TABLE V
OPTICALLY ACTIVE AMINO ACIDS PREPARED FROM THEIR AROMATIC SULFONATES

Amino acid	Registry no. D	Registry no. L	Method	Yield, %	N analysis, % Calcd	N analysis, % Found L	N analysis, % Found D	$[\alpha]^{25}D$, deg (c 2, 5 N HCl) L	$[\alpha]^{25}D$, deg (c 2, 5 N HCl) D
Alanine	338-69-2	56-41-7	Ion exchange	96	15.72	15.72	15.73	+14.6	−14.6
DOPA	5796-17-8	59-92-7	LiOH	96	7.10	7.08	7.11	−12.2[a]	+12.3[a]
Leucine	328-38-1	61-90-5	Ion exchange	95	10.68	10.63	10.64	+15.9	−16.0
Lysine HCl	42334-88-3	10098-89-2	Ion exchange	96	15.34	15.41	15.45	+20.8	−20.8
MDPMA	42334-90-7	42334-89-4	NH_4OH	96	6.28	6.27	6.27	+25.4[b]	−25.4[b]
Serine	312-84-5	56-45-1	Ion exchange	98	13.33	13.37	13.35	+15.0[c]	−15.1[c]
Tryptophan	153-94-6	73-22-3	NH_4OH	95	13.72	13.74	13.73	−32.4[d]	+32.5[d]

[a] 4%, in 1 N HCl, at 20°. [b] $[\alpha]^{25}_{365}$, 1% in 1 N HCl. [c] In 1 N HCl. [d] 1% in H_2O.

by filtration, washed with a small amount of cold water, and dried. By this operation, optically pure crystals of L-Ser-*m*-XS were obtained, yield 8.62 g, $[\alpha]^{25}D$ +4.1° (*c* 4, H_2O).

Preparation of Optically Active Amino Acids.—From optically pure aromatic sulfonates of amino acids, the free amino acids were easily obtained either by neutralization with alkali or by use of an ion exchange resin. In the former, an aqueous solution of aromatic sulfonates was adjusted with alkali to the isoelectric point of the amino acids and cooled in a refrigerator overnight. The crystallized free amino acids were filtered off, washed with cold water, and dried. This method was convenient for sparingly soluble amino acids. For readily soluble amino acids, the latter method was employed. Aromatic sulfonates were taken up in a tenfold amount of water. The solution was passed through an ion exchange column of Amberlite IR-120 (in H form). The column was washed with water and the amino acid was eluted with 2 *N* NH_4OH. The eluate was concentrated, treated with charcoal, and concentrated again until the crystalline precipitate appeared. To the residue MeOH was added and the mixture was allowed to stand in a refrigerator overnight to give the colorless amino acid.

Table V indicates the yields and the specific rotations of optically active amino acids obtained by this process.

For the preparation of L-α-methyl DOPA, the L-MDPMA (50.0 g) obtained above was hydrolyzed with 20% hydrochloric acid (930 ml) and phenol (47 g) for 17 hr. After evaporation, the residue was dissolved in 120 ml of water and adjusted to pH 5.8 with 5 *N* NH_4OH containing a small amount of sodium bisulfite. The precipitate was collected, and further crops were obtained by successive concentrations of the filtrate. The total yield of L-α-methyl DOPA·$^3/_2H_2O$ was 43.6 g (81.6%). Recrystallization from sulfurous acid solution (0.5%) gave a white powder of L-α-methyl DOPA·$^3/_2H_2O$, and drying of the sesquihydrate *in vacuo* at 100° gave the anhydrous form, mp 306–307° dec, $[\alpha]^{25}D$ −5.2°, $[\alpha]^{25}_{578}$ −5.5° (*c* 2, 0.1 *N* HCl). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.63; H, 6.24; N, 6.59.

Acknowledgment.—We thank Dr. S. Miyoshi and Dr. K. Matsumoto in our laboratory for preparation of DL- and D-MDPMA.

Registry No.—DL-MDPMA·$^1/_2$ *p*-PS, 42398-50-5; L-α-methyl DOPA, 555-30-6.

Total Synthesis of *dl*-Prostaglandin E_1

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dl-Prostaglandin E_1 (PGE_1) (**61**) has been synthesized in 14 steps from 2-carboxy-5-oxo-1-cyclopentenehe ptanoic acid (**15**). The synthesis required the development of two mild procedures and a new protecting group. A Moffatt oxidation using a water-soluble carbodiimide converted the carbinol **52** to aldehyde **53**. The Wittig reaction of aldehyde **53** with the tributylphosphorane **36** was used to obtain the enone **54**. Protection of the cyclopentanone carbonyl group was achieved *via* the phenylthiomethyl oxime **48**. This derivative is unaffected by mild oxidative (Moffatt or Collins) or reductive (borohydride) procedures and yet can be readily cleaved back to the unsubstituted oxime with mercury ion catalysis and hence in turn to the ketone.

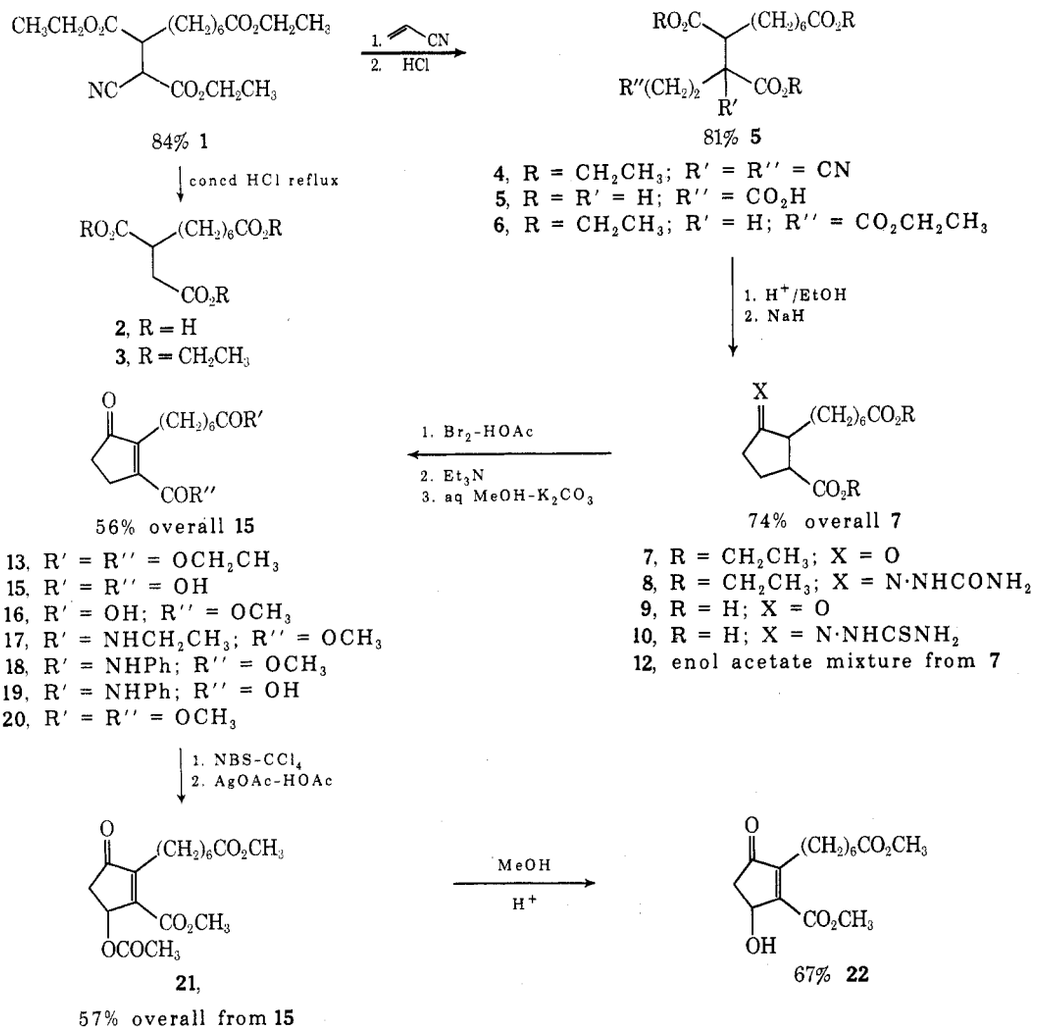
The prostaglandins have, during the past decade, become a major area of biological[1] and clinical investigation.[2] As a consequence of their limited accessibility from natural sources, and the desire to explore the structural requirements for their biological activity, the prostaglandins have become the synthetic targets of many groups.[3] Several of these groups have reported specific syntheses of prostaglandin E_1 (PGE_1)[4] (**61**). We now describe the details of our synthesis of PGE_1.[5]

At the time our efforts commenced there was no significant clinical work published on the prostaglandins which would indicate any important differences between PGE_1 and PGE_2. PGE_1 seemed to be the most appropriate target compound, as it had been converted to PGA_1 and $PGF_1\alpha$[3] and the additional double bond in the carboxylic acid side chain of PGE_2 seemed to pose additional synthetic limitations.

The preparation of an appropriate starting material, **15**, was anticipated as being possible by a process analogous to one of those used to synthesize isosarkomycin, 2-methyl-3-carboxycyclopentenone. The synthesis of Shemyakin[6] was briefly investigated but discarded in favor of the procedure used by Newman.[7]

(1) J. R. Weeks, *Annu. Rev. Pharmacol.*, **12**, 317 (1972).
(2) Research in Prostaglandins (Supplement), Sept 1972, Worcester Foundation.
(3) J. E. Pike, *Fortschr. Chem. Org. Naturst.*, **28**, 313 (1970).
(4) (a) C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Amer. Chem. Soc.*, **94**, 3643 (1972); (b) D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, Z. S. Zelawski, and N. L. Wendler, *Tetrahedron*, **29**, 1447 (1973); (c) E. J. Corey and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 7319 (1971), and references cited therein; (d) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *ibid.*, **91**, 5372 (1969); (e) M. Miyano and M. A. Stealey, *J. Chem. Soc., Chem. Commun.*, 180 (1973).
(5) N. Finch and J. J. Fitt, *Tetrahedron Lett.*, 4639 (1969).
(6) M. M. Shemyakin, M. N. Kolosov, M. G. Karapetyan, and V. Y. Rodionov, *Zh. Obshch. Khim.*, **28**, 2068 (1958); *Chem. Abstr.*, **53**, 2228e (1959).
(7) M. S. Newman and J. L. McPherson, *J. Org. Chem.*, **19**, 1717 (1954).

SCHEME I



Substituting readily available diethyl α-bromoazelate[8] for the ethyl α-bromopropionate used by Newman gave access in good yield to the cyclopentenone diacid **15** (Scheme I). The only critical step in this procedure was to ensure that the addition of acrylonitrile to compound **1** goes to completion (tlc). If adduct **4** is contaminated with unreacted starting material, **1**, hydrolysis gives a crystalline mixture of tetraacid **5** and triacid **2**. The acids **5** and **2** cocrystallize and the presence of **2** in **5** becomes easily evident only after esterification, when the presence of the triester **3** in the tetraester **6** can be readily detected by vpc. After Dieckmann cyclization of **6**, the resultant cyclopentanone diester, **7**, was hydrolyzed to the diacid.[9] Conversion of **7** to the cyclopentenone diester **13** was explored both *via* bromination of the enol acetate mixture **12** and directly of **7** followed by dehydrobromination. Both procedures gave comparable overall yields, and the latter procedure was one step less, so this was employed for the large scale preparations.

Introduction of the hydroxyl group into the cyclopentenone diester **13** (Scheme I), to obtain **22**, also employed well-established procedures.[10] The only ambiguity possible, *i.e.*, that the hydroxyl group of **22** was in position 5 rather than 4 of the cyclopentenone ring, was removed by spectral comparison (particularly the uv shift with base) of the precursor to **22**, the acetoxycyclopentenone diester **21**, with 2-methyl-3-carbomethoxy-4-acetoxycyclopentenone whose structure has been firmly established.[11]

To obtain the appropriate stereochemistry for PGE_1, *i.e.*, trans,trans, it was presumed that silylation of the hydroxycyclopentenone diester **22** would create a functionality, *i.e.*, the siloxy group, large enough to influence the direction of hydrogenation. Thus cis addition of hydrogen to the double bond of siloxycyclopentenone **25** from the side opposite to the siloxy group would yield an all-cis siloxycyclopentanone. Epimerization then at the center α to the carbomethoxy group should lead predominantly to the desired all-trans arrangement. In fact, hydrogenation of the siloxycyclopentanone diester, **25**, over Raney nickel gave a crystalline siloxycyclopentanone, **26**, in almost quantitative yield. A single spot on tlc and crystallinity were taken as indicators of homogeneity. Reaction with methoxyamine in pyridine gave a crystalline

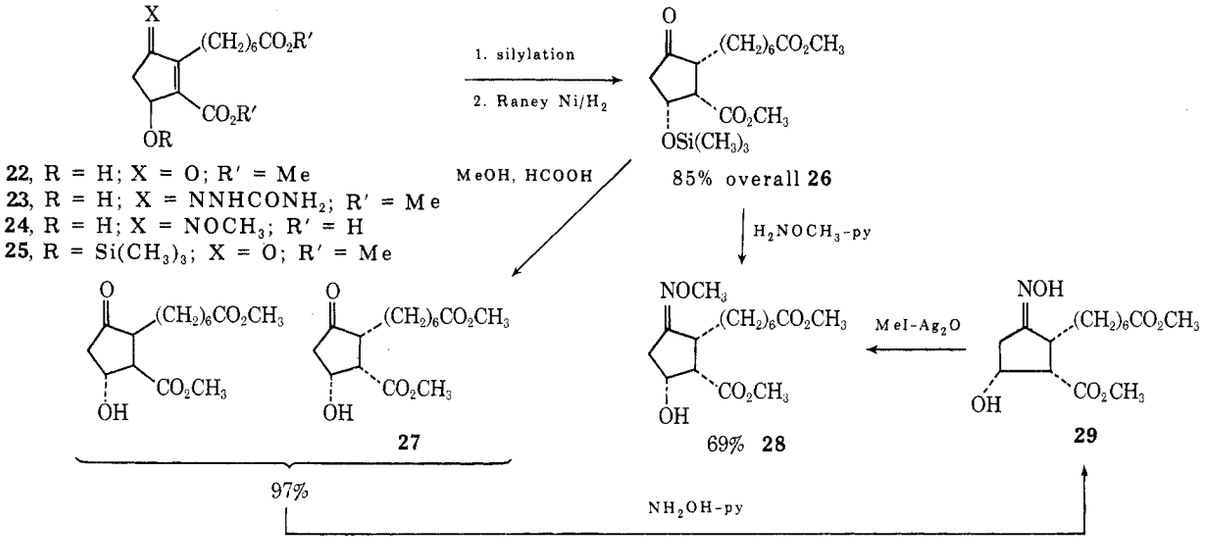
(8) B. Teichmann, *Acta Chim. (Budapest)*, **41**, 331 (1964); *Chem. Abstr.*, **62**, 2704c (1965).

