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The Conversion of Carbohydrate Derivatives into Functionalized Cyclohexanes and Cyclopentanes

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Contents

I. Introduction

Although Nature uses carbohydrates as synthetic precursors of many functionalized carbocyclic compounds, both saturated and aromatic (sections II.A.1 and III.A.1), until recently chemists have paid only slight attention to the possibilities offered by this approach. In the case of benzenoid compounds and cyclopentenones, which are produced in minor amounts on the destructive decomposition of carbohydrates,[1] opportunities are probably confined to the synthesis of products carrying isotopically labeled atoms at specific ring positions. For oxygenated cyclohexane and cyclopentane derivatives, however, excellent opportunities exist, and now a wide range of such compounds have been made from sugars, particular advantage being gained by the passing of chirality from starting material to product. The first rational sugar-to-cyclohexane conversion was carried out in 1948 when H. O. L. Fischer and colleagues prepared nitroinositols from a 6-deoxy-6-nitrohexose by use of a base-catalyzed intramolecular aldol-like cyclization.[2] A further 30 years elapsed before a cyclopentane synthesis was completed.[3]

It is the intention of this review to bring together the range of methods now available for producing functionalized, chiral cyclohexane and cyclopentane derivatives from sugars and to indicate how these have been applied. The progress made in recent years (>80% of the papers to appear on the subject have been published in the last decade) represents a small part of the new age of carbohydrate chemistry in which sugars have changed from being considered unmanageable to being controllable source materials for synthesis of a myriad of complex, chiral compounds. Several reviews have dealt with the use of sugars in the syntheses of natural compounds.[4] Particular attention is drawn to a new survey which concentrates on the use of monosaccharides for the synthesis of natural products which contain carbocyclic ring systems.[337] While it tends to deal with major features of such syntheses, the current review focuses on the chemical features of the cyclization processes.

Credit for much of the developmental work in the field, and especially for demonstrating the use of carbohydrates in the complete synthesis of many complex natural products whose structures incorporate five- and six-membered rings, must go to Prof. Bert Fraser-Reid whose insight, intuition, and perceptive use of developing methodologies have brought achievements which a few years ago would have been unimaginable. He has described his group's work in an article "Carbocycles from Carbohydrates: the Annulated Sugar Approach,"[5] to which readers are referred for a portrayal of the aesthetic features of the topic. Here a somewhat unembellished account of all published work is provided. It represents an extension of surveys carried out in Wellington where carbohydrates have been used in the exploration of routes to carbocyclic compounds of importance in medicine[6] and includes a review of developments relating to an efficient means of converting specific unsaturated sugar derivatives into functionalized cyclohexanone compounds discovered in the course of the work (section II.D.1).[7] This reaction, which involves the direct conversion of hex-5-enopyranosyl derivatives into cyclohexanones, has become well recognized, and there has been a tendency to refer to it as a name reaction after one of us (R. J. F.). An entirely unconnected reaction—the conversion of acylated glycals into 2,3-unsaturated glycopyranosides—has, however, also acquired the same name, and in the interest of avoiding confusion we do not use it.

For the purposes of this survey such simple carbohydrates as glyceraldehyde and the tetritols, and compounds such as tartaric and malic acids, are not considered as starting materials, but cases involving the development of carbocyclic rings from parts of sugar molecules (for example, by diene addition to double bonds of carbohydrate alkenes) are included.

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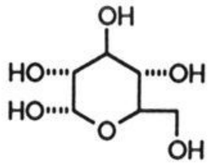
Robin Ferrier did his undergraduate studies and Ph.D. (1957) in the University of Edinburgh, his home town, and was there introduced to carbohydrate chemistry as a member of the Hirst/Aspinall polysaccharide group. On moving to his first teaching position in W. G. Overend's monosaccharide team in Birkbeck College, University of London, he turned to work with simple carbohydrate derivatives—in particular the largely unexpoited unsaturated sugars. A period in 1960–61 in Melvin Calvin's laboratory working on a photosynthesis-related topic served as a life-long stimulus and initiated deep respect for biological/chemical collaboration. In 1970 he went to be Professor of Organic Chemistry in Wellington, New Zealand, and with a small group of research students, turned attention to the utilization of sugars in the synthesis of functionalized cyclohexanes and cyclopentanes with emphasis on compounds of medicinal significance—particularly the prostaglandins, anthracyclinones, and aminoglycoside antibiotics. During this work a Ph.D. student, Richard Furneaux, discovered a novel free-radical substitution reaction by which bromine can be introduced into ring positions of some cyclic sugar derivatives, and this led to studies of the use of radical processes in synthetic carbohydrate/medicinal chemistry. Several projects in applied organic chemistry of special significance in New Zealand have been undertaken. He has been involved with the Royal Society of Chemistry's Specialist Periodical Reports, Carbohydrate Chemistry since its inception in 1967 and, as Senior Reporter, has just delivered Volume 25. Comparison of Volume 1 with the latest reveals how expansive recent progress in organic and biological sugar chemistry has been; the developments in the field, now under review, illustrate the point well.

The representation of molecular structures has posed problems—particularly as the literature appears to contain examples of the use of all possible methods—and a fully consistent system has not been found. While there has been a recent tendency, particularly on the part of authors from outside the carbohydrate tradition, to use plane projections (e.g. **1** for a α-D-glucopyranose; Mills formulae[8] as are used commonly for terpenes and steroids), and while these offer considerable advantage when fused ring systems are involved, in our opinion, they are frequently inferior to Haworth perspective formulae (**2** for the same sugar) in denying the viewer adequate perception of the third dimension. Haworth formulae are therefore often favored—even at the expense of conformational diagrams, since these represent "state" as well as "structure", and the former is often uncertain and/or variable. On occasion, particularly with fused-ring compounds, this has led to the use of mixed representational systems which is clearly imperfect. Hopefully, however, the structures used are unambiguous and helpful.



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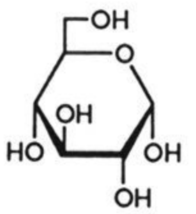

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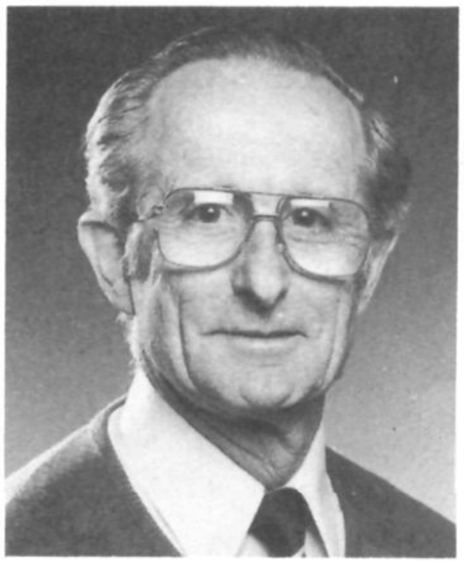


Syd Middleton was born in Australia and worked in industrial and university laboratories while studying for his undergraduate qualifications. His Ph.D. (1960) was taken at the University of Melbourne with Professor W. Davies in the area of heterocyclic chemistry. First teaching appointments were at Royal Melbourne Technical College and Melbourne University, and in 1962 he moved to the newly formed Monash University where he developed a strong interest in alicyclic stereochemistry. A period of study leave with D. M. Brown in Cambridge in 1966 indirectly kindled his interest in carbohydrate chemistry. He is now a Senior Lecturer in Chemistry at Monash where his current research interests are in the areas of stereoselective synthesis of alicyclic compounds, ^{13}C NMR spectroscopy, and organic mass spectrometry.

II. Syntheses of Functionalized Cyclohexanes

A. Carbanion Cyclizations

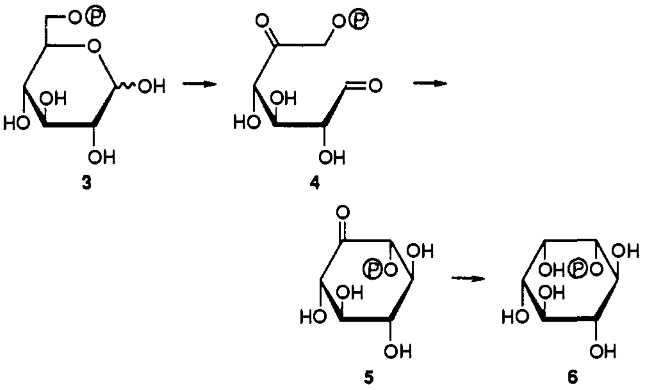
Most reactions employed by synthetic chemists in the key steps of conversions of carbohydrate derivatives into compounds containing cyclohexane rings have involved intramolecular nucleophilic displacements by carbanions or carbanion equivalents. These are treated in this section according to the nature of the stabilization of these nucleophilic species, the reactions of carbanions adjacent to carbonyl groups, phosphorus atoms, and nitro groups being covered. Arbitrarily, metalated carbon centers are covered separately in section II.D. Since corresponding biosynthetic processes bear strong resemblance to some of the reactions dealt with, a short introductory coverage of them is provided.

1. Biosynthesis of Hydroxylated Cyclohexanes

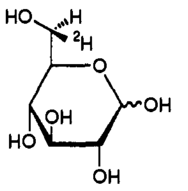
The key step in the natural production of inositols and many of their derivatives is the conversion of D-glucose 6-phosphate (**3**) into *myo*-inositol 1-phosphate (**6**) under the catalytic influence of inositol cyclase, the reaction proceeding by way of the 5-osulose **4** which undergoes aldol cyclization to the inosose phosphate **5** then ketone reduction (Scheme 1).[9,10] From **6** the other naturally occurring inositols and derivatives are produced.[11] The ring-closing step has been elucidated in considerable detail; for example, the *pro*-6*R* hydrogen atom is lost in the process,[12] and there is evidence that the aldehydo group may be bound as a carbinolamine by the side-chain amino group of a lysine unit of the catalyzing enzyme.[11]

Because of their significance as components of the aminoglycoside antibiotics, the biosynthesis of inosamines has been studied at length, and whereas aldol

Scheme 1



condensations of the above kind are involved in some ring closures which lead to these compounds, not all follow this route in detail.[13] In the biosynthesis of the 2-deoxystreptamine component of the antibiotic ribostamycin from D-glucose which was deuterated at both C-6 positions and at one of them specifically (compound 7), for example, the label was incorporated into both of the methylene sites and into the equatorial site (compound 8), respectively.[14] It follows, therefore, that the carbanion/enolate required for aldol ring closure was not, in this case, formed by deprotonation of a labeled analogue of 4, but by a reaction that involved a methylene carbanion. In this way the process bears strong resemblance to that by which D-glucose is converted into shikimic acid (14) from which Nature produces the benzenoid rings of the aromatic amino acids and an extensive range of other metabolites.[15,16]



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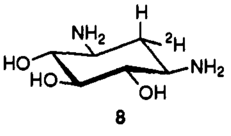

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3-Deoxy-D-*arabino*-heptulosonic acid 7-phosphate (**9**), produced from D-erythose 4-phosphate and phospho enol pyruvate, is the first main intermediate and is converted into 3-dehydroquinic acid (**13**) by an aldol process involving the product **10** of *syn*-β-elimination of phosphoric acid from an initially formed 5-ulose. Reduction then occurs at C-5 to give the extremely unstable, unsaturated hemiacetal **11** which can spontaneously ring open to the enolate **12** which cyclizes by attack of C-7 at C-2. Shikimic acid (**14**) then follows from **13** (Scheme 2).

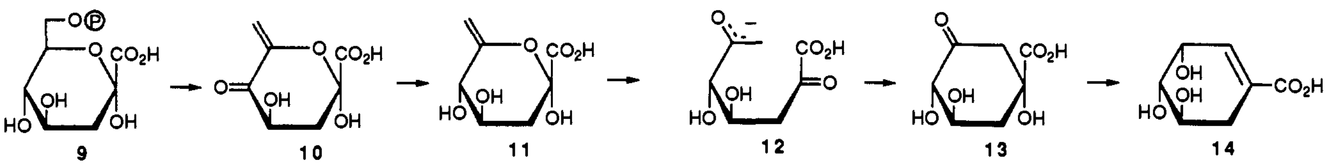
In assessing the enzymic dependence of this route Bartlett and Satake made the *o*-nitrobenzyl α-glycoside of **11** and, by photolysis at pH 7, converted it to 3-dehydroquinic acid in good yield and concluded, not just that the biological derivation of **11** would have resulted in the observed product, but that this step could proceed without the requirement for a specific enzyme.[17]

In the carbocyclization step the alkene proton adjacent to the ring oxygen atom of **11** takes up the equatorial site in the methylene group of the product **13** thereby indicating that the reaction proceeds by way of a chairlike transition state. A further stereochemical observation was that, like several other aldol cyclizations to be described in this review, this reaction resulted in the epimer with axial hydroxyl group at the new chiral center.

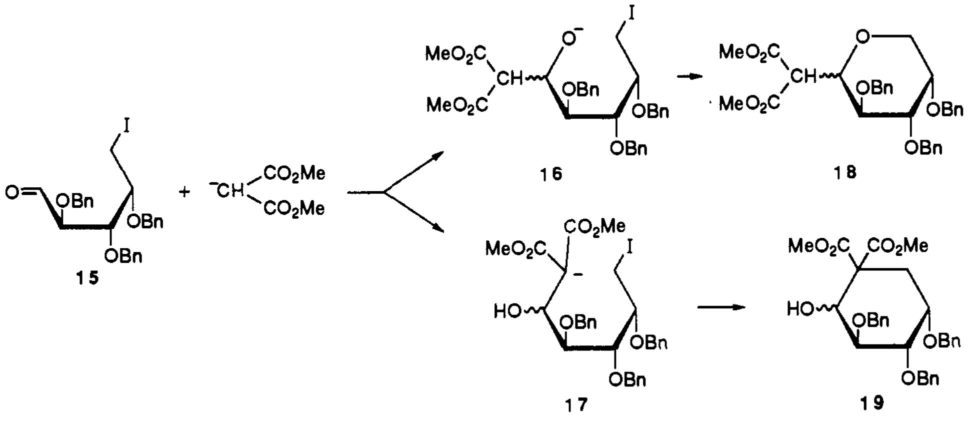
2. Displacements by Enolate Carbanions at Saturated Carbon Centers

Intramolecular nucleophilic displacement reactions of carbohydrate derivatives which result in cyclohexane products require the nucleophilic and electrophilic centers to be in the 1,6-relationship. Cyclizations belonging to this category of simple hexose derivatives appear not to have been reported, but use of *aldehydo*-pentose compounds bearing leaving groups at C-5 has, by a two-carbon chain-extension process, led to easy access to cyclohexanes with single carbon substituents and has been of particular value in the synthesis of

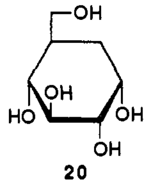
Scheme 2



Scheme 3



carbahexopyranoses.[18] Thus, for example, treatment of the 5-deoxy-5-iodo-L-arabinose derivative **15** with the anion of dimethyl malonate gave the intermediates **16** and **17** (Scheme 3) from which the tetrahydropyrans **18** and the cyclohexanes **19** (isolated as the acetates) were obtained in 33 and 43% yield, respectively, the latter giving access to carba-α-D-glucopyranose (**20**) and via an alkene, the β-L-altrose isomer **21**.[19,20] In related fashion, the D-lyxose mesylate **22** was used to obtain the cyclized adducts **23** from which methyl shikimate (**25**) was derived by way of the tribenzyl ether **24** (Scheme 4).[21,22] Natural shikimic acid also yielded the methyl ester **25**, and thus it has the illustrated absolute configuration.



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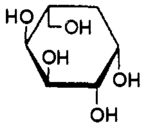

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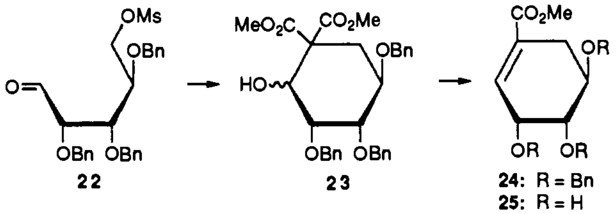
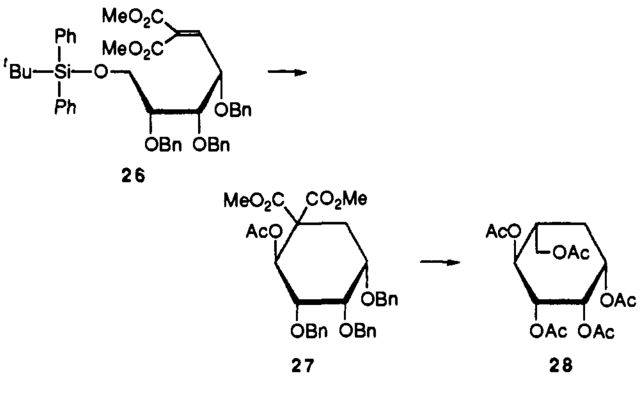
Scheme 4



As means of preparing functionalized cyclohexanes, the reactions illustrated in Schemes 3 and 4, both suffer from the competitive formation of tetrahydropyrans (e.g. **18**), and as a way of avoiding this, the stepwise procedure illustrated in Scheme 5 has been adopted.[23,24]

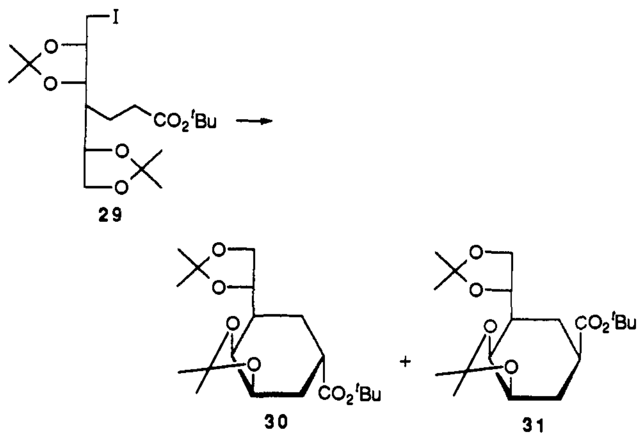
Scheme 5



For example, Knoevenagel condensation of dimethyl malonate with 2,3,4-tri-*O*-benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-D-ribose afforded the alkene **26** which was hydrogenated and disilylated, and the resulting alcohol oxidized to give an aldehyde from which, following aldol cyclization, the acetate **27**, and hence carba-β-L-mannopyranose peracetate **28**, were obtained.

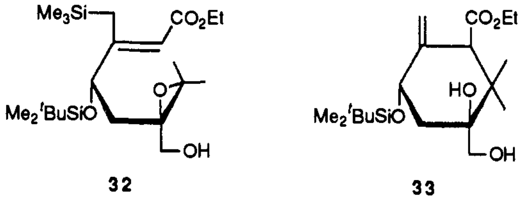
The strategy has been used to give access to more complex cyclohexanes: the anion generated in the branched chain of ester **29** displaced iodide to give the epimers **30** and **31** (68 and 22%, respectively, Scheme 6) from which the anomeric forms of carba-2,3-dideoxy-D-*manno*-octulosonic acid, an analogue of the Gram-negative bacterial polysaccharide component KDO, were obtained.[25]

Scheme 6



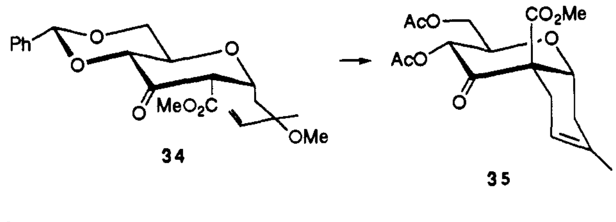
A sophisticated example of a cyclization which involves an enolate carbanion equivalent was carried out with the epoxy–allylsilane **32**, derived by multistep processes from L-arabinose. It underwent an intramolecular nucleophilic displacement reaction when the epoxide ring was activated by addition of boron trifluoride etherate to give the highly functionalized **33** (Scheme 7) in the key step of the synthesis of an enantiomerically pure component of the diterpene taxol.[26] The use of vinylsilane-based cyclizations is noted in section II.E.

Scheme 7



A further conversion of a carbohydrate-based compound into a terpene-related derivative, this time of the sesquiterpenoid trichothecene family, depended in the critical cyclohexane ring-formation step upon nucleophilic displacement with allylic rearrangement, compound **34** affording the cyclized **35** on treatment with tin(IV) chloride and acetic anhydride (Scheme 8).[27]

Scheme 8



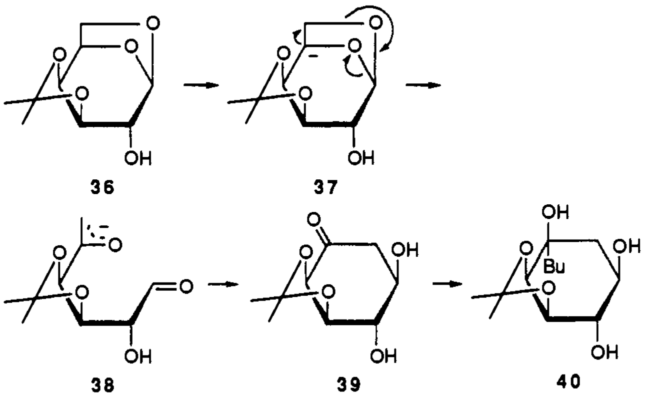
3. Aldol and Aldol-like Reactions

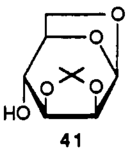
Under this heading reactions of enolates and some enolate equivalents are discussed; cases involving other carbanionic species are considered separately (sections II.A.4, II.A.5, and II.D).

a. Reactions within Sugar Chains. Klemer and Kohla found that 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactose (**36**), on treatment with *n*-butyllithium, gave the *C*-butylinositol derivative **40** in 85% yield.[28]

This can be rationalized by invoking proton abstraction from C-5 and rearrangement of the resulting carbanion **37** to give the enolate **38**, which added in aldol fashion to the formyl group to produce the cyclohexanone **39** with which the nucleophilic reagent gave the final tertiary alcohol **40** (Scheme 9). In the ring closure the reaction resembles a biosynthetic step (section II.A.1) and the mercury(II)-induced cyclization (section II.D.1), but clearly, the direction of attack at the formyl center is governed by different factors. Methyllithium effected an analogous rearrangement, the *C*-methyl analogue of **40** being isolated in 45% yield together with 2% of the epimer at the tertiary center. In a consistent manner, the isomeric 2,3-*O*-isopropylidene-D-*manno*-anhydride **41** gave the carbocycles **42** and **43** (52 and 12%, respectively),[28] and the *altro* isomer **44** afforded **45** (71%)[29] showing that the reaction has some general applicability.

Scheme 9





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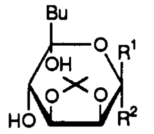
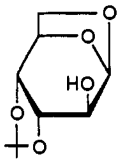


42: R^1 = OH; R^2 = H
43: R^1 = H; R^2 = OH



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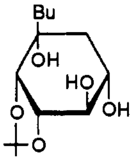

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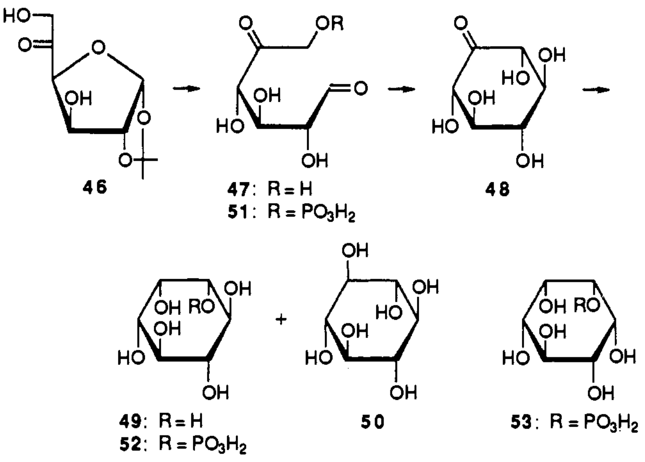
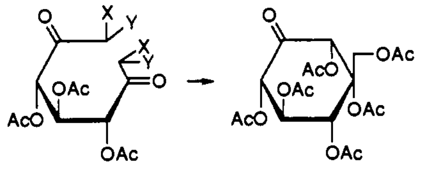
In keeping with these findings, aldol cyclization of 1,5-dicarbonyl carbohydrates affords cyclohexanone derivatives as Kiely and Fletcher first showed by converting D-*xylo*-hexos-5-ulose **47**, formed from the acetal **46**, into the inosose **48** by treatment with alkali. Subsequent reduction with sodium borohydride gave *myo*- and *scyllo*-inositol (**49** and **50**, respectively), thus completing the second chemical conversion of D-glucose into myo-inositol.[30,31] (For the first, see section II.A.5.a.) While this sequence acted as a model for the biosynthesis of the inositols, an even closer biomimetic conversion was carried out by Kiely and Sherman who similarly converted the 1,5-dicarbonyl phosphate **51** into *myo*-inositol 1-phosphate (**52**) and *epi*-inositol 3-phosphate (**53**) (Scheme 10) which were identified by gas chromatography/mass spectrometric methods.[32] In parallel work a Russian group reported that 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexos-5-ulose, on treatment with Dowex 50W resin, gave a product which afforded 6-*O*-benzyl-*myo*-inositol after reduction with sodium borohydride.[33]

In extensions of this work, the bis(diazo ketone) **54** (X, Y = N_2), made from the corresponding D-xylaric acid chloride, underwent cyclization to give compound **55** (35% isolated) on treatment with copper(II) acetate in glacial acetic acid by a process which, however, may have involved intermediate carbenes rather than carbanions.[34] Only 5% of the sought penta-*O*-acetyl analogue **54** (X, Y = H, OAc) was obtained, and in further attempts to produce this perester, the dibromide **56**, obtained from **54** (X, Y = N_2) by treatment with hydrogen bromide, gave the cyclohexenone **60** (50%, characterized by X-ray crystallography) with sodium acetate in ethanol. Intermediates **57**–**59** are thought to be involved in the cyclization process (Scheme 11).[35]

Scheme 10





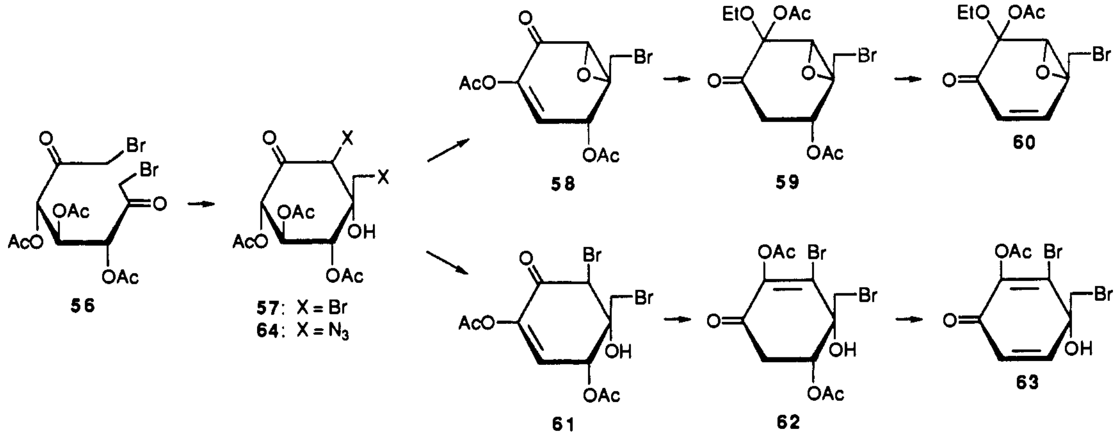
It was then observed that compound **57** was the principal product initially formed when the dibromide **56** was treated with sodium acetate in acetone, but in this solvent (which could not participate in the reaction as did ethanol in giving **60**) reaction continued by way of **61** and **62** to give the dienone **63** as product (Scheme 11).[36,37] Cyclization of bromide **56** to the diazido product **64** was effected by treatment with sodium azide.

b. Reactions Involving Extended- and Branched-Sugar Chains. Opportunities for performing aldol cyclizations are increased in compounds having carbonyl-containing extended or branched chains, and several cyclohexane derivatives have been produced from such compounds.

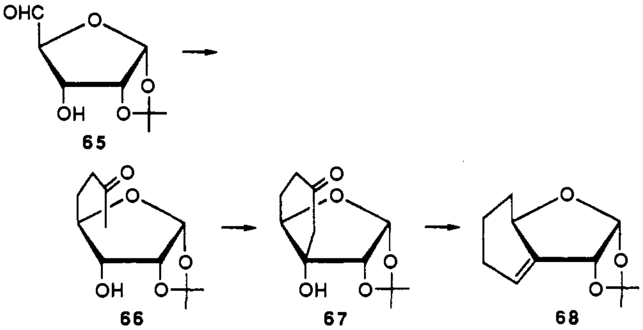
From the D-allose-derived **65** the 1,5-diketone **66** was prepared by application of a Wittig chain extension involving (2-oxopropylidene)triphenylphosphorane, and on base-catalyzed cyclization (DBU in refluxing benzene), the *cis*-fused cyclohexanone product **67** of aldol reaction was obtained. Elimination following methanesulfonylation gave compound **68** and thus an enantiomerically pure 7-oxabicyclo[4.3.0]non-1-ene derivative became available (Scheme 12).[38]

In analogous work aimed at the synthesis of phenanthridone alkaloids, the enal **69**, derived from L-arabinose, was treated with the lithium derivative **70** to give epimers **71** and hence the enone **72** which, on ozonolysis, gave a dicarbonyl product that underwent base-cata-

Scheme 11

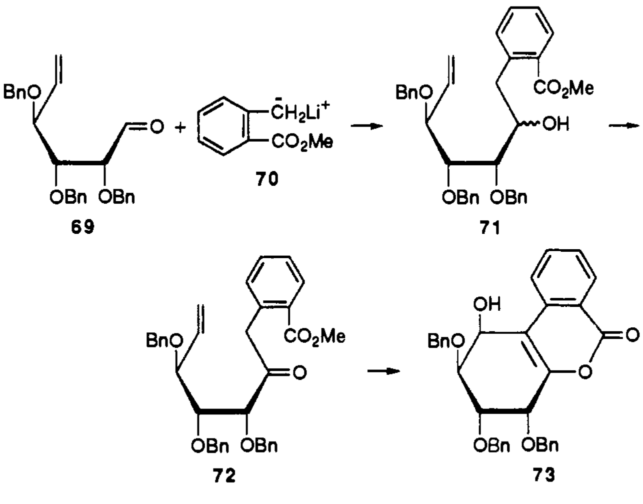


Scheme 12



lyzed cyclization and lactonization to the isocoumarin **73** (Scheme 13) from which alkaloid precursors were obtained.[39]

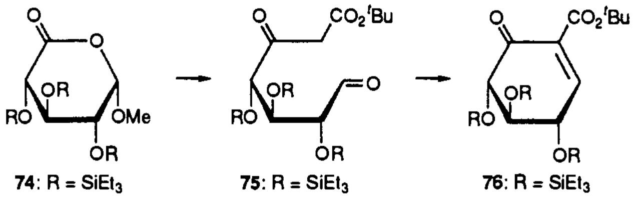
Scheme 13



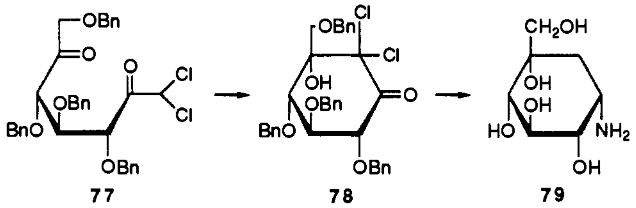
A further, related procedure, developed by Vasella and co-workers, involves the treatment of "pseudo-δ-lactones" with carbanionic reagents. Thus compound **74**, obtained by ozonolysis of the corresponding *exo*-methylene glycoside, when treated with the lithium salt derived from *tert*-butyl acetate, afforded the cyclohexene derivative **76** in 51% yield, presumably by way of the 1,5-dicarbonyl intermediate **75** (Scheme 14). Lithiated dimethyl methylphosphonate and diethyl ethylphosphonate reacted in analogous fashion with a pseudo-δ-lactone of the β-L-*ribo*-series.[40]

In somewhat related work the hept-2,6-diulose derivative **77** was made by treatment of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone with dichloromethyl carbanion followed by oxidation of the adduct with DMSO, trifluoroacetic anhydride, and triethylamine. In the "one-pot" overall procedure the diketone cyclized in 63% yield to **78** from which the naturally occurring *carba*-amino sugar valiolamine **79** was made (Scheme 15).[41] Extensions of the work in the disaccharide series were then used in the synthesis of validamycin G.[42]

Scheme 14

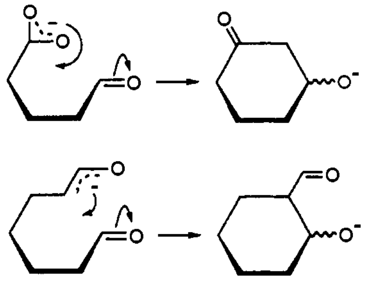


Scheme 15



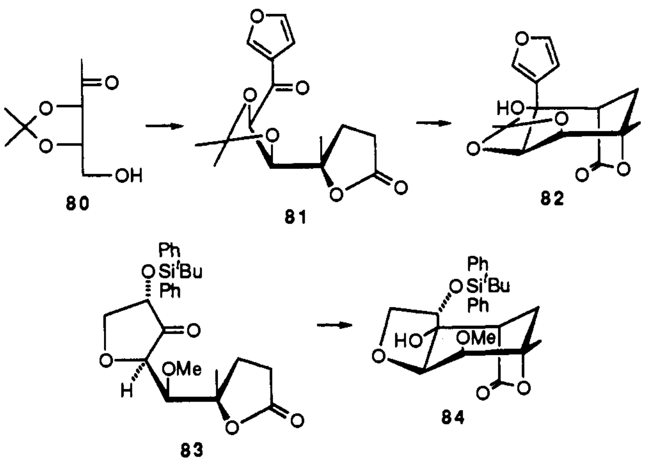
As well as being obtainable from chain-extended 1,5-dicarbonyl moieties by (enol-endo)-*exo*-*trig* processes, cyclohexanes may be produced from 1,7-dicarbonyl compounds [(enol-exo)-*exo*-*trig* closures[43]] (Scheme 16), and Williams and Klinger have used Claisen strategy in this way to produce compound **82**, a synthon for a component of the milbemycin and avermectin family of macrocyclic metabolites. They made the keto–aldono lactone **81** stepwise from the 1-deoxypentulose deriv-

Scheme 16

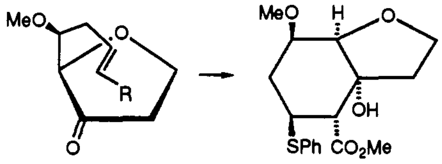


ative **80** using Grignard addition processes at C-2 and subsequently also at C-5 after oxidation to the aldehyde at this position. Treatment of the product with lithium diethylamide afforded the cyclized **82** following C-2 carbanion attack at C-7 which occurred with high efficiency and with a stereoselectivity of 4:1 in favor of the desired isomer (Scheme 17).[44] In an extension of the work compound **83**, synthesized from 1,5-anhydro-D-glucitol, cyclized on treatment with the same base to give **84** which, with the oxahydrindan ring system, is more closely related to the natural product component than is **82**. The yield was 80% showing the preference for *cis*-ring fusion in closures of this type.[45]

Scheme 17



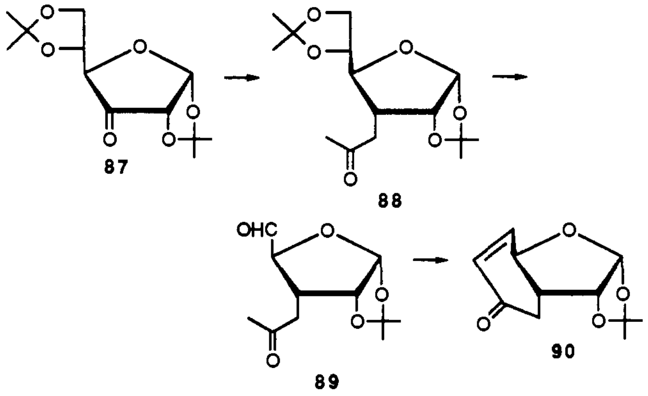
A further approach to the oxahydrindan unit of the avermectins relies on a process induced by thiolate attack at the β-position of the alkene function of the furanone **85**, which was prepared from methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside. The "ate" species derived by reaction of trimethylaluminum with lithium thiophenate gave **86** in high yield as a single product.[46]



