The Ester Enolate Claisen Rearrangement. Construction of the Prostanoid Skeleton[1a]

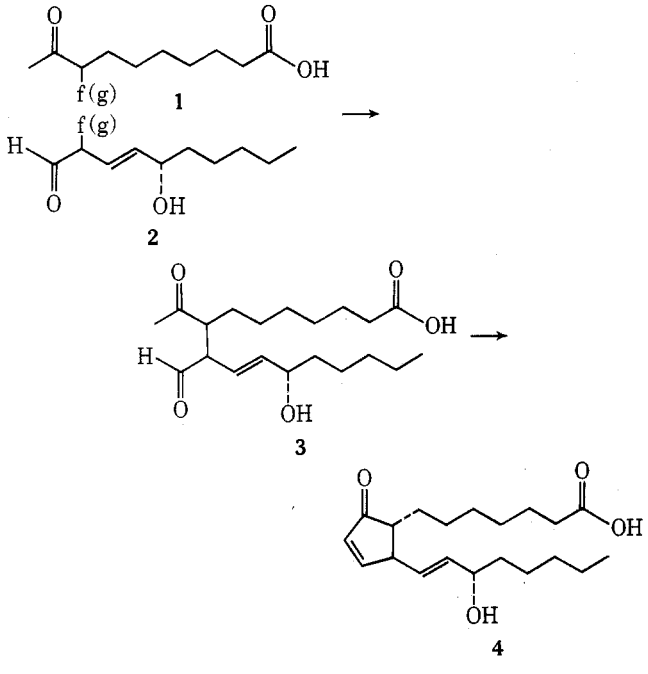
Robert E. Ireland,* Richard H. Mueller, and Alvin K. Willard[1b]

Gates and Crellin Laboratories, California Institute of Technology, Pasadena, California 91125

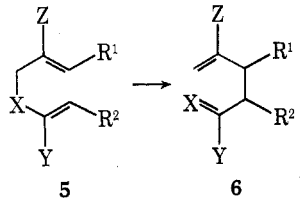
Received November 17, 1975

A convergent synthesis of the prostaglandin skeleton is described. The ester enolate modification of the aliphatic Claisen rearrangement is used to form the key C_8–C_{12} bond. Rearrangement of ester **18** provides the lactone **29** which is converted to the prostanoid **30**. Similarly, the lactone **52**, a potential intermediate in the synthesis of 12-methyl PGA_1, is obtained from ester **51**. Preparation of ester **51** features Claisen rearrangement of ester **38**, which leads to the dienoate **41** after desulfenylation. Model studies of reduction of γ,δ-epoxy-α,β-unsaturated esters to δ-hydroxy-β,γ-unsaturated esters are described. This reduction is accomplished with lithium in ammonia at −78 °C for conversion of epoxy ester **50** to ester **51**.

No family of molecules since the steroids has attracted the interest and effort of synthetic chemists as strongly as have the prostaglandins. Recent efforts have involved the search for flexible synthetic schemes which will allow preparation of a variety of analogues. We report here a synthetic approach which incorporates connection of a "top half" and a "bottom half" of the prostanoid skeleton in a key carbon–carbon bond forming reaction.

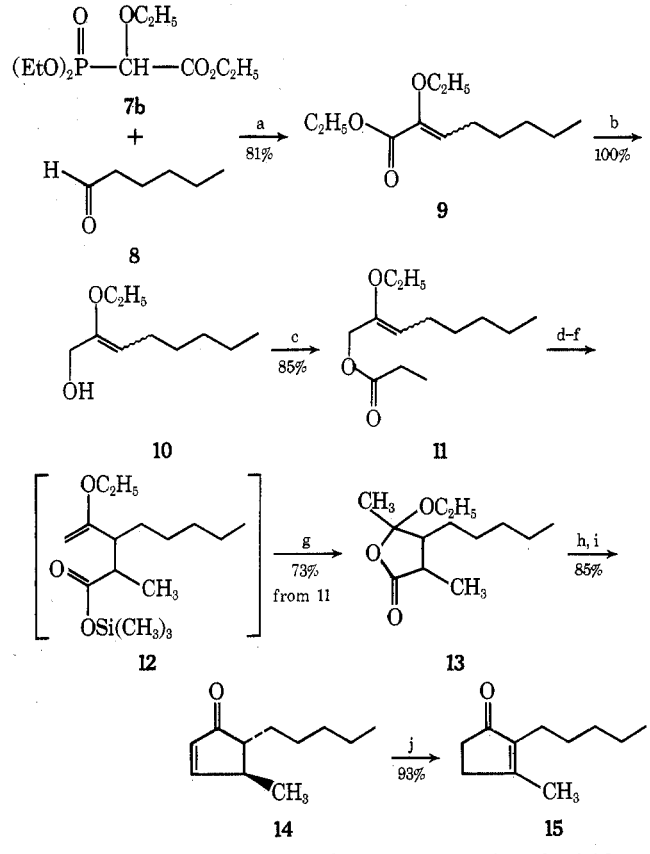


An intriguing possibility for this approach was formation of the carbon–carbon bond with an aliphatic Claisen rearrangement. This reaction (**5** → **6**) would not only provide an efficient means for formation of the desired bond but also would result in the proper number of suitably functionalized carbon atoms for subsequent formation of the cyclopentanone ring system.



The requirements that only one equivalent of each half of the molecule be employed in construction of the precursor **5** and that conditions of the reaction be compatible with a variety of functional groups prompted development of the ester enolate Claisen rearrangement.[2,3]

Scheme I. Synthesis of Dihydrojasmone (15)[a]



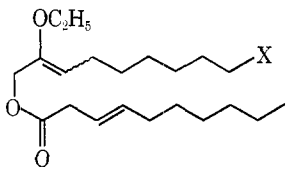
[a] a, NaH, THF; b, $LiAlH_4$, ether; c, propanoic anhydride, pyridine; d, LICA, THF, −78°C; e, TMSCl; f, 65°C, 7 h; g, CH_3SO_3H, EtOH; h, DIBAH, toluene, −78°C; i, NaOH, aqueous CH_3OH, 25°C; j, KOH, aqueous CH_3OH, reflux.

To demonstrate the viability of this approach, synthesis of dihydrojasmone (**15**), a virtual touchstone of cyclopentenone syntheses, was undertaken. The successful route is described in Scheme I.[2]

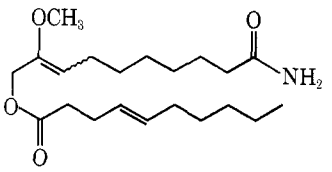
Phosphonates such as **7b**, introduced by Grell and Machleidt,[4] are a useful source of functionalized allylic alcohols such as **10**. When the ester **11** was subjected to enolization with lithium isopropylcyclohexylamide (LICA) and the enolate was trapped with trimethylchlorosilane (TMSCl), rearrangement[3] occurred without incident to give silyl ester **12**. The enol ether functionality not only serves as an ultimate source of a methyl ketone for aldol condensation but also is a convenient handle for reduction

of the silyl ester carbon to the aldehyde oxidation state. This reduction is accomplished by conversion of the silyl ester **12** to the lactone **13** with a trace of acid in ethanol followed by reaction with diisobutylaluminum hydride (DIBAH).[5] Finally, aldol condensation[6] and double bond migration[7] complete this synthesis of dihydrojasmone (**15**).[8]

This same approach was then used for the construction of the prostaglandin skeleton, with initial efforts focused on preparation and transformations of esters **16–18.**



16, X = C≡N
17, X = $CONH_2$



18

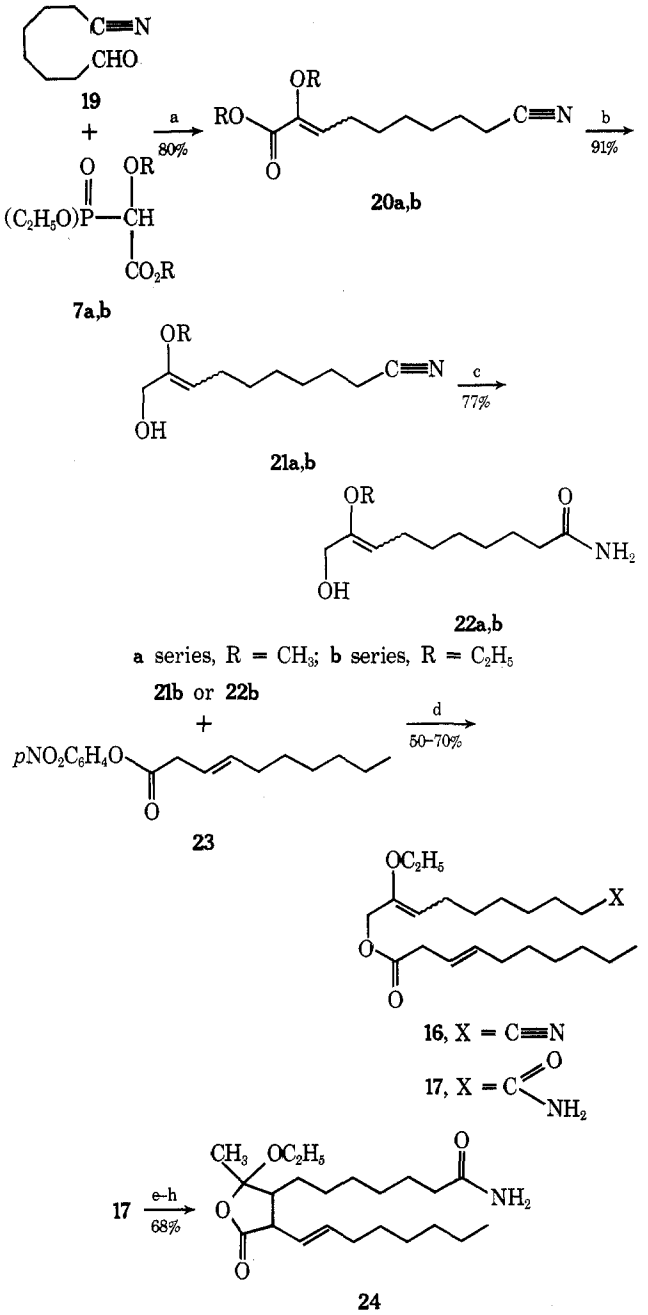
Use of readily available 7-cyanoheptanal (**19**)[9] as a substrate in the Wittig reaction produced equivalent amounts of the geometrical isomers of ester **20** (Scheme II). The methoxy series was adopted in later stages of these studies because it offered the advantage of simpler interpretation of NMR spectra of intermediates in the synthesis. Selective reduction of the cyano esters **20** with lithium borohydride[10] in tetrahydrofuran (THF) provided the desired alcohols **21.** An alternate masked carboxylic acid function, the primary amide **22,** was available by hydration of the nitrile in the presence of the enol ether with basic hydrogen peroxide. Reaction of the alcohol **21** or **22** with the *p*-nitrophenyl ester[11] of the acid in triethylamine was the most satisfactory procedure for preparation of esters fo these γ,δ-unsaturated acids.

With the esters **16** and **17** in hand, their further conversion to cyclopentenone derivatives was investigated. Enolization, silylation, and Claisen rearrangement of cyano ester **16** resulted in a mixture of products containing C-silylated nitrile. The silylation of aliphatic nitriles has now been studied and formation of C-silylated products, even with 1 equiv of base and trialkylchlorosilane, has been demonstrated.[12] Because of this problem, use of the nitrile as a masked carboxylic acid was abandoned in favor of the primary amide. Rearrangement of amide ester **17** proceeded in good yield to provide a intermediate silyl ester which was directly transformed to the lactone **24** with a trace of methanesulfonic acid in ethanol.

Attempted reduction of amide lactone **24** with 1 equiv of diisobutylaluminum hydride[5] resulted in complete recovery of the starting lactone; apparently the reagent is consumed by reaction with the acidic amide proton. The reduction was accomplished with 2 equiv of hydride reagent, but treatment of the reduction product with aqueous base to cause aldol condensation[6] produced neither cyclopentenone nor β-ketol. A possible reason for this is that the acidity of the β,γ-unsaturated aldehyde was resulting in extensive conjugation of the double bond.

