Chem. Soc., Chem. Commun., 460 (1972). It is possible that the centaurepensin isolated by these workers is identical with chlorohyssopifolin reported in ref 13.
(15) J. D. Edwards, T. Matsumoto, and T. Hase, *J. Org. Chem.*, **32**, 244 (1967).
(16) A small amount of an isomeric 3,4-epoxide which was not further characterized was also formed.
(17) S. M. Kupchan and M. Maruyama, *J. Org. Chem.*, **36**, 1187 (1971).
(18) Z. Samek, *Tetrahedron Lett.*, 671 (1970). Although some exceptions to the rule have been found,[4] it seems to be generally applicable to guaianolides.
(19) If the absolute configuration is as postulated, the observation that the CD curves of graminiliatrin and spicatin display negative Cotton effects near 260 nm could be interpreted as providing additional support for the trans fusion of the lactone ring.[20] However, the presence of one or two additional inherently symmetric but asymmetrically perturbed unsaturated ester chromophores in **1b** and **2b** could conceivably affect the CD curve so that the argument is not without pitfalls. A summary of X-ray results for several sesquiterpene lactones of established absolute configuration indicates that a C-6,C-7 trans lactone fusion gives rise to left-handed chirality (*i.e.*, the C=C—C=O torsion angle is negative).[21] Whether there is a direct connection between the chirality of the C=C—C=O grouping and the sign of the Cotton effect is still moot.[22]
(20) W. Stöcklin, T. G. Waddell, and T. A. Geissman, *Tetrahedron*, **26**, 2397 (1970).
(21) A. T. McPhail and G. A. Sim, *Tetrahedron*, **29**, 1751 (1973).
(22) P. J. Cox, W. Herz, and G. A. Sim, *J. Chem. Soc., Perkin Trans. 2*, submitted for publication.
(23) The coupling constants involving H-1, H-2, H-3, H-6, H-7, and H-8 of **1a** and **3** are very similar to those reported for **16** and **18**, respectively, thus providing additional evidence for the stereochemistry assigned to **1a**.
(24) For experimental details see previous papers of this series.
(25) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).
(26) We wish to thank Dr. Thorleif Anthonsen, Institute for Organisk Kjem, Norges Tekniske Hogskole, Trondheim, for the authentic sample.

Total Synthesis of *dl*-9-Deoxyprostaglandin E_1

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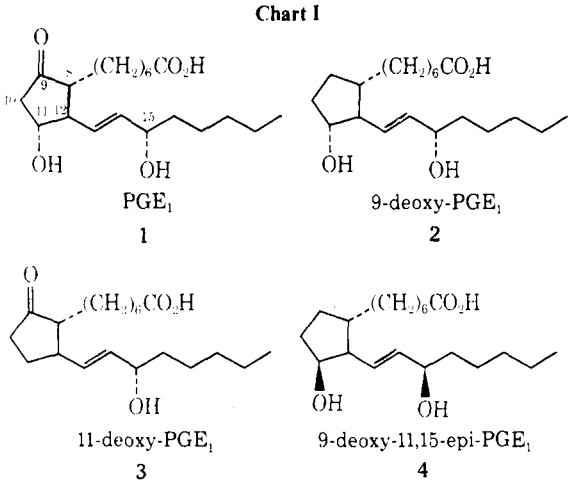
dl-9-Deoxyprostaglandin E_1 (PGE_1) **2** has been synthesized in nine steps from 2-carbomethoxy-3-oxo-1-cyclopenteneheptanoic acid methyl ester **36**. Details are provided of model studies and development of a synthetic procedure for preparation of one of the simplest PGE_1 model compounds **35** which contains all but one of the stereochemical features of PGE_1 **1**.

Extensive work has been carried out for several years with 11-deoxyprostaglandins **3**,[1,2] but only recently have accounts appeared of work with the 9-deoxyprostaglandins **2**.[3-5] These reports have prompted us to describe our synthesis of this type, which was disclosed previously in the patent literature[6] (Chart I).

Chart I

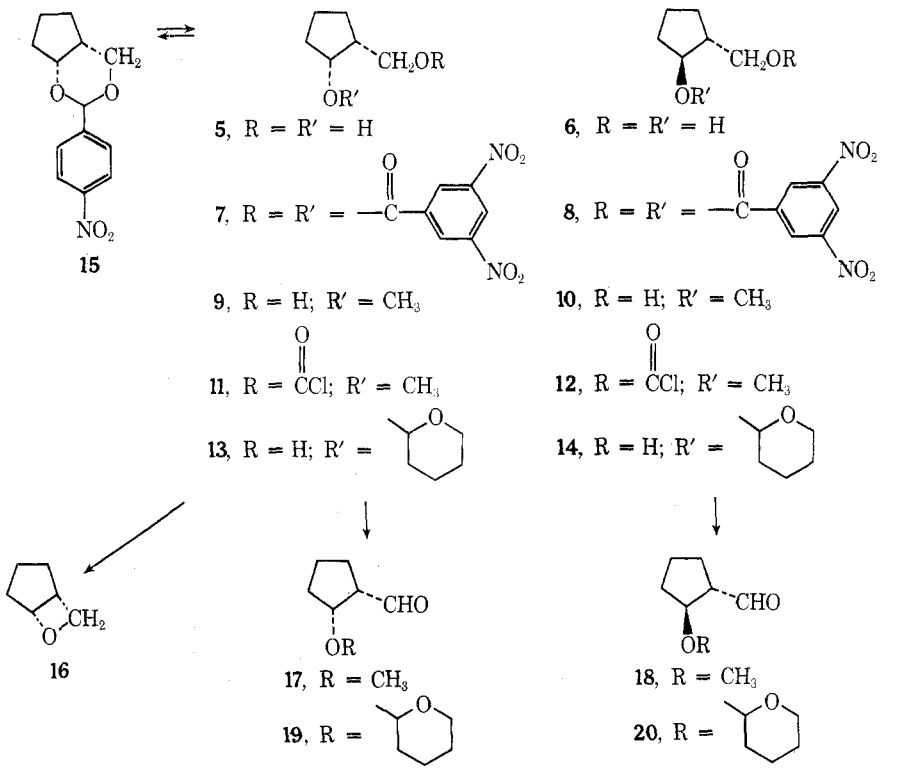


We also now describe the model experiments which were carried out to establish the stereochemical assignments in this synthetic sequence and that used for the synthesis of prostaglandin E_1 **1** itself.[7]

Reaction of a mixture of the carbinols **5** and **6**, obtained by $LiAlH_4$ reduction of a mixture of *cis*- and *trans*-2-carbomethoxycyclopentanols, with *p*-nitrobenzaldehyde dimethyl acetal[8] and acid catalysis yielded only one *p*-nitrobenzylidene cyclic acetal **15**. This was shown to be derived from the cis hydroxycarbinol **5** by cleavage back to this compound, which had been obtained also by $LiAlH_4$ reduction of the low-boiling *cis*-2-carbomethoxycyclopentanol. Separation of the *cis*- and *trans*-2-carbomethoxycyclopentanols could be achieved conveniently by fractional distillation using a spinning band column.[9] The cis assignment to the crystalline 2-hydroxymethylcyclopentanol **5** was rigorously proved by conversion into the oxetane **16** by Kovács *et al.*[10] (Chart II). This selective acetalization was used for assignment of stereochemistry to intermediates **44** and **46** in the 9-deoxyprostaglandin synthesis.

One important synthetic operation we had to accomplish for synthesis of either PGE_1 **1** or 9-deoxy-PGE_1 **2** was attachment of the *trans*-allylic alcohol side chain to the cyclopentane ring. The most attractive route seemed to be reaction of an appropriate cyclopentane aldehyde with a Wittig reagent and then metal hydride reduction of the resultant enone. The snag with this route was that the Wittig reagent could function as base as well as nucleophile and cause at least epimerization of the aldehyde, if not elimination. To explore the viability of this route for use in a prostaglandin synthesis, we therefore decided to attempt synthesis of cis and trans 2-methoxycyclopentane aldehyde **17** and **18**. The mixture of 2-carbomethoxy- and carboethoxycyclopentanols was O-methylated.[11,12] The cis and trans mixture of methoxy carbinols **9** and **10**, obtained by $LiAlH_4$ reduction of the mixture of O-methylated esters, was separated by fractional distillation through a spinning band column. The lower boiling fraction was assigned the cis configuration **9** by correlation with material obtained directly from the pure *cis*-2-carbomethoxycyclopentanol. A similar correlation was carried out for the high-boiling trans isomer **10**. The oxidation of the *trans*-2-hydroxymethyl-1-methoxycyclopentane **10** to the *trans*-2-methoxycyclopentane aldehyde **18** proceeded well with Jones reagent. Unfortunately, Jones reagent did not work for the preparation of the *cis*-2-methoxycyclopentane aldehyde **17** from the cis carbinol **9**. Instead a little used procedure due to Barton[13] was tried on the carbinols **9** and **10** and worked extremely well, providing both cis and trans 2-methoxycyclopentane aldehydes **17** and **18** free of each other. Not surprisingly, the trans aldehyde **18** was more stable and yielded normal

Chart II



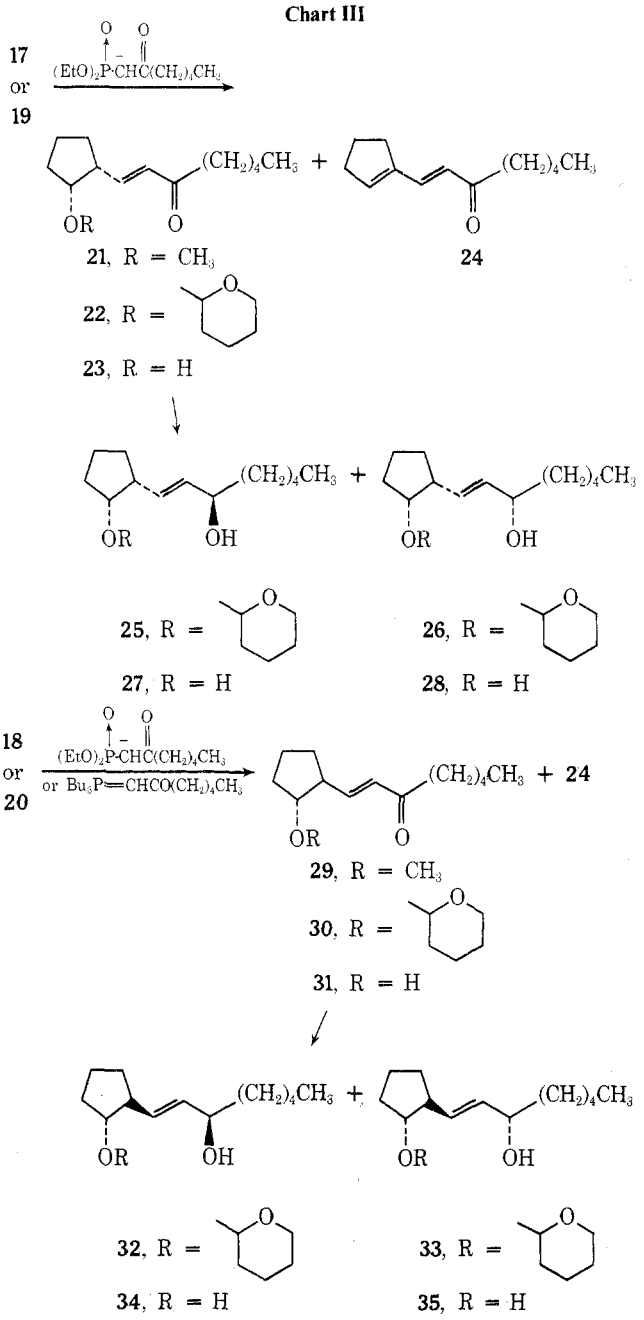
derivatives, *e.g.*, a semicarbazone, whereas cis aldehyde **17** underwent rapid elimination and yielded only derivatives of cyclopentene aldehyde.

