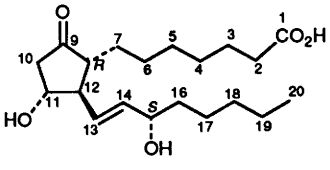
# The Synthesis of Novel Prostaglandin Analogues *via* Cycloaddition Reactions

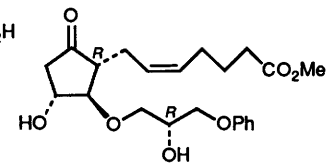
**Eric W. Collington, Harry Finch, and John G. Montana**
*Glaxo Group Research Ltd., Ware, Hertfordshire, SG12 0DP*
**Richard J. K. Taylor** *
*School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ*

The total synthesis of the cyclobutane prostaglandin analogues (**4**) and (**5**), and their subsequent conversion to the γ-lactones (**6**) and (**7**), γ-lactam (**8**) and cyclopentanone (**9**) is described. The cornerstone of the synthetic strategy is the intermolecular [2 + 2] cycloaddition of dichloroketene to a suitably functionalised enol ether.

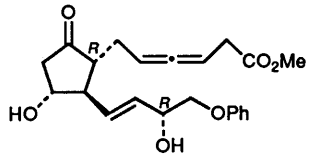
The interest in novel prostaglandins exhibiting pharmacological specificity and increased metabolic stability has led to the synthesis of analogues possessing diverse structural modifications.[1] At present the use of synthetic prostanoids in the treatment of gastric ulcers is attracting considerable attention.[2] Several prostaglandin analogues such as Enprostil (**2**)[3] and Misoprostol (**3**)[4] (Figure 1) have been recognised as potentially useful therapeutic agents in this area. Our own research has shown that prostanoids containing an ether linkage in the lower side-chain, as depicted by GR 35666X (**1**),[5] are potent anti-ulcer compounds.



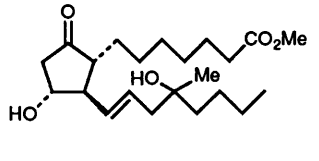
$PGE_1$



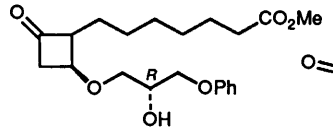
(1)
GR35666X



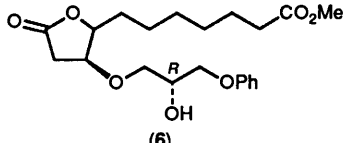
(2)
ENPROSTIL



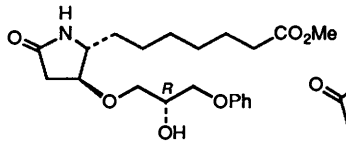
(3)
MISOPROSTOL



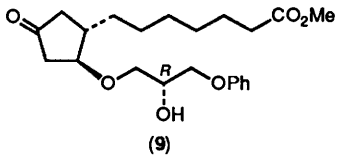
(4)
*trans*—isomer
(5)
*cis*—isomer



(6)
*trans*—isomer
(7)
*cis*—isomer



(8)



(9)

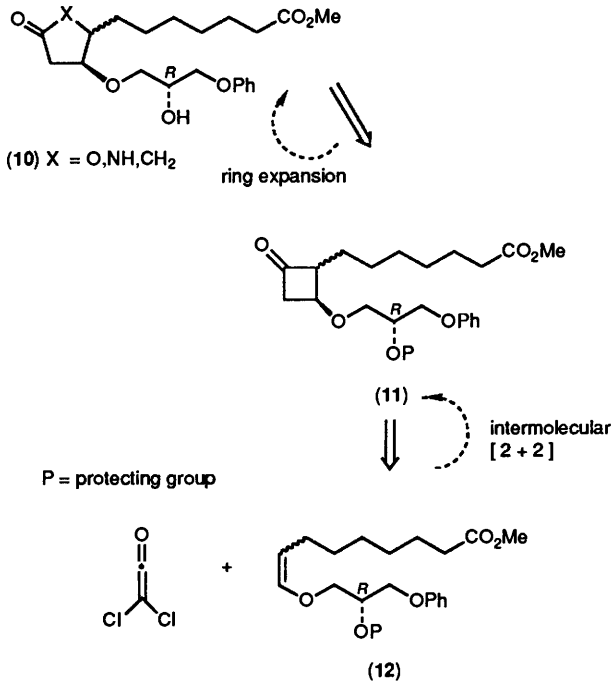
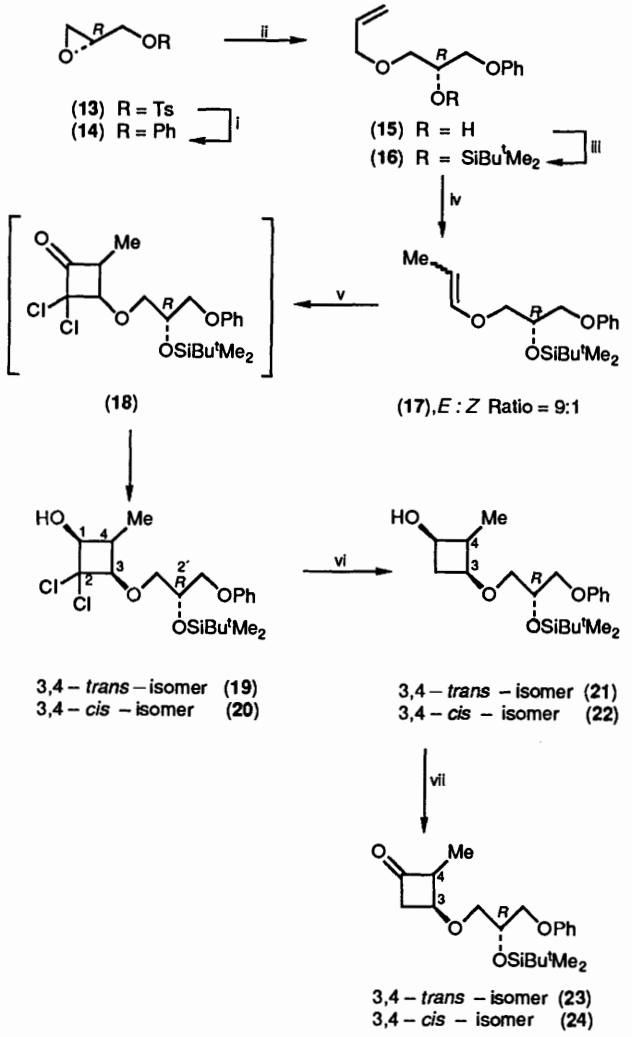



**Figure 1.**

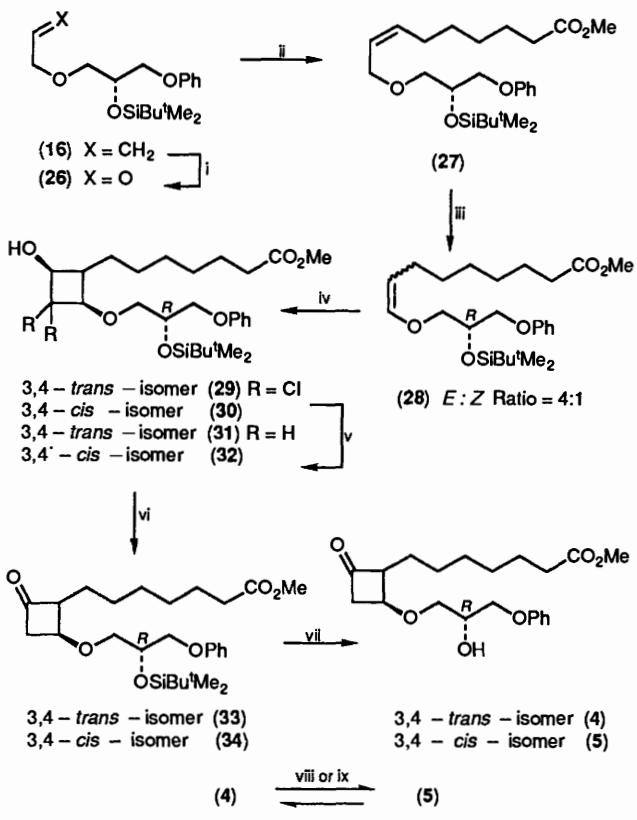
As an extension of this work, we have investigated the pharmacological effects of modifying the cyclopentanone ring of GR 35666X (**1**), with cyclobutanes (**4**) and (**5**), lactones (**6**) and (**7**), lactam (**8**) and cyclopentanone (**9**), as key target molecules. Retrosynthetic analysis (Figure 1) suggested the possibility of preparing the five-membered ring compounds (**10**) by ring-expansion of the corresponding protected cyclobutanones (**11**). An intermolecular [2 + 2] cycloaddition of dichloroketene and a suitably functionalised enol ether (**12**)[6,7] was proposed for the preparation of the crucial cyclobutanone intermediates (**11**).

