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SYNTHESIS OF A PROSTAGLANDIN ENDOPEROXIDE MODEL COMPOUND AND ITS REACTION WITH ELECTRON TRANSFER REAGENTS[1]

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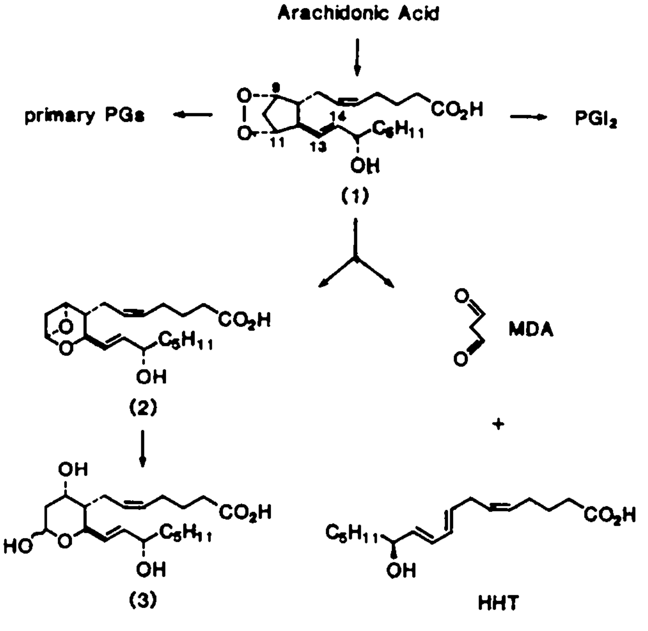
Abstract: 5-*Exo*-phenyl-2,3-dioxabicyclo[2.2.1]heptane (4c) was synthesized as a model compound of prostaglandin endoperoxide (PGH) to mimic the bioconversion of PGH into thromboxane (TX). The reaction of (4c) with various electron transfer reagents was investigated. With the aid of a catalytic amount of ferrous ion, (4c) was successfully converted into the thromboxane B (TXB) skeleton.

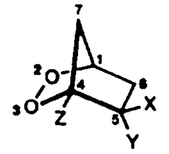
The prostaglandin endoperoxide (PGH_2) (1) plays a central role in the cyclooxygenase system of arachidonic acid metabolism[2] as a substrate for enzymes producing primary prostaglandins (PG), prostacyclin (PGI_2), thromboxane A_2 (TXA_2) (2), and other metabolites like malondialdehyde (MDA) and 12-hydroxy-5,8,10-heptadecatrienoic acid (HHT). TXA_2 (2) is converted into TXB_2 (3) on hydration. Among the cascade-like metabolic pathways shown in Scheme 1, the bioconversion of PGH_2 (1) into TXA_2 (2) is the most complicated and intriguing from the viewpoint of organic reactions and the biosynthetic mechanism remains to be solved. Several hypotheses have been proposed to account for the skeletal rearrangement of the bicyclic moiety. An initiation of peroxy-bond cleavage by electrophilic enzymatic attack at the peroxide oxygen at C-9 (PG numbering) has been suggested.[3] An alternative mechanism proposed is initiated by an electron transfer from metal to peroxy-bond producing a radical anion species.[4] Based on the enzymatic properties of the purified TX synthetase, the heterolytic cleavage of the peroxy-bond, in which the oxygen at C-9 carries a positive charge (opposite to the first proposal), has also been claimed.[5]

Model reactions of 2,3-dioxabicyclo[2.2.1]heptane (4a), the PGH_2 nucleus, under various conditions afforded neither the TXA nor the TXB nucleus,[6] suggesting that the two side chains of (1) may play an important role in the isomerisation of the bicyclic moiety to the 2,6-dioxabicyclo[3.1.1]heptane ring of (2). However, very little is known about the structural features of (1) which govern its modes of reaction. Compound (4a) on thermolysis undergoes mainly cleavage of the C-1-C-7 (Figure 1) bond[6] after the peroxy-bond homolysis, while the 5-vinyl-substituted derivative (4b) fragments at the C-1-C-6 and C-4-C-5 bonds.[7] Several model studies indicate that external chemical factors also control the mode of endoperoxide reaction. Under ionic reaction conditions, (1) undergoes C-9-C-10 (PG numbering) or C-10-C-11 bond cleavage yielding levuglandins accompanied by formation of the primary PG's.[8] On the other hand, one-electron transfer reagents were reported to cleave the C-8-C-9 and C-11-C-12 bonds of (1) to afford MDA and HHT,[9] which corresponds to the other pathway carried out by the TX synthetase.[5]

For the purpose of providing some evidence for chemical interpretation of the biosynthetic mechanism of (1)→(2), the bioconversion was mimicked using a model compound.[10] On designing the model compound of (1), certain assumptions were made. The C-13-C-14 double bond of the ω side-chain of (1) will play the most important role in stabilizing the transition state of the C-11-C-12 bond cleavage because it is driven by the resulting formation of an allylic radical or carbonium ion.[11] Furthermore, the double bond will have non-bonding interaction with some part of the TX synthetase, so the electronic nature of the double bond

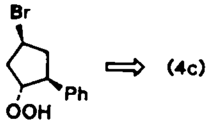


Scheme 1.



(4a) X = Y = Z = H
(4b) X or Y = $CH=CH_2$, Z = H
(4c) X = Ph, Y = Z = H
(4d) X = Z = H, Y = Ph
(4e) X = Y = H, Z = Ph

Figure 1.



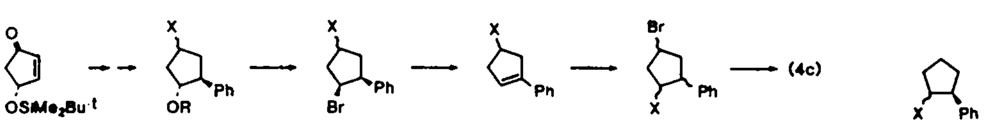
(5)

may be more important than usual. The electronic nature of the double bond can affect the selectivity of the two reactions; TXA_2 formation and/or the MDA and HHT formation. Based on the above assumptions, we have chosen 5-*exo*-phenyl-2,3-dioxabicyclo[2.2.1]heptane (4c) for the simplified endoperoxide model. In this molecule the ω side-chain is substituted by a phenyl group to act as the electronically modified C-13-C-14 double bond equivalent and the α side-chain is removed. We now describe the synthetic methods leading to (4c) and its reactions with various electron transfer reagents.