(9) J. F. Bagli, T. Bogri, R. Deghenghi, and K. Wiesner, *Tetrahedron Lett.*, 465 (1966).

(10) C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964).

(11) N. Finch and E. Schlittler, *Tetrahedron*, **24**, 5421 (1968).

SCHEME II



22, R = H; X = O; R′ = Me
23, R = H; X = NNHCONH$_2$; R′ = Me
24, R = H; X = NOCH$_3$; R′ = H
25, R = Si(CH$_3$)$_3$; X = O; R′ = Me

methyl oxime, **28**, in 69% yield. The mother liquor material contained a second compound, which was assumed to be a syn or anti isomer of **28**. Reaction of siloxycyclopentanone, **26**, with hydroxylamine gave an oxime, **29**, which could be O-methylated to give the same methyl oxime, **28**, as had been obtained directly from **26** with methoxyamine. Serious doubts, for several reasons, developed about whether the methyl oxime mother liquor material was indeed a syn or anti isomer and as epimerization during methyl oxime formation had been excluded[12] these doubts necessarily extended to the homogeneity of **26**. Treatment of this substance with methanolic formic acid at room temperature, to remove the silyl group, yielded a crystalline hydroxycyclopentanone, which by tlc was clearly a mixture of two substances. Both isomers cocrystallized and several recrystallizations were necessary to obtain a homogeneous sample of the major isomer **27** (Scheme II). Compound **27** yielded the same oxime derivatives as could be obtained directly from the siloxycyclopentanone, **26**. The minor isomeric hydroxycyclopentanone was subsequently shown to be a cis,-trans compound derived by hydrogenation from the same side as the siloxy group. This was therefore the origin of the "mother liquor" methyl oxime, rather than syn–anti isomerism. Despite our disappointment in the lack of stereospecificity at the hydrogenation step, our expectations were completely fulfilled on treatment of the major all-cis crystalline methyl oxime, **28**, with base. Hydrolysis with aqueous methanolic potassium carbonate and reesterification with diazomethane yielded an isomeric compound, **32**, which contained only traces of the starting material **28**. That this change involved epimerization at the carbomethoxy group was confirmed by an ir dilution study of the OH region. The crystalline methyl oxime, **28**, showed a concentration-independent behavior expected for a cis arrangement of hydroxyl group and ester, which makes possible a strong *intra*molecular hydrogen bond. The isomeric methyl oxime, **32**, exhibited concentration-dependent behavior and can be reasonably assigned a trans stereochemistry at these centers.[12] Independent work[12] on methyl oximes derived from configurationally unstable ketones demonstrated that under these conditions epimerization α to the methyl oxime was unlikely. Thus the stereochemistry of the epimerized methyl oxime, **32**, can be assigned all trans, assuming cis addition of hydrogen at the reduction step.

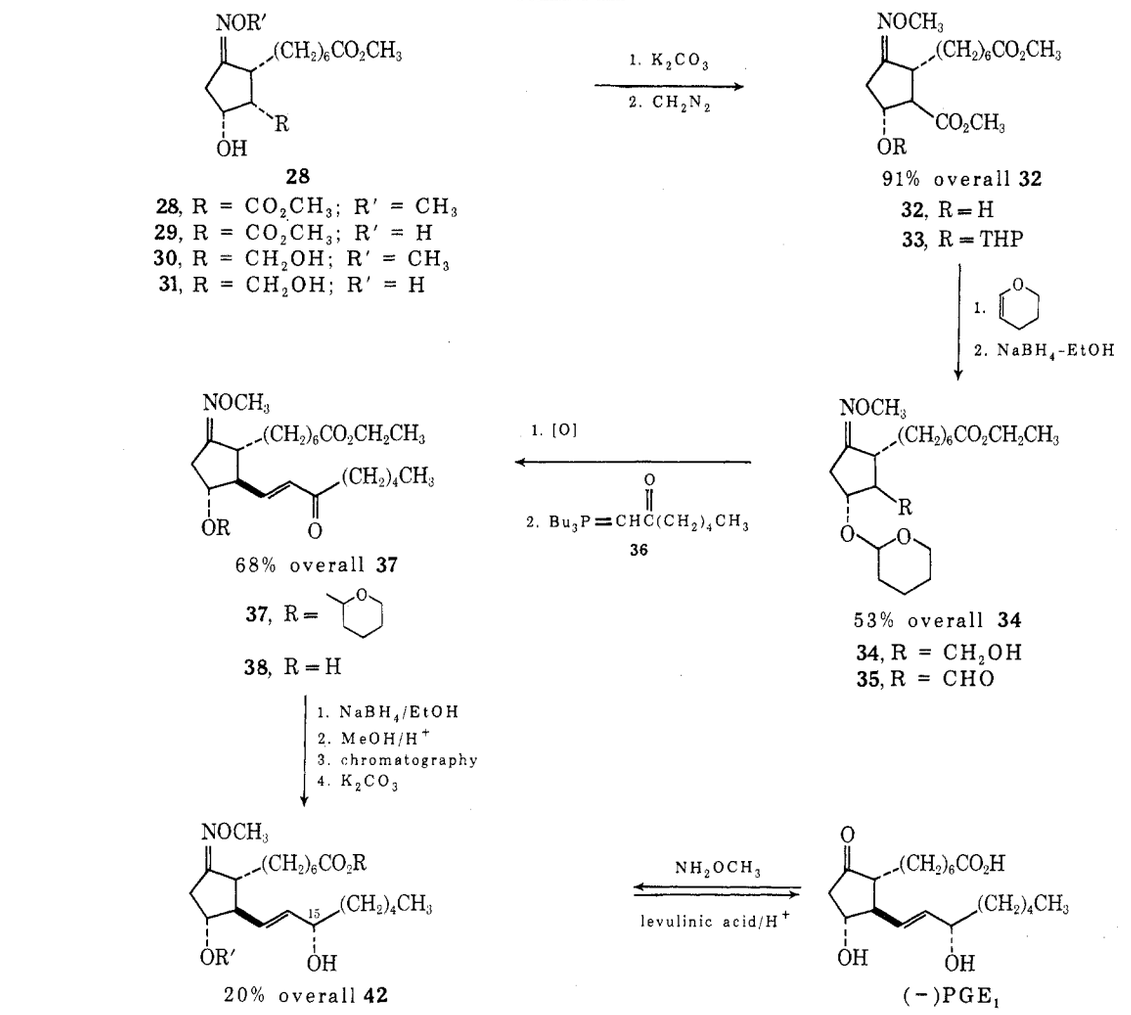
The next step in the sequence called for selectivity between the ester at the end of the chain and that on the ring. Earlier efforts (Scheme I) had provided half-ester acid derivatives of cyclopentenone diacid **15**, *e.g.*, compounds **17** and **18**. Nevertheless, based both on the yields by which they were obtained and the ease of their conversion to the hydroxycyclopentenones, these compounds, **17** and **18**, were not regarded as being useful intermediates, which would provide this selectivity. Therefore, an alternative approach was explored. It had been anticipated that selectivity between the esters would be possible *via* an internal assist from the hydroxy group, *e.g.*, sodium borohydride might be expected to reduce the ester attached to the ring *via* an intermediate alkoxy borohydride. Alas the stereochemical differences evident in the ir study, discussed above, now worked against us. The all-cis crystalline methyl oxime, **28**, was reduced rapidly in good yield to the crystalline diol methyl oxime ester **30**, but epimerized methyl oxime **32** reacted only sluggishly with borohydride and no discrimination was evident in the reduction of the esters. In desperation the dihydropyran addition step was carried out and borohydride reduction repeated on THP ether **33**. For reasons we do not completely understand, **33** gave selective reduction of the ester on the ring and the desired THP methyl oxime ester carbinol, **34**, could be readily separated by chromatography from overreduced material. Nevertheless this step is the poorest in the scheme, except for the cleavage of PGE$_1$ oxime.

Oxidation of carbinol **34** to aldehyde **35** could be effected in almost quantitative yield by a modified Moffatt oxidation[13] using the water-soluble 1-cyclo-

(12) Configurational stability of methyl oximes from epimerizable ketones, the stereochemical assignments to substituted 2-hydroxycyclopentanecarboxylic acids, and other model studies will be discussed in more detail in a subsequent paper.

(13) (a) J. G. Moffatt, *Org. Syn.*, **47**, 25 (1967); (b) N. M. Weinshenker and C. M. Shen, *Tetrahedron Lett.*, 3285 (1972).

SCHEME III



39, R = CH_2CH_3; R′ = H

40, R = CH_2CH_3; R′ =  (epimer mixture at C_{15})

41, R = CH_2CH_3; R′ = H (C_{15} epimer)

42, R = R′ = H

hexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich C-10, 640-2). The excess reagent was readily removed by an ice water wash. In this instance the product would be affected by oxalic acid treatment, normally used to remove excess DCC, the reagent used by Moffatt.[13a] Other modifications of the Moffatt oxidation have been developed by the Alza group.[13b] Reaction of aldehyde **35** with the tributylphosphorane **36** gave the enone **37**. The use of **36** was developed by us because of the instability of the reactant aldehyde **35**. Tributylphosphoranes were known to be more reactive than the conventional triphenylphosphoranes.[14] Thus a Wittig reaction with the tributylphosphorane **36** is possible under milder conditions.

The enone **37** was reduced with sodium borohydride in ethanol at room temperature. Under these conditions with the THP group still present, little conjugate reduction (estimated by nmr) was evident. The mixture of allylic alcohols **40** was treated with methanolic hydrochloric acid to remove the THP group and the mixture of hydroxy allylic alcohols, **39** and **41**, subjected to preparative tlc on alumina plates. The slower moving material, **39**, crystallized. Hydrolysis of this with methanolic potassium carbonate solution gave (±)-PGE_1 methyl oxime, **42**, which was identical spectrally and on tlc with the methyl oxime prepared from (−)-PGE_1[15] (Scheme III).

A variety of methods were investigated for cleavage of the methyl oxime back to PGE_1. Attention was directed to the nonoxidative procedures used for oximes, *i.e.*, reduction or exchange processes. Reaction in levulinic acid or its ethyl ester containing aqueous mineral acid at 4° effected some conversion to PGE_1. However, the yields were poor, and the process was clearly unsuited for providing adequate quantities of prostaglandin analogs. What was needed was an oxime, which could be cleaved more readily. An unsubstituted oxime would be suitable as many mild

(14) A. J. Speziale and D. E. Bissing, *J. Amer. Chem. Soc.*, **85**, 3878 (1963).

(15) We wish to acknowledge help by Swiss colleagues with this comparison during a stay in Basle in 1967 by Neville Finch. CIBA-GEIGY colleagues, Dr. J. Schmidlin obtained the ir spectra, Dr. H. Hurzeler the mass spectra, and Dr. Neher made the tlc comparisons. Dr. U. Scheidegger (Varian, Zurich) obtained nmr spectra on 2 mg by use of a CAT. A sample of (−)-PGE_1 was kindly provided by Professor D. A. vanDorp (Unilever).

