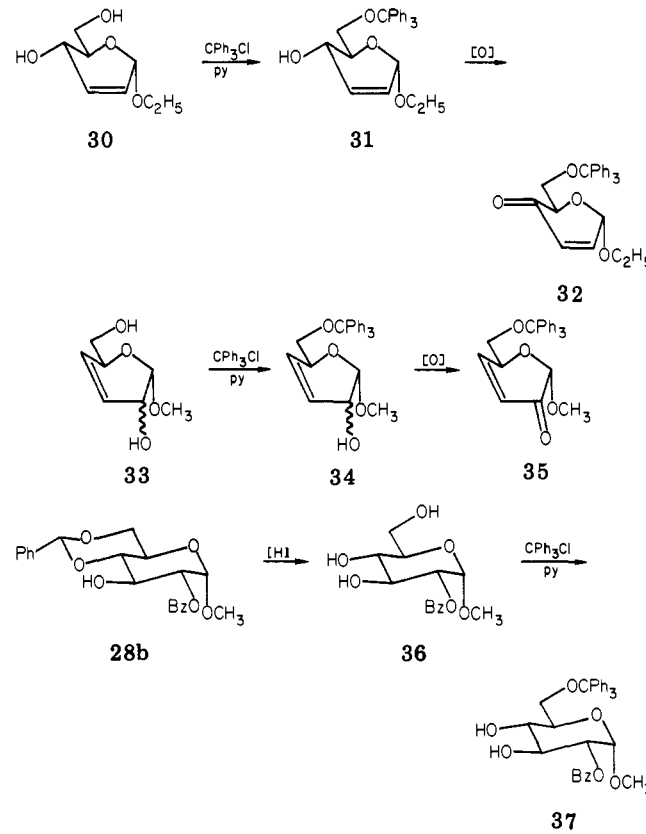
R	R	R^1	R^2	ref
H	Ac	Ac	Ac	69
CH_3	CH_3	Bz	H	63, 70, 71



28 29

	R	R^1	ref
28a	H	H	
28b	Bz	H	72-79
29a	H	H	
29b	Bz	H or Bz	72-75, 78

SCHEME III



30 31 32 33 34 35 28b 36 37

IV. Syntheses of Hexenuloses

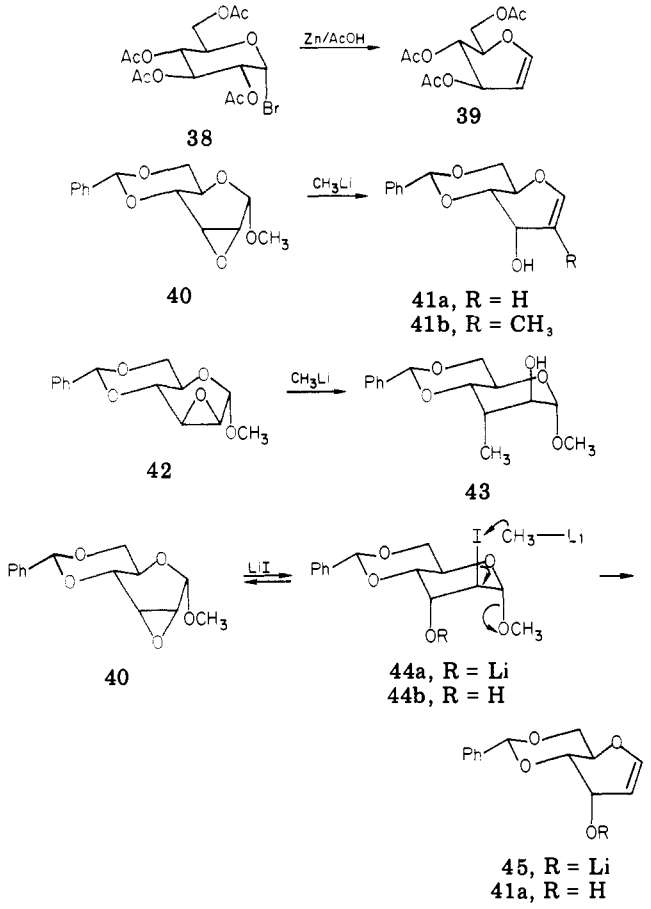
A. General Methods

One general method for incorporating the α,β-unsaturated-keto chromophore, which was first developed by Fraser-Reid and his co-workers,[15,16] has as its final step the oxidation of an allylic alcohol. First the glycoside is functionalized with either a monofunctional (acetate or benzoate) or difunctional (benzylidene) protecting group.[44,45] The free vicinal diols are then converted into the olefin by way of sulfonyloxy groups.[46] Another method leading to hex-2-enopyranosid-4-uloses is treating 2-furylcarbinols with bromine in methanol. The resulting 2,5-dimethoxy-2,5-dihydrofuran derivatives are then treated with mild acid. This method was first published by Achmatowicz and co-workers[18,47] and later by Shono and Matsumura,[48] Torii and his colleagues,[49] and Week and his associates.[50]

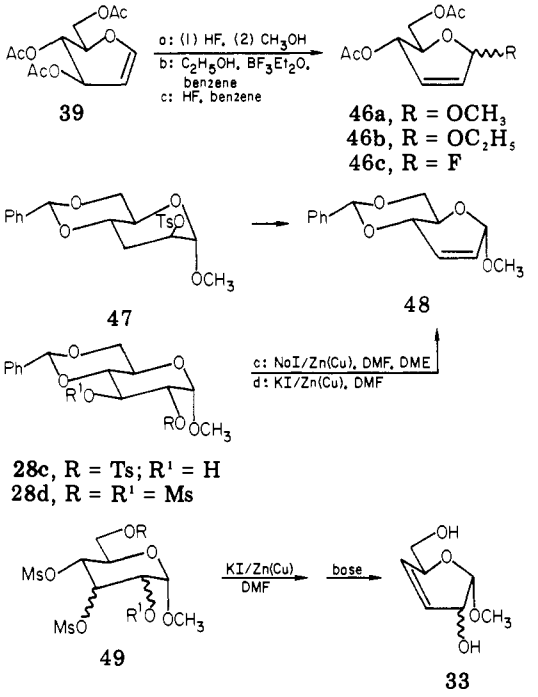
1. Incorporation of the Enone Chromophore

a. Protection of Hydroxyl Groups. Various functional groups are used to protect certain hydroxyl groups.[51] In the syntheses of hexenuloses, the most commonly used protecting groups are (a) benzylidene and isopropylidene (Scheme I),[52-68] (b) acetates and benzoates (Scheme II), and (c) triphenylmethyl (trityl) ether (Scheme III).[63,65,79-85] Two advantages of the alkylidenes are their stability in alkaline solution and their ease of hydrolysis in acid solution. Acid hydrolysis

SCHEME IV



SCHEME V



thus provides a method for removing the alkylidene groups; the benzylidene group may also be removed by hydrogenation over a platinum catalyst. The acetates and benzoates are usually water-insoluble crystalline derivatives. Benzoates are more sluggish in their reactions than acetates, but crystallize more readily. With limiting amounts of the benzoylating reagent, primary hydroxyl groups are selectively esterified. The esters are hydrolyzed slowly by acid, but rapidly by base. Generally, the groups are removed with retention of configuration of the secondary hydroxyl groups. The main purpose of the triphenylmethyl group is to block primary hydroxyl groups.

b. Syntheses of Olefins. The synthesis and chemical reactions of unsaturated sugars have been reviewed by Ferrier[39] and Fraser-Reid.[40] As part of this discussion, it is appropriate to mention some of the general methods for incorporating unsaturation into the glycoside. 1,5-Anhydro-2-deoxyhex-1-enitols are generally prepared by reductive removal of a C-1 halogen and a neighboring C-2 acetate group from an acetylated glycosyl halide.[86-89] Wide variations in the yield of 1,5-anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hex-1-enitol (**39**) (tri-*O*-acetylglucal), obtained by the conventional treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**38**) with zinc dust in aqueous acetic acid (Scheme IV), have been attributed to differences in the activity of the zinc.[90]

Another method reported for the synthesis of 1,5-anhydro-2-deoxyhex-1-enitols, e.g., **41**, is the ring opening of the epoxide group in methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**40**) with methyllithium (Scheme IV).[91-94] The corresponding mannopyranoside **42** does not give an unsaturated sugar, but a 3-*C*-methylaltropyranoside **43**.[93] The nature of R in **41** depends on the quality of the methyllithium: freshly prepared methyllithium results in the formation of **41a**.[92] A plausible mechanism[93,94] for formation of **41a** is opening of the epoxide **40** by iodide ion (found in commercial methyllithium) to form the lithium alkoxide of the iodohydrin **44a** (Scheme IV). Nucleophilic attack on the iodine atom with concomitant elimination of the methoxy group gives the allal derivative **45**, which is then hydrolyzed to **41a**. Evidence for this mechanism was provided by the isolation of the iodohydrin **44b**.[94] This method is limited in scope, because the mannopyranoside **42** gives the branched-chain sugar, and only with methyllithium unsaturated sugars were isolated. Since the method begins with an epoxide, it would not be applicable in molecules where the possibility of oxide ring migration could occur in the precursor.[95]

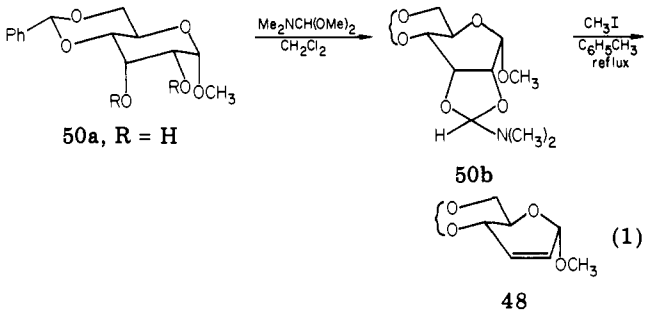
One of the main routes to hex-2-enopyranosides, e.g., **46**, is the high-temperature[96,97] or acid-catalyzed room-temperature[98,99] reaction of alcohols with acylated 1,5-anhydro-2-deoxyhex-1-enitols, e.g., **39** (Scheme V). This proceeds with rearrangement of the double bond and displacement of the C-3 functionality. Ferrier reported that the high-temperature rearrangement gives mixtures of anomers. In a later publication, Ferrier and Prasad[99] described a set of conditions (tri-*O*-acetylglucal (**39**) with alcohols in benzene solution in the presence of boron trifluoride at room temperature) for enhancing the stereospecificity and yields of these reactions in the preparation of compounds such as **46b** (α-OC_2H_5). Unlike hydrogen bromide and hydrogen chloride, hydrogen fluoride does not add directly to **39**, but in benzene solution, it gives **46c**.[100] Alcoholysis of the fluoride affords the corresponding alkyl glycoside derivatives **46a** or **46b** in the same proportions as are obtained on treating **39** directly with alcohols.

Another method involves direct introduction of the 2,3-olefinic double bond. Thus, methyl 4,6-*O*-

benzylidene-α-D-*erythro*-hex-2-enopyranoside (48) was first prepared by Bolliger and Prins[101] from methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α-D-mannopyranoside (47) (Scheme V). This compound (48) has also been prepared from precursors containing C-2 and C-3 functional groups, e.g., epoxide,[102] iodohydrin,[103] episulfide[104,105] thionocarbonate,[104] sulfonate,[104,106] xanthate,[96] thiouranium,[107] and aziridine,[108] and by the action of potassium ethyl xanthate on the disulfonic esters or epoxides.[104] Lemieux and his co-workers[94] described a facile synthesis of 48 from the epoxide 40. This method involves the conversion of the epoxide 41 to the iodohydrin **44b**, and treating the latter compound with methane- or *p*-toluenesulfonyl chloride in refluxing pyridine.

Fraser-Reid and his co-workers[46,63] developed the Tipson–Cohen[109] reaction for the elimination of contiguous secondary sulfonyloxy groups in synthesizing hex-2-eno 48 and hex-3-enopyranosides **33** from **28d** and **49**, respectively (Scheme V). In the former case, the low yield was attributed to the conformational constraints of the 4,6-*O*-benzylidene protecting group,[46] but Seto et al.[110] claimed that the direct elimination of the sulfonyloxy groups is strongly influenced by the anomeric configuration. Recently, Radatus and Clarke[111] reported an improved synthesis of 48 from methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside (**28c**)[112] (Scheme V) by another modification of the Tipson–Cohen method: zinc–copper couple, sodium iodide in dimethylformamide, and dimethoxyethane under reflux. They noted that dimethoxyethane serves to maintain a reaction temperature at 125–130 °C and to precipitate the Lewis acid zinc(II) iodide.

Other methods were recorded in the literature for direct incorporation of unsaturation into a carbohydrate molecule. In 1972, Carnahan and Closson[113] demonstrated that treatment of vicinal dimesylates with anthracene- or naphthalene–sodium results in a high-yield conversion into the corresponding alkenes. Barton and co-workers[114] reported that the reaction of vicinal diol bis(dithiocarbonates) with tri-*n*-butyltin hydride in toluene or benzene gives the corresponding olefin in high yield. Hanessian et al.[115] converted vicinal *cis*-diols **50a** by way of (dimethylamino)methylene acetals **50b** into the corresponding olefin. The trimethylalkylammonium iodide obtained by dissolving the acetals **50b** in toluene and adding iodomethane was heated to the solution's reflux temperature. Since cyclic acetals are intermediates in this sequence, it is only applicable to *cis*-1,2-diols, e.g., **50a** → **50b** → 48 (eq 1).

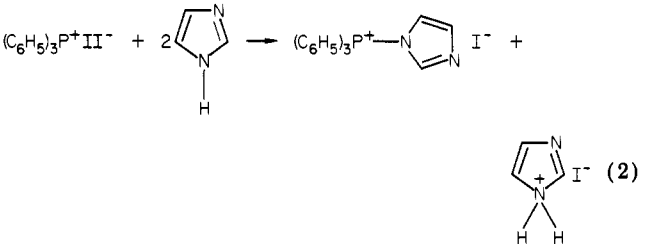


50a, R = H

50b

48 (1)

Garegg and Samuelsson[116,117] noted that the system triphenylphosphine, imidazole, and iodine in toluene is a useful system for a one-step conversion of *trans*-1,2-diols into olefins; triiodoimidazole may be used to avoid the generation of hydrogen iodide. The reagent system was less effective with *cis*-1,2-diols. It was postulated that imidazole or triiodoimidazole probably forms a complex with triphenylphosphine and iodine (eq 2) and that imidazole may also function as a base.



(2)

The same products were obtained in lower yield and over longer reaction times when pyridine was the base.

c. Oxidation of Allylic Alcohols. In 1948, Morton and his co-workers[118] described the first example of allylic alcohol oxidation with precipitated manganese dioxide. Since that time, other unsaturated alcohols, both primary and secondary, have been oxidized with manganese dioxide.[119–121] Oxidations with manganese dioxide have been reviewed by Fatiadi,[122,123] and some reservations about the specificity of these reactions have been expressed by Barakat and co-workers.[124]

Manganese dioxide oxidations in the carbohydrate field have been limited to the stereospecific oxidations of certain allylic alcohols as described by Fraser-Reid and co-workers (Table I).[15,16,63,65,125–127] In these reports and in a report by Collins,[128] anomalies in the oxidation of some epimeric allylic alcohols were observed (Scheme VI) and were discussed in terms of stereochemical effects.[126] However, it was pointed out that there must be factors other than stereochemical (e.g., half-chair conformation or an anomeric effect) responsible for the failure of **41a** or **60** to be oxidized. These anomalies are consistent with the observations made on oxidizing other natural products;[129–134] in manganese dioxide oxidations, many cyclic allylic alcohols favor a particular orientation of their hydroxyl groups.

SCHEME VI

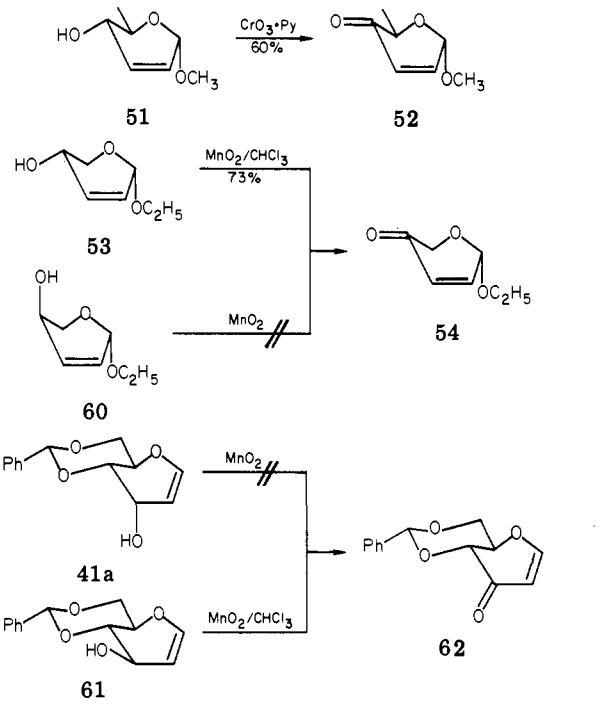
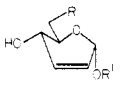
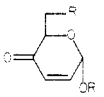
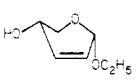
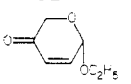
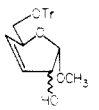
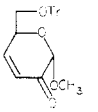
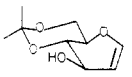
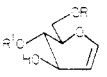
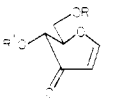
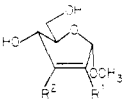
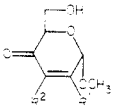


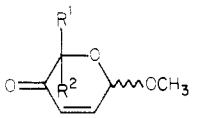
TABLE I. Manganese Dioxide Oxidations of Allylic Alcohols to En-uloses

allylic alcohol	enuloses	time, yield	ref
 51	 52	R = OBz; R¹ = CH_3; 6 h, 53% R = OH; R¹ = C_2H_5; 5 h, 82% R = H; R¹ = C_2H_5; 60 h, 85%	15, 16, 125
 53	 54	7 h, 70%	16, 126
 34	 35	equatorial; 48 h, 94% axial; 40 h, 94%	63
 26	 55	72 h, 73%	65
 56	 57	R = Tr; R¹ = H; 8 h, 85% R = Bz; R¹ = H; 12 h, 26%	65
 58a, R¹ = H; R² = CH_3 58b, R¹ = CH_3; R² = H	 59a, R¹ = H; R² = CH_3 59b, R¹ = CH_3; R² = H	a: 6 h, 77% b: 5.5 h, 68%	127

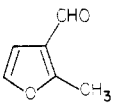
Another reagent which has had widespread utility in the oxidation of allylic alcohols is chromium trioxide[135,136] or its dipyridine complex.[136-139] Fraser-Reid and his co-workers reported on the oxidation of **26**,[65] **34**,[63] **41a**,[45] and **51** (R = H; R¹ = CH_3)[125] using chromium trioxide–pyridine complex in methylene chloride. Collins, on the other hand, found chromium trioxide in pyridine to be the most satisfactory reagent for the oxidation of **41a**.[128]

2. Transformation of Furfuryl Alcohols

Achmatowicz and his co-workers[18,47,140-142] have developed methods for the total synthesis of monosaccharides from furfuryl alcohols; one of the intermediates is the alkyl hex-2-enopyranosid-4-uloses **63**. This method is the reversal of the well-known transformation of sugars into furan compounds. For example, 2-methyl-3-formylfuran (**64**) was obtained on heating a streptose derivative at pH 2–4.



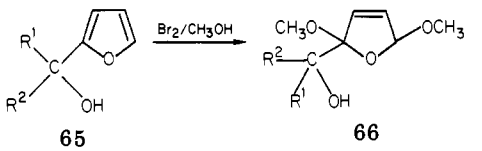
63, R¹ = H, CH_3, CH_2OH
R² = H, CH_3, CH_2OH



64

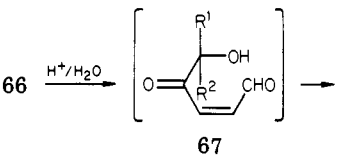
The principle of the method leading to alkyl hex-2-enopyranosid-4-uloses is outlined in Scheme VII. The 2-furylcarbinol **65** is converted into 2,5-dimethoxy-2,5-dihydrofuran **66** by treatment with bromine in methanol. Cleavage of the acetal bonds in **66** is accomplished by hydrolysis with mineral acid, and the dicarbonyl compound **67** immediately cyclizes to the 2,3-dideoxy-hex-2-enopyranos-4-ulose **68**. Compound **68** is then

SCHEME VII

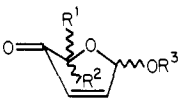


65 66

a, R¹ = R² = H
b, R¹ = CH_3; R² = H
c, R¹ = R² = CH_2OAc
d, R¹ = COOBu; R² = H
e, R¹ = R² = COOEt



67



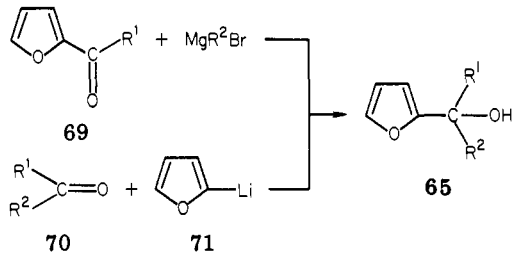
63

68a, R¹ = R² = R³ = H
68b, R¹ = CH_3; R² = R³ = H
68c, R¹ = R² = CH_2OH; R³ = H
68d, R¹ = CH_2OH, H; R² = H, CH_2OH; R³ = H

methylated with methyl orthoformate in the presence of a Lewis acid catalyst to give **63**.

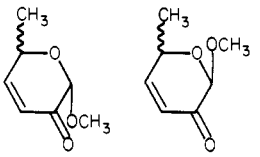
Some variations to this synthetic route were reported by a number of workers: (1) electrolytic methoxylation of the furylcarbinol,[48,49] (2) oxidation of furylcarbinol with peracids,[143,144] (3) cleavage of the acetal bonds in **66** with organic peracids[49,50] or Dowex 50 resin,[48] followed by formic or trifluoroacetic acid in methanol to give **63**, and (4) methylation of **68** with methyl iodide in the presence of silver oxide.[143,144] The furylcarbinol

SCHEME VIII



65 was prepared (Scheme VIII) either from the Grignard reaction of 2-acylfuran **69** with an alkylmagnesium bromide[18,47,140,141] or by the reaction of the ketone **70** with 2-furyllithium **71**.[143,144]

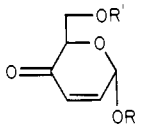
Bognar and Herczegh[145,146] described an analogous procedure for the synthesis of hex-3-enopyranosides **76** starting with 5-methyl-2-furaldehyde (**72**) (Scheme IX). The formyl group of **72** is protected by condensation with 2,3-dimethyl-2,3-butanediol and gives the dioxolane **73**. This is oxidized with bromine–water at pH 3–4 and the resulting unsaturated dioxo compound **74** is not isolated, but immediately reduced with sodium borohydride to give the mixture **75**. Methanolysis of **75** gives the known methyl 3,4,6-trideoxy-DL-hex-3-enopyranosides **76**.[147] Compounds **76**, now possessing the allylic alcohol, can conceivably be oxidized to the corresponding methyl 3,4,6-trideoxy-α-DL-*glycero*-hex-3-enopyranosidulose (**77**) or the corresponding β anomer (**78**).



B. Individual Classes of Hexenuloses

1. Alkyl Hex-2-enopyranosid-4-uloses

a. From Carbohydrate Precursors. **i. 2,3-Dideoxy Sugars.** Among the first recorded examples of incorporation of an α,β-unsaturated-keto functionality into an alkyl pyranoside unit are the reports by Fraser-Reid and his co-workers[15,16] on the syntheses of some alkyl 2,3-dideoxyhex-2-enopyranosid-4-uloses **79** as stable

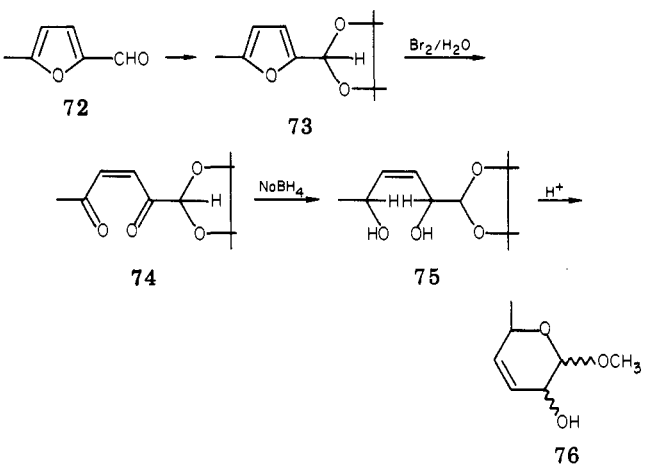


79, R = CH_3, C_2H_5
R′ = H, Ac, Bz, Ts, Tr

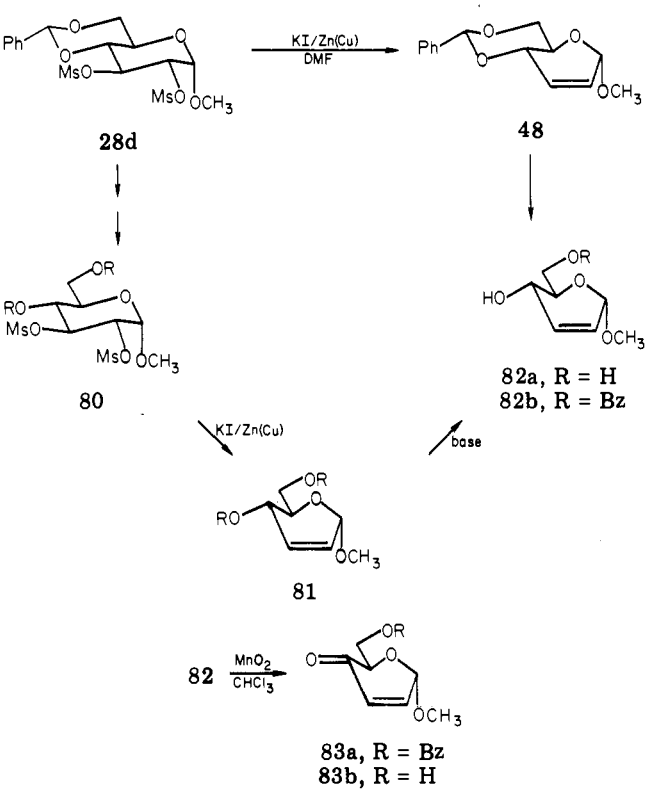
crystalline compounds. The synthesis of ethyl 2,3-dideoxy-α-D-pent-2-enopyranosid-4-ulose (**54**) was also described.[16] These compounds were prepared in high yields by using simple experiments and starting with cheap readily available materials, for example, D-glucose (**21a**) and methyl α-D-glucopyranoside (**21b**).

Earlier, Fraser-Reid and Boctor[46] described the reductive elimination of vicinal sulfonyloxy groups from methyl 2,3-di-*O*-(methylsulfonyl)-α-D-glucopyranosides **28d** and **80** (R = Ac or Bz) with the formation of hex-2-enopyranosides **48** and **81** (R = Ac or Bz), respectively (Scheme X). Acid treatment removes the benzylidene group in **48**, and the resulting diol **82a** was selectively

SCHEME IX



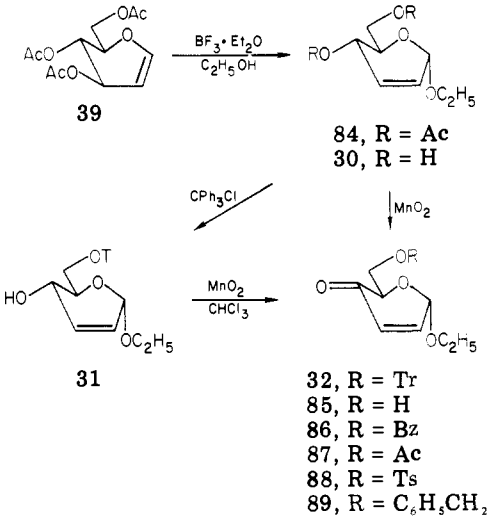
SCHEME X



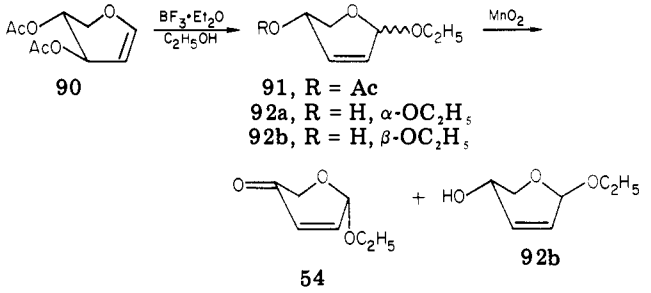
benzoylated at the C-6 hydroxy group to give methyl 6-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**82b**). Alternatively, the reaction mixture **81** (some deacylation at C-4 occurs during the reductive elimination) is deacylated to the diol **82a** and subsequently converted to **82b**. Manganese dioxide[148] oxidizes the allylic alcohol **82b** to methyl 6-*O*-benzoyl-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**83a**) in 53% yield. Attempts to debenzoylate the primary ester of **83a** brought about destruction of the molecule.