Synthesis of the Endoperoxide (4c).[12] —— Previously, we prepared the desired endoperoxide (4c) by the peroxide transfer reaction[13] between bis(tri-*n*-butyltin) peroxide and the bistriflate of *c*-4-phenyl-*r*-1,*c*-3-cyclopentanediol, although the yield was not satisfactory.[14] The double displacement reaction of *c*-2-phenyl-*r*-1,*c*-4-dibromocyclopentane with anhydrous hydrogen peroxide in the presence of silver salt[15] was also attempted. However, this yielded the unexpected 1-phenyl-2,3-dioxabicyclo[2.2.1]heptane (4e) as the major product along with a small amount of (4c).[14]

Consideration of the mechanism for formation of (4e) mentioned above suggests that an intramolecular cyclisation of a bromohydroperoxy compound,[16] like (5), would be a favourable route to the desired (4c). This would avoid the involvement of 2-phenyl-1-cyclopentyl cationic species which rearrange to the benzyl cation.[17] The preparation of the compound (5) was carried out as shown in Scheme 2. The acetoxy isomers (7) and (8)[14] were prepared in three steps starting with 4-*t*-butyldimethylsilyloxycyclopent-2-en-1-one (6). These were separately desilylated and the resulting alcohols (9) and (10) were converted into the inverted bromides (11) and (12), respectively, by 2-chloro-3-ethylbenzoxazolium tetrafluoroborate, tetraethylammonium bromide, and triethylamine in dichloromethane.[14,18] In practice, the compounds from (7, 8) to (11, 12) were handled as a mixture and the latter was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to yield an olefinic compound (13). Hydrolysis of (13) afforded an alcohol (14) in 24 % overall yield from (6). Compound (14) on treatment with triphenylphosphine and carbon tetrabromide was converted into an unstable bromide (15) in 89 % yield.

Dichlorohydroboration was reported to be a good method to prepare hydroperoxides without contamination from the corresponding alcohol.[19] Before applying the reaction to unstable (15), a preliminary experiment using 1-phenyl-1-cyclopentene (16)[20] was run. Dichlorohydroboration of (16) followed by autoxidation and chromatographic separation at 0°C yielded hydroperoxide isomers (19) and (20) in 12 and 32 % yield, respectively. This was accompanied by the formation of alcohols (21) and (22) in 3 and 10 % yield, respectively. The configuration of the hydroperoxy and hydroxy groups relative to the phenyl group was tentatively assigned based on analogy to the literature precedent that 1-methylcyclopentene produced *trans*



(6)

(7) R = SiMe$_2$Bu^t X = β-OAc
(8) R = SiMe$_2$Bu^t X = α-OAc
(9) R = H, X = β-OAc
(10) R = H, X = α-OAc

(11) X = β-OAc
(12) X = α-OAc

(13) X = OAc
(14) X = OH
(15) X = Br
(16) X = H

(17) X = OOH
(18) X = OH

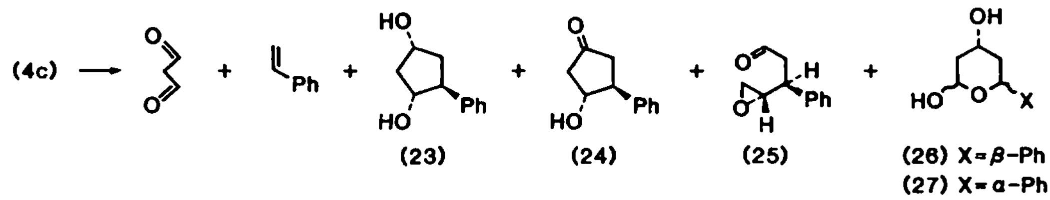
(19) X = β-OOH
(20) X = α-OOH
(21) X = β-OH
(22) X = α-OH

Scheme 2.

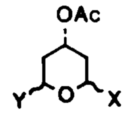
hydroperoxide predominantly.[21] When compound (15) was subjected to the above reaction, hydroperoxide mixtures (17) and alcohol mixtures (18) were formed, but the reproducibility of the reaction was poor. On the other hand, ordinary hydroboration[21] of (15) followed by sequential oxidations with oxygen and hydroperoxide gave consistently modest yields (*ca.* 30 %) of (17) after low temperature chromatography. The formation of the corresponding alcohol is mechanistically unavoidable and alcohol mixture (18) was isolated in 24 % yield. Since the separation of hydroperoxide isomers was not achieved, no direct evidence that (17) contained the desired bromohydroperoxide (5) was obtained. However, the hydroperoxides (17) on treatment with silver (I) oxide in dichloromethane afforded the endoperoxide (4c) in 36 % yield along with a small amount of its *endo*-phenyl isomer (4d). The formation of (4c) suggests that (17) contained (5) as a major isomer, since silver (I) oxide is reported to carry out an intramolecular S_N2-type cyclisation for bromohydroperoxy compounds.[16d] The formation of isomeric (4d) was confirmed by reduction of crude (4d) with stannous chloride into *c*-4-phenyl-*r*-1,*c*-3-cyclopentanediol.

The Reaction of the Endoperoxide (4c). —— It was reported that thromboxane synthetase is like cytochrome P-450 and contains an Fe(III)-heme-thiolate as its active site.[5] Model studies using Fe(III)-porphyrin showed that it acts as a strong nucleophile toward peroxide oxygen and promotes reductive O-O bond cleavage.[22] Considering these findings, the reaction of (4c) with various electron transfer reagents was investigated. Table lists the reagents studied and the yields of the products. Quantitative analyses of MDA and styrene were made by the thiobarbituric acid test[23] and h.p.l.c., respectively. The structures of the reaction products shown in Scheme 3 were confirmed by their independent preparation which will be mentioned in a later section. The production of MDA and styrene was the major mode of reaction in each case, and primary PG-like products (23) and (24) and epoxyaldehyde (25) were formed in varying amounts depending upon the reagent. The formation of these products are interpreted by the well precedented O-O bond cleavage reaction of endoperoxide.[9,24] Noteworthy is the product (26, 27) bearing the 2,4-dihydroxytetrahydropyran ring, the TXB ring moiety, which was found in the case of the Fe(II)-promoted reaction. The compound (26, 27) was isolated as the corresponding diacetate mixture (28, 30a, b) (*vide infra*) and identified by comparison with authentic samples. Electron transfer reagents containing ligands failed to yield the TXB-like product. The difference in mode of reaction between outer-sphere [Fe(II)] and inner-sphere [Ru(II)] radicals was reported in the case of ascaridol,[9,25] but the exact nature of these radicals seems to be too little understood to provide a logical interpretation for the different results from the radical reactions.

