The Total Synthesis of Natural Products

VOLUME 1

Edited by

JOHN ApSimon

Department of Chemistry
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WILEY-INTERSCIENCE, a *Division of John Wiley & Sons, Inc.*
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Preface

Throughout the history of organic chemistry we find that the study of natural products frequently has provided the impetus for great advances. This is certainly true in total synthesis, where the desire to construct intricate and complex molecules has led to the demonstration of the organic chemist's utmost ingenuity in the design of routes using established reactions or in the production of new methods in order to achieve a specific transformation.

These volumes draw together the reported total syntheses of various groups of natural products with commentary on the strategy involved with particular emphasis on any stereochemical control. No such compilation exists at present and we hope that these books will act as a definitive source book of the successful synthetic approaches reported to date. As such it will find use not only with the synthetic organic chemist but also perhaps with the organic chemist in general and the biochemist in his specific area of interest.

One of the most promising areas for the future development of organic chemistry is synthesis. The lessons learned from the synthetic challenges presented by various natural products can serve as a basis for this ever-developing area. It is hoped that this series will act as an inspiration for future challenges and outline the development of thought and concept in the area of organic synthesis.

The project started modestly with an experiment in literature searching by a group of graduate students about six years ago. Each student prepared a summary in equation form of the reported total syntheses of various groups of natural products. It was my intention to collate this material and possibly publish it. During a sabbatical leave in Strasbourg in the year 1968–1969, I attempted to prepare a manuscript, but it soon became apparent that if I was to also enjoy other benefits of a sabbatical leave, the task would take many years. Several colleagues suggested that the value of such a collection

would be enhanced by commentary. The only way to encompass the amount of data collected and the inclusion of some words was to persuade experts in the various areas to contribute. I am grateful to all the authors for their efforts in producing stimulating and definitive accounts of the total syntheses described to date in their particular areas. I would like to thank those students who enthusiastically accepted my suggestion several years ago and produced valuable collections of reported syntheses. They are Dr. Bill Court, Dr. Ferial Haque, Dr. Norman Hunter, Dr. Russ King, Dr. Jack Rosenfeld, Dr. Bill Wilson, Mr. Douglas Heggart, Mr. George Holland, and Mr. Don Todd. I also thank Professor Guy Ourisson for his hospitality during the seminal phases of this venture.

JOHN APSIMON

Ottawa, Canada
February 1972

Contents

THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

The Total Synthesis of Carbohydrates

J. K. N. JONES AND W. A. SZAREK

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1. INTRODUCTION

The carbohydrates comprise one of the major classes of naturally occurring organic compounds. Although the structures of carbohydrates appear to be quite complex, the chemistry of these compounds usually involves only two kinds of functional group, ketone or aldehyde carbonyls and hydroxyl groups. The carbonyl groups normally are not free but are combined with

the hydroxyl groups in hemiacetal or acetal linkages; the carbon of the "masked" carbonyl is known as the anomeric center. When a free sugar is dissolved in an appropriate solvent, a dynamic equilibrium is achieved involving both anomerization and ring isomerization.

A wide variety of sugars has been found in nature and/or synthesized in the laboratory. These include not only the "classical" sugars but also derivatives such as amino, thio, halo, deoxy, branched-chain, and unsaturated sugars. Most synthetic sugars have been obtained by chemical transformations of naturally occurring sugars or their derivatives. In fact, the degree of achievement is such that the synthesis of a new mono-, di-, or trisaccharide can now be undertaken with a fair degree of confidence.

The total synthesis of sugars from noncarbohydrate precursors has also been achieved by many routes. Some methods are long, involved, are stereospecific and result in the formation of one or two sugars only; others are relatively simple but produce complex mixtures of carbohydrates which may resist fractionation. Practically all naturally occurring sugars are optically active. Most synthetic routes which employ noncarbohydrate precursors produce racemic mixtures of sugars which may be difficult to separate into the D and L isomers. However, if enzymes are used to effect condensation of fragments or to remove one or more of the components, optically pure isomers may be isolated. In this chapter the total synthesis of sugars and the related alditols and cyclitols, from noncarbohydrate substances by both specific and nonspecific methods, are discussed. Only compounds containing more than three carbon atoms are considered.

2. BASE-CATALYZED CONDENSATIONS WITH CARBON-CARBON BOND FORMATION. THE FORMOSE REACTION

The formose reaction has attracted the attention of biologists and chemists in recent years because it involves the self-condensation of formaldehyde to produce reducing sugars. This property is of interest in considering the problem of the origin of life on this planet, especially as formaldehyde has been detected in interstellar gases,[1] and also because of the feasibility of using carbon (as formaldehyde) as a possible source of sugars for the growth of microorganisms with the concomitant production of proteins and other complex organic compounds of importance to life and industry.[2]

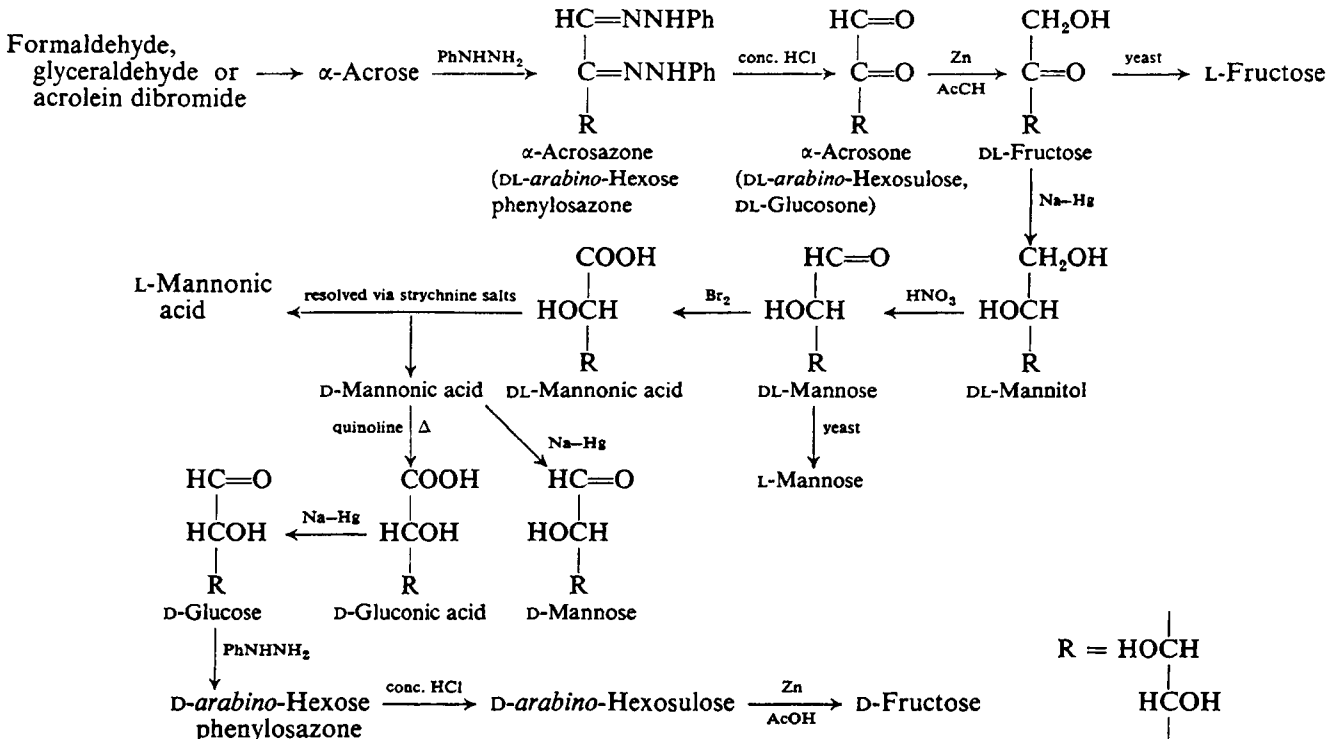
The self-condensation of formaldehyde under the influence of base to yield a sugarlike syrup (methylenitan) was first observed by Butlerow[3] in 1861, when he treated trioxymethylene with calcium hydroxide solution. Calcium carbonate, magnesia, baryta, mineral clay, or even γ-radiation

may also be used.[4] Fischer[5] showed that the sugarlike syrup called formose obtained from gaseous formaldehyde,[6] or methose prepared by the action of magnesium hydroxide suspension on formaldehyde,[7] contained monosaccharides, and that by reacting methose with phenylhydrazine acetate it was possible to obtain two hexose phenylosazones in low yield. Much higher yields were obtained from acrose (see below). Fischer named these derivatives α- and β-acrosazone (the corresponding sugars are α-acrose and β-acrose) and showed that α-acrosazone was DL-*arabino*-hexose phenylosazone (DL-glucose phenylosazone). In a remarkable series of experiments involving chemical and enzymic processes, Fischer was able to achieve the total synthesis from α-acrose of D- and L-glucose, D-gluconic acid, D- and L-mannose, D- and L-mannonic acids, D- and L-mannitol, and of D- and L-*arabino*-hexulose (D- and L-fructose), thus laying the basis for the synthesis of many other sugars. The transformations achieved are shown in Scheme 1.

