C-NUCLEOSIDES, C-NUCLEOSIDE PRECURSORS AND A NOVEL EXOCYCLIC GLYCAL

by

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B.Sc., The University of British Columbia, 1976

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

In the Department of

Chemistry

We accept this thesis as conforming

to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

February 1980

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ABSTRACT

The synthesis of 3-(R and S)-3,4-dihydroshowdomycin (171) and (170) and the novel 3-(S)-(2,3-O-isopropylidene-α-D-ribofuranosyl)succinimide [3-(S)-α-dihydroshowdomycin acetonide 176] are reported. Several functionalized C-glycosides along with the addition products of a novel exocyclic enolic sugar, methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (172), are also described.

Application of the photoamidation reaction to methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-2-enonate (18) yielded 3-(R,S)-(5-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-hydroxy-4-methylpentanoic 1,4-lactone (139) and methyl 4,7-anhydro-8-O-benzoyl-3-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro) octonate (140) and (141). Cyclization of the β-carbamoyl esters 140 and 141 with concomitant debenzoylation with sodium methoxide gave 170 and 171 after removal of the isopropylidene groups.

Isomerization of the carbon-carbon double bond of 18 with sodium azide in a N,N-dimethylformamide solution gave 172 which when photoamidated and treated with sodium methoxide gave compound 176.

Treatment of 18 with sodium azide gave methyl (E)-4,7-anhydro-8-O-benzoyl-2,3,5-trideoxy-D-erythro-oct-2,4-dienonate (178) along with 172. When excess hydrazoic acid was added to the above reaction mixture methyl 4,7-anhydro-3-azido - 8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo, altro-octonate (189) and small amounts of 172 were isolated. Reducing the amount of hydrazoic acid in the latter reaction gave compound 172 as the predominant product with small amounts of 189 along with methyl 3-amino-4,7-anhydro-8-O-benzoyl-2-diazo-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-octonate (192) and (193), respectively. Hydrogenation of 189 in

the presence of 5% palladium on carbon gave the corresponding amino compounds, methyl 3-amino-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo, altro-octonates (190) and (191), respectively. Hydrogenation of 192 and 193 as above in separate reactions gave the corresponding hydrogenolysis products 190 and 191, along with the hydrazones of methyl 3-amino-4,7-anhydro-8-O-benzoyl-3-deoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-2-octulosonate (195) and (196), respectively.

The slow evaporation of the solvent from a diethyl ether-hexane solution of 172 or prolonged storage of 172 exposed to room atmosphere gave 5-O-benzoyl-2,3-O-isopropylidene-D-ribono-1,4-lactone (199), 8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-4-octulofuranosono-1,4-lactone (200), methyl (E)-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-oct-2-en-4-ulofuranosonate (201), methyl 8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-4-octulofuranosonate (202), and methyl 8-O-benzoyl-2-deoxy-5,6-O-isopropylidene-α,β-D-allo (and altro)-4-octulofuranosonate (203) and (204), respectively.

Treatment of 204 with para-toluenesulfonic acid in an azeotroping benzene solution yielded the furan derivative, 2-benzoyloxymethyl-5-(carbomethoxyacetyl)furan (212).

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ACKNOWLEDGEMENTS

I wish to thank Dr. Alex Rosenthal for his guidance, suggestions and patience during the course of this research.

The cooperation and invaluable practical assistance provided by Drs. B. L. Cliff and R. H. Dodd during my period at U.B.C. are gratefully acknowledged.

To Pam and my mother, for their patient understanding during the preparation of this thesis, I wish to express my deepest appreciation.

Finally, the financial support of the University of British Columbia (1976-1979) and the National Research Council of Canada (through Dr. Rosenthal (1979-1980)) is acknowledged.

I. OBJECTIVE

The naturally occurring nucleoside antibiotics represent a diverse group of biological compounds structurally related to the purine and pyrimidine nucleosides and/or nucleotides. The utility of these compounds have been equally diverse in that they have been used as models for conformational and spectroscopic studies, used as probes in the biological systems to elucidate the complex steps involved in converting the genetic message to new biopolymers and in the determination of the stages of other metabolic and anabolic pathways.

The possible and existing chemotherapeutic value of these naturally occurring nucleosides and their analogues and/or homologues however, represent an unlimited use for these compounds. The structural analogues of the common nucleosides, obtained either from natural sources or by synthetic means, have often been found to be antiviral, antibacterial, antifungal, or antitumor in their action.

Four classes of modified nucleosides can be distinguished: (1) nucleosides in which the ribosyl portion is altered by the incorporation and/or elimination of various groups, (2) base-modified nucleosides, in which the common purine or pyrimidine derivative has been altered, (3) C-nucleosides, in which the heterocyclic base is linked to the sugar moiety by a carbon-carbon rather than a carbon-nitrogen bond, and (4) the more recent homo-C-nucleosides, in which a methylene unit resides between the nitrogenous heterocyclic base and sugar moiety. The fact that pyrazofurin (PF) (antiviral and antitumor) exists both as an α (PF) and β (PF_B) (possible antiviral agent) anomers and both exhibit some degree of antibiotic activity is of particular relevance in this present work.

The objective of the work described in this thesis is to synthesize various C-nucleosides and various ketose nucleosides. In the first part of this work, the synthesis of the normal- and α-dihydro derivative of showdomycin by way of photoamidation of unsaturated octonates was studied.

The second part of this thesis is concerned with the synthesis of functionalized precursors to C-nucleosides. The precursors envisioned were the C-glycosyl diamino acid derivatives, the amino and carboxylic groups of the amino acid being potentially amenable to further derivatization and the possibility of cyclization of the vicinal amino groups to give analogues of pyrazofurin. The two routes employed for the synthesis of such precursors were the condensation of sodium azide with an α,β-unsaturated octonate and the azido-nitration of the same unsaturated compound.

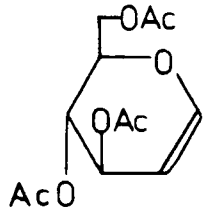
In the third part of this thesis, the derivatives of a novel exocyclic glycal is investigated. Various compounds which are produced from the air oxidation of the glycal are resynthesized using known procedures.

The ketohexose nucleoside psicofuranine which is both antibacterial and antitumor in its activity was found to be absorbed externally by animals but not absorbed in man unless it was converted to the tetraacetate. It seemed plausible the elongation of the hydroxymethyl group at C-2' with a hydrophobic moiety such as carbomethoxymethyl might result in interesting biological consequences. Therefore, the forth and final part of this thesis deals with the attempted synthesis of analogues of psicofuranine utilizing both the novel exocyclic glycal and its acetylated hemiketal derivative. The fusion method and the one-step synthesis of a N-nucleoside using tin tetrachloride and methanesulfonic acid catalysts were employed with the latter compound.

II. INTRODUCTION

1. Unsaturated Sugars

The first laboratory synthesis of an unsaturated sugar derivative dates back to 1913 when Emil Fisher and K. Zach produced triacetyl-D-glucal (1).[1] Since this first synthesis of an enol ether functionality in a carbohydrate, the range of discrete carbohydrate derivatives which possess a carbon-carbon double bond in the sugar chain has increased to cover a large variety of unsaturated sugars which have one or more carbon-carbon double bonds which may be in conjugation with themselves or other functional groups. The increased activity in the last quarter century in this important group of diversified compounds has prompted several reviews.



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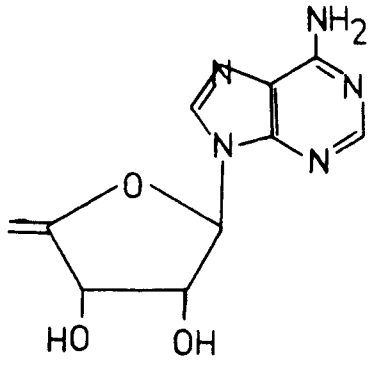
The glycals and their 2-hydroxy derivatives, were dealt with in two earlier papers by Helferich[2] and Blair[3], respectively. A broader scope of this field is reflected in two reviews by Ferrier.[4,5] Recently, Kiss[6] has given an in depth review of β-eliminative degradation of carbohydrates containing activating groups while Feather and Harris[7] reviewed the area of dehydration reactions of carbohydrates. Formation of unsaturated sugars by enlarging the carbon skeleton via the Wittig reaction has been reviewed by Zhdanov.[8]

The present and potential value of the unsaturated sugars in both their direct utility as well as their use as synthetic intermediates is exemplified by the presence of unsaturated carbohydrates in the naturally occurring nucleoside antibiotics Decoyinine[9] [Angustmycin A, 9-β-D-(5,6-

psicofuranoseenyl)-6-amino purine, 2] and Blasticidin S[10] [1-(1′-cytosinyl)-4-[L-3′-amino-5′-(1′′-N-methylguanidino)-valerylamino]-1,2,3,4-tetradeoxy-2,3-dehydro-β-D-erythro-hex-2-ene uronic acid, 3]. The unsaturated carbo-



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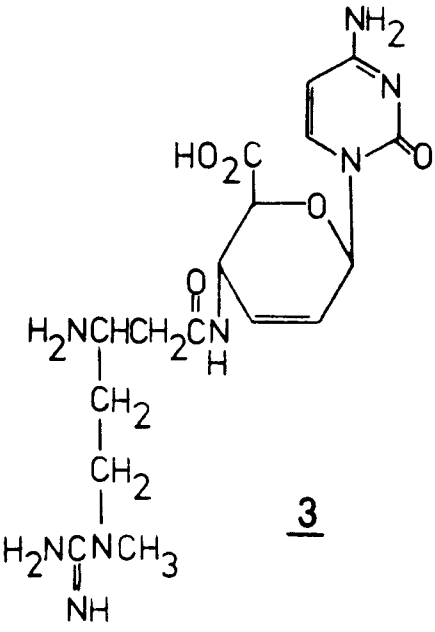

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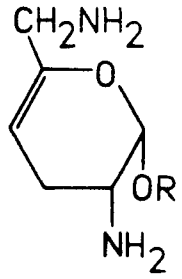
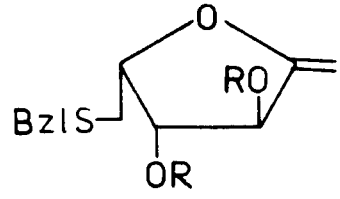
hydrates themselves can have antibiotic behavior as shown by Sisomicin[11] which has the structural component 2,6-diamino-2,3,4,6-tetradeoxy-α-D-glycero-hex-4-enoside (4) and by the antibiotic sugar derivative 6-S-benzyl-2,3-bis-O-(para-nitrobenzoyl)-6-thio-L-xylo-hex-1-enulofuranose[12] (5). The unsaturated



4 R=disaccharide

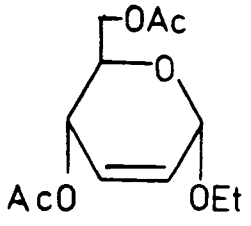


5 R=para-nitrobenzoyl

sugars can be used as synthetic intermediates as shown by these examples:

(1) Ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (6)

is transformed into the antibiotic sugar, Amicetose[13,*] (2,3,6-trideoxy-D-erythro-hexopyranose, 7), (2) 6-chloro-9-(3,4-di-O-acetyl-2-deoxy-α (and β) D-erythro-pentopyranosyl) purines[15] (8) are produced from 3,4-di-O-acetyl-D-arabinal (9) and 6-chloropurine (10), and (3) from 2-methyl-furan (11) was produced the female sex hormone progesterone[16] (12).



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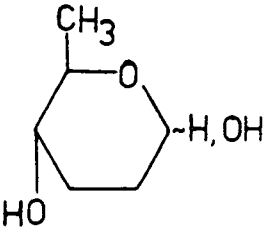

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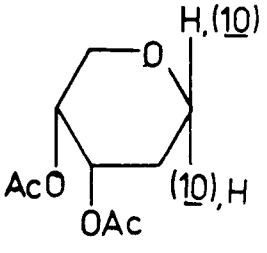

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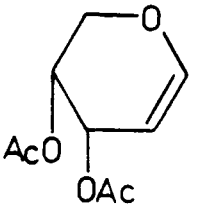

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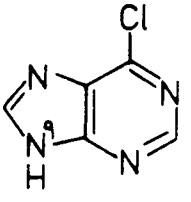

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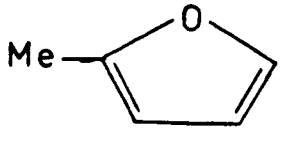

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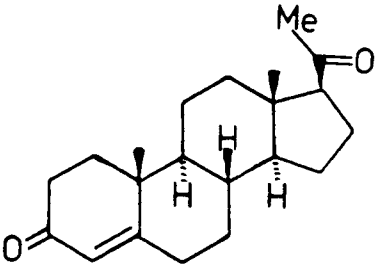

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The discussion on this broad topic however, will be necessarily selective and brief. Reactions of the unsaturated sugars will follow in Sections 2, 3 and 4.

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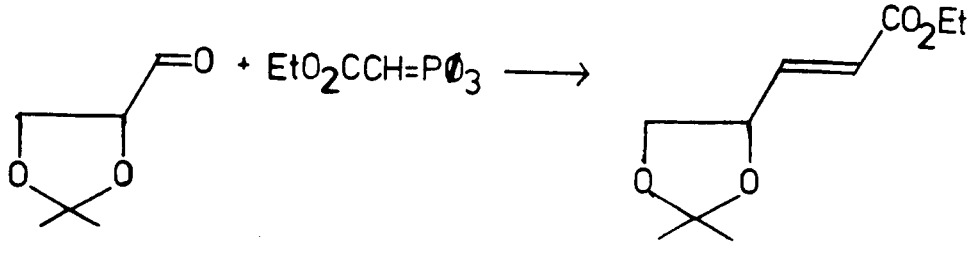
* Amicetose is also a constituent of the antibiotic nucleosides[14] Amicetin, Plicacetin and Bamicetin.

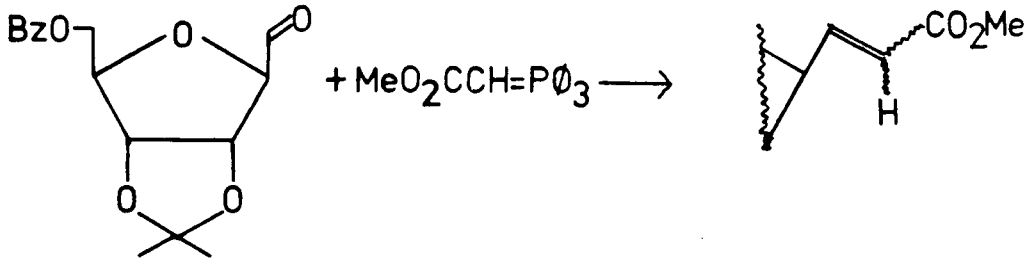
1.1. Synthesis of Unsaturated Sugars.

As one of the few synthetic methods which can elongate the carbon skeleton of an organic molecule along with concomitant introduction of a new carbon-carbon double bond, the Wittig[17] reaction and its modifications[18], has quickly become one of the fundamental synthetic methods of modern organic chemistry, mild reaction conditions, together with high yields and the absence of migration of the bond formed are the main features of this method. The simultaneous insertion of an alkene bond and a carboxyl functionality into a carbohydrate is very attractive in view of possible useful derivatization of both functional groups. The first synthesis of this kind was reported by Kuhn and Brossmer[19]. Thus, 1,2-O-isopropylidene-D-glyceraldehyde (13) and carboethoxymethylenetriphenylphosphorane (14) were condensed to give the higher-carbon unsaturated ester, ethyl 2,3-dideoxy-4,5-O-isopropylidene-D-glycero-pent-2-enonate (15). Moffatt et al[20], in an analogous reaction with 2,5-anhydro-6-benzoyl-3,4-O-isopropylidene-



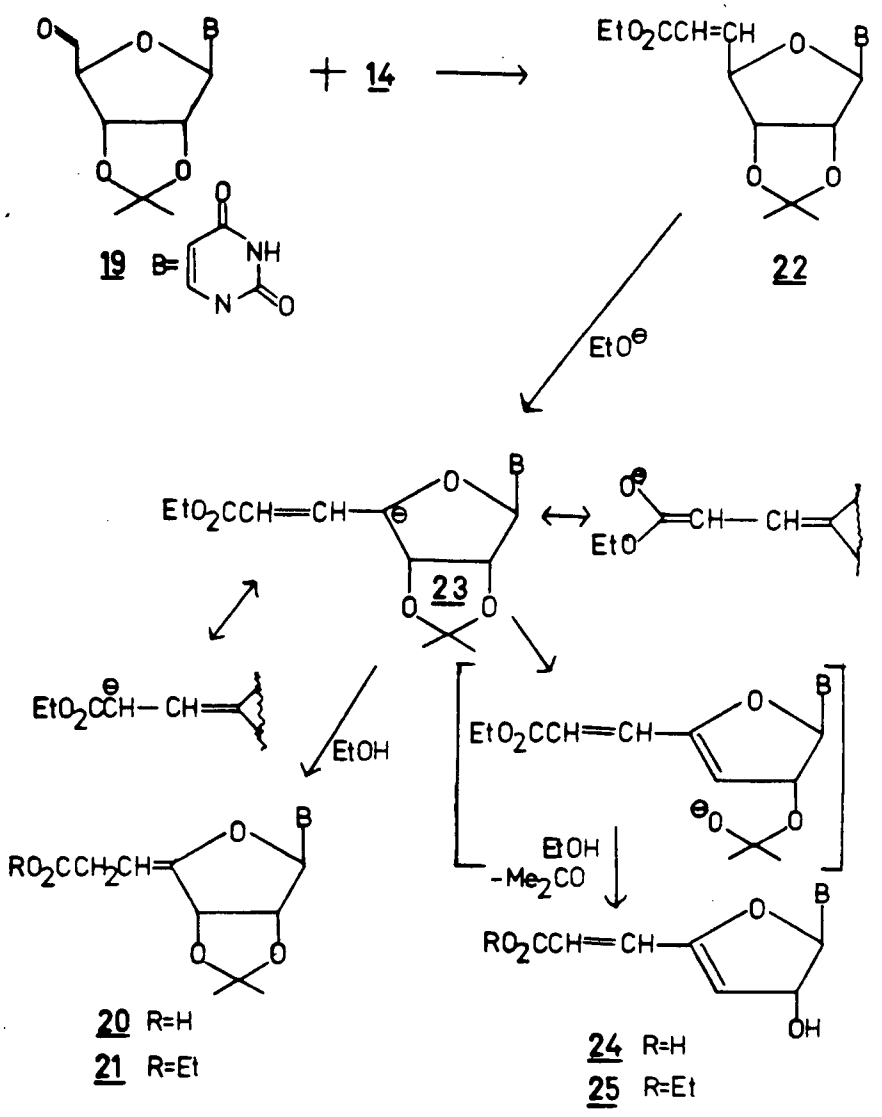
13 14 15

D-allose (16) and carbomethoxymethylenetriphenylphosphorane (17) synthesized methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-2-enonate (18).



16 17 18

Unsaturated sugars can also be synthesized by reactions involving allylic rearrangements[4,5,13] of initially unsaturated carbohydrates. Thus, when Jones and coworkers[8,21] attempted to synthesize a nucleotide analogue by condensing 2′,3′-O-isopropylideneuridine-5′-aldehyde (19) with phosphorane 14 generated *in situ*, four unsaturated carbohydrate derivatives were obtained. Two of the unsaturated derivatives, 1-(5,6-dideoxy-2,3-O-isopropylidene-β-D-*erythro*-hept-4-enofuranosyl uronic acid) uracil (20) and its ethyl ester 21, arose[8] as a result of a base-catalyzed allylic rearrangement of the expected hept-5-enofuranosyl ester 22 *via* the resonance stabilized intermediate anion 23.



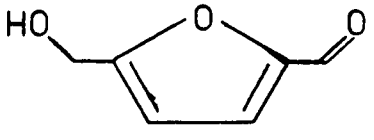
Scheme I

The formation of the other two olefinic carbohydrate derivatives, 1-(3,5,6-trideoxy-β-D-glycero-hept-3,5-dienofuranosyl uronic acid) uracil (24) and its ethyl ester 25 arose from a β-elimination of the, normally alkali stable, O-isopropylidene group.

Although elimination reactions β to activating functions[6] are common in carbohydrate chemistry, the leaving groups usually only have one covalent bond (except epoxides) linking it to the sugar molecule (eg -OMe[22], -OAc[23] and -OSO_2Me[24]). The β-elimination of the O-isopropylidene group (acetone) which has two points of linkage to the carbohydrate molecule,

although rare, does occur. The normally alkali-stable O-isopropylidene group if situated β to an activation group such as the carbonyl of an ester[25] or in a vinylog system such as 22 will, in the presence of an appropriate base, eliminate acetone to give the intermediate activated allylic alkoxide. Other activation groups such as dithioacetals[26] are also capable of enhancing such eliminations.

Unsaturated sugars are also formed from the acid dehydration of carbohydrates and their derivatives. The tertiary alcoholic groups and their derivatives (eg ethers and esters) are particularly susceptible to dehydration[27a]; therefore, it can be expected that cyclic ketose derivatives will dehydrate more readily than the aldoses.[28] The reaction of carbohydrates in alkaline or acidic solutions usually result in a myriad of products[7] but one product which is usually formed in significant quantities is 5-hydroxymethylfurfural (26). The key step in the formation of 26 from sugars is

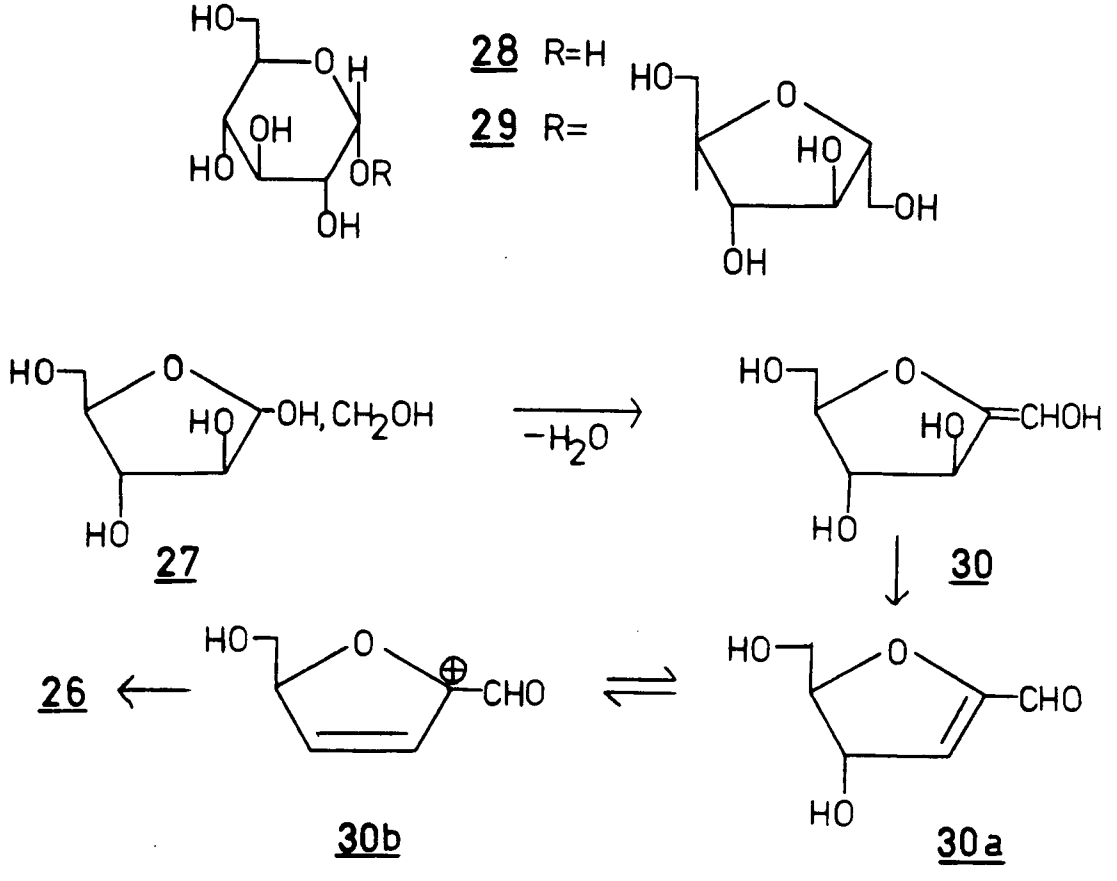


26

the formation of 1,2- and 2,3-enediols.[29,30]

Two mechanisms have been proposed for the formation of compound 26: (1) based on the fact 26 is formed from D-fructose (27) in higher yield and at a much greater rate than is formed from D-glucose (28) (this difference was particularly evident when 26 was prepared from sucrose[31] (29), only the D-fructose (27) portion of the molecule reacted, and D-glucose (28) was recovered in almost quantitative yield), the mechanism[32] states that D-fructose (27) is present in the furanose form, and that the ring remains

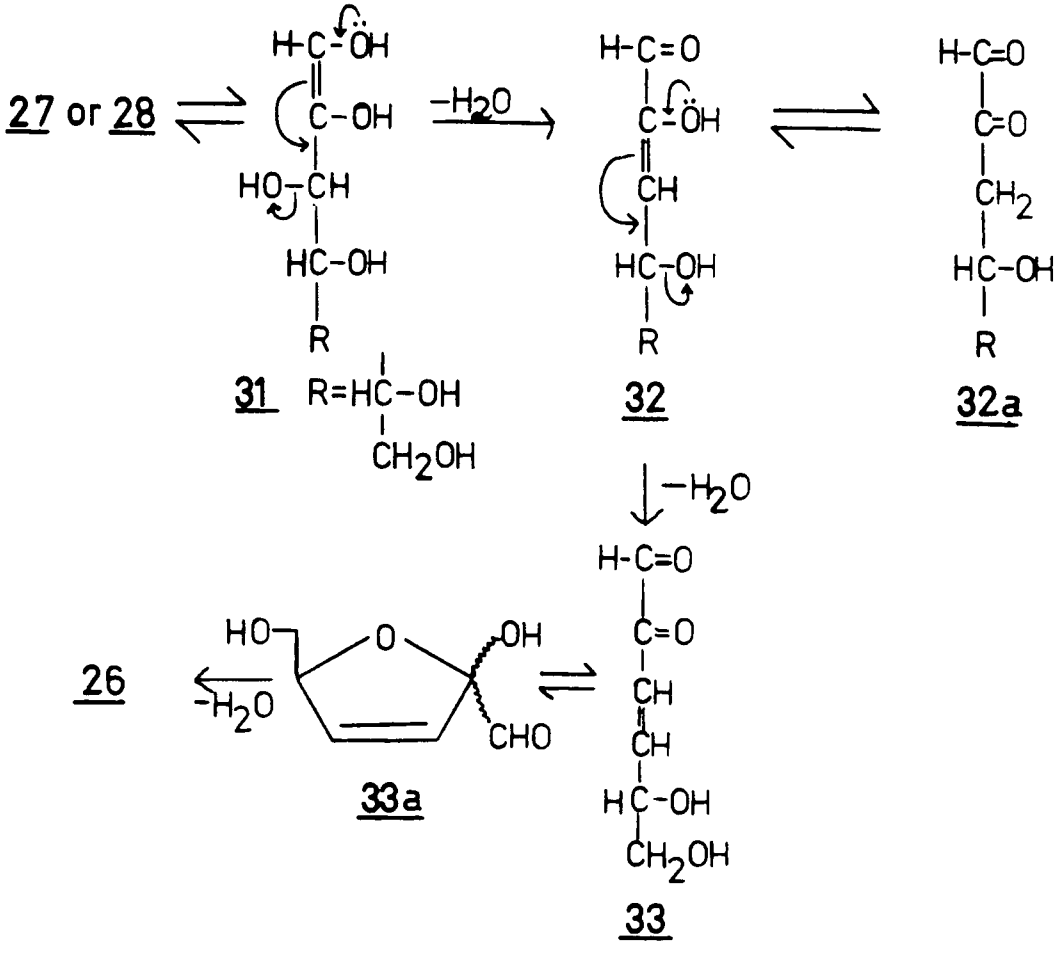
intact. The initial reaction is the elimination of water to form the 1,2-enolic form of 2,5-anhydro-D-mannose (30), and that further dehydration results in compound 26. The necessity for 28 to isomerize to 27 before dehydration accounts for the much lower reaction rate of 28.



Scheme II

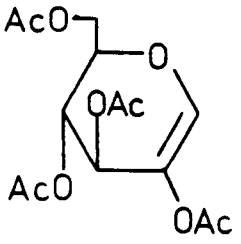
(2) The second mechanism[29,33] proposed suggest that the dehydration proceeds via an acyclic 1,2-enediol 31 which eliminates a molecule of water through β-elimination of a hydroxy group to give 32. Compound 32 undergoes rapid elimination of a second hydroxyl group to give 33. The loss of a third molecule of water occurs after, or simultaneously with the cyclization of

33 and results in the formation of 26.



Scheme III

Other approaches to the synthesis of unsaturated sugars involve the dehydrohalogenation of glycosyl bromides in the presence of nitrogenous bases. Thus, 2,3,4,6-tetra-O-acetyl-1-deoxy-D-arabino-hex-1-enopyranose[34] (34) was obtained in ~80% from its corresponding glycosyl bromide in the presence diethylamine. 1,5-diazabicyclo-[5.4.0]-undec-5-ene (DBU, 35) has been utilized in effecting dehydrohalogenation of glycosyl halides.[35]



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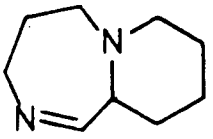

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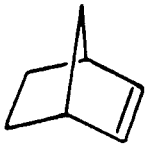
2. Photochemical Reactions

Along with the increased activity in the synthesis of unsaturated sugars and other functionalized carbohydrates in the last two decades, the use of photochemistry with these functionalized carbohydrates has also increased notably. The following discussion will, however, be limited to the application of photoamidation to carbohydrates possessing a single carbon-carbon double bond and the related side reactions of this process. Reactions such as photoelimination and rearrangements is beyond the scope of this thesis and further discussion is unnecessary. Phillips[36a] has dealt with the area of photo-degradation of simple sugars in a review article. Bohm and Abell[36b] have reviewed the stereochemistry of free-radical additions and this topic will be dealt with briefly.

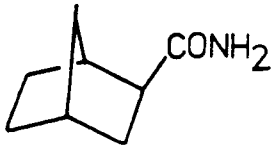
2.1. Photoamidation of Unsaturated Sugars

The addition of carboxamide free radicals to olefins was first reported by Friedman and Shechter[37] less than two decades ago. They found that substituted formamides add to olefins in the presence of peroxides to give products resulting from the addition of both $\cdot CON(CH_3)_2$ and $HCON(CH_3)\dot{C}H_2$ radicals to olefins. In an independent study formamide was reported[38] to have added to olefins in the presence of peroxides at elevated temperatures. The light-induced addition of formamide to terminal olefins was shortly reported by Elad.[39] This initial communication by Elad was soon followed

by four paper by Elad and Rokach[40a)-d)] describing the photoaddition of formamide to terminal olefins[40a], norbornene[40b], nonterminal olefins[40c] and α,β-unsaturated esters.[40d] These photoreactions gave high yields of 1:1 adducts and served as a method of obtaining higher homologous amides and their derivatives from unsaturated compounds. The addition of formamide to the unsaturated compound may occur when induced directly by sunlight (wavelengths of 220-250 nm) but the yields are fairly low (∿20% of the 1:1 adducts). Light filtered through Pyrex (wavelength >300 nm) gave very poor yields of the derived amides but in the presence of acetone as a photoinitiator the reaction proceeded at a greater rate and gave high yields of the desired amide.[40a] With terminal olefins the 1:1 addition products were predominantly formed via an anti-Markovnikov addition. Formamide addition to unsubstituted nonterminal or cyclic olefins was nonregio- and nonstereospecific and products resulting from addition to either carbon of the double bond were formed. However, if steric interactions are significantly different about the olefinic bond, a stereoselective addition of formamide can occur. Thus, the photochemical addition of formamide to norbornene (36) proceeded in a stereoselective manner to give the norbornane-2-exo-carboxamide (37) enantiomorphs, exclusively[40b].



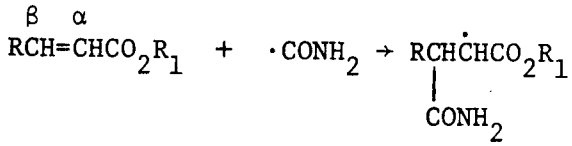
36



37

Therefore, one might expect the possibility of stereochemical induction in suitably sterically hindered olefinic compound in the photoamidation reaction.

When the photoamidation reaction was applied to simple α,β-unsaturated esters, the expected β-addition of the carbamoyl radical to the unsaturated ester occurred to give derivatives of alkalyted succinic acids. e.g.



R_1,R=alkyl groups

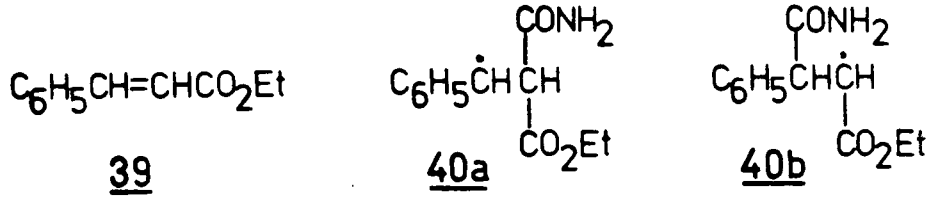
38

As in the case of the photoamidation of the olefins, the orientation of addition of the carbamoyl radical to the carbon-carbon double bond depends upon the relative stabilities of the radicals formed and the stereochemical orientation is dependant on steric factors. In the case of terminal olefins the initial attack is on the primary carbon to produce a secondary radical which is more stable[41] than the primary radical produced upon initial attack at the nonterminal carbon, thereby resulting in a regiospecific addition. With unsubstituted nonterminal olefins, the addition of the carbamoyl radical to either carbon produces secondary radicals, thereby resulting in skeletal isomers. With the simple α,β-unsaturated esters, which is in essence an nonterminal olefin, initial attack of the carbomyl radical to the β carbon results in the formation of a free radical (38) which obtains its stabilization through resonance with the ester group.[40d] Therefore, with the simple alkyl* α,β-unsaturated esters, only products

* with respect to the acid portion of the ester.

resulting from β-addition of the carbamoyl radical were isolated.

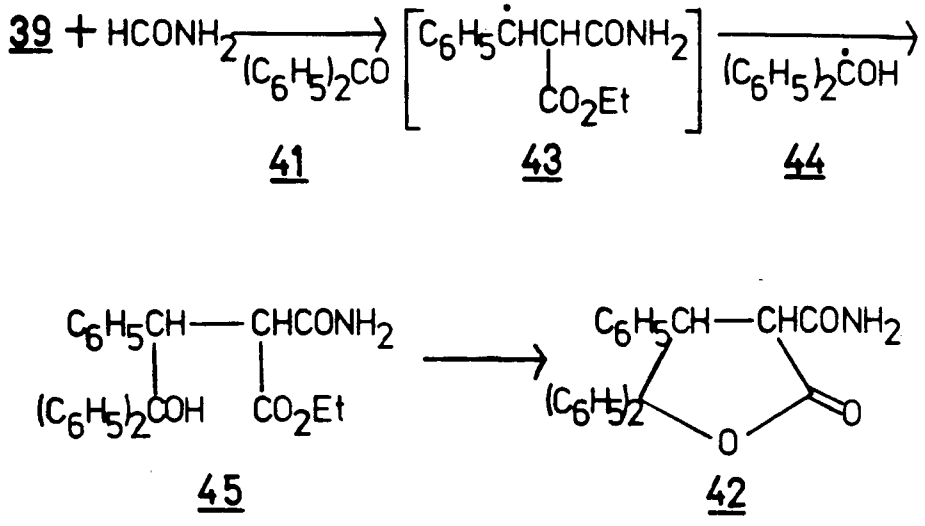
Interesting results occurred when a stabilizing group was introduced at the β position of the unsaturated ester. With ethyl cinnamate (39) the relative stabilities of the two radical intermediates 40a and 40b would determine the orientation of the addition of the carbamoyl radical.



39 40a 40b

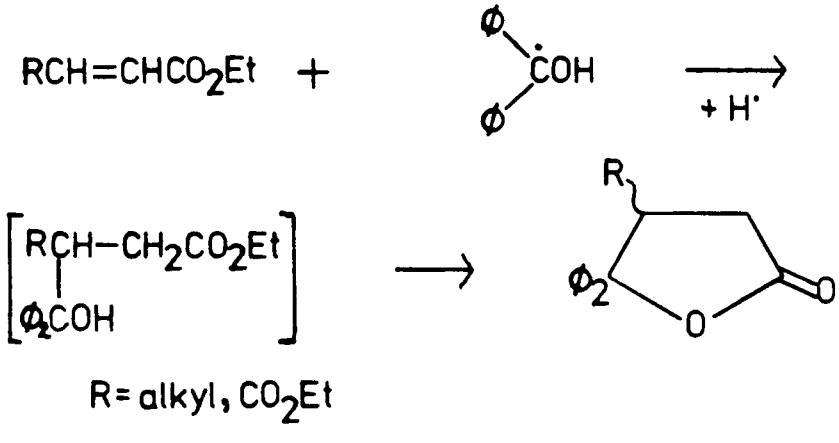
Steric factors should not be ignored but in this particular instance the electronic stabilities are obviously the over-riding factors. A comparison of the stability of free radicals[42] which are stabilized by conjugation with these two functional groups lead to the expectation that a benzyl malonic acid derivative would result from the α-addition of the carbamoyl radical (structure 40a). However, experimental evidence showed that the major product formed from the photoamidation of ethyl cinnamate (39) in the presence of benzophenone (41) as sensitizer, was 2-carbamoyl-3,4,4-triphenyl-γ-butyrolactone (42). As can be seen in the following scheme, the stable intermediate benzylic radical 43 in which the unpaired electron is delocalized over the phenyl group, fails to perform the hydrogen abstraction from formamide. Instead, the intermediate radical 43 forms a 1:1 adduct with a semipinacol radical 44 (or a molecule of benzophenone (41)) thus leading to the amido ester alcohol 45 which, under

the conditions of the reaction, lactonizes to the amido lactone 42.



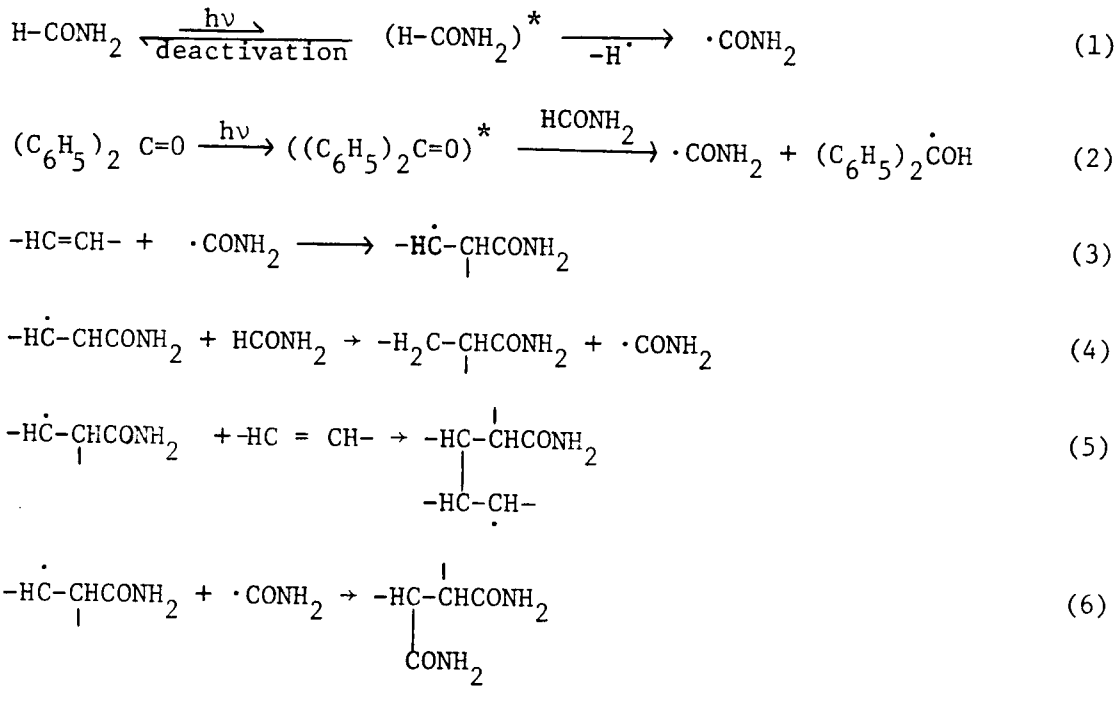
Scheme IV

A side reaction that was detected in the photoamidation reactions sensitized with benzophenone was the addition of the sensitizer to the α,β-unsaturated ester with subsequent lactonization of the γ-hydroxy esters to give the substituted γ-butyrolactones as shown in the following scheme:



Scheme V

The free radical chain mechanism was proposed for the photoamidation reaction. As mentioned previously, the light-induced amidation reaction can occur without an initiator but its presence increases the rate of the reaction and yields are signficiantly higher. The course of the reaction may be illustrated in the following scheme:



Scheme VI

In systems without added sensitizers (ketones) the generation of the carbamoyl radical (step 1) result from either the collapse of the photoactivated (*) formamide molecule or through hydrogen abstraction from formamide by other radicals formed. In the presence of a sensitizer, the photo—activated sensitizer abstracts a hydrogen from the formamide molecule to form the carbamoyl and ketyl radicals (step 2). The olefin which serves a radical scavenger[43] then forms 1:1 adduct (step 3) with the available radicals which leads to the isolated amide and alcoholic products. The desired amide products can be synthesized in high yields by adjusting the concentrations of the appropriate reagents. Reactions (1) and (2) are the initiation steps whereas reactions (3) - (5) are chain propagation steps with (3) and (4) giving 1:1 adduct and reaction (5) leads to 2:1 telomer* or further telomerization can occur to give higher telomer. Chain termination can occur when two radicals combine to form a new sigma-bond as shown in step (6). Alkylated succinamides have been isolated from the photoamidation of terminal olefins[40a] and oxamide isolated when olefin is absent.

The role of the sensitizer, usually acetone or benzophenone, was initially in dispute as to whether its primary role was one of a photo-initiator in which the photoactivated ketone abstracted hydrogen from formamide (step 1) or that of a photosensitizer whereby the photoactivated triplet energy of the ketone was transferred to formamide which would then collapse to form the carbamoyl radical.[40a] This conflict was resolved[44] when the triplet energy of formamide (4.2 eV) was found to be

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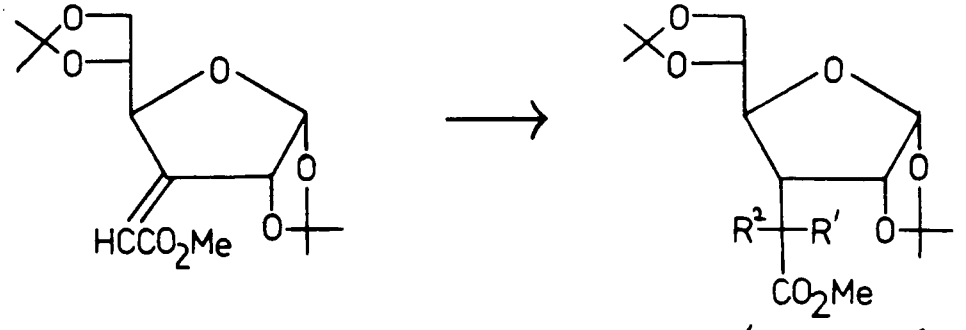
* a n:1 telomer is defined as a molecule formed from n molecules of olefin and one molecule of formamide.

greater than that of either excited triplet acetone (3.5 eV)[45] or benzophenone (3.03 eV)[46]. Therefore, the photosensitization of formamide by these ketones is impossible, and, as a consequence, the only possible mechanism is one in which the formyl hydrogen is abstracted by the $n\rightarrow\pi^*$ triplet of the ketone. Chemical proof is also present in the form of products isolated from the reaction of the intermediate ketyl radicals, such as 2-methyl alkane-2-ols from acetone-initiated photoamidation of olefins and considerable amounts of benzpinacol when benzophenone was used as the photoinitiator.

The application of photochemical addition of formamide to unsaturated sugars has been undertaken by Rosenthal and coworkers in an effort to determine the stereochemical outcome of this reaction on various unsaturated sugars, as well as, utilizing this reaction to synthesize branch chain amido and amino sugars which may be used to synthesize nucleoside analogues. Rosenthal and Ratcliffe[47] photoamidated (Z) and (Z,E)-3-deoxy-3-C-(methoxycarbonyl)-methylene-1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose (46) to afford 3-C-[R and S-carbamoyl(methoxy carbonyl)methyl]-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (47) and (48) by an anti-Markovnikov addition of formamide to the carbon-carbon double bond. The exclusive addition of the carbamoyl radical to



46

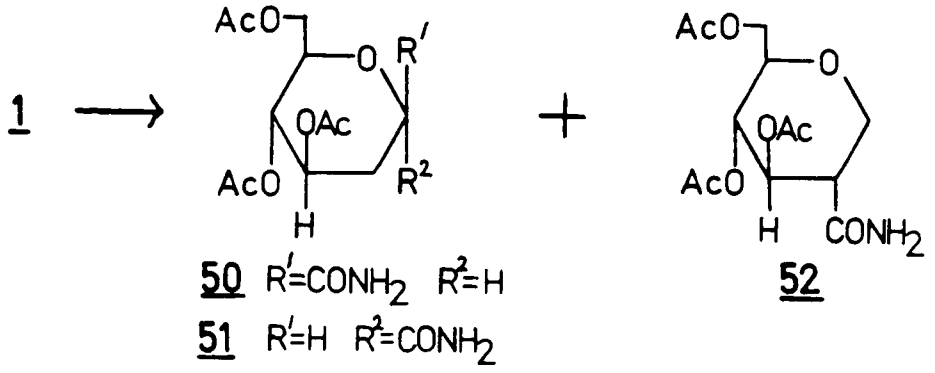
47 $R'=CONH_2$ $R^2=H$

48 $R'=H$ $R^2=CONH_2$

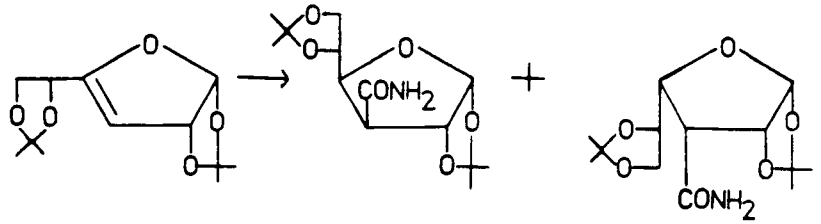
the α-carbon of ester 46 was a result which was surprising in view of Elad's[40d] work with simple α,β-unsaturated ester to afford the corresponding β-carbamoyl esters. However, in view of the work of Rosenthal and co-workers (vide infra) with substituted (enolic) unsaturated sugars which result in an anti-Markovnikov photoaddition of formamide and the previously discussed α-addition of the carbamoyl radical to ethyl cinnamate (38), the possibility of α-carbamoylation to give the intermediate tertiary radical at C-3 was not totally unexpected.[48]

Upon photoamidation of various unsubstituted, mono- and disubstituted, endocyclic, enolic and enediolic unsaturated sugars, Rosenthal and coworkers concluded[47] that, in accord with Elad's[40a),b)] findings with terminal and nonterminal olefins: the photoaddition of formamide proceeds in an anti-Markovnikov fashion and substrates in which both carbons of the unsaturated group bears hydrogen or in which the unsaturated group is fully substituted (with saturated groups), the photoamidation is non-regiospecific.

The stereochemistry of the carbamoyl radical addition and the subsequent hydrogen abstraction step can be rationalized predominantly from the steric environment about the reactive centre of the unsaturated substrate. The cis-1,2-steric interactions provide the predominate directing influence with the attacking species approaching from the least hindered side. The results of these steric interactions are evidenced by the product ratios found by Rosenthal and coworkers.[47,49] Thus, photoamidation of triacetyl-D-glucal (1). Yielded three major carbamoyl sugars 50, 51 and 52 in an approximate ratio of 2:2:3, respectively[50], with product 52 exhibiting a trans-orientation of the carbamoyl group to C-3 acetyl.



When 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enofuranose (53) was irradiated, two formamide adducts 54 and 55 were formed in about equal amounts.[51] This regio- and stereospecific addition was an exclusively trans-hydrocarbomoylation since there was only a single 1,2-cis-interaction in the abstraction step. The addition of the carbamoyl radicals cis to

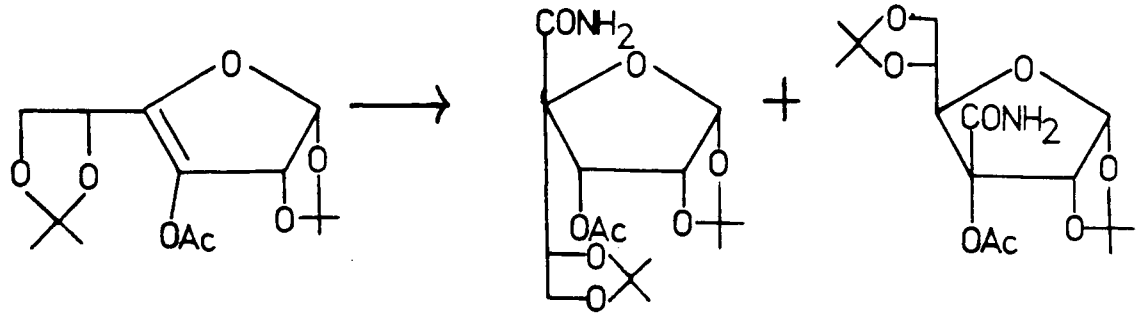


53 54 55

O-2 of 53 (i.e., the endo face of the fused ring system) is not totally surprising in light of the facile displacement reactions of structurally similar substrates when the attacking species is neutral, small and capable of hydrogen bonding to the oxygen on C-2 (e.g., hydrazine[52a] and ammonia[52b]).

Photoamidation of the fully substituted 3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-erythro hex-3-enofuranose (56) afforded carboxamide sugars 57 and 58 in 65 and 26% yields, respectively.[53] Expectedly, the major components added the carbamoyl radical to the exo-face of the substrate with hydrogen abstraction in 57 on the same side due to two 1,2-cis-interactions on the sterically crowded endo-face. The hydrogen abstraction in the synthesis of compound 58 occurs on the endo-face but

on the least hindered position of the fused ring system. Also, the over-all addition is trans since a 1,2-cis-steric repulsion from a carbon (e.g., the carbamoyl group) is expected to be greater than an oxygen (e.g., O-3) which might also provide hydrogen bonding to the hydrogen donor.



56 57 58

2.2. Photochemical cis-trans Isomerization

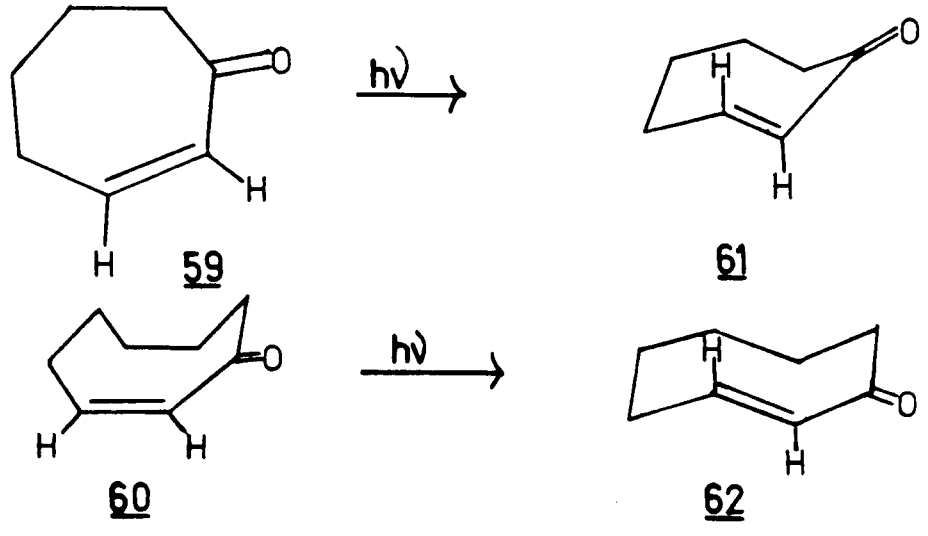
The phenomenon of cis-trans isomerization is well established, not only for thermal ground state reactions[55], but also for excited state reactions.[56,57] The ease with which the carbon-carbon double bond undergoes geometric isomerization upon irradiation has been known for a considerable time, but the details of the reaction remain the subject of many investigations.[58] The dependence of the photochemical equilibrium of olefinic, aromatic and α,β-unsaturated ester systems on concentration temperature and triplet energy have been investigated.[57] However, a detailed discussion on these topics and the mechanism of the photochemical isomerization is beyond the scope of this thesis and only the mechanism and effects of triplet energy will briefly discussed.

In a ground state isomerization the thermal reaction proceeds by way of a non-planar transition common to both cis- and trans-isomers. The transition state will collapse to give a greater proportion of the

thermodynamically more stable isomer, usually the trans-isomer. However, the product composition in the photochemically induced isomerization differs from that in the thermal process and the thermodynamically less stable isomer usually predominates. Irradiation of a trans-isomer will produce an excited species which is usually lower in energy than the corresponding cis-isomer and the geometric isomerization is brought about by a distortion of the excited states initially produced, to an excited state common to both cis- and trans-isomers. The common excited state is termed a phantom state and involves a small activation energy.[57] Collapse of the phantom state to the ground state will afford both cis- and trans-isomers. The cis-isomer is less liable to undergo excitation than the trans-isomer but nevertheless, an excited state population will be obtained from this isomer, and isomerization from cis- to trans- will occur via the phantom state. In this manner, an equilibrium termed a photostationary state is established in which the cis-isomer usually predominates. Therefore, the photostationary state is a function of the extinction coefficient of the two geometric isomers with the isomer with the lower value predominating when the isomerization is brought about by direct irradiation. However, when the geometric isomerization is brought about by triplet sensitization (e.g. from excited triplet acetone or benzophenone), the composition of the photostationary state differs from that of direct irradiation. If the energy of the donor is greater than that of both isomers, then triplet energy transfer to both the cis- and trans-isomer will occur. The initially formed cis- and trans-triplet excited species undergo distortion to the common phantom triplet which, on collapsing to the ground state, affords a mixture of isomers. Because the sensitizer can excite both isomers, the proportion of cis-isomer in the

photostationary state from a sensitized reaction is lower than that obtained from direct irradiation. Sensitizers of high energy (acetone) give photostationary states with approximately the same composition of isomers (∿55% cis), while reducing the energy of the sensitizer gives anomolous results.[57] When the triplet energy of the sensitizer is low but still capable of transferring energy to both isomers, the sensitizer then functions as a true "photocatalyst" and the photostationary mixture approaches that at thermal equilibrium.[57]

Photochemical cis-trans isomerization has led to the synthesis of trans-double bonds in both cis-cyclohept-2-enone (59) and cis-cyclo-oct-2-enone (60) to afford the corresponding trans-isomers 61 and 62 when irradiated with light greater than 300 nm, the isomerization being effected by the $n \rightarrow \pi^*$ excitation.[59] In the case of α,β-unsaturated esters the energy-



transfer from the excited carbonyl compound to the ester has been reported to be efficient and led to cis-trans isomerization or cycloaddition.[57] Thus, with respect to the photoamidation reaction, the quenching of the excited photoinitiator via the sensitization of the α,β-unsaturated ester must be considered. Elad and Rokach[40d] found that when the acetone-initiated

reaction of formamide with ethyl maleate (cis-isomer) or ethyl fumarate (trans-isomer) was carried out under conditions similar to the ones used for isolated double bonds (i.e., limited amount of acetone employed), no addition products of formamide and the unsaturated ester could be detected. However, the recovered starting α,β-unsaturated ester consisted of a mixture of geometric isomers, particularly in the case of ethyl fumarate which was recovered mainly as ethyl maleate (e.g., trans to cis isomerization). Increased amounts of acetone produced some addition of formamide to the above esters but yields were still low. On the other hand, using benzophenone as the photoinitiator the addition of formamide to ethyl fumarate and maleate were achieved in almost quantitative yield. However, the undesirable isomerization still occurred and this energy-transfer step was found to be more efficient and more rapid than the hydrogen abstraction step from formamide.

3. Carbon-Carbon Double Bonds

Hydrocarbons possessing a carbon-carbon double bond have the most basic functional group in organic chemistry. By various simple transformation this functional group may be transformed into a saturated hydrocarbon, an hydrocarbon possessing a higher degree of unsaturation or various other functionalized molecules containing hetero-atoms. This section will deal mainly with addition reactions to compounds possessing a carbon-carbon double bond.

