*Tetrahedron* Vol 29, pp. 1447 to 1456. Pergamon Press 1973 Printed in Great Britain

# A STEREOSELECTIVE TOTAL SYNTHESIS OF (±) PROSTAGLANDIN $E_1$[1,2]

D. TAUB, R. D. HOFFSOMMER, C. H. KUO, H. L. SLATES, Z. S. ZELAWSKI and N. L. WENDLER*

Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Rahway, New Jersey

(*Received in USA* 12 *October* 1972; *Received in the UK for publication* 8 *January* 1973)

**Abstract**—A stereoselective total synthesis of prostaglandin $E_1$ employing 5-methoxyindanone-1 as starting material is described.

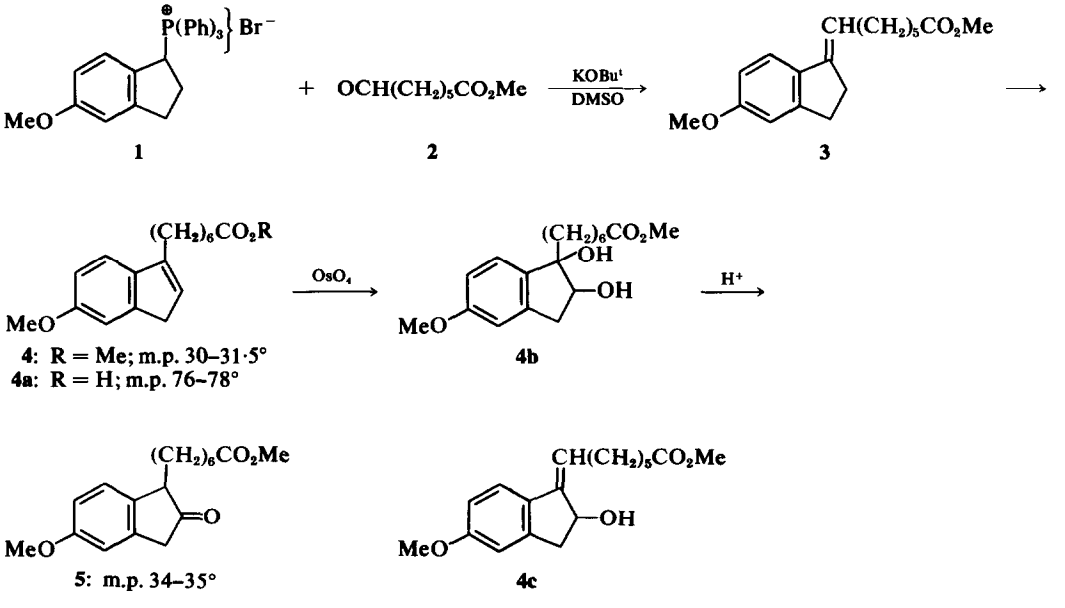
It was the design of the present undertaking to construct the *cis*-hydrindenone system **17** in which it was anticipated that the *exo* orientation of the heptanoic acid side-chain would prevail. Cleavage oxidation of **17** in turn would generate an epimerizable acetyl function thereby securing the proper *trans, trans* geometrical disposition of substituents about the cyclopentanone ring. The subsequent elaboration of the pertinent groups to yield the desired end-functionality constituted the experimental hazard to be enjoined.

Wittig condensation of triphenyl 5-methoxyindanyl phosphonium bromide **1**, derived from 5-methoxyindanone, with methyl 6-formylhexanoate[3]† **2** (KOt-Bu/DMSO) yielded the exocyclic unsaturated ester **3**.‡ The exocyclic olefin **3** was isomerized in turn to the endocyclic isomer **4** m.p. 30–31·5° in chloroform solution containing a catalytic trace of trifluoroacetic acid at 25°. The *endo-exo* equilibrium ratio was 9:1 and the *endo* isomer **4** was obtained pure by crystallization of the mixture from hexane-ether. Equilibration of the mother liquor and saponification to the more easily isolable free acid **4a** m.p. 76–78° raised the overall yield of **4** from **1** to 75–80%.

Hydroxylation of **4** with osmium tetroxide followed by acid catalyzed dehydration of the intermediate diol **4b** (PTSA-benzene) afforded the keto ester **5** m.p. 34–35°. The acid catalyzed con-

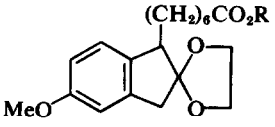
†We obtained **2** from cycloheptanone (see Exptl).

‡Attempted formation of **3** by Wittig condensation of 5-methoxyindanone-1 as the carbonyl component with the ylids derived from $[(C_6H_5)_3P(CH_2)_6CO_2R]^+$ (R=$CH_3$, H) was unsuccessful, although condensation did occur with ethylidene triphenylphosphorane.

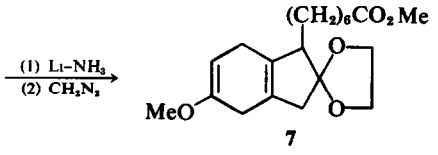


version of **4b** → **5** was observed to proceed at least in part *via* the allylic carbinol **4c** as evidenced by the intermediate formation of the latter on interruption of the reaction. A diversity of oxidative alternatives for the conversion **4** → **5** were examined and found to lack the desired specificity and yield. The more promising approaches involved (a) hydroboration followed by 2-phase sodium dichromate oxidation and (b) conversion to the bromohydrin (NBS-aq. acetone-$CaCO_3$) followed by HBr elimination (MeONa–MeOH).

The keto ester **5** was successively ketalized to **6** and saponified to give the acid **6a** which in turn was submitted to Birch reduction (Li-$NH_3$/THF-t-BuOH) with concluding esterification. Treatment of the Birch reduction product **7** with aqueous acetic acid in tetrahydrofuran at 10° achieved selective enol ether collapse to afford the $\beta,\gamma$-unsaturated ketonic ester **8**. Attempted enol ether cleavage of **7** by the standard oxalic acid-MeOH/THF procedure[4] resulted in a product contaminated with the corresponding dimethyl ketal of **8**. The latter impurity was evidenced by an NMR singlet at $\delta$ 3·10, present also in the spectra of analogous 3,3-dimethyl $\Delta^{5(10)}$-steroids.



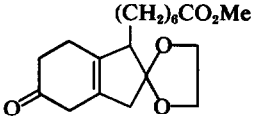

**6**: R = Me
**6a**: R = H



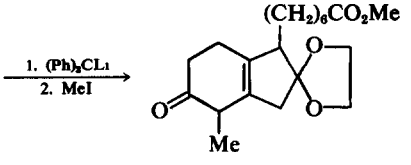

**7**

Attempts to isomerize the double bond of **8** $\beta,\gamma \rightarrow \alpha,\beta$ by base catalysis in methanol resulted in loss of the ketal function and formation of the dienolone methyl ether **9**. The latter on brief treatment with aqueous perchloric acid in tetrahydrofuran yielded the dienolone **9a** m.p. 120–122°; $\lambda_{max}^{MeOH}$ 361 nm ($\epsilon$ 8,200), 314 nm ($\epsilon$ 21,200); $\lambda_{max}^{MeOH/OH^-}$ 361 nm ($\epsilon$ 68,000). By contrast with this finding, acid catalyzed deketalization **8** → **8a** followed by methoxide treatment led to the $\Delta^{1(7a)}$ hydrinden-2,5-dione **8b** $\lambda_{max}^{MeOH}$ 237 nm ($\epsilon$ 12,500). Of the three possible migration sites alpha to the CO functions, the fully substituted 1(7a)-position is preferred.

Methylation of **8** with trityllithium and methyl iodide in hexamethylphosphoramide and tetrahydrofuran resulted exclusively in $\alpha$-methylation to give a single monomethylated compound **10**. In carrying out this methylation, the $\Delta^{\beta,\gamma}$-ketone **8** was first converted to its enolate by addition to a slight excess of lithium triphenylmethyl in THF-HMPT thereby assuring kinetic formation of the desired C-4-enolate anion and avoiding $\Delta^{\beta,\gamma} \rightarrow \Delta^{\alpha,\beta}$ isomerization leading to dienolone **9a**. The enolate anion of **8** thus formed was injected slowly into a large excess of methyl iodide. In this manner yields of better than 90% of the desired monomethylated product **10** were realized with essentially no dimethylated by-product being observed.

