on silica gel (100 g) with toluene–hexane (1:4). The complex **6** was recovered: 71% yield; mp 78 °C; IR (cyclohexane) $\nu_{C\equiv O}$ 2017 (s), 1955 (vs), 1945 (vs); $^{31}P$ NMR ($C_6D_6$) $\delta$ −24.9 (s); $^1H$ NMR ($C_6D_6$) $\delta$ 5.87 (d, 1 H, $^3J_{P-H}$ = 2.9), 6.7–7.5 (m, 15 H, phenyl); $^{13}C$ NMR ($C_6D_6$) $\delta$ 223.79 (s, CO) 117.0 (d, C$\alpha$, phospholyl, $^1J_{C-P}$ = 60.3), 120.0 (d, C$\alpha$, phospholyl, $^1J_{C-P}$ = 63.3) 114.3 (d, C$\beta$, phospholyl, $^2J_{C-P}$ = 5.9), 94.6 (d, CH$\beta$, phospholyl, $^2J_{C-P}$ = 4.4), 135–126 (m, phenyl C); mass spectrum (70 eV, 170 °C), *m/e* (relative intensity) 450 (M, 15), 394 (M − 2CO, 23), 366 (M − 3CO, 100). Anal. Calcd for $C_{25}H_{16}MnO_3P$: C, 66.66; H, 3.55; P, 6.89. Found: C, 66.61; H, 3.75; P, 6.93.

**1-Methyl-2,3,5-triphenylphosphole (7).** A solution containing 0.01 g of lithium and 0.311 g of **3** in 10 mL of THF was stirred for 2 h at room temperature. The mixture became dark brown. A solution containing 0.16 g of $ICH_3$ in 3 mL of THF was then added dropwise, and the mixture was stirred for 1 h at room temperature. The solvent was evaporated, and the residue was chromatographed on silica gel (50 g) with toluene–hexane (1:4). Yellow product **7** was recovered: 0.2 g (61% yield); mp 118 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.31 (d, 3 H methyl, $^2J_{P-H}$ = 1), 7–7.7 (m, 15 H phenyl + 1 H phospholyl); $^{31}P$ NMR ($CDCl_3$) $\delta$ 0.47 (s); mass spectrum (70 eV, 150 °C) *m/e* (relative intensity) 326 (M, 100). Anal. Calcd for $C_{23}H_{19}P$: C, 84.66; H, 5.83; P, 9.51. Found: C, 84.81; H, 5.57; P, 9.62.

**Synthesis of Phosphorins from 1,2,5-Triphenylphosphole and Alkynes 9.** A mixture of alkyne and 1,2,5-triphenylphosphole (molar ratio 1.3:1) was heated in a sealed tube at 230 °C for 4 days. All phosphorins were chromatographed on silica gel (50 g of silica gel/g of product) with toluene–hexane (1:4). **9b** was recrystallized in hexane; **9a,c,d** were purified by vacuum distillation. When the alkyne was not very stable at 230 °C, e.g., phenylacetylene or unreactive, e.g., bis(trimethylsilyl)acetylene, the major product was the hexaphenylbiphospholyl **3**. With stable and reactive alkynes, e.g., tolane, 3-hexyne or phenylmethylacetylene, the reaction was almost complete, and the major product was the phosphorin **9**. Physical and spectroscopic data are presented in Table I.

**Registry No.** 1, 1162-70-5; **3**, 81390-27-4; **5**, 81408-80-2; **6**, 81408-81-3; **7**, 81390-28-5; **9a**, 81390-29-6; **9b**, 79032-30-7; **9c**, 81390-30-9; **9d**, 81390-31-0; phenylacetylene, 536-74-3; bis(trimethylsilyl)-acetylene, 14630-40-1; tolan, 501-65-5; 3-hexyne, 928-49-4; phenylmethylacetylene, 673-32-5; $Mo(CO)_6$, 13939-06-5; $Mn_2(CO)_{10}$, 10170-69-1.

