

## SUGAR ENOLONES: SYNTHESIS, REACTIONS OF PREPARATIVE INTEREST, AND $\gamma$ -PYRONE FORMATION

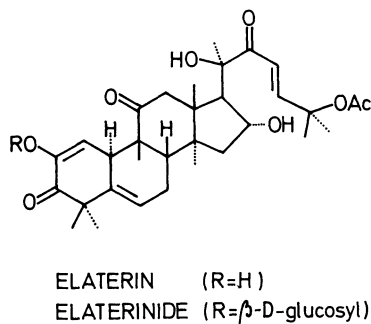
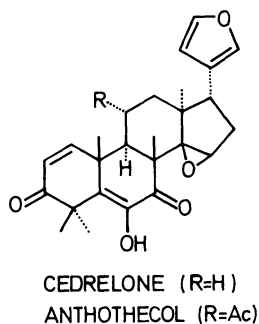
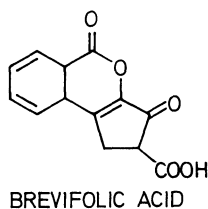
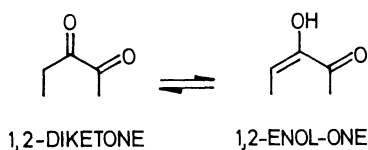
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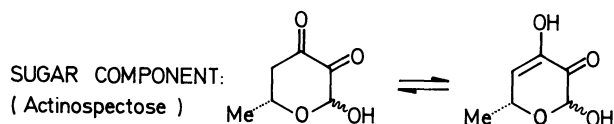
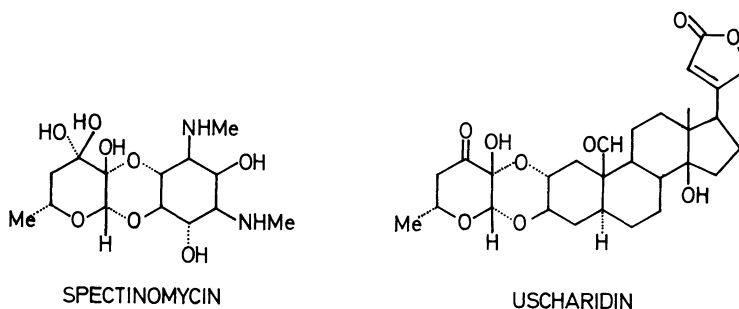
*Abstract* — An account on pyranoid sugar enolones is given with respect to their preparation, their use as educts for the synthesis of a variety of 2-deoxy and 4-deoxy sugars functionalised *via* the enol or carbonyl function, and their conversion into  $\gamma$ -pyrones, allowing an evaluation of the biosynthetic pathways for kojic acid and maltol from carbohydrate precursors.

### INTRODUCTION

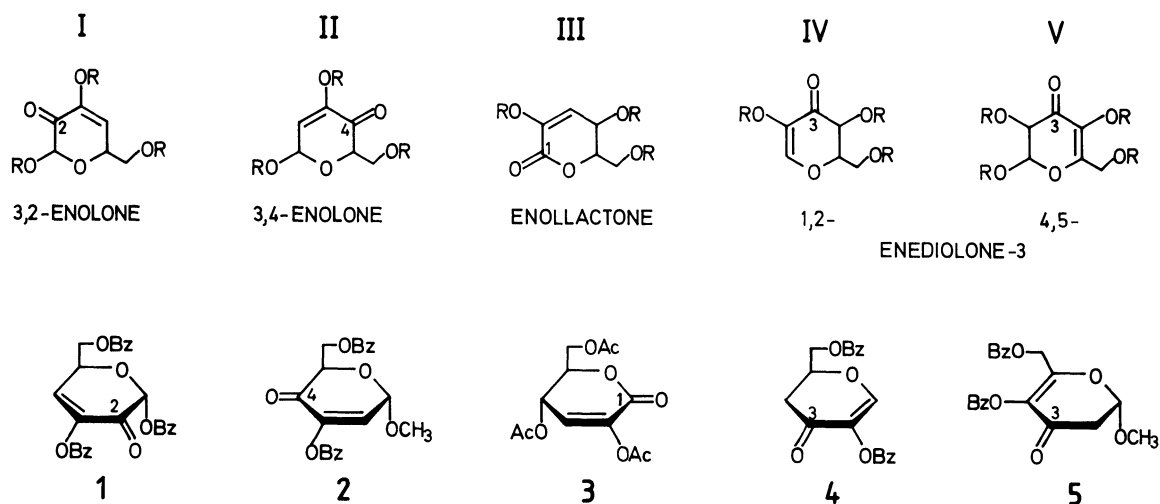
The mono-enol form of a 1,2-diketone, having a carbonyl function situated next to the enol group may be referred to as a 1,2-enolone. This structural unit is often present in natural products, such as, for example, brevifolic acid, a constituent of the ellagitannins (Ref. 1), meliacins like cedrelone and anthothecol (Ref. 2), or triterpenoids of the elaterin type, which are widely distributed in cucurbitaceous and cruciferous plants (Ref. 3).



Sugars containing a 1,2-enolone moiety have not yet been discovered in Nature despite the fact that the fused ring aminocyclitol antibiotic spectinomycin (Ref. 4) as well as uscharidin from the African arrow poison of calotropis (Ref. 5) contain a 2,3-diketosugar in the form of a dioxane type 1-acetal-2-hemiketal. As a free sugar, this 4,6-dideoxy-D-glycero-hexo-2,3-diulose (actinospectose) could be expected to exist in the enolone form, yet, due to its apparent instability towards hydrolytic or pyrolytic conditions, it has eluded isolation and characterisation.



There are only two ways in which the structural features of a 1,2-enolone may be incorporated into a pyranoid ring: (a) in the form of a 4-deoxyhexeno-2-ulose (I), which has the enol function at C-3 and the carbonyl group at C-2, and, hence, may be termed a hexose-3,2-enolone (e.g. actinospectose and 1); (b) as a 2-deoxyhexeno-4-ulose (II), which may be referred to as a hexose-3,4-enolone (e.g. 2). Sugar enolones of types I and II, their preparation, synthetically useful reactions, and conversion into  $\gamma$ -pyrones form the subject of this presentation. Other pyranoid structures that might also be considered as having an enol group next to a carbonyl function, e.g. compounds of types III - V, as enol lactones (e.g. 3) or enediolones (4, 5) may be differentiated from sugar enolones formally as well as chemically, and are only partially considered.

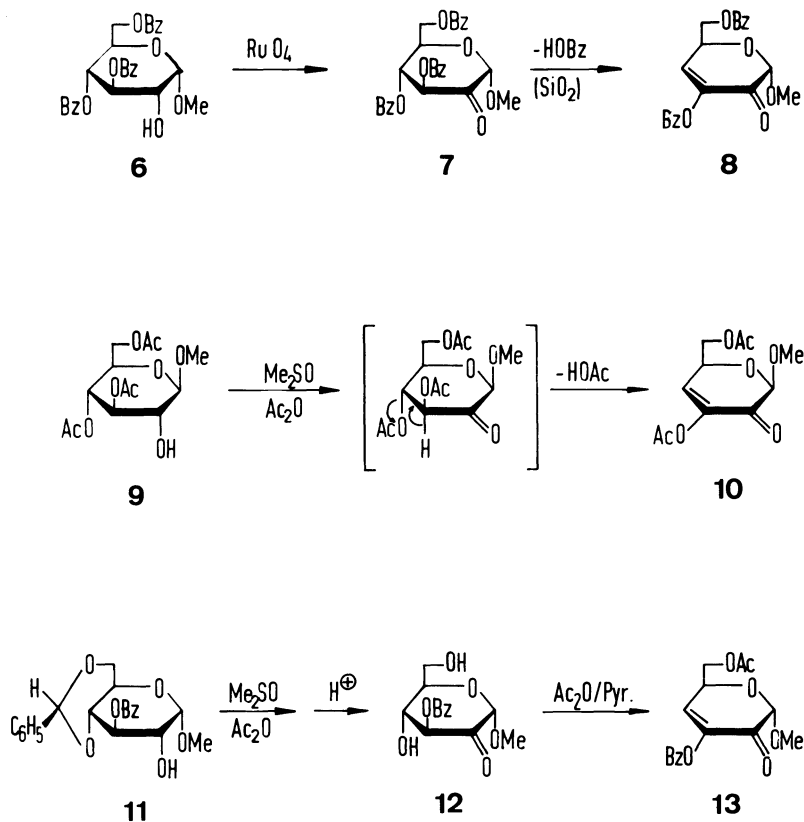


Sugar enolones have long been postulated as possible intermediates in the formation of  $\gamma$ -pyrones from hexose derivatives. Isbell in 1944 (Ref. 6) formulated a hexose-3,2-enolone to mechanistically rationalise the conversion of Maurer's "tetra-acetyl glucosone hydrate" into diacetylkojic acid (Refs. 7, 8), and Lemieux and Wolfrom (Ref. 9) postulated a 3,4-enolone intermediate of type II to account for the ready formation of maltol from the streptose portion of streptomycin on treatment with alkali. However, it is only within the last decade that sugar enolones of types I and II, usually

as acyl derivatives, have been prepared and unambiguously characterised (Refs. 10-24), thereby allowing a systematic evaluation of their synthetic potential in carbohydrate chemistry as well as an assessment of  $\gamma$ -pyrone formation therefrom with respect to the biosynthesis of kojic acid and maltol from carbohydrate precursors.