Another more attractive route originates with tri-*O*-acetylglucal (**39**) (Scheme XI). In 1969, Ferrier and Prasad[99] described an excellent method for obtaining **84** as a crystalline substance in 95% yield from **39**. The diacetate **84** is deacetylated, and the diol **30** oxidized with manganese dioxide to the crystalline hydroxy enone **85** in 82% yield. Ethyl 2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**85**) is extremely labile in the presence of triethylamine. However, it is converted

SCHEME XI

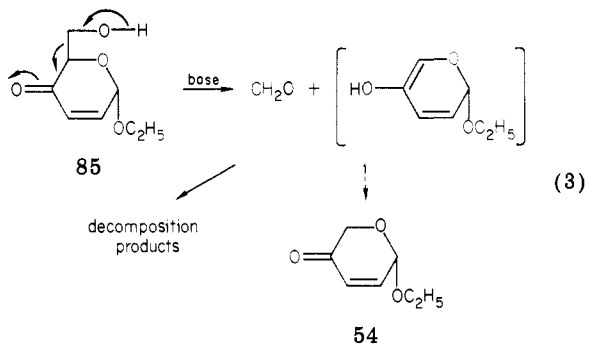


SCHEME XII



into its benzoyl **86**, acetyl **87**, and tosyl **88** derivatives by standard esterification procedures. Unfortunately, attempts to tritylate **85** were unsuccessful: to form **32**, it is more advantageous to first tritylate the diol **30** and then oxidize the 6-*O*-trityl ether **31**.

Theoretically, the primary alcohol **85** could provide a convenient access to the pent-2-enopyranosid-4-ulose **54** by way of a base-induced retro-aldol liberation of formaldehyde (eq 3). However, although 83 mol % of

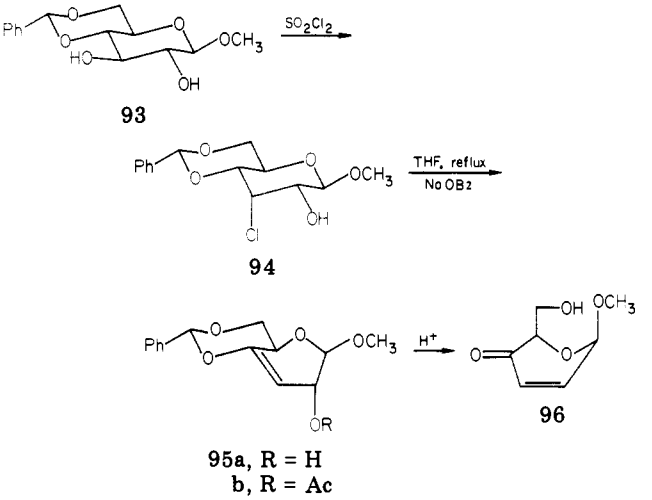


(3)

formaldehyde is liberated when **85** is treated with base, the product showed no evidence for the expected α,β-unsaturated ketone **54**.

A synthesis of 54 starting with 1,5-anhydro-3,4-di-*O*-acetyl-2-deoxy-D-*threo*-pent-1-enopyranose (**90**) (Scheme XII) was designed. Treatment of **90** with ethanol using boron trifluoride as catalyst gives a mixture of products **91** (α- and β-OC_2H_5), which showed only as one spot on thin layer chromatography. However, on deacetylation, two components are detected and isolated by preparative layer chromatography. The substance with the larger R_f value, **92a**, is easily oxidized with manganese dioxide to **54**, while that with the

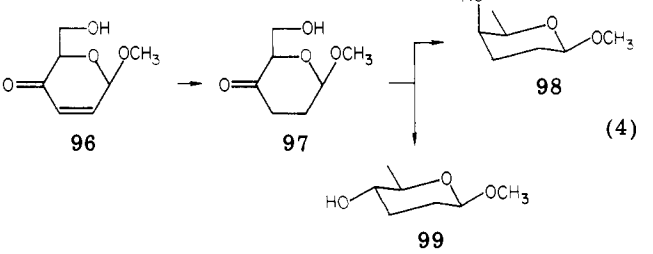
SCHEME XIII



smaller R_f value, **92b**, is resistant to oxidation. Alternatively, the mixture of allylic alcohols **92a** and **92b** is subjected to the above oxidation conditions for 12 h and the pent-2-enopyranosid-4-ulose **54** is readily separated from unchanged **92b** by extraction from aqueous solution with petroleum ether.

Following the reports by the Waterloo group,[15,16] Jones and his co-workers[149] described the synthesis of methyl 2,3-dideoxy-β-D-*glycero*-hex-2-enopyranosid-4-ulose (**96**). Their synthetic approach (Scheme XIII) starts with methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy-β-D-allopyranoside (**94**) which is obtained in 94% yield by reacting methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**93**) with sulfuryl chloride.[150] When **94** is treated with sodium benzoate in tetrahydrofuran at reflux, elimination occurs to give **95a** in 85% yield; **95a** could be converted into the 2-*O*-acetyl derivative **95b**. Reference was made to a comparable elimination by Horton and his collaborators.[151] Acid treatment of **95a** or its acetate **95b** affords the hex-2-enopyranosid-4-ulose **96** in about 70% yield. All of the spectroscopic data were in accord with the structure; the NMR spectrum of **96** was similar to that reported for **83b**.[15,16] However, whereas H-1 in **83b** appears as a doublet devoid of any secondary splitting, the spectrum of **96** shows H-1 with splitting 2.2 and 1.8 Hz for H-2 and H-3, respectively. These values are consistent with a quasi-axial orientation of H-1 in compounds with the C_1 conformation.[152]

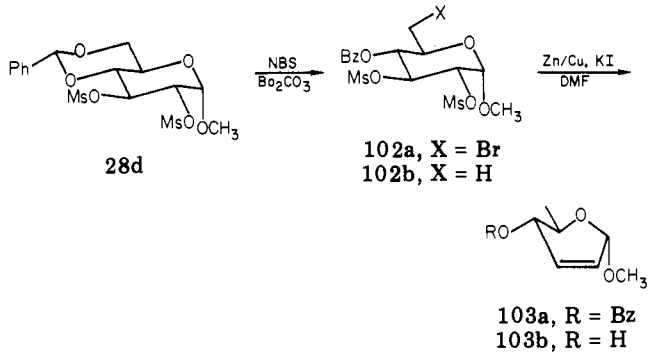
Jones and his co-workers demonstrated the synthetic utility of **96** in a series of reductions leading to methyl 2,3,6-trideoxy-β-D-*threo*-hexopyranoside (methyl β-D-rhodinoside **98**) and methyl 2,3,6-trideoxy-β-D-*erythro*-hexopyranoside (methyl β-D-amicetoside **99**), respectively (eq 4).



(4)

ii. **2,3,6-Trideoxy Sugars.** The L enantiomer of the parent sugars of **98** and **99** are examples of the 2,3,6-

SCHEME XIV



28d

102a, X = Br
102b, X = H

103a, R = Bz
103b, R = H

trideoxyhexoses found in antibiotics. In 1966, Hanessian[153] reviewed the synthesis and chemistry of deoxy sugars. Most of the synthetic routes start with glucose, and only a few commence with unsaturated[154] or other modified sugars.[149] Fraser-Reid and co-workers[125] reported some synthetic routes of alkyl 2,3,6-trideoxyhex-2-enopyranosides **100** and the corresponding hex-2-enopyranosid-4-uloses **52** and **101** from readily accessible and inexpensive starting materials.

100a, X = I; R' = C_2H_5
100b, X = H; R' = C_2H_5

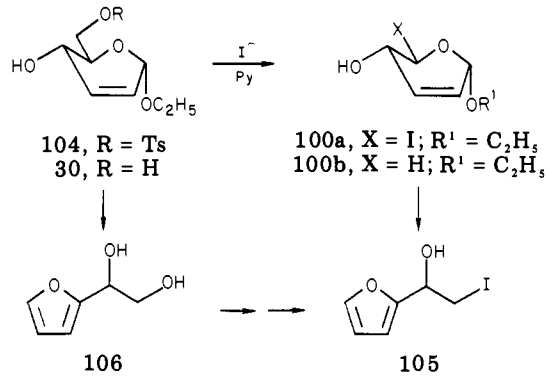
52, R' = CH_3
101, R' = C_2H_5

The classical approach to 6-deoxy sugars involves reductive removal of the corresponding sulfonate ester or iodide with lithium aluminum hydride; this reagent cannot be used on substrates such as **100a**, because double bond migration occurs.[155,156] Consequently, synthetic routes were designed which (1) create the 6-deoxy functionality and then introduce the 2,3-double bond and (2) employ a method of hydrogenolysis that does not affect 2,3-double bonds.

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-(methylsulfonyl)-α-D-glucopyranoside (**28d**) (Scheme XIV) is converted to methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-(methylsulfonyl)-α-D-glucopyranoside (**102a**) in 71% yield with a modification of the Hanessian and Plessas procedure.[157-159] When **28d**, dissolved in a mixture of tetrachloroethylene and carbon tetrachloride, is allowed to react with *N*-bromosuccinimide and barium carbonate, the benzylidene acetal ring opens and gives the monobenzoylated bromodeoxy sugar derivative **102a**. Zinc–copper couple in boiling acetic acid hydrogenolyzes **102a** to a crystalline 6-deoxy compound, **102b**, in 74% yield. A mixture of potassium iodide and zinc–copper couple in dimethylformamide[46,109] reductively eliminates the sulfonyl ester groups of **102b**. The product **103a** undergoes deesterification during the reaction to give **103b** directly. Compound **103b** codistills with the dimethylformamide, contributing to the low yields of **103b**; the overall yield for the conversion **102b** → **103a** → **103b** is 30–40%.

Ethyl 6-iodo-2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**100a**) was chosen as the synthon (Scheme XV) for the method, which involves hydrogenolysis and does not affect the 2,3 unsaturation. It is formed when iodide ion, in acetone or methyl ethyl ketone, displaces the tosyl group of **104**; compound **104** is prepared in 64% yield from **30**. However, under the above conditions **100a** rapidly rearranges to the 2-substituted furan **105**. The structure of **105** was confirmed by spectroscopic data and chemical correlation with the known diol **106** obtained from acid hydrolysis of **30**.[104] A mechanism for the formation of **106** from **82a** (cf. **30**) has been proposed by Zamojski et al.[160] When the iodinolysis of **104** is conducted in a system containing pyridine, **100a** forms in 89% yield without rearrangement to **105**.[125] Deactivated W-2 Raney nickel[161] catalyzes the hydrogenolysis of the iodide **100a** to **100b** without reduction of the double bond. This step occurs in 90% yield, while the yield for the overall sequence **30** → **104** → **100a** → **100b** is about 50%.

SCHEME XV

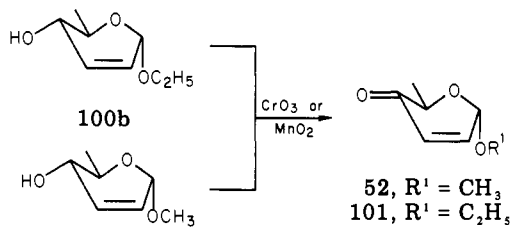


104, R = Ts
30, R = H

100a, X = I; R' = C_2H_5
100b, X = H; R' = C_2H_5

106 105

SCHEME XVI

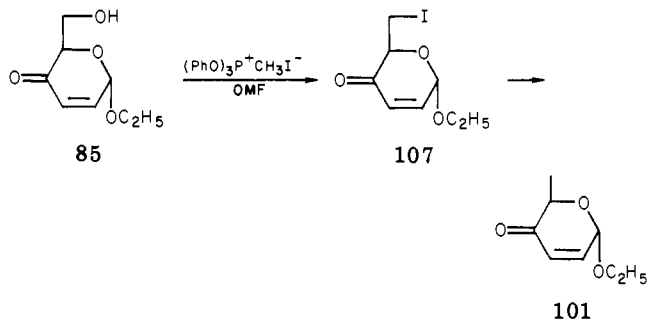


100b

103

52, R' = CH_3
101, R' = C_2H_5

SCHEME XVII



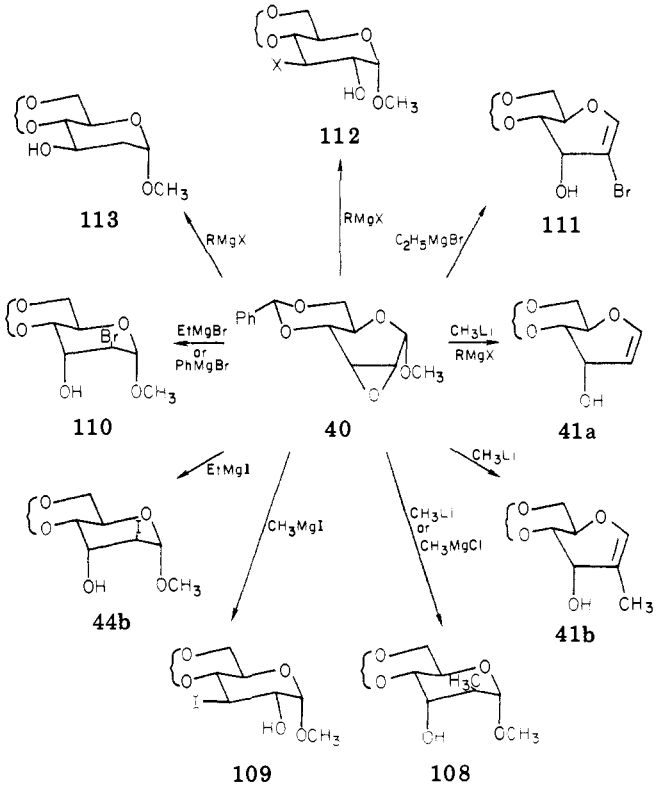
85 107

101

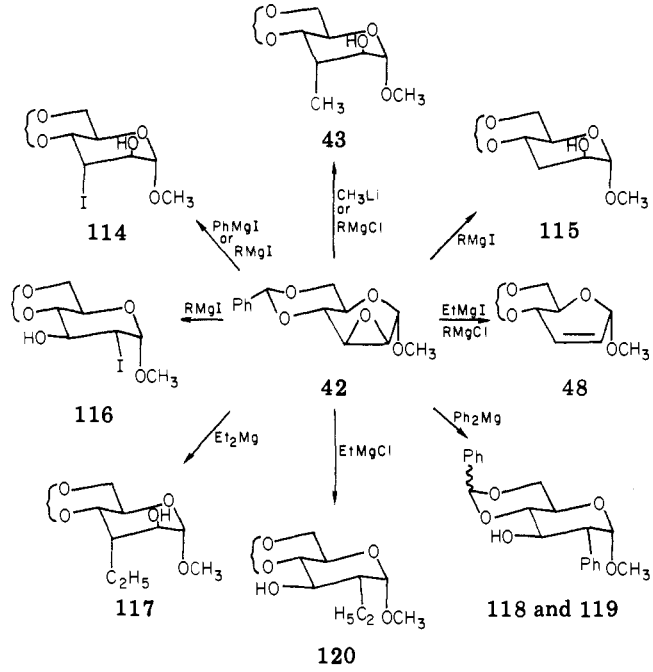
The route outlined in Scheme XIV can be carried out on a large scale; however, the yield in the final step will be low, because the dimethylformamide and product codistill. The alternate route shown in Scheme XV is preferred because of the high yields in each step, the use of low boiling solvents, and the availability of the starting materials. Chromium trioxide oxidizes **103b** to **52** in 60% yield, while manganese dioxide oxidizes **100b** to **101** in 85% yield (Scheme XVI).

The most direct route to ethyl 2,3,6-trideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**101**) (Scheme XVII) starts with the readily prepared ketone **85**.[16] Triphenoxyphosphonium methiodide[162] reacts with **85** in DMF and gives the iodide **107**. Deactivated W-2 Raney nickel promotes the hydrogenolysis of **107** to **101**

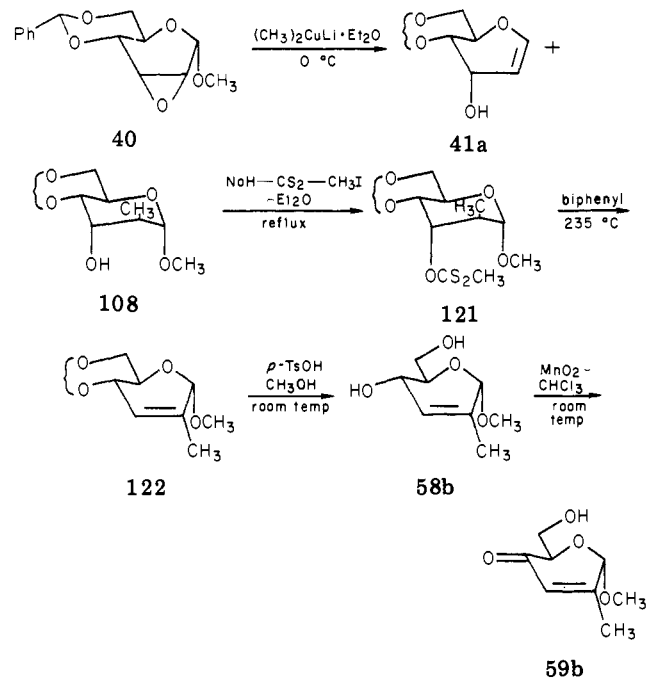
SCHEME XVIII



SCHEME XIX



SCHEME XX



in 42% overall yield. Tri-*n*-butyltin hydride[163] also hydrogenolyzes the iodide **107**, but it is impossible to isolate the product from the inorganic material.

iii. 2,3-Dideoxy-2-*C*(-3-*C*) Branched-Chain Sugars. Branched-chain sugars are another class of modified sugars that have been isolated in large numbers as glycoside components of antibiotics from microorganisms and higher plants.[164] Many methods have been developed for the synthesis of these modified sugars.

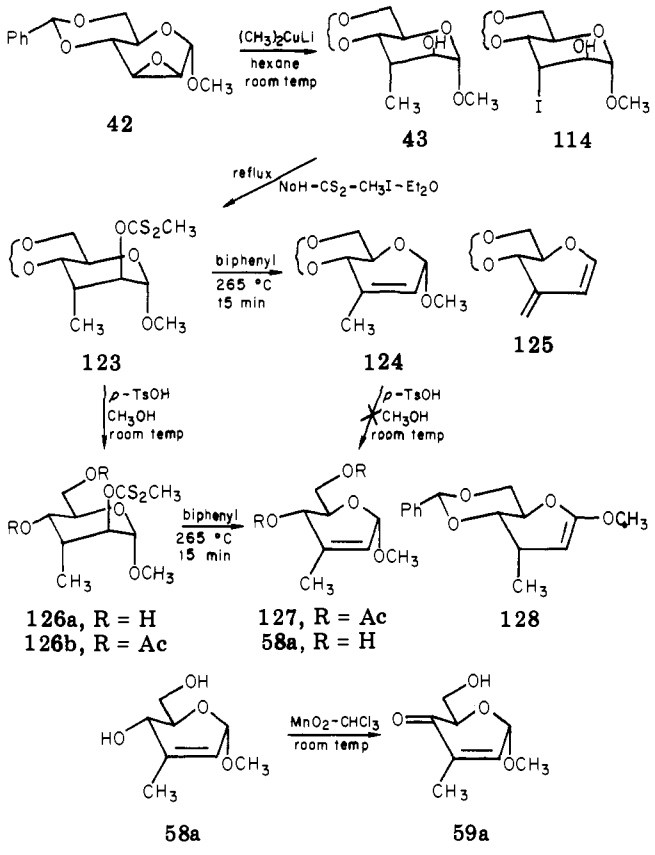
The most common method for introducing branching at C-2 and C-3 is by reacting epoxides **40** and **42**, respectively, with an organometallic reagent. Preference for attack at C-2 or C-3 results from the stereochemistry of the entire molecule[165] and the expected trans diaxial[166] ring opening of the epoxide. However, the reactions of carbohydrate epoxides **40** and **42** with organometallic reagents give rise to a variety of unwanted products as shown in Schene XVIII and Scheme XIX, respectively.[91-93,102,167-171]

In 1975, Fraser-Reid and Hicks[127] reported the syntheses of the C-2 and C-3 methyl derivatives of methyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosid-4-ulose (**83b**) from the readily available epoxides **40** and **42**. In developing their synthetic routes these workers took advantage of the salutary effects which lithium dimethylcuprate[172] has in oxirane cleavage.[173] For example, (1) lithium dimethylcuprate is more reactive and gives higher yields of nucleophilic addition products than alkyllithium, and (2) limited side reactions occur under the mild conditions for oxirane cleavage.

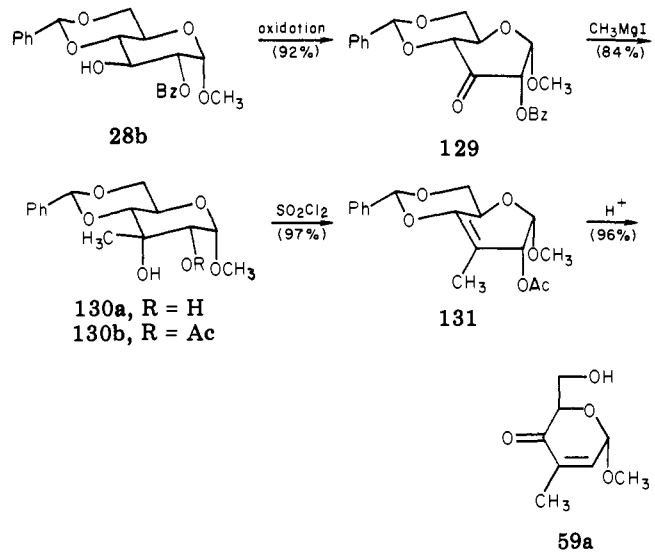
Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**40**) undergoes ring opening when allowed to react with lithium dimethylcuprate in ether at 0 °C[174] (Scheme XX); the desired alcohol **108** crystallizes from the reaction mixture of **108** and **41a** in 65% yield. The yield of **108** increases to 75% by taking advantage of its reluctance to be esterified by acetic anhydride. A mixture of sodium hydride, carbon disulfide, and methyl iodide in refluxing diethyl ether[96] converts **108** to the xanthate ester **121**, which on heating to 235 °C in biphenyl gives **122** in 67% yield based on **108**. Debenzylidation occurs on treating **122** with *p*-toluenesulfonic acid. The resulting diol **58b** is water soluble, and this facile reaction eliminates the need to isolate **122** chromatographically. Thus, the crude pyrolysis product in methanol is treated with *p*-toluenesulfonic acid, and after neutralization and concentration, the crude residue **58b** is partitioned between ether and water. By this procedure the diol **58b** is obtained in 47% yield from **121**. Manganese dioxide in chloroform oxidizes the diol **58b** to the enone **59b** in 68% yield.

Conceptually, conversion of the diastereomeric oxirane **42** to **43** should be achieved through the application of the same series of reactions. However, several

SCHEME XXI



SCHEME XXII



difficulties were encountered and modifications were made where appropriate (Scheme XXI). Lithium dimethylcuprate in ether, benzene, or THF at 0 °C does not effect ring opening of the epoxide **42**, and at room temperature, three unidentified products are formed.[174] However, if the reagent is prepared in hexane at 0 °C, it reacts with **42** at room temperature to give methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-altropyranoside (**43**) in 70% yield; at scales larger than 0.008 mol, appreciable quantities of the iodohydrin **114** form. Fortunately, this can be removed chromatographically by using a silica gel column. The mixture of sodium hydride, carbon disulfide, and methyl iodide in refluxing diethyl ether for 24 h transforms **43** to the 2-*O*-[(methylthio)thiocarbonyl] derivative **123** in 82% yield.

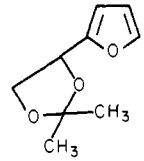
The xanthate ester **123** in biphenyl at 235 °C for 1.0 h pyrolyzes to give diene **125** instead of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-α-D-*erythro*-hex-2-enopyranoside (**124**). A control study showed that the olefin **124** is formed first and this then undergoes pyrolytic 1,4 elimination of methanol to give **125**; the optimum conditions under which **123** pyrolyzes to **124** in 61% yield are 265 °C and 15 min. It should be noted in passing that the xanthate ester **123** contains two available cis hydrogens and could on pyrolysis have given **128**. However, *no* **128** forms during pyrolysis. This selectivity supports the hypothesis that a hydrogen on the carbon bearing oxygen atoms would be less readily removed on pyrolysis of a xanthate ester. Ferrier[96] postulated that the lack of reactivity of these hydrogens was due to the mesomeric interaction between unshared electrons of the oxygen and the incipient π bond.

Unexpectedly, Fraser-Reid and Hicks encountered failure of olefin **124** to undergo acid-catalyzed debenzylidation. This they attributed to the sensitivity of **124** to acid. Therefore, they explored an alternate approach whereby a base-labile protecting group was utilized. *p*-Toluenesulfonic acid in methanol effects debenzylidation of **123** to give diol **126a** in 92% yield. Acetylation by the normal procedures converts **126a** in 83% yield to its diacetate **126b**. This on heating at 265 °C in diphenyl for 15 min is converted to **127** in 66% yield. Sodium carbonate in dry methanol deacylates diacetate **127** to **58a** in 87% yield, and manganese dioxide in chloroform oxidizes **58a** to methyl 2,3-dideoxy-3-*C*-methyl-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**59a**) in 77% yield.

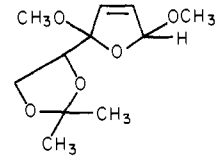
An alternate synthesis of **59a**, devised by Box and his associates,[175] takes advantage of the availability of the 2-*O*-benzoate **28b**.[77] The route, shown in Scheme XXII, embodies the application of a Grignard reaction with a 3-keto-*ribo* sugar, **129**, producing an *allo* compound, **130a**. Subsequent reactions involve dehydration of **130b** and acid treatment of the olefin **131**. Except for the Grignard reaction (84% yield), the yields of the reactions are greater than 90% with an overall yield of 72%. The significance of the route is a general method for the synthesis of 3-*C*-alkyl- or -arylhex-2-enopyranosid-4-uloses.

b. From Noncarbohydrate Precursors. In 1973, Jones and Szarek[16] reviewed the total synthesis of carbohydrates. Several synthetic routes using noncarbohydrate precursors were discussed, in particular, the general approach developed by Achmatowicz and coworkers.[18] One class of intermediates isolated is methyl 2,3-dideoxy-DL-hex- or -pent-2-enopyranosid-4-uloses **63**, and their synthesis is outlined in Scheme VII.

The carbinols **65** and **132** were prepared by chemical transformations of suitably substituted furan derivatives. Furfuryl alcohol (**65a**) was prepared by lithium aluminum hydride (LAH) reduction of furfural. Compounds **65b**, **65d**, **65e**, and **132**[176] were obtained by the

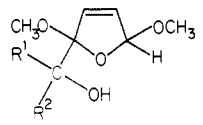


132

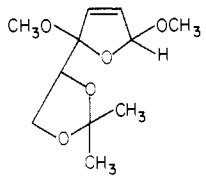


133

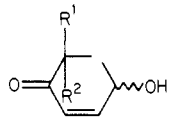
TABLE II. Yields, Boiling Points, and Melting Points



66



133



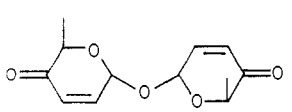
68, R^3 = H

trans-formation	R_1	R_2	yield, %	bp °C (mm)	mp, °C
65a → 66a	H	H	73	71 (1.00)	
65b → 66b	CH_3	H	92	72-74 (1.50)	
65c → 66c	CH_2OAc	CH_2OAc	64	130 (0.60)	
65d → 66d	COOBu	H	73	135 (0.90)	
65e → 66e	COOEt	COOEt	47	132 (0.80)	
132 → 133			76	74 (0.50)	
66a → 68a	H	H	100		54-58
66b → 68b	CH_3	H	98	120 (0.35)	62-65
66c → 68c	CH_2OAc	CH_2OAc	64	150 (0.80)	
133 → 68d	CH_2OH, H	H, CH_2OH	100		

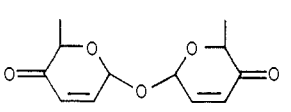
synthetic routes described in the literature. Achmatowicz et al.[18] synthesized the 1,3-diacetate of 2-(2-furyl)glycerol (**65c**) by the following sequence: LAH reduction of the ethyl ester of (2-furyl)tartronic acid (**65e**) and subsequent acetylation of 2-(2-furyl)glycerol.

Oxidative bromination in methanol transforms the 2-furylcarbinols **65** and **132** into the corresponding 2,5-dimethoxy-2,5-dihydrofurans **66** and **133** in high yield (Table II). In a typical experiment, a solution of 2-furylcarbinol in ether and methanol is kept at −35 °C, and bromine in methanol added gradually with stirring. After about 30 min, the reaction mixture is saturated with ammonia gas and allowed to warm to room temperature. Deacetalation occurs when **66a**, **66b**, **66c**, and **133** are treated with a 1–2% sulfuric acid at 20–60 °C, and the dicarbonyl intermediate **67** immediately cyclizes to the 2,3-dideoxy-DL-hex- or -pent-2-enopyranos-4-uloses **68** in high yields (Table II).

Compounds **68** are unstable in aqueous solutions at room temperature. They decompose rapidly when treated with basic agents, and secondary reactions occur while in acid media. For example, when **68b** is stirred for a few days at pH 3–4, it undergoes intermolecular dehydration, yielding two isomeric compounds **134** and **135**.



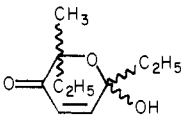
134



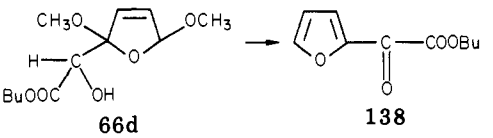
135

The enones **68** only existed in the hemiacetal cyclic form, and their structures were evident from analytical and spectral data. Prior to the report by Achmatowicz and co-workers,[18] acid hydrolysis of 2,5-dialkoxy-2,5-dihydrofurfuryl compounds were reported several times, and the products were assigned acyclic structures or characterized as crystalline derivatives;[177] compound **136** was the only recorded example of a cyclic system.[178]

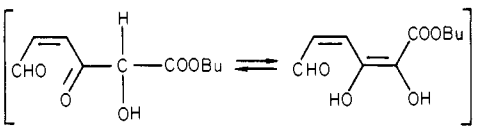
Butyl 2-furylglyoxylate (**138**) is the only product obtained on acid hydrolysis of **66d**. Achmatowicz et al.[18]



136



66d 138



137

reasoned that formation of **138** was a consequence of the easy enolization of the α-hydroxy-β-keto ester system in **137**. This enolization is well-known in the chemistry of ascorbic acid. Acid hydrolysis of **66e** affords ethyl tartronate in 71% yield.