# Prostaglandins. 3. Synthetic Approaches to 11-Deoxyprostaglandins[1]

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A straightforward synthesis is described of *dl-trans*-2-[6-(methoxycarbonyl)hex-2(*Z*)-enyl]-3-formylcyclopentanone (**5**), a versatile intermediate for the synthesis of 11-deoxyprostaglandins and their analogues. Base-catalyzed cyclization of 1,2,4-tris(methoxycarbonyl)butane under kinetically controlled conditions led to (70%) *trans*-2,3-bis(methoxycarbonyl)cyclopentanone (**3**). Treatment of **3** with hot benzyl alcohol gave (80%) *trans*-2-(benzyloxycarbonyl)-3-(methoxycarbonyl)cyclopentanone (**25**), which was purified as its copper chelate. Alkylation of **25** with 6-cyanohex-2-ynol mesylate (**20**) with NaH/dimethoxyethane afforded 82% 2-(6-cyanohex-2-ynyl)-2-(benzyloxycarbonyl)-3-(methoxycarbonyl)cyclopentanone (**26**). Catalytic reduction of **26** in ethanol/pyridine, using a $Pd/BaSO_4$ catalyst followed by warming, gave (91.5%) a 9:1 mixture of *trans*-2-(6-cyanohex-2(*Z*)-enyl)-3-(methoxycarbonyl)cyclopentanone (**27**) and its 2,3-dihydro derivative **29**. Chromatography of the corresponding carboxylic acids gave the pure acid **30** (69% from **26**). Reduction ($NaBH_4$) of the acid chloride (**31**) of acid **30** led to a mixture of diols **32**. Saponification of the nitrile group of **32** afforded the C-1 epimeric mixture of the diol acids **33**, which on $CH_2N_2$ esterification (69% from **31**) and Collins oxidation afforded (92%) the desired **5**. A second route to **5** also was explored. Cyclization (*t*-BuOK/*t*-BuOH) of 4-[2-(methoxycarbonyl)ethyl]-tetrahydrofuran-2-one (**12**) led to *cis*-hexahydro-1*H*-cyclopenta[*c*]furan-1,6-dione (**4**), which when alkylated (*t*-BuOK/*t*-BuOH) with **20** gave (90%) the C-6a alkylation product **35**. Alkaline saponification of **35** led to *trans*-2-(6-cyanohex-2-ynyl)-3-(hydroxymethyl)cyclopentanone (**36**) in only modest yield (15%). A four-step sequence of catalytic reduction, nitrile hydrolysis, acid esterification, and oxidation then gave **5**, in 44% overall yield from **36**.

## Introduction

In a recent paper[3] we described a total synthesis of (+)-prostaglandin $F_{2\alpha}$ (**1**) from chiral precursors. Concurrent with that research, we had established a program to develop a synthetic route to the 11-deoxyprostaglandins which have biological activity[4a] in their own right. A typical representative of this class is 11-deoxyprostaglandin $E_1$ (**2**), which has potent bronchodilating activity.[4b] Other prostanoids of the 11-deoxy series are excellent inhibitors[4c] of gastric juice secretion.

## Synthesis of 2,3-Disubstituted Cyclopentanones

In our earlier work[3] the cyclopentanone intermediates that we had used did not lend themselves to synthesis[5] in

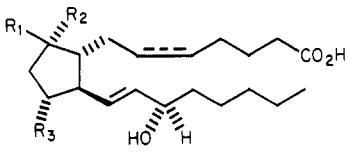
(1) Most of the work described in this paper is the subject of two patents: White, W. L.: Johnson, F. U.S. Patent 4 125 556, Nov 14, 1978 (Appl. May 19, 1971) and U.S. Patent 4 146 553, Mar 27, 1979 (Appl. June 19, 1978).

(2) This author's contributions were made largely prior to 1974, as a member of the Dow Chemical Co., Eastern Research Laboratory, Wayland, MA.

(3) Johnson, F.; Paul, K. G.; Favara, D.; Ciabatti, R.; Guzzi, U. *J. Am. Chem. Soc.* **1983**, *103*, in press.

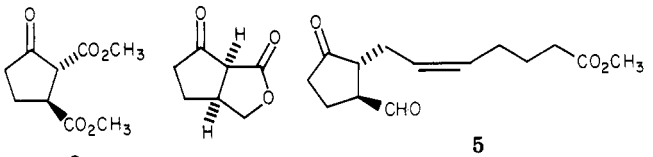
(4) (a) Bartmann, W.; Beck, G.; Lerch, U.; Teufel, H.; Babej, M.; Bickel, M.; Schoelkens, B.; Seeger, K. In "Chemistry Biochemistry and Pharmacological Activity of Prostanoids"; Roberts, S. M., Scheinmann, F., Ed.; Pergamon Press: Elmsford, NY, **1979**, p 195. (b) Greenberg, R.; Smorong, K.; Bagli, J. F. *Prostaglandins* **1976**, *91*, 961. (c) Caten, M. P. L.; Broughton, B. J.; Coffee, E. C. J.; Darnbrough, G.; Palfreyman, M. N.; Parker, T., in ref 4a, p 27.

0022-3263/82/1947-2379$01.25/0 



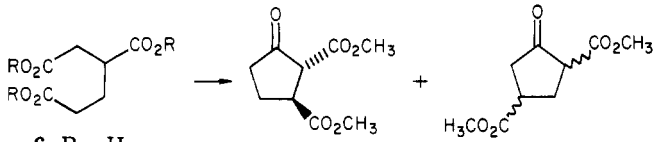
1, $R_1$ = H; $R_2$ = OH; $\Delta^5$ double bond
2, $R_1$, $R_2$ = O; $R_3$ = H; 5,6 saturated

the 11-deoxy series. We, therefore, directed our efforts to two other potential cyclic intermediates, namely, **3** and **4**. Both of these compounds could be expected to allow introduction of the $\alpha$ side chain by direct alkylation. In addition, the further transformation to **5**, an intermediate already demonstrated[6] to be useful in the synthesis of 11-deoxyprostaglandins, could be expected to be reasonably straightforward. The choice of such compounds as **3** and **4** as synthetic intermediates had a second advantage, namely, that they should allow the introduction of a wide variety of $\alpha$ and $\beta$ side chains, an objective clearly desirable in a program also directed toward analogue synthesis.