There are basically four ways in which addition to a double or triple bond can take place. Three of these are two step processes, with an initial attack by a nucleophile, an electrophile, or a free radical. The second step consists of combination of the resulting intermediate with a positive

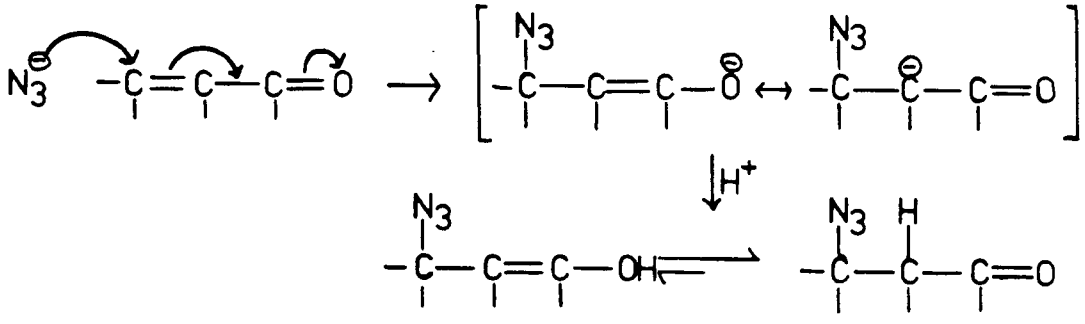
species, a negative species, or a neutral entity, respectively. In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous. The mechanism which is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Pericyclic[66] reactions are beyond the scope of this thesis and no further discussion on this process is necessary. Photochemical free radical additions have been dealt with in detail in the previous section and two non-photochemical methods will be briefly dealt with here. Nucleophilic and particularly electrophilic substitution will be the main focus of this section.

3.1. Nucleophilic Addition to α,β-Unsaturated Esters

The numerous examples of Michael-type addition to conjugated olefins are too varied in substrate and addition products to be discussed at any length. The focus of this section will be the addition of hydrazoic acid and sodium azide to α,β-unsaturated esters.

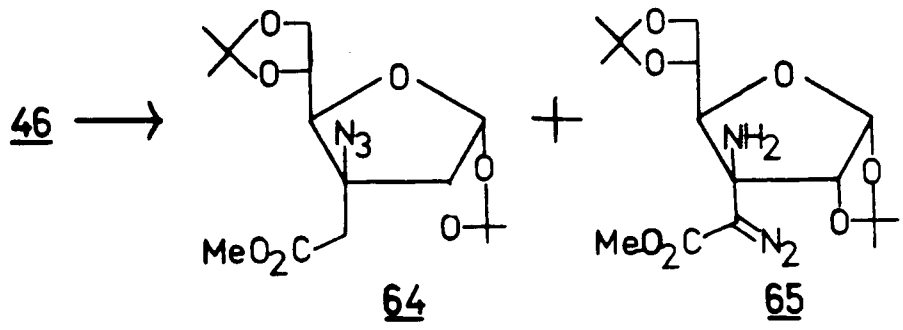
Based on Oliveri-Mandala's[67] addition of hydrazoic acid to benzoquinone in 1915, Boyer[68] in 1951, established that olefins conjugated with electron withdrawing groups (e.g., C=O, -C≡N, $-NO_2$ and ) undergo Michael-type addition reactions with hydrazoic acid to give the corresponding β-azido compound. The α,β-unsaturated carbonyl compounds exhibited intermediate reactivity and the azide products were found to thermally unstable with elimination of hydrazoic acid and nitrogen. The thermal stability of the azides apparently increased with the number and the molecular weight of the substituents on the carbon bearing the azido group[69] or if the azido compound was stored in a high molecular weight solvent (e.g., chloroform).

Since hydrazoic acid is a very weak acid, the mechanism of this reaction is considered to be a 1,4 nucleophilic addition, with protonation of the resulting enolate ion predominantly at the oxygen leading to an enol which tautomerizes. The mechanism is illustrated in Scheme VIII.



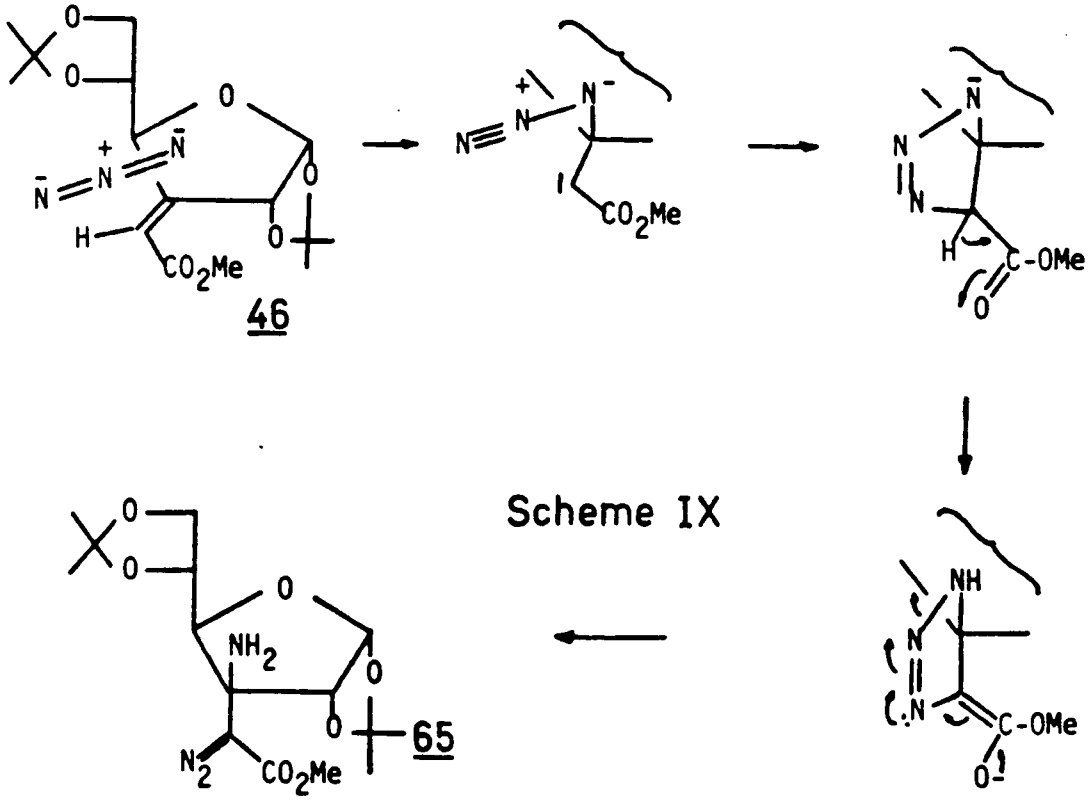
Scheme VIII

The Michael-type addition of hydrazoic acid to various conjugated unsaturated sugars has been studied.[70,71] When Rosenthal and Ratcliffe[72] treated (Z)-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl) methylene-α-D-ribo-hexofuranose (46) with excess sodium azide and hydrazoic acid, the azido-product arising from the stereoselective addition of hydrazoic acid to the double bond to give the gluco-diastereomer (64) was isolated in 80% yield. Interestingly, along with expect addition product a second component isolated in a low yield (7%) was found to be 3-amino-3-deoxy-3-C-[3´-diazo (methoxycarbonyl) methyl]-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (65).



Upon treating the unsaturated sugar 46 with sodium azide in the absence of hydrazoic acid and a non-protic solvent, they isolated the diazo-amino sugar 65 as the major addition product (46%) and the azido sugar 64 in trace amounts (2%).

The mechanistic pathway to the novel diazo-amino sugar 65 is thought to arise from the base-catalyzed tautomerization and bond rearrangement of the charged triazoline which results from the intramolecular cyclization of the azido enolate anion.[73] This mechanism is illustrated in the following scheme.

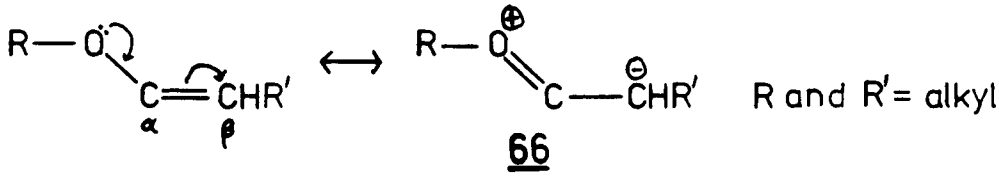


Scheme IX

3.2. Reactions of Enol Ethers

Just as olefinic compounds activated with electron-withdrawing groups undergo numerous nucleophilic addition reactions with the electron-withdrawing group directing the regiospecificity of the reaction, olefins, which are naturally more susceptable to electrophiles than nucleophiles, have enhanced affinity for electrophiles when electron-donating groups are present. As with the electron-withdrawing groups ability to influence the direction of attack in nucleophilic addition reactions, the electron-donating groups also play an important role in the regiospecificity of various addition reactions. This section will deal with various electrophilic, free radical and cyclic additions to the enolic double bond, along with a discussion on the general susceptability of ethers and olefins to air oxidation. Pericyclic and Diels-Alder cyclo-addition[74] reactions are however, beyond the scope of this thesis and will not be discussed.

The mode of addition of ionic reagents to the carbon-carbon double bond of enol ethers (i.e., vinyl ethers) is governed by the mesomeric release of electrons from the oxygen of the ether, which give rise to the contributing canonical structure 66 and directs the electrophile to



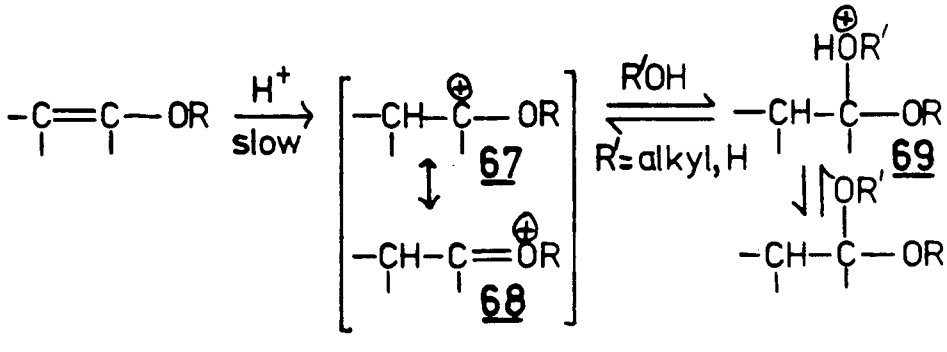
66

the β-carbon. In those reactions which involve a 1,2-cyclic onium ion either the negative inductive or positive mesomeric effect of the enolic

oxygen will exert a directing influence during the approach of the nucleophile in the second step. However, the stereochemistry of the addition which depends upon the characteristics of each reaction and governs the ratio of the initial products may not be obvious in the isolated products due to the epimerization (or anomerization) about the α-carbon due to the activation effect of the enolic oxygen.

3.2.1. Addition of Oxygen and Hydrogen

Enol ethers readily add water or primary alcohols in the presence of acid. Protonation (by the electrophile, H^+) takes place at the β-carbon to give intermediate carbonium ion 67 stabilized by the mesomeric release of electrons to the α-carbon to give contributing structure 68. The intermediate cation then adds a molecule of the hydroxy reagent (ROH) to give the protonated species 69 which looses a proton to give the hemi-ketal or ketal from the addition of water or alcohol, respectively. This mechanism is illustrated in Scheme X. This mechanism is termed an A-SE2 mechanism[75]



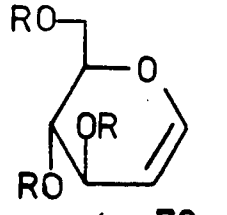
Scheme X

because the substrate (enol ether) is protonated in the rate determining step.

As can be seen from the above scheme, the addition of the nucleophilic reagent is an reversible step catalyzed by the presence of the acid; therefore,

the -OR' groups attached to the α-carbon will approach a thermodynamic equilibrium irregardless of the steric factors affecting the initial addition of the nucleophile.

The acid-catalyzed addition of water to the enolic system of 1,2-deoxy-1-eno sugars (glycals) has been applied with success in the synthesis of numerous 2-deoxy derivatives of pentoses, hexoses, 6-deoxyhexoses, disaccharides, and methylated aldoses.[2,4] The yields of the 2-deoxy products vary considerably and the main by-products are those arising from the hydrolysis of acid-labile groups and products arising from acid-catalyzed elimination reactions. For example, from D-glucal (1,2-dideoxy-D-arabino-hex-1-eno-pyranose, 70, R=H) and D-galactal (1,2-dideoxy-D-lyxo-hex-1-enopyranose, 71, R=H), acid-catalyzed addition of water gave, in addition to the 2-deoxyhexoses (72 and 73 in 42% and 78%, resp.), 3-hydroxy-2-(hydroxmethyl)-2H-pyran (74) in 16% and 1% yield, respectively.[76]



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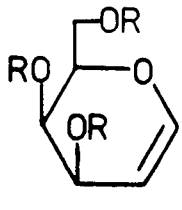

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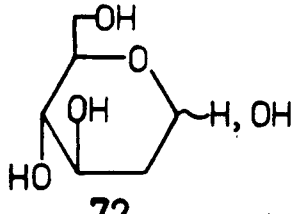

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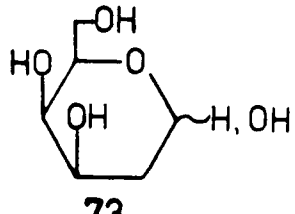

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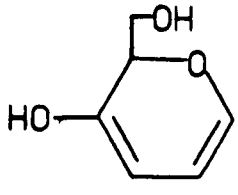
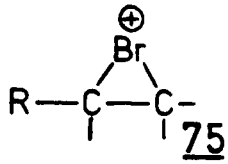


74

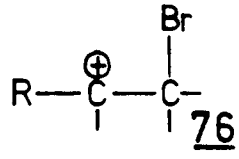
In the acid-catalyzed addition of alcohols to the enolic system of the 1,2-unsaturated sugars, 2-deoxy alkyl glycosides results. In some cases[77] this method of synthesis of the 2-deoxy glycoside is preferred over the glycosidation of the free sugar. As in the hydration of glycols, the competing elimination reaction interferes and various acyclic and unsaturated cyclic products may result, along with the hydrolysis of acid-labile groups.[4]

3.2.2. Addition of Bromine and Bromomethoxylation

In the electrophilic attack of the bromonium ion (Br^+, or a carrier of it) on a simple olefin, the bromonium ion 75 is often an intermediate



75



76

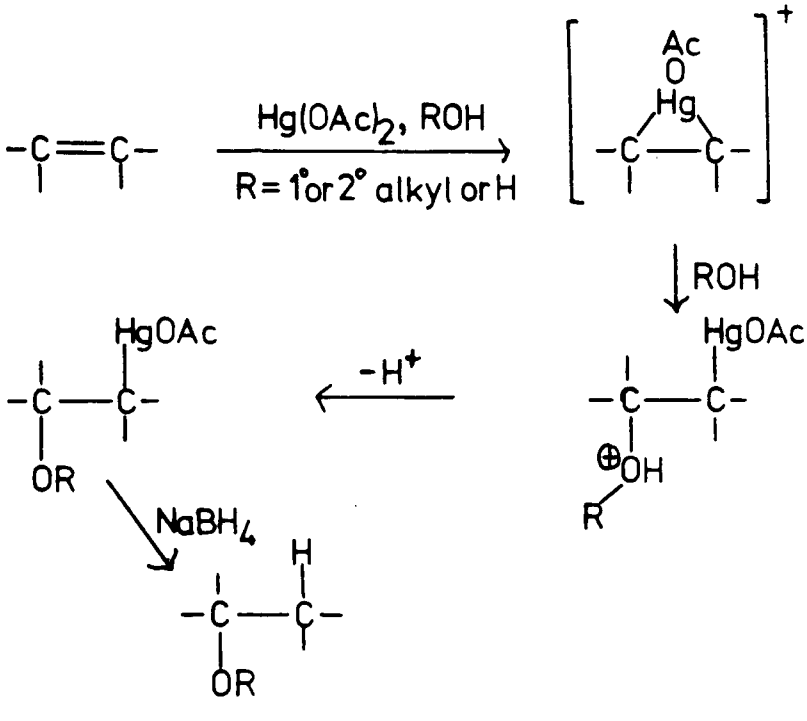
that leads to an attack of the nucleophile from the opposite face (of the double bond) to give stereospecific anti addition.[78] However, a number of examples have been found where addition of bromine is not[79] stereospecifically anti. The results indicate that there is a spectrum of mechanisms between complete brominium-ion 75 formation and complete open-cation formation, with partially bridged bromonium ions in between.[80] The location in this spectrum is determined by the relative abilities of the R-groups to stabilize the open-cation 76. Therefore, where R is an alkoxyl group which gives a relatively stable oxonium cation such as 68, the intermediate cation will possess much open-cation character, thereby lowering the stereoselectivity of the addition reaction.

In a report[81] on the halomethoxylation (addition of X=halogen and $-OCH_3$) of tri-O-acetyl-D-glucal (70, R=Ac) and tri-O-acetyl-D-galactal

(71, R=Ac), the adducts isolated showed significant proportions of α-cis addition products arising from the open-cation.

3.2.3. Methoxymercuration

Another route to the 2-deoxy glycosides is by the use of the oxymercuration reaction.[82a] The enol ethers (or olefins) can be alkylated (or hydrated) quickly, under mild conditions, in high yields without rearrangement or elimination products. The oxymercuration reaction involves the electrophilic addition, to the carbon-carbon double bond, of the mercuric ion to form a cyclic mercurinium ion 77. This ion is then attacked by the nucleophilic solvent (water or 1° or 2° alcohol) to yield the addition product. The net reaction is anti addition and the orientation corresponds to Markovnikov addition of alcohol (or water). The mechanism[82b] is illustrated in Scheme XI.

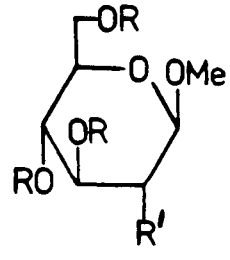


Scheme XI

The attack of the hydroxy reagent is of the S_N2 type, even though the orientation of the addition shows that the nucleophile attacks the more highly substituted carbon-carbon. The seeming contradiction is due to the fact that the transition state in cationic three-membered rings possess much S_N1 character and, therefore the electronic factor play a greater role. Thus, the attack of the nucleophile (ROH) occurs at carbon that can best accommodate the positive charge (i.e., usually the more substituted centre).

The oxymercuration reaction is usually followed by a in situ reductive demercuration with sodium borohydride (see Scheme XI) to give the net Markovinikov addition of water or alcohol to the unsaturated bond. The intermediate oxymercurial if isolated is usually precipitated as the chloride.[83]

Thus, the oxymercuration of tri-O-acetyl-D-glucal (70, R=Ac), after replacement of the ionic acetate by chloride, gave methyl 3,4,6-tri-O-acetyl-2-(chloromercuri)-2-deoxy-β-D-glucopyranoside (78)[84a-b]. Reductive cleavage of the carbon mercury bond and simultaneous deacetylation were brought about



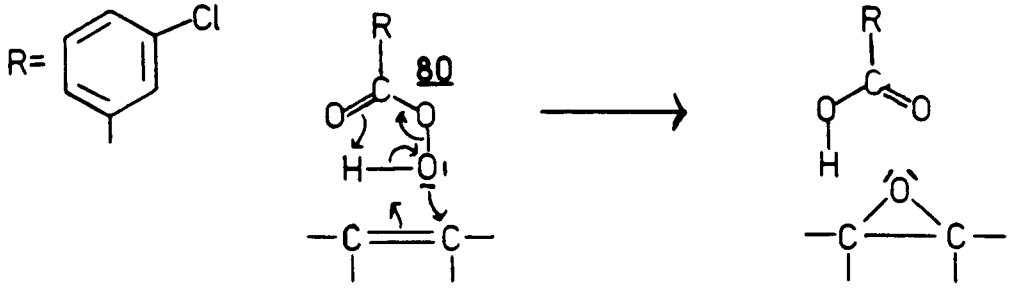
78 R=Ac R'=HgCl 79 R=R'=H

with potassium borohydride in alkaline solution and gave methyl 2-deoxy-β-D-arabino-hexopyranoside (79).

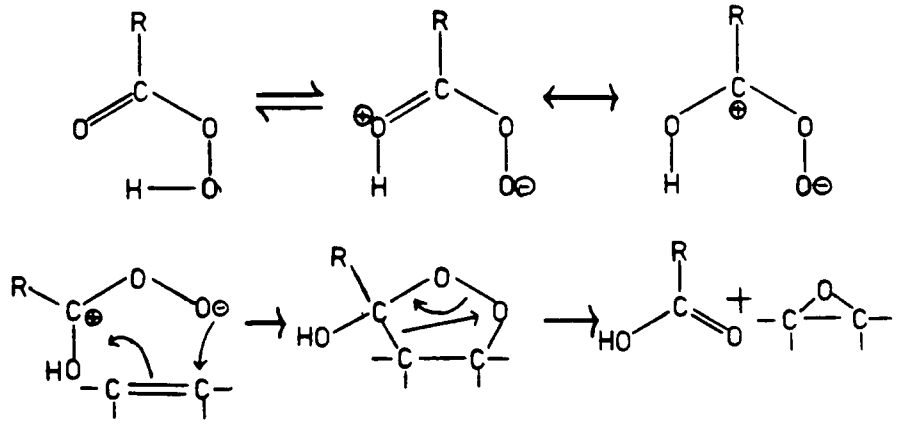
3.2.4. Reaction with meta-Chloroperbenzoic Acid

Another facile method for the synthesis of alkyl or acyl glycosides involves the use of meta-chloroperbenzoic acid (MCPBA, 80) on the glycals. The reaction of olefins with peracid 80 usually permits the isolation of the initially formed expoxide[85a], however, with enol ethers the intermediate epoxy acetals appear to react with the carboxylic acid in the reaction mixture too rapidly to permit isolation.[85b] Therefore, the usual product of treating a glycal with peracid 80 is the α-hydroxy glycosyl esters.

Two mechanisms have been proposed for epoxidation of carbon-carbon double bonds with peracids. The first proposed by Bartlett[86] in 1957 involves the following one-step mechanism.

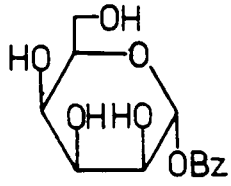


Another, more recent, mechanism which is also in accord with the reaction kinetics, solvent effects and stereochemistry of the reaction involves a two step process as follows.[87]



The key step of this mechanism involves the 1,3-dipolar addition of a tautomer of the peracid. The five-member adduct then rearranges to give the products.

In the hydroxylation of D-galactal (71,R=H) with peroxybenzoic acid a regio- and stereospecific addition of the reagents occurred to give α-D-talopyranosyl benzoate (81).[88] The mechanistic aspects of the opening

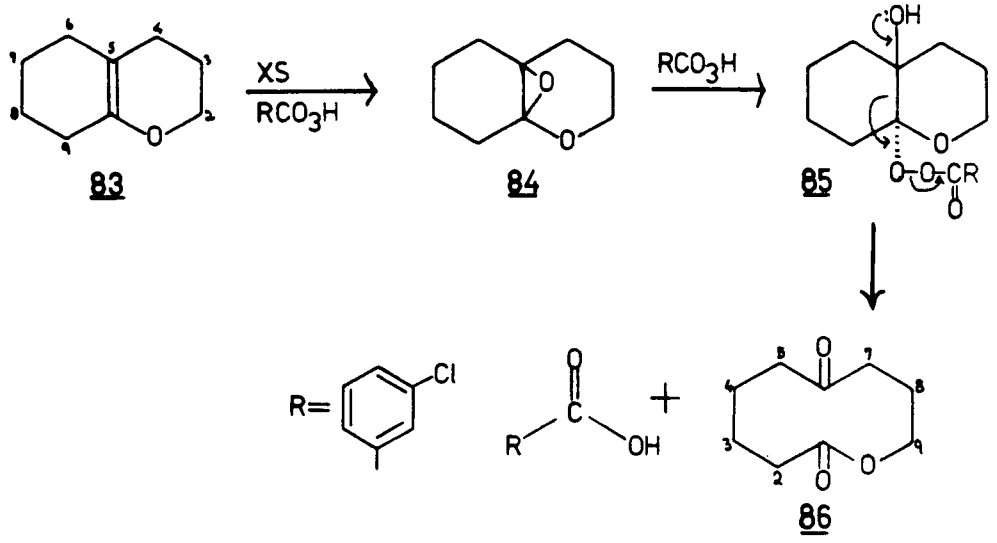


81

82

of the epoxide are identical to those proposed for the oxymercuration reaction (previous section) except the three-membered cationic species is structure 82.

An interesting modification to the hydroxylation reaction with the peracid involves the slow addition of the enolic substrate to an excess of peracid which results in a cleavage of original carbon-carbon double bond. Thus, when Borowitz[89], Gonis and coworkers treated 5,6,7,8-tetrahydrochroman (83) with excess MCPBA 80, they isolated 6-ketononanolide (86) in 92% yield.

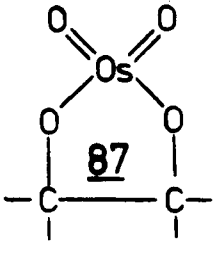


Scheme XII

The mechanism proposed for this cleavage is depicted in Scheme XII and involves the usual formation of the epoxy-acetal 84 from the epoxidation of the enolic double bond, the epoxide 84 reacts with the excess peracid to give the α-hydroxy ketal perester 85 which then decomposes to give 86 and meta-chlorobenzoic acid.

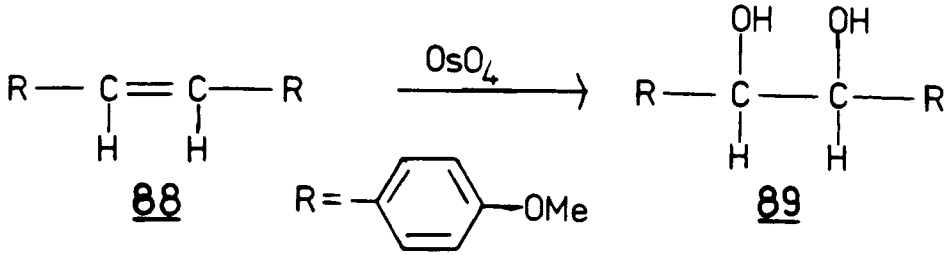
3.2.5. Oxidation with Osmium Tetroxide

Osmium tetroxide[89] adds to carbon-carbon double bonds from the least hindered side for the selective conversion of olefins to cis-1,2-diols.[90] The cyclic osmate ester 87 is an intermediate and can be isolated, but is



usually decomposed in solution, with sodium sulfite in ethanol or other reagents.[90,91a-b] Bases (e.g. pyridine) catalyze the reaction by coordinating with the ester.[90] Electron-withdrawing substituents retard the rate of the inorganic ester formation[92] and strained, unhindered olefins usually react with osmium tetroxide more rapidly than unstrained[93] or sterically hindered olefins.

Hydroxylation of 4,4´-dimethoxystilbene (88) with osmium tetroxide has been achieved[92] to give the corresponding diol (89).



88 89

3.2.6. Oxidation with Molecular Oxygen

Oxidation with molecular oxygen provides another route to the hydroxylation and oxidative cleavage of enolic double bonds. The slow atmospheric oxidation of a C-H bond to a C-O-OH group or any slow oxidation with atmospheric oxygen is termed autoxidation. The initial autoxidation products often react further to give a more complicated mixture and the purpose of this section is to explore some of the possible routes to the hydroxylation and oxidative cleavage of the enolic double bond with these autoxidation intermediates.

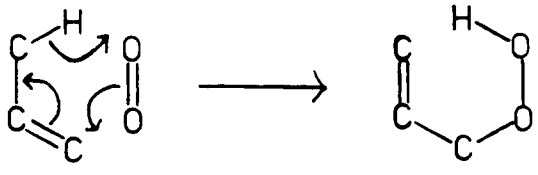
The formation of hydroperoxides from ground state molecular oxygen (a triplet) is a free radical process[94], however, oxygen itself (a diradical) is too unreactive to abstract the hydrogen. The chain must be initiated by the production of some free radicals (eg. R´·) produced by some initiation process, the radical combines with molecular oxygen to give R´-O-O·, a species which can abstract hydrogen. The chain is propagated by the following two steps:

$$R'OO\cdot + RH \longrightarrow R'OOH + R\cdot \qquad (1)$$

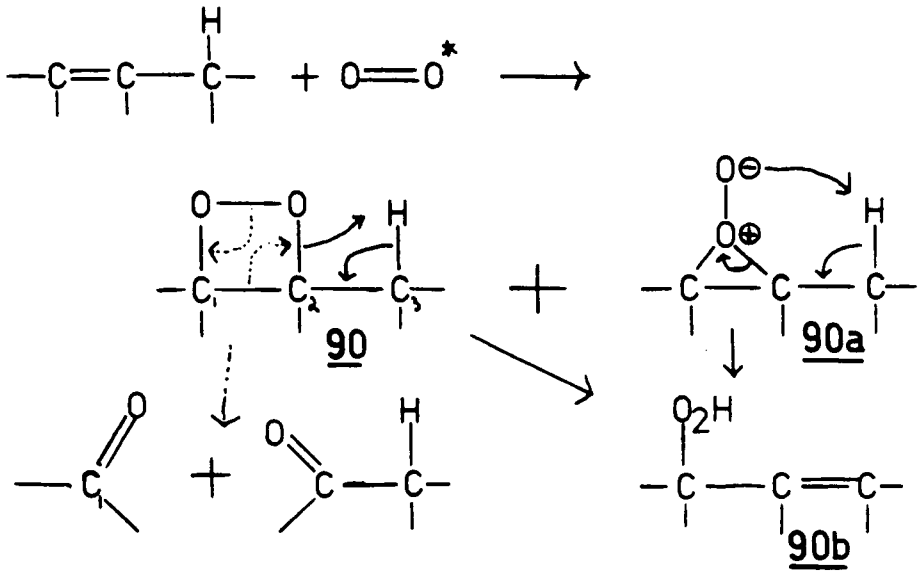
$$R\cdot + O_2 \longrightarrow R\text{-}O\text{-}O\cdot \qquad (2)$$

The C-H bonds which most reactive are tertiary, allylic, and benzylic positions and the α-position of ethers.

Hydroperoxides can also be formed by the direct action of photo-sensitized molecular oxygen on olefins. The active reagent here is the excited singlet state[95] oxygen molecule. This reaction always takes place with 100% allylic rearrangement which is incompatable with a free radical mechanism; therefore, two mechanisms have been proposed for production of hydroperoxides from singlet oxygen. The first mechanism proposed[96] involves a one-step pericyclic mechanism, similar to that of the ene synthesis.[97]



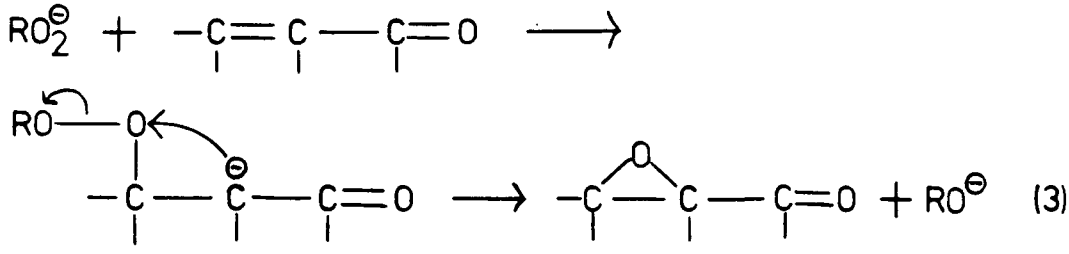
The second mechanism proposed involves the initial addition of singlet oxygen to the double bond to form either a dioxetane intermediate 90 or three-membered dipolar peroxirane 90a. Decomposition of these intermediates by internal proton transfer and bond rearrangements affords the allyl hydroperoxide 90b. Oxidative-cleavage of the carbon-carbon double bond may occur by an alternative decomposition of the dioxetane to give the carbonyl products. These steps are illustrated in Scheme XIII.



90 90a 90b

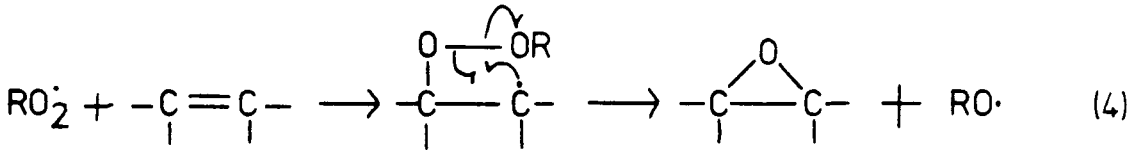
Scheme XIII

The formation of epoxides from the reaction between the hydroperoxides and olefin may take place by at least three routes.[99] The first, and most synthetically useful, involves the base catalyzed addition of the hydroperoxide to α,β-unsaturated carbonyl compounds (reaction 3). The intermediate anion attacks the 0-0 bond to close the epoxide. The epoxides may



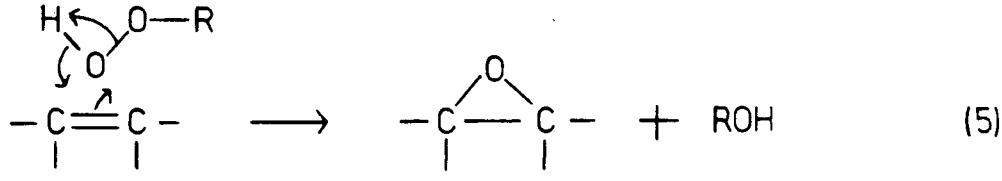
(3)

be formed by the addition of the peroxy radical to the carbon-carbon double bond follow by ring closure and expulsion of an alkoxy radical (reaction 4).



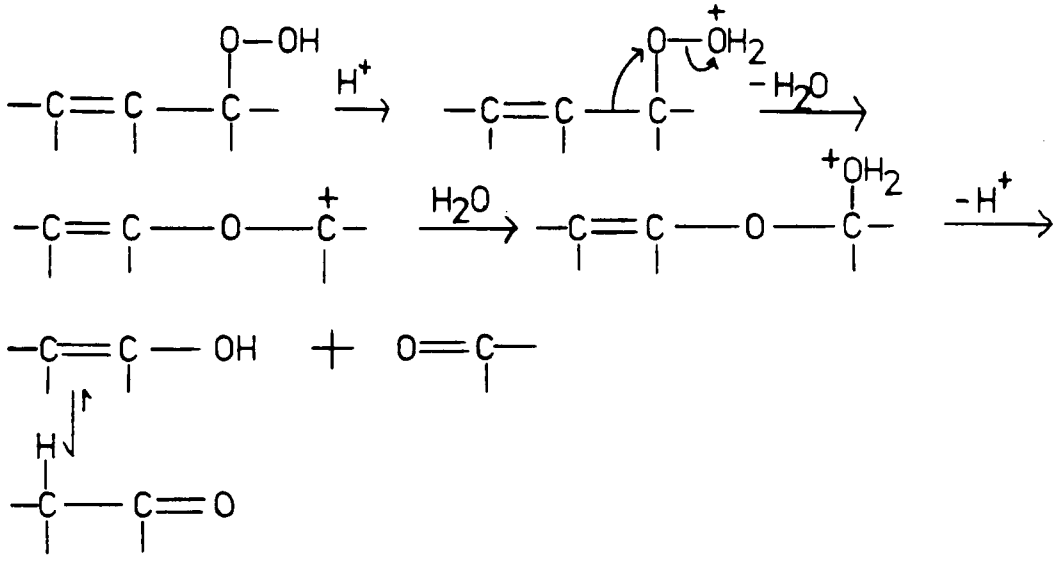
(4)

The third route involves a nonradical nucleophilic displacement by C=C on the oxygen-oxygen bond to give an epoxide in manner similar to that of epoxidation with peracid (reaction 5 and also see Section 3.2.4.).



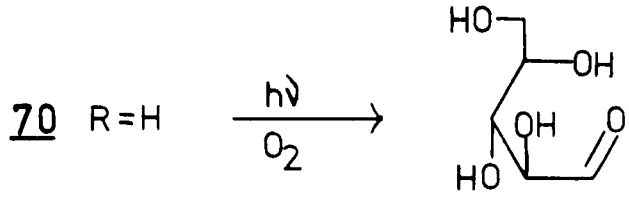
(5)

As was seen in the oxidation of the olefin with singlet oxygen, the reaction could lead to an oxidative cleavage of the olefinic bond. Another route to the cleavage of the original double bond with the formation of two carbonyl compound involves the rearrangement of the allylic hydroperoxide.[100] The mechanism is seen in the following scheme.

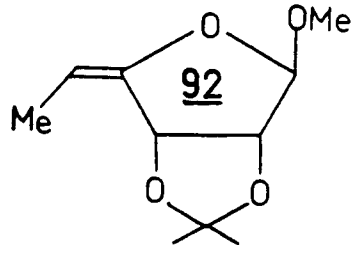


Scheme XIV

When D-glucal (70,R=H) was irradiated[101] in the presence of oxygen, D-arabinose (91), formed by an oxidative cleavage of the double bond, was isolated as the main product. Goodman and co-workers[102] reported that purified samples of methyl 5,6-dideoxy-2,3-O-isopropylidene-β-D-allofuranoside-4-ene (92) slowly polymerized on standing and indicated an increased oxygen content, suggestive of an oxidative polymerization.



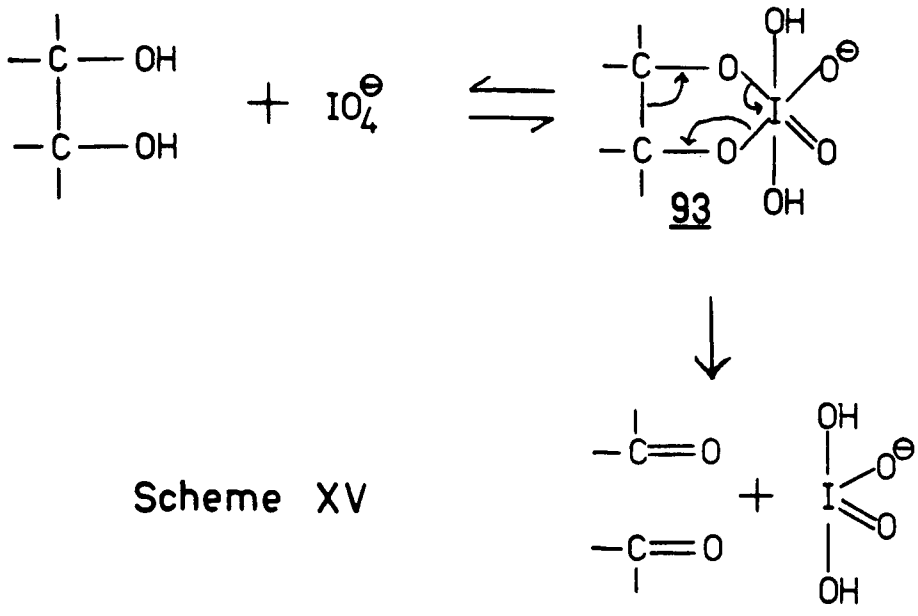
91



92

3.2.7. Periodate Oxidation

As was seen in the previous three sections the enol ethers can be hydroxylated or oxidatively cleaved ina one-step synthesis; however, the hydroxylated products (i.e., α-hydroxy ketone/aldehydes or their corresponding hemi-acetals) can be isolated and then oxidatively cleaved in a subsequent step. 1,2-Glycals, α-hydroxy aldehydes and ketones are easily cleaved by aqueous solutions of sodium periodate[103] resulting in the formation of carbonyl functionalities. The mechanism of the oxidative cleavage[104] involves the rapid and reversible formation of a cyclic periodate ester 93, decomposition of the ester results in the oxidative cleavage of the carbon-carbon bond of the 1,2-diol. This mechanism is shown in Scheme XV.



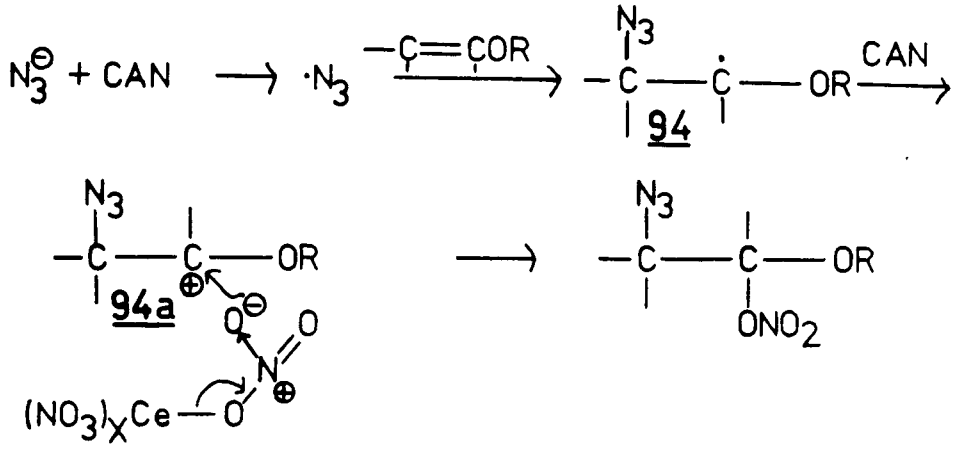
Scheme XV

The reaction, therefore, is limited to substrates that can form the cyclic ester 93.

3.2.8. Azido-Nitration

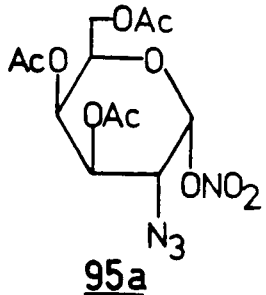
The azido-nitration reaction is a recently developed[105] reaction for the regiospecific addition of azide ($-N_3$) and nitrate ($-ONO_2$) across the enolic double bond. The reaction involves the addition of the enol ether in a suitable solvent to a mixture of ceric ammonium nitrate (CAN) and sodium azide to give the 1:1:1 adduct.

The mechanism proposed[106] for this addition involves both free-radical and ionic intermediates. CAN oxidizes the azide anion to the azido radical which adds to the β-carbon of the enolic substrate. The intermediate radical 94 stabilized by the oxygen is oxidized by another molecule of CAN to give the stabilized oxo-carbonium ion 94a which accepts a nitrate nucelophile associated with leaving CAN complex to give the final addition product. This mechanism is illustrated in the following scheme.

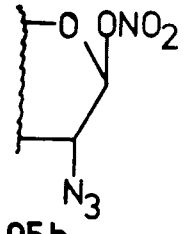


Scheme XVI

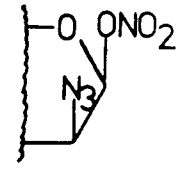
When 3,4,6-tri-O-acetyl-D-galactal (71, R=Ac) was treated with CAN and sodium azide three 2-azido galactopyranosyl nitrates (95a, b and c in 37, 55 and 8% yield resp.).



95a



95b



95c

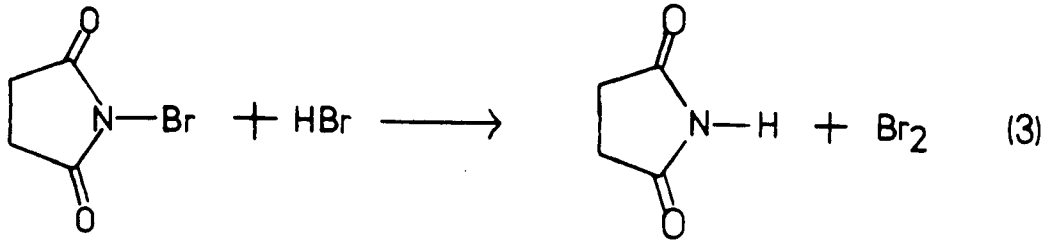
3.2.9. Reaction with N-Bromosuccinimide

Olefins can be halogenated at the allylic position with N-bromosuccinimide (NBS) and when this reagent is used, the reaction is known as the "Wohl-Ziegler bromination". With this reagent an initiator is required and is usually a peroxide or, less often, u.v. light. The reaction is usually quite specific at the allylic position and good yields are obtained. The mechanism is of the free radical type[108] and is initiated by small amounts of Br. Once the bromine radical is formed the main propagation steps are:

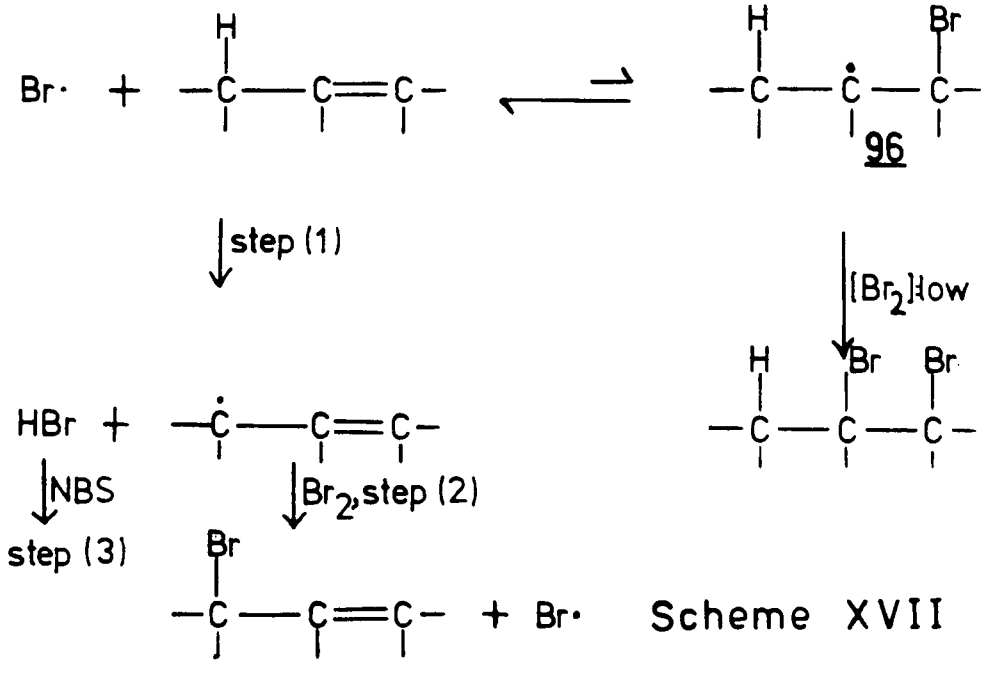
$$Br^{\cdot} + RH \longrightarrow R^{\cdot} + HBr \qquad (1)$$

$$R\cdot + Br_2 \longrightarrow RBr + Br\cdot \qquad (2)$$

The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



Therefore, the function of NBS is provided a source for molecular bromine, in a low, steady-state concentration and to use up the hydrogen bromide liberated in step 1. The fact the concentration of molecular bromine is low provides the proper conditions for allylic substitution rather than addition to the double bond. The atomic bromine adds to the double bond in a equilibrium process and when the concentration of bromine is low, there will not be high probability that the proper species will be in the vicinity once the intermediate radical 96 forms and the equilibrium will lie to the left. This slows the rate of addition so that allylic bromination can compete successfully. This rationale is illustrated below:



Scheme XVII

4. C-Nucleosides

The nucleosides and their analogues are a broad range of compounds in which an unsaturated hetereocycle is attached to a polyhydric alcohol, aldehyde or ketone. The common or normal, naturally-occurring N-nucleosides consist of a pyrimidine or purine base joined by an N-glycosyl linkage to D-ribose. In 1959, Cohn[110] isolated a nucleoside that was different from the previously known N-nucleosides. This compound, which was isolated from an alkaline hydrolysate of calf liver, was found[111a-b] to be 5-(β-D-ribofuranosyl) uracil (pseudouridine, 97), a nucleoside possessing a C-glycosyl linkage. Since then, a number of other C-nucleosides have been isolated (see Figure 1) mainly from fermentation sources.[112] All, except pseudouridine 97 and Indochrome BII (105), possess antibiotic properties.[112,113] The biological activity of the C-nucleosides stems from their structural similarities to the N-nucleoside, which allows the biological system to accept them as metabolites plus the structural dissimilarities which allow for different chemical interactions in the biological system.[114] One of the larger and more important differences is the presence of the glycosidic carbon-carbon bond which has an enhanced hydrolytic stability compared to the more labile carbon-nitrogen bond of the common N-nucleosides.

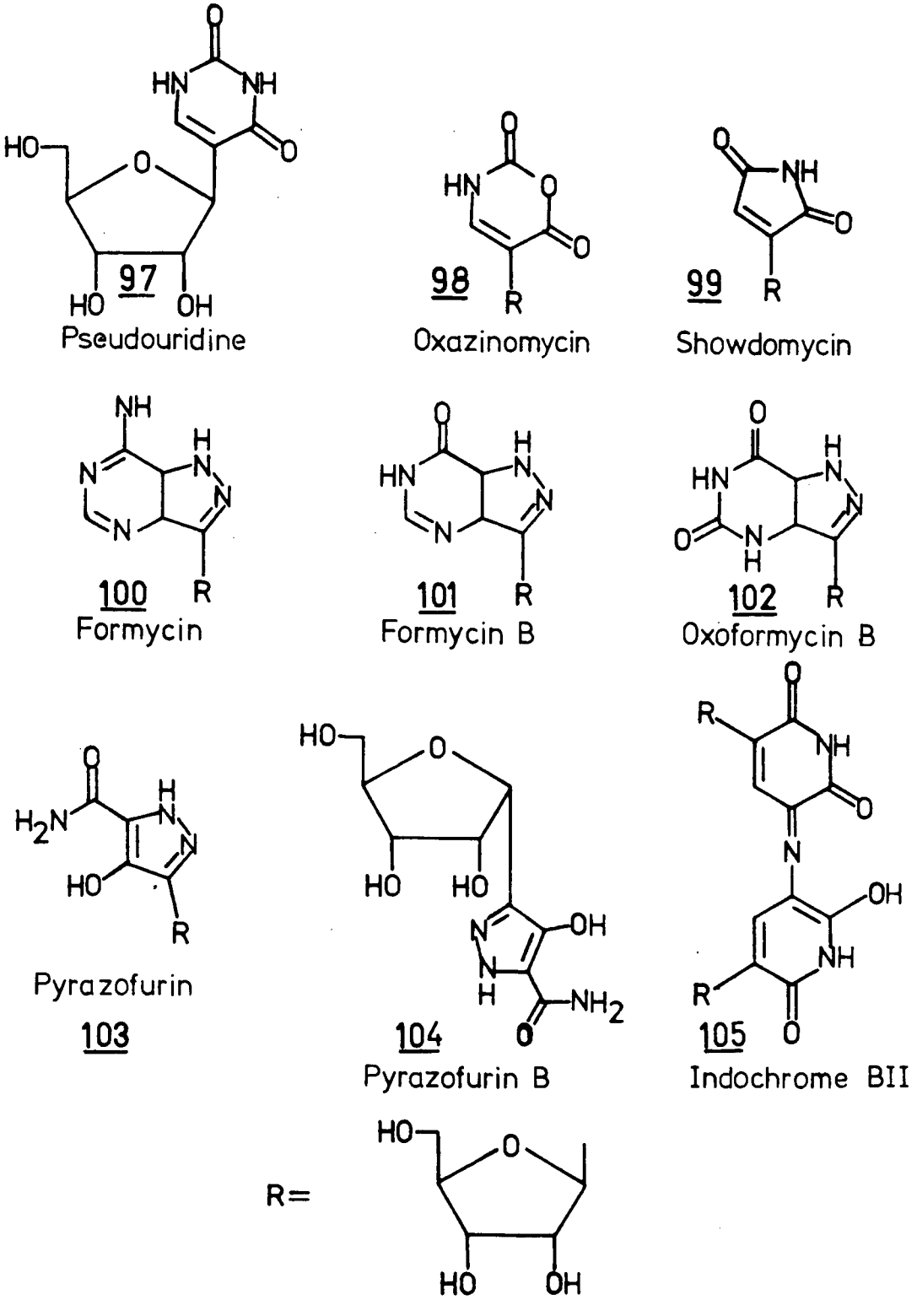


Figure 1: Naturally-Occurring C-Nucleosides

The biological properties[113,116] of the naturally-occurring C-nucleosides along with the synthesis[112,116] of both naturally-occurring C-nucleoside and their analogues have been extensively reviewed. This section, then, will focus its attention on the synthetic approaches to showdomycin (99) and follow with a brief discussion of the general approaches to the synthesis of C-nucleoside precursors.

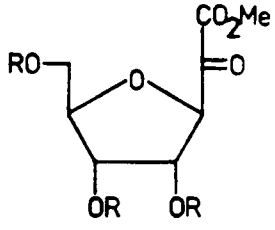
4.1. Showdomycin

Showdomycin (99) was discovered by Nishimura and coworkers[117] in 1964 and is elaborated by Streptomyces showdoensis. The structure of showdomycin has been established[118a-c] as 2-(β-D-ribofuranosyl) maleimide (99) by chemical and spectral analysis and its structure is closely related to pseudouridine (97). Showdomycin exhibits both antibacterial and antitumor activity.[113]

Showdomycin is structurally unique among the C-nucleosides of natural origin, in that it has the five-membered maleimide heterocyclic aglycon. Synthetic approaches to showdomycin must take into account its lability in base, attributable to a rapid Michael type of intramolecular addition of the 5′-hydroxyl group to the double bond.[118a] Two methods[112] have been utilized in the synthesis of C-nucleosides, one involves the direct condensation of the preformed heterocyclic base on the sugar and the other utilizes anomerically functionalized C-β-D-pentofuranosyl derivatives with the hetereocyclic base elaborated from the functionalized 'aglycon'. The successful synthesis of showdomycin have utilized the latter approach.

The first three syntheses of showdomycin were very similar in that each used a stabilized Wittig reagent on the keto 'aglycon' of the sugar to complete the maleic acid portion of the molecule. The first synthesis

was reported in 1970 when Kalvoda, Farkaš and Šorm[119] utilized methyl 4,5,7-tri-O-acetyl-3,6-anhydro-D-allo-heptulosonate (106,R=Ac), which was ingeniously prepared via the ozonolysis of 1-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-2,4,6-trimethoxy benzene (107), as their key intermediate. The keto ester 106 was then condensed with the Wittig reagent (ethoxy-



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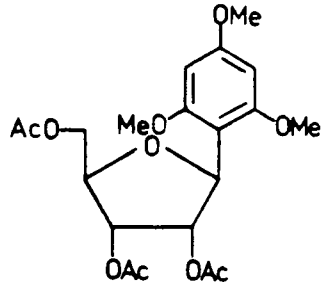
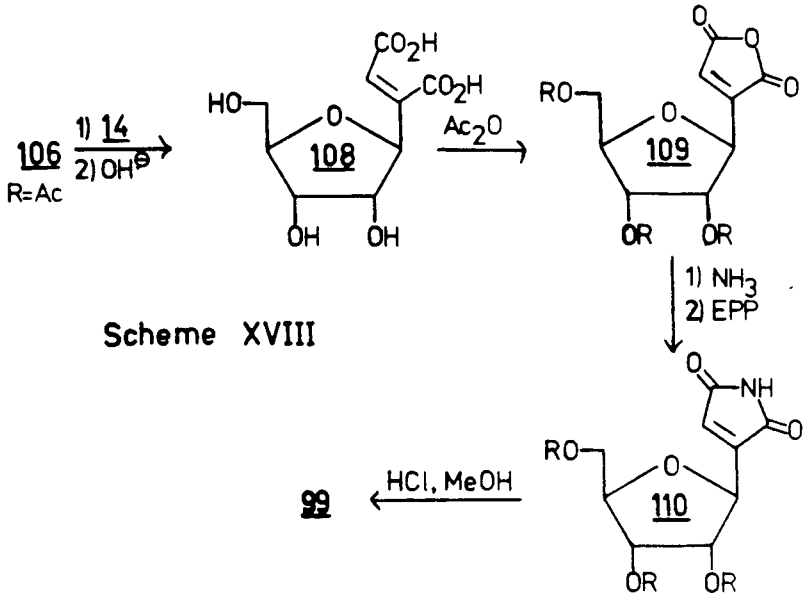


107

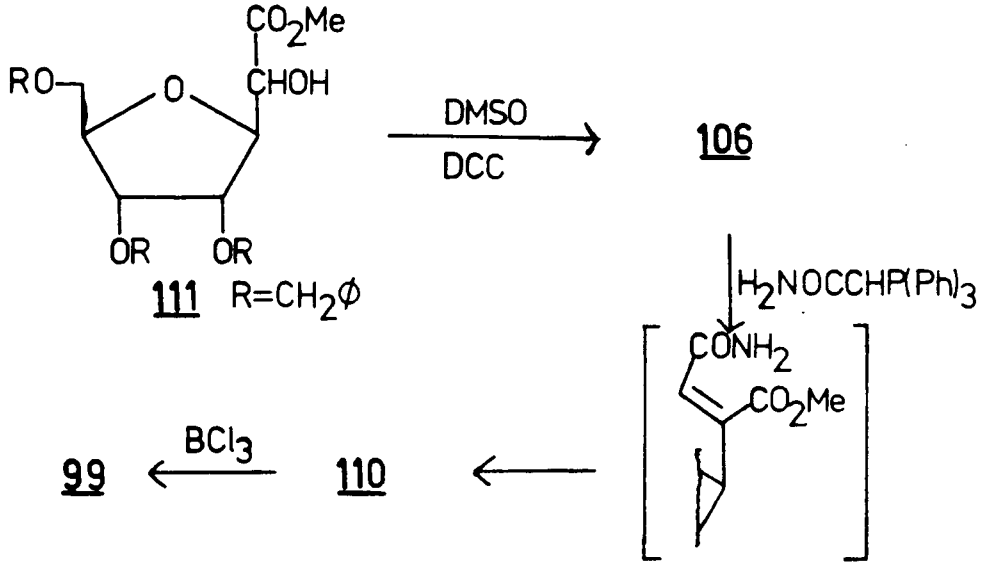
carbonylmethylene)triphenylphosphorane. The resulting mixture of esters (cis and trans) was hydrolyzed, and the cis-acid (108) was cyclized with acetic anhydride to afford the maleic anhydride derivative (109). Treatment with ammonia, and cyclization of the resulting maleamic acid in the presence of ethyl polyphosphate (EPP) gave showdomycin triacetate (110) which, when treated with methanolic hydrogen·chloride, gave crystalline showdomycin (99) (see Scheme XVIII).