The Fe(II)-promoted reaction deserves some comments. Addition of a catalytic amount of ferrous sulfate (0.05 equiv.) to (4c) in degassed aqueous acetonitrile under argon led to a very fast reaction (<1 min) and to the formation of the products listed in the Table. Under the reaction conditions used the formation of Fe(III) is expected.[24a,b] Fe(III) is a Lewis acid and Lewis acid-catalysed decomposition of peroxy compounds is known.[24c,26] This led to a study of the effect of Fe(III) on (4c). When (4c) was treated with ferric sulphate (0.05 equiv.) for 1 min, more than 98% of starting material was recovered. These findings suggest that the above reaction was initiated by the electron supply from Fe(II) to (4c) and the direct decomposition of (4c) by Fe(III) formed during the reaction is probably small, although it can not be entirely ignored.[27] The formation of (26, 27) may follow that shown in Scheme 4 which is based on the Fe(II)-Fe(III) redox process hypothesised by Turner and Hertz.[4] According to the mechanism, the formation of (26, 27) is caused by the generation of benzylic radical species (A) from the radical anion (or the corresponding ferric alkoxide) without undergoing fragmentation to MDA and styrene. In this respect, the phenyl group of (4c) is considered to



Scheme 3.



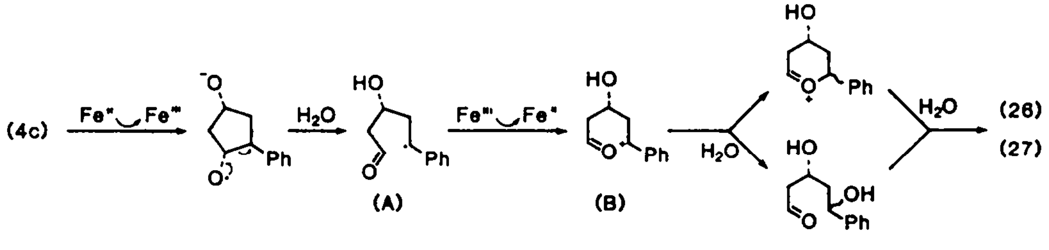
(28) X=β-Ph, Y=β-OAc
(29) X=β-Ph, Y=α-OAc
(30a,b) X=α-Ph, Y=〰OAc

Table. Reaction of (4c) with electron transfer reagents.[9, 24]

Reagents		Time	Solvent	Product and yield (%)[a]					
				MDA	Styrene	(23)	(24)	(25)	(26, 27)
$FeSO_4$	2 eq	30 min	aq. CH_3CN	39[b]	45	1[c]	6[c]	10[c]	3[d]
$FeSO_4$	0.05 eq	<1 min	aq. CH_3CN	+[e]	43	1	5	12	3
Ru(II)$(Ph_3P)_3Cl_2$	0.02 eq	3 hr	$CDCl_3$	+	63	trace	0	14	0
Pd(O)$(Ph_3P)_4$	0.1 eq	16 hr	$CDCl_3$	+	14	11	0	7	0
Rh(I)(Ph_3P)Cl	0.1 eq	16 hr	$CDCl_3$	+	26	17	0	13	0
Co(II)TPP[f]	0.02 eq	42 hr	$CDCl_3$	+	46	trace	0	23	0
Fe(III)TPPCl	0.02 eq	26 hr	$CDCl_3$	+	55	trace	0	28	0
Hemin	0.02 eq	15 min	aq. CH_3CN	+	2	10	0	0	0

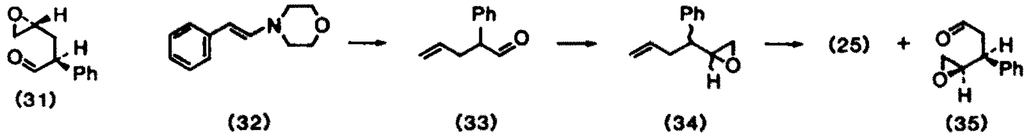
[a] Yield determined by h.p.l.c. except noted. [b] Yield determined by the thiobarbituric acid test. [c] Isolated yield. [d] Isolated yield of the corresponding diacetate. [e] + means positive to the thiobarbituric acid test, but not determined quantitatively. [f] TPP = tetraphenylporphine.

have played the expected role to some extent.[28] The present model failed to undergo stereoselective cyclisation via seco-species (B), giving (26, 27), an isomeric mixture at the carbon bearing a phenyl group. However, it was previously demonstrated that the 11,12-secoprostaglandin analogues containing an α side-chain underwent stereoselective cyclisation to the TXB analogue which bears a *trans* side chain.[11] Accordingly, the involvement of (A) or (B) is not inconsistent with the bioconversion of PGH_2 (1) into TXA_2 (2) in respect to the stereochemistry at C-12. The present study provides some insight into the biosynthetic mechanism of TXA_2 formation from PGH_2.



Scheme 4.

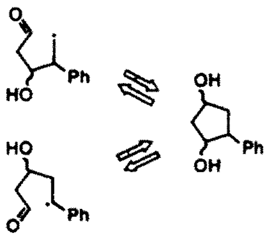
Independent Preparation of the Endoperoxide Reaction Products. —— Based on mechanistic considerations, epoxyaldehyde can be one of two possible structures. The formation of epoxyaldehydes like (25) and (31) are well precedented.[6,9,24d,e] In the n.m.r. spectrum of the epoxyaldehyde obtained, the aldehyde proton was observed as a triplet thereby excluding structure (31). To confirm the gross structure, the compound (25) was prepared as shown in Scheme 5. Phenylacetoaldehyde was first converted into a morpholine enamine (32)[29] and the enamine was reacted with allyl bromide in refluxing acetonitrile followed by hydrolysis to give an allylated product (33) in 46% yield. Treatment of (33) with dimethyloxosulphonium methide[30] afforded a mixture of epoxides (34) in 40% yield. Ozonolysis of the mixture yielded separable epoxyaldehydes in which the more polar isomer, obtained in 39 % yield, was identical to (25). The yield of the other isomer (35) was 42%. The relative configuration of benzylic and epoxy carbon atoms of (25) was assigned based on the mechanism of formation. Since the bonds around the two carbon atoms are not considered to be broken during the reaction,[6] their configurations are retained as depicted.



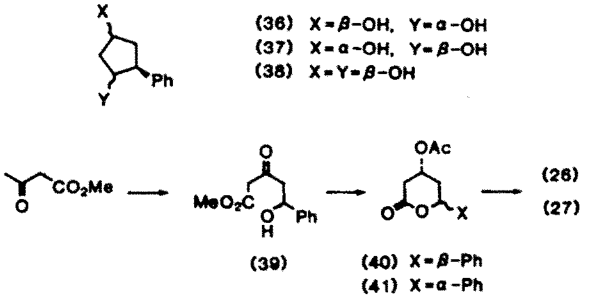
Scheme 5.