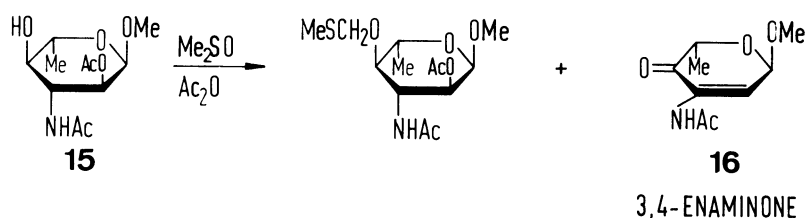
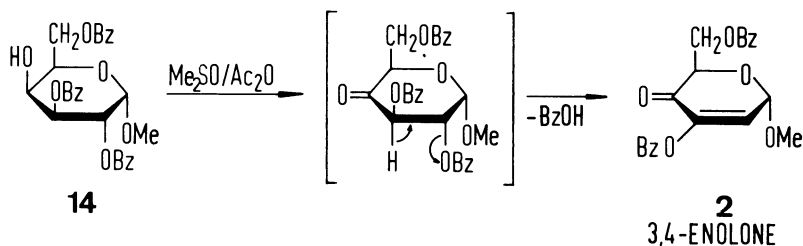
#### SYNTHESIS OF SUGAR ENOLONES

The propensity of acylated hexopyranosiduloses for  $\beta$ -elimination of acyloxy groups is exceptionally facile, as first observed in attempts to purify the uloside (7) obtained by ruthenium tetroxide oxidation of the glucoside (6). Chromatography on silica gel, sufficed to eliminate benzoic acid from the 3,4-position to give the enolone (8) (Ref. 10). Such an elimination reaction may similarly be elicited under the conditions of methyl sulfoxide-acetic anhydride oxidation [the intermediate uloside formed from (9) is not isolable due to its conversion into enolone (11) (Ref. 11)] or on acetylation, as exemplified by glycosidulose (12), which was stable towards the acidic conditions required for de-*O*-benzylidenation, yet readily lost acetic acid on treatment with pyridine-acetic anhydride to give enolone (13) (Ref. 21).



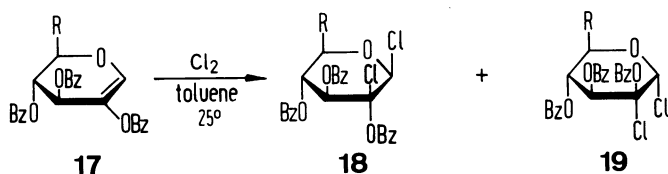
The preparation of hexose-3,4-enolones can similarly be effected. When methyl 2,3,6-tri-*O*-benzoyl- $\alpha$ -D-galactoside (14) was treated with methyl sulfoxide-acetic anhydride the 4-uloside formed is detectable in the reaction mixture by h.m.r. spectroscopy, yet its isolation therefrom in pure form met with difficulties due to its tendency to lose of benzoic acid. After 48 h at room temperature the highly crystalline enolone (2) was isolable (>60 %) (Ref. 23). Since the adduct (14) is available from methyl  $\alpha$ -D-galactoside *via* benzoylation (Ref. 25), (2) is a most readily accessible 3,4-enolone.

For the partially acetylated 3-aminosugar derivative (15) a similar oxidation-elimination sequence may be anticipated, and was experimentally verified, affording in addition to an undesired byproduct, the 4-methylthiomethyl ether, the 3-acetamidoenone (16) which is logically termed a 3,4-enaminone (Ref. 23).



Another approach which has proved to be exceptionally facile and effective for the preparation of 3,2-enolones, involves halogenation of 2-hydroxyglycol esters and subsequent hydrolysis, and can be applied with equal ease to hexose, 6-deoxy-hexose or pentose derivatives. Chlorination or bromination of the benzoyleated hydroxyglycol (17, R = H, Me, CH<sub>2</sub>OBz) in a non-polar solvent proceeds with almost exclusive formation of *cis*-adducts (Refs. 21, 22, 26-28), a course that is easily understood on the basis 1,2-benzoxonium ion intermediates. However, the factors governing the ratios of *cis*-adducts, i.e. a 3:1 preponderance of halogen attack from above the plane of the pyranose ring in the hexose case and an opposite ratio for 6-deoxyhexose derivatives, is less easily rationalised, yet must be due to different conformational arrangements in the 2-hydroxyglycol esters. As in the case of 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hexenitol (31) (Ref. 29), the interconversion equilibrium between the two half-chair conformations (<sup>4</sup>H<sub>5</sub> ⇌ <sup>5</sup>H<sub>4</sub>) in the tetra-benzoyl-hexenitol (17, R = CH<sub>2</sub>OBz) lies on the <sup>5</sup>H<sub>4</sub> side on the basis of n.m.r. data (J<sub>3,4</sub> = 3.9 and J<sub>4,5</sub> = 4.7 Hz in benzene) and in this preferred conformation the axial 4-OBz may exert a significant steric hindrance towards initial chlorine attack at C-2 from the β-side. This restriction is lightened in the 6-deoxyhexose derived glycol (17, R = Me) in which the conformational equilibrium appears to be shifted towards the <sup>4</sup>H<sub>5</sub> form (J<sub>3,4</sub> = 4.5 and J<sub>4,5</sub> = 6.0 Hz), thus preferentially leading to C-2-addition of the chloronium ion from the less hindered α-side. Nonetheless, it is obvious, that further investigations are needed to more concretely explain these steric preferences, in particular with respect to the observation that the product distribution varies somewhat with the polarity of the solvent used for halogenation.

#### CHLORINE ADDITION TO 2-HYDROXYGLYCOL ESTERS



β-D-gluco  
6-deoxy-β-D-gluco  
β-D-xylo

α-D-manno  
α-D-rhamno  
α-D-lyxo

approx. ratio  
R = CH<sub>2</sub>OBz 3:1  
R = Me 1:3  
R = H 2:3

In this context, it may be mentioned that configurational assignments to these dihalides presented a problem. Whereas the configuration at the anomeric carbon could be delineated from the chemical shift of the singlet for H-1, and also from titanium tetrahalide-induced anomerisations (Ref. 22, 26, 27), information on the chirality at the tertiary carbon could be provided only indirectly, i.e. by comparison of their  $^1\text{H}$ - and  $^{13}\text{C}$ -n.m.r. data with those of related compounds of known configuration (Ref. 26), and by an evaluation of their chiroptical properties on the basis of the exciton chirality method the application of which was unambiguous only when the benzoyl chromophores added up to high overall chiralities (Ref. 22). Proof of the configuration at C-2 was furnished by an X-ray crystallographic structure determination of the  $\alpha$ -D-*manno* dichloride (19, R =  $\text{CH}_2\text{OBz}$ ; Ref. 22) and the  $\beta$ -D-*xylo* dichloride (18, R = H; Ref 30). As clearly revealed by Fig. 1, the two chlorine substituents are *cis*, Cl-1 being axial as are BzO-2,3,4.

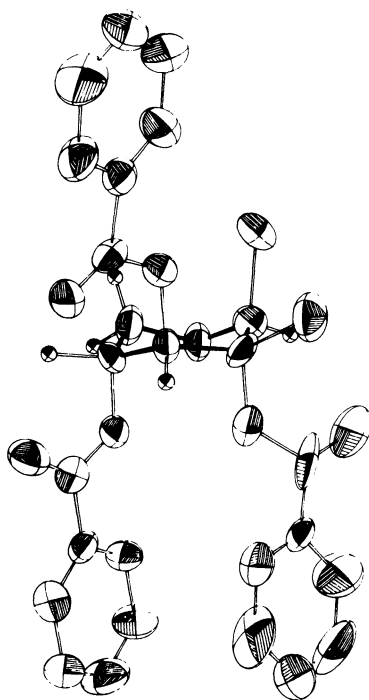


Fig. 1. An ORTEP drawing of 2,3,4-tri-*O*-benzoyl-2-chloro- $\beta$ -D-xylopyranosyl chloride (20) showing thermal ellipsoids (Ref. 30). Hydrogen atoms of the benzene rings have been omitted.