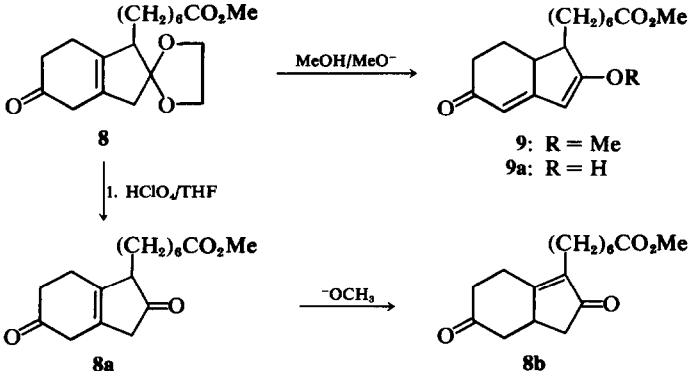



**8**




**10**

Hydrogenation of the methylated $\Delta^{\beta,\gamma}$-ketonic ester **10** over 5% ruthenium on charcoal in ethanol at 1600 p.s.i. formed an intermediate diol that was oxidized with chromic acid to afford predominantly the C-1 *endo* substituted *cis* hydrindandione **11**




**8**

**9**: R = Me
**9a**: R = H

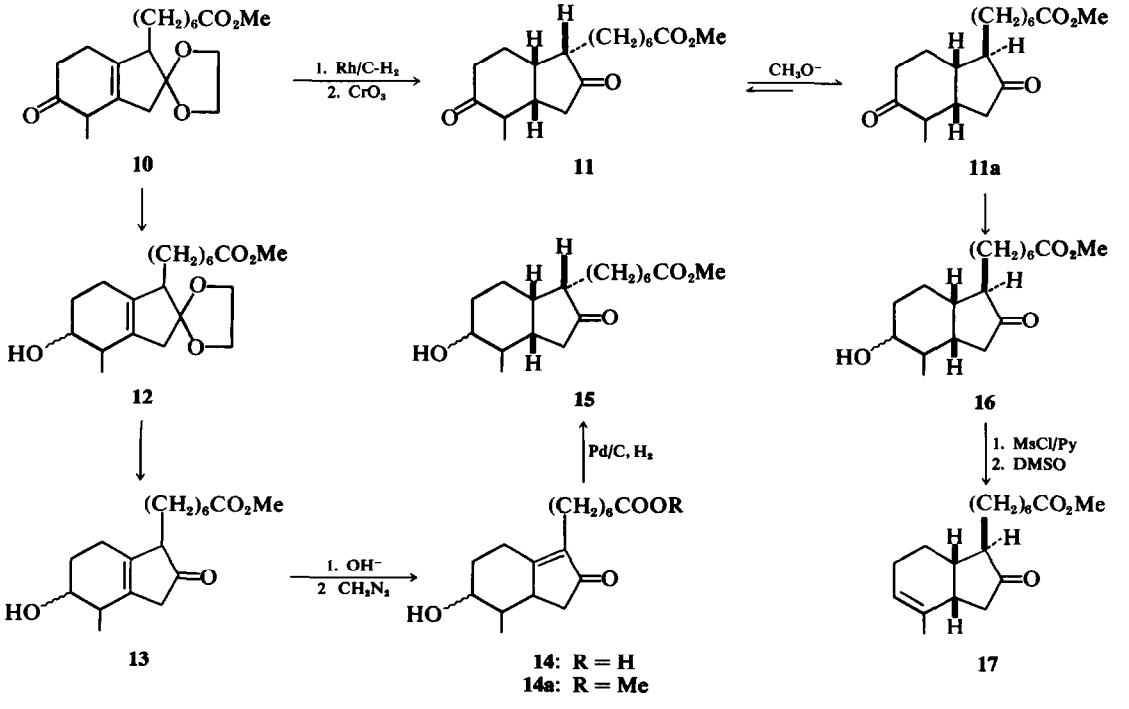
**8a**

**8b**

together with lesser amounts of its C-1 *exo* epimer **11a**. Equilibration with sodium methoxide in methanol reversed the proportion of the two isomers and produced a 5 : 1 ratio of **11a** to **11**, respectively, whereby the predominant *exo* isomer **11a** was the desired one. The orientational assignment is consistent with expectations referred to earlier and is based on the greater steric stability of the side chain in an *exo* orientation to the *cis*-fused hydrindanone system. The diketone **11a** was selectively reduced with lithium tri-t-butoxy aluminum hydride at the 6-ring carbonyl function and the resulting carbinol dehydrated exclusively in the Saytzeff sense by heating its mesylate ester in dimethyl sulfoxide to give the key bicyclic olefinic keto ester **17** in 90% yield.

An alternative route to **17**, and in fact the preferred one for preparative purposes, consisted of initially reducing **10** [$LiAlH(t\text{-}OBu)_3$] to **12** followed by deketalization with aqueous perchloric acid in tetrahydrofuran to give **13**. The double bond of **13** was subsequently isomerized by base to afford the $\Delta^{\alpha,\beta}$-ketone **14**; $\lambda_{max}$ 239 nm ($\epsilon$ 12,700). (Compare conversion **8a** → **8b**). The double bond isomerization was carried out in aqueous methanolic potassium hydroxide to permit the isomerized acid thus obtained to be separated from any by-product triphenylmethane remaining from the methylation step. Diazomethane treatment yielded methyl ester **14a** which was hydrogenated over 10% Pd-C in methanol at 25° and atmospheric pressure to give **15** as a mixture of C-5 epimers. Although this path involved more steps than the ruthenium hydrogenation route, it was nonetheless the more dependable and higher yield sequence. The hydrogenation product **15** was purified by chromatography (60% yield) in the only purification over eight steps from the $\beta$-indanone **5**. Prior isomerization of the C-1 side chain in **15** was not required since the mesylation-desmesylation sequence produced **17** in equilibrated form (90% yield), which was shown by VPC and NMR to consist of 85% of the *exo* epimer as represented by structure **17**. It was not found feasible to separate the minor C-1 *endo* epimer at this stage; consequently the epimeric mixture was processed through the remaining steps of the synthesis and an epimeric separation was effected at the penultimate stage (see later discussion).

The hydrindenone **17** was converted to the ethylene acetal derivative **18** and the latter cleaved by the Lemieux-von Rudloff procedure ($KMnO_4$-$NaIO_4$)[5] to the corresponding acetylcyclopentane propionic acid **19** which in turn was esterified with diazomethane to the corresponding ester **19a**. The acetyl function of the latter had partially epimerized in the basic oxidation medium as indicated by separate NMR singlets at $\delta$ 2·17 (major) and $\delta$ 2·21 (minor). Treatment of this mixture with sodium methoxide in methanol at 25° completed the epimerization to give the desired *all trans* compound **19a** with a single NMR singlet at $\delta$ 2·17. Baeyer-Villiger oxidation of **19a** with *m*-chloroperbenzoic acid proved to be slow and resulted



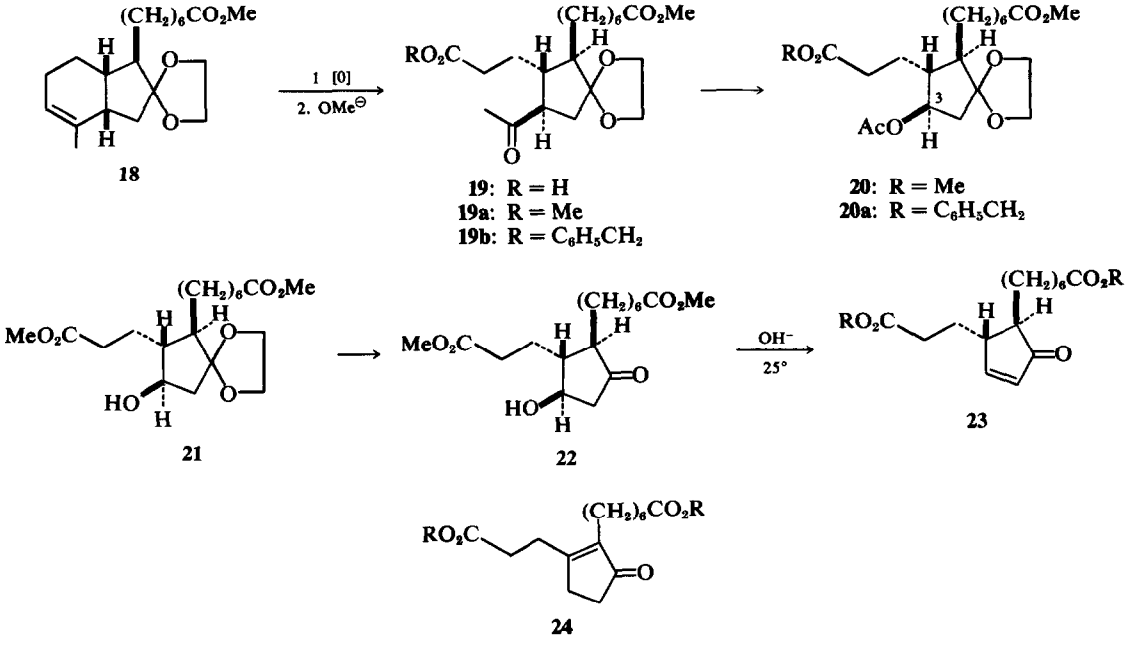
in substantial loss of the acetal function under the acidic conditions of the reaction. Peroxytrifluoroacetic acid in methylene chloride buffered with disodium hydrogen phosphate, on the other hand, was a more efficient reagent; oxygen insertion proceeded with retention of configuration[6] and negligible loss of the ketal group. The acetoxy diester **20** exhibited a singlet δ 2·02 ($MeCO_2$). A 1H multiplet at δ 4·87 is assigned to the C-3 carbinolic hydrogen, and is indicative of *trans* stereochemistry with respect to the substituents at C-2 and C-3. The absence of resonance in the δ 5·1–5·2 region demonstrated the absence of *cis* isomer.*

Deacetylation of **20** with sodium methoxide in methanol led to the hydroxy diester **21** which was successfully deketalized to **22** without β-elimination of the hydroxyl function by employing 1:1 aqueous acetic acid at 22° for 3 hr. This result also foreshadowed success in the analogous projected final step of the synthesis. The β-hydroxycyclopentanone part structure of **22** was substantiated by treatment with a catalytic amount of potassium hydroxide in methanol at 25° to give the chromophore **23**, $\lambda_{max}$ 218 nm, whereas at 90° with excess alkali, **24** $\lambda_{max}$ 238 nm was produced. This behavior parallels that observed for dihydroprostaglandin $E_1$.[8] At this stage, with the substituents on the cyclopentanone ring disposed in the required *trans,trans* arrangement, the major stereochemical problem had been solved. The remaining task involved conversion of the propionic acid residue into the required octenol side chain.