Model studies were first carried out to assess the viability of the [2 + 2] cycloaddition reaction of dichloroketene with an enol ether (Scheme 1).† It was envisaged that the allyl ether (**16**) could be used as a precursor to the model enol ether (**17**), and also as an intermediate in the synthesis of the more complex

† All synthetic compounds were obtained as stereochemical mixtures relative to the fixed *R*-configuration in the lower side chain. The terms *cis* and *trans* refer to the relative orientations of the side-chains on the cyclobutane ring.




**Scheme 1.** *Reagents:* i, PhOH, NaH, DMF, (77%); ii, $CH_2$=$CHCH_2OH$, NaH, THF, (75%); iii, Bu$^t$Me$_2$SiCl, DMF, imidazole, (98%); iv, $(C_8H_{12})IrH_2(PPh_2Me)_2$, (**25**), $H_2$, THF (95%); v, *a*, $Cl_3CCOCl$, Zn–Cu, THF, *b*, $NaBH_4$, EtOH (80% combined overall yield); vi, $Bu_3SnH$, AIBN, PhH, [87% (**21**) and (**22**)]; vii, PCC, NaOAc, $CH_2Cl_2$, [47% (**23**) and (**24**)].




**Scheme 2.** *Reagents:* i, *a*, $O_3$, $CH_2Cl_2$, *b*, $PPh_3$ (96%); ii, *a*, $Ph_3P^+(CH_2)_6CO_2HBr^-$, KOBu$^t$, THF, *b*, $CH_2N_2$, $Et_2O$ (67%); iii, (**25**), $H_2$, THF (76%); iv, *a*, Zn–Cu, $Cl_3CCOCl$, THF, *b*, $NaBH_4$, EtOH, [51% (**29**), 18% (**30**)]; v, $Bu_3SnH$, AIBN, PhH, {(**31**) [71% from (**29**)]}, {(**32**) [88% from (**30**)]}; vi, PCC, NaOAc, $CH_2Cl_2$, mol. sieves, {(**33**) [69% from (**31**)]}, {(**34**) [57%* from (**32**)]}; vii, HF, $H_2O$, MeCN, {(**4**) [98% from (**33**)]}, {(**5**) [79% from (**34**)]}; viii, DBU, $CH_2Cl_2$, (**14**) [75% (**4**):(**5**) = 9:1]; ix, DBU, $CH_2Cl_2$, (**5**) 95% (**4**):(**5**) = 9:1].

* (**33**) (11%) was also isolated from this reaction.

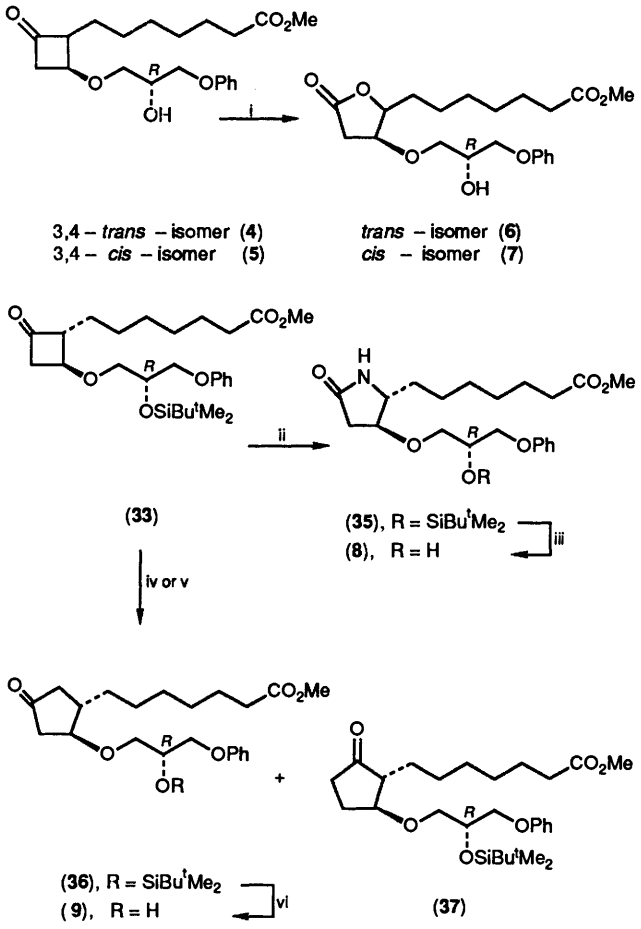
allyl ether (**27**) (Scheme 2). Therefore, a chiral synthesis of the allyl ether (**16**) from commercially available 2*R*-glycidyl tosylate (**13**)[8] was devised. Nucleophilic substitution of the tosylate (**13**) with sodium phenoxide gave the epoxide (**14**). Chiral benzylglycidyl ethers are valuable synthetic intermediates[9,10] and since the completion of this work both *R*-(−)[9] and *S*-(+)[9,10] enantiomers have been prepared from chiral glycidyl tosylates. Nucleophilic cleavage of the epoxide (**14**) with the anion derived from allyl alcohol occurred at the primary site, and the intermediate alcohol (**15**) was protected as the silyl ether (**16**). However, for convenience most of the model studies were carried out using the racemic form of the silyl ether (**16**), derived from the racemic epoxide using the above procedure.

In an attempt to show that Payne Rearrangement[8] had not occurred during nucleophilic substitution of the tosylate (**13**), NMR studies of the alcohol (**15**) using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) were undertaken.[11] These indicated the absence of any of the unwanted *S*-isomer, although the detection limits of this technique were not fully established, and hence it is not possible to state categorically that no rearrangement had taken place.

Isomerisation of the allyl ether (**16**) using the iridium catalyst (**25**)[12] proceeded in excellent yield to give predominantly the *E*-enol ether (**17**). The intermolecular [2 + 2] cycloaddition with dichloroketene, prepared *in situ* by treatment of trichloroacetyl chloride with freshly prepared zinc–copper couple,[7] was successful. However, the dichloroketone (**18**) was unstable to chromatography on silica gel, and direct reduction to the alcohols (**19**) and (**20**) was necessary for product isolation. It should be noted that no attempt was made to separate the diastereoisomers resulting from this reaction. Thus structure (**19**) represents a mixture of (1*S*,3*R*,4*S*,2′*R*) and (1*R*,3*S*,4*R*,2′*R*) diastereoisomers, the 2′*R* configuration being determined by the 2*R*-tosylate (**13**) employed as starting material. [Structures (**4**)–(**9**), (**20**)–(**24**), and (**29**)–(**37**) represent similar diastereomeric mixtures.]† It is noteworthy that the reduction of the ketone (**18**) was stereospecific, with only the β-cyclobutanols (**19**) and (**20**) being formed. Confirmation of the relative stereochemistry of the groups on the cyclobutane ring was achieved by NOE studies. The stereospecific nature of the reduction can be explained if one considers the angle of attack of the hydride nucleophile. The approach of the hydride nucleophile required to generate the α-isomer is sterically hindered by the bulky β-side-chain, whereas hydride attack to produce the β-isomer meets with little steric hindrance.

Dechlorination of the dichloro alcohols (**19**) and (**20**) using

† See footnote on p. 1839.




**Scheme 3.** *Reagents:* i, $AcO_2H$, NaOAC, $CH_2Cl_2$ −15 °C, {(**16**) [94% from (**4**)]}, {(**7**) [89% from (**5**)]}; ii, *a*, MSH, $CH_2Cl_2$, *b*, $SiO_2$ pH = 3.9 (78%); iii, HF, MeCN, $H_2O$ (78%); iv, $CH_2N_2$, $Et_2O$, MeOH, 0–5 °C, 19% (**36**), 19% (**37**), 30% (**33**); v, $TMSCHN_2$, $BF_3$–$OEt_2$, $CH_2Cl_2$, −78 °C, 52% (**36**); vi, HF, MeCN, $H_2O$ (77%).

tributyltin hydride afforded a reasonable yield of the cyclobutanols (**21**) and (**22**), which were oxidised to the ketones (**23**) and (**24**) using pyridinium chlorochromate (PCC).[13]

After the encouraging results of the model study, the same methodology was utilised in the synthesis of the cyclobutane prostaglandins (**4**) and (**5**) (Scheme 2). Ozonolysis of the allyl ether (**16**) and conversion of the aldehyde (**26**) into the alkene (**27**) by Wittig olefination proceeded in excellent yield. Isomerisation of the allyl ether (**27**) into the enol ether (**28**) was less stereoselective than the model system, but still provided predominantly the *E*-isomer. Intermolecular cycloaddition of the enol ether (**28**; *E*:*Z* ratio = 4:1) with dichloroketene and subsequent sodium borohydride reduction afforded the alcohols (**29**) and (**30**).* The two isomers were readily separable by silica gel chromatography and hence were used individually in subsequent reactions.

