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ROUTES TO PROSTAGLANDINS FROM SUGARS

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Abstract - The synthesis of carbocyclic compounds - particularly cyclopentane derivatives - from carbohydrates is discussed and several routes to the advanced prostaglandin intermediates 4 and 5 from the readily available 5,6-dideoxyhex-5-enose triester 43 are then described. One approach involves the 2-aza-3-oxabicyclo[3.3.0]octane intermediate 45; another utilises the bicyclo[3.2.0]heptane derivative 51 produced by a photochemical intramolecular [2+2]cycloaddition reaction applied to the nona-3,8-dienulose compound 50.

INTRODUCTION

The wide ranging physiological activities of the prostaglandins has made these natural products and their analogues of the greatest significance in pharmaceutical science, and the 20 years since they were first structurally identified have seen explosive activity in the study of all aspects of their biology and chemistry (Ref.1). Unlike the steroids, with which as a family they have been compared, they do not accumulate to any extent in mammalian tissue and, although some are obtainable from non-mammalian sources (Ref.2), the desirability of having available versatile synthetic methods for the production of all the naturally occurring members and a wide range of analogues has remained high.

Many methods have been developed for synthesis in the laboratory (Ref.3), the majority being based on achiral starting materials and requiring for the production of the natural materials an optical resolution or an enantioselective step carried out by a biological or chiral chemical reagent. A few procedures, however, have utilised optically pure starting materials: routes to prostaglandins have been opened from the iridoid aucubin (Ref.4) and from (-)malic acid (Ref.5), and the synthesis of prostaglandin $F_{2\alpha}$ (1) from D-*glycero*-D-*gulo*-heptono-γ-lactone (Ref.6), which is commercially available and readily made from D-glucose, represents both a major achievement in controlled organic synthesis and a milestone in the rapidly expanding field of synthesis of non-carbohydrate natural products from sugars (Ref.7). In Fig. 1 the principles involved in this synthesis are illustrated; they depend upon the

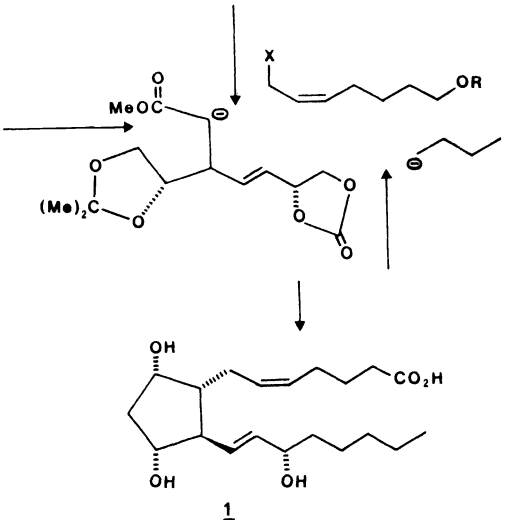

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Fig. 1.

use of a branched-chain unsaturated heptonic acid derivative which provides the carbon atoms of the cyclopentyl ring and the inner portion of the ω-chain as well as means for completing this chain and introducing the α-chain. The application of carbohydrates in the synthesis of prostaglandins is therefore not novel, and several routes to oxa-derivatives and thromboxane B_2 have also been developed from sugars (Ref.8), but rather than produce analogues or use sugars in the sophisticated, all-embracing manner of Stork to produce particular prostaglandins, we selected as our objectives advanced synthetic intermediates related to the core parts of the compounds and which have already provided access to natural products and their analogues.

Retrosynthesis of prostaglandin $F_{2\alpha}$ (1) leads to the dialdehyde 2 which, for practical synthetic purposes, must be selectively protected, for example as a cyclic acetal 3 (R = Me, R' = O or 3 R = Me, R' functionalised alkylidene) (Fig. 2), and since such compounds are

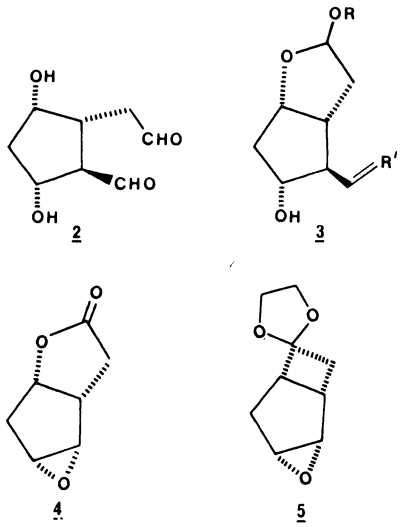


Fig. 2.

available from the epoxylactone 4 (Ref.3) and from the cyclobutanone derivative 5 (Ref.9) these became our primary targets.

SYNTHESIS OF CARBOCYCLIC COMPOUNDS FROM CARBOHYDRATES

As well as providing suitable access to a wide range of non-carbohydrate compounds with *O*- (and sometimes *N*-) heterocyclic structural components and to many chiral acyclic compounds, sugars can be used to obtain functionalised carbocyclic compounds (Ref.7), and while there are several methods for producing cyclohexane derivatives the literature contains only few examples of the preparation of analogous three-, four-, five- and seven-membered cyclic derivatives. No doubt the paucity of data in this area can be attributed to the instability of most carbohydrate derivatives under conditions used for many cyclisation reactions - especially to the presence of oxygenated functions in situations in which they act as good leaving groups, for example when they are β-related to carbonyl functions.