If this were indeed the case, isolation of the double bond was a possible solution. This suggested preparation of ester **18** (Scheme III). Moving the double bond to a position where it would not interfere with the aldol condensation also simplified ester formation; now, the acid chloride **25** served well for preparation of the ester. Rearrangement of ester **18,** using lithium disopropylamide (LDA) and *tert*-butyldimethylchlorosilane (TBSCl),[3,13] led to the silyl ester **26** which, as above, could be converted with acid into the lactone **27.** Reduction with 2 equiv of DIBAH[5] and aldol condensation[6] with aqueous methanolic sodium hydroxide

Scheme II. Preparation and Transformations of Esters 16 and 17[a]



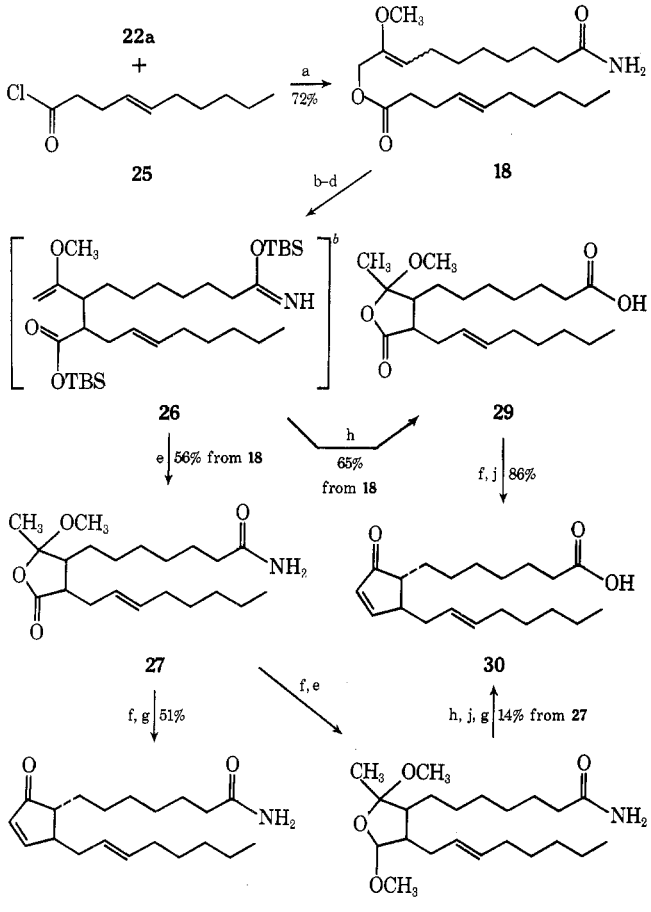
a series, R = CH_3; b series, R = C_2H_5

a, NaH, THF; b, $LiBH_4$, THF; c, H_2O_2, NaOH, aqueous C_2H_5OH; d, Et_3N, 25°C; e, LICA, THF, −78°C; f, TMSCl; g, 67°C, 3.5 h; h, CH_3SO_3H, C_2H_5OH.

provided the cyclopentenone **28.** This verified that the trouble with these reactions on lactone **24** was the position of the double bond.

As the lactone **27** or the cyclopentenone **28,** the molecule could not be subjected to reaction conditions sufficiently vigorous to effect hydrolysis of the primary amide. This hydrolysis was attempted at the intermediate stage. Lactone **27** was reduced as before and the reduction product was protected as the acetal **31.** Saponification of the primary amide, acidic hydrolysis of the acetals, and finally aldol condensation in aqueous alcoholic base gave the cyclopentenone acid **30** in low yield. An alternate point in the synthetic scheme where saponification was possible was immediately after Claisen rearrangement. Basic hydrolysis of the silyl ester **26** followed by neutralization gave the lactone acid **29** in good yield. Reduction, again with 2 equiv of

Scheme III. Synthesis of Prostanoic Acid Derivatives 28 and 30[a]

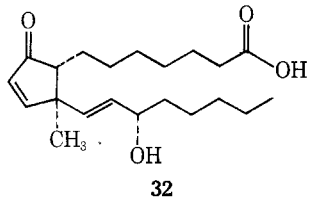


[a] a, Et_3N, CH_2Cl_2, 25°C; b, LDA, THF, −78°C; c, TBSCl; d, 67°C, 3 h; e, CH_3SO_3H, CH_3OH; f, DIBAH, Et_2O, −78°C; g, aqueous NaOH, CH_3OH, 25°C; h, aqueous NaOH, CH_3OH, reflux 16 h, then neutralize; i, HOAc, piperidine, C_6H_6; j, aqueous HCl. [b] TBS = *tert*-butyldimethylsilyl.

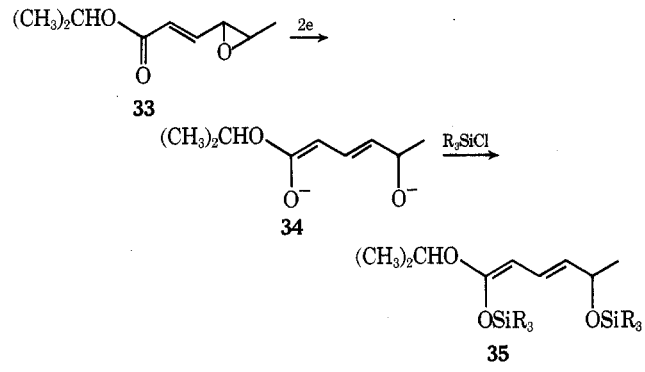
DIBAH,[6] and aldol condensation using piperidinium acetate[14] in refluxing benzene provided the cyclopentenone acid **30** in more satisfactory overall yield.

Having demonstrated that the prostaglandin skeleton could be constructed in this manner, we refocused attention on the problematic double bond in the lower side chain. An alternate solution would be to block apparent conjugation of theouble bond during the aldol condensation; a methyl group should serve this purpose well. The 12-methyl was also attractive because it should block in vivo deactivation of the PGA via migration of the enone double bond to produce the less active PGB structure.

Our synthetic approach to 12-methyl PGA_1 (**32**) would also give us the opportunity to investigate a sequence in which generation of the allylic alcohol functionality in the lower side chain is coupled to enolate formation necessary for the Claisen rearrangement. Two electron reduction of α,β-unsaturated γ,δ-epoxy esters such as **33** should give the enolate **34**. Silylation would provide the silyl ketene acetal **35**. If the alcohol portion of this molecule were an allylic alcohol, this process could be followed by Claisen rearrangement.



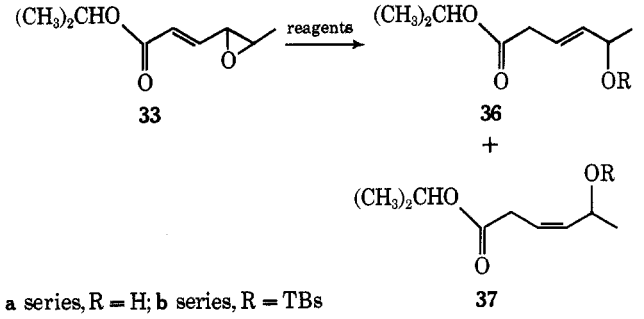
32



Epoxy esters such as **33** are readily available by peracid oxidation[15] of the corresponding dienoic esters. Several reduction methods were examined and are outlined in Table I.

Initial efforts were directed toward finding a system in which both reduction and silylation were possible in the same reaction mixture so that the reduction and Claisen rearrangement could be performed in a single step. A promising system for this transformation was sodium in THF–hexamethylphosphoramide (HMPA).[16,17] During initial attempts, reductions employing these conditions produced a myriad of products but little or none of the desired reduction product. Only under very specific conditions, 2–3 equiv of the Na–HMPA–THF solution added in one portion to a rapidly stirred solution of ester **33** in HMPA–THF at −78 °C followed by addition of TBSCl, could even low yields of the reduction products be obtained. The intermediate silyl ketene acetal **35**, which is formed under these conditions, it readily hydrolyzed to the siloxy esters **36b** and **37b** for analysis. Quenching the reaction mixture with solid ammonium chloride gave nearly identical yield of the alcohols **36a** and **37a** and demonstrated that the problems were arising during reduction, not silylation. A second distinct disadvantage of this method of reduction was that it produced the trans isomer **36b** and the cis isomer **37b** in nearly equal proportions (VPC analysis).

Table I. Reduction of Epoxy Ester 33

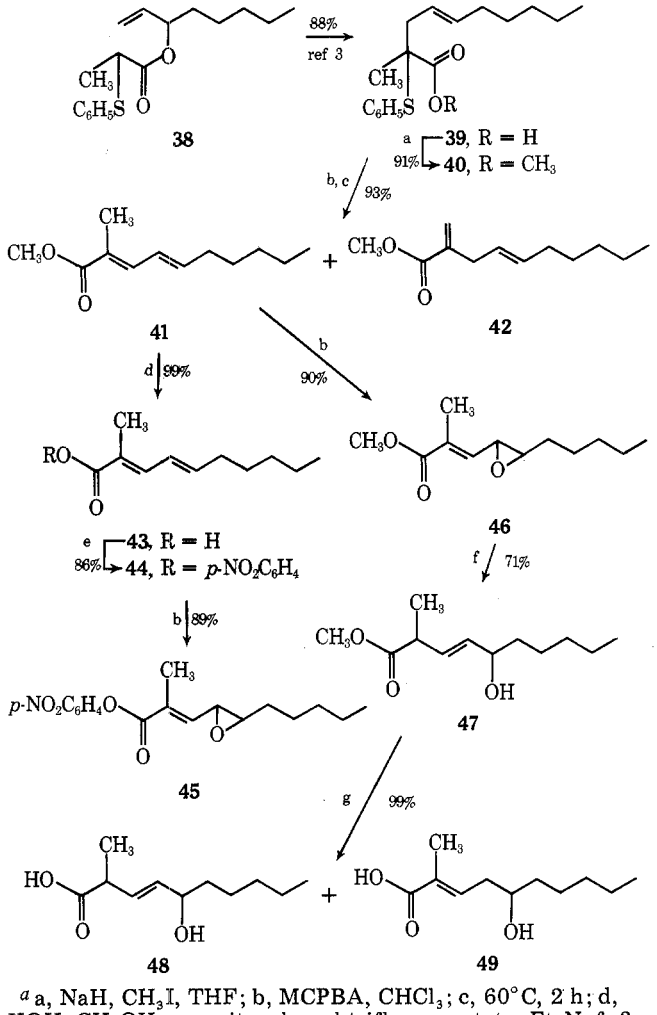


a series, R = H; b series, R = TBs

Entry	Reagents	R	Yield, %[a]	36/37[b]
1	1. 2 equiv Na, HMPA, THF, −78 °C 2. TBSCl 3. HOAc, H_2O	TBS	37	60/40
2	1. 3 equiv Na, HMPA, THF, −78 °C 2. NH_4Cl	H	42	
3	1. Zn, TBSCl, HMPA, THF, 67 °C		0	
4	1. 3 equiv Li, NH_3, THF, −78 °C 2. NH_4Cl	H	79	89/11

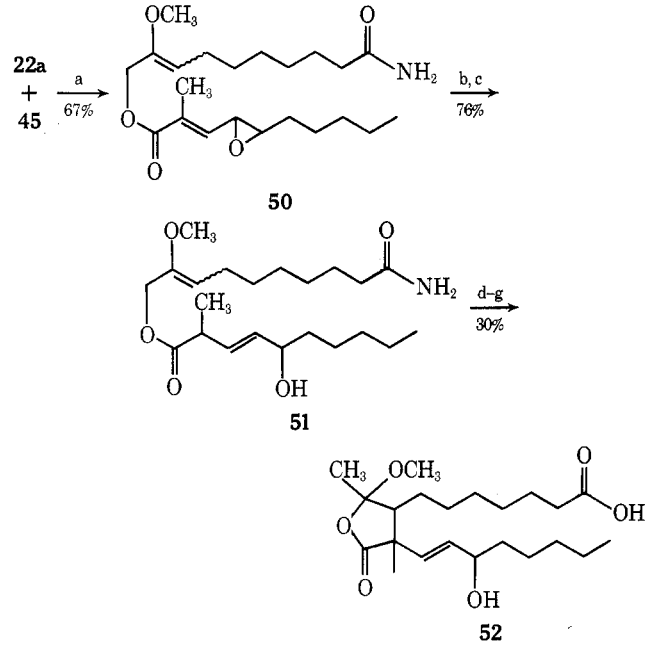
[a] After isolation and chromatography. [b] By VPC analysis.

Scheme IV. Preparation of the Acid Fragment for Ester 50[a]



[a] a, NaH, CH_3I, THF; b, MCPBA, $CHCl_3$; c, 60°C, 2 h; d, KOH, CH_3OH; e, *p*-nitrophenyl trifluoroacetate, Et_3N; f, 3 equiv Li, NH_3, THF, −78°C; g, LiOH, aqueous CH_3OH.

Scheme V. Preparation and Transformations of Ester 50[a]



[a] a, Et_3N, THF, 50°C, 57 h; b, 3 equiv Li, NH_3, THF, −78°C; c, NH_4Cl; d, LDA, THF, −78°C; e, TBSCl, HMPA; f, 67°C, 3 h; g, NaOH, aqueous CH_3OH, then neutralize.

Reduction with a mixture of zinc and TBSCl in HMPA–THF had proven useful in the preparation of silyl ketene acetals from α-bromo esters,[3] but this method failed to reduce the epoxy ester **33**. Finally a high yield of alcohols **36a** and **37a** was realized by reduction with lithium in ammonia–THF. The best results were obtained when the reduction was performed with 3 equiv of lithium at −78 °C for 1 min, and then the reaction mixture was quenched with solid ammonium chloride. In this case an 89:11 ratio of **36a** and **37a** was obtained (VPC analysis). These isomers were easily separated by silica gel chromatography after conversion[18] to the corresponding silyl ethers **36b** and **37b**.