It is remarkable that the  $^1\text{C}_4$  conformation is approximated here more closely than in any other xylose derivative for which a "tetra-axial conformation" has been promulgated (Refs. 31, 32). This situation is clearly born out by the bond distances between axial substituents, in particular that between O-2 and O-4 (Fig. 2), which at 2.67 Å is distinctly shorter than those observed for tri-*O*-benzoyl- $\beta$ -D-xylosyl bromide (21, 2.81 Å) and  $\beta$ -D-xylose tetrabenzoate (22, 2.88 Å). Also, the dihedral angles Cl-1/BzO-2 in (20) and Br-1/BzO-2 in (21) are significantly different deviating from an antiparallel arrangement by only 9.5° (20) compared to 41.8° in (21). For (22) — angular data have not been advanced so far (Ref. 32) — a similarly large aberration from a truly all-axial disposition of benzoyloxy groups is to be deduced.

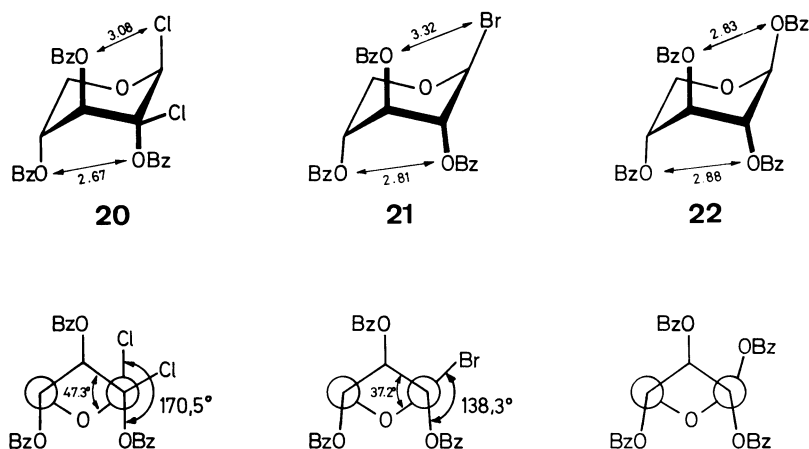
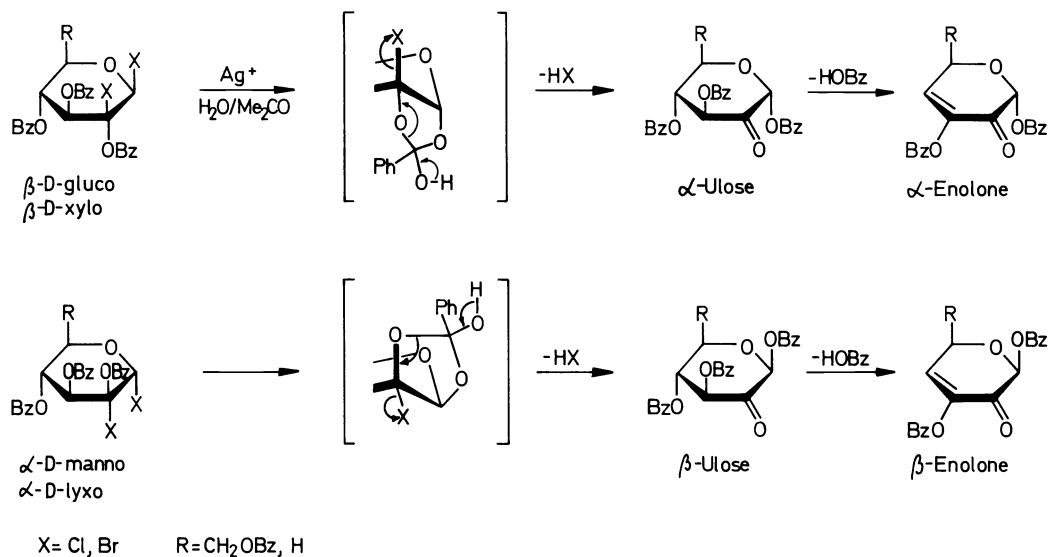


Fig. 2. Conformations and Newman projections of 2,3,4-tri-*O*-benzoyl-2-chloro-β-D-xylopyranosyl chloride (20, Ref. 30), 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl bromide (21, Ref. 31), and tetra-*O*-benzoyl-β-D-xylopyranoside (22, Ref. 32).

These 1,2-dihalo sugars exhibit distinct reactivity differences towards hydrolysis (Refs. 22, 27). The β-D-*gluco*-dibromide, which is the most reactive of the *cis*-adducts, is hydrolysed on treatment with silver carbonate in aqueous acetone at room temperature, to give exclusively the corresponding α-hexosulose, a reaction undoubtedly proceeding *via* initial removal of the anomeric substituent, formation of an orthoester type intermediate, and subsequent extrusion of HX. The β-D-*gluco* dichloride is unaffected under these conditions, and requires prolonged heating for conversion into the α-*ulose*. Hydrolysis of the α-D-*manno* dihalides to give the corresponding β-hexosulose *via* an analogous mechanism is still less readily elicited, the dibromide responding only to prolonged treatment with silver carbonate in aqueous acetone, whereas the dichloride required heating with silver perchlorate.

#### HYDROLYSIS OF BENZOYLATED 1,2-DIHALOHEXOSES

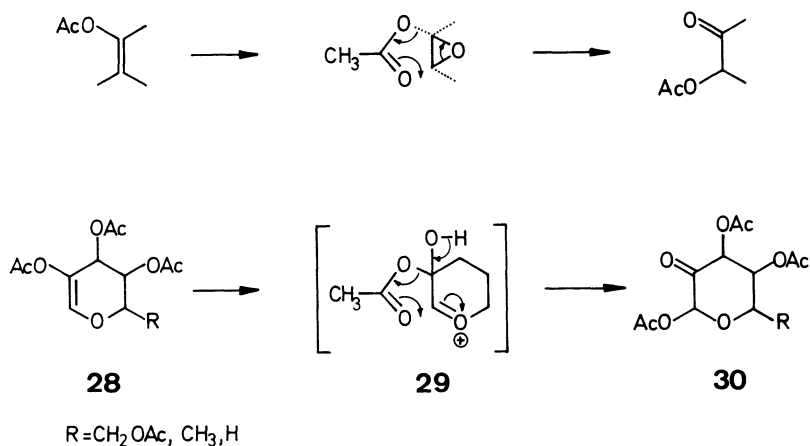




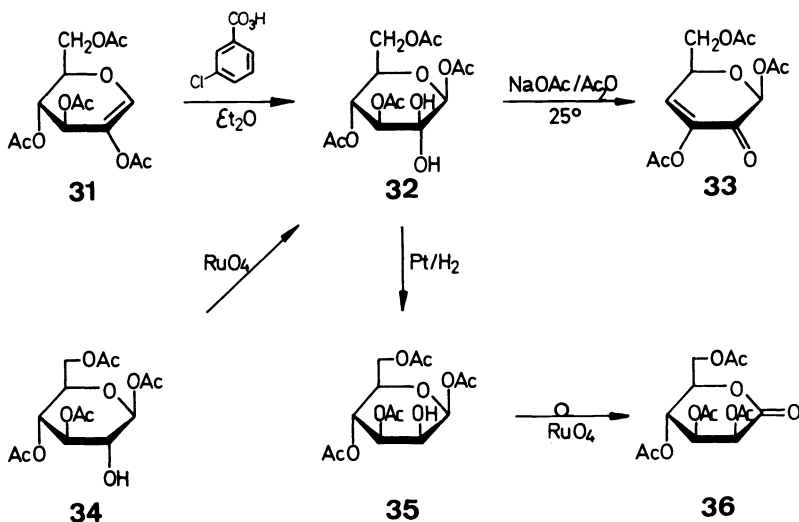
tribenzoate 1 are so close as to be within experimental error. He assigned a 1,2-epoxide structure to the product resulting from chlorination and hydrolysis, quite understandable when considering the techniques available then.

