

The Conversion of Carbohydrate Derivatives into Functionalized Cyclohexanes and Cyclopentanes

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I. Introduction

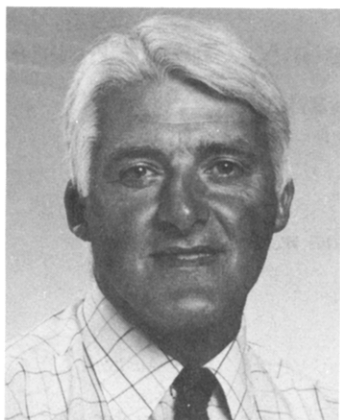
Although Nature uses carbohydrates as synthetic precursors of many functionalized carbocyclic compounds, both saturated and aromatic (sections II.A.1 and III.A.1), until recently chemists have paid only slight attention to the possibilities offered by this approach. In the case of benzenoid compounds 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.^{3b7} While it tends to deal with major features of such syntheses, the current review focuses on the chemical features of the cyclization processes.

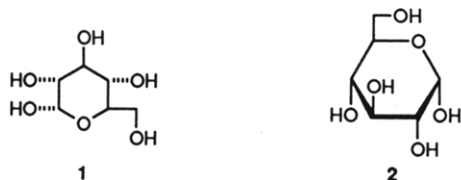
Credit for much of the developmental work in the field, and especially for demonstrating the use of carbohydrates in the complete synthesis of many complex natural products whose structures incorporate five- and six-membered rings, must go to Prof. Bert Fraser-Reid whose insight, intuition, and perceptive 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 medicine⁶ 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.



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 unexploited 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, anthracyclones, 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 formulae⁸ 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



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, ¹³C NMR spectroscopy, and organic mass spectrometry.

which is clearly imperfect. Hopefully, however, the structures used are unambiguous and helpful.

II. Syntheses of Functionalized Cyclohexanes

A. Carbanion Cyclizations

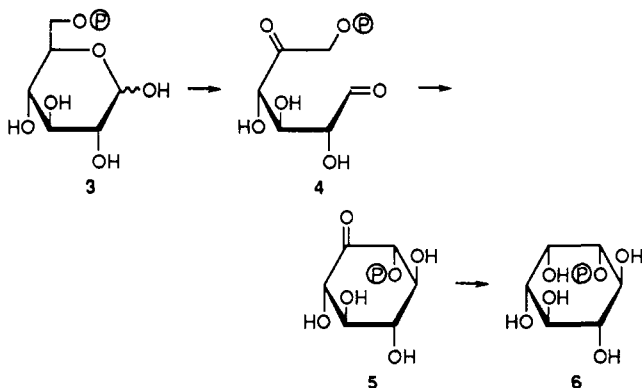
Most reactions employed by synthetic chemists in the key steps of conversions of carbohydrate derivatives into compounds containing cyclohexane rings have involved intramolecular nucleophilic displacements by carbanions or carbanion equivalents. These are treated in this section according to the nature 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

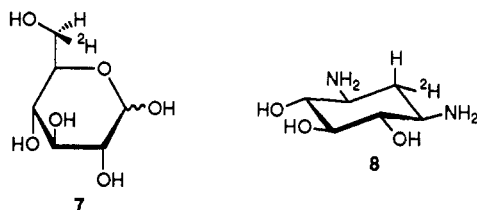
The key step in the natural production of inositols and many of their derivatives is the conversion of D-glucose 6-phosphate (3) into *myo*-inositol 1-phosphate (6) under the catalytic influence of inositol cyclase, the reaction proceeding by way of the 5-osulose 4 which undergoes aldol cyclization to 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*-6R hydrogen atom is lost in the process,¹² and there is evidence that the aldehyde 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

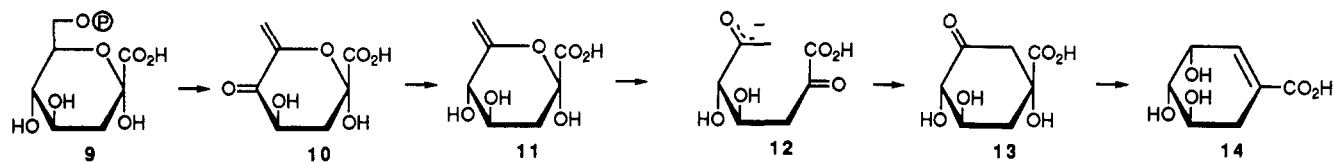


condensations of the above kind are involved in some ring closures which lead to these compounds, not all follow this route in detail.¹³ In the biosynthesis of the 2-deoxystreptamine component of the antibiotic ribostamycin from D-glucose which was deuterated at both C-6 positions and at one of them 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

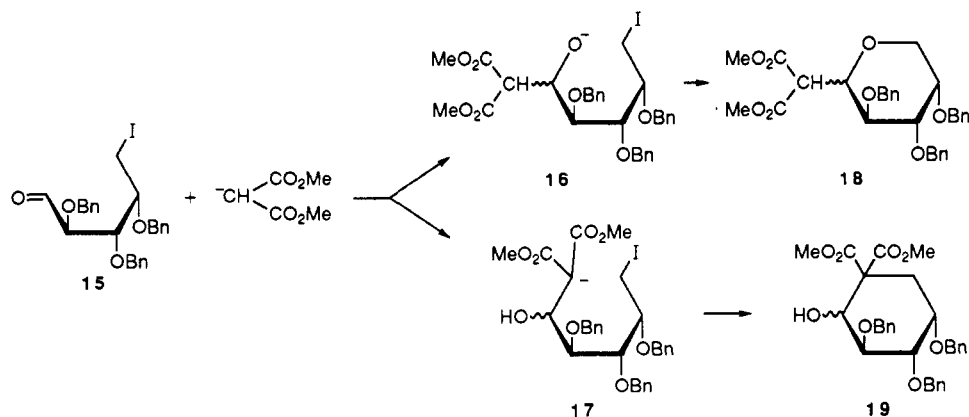


the carbanion/enolate required for aldol ring closure was not, in this case, formed by deprotonation of a labeled analogue of 4, but by a reaction that involved a methylene carbanion. In this way the process bears strong resemblance to that by which D-glucose is converted into shikimic acid (14) from which Nature produces the benzenoid rings of the aromatic amino acids and an extensive range of other metabolites.^{15,16}

Scheme 2



Scheme 3



3-Deoxy-D-*arabino*-heptulosonic acid 7-phosphate (9), produced from D-erythrose 4-phosphate and phosphoenolpyruvate, 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).

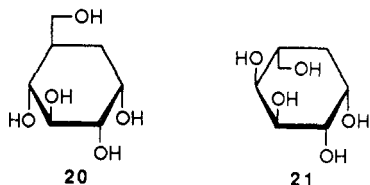
In assessing the enzymic dependence of this route Bartlett and Satake made the *o*-nitrobenzyl α-glycoside of 11 and, by photolysis at pH 7, converted it to 3-dehydroquinic acid in good yield and concluded, not just that the biological derivation of 11 would have resulted in the observed product, but 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

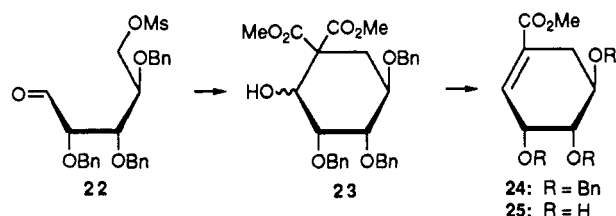
Intramolecular nucleophilic displacement reactions of carbohydrate derivatives which result in cyclohexane products require the nucleophilic and electrophilic centers to be in the 1,6-relationship. Cyclizations belonging to this category of simple hexose derivatives appear not to have been reported, 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

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

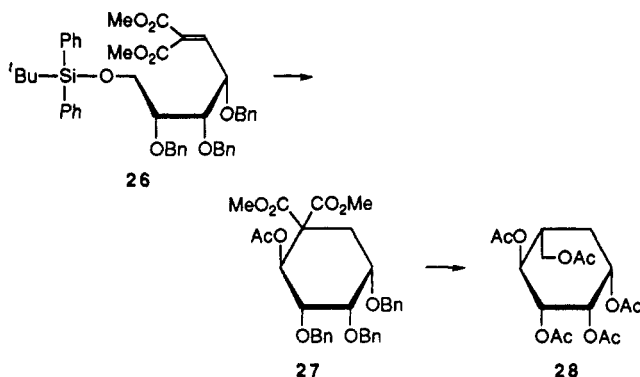
Scheme 4



methyl ester 25, and thus it has the illustrated absolute configuration.

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}

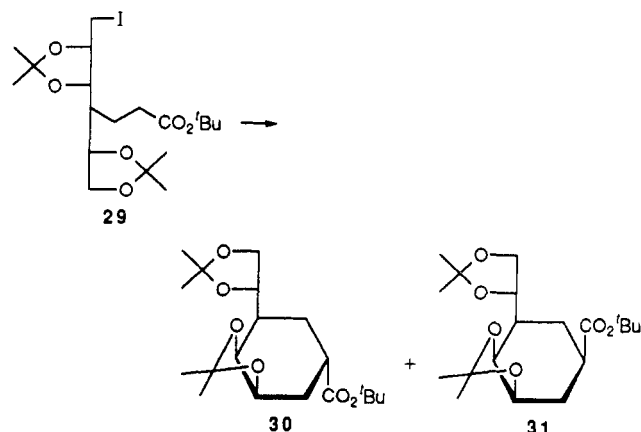
Scheme 5



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-

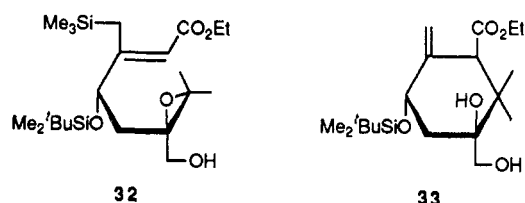
Scheme 6



negative bacterial polysaccharide component KDO, were obtained.²⁵

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

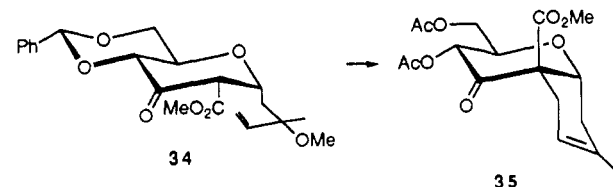
Scheme 7



enantiomerically pure component of the diterpene taxol.²⁶ The use of vinylsilane-based cyclizations is noted in section II.E.

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



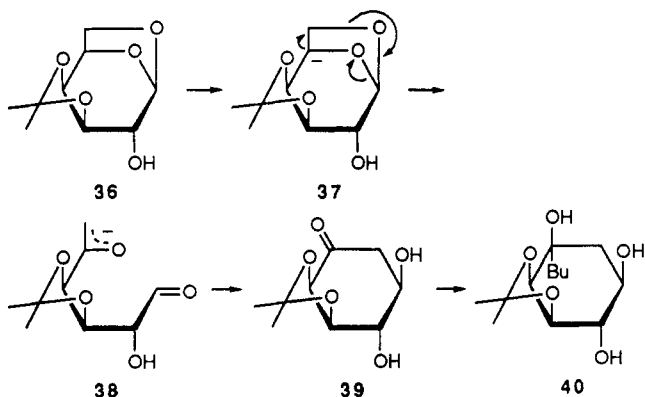
3. Aldol and Aldol-like Reactions

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).

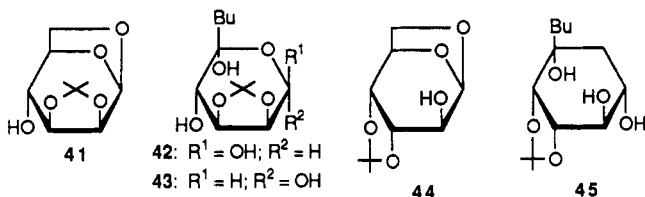
a. *Reactions within Sugar Chains.* Klemer and Kohla found that 1,6-anhydro-3,4-*O*-isopropylidene- β -D-galactose (36), on treatment with *n*-butyllithium, gave the C-butylinositol derivative 40 in 85% yield.²⁸

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

Scheme 9



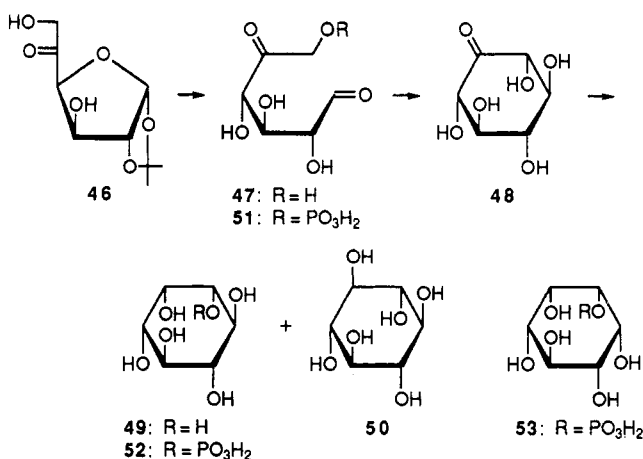
reaction resembles a biosynthetic step (section II.A.1) and the mercury(II)-induced cyclization (section II.D.1), but clearly, the direction of attack at the formyl center is governed by different factors. Methylolithium effected an analogous rearrangement, the C-methyl analogue of **40** being isolated 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.



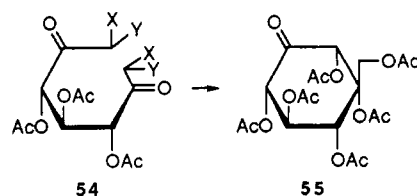
In keeping with these findings, aldol cyclization of 1,5-dicarbonyl carbohydrates affords cyclohexanone derivatives as Kiely and Fletcher first showed by converting *D*-xylo-hexos-5-ulose **47**, formed from the acetal **46**, into the inosose **48** by treatment with alkali. Subsequent reduction with 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 = N₂), made from the corresponding *D*-xylicaric

Scheme 10



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 = N₂) 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

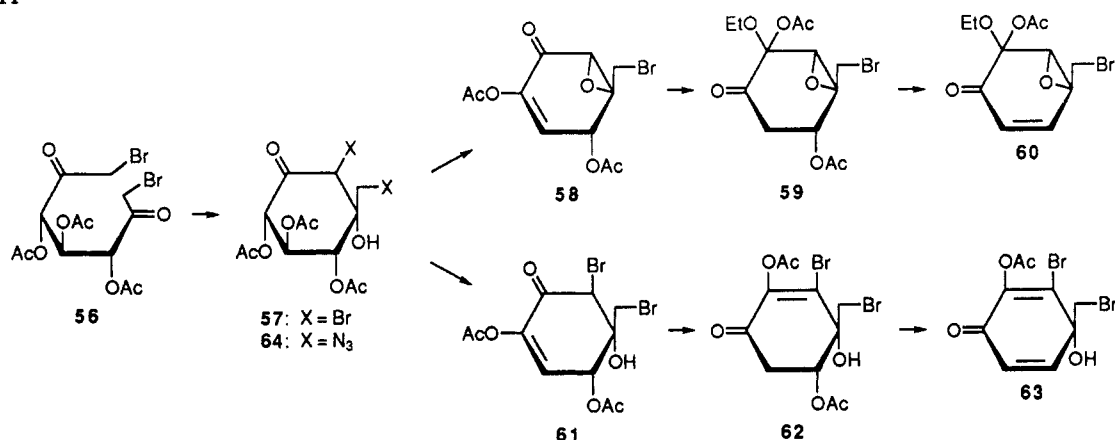
It was then observed that compound **57** was the principal product initially formed when the dibromide **56** was treated with sodium acetate in acetone, but in this solvent (which could not participate in the reaction as did ethanol in giving **60**) reaction continued by way of **61** and **62** to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

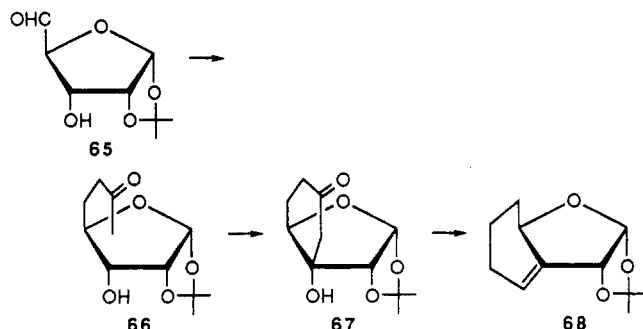
From the *D*-allose-derived **65** the 1,5-diketone **66** was prepared by application of a Wittig chain extension involving (2-oxopropylidene)triphenylphosphorane, and on base-catalyzed cyclization (DBU in refluxing benzene), the *cis*-fused cyclohexanone product **67** of aldol reaction was obtained. 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

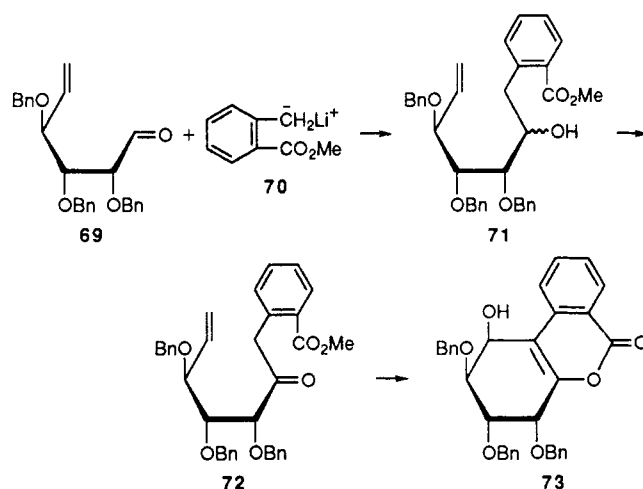


Scheme 12



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

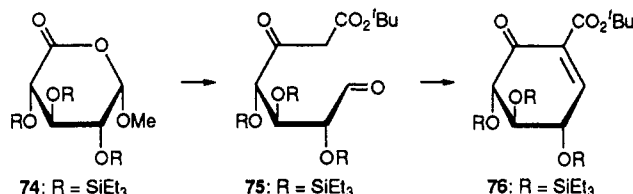
Scheme 13



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

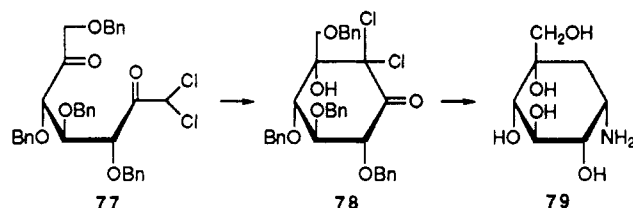
In somewhat related work the hept-2,6-diulose derivative 77 was made by treatment of 2,3,4,6-tetra-*O*-

Scheme 14



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 valioline 79 was made (Scheme 15).⁴¹ Extensions of the work in the disaccharide series

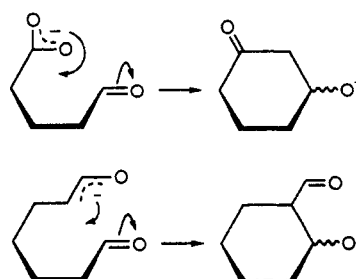
Scheme 15



were then used in the synthesis of validamycin G.⁴²

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 closures⁴³] (Scheme 16),

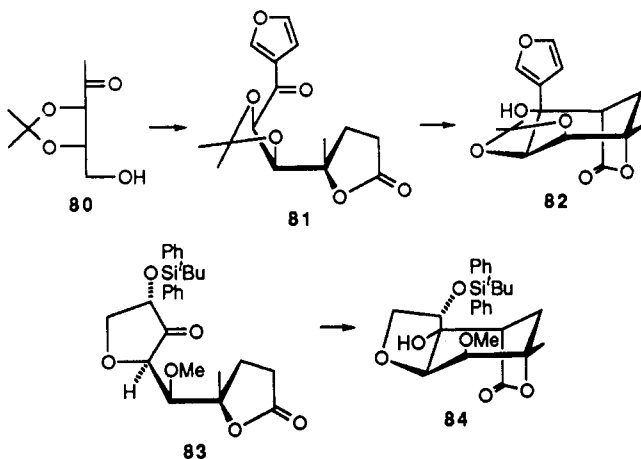
Scheme 16



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-

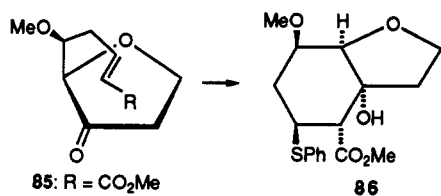
ative **80** using Grignard addition processes at C-2 and subsequently also at C-5 after oxidation to the aldehyde at this position. Treatment of the product with lithium diethylamide afforded the cyclized **82** following C-2 carbanion attack at C-7 which occurred with high efficiency and with a stereoselectivity of 4:1 in favor of the desired isomer (Scheme 17).⁴⁴ In an extension of

Scheme 17



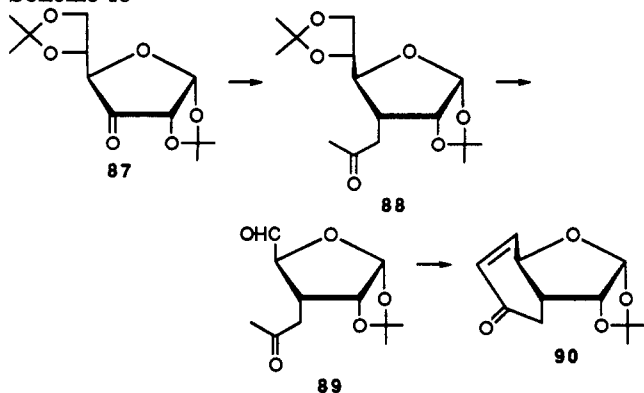
the work compound **83**, synthesized from 1,5-anhydro-D-glucitol, cyclized on treatment with the same base to give **84** which, with the oxahydrindan ring system, is more closely related to the natural product component than is **82**. The yield was 80% showing the preference for *cis*-ring fusion in closures of this type.⁴⁵

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 thiophenolate gave **86** in high yield as a single product.⁴⁶



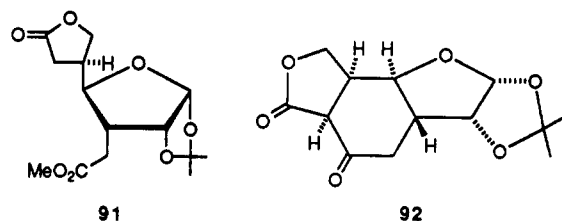
Considerable use has been made of dicarbonyl species having one of the carbonyl groups in branched chains of sugar derivatives. Thus the D-glucose-derived ketone **87** was converted into the branched ketone **88** by use

Scheme 18



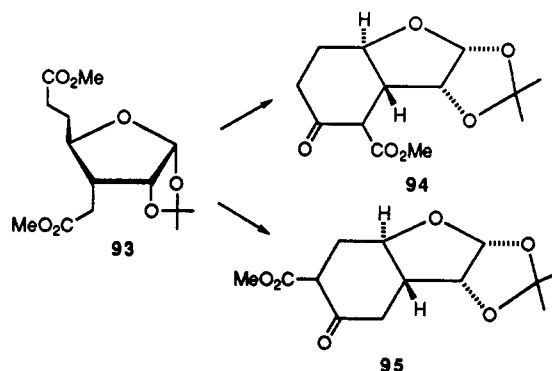
of Wittig methodology. Partial acid hydrolysis and periodate oxidation of the exposed α -diol afforded the "alone" **89** which, after several bases had failed, was aldol cyclized to give the cyclohexanone **90** in 45% yield by use of DBU followed by acetic anhydride and pyridine (Scheme 18). This product afforded access to enantiomerically pure *pseudosugars* and has been used appreciably for this purpose.^{47,48} It also provided access 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 aldehyde and keto functions reversed, to make other highly functionalized cyclohexane derivatives.⁵⁰