Oxidation of the cyclobutanols (**31**) and (**32**) with PCC was successful, although the yields were improved significantly when the reaction was carried out in the presence of 4 Å molecular sieves.[14,15] Also, oxidation of the *cis* cyclobutanol (**32**) gave a small quantity of the *trans* cyclobutanone (**33**). Deprotection of the two ketones (**33**) and (**34**) proceeded in excellent yield providing the prostaglandin analogues (**4**) and (**5**). Base catalysed isomerisation of each of the isomers (**4**) and (**5**) provided an equilibrium mixture containing 10% of the *cis* isomer (**5**) by NMR analysis. This result indicates that the *trans* ketone (**33**) obtained from oxidation of the *cis* alcohol (**32**) was probably generated *via* base catalysed epimerisation of the *cis* ketone (**34**).

Baeyer–Villiger oxidation of the ketones (**4**) and (**5**) using peracetic acid[16] occurred with total regioselectivity and afforded the corresponding γ-lactones (**6**) and (**7**) in excellent yield (Scheme 3). The NMR spectra of these compounds showed a large geminal coupling of the 11-H protons (*J* 18 Hz) at δ 2.80 ppm and δ 2.67 ppm respectively, illustrating the presence of the expected lactone isomers. These results were also in agreement with those observed by Greene and co-workers in the ring expansion of similar prostaglandin analogues.[17]

Similarly, treatment of the cyclobutanone (**33**) with mesitylenesulphonyl hydroxylamine[17,18] followed by passage of the reaction mixture through acid washed silica gel[19,20] gave the γ-lactam (**35**) in 78% yield in a regioselective manner. The structure of the amide isomer (**35**) was confirmed by $^1H$ NMR spectroscopy. A large geminal coupling (*J* 17 Hz) was observed for the 11-H ring protons α to the amide carbonyl group at δ 2.60 ppm.[17] Deprotection of the silyl ether (**35**) using aqueous hydrogen fluoride provided the desired alcohol (**8**).

Ring expansion of the cyclobutanone (**33**) to the cyclopentanones (**36**) and (**37**) using diazomethane was less regioselective.[17] Some success was achieved in the methanol catalysed reaction,[21] with low yields of the two homologated isomers (**36**) and (**37**) being isolated. The Lewis acid catalysed diazomethane ring expansion[21] caused rapid decomposition of the ketone (**33**), however, a modified diazomethane reagent, trimethylsilyldiazomethane,[22] was higher yielding and more regioselective, affording solely the 10-oxo isomer (**36**).

In order to assess the possibility of using these prostaglandin analogues to treat peptic ulcers, their ability to inhibit ethanol-induced lesions in the rat stomach[23] was tested. Unfortunately, none of the compounds described here were more active than $PGE_2$ in this test.

In conclusion, this work demonstrates that a wide range of novel cyclobutane prostaglandin analogues can be obtained in good overall yield *via* [2 + 2] cycloaddition reactions of dichloroketene and a suitably functionalised enol ether. Furthermore, these prostanoids can also be utilised *via* highly regiospecific ring expansion reactions to provide further unique prostanoids.

## Experimental

$^1H$ and $^{13}C$ NMR spectra ($CDCl_3$ solutions) were recorded on a Brücker WM250MHz spectrometer with tetramethylsilane (TMS) as an internal standard. IR spectra were obtained on a Perkin-Elmer 357 spectrometer as a bromoform solution unless otherwise stated. GLC separations were performed on a Perkin-Elmer 8500 machine using a 10 m × 0.22 mm fused silica capillary column. A standard work-up procedure involved addition of ammonium chloride solution to the reaction mixture, followed by extraction of the two phase mixture with the specified solvent. The combined organic extracts were washed with saturated brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the crude product.

Light petroleum refers to the fraction of b.p. 40–60 °C. Ether refers to diethyl ether. Anhydrous tetrahydrofuran (THF) was obtained by distilling the commercial product from sodium and benzophenone under an atmosphere of nitrogen. Anhydrous triethylamine was obtained by distillation of the commercial product from potassium hydroxide. All other reagents were dried by distillation of the respective compounds onto activated 4 Å molecular sieves under a nitrogen atmosphere. Zinc–copper couple,[7] bis(diphenylmethylphos-

* See footnote on p. 1839.

phine)cyclo-octadiene iridium(I)hexafluorophosphate (**25**),[24] t-butyl-*N*-mesitylene-sulphonyloxycarbamate[25] and (6-carboxyhexyl)triphenylphosphonium bromide[26] were prepared according to literature procedures.

Trichloroacetyl chloride was liberated from any trichloroacetic acid and HCl by *in vacuo* distillation of the commercial product prior to use. The distillate was then used immediately. Oil free sodium hydride was prepared by stirring a slurry of commercially available 60% sodium hydride dispersion on oil with anhydrous hexane under a nitrogen atmosphere for 10 min. The solvent was removed by syringe leaving the oil free sodium hydride ready for use.

Column chromatography was performed on Merck Kieselgel 9385 silica gel using flash chromatography.[27] The dimensions of the packed column and the eluant are given. Acid washed silica gel was prepared by adjusting the pH of a slurried suspension of Merck Kieselgel 9385 silica gel in deionised water to 3.8–4.0 by the slow addition of 2M sulphuric acid. After pH equilibration (*ca.* 30 min) the silica gel was filtered off and dried under vacuum (150 °C at 20 mmHg) for 24 h.

(R)-(*Phenoxymethyl*)*oxirane* (**14**).—A solution of phenol (2.81 g, 29.86 mmol) in dry dimethylformamide (DMF) (15 ml) was added to a stirred suspension of oil free sodium hydride (819 mg, 34.13 mmol) in dry DMF (30 ml) at 20 °C under a nitrogen atmosphere. After 30 min a solution of *R*-glycidyl tosylate (**13**) (6.49 g, 28.44 mmol) in dry DMF (15 ml) was added and stirring was continued for 4.5 h. The reaction mixture was partitioned between ice cold aqueous sodium hydroxide (1M; 150 ml) and ether (100 ml). The aqueous phase was extracted with ether (3 × 30 ml), and the combined extracts were washed with water (20 ml) and brine (2 × 20 ml), dried and concentrated under reduced pressure to yield a colourless oil (5.13 g). Purification by flash chromatography (40 mm column, chloroform) yielded a crude sample of the title compound. Further purification by vacuum distillation gave the *title compound* as a colourless oil (3.30 g, 77%) b.p. 90 °C at 0.05 mmHg; $R_f$ 0.31 ($CHCl_3$); (Found: C, 72.3; H, 7.0. $C_9H_{10}O_2$ requires C, 72.0; H, 6.8%); $[\alpha]_D$ −3.6° (*c* 0.33 in $CHCl_3$) [lit.,[9] $[\alpha]_D$ −5.4° (*c* 5 in $C_6H_6$)]; $\nu_{max}(CHBr_3)$ 1 600, 1 505, and 1 259 $cm^{-1}$; $\delta_H$ 2.75 (1 H, q, *J* 3 Hz), 2.94 (1 H, t, *J* 4 Hz), 3.29–3.40 (1 H, m), 3.90–4.02 (1 H, dd, *J* 5 and 11 Hz), 4.15–4.28 (1 H, dd, *J* 3 and 11 Hz), and 6.90–7.30 (5 H, m).