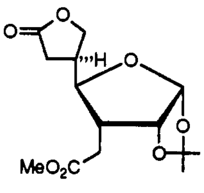
85: R = CO$_2$Me **86**

Considerable use has been made of dicarbonyl species having one of the carbonyl groups in branched chains of sugar derivatives. Thus the D-glucose-derived ketone **87** was converted into the branched ketone **88** by use of Wittig methodology. Partial acid hydrolysis and periodate oxidation of the exposed α-diol afforded the "alone" **89** which, after several bases had failed, was aldol cyclized to give the cyclohexanone **90** in 45% yield by use of DBU followed by acetic anhydride and pyridine (Scheme 18). This product afforded access to enantiomerically pure *pseudo*sugars and has been used appreciably for this purpose.[47,48] It also provided acess to the key intermediate for the synthesis of paniculide B.[49] The same group of Japanese workers have used a dicarbonyl compound akin to **89**, but with the aldehydo and keto functions reversed, to make other highly functionalized cyclohexane derivatives.[50]

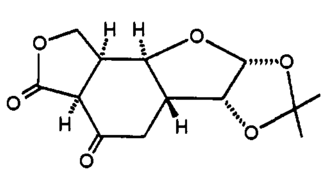
Scheme 18



The lactone ester **91**, prepared by selective routes from D-glucose, gave the keto lactone **92** in 91% yield by Dieckmann cyclization when treated with potassium *tert*-butoxide.[51] Earlier Dieckmann cyclizations had shown that, whereas potassium *tert*-butoxide in refluxing benzene caused the branched-chain uronic acid derivative **93** to give the keto ester **94** derived by way of the carbanion in the C-3 branch chain, the product **95** of the other possible ring-closure process was formed when 18-crown-6 was used in conjunction with this base (Scheme 19).[52]

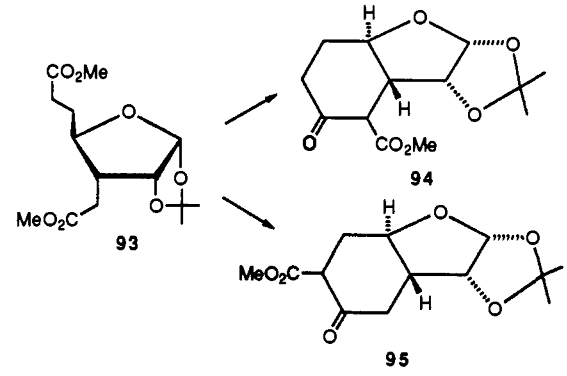


91



92

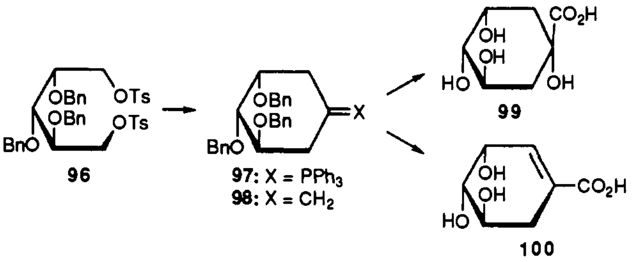
Scheme 19



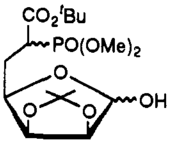
4. Reactions of Phosphorus-Stabilized Species

Following the elegant discovery that short alkanes having halogen or sulfonyloxy substituents at the α- and ω-positions react with methylenetriphenylphosphorane to give carbocyclic products that incorporate a carbon atom derived from the reagent,[53] Bestmann and Heid applied the procedure to the D-arabinitol derivative **96** and obtained the cyclohexylidene ylide **97**. This reaction proceeded by successive nucleophilic displacements of the sulfonyloxy groups and yielded a new Wittig reagent which, by reaction with formaldehyde, gave the cyclohexane and an *exo*-methylene group **98**. From this, quinic acid (**99**) and (−)-shikimic acid (**100**) were derived (Scheme 20) in the first laboratory syntheses of these acids in enantiomerically pure forms.[54]

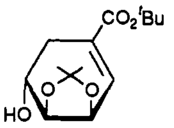
Scheme 20



It has emerged that later approaches to cyclohexane derivatives from carbohydrates which have involved phosphorus-containing intermediates have been most suited to the preparation of compounds with a carbon substituent on the cyclohexane rings, and several such approaches have resulted in improved routes to shikimic acid in its natural enantiomeric form. Thus Fleet's group developed a considerably more efficient synthesis of this acid (39% from D-mannose) by employing an intramolecular cyclization based on the use of a phosphonate-stabilized carbanion bearing an additional stabilizing ester group (Wadsworth–Emmons reaction). Treatment of **101** (which was made from benzyl 2,3-*O*-isopropylidene-5-*O*-triflyl-α-D-lyxofuranoside and the sodium salt of *tert*-butyl (dimethoxyphosphoryl)acetate followed by hydrogenolysis) with sodium hydride in tetrahydrofuran gave the shikimic acid derivative **102** in 73% yield.[55,56] A similar route to shikimic acid and its phosphonate analogue utilized 5,6-alkene analogues of **101**. In the case of the phosphonate synthesis the alkene intermediate isomerized to the 4,5-unsaturated compound, but this did not affect the approach to the final product.[57] The same approach applied to 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-triflyl-α-D-xylose led to 4-*O*-benzyl-3-*epi*-shikimic acid.[58]



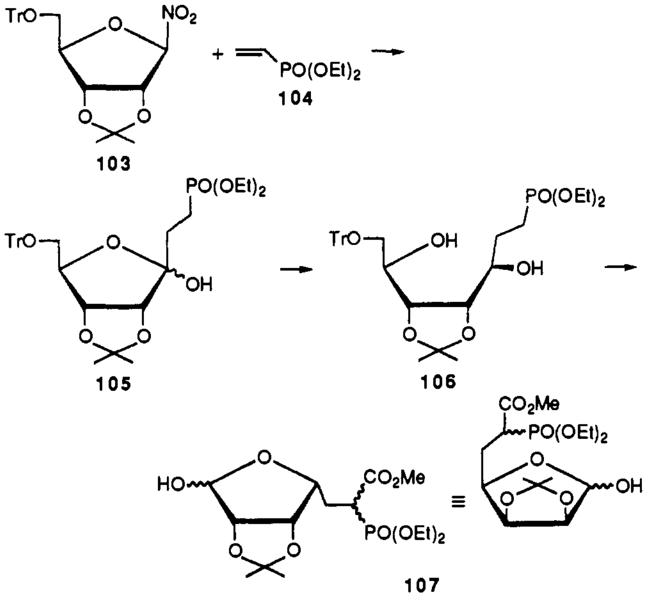
101



102

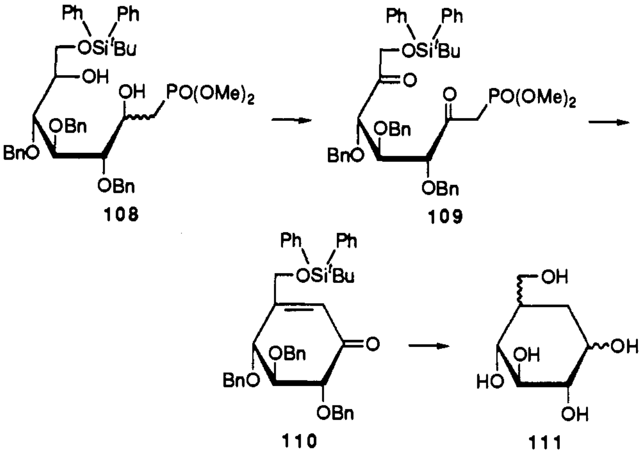
In somewhat parallel fashion Mirza and Vasella used a procedure based on a chain extension at C-1 of the 1-deoxy-1-nitro-D-ribofuranose derivative **103**. On base-catalyzed addition to the vinyl phosphonate **104**, followed by heating the adducts in wet formamide, the anomeric phosphonates **105** were obtained. Reduction with sodium borohydride then afforded the corresponding acyclic diol **106** in good yield and with high stereoselectivity. The product **107** of detritylation, periodate oxidation, and methoxycarbonylation at the position adjacent to the phosphorus atom is a close analogue of **101** and led to (−)-methyl shikimate following an efficient base-catalyzed cyclization (Scheme 21).[59]

Scheme 21



Clearly, the intramolecular phosphonate approach is applicable to the synthesis of carbahexopyranoses and their derivatives. For this purpose Paulsen and von Deyn produced the epimeric phosphonates **108** from 2,3,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-D-glucose by use of dimethyl methylphosphonate and butyllithium. Oxidation of the hydroxyl groups gave the dione **109** which, with base, afforded the enone **110** and hence carba-α- and β-D-glucopyranose and the L-idose epimers at C-5 (**111**, Scheme 22).[60]

Scheme 22

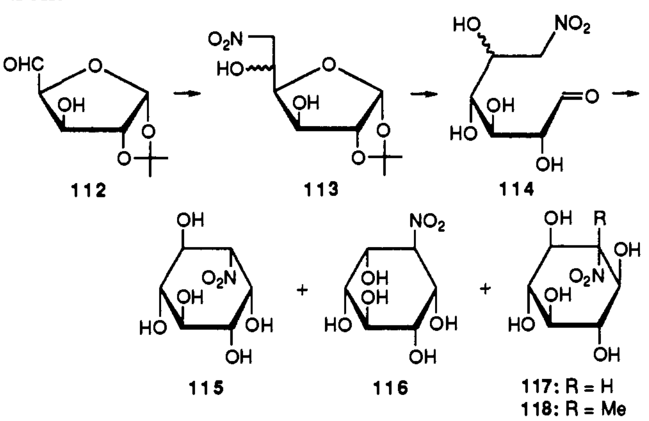


5. Reactions of Nitro-Stabilized Species

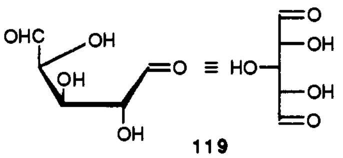
Considerable attention has been paid to cyclohexane derivatives produced by the reaction of carbanions stabilized by nitro groups. Intramolecular reactions have been found to be of appreciable use, and intermolecular processes, involving the use of nitroalkanes have, likewise, been studied on many occasions.

a. Cyclizations of Nitro Sugars. The first chemical conversion of a sugar to a cyclohexane derivative was carried out by H. O. L. Fischer's group[2] who showed that a mixture of 6-deoxy-6-nitro-D-glucose and -L-idose **114**, prepared from the D-glucose-derived **112** and then **113**, on treatment with base, undergoes intramolecular Henry reaction to give mixed deoxynitroinositols which were later identified as the D,L-1-nitro-*myo*-, 3-nitro-*muco*, and nitro-*scyllo*-inositols (**115**–**117**) (Scheme 23).[61] By reduction of the nitro groups and treatment of the derived amines with nitrous acid to convert the amino to hydroxy groups, the first formal conversion of glucose to the inositols was completed.[62] The nitroaldehydes [114] are enantiomerically pure forms of the racemic products of Henry reaction of nitromethane

Scheme 23



with the symmetrical dialdehyde **119** which is derived by acid hydrolysis of **112**. These compounds react further also to give racemic **115–117**, and with nitroethane the *C*-methylinositol derivative **118** can be obtained. In addition, methyl 6-deoxy-6-nitro-D-glucopyranoside in basic conditions affords deoxynitroinositols by a multistep process initiated by abstraction of H-6 and ring opening to give the 5-enal **120**.[63]



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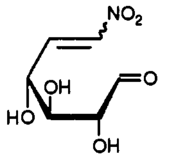
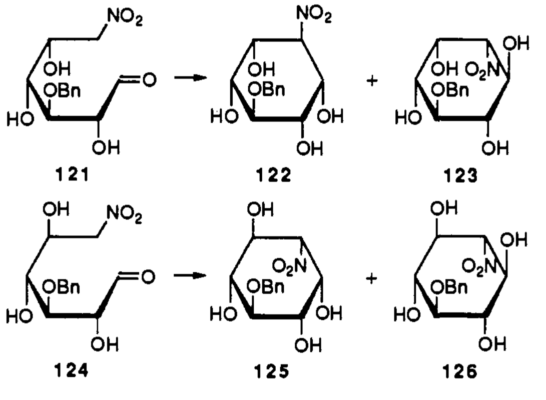


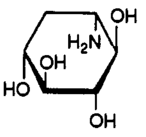
120

Baer and co-workers have also carried out detailed studies of the products formed by the ring closure of 6-deoxy-6-nitrohexoses under kinetic and thermodynamic control. They showed that the glucose derivative **121** gave **122** and **123** in the ratio 3:1 under kinetic control, whereas the L-ido isomer **124** gave **125** (the enantiomer of **123**) and **126** in the same ratio. Base-catalyzed equilibration of these products led to mixtures of **122**, **123**/**125**, and **126** in the proportions 1.5:5.5:1, (Scheme 24),[64] and this and studies of related systems allowed conformational analyses to be carried out on inositol rings bearing nitro and nitronate groups.[65] Related work with 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-6-deoxy-6-nitromaltose, derived from 1,6-anhydromaltose, led to mixed products from which α-D-glucosylated inosamines have been prepared as their peracetates.[66]

Scheme 24



The method's obvious applicability to the preparation of inosamines has led to 1-amino-1-deoxy-*scyllo*-inositol by use of 2,3-di-*O*-benzyl-6-deoxy-6-nitro-D-glucose,[67] and to 3-amino-2,3-dideoxy-D-*myo*-inositol (**127**), an intermediate in the biosynthesis of 2-deoxystreptamine, from 5,6-dideoxy-6-nitro-D-glucose.[68] 2-Deoxystreptamine (**128**) has been prepared from the nitroaldehyde **129** which was derived from a 1-deoxy-1-nitroheptitol.[69] Clearly such inosadiamines could be obtained by application of the nitro sugar cyclization to amino sugar derivatives and, in this way, streptamine and its 2-epimer have also been made, as their peracetates **130** and **131**, respectively, from 2-acetamido-2,6-dideoxy-6-nitro-D-glucose.[70]



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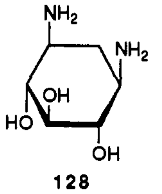

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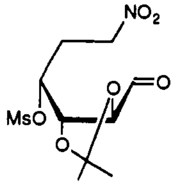

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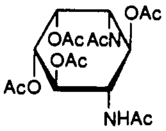

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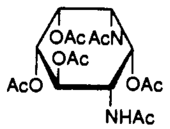
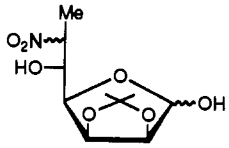


131

A range of inositols and inosamines having carbon substituents on the rings have been made by use of 6-nitrohexose derivatives bearing carbon substituents, and if such groups are attached at C-6, the products contain the nitro group at tertiary ring positions. In this way the heptose compounds **132** have been converted in 70% yield into the thermodynamically favored **133** which served as a model for the preparation of **134** having the ring skeleton of the alkaloid histrionicotoxin.[71]



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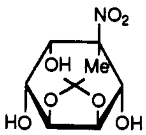

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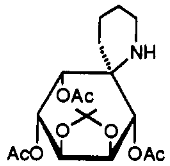
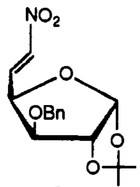


134

Most commonly, branch points have been introduced at C-5 of nitrohexoses by way of 6-deoxy-6-nitro-5-enes, and by this means a range of inositols with branched chains akin to natural products have been obtained by Funabashi, Yoshimura, and colleagues.[72] For example, vinyl addition at C-5 of compound **135** by use of vinylmagnesium bromide gave **136** from which the carba-α-D-glucopyranose derivative **137** was made in 52% yield.[73] Extensions of the work led to the synthesis of a series of branched inositol derivatives—many with dithianyl substituents—and thus, interestingly, to the preparation of **138** which is a derivative of a structural component of tetrodotoxin.[74] Other workers produced validamine (**139**) and the L-*ido*-epimer by use of 6-deoxy-6-nitrohexose derivatives bearing (benzoyloxy)methyl substituents bonded to C-5, and induced ring closures by using potassium fluoride in DMF in the presence of a crown ether.[75]



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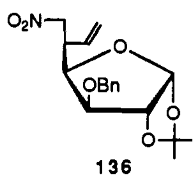

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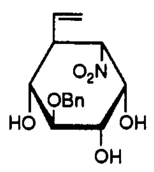

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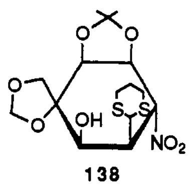

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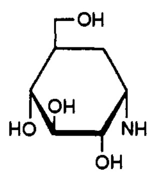
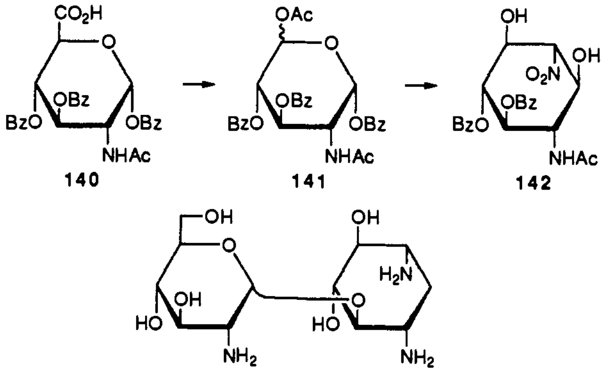


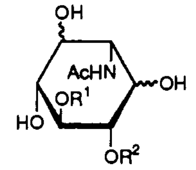
139

b. Dialdehyde–Nitromethane Cyclizations. As pointed out in the last section the 6-deoxy-6-nitroaldohexoses that, in basic solution, cyclize to deoxynitroinositols are the same as the first products of reaction of pentodialdoses with nitromethane; in consequence, condensation of these latter compounds also results in the same inositol derivatives.[76] The *xylo*-dialdose **119** gives the carbocyclic nitro compounds **115–117**,[77] and with nitroethane in place of nitromethane the *C*-methyl derivative **118** can be produced in 14% yield by direct crystallization.[78] Pentodialdoses or their derivatives required for the cyclization under consideration may be prepared from pentose- or hexose-based compounds, but certain aminodeoxy analogues have been made by periodate oxidation of appropriate aminocyclopentanediols and have given access to inosadiamines following cyclization with nitromethane and subsequent reduction.[79]

More novel and very useful access to carbohydrate dialdehydes has been gained by oxidative decarboxylation of hexopyranuronic acids either electrolytically or with lead tetraacetate, the latter causing replacement of the carboxy groups by acetoxy thereby giving compounds that, with base, degrade to the pentodialdoses and hence, in the presence of nitromethane, afford access to deoxynitroinositols and hence inosamines. By the lead tetraacetate-based procedure the acid **140** afforded a route to **142** by way of the pentodialdose cyclic hydrate derivative **141** (Scheme 25),[80] a compound closely related to **142** was made and used to obtain 2-deoxystreptamine pentaacetate,[81] and the kanamycin C component paromamine (**143**) was made from a 2-amino-2-deoxy-D-glucose-substituted 2-amino-2-deoxy-D-glucuronoside.[82] D-Mannose has been converted into (−)-shikimic and (−)-quinic acid by way of deoxynitroinositols derived from methyl tri-*O*-benzyl-α-D-mannopyranosiduronic acid.[81] In an extension of the work hexuronic acid-containing saponins have been converted into inosamines bonded to several sugar units.[83]

Scheme 25





144

R¹ = *O*-α-L-Rhap-(1→2)-*O*-α-L-Rhap-(1→2)-*O*-β-D-Galp
R² = β-D-Glcp

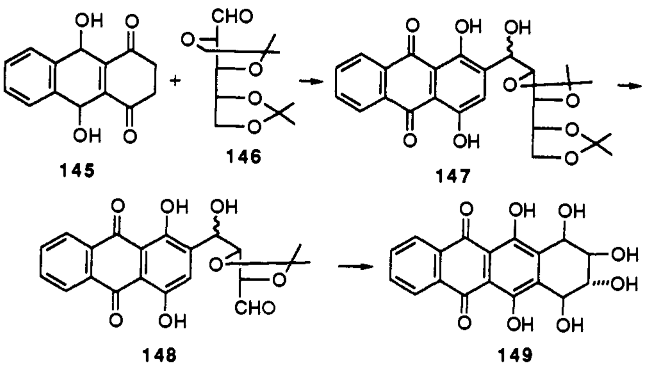
The electrochemical procedure, using uronic acids in cold methanol containing diethylamine, gives unstable products which, with nitromethane and sodium methoxide in methanol, affords nitroinositol derivatives.[84] In this way compounds **144** were produced from a triterpene glycoside of a pentasaccharide, the glycosidic linkage involving a uronic acid precursor of the inosamine moieties.[85]

6. Inter-/Intramolecular Carbanionic Cyclizations

In this section a set of reactions are discussed that involve initial intermolecular carbanion processes followed by second, intramolecular steps.

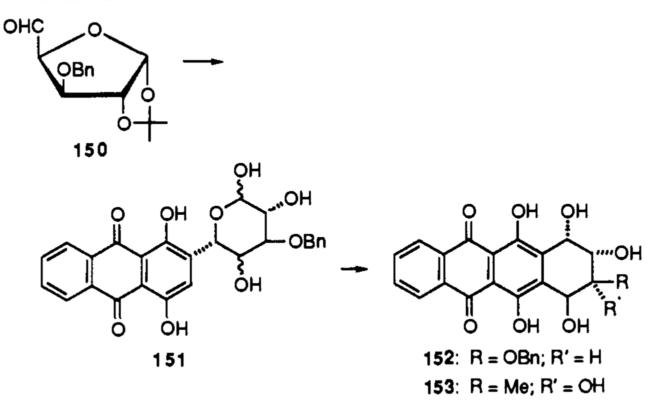
leuco-Quinizarin (**145**) and the D-arabinose-based aldehyde **146**, when treated with aqueous alkali and then with atmospheric oxygen, gave the quinizarin **147** in 56% yield (Marschalk reaction which involves an initial aldol step). From **147**, the aldehyde **148** was made by partial hydrolysis followed by periodate oxidation, and this, when reduced back to the *leuco* form by treatment with alkaline sodium dithionite, cyclized. Further aerial oxidation and acidic hydrolysis gave a tetrahydroxycyclohexane identified as **149** (Scheme 26).[86] Later, analogous work by Shaw and co-workers with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose (**150**) led to compound **151** and hence, by a further aldol process, to the ring closed **152** (Scheme 27).[87]

Scheme 26



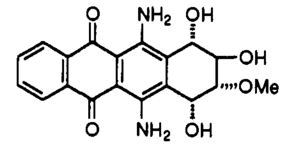
From this point the work was extended by use of branched-chain sugar aldehydes to give compounds such as **153** with a tertiary alcohol function in the D ring[88–90] and thus akin to the anthracyclinones. In this later work reduction to the *leuco* derivatives was conducted with zinc/acetic acid, and the aldol processes

Scheme 27



were effected by use of 1,5-diazabicyclo[4.3.0]non-5-ene in DMF prior to aeration. The diamino **154** was made in extensions of these studies by use of *leuco*-1,4-diaminoanthraquinone.[91]

In closely related studies by a French group compound **145** was condensed with 2-deoxy-3-*C*-(hydroxymethyl)-3,3′-*O*-isopropylidene-D-*glycero*-tetrose (**155**, made from D-isosaccharino-1,4-lactone which is a product of calcium hydroxide-promoted degradation of lactose) in refluxing 2-propanol containing piperidinium acetate which, in effect, reductively removes the benzylic hydroxyl group of the first product. Generation of an aldehyde group from the primary alcohol and cyclization under Marschalk conditions then gave **156**, hydrogenolysis of which over palladium on barium sulfate gave the deoxy analogue **157**. Subsequent use of 3-deoxy-2-*C*-(hydroxymethyl)-2,2′:4,5-di-*O*-isopropylidene-D-*erythro*-pentose (from the same source as **155**) resulted in **158** which is closely related to daunomycinone.[92] Then the same group, using the same methodology and the anion derived from *p*-dimethoxybenzene, made **159** for use in a more traditional route to the anthracyclinones[93] and developed the use of aldehyde **160** and related carbohydrate-based compounds for access to 7,10-dihydroxyanthracyclinones related to **156** and **157**[94] and other compounds of this family.[95]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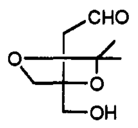
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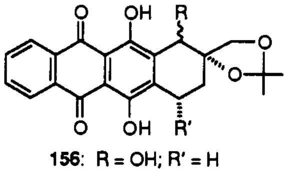
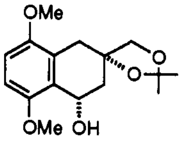

156: R = OH; R' = H
157: R = H; R' = H
158: R = H; R' = OH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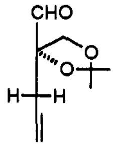
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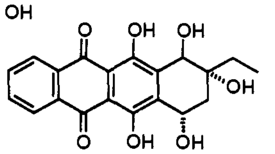
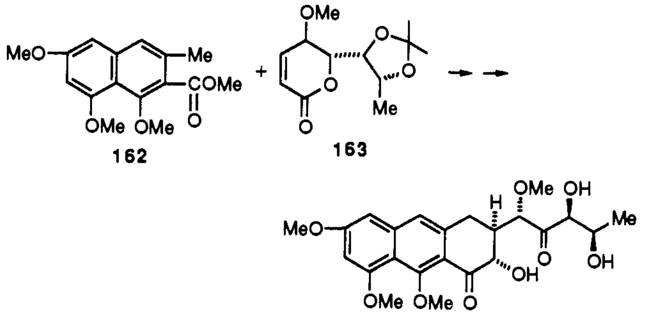

161

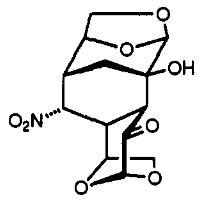
3-*O*-Benzyl-3-*C*-ethyl-4-*O*-trityl-L-*glycero*-tetrose, synthesized from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose, has been applied in the above manner to obtain 4-deoxy-β-rhodomycinone (**161**).[96]

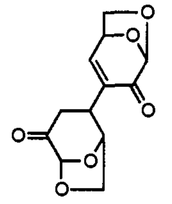
While the above two-stage reactions used four carbon atoms derived from carbohydrate derivatives to form the new cyclohexane ring of the anthracyclinones, several examples have been recorded in which two carbon atoms of a carbohydrate electrophile have combined with four-carbon nucleophilic units in Michael/Claisen processes. Thus, the benzylic anion derived from **162** added to the unsaturated octonic acid derivative **163** in Michael fashion. The first formed product anion and then Claisen-condensed with the methoxycarbonyl group to give the cyclohexanone ring in the key step of the synthesis of **164**, a trimethyl ether of the aglycon olivin of olivomycin A (Scheme 28).[97]

Scheme 28



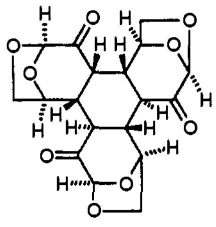
During a later investigation of the Michael addition of nitromethane to levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose) it was discovered that the initial adduct adds to a second molecule of the enone, the available nitronate anion adding in Michael fashion and the anion thus formed at *C*-3 ring closing to the carbonyl group of the first sugar ring. When conditions for its preparation were optimized the product **165** was obtained in 95% yield.[98]


165

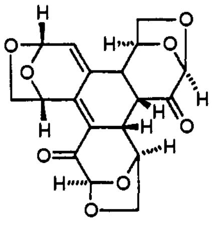

166

It has also been found that levoglucosenone takes part in base-catalyzed cyclohexane ring-forming reactions in the absence of other reagents (such as nitromethane). On heating in aqueous triethylamine it dimerizes following attack by catalytic hydroxide at C-4 to give **166** which then condenses with further levoglucosenone to afford **167** (by Michael-like addition) and **168** (following aldol condensation). Compounds **166**–**168** were isolated in 8, 18, and 56% yield, respectively.[99]

The reverse type of Michael addition is involved in Robinson annulation, application of which in carbohydrate chemistry proves to be surprisingly rare—no doubt because most carbonyl compounds available would be subject to β-eliminative degradation. The case illustrated in Scheme 29 shows that in the absence



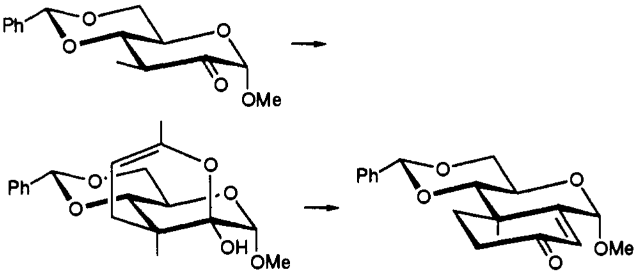
167



168

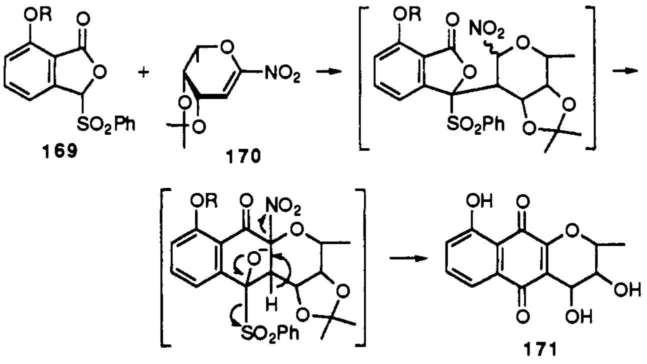
of α-related hydrogen atoms the process can be applied with normal success (yield reported, 58%).[100]

Scheme 29



A very neat synthesis of (−)-cryptosporin (171) relied, in the critical step, on base-catalyzed Michael addition of the anion derived from sulfonyl lactone 169 to the 1-nitroglycal 170, and subsequent intramolecular C-acylation followed by double elimination as indicated in Scheme 30.[101]

Scheme 30

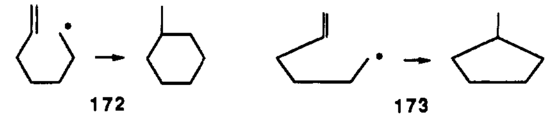


R = MeOCH$_2$CH$_2$OCH$_2$-

B. Free-Radical Cyclizations

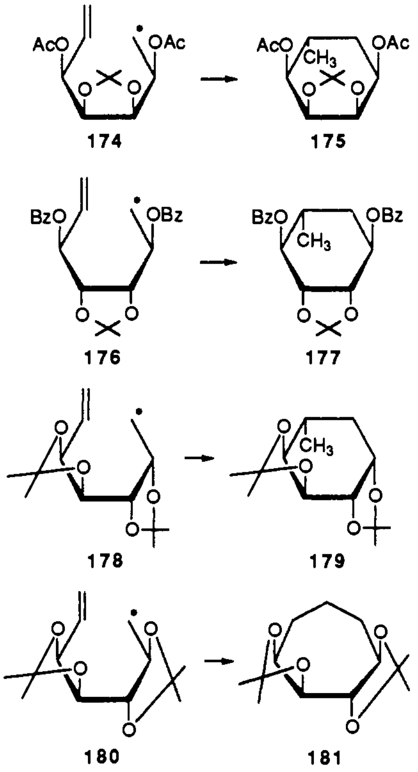
Many fewer instances have been reported of carbohydrate radical cyclizations which have resulted in six-membered rings than in analogous cyclopentanes (section III.B). This is because common carbohydrates offer fewer opportunities to produce required 6-heptenyl radicals 172 than 5-hexenyl species 173, both of which normally cyclize by *exo* processes to give cyclohexanes and cyclopentanes, respectively (Scheme 31).[102] In several cases in which the former have been prepared (from either heptose or extended-chain derivatives or from branched-chain compounds having a radical generating group on the sugar chain and a radical trap in the branching group), the method has proved highly suitable.

Scheme 31

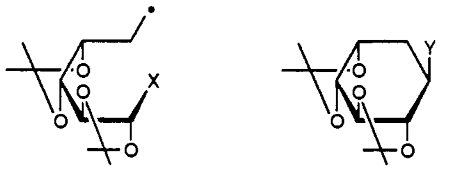


Redlich and co-workers have studied ring closures involving 6-heptenyl species by generating radicals at C-7 of several 1,2-dideoxyhept-1-enitol derivatives and have, in some cases, gained efficient access to carba-6-deoxyhexoses by this approach. Thus the radical 174, derived from the corresponding D-*allo*-iodide by treatment with tributyltin hydride, gave 175 in 87% yield,[103] but the stereochemical and protecting group requirements for efficient ring closure are demanding: D-*galacto* analogue 176 gave 90% yield of 177 and its epimer in the ratio 2:1, but the L-*manno* radical 178 produced the β-L-*altro* 179 in only 51% yield, suggesting that factors associated with strain imposed by the acetal rings were having an effect. That such strain can have major consequences was then vividly demonstrated by the finding that the product derived in 81% yield from the D-*gulo* species 180 was the carbaseptanose 181 (Scheme 32). Seemingly, the transition state leading to the seven-membered cyclic product of *endo* ring closure was better able to accommodate a *trans*-fused dioxolane ring than that of *exo* closure from which the carbahexopyranoses would have been derived. The authors rationalized the observed selectivities in terms of chair- and boatlike transition states for compounds having *threo*- and *erythro*-related substituents at C-3 and C-6 (numbering from the alkene end respectively) and found that benzyl ether groups at these positions were not compatible with efficient cyclizations.

Scheme 32



A related study has been made of the ring closures of radicals derived from a range of 6-bromo-6-deoxyhexose derivatives having different unsaturated radical trapping groups at C-1, and again it was found that the yields and stereoselectivities were greatly dependent on structural factors; they were also very dependent on the nature of the trapping groups. One series studied was the 2,3:4,5-di-*O*-isopropylidene-D-glucos-6-yl species **182** (each member being derived from the corresponding bromide) from which no cyclized products were obtained with the aldehyde **182a** or the nitrile **182b**. However, the oxime **182c**, the enol ethers **182d**, and the unsaturated ester **182e** all afforded good yields of mixed products with the epimers **183** dominating strongly.[104]

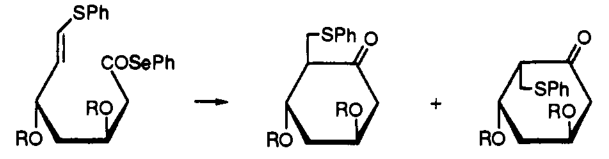


182a: X = CHO
b: X = CN
c: X = CH=NOBn → **c**: Y = CH_2NHOBn
d: X = CH=CHOMe → **d**: Y = CH_2OMe
e: X = $CH=CHCO_2Me$ → **e**: Y = CH_2CO_2Me

183

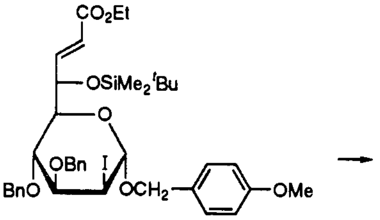
Acyl radicals may also be used in the above type of ring closures, the radical derived from the hept-6-enonic selenoester **184** (prepared from non-carbohydrate sources) cyclizing to give equal proportions of the cyclohexanones **185** and **186** in 90% yield (Scheme 33).[105]

Scheme 33

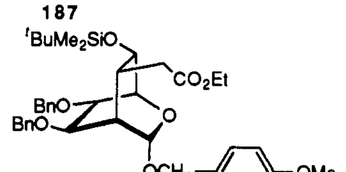


184: R = $SiMe_2{}^tBu$ **185**: R = $SiMe_2{}^tBu$ **186**: R = $SiMe_2{}^tBu$

Fraser-Reid and colleagues have developed this approach by using radicals on sugar rings and have in an extensive study prepared bicyclic products having the anomeric centers intact.[106] In the specific case of the radical derived at *C*-2 of the nonuronic acid derivative **187**, ring closure occurred in the *exo* manner to give the bicyclic **188** in 70% yield (plus epimer, 14%) notwithstanding the fact that the pyranoid ring had to adopt a conformation much distorted from the normal $^4C_1$ chair for radical addition to be possible. A notable feature of **188** and related compounds was that, on hydrolysis of the glycosidic bond, they remained as bicyclic hemiacetals which, for ring opening, had to be converted into dithiane derivatives (e.g. **189**).