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

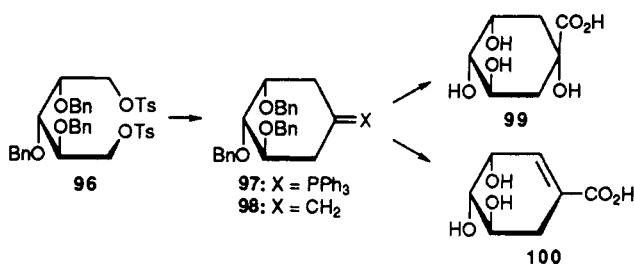
Scheme 19



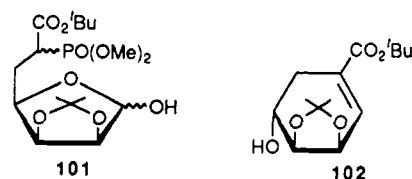
4. Reactions of Phosphorus-Stabilized Species

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

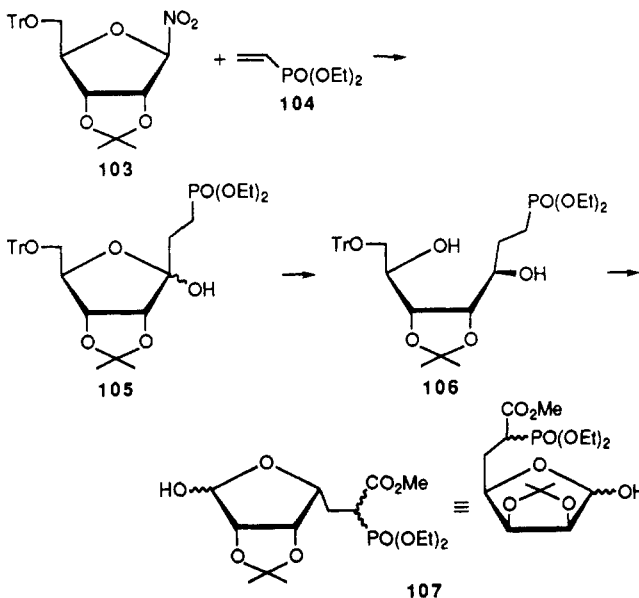


alkene intermediate isomerized to the 4,5-unsaturated compound, but this did not affect the approach to the final product.⁵⁷ The same approach applied to 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-triflyl- α -D-xylose led to 4-*O*-benzyl-3-*epi*-shikimic acid.⁵⁸

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

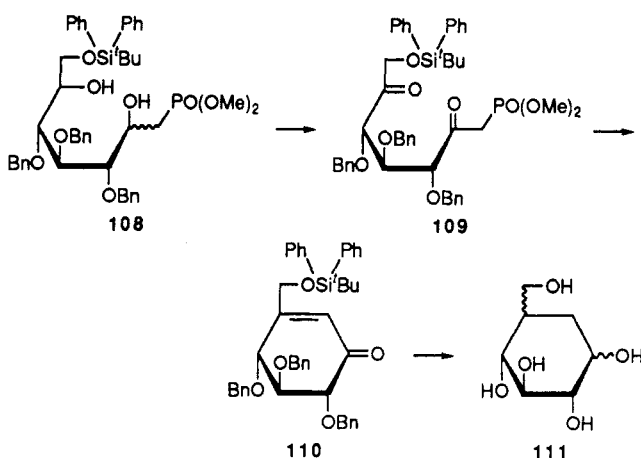
Clearly, the intramolecular phosphonate approach is applicable to the synthesis of carbahehexopyranoses and their derivatives. For this purpose Paulsen and von Deyn produced the epimeric phosphonates 108 from 2,3,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-D-glucose by use of dimethyl methylphosphonate and butyllithium. Oxidation of the hydroxyl groups gave the dione 109 which, with base, afforded the enone 110 and hence

Scheme 21



carba- α - and β -D-glucopyranose and the L-idose epimers at C-5 (111, Scheme 22).⁶⁰

Scheme 22

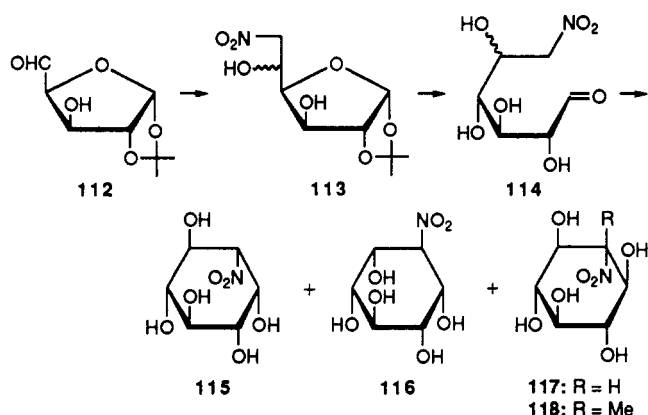


5. Reactions of Nitro-Stabilized Species

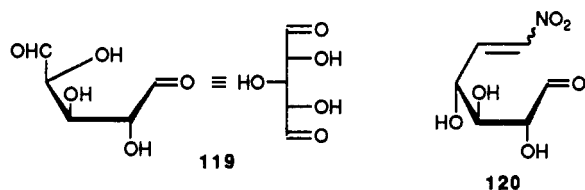
Considerable attention has been paid to cyclohexane derivatives produced by the reaction of carbanions stabilized by nitro groups. Intramolecular reactions have been found to be of appreciable use, and intermolecular processes, involving the use of nitroalkanes have, likewise, been studied on many occasions.

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 group² 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 nitroaldehydes¹¹⁴ are enantiomerically pure forms of the racemic products of Henry reaction of nitromethane

Scheme 23

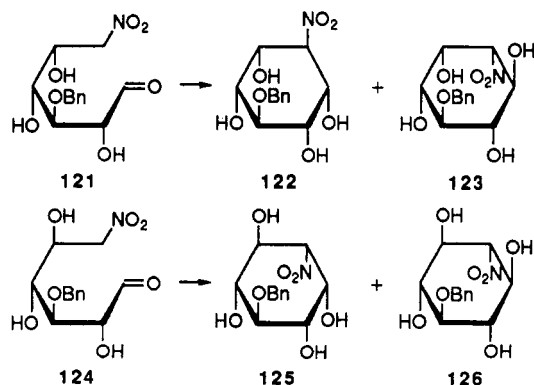


with the symmetrical dialdehyde 119 which is derived by acid hydrolysis of 112. These compounds react further also to give racemic 115–117, and with nitroethane the C-methylinositol derivative 118 can be obtained. In addition, methyl 6-deoxy-6-nitro-D-glucopyranoside in basic conditions affords deoxynitroinositols by a multistep process initiated by abstraction of H-6 and ring opening to give the 5-enal 120.⁶³



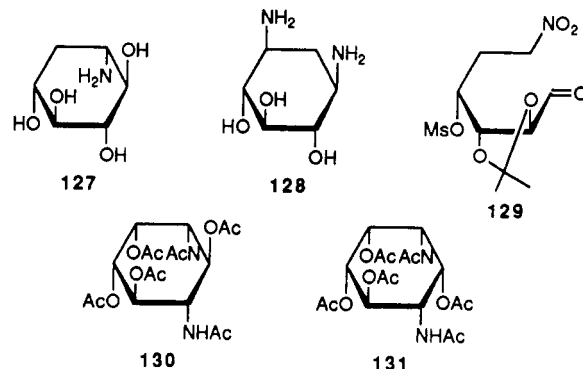
Baer and co-workers have also carried out detailed studies of the products formed by the ring closure of 6-deoxy-6-nitrohexoses under kinetic and thermodynamic control. They showed that the glucose derivative 121 gave 122 and 123 in the ratio 3:1 under kinetic control, whereas the L-ido isomer 124 gave 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

Scheme 24

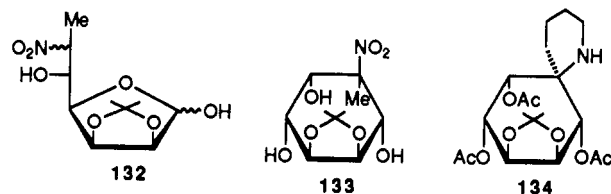


allowed conformational analyses to be carried out on inositol rings bearing nitro and nitronate groups.⁶⁵ Related work with 2,3,2',3',4',6'-hexa-O-acetyl-6-deoxy-6-nitromaltose, derived from 1,6-anhydromaltose, led to mixed products from which α -D-glucosylated inosamines have been prepared as their peracetates.⁶⁶

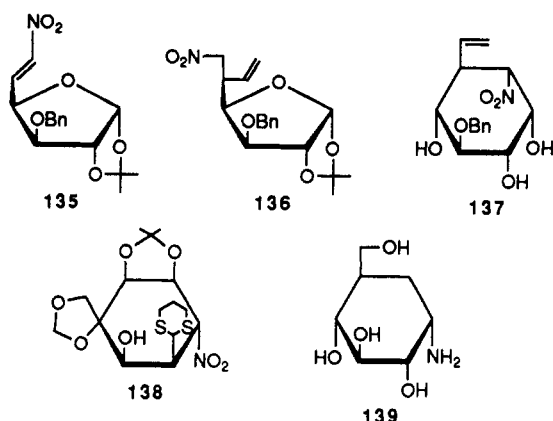
The method's obvious applicability to the preparation of inosamines has led to 1-amino-1-deoxy-*scyllo*-inositol by use of 2,3-di-O-benzyl-6-deoxy-6-nitro-D-glucose,⁶⁷ and to 3-amino-2,3-dideoxy-D-*myo*-inositol (127), an intermediate in the biosynthesis of 2-deoxystreptamine, from 5,6-dideoxy-6-nitro-D-glucose.⁶⁸ 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



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



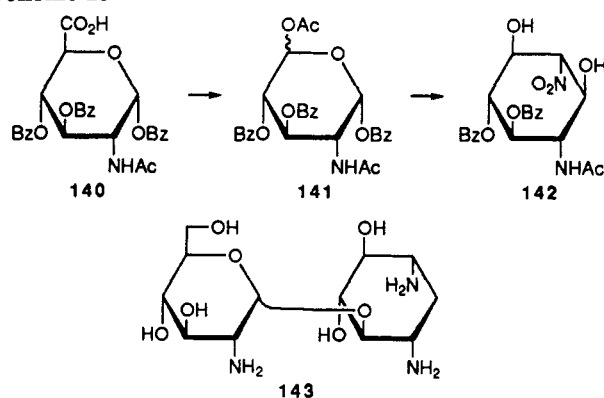
Most commonly, branch points have been introduced at C-5 of nitrohexoses by way of 6-deoxy-6-nitro-5-enes, and by this means a range of inositols with branched chains akin to natural products have been obtained by Funabashi, Yoshimura, and colleagues.⁷² For example, vinyl addition at C-5 of compound 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



b. Dialdehyde-Nitromethane Cyclizations. As pointed out in the last section the 6-deoxy-6-nitroal-dohexoses 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 *xyl*-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 aminocyclopentenediols and have given access to inosadiazines following cyclization with nitromethane and subsequent reduction.⁷⁹

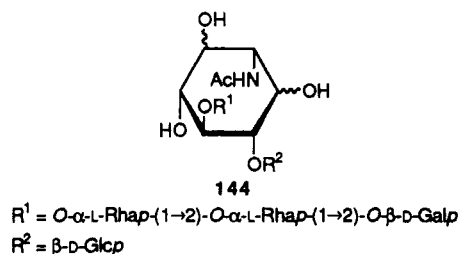
More novel and very useful access to carbohydrate dialdehydes has been gained by oxidative decarboxylation of hexopyranuronic acids either electrolytically or with lead tetraacetate, the latter causing replacement of the carboxy groups by acetoxy thereby giving compounds that, with base, degrade to the 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 com-

Scheme 25



pound 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

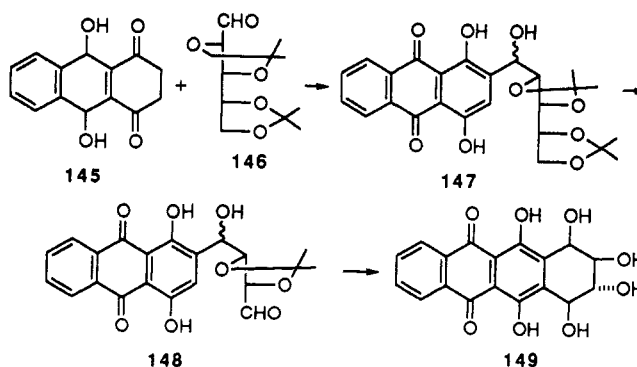
The electrochemical procedure, using uronic acids in cold methanol containing diethylamine, gives unstable products which, with nitromethane and sodium methoxide in methanol, affords nitroinositol derivatives.⁸⁴ In this way compounds 144 were produced from a triterpene glycoside of a pentasaccharide, 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

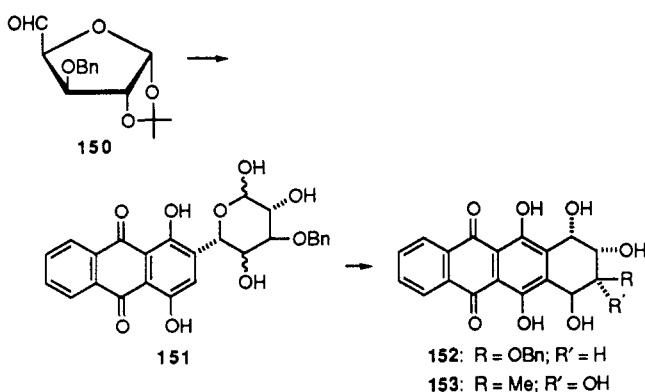
Scheme 26



co-workers with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xyl*-pentodialdofuranose (150) led to compound 151 and hence, by a further aldol process, to the ring closed 152 (Scheme 27).⁸⁷

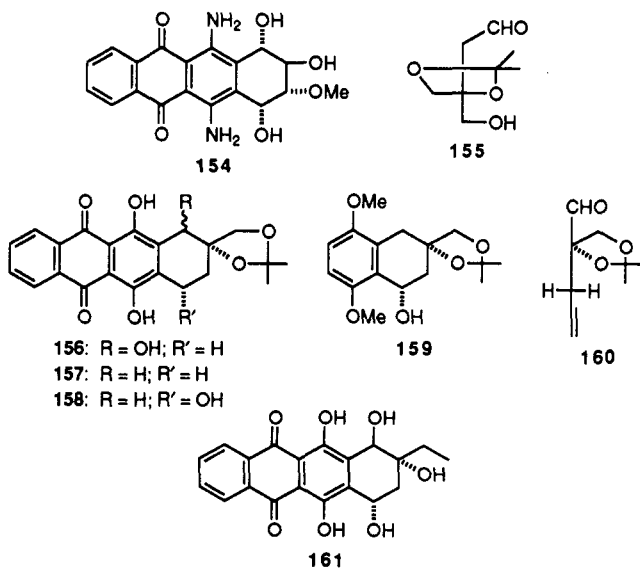
From this point the work was extended by use of branched-chain sugar aldehydes to give compounds such as 153 with a tertiary alcohol function in the D ring^{88–90} and thus akin to the anthracyclonones. In this later work reduction to the *leuco* derivatives was conducted with zinc/acetic acid, and the 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 anthracyclinones⁹³ 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

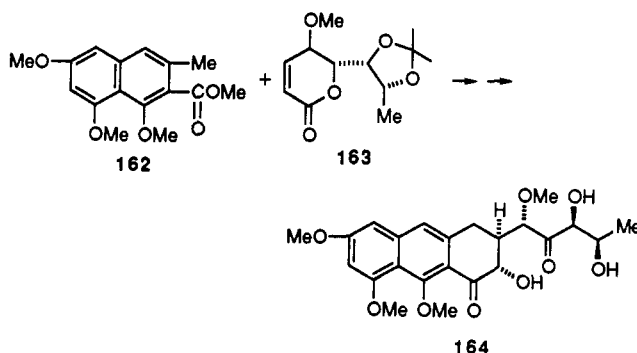


3-*O*-Benzyl-3-*C*-ethyl-4-*O*-trityl-*L*-glycero-tetrose, synthesized from methyl 4,6-*O*-benzylidene-3-deoxy- α -*D*-

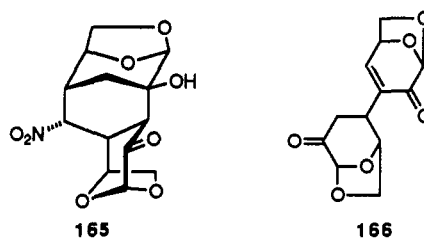
erythro-hexopyranosid-2-ulose, has been applied in the above manner to obtain 4-deoxy- β -rhodomycinone (**161**).⁹⁶

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

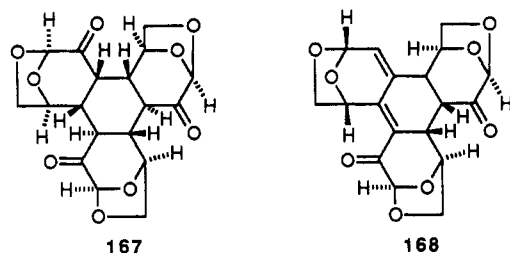


During a later investigation of the Michael addition of nitromethane to levoglucosenone (1,6-anhydro-3,4-dideoxy- β -*D*-glycero-hex-3-enopyranos-2-ulose) it was discovered that the initial adduct adds to a second molecule of the enone, the available nitronate anion adding in Michael fashion and the 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



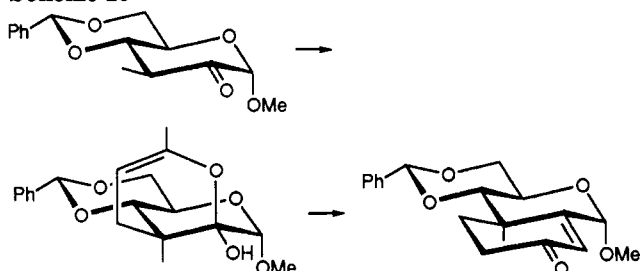
It has also been found that levoglucosenone takes part in base-catalyzed cyclohexane ring-forming reactions in the absence of other reagents (such as nitromethane). On heating in aqueous triethylamine it dimerizes following attack by catalytic hydroxide at *C*-4 to give **166** which then condenses with 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



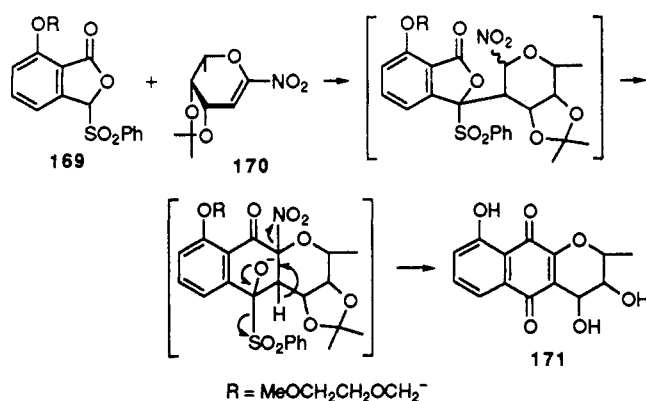
of α -related hydrogen atoms the process can be applied with normal success (yield reported, 58%).¹⁰⁰

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

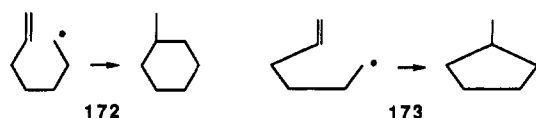
Scheme 30



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

Scheme 31

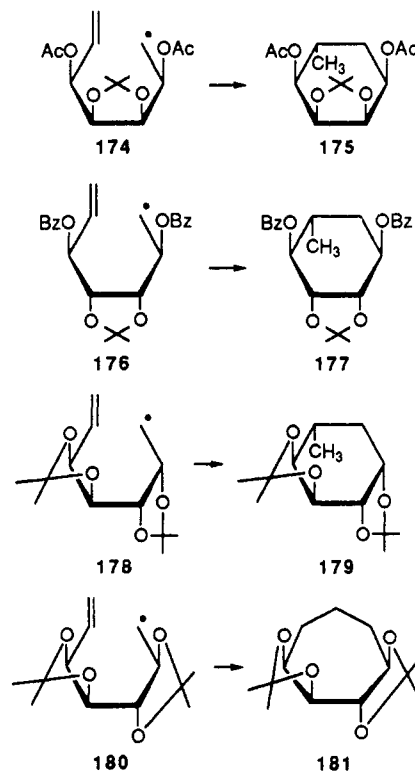


several cases in which the former have been prepared (from either heptose or extended-chain derivatives or from branched-chain compounds having a radical

generating group on the sugar chain and a radical trap in the branching group), the method has proved highly suitable.

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

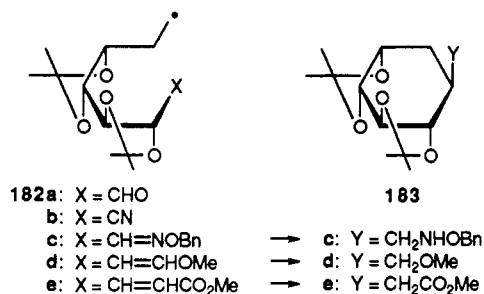
Scheme 32



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.

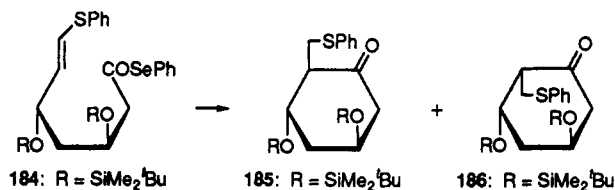
A related study has been made of the ring closures of radicals derived from a range of 6-bromo-6-deoxyhexose derivatives having different unsaturated radical trapping groups at C-1, and again it was found that the yields and stereoselectivities were greatly dependent

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

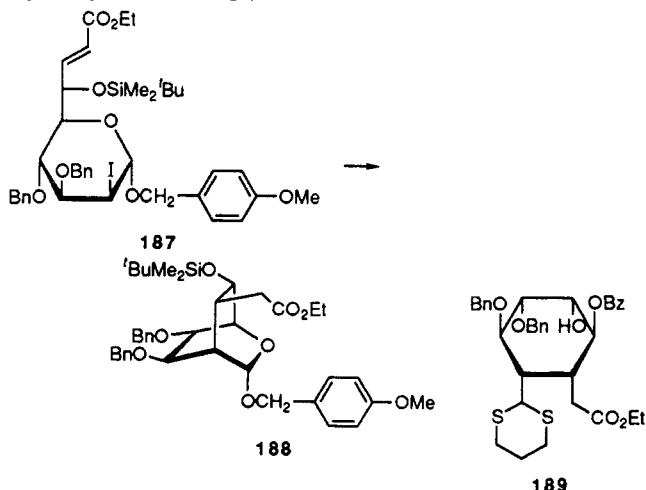


Acyl radicals may also be used in the above type of ring closures, the radical derived from the hept-6-enonic selenoester **184** (prepared from non-carbohydrate sources) cyclizing to give equal proportions of the cyclohexanones **185** and **186** in 90% yield (Scheme 33).¹⁰⁵

Scheme 33



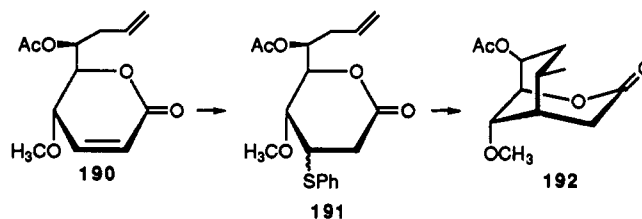
Fraser-Reid and colleagues have developed this approach by using radicals on sugar rings and have in an extensive study prepared bicyclic products having the anomeric centers intact.¹⁰⁶ In the specific case of the radical derived at C-2 of the nonuronic acid derivative **187**, ring closure occurred 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 ⁴C₁ 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**).