Hydroxyketone (24) was obtained in 81% yield upon acid hydrolysis (0.1 N HCl in acetonitrile) of *trans*-3-*t*-butyldimethylsilyloxy-4-phenylcyclopentanone which was prepared by the 1,4-addition of diphenylcopperlithium to (6).[14] Preparation of 1,3-*cis*-diol (23) and X-ray crystallographic analysis of the corresponding diacetate were described in a previous report.[14] It is known that in the reaction of secondary alcohols with lead tetra-acetate, epimerisation of the alcohol occurs via recyclisaton of the radical species formed by β-scission as depicted in Scheme 6.[31] In order to check the possibility of epimeric alcohol formation in the present system, diols (36),[14] (37), and (38) were prepared. The unknown (37) was obtained in an overall 45 % yield starting from compound (10) in three steps; mesylation, inversion with cesium acetate in the presence of 18-crown-6,[32] and hydrolysis of the resulting diacetate. The compound (38) was prepared from (23) by double inversion using the same procedure as described above.[14] Careful h.p.l.c. analysis was performed for the diol fraction of the endoperoxide reaction products to see if any other diol isomers were present as contaminants. The four diols prepared appeared as discrete peaks by h.p.l.c. analysis. Only (23) was found in the reaction products and the other isomers were not detected.

Authentic TXB-like lactols (26) and (27) and their corresponding acetates were prepared according to Scheme 7. Methyl acetoacetate was sequentially treated with sodium hydride and *n*-butyllithium in tetrahydrofuran. The resulting dianion[33] was allowed to react with benzaldehyde to afford hydroxy-ketoester (39) in 89% yield. Sodium borohydride reduction of (39) followed by hydrolysis afforded the diol-acid, which was treated with acetic anhydride to yield an equal amount of two crystalline lactones (40) and (41) in 69% yield. In the n.m.r. spectrum of the less polar lactone (40), the proton on the carbon bearing acetoxy group was observed as a quintet (*J* 4 Hz), while the proton at the same position in the more polar isomer (41) was a triplet of doublets (*J* 6.3, 6.6, and 8.4 Hz). Assuming that the bulkier phenyl group occupies the equatorial position, (40) was assigned as having the acetoxy group *trans* to the phenyl and (41) as *cis*. The lactones (40) and (41) were separately subjected to di-isobutylaluminium hydride reduction to yield lactols (26) and (27), respectively, both in 28% yield. When (26) was treated with acetic anhydride in pyridine, two separable acetates (28) and (29) were obtained in 65 and 6% yield, respectively. On the other hand, acetylation of (27) afforded the corresponding acetates (30a, b) as a 1:1 anomeric mixture in 70% yield. On acetylation of the lactol fraction (26, 27) in the reaction of (4c) with Fe(II), a mixture of three acetates (28) and (30a, b) was



Scheme 6.



Scheme 7.

obtained in an approximate ratio of 2:1:1, respectively. Compound (29) was not isolated probably due to its very small yield after the acetylation.

EXPERIMENTAL

M.p.s were determined on a Yanagimoto micro apparatus and are uncorrected. A Hitachi 260-10 or a JASCO-J-0056 spectrophotometer was used to obtain i.r. spectra. ^1H n.m.r. spectra were obtained with a Varian EM-390 (90 MHz) or a Varian XL-200 (200 MHz) spectrometer in $CDCl_3$ with Me_4Si as the internal reference unless otherwise mentioned. Mass spectra were determined with a Hitachi RMU-8 spectrometer (with e.i., 70 eV). Elemental analyses were performed by the analytical department of these laboratories. Lobar Columns (Merck, silica gel 60, 230-400 mesh, size A or B) were used for column chromatography along with a FMI RP-SY Lab Pump and a Waters R-403 Differential Refractometer unless otherwise stated. T.l.c. plates (Art. 5715) were purchaced from E. Merck and peroxides were detected by a spray of either ferrous thiocyanate or N,N,N',N'-tetramethyl-*p*-phenylenediamine dihydrochloride. H.p.l.c. analyses were carried out on a LiChrosorb SI 60 column (Merck, 10 μ, 4.6 mm x 250 mm) in normal phase operation and a Develosil ODS-7 column (Nomura Chemical Co., 7 μ, 4.6 mm x 250 mm) in reverse phase operation with the following equipment; a Reodyne 7125 injector, a Knauer-64 pump, an Oyobunko Uvilog 5IIIA u.v. detector, and a Hewlett Packard 3390A reporting integrator.

(1R*,2S*,4S*)-4-*Acetoxy-2-phenyl-1-cyclopentanol* (9). —— A solution of the silyl ether (7)[14] (1.50 g, 4.49 mmol) and n-tetrabutyl-ammonium fluoride (1 M in tetrahydrofuran, 5.0 ml) in tetrahydrofuran (15 ml) was stirred at room temperature for 15 h. The mixture was diluted with dichloromethane and washed with water. The organic layer was dried (Na_2SO_4), evaporated, and the residue was chromatographed with n-hexane/ethyl acetate (50/50) as the eluent to give (9) (862 mg, 87%) as a colourless oil. $\nu_{max.}$ ($CHCl_3$) 3560 and 1730 cm^{-1}; δ 7.32 (5H, br s, aryl), 5.40-5.10 (1H, m, 4-H), 4.50-4.10 (1H, m, 1-H), 3.10-1.65 (6H, m, 2-H, 3-H_2, 5-H_2, and OH), and 2.06 (3H, s, COMe); *m/z* 220 (M^+).

(1R*,2S*,4R*)-4-*Acetoxy-2-phenyl-1-cyclopentanol* (10). —— The silyl ether (8)[14] (160 mg, 0.479 mmol) was treated as above yielding (10) (62 mg, 59%) as a colourless oil. δ 7.32 (5H, br s, aryl), 5.40-5.10 (1H, m, 4-H), 4.40-3.90 (1H, m, 1-H), 3.35-1.60 (5H, m, 3-H_2, 2-H, 5-H_2), and 2.02 (3H, s, COMe).

(1S*,3S*,4S*)-1-*Acetoxy-3-bromo-4-phenylcyclopentane* (11). —— A solution of the alcohol (9) (110 mg, 0.5 mmol) and triethylamine (61 mg, 0.6 mmol) in dichloromethane (1.0 ml) was added to a stirred mixture of 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (161 mg, 0.6 mmol), tetraethylammonium bromide (126 mg, 0.6 mmol), and dichloromethane (1.0 ml) at 0°C. After 4 h stirring, the mixture was chromatographed on silica gel (Merck, silica gel 60, 70-230 mesh) with n-hexane/ethyl acetate (90/10) as the eluent. Re-chromatography with the same solvent afforded (11) (54 mg, 38%) as an oil. $\nu_{max.}$ (film) 1736 cm^{-1}; δ 7.30 (5H, br s, aryl), 5.30 (1H, ddd, *J* 3, 6, 18 Hz, 1-H), 4.60 (1H, t, *J* 4 Hz, 3-H), 3.30-2.30 (5H, m, 2-H_2, 4-H, 5-H_2); *m/z* 282 and 284 (M^+).