Scheme XVIII

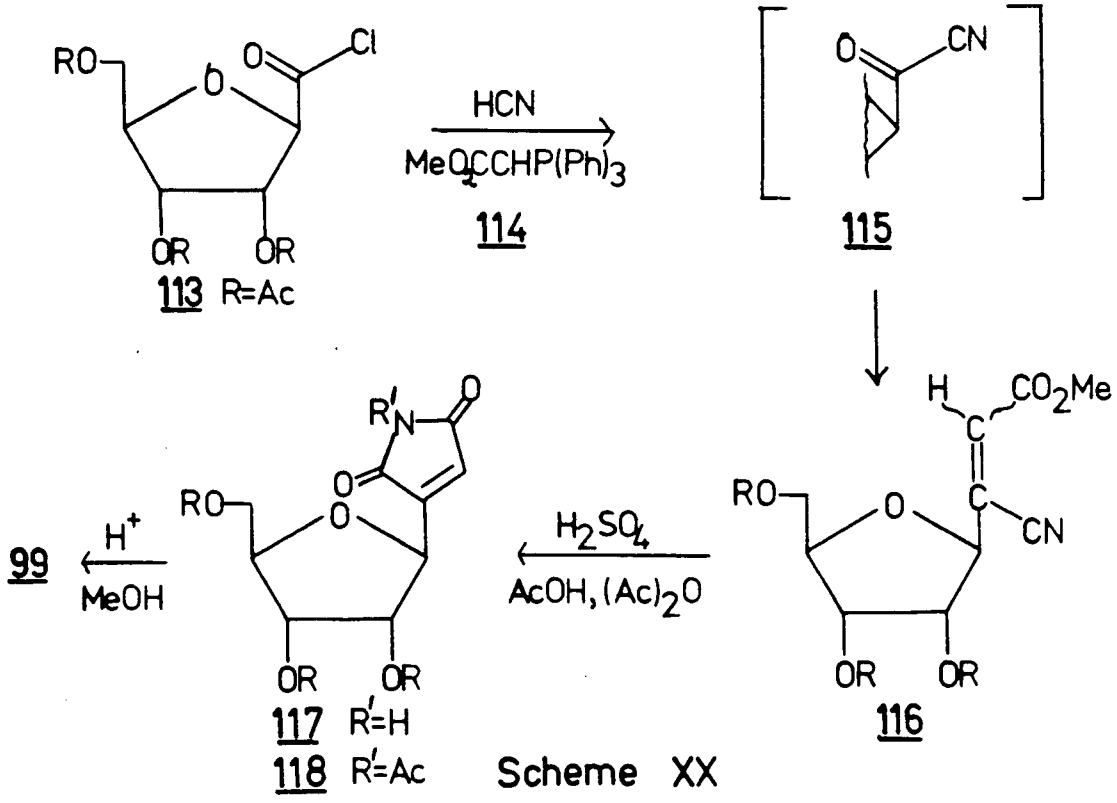
Although yields for the ozonolysis and Wittig reaction were not given showdomycin was isolated in about 16% overall from 108.

Three years later, Trummlitz and Moffat[120] described a two-step synthesis starting from the benzyl analogue (R-Bzl) of the keto ester 106. This key compound was synthesized from the dimethylsulfoxide-dicyclohexylcarbodiimide (DMSO-DCC) oxidation of the epimeric hydroxyl precursor (111). The construction of the ring was achieved in a key, one-step Wittig reaction, utilizing (carbamoylmethylene)triphenylphosphorane Presumably, a spontaneous cyclization of the cis-orient maleamic acid ester (112) intermediate occurred to give the maleimide ring. To avoid hydrogenation of the maleimide ring, the debenzylation was accomplished in good yields by treatment of 111 with boron trichloride to give an overall yield of 29.6% from the epimeric hydroxy ester 111.



Scheme XIX

Kalvoda searched for other routes[121a-b] to showdomycin and in 1976 reported[122] the synthesis of showdomycin *via* the condensation of a stabilized Wittig reagent on an acyl cyanide. The key step in this synthesis involves the *in situ* generation of the acyl cyanide followed by reaction with the Wittig reagent to give the methyl 3-cyano-2-alkenoate. Thus 3,4,6-tri-*O*-acetyl-2,5-anhydro-D-allonyl chloride (113) was treated with hydrogen cyanide in the presence of excess (methoxycarbonylmethylene)triphenylphosphorane (114) to give an intermediary acyl cyanide 115 which is converted to a mixture of *cis* and *trans* isomers of the Wittig adduct 116. The *cis* (or *E*) isomer is cyclized in a mixture of acetic acid, acetic



113 R=Ac

114

115

116

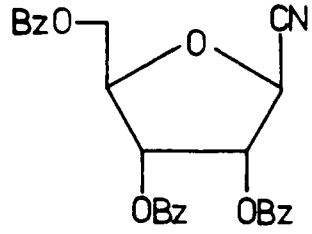
117 R'=H

118 R'=Ac

99

Scheme XX

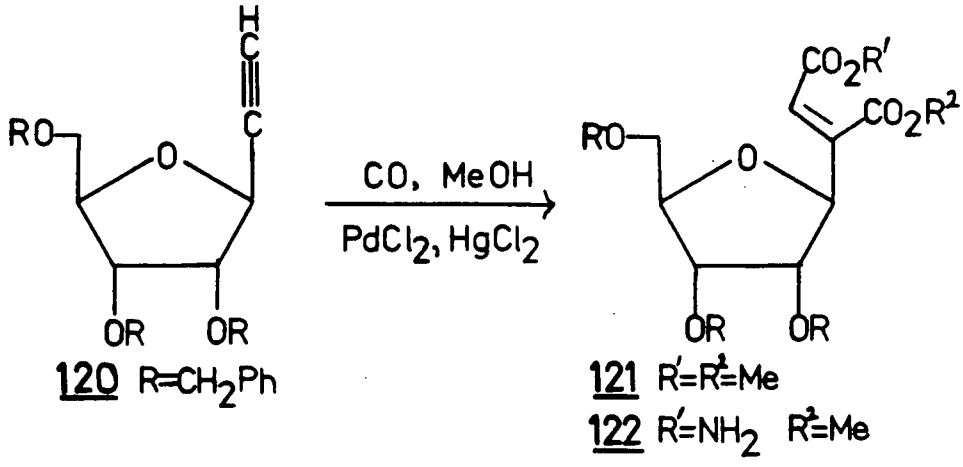
anhydride, and sulfuric acid to give a mixture of the free (117) and N-acetylated (118) maleimides which were de-acetylated in methanolic hydrochloric acid to give showdomycin (99) in an overall yield of 16.7% from the nitrile precursor 119. At first glance Kalvoda's more recent



119

synthesis has an lower overall yield but on closer inspection Trummlitz and Moffatt's procedure also have the nitrile 119 as an intermediate in the total synthesis of showdomycin from ribose. Therefore, Trummlitz and Moffatt's yield of showdomycin is calculate from the common intermediate 119, the overall yield drops from 29.6% to 8.5%, making Kalvoda's synthesis much more appealing.

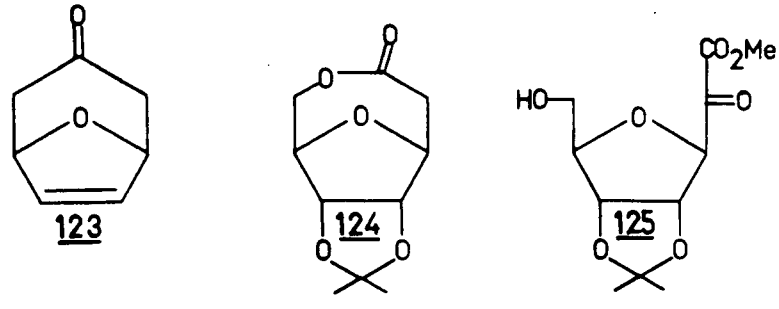
In a very recent paper Buchanan, Edgar and coworkers[123] reported the synthesis of showdomycin (99) using the terminal acetylenic sugar, 2,3,5-tri-O-benzyl-β-D-ribofuranosylethyne (120) as their key intermediate. The key reaction involved the dicarboxylation of the terminal acetylene to the maleic ester derivative 121, in 80% yield, similar to the intermediate in Kalvoda's[119] first synthesis (see Scheme XVIII, structure 108). In a series of transformations similar to Kalvoda's, the intermediate 121 was converted to the maleamic acid derivative 122 and cyclized to the maleimide



with acetyl chloride (cf EPP of Kalvoda[119]). After debenzylation with boron trichloride, showdomycin was isolated in an overall yield of 23% from the ethyne 120 and 8% overall from D-ribose.

The overall yield of showdomycin from D-ribose (calculated from known procedures) using Kalvoda's[122] latest procedure is 10%; therefore, this recent procedure compares favourably.

In a recent preliminary communication, Noyori, Sato, and Hayakawa[128a-b] reported the synthesis of showdomycin starting from noncarbohydrate materials. One of the key steps in this interesting synthesis involves the synthesis of 8-oxabicyclo[3.2.1]oct-6-en-3-one (123) from acetone and furan. Following hydroxylation with osmium tetroxide and isopropylidenation, subsequent Baeyer-Villiger oxidation of the ketone gave a racemic mixture of lactone 124. After resolving the mixture, the C-β-D-glycono-lactone 124 was converted to showdomycin (99) in a seven step sequence involving the formation of a α-keto ester 125 followed by cyclization with the amide stabilized Wittig reagent (cf. Trummlitz and Moffatt[120]).



The yield of showdomycin based on the lactone acetonide 124 was less than 22% and less than 7% based on 123 (cf. 10% based on D-ribose for Kalvoda's[122] procedure). The advantage of this synthesis is the fact the starting materials are readily available and inexpensive, and the α-keto ester intermediate[125] is amenable to the synthesis of other C-nucleosides.[128a]

Other synthetic procedures involving the condensation of a heterocyclic base containing the necessary elements for the maleimide ring directly onto a sugar derivative have been reported[126], however, the final transformation to showdomycin (99) has not been accomplished.[124b]

4.2. C-Nucleoside Precursors

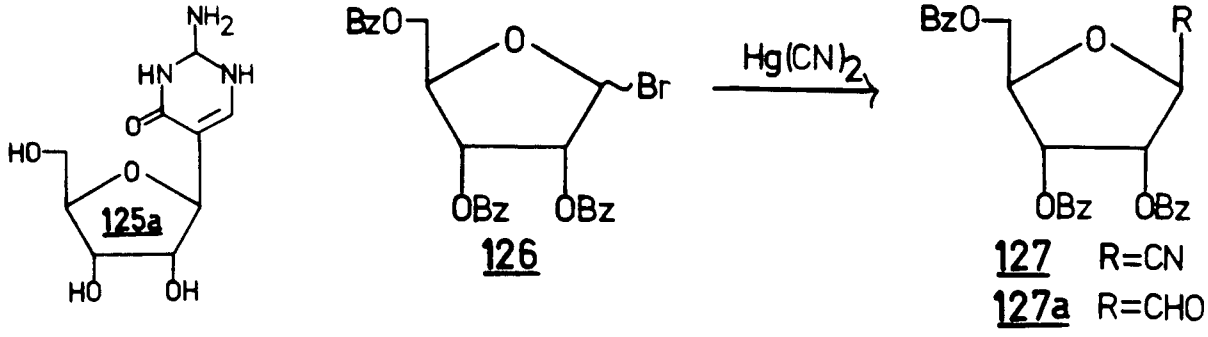
A great number of analogues[112,116] of the naturally-occurring C-nucleosides have been synthesized over the last decade in an effort to obtain chemotheropeutic compounds with specific biological activity. This endeavour has been highlighted by the synthesis[125] of pseudo-isocytidine [5-(β-D-ribofuranosyl)isocytosine (125a)], the first synthetic C-nucleoside to display antitumour properties.[126]

Four synthetic strategies have been employed in the synthesis of novel C-nucleosides. Three of these approaches have been mentioned in the previous section and involve the elaboration[122] of a heterocyclic base from sugar derivative functionalized at C-1 and the second involves the direct coupling of a preformed heterocyclic with an appropriately blocked sugar derivative.[112,116] The third procedure mentioned, prepares the C-nucleoside from noncarbohydrate sources[128a] and the last method involves the modification of naturally-occurring C-nucleosides.

By far the most practical and versatile synthetic route to modified C-nucleosides consists of functionalization of the sugar derivative at

C-1 followed by a stepwise elaboration of a heterocyclic base from this functional group. Two general methods for obtaining these functionalized precursors are available. One involves the intramolecular cyclization of acyclic carbohydrate derivatives[112] which lead[129] to precursor 120 for Buchanan's[123] synthesis of showdomycin (99). The second method involves the formation of a carbon-carbon bond at the anomeric centre formed usually from a glycosyl halide and an appropriate carbanion. The most versatile derivative formed from this latter procedure is the D-ribosyl cyanide derivative which will be discussed in more detail.

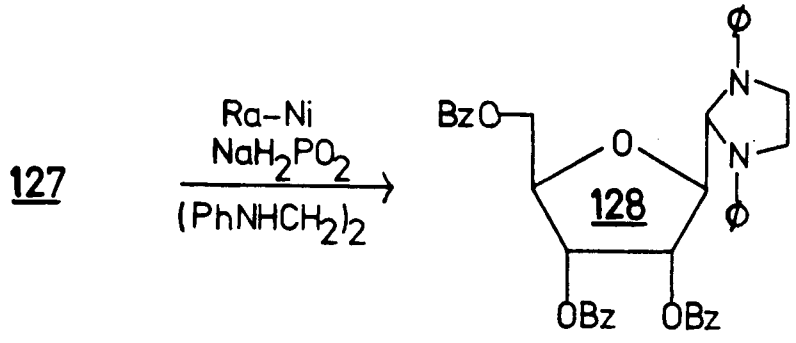
Based on the previous work by Coxon[130], Bobek and Farkas[131] prepared tri-O-benzoyl-β-D-ribofuranosyl cyanide (127 R=CN) in high yield by reacting the bromide 126 with mercuric cyanide. Only the β-isomer was isolated, presumably owing to neighbouring group participation.[112] The orientation of the C-1 substituents is important since,but for a few exceptions,[133,134] only the β-derivatives exhibit therapeutic activities. The value of the ribosyl cyanide 127 is that the various derivatives of the nitrile group have used to elaborate a variety of naturally-occurring C-nucleosides (e.g., showdomycin[120,122] (99), formycin B[134] (101) and oxoformycin (102))



and C-nucleoside analogues.[112]

To this end, Moffatt and coworkers[141a] have prepared 2,5-anhydro-D-allose

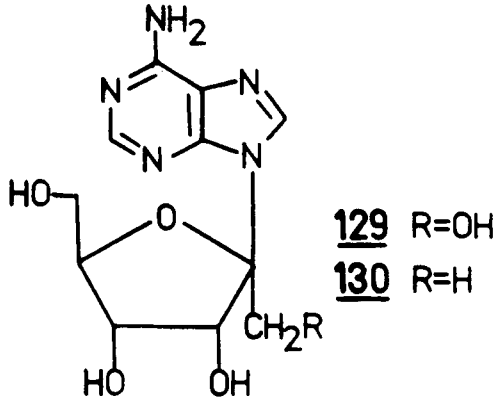
protected with various blocking groups. The key step and key intermediate in formation of these derivatives was the reductive-hydrolysis of the nitrile 127 with Raney nickel and sodium hypophosphite in the presence of 1,2-dianilinoethane to trap the aldehyde as the N,N'-diphenylimidazolidine derivative 128. The aldehyde 127a (R=CHO) could be regenerated



from 128 by mild acid hydrolysis. The aldehyde 127a (R=CHO) or its various protected analogues are key intermediates in the synthesis of a variety of C-nucleosides previously discussed.

5. Ketose N-Nucleosides

The ketose N-nucleosides are a rare group of nucleoside antibiotics of which only two are known. Psicofuranine[113] [angustmycin C, 6-amino-9-(β-D-psicofuranosyl) purine, 129] and decoyinine (2) are antibacterial and

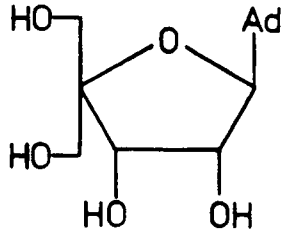


antitumor nucleoside antibiotics elaborated by the Streptomyces. As can be seen in structure 129 (and 2) these nucleosides have the common N-glycosyl

linkage between the sugar and base but the uncommon feature is the hydroxymethyl group at 'C-1' which requires a keto-sugar precursor and which makes the heterocyclic base both acid and base labile. Therefore synthetic approaches to the ketose N-nucleoside must take these properties into consideration.

The synthesis of psicofuranine (129) has been reported by two groups[136a-b] and the synthesis of decoyinine (2) from psicofuranine was reported by Robins and his coworkers.[137]

Farkaš and Šorm[138] synthesized the 1´-deoxy analogue (130) of psicofuranine and found this compound to be inactive against Escherichia coli. A structural isomer 131 of psicofuranine (129) was synthesized by Rosenthal and Ratcliffe[53] via the photoamidation of the enolic sugar 56, however, this analogue no longer possesses the N-ketal structural feature of ketose



131 Ad=Adenyl

nucleosides.

III. RESULTS AND DISCUSSION

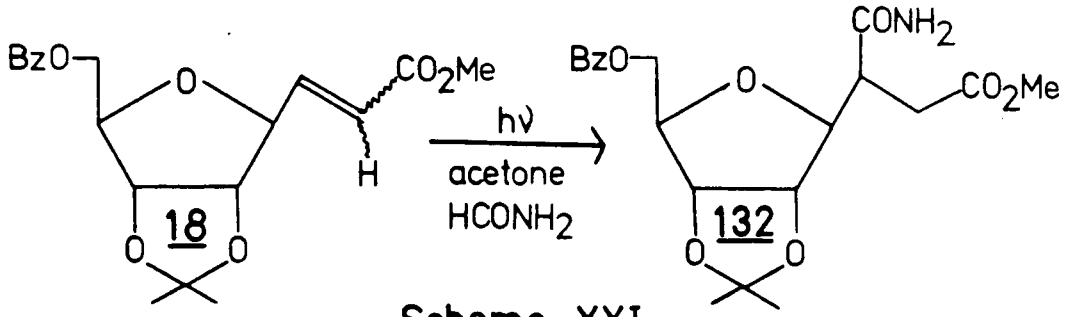
The work to be described has been divided into four basic units. These are: (1) the synthesis of α- and β-dihydroshowdomycin, (2) the synthesis of functionalized precursors to C-nucleosides, (3) the oxidation products of Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-3-enonate (172), a novel exocyclic enolic sugar, and (4) the attempted synthesis of a ketose N-nucleoside. Each unit has been organized according to the outline listed in the table of contents. The mechanistic and stereochemical aspects of the basic chemical reactions have been dealt with in the introduction and a detailed discussion in these areas will only be made where stereochemical assignments appear possible. Details of the experimental procedure and work-up conditions along with spectroscopic data will appear in the experimental section.

1. Synthesis of α- and β-Dihydroshowdomycin: Photoamidation of Methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-2 (and 3)-enonate (18) and (172), respectively.

The work to be presently discussed was undertaken in an attempt to provide a new synthetic path to the antibacterial and antitumor[113] C-nucleoside showdomycin (99). Prior to the start of this work only two practical synthetic routes to showdomycin had been reported.[120,122] Both, however, possessed undesirable synthetic steps such as DMSO-DCC oxidation[120] or reactions involving cyanide reagents.[120,122] In view of the antibiotic properties of showdomycin and the undesirable features of the previous syntheses, the development of a high-yielding, practical synthetic route to this C-nucleoside seemed justified.

Based on the photoamidation of unsaturated sugars by Rosenthal and coworkers[47,51] and on the original photoamidation work by Rokach and Elad[40]

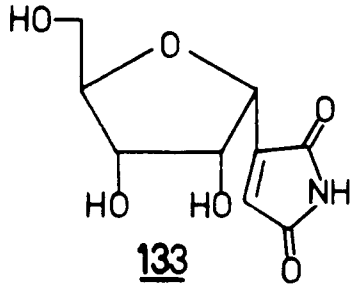
(see Introduction Section 2.1.), it seemed reasonable that photoamidation of the α,β-unsaturated ester sugar derivative 18 should lead to predominant carbamoylation at the β-carbon to give the substituted succinic acid derivative 132 (Scheme XXI), providing the necessary elements for the



Scheme XXI

formation of the maleimide aglycon. Cyclization of 132 followed by dehydrogenation would give the protected showdomycin (99) which could be recovered by mild aqueous acid hydrolysis of the protecting groups.

During the course of this work a novel 3-ene analogue of 18 (described in detail in Section 2.1.) became available and it seemed plausible that this new compound might provide a route to the hitherto unknown α-showdomycin



133

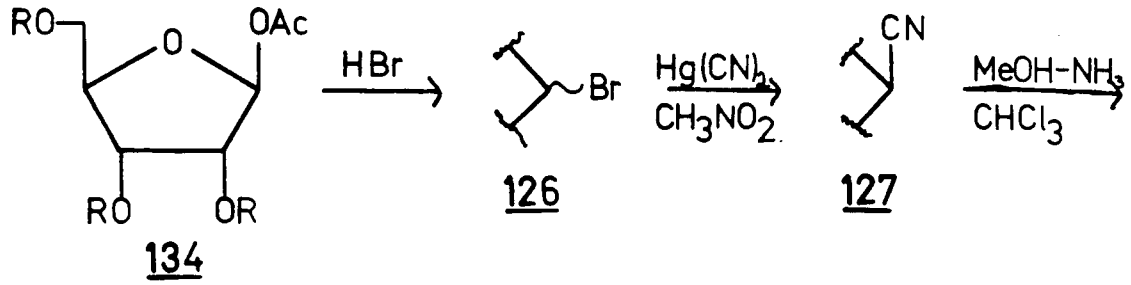
(133). The photoamidation work with this novel compound is described in Sections 1.2. and 1.3.

1.1. Synthesis of normal-(β-) Dihydroshowdomycin via Photoamidation of the Methyl oct-2-enonate 18.

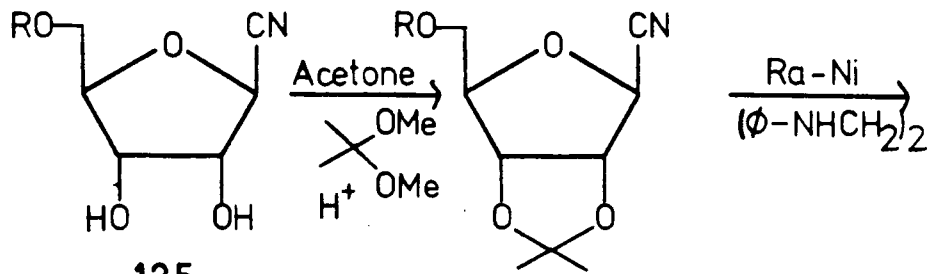
1.1.1. Methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-2-enonate (18).

The title compound was prepared in a five-step process starting from the commercially[139a] available 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribose[140a-b] (134). Compound 134 was converted to the glycosyl bromide 126 with hydrogen bromide. The bromide 126 was then treated with excess mercuric cyanide in nitromethane for 20 hours. The crude 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide[131] (127) was worked up in chloroform solution rather than ethyl acetate to achieve a more efficient removal of the mercuric salts.

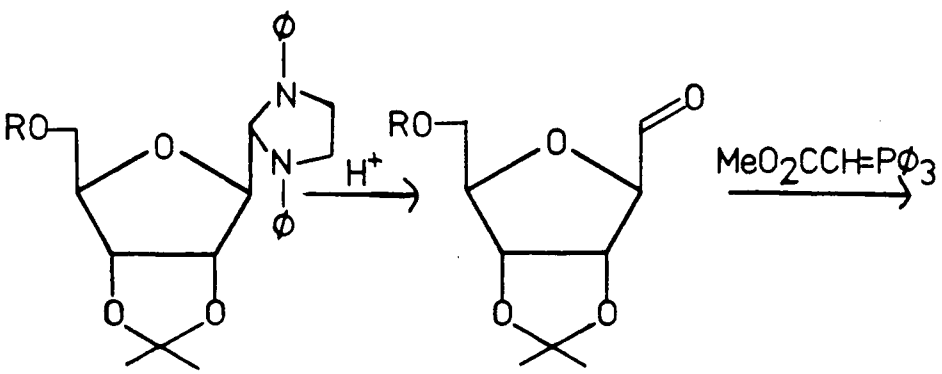
Following the procedure of Moffatt et al.[141a], the cyanide 127 was partially debenzoylated in a chloroform solution of methanolic ammonia to give 5-O-benzoyl-β-D-ribofuranosyl cyanide (135). This vicinal diol 135 was isopropylidenated in a solution of acetone and 2,2-dimethoxypropane with perchloric acid catalyst to afford the 5-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl cyanide (136). The cyanide 136 was reductively hydrolyzed with Raney nickel in presence of 1,2-dianilinoethane to trap the intermediate aldehyde 137 and give 1,3-diphenyl-2-(5-O-isopropylidene-β-D-ribofuranosyl) imidazolidine (138). Finally, the synthesis of the unsaturated ester 18 was achieved by acid-catalyzed hydrolysis of the N-acetal protecting group in acetone-methylene chloride and treating the regenerated aldehyde 137 with(carbomethoxymethylene)triphenylphosphorane in methylene chloride for one hour at room temperature to afford the title compound 18. Column chromatography, with silica gel, of the resulting syrup using 2:1 ether-hexanes as developer afforded a 8:1 mixture of the trans and cis isomers of the title compound. This mixture was used in subsequent reactions without



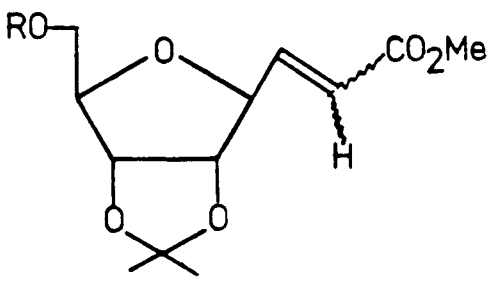
134 126 127



135 136



138 137



18

R=Bz

Scheme XXII

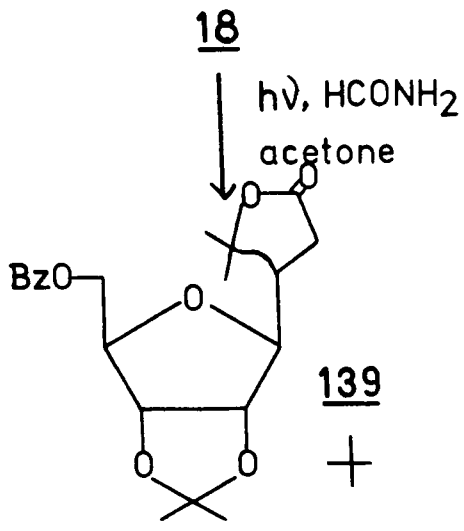
further separation (see Scheme XXII).

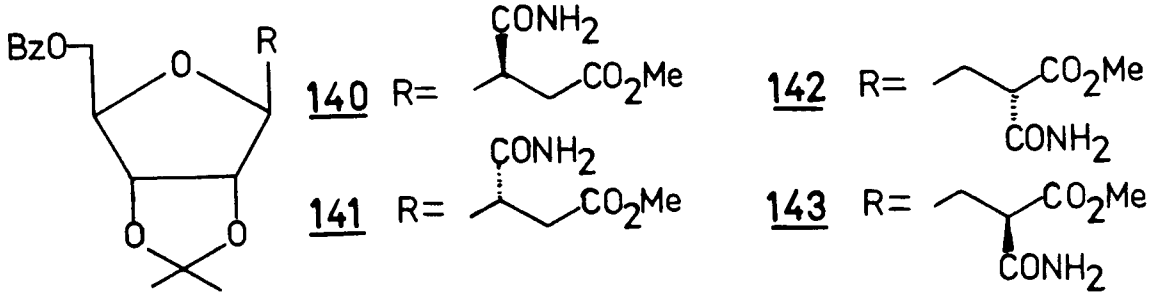
1.1.2. Photoamidation of 18 to give 3-(R,S)-(5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-hydroxy-4-methylpentanoic 1,4-lactone (139), Methyl 4,7-anhydro-8-O-benzoyl-3-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-octonate (140 and 141) and Methyl 4,7-anhydro-8-O-benzoyl-2-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-octonate (142 and 143).

When a solution of the α,β-unsaturated ester sugar derivative 18 in formamide containing acetone and tert-butanol was irradiated through pyrex filter according to Elad's procedure[40], two major product bands could be discerned by t.l.c. of the reaction mixture. The t.l.c. also indicated (by char) significant carbohydrate material of intermediate R_f and lower R_f than the two major bands. Column chromatography on silica gel of the worked-up reaction mixture afforded the two major bands in yields of 10 and 25% yields of the higher and lower R_f bands, respectively.

The faster-moving component was found to be a R,S-mixture of lactone 139 and the slower-moving component was a mixture of the possible formamide addition products 140, 141, 142 and 143.

The lactone mixture 139 was not resolvable by chromatography nor by crystallization from various solvents. The lactones were therefore characterized as a mixture. The n.m.r. spectrum of 139 in benzene-d_6 showed six high-field signals attributed to the methyl resonances. Two of these signals were very strong indicating the overlap of two methyl resonances and the other four were moderate strong for the remaining methyls indicating the presence of eight methyl groups. The loss of the low-field vinylic signals of 18 and the presence of new signals at ca. δ2.2 (three hydrogen





multiplet) suggested addition to the double bond had taken place, also, the methoxy signal of 18 had disappeared possibly due to the hydrolysis of the ester but no low-field signal attributable to a carboxylic acid proton was present.

Moreover, the i.r. spectrum of 139 was free of absorbances above 3000 cm^{-1} and possessed two strong carbonyl signals at 1780 and 1728 cm^{-1} due to the γ-lactone and benzoate, respectively. Also, the absorbance at 1672 cm^{-1} (C=C) of 18 was no longer present. The mass spectrum of 139 possessed a weak signal of 390 for the molecular ion (m^+) and a very strong fragment at 375 (m^+-CH_3) indicative the formation of an acetoxonium ion from the 0-isopropylidene group of 139.[141b]

These results indicate that a ketyl radical [$(CH_3)_2\dot{C}OH$] had added to C-2 of 18 forming a resonance stabilized radical (similar to 38) which abstracts a hydrogen and intramolecularly cyclizes to give the γ-lactones 139 (see Introduction, Section 2.1, Scheme V). Addition of the ketyl radical

to the α-carbon may have occurred (although not isolated) but the resulting β-hydroxy ester would require special conditions[142] to form the necessary β-lactone which would also have an i.r. absorbance of a larger frequency than that observed.[143a] Rokach and Elad[40d] also reported the isolation of γ-lactones from benzophenone-initiated photoamidation of α,β-unsaturated esters.

The structure of amides 140 through 143 could not be elucidated by spectral means alone because these isomers could not be separated by chromatography nor by crystallization. The structures were ultimately established by chemical transformation of the mixture (described below, Sections 1.1.3. and 1.1.4.). Therefore, spectral analysis of the mixture was used to determine the presence of the carbamoyl group and show that formamide did add to the carbon-carbon double bond.

The n.m.r. spectrum of 140-143 in deuterchloroform showed, as with lactone 139, the disappearance of the low-field vinylic protons, with the generation of a broad three-proton multiplet in the δ2.24-3.25 region (H-2 and H-3). The spectrum also showed one broad signal at δ6.40 (one-proton) and two broad signals at δ5.88 and 6.00 (one-proton) which were D_2O-exchangeable, indicating two major amide products. Surprisingly, all three methyl groups were present as singlets. Based on the n.m.r. spectrum and on mechanistic grounds the substituted malonic acid derivatives 142 and 143 were not expected in any appreciable amounts because the α-hydrogen of the malonates resonate[47] at δ3.50-δ3.65 and no appreciable signals were present (except for $OC\underline{H}_3$) in that region and since both olefinic carbons of the olefinic carbon chain possessed hydrogens, β-addition of the carbamoyl radical was expected to occur (Section 2.1.).

The i.r. spectrum of the above amide mixture showed amide peaks at 3180, 3365, 3480 and 1690 cm^{-1}, indicative of a primary amide.[143b] Again the olefinic absorption of 18 was absent. Though a molecular ion (m^+) peak was not observed in the mass spectrum of the mixture 140-143, the characteristic (m^+-CH_3) was predominant along with a strong signal at m/e 376 (m^+-OCH_3) indicating the cyclization of 140 and 141 to form the protonated maleimide fragment. Elemental analysis of 140-143 also established the empirical formula of the mixture to be at 1:1 telomer of 18 and formamide.

Although Rokach and Elad[40d] only isolated alkylated succinic acid derivatives from the photoamidation of α,β-unsaturated esters, the unsaturated acid parent compounds were simple straight chain compounds. Rosenthal and Ratcliffe's[47] substrate 46 (see Introduction, Section 2.1.) was fully substituted at the β-position and gave, exclusively, the malonic acid derivative upon photoamidation and they attributed this reversal to a greater stabilization of the C-3 radical over the alternate radical formed by carbamoyl attack at C-3. However, the high degree of regiospecificity was no doubt aided by the steric bulk of the protected sugar ring attached to C-3 of compound 46. This steric interaction presumably accounts for the presence of the substituted malonic acid derivatives 142 and 143. Surprisingly, the presence of the chiral sugar in 46 did not contribute to the optical induction of the amide products (47 and 48) which were formed in equal amounts. This lack of stereoselectivity is presumably due to the photochemical cis-trans isomerization of the initially geometrically pure starting material (i.e., (Z)-46), brought about by triplet sensitization of the substrate by excited triplet acetone (Section 2.2.). Amides 140 and 141 were found (Subsection 1.1.3.3.) to be synthesized in equal amounts from a predominantly (89%) trans-18 and this lack of optical induction is also attributed to the geometric isomerization of the starting material to

give a photostationary state with approximately the same composition of geometric isomers.

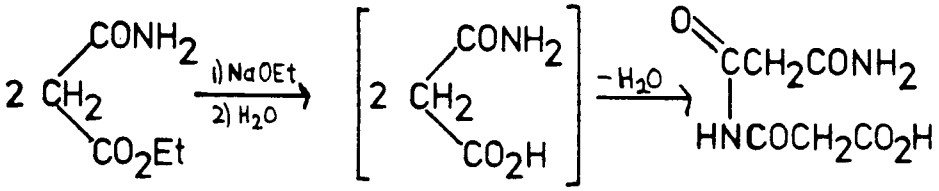
The n.m.r. spectra of other components isolated from the chromatography column indicated more than six protons in the high-field region of the isopropylidene methyls; these compounds were assumed to be other ketyl or acetonyl[40a] radical addition or diradical (not telomers) addition products. Since none of these compounds were isolated pure, these components were not further studied.

The yield of the formamide addition products was rather low (25% cf., Rosenthal and Ratcliffe[47], 45%, and Rokach and Elad[40d], 77-81%). This low yield may be the result of a competition for the excited triplet energy of acetone[40d], the reaction with 18 which leads to a geometric isomerism and the reaction with formamide which leads to hydrogen atom abstraction. When the former process is more efficient than the later, poor yields of formamide-ester adduct result along with an increase in acetone addition products. Rokach and Elad[40d] found that benzophenone provided efficient hydrogen atom abstraction with the isomerization as an unavoidable side reaction and this initiator gave high yields of the desired amide products.

1.1.3. Cyclization of 140 and 141 to give the Glycosylated Succinimide Derivatives

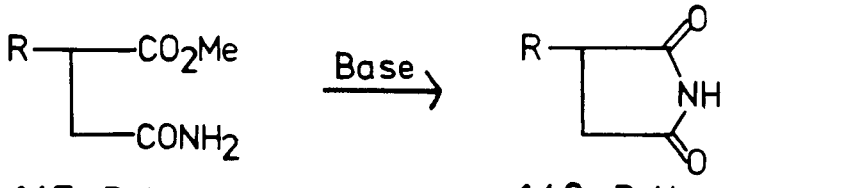
The reaction between amides and esters can either be thermally induced or base-catalyzed.[144] However, disproportionation of primary amides occurs at elevated temperatures and may compete with the ester reaction. Base-catalyzed intramolecular acylation of amides by neighbouring ester groups have been reported.[145a] Treating ethyl malonamate (144) with sodium ethoxide,

de Mouilpied and Rule[145b] found no ring compound but rather, acid 146 resulting from the dimerization of malonamic acid (145); however, when



144 145 146

methyl succinamate (147) was the substrate, succinimide (148) was isolated, albeit in rather small yield. Sondheimer and Holley[145c] found that



147 R=H 148 R=H

149 R=NHCO$_2$CH$_2$Ø 150 R=NHCO$_2$CH$_2$Ø

treatment of carbobenzoxy-L-asparagine methyl ester (149) with sodium hydroxide gave good yields (77%) of the cyclic aminosuccinimide 150. Keeping in mind the thermal instability of sugar derivatives and the base labile groups present, various methods were attempted to form the succinimide aglycon from the amido-esters 140 and 141. The retention of the benzoate group was desirable in the event the subsequent dehydrogenation reaction required protected hydroxyl groups.

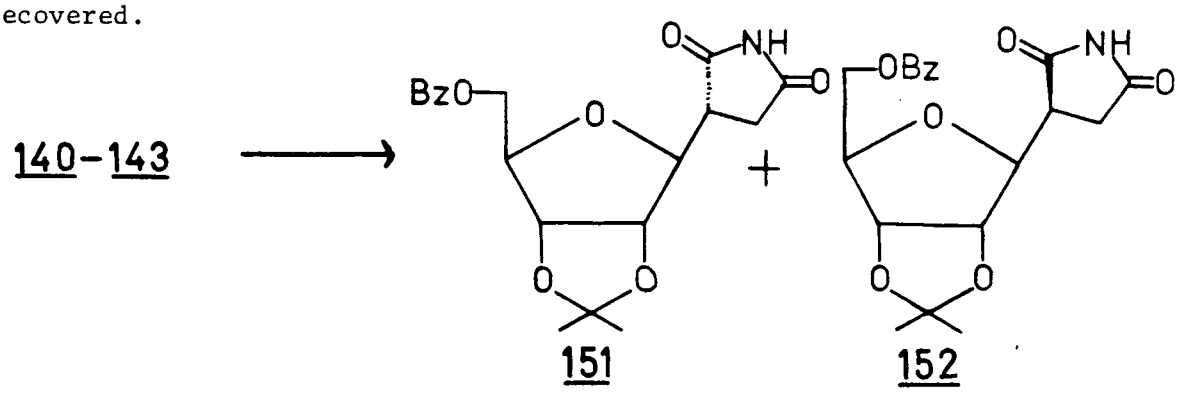
1.1.3.1. Attempted Cyclization of 140 and 141 in Refluxing Solvents

Taking into consideration the base sensitive benzoate and methyl ester, as well as, the thermal instability of the benzoate, refluxing the amide mixture 140-143 in a mildly basic (weakly nucleophilic), high-boiling point solvent appeared to a sensible route to the formation of succinimide ring from 140 and 141. When the amide mixture 140-143 was refluxed in

either pyridine or xylene for five hours no change in the starting mixture was observed.

1.1.3.2. Cyclization of 140 and 141 by Thermal Ring Closure in Absence of a Solvent to Give 3-(R) and (S)-(5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl) succinimide (151) and (152).

When a solvent free sample of amides 140-143 was heated at approximately 200° under reduced pressure (∿100 torr) two higher R_f products could be detected by t.l.c. after a few minutes. Prolonged heating produced larger amounts of the faster moving materials but simultaneously a greater amount of decomposition (charring) of the reaction sample occurred. Initial purification of the reaction mixture on a weakly acidic resin column followed by chromatography on a silica gel plate gave two protected epimeric ribofuranosylsuccinimides 151 and 152 in yields of 6 and 7%, respectively. A small portion (25%) of the starting mixture was also recovered.



The n.m.r. spectrum of the higher R_f (18:4:1 benzene-ethyl acetate-ethanol as developer) succinimide 151 in deuterochloroform indicated the presence of predominantly one compound (∿95% purity, impurity mainly lower R_f succinimide). The spectrum showed two sharp singlets at δ1.38 and 1.57 for the methyl protons of the isopropylidene group, as well as, a loss of the methoxy signal of the methyl ester. The broad signal at δ7.90 was attributed to the imide proton (NH) and an ABM pattern centered at δ3.0 was

assigned to the protons of the succinimide ring (J_{gem} 18.0 Hz). The sugar protons were well separated and assignable (see Experimental).

The n.m.r. spectrum of the lower R_f succinimide 152 in deuterochloroform indicated a second diasteromeric succinimide of lower purity (~90%, mainly contaminated with 151). The imide (NH) proton was at lower field, δ8.20, the succinimide protons exhibited an A_2M spitting centered at δ3.0 (ABM pattern in deuterobenzene) and although the sugar protons signals were within a 50 Hz packet, they were assignable with the aid of irradiations, coupling constants and comparison with a spectrum of 152 in deuterobenzene.

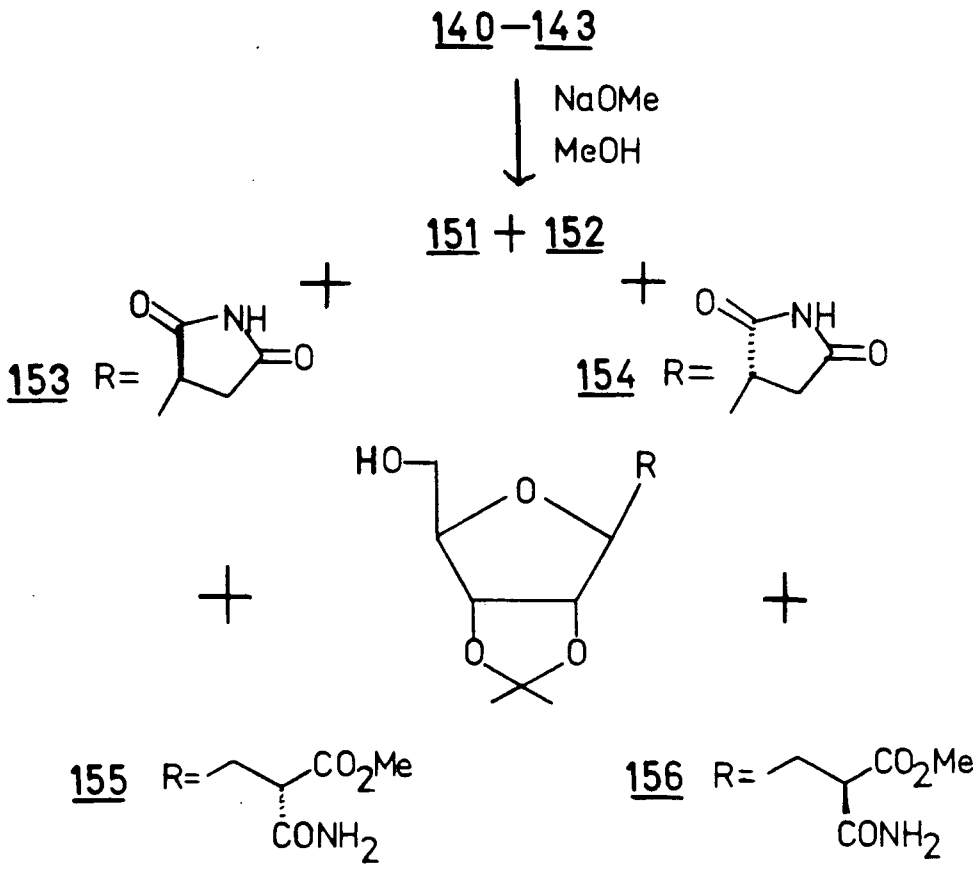
Both succinimide products 151 and 152 were found to possess labile O-isopropylidene protecting groups and storage of the syrups under ambient (room temperature) conditions caused partial hydrolysis of the blocking group. Therefore, the succinimide products containing O-isopropylidene groups should be kept refrigerated and dry. The syrups also had a tendency to crystallize but insufficient quantities prevented recrystallization of these samples.

No other products (e.g., disproportionation products) from the thermal cyclization of the amide mixture were detected; however, due to the low yields of the succinimide products and large amount of decomposition of the reaction mixture no firm conclusion could be made about the composition of the starting amide mixture. Therefore, it was necessary to find a method to selectively derivatize the components of amide mixture without decomposing any of the components. Due to the low solubility of the amides 140-143 in aqueous solvent systems and the possible saponification of the methyl ester or the amide with sodium hydroxide, it was decided that methanolic sodium methoxide would be the most suitable of the base-catalyzed ring-closure procedures.

1.1.3.3. Treatment of Amides 140, 141, 142 and 143 with Methanolic Sodium Methoxide to give 151, 152, 3-(S) and (R)-(2,3-O-isopropylidene-β-D-ribofuranosyl) succinimide [(S) and (R)-dihydroshowdomycin acetonide] (153) and (154), and Methyl 4,7-anhydro-2-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and D-altro)-octonate (155) and (156)

When the amide mixture 140-143 was treated with 0.5 equivalents of methanolic sodium methoxide six compounds, 151, 152, 153, 154, 155 and 156, were produced. These products were separated chromatographically on a column of silica gel to give three major charring components.

The faster-running component was found, by n.m.r. spectroscopy, to be a 50/50 mixture of the protected ribosylsuccinimides 151 and 152 (55% combined yield) previously isolated (Section 1.1.1.2). The fractions of these two stereoisomers were partially resolved but no further attempts were made to separate them because the possible conversion of these succinimide derivatives to the analogous maleimide compound would destroy the chirality of the aglycon to give identical products and the showdomycin (99) five-membered base ring.



The fractions of the second component, eluted from the chromatography column, upon close t.l.c. analysis were also found to consist of two closely overlapping compounds (153 and 154). Fortunately, the 3-S-succinimido derivative 153 was slightly more mobile on the silica gel adsorbant and also charred an initial pink upon spraying with acid and heating (the lower R_f compound 154 charred black).

The structure of compound 153 was easily deduced from its n.m.r. spectrum (in $CDCl_3$, see Figure 2a). The spectrum clearly showed two D_2O-exchangeable protons at δ2.31 and 8.83 for the 5′-primary hyroxyl proton and the succinimide proton, respectively. The methoxy methyl along with the aromatic signals were no longer present while the other protons signals were easily assignable from irradiations and coupling values. Upon changing the spectroscopic solvent to dimethylsulfoxide-d_6, the primary hydroxyl

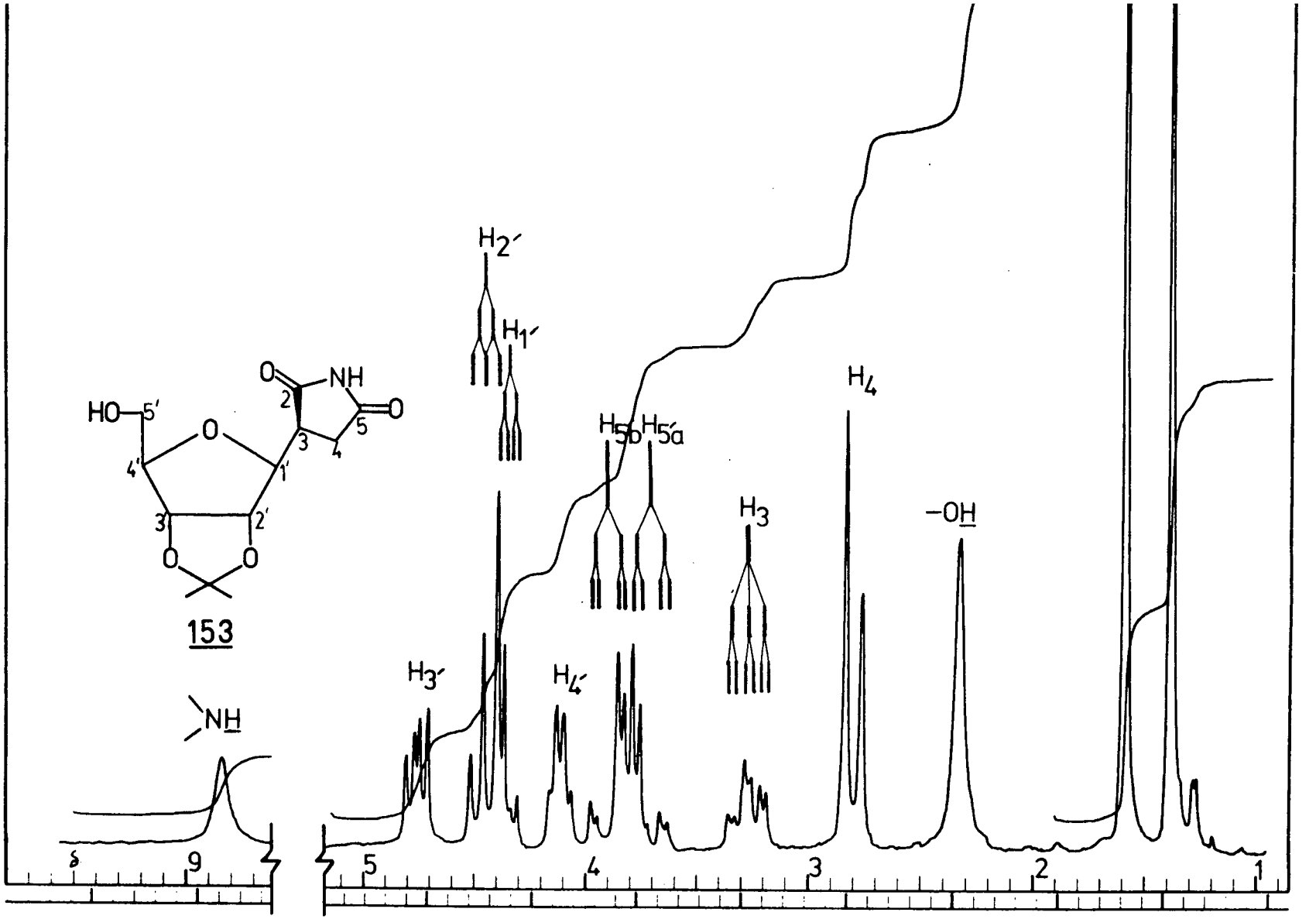


Figure 2A. Partial 100 MHz Proton N.M.R. Spectrum of 3-(S)-(2,3-O-isopropylidene-β-D-ribofuranosyl)succinimide [(S)-dihydroshowdomycin acetonide, 153] in $CDCl_3$.

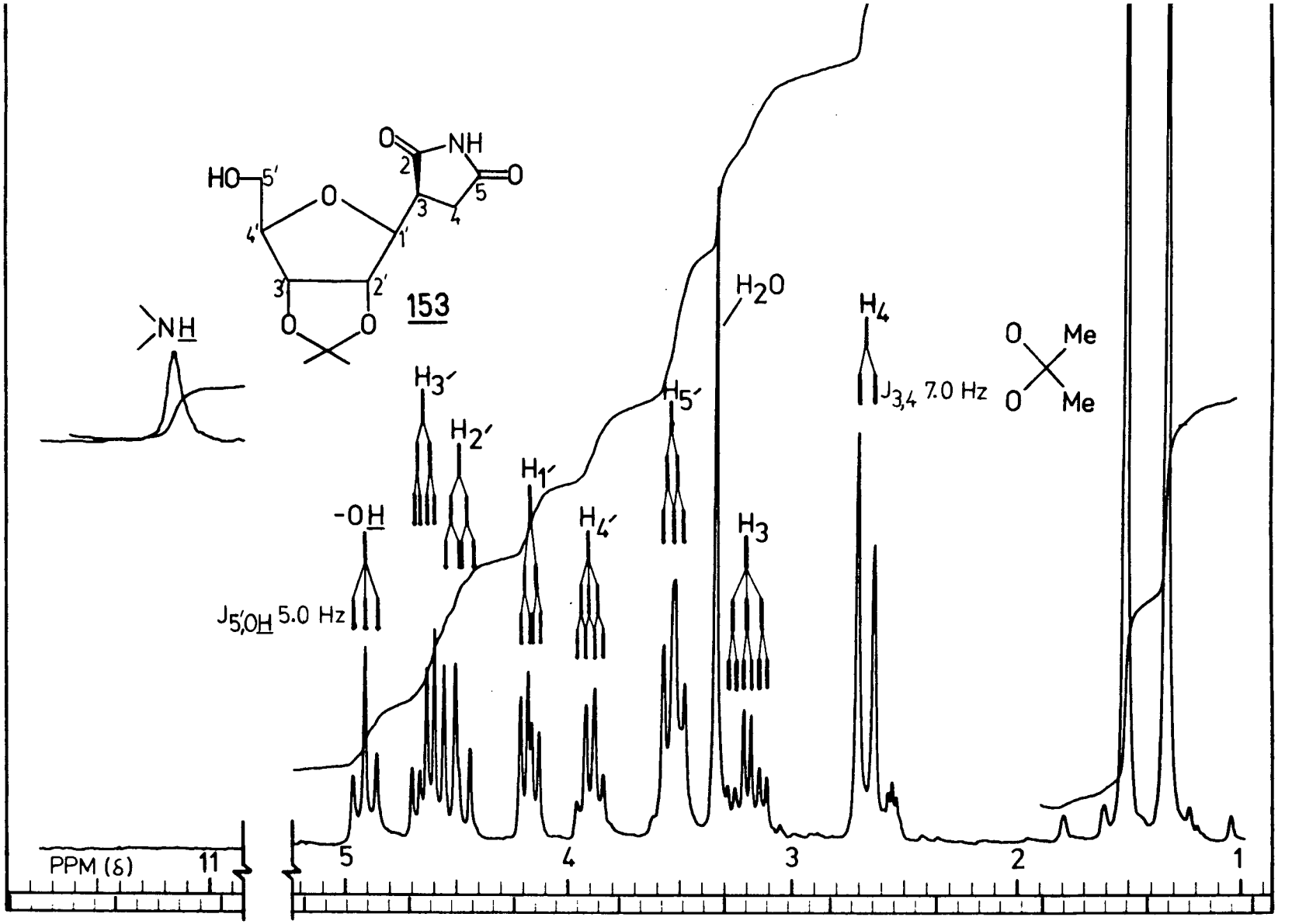


Figure 2B. Partial 100 MHz Proton N.M.R. Spectrum of (S)-Dihydroshowdomycin Acetonide (153) in DMSO-d_6.

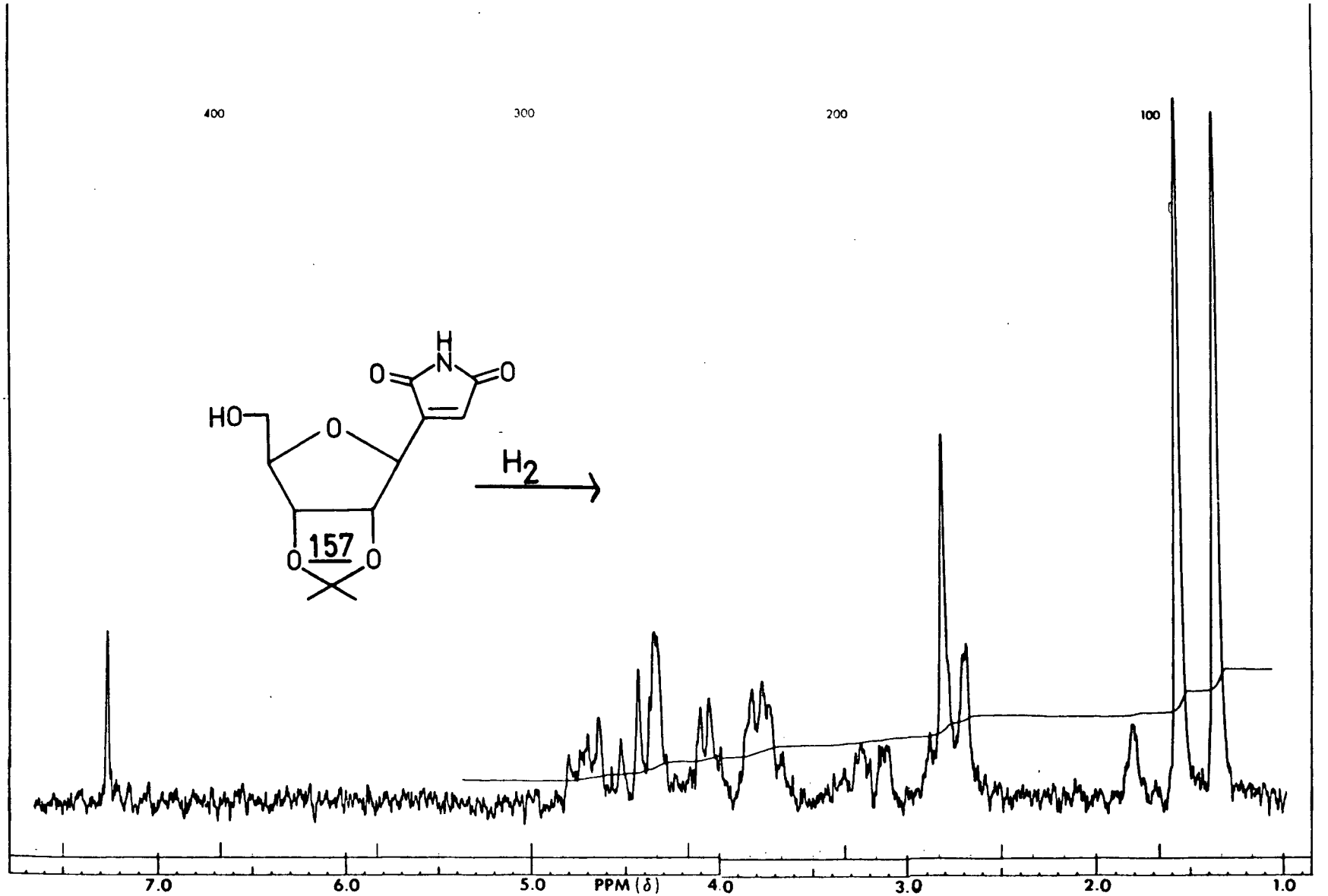
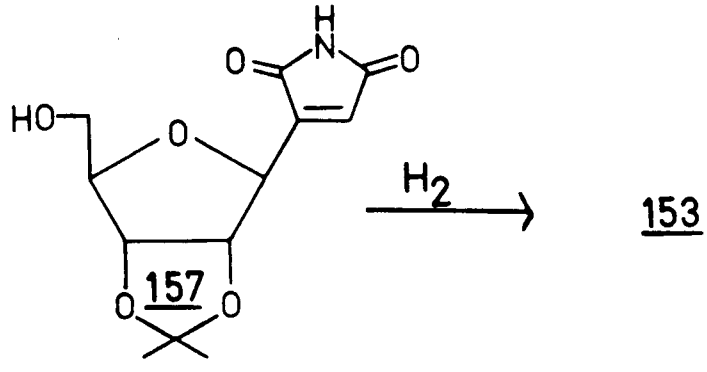


Figure 3. 60 MHz Proton N.M.R. Spectrum of the Hydrogenation Product of Showdomycin Acetonide (157) in $CDCl_3$.