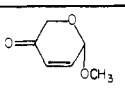
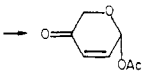
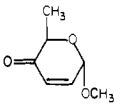
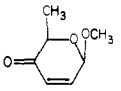
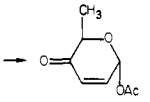
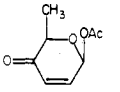
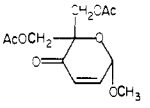
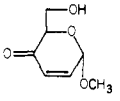
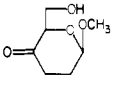
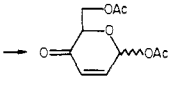
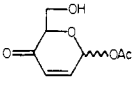
Methyl orthoformate in the presence of boron trifluoride etherate or stannic chloride at room temperature for 40–60 min effects glycosidation of **68**. Under these conditions, the methyl glycosides are obtained in 30–65% yield (Table III) with minimum amounts of side-reaction products, which could arise by addition of methanol to the double bond or ketalization of the C-4 carbonyl group. Methyl glycosides **52**, **141** and **83b**, **96**, obtained from **68b** and **68d**, respectively, are mixture of anomers and are separated by column and preparative gas chromatography. Considerable amounts of 1,6-anhydro-2,3-dideoxy-β-DL-hex-2-enopyranosid-4-ulose (**145**) are formed during the glycosidation of **68d**.

1-*O*-acetyl derivatives **140**, **142** and **143**, and **146** and **147** result when **68a**, **68b**, and **68d** are treated with acetic anhydride in pyridine or in methylene chloride–ethyl acetate solution at 0 °C (Table III). Compound **68a** affords **140** in high yield, **68b** yields both **142** and **143**, and pyranos-4-ulose **68d** gives rise to **146** and certain amounts of **147**; both **146** and **147** were mixtures of anomers. Unequivocal confirmation of their structures follows from IR, UV (Table III) and other spectroscopic data.

Some variations in the procedure of Achmatowicz et al.[18] have been noted by several workers.[48-50,143,144] A comparison of these variations is illustrated in Scheme XXIII. Lefebvre and co-workers[143,144] prepare the furfuryl alcohols by allowing aldehydes or ketones **70** to react with 2-furyllithium derivatives **71** (Scheme VIII). The furfuryl alcohols **65** are then oxidized with *m*-chloroperbenzoic or peracetic acid directly to 2,3-dideoxy-DL-2-enopyranos-4-uloses **68** (R^3 = H), which when treated with a mixture of methyl iodide and silver oxide give the pyranosid-4-uloses **68** (R^3 = CH_3).

Shono and co-worker[48] and Torii et al.[49] obtain their furfuryl alcohols **65** in the usual way, but employ an electrochemical procedure to form the 2,5-dimethoxy-2,5-dihydrofurans **66**. Dowex 50 ion exchange resin, employed by Shono and co-worker,[48] and perchloric acid, used by Torii et al.,[49] catalyze ring expansion of **66** to the pyranos-4-uloses **68** (R^3 = H). Torii et al.[49] prepare their methyl pyranosid-4-uloses by refluxing the

TABLE III. Physical Properties of 2,3-Dideoxy-DL-2-enopyranos-4-uloses

transformation	yield, %	bp (mm) [mp], °C	spectral data: IR ν_{max}, cm^{-1}	spectral data: UV λ_{max}, (ϵ)
68a → 	43	76-81 (23 mm)	1700, 1640	211 (8200)
139 	85	70-80 (0.40 mm) [40-41]	1755, 1705 1635, 1220	217 (11200) 353 (30)
140  68b →	45	82-85 (30 mm)	1700, 1630	211 (8000) 278 (20) 343 (50)
52 	19	82-85 (30 mm)	1700, 1630	212 (8700) 278 (40) 343 (60)
141 	46	80 (0.40 mm)	1755, 1700 1635, 1225	216 (11100) 331 (60)
142 	34	80 (0.40 mm)	1750, 1700 1635, 1235	216 (10900) 346 (40)
143  68c →	30	100 (0.60 mm)	1750, 1695 1640, 1230	215 (9000) 278 345
144  68d →	12	75-80 (10^{-4} mm)	3500, 1700 1640	208 (8800) 345 (30)
83b 	10	75-80 (10^{-4} mm)	3500, 1700 1640	
96 	26	84 (30 mm)	1710, 1695 1610	202 (4900) 234 (4500) 356 (70)
145 	40	100 (10 mm)	1745, 1700 1635, 1230	217 (10600) 271 (170) 346 (30)
146  147	17		1695, 1635 3520, 1745 1220	337 (40) 216 (9100)

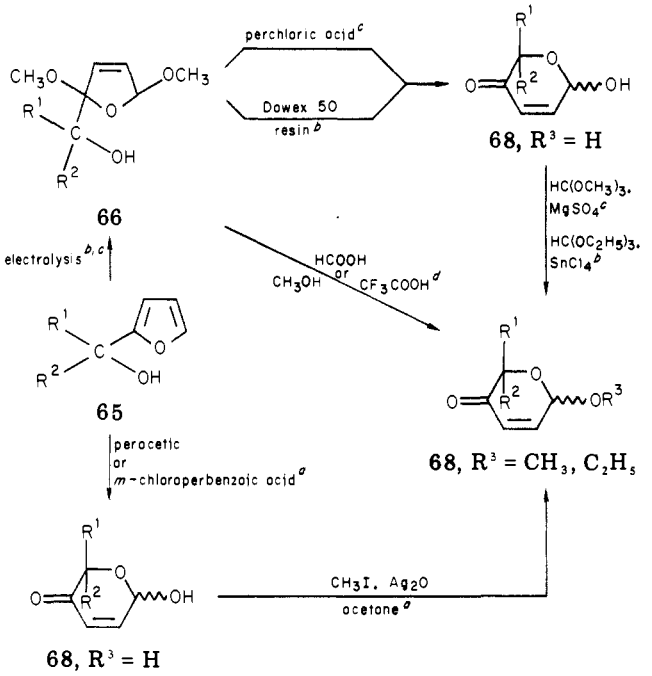
pyranos-4-uloses **68** (R^3 = H) with methyl orthoformate in the presence of magnesium sulfate, while Shono and co-workers[48] used a classical Lewis acid and ethyl orthoformate.

Weeks and collaborators[50] employ the method of Achmatowicz and co-workers[18] for synthesizing the furfuryl alcohols **65** and converting them to 2,5-dimethoxy-2,5-dihydrofurans **66**. However, they found that formic or trifluoroacetic acid in the presence of a protic solvent, for example, methanol, converts the 2,5-dimethoxy-2,5-dihydrofurans **66** directly to alkyl-2-enopyranosid-4-uloses **68** (R^3 = CH_3 or C_2H_5). In all cases, the intermediates and final products are obtained in greater yields. Table IV contains several examples of alkyl pyranosid-4-uloses and their intermediates made by procedures encompassing these variations.

2. *Alkyl Hex-3-enopyranosiduloses*

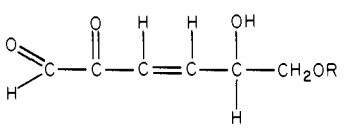
a. From Carbohydrate Precursors. i. **3,4-Dideoxy-6-*O*-methyl Sugars.** A compound of the type **152** was first isolated as its phenylosazone by Wolfrom and co-workers[179] and was shown to be an intermediate

SCHEME XXIII

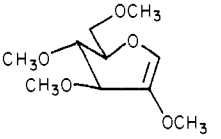


[a] References 143, 144. [b] Reference 48. [c] Reference 49. [d] Reference 50.

in the conversion of 1,5-anhydro-2,3,4,6-tetra-*O*-methyl-D-*arabino*-hex-1-enitol (**154**) to 5-(methoxymethyl)-2-furaldehyde. In 1962, Anet[180] reported the

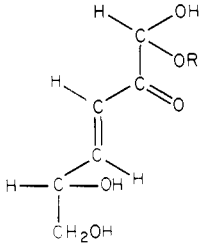


152, R = CH_3
153, R = H

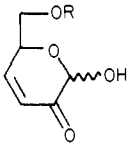


154

isolation of both cis and trans forms of **153** from acid treatment of di-D-fructoseglycine: the trans isomer as its hemiacetal **155** and the cis isomer in its cyclic form **156**. The yield of the trans isomer varied markedly



155

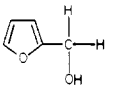
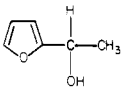
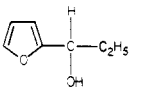
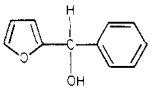
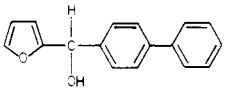
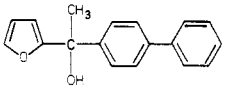


156, R = H
157, R = CH_3

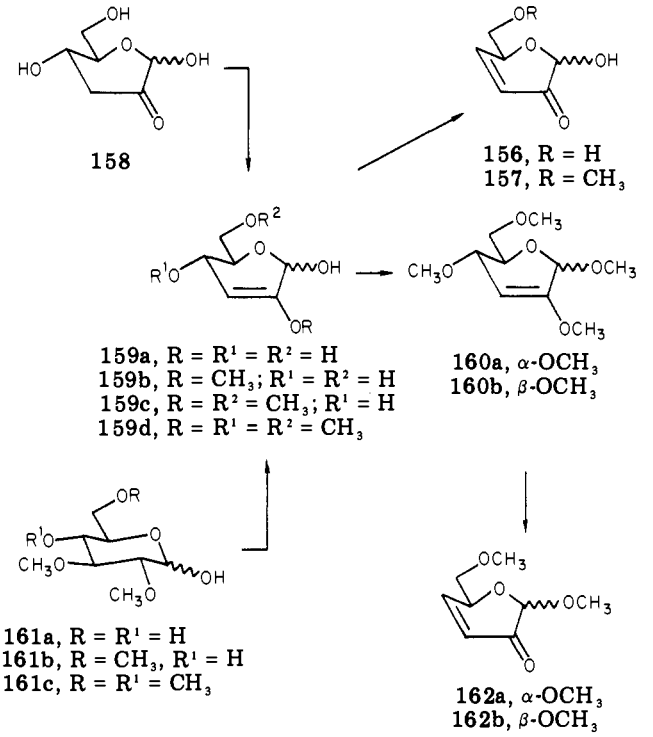
with pH while that of the cis isomer was constant. The trans isomer has been detected in only one reaction, namely, the action of hot dilute acid on D-fructose.

Anet[181,182] described two methods for exclusive formation of the cis isomers **156** and **157** (Scheme XXIV). The basis of the first method is enolization of 3-deoxy-D-*erythro*-hexopyranosulose (**158**) to 3-deoxy-D-*erythro*-hex-2-enopyranose (**159a**) without altering the ring form. Compound **158** dehydrates in two stages when it is heated in dilute acetic acid; the formation of 5-(methoxymethyl)-2-furaldehyde (the second stage) occurs faster; hence the first stage, i.e., formation of **156**, is only accomplished in 1% yield. The key step of the

TABLE IV. Isolated Yields (%) of **66** and **68**

furfuryl alcohol	66	68 (R³) H	68 (R³) CH_3	68 (R³) C_2H_5	ref
	61	60		37	48
	91		77		49
	73		80		50
65a		48			143
	74	81		66	48
	95		87		49
	92		80		50
65b					
	73	100	68		48
	94	98	90		49
148					
		70			143
149					
		75	60		143
150					
		80	70	80	143
151					

SCHEME XXIV



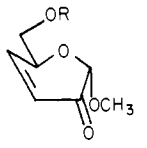
second method is the formation of the 2-*O*-methyl-hex-2-enopyranose **159b**.

3-Deoxy-2-*O*-methyl-D-*erythro*-hex-2-enose (**159b**) was first prepared by Kenner and Richards[183] by treating 2,3-di-*O*-methyl-D-glucose (**161a**) with aqueous calcium hydroxide. The method was improved and extended by Anet[181] to other 2-*O*-methylaldoses, **161b** and **161c**. Thus, 2,3,6-tri-*O*-methyl-D-glucose (**161b**) gives **159c**, while 2,3,4,6-tetra-*O*-methyl-D-glucose (**161c**)

yields the crystalline 2,4,6-tri-*O*-methyl-α-D-*erythro*-hex-2-enopyranose (**159d**). Larger yields of **157** are obtained on acid rearrangement of the 2-*O*-methyl-hex-2-enoses **159b**, **159c**, and **159d**. However, the long reaction times required in synthesizing **159** from **161** make this an impractical method.

Glycosidation of the free sugar **159d**[184] is effected with methyl sulfate in the presence of sodium hydroxide. The methyl α- and β-glycosides **160** are separated by preparative gas–liquid chromatography and then converted by acid treatment into the methyl 3,4-dideoxy-6-*O*-methyl-α- and -β-D-*glycero*-hex-3-enopyranosiduloses (**162**).

ii. 3,4-Dideoxy-6-*O*-acyl Sugars. Bock and Pedersen[185,186] studied the reactions of 1,5-anhydro-2,3,4,6-tetra-*O*-acyl-D-*arabino*-hex-1-enitol (**163**) with hydrogen fluoride. These reactions provided a method for the synthesis of methyl 6-*O*-acyl-3,4-dideoxy-α- and -β-D-*glycero*-hex-3-enopyranosiduloses (**165a** and **165b**) by way of the 2,4,6-tri-*O*-acyl-α- and -β-D-*erythro*-hex-2-enopyranosyl fluorides (**164**) (Scheme XXV). Hex-1-enopyranose **163a** or **163b** in anhydrous hydrogen fluoride at −78 °C is immediately converted to the corresponding hex-2-enopyranosyl fluoride **164a** or **164b**. However, at −30 °C, **163a** or **163b** is completely transformed to the hex-3-enopyranosylulose fluoride **165c** or **165d**. The conversion of **163** to **164** is also achieved with a solution of hydrogen fluoride in benzene. Under these conditions there is no further reaction. However, anhydrous hydrogen fluoride converts **164a** or **164b** to **165c** or **165d**. These products are obtained in almost quantitative yields as unstable syrups but are purified and the anomers separated, with considerable losses, by preparative thin-layer chromatography. Methanol in the presence of catalytic amounts of boron trifluoride causes glycosidation of the fluorides **165c** or **165d**, and the anomeric mixtures of **165a** or **165b** are separated by chromatography. Alternatively, **165a** or **165b** is obtained directly from **163** by prolonged reaction with methanol and boron trifluoride. Holder and Fraser-Reid[63,187] reported the synthesis of some crystalline alkyl 3,4-dideoxy-α-D-*glycero*-hex-3-enopyranosiduloses **166** with readily available starting materials and by way of simple laboratory processes.



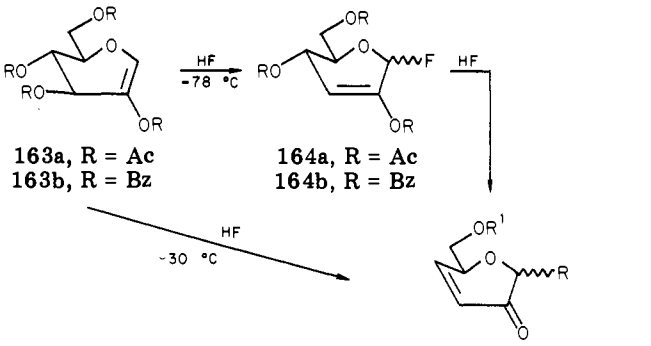
166, R = H, Ac, Bz, Tr

Extensive use was made of acid- and base-labile protecting groups and selective esterification of the secondary hydroxyl groups. Reductive elimination of cis and trans vicinal sulfonyloxy groups served to introduce the double bond into the pyranosides, and manganese dioxide or chromium trioxide was used to oxidize the allylic alcohols.

The synthetic sequence leading to olefin **168** having an equatorial allylic alcohol is illustrated in Scheme XXVI. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**28a**) forms when methyl α-D-glucopyranoside (**21b**) is allowed to react with α,α-dimethoxytoluene under conditions similar to those developed by Evans.[61,62,65] *N*-Benzoylimidazole in chloroform at room temperature then reacts with **28a** and gives **28b**.[76] Catalytic hydrogenolysis removes the benzylidene group, and the resulting monobenzoate **167a** is selectively benzoylated with benzoyl chloride to give **167b**. This three-step route to methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (**167b**) is better in overall yield and easier in execution than direct dibenzoylation of **21b** reported earlier.[71,72] Methanesulfonyl chloride esterifies dibenzoate **167b**, and the resulting 3,4-dimesylate **167c** undergoes reductive elimination by potassium iodide and zinc–copper couple in DMF to a mixture of an allylic alcohol **168a** and its benzoate **168b**. Hydrolysis of this mixture with the triethylamine–methanol–water system affords the diol **168c** as a mobile oil; this was characterized as its di-*O*-*p*-nitrobenzoate ester **168d** and 6-*O*-trityl ether **168e**.

A synthetic sequence (Scheme XXVII) was designed which provided a *cis*-3,4-dimesylate, an axial 2-hydroxy group, and subsequently an axial allylic alcohol. Se-

SCHEME XXV

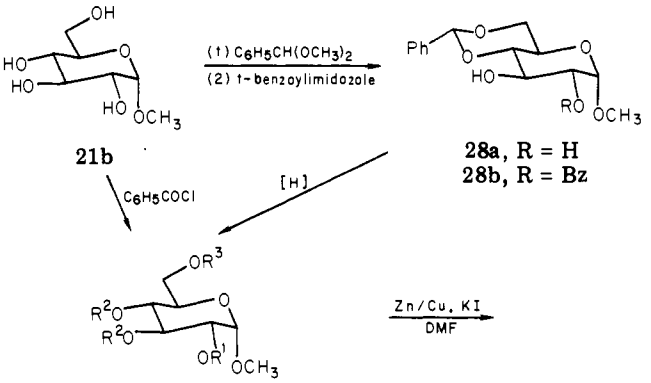


163a, R = Ac
163b, R = Bz

164a, R = Ac
164b, R = Bz

165a, R = OCH_3; R^1 = Ac
165b, R = OCH_3; R^1 = Bz
165c, R = F; R^1 = Ac
165d, R = F; R^1 = Bz

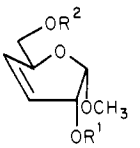
SCHEME XXVI



21b

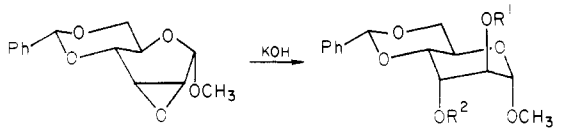
28a, R = H
28b, R = Bz

167a, R^1 = Bz; R^2 = R^3 = H
167b, R^1 = R^3 = Bz; R^2 = H
167c, R^1 = R^3 = Bz; R^2 = Ms
167d, R^1 = R^2 = H; R^3 = CPh_3
167e, R^1 = Bz; R^2 = H; R^3 = CPh_3
167f, R^1 = Bz; R^2 = Ms; R^3 = CPh_3



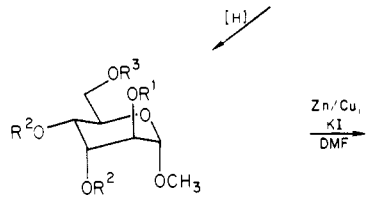
168a, R^1 = H; R^2 = Bz
168b, R^1 = R^2 = Bz
168c, R^1 = R^2 = H
168d, R^1 = R^2 = *p*-nitrobenzoyl
168e, R^1 = H; R^2 = CPh_3

SCHEME XXVII

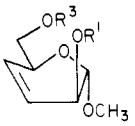


40

29a, $R^1 = R^2 = H$
29b, $R^1 = Bz; R^2 = H$
29c, $R^1 = H; R^2 = Bz$
29d, $R^1 = R^2 = Bz$



169a, $R^1 = Bz; R^2 = R^3 = H$
169b, $R^1 = Bz; R^2 = H; R^3 = CPh_3$
169c, $R^1 = Bz; R^2 = Ms; R^3 = CPh_3$

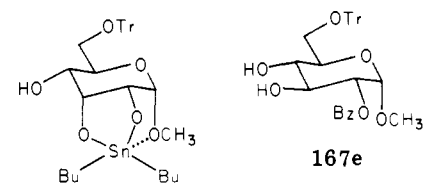


170a, $R^1 = H; R^3 = CPh_3$
170b, $R^1 = Bz; R^3 = CPh_3$

lective benzoylation of the readily available methyl 4,6-*O*-benzylidene-α-D-altropyranoside (**29a**) (obtained from epoxide **40**[57]) with *N*-benzoylimidazole affords 2-*O*-benzoate **29b** as the only benzoylated product.[78] Other methods of benzoylation[73,85] were less practical because of the variable quantities of 3-*O*-benzoate **29c** and 2,3-di-*O*-benzoate **29d** produced. Catalytic hydrogenolysis cleaves the benzylidene group of **29b**, and the resulting monobenzoate **169a** is treated at room temperature[80-82] with a solution of trityl chloride in anhydrous pyridine. The 6-*O*-trityl ether **169b** is not isolated, but is esterified with methanesulfonyl chloride to the crystalline methyl 2-*O*-benzoyl-3,4-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-altropyranoside (**169c**). Potassium iodide and zinc–copper couple in DMF effect the elimination of the methylsulfonyl groups from **169c** with introduction of 3,4 unsaturation. The triethylamine–methanol–water system debenzoylates the mixture **170a** and **170b**, and provides methyl 3,4-dideoxy-6-O-trityl-α-D-*threo*-hex-3-enopyranoside (**170a**).

Corey and co-workers[188] and Hernandez[189] also reported the synthesis of methyl 3,4-dideoxy-6-*O*-trityl-α-D-*erythro*-hex-3-enopyranoside (**168e**). The former group employed the route described by Holder and Fraser-Reid,[63,187] while Hernandez designed an alternate sequence. When methyl α-D-glucopyranoside (**21b**) is allowed to react with trityl chloride in triethylamine, DMF, and catalytic amounts of 4-(dimethylamino)-pyridine,[190] the 6-*O*-trityl ether **167d** forms in 85% yield. Di-*n*-butyltin oxide in refluxing methanol gives di-*n*-butylstannylene derivative **171**.[191] This intermediate provides the necessary activation of C-2 hydroxyl for selective benzoylation with benzoyl chloride in triethylamine and tetrahydrofuran.[191] Under these conditions, **171** is converted to **167e**. The subsequent steps to **168e** were conducted as described by Holder and Fraser-Reid.[63,187] Another instance where *cis*-di-*O*-(methylsulfonyl) groups undergo reductive elimination by the Tipson and Cohen[109] method was communicated by Umezawa et al.[192] in the transformation **172** → **173** → **168b** (Scheme XXVIII). The final stage in the synthesis of the methyl 3,4-dideoxy-α-D-*glycero*-hex-3-enopyranosiduloses, **166**, is the selective oxidation of the C-2 allylic alcohol (Scheme XXIX). Both allylic alcohols **168e** and **170a** are oxidized by manganese dioxide or chromium trioxide in pyridine to the crystalline enone **35**. Hydrogen chloride in chloroform[84] readily detritylates **35** and affords crystalline **166a**.

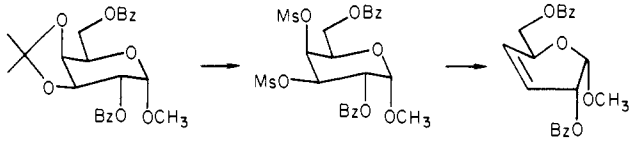
The most economical route to **166a** is outlined in Scheme XXX. This path originates with the previously described monobenzoate **28b**, and the key intermediates **167f** and **168e** are isolated as crystalline derivatives. Compound **166a** was esterified to the benzoate **166b**, *p*-nitrobenzoate **166c**, and acetate **166d**.[185,186]



171

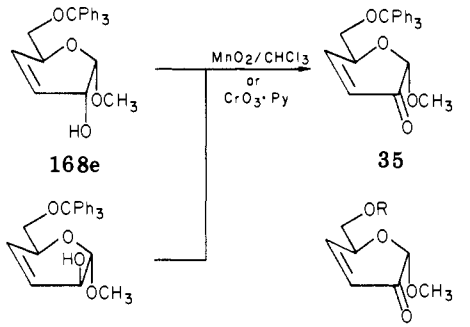
167e

SCHEME XXVIII



172 173 168b

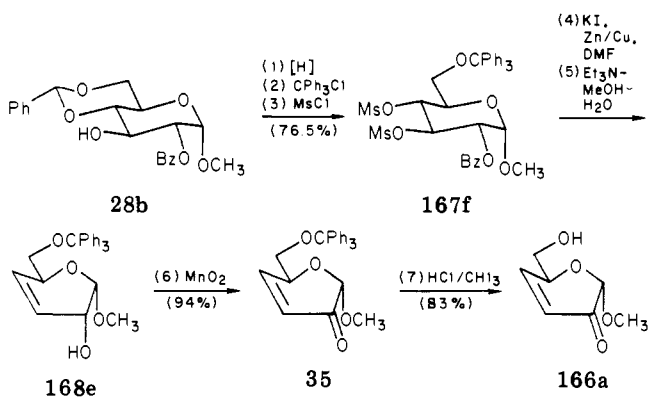
SCHEME XXIX



168e 35 170a

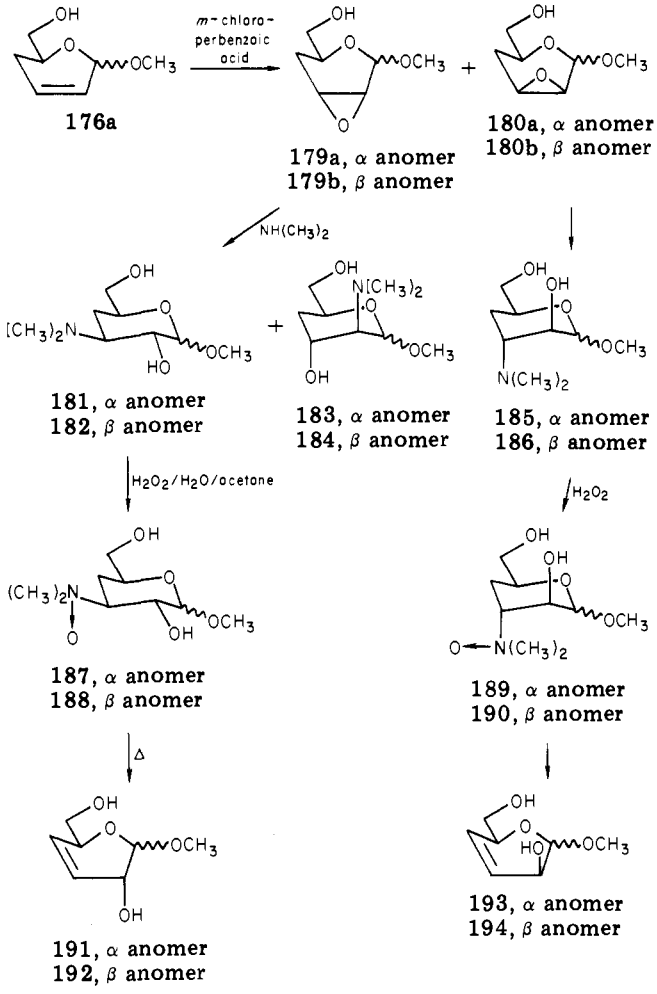
166a, R = H
166b, R = Bz
166c, R = *p*-nitrobenzoyl
166d, R = Ac

SCHEME XXX

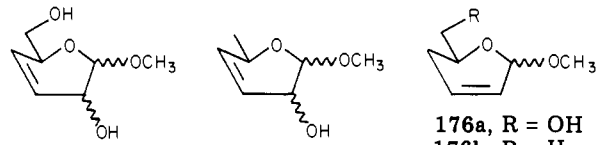


28b 167f 168e 35 166a

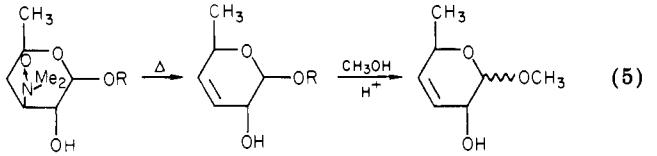
SCHEME XXXI



b. From Noncarbohydrate Precursors Another general approach to the synthesis of methyl 3,4-dideoxy- and 3,4,6-trideoxy-DL-hex-3-enopyranosides **174** and **175** from 2-methoxy-5,6-dihydro-2*H*-pyran derivatives **176** was described by Banaszek and Zamojski.[147] This



method was based upon the observation made by Jones and Rowley[193] during their studies of the structural modifications of erythromycins. They reported that pyrolysis of the desosamine *N*-oxide **177** (eq 5) leads to



(5)

R = macro ring of erythromycins

the unsaturated compound **178**. This on treatment with methanolic hydrogen chloride gives a mixture of methyl 3,4,6-trideoxy-α- and -β-D-*erythro*-hex-3-enopyranosides (**72**).

Epoxidation of *cis*- and *trans*-5,6-dihydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran (**176a**)[194] with *m*-chloroperbenzoic acid (Scheme XXXI) gives the four stereoisomeric epoxides **179a**, **179b**, **180a**, **180b**, which were separated chromatographically into pure components.[195] An aqueous solution of dimethylamine effects opening of the oxirane rings of **179** and **180** to give the *xylo* and *arabino* products **181–186** (Table V). The 3-(dimethylamino)-*xylo*-pyranosides **181** and **182** and -*arabino*-pyranosides **185** and **186** are oxidized with hydrogen peroxide in an acetone–water mixture to the corresponding *xylo* and *arabino* *N*-oxides **187**, **188** and **189**, **190**, respectively, in 90–100% yields. Elimination of *N*,*N*-dimethylhydroxylamine proceeds smoothly on heating each *N*-oxide under reduced pressure with the formation of methyl 3,4-dideoxy-DL-*erythro*- (**191**, **192**) and -*threo* (**193**, **194**)-hex-3-enopyranosides (Table VI).