This hypothetical 1,2-anhydro compound is intriguing since, to our knowledge, a compound of this type has not been prepared. At first thought it might be expected to arise from epoxidation of a hydroxyglycal ester. However, when taking into account the instability of  $\alpha$ -acyloxyepoxides as formed on peroxidation of aliphatic enolesters and their tendency to rearrange into the respective  $\alpha$ -acyloxy-ketones (Ref. 35), it becomes obvious that peracyl hexosuloses (30) are to be expected as peroxidation products of glycal esters. In fact,  $\alpha$ -acyloxyepoxides may not even be intermediates, since an intermediate of type 29 is likely to be formed with subsequent direct elaboration of the carbonyl function (29  $\rightarrow$  30).

#### PEROXIDATION OF ENOLESTERS



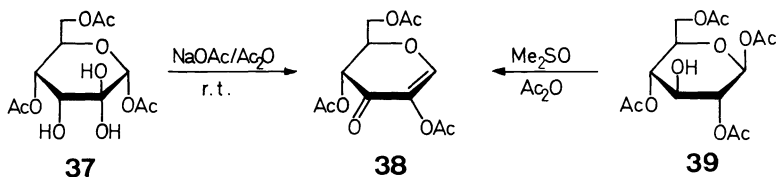
This reaction constitutes an easy approach to acylated hexosuloses, as illustrated, for example, with tetra-*O*-acetyl-2-hydroxyglucal (31) (Ref. 36). When (31) was oxidised with *m*-chloroperbenzoic acid in ether, only one product was formed, namely, 1,3,4,6-tetra-*O*-acetyl- $\beta$ -D-*arabino*-hexosulose, which separated from the reaction mixture as the monohydrate (32). Structural and configurational proof, in revision of previous structural assignments (Ref. 37), was provided by spectral data (C-1 at  $\delta$  92.6 p.p.m. with  $J_{H-1, C-1}$  165 Hz) and by chemical evidence, i.e. by its independent formation on ruthenium tetroxide oxidation of tetra-*O*-acetyl- $\beta$ -D-glucose (34), as well as





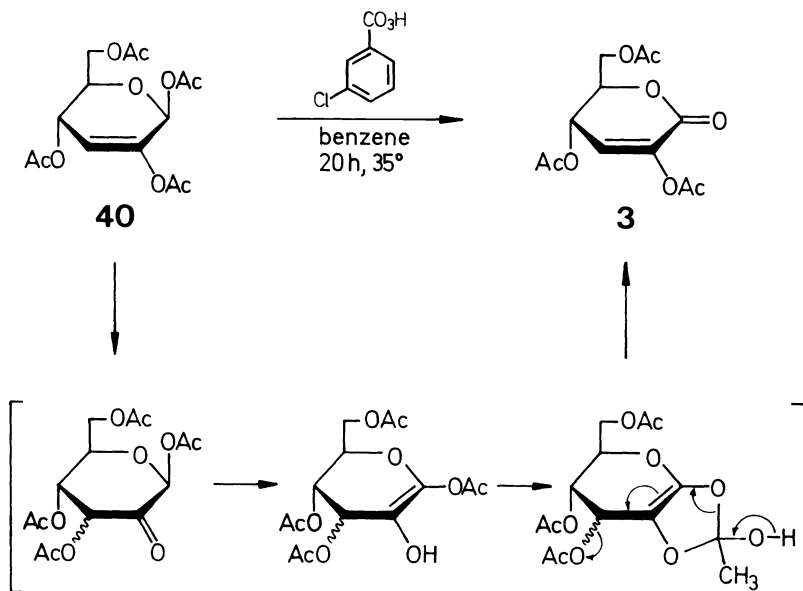
by its preferential hydrogenation to the known (Ref. 38) 1,3,4,6-tetra-*O*-acetyl- $\beta$ -D-mannose (35). It is notable that (35), unlike (34), is not oxidised to the 2-ulose (32) with  $\text{RuO}_4$ , but forms the D-mannono-1,5-lactone (36) instead. Obviously, oxidation is preceded by an *O*-1  $\rightarrow$  *O*-2 acetyl migration, favored by the *cis*-relationship of substituents.

For conversion of ulose (32) into the respective 3,2-enolone very mild conditions, e.g. treatment with sodium acetate-acetic anhydride at room temperature for 2 h, have to be applied, (33) then being formed exclusively (Ref. 36). On longer exposure to these conditions, however, (33) is gradually converted into kojic acid diacetate (cf. below). This ready and exclusive conversion (32)  $\rightarrow$  (33) is contrasted by the behaviour of a close analog of (32), i.e. 1,4,6-tri-*O*-acetyl- $\alpha$ -D-ribo-hexosulose monohydrate (37) towards sodium acetate-acetic anhydride. After 2 h at room temperature the major product obtained was the enediolone (38) (Ref. 39), which appears to be more readily accessible *via* methyl sulfoxide-acetic anhydride oxidation of 1,2,4,6-tetra-*O*-acetyl-D-glucose (39), here, too, elaboration of the carbonyl function at C-3 being followed by 2,1-elimination of acetic acid (Ref. 40). The steric and mechanistic reasons underlying the behaviour of these uloses with respect to their different patterns for  $\beta$ -elimination, i.e. (32)  $\rightarrow$  (33) *versa* (37)  $\rightarrow$  (38), are presently being studied.



A set of reactions analogous to that of (31) - (36) can be carried out with tri-*O*-acetyl-D-xylal (31, H instead of  $\text{CH}_2\text{OAc}$ ), except that the respective  $\alpha$ -pentosulose monohydrate is formed preferentially (Ref. 36). This result indicates that, in the pentose series, attack of the peracid from the  $\beta$ -side is favored in contrast to predominant attack from the  $\alpha$ -side for (31). Thus, steric preferences of hydroxyglycol esters for halogen and for peracid addition are identical, qualitatively at least.

In applying enolester peroxidation to acylated 3-deoxyhex-2-enoses, e.g. (40), one is inclined to expect also hexos-2-uloses *via* acyloxy-epoxide  $\rightarrow$  acyloxyketone rearrangement. However, due to the somewhat more vigorous

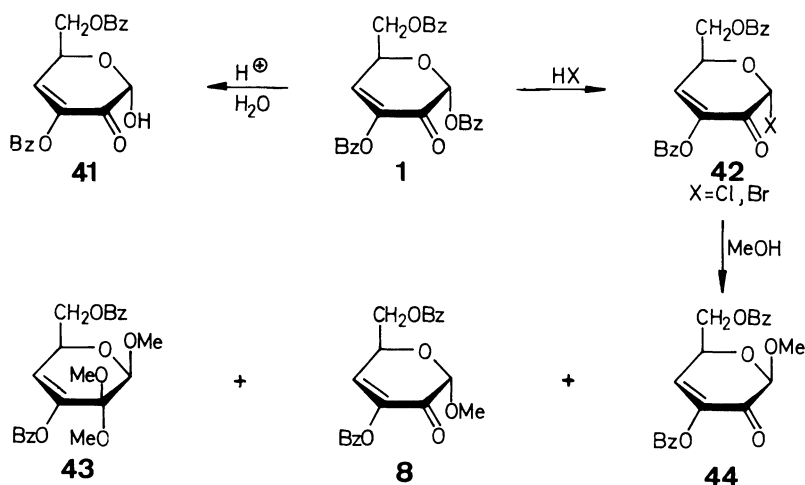


conditions required as compared with those for (31), the intermediate tetra-*O*-acetyl-hexosulose is converted, not unexpectedly in view of a recent, analogous observation (Ref. 41), into the unsaturated lactone (3) *via* enolization, *O*-1 → *O*-2 acetyl migration, and elimination, as illustrated (Ref. 40).

#### REACTIONS OF ENOLONES

The structural features inherent in pyranoid enolones promise high synthetic potential for the preparation of 2-deoxy and 4-deoxy sugars functionalised *via* their carbonyl groups at C-4 and C-2, respectively. Thus, they provide a ready access not only to deoxypyranosuloses, but also to a variety of deoxy, amino, and branched chain sugars.

It is noteworthy that 3,2-enolones are remarkably insensitive towards acid, thus allowing a series of reactions in which the enolone system is retained. Treatment of the enolone (1) with trifluoroacetic acid at 60° affords the 1-hydroxy analog (41), whereas hydrogen chloride-acetyl chloride or hydrogen bromide-acetic acid replace the anomeric substituent by halogen. The corresponding halides (42), which are readily isolable in crystalline form, are versatile intermediates for the synthesis of glycosides *via* alcoholysis, the outcome of which depends on the conditions used. Thus, the β-enolone (44) with only traces of the α-anomer (8) are formed on methanolysis at room temperature, whereas substantial amounts of 8, and the 2,2-dimethyl ketal (43) accumulate on treatment with boiling methanol in the absence of an acid acceptor (Ref. 21).