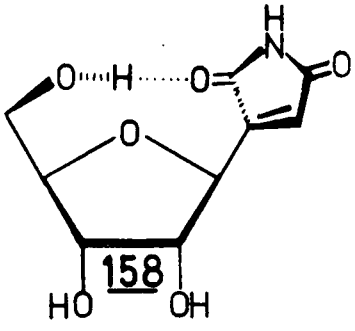
proton shifted downfield to δ4.87 and exhibited a triplet with a coupling value of 5.0 Hz with the vicinal protons on C-5′ (also D_2O-exchangeable); thereby, establishing the presence of the primary hydroxyl group.[146a]

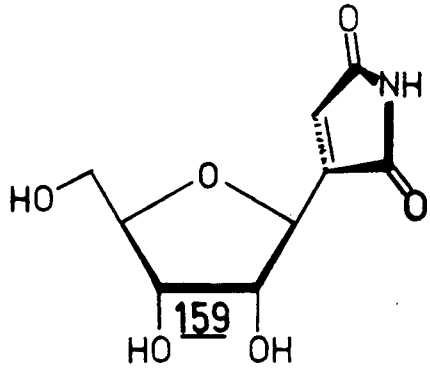
Unequivocal proof of structure of compound 153 came from a comparison of the n.m.r. spectrum of 153 in deuterochloroform with that of the hydrogenation product[146b] of 2′,3′-O-isopropylidene-showdomycin (157) (see Figure 3). The two spectra, except for the position of the D_2O-exchangeable signals, were identical.



In the original paper by Nakagawa et al.[118a], the hydrogenation product 153 was the only succinimide derivative reported. This stereospecific reduction is also supported by the title of n.m.r. spectrum in Figure 3 and in a personal communication with the author. Townsend and coworkers[118c] also reported a highly stereoselective hydrogenation of showdomycin (99) to give the de-isopropylidenated derivative of 153 (see Section 1.1.7.). The selectivity in the hydrogenation of showdomycin (99) or its acetonide 157 may be due to a conformational preference of the maleimide ring. In order to minimize steric interactions with the furanoid ring of 99 or 157, a plane which is perpendicular to the maleimide ring and intercepts the C-3/C-1′ bond would bisect the angle O-4′/C-1′/C-2′. This particular conformation has two possible rotamers 158 and 159 and structure 158 possesses the least amount of steric interaction with H-2′. Structure 158 also is capable of intramolecular hydrogen-bonding between

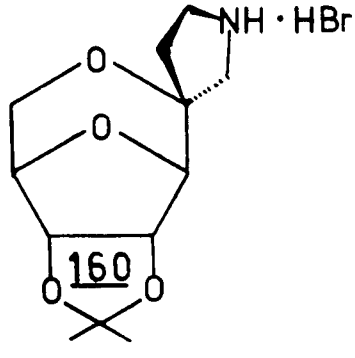
the C-5′ hydroxyl and the C-2 oxo group. The conformational preference of showdomycin to structure 158 has been verified by X-ray analysis[147] and theoretical calculations.[148]





The X-ray analysis also shows that the C-5′ hydroxyl is staggered between O-4′ and C-3′.

If this conformation preference is only slightly affected by the presence of the 2′,3′-O-isopropylidene (either enhancing or lessening the preference) hydrogenation should proceed preferentially from the 'exo-face' (back-side on structure 158) of 158 to give predominantly the 3-S stereoisomer. Therefore it is suggested that the higher R_f dihydroshowdomycin acetonide 153 is the 3-S diastereomer. This conformational preference under reaction conditions is also supported by the synthesis[118b] of N-methylbisdeoxycycloshowdomycin acetonide hydrobromide (160) which from X-ray structure analysis proved to be the 3-S diastereomer.



Compound 160 is synthesized from the base-catalyzed intramolecular Michael-type addition of the 5'-hydroxyl group to the double bond. Addition via structure 158 would lead to the 3-S isomer which was isolated and addition via structure 159 would give the 3-R isomer which was not obtained. Therefore, chemical, structural, and theoretical considerations support the above assignment of compound 153 as the 3-S-succinimide derivative. (See Section 1.1.9. for n.m.r. spectral correlation support.)

Interestingly, compound 153 was found to crystallize quite readily in chloroform to form a 1:1 complex with the solvent. Solutions as low as 0.5% would form crystals at room temperature. The complex was verified by micro-analysis which gave the expected carbon, hydrogen and chlorine content.

The lower R_f, 3-R-succinimide derivative 154 could not be purified as easily as its epimer 153. The n.m.r. spectrum of the lower R_f component isolated by chromatography indicated the presence of at least two minor contaminants. The presence of aromatic signals along with a strong signal in the methoxy region (δ3.5-3.8) suggested trans-esterification products either inter- or intramolecularly formed. Pure 154 was obtained by selective crystallization and its n.m.r. spectrum in dimethylsulfoxide-d_6 (Figure 4) showed no aromatic nor methoxy resonances and possessed a D_2O-exchangeable signal at δ11.15 for the imide proton. The other proton signals were again well separated and easily assignable by coupling values and irradiations. The mass spectra of 153 and 154 were nearly identical possessing a very weak peak of 272 ($m^+ + H$) and a very strong expected signal at 256 ($m^+ - CH_3$) from the formation of the acetoxonium ion.

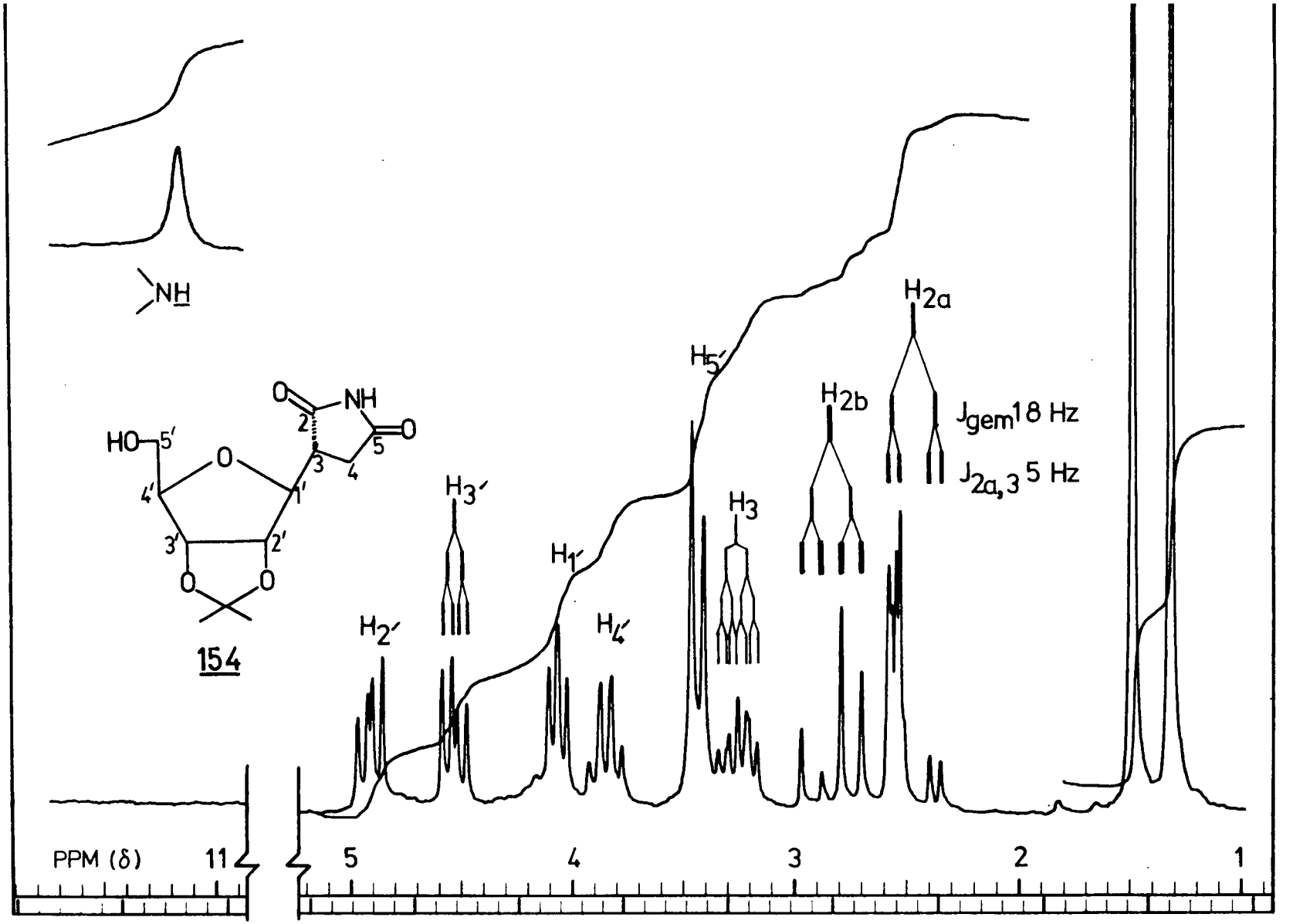


Figure 4. Partial 100 MHz Proton N.M.R. Spectrum of 3-(R)-(2,3-O-isopropylidene-β-D-ribofuranosyl)succinimide [(R)-dihydroshowdomycin] (154) in DMSO-d_6.

The third and final component eluted from the silica gel column consisted of a mixture of the α-carbamoylation adducts 155 and 156. These components could not be chromatographically separated nor could they be crystallized. The i.r. spectrum of this mixture showed amide peaks at 3500, 3360 (N-H), 1680 (C=O) and 1580 cm^{-1} (Amide II)[143b] (1725 cm^{-1} (CO_2Me)). Expectedly, no olefinic absorbances were present. The exact composition of this mixture is unknown since the n.m.r. spectrum in deuterochloroform showed only singlets for the methyl signals. The basis for assignment of this component as a mixture of the α-carbamoyl esters is based on chemical shifts in the n.m.r. spectrum of the above mixture. The H-3 resonance occurs at fairly high field (δ2.20) which indicates the presence of a methylene group which does not have electron withdrawing groups directly bonded. The methylene group is broad and does not possess any fine structure indicating the presence of a mixture. A low-field multiplet at δ4.68 assigned to either H-5 or H-6 possess five signals also indicating a mixture of compounds. The final evidence for the malonamic esters structure comes from the position of α-hydrogen (δ3.51) which is in close agreement to previous α-hydrogen of this structure (Rosenthal and Ratcliffe[47], δ3.53) and which resonate at lower-field than the α-hydrogens of the β-carbamoylation products. Two broad D_2O-exchangeable signals were also present at δ6.40 and 6.80 indicating the possibility of a 50:50 mixture or else a non-equivalence of the amide protons. The mass spectrum spectrum exhibited a strong acetoxonium peak at 288 ($m^+ - CH_3$).

1.1.4. Debenzoylation of Compounds 151 and 152 to give 153 and 154

Treatment of an equal mixture of the protected ribosylsuccinimides 151 and 152 with sodium methoxide gave two closely overlapping bands on the t.l.c. plate. Chromatography of these components on a column of silica gel gave

two compounds which had n.m.r. spectra identical to the (R) and (S)-dihydroshowmycin (153) and (154) isolated in the preceding section.

Unfortunately, neither starting compounds 151 nor 152 was debenzoylated as a pure compound nor as a predominant component in a mixture of the two in order to directly relate the benzoylated and corresponding debenzoylated dihydroshowdomycin derivatives. However, based on the fact that the lower R_f benzoylated compound 152 chars pink as does the higher R_f debenzoylated compound 153, along with the fact that the n.m.r. spectra of these two compounds have H-3′ at lower field than H-2′ and that the succinimide protons exhibit an A_2M splitting pattern, the lower R_f benzoylated compound 152 is tentatively assigned the 3-S configuration.

Analogously, the other two dihydroshowdomycin derivatives (151 and 154) both char black and the n.m.r. spectra have H-2′ at lower field than H-3′ and the succinimide protons exhibit an ABM splitting pattern. Therefore, the higher R_f benzoylated compound 151 is tentatively assigned the opposite, 3-R, configuration. (See Section 1.1.9. for a discussion on the significance of these chemical shifts).

1.1.5. Attempted Dehydrogenation of Succinimide and its Alkylated Derivatives.

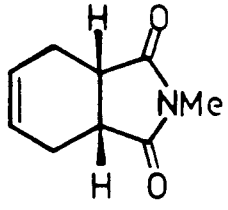
Dehydrogenation of six-membered alicyclic or heterocyclic five- and six-membered rings may be achieved in a number of ways.[149a] However, the dehydrogenation of an aliphatic compound to give a double bond in a specific location is much more difficult unless the new double bond can be in conjugation with a double bond or an unshared pair of electrons already present. The dehydrogenation process is also enhanced by the presence of unsaturation in the substrate.[149b] There are three types of reagents most frequently used to effect dehydrogenation or aromatization. They are[149c]:

1) Hydrogenation catalyst such as platinum, palladium and nickel. In this case the reaction is the reverse of double bond hydrogenation.

2) The elements sulfur and selenium (and selenium dioxide).

3) Quinones, which are reduced to the corresponding hydroquinone. The more reactive and most widely used is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

For example, treatment of the unsaturated fused-ring succinimide compound 161 with nickel peroxide[150] gave the corresponding aromatic compound, N-methylphthalimide (162), in 62% yield while no attempts were made to dehydrogenate the corresponding saturated compound 163.



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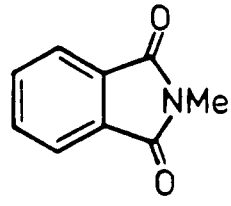

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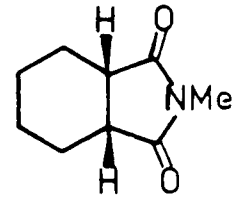


163

1.1.5.1 Palladium and Succinimide

When a mixture of succinimide, biphenyl (B.P. 254-255°) and 10% palladium on charcoal was refluxed for 25 hours while carbon dioxide was passed through the solution, succinimide was quantitatively recovered. No attempts were made to modify this reaction.

1.1.5.2. Treatment of Compound 151, 152, 153 and 154 with Nickel Peroxide

Treatment of the protected ribosylsuccinimides 151 and 152 in refluxing xylene with nickel peroxide[149c,150,151] for 60 hours produced only broad u.v. active slow charring bands and base-line materials. The isolated crude syrup was five-times the starting materials weight; therefore,

polymerized solvent along with decomposed carbohydrate materials were presumably the main components and were not further analyzed.

Treatment of the debenzoylated succinimide derivatives 153 and 154 with nickel peroxide in refluxing benzene for 26 hours gave negative results. The starting material was present but no u.v. active component was produced.

Treatment of 153 and 154 with nickel peroxide in water for 7 days also gave negative results.

Difficulties were anticipated with use of the nickel peroxide oxidative dehydrogenation process because the presence of a methoxymethyl substituent on the cyclic substrate was reported[150] to decrease the efficiency of the dehydrogenation process. Also, all the substrates utilized possessed endocyclic unsaturations which lead to aromatic products upon dehydrogenation.

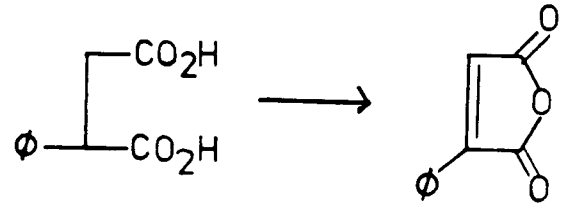
1.1.5.3. Attempted Dehydrogenation of Compounds 153 and 154 with DDQ.

Treatment of the ribosylsuccinimides 153 and 154 with DDQ[149a-c,152a,b] in refluxing dioxan for 3 days gave the anticipated precipitation of the dihydroquinone; however, chromatography of the reaction mixture gave no u.v. active charring bands.

This result was not totally unexpected since Evan et al.[150], reported that DDQ gave poorer results with oxazolines compare to dehydrogenation with nickel peroxide.

As for the other methods mentioned in the introduction to this section (1.1.5), the use of sulfur require dehydrogenation in a melt[149c] (∿250°) in which the starting carbohydrate is not expected to be very stable. The same problem exists with the use of elemental selenium[149c].

The use of the selenium dioxide[149c] reagent, however, may give the desired result since Barnes and Barton[153] reported the dehydrogenation of cis hydrogens from triterpenoid 1,4-diketones to enediones. However, Hill[154] showed that phenylsuccinic acid (164) can be dehydrogenated with selenium dioxide to give phenylmaleic anhydride (165) but the phenyl group appears essential to the reaction since succinic acid and ethylsuccinic acid do not react.



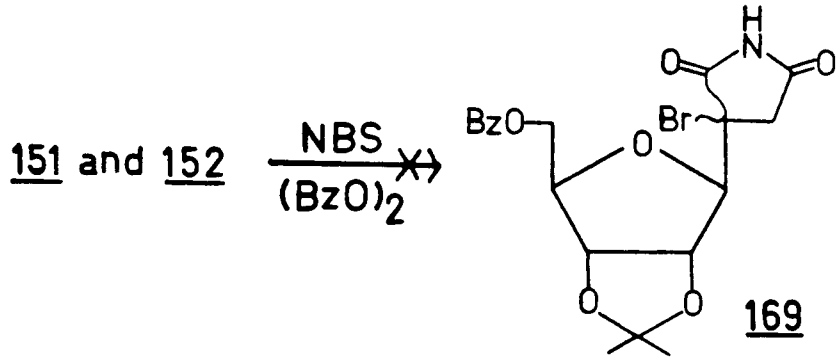
164 165

The high degree of difficulty in dehydrogenating the succinimide ring to the corresponding maleimide in one step is exemplified by the Russian[155] process in which succinimide was heated to 300-400° in the presence of a Vanadium oxide catalyst to give maleimide.

1.1.6. Attempted Synthesis of (R,S)-3-Bromo-3-(5-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)succinimide (169).

Due to the difficulty involved with a one step dehydrogenation of an alkylated succinimide it was thought that substitution of an eliminatable group at the tertiary α-position of the alkylated succinimides 151 and 152 might lead to the desired maleimide product. The difficulty in this approach was due to the fact that the carbohydrate moiety also possesses tertiary hydrogen on the furanoid ring.

It was hoped that treatment of the protected sugars 151 and 152 with NBS would lead to selective bromination at C-3 to give tertiary bromide (169) or perhaps directly to unsaturated maleimide product.[156,157a,b]

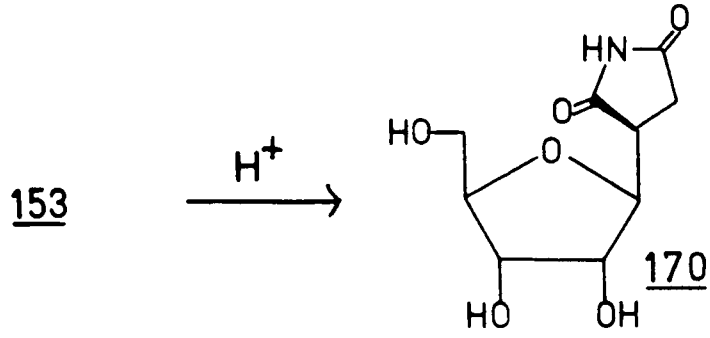


1.1.6.1. Treatment of 151 and 152 with NBS.

When 151 and 152 were treated with NBS and benzoyl peroxide in refluxing carbontetrachloride for 32 minutes, a five-component mixture resulted. The n.m.r. spectrum of the major higher R_f (cf. starting material) band in deuterochloroform indicated the presence of the tertiary hydrogen of the alkylsuccinimide along with an absence of any vinylic protons (ca. δ6.8[118c]) due to an alkylmaleimide group.

1.1.7. 3-(S)-(β-D-ribofuranosyl)succinimide (170)

Treatment of the (S)-dihydroshowdomycin acetonide (153) with a solution of 3:1 trifluoroacetic acid-methanol gave the de-isopropylidenated compound 170 in almost quantitative yield. The clear syrup was purified by chromatography on Bio-Rex 70 cation exchange resin (H^+ form).

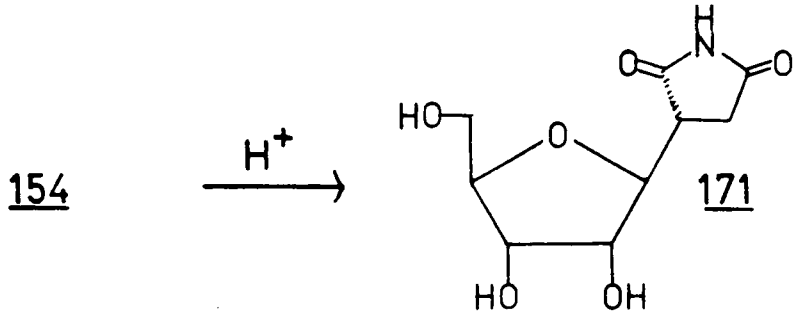


The n.m.r. spectrum of (S)-dihydroshowdomycin (170) in dimethylsulfoxide-d_6 was consistent with the assigned structure, having three D_2O-exchangeable proton at δ4.63 and one at δ11.0. From the coupling values and chemical shifts of the remaining signals, the doublet of doublets at δ4.06 was assigned to H-1′. This assignment was confirmed

when irradiation of H-3 collapsed this signal to a doublet. The coupling constant between H-1′ and H-3 ($J_{3,1'}$) was 2.0 Hz which increased to 2.5 Hz upon changing the spectroscopic solvent to D_2O containing a few drops acetic acid-d_4. This latter value is identical to the value reported by Townsend and coworkers[118c] for the major product of the hydrogenation of showdomycin (99).

1.1.8. 3-(R)-(β-D-ribofuranosyl)succinimide (171)

Identical treatment of the (R)-acetonide 154 as above gave 3-(R)-dihydroshowdomycin (171). The n.m.r. spectrum of 171 in dimethylsulfoxide-d_6 again possessed three mid-field and one low-field D_2O-exchangeable protons. As with its acetonide and benzoylated acetonide precursors (154



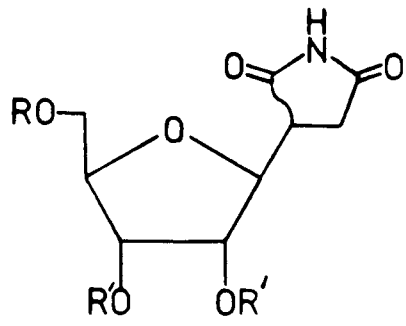
and 151, resp.), the H-2′ signal of 171 resonated at lower field than its H-3′ signal (δ4.30 and 4.00, resp.). (This pattern was also retained for the 3-S-isomers 152, 153 and 170 with H-3′ resonating at lower-field). The coupling constant $J_{3,1'}$ for 171 was 6.0 Hz; therefore, this isomer, expectedly is not the same as Townsend's[118c] major hydrogenation product.

1.1.9. General Considerations

As mentioned in Section 1.1.4. the positions of the n.m.r. resonances of H-2′ and H-3′ of compounds 151, 152, 153 and 154 (along with other information) were used to assign the configuration of C-3 of compounds 151 and 152. The question arises as to why the relative positions of these two resonances change in going from the 3-R-to the 3-S-isomer. From molecular

models of compounds 153 and 154, if, based on steric grounds, the preferred conformation of the aglycon is one in which hydrogens H-3 and H-1′ are in a trans or anti relationship then the furanoid and maleimide rings would also be in a trans relationship. From a first-order analysis of the observed coupling constants between H-3 and H-1′ of the various ribosylsuccinimide derivatives and their calculated dihedral angles[158], it is suggested that a possible explanation to the reversal of the H-3′ and H-2′ resonances is due to the anisotropic shielding[159] of H-2′ by the C-2 carbonyl of the maleimide ring of the 3-S-isomers. Molecular models of these compounds show that rotation about the'glycosidic' bond (C-3/C-1′) is restricted due to steric interference with H-2 which would cause deshielding of H-2′ (therefore, lower-field resonance) due to intramolecular van der Waals forces[159]; however, as the figures in Table I indicate,the preferred conformation is one in which the dihedral angle between H-3 and H-1′ is between 119 and 134.6°. This preferred conformation would only allow one of the diastereomers to position a carbonyl group (C-2 carbonyl of the S-isomer) of the maleimide ring over H-2′ to cause and anisotropic effect. Therefore, the 3-S-ribofuranosylsuccinimides (152, 153 and 170) might be expected to possess higher H-2′ resonances which is indeed observed.

Table I. Calculated Dihedral Angles between H-3 and H-1′



Compound and Chirality (C-3)		Solvent	Chem. Shift(δ) H-2′	H-3′	$J_{3,1'}$ (Hz)	Dihedral Angle
151-R 152-S	R=Bz R′-R′=Ip[a]	$CDCl_3$	5.25	4.75	2.5	123
		$CDCl_3$	4.54	4.72	3.8	131
153-S 154-R	R=H R′-R′=Ip[a]	DMSO-d_6	4.46	4.61	3.5	129
		DMSO-d_6	4.90	4.51	4.0	132
170-S 171-R	R=R′=H	DMSO-d_6	3.60	3.83	2.0[b]	119.3
		D_2O	4.30	4.00	4.4	134.6

a) Ip = Isopropylidene b) 2.5 Hz in D_2O (123°)

From the above table and the above discussion, it can be seen that the reversal of the two resonances H-2′ and H-3′ is due to large shifts in H-2′ rather than complementary shifts in H-2′ and H-3′. It might also be suggested that the large chemical shift of H-2′ in the R-isomers may be due to an enhanced steric deshielding due to electric dipole repulsions of the furanoid oxygen and the carbonyl group of C-2. This electronic repulsion tends to bring the C-4 methylene group and the C-2′ hydrogen into closer proximity and thereby increase the van der Waals repulsion causing a downfield shift in H-2′ and H-4. This downfield shift in H-4, although not as predominant as H-2′, is observed for the R-isomers (see Experimental). For the S-isomer, this electronic interaction is minimized and might even provide attractive forces which may explain the stability of the nearly eclipsed conformation, with respect to the substituents on C-3 and C-1′ of the S-isomer. This evidence, therefore, supports the stereochemical assignments made previously (Section 1.1.3.3.) for the β-D-ribofuranosylsuccinimide derivatives.

It should be noted that the acetonides of these succinimide derivatives are very labile and unless they are crystalline, the stored syrups will slowly de-isopropylidenate. Therefore, the syrups should be stored in a

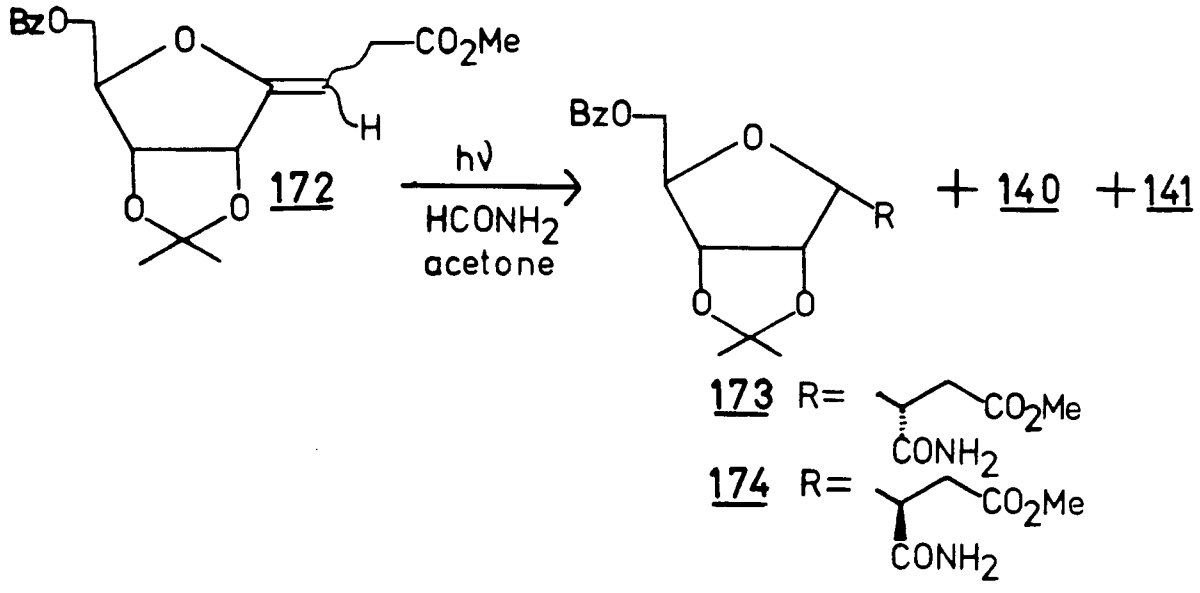
cool and dry container.

1.2. Synthesis of α-Dihydroshowdomycin Acetonide via Photoamidation of Methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (172).

1.2.1. Photoamidation of 172 to give 140, 141, Methyl 4,7-anhydro-8-O-benzoyl-3-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-gluco (and manno)-octonate (173) and (174), respectively.

Irradiation of the methyl oct-3-enonate 172 (~95:5 ratio of Z-to E-isomers, resp., details of its synthesis to be discussed in Section 2.), by the same procedure used for the irradiation of the methyl oct-2-enonate 18 produced a mixture that possessed a band on t.l.c. which was identical in R_f to that of amides 140-143 produced from the latter unsaturated compound. Spectral analysis of this band indicated a mixture of amide products also, but only after chemical transformation (see following section) was this band found to consist of the previously isolated (Section 1.1.2.) amides 140 and 141 and the new carbamoyl products 173 and 174. Column chromatography of the irradiation mixture failed to separate any of the four components and crystallization of this mixture did not affect its composition.

As with the n.m.r. spectrum of amides 140-143, this new mixture exhibited three broad peaks at ca. δ6.2 and a broad three-proton multiplet in the δ2.4 to 3.4 region. The i.r. spectrum possessed a strong primary amide band[143b] at 1685 cm^{-1}.

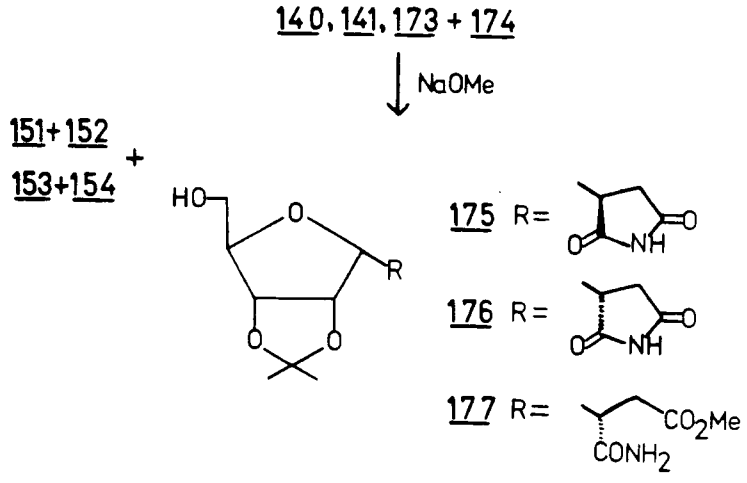


1.2.2. Treatment of Amides 140, 141, 173 and 174 with Methanolic Sodium Methoxide to give 151, 152, 153, 154, 3-(R) and (S)-(2,3-O-Isopropylidene-α-D-ribofuranosyl)succinimide [(R) and (S)-α-dihydroshowdomycin Acetonide] (175) and (176) and Methyl 4,7-anhydro-3-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-gluco-octonate (177), respectively.

When the amide mixture 140, 141, 173 and 174 was treated with 0.12 equivalents of sodium methoxide a multicomponent mixture was seen on the t.l.c. of the reaction mixture. Column chromatography of the worked-up reaction mixture gave compounds 151, 152, 153, 154, 175, 176 and 177.

The n.m.r. spectrum of the faster moving band indicated partially resolved fractions of the previously isolated (see Sections 1.1.1.2 and 1.1.3.3.) β-ribosylsuccinimides 151 and 152, present in an overall ratio of 4:6 (∿20% combined yield), respectively. The n.m.r. spectrum of these fractions also showed minor components which are presumably the 'α'-analogues of 151 and 152. This presumption is based on the isolation (vide infra) of the debenzoylated α-ribosylsuccinimides 175 and 176 and

the presence of a prominant doublet of doublets at ca. δ4.94 in the n.m.r. spectra which is also present in the spectra of the debenzoylated α-compounds but in none of the β-ribosylsuccinimide compounds.



The first of the slower-moving components eluted from the column was compound 153, the n.m.r. spectrum of which was identical to the 3-(S)-dihydroshowdomycin (153) previously isolated (Section 1.1.3.3.). This compound was followed by a mixture of two ribosylsuccinimide acetonides whose n.m.r. spectrum identified the minor component as the previously isolated 3-(R)-dihydroshowdomycin (154) (30% of this mixture). The n.m.r. spectrum also showed the loss of the benzoate and methyl ester of the starting compounds and possessed two D_2O-exchangeable protons at δ2.07 and 9.00 for the primary hydroxyl and imide groups. Of particular significance is the presence of a prominent doublet of doublets at δ4.75 which is also present for a pure α-ribosylsuccinimide described below. Therefore, the major component of this mixture is tentatively assigned as 3-(R)-(2,3-O-isopropylidene-α- D-ribofuranosyl)succinimide [(R)-α-dihydroshowdomycin acetonide] (175). (Assignment of the new chiral center to be discussed below).

Continued elution of the column gave the 3-(S)-α-ribosylsuccinimide acetonide 176 in 12% yield as a pure isomer. The n.m.r. spectrum of 176

also showed the loss of the benzoate and methyl ester groups. Two broad D_2O-exchangeable signals at δ2.16 and 8.28 for the primary hydroxyl and imide protons, respectively, were also present. The mass spectrum of 176 was very similar to that of its β-analogues in possessing a protonated molecular ion at 272 (m+1) and a very strong acetoxonium fragment at 256 ($m-CH_3$).

The configurational assignment of the new chiral center at C-3 of the succinimide ring is based on model studies of the two diastereomers 175 and 176 and on the coupling constants between H-3 and H-1′ (i.e. $J_{3,1'}$). With $J_{3,1'}$ of 175 equal to 2.0 Hz and 8.0 Hz for 176, the respective dihedral angles calculated from the Karplus[158] relationship are 59(119) and 159°(9°), respectively. From models or diagrams of these two compounds it can be seen that the cis-relationship between the O-isopropylidene group and the succinimide ring greatly hinders rotation about C-3 and C-1′ bond. From calculated dihedral angles and models of the two isomers it can be seen that the 3-R isomer would prefer the smaller dihedral angle of 59° while the 3-S isomer prefers the larger dihedral angle of 159°. [The values in parenthesis represent unstable conformers.] These preferences are based mainly on steric considerations but it appears as though the electrostatic repulsions are also minimized. Therefore, the lower R_f, α-product 176 is tentatively assigned the 3-S configuration and the higher R_f, α-product 176 the 3-R configuration.

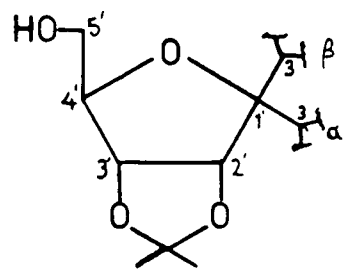
The final component isolated, compound 177, was found to be an uncyclized, debenzoylated amide. This pure stereoisomer was found to possess a strong carbonyl absorption at 1732 and 1678 cm^{-1} in the infrared for the methyl ester and primary amide[143b], respectively. The i.r. spectrum also showed a broad peak at about 3450 with two sharp absorbances overlapping it at 3500 and 3410 cm^{-1}, indicating the presence of a hydroxyl group and

the primary amide N-H stretching bands. For these two latter groups the n.m.r. spectrum of 177 in dimethylsulfoxide-d_6 possessed a single-proton, D_2O-exchangeable triplet at δ4.80 for the C-8 primary hydroxyl and two broad D_2O-exchangeable signals at δ6.77 and 7.24 of the carbamoyl group. Moreover, the n.m.r. spectrum possessed three sharp, three-proton singlets of δ3.57, 1.42 and 1.28 for the methoxy methyl and the isopropylidene methyls, respectively. The mass spectrum possessed a protonated molecular ion peak 304 (m+1) and micro-analysis confirmed the empirical formula.

Assignment of the configuration of C-3 and C-4 of this amide is again based on n.m.r. evidence. As can be seen in Table II, the coupling constants between the furanoid hydrogens of the α-series of compounds are very similar, especially the $J_{3',4'}$ values relative to the β-series. This difference and magnitude of the $J_{3',4'}$ values have been observed for a series of 2',3'-O-isopropylidenated C-α and β-D-ribofuranosides.[167] The assignment of the chirality of C-3 is based on the coupling values $J_{3,1'}$ of the α-series. If the conformational preference about C-3 and C-1' does not change significantly from the cyclic and acyclic compounds then amide 177 can be assigned the 3-S-configuration. This assumption should be valid since the conformations assigned to succinimides 175 and 176 (vide supra) are roughly in staggered conformations with steric and repulsive electronic interactions minimized. The 3-S-α-ribosylsuccinimide 176 is expected to retain its trans-orientation of H-3 and H-1' in the open-chain form (i.e., amide 177) since the above interactions are still minimized. This conformation should give maximum coupling interaction between H-3 and H-1', thereby resulting in the observed $J_{3,4}$ value of 10 Hz. The 3-R-α-ribosylsuccinimide 175 is also expected to retain its conformation in the open-chain form and, therefore, lower $J_{3,1'}$ value, since the rotamer in which H-3 and H-1' are trans-orientated would

bring about an unfavourable steric and electronic interaction between the C-3-carbamoyl group and O-2′. Therefore, it is suggested that 177 has the α-3-S-configuration.

Table II. Coupling Constants and Optical Rotations of the 'α-' and 'β-' D-Ribosylsuccinimide Derivatives and their H-1′ Chemical Shifts.



Compd.	C-1′&C-3 config[n.]	$[\alpha]_D^{**}$	Solvent	$J_{3,1'}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	δH-1
153	β-3-S	-9.27	$CDCl_3$	3.3	6.0	6.0	3.5	4.34
			DMSO	3.3	5.0	6.5	4.0	4.14
154	β-3-R	-35.3	DMSO	4.0	4.5	6.5	4.5	4.04(4.14)
175	α-3-R	+8.04*	$CDCl_3$	2.0	3.5	6.0	0.0	4.56
176	α-3-S	-1.0	$CDCl_3$	8.0	3.8	6.0	1.0	4.47
177	α-3-S	+16.1	H_2O	10.0	3.5	6.0	0.0	4.18(4.23)

* contaminated with approx. 30% compd. 154.
** optical rotations measured in methanol solution.
( ) values in parenthesis are in $CDCl_3$.

Generally speaking, the spectral characteristics of the α and β compounds listed in Table II are consistent with the spectral properties of 2′,3′-O-isopropylidenated C-α and β-D-ribofuranosides. The 'anomeric' proton (H-1′) is generally downfield in the α-anomer and the optical rotation is more positive in the α-anomer which is consistent with Hudson's rules.[53,167,168]

The surprisingly low degree of stereoselectivity in both steps of this photoamidation reaction is not obviously clear but the fact that

isolated double bonds have been photochemically isomerized using benzophenone[56] indicated that an alkene possessing an auxochrome such as an alkoxyl group (as in the methyl oct-3-enonate 172) should be more efficiently[159e] sensitized via the n→π* transition[43b] with a higher energy sensitizer such as excited triplet acetone (see Introduction, Sections 2.1. and 2.2.). The lack of a vicinal chiral group may also contribute to the low stereoselectivity of carbamoylation step. The hydrogen abstraction step however was expected to proceed with a higher degree of selectivity irregardless of the stereoselectivity of the initial addition step (see Introduction, Section 2.1.). In view of the stereospecificity of the hydrogen abstraction step in the photoamidation of unsaturated sugars 46, 53 and 56, the lack specificity here can perhaps be attributed to the 8-O-benzoyl group of 172 which might provide either steric or electronic interactions on the exo-face to counteract the steric repulsion in the endo-face of the fused-ring system. The regiospecificity in the initial reaction is expected due to the anti-Markovnikov orientation of the photoamidation reaction.

A final question which might be asked about this latter chemical transformation of the mixture of amides is why was there a reactivity difference between the α- and β-anomers towards debenzoylation. Two possible answers are immediately obvious; first, if cyclization occurs before debenzoylation the perhaps the conjugate base of the 'β'-imide provides both steric and predominantly electrostatic repulsion to the methoxide anion, both forces which are minimized in the α-anomer; secondly, if debenzoylation occurs before cyclization perhaps the conjugate base of the β-amide again provides both steric and electrostatic repulsion which

is again minimized in the α-isomer. Therefore, either mechanism provides for a predominance of the debenzoylated α-anomers if a catalytic amount of base is used.

2. Synthesis of Functionalized Precursors to C-Nucleosides

The importance of the natural and synthetic C-Nucleosides as anti-tumor and antibiotic agents was emphasized in the Introduction (Section 4.). The synthesis of analogues of these biologically important compounds has thus been pursued in a desire to produce more active and more selective derivatives with less toxic and other undesirable characteristics.[112,116] Several synthetic pathways to possible intermediates of new analogues are described in this section. Each synthesis involves the use of azide reagents as either an acid, base, nucleophile, free-radical or organic intermediate.

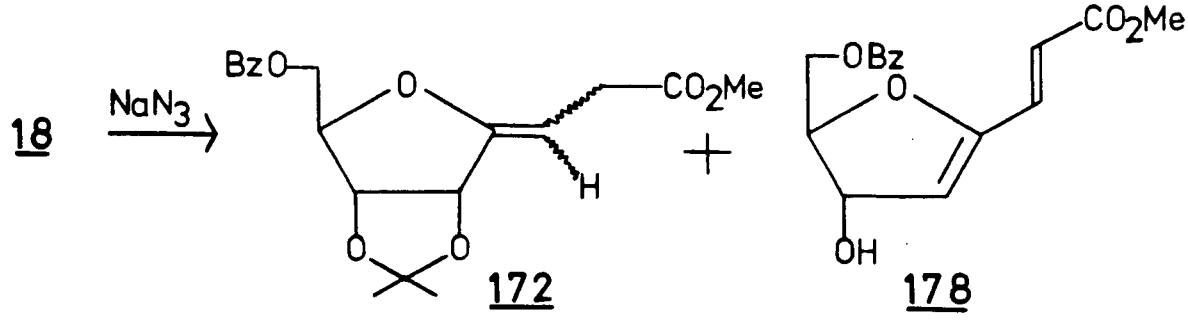
The first part of the work to be described is based on the synthesis of branched-chain glycosyl amino-acids by Rosenthal and Ratcliffe[72] who added hydrazoic acid and sodium azide to an unsaturated sugar. The second part of this section is based on the azido-nitration of unsaturated sugars by Lemieux and Ratcliffe.[105]

2.1 Synthesis of Unsaturated and Amino Sugars

2.1.1. Attempted Addition of Sodium Azide to the Methyl oct-2-enonate 18 to yield Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo—oct-3-enonate (172) and Methyl (E)-4,7-anhydro-8-O-benzoyl-2,3,5-trideoxy-D-erythro-oct-2,4-dienonate (178).

When a solution of the methyl oct-2-enonate 18 (see Section 1.1.1.) in N,N-dimethylformamide was heated at 50-55° in the presence of excess sodium azide, two new unsaturated compounds, 172 and 178, were isolated in 21.5 and 51.5% yield, respectively, from the chromatographed reaction mixture

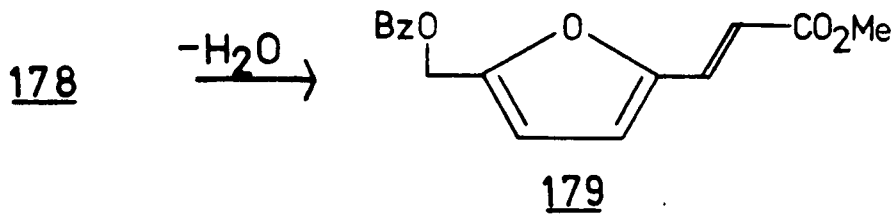
after work-up. T.l.c. of the reaction mixture with various solvent systems indicated that the reaction had only gone to partial completion after 21 hours, with no significant changes in its composition after an additional 24 hours at 50-55°. After an additional 48 hours at approximately 63°, the unchanged mixture was worked-up. Upon side-by-side development of the starting compound 18 with the reaction mixture on a t.l.c. plate, it was observed that the faster-moving component of the reaction mixture had the same R_f as 18 but the initial charring coloration differed, with 18 producing an orange colour and the reaction mixture producing a dull grey and bright purple colouration for its faster-moving and slower-moving components, respectively, indicating the consumption of the starting material.



The slower-moving component, 178, was easily identified as the acetone elimination product from an inspection of its n.m.r. spectrum which indicated the loss of the O-isopropylidene group along with the presence of only one D_2O-exchangeable doublet at δ2.57 for the secondary hydroxyl at C-5 and with the loss of one furanoid hydrogen (H-4) and the shift of another (H-5) to the enolic region[159b] at δ5.52. Moreover, the stereochemical purity of this compound is also in evidence from the n.m.r. spectrum, in which the vinylic protons of C-2 and C-3 are present as sharp doublets at δ6.29 and 7.13 with a coupling constant of 16.0 Hz indicative

of the trans-(or E-) isomer.[160] The i.r. spectrum of this crystalline material is also consistent with the assigned structure 178: 1) the hydroxyl absorbed at 3500 cm^{-1} to give a broad band, 2) the methyl ester exhibited a moderate shift (starting material[20], 18, at 1730 cm^{-1}) to lower frequency (1712 cm^{-1}) due to extended conjugation[159c], 3) the C-2/C-3 double bond exhibited a similar shift[159d] (i.e., from 1672 to 1660 cm^{-1}) and 4) a moderate band at 1607 cm^{-1} can be assigned to the new carbon-carbon double bond between C-4 and C-5 with the low frequency attributable to a combination of ring strain, conjugation and the presence of an electronegative substituent.[159d] The mass spectrum of the dienonate 178 also provides a great deal of supportive evidence for the assigned structure. The first four major signals at 304, 286, 272 and 254 (relative intensity, 1.4:1.4:1:2, resp.) represent the molecular ion (m^+) and the loss of water, methanol and the combined loss of both, respectively. The relative strength of the molecular ion and its loss of groups possessing even numbers of electrons indicate the high degree of stability of enolic radical cationic species. This stability has also been exhibited by other enolic sugars which also possess strong molecular ion signals relative to corresponding non-enolic or saturated compounds[161] (also, see compd. 172 below and compd. 220 in Section 4.).

The dienonate 178 in its crystalline form is quite unreactive and can be stored at room temperature; however, as a syrup, the unprotected compound reacts further to form both lower and higher R_f materials. Isolation of the single higher by-product gave 2-benzoyloxymethyl-5-((E)-carbomethoxyethylene)furan (179) which has been isolated by Moffatt et al.,[20] and results from a dehydration of 178. Compound 178 can be synthesized as the sole product in 64% by an increase in the initial reaction temperature in the absence hydrazoic acid.



179

The structure of the minor component, 172, is also consistent with the various spectral data. Additional proof of its structure comes from various chemical transformations. This section will deal with the spectral characterization and provide evidence for the stereochemistry of the enolic double-bond. Following subsections (2.1.1.1., 2.1.1.2., 2.1.1.3. and 2.1.1.4.) will deal with several addition products of the oct-3-enonate 172 and in Section 3, air oxidation products of 172 will be explored.

The methyl oct-3-enonate 172 has been synthesised following the method outlined above and in higher yields under modified conditions (see Section 2.1.3.). In each case, one and the same geometric isomer of 172 predominated (usually ∿95% as determined by the n.m.r. spectrum of the mixture) and can be partially resolved by column chromatography on silica gel. For convenience, the n.m.r. spectrum of the major (Z)-isomer (vide infra) will be discussed; however, the important and resolvable resonances of the minor (E)-isomer will be dealt with when the geometric assignment is discussed. With the anticipated addition of sodium azide to the double bond (see Introduction: Section 3.1.) and the known reactivity of organic azide compounds (e.g., formation of nitrenes or 1,3-dipolar cycloadditions to unsaturated compounds)[162], the assignment of the n.m.r. spectrum (see Figure 5) of faster-moving chromatographic component to the unsaturated compound 172 was not immediately clear since the vinylic protons

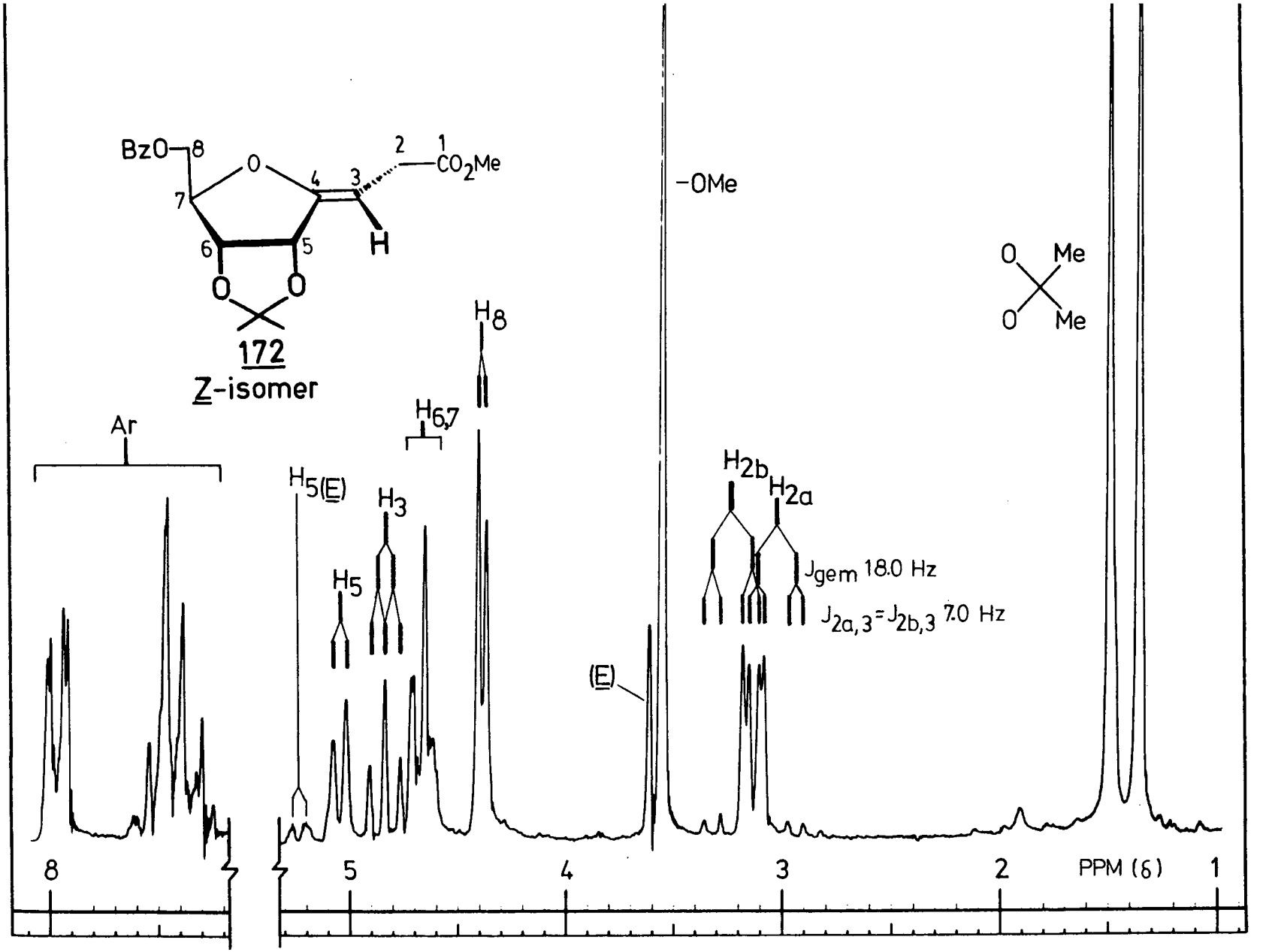


Figure 5A. Partial 100 MHz Proton N.M.R. Spectrum of Methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (172). A 5:95 ratio of the E- to Z-isomers in $CDCl_3$.

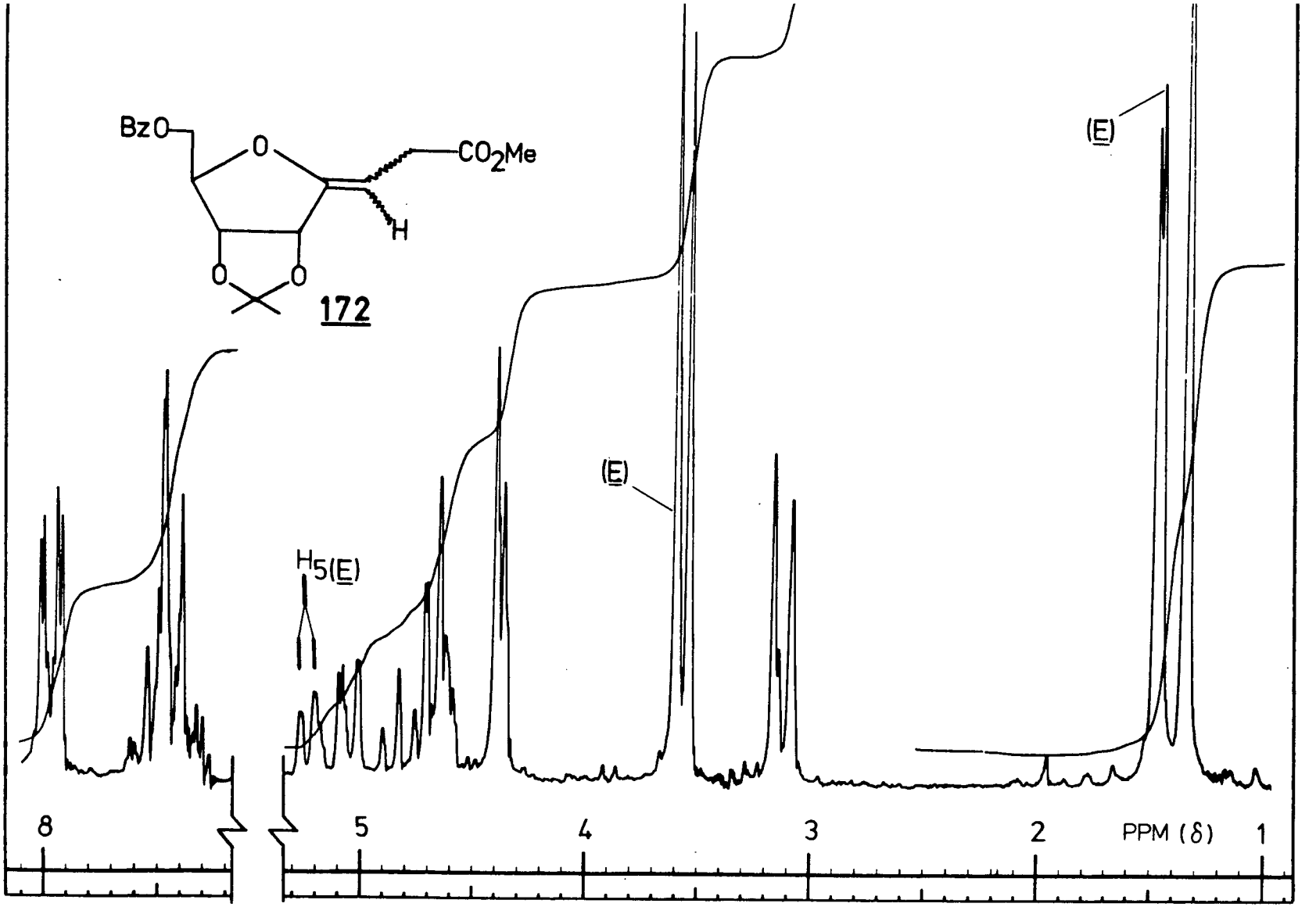


Figure 5B. Partial 100 MHz Proton N.M.R. Spectrum of Methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (172). A 55:45 ratio of the E- to Z-isomers in $CDCl_3$.

of the starting material (see Figure 5) was no longer present nor did the i.r. spectrum indicate the presence of an carbon double-bond (vide infra). Moreover, the n.m.r. spectrum showed a relatively low-field methylene ABX pattern at ca. δ3.12; however, the spectrum did not indicate any sort of dimerization since the methyl groups were sharp singlets and H-8 appeared as a doublet. The spectrum also integrated for the same number of protons as the starting material. The identification of this component as the 3-ene isomer of the starting material enabled the assignment of the broadened doublet δ5.03 to H-5 with the broadening due to allylic coupling with H-3 which was present as a pseudo-triplet at δ4.82. It might also be suggested that presence of the hydrogens of C-8 as a doublet indicates an averaging of environments of these diastereomeric hydrogen due to freer rotation about the C-7/C-8 bond (observed in 178 also).