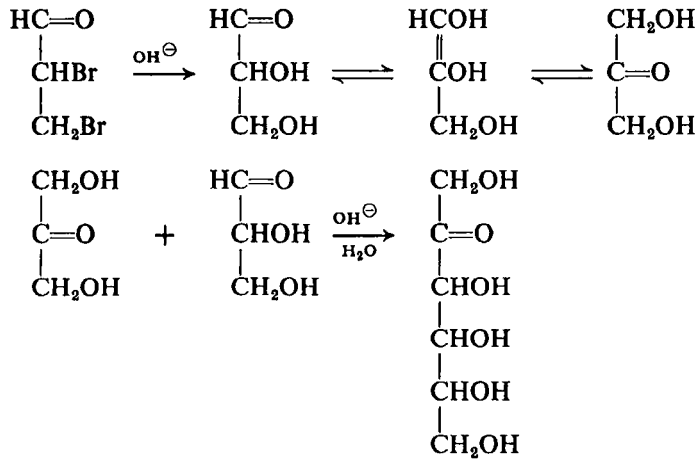
β-Acrosazone was later identified as DL-*xylo*-hexose phenylosazone (DL-sorbose phenylosazone), which can be derived from DL-glucose, DL-idose, and DL-*xylo*-hexulose (DL-sorbose).[8] However, there has been a suggestion that β-acrosazone is really the phenylosazone of DL-dendroketose (see below). Fischer and Tafel[9] observed that 2,3-dibromopropionaldehyde (acrolein dibromide) when treated with dilute alkali yielded products which reacted like sugars (hence the name "acrose"). DL-Glyceraldehyde[10] also gave products that possessed the properties of sugars when treated similarly. Fischer and Tafel[9] explained the formation of acrose as an aldol-type condensation between DL-glyceraldehyde and 1,3-dihydroxypropanone (dihydroxyacetone), the latter compound being formed by a base-catalyzed isomerization from DL-glyceraldehyde (see Scheme 2).

H. O. L. Fischer and E. Baer[11] showed that D-glyceraldehyde and 1,3-dihydroxypropanone react in basic solution to yield D-*arabino*-hexulose and D-*xylo*-hexulose as major products. This reaction is a general reaction and novel sugars can be produced if D-glyceraldehyde is replaced by L-glyceraldehyde or by other aldehydes (see below). It is interesting that the biological origin of D-*arabino*-hexulose follows a similar route, but sugar phosphates and enzymes (aldolases) are involved.[12] In all cases the *threo* configuration is favored at the newly formed asymmetric centres but condensations involving enzyme-catalyzed reactions[13] usually yield the D-*threo* configuration only.

The conversion of formaldehyde to formose involves a complex series of reactions which have been rationalized by Breslow,[14] who suggested that two processes are involved in the formation of glycolaldehyde from formaldehyde. The first is a slow condensation of two molecules of formaldehyde to form glycolaldehyde, which then reacts rapidly with a further molecule of formaldehyde to produce glyceraldehyde. Part of this is then converted to


Formaldehyde, glyceraldehyde or acrolein dibromide
α-Acrose
PhNHNH2
α-Acrosazone (DL-arabino-Hexose phenylosazone
conc. HCl
α-Acrosone (DL-arabino-Hexosulose, DL-Glucosone)
Zn
AcOH
DL-Fructose
yeast
L-Fructose
Na–Hg
DL-Mannitol
HNO3
DL-Mannose
Br2
DL-Mannonic acid
resolved via strychnine salts
L-Mannonic acid
D-Mannonic acid
quinoline
Δ
Na–Hg
L-Mannose
D-Glucose
D-Gluconic acid
D-Mannose
PhNHNH2
D-arabino-Hexose phenylosazone
conc. HCl
D-arabino-Hexosulose
Zn
AcOH
D-Fructose
R = HOCH HCOH HCOH CH2OH
(only the D isomers of DL mixtures are shown)

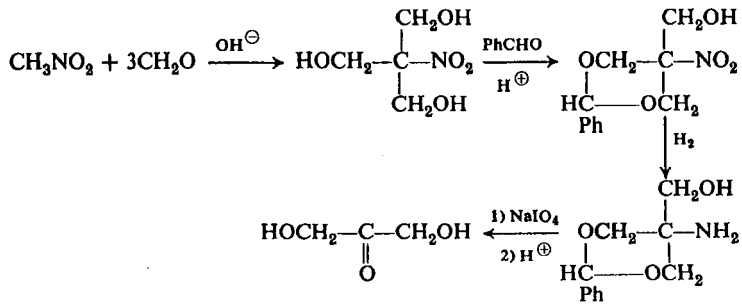
Scheme 1



Scheme 2

1,3-dihydroxypropanone,* which then rapidly reacts with formaldehyde to yield tetrulose and then tetrose, which then breaks down to two molecules of glycolaldehyde. The reaction is thus autocatalytic and is formulated as shown in Scheme 3. The rate of formose formation is dependent upon the metal cation of the base used. It is more rapid with those bases that form chelate compounds with enediols, which are intermediates in the foregoing reaction: thallium hydroxide > calcium hydroxide > sodium hydroxide. It follows that the composition of formose will depend upon the base used, the concentration of the reactants, and the temperature and time of reaction. Short periods of reaction favor the formation of lower molecular weight ketose sugars, longer periods of reaction yield more aldose sugars, while high concentration of alkali and long periods of heating yield saccharinic acids[16] and other products resulting from the decomposition of sugars by

* 1,3-Dihydroxypropanone has been prepared by Marei and Raphael[15] from nitromethane and formaldehyde:



$$CH_2O + HOCH_2—CHO \rightleftarrows HOCH_2—CHOH—CHO \rightleftarrows HOCH_2—CO—CH_2OH$$

$$CH_2O + HOCH_2—CO—CH_2OH \rightleftarrows HOCH_2—CHOH—CO—CH_2OH \rightleftarrows HOCH_2—CHOH—CHOH—CHO$$

$$HOCH_2—CHOH—CHOH—CHO \rightleftarrows 2\ HOCH_2—CHO$$

Scheme 3

alkali. With the advent of paper chromatography and gas-liquid chromatography, it has been possible to detect all eight aldohexose sugars, all four hexuloses, the four pentoses, two pentuloses, all possible tetroses, dendroketose, and three heptuloses.[17–19] Recently, sugars prepared by base-catalyzed condensation of formaldehyde were analyzed by combined gas-liquid chromatography and mass spectrometry; both branched and straight-chain products were detected.[19a] Cannizzaro reaction of formaldehyde proceeds in alkaline medium in conjunction with the formose reaction to produce aldoses and ketoses, and it has been shown[19b] that the extent of the two reactions is a function of the catalyst used. In a study with calcium hydroxide as catalyst, it was found that the ratio of branched-chain sugar derivatives, such as (hydroxymethyl)glyceraldehyde and apiose (see below), and straight-chain products could be controlled by manipulation of the reaction conditions. The branched products are very readily reduced by a crossed-Cannizzaro reaction with formaldehyde and large quantities of species such as (hydroxymethyl)glycerol are produced. Formose solutions are decomposed by microorganisms if allowed to stand in an open vessel in the laboratory.[20] Glycolaldehyde itself polymerizes under the influence of base to yield tetroses, hexoses, and other sugars.[21] Methoxyacetaldehyde polymerizes in aqueous potassium cyanide solution forming 2,4-dimethoxyaldotetroses:[22]

$$CH_3OCH_2—CHO + CH_3OCH_2—CHO \xrightarrow[\text{or } K_2CO_3]{KCN} CH_3OCH_2—CHOH—CHOCH_3—CHO$$

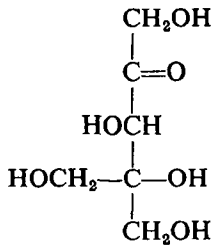
The polymerization of formaldehyde to yield sugars is, therefore, a very complicated process. For example, the formation of pentoses from formaldehyde may proceed via several routes. Glycolaldehyde and 1,3-dihydroxypropanone may react to form pentuloses, which subsequently are isomerized to pentoses, or formaldehyde and a tetrulose may combine to yield pent-3-uloses, which then isomerize to pentuloses and pentoses, or glyceraldehyde and glycolaldehyde may combine to form pentoses. To test these hypotheses, Hough and Jones[23] treated mixtures of glycolaldehyde and 1,3-dihydroxypropane and of glyceraldehyde and glycolaldehyde with lime water and found that pentoses were produced along with several other sugars. They were able to isolate arabinose, ribose, and xylose, as phenylhydrazones, from the complex mixture of sugars that results from the two reactions previously described.

Very recently, it was shown[23a] that it is possible, by making use of the hexokinase reaction, to extract some specific sugars from the complex synthetic formose sugars. The enzyme hexokinase is known to transfer the terminal phosphate of ATP to D-glucose:

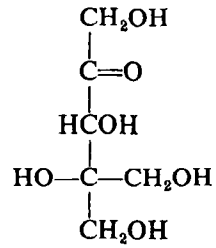
$$\text{D-glucose} + \text{ATP} \xrightarrow{\text{hexokinase}} \text{D-glucose 6-phosphate} + \text{ADP}$$

However, the enzyme is not totally specific for glucose, other hexoses such as fructose and mannose being also susceptible to phosphorylation. The basis of the method of extraction involves phosphorylation of some hexoses by this means, which are then retained on a column of anion-exchange resin (together with unreacted ATP and formed ADP), while other unreacted, neutral components of the formose mixture pass through the column. The sugar phosphates are then eluted by a salt solution of appropriate concentration, and the unsubstituted hexoses are obtained by a phosphatase reaction.