187



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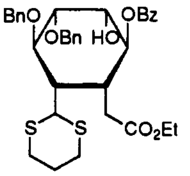
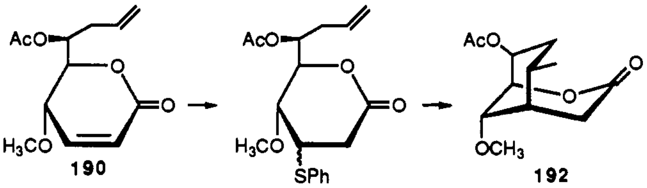


189

An ingenious related cyclohexane synthesis utilizes a one-pot procedure based on the selective addition of benzenethiol to the conjugated double bond of non-2,8-dienonic acid lactones. For example, the epimeric adducts **191** were made by reaction of the thiol in the presence of triethylamine with the enone **190** and, without isolation, were treated with tributyltin hydride and AIBN to give 77% of compound **192** together with 6% of the epimer at C-8 (Scheme 34).[107]

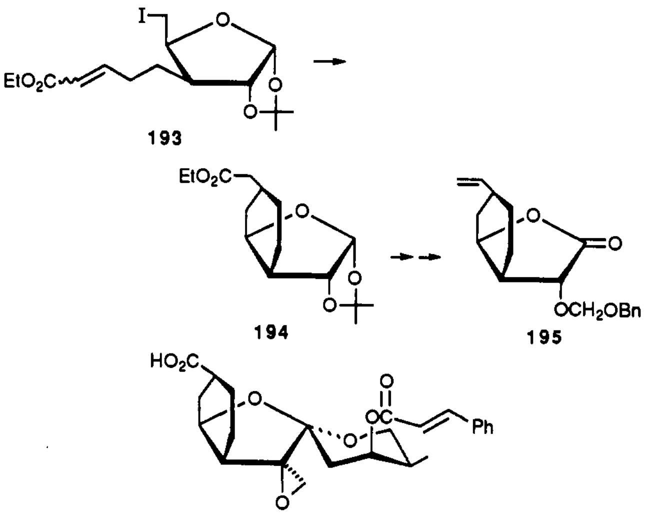
Scheme 34



190 **191** **192**

Parallel work has been carried out in the furanoid series with compounds having radical traps in branched chains. Use of the 5-iodopentose derivatives **193**, made by Wittig procedures from the corresponding aldehyde, gave compound **194** and its epimer in 74 and 85% combined yields from the (*E*)- and (*Z*)-alkenes, respectively, the epimeric ratio being 2:1 and 9:1 in favor of **194** in each case. The major isomer gave access to **195** (Scheme 35) which is a key intermediate in a synthesis of (+)-phyllanthocin **196**, an anti-P388 leukemia plant product. Radical cyclization of the aldehyde precursor of **193** gave the cyclohexanol epimers in 55% yield, but the corresponding nitrile was almost unreactive as a radical trap.[108]

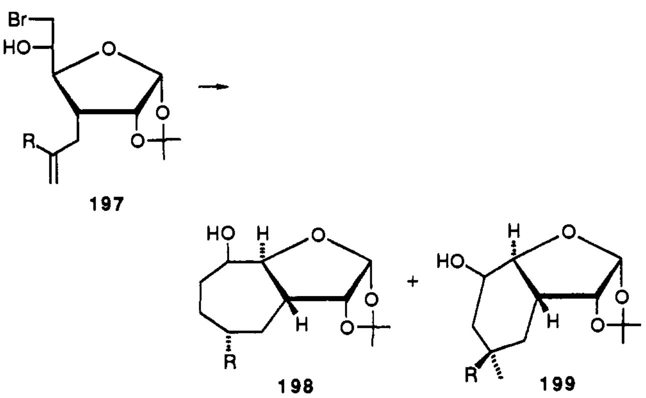
Scheme 35



193 **194** **195** **196**

As was to be expected for C-3 epimers of compounds like **193**, from which *trans*-ring junctions would be established on ring closure, radical cyclizations by the normal *exo* mode proved more difficult, compound **197** (R = H) giving 44% of the product **198** (R = H) of *endo* closure and only 33% of the *exo* product **199** (R = H) (Scheme 36). When an additional methyl group was present at the site of *exo* attack (compound **197**, R = Me) no cyclization at this center was detected, the only

Scheme 36



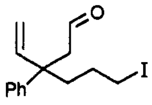
197

198

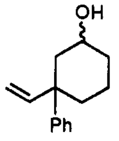
199

cyclized product being the *endo* compound **198** ($R =$ Me, 25%).[109] Related cyclizations were then performed with analogues of **197** in which the double bonds were components of oxime groups or of α,β-unsaturated esters. In the former cases cyclohexanes were produced having alkoxyamino substituents, and the yields were 30%; in the latter series yields were 80% of products having (alkoxycarbonyl)methyl substituents. In all cases, epimeric pairs were produced with α-isomers predominanting strongly.

In the course of their extensive work in this area of synthesis, Fraser-Reid and co-workers encountered with surprise the relative ease with which some carbon free radicals cyclize intramolecularly with appropriate aldehydo groups to give cyclohexanols in preference to forming cyclopentane rings with alkenes. For example, the main products of ring closure of the primary radical derived from **200** were the six-membered alcohols **201** (85%),[110] and consistent with this, the tribranched carbohydrate iodide **202** afforded a radical which preferentially reacted directly to give **203** (Scheme 37).

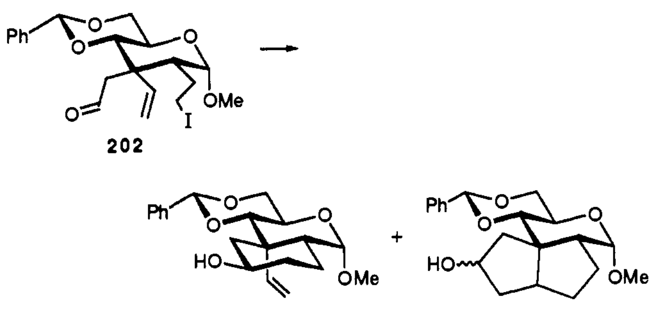


200



201

Scheme 37



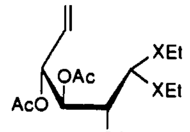
202

203

204

Concurrently, however, some *exo* closure did occur with the alkene, subsequent reaction with the aldehyde leading to **204** (total yield 91%, **203**/**204**, 4:1). Replacement of the vinyl group of **202** by a methoxyl group gave the analogue of **203** in high yield establishing that the formation of products of this kind was not a peculiar feature of **202**.[111] In a more extensive assessment of aldehyde groups as radical traps they showed clearly that several factors can diminish their efficiency—particularly the presence of α-oxygen atoms—and they concluded that care should be taken in selecting substrates for cyclizations.[112] (See also section III.B.3.)

An early report that exposure of the acetals **205** and **206** to ultraviolet irradiation proceeded by a radical *endo* process to give cyclohexyl products has apparently not been confirmed.[113] However, dithioacetals can be used as radical sources for cyclization processes (section III.3.B.1.b).



205: X = O
206: X = S

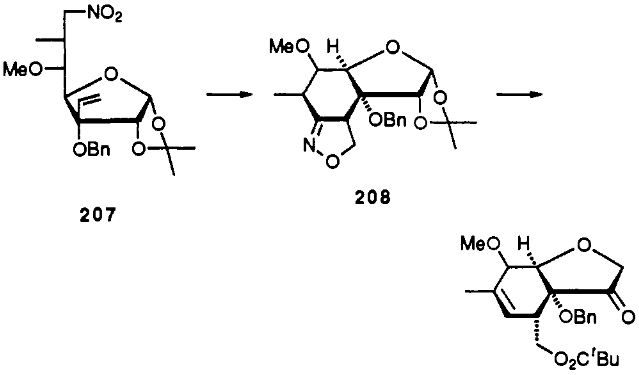
C. Cycloaddition Reactions

A range of cycloaddition processes have been applied to produce cyclohexane derivatives; Diels–Alder reactions of various kinds have been of particular value while 1,3-dipolar cycloadditions appear to have been undervalued. During the preparation of this review the proceedings of an American Chemical Society symposium on "Cycloaddition Reactions in Carbohydrate Chemistry" have been published.[114] Readers are referred to this for a more extensive coverage of the subject than can be provided here.

1. 1,3-Dipolar Cycloadditions

Such reactions have been used less frequently to produce cyclohexane derivatives than five-membered carbocycles (section III.C.1) from sugar derivatives, but a few examples have been described of efficient syntheses of compounds containing functionalized six-membered rings. Thus the 7-deoxy-7-nitroheptose derivative **207**, prepared from the corresponding 3-*C*-vinyl-D-*allo*-hexodialdofuranose, when converted to the corresponding nitrile oxide (by use of phenyl isocyanate and triethylamine), spontaneously underwent intramolecular [1,3]-dipolar cycloaddition to give the isoxazoline **208** in 74% yield. This was converted into **209**, a synthon for the oxahydrindene portion of the avermectins (Scheme 38).[115]

Scheme 38



207

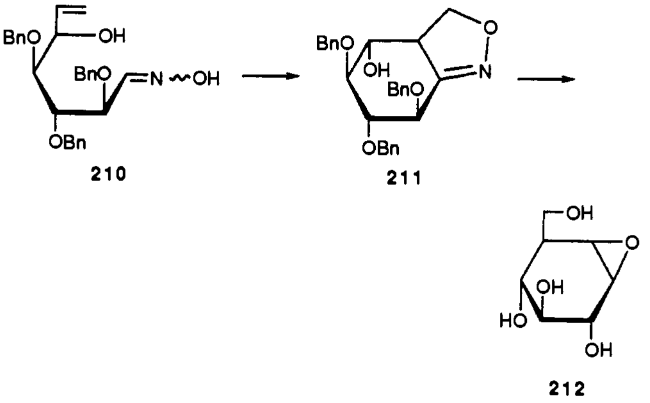
208

209

Nitrile oxides may also be prepared by oxidation of oximes with hypochlorite, and in this way the oxime

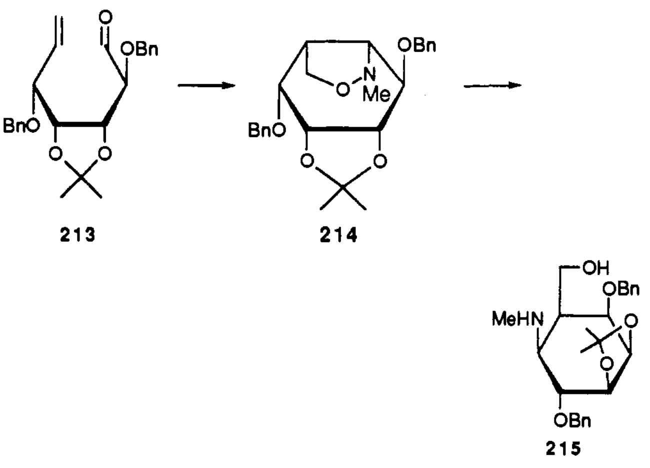
210 of a hept-6-enose derivative (made by Wittig methylenation of a D-idopyranoside 6-aldehyde, followed by acid-catalyzed hydrolysis) was converted into the bicyclic **211** in 70% yield and hence into cyclophellitol (**212**, Scheme 39) which is a β-D-glucosidase inhibitor produced by the mushroom *Phellinus* sp.[116,117] In a similar manner an isomer of **212** with the epoxide oxygen atom on the α-side of the ring was produced by analogous treatment of the D-*galacto* isomer of **210** (inverted stereochemistry at C-2 and C-3). In this case, however, the cyclization step gave mainly the isoxazoline with the "wrong" stereochemistry at the cyclohexane ring position bearing the carbon-bonded substituent—a problem which was largely removed during hydrogenolysis in acidic conditions under which the intermediate ketone underwent epimerization at the center in question.[117]

Scheme 39



Analogous nitrone cycloaddition processes offer a further satisfactory route to cyclohexanes which has not been exploited to any great extent. From 2,3:5,6-di-*O*-isopropylidene-D-mannose the enal **213** was obtained by use of the key steps of vinyl Grignard addition at C-1 and preferential hydrolysis of the acetal at C-5,6 then periodate oxidation of the released diol. With *N*-methylhydroxylamine, nitrone formation occurred followed by cyclization to give **214** with 6:1 stereoselectivity, indicating that the orientation of the group at C-2 (aldose numbering) largely determines the direction of ring closure. From compound **214** the carbasugar analogue **215** was derived by hydrogenolysis (Scheme 40).[117] In closely related work isoxazolines (cf. **211**) and isoxazolidenes (cf. **214**) have been derived from 2,3,4,5-tetraethers of 6,7-dideoxy-D-*ido*- and D-*gulo*-hept-6-enoses (cf. **213**).[118]

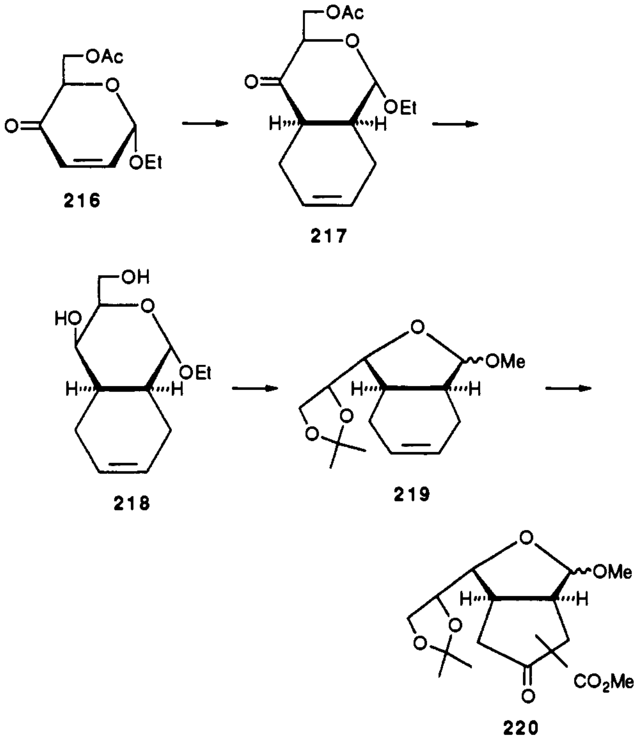
Scheme 40



2. [4 + 2] Cycloadditions

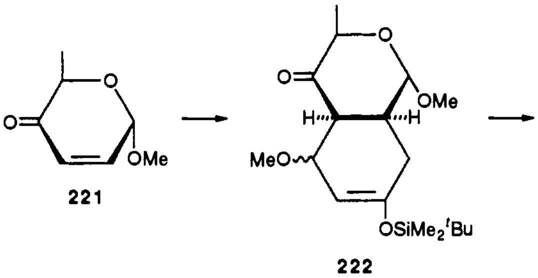
a. Reactions of Carbohydrate Dienophiles (cf. section III.C.2 for further relevant material). Major impetus was provided to Fraser-Reid's pioneering work on annulated pyranosides by the finding, in his laboratory, of conditions for the efficient Diels–Alder addition of 1,3-butadiene to the carbohydrate-derived enone **216**. At −60 °C in dichloromethane in the presence of an excess of aluminum chloride, highly selective reaction occurred to give **217** (81%), and from this the diol **218** was obtained by use of lithium aluminum hydride, also in high yield (Scheme 41). On treatment with methanolic hydrogen chloride **218** was converted to a mixture of the corresponding methyl pyranosides and the isomeric furanosides in the ratio 1:6. Isolation of the latter was effected by way of compounds **219** from which cyclopento derivatives **220** were obtained by use of ruthenium dioxide/sodium periodate to cleave the double bond, diazomethane to give the dimethyl ester and potassium *tert*-butoxide to effect Dieckmann cyclization. Decarbomethoxylation by heating with sodium chloride in moist DMSO gave the corresponding cyclopentanes (section III.C.2). It was of importance to note that, whereas this cyclohexane to cyclopentane ring contraction occurred efficiently, the analogous reaction applied to the diacetate of **218** did not proceed because of the failure of the Dieckmann reaction in this case.[119] Polish workers had earlier obtained analogous results on condensing various 1,3-dienes with racemic 2-methoxy-5-oxo-5,6-dihydro-2*H*-pyran under high pressure.[120]

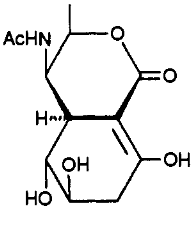
Scheme 41



With these methods in hand Fraser-Reid and Abdur Rahman synthesized the *N*-acetyl derivative **223** of the major part of the antibiotic actinobolin using the 6-deoxy-D-hexose-based enone **221** which, with the appropriate Danishefsky diene, afforded the key intermediate **222** (Scheme 42).[121] Other workers have opened the carbohydrate ring of compound **218** with benzene-1,2-dithiol and titanium tetrachloride to give the dithioacetal **224** from which the cyclohexene carboxylic acid **225** was produced for use in the synthesis of optically pure compactin.[122] A further extension of the work has been to the preparation of benzannelated pyranosides by use of enones like **216** and 1-methoxy-1,3-butadiene which afforded compounds such as **226** which may be aromatized by use of DDQ to **227**.[123]

Scheme 42





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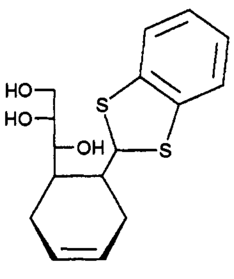

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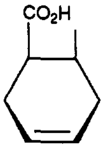

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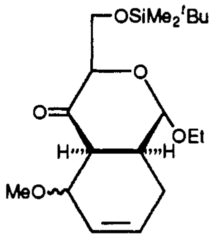

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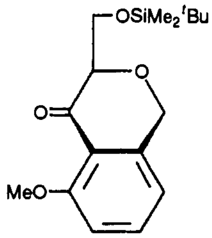
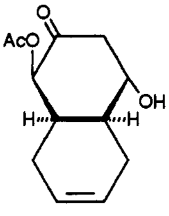
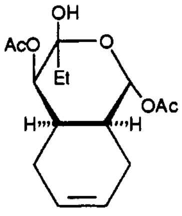


227

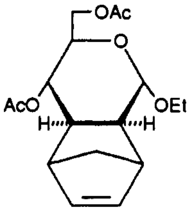
Elimination of hydrogen iodide from C-5–C-6 of the 4-*O*-acetyl-6-deoxy-6-iodo derivative of **218** gave the *exo*-alkene which was rearranged to the ketone **228** (section II.D.1) from which the triol **229**, which represents the AB ring system of *β*-rhodomycinone, was obtained.[124] In the course of this work it was noted that *cis*-fused bicyclic ketones related to **217** epimerize at C-3 to give *trans*-fused products—a matter also noted in closely parallel work which revealed that the double bond of ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-*α*-D-*erythro*-hex-2-enopyranoside is adequately active as a dienophile to accept cyclopentadiene and produce **230** (stereochemistry not fully determined).[125]



228



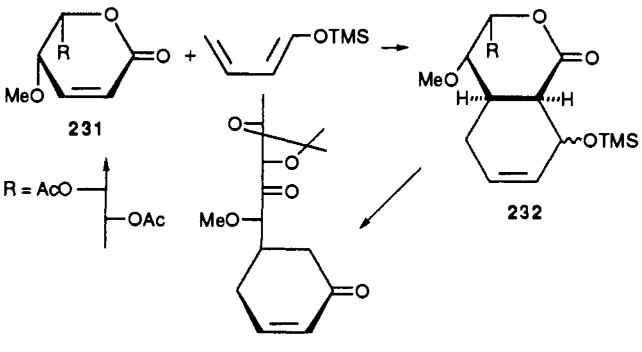
229



230

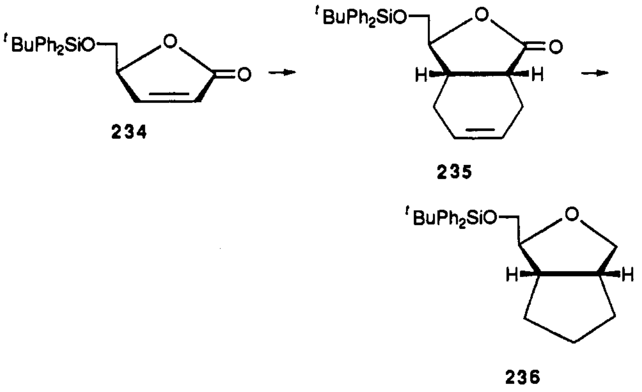
That 2,3-unsaturated aldonic acid lactones can also be employed as dienophiles was shown by Frank *et al.*[126] who treated compound **231**, which was prepared following Wittig extension of 3,4-*O*-isopropylidene-2-*O*-methyl-D-fucal, with 1-[(trimethylsilyl)oxy]butadiene to obtain, in 83% yield, the mixed adducts **232**. From these, a synthon for the aureolic acid aglycon **233** was produced (Scheme 43).

Scheme 43



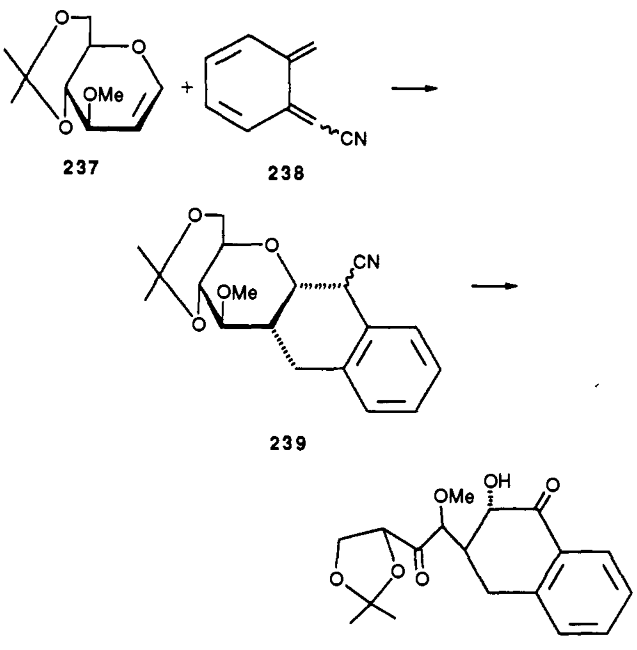
The use of the butenolide **234**, made from D-ribono-*γ*-lactone, to obtain the Diels–Alder adduct **235** and hence the 2-oxabicyclo[3.3.0]octane **236** (Scheme 44) further illustrates the potential of unsaturated carbohydrate lactones.[127]

Scheme 44



1,2-Dideoxyald-1-enopyranose (glycal) derivatives, being vinyl ethers with electron-rich double bonds, are less reactive as dienophiles, but they have been used to prepare benzocyclohexanes from carbohydrates by Franck and John in an elegant synthesis of the model aureolic acid aglycon **240**. Addition of the *o*-xylylene **238** to the D-glucal derivative **237** gave 65% of the epimers **239** (together with isomers formed because of incomplete regio- and stereospecificity) which were converted efficiently into the required **240** (Scheme 45), the key step being an acid-catalyzed elimination β- to the nitrile group which caused opening of the pyranoid ring.[128]

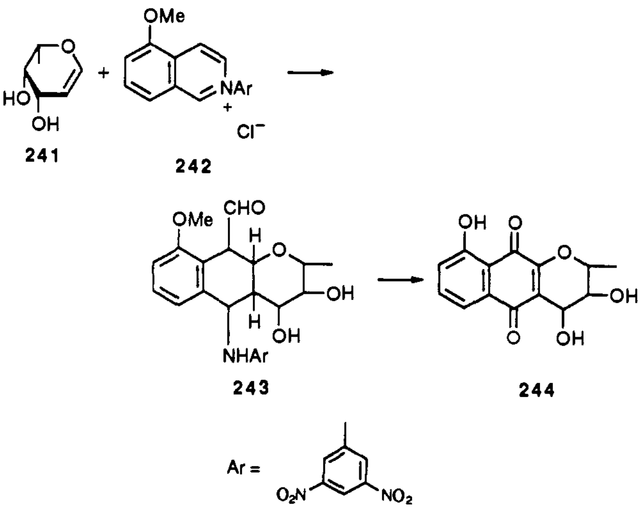
Scheme 45



237 238 239 240

From the same group then came an elegant synthesis of (–)-cryptosporin (**244**) which used L-fucal **241** and the isoquinolinium salt **242** in an application of an inverse electron demand Diels–Alder process. The initial product, which formed at 55–60 °C in methanol, on acid-catalyzed hydrolysis gave 95% of the aldehyde **243** which was converted to **244** in eight steps (Scheme 46).[129] Another synthesis of this compound is referred to in section II.A.6.

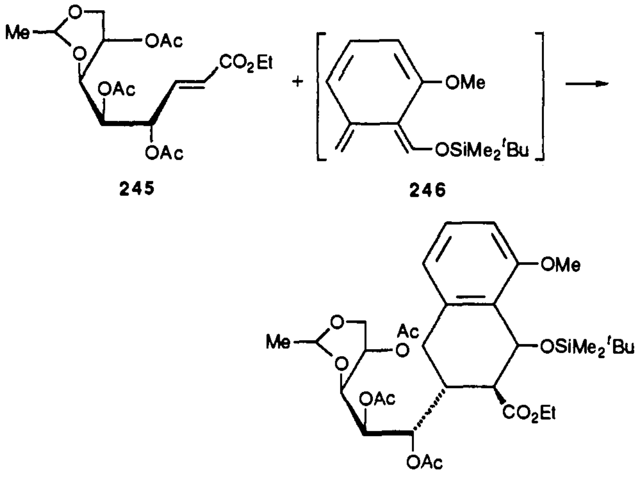
Scheme 46



241 242 243 244

The same group then examined the preferred direction of attack of an *o*-xylylene at double bonds of some acyclic alkenes and concluded that allylic *syn*-oxygen-bonded substituents give rise to unfavorable orbital interactions in the transition state thereby favoring reaction at the face opposite of the oxygen function. In this way the adduct **247** dominanted in the products of reaction of the alkene **245** with **246** which was derived from the corresponding benzocyclobutene (Scheme 47).[130] (See also Scheme 53.)

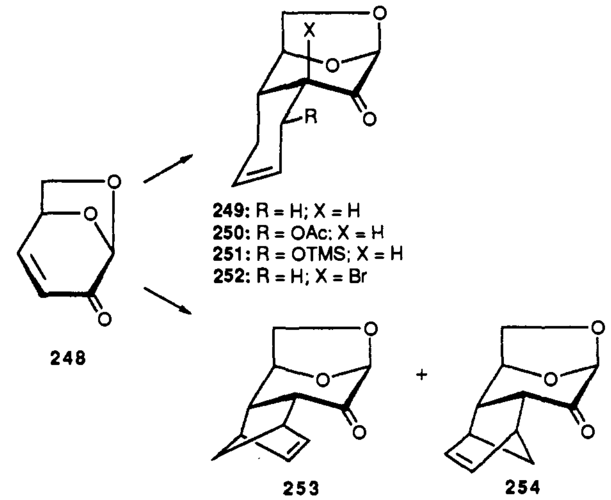
Scheme 47



245 246 247

Considerable attention has been paid to the adducts derived from the cellulose pyrolysis product "levoglucosenone" **248** which have given access to several compounds of value in natural product synthesis. With this enone, *exo* addition of dienes is favored, 1,3-butadiene giving crystalline **249** in 95% yield following reaction at 160 °C.[131] For cyclic dienes the situation is more complex, the alkene group developed during the reaction being able to adopt *exo* or *endo* orientations with respect to the pyranoid ring, and cyclopentadiene giving the isomeric *exo* adducts **253** and **254** in 65 and 16% yield, respectively, following heating together or in boiling chlorobenzene.[131-133] 1,3-Cyclohexadiene, 1,3-diphenylisobenzofuran,[131] and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene[133] also give products of cycloaddition in high yield. Further functionalized derivatives became available by use of modified dienes,

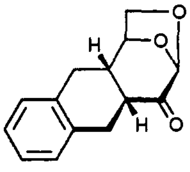
Scheme 48



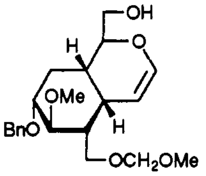
249: R = H; X = H
250: R = OAc; X = H
251: R = OTMS; X = H
252: R = H; X = Br

248 253 254

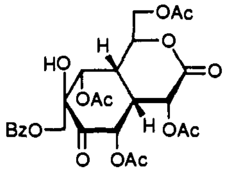
1-acetoxy- and 1-[(trimethylsilyl)oxy]-1,3-butadiene reacting efficiently to afford **250** and **251**, respectively.[134] A bromine atom can be made available at C-3 (compound **252**) by reaction between 1,3-butadiene and 3-bromolevoglucosenone (Scheme 48)[131,135] and the benzannelated product **255** can be made in 53% yield by means of an *o*-xylylene cycloaddition process.[136] From the acetate **250** the advanced reserpine intermediate **256**[134] and the oxadecalone segment **257** of tetrodotoxin[137] have been synthesized, and the gaunidinium portion **258** of the same toxin has been produced from the bromine **252**.[135] *allo*-Yohimban **259** was made in enantiomerically pure form by a 12-step synthesis from the parent adduct **249**.[138]



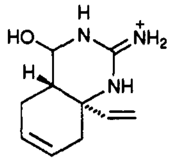
255



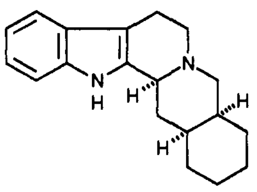
256



257



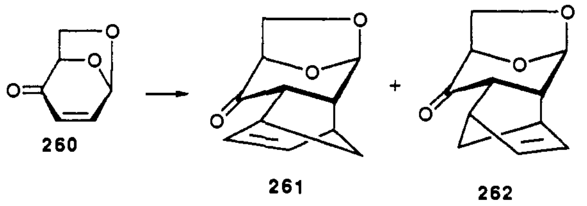
258



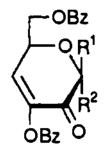
259

Because of its relatively low availability, fewer studies have been carried out on "isolevoglucosenone" (**260**), but when treated with cyclopentadiene, with zinc chloride present as catalyst, it gave both products **261** and **262** of "down" addition in 82% yield and in the proportions 4:1 (Scheme 49).[139]

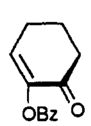
Scheme 49



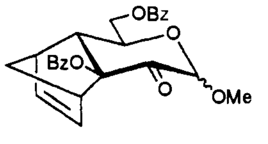
An interesting general observation to come from a comparison of the relative reactivities of pyranoid α,β-unsaturated ketones and carbocyclic analogues was that the former are more reactive as dienophiles in most cases.[140] Similar findings were reported in studies of the addition of cyclopentadiene to four similar enolones including the epimers **263** and **264** which underwent cycloadditions thermally, under high pressure, or with Lewis acid catalysis, while the carbocyclic analogue **265** failed to react. This was attributed in part to the effect of the ring oxygen atoms' lowering of the LUMO of the π systems of the pyranoid rings. Best yields of products and best stereoselectivities were found under high pressure (15 kbar). For example, under these conditions, the α- and β-anomers (**263** and **264**) gave the α-*endo*, α-*exo*, β-*endo*, and β-*exo* adducts **266**, **267**, **268**, and **269** in the proportions 7:7:75:11 and 86:12:1:1, respectively. The latter enolone, having both substituents on the same (β) face of the ring, reacted considerably faster than did its anomer and with higher selectivity. Clearly, the group at the anomeric center played a dominant role in determining the face of the double bond which was approached by the diene.[141]



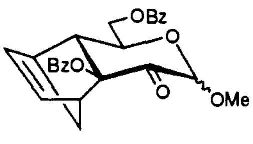
263: R^1 = H; R^2 = OMe
264: R^1 = OMe; R^2 = H



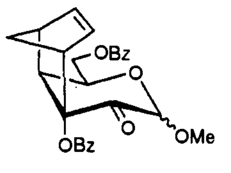
265



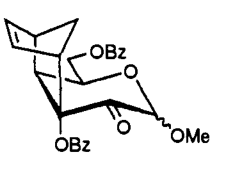
266



267



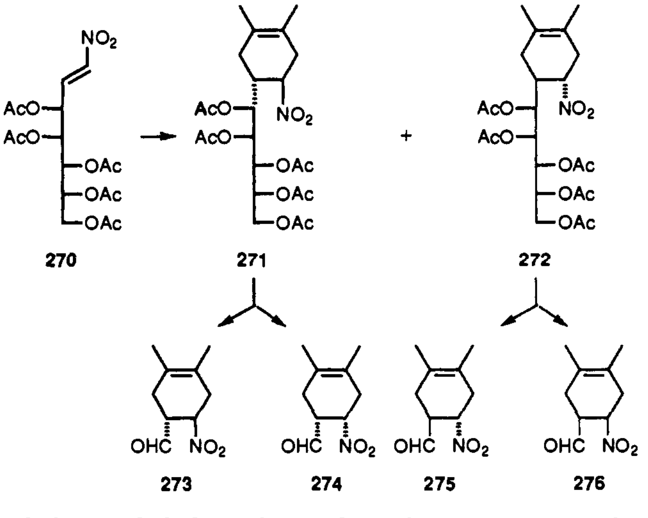
268



269

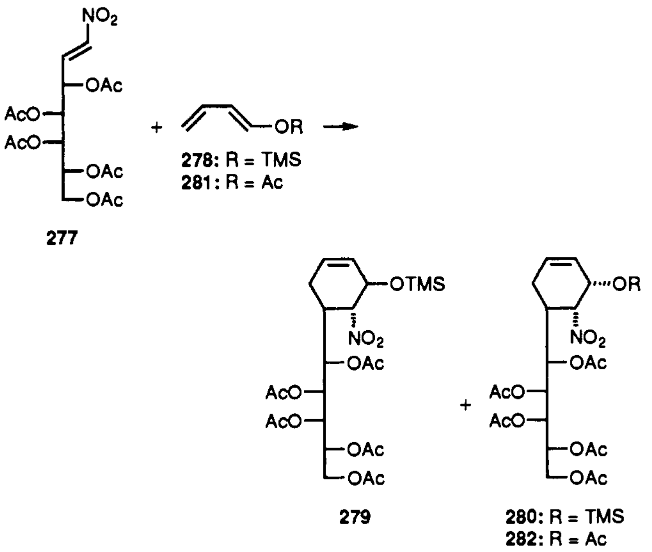
Considerable interest has also been taken in the reactions undergone between acyclic carbohydrate dienophiles and dienes because of the value of the products as sources of relatively simple, but highly functionalized cyclohexanes and (from the adducts produced with cyclopentadiene) cyclopentanes (see section III.C.2.a). For example, reaction of the (*E*)-nitroalkene **270** available from D-mannose, with 2,3-dimethylbutadiene in refluxing toluene gave the *trans*-related adducts **271** and **272** in the ratio 1.9:1. Under acidic conditions each was directly deacetylated, and the resulting polyols were degraded with periodate to give the aldehydes **273** and **275**, respectively. Under basic conditions, however, each adduct partially epimerized and thus afforded access to the isomeric aldehydes **274** and **276**, respectively (Scheme 50).[142] An extension of the work led to the finding that reaction of the D-*galacto*-nitroalkene **277** with 1-[(trimethylsilyl)oxy]-butadiene (**278**) gave the products **279** and **280** of attack of the diene at the *si* face of the dienophile, presumably

Scheme 50



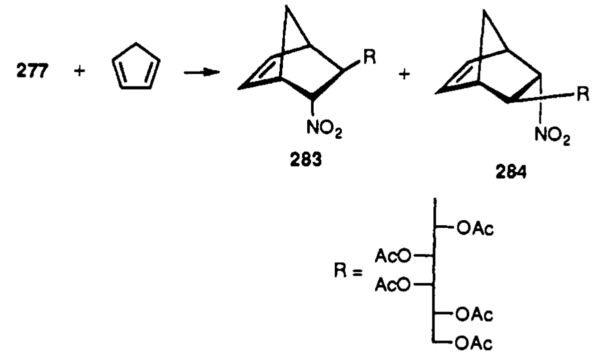
because of the directing effect of the allylic ester group. With 1-acetoxybutadiene (**281**), however, not only is diastereofacial specificity observed, but there is also *endo* specificity, compound (**282**) being the only product observed (75% yield) (Scheme 51).[143]

Scheme 51



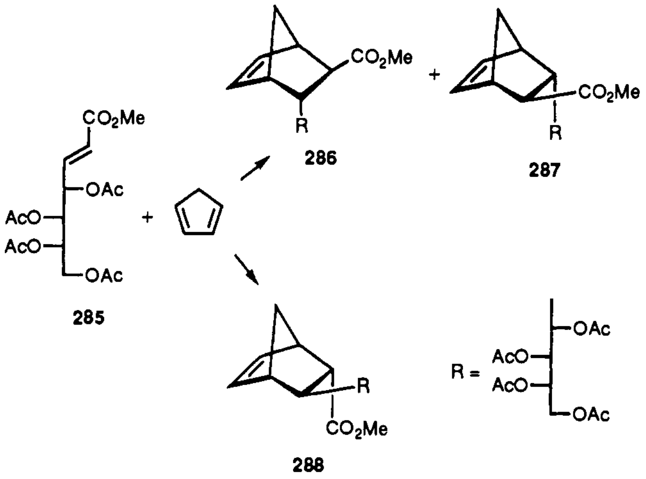
When cyclopentadiene was then used with nitroalkenes **270**, **277**, and the D-*gluco* isomers, all four possible *trans*-related products were formed in each case, compound **277**, for example, giving the nitro-*endo* compounds **283** and **284** (37 ± 2% each) as main products (Scheme 52). The stereochemistries were established by X-ray diffraction analysis of two of the D-*manno* adducts[144] followed by correlations of deacetylation–periodate oxidation products.[145]

Scheme 52



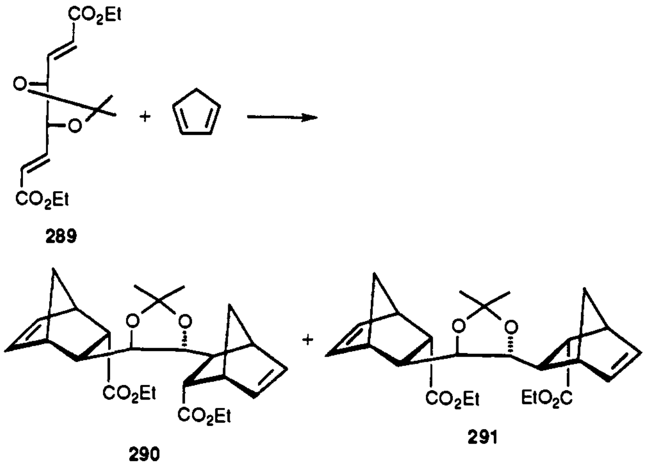
Analogous studies have been carried out by Horton's group using the (*E*)-unsaturated aldonic ester **285**, derived by Wittig extension of 2,3,4,5-tetra-*O*-acetyl-L-arabinose. Again all four *trans*-related adducts were obtained in significant proportions, but compound **286** was isolated in 40% yield, and **287** was formed in 27% yield showing, that in this case, thermal cycloaddition favored the products with the electron-withdrawing group in the *exo* orientation. When this condensation, however, was repeated at 0 °C in the presence of aluminum chloride, the product ratios altered and **288**, with the methoxycarbonyl group *endo*, was produced in 58% yield (36% isolated) (Scheme 53).[146] The work was also carried out with D-arabinose as starting sugar and the enantiomers of **286** and **288** were therefore obtainable,[147] and thus access to all four *trans*-disubstituted norbornenes was gained. The use of compounds derived in this way for the making of cyclopentanes is referred to in section III.C.2.a.