The i.r. spectrum of 172 exhibited a splitting of the carbonyl absorbances with the higher frequency band at 1743 cm^{-1} indicating the deconjugation of the methyl ester.[159c] The carbon-carbon double bond absorbance of the 2-enonate 18 was no longer resolvable but the presence of a shoulder at ca. 1710 cm^{-1} might be attributable to an up-frequency shift of the double-bond due to deconjugation in the presence of an electronegative substituent.[159d] Goodman and coworkers[102] reported an absorption at ca. 1700 cm^{-1} for the exocyclic enolic acetal 92; therefore, the above assignment appears valid.

The mass spectrum of the two unsaturated sugars 18 and 172 also warrant direct comparison. The peak ratios of the first four ions are 1.0:0.4:1.0:2.0 for the 3-ene 172 and 1.0:21.5:12.2:11.2 for the 2-ene 18 representing (m^+), (m^+-CH_3), (m^+-OCH_3), and (m^+-acetone), respectively. Clearly, the

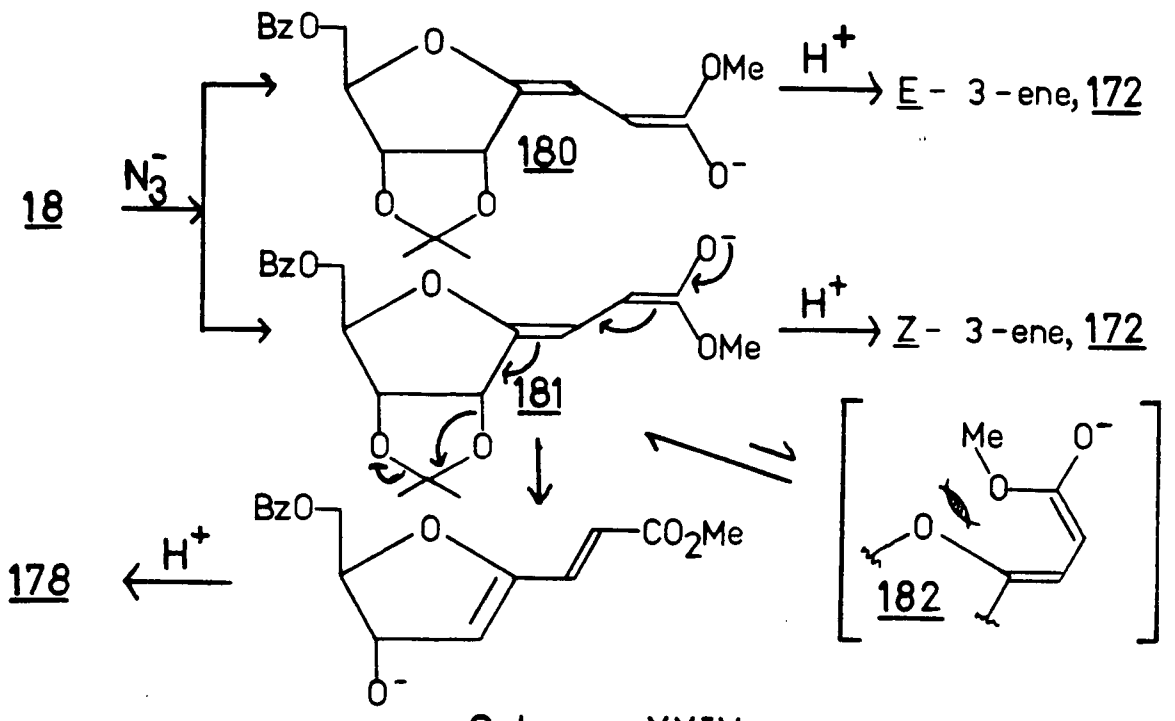
stability of the molecular ion of 172 indicates the stabilizing effect of the enolic system in forming an allylic cationic radical.

The assignment of the geometric configuration of the 3-ene 172 is primarily based on chemical shift of the enolic hydrogen H-3 and, to a lesser extent, on the allylic hydrogen H-5. H-3 of the major isomer resonates at δ4.82, the assignment of which is confirmed by irradiation of the pair of doublets of doublets at ca. δ3.12 (H-2a and H-2b) which collapses the pseudo-triplet of H-3 to a singlet. H-3 of the minor isomer resonates at lower-field (ca. δ5.08). Since the net shielding effect[163] from the alkoxyl (0.7) and alkoxymethyl (i.e., C-5) groups of the enolic system on H-3 in the Z-isomer (i.e., furanoid oxygen and C-2 are cis) is expected to be greater than that of the E-isomer, we can tentatively assign the isomer with the higher-field H-3 resonance to the Z-isomer (i.e., the isomer predominantly formed). Secondary support for this assignment comes from the chemical shift of the H-5 signal, in the minor isomer which has been tentatively assigned the E-configuration in which C-5 and C-2 are in a cis-relationship H-5 resonates at lower-field. This down-field shift might be attributed to a steric deshielding of H-5 by the substituents on C-2. Although the steric deshielding of the C-2 hydrogen are not clearly evident, the downfield shift of the methyl ester is clearly seen, indicating a mutual deshielding of the cis-groups.

Confirmatory evidence for the geometric assignment of the isomers was sought in the carbon-13 n.m.r. spectrum of the two isomers. It has been observed that α-carbons in cis-olefins are appreciably shielded relative to those in the corresponding trans-isomers.[164] The C-13 n.m.r. spectrum showed a down-field shift for C-2 and an up-field shift for C-5 in going from the major (previously assigned Z-isomer) to minor E-isomer; therefore,

this result cannot be considered direct confirmatory evidence for the geometric assignment. However, it should be pointed out that although literature information on substituted enol ethers is lacking, the influence of cis-methyl groups is known and, therefore, irregardless of the relative effect of the cis- and trans-alkoxyl group on C-2, C-5 should experience the steric shielding of C-2 with respect to its interaction with H-3 in the E- and Z-isomers of 3-enonate 172, respectively. Therefore, the anomolous results of the C-13 n.m.r. spectrum partially support the Z-assignment of the major isomer.

The stereoselectivity of this base-catalyzed isomerization presumably results from a requirement in which the π-orbitals of α,β-unsaturated ester 18 must be parallel with the C-4/H-4 bond in order to effect deprotonation of C-4. This requirement allows for two possible conformations of 18, one leading to the E-extended enolate 180 and the other to the Z-extended enolate 181.[6a] Models studies of 18 suggest that the conformational precursor to the E-enolate 180 experiences greater steric interaction with C-5 (therefore, higher energy transition state) than the corresponding precursor to 181 which leads to a predominance of Z-enolate 181 and the Z-isomer of 172 (i.e., the predominant isomer isolated).



Scheme XXIV

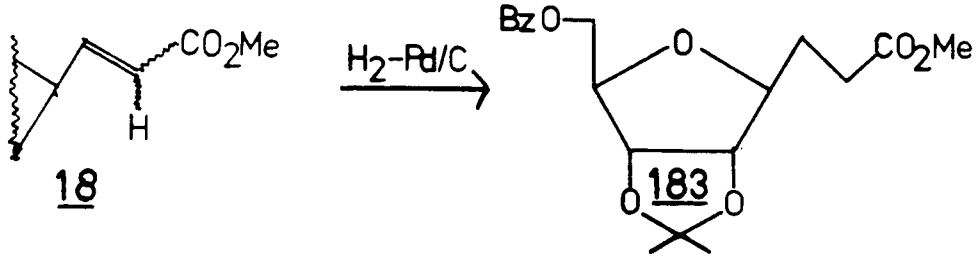
As can be seen from the above scheme, the original carbon double-bond is now part of a conjugated enolate system and rotation about C-2/C-3 bond is made easier. The trans- or E starting material 18 leads directly to a transoid or s-trans conformation (180 and 181) while the inherent steric instability of the cisoid or s-cis conformation probably leads to a rotation about C-2/C-3 in the transition state in the deprotonation of Z-18. The high degree of thermodynamic instability of 182 (and its E-analogue) then give a probable explanation for the stereoselective synthesis of the Z-isomer of 178.

Although the isomerization and elimination reaction involved here is rather unusual, there is precedent[21] for such a stereoselective dual reaction taking place with analogous compound such as 22 (see Introduction, Section 1.1.). The lack of any azide addition products here might be due to the ease in which the acyclic activating groups in 18 and 22 align themselves with the activated hydrogen leading to ready deprotonation whereas compound 46 (Introduction, Section 2.1.) requires a strained ring conformation to achieve the same alignment. Also, β-azido carbonyl compounds

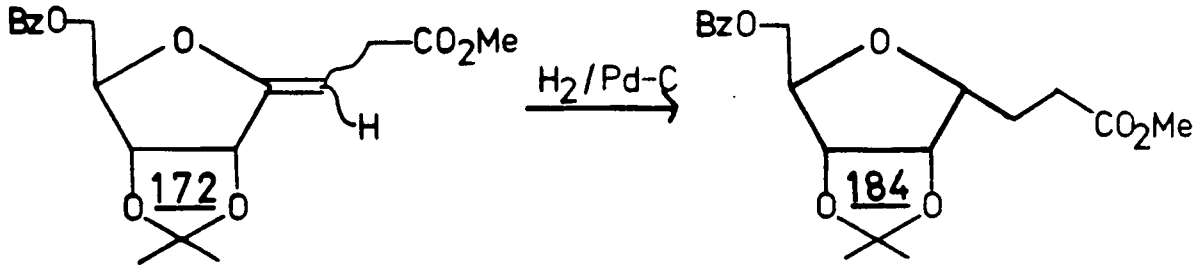
have been reported[165] to be fairly unstable and undergo β-elimination to regenerate the α,β-unsaturated carbonyl precursor. Therefore, an equilibrium between the starting material 18 and an azido adduct might have occurred with the isomerization and elimination reaction irreversably consuming starting material. The isomerization reaction is presumed to be irreversable since treatment of 172 under the same conditions as 18 does not give any 18 nor 178. Several derivatives of 172 will now be described before modifications to this reaction are reported.

2.1.1.1. Hydrogenation of 18 and 172 to give Methyl 4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-α-D-allo (and altro)-octonate (183) and (184), respectively.

Catalytic hydrogenation of the methyl oct-2-enonate 18 and oct-3-enonate 172 in separate reductions gave two epimeric saturated compounds 183 and 184, respectively. The characteristic changes in each starting compound will be described first before a direct comparison is made between the two products.



The vinylic hydrogens of 18 were no longer present in the n.m.r. spectrum of the hydrogenation product, 183, and two high-field methylene multiplets were present at ca. δ1.96 and 2.44. The stereochemical purity of this compound was exemplified by three sharp methyl resonances. The i.r. spectrum showed a small shift[159c] in the saturated methyl ester to 1738 cm^{-1} (cf. 1730 of 18) and a disappearance of the carbon-carbon double bond absorption at 1672 cm^{-1}.



The hydrogenation product 184, the 'α'-analogue of 183, produced a n.m.r. spectrum in deuterochloroform which indicated and up-field shift in the C-2 methylene to ca. δ2.58 and a new methylene multiplet at ca. δ2.08. The methyl groups of 184 were also present as sharp singlets. The i.r. spectrum of 184 retained the close doublet for the carbonyls (1738 for the methyl ester and 1727 cm^{-1} for the benzoate, cf. above) but the moderate shoulder at 1710 cm^{-1} (C=C) was no longer present.

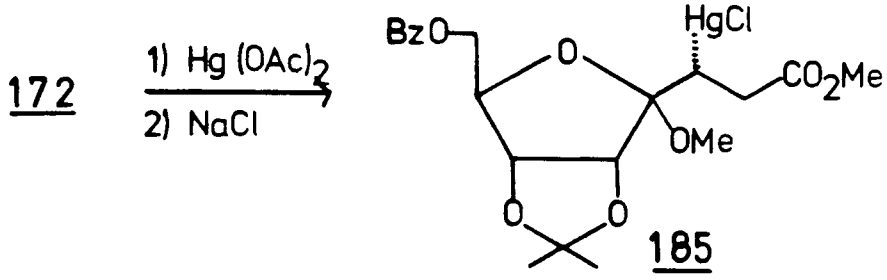
Both saturated compounds 183 and 184 exhibit weak molecular ions at 364 in the mass spectrum and very strong acetoxonium and acylium fragments. As seen above, the carbonyl absorbances are nearly identical in the i.r. spectrum of these compounds. The otpical rotation of these anomers are -11.4 and -9.0° for 183 and 184, respectively. This result indicates a very low contribution of chiral centre at C-4 to the overall rotation of the anomers.[166] The above information shows the similarity and purity of the two compounds, therefore, there is a need to show their differences and probable stereochemistry.

Based on mechanistic grounds[85] and on the fact that different products are formed in the two hydrogenations, the 'β-anomer' 18 should retain its stereochemistry (i.e. C-4) after hydrogenation. The hydrogenation of the 3-enonate 172 should proceed from the least hindered side[102,185] (i.e., away from the O-isopropylidene) to give the 'α-anomer'. The differences in the n.mr. spectra of these two 'anomeric' isomers support the above assignment. H-4 resonates of δ3.93 and 4.07 for compounds 183 and 184, respectively. As was seen with the α and β-dihydroshowdomycin acetonides

(Section 1.2.2.) the 'anomeric' proton (H-4) of the 'α-anomers' are consistently downfield of the 'β-anomers'.[167] Therefore, the hydrogenation product of the 3-enonate 172 (i.e., compd. 183) can be tentatively assigned the 'α'-configuration (eg. D-altro) and compound 184 the 'β'-configuration. Additional supportive evidence is also found in the chemical shift differences of the gem-dimethyl groups of the O-isopropylidene group of 183 and 184. In the 'β-anomer' 183 the resonances of the gem-dimethyls are separated by 20 Hz while the resonances of the gem-dimethyls of the 'α-anomer' 184 are separated by 17 Hz. This difference is consistent with the larger chemical shift differences of the gem-dimethyl groups of isopropylidenated β-C-glycosides.[167] Although not as significant alone[166], the 'α-anomer' 184 shows a more positive rotation expected for an α,β-pair of 'anomers'.[53,167,168]

2.1.1.2. Methyl (methyl 8-O-benzoyl-3-(chloromercuri)-2,3-dideoxy-5,6-O-isopropylidene-α-D-altro-4-octulofuranosid)onate (185)

When a solution of the methyl oct-3-enonate 172 in absolute methanol was treated with mercuric acetate followed by sodium chloride, the chromatographed reaction mixture readily gave crystalline 185 from a methanol solution.



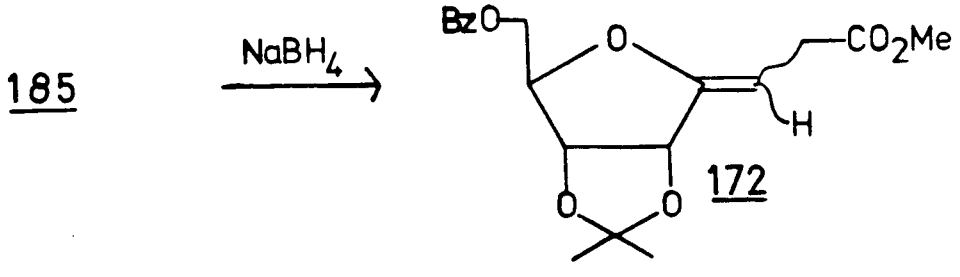
The carbonyl region in the i.r. spectrum of 185 indicated the loss of the shoulder at 1710 cm^{-1} due to the carbon-carbon double bond and the mass spectrum exhibited a complex pattern at the anticipated regions due to the isotopes of chlorine and mercury. The chemical analysis was

consistent with the empirical formula of 185 and the n.m.r. spectrum exhibited four sharp methyl resonances.

The predominance of the α-D-altro isomer is expected on mechanistic grounds. As in the hydrogenation of 172 (predominantly Z-isomer), the 5,6-O-isopropylidene group is expected to hinder the approach of the mercuric reagent from the α-face to give the intermediate 'β'-3,4-mercurium ion which leads to the methyl α-D-altro-glycoside 185 from an overall trans-addition[4] to the double bond of the Z-isomer of 172 (i.e., the α-D-allo-glycoside would form from the E-isomer of 172). The attempted reductive-demercuration of 185 is described in the next subsection.

2.1.1.2.1. Reduction of 185 with Sodium Borohydride to Yield 172

Treatment of an ethanolic solution of the organomercury compound 185 with sodium borohydride resulted in the expected precipitation of elemental mercury; however, the sugar derivative isolated after column chromatography proved not to be the corresponding methyl glycoside[4] but a product arising from a reductive-elimination to regenerate the enolic precursor 172 of 185.



The n.m.r. spectrum of the different fractions isolated from column chromatography indicated an enhancement of the weak signals present in compound 172 previously isolated. These enhanced signals were attributed to the E-isomer of 172 and were predominant in the faster-moving portion of the eluent. Expectedly, the optical rotation of an 55:45 molar ratio

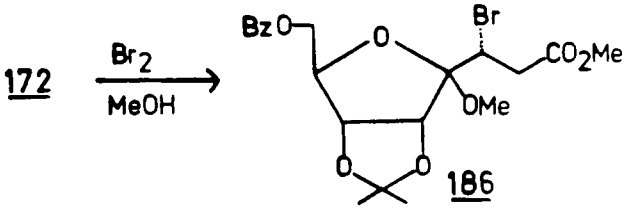
of the E-to Z-isomers exhibited the same strong negative rotation of a predominantly (∿95%) Z-mixture of 172(-167 and -156, resp.). The overall ratio of the E- to Z-isomer of 172 was found to be 42:58.

The de-alkoxymercuration reaction is usually accomplished under acidic conditions and with a high degree of stereoselectivity[82b]; therefore, the elimination seen here must proceed by a different mechanism.

2.1.1.3. Methyl (methyl 8-O-benzoyl-3-bromo-2,3-dideoxy-5,6-O-isopropylidene-α-D-altro-4-octulofuranosid)onate (186)

Bromomethoxylation[4,5,169] of a 95 to 5 mixture of the Z to E-isomers of the methyl oct-3-enonate 172 in a methanol solution in the presence of silver carbonate produced a mixture of adducts which after column chromatography on silica gel gave a major component (41% yield) which is tentatively assigned the α-D-altro-glycoside 186. Several slower-moving minor components were also isolated, but due to their thermal instability, the clear syrups turned into black tars before any spectral analysis could be initiated.

The n.m.r. spectrum of 186 exhibited a clearly defined ABX system for H-2 and H-3 and showed four sharp methyl resonances. The i.r. spectrum again showed a loss of the shoulder at 1710 cm^{-1} in the carbonyl band but more significantly, the mass spectrum of 186 indicated a trace molecular ion and strong acetoxium ion doublets (i.e. due to Br 79 and 81) and a very strong singlet at 307 (m^+-$CHBrCH_2CO_2Me$) due to the C-4 stabilized carbonium ion from a C-3/C-4 cleavage. The stereochemical assignment of 186 implies an overall trans-addition of the reagents which have been observed for other enolic sugars.[5]

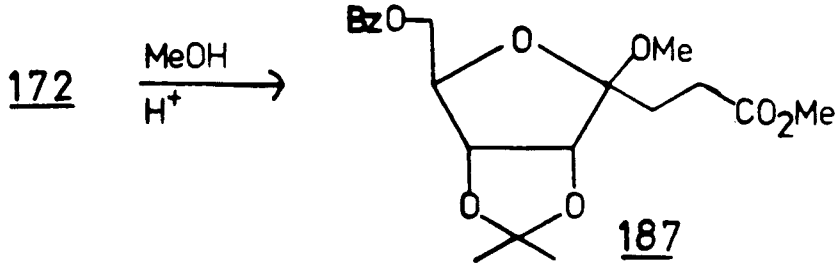


2.1.1.3.1. Attempted Hydrogenolysis[85d] of 186.

When the bromoglycoside 186 was hydrogenated in methanolic potassium hydroxide in the presence of 5% palladium on carbon[170], t.l.c. of the reaction mixture showed lower R_f plus base-line materials but none of these could be clearly resolved and further attempts to isolate the products were not initiated. Also, none of the components had the R_f of the expected debrominated methyl glycoside.

2.1.1.4. Methyl(methyl 8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-4-octulofuranosid)onate (187)

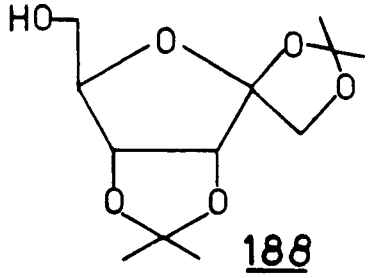
When a solution of the methyl oct-3-enonate 172 (95:5 mixture of the E to Z-isomers) in pyridine, acetic acid, methanol, and water was allowed to stand for several months, a high R_f band (relative to 172) was isolated from the myriad of products to give the methyl glycoside 187. The i.r. and



n.m.r. spectra were completely consistent with the proposed structure. The mass spectrum possessed the acetoxonium fragment plus the C-4 stabilized carbonium fragment at 307 ($m^+-CH_2CH_2CO_2Me$).

Since the methyl glycoside was formed under equilibrium conditions, the assignment of the anomeric centre (C-4) is based on the work of Moffatt and coworker[167] who found that fused five-member rings with epimerizable substituents (i.e. C-glycosides of 2,3-O-isopropylidene-D-ribofuranose) under equilibrium conditions prefer a cis-orientation of the isopropylidene and the 'non-polar' group. The study also indicated that these glycosides

with polar substituents (e.g., OH,OR,Cl,NH_2) prefer to adopt a 1,2-trans-relationship. These results are also consistent with the various derivatives of D-psicose.[171] For example, the main component in a equilibrium mixture of D-psicose in acetone is 1,2:3,4-di-O-isopropylidene-β-D-psicofuranose (188).



188

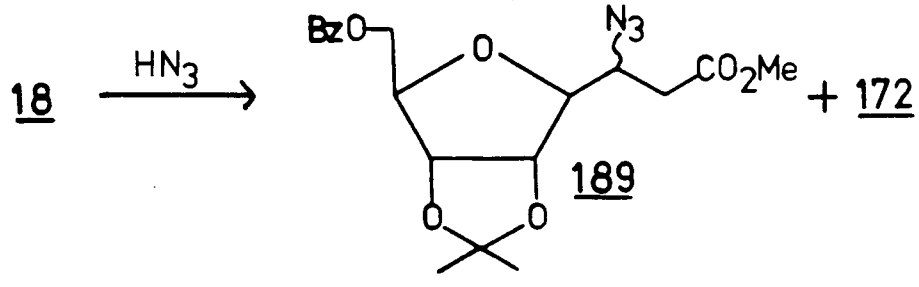
Therefore, the methyl glycoside isolated is tentatively assigned the β-configuration. The chemical shifts of H-5 and H-6 (δ4.49 and 4.79, resp.) also support this assignment (see Section 3.1.2. for discussion of this topic).

2.1.2. Addition of Hydrazoic Acid to the Methyl oct-2-enonate 18 to Yield 172 and Methyl 4,7-anhydro-3-azido-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo, altro-octonate (189).

Due to the lack of addition products in section 2.1.1., the original procedure of Rosenthal and Ratcliffe[72] (see Introduction, Section 3.1.) to obtain azido-compounds from an unsaturated isopropylidenated sugar was used. Therefore, treatment of the 2-enonate 18 in N,N-dimethylformamide with hydrazoic acid in the presence of sodium azide produced the expected epimeric mixture of the 3-azido compounds 189. Chromatography of the worked-up reaction mixture gave one major band, the n.m.r. spectrum of which indicated a mixture of similar compounds (e.g., singlets for the isopropylidene methyls and a close doublet (∿2 Hz) for the methoxyl methyl of the epimers of 189) plus a small amount (<10%) of the methyl oct-3-enonate

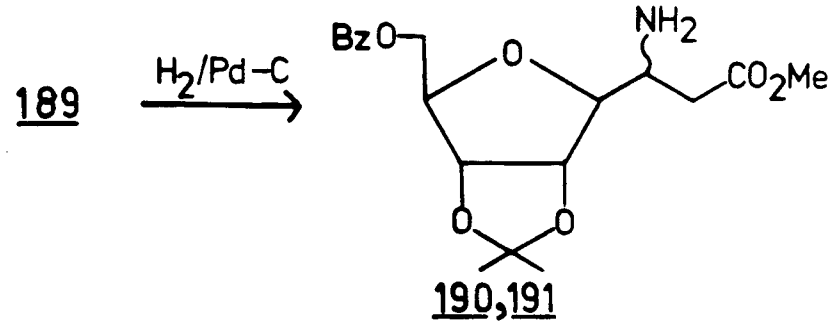
172 as evidenced by the presence of its H-2 and methoxyl methyl signal at ca. δ3.05 and 3.50, respectively. The i.r. spectrum of this band possessed a strong doublet at 2110 and 2140 cm^{-1} indicating the presence of two azido components.[143c] The epimeric azides were isolated pure as their corresponding amino derivatives (following subsection).

Two other minor impure components were also isolated and were later (Section 2.1.3.) shown to be the desired α-diazo-esters 192 and 193.



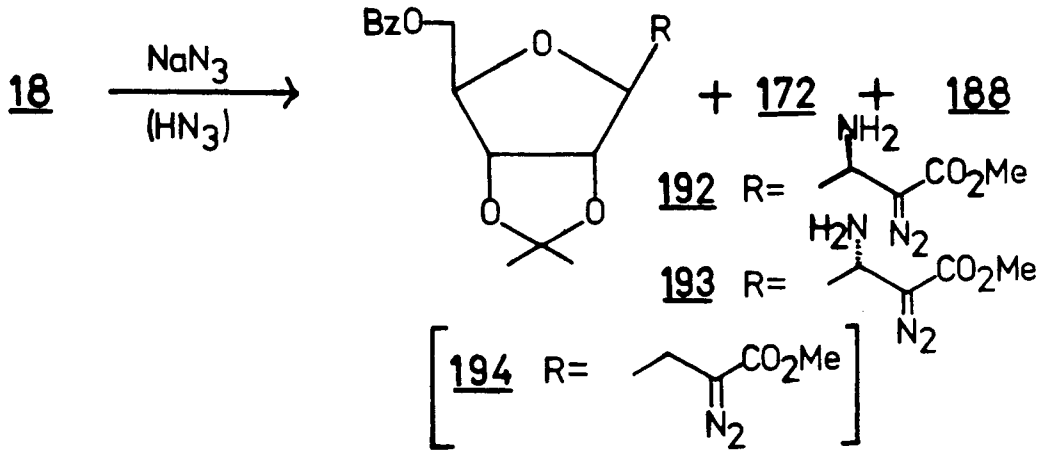
2.1.2.1. Methyl 3-amino-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-octonate (190) and (191).

Hydrogenation of the contaminated (with 172) epimeric azido mixture 189 in the presence of 5% palladium on charcoal as catalyst[72] gave the corresponding amino compounds 190 and 191 as a chromatographically homogeneous mixture. The n.m.r. spectrum of this mixture in deuterochloroform was entirely consistent with a composite spectrum made up from the individual amines 190 and 191 (see Section 2.1.3.1.). The composite spectrum also indicated a predominance (∿67%) of the D-glycero-D-allo epimer (e.g., 3-S-isomer; see Section 2.1.3.) 190 which might explain the stronger band at 2140 cm^{-1} of the azido doublet in the i.r. spectrum of 189. This result indicates a small degree of stereselectivity in this nucleophilic addition reaction which was lacking in the photoamidation reaction (Sections 1.1.3.1. and 1.2.2.).



2.1.3. Addition of Sodium Azide to 18 to give 172, 189, and Methyl 3-amino-4,7-anhydro-8-O-benzoyl-2-diazo-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-octonate (192) and (193), respectively.

With the production of small quantities of lower R_f compounds (Section 2.1.2.) which showed absorption bands at ca. 2100 cm^{-1}, the results which parallel those of Rosenthal and Ratcliffe[72], the addition reaction was modified to increase the yield of these minor components but keeping in mind the susceptability of the substrate to elimination of acetone. The optimum conditions for the synthesis of the α-diazo-esters, 192 and 193, using hydrazoic acid, excess sodium azide, and N,N-dimethylformamide as solvent was determined (see Experimental) but the yield of 192 and 193 were still very low, 9 and 6%, respectively. The main product was the methyl oct-3-enonate 172 (∿70%), of which the chromatographically faster-running portion was contaminated with small portions of the azido mixture 189. Higher concentration of the acid produced larger portions of 189 and decreased 192 and 193. Lower concentrations of acid, replacement of the hydrazoic acid by excess ammonium chloride[172] or the usage of hexamethylphosphoramide as catalyst resulted in the elimination of acetone to give 178 which has the same relative R_f (ether-hexane as developer) as 193 and also resulted in lower yields of 192 and 193.



The two diastereomers 192 and 193 were easily separable by column chromatography on silica gel. Both compounds showed characteristic absorbances in their i.r. spectra at 3400, 3340, 2100 and 1698 cm^{-1} for the primary amine, conjugated diazo, and α-diazo-carbonyl ester, respectively.[72,143d,173] The benzoate carbonyl remained unchanged at 1730 cm^{-1}. The n.m.r. spectrum of both possessed a broad two-proton D_2O-exchangeable singlet at ca. δ1.64 which confirms the presence of the primary amine. The mass sepctrum of both diazo compounds showed characteristic fragments at 377 (M^+-N_2) and 362 (M^+-N_2-Me).[48b,174]

A tentative assignment of the configuration at C-3 is based on Brewster's Rules[175] and Hudson's Rules of Isorotation.[168] The molecular rotation of the high and low R_f (using 2:1 ether-hexanes as developer) β-amino-α-diazo-esters (on silica gel) are -194 and +84°, respectively. Application of Hudson's Rules predicts a value of -55° for the molecular rotation of a non-functionalized C-3 analogue of the above epimers depicted in structure 194. An analogous compound to 194 is compound 183 (see Section 2.1.1.1.) which has a molecular rotation of -41.5°. This close agreement suggest an application of Brewster's Rule to the chiral center at C-3 and if the polarizabilities of substituents decrease in the order $C_2>C_4>NH_2>H$, then Brewster's Rule predicts a higher positive rotation for the 3-S or

D-glycero-D-allo diastereomer. The lower-R_f diazo compound 192 has the greater positive rotation and it is therefore suggested to possess the 3-S-configuration and the higher R_f diazo component 193, the corresponding 3-R-configuration (i.e., D-glycero-D-altro).

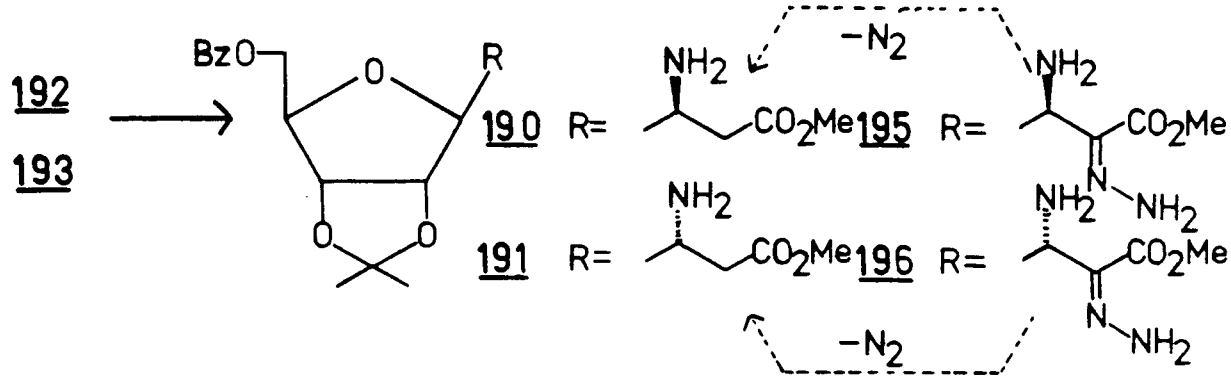
2.1.3.1. Hydrogenation of 192 and 193 to give 190, 191 and Methyl 3-amino-4,7-anhydro-8-O-benzoyl-3-deoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-2-octulosonate Hydrazone (195) and (196), respectively.

Hydrogenation of the diazo compounds 192 and 193 (in separate reactions) in the presence of palladium catalyst gave the corresponding β-amino compounds 190 and 191 (30 and 40%, resp.) and β-amino hydrazones 195 and 196 (26 and 16%, resp.), respectively.[176] The structures were readily deduced from their i.r. and n.m.r. spectra.

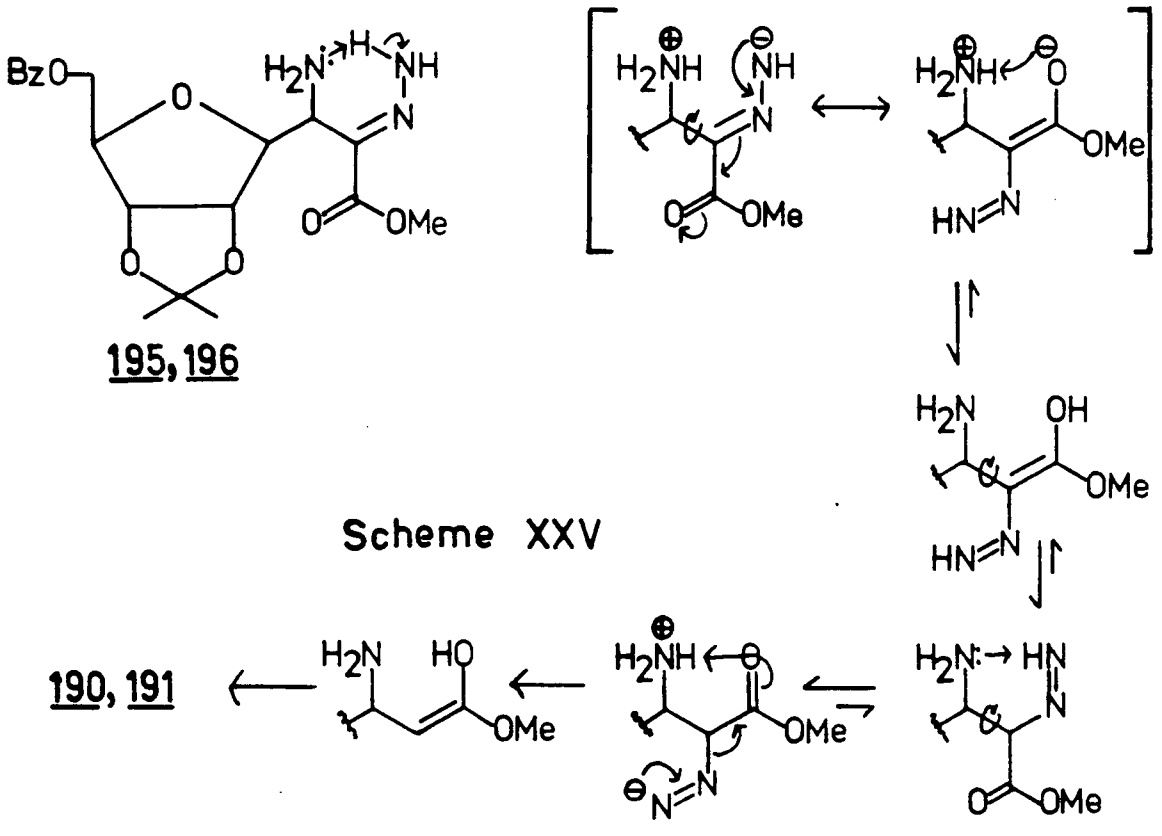
Both β-amino compounds, 190 and 191, possessed the characteristic absorption bands at 3405, 3340, 1740 and 1730 cm^{-1} for the primary amine[143d] and esters groups[159c] in their i.r. spectra. Both amines possessed surprisingly sharp two-proton singlets at ca. δ1.58 in their n.m.r. spectra which exchanged with D_2O and, moreover, resolvable ABX systems were present for the new methylene groups, the presence of which caused an up-field shift in H-3. The mass spectrum of 190 contained a significant molecular ion (m^+) signal plus a strong acetoxonium fragment (m^+-CH_3) at 364.[141b] Chemical analysis for both amines confirmed the empirical formulas.

The structure of hydrazones 195 and 196 was deduced primarily from their chromatographic mobility, n.m.r. spectra and decomposition products. Both hydrazones have significantly lower R_f's than 190 and 191 a fact which is exemplified by the presence of two broad, two-proton D_2O-exchangeable singlets in the n.m.r. spectra at ca. δ1.78 and 8.40. Compared to their

diazo precursors, the n.m.r. spectrum of both hydrazones presented H-3 as a broad resolvable doublet. Hydrazone 195 originating from the lower R_f diazo compound 192 was crystallizable and gave the expected chemical analysis but syrups of both compounds 195 and 196 stored at room temperature or reduced temperature (∿5°) would slowly show increasing amounts of a higher R_f material with identical mobilities to that of the β-amino compounds 190 and 191, respectively. Chromatographic separation of this higher R_f component gave n.m.r. spectra which were identical to the corresponding β-amino compounds.



The transformation of the hydrazones 195 and 196 to the corresponding β-amino compounds 190 and 191, respectively, presumably occurs by a mechanism similar to that of the Wolff-Kishner[177] reduction. The base in this reduction being the primary amine at C-3 and the mild conditions of the transformation attributable to the stabilizing effect of the ester carbonyl on the intermediate anions. Whether the reduction is intramolecularly or intermolecularly catalyzed cannot be distinguished at this time (although both pathways might be operating simultaneously). For simplicity the following scheme depicts the intramolecular-route.

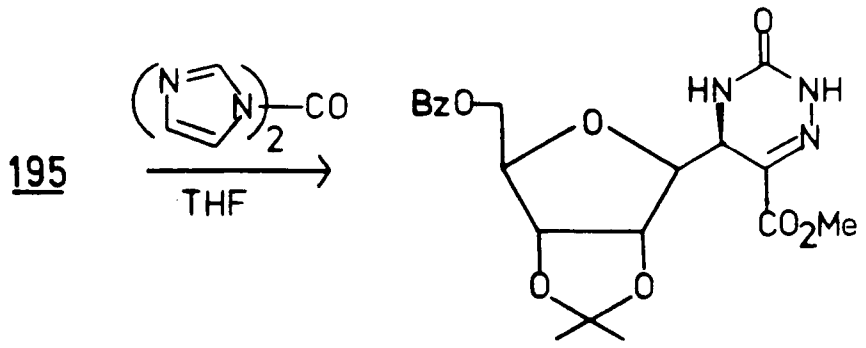


195, 196

Scheme XXV

2.1.3.2. Attempted Ring Closure of 195 with N,N'-Carbonyldiimadazole (197) to give 5-(S)-(5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribo-furanosyl)-6-carbomethoxy-4,5-dihydro-2H-as-triazin-3-one (198).

In a desire to synthesize an analogue of the C-nucleoside pyrazofurin[112,178] (see Introduction, Section 4.), it was hoped that the introduction of a carbonyl group in the preparation of a six-membered heterocyclic system starting from the aminohydrazones 195 and 196 would lead to products amenable to aromatization and result in the synthesis of an analogue of pyrazofurin. Thus, treatment of the crystalline aminohydrazone 195 with 197 in refluxing tetrahydrafuran gave a major higher R_f product which has been tentatively assigned structure 198.[179a,b]



198

The i.r. spectrum of 198 showed absorbances at 3410, 3300 and 3270 cm^{-1} for the N-H stretching and possessed a new carbonyl absorbance at 1665 cm^{-1} indicative of a urea type compound.[159g] The n.m.r. spectrum in DMSO-d_6 contained several low-field non-aromatic signals, the lowest of which (∂9.32) disappeared quickly upon addition of D_2O. The methyl resonances were also present as sharp peaks. The mass spectrum of 198 significantly showed strong fragments at 418, 277 and 156 representing the acetoxium ion (m^+-CH_3), the sugar fragment (i.e., C-1′/C-5 cleavage) and the aglycon, respectively.

2.2. Attempted Synthesis of a Vicinal Diazido Sugar

2.2.1. Treatment of 18 with Sodium Azide and Ceric Ammonium Nitrate (CAN).

The C-nucleoside pyrazofurin (103)[178] possesses strong antiviral activity and it was thought that a re-arrangement of the bond sequence in the aglycon might provide interesting biological consequences. Based on the proposed mechanism of the azido-nitration reaction (see Introduction, Section 3.2.8.) and on the work done by other researcher on the addition of azide radicals to unsaturated esters (e.g., compd. 18 which undergoes a free-radical addition in the photoamidation reaction, see Introduction, Section 2.1.), it was hoped that the treatment of the methyl oct-2-enonate 18 with CAN and sodium azide might give a vicinal diazido adduct[180] which might lead to a structural isomer of pyrazofurin (103).[112,178] Thus,

following the method described by Ratcliffe[105], compound 18 was treated with CAN and sodium azide at -33 to -22° in acetonitrile for fifteen hours. T.l.c. of the reaction mixture indicated 10 to 15% consumption of starting material with two new higher R_f components. Chromatography of the reaction mixture on silica gel gave unreacted starting material (∿73%) and two minor components in 8 and 2% yields (based on starting material and azido allylic substitution, vide infra) with the faster-moving component predominating. The n.m.r. spectra of both components showed them to be impure with the presence of low-field vinylic doublets (16 Hz) (i.e., an isolated AB system). The i.r. spectrum of both components possessed sharp bands and ca. 2120 cm^{-1} ($-N_3$)[143c] and the major component possessed a strong mass spectral peaks at 388 (m^+-CH_3), 375(m^+-N_2), and 361(m^+-N_3) suggesting allylic substitution rather than addition took place. The low yields of these impure products and the lack of any isolated addition products[181] precluded further work on this reaction.

3. Oxidation and Hydration Products of Methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (172).

The 3-enonate 172, obtained by a base-catalyzed isomerization of the methyl oct-2-enonate 18[20] (see Section 2.1.1., 2.1.2., and 2.1.3.), when allowed to stand in a etheral solvent system or as a syrup exposed to ambient conditions (e.g., air, light, moisture, room temperature) for prolonged periods will slowly react with atmospheric moisture, oxygen, or ether autoxidation[27b] products to give a myriad of carbohydrate products. This section will present (i) those carbohydrate products which have been isolated pure, (ii) possible mechanism of formation, (iii) assignment of sterochemistry, (iv) methods and results of reactions to selectively obtain some of these products, and (v) derivatives of the ketal products.

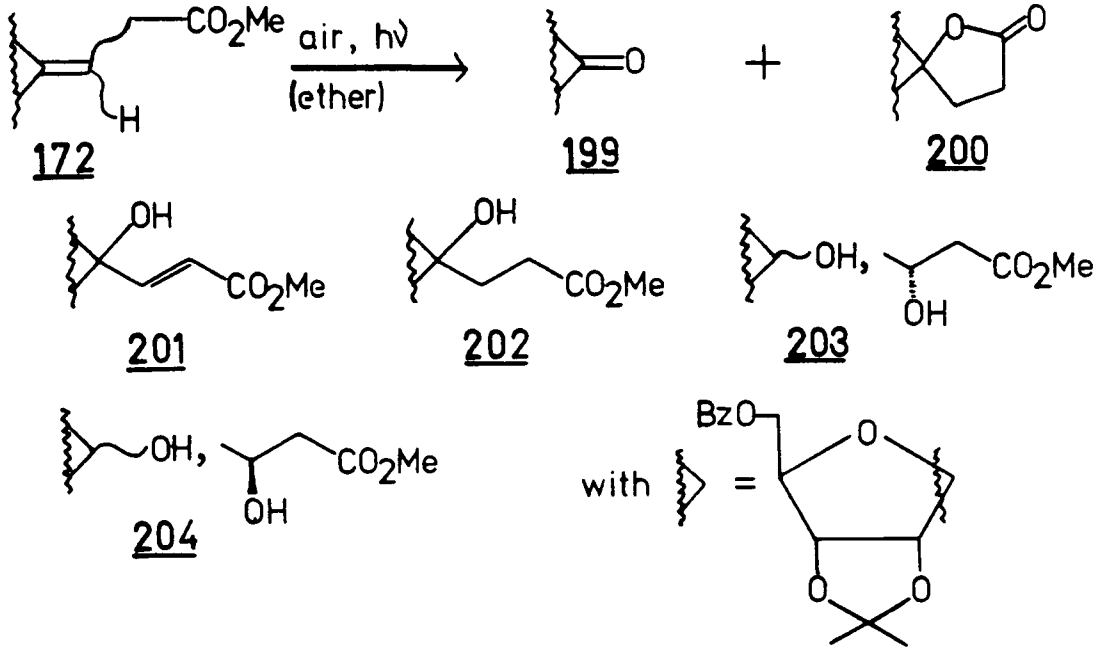
The oxidation and hydration products will be presented in order of chromatographic mobility, starting with the faster-moving components and will be followed by their chemical synthesis and derivatization.

The rate of the autoxidation process is dependent to the carbon-hydrogen bond strengths[182] of the substrates and the α-position of ethers and, in particular, the C-2 position of the 3-enonate is susceptable to autoxidation since the secondary hydrogens are 'α' to an carbonyl and allylic to a substituted enol ether group. The susceptability of 172 to autoxidation is exemplified by reports of facile peroxide formation[183] or oxidative polymerization[102] (e.g. compound 92) of similarly activated compounds.

3.1. 5-O-Benzoyl-2,3-O-isopropylidene-D-ribono-1,4-lactone (199), 8-O-Benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-4-octulofuranosono-1,4-lactone (200), Methyl(E)-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-oct-2-en-4-ulofuranosonate (201), Methyl 8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-4-octulofuranosonate (202), Methyl 8-O-benzoyl-2-deoxy-5,6-O-isopropylidene-α,β-D-allo (and altro)-4-octulofuranosonate (203) and (204), respectively.

When the methyl oct-3-enonate 172, contained in open test-tubes, was left in the chromatographic solvent (2:1 ether-hexanes) used for its purification and the solvents allowed to slowly evaporate while exposed to light and atmosphere of the room or when stored as a syrup in a stoppered glass flask, t.l.c. of the remaining syrup using 2:1 ether-hexanes as developer showed two major lower R_f products. Lesser amounts of intermediate and lower R_f charring materials were also observed (all slower moving than 172). Preliminary separation of the mixture was achieved by gradient elution of the syrupy mixture on a column of silica gel using

ether-hexanes. The various bands were isolation and rechromatographed with suitable solvent systems (see Experimental) to achieve separation of some of the many components. Thus, compounds 199, 200, 201, 202, 203 and 204 were isolated in 3.5, 8.2, 0.3, 2.7, 4.5 and 17.6% yields, respectively with compounds 203 and 204 as the major lower R_f products mentioned above since compounds 172 and 199-202 possessed similar R_f's using 2:1 ether-hexanes as developer.



The i.r. spectrum of the ribono-1,4-lactone 199 gave a strong absorption of 1802 cm^{-1} indicating the presence of the five-membered lactone ring.[143a] The n.m.r. spectrum of 199 clearly showed the absence of the methyl peak of the methyl ester and showed the easily resolvable multiplet of the ribo-sugar protons between δ4.44 and 4.94. The mass spectrum of 199 possessed a weak signal at 293 which was attributed to the protonated parent molecule and an extremely intense acetoxonium fragement at 277 (m^+-CH_3). The structure of 199 was also proven by chemical

synthesis. Treatment of the methyl oct-3-enonate 172 with excess meta-chloroperbenzoic acid (see Introduction, Section 3.2.4.) or oxidative cleavage of the vicinal hydroxy hemiketals 203 or 204 with periodate gave lactone 199. The spiro-lactone 200 exhibited the characteristic i.r. carbonyl peak at 1800 cm^{-1} while the n.m.r. spectrum showed four high-field methylene signals at ca. 2.60 along with the absence of the methoxy methyl group. The mass spectrum again showed a trace molecular ion signal (348) and a very intense acetoxium fragment at 333 (m^+-CH_3).

The unsaturated ketal 201 was isolated as a syrup and gave broad absorption bands at 3440 and 1720 cm^{-1} for the hydroxyl group and degenerate carbonyl groups, respectively. The n.m.r. spectrum of 201 in DMSO-d_6 contained three sharp methyl resonances and a pair of doublets at δ4.56 and 4.96 for H-5 and H-6, respectively. The assignment of the doublets is based on a slight broadening of the low-field doublet attributable to a small interaction with H-7 and on the fact these doublets are in similar positions in the n.m.r. spectrum of the saturated ketal 202 in which the low-field doublet is further split by ca. 1.0 Hz. Moreover, two sharp doublets ($J_{2,3}$ 16.0 Hz) at δ6.14 and 6.87 (H-2 and H-3, resp.) in the spectrum of 201 confirms the presence of an α,β-unsaturated ester grouping in the trans-orientation[160] and a sharp, D_2O-exchangeable, one proton singlet at δ6.89 suggests the presence of a tertiary hydroxyl.[146a] The mass spectrum showed a weak moelcular ion (378) and the anticipated acetoxium fragment at 363 (m^+-CH_3).

The saturated ketal 202 produced a broad absorption band at 3430 cm^{-1} in its i.r. spectrum indicating the presence of a hydroxyl group. The n.m.r. spectrum of 202 in DMSO-d_6 confirmed this assignment by the presence of a sharp, one-proton singlet at δ6.16 which disappeared upon addition of D_2O;

moreover, two high-field methylene groups along with a doublet ($J_{5,6}$ 6.0 Hz) for H-5 at δ4.44 and doublet of doublets ($J_{6,7}$ 1.0 Hz) for H-6 at δ4.86 were also present. The mass spectrum contained the acetoxonium fragment (m^+-CH_3) at 365 and weaker fragment at 363 (m^+-OH) due to the loss of the C-4 hydroxyl and resulting in an C-4 oxo-carbonium fragment.

The next component isolated was the higher R_f vicinal hydroxy β-ketal of 203 which was readily crystallized from dichloromethane-hexanes. The i.r. spectrum of 203 contained a broader and more intense absorption band at 3480 cm^{-1} than the previous two ketals which suggest the presence of more than one hydroxyl group. The n.m.r. spectrum of 203 in DMSO-d_6 possessed a sharp, one-proton singlet and doublet at δ5.25 and 6.08, respectively, both of which disappeared upon addition of D_2O. H-6 and H-5 were present as doublets at δ4.95 and ca. 4.52, respectively. This assignment was confirmed by a comparison with the n.m.r. spectrum of 203 in deuterochloroform which showed H-6 to be lower-field, broadened doublet ($J_{5,6}$ 6.0 Hz in both solvents). The n.m.r. spectrum of 203 in DMSO-d_6 produced a splitting in the methyl resonances upon addition of D_2O. These new signals were attributed to the presence of the α-anomer of 203, the presence of which was caused by the D_2O/HDO-catalyzed anomerization of the β-anomer of 203.[13b] The mass spectrum and chemical analysis corroborated the assigned empirical formula of 203.

The syrupy, lower R_f, vicinal hydroxy-ketal 204 was isolated as the major component (17.6%). The major differences between the two hydroxy-ketals 203 and 204 are their chromatographic mobility, their ability to form crystals, their optical rotation (-29.1 and +9.27° for 203 and 204, resp.) and their n.m.r. spectra. In regards to the latter, the n.m.r. spectrum of 204 in DMSO-d_6 indicated a 2:1 ratio of anomers which increased

(to approx. 4:1) upon addition of D_2O. The addition of D_2O also resulted in the loss of two singlets and a doublet at δ5.95, 5.60 and 5.29, respectively. The loss of a second doublet at ca. δ4.89 may have occurred but was obscured by an overlapping signal and a change in anomeric ratios.

3.1.1. Possible Mechanistic Pathways to Compounds 199 to 204.

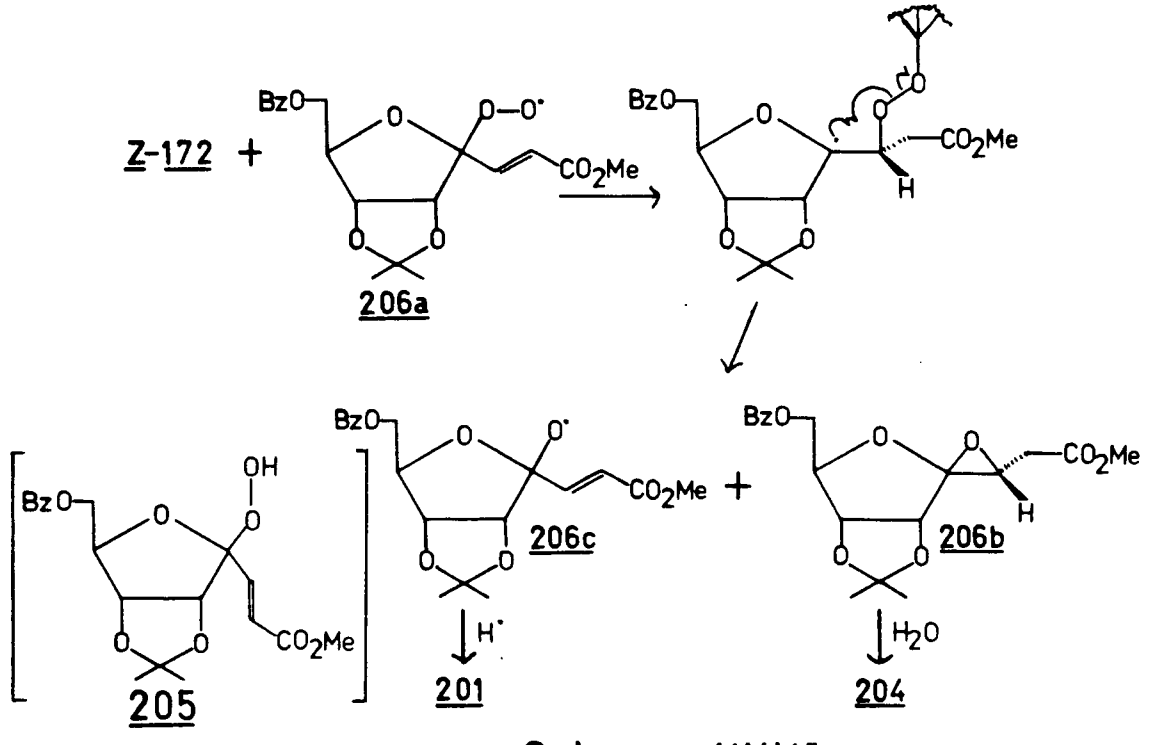
Although the mechanistic pathways to the above carbohydrates (199 to 204, inclusive) have not been investigated, the known reactions of olefins with oxygen and hydroperoxides and their radical precursors will be applied here to rationalize the formation of the above products from the methyl oct-3-enonate 172. References to structures of intermediates, reactions, and reaction schemes will be found in section 3.2.6. of the Introduction. Although several routes might lead to the desired product, the shortest and most probable route(s) will be presented.

The pathway to the ribono-1,4-lactone 199 can be envisioned as proceeding through the formation of a dioxetane intermediate[95,184a,b] such as 90, formed by the addition singlet oxygen to the 3-enonate 172, and subsequent decomposition of intermediate to give the carbonyl compound 199 (see Scheme XIII). A second route which involves triplet ground state oxygen requires the autoxidation of the 3-enonate 172 to the unsaturated peroxy ketal 205 which undergoes rearrangement (Scheme XIV) to give lactone 199. Other routes involving the hemiketals 201-204 or their precursors (vide infra) might provide a route to 199 via the Baeyer-Villiger rearrangement or a reaction similar to one depicted in Scheme XII (see Introduction, Section 3.2.4.).

The spiro-lactone 200, obviously arises from an intramolecular cyclization of the saturated hemiketal 202 or its precursor.

The unsaturated hemiketal 201 can come about by two routes; the first,

involves the dehydration of either of the β-hydroxy esters 203 or 204 to give 201 directly. The second route involves the peroxy-radical precursor (206a) to the peroxy hemiketal 205. This radical adds to a molecule of the 3-enonate 172 which then rearranges to form an epoxide of 172 (compd. 206b) and the alkoxy radical of 201 (compd. 206c, see Scheme XXVI below) which abstracts a hydrogen atom to give 201 (which also results in the propagation of the autoxidation process).



Scheme XXVI

The saturated hemiketal 202 obviously results from a hydration of the enol ether 172 (see Introduction, Section 3.2.1.). Intramolecular cyclization of 202 gives the spiro-lactone 200.

The hydroxy hemiketals 203 and 204 can arise from epoxide procursors as depicted in Scheme XXVI (vide infra) which hydrate to give the desired products. If other readily oxidizable substrates such as ethyl ether are present, the peroxide radical formed (similar to 206a) will also

compete for substrate 172. Another route to 203 and 204 and their oxirane precursors involve the hydroperoxide 205 and the hydroperoxides of ethyl ether. These hydroperoxides might react with 172 in a manner analogous to peracid reactions (see Introduction, Section 3.2.4.) with carbon-carbon double bonds (see Reaction (5)). The peroxy hemiketal structure of these hydroperoxides should enhance this latter mechanism and result in another pathway to 201. Hydration of 201 would also give to 203 and 204, although this hydration is not expected to contribute significantly.