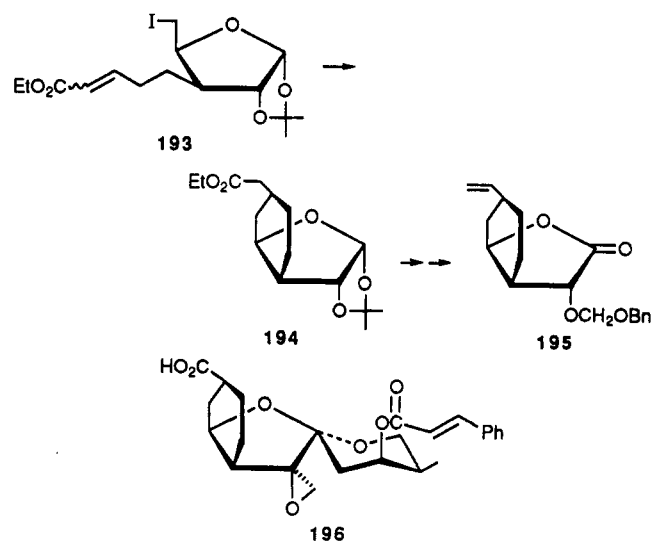
An ingenious related cyclohexane synthesis utilizes a one-pot procedure based on the selective addition of benzenethiol to the conjugated double bond of non-2,8-dienonic acid lactones. For example, the epimeric adducts **191** were made by reaction of the thiol in the presence of triethylamine with the 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



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

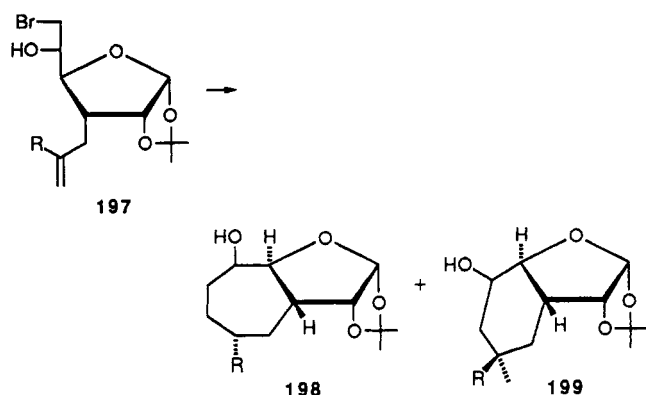
Scheme 35



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

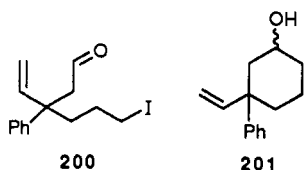
As was to be expected for C-3 epimers of compounds like **193**, from which *trans*-ring junctions would be established on ring closure, radical cyclizations by the normal *exo* mode proved more difficult, compound **197** (R = H) giving 44% of the product **198** (R = H) of *endo* closure and only 33% 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



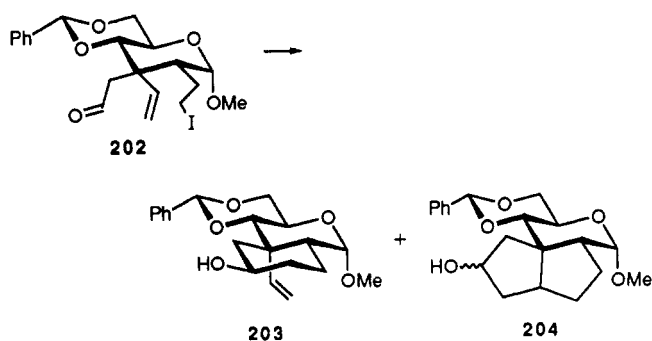
cyclized product being the *endo* compound 198 ($R = \text{Me}$, 25%).¹⁰⁹ Related cyclizations were then performed with analogues of 197 in which the double bonds were components of oxime groups or of α,β -unsaturated esters. In the former cases cyclohexanes were produced having alkoxyamino substituents, 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 predominant 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 aldehyde 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).

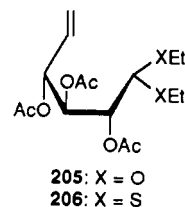
Scheme 37



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).



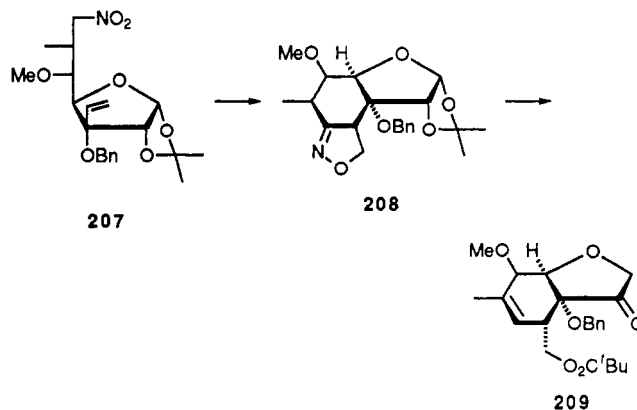
C. Cycloaddition Reactions

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

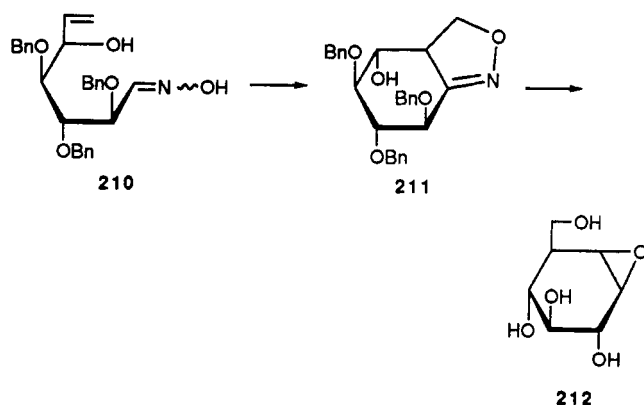
Scheme 38



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

210 of a hept-6-ene 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

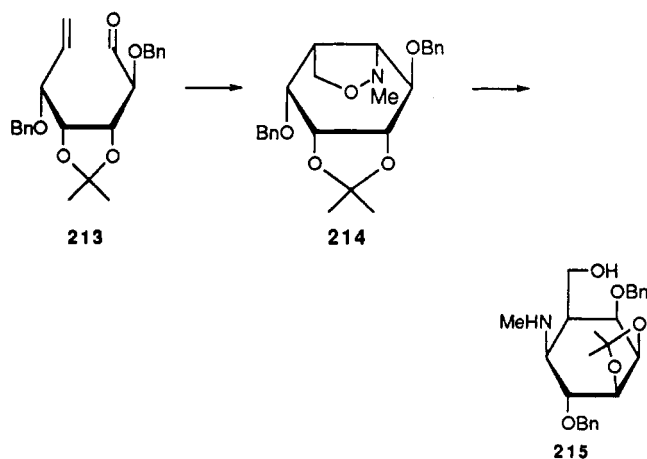
Scheme 39



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

Analogous nitron 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, nitron 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

Scheme 40

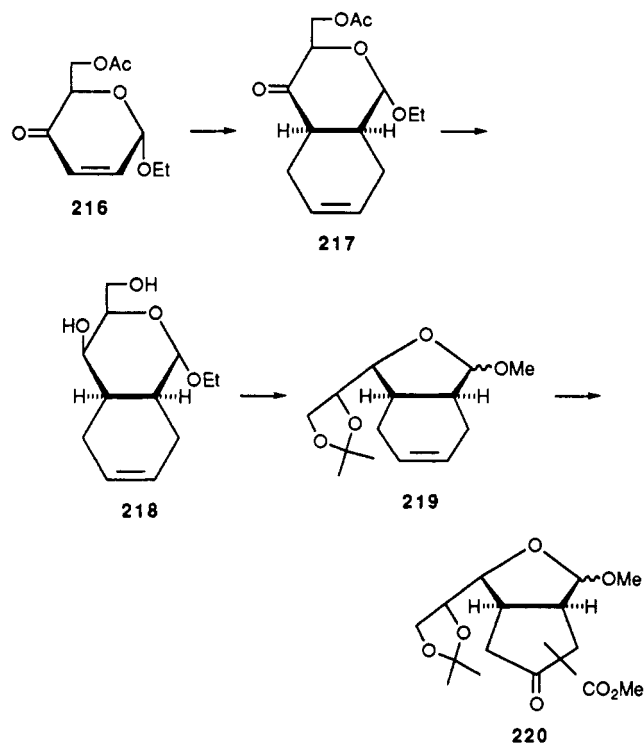


(cf. 211) and isoxazolidenes (cf. 214) have been derived from 2,3,4,5-tetraethers of 6,7-dideoxy-D-ido- and D-gulo-hept-6-enoses (cf. 213).¹¹⁸

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

Scheme 41

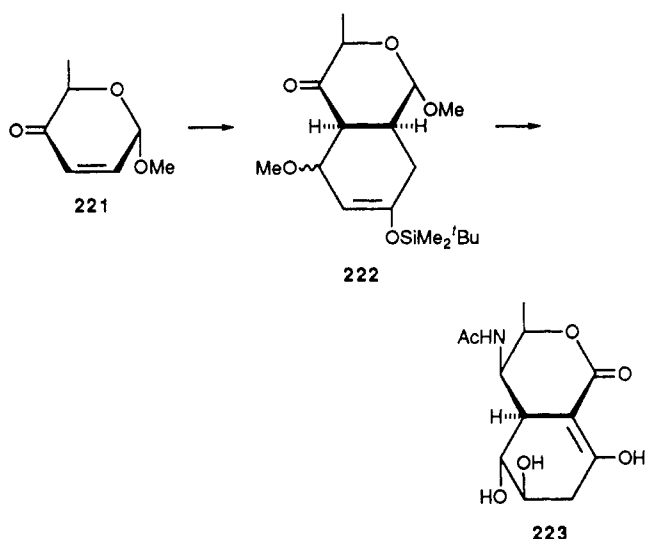


treatment with methanolic hydrogen chloride 218 was converted to a mixture of the corresponding methyl pyranosides and the isomeric furanosides in the ratio 1:6. Isolation of the latter was effected by way of compounds 219 from which cyclopento derivatives 220 were obtained by use of ruthenium dioxide/sodium 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-2H-pyran under high pressure.¹²⁰

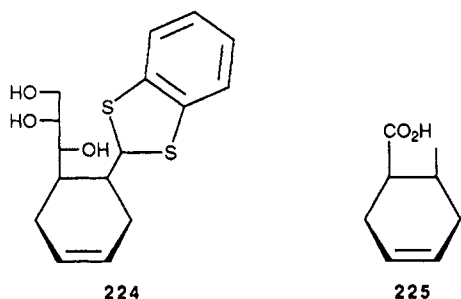
With these methods in hand Fraser-Reid and Abdur Rahman synthesized the *N*-acetyl derivative 223 of the

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

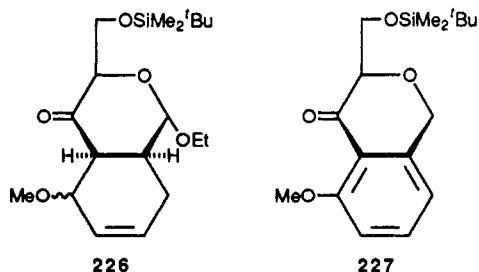
Scheme 42



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

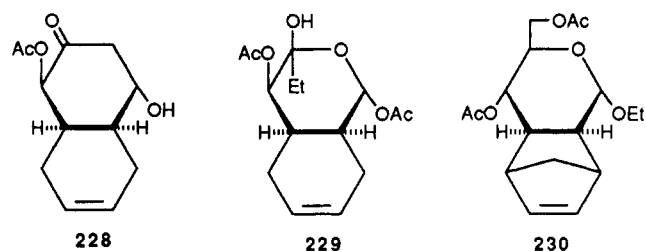


the work has been to the preparation of benzannulated pyranosides by use of enones like **216** and 1-methoxy-1,3-butadiene which afforded compounds such as **226** which may be aromatized by use of DDQ to **227**.¹²³



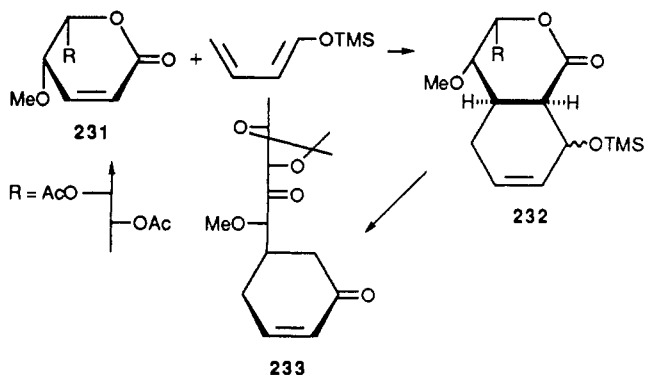
Elimination of hydrogen iodide from C-5–C-6 of the 4-*O*-acetyl-6-deoxy-6-iodo derivative of **218** gave the *exo*-alkene which was rearranged to the ketone **228** (section II.D.1) from which the triol **229**, which represents the AB ring system of β -rhodomycinone, was obtained.¹²⁴ In the course 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



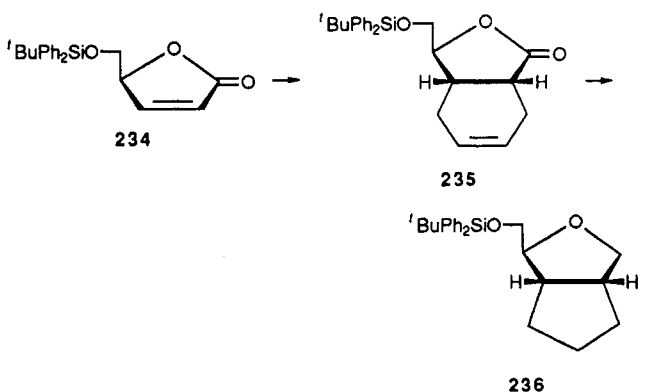
That 2,3-unsaturated aldonic acid lactones can also be employed as dienophiles was shown by Frank *et al.*,¹²⁶ who treated compound **231**, which was prepared following Wittig extension of 3,4-*O*-isopropylidene-2-*O*-methyl-D-fucal, with 1-[(trimethylsilyl)oxy]butadiene to obtain, in 83% yield, the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

Scheme 44

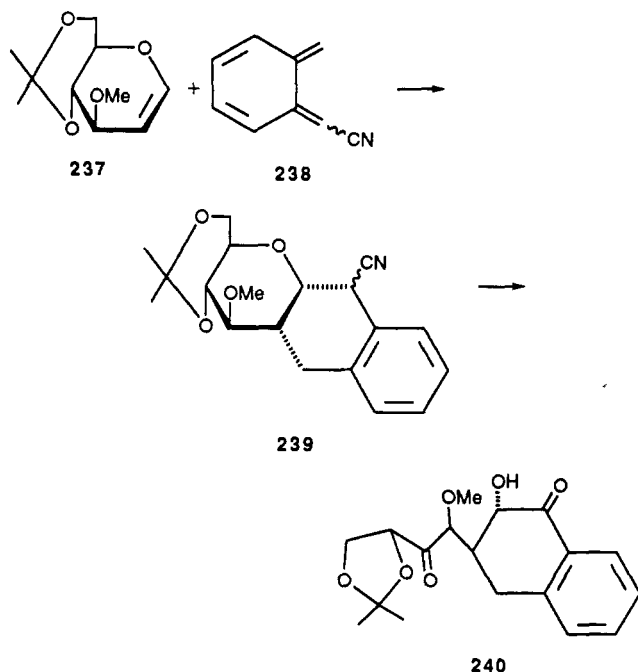


further illustrates the potential of unsaturated carbohydrate lactones.¹²⁷

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),

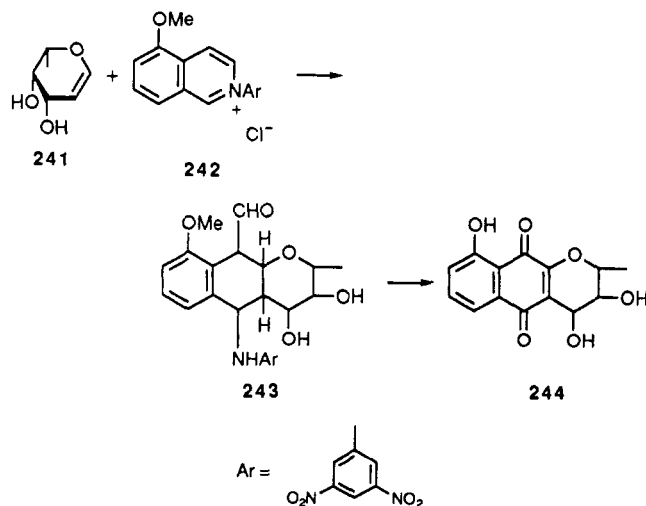
Scheme 45



the key step being an acid-catalyzed elimination β - to the nitrile group which caused opening of the pyranoid ring.¹²⁸

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.

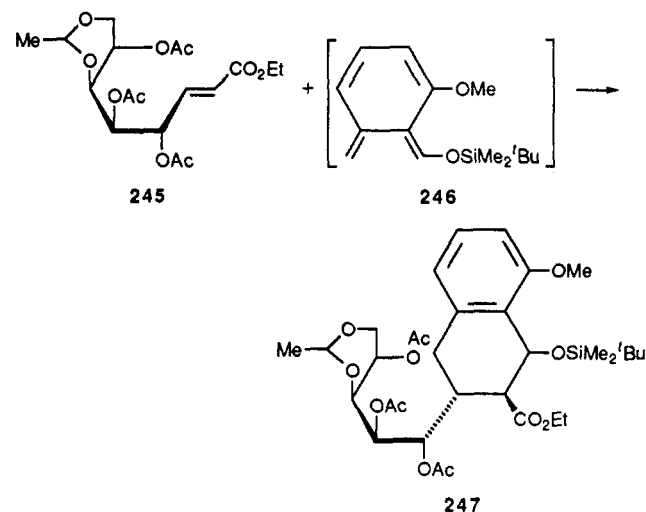
Scheme 46



The same group then examined the preferred direction of attack of an *o*-xylylene at double bonds of some

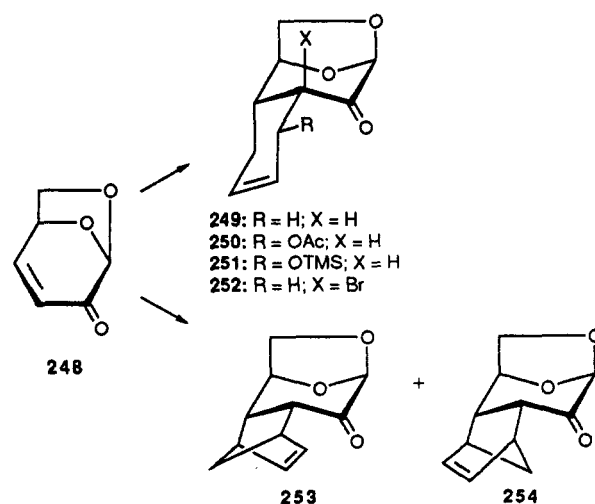
acyclic alkenes and concluded that allylic *syn*-oxygen-bonded substituents give rise to unfavorable orbital interactions in the transition state thereby favoring reaction at the face opposite of the oxygen function. In this way the adduct **247** dominated in the products of reaction of the alkene **245** with **246** which was derived from the corresponding benzocyclobutene (Scheme 47).¹³⁰ (See also Scheme 53.)

Scheme 47

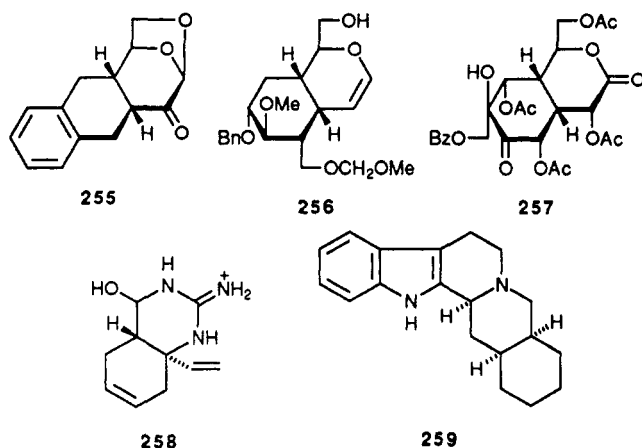


Considerable attention has been paid to the adducts derived from the cellulose pyrolysis product “levoglucosenone” **248** which have given access to several compounds of value in natural product synthesis. With this enone, *exo* addition of dienes is favored, 1,3-butadiene giving crystalline **249** 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-dimethoxycyclopentadiene¹³³ also give products of cycloaddition in high yield. Further functionalized derivatives became available by use of modified dienes,

Scheme 48

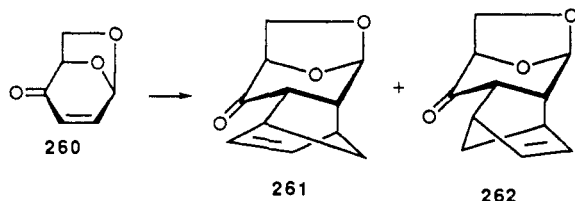


1-acetoxy- and 1-[(trimethylsilyl)oxy]-1,3-butadiene reacting efficiently to afford **250** and **251**, respectively.¹³⁴ A bromine atom can be made available at C-3 (compound **252**) by reaction between 1,3-butadiene and 3-bromovogluosenone (Scheme 48)^{131,135} and the benzannulated product **255** can be made in 53% yield by means of an *o*-xylene cycloaddition process.¹³⁶ From the acetate **250** the advanced reserpine intermediate **256**¹³⁴ and the oxadecalone segment **257** of tetrodotoxin¹³⁷ 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

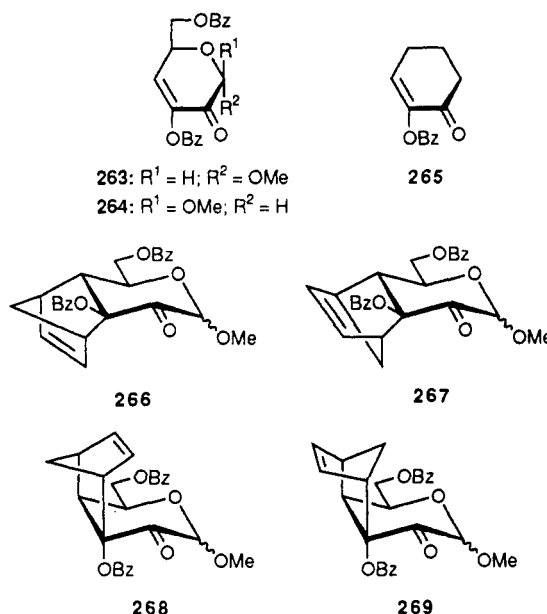


Because of its relatively low availability, fewer studies have been carried out on "isolevoglucosenone" (**260**), but when treated with cyclopentadiene, with zinc chloride present as catalyst, it gave both products **261** and **262** of "down" addition in 82% yield and in the proportions 4:1 (Scheme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

Scheme 49



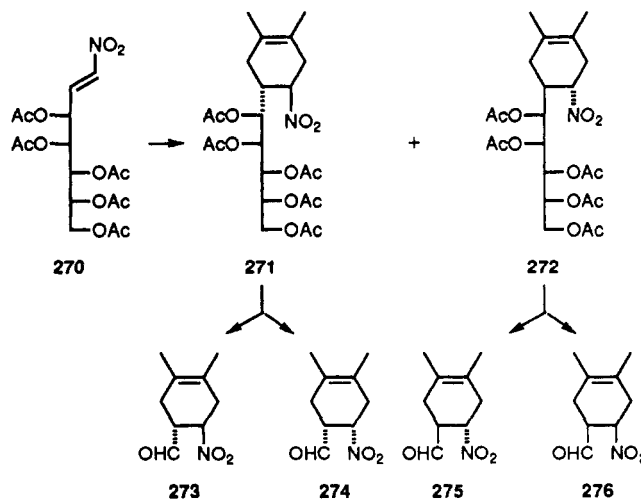
An interesting general observation to come from a comparison of the relative reactivities of pyranoid α,β -unsaturated ketones and carbocyclic analogues was that the former are more reactive as dienophiles in most cases.¹⁴⁰ Similar findings were reported in studies of the addition of cyclopentadiene 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