The stereochemical assignment for these two isomers rests on infrared spectral data.[19] The major isomer exhibits a medium band at 970 cm^{-1}, indicative of a trans-disubstituted ethylene. No such band is present in the ir spectrum of the minor isomer.

Since the one-step process was effectively ruled out by the necessity of performing the reduction in ammonia, enolization of the reduction products had to be examined. Enolization of both the hydroxy esters **36a** and **37a** and the siloxy esters **36b** and **37b** with LDA followed by trapping with TBSCl gave the silyl ketene acetal **35**. Competing elimination was not a problem.

Efforts then turned to synthesis of the epoxy ester **50** or its reduced derivative **51**. The acid fragment for these esters was prepared as described in Scheme IV. The α-(phenylthio) ester **40** was readily available via Claisen rearrangement of allylic ester **38**[3] followed by esterification. Desulfenylation[20] by mild heating of the sulfoxides obtained by oxidation with MCPBA produced a mixture of unsaturated esters **41** and **42** in the ratio 78:22. The mixture of diastereomeric sulfoxides obtained in the oxidation was separated by silica gel chromatography, and the sulfoxides were independently pyrolyzed. The more mobile isomer gave the olefins in a 68:32 ratio (**41**:**42**) and the less mobile isomer in 90:10 ratio.

This synthesis of ester **41** also serves to demonstrate the possibility of employing the Claisen rearrangement for formation of a carbon–carbon double bond. The sulfur functionality serves to mask this double bond until a convenient stage is reached in the synthesis.

Oxidation of ester **41** with MCPBA[15] produced the epoxy ester **46** in high yield. The presence of only one geometrical isomer of this epoxy ester is clearly demonstrated by NMR analysis. This indicates that ester **41** is cleanly the *E,E* isomer. Attempts to saponify the epoxy ester **46** in order to obtain the corresponding acid were not encouraging. This sensitive epoxy acid was obtained in varying states of purity and attempted purification led to extensive decomposition.

The alternative approach of using the acid portion in already reduced form was also investigated. Epoxy ester **46** was reduced under the same conditions described above and gave a mixture of two separable components (93:7). The major component was assigned the trans stereochemistry **47** based on results obtained with ester **33**. The minor isomer was tentatively assigned cis stereochemistry. Saponification of ester **47** gave a mixture of acids containing 70% of the unsaturated acid **48** and 30% of the conjugated isomer **49**.

Since the difficulty in both of these approaches arose during attempted saponification of the methyl ester in order to prepare some activated ester derivative suitable for esterification, saponification of the ester at an earlier, less sensitive stage was desirable.

Hydrolysis of the dienoic ester **41** proceeded without difficulty. The *p*-nitrophenyl ester **44**[11] of the resulting acid

43 was sufficiently stable to permit partial purification by rapid chromatography on silica gel. This derivative was also readily oxidized with MCPBA[15] to provide the epoxy ester **45.** When stirred with the alcohol **22a** in THF–triethylamine, epoxy ester **45** was converted to the target ester **50** through ester exchange (Scheme V).

Reduction of ester **50** to hydroxy ester **51** proceeded normally. The minor isomer (cis?) found in the reduction of ester **46** was not detected but was probably present in the mixture.

Initial attempts to carry this ester on to 12-methyl PGA_1 (**32**) met with serious difficulties. Rearrangement and basic hydrolysis gave the lactone **52** in only 30% yield. The unsaturated acid **43** was a major side product. Reduction of lactone **52** with 3 equiv of DIBAH proceeded smoothly but attempted aldol condensation did not produce cyclopentenone under mild (piperidinium acetate[14]) or harsh (aqueous methanolic sodium hydroxide[6]) conditions. In view of these difficulties and in face of a report that 12-methyl PGA_2 was inactive,[21] the synthesis was not pursued further.

Although difficulties arose in late stages of some of the syntheses described here, the potential of the ester enolate Claisen rearrangement in convergent synthesis of complex organic molecules has been demonstrated. Particularly, the compatibility of this reaction with a wide variety of functionality should make it a useful addition to the synthetic chemist's armory of reactions.

Experimental Section[22]

Methyl Diethoxyphosphinylmethoxyacetate (7a). The procedure of Grell and Machleidt[4] was followed to prepare the phosphonate **7a** from methyl dimethoxyacetate: bp 110 °C (0.3 mm); NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7 Hz, CH_3CH_2O–), 3.52 (s, 3 H, ether CH_3O–), 3.83 (s, 3 H, ester CH_3O–), 4.22 (m, 5 H, $CHCO_2$– and CH_3CH_2O); ir (neat) 1750 (C=O), 1260, 1120, 1015, 970 cm^{-1}.

Anal. Calcd for $C_8H_{17}O_6P$: C, 40.00; H, 7.13. Found: C, 40.12; H, 7.08.

Ethyl 2-Ethoxy-2-octenoate (9). A stirred suspension of 2.78 g (0.116 mol) of sodium hydride (mineral oil free) in dry THF was treated during 30 min with the dropwise addition of 30.0 g (0.112 mol) of phosphonate **7b.** Following the addition, the reaction mixture was stirred for an additional 30 min and then cooled to 0 °C. Hexanal (11.2 g, 0.112 mol) was added dropwise to this solution over a 30-min period. Near the end of the addition, a gummy precipitate formed. The reaction mixture was stirred for an additional 30 min at 25 °C and then treated with 50 ml of water. Benzene extraction,[23] including an aqueous ammonium chloride wash, followed by distillation of the residue afforded 19.5 g (81%) of a mixture (1:3) of unsaturated esters **9:** bp 60–63 °C (0.08 mm); NMR ($CDCl_3$) δ 0.87 (br t, 3 H, $-CH_2CH_2CH_3$), 1.33 (t, 6 H, J = 7 Hz, $-OCH_2CH_3$), 3.73 (br t, 2 H, J = 7 Hz, $=COCH_2CH_3$), 4.24 and 4.21 (q's, 2 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.24 and 5.26 (t's 1 H, ratio 1:3, J = 7 and 7.5 Hz, vinylic H's); ir ($CHCl_3$) 1725 (C=O), 1640 (C=C), 1380, 1160, 1040 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.34; H, 10.38.

2-Ethoxy-2-octenyl Propanoate (11). To a suspension of 2.0 g (53 mmol) of lithium aluminum hydride in 120 ml of dry ether was added 10.0 g (47 mmol) of the esters **9** over a 30-min period. Following the addition, the reaction mixture was stirred for an additional 15 min before excess hydride was destroyed by addition of ethyl acetate. Work-up according to the procedure of Fieser[24] afforded 7.75 g of crude alcohols **10** which were used without further purification. This material was treated with 15 g of propanoic anhydride in 20 ml of dry pyridine at 25 °C for 20 h. Distillation of the reaction mixture gave 8.9 g (85%) of the ester **11:** bp 72–85 °C (0.1 mm); NMR ($CDCl_3$) δ 2.33 (q, 2 H, J = 7 Hz, $CH_3CH_2CO_2$–), 3.65 (q, 2 H, J = 7 Hz, CH_3CH_2O–), 4.57 and 4.62 (s's, 2 H, $-OCH_2C$=C), 4.64 and 4.86 (t's, 1 H, J = 7 Hz, vinylic H's); ir (neat) 1725 (C=O), 1640 cm^{-1} (C=C).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.58; H, 10.50.

5-Ethoxy-3,5-dimethyl-4-pentyloxacyclopentan-2-one (13). A solution of 7.1 mmol of LICA in 20 ml of dry THF was cooled to −78 °C. To this rapidly stirred solution was added 1.50 g (6.6 mmol) of ester **11** over 3 min. Following the addition, 0.850 ml (6.7 mmol) of TMSCl was added in one portion and the reaction mixture was stirred at −78 °C for an additional 3 min. The cooling bath was removed and the reaction mixture was allowed to warm to 25 °C. The mixture was then stirred at reflux for 7 h to effect rearrangement. After cooling to 25 °C the reaction mixture was treated with 2 ml of ethanol and sufficient methanesulfonic acid to obtain pH 1–2. Extraction[23] with petroleum ether afforded 1.6 g of a yellow oil which was evaporatively distilled at 80 °C (0.2 mm) to give 1.1 g (73%) of the lactone **13.** A portion of this material (400 mg) was purified further by medium-pressure chromatography[22] on 2.5 × 50 cm of silica gel with 50% dichloromethane–benzene. Elution with 550 ml of this solvent system gave the analytical sample: NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7 Hz, CH_3), 1.40 (d, 3 H, J = 8 Hz, CH_3CH–), 3.63 (q, 2 H, J = 7 Hz, $-CH_2O$–); ir (neat) 1792 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.46; H, 10.49.

4-Methyl-5-pentyl-2-cyclopentenone (14). A solution of 450 mg (2.0 mmol) of lactone **13** in 10 ml of dry toluene was cooled to −78 °C. To this stirred solution was added 2.4 ml (2.3 mmol) of DIBAH in benzene over 5 min. The reaction mixture was stirred for 30 min at −78 °C and then treated with 0.5 ml of methanol and allowed to warm to 25 °C. Benzene extraction[23] gave 440 mg of a colorless oil which was dissolved in 10 ml of methanol and treated with 10 ml of 5% aqueous sodium hydroxide solution. This mixture was stirred at 25 °C for 20 min after which benzene extraction[23] and evaporative distillation of the residue at 80 °C (1 mm) gave 280 mg (85%) of colorless cyclopentenone **14:** NMR ($CDCl_3$) δ 0.90 (br t, 3 H, J = 7 Hz, CH_3CH_2–), 1.22 (d, 3 H, J = 7 Hz, CH_3CH–), 6.14 (dd, 1 H, J = 6 and 2 Hz, =CHC=O), 7.55 (dd, 1 H, J = 6 and 2.5 Hz, CH=C–C=C); ir (neat) 1710 (C=O), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.49; H, 10.90.

3-Methyl-2-pentyl-2-cyclopenten-1-one (15). A mixture of 118 mg (0.711 mmol) of cyclopentenone **14** and 200 mg of potassium hydroxide in 10 ml of water and 5 ml of methanol was stirred at reflux for 40 min. Extraction[23] with dichloromethane and evaporative distillation of the residue at 80 °C (1 mmol) gave 110 mg (93%) of colorless dihydrojasmone (**15**): NMR δ 0.88 (br t, 3 H, J = 7 Hz, CH_3), 1.2 (m, 6 H), 2.05 (s, 3 H, $C=CCH_3$); ir (neat) 1700 (C=O), 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.55; H, 10.95.

Methyl 9-Cyano-2-methoxynon-2-enoate (20a). To a mechanically stirred suspension of 2.64 g (0.11 mol) of sodium hydride (mineral oil free) in 150 ml of dry THF was added 24.0 g (0.10 mol) of phosphonate **7a** over 40 min. The mixture was stirred for an additional 1 h and then cooled to 0 °C. During 30 min, the reaction mixture was treated with 13.9 g (0.1 mol) of 7-cyanoheptanal (**19**) while vigorous stirring was maintained. Toward the end of the addition a gummy precipitate formed. The reaction mixture was allowed to warm gradually to 25 °C over 1 h. After cautious addition of 80 ml of water, ether extraction[23] gave a slightly orange liquid which was subjected to short path distillation to give 17.9 g (80%) of the cyano esters **20a,** bp 120–128 °C (0.015 mm). NMR analysis indicated that this was approximately an equal mixture of double bond isomers. A portion of this material (378 mg) was purified further by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 30% ether–petroleum ether at a flow rate of 1 ml/min. Elution with 150 ml gave 174 mg of the Z isomer. An analytical sample was prepared by evaporative distillation at 110 °C (0.001 mm); NMR ($CDCl_3$) δ 3.67 (s, 3 H, ether CH_3O–), 3.78 (s, 3 H, ester CH_3O–), 6.23 (t, 1 H, J = 7 Hz, vinylic H); ir ($CHCl_3$) 2250 (C≡N), 1720 (C=O), 1651 (C=C), 1270, 1120, 990 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.09; H, 8.43; N, 6.26.

Further elution with 10 ml of the same solvent system gave 68 mg of a mixture of the E and Z isomers. Continued elution with 80 ml of this solvent system gave 123 mg of the E isomer. An analytical sample was prepared by evaporative distillation at 110 °C (0.001 mm): NMR ($CDCl_3$) δ 3.58 (s, 3 H, ether CH_3O–), 3.78 (s, 3 H, ester CH_3O–), 5,20 (t, 1 H, J = 7 Hz, vinylic H); ir ($CHCl_3$) 2250 (C≡N), 1725 (C=O), 1640 (C=C), 1376, 1170, 1130 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.00; H, 8.48; N, 6.19.