3.1.2. Stereochemistry of 200-204.

The sterochemistry of the ketals of the methyl oct-3-enonate 172 has been briefly discussed in section 2.1.1.4 when the methyl glycoside 187 of the saturated hemiketal 202 was isolated. The conclusion reached in that discussion was that under equilibrium conditions ketals with an O-isopropylidene group at the 3,4-position of the furanoid ring (ie., the 2,3-position of aldofuranoses) prefer the β-configuration. A further correlation arising from the proton n.m.r. of the psicose derivatives concerns the chemical shifts of H-2 and H-3 (aldofuranose ring or H-5 and H-6 in the octulosonates under discussion).[171] The H-3 chemical shifts in the β-D-psicofuranosides were consistently downfield from the H-2 chemical shifts by 0.14 part per million (ppm) or more and in the α-anomers H-3 was up-field from H-2 (see Section 3.3.2. for an example of this shift in H-3). Another correlation which has been found for these isopropylidenated derivatives is that the chemical shift differences in the gem-dimethyl groups of the C-glycosides[167] have greater differences when the isopropylidene group and the anomeric substituent are in a trans-relationship. Both studies also showed that both the α-O and C-glycosides shows a greater

positive optical rotation.

In all four of the 2,3-dideoxy-4-octulofuranose derivatives 187, 201, 202 and 203, the β-configuration was given to the anomeric centre. These tentative assignments are basedon the above thermodynamic considerations and on the relative positions the H-5 and H-6 resonances. Only one anomer was isolated in each case (therefore, assigned the more stable β-configuration) and H-6 was consistently lower-field than H-5 (consistent with the β-configuration).

For the hydroxy hemiketals 203 and 204, two new chiral centres are present and both compounds exhibit an equilibrium in a DMSO-d_6/D_2O solvent system. The assignment of the stereochemistry at C-3 is based on the stereochemistry of the methyl oct-3-enonate 172 which has been determined (Section 2.1.) to be predominantly the Z-isomer and on the stereoselectivity of addition reactions to 172 and other exocyclic double bonds with similar steric environments. With substrates such 172, 46, and 92, hydrogenation,[102,185] hydroxylation with osmium tetroxide or permanganate[186], or hydroboration[102], all proceed from the side opposite of the isopropylidene group (i.e., the least hindered side). The hydroxylation of 172 with osmium tetroxide and meta-chloroperbenzoic acid gave predominantly the lower R_f hydroxy hemiketal 204, results which are analogous to the air oxidation of 172. Therefore, whatever the mechanism and stereochemical selectivity of the latter process, the former results indicate that topside (β-face) attack by the hydroxylation reagents on the major Z-isomer of 172 will give the 3-R-isomer (i.e., D-altro-isomer) 204 and topside attack on the E-isomer of 172 will give the 3-S-isomer (i.e., D-allo-isomer) 203 (for additional support see Section 3.3.2.).

The fact that the ratio of the two components present in the proton

n.m.r. spectrum of both hydroxy hemiketals 203 and 204 can be varied by the addition of D_2O is sufficient evidence to prove that the components in both compounds are anomeric or tautomeric components of the same parent carbohydrate. The synthesis of ribono-1,4-lactone 199 from 203 or 204 by periodate cleavage corroborates the vicinal orientation of the carbonyl at C-4 and hydroxyl at C-3. Additional proof of this structure for 203 and 204 is obtained by the isolation of 203 and 204 from the hydroxylation of the oct-3-enonate 172 with osmium tetroxide and meta-chloroperbenzoic acid.

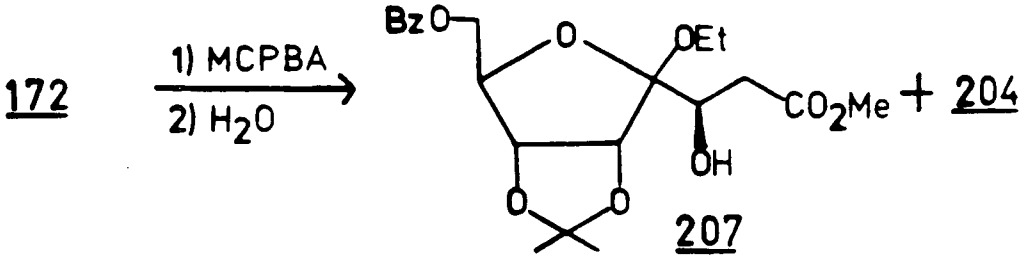
Although the proton n.m.r. spectra of 203 and 204 could not unequivocally establish whether or not a mixture of cyclic or acyclic and cyclic modifications of the parent carbohydrate were present in solution, the fact that a one-proton singlet and one-proton doublet (combined integration in the mixtures) which disappeared upon addition of D_2O did strongly suggest the presence of two cyclic modifications. This conclusion was supported by the fact that D-psicose and its 6-O-methyl derivative existed only in cyclic modications either in D_2O or DMSO-d_6 solution.[54] Confirmatory evidence for this conclusion was found in the carbon-13 n.m.r. spectra of 203 and 204 which contained only two carbonyl resonances (i.e., the benzoate and methyl ester) and a pair of ketal doublets (i.e., C-4 and the quaternary carbon of the isopropylidene group of the anomers) for both compounds; thus, providing unequivical support for the presence of the two anomers rather than a mixture of cyclic and acyclic tautomers.

Based on the discussion presented earlier in this subsection, the β-anomers of 203 and 204 would be expected to predominate. Support for this anticipated predominance comes from a variety of spectroscopic correlations. In the D-psicose series the anomeric hydroxyl proton proton was found to resonate at lower field in its β-furanose configuration[54] - ketose 203 and 204 had stronger low-field singlets. The β-anomer of D-psicose and its

derivatives produces its anomeric C-13 signal downfield from that of the α-anomer[54,187] - the low-field signal of the C-4 doublet of 203 and 204 predominated. The cis-orientation of C-3 and O-5 produces a smaller chemical shift difference in the gem-dimethyl group of the acetonides[167] - the major anomeric component of 203 and 204 chemical shift difference of ca. 15 Hz while the minor component has a difference of ca. 21 Hz; therefore, the major component possesses a cis-orientation of the isopropylidene and C-4 side chain (i.e., the β-anomer). Finally, the H-5 resonances of major anomers are found to be a sharp doublet at significantly higher field than H-6 thereby providing additional support for the predominance of the β-anomer.[171]

3.2. Treatment of 172 with meta-Chloroperbenzoic Acid (MCPBA) to ield Methyl (ethyl 8-O-benzoyl-2-deoxy-5,6-O-isopropylidene-β-D-altro-4-octulofuranosid)onate (207) and Compound 204.

Treatment of a dichloromethane solution of the methyl oct-3-enonate (172) with MCPBA gave a major product which was higher in R_f than the desire vicinal hydroxy hemiketals, 203 and 204. The hemiketal 204 was isolated in 10% yield after column chromatography of the reaction mixture but the ethyl glycoside 207 was isolated in 39%.



The i.r. spectrum of 207 possessed a broad band at 3560 cm^{-1} indicating the presence of a hydroxyl group and a broad carbonyl band 1727 cm^{-1}. The

n.m.r. spectrum of 207 in DMSO-d_6 exhibited three methyl groups and A_3B_2 quartet and triplet for the ethyl group at δ3.61 and 1.07, respectively. Moreover, H-6 was present as a broadened doublet at δ4.87 compared to 4.67 for H-5 which suggest the presence of the β-anomer. Since only one isomer of 207 was isolated, thermodynamic considerations similar to those for compounds 201-204 suggest that the β-anomer predominates (see previous section).

Compound 207 probably arises from the acid-catalyzed opening of the intermediate epoxide (e.g., compd. 206b) in the presence of trace alcohol used to stabilized halogenated solvents.

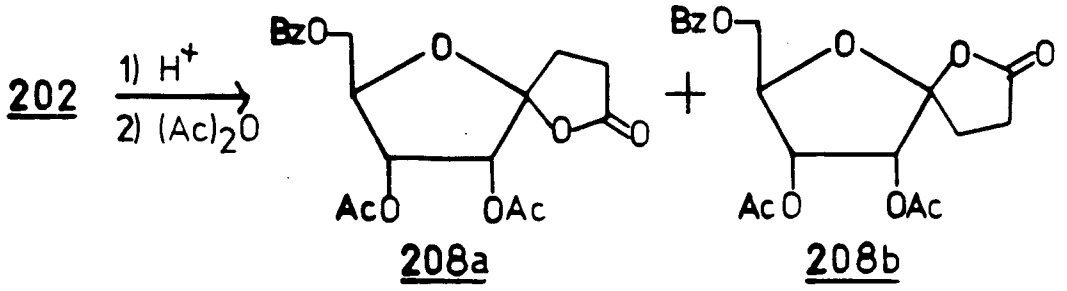
3.3. Derivatives of Ketals 202-204

The purpose of the synthesis of derivatives of ketals 202-204 was two-fold. First, the derivatives might give crystalline compounds (i.e., ketal 204 is a syrup) which are anomerically stable and thus, amenable to unambiguous characterization and possibly corroborate the configuration of C-3 of ketals 203 and 204. Secondly, it was hoped that some of these derivatives might lead to precursors of analogues of ketose N-nucleosides (see Section 4. and Introduction, Section 5.).

3.3.1. 5,6-Di-O-acetyl-8-O-benzoyl-2,3-dideoxy-α(andβ)-D-ribo-4-octulofuranosono-1,4-lactone (208a) and (208b), respectively

Treatment of the saturated hemiketal 202 with 80% aqueous trifluoroacetic acid followed by acetic anhydride give the spiro-lactones 208a and 208b in 24 and 34% yield, respectively. The n.m.r. spectra of 208a and 208b showed the loss of the methyl ester methyl group along with the shift of two of the furanoid hydrogens to lower-field. This acetylated lactone structure was confirmed by the presence of three carbonyl bands at ca. 1730,

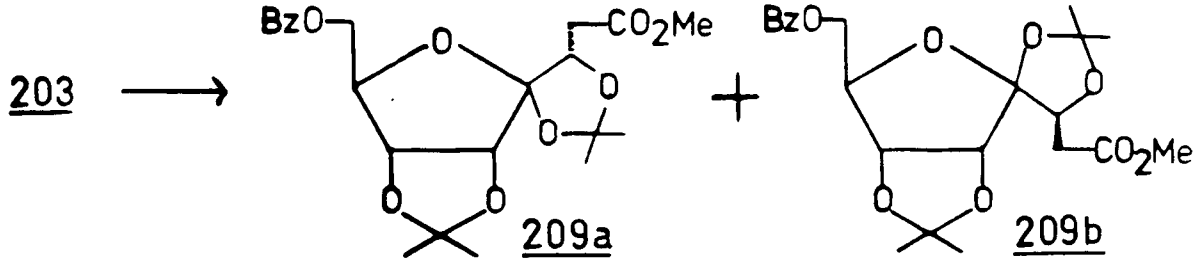
1760 and 1805 cm^{-1} for the five-membered lactone[143a], acetates and benzoates, respectively.



The assignment of the anomeric configuration is again based on the positions of the H-6 resonance in the n.m.r. spectrum.[171] The chromatographically more mobile component (compd. 208a) possessed a higher-field (0.17 ppm) H-6 signal and is therefore assigned the α-configuration and thus the β-configuration for 208b. This assignment is also supported by the more positive optical rotation for 208a (eg., +57.5° cf. -11.1° for 208b).

3.3.2. Methyl 8-O-benzoyl-2-deoxy-3,4:5,6-di-O-isopropylidene-α(and β)-D-allo-4-octulofuranosono-1,4-lactone (209a) and (209b), respectively.

Treatment of the vicinal hydroxy hemiketal 203 with trifluoroacetic acid, 2,2-dimethoxypropane, and acetone gave an anomeric pair of diacetonides 209a and 209b in 75 and 12% yields, respectively, the n.m.r. spectrum of both diacetonides showed five, sharp three-proton singlets for the methyl groups and an overlapping multiplet for H-3, H-5 and H-6. The multiplet for H-3 was easily resolved due to the coupling with H-2a and H-2b which enabled a facile assignment of H-5 and H-6 since H-6 was present as a broadened doublet.

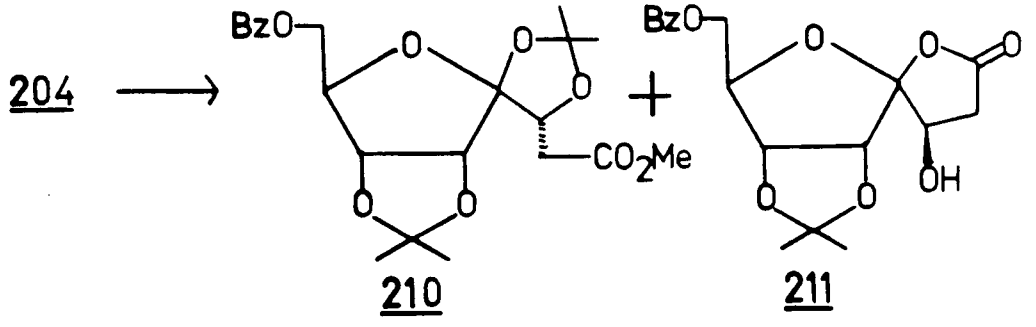


The configuration of the two anomers was again assigned on the basis of the relative chemical shifts of H-5 and H-6. The position of H-5 and H-6 in the α-anomer was δ4.76 and 4.66 and δ4.65 and 4.85 in the β-anomer, respectively; therefore, these relative chemical shifts support the assigned configurations with secondary support provided by optical rotation measurements (i.e., α-anomer possessing a more positive rotation). Additional spectroscopic correlation which supports the anomeric assignment along with the configurational assignment of C-3 was found in the chemical shift of H-2a and H-2b of the β-anomer 209b. H-2b resonates at significantly lower field relative to H-2a (0.52 ppm) - this difference has been observed in other di-O-isopropylidenated spiro-ketals and has been attributed to the deshielding effect of the oxygen at C-5.[188] Therefore, it can be seen from models of the various diastereomers that only the diacetonide of the β-anomer of the D-allo-octulose 203 (i.e., compd. 209b) can attain an orientation wherein the hydrogens of H-2 are in close proximity to O-5 in a conformationally confined system where one hydrogen on C-2 projects into the space occupied by one of the lone pairs on O-5; thus, supplying supportive evidence for the configurational assignment of C-3 in compounds 203 and 204.

3.3.3. Methyl 8-O-benzoyl-2-deoxy-3,4:5,6-di-O-isopropylidene-β-D-altro-4-octulofuranosonate (210) and 8-O-benzoyl-2-deoxy-5,6-O-isopropylidene-β-D-altro-4-octulofuranono-1,4-lactone (211).

Treatment of epimeric hemiketal 204 as above gave only one diacetonide 210 in 33% yield and a lactone 211 in 10% yield. The chemical and spectroscopic analyses of 210 were completely consistent with the proposed structure. The anomeric configuration of 211 is tentatively assigned the β-configuration and is based on the chemical shift of H-5 and H-6 (i.e., H-6 lower field

than H-5 cf. compds. 209a and 209b) with the optical rotation again providing secondary support.



210 211

The structure of compound 211 was evident from the loss of the methoxy methyl group of 204 in the n.m.r. spectrum of 211; moreover, the presence of a broad, single-proton triplet which disappeared upon addition of D_2O and resulted in the collapse of a high-field multiplet to a doublet of doublets (i.e., H-2b) and a mid-field doublet of doublets to a doublet (i.e., H-3) suggested a rather rigid spiro-lactone structure. I.r. absorbances at 3580 and 1812 cm^{-1} supported the presence of the hydroxyl and five-membered lactone groups.[143a]

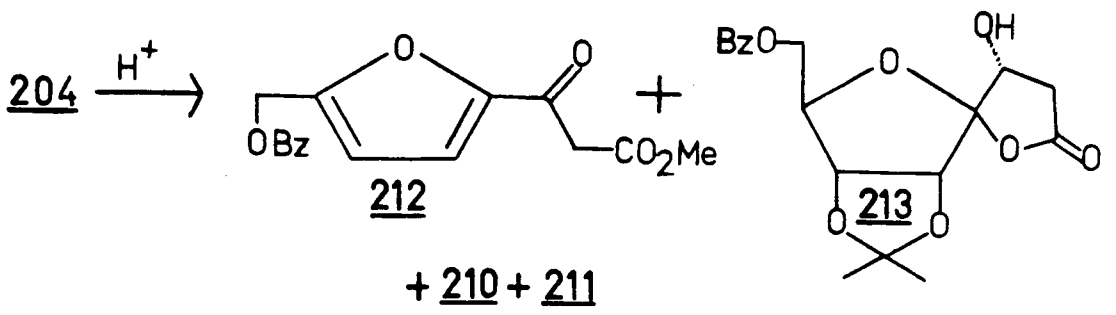
Comparison of lactone 211 with a chromatographically less mobile spiro-lactone (compd. 213; see Section 3.2.4.) isolated from a later synthesis starting with 204 suggested the β-configuration for 211 (e.g., from a comparison of chemical shifts of H-6 and optical rotations). Models of the spiro-lactone 211 indicate a sterically hindered spiro-system wherein O-3 and O-5 are in close proximity (cf. compd. 209b); however, this steric interaction might be stabilized by possible hydrogen-bonding between the C-3 hydroxyl and O-5. These two interactions produce a conformationally rigid spiro-system which results in a favourable orientation for a four-bond coupling between the hydroxyl proton and H-2b (2.0 Hz). Proton-proton spin-coupled interactions through four bonds has been observed for conformationally favourable rigid systems and the presence of a

heteroatom in the path between these interacting protons enhance this interaction.[189] The conformational immobility of 211 is also exemplified be the lack of an observable coupling interaction between H-2a and H-3.

3.3.4. Compounds 210, 211, 2-Benzoyloxymethyl-5-(carbomethoxyacetyl) furan (212) and 8-O--Benzoyl-2-deoxy-5,6-O-isopropylidene-α-D-altro-4-octulofuranosono-1,4-lactone (213) from 204.

When the hemiketal 204 was continuously azeotroped in a benzene solution in the presence of para-toluenesulfonic acid, four components, compounds 210, 211, 212 and 213, were isolated from the reaction mixture in 1.3, 39, 11 and 2% yields, respectively. The n.m.r. spectrum of the substituted furan derivative 212 showed three singlets and two doublets along with the benzoate signals and the i.r. spectrum of 212 exhibited three carbonyl bands at 1750, 1730 and 1670 cm^{-1} for the methyl ester, benzoate and conjugated ketone, respectively. The U.V. spectrum of 212 exhibited a strong absorption band at 276 nm which is consistent with the assigned structure.[190]

The acid-degradation of 204 to 212 probably arose from a series of eliminations similar to those outlined in schemes II and III (see Introduction, Section 1.1.). The O-isopropylidene group of 204 might have hydrolyzed before the degradation process to give acetone which reacts with 204 to give the diacetonide 210 or the vicinal hydroxy hemiketal 204 might have reacted with an intermediate in the degradation reaction which results in an exchange reaction to give intermediates which lead to 210 and 212, respectively. The latter route is expected to predominate.[194]

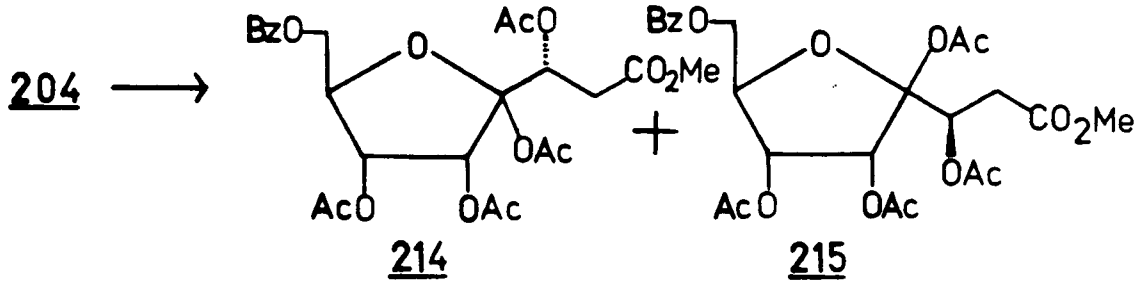


+ 210 + 211

Similar to its β-anomer 211, spiro-lactone 213 indicated the loss of methoxy methyl group of 204 in its n.m.r. spectrum. Also, H-3 showed significant broadening due to coupling with the hydroxyl proton. This interaction disappeared upon addition of D_2O and H-3 collapsed to a sharp triplet which when irradiated collapsed H-2a and H-2b to a pair of doublets. The i.r. spectrum confirmed the presence of the above functional groups with absorbances at 3500 and 1805 cm^{-1} for the hydroxyl and five-membered lactone[143a], respectively.

3.3.5. Methyl 3,4,5,6-tetra-O-acetyl-8-O-benzoyl-2-dexoy-α(andβ)-D-altro-4-octulofuranosonate (214) and (215), respectively.

Treatment of the hemiketal 204 with 80% trifluoroacetic acid and acetylation of the resulting mixture with acetic anhydride gave two tetra-acetates 214 and 215 in 7 and 25% yields, respectively. Separation of the two anomers on a column of silica gel gave the faster-moving β-anomer 215 followed by the α-anomer 214. The n.m.r. spectrum of both anomers in deuterochloroform showed five sharp methyl resonances and three single-proton multiplets at lower-field due to the acetylated secondary hydroxyls of H-3, H-5 and H-6. H-6 of the faster-moving component was at lower-field than the slower-moving tetraacetate (δ5.80 and 5.44, resp.) and was assigned the β-configuration.[171] The faster-moving tetraacetate also possessed a smaller positive rotation. The i.r. of both compounds possessed a strong band a ca. 1757 cm^{-1} and at strong shoulder at ca. 1731 cm^{-1} for the acetates



and benzoate groups, respectively.

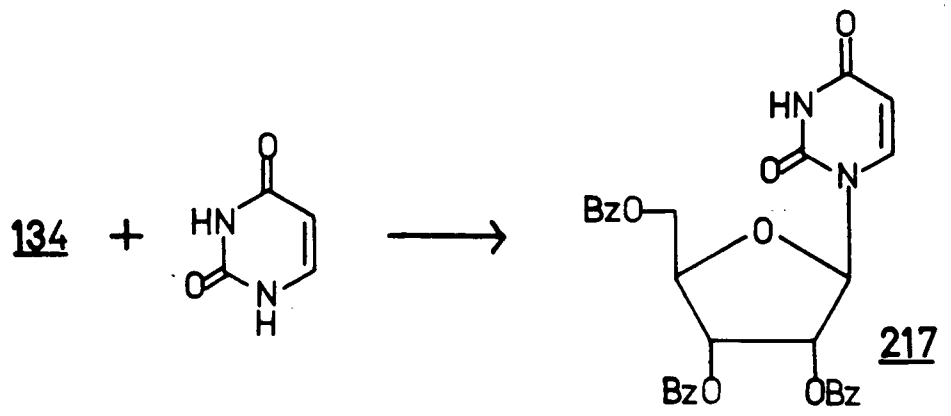
Attempted hydrogenation of the α-anomer 214 in the presence of platinum catalyst failed. The recovery of 214 supports the assigned cyclic structure of the tetraacetate.

4. Attempted Synthesis of Analogues of Psicofuranine (129).

The ketose N-nucleosides[113], of which psicofuranine (129) is one of its two known natural members, are a rare group of nucleoside antibiotics. The availability of two novel epimeric homologues of D-psicose, namely methyl 8-O-benzoyl-2-deoxy-5,6-O-isopropylidene-D-allo (and altro)-4-octulofuranosonate (203) and (204), respectively (Section 3.1.), prompted an investigation into the feasability of synthesis of a homologue of the antibacterial and antitumor nucleoside psicofuranine (129).

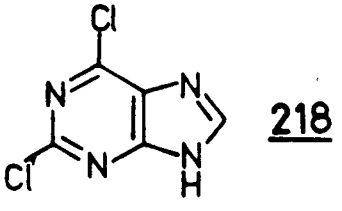
Farkaš and Šorm[136b] reported the synthesis of psicofuranine (129) in 4.6% yield starting from the benzoylated methyl psicofuranosides via the condensation of the mercuric chloride salt of N-benzoyl-adenine on the corresponding sugar bromide. Several attempts were made to condense a purine or pyrimidine base onto derivatives of ketose 204; however, none of the attempts gave any significant amount of nucleoside material. The synthetic strategies will, therefore, be only briefly discussed. Synthetic methods[112,116,191a] and mechanisms[192] of the condensation reactions have been thoroughly reviewed and will not be dealt with here.

a) Following the method of Vorbrüggen and Bennua[193], the acylated D-ribofuranoside 134 was condensed with uracil (216) to give 2′,3′,5′-tri-O-benzoyl-uridine (217) in 69% yield. Substitution of 134 with the acylated

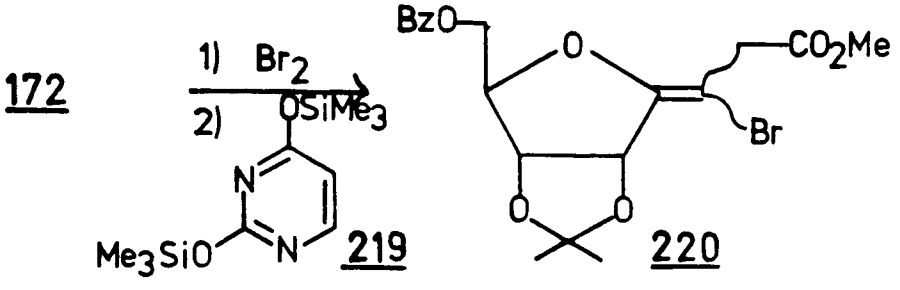


methyl 4-octulofuranosonate 214 gave a multicomponent mixture, none of which could be reconciled with the desired adduct.

b) Utilization of the fusion procedure[191b] with 214 and 2,6-dichloropurine (218) also gave negative results.



c) An attempt to utilize the methyl oct-3-enonate 172 directly[4] in the synthesis of a ketose N-nucleoside was also unsuccessful. Thus, the addition of bromine to 172 followed by bis(trimethylsilyl)thymine (219) gave a predominantly faster-moving product upon silica gel chromatography. This unstable product has been tentatively assigned as methyl (E,Z)-4,7-anhydro-8-O-benzoyl-3-bromo-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (220).



The n.m.r. spectrum of 220 showed a broadening of the isopropylidene methyl signals and doublets for H-2 and the methoxy methyl. The mass spectrum of 220 showed a very intense molecular ion doublet of 440/442 due to the bromine isotopes and the strength of the signal supports the enolic structure for 220. The facile loss of hydrogen bromide from bromine adducts of enolic compounds has been reported[102] and the possible catalytic activity of amino compounds in the elimination to give enolic compounds has also been used synthetically (see Introduction, Section 1.1.).

IV EXPERIMENTAL

1. General Methods

P.m.r. spectra were determined in chloroform-d or dimethyl sulfoxide-d_6 with tetramethylsilane as the internal standard (set at δ=0) or in deuterium oxide with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as the external standard (set at δ=0) by using a Varian HA-100, Varian XL-100, Bruker 270 or Bruker 400 spectrometer. Values given for coupling constants are first order. Carbon-13 n.m.r. spectra were determined in chloroform-d or dimethylsulfoxide-d_6 with tetramethylsilane as the internal standard by using a Varian CFT-20 spectrometer. Optical rotations were measured at ambient temperature with a Perkin-Elmer Model 141 automatic polarimeter. Infrared spectra were recorded on a Perkin-Elmer 710B or 727B spectrometer. All melting points were done on a Leitz microscope heating stage, Model 350, and are corrected *via* a calibration curve. Mass spectra were determined on a Varian/MAT CH4B or Kratos MS902 low resolution or a Kratos MS50 hi-resolution spectrometer. Ultraviolet spectra were recorded on a Cary 15 spectrometer. Reaction temperatures were measured *via* an external oil bath unless otherwise stated. Elemental analyses were performed by Mr. P. Borda of the Microanalytical Laboratory of the University of British Columbia.

2. Chromatography

2.1. Column Chromatography

Silica gel column chromatography was performed using *silica gel H for thin layer chromatography* (Merck). The ratio of substrate to absorbent was approximately 1:100 (w/w) and the ratio of column length to diameter was approximately 10:1. Columns were pressurized above the solvent reservoir at 8-12 p.s.i. providing flow rates of 30-500 ml h^{-1}.

2.2. Thin Layer Chromatography

All thin layer chromatography was performed using silica gel (Camag) containing 5% calcium sulfate. Compounds were detected by ultraviolet absorption and/or by spraying with 50% sulfuric acid followed by heating on a hot plate.

3. Abbreviations

The abbreviations used in the following descriptions are as follows: n.m.r.(nuclear magnetic resonance), p.m.r.(proton magnetic resonance), u.v.(ultraviolet), i.r.(infrared), m.p.(melting point), t.l.c.(thin layer chromatography), DMF(N,N,-dimethylformamide), DMSO(dimethyl sulfoxide), THF(tetrahydrofuran), MeOH(methanol), s(singlet), d(doublet) dd(doublet of doublets), t(triplet), q(quartet), and m(multiplet).

4. (R) and (S)-Dihydroshowdomycin (171) and (170), respectively.

4.1. Synthesis of Methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-2-enonate (18) from 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (134).

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl Cyanide (127)

Dry gaseous hydrogen bromide (passed through granular P_2O_5) was bubbled through a stirred solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 134 (126 g, 0.25 mol) in anhydrous benzene (500 ml). The mixture was cooled in an ice bath while the gas flow was carefully maintained to retain a positive gas pressure. The solution was saturated and gas flow continued for 60 min after which the gas inlet and ice bath were removed and the reaction mixture was allowed to stand at room temperature for an additional 45 minutes. Dry nitrogen gas was passed through the solution to displace the hydrogen bromide and the solution was evaporated under reduced pressure (bath temperature 40°C) and the residue coevaporated with 400 ml anhydrous benzene. The resulting amber syrup was dissolved in nitromethane (300 ml)

(dried by distillation over P_2O_5), powdered mercuric cyanide (125 g, 0.485 mol)(predried at 140°, 0.10 mm Hg for 24 hours) added and a drying tube was then attached to the reaction flask (performed in a dry-box). The mixture was stirred for 20 hours at room temperature after which the insoluble portion was filtered off and washed with benzene to yield a greenish filtrate. The combined filtrates were evaporated under reduced pressure and the resulting syrup was dissolved in chloroform (2.0ℓ) and washed with 5% aqueous potassium iodide (2 x 200 ml) and water (2 x 100 ml), dried over sodium sulfate, evaporated under reduced pressure, and the crude syrup dissolved in ethanol (200 ml). Approximately half the ethanol was evaporated under reduced pressure, the concentrate seeded and allowed to crystallize at room temperature over-night. The crystalline mass was triturated with a mixture of ethanol-ether (85:15, 100 ml), the crystals collected and washed with ethanol. The filtrates were combined, evaporated and the residue crystallized from ethanol over several weeks with periodic evaporation (under reduced pressure) of small portions of ethanol until a brown oil formed after which the crystalline ribosyl cyanide 127 was collected and washed with ethanol (overall yield: 96.5 g, 81.6%)(lit.~88%); m.p. 78-80.5°, (lit.[131] m.p.78.5-80°); n.m.r. (60 MHz, $CDCl_3$): δ4.91(d,1H, $J_{1,2}$ 4.0 Hz,H-1)(lit.[131] δ4.425,d,H-1); $[\alpha]_D^{24}$ + 23.9 (c0.5,$CHCl_3$), (lit.[131] + 23.8 (c0.5,$CHCl_3$)). Final verification of structure was evident in the following derivatizations.

5-O-Benzoyl-β-D-ribofuranosyl Cyanide (135)

A solution of the blocked ribosyl cyanide 127 (90 g) in anhydrous chloroform (900 ml) was added to a stirred, ice-cooled solution of saturated methanolic ammonia (1350 ml) and kept in an ice bath for 4.5 h. The solvent was then evaporated under reduced pressure (in 500 ml portions), and the resulting

clear syrup was dissolved in ethyl acetate (300 ml), washed with saturated aqueous sodium bicarbonate (30 ml), water (30 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield a clear syrup. The residual syrup was allowed to crystallize from benzene-hexane overnight in the refrigerator to give the crystalline partially unblocked cyanide 135 (37.2 g,72.5%)(lit.[141a] 83%); m.p. 117-118.5, (lit.[141a] 117-117.5(118)). Smaller scale reactions were found to give yields comparable to the literature yield.

5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl Cyanide (136)

To a solution of 70% perchloric acid (3.6 ml), 2,2-dimethoxypropane (30 ml), and acetone (180 ml) was added the partially unblocked ribosyl cyanide 135 (25.0 g). The resulting dark red solution was stirred at room temperature for 2 h. The reaction mixture was then neutralized (as indicated by litmus paper) with ammonium hydroxide and evaporated, leaving a residue which was dissolved in chloroform (250 ml) and washed with water (2 x 25 ml). The organic layer was dried over anhydrous sodium sulfate, evaporated and the crude yellow syrup crystallized from ether-hexane to yield the isopropylidenated cyanide 136 (26.4 g, 91.6%) (lit.[141a] 95%); m.p. 62° (lit.[141a] 60-61).

1,3-Diphenyl-2-(5-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl) imidazolidine (138)

To a suspension of Raney nickel (100 g)[195,*], 1,1-dianilinoethane (27 g), and sodium hypophosphite (55 g) in 212 ml of a mixture of pyridine, acetic acid and water (2:1:1) was added to the blocked ribosyl cyanide 136 (26.35 g) which resulted in a vigorous exothermic reaction with an evolution of vapors. The mixture was stirred vigorously for 1 h. The mixture was then filtered[**]

* The Raney nickel was measured by activating 200 g of Raney nickel alloy.
**The Raney nickel was still very active, so that caution must be exercised during the filtration and washing.

and the residue washed thoroughly with chloroform. The combined filtrates were diluted to a volume of 4.5 ℓ with chloroform. This mixture was divided into 3 portions and each portion was washed with water (2 x 300 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to yield a partially crystalline syrup that completely solidified under vacuo, over-night, at room temperature. The solid mass was triturated with methanol to yield a yellow paste that was filtered, washed with methanol and dried to yield the blocked ribosyl imidazolidine 138 (32.5 g, 74.5%) (lit.[141a] 78%); m.p. 144.5-148 (lit.[141a] 144-145).

Carbomethoxymethylenetriphenylphosphorane (17)[196]

To a stirred solution of triphenylphosphine (135 g, 0.51 mol) in benzene (600 ml) was added dropwise methyl bromoacetate (76 g, 0.50 mol) over 30 min resulting in a mildly exothermic reaction which precipitated the phosphonium bromide. The mixture was cooled in the refrigerator for 3h, filtered and washed with a small portion of benzene. The filtrate was concentrated until crystals appeared and allowed to cool overnight in the refrigerator. The second batch of the bromide was collected and dried (combined yield; 182 g,85%).

To a stirred solution of carbomethoxymethyltriphenylphorphonium bromide (182 g) in water (4 ℓ) was added slowly a 1N aqueous sodium hydroxide solution until the reaction mixture was alkaline to phenolphthalein. The pink, milky slurry was filtered and washed with water to neutrality. The filter cake was then transferred in small portions to a flask containing stirring methylene chloride (250 ml) and sufficient methylene chloride was added to permit complete dissolution of the crude, wet phosphorane. The aqueous phase was withdrawn and the organic phase washed with water, dried, evaporated and recrystallized from ethyl acetate-petroleum ether (30-60) to yield the

triphenylphosphorane 17 (128g,77%); m.p. 170.5-172 (lit.[196a,b] 162-163°, 170-172° respectively); n.m.r. (60 MHz, $CDCl_3$); δ2.74(s,1H,H-2), 3.43(s,3H,$-OCH_3$) and 7.17-7.74(m,15H,Ar).

Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-2-enonate (18).

To a stirred solution of the blocked ribosyl imidazolidine 138 (12.5 g, 25 mmol) and methylene chloride (250 ml) in an ice-water bath was added a solution of p-toluenesulfonic acid monohydrate (13.0 g, 68.5 mmol) in acetone over 10 min. The resulting mixture was stirred an additional 20 min. The mixture was then filtered through celite directly onto solid sodium hydrogen carbonate (5.0 g) and the residue washed with methylene chloride. The combined filtrates were filtered through CELITE and evaporated to yield a clear syrup which produced a wide band on the t.l.c. plate (2:1 ether-hexanes as developer) with the absence of any starting compound. This syrup of the anhydroaldehyde 137 was immediately dissolved in a solution of the phosphorane 17 (16.6 g) in methylene chloride (125 ml) and stirred for 1 h at room temperature. The mixture was evaporated and triphenylphosphine oxide solidified in the resulting syrup. The mixture was triturated with a minimum of methylene chloride, filtered, washed with methylene chloride and the filtrates evaporated to yield a golden syrup which was chromatographed on silica gel (500 g) using 2:1 ether-hexanes as developer. The major chromatographically pure band was collected to yield the unsaturated ester 18 (7.45 g,82%)(lit.[20] 88%) as a colorless syrup that was shown to be mixture of geometric isomers by n.m.r. (∿8:1) with the E-isomer predominating: $\nu_{max}^{CCl_4}$ 1730(C=O), 1670 cm^{-1}(-C=C-)(lit.[20] ν_{max}^{film}1730 cm^{-1}); n.m.r. (100 MHz,$CDCl_3$) δ1.29 and 1.52(s,3H,$C(CH_3)_3$), 3.62

(s,3H,-OMe), 6.11(dd,1H,$J_{2,3}$ 16 Hz,$J_{2,4}$ 1.5 Hz,H-2), 6.99(dd,1H,$J_{3,4}$ 4.0 Hz, H-3)(lit.[20] n.m.r. δ1.38 and 1.60, $C(C\underline{H}_3)_2$; 3.73, -OMe; 6.21, H-2; 7.10, $J_{3,4}$ 3.5 Hz,H-3; respectively).

4.2 Photoamidation of Unsaturated Sugars

Photoamidation reactions were carried out using a procedure previously described[50]. The light source in these reactions was a Hanova 450 W type L lamp. The photochemical reactions were carried out by placing the lamp and a pyrex filter inside a water cooled quartz immersion well apparatus which was placed inside a 3-necked pyrex vessel containing the reaction solvents (capacity with lamp ∿300 ml). The photolysis mixture was agitated via a magnetic stirring bar and the whole apparatus wrapped in aluminum foil. Distilled tert-butanol, spectrograde acetone and reagent grade formamide were used. All photochemical reaction mixtures were deoxygenated with nitrogen overnight and during the course of the irradiations.

Photoamidation of Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-2-enonate (18) to Yield 3-(R,S)-(5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-hydroxy-4-methyl-pentanoic 1,4-lactone (139), Methyl 4,7-anhydro-8-O-benzoyl-3-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-octonate (140), (141) and Methyl 4,7-anhydro-8-O-benzoyl-2-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-octonate (142), (143), respectively.

A solution of the α,β-unsaturated ester 18 (3.7 g), acetone (15 ml), tert-butanol (15 ml) and formamide (30 ml) was added slowly to a mixture of tert-butanol (10 ml) and formamide (200 ml) contained in the photolysis cell over 3.5 h. The mixture was irradiated during the addition and continued

for 25 h (or until all of the starting material had been consumed, as evidenced by t.l.c. of the reaction mixture using 8:4:1 benzene-ethylacetate-ethanol as developer). The reaction mixture was then concentrated by removal of the tert-butanol and acetone under reduced pressure at ∿50°. The resulting solution in formamide was diluted with saturated aqueous sodium chloride (200 ml), extracted with dichloromethane (4 x 200 ml), the combined extracts concentrated to approximately 100 ml and the concentrated extracts were then washed with saturated aqueous sodium chloride (50 ml). The organic phase was collected, dried over anhydrous sodium sulfate, filtered and evaporated to yield a crude syrup (3.9 g). Chromatography of this syrup on silica gel (470 g) using 8:4:1 benzene-ethyl acetate-ethanol as developer gave crude lactone (139) as a clear syrup (1.46 g) which was contaminated with lower R_f impurities. This mixture was later rechromatographed using a weaker solvent system.

Continued elution of the chromatography column gave, as a single amide band, compounds 140, 141, 142 and 143 (combined yield: 1.3 g, 31%). The amide band was shown to be a mixture of the four isomers by n.m.r. and by derivatization with sodium methoxide. The derivatization mixture indicated that photoamidation of compound 18 favors β-addition to α-addition by an approximate ratio of 10:1 and that compounds 140 and 141 were formed in equal amounts. Since the amides could not be separated by chromatography nor fractional crystallization, they were charactered as a mixture of four amides. An analytical sample was obtained by crystallization from chloroform-hexane: m.p. 141-145° (fine neeldes); $[\alpha]_D^{25}$ -29.5 (c1.0, $CHCl_3$); $\nu_{max}^{CCl_4}$ 3180, 3365, 3480 (broad, NH_2), 1690 (amide, C=O), 1727, 1738 cm^{-1} shoulder (esters, C=O); n.m.r. (100 MHz, $CDCl_3$) δ1.33 and δ1.53(s,3H,C(CH_3)$_2$), δ1.98-3.25(m,2.5H,H-2,H-3), 3.64 with 3.71 side band (s,3H,-OCH_3), 3.94-4.80

(m,6H,H-4,H-5,H-6,H-7,H-8), 5.96,6.08,6.43 (broad s,2H total,$N\underline{H}_2$, exchangeable with D_2O, 7.52(m,3H,Ar), 8.06(m,2H,Ar); mass spectrum: m/e 392 (m^+-CH_3), 376(m^+-OCH_3).

Anal. Calc. for $C_{20}H_{25}NO_8$:C,58.96;H,6.14;N,3.44. Found:C,58.76;H,6.14; N,3.50.

Rechromatography of the high R_f (with respect to the amides) components on silica gel using 40:8:1 to 5:4:1 benzene-ethyl acetate-ethanol gradient, yielded only one chromatographically homogeneous band, consisting of the diastereomeric mixture of lactone 139 (0.45 g, 11%, ~50/50 mixture). The lactones were inseparable on t.l.c. and could not be crystallized from various solvents: $[\alpha]_D^{23}$-23.4 (c1.4, $CHCl_3$) ; $\nu_{max}^{CCl_4}$ 1728(benzoate,C=0), 1780(lactone,C=0); n.m.r.(100 MHz, C_6D_6),(isomer no.1), δ1.08, 1.18, 1.30 and 1.43(s,3H,4x$C\underline{H}_3$), 2.24(d(overlapping H-2b,1H,$J_{2a,3}$ 9 Hz,H-2a), 2.25 (d(overlapping H-2a),1H,$J_{2b,3}$ 11 Hz,H-2b), 3.66(pseudo-t,1H,$J_{3,1'}$ and $J_{1',2'}$ 6 Hz,H-1'), (isomer no.2), δ1.14(s,6H,2xCH_3),118 and 2.40(s,3H,2xCH_3), 2.38(d(overlapping H-2b),1H,$J_{2a,3}$ 8 Hz,H-2a), 2.39(d(overlapping H-2a),1H, $J_{2b,3}$ 9 Hz,H-2b), 3.225(pseudo-t,1H,$J_{3,1'}$ and $J_{1',2'}$ 4.5 Hz,H-1'), (combined isomers), δ1.84-2.12(m,1H,H-3), 3.91-4.42(m,5H,H-2',H-3',H-4',H-5), 7.12 (broad s(overlapping C_6D_6), 5.3H,Ar), 8.10(m,2H,Ar). Irradiation of the multiplet at δ1.94 partially collapsed the pair of pseudo-triplet at δ3.64 to a broad triplet. Irradiation of the pair of pseudo-triplets at δ3.64 collapsed the multiplet a δ1.94 to a broad quartet($J_{2,3}$ 8 to 12 Hz); mass spectrum m/e 390(m^+), 375(m^+-CH_3), 332(m^+-Acetone).

Anal. Calc. for $C_{21}H_{26}O_7$: C,64.60; H,6.72. Found: C,63.88; H,6.77.

Attempted Cyclization of Compounds 140 and 141 by Refluxing in Basic Solvent

A mixture of the amides 140, 141, 142 and 143 (125 mg) was dissolved in pyridine (6 ml) and refluxed (bath temperature: 135-145°) for 5h. T.l.c.

of the solution showed only one charring band identical to that of the starting materials.

Attempted Cyclization of Compounds 140 and 141 by Refluxing in High Boiling Point Solvent

A mixture of the amides 140, 141, 142, and 143 (22 mg) was dissolved in xylene (1 ml) and refluxed for 5h. T.l.c. of the solution showed only one charring band which was identical to the starting amides.

Cyclization of Compounds 140 and 141 by Thermal Ring Closure in the Absence of a Solvent to give 3-(R) and (S)-(5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)succinimide (151) and (152), respectively.

A round bottom flask containing a mixture of amides 140, 141, 142 and 143 (130 mg) equipped with two traps in series joined together by standard-taper ground glass joints was placed in a Kugelruhr vacuum distillation apparatus. The reaction flask along with the first trap was placed in the heated compartment, the internal pressure was reduced (∿100 torr), and the reaction flask heated to 200-217° (surrounding air temperature) for 45 min while the flask was gently rocked. After this time the material in the flask had begun to char. The apparatus was allowed to cool and then the reaction flask and central trap was rinsed out with methanol to give a brown suspension which was filtered and evaporated to yield a brown syrup (72 mg). The syrup was dissolved in a small amount of methanol and applied to a column of Bio-Rex 70(H^+) resin (∿90 ml) and eluted with methanol. The major higher R_f (0.42 using 15:4:1 benzene-ethyl acetate-ethanol as developer) material was isolated (26 mg) and rechromatographed on a silica gel plate (15x20 cm, 1.0 mm, x2 with 18:4:1 mixture of the above solvents) to yield two partially overlapping bands. Careful removal and elution of the faster-moving component gave compound 151 as a

clear syrup (7.0 mg,6%,>95% purity); n.mr. (100 MHz,$CDCl_3$) δ1.38 and 1.57(s,3H,C($C\underline{H}_3$)$_2$), 2.71(dd(overlapped by H-4b),1H,J_{gem} 18.0 Hz,$J_{3,4a}$ 8.0 Hz, H-4a), 2.93(dd(overlapped by H-4a),1H,J_{gem} 18.0 Hz,$J_{3,4b}$ 8.0 Hz,H-4b), 3.26 (m,1H,$J_{3,1'}$ 2.5 Hz,H-3), 4.14-4.33(m,2H,H-1′,H-4′), 4.39-4.62(m,2H,H-5′), 4.74(dd,1H,$J_{2',3'}$ 7.0 Hz,$J_{3',4'}$ 4.8 Hz,H-3′), 5.25(dd,1H,$J_{1',2'}$ 4.0 Hz, H-2′), 7.55(m,3H,Ar), 7.90(broad s,1H,N$\underline{H}$), 8.09(m,2H,Ar). Irradiation of the doublet of doublets at δ5.25 or the multiplet at δ3.26 partially collapsed the high field portion of the multiplet at δ4.14-4.33. The 100 MHz spectrum with benzene-d_6 solvent confirmed the assignment order as: H-1′,H-4′,H-5′, H-3′ and H-2′ from high- to low-field.

Removal and extraction of the slower-moving component from the plate afforded the epimeric 3-$\underline{S}$ compound $\underline{152}$ (8.5 mg,7%,>90% with compound $\underline{151}$ as the main impurity), n.m.r. (100 MHz, $CDCl_3$) δ1.37 and 1.58(s,3H,C($C\underline{H}_3$)$_2$), 2.73(d,2H,$J_{3,4}$ 7.0 Hz,H-4), 3.19(m,1H,H-3), 4.32(pseudo-q(partially overlapped by H-1′),1H,$J_{3',4'}$ 4.0 Hz, $J_{4',5'}$ 4.0 Hz,H-4′), 4.38(dd(partially overlapped by H-4′),1H,$J_{3,1'}$ 3.8 Hz,$J_{1',2'}$ 5.3 Hz,H-1′), 4.51(d,2H,H-5′), 4.54(dd(partially overlapped by H-5′),1H,$J_{1',2'}$ 5.3Hz,$J_{2',3'}$ 6.5 Hz,H-2′), 4.72(dd,1H,H-3′), 7.56(m,3H,Ar), 8.05(m,2H,Ar), 8.20(broad s(partially buried under the low-field aromatic resonances),1H,N$\underline{H}$). Irradiation of the multiplet at δ3.19 partially collapsed the doublet of doublet at δ4.38 to a doublet ($J_{1',2'}$ 5.3Hz) overlapping two of the low-field signals of the H-4′ pseudo-quartet.

The higher R_f minor component eluted by the resin column was, therefore, not analyzed and a small portion (33 mg,25%) of starting material was recovered.

Treatment of a Mixture of the Amides 140, 141, 142, and 143 with Methanolic Sodium Methoxide to Yield (151), (152), 3(S) and (R)-(2,3-O-isopropylidene-β-D-ribofuranosyl)succinimide[(S) and (R)-dihydroshowdomycin acetonide], (153), (154), and Methyl 4,7-anhydro-2-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and D-altro)-octonate (155) and (156), resp.

To a stirred solution of the amides 140, 141, 142, and 143 (330 mg, ∿45:45:5:5 mixture, resp.) in anhydrous methanol (33 ml) was added methanolic sodium methoxide (2.0 ml,0.2N) in 0.2 ml portions over 2.5 h at room temperature under dry nitrogen atmosphere. The reaction mixture was then neutralized with sufficient Bio Rex 70(H^+) resin (in methanol) as indicated by pH paper. The mixture was filtered and the methanol evaporated under reduced pressure to yield a crude syrup (400 mg) which released the sweet odor of an ester (e.g. methyl benzoate). Preliminary purification of the syrup on silica gel (35 g) using a 15:4:1 to 5:4:1 benzene-ethyl acetate-ethanol gradient as developer yielded the blocked ribosyl succinimides 151 and 152 (168 mg, 55%) as partially resolved (by t.l.c. using 15:4:1 developer) fractions which by n.m.r. were shown to be identical to the succinimides produced by the thermal ring closure of the starting amides (see page 148).

Continued elution of the chromatography column gave a mixture of imides 153 and 154 (86 mg,28%)(which were later rechromatographed) and a final band of the debenzoylated, α-addition amides 155 and 156 (21.5 mg,9%).

Very careful chromatography of the mixture of acetonides 153 and 154 in small portions (∿30 mg) on silica gel (6.0 g) using 8:4:1 benzene-ethyl acetate-ethanol as developer afforded a slightly higher R_f (0.329) pink charring band which could be induced to crystallize rapidly in a chloroform solution to yield a 1:1 complex with the solvent (chloroform): m.p. 77.5-80.5° (neeldes).

Anal. Calc. for $C_{12}H_{17}NO_6 \cdot CHCl_3$:C,39.96;H,4.65;Cl,27.23;N,3.56. Found:C,40.04;H,4.47;Cl,27.11;N,3.63.

Recrystallization of the same higher R_f band from hexane-benzene-ethanol yielded crystals of 153 which were free of solvent; m.p.123-125° (lit.[118a] 173-174°); $[\alpha]_D^{25}$ -9.27°(c1.0,$CHCl_3$); $\nu_{max}^{CHCl_3}$ 3475,3410(NH), 3225(broad,OH),1725,1780 cm^{-1} weak shoulder (amide carbonyl); n.m.r. (100 MHz,DMSO-d_6) δ1.29 and 1.47(s,3H,C(CH_3)$_2$), 2.63(d,2H,$J_{3,4}$ 7.0 Hz,H-4), 3.16(t of d,1H,$J_{3,4}$ 7.0 Hz,$J_{3,1'}$ 3.5 Hz,H-3), 3.49(dd,2H,$J_{4',5'}$ 4.0Hz,$J_{OH,5'}$ 5.0Hz, collapses to a doublet of 4.0Hz upon addition of D_2O,H-5'), 3.87 (pseudo-q,1H,$J_{4',5'}$ 4.0 Hz,$J_{3',4'}$ 4.0Hz,H-3'), 4.14(dd,1H,$J_{3,1'}$ 3.5Hz, $J_{1',2'}$ 5.0Hz,H-1'), 4.46(dd,1H,$J_{1',2'}$ 5.0Hz,$J_{2',3'}$ 6.5Hz,H-2'), 4.61(dd, 1H,$J_{2',3'}$ 6.5Hz,$J_{3',4'}$ 4.0Hz,H-3'), 4.87(t,1H,$J_{OH,5'}$ 5.0Hz,OH,exchangeable with D_2O), 11.13(broad s,1H,NH,exchangeable with D_2O). Irradiation of the pseudo-quartet at δ3.87 partially coallpsed the doublet of doublets of δ4.61 to a broad doublet and collapsed the doublet of doublets at δ3.49 to a doublet. Irradiation of the triplet of doublets at δ3.16 collapsed the doublet of doublets at δ4.14 to a doublet and collapsed the doublet at δ2.63 to a broad singlet m/e 272(m^++H), 256(m^+-CH_3), 240(m^+-OCH_3).

Anal. Calc. for $C_{12}H_{17}NO_6$:C,53.13;H,6.32;N,5.16. Found:C,53.00; H,6.38;N,5.10.

Continued elution of the acetonide mixture yielded the 3-R-diastereomer (154) as a clear syrup which was crystallized in methanol: m.p. 159.5-161° (granular); $[\alpha]_D^{25}$ -35.3° (c0.5,CH_3OH), $\nu_{max}^{CHCl_3}$ 3500(broad), 3420(sharp,NH), 3250(broad, OH), 1725, 1785 cm^{-1} weak shoulder (imide carbonyls); n.m.r. (100 MHz,DMSO-d_6) δ1.30 and 1.46(s,3H,C(CH_3)$_2$), 2.45(dd(partially obscured by DMSO),1H,J_{gem} 18.0Hz,$J_{3,4a}$ 5.0Hz,H-4a), 2.82(dd,1H,J_{gem} 18.0Hz,$J_{3,4b}$ 9.0Hz,H-4b), 3.24 (m,1H,$J_{3,4b}$ 9.0Hz,$J_{3,4a}$ 5.0Hz,$J_{3,1'}$ 4.0Hz,H-3), 3.42(d,2H,$J_{4',5'}$ 5.0Hz,H-5'),

3.83(pseudo-q,1H,$J_{4',5'}$ 5.0Hz,$J_{3',4'}$ 4.5Hz,H-4'), 4.05(pseudo-t,1H, $J_{1',2'}$ 4.5Hz,$J_{3,1'}$ 4.0Hz,H-1'), 4.51(dd,1H,$J_{2',3'}$ 6.5Hz,$J_{3',4'}$ 4.5Hz,H-3'), 4.90(dd,1H,$J_{2',3'}$ 6.5Hz,$J_{1',2'}$ 4.5Hz,H-2'), 11.15(broad s,1H,NH,exchangeable with D_2O). Irradiation of the pseudo-quartet at δ3.83 collapsed the doublet of doublets at δ4.51 to a doublet($J_{2',3'}$ 6.5Hz) while the doublet at δ3.42 collapsed to a broad singlet. Irradiation of the doublet of doublets at δ4.90 collapsed the pseudo-triplet at δ4.05 to a broad doublet while the collapse of the doublet of doublets at δ4.51 to a singlet appear anomolous due to its proximity to the irradiation frequency. Irradiation of the pseudo-triplet at δ4.05 collapsed the doublet of doublets at δ4.90 to a doublet ($J_{2',3'}$ 7.0Hz) while the multiplet at δ3.24 collapsed to a doublet of doublets ($J_{3,4a}$ 5.0Hz and $J_{3,4b}$ 9.0Hz); mass spectrum; m/e 272 (m^++H), 256(m^+-CH_3), 240(m^+-OCH_3).

Anal. Calc. for $C_{12}H_{17}NO_6$:C,53.13;H,6.32;N,5.16. Found:C,53.08; H,6.45; N,5.16.

Rechromatography of amides 155 and 156 failed to separate the two diastereomers nor could they be crystalled from various solvents:n.m.r. (mixture, 100MHz,$CDCl_3$) δ1.34 and 1.52(s,3H,C(CH_3)$_2$), 2.20(broad band without fine structure, approx.2H,H-3),3.51(m,1H,H-2), 3.69(d,2H,$J_{7,8}$ 3.5Hz,H-8), 3.77(s,3H,-OCH_3), 4.02(m,2H,H-4,H-7), 4.40(dd,1H,H-5 or H-6) 4.68(m,1H,H-5 or H-6), 6.40 and 6.80(broad s,1H,NH_2); $[\alpha]_D^{23}$-16 (c1.3, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3500, 3360 (N-H), 1725 (-CO_2Me), 1680 (-$CONH_2$), 1580 cm^{-1} (N-H); mass spectrum; m/e 304 (m^++H), 288 (m^+-Me), 272 (m^+-OCH_3).

Debenzoylation of Compounds 151 and 152 to give compounds 154 and 153,resp.

To a stirred solution of a mixture (∿50/50) of the blocked succinimides 151 and 152 (100 mg) in anhydrous methanol (10 ml) was added methanolic sodium methoxide (1.0 ml,0.2N) in 0.2 ml portions over 1.5h at room temperature under dry nitrogen atmosphere. T.l.c. of the reaction mixture using 8:4:1

benzene-ethyl acetate-ethanol as developer showed complete consumption of starting materials and two overlapping lower R_f (0.33 and 0.31) bands identical to that of compounds 153 and 154. After neutralization of the reaction mixture with Bio-Rex 70(H^+) resin, filtration, and evaporation of the methanol, the crude syrup (109 mg) was chromatographed in small portions (∿30 mg) on silica gel (6.0 g) using 8:4:1 benzene-ethyl acetate-ethanol as developer to achieve results described previously. Thus, compounds 153 and 154 obtained from 151 and 152 were identical (by n.m.r.) to those of 153 and 154 obtained from treating the amide mixture, from the photoamidation of 18, with sodium methoxide.

Attempted Dehydrogenation of Succinimide with Palladium.

A mixture of succinimide (28 mg), biphenyl (11 g) and 10% palladium on charcoal (102 mg) was heated until reflux (∿270° external temperature). A slow stream of dry carbon dioxide gas was passed through the refluxing mixture which was heated for 25 h. The reaction mixture was then allowed to cool (∿100°C) and was extracted with hot water (2x12 mls). The combined extracts were filtered and evaporated to yield a crystalline residue (28 mg) the n.m.r. of this product was identical to that of the starting succinimide.