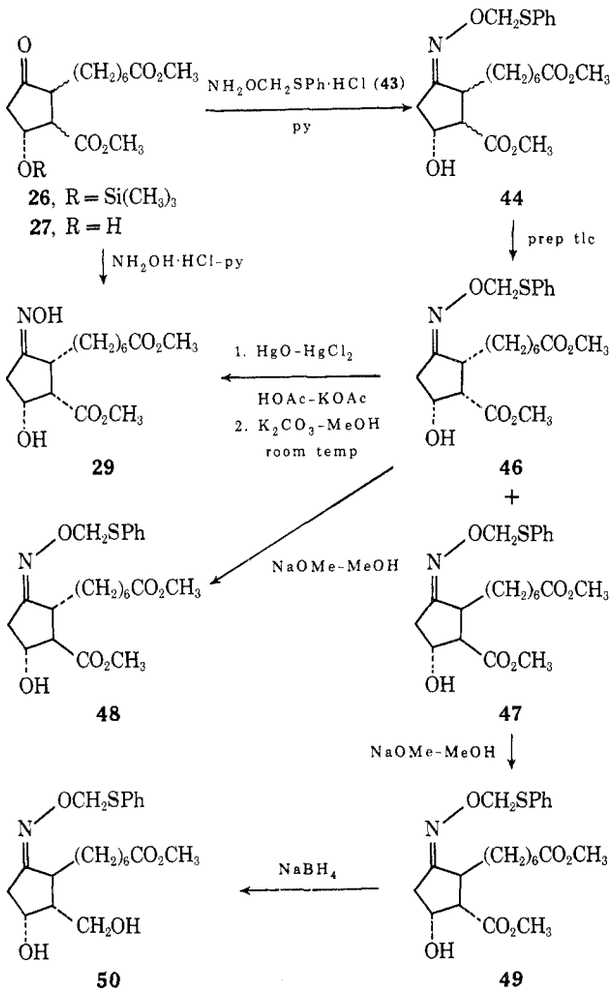
methods are available for conversion of oximes back to ketones.[16] However, unsubstituted oximes will not survive even the mild oxidation conditions of the Moffatt oxidation;[17] so an appropriate protecting group was required. After several investigations[18] one particularly satisfactory reagent was discovered which should have broad applicability for the protection of sensitive ketones, phenylthiomethoxamine **43**. This was prepared and treated with a variety of ketones. The phenylthiomethyl oximes were cleaved back to the unsubstituted oximes in a two-step procedure. Treatment with a mixture of mercuric oxide and mercuric chloride in potassium acetate–acetic acid gave the acetoxymethyl oxime which was unstable and collapsed to the unsubstituted oxime on treatment with methanolic potassium carbonate in the cold.[19]

While this procedure involves multiple operations it is well suited for telescoping, and overall yields are excellent.

The siloxycyclopentanone **26** or the desilylated material **27** reacted with phenylthiomethoxyamine hydrochloride (**43**) in pyridine to give a crystalline product, **44**, in excellent yield. As with other derivatives in this series both isomers had cocrystallized. The major isomer, the all-cis compound **46**, was separated on the first occasion by preparative tlc and fully characterized along with the minor isomer **47**. Application of the cleavage conditions to **46** gave the unsubstituted oxime **29**, which was identical with that obtained as the major product from the reaction of hydroxylamine on the siloxycyclopentanone **26** (Scheme IV). After appropriate experiments on model compounds,[19] to confirm the stability of the new group to oxidation conditions, the scheme proceeded with compound **44** as an intermediate. The epimerization step was first carried out on the separated isomers **46** and **47**. They were separately converted by methanolic sodium methoxide at reflux almost exclusively into epimeric substances (Scheme IV). That the epimerization involved the center α to the carbomethoxy group in both cases was evident from the fact that the minor isomer **47** which was resistant to sodium borohydride reduction was epimerized to **49**. This was smoothly reduced to the crystalline diol ester **50** by sodium borohydride (Scheme IV), thus establishing that the ester and hydroxyl group were cis to one another in **49**. The reverse situation pertained to **46**, as its epimer, **48**, could be converted to a diol ester with sodium borohydride only *via* the THP derivative **51**, which, as we have shown above, is the behavior of a trans arrangement of ester and hydroxyl group.

In view of the lack of stereospecificity in the hydrogenation of the cyclopentenone diester **22** and the absence of a readily purifiable crystalline derivative, such as existed in the methyl oxime sequence, it was clearly necessary to achieve stereochemical homogeneity by means of chromatography. It turned out that separation after epimerization, *i.e.*, of **48** from **49** (Scheme IV)

SCHEME IV



by chromatography, was quite easy. Furthermore as silylation of the cyclopentenone *22* achieved very little in the way of increasing the stereospecificity of the hydrogenation step, it was clear that the process from *22* to **48** could be telescoped (Scheme V). Hydrogenation of *22* with Raney nickel yielded a mixture of the hydroxycyclopentanone, **27**, and its isomer (Scheme II), which was not purified but treated directly with phenylthiomethoxlamine hydrochloride, **43**, in pyridine. The mixture of oximes **46** and **47** (Scheme IV) was epimerized with sodium methoxide and the major isomer, **48**, separated by preparative tlc. **48** was obtained in 48% overall yield from *22*.

A publication by Miyano[20] described an alternative reduction scheme, using zinc and acetic acid, on a related compound. Using this process it was possible to proceed in two steps from hydroxycyclopentenone, *22*, to **48** with approximately the same overall yield. Transformation of **48** into a prostaglandin (Scheme V) proceeded in a manner analogous to that for the methyl oxime **32** (Scheme III). Particular attention was directed at the poor step, *i.e.*, selective borohydride reduction of the esters of the THP ether **51**. Interestingly the ester exchange noted with the analogous process in the methyl oxime case, *i.e.*, **33** to **34** in Scheme

(16) (a) G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 195 (1971); (b) A. McKillop, J. D. Hunt, R. D. Naylor, and E. C. Taylor, *J. Amer. Chem. Soc.*, **93**, 4918 (1971); (c) E. J. Corey and J. E. Richman, *ibid.*, **92**, 5276 (1970), and references cited therein.

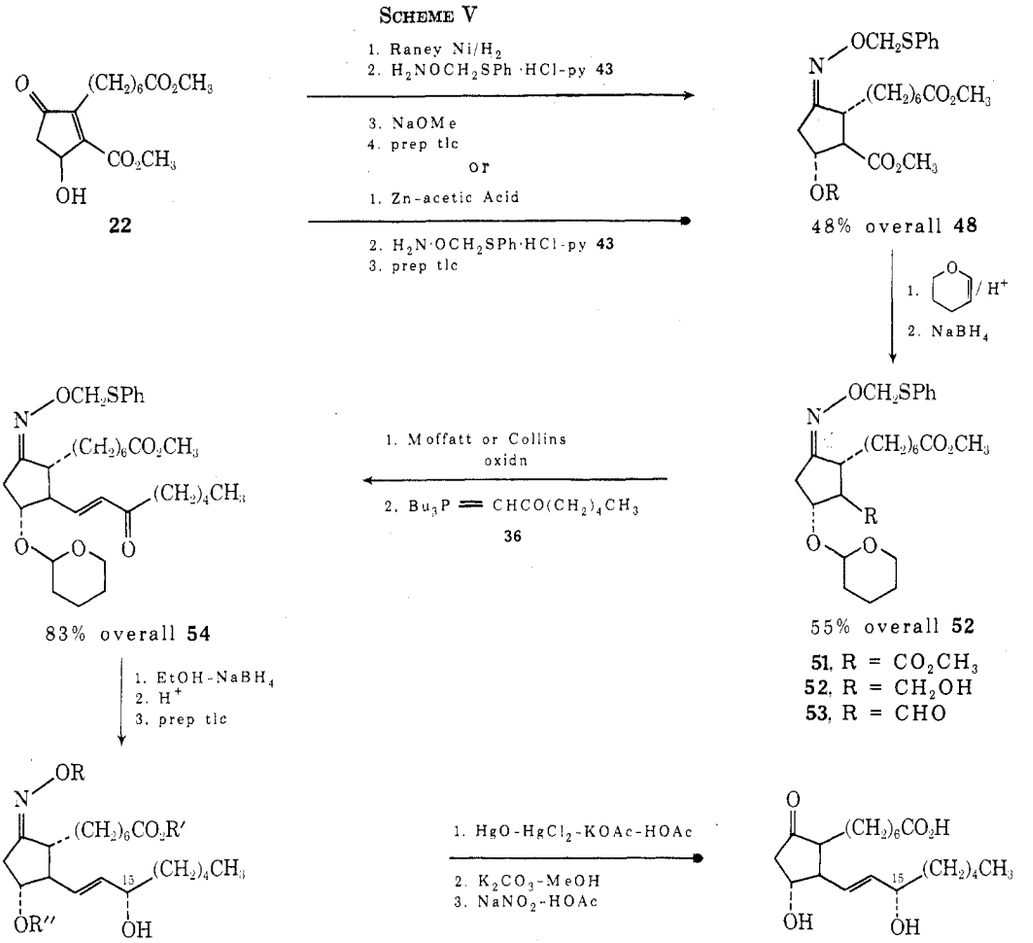
(17) A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).

(18) N. Finch, U. S. Patent 3,657,328 (1972).

(19) I. Vlattas, L. DellaVecchia, and J. J. Fitt, *J. Org. Chem.*, **38**, 3749 (1973).

(20) M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, **37**, 1810 (1972).

SCHEME V



55, R = CH_2SPh; R′ = CH_3; R″ =  (C_{15} mixture)

56, R = CH_2SPh; R′ = CH_3; R″ = H
57, R = CH_2SPh; R′ = CH_3; R″ = H (C_{15} epimer)
58, R = CH_2OCOCH_3; R′ = CH_3; R″ = H
59, R = R = H; R′ = CH_3 (*dl*-PGE_1 oxime methyl ester)
60, R = R′ = R″ = H (*dl*-PGE_1 oxime)
62, R = CH_2OCOCH_3; R′ = CH_3; R″ = H (C_{15} epimer)

III, did not occur in the transformation of **51** to **52**[21] (Scheme V).

The reasons for the absence of exchange in the latter case are not clear. An especially interesting observation was that the "starting material" recovered from the borohydride reduction of the THP ether, **51**, was resistant to further reduction. Nevertheless, cleavage by acid back to the hydroxy diester **48** and re-formation of **51** from this product, yielded material which would again undergo selective reduction of the ester groups, to the extent of about 50%, to yield the carbinol ester **52** (Scheme V). From this we infer that **51** is a 1:1 mixture of epimers only one of which has the geometry suitable for assisting the reduction.

Finally, removal of the ketone protecting group from **56** (Scheme V) proceeded as for the model ketones,[19] *via* the acetoxymethyl oxime **58**. However, cleavage of **58** to the unsubstituted oxime could in this case be accomplished incidental to ester hydrolysis to give (±)-PGE oxime, **60**, directly.

The final step, *i.e.*, nitrosation of (±)-PGE_1 oxime **60** into (±)-PGE_1 **61** was the poorest step in the entire scheme. This was disappointing, especially in view of the claims that oximation was a suitable method for protecting the ketone function of PGE_1.[22] Nevertheless nitrosation provided a clean product which could be crystallized directly. The racemic PGE_1 obtained was identical by spectra (nmr, ir) and tlc behavior[23] with an authentic sample of (−)-PGE_1. Our material showed no depression of melting point on admixture with (±)-PGE_1.[24] Some additional work to improve the conversion of PGE_1 oxime **60** to PGE_1 **61**, using some of the newer procedures,[16] will be undertaken.

(21) E. Schenker in "Newer Methods of Preparative Organic Chemistry," Vol. IV, W. Foerst, Ed., Verlag Chemie, Weinheim, 1968, pp 224–225.

(22) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

(23) K. Gréen and B. Samuelsson, *J. Lipid Res.*, **5**, 117 (1964).

(24) We are indebted to Dr. U. Axen of the Upjohn Co. for a gift of racemic PGE_1.

Experimental Section[25]

Ethyl 2-Cyano-3-ethoxycarbonyl-1,10-decanedioate (1).—Sodium hydride (75.0 g, 3.13 *M* as a 59.8% dispersion in mineral oil) was suspended in 1,2-dimethoxyethane (1.5 l., dried over $LiAlH_4$ and distilled) and ethyl cyanoacetate (352 g, 3.12 *M*) added dropwise over 2 hr. The mixture was refluxed for 1 hr to complete reaction and cooled to room temperature. Ethyl 2-bromoazelate (733 g, 2.27 *M*) was added over a 2.5-hr period and refluxed for 3.5 hr after the addition. The solvent was removed *in vacuo* and the residue slurried in water and acidified with 2 *N* HCl. This was ether extracted and the ether extract washed with water and salt solution. The ether was removed *in vacuo* and the residue distilled to give **1** [670 g (84%), bp 190–205° (0.70 mm)]. Redistillation [bp 144° (0.05 mm)] gave the analytical sample: nmr δ 4.12 (m, 7), 3.07 (m, 1); ir (film) 2225 (w), 1735 (s), 1470 (m), 1375 (m), 1028 cm^{-1} (m).

Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.82; H, 8.22; N, 3.94. Found: C, 61.15; H, 8.27; N, 4.04

3-Carboxy-1,10-decanedioic Acid (2).—Ethyl 2-cyano-3-ethoxycarbonyl-1,10-decanedioate (**1**) (10.0 g, 28.2 m*M*) was mixed with concentrated HCl (70 ml) and refluxed for 24 hr. The mixture was filtered to remove an insoluble solid and the filtrate extracted with ethyl acetate. Removal of the ethyl acetate gave a wax that became a white solid on trituration with CH_2Cl_2. Recrystallization from $CHCl_3$ gave the triacid **2**: mp 55–58°; ir 1705 (s), 1215 (m), 930 cm^{-1} (m); nmr (DMSO) δ 2.38 (m, 5), 1.41 (m, 10).

Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.43; H, 7.42.

Ethyl 3-Ethoxycarbonyl-1,10-decanedioate (3).—The triacid **2** was esterified by reaction in ethanol and benzene with a catalytic amount of H_2SO_4. After work-up the oil was distilled to give the triester **3**: bp 217–225° (8.5 mm); ir (film) 1734 (s), 1375 (m), 1030 (m), 858 cm^{-1} (m); nmr δ 4.18 (overlapping quartets, 6), 2.55 (m, 5).

Anal. Calcd for $C_{17}H_{30}O_6$: C, 61.79; H, 9.15 Found: C, 61.63; H, 9.14.