(R)-1-*Phenoxy*-3-(*prop*-2-*enyloxy*)*propan*-2-*ol* (**15**).—A solution of allyl alcohol (25.5 ml, 0.41 mol) in dry THF (80 ml) was added over 20 min to a stirred suspension of oil free sodium hydride (2.96 g, 0. 12 mol) in dry THF (80 ml) at 50 °C under a nitrogen atmosphere. The resultant suspension was stirred at 50 °C for 15 min. A solution of the epoxide (**14**) (8.51 g, 0.06 mol) in dry THF (80 ml) was added over 20 min and the resultant solution was stirred at 50 °C for 24 h. Standard work-up using dichloromethane as solvent gave a yellow oil (10.3 g). Purification by flash chromatography [10 cm column; ether–light petroleum (1:3)] yielded the *title compound* as a straw coloured oil (9.30 g, 75%); $R_f$ 0.12 (ether–light petroleum, 1:3); (Found: C, 69.0; H, 8.0. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%; $[\alpha]_D$ −3.0° (*c* 0.56 in MeOH); $\nu_{max}$ 3 580, 1 600, and 1 500 $cm^{-1}$; $\delta_H$ 2.60 (1 H, d, *J* 5 Hz), 3.55–3.65 (2 H, m), 4.00–4.10 (4 H, m), 4.20–4.25 (1 H, m), 5.20–5.35 (2 H, m), 5.90–6.00 (1 H, m), and 6.90–7.30 (5 H, m).

(R)-*t-Butyldimethyl*[1-(*phenoxymethyl*)-2-(*prop*-2-*enyloxy*)*ethoxy*]*silane* (**16**).—t-Butylchlorodimethylsilane (269 mg, 1.80 mmol) was added to a stirred solution of the alcohol (**15**) (300 mg, 1.44 mmol) and imidazole (244 mg, 3.60 mmol) in dry DMF (5 ml) under a nitrogen atmosphere. After 18 h water (40 ml) was added and the aqueous phase was extracted with ether (3 × 40 ml). The combined extracts were washed with brine (20 ml), dried and concentrated under reduced pressure to yield a colourless oil (463 mg). Purification by flash chromatography [20 mm column; ether–light petroleum (1:10)] yielded the *title compound* as a colourless oil (445 mg, 98%); $R_f$ 0.60 (ether–light petroleum, 1:10); (Found: C, 67.0; H, 9.4. $C_{18}H_{30}O_3Si$ requires C, 66.9; H, 9.3%); $[\alpha]_D$ −8.9° (*c* 0.54 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 1 600, 1 510, and 1 248 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 3.45–3.60 (2 H, m), 3.92–4.05 (4 H, m), 4.10–4.25 (1 H, m), 5.12–5.30 (2 H, m), 5.80–5.95 (1 H, m), and 6.90–7.30 (5 H, m).

[R-(E)]-*t-Butyldimethyl*[1-(*phenoxymethyl*)-2-(*prop*-1-*enyloxy*)*ethoxy*]*silane* (**17**).—The iridium complex (**25**) (3 mg, 5.3 μmol) was added to a solution of the allyl ether (**16**) (110 mg, 0.37 mmol) in dry THF (2 ml), under a nitrogen atmosphere. The suspension was degassed and stirred under a hydrogen atmosphere for *ca.* 30 sec (until a colourless solution was obtained). The solution was degassed again, and stirred under a nitrogen atmosphere for 2.5 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography [10 mm column; ether–light petroleum (1:10)] to yield the *title compound* as a colourless oil (105 mg, 95%); $R_f$ 0.50 (ether–light petroleum, 1:20); (Found: C, 67.1; H, 9.2. $C_{18}H_{30}O_3Si$ requires C, 66.9; H, 9.3%); $[\alpha]_D$ −4.5° (*c* 0.18 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 1 600, 1 500, and 1 247 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.55 (3 H, dd, *J* 2 and 2 Hz), 3.64–4.04 (4 H, m), 4.22 (1 H, m), 4.69–4.79 (1 H, m), 5.97 (1 H, d, *J* 9 Hz, MeCH=C*H*, *Z*-isomer), 6.24 (1 H, d, *J* 16 Hz, MeCH=C*H*, *E*-isomer), and 6.90–7.30 (5 H, m).

[1α,3α(R),4α]-*and*[1α,3α(R),4β]-2,2-*Dichloro*-3-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-4-*methylcyclobutanol* (**19**) *and* (**20**).—A solution of freshly distilled trichloroacetyl chloride (0.09 ml, 0.75 mmol) in dry THF (5 ml) was added over 5 min to a stirred suspension of the enol ether (**17**) (*E*:*Z* ratio = 9:1) (219 mg, 0.74 mmol) and freshly prepared zinc–copper couple (176 mg, 2.72 mmol) in dry THF (3 ml) under a nitrogen atmosphere. After 20 min the excess zinc was filtered off and the filtrate was cooled to 0–5 °C. A preformed solution of sodium borohydride (51 mg, 1.36 mmol) in ethanol (10 ml) was added and the reaction mixture was stirred at 0–5 °C for 20 min. Brine (50 ml) was added and the aqueous phase was extracted with dichloromethane (3 × 30 ml). The combined extracts were dried and concentrated under reduced pressure to yield an orange oil (372 mg). Purification by flash chromatography [25 mm column; ether–light petroleum (1:3)] yielded the title compound (**19**) as a colourless oil (156 mg, 50%); $R_f$ 0.19 (ether–light petroleum, 1:3); $\nu_{max}(CHBr_3)$ 3 560, 3 350, 1 600, 1 510, and 1 246 $cm^{-1}$; $\delta_H$ 0.12 (6 H, s), 0.90 (9 H, s), 1.27 (3 H, 2 × d, *J* 7 and 7 Hz), 1.93 (1 H, m), 2.14 (1 H, d, *J* 2 Hz), 3.24–3.28 (1 H, 2 × t, *J* 7 and 7 Hz), 3.45 (1 H, m), 3.60–3.70 (2 H, m), 3.85–4.13 (3 H, m), and 6.90–7.30 (5 H, m); $\delta_C$ 158.70 (ArC), 129.40 (ArC), 120.80 (ArC), 114.50 (ArC), 89.05 (4-C), 78.40 (3-C), 72.60 (5-C), 72.00 and 71.80 [8-C (diastereoisomers)], 70.30 and 70.20 [9-C (diastereoisomers)], 69.60 (7-C), 44.00 (2-C), 25.80 [SiC(*Me*)$_3$], 18.02 [Si*C*(Me)$_3$], 15.50 (1-C), and −4.56 and −4.71 [OSi*Me*$_2$, (diastereoisomers)].

Further elution gave a (2:1) mixture of the stereoisomers (**19**) and (**20**) from this reaction (89 mg, 30%). The two isomers were distinguished by $^{13}C$ NMR spectroscopy. The stereoisomer (**20**) showed the same $^{13}C$ NMR spectrum except for $\delta_C$ 74.20 (3-C), 37.40 (2-C), and 6.40 (1-C).

(1α,2α,3α)- *and* (1α,2β,3α)-3-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-2-*methylcyclobutanol* (**21**) *and* (**22**).—A solution of the α,α-dichlorocyclobutanols (**19**) and (**20**) (ratio

2:1) (126 mg, 0.29 mmol), tributyltin hydride (0.3 ml, 1.16 mmol) and 2,2′-azobis(2-methylpropionitrile) (5 mg, 0.02 mmol) in dry benzene (5 ml) was heated at reflux under a nitrogen atmosphere for 48 h. During this period, further tributyltin hydride (0.3 ml) and 2,2′-azobis(2-methylpropionitrile) (5 mg) were added after 8 h and 24 h respectively. The solvent was removed under reduced pressure and the residue (1.3 g) was purified by flash chromatography [30 mm column; ether–light petroleum (1:3)] to yield the title compounds as a colourless oil [92 mg, 87%, ratio (**21**):(**22**) = 3:2]; $R_f$ 0.30 (ether–light petroleum, 1:1); $\nu_{max}(CHBr_3)$ 3 590, 1 600, 1 500, and 1 246 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.19 (3 H, d, *J* 7 Hz), 1.62 (1 H, d, *J* 3 Hz), 1.67 (1 H, m), 1.93 (1 H, m), 2.62 (1 H, m), 3.17 (1 H, m), 3.35–3.53 (3 H, m), 3.80–4.13 (3 H, m), and 6.90–7.30 (5 H, m); $\delta_C$ 158.80 (ArC), 129.41 (ArC), 120.60 (ArC), 114.52 (ArC), 72.65 (5-C), 70.50 (8-C), 70.30 (9-C), 69.94 (7-C), 66.50 (3-C), 49.56 and 49.51 [2-C (diastereoisomers)], 38.40 (4-C), 25.80 [SiC(*Me*)$_3$], 18.30 [Si*C*(Me)$_3$], 16.20 (1-C), and −4.62 to −4.57 [Si*Me*$_2$, (diastereoisomers)].

