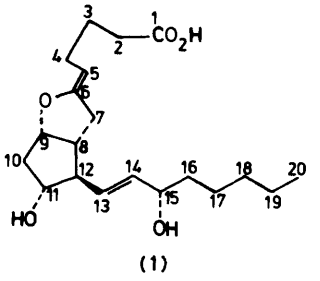
Synthetic Approaches to 11-Deoxyhomoprostacyclin Analogues

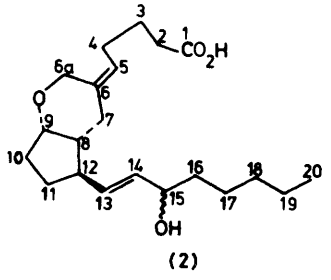
By **Andrew J. Dixon** and **Richard J. K. Taylor,***† The Chemistry Department, The Open University, Milton Keynes MK7 6AA
Roger F. Newton,* **Alan H. Wadsworth,** and **Graham Klinkert,** Glaxo Group Research Ltd., Ware, Hertfordshire SG12 0DJ

A number of synthetic approaches to the title compounds are described. The key synthetic intermediates, the allylcyclopentanone (4) and the methoxyallylcyclopentanone (30) have been prepared from cyclopent-2-enone using the organocuprate conjugate-addition–enolate-alkylation reaction. The selective functionalisation of the allylic double bond in the ketone (4) and protected derivatives of the alcohol (7) has been attempted using bromine in acetic acid, *N*-bromosuccinimide in aqueous dimethyl sulphoxide, and iodine–silver chromate. A number of interesting observations made during these investigations are reported. A successful synthesis of *Z*- and *E*-11-deoxyhomoprostacyclin (2) and (3) from the methoxyallylcyclopentanone (30) is described.

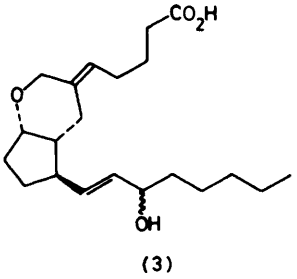
THE remarkable biological properties of prostacyclin (PGI_2) (1) have stimulated an intense research effort to prepare synthetic analogues that are sufficiently stable to be used therapeutically.[1] As part of our programme to prepare 11-deoxyprostaglandin analogues using the organocuprate conjugate-addition–enolate-alkylation reaction [2] we set out to synthesise the homoprostacyclin analogues (2) and (3). We anticipated that by replacing the labile enol-ether moiety of prostacyclin with an allylic ether grouping in (2) and (3) we would obtain the desired stability.



(1)



(2)

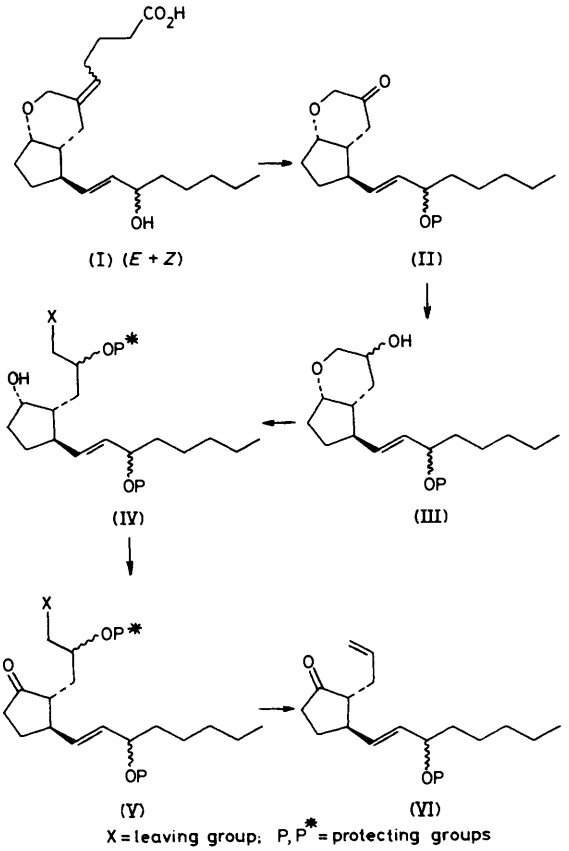


(3)

a; 15*S*
b; 15*R*

Prostacyclin numbering scheme for compounds (1)—(3)

A retrosynthetic analysis enabled several synthetic approaches to be identified but the most appealing from our viewpoint was the one illustrated in Scheme 1. The target molecules (I) should be formed from the ketone (II) by way of the Wittig reaction, and (II) in turn should be readily formed from the alcohol (III) which could well be prepared by the cyclisation of a protected halohydrin (IV) followed by selective deprotection; compound (IV)



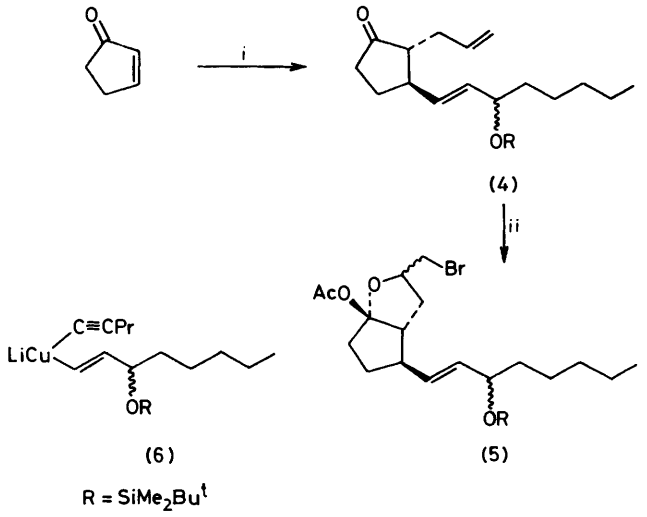
SCHEME 1 Retrosynthetic analysis

in turn should be available from the reduction of the ketone (V). Finally we envisaged that the regioselective functionalisation of the allyl cyclopentanone (VI) should lead to compound (V).

A synthetic route of this type was particularly attractive as we have recently devised a convergent synthesis of the allyl cyclopentanone (4) using the organocuprate

† *Present address:* School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ.

conjugate-addition–enolate-alkylation reaction as shown in Scheme 2.[2,*] We hoped to prepare a compound of type (V) (Scheme 1) by treatment of the ketone (4) with bromine in acetic acid. However, the keto-group participated in this reaction, the product being the bicyclic acetate (5) which underwent ready hydrolysis on silica to give the corresponding hemiacetal (5; Ac replaced by H).



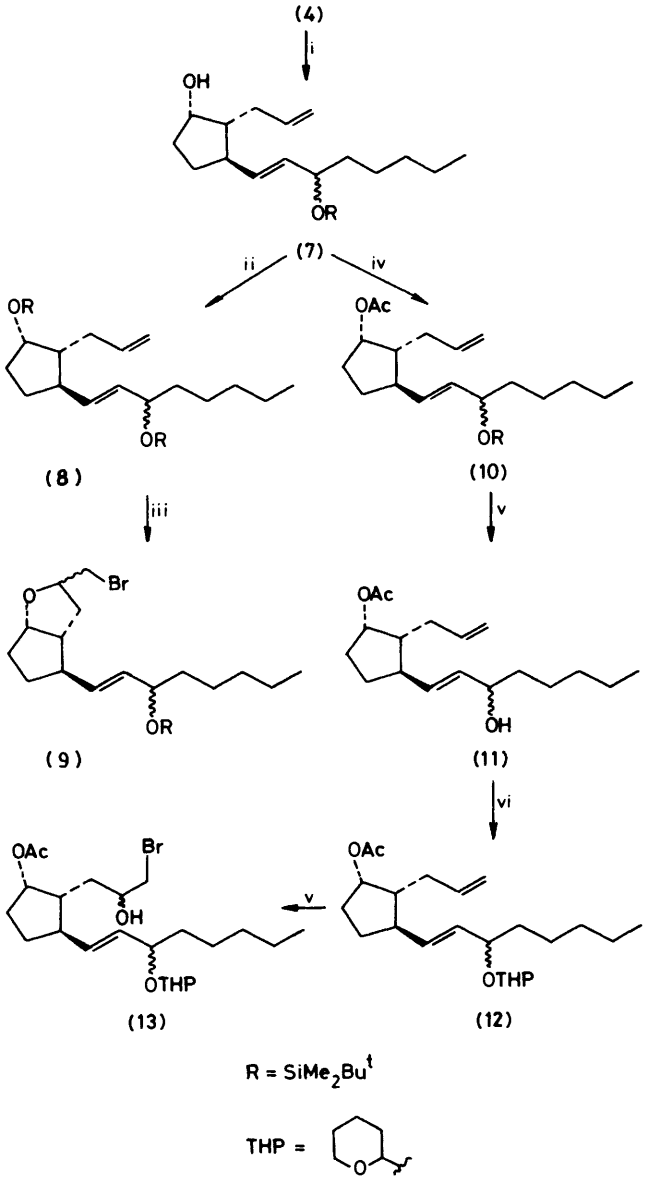
SCHEME 2 *Reagents*: i, (6), Et_2O, −78 °C then allyl bromide–liquid NH_3 (ref. 2); ii, Br_2, AcOH

In an attempt to overcome interference by the oxygen substituent at C-1, the ketone (4) was stereoselectively reduced to the alcohol (7) in 92% yield using potassium tri-s-butylborohydride (Scheme 3) as previously described (ref. 2). Treatment of the corresponding t-butyldimethylsilyl ether (8) with bromine in acetic acid, however, gave only the bicyclic ether (9), again resulting from neighbouring-group participation by the 1-oxygen substituent of compound (8).