Scheme 53



Consistent with the finding that compound **288** was formed in the presence of aluminum chloride, the D-mannitol-derived **289** gave adducts **290** and **291** (3:2) on treatment with cyclopentadiene in dichloromethane at −20 °C with added diethylaluminum chloride (Scheme 54).[148]

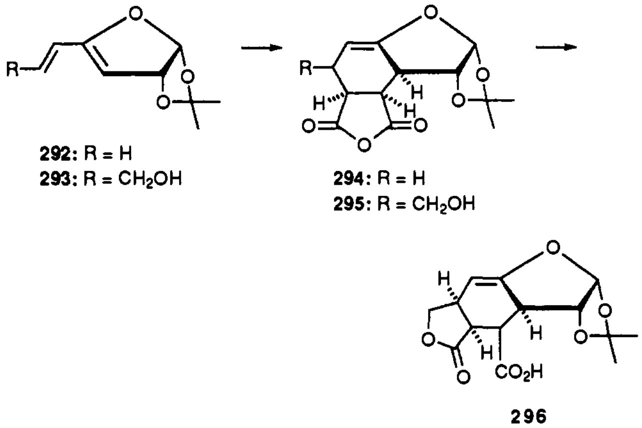
Scheme 54



b. Reactions of Carbohydrate Dienes. This section does not cover Diels–Alder reactions of such compounds as 1,3-butadienyl glycosides in which the diene is not part of the sugar moiety. Elegant work of this type, in which the carbohydrate acts as a chiral auxiliary, has, for example, led to the synthesis of (+)-daunomycinone.[149] (See ref 114 for discussions of the topic).

1,3-Dienes can be produced within normal sugar chains, in extensions of them from the reducing end or from the nonreducing end, or they may involve carbon atoms in branched chains: examples of Diels–Alder reactions dependent on all these diene types have been reported recently. Again Fraser-Reid led the way by noting the efficient addition of maleic anhydride to the hexofuranose derivative **292** to give **294**,[150] and subsequently, on repetition of the reaction with the heptose analogue **293**, the lactone **296** was produced by way of **295** which underwent spontaneous rearrangement

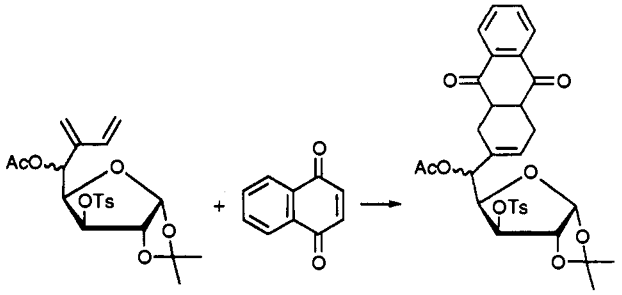
Scheme 55



292: R = H
293: R = CH$_2$OH
294: R = H
295: R = CH$_2$OH
296

(Scheme 55).[151] Extensions of the work have led to cycloadducts derived from a hepturonic ester analogue of **293**,[152] and from heptopyranose dienes akin to **292**.[153] Related studies by Russian workers have employed the dienes **297** and naphthazarin to obtain products **298** (Scheme 56) which are analogues of quinone antibiotics.[154]

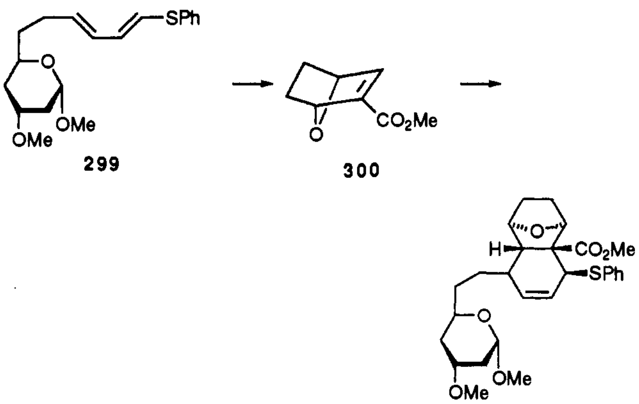
Scheme 56



297 **298**

An elegant example of the use of a chain-extended carbohydrate diene utilized Diels–Alder cyclization of compound **299** made by Wittig extension of an octopyranoside-8-aldehyde and the enantiomerically pure 7-oxabicyclo[2.2.1]heptane ester **300** which gave the *exo* adduct **301** in 70% yield (Scheme 57) in the key

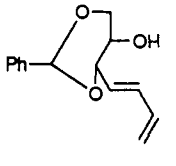
Scheme 57



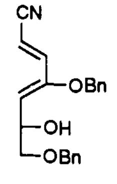
299 **300** **301**

step of a synthesis of the hypocholesterolemic compound (+)-compactin.[155]

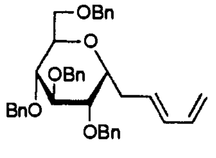
Dienes formed by extensions of sugar chains from the reducing end condensing with dienophiles are as follows: compound **302**, produced by Wittig methylenation of the 2-enal which is readily available from 3-*O*-acetyl-4,6-*O*-benzylidene-D-allal (the products afforded a new synthetic approach to forskolin);[156] nitrile **303**, formed in moderate yield from 2,3,5-tri-*O*-benzyl-D-arabinose on treatment with diethyl (cyanomethyl)phosphonate and base;[157] the *C*-glycosidic product **304** of reaction of 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranose with (*E*)-1-(trimethylsilyl)penta-2,4-diene in the presence of boron trifluoride etherate.[158]



302

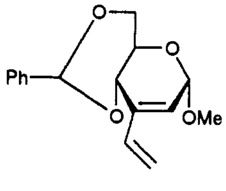


303

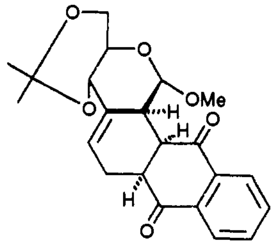


304

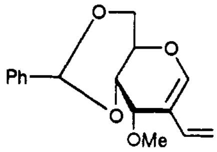
In a study of new means of gaining access to enantiomerically pure anthracyclinones the branched-chain diene **305** was cyclized with naphthazarin and gave 85% of adduct **306** indicating that the allylic substituents in **305** exerted strong directional control over the addition leading mainly to the product of *β-exo* cyclization. Similar results were obtained with maleic anhydride and dimethyl acetylenedicarboxylate; with dimethyl furamarate two products were formed in similar proportions.[159] Other workers obtained analogous results with this diene, and with the isomer of **305** having the vinyl group at C-2.[160] From compound **307** and maleic anhydride the adduct **308** was obtained exclusively and, similarly, the C-3 epimer of **307** gave the product with new rings fused *anti* to the methoxy group.[161]



305



306



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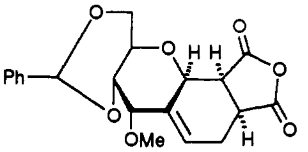


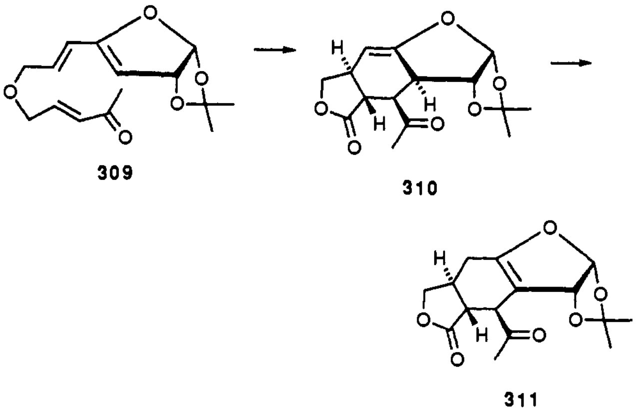
308

c. *Intramolecular Reactions.* Few, if any, examples of such processes had been reported for carbohydrate derivatives by the mid 1980s when the general topic of intramolecular Diels–Alder reactions was extensively reviewed,[162] but since then several instances have been described which illustrate the powerful synthetic potential of the approach. In some cases the dienophiles or one of the diene double bonds of the dienes were within carbohydrate rings; in others fully acyclic compounds have been cyclized by the process, two new rings being formed in all such cyclizations.

The earliest example of this type of process applied to a carbohydrate derivatives was again provided by

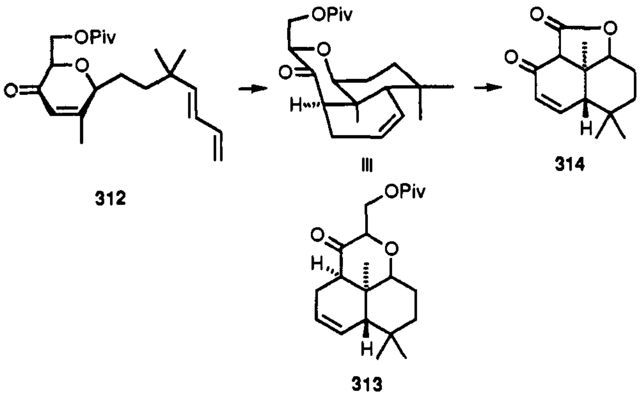
Fraser-Reid's group who showed that the unsaturated ester **309** of a heptose-based diene underwent cyclization initially to give mainly the product **310** derived from the *anti-β*-face transition state. This initial product, under the conditions of the reaction, underwent rearrangement to the isomer **311** having the double bond within the furanoid ring (Scheme 58).[163]

Scheme 58

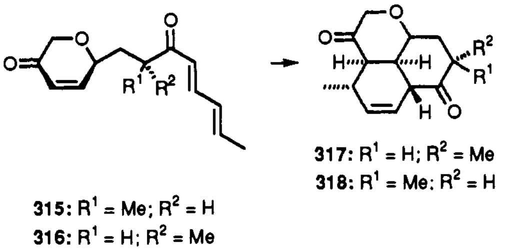


From the same group then came a report of the value of this approach in the synthesis of functionalized *trans*-decalins illustrated by the preparation of **314**, an advanced intermediate in the synthesis of forskolin. Heating of the *C*-glycosidic enone **312** in refluxing xylene for 48 h caused 30% conversion to the *trans*-decalin **313** derived by way of the *cis-anti* transition state.[162] (The enone **312** was made from an alkyne produced following addition of lithium acetylide to the carbonyl group of tetra-*O*-benzyl-D-glucono-δ-lactone.) Sodium chromate then caused allylic oxidation to the enone and concurrent Baeyer–Villiger-like oxygen insertion in the –C(=O)–C–O– sequence of the pyranoid ring to convert it to –C(=O)–O–C–O–. On treatment with sodium methoxide in methanol the product collapsed to the simple lactone unit of **314** (Scheme 59).[164]

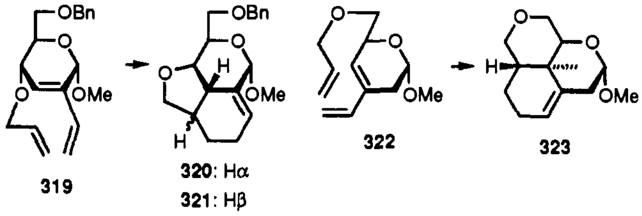
Scheme 59



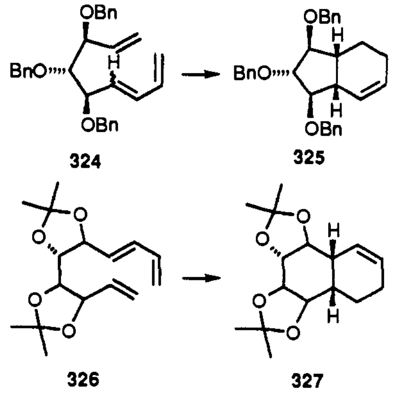
In parallel studies French workers isolated single, crystalline products **317** and **318** of the separate thermal cyclizations of the epimers **315** and **316** which had been produced from 3,4-di-*O*-acetyl-L-arabinal. As for compound **313**, **317** and **318** were derived from the *cis-anti* transition state.[165]



In the case of the allyl ether **319**, in which the diene is partly within a pyranoid ring, the epimers **320** and **321** were produced (80%) in the ratio 3:1, the lack of stereospecificity being apparently consequent upon the adoption of the *cis-syn* as well as the *cis-anti* transition state. On the other hand **322** gave the expected **323**, exclusively, but when an ethyl fumaroyl ester group was used in place of the allyl ether of **322**, epimerized products were isolated.[166]



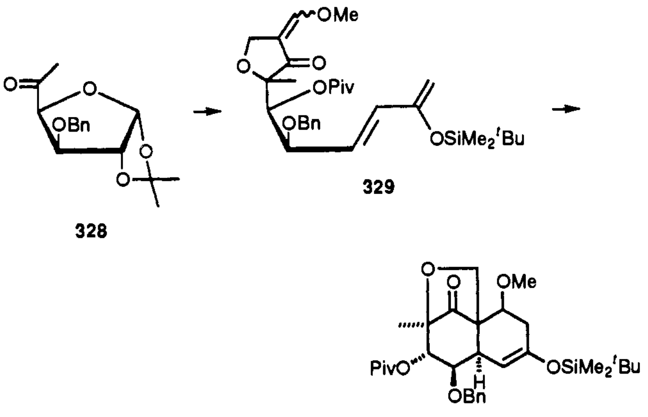
In the area of acyclic compounds that contain both a diene and a suitably situated dienophile in the same carbon chain, carbohydrate structures can be incorporated in a largely unmodified form or after major alteration. In the first category come the mixed isomers **324**, synthesized from 2,3,4-tri-*O*-benzyl-D-xylose by successive Wittig extensions from each terminal carbon atom, which gave **325** in 83% yield on heating in toluene at 160 °C, suggesting that thermal interconversion of isomers occurred either before or after cyclization.[167] Continuation of the work revealed that both the (*E*)-**326** and the (*Z*)-isomer of the D-glucose-based deca-1,3,9-trienitol gave the corresponding *cis*-decalin **327** and in this case it was shown that thermal isomerization of the (*Z*)-isomer occurred prior to cycloaddition.[188]



A much more complex application was to the synthesis of **330**, a compound closely related to the bitter principal quassimarin. From the D-glucose-based ketone **328** the multifunctionalized **329** was synthesized in 10 steps commencing with highly selective 1-lithio-3,3-diethoxypropyne addition to the carbonyl group. *Cis-anti* cyclization of **329** with the aid of trimethylaluminum gave the required **330** in 62% yield (impressively 24% from **328**) (Scheme 60).[169]

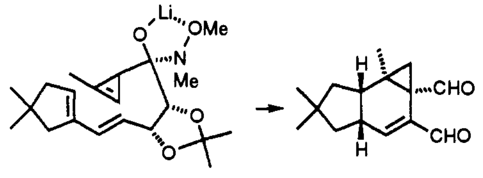
Other examples of natural products synthesized from carbohydrate-derived substrates are the antibiotic (+)-

Scheme 60

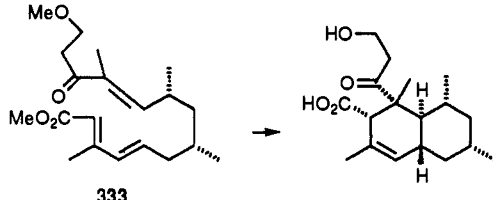


328 329 330

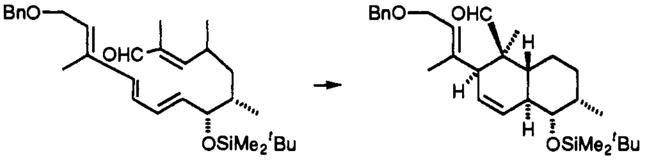
isovelleral **332** by way of the intermediate **331** (from 2,3-*O*-isopropylidene-L-erythruronic acid);[170] the mycotoxin diplodiatoxin **334** from **333** which was elaborated from methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-α-D-allopyranoside;[171] and the fragment **336** of tetronolide from **335** and, initially, methyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose and hence methyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-2,4-di-*C*-methyl-D-*lyxo*-hexopyranoside.[172]



331 332



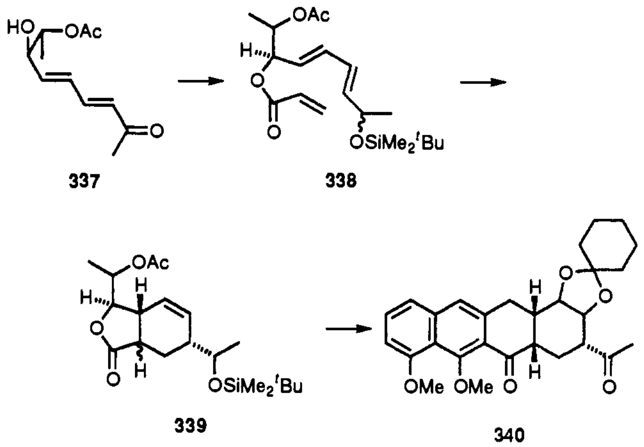
333 334



335 336

A further use of the approach utilized a carbohydrate diene and the double bond of an introduced acrylate ester. Di-*O*-acetyl-L-rhamnal served as a means of preparing the dienone **337** which was converted to the acrylate and reduced, and the resulting alcohol was silylated to give **338** which, on heating in toluene at 210 °C for 3 days, gave mixed epimers **339** (Scheme 61) and an isomer with alternative configuration at the allylic branching center in the ratios 2.5:2.5:1. Treatment with base of the *trans* isomer of **339** caused isomerization to the more stable *cis*-fused compound which was then converted to **340**, a close relative of the aglycon of the anthracycline antibiotic (−)-pillaromycin A.[173]

Scheme 61



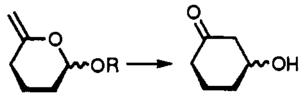
337 338 339 340

D. Cyclizations Involving Organometallic Intermediates

The treatment of cyclizations proceeding by way of organomercury intermediates might have been presented with carbanionic processes in section II.A. It is given here be consistent with section III.D.

1. Cyclizations Involving Organomercury Intermediates

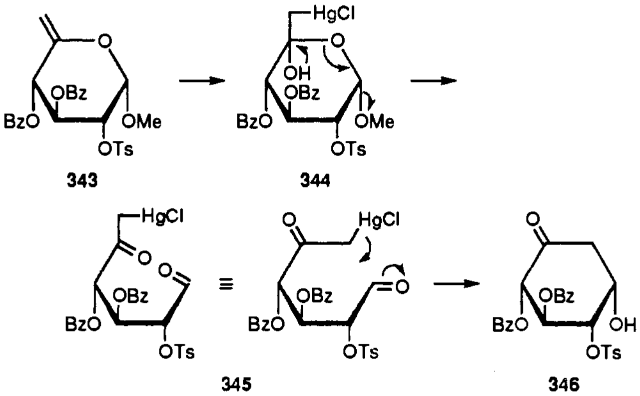
A convenient procedure for converting carbohydrate derivatives into cyclohexanone analogues (in outline **341** → **342**) was first observed when the alkene (**343**) was treated in refluxing aqueous acetone in the presence of a molar equivalent of mercury(II) chloride.[7] Under these mild conditions the rearrangement reaction was complete in 4.5 h and the product **346** crystallized from the cooled reaction solution. The yield was 83%, and this figure was increased to 89% on replacement of the chloride reagent by mercury(II) acetate.[174]



341 342

In the course of the reaction, regiospecific hydroxymercuration of the vinyl ether component of **343** occurs to give the unstable hemiacetal **344** which loses methanol to afford the dicarbonyl intermediate **345**. This then takes part in an aldol-like, intramolecular cyclization to give the cyclohexanone **346** (Scheme 62).

Scheme 62

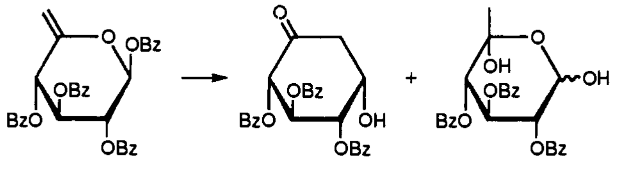


343 344 345 346

Compound **345** exists in aqueous media in the hydrated, cyclic form from which it can be isolated by removal of water. After such isolation, and on treatment with hydrogen sulfide to activate the methylene carbanion, it undergoes similar cyclization to give **346** (67% isolated).[174]

In a closer study of the reaction, the tetrabenzoate **347** gave the analogous ketone **348** (mercury(II) chloride; 55% yield after chromatographic separation) together with the cyclic diol **349** (Scheme 63) which was assumed to arise by hydrolysis of the mercury-containing analogue of the intermediate **345**. Since such hydrolysis would be subject to acid catalysis, it became desirable to carry out the cyclization by use of a mercury salt that would not give a strong acid as byproduct, and in consequence, mercury(II) acetate was assessed as cyclizing reagent and it gave the product **348** in 93% yield. Several related cyclizations were likewise facilitated by use of this salt.[174]

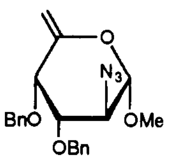
Scheme 63



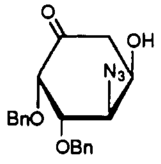
347 **348** **349**

Consistent with the reaction path outlined in Scheme 62, 6-deoxyhex-5-enopyranosyl compounds undergo methoxymercuration to give acetals at C-5 which hydrolyze under acid conditions to afford the hydroxycyclohexanones.[175] Similar hydrolysis of the initial alkenes, however, results in extensive formation of 6-deoxyhexos-5-ulose derivatives following protonation rather than mercuration at C-6,[176] thus showing that the mercury-containing intermediates are required for efficient carbocyclization.

Contrary to the supposition that mercury salts of weak acids best facilitate the reaction, mercury(II) trifluoroacetate proved appreciably more effective than mercury(II) chloride in converting the azidoalkene **350** into cyclohexanone **351** in aqueous acetone even at room temperature,[176] and a further valuable alternative procedure involves the use of catalytic amounts of mercury(II) sulfate in 1,4-dioxane containing aqueous sulfuric acid at 60–80 °C.[177] Under these conditions the cyclizations proceed (presumably by way of species analogous to **345**) to give the cyclohexanones and regenerate active inorganic mercury species. By this means the 3-tosylate **352** was converted into the expected product **353** in 72% yield, whereas, with mercury(II) chloride, *p*-toluenesulfonic acid was eliminated and the enone **354** was isolated in poor yield as the only product (Scheme 64).[177] An example has been reported of the use of the mercury(II) sulfate method to convert a methyl 3-amino-2,3,6-trideoxy-α-D-*erythro*-hex-5-enopyranoside derivative into the corresponding cyclohexanone in quantitative yield.[178]

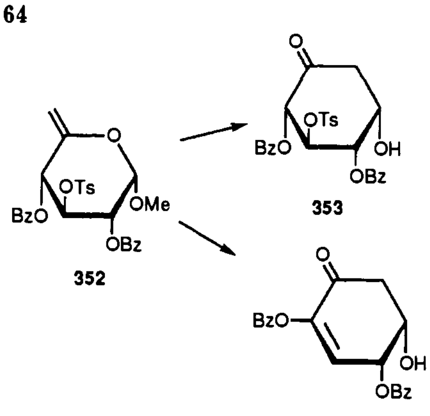


350



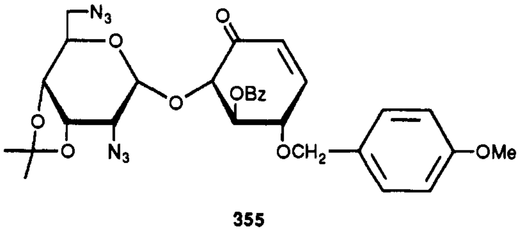
351

Scheme 64

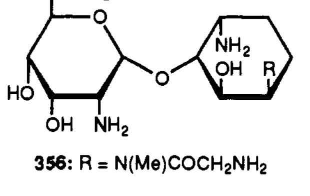


A later study of the reaction[179] was aimed at further minimizing the severity of the conditions and at reducing the proportions of mercury salt used, and thus alleviating reported problems associated with the occurrence of side reactions[177,178] and with product isolation.[176] It was established that mercury(II) chloride, oxide, acetate, and trifluoroacetate, used in catalytic quantities (0.1 mol equiv), all enabled the reaction of methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside (Table 1, entry 6) to proceed effectively even at room temperature, the trifluoroacetate requiring a few hours to permit the reaction to go to completion, the chloride and acetate requiring a few days, and the oxide more than one week. Mercury(II) trifluoroacetate used in 10% molar proportions emerged as a very efficient reagent; subsequent reports record its use at concentrations even down to 1 mol %.[180,181]

While some of the carbocyclic products available by this method (e.g. tosylate **353**) have leaving groups which take part in elimination reactions to give conjugated enones with particular ease, all products of the reaction have hydroxyl groups that can lead to enones formed by the alternative β-elimination procedures. Products of elimination of this kind have been formed when the ring closure processes have been carried out under conditions more vigorous than those required to cause ring closure (e.g. **352** → **354**),[177] or by induction of elimination by rendering the hydroxyl groups of initial products more susceptible by methanesulfonylation[182-184] or acetylation.[173,175,185] Enones derived by this type of elimination reaction are readily available and are of considerable synthetic value, the antimicrobial amino-

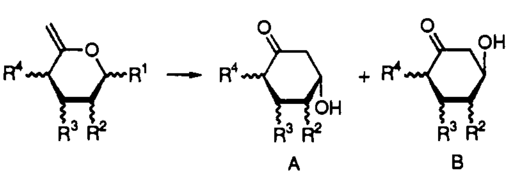


355



356: R = $N(Me)COCH_2NH_2$

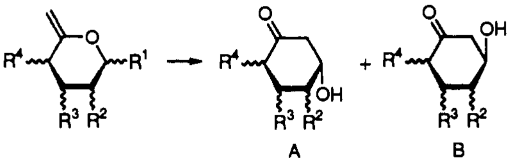
Table 1. Functionalized Cyclohexanones from 6-Deoxyhex-5-enopyranosyl Derivatives[a]



					yield (%)		
entry	R1	R2	R3	R4	A	B	ref(s)
1	OMe(b)	OTs(b)	OBz(a)	OBz(b)	89		174
2	OMe(a)	H	OBz(a)	OBz(b)	82		187
3	OMe(b)	H	H	OBz(b)	24	18	187
4	OMe(b)	OBn(b)	OBn(a)	OBn(b)	68[b]	17	185, 194
5	OMe(b)	OBn(b)	OBn(a)	OAc(b)	68[b]	17	199, 200
6	OMe(b)	OBn(b)	OBn(a)	OAc(b)	85	11	179
7	OMe(b)	OBn(a)	OBn(b)	OAc(b)	16	64	179
8	OMe(b)	OBn(b)	OBn(a)	OAc(a)	72	18	179
9	OMe(b)	H	OCH_2OMe(b)	OBz(b)	4	82	179
10	OMe(b)	OBz(b)	OTs(a)	OBz(b)	72		177
11	OMe(b)	OBz(b)	OBz(a)	OBz(a)	99		177
12	OMe(b)	OMe(b)	OMe(a)	OBz(a)	73		177
13	OMe(b)	OBz(a)	OBz(a)	OBz(b)	83		177
14	OMe(b)	OMe(a)	OMe(b)	OBz(b)		50	177
15	OMe(b)	H	OMe(a)	OBn(b)	70[b]	14	184
16	SPh	OMeBn(b)	OBn(a)	[c](b)	67		185
17	OAc(a)	OAc(b)	OAc(a)	[d](b)	83		198, 201
18	OBz(a)	OBz(b)	OBz(a)	OBz(b)	93		174
19	O(b)-$C(CH_3)_2$-O(b)		O(a)-$C(CH_3)_2$-O(a)		40		202

[a] The notations a and b relating to the substituents imply that they are, respectively, above or below the rings in the Haworth perspective formulae. [b] Epimers were not separated. [c] 2,6-Diazido-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-allopyranosyl. [d] Tetra-*O*-acetyl-α-D-glucopyranosyl.

Table 2. Functionalized Cyclohexanones from Amino-6-deoxy-hex-5-enopyranosyl Derivatives[a]



					yield (%)		
entry	R1	R2	R3	R4	A	B	ref(s)
1	OMe	NHAc(b)	$OCHMeCO_2Bn$(a)	OAc(b)	90(52)[b]	10	189
2	OMe(b)	BnNCbz(b)	OBn(a)	OBn(b)	66	9	189
3	OMe(b)	NHCbz(b)	OBz(a)	OBz(b)	71		191
4	OMe(b)	NHBz(b)	OBz(a)	OBz(b)	36		197
5	OMe(b)	BnNCbz(b)	OBn(a)	OBn(b)	75		192
6	OMe(b)	BnNCbz(b)	OBn(a)	MeOBn(b)	75		192
7	OMe(b)	NHBz(b)	OAc(a)	OAc(b)	68		175
8	OMe(b)	N_3(a)	OBn(b)	OBn(b)		75	176
9	OMe(b)	H	N_3(a)	OBz(b)	82		187,191
10	OMe(b)	H	NHBz(b)	OBn(b)		100	178
11	OMe(a)	H	NHBz(b)	OBz(b)		81	187
12	OMe(a)	H	$NHCOCF_3$(b)	OBz(b)		86	187

[a] The notations a and b relating to the substituents imply that they are above or below the rings in the Haworth perspective formulae. [b] Isolated yield.

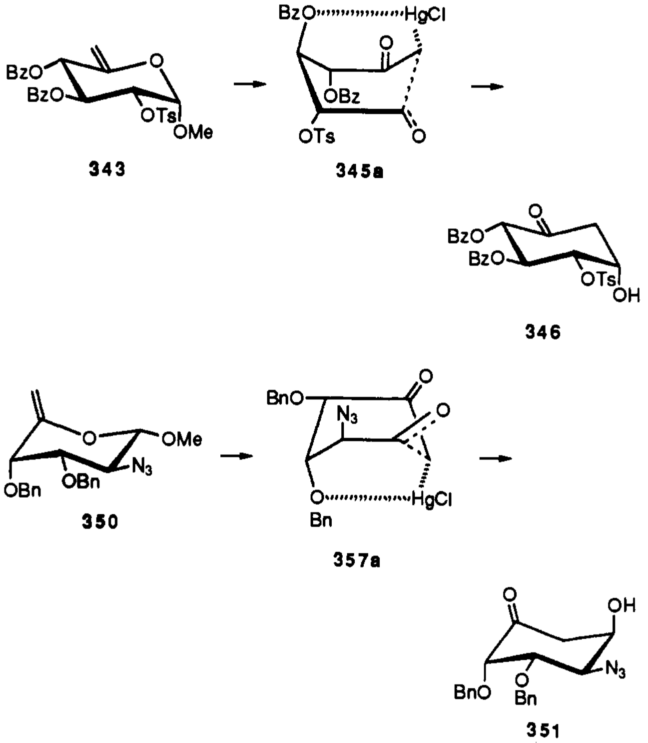
glycoside pseudodisaccharide **356**, for example, having been prepared from the maltose-derived enone **355**.[185]

In Table 1 results obtained by carrying out this rearrangement reaction on simple 6-deoxyhex-5-enopyranosyl compounds are listed, while Table 2 records similar data relevant to analogous alkenes derived from amino sugar derivatives. Particular interest in the products of the reaction of the latter alkenes stems from the occurrence of inosamines and related hydroxylated cyclohexylamine derivatives as components of many aminoglycoside antibiotics and other natural products.[186]

A notable feature of the mercury(II)-induced reaction, clearly apparent from Tables 1 and 2, is the high stereoselectivity shown in the great majority of cases. Commonly, single diastereoisomers are isolated in high yield as the only recorded products, and the process has, on occasion, been considered to be stereospecific. Tables 1 and 2 indicate that this is not, however, a good generalization, but it can also be noted that the few cases in which minor isomers have been recorded all involve compounds with ether groups at C-3 of the starting materials. Whether this is a significant factor remains to be established.

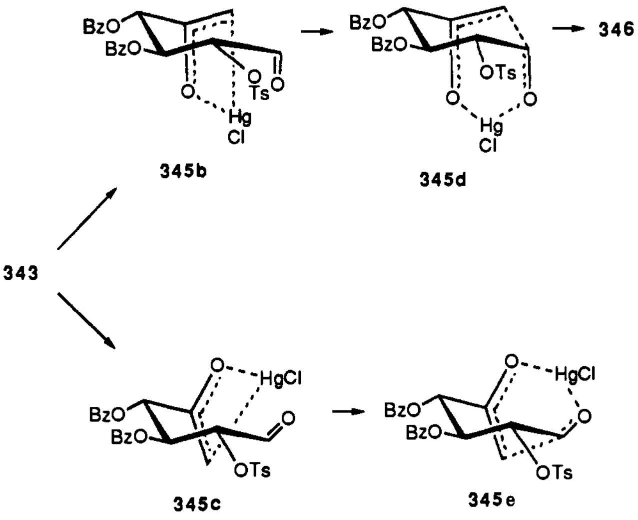
First attempts to rationalize the high stereoselectivity of the ring closure reaction proposed a dependence of the configurations at the generated alcohol centers on the preferred conformations of the unsaturated starting materials,[177] but it was later recognized that there is a strong correlation between the orientations of hydroxyl groups in the preponderant products and those at the β positions to them—i.e. at C-3 of the carbohydrate starting materials. Thus the generated hydroxyl groups and the C-3 substituents are *trans* related to each other[187] (e.g. compounds with R^3 above the plane of the ring—designated a in the tables—give products designated A). Rationalization for this, involving coordination between the mercury atoms of the intermediates (e.g. **345**) and the electronegative substituents at C-3, by which the aldehydo groups are constrained in *exo* orientations and the C-6 nucleophiles are required to attack from the directions shown, is illustrated in Scheme 65. According to this hypothesis, therefore, compound **343** gives **346** by way of the transition state **345a**; likewise, compound **350** (Table 2, entry 8) gives **351**, with the alternative configuration at the new asymmetric center, by way of **357a**.

Scheme 65

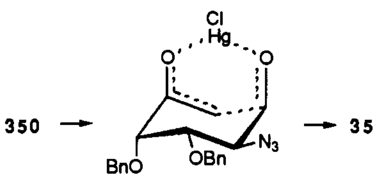


A third hypothesis, which is developed somewhat here, invokes coordination between the mercury atoms of intermediates and the oxygen atoms of the aldehydic groups while retaining features of the conformations of the starting alkenes. In the case of compound **343** the C-5–C-6 portion of intermediate **345** has mercury enolate character which can be represented in the rotamers **345b** and **345c**, both allowing access of C-6 to C-1—particularly when the delocalization is extended to involve the aldehydic oxygen atom (**345d** and **345e**). Of these transition states the former (having a chair conformation) is favored with respect to the latter (a boat) and determines the main reaction product **346** (Scheme 66).[188] This interpretation, which in effect rationalizes the initial conformational correlation,[177] has considerable appeal, but, on the basis of current evidence, does not negate that represented in Scheme 65 and means of choosing between them is awaited with interest. Apparently the only evidence currently available comes from unpublished work on fused ring systems. It favors the conformational/carbonyl coordination hypothesis and is mentioned briefly at the end of this section. Applied to compound **350**, the new hypothesis[188] proposes that **357b** represents the transition state adopted in passing from the $^1C_4$ chair starting material to **351** (Scheme 67).