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

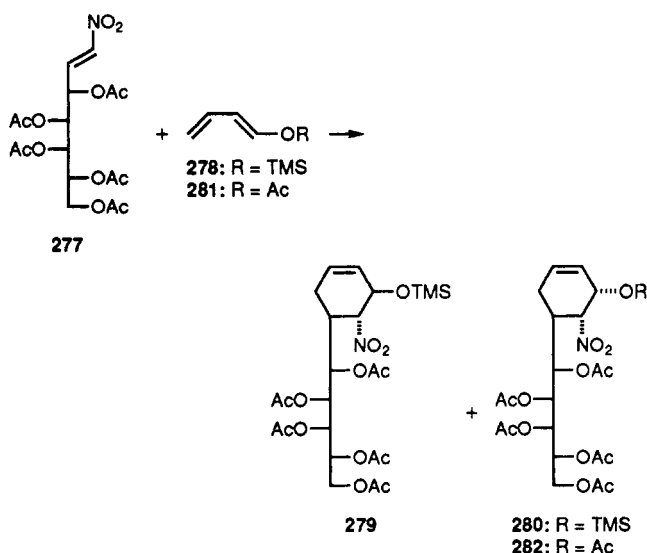
Scheme 50



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

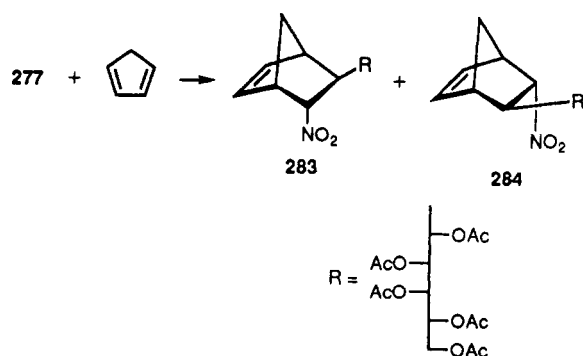
because of the directing effect of the allylic ester group. With 1-acetoxybutadiene (281), however, not only is diastereofacial specificity observed, but there is also *endo* specificity, compound (282) being the only product observed (75% yield) (Scheme 51).¹⁴³

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** ($37 \pm 2\%$ each) as main products (Scheme 52). The stereochemistries were

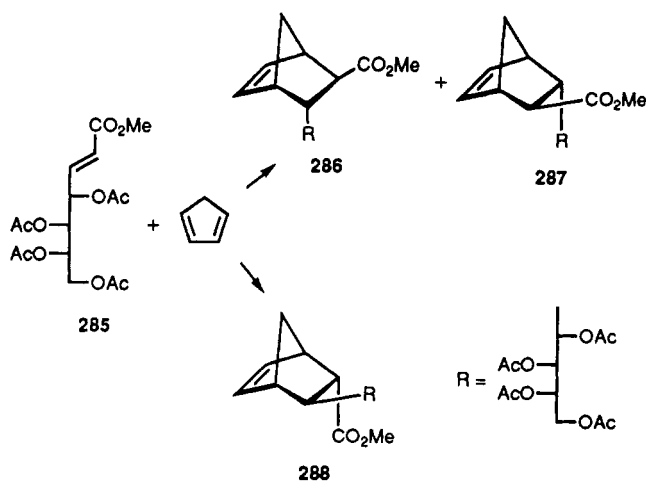
Scheme 52



established by X-ray diffraction analysis of two of the D-manno adducts¹⁴⁴ followed by correlations of deacetylation-periodate oxidation products.¹⁴⁵

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

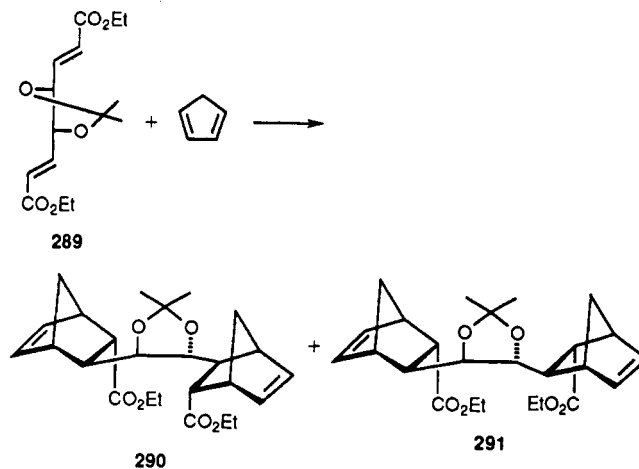
Scheme 53



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.

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

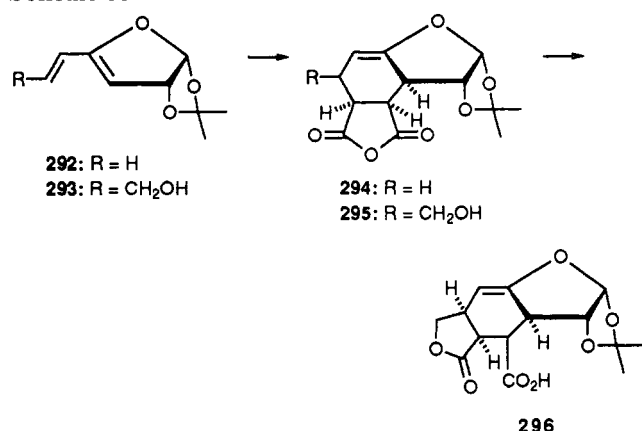
Scheme 54



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).

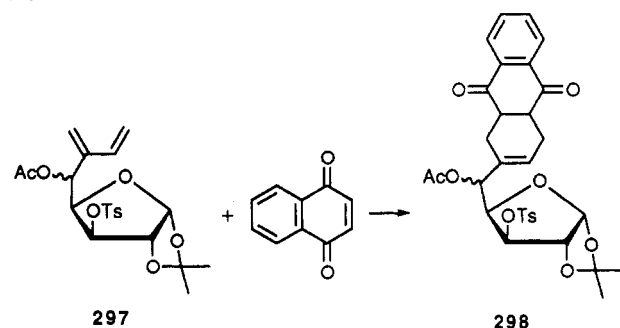
1,3-Dienes can be produced within normal sugar chains, in extensions of them from the reducing end or from the nonreducing end, or they may involve carbon atoms in branched chains: examples of Diels-Alder reactions dependent on all these diene types have been reported recently. Again Fraser-Reid led 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



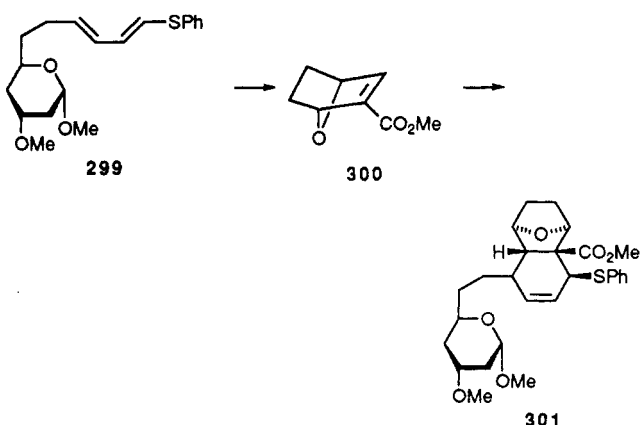
(Scheme 55).¹⁵¹ Extensions of the work have led to cycloadducts derived from a hepturonic ester analogue of **293**,¹⁵² and from heptopyranose dienes akin to **292**.¹⁵³ Related studies by Russian workers have employed the dienes **297** and naphthazarin to obtain products **298** (Scheme 56) which are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

Scheme 56



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

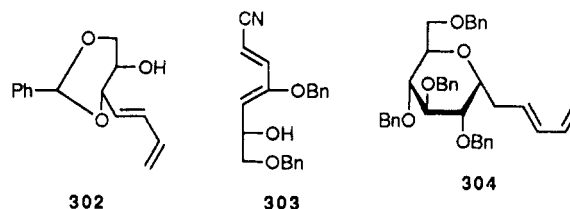
Scheme 57



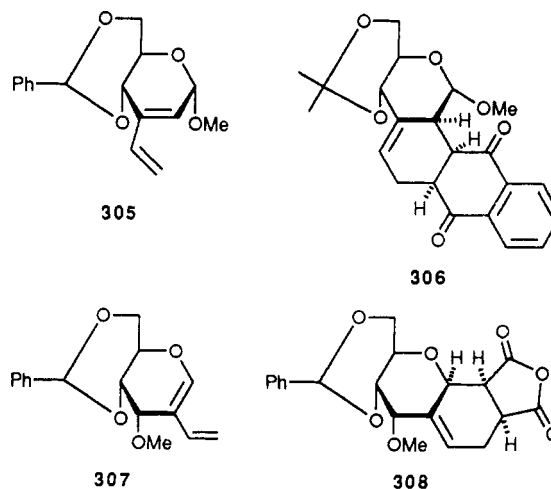
step of a synthesis of the hypocholesterolemic compound (+)-compactin.¹⁵⁵

Dienes formed by extensions of sugar chains from the reducing end condensing with dienophiles are as

follows: compound **302**, produced by Wittig methylation 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



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

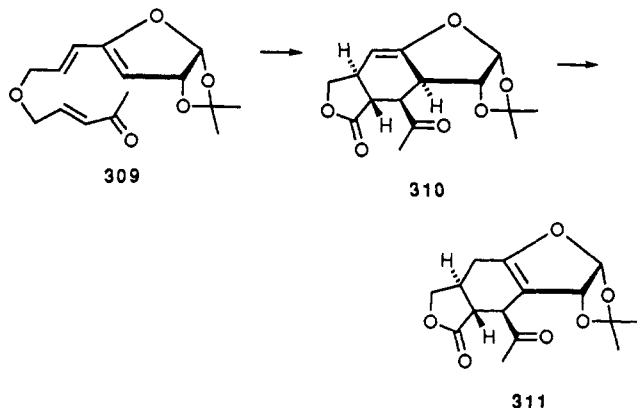


c. Intramolecular Reactions. Few, if any, examples of such processes had been reported for carbohydrate derivatives by the mid 1980s when the general topic of intramolecular Diels–Alder reactions was extensively reviewed,¹⁶² but since then several instances have been described which illustrate the powerful 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

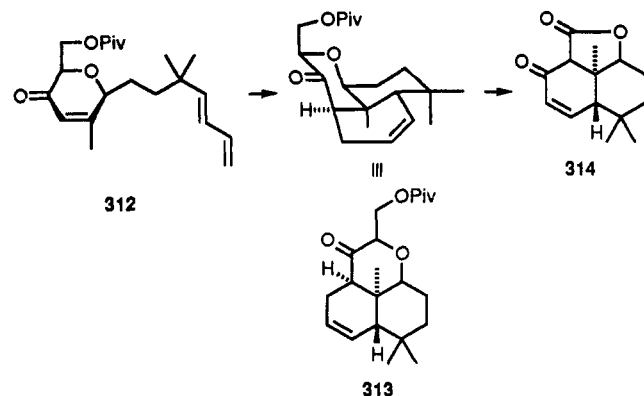
Fraser-Reid's group who showed that the unsaturated ester **309** of a heptose-based diene underwent cyclization initially to give mainly the product **310** derived from the *anti*- β -face transition state. This initial product, under the conditions of the reaction, underwent rearrangement to the isomer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

Scheme 58



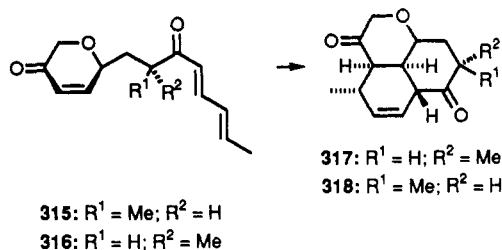
From the same group then came a report of the value of this approach in the synthesis of functionalized *trans*-decalins illustrated by the preparation of **314**, an advanced intermediate in the synthesis of forskolin. Heating of the *C*-glycosidic enone **312** in refluxing xylene for 48 h caused 30% 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 $-\text{C}(=\text{O})-\text{C}-\text{O}-$ sequence of the pyranoid ring to convert it to $-\text{C}(=\text{O})-\text{O}-\text{C}-\text{O}-$. On treatment with sodium methoxide in methanol the product collapsed to the simple lactone unit of **314** (Scheme 59).¹⁶⁴

Scheme 59

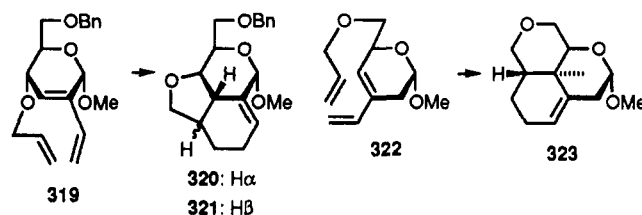


In parallel studies French workers isolated single, crystalline products **317** and **318** of the separate thermal cyclizations of the epimers **315** and **316** which had been produced from 3,4-di-*O*-acetyl-L-arabinal. As for compound **313**, **317** and **318** were derived from the *cis*-*anti*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

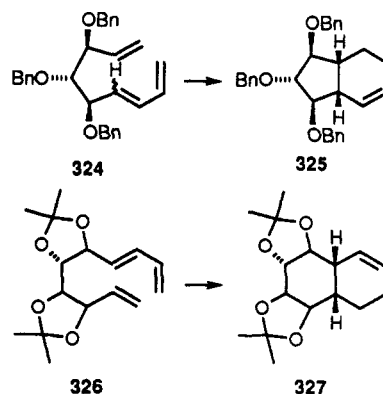
In the case of the allyl ether **319**, in which the diene is partly within a pyranoid ring, the epimers **320** and **321** were produced (80%) in the ratio 3:1, the lack of



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



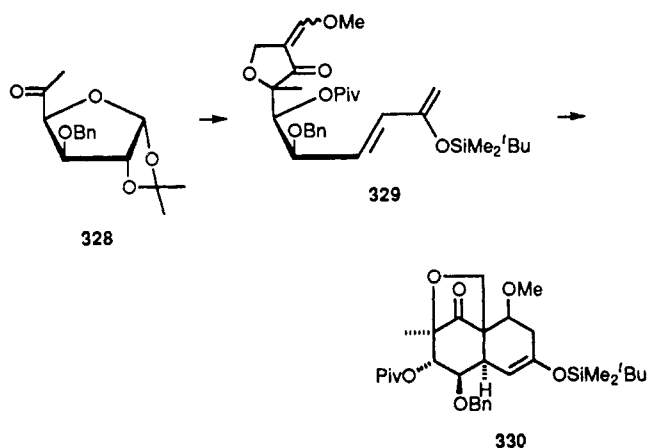
In the area of acyclic compounds that contain both a diene and a suitably situated dienophile in the same carbon chain, carbohydrate structures can be incorporated in a largely unmodified form or after major alteration. In the first category come the mixed isomers **324**, synthesized from 2,3,4-tri-*O*-benzyl-D-xylose 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 decal-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.¹⁶⁸



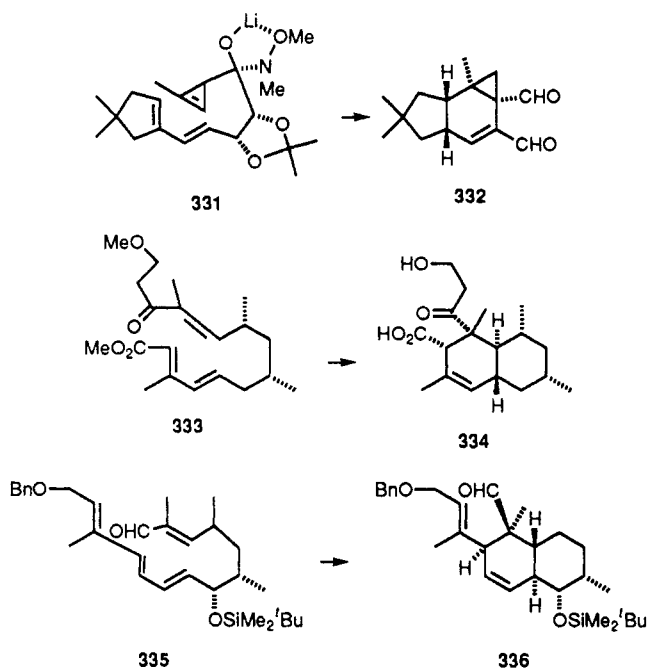
A much more complex application was to the synthesis of **330**, a compound closely related to the bitter principal quassamarin. From the D-glucose-based ketone **328** the multifunctionalized **329** was synthesized in 10 steps commencing with highly selective 1-lithio-3,3-diethoxypropyne addition to 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

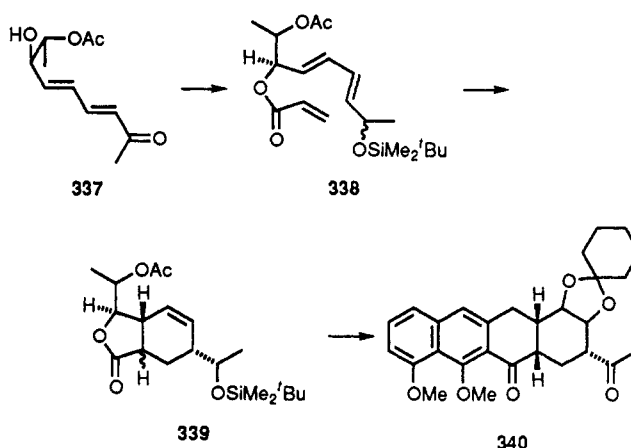


isovelleral 332 by way of the intermediate 331 (from 2,3-*O*-isopropylidene-L-erythruronic acid);¹⁷⁰ the mycotoxin diploidiatoxin 334 from 333 which was elaborated from methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl- α -D-allopyranoside;¹⁷¹ and the fragment 336 of tetronolide from 335 and, initially, 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



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

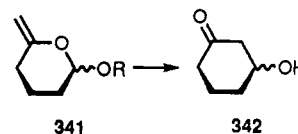


D. Cyclizations Involving Organometallic Intermediates

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

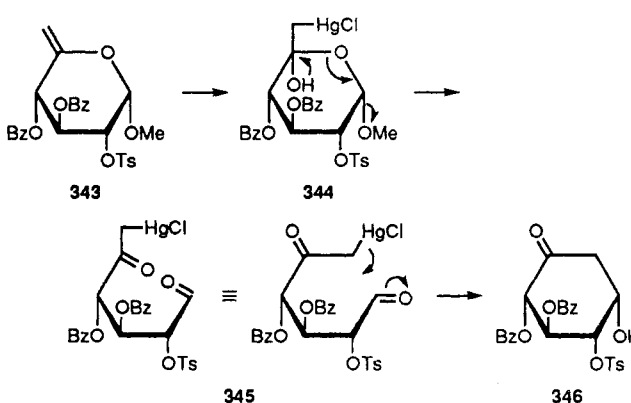
A convenient procedure for converting carbohydrate derivatives into cyclohexanone analogues (in outline 341 \rightarrow 342) was first observed when the alkene (343)



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

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).

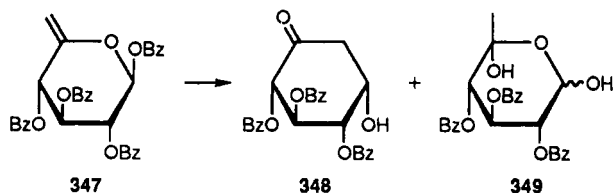
Scheme 62



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

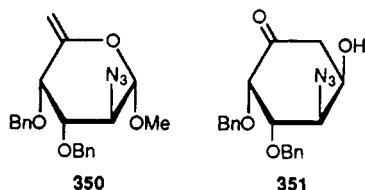
Scheme 63



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

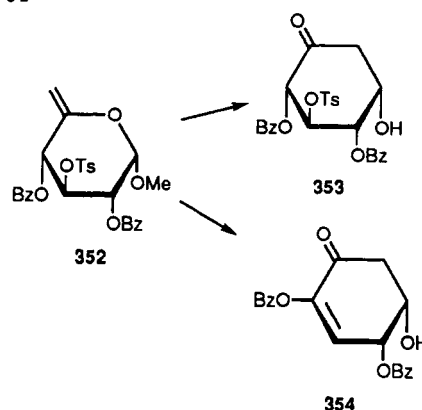
Consistent with the reaction path outlined in Scheme 62, 6-deoxyhex-5-enopyranosyl compounds undergo methoxymercuration to give acetals at C-5 which hydrolyze under acid conditions to afford the hydroxycyclohexanones.¹⁷⁵ Similar hydrolysis of the initial alkenes, however, results in extensive formation 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-

Scheme 64



hex-5-enopyranoside derivative into the corresponding cyclohexanone in quantitative yield.¹⁷⁸

A later study of the reaction¹⁷⁹ 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-xylohex-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** \rightarrow **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-

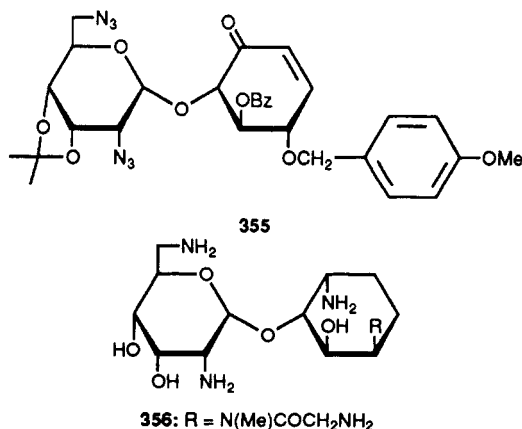
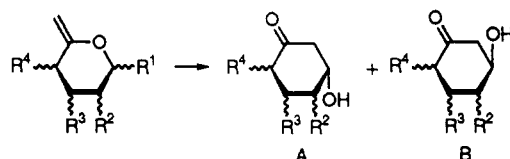
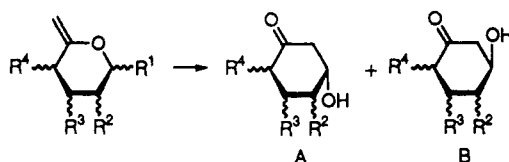


Table 1. Functionalized Cyclohexanones from 6-Deoxyhex-5-enopyranosyl Derivatives^a

entry	R ¹	R ²	R ³	R ⁴	yield (%)		ref(s)
					A	B	
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 ₂ OMe(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

entry	R ¹	R ²	R ³	R ⁴	yield (%)		ref(s)
					A	B	
1	OMe	NHAc(b)	OCHMeCO ₂ Bn(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.

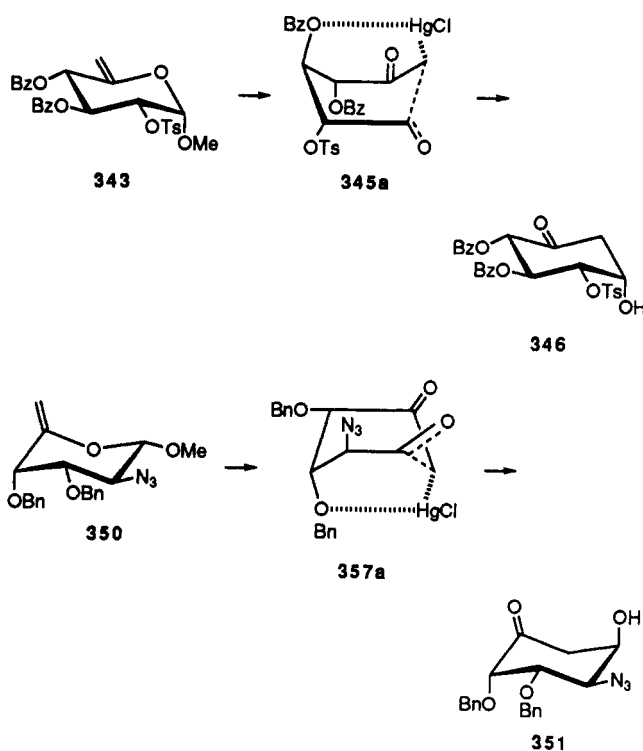
glycoside pseudodisaccharide **356**, for example, having been prepared from the maltose-derived enone **355**.¹⁸⁵

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 other¹⁸⁷ (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 aldehyde 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,

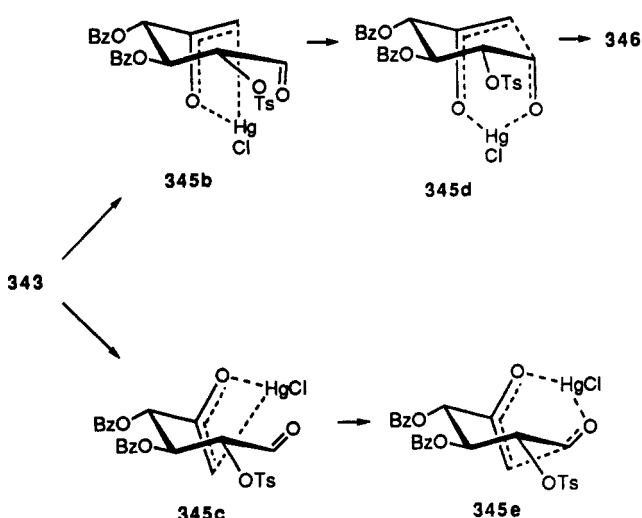
Scheme 65



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.