Preparation of Nickel Peroxide

Following the procedure of Nakagawa, Konaka and Nakata[151], a solution of sodium hydroxide (42 g) in 5.3% aqueous sodium hypochlorite (300 ml) was added dropwise to a mechanically stirred solution of nickel sulfate-hexahydrate (130 g) in water (300 ml). The addition was completed in 10 min and the mixture was stirred for an additional 30 min at room temperature. Attempts to filter and wash the fine nickel peroxide suspension failed due to clogging of the filtration apparatus (i.e., Whatman no.1 filter paper and sintered glass). A portion of the suspension was removed, transfered to centrifuge

bottles (200 ml capacity/bottle), centrifuged, the supernatant removed, fresh distilled water added (∿150 ml suspension), and recentrifuged. This process was continued until part of the suspension failed to separate indicating the removal of the excess base. The supernatant was discarded and the residue was filtered, dried under vacuo, and crushed to a powder.

The activity of the nickel peroxide was determined iodometrically to be: 1.7×10^{-3} g-atom oxygen/g nickel peroxide.

Attempted Dehydrogenation of the Ribosyl Succinimides using Nickel Peroxide.

A solution of the blocked ribosyl succinimides 151 and 152 (42 mg, 0.11 mmol) in xylene (2 ml) was added to nickel peroxide (200 mg, ∿3 equiv., activity: 1.7×10^{-3} equiv/g NiO_2). The mixture was refluxed for 60 h after which the reaction mixture was allowed to settle, the supernatent solution removed and filtered through celite. Evaporation of the solvent under reduced pressure resulted in a pale green syrup (220 mg) which produced four wide bands and baseline material on t.l.c. with various developers. Attempts to isolate the carbohydrate product from this mixture were not considered.

Similar treatment of compounds 153 and 154 in refluxing benzene for 26 h did not give any products of different R_f nor did the charring bands absorb U.V. light.

Treatment of compounds 153 and 154 at room temperature with nickel peroxide (50 equiv.) for 7 days using water as the solvent failed to produce any U.V. active charring bands.

Attempted Dehydrogenation of Compounds 153 and 154 with Dicyanodichloroquinone (DDQ).

A solution of a 60:40 mixture of the ribosyl succinimides 153 and 154 (20 mg) and dicyanodichloroquinone in dioxan (1.5 ml) was refluxed for

3 days. The mixtures was cooled, filtered and the off-white solids (25 mg) washed with dioxan (2.0 ml). The combined filtrates were then evaporated to give a crude syrup (43 mg) which on t.l.c. showed two broad U.V. active bands (9:1 ethyl acetate-ethanol developer). The higher R_f (0.23-0.36) U.V. active band also overlapped a charring band (R_f 0.27). Chromatography of the syrup on silica gel (5.0 g) using 9:1 ethylacetate-ethanol as developer yielded the charring band as a clear syrup (12.5 g) which did not absorb U.V. light. Further analysis of this band, therefore, was not attempted.

Attempted Synthesis of (R,S)-3-Bromo-3-(5′-O-benzoyl-2′,3′-O-isopropylidene-β-D-ribofuranosyl)succinimide (169).

A mixture of the blocked ribosyl succinimides 151 and 152 (85 mg, 0.23 mmol), N-bromosuccinimide (50 mg, 0.29 mmol), and benzoyl peroxide (5 mg) in 5 ml anhydrous carbon tetrachloride was refluxed under anhydrous conditions. After reflux for a few minutes, most of the solid material had gone into solution. After 17 min of reflux, an oil began to separate from the reaction mixture. The mixture was refluxed an additional 15 min after which it was cooled, diluted with chloroform (6 ml), washed with 5% aqueous sodium hydrogen carbonate, and dried over anhydrous sodium sulfate. Evaporation of the solvents under reduced pressure and chromatography of the residual syrup on a t.l.c. plate using 20:4:1 benzene-ethylacetate-ethanol as developer (developed twice) gave a five-component mixture. Isolation of the major band (R_f 0.43) gave a clear syrup (11 mg) which by n.m.r. showed a mixture of compounds which still retained H-3 of the succinimide ring. Further analyses of this band and the other minor components were not pursued.

3-(S)-(β-D-ribofuranosyl)succinimide (170), from Compound 153.

A solution of acetonide 153 (124 mg) in 3:1 trifluoroacetic acid-methanol (4.0 ml) was stirred for 45 min at room temperature. After evaporation of the solvents under reduced pressure, the residual syrup was chromatographed on a column of Bio-Rex 70(H^+) resin which was developed with water to yield (S)-dihydroshowdomycin 170 as a clear syrup (96 mg, 91%). An analytic sample was obtained by crystallization from benzene-acetone; m.p. 136-140° (leaflets); $[\alpha]_D^{23}$ -10.2° (c3.4,H_2O); n.m.r. (100 MHz, DMSO-d_6) δ2.48(dd (partially obscured by DMSO), 1H,J_{gem} 17.5Hz,$J_{3,4a}$ 9.0Hz, H-4a), 2.72(dd,1H,J_{gem} 17.5Hz,$J_{3,4b}$ 5.0Hz,H-4b), 3.06(m,1H,H-3),3.43(d,2H, $J_{4',5'}$ 4.0Hz,H-5'), 3.60(dd (partially obscured by H-4'),1H,$J_{1',2'}$ 8.0Hz, $J_{2',3'}$ 5.5Hz,H-2'), 3.70(m,1H,H-4'), 3.83(dd,1H,$J_{2',3'}$ 5.5Hz,$J_{3',4'}$ 3.0Hz, H-3'); 4.06(dd,1H,$J_{3,1'}$ 2.0Hz,$J_{1',2'}$ 8.0Hz,H-1'), 4.54(broad s,3H,3xOH, exchangeable with D_2O), 11.0(broad s,1H,NH, exchangeable with D_2O). Irradiation of the doublet of doublets at δ4.06 collapsed the doublet of doublet at δ3.60 to a doublet ($J_{2',3'}$ 5.5Hz) while the multiplet at δ3.06 collapsed to a doublet of doublets ($J_{3,4a}$ 9.0Hz and $J_{3,4b}$ 5.0Hz). Irradiation of the multiplet at δ3.06 collapsed the doublet of doublets at δ4.06 to a doublet ($J_{1',2'}$ 8.0Hz): n.m.r. (100MHz,D_2O-D_3CCO_2D) δ4.13 (dd,1H,$J_{3,1'}$ 2.5Hz,$J_{1',2'}$ 7.0Hz,H-1'), (lit.[118c] n.m.r. (60MHz,D_2O-D_3CCO_2D, internal D.S.S. standard) δ4.50($J_{3,1'}$ 2.5Hz)); mass spectrum:m/e 232(m^++H), 213(m^+-H_2O), 200(m^+-CH_2OH).

Anal. Calc. for $C_9H_{13}NO_6$:C,46.75;H,5.67;N,6.06. Found: C,47.21; H,5.76;N,6.06.

3-(R)-(β-D-ribofuranosyl)succinimide (171) from Compound 154.

A solution of acetonide 154 (98 mg) in 3:1 trifluoroactic acid-methanol (4.0 ml) was stirred for 45 min. at room temperature. After evaporation of

the solvents under reduced pressure, the resulting syrup was chromatographed on a column of Bio-Rex 70(H^+) resin and eluted with water to yield (R)-dihydroshowdomycin (171) as a clear syrup (72.5 mg, 87%). The syrup failed to crystallize from a variety of solvents: $[\alpha]_D^{25}$ -16.6° (c3.4,H_2O), n.m.r. (270 and 400MHz,D_2O) δ2.72(dd,1H,J_{gem} 19.0Hz,$J_{3,4a}$ 4.3Hz,H-4a), 3.00(dd, 1H,J_{gem} 19.0Hz,$J_{3,4b}$ 9.4Hz,H-4b), 3.33(m,1H,H-3), 3.54(dd,1H,J_{gem} 12.3Hz, $J_{4',5'a}$ 5.6Hz,H-5'a),3.69(dd,1H,J_{gem} 12.3Hz,$J_{4',5'b}$ 3.6Hz,H-5'b), 3.87 (m,1H,H-4'),4.00(pseudo-t,1H,$J_{2',3'}$ 6.0Hz,$J_{3',4'}$ 4.8Hz,H-3'), 4.05(q,1H, $J_{3,1'}$ 4.4Hz,$J_{1',2'}$ 6.2Hz,H-1'),4.30(pseudo-t,1H,$J_{1',2'}$ 3.0Hz,$J_{2',3'}$ 3.0Hz, H-2'). Irradiation of the multiplet at δ3.33 collapsed the doublet of doublets at δ4.05 to a doublet($J_{1',3'}$ 6.4Hz) while the doublet of doublets at δ2.72 and δ3.00 collapsed to two doublets with $J_{4a,4b}$ 19Hz.

5. 3-(S)-α-Dihydroshowdomycin Acetonide

Photoamidation of Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (172) to yield Diastereomers 140, 141, Methyl 4,7-anhydro-8-O-benzoyl-3-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-gluco (and manno)-octonate (173), (174), respectively.

A solution of the enol ether 172 (6.0 g), acetone (15 ml), tert-butanol (15 ml) and formamide (30 ml) was added over 3h to a mixture of tert-butanol (10 ml) and formamide (200 ml) contained in a photolysis cell. The mixture was irradiated during the addition and continued for 4 days (or until all of the starting material had been consumed, as evidenced by t.l.c. of the reaction mixture using 8:4:1 benzene-ethylacetate-ethanol as developer). The reaction mixture was then concentrated by removal of the tert-butanol and acetone under

reduced pressure at ∿55°. The resulting solution in formamide was diluted with saturated aqueous sodium chloride (200 ml), extracted with dichloromethane (4x200 ml), the combined extracts concentrated to approximately 100 ml and the concentrated solution then washed with saturated aqueous sodium chloride (50 ml). The organic phase was collected, dried over anhydrous sodium sulfate, filtered and evaporated to yield a crude syrup which was chromatographed on silica gel (465 g) using 9:1 benzene-ethanol as developer. Isolation of the band corresponding to the amides previously synthesized (see photoamidation of compd. 18) gave a clear syrup (1.5 g, 22%). The amide band was shown to be a mixture of the diastereomeric amides 140, 141, 173 and 173 by n.m.r. and by conversion of the amides to cyclic imides. An analysis of the n.m.r. spectra of the above imides indicated an approximately 2:1 ratio of the α to β-anomers* of the amides. An analytical sample of a mixture of the amides was obtained by crystallization from chloroform-hexane; m.p. 180-185° (amorphous solid); $[\alpha]_D^{23}$ + 3.6° (c1.0, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3410, 3515(N-H), 1722(ester carbonyls), 1685(amide carbonyl), 1596 cm^{-1}(amide II band); n.m.r.(100MHz,$CDCl_3$) δ1.34 and 1.54(s,3H,$C(CH_3)_2$), 2.41-3.44(m,3H,H-2,H-3), 3.65(s,3H,$-OCH_3$), 4.05-4.85(m,6H,H-4 to H-8), 5.97, 6.19,6.49(broad overlapping singlets, approx.2H,NH_2), 7.54(m,3H,Ar), 8.05(m, 2H,Ar); mass spectrum: m/e 392(m^+-CH_3), 376(m^+-OCH_3).

Anal. Calc. for $C_{20}H_{25}NO_8$:C,58.96;H,6.19;N,3.44. Found:C,58.60; H,6.05;N,3.39.

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* used in the extended sense

Treatment of a Mixture of the Amides 140, 141, 173, and 174 with Methanolic Sodium Methoxide to yield 151, 152, 153, 154, 3-(R) and (S)-(2,3-O-Isopropylidene-α-D-ribofuranosyl)succinimide (175),(176), Methyl 4,7-anhydro-3-C-carbamoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-gluco-octonate (177), respectively.

To a stirred solution of amides 140, 141, 173, and 174 (400 mg) in anhydrous methanol (15 ml) was added methanolic sodium methoxide (0.4 ml, 0.2N). The mixture was allowed to stir at room temperature under dry nitrogen atmosphere for 8h after which time t.l.c. of the reaction mixture (9:5:1 benzene-ethylacetate-ethanol as developer) indicated the presence of the starting compounds (R_f 0.28) and higher and lower R_f materials. An additional 0.1 ml of the methanolic sodium methoxide solution was added and the mixture was allowed to stir overnight (14h). T.l.c. analysis of the reaction mixture showed little change so that the reaction was terminated by neutralization of the solution with Bio-Rex 70(H^+) resin (as indicated by pH paper). The mixture was filtered, evaporated and the residual syrup partitioned between chloroform-water (25:25, V/V) to separate the water soluble components (195 mg, crude syrup) from the organic solvent soluble components (240 mg, crude syrup).

The syrup from the chloroform soluble layer was dissolved in a small quantity of methanol, applied to a column (23 x 2.6 cm) of Bio-Rex 70(H^+) resin and eluted with methanol. The slower-moving colorless component was isolated and the solvent removed to yield a partially crystalline syrup (185 mg). T.l.c. of this syrupy mixture using 1:1 benzene-ethylacetate as developer indicated two bands, a major broad band (R_f 0.32-0.43) and a lower R_f (0.13) minor narrow band corresponding to the starting amides. Column chromatography on silica gel (15 g) of the syrup using a 2:1 to 1:1

benzene-ethyl acetate gradient afforded mainly the blocked ribosyl succimides 151 and 152 (∿60% of isolated material) plus other minor components (∿40%)(total: 124 g, 34% based on 151 and 152) as partially resolved fractions as indicated by their n.m.r. spectra. The head and tail of this broad band corresponded mainly to the 'β' ribosyl succinimides 151 and 152, respectively, previously isolated while the central portion of the band corresponded to a mixture of the above and other unidentified materials. Further purification or characterization of these mixtures was not attempted.

The syrup from the water soluble portion of the reaction mixture was dissolved in a small quantity of water, applied to a column (33.0 x 3.5 cm) of Bio-Rex 70(H^+) resin and eluted with water to yield 3 major bands. T.l.c. of the faster-moving band on silica gel using 5:4:1 benzene-ethyl acetate-ethanol as developer indicated two major bands, a broad higher R_f (0.33) band charring pink on the faster-moving portion of the band and a narrower low R_f (0.24) band which charred more uniformly.

The first band (85 mg) eluted from the resin column was therefore rechromatographed on silica gel (5 g) in two portions using 5:4:1 benzene-ethyl acetate-ethanol as developer. A portion of the faster-moving, pink-charring band was isolated pure (5.0 mg, 2%) and was found to be identical, by n.m.r. spectroscopy and by the melting point of the 1:1 crystalline complex with chloroform, to the 3-S-(β-ribosyl)succinimide 153 previously synthesized. Continued elution of the column gave a portion (21 mg, 7.5%) of the higher R_f band which was free of the pink charring material. The n.m.r. spectrum of this fraction indicated the presence of two compounds the major component (∿2:1) being the α-3-(R)-ribosylsuccinimide acetonide 175 and the minor component being the previously synthesized lower R_f β-3-R-isomer 154. The

pure α-anomer could not be obtained by chromatography nor by crystallization; therefore, the optical rotation of the 2:1 mixture of the α/β is reported along with a tentative n.m.r. assignment: $[\alpha]_D^{25}$ + 8.04° (c2.0,MeOH); n.m.r. (100MHz,$CDCl_3$) δ1.30 and 1.47(s,3H,C(CH_3)$_2$), 2.70 (dd,1H,J_{gem} 19.0Hz,$J_{3,4a}$ 10.0Hz,H-4a), 2.86(dd,1H,J_{gem} 19.0Hz,$J_{3,4b}$ 5.0Hz,H-4b), 3.17(m,1H,H-3), 3.60(d,2H,$J_{4',5'}$ 4.5Hz,H-5'), 2.07(broad s, approx. 1H,OH), 4.14(t,1H,$J_{4',5'}$ 4.5Hz,H-4'), 4.56(dd,1H,$J_{3,1'}$ 2.0Hz, $J_{1',2'}$ 3.5Hz,H-1'), 4.70(d,1H,$J_{2',3'}$ 6.0Hz), 4.75(dd,1H,$J_{1',2'}$ 3.5Hz,$J_{2',3'}$ 6.0Hz,H-2'), 9.00(broad s, approx.1H,NH).

Continued elution of the column gave the low R_f α-3-(S)-ribosylsuccinimide acetonide 176 (32 mg,12%) as pure diastereomer easily separable from the other three and crystallized in chloroform: m.p. 141.5-144.5°; $[\alpha]_D^{25}$ -1.0° (c0.5,MeOH); n.m.r. (100MHz,$CDCl_3$) δ1.22 and 1.41(s,3H,C(CH_3)$_2$), 2.16(broad s,1H,OH, exchangeable with D_2O), 2.68(dd,1H,J_{gem} 18.5Hz,$J_{3,4a}$ 9.5Hz,H-4a), 2.96(dd,1H,J_{gem} 18.5Hz,$J_{3,4b}$ 5.0Hz,H-4b), 3.40(m,1H,H-3), 3.63 (broad d,2H,$J_{4',5'}$ 4.0Hz,H-5'), 4.22(broad t,1H,$J_{4',5'}$ 4.0Hz,H-4'), 4.40(dd, 1H,$J_{3,1'}$ 8.0Hz,$H_{1',2'}$ 3.8Hz,H-1'), 4.65(dd,1H,$J_{2',3'}$ 6.0Hz,$J_{3',4'}$ 1.0Hz, H-3'), 4.76(dd,1H,$J_{2',3'}$ 6.0Hz,$J_{1',2'}$ 3.8Hz,H-2'), 8.28(broad s,1H,NH, D_2O-exchangeable); mass spectrum; m/e 272(m^++H), 256(m^+-CH_3), 240(m^+-$HOCH_2$).

Anal. Calc. for $C_{12}H_{17}NO_6$:C,53.13;H,6.32;N,5.16. Found:C,53.35; H,6.38;N,5.17.

The final slower moving bands of the water soluble components was found to be minor component. Rechromatography of this component (33 mg) on silica gel (5.0 g) using 5:4:1 benzene-ethyl acetate-ethanol yielded only one chromatographically and stereochemically pure band of the debenzoylated, α-3-(S)-amide 177 (17 mg, 6%); m.p. 161-163°; $[\alpha]_D^{25}$ + 16.1° (c1.5,$CHCl_3$);

$\nu_{max}^{CHCl_3}$ 3500, 3410 (broad,NH,OH), 1732 (ester carbonyl) 1678 (amide carbonyl), 1593 cm^{-1} (amide II band); n.m.r. (100 MHz,D_2O) δ1.38 and 1.53(s,3H,C($\underline{CH}_3$)$_2$), 2.69(d,2H,$J_{2,3}$ 7.5Hz,H-2), 3.14(m,1H,H-3) 3.60(d, 2H,$J_{7,8}$ 6.0Hz,H-8), 3.70(s,3H,-O$\underline{CH}_3$), 4.13(dd(overlapped by H-7),1H,$J_{3,4}$ 10.0Hz,$J_{4,5}$ 3.5Hz,H-4), 4.16(t(overlapped by H-4),1H,$J_{7,8}$ 6.0Hz,H-7), 4.82(d,1H,$J_{5,6}$ 6.0Hz,H-6), 4.95(dd,1H,$J_{4,5}$ 3.5Hz,$J_{5,6}$ 6.0Hz,H-5); mass spectrum: m/e 304(m^++H), 288(m^+-CH_3), 272(m^+-OCH_3/$HOCH_2$).

Anal. Calc. for $C_{13}H_{21}NO_7$: C,51.48; H,6.98;N,4.62. Found: C,51.01; H,7.00;N,4.58.

6. Unsaturated, Azido, Diazo and Amino Sugars

Treatment of Compound 18 with Sodium Azide to Yield Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (172) and Methyl (E)-4,7-anhydro-8-O-benzoyl-2,3,5-trideoxy-D-erythro-oct-2,4-dienonate (178).

A mixture of the methyl oct-2-enonate 18 (88 mg) and sodium azide (89 mg) in anhydrous DMF (4.5 ml) was sealed (rubber septum) in a flask under dry nitrogen atmosphere and stirred for 45h at 50-55°. After increasing the temperature to 60-65°, the reaction mixture was stirred for an additional 48h. The mixture was then evaporated under vacuo to remove the volatile components. The residue was dissolved in a mixture of 1:1 dichloromethane and saturated aqueous sodium chloride (10 ml). The organic layer was separated and the aqueous suspension extracted twice with dichloromethane (2x5 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated, leaving a crude syrup which was chromatographed on silica gel (10 g) using 2:1 ether-hexanes as developer.

The faster-moving component, compound 172, was isolated as a clear syrup (18 mg, 20.5%) and was found to be a 9:1 mixture of the Z and E isomers, respectively, from n.m.r.; $[\alpha]_D^{25}$ - 156.3 (c 0.95,$CHCl_3$); $\nu_{max}^{CCl_4}$

1743, 1733 (methyl ester and benzoate carbonyls, resp.) and 1710 cm^{-1} shoulder (C=C); n.m.r. (100MHz,$CDCl_3$) δ1.33 and 1.46(s,3H,C($\underline{CH_3}$)$_2$), 3.02(dd,1H,J_{gem} 18.0Hz,$J_{2a,3}$ 7.0Hz,H-2a), 3.22(dd,1H,$J_{2b,3}$ 7.0Hz,H-2b), 3.53(s,3H,-OCH_3), 4.37(d,2H,$J_{7,8}$ 4Hz,H-8), 4.59-4.71(m,2H,H-7,H-6), 4.82 (pseudo-t,1H,$J_{2a,3}$ and $J_{2b,3}$ 7.0Hz,H-3), 5.03 (broad-d,1H,$J_{5,6}$ 5.5Hz,H-5), 7.46(m,3H,Ar), 7.95(m,2H,Ar). Irradiation of the two doublet of doublets at δ3.02 and 3.22 collapsed the pseudo-triplet at δ4.82 to a singlet. (A 270 MHz n.m.r. spectrum of 172 confirmed these assignments) C-13 n.m.r. (20 MHz, $CDCl_3$, proton decoupled) δ25.73 and 26.92(C($\underline{CH_3}$)$_2$), 30.73(C-2),51.60 (-O$\underline{CH_3}$), 64.79(C-8), 79.85, 8.53(C-6 and C-7), 83.79(C-5), 94.71(C-3), 113.23 ($\underline{C}$(CH_3)$_2$), 128.53,129.67,130.94,133.31(Ar), 156.55(C-4), 166.00(A.$\underline{C}$=O), 172.10($\underline{CO_2}CH_3$); mass spectrum: m/e 362(m^+), 347(M^+-15), 330(m^+-CH_3OH), 304(m^+-Acetone).

Although neither geometric isomers could be isolated free from the other (especially the minor E-isomer), varying concentrations of each would allow some specific spectral data for the E-isomer of 172. A 55:45 mixture (see Reduction of compound 185) of the E to Z geometric isomers gave the following data: n.m.r. (100MHz,$CDCl_3$) δ1.33 and 1.44(s,3H,C(CH_3)), 3.58(s, 3H,-O$\underline{CH_3}$), 5.08(H-3), 5.22(broad d,H-5); C-13 n.m.r. (20MHz,$CDCl_3$) δ25.93 and 26.92 (C($\underline{CH_3}$)$_2$), 31.62(C-2), 79.28, 80.92 (C-6 and C-7), 82.90(C-5), 94.29(C-3), 157.73(C-4), 172.66($\underline{CO_2}$Me), all other bands were degenerate with the Z-isomer; $[\alpha]_D^{23}$ -167(c 1.0,$CHCl_3$).

Anal. Calc. for $C_{19}H_{22}O_7$: C,62.97;H,6.12. Found: C,63.30;H,6.06.

Continued elution of the column gave the dienonate 178 as a clear syrup (38 mg, 51.5%). The characterization of 178 appears in the subsection directly below.

Methyl(E)-4,7-anhydro-8-O-benzoyl-2,3,5-trideoxy-D-erythro-oct-2,4-dienonate (178)

A mixture of the E(and Z)-2,3-unsaturated ester 18 (0.57, 1.6 mmol), and sodium azide (0.5 g, 77 mmol) in anhydrous DMF (50 ml) under nitrogen atmosphere in a sealed (rubber septum) flask was stirred for 24 h at 85-90°. The solvent was then evaporated in vacuo with the water bath temperature kept below 50°. The resulting syrup was dissolved in a 1:1 mixture of dichloromethane and saturated aqueous sodium chloride (30 ml). The organic layer was separated and the aqueous suspension extracted twice with dichloromethane (2x15 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated, leaving a crude syrup which was chromatographed on silica gel (42 g) using 1:1 benzene-ethyl acetate as developer. The major band was collected and evaporated to yield a clear syrup which on storage under vacuum produced a crystalline mass of compound 178 (0.306 g, 64%). Compound 178 was recrystallized from benzene-hexane to yield fine neeldes: m.p. 99.5-102°; $[\alpha]_D^{28}$ + 98.68 (c1.26,$CHCl_3$); $\nu_{max}^{CHCl_3}$ 3500 (broad,OH), 1712 and 1725 (-CO_2Me and PhCO_2- carbonyls, respectively), 1660 and 1607 cm^{-1} (-C=C-); n.m.r. (100 MHz,$CDCl_3$): δ2.57(d,1H,$J_{6,OH}$ 7.5Hz, OH, exchangeable with D_2O), 3.74(s,3H,-OCH_3), 4.42(d,2H,$J_{7,8}$ 5.0Hz,H-8), 4.74 (t of d,1H,$J_{7,8}$ 5.0Hz,$J_{6,7}$ 3.0 Hz,H-7), 4.95(d of t,1H,$J_{6,OH}$ 7.5Hz, $J_{6,7}$ 3.0Hz, collapses to a doublet of 3.0Hz upon D_2O exchange,H-6), 5.52(d,1H, $J_{5,6}$ 3.0Hz,H-5), 6.29(d,1H,$J_{2,3}$ 16.0Hz,H-2), 7.13(d,1H,$J_{2,3}$ 16.0Hz,H-3), 7.30-8.06(m,5H,Ar); mass spectrum: m/e 304(m^+), 286(m^+-H_2O), 272(m^+-CH_3OH).

Anal. Calc. for $C_{16}H_{16}O_6$: C,63.15;H,5.30. Found: C,63.01;H,5.46.

2-Benzoyloxymethyl-5-((E)-carbomethoxyethylene)furan (179).

Prolonged (several months) storage of the methyl oct-2,4-dienonate 178 produced a dark amber syrup which by t.l.c. showed both baseline and

higher R_f charring materials (9:1 benzene-ethyl acetate developer) and an absence of starting compound 178. The residual syrup (200 mg) was chromatographed on silica gel (10 g) using 15:1 benzene-ethyl acetate as developer. Collection of the high R_f (0.32) band yielded the substituted furan 179 (14 mg, 7%); n.m.r. (100 MHz, $CDCl_3$) δ3.73(s,3H,$-OCH_3$), 5.28(S,2H,H-8), 6.31 (d,1H,$J_{2,3}$ 16Hz,H-2), 6.49 and 6.54(d,1H,$J_{5,6}$ 3.5Hz,H-5,H-6), 7.37(d,1H,$J_{2,3}$ 16Hz,H-3), 7.43(m,3H,Ar) 8.01(m,2H,Ar). This n.m.r. data was identical to those obtained by Moffat et al[20] for compound 179.

Catalytic Hydrogenation of 18 to yield Methyl 4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-octonate (183)

A solution of the methyl oct-2-enonate 18 (147 mg) in methanol (10 ml) was hydrogenated at 60 p.s.i. for 48 h at room temperature in the presence of 5% palladium on charcoal (60 mg) as catalyst. The mixture was filtered and evaporated to yield a clear syrup (134 mg) which was shown by t.l.c. to be homogeneous with a R_f slightly lower than the starting unsaturated compound (R_f 0.36 with 4:1 benzene-ethyl acetate developer). Chromatography of the syrup on silica gel (12 g) using 4:1 benzene-ethylacetate developer gave the saturated methyl octonate 183 (127 mg, 82%): $[\alpha]_D^{25}$ -11.4(c1.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1727, 1738 cm^{-1} shoulder (C=0); n.m.r. (100 MHz,$CDCl_3$) δ1.30 and 1.50 (s,3H,$C(CH_3)_2$), 1.78-2.04(m,2H,H-3), 2.35-2.51(m,2H,H-2), 3.58(s,3H,$-OCH_3$), 3.84-4.02(m,1H,H-4),4.14-4.67(m,5H,H-5 to H-8), 7.48(m,3H,Ar), 8.03(m,2H,Ar). Irradiation of the multiplet at δ1.94 partially collapsed the multiplet structure at δ3.92 but no discernable information on the coupling at H-4 with H-3 nor H-5 could be ascertained. Mass spectrum: m/e 364(m^+), 349 (m^+-CH_3), 333(m^+-OCH_3).

Anal. Calc. for $C_{19}H_{24}O_3$: C,62.63; H,664. Found: C,62.71;H,6.66.

Catalytic Hydrogenation of 172 to yield Methyl 4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-altro-octonate (184).

A solution of the methyl oct-3-enonate 172 (192 mg) in methanol (10 ml) was hydrogenated at atmospheric pressure for 10h at room temperature in the presence of 5% palladium on charcoal (85 mg) as catalyst. The mixture was then filtered and evaporated under reduce pressure to give a crude syrup which by t.l.c. was shown to contain charring materials having higher and lower R_f than the starting unsaturated sugar. Chromatography of the crude mixture on silica gel (17 g) using 4:1 benzene-ethylacetate as developer afforded the saturated compound 184 (97 mg, 50%) as a colorless syrup which solidified on standing but could not be crystallized from various solvents. An analytical sample was prepared by distillation under reduced pressure (0.02 mm, 100°) to give solid 184; m.p. 43.5-45.5°C; $[\alpha]_D^{25}$ -9.0(c1.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1727, 1738 cm^{-1} shoulder (C=O); n.m.r. (100 MHz,$CDCl_3$) δ1.36 and 1.52 (s,3H,$C(CH_3)_2$), 1.94-2.16(m,2H,H-3), 2.42-2.58(m,2H,H-2), 3.66(s,3H,-OMe), 4.07(t of d,1H,$J_{3,4}$ 6.0Hz,$J_{4,5}$ 3.0Hz,H-4), 4.22-4.55(m,3H,H-7,H-8), 4.68-4.83(m,2H,H-5,H-6), 7.54(m,3H,Ar), 8.06(m,2H,Ar). Irradiation of the multiplet at δ2.06 collapsed the triplet of doublets at δ4.07 to a doublet ($J_{4,5}$ 3.0Hz); mass spectrum: m/e 364(m^+), 349(m^+-CH_3), 333(m^+-OCH_3).

Anal. Calc. for $C_{19}H_{24}O_7$:C,62.63;H,6.64. Found: C,62.81;H,6.71.

Methyl(methyl 8-O-benzoyl-3-(chloromercuri)-2,3-dideoxy-5,6-O-isopropylidene-α-D-altro-4-octulofuranosid)onate (185).

To a stirred solution of the methyl oct-3-enonate 172 (0.8 g) in methanol (40 ml) was added mercuric acetate (0.8 g). The resulting thick suspension was stirred for 1h after which the mixture was refluxed for 15 min to give a clear solution. After the solution was allowed to cool, sodium chloride (0.3 g) and acetic acid (0.05 ml) were then added and the mixture was refluxed

for an additional hour. T.l.c. of the reaction mixture indicated complete consumption of the starting compound and indicated a new lower R_f (0.39) compound using 2:1 ether-hexanes as developer. The reaction mixture was filtered and evaporated and the residual syrup (1.23 g) chromatographed on silica gel (60 g) using the above developer to yield the organo-mercury compound 185 (1.14 g, 82%) as a partially crystalline, hard syrup which was recrystallized from methanol: m.p. 118.5-120.5°; $[\alpha]_D^{25}$ -32.1(c2.0,$CHCl_3$); $\nu_{max}^{CDCl_3}$ 1718, 1722 cm^{-1} (carbonyls); n.m.r. (100MHz,$CDCl_3$) δ1.34 and 1.53 (s,3H,$C(CH_3)_2$), 2.79-3.21(m,approx.3H,H-2,H-3), 3.37(s,3H,$-OCH_3$), 3.75(s,3H, $-CO_2CH_3$), 4.27-4.46(m,3H,H-7,H-8), 4.53(sharp d,1H,$J_{5,6}$ 6.0Hz,H-5), 4.82(broad d,1H,$J_{5,6}$ 6.0Hz,$J_{6,7}$ <1.0Hz,H-6), 7.55(m,3H,Ar), 8.12(m,2H,Ar). The mass spectrum was a complex pattern due to 5 abundant mercury isotopes and 2 chlorine isotopes. The complex patterns were present at: 630(m^+), 615 (m^+-CH_3), 599(m^+-OCH_3).

Anal. Calc. for $C_{20}H_{25}ClHgO_8$: C,38.16;H,4.00;Hg,31.87. Found: C,38.02; H,4.00;Hg,31.55.

Reduction of Compound 185 to Give Compound 172.

A mixture of the mercuric compound 185 (350 mg, 0.56 mmol) in ethanol (12 ml) was gently heated over a steam bath until the sugar completely dissolved. The solution was allowed to cool with stirring and then sodium borohydride (27 mg, 0.7 mmol) was added to the solution in six portion. The solution turned a darker opaque grey after each addition of the reducing agent. After 3 min, the mixture was concentrated (∿1 ml) under reduced pressure and the concentrate dissolved in a mixture of ether (10 ml) and water (4 ml). The resulting mixture was stirred for several minutes and then the aqueous layer along with the liberated elemental murcury was withdrawn and the organic layer washed with 1N HCl (2x5 ml), water (5 ml) and

dried over anhydrous sodium sulfate. T.l.c. of the organic phase indicated only one band slightly lower in R_f than the starting material (using 4:1 benzene-ethylacetate as developer, R_f 0.48 and 0.55,resp.). The solution was then filtered and evaporated and the residual syrup (255 mg) chromatographed on a column of silica gel (16.5 g) using 4:1 benzene-ethyl acetate as developer giving back the unsaturated compound 172 (185 mg, 92%) as a clear syrup. This reaction, however, gave a mixture of the methyl(E,Z) oct-3-enonate 172 that was significantly richer in the E isomer (approx. 8:10 of the E to Z isomers,resp.). One fraction collected had 55% of the E isomer and was used to determine some of the characteristics of this minor isomer (see page 163).

Methyl(methyl 8-O-benzoyl-3-bromo-2,3-dideoxy-5,6-O-isopropylidene-α-D-altro-4-octulofuransid)onate (186).

To a mixture of the methyl oct-3-enonate 172 (0.8 g, 2.2 mmol), powdered Drierite (0.8 g), silver carbonate (0.8 g) in anhydrous methanol (13 ml) was slowly added bromine (2.75 ml of an 0.8 Molar methanolic solution) while the mixture was stirred. The reaction quickly consumed the added bromine evidenced by the loss of color after the addition of the bromine solution. The mixture was stirred 1.8 h, then filtered through celite and the solid materials washed with chloroform (3x5 ml). The combined filtrates were evaporated under reduced pressure and the residue redissolved in chloroform (75 ml) and washed with water (15 ml), 5% aqueous sodium hydrogen carbonate (15 ml) and water (2 x 15 ml). The organic phase was then dried over anhydrous sodium sulfate overnight. T.l.c. of the organic phase using 9:1 benzene-ethyl acetate as developer indicated two prominent charring components, the major component (R_f 0.456) moving faster than the starting compound (R_f 0.294) and the minor

component moving at a similar rate (R_f 0.280). The organic layer was evaporated at reduced pressure and the residual syrup (0.83 g) chromatographed on silica gel (67 g) using 9:1 benzene ethyl acetate as developer. Isolation of the faster-moving component gave the methyl bromoglycoside 186 (0.424 g, 41%) as a clear syrup which turned black upon heating or prolonged storage at room temperature: $[\alpha]_D^{25}$ -13.9° (c1.34,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1728, 1740 cm^{-1} shoulder (carbonyls); n.m.r. (100 MHz,$CDCl_3$) δ1.34 and 1.54(s,3H,$C(CH_3)_2$), 2.94(dd,1H,J_{gem} 16.5Hz,$J_{2a,3}$ 10.0Hz,H-2a), 3.31(s,3H, $-OCH_3$), 3.41(dd(partially buried under $-OCH_3$),1H,J_{gem}~16.5Hz,$J_{2b,3}$ 3.5Hz, H-2b), 3.68(s,3H,$-CO_2CH_3$), 4.32(d(overlapped by H-8b),1H,$J_{7,8a}$ 8.5Hz,H-8a), 3.34(d(overlapped by H-8a),1H,$J_{7,8b}$ 5.5Hz,H-8b), 4.41-4.53(m,1H,H-7), 4.60 (d,1H,$J_{5,6}$ 6.0Hz,H-5), 4.75(dd(partially obscured by H-3),1H,$J_{5,6}$ 6.0Hz, $J_{6,7}$ 2.0Hz,H-6), 4.84(dd,1H,$J_{2a,3}$ 10.0Hz,$J_{2b,3}$ 3.5Hz,H-3), 7.45(m,3H,Ar), 8.02(m,2H,Ar). Irradiation of the doublet of doublets at δ3.41 collapsed the doublet of doublets at δ4.84 to a doublet with $J_{2a,3}$ 10.0Hz, mass spectrum: m/e 459/457(m^+-CH_3), 443/441(m^+-OCH_3), 307($m^+-CHBrCH_2CO_2Me$).

Anal. Calc. for $C_{20}H_{25}BrO_8$:C,50.75;H,5.32;Br,16.88. Found: C,49.59; H,5.10;Br,16.47.

Several minor lower R_f charring components were also isolated but these decomposed before they were characterized.

Attempted Hydrogenolysis of 186

To a prehydrogenated mixture of potassium hydroxide (18 mg) and 5% palladium on carbon (25 mg), in methanol (5 ml) was added a solution of the bromo methyl glycoside 186 (130 mg) in methanol (5 ml). The resulting mixture was vigorously stirred overnight under hydrogen atmosphere (~760 torr). After neutralizing the reaction mixture with Bio-Rex 70 (H^+) resin, the mixture was filtered and evaporated. T.l.c. of the syrup with 2:1 ether-

hexanes as developer gave only lower R_f (0.143) and baseline material (R_f for compound 172 and 186, 0.43 and 0.50, resp.).

Methyl(methyl 8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-α(or β)-D-ribo-4-octulofuranosid)onate (187).

In an attempt to obtain the azido compound 189 free from the methyl oct-3-enonate 172, a sample of a mixture of compounds 189 and 172 was dissolved in a mixture of pyridine, acetic acid, and methanol and then water added until the solution turned cloudy. The solution was then stored for several months. T.l.c. of the solution using 2:1 ether-hexanes as developer indicated a myriad of products ranging from the baseline to the starting compounds. Evaporation of the solvents gave a dark whisky colored syrup (4.6 g) which was chromatographed on silica gel (230 g) using 2:1 ether-hexane as developer. Isolation of a portion (0.53 g) of the eluent which had the same R_f as the starting compounds, indicated the presence of the azido compound 189 by i.r. spectroscopy and the n.m.r. spectrum indicated the presence of a new methyl resonance (∿2H) at δ3.15. This sample was hydrogenated in methanol (35 ml) at atmospheric pressure for 18 hours in the presence of 5% palladium on carbon. After filtration and evaporation of the methanol solution, the residual syrup (490 mg) was chromatographed on silica gel (45 g) using 4:1 benzene-ethyl acetate to give the methyl glycoside 187 (182 mg) as a partially crystalline syrup which was recrystallized from benzene-hexane: m.p. 73-74.5°; $[\alpha]_D^{24}$ -35.1(c2.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1724 (benzoate), 1740 cm^{-1} ($-CO_2CH_3$); n.m.r. (100 MHz,$CDCl_3$) δ1.34 and 1.51(s,3H,$C(CH_3)_2$), 2.08-2.57(m,4H,H-2,H-3), 3.22(s,3H,$-OCH_3$),3.71(s,3H,$-CO_2CH_3$), 4.31-4.48(m, 3H,H-7,H-8), 4.49(d(overlapped by H-7 and H-8 multiplet),1H,$J_{5,6}$ 6.0Hz,H-5), 4.79(broad d,1H,$J_{5,6}$ 6.0Hz,H-6), 7.54(m,3H,Ar), 8.10(m,2H,Ar); mass spectrum; m/e 379(m^+-CH_3), 363(m^+-OCH_3), 307($m^+-CH_2CH_2CO_2CH_3$).

Anal. Calc. for $C_{20}H_{26}O_8$;C,60.90;H,6.65. Found:C,61.25;H,6.61.

Addition of Hydrazoic acid to Compound 18 in the Presence of Sodium Azide to Give 172 and Methyl 4,7-anhydro-3-azido-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-(allo,altro)-octonate (189).

To an azeotropically dried mixture of the methyl oct-2-enonate 18 (1.0 g) was added sodium azide (0.44 g), anhydrous DMF (35 ml), and hydrazoic aeid (7.0 ml of a 1.39N solution of HN_3 in $CHCl_3$). The mixture was sealed (rubber septum) and stirred for 4 days at 52-55°. The resulting opaque, pale orange mixture was evaporated in vacuo and the residue dissolved in a 1:1 mixture of dichloromethane and saturated aqueous sodium chloride (50 ml). The aqueous phase was extracted with dichloromethane (25 ml) and the combined organic extracts dried over anhydrous sodium sulfate. Following filtration and evaporation of the organic extracts, t.l.c. of the residual syrup indicated a single major band identical in R_f to the starting compound. The infrared spectrum of this syrup, however, indicated a new absorption at 2110 cm^{-1} indicative of the azido functional group. Chromatography of this syrup on silica gel (100 g) using 1:1 hexanes-ether as developer yielded fractions containing mainly the azido mixture 189 (∿60:40) and increasing amounts of the methyl oct-3-enonate 172 ranging from less than 5% in the faster moving portion of the band to approximately 25% in the tail and of the azido band (∿72% yield of 189). No attempts were made to isolate compound 189 in a pure state: $\nu_{max}^{CCl_4}$ 1732, 1745 shoulder (benzoate and $-CO_2Me$,resp.), 2140, 2110 cm^{-1} shoulder (azide); n.m.r. (100 MHz,DMSo-d_6) δ1.32 and 1.48(s,3H,C(CH_3)$_2$), 2.30-2.84(m,2H,H-2),3.60,3.61(two overlapping singlets,3H,-OCH_3),3.90-4.14(m,2H,H-3,H-4), 4.28-4.53(m,3H,H-7,H-8), 4.68-4.84(m,2H,H-5,H-6), 7.56(m,3H,Ar), 8.01(m,2H,Ar); mass spectrum: m/e 405(m^+), 390(m^+-CH_3), 377(m^+-N_2).

Continued elution of the chromatography column with an increasing percentage of ether (2:1,3:1, and 4:1,ether-hexane) produced two minor components which proved to be impure from their n.m.r. spectra but possessed absorption bands at ca. 2100 cm^{-1} in their i.r. spectra. These components were later isolated in higher yield and purity (see compounds 192 and 193 below).

Hydrogenation of Compound 189 to give a Mixture of Methyl 3-amino-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-(allo, altro)-octonate (190) and (191), respectively.

A solution of the (R,S) azido mixture 189 (∿725 mg) in methanol (100 ml) was hydrogenated at atmospheric pressure for 13 h at room temperature in the presence of 5% palladium on charcoal (260 mg, prehydrogenated) as catalyst. After filtration and evaporation of the reaction mixture, t.l.c. of the residual syrup indicated a new lower R_f spot identical to the amino compounds 190 and 191 isolated below. Chromatography of the syrup on silica gel (60 g) using 9:1 benzene-ethanol as developer yielded a chromatographically pure syrup (625 mg, ∿92%) that was an approximately 2:1 mixture of compound 190 to 191 by n.m.r.

Treatment of Compound 18 with Sodium Azide in the Presence of Hydrazoic acid to give Compounds 172, 189, and Methyl 3-amino-4,7-anhydro-8-O-benzoyl-2-diazo-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo (and altro)-octonate (192) and (193), respectively.

To an azeotropically dried mixture of the (E,Z) oct-2-enonate 18 (2.4 g, 50 mmol) was added sodium azide (1.2 g), anhydrous DMF (72 ml), and hydrazoic acid (0.83 ml of a 2.17 N solution of NH_3 in $CHCl_3$). The mixture was sealed (rubber septum), wrapped in aluminum foil and stirred for 4d at 52-55°. The resulting opaque, pale orange mixture was evaporated in vacuo and the residue

dissolved in a 1:1 mixture of dichloromethane and saturated aqueous sodium chloride (100 ml). The aqueous phase was extracted with dichloromethane (50 ml) and the combined organic extracts dried over anhydrous sodium sulfate and evaporated to yield a bright yellow syrup (2.7 g). Chromatography of this syrup on silica gel (200 g) with a gradient of 1:1 hexane ether to 100% ether as developer yielded a faster-moving component having the same R_f as the starting compound 18. This component (1.7 g, ∿70%) was a mixture of methyl oct-3-enonate 172 and hydrazoic addition product 189. The head of this band was richer in compound 189 as evidenced by a decreasing intensity of the band at 2120 cm^{-1} (N_3) in subsequent fractions of this band. From the n.m.r. spectrum (in $CDCl_3$) of this faster-moving component, the azide 189 was found to be less than 5% of this band.

Continued elution of the chromatography column resulted in an observable, definitive separation of two slower-moving yellow components on the column. Collection of the first band gave a bright yellow syrup of the altro-β-amino-α-diazo octonate 193 (180 mg, 6%); $[\alpha]_D^{28}$ -47.8° (c0.56,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3400, 3340 (weak, $-NH_2$), 2105($-N_2$), 1734(benzoate), 1697 cm^{-1} ($-CO_2CH_3$); n.m.r. (100MHz,$CDCl_3$) δ1.31 and 1.50(s,3H,c(CH_3)$_2$), 1.63(broad s(partially overlapped by C(CH_3)$_2$),2H,NH_2, exchangeable with D_2O), 3.72(s,3H,$-OCH_3$), 3.91(broad m, 1H,H-3), 4.08(pseudo-t,1H,$J_{3,4}$ and $J_{4,5}$ 4.0Hz,H-4), 4.26(pseudo-q,1H,$J_{6,7}$ 3.5 Hz,$J_{7,8}$ 4.5Hz,H-7), 4.45(d,2H,$J_{7,8}$ 4.5Hz,H-8), 4.63(dd,1H,$J_{5,6}$ 7.0Hz,$J_{4,5}$ 4.0Hz,H-5(6)), 4.77(dd,1H,$J_{5,6}$ 7.0Hz,$J_{6,7}$ 3.5Hz,H-6(5)), 7.49(m,3H,Ar), 8.04 (m,2H,Ar); mass spectrum: m/e 377(m^+-N_2), 362($m^+-(N_2+CH_3)$), 345($m^+-(N_2+HOCH_3)$), 330(345-CH_3). Metastable peak at approximately 316 which could be attributed to 377 fragmenting to 345 or 345 fragmenting to 330. The former is favored due to their comparable intensities.

Further elution of the column yielded the slower-moving diazo compound

192 (264 mg, 9%); $[\alpha]_D^{28}$ + 20.7° (c1.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3400, 3340($-NH_2$), 2102 (diazo), 1730(benzoate), 1698 cm^{-1} ($-CO_2CH_3$); n.m.r.(100MHz,$CDCl_3$) δ1.30 and 1.50(s,3H,$C(CH_3)_2$), 1.66(broad s(partially overlapped by CH_3 at δ1.50), 2H,NH_2, exchangeable with D_2O), 3.70(s,3H,$-OCH_3$), 3.96(broad m,1H,H-3), 4.05(dd,1H,approx. 4.0 and 5.5Hz,H-4), 4.18-4.30(m,1H,H-7), 4.41(d,1H, $J_{3,8a}$ 2.0Hz,H-8a), 4.45(d,1H,$J_{7,8b}$ 2.5Hz,H-8b), 4.62-4.67(m,2H,H-5,H-6), 7.48 (m,3H,Ar), 8.01(m,2H,Ar); mass spectrum: identical to compound 193.

Anal. Calc. for $C_{19}H_{23}N_3O_7$:C,56.29;5.72;N,10.36. Found: C,60.78; H,6.54; 3.10.

Compound 192 was dried at 78° for 18 h *in vacuo* prior to micro-analysis. If elimination of nitrogen did occur to give the aziridine derivative, analysis should give:

$C_{19}H_{23}NO_7$:C,60.5;H,6.2;N,3.7.

Catalytic Hydrogenolysis and Hydrogenation of Compound 193 to give Methyl 3-amino-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-altro -octonate (191) and Methyl 3-amino-4,7-anhydro-8-O-benzoyl-3-deoxy-5,6-O-isopropylidene-D-glycero-D-altro -2-octulosonate Hydrazone (196).

A solution of the diazo compound 193 (1.16 g) in methanol (75 ml) was hydrogenated at atmospheric pressure for 3 h at room temperature in the presence of 5% palladium on charcoal (190 mg, prehydrogenated) as catalyst. The mixture was filtered and evaporated to yield a pale yellow syrup which on t.l.c. using 9:1 benzene-ethanol as developer gave two new lower R_f (0.35 and 0.16) bands. The higher R_f band, however, also overlapped a faster moving, minor, broad band. Chromatography of the crude syrup on silica gel (124 g) using 9:1 benzene-ethanol as developer gave a portion of the high R_f (0.35) β-amino compound 191 (0.32 g, 30%) free of higher R_f impurities: $[\alpha]_D^{25}$ -12.8°

(c1.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3405, 3340 (weak,N-H), 1730, 1740 cm^{-1} shoulder(benzoate and $-CO_2CH_3$, resp.); n.m.r. (100MHz,$CDCl_3$) δ1.33 and 1.53(s,3H,$C(CH_3)_2$), 1.56(s(buried under CH_3 at δ1.53),2H,NH_2, exchangeable with D_2O), 2.34 (dd,1H,J_{gem} 16.0Hz,$J_{2a,3}$ 9.0Hz,H-2a), 2.58(dd,1H,J_{gem} 16.0Hz,$J_{2b,3}$ 4.0Hz, H-2b), 3.18-3.36(broad m,1H,H-3), 3.62(s,3H,$-OCH_3$), 3.81-3.90(m,1H,H-4), 4.14-4.30(m,1H,H-7), 4.44(d,1H,$J_{7,8a}$ 4.0Hz,H-8a), 4.45(d,1H,$J_{7,8b}$ 4.0Hz, H-8b),4.59-4.69(m,2H,H-5,H-6), 8.46(m,3H,Ar), 8.02(m,2H,Ar). Irradiation of the multiplet centered at δ4.62 collapsed the multiplet at δ3.81-3.90 to a doublet with $J_{3,4}$ 5.0Hz. Irradiation of the broad multiplet at δ3.24 collapsed the doublet of doublets at δ2.34 and 2.58 to doublets (J_{gem} 16.0Hz) while the multiplet at δ3.85 partially collapsed.

Anal. Calc. for $C_{19}H_{25}NO_7$: C,60.15;H,6.64;N,3.69. Found: C,59.92;H,6.58; N,3.71.

Further elution of the column gave the hydrazone 196 (0.31 g, 26%) as a clear syrup which could not be crystallized from various solvents: n.m.r. (100MHz,$CDCl_3$) δ1.32 and 1.52(s,3H,$C(CH_3)_2$), 1.78(broad s,2H,NH_2, exchangeable with D_2O), 3.69(s,3H,$-OCH_3$), 3.86(broad d,1H,$J_{3,4}$ ~4.0Hz,H-3), 4.16-4.28 (pseudo-q(overlapping bands),2H,approx. 4.0Hz between the four resonance signals,H-4,H-7), 4.42(d,1H,$J_{7,8a}$ 4.0Hz,H-8a), 4.44(d,1H,$J_{7,8b}$ 4.0Hz,H-8b), 4.58(dd,1H,$J_{4,5}$ 4.0Hz,$J_{5,6}$ 7.0Hz,H-5), 4.68(dd,1H,$J_{5,6}$ 6.0Hz,$J_{6,7}$ 3.0Hz,H-6), 7.46(m,3H,Ar), 8.03(m,2H,Ar), 8.47(broad s,2H, $-NNH_2$, exchangeable with D_2O); $\nu_{max}^{CCl_4}$ 3400, 3350, 3300 (weak,$-N-H_2$), 3310, 3270(weak,$-NNH_2$), 1725(benzoate), 1700 ($-CO_2CH_3$), 1570 cm^{-1}(broad,-C=N-).

Catalytic Hydrogenolysis and Hydrogenation of Compound 192 to give Methyl 3-amino-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-glycero-D-allo-octonate (190) and Methyl 3-amino-4,7-anhydro-8-O-benzoyl-3-deoxy-5,6-O-isopropylidene-D-glycero-D- allo 2-octulosonate Hydrazone (195).

A solution of the diazo compound 192 (670 mg) in methanol (55 ml) was hydrogenated at atmospheric pressure for 3 h at room temperature in the presence of 5% palladium on charcoal (200 mg, prehydrogenated) as catalyst. The mixture was filtered and evaporated to yield a light yellow syrup (613 mg) which on t.l.c. using 9:1 benzene-ethanol as developer gave two new lower R_f (0.30 and 0.22) component and indicated the complete consumption the starting compound (R_f 0.40). Chromatography of the crude syrup on silica gel (45 g) using the above 9:1 solvent pair as developer gave the β-amino compound 190 (249 mg, 40%) as a clear syrup: $[\alpha]_D^{25}$ -11.0 (c2.4,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3405, 3340 (weak,N-H), 1730, 1740 cm^{-1} shoulder (benzoate and $-CO_2CH_3$ resp.); n.m.r. (100MHz,$CDCl_3$) δ1.32 and 1.52(s,3H,$C(CH_3)_2$), 1.61(s,2H,NH_2, exchangeable with D_2O), 2.28(dd,1H,J_{gem} 16.0Hz,$J_{2a,3}$ 9.0Hz,H-2a), 2.60(dd, 1H,J_{gem} 16.0Hz,$J_{2b,3}$ 4.0Hz,H-2b), 3.24-3.41(m,1H,H-3), 3.60(s,3H,$-OCH_3$), 3.76(dd,1H,$J_{3,4}$ 6.0Hz,$J_{4,5}$ 4.0Hz,H-4), 4.19(pseudo-q,1H,$J_{7,8a}$ and $J_{7,8b}$ 4.0Hz,$J_{6,7}$ 4.0Hz,H-7), 4.34(dd(partially overlapped by H-7 and H-8b),1H, J_{gem} 11.5Hz,$J_{7,8a}$ 4.0Hz,H-8a), 5.48(dd(partially overlapped by H-8a and H-5(6)), J_{gem} 11.5Hz,$J_{7,8b}$ 4.0Hz,H-8b), 4.57(dd,1H,$J_{4,5}$ 4.0Hz,$J_{5,6}$ 6.5Hz,H-5), 4.71(dd,1H,$J_{6,7}$ 4.0Hz,H-6) 7.44(m,3H,Ar), 8.00(m,2H,Ar); mass spectrum: m/e 379(m^+), 364(m^+-CH_3), 348(m^+-OCH_3).

Anal. Calc. for $C_{19}H_{25}NO_7$:C,60.15;H,6.64;N,3.69. Found: C,60.06; H,6.49;3.61.

Further elution of the column gave hydrazone 195 (110 mg, 16%) as a viscous syrup which was crystallized from hexane-ethylacetate: m.p. 109.5-111°; n.m.r. (100MHz,$CDCl_3$) δ1.34 and 1.52(s,3H,$C(CH_3)_2$), 1.78(broad s,2H, $-NH_2$, exchangeable with D_2O), 3.68(s,3H,$-OCH_3$) 3.94(broad d,1H,$J_{3,4}$ 6.5Hz, H-3), 4.10-4.28(m,2H,H-4,H-7), 4.42(m,2H,$J_{7,8}$ ∿3.0Hz,H-8), 4.62(dd,1H,

$J_{4,5}$ 3.7Hz,$J_{5,6}$ 6.0Hz,H-5), 4.74(dd,1H,$J_{5,6}$ 6.0Hz,$J_{6,7}$ 3.5Hz,H-6), 7.48(m, 3H,Ar), 8.02(m;2H,Ar), 8.36(broad s,approx.2H, $-NNH_2$, exchangeable with D_2O); mass spectrum: m/e 407(m^+), 398(m^+-CH_3).

Anal. Calc. for $C_{19}H_{25}N_3O_7$:C,56.01;H,6.19;N,10.31. Found: C,56.00; H,6.25;N,10.23.

Attempted Cyclization of Compound 195 with N,N'-Carbonyldiimidazole (197) to give 5-(S)-(5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-6-carbomethoxy-4,5-dihydro-2H-as-triazin-3-one (198)

A solution of the hydrazone 198 (63 mg) and N,N'-carbonyldiimidazole (∿30 mg) in anhydrous THF (2.4 ml) was mildly refluxed for 1.5 h. The mixture was then cooled and the THF evaporated. The residual syrup was dissolved in a small amount of dichloromethane, applied to three t.l.c. plates (15x20 cm, 1.0mm) and developed with 15:8:2 benzene-ethylacetate-ethanol to give 4 major bands. The slowest moving band at R_f 0.11 was identical by n.m.r. spectroscopy to imidazole. The intermediate bands of R_f 0.22 and 0.385 were mixtures by n.m.r. and no further attempts to purify them were made. The faster-moving band at R_f 0.56 (44 mg, 65%) was the most prominent of the charring bands and possessed single peaks for its methyl resonances in the n.m.r. spectrum: n.m.r. (100MHz, DMSO-d_6, assignments are tentative and are based on compound 198) δ1.24 and 1.43(s,3H,C($\underline{CH_3}$)$_2$), 3.57 (s,3H,$-OCH_3$), 4.00-4.36(m,4H,H-1',H-4',H-5'), 4.74-4.92(m,3H,H-5,H-2',H-3'), 6.38(d,2/3H,∿8.0Hz,no assignment), 7.10(broad s,2/3H, no assignment), 7.60 (m,3H,Ar), 8.12(m,2H,Ar), 9.32(broad s,1H,N(2)-$\underline{H}$, exchangeable with D_2O); mass spectrum: m/e 431(m^+-2H), 418(m^+-CH_3); $\nu_{max}^{CCl_4}$ 3410, 3300, 3270(NH), 1725 (PhCO), 1700($-CO_2Me$), 1665(HN-CO-NH), ∿1550 cm^{-1}(C=N).