The *trans* keto acid **19** was converted into its benzyl ester **19b** with phenyldiazomethane and the latter treated in the Baeyer-Villiger oxidation to yield **20a**. Hydrogenolysis of **20a** over 10% palladium on charcoal in ethyl acetate yielded the acetoxy half-acid ester **25**. Irradiation of a solution of **25** in pyridine-benzene in the presence of lead tetraacetate and copper acetate according to the method of Bacha and Kochi,[9] proceeded with eliminative decarboxylation and the formation of the olefin **26** (35–40%). Cleavage oxidation ($OsO_4$-$NaIO_4$)[10] of of the olefin **26** gave a high yield of aldehyde **27** which was condensed directly with ylid derived from dimethyl 2-oxoheptylphosphonate[2a] to yield the derivative **28** of 15-dehydroprostaglandin $E_1$, $\lambda_{max}$ 228 nm (ε 14,000). Reduction of **28** with sodium borohydride in methanol at −5° proceeded as anticipated to give a chromatographically separable ~1:1 mixture of the $C_{15}$-epimeric carbinols **29** (15 S) and **29a** (15 R). The 15 R isomer **29a** was efficiently oxidized with manganese dioxide back to the 15-keto precursor **28**. The more polar 15S isomer **29** on basic hydrolysis yielded crystalline (±) prostaglandin $E_1$ dioxalane **30**, m.p. 81–83°. Removal of the dioxalane blocking group of **30** with 1:1 aqueous acetic acid at 20–25° for 3 hr yielded directly crystalline (±) prostaglandin $E_1$, m.p. 112–113° identical by TLC, IR, NMR and MS (methyl ester) criteria with natural (−) prostaglandin $E_1$.

On the other hand, when the deblocking operation was effected on *total crude* dioxalane deriva-

*The corresponding carbinolic hydrogen in esters of *trans* and *cis* 2-acetoxycyclopentanepropionic acid absorbed at δ 4·78 and δ 5·16, respectively.[7]



tive **30** there was afforded in addition to (±) $PGE_1$ a small amount of a minor component identified as (±) 8-*iso*-$PGE_1$ m.p. 96–98° (reported[2b] 101–102°). Equilibration of the latter (KOAc–EtOH)[11] led to (±) $PGE_1$. The (±) 8-*iso*-$PGE_1$ derived from crude **30** originated from the minor amount of endo-side chain isomer present at equilibrium in the *cis*-hydrindenone **17** (*cf* earlier discussion).

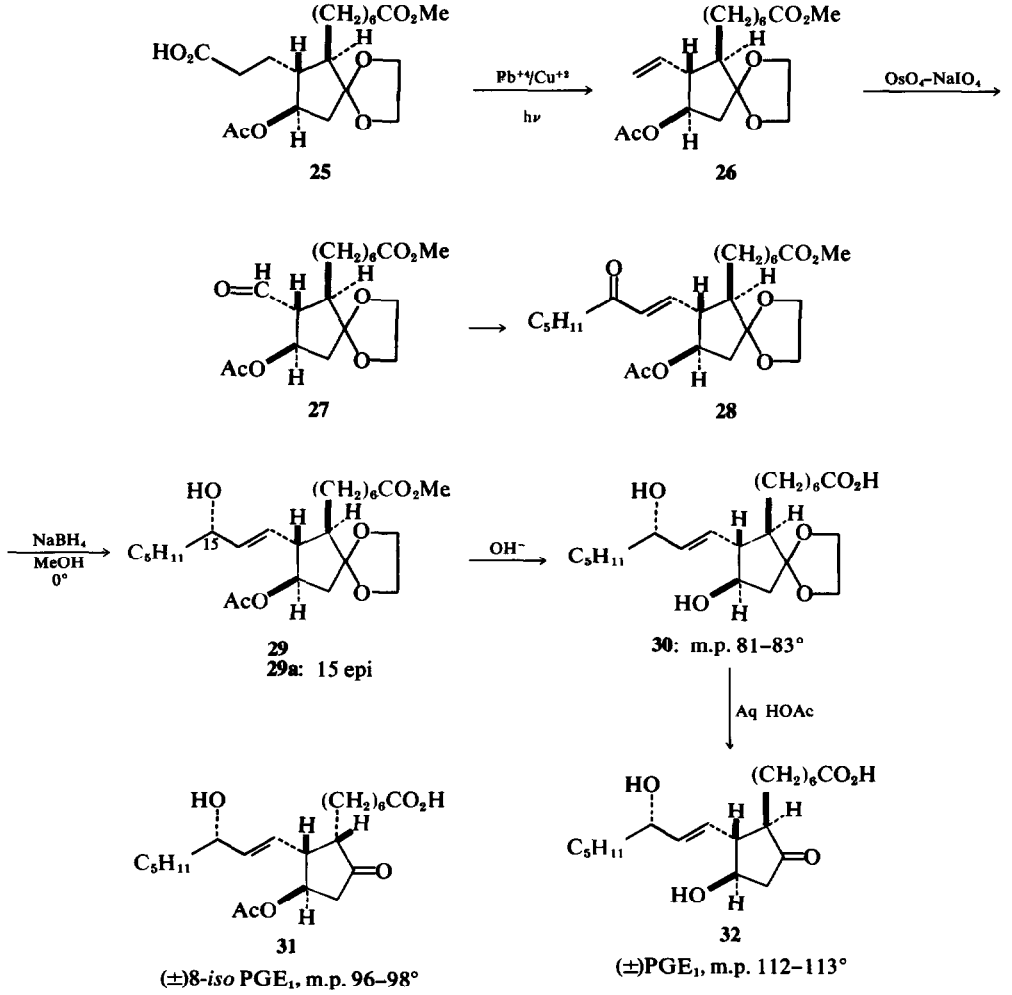
## EXPERIMENTAL

M.ps were taken on a microscope hot-stage apparatus and are uncorrected. UV spectra were determined in MeOH on a Cary model 11 PMS spectrometer and IR spectra on a Perkin-Elmer Infracord instrument. NMR spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. TLC was carried out on silica gel G coated glass plates and column chromagraphy on silica gel H columns by the "dry column" technique. The proper elution system was determined by TLC probes, and fractions were collected automatically. VPC determinations were carried out on a Varian-Aerograph No. 200 instrument employing a 5 ft × 0·25 in. 20% S.E. 30 on Chrom W Column

*5-Methoxyindanone*[12a]. This substance was prepared by cyclization of *m*-methoxyphenylpropionic acid in polyphosphoric acid[12b] at 45–50° for 4 hr; m.p. 108–110° (from MeOH); yield 70–75%. Under these conditions formation of the 7-methoxy isomer was minimized.

*Triphenyl 5-methoxyindanylphosphonium bromide* **1**. To a stirred soln of 50 g 5-methoxyindanol (prepared by $NaBH_4$–EtOH reduction of 5-methoxyindanone[13]) in 750 ml $CH_2Cl_2$ was added 102·3 g triphenylphosphine hydrobromide[14] in portions over 5 min. The mixture was stirred for 1 hr and then concentrated to dryness under vacuum. Crystallization of the residue from acetone (250 ml) gave **1** as a white powder, 142 g (95%), m.p. 210–212°. (Found: C, 68·56; H, 5·49; P, 6·11; Br, 16·08. Calc. for $C_{28}H_{26}OPBr$: C, 68·70; H, 5·36; P, 6·33; Br, 16·33%).

*Methyl 6-formlhexanoate* **2**. This compound was obtained in two steps from cycloheptanone. Persulfuric acid-methanol oxidation of cycloheptanone by the procedure of Robinson and Smith[15] for the corresponding ethyl ester led to methyl 7-hydroxyheptanoate. Improved



yields resulted on extending the room temp reaction time to 42–48 hr and omitting the 6 hr reflux period; yield 30 g (70%), b.p. 91–94°/0·1 mm. The distilled material contained *ca* 5% of dimethyl pimelate (VPC) as a minor impurity which was removed during the next step.