(1R*,3S*,4S*)-1-*Acetoxy-3-bromo-4-phenylcyclopentane* (12). —— The alcohol (10) (1.0 g, 4.545 mmol) was treated as above yielding the bromide (12) (461 mg, 36%) as a colourless oil. δ 7.30 (5H, br s, aryl), 5.60-5.30 (1H, m, 1-H), 4.82-4.56 (1H, m, 3-H), 3.64-3.36 (1H, m, 4-H), 3.10-1.90 (4H, m, 2-H_2, 5-H_2), and 2.00 (3H, s, COMe); *m/z* 282 and 284 (M^+).

1-*Acetoxy-3-phenyl-3-cyclopentene* (13). —— A mixture of the bromide (11) (338 mg, 1.194 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (272 mg, 1.791 mmol) in tetrahydrofuran (4.0 ml) was stirred at room temperature for 15 h and the resulting solid was removed by filtration. The filtrate was evaporated and the residue was chromatographed with n-hexane/ethyl acetate (95/5) as the eluent to afford (13) (212 mg, 88%) as needles, m.p. 42-44°C (from pet. ether, lit.[34] 42-44°C); $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}; δ 7.50-7.10 (5H, m, aryl), 6.06 (1H, t, *J* 2 Hz, 4-H), 5.60-5.30 (1H, m, 1-H), 3.25-2.35 (4H, m, 2-H_2, 5-H_2), and 2.02 (3H, s, COMe).

3-*Phenyl-3-cyclopenten-1-ol* (14). A mixture of the acetate (13) (454 mg, 2.248 mmol) and potassium carbonate (372 mg, 2.697 mmol) in methanol (10 ml) was stirred at room temperature for 1 h. Water and dichloromethane were added and layers were separated. The organic layer was dried (Na_2SO_4) and evaporated to give a solid which was recrystallized to afford (14) (354 mg, 98%) as needles, m.p. 79-81°C (ether, lit.[34] 79-81°C). δ 7.50-7.15 (5H, m, aryl), 6.08 (1H, t, *J* 2 Hz, 4-H), 4.75-4.40 (1H, m, 1-H), 3.15-2.30 (4H, m, 2-H_2, 5-H_2), and 2.00 (1H, br s, OH).

1-Bromo-3-phenyl-3-cyclopentene (15). —— A solution of the alcohol (14) (640 mg, 4 mmol), carbon tetrabromide (1.336 g, 4 mmol), and triphenyl phosphine (2.096 g, 8 mmol) in dichloromethane (20 ml) was stirred at 0°C for 5 h. The mixture was chromatographed (n-hexane) to give (15) (796 mg, 89%) as an unstable oil (m.p. below 25°C), (Found: C, 59.05; H, 5.1. $C_{11}H_{11}Br$ requires C, 59.2; H, 4.95%); δ 7.30 (5H, br s, aryl), 6.02 (1H, t, *J* 1 Hz, 4-H), 4.74-4.44 (1H, m, 1-H), 3.30-2.90 (4H, m, 2-H_2, 5-H_2); *m/z* 222 and 224 (M^+).

Hydroboration-autoxidation of 1-Phenyl-1-cyclopentene (16). —— Dichloroborane ether complex (6.6 M, 0.2 ml, prepared from lithium borohydride and boron trichloride in ether) was added to a stirred solution of (16) (144 mg, 1.0 mmol) in n-pentane (1.0 ml) at 0°C under a nitrogen atmosphere. Boron trichloride (2.0 M in n-hexane, 0.5 ml) was added to the mixture. After 15 min, the mixture was cooled to -78°C and ether (2.0 ml) was added. Oxygen gas was bubbled into the resulting solution for 15 min. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ether. The organic layer was dried (Na_2SO_4), evaporated, and the residue was chromatographed at 0°C. Elution with n-hexane/ethyl acetate (90/10) gave (19) (21 mg, 12%) as a colourless oil. $\nu_{max.}$(film) 3510 cm^{-1}; δ 7.30 (6H, br s, aryl and OOH), 4.85-4.55 (1H, m, 1-H), 3.30-2.95 (1H, m, 2-H), and 2.40-1.60 (6H, m, $CH_2 \times 3$); *m/z* 178 (M^+).

Further elution with the same solvent gave (20) (57 mg, 32%) as a clourless oil. $\nu_{max.}$(film) 3510 cm^{-1}; δ 7.94 (1H, s, OOH), 7.30 (5H, br s, aryl), 4.54 (1H, dd, *J* 4, 7 Hz, 1-H), 3.30-2.95 (1H, m, 2-H), and 2.50-1.60 (6H, m, $CH_2 \times 3$); *m/z* 178 (M^+).

Further elution with the same solvent gave (21) (5 mg, 3%) as a colourless oil. δ 7.30 (5H, br s, aryl), 4.32 (1H, br t, *J* 3 Hz, 1-H), 3.25-2.90 (1H, m, 2-H), 2.40-1.60 (6H, m, $CH_2 \times 3$), and 1.12 (1H, d, *J* 3 Hz, OH); *m/z* 162 (M^+).

Further elution with the same solvent gave (22) (17 mg, 10%) as a colourless oil. δ 7.30 (5H, br s, aryl), 4.30-3.95 (1H, m, 1-H), 3.05-2.65 (1H, m, 2-H), and 2.40-1.30 (7H, m, $CH_2 \times 3$ and OH); *m/z* 162 (M^+).

Hydroboration-autoxidation of 1-Bromo-3-phenyl-3-cyclopentene (15). —— A mixture of the bromide (15) (400 mg, 1.79 mmol) and borane-tetrahydrofuran complex (1.0 M, in tetrahydrofuran, 0.9 ml) in tetrahydrofuran (10 ml) was refluxed for 1 h under a nitrogen atmosphere. The mixture was cooled to -78°C and oxygen gas was bubbled into the mixture for 1.5 h. The mixture was warmed to 0°C and oxygen gas bubbling was continued for an additional 0.5 h, after which 30% hydrogen peroxide (0.4 ml) was added and stirring continued at 0°C for an additional 0.5 h. Dichloromethane was added and the organic layer was washed with deionized water, dried (Na_2SO_4), and evaporated. The residue was chromatographed at 0°C with n-hexane/ethyl acetate (85/15) to give the stereoisomers of *4-bromo-2-phenyl-1-cyclopentylhydroperoxide* (17) (126 mg, 27%) as an unstable oil. δ 8.05 (1H, s, OOH), 7.30 (5H, br s, aryl), 4.80-4.50 (1H, m, 1-H), 4.50-4.08 (1H, m, 4-H), and 3.25-1.96 (5H, m, 2-H, $CH_2 \times 2$); *m/z* 256 and 258 (M^+).