trans- *and* cis-3-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-2-*methylcyclobutanone* (**23**) *and* (**24**).—Pyridinium chlorochromate (71 mg, 0.33 mmol) was added to a stirred suspension of sodium acetate (66 mg, 0.81 mmol) and the alcohols (**21**) and (**22**) (80 mg, 0.22 mmol) in dry dichloromethane (5 ml) at 0–5 °C under a nitrogen atmosphere. The resultant suspension was stirred at 0–5 °C for 3 h and 20 °C for 2.5 h. Further pyridinium chlorochromate (71 mg) and sodium acetate (66 mg) were added and stirring was continued for 3 h. The reaction mixture was filtered through a silica pad (acid-washed, pH = 3.9). The filtrate was washed with copper sulphate solution (10%; 2 × 20 ml) and brine (20 ml), dried and concentrated under reduced pressure to yield a colourless oil (79 mg). Purification by flash chromatography using acid washed silica (pH = 3.9) [20 mm column; ether–light petroleum (1:3)] yielded the *title compound* (**23**) as a colourless oil (16 mg, 20%); $R_f$ 0.37 (ether–light petroleum, 1:3); (Found: C, 65.4; H, 8.9. $C_{20}H_{32}O_4Si$ requires C, 65.8; H, 8.8%); $\nu_{max}(CHBr_3)$ 1 780, 1 600, 1 505, and 1 248 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.18 (3 H, d, *J* 6 Hz), 3.00–3.20 (2 H, m), 3.24–3.28 (1 H, m), 3.50–3.70 (2 H, m), 3.85–4.05 (3 H, m), 4.20 (1 H, m), and 6.90–7.30 (5 H, m); $\delta_C$ 207.50 (3-C), 158.70 (ArC), 129.40 (ArC), 120.80 (ArC), 114.40 (ArC), 72.90 (5-C), 71.66 and 71.74 [8-C (diastereoisomers)], 70.40 (9-C), 69.01 (7-C), 61.40 (2-C), 51.47 (4-C), 25.80 [SiC(*Me*)$_3$], 18.20 [Si*C*(Me)$_3$], 12.00 (1-C), and −4.60 to −4.56 [Si*Me*$_2$ (diastereoisomers)].

Further elution gave a mixture of the *trans* and *cis* isomers (**23**) and (**24**) (14 mg, 18%) and then the *cis* cyclobutanone (**24**) (7 mg, 9%). The *cis* isomer (**24**) was distinguished from its stereoisomer by $^{13}C$ NMR spectroscopy; $\delta_C$ 209.80 (3-C), 67.87 (5-C), 58.60 (2-C), 51.98 (4-C), and 7.55 (1-C).

(R)-2-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-*ethanal* (**26**).—Ozone was bubbled through a stirred solution of the alkene (**16**) (865 mg, 2.94 mmol) and Sudan III (2 mg) in dry dichloromethane (15 ml) at −78 °C. After 1.5 h the reaction vessel was purged with nitrogen, and triphenylphosphine (1.72 g, 6.56 mmol) was added. The reaction mixture was allowed to warm to 20 °C over 1 h and then concentrated under reduced pressure to yield a pink solid (3.24 g). Purification by flash chromatography [50 mm column; ether–light petroleum (1:3)] yielded the *title compound* as a tan coloured oil (837 mg, 96%); $R_f$ 0.40 (ether–light petroleum, 1:1); (Found: C, 62.9; H, 8.7. $C_{17}H_{28}O_4Si$ requires C, 62.9; H, 8.6%); $[\alpha]_D$ −4.9° (*c* 0.39 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 1 734, 1 600, and 1 248 $cm^{-1}$; $\delta_H$ 0.15 (6 H, s), 0.90 (9 H, s), 3.50–3.55 (2 H, m), 3.75–4.15 (5 H, m, 5-H), 6.90–7.30 (5 H, m), and 9.62 (1 H, s).

[R-(Z)]-*Methyl* 9-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]*non*-7-*enoate* (**27**).—A mixture of potassium t-butoxide (350 mg, 3.12 mmol) and 6-(carboxyhexyl) triphenylphosphonium bromide (735 mg, 1.56 mmol) in dry THF (10 ml) was stirred at 20 °C under a nitrogen atmosphere for 1 h. A solution of the aldehyde (**26**) (155 mg, 0.52 mmol) in dry THF (10 ml) was added and stirring was continued for 4 h. Standard work-up using ether as solvent yielded an orange gum. The residue was dissolved in ether (10 ml) and treated with an excess of ethereal diazomethane. The reaction vessel was purged with nitrogen and concentrated under reduced pressure to yield an orange solid (489 mg). Purification by flash chromatography [30 mm column; ether–light petroleum (1:8)] yielded the *title compound* as a pale yellow oil (156 mg, 67%); $R_f$ 0.37 (ether–light petroleum, 1:8); (Found: C, 66.5; H, 9.6. $C_{25}H_{42}O_5Si$ requires C, 66.6; H, 9.4%); $[\alpha]_D$ −60.0° (*c* 0.56 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 1 738, 1 600, 1 500, and 1 246 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.30–1.40 (4 H, m), 1.60 (2 H, m), 2.05 (2 H, m), 2.30 (2 H, t, *J* 7 Hz), 3.50–3.55 (2 H, m), 3.70 (3 H, s), 3.80–4.20 (5 H, m), 5.50–5.60 (2 H, m), and 6.90–7.30 (5 H, m); ($t_R$ 14.62 min, 74.9%; $t_R$ 14.72 min, 25.1%; Temp. = 100–300 °C).

[R-(E)] *and* [R-(Z)]-*Methyl* 9-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]*non*-8-*enoate* (**28**).—A suspension of the allyl ether (**27**) (4.6 g, 10.20 mmol) and the iridium complex (**25**) (400 mg, 498 μmol) in dry THF (30 ml) was degassed and stirred under a hydrogen atmosphere for *ca.* 3 min. The resultant solution was degassed again and stirred under a nitrogen atmosphere for 2 days. The solvent was removed under reduced pressure and the residue was purified by flash chromatography [10 cm column; ether–light petroleum (1: 10)] to yield the *title compound* as a colourless oil (3.48 g, 76%; *E*:*Z* ratio = 4:1); $R_f$ 0.45 (ether–light petroleum, 1:10); (Found: C, 66.8; H, 9.4. $C_{25}H_{42}O_5Si$ requires C, 66.6; H, 9.4%); $[\alpha]_D$ −7.5° (*c* 0.32 in MeOH); $\nu_{max}(CHBr_3)$ 1 735, 1 600, 1 505, and 1 245 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.25–1.31 (6 H, m), 1.55 (2 H, m), 1.85 (2 H, m), 2.30 (2 H, m), 3.67 (3 H, s), 3.70–4.05 (4 H, m), 4.10–4.30 (1 H, m), 4.70–4.83 (1 H, dt, *J* 5 and 12 Hz), 5.95 (1 H, d, *J* 6 Hz, *Z*-isomer), 6.25 (1 H, d, *J* 13 Hz, *E*-isomer), and 6.90–7.30 (5 H, m).

[1α,2β(R),4β] *and* [1α,2α(R),4α] *Methyl* 3,3-*Dichloro*-2-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-4-*hydroxycyclobutylheptanoate* (**29**) *and* (**30**).—A solution of freshly distilled trichloroacetyl chloride (0.16 ml, 1.39 mmol) in dry THF (10 ml) was added over 10 min to a stirred suspension of the enol ether (**28**) (472 mg, 1.05 mmol, *E*:*Z* ratio = 4:1) and freshly prepared zinc–copper couple (270 mg, 4.17 mmol) in dry THF (5 ml) under a nitrogen atmosphere. The resultant suspension was stirred at 20 °C for 20 min, the excess zinc–copper couple was filtered off and the filtrate was diluted with ethanol (20 ml). The solution was cooled to 0–5 °C and sodium borohydride (306 mg, 8.08 mmol) was added. After 15 min brine (30 ml) was added and the aqueous phase was extracted with ether (3 × 30 ml). The combined extracts were dried and concentrated under reduced pressure to yield a brown oil (480 mg). Purification by flash chromatography [30 mm column; ether–light petroleum (1:4)] yielded the *title compound* (**30**) as a colourless oil (106 mg, 18%); $R_f$ 0.34 (ether–light petroleum, 1:2); (Found: C, 57.8; H, 8.2; Cl, 12.7. $C_{27}H_{44}Cl_2O_6Si$ requires C, 57.5; H, 7.9; Cl, 12.6%); $[\alpha]_D$ −6.9° (*c* 0.30 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 3 550, 1 728, 1 600, and 1 248 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.20–1.70 (10 H, m), 1.95 (1 H, m), 2.20–2.35 (2 H, m), 2.44–2.48 (1 H, dd, *J* 4 and 11 Hz), 3.25 (1 H, m), 3.48 (1 H, m), 3.60–3.72 (2 H, m), 3.66 (3 H, s), 3.80–4.02 (2 H, m), 4.21 (1 H, m), and 6.90–7.30 (5 H, m); $\delta_C$ 174.20 (1-C), 158.70 (ArC), 129.40 (ArC), 120.80 (ArC), 114.40 (ArC), 91.32 (10-C),

82.04 (11-C), 75.15 (9-C), 71.68 (14-C), 70.24 (15-C), 69.47 (13-C), 51.50 (1-OMe), 42.56 (8-C), 34.00 (2-C), 21.89 (7-C), 26.80–28.98 (4-C, 5-C, and 6-C), 25.80 [SiC(*Me*)$_3$], 24.80 (3-C), 18.17 [Si*C*(Me)$_3$], and −4.65 to −4.70 [Si*Me*$_2$ (diastereoisomers)].