To a stirred solution of 48 g of the above methyl 7-hydroxyheptanoate in 120 ml DMSO and 270 ml triethylamine maintained at 20–25° was added dropwise 143·3 g pyridine-$SO_3$ complex in 450 ml DMSO.[16] After 3 hr at 25° the mixture was chilled, poured onto crushed ice, acidified with 2·5N N HCl and thoroughly extracted with ether. The ether extract was washed with 5% $KHCO_3$ aq, NaCl aq, dried over $MgSO_4$ and concentrated to dryness to give **2** as a pale yellow oil 46·7 g (98%) 85% pure by VPC. Distillation yielded 28·5 g (60%) pure **2**, b.p. 62°/0·1 mm. On standing the aldehyde was slowly converted to a cyclic trimer. If it was not used within 48 hr, the aldehyde was stored as the bisulfite addition product prepared by stirring an ether soln of **2** with an excess of 50% $NaHSO_3$ aq at 5° and filtering the crystalline bisulfite addition product. Regeneration of **2** from its bisulfite addition product was effected by stirring with sat $Na_2CO_3$ aq at 10° and extraction of **2** with ether.

*5-Methoxy-1-indeneheptanoic acid methyl ester* **4**. To a stirred soln of 9·63 g t-BuOK in 60 ml DMSO maintained under $N_2$ was added 40 g of **1** in 300 ml DMSO. After 5 min 12·9 g of **2** was added dropwise just discharging the ylid red color. The mixture was stirred 1 hr and then poured into 1000 ml $H_2O$ and 350 ml hexane. Precipitated triphenylphosphine oxide was filtered off and the filtrate extracted with ten 75 ml portions hexane. The latter extracts were washed successively with 1:1 DMSO-$H_2O$ (4×250 ml), $H_2O$ (4×250 ml) and sat NaCl aq (300 ml) and dried over $MgSO_4$. Removal of solvent yielded 20·1 g crude *exocyclic indanyl ester* **3** as a pale yellow oil; NMR ($C_6D_6$) δ 2·69 (4H, m. $ArCH_2CH_2C=$), 3·40 (3H, s, OMe), 3·42 (3H, s, OMe), 5·70 (1H, m. vinyl H), 6·5–7·5 (3H, Ar).

To a soln of **3** (20·1 g) in $CHCl_3$ (200 ml) was added 5 drops trifluoroacetic acid. After 4·5 hr at 20–25° the soln was concentrated under vacuum and the residue crystallized from hexane to give 17·4 g (74%) of **4** m.p. 30–31·5°; $\lambda_{max}^{MeOH}$ 261 nm (13,600); NMR ($CDCl_3$) δ 3·30 (2H, broad s, $ArCH_2CH=$), 3·65 3H, s, ester $OCH_3$); 3·81 (3H, s, $ArOCH_3$), 6·06 (1H, m, vinyl H), 6·75–7·35 (3H, Ar). (Found: C, 74·73; H, 8·33. Calc. for $C_{18}H_{24}O_3$: C, 74·97; H, 8·39%.)

Saponification of the mother liquors (2·7 g) in aqueous methanolic KOH at room temp and crystallization of the product from ether hexane gave **4a** (0·63 g) m.p. 76–78°. (Found: C, 73·95; H, 8·02. Calc. for $C_{17}H_{22}O_3$: C, 74·40; H, 8·08%). Esterification of **4a** with diazomethane yielded crystalline **4** (total yield 77% from **1**).

*5-Methoxy-2-oxo-1-indanheptanoic acid methyl ester* **5**. To a stirred soln of 10·25 g of **4** in 40 ml pyridine maintained at 15–20° was added 9·0 g $OsO_4$ in 60 ml pyridine. After 18 hr at room temp the mixture was added to a soln of $NaHSO_3$ (16·2 g) in 270 ml water and 180 ml pyridine [17] and stirred for 1 hr. The mixture was extracted with chloroform and worked up in the usual manner to give the glycol ester, *5-methoxy1,2-dihydroxy-1-indanheptanoic acid methyl ester* **4b** as a viscous yellow oil (11·2 g); IR ($CHCl_3$) 2·85, 2·95, 5·78 μ.

The total glycol product in 50 ml benzene was added dropwise with stirring to 6·5 g anhydrous *p*-toluenesulfonic acid in 10 ml benzene at 50°. After 4 hr at room temp the mixture was decanted, the solid washed with benzene and the combined benzene extracts washed successively with 5% $KHCO_3$ aq, water, sat NaCl aq, dried over $MgSO_4$, treated with charcoal, and concentrated to dryness under vacuum. Crystallization of the residue from ether-hexane gave 8·03 g (74% from **4**) of **5** m.p. 34–35°; IR ($CHCl_3$) 5·72, 5·78 μ; NMR ($CDCl_3$) δ 3·50 (2H, s, $ArCH_2CO$), 3·67 (3H, s, ester $OCH_3$), 3·83 (3H, s, $ArOCH_3$). (Found: C, 70·71; H, 7·52. Calc. for $C_{18}H_{24}O_4$: C, 71·04; H, 7·95%).

Dry column chromatography of the mother liquors yielded an additional 0·56 g (6%) of crystalline **5**

The 2,4-dinitrophenylhydrazone had m.p. 115–116° (Found: C, 59·46; H, 5·89; N, 11·65. Calc. for $C_{24}H_{28}N_2O_7$: C, 59·49; H, 5·83; N, 11·56%).

*5-Methoxy-2-oxo-1-indanheptanoic acid methyl ester ethylene acetal* **6**. A mixture of **5** (16·0 g), ethylene glycol (24 ml) and *p*-toluenesulfonic acid monohydrate (0·36 g) in benzene (650 ml) was refluxed with water separation (Dean-Stark trap) for 22 hr under $N_2$. The mixture was cooled, made basic with 5% $K_2CO_3$ aq, washed with water, sat NaCl aq dried over $Na_2SO_4$ and concentrated to dryness under vacuum to give **6** (16·3 g) as an oil; IR ($CHCl_3$) 5·78, 10·50 μ; NMR ($CDCl_3$) δ 3·48 (4H, s, $—OCH_2CH_2O—$); 3·67 (3H, s, ester $OCH_3$), 3·75 (3H, s, $ArOCH_3$).

Completion of cyclic acetal formation was shown by VPC; single peak Rt 13·2 min at 275°.

*5-Methoxy-2-oxo-1-indanheptanoic acid ethylene acetal* **6a**. To a soln of **6** (16·3 g) in MeOH (175 ml) under $N_2$ was added a soln of 5·3 g KOH in 88 ml MeOH-water (3:1). The mixture was stirred at room temp for 18 hr, concentrated to remove the MeOH, diluted with water and washed with benzene-hexane (1:1). Chloroform (200 ml) was added followed by 10% $NaH_2PO_4$ aq to pH 5-6. The mixture was extracted with $CHCl_3$ and the latter extract washed with sat NaCl aq, dried over $Na_2SO_4$ and concentrated under vacuum to give **6a** as a viscous oil (14·3 g) pure by TLC ($R_f$ 0·5, 20% MeOH-$CHCl_3$).

*2-Oxo-5-methoxy-4,7-dihydro-1-indanheptanoic acid methyl ester 2-ethylene acetal* **7**. A soln of **6a** (11·3 g) in 290 ml of 1:1 THF-t-BuOH was added dropwise to a stirred soln of liquid $NH_3$ (290 ml). Li ribbon (4·05 g) in 1·5″ strips was added over 4 hr to the mixture which was maintained at gentle reflux by appropriate dry ice-acetone cooling. After an additional 30 min, MeOH (100 ml) was added and the $NH_3$ evaporated overnight in a slow stream of $N_2$. Water (250 ml) was then added and the mixture was concentrated under vacuum to remove most of the THF and t-BuOH present. Additional water was added, the mixture was extracted twice with ether, brought to pH 5·5 with 10% $NaH_2PO_4$ aq and extracted with $CHCl_3$. The latter extract was washed with sat NaCl aq dried over $Na_2SO_4$ and concentrated under vacuum to give the Birch reduction product acid (11·2 g). To a soln of the latter in ether (25 ml) was added excess ethereal diazomethane. Removal of volatiles under vacuum yielded the reduced ester **7**; (11·3 g) IR ($CHCl_3$) 5·75, 6·01, 10·50, 10·82 μ; NMR ($C_6D_6$) δ 2·77 (4H, broad s, allylic H); 3·35 (3H, s, enol Me), 3·40 (3H, s, ester OMe), 3·57 (4H, s, $—OCH_2CH_2O—$), 4·58 (1H, m, vinyl H).

*2,5-Dioxo-4,5,6,7-tetrahydro-1-indanheptanoic acid methyl ester 2-ethylene acetal* **8**. To a stirred soln of 9·4 g of **7** in 18 ml THF at 10° was added dropwise 108 ml 1:1 AcOH-water. The mixture was maintained at 10° for 5 hr, poured into excess ice cold $KHCO_3$ aq and extracted with benzene-hexane (9:1). The organic extract was

washed with sat NaCl aq, dried over $Na_2SO_4$ and concentrated under vacuum to yield **8** (8·92 g; 97%) as a viscous oil; IR (neat) 5·75, 5·82, 10·50 $\mu$; NMR ($C_6D_6$) $\delta$ 3·40 (3H, s, ester $OCH_3$), 3·57 (4H, s, $-OCH_2CH_2O-$).