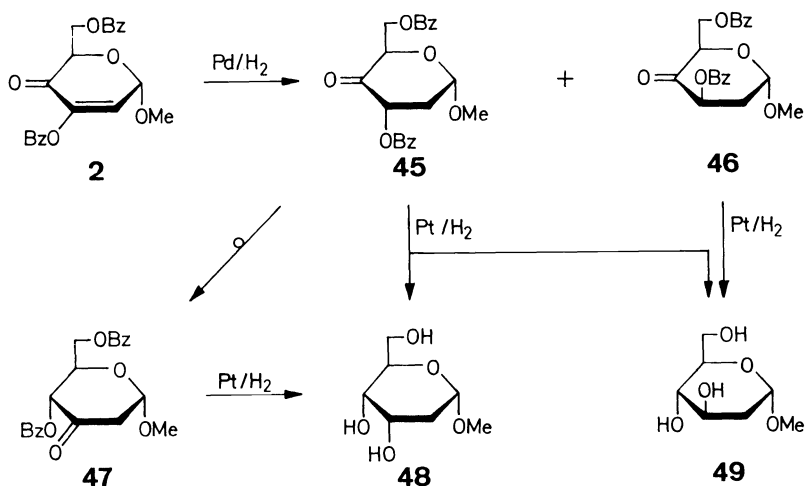
In contrast, 3,4-enolones are considerably more sensitive towards acid. Although stable towards acetic acid, the enolone (2) undergoes profound changes on dissolution in trifluoroacetic acid, the optical rotation being lost within minutes owing to acid catalysed 4,5-enolisation and subsequent elaboration of the  $\gamma$ -pyrone system by expulsion of the anomeric substituent (see below).

However, hydrogenation and hydride reduction may be performed readily. Utilising palladium on charcoal, the olefinic double bond in (2) can be saturated without affecting the carbonyl group, resulting in a 3:1 mixture of the 2-deoxyhexosid-4-uloses with *erythro* (45) and *threo* configurations (46). On hydrogenation, using platinum as the catalyst for saturation of the C=O group, and subsequent de-*O*-benzoylation, a 2:1 mixture of the 2-deoxy-*ribo*-(48) and 2-deoxy-*arabino*-hexosides (49) was obtained, which was readily fractionated, thus affording an alternate, facile access to these compounds *via* 3,4-enolones (Ref. 42).

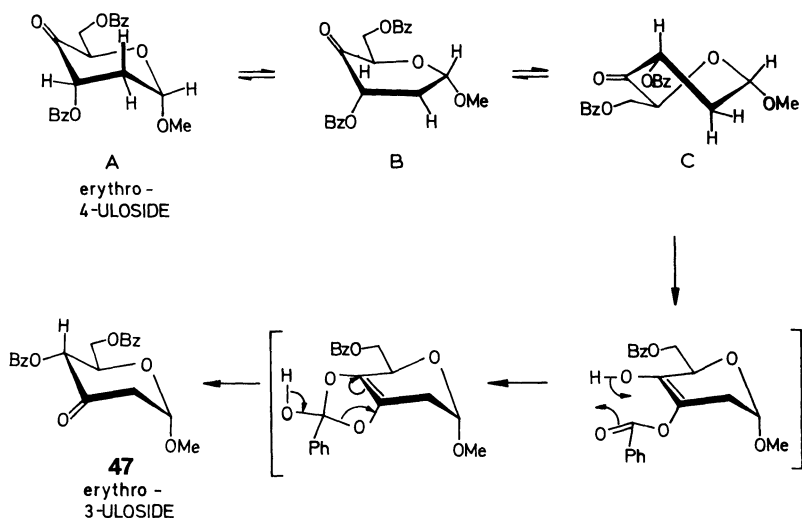
The characterisation of ulosides of the type (45) and (46) was impeded for several reasons. Neither compound could be crystallised from the mixture and column chromatography on silica gel afforded syrupy *erythro*-4-uloside, the *threo*-isomer and another, highly crystalline product, that turned out to be

the *erythro*-3-uloside (47), obviously formed exclusively from (45), since the 3-epimer (46) is stable in contact with silica gel (Ref. 42).

## 3,4 - ENOLONE: HYDROGENATION

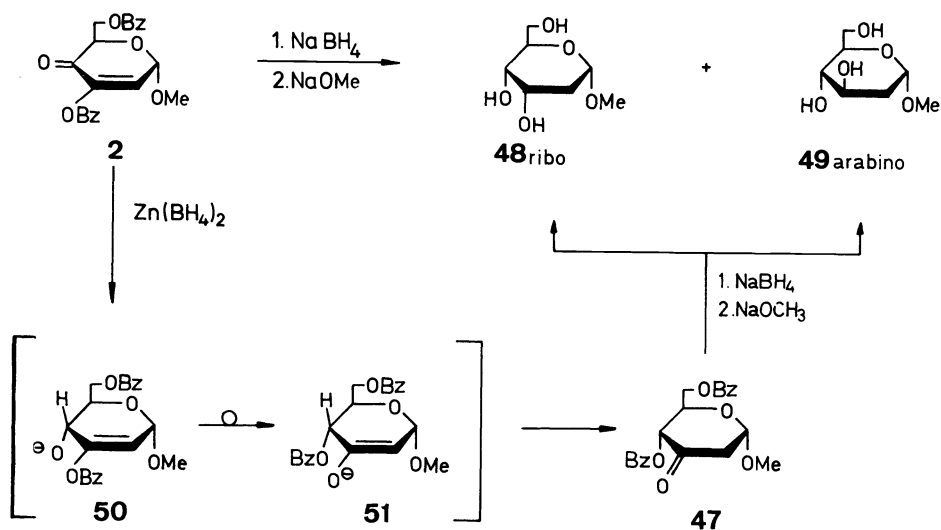


The conversion (45) $\rightarrow$ (47), which can also be effected thermally, may be rationalised on the basis of a 3,4-enolisation followed by an *O*-3 $\rightarrow$ *O*-4-benzoyl migration *via* an enediol-orthoacid intermediate and subsequent reketonisation, as illustrated. The skew conformation C adopted by (45) on the basis of n.m.r. data, the utilisation of the quasi-axial proton (H-3) for the initial enolisation, and the preferential axial attachment of a proton at C-4 in the final step, reasonably account for the remarkable stereoselectivity of the reaction as well as for the higher propensity of *erythro*-4-uloside (45) to undergo this rearrangement. Apparently, in the *threo* epimer (46) which exists in an only slightly distorted  ${}^4C_1$  conformation according to its proton coupling patterns, the axially disposed H-3 is less amenable to enolisation than the quasi-axial H-3 in (45).

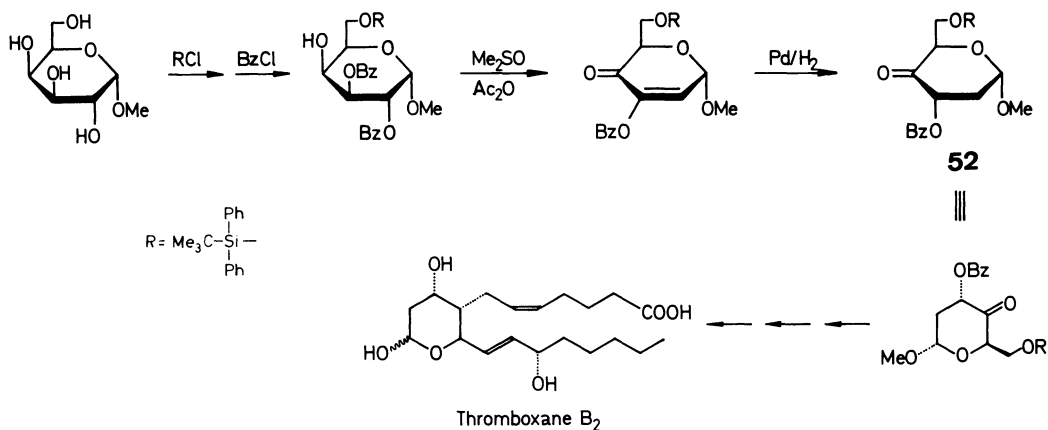


When the 3,4-enolone (2) was reduced with sodium borohydride a similar 2:1 mixture of 2-deoxyhexosides (48) and (49) was obtained, but *via* a different mechanism: preferential addition of the hydride species to the carbonyl carbon from the less hindered  $\beta$ -side (2 $\rightarrow$ 50) is followed by an *O*-3 $\rightarrow$ 0-4 benzoyl migration, thus liberating the carbonyl group at C-3. Subsequently, the resulting *erythro*-3-uloside (47), is reduced with a preponderance of hydride attack from the  $\beta$ -side to yield (48) and (49). This rationalisation was proved by the isolation of (47), in 44% yield, on reduction of (2) with the less reactive zinc borohydride. Apparently the enolate (51) in the form of its zinc complex is stable towards hydride addition. Further substantiation was provided by the formation of a specifically C-4 deuterated *erythro*-3-uloside (47) on treatment with zinc borodeuteride and by the 1.6:1 preference of (47) for hydride addition from the  $\beta$ -side on sodium borohydride reduction (Ref. 42).