**3** **4** **5**

The keto diester **3** was already known[7] to the literature in admixture with its 2,4-bis(methoxycarbonyl) isomer **8**, having been obtained by the Dieckmann cyclization of esters of **6**. The trimethyl ester **7**, necessary for this cyclization, had been prepared in the past by divers methods.[7] However, for large-scale work we consider that the most convenient consists of the nitric acid oxidation[8] (catalyzed by copper powder and ammonium vanadate) of the commercially-available methyl cyclohex-3-enecarboxylate to give the acid **6** followed by esterification under the conditions of Clinton and Laskowski.[9] The overall yield of **7** is 65% and reactions on a 5-mol scale can be performed with little trouble.

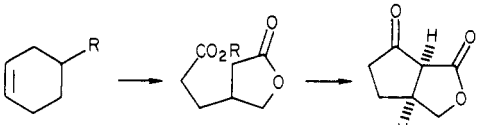


**6**, R = H
**7**, R = $CH_3$ **3** **8**

In the earlier work[7,10] on the cyclization of the esters of **6**, it could be noted that although variations in the choice of solvent seemed to change the ratios of **3** to **8**, the desired isomer **3** could not be obtained to the exclusion of the other. Our own experiments with **7** initially did not lead to any improvement. Cyclization in xylene solution of 80 °C with sodium hydride and a trace of methanol, for example, led to a 74% yield of **3** and **8** in a ratio of 4:1, and although these isomers cannot be separated by distillation, the method of Ruzicka[10] allows **3** at least to be separated in a pure state.

In this procedure **3** is extracted selectively into aqueous solution by a mixture of equal volumes of 2 N sodium carbonate and saturated sodium bicarbonate solutions. Acidification then gives *trans*-2,3-bis(methoxycarbonyl)-cyclopentanone (**3**) in a pure state as judged by GLC and $^1$H NMR analyses. However, this could not be regarded as a suitable solution to the problem because the yield of pure **3** could not be raised above 40%. A reexamination of our own results and those of previous workers then indicated that all previous cyclizations had been performed with use of conditions under which **3** and **8** might be interconverted (via **7**), i.e., under conditions of thermodynamic control. Logic suggested that because of the inductive effect of the methoxycarbonyl at C-3, the hydrogens at C-2 in **7** ought to be more acidic than those at C-5. Thus, cyclization ought to be faster kinetically at C-2 than at C-5. In an attempt to exploit this idea, the cyclization was repeated so that the temperature never rose above 25 °C, heat evolution being controlled by an ice bath. This immediately bore results, for after acidic workup the product isolated now contained >90% of **3**, as indicated by GLC. Fortuitously one of the batches crystallized after distillation, and thereafter purification could be accomplished directly by one recrystallization from ether/petroleum ether. Yields of 70% of pure **3** were obtained routinely, even on a 0.6-mol scale.

The synthesis[11] of **4** again started from a substance available in bulk, namely, **9**. Reduction[12] of **9** with sodium borohydride gave **10**, which on ozonolysis, followed by treatment with peracetic acid, led to the lactonic acid **11**. Fischer–Speier esterification then gave the methyl ester **12** in 75% overall yield. Attempts to cyclize **12** under