Further elution afforded the isomeric mixture of *4-bromo-2-pheny-1 -lcyclopentanol* (18) (103 mg, 24%) as an unstable oil. δ 7.30 (5H, br s, aryl), 4.70-4.30 (2H, m, 1-H, 4-H), 3.15-1.80 (6H, m, 2-H, OH, $CH_2 \times 2$); *m/z* 240 and 242 (M^+).

(1R*,4R*,5S*)-*5-Phenyl-2,3-dioxabicyclo-*[2.2.1]*heptane* (4c). —— Silver (I) oxide (150 mg, freshly prepared from 1N silver nitrate and 10% sodium hydroxide) was added to a stirred solution of the bromohydroperoxide (17) (130 mg, 0.506 mmol) in dichloromethane (4.0 ml) at 0°C. The mixture was stirred at 0°C for 3 h and filtered through a pad of Celite. The filtrate was evaporated and the residue was chromatographed at 0°C with n-hexane/ethyl acetate (90/10) as the eluent yielding (4c) (32 mg, 36%) as needles, m.p. 38-40°C (pet. ether), which was identical with the authentic material.[14]

Reaction of Endoperoxide (4c) *with Ferrous Sulphate.* —— Ferrous sulphate (1.0 M in water, 0.7 ml) was added to a stirred solution of the endoperoxide (4c) (62 mg, 0.352 mmol) in acetonitorile (1.0 ml) and water (1.0 ml) at 0°C. After 0.5 h stirring, a small amount of this mixture was used for quantitative analyses of malonaldehyde (using a colour reaction with thiobarbituric acid and monitoring of its absorption at 532 nm), and of styrene (using reverse phase h.p.l.c. with acetonitrile/water (60/40), 1 ml/min, t_R = 9.6 min). The rest of the mixture was extracted with dichloromethane and the organic layer was dried (Na_2SO_4), evaporated and the residue was chromatographed. Elution with n-hexane/ethyl acetate (40/60) gave the epoxyaldehyde (25) (6.0 mg, 10%) as an oil, which was identical with the authentic sample described below.

Further elution with the same solvent afforded the hydroxy-ketone (24) (4 mg, 6%) as needles, m.p. 51-52°C (ethanol/water), which was identical with the authentic sample described below.

Elution with ethyl acetate afforded a mixture of the lactol (26) and (27), which was identical with the authentic samples described below. Confirmation of the identification was carried out by reverse phase h.p.l.c. with acetonitrile/water (20/80), 1 ml/min, t_R = 7.38 min for (26), t_R = 6.52 and 7.83 min for (27). The mixture of the lactols (26) and (27) mentioned above was treated with acetic anhydride and pyridine for 2 h at room temperature to give the acetate mixture (28) and (30a, b) (5 mg, 3% from (4c)), which was identical with the authentic sample described below. Confirmation was by reverse phase h.p.l.c. with methanol/water (50/50), 1 ml/min, t_R = 19.2 min and by normal phase h.p.l.c. with dichloromethane/metanol (500/1), 1 ml/min, t_R = 11.9 min.

Further elution with ethyl acetate gave the diol (23) (0.6 mg, 1%), which was identical with the authentic sample[14] as shown by reverse phase h.p.l.c. with acetonitrile/water (20/80), 1 ml/min, t_R = 9.38 min and normal phase h.p.l.c. with dichloromethane/methanol (96/4), 1 ml/min, t_R = 15 min. Treatment of the diol (23) with acetic anhydride and pyridine gave the diacetate, which was also identical with the authentic sample[14] as shown by reverse phase h.p.l.c. with methanol/water (60/40) 1 ml/min, t_R = 15.4 min and normal phase h.p.l.c. with dichloromethane/methanol (500/1), 1 ml/min, t_R = 16.4 min.

(3R*,4S*)-3-*Hydroxy-4-phenyl-1-cyclopentanone* (24). —— A mixture of (3R*,4S*)-3-*t-butyldimethylsilyloxy-4-phenyl-1-cyclopentanone*[14] (1.54 g, 5 mmol) and 0.1 N hydrochloric acid (5.0 ml) in acetonitrile (15 ml) was stirred at room temperature for 20 h. The mixture was extracted with dichloromethane, and the organic layer was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. Chromatography of the residue with n-hexane/ethyl acetate (50/50) afforded (24) (716 mg, 81%) as needles, m.p. 51-52°C (ethanol/water), (Found: C, 71.3; H, 7.15. $C_{11}H_{12}O_2 \cdot 0.5H_2O$ requires C, 71.35; H, 7.1%); $\nu_{max.}$ ($CHCl_3$) 3400 and 1740 cm^{-1}; δ 7.30 (5H, br s, aryl), 4.36 (1H, quartet-like, *J* 7 Hz, 3-H), 3.30 (1H, dt, *J* 7, 7 Hz, 4-H), 2.95-2.05 (5H, m, 2-H_2, 5-H_2, OH); *m/z* 176 (*M*+).

(E)-β-*Morpholinostyrene* (32). —— Morpholine (0.87 g, 10 mmol) was added dropwise to a stirred solution of phenylacetoaldehyde (1.20 g, 10 mmol) in benzene (20 ml). The crystals formed were collected by filtration to give (32) (1.88 g, quantitative), which was used in the next step without purification. δ 7.45-6.95 (5H, m, aryl), 6.65 and 5.45 (each 1H, each d, *J* 15 Hz, vinyl), and 3.78 and 3.04 (each 4H, each t, *J* 6 Hz, CH_2 x 4).

2-*Phenyl*-4-*penten*-1-*al* (33). A mixture of the enamine (32) (1.88 g, 10 mmol) and allyl bromide (1.21 g, 10 mmol) in acetonitrile (20 ml) was refluxed for 7 h and evaporated. The residue was refluxed with water (50 ml) for 1 h, and extracted with n-hexane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. Chromatography with n-hexane afforded (33) (779 mg, 49%) as an oil. δ 9.66 (1H, d, *J* 1 Hz, CHO), 7.55-7.05 (5H, m, aryl), 5.95-5.30 (1H, m, 4-H), 5.20-4.85 (2H, m, 5-H_2), 3.85 (1H, td, *J* 1, 6 Hz, 2-H), and 3.00-2.20 (2H, m, 3-H_2).