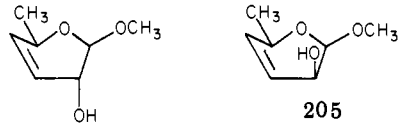
TABLE V. Reaction Products of Epoxides 179, 180, 195, and 196 with Aqueous Dimethylamine

epoxide	reaction time, h	products	yield, %
179a	48	181	84
		183	10
179b	48	182	73
		184	15
180a	12	185	100
180b	12	186	100
195	56	197	75
		198	12
196	1	199	85

TABLE VI. Products from Pyrolysis of *N*-Oxides 187, 188, 190, 200, 201

N-oxide	product	yield, %
187	191	67
188	192	59
189	193	66
190	194	64
200	202	68
201	203	76

The synthesis of methyl 3,4,6-trideoxy-α-DL-*erythro*-hex-3-enopyranoside (**202**) and the isomeric *threo*-hex-3-enopyranoside (**203**) starts with *trans*-5,6-dihydro-2-methoxy-6-methyl-2*H*-pyran (**176b**) and follows the same pathway (Scheme XXXII).[147,196] Anomerization of both **202** and **203** with methanolic hydrogen chloride and separation of the resulting α,β anomeric mixtures by column chromatography give the corresponding β anomers **204** and **205**.

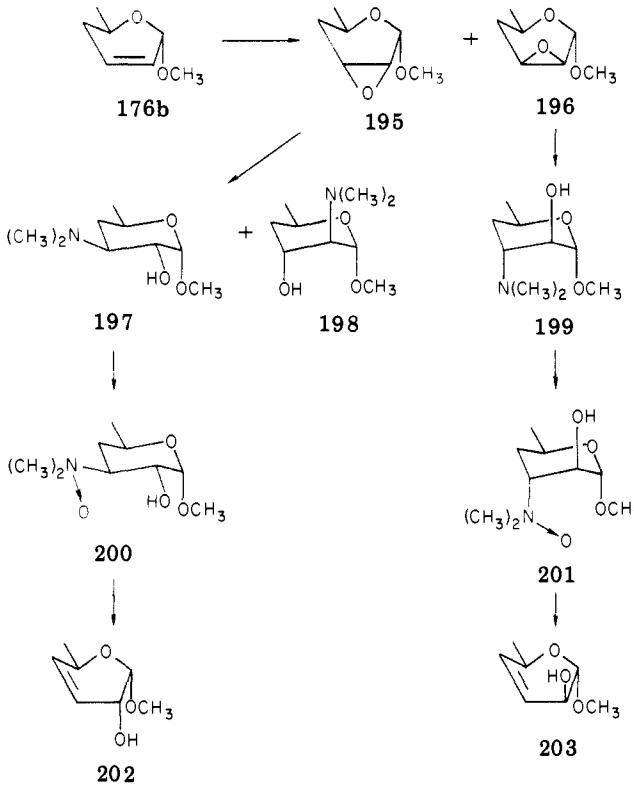


An alternate approach to the synthesis of racemic methyl 3,4,6-trideoxy-DL-*threo*- and -DL-*erythro*-hex-3-enopyranosides (**202**) and (**203**) from 5-methyl-2-furaldehyde (**72**) was reported by Bognar and Herczegh[146] (Scheme IX).

3. 1,5-Anhydrohex-1-en-3-uloses

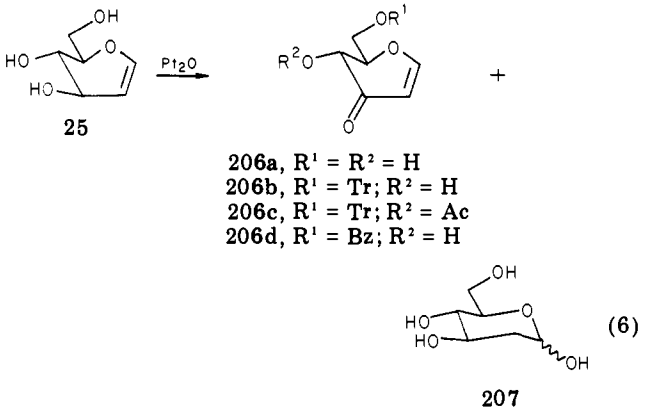
a. Direct Oxidation of Allylic Alcohol. These compounds are late arrivals on the chemical scene, considering their close relationship to D-glucal (**25**), a compound long known[197] to carbohydrate chemists. In 1966, Heyns and Gottschalck[23] reported that platinum oxide,

SCHEME XXXII



in an oxygen atmosphere, oxidizes **25**. The products of the reaction (eq 6) are 1,5-anhydro-2-deoxy-hex-1-en-3-ulose (**206a**) (1.5%), 2-deoxy-D-glucopyranose (**207**), and carboxylic acids. Formation of **207** was assumed to occur during workup by the addition of water to **25**. Later, Tronchet and co-workers[24] obtained higher yields (60–80%) of **206a** by using Fetizon's reagent (silver carbonate–Celite).

P. M. Collins[128] described the synthesis of 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*erythro*-hex-1-

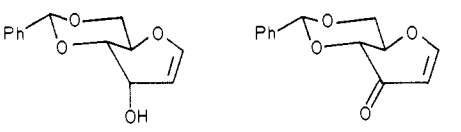


206a, $R^1 = R^2 = H$
206b, R^1 = Tr; R^2 = H
206c, R^1 = Tr; R^2 = Ac
206d, R^1 = Bz; R^2 = H

(6)

207

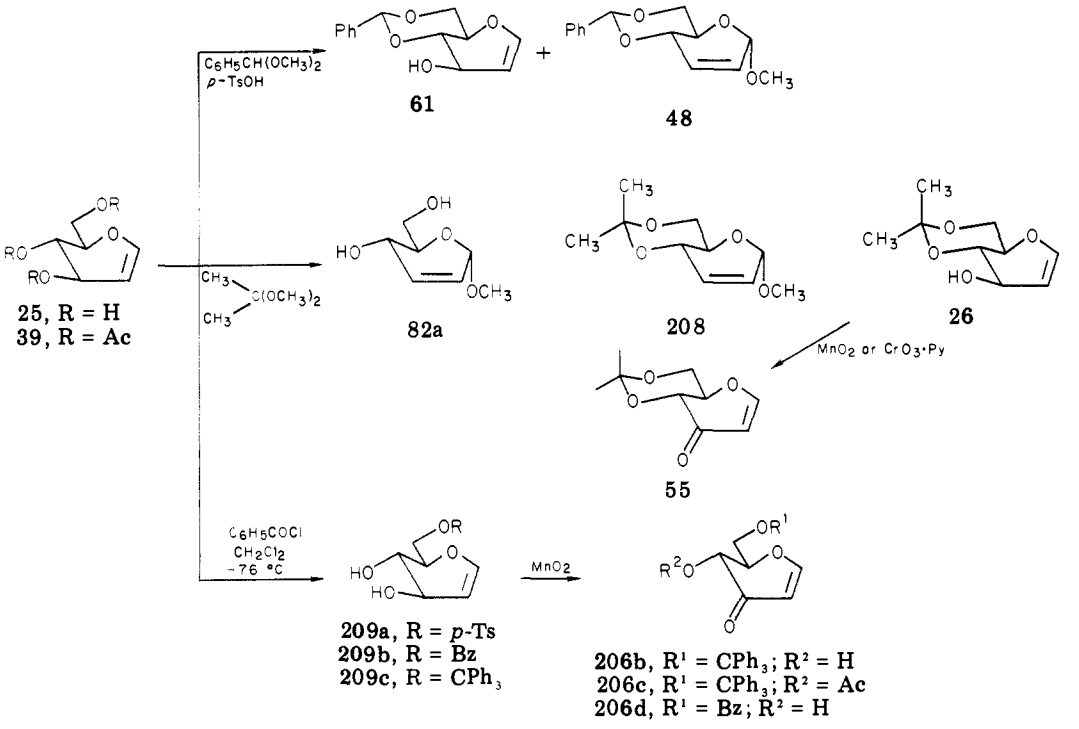
en-3-ulose (**62**) from **41a**.[91-94] Treatment of **41a** with



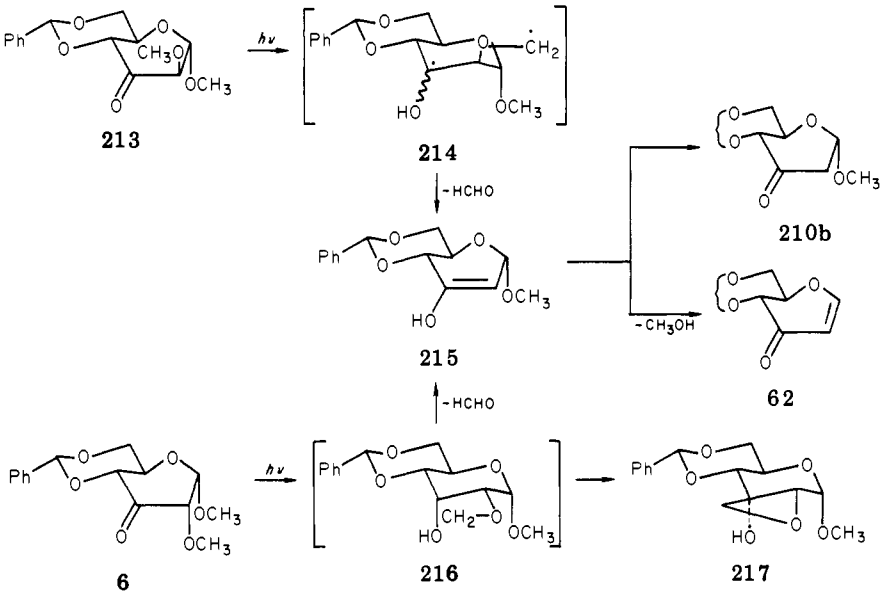
chromium trioxide in pyridine gives **62** in 75–80% yield. Other oxidizing agents were tried: (1) manganese dioxide, a reagent recommended for the oxidation of allylic alcohols, had little effect, (2) ruthenium dioxide attacked the double bond, and (3) methyl sulfoxide and sulfur trioxide–pyridine complex did give some enone, but the maximum yield of **62** was 30%.

A rapid route to 1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-uloses **62** and **206** containing acid- or base-labile protecting groups was reported by Fraser-Reid and associates.[65] Glucal (**25**) (Scheme XXXIII) was chosen as starting material because of its ready availability from tri-*O*-acetylglucal (**39**), and the presence of an allylic hydroxy group. Benzylidenation of **25** with benzaldehyde and zinc chloride[52,53,92] does not give **61** in large quantities, and on treatment with α,α-dimethoxytoluene in the presence of *p*-toluenesulfonic acid at room temperature, a number of products are formed.

SCHEME XXXIII



SCHEME XXXIV

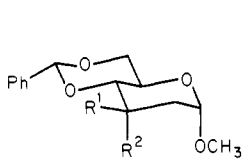


One of the products is **48**, formed in large quantities early in the reaction. Acetonation proved to be more controllable than benzylidenation. Thus, 2,2-dimethoxypropane in DMF acidified to pH 3 with *p*-toluenesulfonic acid effects acetonation of **25**. After 45 min, a reaction mixture is obtained from which **26** was separated chromatographically as an oil in 44% yield. When the reaction time is 2 h, two additional substances **82a** and **208** form.

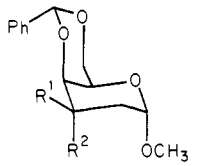
Manganese dioxide in chloroform oxidizes **26** slowly to 1,5-anhydro-4,6-*O*-isopropylidene-2-deoxy-D-*erythro*-hex-1-en-3-ulose (**55**) in 73% yield. Alternatively, the oxidation is accomplished in 15 min with chromium trioxide–pyridine in methylene chloride with a 77% yield. Fraser-Reid and co-workers[65] found it more practical to oxidize the crude acetonation product directly. Therefore, if **39** is deacylated by the methanol–water–triethylamine method and oxidation of **26** done with the chromium trioxide complex, **55** is obtained in 20% yield from **39** in 3–4 h without purification of intermediates.

1,5-Anhydro-2-deoxyhex-1-en-3-uloses **206**, containing base-labile groups, were prepared by taking advantage of the high reactivity which the primary alcohol has displayed in the preparation of 6-*O*-(*p*-tolylsulfonyl)-D-glucal (**209a**).[198] In one instance, D-glucal (**25**) (Scheme XXXIII) is benzoylated with benzoyl chloride in a mixture of pyridine and methylene chloride at −76 °C. The 6-*O*-benzoyl-D-glucal (**209b**) is then oxidized with manganese dioxide in chloroform for 12 h to give 1,5-anhydro-6-*O*-benzoyl-2-deoxy-D-*erythro*-hex-1-en-3-ulose (**206d**) in 26% yield. A sequence leading to **206c** was also described. D-Glucal (**25**) is tritylated to **209c** with trityl chloride, and manganese dioxide then oxidizes **209c** to **206b**. Acetic anhydride acetylates **206b** to 1,5-anhydro-4-*O*-acetyl-6-*O*-(triphenylmethyl)-2-deoxy-D-*erythro*-hex-1-enopyran-3-ulose (**206c**).

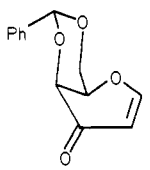
b. Photolysis of Methyl 2-O-Methylhexopyranosid-3-uloses. Collins and his associates observed the formation of 1,5-anhydro-2-deoxyhex-1-en-3-uloses during the oxidation of 2-deoxy-α-D-*lyxo*-hexopyranosides[25] and the photolysis of 2-*O*-methyl-α-D-hexopyranosid-3-ulose.[26,27] Whereas chromium trioxide–pyridine oxidizes a 2-deoxy-α-D-*arabino*-hexopyranoside (**210a**) to the *erythro*-hexopyranosid-3-ulose **210b**, it does not convert the *lyxo*-hexopyranoside **5** to the corresponding *threo*-hexopyranosid-3-ulose **211**. Instead, 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*threo*-hex-1-en-3-ulose (**212**) is obtained, presumably by elimination of methanol after oxidation. Evidence for this assumption



210a, R^1 = OH; R^2 = H
210b, $R^1 + R^2$ = O



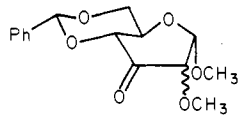
5, R^1 = OH; R^2 = H
211, $R^2 + R^1$ = O



212

came from the observation that **212** was obtained by heating **211** in 0.1 M pyridine in perchloric or hydrochloric acid. In pyridine alone, the starting ketone **211** is recovered; this establishes that acid catalyzes the elimination. Collins and his colleagues proposed that the rigidity of the trans ring fusion in **210** prevents elimination of methanol from **210b**. Ruthenium tetroxide oxidizes both **210a** and **5** to the ketones **210b** and **211** in better yields and without elimination of methanol.

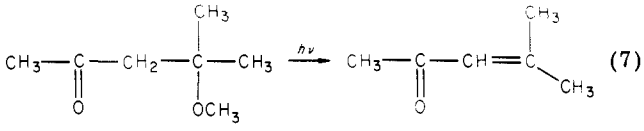
Methyl 2-*O*-methyl-α-D-pyranosid-3-uloses **213** have been reported to give type II photolytic cleavages. The



6, equatorial OCH_3 at C-2
213, axial OCH_3 at C-2

stereochemistry of the 2-*O*-methyl group effects the photochemical outcome. Irradiation of a 0.5% solution of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*arabino*-

hexopyranosid-3-ulose (213) (Scheme XXXIV) in benzene effects a 60% conversion to three products: the *ribo* isomer 6 (3%), 1,2-dideoxy-*erythro*-hex-1-enopyran-3-ulose 62 (46%), and 2-deoxy-*erythro*-hexopyranosid-3-ulose 210b (5%). A 1,4 elimination of methanol from the enol intermediate 215 was invoked to account for the formation of 62; this type of elimination product has also been observed in the photolysis of 4-methyl-4-methoxy-2-pentanone (218) (eq 7).[199]



218 219 (7)

The *ribo* isomer 6 undergoes photolysis more rapidly than the *arabino* compound 213 under similar conditions (Scheme XXXIV). Partial separation of the photochemical mixture was accomplished by preparative thin-layer chromatography, and the compounds identified are the starting material 6 (6%), a mixture (9:1) of 62 and 210b (4%), and 65% of an oxetanol 217, a product not unexpected in an α ketone photolysis.[200,201]

4. Alkyl Hex-4-enopyranosid-3-uloses

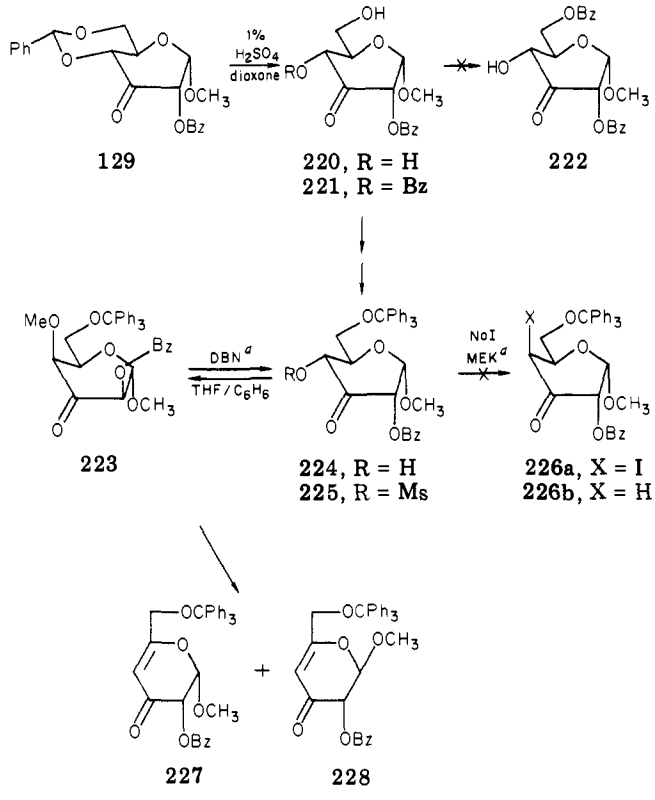
This class of compounds, like the 1,5-anhydro-2-deoxy-hex-1-eno-3-uloses 55, 62, 206, and 212, are vinylogous ethers and could possibly undergo similar conjugate 1,4 addition reactions.[202-205] Therefore, hex-4-enopyranosid-3-uloses are potential synthons for preparing pyranosides containing a variety of substituents at C-5.

Ferrier[38,39] reviewed several methods for introducing unsaturation between C-4 and C-5. Recent examples involving (a) elimination from aldehyde or uranate derivatives,[206-208] (b) allylic rearrangement of the 5,6 double bond with leaving groups at C-4[209,210] and (c) the Cope and Hofmann eliminations from C-4 *N*-oxide and quaternary ammonium salt, respectively,[211] have been reported. In 1978, Fraser-Reid and Yunker[28] described the introduction of 4,5 unsaturation by β elimination of sulfonic acid from a 4-(methylsulfonyl)hexopyranosid-3-ulose in their synthesis of methyl 2-*O*-benzoyl-4-deoxy-6-*O*-(triphenylmethyl)-α-D- and -β-L-*glycero*-hex-4-enopyranosid-3-uloses (227 and 228) (Scheme XXXV).

Debenzylidenation of the readily available ketone 129[76] is effected by heating in dioxane containing 1% sulfuric acid for 3 h. Selective benzoylation of 220 does not give the dibenzoate 222, but rather 221. Triphenylmethyl chloride effects tritylation of the primary hydroxyl group of 220 to give 224, and then the 4-*O*-mesylate 225 is prepared by treating 224 with methanesulfonyl chloride in pyridine. These conditions for preparing the sulfonic ester were adopted because unreproducible results were obtained with *p*-toluenesulfonyl chloride and methanesulfonyl chloride and triethylamine in methylene chloride gave an unexpected sultone.[212] The three steps leading to 225, 129 → 220, 220 → 224, 224 → 225, were carried out in 93%, 77%, and quantitative yields, respectively.

Treatment of the 4-*O*-(methylsulfonyl)hexopyranosid-3-ulose 225 with sodium iodide in methyl ethyl ketone does not give the expected iodide 226a;

SCHEME XXXV[a]



[a] MEK, methyl ethyl ketone; DBN, diazabicyclononane.

instead, the 4-deoxy compound 226b was identified as the major product. Alternatively, when the methanesulfonate 225 is treated with diazobicyclononene in tetrahydrofuran–benzene solution at room temperature, a very facile reaction occurs. Column chromatography of the reaction product gave 39% of a mixture of the α-D-*glycero* (227) and β-L-*glycero* (228) derivatives in a 58:42 ratio. The low yield was partly due to considerable detritylation which occurred during the reaction.

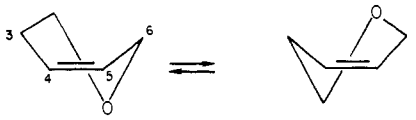
A synthetic sequence designed to incorporate the α,β-unsaturated-keto chromophore into a carbohydrate molecule is a challenge in view of the abundance, variety, and stereochemical relationships of the hydroxyl groups. The deployment of protecting groups coupled with the availability of modern chemical reagents has simplified efforts in preparing suitably substituted derivatives for use as intermediates in synthetic sequences leading to carbohydrate enones. The attractive features of the methods employed for synthesizing the hexenopyranosuloses are (1) the simplicity and ease of execution of the reactions, (2) the high yields of important intermediates and final products, (3) the low cost and availability of the reagents, and (4) the limited use of chromatographic techniques. More important is the fact that the intermediates, final products, and their derivatives are crystalline compounds. Methods originating with glycosides lead to one enantiomer of the carbohydrate enone, while methods involving furfurylcarbinols give rise to racemic mixtures.

V. Spectroscopic and Conformational Analysis

A. NMR Spectroscopy and Conformational Analysis

Dihydropyrans, like cyclohexene, exist in two conformations: half-chair and half-boat. However, because

SCHEME XXXVI



3,6-dihydro-2*H*-pyran

229

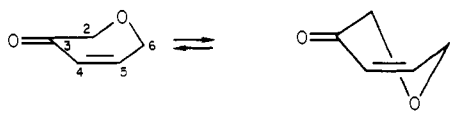
5,6-dihydro-2*H*-pyran

230

2,3-dihydro-4*H*-pyran

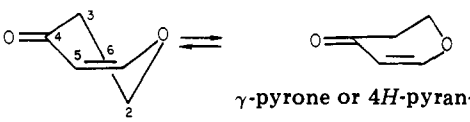
231

SCHEME XXXVII



α-pyrone or 2*H*-pyran-3-one

232



γ-pyrone or 4*H*-pyran-4-one

233

of strain, the half-chair is more stable.[213,214] In fact, Wells and Malloy reported[215] that 3,6-dihydro-2*H*-pyran (**229**) exists in a half-chair conformation with oxygen on one side of the plane formed by C-3, C-4, C-5, and C-6 (Scheme XXXVI); the position of the equilibrium depends on such factors as the anomeric effect[216] found in glycosides. Examples of 2,3-dihydro-4*H*-pyrans (**231**) are found in glycal chemistry[217,218] and conformational assignments were made in terms of the half-chair conformer (Scheme XXXVI). The carbonyl function of the α,β-unsaturated-keto chromophore introduces a third sp^2 hybridized carbon into the six-membered ring in dihydropyran. A consequence of this is a plane containing five adjacent atoms and a sixth atom above or below the plane (Scheme XXXVII).[219]

Several physical methods have been employed in conformational analysis,[213] and the application of some of them in the analysis of sugars and their derivatives was reviewed by a number of authors.[43,220] However, only proton magnetic resonance (^{1}H NMR) and ^{13}C magnetic resonance (^{13}C NMR) spectroscopic analyses will be discussed in this review. In describing NMR spectroscopy as a tool for conformational analysis, Durette and Horton[220] noted, "Since the pioneering work of Lemieux and co-workers[221]...this physical method has developed into the most powerful and direct technique for the investigation of the conformational aspects of sugars and their derivatives in solution."

Proton magnetic resonance (^{1}H NMR) spectroscopy is most widely used,[222-224] and up until 1964, no other nucleus in carbohydrates and their derivatives had been studied; in most cases, the conformation of the molecules is based solely on ^{1}H NMR. The first ^{13}C nuclear magnetic resonance papers to deal with carbohydrate structures were published in 1969; the authors[225-228] were particularly interested in identification and distribution of anomers. Since then, ^{13}C NMR has had widespread utility in conformational analysis of biological molecules[229] and in particular carbohydrates.[230] Achmatowicz and his associates[231-237] employed mainly ^{1}H NMR spectra and to a lesser extent ^{13}C NMR spectra in the conformational analysis of dihydropyran derivatives. ^{13}C magnetic resonance spectroscopy has not been widely used in conformational analysis of olefinic or α,β-unsaturated-keto sugars. Only two systematic studies have been reported: Achmatowicz et al.[234] on 2-substituted-6-alkoxy-3,6-dihydro-2*H*-pyrans (2,3-unsaturated sugars) and Guthrie et al.[238] on the study of glycals; there is a brief discussion of the ^{13}C NMR spectra of 2-substituted-6-methoxy-3,6-dihydro-2*H*-pyran-3-ones (hex-2-enopyranosid-4-uloses) to corroborate the configurational assignments made by analysis of ^{1}H NMR spectra.[237]

1. *Proton Nuclear Magnetic Resonance*

The characteristic chemical shifts and coupling constants of olefinic protons in the ^{1}H NMR spectra of dihydropyrans and -pyrones are well documented.[239] Typical spectroscopic features of some olefinic systems found in unsaturated sugars are summarized in Table VII, and the parameters are similar to those observed for dihydropyrans and -pyrones.

The conformational equilibrium is determined from the coupling constants of (a) vicinal and allylic protons in the —CH=CH—CH system on the basis of Garbisch[240] equations

$$J_{vic} = \begin{cases} 6.6\cos^2\phi + 2.6\sin^2\phi & 0° \le \phi \le 90° \\ 11.6\cos^2\phi + 2.6\sin^2\phi & 90° \le \phi \le 180° \end{cases}$$

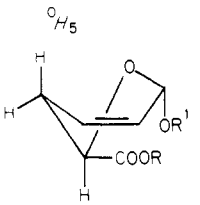
$$J_{allyl} = \begin{cases} 1.3\cos^2\phi + 2.6\sin^2\phi & 0° \le \phi \le 90° \\ -2.6\sin^2\phi & 90° \le \phi \le 180° \end{cases}$$

and (b) vicinal protons in the H—C—C—H system by the Karplus[241] equations.

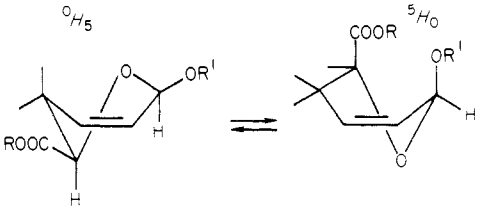
$$J = \begin{cases} 8.5\cos^2\phi - 0.3 & 0° \le \phi \le 90° \\ 9.5\cos^2\phi - 0.3 & 90° \le \phi \le 180° \end{cases}$$

These equations are semiempirical, and their parameters have been obtained from data for carbocyclic systems. It is not surprising therefore that Anet[184] observed some variations from these equations.

The structures of *cis*- and *trans*-6-alkoxy-3,6-dihydro-α-pyran-2-carboxylic esters are analogous to those of the hex-2-enopyranosides. A study of the ^{1}H NMR spectra of these esters[231] shows that the trans isomer **240** exists exclusively in the conformation with the ester function equatorial and the alkoxy group axial ($^0H_5$). This is based on the large sum of coupling constants (15.6 ± 0.1 Hz) for H-5 and H-4_{ax} and H-5 and H-4_{eq} (carbohydrate numbering) with dihedral angles of 170° and 50°, respectively. Conformational analysis leads to the same conclusion. Both the equatorial orientation of the carboalkoxy group and anomeric effect of pseudoaxial groups should favor the $^0H_5$ conformation of the trans adduct. In the case of the cis isomer **241**, there is an equilibrium in which the ester and the alkoxy groups exist in either the equatorial–



240

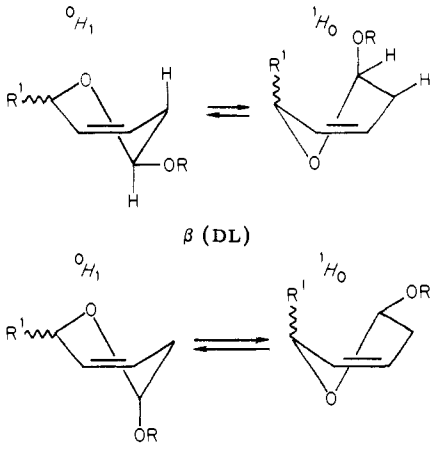


241

pseudoequatorial ($^{O}H_5$) or axial–pseudoaxial ($^{5}H_O$) relationships. The $^{5}H_O$ conformation is more stable despite the 1,3-diaxial interaction, and this preference is a result of the stabilizing effect of the anomeric pseudoaxial alkoxy group. This conformational analysis supports the observed small sum of coupling constants (~7 Hz) for H-5 and H-4_{ax} and H-5 and H-4_{eq} with dihedral angles of 50° and 70°, respectively.

The conformational assignment of pairs of 2*H*-pyran-3-ones (**232**, Scheme XXXVII) like the 2*H*-pyrans is also based on ^{1}H NMR spectra. Isomers with trans configuration of the 1-alkoxy and 5-alkyl substituents (carbohydrate numbering) and in which there is a pseudoequatorial proton at C-1 were identified by their large $J_{1,2}$ and small $J_{1,3}$ values. On the other hand, isomers with relatively smaller $J_{1,2}$ and larger $J_{1,3}$ values were assigned the cis configuration. The position of the equilibrium due to the nature of the 5-alkyl group is shown in Table VIII.