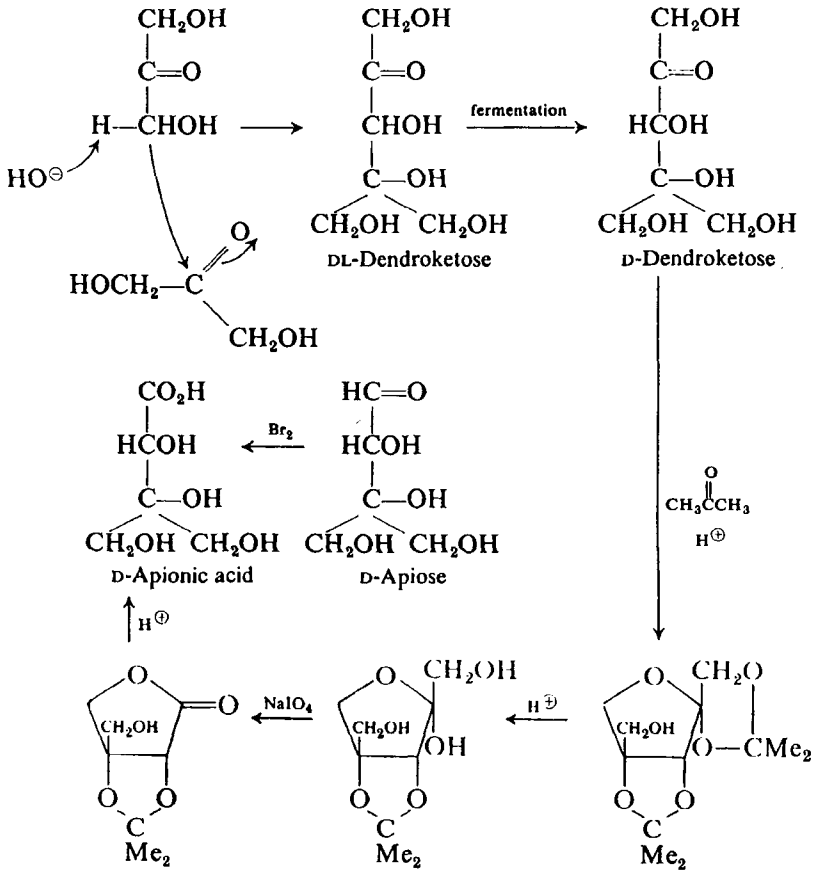
The branched-chain sugar DL-dendroketose mentioned earlier was first isolated by Utkin,[24] who prepared it by adding sodium hydroxide to a solution of 1,3-dihydroxypropanone in water. It is formed so easily and in such high yield that it seems remarkable that it has not appeared in any natural product. Moreover, it is metabolized completely by baker's yeast.[25] Like the branched-chain sugar apiose,[26] hemiacetal formation results in the formation of a new optically active center with the possible formation of eight isomers from the D and L forms of dendroketose. Utkin was able to isolate D-dendroketose (4-*C*-hydroxymethyl-D-*glycero*-pentulose) when he observed that a microorganism which accidentally contaminated a solution of DL-dendroketose, metabolized the L-isomer only. He was able to prove the absolute configuration of the nonmetabolized material by relating it to D-apiose,[27] a sugar of known absolute configuration, by the series of reactions indicated in Scheme 4. It may be significant that D-dendroketose, which remained after fermentation of the DL mixture, possesses a potential L-*threo* disposition of hydroxyl groups at C-3 and C-4, while L-dendroketose which possesses a potential D-*threo* configuration at C-3 and C-4 is metabolized:



L-Dendroketose
(metabolized)



D-Dendroketose
(not metabolized)



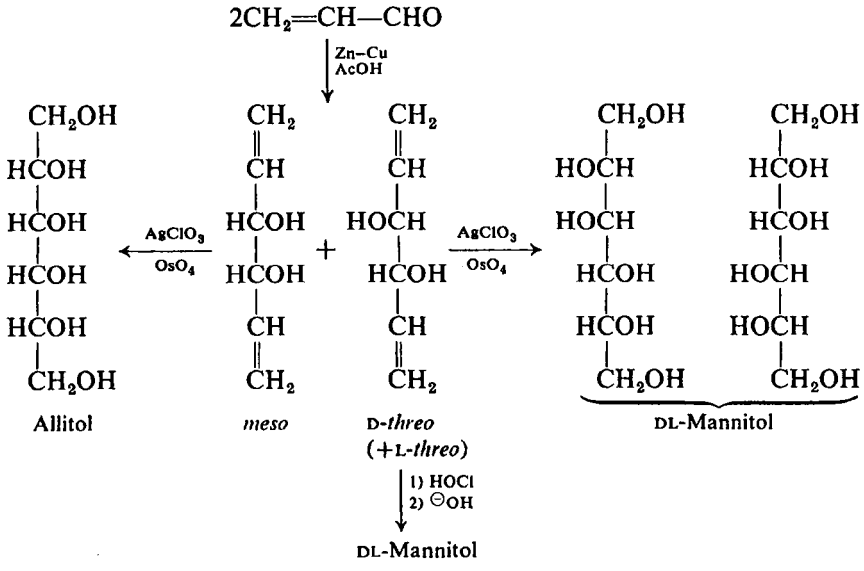
Scheme 4

3. SYNTHESES FROM ACETYLENIC AND OLEFINIC PRECURSORS

The directed synthesis of carbohydrates from noncarbohydrate precursors in most cases involves the preparation of compounds of acetylene. These acetylenic intermediates may be converted into *cis*- or *trans*-ethylenic derivatives dependent upon the mode of reduction of the acetylene. A further advantage of this approach is that the ethylene may then be hydroxylated in a *cis* or *trans* fashion, as decided by the mode of oxidation. In some cases steric effects may be used to force the predominant formation of one of the DL forms. This procedure is particularly effective when the hydroxylation of a ring compound is involved.

Several workers, chief among whom are Lespieau, Iwai, and Raphael, have synthesized carbohydrate derivatives from acetylenic and olefinic precursors. Stereochemical problems of hydroxylation were minimized either by *cis*-hydroxylation of double bonds of known stereochemistry using potassium permanganate or osmium tetroxide, or by epoxidation of double bonds of known stereochemistry followed by opening of the epoxide ring, with resulting *trans*-hydroxylation of the double bond.

Griner[28] appears to be one of the first to attempt the synthesis of sugar alcohols. He observed that when acrolein was hydrogenated by means of a zinc-copper couple and acetic acid, dimerization occurred and divinylglycol (CH_2=CH—CHOH—CHOH—CH=CH_2) resulted. This may exist in *meso* or DL modifications. Griner obtained the aid of LeBel to isolate a mold which would preferentially metabolize one of the isomers. In this, LeBel was successful. Griner had expected to obtain an optically active material but obtained a product devoid of activity and concluded that the *meso* form only was present. Lespieau[29] later showed this conclusion to be erroneous. Griner attempted to oxidize the divinylglycol, with permanganate solution, to a hexitol, but was unsuccessful. Later, in a brief note,[30] Griner stated that addition of two molecules of hypochlorous acid to divinylglycol gave a divinylglycol dichlorohydrin from which, after treatment with base, he was able to isolate DL-mannitol. Lespieau[31] repeated the attempted hydroxylation of divinylglycol but used osmium tetroxide-silver chlorate as the hydroxylating agent, and obtained allitol and DL-mannitol (see Scheme 5).



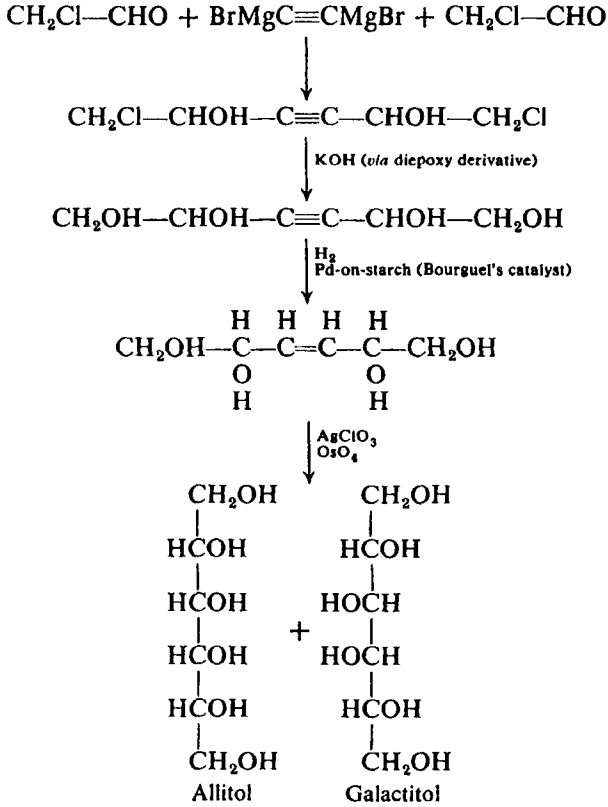
Scheme 5

Hence, assuming *cis* addition of the new hydroxyl groups, allitol arises from the *meso* compound and DL-mannitol from DL-divinylglycol. In a second method of synthesis,[32] involving the Grignard reagent derived from acetylene and chloroacetaldehyde, divinylacetylene dichlorohydrin

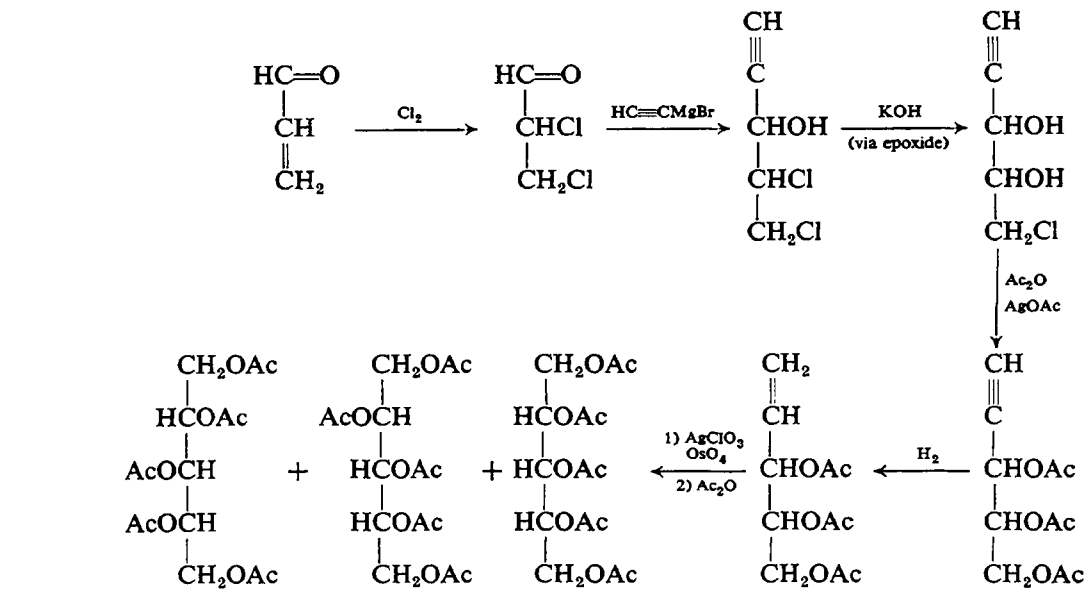
$$(CH_2Cl—CHOH—C{\equiv}C—CHOH—CH_2Cl),$$

was prepared, converted to the hexynetetrol, and reduced to the corresponding ethylene derivative. Hydroxylation of the product by means of osmium tetroxide-silver chlorate gave galactitol and allitol. The ethylene derivative, therefore, had the *meso* configuration (see Scheme 6).