Scheme 66



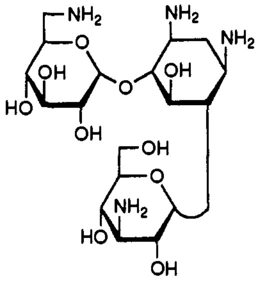
Scheme 67



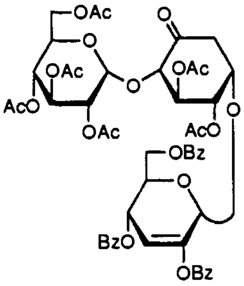
357b

Because of the major significance of highly functionalized cyclohexane derivatives in several groups of bioactive substances, this rearrangement reaction has been put to practical use on several occasions. 2-Deoxystreptamine, for example, which occurs extensively in glycosylated forms in many aminoglycoside antibiotics, e.g. kanamycin A (**358**),[186] and related amino- and diaminocyclohexane compounds, have been synthesized in the course of studies of these medicinals by performing the rearrangement reaction on aminohexose alkenes,[175,176,178,183,189–193] or by aminating cyclohexanone products[182,194–196] or both.[197] Compound **356** indicates the type of relevant aminated carbadisaccharide derivative that is available by the application of the reaction to an unsaturated disaccharide derivative,[185] and the unsaturated **359**,[198] prepared by glycosylation of a maltose-derived glucopyranosylcyclohexanone, suggests an approach to compounds akin to kanamycin A (**358**) and related antibiotics.

In a similar fashion, the structural similarity of the cyclohexanone derivatives obtainable by the "mercury method" to "carba-pyranoid" sugars, i.e. sugar-like cyclohexane derivatives having the ring oxygen atoms replaced by methylene group,[204] has led to the synthesis of several carbahexoses[178,193,199,203,205,206] which are of

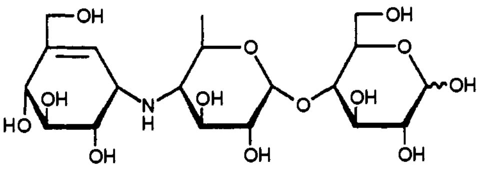


358

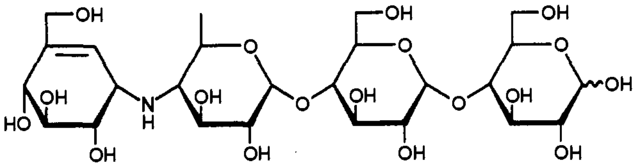


359

considerable interest as enzyme inhibitors. Thus, for example, the carba trisaccharide glucosidase inhibitor **360**, related to the naturally occurring α-glucosidase inhibitor acarbose (**361**), has been prepared.[205]



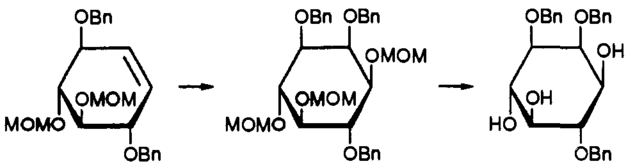
360



361

Of particular interest has been the application of the method to the preparation of derivatives of inositols themselves—especially some from which *myo*-inositol 1,4,5-triphosphate, the intracellular secondary messenger in many signal transduction processes, can be made. The first approach involves *cis* hydroxylation of the double bond of compound **362**, made following sodium borohydride–cerium trichloride reduction of the carbonyl group of the enone produced by normal methods. Selective benzylation was effected by way of a tin-containing intermediate to give access to the fully substituted **363** from which the acetal groups were removed to afford 2,3,6-tri-*O*-benzyl-*myo*-inositol (**364**, Scheme 68), an ideal precursor for the desired triphosphate.[207]

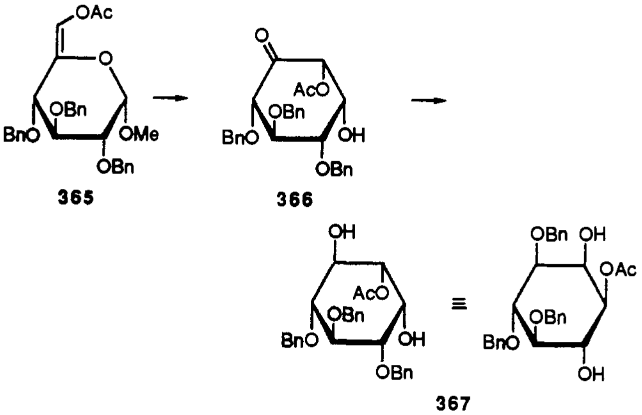
Scheme 68

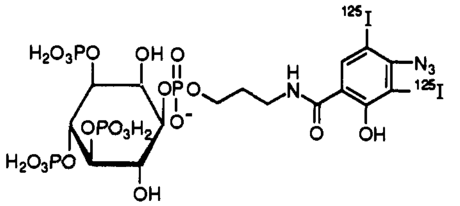


362 **363** **364**

In the second approach two other reports described, for the first time, application of the mercury salt method to hex-5-enopyranosyl compounds, i.e. alkenes bearing oxygen substituents at C-6 and made from the corresponding 6-aldehydes. These underwent cyclization in the normal way to give inosose derivatives rather than deoxy analogues and afforded more direct access to inositols. For example, the (*Z*)-alkene **365**, prepared by Bender and Budhu with 95% stereoselectivity from the corresponding aldehyde by treatment with acetic anhydride and potassium carbonate in hot acetonitrile, with mercury(II) trifluoroacetate in aqueous acetone at 0 °C, gave 85% of cyclized products comprising 85% of compound **366** and 15% of the epimer with the equatorial hydroxyl group. A total of 59% of the main product **366** was isolated by chromatography, and this was reduced with complete specificity to the *myo*-D-inositol derivative **367** by use of sodium triacetoxyborohydride (Scheme 69).[208] Similar results were obtained by Estevez and Prestwich using *p*-methoxybenzyl protecting groups, and they proceeded to make *myo*-D-inositol 1,3,4,5-tetrakis(phosphate) with the ester group at C-1 "tethered" to a radioiodinated photoaffinity label (**368**).[209]

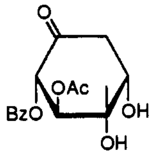
Scheme 69



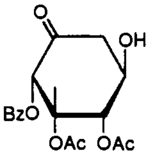


368

The occurrence in nature of *C*-methylcyclitols, e.g. laminitol, has led to application of the mercury-based reaction in this area.[210] Thus, compounds **369**–**371** (and several related ketones) were made from the corresponding branched methyl 6-deoxyhex-5-enopyranosides with 70%, 83% and 45% yields, respectively.



369



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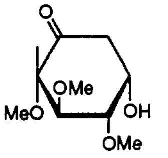
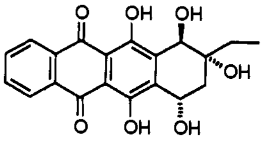


371

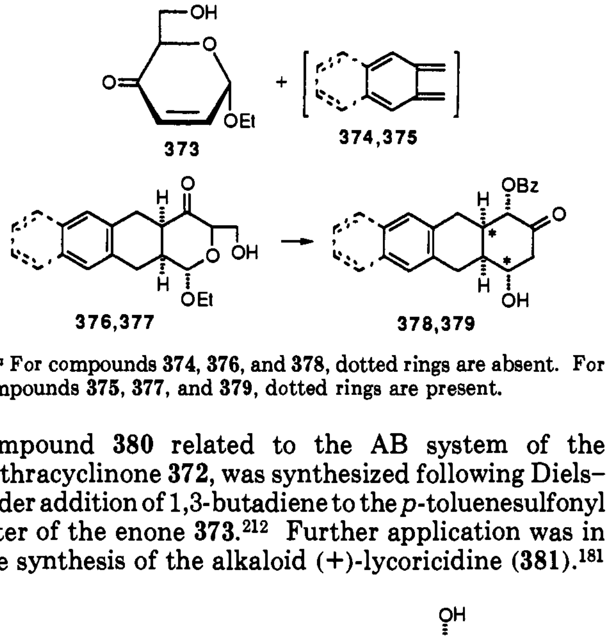
Consistent with both the O-1 and the O-3 coordination hypotheses (see above), the first two products have the hydroxyl group at the new asymmetric center *trans* related to the ester group at C-3, while no strong selectivity was shown with compound **371** which was formed together with 36% of its epimer. This again may suggest that ether groups at C-3 have less mercury(II) coordinating effect, and hence less directing influence, than do ester groups, but it does not appear to help choose between the two main hypotheses.

Extensions of the use of the reaction can give access to highly functionalized components of non-carbohydrate compounds such as the anthracyclinone β-rhodomycinone (**372**). Thus, the *o*-xylylenes **374** and **375**, generated from the corresponding dibromides by treatment with zinc dust in an ultrasonic field, underwent cycloaddition reactions with the D-glucose-derived enone **373** to give adducts **376** and **377**, respectively, from which the tri- and tetracyclic **378** and **379** were obtained following reduction of the carbonyl groups, conversions of the hydroxymethyl groups to *exo*-alkenes, and application of the mercury rearrangement reaction, (Scheme 70).[211] In closely related work, compound **380** related to the AB system of the anthracyclinone **372**, was synthesized following Diels–Alder addition of 1,3-butadiene to the *p*-toluenesulfonyl ester of the enone **373**.[212] Further application was in the synthesis of the alkaloid (+)-lycoricidine (**381**).[181]

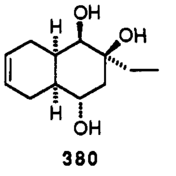


372

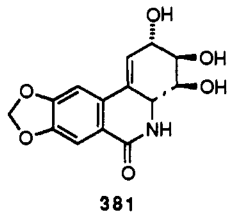
Scheme 70[a]



[a] For compounds **374**, **376**, and **378**, dotted rings are absent. For compounds **375**, **377**, and **379**, dotted rings are present.



380

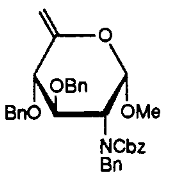


381

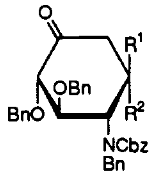
The isolation of compounds **378** and **379** in 68 and 65% yield, respectively, from the corresponding 5-enopyranosides and of 70% of the isomer of **378** having altered stereochemistries at the asterisked centers from the alkene derived from the *trans*-fused C-3 (carbohydrate numbering) epimer of compound **376**,[213] allow further comment on the stereochemistry of the cyclization process. In these cases (at least) the selectivities exhibited depend on factors other than coordination of the inorganic species of mercury-containing intermediates to electronegative substituents at C-3 (carbohydrate numbering) of the starting materials, and therefore conformational factors, with probable coordination involving the carbonyl groups, are indicated as the features upon which the stereochemistry depends.

2. Cyclizations Promoted by Palladium(II) Salts

S. Adam first reported that the cyclohexanone synthesis from 6-deoxyhex-5-enopyranosyl derivatives, which is normally carried out by use of mercury(II) salts (section II.D.1), can be effected with catalytic amounts of Pd(II) salts in the presence of aqueous sulfuric acid.[214] While the mechanism of the palladium-promoted process is not known in detail, it gives similar, but not identical, results to that undergone in the presence of mercury(II) compounds. Compound **382** thus afforded 70% of the products **383** and **384** in the ratio 3:2 when heated at 80 °C for 45 min with palladium chloride (0.2 mol equiv) in dioxane–aqueous sulfuric acid, while 75% of these products were isolated following use of mercury(II) sulfate (0.027 mol equiv) under the same conditions for 3 h; the ratio of products, however, was 7:1 (Table 2, entry 2).[189] Initial evidence that some applications of the palladium method can lead to products with good stereoselectivity (and other to enones) has appeared.[338]



382

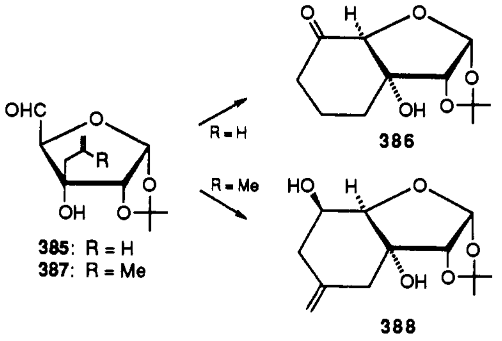


383: $R^1 = H$; $R^2 = OH$
384: $R^1 = OH$; $R^2 = H$

3. Cyclizations Promoted by Rhodium(I) Compounds

5-Hexenals, when treated with rhodium(I) compounds, undergo "hydroacylation" to give methylcyclopentanones. It was therefore expected that the *C*-allyl-D-ribose derivative **385** (R = H) would afford access to a highly functionalized cyclopentane. Instead, the cyclohexanone **386** was obtained in 60% yield by use of catalytic amounts of $[(Ph_3P)_2RhCl]_2$ in dichloromethane under 1 atm of ethylene at 25 °C. A similar result was obtained with the analogue bearing a methyl group at C-1 of the branching substituent, but when a methyl group was present at C-2′ (**387**), an ene reaction occurred to give compound **388** (Scheme 71).[215]

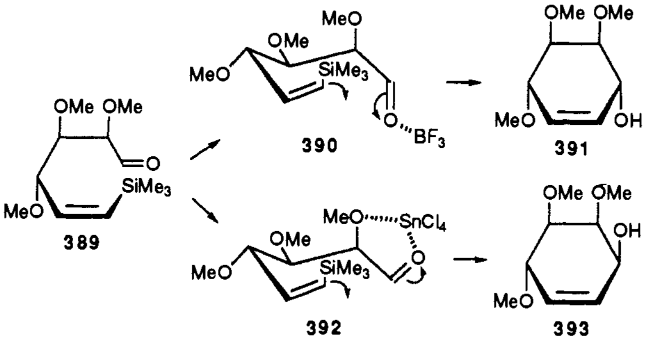
Scheme 71



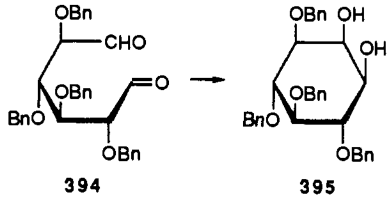
E. Other Reactions

A cyclization process akin to many of the carbanionic reactions described in section II.A.3.a, but which affords cyclohexene products directly, is based on the use of a vinylsilane group within an aldehydocarbohydrate. Compound **389** was prepared from 2,3,4-tri-*O*-methyl-L-arabinose diethyl dithioacetal and cyclized by treatment with Lewis acids the nature of which exerted dramatic control over the stereochemistry of the reaction. When boron trifluoride was used coordination control (transition state **390**) afforded conduritol (**391**; 86%, selectivity >30:1), whereas with tin(IV) chloride chelation control (transition state **392**) gave the product **393** with the 1,2-*cis*-hydroxyl,methoxyl relationship (68%, similar selectivity, Scheme 72).[216]

Scheme 72



McMurry-like cyclization of the dialdose **394**, by use of titanium(IV) chloride and zinc–copper couple, gave one of the expected *cis*-diols (**395**), together with significant proportions of both *trans*-dihydroxy compounds.[217]



Cyclization of a bis(diazo ketone) to give a cyclohexanone derivatives by a process that probably involved a carbene was noted in section II.A.3.a.

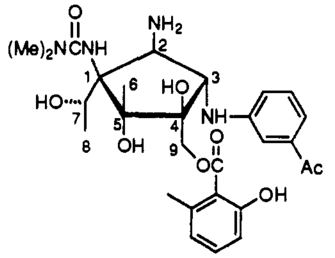
III. Syntheses of Functionalized Cyclopentanes

A. Carbanion Cyclizations

1. Biosynthesis of Hydroxylated Cyclopentanes

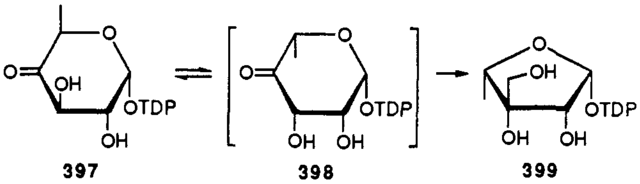
In addition to playing a central role in the biosynthesis of functionalized cyclohexanes such as the inositols (section II.A.1), D-glucose also serves as the biosynthetic precursor of a number of cyclopentane analogues, and in each case formation of the alicyclic ring may again involve an aldol reaction.

The earliest investigations in this area were carried out by Rinehart's group who used ^{13}C-labeling experiments to show that C-3 and C-9 of the antibiotic pactamycin **396** were derived from C-1 and C-6 respectively of D-glucose, while C-6, C-7, and C-8 of the antibiotic all derived from methionine.[218] Such labeling patterns would be expected if the sugar underwent initial conversions to either a 4-ulose or a hexodialdose (or a biochemical equivalent), thereby affording a stabilized carbanion at C-5 and facilitating aldol cyclization between these center and C-1. The resulting carbon–carbon bond would thus become the (C-3)–(C-4) bond of pactamycin. It was pointed out, however, that the observed labeling patterns would also result if D-glucose was initially converted into an inosose (see section II.A.1) which then underwent a ring contraction analogous to that involved in the formation of thymidine diphosphodihydrostreptose (**399**) from thymidine diphospho-6-deoxy-D-*xylo*-hexos-4-ulose (**397**) *via* the isomeric enzyme-bound L-*lyxo*-hexos-4-ulose **398** (Scheme 73).[219]



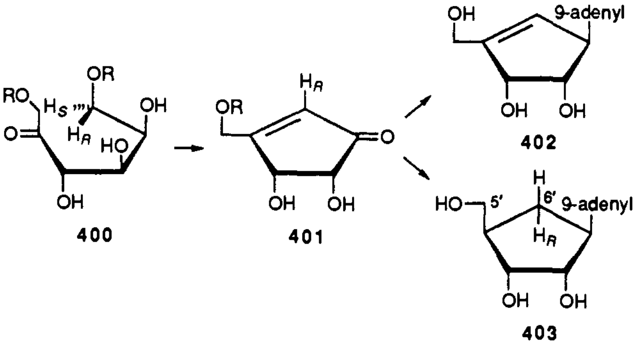
396

Scheme 73



The cyclopentane moiety of the carbanucleoside antibiotic aristeromycin **403** is also derived from D-glucose (Scheme 74), appropriate ^{13}C-labeling experiments indicating that C-1 and C-6 of the hexose correspond to C-5′ and C-6′, respectively, of the antibiotic.[220] Formation of the cyclopentane ring of **403** thus involves bonding of C-2 and C-6 of D-glucose, and possibly proceeds through the intermediacy of the phosphorylated fructose **400** (R = PO_3H_2). Additional results obtained by use of specifically tritiated and deuterated forms of D-glucose suggest that the conversion proceeds via the intermediate cyclopentenone **401** (R = PO_3H_2) formed from **400** by elimination of H-5–OR, aldol-like cyclization, and subsequent elimination. The intermediacy of the enone **401** is supported by the concurrence of the unsaturated antibiotic neplanocin A (**402**) with aristeromycin. Significantly, the overall process leading from D-glucose to aristeromycin results in specific loss of the *pro*-6*S* hydrogen atom of the proposed intermediate **400**, thus indicating that the stereochemical outcome of the reaction is the

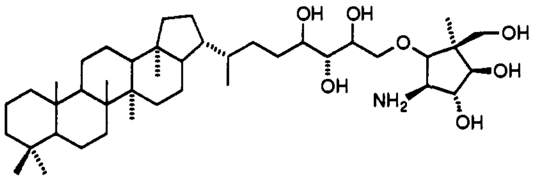
Scheme 74



reverse of that of the formally analogous cyclization of glucose 6-phosphate to *myo*-inositol 1-phosphate (see section II.A.1).

Very recently, details of the steps involved in the conversion of the enone **401** into aristeromycin (**403**) have been elucidated using doubly labeled forms of D-glucose.[221] The chemical synthesis of carbocyclic nucleosides like **402** and **403** has been reviewed.[222]

Initial experiments showed that formation of the polyfunctionalized cyclopentane moiety of the triterpene hopanoid ether **404**, a membrane reinforcer of prokaryote bacteria, could also involve aldol cyclization of a D-fructose derivative.[223] Additional experiments with ^{13}C-labeled D-glucose showed, however, that the overall process involves C–C bond formation between C-1 and C-5 rather than between C-2 and C-6 as in the case of aristeromycin (**403**) and (presumably) neplanocin A (**402**).[224]



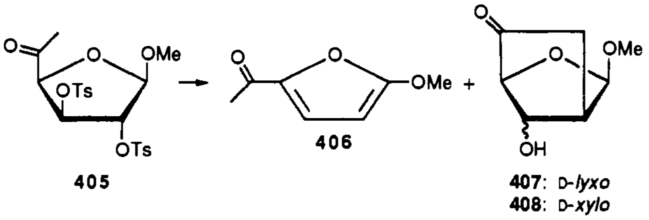
404

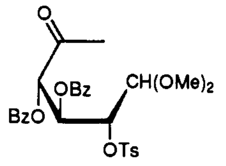
2. Displacements by Enolate Carbanions at Saturated Carbon Centers

The carbanionic centers required for this type of reaction have been generated most commonly by proton abstraction from positions α to ketone, ester, amide, or nitrile groups. Cases which involve stabilization of the carbanion by other groups are considered in sections III.A.4 and III.A.5.

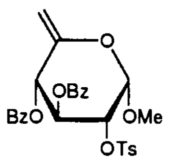
Only limited success attended early attempts to obtain cyclopentane derivatives from carbohydrate-derived precursors through use of reactions of this type. Thus, while the D-glucofuranose derivative **405** afforded the bicyclic ketone **407** (or possibly its isomer **408**), in 34% isolated yield on treatment with DBU at 5 °C, the main product (65% isolated yield) was the furan **406** (Scheme 75). In an effort to improve the yield of the bicyclic product, the 3-*O*-methyl analogue of the ditosylate **405** was treated as before, but no cyclization was observed.[225] Attention was then directed toward the tosylate **409** which, on cyclization, would give a cyclopentanone derivative, but all attempts to obtain the required acetal from the glucose-derived enopyranoside **410** were unsuccessful. A fortunate outcome of the study, however, was the finding that the C-6 mercuriated form of the free sugar analogue of **409** readily cyclized to give a cyclohexanone derivative (section II.D.1).

Scheme 75





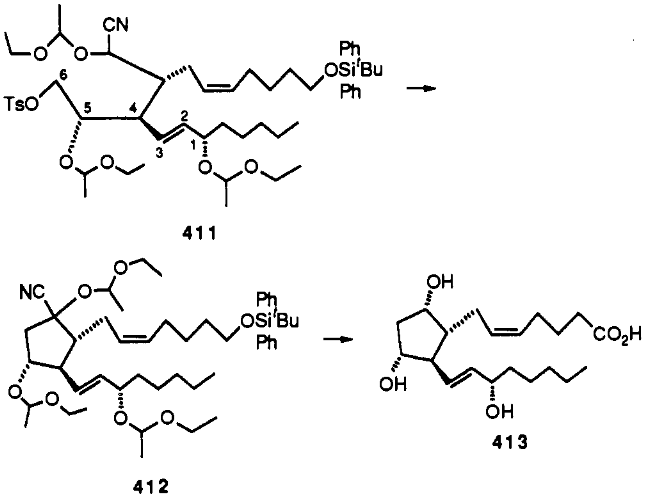
409



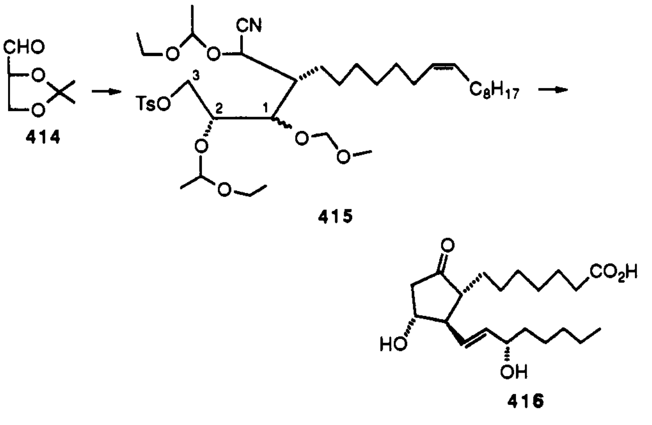
410

That ring closures of the above intended kind can be successful was emphatically shown by Stork *et al.* who converted the highly functionalized, acyclic tosylate **411** (which was prepared from D-glucose, the carbon atoms of which are numbered in the formula) to the cyclopentane derivative **412** in good yield.[226] This was the key step of their total synthesis of prostaglandin F$_{2\alpha}$ (**413**) by chiral transfer from D-glucose (Scheme 76) which stands as a landmark in the use of carbohydrates in the synthesis of non-carbohydrate natural products. While potassium hexamethyldisilazide was used as the requisite base for the cyclization, the corresponding sodium disilazide was employed to effect the analogous cyclization of the acyclic tosylate **415** which was derived from D-mannitol via 2,3-*O*-isopropylidene-D-glyceraldehyde (**414**) the carbon atoms of which are indicated. The product was subsequently converted into prostaglandin E$_1$ (**416**) having the correct absolute configuration (Scheme 77).[227]

Scheme 76

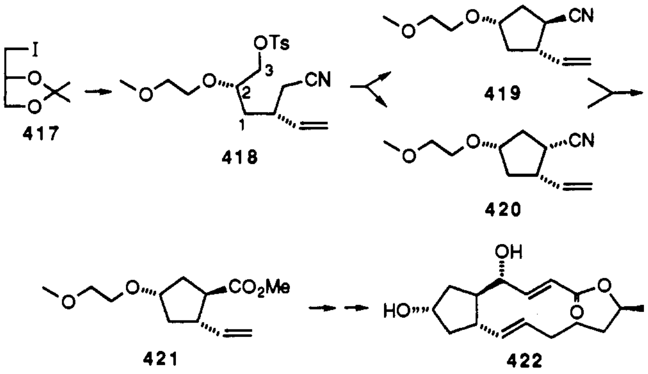


Scheme 77



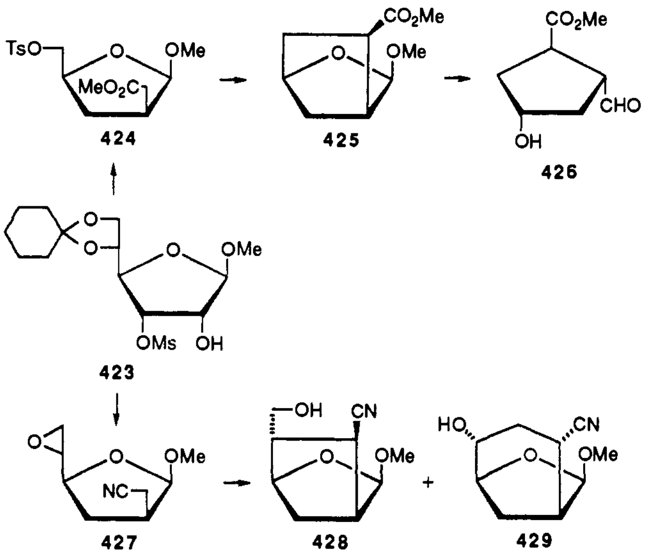
The iodide **417**, also available from 2,3-*O*-isopropylidene-D-glyceraldehyde, provided Mori *et al.* with a convenient starting point for their synthesis of the tosylate **418** which, on treatment with sodium hexamethyldisilazide in refluxing benzene, readily afforded a 92:8 mixture of the stereoisomeric cyclopentane derivatives **419** and **420**, respectively.[228] After alkaline hydrolysis, followed by treatment with diazomethane, these gave the single methyl ester **421** which was eventually converted into the biologically active macrocyclic lactone (+)-brefeldin A (**422**, Scheme 78).

Scheme 78



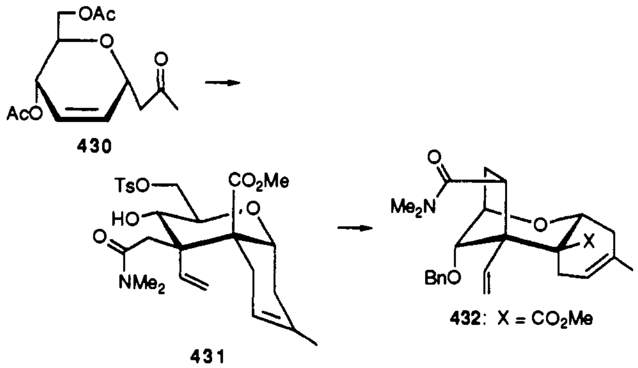
Alternative approaches to the synthesis of brefeldin A and prostaglandins from carbohydrate-derived precursors were developed by Ohrui and Kuzuhara.[229] The D-allofuranoside **423** was converted in six steps to the tosylate **424** which was then treated with lithium hexamethyldisilazide in dimethoxyethane/hexamethylphosphoric triamide (1:1) at room temperature. The bicyclic product **425**, obtained in 90% yield, was subsequently hydrolyzed at room temperature to give the cyclopentane derivative **426** (Scheme 79) the functionality and stereochemistry of which are consonant with its projected conversion into (+)-brefeldin A (**422**). The allofuranoside **423** was also converted by five steps to the epoxide **427** which, on treatment with lithium hexamethyldisilazide in tetrahydrofuran at room temperature, afforded a 1:1 mixture of the bicyclic cyclopentane and cyclohexane derivatives **428** and **429**. The former, resulting from carbanion attack at the more substituted carbon atom of the epoxide ring in **427**, in principal, could be used in the chiral synthesis of prostaglandins.

Scheme 79

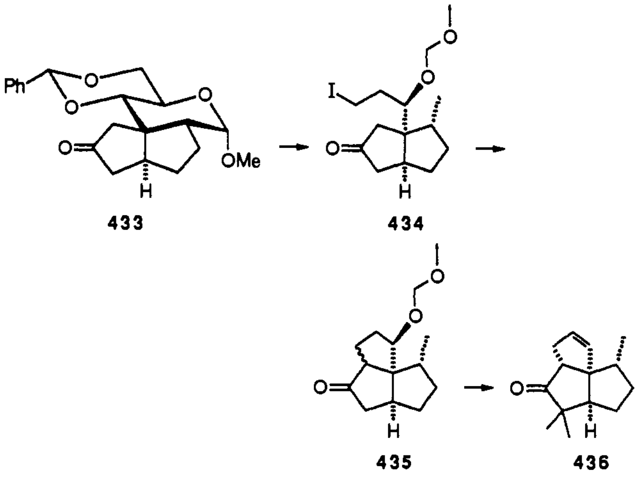


Two further very elegant instances of cyclopentane ring formation by intramolecular nucleophilic displacement are found in the stereocontrolled syntheses of polycyclic systems developed by Fraser-Reid's group. In the first of these, the *cis*-fused (and thus conformationally mobile) oxadecalin derivative **431**, obtained from the readily available *C*-glycopyranoside **430**, was treated with potassium hexamethyldisilazide in order to effect conversion to the tricyclic trichothecene derivative **432** which was isolated as a single, optically active diastereomer (Scheme 80).[230] The second case involved cyclization of the keto iodide **434** to the triquinane **435** from which the silphinene skeleton **436** was subsequently obtained (Scheme 81).[231] Compound **434** was conveniently derived from the branched-chain pyranoside **433** the synthesis of which is considered in section III.B.1.c.

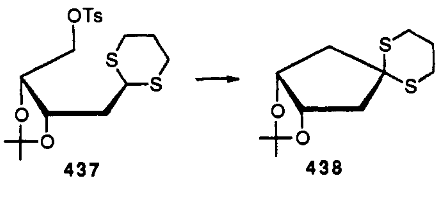
Scheme 80



Scheme 81



That carbanions derivable from 1,3-dithianes can be used to form cyclopentane rings is illustrated by the finding that, on treatment with *n*-butyllithium at –30 °C, compound **437** is converted into **438** in 71% yield.[232]

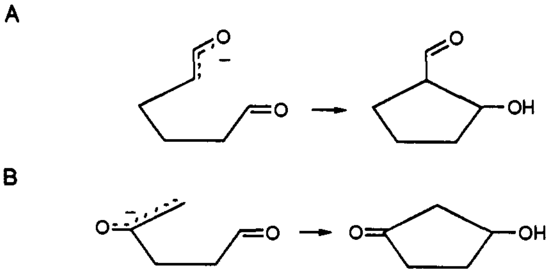


3. *Aldol and Aldol-like Reactions*

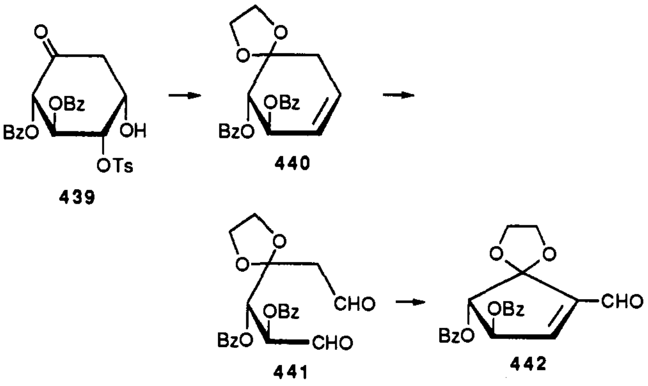
Under this general heading it is convenient to consider cases in which formation of cyclopentane derivatives involves intramolecular nucleophilic attack at aldehyde, ketone, or ester carbonyl groups by simple enolate (or equivalent) centers generated in *any* way. Cases involving attack by other types of carbanionic centers are again considered separately (sections III.A.4 and III.A.5).

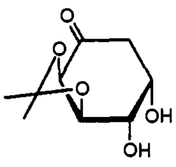
a. Reactions with Sugar Chains. The ring-forming steps in reactions of this type involve either 5-(enol-exo)-*exo-trig* or 5-(enol-endo)-*exo-trig* processes (Scheme 82; A and B respectively),[43] and in most cases the resulting β-ketols undergo dehydration to give thermodynamically stable conjugated enones. Several different methods have been used to generate the required enolates, the most straightforward and commonly used method involving deprotonation of appropriate dicarbonyl compounds. Thus, the cyclohexanone derivative **439**, obtained from methyl α-D-glucopyranoside (see section II.D.1), proved to be a convenient source of the cyclohexene **440** and hence the 1,6-dialdehyde **441**. Aldol cyclization of **441** using pyrrolidinium acetate in benzene then gave the unsaturated aldehyde **442** (Scheme 83) via a kinetically favored cyclization step of type A (Scheme 82).[233] Protection of the carbonyl function at C-1 of **439** may well have been important for the success of the overall sequence, however, since attempts to obtain the related enal **444** by periodate cleavage of the diol **443** and aldol cyclization of the resulting dial were unsuccessful. Indeed, the cyclization **441** → **442** seems to be the only recorded instance of cyclopentane ring formation from a carbohydrate-derived 1,6-dicarbonyl compound.