Ethyl 2-Cyano-2-(2-cyanoethyl)-3-ethoxycarbonyl-1,10-decanedioate (4).—Sodium (6.0 g, 0.26 *M*) was allowed to react with anhydrous ethanol (1.5 l.) and cooled to −5° (ice–salt bath). The triester nitrile **1** (1100 g, 3.1 *M*) was added dropwise over 1 hr. Acrylonitrile (200 g, 3.8 *M*) was added dropwise over 1.75 hr with continued cooling and stirring. After addition, the reaction was equilibrated to room temperature and stirred for 18 hr. Examination by tlc (silica gel, benzene–$CHCl_3$ 1:9) indicated that the starting material had been converted to product. The solvent was removed *in vacuo* and the residue shaken between ether and water. The ether extract was washed with water and saturated NaCl solution and dried ($MgSO_4$), and the solvent was removed giving **4** (1230 g, 2.92 *M*, 94% yield). This residue was used for the preparation of the tetraacid **5** without further purification.

A small amount was distilled giving the analytical sample: bp 181–183° (0.10 mm); nmr δ 4.25 (overlapping quartets, 6); ir (film) 2250 (w), 1735 (s), 1370 (m), 1020 (m), 850 cm^{-1} (m).

Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.74; H, 7.90; N, 6.86. Found: C, 61.50; H, 8.01; N, 6.79.

4,5-Dicarboxy-1,12-dodecanedioic Acid (5).—The dicyano triester **4** (660 g, 1.62 *M*) was mixed with concentrated HCl (2.5 l) and heated to reflux, utilizing an air condenser. After 6 hr, an additional 400 ml of concentrated HCl was added, a water condenser attached, and the mixture refluxed 18 hr. The reaction mixture was concentrated to one-third volume *in vacuo* and water added to dissolve the precipitated NH_4Cl. This was extracted with ethyl acetate which was washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate–CH_2Cl_2 to give compound **5** (414.5 g, 81%) as a white solid, mp 130–134°. Recrystallization from ethyl acetate gave the analytical sample: mp 143–145°; ir 1712 (s), 1440 (m), 1210 (m), 925 cm^{-1} (m); nmr (NaOD) δ 2.42 (m, 6), 1.48 (m, 12).

Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97 Found: C, 53.01; H, 7.09.

(25) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument as $CDCl_3$ solutions and ir spectra as Nujol mulls, unless otherwise indicated. Mass spectra were obtained on a M.S.9 instrument, at 70 eV.

Ethyl 4,5-Diethoxycarbonyl-1,12-dodecanedioate (6).—The tetraacid **5** (300 g, 0.945 *M*) was dissolved in anhydrous ethanol (330 ml) and benzene (550 ml) and concentrated H_2SO_4 (5 ml) added. This was heated to reflux and a Dean-Stark water trap attached. After 18 hr, the water was no longer forming and slightly more than the theoretical amount already collected, the heating was discontinued. The solvents were removed *in vacuo* without heating above room temperature. The residue was dissolved in ether and shaken with water and 10% $KHCO_3$ solution. The ether was removed and the residue distilled to give compound **6** [325.1 g (80%), bp 205–210° (0.2 mm)]. Redistillation [bp 192–194° (0.13 mm)] gave the analytical sample: nmr δ 4.16 (overlapping quartets, 8), 2.48 (m, 6); ir (film) 1737 (s), 1380 (m), 1035 (m), 858 cm^{-1} (w); vpc [2% DEGS on Anachrom ABS (110–120 mesh) at 300°] retention time of compound **6** 18.4–27.2 min, retention time of compound **3** 2.8 min.

Anal. Calcd for $C_{22}H_{38}O_8$: C, 61.37; H, 8.90. Found: C, 62.03; H, 9.05.

Ethyl 2-Ethoxycarbonyl-5-oxocyclopentaneheptanoate (7).—Sodium hydride (38 g, 1.59 *M* as a 57.2% dispersion in mineral oil) was suspended in dry ethyl ether (500 ml) and cooled to 3–4° (cold room). Ethanol (5 ml) was added and after stirring 20 min a cold (3–4°) solution of the tetraester **6** (562.5 g, 1.31 *M*) in dry ether (1.5 l.) was added dropwise over 5 hr. The internal temperature was at 3–4° during the addition and while stirring for an additional 5 days. Hydrochloric acid (400 ml, 2 *N*) was added and the mixture stirred at room temperature for 2 hr. The ether layer was separated, washed with saturated NaCl solution, and removed. The residue from the ether layer (positive $FeCl_3$ test) was mixed with 6.0 *N* HCl (1.0 l.) and refluxed 24 hr. The cooled mixture was extracted with ether, which was washed with saturated NaCl solution. The ether was removed and the residue (negative $FeCl_3$) mixed with benzene (1.6 l.), ethanol (650 ml), and H_2SO_4 (2.5 ml). This was heated to reflux and a Dean-Stark water trap attached. After 48 hr, the solvents were removed *in vacuo*, without heating, and the residue dissolved in ether and shaken with water and $KHCO_3$ solution. The ether was removed and the residue distilled to give compound **7** [376.2 g (92%), bp 201–205° (0.45 mm)], vpc [Supelcoport 80/100, 3% coating SP-2250 at 220°] major retention time 9.3, minor 10.2 (9:1). Redistillation [bp 160–164° (0.10 mm)] gave the analytical sample: nmr δ 4.18 (overlapping quartets, 4), 2.40 (m, 8); ir (film) 1728 (s), 1465 (m), 1378 (m), 1030 (m), 855 cm^{-1} (w).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.44; H, 9.23.

The semicarbazone **8** of the cyclopentanone diester **7** was prepared and had mp 114–117° (ethanol–water); nmr δ 4.17 (overlapping quartets, 4), 2.45 (m, 7); ir ($CHCl_3$) 3515 (w), 3380 (w), 1735 (s), 1690 (s), 1560 (s), 1380 cm^{-1} (m).

Anal. Calcd for $C_{18}H_{31}N_3O_5$: C, 58.51; H, 8.46; N, 11.37. Found: C, 58.34; H, 8.29; N, 11.16.

2-Carboxy-5-oxocyclopentaneheptanoic Acid (9).—The cyclopentanone diester **7** (10 g) was mixed with 10% aqueous KOH (60 ml), and ethanol was added to effect complete solution. After stirring 18 hr at room temperature the solution was extracted with ether, which was discarded. The aqueous phase was acidified with concentrated HCl and extracted with ether. The ether was shaken with saturated NaCl solution and removed to give **9** as a very viscous oil (7.6 g, 92.5%): nmr δ 2.52 (m, 8), 1.55 (m, 10); ir (film) 1735 (s), 1702 (s), 1405 (m), 1040 (m), 870 cm^{-1} (w).

The thiosemicarbazone, **10**, of the cyclopentanone diacid **9** was prepared. The cyclopentanone diacid **9** (550 mg) was dissolved in 50% aqueous acetic acid (10 ml), and thiosemicarbazide (219 mg) was added. The mixture was heated to boiling to obtain a solution; water was added until a slight turbidity persisted. On cooling a white precipitate formed. Recrystallization from water afforded the analytical sample of **10**: 510 mg; mp 160–162°; nmr (DMSO) δ 2.59 (m, 4), 2.20 (m, 3); ir 3420 (w), 3140 (m), 1695 (s), 1600 (s), 1510 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{23}N_3O_4S$: C, 51.05; H, 7.04; N, 12.75. Found: C, 51.33; H, 7.00; N, 12.99.

Ethyl 2-Ethoxycarbonyl-5-oxocyclopentaneheptanoate Enol Acetate (12).—The cyclopentanone diester **7** (95.5 g, 0.306 *M*) was dissolved in isopropenyl acetate (61.2 g, 0.612 *M*), and *p*-toluenesulfonic acid (1.0 g) was added. The solution was refluxed for 18 hr, cooled, and added to excess 10% K_2CO_3 solution. This was ether extracted, the ether removed, and the residue

distilled. The major fraction [bp 168–175° (0.1 mm)] was the mixture of the enol acetates **12** (92.1 g, 85%): nmr δ 4.15 (pair of quartets, 4), 2.47 (m, 8); ir (film) 1755 (m), 1733 (s), 1375 (m), 1030 (m) cm^{-1}; vpc (2% Degs on Anachrom ABS (110–120 mesh) at 200°) 7.7 and 9.3 min (5:3).

Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.86; H, 8.55.

Ethyl 2-Ethoxycarbonyl-5-oxo-1-cyclopenteneheptanoate (13). Formed *via* the Enol Acetate.—The cyclopentanone diester enol acetates **12** (48 g, 0.135 *M*) were dissolved in dry CCl_4 (100 ml, dried by passage through neutral activity I Al_2O_3) and cooled to −5° (ice–salt bath). Bromine (21.6 g, 0.135 *M*) dissolved in dry CCl_4 (100 ml) was added dropwise over 0.5 hr, with continued cooling. The bromine color was discharged immediately on addition. After stirring an additional 0.5 hr, triethylamine (27.3 g, 0.27 *M*) was added, and the mixture was refluxed for 2 hr and stirred overnight at room temperature. The mixture was filtered to remove the precipitated salt. The filtrate was evaporated *in vacuo* and the residue vacuum distilled to give **13** [28.5 g (68%); bp 153–154° (0.1 mm)]: nmr δ 4.18 (overlapping quartets, 4), 2.46 (m, 8); ir (film) 1735–1705 (broad s), 1635 (w), 1375 (m), 1095 (m), 855 (m), 755 cm^{-1} (m); uv λ_{max} (MeOH) 246 mμ (γ 9700).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.89; H, 8.69.

Ethyl 2-Ethoxycarbonyl-5-oxo-1-cyclopenteneheptanoate (13). Directly from the Cyclopentanone Diester 7.—The cyclopentanone diester **7** (306 g, 0.97 *M*) was dissolved in glacial acetic acid (500 ml) and to it added a solution of bromine (155 g, 0.97 *M*) in glacial acetic acid (250 ml) dropwise over 1.75 hr while stirring at room temperature. After an additional 2 hr, the solvent was removed *in vacuo*. The residue was dissolved in ether and shaken with water and 10% $KHCO_3$ solution. The residue from the ether was dissolved in CCl_4 (1.2 l., dried by passage through neutral activity I Al_2O_3); to it was added triethylamine (101 g, 1.0 *M*). The mixture was refluxed for 8 hr and filtered and the residue from the filtrate vacuum distilled to give **13** [190 g (61%), bp 165–173° (0.3 mm)], which was identical (ir, nmr, vpc) with that obtained from the enol acetate.

The semicarbazone **14** of the cyclopentenone diester **13** was prepared in the usual way and had mp 87–88° (ethanol–water); nmr δ 4.08 (overlapping quartets, 4), 2.47 (m, 8); ir ($CHCl_3$) 3510 (w), 3370 (w), 1720 (s), 1685 (s), 1600 (w), 1560 cm^{-1} (s); uv λ_{max} (MeOH) 298 mμ (ε 23,640).

Anal. Calcd for $C_{18}H_{29}N_3O_5$: C, 58.83; H, 7.96; N, 11.44. Found: C, 58.89; H, 7.99; N, 11.43.

2-Carboxy-5-oxo-1-cyclopenteneheptanoic Acid (15).—The cyclopentenone diester **13** (75.5 g, 0.243 *M*) was dissolved in methanol (800 ml), and 15% K_2CO_3 (800 ml) was added. The mixture was refluxed for 2 hr, cooled, and most of the solvent removed *in vacuo*. The residue was diluted with water and ether extracted. The ether extract was discarded. The aqueous phase was acidified with concentrated HCl, saturated with NaCl, and extracted with ether. The residue from the ether layer was recrystallized from benzene to give **15** [57.6 g (93%), mp 81–83°]. Recrystallization from water afforded the analytical sample: mp 95–96°; nmr δ 2.55 (m, 8), 1.55 (m, 8); ir 1710 (s), 1665 (s), 1215 (s), 905 (m), 720 cm^{-1} (m); uv λ_{max} (MeOH) 245 mμ (ε 12,690).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.51; H, 7.32.

2-Methoxycarbonyl-5-oxo-1-cyclopenteneheptanoic Acid (16).—The cyclopentenone diacid **15** (5.32 g, 0.021 *M*) was dissolved in ether (200 ml) and to it added ethereal diazomethane (0.0233 *M*) slowly with vigorous stirring. After stirring an additional 0.5 hr the ether solution was extracted with 10% $KHCO_3$ solution. The basic solution was acidified with concentrated HCl, saturated with NaCl, and extracted with ether. The ether was removed to give **16** [3.66 g (65%)] as an oil: nmr δ 3.86 (s, 3), 2.55 (m, 8), 1.53 δ (m, 8).

***N*-Ethyl-2-methoxycarbonyl-5-oxo-1-cyclopenteneheptanoic Acid Amide (17).**—Trisethylaminoboron[26] (600 mg) was dissolved in dry benzene (10 ml, dried over Na wire), and, while stirring at room temperature, a solution of the half-ester acid **16** (1.0 g) in dry benzene (15 ml) was added over a period of 15 min. After stirring 3 days, 1 *N* HCl was added and the benzene layer separated. It was shaken with water and saturated NaCl solution and dried ($MgSO_4$). The residue from the benzene was chromatographed over silica gel and the product eluted as a crystalline solid with methylene chloride–ethyl acetate (1:1). Recrystallization from ether–hexane afforded the analytical sample of **17** (230 mg, mp 57–58°): nmr δ 3.87 (s, 3), 3.31 (m, 2), 1.13 (t, 3); ir (m), 1725 (s), 1705 (s), 1670 (w), 1645 (s), 1555 cm^{-1} (m); uv λ_{max} (MeOH) 246 mμ (ε 13,070).

Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; 8.53; N, 4.74. Found: C, 64.85; H, 8.59; N, 5.05.

***N*-Phenyl-2-carboxy-5-oxo-1-cyclopenteneheptanoic Acid Amide (19).**—The half-ester acid **16** (5.1 g) was dissolved in dry ether (100 ml), and oxalyl chloride (2.5 ml) was added with stirring at room temperature. After 3 hr the solvent and excess oxalyl chloride were removed *in vacuo*. The residue was dissolved in ether (150 ml), and aniline (4 ml) was added with vigorous stirring. After 1 hr the mixture was shaken with water, 1 *N* HCl, and 10% $KHCO_3$ solution. The residue from the ether layer was chromatographed over silica gel and the methyl ester of compound **18** eluted as viscous wax-like oil with ethyl acetate–methylene chloride (1:3) (3.96 g): nmr δ 7.29 (m, 5), 3.84 (s, 3), 2.47 (m, 8); ir (film) 3295 (m), 1728 (s), 1703 (s), 1670 (m), 1620 (s), 1460 (s), 770 (m), 705 cm^{-1} (m).

This half-ester anilide **18** (350 mg) was dissolved in methanol (10 ml) and 10% K_2CO_3 solution (10 ml) and refluxed for 2 hr. After cooling it was diluted with water and extracted with ether. The aqueous phase was acidified with concentrated HCl, saturated with NaCl, and extracted with ether. Removal of the ether gave an oil that crystallized. Recrystallization from ethyl acetate gave the analytical sample of **19** (180 mg): mp 166–168°; nmr (NaOD) δ 7.21 (m, 5), 2.73 (m, 2), 2.23 (m, 6); ir 3304 (w), 1712 (s), 1665 (s), 1602 (m), 1538 (m), 1210 (m), 768 (w), 725 cm^{-1} (w); uv λ_{max} (MeOH) 242 mμ (ε 26,140).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69,28; H, 7.04; N, 4.25. Found: C, 69.05; H, 7.14; N, 4.15.

Methyl 2-Methoxycarbonyl-5-oxo-1-cyclopenteneheptanoate (20).—The cyclopentenone diacid **15** (52.5 g, 0.207 *M*) was dissolved in ethyl ether (1.0 l.), and, with stirring at room temperature, ethereal diazomethane added until the yellow color persisted. After 0.5 hr the solution was concentrated to half volume by steam bath. It was shaken with 10% $KHCO_3$ solution. The residue from the ether layer was distilled to give **20** [50.6 g, (87%), bp 146° (0.1 mm)]: nmr δ 3.87 (s, 3), 3.66 (s, 3), 2.49 (m, 8); ir (film) 1735–1700 (s), 1630 (w), 1438 (m), 1095 (w), 753 cm^{-1} (w); uv λ_{max} (MeOH) 246 mμ (ε 9630).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.47; H, 7.84.

Methyl 2-Methoxycarbonyl-3-acetoxy-5-oxo-1-cyclopenteneheptanoate (21).—The cyclopentenone dimethyl ester **20** (25.4 g, 0.09 *M*) was dissolved in CCl_4 (225 ml, dried by passage through neutral activity I Al_2O_3), and *N*-bromosuccinimide (19.5 g, 0.11 *M*) was added. A catalyst, 2,2′-azobis(2-methylpropionitrile) (400 mg), was added, and the mixture was refluxed for 1 hr. The floating suspended solid was removed by filtration.

The residue from the filtrate was dissolved in glacial acetic acid (175 ml), and silver acetate (22.6 g, 0.135 *M*) was added. This mixture was refluxed for 1 hr, cooled, and filtered. The filtrate was diluted with ether and extracted with water and 10% $KHCO_3$ solution. The residue from the ether was vacuum distilled to give **21** [17.4 g (47%), bp 169–170° (0.01 mm)]: nmr δ 6.08 (m, 1), 3.88 (s, 3), 3.65 (s, 3), 2.06 (s, 3); ir (film) 1725 (s) 1640 (w), 1440 (m), 1230 cm^{-1} (s); uv λ_{max} (MeOH) 238 mμ (ε 12,830), basified with 0.1 *N* KOH 252 (ε 7710), 422 mμ (ε 8380).[11]

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 60.38; H, 7.21.

Methyl 2-Methoxycarbonyl-3-hydroxy-5-oxo-1-cyclopenteneheptanoate (22).—The acetoxycyclopentenone diester **21** (32.5 g, 0.0956 *M*) was dissolved in cold 2.4 *N* methanolic HCl (450 ml) and stirred at room temperature. After 4 hr the solvent was removed *in vacuo* and the residue dissolved in ether and shaken with water (until the aqueous washes were neutral). The residue from the ether layer was chromatographed over silica gel and **22** eluted with methylene chloride–ethyl acetate (3:2) [19.0 g (67%), bp 156–158° (0.01 mm)]: nmr δ 5.15 (m, 1), 3.92 (s, 3), 3.66 (s, 3); ir (film) 3460 (m), 1720 (s), 1636 (w), 1440 cm^{-1} (m); uv λ_{max} (MeOH) 237 mμ (ε 11,700).

Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.11; H, 7.60.

The semicarbazone, **23**, of the hydroxycyclopentenone diester **22** was prepared: mp 140–141° (methanol–water); ir 3514

(26) D. W. Aubrey and M. F. Lappert, *J. Chem. Soc.*, 2927 (1959).

(w), 3304 (m), 1735 (s), 1715 (s), 1672 (s), 1610 cm^{-1} (m); uv λ_{max} (MeOH) 296 mμ (ϵ 23,850).

Anal. Calcd for $C_{16}H_{25}N_3O_6$: C, 54.07; H, 7.09; N, 11.83. Found: C, 53.77; H, 7.06; N, 12.07.

The *O*-methyl oxime, **24**, of the hydroxycyclopentenone diacid was prepared by dissolving the ketone in dry pyridine (molecular sieves, type 4A) and adding an excess of methoxyamine hydrochloride. After 2 days at room temperature the solvent was removed *in vacuo*, the residue was dissolved in ether–water, and the ether layer reshaken with water. The residue from the ether was the diester of **24** as a low melting waxy solid.

This wax was dissolved in methanol–10% K_2CO_3 solution (1:1) and refluxed for 1.5 hr. Work-up in the usual manner gave **24**: mp 102–104° (ether–hexane); nmr δ 5.08 (m, 1), 3.98 (s, 3), 2.72 (m, 4), 2.33 (m, 2); ir ($CHCl_3$) 3585 (w), 1685 (s), 1610 (m), 1040 cm^{-1} (s); uv λ_{max} (MeOH) 269 mμ (ϵ 14,800).

Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.49; H, 7.39; N, 4.87.

Methyl 2-Methoxycarbonyl-3-trimethylsiloxy-5-oxo-1-cyclopenteneheptanoate (25).—The hydroxycyclopentenone diester **22** (18.9 g, 0.051 *M*) was dissolved in dry ether (500 ml) and mixed with trimethylsilyl chloride (19 ml). With vigorous stirring at room temperature triethylamine (33 ml) was added dropwise causing immediate precipitation of triethylamine hydrochloride. After 2 hr the mixture was filtered. The filtrate was shaken with water and saturated NaCl solution. The residue from the ether layer was chromatograhed over silica gel, and **25**, an oil (21.1 g, 90%), was eluted with ethyl acetate–methylene chloride (1:9): nmr δ 5.15 (m, 1), 3.88 (s, 3), 3.63 (s, 3), 0.18 (s, 9); ir (film) 1722 (s), 1640 (w), 1440 (m), 1258 (s), 845 cm^{-1} (s).

Methyl 2-Methoxycarbonyl-3-trimethylsiloxy-5-oxocyclopentaneheptanoate (26).—The trimethylsiloxycyclopentenone diester **25** (9.8 g, 0.0265 *M*) was dissolved in methanol (125 ml), and Raney nickel catalyst (1.0–2.0 g, wet with methanol) was added. The reduction was conducted at an initial hydrogen pressure of 48 psi, at room temperature. After 3.5 hr slightly more than the theoretical amount of hydrogen was consumed. The mixture was filtered through Celite which was washed well with methanol. Evaporation of the filtrate gave compound **26** (9.21 g, 93.5%) as an oil that crystallized (mp ≈22–24°) on standing in the cold. Although satisfactory microanalysis could not be obtained, the spectra concur with the assigned structure: nmr δ 4.61 (m, 1), 3.69 (s, 3), 3.63 (s, 3), 2.38 (m, 6), 0.14 (s, 9); ir (film) 1738 (s), 1440 (m), 1255 (s), 845 cm^{-1} (s).

Methyl 2-Methoxycarbonyl-3-hydroxy-5-oxocyclopentaneheptanoate (27).—The trimethylsiloxycyclopentanone diester **26** (7.25 g, 0.0195 *M*) was dissolved in methanol (200 ml), and formic acid (1 ml) was added. After stirring 3 hr at room temperature the solvent was removed *in vacuo*. The oily residue (5.72 g, 97.5%), which crystallized on standing, showed two spots on tlc (silica gel, ethyl acetate–methylene chloride 1:4, two developings) a minor R_f 0.565 and a major R_f 0.495. Recrystallization from ether gave a white solid (4.79 g, mp 68–70°) which was predominantly the polar isomer. Further recrystallizations from ether gave pure polar material, the all-cis configuration of **27**: mp 72–73°; nmr δ 4.62 (m, 1), 3.74 (s, 3), 3.68 (s, 3), 3.46 (m, 2); ir ($CHCl_3$) 3480 (w), 1736 (s), 1435 cm^{-1} (m); mass spectrum *m/e* 300 (M), 282 (M − H_2O), 269 (M − OCH_3).

Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.26; H, 8.26.

The *O*-Methyl Oxime (28) of the Cyclopentanone Diester 27.—Trimethylsiloxycyclopentanone diester **26** (8.6 g, 0.0231 *M*) was dissolved in pyridine (100 ml, dried over molecular seives), and *O*-methylhydroxylamine hydrochloride (9.8 g) was added. After 24 hr at room temperature the pyridine was removed *in vacuo*. The residue was shaken between ether and water. The residue from the ether layer was recrystallized (ether–hexane) to give compound **28** (5.2 g, 69%). A further recrystallization from hexane gave the analytical sample: mp 46–47°; nmr δ 4.48 (q, 1), 3.84 (s, 3), 3.72 (s, 3), 3.64 (s, 3); ir 3380 (m), 1730 (s), 1655 (w), 1043 cm^{-1} (s); tlc [ethyl acetate–chloroform (1:1 two developings)] R_f 0.635.

Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.43; H, 8.35; N, 4.24.

The Oxime (29) of the Cyclopentanone Diester 27.—Trimethylsiloxycyclopentanone diester **26** (525 mg) was dissolved in dry pyridine (25 ml), and hydroxylamine hydrochloride (1.5 g) was added. After 24 hr at room temperature the pyridine was removed *in vacuo* and the residue shaken between ether and water. The crystalline residue from the ether layer was recrystallized (benzene–hexane) to give **29** (320 mg): mp 97–98°; nmr δ 4.50 (m, 1), 3.74 (s, 3), 3.67 (s, 3); ir 3390 (m), 3250 (m), 1730 (s), 1190 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.08; H, 7.73; N, 4.57.

Preparation of *O*-Methyl Oxime 28 from Oxime 29.—Oxime **29** (100 mg) was dissolved in acetonitrile (2 ml, dried by passage through Al_2O_3 neutral activity I) and methyl iodide (3 ml). The solution was warmed to 45° and Ag_2O (11 mg) was added. After 1 hr an additional 11 mg of Ag_2O was added. This process was repeated every hour until a total of 66 mg of Ag_2O was added. After 20 hr, the mixture was diluted with $CHCl_3$ and filtered. The residue from the filtrate was chromatographed over silica gel, and the crystalline solid (48 mg) eluted with methylene chloride-ethyl acetate (4:1) was shown to be the methyl oxime, **28**, by tlc, melting point, and mixture melting point.

Methyl 2-Hydroxymethyl-3-hydroxy-5-methoxyiminocyclopentaneheptanoate (30).—*O*-methyl oxime **28** (3.0 g) was dissolved in ethanol (100 ml), and $NaBH_4$ (2.0 g) was added. After stirring 2 hr, another 1.0 g $NaBH_4$ was added. After an additional 1.5 hr, the ethanol was removed *in vacuo* and the residue shaken between ether and water. The residue from the ether layer was chromatographed over silica gel. Compound **30**, 1.71 g, was eluted with ethyl acetate–methylene chloride (3:2). Recrystallization from ether gave the analytical sample: mp 86–88°; nmr δ 3.83 (s, 3), 3.65 (s, 3); ir 3290 (s), 1735 (s), 1650 (w), 875 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{27}NO_6$: C, 59.78; H, 9.03; N, 4.65. Found: C, 60.09; H, 9.17; N, 4.70.

Methyl 2-Hydroxymethyl-3-hydroxy-5-hydroxyiminocyclopentaneheptanoate (31).—Oxime **29** (630 mg) was dissolved in ethanol (30 ml), and $NaBH_4$ (630 mg) was added. After stirring 2 hr at room temperature an additional 630 mg of $NaBH_4$ was added. After a total of 4.5 hr, the solvent was removed *in vacuo* and the residue shaken between ether and water. The residue from the ether layer was chromatographed over silica gel. Unreacted starting material **29** (350 mg) was eluted with ethyl acetate–methylene chloride (3:7), and compound **31** (180 mg, 71% based on recovered starting material) was eluted with ethyl acetate-methylene chloride (3:2). Recrystallization from ether gave the analytical sample: mp 79–80°; nmr δ 4.48 (m, 1), 3.67 (s, 3); ir 3210 (s), 1730 (s), 1677 cm^{-1} (w).

Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.51; H, 8.77; N, 4.87. Found: C, 58.83; H, 8.91; N, 4.53.

Epimerization of Methyl Oxime 28 to 32.—Methyl oxime **28** (8.6 g, 0.0261 *M*) was dissolved in methanol (250 ml) and 10% K_2CO_3 solution (250 ml) and refluxed for 2 hr. After cooling to room temperature it was extracted with ether, which was discarded. The aqueous layer was cooled in an ice bath, acidified with concentrated HCl, saturated with $(NH_4)_2SO_4$, and extracted with ether. The residue from the ether layer was dissolved in ether (75 ml) and treated with excess ethereal diazomethane. After 1 hr at room temperature, the solution was extracted with 10% $KHCO_3$ solution, dried over $MgSO_4$, and evaporated to give **32** (7.85 g, 91%), homogeneous on tlc: nmr δ 4.39 (m, 1), 3.82 (s, 3), 3.74 (s, 3), 3.63 (s, 3); ir (film) 3465 (m), 1730 (s), 1650 (w), 1435 (m), 1040 cm^{-1} (s); tlc [ethyl acetate–chloroform (1:1, two developings)] R_f 0.70.

Tetrahydropyranyl Ether (33) of 32.—**32** (2.75 g) was dissolved in methylene chloride (100 ml) and to it added 2,3-dihydro-γ-pyran (1.5 g) and picric acid (50 mg). After 18 hr, the solution was shaken with water and 10% $KHCO_3$ solution. The residue from the methylene chloride layer chromatographed over silica gel and **33** (3.28 g, 95%) eluted with ethyl acetate–methylene chloride (1:9): nmr δ 4.62 (m, 1), 4.36 (m, 1), 3.82 (s, 3), 3.73 (s, 3), 3.64 (s, 3); ir (film) 1732 (s), 1630 (w), 1438 m), 1200 (s), 1170 (s), 1042 cm^{-1} (s).

Borohydride Reduction of 33 to 34.—**33** (10.2 g, 0.0247 *M*) was dissolved in anhydrous ethanol (300 ml) and to it was added $NaBH_4$ (21.5 g) portionwise over 3.5 hr while stirring at room temperature. After that time, the mixture was diluted with water and extracted with ether. The ether layer was reshaken with water and saturated NaCl solution. The residue from the ether layer was chromatographed over silica gel and unreacted starting material (**33**, 2.09 g) eluted with ethyl acetate–methylene chloride (1:4). **34** (4.15 g, 53% based on recovered starting material) was eluted with ethyl acetate–methylene chloride (2:3). Ester exchange occurred during this reaction and **34** was isolated

as the ethyl ester: nmr δ 4.66 (m, 1), 4.12 (q, 2), 3.84 (s,3); ir (film) 3440 (m), 1730 (s), 1650 (w), 1195 (s), 1040 cm^{-1} (s).

Moffatt Oxidation of 34 to 35.—**34** (1.45 g) was dissolved in benzene (20 ml, dried over Na wire) and dimethyl sulfoxide (20 ml, dried over molecular seives) and cooled to 4°. Then dry pyridine (0.47 ml), trifluoroacetic acid (0.26 ml), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich No. C-10,640-2) (1.5 g) were added in that order. After stirring 24 hr at 4°, the mixture was poured into ice water and extracted with ether. The ether layer was reshaken with ice water, dried ($MgSO_4$), and evaporated to dryness *in vacuo*, to give **35** [1.35 g (93%)]: nmr δ 9.76 (m, 1), 4.61 (m, 1), 4.13 (q, 2), 3.83 (s, 3); ir (film) 2720 (w), 1725 (s), 1650 (w), 1440 (m), 1030 cm^{-1} (s).

Preparation of 1-Tributylphosphoranylidene-2-heptanone (36).—1-Chloro-2-heptanone[27] (5.0 g, 0.0337 *M*) was added to a solution of tri-*n*-butylphosphine (6.8 g, 0.0337 *M*) in chloroform (35 ml). The mixture was refluxed for 1 hour, and then the solvent was removed. A portion of the residue (5 g, 0.0156 *M*) was slurried in water (100 ml). The water was extracted (ether) and filtered. The clear aqueous solution was basified (15 ml of 2 *N* NaOH), with stirring (5 min) and extracted (ether). The ethereal extracts were dried ($MgSO_4$), and the ether was removed. The residue was distilled. The main fraction, 1-tributylphosphoranylidene-2-heptanone (**36**, 2.4 g, 0.0077 *M*, 49%), had bp 140–143° (0.01 mm); nmr δ 3.14 (s, <1), 2.06 (t, 2); ir (film) 1530 (s), 1470 (m), 1402 (s) cm^{-1}. This substance, **36**, colors rapidly on exposure to air. It was not possible to obtain a satisfactory elemental analysis.

Wittig Reaction of Aldehyde 35 to Enone 37.—**35** (1.35 g) was mixed with-1-tributylphosphoranylidene-2-heptanone **36** (1.3 g) in ether (50 ml) and stirred at room temperature. After 1.5 hr, the solvent was removed and the residue chromatographed over silica gel. The enone **37** [1.24 g (74%)] was eluted with ethyl acetate–methylene chloride (1:19): nmr δ 6.82 (m, 1), 6.1 (m, 1), 4.61 (m, 1), 4.15 (m, 4), 3.83 (s, 3), 0.90 (m, 3); ir (film) 1735 (s), 1695 (m), 1670 (m), 1625 (m), 1030 cm^{-1} (s); uv λ_{max} (MeOH) 225 mμ (ϵ 15,200).

Hydrolysis of Enone 37 to 38.—**37** (780 mg) was dissolved in methanol (75 ml), and 1 *N* HCl (1 ml) was added. The mixture was stirred at room temperature under a N_2 atmosphere. After 3 hr most of the methanol was removed *in vacuo* at room temperature. The residue was dissolved in ether and shaken with water. The residue from the ether layer was chromatographed on silica gel, and **38** (230 mg) was eluted with ethyl acetate–methylene chloride (1:9). It was homogeneous on tlc: nmr δ 6.76 (m, 1), 6.20 (m, 1), 3.81 (s, 3), 2.45 (complex multiplet, 8), 0.91 (m 3).

Borohydride Reduction of Enone 38 to 39.—**38** (230 mg) was dissolved in ethanol (10 ml) and $NaBH_4$ (440 mg) added. Stirred at room temperature for 2 hr the solvent was removed *in vacuo* at room temperature; the residue was shaken between ether and water. Removal of the ether gave an oil, 195 mg. A major component of this oil was **39** as indicated by tlc [alumina GF, cyclohexane–dioxane–ethyl acetate (7:2.5:0.5)] and nmr.

Borohydride Reduction of Enone 37 to 40.—**37** (3.6 g) was dissolved in ethanol (250 ml), and $NaBH_4$ (7.2 g) was added. After stirring 1.5 hr at room temperature, the mixture was poured into ice water and extracted with ether (three times). The ether layer was reshaken with water and saturated NaCl solution. The residue from the ether layer was chromatographed over silica gel and **40**, 2.54 g, as an oil, eluted with ethyl acetate–methylene chloride (1:9): nmr δ 5.61 (m, 2), 4.69 (m, 1), 3.83 (s, 3), 0.91 (m, 3): ir (film) 3415 (m), 1732 (s), 1650 (w), 1040 cm^{-1} (s).

Hydrolysis of 40 to 39.—**40** (740 mg) was dissolved in methanol (60 ml), and 1 *N* HCl (1 ml) was added. Stirred overnight at room temperature, it was poured into cold water and extracted with ether (twice). The ether layer was reshaken with water and saturated NaCl solution and dried over $MgSO_4$. The residue from the ether layer was preparatively separated [alumina GF, cyclohexane–dioxane–ethyl acetate (7:2.5:0.5)] and two major bands isolated. The nonpolar band, **41**, R_f 0.33, was an oil (220 mg). The polar band gave **39** (228 mg), R_f 0.20, which crystallized on standing in the cold. Recrystallization from ether–pentane gave the analytical sample: mp 67–68°; nmr δ 5.61 (m, 2), 3.82 (s, 2), 2.28 (m, 2), 0.93 (m, 3); ir ($CHCl_3$) 3590 (w), 3375 (m), 1728 (s), 1650 (w), 1465 (m), 1045 cm^{-1} (s); mass spectrum *m/e* 411 (M), 393 (M − H_2O), 380 (M − CH_3O).

Anal. Calcd for $C_{23}H_{41}NO_5$: C, 67.12; H, 10.04; N, 3.40. Found: C, 67.52; H, 10.26; N, 3.31.

***dl*-PGE$_1$ Methyl Oxime (42) from 39.**—**39** (220 mg) was dissolved in methanol (35 ml), and 10% K_2CO_3 solution (35 ml) was added. The mixture was refluxed on the steam bath for 2 hr. On cooling, the reaction was diluted with water and extracted with ether. The aqueous layer was cooled in an ice bath, acidified with 2 *N* HCl, saturated with NaCl, and extracted with ether twice. The ether was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give *dl*-PGE_1 methyl oxime, **42**, as a solid. Recrystallization from ether–pentane gave the analytical sample (144 mg): mp 97–99°; nmr δ 5.50 (m, 2), 4.05 (m, 1), 3.78 (s, 3), 0.91 (m, 3); ir (CH_2Cl_2) 3610 (m), 3400 (m), 1710 (s), 1044 cm^{-1} (s); mass spectrum *m/e* 383 (M), 365 (M − H_2O), 347 (M − $2H_2O$), 334 (M − H_2O, CH_3O).

Anal. Calcd for $C_{21}H_{37}NO_5$: C, 65.76; H, 9.72; N, 3.65. Found: C, 66.15; H, 9.73; N, 3.62.

PGE_1 was converted to a syn–anti mixture of methyl oximes by aforementioned procedures. The product was chromatographed on Mallinckrodt silicic acid [100–120 mesh, well washed (methanol), and reactivated (120°, 18 hr)] using chloroform–methanol (99:1) as eluent. The faster moving isomer was crystallized [mp 55–57° (aqueous methanol)]. The ir, nmr, and mass spectra of this compound were identical with those of **42** as was its mobility on tlc [silica gel, $CHCl_3$–methanol–acetic acid–H_2O (90:8:1:0.7)].[15]

Cleavage of Methyl Oxime 42.—*dl*-PGE_1 methyl oxime **42** (63 mg) was dissolved in a solution of levulinic acid (0.9 ml) and 13% aqueous $HClO_4$ (0.1 ml), precooled to 3°. After 48 hr at 3° the solution was diluted with cold ether and extracted with cold water (four times). The ether layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* below room temperature. The residue was chromatographed on silicic acid [100–120 mesh, well washed (methanol), and reactivated (120°, 18 hr)]. An oil (2 mg) eluted with $CHCl_3$–MeOH (97:3) was identical with PGE_1 (R_f 0.27; $CHCl_3$–MeOH–HOAc–H_2O, 90:8:1.0:0.7) on tlc and gave the typical uv shift with base. All attempts to crystallize the oil were unsuccessful.

Phenylthiomethoxyamine Hydrochloride (43).—Thiophenol (110.2 g, 1.0 *M*) and paraformaldehyde (45.0 g, 0.5 *M*) were mixed together and cooled to −15°. Anhydrous HCl gas was bubbled into the mixture and within 5 min the temperature rose to 22°; HCl addition was stopped during the exothermic reaction. When the temperature returned to −15° the HCl addition was continued for 3 hr. The mixture was warmed to room temperature and anhydrous $CaCl_2$ was added with stirring. This mixture was filtered, and the filtrate distilled to give chloromethyl phenyl sulfide (63.4 g, 40% yield): bp 62–63° (0.1 mm) [lit.[28] 106–7° (13 mm)]; nmr δ 7.42 (m, 5), 4.85 (s, 2). *N*-Hydroxyphthalimide (81.5 g, 0.5 *M*), triethylamine (49.6 g, 0.49 *M*), and chloromethyl phenyl sulfide (63.4 g, 0.4 *M*) were mixed together in dry tetrahydrofuran (830 ml) and refluxed for 15 hr. The mixture was filtered and the residue from the filtrate was dissolved in CH_2Cl_2 and shaken with 10% $KHCO_3$ solution (five times) and water. The residue from the CH_2Cl_2 layer was recrystallized from CH_2Cl_2–ether to give *N*-phenylthiomethoxyphthalimide (75.0 g, 66% yield): mp 88–88.5°; nmr δ 7.50 (m, 9), 3.58 (s, 2); ir (KBr) 1785 (w), 1725 (s), 1605 (w), 970 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.16; H, 3.89; N, 4.91 Found: C, 62.90; H, 3.91; N, 4.86.

N-Phenylthiomethoxyphthalimide (75.0 g, 0.26 *M*) and hydrazine hydrate (13.5 g, 0.27 *M*) were mixed together in 95% ethanol (600 ml) and refluxed for 4.5 hr. After cooling to room temperature the mixture was filtered. The filtrate was concentrated *in vacuo* to a very small volume, diluted with ether, and cooled to 0°. After 1 hour at 0° it was filtered. The residue from the filtrate was distilled to give phenylthiomethoxyamine (30.2 g, 75% yield): bp 82–94° (0.1 mm); nmr δ 7.35 (m, 5), 5.57 (s, 2), 5.00 (s, 2); ir (film) 3300 (m), 3050 (m), 2910 (m), 1585 (s), 990 cm^{-1} (s).