Addition of the side chain was achieved by reaction of the aldehydes **17** and **18** with the sodio derivative of diethyl (2-oxoheptyl)phosphonate[14,25] (Chart III).

To our satisfaction, the cis methoxy aldehyde **17** gave exclusively the cis methoxy enone **21**, and the trans methoxy aldehyde **18** the trans enone **29**. Thus, while in both cases, some elimination to the dienone **24** was observed, in neither case did epimerization take place. This was especially evident in the nmr spectra of the enones **21** and **29** as the $-OCH_3$ signal was at different positions (δ 3.26 and 3.30, respectively) and the presence of one in the other would have been obvious. More interestingly though, the position and splitting of the β vinyl H was also quite distinctive, and was obviously to be of value in stereochemical assignments to the allylic alcohol side chain in the more complex molecules we intended to prepare.

Use of the 2-methoxycyclopentane aldehydes **17** and **18** was predicated on their ease of preparation and the utility of a methoxy group as an nmr marker. To be of use as intermediates for a prostaglandin synthesis, it was obviously necessary to explore the sequence with a group which could be more easily converted into a free hydroxyl group. For this purpose tetrahydropyranyloxy was chosen. Preparation of the cis and trans tetrahydropyranyloxy carbinols **13** and **14** proceeded uneventfully. Unfortunately, they did not stand up to the phosgene treatment necessary for the Barton oxidation.[13] Instead the Moffat oxidation[15] was employed, modified by the use of the water-soluble 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate.[26] Using this variant, excellent yields of the cis and trans 2-tetrahydropyranyloxycyclopentane aldehydes **19** and **20** could be obtained from the carbinols **13** and **14**. This modified Moffat oxidation was subsequently used in our synthesis of PGE_1.[7] Reaction of the *cis*-2-tetrahydropyranyloxycyclopentanecarboxaldehyde (**19**) with the sodio derivative of diethyl (2-oxoheptyl)phosphonate yielded the desired enone **22**, plus some dienone **24**. At this point it was decided to investigate alternative "side-chain addition reagents," which would not cause material loss *via* elimination. One criterion to be met would be reduced basicity. The preformed redistilled ylid 1-tributylphosphoranylidene-2-heptanone met this criterion. This variant of the usual Wittig reagent gave an excellent yield of the desired enone **30** from the trans 2-tetrahydropyranyloxycyclopentane aldehyde **20**. The tetrahydropyranyl group was readily removed from both enones to give the hydroxy enones **23** and **31**. The inspection of the β vinyl H in the nmr spectra, which was less complex than in the tetrahydropyranyl derivatives **22** and **30**, as these were epimeric mixtures at the tetrahydropyranyl group, could now be made and the absence of epimerization α to the aldehyde in either side-chain addition process be assured. We now encountered a further problem in that sodium borohydride reduction of the hydroxy enones **23** and **31** gave substantial amounts of products derived from conjugate addition of hydride, based on a substantial reduction in the integrated area of the vinyl region in the nmr spectra of the products. This presumably occurs *via* intramolecular hydride addition from the alkoxyborane formed from the free alcohol. This was very simply resolved by carrying out the sodium borohydride reduction on the tetrahydropyranyloxy enones **22** and **30**, and cleaving the tetrahydropyranyl ether after reduction. Only a cursory investigation of these last two steps was made with the *cis*-tetrahydropyranyloxy enone **22** and the final diols **27** and **28** were not characterized. Attention was directed to the natural PGE_1 trans stereochemistry. Sodium borohydride reduction of the *trans*-2-tetrahydropyranyloxy enone **30** gave a complex mixture of epimers **32** and **33**. On removal of the tetrahydropyranyl group, the trans diols **34** and **35** were readily separable by silica gel column chromatography. Although stereochemical assignments could not rigorously be made, based on their chromatographic behavior, one could conjecture that the slower moving epimer **35** had the stereochemistry of PGE_1 at the allylic alcohol. Thus, the diol **35** had the stere-

Chart III



ochemistry of PGE_1 at three of its four asymetric centers and also the trans arrangement of the olefin. The stereochemistry of the olefin followed from the method of synthesis *via* a stabilized phosphorus ylid. This had also been confirmed by the coupling constant between the α and β protons in the nmr spectrum of the enone precursor **30**.

Thus, having developed a satisfactory process for conversion of 2-alkoxy cyclopentane aldehydes into compounds such as the diol **35**, which had almost all of the stereochemical features of PGE_1, it seemed appropriate to consider application of the process to a cyclopentane aldehyde with the heptanoic acid side chain of PGE_1 attached.

The choice of starting material for the synthesis of such a cyclopentane aldehyde was the readily available 2-carbomethoxy-3-oxo-1-cyclopenteneheptanoic acid methyl ester[16] **36** (Chart IV). Sodium borohydride reduction of this diester **36** yielded a mixture of two hydroxy diesters **38** and **39**, along with varying amounts of carbinols **42** and **43**, resulting from overreduction. The same two diesters **38** and **39** were also obtained from the cyclopentanone diester **37** by sodium borohydride reduction; therefore, we may presume that they differ only in the stereochemistry of the cyclopentanol carbon C_{11}. The assignment of the faster moving epimer **38** as having the cis arrangement of cyclopentanol hydroxyl and carbomethoxy groups was assured by an infrared study of the OH stretching region as a function of concentration, as was done for the simpler case of the *cis*- and *trans*-2-carbomethoxycyclopentanols.[17] This was confirmed by the rapid selective reduction of the hydroxy diester **38** to the diol ester **42** by sodium borohydride. This diol ester **42** was characterized as the *p*-nitrobenzylidine acid **46**, a process shown in the unsubstituted cyclopentane case to be specific for a cis arrangement of the hydroxy and ester groups (*i.e.*, diol **5** → *p*-nitrobenzylidine acetal **15**). The most convenient synthesis of the trans hydroxy diester **39** took advantage of the more rapid reduction of the cis hydroxy diester **38**. The cyclopentenone diester **36** reacted with excess sodium borohydride at room temperature, rather than 4°. This converted all the *cis*-hydroxy diester **38** formed into the carbinol **42**, enabling the trans hydroxy diester to be isolated by a filtration through silica gel rather than careful chromatography.

In order to strengthen further the stereochemical assignments, the hydroxy diesters **38** and **39** were hydrolyzed to the crystalline diacids **40** and **41** under conditions known to epimerize such an arrangement on a cyclopentane ring, if it were all cis.[7,18]

Reesterification of the hydroxy diacids **40** and **41** with diazomethane regenerated the same hydroxy diesters **38** and **39**.

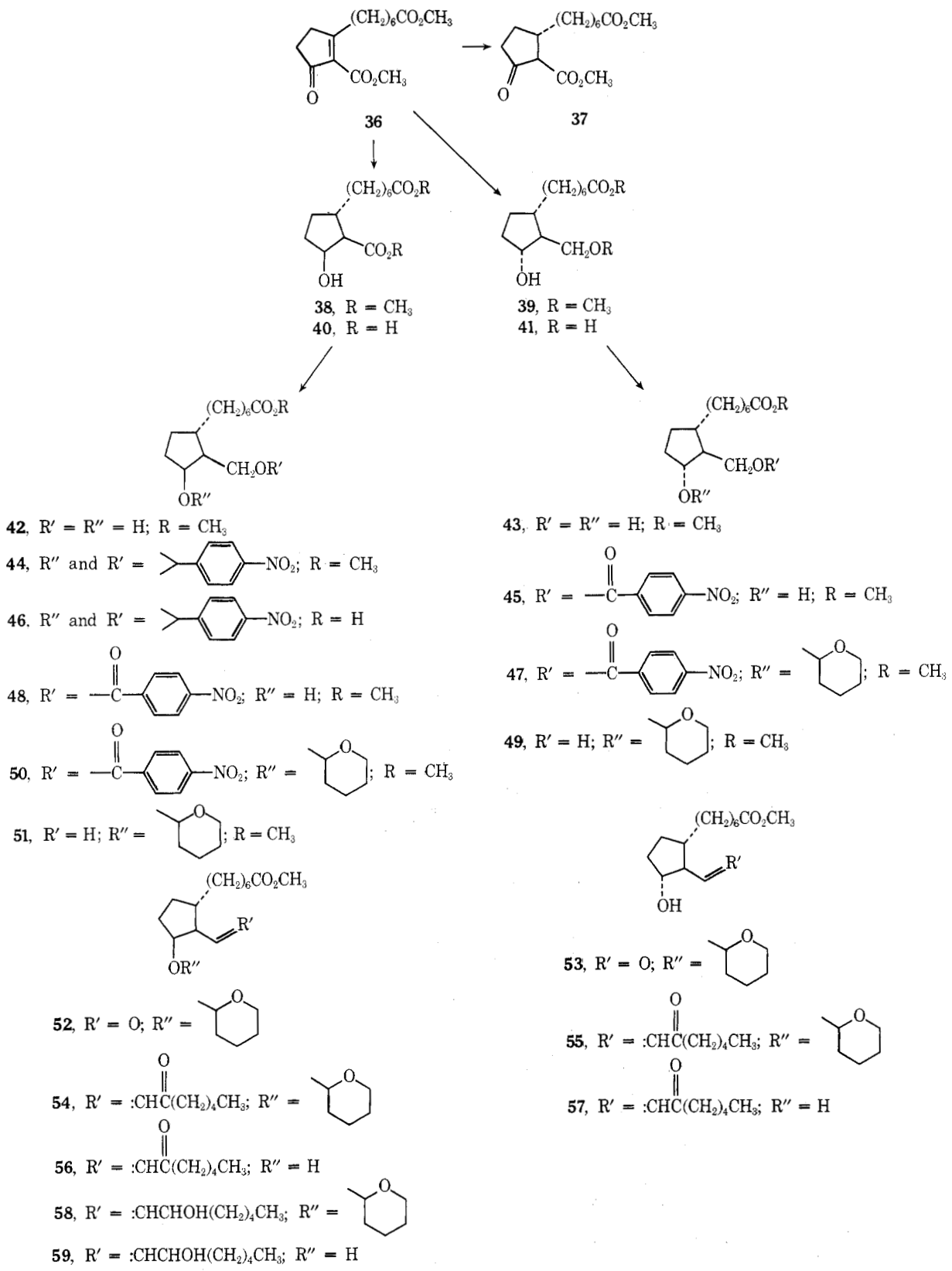
Conversion of the hydroxy diesters **38** and **39** into the tetrahydropyranyloxy aldehydes **52** and **53** was performed slightly differently from that done in the unsubstituted cyclopentane cases, where the *cis*- and *trans*-2-carbomethoxycyclopentanols were converted into the tetrahydropyranyloxy aldehydes **19** and **20**. This was necessitated by the presence of two ester groups in the hydroxy diesters **38** and **39**. Fortunately, with these compounds, access to the diol esters **42** and **43** from the hydroxy diesters **38** and **39** was easier than in the analogous case in the PGE_1 synthesis.[7] Reduction of the cis hydroxy ester **38** to the diol ester **42** did occur faster than reduction of the trans hydroxy ester **39** to the diol ester **43**. However, reduction by sodium borohydride of the carbomethoxy group on the cyclopentane ring, even with the trans hydroxy ester **39**, was substantially faster than reduction of the heptanoic ester. Thus, the diol esters **42** and **43** were best prepared directly from the cyclopentenone diester **36**, by permitting extensive overreduction. The mixture of diol esters **42** and **43**, obtained from a rough column chromatography, was para-nitrobenzoylated. The pure cis *p*-nitrobenzoate **48** and trans *p*-nitrobenzoate **45** could be isolated by preparative thick layer chromatography. The assignment of structure was assured by preparation of the cis *p*-nitrobenzoate **48** from the purified diol ester **42**.