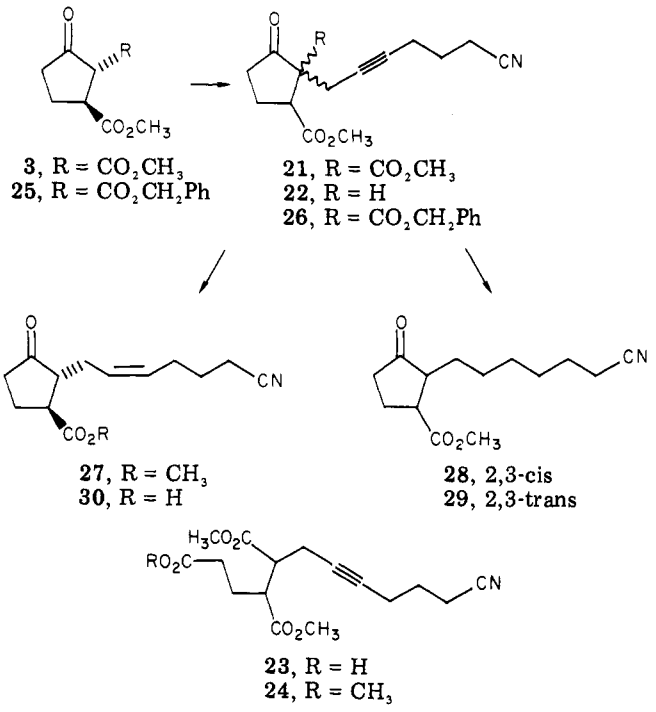


**9**, R = CHO **11**, R = H
**10**, R = $CH_2OH$ **12**, R = $CH_3$ **4**

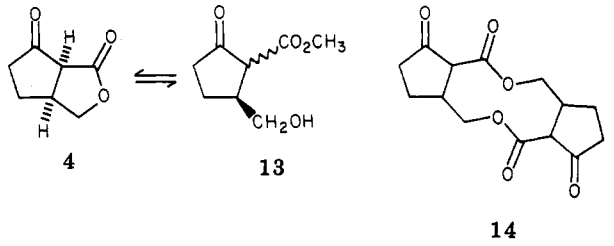
normal Dieckmann conditions ($CH_3ONa/CH_3OH$) or by means of NaH/DME led to only small quantities of the desired **4**. Much better yields were obtained by using *t*-BuOK/*t*-BuOH at <20 °C. However, **4** is not obtained pure directly. Apparently the cyclization initially gives **4**, but this then, in part, is opened by the methoxide ion released in the initial step of the process to give **13**. However, despite these complications, if during the isolation procedure the crude product is heated briefly to 160 °C, **13** is reconverted to **4** and the latter can be obtained in 63% yield. A trace amount of crystalline dimer also is obtained. Initially we thought that this compound had structure **14** and was derived from the interactions of **4** and **13**. However, the spectroscopic data do not support this. In particular, in the mass spectrum there is a major loss of a fragment of mass 73 ($C_3H_5O_2$ or $C_4H_9O$) which is difficult to reconcile with structure **14**. In addition, the

(5) For a recent review of other syntheses in the 11-deoxy series, see Mitra, A. In "The Synthesis of Prostaglandins"; Wiley: New York, 1977; pp 337–352.
(6) Bagli, J.; Bogri, T. *Tetrahedron Lett.* **1972**, 3815.
(7) Kay, F. W.; Perkin, W. H. *J. Chem. Soc.* **1906**, *89*, 1640. Shemyakin, M. M.; Schchukina, L. A.; Vinogradova, E. I; Kolosov, M. N.; Vdovina, R. G.; Karapetyan, M. G.; Rodionov, V. Ya.; Ravdel, G. A.; Shvetsov, Yu. B.; Bamdas, E. M.; Chaman, E. S.; Ermolaev, K. M.; Semkin, E. P. *Zh. Obschch. Khim.* **1957**, *27*, 742. Toki, K. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 233. Kasturi, T. R. *Ind. Inst. Sci., Golden Jubilee Res. Vol. 1909–1959*, 40 (*Chem. Abstr. 55*, 23371). Vul'fson, N. S.; Zaretskii, V. I. *Zh. Obshc. Khim.* **1964**, *34*, 828 (*Chem. Abstr. 60*, 15757).
(8) Lynn, J. W.; Roberts, R. L. U.S. Patent 3118935 (Jan 21, 1964).
(9) Clinton, R. O.; Laskowski, S. C. *J. Am. Chem. Soc.* **1948**, *70*, 3135.
(10) Ruzicka, R.; Almeida, A. B.; Brock, A. *Helv. Chim. Acta* **1934**, *17*, 183.
(11) After this work was completed, the synthesis of **4**, by essentially the same method, was reported by Boeckmann, R. K.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752. A different synthesis has been reported by Goldsmith, D. J.; Thottathil, J. K. *Tetrahedron Lett.* **1981**, 2447. A general approach to this type of bicyclic structure also has been described recently [Morizawa, Y.; Hiyama, T.; Nozaki, H. *Ibid.* **1981**, 2297] although the parent compound, **4**, was not reported.
(12) Skinner, C. G.; Ravel, J. M.; Shive, W. *Arch. Biochem. Biophys.* **1959**, *80*, 416.

Scheme I

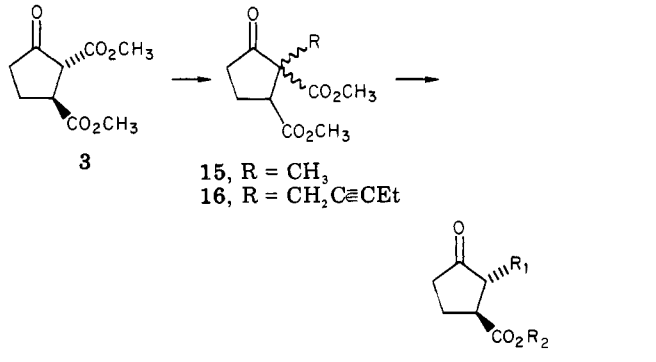


material does not give a color with $FeCl_3$ solution, indicating the absence of an enolic system. Further investigation of this compound was not pursued.