10-Hydroxy-9-methoxydec-8-enenitrile (21a). To a vigorously stirred suspension of 685 mg (18 mmol) of sodium borohydride and 1.56 g (18 mmol) of anhydrous lithium bromide[10] in 20 ml of

dry THF was added 2.0 g (8.89 mmol) of the cyano ester **20a**. This mixture was stirred at 25 °C for 52 h. At the end of this period, 20 ml of water was added and the reaction mixture was stirred for 40 min. After addition of another 20-ml portion of water, ether extraction[23] gave 2.1 g of a colorless oil which still contained some ester (ir analysis). This material was subjected again to the same treatment and gave 1.59 g (91%) of the crude cyano alcohol **21a** as a colorless liquid. A portion of this material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 80% ether–petroleum ether at a flow rate of 1 ml/min followed by evaporative distillation at 100 °C (0.001 mm) and gave the analytical sample: NMR ($CDCl_3$) δ 3.54 and 3.65 (s, 3 H total, CH_3O), 4.13 (br s, 2 H, $-CH_2O-$), 4.6 (m, 1 H, vinylic H's); ir ($CHCl_3$) 3600 and 3470 (OH), 2250 (C≡N) 1670 (C=C), 1465, 1140, 1110, 1055, 1015 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; h, 9.71; N, 7.10. Found: C, 66.87; H, 9.59; N, 7.01.

10-Hydroxy-9-methoxydec-8-enamide (22a). A solution of 1.97 g (10.0 mmol) of the crude cyano alcohol **21a** in 50 ml of ethanol was added in one portion to an ice-cooled, stirred mixture of 90 ml of 10% aqueous hydrogen peroxide and 3 ml of 40% aqueous sodium hydroxide solution. After 10 min the ice bath was removed and the reaction mixture was stirred at room temperature for 2 h. Dichloromethane extraction[23] gave 1.65 g (77%) of a white solid. A portion of this material (130 mg) was purified further by medium-pressure chromatography[22] on a 1.25 × 50 cm of silica gel with 50% acetone–ether at a flow rate of 1 ml/min. Elution with 265 ml of this solvent system gave 101 mg of a white solid. One recrystallization from ehter containing a small amount of dichloromethane gave the analytical sample as a mixture of double bond isomers: mp 51–58 °C; NMR ($CDCl_3$) δ 3.53 and 3.65 (s, 3 H total, CH_3O-), 4.09 (m, 2 H, CH_2O-), 4.8 (m, 1 H, vinylic H), 6.0 (br s, 2 H, NH_2); ir ($CHCl_3$) 3700–3100 (several bands, OH, NH_2), 1675 (C=O), 1590, 1465, 1390, 1010 cm^{-1}.

Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.41; H, 9.88; N, 6.46.

Ethyl 9-Cyano-2-ethoxynon-2-enoate (20b). In a manner similar to that described for the methyl derivative **20a**, phosphonate **7b** and cyano aldehyde **19** were converted into a mixture of esters **20b** (84%): bp 120–136 °C (0.1 mm); NMR ($CHCl_3$) δ 2.33 (m, 4 H, $=CCH_2-$ and $-CH_2C\equiv N$), 4.25, 4.21, and 3.75 (q's, 4 H total, J = 7 Hz, CH_3CH_2O-), 6.21 and 5.22 t's, 1 H total, J = 7 Hz, vinylic H); ir (neat) 2250 (C≡N), 1725 (C=O), 1640 cm^{-1} (C=C).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.39; H, 9.13; N, 5.57.

9-Ethoxy-10-hydroxydec-8-enenitrile (21b). In a manner similar to that described for cyano alcohol **21a**, the mixture of esters **20b** was reduced with lithium borohydride[10] to give the cyano alcohol **21b** (100%): NMR ($CDCl_3$) δ 3.66 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 4.12 (br s, 2 H, $=CCH_2O-$), 4.4 (m, 1 H, vinylic H); ir ($CHCl_3$) 3600 and 3470 (OH), 2240 (C≡N), 1665 (C=C), 1385, 1105, 1050, 1010 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.2;; H 10.09; N, 6.60.

9-Ethoxy-10-hydroxydec-8-enamide (22b). In a manner similar to that described for hydroxy amide **22a**, the cyano alcohol **21b** was converted into the hydroxy amide **22b** (72%): NMR ($CDCl_3$) δ 3.15 (br s, 1 H, OH), 3.68 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 4.13 and 4.10 (s, 2 H total, $-CH_2OH$), 4.47 and 4.76 (t, 1 H total, J = 7.5 and 8 Hz, vinylic H), 6.2 (br s, 2 H, NH_2); ir ($CHCl_3$), 3700–3150 (several bands, OH, NH_2), 1675 (C=O, C=C), 1590 cm^{-1}.

Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.79; H, 10.17; N, 6.14.

9-Cyano-2-ethoxy-2-nonenyl (*E*)-3-Decenoate (16). To a solution of 1.40 g (6.0 mmol) of *p*-nitrophenyl trifluoroacetate[11] in 3 ml of dry pyridine was added 1.0 g of (*E*)-3-decenoic acid.[25] This mixture was stirred for 2 h at 25 °C. Pentane extraction,[23] including an acid wash and a base wash, gave 1.37 g (80%) of *p*-nitrophenyl (*E*)-3-decenoate (**23**) which was not purified further: NMR ($CDCl_3$) δ 2.07 (m, 2 H, $=CCH_2$), 3.30 (d, 2 H, J = 5 Hz, $=CCH_2CO_2-$), 5.65 (m, 2 H, CH=CH), 7.25 (d, 2 H, J = 8 Hz, aromatic H's), 8.25 (d, 2 H, J = 8 Hz, aromatic H's); ir (neat) 1765 (C=O), 1620, 1595, 1530, 1495, 1350, 1115 cm^{-1}.

This crude *p*-nitrophenyl ester **23** was dissolved in 3 ml of dry triethylamine and was treated with 1.3 g (6.1 mmol) of the cyano alcohol **21b**. This mixture was stirred at 25 °C for 16 h. Pentane extraction,[23] including a base wash, gave 1.6 g of an oil which was filtered through 7 g of silica gel with benzene to give 1.14 g (50%) of cyano ester **16** as a colorless oil: NMR ($CDCl_3$) δ 2.96 (br d, 2 H, J = 4 Hz, $-CH_2CO_2-$), 3.63 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 4.48 (s, and t, 3 H, J = 7 Hz, $-OCH_2C=CH-$), 5.50 (m, 2 H, CH=CH); ir (neat) 2250 (C≡N), 1737 (C=O), 1668 cm^{-1} (C=C).

Anal. Calcd for $C_{22}H_{37}NO_3$: C, 72.69; H, 10.26; N, 3.85. Found: C, 72.69; H, 10.27; N, 3.78.

9-Carbamoyl-2-ethoxy-2-nonenyl (*E*)-3-decenoate (17). The *p*-nitrophenyl ester **23** (4.8 mmol) was added to 1.0 g (4.4 mmol) of the hydroxy amide **22b** in 2 ml of dry triethylamine. This mixture was stirred for 36 h at 25 °C. Ether extraction,[23] including a base wash, gave a yellow oil which was purified by chromatography of 10 g of silica gel with 300 ml of ether. The ether fraction contained 1.4 g (83%) of a slightly yellow oil which solidified upon standing. A portion of this material was recyrstallized from petroleum ether to afford the analytical sample: mp 53–54 °C; NMR ($CDCl_3$) δ 3.03 (d, 2 H, J = 5 Hz, CH_2CO_2-), 3.68 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 4.60 (s and t, 3 H, J = 7 Hz, $CH_2C=CH-$), 5.53 (m, 2 H, CH=CH), 5.8 (br, 2 H, NH] $_2$); ir ($CHCl_3$) 1725 (ester C=O), 1675 (amide C=O), 1590, 1115, 1060, 965, 910 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.34; H, 10.27; N, 3.64.

4-(6-Carbamoylhexyl)-5-ethoxy-5-methyl-3-(1-octenyl)oxacyclopentan-2-one (24). A solution of 1.64 mmol of LICA in 3 ml of dry THF was cooled to −78 °C. To this rapidly stirred mixture was added a solution of 206 mg (0.54 mmol) of ester **17** in 1 ml of dry THF over 35 s. After an additional 2 min at −78 °C, 0.250 ml (1.95 mmol) of TMSCl was added in one portion. The reaction mixture was stirred for an additional 3 min at −78 °C and then allowed to warm to 25 °C. The mixture was then stirred at reflux for 3.5 h to effect rearrangement. After cooling to 25 °C, the mixture was treated with 0.1 ml of ethanol and sufficient methanesulfonic acid to give pH 1–2. Immediate dichloromethane extraction[23] afforded 227 mg of a yellow oil. This material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 20% acetone–benzene. Elution with 300 ml of this solvent mixture afforded 141 mg (68%) of the lactone amide **24** as a colorless oil: NMR ($CDCl_3$) δ 1.60 [s, 3 H, $CH_3C(O)_2-$], 3.66 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 5.5–6.3 (br m, 4 H, CH=CH and NH_2); ir ($CHCl_3$) 3700–3150 (several bands, NH_2), 1765 (lactone C=O), 1675 (amide C=O), 1590 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.10; H, 10.30; N, 3.71.

(*E*)-4-Decenoyl Chloride (25). A solution of 1.37 g (8.05 mmol) of (*E*)-4-decenoic acid[3] in 15 ml of dry benzene was treated with 1.4 ml (1.90 g, 16 mmol) of thionyl chloride. This mixture was stirred at reflux for 1 h. After the reaction mixture had cooled to 25 °C, the benzene and excess thionyl chloride were removed by rotary evaporation at reduced pressure followed by addition and similar removal of a second 15-ml portion of benzene. The residue was evaporatively distilled at 50–55 °C (0.05 mm) and 1.41 g (93%) of the acid chloride as a colorless liquid: NMR ($CDCl_3$) δ 2.95 (m, 2 H, C-2 H's), 5.45 (m, 2 H, CH=CH); ir ($CHCl_3$) 1800 (C=O), 1405, 970, 915, 730, 685 cm^{-1}.

9-Carbamoyl-2-methoxy-2-nonenyl (*E*)-4-Decenoate (18). A solution of 1.37 g (6.37 mmol) of the hydroxy amide **22a** and 3.53 ml (2. 55 g, 25 mmol) of dry triethylamine in 25 ml of dry dichloromethane was cooled to 0 °C. To this stirred solution was added 1.20 g (6.37 mmol) of the acid chloride **25** in 10 ml of dichloromethane. The reaction mixture was allowed to warm to 25 °C over 1 h and then was stirred for 11 h. Extraction[23] with 10% dichloromethane–ether, including a base wash, gave 2.02 g of a yellow oil which crystallized upon standing. This material was purified by medium-pressure chromatography[22] on 2.5 × 50 cm of silica gel with 40% acetone–ether at a flow rate of 2 ml/min. After elution with 210 ml of this solvent system, the next 160 ml afforded 1.60 g (72%) of the ester **18** as a white, waxy solid containing two isomers. A portion of this material was recrystallized from hexane and gave white platelets: mp 52.5–60 °C; NMR ($CDCl_3$) δ 3.47 and 3.55 (s, 3 H total, CH_3O), 4.57 (m, 2 H, $-CH_2O-$), 4.8 (m, 1 H, enol ether vinylic H), 5.42 (m, 2 H, CH=CH), 5.7 (br, 2 H, NH_2); ir ($CHCl_3$) 3540, 3500, and 3420 (NH_2), 1730 (ester C=O), 1675 (amide C=O), 1590, 1160, 1120, 1070, 970 cm^{-1}.

Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.64; H, 10.13; N, 3.84.

4-(6-Carbamoylhexyl)-5-methoxy-5-methyl-3-(2-octenyl)oxacyclopentan-2-one (27). A solution of 1.5 mmol of LDA in 3.0 ml of dry THF was cooled to −78 °C. To this rapidly stirred solution was added 184 mg (0.5 mmol) of the ester **18** in 1 ml of THF over 1 min. After an additional 2 min at −78 °C, 1.0 ml (1.52 mmol) of TBSCl in HMPA was added in one portion. This mixture was stirred at −78 °C for an additional 2 min after which the cooling bath was removed and the reaction mixture was allowed to

warm to 25 °C over 20 min. The reaction mixture was then stirred at reflux for 3.5 h. Extraction[23] with 75% ether–petroleum ether afforded 369 mg of a nearly colorless oil. This oil was dissolved in 3 ml of THF and 1 ml of methanol; one drop of methanesulfonic acid was added and the mixture was stirred for 35 min at 25 °C. Extraction[23] with 75% ether–petroleum ether, including a base wash, gave 198 mg of a colorless oil. This material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 25% acetone–ether at a flow rate of 1 ml/min. After elution with 110 ml of this solvent system, the next 10 ml gave 45 mg of a mixture of compounds which by NMR analysis appeared to contain 50% of the desired lactone. Continued elution with 65 ml of the same solvent system gave 102 mg (56%) of a mixture of diasteriomers of the lactone **27** as a colorless oil: NMR ($CDCl_3$) δ 1.35 (br s, methylenes), 1.43 and 1.53 [s, 3 H total, $CH_3C(O)_2$–], 3.33 (br s, 3 H, CH_3O–), 5.5 (br m, 4 H, CH=CH and NH_2): ir ($CHCl_3$) 1765 (lactone C=O), 1680 (amide C=O), 1590, 1385, 975, 910 cm^{-1}.

Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.72; H, 9.99; N, 3.62.

5-(6-Carbamoylhexyl)-4-(2-octenyl)-2-cyclopentenone (28). A. Reduction with DIBAH. A solution of 102 mg (0.278 mmol) of lactone **27** in 4 ml of dry ether was cooled to −78 °C. To this stirred solution was added 0.885 ml (0.612 mmol) of a solution of DIBAH in benzene over a period of 3 min. The reaction mixture was stirred at −78 °C for an additional 30 min, then 0.15 ml of methanol was added to the mixture and the cold bath was removed. After the reaction mixture had warmed to 25 °C, 0.15 ml of water and 0.2 g of Celite were added. The reaction mixture was stirred vigorously for 15 min. Anhydrous sodium sulfate (0.2 g) was again subjected to vigorous stirring for 15 min. The reaction mixture was then filtered with the aid of 75 ml of ether. The filtrate was evaporated at reduced pressure and gave 95 mg (92%) of a crude lactol which was not purified further.

B. Aldol Condensation. A solution of 69 mg of (0.187 mmol) of the crude lactol in 5 ml of ethanol and 5 ml of 5% aqueous sodium hydroxide solution was stirred for 20 min at 25 °C. Ether extraction[23] gave 53 mg of a colorless oil. This material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 30% acetone–ether at a flow rate of 1 ml/min. After elution with 120 ml of this solvent system, continued elution with 35 ml afforded 33 mg (51%) of the cyclopentenone **28** as a colorless oil: NMR ($CDCl_3$) δ 2.05 (t, 2 H, J = 7 Hz, CH_2C=O), 5.42 (m, 2 H, CH=CH), 5.73 (m, 2 H, NH_2), 6.10 (dd, 1 H, J = 6 and 1 Hz, =CHC=O), 7.56 (dd, 1 H, J = 6 and 2 Hz, CH=C–C=O); ir ($CHCl_3$) 3550–3100 (several bands, NH_2), 1685 (enone and amide C=O), 1590, 970 cm^{-1}; uv (EtOH) λ_{max} 219 nm (ϵ 10 000).

Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.05; H, 10.47; N, 4.41.

4-(6-Carboxyhexyl)-5-methoxy-5-methyl-3-(2-octenyl)oxacyclopentan-2-one (29). A solution of 2.04 mmol of LDA in 7 ml of dry THF was cooled to −78 °C. To this stirred solution was added 1.8 ml of dry HMPA followed by 250 mg (0.679 mmol) of the ester **18** in 2 ml of THF over 4 min. The reaction mixture was stirred for an additional 2 min and then 0.59 ml (2.04 mmol) of TBSCl in hexane was added. After an additional 2 min at −78 °C, the cold bath was removed and the reaction mixture was allowed to warm to 25 °C. The mixture was then stirred at reflux for 3 h. Extraction[23] with 75% ether–petroleum ether gave a nonmobile oil. This material was stirred at reflux in a solution of 1.2 g of sodium hydroxide, 6 ml of water, and 15 ml of methanol for 16 h. The cooled reaction mixture was poured into 30 ml of water and extracted with three 25-ml portions of ether (extracts discarded). The basic solution was cooled to 0 °C and acidified by addition of 90 ml of 0.4 N H_2SO_4 with stirring. Dichloromethane extraction[23] gave 220 mg of an oil. This material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with petroleum ether–dichloromethane–THF–acetic acid (50:10:3:2) at a flow rate of 1 ml/min. After elution with 60 ml of this solvent system, continued elution with 50 ml gave 162 mg (65%) of a mixture of diastereomers of the lactone acid **29** as a colorless oil: NMR ($CDCl_3$) δ 1.43 and 1.53 [s, 3 H total, $CH_3C(O)_2$–], 3.36 (s, 3 H, CH_3O–), 5.65 (m, 2 H, CH=CH); ir ($CHCl_3$) 1765 (lactone C=O), 1710 (acid C=O), 1380, 975 910 cm^{-1}.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.45; H, 9.85. Found: C, 68.42; H, 9.72.

5-(6-Carboxyhexyl)-4-(2-octenyl)-2-cyclopentenone (30). A. Reduction with DIBAH. A solution of 168 mg (0.450 mmol) of the lactone acid **29** in 15 ml of dry ether was cooled to −78 °C. To this stirred solution was added 1.17 ml (1.01 mmol) of DIBAH in benzene over a 4-min period. The reaction mixture was then stirred at −78 °C for an additional 30 min. The mixture was then treated with 0.6 ml of methanol to quench excess hydride and was stirred for an additional 5 min at −78 °C. The reaction mixture was then rinsed into a mixture of 5 ml of acetic acid and 10 g of ice with 25 ml of ether. This mixture was stirred for 5 min, after which ether extraction[23] afforded 166 mg (quantitative crude yield) of a keto aldehyde: NMR ($CDCl_3$) δ 1.33 (m, $-CH_2$–), 2.16 and 2.23 (s, 3 H total, CH_3C=O), 5.38 (m, 2 H, CH=CH), 9.41 (br s, 1 H, CO_2H), 9.69 (m, 1 H, CHO).

B. Aldol Condensation. This keto aldehyde was dissolved in 15 ml of dry benzene and was treated with 5.7 μl of acetic acid and 9.9 μl of piperidine. This mixture was stirred at reflux with continuous removal of water by means of a Dean-Stark apparatus charged with 4A molecular sieves. After 4.75 h, TLC analysis indicated that some starting keto aldehyde remained. The reaction mixture was again treated with 5.7 μl of acetic acid and 9.9 μl of piperidine and reflux was continued for 2 h. Ether extraction,[23] including a wash with 20% aqueous sodium dihydrogen phosphate solution, gave 197 mg of a slightly yellow oil. Purification by preparative TLC[22,26] on 13 × 20 × 0.2 cm of silica gel with hexane–dichloromethane–THF–acetic acid (30:10:5:3) afforded 126 mg (86% from lactone **29**, R_f 0.23–0.38) of cyclopentenone **30** as a colorless oil: NMR ($CDCl_3$) δ 5.44 (m, 2 H, CH=CH), 6.15 (dd, 1 H, J = 6 and 1 Hz, =CHC=O), 7.60 (dd, 1 H, J = 6 and 2 Hz, CH=CC=O), 10.07 (br s, 1 H, CO_2H); ir ($CHCl_3$) 3400–2600 (CO_2H), 1705 (enone and acid C=O), 1590, 950 cm^{-1}; uv (EtOH) λ_{max} 219 (ϵ 9400).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.90; H, 9.90.

3-(6-Carbamoylhexyl)-2,5-dimethoxy-2-methyl-4-(2-octenyl)oxacyclopentane (31). A solution of 133 mg (0.361 mmol) of the crude lactol, which resulted from reduction of lactone **27** (vide supra), in 7 ml of methanol was cooled to 0 °C. To this solution was added one drop of methanesulfonic acid and the reduction mixture was stirred at 0 °C for 3 h. Ether extraction,[23] including a base wash, gave 128 mg (93%) of a slightly brown oil. A portion of this material (75 mg) was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 30% acetone–ether at a flow rate of 1 ml/min. After elution with 135 ml of this solvent, continued elution with 125 ml afforded 53 mg of a mixture of several diastereomers of the bis acetal **31** as a colorless oil: NMR ($CDCl_3$) δ 3.27, 3.32, 3.37, and 3.40 (s, CH_3O), 4.65 (m, 1 H, –OCHO–), 5.43 (m, 2 H, CH=CH), 5.68 (m, 2 H, NH_2); ir ($CHCl_3$) 1675 (amide C=O), 1590, 1380, 1100, 975 cm^{-1}.

Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 68.91; H, 10.76; N, 3.66.

Preparation of Cyclopentenone 30 from Bis Acetal 31. A solution of 128 mg (0.334 mmol) of the crude bis acetal **31** in 25 ml of methanol and 8 ml of 20% aqueous sodium hydroxide solution was stirred at reflux for 8 h. The reaction mixture was poured into 150 ml of pH 7 buffer (Beckman) containing a small amount of bromothymol blue. The blue solution was neutralized by dropwise addition of concentrated hydrochloric acid at 0 °C until a light green color was obtained. Dichloromethane extraction[23] gave 95 mg of a brown oil. This material was partially purified by filtration through 15 g of silica gel. Elution with 40 ml of ether gave 48 mg of an oil. This material was dissolved in 7.5 ml of THF and 3 ml of water. To this solution was added 0.3 ml of concentrated hydrochloric acid and the mixture was stirred at 25 °C for 1.5 h. At the end of this period, 0.75 ml of 40% aqueous sodium hydroxide solution and 3 ml of methanol were added. The reaction mixture was stirred at 25 °C for 25 min. The reaction mixture was then poured into 20 ml of 5% hydrochloric acid. Ether extraction[23] gave 44 mg of an orange oil. Chromatography of this material on 15 g of silica gel with 30 ml of 75% ether–petroleum ether, 30 ml of 90% ether–petroleum ether, and finally 60 ml of ether gave 15 mg (14% from lactone **27**) of the cyclopentenone acid **30**.

Isopropyl 4,5-Epoxy-2-hexenoate (33). A solution of 5.8 g (37.7 mmol) of isopropyl sorbate in 100 ml of dichloromethane was cooled to 0 °C. To this solution was added 11.5 g (56.5 mmol) of 85% *m*-chloroperbenzoic acid during a 10-min period. Following this addition, the reaction mixture was stirred at 0 °C for 30 min and at 25 °C for 4 h. Excess peracid was then destroyed by dropwise addition of 10% aqueous sodium bisulfite solution and the product was isolated by ether extraction,[23] including a base wash. The residual liquid was purified by chromatography on 200 g of silica gel. After elution with 500 ml of 10% ether–petroleum ether and then 250 ml of 20% ether–petroleum ether, continued elution with the latter solvent system gave 4.9 g (76%) of the epoxy ester **33**. An analytical sample was obtained by preparative VPC[22] (200 °C, 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple)

followed by evaporative distillation at 40 °C (0.08 mm): NMR ($CDCl_3$) δ 1.25 [d, 6 H, J = 6 Hz, $(CH_3)_2C$], 1.35 (d, 3 H, J = 6 Hz, C-6 H), 2.95 (q of d, 1 H, J = 5 and 2 Hz, C-5 H), 3.13 (dd, 1 H, J = 6 and 2 Hz, C-4 H), 5.07 [septet, 1 H, J = 6 Hz, $(CH_3)_2CHO$–], 6.07 (d, 1 H, J = 15 Hz, C-2 H), 6.67 (dd, 1 H J = 15 and 6 Hz, C-3 H); ir ($CHCl_3$) 1710 (C=O), 1660 (C=C), 1110, 975, 940, 830 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.52; H, 8.36.

Reduction of Ester 33. A. With Lithium in Ammonia. A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to −78 °C. To this stirred solution was added 63 mg (9 mmol) of lithium wire in six freshly cut pieces. After 10 min at −78 °C, a solution of 510 mg (3 mmol) of the ester **33** in 2 ml of dry THF was added to the rapidly stirred reaction mixture as fast as possible. After 40 s, the blue color faded and 9 g of solid ammonium chloride was added. Stirring was continued at −78 °C for 2 min, after which the cooling bath was removed and ammonia allowed to evaporate over 4 h. Dichloromethane extraction[23] gave 480 mg of a colorless oil which was purified further by chromatography on 15 g of silica gel with 50% ether–petroleum ether. After elution with 40 ml of this solvent mixture, continued elution with 80 ml gave 410 mg (79%) of a mixture of alcohols **36a** and **37a**. Analysis by VPC[22] (160 °C, 8 ft × 0.25 in. 10% Carbowax 20M 60 ml/min, thermocouple) indicated that the mixture contained an 89:11 ratio of isomers: NMR ($CDCl_3$) δ 1.22 [d, 6 H, J = 6 Hz, $(CH_3)_2C$], 1.25 (d, 3 H, J = 6 Hz, C-6 H's), 2.3 (br, 1 H, OH), 3.00 (m, 2 H, C-2 H's), 4.27 (m, 1 H, C-5 H), 5.00 [septet, 1 H, J = 6 Hz, $(CH_3)_2CH$–], 5.67 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 3600 and 3400 (OH), 1720 (C=O), 1375, 1110, 1060, 970 cm^{-1}.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.70; H, 9.44.