In the alternative procedure depicted in Scheme 3 the alcohol (7) was converted into the acetate (10) which was treated with *N*-bromosuccinimide (NBS) in aqueous dimethyl sulphoxide (DMSO) [3] in order to prepare the corresponding bromohydrin. The only product isolated under these conditions, however, was the desilylated alcohol (11) which was obtained in 79% yield. We have since shown [4] that the use of NBS in aqueous DMSO is a useful alternative to the standard procedures [5] for removal of t-butyldimethylsilyl protecting groups. To avoid this complication the 3′-tetrahydropyranyloxy-derivative (12) was formed which, on treatment with NBS in aqueous DMSO, was cleanly converted into the bromohydrin (13).

Straightforward protecting-group manipulation should convert compound (13) into an intermediate of type (IV) which could presumably be readily transformed into the target molecules (2) and (3) by the procedure shown in Scheme 1. Our belief that this synthetic route could be successful was reinforced when Skuballa published a synthesis of the 11α-hydroxylated † derivatives of compounds (2) and (3) using a similar approach (Scheme 4).[6]

In view of the length of the bromohydrin route we sought a more direct synthesis by investigating alternative methods of functionalising the allyl side-chain. Approaches involving the regioselective epoxidation [2] and nitromercuriation of the alcohol (7), which again illustrated the facile involvement of the alcohol oxygen substituent, were unsuccessful. We next decided to investigate the direct conversion of the allyl double bond



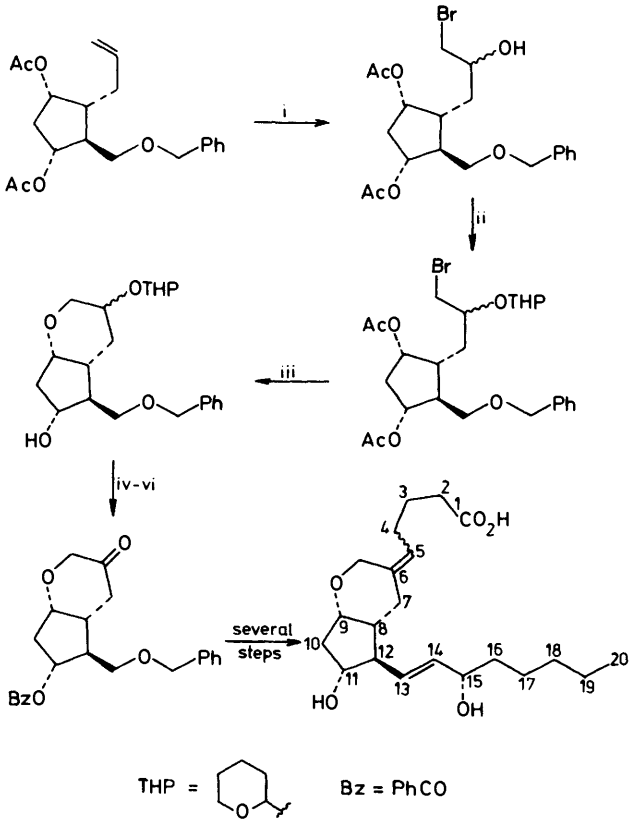
SCHEME 3 *Reagents*: i, $KBHBu^s_3$ (ref. 2); ii, Bu^tMe_2SiCl; iii, Br_2, AcOH; iv, Ac_2O; v, NBS, DMSO–H_2O; vi, $CH_2[CH_2]_2CH{=}CH{\cdot}O$, H^+

* All synthetic compounds are racemic mixtures of 3′*R*- and 3′*S*-diastereoisomers. Systematic numbering is used throughout the text unless it is indicated that prostaglandin/prostacyclin numbering [see (2)] is being employed.

† Prostaglandin numbering scheme.

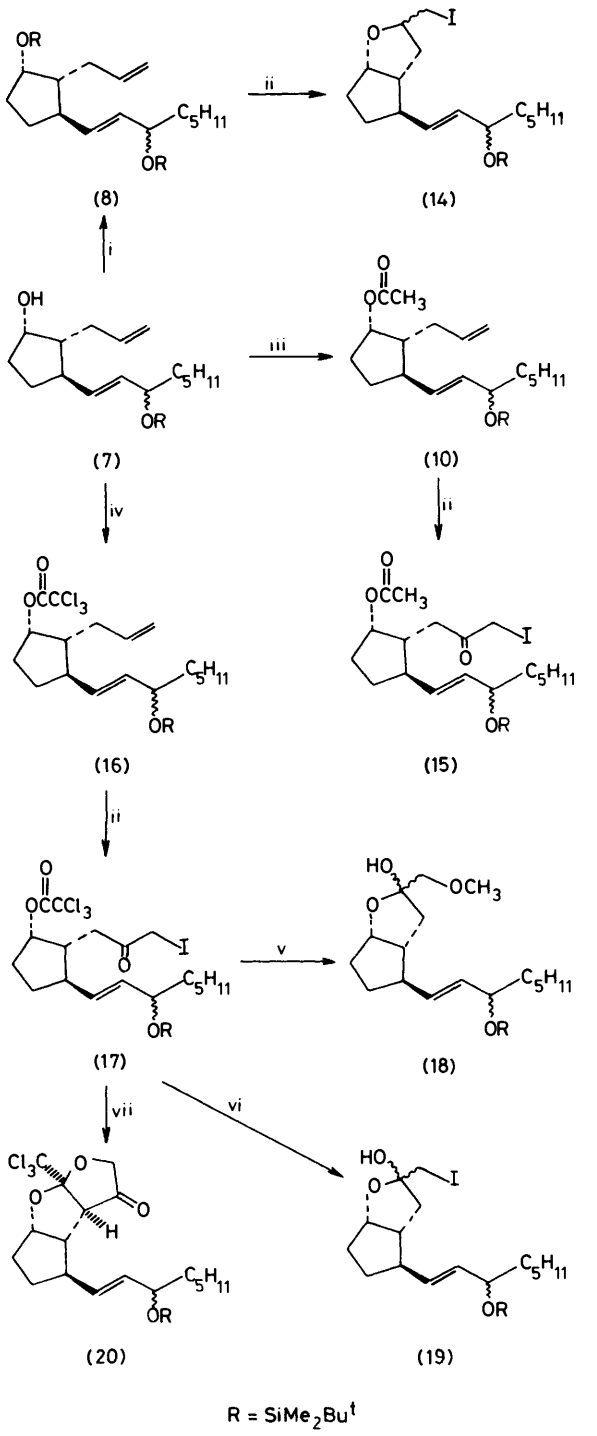
into an α-iodo-ketone using a recently reported procedure.[7] The results are shown in Scheme 5.

Reaction of the t-butyldimethylsiloxy-derivative (8) with silver chromate and iodine in accordance with the published procedure [7] gave only the bicyclic ether (14) in 82% yield. The same product was obtained from the corresponding reaction with the tetrahydropyranyloxy-derivative of the alcohol (7) and presumably results from the intramolecular interception of the intermediate



SCHEME 4 (ref. 6) *Reagents*: i, NBS, DMSO–H_2O; ii, $CH_2[CH_2]_2CH{=}CH{\cdot}O$, H^+; iii, KOH; iv, BzCl; v, H^+; vi, Jones oxidation

iodonium ion by the oxygen substituent. Reaction of the acetate (10) under the same conditions, however, gave the required iodo-ketone (15). The regioselectivity observed in this reaction is noteworthy; products resulting from reaction at the disubstituted double bond were not observed. Unfortunately, all attempts to remove the acetate protecting group from compound (15) and effect cyclisation to produce a compound of type (II) (Scheme 1) were unsuccessful. The conversion of the ketone (15) into the corresponding acetal was tried using a number of reagents but these reactions also failed. In view of these results it was concluded that the ideal protecting group for the hydroxy-group of the alcohol (7) would have similar electronic characteristics to the acetate group but would be easily removable under mild conditions. The trichloroacetate group seemed ideal [8,9] and so the alcohol (7) was converted into its trichloroacetate (16)



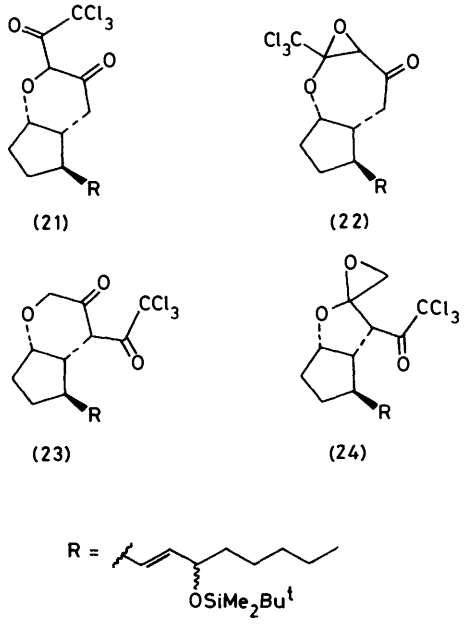
SCHEME 5 *Reagents*: i, Me_2Bu^tSiCl; ii, Ag_2CrO_4–I_2; iii, Ac_2O; iv, $(CCl_3CO)_2O$; v, MeOH–NH_3; vi, NH_3, MeOH–Et_2O (1 : 9); vii, $N[CH_2]_5CH{=}N(CH_2)_2CH_2$, Et_2O

using trichloroacetic anhydride and pyridine.[8] Reaction of the ester (16) with silver chromate and iodine gave the expected α-iodo-ketone (17) in 44% yield. The removal of the trichloroacetate protecting group was first attempted using ammonia gas in diethyl ether [9] but

this proved to be ineffective. We found that deprotection could be achieved efficiently with ammonia in anhydrous methanol but, unfortunately, displacement of iodine by methoxide ion also occurred giving the bicyclic hemiacetal (18) in 84% yield. The use of ether–methanol (9 : 1) as solvent for the ammonolysis reaction reduced the quantity of compound (18) produced and enabled the required iodide (19) to be obtained in 45% yield.