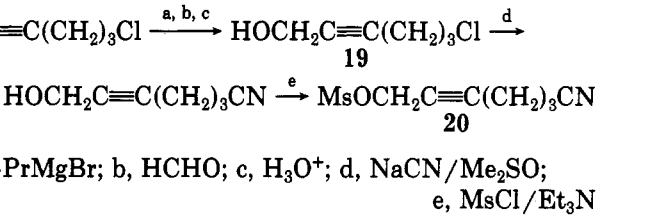


## Introduction of the α Side Chain

Prior to attempts to introduce the complete α side chain, some simple alkylation experiments were performed with **3**. Treatment of the sodium salt of **3** in 1,2-dimethoxyethane with methyl iodide afforded a mixture of isomers, **15**, which when subjected to acid hydrolysis gave the keto acid **17** as a single crystalline product. This was found



to be identical with an authentic sample prepared by an unambiguous route according to Newman and McPherson,[13] thus proving absolutely not only the structure of **3** but also demonstrating that the desired C-alkylation could be accomplished. Alkylation with pent-2-ynyl mesylate (an easily available model for the slightly more complex side chain that we planned to use) also led to an 80% yield of a mixture of C-2 stereoisomers (**16**) but in this case was accompanied also by 5–7% of the product of O-alkylation. The latter was easily removed, however, by chromatography. The removal of the 2-methoxycarbonyl group of **16** was effected by treatment with 3 equiv of lithium iodide dihydrate in boiling collidine.[14] This afforded **18** in 61% yield after distillation, and it is interesting to note that the 3-methoxycarbonyl group resisted demethylation under these conditions. The alkylating agent **20** required for the introduction of the prostaglandin α side chain was prepared[15] via the chloro alcohol **19** as shown.



a, *i*-PrMgBr; b, HCHO; c, $H_3O^+$; d, $NaCN/Me_2SO$; e, $MsCl/Et_3N$

This method is adaptable to large-scale synthesis and **20** was prepared routinely in 50–60-g quantities, in 50% overall yield.

The alkylation of **3** with **20** was then conducted, using the conditions described for the preparation of **16**, and led to a 95% yield of a mixture of C- and O-alkylated products. From this the highly dominant C-alkylated product **21** (a C2–C3 cis and trans mixture) was separated in 86% yield by chromatography over silica gel as a viscous faintly yellow oil (Scheme I). The removal of the 2-methoxycarbonyl group, however, proved to be unexpectedly difficult. The use of lithium iodide/collidine, which had served so well in the case of **16**, led not only to **22** (50%) but also to the product of ring cleavage, whose structure was assigned as a mixture of diastereoisomers represented by **23**, by a spectroscopic examination of their methyl esters (**24**). Slightly better results were obtained when $Me_2SO/NaCl$[16] at 160 °C was used, in place of LiI/collidine, and although **22** is easily separable from **23**, the method was not practicable for large-scale work. We, therefore, retraced our steps and converted **3** to the mono(benzyloxycarbonyl) derivative **25** by the method of Baker et al.[17] and purified it via its copper chelate. The alkylation of **25** to **26** proceeded smoothly, giving better than an 80% yield, after chromatographic removal of the O-alkylated contaminant. Exhaustive reduction of **26** with hydrogen and a palladium-on-carbon catalyst, in ethyl acetate, then led quantitatively to a 1:1 mixture, as might be expected, of the cis and trans isomers **28** and **29**, respectively. On the other hand, when a palladium-on-calcium carbonate catalyst was used in ethanol/pyridine as the solvent, the product, obtained in quantitative yield, comprised solely the trans isomer **29**. Finally, when a palladium-on-barium sulfate catalyst was utilized under

(13) Newman, M. S.; McPherson, J. L. *J. Org. Chem.* **1954**, *19*, 1717.

(14) Elsinger, F. *Org. Synth.* **1965**, *45*, 7.

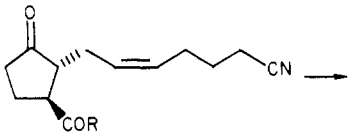
(15) We thank Dr. D. Favara (Gruppo Lepetit Spa, Milano, Italy) for the experimental details for the preparation of **19**, **20**, and its mesylate. Although the chloroalcohol **19** has been prepared several times in the past, the simplest method is that of the French workers: Marzak, I.; Guermont, J. P. *C. R. Hebd. Seances Acad. Sci.* **1956**, *242*, 141; Marzak-Fleury, A. *Ibid.* **1964**, *259*, 4071. We report experimental details for this compound because the original publications did not contain them.

(16) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957.

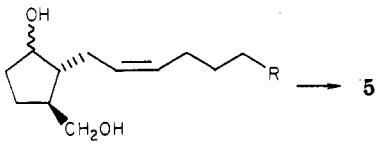
(17) Baker, B. R.; Schaub, R. E.; Querry, M. V.; Williams, J. H. *J. Org. Chem.* **19528** *17*, 77.

the latter conditions, the reduction became very slow after the absorption of 2 equiv of hydrogen and it was possible (after warming to promote decarboxylation) to isolate a product that contained 90% of the desired *trans*-2-(6-cyanohex-2(*Z*)-enyl)-3-(methoxycarbonyl)cyclopentanone (**27**), together with 10% of the 2,3-dihydro isomer **29**. When the mixture was saponified by aqueous methanolic sodium carbonate, and the product was purified by careful chromatography over silica gel, the pure acid **30**, devoid of overreduction products, could be isolated in 69% overall yield from **26**.