Isopropyl (*E*)-5-(*tert*-Butyldimethylsilyloxy)-3-hexenoate (36b) and Isopropyl (*Z*)-5-(*tert*-Butyldimethylsilyloxy)-3-hexenoate (37b). Following the procedure of Corey,[18] a mixture of 462 mg (2.69 mmol) of the alcohols **36a** and **37a** from the lithium in ammonia reduction above, 483 mg (3.22 mmol) of TBSCl, and 457 mg (6.73 mmol) of imidazole in 5 ml of dry DMF was stirred at 25 °C for 17 h. Pentane extraction[23] gave 731 mg of a slightly yellow oil which was filtered through 15 g of silica gel with 80 ml of 5% ether–petroleum ether. This afforded 526 mg (68%) of a colorless oil. Analysis by VPC[22] (160 °C, 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple) indicated that this consisted of two isomeric components. The minor isomer (10%) had a retention time of 11.5 min; the major isomer (90%) had a retention time of 13.0 min. These isomers were separated by medium-pressure chromatography[22] on 0.9 × 60 cm of silica gel with 5% ether–petroleum ether at a flow rate of 0.5 ml/min. The more mobile component was the minor isomer which was assigned the Z stereochemistry **37b**. An analytical sample was prepared by evaporative distillation at 50 °C (0.05 mm): NMR ($CDCl_3$) δ 0.03 [s, 6 H, $(CH_3)_2Si$], 0.87 [s, 9 H, $(CH_3)_3CSi$], 1.18 (d, 3 H, J = 6 Hz, C-6 H's), 1.22 [d, 6 H, J = 6 Hz, $(CH_3)_2C$], 1.37 (d, 2 H, J = 5 Hz, C-2 H's), 4.5 (m, 1 H, C-5 H), 5.00 [septet, 1 H, J = 6 Hz, $(CH_3)_2CH$–], 5.55 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 1725 (C=O), 1260, 1110, 915, 875, 835 cm^{-1}, no band at 970 cm^{-1}.

Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.94; H, 10.58.

The less mobile component was the major isomer and was assigned the E stereochemistry **36b**. An analytical sample was prepared by evaporative distillation at 50 °C (0.05 mm): NMR ($CDCl_3$) δ 0.05 [s, 6 H, $(CH_3)_2Si$], 0.90 [s, 9 H, $(CH_3)_3CSi$], 1.20 (d, 3 H, J = 6 Hz, C-6 H's), 1.22 [d, 6 H, J = 6 Hz, $(CH_3)_2C$], 2.98 (d, 2 H, J = 5 Hz, C-2 H's), 4.27 (m, 1 H, C-5 H), 5.02 [septet, 1 H, J = 6 Hz, $(CH_3)_2CHO$–], 5.5 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 1720 (C=O), 1260, 1110, 970, 910, 835 cm^{-1}.

Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 63.00; H, 10.58.

Reduction of Ester 33. B. With Sodium in HMPA–THF, Followed by Silylation with TBSCl. A solution of sodium in HMPA–THF was prepared according to the procedure of House.[17] Titration of an aliquot of this solution with *sec*-butyl alcohol in xylene indicated that it was 0.35 M in sodium. Addition of a second aliquot to water followed by titration with standard HCl to a phenolphthalein endpoint indicated that the solution was 0.32 M in total base.

A solution of 170 mg (1 mmol) of ester **33** in 13.7 ml of THF was cooled to −78 °C. To this rapidly stirred solution was added 5.88 ml (2.0 mmol) of the Na–HMPA–THF solution in one portion. Decolorization occurred after 70 s. After an additional 2 min at −78 °C the yellow solution was treated with 0.65 ml (2.2 mmol) of TBSCl in hexane and was stirred at −78 °C for an additional 2 min. The cooling bath was then removed and the reaction mixture was stirred at 25 °C for 20 min. Pentane extraction[23] gave a yellow oil which was dissolved in 5 ml of THF and treated with 1 ml of 70% aqueous acetic acid solution. This solution was stirred at 25 °C for 1 h to effect hydrolysis of the silyl ketene acetal. Pentane extraction,[23] including a base wash, gave a nearly colorless oil which was purified by chromatography on 10 g of silica gel with 10% ether–petroleum ether. Elution with 35 ml of this solvent mixture gave 113 mg (39%) of a mixture of silyl ethers **36b** and **37b**. Analysis by VPC[22] (160 °C 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple) indicated that this material consisted of a mixture of Z silyl ether **37b** (40%) and E silyl ether **36b** (60%).

C. With Sodium in HMPA–THF Followed by Protonation. A solution of sodium in HMPA–THF[17] was prepared as in B above. Titration of total base with standard HCl indicated that the solution was 0.256 M in sodium. A solution of 170 mg (1.0 mmol) of ester **33** in 43 ml of dry THF and 4 ml of dry HMPA was cooled to −78 °C. To this rapidly stirred solution was added 11.7 ml (3.0 mmol) of the Na–HMPA–THF solution in one portion. The blue color persisted and was discharged after 1 min by addition of 9 g of sodium ammonium chloride. After an additional 2 min at −78 °C, the reaction mixture was allowed to warm to 25 °C over 30 min. Pentane extraction gave 127 mg of a yellow oil which was purified by chromatography on 15 g of silica gel with 50% ether–petroleum ether. After elution with 54 ml of this solvent mixture, continued elution with 40 ml gave 73 mg (42%) of a mixture of alcohols **36a** and **37a**.

D. With Zinc in HMPA–THF.[3] A mixture of 340 mg (2.0 mmol) of epoxy ester **33**, 600 mg (4 mmol) of TBSCl, and 0.5 g of zinc dust in 10 ml of dry THF and 2.5 ml of dry HMPA was stirred at reflux for 16 h. Pentane extraction[23] gave a colorless oil. NMR analysis indicated that this material consisted of only the starting ester **33**.

Enolization of Hydroxy Esters 36a and 37a. A solution of 2.2 mmol of LDA in 20 ml of dry THF was cooled to −78 °C. To this solution was added 4.0 ml of dry HMPA. This rapidly stirred solution was treated with the dropwise addition of 172 mg (1.0 mmol) of a mixture of the hydroxy ester **36a** (90%) and **37a** (10%) in 2 ml of dry THF over 4 min. Following the addition, the reaction mixture was stirred at −78 °C for an additional 2 min and then 0.65 ml (2.2 mmol) of TBSCl in hexane was added in one portion. After an additional 2 min, the reaction mixture was allowed to warm to 25 °C and was stirred for 30 min. Pentane extraction[23] gave a slightly yellow oil which contained none of the starting esters and was identified as the ketene acetal **35** (NMR analysis). This material was dissolved in 5 ml of THF and was treated with 1 ml of 70% aqueous acetic acid. After 1.5 h, VPC[22] analysis (160 °C, 6 ft × 0.125 in., 4% SE-30, 60 ml/min, flame ionization) employing hexadecane as an internal standard (corrected for sensitivities) indicated that the siloxy esters **36b** and **37b** were present in 56% yield. VPC[22] analysis (160 °C, 8 ft × 0.25 in., 10% Carbowax 20M, 60 ml/min, thermocouple) demonstrated that the mixture consisted of 90% of the E ester **36b** and 10% of the Z ester **37b**.

Enolization of the Siloxy Esters 36b and 37b. A solution of 0.6 mmol of LDA in 5 ml of dry THF was cooled to −78 °C and 1.0 ml of dry HMPA was added. To this rapidly stirred mixture was added a solution of 143 mg (0.5 mmol) of a mixture of the silyl ethers **36b** (90%) and **37b** (10%) and 90 mg (0.6 mmol) of TBSCl in 0.5 ml of dry THF over 4 min. After an additional 2 min at −78 °C, the reaction mixture was allowed to warm to 25 °C and was stirred for 30 min. Pentane extraction[23] gave a slightly yellow oil which contained none of the starting esters **36b** or **37b** (NMR analysis). The ketene acetal was hydrolyzed and the reaction mixture analyzed as described above. The siloxy esters were present in 64% yield. This consisted of ester **36b** (90%) and ester **37b** (10%).

Methyl (*E*)-2-Methyl-2-(phenylthio)-4-decenoate (40). A solution of 3.37 g (11.53 mmol) of (*E*)-2-methyl-2-(phenylthio)-4-decenoic acid[3] in 40 ml of dry HMPA was treated with 353 mg of sodium hydride (minrral oil free) in small portions over a 10-min period. Following the addition, the reaction mixture was stirred at 25 °C for 1.25 h and then treated with 2.49 ml (5.68 g, 40 mmol) of iodomethane in one portion. This mixture was stirred at 25 °C for 3 h and then diluted with 100 ml of 5% hydrochloric acid solution. Ether extraction,[23] including a wash with 10% aqueous sodium thiosulfate solution, gave 3.40 g of a slightly yellow oil. This material was purified by chromatography on 170 g of silica gel with 5% ether–petroleum ether. After elution with 540 ml of this solvent system, continued elution with 360 ml gave 3.21 g (91%) of the methyl ester **40**. An analytical sample was prepared by evaporative distillation at 120° (0.05 mm): NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3),

2.00 (m, 2 H), 1.8–2.9 (4 H), 5.43 (m, 2 H, CH=CH), 7.4 (m, 5 H, C_6H_5); ir ($CHCl_3$) 1725 (C=O), 1435, 1375, 1025, 970 cm^{-1}.

Anal. Calcd for $C_{18}H_{26}O_2S$: C, 70.56; H, 8.55; S, 10.46. Found: C, 70.62; H, 8.62; S, 10.49.

Methyl (*E,E*)-2-Methyl-2,4-decadienoate (41) and Methyl (*E*)-2-Methylene-4-decenoate (42). A solution of 3.0 g (9.80 mmol) of the α-(phenylthio) ester **40** in 125 ml of dichloromethane was cooled to 0 °C. To this stirred solution was added a solution of 1.99 g (9.80 mmol) of 85% *m*-chloroperbenzoic acid in 25 ml of dichloromethane over a period of 1 h. Following the addition, the reaction mixture was stirred at 0° for an additional 1 h. Ether extraction,[23] including a base wash, gave a mixture of sulfoxides. This material was dissolved in 65 ml of carbon tetrachloride and was stirred at 60 °C for 2 h. The reaction mixture was cooled to 25 °C and the solvent was removed at reduced pressure. The residue was partially purified by passage through 100 g of silica gel with 200 ml of 30% ether–petroleum ether and afforded 2.0 g of a colorless oil. VPC[22] analysis (200 °C, 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple) indicated that this material consisted of only two volatile components. The minor component (retention time 3.5 min) accounted for 22% of the mixture and the major component (retention time 7.5 min), 78%. These isomers could be separated by medium-pressure chromatography[22] on 2.5 × 50 cm of silica gel with 2% ether–petroleum ether at a flow rate of 2 ml/min. After elution with 380 ml of this solvent system, continued elution with 300 ml gave 387 mg (20%) of the minor component which was identified as the α-methylene ester **42.** An analytical sample was prepared by evaporative distillation at 60° (0.1 mm): NMR ($CDCl_3$) δ 0.5–1.5 (9 H), 2.0 (m, 2 H, C-6 H's), 3.0 (m, 2 H, C-3 H's), 3.77 (s, 3 H, CH_3O), 5.50 (m, 3 H, vinylic H's). 6.15 (br s, 1 H, vinylic H syn to ester); ir ($CHCl_3$) 1715 (C=O), 1630 (C=C), 1435, 1140, 975, 950 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.38; H, 10.18.

After elution with an additional 20 ml of the same solvent system, continued elution with 430 ml gave 1.411 g (73%) of the major isomer which was identified as the fully conjugated isomer **41.** An analytical sample was prepared by evaporative distillation at 60°C (0.05 mm): NMR ($CDCl_3$) δ 0.7–1.6 (9 H), 1.90 (br s, 3 H, vinylic CH_3), 2.2 (m, 2 H, C-6 H's), 3.71 (s, 3 H, CH_3O–), 6.23 (m, 2 H, C-4 H and C-5 H), 7.13 (br d, 1 H, J = 8 Hz, C-3 H); ir ($CHCl_3$) 1700 (C=O), 1640 and 1610 (C=C), 1435, 1110, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.42; H, 10.16.

In a separate experiment it was possible to separate and independently pyrolyze the two diastereomeric sulfoxides. The mixture of sulfoxides from oxidation of 2.0 g (6.54 mmol) of the ester **40** was subjected to chromatography on 200 g of silica gel. After elution with 400 ml of 30% and 300 ml of 40% ether–petroleum ether, continued elution with 225 ml of 50% ether–petroleum ether gave 712 mg of the more mobile sulfoxide contaminated with decomposition products. Further elution with 150 ml of the same solvent mixture gave 346 mg of the less mobile sulfoxide, also contaminated with decomposition products. Rapid rechromatography on 50 g of silica gel with 60% ether–petroleum ether afforde pure samples of each of the sulfoxides.