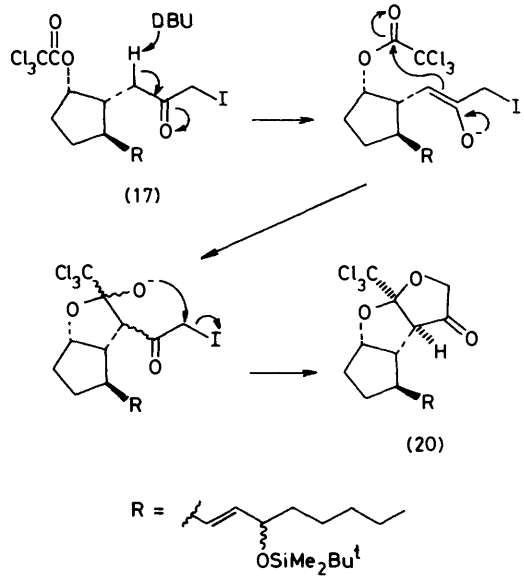
The hemiacetal (19) was treated with a variety of base–solvent combinations in the hope of effecting cyclisation to a compound of type (II) (Scheme 1). Unfortunately, these reactions failed to produce the desired product. Attempts to acetalise compound (17) prior to removal of the trichloroacetate group also failed.

An interesting observation we made was that when the ester (17) was treated with the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ether at room temperature all the starting material disappeared after 3 h and chromatographic separation of the mixture gave a major product in 23% yield. Microanalysis and mass spectroscopy indicated that HI had been removed during the course of the reaction. A number of possible structures, *e.g.* (20) (Scheme 5) and (21)—(24) were considered for this compound, based on the mechanistic premise that ketone enolisation was followed by reaction of the enolate and subsequent elimination of iodide.



Comparison of these structures with the observed spectroscopic data suggest that compound (20) is the reaction product. A possible mechanism for its formation is shown in Scheme 6.

The i.r. spectrum of compound (20) in $CHBr_3$ shows a single carbonyl stretching band at 1 760 cm^{-1}; the reported [10] value for 3-oxacyclopentanone is 1 764 cm^{-1}. The ^{13}C- and ^{1}H-n.m.r. spectra of compound (20), full details of which are given in the Experimental section,



SCHEME 6 Postulated mechanism for the formation of compound (20) from the ester (17)

were also in accord with the assigned structure. Critical ^{13}C- and ^{1}H-n.m.r. data are shown in the Table.

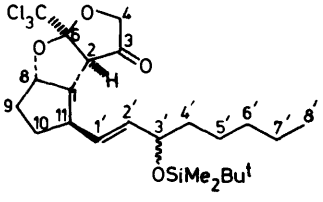
Critical n.m.r. data for compound (20)

(a) ^{1}H N.m.r.

Chemical shift (δ) $CDCl_3$	Chemical shift (δ) C_6D_6	Coupling constants (Hz)	Assignment	Coupling constants (Hz) [c]
4.91	4.32	6 6 2	8	$J_{1,8} = 6$
4.47	4.0 [a]	16.5 (C_6D_6 only)	4	$J_{1,11} = 9.5$
3.20	3.20	2	2 [b]	$J_{1,2} = 2$
2.75	2.60	—	11	$J_{4}(gem.) = 16.5$
2.38	1.92	9.5 6 2	1	

(b) ^{13}C N.m.r.[d]

Chemical shift in $CDCl_3$ (Multiplicity)	Assignment
210.5 (s)	3
120.1 (s)	6
100.3 (s)	CCl_3
88.0 (d)	8
75.5 (t)	4
56.0 [e] (d)	2
56.0 [e] (d)	1

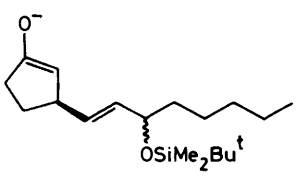


[a] Centre of AB system (singlet in $CDCl_3$). [b] Two doublets (presumably for the two C-3′ diastereoisomers). [c] Confirmed by spin-decoupling experiments. [d] Some signals were paired, presumably due to the presence of C-3′ diastereoisomers. [e] 4 Signals within 0.2 p.p.m.

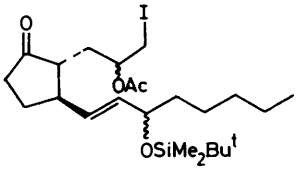
In the ^{13}C n.m.r. spectrum only one carbonyl resonance was observed [ruling out structures (21) and (23)] and its chemical shift (210.5 p.p.m.) was characteristic of a normal ketone rather than a trichloromethyl ketone (C=O in 1,1,1-trichloroacetone resonates at δ_C 180.3 p.p.m [11]) or an ester carbonyl. The trichloromethyl signal at δ_C 100.3 p.p.m. is also in the region expected (δ_{CCl_3} is 95 p.p.m. in 1,1,1-trichloroethane [12]).

In the ^{1}H n.m.r. spectrum the large *geminal* coupling

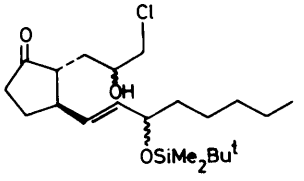
constant of the C-4 methylene group is in accord with a methylene adjacent to carbonyl [*cf.* the spectrum of compound (35)]; the *geminal* coupling constant in oxirans is small [13] and so structure (24) can be discounted. The splitting pattern and chemical shift (δ 4.91) of the C-8 methine proton are characteristic of the C-1 proton in a 2-oxabicyclo[3.3.0]octane system [*cf.* the spectra of compounds (9), (14), (18), and (19)]. This rules out structure (22) which can also be discounted for several other reasons. The remaining chemical shifts and coupling constants are consistent with structure (20) and the small value for $J_{1,2}$ suggests that it is in the *cis-transoid-cis* configuration.



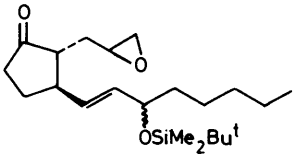
(25)



(26)



(27)

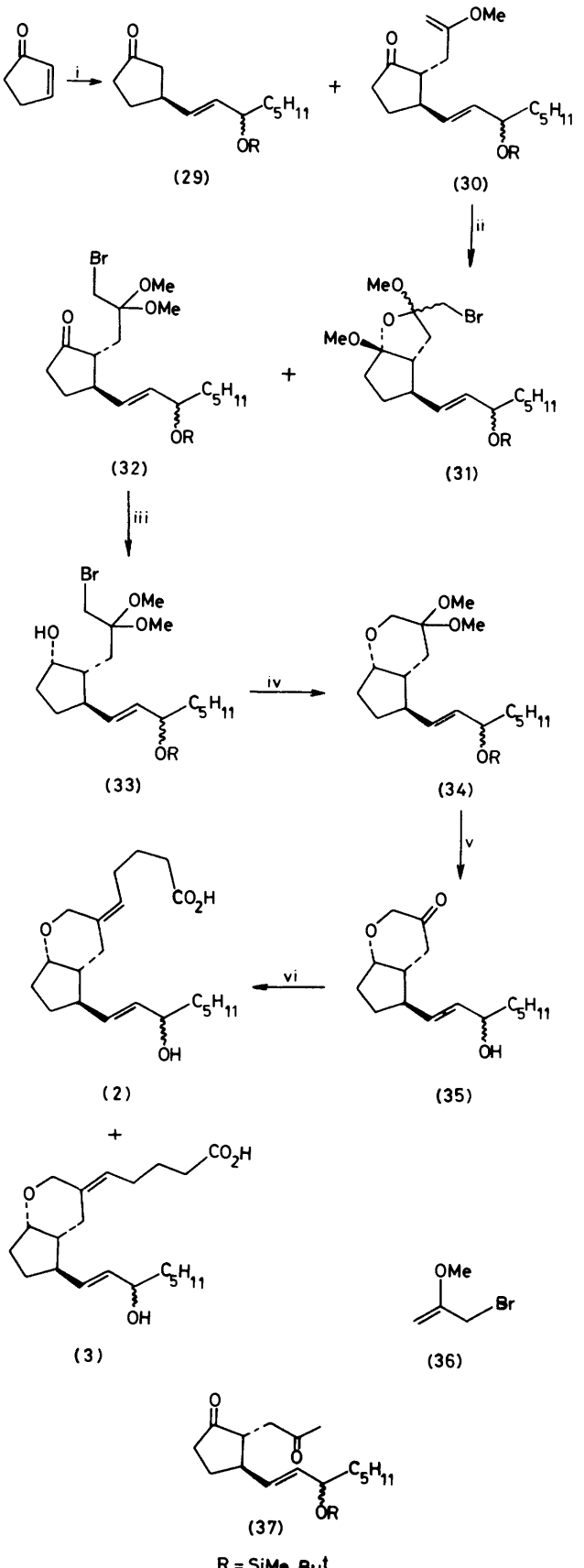


(28)

In view of the problems encountered in trying to functionalise the allyl side-chain, our efforts were directed towards introducing a prefunctionalised α-side-chain during the conjugate-addition–enolate-alkylation reaction. Attempts to alkylate the intermediate enolate (25) with 2-acetoxy-1,3-di-iodopropane and epichlorohydrin in order to prepare compounds (26) and (27) [or (28)] respectively, were unsuccessful.