The completion of the synthesis of **5** was then carried out as shown below. Reduction of the acid chloride **31** of acid **30**, by means of excess sodium borohydride in aqueous dioxane,[18] afforded a mixture of diols **32**, which were hydrolyzed to the corresponding carboxylic acids, using aqueous methanolic potassium hydroxide. Treatment of the latter with diazomethane then led to the methyl esters **34**, the overall yield from **30** being 69%, and no formal purification is required. The final step, the conversion of the mixture of esters **34** to the desired keto aldehyde **5**, was accomplished by Collins oxidation in 92% yield in methylene chloride.[19] The product **5**, a colorless mobile oil, proved to be a single compound and was judged to be pure by both chromatographic and spectroscopic techniques. Its physical constants were identical with those reported in the literature.[6]



**30**, R = OH
**31**, R = Cl



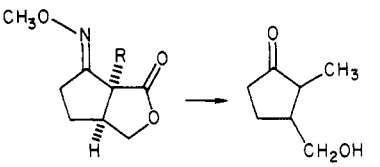
**32**, R = CN
**33**, R = $CO_2H$
**34**, R = $CO_2CH_3$

Having achieved our objective starting from intermediate **3**, we now turned our attention to intermediate **4**. The basis of our studies with this compound was the hope that some of the problems associated with the synthesis beginning with **3** could be avoided. Most noteworthy of these were (a) our inability to control completely the double reduction of the acetylenic benzyl ester **26** to give solely **27** and (b) the somewhat tedious sequence of steps associated with the conversion of the 3-methoxycarbonyl group to an aldehyde.

Alkylation of the potassium salt of **4** in *tert*-butyl alcohol with 6-cyanohex-2-ynyl mesylate (**20**) proceeded smoothly at room temperature to give the desired product, **35**, in 90% yield (Scheme II). Nevertheless, the hydrolysis of **35** proved to be the Achilles' heel of this approach. Attempts to convert **35** to **36** under acidic conditions did not give rise to discrete products. On the other hand, whereas specific basic conditions did lead to modest yields (15%) of the desired substance **36**, the major product was a mixture of acids, **37**, derived from an initial cleavage of the cyclopentanone ring. Even very mild basic conditions produced mainly **37**.

(18) Chaiken, S. W.; Brown, H. C. *J. Am. Chem. Soc.* **1949**, *71*, 122.
(19) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

In an attempt to avoid the low yields of **36** that were obtained in the hydrolysis step, a model study was made of the methoxime (**41**) of **4**. Alkylation of the potassium salt of **41** with methyl iodide smoothly led to the desired compound **42**. However, in this case, base hydrolysis merely led to opening of the lactone ring without decarboxylation and acidification simply regenerated **42**. When the base hydrolysis of **42** was conducted at 160 °C in a sealed tube for 1 h in the presence of copper powder, only a trace amount of a neutral fraction was obtained which, from its mass spectral characteristics [$m/z$ 128 ($M^+$)] appeared to be the desired compound **43**. Nevertheless it was accompanied by recovered **42** and much dark tarry material. Further attempts to develop an efficient method of converting **35** to **36**, therefore, were abandoned at this point.



**41**, R = H
**42**, R = $CH_3$

**43**

It is unfortunate that **36** could be produced in only low yield since its conversion to **5** proved to be relatively simple. Catalytic reduction in pyridine with a palladium-on-barium sulfate catalyst led to **38** (82% yield) with no overeduction, and the latter on strong base hydrolysis then afforded the acid **39**. This, without characterization, was converted directly to the methyl ester **40**, using diazomethane, and oxidation of the latter with Collins reagent gave **5**, identical in all respects with the sample prepared previously.