Reaction of these cis and trans *p*-nitrobenzoates **48** and **45** with dihydropyran gave the tetrahydropyranyl ethers **50** and **47**. Methanolysis of these compounds gave the desired tetrahydropyranyloxy carbinol esters **51** and **49**, which could be oxidized to the tetrahydropyranyloxy aldehydes **52** and **53** by either the modified Moffat procedure as used for the cyclopentane derivatives **13** and **14**, or by the use of Collins' reagent.[19]

The cis tetrahydropyranyloxy aldehyde **52** underwent very facile elimination to the cyclopentene aldehyde which was characterized as the semicarbazone.

Reaction of the cis and trans tetrahydropyranyloxy aldehydes **52** and **53** with 1-tributylphosphoranylidine-2-

Chart IV



heptanone gave the enones **54** and **55**. These were reduced with sodium borohydride and the tetrahydropyranyloxy group cleaved with acid. However, an alternative procedure using zinc borohydride,[20] which gives less conjugate reduction, also enabled the hydroxy enones **56** and **57** to be utilized. This was helpful, as comparison of the nmr spectra of **56** and **57** with those of the model compounds **23** and **31** reassured us of the stereochemical assignments, which had been made to these compounds. Reduction with zinc borohydride gave in each case a 1:1 mixture of allylic alcohols epimeric at C_{15}. These were separated by preparative thick layer chromatography. By analogy with the PGE_1 case, the slower moving band from the reduction of the trans hydroxy enone **57** was assigned the PGE_1 configuration. Hydrolysis of the ester gave the beautifully crystalline acid, mp 76–78°, *dl*-9-deoxy-PGE_1 **2**. The C_{15} epimer was not

crystalline; however this is analogous to the situation with *dl*-PGE$_1$ and *dl*-15-epi-PGE$_1$.[21]

The slower moving band from the preparative tlc plate of the zinc borohydride reduction of the cis hydroxy enone **56** also yielded a crystalline acid, mp 71–72°, on hydrolysis, which was assigned the 11,15-epi configuration **4**. The C_{15} epimer, obtained by hydrolysis of the faster moving band, was a waxy solid which could not be satisfactorily recrystallized.

All four compounds from the synthesis showed prostaglandin-like effects in various biological tests.[22] These effects were more pronounced, with a given dose, from the crystalline acids 9-deoxy-PGE$_1$ **2** and 9-deoxy-11,15-epi-PGE$_1$ **4**, thus providing support for the stereochemical assignments.

Experimental Section[23]

Preparation of *cis*- and *trans*-2-Carbomethoxycyclopentanols. Commercial 2-carboethoxycyclopentanone (190 g), as a mixture of methyl and ethyl esters, was hydrogenated in ethanol (200 ml) at 55 psi over PtO_2 (10 g) until a negative $FeCl_3$ test was obtained (several hours). The catalyst and solvent were removed and the residue was distilled to give 167 g, bp 71–87° (1.5 mm).

A portion (33 g, 0.2 mol) of this material was stirred at room temperature with 10% aqueous KOH (250 ml) until a clear solution was obtained (4 hr). This solution was extracted with ether, acidified with concentrated HCl, saturated with NaCl, and extracted with ether. The extracts were dried ($MgSO_4$) and the ether was removed. The viscous oil (26.5 g) was redissolved in ether and treated with excess ethereal diazomethane. The ethereal solution was washed with 10% $KHCO_3$ and dried ($MgSO_4$) and the ether removed. The resulting oil (33.0 g) was distilled through a Nester Faust spinning band column using a water aspirator. Two principal fractions were collected: the cis isomer, bp 95–97° (15.3 g); and the trans isomer, bp 110–112° (13.3 g). The homogeneity was checked by tlc (silica gel eluted by HCO_2H–$CHCl_3$ 5:95).

***trans*-2-Hydroxymethylcyclopentanol 6 and the *p*-Nitrobenzylidine Derivative of *cis*-2-Hydroxymethylcyclopentanol 15.** The mixture of hydroxy esters from PtO_2 hydrogenation of commercial 2-carboethoxycyclopentanone (5.01 g, 0.032 mol) was refluxed in ether (200 ml) overnight with excess $LiAlH_4$. The excess $LiAlH_4$ was decomposed with saturated Na_2SO_4 solution and the ether separated. The aqueous solution was made strongly acid (10 *N* H_2SO_4) to dissolve the precipitated solids and was continuously extracted overnight with ether. The combined ethereal extracts were dried ($MgSO_4$), and the ether was removed to yield an amber oil (**5** + **6**), 3.3 g (90%).

This amber oil (506 mg, 4.35 mmol) was dissolved in benzene (15 ml), and *p*-nitrobenzaldehyde dimethyl acetal[8] (426 mg, 2.16 mmol) and a few crystals of *p*-toluenesulfonic acid were added. The mixture was refluxed for 2.5 hr; the benzene was concentrated to half-volume and added directly to an alumina column (13 g, neutral I) made up in benzene. Elution by benzene yielded **15** as an oil (467 mg, 1.87 mmol 43%) which crystallized, mp 86–88°. Recrystallization from hexane yielded colorless needles; mp 88–89°; ir (Nujol) 1610 (m), 1525 (s), 1328 (s), 1100 (s) cm; uv λ_{max} (MeOH) 263 mμ (ε 11,780); nmr ($CDCl_3$) δ 7.99 (m,4), 5.54 (s,1), 4.37 (m,1), 4.21 (broad singlet, 2).

Anal. Calcd for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.45; H, 6.20; N, 5.04.

Elution of the column with ethyl acetate gave an amber-colored oil (260 mg, 2.24 mmol, 51%). Several such column strippings were combined and distilled. A main fraction was collected of *trans*-2-hydroxycyclopentanol **6**: bp 82–83° (0.1 mm); ir (film) 3320 (s), 1430 (m), 1335 (m), 1020 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.00 (m, 1), 3.62 (complex multiplet, 2).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.77; H, 10.29.

$LiAlH_4$ reduction in ether of the *trans*-2-hydroxycyclopentanecarboxylic acid methyl ester obtained by fractional distillation yielded an oil identical (tlc,[24] ir, nmr) with that obtained from the above column strippings.

***cis*-2-Hydroxymethylcyclopentanol 5 *via* the *p*-Nitrobenzylidine Acetal 15.** The *p*-nitrobenzylidine acetal **15** (1 g, 4.02 mmol) was stirred in methanol (25 ml), and Brady's reagent (0.8 g of 2,4-dinitrophenylhydrazine, 1.6 ml of concentrated H_2SO_4, 12 ml of MeOH, and 4 ml of water) was added dropwise during 30 min. The mixture was stirred overnight at room temperature. The yellow precipitate was collected (1.19 g, 3.59 mmol, 89%), mp 321–323° dec (lit value for *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone, mp 320°). The filtrate was diluted with saturated $(NH_4)_2SO_4$ solution and continuously extracted overnight with ether. The ether was dried ($MgSO_4$) and removed. The residue (500 mg) was distilled in a short path apparatus to give a colorless oil, bp 81–83° (0.5 mm) (300 mg, 2.58 mmol, 64%), which crystallized on standing, mp 31–34°. Recrystallized from ether–pentane to give *cis*-2-hydroxymethylcyclopentanol **5**: mp 33–34°; ir (film) 3295–3345 (broad, s), 1005 (s), 930 (m) cm^{-1}; nmr ($CDCl_3$) δ 4.34 (m, 1), 3.73 (doublet, 2).

Anal. Calcd for $C_6H_{12}O_2$; C, 62.04; H, 10.41. Found: C, 62.03; H, 10.39.

$LiAlH_4$ reduction in ether of the *cis*-2-hydroxycyclopentanecarboxylic acid methyl ester obtained by fractional distillation yielded a crystalline diol, mp 33–34°, identical (tlc,[24] melting point, mixture melting point, ir, nmr) with that obtained by regeneration from the cyclic acetal.

The Bis-3,5-dinitrobenzoate of *trans*-2-Hydroxymethylcyclopentanol (8). *trans*-2-Hydroxymethylcyclopentanol (**6**) (0.9 g, 7.76 mmol) was dissolved in dry pyridine (25 ml) and with stirring 3,5-dinitrobenzoyl chloride (4.31 g, 18.66 mmol) was added slowly. The mixture was stirred at room temperature overnight. The pyridine was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and passed through an alumina column (neutral I) made up in and eluted by CH_2Cl_2. The eluted solids (2.79 g, 4.72 mmol, 61%) were recrystallized from CH_2Cl_2–hexane to give the trans bis-3,5-dinitrobenzoate (**8**): mp 152–154°; ir (Nujol) 1720 (s), 1630 (m), 1545 (s), 720 (s) cm^{-1}; nmr (DMSO) δ 8.89 (m, 6), 5.49 (m, 1), 4.51 (m, 2).

Anal. Calcd for $C_{20}H_{16}N_4O_{12}$: C, 47.62; H, 3.20. Found: C, 47.85; H, 3.62.

