ApSimon

The Total Synthesis of Natural Products

VOLUME 1

INTERSCIENCE

The Total Synthesis of Natural Products

VOLUME 1

Edited by

JOHN ApSimon

Department of Chemistry
Carleton University, Ottaw

WILEY-INTERSCIENCE, a Division of John Wiley & Sons, Inc.
New York · London · Sydney · Toronto

Library of Congress Cataloging in Publication Data:

ApSimon, John.
The total synthesis of natural products.

Includes bibliographical references.
1. Chemistry, Organic—Synthesis. I. Title.

QD262.A68 547′.2 72-4075
ISBN 0-471-03251-4

Printed in the United States of America

10 9 8 7 6 5 4 3 2

Contributors to Volume 1

U. Axen, Upjohn Company, Kalamazoo, Michigan
F. M. Dean, University of Liverpool, England
A. H. Jackson, University College, Cardiff, United Kingdom
F. Johnson, Dow Chemical Company, Wayland, Massachusetts
J. K. N. Jones, Queen's University, Kingston, Ontario
S. A. Narang, National Research Council of Canada, Ottawa
J. E. Pike, Upjohn Company, Kalamazoo, Michigan
W. P. Schneider, Upjohn Company, Kalamazoo, Michigan
K. M. Smith, University of Liverpool, England
W. A. Szarek, Queen's University, Kingston, Ontario
R. H. Wightman, Carleton University, Ottawa, Ontario

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 Carbohydrates

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

Department of Chemistry, Queen's University, Kingston, Ontario, Canada

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]

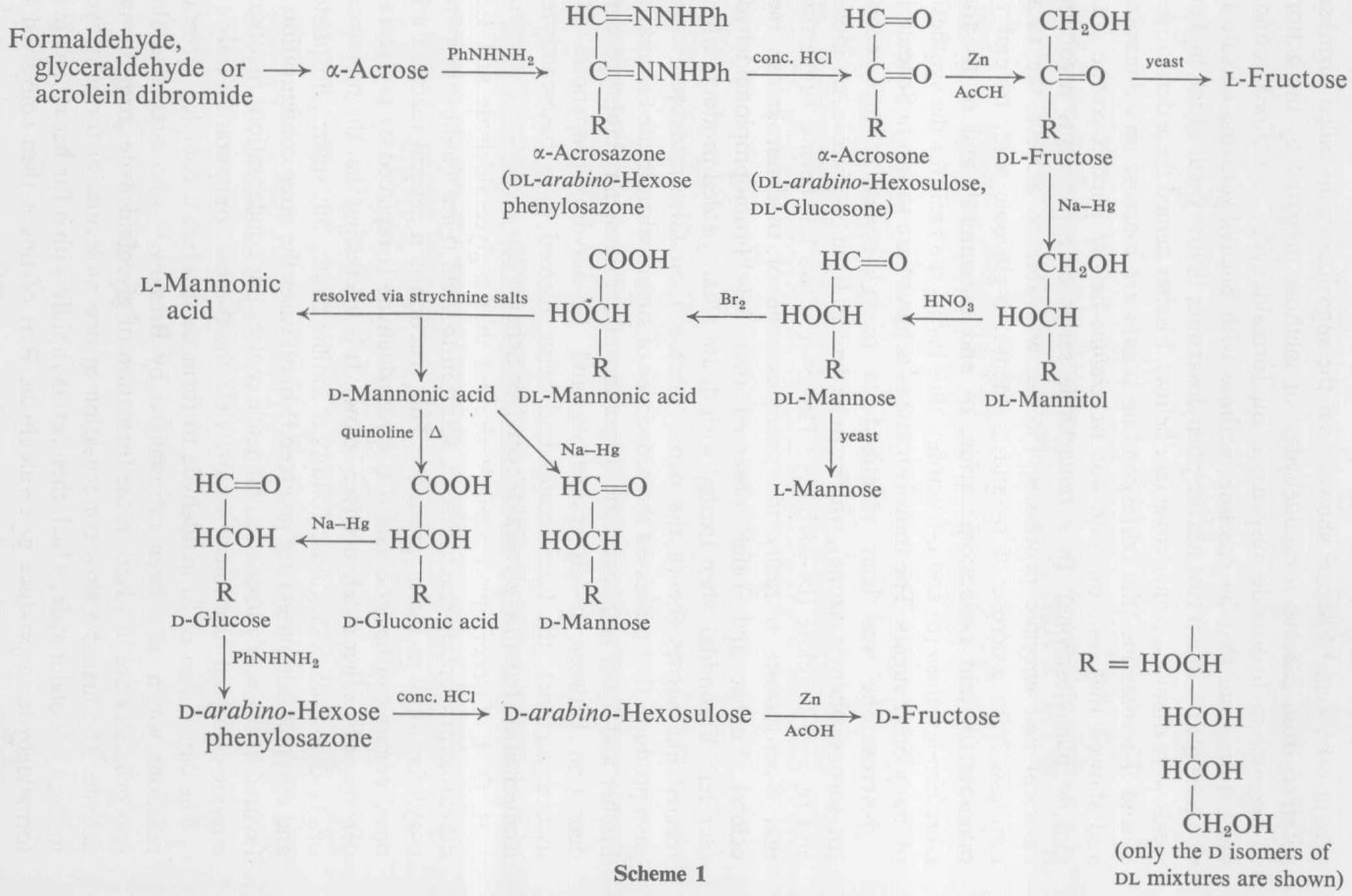
The self-condensation of formaldehyde under the influence of base to yield a sugarlike syrup (methylenitan) was first observed by Butlerow[3] in 1861, when he treated trioxymethylene with calcium hydroxide solution. Calcium carbonate, magnesia, baryta, mineral clay, or even γ-radiation