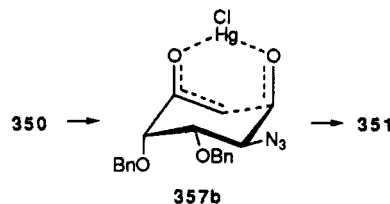
A third hypothesis, which is developed somewhat here, invokes coordination between the mercury atoms of intermediates and the oxygen atoms of the aldehydic groups while retaining features of the conformations of the starting alkenes. In the case of compound 343 the C-5–C-6 portion of intermediate 345 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

Scheme 66



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 hypothesis¹⁸⁸ proposes that 357b represents the transition state adopted in passing from the 1C_4 chair starting material to 351 (Scheme 67).

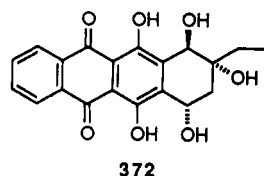
Scheme 67



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.

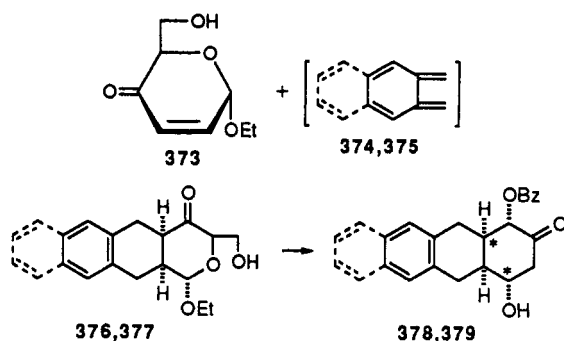
In a similar fashion, the structural similarity of the cyclohexanone derivatives obtainable by the “mercury method” to “carba-pyranoid” sugars, i.e. sugar-like cyclohexane derivatives having the ring oxygen atoms replaced by methylene group,²⁰⁴ has led to the synthesis of several carbahexoses^{178,193,199,203,205,206}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

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*-xylenes 374 and 375,



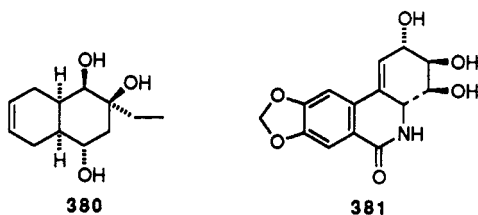
generated from the corresponding dibromides by treatment with zinc dust in an ultrasonic field, underwent cycloaddition reactions with the D-glucose-derived enone 373 to give adducts 376 and 377, respectively, from which the tri- and tetracyclic 378 and 379 were obtained following reduction of the carbonyl groups, conversions of the hydroxymethyl groups to *exo*-alkenes, and application of the mercury rearrangement reaction, (Scheme 70).²¹¹ In closely related work,

Scheme 70^a



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

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

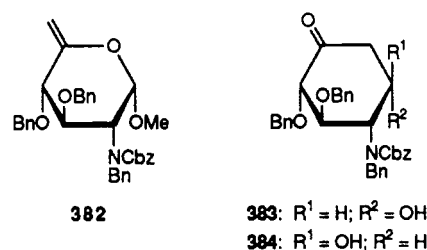


The isolation of compounds 378 and 379 in 68 and 65% yield, respectively, from the corresponding 5-enopyranosides and of 70% of the isomer of 378 having altered stereochemistries at the asterisked centers from the alkene derived from the *trans*-fused C-3 (carbohydrate numbering) epimer of compound 376,²¹³ 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 coor-

dination involving the carbonyl groups, are indicated as the features upon which the stereochemistry depends.

2. Cyclizations Promoted by Palladium(II) Salts

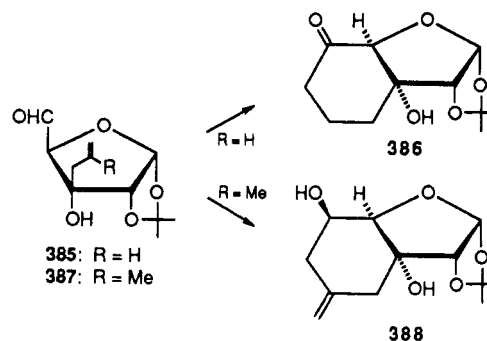
S. Adam first reported that the cyclohexanone synthesis from 6-deoxyhex-5-enopyranosyl derivatives, which is normally carried out by use of mercury(II) salts (section II.D.1), can be effected with catalytic amounts of Pd(II) salts in the presence of aqueous sulfuric acid.²¹⁴ While the mechanism of the 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



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 [(Ph₃P)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

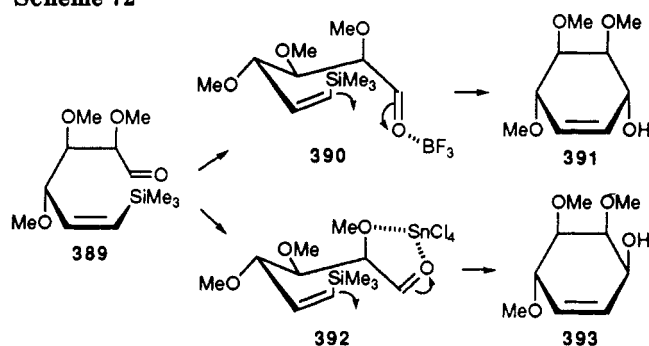


E. Other Reactions

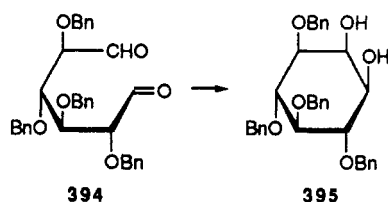
A cyclization process akin to many of the carbanionic reactions described in section II.A.3.a, but which affords cyclohexene products directly, is based on the use of a

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.

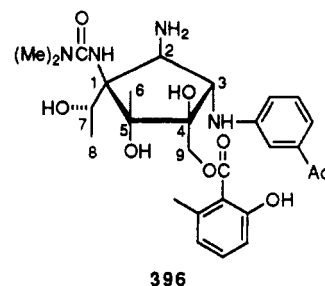
III. Syntheses of Functionalized Cyclopentanes

A. Carbanion Cyclizations

1. Biosynthesis of Hydroxylated Cyclopentanes

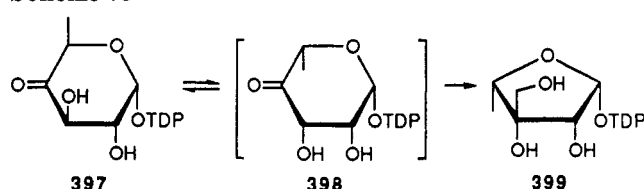
In addition to playing a central role in the biosynthesis of functionalized cyclohexanes such as the inositols (section II.A.1), D-glucose also serves as the biosynthetic precursor of a number of cyclopentane analogues, and in each case formation of the alicyclic ring may again involve an aldol reaction.

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-



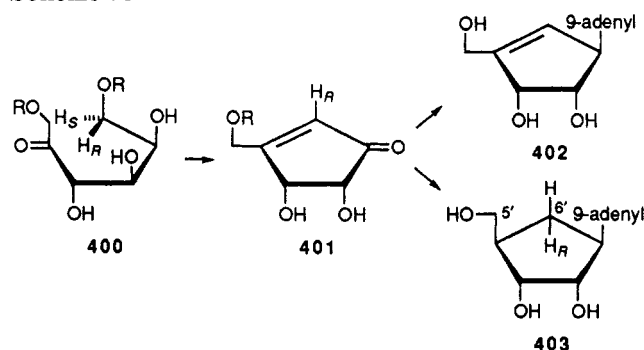
4) bond of pactamycin. It was pointed out, however, that the observed labeling patterns would also result if D-glucose was initially converted into an inosose (see section II.A.1) which then underwent a ring contraction analogous to that involved in the formation of thymidine diphosphodihydrostreptose (**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

Scheme 73



The cyclopentane moiety of the carbanucleoside antibiotic aristeromycin **403** is also derived from D-glucose (Scheme 74), appropriate ^{13}C -labeling ex-

Scheme 74

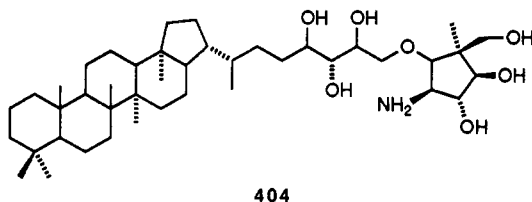


periments indicating that C-1 and C-6 of the hexose correspond to C-5' and C-6', respectively, of the antibiotic.²²⁰ Formation of the cyclopentane ring of **403** thus involves bonding of C-2 and C-6 of D-glucose, and possibly proceeds through the intermediacy of the phosphorylated fructose **400** (R = 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*-6S hydrogen atom of the proposed intermediate **400**, thus indicating that the stereochemical outcome of the reaction is the

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 ¹³C-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) nep-lanocin A (**402**).²²⁴

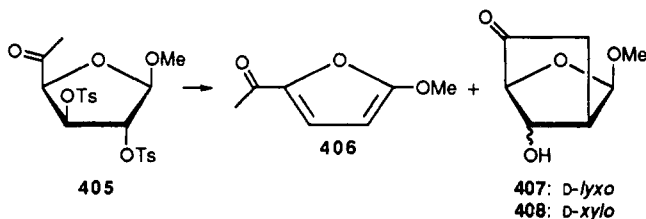


2. Displacements by Enolate Carbanions at Saturated Carbon Centers

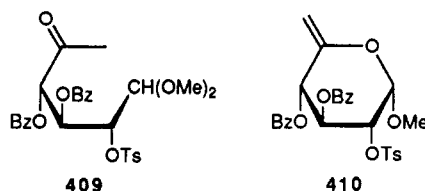
The carbanionic centers required for this type of reaction have been generated most commonly by proton abstraction from positions α to ketone, ester, amide, or nitrile groups. Cases which involve stabilization of the carbanion by other groups are considered in sections III.A.4 and III.A.5.

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

Scheme 75

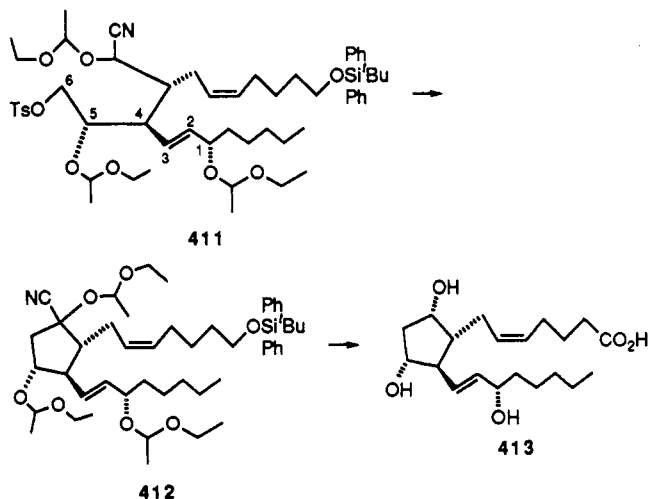


bicyclic product, the 3-O-methyl analogue of the ditosylate **405** was treated as before, but no cyclization was observed.²²⁵ Attention was then directed toward the tosylate **409** which, on cyclization, would give a cyclopentanone derivative, but all attempts to obtain the required acetal from the 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).



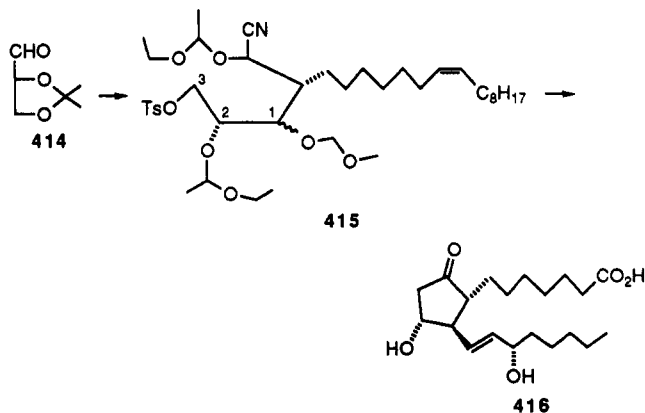
That ring closures of the above intended kind can be successful was emphatically shown by Stork *et al.* who converted the highly functionalized, acyclic tosylate **411** (which was prepared from D-glucose, the carbon atoms of which are numbered in the formula) to the cyclopentane derivative **412** in good yield.²²⁶ This was the key step of their total synthesis of prostaglandin F_{2α} (**413**) by chiral transfer from D-glucose (Scheme 76)

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 E₁ (**416**) having the correct absolute configuration (Scheme 77).²²⁷

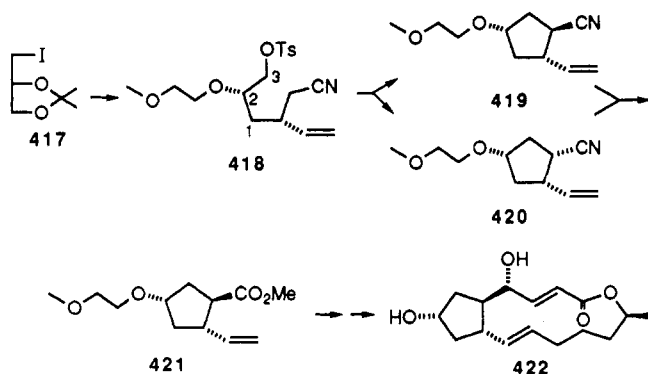
Scheme 77



The iodide **417**, also available from 2,3-O-isopropylidene-D-glyceraldehyde, provided Mori *et al.* with a

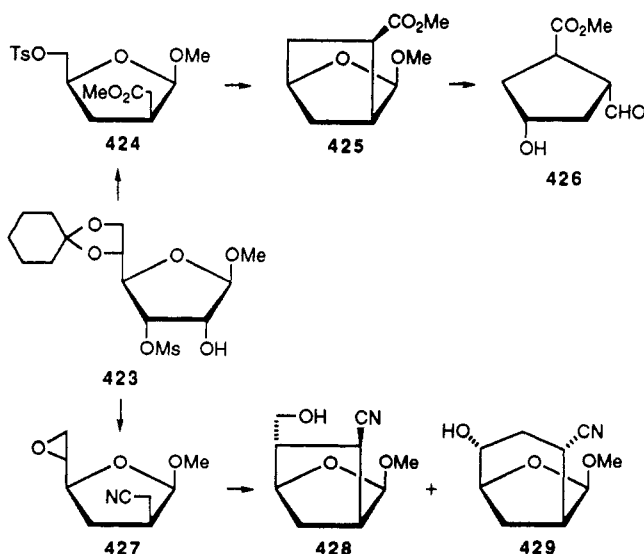
convenient starting point for their synthesis of the tosylate **418** which, on treatment with sodium hexamethyldisilazide in refluxing benzene, readily afforded a 92:8 mixture of the stereoisomeric cyclopentane derivatives **419** and **420**, respectively.²²⁸ After alkaline hydrolysis, followed by 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 Ohri 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

Scheme 79

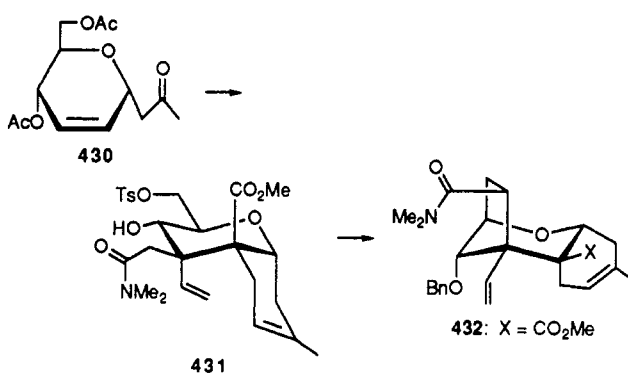


functionality and stereochemistry of which are consonant with its projected conversion into (+)-brefeldin A (**422**). The allofuranoside **423** was also converted by five steps to the epoxide **427** which, on treatment with lithium hexamethyldisilazide in tetrahydrofuran at room temperature, afforded 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.

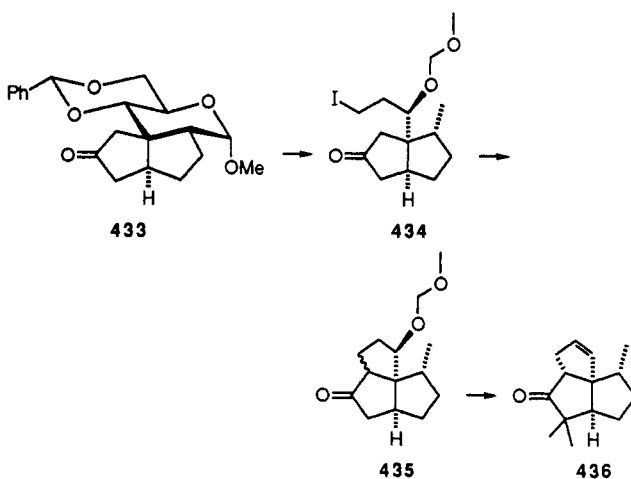
Two further very elegant instances of cyclopentane ring formation by intramolecular nucleophilic displacement are found in the stereocontrolled syntheses of polycyclic systems developed by Fraser-Reid's group. In the first of these, the *cis*-fused (and thus conformationally mobile) oxadecalin derivative **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

Scheme 80



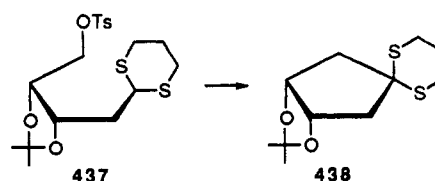
involved cyclization of the keto iodide **434** to the triquinane **435** from which the silphinene skeleton **436** was subsequently obtained (Scheme 81).²³¹ Compound

Scheme 81



434 was conveniently derived from the branched-chain pyranoside **433** the synthesis of which is considered in section III.B.1.c.

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

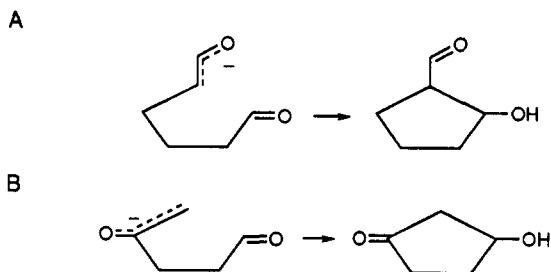


3. Aldol and Aldol-like Reactions

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).

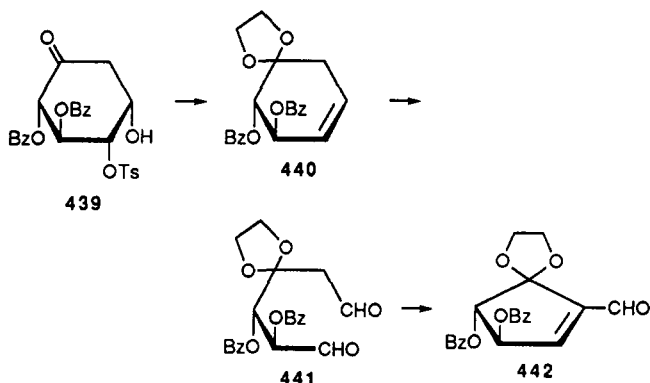
a. Reactions with Sugar Chains. The ring-forming steps in reactions of this type involve either 5-(enol-*exo*)-*exo-trig* or 5-(enol-*endo*)-*exo-trig* processes (Scheme 82; A and B respectively),⁴³ and in most cases the

Scheme 82



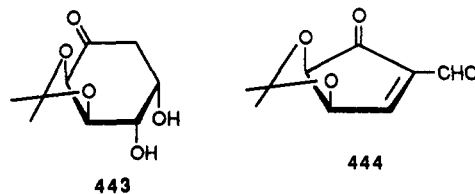
resulting β -ketols undergo dehydration to give thermodynamically stable conjugated enones. Several different methods have been used to generate the required enolates, the most straightforward and commonly used method involving deprotonation of appropriate dicarbonyl compounds. Thus, the cyclohexanone 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

Scheme 83



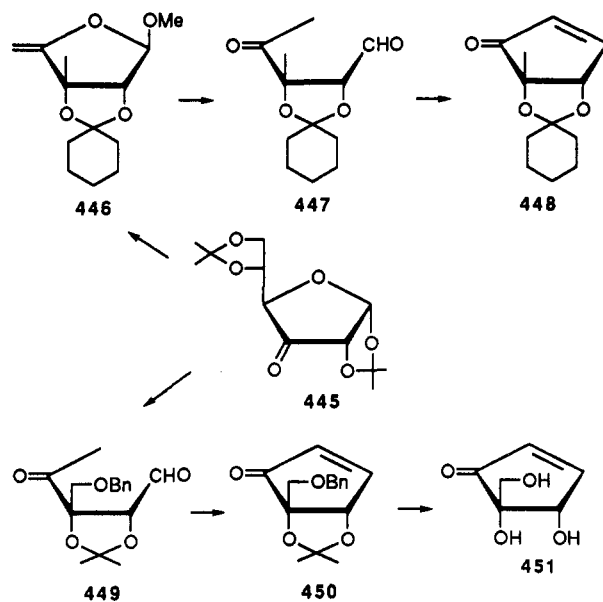
cyclization step of type A (Scheme 82).²³³ Protection of the carbonyl function at C-1 of 439 may well have been important for the success of the overall sequence, however, since attempts to obtain the related enal 444 by periodate cleavage of the diol 443 and aldol cyclization of the resulting dial were unsuccessful. Indeed, the cyclization 441 \rightarrow 442 seems to be the only recorded instance of cyclopentane ring formation from a carbohydrate-derived 1,6-dicarbonyl compound.