The Bis-3,5-dinitrobenzoate of *cis*-2-Hydroxymethylcyclopentanol (7). *cis*-2-Hydroxymethylcyclopentanol (**5**) (438 mg, 3.77 mmol) reacted with 3,5-dinitrobenzoyl chloride in pyridine in an analogous manner. The CH_2Cl_2 eluted solids (1.52 g, 3.01 mmol, 80%) were crystallized from CH_2Cl_2–hexane to the cis bis-3,5-dinitrobenzoate **7**: mp 172–174°; ir (Nujol) 1725 (s), 1625 (m), 1545 (s), 718 (s), cm^{-1}; nmr (DMSO) δ 8.91 (m, 6), 5.67 (m, 1), 4.56 (doublet, 2).

Anal. Calcd for $C_{20}H_{16}N_4O_{12}$: C, 47.62; H, 3.20. Found: C, 47.63; H, 3.36.

Preparation of *cis*- and *trans*-2-Hydroxymethylcyclopentanol Methyl Ether 9 and 10. The mixture of hydroxy esters from PtO_2 hydrogenation of commercial 2-carboethoxycyclopentanone (45 g, 0.312 mol) was dissolved in acetonitrile (200 ml) and methyl iodide (160 ml). Ag_2O (80 g) was added. The mixture was refluxed and stirred overnight. The solids were removed by filtration and the solvents removed. The residue was distilled at the aspirator. The main fraction, bp 81–86° (34.6 g, 0.219 mol, 70%), was used for reduction directly.

The mixture of methoxy esters (52 g, 0.329 mol) was refluxed with $LiAlH_4$ (35 g) in dry 1,2-dimethoxyethane (350 ml) overnight. The excess $LiAlH_4$ was decomposed with saturated Na_2SO_4 solution and ether extracted. Removal of the ether gave an oil (35 g, 0.269 mol, 82%) which was distilled through a Nester Faust spinning band column at the aspirator. Two main fractions were collected.

cis-2-Hydroxymethylcyclopentanol methyl ether **9**: bp 75–76°; ir (film) 3400 (broad, s), 1080 (s), 1035 (m) cm^{-1}; nmr ($CDCl_3$) δ 3.72 (m, 3), 3.30 (s, 3).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.43; H, 10.68.

trans-2-Hydroxymethylcyclopentanol methyl ether **10**: bp 84–85°; ir (film) 3410 (s), 1470 (m), 1372 (m), 1080 (s) cm^{-1}; nmr ($CDCl_3$) δ 3.58 (m, 3), 3.29 (s, 3).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.77; H, 11.05.

The stereochemical assignments were checked by a CCl_4 dilution ir study which showed evidence of strong intramolecular hydrogen bonding in the cis isomer **9** and only intermolecular hydrogen bonding in the trans **10**.

***cis*-2-Methoxycyclopentanecarboxylic Acid Methyl Ester.** *cis*-2-Hydroxycyclopentanecarboxylic acid methyl ester (2 g, 0.0139 mol) was dissolved in CH_3CN (15 ml) and CH_3I (15 ml). The mixture was stirred at reflux overnight with Ag_2O (5 g). Methylation was complete based on tlc (silica gel–$CHCl_3$). The solids were removed by filtration and the filtrate concentrated to dry-

ness, and the residue (2.16 g) was distilled at the aspirator, to give *cis*-2-methoxycyclopentanecarboxylic acid methyl ester: bp 80° (1.5 g, 0.00948 mol, 68%); nmr ($CDCl_3$) δ 3.99 (m, 1), 3.70 (s, 3), 3.29 (s, 3), 2.83 (m, 1).

***cis*-2-Hydroxymethylcyclopentanol Methyl Ether 9.** *cis*-2-Methoxycyclopentanecarboxylic acid methyl ester (800 mg, 5.06 mmol) was dissolved in dry 1,2-dimethoxyethane. $LiAlH_4$ (2 g) was added and the mixture refluxed overnight. The excess reagent was decomposed with saturated Na_2SO_4 solution and made acidic (HCl) and ether extracted. The ether was dried and removed and the residue (1 g) distilled in a short path apparatus at the aspirator. The main fraction, bp 85–86°, was identical (tlc, ir, nmr) with the lower-boiling fraction compound **9** from the spinning band distillation of the cis/trans mixture of 2-methoxycyclopentanols.

***trans*-2-Hydroxymethylcyclopentanol Methyl Ether 10.** *trans*-2-Hydroxycyclopentanecarboxylic acid methyl ester was O-methylated and reduced by $LiAlH_4$ analogously to the cis ester. The main fraction had bp 77° (aspirator) and was identical (tlc, ir, nmr) with the higher-boiling fraction compound **10** from the spinning band distillation of the cis/trans mixture of 2-methoxycyclopentanols.

***trans*-2-Methoxycyclopentanecarboxaldehyde (18) *via* Jones Oxidation.** *trans*-2-Hydroxymethylcyclopentanol methyl ether **10** (1 g, 7.68 mmol) was dissolved in acetone (10 ml). The solution was cooled to 0° (ice–salt bath) and treated dropwise with Jones reagent (1 ml). On completing the addition, the mixture was diluted with ice-cold salt solution and ether extracted. The ethereal extract was washed with ice-cold 10% $KHCO_3$ and the ether removed. The residue (800 mg, 6.24 mmol, 81%) contained only a trace of the starting alcohol **10** by the tlc (silica gel–$CHCl_3$) and consisted of a single faster moving material. Attempts to distil this material to obtain an analysis were not successful. The spectra were satisfactory for *trans*-2-methoxycyclopentanecarboxaldehyde (18): ir (film) 1721, 1092 cm^{-1}; nmr ($CDCl_3$) δ 9.72 (m, 1), 4.02 (m, 1), 3.30 (s, 3), 2.79 (m, 1).

The aldehyde was characterized as the semicarbazone; mp 178° (methanol); ir (Nujol) 3450 (m), 3210 (m), 3150 (m), 1692 (s), 1573 (m) cm^{-1}; uv λ_{max} (MeOH) 228 mμ (ε 14,010).

Anal. Calcd for $C_8H_{15}N_3O_2$: C, 51.87; H, 8.16; N, 22.69. Found: C, 51.78; H, 8.18; N, 22.83.

***trans*-2-Methoxycyclopentanecarboxaldehyde (18) *via* Barton Oxidation.** *trans*-2-Hydroxymethylcyclopentanol methyl ether **10** (11.1 g, 0.0852 mol) was dissolved in a 12.5% benzene solution of phosgene (150 ml). The solution was stirred overnight at room temperature, and the solvents were removed at the aspirator. The residue was distilled and the main fraction was the chloroformate **12:** bp 72–3° (1.5 mm) (14.03 g, 0.0728 mol, 85%); ir (film) 1770–1790 (broad, s), 1150 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.27 (doublet, 2), 3.52 (m, 1), 3.28 (s, 3).

Anal. Calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80; Cl, 18.41. Found: C, 49.90; H, 6.89; Cl, 18.53.

The trans 2-methoxychloroformate **12** (8.62 g, 0.0451 mol) was cooled to ~5° and dry DMSO (25 ml) added slowly. The temperature rose (30°) and gas evolution was evident. The solution was stirred at room temperature for 25 min. Dry triethylamine (6.4 ml) was added dropwise; again the reaction was slightly exothermic and a precipitate developed. The mixture was stirred at room temperature for 25 min and then poured onto ice–water and ether extracted. The ethereal extract was dried ($MgSO_4$) and evaporated. The residue (5.5 g, 0.0429 mol, 95%) contained only traces of *trans*-2-hydroxymethylcyclopentanol methyl ether **10** by tlc (silica gel–$CHCl_3$). This was distilled and the main fraction (3.5 g, 0.0273 mol, 60%), bp 41–46° (2.5 mm), was identical (tlc, ir, nmr) with the trans 2-methoxycyclopentane aldehyde **18** prepared by the Jones oxidation.

***cis*-2-Methoxycyclopentanecarboxaldehyde (17) *via* the Barton Oxidation.** *cis*-2-Hydroxymethylcyclopentanol methyl ether **9** (5.47 g, 0.042 mol) was converted into the chloroformate **11** in a manner analogous to the trans compound **12.** This was treated with DMSO and in turn with triethylamine. The resulting oil (5.0 g, 0.039 mol, 93%) was distilled. The main fraction was cis 2-methoxycyclopentane aldehyde **17** (3.63 g, 0.028 mol, 67%): bp 44–51° (1.8 mm); ir (film) 2740 (w), 1723 (s), 1035 (s) cm^{-1}; nmr ($CDCl_3$) δ 9.79 (m, 1), 4.17 (m, 1), 3.28 (s, 3). Satisfactory analysis could not be obtained although the material contained only traces of impurities (cyclopentene aldehyde and the starting alcohol) by tlc (silica gel–$CHCl_3$). Also, attempts to obtain derivatives were unsuccessful. Reaction with thiosemicarbazide gave the thiosemicarbazone of cyclopentene aldehyde, mp 175° (aqueous acetic acid).

Anal. Calcd for $C_7H_{11}N_3S$: C, 49.61; H, 6.55; N, 24.83. Found: C, 49.29; H, 6.42; N, 24.80.

Wadsworth–Emmons Reaction with *trans*-2-Methoxycyclopentanecarboxaldehyde (18). Diethyl (2-oxoheptyl)phosphonate[25] (10.97 g, 0.0438 mol) was dissolved in dry DMSO (60 ml) and treated with NaH (0.957 g, 0.0399 mol) for 1 hr at room temperature. Then *trans*-2-methoxycyclopentanecarboxaldehyde (18) (5.1 g, 0.0398 mol) in dry DMSO (25 ml) was added dropwise with stirring at room temperature. The mixture was stirred overnight and poured into ice–water and ether extracted. The ether was dried ($MgSO_4$) and removed *in vacuo*. The residue, an amber oil (10.5 g), was chromatographed over silica gel (215 g) eluted by CH_2Cl_2. The early eluates contained artefacts, but a main fraction was collected (1.35 g, 0.007 mol, 18%) which was distilled. The bulk distilled at 99–101° (0.35 mm) to give the dienone **24** as a clear oil (951 mg, 4.95 mmol, 12%): ir (film) 1685 (m), 1660 (s), 1610 (s), 1590 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.37 (d, 1), 6.21 (m, 1), 5.98 (d, 1), 2.50 (m, 6), 0.89 (m, 3); uv λ_{max} (MeOH) 222 mμ (ε 3,430), 284 (22,260).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.63; H, 10.46.