Derivatives of alkyl hex-3-enopyranosides (2-alkoxy-6-(hydroxymethyl)-3,6-dihydro-α-pyran) like those of alkyl hex-2-enopyranosides exist in a half-chain equilibrium **244**. However, the position of the equilibrium



β (DL)

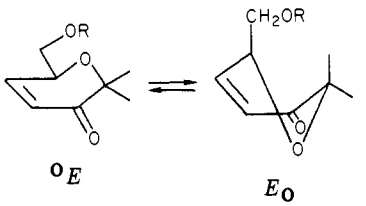
α (DL)

244

is influenced not only by the anomeric effect but also by the 1,3-axial–pseudoaxial repulsion and the allylic effect[242] of the 2-acetoxy substituent. The conformational equilibria for a number of compounds (Table IX) were determined from the magnitude of the vicinal coupling constant $J_{1,2}$; the values of $J_{1,2}$ are weighted averages of the corresponding coupling constants of the two conformers present in the equilibrium mixture.

The anomeric effect plays a decisive role in shifting the equilibrium of **245** and **246** to conformers with axial methoxy groups, and the magnitude of its effect, in **245** for example, increases with decreasing polarity of the solvent. In compound **246b**, the great preponderance of $^{1}H_O$ when compared with that for **245b** is attributed to an allylic effect.[242] This is due to the preference of polar substituents in allylic positions for the pseudoaxial orientation. A methyl, hydroxymethyl, or acetoxymethyl group at C-5 causes a shift exclusively to the $^{O}H_1$ conformer in the *α-threo* compounds **251a**, **252a**, and **253a**; in this conformation there are the preferred axial C-1 methoxy group, a pseudoaxial C-2 acetoxy or hydroxy, and the pseudoequatorial C-5 substituents. The preferred pseudoequatorial orientation of the C-5 substituents is indicated by the higher proportion of $^{O}H_1$ in **248a**, **249a**, and **250a** than that observed in **245a** and **246a**. In the *β-threo* (**251b**, **252b**, **253b**), and *β-erythro* (**247b**, **248b**, **249b**, **250b**) series, there is a 1,3-axial–pseudoaxial interaction between the C-1 methoxy and the C-5 substituents that is strong enough to destabilize a $^{1}H_O$ conformation. Consequently, these compounds show a preponderance of the $^{O}H_1$ conformer. Because of the allylic effect of the C-2 acetoxy group, the contributions of the $^{1}H_O$ anomer to the equilibrium is higher in **248b** and **250b** than it is in **251b** and **253b**.

The rigidity of the α,β-unsaturated carbonyl system limits the hex-3-enopyranosiduloses to two envelope conformations, **254**. In 1965, Anet[184] described the



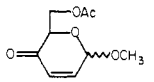
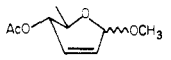
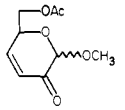
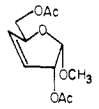
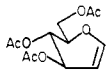
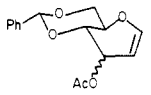
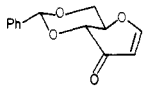
254

conformational analysis of anomeric pairs of methyl 3,4-dideoxy-6-*O*-methyl-hex-3-enopyranosiduloses. The ^{1}H NMR spectra of both α and β anomers show small vicinal coupling for $J_{4,5}$ and relatively large allylic coupling for $J_{3,5}$ (Table X); this indicates a dihedral angle of near 90°.[240,243] Therefore, both anomers exist in the ^{O}E conformation, with H-5 perpendicular to the ring.

The multiplicity of H-1 and H-3 provided information for the assignment at the anomeric center. Long-range couplings in the system H—C—C(=O)—C—H have maximum values when the two protons and three carbons are in the same plane. Therefore, the larger $J_{1,3}$ values (Table X) are consistent with the α isomers; similar values for $J_{1,3}$ were reported by Bock and Pedersen[186] for pairs of 6-*O*-acetyl derivatives and by Holder and Fraser-Reid[63] for the parent compound, made from methyl α-D-glucopyranoside. The anomeric proton of the β anomer displays a long-range coupling ($J_{1,5}$ ~ 1.1 Hz) that could arise by either a four-σ-bond coupling or through a six-bond coupling involving the π electrons of the unsaturated system. In each pair of hex-3-enopyranosiduloses, the shielding of H-1 is larger when H-1 is equatorial (Table X). This is the reverse situation normally found with pyranoside systems.[221]

Proton nuclear magnetic resonance spectroscopy played an important role in the conformational analysis

TABLE VII. Chemical Shifts (δ) and Coupling Constants (Hz) of Olefinic Protons of Hexenopyranoses, Hex-1-enitols, and Their Hex-en-uloses

compound	anomer	H-1	H-2	H-3	H-4	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	ref
	α		6.83	6.04		3.50	10.50		18
	β		6.83	6.10		2.20	10.70		18
20, α anomer 234, β anomer									
	α		5.30			not measured			18
	β		5.65–6.00			not measured			18
81, R = Ac, α anomer 235, β anomer									
	α			6.17	6.97			10.70	186
	β			6.22	7.03			10.70	186
166d, α anomer 165a, β anomer									
	α			5.72	5.85	4.20	1.60	10.20	186
236									
	β			5.85	6.05	2.80		10.00	186
237									
		6.53	4.81			6.40	3.20	not measured	217
39									
		6.46	4.99			6.00	2.00	7.50	92
		6.44	4.88			6.00	5.70	3.50	92
238, axial 239, equatorial									
		7.30	5.48			6.00			128
68									

of *O*-acetylglycals.[217,218] Assignments of chemical shifts and coupling constants (Table XI) were made on the basis of equal splitting in the different multiplets and also through systematic double resonance experiments. Other experiments such as weak field "tickling" and internuclear double resonance (INDOR) confirmed the assignment and sign of long-range couplings; the addition of a shift reagent produced simple spectra on which spin-decoupling and INDOR experiments were performed. One notable feature of the ^{1}H NMR spectra is the low-field absorptions in the ranges δ 6.0–6.6 and 4.5–5.1 with couplings of approximately 6 Hz. These absorptions were assigned to H-1 and H-2, respectively, because of the similarities in chemical shifts for the olefinic protons of 2,3-dihydrofuran and 2,3-dihydropyran;[239] similar values were recorded for the 4,6-*O*-benzylidene analogues **238** and **239** (Table VII)[92] and 1,5-anhydro-4-*O*-acetyl-2,3,6-tri-deoxy-D-*erythro*- and -*threo*-hex-1-enitols **258** (*cis* and *trans*-3-acetoxy-2-methyl-2,3-dihydro-γ-pyrans).[236]

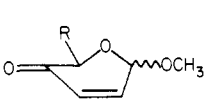
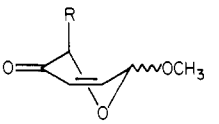
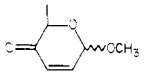
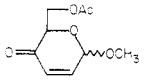
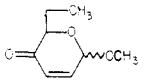
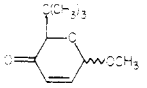
Distinctions between the two conformations $^4H_5$ and $^5H_4$ were made on the basis of $J_{3,4}$ or $J_{3',4}$ and $J_{4,5}$. The magnitude of the vinyl–allylic coupling $J_{2,3}$ or $J_{2,3'}$ determines the orientation of H-3. These couplings depend on the angle the allylic proton makes with the olefinic plane and are smallest when the angle is 90°.[240,243] There are two schools of thought regarding the low value 6.8 Hz for $J_{4,5}$ in **254**-equatorial; the accepted range for axial–axial couplings is 8–12 Hz. Ferrier,[242] Hall and Johnson,[217] and Chalmers and Hall[215] attribute the low coupling to the flattening of the ring. Achmatowicz and his co-workers[236] feel that the low value (6.6 Hz in **258**-equatorial and 6.8 Hz in **254**-equatorial) was due to the existence of an equilibrium half-chair conformation with $^4H_5$ and $^5H_4$ conformers. The most sensitive indicator to conformational change is the coupling $J_{2,4}$. It is large when H-4 is equatorial and not observed when H-4 is axial.

Chalmers and Hall[218] considered various allylic and nonallylic interactions to account for the conformational preferences of the glycals.

2. ^{13}C Nuclear Magnetic Resonance

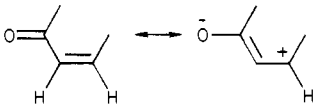
Although ^{13}C NMR spectroscopy provides the same types of information as ^{1}H NMR, only the chemical shifts are the most useful parameters.[244] Chemical shifts are directly influenced by the electron density associated with the particular atom and are also de-

TABLE VIII. Coupling Constants (Hz) and Conformer Population (%) of Methyl Hex-2-enopyranosid-4-uloses

compound	$J_{1,2}$	$J_{1,3}$	 α	β	 α	β
	3.30	0.50	93		7	
	1.90	1.50		78		22
52, α isomer 141, β isomer						
	3.50	0.50	98		2	
	2.20	1.70		73		27
20, α isomer 234, β isomer						
	3.30	0.50	93		7	
	1.70	1.50		88		12
242a, α isomer 242b, β isomer						
	3.45	0.50	100		0	
	1.45	1.75		100		0
243a, α isomer 243b, β isomer						

pendent on the nature and orientation of a substituent on that atom and to a lesser extent on those of neighboring substituents. Two generalizations, germane to this discussion, were formulated on the basis of comparative studies of anomeric monosaccharides,[245,246] cyclohexane derivatives,[247] and some inositols and their *O*-methyl derivatives:[248] (1) axial substituents are associated with increased shielding to which it is attached and (2) an axial hydrogen atom in a 1,3-axial relationship with an axial substituent is associated with shielding to the ^{13}C nucleus to which it is attached (γ effect). Marr and Stothers[249] reported some typical olefinic chemical shifts in cyclohexene and cyclohexenone along with the carbonyl carbon shift.

Achmatowicz and co-workers[234] employed ^{13}C NMR spectroscopy to confirm the conformations of methyl 2-enopyranosides and methyl 2-enopyranosiduloses (3,6-dihydropyrans and dihydropyrones); the conformations of these compounds were assigned on the basis of ^1H NMR and conformational analysis. A comparison of the ^{13}C NMR spectra of methyl 2,3,4-trideoxypent-2-enopyranoside (**259**) and some C-5 derivatives **260**, **261**, and **262** (Table XII) leads to the unequivocal assignments of C-5 and the *O*-methoxy carbons. The signals at 127.7–129.3 ppm were assigned to C-2 and those at higher field (126.6–127.7 ppm) to C-3. By comparing the spectra of **261**-α and **261**-β with those of the derivatives deuterated at the hydroxymethyl group, it was possible to distinguish between the hydroxymethyl group and the C-5 signals. Also in compound **262** there is the expected downfield shifting of the CH_2OH signal. One noticeable feature in the spectra of **259–262** is that there is no significant change in the chemical shifts of the olefinic protons (cf. 127.4 ppm for cyclohexene) due to the anomeric methoxy group. However, the appearance of C-2 at 144.7–147.6 ppm in **263** may be due to the polarization of the π electron away from C-2.

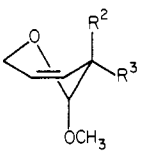
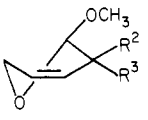
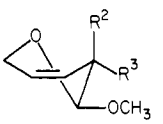
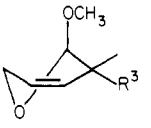
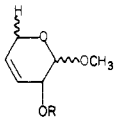
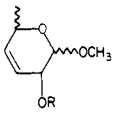
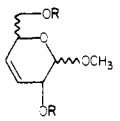
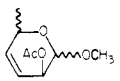
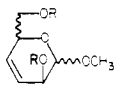


There also appears to be a shielding effect (~ 3 ppm) of C-3 in the trans isomer of **263**; this is not observed in **260–262**.

The shielding effect of the axial substituent on both the α and γ carbon atoms featured in differentiating between α and β anomers. In the α anomer, C-1 was shifted upfield by 1.0–2.5 ppm, while the magnitude for the C-5 shift was at 2.9–4.5 ppm. In compounds **260–263** the steric hindrance of the C-5 substituent along with the anomeric effect stabilizes the α anomer in the $^OH_5$ conformation with an axial OCH_3 at C-1 and an equatorial CH_2OR at C-5. These steric effects act in the opposite directions in the β anomer; therefore both half-chair forms of **260–263** exist in equilibrium ($^OH_5 \leftarrow {}^5H_O$).

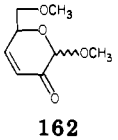
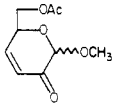
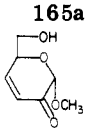
Qualitative analyses of the C-5 and C-4 chemical shifts were employed to estimate the position of the equilibrium. The measured differences of the C-5 chemical shifts in **261**, **262**, and **263** compared favorably with those of C-5 in *cis*- and *trans*-4-*tert*-butylcyclohexanols and α- and β-glucopyranosides[245] (4.7 and 4.2 ppm). In both classes of model compounds the shift to higher field was due to the axial group effect in the cis (β) isomers. Therefore, in an analogous fashion, the β anomers of **261**, **262**, and **263** exist exclusively in the $^OH_5$ conformation. The difference in C-5 chemical shift

TABLE IX. Coupling Constants ($J_{1,2}$) and Conformer Distribution of Methyl DL-Hex-3-enopyranosides

compound[a]	$J_{1,2}$	solvent				
	α 4.20	C_6D_6	100	0		
	3.75	$CDCl_3$	75	25		
	3.55	$(CD_3)_2SO_2$	64	36		
	3.50	D_2O	61	39		
	β 1.75	C_6D_6			79	21
245, R = H; R^3 = OH; R^2 = H	2.75	$CDCl_3$			64	36
246, R = Ac; R^3 = OAc; R^2 = H	3.15	$(CD_3)_2SO_2$			58	42
	2.88	D_2O			62	38
	α 3.75	$CDCl_3$	75	25		
	β 0.75	$CDCl_3$			6	94
	α 3.72	$CDCl_3$	72	28		
	β 6.00	$CDCl_3$			85	15
	α 4.20	$CDCl_3$	100	0		
	β 5.63	$CDCl_3$			78	22
247, R = H; R^3 = OH; R^2 = H						
248, R = Ac; R^3 = OAc; R^2 = H						
	α 3.80	$CDCl_3$	78	22		
	β 5.95	$CDCl_3$			84	16
	α 4.20	$CDCl_3$	100			
	β 4.75	$CDCl_3$			66	34
249, R = H; R^3 = OH						
250, R = Ac, R^3 = OAc						
	α *b*	$CDCl_3$	100			
	β 2.70	$CDCl_3$			83	17
251, R^2 = OAc						
	α 4.20	$CDCl_3$	100	0		
	β 2.40	$CDCl_3$			100	0
	α *b*	$CDCl_3$	100			
	β 2.98	$CDCl_3$			73	27
252, R = H; R^2 = OH						
253, R = Ac; R^2 = OAc						

[a] a = α anomer, b = β anomer. [b] Coupling constant not measured.

TABLE X. Chemical Shifts (δ) and Coupling Constants (Hz) of Methyl D-Hex-3-enopyranosiduloses

compound	chemical shift of H-1, δ	$J_{1,3}$	$J_{1,5}$	$J_{3,5}$	$J_{4,5}$	ref
	α 4.92	0.75	0.30	2.70	1.70	184
	β 5.02	0.20	1.10	2.60	2.30	185
162						
	α 4.80	0.80		2.50	1.80	186
	β 4.82	0.40		2.00	3.00	186
165a						
	α 4.8	~1.00		2.70	1.00	63
166a						

in **260** is significantly less, and may be attributed to some contributions from the ^5H_O conformer. A similar conclusion was arrived at from an analysis of the C-4 chemical shifts. In the pairs of anomers **261**, **262**, and **263** the chemical shifts are approximately the same. This suggests that the C-5 substituents are in the equatorial orientation in both the α and β anomers. The difference of ~2.0 ppm in the C-4 chemical shift of **260** was due to the contributions of the ^5H_O and $^OH_5$ conformers to the equilibrium. Achmatowicz et al. reasoned that the shifting of the conformational equilibrium toward ^5H_O in **260**-β is a consequence of the smaller steric hindrance of carbomethoxy group as compared with hydroxymethyl and acetoxymethyl groups and the tendency of the anomeric OCH_3 to adopt an axial configuration.

Guthrie and co-workers[238] reported results (Table XIII) from a study of the ^{13}C NMR spectra of D-allal and D-glucal; 2,3-dihydro-4*H*-pyran (**264**) served as a model compound for the study. Assignments of ^{13}C resonances were established mainly by chemical shift considerations. However, in some instances, the use of lanthanide shift reagent and proton chemical shift correlations were employed for unequivocal assignments of certain resonances.

The ^{13}C NMR spectra of these compounds display two low-field resonances at 142–146 ppm and 99–104 ppm. The former resonance was assigned to the oxygenated sp^2 carbon (C-1) and the latter to the nonoxygenated sp^2 carbon (C-2). These values when com-

TABLE XI. Conformation, Olefinic Chemical Shifts (δ), and Coupling Constants (Hz) of Acetyl-D-glycals

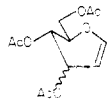
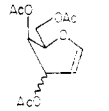
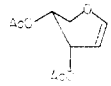
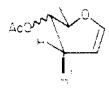
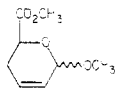
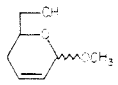
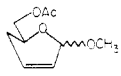
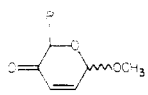
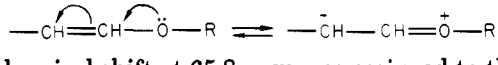
compound	epimer	conformation	H-1	H-2	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	ref
	axial	$^4H_5$	6.22	4.68	6.00	5.90	3.90	10.10	218
	equatorial	$^4H_5$	6.53	4.81	6.40	3.20	6.40	6.80	217, 218
254									
	axial	$^4H_5$	6.18	5.04	5.80	5.20	2.50	1.50	218
	equatorial	$^4H_5$	6.16	4.54	6.30	2.50	4.60	1.80	218
255									
	cis (ax-eq)	$^4H_5$	6.33	4.66	6.00	4.90	4.20	9.30	218
256									
	trans (ax-ax)	$^5H_4$	6.36	4.93	6.20	4.60	2.70	2.20	218
257									
	axial	$^4H_5$ (75%); $^5H_4$ (25%)	6.37	4.61	6.20	4.5 ($J_{2,3}$); 3.0 ($J_{2,3}'$)		1.0	236
	equatorial	$^4H_5$ (65%); $^5H_4$ (25%)	6.25	4.57	6.20	4.2 ($J_{2,3}$); 3.3 ($J_{2,3}'$)	6.2 ($J_{3,4}$); 7.1 ($J_{3',4}$)	6.6	236
258									

TABLE XII. ^{13}C Nuclear Magnetic Resonance Chemical Shifts (ppm) of Methyl 2,3,4-Trideoxypent-2-enopyranosides and -2-enopyranosid-4-uloses

compound		C-1	C-2	C-3	C-4	C-5	ΔC-1	ΔC-5	CH_2OH
		95.4	129.3	126.7	25.5	57.7			
259									
	β	96.6	127.7	126.5	26.1	69.2	1.0	2.9	
	α	95.6	127.7	126.0	27.7	66.3			
260									
	β	97.7	129.1	126.4	27.0	73.4	1.8	5.3	65.3
	α	95.9	129.1	127.7	27.0	65.2			
261									
	β	97.0	127.9	127.7	26.7	69.8	1.4	4.4	66.4
	α	95.6	128.3	126.6	27.1	65.4			66.8
262									
	(H)	94.5	145.6	128.0	195.5	66.0			
	$(CH_3)_\beta$	96.7	147.6	128.3	197.4	74.7	2.2	4.5	
	$(CH_3)_\alpha$	94.5	144.7	127.3	197.6	70.2			

263, R = H
R = CH_3

pared with the olefinic absorptions found in **259–262** clearly indicate a significant polarization of the π electron cloud toward C-2. In compound **264** the low-



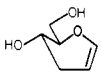
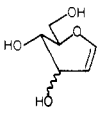
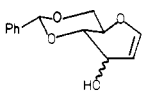
field chemical shift at 65.8 ppm was assigned to the C-5 resonance. Substition of the hydroxymethyl group at C-5 introduces shielding and causes a large downfield shift to 75.7 ppm in **265**. In neither **264** nor **265** was it possible to distinguish between C-3 and C-4. However, in **266** the equatorial hydroxy substituent resulted in the shift downfield of C-4 to 63.8 ppm.

Analysis of the ^{13}C spectra of glucal and allal (**267**) or their 4,6-*O*-benzylidene derivatives **268** was facilitated by chemical shifts considerations and comparison with 3-deoxyglycal. By this approach, Guthrie and his associates[238] made assignments for C-1, C-2, C-5, and C-6. Proton chemical shift was employed to differentiate between C-3 and C-4 in glucal and allal, while a distinction between the methine carbons C-3, C-4, and C-5 and the benzylidene carbon was made possible through the lanthanide-induced shift effect. The higher shielding on carbons 3 and 5 due to the axial hydroxy substituent is evident from the appearance of C-3 and C-5 resonances at higher field in allal and its derivatives.

B. IR and UV Spectroscopy

The characteristic stretching absorptions for olefins, ethers, and ketones and the effect on their position and intensities due to conjugation are well documented.[250]

TABLE XIII. ^{13}C Nuclear Magnetic Resonance Chemical Shifts (ppm) of 2,3-Dihydro-4*H*-pyran, Glucal, and Allal and Their Derivatives

compound	epimer	C-1	C-2	C-3	C-4	C-5	C-6
 264		144.5	100.6	19.9 – 23.2		65.8	
 265		143.5	100.7	19.4 – 24.1		75.1	65.0
 266		142.3	99.7	27.9	63.8	79.4	61.2
 267	equatorial axial	144.6 146.2	103.8 101.3	69.7 62.5	69.2 67.0	79.1 74.8	61.0 61.3
 268	equatorial axial	143.9 146.0	103.5 101.1	66.3 60.0	80.5 78.2	68.2 63.9	68.2 68.3

Whereas unconjugated olefins usually show moderate to weak absorptions in the 1660–1640-cm^{-1} range, cycloolefins show weak absorptions. Conversely, vinyl ethers are characterized by their higher intensities and appearance as doublets at 1660–1610 cm^{-1}.[251] Glycals and their derivatives show intense absorptions for –C=C– near 1650 cm^{-1}.[96] The absorption of the olefin in conjugation with a carbonyl group occurs at lower frequencies (1647–1621 cm^{-1}). In the spectra of aliphatic ethers, the most characteristic absorption is a strong band in the 1124–1030-cm^{-1} region; unsaturated cyclic compounds show absorptions at higher frequencies. The delocalization of the π electrons of carbonyl due to conjugation olefin causes absorption of the carbonyl to appear at lower wave numbers, i.e., 1700–1674 cm^{-1}. The IR spectra of hexenopyranoses and hexenopyranosuloses show characteristic absorptions (Table XIV) in keeping with these observations.

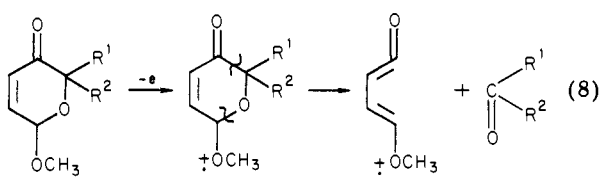
Ultraviolet (UV) spectra of α,β-unsaturated ketones are characterized by an intense $\pi \rightarrow \pi^*$ absorption at 215–250 nm (ϵ_{max} usually 10 000 to 20 000) and a weak $n \rightarrow \pi^*$ at 310–330 nm.[252] A β-ether substituent causes a large bathochromic shift, due to the interactions of the nonbonding electrons on the oxygen with the conjugated system. The pyranosiduloses absorb at about 220 nm (ϵ_{max} 9000) (Table XIV). In contrast, the pyranosuloses show absorptions at 260 nm (ϵ_{max} 8048) (Table XIV), which corresponds favorably with the maxima for 2,3-dihydropyrones.[253]

C. Mass Spectroscopy

Mass spectrometry has become an important analytical tool in carbohydrate chemistry. Its usefulness in determining ring size[254-256] and location of unsaturation[257] is well established. Holder and Fraser-Reid[258] studied the mass spectra of some carbohydrate enones and concluded that the main fragmentation pathways are direct loss of ring substituents while retaining the pyranosidulose ring and a retro-Diels–Alder type cleavage. Accurate mass measurements of salient fragment ions and recognition of appropriate metastable peaks support the proposed fragmentation pathways. Achmatowicz and Grynkiewicz[259] established the fragmentation patterns from a comparative study of 2,3-dideoxypent- or -hex-2-enopyranosuloses, the methyl glycosides, and the C-5 and C-6 deuterium-labeled derivatives.

1. Retro-Diels–Alder Fragmentation

In the case of **85** and **87**, cleavage of the C-4–C-5 and C-1–O (ring) bonds leads to the ion m/e 112 (Scheme XXXVIII), while with **166a**, a similar cleavage involving C-1–C-2 and C-5–O (ring) affords the ion m/e 98; ratio of the intensities of the peaks at m/e 112 and 98 is different for each enone. The effect of substitution on the para position of the enone is manifested not only in the intensity of the ions from the first stage fragmentation but also in the decomposition of the resulting ions of similar or identical composition. Achmatowicz and Grynkiewicz[259] proposed a similar fragmentation (eq 8) for the mass spectra of methyl pent- and hex-2-



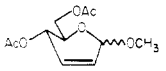
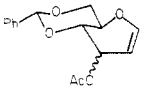
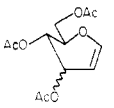
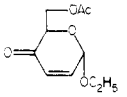
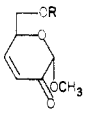
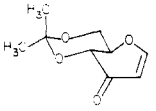
(8)

269 **270**

enopyranosiduloses **269** and obtained the same ion **270** at m/e 98 regardless of C-5 and C-6 deuterium label. Other structurally related compounds for which the retrodiene breakdown under electron impact has been proposed are cyclohexenones,[260,261] 5,6-dihydropyrans,[262] and 2,3-unsaturated monosaccharides.[257]

The charged radicals m/e 112 obtained from **85** or **87** and m/e 98 from **166a** are similar in structure and could undergo fragmentations common to both. Two such pathways are possible (Scheme XXXVIII): (1) McLafferty rearrangements[263] and (2) loss of carbon monoxide. With regard to (1), the ions m/e 112 and

TABLE XIV. IR and UV Spectral Data of Hexenopyranoses and Hex-1-enitols, and Their Hex-en-uloses

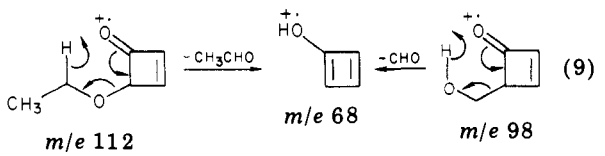
compound	IR, ν_{max}, cm^{-1}	functional group	UV λ_{max}, nm	UV ϵ	ref
 81, α anomer 235, β anomer	1655[a]	—C=C—			18
 238, axial 239, equatorial	ax 1652[b] eq 1668[b]	—O—C=C			92 92
 254	ax 1650[c] eq 1645[c]	—O—C=C			218 218
 87	1648[c]	—C=C—C=O	210[d]	7800	16
 184, R = CH_3 166a, R = H	CH_3 1622[c] 1705 H 1653 1700	—C=C— C=O —C=C— C=O	228[e] 222[f]	9500 9521	184 63
 55	1250[c] 1060 1600 1700	C=C—O— C=C—C=O C=O	260[d]	8048	65

[a] KBr disk. [b] Nujol. [c] Chloroform. [d] Ethanol. [e] Water. [f] Methanol.

TABLE XV. High-Resolution Mass Spectral Data of Hex-2-enopyranosid-4-ulose 85

obsd	calcd	elemental composition
29.0027	29.0027	CHO (62.5%)
29.0396	29.0391	C_2H_5 (37.5%)
55.0183	55.0184	C_3H_3O
84.0203	84.0211	$C_4H_4O_2$ (31.5%)
84.0565	84.0575	C_5H_8O (68.5%)
112.0531	112.0524	$C_6H_8O_2$
172.0736	172.0735	$C_8H_{12}O_4$ (M^+)

m/e 98 lose acetaldehyde and formaldehyde, respectively, with the formation of diene m/e 68 (eq 9).