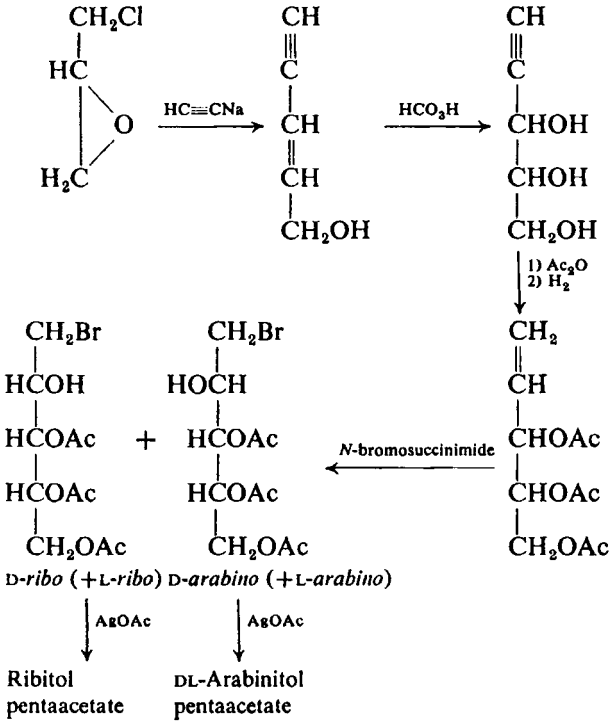
Lespieau[33] also synthesized ribitol and DL-arabinitol using acrolein dichloride and acetylene as starting materials as shown in Scheme 7. Raphael[34] improved on these syntheses by using epichlorohydrin and acetylene as starting materials, and performic acid as the oxidizing agent (see Scheme 8).



Scheme 6


HC=O
CH
CH2
Cl2
HC=O
CHCl
CH2Cl
HC≡CMgBr
CH
C
CHOH
CHCl
CH2Cl
KOH
(via epoxide)
CH
C
CHOH
CHOH
CH2Cl
Ac2O
AgOAc
CH
C
CHOAc
CHOAc
CH2OAc
H2
CH2
CH
CHOAc
CHOAc
CH2OAc
1) AgClO3
OsO4
2) Ac2O
CH2OAc
HCOAc
AcOCH
AcOCH
CH2OAc
+
CH2OAc
AcOCH
HCOAc
HCOAc
CH2OAc
+
CH2OAc
HCOAc
HCOAc
HCOAc
CH2OAc
DL-Arabinitol
pentaacetate
Ribitol
pentaacetate

Scheme 7

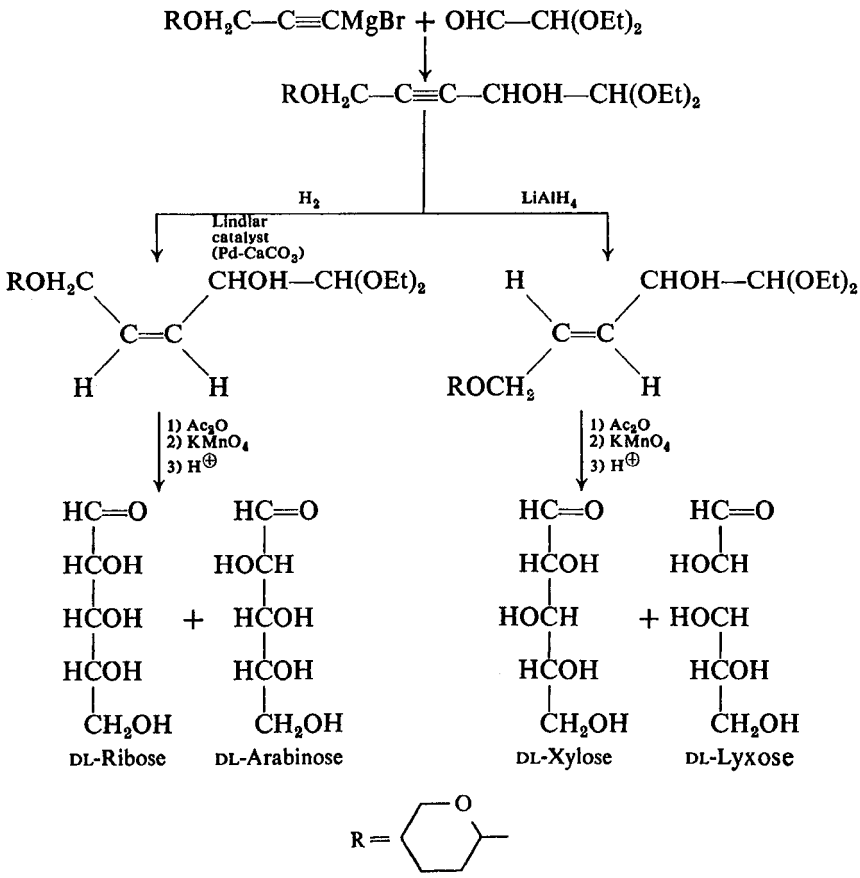


Scheme 8

Iwai and his associates in Japan have achieved several total syntheses of pentose sugars using acetylenic compounds. Iwai and Iwashige[35] condensed the Grignard reagent derived from 3-(tetrahydropyranyl-2′-oxy)-propyne with 2,2-diethoxyacetaldehyde to yield 1,1-diethoxy-5-(tetrahydropyranyl-2′-oxy)pent-3-yn-2-ol, which, on reduction with lithium aluminum hydride, yields the *trans*-olefin. Catalytic hydrogenation, on the other hand, yields the *cis*-olefin. Acetylation of these products, followed by *cis* hydroxylation of the double bonds, affords products which, after hydrolysis of the acetal residues, yield the four DL-pentose sugars (see Scheme 9).

Iwai and Tomita have achieved a stereospecific synthesis of DL-arabinose[36] and a synthesis of a mixture[37] of DL-arabinose and DL-ribose as shown in Scheme 10.

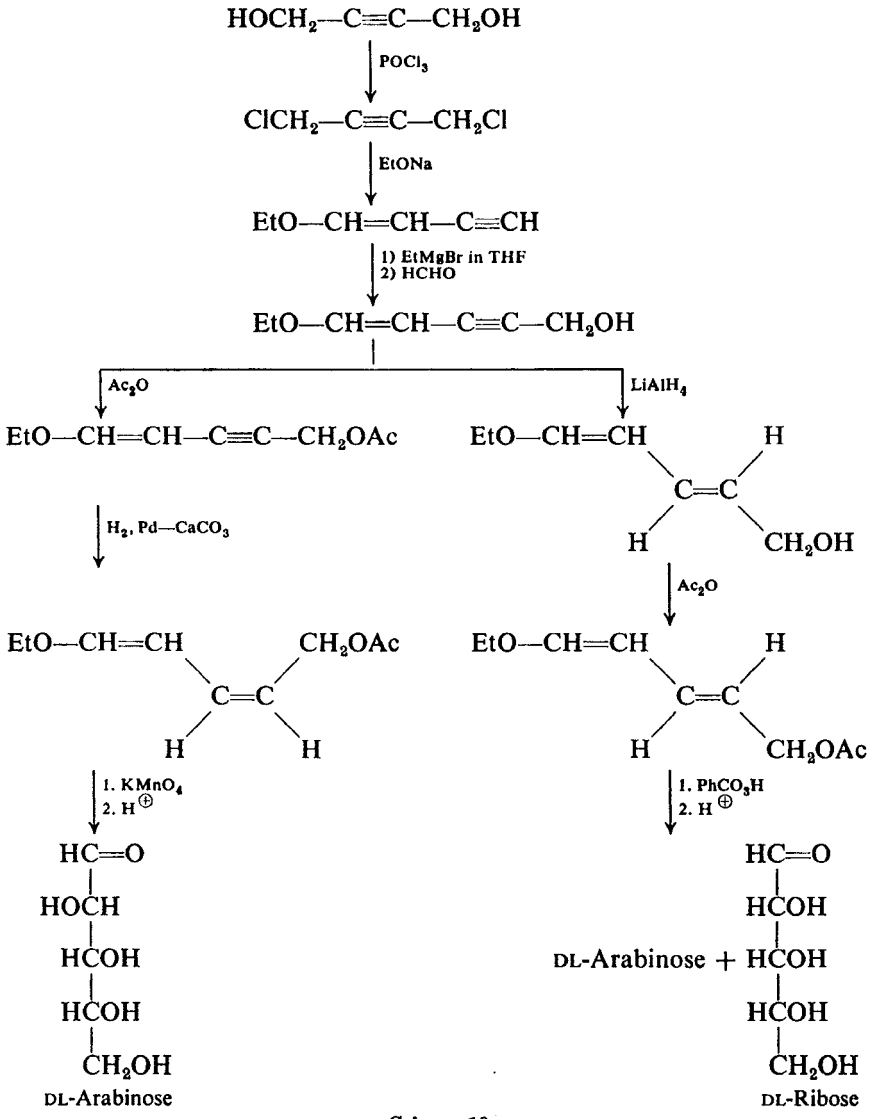
DL-Ribose has been synthesized[38] stereospecifically by oxidative hydroxylation of 2-ethoxy-5-(tetrahydropyranyl-2′-oxy)methyl-2,5-dihydrofuran (see Scheme 11), which was obtained by hydrogenation of DL-1,1-diethoxy-5-(tetrahydropyranyl-2′-oxy)pent-2-yn-4-ol. This acetylenic compound was prepared by the Grignard reaction of (tetrahydropyranyl-2′-oxy)acetaldehyde with propargyl diethyl acetal magnesium bromide. One method for the



Scheme 9

preparation of (tetrahydropyranyl-2′-oxy)acetaldehyde involved ozonolysis of the tetrahydropyranyl ether of allyl alcohol. This synthesis of DL-ribose is the first example, in this chapter, of a total synthesis of a sugar, which involved a furan derivative; other examples are discussed in Section 6.