The principal fraction was eluted by 5–10% ethyl acetate–CH_2Cl_2 (4.51 g, 0.0201 mol, 50%). This was distilled and the center fraction (2.656 g, 0.0118 mol, 29%), bp 110–111° (0.3 mm), was the trans methoxy enone **29:** ir (film) 1690 (m), 1670 (s), 1625 (s) 1100 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.80 (pair of doublets, 1), 6.10 (d, 1), 3.56 (m, 1), 3.30 (s, 3), 0.90 (m, 3); uv λ_{max} (MeOH), 228 mμ (ε 12,700).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.83; H, 10.52.

Wadsworth–Emmons Reaction with Cis 2-Methoxycyclopentane Aldehyde 17. The cis 2-methoxycyclopentane aldehyde **17** (2.7 g, 21.1 mmol) reacted with diethyl (2-oxoheptyl)phosphonate[25] (5.8 g, 23.2 mmol) in an analogous manner. The principal chromatographic fraction (3.31 g, 14.8 mmol, 70%) was eluted by 5% ethyl acetate in CH_2Cl_2 from silica gel. This was distilled and the main fraction (2.59 g, 11.5 mmol, 55%), bp 91–5° (0.02 mm), was the cis methoxy enone **21:** ir (film) 1700 (m), 1675 (s), 1630 (s), 1090 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.96 (pair doublets, 1), 6.05 (d, 1), 3.64 (m, 1), 3.26 (s, 3), 0.89 (m, 3); uv λ_{max} (MeOH) 228 mμ (ε 12,450).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.73; H, 10.72.

***trans*-2-Tetrahydropyranyloxycyclopentanecarboxylic Acid Methyl Ester.** *trans*-2-Hydroxycyclopentanecarboxylic acid methyl ester (4.583 g, 0.0318 mol) was dissolved in CH_2Cl_2 (15 ml). 2,3-Dihydro-γ-pyran (3.21 g, 0.0382 mol) and concentrated HCl (3 drops) were added and the mixture was shaken. After standing at room temperature for 1 hr, the reaction was checked by tlc (silica gel–benzene), then washed (10% aqueous $KHCO_3$), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was distilled and the main fraction was the trans THP ether methyl ester (5.785 g, 0.0253 mol, 80%): bp 98–100° (0.1 mm); ir (film) 1730 (s), 1200 (s), 1032 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.65 (m, 1], 441 (m, 1), 3.66 (s, 3), 3.22–4.15 (complex multiplet, 2).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.94; H, 8.99.

***cis*-2-Tetrahydropyranyloxycyclopentanecarboxylic Acid Methyl Ester.** *cis*-2-Hydroxycyclopentanecarboxylic acid methyl ester reacted in an exactly analogous way to give an 80% yield of the *cis*-THP ether methyl ester: bp 100–105° (0.1 mm); ir (film) 1745 (s), 1250 (s), 1025 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.71 (m, 1), 4.45 (m, 1), 3.71 (s, 3), 3.28–4.10 (complex multiplet, 2).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.24; H, 8.87.

***trans*-2-Hydroxymethylcyclopentanol THP Ether (14).** The trans THP methyl ester (23.89 g, 0.105 mol) was added to $LiBH_4$ (6 g) in ether (250 ml). The mixture was refuxed for 3 hr, allowed to stand overnight at room temperature, and then washed with water. The ether was removed to give an oil (19.2 g). This was distilled and the main fraction was the trans THP carbinol **14** (17.17 g, 0.086 mol, 82%): bp 90–96° (0.01 mm); ir (film) 3432 (s), 1135 (m), 1075 (m), 1025 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.64 (m, 1), 3.90 (m, 2), 3.56 (m, 2).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.99; H, 9.89.

***cis*-2-Hydroxymethylcyclopentanol THP Ether (13).** The cis THP ester (23.4 g, 0.102 mol) was reduced by $LiBH_4$ in ether and worked up as previously described to give a principal fraction: bp 110° (0.1 mm) which was the cis THP carbinol **13** (16.43 g, 0.082 mol, 80%); ir (film) 3450 (s), 1350 (m), 1025 (s) cm^{-1}; nmr

($CDCl_3$) δ 4.63 (m, 1), 4.27 (m, 1), 3.35–4.17 (complex multiplet, 4).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.87; H, 10.06.

***trans*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (20).** The *trans*-2-tetrahydropyranyloxycyclopentylcarbinol (14) (6.25 g, 0.0312 mol) was dissolved in a mixture of dry benzene (250 ml) and dry DMSO (250 ml) and cooled to 4° in ice. Dry pyridine (4.5 ml), trifluoroacetic acid (3.4 ml), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[26] (60 g, 0.142 mol) were added and the mixture stirred for 5 days at 0–4°. The reaction was diluted with ice–water and extracted with ether. Removal of the ether gave an oil which was distilled. The main fraction, bp 77–82° (0.06 mm) (4.97 g, 0.0251 mol, 80%), did not give a satisfactory elemental analysis, but was principally the trans aldehyde **20** based on ir (film) 2710 (w), 1722 (s), 1035 (s) cm^{-1}; nmr ($CDCl_3$) δ 10.55 (m, 1), 4.63 (m, 1), 4.42 (m, 1).

***cis*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (19).** The *cis*-2-tetrahydropyranyloxycyclopentylcarbinol (13) (10 g, 0.0499 mol) was oxidized analogously to give after distillation a main fraction, bp 80–83° (0.05 mm) (8.49 g, 0.0428 mol, 86%), which was the cis aldehyde **19** based on ir (film) 2720 (w), 1720 (s), 1130 (s), 1020 (s) cm^{-1}; nmr ($CDCl_3$) δ 9.93 (m, 1), 4.68 (m, 1), 4.41 (m, 1).

Wadsworth–Emmons Reaction with *cis*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (19). *cis*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (19) (897 mg, 4.52 mmol) was dissolved in dry DMSO (5 ml) and added dropwise to a solution of diethyl (2-oxoheptyl)phosphonate[25] (1.515 g, 6.05 mmol) in DMSO (10 ml) which had been treated with 1 equiv of NaH for 1 hr. The mixture was stirred overnight at room temperature, diluted with water, and extracted with ether. The ether was removed and the residue chromatographed on silica gel made up in CH_2Cl_2 and eluted by ethyl acetate–CH_2Cl_2 (1:19 and 1:9). The main fraction was the cis tetrahydropyranyloxy enone **22** (856 mg, 2.91 mmol, 64%) which was characterized spectrally: ir (film) 1742 (s), 1725 (m), 1700 (m), 1680 (s), 1635 (m) cm^{-1}; nmr ($CDCl_3$) δ 6.58–7.08 (complex multiplet, 1), 6.12 (d, 1), 4.67 (m, 1), 4.25 (m, 1), 0.89 (m, 3); uv λ_{max} (MeOH) 228 mμ (ε 9751). Forerun material from the column chromatography was characterized as the 2,4-dinitrophenylhydrazone of the dienone **24:** mp 126–128° (aq MeOH): ir (Nujol) 3310 (w), 1615 (s), 1595 (s), 1310 (s) cm^{-1}; nmr ($CDCl_3$) δ 9.05 (d, 1), 8.10 (m, 2), 6.98 (m, 1), 6.27 (m, 2), 0.91 (m, 3); uv λ_{max} (MeOH) 225 mμ (ε 16,720), 265 (17,470), 301 (13,770), 387 (29,560).

Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.27; H, 6.48. Found: C, 60.93; H, 6.71.

Wittig Reaction with *trans*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (20). *trans*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (20) (6.7 g, 0.0338 mol) was dissolved in ether (150 ml), and 1-tributylphosphoranylidene-2-heptanone[7] (10.15 g, 0.033 mol) was added. The mixture was stirred overnight at room temperature. The ether was removed; the residue was dissolved in CH_2Cl_2 and filtered through a silica gel column (450 g) made up in CH_2Cl_2. A main fraction (8.4 g, 0.0285 mol, 84%) was eluted by ethyl acetate–CH_2Cl_2 (1:9) which based on spectra [ir (film) 1725 (m), 1695 (m), 1675 (s), 1630 (m), 1135 (s), 1020 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.70–7.21 (complex multiplet, 1) 6.07 (d, 1), 4.61 (m, 1), 4.23 (m, 1), 0.88 (m, 3)] was the desired trans tetrahydropyranyloxy enone **30.** Attempts to distil this product gave a main fraction, bp 135° (0.05 mm), but some decomposition occurs and a satisfactory elemental analysis could not be obtained. The material was used for the next step directly from the chromatography.

The Trans 2-Hydroxy Enone 31. The trans tetrahydropyranyloxy enone **30** (2.76 g, 9.37 mmol) was dissolved in 10% methanolic oxalic acid (30 ml) and allowed to stand at room temperature for 5 hr. The methanol was removed. The residue was dissolved in excess 10% aqueous $KHCO_3$ solution and ether. The ether was separated, dried, and removed. The residue was chromatographed on silica gel (60 g) made up in ethyl acetate–CH_2Cl_2 (1:9). Elution yielded 218 mg, principally starting material. Elution with a 1:4 mixture yielded the principal fraction (1.713 g, 8.15 mmol, 87%), which was distilled in a short path apparatus. The main fraction, bp 118–119° (0.03 mm) (1.192 g, 5.67 mmol, 60%), was the hydroxy enone **31:** ir ($CHCl_3$) 3620 (w), 3465 (w), 1690 (s), 1665 (s), 1625 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.83 (pair doublets, 1), 6.17 (d, 1), 4.02 (m, 1), 2.55 (m, 2), 0.89 (m, 3); uv λ_{max} (MeOH) 230 mμ (ε 14,070).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.48; H, 10.78.

Borohydride Reduction of the Trans 2-Tetrahydropyranyloxy Enone 30. The trans tetrahydropyranyloxy enone **30** (3.558 g, 0.0121 mol) was dissolved in methanol (20 ml) and cooled to −5°. $NaBH_4$ (2 g) was added portionwise with stirring and cooling, making sure that the temperature did not rise above 5°; reaction time was 1 hr. Completion of the reaction was checked by tlc (silica gel–$CHCl_3$). The methanol was removed *in vacuo.* The residue was dissolved in salt solution and extracted with ether. The ether was removed and the residue (3.64 g) chromatographed on silica gel (100 g). The main fraction was eluted by ethyl acetate–CH_2Cl_2 (1:9) (2.79 g, 0.0094 mol, 78%), which was distilled to give a mixture of the alcohols **32** and **33:** bp 130–134° (0.03 mm); ir (film) 3460 (m), 1450 (m), 1350 (m), 1130 (s), 1030 (s) cm^{-1}; nmr ($CDCl_3$) δ 5.58 (m, 2), 4.64 (m, 1), 3.92 (m, 3), 0.92 (m, 3).

Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88. Found: C, 72.81; H, 11.13.