Treatment of Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-allo-oct-2-enonate (18) with Ceric Ammonium Nitrate (CAN) and

Sodium Azide.

A solution of the enonate 18 (362 mg) in anhydrous acetonitrile (5.4 ml) was cooled to -25° under nitrogen atmosphere. This cooled solution was transfered via a syringe to a mixture of solid CAN (1.29 g) and sodium azide (0.06 g). The resulting mixture was vigorously stirred for 15 h at -33 to -22°. Cold ethyl ether (5 ml) was added and the resulting mixture filtered and the solid residue washed with ether (2x2 ml). The combined filtrates were washed with ice cold water (4x5 ml), dried over anhydrous sodium sulfate, filtered and evaporated to give a yellow syrup (398 mg). Column chromatography of the syrup on silica gel (50 g) with 20:1 benzene-ether as developer gave two faster-moving components (31 mg and 8 mg, 8.5 and 2%, resp., based on the molecular weight of 18) which proved to be impure upon inspection of their n.m.r. spectra.

The major slower-moving band (260 mg, 73%) had the same R_f and i.r. spectrum as 18.

7. Hemiketals, γ-Lactones, and Alkyl and Acyl Ketals

Air Oxidation and Hydration of Methyl (E,Z)-4,7-anhydro-8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (172) to yield 5-O-Benzoyl-2,3-O-isopropylidene-DOribono-1,4-lactone (199), 8-O-Benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribono-4-octulofuranosono-1,4-lactone (200), Methyl(E)-8-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-oct-2-en-4-ulofuranosonate (201),Methyl 8-O-benzoyl-2,3-dideoxy-5,6-O-isopropylidene-β-D-ribo-4-octulofuranosonate (202), Methyl 8-O-benzoyl-2-deoxy-5,6-O-isopropylidene-α,β-D-allo (and altro)-4-octulofuranosonate (203) and (204), respectively.

The methyl oct-3-enonate 172 (approx. 13.5 g) which was synthesized in various attempts to improve the yield of the β-amino-α-diazo compounds 192 and 193 was allowed to stand for prolonged periods (1.5-9 months) as a syrup

or in the chromatography developer (2:1 ether-hexanes). In the cases where compound 172 was left in the developer both solvents had completely evaporated leaving a pale yellow syrup. T.l.c. analysis of these syrups indicated that the unsaturated compound had reacted further to form products ranging in R_f (using 2:1 ether-hexanes as developer) from the base-line to the starting compound.

The various fractions and syrups were collected to give a deep whisky colored syrup (∿15 g) which was chromatographed on silica gel (400 g) using a gradient of 1:1 (600 ml), 2:1 (600 ml), 4:1 (315 ml) ether-hexanes and 100% ether to achieve a crude separation of the components. The eluent which contained charring compounds was isolated as seven bands (A to G) according to descending R_f using ether-hexanes as developer.

Fraction A (∿2.0 g): This fraction had the same R_f as the starting methyl oct-3-enonate 172. The n.m.r. spectrum indicated a preponderance (∿70%) of 172 (resonance at ∿δ3.14,H-2) and the splitting of the methyl peaks at δ1.6 and 3.6 indicated a second component. The i.r. spectrum of this mixture had an absorption of ∿2120 cm^{-1} indicative of the azido compound 189.

Fraction B (2.14 g): The i.r. spectrum of this component possessed a broad, weak absorption band at 3350 cm^{-1} and a stronger, sharper peak at 1804 cm^{-1}. T.l.c. of this fraction using 1:1 ether-hexane as developer indicated the possibility of 3 overlapping bands which were slower-moving than the starting compound 172. A change of the developer to 4:1 benzene-ethyl acetate, however, gave better separation to show 3 distinct components plus a minor charring band just above the base-line (R_f 0.41, 0.35, 0.28 and 0.03 with compd. 202 at 0.38).

Rechromatography of this fraction on silica gel (250 g) using 4:1 benzene-ethyl acetate as developer afforded the ribonic, 1,4-lactone 199

(375 mg, 3.5%*) as the faster-moving component which crystallized under vacuo. Recrystallization of this component from benzene-hexane gave an analytical sample: m.p. 101.5-102.5°; $\nu_{max}^{CCl_4}$ 1802(lactone), 1733 cm^{-1}(benzoate); $[\alpha]_D^{25}$ -50.4°(c1.5,$CHCl_3$); n.m.r. (100MHz,$CDCl_3$) δ1.40 and 1.51(s,3H,$C(CH_3)_2$), 4.52(dd,1H,J_{gem} 12.3Hz,$J_{4,5a}$ 3.0Hz,H-5a), 4.69(dd,1H,J_{gem} 12.3Hz,$J_{4,5b}$ 2.5Hz, H-5b), 4.79 and 4.87(d,1H,$J_{5,6}$ 6.0Hz,H-5,H-6), 4.92(pseudo-t,1H,H-4), 7.56(m, 3H,Ar), 7.96(m,2H,Ar); mass spectrum: m/e 293(m^++H), 277(m^+-CH_3).

Anal. Calc. for $C_{15}H_{16}O_6$:C,61.64;5.52. Found: C,61.49;5.50.

Continued elution of the chromatography column gave the keto 1,4-lactone 200 (1.03g, 8.2%) as a partially crystalline syrup which was recrystallized from benzene-hexane; m.p.101-102.5°; $[\alpha]_D^{25}$ -49.9(c1.5,$CHCl_3$); $\nu_{max}^{CCl_4}$1800 (lactone), 1725 cm^{-1} (benzoate); n.m.r. (100MHz,$CDCl_3$) δ1.37 and 1.51(s,3H,$C(CH_3)_2$), 2.24-2.89(m,4H,H-2,H-3), 4.42(d(overlapping H-8b),1H,$J_{7,8a}$ 7.5Hz,H-8a), 4.43(d(overlapping-H-8a),1H,$J_{7,8b}$ 5.0Hz), 4.60(broad dd,1H,H-7), 4.77(d,1H,$J_{5,6}$ 6.0Hz,H-5), 4.92(dd,1H,$J_{5,6}$ 6.0Hz,$J_{6,7}$ ∿1.0Hz,H-6), 7.54 (m,3H,Ar), 8.08(m,2H,Ar); mass spectra: m/e 348(m^+), 333(m^+-CH_3), 213(m^+-$PhCO_2CH_2$).

Anal. Calc. for $C_{18}H_{20}O_7$:C, 62.06;H,5.79. Found: C,61.94; H,5.66.

Further elution of the column gave fractions which by t.l.c. with the 4:1 solvent pair were mixtures of a least two compounds overlapped by a broader, more diffused band. Continued elution of the column eventually gave the lower R_f spot (0.28) as a chromatographically pure compound. The mixture (fraction B-A) was later rechromatographed and the slower-moving component was collected to give the saturated ketal 202 (370 mg, 2.7%) as a partially crystalline syrup which was recrystallized from chloroform-hexane; m.p. 109-112.5°; $[\alpha]_D^{25}$ -2.7°(c1.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3430(broad,OH), 1727 cm^{-1} (esters); n.m.r. (100MHz,DMSO-d_6) δ1.28 and 1.41(s,3H,$C(CH_3)_2$), 1.92-1.16

* yields here will be based on 13 g of compd. 172 consumed.

(m,2H,H-3), 1.30-1.46(m(partially obscured by DMSO-d_6),2H,H-2), 3.60 (s,3H,-OC$\underline{H}_3$), 4.24(broad dd,1H,H-7) 4.37(d(overlapped by H-8b),1H,$J_{7,8a}$ 4.0Hz,H-8a), 4.40(d(overlapped by H-8a),$J_{7,8b}$ 10.5Hz,H-8b), 4.44(d,1H, $J_{5,6}$ 6.0Hz,H-5), 4.86(dd,1H,$J_{5,6}$ 6.0Hz,$J_{6,7}$ 1.3Hz,H-6), 6.16(sharp s,1H, O$\underline{H}$, exchangeable with D_2O), 7.62(m,3H,Ar), 8.02(m,2H,Ar); mass spectrum: m/e 365(m^+-CH_3), 349(m^+-OCH_3), 333(m^+-($HOCH_3$ + CH_3)).

Anal. Calc. for $C_{19}H_{24}O_8$:C,59.99;H,6.36. Found: C,59.87;H,6.36.

Rechromatography of the above mixture (320 mg)(fraction B-A) on silica gel (17 g) using 29:1 benzene-ethanol as developer removed the broad, diffuse band from the overlapping pairs of compounds. A portion of the lower R_f material was isolated pure and was identical to ketal 202 (190 mg). The remaining mixture (108 mg) was again rechromatographed on silica (17 g) using 4:1 benzene-ethyl acetate to afford the unsaturated ketal 201 (28 mg, 0.3%) as a clear syrup: $\nu_{max}^{CCl_4}$ 3440,(broad,OH), 1720 cm^{-1}(broad, benzoate and unsaturated ester); n.m.r. (100MHz, DMSO-d_6) δ1.27 and 1.41(s,3H,C(C$\underline{H}_3$)$_2$), 1.72(s,3H,-OC$\underline{H}_3$), 4.22(broad s,3H,H-7,H-8), 4.56(d,1H,$J_{5,6}$ 5.5Hz,H-5), 4.96 (d,1H,$J_{5,6}$ 6.0Hz,H-6), 6.14(d,1H,$J_{2,3}$ 16.0Hz,H-2), 6.87(d,1H,$J_{2,3}$ 16.0Hz,H-3), 6.89(sharp s,1H,O$\underline{H}$, exchangeable with D_2O), 7.62(m,3H,Ar), 8.04(m,2H,Ar); mass spectra: m/e 378(m^+), 363(m^+-CH_3), 347(m^+-OCH_3); $[\alpha]_D^{23.5}$-25.4 (c1.24,$CHCl_3$).*

Anal. Calc. for $C_{19}H_{22}O_8$:C,60.31;H,5.86.

Found: (Syrup) C,60.62;H,5.99; (Solid)** C,60.61;H,6.00.

Further elution of the column gave a mixture of ketals 201 and 202 (40 mg; a 30:70 ratio, resp.) and a final sample of the pure ketal 202 (55 mg, 3.8% overall yield).

*The n.m.r. spectrum of compd. 201 in $CDCl_3$ indicated a 4:1 mixture of anomers.
**Solid: M.P. 78-88°.

Fraction C(0.55 g): The i.r. spectrum of this component possessed two broad bands at approximately 3400 and 3500 cm^{-1} and a strong broad carbonyl at 1722 cm^{-1}. T.l.c. of this fraction with various solvent systems gave a broad charring band in which no major component could be detected nor could any appreciable separation of components be seen.

Chromatography of the syrup on silica gel (60 g) using 4:1 benzene-ethyl acetate yielded one chromatographically pure band which from its n.m.r. spectrum indicated a mixture of compounds. Due to the relative small amount of sample and the number of compounds observed for this chromatographic region, no further attempts were made to separate the various components.

Fraction D (1.5 g): The i.r. spectrum of this fraction had a broad band at 3500 cm^{-1}, a weak band at 1810 cm^{-1} and a strong carbonyl absorption at 1727 cm^{-1}. T.l.c. of the syrup using 4:1 ether-hexanes as the developer showed two charring bands (R_f 0.32 and 0.37) with the higher R_f band predominating. However, if 2:1 benzene-ethyl acetate was used as the mobile phase, two bands could still be observed but the faster-moving material was much more diffuse (R_f 0.27 to 0.47) and the slower-moving, major component at R_f 0.22 was a much narrower band.

Therefore, the crude syrup (1.2 g) was rechromatographed on silica gel (95 g) using 4:1 ether-hexane as developer to give the faster-moving component (0.96 g) as clear syrup. The slower-moving component was found to be chromatographically identical to the major band in fraction E and were combined. T.l.c. of the higher R_f band using the benzene-ethyl acetate developer still gave the previously described diffuse bands; therefore, this syrup was again rechromatographed but using 4:1 benzene-ethyl acetate as developer to yield the hydroxy ketal 203 (0.64 g, 4.5%) as a white crystalline mass which was recrystallized from dichloromethane-hexanes to

give fine needles: m.p. 126-128° (smaller crystals), 130-132° (larger crystals); $[\alpha]_D^{23}$ -29.1° (c2.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3480(broad,OH), 1725 cm^{-1} (esters); n.m.r.(100MHz,DMSO-d_6) δ1.30 and 1.45(s,3H,C(CH_3)$_2$), 2.28-2.70 (m(obscured by the DMSO resonance), 4H(incl. DMSO),H-2), 3.64(s,3H, -OCH_3), 4.14-4.56(m,5H,H-3,H-5,H-7,H-8), 4.95(d,1H,$J_{5,6}$ 6.0Hz,H-6), 5.25(d,1H, $J_{3,OH}$ 5.5Hz,CHOH, exchangeable with D_2O), 6.08(sharp s,1H,COH, exchangeable with D_2O, 7.70(m,3H,Ar), 8.08(m,2H,Ar). Addition of D_2O to the n.m.r. sample induced a splitting in the methyl resonances to give approximately 20% intensity to the new resonances. These occurred at δ1.36, 1.50 and 3.59. The n.m.r. spectrum using deuterochloroform as solvent clearly indicated the C-2 methylene hydrogens and also showed the keto sugar as a 4:1 ratio of the α and β anomers, respectively; C-13 n.m.r. (20MHz, DMSO-d_6, proton-decoupled) major isomer-δ24.86 and 26.38(C(CH_3)$_2$), 37.69(C-2), 51.13(OCH_3), 66.03(C-8), 69.16(C-3), 82.75 (degenerate), 84.72(C-5,C-6,C-7), 107.39(C-4), 111.89(C(CH_3)$_2$), 165.47(PhC=O), 171.56(CO_2Me); minor isomer-δ25.39 and 26.38(C(CH_3)$_2$), 37.09 (C-2), 51.13(OCH_3), 64.74(C-8), 70.49(C-3), 78.97, 79.85, 81.00(C-5,C-6, C-7), 104.30(C-4), 114.42(C(CH_3)$_2$), 165.47(PhC=O), 171.74(CO_2Me). The aromatic signals centered at δ120 were not assigned. High res. mass spectrum (deviation): m/e 396.1440(1.9,m^+), 381.1193(0.7,m^+-CH_3), 349.0927(0.4,m^+-(CH_3+CH_3OH)), 293.1028(0.3,m^+-$CHOHCH_2CO_2CH_3$).

Anal. Calc. for $C_{19}H_{24}O_8$:C,57.57;H,6.10. Found: C,58.06;H,6.46.

Fraction E (4.7 g): This fraction was mainly contaminated with slower-moving pale yellow impurities. The i.r. spectrum possessed a broad, weak band at 3530 cm^{-1} and a strong band at 1725 cm^{-1}. The amber syrup was rechromatographed on silica gel (230 g) using 19:1 benzene-ethanol as developer to give the epimeric hydroxy ketal 204 (2.5 g,17.6%) as a clear syrup which failed to crystallize from various solvents, $[\alpha]_D$ + 9.27(c1.1,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3510

(broad,OH), 1720 cm^{-1}(esters); n.m.r. (100MHz,DMSO-d_6, minor isomer in parenthesis) δ1.33(1.36) and 1.48(1.57)(s,3H,C($\underline{CH_3}$)$_2$), 2.34-2.80(m(obscured by DMSO), 3H(incl.DMSO),H-2), 3.65(3.63)(S,3H,-OCH_3), 3.84-4.92(m,6H,H-3,H-5, H-6,H-7,H-8), 5.29(d,approx. 1/2H,$J_{3,OH}$ 6.5Hz,CHO$\underline{H}$, exchangeable with D_2O), 5.95 (5.60)(sharp s (broad s), approx. 2/3H (1/3H), CO$\underline{H}$, exchangeable with D_2O), 8.65(m,3H,Ar), 8.05(m,2H,Ar). α to β ratio was approximately 2:1 using DMSO-d_6 as solvent. Addition of D_2O to the solution increased the ratio to approximately 4:1 (α to β, resp.). The n.m.r. spectrum in C_6D_6 gave two broad doublets at δ3.56 and 3.62 with $J_{3,OH}$ 7.0Hz for the 2°-hydroxyls and a sharp singlet at δ4.59 for the 3°-hydroxyl, all of which were exchangeable with D_2O. A similar pattern also occurred in deuterochloroform for the 2°-hydroxyls; mass spectrum; m/e 396(m^+), 381(m^+-CH_3), 365(m^+-OCH_3), 293(m^+-$CHOHCH_2CO_2CH_3$); C-13 n.m.r. (20MHz,DMSO-d_6, proton-decoupled) major isomer-δ25.21 and 26.66(C($\underline{CH_3}$)$_2$), 36.63 (C-2), 66.19(C-8), 67.72(C-3), 82.44, 83.54, 84.94(C-5,C-6,C-7), 107.34(C-4), 112.03($\underline{C}$(CH_3)$_2$), 165.62(Ph$\underline{C}$=0), 172.19 ($\underline{C}O_2$Me); minor isomer-δ25.50 and 26.66(C($\underline{CH_3}$)$_2$), 36.33(C-2), 51.19($O\underline{CH_3}$), 65.05 (C-8), 70.57(C-3), 79.94, 80.68, 81.23(C-5,C-6,C-7), 105.07(C-4), 113.94($\underline{C}$ (CH_3)$_2$), 165.62(Ph$\underline{C}$=0), 172.19($\underline{C}O_2$Me). The aromatic signals were not assigned.

Anal. Calc. for $C_{19}H_{24}O_8$:C,57.57;H,6.10. Found: C,57.24;H,6.18.

Fraction F (∿3.0 g): This pale yellow syrup did not give any definitive bands upon t.l.c. analysis; therefore, no attempts were made to determine its composition.

Synthesis of 199 from 172 Using Excess meta-Chloroperbenzoic acid.

Using a modification of the procedure of Borowitz et al[89a], a solution of the methyl oct-3-enonate 172 (362 mg, 1.0 mmol) in anhydrous 1,2-dichloroethane (3.0 ml) was added to an ice-cooled, stirred, partial suspension of

meta-chloroperbenzoic acid (530 mg, 3.1 mmol) in 1,2-dichloroethane (4.0 ml) over 15 min. The ice-bath was then removed and the mixture stirred for 4 days at room temperature. The reaction mixture remained cloudy during the course of the reaction and a small amount of precipitate was present at the end of the 4 days. The mixture was then filtered, diluted to 15 mls with dichloromethane, the resulting solution washed with 7% aqueous sodium hydrogen carbonate (5 ml), water (5 ml) and the organic phase was dried over anhydrous sodium sulfate. After filtration and evaporation of the organic phase, the residual syrup (142 mg) was chromatographed on silica gel (17 g) using 9:1 benzene-ethylacetate as developer to afford the lactone 199 (49 mg, 17%), the n.m.r. spectrum of which was identical to the lactone 199 isolated from the air oxidation of 172.

Treatment of Compound 172 with meta-Chloroperbenzoic Acid in the Presence of Ethanol to give Compound 204 and Methyl (ethyl 8-O-benzoyl-2-deoxy-5,6-O-isopropylidene- β -D-altro-4-octulofuranosid)onate (207).

To a stirred solution of the methyl oct-3-enonate 172 (180 mg, 0.5 mmol) in reagent grade dichloromethane (4.0 ml) at 0° was added dropwise a solution of meta-chloroperbenzoic acid (114 mg, 0.65 mmol) in dichloromethane (2 mls). The reaction was stirred at 0° for 1 h after which the mixture was allowed to reach room temperature and stirring was continued for an additional 2 h. The excess peracid was destroyed with 10% aqueous sodium sulfite (3.5 ml). The aqueous layer was extracted with dichloromethane, the organic layers were combined and washed with saturated aqueous sodium hydrogen carbonate (5 ml), water (5 ml) and then dried over anhydrous sodium sulfate. Removal of the drying agent by filtration and evaporation of the solvent gave a clear syrup (195 mg) which by t.l.c. using 4:1 benzene-ethyl acetate showed two major components at R_f 0.275 and 0.13. The syrup was applied to a column

of silica gel (30 g) and eluted with a gradient of benzene-ethyl acetate (4:1,60 ml; 3:1,20 ml; 2:1,36 ml; 1.5:1,53 ml). The faster-moving component was collected to give the ethyl glycoside 207 (85 mg,39%) as a clear syrup: $[\alpha]_D^{25}$ -13(c0.6,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3560(broad,OH), 1727 cm^{-1}(esters); n.m.r.(100MHz,DMSO-d_6) δ1.07(t,3H,J_{CH_3,CH_2} 7.0Hz, $-OCH_2\underline{CH_3}$), 1.32 and 1.48 (s,3H,$C(\underline{CH_3})_2$), 2.49(dd(partially buried under DMSO),1H,J_{gem} ~15.0Hz,$J_{2a,3}$ 9.5Hz,H-2a), 2.76(dd,1H,J_{gem} 15.0Hz,$J_{2b,3}$ 3.5Hz, H-2b), 3.61(q(partially buried under $-OC\underline{H_3}$),1H,J_{CH_3,CH_2} 7.0Hz, $-OC\underline{H_2}CH_3$), 3.62(s,3H, $-OC\underline{H_3}$), 4.24-4.47(m, 4H,H-3,H-7,H-8), 4.67(d,1H,$J_{5,6}$ 6.0Hz,H-5), 4.79(broad s (buried under H-5 and H-6),1H,O<u>H</u>, exchangeable with D_2O), 4.87(broad d,1H,$J_{5,6}$ 6.0Hz,H-6), 7.66(m,3H,Ar), 8.05(m,2H,Ar). Irradiation of the triplet at δ1.07 collapsed the quartet at δ3.61 to a singlet; mass spectrum: m/e 424(m^+), 409(m^+-CH_3), 321($m^+-CHOHCH_2CO_2CH_3$).

Anal. Calc. for $C_{21}H_{28}O_9$:C,59.43;H,6.65. Found: C,59.70;H,6.87.

Continued elution of the column gave the ketal 204 (20 mg, 10%) as a clear syrup which had the same R_f (0.254 and 0.232) using 2:1 benzene-ethylacetate and 1:4 hexane-ether as the ketal previously isolated. The n.m.r. spectra of these two ketals were also identical.

Treatment of Compound 172 with Osmium Tetroxide to give Ketals 203 and 204

To a stirred solution of the methyl oct-3-enonate 172 (195 mg, 0.54 mmol) in anhydrous pyridine (2.0 ml) was added solid osmium tetroxide (138 mg, 0.58 mmol). The resulting brown solution grew darker as the reaction progressed. After 22 h, a 5% solution of aqueous sodium hydrogen sulfite was added and the mixture rigorously stirred for 10 min. The mixture was then extracted with chloroform (10 ml and 2x5 ml), and the combined organic extracts washed with water (10 ml) and dried over anhydrous sodium sulfate. After removal

of the drying agent by filtration and evaporation of the solution, xylene (3x4 ml) was added and evaporated at reduced pressure to remove the residual pyridine. The remaining brown syrup was chromatographed on silica gel (16 g) using 14:7:4 benzene-ethylacetate-ether as developer to give ketal 203 (6 mg, 3%) as the faster-moving minor component and ketal 204 (80 mg, 37.5%) as the slower-moving major component. The n.m.r. spectra of both ketals were identical to those obtained from the air oxidation of compound 172 and a crystalline sample of ketal 203 melted at 123-128° in agreement with previous results.

Treatment of Ketal 203 with Sodium Periodate to give Lactone 199

To a stirred solution of the hydroxy hemi-ketal 203 (23 mg) in ethanol (0.5 ml) shielded with foil was added a solution (0.5 ml) of sodium periodate (570 mg) and sodium hydrogen carbonate (36 mg), in water (10 ml). T.l.c. of the mixture after 4 h indicated a higher R_f spot and a slower-moving material approximately the same R_f as starting material. The reaction was allowed to run for 30 days after which the reaction mixture was coevaporated with xylene (3 ml) and the residue dissolved in ethylacetate, filtered and resulting solution evaporated to give a crude syrup (29 mg). Chromatography of this syrup on a preparative silica gel plate (15x20 cm,250 μm) using 3:2 ether-hexanes as developer gave a minimum of five components (detected via a U.V. lamp). Isolation of the components gave only one band which was greater than 2 mg. This major band (7.5 mg, 44%) had the same R_f (0.45 on the above plate) as lactone 199 and the n.m.r. spectra were identical.

Treatment of Compound 204 with Sodium Periodate to give Compound 199 and 211

To a stirred solution of the hydroxy hemi-ketal 204 (60 mg) in methanol (1.3 ml) protected with foil was added a solution of sodium periodate (60 mg) in water (1.3 ml). The solution was stirred for 30 days after which the mixture was filtered and coevaporated with toluene (2x3 ml), redissolved in

ethyl acetate, filtered and evaporated to yield a crude syrup (68 mg). The syrup was chromatographed on a preparative t.l.c. plate (20x20 cm, 1.5 mm) using 1.5:1 ether-hexanes as developer to give 3 U.V. active components. The faster-moving band at R_f 0.48 was collected to give the crystalline lactone 199 (22 mg,50%) which had an n.m.r. spectrum identical to the one obtained for compound 199 isolated from the air oxidation of the methyl oct-3-enonate 172.

The intermediate band (R_f 0.29) was extracted to yield an impure sample of spiro-lactone 211 (3 mg). The n.m.r. spectrum of this syrup showed that it was predominantly the spiro-lactone 211 synthesized in a later reaction.

The slower-moving band (R_f 0.22) yielded a syrup (5.5 mg) which by n.m.r. spectroscopy showed a mixture of 3 compounds. Due to the small amount of material no further attempts were made to purify the last two bands.

5,6-Di-O-acetyl-8-O-benzoyl-2,3-dideoxy-α(and β)-D-ribo-4-octulofuranosono-1, 4-lactone (208a) and (208b), respectively.

A solution of the ketal 202 (245 mg) in 80% aqueous trifluoroacetic acid was stirred for 0.5 h at room temperature after which toluene (6 ml) was added and the mixture evaporated under reduced pressure. The treatment with toluene was repeated twice and the residual syrup was dissolved in a solution of acetic anhydride (3 ml), acetic acid (1.5 ml) and para-toluenesulfonic acid monohydrate (600 mg) and stirred overnight at room temperature. To the resulting brown solution was added sodium acetate (0.56 g) and the reaction mixture stirred for 15 min. Xylene (6 ml) was added and the mixture was evaporated under reduced pressure. The treatment with xylene was repeated twice and resulting slurry was triturated with benzene (25 ml) and the mixture

filtered. The solid residue was washed with benzene (2x15 mls) and the combined filtrates evaporated under reduced pressure to give crude syrup which was chromatographed on silica gel (40 g) using 4:1 benzene-ethyl acetate as developer to afford two major bands. The faster moving band gave lactone 208a (60 mg,24%) as a clear syrup: $[\alpha]_D^{22}$+57.7° (c1.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1805 (lactone), 1752 (acetates), 1730 cm^{-1} (benzoate); n.m.r. (100MHz,$CDCl_3$) δ2,14 and 2.16(s,3H,2xCH_3), 2.27-2.45(m,2H,H-3), 2.57-2.81(m,2H,H-2), 4.46 (dd,1H,J_{gem} 11.0Hz,$J_{7,8a}$ 3.5Hz,H-8a),4.59(pseudo-q(partially overlapped by H-8a),1H,H-7),4.62(dd,1H,J_{gem} 11.0Hz,$J_{7,8b}$ 2.0Hz,H-8b), 5.21(d,1H,$J_{5,6}$ 7.0Hz, H-5), 5.43(dd,1H,$J_{5,6}$ 7.0Hz,$J_{6,7}$ 2.5Hz,H-6), 7.57(m,2H,Ar), 8.08(m,1H,Ar); mass spectra: m/e 392(m^+), 347(m^+-CO_2H), 336(m^+-CH_2CH_2CO) 270(m^+-$PhCO_2H$), 257(m^+-$PhCO_2CH_2$).

Anal. Calc. for $C_{19}H_{20}O_9$:C,58.16;H,5.14. Found:C,58.31;H,5.29.

The slower moving prominant band gave the anomeric lactone 208b (86 mg, 34%) also as a clear syrup: $[\alpha]_D^{22}$ -11.1 (c2.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1805 (lactone), 1765, 1758 (acetates), 1730 cm^{-1} (benzoate); n.m.r. (100MHz,$CDCl_3$) δ2.03 and 2.18(s,3H,2xCH_3), 2.28-2.45(m,2H,H-3), 2.57-2.82(m,2H,H-3), 4.41-4.65(m,3H, H-7,H-8), 5.52(d,1H,$J_{5,6}$ 4.5Hz,H-5) 5.60(dd,1H,$J_{6,7}$ 2.5Hz,H-6), 7.56(m,3H, Ar); 8.14(m,2H,Ar); mass spectrum: identical to 208a.

Anal. Calc. for $C_{19}H_{20}O_9$: C,58.16; H,5.14.

Found: C, 58.44; H,5.13.

Methyl 8-O-benzoyl-2-deoxy-3,4:5,6-di-O-isopropylidene-α(and β)-D-allo-4-octulofuranosonate (209a) and (209b), respectively.

A dark orange solution of 2:2:1 (V/V) 2,2 dimethoxypropane-acetone-trifluoroacetic acid (5 ml) was added to the hydroxy ketal 203 (335 mg) and the resulting solution was stirred at room temperature for 2.5 d. Toluene

(2x4 ml) and benzene (4 ml) were evaporated from the reaction mixture to give a crude dark brown syrup which on t.l.c. using 9:1 benzene-ethyl acetate as developer gave 2 charring bands (R_f 0.28 and 0.35) with the slower-moving band predominating. Chromatography of the syrup on silica gel (38 g) using the above solvent pair gave the β-ketal methyl ester 209b (43 mg, 12%) as a clear syrup: $[\alpha]_D^{23}$ -59.1° (c1.1,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1747 ($-CO_2CH_3$), 1732 cm^{-1}(benzoate); n.m.r. (100MHz,$CDCl_3$) δ1.33,1.43,1.46 and 1.48(s,3H,2xC(CH_3)$_2$), 2.54(dd,1H,J_{gem} 16.0Hz,$J_{2a,3}$ 9.7Hz,H-2a), 3.16(dd, 1H,J_{gem} 16.0Hz,$J_{2b,3}$ 4.0Hz,H-2b), 3.74(s,3H,-OCH_3), 4.45(s,3H,H-7,H-8), 4.65(d,1H,$J_{5,6}$ 6.0Hz,H-5), 4.82(dd(partially overlapped by H-6),1H,$J_{2a,3}$ 9.7Hz,$J_{2b,3}$ 4Hz,H-3), 4.85(broad d,1H,$J_{5,6}$ 6.0Hz,H-6), 7.52(m,3H,Ar), 8.08 (m,2H,Ar); mass spectrum: m/e 436(m^+), 421(m^+-CH_3), 405(m^+-OCH_3).

Continued elution of the chromatography column gave the α-ketal methyl ester 209b (277 mg, 75%) as a clear syrup which could not be crystallized from various solvent: $[\alpha]_D^{24}$ -13.6(c1.1,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1733 cm^{-1} (esters); n.m.r. (100MHz,$CDCl_3$) δ1.38, 1.42, 1.52 and 1.62(s,3H,2xC(CH_3)$_2$), 2.59(dd (partially overlapped by H-2b),1H,J_{gem} 17.0Hz,$J_{2a,3}$ 6.0Hz,H-2a), 2.76(dd (partially overlapped by H-2a),1H,J_{gem} ~17.0Hz,$J_{2b,3}$ 6.0Hz,H-2b), 4.58(s,3H, -OCH_3), 4.47(broad s,3H,H-7,H-8), 4.58(pseudo-t,1H,$J_{2a,3}$ and $J_{2b,3}$ 6.5Hz, H-3), 4.66(broad d,1H,$J_{5,6}$ 7.0Hz,H-6), 4.76(d,1H,$J_{5,6}$ 7.0Hz,H-5), 7.53(m,3H, Ar), 8.04(m,2H,Ar); mass spectrum: m/e 436(m^+), 421(m^+-CH_3), 405(m^+-OCH_3).

Anal. Calc. for $C_{22}H_{28}O_9$:C,60.54;H,6.47. Found: C,60.72;H,6.45.

Methyl 8-O-benzoyl-2-deoxy-3,4:5,6-di-O-isopropylidene-β-D-altro-4-octulofuranosonate (210), 8-O-benzoyl-2-deoxy-5,6-O-isopropylidene-α-D-altro-4-octulofuranosono-1,4-lactone (211).

A solution of acetone (8 ml), 2,2-dimethoxypropane (2 ml) and trifluoroacetic acid (2 ml) was added to the hydroxy hemiketal 204 (370 mg)

and the resulting dark red solution stirred for 2 days. Coevaporation with xylene (2x4 ml) gave a dark syrup which was chromatographed on a column of silica gel (40 g) using a gradient of 9:1 to 1:1 benzene-ethyl acetate as developer. Collection of the faster-moving U.V. active, charring band gave the di-isopropylidenated derivative 210 (136 mg, 33%) as a clear syrup: $[\alpha]_D^{24}$ -36.0°(c1.0,$CHCl_3$); $\nu_{max}^{CCl_4}$ 1748(-CO_2Me), 1730 cm^{-1}(benzoate); n.m.r. (100MHz,$CDCl_3$) δ1.32, 1.37, 1.43 and 1.48(s,3H,2xC(CH_3)$_2$), 2.80(d(overlapped by H-2b),1H,$J_{2a,3}$ 7.0Hz,H-2a), 2.81(d(overlapped by H-2a),1H,$J_{2b,3}$ 5.0Hz,H-2b), 3.74(s,3H,-OCH_3), 4.42-4.49(m,3H,H-7,H-8), 4.73 and 4.84(d(overlapped by H-3), 2H,$J_{5,6}$ 6.0Hz,H-5,H-6), 4.75(dd(partially overlapped by H-5 and H-6), $J_{2a,3}$ 7.0Hz,$J_{2b,3}$ 5.0Hz,H-3), 7.52(m,3H,Ar) 8.10(m,2H,Ar); mass spectrum: m/e 436 (m^+), 421(m^+-CH_3), 405(m^+-OCH_3).

Anal. Calc. for $C_{22}H_{28}O_9$;C,60.54;H,6.47. Found:C,60.30; H,6.57.

Continued elution of the column gave the spiro β-1,4-lactone 211 (34 mg,10%) as a clear syrup: $[\alpha]_D^{22}$ -43.4(c0.7,$CHCl_3$); $\nu_{max}^{CCl_4}$ 3580 (OH), 1812 (lactone), 1730 cm^{-1}(benzoate); n.m.r. (100MHz,$CDCl_3$) δ1.40 and 1.57(s,3H, C(CH_3)$_2$), 2.54(d,1H,J_{gem} 17.5Hz,H-2a), 2.91(d,1H,J_{gem} 17.5Hz,$J_{2b,3}$ 4.7Hz,H-2b), 4.42(d(overlapped by H-8b),1H,$J_{7,8a}$ 7.5Hz,H-8a), 4.43(d(overlapped by H-8a), 1H,$J_{7,8b}$ 6.0Hz,H,8b), 4.52(d,1H,$J_{2a,3}$ 4.5Hz,H-3), 4.67(dd,1H,$J_{7,8a}$ 7.5Hz, $J_{7,8b}$ 6.0Hz,H-7), 4.95 and 5.03(d,1H,$J_{5,6}$ 6.0Hz,H-5,H-6), 7.54(m,3H,Ar), 8.10(m,2H,Ar), 3.32(broad s,1H,OH, exchangeable with D_2O); mass spectrum: m/e 364(m^+), 399(m^+-CH_3), 277(m^+-(CH_3+$CHOHCH_2CO$).

Anal. Calc. for $C_{18}H_{20}O_8$:C,59.33;H,5.53. Found: C,59.29;H,5.69.

Treatment of Ketal 204 with para-Toluenesulfonic Acid Monohydrate to give Compound 210, 211, 2-Benzoyloxymethyl-5-(carbomethoxyacetyl)furan (212), and 8-O-Benzoyl-2-deoxy-5,6-O-isopropylidene-β-D-altro-4-octulofuranosono-1,4-lactone (213)

To a gently azeotroping solution of ketal 204 (220 mg) in benzene (25 ml) was added a suspension of para-toluenesulfonic acid monohydrate (23 mg) in benzene (10 ml) over 15 min while the reaction reaction mixture was maintained at a volume of 20 to 25 ml. The solid residue from the suspension was washed into the reaction flask with methanol (0.5 ml) and sufficient fresh benzene was added to the azeotroping mixture to maintain the above volume. After a further 45 min, the mixture was allowed to cool and was then washed with saturated aqueous sodium hydrogen carbonate (6 ml), water (6 ml) and dried over anhydrous sodium sulfate. Removal of the solids by filtration and evaporation of the benzene under reduced pressure gave a bright yellow syrup which was chromatographed on a column of silica gel (10 g) using a gradient of 4:1 to 1:1 benzene-ethylacetate as developer. A fast-moving component was quickly eluted to give the diisopropylidenated derivative 210 (3 mg, 1.3%) which produced a n.m.r. spectrum identical to the one obtained previously.

Continued elution of the column gave the disubstituted furan derivative 212 (19 mg, 11%) as a clear syrup: λ_{max}^{MeOH} 228 nm (ε26,400), 276 nm (ε27,800); $\nu_{max}^{CHCl_3}$ 1750 ($-CO_2Me$), 1730(benzoate), 1670 cm^{-1} (ketone); n.m.r. (100MHz, $CDCl_3$) δ3.74(s,3H,OCH_3), 3.88(s,2H,H-2), 5.39(s,2H,H-8), 6.67(d,1H,$J_{5,6}$ 3.5Hz,H-6), 7.28(d,1H,$J_{5,6}$ 3.5Hz,H-5), 7.54(m,3H,Ar), 8.09(m,2H,Ar). Irradiation of the doublet at δ6.67 collapsed to doublet at δ7.28 to a singlet; mass spectrum: m/e 302(m^+), 229($m^+-CH_2CO_2CH_3$).

Anal. Calc. for $C_{16}H_{14}O_6$:C,63.57;H,4.75. Found:C,63.39;H,4.75.

Further elution of the column gave the spiro α-1,4-lactone 211 (79 mg, 39%) as a clear syrup: n.m.r. (100MHz,$CDCl_3$) δ1.39 and 1.56(s,3H,$C(CH_3)_2$), 2.52

(d,1H,J_{gem} 17.0Hz,H-2a), 2.91(m,1H,J_{gem} 17.5Hz,$J_{2b,3}$ 5.0Hz,$J_{2b,OH}$ 2.0Hz, H-2b, addition of D_2O collapses m to a doublet of doublets with $J_{2b,3}$ 5.0Hz and J_{gem} 17.5Hz), 3.36(broad pseudo-t,1H,$J_{2b,OH}$ 2.0Hz,$J_{3,OH}$ 1.7Hz,OH, exchangeable with D_2O), 4.42(d(overlapped by H-8b),1H,$J_{7,8a}$ 7.5Hz,H-8a), 4.43 (d(overlapped by H-8a),1H, $J_{7,8b}$ 6.0Hz,H-8b), 4.53(dd,1H,$J_{2b,3}$ 4.7Hz,$J_{3,OH}$ 1.7Hz,H-3, the doublet of doublets collapsed to a doublet of 4.5Hz upon addition of D_2O). The remainder of the spectrum was identical to the spectrum of compound 211 previously produced. Irradiation of the doublet of doublet at δ4.53 collapsed the multiplet at δ2.91 to a doublet of doublets (J_{gem} 17.0Hz and $J_{2b,OH}$ 2.0Hz). The addition of D_2O produced a spectrum which was identical to the one previously obtained from compound 211 in deuterochloroform and D_2O.

Continued elution of the column with 1:1 benzene-ethyl acetate gave the spiro β-1,4-lactone 213 (3.5 mg, 2%) as a clear syrup: $[\alpha]_D^{22}$ -14.3 (c0.35, $CHCl_3$); $\nu_{max}^{CCl_4}$ 3500 (weak,broad,OH), 1805(lactone), 1727 cm^{-1}(benzoate); n.m.r. (100MHz,$CDCl_3$) δ1.38 and 1.65(s,3H,C(CH_3)$_2$), 1.72(broad s(overlapped by CH_3),1H,OH, exchangeable with D_2O), δ2.57(dd,1H,J_{gem} 17.5Hz,$J_{2a,3}$ 6.5Hz, H-2a), 2.83(dd,1H,J_{gem} 17.5Hz,$J_{2b,3}$ 6.5Hz,H-2b), 4.38(broad pseudo-t,1H, $J_{2,3}$~6.5Hz,H-3,addition of D_2O produces a sharp triplet with $J_{2,3}$ 6.5Hz), 4.62(d(overlapped by H-8b),1H,$J_{7,8a}$ 4.0Hz,H-8a), 4.63(d(overlapped by H-8a), 1H,$J_{7,8b}$, 2.0Hz,H-8b), 4.75(d,1H,$J_{5,6}$ 6.0Hz,H-5), 4.86(dd,1H,$J_{5,6}$ 6.0Hz, $J_{6,7}$ 2.0Hz,H-6) approx. 4.82(m(buried under H-5 and H-6),1H,H-7), 8.58(m,3H, Ar), 8.09(m,2H,Ar). Irradiation of the broad pseudo-triplet at δ4.38 collapsed the doublet of doublet at δ2.57 and 2.83 to doublets (J_{gem} ~17.5Hz); mass spectrum: m/e 349(m^+-CH_3), 293(m^++H-$CHOHCH_2CO$), 235(293-acetone).

Treatment of Compound 204 with Trifluoroacetic Acid and Acetic Anhydride to give 3,4,5,6-tetra-O-acetyl-8-O-benzoyl-2-deoxy-α(and β)-D-altro-4-octulofuranosonate (214) and (215), respectively.

A solution of the hydroxy hemiketal 204 (240 mg) in 80% aqueous trifluoroacetic acid was stirred for 20 min after which toluene (6 ml) was added and the resulting mixture was evaporated under reduced pressure to one half the volume. Another aliquot of toluene (2 ml) was added and the mixture evaporated to dryness. The residual syrup was dissolved in a mixture of acetic anhydride (2 ml), acetic acid (1 ml) and para-toluenesulfonic acid monohydrate (200 mg) and stirred a 0° for 3 h. Sodium acetate hydrate (250 mg) was then added to the mixture and stirred for an additional 15 min. The mixture was coevaporated with toluene (2x5 ml) to give a crude syrup which was then dissolved in a 1:1 mixture of chloroform-water (20 ml). The aqueous phase was extracted with chloroform (2x10 ml) and the combined extracts washed with water (5 ml) and dried over anhydrous sodium sulfate overnight.

The drying agent was removed by filtration and the resulting solution evaporated to give a crude brown syrup which was chromatographed on a column of silica gel (40 g) using 4:1 benzene-ethyl acetate as developer to give the β-tetraacetate 215 (23 mg, 7%) as a clear syrup: $[\alpha]_D^{22}$ + 10.7° (c1.4, $CHCl_3$); $\nu_{max}^{CCl_4}$ 1752(acetates), 1730 cm^{-1} (benzoate), n.m.r. (100 MHz,$CDCl_3$) δ1.96, 2.03,2.04 and 2.14 (s,3H,4xCH_3), 2.66(dd,1H,J_{gem} 15.7Hz,$J_{2a,3}$ 8.3Hz, H-2a), 3.06(dd,1H,J_{gem} 15.7Hz,$J_{2b,3}$ 4.5Hz,H-2b), 3.68(s,3H,-OCH_3), 4.36-4.71(m,3H,H-7,H-8), 5.82(pseudo-q(overlapped by H-6),$J_{2a,3}$ 8.3Hz,$J_{2b,3}$ 4.5Hz, H-3), 5.80(pseudo-t(overlapped by H-3),$J_{5,6}$ 6.0Hz,$J_{6,7}$ 6.0Hz,H-6), 6.04(d, 1H,$J_{5,6}$ 6.0Hz,H-5), 7.55(m,3H,Ar), 8.10(m,2H,Ar).

Continued elution with 4:1 benzene-ethyl acetate gave the anomeric α-tetraacetate 214 (80 mg, 25%) as a clear syrup: $[\alpha]_D^{22}$ +21.7 (c0.9,$CHCl_3$);

$\nu_{max}^{CCl_4}$ 1762 (very strong, broad band of the acetates), 1733 cm^{-1} (benzoate); n.m.r. (100 MHz,$CDCl_3$) δ1.83 and 2.02(s,3H,2xCH_3), 2.08(s,6H,2xCH_3), 2.57 (dd,1H,J_{gem} 16.0Hz,$J_{2a,3}$ 8.0Hz,H-2a), 2.85(dd,1H,J_{gem} 16.0Hz,$J_{2b,3}$ 5.0Hz, H-2b), 3.58(s,3H,-OCH_3), 4.45(dd,1H,J_{gem} 12.0Hz,$J_{7,8a}$ 2.7Hz,H-8a), 4.54-4.67 (m,1H,H-7), 4.77(dd,1H,J_{gem} 12.0Hz,$J_{7,8b}$ 2.0Hz,H-8b), 5.33(dd,1H,$J_{5,6}$ 5.5Hz, $J_{6,7}$ 7.3Hz,H-6), 5.49(d,1H,$J_{5,6}$ 5.5Hz,H-5), 6.02(dd,1H,$J_{2a,3}$ 8.0Hz,$J_{2b,3}$ 5.0Hz,H-3), 7.68(m,3H,Ar) 8.09(m,2H,Ar). Irradiation of the doublet of doublets at δ6.02 collapsed the two doublet of doublets at δ2.57 and 2.85 to doublets with J_{gem} 16.0Hz. Irradiation of the multiplet at δ4.61 collapsed the doublet of doublets at δ5.33 to a doublet with $J_{5,6}$ 5.5Hz; mass spectra: m/e 524(m^+), 493(m^+-OCH_3), 465(m^+-O_2CCH_3), 379(m^+-$CH(OAc)CH_2CO_2CH_3$).

8. Attempted Synthesis of a Ketose N-nucleoside

2',3',5'-Tri-O-benzoyl-uridine (217)

Following the method of Vorbrüggen and Bennua[193], a mixture of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (134) (526 mg, 1.04 mmol) and uracil (216)(119 mg, 1.08 mmol) was azeotropically dried with toluene and then a solution of trimethylchlorosilane (0.10 ml), hexamethyldisilazane (0.17 ml), stannic chloride (0.14 ml) in anhydrous acetonitrile (15 ml) was added and the resulting solution stirred at room temperature for 2 h. The reaction mixture was then poured into a stirred mixture of ice-cooled dichloromethane (75 ml) and saturated aqueous sodium hydrogen carbonate (30 ml) and stirred for 10 min. The organic phase was separated and the emulsified residue was extracted with dichloromethane (20 ml). The organic extracts were combined and dried over anhydrous sodium sulfate prior to evaporation to give a clear syrup (557 mg). Column chromatography of the product on silica gel (40 g) using 2:1 benzene-ethylacetate as developer yielded the benzoylated uridine

derivative 217 (398 mg, 69%, lit[193] 83%) as a partially crystalline syrup which was recrystallized from chloroform-hexanes; m.p. 146.5-149° (lit[193] 146-148°).

Two smaller scale reaction with 40 mg of compound 134 gave comparable yields.

Attempted Synthesis of Methyl[1-(3,5,6-tri-O-acetyl-8-O-benzoyl-2-deoxy-α(and/or β)-D-altro-4-octulofuranosyl)uracil]onate from Compound 214.

(a) To an azeotropically dried mixture of the acetylated ketose 214 (40 mg) and uracil (9 mg) was added 1.1 ml of the same silating mixtured used in the synthesis of compound 217 (see previous page). The mixture was stirred at room temperature for 3 days after which time the mixture was poured into an ice-cooled mixture of dichloromethane (4 ml) and saturated aqueous sodium hydrogen carbonate (2 ml). The mixture was vigorously stirred for 10 min and the organic phase withdrawn and dried over sodium sulfate. Removal of the drying agent by filtration and evaporation of the solvents under reduced pressure gave a crude syrup (20 mg) which was chromatographed on a preparative t.l.c. plate (15x20 cm, 1.0 mm) to give six components none of which from their n.m.r. spectra in DMSO-d_6 exhibited any low-field hydrogens (eg NH) nor a doublet at ∿δ5.5-6.0 for H-5 of the uracil moiety.

(b) A mixture of the acetylated ketose 214 (60.5 mg) and uracil (13.8 mg) was azeotroped with benzene (2 ml). To the residue was added a solution of trifluorosulfonic acid (12 μℓ), trimethylchlorosilane (18 μℓ), hexamethyldisilazane (27 μℓ) and acetonitrile (1.6 ml). This mixture was protected with a phosphorus pentoxide drying tube and refluxed for 22 h after which time the cool solution was poured into a vigorously stirred ice-cooled mixture of dichloromethane (3 ml) and saturated aqueous sodium hydrogen carbonate (2 ml). The aqueous phase was extracted with dichloromethane and the combined organic extracts

dried over anhydrous sodium sulfate. T.l.c. of the extract indicated the presence of at least six components, none of which predominated nor exhibited strong U.V. activity; therefore, the mixture was not analyzed further.

Application of the Fusion Reaction [191b] to Compound 214

(a) A mixture of compound (214) (100 mg, 0.2 mmol) and2,6-dichloropurine (218) (62 mg, 0.3 mmol) was azeotropically dried with toluene (5 ml) and the residual mixture fused at 150-155° (bath temperature) to a clear melt which was stirred for 30 min at 15 torr. The darkened melt was then allowed to cool and t.l.c. analysis of the mixture indicated only one charring band that absorbed u.v. light and had the same R_f as the starting compound.

(b) Para-toluenesulfonic acid monohydrate (12 mg) was added to the above mixture and this new mixture was azeotropically dried with toluene (3 ml). The residue was fused at 150-155° to a clear, light brown melt which was stirred for 30 minutes at 15 torr. T.l.c. of the cooled melt gave the same results of part (a).

Bis(trimethylsilyl)thymine (219)

A suspension of powdered thymine (5.16 g, predried at 100°/0.10 torr for 1 h) in distilled hexamethyldisilazane (32 ml) and trimethylchlorosilane (10 drops) was refluxed for 12 h after which time very little change was observed in the suspension. The suspension was then allowed to cool and solid ammonium sulfate (140 mg) was added to the mixture which was again refluxed. After 10 h all of the thymine had gone into solution and the excess hexamethyldisilazane was then removed under vacuo. The residual amber syrup was dissolved in anhydrous 1,2-dichloroethane (67 ml, ∿0.5M solution) and

used in subsequent reactions without further purification.

Synthesis of Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-3-bromo-2,3-dideoxy-5,6-O-isopropylidene-D-ribo-oct-3-enonate (220) from 172

To a solution of the methyl oct-3-enonate 172 (174 mg, 0.5 mmol) in anhydrous 1,2-dichloroethane (2 ml) was added bromine (∿0.5 ml of a 1.0M solution of bromine in 1,2-dichloroethane). The solution was stirred for 10 min at room temperature after which time bis(trimethylsilyl)thymine (219)(1.0 ml of a ∿0.5M solution of 219 in 1,2-dichloroethane) was added followed by tin tetrachloride (0.06 ml, 1.0 equiv in 1.0 ml 1,2-dichloroethane). The mixture was stirred at room temperature for 16 h after which time t.l.c. analysis of the reaction mixture indicated complete consumption of the starting compound and the presence of one faster-moving component (R_f 0.443, starting compound 0.385 using 4:1 benzene-ethylacetate as developer) which had the same weak U.V. activity as the starting compound. The mixture was diluted with chloroform (5 ml) and washed with saturated aqueous sodium hydrogen carbonate (2x3 ml) and water (3 ml) and dried over anhydrous sodium sulfate. Filtration and evaporation of the organic phase gave a crude dark syrup which was chromatographed on a column of silica gel (10 g) using 4:1 benzene-ethylacetate as developer to give Methyl(E,Z)-4,7-anhydro-8-O-benzoyl-3-bromo-2,3-dideoxy-5,6-isopropylidene-D-ribo-oct-3-enonate (220) (72 mg, 34%) as a clear syrup which from its n.m.r. spectrum was a 2:1 ratio of the geometric isomers: $\nu_{max}^{CCl_4}$ 1750($-CO_2CH_3$), 1732(benzoate), 1692 cm^{-1}(C=C); n.m.r. (100MHz, DMSO-d_6, major(M) and minor(m) isomers) δ1.34 and 1.40(s,3H,C(CH_3)$_2$), 3.46-M, 3.50-m(s,2H,H-2), 3.58-m, 3.62-M(s,3H,OCH_3), 4.46(d,2H,$J_{7,8}$ ∿3.2Hz,H-8), 4.89 (t,1H,$J_{7,8}$ 3.4Hz,H-7), 5.03(d,1H,$J_{5,6}$ 6.0Hz,H-6), 5.31-m,5.47-M(d,1H,$J_{5,6}$ 6.0Hz,H-5), 7.64(m,3H,Ar), 7.98(m,2H,Ar). Addition of D_2O does not affect the above resonances; mass spectrum; m/e 440/442(m^+), 425/427(m^+-CH_3), 408/410

(m^+-CH_3OH), 261/263(m^++H-BzOH-Acetone).

Storage of compound 220 at room temperature as a syrup or in solution (chloroform) resulted in a slow auto-catalytic decomposition giving a black charred solid or solution. Heating compound 220 under vacuo at 65° for several hours also produced a black char.

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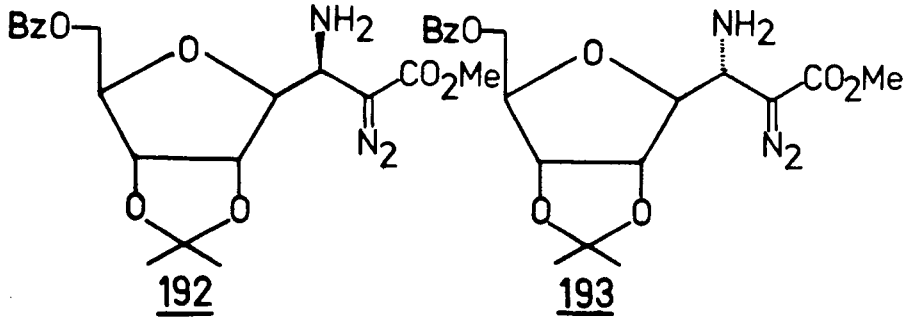
ADDENDUM

1) Re: Stereochemical Assignment of Compounds 192 and 193.



192 193

Additional supportive evidence for the stereochemical assignment made for C-3 of the diazo-amino compounds above (see page 114), comes from an application of Cram's Rule* to the nucleophilic addition of the azide anion to the unsaturated ester 18 (see page 7 and 113). The preponderant epimer predicted is the 3-S-epimer. The major diazo-amino compound isolated was compound 192 which was previosly assigned the 3-S- or D-glycero-D-allo-configuration. Significantly, the major amino epimer determined for the amino mixture, isolated from the hydrogenation of azide 189 (see pages 111-12), was the amino compound 190 (i.e.,the hydrogenolysis product of 192).

Therefore, the predominant epimers (the 3-S-epimer of 189 and compd. 192) predicted by Cram's Rule were shown to be stereochemically identical and were also the same stereochemistry as previously assigned.

2) Re: Sterochemical Assignment of the Anomer Centre of the Ketofuranoses.

The stereochemical assignments of the anomeric centres of the isopropylidenated ketofuranoses (see Results and Discussion, section 3.) were partially made on the basis of the work of Moffatt and coworkers[167] on

*see reference 8, page 263 and reference (64) cited therein.

isopropylidenated C-glycosides. An extention of the C-13 n.m.r. work by Cousineau and Secrist* has shown that a cis-orientation of the alkyl side-chain (at C-4) and the 5,6-O- isopropylidene group (i.e., the β-octulofuranoses) results in a higher-field resonance for the isopropylidene methyls and quaternary carbon. The chemical shift values given for the quaternary carbon are 114.5±0.6 ppm and 112.7±0.6 ppm for the trans- and cis-orientated compounds, respectively. These values are in close agreement with the values found for the C-13 n.m.r. values found for the compounds listed in Table III.

Table III. C-13 N.M.R. Chemical Shifts** of the 5,6-O-Isopropylidene Quaternary Carbon and High-field Methyl of Various Ketofuranosides.

Compd.	anomer assignment	Chemical Shift	
		Quaternary Carbon	High-field Methyl
187	β	112.00	-
203	α	114.42	25.39
	β	111.89	24.86
204	α	113.94	25.50
	β	112.03	25.21
209a	α	114.62	-
209b	β	112.20	-
(172	-	113.23	-)

**Parts Per Million (ppm) from TMS.

As the table clearly shows, the quaternary carbons of the β-anomers (thus, a cis-orientation of the C-4 alkyl side-chain and the isopropylidene group) resonate at ∿112 ppm while the α-anomers resonate at ∿114 ppm. Interestingly, compound 172 in which the alkyl chain is neither 'α' nor 'β' has its quaternary carbon signal at 113.23 ppm, intermediate in chemical shift.

*T.J.Cousineau and J.A.Secrist III, J. Org. Chem., 44, 4351, 1979.