Scheme 82



Scheme 83





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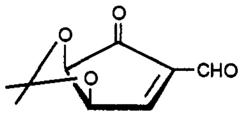
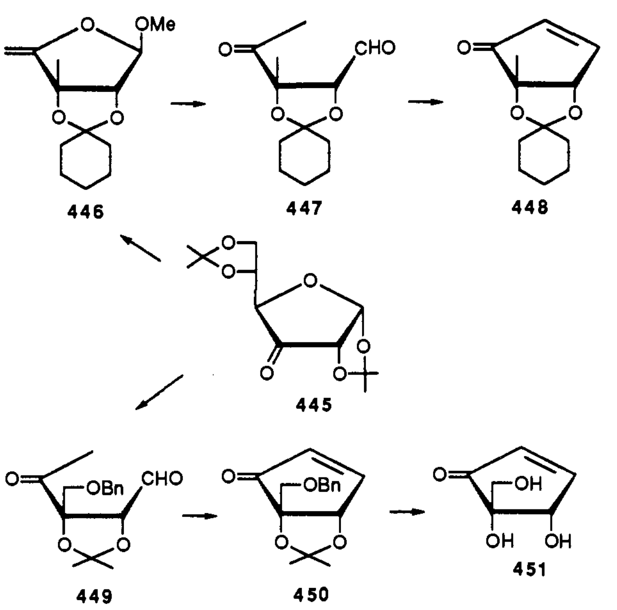


444

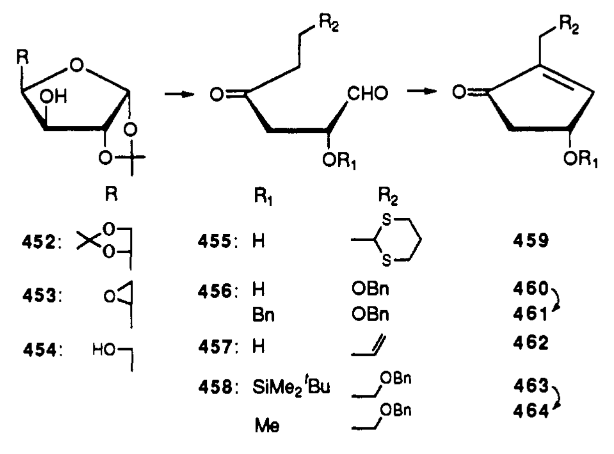
Formation of cyclopentane derivatives from carbohydrate-derived 1,4-dicarbonyl compounds, on the other hand, is well documented, despite the fact that the cyclization step in such reactions involves a kinetically disfavored process[43] of type B (Scheme 82). The earliest reported cases came from Moffatt's group who successfully converted the α-D-*ribo*-hexofuranos-3-ulose derivative **445** into the unsaturated glycoside **446** which was then selectively hydrolyzed to the keto aldehyde **447**.[3] Surprisingly, aldol cyclization of this compound could not be effected under either basic or acidic conditions, but enone **448** was obtained by use of neutral alumina at 100–120 °C. In a similar fashion, **445** was also converted into the keto aldehyde **449** and hence the enone **450** and, ultimately, the antibiotic pentenomycin I (**451**) (Scheme 84). Achab and Das also experienced difficulty effecting aldol cyclization of the keto aldehyde **455**, obtained in nine steps from di-*O*-isopropylideneglucose **452**, but they eventually obtained the potential prostaglandin E_2 precursor **459** in 35% yield by use of 0.1 M sodium hydroxide. These conditions were also used to obtain the enones **460** and **462** from keto aldehydes **456** and **457** respectively, in turn produced from the epoxide **453** and the α-D-xylofuranose derivative **454**, respectively (Scheme 85).[234-236] The di-*O*-benzyl ether **461** made from **460** had previously been prepared by Elliott *et al.* via a different route and subsequently utilized in an alternative synthesis of pentenomycin I **451**.[237]

Scheme 84



Diacetone glucose **452** was also used by Umani-Ronchi *et al.* as starting material for their synthesis of keto aldehyde **458**, and aldol cyclization again proved difficult to effect.[238] Treatment with barium hydroxide in methanol at room temperature, however, eventually afforded the enantiomerically pure silyloxy enone **463** in 33% yield, together with appreciable amounts of the corresponding methoxy enone **464** and its enantiomer. Formation of these products seems likely to have

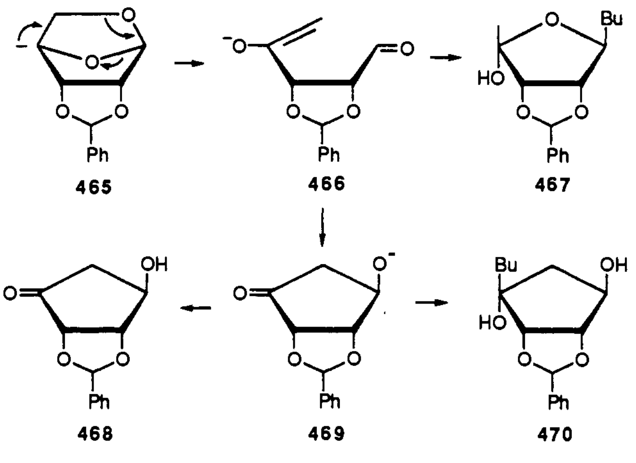
Scheme 85



involved a series of reactions initiated by conjugate addition of methanol to the silylated enone.

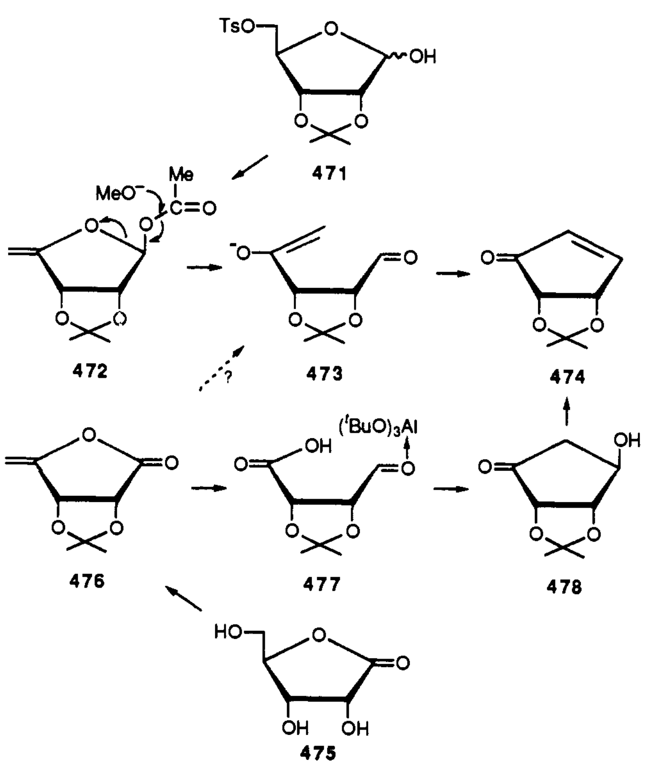
While 1,4-dicarbonyl compounds are the most common precursors of enolates of type B (Scheme 82), other sources have been found. Thus, Klemer and Kohla treated 1,5-anhydro-2,3-*O*-benzylidene-β-D-ribofuranose with lithium diisopropylamide, thereby (presumably) forming carbanion **465**, enolate **466**, cycloalkoxide **469**, and finally the β-ketol **468**.[239] On treating the same anhydride with butyllithium, **466** and **469** were again formed, but further reaction between each of these species and the alkyllithium occurred under the reaction conditions used, so that aqueous workup in this case afforded a mixture of the cyclopentanetetrol derivative **470** and the furanose derivative **467**, the latter predominating (Scheme 86). The reactions involved in the formation of **470** are analogous to those observed when anhydropyranose derivatives are treated with alkyllithium (see Section II.A.3.a), but in these latter cases the intermediates enolates (corresponding to **466**) apparently cyclize to the appropriate cyclohexanone derivatives before they are able to react further with the alkyllithium.

Scheme 86

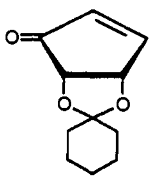


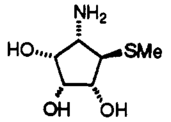
Ohrui's group has effectively converted the ribofuranose derivative **471** into the unsaturated acetate **472** from which the enolate **473**, and hence the (4*S*,5*S*)-cyclopentenone **474** (80% yield), were obtained on treatment with catalytic amounts of sodium methoxide in boiling methanol (Scheme 87).[240,241] Enone **474** was also obtained by Bélanger and Prasit in six steps from D-ribono-γ-lactone (**475**) via the enol lactone **476**.[242] The alicyclic ring was formed in high yield by use of 1 equiv of lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran followed by quenching with aqueous ammonium chloride. Dehydration of the resulting β-ketol **478** was then effected by treatment with methanesulfonyl chloride in pyridine. In principle, reaction of **476** with the hydride reagent might have been expected to involve formation and subsequent cyclization of the enolate **473** but, on the basis of NMR evidence, Bélanger and Prasit suggested that alicyclic ring formation proceeds via the enol complex **447**, considered to be formed during the course of the subsequent quenching with aqueous ammonium chloride.

Scheme 87



In more recent work, Bélanger and Prasit's approach has been applied to the synthesis of the enone **479** which was subsequently converted into the glycoprotein processing inhibitor, mannostatin A (**480**).[243]

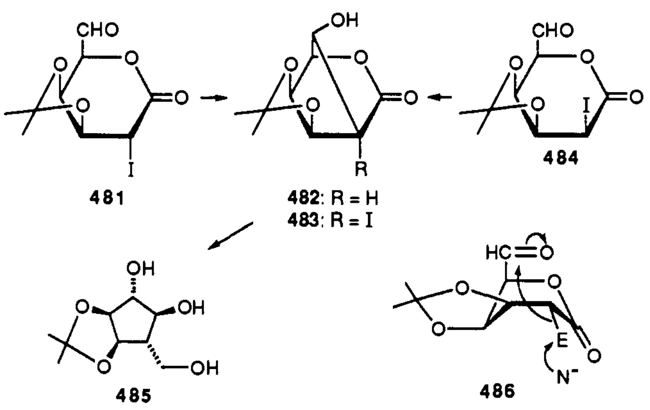

479



480

A novel type of carbocyclization occurred when the α-iodolactone **481** was treated with lithium iodide in tetrahydrofuran, the derived C-2 anion attacking C-6 to give the cyclopentane compound **482** in good yield. From this the triol **485** was obtained by reduction. Relevant also is the reaction undergone by the C-2 epimer **484** which gave only about 10% of **482**, the major product being the iodine-containing analogue **483** derived via the C-2 carbanion formed by deprotonation

Scheme 88

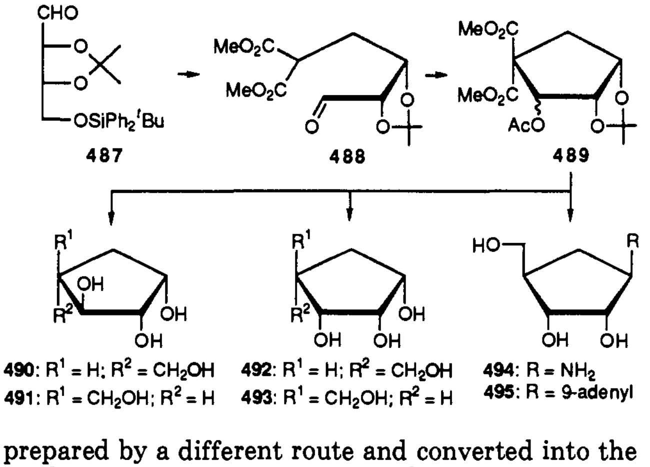


rather than loss of I$^+$ (Scheme 88).[244] For these cyclizations to occur the $^4B_1$ conformation would have been imposed on the pyranoid rings, and the results obtained show, as expected, that nucleophilic attack at C-6 is initiated by iodide attack at the quasiequatorial electrophilic iodine or hydrogen atoms (E), respectively. (See **486** in Scheme 88.)

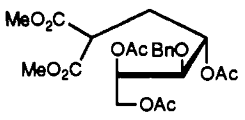
b. Reactions Involving Extended- and Branched-Sugar Chains. Studies involving synthesis of cyclopentane derivatives from sugars having extended carbon chains seem to have been carried out entirely by workers at Keio University, Yokahama, where chain extensions were invariably effected by Knoevenagel condensation of dimethyl malonate with appropriate aldehydes, followed by borohydride reduction of the resulting unsaturated diesters. (For other examples of the use of this type of methodology see Sections II.A.2 and II.A.3.b.) The work has led in particular to access to the carbafuranose series of compounds.

In one set of experiments in this area, Tadano *et al.* converted D-glucose into the D-erythrose derivative **487** the carbon chain of which was then extended in the manner indicated above. Desilylation of the product, followed by PCC oxidation, gave aldehyde **488** which cyclized spontaneously under the reaction conditions used. Acetylation then afforded a mixture of the epimeric acetates **489** which was eventually transformed into carba-β-L-arabinofuranose (**490**), carba-α-D-xylofuranose (**491**), carba-β-L-lyxofuranose (**492**), carba-α-D-ribofuranose (**493**), and the aminotriol **494** (Scheme 89).[23,24,245] The last compound had previously been prepared by a different route and converted into the antibiotic (−)-aristeromycin (**495**).[246]

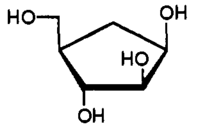
Scheme 89



A second set of experiments involved the chain-extended compound **496** which was made from 2,4,5-tri-*O*-acetyl-3-*O*-benzyl-D-xylose and used to prepare carba-β-D-arabinofuranose (**497**). The procedures involved work with a lactone intermediate and an inversion via a ketone at C-1 (carbohydrate nomenclature).[247]



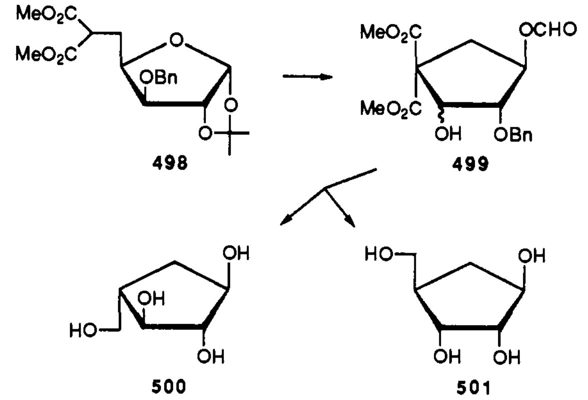
496



497

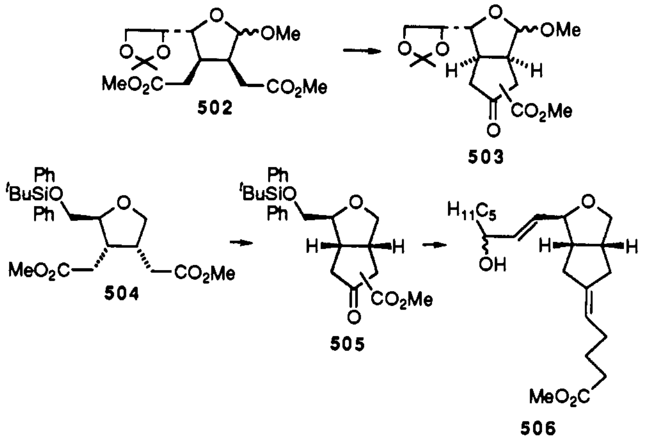
Most recently, Tadano *et al.* have used a similar approach with the chain-extended diester **498**.[248] Removal of the acetal protecting group, followed by cleavage of the resulting diol with periodate and spontaneous aldol cyclization of the product, afforded a mixture of epimeric cyclopentane derivatives **499** from which carba-α-L-arabinofuranose (**500**) and carba-β-D-ribofuranose (**501**) were derived (Scheme 90).

Scheme 90



Cyclopentane derivatives may also be formed through aldol-like cyclizations within branched rather than extended sugar chains, as illustrated by the successful Dieckmann cyclization of diesters **502** and **504** the synthesis of which can be achieved from cyclohexenes derived by Diels–Alder additions of butadiene to unsaturated glycosides (section II.C.2.a).[249,250] In each case, decarbomethoxylation of the resulting mixture of regioisomeric keto esters, **503** and **505**, respectively, was

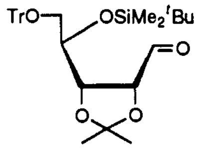
Scheme 91



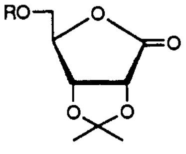
effected by use of the procedure of Krapcho *et al.*[251] (heating with sodium chloride in moist DMSO). The cyclopentanone derivative thereby obtained from keto esters **505** was subsequently transformed into a mixture of epimers **506** whose structures are analogous to those of prostacyclin and carbacyclin (Scheme 91).[252]

4. Reactions of Phosphorus-Stabilized Species

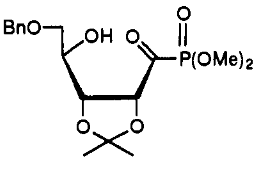
Reactions involving aldol-like cyclization of carbanions which are stabilized both by neighboring phosphonate and carbonyl groups have been put to good use in the enantioselective synthesis of cyclopentane derivatives from carbohydrates. Remarkably, however, in all cases reported to date the intermediate compounds to have been cyclized have been of the same structural type (Schemes 92 and 93). In their initial work in this area, Lim and Marquez used aldehyde **507** which was treated with lithium dimethyl methylphosphonate.[253] The resulting mixture of diastereomeric alcohols was oxidized with Swern's reagent to give a keto phosphonate which, after desilylation and further Swern oxidation, gave the diketo phosphonate **517a**. Cyclization of this latter compound to enone **518a** was then effected in 30% yield by heating with anhydrous potassium carbonate and 18-crown-6 in toluene.



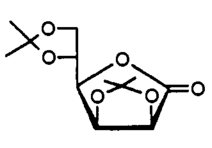
507



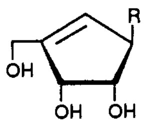
508: R = Bn
509: R = Tr



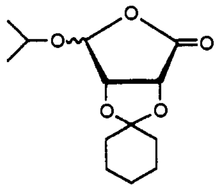
510



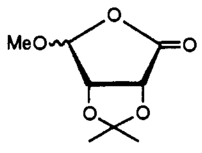
511



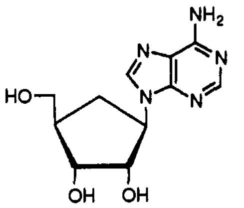
512: R = 9-adenyl
513: R = cytosyl



514



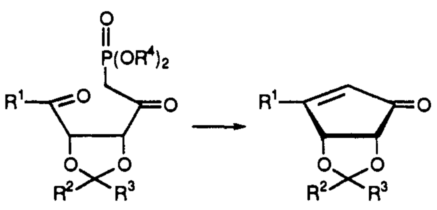
515



516

In later work, Lim and Marquez used D-ribono-γ-lactone to obtain lactone **508** which was again treated with lithium dimethyl methylphosphonate and the resulting hemiketal, on reaction with sodium methoxide in methanol, gave the ring-opened **510** which was oxidized to the diketone **517b** with Collins' reagent.[254] The same type of approach was used by Altenbach *et al.* to obtain diketo phosphonate **517c** from ribonolactone derivative **509**,[255] and subsequently by Huber and Vasella to prepare phosphonate **519a** from the D-mannonolactone derivative **511**.[256] In each of these latter cases, however, potassium *tert*-butoxide was used (rather than sodium methoxide) to effect isomerization of the relevant hemiketal to the corresponding open-chain hydroxy ketone, and activated DMSO was used (rather than Collins' reagent) to oxidize the hydroxy ketone to the diketo phosphonate.

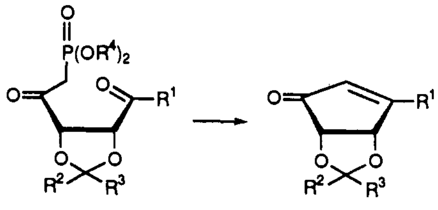
Scheme 92



517a–e **518a–e**

	R^1	R^2	R^3	R^4	ref
a	TrOCH$_2$	Me	Me	Me	253
b	BnOCH$_2$	Me	Me	Me	254
c	TrOCH$_2$	Me	Me	Et	255
d	H	– (CH$_2$)$_5$	–	Me	260
e	H	Me	Me	Me	261

Scheme 93



519a–c **520a–c**

	R^1	R^2	R^3	R^4	ref
a		Me	Me	Et	256
b	H	– (CH$_2$)$_5$	–	Me	260
c	H	Me	Me	Me	261

Cyclizations of phosphonates **517b**, **517c**, and **519a** to the corresponding enones **518b**, **518c**, and **520a**, respectively, were effected by heating with either potassium carbonate or potassium hydrogencarbonate and 18-crown-6 in a hydrocarbon solvent. In the case of **517b**, however, cyclization was preceded by partial base-catalyzed epimerization at carbons 3 *and* 4 of the diketone, with the result that some of the optical antipode of **518b** was also produced.[254b] Fortunately, the racemic enone crystallized preferentially, thereby allowing the enantiometically pure enone **518b** to be recovered from the mother liquor. It was eventually transformed into the carbocyclic nucleoside (−)-neplanocin A (**512**) and its pyrimidine analogue **513**,[254,257,258] while the racemic enone was used as starting material for syntheses of (±)-neplanocin F and (±)-psicoplanocin A.[259]

D-Ribono-γ-lactone was also used as starting material by Borchardt's group.[260] In this case, however, the lactone was converted by three steps (including a periodate oxidation) into the acetal lactones **514** which were then treated with lithium dimethyl methylphosphonate. The resulting aldehydo keto phosphonate

517d underwent spontaneous aldol cyclization under the conditions used and gave the parent enone **518d** in 80% overall yield from **514**, or 65% from ribonolactone. The enantiomeric enone **520b** was obtained in similar fashion in 44% overall yield from D-mannose via the optical antipode of acetal lactones **514** and **519b**.[260] (For an alternative synthesis of enone **520b** from D-ribonolactone see section III.A.3.a.)

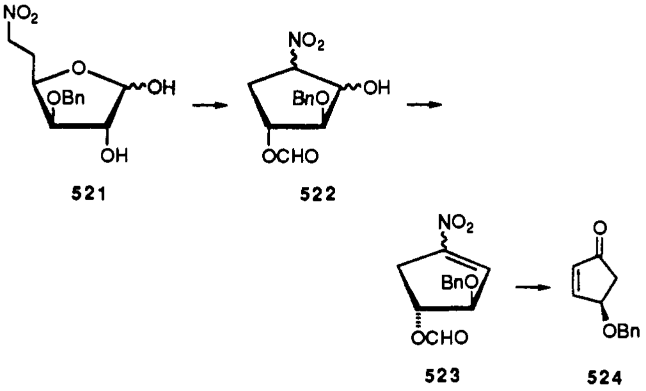
More recently, the same group has also reported the analogous stereoselective synthesis of enone **518e** and its enantiomer **520c** from the acetal lactones **515** and their enantiomers respectively, these latter compounds being obtained by new, three-step syntheses from D-lyxose and D-ribose, respectively.[261] The intermediates **517e** and **519c** were not isolated, and the overall yields of **518e** and **520c** from these readily available sugars were 42 and 41%, respectively. (For alternative syntheses of enone **520c** from D-ribose and D-ribonolactone see section III.A.3.a.)

Enones **518d**, **518e**, **520b**, and **520c** are all potentially very useful as chiral starting materials for the synthesis of more complex molecules, as is well illustrated by the successful conversion of **520b** into mannostatin A (see section III.A.3.a), of **520c** into neplanocin A (**512**),[262] and of **518d** into aristeromycin (**516**),[263,264] neplanocin A (**512**),[264] and neplanocin analogues.[260]

5. Reactions of Nitro-Stabilized Species

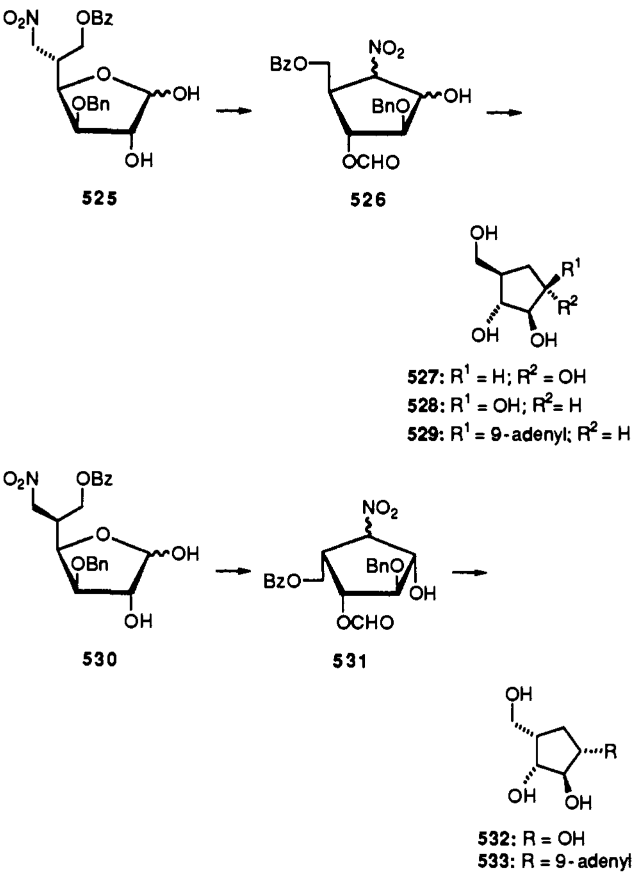
a. Cyclizations of Nitro Sugars. Reported syntheses of cyclopentane derivatives by cyclization of nitro sugars have all used di-*O*-isopropylideneglucose as starting material. In the simplest case, Torii *et al.* initially converted the glucose derivative into nitrofuranose **521** which was then treated with periodate. The resulting open-chain aldehyde, on reaction with triethylamine in DMF at room temperature, cyclized to give a mixture of stereoisomeric nitrocyclopentanols **522** which was readily converted into enone **524** via the nitroalkene **523**, a useful chiral prostaglandin synthon (Scheme 94).[265]

Scheme 94



In similar fashion, Kitagawa's group has made the epimeric nitrofuranoses **525** and **530**,[266] and from them the nitrocyclopentanols **526** and **531**, respectively (Scheme 95).[267] In doing so, they cleaved the furanose rings by reaction with lead tetraacetate in benzene at room temperature, while cyclization of the resulting open-chain aldehydes was achieved by treatment with potassium fluoride and 18-crown-6 in DMF at 2 °C. Standard reactions were then used to convert the mixture of cyclopentanols **526** into both carba-α-D-arabinofuranose **527** and its β-epimer **528**, while cyclopentanols **531** similarly afforded carba-β-L-xylofuranose **532**. Cyclopentanols **526** and **531** also served as convenient starting materials for the latter synthesis of carbocyclic nucleosides **529** (cyclaridine) and **533**, respectively.[288]

Scheme 95

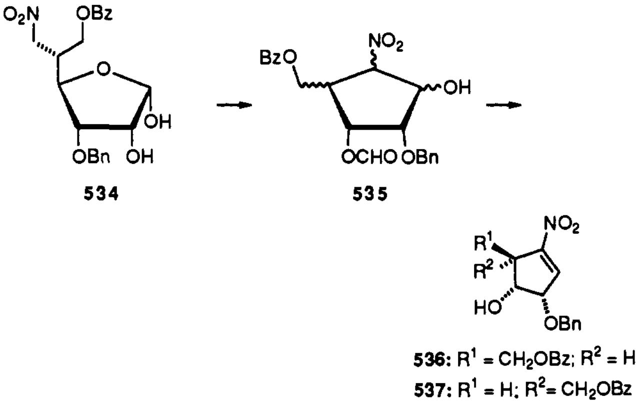


527: $R^1 = H$; $R^2 = OH$
528: $R^1 = OH$; $R^2 = H$
529: $R^1 = 9\text{-adenyl}$; $R^2 = H$

532: R = OH
533: R = 9-adenyl

In the work described above, the intermediate nitrofuranoses **525** and **530** were stereochemically discrete at C-5, thereby ensuring corresponding stereochemical integrity at C-4 in the derived nitrocyclopentanols **526** and **531**, and hence in the final products **527–529**, **532**, and **533**. In more recent work, however, Yoshikawa *et al.* have successfully applied this methodology to the C-5 epimeric mixture of nitrofuranoses **534** which afforded a complex set of isomeric nitrocyclopentanols **535**.[269] When these were treated with

Scheme 96

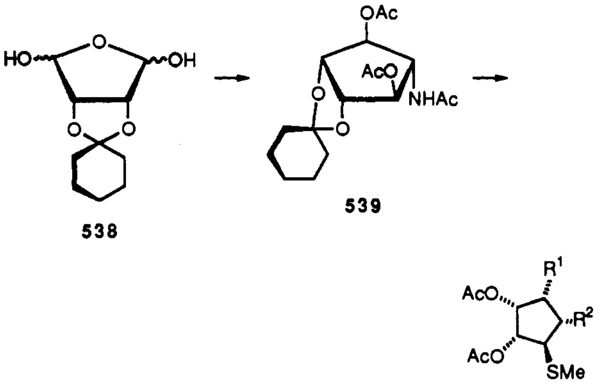


536: $R^1 = CH_2OBz$; $R^2 = H$
537: $R^1 = H$; $R^2 = CH_2OBz$

acetic anhydride a simple mixture of the two epimeric nitrocyclopentenes **536** and **537** was obtained (Scheme 96). After separation, these latter compounds were converted into a number of other highly substituted cyclopentane derivatives; of particular signifiance, in this regard, is the successful conversion of isomer **536** into (−)-aristeromycin. (For an alternative synthesis of this compound from carbohydrate-derived precursors, see Section III.A.4.)

b. Dialdehyde–Nitromethane Cyclizations. It appears that Angyal's early work on reactions of this type is the first recorded case in which cyclopentane derivatives were formally obtained from a carbohydrate-derived precursor. Specifically, 2,3-*O*-cyclohexylidene-*erythro*-tetrodialdose, obtained by periodate cleavage of a cyclohexylidene derivative of *myo*-inositol, and existing in the form of its cyclic hydrate **538**, was treated with nitromethane and sodium methoxide. The resulting *aci*-nitro salt was then acidified, whereupon a mixture of at least four isomeric nitrocyclopentanediols was obtained.[270,271] Catalytic reduction of these, followed by acetylation, afforded a mixture of products from which triacetyl derivative **539** was obtained in 40% yield.[272] Compound **539** has seen wide use as a starting material for the synthesis of a variety of isomeric cyclopentanepentols,[273] aminocyclopentanetetrols,[274] and diaminocyclopentanetriols,[275] all of which are optically inactive. Most recently, **539** has also been transformed into racemic forms of mannostatin A tetraacetate (**540**) and its regioisomer **541** (Scheme 97).[276]

Scheme 97



538

539

540: R¹ = OAc; R² = NHAc
541: R¹ = NHAc; R² = OAc

B. Free-Radical Cyclizations

Prior to 1985, schemes devised for the synthesis of carbocycles from carbohydrate-derived precursors made no use of radical reactions. In that year, however, Wilcox and Thomasco reported the successful cyclization of radicals derived from unsaturated halo sugars,[277] and subsequent activities by the Texas group and by other groups, notably those of RajanBabu[278] and Fraser-Reid,[5] have convincingly shown that radical reactions are highly suited to the formation of cyclopentane derivatives from carbohydrates.

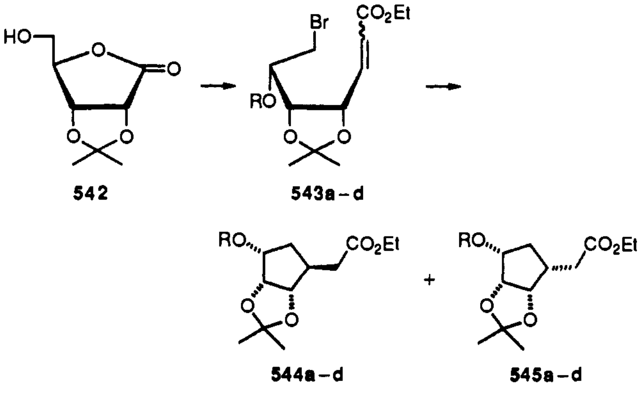
In reviewing work in this area, it is convenient to concentrate initially on "simple" cases in which starting compounds contain radical sources and single radical-acceptor groups. More complex cases are then dealt with.

1. Simple Cyclizations of 5-Hexenyl Radicals

a. Cyclizations within Sugar Chains. Considering the number of cyclopentane derivatives that have been made using carbohydrate-based 5-hexenyl radicals it is surprising that apparently only a few instances of the use of radicals and radical traps both derived within a common sugar chain have been recorded, and all involve cyclizations on to oximo groups. (See section III.B.4.) In addition, however, a closely related radical-based reduction cyclization of unsaturated aldehydes is noted in section III.B.6.

b. Cyclizations within Extended Sugar Chains. Using the D-ribono-γ-lactone acetal **542** as starting material, Wilcox and Thomasco prepared the series of stereoisomeric unsaturated bromo esters **543** which were separated chromatographically and individually treated with tributyltin hydride and radical initiator to give the cyclopentane derivatives **544** and **545** (Scheme 98).[277]

Scheme 98



542 **543a–d**

544a–d **545a–d**

a, R = H; **b**, R = Ac; **c**, R = Bz; **d**, R = Piv

The yields and isomer ratios obtained are shown in Table 3 and clearly indicate that cyclization of the (*Z*)-isomers proceeds with a greater degree of stereocontrol. Moreover, for each (*Z*)-ester, the predominant cyclopentane derivative obtained has the side chain containing the ester group in the *exo* orientation **544**. Such an outcome would be expected if 5-*exo-trig* radical cyclization proceeds via a "chairlike" transition state, as originally proposed by Beckwith *et al.*[279] with the substituents at C-2 and C-4 (with respect to the radical center) preferentially occupying quasiequatorial positions.

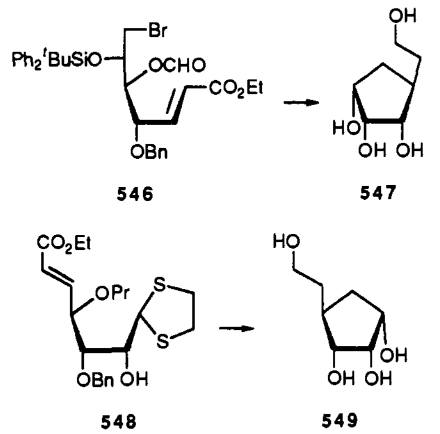
Table 3. Cyclization of 5-Hexenyl Bromides 543[277]

starting compound	products	product ratio 544:545	total yield (%)
(*Z*)-**543a**	**544a, 545a**	6:1	80[a]
(*E*)-**543a**	**544a, 545a**	2:1	80
(*Z*)-**543b**	**544b, 545b**	5:1	80
(*E*)-**543b**	**544b, 545b**	1:1	82
(*Z*)-**543c**	**544c, 545c**	10:1	89
(*E*)-**543c**	**544c, 545c**	1:1.2	87
(*Z*)-**543d**	**544d, 545d**	11:1	87

[a] Jones and Roberts (ref 280) have also reported obtaining the enantiomers of **544a** and **545a** (isomer ratio again 6:1) in 87% isolated yield from the enantiomer of (*Z*)-**543a**, in turn obtained from L-ribono-γ-lactone.

In closely parallel work the radical precursors **546** and **548**, each derived from D-allose, were radical cyclized to give major products from which the enantiomeric tetrols **547** and **549** were made (Scheme 99).[281]

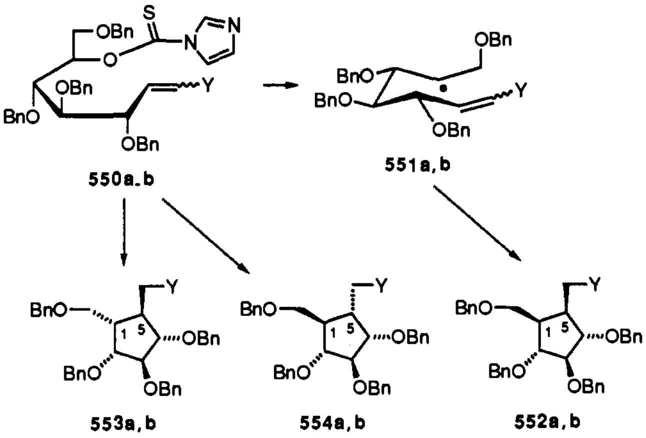
Scheme 99



In the latter case normal tributyltin hydride reaction gave the desulfurized, cyclized product of radical addition but in only 26% yield because, it was speculated, the second C–S bond cleavage was not favored by the reaction conditions.

Whereas each of the foregoing cases may have involved cyclization of acyclic, *primary* radicals, investigations by RajanBabu and co-workers[282] were concerned with cases involving both acyclic and cyclic *secondary* radicals. The acyclic species of interest were generated from the glucose-derived imidazolecarbothioates **550** by reaction with tributyltin hydride and AIBN as radical initiator, and in each case the ensuing cyclization yielded three stereoisomeric cyclopentane derivatives **552**, **553**, and **554** (Scheme 100).

Scheme 100

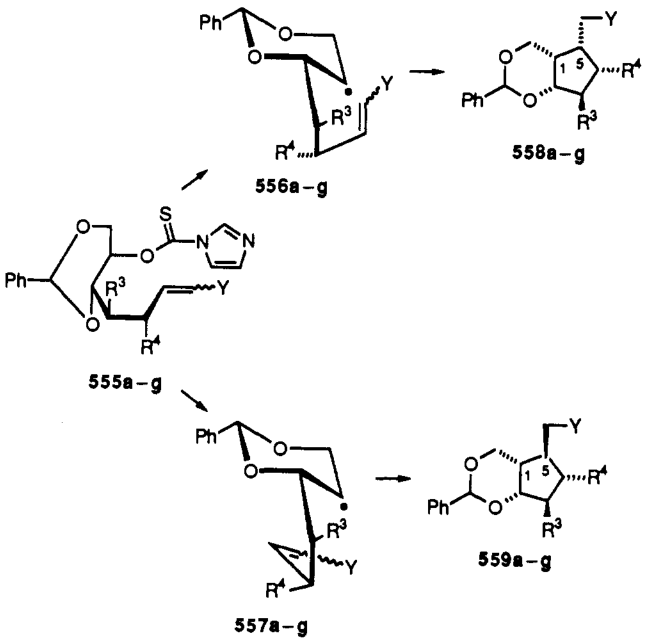


a, Y = H; **b**, Y = OMe

Of these the first were strongly favored whether Y was H or OMe (*Z* or *E*) as expected if the intermediate radicals cyclize from the "chairlike" conformation **551**.