The PGE_1 Model Compounds 34 and 35. The trans tetrahydropyranyloxy alcohol mixture **32** and **33** (3 g, 0.0101 mol) was dissolved in methanol (300 ml), and 1.0 *N* HCl (4 ml) was added. The mixture was stirred at room temperature for 1 hr. Based on tlc (silica gel eluted by ethyl acetate–chloroform 1:4) the reaction was completed. It was diluted with salt solution and extracted by ether. The ethereal extracts were dried ($MgSO_4$) and the ether removed. The residue (1.99 g, 0.0094 mol, 93%) was chromatographed on silica gel (60 g) made up in ethyl acetate–CH_2Cl_2 (1:9). The progress of the chromatography was followed by tlc fractions were combined on the basis of the tlc data. Three main fractions were obtained by elution with ethyl acetate–CH_2Cl_2 (1:4). The first fraction (640 mg, 0.00301 mol, 30%) was exclusively the faster moving epimer **34.** This was distilled, bp 120–125° (0.05 mm); nmr ($CDCl_3$) δ 5.58 (m, 2), 3.91 (m, 2), 0.88 (m, 3).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.32; H, 11.29.

The second fraction (385 mg, 0.00181 mol, 18%) was a mixture of both epimers **42** and **43.**

The third fraction (665 mg, 0.00313 mol, 31%) was exclusively the slower moving epimer **35.** This was also distilled, bp 120–128° (0.05 mm); nmr ($CDCl_3$) δ 5.51 (m, 2), 3.82 (m, 2) 0.88 (m, 3).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.67; H, 11.22.

Borohydride Reduction of the Cyclopentenone Diester 36 to the Cyclopentanol Diester 38. The cyclopentanone diester[16] **36** (12.5 g, 0.0442 mol) was dissolved in methanol (250 ml) and cooled in an ice bath. With stirring $NaBH_4$ (6.5 g) was added portionwise during 1.5 hr such that the temperature remained around 5°. Stirring was continued for a further 30 min. The methanol was removed *in vacuo.* The residue was shaken with ice–saturated NaCl solution and ether. The ether was separated, dried ($MgSO_4$), and removed. The residue (12.9 g) was chromatographed on alumina (580 g of neutral III) made up in CH_2Cl_2. Elution by CH_2Cl_2 gave a colorless oil **38** (6.23 g, 0.0217 mol, 49%) which was homogeneous based on tlc (silica gel–ethyl acetate) This diester **38** was characterized by hydrolysis to the crystalline diacid **40.**

Hydrolysis of the Cyclopentanol Diester 38 to the Diacid 40. The cyclopentanol diester **38** (104 mg, 0.363 mmol) was dissolved in methanol (3 ml), and 10% aqueous K_2CO_3 (3 ml) was added. The mixture was refluxed for 1 hr, concentrated *in vacuo,* and diluted with water; ether was extracted. The aqueous part was acidified and reextracted with ether. Removal of the ether gave a colorless oil (107 mg) which crystallized slowly. This was recrystallized from ether–petroleum ether to give the cyclopentanol diacid **40** (74 mg, 0.286 mmol, 79%): mp 100–101°; ir (Nujol) 3425 (m), 1705 (broad, s) 1300 (m) cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.20; H, 8.49.

In a repeat experiment, the crude diacid **40** instead of being recrystallized was redissolved in ether and treated with excess diazomethane. Removal of the ether gave an oil **38** which was identical (ir, tlc) with original diester **38.**

Borohydride Reduction of the Cyclopentanol Diester 38 to the Diol Ester 42. The cyclopentanol diester **38** (2.6 g, 9.08 mmol) was dissolved in methanol (75 ml) and cooled to 4° in ice. $NaBH_4$ (1.7 g) was added with stirring and the reaction allowed to warm to room temperature. By tlc (silica gel–ethyl acetate–chloroform 1:4) the reaction was half-complete. Further $NaBH_4$ (250 mg) was added and the mixture stirred overnight at room temperature. The reaction was diluted with water and extracted with ether. The ether was removed and the residue chromatographed on silica gel (60 g) made up in ethyl acetate–CH_2Cl_2 (2:3). Elution with this mixture yielded a forerun (460 mg) which was principally the starting diester **38** (ir, tlc). The principal fraction was the diol ester

42 eluted by ethyl acetate–CH_2Cl_2 (4:1) (1.8 g, 6.97 mmol, 76%): ir (film) 3380 (broad, s), 1735 (s), 1440 (m) cm^{-1}; nmr ($CDCl_3$) δ 4.38 (m, 1), 3.68 (s, 3), 3.62 (m, 2), 2.33 (t, 2).

This material was characterized as the *p*-nitrobenzylidene acetal. The diol ester **42** (390 mg, 1.51 mmol) was dissolved in benzene (35 ml). *p*-Nitrobenzaldehyde dimethyl acetal[8] (300 mg, 1.52 mmol) and *p*-toluenesulfonic acid (a few crystals) were added. The mixture was refluxed overnight, then filtered through alumina (20 g, neutral III) made up in benzene and eluted by benzene. The eluates were concentrated to dryness to give a pale yellow waxy solid **44** (534 mg, 1.36 mmol, 90%); ir (film) 1732 (s), 1610 (m), 1525 (s), 1350 (s), 850 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.90 (m, 4), 5.53 (m, 1), 4.38 (m, 1), 4.20 (m, 2), 3.66 (s, 3).

A portion (225 mg, 0.575 mmol) of this ester **44** was hydrolyzed by reflux for 30 min in methanol (10 ml) and aqueous 10% K_2CO_3 (10 ml) to yield a crystalline acid **46** (185 mg, 0.49 mmol, 85%), mp 115–117°, which was recrystallized from ether–pentane to give the analytical sample: mp 115–117°; ir (Nujol) 1700 (s), 1610 (w), 1520 (s), 840 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.91 (m, 4), 5.52 (m, 1), 4.38 (m, 1), 4.19 (m, 2), 2.35 (t, 2).

Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.32; H, 7.12; N, 3.54.

Borohydride Reduction of the Cyclopentenone Diester 36 to the Trans Cyclopentanol Diester 39. The cyclopentenone diester[16] **36** (3.14 g, 11.1 mmol) was dissolved in methanol (90 ml) and cooled in a cold water bath. $NaBH_4$ (3.14 g) was added portionwise during 2.5 hr such that the temperature did not rise above room temperature. The bath was removed and the reaction stirred at room temperature for a further 2.5 hr. The methanol was removed *in vacuo*. The residue was shaken with water and ether. The ethereal layer was separated and the ether removed. The residue was chromatographed over silica gel, made up in CH_2Cl_2. Only traces of material were eluted with CH_2Cl_2. A major fraction was eluted by ethyl acetate–CH_2Cl_2 (2:3) which was the trans hydroxy ester **39** (1.04 g, 3.63 mmol, 33%); ir (film) 3465 (m), 1735 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.37 (m, 1), 3.72 (m, 2), 3.65 (s, 3), 2.30 (t, 2).

Elution of the column by ethyl acetate gave a mixture of diols **42** and **43** which were utilized later [1.27 g, 4.92 mmol, 44%); ir (film) 3390 (s), 1738 (s) cm^{-1}].

The trans hydroxy diester **39** was hydrolyzed by refluxing aqueous 10% K_2CO_3 as for the cis isomer **38**, to yield the diacid **41**: mp 70–71° (ether); ir (Nujol) 3365 (m), 1700 (broad, s), 1200 (s) cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.75; H, 8.75.

A portion of the diacid **41** was redissolved in ether and reesterified with the diazomethane. The hydroxy diester **39** thus obtained was identical (tlc, ir, nmr) with that obtained from the original column chromatography of the borohydride reduction of **36**.

Borohydride Reduction of the Cyclopentanone Diester 37. The cyclopentanone diester[16] **37** (460 mg, 1.62 mmol) was dissolved in methanol (25 ml) and cooled in an ice bath to 4°. $NaBH_4$ (230 mg) was added portionwise during 15 min so that no appreciable temperature rise was noted. The reaction was stirred for a further 45 min, diluted with NaCl solution, and extracted with ether. The ether was removed and the residue (415 mg) was compared on tlc (silica gel–ethyl acetate–chloroform 1:4) with the reaction products obtained from $NaBH_4$ reductions of the cyclopentenone diester **36** and the purified cis and trans hydroxy diesters **38** and **39**. No new products were evident. The composition of the reaction mixtures varied only as to the extent of reduction. The residue was chromatographed on silica gel (15 g), made up in ethyl acetate–CH_2Cl_2 (1:19), and eluted with this mixture. The first major fraction was the cis hydroxy ester **38** (300 mg, 1.047 mmol, 65%) identical (ir, tlc, nmr) with that prepared directly from the cyclopentenone diester **36**. Subsequent elution by ethyl acetate–CH_2Cl_2 (2:3) yielded the trans hydroxy ester **39** (86 mg, 0.30 mmol, 18%) identical (ir, tlc, nmr) with that obtained from the cyclopentenone diester **36**.

Mono-para-nitrobenzoylation of the Cis Diol Ester 42. The cis diol ester **42** (4.87 g, 0.0188 mol) was dissolved in dry pyridine (125 ml), and *p*-nitrobenzoyl chloride (4 g, 0.0215 m mol) was added. The mixture was stirred overnight at room temperature. The pyridine was removed *in vacuo*. The residue was shaken with water and ether. The ether was separated and removed. The residue (8 g) was chromatographed on silica gel (240 g) made up in ethyl acetate–CH_2Cl_2 (1:19) and eluted with this mixture. The first fractions consisted of bis-*p*-nitrobenzoate (2.037 g, 0.00366 mol, 19%). The major fraction eluted by ethyl acetate–CH_2Cl_2 (1:9) and (3:17) was the desired mono-*p*-nitrobenzoate **48** (5.26 g, 0.0129 mol, 69%): ir (film) 3490 (m), 1720 (s), 1610 (m), 1539 (s), 720 (s), cm^{-1}; nmr ($CDCl_3$) δ 8.18 (s, 4), 4.41 (complex multiplet, 3), 4.65 (s, 3), 2.30 (t, 2).

Mono-*p*-nitrobenzoates of the Cis and Trans Diol Esters 42 and 43. The ethyl acetate column strippings from the borohydride reduction of the cyclopentenone diester **36** to the trans hydroxy ester **39** (1.53 g, 5.92 mmol) (see above) were dissolved in dry pyridine (40 ml) and *p*-nitrobenzoyl chloride (1.2 g, 6.45 mmol) in pyridine (10 ml) added dropwise. The reaction mixture stood overnight at room temperature. The pyridine was removed *in vacuo*. The residue was shaken with water and ether. The ether layer was washed, dried ($MgSO_4$), and concentrated to dryness. The residue (2.54 g) was chromatographed on six preparative silica gel plates eluted twice with ethyl acetate–chloroform (1:9). Some starting diols were still evident, as were the bis-*p*-nitrobenzoates close to the solvent front. The two central bands were removed and eluted. The faster moving band (R_f 0.61) (1.38 g, 3.39 mmol, 57%) was the cis mono-*p*-nitrobenzoate **48** identical (ir, nmr, tlc) with that obtained directly from the purified cis diol ester **42**. The slower moving band (R_f 0.48) (433 mg, 1.06 mmol, 18%) was the trans mono-*p*-nitrobenzoate **45**: ir (film) 3430 (m), 1725 (s), 1605 (m), 1550 (s), 730 (s) cm^{-1}; nmr ($CDCl_3$) δ 8.25 (s, 4), 4.20 (complex multiplet, 3), 3.64 (s, 3), 2.31 (t, 2).