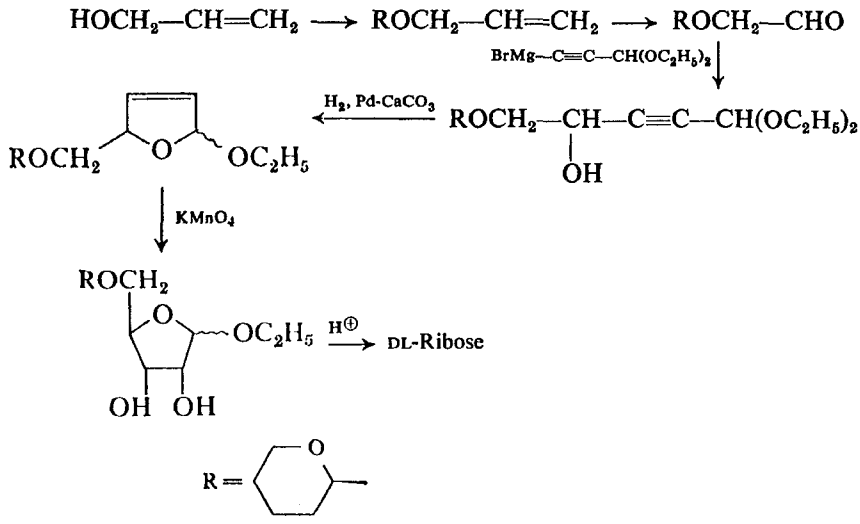
Total syntheses of deoxypentose sugars have also been reported. Hough[39] described a preparation of the biologically important 2-deoxy-D-*erythro*-pentose (2-deoxy-D-ribose) which involves the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde with allylmagnesium bromide. Hydroxylation of the resultant 5,6-*O*-isopropylidene-1-hexene-D-*erythro*-4,5,6-triol gave a mixture of products. Periodate oxidation of the hexitol derivatives, followed by hydrolysis, afforded almost exclusively 2-deoxy-D-*erythro*-pentose (Scheme 12). Another preparation of this sugar has also been achieved[40] using 2,3-*O*-isopropylidene-D-glyceraldehyde as a starting material, by condensation



Scheme 10

with acetaldehyde in the presence of anhydrous potassium carbonate; 2-deoxy-D-xylose was also obtained.

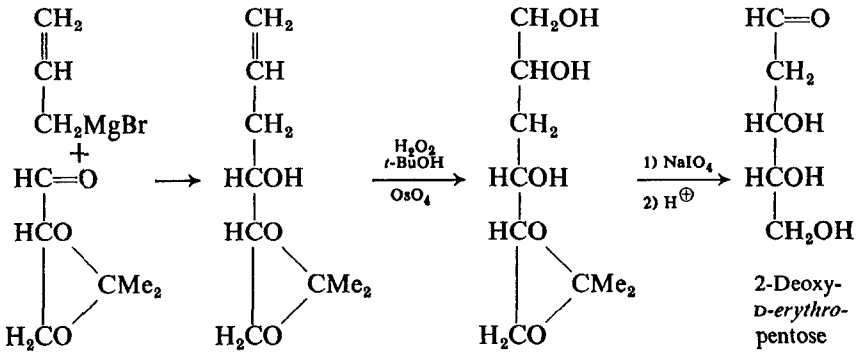
Fraser and Raphael[41] have synthesized 2-deoxy-DL-*erythro*-pentose from but-2-yne-1,4-diol (Scheme 13). This compound was converted into 1-benzoyloxy-4-bromobut-2-yne (**1**) by monobenzoylation and treatment of the resultant half-ester with phosphorus tribromide. Condensation of



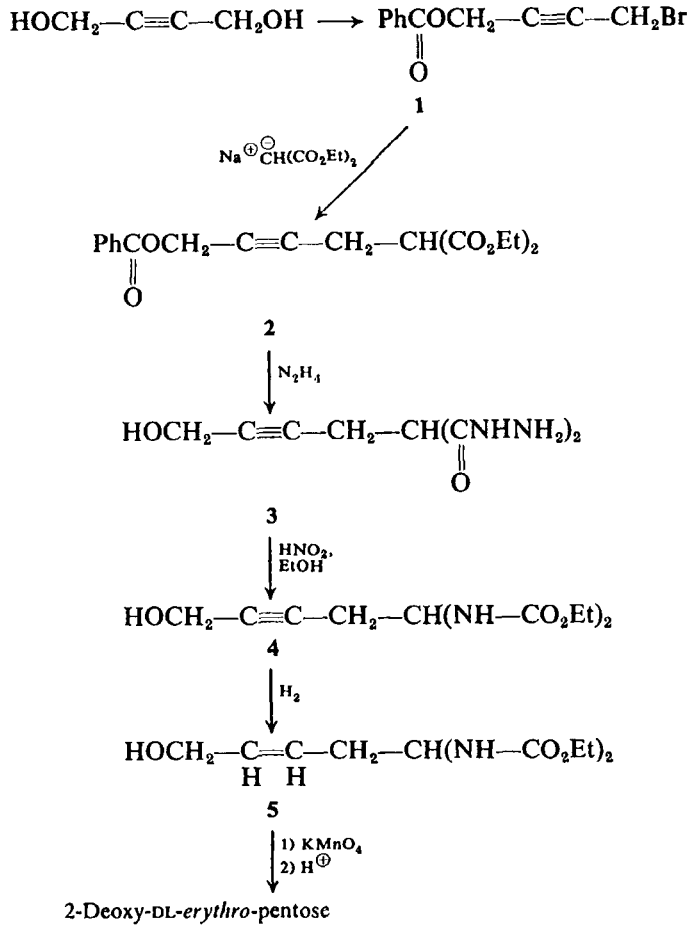
Scheme 11

1-benzoyloxy-4-bromobut-2-yne with ethyl sodiomalonate gave ethyl 5-benzoyloxypent-3-yne-1,1-dicarboyxlate (**2**), which was converted into the dihydrazide **3**. Compound **3** was then subjected to a double Curtius rearrangement; reaction with nitrous acid, followed by treatment of the resultant diazide with ethanol, afforded the acetylenic diurethane **4**. Catalytic hemihydrogenation of **4** gave the *cis*-ethylenic diurethane **5**. *cis*-Hydroxylation of **5**, followed by acid-catalyzed hydrolysis of the resultant *erythro*-triol, gave finally a small yield of 2-deoxy-DL-*erythro*-pentose.

Weygand and Leube[42] have also prepared 2-deoxy-DL-*erythro*-pentose (and 2-deoxy-DL-*threo*-pentose or 2-deoxy-DL-xylose) from an acetylenic precursor, 1-methoxy-1-buten-3-yne (**6**). Treatment of **6** with formaldehyde



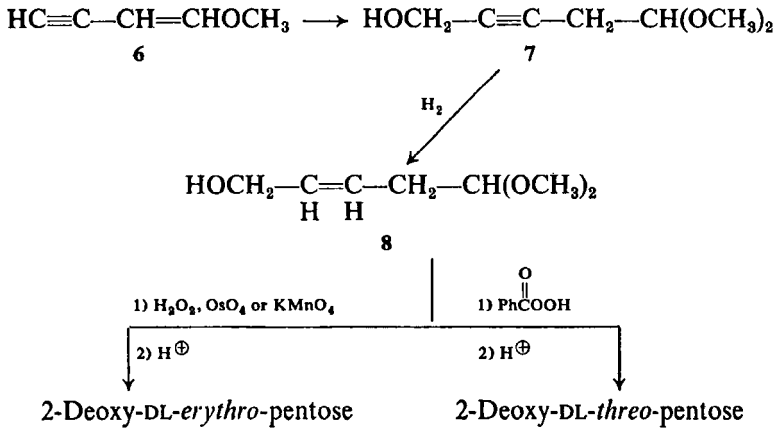
Scheme 12



Scheme 13

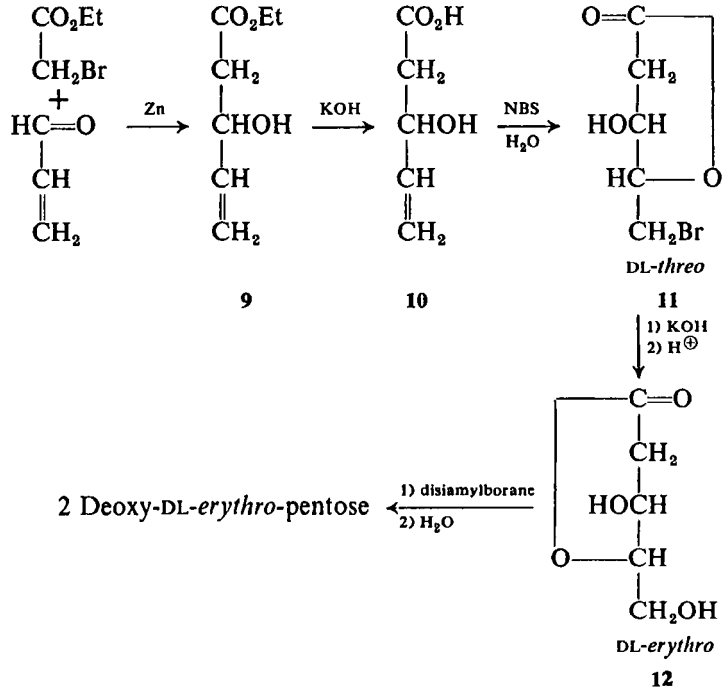
in methanol at 45–55° gives 1-methoxy-1-penten-3-yn-5-ol, but at 65–85° the dimethyl acetal **7** was produced. Hemihydrogenation of **7** over a Lindlar catalyst gave the corresponding ethylene **8**. Hydroxylation of **8** with osmium tetroxide and hydrogen peroxide in *t*-butanol, followed by acid-catalyzed hydrolysis, gave 2-deoxy-DL-*erythro*-pentose, whereas the use of peroxybenzoic acid afforded 2-deoxy-DL-*threo*-pentose (see Scheme 14).