The use of 2-methoxyallyl bromide (36) in the alkylation reaction, however, ultimately led to the successful synthesis of the target molecules (Scheme 7).[14]

Treatment of cyclopent-2-enone with the cuprate reagent (6) and alkylation of the intermediate enolate with 2-methoxyallyl bromide [15] in liquid ammonia gave a mixture of the desired product (30) and the non-alkylated ketone (29). A similar mixture was obtained from the two-step conjugate-addition–silyl-trapping procedure [2,16] but the overall yield of (30) was slightly lower. Compounds (29) and (30) have very similar chromatographic properties in several solvent systems



(29) (30) (32) (31) (33) (34) (2) (35) (3) (36) (37)

R = $SiMe_2Bu^t$

SCHEME 7 *Reagents*: i, Either: (6), ether, −78 °C then (36), liquid NH_3 or: (a) (6), ether, −78 °C then Me_3SiCl, (b) LiNH, then (36), liquid NH_3; ii, Br_2, MeOH, NaOAc, −78 °C; iii, $KBHBu^s_3$, THF, −40 °C; iv, NaH, THF, reflux, 2 d; v, 10% oxalic acid, SiO_2, CH_2Cl_2, r.t., 2 d; vi, $Ph_3\overset{+}{P}[CH_2]_4CO_2H\bar{B}r$, $KOBu^t$, THF, r.t., 2 h

and this, together with the ease with which the enol-ether (30) underwent hydrolysis to give the diketone (37), made purification of the desired compound (30) difficult. Separation of compounds (29) and (30) was eventually achieved by careful chromatography on silver nitrate-impregnated silica gel. Bromination of the enol-ether (30) in methanol gave the desired α-bromoacetal (32) (44% yield), together with the bicyclic acetal (31) (18% yield) resulting from neighbouring-group participation by the keto-group of the cyclopentanone (30). The most convenient procedure for the preparation of compound (32) was found to be the direct bromination of the crude product from the conjugate addition reaction [(29) + (30)], followed by chromatography to separate the desired product (32) from compounds (29) and (31). Stereospecific reduction of the ketone (32) with potassium tri-s-butylborohydride gave the *r*-1,*c*-2,*t*-3-cyclopentanol (33) which underwent slow cyclisation on treatment with sodium hydride in tetrahydrofuran (THF) to give the ether (34), removal of the protecting groups of which using aqueous oxalic acid on silica gel [17] produced the key bicyclic ketone (35).

Completion of the synthesis was accomplished by treating the ketone (35) with the Wittig reagent derived from (4-carboxybutyl)triphenylphosphonium bromide. This reaction gave a mixture of *Z*- and *E*-homoprostacyclin (2) and (3), together with dec-5-enedioic acid derived from self-condensation of the Wittig reagent. Purification by short-path chromatography on silica gel acidified to pH *ca.* 4.5 with trifluoroacetic acid gave, in order of increasing polarity, the 5*E*-15β-diastereoisomer (3b),* an inseparable mixture of the 5*E*-15α- and 5*Z*-15β-diastereoisomers (3a) and (2b), respectively, and finally the 5*Z*-15α-diastereoisomer (2a). The assignment of stereochemistry at C-15 was based on the general rule that the 15α-epimer is usually more polar on t.l.c. than the 15β-epimer.[18] The 5*E*- and *Z*-configurations were readily assigned by ^{1}H n.m.r. spectroscopy; the *Z*-isomers exhibit a characteristic AB system (*J* 15 Hz) for the 6a-protons,* whereas the *E*-isomers show only a broad, ill defined, multiplet. Similar coupling patterns were recorded for the 6a-protons in the corresponding 11α-hydroxylated * homoprostacyclin analogues.[6]

The chromatographic procedure described above gave compounds (2) and (3) contaminated by small amounts of dec-5-enedioic acid. An alternative and more efficient method of purification consisted of treatment of the crude product from the Wittig reaction with excess of t-butyldimethylsilyl chloride (silylester- but not silylether-formation occurred) followed by flash-chromatographic separation: the di-t-butyldimethylsilyl ester of dec-5-enedioic acid is very non-polar and was readily removed, and lastly saponification.

Neither acid, (2) or (3), was sufficiently active as an inhibitor of collagen-induced platelet aggregation to warrant further investigation.

* Prostacyclin numbering scheme.

EXPERIMENTAL †

^{1}H- and ^{13}C-N.m.r. spectra were recorded on Perkin-Elmer R12B, Bruker WP60, Varian EM390, Varian XL200, or Bruker WM250 spectrometers. I.r. spectra were obtained on a Pye-Unicam SP1050 spectrophotometer. Mass spectra were obtained on a Kratos-AEI MS30/74 or MS50 instrument. A normal ethereal work-up consisted of three extractions with diethyl ether, washing the combined extracts with saturated brine, drying with anhydrous magnesium sulphate, and removal of the solvent under reduced pressure. Petroleum is light petroleum (b.p. 60—80 °C).

Column chromatography (medium pressure) was carried out using silica gel H (Merck 7736). T.l.c. was carried out with Camlab ' Polygram ' pre-coated silica plates, and Merck 2 mm-thickness preparative plates were used for preparative t.l.c.

Pent-1-ynylcopper,[19] *trans*-3-(t-butyldimethylsilyloxy)-oct-1-enyl iodide,[20] silver chromate,[7] and 2-methoxyallyl bromide (36) [15] were prepared according to published procedures. Compounds (4) and (7) were prepared as described in reference 2. Solvents were dried and purified using standard procedures.

1β-*Acetoxy*-3-*bromomethyl*-6β-[(*E*)-3-(*t-butyldimethylsiloxy*)*oct*-1-*enyl*]-cis-α-2-*oxabicyclo*[3.3.0]*octane* (5).—The ketone (4) [2] (1.00 g, 2.74 mmol) was dissolved in glacial acetic acid (25 ml) containing anhydrous sodium acetate (1.21 g, 38.70 mmol) and the mixture was stirred under nitrogen. A freshly prepared solution of bromine (480 mg, 3.01 mmol) in glacial acetic acid (10 ml) was added during 30 min. After a further 30 min the mixture was poured into diethyl ether containing anhydrous potassium carbonate (85 g) to neutralise the acetic acid and was then given a normal ethereal work-up. Column chromatography using diethyl ether–petroleum (1 : 19) as eluant afforded pure compound (5) (200 mg, 15%) as an oil [R_F 0.25; diethyl ether–petroleum (1 : 9) as eluant]; $\nu_{max.}$ (neat) 1 740 cm^{-1}; δ($CDCl_3$) 5.60—5.30 (2 H, m, CH=CH), 5.2—4.4 (1 H, m, C*H*CH_2Br), 4.05 (1 H, m, CHOSi), 3.50 (2 H, d, *J* 6 Hz, CH_2Br), 2.0 (3 H, s, $COCH_3$), 0.88 [total 12 H, s and m, $SiC(CH_3)_3$ and CH_2CH_3], 0.03 [6 H, s, $Si(CH_3)_2$], and 3.00—1.10 (total 16 H, m, remainder); *m/z* 444 and 442 (M^+ — AcOH), 431 and 429 ($M^+ - C_5H_{11}$), and 387 and 385 [M^+ — $C(CH_3)_3$ — AcOH] [Found: (M^+ — AcOH), 444.1902 and 442.1898. $C_{22}H_{39}BrO_2Si$ requires *m/z*, 444.1883 and 442.1903].

c-2-*Allyl*-r-1-(*t-butyldimethylsiloxy*)-t-3-[(*E*)-3-(*t-butyldimethylsiloxy*)*oct*-1-*enyl*]*cyclopentane* (8).—The alcohol (7) [2] (200 mg, 0.55 mmol) was dissolved in dimethylformamide (DMF) (10 ml) and then imidazole (93 mg, 1.38 mmol) and t-butylchlorodimethylsilane (99 mg, 0.66 mmol) were added. The mixture was stirred at ambient temperature for 2 d. Reaction was not complete after this time, so the mixture was heated to 50 °C in a water-bath for 3 h and was then poured into saturated brine and extracted once with ether. The extract was washed once with water to remove DMF and was then evaporated to dryness under reduced pressure to yield an oil (250 mg), column chromatography of which [diethyl ether–hexane (1 : 49) as eluant] gave the pure *product* (8) (167 mg, 64%) as an oil [R_F 0.60; diethyl ether–hexane (1 : 19)]; δ($CDCl_3$) 6.10—4.67 (total 5 H, m, CH=CH and $CH=CH_2$), 4.22—3.75 (2 H, m, 2 × CHOSi), 0.85 [total 21 H, s and m, 2 × $SiC(CH_3)_3$ and CH_2CH_3], and 0.00

† Systematic numbering schemes are used throughout the Experimental section.

[12 H, s, 2 × $Si(CH_3)_2$]; *m/z* 465 ($M^+ - CH_3$), 423 [$M^+ - C(CH_3)_3$], and 409 ($M^+ - C_5H_{11}$) [Found: ($M^+ - CH_3$), 465.3567. $C_{27}H_{53}O_2Si_2$ requires *m/z*, 465.3584].