Further elution gave the *trans*-isomer (**29**) as a colourless oil (300 mg, 15%). This isomer could be distinguished from the *cis* isomer (**30**) by $^{13}$C NMR, the peaks that appeared different in the *trans* isomer are shown below (see above for comparison); $R_f$ 0.30 (ether–light petroleum, 1:2); (Found: C, 57.8; H, 8.2; Cl, 12.8. $C_{27}H_{44}Cl_2O_6Si$ requires C, 57.5; H, 7.9; Cl, 12.6%); $[\alpha]_D$ −9.0° (*c* 0.37 in $CHCl_3$); $\delta_C$ 89.12 (10-C), 83.94 (11-C), 48.90 (8-C), and 31.31 (7-C).

[1α,2β(R),4β]-*Methyl* 2-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-4-*hydroxycyclobutylheptanoate* (**31**).—The *title compound* was prepared from the dichloro alcohol (**29**) (180 mg, 0.31 mmol), tributyltin hydride (2.26 ml, 8.40 mmol), and 2,2′-azobis(2-methylpropionitrile) (87 mg, 0.35 mmol) in 71% yield (108 mg) using the procedure described for compounds (**21**) and (**22**); $R_f$ 0.24 (ether–light petroleum, 1:1); (Found: C, 65.7; H, 9.6. $C_{27}H_{46}O_6Si$ requires C, 65.6; H, 9.4%); $[\alpha]_D$ −5.0° (*c* 0.28 in $CHCl_3$); $\nu_{max}$($CHBr_3$) 3 600, 1 728, 1 600, 1 500, and 1 248 cm$^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.20–1.70 (12 H, m), 2.05 (1 H, m), 2.29 (2 H, t, *J* 7 Hz), 2.66 (1 H, m), 3.21 (1 H, dq, *J* 4 and 11 Hz), 3.35–3.55 (3 H, m), 3.67 (3 H, s), 3.80–4.13 (3 H, m), and 6.90–7.30 (5 H, m); $\delta_C$ 174.20 (1-C), 158.80 (ArC), 129.30 (ArC), 120.60 (ArC), 114.40 (ArC), 71.60 and 71.50 [11-C (diastereoisomers)], 70.50 and 70.40 [14-C (diastereoisomers)], 70.00 (15-C), 69.50 (13-C), 65.60 (9-C), 54.70 (8-C), 51.40 (1-OMe), 38.30 (10-C), 34.00 (2-C), 32.20 (7-C), 29.30 (4-C), 29.00 (5-C), 27.00 (6-C), 25.80 [SiC(*Me*)$_3$], 24.80 (3-C), 18.20 [Si*C*(Me)$_3$], and −4.66 to −4.59 (Si*Me*$_2$).

[1α,2α(R),4α]-*Methyl* 2-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-4-*hydroxycyclobutylheptanoate* (**32**).—The *title compound* was prepared from the dichloro alcohol (**30**) (30 mg, 0.05 mmol), tributyltin hydride (0.16 ml, 0.60 mmol) and 2,2′-azobis(2-methylpropionitrile) (5 mg, 0.02 mmol) in 88% yield (14 mg) using the procedure described for compounds (**21**) and (**22**); $R_f$ 0.21 (ether–light petroleum, 1:1); (Found: C, 65.7; H, 9.5. $C_{27}H_{46}O_6Si$ requires C, 65.6; H, 9.4%); $[\alpha]_D$ −8.0° (*c* 0.36 in $CHCl_3$). Again, the major analytical difference with the *trans* isomer (**31**) was illustrated by $^{13}$C NMR. The major differences being $\delta_C$ 46.57 (8-C), 28.44 (6-C), and 22.21 (7-C).

[1α,2β(R)]-*Methyl* 2-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-4-*oxocyclobutylheptanoate* (**33**).—Pyridinium chlorochromate (657 mg, 3.03 mmol) was added to a stirred suspension of the alcohol (**31**) (506 mg, 1.01 mmol), sodium acetate (586 mg, 7.07 mmol) and powdered 4 Å molecular sieves (500 mg) in dry dichloromethane (25 ml) at 0–5 °C under a nitrogen atmosphere. The resultant suspension was stirred at 0–5 °C for 2 h. The suspension was filtered through a silica pad (acid washed, pH = 3.9), and the filtrate was washed with copper sulphate solution (20%; 2 × 20 ml) and brine (20 ml), dried and concentrated under reduced pressure to yield a brown oil (605 mg). Purification by flash chromatography on acid washed silica (pH = 3.9) [30 mm column; ether–light petroleum (1:2)] yielded the *title compound* as a colourless oil (346 mg, 69%); $R_f$ 0.60 (ether–light petroleum, 1:1); (Found: C, 65.7; H, 9.1. $C_{27}H_{44}O_6Si$ requires C, 65.8; H, 9.0%); $[\alpha]_D$ −0.7° (*c* 0.28 in $CHCl_3$); $\nu_{max}$($CHBr_3$) 1 778, 1 730, 1 600, 1 510, and 1 248 cm$^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.20–1.70 (10 H, m), 2.28 (2 H, t, *J* 7 Hz), 2.90–3.20 (3 H, m), 3.50–3.60 (2 H, m), 3.67 (3 H, s), 3.90–4.00 (3 H, m), 4.18 (1 H, m), and 6.90–7.30 (5 H, m); $\delta_C$ 207.80 (9-C), 174.10 (1-C), 158.70 (ArC), 129.40 (ArC), 120.80 (ArC), 114.40 (ArC), 71.65 and 71.55 [11-C (diastereoisomers)], 70.67 (14-C), 70.31 (15-C), 69.80 (13-C), 66.76 and 66.73 [8-C (diastereoisomers)], 51.44 (10-C), 51.40 (1-OMe), 34.00 (2-C), 29.09 (5-C), 28.70 (4-C), 27.49 (7-C), 26.96 (6-C), 25.80 [Si(*Me*)$_3$], 24.90 (3-C), 18.20 [Si*C*(Me)$_3$], and −4.55 to −4.86 [Si*Me*$_2$ (diastereoisomers)].

[1α,2α(R)]-*Methyl* 2-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-4-*oxocyclobutylheptanoate* (**34**).—The title compound was prepared from the alcohol (**32**) (256 mg, 0.52 mmol), pyridinium chlorochromate (338 mg, 1.56 mmol), sodium acetate (259 mg, 3.12 mmol) and powdered 4 Å molecular sieves (250 mg) in 57% yield (141 mg) using the procedure described for compound (**33**). The analytical differences compared to the *trans* isomer (**33**) are: $R_f$ 0.55 (ether–light petroleum, 1:1); $[\alpha]_D$ −6.7° (*c* 0.34 in $CHCl_3$); $\delta_H$ 4.32 (1 H, m); $\delta_C$ 209.40 (9-C), 71.49 (15-C), 64.01 and 63.97 [8-C (diastereoisomers)], and 23.55 (7-C).

The *trans* isomer (**33**) was also isolated from this reaction as a colourless oil (26 mg, 11%) and was identical to the sample previously described according to TLC and NMR analysis.