In sharp contrast to the results obtained with **550** (Y = H or OMe) cyclization of the corresponding benzylidene acetals **555a** and **555b** afforded only one product in each case (Scheme 101). Moreover, the products obtained were of the 1,5-*trans* type **559**. This situation may be rationalized if it is assumed that cyclization occurs in each case via the chair–boat cyclization transition state **557** in which steric interactions specifically involving the benzyloxy group at C-4 are minimized. Support for such a proposal is provided by the finding that 1,5-*trans* products **559** are also formed stereoselectively from carbothioates **555c** and **555d** in each of which R^4 is again a benzyloxy group, whereas 1,5-*cis* products **558** are formed preferentially from carbothioates **555e**, **555f** and **555g** in each of which R^4 is a hydrogen atom. In these latter cases, cyclization presumably occurs while the intermediate radicals are preferentially in chair–chair conformations **556** analogous to the simple chair conformations **551**. Preferential formation of the 1,5-*cis* product (epimer of **558a** at C-4) on cyclization of the mannose-derived carbothioate (epimer of **555a** at C-3) may also be rationalized in similar manner. The galactose-derived radical, however, led to the isomer of **559a** epimeric at C-1 and C-2.[282c]

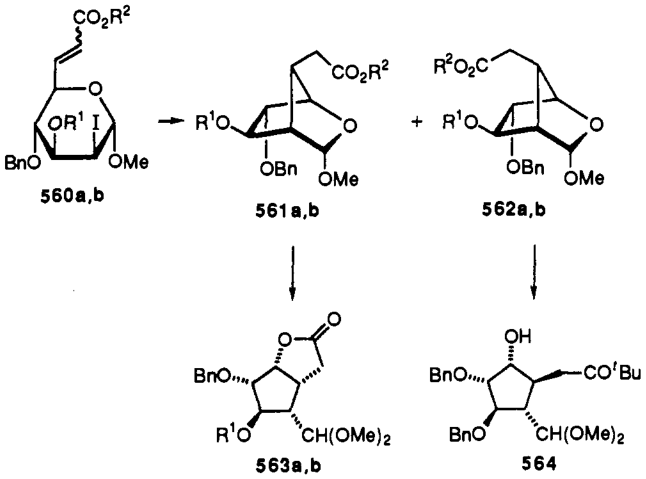
Scheme 101



	Y	R^3	R^4
a	H	OBn	OBn
b	OMe	OBn	OBn
c	H	H	OBn
d	OMe	H	OBn
e	H	OBn	H
f	OMe	OBn	H
g	H	H	H

In each of the above examples, the atom to which the free radical bonds was the anomeric center of the parent sugar the stereoregulating properties of which, however, were largely lost; such was not the case in syntheses carried out by Fraser-Reid's group.[106] Using D-glucal as starting material, these workers prepared the chain-extended unsaturated iodides **560** which were treated with tributyltin hydride and AIBN to give **561** and **562** in 80–90% total yield. Esters **561a** and **561b** were readily transformed into the *cis*-fused lactones **563a** and **563b**, respectively, by simple acid-catalyzed methanolysis, but ester **562b**, under the same conditions, gave the dimethyl acetal **564** (Scheme 102).

Scheme 102

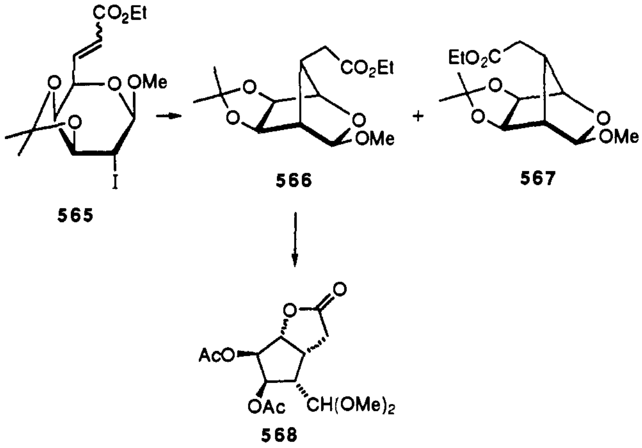


a, R^1 = Bz, R^2 = Et; b, R^1 = Bn, R^2 = ^{t}Bu

The proportions the oxabicycloheptanes obtained from the esters **560** vary somewhat, but the isomers in which the side chain at C-7 is *anti* to the *exo*-oriented substituent at C-5 always predominated. Furthermore, whereas the isomer ratios depended on the nature of the ester alkyl groups, *tert*-butyl giving best selectivity, the stereochemistry of the double bonds had only a minor effect on the steric course of the reactions.

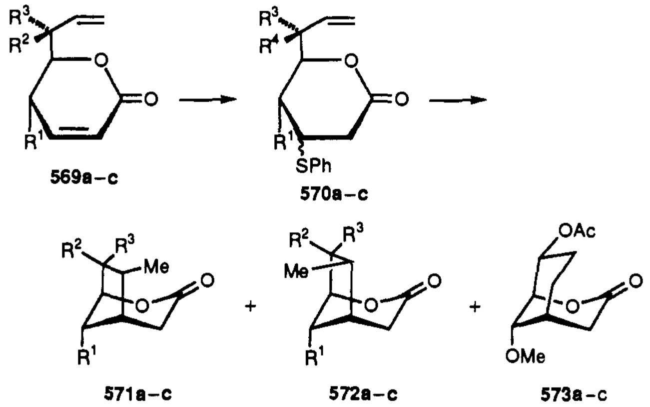
Fraser-Reid *et al.* also investigated analogous cyclizations of the unsaturated iodides **565**, derived from D-galactal, to **566** and **567**, and found that the former, obtained now with specificity or high selectivity from each geometric isomer, was easily converted into the synthetically useful lactone **568** (Scheme 103).[106]

Scheme 103



Radical cyclizations closely related to those studied by Fraser-Reid *et al.* have been investigated by López and co-workers.[283] Using carbohydrate-derived unsaturated lactones **569** as starting materials, they prepared the thioethers **570** by conjugate addition of benzenethiol in the presence of triethylamine. Without isolation, the thioethers were then treated with tributyltin hydride and AIBN to produce the bicyclic lactones **571** and **572** by 5-*exo-trig* radical addition processes (Scheme 104). In the case of **569b**, some 6-*endo-trig* addition also occurred to give **573**. The yields of the different products shown in the scheme imply that cyclization of the intermediate radicals takes place preferentially while these radicals adopt conformations which minimize allylic strain associated with the terminal double bond. Whether these conformations are "chairlike" or "boatlike" seems to be less important.

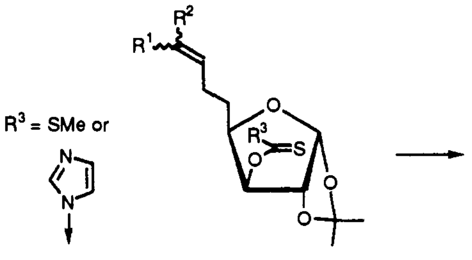
Scheme 104



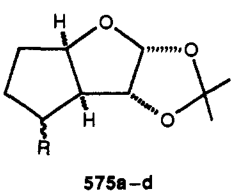
	R^1	R^2	R^3	571	572	573	% yield
a	OMe	OAc	H	4	1	0	92
b	OMe	H	OAc	1.2	2.5	1	78
c	Me	H	Me	1	1	0	72

Contelles *et al.* have also recently used sugar derivatives containing extended, unsaturated carbon chains as substrates for 5-hexenyl radical cyclizations.[284] Specifically, diacetone glucose was converted into a series of oct-7-enofuranose derivatives **574a–d** (both isomers) which were then separately treated with tributyltin hydride and AIBN to give mixtures of the stereoisomeric tricyclic acetals **575a–d** (Scheme 105).

Scheme 105



	R^1	R^2
a	H	CO_2Me
b	Me	CO_2Me
c	H	OMe
d	H	H

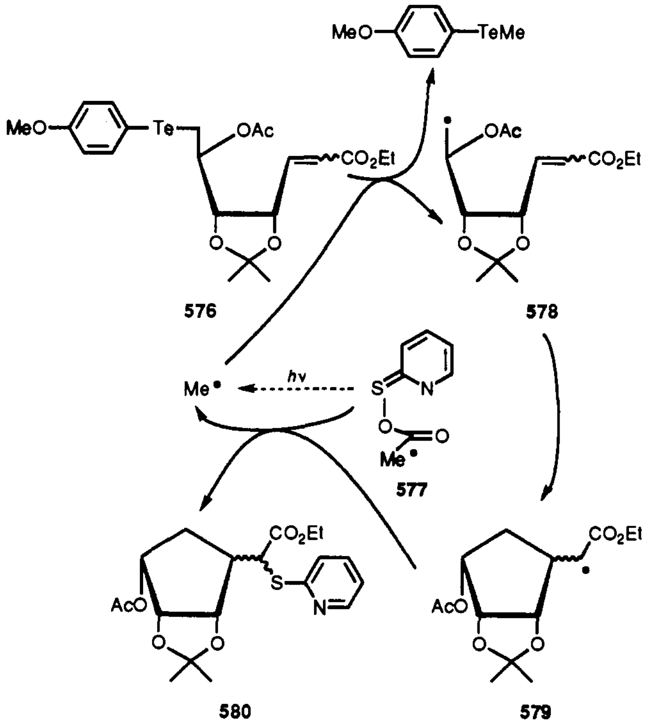


R	R_{endo}:R_{exo}	% yield
CH_2CO_2Me	90:10	80
$CH(Me)CO_2Et$	68:14:12:6	76
CH_2OMe	91:9	30
Me	91:9	40

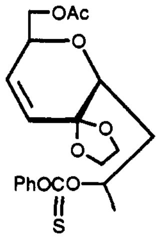
The total yields of the products were markedly dependent on the nature of the groups attached to the olefinic double bonds of the substrates, but the isomer ratios for the products were effectively the same in each case. The major isomers of **575a,b** had the *S* configuration at *C*-7 (sugar numbering) i.e. they had the substituents R *endo* with respect to the oxabicyclo[3.3.0]octane rings, as expected if 5-*exo-trig* radical cyclization proceeds via a "chairlike" transition state.[279] It seems probable that the major isomers **575c,d** had the same configuration at C-7.

In each of the examples discussed thus far in this section, the requisite 5-hexenyl radicals were produced by use of tributyltin hydride with AIBN as radical initiator. Practical difficulties (notably reduction of the first-formed radicals) commonly attend the use of this system; however, a new method recently reported by Barton and co-workers is of particular interest.[285] A radical-exchange reaction between D-ribose-derived anisyl tellurides **576** and methyl radicals initially generated photochemically from the 2-thiopyridone derivative **577** give 5-hexenyl radicals **578** which undergo the usual 5-*exo-trig* cyclization to **579** which react with the thiopyridone derivative **577** to produce the final alicyclic products **580** together with methyl radicals which are then available to continue the chain reaction (Scheme 106). The cyclopentanes were obtained in 85% total yield, the 1,4-*cis*- and 1,4-*trans*-substituted isomers being formed in the proportions 11:89.

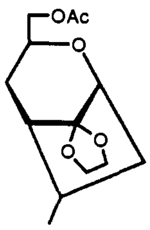
Scheme 106



That radical cyclizations can be used to make the 2-oxabicyclo[3.2.1]octane ring systems of the sesquiterpene trichothecenes was demonstrated by tributyltin hydride-promoted ring closure of the anhydrononit-2-yl radical derived from the *C*-glycosidic compound **581** to give **582** (35% unoptimized).[286] Presumably because of unfavorable dipolar factors, the enone precursor of **581** did not cyclize.



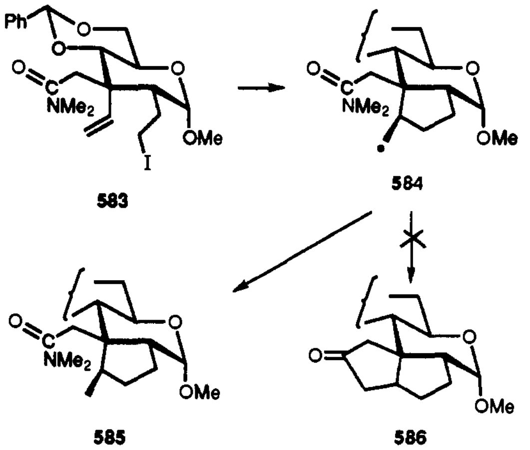
581



582

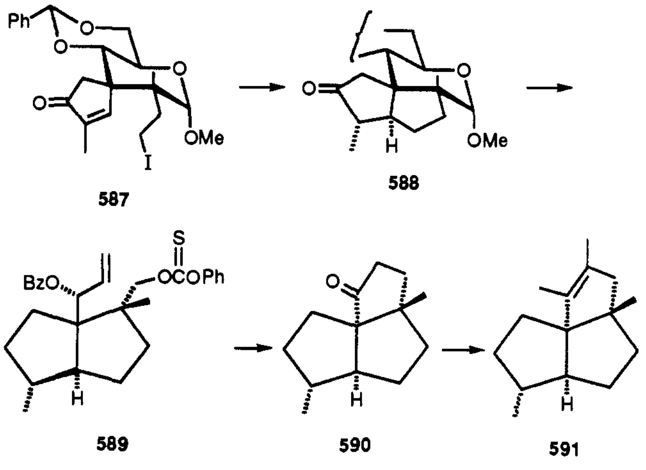
c. Cyclizations within Branched Sugar Chains. Radical cyclizations of this type were first reported by Fraser-Reid's group, the simplest case involving conversion of the triply branched D-mannose-derived unsaturated iodide **583** to the methylcyclopentane derivative **585** on treatment with tributyltin hydride (Scheme 107).[287,288] Cyclization of the initially formed carbon-centered radical is undoubtedly facilitated here by the *cis* relationship between the iodoethyl and vinyl groups since this arrangement necessarily leads to the energetically favored formation of a *cis*-6/5 ring junction in the intermediate cyclopentylmethyl radical **584**. This radical then undergoes quenching by reaction with the tin hydride to give the final product **585** rather than intramolecular trapping by the amide group to give the pyranosidic diquinane **586**.

Scheme 107

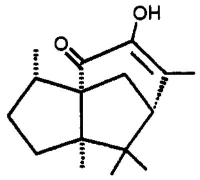


The closely related diquinane **588** was subsequently obtained, however, through a simple radical cyclization based on the iodide **587**, also derived from D-man-

Scheme 108



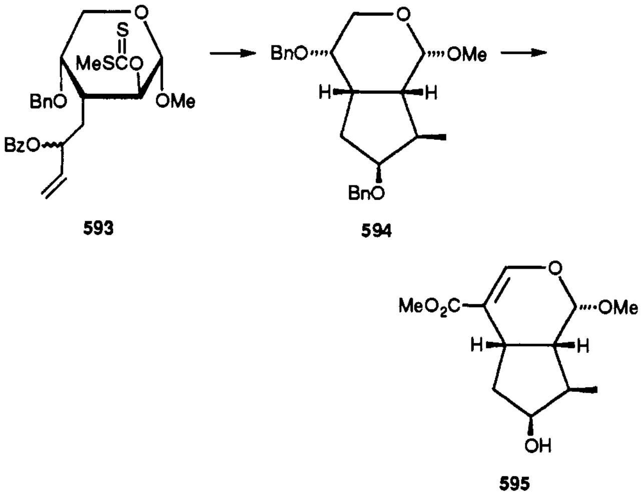
nose.[288,289] Compound **588** was then converted into the monothiocarbonate **589** which, on treatment with tributyltin hydride, underwent smooth 5-*exo-trig* radical cyclization, thereby ultimately permitting stereoselective synthesis of the angularly fused triquinanone **590** and hence the hydrocarbon (−)-silphiperfolene **591** (Scheme 108).[290] In a related fashion, but involving triply branched enyne intermediates, the related (−)-α-pipitzol (**592**) was made[290] among several highly substituted diquinanes.[291] (See also section III.B.5.)



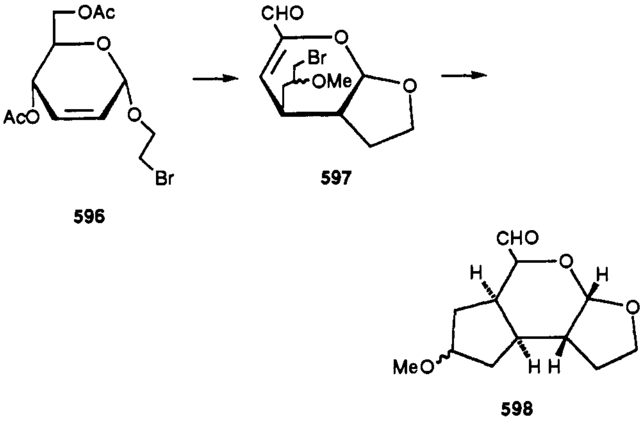
592

In a simpler example the *cis*-fused cyclopentanopyranoside **594** was obtained stereoselectively on treating the unsaturated dithiocarbonate **593** (made from methyl 2,3-anhydro-α-D-lyxopyranoside) with AIBN/tributyltin hydride (Scheme 109) and converted into the iridoid glycoside aglycon, 1-α-*O*-methylloganin (**595**).[292] In reciprocal fashion, the radical being in the branch and the trap within the sugar chain, analogous cyclopentanopyranosides **598** were synthesized by 5-*exo-trig* cyclization of radicals derived from a mixture of epimeric bromoenals **597** prepared following cyclization of **596** by allyltributyltin/AIBN which caused concurrent introduction of branch points at C-2 and C-3 (Scheme 110).[293]

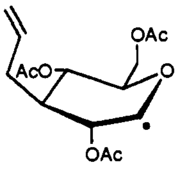
Scheme 109



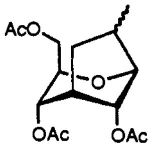
Scheme 110



Finally, Giese *et al.* developed an alternative route to 2-oxabicyclo[3.2.1]octanes **600** (59%, mainly *exo*) (cf. **582**) by usual treatment of the corresponding 3-*C*-allyl-α-D-glucopyranosyl iodide.[294] Formation of such products indicates that the reacting conformation of the intermediate radical has the allyl group at C-3 axially disposed in either a $^1C_4$ chair or the boat **599**. Additional ESR evidence provided by Giese *et al.* suggests that the latter of these alternatives is the more likely.[295]



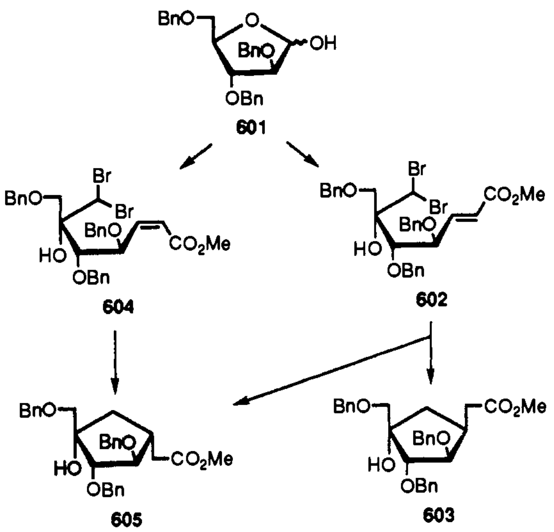
599



600

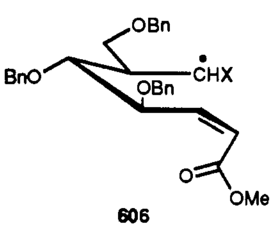
d. Cyclizations within Sugar Chains Which Are Both Extended and Branched. Mention has already been made of the pioneering work of Wilcox and Thomasco in effecting radical cyclization within simple extended sugar chains (see section III.B.1.b). In subsequent investigations, Wilcox and Gaudino caused analogous cyclizations of the unsaturated *gem*-dibromo esters **602** and **604** (Scheme 111), both of which were obtained from the commercially available D-arabinofuranose triether **601** through a six-step reaction sequence which led to initial extension and then branching of the sugar chain. The steric course of cyclization of the radicals derived from the two esters on treatment with AIBN/tributyltin hydride was critically dependent upon the stereochemistry about the olefinic double bond. Thus, whereas cyclization of the (*E*)-ester **602** proceeded to give **603** and **605** without any stereocontrol, the corresponding reaction of the (*Z*)-ester **604** proceeded with stereospecificity to give only ester **605** which was subsequently converted into

Scheme 111

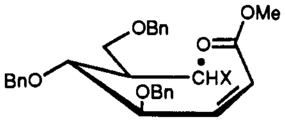


carba-β-D-fructofuranose and the corresponding 6-phosphate derivative.[296,297]

The exclusive formation of product **605** in the latter case indicates that ring closure is effected with the intermediate radical in the "chairlike" conformation **606** which allows for ready overlap between the radical center at C-1 and the unsaturated center at C-5 while minimizing steric interactions involving the terminal ester group; it also permits the relatively bulky substituents at C-2, C-3, and C-4 to occupy quasiequatorial positions. Cyclization via the alternative "boatlike" conformation **607** would be expected to lead to the formation of product **603**, but this pathway is presumably precluded by unfavorable steric interactions in **607** between the ester group and the benzyloxy group at C-4. Moreover, the absence of any such unfavorable interactions in the radicals derived from the (*E*)-ester **602** could well be responsible for the lack of stereocontrol in the cyclization of this compound.



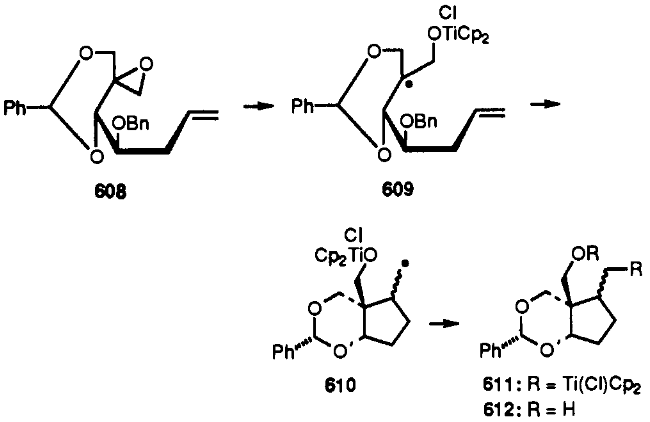
606

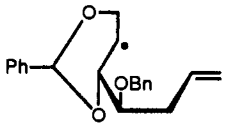


607

Another example of stereoselective ring closure within a sugar chain which is both extended and branched was observed by Nugent and RajanBabu on treating the epoxyalkene **608** with 2 molar equiv of bis(cyclopentadienyl)titanium(III) chloride in anhydrous THF.[298] After quenching the reaction with aqueous acid, a mixture of epimeric *cis*-fused products **612** was obtained in 70% total yield via **610** and **611**, the *endo*/*exo* isomer ratio being 83:17 (Scheme 112). The steric course of cyclization of the initially formed tertiary radical **609** is thus effectively the same as that found for the structurally analogous secondary radical **613** (see section III.B.1.b). The high degree of stereoselectivity observed in the case of radical **609** contrasts sharply, however, with that observed with the related acyclic radical **615** derived in similar fashion from epoxyalkene **614** (Scheme 113). In this latter case, a 45:30:15:10 mixture of the four possible stereoisomeric cyclopentane derivatives **616** is produced.

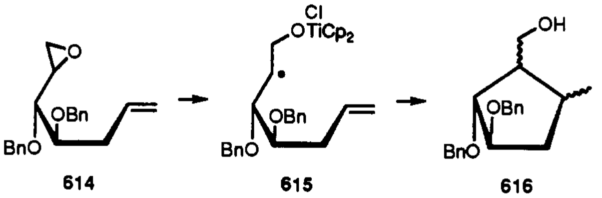
Scheme 112





613

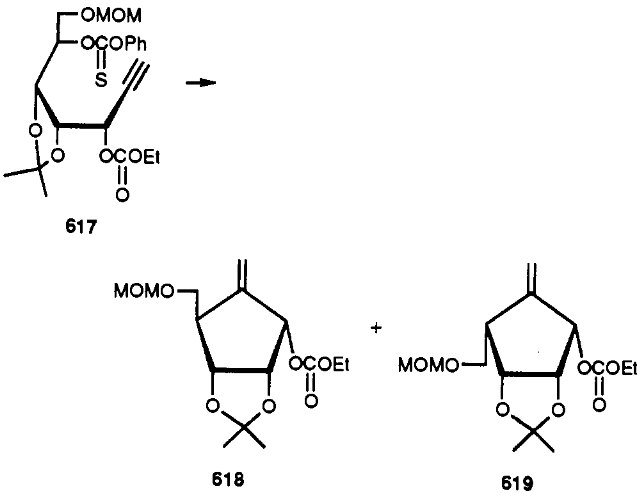
Scheme 113



2. Simple Cyclizations of 5-Hexynyl Radicals

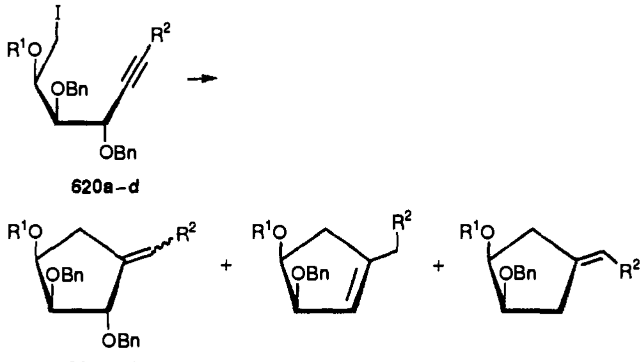
Although carbon–carbon triple bonds are well known to act as effective radical acceptors in 5-*exo-dig* radical cyclizations,[102,299] there have been only a few cases in which "simple" (as distinct from "competitive and serial") reactions of this type have been used to construct cyclopentane rings from carbohydrate-derived precursors. In the first such case, Gaudino and Wilcox used the D-ribose-based alkyne **617** which was heated with AIBN/tributyltin hydride in benzene.[300] A mixture of the epimeric cyclopentanes **618** and **619** (isomer ratio 6.4:1) was thereby obtained in 63% yield (Scheme 114), the dominant *exo* isomer **618**, a carba-α-D-ribose derivative, being isolated in 30% overall yield from 2,3-*O*-isopropylidene-5-*O*-(methoxymethyl)-D-ribose.

Scheme 114



In the above work, the ethynyl group involved in the radical cyclization was introduced in toto during synthesis of compound **617**. Doutheau and co-workers, on the other hand, used Wittig reactions applied to 2,3-di-*O*-benzyl-4,5-*O*-isopropylidene-L-arabinose as means for preparing the series of iodoalkynes **620a-d** in which one carbon of the triple bond corresponds to C-1 of the aldose derivative.[301] On treatment with AIBI/triphenyltin hydride in boiling benzene, these iodides afforded the corresponding 5-hexynyl radicals, but the products (**621**) of subsequent 5-*exo-dig* cyclization were isolated in only low yields (Scheme 115). The major products in each case, **622** and **623**, lacked one of the benzyloxy groups of the original iodides **620** presumably

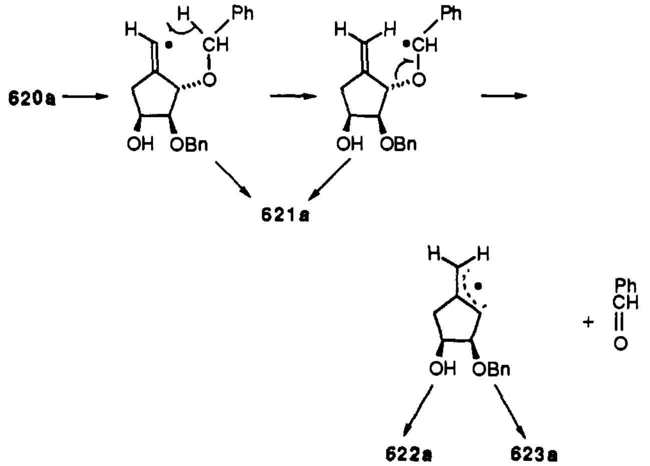
Scheme 115



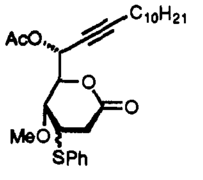
	R¹	R²	% yield 621a-d	622a-d	623a-d
a	H	H	8	62	18
b	H	Me	16	50	29
c	H	$SiMe_3$	3	63	11
d	Ac	CO_2Me	0	19	44

because 5-*exo-dig* cyclization was followed by intramolecular hydrogen atom transfer and then elision of benzaldehyde, as shown in Scheme 116 for the case of the parent iodide **620a**.

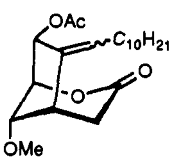
Scheme 116



In an example of bicyclic ring formation by this approach, the sulfide **624**, made by conjugate addition of benzenethiol to the corresponding unsaturated aldono-γ-lactone, on treatment with AIBN/tributyltin hydride, yielded a 1:1 mixture of the stereoisomeric bicyclic lactones **625**.[283]



624



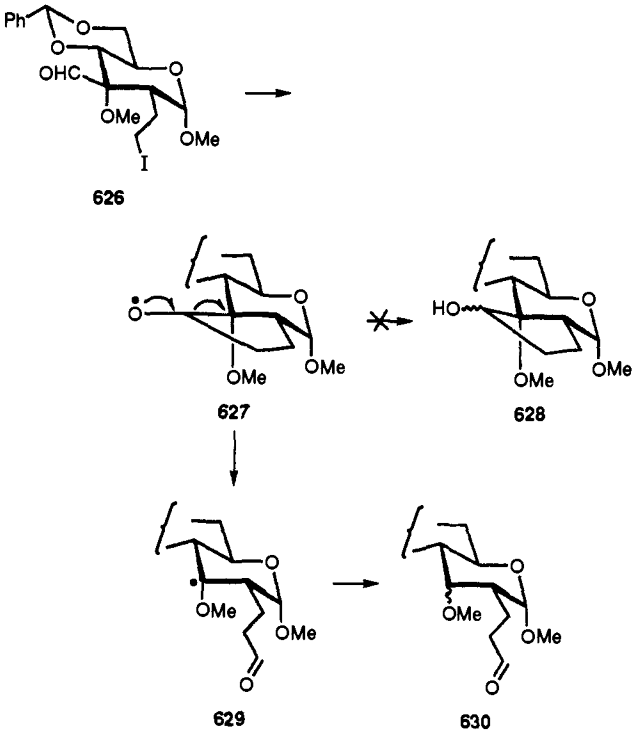
625

The overall total yield of these products was only 20%, however, which is much less than the yields of analogous bicyclic products obtained on application of the same methodology to sulfides having alkenyl rather than alkynyl side chains (see section III.B.1.b).

3. Simple Cyclizations of 5-Oxoalkyl Radicals

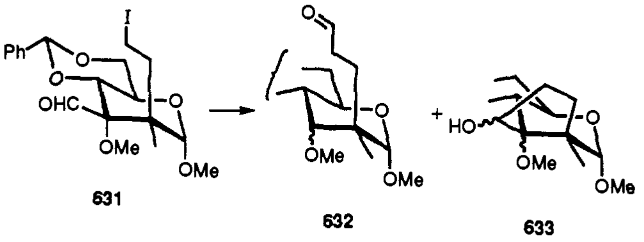
Their observations that aldehyde groups can act as efficient intramolecular radical traps and lead to cyclohexanol rings (section II.B) led Tsang and Fraser-Reid to investigate their use in the preparation of cyclopentanols.[111] The iodopyranoside **626**, on treatment with AIBN/tributyltin hydride, gave the two epimeric methoxyaldehydes **630** in high yield rather than the desired cyclopentanopyranosides **628** (Scheme 117). This situation presumably arises because the initially formed primary alkyl radical interacts with the neighboring aldehyde group, as desired, but the resulting cycloalkoxy radicals **627** undergo β-scission to give the stabilized methoxyalkyl radical **629** and hence the aldehyde translocation products **630**.

Scheme 117

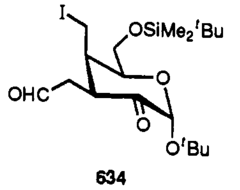


Analogous products **632** were similarly obtained in 50% yield from the iodopyranoside **631** under the same experimental conditions, but in this case a significant proportion of the intermediate cycloalkoxy radicals did not undergo β-scission and the desired cyclopentanopyranosides **633** were obtained in 28% total yield with the isomer ratio of 1:1 (Scheme 118).[111]

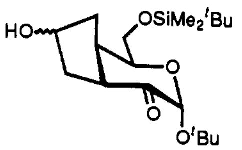
Scheme 118



The suitability of the above approach to the synthesis of cyclopentane derivatives is thus seen to be critically dependent on the extent to which β-scission intervenes, and in the cases of iodides **626** and **631** this scission is facilitated by the methoxy groups at C-3 which stabilize the intermediate radicals e.g. **629**. With compound **626**, β-scission of the derived **627** is further facilitated by the release of steric strain involved in the *trans*-fused cyclopentanopyran system. As with iodide **631**, the interacting ring substituents are *cis* related in compound **634** which afforded the cyclopentanopyranosides **635** in 70% total yield and isomer ratio 5:1. No aldehyde translocation products analogous to **630** and **632** were produced in this case.



634



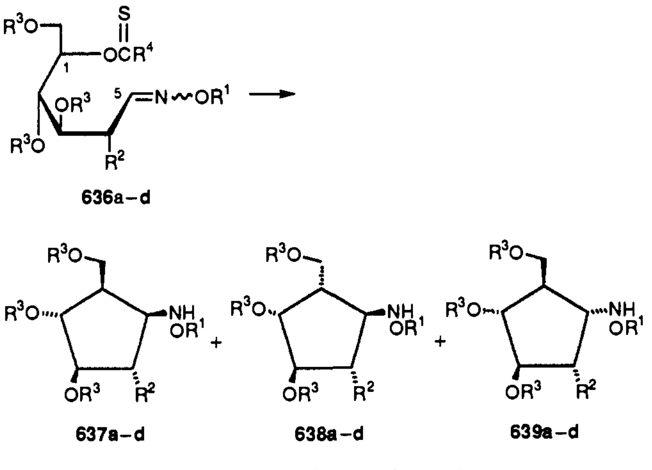
635

Work with model compounds has shown how cycloalkanols can be readily formed from ω-formylalkyl radicals, cyclohexanol production being particularly favored—even in the presence of accessible double bonds.[110,302]

4. Simple Cyclizations of 5-Oximinoalkyl Radicals

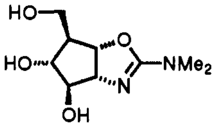
The problem of β-scission encountered above (section III.B.3) with reactions which involve the use of aldehyde groups as radical acceptors is especially acute in cases where an oxygen-bonded substituent is attached to the α-carbon of the initial aldehyde. No such problem is encountered, however, in analogous reactions which utilize *O*-alkyl aldoxime groups as radical acceptors. Thus, despite the fact that the glucose-derived oximes **636a-c** all have either a methoxy or a benzyloxy substituent attached to the carbon α to the oximino group, they afford high total yields (~90%) of cyclopentane derivatives on treatment with AIBN/tributyltin hydride (Scheme 119). Specifically, Bartlett *et al.* found that ethers **636a,b** gave high yields of 63:37 mixtures of cyclopentanes **637a,b** and **638a,b** and ether **636c** gave a 60:31:9 mixture of cyclopentanes **637c**–**639c**.[303] In each case there is thus a preponderance of the 1,5-*cis* product **637** to be expected if cyclization again occurs while the intermediate radical preferentially adopts a "chairlike" conformation having the substituents at C-2, C-3, and C-4 in quasiequatorial orientations.

Scheme 119



	R1	R2	R3	R4
a	Bn	OBn	Bn	Ph
b	Me	OBn	Bn	Ph
c	Bn	OMe	Me	Ph
d	Bn	NHCbz	Ac	Imid

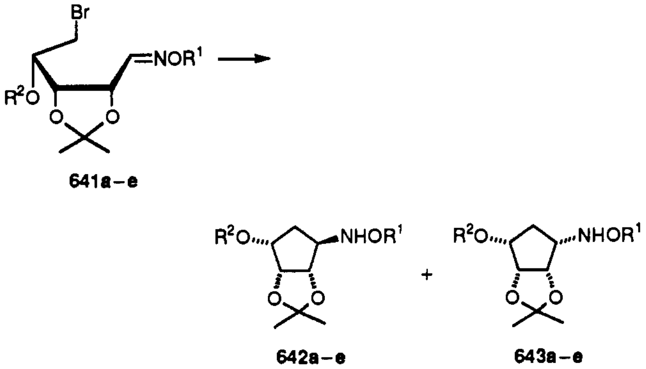
Simpkins *et al.* have effected the analogous radical cyclization of oxime ether **636d**, derived from D-glucosamine, and thereby obtained a mixture of the cyclopentane derivatives **637d**-**639d**, from which product **638d** was isolated in 12% yield.[304] Derivatives **637d** and **639d** on the other hand, could only be obtained as an inseparable mixture (54% total yield), but fortunately it proved possible to convert *both* isomers into the target compound, allosamizoline (**640**), the aglycon of the chitinase inhibitor allosamidin.