The more mobile isomer (isomer A, R_f[22] 0.21, 30% ether–petroleum ether, 523 mg) was characterized by the following spectral data: NMR ($CDCl_3$) δ 1.17 (s, 3 H, CH_3), 1.9 (m, 2 H, $=CCH_2$–), 2.60 (d, 1 H, J = 7 Hz, C-3 H), 2.88 (d, 1 H, J = 6 Hz, C-3 H), 3.60 (s, 3 H, CH_3O), 5.43 (m, 2 H, CH=CH), 7.48 (s, 5 H, C_6H_5); ir ($CDCl_3$) 1720 (C=O), 1370, 1080, 1035, 970 cm^{-1}.

The less mobile isomer (isomer B, R_f[22] 0.12 30% ether–petroleum ether, 144 mg) was characterized by the following spectral data: NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.9 (m, 2 H, $=CCH_2$–), 2.37 (d, 1 H, J = 7 Hz, C-3 H), 2.60 (d, 1 H, J = 6 Hz, C-3 H), 3.63 (s, 5 H, C_6H_5); ir ($CHCl_3$) 1725 (C=O), 1375, 1085, 1045, 975, 910 cm^{-1}.

Each sulfoxide was heated in carbon tetrachloride at 60 °C for 2 h. The products were isolated as described above and analyzed by VPC[22] (200 °C, 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple). The following results were obtained.

Sulfoxide	41/42	Yield of olefins
Isomer A (high R_f)	68/32	99% from sulfoxide
Isomer B (low R_f)	90/10	97% from sulfoxide
Original mixture	78/22	93% from ester **40**

Methyl 4,5-Epoxy-2-methyl-2-decenoate (46). The unsaturated ester **41** (3.1 g, 15.8 mmol) was dissolved in 100 ml of chloroform and 40 mg of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide,[27] a free-radical inhibitor, was added. To this solution was added 4.02 g (19.8 mmol) of 85% *m*-chloroperbenzoic acid and the resulting solution was stirred at 25 °C for 6 h. Ether extraction,[23] including a base wash and a 10% aqueous sodium bisulfite wash, gave the crude epoxy ester **46** which was purified by medium-pressure chromatography[22] on 2.5 × 50 cm silica gel with 10% ether–petroleum ether at a flow rate of 2.7 ml/min. After elution with 560 ml of this solvent mixture, continued elution with 300 ml afforded 3.0 g (90%) of the epoxy ester **46** as a colorless oil. An analytical sample was prepared by evaporative distillation at 70 °C (0.1 mm): NMR ($CDCl_3$) δ 0.5–1.7 (11 H), 1.98 (d, 3 H, J = 1.5 Hz, C-2 CH_3), 2.88 (m, 1 H, C-5 H), 3.33 (dd, 1 H, J = 2 and 8 Hz, C-4 H), 3.75 (s, 3 H, CH_3O–), 6.30 (br d, 1 H, J = 8 Hz, C-3 H); ir ($CHCl_3$) 1715 (C=O), 1655 (C=C), 1435, 1315, 1260, 1160, 1105, 915, 870 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.84; H, 9.42.

Methyl (*E*)-5-Hydroxy-2-methyl-3-decenoate (47). A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to −78 °C. To this stirred solution was added 63 mg (9 mmol) of lithium wire in six pieces. This solution was stirred for 10 min at −78 °C and then 636 mg (3.0 mmol) of epoxy ester **46** in 2 ml of THF was added in one portion. The blue color persisted for 1 min at which time it was discharged by addition of 9 g of solid ammonium chloride. After an additional 2 min at −78 °C, the cooling bath was removed, 75 ml of hexane was cautiously added to the reaction mixture, and the ammonia was allowed to evaporate over 4 h. Ether extraction[23] gave 595 mg of colorless oil which was purified by chromatography on 50 g of silica gel with 40% ether–petroleum ether. After elution with 80 ml of this solvent system, contined elution with 20 ml gave 26 mg (4%) of a minor isomer which was tentatively assigned *Z* stereochemistry of ester **47.** An analytical sample was prepared by evaporative distillation at 90 °C (0.05 mm): NMR ($CDCl_3$) δ 0.9–1.5 (12 H), 1.97 (m, 2 H, C-6 H's), 2.5 (m, 2 H, C-2 H and OH), 3.68 (s, 3 H, CH_3O–), 4.28 (m, 1 H, C-5 H), 5.57 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 3600–3400 (OH), 1725 (C=O), 1455, 1005, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.36; H, 10.32.

After elution with an additional 10 ml of the same solvent system, continued elution with 85 ml gave 440 mg (69%) of the major *E* isomer **47.** An analytical sample was prepared by evaporative distillation at 90 °C (0.05 mm): NMR ($CDCl_3$) δ 0.5–1.9 (15 H), 3.13 (m, 1 H, C-2 H), 3.68 (s, 3 H, CH_3O–), 4.07 (m, 1 H, C-5 H), 5.67 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 3600 and 3550–3400 (OH), 1725 (C=O), 1455, 1045, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.22; H, 10.30.

Attempted Hydrolysis of Hydroxy Ester 47. A solution of 140 mg (0.654 mmol) of epoxy ester **46** and 157 mg (6.54 mmol) of lithium hydroxide[28] in 4.7 ml of methanol and 1.6 ml of water was stirred at 25 °C for 2.5 h. After dilution with water and acidification with concentrated hydrochloric acid, ether extraction[23] gave 129 mg (99%) of a nearly colorless oil. TLC[22] analysis (ether) indicated that this consisted of two acid components, the more mobile of which quenched fluorescence. An ether solution of 32 mg of this material was treated with excess diazomethane[29] for 20 min at 0 °C. The excess diazomethane was destroyed by dropwise addition of acetic acid after which ether extraction[23] gave 33 mg of a colorless oil. This material showed only one spot by TLC analysis (50% ether–petroleum ether). Purification was accomplished by medium-pressure chromatography[22] on 0.9 × 60 cm silica gel with ether at a flow rate of 0.5 ml/min. After elution with 26 ml of this solvent, continued elution with an additional 14 ml afforded 31 mg (91%) of a colorless oil. NMR analysis indicated that this consisted of 70% of ester **47** [δ 3.68 (s, CH_3O)] and 30% of another methyl ester [δ 3.73 (s, CH_3O) and 6.90 (br t, J = 7 Hz, vinylic H)] which was tentatively assigned the structure of the methyl ester arising from conjugated acid **49.** Similar results were obtained when the saponification was attempted with potassium hydroxide in methanol.

(*E,E*)-2-Methyl-2,4-decadienoic Acid (43). A mixture of 3.0 g (15.3 mmol) of the methyl ester **41** and 1.5 g of potassium hddroxide in 10 ml of methanol was stirred at reflux for 1.5 h. The reaction mixture was then diluted with 100 ml of water and extracted with two 50-ml portions of ether (extracts discarded). After acidification of the basic solution with concentrated hydrochloric acid, ether extraction[23] gave 2.76 g (99%) of the acid **43** as white crystals,

mp 53–56 °C. The analytical sample was prepared by two recrystallizations of this material from petroleum ether at −20 °C: NMR ($CDCl_3$) δ 0.6–1.8 (9 H], 1.93 (br s, 3 H, C-2 CH_3), 2.2 (m, 2 H, C_6H_5), 6.2 (m, 2 H, C-4 H and C-5 H), 7.3 (d, 1 H, J = 10 Hz, C-3 H), 11.0 (br s, 1 H, CO_2H); ir ($CHCl_3$) 3500–2500 (CO_2H), 1680 (C=O), 1250, 1035, 970 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.34; H, 9.75.

9-Carbamoyl-2-methoxy-2-nonenyl (*E*)-4,5-Epoxy-2-methyl-3-decenoate (50). A. *p*-Nitrophenyl 2-Methyl-2,4-decadienoate (44). A solution of 2.65 g (14.56 mmol) of unsaturated acid **43** in 20 ml of dry triethylamine was cooled to 0 °C. To this solution was added 3.42 g (14.56 mmol) of *p*-nitrophenyl trifluoroacetate[11] in one portion. This homogeneous solution was stirred at 0 °C for 30 min, during which an orange lower layer separated. Stirring was then continued for 3 h at room temperature. Ether extraction,[23] including a base wash and a 20% aqueous monosodium phosphate wash, gave an orange oil which was passed through 50 g of silica gel with 300 ml of dichloromethane. This afforded 3.8 g (86%) of the *p*-nitrophenyl ester **44** as a slightly yellow oil: NMR ($CDCl_3$) δ 0.6–1.6 (9 H), 2.07 (br s, 3 H, C-2 CH_3), 2.2 (m, 2 H, C-6 H's), 6.3 (m, 2 H, C-4 and C-5 H), 7.32 (d, 2 H, J = 9 Hz, aromatic), 8.28 (d, 2 H, J = 9 Hz, aromatic).

B. *p*-Nitrophenyl 4,5-Epoxy-2-methyl-2-decenoate (45). The *p*-nitrophenyl ester **44** (3.8 g, 12.54 mmol) was dissolved in 100 ml of chloroform. To this solution was added 3.19 g (15.68 mmol) of 85% *m*-chloroperbenzoic acid and 40 mg of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide.[27] This mixture was stirred for 2 h at 25 °C and for 2 h at reflux. Ether extraction,[23] including a 10% aqueous sodium bisulfite wash and a base wash, followed by passage of the residue through 40 g of silica gel with 240 ml of dichloromethane, gave 3.55 g (89%) of the epoxy ester **45** as a slightly yellow oil: NMR ($CDCl_3$) δ 0.5–1.9 (11 H), 2.13 (d, 3 H, J = 1.5 Hz, C-2 CH_3), 3.0 (m, 1 H, C-5 H), 3.45 (dd, 1 H, J = 2 and 8 Hz, C-4 H), 6.60 (br d, 1 H, J = 9 Hz, C-3 H), 7.30 (d, 2 H, J = 9 Hz, aromatic), 8.30 (d, 2 H, J = 9 Hz, aromatic).

C. Preparation of Ester 50. A solution of 1.76 g (8.2 mmol) of the hydroxy amide **22a** and 2.62 g (8.2 mmol) of the *p*-nitrophenyl ester **45** in 5 ml of dry THF and 5 ml of dry triethylamine was stirred at 50 °C for 57 h. Extraction[23] with 30% dichloromethane–ether, including a base wash, gave 3.2 g of an orange semisolid. This material was purified by medium-pressure chromatography[22] on 2.5 × 50 cm of silica gel with 30% acetone–ether at a flow rate of 2 ml/min. After elution with 300 ml of this solvent system, continued elution with 240 ml gave 2.17 g (67%) of the epoxy ester **50** as a nearly colorless oil which solidified upon standing. A portion of this waxy solid was dried at reduced pressure to provide the analytical sample: NMR ($CDCl_3$) δ 0.5–1.9 (19 H), 2.02 (s, 3 H, vinylic CH), 2.10 (m, 4 H, $=CCH_2C-$ and CH_2CONH_2), 2.8 (m, 1 H, C-5 H, epoxide), 3.33 (dd, 1 H, J = 2 and 8 Hz, C-4 H, epoxide), 3.50 and 3.60 (s, 3 H total, CH_3O-), 4.62 and 4.65 (s, 2 H total, $=CCH_2O-$), 5.5 (br, 2 H, NH_2), 6.30 (br d, 1 H, J = 8 Hz, $CH=C-CO_2-$); ir ($CHCl_3$) 3530, 3490 and 3400 (NH_2), 1710, (C=O, ester), 1675 (C=O, amide), 1590, 1310, 1155, 870 cm^{-1}.

Anal. Calcd for $C_{22}H_{37}NO_5$: C, 66.81; H, 9.43; N, 3.54. Found: C, 66.90; H, 9.48; N, 3.49.

9-Carbamoyl-2-methoxy-2-nonenyl 5-Hydroxy-2-methyl-3-decenoate (51). A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to −78 °C. To this stirred solution was added 21 mg (3 mmol) of lithium wire in three pieces. This solution was stirred for 10 min at −78 °C, after which 395 mg (1 mmol) of the epoxy ester **50** in 2 ml of dry THF was added in one portion. The blue color persisted for 1 min after which it was discharged by addition of 9 g of solid ammoniun chloride. After an additional 2 min at −78 °C, the cooling bath was removed and the ammonia was allowed to evaporate over 4.5 h. Dichloromethane extraction[23] gave 345 mg of a yellow oil which was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 30% acetone–ether. After elution with 110 ml of this solvent system, continued elution with 75 ml afforded 290 mg (73%) of the hydroxy ester **51**. A portion of this material was dried at reduced pressure to provide the analytical sample: NMR ($CDCl_3$) δ 0.5–1.9 (22 H), 2.08 (m, 4 H, $=CCH_2C-$ and CH_2CONH_2), 3.1 (m, 1 H, $-CHCO_2-$), 3.50 and 3.57 (s, 3 total, CH_3O-), 4.05 (m, 1 H, −CHOH), 4.53 and 4.60 (s, 2 H total, $=CCH_2O-$), 5.63 (m, 4 H, CH=CH and NH_2); ir ($CHCl_3$) 3600–3250 (OH and NH_2), 1725 (C=O, ester), 1675 (C=O, amide), 1590, 1460, 970, 915 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_5$: C, 66.47; H, 9.89; N, 3.52. Found: C, 66.44; H, 9.76; N, 3.45.