Much the most common type of reaction used to form C-C bonds within sugar derivatives involves the displacement of electrons from one carbon centre by electrons available at another (Fig. 3a). Frequently carbanionic activation is provided by α-carbonyl groups and other carbonyl groups suffer attack in intramolecular aldol reactions, and in this way, for example, a biomimetic synthesis of an inosose phosphate from D-*xylo*-hexos-5-ulose 6-phosphate has been effected (Ref.10). Many inositol derivatives have been produced by reactions of this general mechanistic category (Ref.11), some less usual variants involving (i) the treatment of 6-deoxyhex-5-enopyranosyl compounds with a mercury(II) salt in aqueous media (Ref.11,12), (ii) the reaction of 2,3,4-tri-*O*-benzyl-1,5-di-*O*-toluene-*p*-sulphonyl-D-arabinitol with methylenetriphenylphosphorane (Ref.13), (iii) the base-catalysed cyclisation of a 1,7-dibromo-1,7-dideoxy-*xylo*-hept-2,6-diulose triacetate to an epoxyinosose derivative (Ref.14),

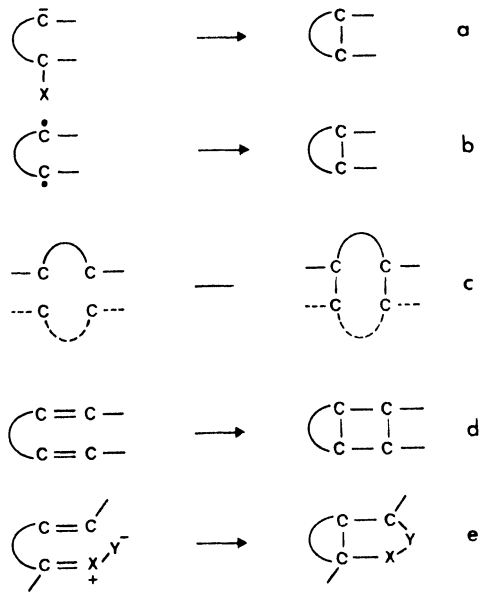


Fig. 3.

and (iv) the cyclisation of the analogous 1,7-bis(diazo) compound which occurs on heating in acetic acid in the presence of copper(II) acetate (Ref.15).

Occasional use has been made of this strategy (Fig. 3a) to produce cyclopropanes from carbohydrate derivatives. Bonding has been effected between C-3' and C-5' of nucleosides by based-catalysed displacement of sulphonoyloxy groups (Ref.16) and by electrolysis of 3',5'-dideoxy-3',5'-di-iodo derivatives (Ref.17). Otherwise, branched-chains have been introduced into sugar derivatives and bonding has then been effected by standard nucleophilic methods between one α-related carbon atom in the sugar and one in the side chain (Ref.18), and an elegant method of directly converting epoxides to cyclopropane derivatives involves the analogous reaction of a branched-chain intermediate formed by use of ethyl diethoxyphosphonylacetate (Ref.19). The reaction has been applied in synthetic studies in the chrysanthemic acid series (Ref.20). Route a (Fig. 3) does not represent a suitable method of making cyclobutanes from carbohydrates, but there are a few references to its application to produce cyclopentane (see below) and cycloheptane (Ref.21) derivatives.

A second strategy for bonding two carbon atoms within a sugar chain depends upon radical coupling (Fig. 3b). Photolysis of 1,3,4,5,6-penta-*O*-acetyl-*keto*-D-fructose and -L-sorbose affords a cyclobutane derivative produced by a Norrish Type II process which involves hydrogen abstraction from C-5 and bonding of this atom to C-2 (Ref.22). Similar treatment of 5,6-dideoxy-*xylo*-hex-5-enose diethyldithioacetal affords a dideoxyinososе diethyldithioacetal by a radical addition process (Ref.23).

A third general procedure involves the construction of carbocyclic rings partly from carbon atoms of the sugars and partly from atoms derived from other sources (Fig. 3c), and the simplest example of this is the derivation of cyclopropanes by application of the Simmons Smith reaction to unsaturated sugar derivatives (Ref. 24). In analogous fashion photochemical [2 + 2] cycloaddition has been effected between a pyranoid enone and ethylene and vinyl acetate to give cyclobutane derivatives (Ref.7b), and buta-1,3-diene has been condensed with the same type of carbohydrate compound in a Diels-Alder reaction to give products with pyranoid rings fused to cyclohexene (Ref.25). Cyclopentadiene undergoes similar [4 + 2] cycloaddition reactions with ald-2-enonic acid esters to afford norbornene adducts (Ref.26).

It appears that the intramolecular cycloaddition strategies illustrated in Fig. 3 (d and e) are largely untested, and this lecture will describe their applications to the synthesis of the advanced prostaglandin intermediates 4 and 5.