*Dienolone methyl ether* **9**. To a stirred soln of **8** (610 mg) in 8 ml dry MeOH maintained under $N_2$ was added 4 ml of 1·0 N methanolic NaOMe. After 1 hr a TLC probe (5% acetone-$CHCl_3$) indicated complete conversion to more polar entities. The mixture was added to conc $NaH_2PO_4$ aq and extracted with $CHCl_3$. The latter extract was washed with 5% $KHCO_3$ aq, conc NaCl aq, dried over $Na_2SO_4$ and concentrated to dryness on the water pump to give the crude **9** (157 mg) as an oil $\lambda_{max}^{CH_3OH}$ 313 nm ($\epsilon$ 24,000) no change on adding NaOH; IR ($CHCl_3$) 5·75 (strong), 6·10, 6·18, 6·35 $\mu$ (very strong) the 10·5 ethylene acetal band was absent. The NMR spectra in $C_6D_6$ and $C_6D_6+D_2O$ were identical indicating the absence of active H. $\delta$ 3·42 (s, 3H COOMe), 3·18 (s ~ 1·5H enolic OMe, 3·74 (s ~ 1·5H enolic OMe), 4·98 (broad s, ~0·5H), 5·10 (broad s, ~0·5H), 6·00 (broad s, 1H). The data suggest the presence of two species—presumably **9** and the alternative 2-oxo-5-methoxy formulation.

*Dienolone* **9a**. The dienolone **9** (400 mg) was kept 75 min in 8 ml THF and 8 ml 1·5N $HClO_4$ at room temp. The mixture was added to cold water and extracted with chloroform. The organic extract was washed with 5% $KHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness. The solid residue was crystallized from ether to give **9a** (250 mg) m.p. 120–122°; $\lambda_{max}^{MeOH}$ 361 nm ($\epsilon$ 8,200), 314(21,200), 230(2,900); $\lambda_{max}^{MeOH+OH^-}$ 361 nm ($\epsilon$ 68,000), 223(6,000); IR (njl) 5·75, 6·10, 6·30–6·70 $\mu$ (very strong). (Found: C, 69·81; H, 8·53. Calc. for $C_{17}H_{24}O_4$: C, 69·83; H, 8·27%).

*Δ-1(7a)-2,5-dioxo-1-hydrindenheptanoic acid methyl ester* **8b**. A soln of **8** (200 mg) in 3 ml THF and 3 ml 1·5 N $HClO_4$ was kept 90 min at room temp. Work up as for **9a** yielded the unconjugated enedione **8a** (150 mg) as a colourless oil; IR ($CHCl_3$) 5·72, 5·78, 5·83 $\mu$ (no 10·5 ethylene acetal band).

To this material in 3 ml MeOH under $N_2$ was added 1 ml 1N methanolic NaOMe. After 90 min at room temp, the mixture was worked up as for **9** to give **8b** as a pale yellow oil (110 mg); $\lambda_{max}^{MeOH}$ 237 nm ($\epsilon$ = 12,500) with minor maxima at 312 and 362 nm; IR ($CHCl_3$) 5·75, 5·82. 5·90, 6·03 $\mu$.

*4-Methyl-2,5-dioxo-4,5,6,7-tetrahydro-indanheptanoic acid methyl ester 2-ethylene acetal* **10**. A soln of trityl lithium in THF–HMPT was prepared as follows: Ethereal MeLi (25 ml, 2·004M) was concentrated to dryness under vacuum and the residue maintained under $N_2$. A soln of 2·24 g triphenylmethane in 46 ml THF (freshly distilled from LAH) was added at 0–5° with stirring. The mixture was stirred for 3·5 hr at 20° (negative Gilman test for MeLi) and then diluted with 46 ml of HMPT (dried over molecular sieves and distilled at reduced press). Titration of an aliquot vs cyclohexanone showed the trityl lithium titer to be 0·486M.

To 16·5 ml of this trityl lithium soln (8·02 m mol) was added by syringe under $N_2$ with stirring 2·68 g (7·98 m mol) of the $\Delta^{\beta,\gamma}$-ketone **8** in 25 ml THF.

The resultant enolate soln was added dropwise by syringe with stirring to 33 ml MeI. After 5 min the mixture was poured into a chilled mixture of AcOH (6 ml) water (10 ml), benzene (50 ml) and hexane (50 ml). Dil $KHCO_3$ aq was added to neutralize the excess AcOH, the layers were separated and the aqueous phase extracted with benzene. The combined organic extracts were washed with water, sat NaCl aq, dried over $Na_2SO_4$ and concentrated to dryness under vacuum.

The product (3·18 g) was freed from triphenylmethane by dry column chromatography on silica gel (32 g) eluting with $CHCl_3$ to afford 2·50 g (90%) pure **10** as a colorless oil; NMR ($CDCl_3$) $\delta$ 1·07 (3H, d, J = 7, C-4 Me), 3·40 (3H, s), 3·58 (4H, s). (Found: C, 68·97; H, 8·63 Calc. for $C_{20}H_{30}O_5$: C, 68·54; H, 8·63%).

For preparative purposes chromatographic separation of triphenylmethane was not required. It was removed by extraction from the carboxylic acid intermediate **14** generated two steps later.

*4-Methyl-2-oxo-5-hydroxy-4,5,6,7-tetrahydro-1-indanheptanoic acid methyl ester-2-ethylene acetal* **12**. To a stirred soln of 9·29 g methylated $\Delta^{\beta,\gamma}$-ketone **10** containing ~10% triphenyl methane) in 100 ml THF at 0° was added a soln of 13·5 g lithium tri-t-butoxy aluminum hydride in 250 ml THF. After 4 hr at 0° sat $Na_2SO_4$ aq (100 ml) was added dropwise and THF removed under vacuum. EtOAc was added and the inorganic salts were filtered off and washed with EtOAc. The filtrate was extracted further with EtOAc and the organic extract was washed with sat NaCl aq dried over $Na_2SO_4$ and the solvent removed under vacuum to give **12** as a colorless oil; 9·30 g; IR (neat) 2·85, 5·75, 10·50 $\mu$; NMR ($C_6D_6$) $\delta$ 1·06 (3H, d, J = 7), 3·40 (3H, s), 3·60 (4H, s).

*4-Methyl-2-oxo-5-hydroxy-4,5,6,7-tetrahydro-1-indanheptanoic acid methyl ester* **13**. The ester **12** (9·3 g) in 95 ml THF was hydrolyzed as in the case of **9a** (see above) by stirring at 0–5° with 95 ml cold 1·5N $HClO_4$ to give **13** as an oil (8·37 g); IR ($CHCl_3$) 2·85, 5·75 $\mu$; NMR ($C_6D_6$) $\delta$ 0·88 (3H, d, J = 7), 3·40 (3H, s), 3·80 (1H, broad s, H—C—OH).

*Δ-1(7a)-4-Methyl-2-oxo-5-hydroxy-1-hydrindanheptanoic acid methyl ester* **14a**. The ester **13** (8·37 g) in 67 ml MeOH was hydrolyzed under $N_2$ at 20° with a soln of KOH (6 g) in 90 ml $H_2O$ and 58 ml MeOH for 20 hr to afford **14** (8·51 g); IR ($CHCl_3$) 2·85–3·2, 5·82, 5·90, 6·06 $\mu$.

The total acid product **14** (8·35 g) on esterification with ethereal $CH_2N_2$ yielded **14a** (8·80 g); $\lambda_{max}^{CH_3OH}$ 239 m$\mu$ (13,500); IR (film) 2·86, 5·71, 5·90, 6·05 $\mu$; NMR ($C_6D_6$) $\delta$ 0·88 (3H, d, J = 7), 3·40 (3H, s) 3·80 (1H, broad s).

*4-Methyl-2-oxo-5-hydroxy-cis-hydrindan-1-heptanoic acid methyl ester* **15**. 10% Pd-C (3·8 g) was added cautiously under $N_2$ to 85 ml MeOH. Unsaturated ester **14a** (3·8 g) in 75 ml MeOH was added and hydrogenation conducted at 1 atm and 25°. Completion of the hydrogenation (4–6 hr) was best determined by disappearance of the conjugated CO band at 5·90 $\mu$ (IR) of an aliquot at which point $H_2$ uptake was 10–15% over theory. The catalyst was removed by filtration, the filtrate taken to dryness and the residue chromatographed on 150 g of silica gel, eluting with 12% acetone-$CHCl_3$. Hydrogenolysis products (~600 mg) in which one (*m/e* 296) or two (*m/e* 280) oxygens were gone were eluted first, followed by 2·42 g (~65%) of the desired ketol (*m/e* 310) as a two-component mixture (TLC, $R_F$ = 0·2–0·3) probably epimeric at C-4 and/or C-5. The major component had IR ($CHCl_3$) 2·72, 2·86, 5·72, 5·78 $\mu$; NMR ($CDCl_3$) $\delta$ 1·05 3H, d, J = 7), 3·64 (3H, s), 3·90 (1H, m). (Found: C, 74·00; H, 9·45. Calc. for $C_{18}H_{30}O_4$: C, 74·00; H, 9·65%).