3-*Bromomethyl*-6β-[(*E*)-3-(*t-butyldimethylsiloxy*)*oct*-1-*enyl*]-cis-α-2-*oxabicyclo*[3.3.0]*octane* (9).—The olefin (8) (50 mg, 0.10 mmol) was dissolved in glacial acetic acid (5 ml) containing anhydrous sodium acetate (40 mg, 0.50 mmol) and NBS (20 mg, 0.11 mmol). The mixture was stirred at ambient temperature under nitrogen for 3 h. Anhydrous potassium carbonate (12 g) was added to neutralise the acetic acid and the mixture was given a normal ethereal work-up. The resulting oil (56 mg) was purified by column chromatography [diethyl ether–petroleum (1 : 19) as eluant] giving *compound* (9) (20 mg, 45%) as an oil [R_F 0.44; diethyl ether–petroleum (1 : 9)]; δ($CDCl_3$) 5.65—5.35 (2 H, m, CH=CH), 4.85—3.80 (total 3 H, m, CHOSi and HCO-CH), 3.55—3.30 (2 H, m, CH_2Br), 0.88 [total 12 H, m, and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.04 [6 H, s, $Si(CH_3)_2$], and 2.70—1.10 (total 16 H, m, remainder).

r-1-*Acetoxy*-c-2-*allyl*-t-3-[(E)-3-(*t-butyldimethylsiloxy*)-*oct*-1-*enyl*]*cyclopentane* (10).—The alcohol (7) (536 mg, 1.46 mmol) was dissolved in toluene (30 ml) containing pyridine (2.313 g, 29.20 mmol) and acetic anhydride (2.985 g, 29.20 mmol). The mixture was stirred at ambient temperature for 2 d. A normal ethereal work-up, with an extra (dilute hydrochloric acid) wash to remove pyridine, afforded the *acetate* (10) (580 mg, 97%) as an oil, pure by t.l.c. [R_F 0.26; diethyl ether–hexane (1 : 9)]; $\nu_{max.}$ (neat) 1 740 cm^{-1}; δ($CDCl_3$) 6.00—4.80 (total 6 H, m, CH=CH, $CH=CH_2$, and CHOAc), 4.02 (1 H, m, CHOSi), 2.00 (3 H, s, $COCH_3$), 0.85 [total 12 H, m, and s, CH_2CH_3 and $OSiC(CH_3)_3$], 0.00 [6 H, s, $OSi(CH_3)_2$], and 2.60—1.10 (total 16 H, m, remainder); *m/z* 393 ($M^+ - CH_3$), 351 [$M^+ - C(CH_3)_3$], and 337 ($M^+ - C_5H_{11}$) (Found: C, 70.7; H, 10.9. $C_{24}H_{44}O_3Si$ requires C, 70.5; H, 11.0%).

r-1-*Acetoxy*-c-2-*allyl*-t-3-[(E)-3-*hydroxyoct*-1-*enyl*]*cyclopentane* (11).—To a solution of the silyl ether (10) (250 mg, 0.612 mmol) in DMSO–water (18 : 1; 19 ml) was added NBS (109 mg, 0.612 mmol) in one portion and the mixture was stirred at ambient temperature for 1 6 h. A normal ethereal work-up was followed by column chromatography with diethyl ether–petroleum (1 : 4) as eluant to give the *alcohol* (11) (143 mg, 79%) as an oil [R_F 0.22; diethyl ether–petroleum (1 : 1)]; $\nu_{max.}$ (neat) 3 415 and 1 740 cm^{-1}; δ($CDCl_3$) 6.25—4.80 (total 6 H, m, CH=CH, $CH=CH_2$, and CHOAc), 4.15 (1 H, m, CHOH), 2.00 (3 H, s, $COCH_3$), 0.85 (3 H, m, CH_2CH_3), and 2.80—0.90 (total 17 H, m, remainder); *m/z* 276 ($M^+ - H_2O$) and 223 ($M^+ - C_5H_{11}$) [Found: ($M^+ - H_2O$), 276.2092. $C_{18}H_{28}O_2$ requires *m/z*, 276.2089].

r-1-*Acetoxy*-c-2-*allyl*-t-3-[(E)-3-(*tetrahydropyran*-2-*yloxy*)-*oct*-1-*enyl*]*cyclopentane* (12).—To a solution of the alcohol (11) (330 mg, 1.12 mmol) in benzene (40 ml) was added dihydropyran (283 mg, 3.36 mmol) and phosphoryl chloride (one drop) and the mixture was stirred at ambient temperature overnight. A normal ethereal work-up, which included a sodium hydrogencarbonate-wash to remove any acid, was followed by column chromatography [diethyl ether–hexane (1 : 19) as eluant] to give the ether (12) (424 mg, 93% as an oil [R_F 0.14; diethyl ether–hexane (1 : 9)]; $\nu_{max.}$ (neat) 1 735 cm^{-1}; δ($CDCl_3$) 6.10—4.50 (total 7 H, m, $CH=CH_2$, CH=CH, CHOAc, and OCHO), 1.97 (3 H, s, $COCH_3$), and 3.1—0.7 (total 28 H, m, remainder); *m/z* 307 ($M^+ - C_5H_{11}$) (Found: C, 72.7; H, 10.0. $C_{23}H_{38}O_4$ requires C, 73.0; H, 10.1%).

r-1-*Acetoxy*-c-2-(3-*bromo*-2-*hydroxypropyl*)-t-3-[(E)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*cyclopentane* (13).—To a solution of the olefin (12) (370 mg, 0.98 mmol) in DMSO–water (18 : 1; 57 ml) was added NBS (191 mg, 1.08 mmol) and the mixture was stirred at ambient temperature for 3 h. Following a normal ethereal work-up, the resulting oil was purified by column chromatography [diethyl ether–petroleum (3 : 17) as eluant] which gave the *bromohydrin* (13) (344 mg, 74%) as an oil [R_F 0.15; diethyl ether–petroleum (1 : 1)]; $\nu_{max.}$ (neat) 3 450 and 1 735 cm^{-1}; δ($CDCl_3$) 5.65—5.05 (total 3 H, m, CH=CH and CHOAc), 4.65 (1 H, m, OCHO), 4.40—3.10 (total 6 H, m, OCH_2, CH_2Br, CHOH, and CHOTHP), 2.00 (3 H, s, $COCH_3$), and 3.15—0.55 (total 26 H, m, remainder); *m/z* 372 (M^+ — THP·OH), 314 (M^+ — THP·OH — AcOH), 301 (M^+ — THP·OH — C_5H_{11}), and 243 (M^+ — THP·OH — AcOH — C_5H_{11}) [Found: (M^+ — THP·OH), 374.1361 and 372.1313. $C_{18}H_{29}BrO_3$ requires *m/z*, 374.1280 and 372.1301).

6β-[(E)-3-(*t-Butyldimethylsiloxy*)*oct*-1-*enyl*]-3-*iodomethyl*-cis-α-2-*oxabicyclo*[3.3.0]*octane* (14).—Silver chromate (244 mg, 0.78 mmol) and powdered 4A molecular sieves (250 mg) were suspended in dichloromethane (3 ml) under nitrogen and the mixture was cooled to 0 °C. Iodine (236 mg, 0.93 mmol) was added, followed by pyridine (33 mg, 0.31 mmol), and the suspension was stirred at 0 °C under nitrogen for 5 min. A solution of the olefin (8) (298 mg, 0.62 mmol) in dichloromethane (1.5 ml) was then added and the mixture was stirred at 0 °C for 30 min. The mixture was then filtered through a pad of Celite, and the residue was washed with diethyl ether. The combined filtrate and washings were washed with 10% aqueous sodium thiosulphate and then with saturated brine and the solvents were removed under reduced pressure. The crude mixture was purified by column chromatography [diethyl ether–hexane (1 : 24) as eluant] to afford the *product* (14) (250 mg, 82%) as an oil [R_F 0.38; diethyl ether–hexane (1 : 9)]; δ($CDCl_3$) 5.55—5.33 (2 H, m, CH=CH), 4.81—3.56 (total 3 H, m, CHOSi, 1-H, and $CHCH_2I$), 3.27 and 3.20 (total 2 H, 2 × d, *J* 4) and 4 Hz, CH_2I), 0.86 [total 12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 3.00—1.05 (total 16 H, m, remainder); *m/z* 477 ($M^+ - CH_3$), 435 [$M^+ - C(CH_3)_3$], and 421 ($M^+ - C_5H_{11}$) (Found: C, 53.85; H, 8.60. $C_{22}H_{41}IO_2Si$ requires C, 53.64; H, 8.39%).

r-1-*Acetoxy*-t-3-[(E)-3-(*t-butyldimethylsiloxy*)*oct*-1-*enyl*]-c-2-(3-*iodo*-2-*oxopropyl*)*cyclopentane* (15).—Silver chromate (394 mg, 1.25 mmol) and powdered 4A molecular sieves (400 mg) were suspended in dry dichloromethane (5 ml) under nitrogen and the mixture was cooled to 0 °C. Iodine (380 mg, 1.50 mmol) was added, followed by pyridine (54 mg, 0.50 mmol) and the suspension was stirred at 0 °C under nitrogen for 5 min. A solution of the olefin (10) (408 mg, 1.00 mmol) in dichloromethane (2 ml) was added and the suspension was stirred at 0 °C for 30 min, then at ambient temperature for a further 2 h. Work-up as for compound (14), followed by column chromatography [diethyl ether–hexane (1 : 9) as eluant] gave, first, unchanged olefin (10) (46 mg, 11%) as an oil, followed by the pure *iodo-ketone* (15) (222 mg, 46% based on converted starting material) as an oil [R_F 0.52; diethyl ether–hexane (2 : 3)]; $\nu_{max.}$ (neat) 1 740 and 1 715 cm^{-1}; δ($CDCl_3$) 5.52—5.03 (total 3 H, m, CH=CH and CHOAC), 4.13—3.87 (1 H, m, CHOSi), 3.71 (2 H, s, CH_2I), 2.87—2.62 [2 H, m, $CH_2C(O)$], 1.99 (3 H, s, $OCOCH_3$), 0.85 [total 12 H, m, and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 2.62—1.04 (total 14 H, m, remainder); *m/z* 493 [$M^+ - C(CH_3)_3$] and 479 ($M^+ - C_5H_{11}$) (Found: C,