(2S*,3S*)- *and* (2R*,3S*)-1,2-Epoxy-3-*phenyl*-5-*hexene* (34). —— A mixture of dimethylsulphoxide (5.0 ml) and sodium hydride (50% dispersion in mineral oil, 210 mg, 4.375 mmol) was stirred at 70°C for 0.5 h. Trimethylsulphoxonium iodide (962 mg, 4.375 mmol) was added to the mixture and stirred at room temperature for 0.5 h. The aldehyde (33) (700 mg, 4.375 mmol) was added to the mixture at room temperature. After 0.5 h stirring at room temperature, the mixture was extracted with n-hexane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue gave the epoxide (34) (305 mg, 49%) as an oil. δ 7.25 (5H, br s, aryl), 5.95-5.40 (1H, m, 5-H), 5.15-4.80 (2H, m, 6-H_2), 3.15-2.95 (1H, m, 2-H), and 2.75-2.30 (5H, m, 1-H_2, 3-H, 4-H_2).

(3S*,4S*)-4,5-*Epoxy*-3-*phenyl*-1-*pentanal* (25) *and* (3S*,4R*)-4,5-*Epoxy*-3-phenyl-1-*pentanal* (35). —— Ozone was bubbled into a solution of the olefin (34) (280 mg, 1.61 mmol) in dichloromethane (19 ml) at -78°C for 10 min. Dimethyl sulphide (0.5 ml) was added to the mixture at -78°C and the mixture was warmed to room temperature. The mixture was evaporated and the residue was chromatographed. Elution with n-hexane/ethyl acetate (70/30) afforded the aldehyde (35) (120 mg, 42%) as an oil. $\nu_{max.}$ (film) 1715 cm^{-1}; δ 9.75 (1H, t, *J* 1 Hz, CHO), 7.30 (5H, br s, aryl), and 3.20-2.50 (6H, m, 5-H_2, 4-H, 3-H, 2-H_2); *m/z* 176 (*M*+).

Further elution with the same solvent afforded (25) (110 mg, 39%) as an oil. $\nu_{max.}$ (film) 1715 cm^{-1}; δ 9.75 (1H, t, *J* 1 Hz, CHO), 7.30 (5H, br s, aryl), 3.56-3.30 (1H, m, 3-H), 3.22-3.06 (1H, m, 4-H), 2.90-2.66 (3H, m, 2-H_2, 5-H), and 2.55-2.45 (1H, m, 5-H); *m/z* 176 (*M*+).

(1R*,3S*,4S*)-4-*Phenyl*-1,3-*cyclopentanediol* (37). —— Mesyl chloride (106 mg, 0.93 mmol) and triethylamine (94 mg, 0.93 mmol) were added to a stirred solution of the alcohol (10) (170 mg, 0.77 mmol) in dichloromethane (2.0 ml) at 0°C. After 2 h stirring, n-hexane and water were added to the mixture and the organic layer was washed with water, and dried (Na_2SO_4). Evaporation and recrystallisation of the residue afforded the mesylate of (10) (173 mg, 75%) as needles; m.p.71-72°C (ether-n-hexane); $\nu_{max.}$ ($CHCl_3$) 1730 and 1360 cm^{-1}; δ 7.28 (5H, br s, aryl), 5.34-5.10 (1H, m, 1-H), 5.00-4.75 (1H, m, 3-H), 3.52 (1H, dt, *J* 9, 10 Hz, 4-H), 2.95-1.85 (4H, m, 2-H_2, 5-H_2), 2.58 (3H, s, SO_2Me), and 2.02 (3H, s, COMe); *m/z* 203 (*M*+-$MeSO_3$).

The mesylate of (10) (170 mg, 0.57 mmol) was refluxed with cesium acetate (329 mg, 1.71 mmol) and 18-crown-6 (75 mg, 0.29 mmol) in toluene (5.0 ml) for 6 h. n-Hexane was added and the mixture was washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue with n-hexane/ethyl acetate (80/20) afforded (1R*,3S*,4S*)-1,3-*diacetoxy-4-phenylcyclopentane* (101 mg, 68%) as a colourless oil. $\nu_{max.}$ (film) 1730 cm^{-1}; δ 7.26 (5H, br s, aryl), 5.65-5.30 (2H, m, 1-H, 3-H), 3.70-3.35 (1H, m, 4-H), 2.75-2.00 (4H, m, 2-H_2, 5-H_2), and 2.05 and 1.75 (each 3H, each s, COMe x 2); *m/z* 262 (*M*+).

A solution of the diacetate prepared above (90 mg, 0.34 mmol) and sodium methoxide (44 mg, 0.82 mmol) in methanol (1.0 ml) was stirred at room temperature for 1 h. Aqueous ammonium chloride and dichloromethane were added to the mixture, and layers were separated. The organic layer was dried (Na_2SO_4) and evaporated, and the residue was chromatographed. Elution with ethyl acetate gave (37) (53 mg, 88%) as a colourless oil; $\nu_{max.}$ (film) 3540 cm^{-1}; δ 7.28 (5H, br s, aryl), 4.60-4.44 and 4.40-4.24 (each 1H, each m, 1-H, 3-H), 3.65-3.30 (1H, m, 4-H), and 2.56-1.70 (6H, m, 2-H_2, 5-H_2, OH x 2); *m/z* 178 (*M*+).

Methyl 5-*Hydroxy*-3-*oxo*-5-*phenylpentanoate* (39). —— Methyl acetoacetate (9.28 g, 80 mmol) was added dropwise to a stirred suspension of sodium hydride (50% dispersion in mineral oil, 4.752 g, 88 mmol) in tetrahydrofuran (200 ml) over 10 min at 0°C. n-Butyllithium (15% in n-hexane, 50.96 ml, 80 mmol) was added to the reaction mixture at 0°C over 10 min. Benzaldehyde (8.48 g, 80 mmol) was added to the mixture at 0°C and stirred at the same temperature for 15 min. The mixture was poured into ice-water, neutralized with 10% hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), evaporated, and the residue was chromatographed. Elution with n-hexane/ethyl acetate yielded (39) (15.76 g, 89%) as an oil. $\nu_{max.}$ (film) 1749 cm^{-1}; δ 7.30 (5H, br s, aryl), 5.20-4.96 (1H, m, 5-H), 3.64 (3H, s, OMe), 3.42 (2H, s, 2-H_2), and 2.95-2.80 (2H, m, 4-H_2).