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 process⁴³ 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

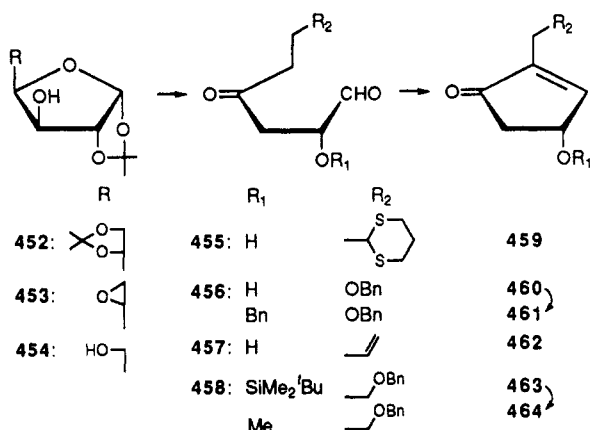
Scheme 84



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 E₂ 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

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

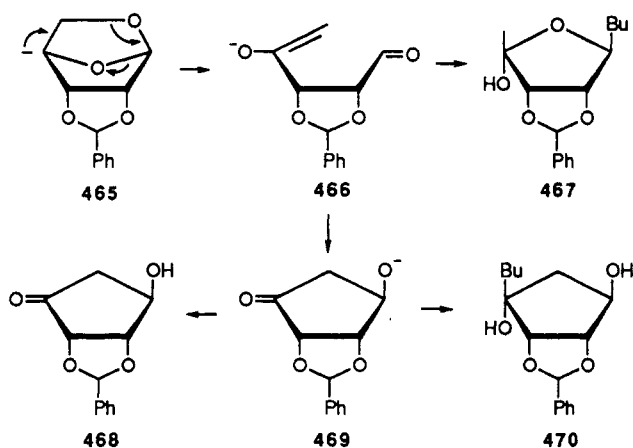
Scheme 85



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, Klemmer 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 alkyl lithium 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

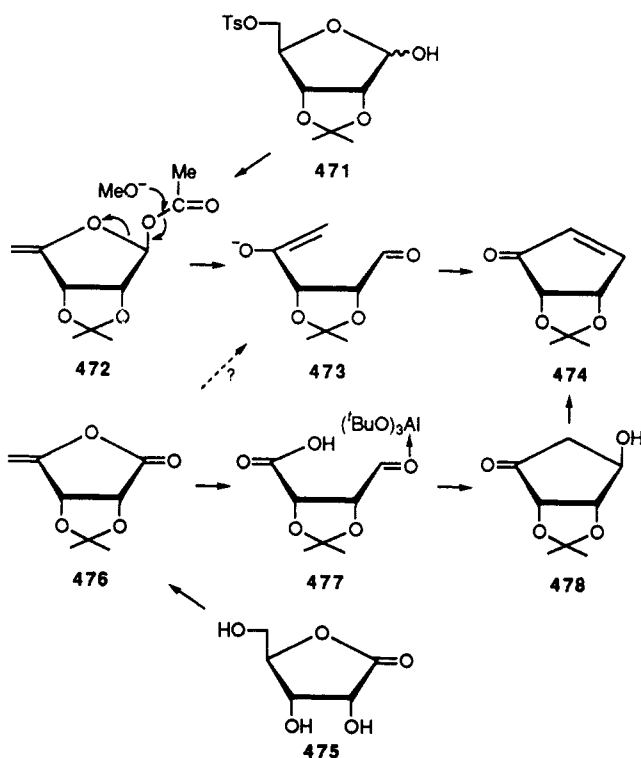
Scheme 86



the formation of **470** are analogous to those observed when anhydropyranose derivatives are treated with alkyl lithium (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 alkyl lithium.

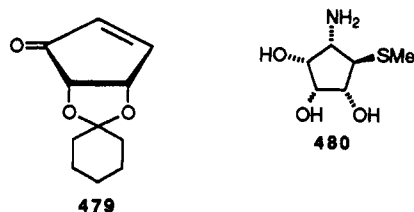
Ohrui's group has effectively converted the ribofuranose derivative **471** into the unsaturated acetate **472** from which the enolate **473**, and hence the (4*S*,5*S*)-cyclopentenone **474** (80% yield), were obtained on treatment with catalytic amounts of sodium methoxide in boiling methanol (Scheme 87).^{240,241} Enone **474** was also obtained by Bélanger and Prasit in six steps from

Scheme 87



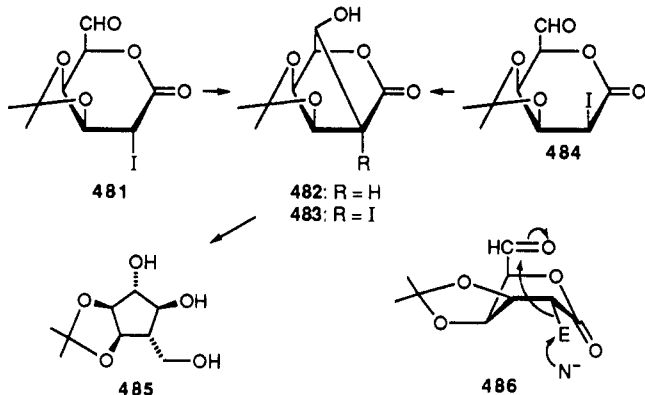
D-ribo- γ -lactone (**475**) via the enol lactone **476**.²⁴² The alicyclic ring was formed in high yield by use of 1 equiv of lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran followed by quenching with aqueous ammonium chloride. Dehydration of the resulting β -ketol **478** was then effected 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.

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



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

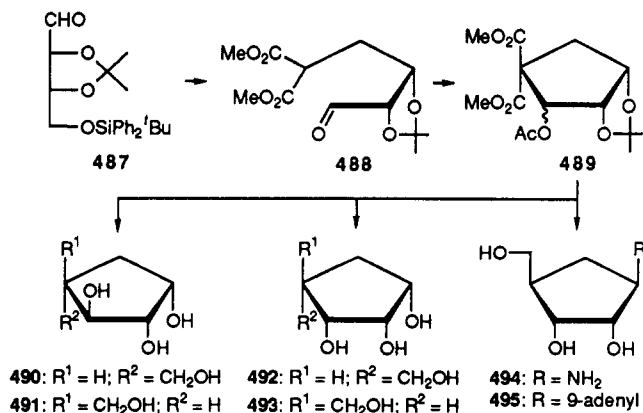


rather than loss of I^+ (Scheme 88).²⁴⁴ For these cyclizations to occur the 4B_1 conformation would have been imposed on the pyranoid rings, and the results obtained show, as expected, that nucleophilic attack at C-6 is initiated by iodide attack at the quasiequatorial electrophilic iodine or hydrogen 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, Yokohama, 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 carba-furanose series of compounds.

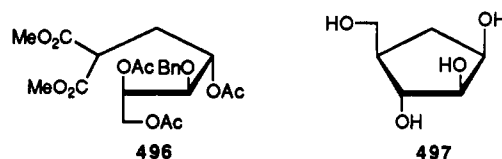
In one set of experiments in this area, Tadano *et al.* converted D-glucose into the D-erythrose derivative 487 the carbon chain of which was then extended in the manner indicated above. Desilylation of the product, followed by PCC oxidation, gave aldehyde 488 which cyclized spontaneously under the reaction 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

Scheme 89



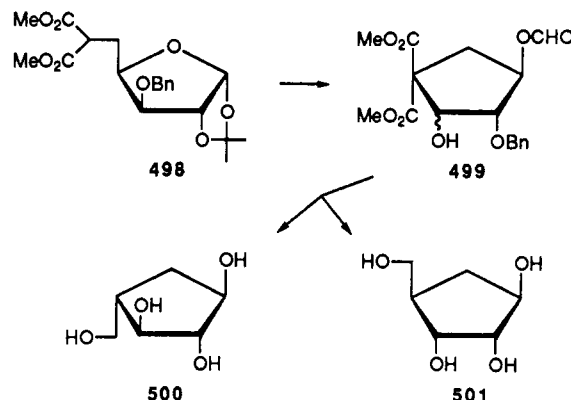
prepared by a different route and converted into the antibiotic (-)-aristeromycin (495).²⁴⁶

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



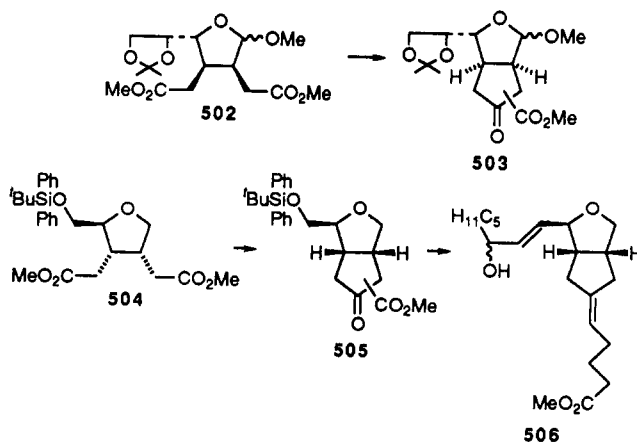
Most recently, Tadano *et al.* have used a similar approach with the chain-extended diester 498.²⁴⁸ Removal of the acetal protecting group, followed by cleavage of the resulting diol with periodate and spontaneous aldol cyclization of the product, afforded a mixture of epimeric cyclopentane derivatives 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

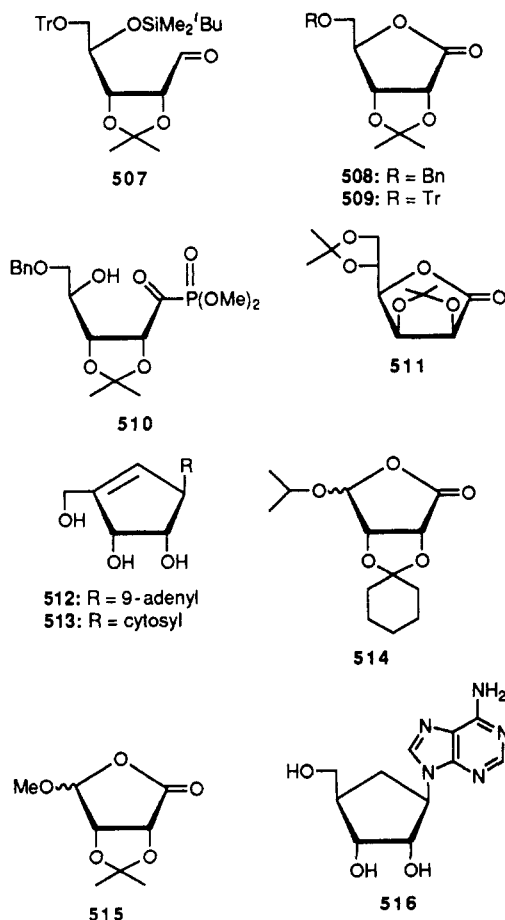
Scheme 91



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

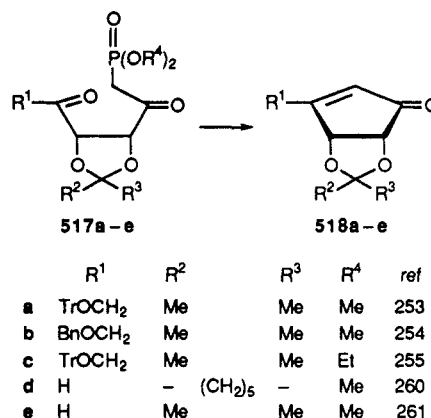
Reactions involving aldol-like cyclization of carbanions which are stabilized both by neighboring phosphonate and carbonyl groups have been put to good use in the enantioselective synthesis of cyclopentane derivatives from carbohydrates. Remarkably, however, in all cases reported to date the intermediate 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



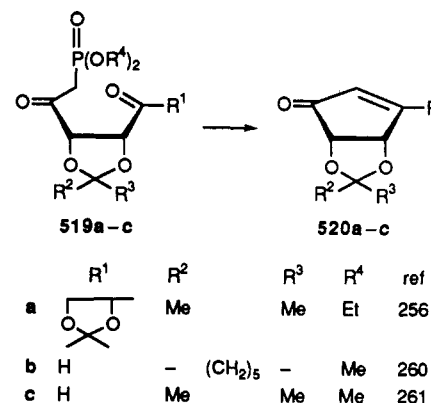
treated with lithium dimethyl methylphosphonate.²⁵³ The resulting mixture of diastereomeric alcohols was oxidized with Swern's reagent to give a keto phosphonate which, after desilylation and further Swern oxidation, gave the diketo phosphonate **517a**. Cyclization of this latter compound to enone **518a** was then effected in 30% yield by heating with anhydrous potassium carbonate and 18-crown-6 in toluene.

In later work, Lim and Marquez used D-ribo- 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*

Scheme 92



Scheme 93



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.

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 enantiometrically 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.)

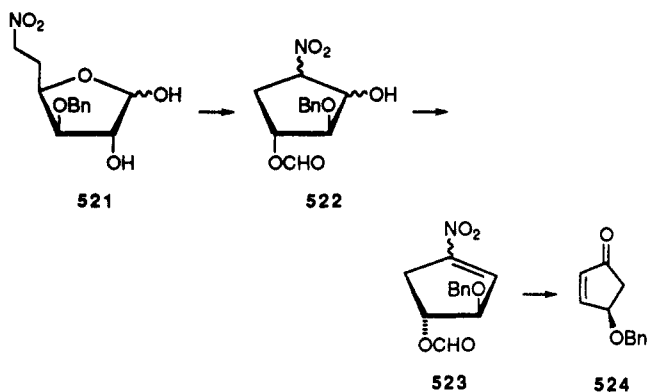
More recently, the same group has also reported the analogous stereoselective synthesis of enone **518e** and its enantiomer **520c** from the acetal lactones **515** and their enantiomers respectively, these latter compounds being obtained by new, three-step syntheses from D-lyxose and D-ribose, respectively.²⁶¹ 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

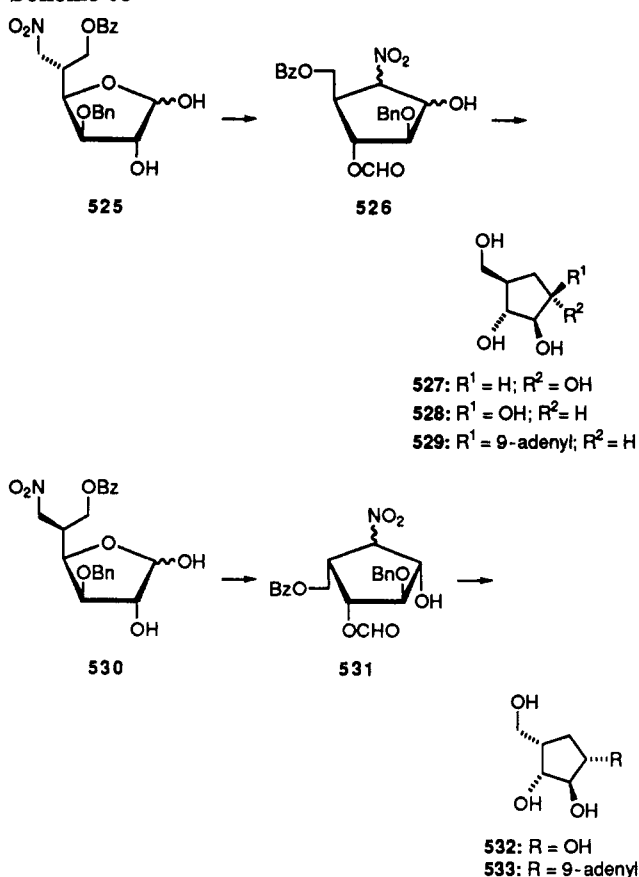
a. Cyclizations of Nitro Sugars. Reported syntheses of cyclopentane derivatives by cyclization of nitro sugars have all used di-*O*-isopropylidene-glucose as starting material. In the simplest case, Torii *et al.* initially converted the glucose derivative into nitrofuranose **521** which was then treated 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

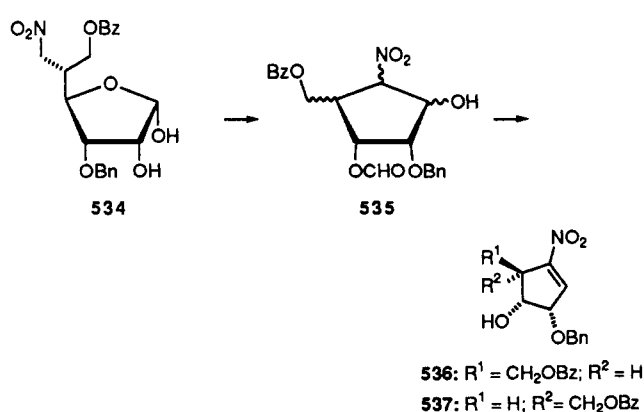
Scheme 95



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.²⁶⁸

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

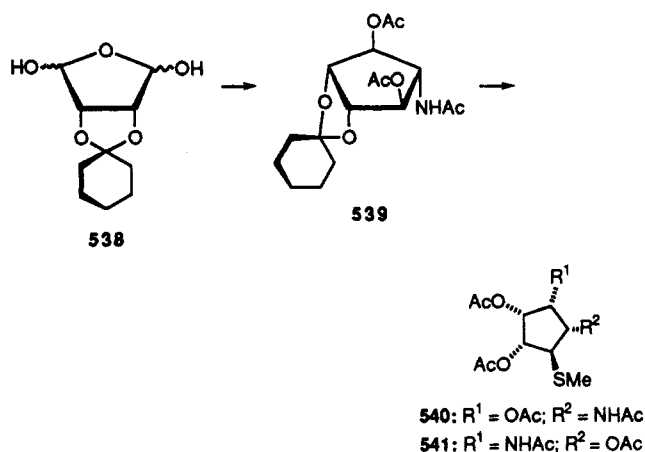
Scheme 96



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 significance, 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 manostatins A tetraacetate (**540**) and its regioisomer **541** (Scheme 97).²⁷⁶

Scheme 97



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 RajanBabu²⁷⁸ 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-

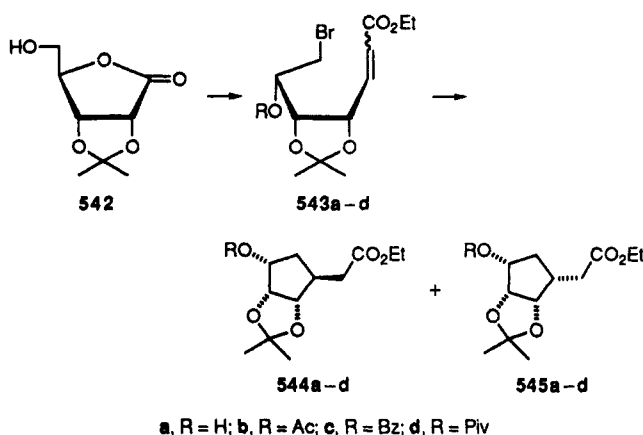
acceptor groups. More complex cases are then dealt with.

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-ribo- 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



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.

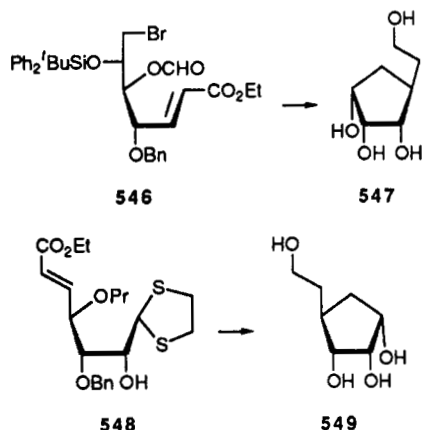
Table 3. Cyclization of 5-Hexenyl Bromides **543**²⁷⁷

starting compound	products	product ratio 544 : 545	total yield (%)
(<i>Z</i>)- 543a	544a , 545a	6:1	80 ^a
(<i>E</i>)- 543a	544a , 545a	2:1	80
(<i>Z</i>)- 543b	544b , 545b	5:1	80
(<i>E</i>)- 543b	544b , 545b	1:1	82
(<i>Z</i>)- 543c	544c , 545c	10:1	89
(<i>E</i>)- 543c	544c , 545c	1:1.2	87
(<i>Z</i>)- 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-ribo- 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

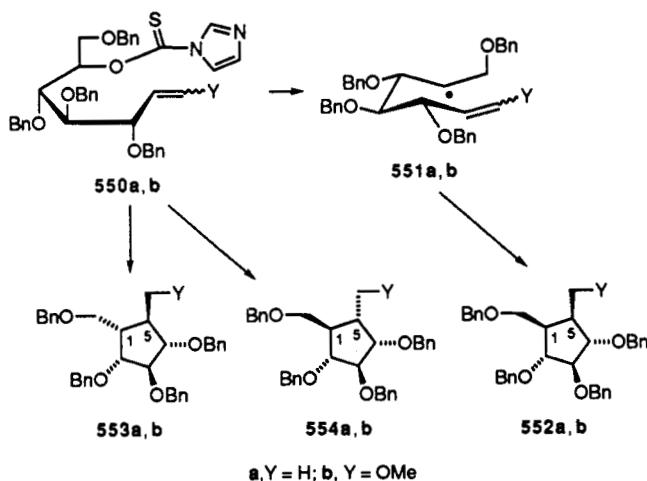
Scheme 99



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-workers²⁸² were concerned with cases involving both acyclic and cyclic *secondary* radicals. The acyclic species of interest were generated from the glucose-derived imidazole-carbothioates **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).

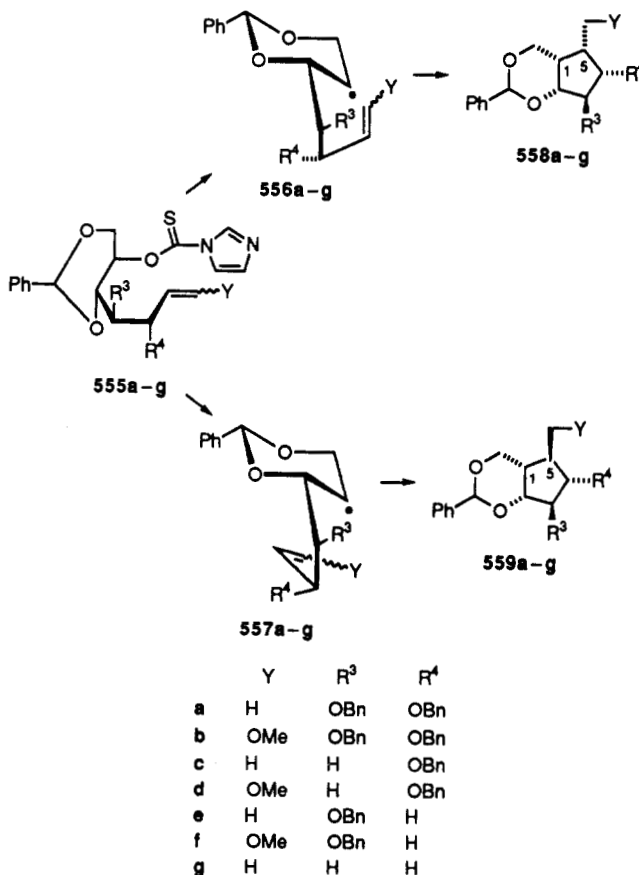
Scheme 100



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

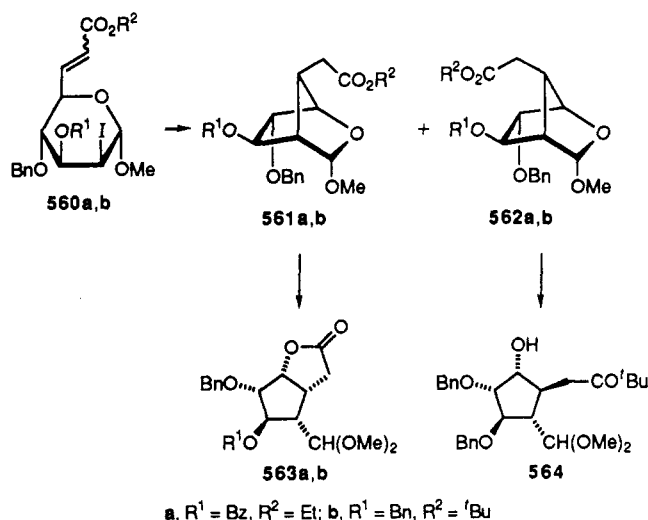
Scheme 101



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 R⁴ is again a benzyloxy group, whereas 1,5-*cis* products **558** are formed preferentially from carbothioates **555e**, **555f** and **555g** in each of which R⁴ 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}

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).

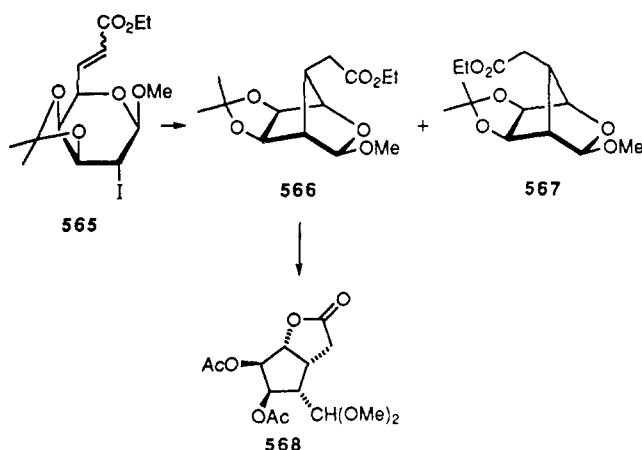
Scheme 102



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.