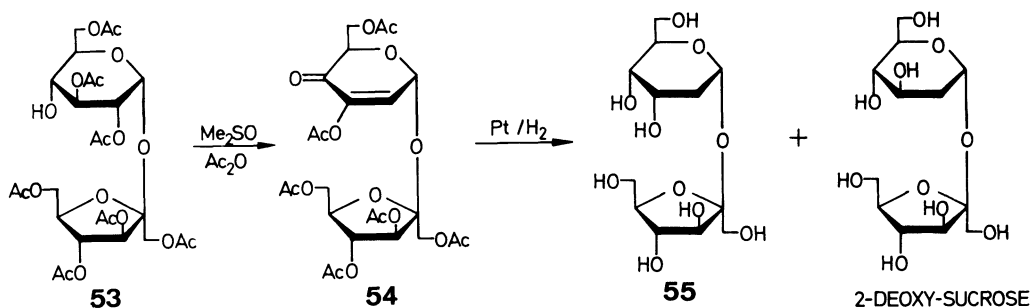
## 3,4-ENOLONE: Hydride Addition



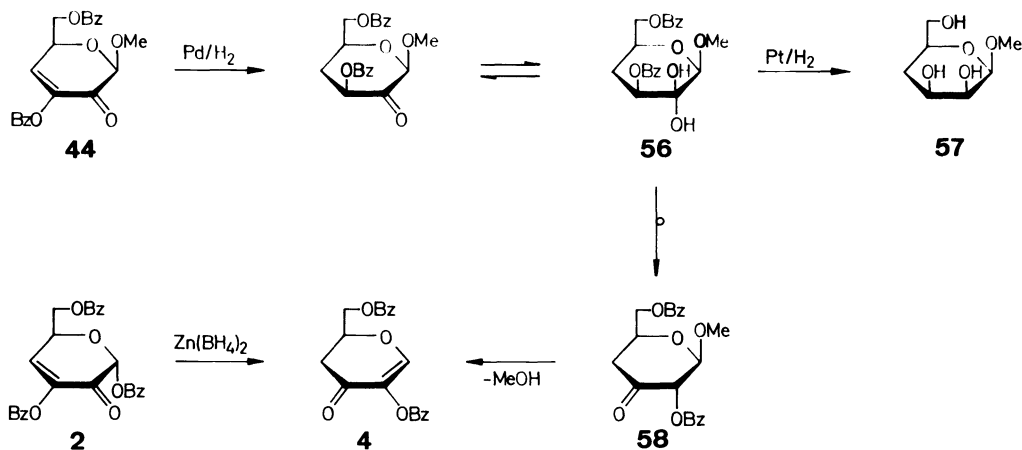
These reactions demonstrate the utility of 3,4-enolones and it is to be expected that Michael and Grignard type additions, presently being studied, will follow an analogous steric course. Two synthetic applications may be noted. First, a facile preparation of the 2-deoxy-D-*erythro*-4-uloside (52), which served as a chiral precursor in the synthesis of thromboxane B<sub>2</sub> (Ref. 43), in four simple steps from methyl  $\alpha$ -D-galactoside, i.e. 6-*O*-silylation with *tert*-butyldiphenylsilyl chloride, benzoylation, oxidation with methyl sulfoxide-acetic anhydride to the enolone, and hydrogenation. Since the last step proceeded almost stereospecifically, the high overall yield of (52) (Ref. 44) compared favorably with that for its 8-step preparation (Ref. 43) from methyl  $\alpha$ -D-glucoside.



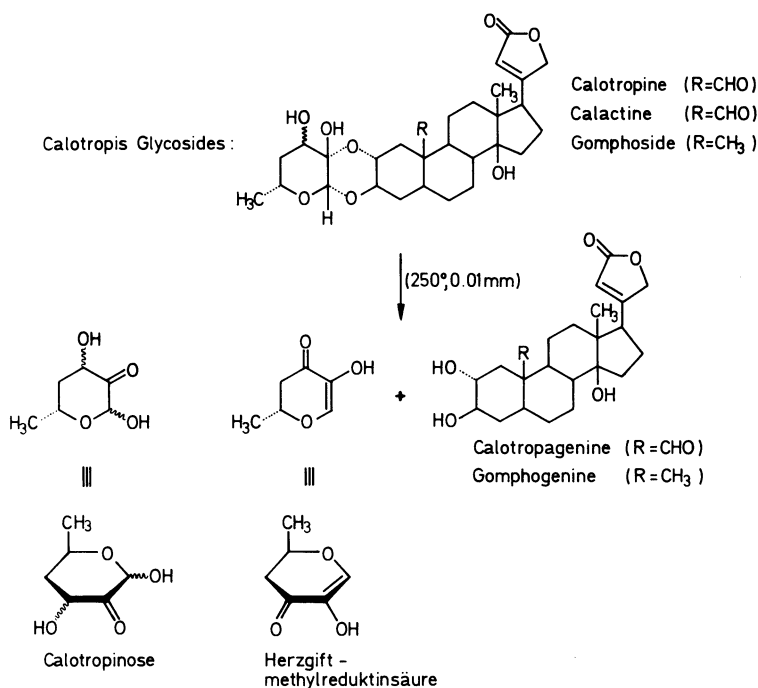
Secondly, a similar sequence applied to partially acylated disaccharides allows the ready preparation of 2-deoxydisaccharides, as exemplified for sucrose hepta-acetate (53) (Ref. 45), which upon conversion into its enolone (54) and subsequent reduction (or hydrogenation) afforded a mixture of products, containing mainly 2-deoxysucrose and its 3-epimer (55) (Ref. 46).



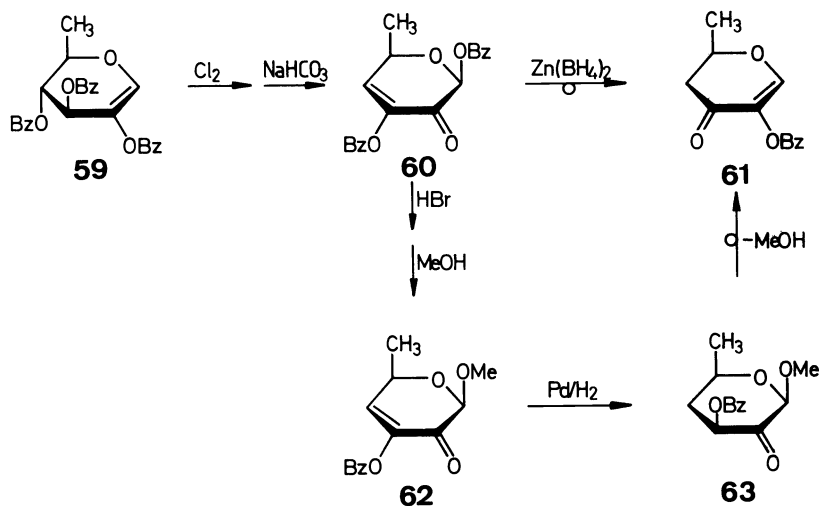
The 3,2-enolones are also highly useful as synthetic intermediates. In an essentially stereospecific hydrogenation, the enolone (44) afforded the 4-deoxy-*threo*-2-uloside as its monohydrate (56), which on hydrogenation, gave almost exclusively methyl 4-deoxy- $\beta$ -D-lyxoside (57), only traces of another isomer were detectable by t.l.c. In contact with silica gel, or on prolonged storage, (56) undergoes an *O*-3 $\rightarrow$ 0-2 benzoyl migration to the *erythro*-2-uloside (58), which, not unexpectedly in view of many similar reactions, is readily converted into dibenzoyl-2,3-dihydrokojic acid (4) by expulsion of the anomeric substituent. However, the latter product is more easily prepared from the enolone (2) by zinc borohydride reduction in a manner similar to that observed for the conversion of (2) into (47), followed by elimination of benzoic acid from the 1,2-positions (Ref. 42).