Synthesis of cyclopentane derivatives from carbohydrates

Although the occasional cyclopentane derivative has been noted amongst the products of major degradation of sugars and their derivatives, few formal syntheses have been recorded. Both types of products of the above mentioned Diels Alder reactions have been utilised to produce cyclopentanes (Fig. 4). Acid catalysed ring contraction of the bicyclic product made from a dideoxyhex-2-enopyranoside using butadiene led to the furanoside derivative 6 the double bond of which was oxidatively cleaved and the dimethyl ester of the product on treatment with

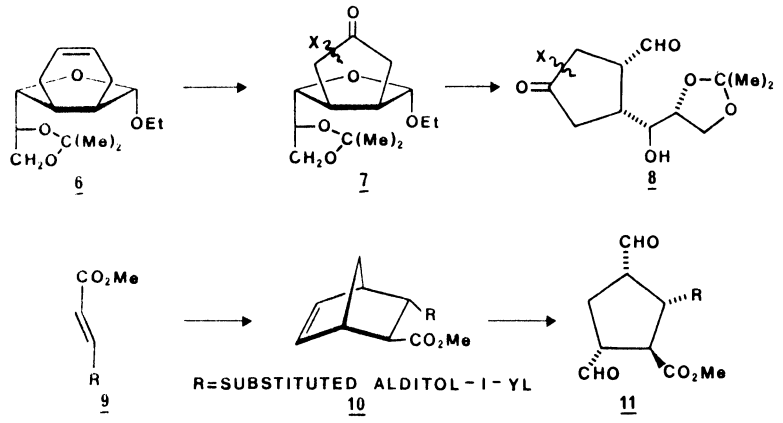


Fig. 4.

base afforded mixed cyclopentane derivatives 7 (X = CO_2Me) which were readily de-esterified and decarboxylated to give the disubstituted cyclopentanone 7 (X = H) (Ref.25). The aldehydes 8 (X = H or CO_2Me) would be derivable. In related fashion, the cyclopentadienyl products 10, obtained from unsaturated aldonic acid derivatives 9, gave rise to the tetrasubstituted compounds 11 with defined absolute and relative stereochemistries (Ref.26).

With one notable exception (see below) the few other examples of carbohydrate → cyclopentane conversions which have been described belong to category a (Fig. 3). Pentenomycin (13) was synthesised by base-catalysed cyclisation of the branched-chain aldulose 12 (Ref.27) (Fig. 5),

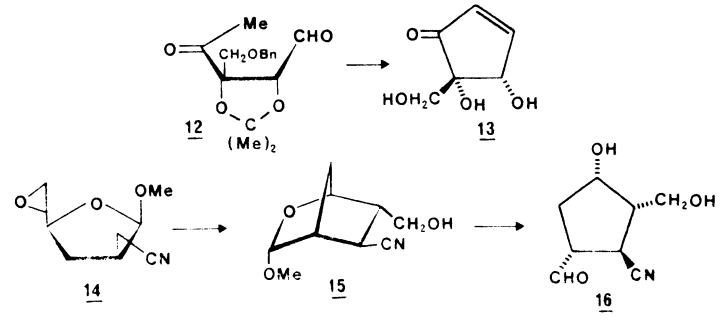


Fig. 5.

and it is noteworthy that the authors reported difficulty with this step. Likewise, the branched-chain nitrile 14 afforded the bicyclic product 15 and hence the aldehyde 16 in studies related to prostaglandin synthesis (Ref.28), and an analogous approach was adopted in the preparation of a brefeldin A precursor which contains a related substituted cyclopentyl ring (Ref.28). In a total synthesis of this compound in its natural enantiomeric form the cyclopentane ring was formed by base treatment of a 5-tosyloxy-hexanonitrile derivative produced from a D-glyceraldehyde compound (Ref.29).

Of seemingly particular interest is a new reaction introduced by Trost and Runge (Ref.30) by which 2-alkylidene-5-vinyltetrahydrofurans can be converted into cyclopentanone derivatives by heating in inert solvents in the presence of catalytic Pd (0) compounds (Fig. 6). In

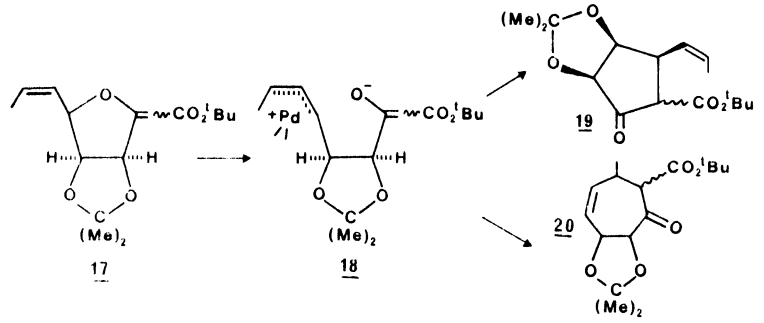
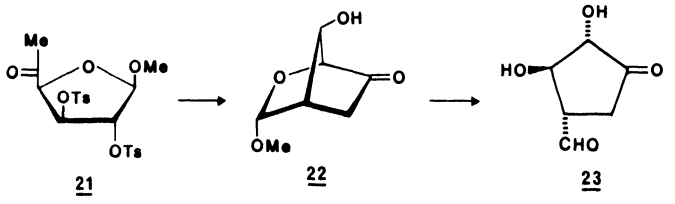


Fig. 6.

this way, for example, the diene 17, obtainable from D-mannose, has been converted into the cyclopentanone 19 via the allyl-palladium ionic intermediate 18 by use of a polymer-bound catalyst. Alternatively, when the sterically less demanding $(Ph_2PCH_2CH_2PPh_2)_2Pd$ was used the carbon nucleophile attacked at the other end of the allylic group to result in the formation of the cycloheptane derivative 20.