A more recent synthesis of 2-deoxy-DL- and L-*erythro*-pentose has been reported by Nakaminami et al.[43] The first step (see Scheme 15) was a Reformatsky reaction of ethyl bromoacetate with acrolein to give the β-hydroxy ester **9**. Compound **9** was hydrolyzed by aqueous potassium hydroxide to give the DL-acid **10**, which was treated in an aqueous solution



Scheme 14

with *N*-bromosuccinimide to afford the DL-bromolactone **11**. Successive basic and acidic hydrolysis gave "2-deoxy-DL-ribonolactone" (**12**). Treatment of **12** with disiamylborane [bis(3-methyl-2-butyl)borane], and hydrolysis of the resultant tris(disiamylborinate) ester, yielded 2-deoxy-DL-*erythro*-

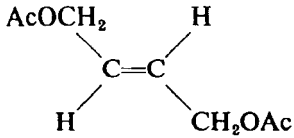


Scheme 15

pentose. The preparation of 2-deoxy-L-*erythro*-pentose involved treatment of the racemic hydroxy acid **10** with a half equivalent of quinine and decomposition of the salt to yield (-)-**10**, which was then subjected to the same reactions as in the case of the racemic compounds.

2,3-Dideoxy-DL-pentose has been synthesized by Price and Balsley[44] by the Claisen rearrangement of allyl vinyl ether to 4-pentenal, conversion to the methyl acetal, and permanganate oxidation (see Scheme 16).

Total syntheses of tetroses and tetritols from olefinic precursors have also been achieved, using reactions which have already been described in this section. Thus Raphael[45] obtained erythritol tetraacetate by treatment of *trans*-2-butene-1,4-diol diacetate (**13**) with peroxyacetic acid, followed by complete acetylation, whereas similar treatment of the *cis* compound **14** produced DL-threitol tetraacetate:



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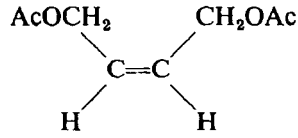
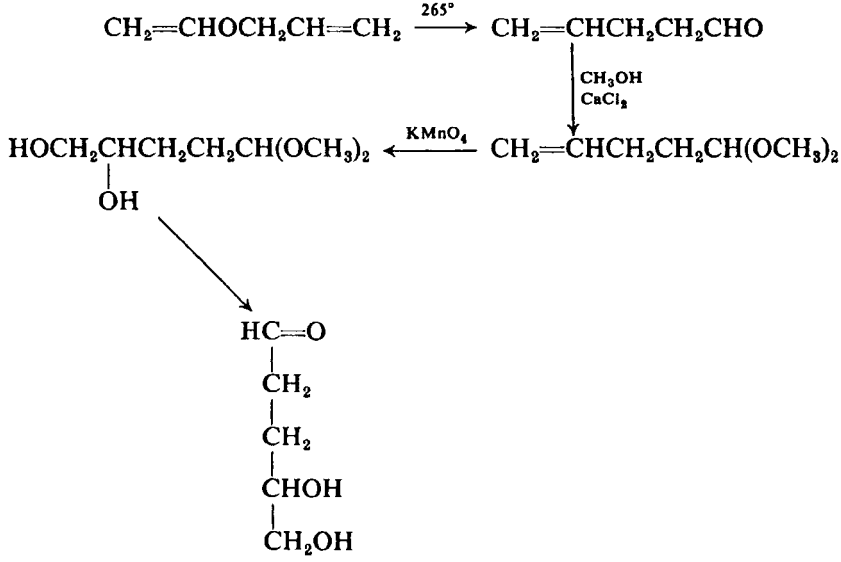


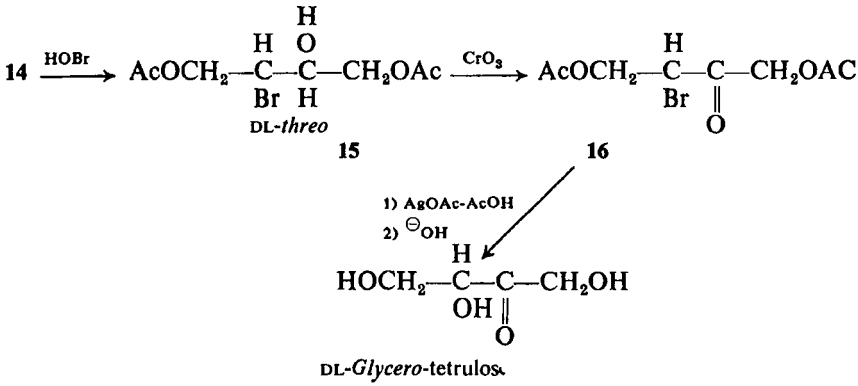
14

As usual, *cis*-hydroxylation of the *cis*-diacetate yielded erythritol tetraacetate, after complete acetylation, and the *trans*-diacetate gave DL-threitol tetraacetate, on treatment with osmium tetroxide and hydrogen peroxide in



Scheme 16

t-butanol and complete acetylation of the product. *trans*-Addition of hypobromous acid to the *cis* and *trans* compounds (**14** and **13**) was smoothly effected to give the *threo*- (**15**) and *erythro*-2-bromobutane-1,3,4-triol 1,4-diacetates (see Scheme 17). Chromium trioxide oxidation of either the *erythro*- or the *threo*-bromohydrin gave the same ketone, 2-bromo-1,4-diacetoxybutan-3-one (**16**), which, on treatment with silver acetate in acetic acid, yielded DL-*glycero*-tetrulose triacetate. Hydrolysis with baryta then gave DL-*glycero*-tetrulose. Other examples of the preparation of tetritol derivatives from olefinic precursors are known.[45a] Kiss and Sirokmán[45b] synthesized *erythro*-2-amino-1,3,4-trihydroxybutane stereospecifically from *trans*-1,4-dibromo-2-butene.

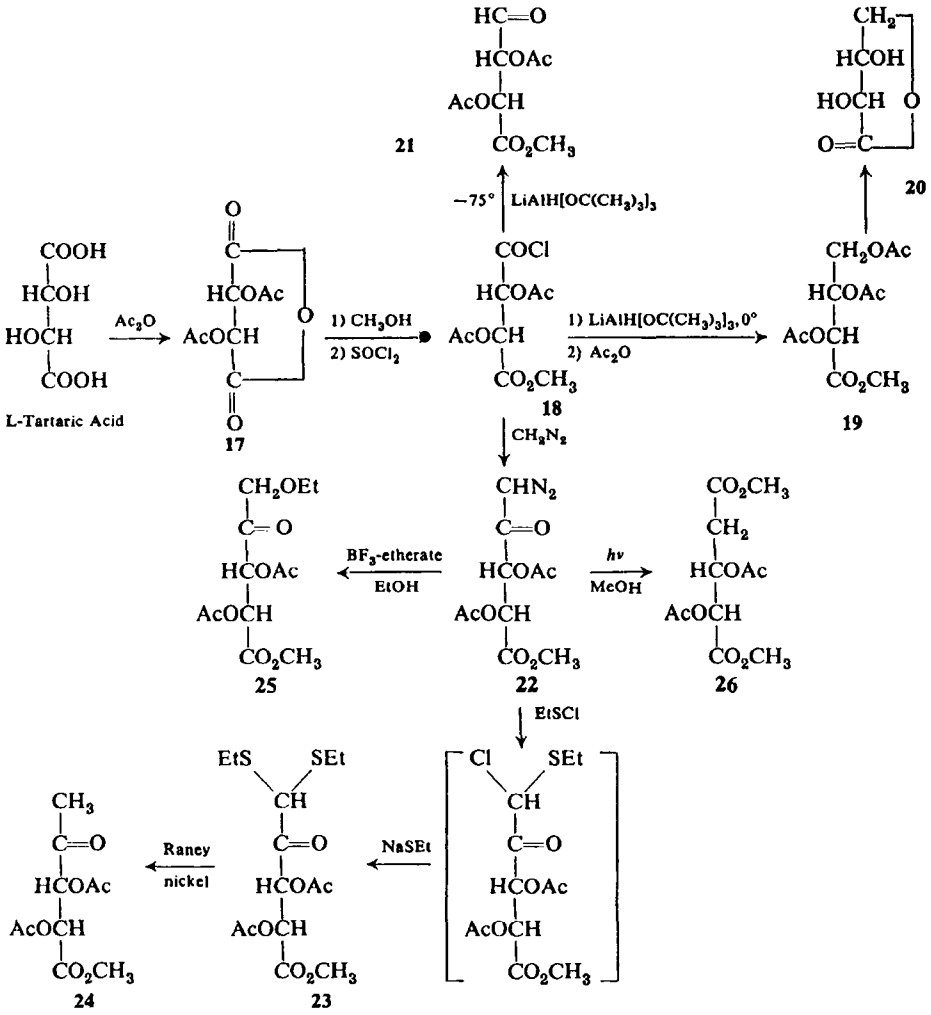


Scheme 17

Walton[46] has prepared D-threose and D-erythrose by a method similar to that employed by Hough[39] for the synthesis of 2-deoxy-D-*erythro*-pentose. Thus addition of vinylmagnesium chloride to 2,3-*O*-isopropylidene-*aldehydo*-D-glyceraldehyde gave a mixture of epimeric pentene derivatives, which were separated by gas-liquid chromatography. Ozonolysis followed by acid-catalyzed hydrolysis of each epimer afforded D-threose and D-erythrose, each in approximately 40% yield. A similar study has been made by Horton et al.[47] In that work, however, the first step was ethynylation of 2,3-*O*-isopropylidene-*aldehydo*-D-glyceraldehyde to give a 44:56 mixture of 4,5-*O*-isopropylidene-1-pentyne-D-*erythro* (and D-*threo*)-3,4,5-triol.