52.15; H, 7.9; I, 23.3. $C_{24}H_{43}IO_4Si$ requires C, 52.35; H, 7.87; I, 23.05%).

t-2-*Allyl*-(r-1)-[(E)-3-(*t-butyldimethylsiloxy*)*oct*-1-*enyl*]-t-3-*trichloroacetoxycyclopentane* (16).—To a solution of trichloroacetic anhydride (476 mg, 20 mmol) and pyridine (320 mg, 4.0 mmol) in toluene (25 ml) was added a solution of the alcohol (7) (366 mg, 1.0 mmol) in toluene (5 ml). After 5 min the mixture was given a normal ethereal work-up with an extra hydrochloric-acid wash to remove pyridine. The crude material was purified by column chromatography [diethyl ether–hexane (1 : 99) as eluant] which gave the *product* (16) (430 mg, 84%) as an oil [R_F 0.52; diethyl ether–hexane (1 : 19)]; $\nu_{max.}$ (neat) 1 765 cm^{-1}; $\delta(CDCl_3)$ 6.15—4.70 (total 6 H, m, CH=CH, $CH{=}CH_2$, and CHOCO), 4.10—3.80 (1 H, m, CHOSi), 0.83 [total 12 H, m, and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 2.65—1.00 (total 16 H, m, remainder).

r-1-[(E)-3-(*t-Butyldimethylsiloxy*)*oct*-1-*enyl*]-t-2-(3-*iodo*-2-*oxopropyl*)-t-3-*trichloroacetoxycyclopentane* (17).—Silver chromate (394 mg, 1.25 mmol) and powdered 4A molecular sieves (400 mg) were suspended in dichloromethane (5 ml) under nitrogen and the mixture was cooled to 0 °C. Iodine (380 mg, 1.50 mmol) was added, followed by pyridine (54 mg, 0.50 mmol), and the mixture was stirred at 0 °C under nitrogen for 5 min. A solution of the trichloroacetate (16) (512 mg, 1 mmol) in dichloromethane (2 ml) was then added and the mixture was stirred at 0 °C for 30 min, then at ambient temperature for a further 2 h. Identical work-up as for compound (14), followed by column chromatography [diethyl ether–hexane (1 : 99) as eluant] gave the *product* (17) (288 mg, 44%) as an oil [R_F 0.44; diethyl ether–hexane (1 : 9)]; $\nu_{max.}$ (neat) 1 765 and 1 715 cm^{-1}; $\delta(CDCl_3)$ 5.55—5.20 (total 3 H, m, CH=CH and CHOCO), 4.15—3.80 (1 H, m, CHOSi), 3.70 (2 H, s, CH_2I), 2.97—2.72 (2 H, m, CH_2CO, 0.82 [total 12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.02 and 0.00 [total 6 H, 2 × s, $Si(CH_3)_2$], and 2.60—1.00 (total 14 H, m, remainder).

6β-[(E)-3-(*t-Butyldimethylsiloxy*)*oct*-1-*enyl*]-3-*hydroxy*-3-*methoxymethyl*-cis-α-2-*oxabicyclo*[3.3.0]*octane* (18).—A solution of the iodo-ketone (17) (150 mg, 0.23 mmol) in methanol (10 ml), saturated with dry ammonia gas, was kept for 5 min. It was then given a normal ethereal work-up and the residue was purified by column chromatography [diethyl ether–petroleum (1 : 4) as eluant], to give the *product* (18) (80 mg, 84%) as an oil [R_F 0.09; diethyl ether–petroleum (3 : 7)]; ν_{max} (neat) 3 480 and 1 735w cm^{-1}; $\delta(CDCl_3)$ 5.50—5.30 (2 H, m, CH=CH), 4.76—4.43 (1 H, m, 1-H), 4.14—3.80 (1 H, m, CHOSi), 3.73—3.47 (total 3 H, m, CH_2OMe and OH), 3.04 and 3.00 (total 3 H, 2 × s, OCH_3), 0.83 [total 12 H, m, and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, m, $Si(CH_3)_2$], and 2.80—1.00 (total 16 H, m, remainder); *m/z* 381 ($M^+ - OCH_3$), 355 [$M^+ - C(CH_3)_3$], and 341 ($M^+ - C_5H_{11}$) [Found: ($M^+ - OCH_3$), 381.2807. $C_{22}H_{41}O_3Si$ requires *m/z* 381.2825].

6β-[(E)-3-(*t-Butyldimethylsiloxy*)*oct*-1-*enyl*]-3-*hydroxy*-3-*iodomethyl*-cis-α-2-*oxabicyclo*[3.3.0]*octane* (19).—A mixture of methanol (2 ml) and ether (18 ml) was saturated with dry ammonia gas, the iodo-ketone (17) (200 mg, 0.31 mmol) was added, and the mixture was kept at 4 °C overnight. Evaporation of the solvent under reduced pressure, followed by column chromatography [diethyl ether–hexane (1 : 9) as eluant] gave the pure *product* (19) (70 mg, 45%) as an oil [R_F 0.41; diethyl ether–hexane (3 : 7)]; $\nu_{max.}$ (neat) 3 400 cm^{-1}; $\delta(CDCl_3)$ 5.45—5.25 (2 H, m, CH=CH), 4.80—4.50 (1 H, m, 1-H), 4.07—3.75 (1 H, m, CHOSi), 3.50—3.35 (2 H, m, CH_2I), 0.80 [total 12 H, m, and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 2.87—1.00 (total 17 H, m, remainder); *m/z* 508 (M^+), 490 ($M^+ - H_2O$), 451 [$M^+ - C(CH_3)_3$], and 437 ($M^+ - C_5H_{11}$) (Found: M^+, 508.1845. $C_{22}H_{41}IO_3Si$ requires *M*, 508.1828).

11β-[(E)-3-(*t-Butyldimethylsiloxy*)*oct*-1-*enyl*]-6α-*trichloromethyl*-5,7-*dioxatricyclo*[6.3.0.$0^{2,6}$]*undecan*-3-*one* (20).—To a solution of the iodo-ketone (17) (327 mg, 0.50 mmol) in ether was added DBU (88 mg, 0.55 mmol) and the mixture was stirred at ambient temperature for 3 h. The white precipitate which formed was filtered off on Celite and was washed well with diethyl ether. The filtrate and washings were evaporated to dryness under reduced pressure and the residue was purified by column chromatography [diethyl ether–hexane (5 : 195) as eluant] to give the *product* (20) (61 mg, 23%) as an oil [R_F 0.25; diethyl ether–hexane (3 : 17)]; $\nu_{max.}$($CHBr_3$) 1 760 cm^{-1}; $\delta(CDCl_3)$ 5.65—5.45 (2 H, m, CH=CH), 4.91 (1 H, m, 8-H), 4.47 (2 H, s, CH_2O), 4.10 (1 H, m, CHOSi), 3.20 (1 H, d, *J* 2 Hz, 2-H), 2.75 (1 H, m, 11-H), 2.38 (1 H, m, 1-H), 0.85 [total 12 H, m, and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 2.2—1.0 (total 12 H, m, remainder); δ_C ($CDCl_3$) several of these signals were paired presumably due to the presence of C-3′ diastereoisomers) 210.5 (s), 135.6 (d), 129.7 (d), 120.1 (s), 100.3 (s), 88.0 (d), 75.5 (t), 73.4 (d), 56.0 (2 × d), 47.2 (d), 38.5 (t), 33.1 (t), 31.9 (t), 31.0 (t), 26.0 (q), 25.06 (t), 22.7 (t), 18.4 (s), 14.0 (q), −4.0 (q), and −4.6 (q); *m/z* 509 ($M^+ - CH_3$), 467 [$M^+ - C(CH_3)_3$], and 453 ($M^+ - C_5H_{11}$) (Found: C, 54.65; H, 7.3. $C_{24}H_{39}Cl_3O_4Si$ requires C, 54.80; H, 7.53%).

trans-3-[(E)-3-(*t-Butyldimethylsiloxy*)*oct*-1-*enyl*]-2-(2-*methoxyallyl*)*cyclopentanone* (30).—(*a*) ' *One-pot* ' *procedure*. n-Butyl-lithium (27.5 mmol) was added to a stirred solution of 3-(t-butyldimethylsiloxy)oct-1-enyl iodide (9.2 g, 25 mmol) in diethyl ether (20 ml) under nitrogen at −78 °C. After 1 h a freshly prepared solution of pent-1-ynylcopper (3.43 g, 26.25 mmol) in diethyl ether (20 ml) and hexamethylphosphorus triamide (9.8 ml, 52.5 mmol) were slowly added in turn and the mixture was stirred for a further 1 h at −78 °C to ensure complete formation of the cuprate (6). A solution of cyclopent-2-enone (3.07 g, 32.5 mmol) in diethyl ether (50 ml) was added very slowly over 30 min to the solution of the salt (6) and the mixture was stirred for a further 1 h at −78 °C. Dry liquid ammonia was then added, followed by 2-methoxyallyl bromide (36) (18.88 g, 125 mmol). The cooling bath was removed and the ammonia was allowed to evaporate off overnight. The mixture was then poured into distilled water and given a normal ethereal work-up. The crude mixture was purified by column chromatography on silica containing 2% by weight of triethylamine with diethyl ether–hexane (3 : 97) as eluant to give a mixture of the desired product (30) and 3*S*-[(*E*)-3-(t-butyldimethylsiloxy)oct-1-enyl]cyclopentanone (29) (1.487 g). Both compounds were coincident on t.l.c. [R_F 0.23; diethyl ether–hexane (1 : 9)]. The mixture was separated by column chromatography on silica gel impregnated with silver nitrate as follows. A slurry of silica gel (25 g) and 10% aqueous silver nitrate (50 ml) was prepared and dried in an oven at 130 °C overnight, and was then pulverised and packed into a column in the usual way. The mixture was then chromatographed on this column with diethyl ether–hexane (1 : 19) as eluant to give pure *product* (30) (1.58 g, 16%) as an oil; $\delta(CDCl_3)$ 5.50—5.38 (2 H, m, CH=CH), 4.07—3.93 (1 H, m, CHOSi), 3.30 (2 H, s, $C{=}CH_2$), 3.45 (3 H, s, OCH_3), 0.79 [total 12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.03 and 0.00 [total 6 H, 2 × s,

$Si(CH_3)_2$], and 2.9—1.1 (total 16 H, m, remainder); *m/z* 394 (M^+), 337 [$M^+ - C(CH_3)_3$], and 323 ($M^+ - C_5H_{11}$) (Found: M^+, 394.2926. $C_{23}H_{42}O_3Si$ requires *m/z*, 394.3903).