4-(6-Carboxyhexyl)-3-(3-hydroxyoctenyl)-5-methoxy-3,5-dimethyloxacyclopentan-2-one (52). A solution of 2.78 mmol of LDA in 10 ml of dry THF was cooled to −78 °C. Following addition of 2.4 ml of dry HMPA, 285 mg (0.718 mmol) of the ester **51** in 2 ml of THF was added dropwise over 4 min to the rapidly stirred solution. After an additional 2 min at −78 °C, 0.840 ml (2.87 mmol) of TBSCl in hexane was added in one portion and stirring was continued for 2 min at −78 °C. The cooling bath was removed and the reaction mixture was allowed to warm to 25 °C, after which the mixture was stirred at reflux for 3 h. Extraction[23] with 75% ether–petroleum ether gave 508 mg of a yellow oil. This material was stirred at reflux with 1.2 g of sodium hydroxide in 6 ml of water and 15 ml of methanol for 16 h. After dilution with water, the reaction mixture was extracted into two 50-ml portions of ether (extracts discarded) and then acidified by addition of 80 ml of 0.4 N sulfuric acid to the ice-cooled, stirred solution. Dichloromethane extraction[23] gave 237 mg of a brown semisolid. This was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with petroleum ether–dichloromethane–THF–acetic acid (50:10:3:2). Following elution with 40 ml of this solvent system, continued elution with 10 ml gave 40 mg of the unsaturated acid **41**. Continued elution with 40 ml gave 44 mg of material which was tentatively identified as the *tert*-butyl dimethylsilyl ether of the desired lactone **52**: NMR ($CDCl_3$) δ 0.07 [s, 6 H, $(CH_3)_2Si$], 0.92 [s, 9 H, $(CH_3)_3CSi$], 2.13 (m, 2 H, $-CH_2CO_2-$), 3.37 (s, 3 H, CH_3O-), 4.07 (m, 1 H, CHOSi), 5.63 (m, 2 H, CH=CH).

After elution with an additional 295 ml of the same solvent system, continued elution with 200 ml gave 65 mg (30%) of the desired lactone acid **52** as a colorless oil. A portion of this material was dried at reduced pressure and provided the analytical sample: NMR ($CDCl_3$) δ 0.6–2.0 (28 H), 2.3 (m, 2 H, CH_2CO_2-), 3.36 (s, 3 H, CH_3O), 4.12 (m, 1 H, −CHOH), 5.7 (m, 2 H, CH=CH), 6.2 (br, 2 H, OH and CO_2H); ir ($CHCl_3$) 3600–3400 (OH), 3200–2600 (CO_2H), 1760 (C=O, lactone), 1710 (C=O, acid), 1380, 1030, 970, 910 cm^{-1}.

Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61. Found: C, 66.52; H, 9.67.

Registry No.—**7a,** 16141-79-0; **7b,** 57679-65-9; **8,** 66-25-1; (*E*)-**9,** 57679-66-0; (*Z*)-**9,** 57679-67-1; (*E*)-**10,** 57679-68-2; (*Z*)-**10,** 57679-69-3; **11,** 38134-43-9; **13,** 38134-44-0; **14,** 57679-70-6; **15,** 1128-08-1; **16,** 57679-71-7; **17,** 57679-72-8; (*EE*)-**18,** 57679-73-9; (*EZ*)-**18,** 57679-74-0; **19,** 13050-09-4; (*E*)-**20a,** 57679-75-1; (*Z*)-**20a,** 57679-76-2; (*E*)-**20b,** 57679-77-3; (*Z*)-**20b,** 57679-78-4; **21a,** 57679-79-5; **21b,** 57679-80-8; (*E*)-**22a,** 57679-81-9; (*Z*)-**22a,** 57679-82-0; **22b,** 57679-83-1; **23,** 57679-84-2; **24,** 57679-85-3; **25,** 57679-86-4; **27,** 57679-87-5; **28,** 57679-88-6; **29,** 57679-89-7; **30,** 57679-90-0; **31,** 57679-91-1; **33,** 27981-16-4; **36a,** 57679-92-2; **36b,** 57679-93-3; **37a,** 57679-94-4; **37b,** 57679-95-5; **40,** 57679-96-6; **40** sulfoxide isomer 1, 57679-97-7; **40** sulfoxide isomer 2, 57679-98-8; **41,** 57679-99-9; **42,** 57680-00-9; **43,** 57680-01-0; **44,** 57680-02-1; **45,** 57680-03-2; **46,** 57680-04-3; **47,** 57680-05-4; **50,** 57680-06-5; **51,** 57680-07-6; **52,** 57680-08-7; **52** TBS ether, 57680-09-8; *p*-nitrophenyl trifluoroacetate, 658-78-6; (*E*)-3-decenoic acid, 53678-20-9; (*E*)-4-decenoic acid, 57602-94-5; isopropyl sorbate, 55584-26-4.

References and Notes

(1) (a) Grateful acknowledgment is made for support for this work by the National Science Foundation and the National Institutes of Health. (b) National Science Foundation Predoctoral Fellow, 1972–1975.
(2) R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94,** 5897 (1972).
(3) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, in press.
(4) W. Grell and H. Machleidt, *Justus Liebigs Ann. Chem.*, **699,** 53 (1966).
(5) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91,** 5675 (1969); J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **46,** 2799 (1963); G. Saucy and R. Borer, *ibid.*, **54,** 2121 (1972).
(6) D. P. Strike and H. Smith, *Tetrahedron Lett.*, 4393 (1970).
(7) G. Stork, G. L. Nelson, F. Rouessac, and O. Gringore, *J. Am. Chem. Soc.*, **93,** 3091 (1971).
(8) R. A. Ellison, *Synthesis*, 397 (1973).
(9) M. Ohno, N Naruse, and I. Terasawa, "Organic Syntheses", Collect Vol. V, Wiley, New York, N.Y., 1973, p 266.
(10) H. C. Brown, "Hydroboration", W. A. Benjamin, New York, N.Y., 1962, p 245.
(11) S. Sakakibara and N. Inukai, *Bull. Chem. Soc. Jpn.*, **37,** 1231 (1964).
(12) D. S. Watt, *Synth. Commun.*, **4,** 127 (1974).
(13) M. W. Rathke and D. F. Sullivan, *Synth. Commun.*, **3,** 67 (1973).
(14) P. M. McCurry, Jr., and K. Abe, *Tetrahedron Lett.*, 1387 (1974).
(15) P. L. Stotter and J. B. Eppner, *Tetrahedron Lett.*, 2417 (1973); G. A. Koppel, *ibid.*, 1507 (1972).
(16) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6,** 1046 (1967); *Bull. Soc. Chim. Fr.*, 791 (1968).
(17) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Am. Chem. Soc.*, **92,** 2783 (1970); H.

O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *ibid.*, **92**, 2800 (1970).
(18) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(19) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, New York, N.Y., 1956, pp 40–42.
(20) B. M. Trost and T. N. Salzmann, *J. am. Chem. Soc.*, **95**, 6840 (1973).
(21) E. J. Corey, C. S. Shiner, R. P. Volante, and C. R. Cyr, *Tetrahedron Lett.*, 1161 (1975).
(22) Boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-60 spectrometer. Chemical shifts are reported as δ values in parts per million relative to Me_4Si (δ Me_4Si 0.0 ppm) as an internal standard. Deuteriochloroform for NMR and chloroform for ir spectra were filtered through neutral alumina before use.

Vapor phase chromatographic (VPC) analyses were determined on either a Hewlett-Packard 5750 equipped with a flame ionization detector or a Varian 920 equipped wihh a thermal conductivity detector using helium as the carrier gas under the indicated conditions. The indicated liquid phase was absorbed on 60–80 mesh Chromosorb W AW DMCS.

Silica gel columns used the 0.05–0.2-mm silica gel manufactured by E. Merck & Co. Darmstadt, Germany. Acidic silica gel refers to Silicar CC-4 special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Mo. Preparative medium-pressure chromatography was performed using glass columns of the indicated length and diameter with fittings supplied by Laboratory Data Control, Riviera Beach, Fla., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck & Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

Analytical thin layer chromatography was conducted on 2.5 × 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck & Co., Darmstadt, Germany.

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride; pyridine, triethylamine, diisopropylamine, *N*-isopropylcyclohexylamine, trimethylchlorosilane (TMSCl), hexamethylphosphoramide (HMPA), benzene, and toluene were distilled from calcium hydride; dimethylformamide (DMF) was dried over 4A molecular sieves and fractionally distilled at reduced pressure; methanol was dried over 3A molecular sieves; ammonia was distilled from a blue solution of sodium directly into the reaction flask; dichloromethane, methyl iodide, and hexane was distilled from phosphorus pentoxide. Petroleum ether refers to the Analyzed Reagent grade hydrocarbon fraction, bp 30–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Diisobutylaluminum hydride (DIBAH) was used as a standard solution in benzene (ca. 1.0 M). Lithium isopropylcyclohexylamide (LICA) and lithium diisopropylamide (LDA) were prepared as described previously.[3] Standard solutions of *tert*-butyldimethylchlorosilane (TBSCl) in hexane (ca. 3.3 M) or HMPA (ca. 1.5 M) were employed.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(23) In cases where the products were isolated "by solvent extraction", the procedure generally followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic layers were washed with several portions of water followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the organic solution with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, espectively, prior to the aforementioned wash with water.
(24) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 584.
(25) M. Gouge, *Ann. Chim. (Paris)*, **6**, 648 (1951).
(26) N. H. Anderson, *J. Lipid Res.*, **10**, 316 (1969).
(27) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, H. Kakoi, *J. Chem. Soc., Chem. Commun.*, **64**, (1972).
(28) E. Andre and J. Henry, *C. R. Acad. Sci.*, **263**, 1084 (1966).
(29) H. M. Fales, T. M. Jaouni, and J. F. Babashak, *Anal. Chem.*, **45**, 2302 (1973).

Carbon-13 Nuclear Magnetic Resonance Spectra of Morphine Alkaloids[1]

Frank I. Carroll,*[2a] Charles G. Moreland,[2b] George A. Brine,[2a] and John A. Kepler[2a]

Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina 27709, and Department of Chemistry, North Carolina State University at Raleigh, Raleigh, North Carolina 27607

Received September 22, 1975

Carbon-13 chemical shifts were measured for 25 morphine, 14-hydroxymorphine, and 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine compounds. The signal due to each carbon was assigned. The ^{13}C assignments of the protonated carbons were aided by single frequency off-resonance decoupling experiments and were confirmed in questionable cases by deuterium labeling experiments. Substituent effects were used to assign chemical shifts to nonprotonated as well as protonated carbons. Comparison of the chemical shifts of the morphine and 14-hydroxymorphine systems to those of the 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine systems showed that the spatial configuration of rings A, B, and D of the two systems was similar. The ^1H and ^{13}C NMR data for the various compounds were compared.

It has been demonstrated that natural abundance carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy is an extremely useful physical method for the structure elucidation of alkaloids. Although several papers have presented correlations of structure with ^{13}C NMR spectra for many classes of alkaloids,[3] only limited studies have been reported for the physiologically and sociologically important morphine series of alkaloids.[4,5]

As a result of the continuing interest in the chemistry and pharmacology of the morphine class of alkaloids, we have synthesized many of the more active morphine type narcotics and narcotic antagonists as well as several of their biotransformation products. In this paper we present a study of the ^{13}C NMR spectra of the morphine alkaloids **1–11** shown in Chart I. The structures shown in Chart I are planar representations of the various morphine systems and illustrate the numbering used throughout this paper.

X-ray analysis of morphine (**1a**) hydriodide has shown that ring B is rigidly held in a distorted half-chair form and that rings C and D possess a boat and a chair form, respectively, with the 6α substituent in a bowsprit orientation.[6] ^1H NMR studies have shown that morphine as well as other Δ^7-morphine type alkaloids including 14-hydroxy analogues possess a similar conformation.[7] In contrast the ^1H NMR data[7] and chemical behavior[8] show that ring C of the C-7, C-8 saturated compounds such as **2a, 2b, 7a,** and **7b** exists in a chair conformation in which the 6α substituent is axial. The absolute stereochemistry of 19-propylthevinol (**9c**) hydrobromide has been established by an x-ray crystallographic study and shown to be as represented in struc-