640

In parallel work, Marco-Contelles *et al.* have successfully cyclized a series of oxime ethers **641** readily prepared from 5-bromo-5-deoxy-2,3-*O*-isopropylidene-α-D-ribofuranose.[305] In each case cyclization was effected by treating the oxime ether in the usual way (Scheme 120). Preferential formation of the *exo* products **642** clearly occurs in all cases.

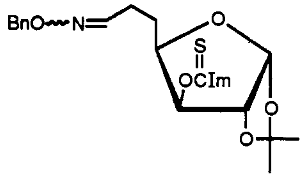
Scheme 120



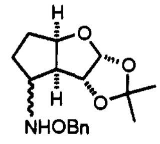
	R1	R2	% yield	642:643[a]
a	Bn	H	75	100:0
b	Bn	Si(Me)$_2$^{t}Bu	53	100:0
c	Bn	Ac	52	100:0
d	Bn	Bz	58	89:11
e	Me	Bz	71	82:20

[a] Mixture of *syn* (70%) and *anti* (30%) oximes used in each case.

More recently, the same group efected the stereoselective radical cyclization of a mixture of the stereoisomeric oxime ethers **644** derived from diacetone glucose.[306] The resulting mixture of epimeric *O*-benzylhydroxylamines **645** was obtained in 55% yield with 80% diastereomeric excess, the major isomer having the *S* configuration at C-7 (sugar numbering), as would be expected if cyclization proceeds via the usual "chairlike" transition state. The course of the reaction is thus entirely analogous to that observed for the cyclization of structurally related unsaturated esters (see section III.B.1a).



644

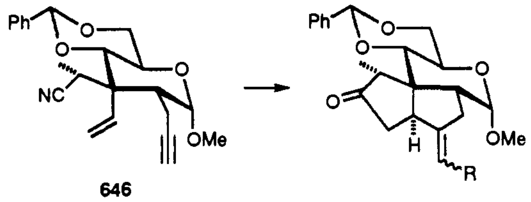


645

5. Competitive and Serial Radical Cyclizations

In an extension of their work on the synthesis of diquinane systems on carbohydrate templates (section III.B.1.c) Fraser-Reid's group carried out a tributyltin hydride-induced serial cyclization on enyne **646** to give the alkenylstannane **647** which, on stirring with silica gel afforded **648** (65% from **646**) (Scheme 121).[291] It was this methodology that led to (−)-α-pipitzol (**592**).[290]

Scheme 121

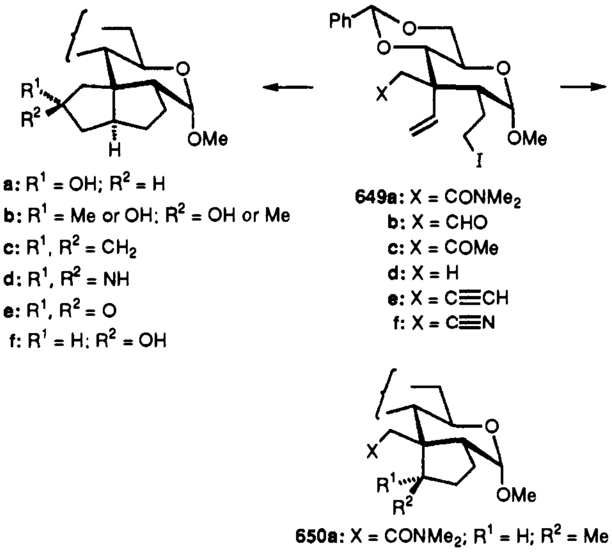


646

647: R = $SnBu_3$
648: R = H

Previously, in closely related work, the same group had shown that whereas the amido iodide **649a** undergoes radical cyclization to give **650a** (Scheme 107), the analogue **649b** with an aldehydo group in place of the amido function preferentially cyclized onto the aldehyde (6-*exo-trig*) (73%), but also gave minor amounts (18%) of the diquinane **651a** derived by consecutive 5-*exo-trig* cyclizations[111a,288] (Scheme 122).

Scheme 122



651a: R^1 = OH; R^2 = H
b: R^1 = Me or OH; R^2 = OH or Me
c: R^1, R^2 = CH_2
d: R^1, R^2 = NH
e: R^1, R^2 = O
f: R^1 = H; R^2 = OH

649a: X = $CONMe_2$
b: X = CHO
c: X = COMe
d: X = H
e: X = C≡CH
f: X = C≡N

650a: X = $CONMe_2$; R^1 = H; R^2 = Me
b: X = COMe; R^1 = H; R^2 = Me
c: X = COMe; R^1 = Me; R^2 = H

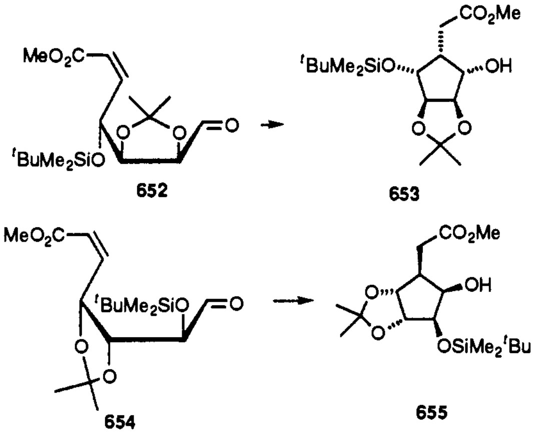
Surprisingly, no 6-*exo-trig* cyclization occurred with the methyl ketone **649c**, the main products now being the reduced **649d** (15%), the "simple" 5-*exo-trig*-derived **650b** (23%) and the diquinane **651b**.[111b]

By use of the alkyne **649e** and nitrile **649f** the diquinanes **651c** and **651d** were formed in high yields and as sole products by consecutive 5-*exo-trig* and 5-*exo-dig* processes,[111a,288] and from the imine **651d**, the ketone **651e** and hence the alcohol **651f** were obtained.

6. Reductive Cyclization of Unsaturated Aldehydes

A totally different radical-based route to cyclopentanes involving the use of samarium diiodide (2 equiv) as a one-electron reducing agent has recently been developed by Enholm and colleagues.[307] Intramolecular coupling between the aldehydic and electron-deficient alkene carbon atoms of compounds such as **652** and **654**, which were made from pentose derivatives by Wittig extension at C-1 followed by oxidation at C-5, is promoted by this reagent, the hydrogen required for the completion of the processes being provided by methanol added to the solvent THF. A notable feature of the reaction is the high and unexpected stereoselectivity observed in some instances. Thus the (*Z*)-alkenes **652** and **654** afforded the cyclopentenes **653** and **655** (~65% yield) with substituents at the new asymmetric centers *syn* to each other (Scheme 123) together with ≤1% of their distereoisomers. On the other hand, (*E*)-alkenes tend to give *anti*-related products with somewhat less selectivity.

Scheme 123



652 **653**

654 **655**

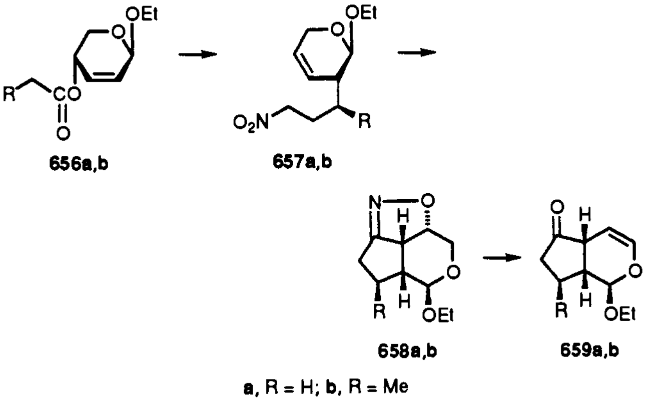
C. Cycloaddition Reactions

1. 1,3-Dipolar Cycloadditions

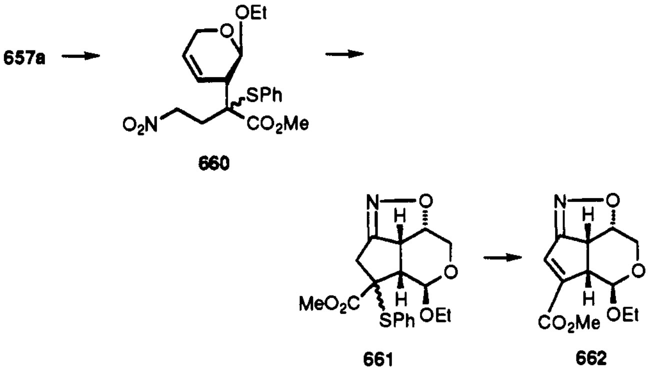
Intramolecular reactions of this type have been found to be extremely useful for the synthesis of five-membered carbocycles, the ring-forming steps involving either nitrile oxides or nitrones (derived from 5-enals) as the key intermediates. These are produced *in situ* and intramolecularly trapped by alkene groups to give cyclopentanoisoxazolines and cyclopentanoisoxazolidines, respectively (c.f. section II.C.1).

Reactions proceeding via nitrile oxides have been extensively utilized by Curran's group for the synthesis of iridoid cyclopentopyran derivatives. Thus, the D-xylal-derived ethyl β-glycosides **656a,b** were converted, by use of the Ireland–Claisen rearrangement in the key step, to the unsaturated nitroacetals **657a,b** which, on treatment with methyl isocyanate and triethylamine, readily afforded the corresponding nitrile oxides. Cyclization of these latter intermediates then gave the Δ^2-isoxazolines **658a,b** (50–60% yield) and hence the oxahydroindenones **659a,b** (Scheme 124). The nitroacetals **660**, prepared from **657a**, were similarly converted to the diastereomeric Δ^2-isoxazolines **661** in essentially quantitative yield. Oxidation of the sulfide groups followed by thermolysis of the resulting sulfoxides then afforded the unsaturated ester **662** as a single stereoisomer in 59% yield (Scheme 125).[308]

Scheme 124



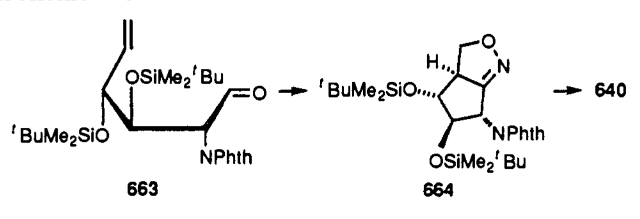
Scheme 125



In an analogous manner, the C-1 epimer of **656a** gave the corresponding epimer of **662** which was then utilized in a highly stereoselective synthesis of (–)-specionin, an iridoid with potent antifeedant activity against the Eastern spruce budworm.[308,309]

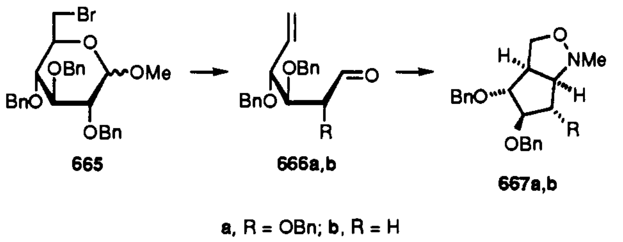
Tatsuta and colleagues have also utilized a nitrile oxide as intermediate in their recent synthesis of (–)-allosamizoline (**640**) from the 2-deoxy-2-*N*-phthalimido-D-glucose-derived enal **663** via the Δ^2-isoxazoline **664** (Scheme 126). The nitrile oxide was generated in this case by the action of hypochlorite on the oxime of **663**.[310]

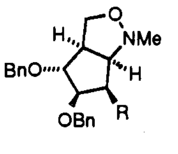
Scheme 126



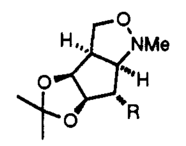
Reactions of this category involving nitrones as intermediates were first carried out by Bernet and Vasella who showed that 6-bromo-6-deoxyglucopyranosides **665**, on treatment with zinc and ethanol, undergo reductive ring opening to the corresponding acyclic 5,6-dideoxyhex-5-enose **666a** together with a small amount of **666b** formed by reductive elimination (Scheme 127). Reaction of the mixture of **666a** and **666b** with *N*-methylhydroxylamine then readily affords the corresponding unsaturated nitrones which undergo spontaneous cyclization to the 2-aza-3-oxabicyclo[3.3.0]-octane derivatives **667a** (yield 80%) and **667b** (yield 5%), respectively.[311a] Compounds **668a,b** (yields 64% and 5% respectively)[311b] and **669a,b** (72–78%) together with **669c** (5–7%)[311c] were synthesized by the same procedure from a 6-bromo-6-deoxy-D-mannoside and -galactoside, respectively, and the D-mannose-derived **668a** was used to obtain the potent α-mannoside inhibitor **670**.[312]

Scheme 127



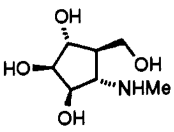


668a: R = OBn
b: R = H

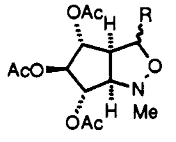


669a: R = OBn
b: R = OSiMe₂ᵗBu
c: R = H

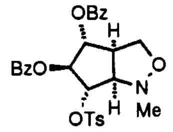
Application of this methodology to appropriate D-glucose derivatives provided ready access to the 2-aza-3-oxabicyclo[3.3.0]octane derivatives **671** (49%), **672** (54%), and **673** (73%),[313] the last of these being subsequently transformed into the *endo*-epoxy lactone **674**, a key intermediate in one synthetic route to prostaglandins.[314]



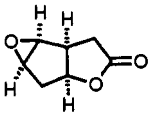
670



671: R = H
672: R = SPh



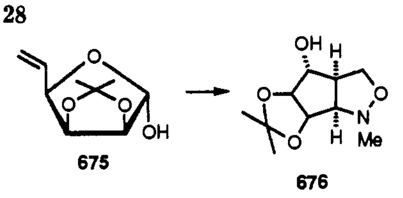
673



674

Carbohydrate-derived unsaturated lactols also afford the corresponding acyclic nitrones on reaction with *N*-methylhydroxylamine, and spontaneous intramolecular 1,3-dipolar cycloaddition again ensues. In this way Bernet and Vasella obtained the *cis–anti–cis* tricyclic product **676** in 84% yield from the lactol **675**[311b] (Scheme 128), while Shing *et al.* prepared the epimeric

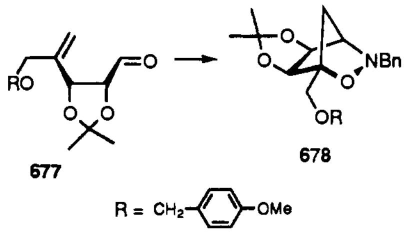
Scheme 128



alcohol product in 94% yield from the D-ribose-derived C-4 epimer of **675**.[315]

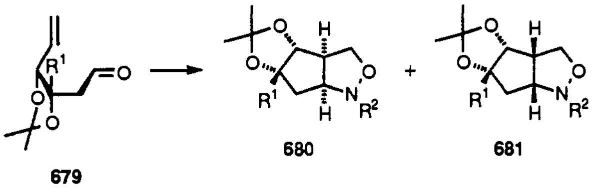
One example has been found in which a 4-enal has been used to make a cyclopentane derivative, the reaction occurring by reverse addition of the nitrone to the alkene and giving a bicyclo[2.2.1]heptane system. Thus the enal **677**, obtained from L-*erythro*-pentulose (L-ribulose) in six steps (70% yield), on treatment with *N*-benzylhydroxylamine, gave a 84% yield of the bicycloheptane analogue **678** (Scheme 129) which was subsequently transformed into (−)-neplanocin A (**512**).[316]

Scheme 129



A detailed study of intramolecular nitrone/alkene cycloaddition reactions by Baldwin and Gedon has recently shown that the stereochemical outcome is very sensitive to the substituent on the nitrone nitrogen atom.[317] Carbohydrate-derived substrates studied included enals of type **679** which were treated with a series of N-substituted hydroxylamines (R^2NHOH). Mixtures of *cis–anti–cis* (**680**) and *cis–syn–cis* (**681**) tricyclic products were thereby obtained (Scheme 130), the isomer ratios varying from 2:1 to greater than 20:1.

Scheme 130



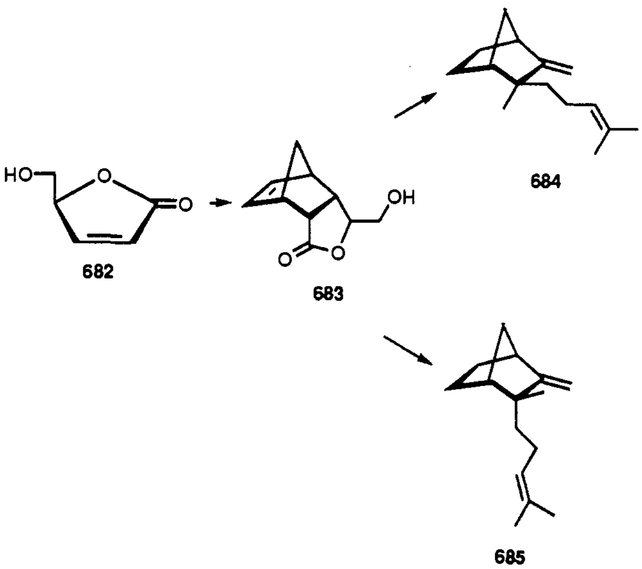
R^1 = H, Me, ^{i}Pr; R^2 = Me, (*R*)- and (*S*)-CHMePh, (*R*)- and (*S*)-CH^{i}PrCH$_2$OMe, (*R*)-CH^{i}PrCO$_2$Me

2. [4 + 2] Cycloadditions

a. Reactions of Carbohydrate Dienophiles. A number of Diels–Alder reactions of carbohydrate dienophiles with cyclopentadiene have already been considered in section II.C.2.a since in each case the adduct formed contains a new six-membered carbocyclic unit. The adducts in question, however, also incorporate new five-membered carbocyclic rings, and therefore these reactions could equally well have been considered in the present section of this review. Likewise, additional examples which are now considered under the heading of "syntheses of cyclopentanes" are equally relevant to the earlier discussion.

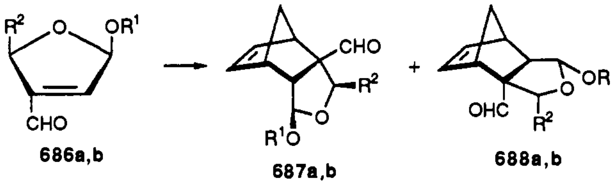
On heating with a large excess of cyclopentadiene at 140 °C, the D-mannitol-derived buten-2-olide **682** gave the crystalline *endo* adduct **683** (60% isolated yield) which served as a convenient common starting material for elegant stereocontrolled syntheses of (+)-β-santolene **684**, (+)-*epi*-β-santolene **685**, and their respective enantiomers, these compounds being well-known constituents of East Indian sandalwood oil (Scheme 131).[318]

Scheme 131



As expected, the Diels–Alder reaction between cyclopentadiene and the D-arabinose-derived carboxaldehyde **686a** also involves almost exclusive addition to the less hindered face of the dienophile, but surprisingly the adduct **687a** is formed in much greater proportions than the isomer **688a**, the ratio varying from 2:1 to 4:1 depending on the temperature at which the reaction is performed (Scheme 132). These results were checked by repeating the reaction with the enantiomer of **686a**. High p-facial selectivity was also observed in the reaction of cyclopentadiene with the more highly substituted aldehyde **686b** (obtained from methyl β-D-glucopyranoside), but the (**687b**/**688b**) ratio was noticeably lower (1.3:1) in this case.[319]

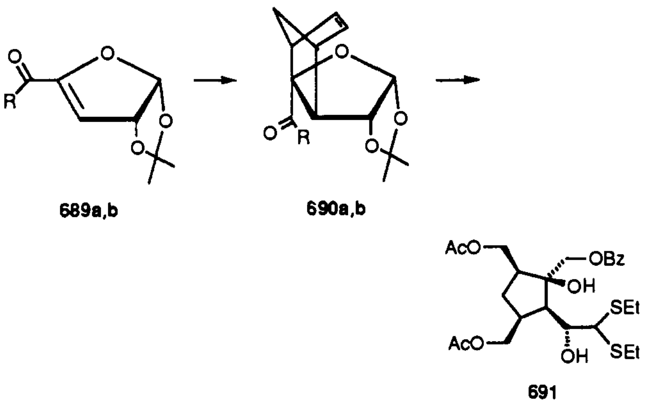
Scheme 132



a, R^1 = Bn, R^2 = H; **b**, R^1 = Me; R^2 = CH$_2$OSiMe$_2$^{t}Bu

The reactions of aldehyde **689a** and ketone **689b** with cyclopentadiene afforded the adducts **690a** and **690b**, respectively, as single diastereomers in 90 and 98% yields. The additions thus occur exclusively on the more accessible face of the dienophile and, for reasons which are not apparent, are entirely *exo* selective. Adduct **690a** was subsequently transformed into the highly functionalized cyclopentane derivative **691** (Scheme 133).[320]

Scheme 133

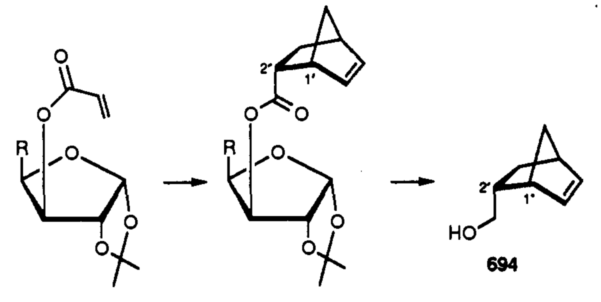


689a,b 690a,b 691

a, R = H; b, R = Me

Diastereoselectivity in the Diels–Alder reactions of cyclopentadiene with the acrylate esters **692a,b** (both derived from di-*O*-isopropylideneglucose) was effected by initially converting the esters to the corresponding trimethylsilyl ethers which were subsequently treated with titanium tetrachloride at −78 °C. Reaction of the resulting complexes with cyclopentadiene then led to highly stereoselective formation of the *endo* adducts **693a,b** both of which gave the (1′*R*,2′*R*)-norbornenylmethanol (**694**) on reductive cleavage (Scheme 134).[321,322]

Scheme 134



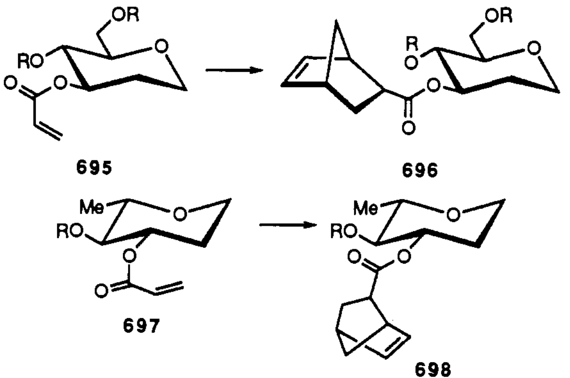
692a,b 693a,b 694

a, R = CH(OH)CH$_2$OH; b, R = CH$_2$OH

Acrylate esters **695** and **697** have also been used as chiral templates for stereoselective cycloaddition reactions with cyclopentadiene, best results being obtained when the esters were treated with diisopropoxytitanium dichloride prior to addition of the diene. In this way compound **695** gave almost exclusively the (1′*R*,2′*R*)-*endo* adduct **696** while ester **697** gave the (1′*S*,2′*S*)-*endo* adduct **698** (Scheme 135), again with very high selectivity.[322,323]

Mention has already been made (see section II.C.2.a) of the fact that two *trans*-disubstituted norbornenes of type **699** and two of type **701** (Scheme 136) may be obtained by cycloaddition of cyclopentadiene to the appropriate (*E*)-unsaturated aldonic ester under either thermal or Lewis acid-catalyzed conditions. Subsequent oxidative cleavage of the carbon–carbon double bond of these norbornenes has provided access to the corresponding tetrasubstituted cyclopentane derivatives **700** and **702**, respectively, and hence to a variety of other chiral cyclopentanes. Moreover, it has recently been shown that analogous *cis*-disubstituted norbornenes may be obtained in high yield and with high stereoselectivity by use of appropriate (*Z*)-unsaturated aldonic esters in these addition reactions, thereby providing potential access to an even wider range of isomeric cyclopentane derivatives.[146,324–326]

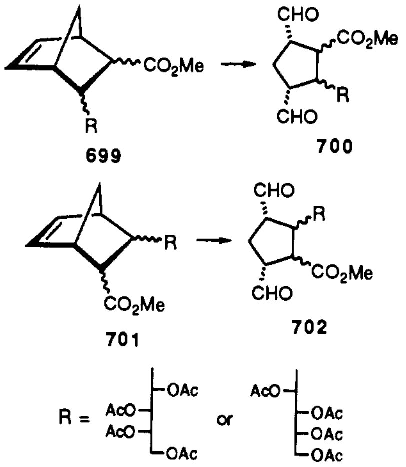
Scheme 135



695 696 697 698

R = pivaloyl

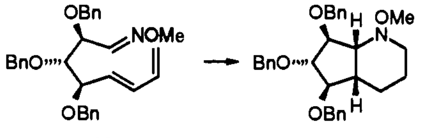
Scheme 136



699 700 701 702

b. Intramolecular Reactions. Intramolecular [4 + 2] cycloaddition reactions of 1,3,8-nonatrienes result in the formation of products which necessarily incorporate new six- *and* five-membered carbocyclic units. Formation of the indene derivative **325** on heating the triene **324** in toluene at 160 °C (section II.C.2.c) involves one such reaction, and cyclization of the related oximes **703** to the azaindene derivative **704** (Scheme 137) under the same conditions is analogous.[167b,327]

Scheme 137

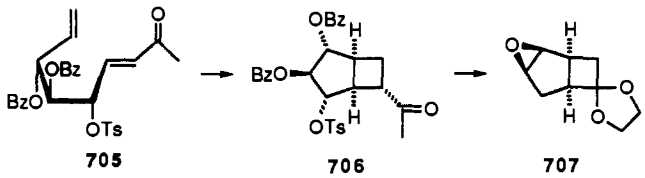


703 704

3. [2 + 2] Cycloadditions

There has apparently been only one recorded instance in which a sugar-derived 1,6-hexadiene has been induced to undergo an intramolecular [2 + 2] cycloaddition reaction, thereby forming a new bicyclo[3.2.0]heptane ring system. On irradiation at 350-nm in dilute benzene solution, the nona-3,8-dienulose derivative **705** gave the bicyclic product **706** (86% yield) from which the prostaglandin intermediate **707** was subsequently derived (Scheme 138).[328,329] Compound **706** was also used as a convenient starting point for two new syntheses of another prostaglandin intermediate, the *endo*-epoxy lactone **674**, previously obtained by other means (section III.C.1).[314]

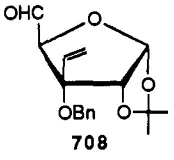
Scheme 138



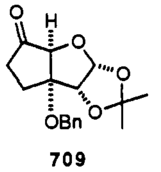
D. Cyclizations Involving Organometallic Intermediates/Complexes

While functionalized cyclohexanes are readily made via mercury- or palladium-containing intermediates from hex-5-enopyranosyl derivatives (sections II.D.1 and II.D.2), there are no analogous routes to cyclopentanes. Efforts to carbocyclize 4-enofuranosyl compounds resulted only in elimination processes or in the hydration of the double bonds, the cyclizations being disfavored by their (enol-endo)-5-*exo-trig* character.[330] However, several other metal-dependent routes to cyclopentane ring systems have been identified recently, their reported efficiencies suggesting that they hold considerable potential as good synthetic methods.

In the same way that compound **385**, with a vicinal formyl and allyl group, underwent cyclohexane ring formation by the linking of the carbon atoms of these groups, the formyl/vinyl system of compound **708** reacted to give the 2-oxabicyclo[3.3.0]octane **709** quantitatively (60% isolated) in another example of rhodium(I) hydroacylation followed by extrusion of the metal. Catalytic amounts of $[(Ph_3P)_2RhCl]_2$ were used at 75 °C in dichloromethane under ethylene.[215]

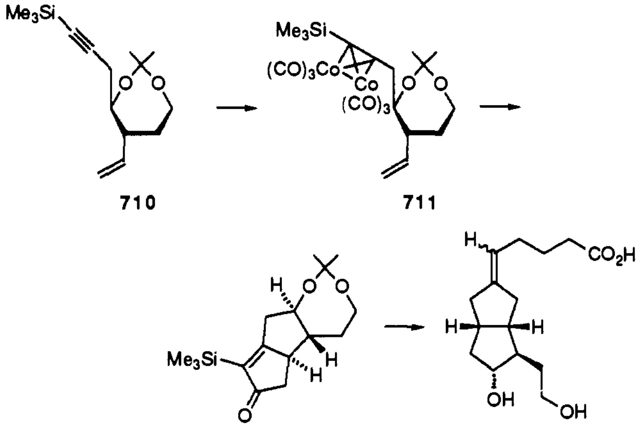


708

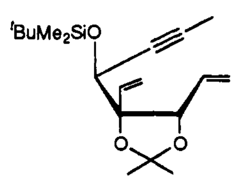


709

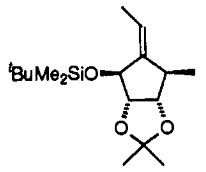
Scheme 139



Three different metal-dependent conversions of carbohydrate-based 1,6-enynes into products containing cyclopentane rings have been described recently. The first employs the Pauson–Khand reaction whereby the D-ribono-γ-lactone-derived compound **710** was converted into the alkyne $Co_2(CO)_6$ complex **711** which, on heating under carbon monoxide with tri-*n*-butylphosphine oxide in heptane for 3 days, gave 45% of the bicyclo[3.3.0]octenone derivative **712** from which the prostaglandin-related carbocyclic analogue **713** was made (Scheme 139).[331] Secondly, the L-*lyxo*-enyne **714** reductively cyclized in good yield mainly to the *exo*-methylene compound **715**, with the substituent *exo* at the new asymmetric center, on treatment with bis(cyclopentadienyl)zirconium dichloride in the presence of magnesium and mercury(II) chloride **332**, and thirdly it was shown that cyclizations involving allylic rearrangement of the ene can be accomplished by use of π-allyl palladium complexes.[333] Thus **716** gave the bicyclic glycal derivative **717** in excellent yield on treatment with tris(dibenzylideneacetone)dipalladium chloroform complex, triphenylphosphine and acetic acid. Likewise, the 3-ene isomer of **716**, having the branched group at C-2, afforded the bicyclic product having the ring junction at C-2 and C-3 and the double bond at C-4 and C-5 (78%). 1,6-Dienes also take part in reactions of similar type, the *C*-glycoside **718** losing acetic acid to give **719** in 72% yield with $Pd(PPh_3)_4$ in acetic acid at 80 °C (Scheme 140).

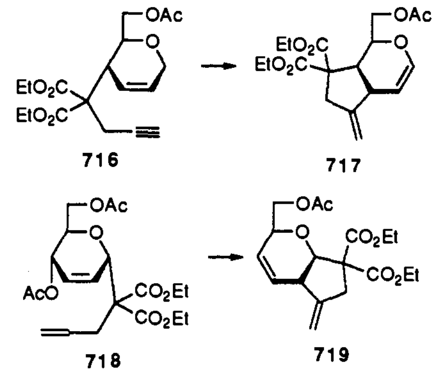


714



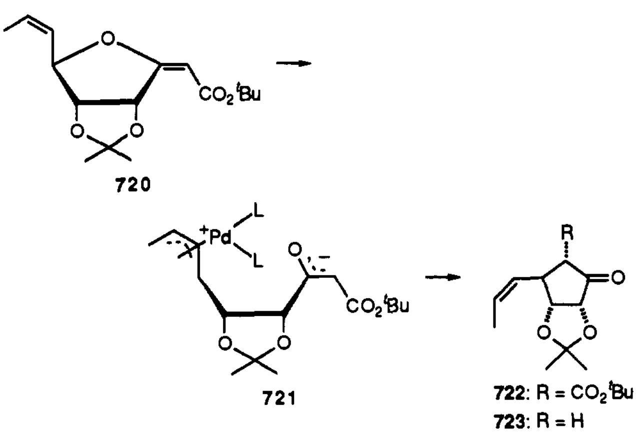
715

Scheme 140



In the case of the 1,6-diene **720**, spanned at C-3 and C-6 (aldonic acid numbering) by an oxygen bridge, the complex formed with Pd(0) at C-6, 7, 8 releases the enolate palladium complex **721** which then can cyclize to give cyclopentanone **722** or a cycloheptanone (Scheme 141).[334] While several Pd(0) complexes induced formation of the latter, a polymer-bound modification of $Pd(PPh_3)_4$, used with *O*,*N*-bis(trimethylsilyl)acetamide to remove protic contaminants, led to 98% of the enol

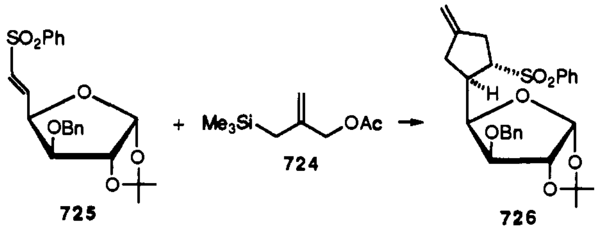
Scheme 141



silyl ether of **722** which could readily be decarboxylated to give **723**.

A further application of palladium chemistry is to [3 + 2] cycloadditions undergone by electron-deficient alkenes and the trimethylenemethane–palladium complex formed from the allylic ester **724** and palladium acetate. The unsaturated sulfone **725** gave, in quantitative yield, the adduct **726** together with minor amounts (12%) of a diastereomer (Scheme 142).[335]

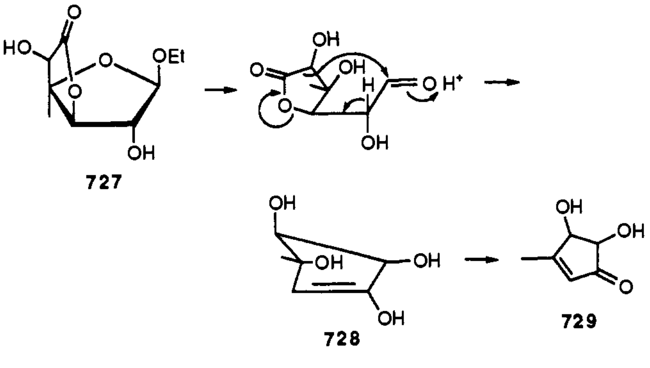
Scheme 142



E. Other Reactions

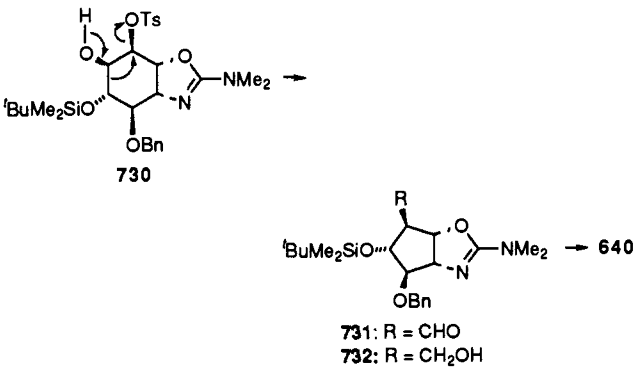
On treatment with acid the branched-chain furanosiduronolactone **727** loses carbon dioxide and water to give the cyclopentenone **729** by a reaction which may involve hydrolysis of the glycosidic bond followed by β-elimination, decarboxylation, and attack of C-5 at C-1 to give the intermediate enol **728**. Ketone formation and further β-elimination would then give **729** (Scheme 143).[336]

Scheme 143



When treated with L-selectride in THF at 65 °C the D-glucosamine-derived cyclohexanooxazoline derivative **730** afforded the ring-contracted aldehyde **731** and hence the corresponding alcohol **732** in 86% overall yield. Subsequent deprotection of **732** led directly to (−)-allosamidin **640**, (Scheme 144).[183] For alternative syntheses of this compound see sections III.B.4 and III.C.1.

Scheme 144



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