Another outgrowth from sugar-3,2-enolones stemmed from the carbohydrate portion of certain cardiac glycosides. The dihydrokojic acid derivative (4) exhibits a close structural relationship to the so-called Herzgift-Methylreduktinsäure, a dihydroallomaltol of high positive optical rotation, obtained on thermal decomposition of calotropis constituents such as calotropine, calactine, gomphoside, and others (Refs. 5, 47). Pyrolytic conditions are required, since dioxane-type glycosidic linkages are stable towards acid hydrolysis, and alkali treatment results in the formation of benzoic acid rearrangement products. Thus, it has not been possible to isolate and characterise the sugar unit of these glycosides, which is a 4,6-dideoxy-D-hexosulose of as yet unclarified configuration at C-3, and which we have named calotropinose.



A facile access to calotropinose-type sugars is provided by the 6-deoxyhexose-derived enolone (60), readily prepared from tri-*O*-benzoyl-hydroxyglycal (59) by low temperature chlorination, hydrolysis, and elimination of benzoic acid (Ref. 48) in a sequence analogous to that used in the hexose series (23+1). When treated with zinc borohydride, (60) was converted into enediolone (61), which is the *O*-benzoyl derivative of the calotropis-derived Herzgift-Methylreduktinsäure. Like the latter, (61) had a high positive optical rotation, proving the absolute configuration of the methyl bearing carbon atom in the calotropis glycosides to be D (or R) as has previously been deduced (Ref. 49) from the optical rotation of periodate oxidation products. On saturation of the enolic double bond in the enolone (62), a 4,6-dideoxy- $\beta$ -D-*threo*-hexosidulose (63) was obtained, which is either the *O*-benzoyl derivative of methyl calotropinoside or of its 3-epimer (Ref. 48). Moreover, as readily revealed on closer inspection of the enolone formulae (the carbonyl group at C-3 is only masked in the form of the enol ester) (60) and (62) are derivatives of actinospectose, the sugar portion of spectinomycin. Since the inosadamine portion of this antibiotic has already been synthesised (Ref. 50), the work now in progress with these enolones should eventually lead to its total synthesis.

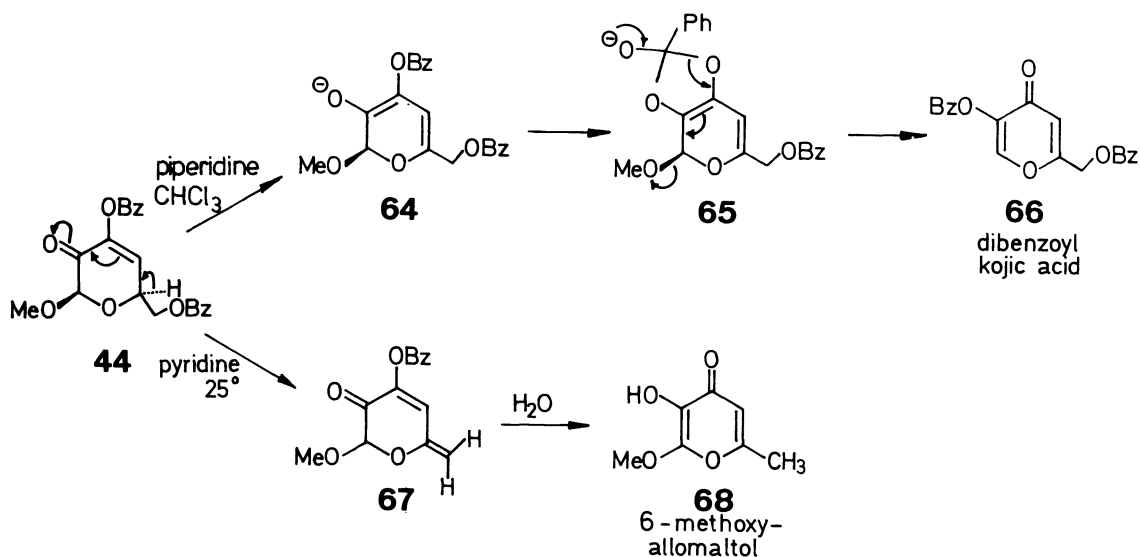


FORMATION OF  $\gamma$ -PYRONES FROM SUGAR ENOLONES

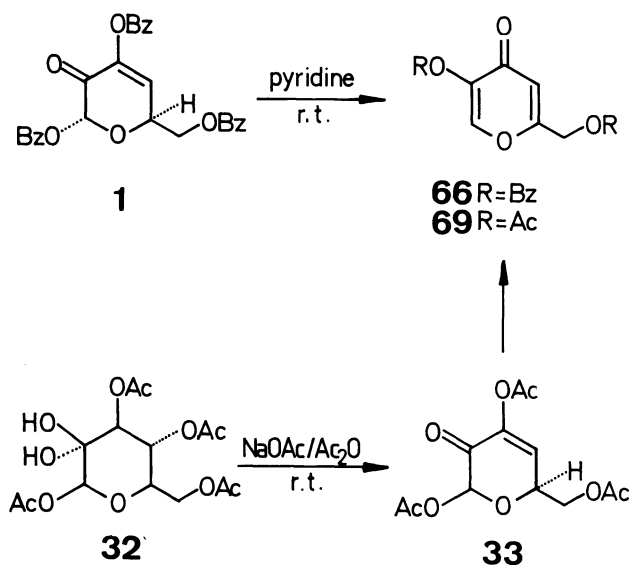
Sugar-3,2-enolones, and even more so their 3,4-enolone analogs, are readily converted into the  $\gamma$ -pyrone system with a kojic acid and maltol type substitution pattern.

Under mild basic conditions (piperidine in chloroform at room temperature) the enolone glycoside (44) was smoothly converted into dibenzoyl kojic acid (66), undoubtedly *via* abstraction of the proton vinylogous to the carbonyl group to form the enolate (64) which undergoes *O*-4→*O*-3 benzoyl migration through an orthoacid type intermediate (65) with concomitant expulsion of the anomeric substituent (Refs. 20, 21).

However, in anhydrous pyridine at room temperature a different pathway was followed, namely, elimination of benzoic acid from the 5,6-positions with the formation of the dienone (67) and another product together with minor components, all different from kojic acid or its derivatives. Although (67) could not be isolated, its presence in pyridine solution was proved by n.m.r. spectroscopy, as well as by subsequent hydrolysis to 6-methoxyallo maltol (68) (Refs. 20, 21).

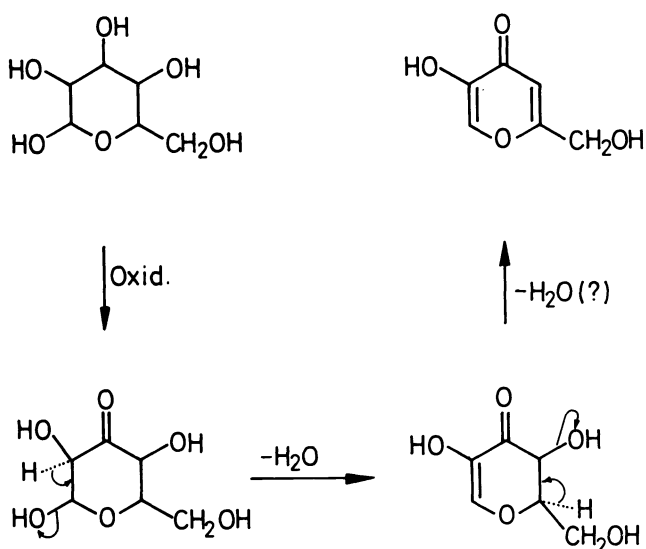


However, the latter course is only observed with glycosides. 1-Acyloxy-enolones, such as (1) and (33), give kojic acid derivatives exclusively in pyridine solution (Refs. 17, 18, 20, 21) or thermally. On longer exposure to sodium acetate-acetic anhydride, ulose (32) was exclusively converted during 2 h into (33), whereas after 24 h a mixture of (33) and (69) had accumulated. Treatment with methyl sulfoxide-acetic anhydride (Ref. 40) gave the same result. On the basis of these results the formation of diacetyl kojic acid (69) on methyl sulfoxide-acetic anhydride oxidation of 1,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucose (Refs. 11, 41, 51) is readily comprehensible.