4. SYNTHESES FROM TARTARIC ACID AND OTHER NATURALLY OCCURRING ACIDS

The potential of the tartaric acids as possible precursors in the synthesis of tetroses and related compounds was recognized by Emil Fischer as early



Scheme 18

as 1889;[48] however, he was unsuccessful in attempts to reduce tartaric acid. In 1941 Lucas and Baumgarten[49] reported a solution to this problem, and achieved a synthesis of L-threitol. More recently, Bestmann and Schmiechen[50] employed L-tartaric acid for the synthesis of a variety of tetrose and pentose derivatives (see Scheme 18). A key intermediate in that work[50] was the acid chloride of monomethyl di-*O*-acetyl-L-tartrate (**18**). Compound **18** was also an intermediate in the work of Lucas and Baumgarten.[49] Its preparation involved heating L-tartaric acid with acetic anhydride to give di-*O*-acetyl-tartaric anhydride (**17**), which reacts vigorously with methanol to give

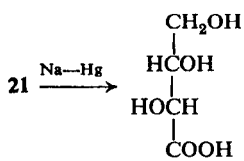
monomethyl di-*O*-acetyltartrate; the latter compound was then converted into **18** by treatment with thionyl chloride. The acid chloride group in **18** was reduced to a hydroxymethyl group by Bestmann and Schmiechen, on treatment with lithium tri-*t*-butoxyaluminum hydride at 0°; the reduced product was isolated as methyl tri-*O*-acetyl-L-threonate (**19**), which was converted into L-threono-1,4-lactone (**20**). When the reduction of **18** with lithium tri-*t*-butoxyaluminum hydride was performed at −75°, methyl 2,3-di-*O*-acetyl-L-threuronate (**21**) was produced; Lucus and Baumgarten[49] had obtained this compound by a Rosenmund reduction of **18**.*

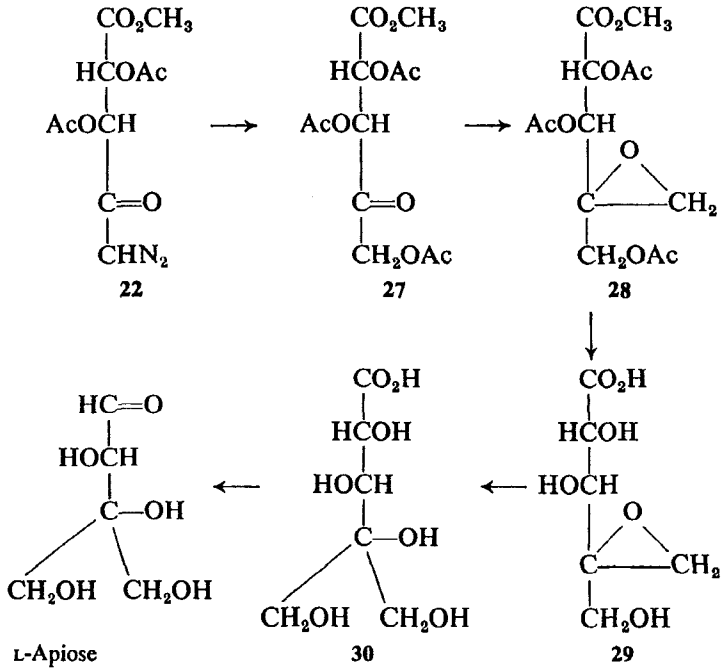
The acid chloride **18** could be transformed with diazomethane into the diazoketone **22**.[51,52] Compound **22** was converted by Bestmann and Schmiechen[50] into the diethyl dithioacetal **23** by a reaction with ethylsulfenyl chloride, followed by treatment of the intermediate 1-chloro-1-ethylthio derivative with sodium thioethoxide. Desulfurization of **23** with Raney nickel gave methyl 2,3-di-*O*-acetyl-5-deoxy-L-*threo*-4-pentulosonate (**24**). Treatment of the diazoketone **22** with boron trifluoride-etherate in ethanol afforded methyl 2,3-di-*O*-acetyl-5-*O*-ethyl-L-*threo*-4-pentulosonate (**25**). Compound **25** had been obtained earlier by Ultée and Soons,[52] by treatment of **22** with cupric oxide in ethanol, instead of the expected Wolff rearrangement product. A Wolff rearrangement of the diazoketone **22** was achieved by Bestmann and Schmiechen by irradiation with ultraviolet light of a methanol solution of **22**; the product was di-*O*-acetyl-2-deoxy-L-*threo*-pentaric acid dimethyl ester (**26**).

The diazoketone **22** has also been utilized in a synthesis of the branched-chain sugar (see also Section 7C) L-apiose by Weygand and Schmiechen[51] (Scheme 19). Treatment of **22** with acetic acid in the presence of copper powder gave methyl 2,3,5-tri-*O*-acetyl-4-pentulosonate (**27**), which was converted into methyl 2,3,5-tri-*O*-acetyl-4,4′-anhydro-4-*C*-hydroxymethyl-L-*threo*-pentonate (**28**) with diazomethane. The opening of the epoxide ring, after saponification of **28** to give **29**, was achieved with a strongly acidic ion-exchange resin; the resultant product (**30**) was finally converted into L-apiose by a Ruff degradation procedure (oxidative decarboxylation of the calcium salt of **30** with hydrogen peroxide in the presence of ferric acetate).

Some deoxy sugar derivatives have been obtained by Lukes et al.[53] from

* Reduction of methyl 2,3-di-*O*-acetyl-L-threuronate (**21**) with sodium amalgam gave L-threonic acid, which was characterized as the brucine salt:[49]

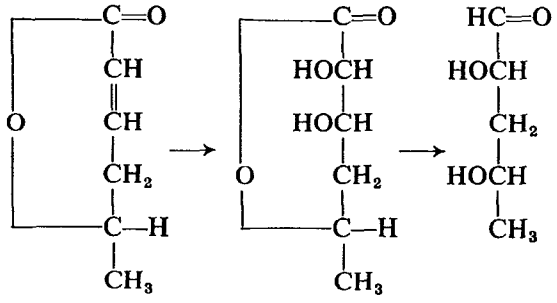




Scheme 19

L-parasorbic acid (**31**), which was isolated from *Sorbus aucuparia* berries. Hydroxylation of **31** with osmium tetroxide and sodium chlorate gave 4,6-dideoxy-L-*ribo*-hexonic acid 1,5-lactone (**32**). The calcium salt of the acid was then subjected to a Ruff degradation to afford 3,5-dideoxy-L-*erythro*-pentose (**33**) (Scheme 20).

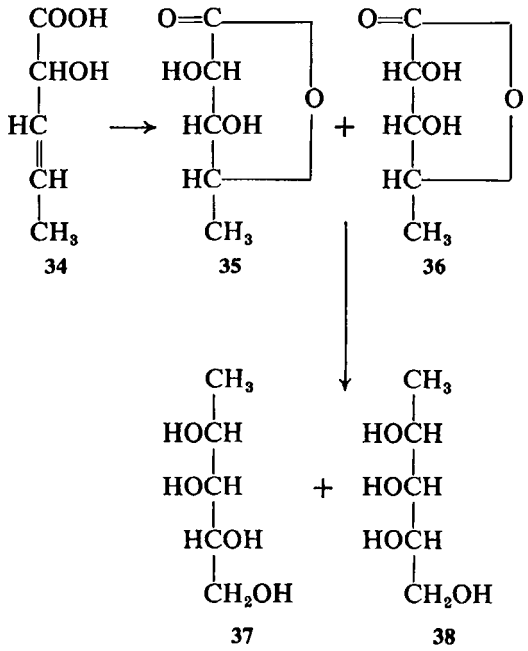
A study, similar to the foregoing, is the stereospecific *trans*-hydroxylation of angelactinic acid (**34**).[54,55] Jary and Kefurt[55] found that hydroxylation of



Scheme 20

34 with peroxyacetic acid gave the lactones of 5-deoxy-DL-arabinonic acid and 5-deoxy-DL-ribonic acid (**35** and **36**) in the ratio of 2.8: 1. These compounds were converted into 1-deoxy-DL-lyxitol (**37**) and 1-deoxy-DL-ribitol (**38**) by treatment of the lactones with lithium aluminum hydride in tetrahydrofuran (see Scheme 21; only one isomer of DL mixtures is shown).