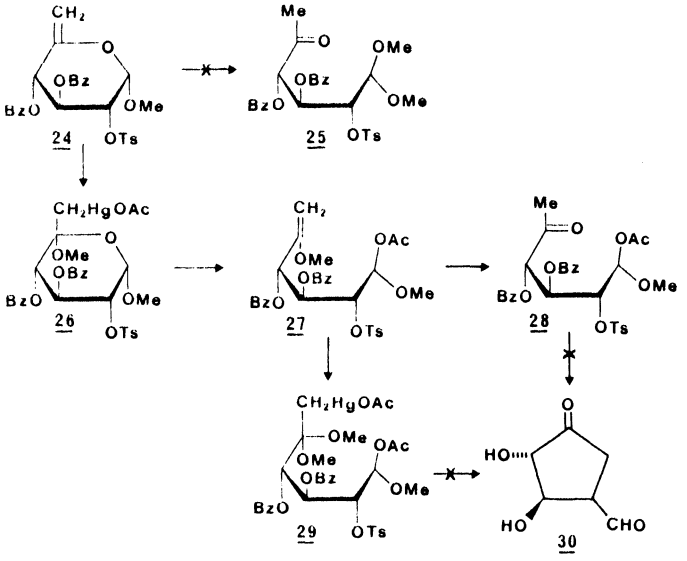
Our first attempts to prepare a cyclopentane derivative involved base-catalysed treatment of the methyl ketone 21 (Fig. 7), and whereas evidence was obtained for the production of some of



21 22 23

Fig. 7.

the bicyclic product 22, formed presumably by way of the D-*ribo*-epoxide, and from which the formylcyclopentane 23 should be accessible, it was clear that this approach was unsound because the carbocyclic ring closure reaction was inevitably accompanied by significant elimination reactions which led to a furan derivative (Ref.31). With the expectation that the avoidance of a strained intermediate like compound 22 would favour the desired ring closure, consideration was given to acyclic species (e.g. 25) and to their production from the alkene 24 (Fig. 8). Unfortunately acid catalysed methanolysis of this compound does not occur by protonation at the ring oxygen atom and solvent attack at C-1, but by protonation at



24 25 26 27 28 29 30

Fig. 8.

C-6 and the product retains the pyranose ring and has a new acetal centre at C-5 (Ref.11,32). It proved possible, however, to make an analogue of compound 25 by methoxymercuration of the alkene 24 and treatment of the product (26) with acetyl chloride in pyridine which resulted in demercuration and acetylation at the ring oxygen atom to give the new vinyl ether 27 which afforded the acyclic methyl ketone 28 with mild acid. However, compound 27 did not give good access to the cyclopentanone 30, neither did its product of methoxymercuration (29) which had attractive nucleophilic character at C-6 and a leaving group at C-2 (Ref.33).

In compound 28 carbanionic activity was induced by the carbonyl function, and in the mercurial (29) by the metal atom, and attention then turned to compounds which had C-6 bonded to both types of function and hence doubly activated. To this end the alkene 24 was treated in refluxing aqueous acetone with mercury(II) chloride and afforded in this way the cyclohexanone 33 in high yield (Ref.11). Subsequently it has been shown (Ref.34) that mercury(II) acetate in the same solvent first adds to the double bond to give the intermediate 31, and from this the acyclic mercurial 32 with the required functionality at C-5, C-6 was obtained, but this substance was formed with concurrent release of an aldehydic centre, and it is with this that the nucleophilic C-6 reacts rather than C-2 and the product

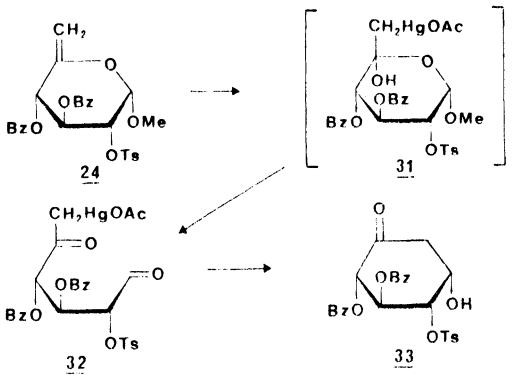


Fig. 9.

was again the cyclohexanone 33 (Fig. 9).

So far, therefore, the above approach had not yielded a good new cyclopentane synthesis, but a welcome by-product was the discovery of a useful means for preparing deoxyinososes (Refs. 11,12). Combination of this procedure with a photochemical reaction we have recently discovered by which bromine can be introduced at C-5 of certain pyranoid derivatives (Ref.35) has led to convenient new means of converting, for example, penta-*O*-benzoyl-β-D-glucopyranose (34) into the deoxyinosose triester 37 by way of the bromide 35 and the alkene 36 (Ref.12) (Fig. 10), and in related fashion octa-*O*-acetyl-β-D-maltose has been converted into an α-D-

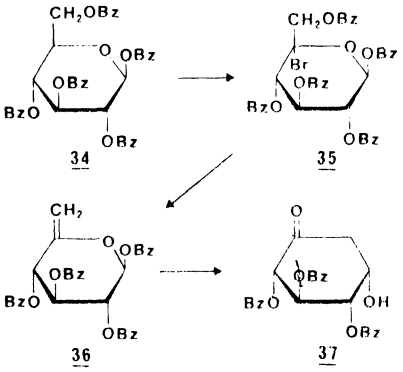


Fig. 10.

glucopyranosyl substituted inosose derivative (Ref.12, see also Ref.36) which is of potential value in aminoglycoside antibiotic synthesis.