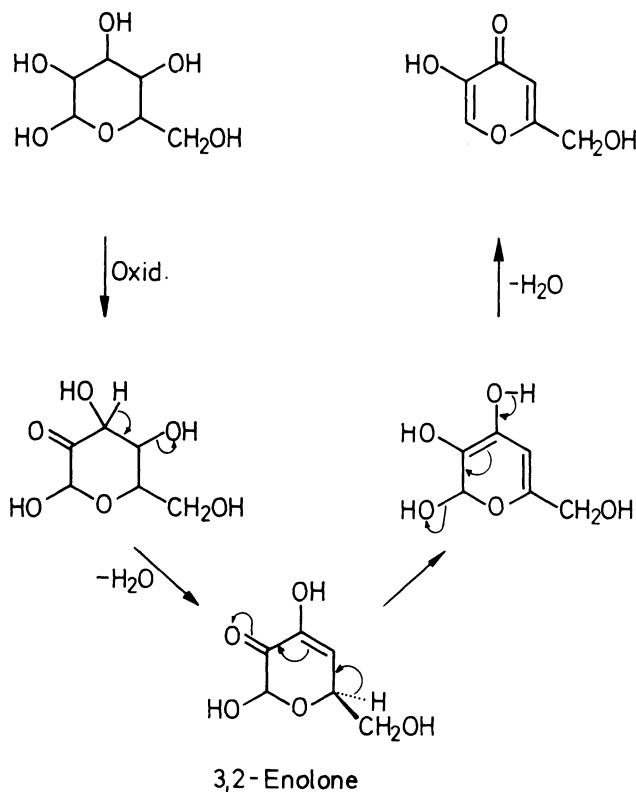
This ready, mechanistically plausible, conversion of hexose-3,2-enolones into kojic acid also has implications for the biological formation of this  $\gamma$ -pyrone. A large number of fungi, mainly belonging to the genus *Aspergillus* and *Penicillium*, produce kojic acid from carbohydrate sources (Refs. 52, 53), the major biosynthetic pathway comprising the utilisation of D-glucose with retention of the pyranoid carbon skeleton, as evidenced by  $^{14}\text{C}$  and  $^3\text{H}$ -labeling studies (Refs. 54, 55). That the structure of kojic acid may be arrived at merely by simple oxidation and dehydration of a hexopyranose has always been "an enticing carrot for chemical donkeys" (Ref. 56), one relevant early bio-synthetic concept being the so-called "carving out" theory, comprising oxidation at C-3 and removal of two molecules of water, one from each side (Refs. 57-59). However, the second elimination of water is less readily rationalised since it utilises a proton not activated by a neighboring carbonyl function, especially when considering that the biological entities are most probably the 1-phosphates, thus enhancing the first elimination step.

#### Conversion of Hexoses into Kojic acid by Fungi (*Aspergillus oryzae*)



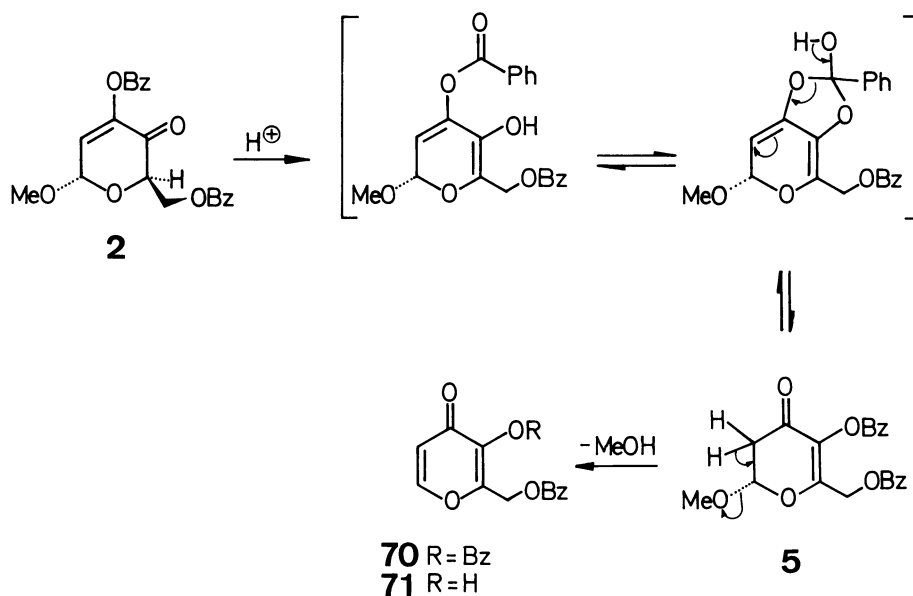


A pathway involving a 3,2-enolone intermediate appears to be more in line with present organic and biosynthetic mechanistic concepts as well as with the apparent ability of *Aspergillus flavus-oryzae* molds to form glucosone from glucose (Ref. 60). It involves oxidation at C-2, elimination of water from the resulting glycosid-2-ulose, and stabilisation of the enolone as the  $\gamma$ -pyrone by enolisation and extrusion of the anomeric substituent. These biosynthetic implications are limited to the apparently exclusive formation of kojic acid by molds of the *Aspergillus flavus-oryzae* group, in contrast to the production of several  $\gamma$ -pyrones, among them kojic acid, by bacteria, e.g. by *Gluconoacetobacter liquefaciens* (Refs. 61, 62) or *Acetobacter cerinus* (Ref. 63), that appears to proceed via 5-ketofructose (Ref. 64) or 2,5-diketogluconate (Ref. 62).

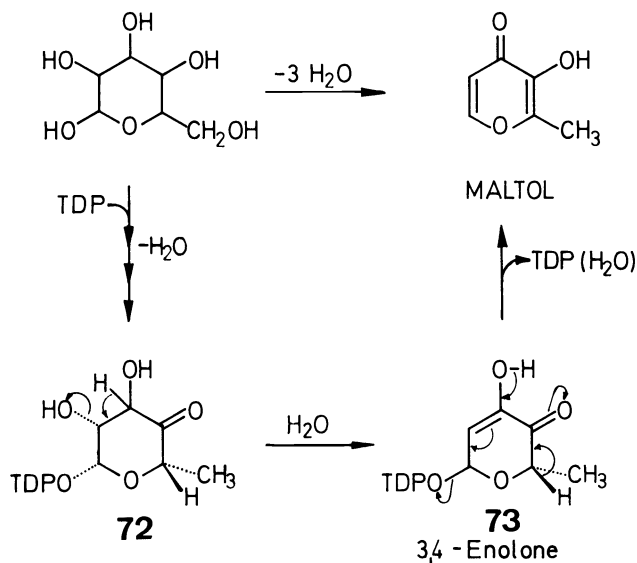


Similar implications are associated with the ready conversion of 3,4-enolones into derivatives of maltol. As already mentioned, dissolution of (2) in trifluoroacetic acid results in the formation of benzoyloxymaltol (71). Under somewhat less forcing conditions this transformation is traceable in more detail. Treatment of (3) with trichloroacetic acid in chloroform afforded a mixture of products from which (70) and the enediol glycoside (5) could be isolated (Ref. 23). Thus, this conversion is reasonably explained by an initial 4,5-enolisation followed by an intramolecular O-3→O-4 benzoyl migration to give (5) from which methanol, and under strongly acidic conditions benzoic acid also is removed (5→70→71).

The tendency of 2 to generate a  $\gamma$ -pyrone with a maltol-type substitution pattern provides the first direct evidence for the postulated occurrence of 3,4-enolone intermediates in the formation of maltol from the streptose portion of streptomycin (Ref. 9) and from a 6-deoxyhex-4-ulose (Ref. 66), as well as in the partial conversion of a hexosid-3-ulose into a derivative of hydroxymaltol (Ref. 65).



In view of these results one is tempted to speculate on the biosynthesis of maltol from carbohydrate sources, a process that unlike the kojic acid formation requires no oxidation step, but simply the removal of 3 moles of water. This conversion may well occur *via* a 6-deoxyhexo-4-ulose in the form of its thymidine diphosphate derivative (72), which has been recognised as an intermediate in the biosynthesis of L-rhamnose (Ref. 67) and probably is also involved in the bioformation of L-streptose (Ref. 68). Elimination of water from the 2,3-position then can elaborate the 3,4-enolone (73) from which maltol is formed by regeneration of TDP.



However, when considering the fact that maltol is produced simply by heating sugar, such as roasting malt or cooking food, the question arises as to whether the occurrence of maltol in coniferous trees (Refs. 69-73) and in other plants (Refs. 74-78) is the result of an enzymatic process, or a purely chemical dehydration reaction. Besides, maltol isolated from natural sources may even be an artefact in some cases, since steam distillation (Refs. 71, 77) and sublimation (Refs. 74, 76) preceded its obtention from plant extracts.

Thus, whereas clear indications may be derived from chemical reactions of sugar-3,2-enolones with respect to the biosynthesis of kojic acid by fungi, it remains to be established whether the maltol formation in plants is an enzymatic or a chemical process, and only in the former case, a 3,4-enolone of type (73) is likely to be the intermediate.

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