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.

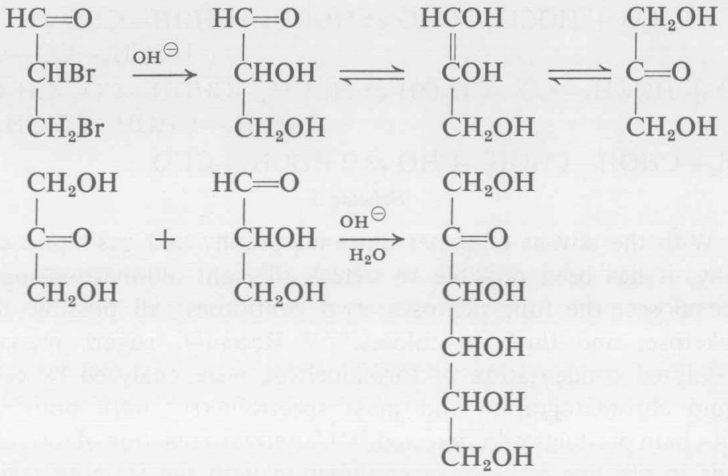
β-Acrosazone was later identified as DL-*xylo*-hexose phenylosazone (DL-sorbose phenylosazone), which can be derived from DL-glucose, DL-idose, and DL-*xylo*-hexulose (DL-sorbose).[8] However, there has been a suggestion that β-acrosazone is really the phenylosazone of DL-dendroketose (see below). Fischer 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



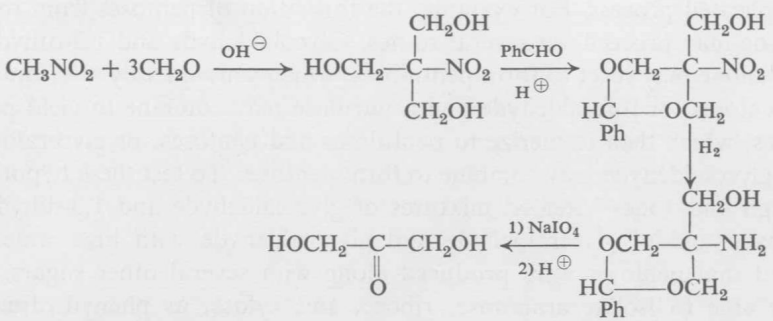
Scheme 1



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]