(4R*,6S*)- *and* (4R*,6R*)-4-*Acetoxy*-6-*phenyltetrahydropyran*-2-*one* (40) *and* (41). —— Sodium borohydride (578 mg, 15.20 mmol) was added to a stirred solution of the ketone (39) (9.0 g, 40.54 mmol) in methanol (40 ml) at 0°C and stirred for 0.5 h. Dichloromethane and water were added to the mixture and the organic layer was dried (Na_2SO_4) and evaporated. The residue was stirred with lithium hydroxide monohydrate (1.702 g, 40.52 mmol) in methanol (40 ml) at room temperature for 15 h. The mixture was evaporated and the residue was stirred with acetic acid (3.0 ml) and acetic anhydride (20 ml) at room temperature for 3 h. Evaporation of the mixture and chromatography of the residue with n-hexane/ethyl acetate (50/50) afforded a 1:1 mixture of (40) and (41) (6.35 g, 69%). A part of the mixture was chromatographed again with n-hexane/ethyl acetate (80/20) as the eluent to give (40) as needles; m.p. 87-88°C (n-hexane); (Found: C, 66.65; H, 6.05. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.0%); $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}; δ 7.30 (5H, br s, aryl), 5.62 (1H, dd, *J* 4, 10 Hz, 6-H), 5.32 (1H, quintet, *J* 4 Hz, 4-H), 2.90-2.80 (2H, m, 5-H_2), 2.50-1.90 (2H, m, 3-H_2), and 2.12 (3H, s, COMe); *m/z* 234 (*M*+).

Further elution with the same solvent gave (41) as needles, m.p. 85-86°C (n-hexane); (Found: C, 66.6; H, 6.1. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.0%); $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}; δ 7.38 (5H, br s, aryl), 5.32 (1H, ddd, *J* 6.3, 6.6, and 8.4 Hz, 4-H), 5.24 (1H, dd, *J* 4, 12 Hz, 6-H), 3.05 (1H, ddd, *J* 0.7, 6.3, and 18 Hz, 5-H), 2.64 (1H, dd, *J* 5, 18 Hz, 3-H), 2.70-1.70 (2H, m, 3-H, 5-H), and 2.02 (3H, s, COMe); *m/z* 234 (*M*+).

(2R*,4R*,6S*)- *and* (2S*,4R*,6S*)-6-*Phenyltetrahydropyran*-2,4-*diol* (26). —— Diisobutylaluminium hydride (1.0 M in dichloromethane, 4.0 ml) was added to a stirred solution of the lactone (40) (468 mg, 2.0 mmol) in tetrahydrofuran (5.0 ml) at -78°C. After stirring 1 h at this temperature, aqueous ammonium chloride was added slowly at room temperature. The mixture was filtered through a pad of Celite, and the layers were separated. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed with n-hexane/ethyl acetate (50/50) as the eluent to give (26) (110 mg, 28%) as needles (dichloromethane/n-hexane), m.p. 116-118°C (Found: C, 67.55; H, 7.25. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.25%); δ 7.36 (5H, br s, aryl), 5.50-4.85 (2H, m, 2-H, 6-H), 4.35-4.05 (1H, m, 4-H), 4.02 (2H, br s, OH x 2), and 2.15-1.50 (4H, m, 3-H_2, 5-H_2); *m/z* 194 (*M*+).

(2R*,4R*,6R*)- *and* (2S*,4R*,6R*)-*6-Phenyltetrahydropyran-2,4-diol* (27). —— The lactone (41) (174 mg, 0.743 mmol) was treated with diisobutylaluminium hydride as above to afford (27) (40 mg, 28%) as a syrup (Found: C, 66.9; H, 7.45. $C_{11}H_{14}O_3{\cdot}0.2H_2O$ requires C, 66.8, H, 7.25%); $\nu_{max.}$($CHCl_3$) 3580 cm^{-1}; δ 7.32 (5H, br s, aryl), 5.55-3.60 (3H, m, 2-H, 4-H, 6-H), 2.45-1.90 (4H, m, 3-H_2, OH x 2), 1.80-1.20 (2H, m, 5-H_2); m/z 194 (*M* +).

(2S*,4R*,6S*)- *and* (2R*,4R*,6S*)-*2,4-Diacetoxy-6-phenyltetrahydropyran* (28) and (29). —— A mixture of the lactol (26) (60 mg, 0.309 mmol), acetic anhydride (0.5 ml), and pyridine (0.5 ml) was allowed to stand at room temperature for 15 h. The mixture was evaporated and the residue was chromatographed. Elution with n-hexane/ethyl acetate (80/20) as the eluent gave the diacetate (28) (56 mg, 65%) as needles, m.p. 81-83°C (n-hexane), (Found: C, 64.85; H, 6.7. $C_{15}H_{18}O_5$ requires C, 64.75; H, 6.55%); $\nu_{max.}$ ($CHCl_3$) 1735 cm^{-1}; δ 7.32 (5H, br s, aryl), 6.15 (1H, dd, *J* 4, 9 Hz, 2-H), 5.36 (1H, quintet, *J* 3 Hz, 4-H), 4.95 (1H, dd, *J* 4, 10 Hz, 6-H), 2.12 and 2.04 (each 3H, each s, COMe x 2), and 2.02-1.66 (4H, m, 3-H_2, 5-H_2); *m/z* 278 (*M* +).

Further elution with the same solvent afforded (29) (5 mg, 6%) as an oil. $\nu_{max.}$ (film) 1735 cm^{-1}; δ 7.35 (5H, br s, aryl), 6.40-6.25 (1H, m, $W_{1/2}$ 6 Hz, 2-H), 5.35-5.14 (2H, m, 4-H, 6-H), 2.14 and 2.08 (each 3H, each s, COMe x 2), and 2.45-1.70 (4H, m, 3-H_2, 5-H_2); *m/z* 279 (*MH* +).

(2R*,4R*,6R*)- *and* (2S*,4R*,6R*)-*2,4-Diacetoxy-6-phenyltetrahydropyran* (30a, b). —— The lactol (27) (35 mg, 0.18 mmol) was treated as above to yield the 1:1 mixture of (30a) and (30b) (35 mg, 70%) as an oil (Found: C, 64.55; H, 6.6. $C_{15}H_{18}O_5$ requires C, 64.75; H, 6.5%); $\nu_{max.}$ (film) 1735 cm^{-1}; δ 7.32 (5H, br s, aryl), 6.50-6.40 (0.5H, m, $W_{1/2}$ 6 Hz, 2-H), 5.86 (0.5H, dd, *J* 2, 10 Hz, 2-H), 5.55-5.00 (1H, m, 4-H), 4.96 (0.5H, dd, *J* 2, 12 Hz, 6-H), 4.56 (0.5H, dd, *J* 2, 12 Hz, 6-H), 2.45-1.55 (4H, m, 3-H_2, 5-H_2), and 2.10 and 2.02 (each 3H, each s, COMe x 2); *m/z* 278 (*M* +).

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