It now, clearly, became of interest to determine whether cyclopentane compounds could be produced by this method from aldofuranose derivatives with exocyclic double bonds at C-4, and to this end the photobromination of several saturated furanosyl derivatives was examined. On treatment in carbon tetrachloride with bromine under bright light the β-D-glucofuranose ester 38, and also the corresponding D-*galacto*-isomer which has the alternative configuration at C-4, gave the product 39 having bromine at this position (Fig. 11). Reaction with zinc

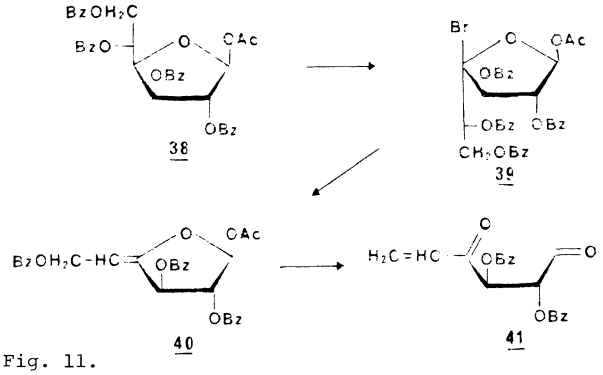


Fig. 11.

and acetic acid caused elimination of benzoyl hypobromite and the production of the *exo*-alkene 40 together with smaller proportions of the *endo*-isomer. By analogy with the reaction 24 → 33 (Fig. 9) the former (40), on treatment with mercury(II) salts, would be expected to lead to a cyclopentanone derivative having C-1 bonded to C-5, but none of this product was obtained; instead, mercuration occurred as expected at C-5 but the intermediate lost the benzoyloxy group from C-6 and the acyclic dicarbonyl alkene 41 was formed (Ref.34). In an attempt to establish the viability of the anticipated ring closure reaction a 5-deoxypent-4-enofuranose analogue of the alkene 40, i.e. a compound which could mercurate at C-5 but which could not react as did 40, was treated with mercury(II) salts in aqueous solution but again no cyclopentanes were formed. In this case, a pentose analogue of the acyclic mercurial 32 was obtained, and all attempts to cause it to ring close resulted in the simple cleavage of the C-Hg bond and the generation of a 5-deoxypentose product. Baldwin and Kruse (Ref.37) have shown that enolate anions do not readily undergo alkylation by 5-*endo*-Trig processes, and we assume, in consequence, that the acyclic pentose mercurial analogue of compound 32 reacted as an enolate anion rather than as a fully associated species and that the ring closure was impeded by stereoelectronic factors operating at C-4 and C-5. By analogy, it becomes clear that the ring closure reactions 12 → 13 (Fig. 5) and 21 → 22 (Fig. 7) are similarly disfavoured, and it is noteworthy, therefore, that neither proceeded without difficulty.

Failure to obtain functionalised cyclopentanes by way of mercurial intermediates has led us to study methods based on ring contraction of newly available deoxyinososes (e.g. 33) which can be made by this policy (Ref.34), but we have concurrently found that two intramolecular cycloaddition reactions which utilise the approaches represented in Fig. 3d and 3e were highly suitable for our purposes. Bernet and Vasella first illustrated the use of the latter 1,3-dipolar cycloaddition type of reaction in carbohydrate chemistry when they showed (Ref.38) that 6-bromo-6-deoxyhexopyranosyl compounds, on treatment in ethanol with zinc, undergo ring-opening to afford corresponding acyclic 5,6-dideoxyhex-5-enoses which, with *N*-methylhydroxylamine, give nitrones and hence 2-aza-3-oxabicyclo[3.3.0]octane products formed by a 1,3-dipolar addition reaction. The conditions are attractively mild and the reactions efficient, and when applied to the 6-deoxy-6-iodo-derivative 42, which is the readily available precursor of the alkene 24, gave the crystalline isoxazolidine 45 in 73% yield by way

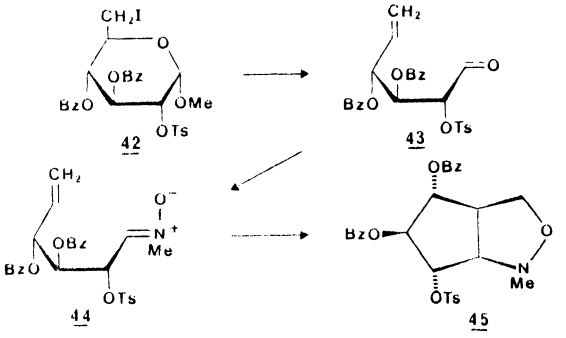


Fig.12.

of the enal 43 and the nitrone 44 (Fig. 12), and this has provided us with a source of the prostaglandin intermediate 4. The aldehyde 43 has also been used as a key intermediate in the synthesis of the second target compound (5).