*Ketols* **15** *and* **16** *via hydrogenation of* **10**. A soln of methylated Δ-β,γ-ketonic ester **10** (2·45 g containing *ca* 0·3 g triphenylmethane) in EtOH (220 ml) was hydrogenated at 1600 p.s.i. and 50° for 20 hr over 3·00 g 5% ruthenium on charcoal catalyst. The mixture was filtered

through celite, the filter pad washed thoroughly with MeOH, and the combined filtrate and washings taken to dryness under vacuum to give 1·86 g of a saturated polar product (largely epimeric diols corresponding to **11**) containing OH and ester functionality and lacking ethylene acetal and CO functionality.

This material in ether (25 ml) and benzene (5 ml) was oxidized with sodium dichromate in $H_2SO_4$ aq by the procedure of Brown and Garg[18] and the product chromatographed on 110 g silica gel eluting with 4% acetone-$CHCl_3$ to give 660 mg of **11** and **11a** with the former predominating (VPC 275° peaks at 12 and 11 min, respectively). The dione mixture was equilibrated in MeOH (8 ml) containing 0·5 ml of 1N methanolic NaOMe. After 2 hr the mixture was added to cold dil HCl and extracted with $CHCl_3$ in the usual manner. The product (630 mg) was now 80:20 **11a**:**11** (VPC); mass of each component 308 (MS); IR ($CHCl_3$) 5·72, 5·78, 5·84 $\mu$; NMR ($CDCl_3$) $\delta$ 1·07 (3H, d, J = 7); 3·67 (3H, s).

To a stirred soln of the equilibrated saturated dione product (600 mg) in dry THF (10 ml) at 0° was added dropwise (5 min) a chilled soln of lithium aluminum tri-*t*-butoxide (1·0 g) in THF (15 ml). After 90 min at 0° a TLC probe indicated completion of the reaction and cold sat $Na_2SO_4$ was added dropwise. Chloroform was added, the mixture was filtered and the ppt washed with $CHCl_3$. Water was added to the filtrate, the mixture was extracted with $CHCl_3$, and the latter extract washed with sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness under vacuum. The residue (590 mg) consisted of isomeric **16** and **15** in the ratio 80:20 (VPC); mass of each component 310 (MS); IR ($CHCl_3$) 2·72, 2·80–2·87, 5·72, 5·78 $\mu$; NMR ($CDCl_3$) $\delta$ 1·07 (3H, d, J = 7), 3·66 (3H, s), 3·91 (1H, m) The physical measurements were similar to those of the ketol product obtained from **14a**.

*4-Methyl-2-oxo-*cis*-hydrind-4-ene-1-heptanoic acid methyl ester* **17**. Methanesulfonyl chloride (6 ml) in pyridine (12 ml) was added at 0° to a stirred soln of **15** (2·44 g—prepared by hydrogenation of **14a**) in pyridine (24 ml). After 18 hr at 0° the mixture was added to ice water and extracted with ether. The ether extract was washed with cold dil HCl, dil $NaHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$ and concentrated under vacuum. The crude mesylate (3·1 g; IR (film) 5·72, 6·95, 7·40, 8·50 $\mu$) was dissolved in DMSO (32 ml) and the soln kept at 100° under $N_2$ for 6 hr. The soln was cooled, added to ice water and extracted thoroughly with hexane. The latter extract was washed with water (4X), sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness. Chromatography of the residue (2·3 g) on silica gel (45 g) eluting with 2% acetone-$CHCl_3$ yielded **17** as a colorless oil (1·35 g); IR ($CHCl_3$) 5·73, 5·79 $\mu$; NMR ($CDCl_3$) $\delta$ 1·67* (3H, t, J = 1·5), 3·65 (3H, s), 5·50* (1H, m); VPC ret time 7·4 min (85%), 8·0 min (15%); MS *m/e* 292 for each component. (Found: C, 69·79; H, 9·67. Calc. For $C_{18}H_{28}O_3$: C, 69·64; H, 9·74%).

The 2,4-dinitrophenylhydrazone had m.p. 92–95° (Found: C, 60·73; H, 6·87; N, 11·75. Calc. for $C_{24}H_{32}O_6N_4$: C, 61·00; H, 6·83; N, 11·86%).

For preparative purposes it was not necessary to chromatograph **17** obtained by hexane extraction of the demesylation reaction mixture. Further extraction with chloroform yielded a mixture of **17** and primarily unchanged mesylate which on retreatment with DMSO at 100° yielded additional **17**. From 15·91 g of **15** a total of 13·49 g (90%) of **17** containing traces of polar impurities (TLC) was obtained.

Identical results were obtained on mesylation-demesylation of the ketol mixture (**16**+**15**) derived from the diones (**11a**+**11**).

*4-Methyl-2-oxo-*cis*-hybrind-4-ene-1-heptanoic acid methyl ester ethylene acetal* **18**. A mixture of **17** (11·85 g), ethylene glycol (27 ml) and *p*-toluenesulfonic acid monohydrate (300 mg) in benzene (600 ml) was refluxed with water separation (Dean-Stark trap) for 20 hr under $N_2$. Work up as in the preparation of **6** led to **18** (12·6 g); IR ($CHCl_3$) 5·75, 10·52 $\mu$; NMR ($CDCl_3$) $\delta$ 1·63 (3H, broad s), 3·67 (3H, s), 3·90 (4H, unsym. d), 5·50 (1H, m).

*trans,trans-3-Acetyl-2-[2-carbomethoxyethyl]-5-oxocyclopentane-heptanoic acid methyl ester, 5-cyclic ethylene acetal* **19a**. To a mechanically stirred soln of **18** (5·25 g) t-BuOH (380 ml) and water (10 ml) at 15° was added a mixture of $K_2CO_3$ (5·46 g), $NaIO_4$ (21·12 g) and $KMnO_4$ (250 mg) in water (1140 ml).[5] After 22 hr at room temp the mixture was concentrated on the water pump until most of the t-BuOH had been removed. Ethylene glycol (1 ml) was added and the mixture was extracted with benzene–ether 1:1 to remove neutral material. The aqueous phase was made acidic (pH ~ 4–5) with granular $NaH_2PO_4$ and extracted 4X with EtOAc. The latter extract was dried over $Na_2SO_4$ and concentrated to dryness under vacuum to give **19** (5·22 g) as a *cis-trans* acetyl isomer mixture; IR (neat) 2·8–3·3, 5·75, 5·85, 10·55 $\mu$.

The ester **19a** (5·25 g) was obtained with diazomethane in ether; IR ($CHCl_3$) 5·75, 10·55 $\mu$; NMR ($CDCl_3$) $\delta$ 2·17 (s, major), 2·21 (s, minor) (3H–acetyl), 3·70 (s, 6H), 3·93 (s, 4H).

Equilibration to all *trans* **19a** was accomplished in dry MeOH (25 ml) (refluxed over Mg for 2 hr and then distilled) to which was added 3 ml of 1·3N methanolic NaOMe under $N_2$. After 18 hr at 20° the mixture was added to excess conc $NaH_2PO_4$ aq, MeOH was removed on the water pump and the product was isolated by EtOAc extraction. The physical properties of *trans,trans* **19a** were similar to those of unequilibrated **19a** except for the presence of only one acetyl singlet ($\delta$ 2·17–3H) in the NMR; TLC (5% acetone–$CHCl_3$) essentially single spot $R_f$ 0·5; mol wt (mass spec) 398; calc. 398.

*trans,trans-3-Acetyl-2-[2-carbobenzyloxy]-5-oxocyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal* **19b**. The acid **19** equilibrated as in the case of **19a** by treating 5 g in dry MeOH (35 ml) with 9·0 ml of 1·67 M methanolic NaOMe under $N_2$ gave 4·75 g of *trans,trans* **19**. Completion of the equilibration was determined by converting 50 mg to **19a** the NMR spectrum of which showed one acetyl singlet ($\delta$ 2·17).

To the equilibrated acid **19** (4·65 g) in ether (20 ml) was added ethereal phenyldiazomethane[19] in portions until the soln remained orange for several hours and a TLC probe showed the absence of **19** (total time ~18 hr). The solvent was removed and the residue chromatographed on 170 g of silica gel eluting with 5% acetone–$CHCl_3$ to give 3·05 g of benzyl ester **20a** as a colorless oil; IR ($CHCl_3$) 5·77, 5·80, 5·83, 10·55 $\mu$; NMR ($CDCl_3$) $\delta$ 2·09 (s, 3H), 3·60 (s, 3H), 3·83 (s, 4H) 5·07 (s, 2H), 7·30 (s, 5H). (Found: C, 68·52; H, 8·12. Calc. for $C_{27}H_{38}O_7$: C, 68·33; H, 8·07).

*trans,trans-3-Acetoxy-2-[2-carbomethoxyethyl]-5-oxocyclpentaneheptanoic acid methyl ester 5-cyclic ethylene acetal* **20**. Peroxytrifluoracetic acid in $CH_2Cl_2$ was prepared by the procedure of Pagano and Emmons[20] from

*Asymmetry present in the olefinic methyl and hydrogen bands is ascribed to the minor C-1 *endo* isomer.