THP Ether of the Cis Mono-*p*-nitrobenzoate (50). The cis mono-*p*-nitrobenzoate **48** (1.10 g, 2.70 mmol) was dissolved in methylene chloride (70 ml). 2,3-Dihydro-γ-pyran (0.75 ml, 8.1 mmol) and picric acid (50 mg) were added and mixture stirred for 18 hr at room temperature. The solvent was removed *in vacuo*. The residue was dissolved in ether and washed (10% aqueous $KHCO_3$ and H_2O). The ether was removed. The residue (1.36 g, 2.7 mmol) which was free of starting alcohol based on tlc (silica gel–ethyl acetate–chloroform 1:9) was characterized spectrally as the tetrahydropyranyl ether **50**: ir (film) 1735 (s), 1723 (s), 1612 (m), 1278 (s), 720 (s), cm^{-1}; nmr ($CDCl_3$) δ 8.25 (s, 4), 4.47 (m, 4), 3.66 (s, 3), 3.55 (m, 3), 2.28 (t, 2). It was then utilized for the next step.

The trans mono-*p*-nitrobenzoate **45** (320 mg, 0.785 mmol) in an exactly analogous process yielded the tetrahydropyranyl ether **47** [400 mg; nmr ($CDCl_3$) δ 8.23 (s, 4), 4.45 (m, 4), 3.65 (s, 3), 3.60 (m, 3), 2.26 (t, 2)] homogeneous on tlc (silica gel–ethyl acetate–chloroform 1:9).

The Cis THP Carbinol 51. The cis tetrahydropyranyloxy *p*-nitrobenzoate **50** (1.48 g, 3.01 mmol) was dissolved in methanol (75 ml), and aqueous 10% K_2CO_3 solution (22 ml) was added. The mixture was stirred at room temperature for 40 min, diluted with water, and extracted with ether. The ether extract was washed (H_2O), dried ($MgSO_4$), and concentrated to dryness to yield the cis tetrahydropyranyl carbinol **51** [(1.05 g, 3.06 mmol; ir (film) 3450 (m), 1735 (s), 1025 (s) cm^{-1}; nmr ($CDCl_3$) δ 3.67 (s, 3), 2.31 (t, 2)] which was homogeneous on tlc (silica gel–CH_2Cl_2–ethyl acetate 4:1).

The Trans THP Carbinol 49. The trans tetrahydropyranyloxy *p*-nitrobenzoate **47** (445 mg, 0.90 mmol) was hydrolyzed in an analogous way to give the trans tetrahydropyranyl carbinol **49** (300 mg, 0.88 mmol) homogeneous on tlc.

The Cis THP Aldehyde 52. *Via* Moffat Oxidation. The cis THP carbinol **51** (365 mg, 1.06 mmol) was dissolved in dry benzene (15 ml) and dry DMSO (15 ml) and cooled to 4° in an ice bath. Dry pyridine (0.15 ml), trifluoroacetic acid (0.1 ml), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[26] (2.2 g, 5.3 mmol) were added and the mixture stirred at 4° for 4 days. The reaction was diluted with ice–water and ether extracted. The ethereal extract was washed (ice–water), dried ($MgSO_4$), and concentrated to dryness. The residue (360 mg, 1.05 mmol 98%) was the cis tetrahydropyranyloxy aldehyde **52** [ir (film), 2700 (w), 1740 (s), 1710 (s), 1440 (m), 1030 (m), 1020 (m) cm^{-1}; nmr ($CDCl_3$) δ 9.75 (m, 1), 3.63 (s, 3), 2.38 (complex multiplet, 3)] homogeneous by tlc (silica gel–CH_2Cl_2–ethyl acetate 9:1).

***Via* Collins Oxidation.** The cis THP carbinol **51** (545 mg, 1.6 mmol) was dissolved in dry CH_2Cl_2 (150 ml). A solution of pyridine dichromate (2.5 g, 9.6 mmol) in dry CH_2Cl_2 (50 ml) was added in one portion with stirring. The mixture was stirred for 15 min at room temperature. Then the CH_2Cl_2 was decanted, washed with water, and removed *in vacuo*. The residue (505 mg, 1.48 mmol, 92%) was identical (tlc, ir, nmr) with the aldehyde **52** prepared *via* the modified Moffatt procedure as described above.

The trans THP carbinol **49** (332 mg, 0.97 mmol) was oxidized *via* the pyridine dichromate procedure to yield the trans THP aldehyde **53** (330 mg, 100%) homogeneous on tlc (silica gel–CH_2Cl_2–ethyl acetate 9:1).

Elimination to the Cyclopentene Aldehyde of the Cis THP

Aldehyde 52. The cis THP aldehyde **52** (236 mg, 0.69 mmol) was dissolved in benzene (10 ml). Piperidine (2 drops) and acetic acid (1 drop) were added and the mixture was warmed in a steam bath for 30 min. The entire mixture was added to an alumina column (15 g, neutral III) made up in CH_2Cl_2–ethyl acetate (1:19) and eluted by that mixture. The material first eluted was the cyclopentene aldehyde. This crude cyclopentene aldehyde was characterized as the semicarbazone, mp 115–116° (aq MeOH); ir (Nujol) 3445 (m), 3150 (m), 1725 (m), 1680 (s), 1590 (m) cm^{-1}; uv λ_{max} (EtOH) 267 mμ (ε 28,560).

Anal. Calcd for $C_{15}H_{25}N_3O_3$: C, 60.99; H, 8.53; N, 14.23. Found: C, 60.84; H, 8.92; N, 14.58.

Wittig Reaction on the Cis THP Aldehyde 52 to the Enone 54. The cis tetrahydropyranyloxy aldehyde **52** (500 mg, 1.47 mmol) and 1-tributylphosphoranylidene-2-heptanone[7] (900 mg, 2.87 mmol) were dissolved in dry THF (30 ml) and refluxed for 3 days. The THF was removed and the residue chromatographed on preparative silica gel plates eluted by ethyl acetate–CH_2Cl_2 (1:19). The main band (R_f 0.71) was removed and eluted to give the cis tetrahydropyranyloxy enone **54** (390 mg, 0.89 mmol 61%); ir (film) 1738 (s), 1675 (m), 1630 (m), 1445 (m), 1027 (s), cm^{-1}; nmr ($CDCl_3$) δ 6.73 (m, 1), 6.02 (m, 1), 3.63 (s, 3), 2.35 (m, 5), 0.89 (m, 3).

Wittig Reaction on the Trans THP Aldehyde 53 to the Enone 55. The trans tetrahydropyranyloxy aldehyde **53** (330 mg, 0.97 mmol) reacted with 1-tributylphosphoranylidene-2-heptanone[7] (608 mg, 1.94 mmol) in THF, and worked up analogously to yield a principal fraction from the plate at R_f 0.62 of the trans tetrahydropyranyloxy enone **55** (212 mg, 0.485 mmol, 50%): nmr ($CDCl_3$) δ 6.75 (m, 1), 6.11 (m, 1), 3.65 (s, 3), 2.40 (m, 5), 0.90 (m, 3).

The Cis Hydroxy Enone 56. The cis tetrahydropyranyloxy enone **54** (380 mg, 0.87 mmol) was dissolved in methanol (30 ml) and 2*N* HCl (0.5 ml) was added. The mixture stood at room temperature for 18 hr. The methanol was removed *in vacuo*. The residue was dissolved in ether and washed with water twice. The ether was removed and the residue chromatographed on preparative silica gel plates eluted by ethyl acetate–CH_2Cl_2 (4:1). The central band (R_f 0.54) was removed and eluted to give the cis hydroxy enone **56** (105 mg, 34%): nmr ($CDCl_3$) δ 6.80 (m, 1), 6.20 (m, 1), 4.28 (m, 1), 3.67 (3), 2.35 (m, 5), 0.91 (m, 3).

The Trans Hydroxy Enone 57. Trans tetrahydropyranyloxy enone **55** (210 mg, 0.48 mmol) reacted in an analogous manner with methanolic HCl to give the trans hydroxy enone **57** (160 mg, 0.45 mmol, 95%), homogeneous on tlc (silica gel–ethyl acetate–CH_2Cl_2 4:1): nmr ($CDCl_3$) δ 6.75 (m, 1), 4.15 (m, 1), 4.05 (m, 1), 3.65 (s, 3), 2.39 (m, 5), 0.89 (s, 3).

9-Deoxy-PGE$_1$ 2. The trans hydroxy enone **57** (160 mg, 0.45 mmol was dissolved in ether (25 ml), and an ethereal solution of $Zn(BH_4)_2$ (20 ml) was added. The mixture was stirred at room temperature for 1.5 hr. Water was added and acetic acid added dropwise until the emulsion broke. The ether was separated and removed. The residue was chromatographed on preparative silica gel plates eluted by ethyl acetate–CH_2Cl_2 (1:1).

The faster moving band (R_f 0.46) (52 mg, 32%) was eluted and dissolved in methanol (5.5 ml) and 10% aqueous K_2CO_3 (5.5 ml). The mixture was refluxed for 2 hr and then concentrated *in vacuo*. The residue was diluted with water, extracted with ether, acidified (2 HCl), and reextracted with ether. Removal of the ether gave the *dl*-9-deoxy-15-epi-PGE$_1$ as a viscous oil (43 mg, 90%) homogeneous by tlc (silica gel–benzene–dioxane–acetic acid 10:10:05, R_f 0.48): ir ($CHCl_3$), 3610 (w), 3400 (m), 1710 (s), 1600 (w), cm^{-1}; mass spectrum, *m/e* 322 (M − H_2O), 304 (M − $2H_2O$), 278 (M − H_2O, CO_2).

The slower moving band (R_f 0.22) (42 mg, 26%) was eluted and hydrolyzed in an analogous manner with methanolic K_2CO_3 solution. Removal of the final ether gave a colorless oil which crystallized (30 mg, 81%). This was homogeneous by tlc (silica gel–benzene–dioxane–acetic acid 10:10:05, R_f 0.46). Recrystallization from ether–hexane gave *dl*-9-deoxy-PGE$_1$ **2**: mp 76–78°; mass spectrum *m/e* 322 (M − H_2O), 304 (M − $2H_2O$), 278 (M − H_2O, CO_2).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.64; H, 10.51.

9-Deoxy-11,15-epi-PGE$_1$ 4. The cis hydroxy enone **56** (360 mg, 1.02 mmol) was reduced in ether with ethereal $Zn(BH_4)_2$ in an analogous manner and worked up by preparative tlc.