SYNTHESIS OF THE EPOXYLACTONE 4 FROM THE ISOXAZOLIDINE 45 (Ref.39)

Isoxazolidine rings can be reductively ring opened by cleavage of the N-O bond, and the resulting amines may then react intramolecularly with other functional groups present (Ref.40), and when compound 45 was treated with Raney nickel it gave the epimine 46 (Fig. 13) thus establishing the stereochemical relationship between the nitrogen substituent and the sulphonyloxy group on the cyclopentane ring of the starting material (45) and hence the stereochemistry of the ring junction. Conversion of the epimine in near quantitative yield to the corresponding alkene was effected by use of *m*-chloroperbenzoic acid (Ref.41), and the side chain was extended by cyanide treatment of the tosyl ester. Iodolactonisation (Ref.42) of the derived acid 47 led to the iodide 48 which was characterised by X-ray diffraction analysis (Ref.43), and reduction with tributyltin hydride and deacylation afforded the diol 49. Since α-diols can be converted directly into epoxides by the combined use of diethyl azodicarboxylate and triphenylphosphine which usually give intermediate phosphonium salts from the more accessible alcohol groups and hence retain the more hindered oxygen atoms (Ref.44), compound 49 was dehydrated with these reagents but it gave only the unexpected *exo*-epoxide. That is, the relatively hindered *endo*-hydroxyl group at C-7 had been removed following, it is presumed, stabilisation of its triphenylphosphonium derivative by the

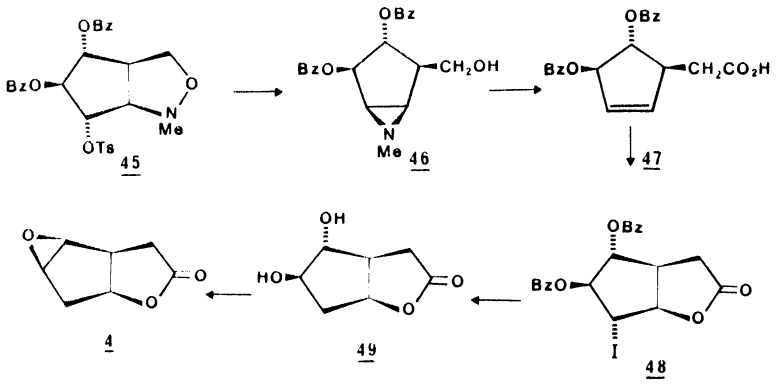


Fig. 13.

lactone oxygen atoms. An alternative reagent for the direct dehydration of α-diols - toluene-*p*-sulphonylimidazole (Ref.45) - reacted according to expectations based on steric considerations and led to the required *endo*-epoxide (4). Use of this product in this same enantiomeric form and in the racemic form as a prostaglandin precursor is well established (Ref.46).

SYNTHESIS OF THE EPOXYLACTONE 4 AND THE CYCLOBUTANONE DERIVATIVE 5 FROM THE DIENONE 50

Many examples of photochemical [2 + 2] cycloaddition reactions between alkenes and the vinyl groups of conjugated enones are in the literature (Ref.47), and frequently they involve intramolecular processes. Although in such cases the enones are often cyclic and the alkene groups are contained in side chains, we visualised such a process affording compounds of value if it could be applied to conjugated enones derived from the enal 43. Treatment with the anion of diethyl propan-2-onylphosphonate afforded the required dienone 50 which, on irradiation at 350 nm, was converted in good yield (values in excess of 80% have been obtained but usually yields were near 60%) into the crystalline bicyclic ketone 51 (Fig. 14). Since this has similarities to the isoxazolidine 45, and since functionalised

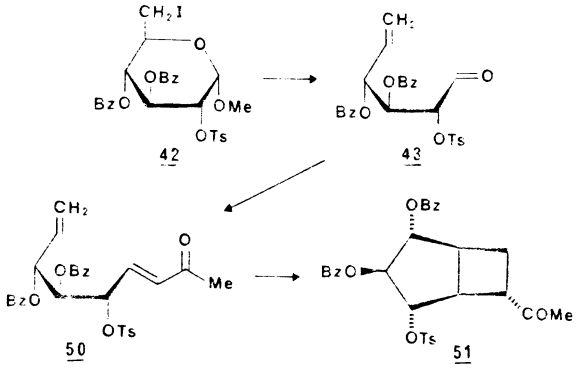


Fig. 14.

bicyclo[3.2.0]heptanes have proved valuable in prostaglandin synthesis (Ref.9) we investigated its use as a precursor of compounds 4 and 5.

Of pre-eminent importance for the conversion of the methyl ketone 51 into the target compounds is the reductive removal of the sulphonyloxy group, and the remaining α-diester system must be converted into an epoxide with the *endo*-stereochemistry. Fortunately, during the additionally required refunctionalisation of the cyclobutane ring, data became available which assisted with these requirements. Whereas in the case of the isoxazolidine 45 the tosyloxy-group was removed by the intramolecular amino-group, we have found three analogous means of displacing this group in the case of the bicyclo[3.2.0]heptane compounds: (i) use of the carbanion obtainable at C-7 and stabilised by the carbonyl group of compound 51, (ii) use of the electrons of the C-1 — C-7 bond of a derived C-7 alcohol, and (iii) use of the oxyanion obtainable at O-3 following base-catalysed deacylation of cyclobutanone derivatives.