90% $H_2O_2$ (6·6 ml), trifluoracetic anhydride (42 ml) in $CH_2Cl_2$ (60 ml) and stored at 0°. Just before use the trifluoracetic acid present was neutralized by addition of powdered $Na_2HPO_4$ (40 g) in portions with stirring at 0° and the supernatant soln utilized as the oxidant. The peracid titer at this point was ~0·35 M.

To a stirred soln at 0° of **19a** (4·50 g) in $CH_2Cl_2$ (25 ml) was added 40 g powdered $Na_2HPO_4$ and 45 ml of the above peracid soln and the mixture stirred at room temp. The course of the reaction was followed by TLC (15% acetone–$CHCl_3$), the product being slightly more mobile than the starting material. Additions of the above peracid reagent (40 ml) were made after 4 hr and 18 hr. After 24 hr the mixture was filtered and the ppt washed with $CH_2Cl_2$. The filtrate was washed with $NaHSO_3$ aq, $KHCO_3$ aq, sat NaCl aq, dried over $Na_2SO_4$ and concentrated to dryness to give **20** (4·25 g) as a colorless oil; IR ($CHCl_3$) 5·72, 5·78, 8·0, 10·54 $\mu$; NMR ($CDCl_3$) $\delta$ 2·02 (s, 3H), 3·67 (s, 6H), 3·88 (s, 4H), 4·87 (m, 1H).

trans,trans-3-*Hydroxy*-2-[2-*carbomethoxyethyl*]-5-*oxocyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal* **21**. To a soln of **20** (3·48 g) in 20 ml dry MeOH under $N_2$ was added 4 ml of 1·27N methanolic NaOMe After 90 min at room temp the soln was chilled, added to excess cold $NaH_2PO_4$ aq and the MeOH removed on the water pump. The crude product was isolated by EtOAc extraction and purified by chromatography on silica gel eluting with 25% acetone–$CHCl_3$. Single spot ($R_f$ ~ 0·5) **21** (1·81 g) was obtained; IR ($CHCl_3$) 2·75, 2·85, 5·75, 10·55 $\mu$; NMR ($C_6D_6$) $\delta$ 3·40 (s, 6H), 3·50 (s, 4H), 3·77 (m, 1H).

trans,trans-3-*Hydroxy*-2-[2-*carbomethoxyethyl*]-5-*oxocyclopentaneheptanoic acid methyl ester* **22**. The diester **21** (7 mg) was kept in 0·5 ml of 1:1 aqueous AcOH at 22° for 3 hr. Toluene (5 ml) was added and the soln was pumped to dryness under vacuum. The residue (**22**) had the same TLC mobility as the starting material, but lacked the ethylene acetal IR band at 10·55 $\mu$; IR ($CHCl_3$) 2·78, 2·90, 5·75 $\mu$. A sample (1·7 mg) in MeOH (50 ml) was transparent in the UV. However, on addition of 1 drop of 5% KOH aq both to the MeOH reference and to the sample a strong maximum appeared at 218 nm. When 5 cc of 2M KOH in 80% MeOH was added and the sample kept at 90° for 1 hr the maximum shifted to 238 nm.

trans,trans-3-*Acetoxy*-2-[2-*carbobenzyloxethyl*]-5-*oxocyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal* **20a**. Utilizing the procedure of the earlier experiment **19b** (1·90 g) in $CH_2Cl_2$ (20 ml) buffered with $Na_2HPO_4$ (25 g) was treated with buffered $CF_3CO_3H$ reagent (3 × 20 ml). Work up gave 1·70 g of **20a**; IR ($CHCl_3$) 5·73, 5·80, 8·05, 10·55 $\mu$; NMR ($CDCl_3$) $\delta$ 1·98 (s, 3H), 3·63 (s, 3H), 3·87 (s, 4H), 5·13 (s, 2H), 7 33 (s, 5H).

trans,trans-3-*Acetoxy*-2-[2-*carboxyethyl*]-5-*oxocyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal* **25**. A soln of 1·63 g of **20a** in EtOAc (20 ml) was added to a pre-reduced suspension of 10% Pd-C catalyst (750 mg) in EtOAc (20 ml). Hydrogenation was carried out at 25° and 1 atm and 1 molar equiv was absorbed in 25 min. The mixture was filtered, the ppt washed with EtOAc and the filtrate concentrated to dryness. The residue was dissolved in 1.1 ether hexane and extracted with $KHCO_3$ aq. The latter extract was acidified with powdered $NaH_2PO_4$ and extracted with EtOAc. The EtOAc extract was dried over $Na_2SO_4$ and concentrated to dryness to give **25** (1 32 g) IR (neat) 2·8–3·3, 5·78, 5·88, 8·10, 10·55 $\mu$.

trans,trans-3-*Acetoxy*-2-*vinyl*-5-*oxycyclopentaneheptaacid methyl ester 5-cyclic ethylene acetal* **26**. To a soln of **25** (1·30 g) in 22 ml benzene under $N_2$ was added pyridine (880 mg). $Cu(OAc)_2 \cdot H_2O$ (45 mg) and $Pb(OAc)_4$[21] (1·490 g).[9] The mixture was stirred in the dark for 30 min and then photolyzed at 3500 Å in a Rayonet photochemical reactor (t = 30°) for 70 min at which time a starch iodide test for $Pb(OAc)_4$ was negative. Ether and cold water followed by powdered $NaH_2PO_4$ were added. The mixture was extracted with ether, the organic phase washed with water, $KHCO_3$ aq, sat NaCl aq, dried over $Na_2SO_4$ and concentrated to dryness to give crude **26** (490 mg). Treatment of the $KHCO_3$ aq extract with solid $NaH_2PO_4$ and extraction with EtOAc yielded 650 mg of recovered **25**. The latter was retreated as above to give 220 mg of neutral **26** and 285 mg of recovered **25**.

Combined neutral product (1·56 g) derived from 2·215 g consumed acid **25** was chromatographed on 100 g silica gel eluting with 5% acetone–$CHCl_3$ to give 730 mg (37%) pure **26**, $R_f$ ~ 0·4; IR ($CHCl_3$) 5·73, 5·77, 6·20, 8·00, 10·55, 10 85 $\mu$, NMR ($CDCl_3$) $\delta$ 2·01 (d, J ~ 1·5, acetoxy Me split by vinyl H), 3·63 (s, 3H), 3·88 (broad s, 4H), 4·6–5·8 (m, 3H).

trans,trans-3-*Acetoxy*-2-*formyl*-5-*oxocyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal* **27**. To a soln of **26** (325 mg) in pure THF (9 ml) stirred under $N_2$ was added 1·8 ml 1% $OSO_4$ aq (18 mg $OsO_4$). Within 10 min the mixture turned black and sodium periodate (880 mg) in water (6 ml) was added over 15 min. After 2 hr the precipitated sodium iodate was filtered, washed with EtOAc and the filtrate washed with sat NaCl aq. Benzene was added to the organic phase, which was dried over $Na_2SO_4$, treated with charcoal, filtered and the nearly colorless filtrate concentrated to dryness to give **27** (318 mg); IR (neat) 3·7, 5·77, 5·80, 10·55 $\mu$.

15-*Dehydroprostaglandin* $E_1$ *methyl ester acetate, 9-cyclic ethylene acetal* **28**. Dimethyl 2-oxoheptylphosphonate[2a] (230 mg) in 4 ml THF was added to a suspension of 48 mg of 50% sodium hydride-white oil dispersion at 0° under $N_2$. After stirring at 0° for 20 min **27** (318 mg) in 4 ml THF was added and the mixture allowed to warm to room temp. After 4 hr the mixture was chilled, added to 75 ml cold conc $NaH_2PO_4$ aq and extracted with EtOAc. The latter extract was washed with sat NaCl aq, dried over $Na_2SO_4$ and concentrated to dryness The crude product (920 mg) from two runs was chromatographed over 35 g of silica gel eluting with 5% acetone-$CHCl_3$ to give 370 mg pure Wittig product **28** and 200 mg of earlier fractions containing 75% of **28** and ~15–20% of the corresponding dienone (UV, TLC). Since these fractions could be utilized in the borohydride reduction, the effective yield of **28** was 520 mg (65%) The material was a colorless oil, $\lambda_{max}^{CH_3OH}$ 228 nm (14,000); IR ($CHCl_3$) 5·77, 5·90, sh, 6·00, 6·15, 8·05, 10·20, 10·55 $\mu$; NMR ($CDCl_3$) $\delta$ 1·03 (t, J = 6, 3H), 2·00 (s, 3H), 3·67 (s, 3H), 3·92 (s, 4H), 4·93 (m, 1H), 6·07 (d, J = 16, 1H), 6·67 (d, d, J = 8, J = 16, 1H). (Found: C, 66·28; H, 8·69. Calc. for $C_{25}H_{40}O_7$: C, 66·34; H, 8·91%).