(*b*) *Silyl trapping procedure.* The above procedure was repeated as far as the slow addition of the cyclopent-2-enone solution followed by stirring for 1 h at −78 °C. THF (50 ml) was then added, followed by a mixture of trimethylsilyl chloride (15 ml) and triethylamine (20 ml). The mixture was left to warm to ambient temperature (*ca.* 1 h), ice was then added to quench the excess of trimethylsilyl chloride, and the mixture was extracted with hexane (3 × 200 ml). The combined extracts were washed with ice-cold 2% sulphuric acid (4 × 75 ml) to precipitate the copper–HMPA complex, then with 8% aqueous sodium hydrogen carbonate (100 ml). The extracts were dried and evaporated under reduced pressure. Distillation of the residue gave 3-[(*E*)-3-(t-butyldimethylsiloxy)oct-1-enyl]-1-trimethylsiloxycyclopent-1-ene (b.p. 100—125 °C at 0.1 mmHg) (6.6 g, 66%) as an oil (R_F 0.55; hexane); δ($CDCl_3$) 5.7—5.1 (2 H, m, CH=CH), 4.52 (1 H, m, 2-H), 4.00 (1 H, m, CHOSi), 3.20 (1 H, m, 3-H), 0.88 [total 12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.09 [9 H, s, $OSi(CH_3)_3$] 0.00 [6 H, s, $Si(CH_3)_2$], and 2.3—1.0 [total 12 H, m, remainder).

A solution of the silyl enol-ether (3.96 g, 10 mmol) in THF (30 ml) was added to a solution of lithium amide (11 mmol) in distilled liquid ammonia (50 ml) at −78 °C. The mixture was warmed to −40 °C for 30 min to ensure complete formation of the enolate, and then a solution of 2-methoxyallyl bromide (36) (3.32 g, 22 mmol) in THF (15 ml) was added rapidly; the cooling bath was removed and the ammonia was allowed to boil off overnight. The mixture was then poured into distilled water, given a normal ethereal work-up and purified by column chromatography [as in experiment (a)] giving the title compound (30) (390 mg, 10%).

trans-[(E)-3-(*t-Butyldimethylsiloxy*)*oct*-1-*enyl*]-2-(2-*oxopropyl*)*cyclopentanone* (37).—To a solution of the aforementioned mixture of the enol-ether (30) and the ketone (29) (total 150 mg) in THF (5 ml) was added 10% aqueous oxalic acid (0.25 ml) and the mixture was stirred at ambient temperature. After 2 h the oxalic acid was neutralised by the addition of saturated aqueous sodium hydrogen carbonate (1 ml) and the mixture was given a normal ethereal work-up. The resulting oil was purified by preparative t.l.c. [diethyl ether–petroleum (1 : 4)]; extraction of the material of R_F 0.20 gave the *product* (37) (55 mg) as an oil; $\nu_{max.}$ (neat) 1 745 and 1 725 cm^{-1}; δ($CDCl_3$) 5.60—5.40 (2 H, m, CH=CH), 4.15—4.00 (1 H, m, CHOSi), 2.18 (3 H, s, $COCH_3$), 0.92 [total 12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.04 and 0.06 [total 6 H, 2 × s, $Si(CH_3)_2$], and 2.80—1.15 (total 16 H, m, remainder); *m/z* 365 ($M^+ - CH_3$), 323 [$M^+ - C(CH_3)_3$], and 309 ($M^+ - C_5H_{11}$) {Found: [$M^+ - C(CH_3)_3$], 323.2060. $C_{18}H_{31}O_3Si$ requires *m/z*, 323.2042}.

trans-2-(3-*Bromo*-2,2-*dimethoxypropyl*)-3-[(E)-3-(*t-butyldimethylsiloxy*)*oct*-1-*enyl*]*cyclopentanone* (32).—To a solution of the enol ether (30) (110 mg, 0.28 mmol) in methanol (5 ml) was added anhydrous sodium acetate (90 mg, 1.12 mmol) and the mixture was cooled to −78 °C. A solution of bromine (48 mg, 0.31 mmol) in methanol (3 ml) was added slowly to the stirred mixture. After 10 min the mixture was poured into aqueous sodium hydrogen carbonate and given a normal ethereal work-up. Purification by column chromatography [ethyl acetate-petroleum (1 : 19) as eluant] afforded, first, 3-bromomethyl-6β-[(*E*)-3-(t-butyldimethylsiloxy)oct-1-enyl]-1β,3-dimethoxy-*cis*-α-2-oxabicyclo[3.3.0]octane (31) (25 mg, 18%) as an oil [R_F 0.57; ethyl acetate–petroleum (1 : 9)]; δ($CDCl_3$) 5.38 (2 H, m, CH=CH), 4.1—3.0 (total 9 H, m and 4 × s, CHOSi, 2 × OCH_3, and CH_2Br), 0.80 [total 12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 2.40—1.00 (total 16 H, m, remainder), then the desired *product* (32) (62 mg, 44%) as an oil [R_F 0.27; ethyl acetate–petroleum (1 : 9)]; $\nu_{max.}$ (neat) 1 740 cm^{-1}; δ($CDCl_3$) 5.8—5.3 (2 H, m, CH=CH), 4.07 (1 H, m, CHOSi), 3.7—3.3 (2 H, m, CH_2Br), 3.2 and 3.15 (total 6 H, 2 × s, 2 × OCH_3), 0.85 [total 12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 2.7—1.1 (total 16 H, m, remainder); *m/z* 474 ($M^+ - OCH_3$) and 448 [$M^+ - C(CH_3)_3$] [Found: ($M^+ - OCH_3$), 473.2073 and 475.2076. $C_{23}H_{42}BrO_3Si$ requires *m/z*, 473.2086 and 475.2066).

c-2-(3-*Bromo*-2,2-*dimethoxypropyl*)-t-3-[(E)-3-(*t-butyldimethylsiloxy*)*oct*-1-*enyl*]*cyclopentan*-r-1-*ol* (33).—A solution of potassium tri(s-butyl)borohydride (Aldrich K-Selectride, 1.07 mmol) in THF was slowly added to a stirred solution of the ketone (32) (270 mg, 0.534 mmol) in THF (30 ml) under nitrogen at −40 °C. The temperature was allowed to rise to 0 °C over 1 h and the excess of reagent was then hydrolysed by the careful addition of water. 3M Aqueous sodium hydroxide (0.3 ml, 0.587 mmol) was then added, followed by 30% aqueous hydrogen peroxide (0.35 ml, 2.88 mmol) to oxidise the borane. The mixture was stirred at 0 °C for 1 h. A normal ethereal work-up gave an oil which was purified by column chromatography [diethyl ether–hexane (1 : 4) as eluant] to afford the *alcohol* (33) (250 mg, 93%) as an oil [R_F 0.32; diethyl ether–hexane (1 : 1)]; $\nu_{max.}$ (neat) 3 500 cm^{-1}; δ($CDCl_3$) 5.4—5.2 (2 H, m, CH=CH), 4.3—3.75 (total 2 H, m, CHOH and CHOSi), 3.75—3.10 (total 8 H, m, CH_2Br and 2 × OCH_3), 0.83 [total 12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 2.40—1.03 (total 17 H, m, remainder); *m/z* 419.417 ($M^+ - H_2O - C_5H_{11}$) [Found: ($M^+ - H_2O - C_5H_{11}$), 419.1485 and 417.1462. $C_{19}H_{34}BrO_3Si$ requires *m/z*, 419.1480 and 417.1460].

7β-[(E)-3-(*t-Butyldimethylsiloxy*)*oct*-1-*enyl*]-4,4-*dimethoxy*-cis-α-2-*oxabicyclo*[3.4.0]*nonane* (34).—To a solution of the alcohol (33) (190 mg, 0.38 mmol) in THF (50 ml) was added 50% sodium hydride in oil (36 mg, 0.76 mmol), the mixture was boiled under reflux for 2 d, and then poured into distilled water and given a normal ethereal work-up. Column chromatography [diethyl ether–hexane (1 : 9) as eluant] gave the *cyclic ether* (34) (92 mg, 58%) as an oil [R_F 0.35; diethyl ether–hexane (1 : 4)]; δ($CDCl_3$) 5.6—5.1 (2 H, m, CH=CH), 4.2—3.7 (total 2 H, m, CHOSi and CHO), 3.35—2.9 (total 8 H, m, OCH_2 and 2 × OCH_3), 0.80 [total 12 H, m, and s, CH_2CH_3 and $SiC(CH_3)_3$], 0.00 [6 H, s, $Si(CH_3)_2$], and 2.9—1.1 (total 16 H, m, remainder); *m/z* 395 ($M^+ - OCH_3$) [Found: ($M^+ - OCH_3$), 395.2955. $C_{23}H_{43}O_3Si$ requires *m/z* 395.2981] (Found: C, 67.60; H, 10.95. $C_{24}H_{46}O_4Si$ requires C 67.55; H, 10.87%).