The faster moving band (R_f 0.49) (81 mg, 22%) was hydrolyzed by methanolic K_2CO_3 solution as described above to give *dl*-9-deoxy-11-epi-PGE$_1$ as a wax (71 mg, 90%) homogeneous on tlc (silica gel–benzene–dioxane–acetic acid 10:10:05, R_f 0.55): nmr ($CDCl_3$) δ 5.61 (m, 2), 4.16 (m, 2), 0.93 (m, 3); mass spectrum *m/e* 322 (M − H_2O), 304 (M − $2H_2O$), 278 (M − H_2O, CO_2).

The slower moving band (R_f 0.33) (93 mg, 26%) was hydrolyzed by methanolic K_2CO_3 solution as described above to give *dl*-9-deoxy-11,15-epi-PGE$_1$ **4** (81 mg, 91%) which crystallized and was homogeneous on tlc (silica gel–benzene–dioxane–acetic acid 10:10:0.5, R_f 0.50). Recrystallization from ethyl acetate gave the analytical sample: mp 71–72°; nmr ($CDCl_3$) δ 5.58 (m, 2), 4.12 (m, 2), 0.92 (m, 3); mass spectrum *m/e* 322 (M − H_2O), 304 (m − $2H_2O$), 278 (M − H_2O, CO_2).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.73; H, 10.76.

9-Deoxy-11,15-epi-PGE$_1$ 4 *via* $NaBH_4$ Reduction. The cis tetrahydropyranyloxy enone **54** (2.75 g, 6.4 mmol) was dissolved in 95% ethanol (150 ml). To the well-stirred solution at room temperature was added $NaBH_4$ (5.5 g). After 30 min, the reaction was diluted with water, and ether was extracted. Removal of the ether gave a residue which was chromatographed on silica gel (75 g) made up in CH_2Cl_2. The main fraction, the mixture of allylic alcohols **58** (2.09 g, 4.76 mmol, 74%), was eluted by ethyl acetate–CH_2Cl_2 (1:6): ir (film) 3440 (m), 1733 (s), 1017 (s) cm^{-1}; nmr ($CDCl_3$) δ 5.54 (m, 2), 4.61 (m, 1), 3.67 (s, 3), 0.91 (m, 3).

The mixture of allylic alcohols **58** (2.05 g, 4.67 mmol) was dissolved in methanol (125 ml) and 1 *N* HCl (3 ml) added. The mixture was stirred at room temperature for 2.5 hr and diluted with water, and ether was extracted. The ether was removed and the residue **59** (1.62 g, 4.57 mmol, 98%) was chromatographed on silica gel (60 g). Two chromatographically pure fractions (tlc) were eluted. The faster one eluted by ethyl acetate–CH_2Cl_2 (1:4) (0.518 g, 1.46 mmol, 31%) was identical (ir, nmr, tlc) with *dl*-9-deoxy-11-epi-PGE$_1$ methyl ester from the preparative tlc plates. The slower fraction (0.530 g, 1.49 mmol, 32%) eluted by ethyl acetate–CH_2Cl_2 (2:3) was identical (ir, nmr, tlc) with the *dl*-9-deoxy-11,15-epi-PGE$_1$ methyl ester from the preparative tlc plates.

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Registry No.—**2,** 53317-71-8; **4,** 53317-72-9; **5,** 53229-67-7; **6,** 53229-68-8; **7,** 53229-69-9; **8,** 53293-20-2; **9,** 53229-70-2; **10,** 53229-71-3; **11,** 53229-72-4; **12,** 53229-73-5; **13** (or **14**), 53229-74-6; **15,** 53229-75-7; **17,** 53229-76-8; **18,** 53229-77-9; **18** semicarbazone, 53229-78-0; **19** (or **20**), 53229-79-1; **21,** 53229-80-4; **22,** 53229-81-5; **24,** 53229-82-6; **24** 2,4-DNPH, 53229-83-7; **29,** 53275-01-7; **31,** 53229-84-8; **32** (or **33**), 53229-85-9; **34,** 53229-89-3; **35,** 53275-05-1; **36,** 39493-34-0; **37,** 53229-86-0; **38,** 53229-87-1; **39,** 53275-02-8; **40,** 53229-88-2; **41,** 53275-03-9; **42,** 53275-04-0; **43,** 53275-06-2; **44,** 53229-90-6; **45,** 53275-07-3; **46,** 53229-91-7; **47** (or **50**), 39493-38-4; **48,** 53275-08-4; **49** (or **51**), 39493-39-5; **52** (or **53**), 38460-69-4; **54,** 53275-09-5; **55,** 53275-10-8; **56,** 53317-73-0; **57,** 53275-11-9; **58** 15α-OH, 53275-12-0; **58** 15β-OH, 53275-13-1; 2-carboethoxycyclopentanone, 53229-92-8; 2-carbomethoxycyclopentanone, 53229-93-9; *cis*-2-carbomethoxycyclopentanol, 53229-94-0; *trans*-2-carbomethoxycyclopentanol, 53229-95-1; *p*-nitrobenzaldehyde dimethyl acetal, 881-67-4; 3,5-dinitrobenzoyl chloride, 99-33-2; 1-cyclopentene-1-carboxaldehydethiosemicarbazone, 53229-96-2; diethyl (2-oxoheptyl)phosphonite, 3450-65-5; 2,3-dihydro-γ-pyran, 110-87-2; 2-tetrahydropyranyloxycyclopentanecarboxylic acid methyl ester, 53229-97-3; 1-tributylphosphoranylidene-2-heptanone, 35563-52-1; *p*-nitrobenzoyl chloride, 122-04-3; 2-formyl-2-cyclopentene-1-heptanoic acid methyl ester semicarbazone, 53229-98-4; *dl*-9-dioxy-15-epi-PGE$_1$, 53317-74-1; *dl*-9-dioxy-11-epi-PGE$_1$, 53317-75-2.

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(23) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr were obtained on a Varian A-60 unless otherwise stated. Mass spectra were obtained on an MS9 instrument at 70 eV.
(24) Homogeneity of the *cis*- and *trans*-2-hydroxymethylcyclopentanols was most conveniently checked by tlc using Silica Gel GF eluted by benzene–chloroform–formic acid–isopropyl alcohol (2:8:2:1).
(25) Dimethyl (2-oxoheptyl)phosphonate is now available from Aldrich Chemical Co.
(26) Available from the Aldrich Chemical Co.

Intramolecular Friedel–Crafts Reaction of 3-Cyclohexen-1-acetyl Chloride and Its 4-Methyl Analog[1]

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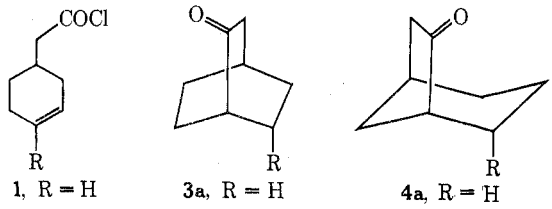
Stannic chloride catalyzed cyclization of 3-cyclohexen-1-acetyl chloride (**1**) yielded a mixture of 6-chlorobicyclo[2.2.2]octan-2-one (**3b**) and 2-chlorobicyclo[3.2.1]octan-7-one (**4b**). Reductive fragmentation of **3b** and **4b** with lithum aluminum hydride gave 2-(3-cyclohexenyl)ethanol. Treatment of the keto chloride mixture with DBN–HMPA gave bicyclo[3.2.1]oct-3-en-6-one (**9**) as the only elimination product. Cyclization of 4-methyl-3-cyclohexen-1-acetyl chloride (**2**) followed by DBN–HMPA elimination furnished 4-methylbicyclo[3.2.1]oct-3-en-6-one (**15**) in good yield. These intramolecular Friedel–Crafts acylations provide a regioselective synthetic route to bicyclo[3.2.1]octane systems containing differentiated functionality in two bridges.

The intramolecular Friedel–Crafts acylation of aliphatic substrates to give fused-ring products is well documented.[2,3] This method also provides an attractive synthetic route to bicyclic derivatives characterized by differentiated functionality in two bridges.[4] An investigation of the Lewis acid catalyzed cyclization of 3-cyclohexen-1-acetyl chloride (**1**) and its 4-methyl analog **2** was undertaken to evaluate further this approach to functionalized bicyclooctane skeletons.

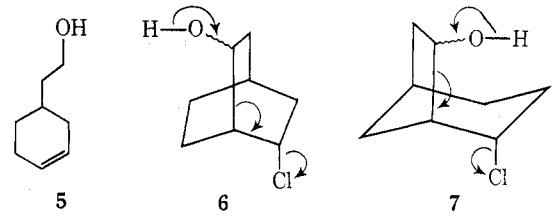
Treatment of acid chloride **1** with stannic chloride in carbon disulfide (−15°, 1 hr) yielded a mixture of three bicyclic keto chlorides (ratio 11:6:6) in 90% yield. Reduction of this mixture with tri-*n*-butyltin hydride gave two ketones which were identified as bicyclo[2.2.2]octan-2-one (**3a**) and bicyclo[3.2.1]octan-6-one (**4a**) by comparison with authentic materials. Separation of the keto chloride mixture and reduction of the individual components revealed that the major isomer furnished **3a**, one minor isomer gave **4a**, and the other minor isomer was not reduced under these conditions. Assignment of structure **3b** to the major keto chloride component and structure **4b** to one of the minor isomers was based on the observation that treatment of the keto chloride mixture with lithium aluminum hydride gave alcohol **5** in 75% yield. A reductive fragmentation[4a] of **3b** and **4b** (see arrows in **6** and **7**) readily accounts for the formation of **5** and suggests the anti disposition of the carbonyl group and the chlorine atom shown in **3b** and **4b**.



1, R = H
2, R = Me

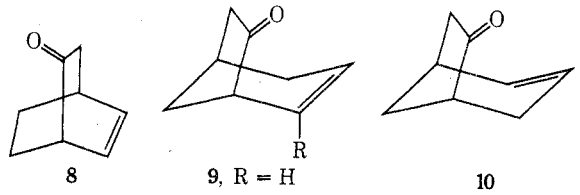
3a, R = H
b, R = Cl

4a, R = H
b, R = Cl



5 6 7

When the initial keto chloride mixture was heated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in hexamethylphosphortriamide (HMPA) solution (115°, 5 hr) a *single* bicyclic keto olefin was isolated together with recovered keto chloride(s). Vpc comparison of this new material with known samples of the possible elimination products, 8[5] and a mixture[6] of **9** and **10**, indicated that it was one of the bicyclo[3.2.1]octenes **9** or **10**. Initial structural assignment as



8 9, R = H
15, R = CH_3 10

9 was made on the basis of the lanthanide shift nmr analysis method of Willcott and Davis[7] (see Experimental Section for details) and was confirmed by comparion with authentic **9**.[8] The reluctance of keto chloride **3a** to undergo