(9)

Further loss of acetylene from ion m/e 68 generates the species m/e 42. This is the most intense peak in **166a** while in **85** and **87** it has relative intensities of 14% and 7.5%, respectively. Loss of carbon monoxide from m/e 112 gives the cyclopropene radical ion $[C_5H_8]^{+\cdot}$, m/e 84, as the most abundant peak in **85** and **87**. Similarly, loss of carbon monoxide from cyclobutenone, m/e 98, gives (hydroxymethyl)cyclopropene, m/e 70 (63.5% relative intensity). Fragmentations similar to these had been proposed for cyclohexenones.[260,261]

TABLE XVI. Metastable Peaks of Some Transitions in the Mass Spectra of Hexenopyranosiduloses 85, 87, and 166a

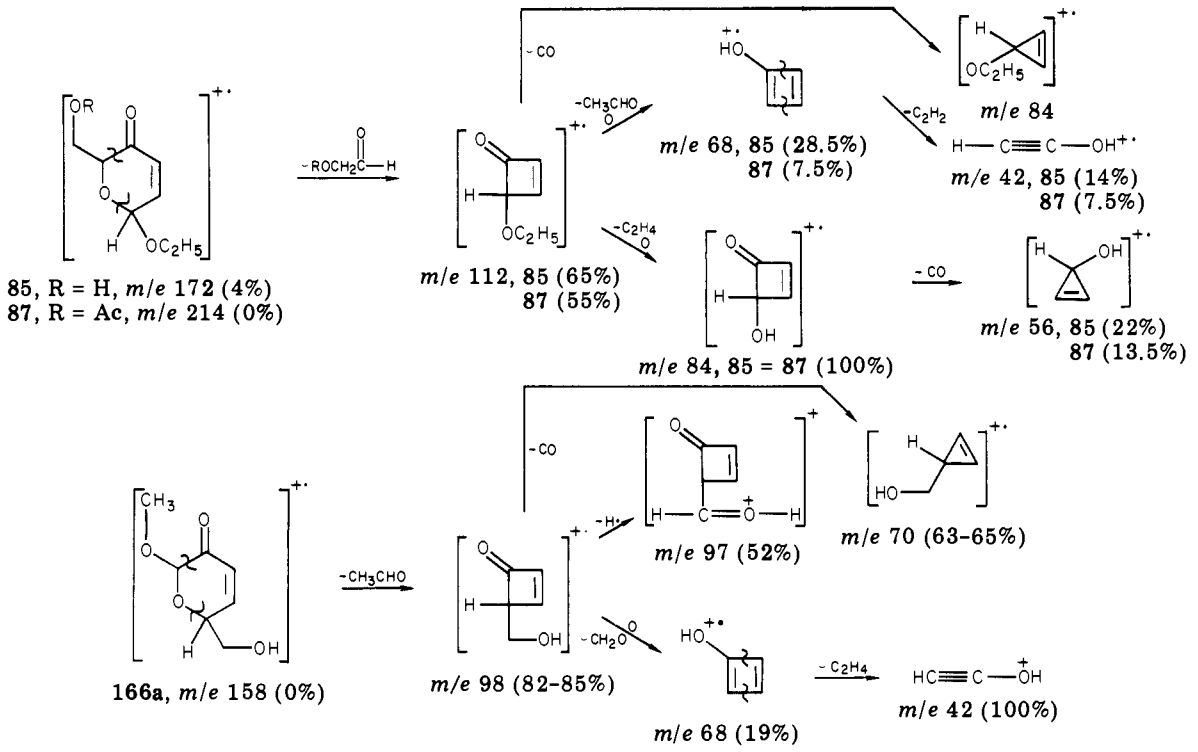
transition	compound	obsd	calcd
112 → 84	85	63.20	63.00
	87	63.20	63.00
84 → 56	85	37.10	37.33
	87	37.10	37.33
98 → 70	166a	50.00	50.00
68 → 42	166a	25.70	25.90
172 → 142	85	117.00	117.23
127 → 97	85	74.00	74.08
169 → 109	87	70.00	70.30
154 → 109	87	77.00	77.14

Precedent for the third decomposition of ion m/e 112 is found in the fragmentation of allylic ethers.[264] On this basis, ethylene is lost from the ethoxy group by way of a hydrogen transfer through a four-membered intermediate, with the formation of 4-hydroxycyclobut-2-enone, $[C_4H_4O_2]^{+\cdot}$, m/e 84. This can lose carbon monoxide with the formation of cyclopropenol, m/e 56. High resolution studies of **85**, summarized in Table XV, verify that m/e 84 is a doublet. Further support for the analyses in Scheme XXXVIII is given by the observation of metastable peaks (Table XVI) for the transitions m/e 112 → m/e 84, 84 → 56, 98 → 70, 68 → 42.

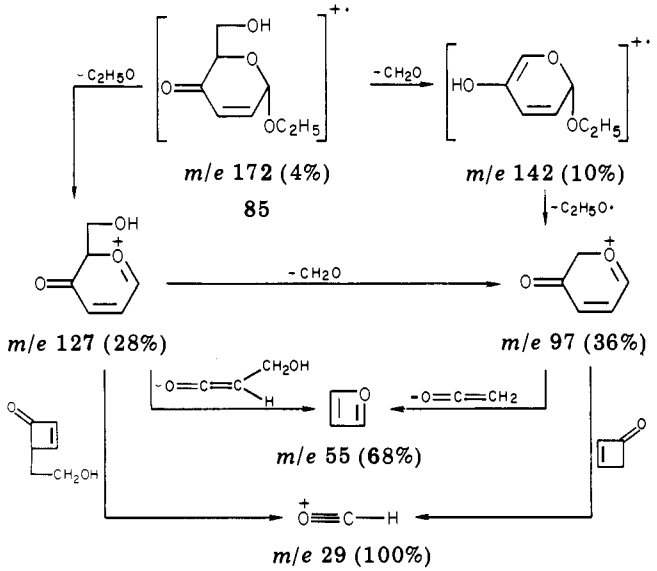
2. Retention of the Pyranosidulose Ring

As with other alkyl pyranosides,[265] the mass spectra of alkyl pent- and hex-2-enopyranosiduloses show the

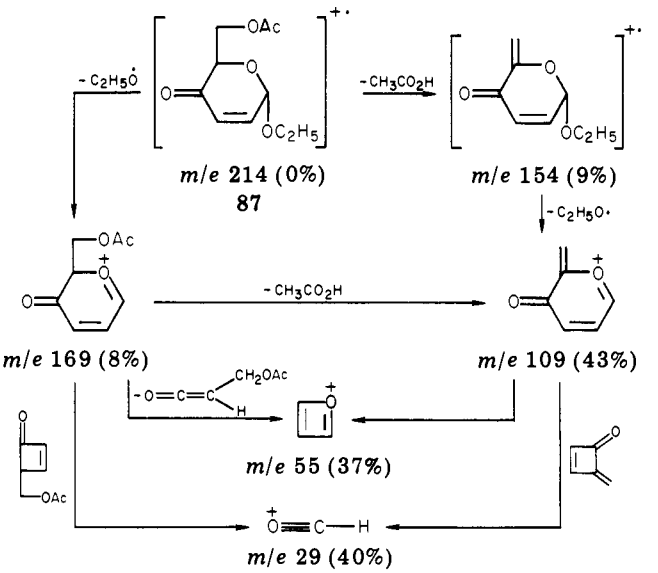
SCHEME XXXVIII



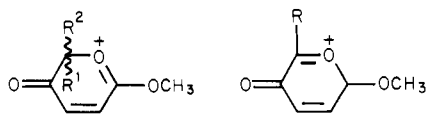
SCHEME XXXIX



SCHEME XL



characteristic M – alkoxy peak: M – 31 from methyl and M – 45 from ethyl pyranosiduloses. Achmatowicz and Grynkiewicz[259] attribute the low-intensity M – 1 peak to the anomeric hydrogen abstraction to give ion **271** since no M – 2 peaks appeared in the spectra of C5

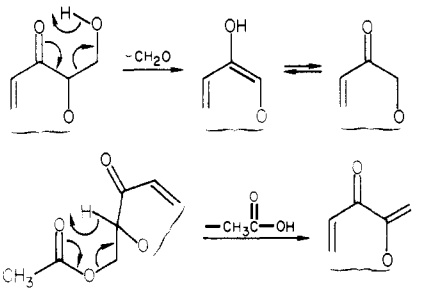


271 **272**

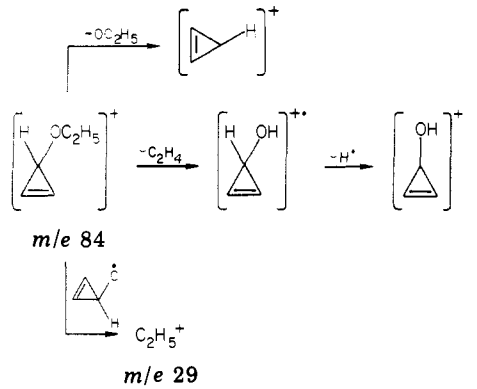
deuterated compounds. The lack of M – 15 fragment from **269** (R′ = CH_3) indicates that oxonium ions without C-6 methyl (**272**) are not formed during fragmentation.

For each of the enones **85** and **87**, ions were produced by loss of OC_2H_5 to give *m/e* 127 (28% relative intensity) and *m/e* 169 (8%), respectively (Schemes XXXIX, XL). A very interesting decomposition of the molecular ions is the loss of acetaldehyde from **85** to give ion *m/e* 142 (10%) or acetic acid from **87** to give *m/e* 154 (9%). The charged radicals *m/e* 142 and *m/e* 154 can also lose the aglycon OC_2H_5 to give the ions *m/e* 97 (36%) and 109 (43%), respectively. The loss of acetaldehyde from *m/e* 127 and acetic acid from *m/e* 169 to give oxonium ions *m/e* 97 and *m/e* 109, respectively, was also proposed as one of their modes of fragmentation. In view of the fact that neither alkyl group nor hydrogen atom is removed from C-5 with formation of **272** during fragmentation of **269**, an alternate mechanism[263] involving a six-centered transition state is proposed to account for the loss of acetic acid or formaldehyde (Scheme XLI). Metastable peaks (Table XVI) were observed for the transitions *m/e* 172 → 142

SCHEME XLI



SCHEME XLII



and 127 → 97 in **85** and for *m/e* 154 → 109 and 169 → 109 in **87**.

Two other fragmentations of *m/e* 127 and 169 are loss of a ketene and the generation of an alkylcyclobutenone with the formation of *m/e* 55 and 29, respectively. The origins and relative intensities of these ions are shown in Schemes XXXIX and XL. Another parent ion for *m/e* 55 and 29 is the ethyl cyclopropenyl ether, $[C_5H_8O]^{+\cdot}$, *m/e* 84. This can undergo the typical fragmentation of allylic ethers[264] by losing ethylene to form cyclopropenol, *m/e* 56 (Scheme XLII), which by loss of hydrogen forms the protonated cyclopropenone, *m/e* 55. A second course of fragmentation for the ether *m/e* 84 is that in which rapture occurs on either side of the oxygen atom, the charge being retained by the hydrocarbon moiety. One of these entities is the ion *m/e* 29. Accurate mass measurements show that *m/e* 55 has the elemental composition C_3H_3O and *m/e* 29 exists as a doublet with elemental compositions of CHO and C_2H_5.

NMR, IR, UV, and mass spectroscopic measurements have been used extensively in the structural elucidation of hexenopyranosuloses and their derivatives. The IR and UV spectra of the carbohydrate enones show absorptions characteristic of the α,β-unsaturated-keto chromophore. One notable UV absorption is at 260 nm which is typical of 2,3-dihydro-4*H*-pyrones. Supporting these observations is the fact that on electron impact the main fragmentation pathway of the carbohydrate enones is a retro-Diels–Alder type cleavage. The primary fragments contain the substituents that were in the γ position of the molecular ion. Therefore, recognition of these primary fragments could provide a means of allocating the position of the α,β-unsaturated-keto chromophore in the hex- or pentenopyranosiduloses.

NMR spectroscopy proved to be a valuable tool in effectively resolving the conformational and configurational features in hexenopyranosuloses. The conformational equilibrium was determined by the magnitude of proton coupling constants in the ^1H NMR spectra and the chemical shifts in the ^{13}C NMR spectra. Conformational analysis confirmed the observed coupling constants which are usually weighed averages of the conformers. Supporting evidence was also obtained from the multiplicity and relative absorptions of the anomeric protons.

VI. Reactions

Hexenopyranosuloses are remarkable versatile classes of synthetically useful carbohydrate molecules due mainly to the propensity of the α,β-unsaturated-keto chromophore to undergo various chemical reactions. The conjugation enables the molecules to participate in reactions not only characteristic of the individual functional groups but also distinctive of the conjugated system. Hex-2-enopyranosid-4-uloses were chosen as models in synthetic manipulations because of their ready availability[16,18] and the possibility to produce 3-deoxy and 2-substituted sugars of biological interest.

Reactions of hex-2-enopyranosid-4-uloses occur in the ground or excited states. In the first category are reductions, and these may be metal hydride reductions of the carbonyl group[18,47] or catalytic hydrogenation of the olefinic function.[16,149] The enones may be annulated through dipolar cycloaddition[266,267] or Diels–Alder reaction.[268-271] Other reactions, typical of the individual functional groups, include the Wittig reaction,[85,272] epoxidation,[48-50] and cis hydroxylation.[273] Nucleophilic 1,4 additions to α,β-unsaturated-keto chromophore constitute one of the most widely used reactions in the synthetic reactions of hex-2-enopyranosid-4-uloses. The addends may be metalloorganic species[205] or anions such as dithiane,[204] azide,[274-276] amines,[277] nitro ethyl, cyanoacetates, nitroalkanes, or β-dicarbonyl compounds.[278] In the second category of reactions are photoinduced additions of alcohols,[279] ketals, acetals, or polyfunctional species[280] and cyclobutane formation from suitably substituted olefins.[281] It would be beyond the scope of this review to discuss the stereochemical outcome of these reactions except to mention directional effects due to the aglycon group or delocalization of the olefinic π electrons.

A. Ground State

1. Reduction

Methyl hex- or pent-2-enopyranosid-4-uloses are reduced to allylic alcohols with sodium borohydride ($NaBH_4$) in tetrahydrofuran–water solution or with lithium aluminum hydride (LAH) in ether.[18,47] Under these conditions, only the keto function is reduced. In general, no more than two stereoisomeric compounds are formed[18,47,141,282-284] (Scheme XLIII, Table XVII), and they are separated by chromatography. The scope of this reduction has been explored extensively, and because of its stereoselectivity, it is one of the steps in the total synthesis of monosaccharides from noncarbohydrate molecules.[140-142,282-284]

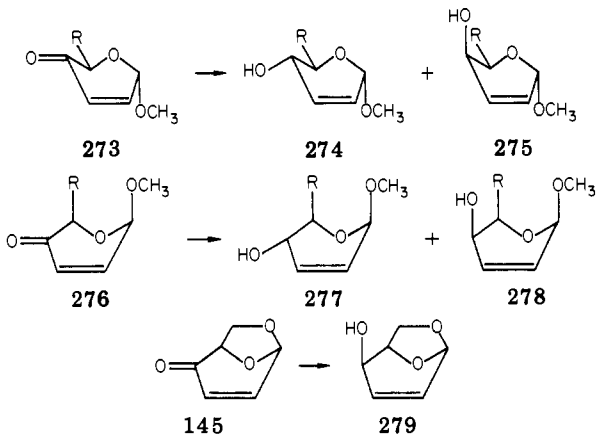
Stereoselectivity of the LAH or $NaBH_4$ reductions is due to stereoelectronic and conformational factors.[219] The conformational factor is connected with the thesis that compounds react in the most stable conformation of the ring. Conformational analysis establishes that

TABLE XVII. Yield and Isomer Composition of Reduced Enones

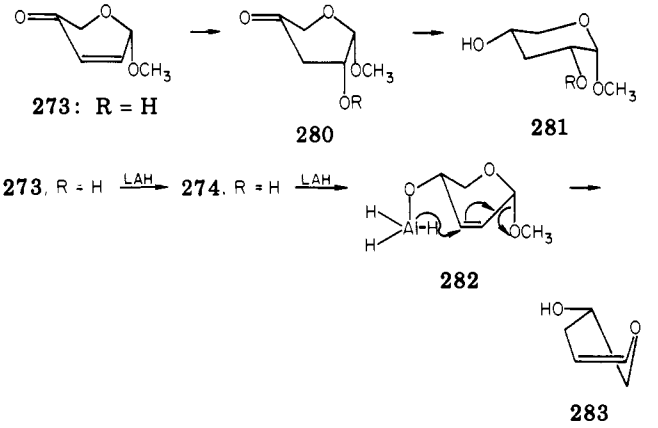
enone	reduction system	yield, %	products			ratio, %	ref
273, R = H	$NaBH_4$, THF/H_2O	>82	274		275	90:10	18
		92	274		275	90:8	47
	LAH, ether	low	274		275	*a*	47
R = CH_3	$NaBH_4$, THF/H_2O	96	274		275	85:15[b]	18
	LAH/ether		274			*b*	282
R = CH_2OH	$NaBH_4$, THF/H_2O	71[c]	274			100	18
		96					141
	LAH/ether		274		275	90:10	141
R = CH_2NO_2	LAH		274			*d*	283
R = CH_2NHAc	LAH		274			*d*	283
276, R = CH_3	$NaBH_4$, THF/H_2O	69[c]	277			*e*	18
	LAH/ether		277		278	50:50	282
R = CH_2OH	$NaBH_4$, THF/H_2O	46[c]	277			100	18
		79	277		278	90:10	141
	LAH/ether		277		278	50:50	141
R = CH_2OBn[f,g]	$NaBH_4$, THF/H_2O		274	277	278	42:21:10	284

[a] Mainly 274 with a trace of 275. [b] Almost exclusively 274. [c] Analyzed as acetate. [d] Mainly 274. [e] Predominant isomer is 277. [f] Bn = $PhCH_2$. [g] Mixture of 273 and 276 (7:3).

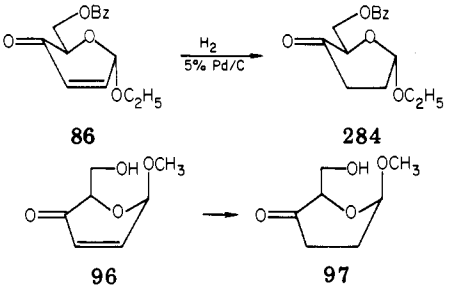
SCHEME XLIII



SCHEME XLIV



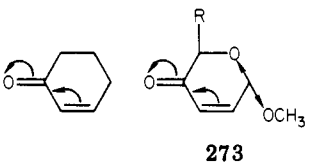
SCHEME XLV



enones **273** and **276** exist in ${}^{O}E \rightleftarrows E_O$ equilibrium and that the position of the equilibrium is influenced significantly by the anomeric effect. The α-D sugars exist almost exclusively in the ${}^{O}E$ conformer while the β-D anomers contain more E_O conformer; in both cases the aglycon group in the more stable conformer has an axial or pseudoaxial orientation. The envelope conformation allows a perpendicular approach of the hydride ion to both sides of the carbonyl group.

Assigning the stereochemistry at C-4 followed from examination of the ^1H NMR of the allylic alcohols. A predominance of the equatorial allylic alcohol is in keeping with Barton's rule[285] for the reduction of unhindered ketones; in general, reduction with LAH or $NaBH_4$ affords the equatorial epimer if the ketone is unhindered and the axial epimer if the ketone is hindered. Consistent with Barton's rule, the 1,6-anhydrohex-2-enopyranos-4-ulose **145** gave **279** on reduction with $NaBH_4$ (Scheme XLIII). Because of steric hindrance due to the 1,6-anhydro bridge, attack by the reducing agent would be expected to take place from the opposite side of the ring.

Reducing methyl pent-2-enopyranosid-4-ulose (**273**, R = H) with sodium borohydride in alcoholic or aqueous alcoholic solutions gives products that result from addition of alcohols to the double bond (Scheme XLIV). The competing reaction with carbocyclic α,β-unsaturated ketones or aldehydes is reduction of the double bond.[286] Achmatowicz and Bukowski[47] employed the hard and soft acid and base concept to explain the differences in reactivity of **273** and cyclohex-2-en-1-one.

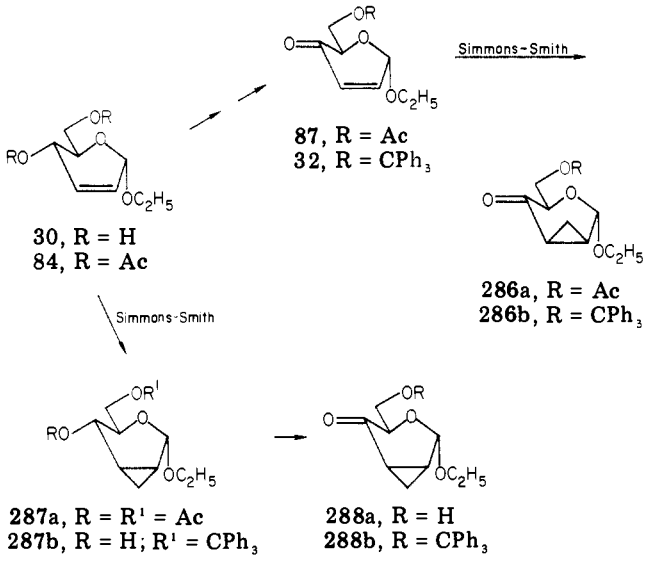


273

The β carbon atom in **273** is a harder acidic center. Since an alcohol is a hard base while hydride ion is a soft base, the former would react more readily with **273**. The order of reactivity is the reverse with cyclohex-2-en-1-one.

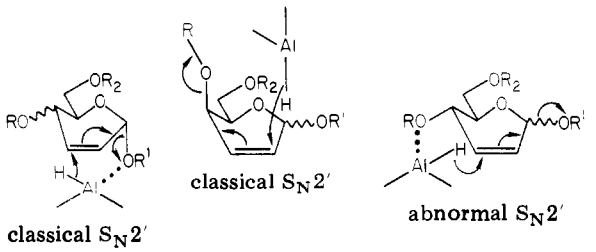
Selective reduction of the olefinic double bond of hex-2-enopyranosid-4-uloses is accomplished more effectively by catalytic hydrogenation (Scheme XLV). Reduction of **86** over 5% palladium on charcoal in ethyl acetate at room temperature gives the saturated ketone

SCHEME XLVI



284.[16] On the other hand, hydrogenation of **96** in the presence of palladium black, in ethanol, affords after 2 days mainly **97** isolated in 45% yield; thin layer chromatography revealed the presence of several other unidentifiable components. However, when a W-4 Raney nickel catalyst is used, compound **97** is obtained in 72% yield after 30 min.[149]

Although the LAH reduction of the hex-2-enopyranosid-4-uloses is as stereoselective as the $NaBH_4$ reduction, the yield of the allylic alcohol is low due to the formation of a 3-deoxyglycal.[47] This is the only product formed when the reduction was allowed to proceed overnight. The formation of glycals is quite interesting in that the ketone is reduced initially to the allylic alcohol, and this then assists in the reductive cleavage of the aglycon group with concomitant migration of the double bond (Scheme XLIV). This reductive rearrangement of hex-2-enopyranosides under the influence of LAH to vinyl ethers was first reported by Fraser-Reid and Radatus[287] as a ready synthetic route to 3-deoxyglycals. In subsequent publications, Fraser-Reid and co-workers[155,156] examined some mechanistic aspects of the reaction. Results suggest that the rearrangements take place by way of one of the mechanisms expressed in **285**.

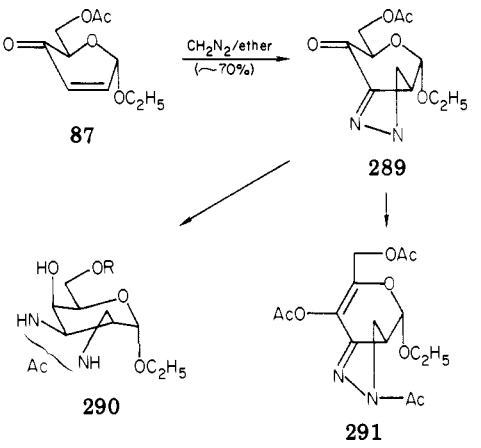


285

2. Annulation

Fraser-Reid and Carthy[266] recorded the first annulation reaction of hexenopyranosiduloses. Addition of methylene across the olefinic double bond occurs when methylene iodide is allowed to react with ethyl hex-2-enopyranosid-4-ulose **87** under Simmons–Smith reaction conditions (Scheme XLVI). The stereochemistry of the cyclopropyl ring in **286** was based on a direct

SCHEME XLVII

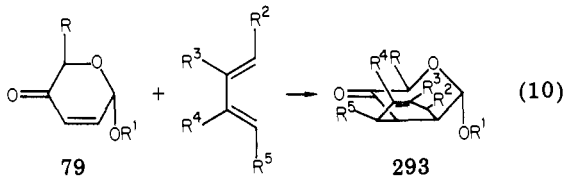


comparison of the ^1H NMR spectrum of the 6-*O*-trityl ether **286b** with that of **288b** which has the *ribo* configuration and whose synthesis is shown in Scheme XLVI.

In the ^1H NMR spectra of **288b** and **286b**, H-1 appears as a singlet. However, it occurs at δ 5.55 in **288b** and at δ 5.17 in **286b**. In an earlier publication, Radatus and Fraser-Reid[288] commented on the shielding effect of cyclopropyl group on vicinal cis-oriented protons. This effect apparently contributes to the lower frequency of H-1 in **286b**. Differences in stereochemical outcome of the Simmons–Smith cyclopropanation are worthy of note. The incoming methylene adds syn to the ethoxy group in **84**, whereas in **87** the addition is syn to the acetoxy group. The acetoxy group apparently provides greater directing influence to the incoming methylene than does the allylic ethoxy group.

Diazomethane and its derivatives react with ketones and olefins usually under very mild conditions to yield a variety of interesting and often useful products. With most ketones, the reaction results in homologation of the ketone or formation of an epoxide,[289,290] and with olefins, Δ^2-pyrazolines are the main classes of compounds formed. Reactions of diazomethane and its derivatives with α,β-unsaturated ketones involve the olefinic unsaturation.[291] Fraser-Reid and co-workers[267] reported that when diazomethane is allowed to react with **87** a pyrazoline **289** is formed (Scheme XLVII). The accumulated spectroscopic evidence is in agreement with a Δ^2-pyrazoline. This class of bimolecular heterocyclic compounds is novel in its own right and well suited for synthetic transformations into branched-chain amino sugars. Of particular interest are formation of a triacetate **291**, which has some antithrombic activity, and the cleavage of the N–N bond to provide a branched-chain diamino sugar, **290** (Scheme XLVII).

Structural features in hex- or pent-2-enopyranosid-4-uloses make them attractive dienophiles in Diels–Alder reactions: (1) the cis olefinic function will lead to a series of cis adducts; (2) there are present two readily distinguishable one and two carbon fragments; (3) the activating C-4 keto function offers the potential for attaching carbon units; and (4) the fixed stereochemistry allows for diastereoface-differentiating reactions.[270] The reactivity of the 2-enopyranosid-4-uloses is evident from the observation that **79** condenses in high yield and with stereoselectivity with a number of dienes **292** (eq 10). Condensation reactions have oc-



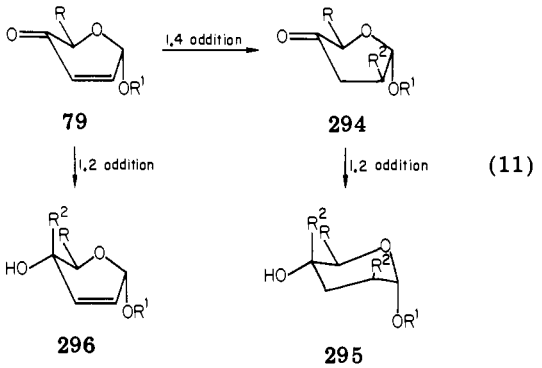
(10)

79 292 293

curred at temperatures ranging from room temperatures for cyclopentadiene to 130 °C for *trans,trans*-hexa-2,4-diene (Table XVIII); the diene and dienophile in 1,2-dimethoxyethane are heated in a seal tube. Jurczak and Tkacz[269] demonstrated that under high pressure and mild conditions (20 ± 2 °C), the dienophile **79** (R = H; $R^1 = CH_3$) condenses with a number of dienes to give adducts in high yields (Table XVIII). Fraser-Reid et al.[271] reported that the high temperature procedure for the condensation of **79** ($R = CH_2OAc$; $R^1 = C_2H_5$) with butadiene leads to extensive decomposition. However, aluminum chloride enhances the reactivity of the dienophile; other Lewis acid catalysts known for enhancing reactivity of dienophiles[292] are ineffective. These diene–dienophile condensations occur with a high degree of stereoselectivity, and the correct stereochemistry at the ring junction was deduced by ^1H NMR spectroscopy.[268] The values of all coupling constants confirm a cis-endo stereochemistry.

3. Nucleophilic Additions

Most of the reports describing nucleophilic additions dealt with 1,4 addition of nucleophiles to hex-2-enopyranosid-4-uloses. However, there are some instances of 1,2 additions across the keto function (eq 11). In



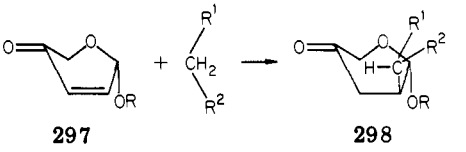
(11)

79 294 296 295

all cases, additions occur with a high degree of stereoselectivity due in part to the stereoelectronic and directional effects of the aglycon group. The nucleophiles approach the planar substrate from the face opposite the aglycon.[278]

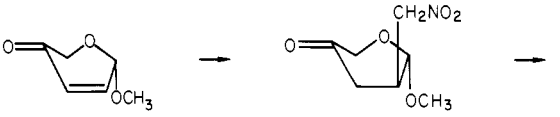
a. Michael Additions. The normal conditions for Michael additions to hex-2-enopyranosid-4-uloses cannot be employed because of the sensitivity and ease of decomposition of the enones on contact with alkaline solution. This fact notwithstanding, Achmatowicz and co-workers[278] searched for suitable reaction conditions that would generate nucleophiles from molecules with an active methylene group. Some success was achieved in the presence of a potassium bicarbonate suspension in ether; however, the results were not reproducible. More consistent results (Scheme XLVIII) were obtained when the catalyst was a saturated alcoholic solution of potassium bicarbonate; some of the solvents used include methanol, 2-propanol, and 2-methyl-2-propanol. When nitromethane was the addend, two products are

SCHEME XLVIII

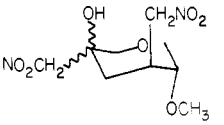


297 298

R	R^1	R^2	system	yield, %
CH_3	H	NO_2	$KHCO_3/CH_3OH$	71
CH_3	CH_2CH_3	NO_2	$KHCO_3/(C_2H_5)_2O$	85
CH_3	$CO_2C_2H_5$	NO_2	$KHCO_3/CH_3OH$	79
CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	K_2CO_3/CH_3OH	77
CH_3	CN	$CO_2C_2H_5$	$KHCO_3/CH_3OH$	80
CH_3	$COCH_3$	$CO_2C_2H_5$	$KHCO_3/(CH_3)_2CHOH$	93
CH_3	$COCH_3$	$COCH_3$	$KHCO_3/CH_3OH$	85
H	$COCH_3$	$CO_2C_2H_5$	$KHCO_3/CH_3OH$	90
COC_6H_5	$COCH_3$	$CO_2C_2H_5$	$KHCO_3/CH_3OH$	88

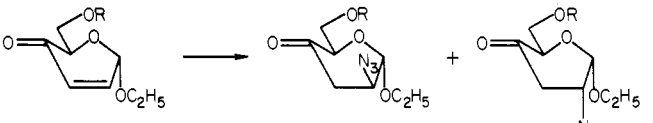


79, R = H; $R^1 = CH_3$ 298, R^1 = H; $R^2 = NO_2$; R = CH_3



299

SCHEME XLIX



88, R = CPh_3
85, R = H
86, R = Bz

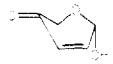
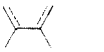
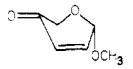
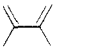
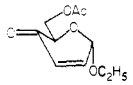
300 301

isolated from the reaction mixture. Spectroscopic analyses establish that one product, **298** (R = H; $R^2 = NO_2$), resulted from a 1,4 addition, and the other, **299**, was the result of both 1,4 and 1,2 additions.