Anal. Calcd for C_7H_9NOS: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.40; H, 5.99; N, 9.16.

Phenylthiomethoxyamine (3.0 g, 0.0193 *M*) was dissolved in ether (50 ml), and excess ethereal–HCl was added causing the immediate formation of a white precipitate. Filtration gave

(27) S. Archer, M. J. Unser, and E. Froelich, *J. Amer. Chem. Soc.*, **78**, 6182 (1956).

(28) H. Bohme and H. P. Teltz, *Justus Liebigs Ann. Chem.*, **620**, 1 (1959).

phenylthiomethoxyamine hydrochloride (**43**, 3.57 g, 96.5%). Recrystallization from ethyl acetate–methanol gave the analytical sample: mp 110–112° dec; nmr (DMSO) δ 7.47 (m, 5), 5.68 (s, 2); ir 2660 (s), 1585 (w), 1570 (w), 1005 (s), 860 cm^{-1} (s).

Anal. Calcd for $C_7H_9NOS \cdot HCl$: C, 43.86; H, 5.26; N, 7.31. Found: C, 43.93; H, 5.39; N, 7.41.

The Phenylthiomethyl Oxime (44) of 27.—The crystalline residue from the preparation of **27** (5.55 g) was dissolved in pyridine (150 ml, dried over molecular sieves), and phenyl mercaptomethylhydroxylamine hydrochloride (**43**) (4.94 g) was added. After stirring 24 hr at room temperature the pyridine was removed *in vacuo*. The residue was dissolved in ether and shaken with water, 0.2 *N* HCl, and water again. The residue from the ether (8.54 g) crystallized on standing.

A portion of this residue was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give the major product **46** (R_f = 0.64), a white crystalline solid: mp 53–55° (ether–hexane); nmr δ 7.33 (m, 5), 5.46 (s, 2), 4;55 (m, 1), 3.70 (s, 3), 3.66 (s, 3), 2.75 (m, 2) 2.28 (m, 2); ir (KBr) 3240 (m), 1731 (s), 1030 cm^{-1} (m); mass spectrum *m/e* 437 (M).

Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.62; H, 7.18; N, 3.12.

A minor product, **47**, R_f 0.57, was also isolated: nmr δ 7.31 (m, 5), 5.46 (s, 2), 4.49 (m, 1), 3.73 (s, 3), 3.66 (s, 3), 2.65 (m, 2), 2.27 (m, 2).

Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.40; H, 7.14; N, 3.20. Found: C, 61.19; H, 7.37; N, 3.32.

Conversion of 46 to Oxime 29.—**46** (25 mg) was dissolved in glacial acetic acid (3 ml), and with stirring at room temperature a solution of $HgCl_2$ (105 mg), KOAc (90 mg), and H_2O (44 mg) in 3 ml glacial acetic acid was added. A white precipitate formed after 1 hr, and, after a total of 2.5 hr, the mixture was diluted with acetone and H_2S was bubbled into it until a black precipitate formed. The mixture was filtered through Celite and the filtrate evaporated to dryness *in vacuo*. This residue was dissolved in ether–water. The ether layer was reshaken with water and dried over $MgSO_4$. The residue from the ether layer was dissolved in methanol (4 ml), and 10% K_2CO_3 solution (1 ml) was added. After 35 min at room temperature the solution was diluted with ether and washed with water. The residue from the ether layer was recrystallized from ether to give **29**, 12 mg, identical by tlc, melting point, and mixture melting point with the material from oximation of siloxycyclopentanone diester, **26**.

Epimerization of 46 to 48.—**46** (125 mg) was dissolved in anhydrous methanol (7 ml), and a solution of Na (2 mg) in anhydrous methanol (2 ml) was added. Refluxed for 20 hr under N_2, the solution was cooled, diluted with ether, and shaken with water. The residue from the ether layer was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give **48** as an oil (103 mg, R_f 0.605): nmr δ 7.36 (m, 5), 5.45 (s, 2), 4.35 (m, 1), 3.73 (s, 3), 3.65 (s, 3), 2.05–3.4 (complex multiplet, 7).

Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.27; H, 7.13; N, 3.11.

Epimerization of 47 to 49.—**47** (62 mg) was dissolved in anhydrous methanol (5 ml), and a solution of Na (1.0 mg) in anhydrous methanol (2 ml) was added. Refluxed 20 hr under N_2, the solution was cooled, diluted with ether, and shaken with water. The residue from the ether layer was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give **49** as an oil (55 mg, R_f 0.44): nmr δ 7.38 (m, 5), 5.43 (s, 2), 4.37 (m, 1), 3.72 (s, 3), 2.87 (complex multiplet, 5), 2.24 (m, 2).

Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.74; H, 7.38; N, 3.28.

Borohydride Reduction of 49 to 50.—**49** (710 mg) was dissolved in methanol (35 ml). While stirring at room temperature, $NaBH_4$ (840 mg) was added portionwise over 2 hr. After 2.5 hr, the mixture was poured into ice water and extracted with ether. The ether was shaken with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue from the ether layer was recrystallized from ether to give **50**, 540 mg: mp 56–57°; nmr δ 7.33 (m, 5), 5.42 (s, 2), 3.66 (s, 3), 2.1–2.8 (complex multiplet, 5); ir 3350 (m), 1738 (s), 1020 cm^{-1} (s).

Anal. Calcd for $C_{21}H_{31}NO_5S$: C, 61.59; H, 7.63; N, 3.42. Found: C, 61.67; H, 7.75; N, 3.42.

Preparation of 48 Directly.—The crude crystalline mixture of compounds **46** and **47** (7.0 g) was dissolved in anhydrous methanol (250 ml), and a solution of Na (105 mg) in anhydrous methanol (50 ml) was added. Refluxed for 20 hr under N_2, the solvent was removed *in vacuo*. The residue was dissolved in ether and shaken with water and saturated NaCl solution. The residue was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give **48** (3.24 g, 40.5% overall from **22**) and **49** (1.21 g, 15% overall from compound **22**).

48 by Catalytic Reduction of 22 and a Telescoped Sequence.—**22** (9.5 g) was dissolved in methanol (130 ml), and Raney nickel catalyst (2.0–3.0 g, wet with methanol) was added. The mixture was reduced at an initial hydrogen pressure of 47 psi, at room temperature. After 24 hr, slightly more than the theoretical amount of hydrogen absorbed; the mixture was filtered through Celite.

The residue from the filtrate, **27** by ir, nmr, and tlc (8.21 g), was dissolved in pyridine (175 ml, dried over molecular seives) and *O*-phenylmercaptomethylhydroxylamine hydrochloride (**43**) (7.4 g) was added. After 48 hr at room temperature the pyridine was removed *in vacuo*. The residue was partitioned between ether and water. The ether layer was shaken with 0.1 *N* HCl and water.

The residue from the ether, **44** by ir, nmr, and tlc (12.5 g), was dissolved in anhydrous methanol (400 ml); a solution of Na (150 mg) in anhydrous methanol (15 ml) was added; and the mixture was refluxed 20 hr under a nitrogen atmosphere. Most of the methanol was removed *in vacuo* without heating above room temperature. The residue was dissolved in ether and shaken with water.

The residue from the ether layer (11.7 g) was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give **48**, identified by tlc and nmr (6.81 g, 48% overall from **22**).

The material corresponding to **49** (1.93 g, 14% overall from **22**) was also isolated.

48 from 22 by Zinc–Acetic Acid Reduction.—**22** (1.0 g) was dissolved in glacial acetic acid (40 ml), and Zn dust (2.0 g) was added. After 20 hr of vigorous stirring at room temperature the mixture was diluted with ether and filtered. The filtrate was evaporated to dryness *in vacuo* without heating above room temperature. The residue was dissolved in ether and shaken with water.

The residue from the ether layer (980 mg) was dissolved in pyridine (50 ml, dried over molecular seives); *O*-phenylmercaptomethylhydroxylamine hydrochloride (**43**) was added. After 48 hr at room temperature the pyridine was removed *in vacuo*. The residue was partitioned between ether and water. The ether layer was shaken with 0.1 *N* HCl and water.

The residue from the ether layer was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give **48** by tlc and nmr (685 mg, 47% overall from **22**) and **49** (309 mg, 21% overall from **22**).

Tetrahydropyranyl Ether of 48.—**48** (3.2 g, 7.34 m*M*) was dissolved in methylene chloride (200 ml, dried over molecular sieves) and to it added 2,3-dihydro-γ-pyran (2.1 ml) and picric acid (210 mg). After stirring 18 hr at room temperature the solution was shaken with water and 10% $KHCO_3$ solution. The residue from the methylene chloride layer was chromatographed over silica gel and **51** (3.76 g, 98.5%) eluted with ethyl acetate–methylene chloride (1:9): nmr δ 7.35 (m, 5), 5.45 (s, 2), 4.61 (m, 1), 3.72 (s, 3), 3.66 (s, 3); ir (film) 1732 (s), 1655 (w), 1585 (s), 1015 cm^{-1} (s).

Borohydride Reduction of 51 to 52.—**51** (3.7 g, 7.1 m*M*) was dissolved in ethanol (200 ml), and $NaBH_4$ (4.0 g) was added portionwise over a 4-hr period at a rate of 1.0 g/hr. After 4.5 hr, the solvent was removed *in vacuo* and the residue shaken between ether and water. The residue from the ether layer was preparatively separated (silica gel; ethyl acetate–methylene chloride, 1:4) to give unreacted starting material (1.03 g, R_f 0.86) and **52** (1.44 g, 57% based on recovered starting material, R_f 0.42): nmr δ 7.38 (m, 5), 5.46 (s, 2), 4.65 (m, 1), 3.67 (s, 3); ir (film) 3410 (m), 1730 (s), 1648 (w), 1580 (w), 1010 cm^{-1} (s).

Recyclization of Recovered Material from the Borohydride Reduction of 51.—**51** (1.55 g, recovered from the preparation of compound **52**) was dissolved in methanol (120 ml), and 1 *N* HCl (3 ml) was added. After stirring 18 hr at room temperature, the solvent was removed *in vacuo* at room temperature, the residue was dissolved in ether, and shaken with water. The residue from the ether layer was chromatographed over silica gel and **48**, 880 mg (68%), eluted with ethyl acetate–methylene chloride (1:9).

48 (880 mg) was dissolved in methylene chloride (60 ml), and

2,3-dihydro-γ-pyran (0.6 ml) and picric acid (60 mg) was added. After 18 hr at room temperature the solution was shaken with water and 10% $KHCO_3$ solution. The residue from the methylene chloride layer [**51** by tlc, 1.05 g (100%)] was dissolved in ethanol (50 ml); $NaBH_4$ (1.9 g) was added portionwise over 4 hr with stirring at room temperature. After 4.5 hr most of the solvent was removed *in vacuo* at room temperature. The residue was dissolved in ether–water. The ether layer was reshaken with water (twice). The residue from the ether layer was preparatively separated (silica gel; ethyl acetate–methylene chloride, 1:4) to give unreacted starting material, **51** (420 mg, R_f 0.86) and **52** (435 mg, 73% based on recovered starting material, R_f 0.42).

The Collins Oxidation of 52 to Aldehyde 53.—**52** (305 mg) was dissolved in methylene chloride (40 ml, dried over molecular sieves), and with stirring at room temperature a solution of freshly prepared pyridine dichromate (1.07 g) in dry methylene chloride (150 ml) was added in one portion. After stirring 10 min, the CH_2Cl_2 was decanted into a separatory funnel containing water. The CH_2Cl_2 layer was reshaken with water (twice) and dried over $MgSO_4$. Removal of the solvent gave **53** (290 mg) homogeneous on tlc: nmr δ 9.75 (m, 1), 7.4 (m, 5), 5.4 (s, 3), 4.61 (m, 1), 3.61 (s, 3).

This residue was used immediately without further purification or identification.

The Moffatt Oxidation of 52 to Aldehyde 53.—**52** (725 mg) was dissolved in dimethyl sulfoxide (19 ml, dried over molecular sieves) and benzene (19 ml, dried over sodium wire) and cooled to 4°. Then dry pyridine (175 mg), trifluoroacetic acid (210 mg), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich No. C-10,640-2) (2.5 g) were added in that order. After stirring 72 hr at 4°, the reaction mixture was poured into ice water and extracted with ether. The ether was reshaken with water, dried over $MgSO_4$, and evaporated *in vacuo* to give **53** (710 mg), identical with the aldehyde derived from the Collins oxidation by nmr and tlc.

The Wittig Reaction on 53 to Give 54.—**53** (290 mg) and 1-tributylphosphoranylidene-2-heptanone (**43**) (450 mg) were mixed together in ether (20 ml) and stirred at room temperature. After 18 hr, the ether was removed and the residue preparatively separated (silica gel; ethyl acetate–methylene chloride, 1:9) to give **54** [302 mg, 87.5%; R_f 0.83; nmr δ 7.37 (m, 5), 6.77 (m, 1), 6.22 (m, 1), 5.45 (s, 2), 4.61 (m, 1), 3.65 (s, 3), 0.92 (m, 3)] as an oil.

Borohydride Reduction of Enone 54 to 55.—**54** (440 mg) was dissolved in ethanol (30 ml), and $NaBH_4$ (450 mg) was added portionwise over a 5-min period. The mixture was stirred at room temperature for 0.5 hr. The solution was poured into ice water and extracted twice with ether. The ether layer was reshaken with water, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue **55** (430 mg) was used in the next step without further purification or identification.