*Prostaglandin* $E_1$ *methyl ester acetate, 9-cyclic ethylene acetal* **29** *and its* 15 R *epimer* **29a**. To a stirred soln of **28** (350 mg) in 7 ml MeOH at −5° under $N_2$ was added a chilled soln of 29 mg $NaBH_4$ in 3 ml MeOH. After 30 min at ~−5° the mixture was added to ice-cold $NaH_2PO_4$ soln (75 ml) and extracted with EtOAc. The extract was dried over $Na_2SO_4$ and concentrated to dryness. The residue (350 mg) was chromatographed over 38 g of silica gel eluting with 12% acetone–$CHCl_3$ to give as

colorless oils **29a** (150 mg) $R_f = 0{\cdot}61$, mixed fractions (28 mg—mainly **29**) and **29** (125 mg $R_f = 0{\cdot}68$). The respective IR ($CHCl_3$) spectra were essentially identical, 2·78, 2·90, 5·73, 5·79, 8·05, 10·25, 10·55 $\mu$.

*Manganese dioxide oxidation of* **29a** *to* **28**. A soln of **29a** (150 mg) in 3 ml EtOAc was added to a suspension of active $MnO_2$[22] (2·5 g) in 15 ml EtOAc. The mixture was stirred at room temp for 16 hr, filtered, and the ppt washed with acetone. Concentration of the filtrate and washings under vacuum gave 145 mg of single spot **29a** (TLC 10% acetone–$CHCl_3$); $\lambda_{max}^{MeOH}$ 228 m$\mu$ (13,600).

*Prostaglandin* $E_1$, *9-cyclic ethylene acetal* **30**. To a stirred soln of **29** (120 mg) in 3·5 ml MeOH under $N_2$ at 0° was added dropwise a soln of KOH (130 mg) in 8 ml MeOH. The cloudy mixture was allowed to warm to room temp. It became clear in 30 min. After 3 hr MeOH was removed on the water pump, water was added and a few mg of neutral material was removed by extraction with hexane-ether. Powdered $NaH_2PO_4$ was added to pH 5 and the mixture was extracted with EtOAc. The latter extract was dried over $Na_2SO_4$ and concentrated to dryness to yield 105 mg of crude **30**. TLC using Andersen's F-6 system[23] (EtOAc:acetone:AcOH—90:10:1) showed the presence of two components; the major had $R_f$ 0·3 and the minor $R_f$ 0·37. Trituration with ether-hexane led to the crystalline major component **30**; prisms from EtOAc-hexane m.p. 81–83°; IR ($CHCl_3$) 2·8–3·3, 5·85, 10·30, 10·55 $\mu$. (Found: C, 66·26; H, 9·51. Calc. for $C_{22}H_{38}O_6$; C, 66·30; H, 9·61%).

In another run, chromatography of 50 mg of crude **30** on 6·5 g silica gel eluting with the F-6 system gave 29 mg of crystalline **30** and 6 mg of the more mobile component. The IR spectrum of the latter was similar to that of crystalline **30** and the substance is formulated as the ethylene acetal of 8-iso $PGE_1$ (see below).

(±) *Prostaglandin* $E_1$ **32**. A soln of single spot ethylene acetal **30** (40 mg) in 1:1 AcOH-water (3·5 ml) was kept at 25° for 3 hr. Cold conc $NaH_2PO_4$ aq was added and the mixture extracted with EtOAc. The latter extract was washed with sat NaCl aq, dried over $Na_2SO_4$, toluene added and the soln taken to dryness under vacuum at 20–25°. The crystalline residue (35 mg) on crystallization from EtOAc-hexane gave **32** as hexagonal plates (20 mg) m.p. 112–113°; 2nd crop 7 mg m.p. 110–112°. The crystalline residue contained minor mobile impurities (TLC F-6 system). Both crystalline crops were single spot. First crop material was identical with natural (−) $PGE_1$ by TLC behavior in three systems (F-6[23], A-1[24], A-IX[24]), as well as by comparison of the respective IR and NMR spectra and the mass spectra of the methyl esters. (Found: C, 67·48; H, 9·55. Calc. for $C_{20}H_{34}O_5$: C, 67·76; H, 9·67%).

8-*iso-Prostaglandin* $E_1$ **31**. When crude **30** (80 mg) was deblocked as in the preceding experiment, the product (65 mg) on crystallization gave low melting $PGE_1$ **32** (43 mg m.p. 100–105°) raised to 110–112° on two recrystallizations. TLC examination of the mother liquors (F-6 system) showed the presence of a slightly more mobile component. It was isolated by preparative TLC of 30 mg of mother liquor material on 8″ × 8″ Analtech 250 $\mu$ silica gel plates (F-6 system) visualizing the bands by water spray to yield 6 mg of single spot (±) 8-iso $PGE_1$ **31** m.p. 96–98° (reported m.p. 101–102°[22b]). Equilibration of 4 mg of **31** in 95% ethanolic AcOK for 90 hr[11] led to the $PGE_1$-8-iso $PGE_1$ equilibrium mixture in which $PGE_1$ greatly predominated. Isolation by preparative TLC (F-6 system) led to single spot $PGE_1$ **32**, m.p. 106–110°.

## REFERENCES


[1]For a preliminary account of this work see: D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, Z. S. Zelawski and N. L. Wendler, *Chem. Comm.* 1258 (1970)

[2]For other syntheses of Prostaglandin $E_1$ see: [a]E. J. Corey, N. H Anderson, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas and R. H. Winter, *J. Am. Chem. Soc.* **90**, 3245 (1968); E. J. Corey, I. Vlattas, N. H. Anderson and K. Harding, *Ibid.* 3247; E. J. Corey, R. Noyori and T. K. Schaaf, *Ibid.* **92**, 2586 (1970); [b]W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike and J. L. Thompson, *Ibid.* **91**, 5372 (1969); U. Axen, F. A. Lincoln and J. L. Thompson, *Chem. Comm* 303 (1969); [c]H. L. Slates, Z. S. Zelawski, D. Taub and N. L. Wendler, *Ibid.* 304 (1972), [d]C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti and M. Casey, *J. Am. Chem. Soc.* **94**, 3644 (1972); [e]J. Fried, C. H. Lin, J. C. Sih, P. Dalven, G. F. Cooper, *Ibid.* **94**, 4342 (1972); J. Fried, J. C. Sih, C. H. Lin and P. Dalven, *Ibid.* **94**, 4343 (1972); [f]A. F. Kluge, K. G. Untch and J. H. Fried, *Ibid.* **94**, 7827 (1972)

[3]W. M. McLamore, W. D. Celmer, J. V. Bogert, F. C. Pennington, B. A. Sobin and I. A. Solomons, *Ibid.* **75**, 105 (1953)

[4]*cf.* A. J. Birch, G. A. Hughes, G. Kruger and G. S. R. Subba Rao, *J. Chem. Soc.* 5889 (1964)

[5]R. U. Lemieux and E. von Rudloff, *Canad. J. Chem.* **33**, 1701 (1955); E. von Rudloff, *Ibid.* **34**, 1413 (1956)

[6]R. B. Turner, *J. Am. Chem. Soc.* **72**, 878 (1950): T. F. Gallagher and T. H. Kritchevsky, *Ibid.* **72**, 882 (1950)

[7]See also P. Kurath, W. Cole, J. Tadanier, M. Freifelder, G. R. Stone and E. V. Schuber, *J. Org. Chem.* **28**, 2189 (1963); J. Bagli and T. Bogri, *Tetrahedron Letters* 5 (1967)

[8]S. Bergstrom, R. Ryhage, B. Samuelsson and J. Sjovall, *J. Biol. Chem.* **238**, 3555 (1963)

[9]J. D. Bacha and J. K. Kochi, *Tetrahedron* **24**, 2215 (1968)

[10]R. Pappo, D. S. Allen, Jr., R. U. Lemieux and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956)

[11]J. E. Pike, F. H. Lincoln and W. P. Schneider, *Ibid.* **34**, 3552 (1969)

[12a]C. K. Ingold and H. A. Piggott, *J. Chem. Soc.* 1469 (1923); [b]A. J. Birch, J. A. K. Quartey and H. Smith, *Ibid.* 1768 (1952)

[13]J. Sam and T. C. Snapp, *J. Pharm. Sci.* **54**, 756 (1965)

[14]J. D. Surmatis and A. Ofner, *J. Org. Chem.* **28**, 2735 (1963)

[15]R. Robinson and L. H. Smith, *J. Chem. Soc.* 371 (1937)

[16]Procedure of J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.* **89**, 5505 (1967)

[17]*cf.* procedure of J. S. Baran, *J. Org. Chem.* **25**, 257 (1960)

[18]H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.* **83**, 2952 (1961)

[19]P. Yates and B. L. Shapiro, *J. Org. Chem.* **23**, 759 (1958)

[20]A. S. Pagano and W. D. Emmons, *Org. Syn.* **49**, 47 (1969)

[21]L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Vol. 1, p. 537. Wiley, N.Y. (1967)

[22]J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1094 (1952)

[23]N. H. Andersen, *J. Lipid. Res.* **10**, 316 (1969)

[24]K. Green and B. Samuelsson, *Ibid.*, **5**, 117 (1964)