Displacement of the sulphonyloxy group of ketone 51 by the carbanion at C-7

There are several examples in the literature of the displacement of *exo*-leaving groups at C-2 of bicyclo[3.2.0]heptan-6-ones by C-7 carbanions with the resultant formation of stable tricyclo[3.2.0.$0^{2,7}$]heptan-6-ones (Ref.9), and in analogous fashion the methyl ketone 51, on treatment with DBU, gave the crystalline tricyclic ketone 52 in high yield (Fig. 15).

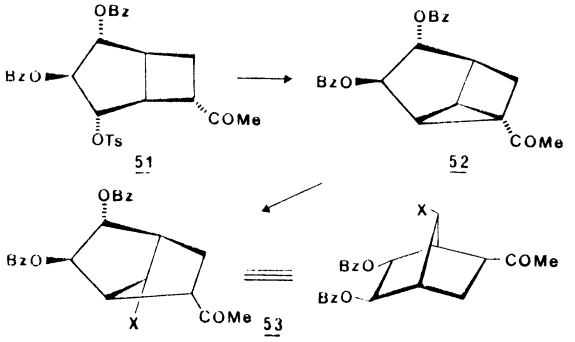


Fig. 15.

Should this compound react with nucleophiles in "*quasi*-Michael" fashion by attack at the carbon atom previously bearing the sulphonyloxy group it would offer means of removing this ester in the required fashion from the precursor (51). However, in keeping with the behaviour of analogues (Ref.9), the tricyclic compound gave a set of 7-substituted norbornyl derivatives (53, X = H, I, Br, OAc, SPh) as shown, the "*quasi*-Michael" attack occurring at the alternative electrophilic centre and leading to cleavage of the bond common to the two smallest rings. This approach therefore did not lead to the target products, but it is noted incidentally that one synthetic route to the prostaglandins depends upon analogous products of norbornanes bearing similarly introduced nucleophiles at C-7 (Ref.9).

Displacement of the sulphonyloxy group of alcohol 54 by the C-1 — C-7 bond electrons

Treatment of the methyl ketone 51 with trifluoroperacetic acid (Ref.48) gave the expected Baeyer-Villiger product i.e. the analogous *exo*-acetate from which the alcohol 54 was derived by selective deacetylation. Since this compound, on oxidation, gave a cyclobutanone from which the epimeric alcohol was derived by reduction with sodium borohydride, and since such reduction occurs predominantly from the *exo*-direction to give *endo*-products (Ref.49), the former alcohol 54 can be assigned the *exo*-configuration.

A most convenient method of opening the cyclobutyl ring was discovered when the alcohol 54 was treated with sodium hydride since the oxyanion collapsed to give an aldehydic group and the C-1 — C-7 electrons displaced the sulphonyloxy group (Fig. 16). The unsaturated

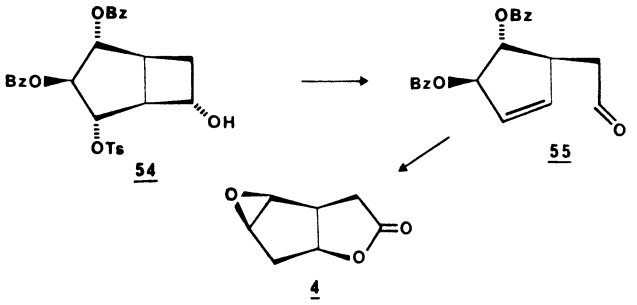


Fig. 16.

aldehyde 55 was thus produced with high efficiency and characterised by its conversion to the acid 47 and the iodolactone 48 which are intermediates in the route from the isoxazolidine 45 to the epoxylactone 4. The sequence 43 → 50 → 51 → 54 → 55 → 47 → 48 → 4 represents a new access to our first target and has the advantage of providing the two-carbon side chains directly. Apart from the synthesis of the dienone 50 from iodide 42 and its photochemical transformation into the bicyclic ketone 51, each of which gives about a 60% yield, all of the steps in the procedure can be conducted with high efficiency.

Displacement of the sulphonyloxy group of acetals 56, (X = S or O) by the anion at O-3

Since nucleophilic opening of the epoxide ring of the cyclobutanone derivative 5 occurs

appreciably more selectively than that of the epoxylactone 4 to give compounds with two appropriate ring substituents related to 3 (Ref.9), it was attractive to use the methyl ketone 51 and a strategy which involved retention of the regiocontrolling cyclobutane ring at the point of nucleophilic opening of the epoxide ring. The known compound 5 therefore was selected as the next synthetic objective. In consequence, the alcohol 54 was oxidised to the corresponding ketone and converted to the dithioacetal 56 (X = S)[this compound being initially more readily prepared than the oxygen analogue 56 (X = O)]. Attempts to displace the sulphonyloxy group of the thioacetal 56 (X = S) (and also the methyl ketone 51 and the acetate of alcohol 54) with nucleophiles which could have permitted deoxygenation at C-2 did not lead specifically to the desired products - either mixtures were produced or 3-substituted products resulted. In the case of the reduction of the dithioacetal 56 (X = S) with lithium aluminium hydride the product appeared to be a 2,4-diol produced conceivably from an *endo*-2,3-epoxide which was attacked at C-3 by the hydride coordinated to the hydroxyl group at C-4. When, however, compound 56 (X = S) was treated with potassium carbonate in methanol, debenzoylation took place and O-3 concurrently displaced the tosyloxy anion to give the crystalline epoxide 57 (X = S) specifically (Fig. 17). It was anticipated by