Hydrolysis of 55 to 56 and 57.—**55** (430 mg) was dissolved in methanol (60 ml), and 0.1 *N* HCl (1.25 ml) was added. Stirred at room temperature 20 hr. The solvent was removed *in vacuo* without heating above room temperature. The residue was dissolved in ether and shaken with water. The residue from the ether layer was preparatively separated [silica gel, ethyl acetate–methylene chloride (3:7), two developings] to give **56** (132 mg) as a crystalline solid (R_f 0.51; ethyl acetate–methylene chloride, 1:1).

Recrystallization from ether–hexane gave the analytical sample: mp 52–54°; nmr δ 7.45 (m), 5.48 (m, 2), 5.42 (s, 2), 3.64 (s, 3), 0.90 (m, 3); ir ($CHCl_3$) 3605 (m), 3415 (m), 1727 (s), 1585 (w), 1018 cm^{-1} (s); mass spectrum *m/e* 505 (M), 473 (M − $HOCH_3$), 366 (M − OCH_2SPh).

Anal. Calcd for $C_{28}H_{43}NO_5S$: C, 66.51; H, 8.57; N, 2.77. Found: C, 66.55; H, 8.51; N, 2.78.

The less polar band was **57** (143 mg as an oil; R_f 0.64, ethyl acetate–methylene chloride, 1:1): nmr δ 7.39 (m, 5), 5.59 (m, 2), 5.45 (s, 2), 3.63 (s, 3), 0.92 (m, 3); ir ($CHCl_3$) 3610 (m), 3450 (w), 1727 (s), 1582 (w), 1020 cm^{-1} (s).

Cleavage of 56 to 58.—**56** (72 mg) was dissolved in glacial acetic acid (5 ml), and a solution of mercuric chloride (230 mg), potassium acetate (210 mg) and mercuric oxide (100 mg) in glacial acetic acid (7.5 ml) was added in one portion. The mixture was stirred at room temperature for 0.5 hr; a white precipitate formed after 10 min. The mixture was diluted with acetone and H_2S bubbled into it until a black precipitate formed. This mixture was filtered through Celite, which was washed well with acetone and ether. The filtrate was evaporated *in vacuo* at room temperature. The residue was dissolved in ether–water. The ether layer was reshaken with water, dried over $MgSO_4$ and evaporated under aspirator pressure to give **58** (61 mg) as an oil: homogeneous on tlc; nmr δ 5.63 (m, 4), 4.00 (m, 2), 3.66 (s, 3), 2.23 (complex multiplet, 7), 0.92 (m, 3).

Formation of the *dl*-PGE_1 Oxime Methyl Ester 59 from 58.—**58** (34 mg) was dissolved in methanol (3 ml) and 10% K_2CO_3 solution (0.5 ml) added. Stirred at room temperature for 0.5 hr. Most of the methanol was removed by aspirator; the residue was dissolved in ether and shaken with water and saturated NaCl solution. The ether layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a crystalline residue. Recrystallization from ether–hexane gave the analytical sample of **59** (17 mg): mp 105–107°; nmr δ 5.59 (m, 2), 3.68 (s, 3), 0.98 (m, 3); ir (KBr) 3360 (s), 1738 (m), 1708 (s, internally bonded carbonyl), 1660 (w), 935 cm^{-1} (m); mass spectrum *m/e* 383 (M), 367 (M − O), 366 (M − OH).

Anal. Calcd for $C_{21}H_{37}NO_5$: C, 65.76; H, 9.72; N, 3.65. Found: C, 65.85; H, 9.92; N, 3.75.

***dl*-PGE_1 Oxime and *dl*-PGE_1 from 58.**—**58** (68 mg) was dissolved in methanol (6.8 ml) and 10% K_2CO_3 solution (1.13 ml) was added; after stirring at room temperature for 4 days, the solvent was removed *in vacuo* at room temperature. The residue was crystallized with ether–methylene chloride to give crystals of *dl*-PGE_1 oxime **60**: mp 123–5°; nmr (drop of DMSO added to $CDCl_3$) δ 5.52 (t, 2), 3.10 (d, 1), 2.92 (d, 1); ir (KBr) 3390 (s), 1680 cm^{-1} (s). Spectra and tlc behavior were identical with those of a sample of *l*-PGE_1 oxime.

Anal. Calcd for $C_{20}H_{35}NO_5$: C, 65.01; H, 9.55; N, 3.79. Found: C, 64.87; H, 9.78; N, 3.47.

The mother liquor and crystals were recombined and dissolved in glacial acetic acid (3.5 ml) and cooled to 10°. Then 10% aqueous $NaNO_2$ solution (1.5 ml) was added and the reaction was stirred at 10° for 1 hr. An additional 1.5 ml of 10% $NaNO_2$ solution was added and the reaction was allowed to warm to room temperature over 15 min. The mixture was shaken between water and ethyl acetate–ether (3:1). The organic layer was reshaken with water and saturated NaCl solution, dried over $MgSO_4$, and evaporated *in vacuo* at room temperature. The residue was dissolved in ethyl acetate (0.2 ml) and allowed to stand at −5° overnight. *dl*-PGE **61** (8 mg) crystallized out, mp 112–115°, no melting point depression on admixture with authentic *dl*-PGE_1.[24] The nmr and ir were identical with those of authentic PGE_1. Tlc examination (solvent systems AI and MI[23]) also showed that they were identical.

Cleavage of 57 to 62.—**57** (78 mg) was dissolved in glacial acetic acid (5.5 ml) and a solution of mercuric chloride (250 mg), potassium acetate (218 mg), and mercuric oxide (105 mg) in glacial acetic acid (8.0 ml) was added in one portion. After the mixture stirred for 0.5 hr at room temperature, a white precipitate was present. The mixture was diluted with acetone, and H_2S was bubbled into it until a black precipitate formed. It was filtered through Celite, which was washed well with acetone and ether. The filtrate was evaporated in vacuo at room temperature. The residue was dissolved in ether–water. The ether layer was reshaken with water, dried ($MgSO_4$), and evaporated to give **62** (71 mg) as an oil: homogeneous on tlc; nmr δ 5.67 (m, 4), 4.12 (m, 2), 3.67 (s, 3), 2.25 (complex multiplet, 7), 0.91 (m, 3).

***dl*-C_{15}-Epi-PGE_1 (63) from 62.**—**62** (132 mg) was dissolved in methanol (13.2 ml) and 10% K_2CO_3 solution (2.2 ml) added. After stirring at room temperature for 4 days, the solvent was removed *in vacuo*. The residue was dissolved in glacial acetic acid (6.5 ml) and stirred at 10°. Then 10% aqueous $NaNO_2$ solution (2.75 ml) was added and the solution was stirred at 10° for 1 hr. An additional 2.75 ml of 10% $NaNO_2$ solution was added and the reaction mixture was allowed to warm to room temperature over a 20-min period. The solution was shaken between water and ethyl acetate–ether (3:1). The organic layer was reshaken with water and saturated NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo* at room temperature. The residue from the organic layer was preparatively separated (silica gel; benzene–dioxane–acetic acid, 20:20:1) to give C_{15} *dl*-Epi-PGE_1 **63** (21 mg): nmr δ 5.69 (m, 2), 4.16 (m, 2), 2.36 (m, 3), 0.92 (m, 3); homogeneous on tlc (solvent systems AI and MI[23]).

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Registry No.—1, 25407-85-6; 2, 42334-95-2; 3, 42334-96-3; 4, 23166-56-5; 5, 23166-57-6; 6, 23266-13-9; 7, 23166-58-7; 8, 23166-59-8; 9, 42335-01-3; 10, 42335-02-4; 12 4-ene, 26047-64-3; 12 5-ene, 26060-68-4; 13, 23166-53-2; 14, 23166-54-3; 15, 23166-52-1; 16, 42335-08-0; 17, 42335-09-1; 18, 42335-10-4; 19, 42335-11-5; 20, 25346-53-6; 21, 42335-13-7; 22, 42335-14-8; 23, 42335-15-9; 24, 42335-16-0; 25, 42398-33-4; 26, 26258-31-1; 26 epimer, 42447-95-0; 27, 42335-17-1; 27 epimer, 42335-18-2; 28, 25455-39-4; 28 epimer, 42335-20-6; 29, 42335-21-7; 29 epimer, 42398-34-5; 30, 42335-22-8; 31, 42335-23-9; 32, 25348-52-1; 33, 25348-53-2; 34, 25348-54-3; 35, 42335-27-3; 36, 35563-52-1; 37, 25348-56-5; 38, 42335-30-8; 39, 42335-31-9; (R)-40, 42335-32-0; (S)-40, 42335-33-1; 42, 25455-41-8; 43, 41108-24-1; 46, 42335-36-4; 47, 42335-37-5; 48, 42335-38-6; 49, 42335-39-7; 50, 42398-35-6; 51, 42335-40-0; 52, 42335-41-1; 53, 42335-42-2; 54, 42398-36-7; (R)-55, 42335-43-3; (S)-55, 42334-36-1; 56, 42334-37-2; 57, 42334-38-3; 58, 42334-39-4; 59, 42334-40-7; 60, 42334-41-8; 61, 20348-58-7; 62, 42334-43-0; 63, 20897-96-5; ethyl 2-bromoazelate, 760-95-2; thiophenol, 108-98-5; chloromethyl phenyl sulfide, 7205-91-6; N-hydroxyphthalimide, 524-38-9; N-phenylthiomethoxyphthalimide, 41108-32-1; phenylthiomethoxyamine, 41108-23-0.

A General Synthetic Approach to the Eudesmane Class of Sesquiterpenes

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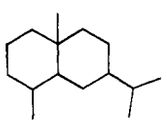
A versatile synthetic approach to the eudesmane class of sesquiterpenes is described. The key intermediate in the synthetic scheme is 6-methoxy-10-methyl-$\Delta^{6,7}$-octal-1-one (4). Elaboration of 4 into precursors which have been used in previous eudesmane sesquiterpene synthesis was accomplished in two manners. Wittig olefination of 4 with methylenetriphenylphosphorane followed by acid hydrolysis gave 1-methylene-10-methyl-6-decalone (10) which has previously been converted to atractylon and isoalantolactone. Incorporation of a carbomethoxy group at C-7 and removal of the carbonyl group at C-6 transformed 4 eventually into 7-carboxy-10-methyl-1-decalone (11) which has previously been converted to β-eudesmol.

The eudesmane class (see **1** for the general substitution pattern) of decalin sesquiterpanes has recently received considerable synthetic attention, especially β-eudesmol (2).[1] As part of our own synthetic studies,



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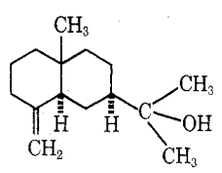
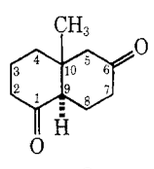


2

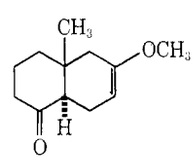
we have developed a general approach which allows elaboration from a common intermediate into diverse members of the eudesmane class. The synthesis of this intermediate and its conversion into compounds used in other eudesmane sesquiterpene syntheses is the subject of this paper.

Our scheme was based on the use of a synthon of the diketone **3**. This type of intermediate, properly protected so that the carbonyl functions could be operated on selectively, would allow elaboration at both C-1 and C-7 as is required for the synthesis of the eudesmane sesquiterpenes. Also the presence of the carbonyl groups at C-1 and C-6 would allow stereochemical control of the ring fusion and the group at C-7 by equilibration at these centers. Finally the carbonyl function at C-6 would allow the synthesis of other eudesmane sesquiterpenes, such as the furanosesquiterpene atractylon,[2] not readily accessible by the earlier cited synthetic routes.



3

Our choice and initial synthetic goal for the protected diketone was the keto–enol ether **4**. This was conveniently prepared as outlined in Scheme I. Following a modified procedure of Birch,[3a] we prepared keto enol ether **8**[3] in good yield. Birch had suggested that prior reduction of the carbonyl group at C-1 to a hydroxyl group should increase the yield of enol ether–alcohol **7** in the subsequent Birch reduction step. This indeed proved correct as reduction of **5** with sodium borohydride to **6** followed by Birch reduction as previously described[3a] afforded crystalline **7** in 90% yield, whereas direct reduction of **5** gave yields on the order of 60%. Oppenauer oxidation of **7**[3a] gave crystalline enol ether–ketone **8** in yields in excess of 90%. Treatment of **8** with lithium dimethylcopper(I) gave the desired 1,4-addition product as an epimeric mixture at C-9. Under the aqueous work-up conditions the trans-fused product **4** predominated, constituting ~70%



4

(1) For some previous syntheses of members of the eudesmane class, especially β-eudesmol, see (a) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); (b) D. C. Humber, A. R. Pinder, and R. A. Williams, *ibid.*, **32**, 2335 (1967); (c) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968); (d) J. A. Marshall and M. T. Pike, *J. Org. Chem.*, **33**, 435 (1968); (e) J. W. Huffman and M. L. Mole, *Tetrahedron Lett.*, 501 (1971); *J. Org. Chem.* **37**, 13 (1972); (f) R. G. Carlson and E. G. Zev, *ibid.*, **37**, 2468 (1972).

(2) S. Taki and G. Hongo, *J. Pharm. Soc. Jap.*, **44**, 539 (1925). H. Hikino, Y. Hikino, and I. Yoshioka, *Chem. Pharm. Bull.*, **10**, 641 (1962); **12**, 755 (1964).

(3) (a) A. J. Birch, J. A. K. Quartey, and H. Smight, *J. Chem. Soc.*, 1769 (1952); (b) A. J. Birch, *Proc. Roy. Soc. N. S. W.*, **83**, 245 (1949); (c) N. N. Gaidamovich and I. V. Torgov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1682 (1961).