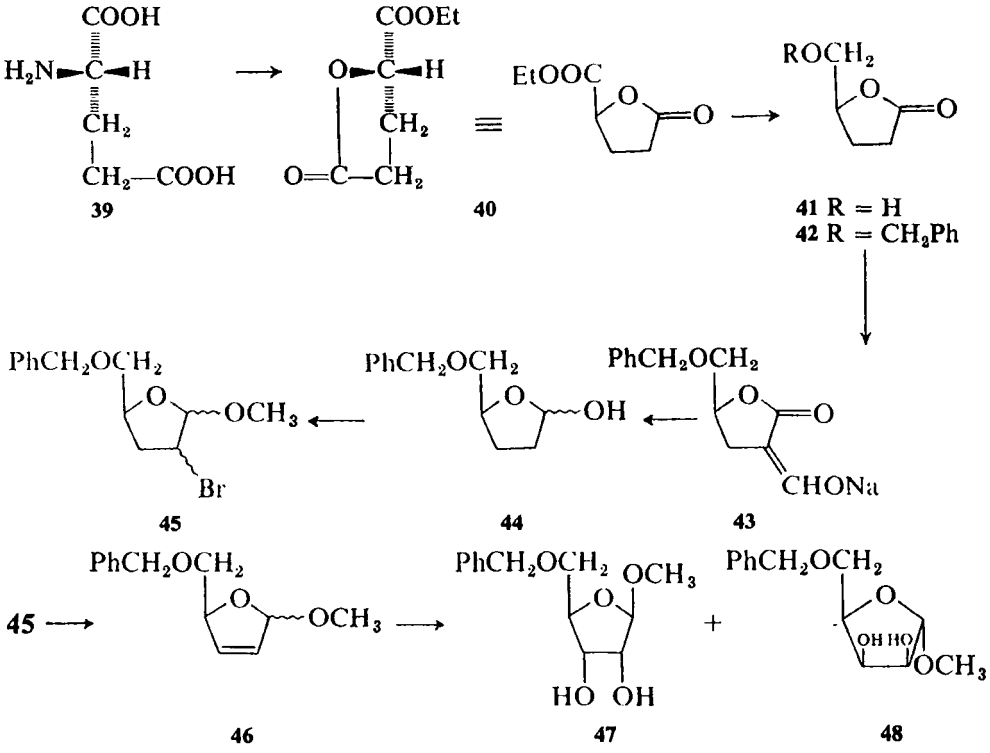
Very recently, Koga et al.[56] described a new synthesis of D-ribose from L-glutamic acid (**39**) without the necessity of resolution at intermediate



Scheme 21

stages; the asymmetric center of **39** became C-4 in D-ribose (see Scheme 22). The amino acid was deaminated to give, after esterification, the lactone ester **40**; this deamination was considered to proceed with full retention of configuration, because of the participation of the neighboring carboxyl group. Reduction of **40** with sodium borohydride in ethanol afforded the lactone alcohol **41**, which was converted into the benzyl ether **42**. Treatment of **42** with sodium and ethyl formate in ether gave the sodium salt **43**, which, on being heated in acidic aqueous dioxane, afforded 5-*O*-benzyl-2,3-dideoxy-D-pentofuranose (**44**), as a result of hydrolysis of the lactone ring, decarboxylation, and subsequent ring closure. Compound **44** was converted into a mixture of glycosides (see Section 6) which, on treatment with bromine and calcium carbonate, gave the monobromo derivative **45** as a mixture of

diastereomers. Base-catalyzed dehydrobromination of **45** afforded the unsaturated derivative **46**. Surprisingly, hydroxylation of **46** with potassium permanganate or with osmium tetroxide gave a mixture of methyl 5-*O*-benzyl-β-D-ribofuranoside (**47**) and methyl 5-*O*-benzyl-α-D-lyxofuranoside (**48**). Compounds **47** and **48** could be separated as their acetonides or diacetates; alternatively, D-ribose could be isolated as its "anilide" by hydrogenation of the hydroxylation product to remove the benzyl group, followed by acid-catalyzed hydrolysis, and then treatment with aniline.



Scheme 22

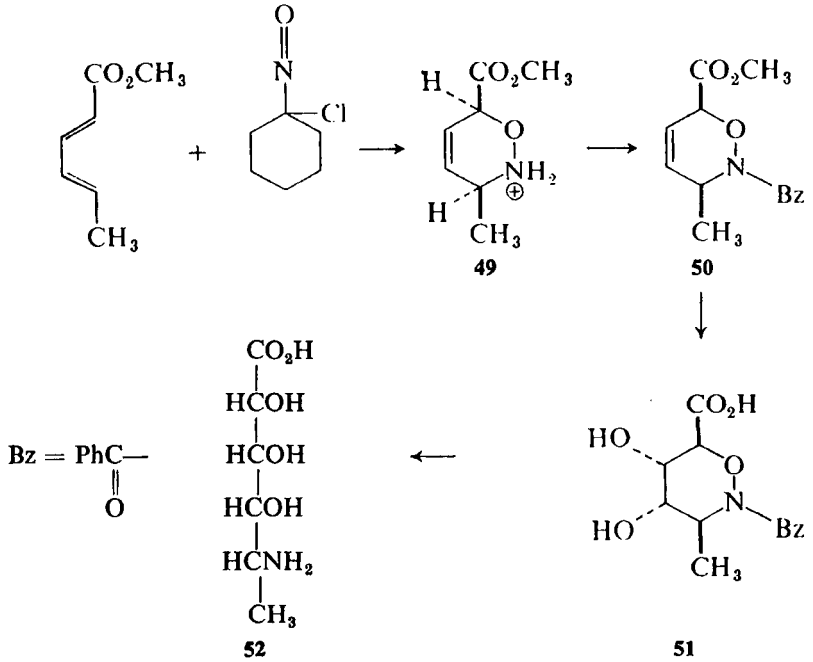
Another synthesis of a sugar derivative from an amino acid (L-aspartic acid), and a synthesis involving both pyruvic acid and glycine, are discussed in Section 7A.

5. THE DIELS-ALDER REACTION

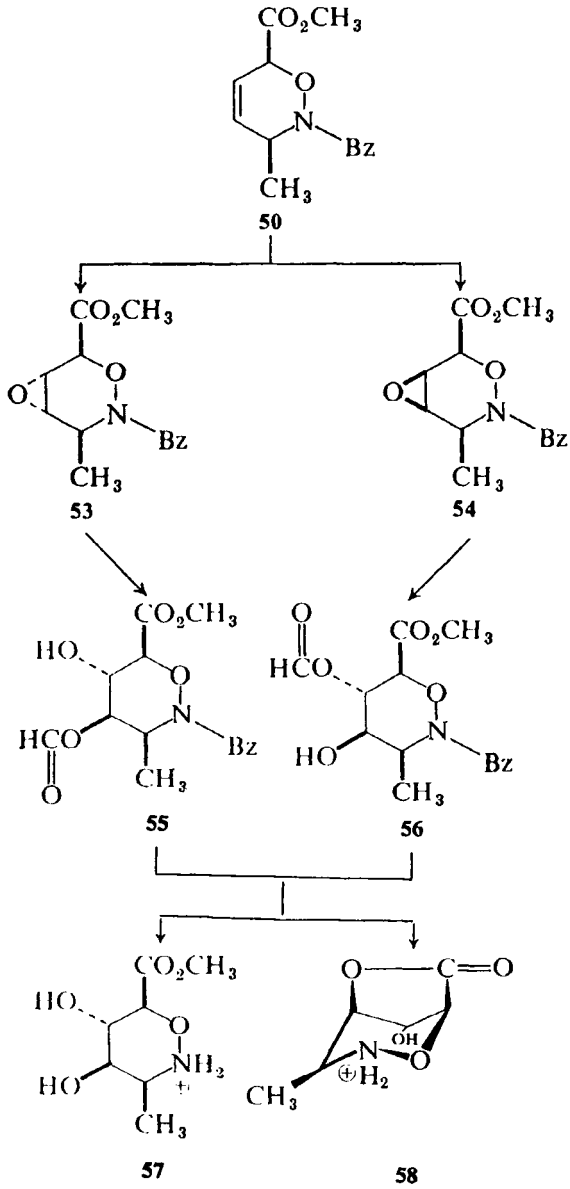
The Diels-Alder reaction has been employed by a number of workers for the preparation of dihydropyrans as substrates for the synthesis of a wide

range of monosaccharides. These examples are discussed in Section 6, which is specifically concerned with the synthesis of sugars from pyran derivatives. In this section, the use of Diels-Alder condensations in two very elegant, total syntheses of novel carbohydrates is described.

The first example is that of Belleau and Au-Young,[57] whose objective was the total synthesis of amino sugars (Section 7A). They utilized the dienophilic properties of 1-chloro-1-nitrosocyclohexane and condensed it with methyl sorbate to yield *cis*-3-methyl-6-methoxycarbonyl-3,6-dihydro-1,2-oxazine hydrochloride (**49**). This Diels-Alder adduct is formed in a stereospecific manner, the *cis*-adducts only being formed when the diene has the *trans*, *trans* geometry, as is present in methyl sorbate. The adduct possesses a double bond at positions 4 and 5 and may therefore be hydroxylated to yield, after ring cleavage, 5-amino-5,6-dideoxy-DL-hexonic acids. The possible formation of a 2-amino-2-deoxy derivative was eliminated when the adduct, after hydrogenation and ring-opening, was shown to be an α-hydroxy acid and not an α-amino acid. When the *N*-benzoate of the adduct **50** was hydroxylated with osmium tetroxide-pyridine complex, attack of the reagent occurred from the least hindered side, and the diol-*N*-benzoyl-acid **51** resulted. Mild hydrolysis of **51**, followed by catalytic hydrogenation over Adam's catalyst, furnished 5-amino-5,6-dideoxy-DL-allonic acid (**52**) (see Scheme 23).



Scheme 23



Scheme 24