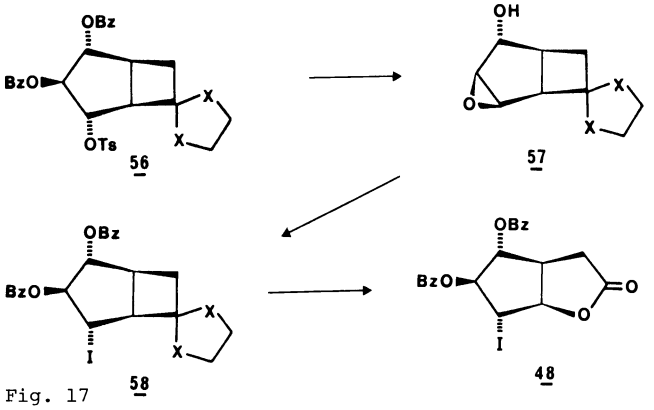


Fig. 17

analogy (Ref.9) that this would react with nucleophiles preferentially at C-2 in the desired fashion, and with sodium iodide and catalytic acid it gave, following benzoylation, the 2-iodo-product 58 (X = S) almost quantitatively. Hydrolysis of the thioacetal and Baeyer-Villiger oxidation gave the previously characterised iodolactone 48 which establishes the structure of the epoxide 57 (X = S) and its highly specific mode of reaction with iodide.

These procedures were then repeated on the oxygen analogue 56 (X = O) and the hydroxyepoxide 57 (X = O) and the iododiacetate (59) were obtained uneventfully. When, however, the latter was treated with tributyltin hydride in the presence of a radical initiator, direct dehalogenation did not occur as was the case with the lactone analogue (48). Instead, ring opening took place which resulted in the production of the cyclopentene acetal 60 (Fig. 18) by a radical reaction comparable with that observed with the alcohol 54 when it

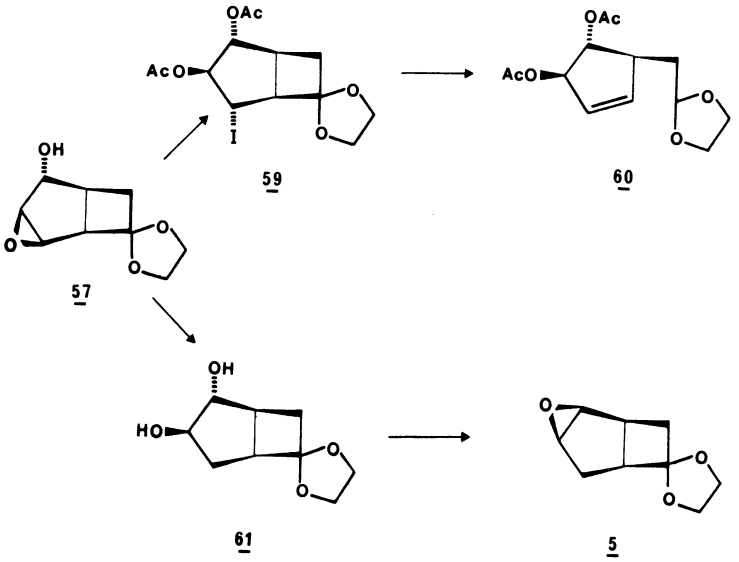


Fig. 18

was treated with base (54 → 55).

Direct reduction of the epoxide 57 (X = O) appeared to afford a 2,4-related diol, and therefore lithium aluminium hydride reduction was applied to the derived *tert*-butyldimethylsilyl ether and the product, after acid-catalysed desilylation, was the required diol 61 which, on dehydration with toluene-*p*-sulphonylimidazole, afforded the *endo*-epoxide 5 as required. At the time of reporting, however, we have to record that this epoxidation was surprisingly non-specific and that approximately equal proportions of this epoxide and the *exo*-isomer were produced. In view of the analogous, specific conversion of the related diol 49 into the epoxide 4 this was unexpected.

In summary, the interconversions outlined in Fig. 19 have been developed for the synthesis of the advanced prostaglandin intermediates 4 and 5 from the readily available methyl α-D-glucopyranoside derivative 42.

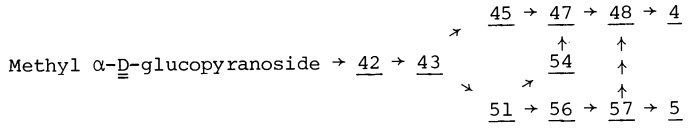


Fig. 19.

Acknowledgements - S.R. Haines carried out the work referred to in Fig. 11 and Dr. P.C. Tyler completed the synthesis of compound 5 from the acetal 56 (X = O).

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