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

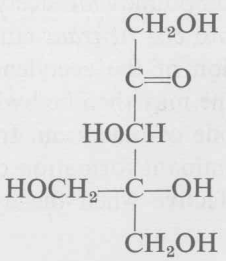
The polymerization of formaldehyde to yield sugars is, therefore, a very complicated process. For example, the formation of pentoses from formaldehyde may proceed via several routes. Glycolaldehyde and 1,3-dihydroxypropanone may react to form pentuloses, which subsequently are isomerized to pentoses, 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:

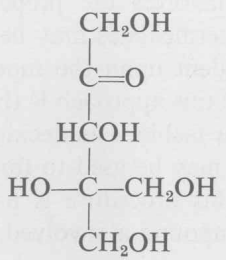
$$\text{D-glucose} + \text{ATP} \xrightarrow{\text{hexokinase}} \text{D-glucose 6-phosphate} + \text{ADP}$$

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.

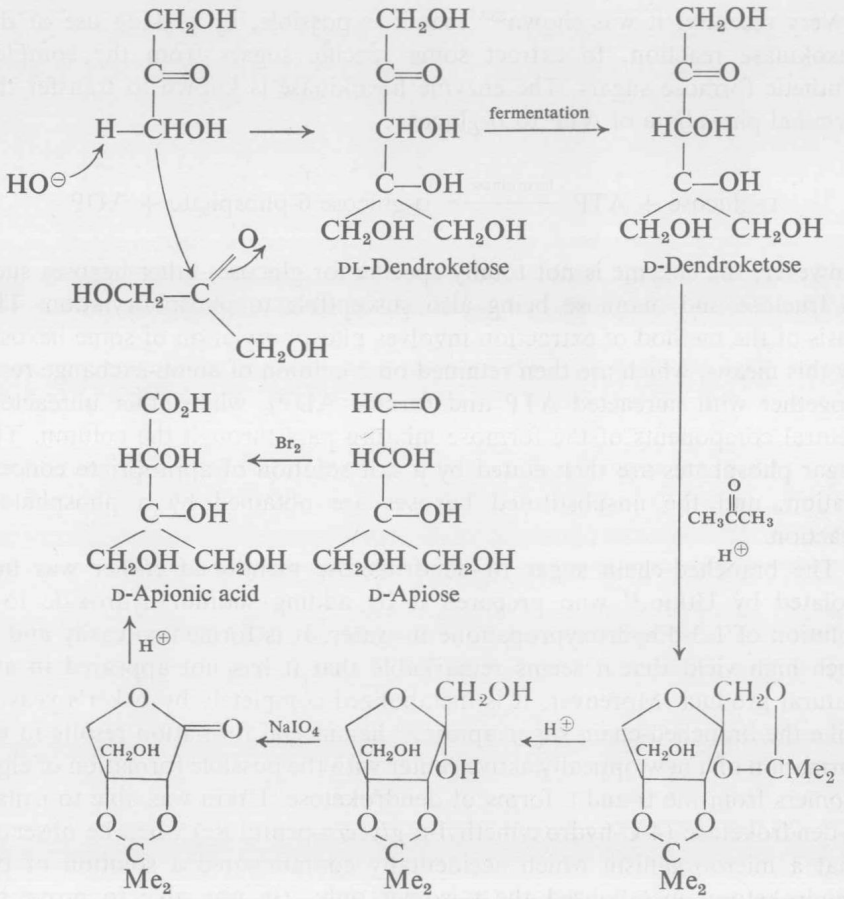
The branched-chain sugar DL-dendroketose mentioned earlier was first isolated by Utkin,[24] who prepared it by adding sodium hydroxide to a solution of 1,3-dihydroxypropanone in water. It is formed so easily and in such high yield that it seems remarkable that it has not appeared in any natural product. 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)