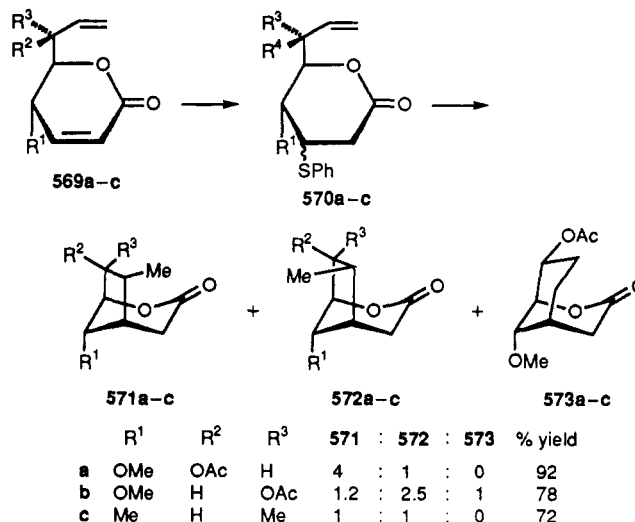
Fraser-Reid *et al.* also investigated analogous cyclizations of the unsaturated iodides **565**, derived from D-galactal, to **566** and **567**, and found that the former, obtained now with specificity or high selectivity from each geometric isomer, was easily converted into the synthetically useful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

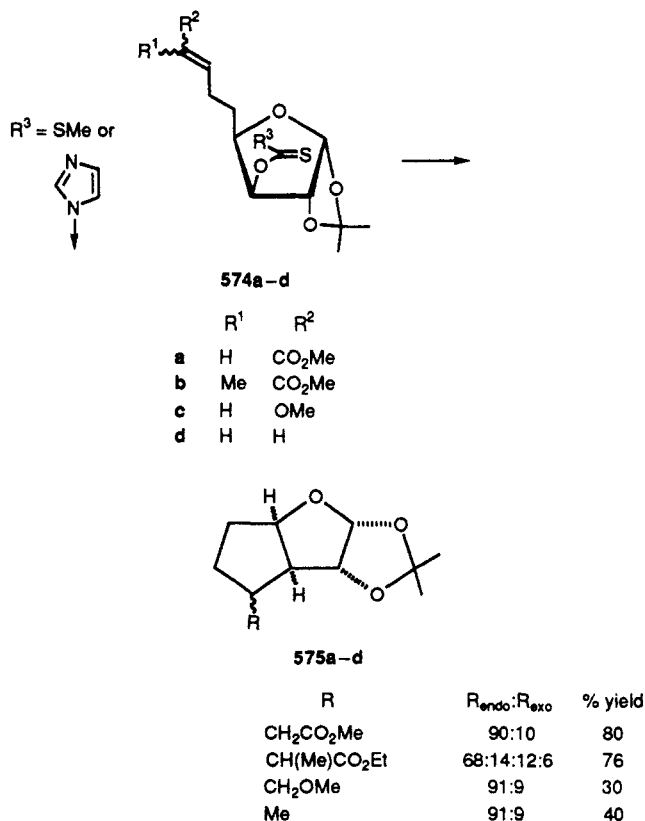
Scheme 104



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.

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

Scheme 105

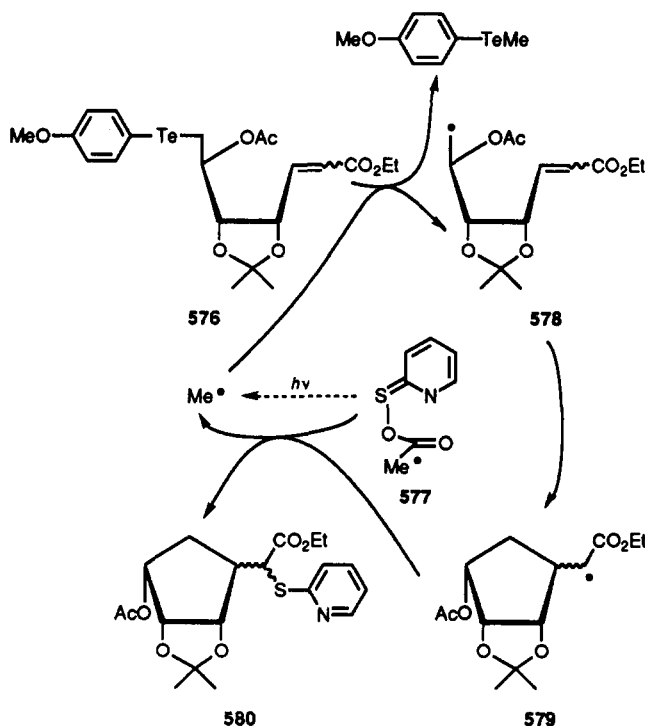


isomers) which were then separately treated with tributyltin hydride and AIBN to give mixtures of the stereoisomeric tricyclic acetals **575a-d** (Scheme 105).

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.

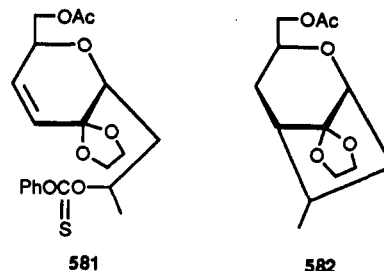
In each of the examples discussed thus far in this section, the requisite 5-hexenyl radicals were produced by use of tributyltin hydride with AIBN as radical initiator. Practical difficulties (notably reduction of the first-formed radicals) commonly attend the use of this system; however, a new method 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%

Scheme 106



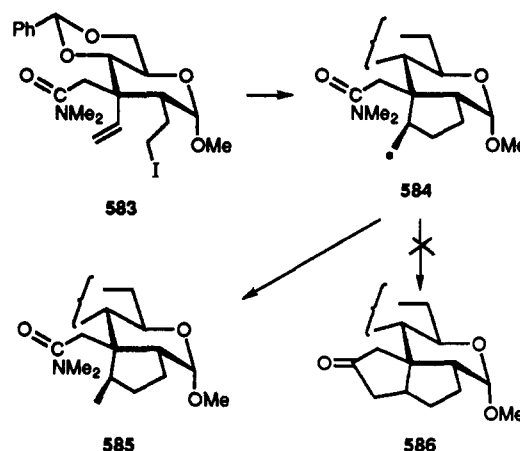
total yield, the 1,4-*cis*- and 1,4-*trans*-substituted isomers being formed in the proportions 11:89.

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.



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

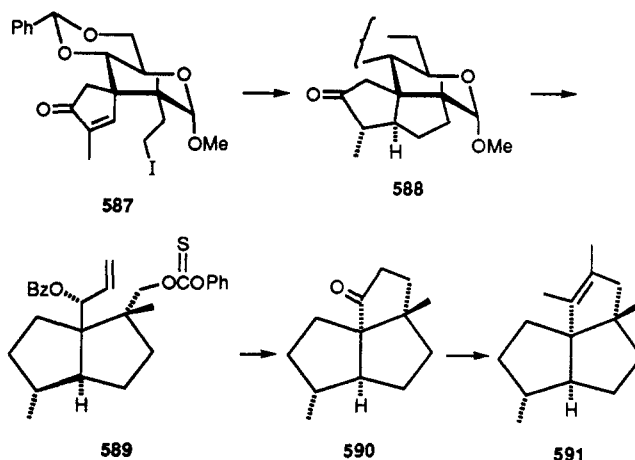
Scheme 107



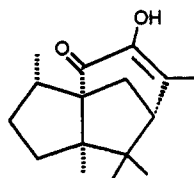
carbon-centered radical is undoubtedly facilitated here by the *cis* relationship between the iodoethyl and vinyl groups since this arrangement necessarily leads to the energetically favored formation of a *cis*-6/5 ring junction in the intermediate cyclopentylmethyl radical **584**. This radical then 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**.

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



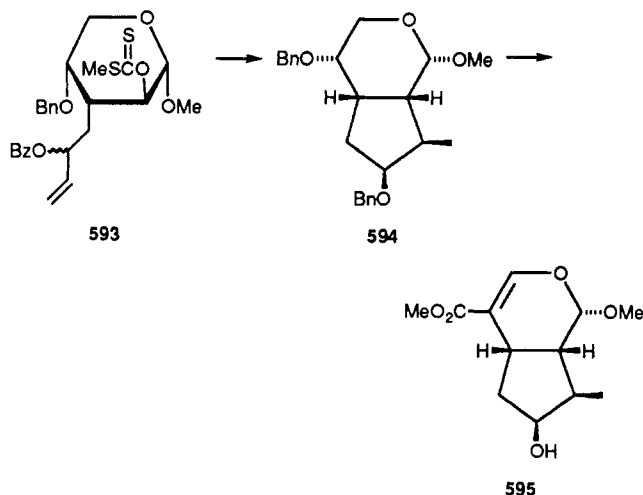
nose.^{288,289} Compound **588** was then converted into the monothiocarbonate **589** which, on treatment with tributyltin hydride, underwent smooth 5-*exo-trig* radical cyclization, thereby ultimately permitting stereoselective synthesis of the angularly fused triquinanone **590** and hence the hydrocarbon (-)-silphiperfolene **591** (Scheme 108).²⁹⁰ In a related fashion, but involving triply branched enyne intermediates, the related (-)- α -pipitzol (**592**) was made²⁹⁰ among several highly substituted diquinanes.²⁹¹ (See also section III.B.5.)



592

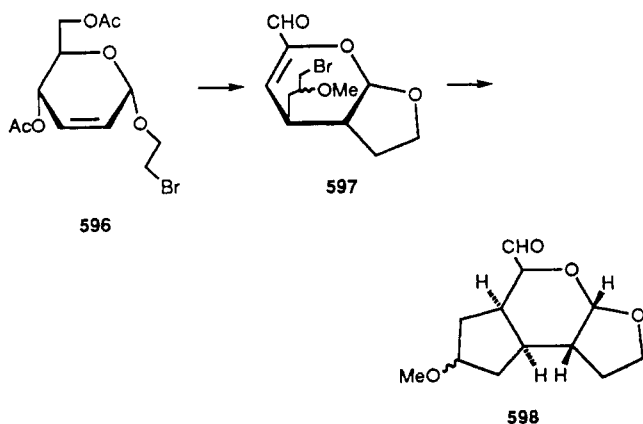
In a simpler example the *cis*-fused cyclopentanopyranoside **594** was obtained stereoselectively on treating the unsaturated dithiocarbonate **593** (made from methyl 2,3-anhydro- α -D-lyxopyranoside) with AIBN/tributyltin hydride (Scheme 109) and converted into the iridoid

Scheme 109



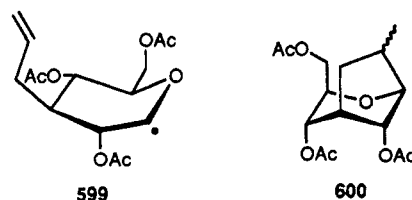
glycoside aglycon, 1- α -O-methylloganin (**595**).²⁹² In reciprocal fashion, the radical being in the branch and the trap within the sugar chain, analogous cyclopent-

Scheme 110



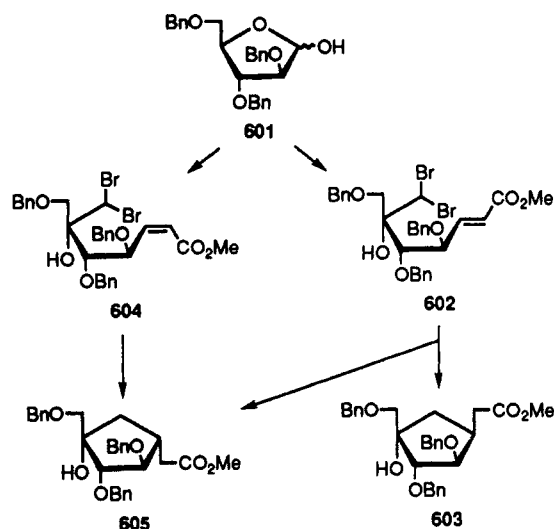
tanopyranosides **598** were synthesized by 5-*exo-trig* cyclization of radicals derived from a mixture of epimeric bromoenals **597** prepared following cyclization of **596** by allyltributyltin/AIBN which caused concurrent introduction of branch points at C-2 and C-3 (Scheme 110).²⁹³

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



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

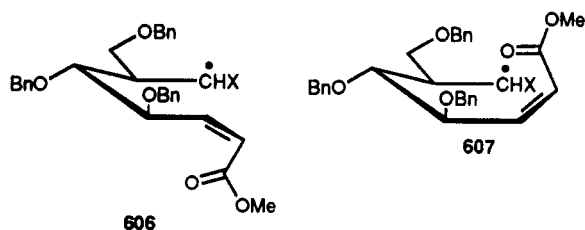
Scheme 111



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

carba- β -D-fructofuranose and the corresponding 6-phosphate derivative.^{296,297}

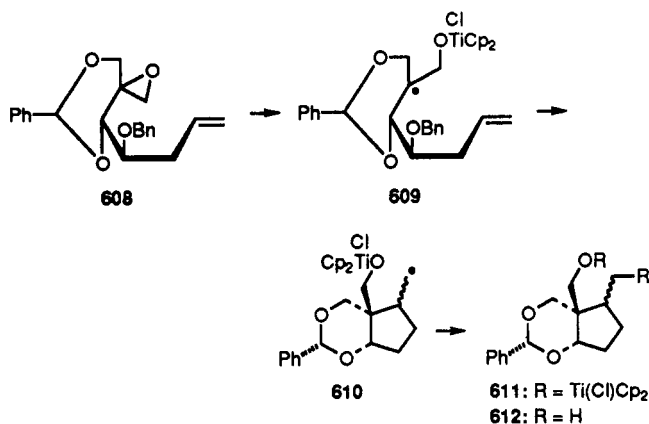
The exclusive formation of product **605** in the latter case indicates that ring closure is effected with the intermediate radical in the "chairlike" conformation **606** which allows for ready overlap between the radical center at C-1 and the unsaturated center at C-5 while minimizing steric interactions 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



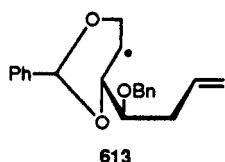
interactions in the radicals derived from the (*E*)-ester **602** could well be responsible for the lack of stereocontrol in the cyclization of this compound.

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

Scheme 112

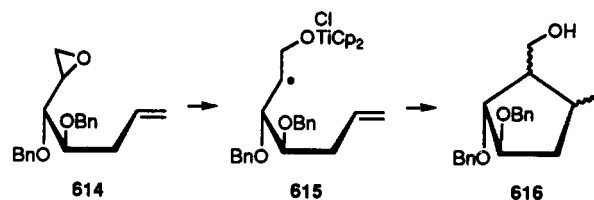


cyclization of the initially formed tertiary radical **609** is thus effectively the same as that found for the structurally analogous secondary radical **613** (see section III.B.1.b). The high degree of stereoselectivity observed



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

Scheme 113

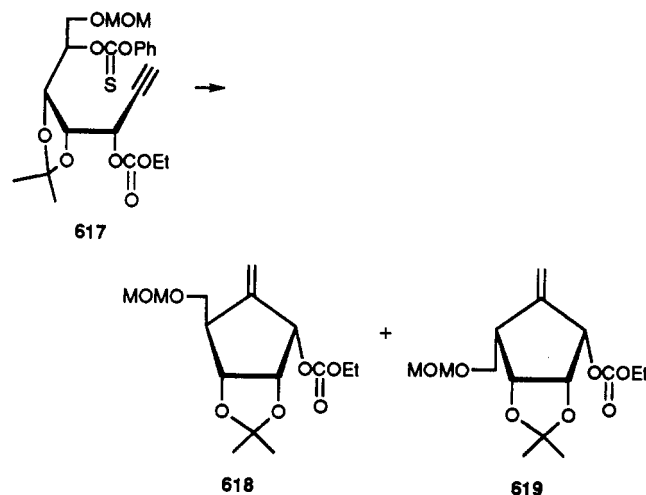


of the four possible stereoisomeric cyclopentane derivatives **616** is produced.

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),

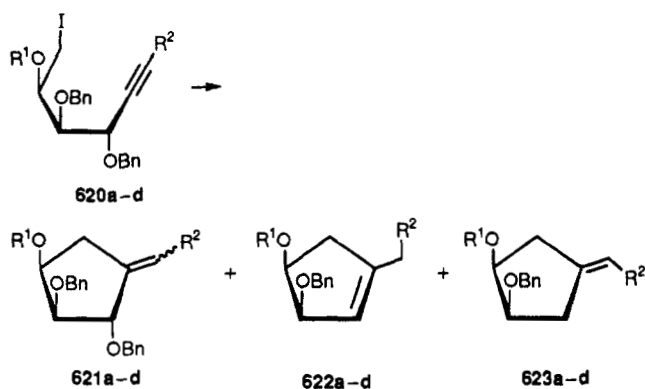
Scheme 114



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.

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

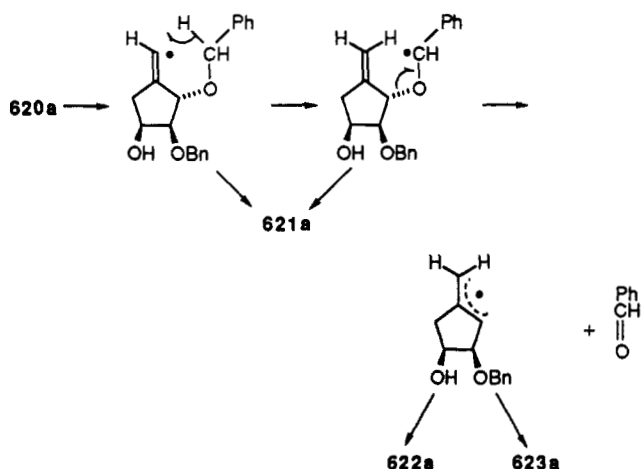
Scheme 115



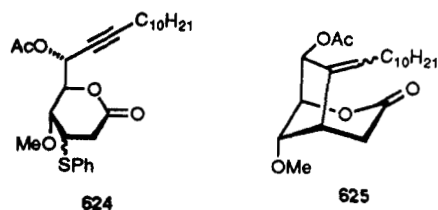
R ¹	R ²	% yield		
		621a-d	622a-d	623a-d
a	H	8	62	18
b	H	16	50	29
c	H	3	63	11
d	Ac	0	19	44

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



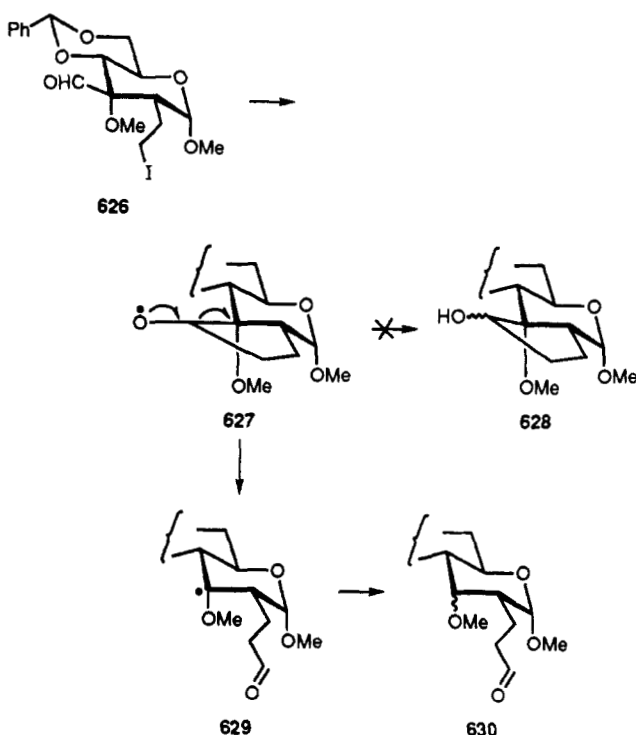
The overall total yield of these products was only 20%, however, which is much less than the yields of analogous bicyclic products obtained on application of the same

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 cyclopentanol.¹¹¹ The iodopyranoside **626**, on treatment with AIBN/tributyltin hydride, gave the two epimeric methoxyaldehydes **630** in high yield rather than the desired cyclopentanoxyranosides **628** (Scheme 117). This situation presumably arises because the

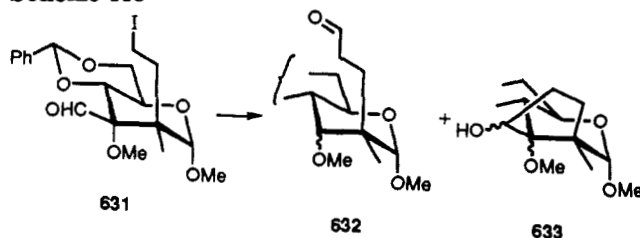
Scheme 117



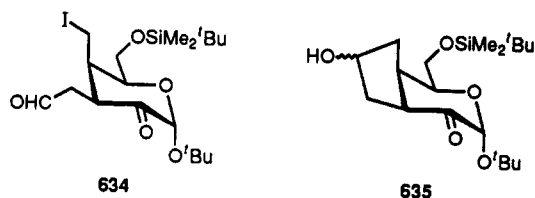
initially formed primary alkyl radical interacts with the neighboring aldehyde group, as desired, but the resulting cycloalkoxy radicals **627** undergo β -scission to give the stabilized methoxyalkyl radical **629** and hence the aldehyde translocation products **630**.

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 cyclopentanoxyranosides **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.

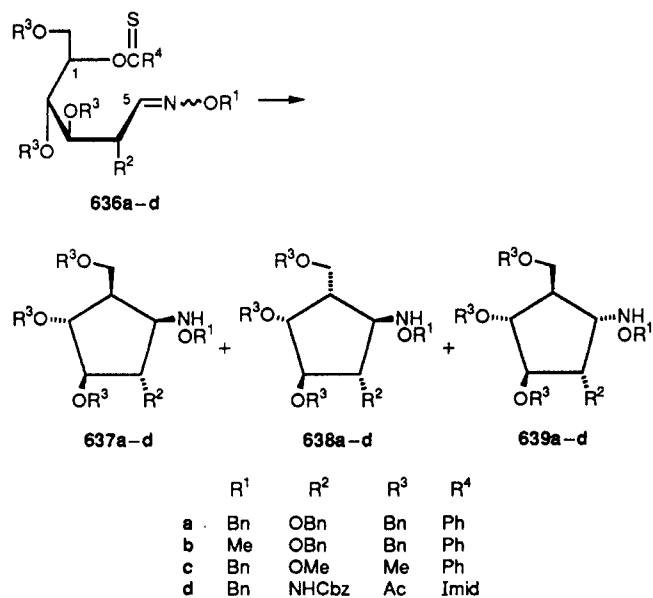


Work with model compounds has shown how cycloalkanols can be readily formed from ω -formylalkyl radicals, cyclohexanol production being particularly favored—even in the presence of accessible double bonds.^{110,302}

4. Simple Cyclizations of 5-Oximinoalkyl Radicals

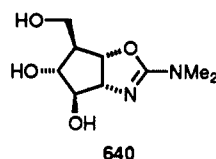
The problem of β -scission encountered above (section III.B.3) with reactions which involve the use of aldehyde groups as radical acceptors is especially acute in cases where an oxygen-bonded substituent is attached to the α -carbon of the initial aldehyde. No such problem is encountered, however, in 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 ($\sim 90\%$) of cyclopentane derivatives on treatment with AIBN/tributyltin hydride (Scheme 119). Specifically, Bartlett *et al.* found that ethers **636a,b** gave high yields of **637**

Scheme 119



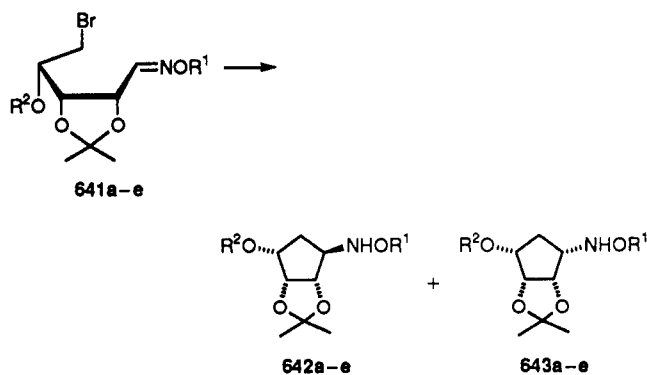
mixtures of cyclopentanes **637a,b** and **638a,b** and ether **636c** gave a 60:31:9 mixture of cyclopentanes **637c-639c**.³⁰³ In each case there is thus a preponderance of the 1,5-*cis* product **637** to be expected if cyclization again occurs while the intermediate radical preferentially adopts a "chairlike" conformation having the substituents at C-2, C-3, and C-4 in quasiequatorial orientations.