[1α,2β(R)]-*Methyl* 2-(2-*Hydroxy*-3-*phenoxypropoxy*)-4-*oxocyclobutylheptanoate* (**4**).—Aqueous hydrogen fluoride (40%; 0.02 ml, 0.53 mmol) was added to a stirred solution of the silyl ether (**33**) (76 mg, 0.15 mmol) in acetonitrile (2 ml) at 0–5 °C. The resultant solution was stirred at 0–5 °C for 1.5 h and 20 °C for 3.5 h. Further hydrogen fluoride (0.02 ml) was added and stirring was continued for 1.5 h. Standard work-up using ether as solvent gave a colourless oil (69 mg). Purification by flash chromatography [20 mm column; ether–light petroleum (3:1)] yielded the *title compound* as a colourless oil (56 mg, 98%); $R_f$ 0.22 (ether–light petroleum, 3:1); (Found: C, 66.3; H, 8.2. $C_{21}H_{30}O_6$ requires C, 66.6; H, 8.0%); $[\alpha]_D$ +0.5° (*c* 0.41 in $CHCl_3$); $\nu_{max}$($CHBr_3$) 3 480, 1 780, 1 738, 1 600, and 1 500 cm$^{-1}$; $\delta_H$ 1.20–1.75 (10 H, m), 2.30 (2 H, t, *J* 7 Hz), 2.55 (1 H, m), 2.90–3.30 (3 H, m), 3.60–3.70 (2 H, m), 3.66 (3 H, s), 3.95–4.10 (3 H, m), 4.15–4.25 (1 H, m), and 6.90–7.30 (5 H, m).

[1α,2α(R)]-*Methyl* 2-(2-*Hydroxy*-3-*phenoxypropoxy*)-4-*oxocyclobutylheptanoate* (**5**).—The *title compound* was prepared from the silyl ether (**34**) (120 mg, 0.24 mmol) and 40% aqueous hydrogen fluoride (0.02 ml, 0.53 mmol) in 79% yield (71 mg) using the above procedure. All analytical data was comparable to the *trans* isomer (**4**) except the following: $R_f$ 0.33 (ether–light petroleum, 5:1); (Found: C, 66.5; H, 8.1. $C_{21}H_{30}O_6$ requires C, 66.6; H, 8.0%); $[\alpha]_D$ −2.4° (*c* 0.49 in $CHCl_3$); $\delta_H$ 4.30–4.40 (1 H, m, 14-H).

*Isomerisation of* [1α,2α(R)] *and* [1α,2β(R)]-*Methyl* 2-(2-*Hydroxy*-3-*phenoxypropoxy*)-4-*oxocyclobutylheptanoate* (**4**) *and* (**5**).—One drop of 1,8-diazabicyclo[5.4.0]undec-7-ene was added to a stirred solution of the ketone (**5**) (8 mg) in dichloromethane (5 ml) at 20 °C. After 4 h the reaction mixture was purified directly by flash chromatography on acid washed silica (pH = 3.9) [10 mm column; ether–light petroleum (5:1)] to yield a mixture of the *trans* isomer (**4**):*cis* isomer (**5**) (9:1) as a colourless oil (6 mg, 95%). The isomer ratio was determined by NMR, utilising integration of the 12-H [4.15–4.25 (12-H, *trans* isomer); 4.30–4.40 (12-H, *cis* isomer)]. For the remaining analytical data see above.

Isomerisation of the *trans* isomer (**4**) (6 mg) under identical conditions to those described above gave an identical mixture of the *cis* and *trans* isomers (**4**) and (**5**) as a colourless oil (5 mg, 75%).

[2α,3β(R)]-*Methyl Tetrahydro*-3-(2-*hydroxy*-3-*phenoxypropoxy*)-5-*oxo*-2-*furylheptanoate* (**6**).—Peracetic acid (5.26M in acetic acid; 0.13 ml, 0.65 mmol) was added to a stirred suspension of the ketone (**4**) (91 mg, 0.24 mmol) and sodium

acetate (65 mg, 0.78 mmol) in dry dichloromethane (4 ml) at −15 °C under a nitrogen atmosphere. After stirring the reaction mixture for 1 h at −15 °C and 6.5 h at −25 °C, it was allowed to warm to 20 °C and diluted with dichloromethane (10 ml). The organic phase was washed consecutively with sodium sulphite solution (1.5M; 15 ml), sodium bicarbonate solution (8%, 15 ml) and brine (15 ml), dried and concentrated under reduced pressure to yield a colourless oil (101 mg). Purification by flash chromatography on acid washed silica (pH = 3.9) [15 mm column; ether–light petroleum (4:1)] yielded the *title compound* as a colourless oil (89 mg, 94%); $R_f$ 0.20 (ether–light petroleum, 5:1); (Found: C, 63.6; H, 7.6. $C_{21}H_{30}O_7$ requires C, 63.9; H, 7.6%); $[\alpha]_D$ +0.5° (*c* 0.39 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 3 590, 1 778, 1 730, 1 600, and 1 500 $cm^{-1}$; $\delta_H$ 1.30–1.70 (10 H, m), 2.30 (2 H, t, *J* 8 Hz), 2.50 (2 H, m), 2.80 (1 H, dd, *J* 6 and 18 Hz), 3.60–3.65 (2 H, m), 3.69 (3 H, s), 3.95–4.05 (3 H, m), 4.15 (1 H, m), 4.45 (1 H, m) and 6.90–7.30 (5 H, m); $\delta_C$ 174.50 (10-C), 174.10 (1-C), 158.40 (ArC), 129.60 (ArC), 121.40 (ArC), 114.50 (ArC), 85.00 and 84.90 [12-C (diastereoisomers)], 79.60 (8-C), 70.24 (15-C), 69.06 (16-C), 68.50 (14-C), 51.40 (1-OMe), 34.90 (11-C), 33.90 (2-C), 33.40 (7-C), 29.20 (5-C), 28.80 (4-C), 24.90 (6-C), and 24.70 (3-C).

[2α,3α(R)]-*Methyl Tetrahydro*-3-(2-*hydroxy*-3-*phenoxypropoxy*)-5-*oxo*-2-*furylheptanoate* (**7**).—The *title compound* was prepared from the ketone (**5**) (28 mg, 0.07 mmol), peracetic acid (0.04 ml) and sodium acetate (20 mg, 0.23 mmol) in 89% yield (24 mg) using the above procedure; $R_f$ 0.14 (ether–light petroleum, 5:1); (Found: C, 63.7; H, 7.9. $C_{21}H_{30}O_7$ requires C, 63.9; H, 7.6%); $[\alpha]_D$ +0.4° (*c* 0.51 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 3 580, 1 775, 1 725, 1 600, and 1 510 $cm^{-1}$; $\delta_H$ 1.20–1.90 (10 H, m), 2.28 (2 H, dd, *J* 2 and 7 Hz), 2.58–2.62 (1 H, d, *J* 6 Hz), 2.67 (2 H, d, *J* 18 Hz), 3.50–3.75 (2 H, m), 3.67 (3 H, s), 3.95–4.06 (2 H, m), 4.14–4.17 (2 H, m), 4.43 (1 H, m), and 6.90–7.30 (5 H, m); $\delta_C$ the $^{13}C$ NMR was identical to the *trans* isomer (**6**) apart from the following: 84.00 (12-C), 76.70 (8-C), and 35.90 (11-C).

[2α,3β(R)]-*Methyl* 3-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]*tetrahydro*-5-*oxo*-1H-*pyrrol*-2-*ylheptanoate* (**35**).—Butyl-*N*-mesitylenesulphonyloxycarbamate (80 mg, 0.30 mmol) was added to trifluoroacetic acid (0.3 ml, 3.90 mmol) at 0–5 °C.[15] After 10 min the reaction mixture was poured into a stirred emulsion of ice-water and dichloromethane (1:1, 20 ml). The aqueous layer was removed and the organic phase was washed with sodium bicarbonate solution (8%; 10 ml), dried and concentrated to a small volume (*ca.* 5 ml).

The solution of mesitylene sulphonyl hydroxylamine was added to a stirred solution of the ketone (**33**) (98 mg, 0.19 mmol) in dichloromethane (3 ml) at 20 °C. The resultant solution was stirred at 20 °C for 5 h and then purified directly by flash chromatography on acid washed silica (pH = 3.9) [25 mm column; ether–light petroleum (1:2) ⟶ 10% methanol in ether] to yield the *title compound* as a pale yellow oil (74 mg, 78%); $R_f$ 0.26 ($Et_2O$); (Found: C, 63.8; H, 8.6; N, 2.9. $C_{27}H_{45}NO_6Si$ requires C, 63.9; H, 8.9; N, 2.8%); $[\alpha]_D$ −5.8° (*c* 0.26 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 3 425, 1 725, 1 690, 1 600, 1 500, and 1 245 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.25–1.70 (10 H, m), 2.25–2.40 (3 H, m), 2.60 (1 H, dd, *J* 2 and 17 Hz), 3.45–3.60 (3 H, m), 3.67 (3 H, s), 3.80–4.00 (3 H, m), 4.10–4.20 (1 H, m), and 6.90–7.30 (5 H, m).