## Experimental Section[20]

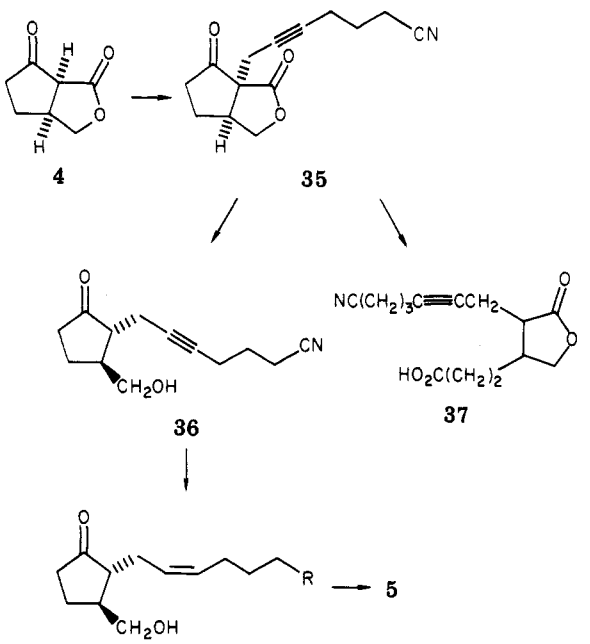
**1,2,4-Tricarboxybutane (6).** To a mechanically stirred mixture of nitric acid (2150 g, 71%) water (900 mL), ammonium vanadate (2.2 g), and copper powder (5.5 g) was added methyl cyclohex-3-enecarboxylate (700 g) during 2 h. The reaction was exothermic and the temperature of the mixture was kept at 50–55 °C by an ice bath. After a further 2 h at this temperature the cooling bath was removed and the green solution was stirred at 25 °C for 48 h. The volatiles were removed cautiously at reduced pressure and the viscous residue was triturated in an ice–salt bath with $CH_2Cl_2$ (1 L). The resulting crude solid was removed by filtration, using a sintered-glass funnel, and washed well with $CH_2Cl_2$. The still damp solid was dissolved at reflux in EtOAc (2.1 L), decolorized by treatment with activated charcoal (30 g), and rapidly filtered while hot through Celite. The faintly yellow solution was diluted immediately with $CH_2Cl_2$ (2.1 L) and allowed to stand overnight. This afforded 1,2,4-tricarboxybutane (779 g, 82%) as colorless rhombohedral crystals, mp 118.5–120 °C (lit.[8] mp 124 °C). A sample recrystallized from EtOAc had mp 123–124 °C.

Anal. Calcd for $C_7H_{10}O_6$: C, 44.21; H, 5.30. Found: C, 43.97; H, 5.09.

**1,2,4-Tris(methoxycarbonyl)butane (7).** A mechanically stirred mixture of 1,2,4-tricarboxybutane (500 g), $CH_3OH$ (800

(20) All melting points were determined with a Thomas-Hoover "Uni-Melt" capillary melting-point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 grating spectrometer using NaCl plates. $^1H$ NMR spectra were recorded on a Varian MV-14 instrument at 60 MHz using $Me_4Si$ as an internal standard and are measured in δ. Mass spectra were recorded on either an AEI MS 12 or an MS 30 instrument. Column chromatography was performed on columns packed with J. T. Baker ("Baker Analyzed") silica gel powder (60–200 mesh). Elution systems were established by preliminary TLC, using Brinkmann TLC silica gel precoated glass plates (60-F254). Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, TN.

Scheme II



4 35 36 37

38, R = CN
39, R = $CO_2H$
40, R = $CO_2CH_3$

g), concentrated sulfuric acid (10 mL), and 1,2-dichloroethane (2.35 L) was heated under reflux for 6 h. The lower layer was reduced to small bulk under reduced pressure and the residual liquid was diluted with benzene (1 L), washed with saturated $NaHCO_3$ solution (2 × 500 mL) and then brine (3 × 500 mL), and finally dried ($MgSO_4$). The yellow oil obtained after removal of the benzene was fractionated, using a 15 in. Vigreaux column, and afforded the desired triester **7** (482 g, 79%) as a colorless mobile oil: bp 98–101 °C (0.1 mmHg); IR (neat) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.33 (m, 7 H), 3.67 (s, 6 H, $OCH_3$), 3.70 (s, 3 H, $OCH_3$).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.64; H, 7.01.

***trans*-2,3-Bis(methoxycarbonyl)cyclopentanone (3).** To a stirred suspension of sodium hydride (30.5 g of 57% NaH in mineral oil) in anhydrous *p*-xylene (450 mL) was added 20 mL of a solution of 1,2,4-tris(methoxycarbonyl)butane (142.5 g), MeOH (1.0 mL), and *p*-xylene (125 mL). As soon as effervescence commenced, the remainder of the solution was added dropwise during 1.5 h, the temperature of the reaction mixture being maintained at 20–25 °C during this operation. Stirring was continued for 20 min and the viscous mixture was then diluted with water (200 mL). The aqueous phase was separated and immediately acidified by addition to cold 1.68 M citric acid solution, with stirring. The crude product was extracted with EtOAc (3 × 250 mL), and the combined extracts were washed with water (100 mL) and brine (2 × 100 mL) and then dried ($MgSO_4$). The filtered solution was stirred briefly with activated charcoal (7 g) and filtered through Celite, and the solvent was then removed under reduced pressure. The residue which solidified on cooling was recrystallized from $Et_2O$/petroleum ether (bp 30–60 °C), affording pure **3** (84.0 g, 70%) as colorless needles: mp 49–50 °C; IR (film) 1750, 1727 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.49 (m, 4 H, $CH_2CH_2$), 3.58 (m, 2 H, COCHCHCO), 3.74 (s, 3 H, β-$CO_2CH_3$), 3.79 (s, 3 H, α-$CO_2CH_3$).