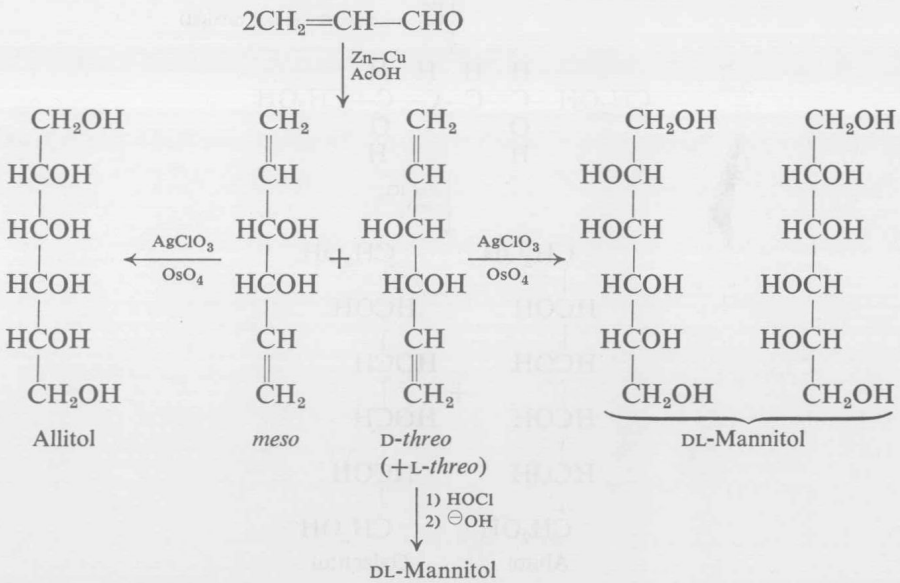
Scheme 4

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).



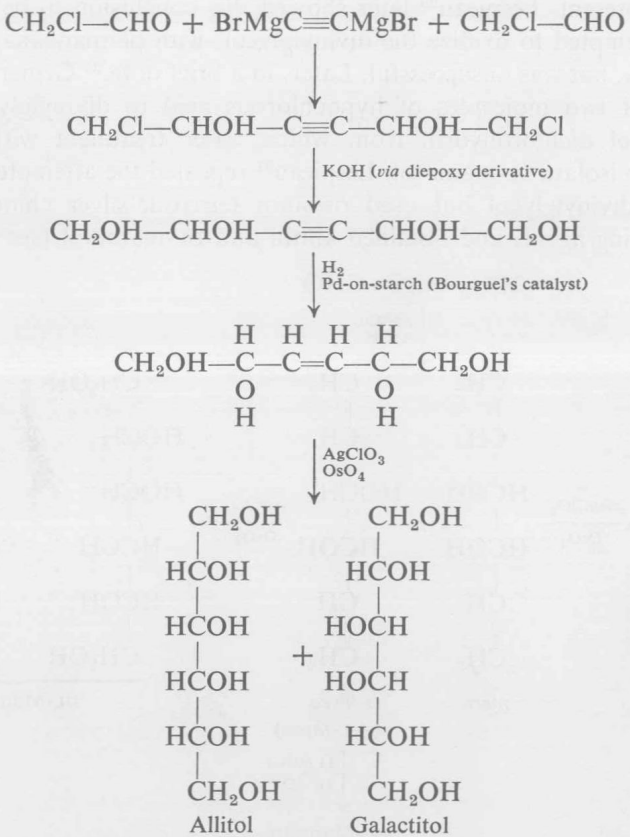
Scheme 5

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