[2α,3β(R)]-*Methyl Tetrahydro*-3-(2-*hydroxy*-3-*phenoxypropoxy*)-5-*oxo*-1H-*pyrrole*-2-*heptanoate* (**8**).—The *title compound* was prepared from the silyl ether (**35**) (61 mg, 0.12 mmol) and 40% aqueous hydrogen fluoride (0.012 ml, 0.38 mmol) in 78% yield (42 mg) using the procedure described for compound (**4**); $R_f$ 0.25 (EtOAc); (Found: C, 63.7; H, 8.0; N, 3.8. $C_{21}H_{31}NO_6$ requires C, 64.0; H, 7.9; N, 3.6%); $[\alpha]_D$ −1.6° (*c* 0.25 in MeOH); $\nu_{max}(CHBr_3)$ 3 435, 1 730, 1 700, 1 600, and 1 500 $cm^{-1}$; $\delta_H$ 1.25–1.70 (10 H, m), 2.25–2.40 (3 H, m), 2.50 (1 H, m), 2.60 (1 H, dd, *J* 2 and 17 Hz), 3.45–3.60 (3 H, m), 3.67 (3 H, s), 3.80–4.00 (3 H, m), 4.15–4.20 (1 H, m), and 6.90–7.30 (5 H, m).

[1α,2β(R)]-*Methyl* 2-[2-(*t-Butyldimethylsilyloxy*)-3-*phenoxypropoxy*]-4-*oxocyclopentylheptanoate* (**36**).—Trimethylsilyldiazomethane (10% in hexane; 26 mg, 0.23 mmol) was added to a stirred solution of the ketone (**33**) (83 mg, 0.16 mmol) and boron trifluoride–diethyl ether (0.03 ml, 0.23 mmol) in dry dichloromethane (3 ml) at −78 °C under a nitrogen atmosphere. The resultant solution was stirred at −78 °C for 1 h. Standard work-up using ether as solvent yielded a colourless oil (86 mg). Purification by flash chromatography on acid washed silica (pH = 3.9) [25 mm column; ether–light petroleum (1:2)] yielded the title compound as a colourless oil (42 mg, 52%); $R_f$ 0.14 (ether–light petroleum, 1:3); $[\alpha]_D$ −2.9° (*c* 0.82 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 1 735, 1 600, 1 500, and 1 248 $cm^{-1}$; $\delta_H$ 0.10 (6 H, s), 0.90 (9 H, s), 1.10–1.70 (10 H, m), 1.88 (1 H, dd, *J* 6 and 18 Hz), 2.10–2.50 (5 H, m), 2.53 (1 H, d, *J* 4 Hz), 3.45–3.60 (2 H, m), 3.67 (3 H, s), 3.82–4.00 (3 H, m), 4.15 (1 H, m), and 6.90–7.30 (5 H, m); $\delta_C$ 216.20 (10-C), 174.20 (1-C), 158.80 (ArC), 129.40 (ArC), 120.80 (ArC), 114.40 (ArC), 82.10 (12-C), 71.27 and 70.31 [15-C (diastereoisomers)], 70.51 (16-C), 69.60 (14-C), 51.40 (1-OMe), 43.80 (11-C), 42.70 (9-C), 41.90 (8-C), 34.00 (2-C), 33.20 (7-C), 29.30 (4-C), 29.00 (5-C), 27.60 (6-C), 25.80 [SiC(*Me*)$_3$], 24.80 (3-C), 18.20 [Si*C*(Me)$_3$], and −4.59 to −4.68 [Si*Me*$_2$ (diastereoisomers)].

[1α,2β(R)]-*Methyl* 2-(2-*Hydroxy*-3-*phenoxypropoxy*)-4-*oxocyclopentylheptanoate* (**9**).—The *title compound* was prepared from the silyl ether (**36**) (45 mg, 0.09 mmol) and 40% aqueous hydrogen fluoride (0.012 ml, 0.38 mmol) in 77% yield (27 mg) using the procedure described for compound (**4**); $R_f$ 0.29 (ether–light petroleum, 3:1); (Found: C, 67.6; H, 8.1. $C_{22}H_{32}O_6$ requires C, 67.3; H, 8.2%); $[\alpha]_D$ +0.6° (*c* 0.33 in $CHCl_3$); $\nu_{max}(CHBr_3)$ 3 580, 3 450, 1 736, 1 600, and 1 500 $cm^{-1}$; $\delta_H$ 1.25–1.65 (10 H, m), 1.85 (1 H, dd, *J* 6 and 18 Hz), 2.20–2.35 (5 H, m), 2.50–2.60 (2 H, m), 3.60–3.65 (2 H, m), 3.67 (3 H, s), 3.80–4.05 (3 H, m), 4.15 (1 H, m), and 6.90–7.30 (5 H, m).

## References


1 A. Mitra, 'The Synthesis of Prostaglandins,' Wiley Interscience, New York, 1977; 'New Synthetic Routes to Prostaglandins and Thromboxanes,' eds. S. M. Roberts and P. Scheinmann, Academic Press, London, 1982; R. F. Newton, S. M. Roberts, and R. J. K. Taylor, *Synthesis*, 1984, 449.

2 S. J. Sontag, *Drugs*, 1986, **32**, 445; S. J. Sontag and E. J. Hines, *Am. J. Gastroenterol.*, 1986, **81** (11), 1021; D. Branski, P. Sharoh, and A. Abrahamov, *J. Pediatr. Gastroenterol. Nutr.*, 1986, **5** (6), 853.

3 R. M. Eglen, C. M. Cornett, L. K. Dubuque, L. L. Jacobson, W. W. Montgomery, and R. L. Whiting, *Br. J. Pharmacol.*, 1989, **96**, 175P; J. J. Reeves, K. T. Bunce, R. L. G. Sheldrick, and R. Stables, *ibid.*, 1988, **95**, 805P.

4 P. W. Collins, E. Z. Dajani, D. R. Driskill, M. S. Bruhn, C. J. Jung, and R. Pappo, *J. Med. Chem.*, 1977, **20** (9), 1152.

5 E. W. Collington, H. Finch, and D. B. Judd, BP 2,174,702A/1986.

6 A. E. Greene and F. Charbonnier, *Tetrahedron Lett.*, 1985, **26**, 5525.

7 W. T. Brady, *Tetrahedron*, 1981, **37**, 2949.

8 J. M. Klunder, S. Y. Ko, and K. B. Sharpless, *J. Org. Chem.*, 1986, **51**, 3710; Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.

9 H. S. Bynn and R. Bittman, *Tetrahedron Lett.*, 1989, **30**, 2751.

10 J. M. Klunder, T. Onami, and K. B. Sharpless, *J. Org. Chem.*, 1989, **54**, 1295.

11 D. J. Hoover and W. H. Pirkle, *Top. Stereochem.*, 1982, 263.

12 D. Baudry, M. Ephritikhine, and H. Felkin, *J. Chem. Soc., Chem. Commun.*, 1978, 694.
13 G. Piancatelli, A. Scettri, and M. D'Auria, *Synthesis*, 1982, 245.
14 C. L. Stevens, S. Czernecki, C. Georgoulis, and K. Vijayakumaran, *Tetrahedron Lett.*, 1985, **26**, 1699.
15 K. Antonakis and J. Herscovici, *J. Chem. Soc., Chem. Commun.*, 1980, 561.
16 H. O. House, 'Modern Synthetic Reactions 2nd Ed.,' pp. 321–329, W. A. Benjamin, New York, 1972.
17 A. E. Greene, J. P. Deprés, and P. Crabbé, *Tetrahedron*, 1981, **37**, 621.
18 Y. Tamura, J. Minamiikawa, and M. Ikeda, *Synthesis*, 1977, 1.
19 A. Costa, R. Mestres, and J. M. Riego, *Synth. Commun.*, 1982, **12**, 1003.
20 G. A. Olah and A. P. Fung, *Synthesis*, 1979, 537.
21 H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Am. Chem. Soc.*, 1960, **82**, 4099.
22 N. Hashimoto, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, 1982, **30**, 119.
23 E. R. Lacy and S. Ito, *Gastroenterology*, 1982, **83**, 619.
24 L. M. Haines and E. Singleton, *J. Chem. Soc., Dalton Trans.*, 1972, 1891.
25 J. G. Krause, *Synthesis*, 1972, 140.
26 K. Kato, S. Ohkawa, S. Terao, Z. Terashita, and N. Nishikawa, *J. Med. Chem.*, 1988, **28**, 287.
27 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

*Paper* 9/03530C
*Received* 17*th August* 1989
*Accepted* 18*th December* 1989