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.



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

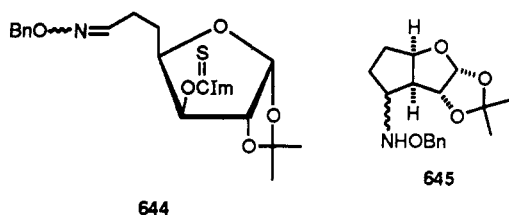


	R ¹	R ²	% yield	642:643 ^a
a	Bn	H	75	100:0
b	Bn	Si(Me) ₂ ^t Bu	53	100:0
c	Bn	Ac	52	100:0
d	Bn	Bz	58	89:11
e	Me	Bz	71	82:20

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

More recently, the same group effected 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

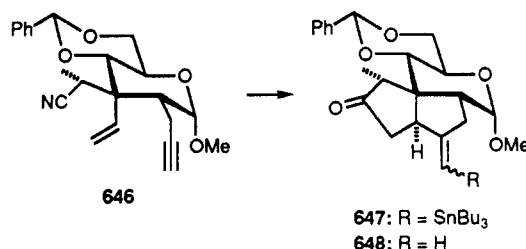
is thus entirely analogous to that observed for the cyclization of structurally related unsaturated esters (see section III.B.1a).



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

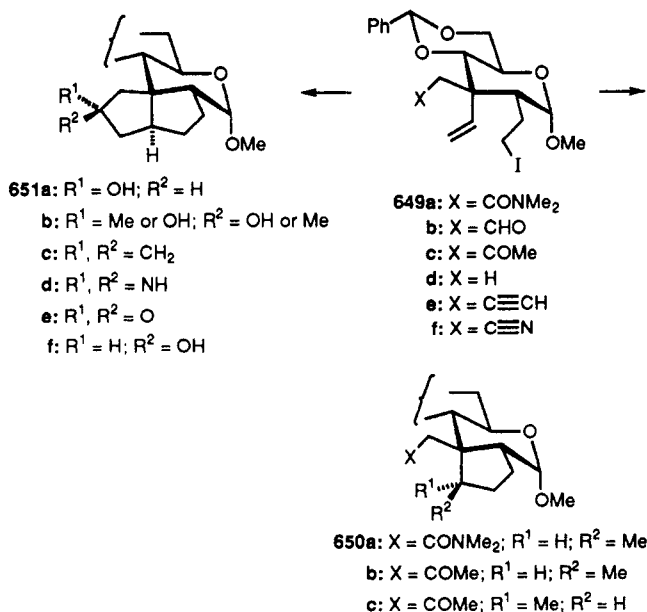
Scheme 121



was this methodology that led to (–)- α -pitzol (**592**).²⁹⁰

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 aldehyde 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



Surprisingly, no 6-*exo-trig* cyclization occurred with the methyl ketone **649c**, the main products now being

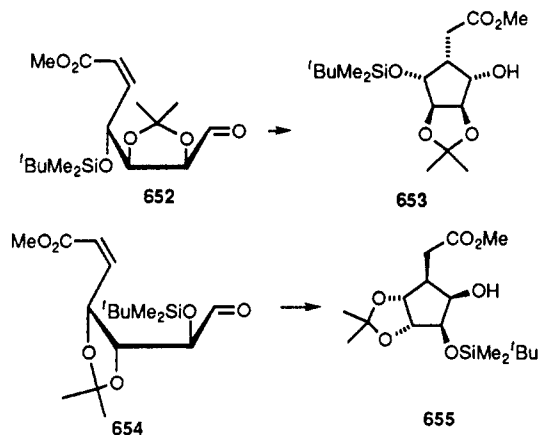
the reduced **649d** (15%), the “simple” 5-*exo-trig*-derived **650b** (23%) and the diquinane **651b**.^{111b}

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 cyclopentenones **653** and **655** (~65% yield) with substituents at the new asymmetric centers *syn* to each other (Scheme 123)

Scheme 123



together with $\leq 1\%$ of their distereoisomers. On the other hand, (*E*)-alkenes tend to give *anti*-related products with somewhat less selectivity.

C. Cycloaddition Reactions

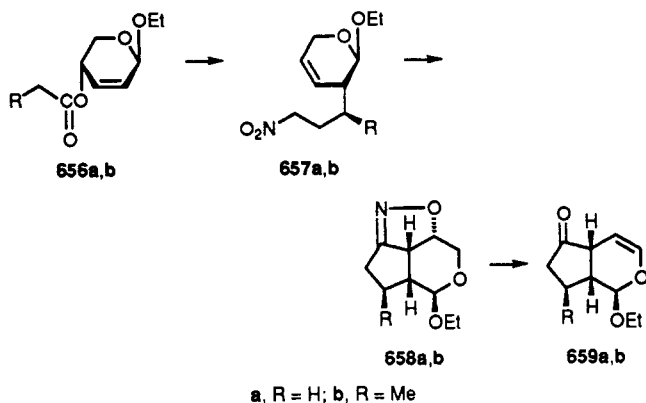
1. 1,3-Dipolar Cycloadditions

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

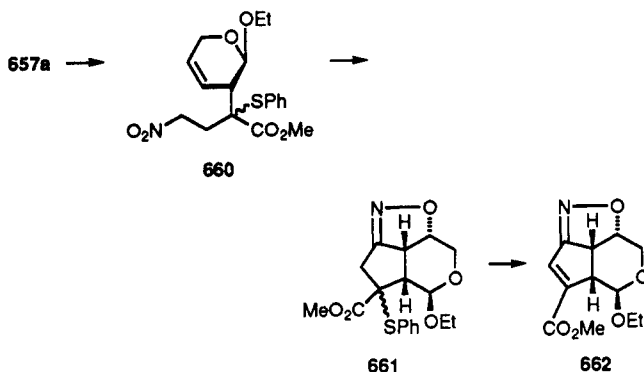
oxides. Cyclization of these latter intermediates then gave the Δ^2 -isoxazolines **658a,b** (50–60% yield) and hence the oxahydroindenones **659a,b** (Scheme 124). The

Scheme 124



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

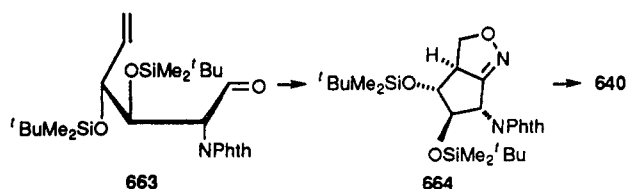
Scheme 125



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

Scheme 126

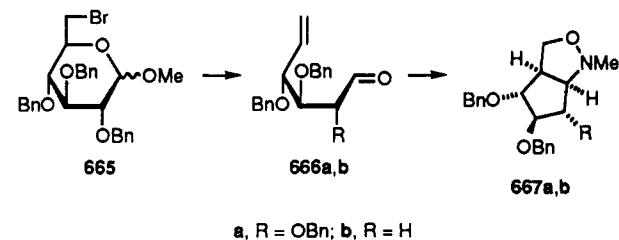


case by the action of hypochlorite on the oxime of **663**.³¹⁰

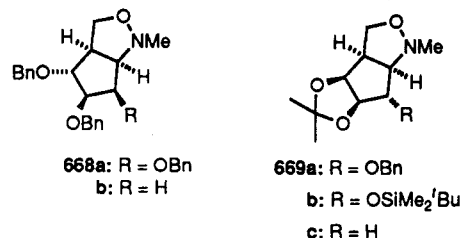
Reactions of this category involving nitrones as intermediates were first carried out by Bernet and Vasella who showed that 6-bromo-6-deoxyglucopyranosides **665**, on treatment with zinc and ethanol,

undergo reductive ring opening to the corresponding acyclic 5,6-dideoxyhex-5-ene **666a** together with a small amount of **666b** formed by reductive elimination (Scheme 127). Reaction of the mixture of **666a** and

Scheme 127

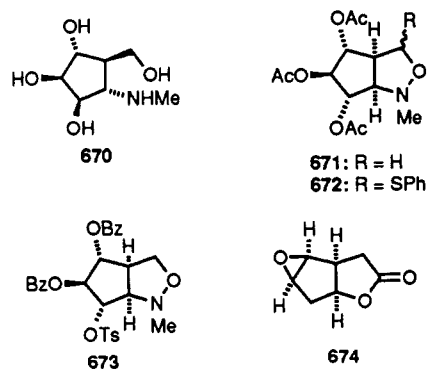


666b with *N*-methylhydroxylamine then readily affords the corresponding unsaturated nitrones which undergo spontaneous cyclization to the 2-aza-3-oxabicyclo[3.3.0]octane derivatives **667a** (yield 80%) and **667b** (yield 5%), respectively.^{311a} Compounds **668a,b** (yields 64% and 5% respectively)^{311b} and **669a,b** (72–78%) together with **669c** (5–7%)^{311c} were synthesized by the same



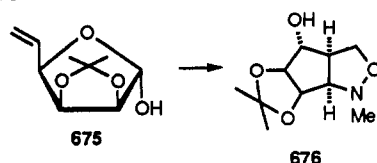
procedure from a 6-bromo-6-deoxy-D-mannoside and -galactoside, respectively, and the D-mannose-derived **668a** was used to obtain the potent α -mannoside inhibitor **670**.³¹²

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



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

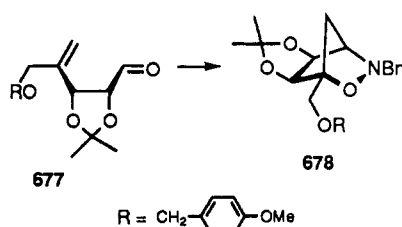
Scheme 128



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 nitron 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

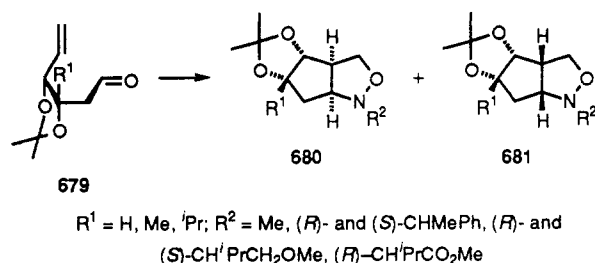
Scheme 129



subsequently transformed into (-)-neplanocin A (512).³¹⁶

A detailed study of intramolecular nitron/alkene cycloaddition reactions by Baldwin and Gedon has recently shown that the stereochemical outcome is very sensitive to the substituent on the nitron nitrogen atom.³¹⁷ Carbohydrate-derived substrates studied included enals of type 679 which were treated with a series of N-substituted hydroxylamines ($R^2\text{NHOH}$). 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

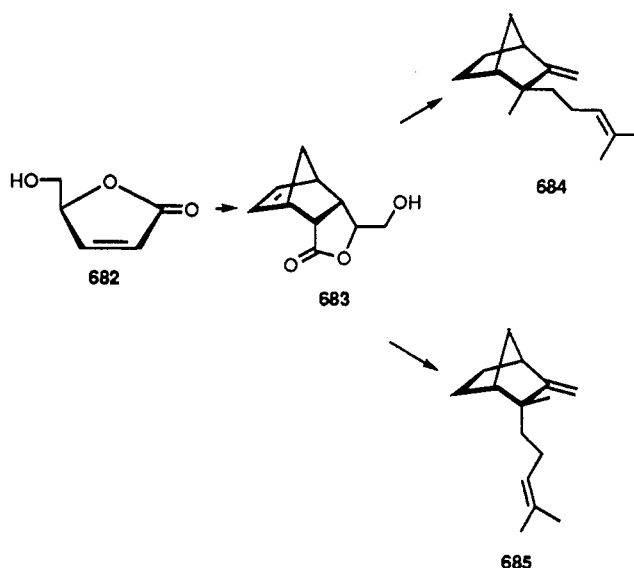


2. [4 + 2] Cycloadditions

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.

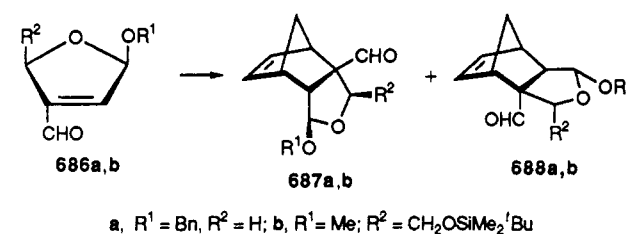
On heating with a large excess of cyclopentadiene at 140 °C, the D-mannitol-derived buten-2-olide 682 gave the crystalline *endo* adduct 683 (60% isolated yield) which served as a convenient common starting material for elegant stereocontrolled syntheses of (+)- β -santolene 684, (+)-*epi*- β -santolene 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

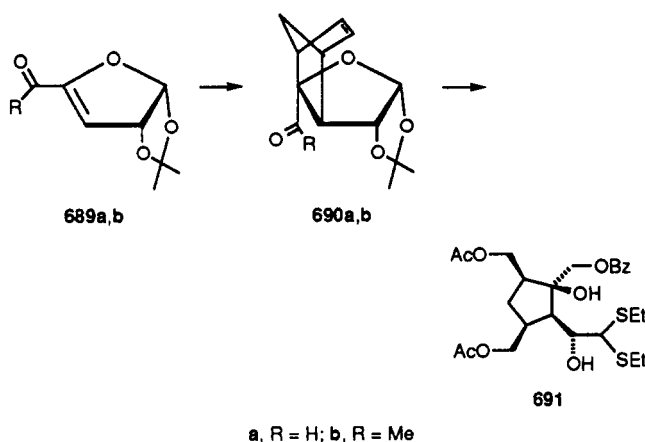
Scheme 132



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

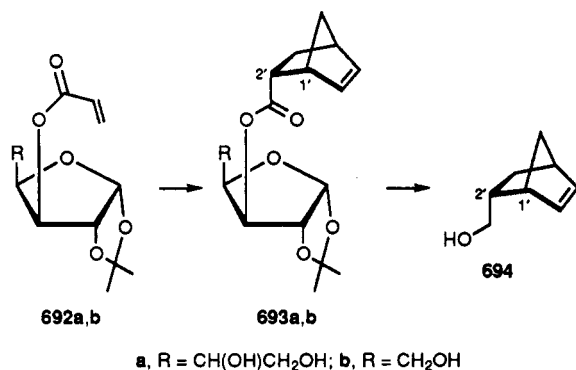
The reactions of aldehyde 689a and ketone 689b with cyclopentadiene afforded the adducts 690a and 690b, respectively, as single diastereomers in 90 and 98% yields. The additions thus occur exclusively on the more accessible face of the dienophile and, for reasons which are not apparent, are entirely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

Scheme 133



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*)-norbornenyl-methanol (**694**) on reductive cleavage (Scheme 134).^{321,322}

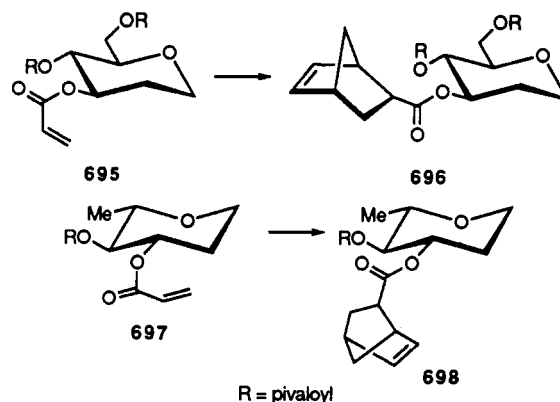
Scheme 134



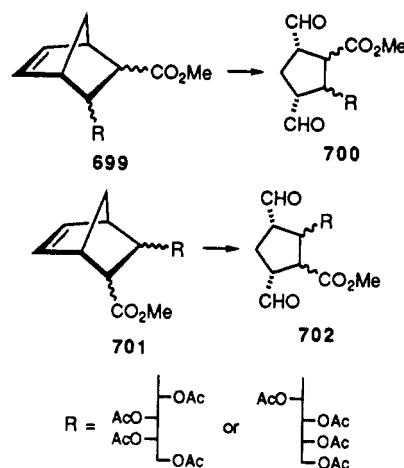
Acrylate esters **695** and **697** have also been used as chiral templates for stereoselective cycloaddition reactions with cyclopentadiene, best results being obtained when the esters were treated with diisopropoxytitanium dichloride prior to addition of the diene. In this way compound **695** gave 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

Scheme 135



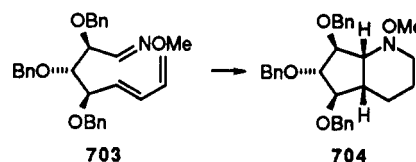
Scheme 136



aldonic esters in these addition reactions, thereby providing potential access to an even wider range of isomeric cyclopentane derivatives.^{146,324-326}

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

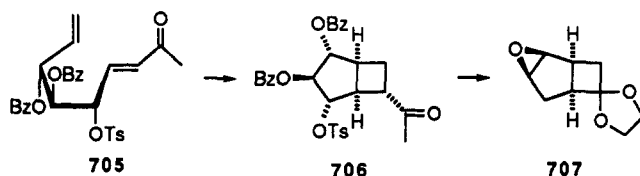


3. [2 + 2] Cycloadditions

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

Scheme 138

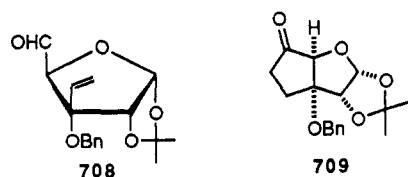


as a convenient starting point for two new syntheses of another prostaglandin intermediate, the *endo*-epoxy lactone **674**, previously obtained by other means (section III.C.1).³¹⁴

D. Cyclizations Involving Organometallic Intermediates/Complexes

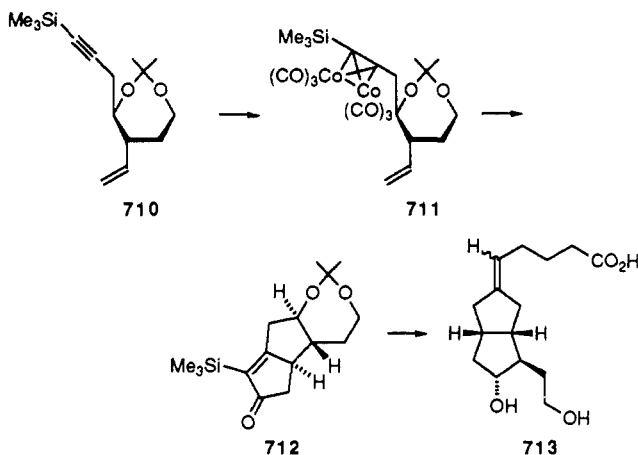
While functionalized cyclohexanes are readily made via mercury- or palladium-containing intermediates from hex-5-enopyranosyl derivatives (sections II.D.1 and II.D.2), there are no analogous routes to cyclopentanes. Efforts to carbocyclize 4-enofuranosyl compounds resulted only in elimination processes 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 $[(\text{Ph}_3\text{P})_2\text{RhCl}]_2$ were used at 75 °C in dichloromethane under ethylene.²¹⁵

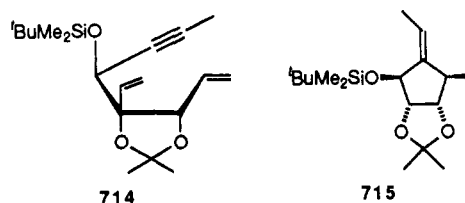


Three different metal-dependent conversions of carbohydrate-based 1,6-enynes into products containing cyclopentane rings have been described recently. The first employs the Pauson-Khand reaction whereby the D-ribo- γ -lactone-derived compound **710** was converted into the alkyne $\text{Co}_2(\text{CO})_8$ 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 rear-

Scheme 139

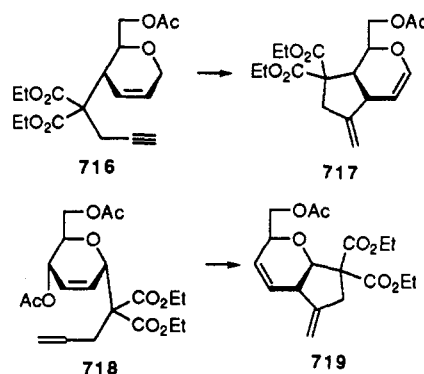


angement of the ene can be accomplished by use of π -allyl palladium complexes.³³³ Thus **716** gave the



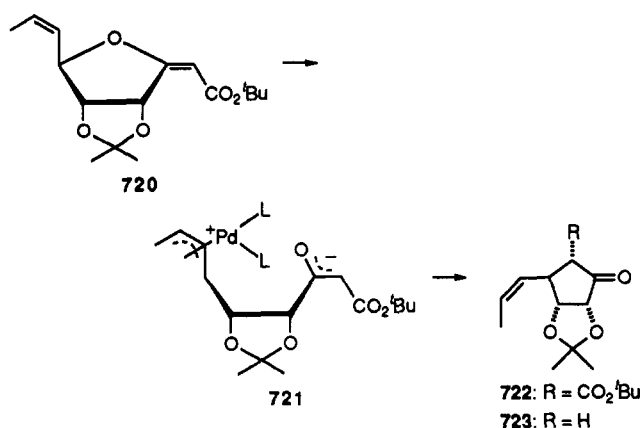
bicyclic glycol derivative **717** in excellent yield on treatment with tris(dibenzylideneacetone)dipalladium chloroform complex, triphenylphosphine and acetic acid. Likewise, the 3-ene isomer of **716**, having the branched group at C-2, afforded the bicyclic product having the ring junction at C-2 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 $\text{Pd}(\text{PPh}_3)_4$ in acetic acid at 80 °C (Scheme 140).

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 $\text{Pd}(0)$ 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 $\text{Pd}(0)$ complexes induced formation of the latter, a polymer-bound modification of $\text{Pd}(\text{PPh}_3)_4$, used with *O,N*-bis(trimethylsilyl)acetamide to remove protic contaminants, led to 98% of the enol

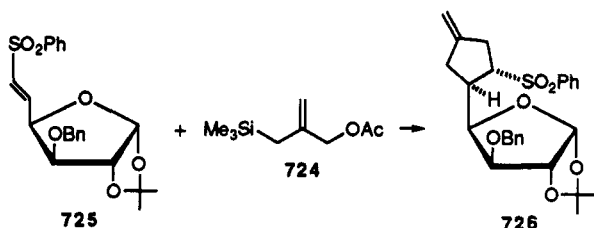
Scheme 141



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

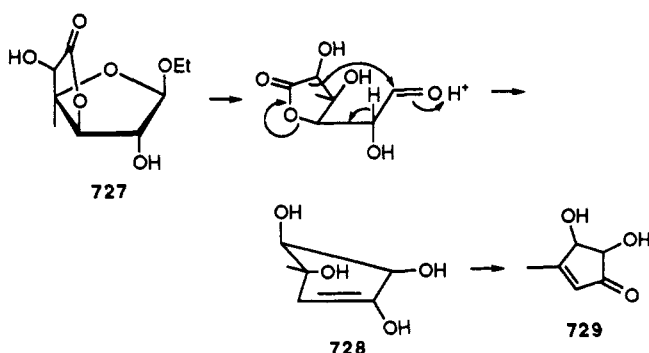
Scheme 142



E. Other Reactions

On treatment with acid the branched-chain furano-siduronolactone **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

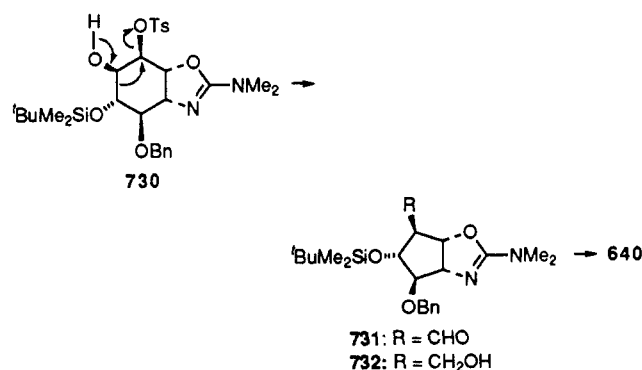
Scheme 143



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

Scheme 144



syntheses of this compound see sections III.B.4 and III.C.1.

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