7β-[(E)-3-*Hydroxyoct*-1-*enyl*)]-cis-α-2-*oxabicyclo*[3.4.0]-*nonan*-4-*one* (35). A slurry of 230—400 mesh silica gel (1 g) in dichloromethane (3 ml) was treated with 10% aqueous oxalic acid (0.1 ml) and the slurry was stirred until the aqueous phase disappeared (30 min). A solution of the acetal (34) (100 mg, 0.23 mmol) in dichloromethane (0.5 ml) was added and the mixture was stirred for 2 d at ambient temperature. Solid anhydrous sodium carbonate was added to neutralise the oxalic acid and, after being stirred for 5 min, the mixture was filtered and the residue was washed well with diethyl ether. Evaporation of the combined filtrate and washings under reduced pressure, followed by preparative t.l.c.

[diethly ether] of the residue gave, from the band of R_F 0.37, the *ketone* (35) (48 mg, 79%) as a semi-crystalline solid; $\nu_{max.}$(CHCl$_3$) 1 737 cm^{-1}; δ 5.7—5.3 (2 H, m, CH=CH), 4.1 and 3.75 (2 H, AB, *J* 18 Hz, CH_2CO), 4.02—3.9 (total 2 H, m, C*H*OH and 1-H), 0.88 (3 H, m, CH_2CH_3), and 2.8—1.1 (total 17 H, m, remainder); δ_C (CDCl$_3$; 25.2 MHz) 210.7 (C=O), 133.7 and 132.0 (C=C), 72.8 [O*C*(=O)], and 72.6 and 72.4 p.p.m. (epimers) (COH); *m/z* 266 (M^+), 248 ($M^+ - H_2O$), and 195 ($M^+ - C_5H_{11}$) (Found: M^+ 266.1906; C, 72.45; H, 9.85. $C_{16}H_{26}O_3$ requires *M*, 266.1882; C, 72.14; H, 9.84%).

(Z)- *and* (E)-4-(4-*Carboxybutylidene*-7β-[(E)-3-*hydroxyoct*-1-*enyl*]-cis-α-2-*oxabicyclononane* (2) *and* (3), *respectively*.—A solution of 4-carboxybutyltriphenylphosphonium bromide (886 mg, 2 mmol) and potassium t-butoxide (448 mg, 4 mmol) in THF (10 ml) was stirred under nitrogen at room temperature for 30 min. A solution of the ketone (35) (70 mg, 0.26 mmol) in THF (5 ml) was then added in a single portion to the deep red solution of the Wittig reagent. The mixture was stirred at room temperature for 16 h and was then poured into saturated aqueous ammonium chloride (150 ml). A normal ethereal work-up gave a pale-yellow gum which was purified by short-path column chromatography on silica gel (Merck 7729; 20 g) acidified to pH *ca.* 4.5 with trifluoroacetic acid (60 mg) with ethyl acetate–petroleum as eluant to give, first, the (4-*exo*-E)-(3′R)-*diastereoisomer* (3b) (21 mg) as a solid (m.p. 77—82 °C); R_F 0.22 [1% AcOH in ethyl acetate–petroleum (35 : 65)]; $\nu_{max.}$(CHBr$_3$) 3 590, 3 500—2 500, and 1 710 cm^{-1}; δ(CDCl$_3$) 7.10 (total 2 H, s, OH and CO_2H), 5.50—5.30 (total 3 H, m, CH=CH and δ-H), 4.10—3.90 (total 4 H, m, CH_2O, 1-H, and C*H*OH), 2.60—0.80 (total 25 H, m, remainder); δ_C (CDCl$_3$) 177 (s, C=O), 135.6 (d, C-2′), 133.5 (d, C-1′), 132.9 (s, C-4), 125.1 (d, C-δ), 80.9 (d, C-1), 73.7 (d, C-3′), 72.9 (t, C-3), and 47.1—13.9 p.p.m. (13 consistent signals, remainder); *m/z* 350 (M^+), 332 ($M^+ - H_2O$), and 279 ($M^+ - C_5H_{11}$) [Found (NH$_3$ c.i.m.s.): $(M + NH_4)^+$, 368.2830. $C_{21}H_{34}O_4 \cdot NH_4$ requires *m/z*, 368.2801).

This was followed by an inseparable mixture of the (4-exo-E)-(3′S)- *and* (4-exo-Z)-(3′R)-*diastereoisomers* (3a) and (2b), respectively, (9 mg; *ca.* 60 : 40) as a gum; R_F 0.17 [1% AcOH in ethyl acetate–petroleum (35 : 65)]; δ(CDCl$_3$) 5.60—5.45 (total 4 H, m, 2 × CH=CH), 5.37 (*ca.* 1 H, m, *E*-vinyl H), 5.18 (*ca.* 1 H, *Z*-vinyl H), 4.45 and 3.79 (total *ca.* 2 H, AB, *J* 15 Hz, 3-H_2 in *Z*-isomer), 4.10—3.90 (total *ca.* 6 H, m, 2 × 1-H, 2 × C*H*OH, and 3-H_2 in *E*-isomer), and 2.80—0.80 (total 54 H, m, remainder); δ_C (CDCl$_3$) as for (3b) *except* 72.9 and 65.7 [C-3 in (3a), (2b), respectively], 42.8 and 44.0 [C-6 in (3a), (2b), respectively), and 25.0 and 32.5 p.p.m. [C-5 in (3a), (2b), respectively) [Found (NH$_3$ c.i.m.s.): $(M + NH_4)^+$, 368.2825. $C_{21}H_{34}O_4 \cdot NH_4$ requires *m/z*, 368.2801).

The third major fraction (9 mg), which was contaminated by a small amount of dec-5-enedioic acid, contained the (4-exo-Z)-(3′S)-*diastereoisomer* (2a) (9 mg) as a gum; R_F 0.14 [1% AcOH in ethyl acetate–petroleum (35 : 65)]; δ(CDCl$_3$) main distinguishing absorptions as follows: 5.18 (1 H, m, δ-H) and 4.48 and 3.79 (total 2 H, AB, *J* 15 Hz, CH_2O) [Found (NH$_3$ c.i.m.s.): $(M + NH_4)^+$, 368.2811. $C_{21}H_{34}O_4 \cdot NH_4$ requires *m/z*, 368.2801).

Further purification could be achieved by treatment with a small molar excess of t-butyldimethylsilyl chloride and triethylamine in dichloromethane. After 20 min a normal ethereal work-up, in which the extracts were also washed with a buffered pH 6.5 solution, gave the corresponding silyl esters. Flash chromatography on silica (Merck 9385) using 10—25% ethyl acetate–petroleum gave the di-t-butyldimethylsilyl ester of dec-5-enedioic acid, followed by the t-butyldimethylsilyl esters of compounds (2) and (3). Saponification with 2M NaOH in ethanol at room temperature for 5 h, followed by acidification and normal ethereal work-up, gave pure samples of the acids (2) and (3).

We are grateful to the S.E.R.C. and Glaxo Group Research for financial support (C.A.S.E. to A. J. D.).

[2/015 *Received*, 6*th January*, 1982]

REFERENCES

[1] For a review of the synthesis and biological properties of prostacyclin and prostacyclin analogues see K. C. Nicolaou, G. P. Gasic, and W. E. Barnette, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 293.
[2] A. J. Dixon, R. J. K. Taylor, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1407.
[3] D. R. Dalton, J. B. Hendrickson, and D. G. Jones, *Chem. Commun.*, 1966, 591.
[4] R. J. Batten, A. J. Dixon, R. J. K. Taylor, and R. F. Newton, *Synthesis*, 1980, 235.
[5] E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190; R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 1979, 3981 and references therein.
[6] W. Skuballa, *Tetrahedron Lett.*, 1980, **21**, 3261.
[7] G. Cardillo and M. Shimizu, *J. Org. Chem.*, 1977, **42**, 4268.
[8] A. F. Cook and D. T. Maichuk, *J. Org. Chem.*, 1970, **35**, 1940.
[9] K. Takeo, *Carbohydr. Res.*, 1976, **48**, 290 and references therein.
[10] B. T. Buzzi, P. R. Olivato, R. Rittner, C. Trufer, H. Viertler, and B. Wladishaw, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1294.
[11] J. B. Stothers and P. C. Lauterbur, *Can. J. Chem.*, 1964, **42**, 1563.
[12] G. Miyajima and K. Takahashi, *J. Phys. Chem.*, 1971, **75**, 331.
[13] 'Progress in N.M.R. Spectroscopy,' eds. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Pergamon, 1969, vol. 5, p. 184.
[14] Preliminary communication; A. J. Dixon, R. J. K. Taylor, R. F. Newton, and A. Wadsworth, *Tetrahedron Lett.*, 1982, 23, 327.
[15] R. M. Jacobsen, R. A. Raths, and J. H. McDonald, *J. Org. Chem.*, 1977, **42**, 2545.
[16] J. W. Patterson and J. H. Fried, *J. Org. Chem.*, 1974, **39**, 2506; E. S. Binkley and C. H. Heathcock, *ibid.*, 1975, **40**, 2156.
[17] F. Huet, A. Lechevalier, M. Pellet, and J. M. Conia, *Synthesis*, 1978, 63.
[18] O. G. Plantema, H. de Koning and H. D. Huisman, *J. Chem. Soc., Perkin Trans. 1*, 1978, 304 and references therein.
[19] C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071.
[20] E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, 1972, **94**, 7210.