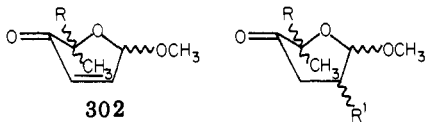
Gero and his associates[274,275] described the conjugate 1,4 addition of azide ion to hex-2-enopyranosid-4-ulose as one of the key steps in the synthesis of the diamino sugar component of some aminoglycoside antibiotics. The elements of hydrazoic acid add to the carbon–carbon double bond of the α,β-unsaturated-keto chromophore when **88** is treated with sodium azide in acetic acid at room temperature (Scheme XLIX). During the course of the reaction, the kinetically favored product **300** (R = Ts) forms first, and this gradually transforms into the thermodynamically more stable substance **301** (R = Ts). After 5 h, the equilibrium mixture comprises D-*erythro* and D-*threo* isomers **301** and **300** (R = Ts) in the ratio 6:4; a similar trend was observed with **85** and **86**.

In contrast, however, Sakakibara and his colleagues[276] noticed that when **85** or **86** is allowed to react with hydrazoic acid in chloroform, only the *threo*-pyranosidulose **300** (R = Bz) or **300** (R = H) is formed (Scheme XLIX). Other solvent systems include chloroform–tetrahydrofuran (1:5) and dimethyl sulfoxide. No reaction was observed in benzene or in the chloro-

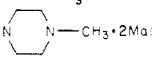
TABLE XVIII. Conditions, Yields, and Isomer Distribution of Diels-Alder Adducts

dieneophile	diene	conditions	yield, %	isomer ratio	ref
		100 °C, 16 h	62	57:43	268
		120 °C, 24 h	82	68:32	268
79, R = R¹ = H		130 °C, 24 h	39	68:32	268
		120 °C, 24 h	50	100	268
		25 °C, 72 h	75	100	268
		100 °C, 24 h	65	93:7	270
		10.9 kbar, 20 °C, 24 h	73	98:2	269
79, R = CH_3; R¹ = H		100 °C, 24 h	80	92:8	270
		11.0 kbar, 20 °C, 24 h	91	98:2	269
		100 °C, 24 h	45	92:8	270
		10.5 kbar, 20 °C, 24 h	51	99:1	269
		100 °C, 24 h	54	95:5	270
		10.9 kbar, 20 °C, 24 h	60	100	269
		$AlCl_3$, CH_2Cl_2 -78 °C, 2.5 h	78	100	172
79, R = C_2H_5; R¹ = CH_2OAc					

SCHEME L



302 303

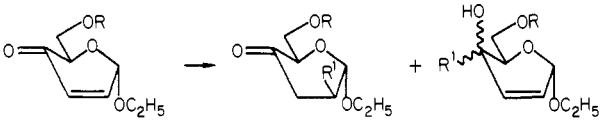
R¹	yield, %
$N(CH_3)_2$·HCl	80
$NHCH_3$·HCl	91
	88
morpholino	75

form–tetrahydrofuran–water (1:5:3) system. The addition of hydrazoic acid was monitored by ^1H NMR spectroscopy, and no epimerization was observed even in dimethyl sulfoxide. Sakakibara's group explained the preponderance of axial attack of azide ion in terms of stereoelectronic control and steric hindrance by the aglycon group.

A Michael addition of amines to enone **302** dissolved in ether, benzene, or THF gives the 2-amino derivative (Scheme L).[277] The technique used to prepare the amine adduct **303** varied according to the nature of the amine: gaseous amines were bubbled through a benzene or ether solution of the enone and liquid amines were simply added to an ether solution of the enone; if an aqueous solution of the amine is available, then it is used as such, and tetrahydrofuran is used as the solvent for the reaction.

b. Copper-Induced 1,4 Additions. The most useful information of copper-induced alkylation of carbohydrate enones came from studies of conjugate addition of lithium dialkylcuprate reagents (Scheme LI).[205,293] In the reactions of hex-2-enopyranosid-4-uloses **32** or **85** and hex-3-enopyranosiduloses **35** with lithium dialkylcuprate, there is formed in each case a 1,4 adduct, **304** or **306**, with the alkyl group in an axial orientation; 1,2 addition products **305** were observed in some cases.

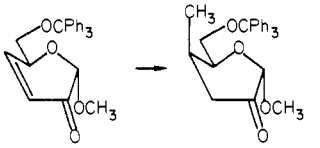
SCHEME LI



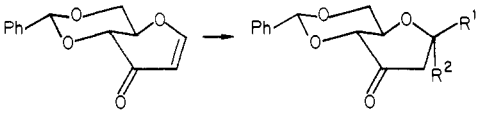
32, R = CPh_3
85, R = H

304 305

a, R = H; R¹ = CH_3
b, R = CPh_3; R¹ = CH_3
c, R = H; R¹ = $CH=CH_2$



35 306



62 307

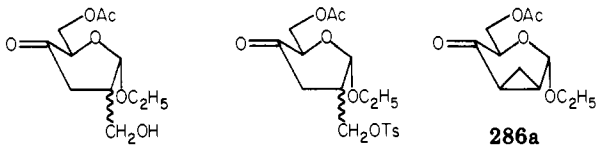
R¹ = H; R² = CH_3
R¹ = CH_3; R² = H

On the other hand, 1,4 additions to 1,5-anhydro-2-deoxyhex-1-en-3-uloses are not stereoselective, and complex mixtures are obtained. Thus, the reaction of **62** with lithium dimethylcuprate gave two conjugate addition products **307**, and there was no evidence of 1,2 addition. Grignard reagents or alkyllithiums in the presence of catalytic or stoichiometric amounts of copper have also been employed.

Some of the factors which influence the yield of the 1,4 adduct are as follows: (1) structure variation of the substrate—tritylated enone **35** is superior to parent enone **85**, and the system with the vinylogous ether gives lower yields; (2) amount of copper(I) species—stoichiometric quantities lead to higher yields than catalytic amounts; and (3) the origin of the lithium

dialkylcuprate complex—the yield is less with the heterogeneous system (copper(I) iodide and methyllithium in ether) than with the homogeneous system (soluble tri-*n*-butylphosphine complex and methyllithium in ether). The method using the heterogeneous system is preferred since preparation of phosphine complex and chromatography of the reaction product to remove the liberated phosphine are both avoided.

Originally, the alkyl group in the 1,4 adduct **304b** was assigned an equatorial orientation.[293] In **304b**, H-1 is located at 4.71 ppm with an observed splitting of 4.0 Hz which seemed consistent with cis hydrogens as seen in α-D-glucopyranosides. However, when it was demonstrated that the product **308** from the photochemical addition of methanol to enone **87** was transformed to the cyclopropapyranosid-4-ulose **286a**



308 **309** **286a**

H-1, δ 4.8, $J_{1,2} \simeq 4.0$ Hz

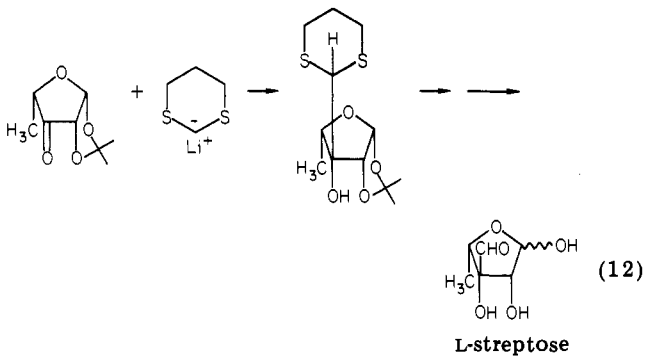
of known stereochemistry,[279] the assignment in **304b** was reexamined. Reduction of **304b** gives a mixture of 3-deoxyglycosides **310** with coupling constants of 0.0 and 2.6 Hz. These values are definitive evidence for

304b **310**

H-1, δ 4.71, $J_{1,2} = 4.0$ Hz $J_{1,2} = 0.0$ and 2-6 Hz

a diequatorial relationship of H-1 and H-2. Assignment of the stereochemistry at C-1 in **307** was based on the general rule that in pyranoid rings, the equatorial protons resonate at a lower field than constitutionally similar axial protons. The stereochemistry at C-4 in **306** was based on the information obtained from the C-3 methylene protons. Paulsen and co-workers[294] also reported similar 1,4-addition reactions of enones **52**, **311**, and **314** with lithium dimethylcuprate or vinylmagnesium bromide in the presence of copper(I) chloride (Scheme LII).

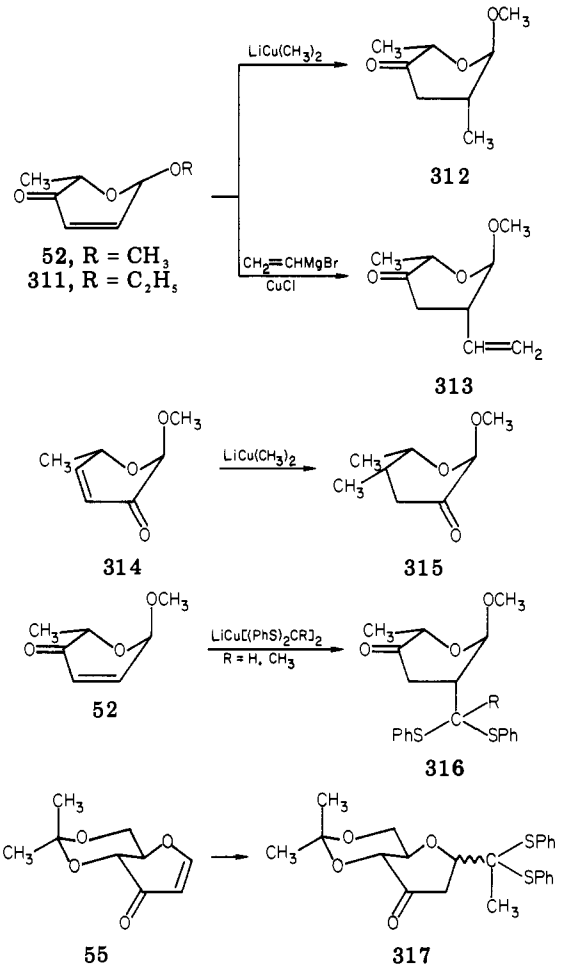
c. Additions of 1,3-Dithiane Species. Paulsen and his collaborators[204,295] developed the 1,3-dithiane procedure of Seebach[296] for the synthesis of complex, branched-chain carbohydrates containing a functionalized side chain; the best example is the synthesis of L-streptose (eq 12). The main application of this method is addition reactions to carbonyl compounds.



(12)

L-streptose

SCHEME LII

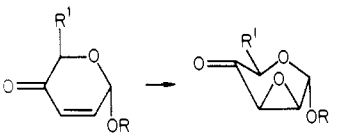


The 1,3-dithiane anion under controlled 1,4-addition conditions, that is, in the presence of copper catalyst, adds only to certain substrates **52** and **55** (Scheme LII).[294,297] However, an anion of 2-carbethoxy-1,3-dithiane (**318**), which is more stable and easy to prepare, adds stereoselectively to the enones **52** and **55** and gives 1,4-addition products **319** and **323** in high yields (Scheme LIII). When the enolate **320** is reduced, only the side chain is reduced, and this provides an easy route to **322**. As in the case with the cuprate additions, the new side chain adds to the molecule always from the side opposite to the aglycon group. Another variation in the dithiane method lies in the application of a dianion of 2-(hydroxymethyl)-1,3-dithiane **325**. The procedure is suitable for the introduction of functionalized side chains containing the α-keto(hydroxymethyl) group.

4. Epoxidation and Cis Hydroxylation

Despite their sensitivity to basic media, the enones **79** are converted to the epoxides **327** when treated with hydrogen peroxide in the presence of a cold solution of sodium hydroxide or sodium carbonate (Table XIX). In each case, only one isomer is isolated, indicating the stereoselectivity of the reaction. The stereochemistry of the epoxidation of enones **79** is influenced by the aglycon group's directing effect. Thus, the oxirane ring forms by axial attack from the least hindered face of the molecule.

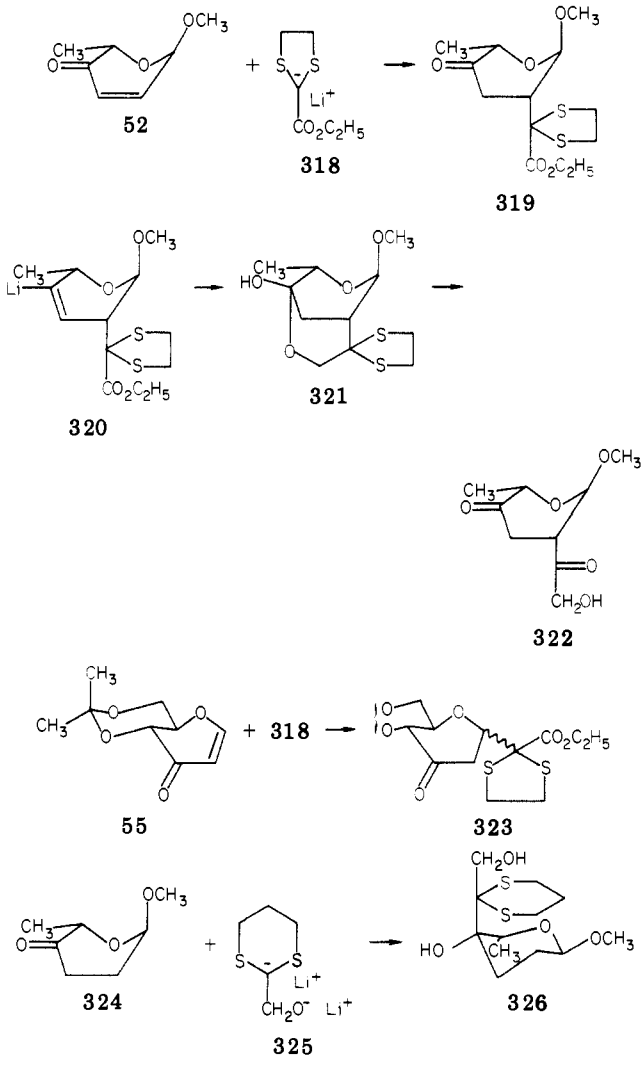
TABLE XIX



79 327

substituents R	substituents R′	solvent	base	conditions H_2O_2, %	conditions temp, °C	conditions time, h	yield, %	ref
C_2H_5	H	methanol	1% NaOH	30	-20	1	26	48
	CH_3	methanol	1% NaOH	30	-20	1	66	48
CH_3	CH_2H_5	methanol	1% NaOH	30	-20	1	48	48
CH_3	H	ether	5% Na_2CO_3	15	5	3	89	49
	CH_3	ether	5% Na_2CO_3	15	10	3	90	49
	CH_3	methanol	5% Na_2CO_3	15	0-3	3	93	49
	CH_3	water	5% Na_2CO_3	15	0-5	3	90	49
	C_2H_5	ether	5% Na_2CO_3	15	5	3	88	49
CH_3	H	2-propanol	1 M NaOH	30	0-5	1	85	50
	CH_3	2-propanol	1 M NaOH	30	0-5	1	85	50
CH_3	CH_2OBz	methanol	6 M NaOH	30	0	1	63	276

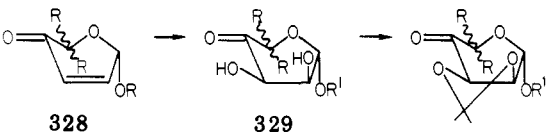
SCHEME LIII



52 318 319 320 321 322 55 323 324 325 326

In cis hydroxylation of the enones, most of the common cis hydroxylating reagents (Milas or Woodward) were unsatisfactory. However, silver chlorate in the presence of a catalytic amount of osmium tetroxide effects cis hydroxylation of enones **328** (Scheme LIV).[273] In each case, a single product, **329**, is formed and the product was characterized as the isopropylidene acetal **330**. The cis hydroxylation was assumed to occur trans to the C-1 substituent because of steric hindrance.

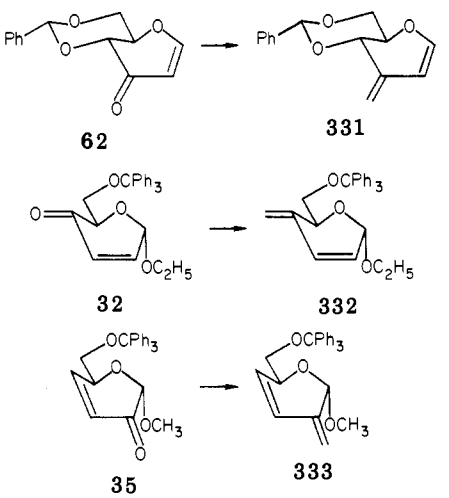
SCHEME LIV



328 329 330

R	R′	yield, %
H	CH_3	49
H	Bz	43
CH_3	CH_3	58

SCHEME LV

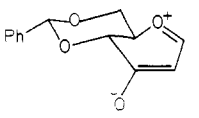


62 331 32 332 35 333

5. Miscellaneous Reactions

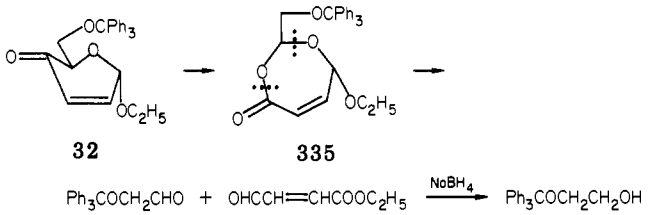
Other typical reactions of olefins or ketones which have been reported for the carbohydrate enones include Wittig reaction and Baeyer–Villiger oxidation.

Wittig methylenation of carbohydrate enones is one of the routes developed for the synthesis of conjugated dienes.[272,298] Thus, the reaction of methylenetriphenylphosphorane with an ethereal solution of the enone **62** results in the formation of a 1,5-anhydro-2,3-dideoxy-3-*C*-methylene-D-*erythro*-hex-1-enitol, **331** (Scheme LV). The low yield of **331** was attributed to the large contribution of the charged species **334** in



334

SCHEME LVI

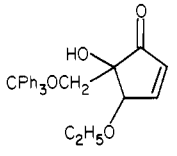


32 335

$Ph_3COCH_2CHO + OHCCH{=}CHCOOC_2H_5 \xrightarrow{NaBH_4} Ph_3COCH_2CH_2OH$

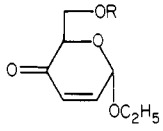
which the positive charge is delocalized from C-3 to the ring oxygen. Accordingly other arrangements of the chromophore in enones **32** and **35** where the ring-oxygen atom is in the δ position give the conjugated dienes **332** and **333** (Scheme LV) in yields greater than 60%.

The classical Baeyer–Villiger reaction proceeds quite smoothly when ethyl 6-*O*-(triphenylmethyl)-α-D-*erythro*-hex-2-enopyranosid-4-ulose (**32**) is oxidized with peracetic acid (Scheme LVI).[299] There is a pronounced downfield shift of the C-5 proton of the product, indicating oxygen insertion in the sugar ring. Sodium borohydride reaction conditions open the lactone ring ultimately producing a 2-(triphenylmethoxy)ethanol. Hauser[299] also recorded a base-induced rearrangement of **32**, yielding an α-hydroxy-α,β-unsaturated 5-membered cyclic ketone, **336**.

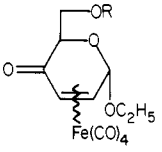


336

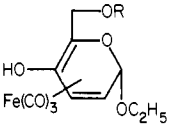
When a benzene solution of enone **85** is allowed to react with $Fe_2(CO)_9$ and the reaction mixture chromatographed on a silica column, starting material and three products are isolated.[300] Two of these are the



85, R = H
32, R = Tr



337a, R = H
337b, R = Tr



338

diastereomeric pair **337a** resulting from the two modes of addition of the iron carbonyl, and the other is triiron dodecacarbonyl ($Fe_3(CO)_{12}$). There was no evidence of the tricarbonyl complex **338**. A similar reaction was observed for **32**, but no triion dodecacarbonyl was found.

B. Excited State

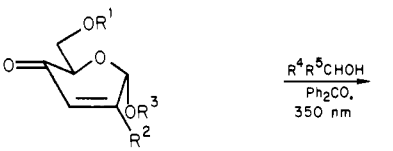
The photochemistry of organic molecules possessing the α,β-unsaturated carbonyl function has been studied extensively.[301-306] Little was known of photochemical reactions displayed by enones that possess an endocyclic oxygen atom[307] until the reports describing photodimerization and addition of olefins to 1,2-dideoxy-D-hex-1-eno-3-ulose[281] and the 1,4 addition of oxycarbinyl species to the α,β-unsaturated-keto chromophore of hexenopyranosuloses.[279,280]

1. Addition of Oxycarbinyl Species

Introducing of branching into hexenopyranosuloses by photosensitized addition of oxycarbinyl species[279,280] was first reported by Fraser-Reid and co-workers.[293] They noted that irradiation of alkyl hex-2-enopyranosid-4-uloses **339** in alcohols containing benzophenone at 350 nm produces hexopyranosid-4-uloses **340** bearing a carbinol residue at the β position (Scheme LVII). Originally[293] it was assumed that the residue was in the most favored equatorial orientation. Later[279] it was shown that the alkylations occur from the less hindered side and are completely stereo- and regioselective. The presence of a β substituent on the enone system does not affect the stereochemistry of the photoalkylation. Photochemical addition of methanol to hex-1-enopyran-3-uloses **206** or hex-3-enopyranosiduloses **166** are not stereospecific, and mixtures of *C*-glycosides **341** or 4-*C*-alkylhexopyranosiduloses **342** are isolated (Scheme LVII).

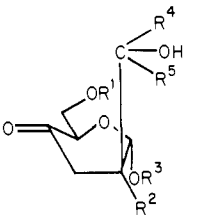
With alkyl hex-2-enopyranosid-4-uloses **339**, a single 1,4 adduct, **340**, with methanol or ethanol is isolated in 50–75% yield. The ease with which the 1,4 adduct with

SCHEME LVII



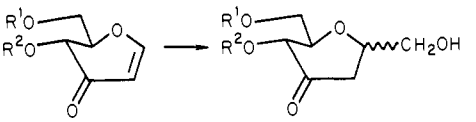
339

a, $R^1 = H; R^2 = H; R^3 = C_2H_5$
b, $R^1 = Ac; R^2 = H; R^3 = C_2H_5$
c, $R^1 = CPh_3; R^2 = H; R^3 = C_2H_5$
d, $R^1 = CPh_3; R^2 = CH_3; R^3 = CH_3$



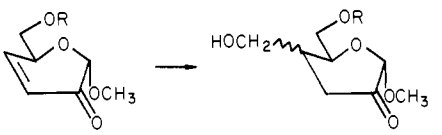
340

a, $R^1 = R^2 = R^4 = R^5 = H; R^3 = C_2H_5$
b, $R^1 = Ac; R^2 = R^4 = R^5 = H; R^3 = C_2H_5$
c, $R^1 = CPh_3; R^2 = R^4 = R^5 = H; R^3 = C_2H_5$
d, $R^1 = CPh_3; R^2 = CH_3; R^4 = R^5 = H; R^3 = CH_3$
e, $R^1 = Ac; R^2 = R^4 = H; R^5 = CH_3; R^3 = C_2H_5$
f, $R^1 = R^2 = H; R^4 = R^5 = CH_3; R^3 = C_2H_5$
g, $R^1 = CPh_3; R^2 = H; R^4 = R^5 = CH_3; R^3 = C_2H_5$



206 341

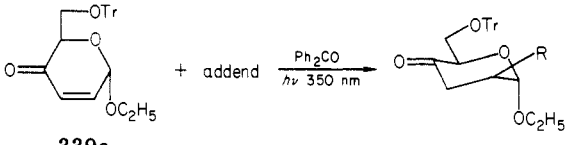
a, $R^1 + R^2 = HCPh$
b, $R^1 + R^2 = C(CH_3)_2$
c, $R^1 = Bz; R^2 = H$
d, $R^1 = CPh_3; R^2 = Ac$



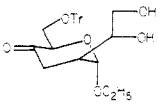
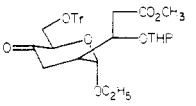
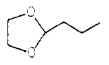
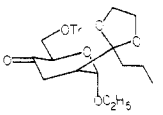
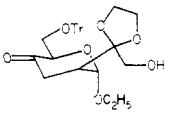
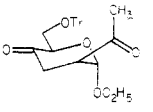
166 342

a, R = H
b, $R = CPh_3$

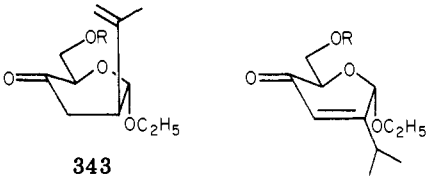
TABLE XX



339c 345

addend	time, h	product	yield, %
	4.0	 346	75-79
	5.5	 347	74
	2.0	 348	62
	4.0	 349	42
CH_3CHO	5.0	 350	67

2-propanol may lose water to give **343** or **344** made it difficult to isolate **340f** or **340g** pure.



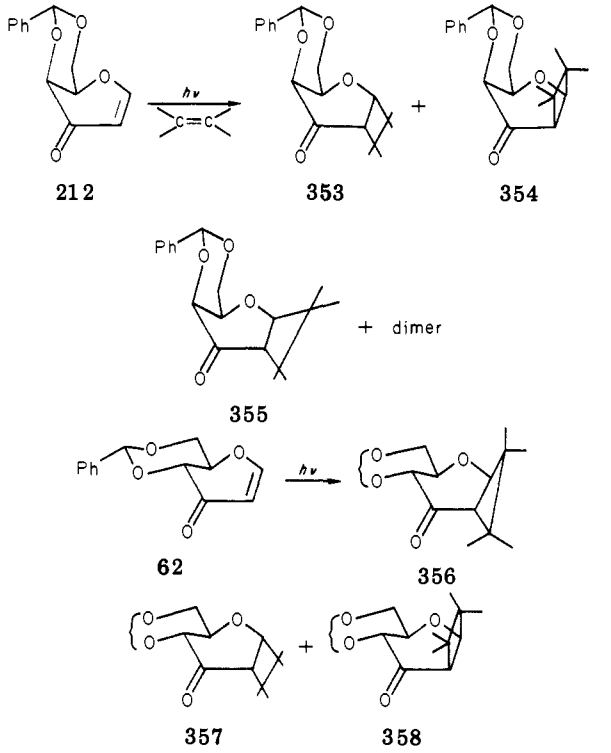
343 344

Irradiation of enones **206a** and **206b** in methanol gives mixtures of adducts in poor yield. However, the conformationally mobile system **206d** gives mixture **341d** (ratio 7:3 axial:equatorial) in about 65% yield. Under similar reaction conditions with enones **166**, mixtures (ratio 3:1 axial:equatorial) of 1,4 adducts **342** are formed in 50% yield.[85]

The simplicity and ease of execution of the photoaddition of simple alcohols to hexenopyranosuloses led Fraser-Reid and his groups[308,309] to explore photoaddition of other oxycarbinyl species, e.g., polyfunctional alcohols (diol, hydroacylate), acetals, dioxalanes, and aldehydes. These oxycarbinyl species undergo photochemical-induced conjugate addition to various ethyl hex-2-enopyranosid-4-uloses **339** and afford 1,4-ketals, 1,4-keto ketals, and 1,4-diketones; Table XX illustrates some of the photoadducts obtained with **339c**.

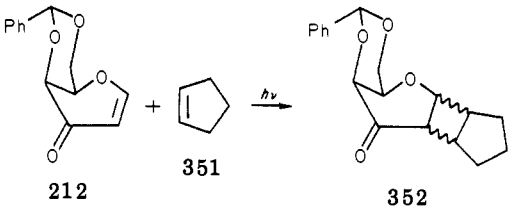
These photoadditions are regiospecific and frequently stereoselective with respect to the substrate, and there is a high degree of regiospecificity regarding the addend.

SCHEME LVIII



2. Addition of Olefins

Few examples of photochemical additions of olefins to carbohydrate enones have been reported,[281,308] and these are concerned with the photoannulation of hex-1-enopyran-3-uloses. Under these conditions some dimerization of the enones was observed. In 1972, Collins and Whitton[310] described the addition of cyclopentene to 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*threo*-hex-1-en-3-ulose (**212**) dissolved in dichloromethane (eq 13). ^1H NMR spectroscopy of the mixture



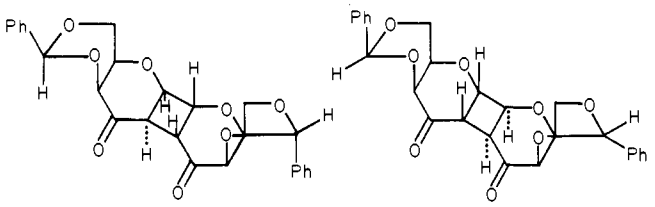
212 351 352 (13)

proved it to be an isomeric mixture of ketonic products; mixtures of cis- and trans-fused products are usually formed in photoannulation of 2-cyclohexenones with simple olefins. However, the stereochemistry at the ring junction could not be identified because of the complexity in the high-field region of the ^1H NMR spectrum. This problem was overcome by using 2,3-dimethyl-2-butene.

A 1% solution of **212** in methylene chloride containing 2,3-dimethyl-2-butene on irradiation gives a mixture (80% conversion) of three cyclobutane adducts, **353**, **354**, and **355**, and a dimer (Scheme LVIII). The structures of the photoadducts were deduced on the basis of their ^1H NMR spectra and their response to base. The spectra of **353** and **354** are unaffected by base, and each compound was assumed to be cis. The other isomerizes to **354**, indicating that it possesses a trans-fused ring system. Additional structural information came from comparisons of ^1H NMR data of acetate derivatives with the data of classical sugar

acetates. In a similar fashion, the 1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose **62** affords three isomeric cyclobutane adducts, **356**, **357**, and **358** (Scheme LVIII).

Further support for assigning a dimeric structure to the fourth photoadduct came from a study in the absence of olefin. Under these conditions the only detectable product was the dimer. Conversely, on irradiation of **212** in the presence of a 20-fold excess of dimethylbutane, only a trace of the dimer was observed. An observation worthy of note is the stability of the dimer in base. The significance of this is that the fusion at C-1 and C-2 in both pyranoid rings must be cis. The simple nature of the ^{1}H NMR spectrum and the appearance of C-2 and C-1 as broadened doublets at δ 3.60 and 4.52, respectively, strongly indicated a head-to-head adduct as shown in **359** or **360**.



359 360

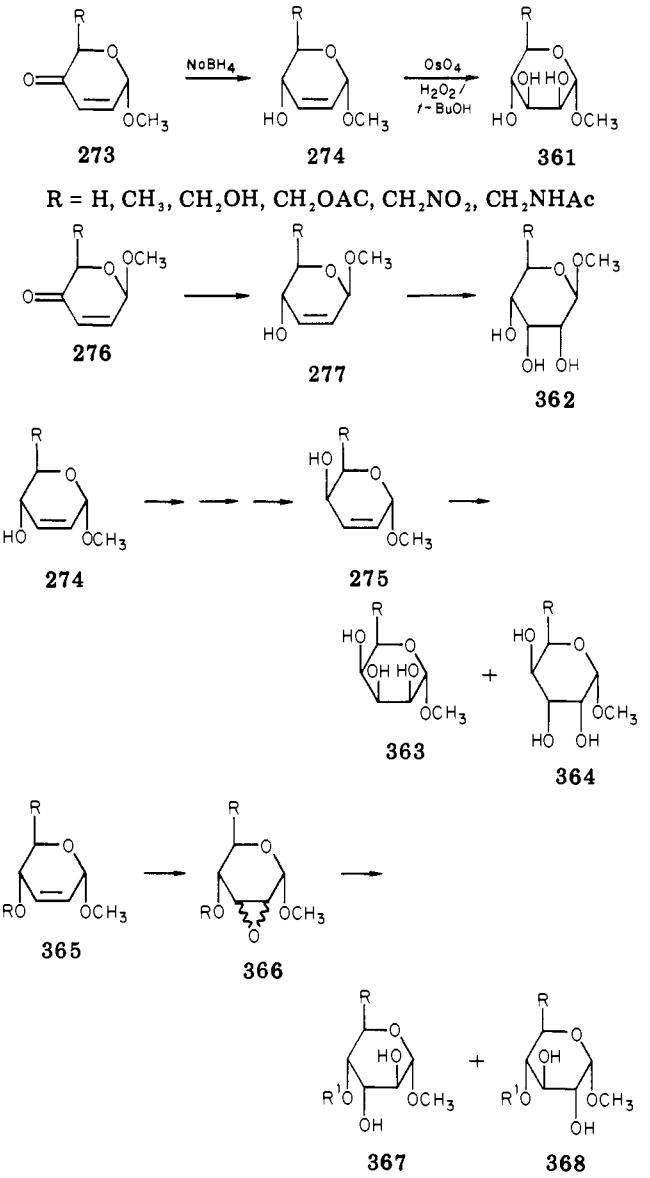
VII. Applications

The statement, "there are four attributes possessed by carbohydrate derivatives which make them ideal chiral synthons",[17] is very applicable to enones. They are synthesized from carbohydrate or noncarbohydrate precursors and in the former case exist in one or the other enantiomeric forms (D or L). By design, the enones posses a variety of functional groups for chemical manipulations, and the reactions are highly stereo- and in some cases regioselective. ^{1}H NMR spectroscopy usually is sufficient for assigning the correct structure for reaction products; however, in some cases caution is advised. Some aspects of these inherent characteristics are exemplified in the stereoselective syntheses of monosaccharides and some amino, deoxy, and branched-chain sugars of biological interest. Fraser-Reid and Anderson[17] reviewed the application of hex-2-enopyranosid-4-uloses in the asymmetric syntheses of natural products by way of annulated pyranosid-4-uloses and pointed out the presence of functionalities capable of various chemical manipulations.

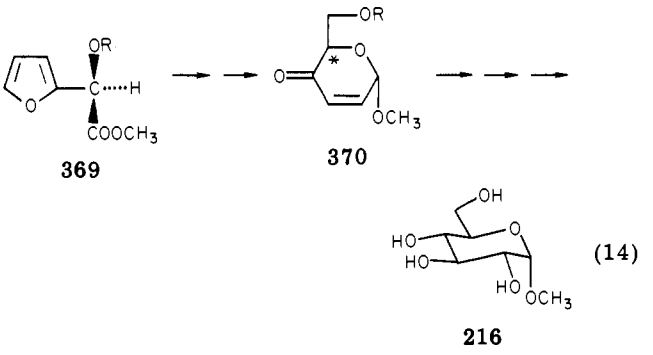
A. Syntheses of Monosaccharides

Enones are key intermediates in the syntheses of monosaccharides from noncarbohydrate precursors.[140-142,282-284] The stereochemical relationships at C-2, C-3, and C-4 are determined by a judicious choice of reaction sequences—reduction of ketone and cis hydroxylation or epoxidation followed by oxirane ring opening of olefin (Scheme LIX). This route[18] affords racemic mixtures, and the optically pure sugar is obtained by resolution; the absolute stereochemistry is assigned by comparison with the naturally occurring sugar. Optically pure monosaccharides of the desired absolute configuration can be obtained by starting with enantiomerically pure 2-furylcarbinol of known absolute configuration. This approach is exemplified by the total synthesis of methyl α-L- and α-D-glucopyranosides **284**

SCHEME LIX



from (*R*)- and (*S*)-2-furylglycolic acids **369**,[311] respectively (eq 14).

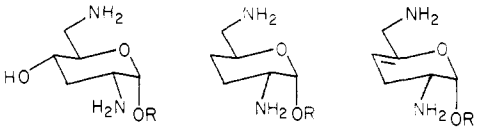


(14)

B. Syntheses of Modified Sugars

1. Carbohydrate Precursors

a. Aminohexopyranosides. 2,6-Diaminotri- or tetradeoxyhexopyranosides are constituents of a number of polynuclear amino glycoside antibiotics.[312,313] Tobrosamine (**371**)[274] is one of the units found in tobramycin, and sisosamine (**373**) and purpurosamine (**372**)[314] are constituents of sisomicin and gentamicin C_{1a}, re-

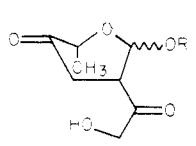


371 372 373

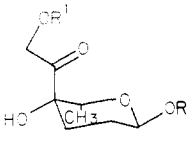
spectively. Three features common in these structures are (1) the α-D-aglycon group, (2) the equatorial C-2 amino function, and (3) the 3-deoxy aspect.

Gero and his co-workers[274,314] reported syntheses of these amino sugars from the readily available hex-2-enopyranosid-4-ulose **88** (Scheme LX). The key step in these syntheses is the nucleophilic 1,4 addition of azide ion to the α,β-unsaturated-keto chromophore in **88**. Ketone **301a** on treatment with sodium borohydride, followed by catalytic hydrogenation in acetic anhydride, was transformed to **375a**. A displacement of the tosyl group in **375a** with sodium azide in DMF followed by catalytic reduction in acetic anhydride afforded **376**. The ^{1}H NMR data of **376** is in agreement with those reported for the methyl α-D-glycoside of *N,N*-diacetyltobrosamine. A series of reactions involving borohydride reduction and treatment of alcohol **374a**, with sulfuryl chloride in pyridine, smoothly converts the keto azide **301a** into **377**. Raney nickel in hydrazine hydrate effects dechlorination of **377** and at the same time reduces the C-2 azide; the free base is then acylated by normal procedures, giving **378**. Sodium azide displacement followed by reduction in acetic anhydride completes the synthesis of **379**. A similar azide displacement in hexamethylphosphoric triamide followed by selective hydrogenation and N-acylation converts **377** into **381**. Mercaptolysis of **379** and **381** followed by N-acylation gave compounds identical with those obtained from sisomicin and gentamicin. Gero's group[275] also used this method to synthesize lividosamine **375b** (Scheme LX), one of the sugar components of the antibiotic lividomycin b.

b. Pillarose. One of the components of pillaromycin A,[315] a member of the anthracycline group of antibiotics, is a highly modified monosaccharide, pillarose. Its original structure[316] was thought to be a 2,3,6-trideoxyhexopyranosid-4-ulose, **382**, containing a two-carbon



382

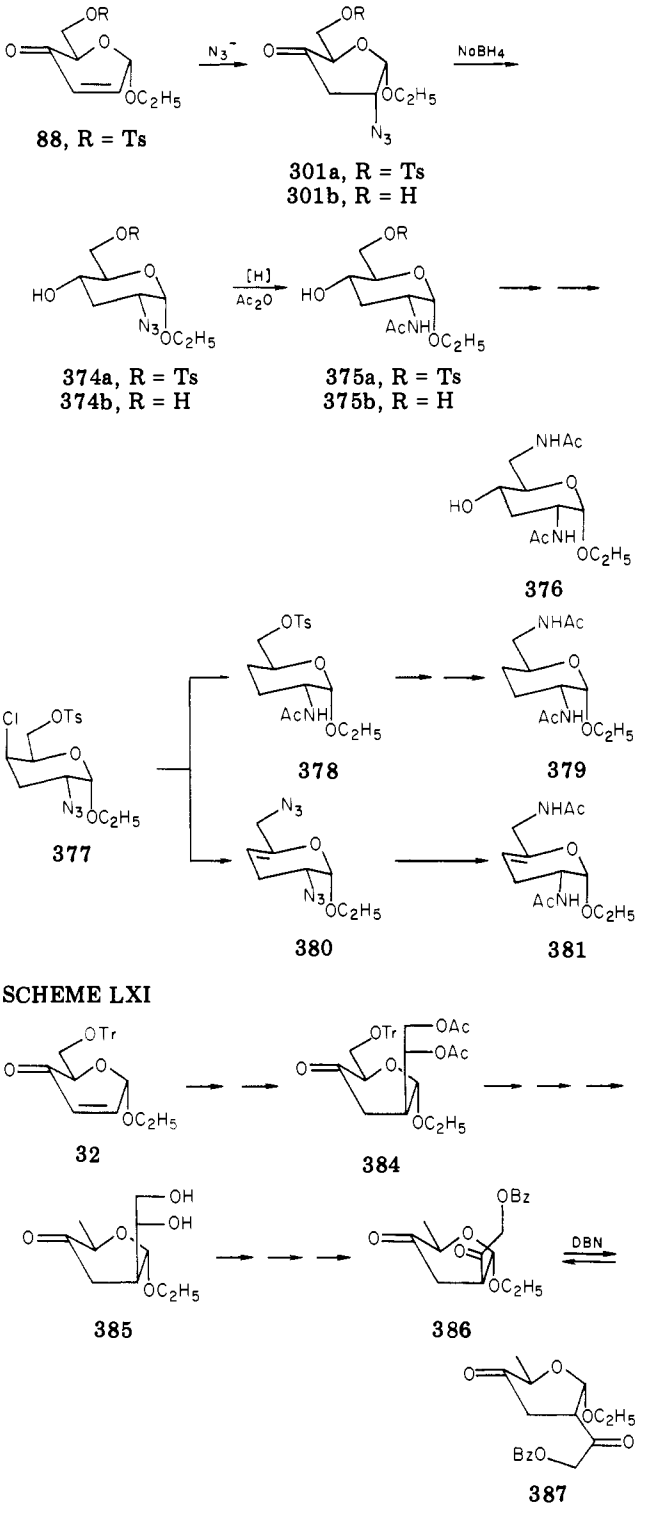


383a, R = CH_3; R^1 = Bz

branch at C-2. However, X-ray crystallographic[317] and mass spectral data established that pillarose is in fact a C-4 branched-chain hexopyranose, **383**. Further confirmation came from synthetic studies conducted by Fraser-Reid and Walker.[318,319] As there was no clear evidence of relative stereochemistry at the asymmetric centers, routes were designed for all related structures. Later Paulsen and co-workers[320] and Brimacombe and associates[321] developed other synthetic routes for pillarose.

The pivotal reaction in the synthesis of the C-2 branched-chain structure was a stereoselective photoaddition to hex-2-enopyranosid-4-ulose (Scheme LXI). In the event, addition of ethylene glycol to enone **32** and acylation of the resulting diol give **384** in 80% yield. Two sequences of standard reactions effect the trans-

SCHEME LX



88, R = Ts

301a, R = Ts
301b, R = H

374a, R = Ts
374b, R = H

375a, R = Ts
375b, R = H

376

377

378

379

380

381

SCHEME LXI

32

384

385

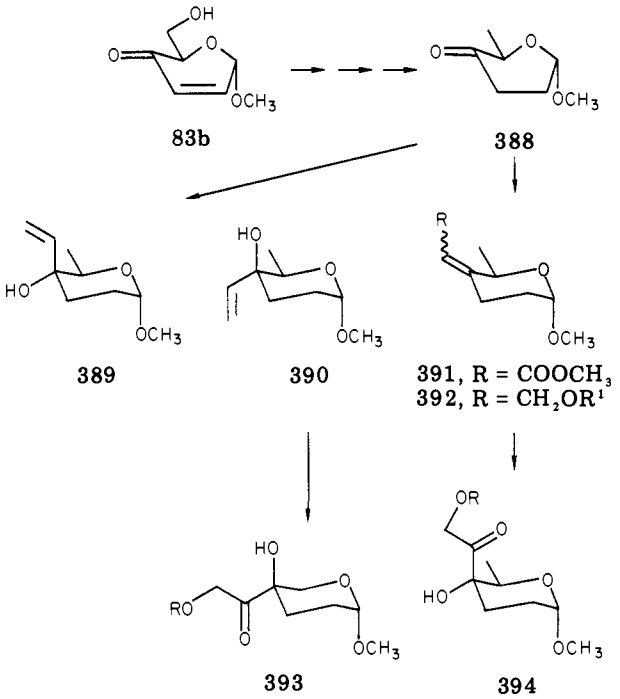
386

387

formation of **384** to **386**. Treatment of **386** with 1,5-diazabicyclo[4.3.0]non-5-ene brings about epimerization at C-2, and the epimers **386** and **387** were separated as their benzoates. The ^{1}H NMR spectra of **386**, **387**, and methyl 8-*O*-benzoylpillaroside (**383a**) show striking differences in the chemical shifts of H-1, H-2, and H-3.

Routes leading to the C-4 branched-chain compounds **393a** and **394a** originated with enone **83b** (Scheme LXII), albeit it was obtained by a lengthy process.[16] Standard reactions were employed to convert **83b** to **388**, and the key steps in the syntheses were the Wadsworth–Emmons–Wittig reaction with trimethyl phosphonoacetate and the 1,2 addition of vinyl-

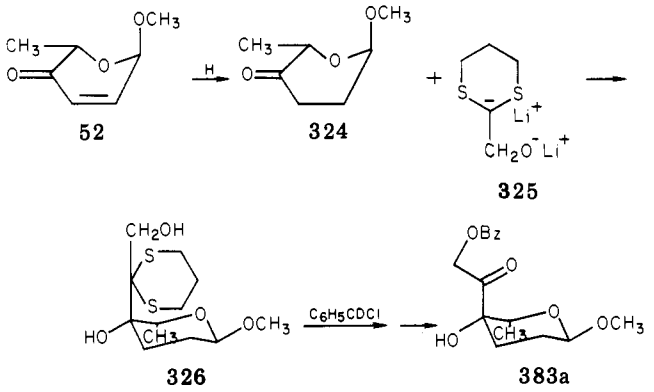
SCHEME LXII



83b 388 389 390 391, R = $COOCH_3$ 392, R = CH_2OR^1 393 394

a, R = Bz
b, R = CPh_3
c, R = H

SCHEME LXIII

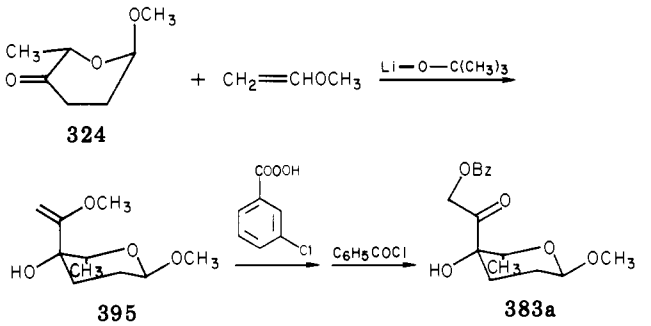


52 324 325 326 383a

magnesium bromide. In the first case, the mixture of esters **391** is reduced, and the alcohols are protected as the tritylates **392** (R = Tr). Hydroxylation with osmium tetroxide followed by oxidation with the Pfitzner–Moffat reagent gives **394b**; detritylation and benzoylation complete the synthesis of **394a** as a noncrystalline compound. The allylic alcohols **389** and **390** from the Grignard reaction were separated by column chromatography. The major isomer **390**, in whose ^1H NMR spectrum H-1 appears as a doublet, is oxidized with osmium tetroxide, and the ketol **393c** is benzoylated to give a crystalline benzoate **393a**. A comparison of the ^1H NMR and optical rotation data indicates that **393a** is the D enantiomer of **383a**.

The key step in the elegant synthesis developed by Paulsen and co-workers[320] is the C–C linkage by nucleophilic addition of the dianion **325** (Scheme LXIII). Benzoylation of the adduct **326** followed by desulfurization leads to the pillaroside **383a**. Another direct approach[321] involves the 1,2 stereoselective addition of (1-methoxyvinyl)lithium to **324** (Scheme LXIV). The adduct **395** on oxidation with *m*-chloroperbenzoic acid

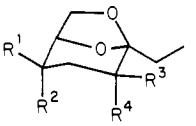
SCHEME LXIV



324 395 383a

in wet ether followed by benzoylation furnishes methyl 8-*O*-benzoylpillaroside (**383a**). In both cases the physical and spectroscopic properties are in agreement with those of the corresponding derivative of natural pillarose.

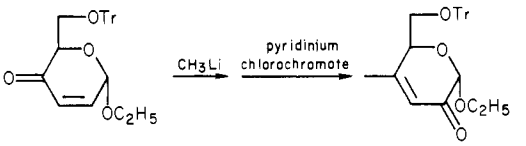
c. Multistriatins Multistriatins belong to a class of novel bicyclic ketals found in the European elm bark beetle.[322] The distinguishing feature in their structures **396** is the 1,3-di-*C*-methyl arrangements. Fraser-Reid



396

	R^1	R^2	R^3	R^4	
a = CH_3	H	H	CH_3	γ	
b = CH_3	H	H	H	α	
c = H	CH_3	CH_3	H	δ	
d = H	CH_3	CH_3	CH_3	β	

and co-workers[323] described stereoselective syntheses of the di-*C*-methylpyrano moieties from hexenopyranosiduloses **32**, **35**, and **397**; the syntheses of **32** and **35** were discussed earlier; and **397** is obtained by a two-step process from **32** (eq 15).



32, R = Tr 397 (15)

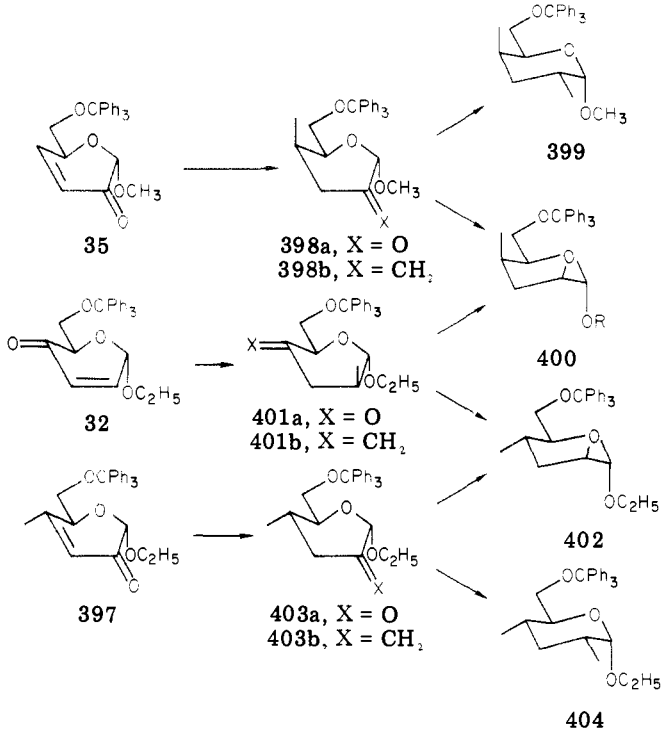
The 1,3-dimethyl diastereomer systems from **35** and **32** are generated by stereoselective dimethylcuprate addition to the enone system (Scheme LXV). This nucleophilic addition is followed by a Wittig reaction on the corresponding ketones **398a** and **401a** and hydrogenation of the newly formed alkenes **398b** and **401b**. Establishing the 1,3-dimethyl system from **397** involves first hydrogenation of the olefinic double bond, then a Wittig reaction followed by hydrogenation of the exocyclic double bond.

The total synthesis of the multistriatins skeleton from the enones was accomplished from model studies with the 6-*O*-benzyl ether **89** leading to α-multistriatin.[17,323] Other stereoselective syntheses of α-multistriatin from D-mannitol and D-glucose have been published.[324,325]

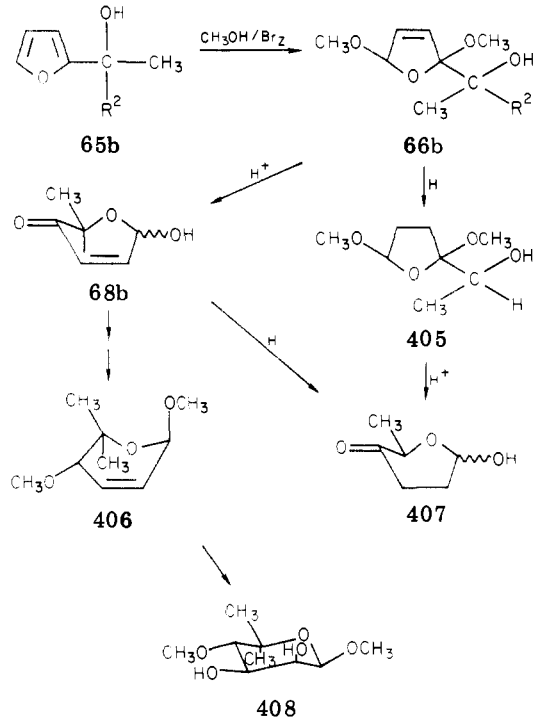
2. Furfuryl Alcohol Precursors

a. Noviose and Cinerulose A. The structure of noviose, the sugar component of the antibiotic novobiocin, is established as 4-*O*-methyl-5,5-dimethyl-L-lyxose. Achmatowicz and co-workers[326] developed an

SCHEME LXV



SCHEME LXVI

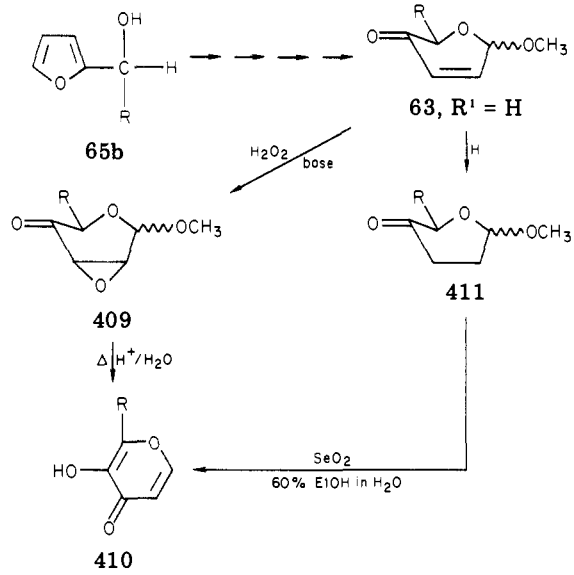


efficient stereoselective synthesis of methyl β-DL-novioside **408** from a furfuryl alcohol, **65b**. This method (Scheme LXVI) is noteworthy since it demonstrates the general method of the total synthesis of an antibiotic sugar from a noncarbohydrate precursor.

Cinerulose A, a hexopyranos-4-ulose (**407**), was synthesized by Achmatowicz and Szechner[327] following the principles developed earlier for monosaccharide synthesis.

b. Maltol The 3-hydroxy-4*H*-pyran-4-one nucleus is found in maltol and its related compounds **410**; these are of interest because of their usefulness as flavoring agents. For a long time, the only practical synthetic

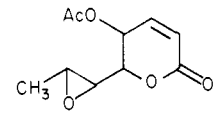
SCHEME LXVII



route was from kojic acid.[328] Groups headed by Shono,[48] Tori,[49] and Weeks[50] reported efficient syntheses of 2-alkyl-3-hydroxy-4*H*-pyran-4-one **410** by way of alkyl pent-2-enopyranosid-4-ulose **63** (Scheme LXVII). The steps leading to **410** involve epoxidation of **63** and acid-catalyzed rearrangement of **409**. Alternatively, the synthesis may be accomplished via the hexopyranosid-4-ulose **411**.

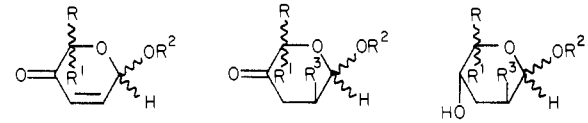
VIII. Biological Activity

Hexenopyranosiduloses and their derivatives bear such a close resemblance to the modified sugars found in antibiotics that it is not difficult to imagine that they themselves possess some biological activity. This idea is strengthened by the occurrence of a structurally related antibiotic, asperlin **412**,[329] and the evidence from



412

the results of two independent studies: Lefebvre's group[144] was concerned with the biological properties of hex-2-enopyranos-4-uloses and their C-1 derivatives **413**, while Georgiadis[277] investigated the activity of C-2 amino hexopyranosuloses **414** and hexopyranoses **415**.



413 414 415

R = H, CH_3
R^1 = p-$C_6H_5C_6H_4$--
R^2 = H, CH_3, CH_3CO, CH_3OCO, $CONHCH_3$, $CON(CH_3)_2$
R^3 = $N(CH_3)_2$, $NHCH_3$, morpholino, 4-methyl-1-piperazinyl

The three classes of compounds, particularly those with a C-5 biphenylyl or similar residue, display anticoccidal and/or antimicrobial activities during in vitro screening; the nature of the aglycon influence both the degree and type of activity.

In general, the enones, their C-1 derivatives **413** and C-2 amino adducts **414** are active antimicrobial agents.

They exhibit activity against Gram-positive bacteria but are inactive against Gram-negative organisms. Although the C-1 derivatives, particularly the ethers, are the most effective agents, carbamates are generally inactive. As for antifungal activity, all hexeno- and hexopyranosid-4-uloses acted mostly against *Microsporum gypseum* and *Trichophytum granulosum* organisms, while little activity was observed against *Candida albicans*. The more stable C-4 hydroxy derivatives **415** are ineffective as antibacterial and antifungal agents. The antimicrobial activity of the amino adducts (in vitro) was of the same order of magnitude as the enones, and this suggests that such activity may be due to a retro-Michael reaction.

Both classes of amino adducts are by far more active as coccidiostats than the hexenopyranosid-4-uloses. Of the C-1 derivatives of the enones, the most effective agents are the carbamates. The activity of these agents was demonstrated during in vivo screening studies in chickens experimentally infected with *Eimeria tenella*. In general, the smaller the amino substituent, the better the anticoccidial activity, and the amino adducts retained their activity when they are reduced. Therefore, the coccidiostatic activity is not necessarily linked to the hex-2-enopyranosid-4-ulose nucleus.

Fraser-Reid and co-workers[267] observed mild antithrombic activity of the triacetylpyranopyrazoline **291**. These compounds add to the vast numbers of synthetic or naturally occurring modified carbohydrates with biological activity.

IX. Summary and Conclusions

Following the original reports describing the synthesis of novel carbohydrate enones, several research groups investigated various aspects of hexenopyranosulose chemistry. Two general methods were developed for their syntheses: one involves the incorporation of the α,β-unsaturated-keto chromophore into readily available glycopyranosides, and the principle of the other is the transformation of furfuryl alcohols. Use of ^{1}H NMR and to a lesser extent ^{13}C NMR spectroscopy is commonplace in structural elucidation of enones and their reaction products; the most useful information is that obtained from conformation analysis. The behavior of the enones on electron impact was examined and the main fragmentation pathway is a retro-diene fragmentation.

The variety of the reactions reported for the enones, both in the ground and excited states, is an indication of their synthetic utility. One noticeable feature in the chemistry of the hexenopyranosuloses is the high degree of stereoselectivity associated with these reactions. This is most desirable in the asymmetric synthesis of naturally occurring sugars and other optically active compounds. In this respect, the enones are attractive starting materials, and this is evident from the number of research programs in which enones have been used as chiral synthons.

The enones and their derivatives were found to possess good in vitro antimicrobial activities. Some derivatives and adducts exhibited in vivo anticoccidial effects.

During the past two decades, major advances have been made in the study of hexenopyranosuloses, and this is likely to continue for many years to come.

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