Anal. Calcd for $C_9H_{12}O_5$: C, 53.99; H, 6.04. Found: C, 53.92; H, 6.01.

The (2,4-dinitrophenyl)hydrazone crystallized (MeOH) as golden, felted needles, mp 145.0–146.5 °C.

Anal. Calcd for $C_{15}H_{16}N_4O_8$: C, 47.37; H, 4.24; N, 14.73. Found: C, 47.41; H, 4.24; N, 14.71.

**4-[2-(Methoxycarbonyl)ethyl]tetrahydrofuran-2-one (12).** 1,2,5,6-Tetrahydrobenzyl alcohol (112 g) was dissolved in a mixture of glacial acetic acid (720 mL) and water (80 mL), and the mixture was cooled in an ice bath and treated with a stream (6 $ft^3$/min) of ozonized oxygen. After 7.5 h ozone became detectable (trap containing acidic iodide) in the effluent oxygen and the passage of gas was discontinued. The solution was allowed to warm to 10 °C and aqueous peracetic acid (40%, w/v; 225 mL), at 5 °C, was added in 25-mL portions. The temperature rose spontaneously but was held just below 30 °C by cooling the solution in a cold water bath. The mixture was heated cautiously at 80 °C for 2 h and allowed to stand overnight at 25 °C. Excess peroxide was destroyed by the addition of a solid mixture of potassium metabisulfite (40 g) and potassium acetate (40 g), and the solvents then were removed under reduced pressure. The residual pasty mass containing **11** was diluted with $CH_3OH$ (800 mL) and HCl gas was passed through the solution for 30 min. Precipitated potassium salts were removed by filtration, and the filtrate was heated under reflux for 20 h. The excess $CH_3OH$ was removed under reduced pressure at <60 °C and the resulting oil was teemed into water (1.2 L). The mixture was extracted with $CH_2Cl_2$ (3 × 250 mL) and the organic extract was washed with 10% brine (100 mL) and dried ($MgSO_4$). Removal of the solvent then afforded a pale-yellow oil which on distillation afforded the lactonic ester **12** (107 g; bp 129–33 (0.15 mmHg); 62% yield, 94% pure): IR (neat) 1770, 1735, 1437, 1177, 1020 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.71 (m, 2 H, Et 1-H), 1.95–2.65 (m, 5 H, Et 2-, 3-, 4-H), 3.58 (s, 3 H, $OCH_3$) 3.92 (q, OH, 5-H), 4.33 (q, 1 H, 5-H); mass spectrum, *m/z* (relative intensity) 172 (1), 154 (34), 141 (92), 122 (79), 112 (100), 98 (98), 97 (65), 74 (68). Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.79; H, 7.20.

***cis*-Hexahydro-1*H*-cyclopenta[*c*]furan-1,6-dione (4).** Potassium metal (4.4 g) was dissolved in dry *t*-BuOH (250 mL) under $N_2$ and the resulting solution was maintained at 20 °C by means of an external cold-air stream, while a solution of the lactonic ester **12** (16.7 g) in *t*-BuOH (50 mL) was added with vigorous stirring during 35 min. After a further 35 min a solution of anhydrous oxalic acid (5.5 g) in the same solvent (55 mL) was added in one portion and rapid stirring was maintained for 10 min. The precipitate was removed by filtration and washed with dry *t*-BuOH (50 mL), and then discarded. The combined filtrates were taken to small bulk under reduced pressure and afforded an oil (12 g) whose GLC showed the presence of product and starting material in the ratio 86:14. The infrared spectrum, however, showed strong absorption for OH in the 3300-$cm^{-1}$ region, indicating that some ring opening had occurred to give 3-(hydroxymethyl)-2-(methoxycarbonyl)cyclopentanone (**13**). The latter compound was not fully characterized, however. The oil then was added to water (80 mL) and the resulting solution was extracted with $Et_2O$ (40 mL) and this extract after the usual isolation procedure led to an oily solid (0.5 g), which is discussed later. The aqueous phase was now extracted with $CH_2Cl_2$ (6 × 30 mL) and this, after being dried, afforded a colorless oil (10.2 g). The latter was heated to 160 °C under vacuum for 30 min, cooled, and crystallized from EtOH/EtOAc (1:1; 12 mL) to give the desired product **4**, as large crystals, mp 51–55 °C (8.8 g, 63%), suitable for further work. A sample recrystallized from the same solvents gave the pure keto lactone: mp 55–56 °C; IR (neat) 1775, 1725, 1470, 1400, 1365, 1190, 1142, 1048, 1012, 996, 965 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.92 (m, 1 H), 2.41 (m, 3 H), 3.39 (m, 2 H), 4.20 (q, 1 H, 3-H), 4.56 (q, 1 H, 3-H); mass spectrum, *m/z* (relative intensity) 140 (37), 110 (13), 95 (25), 85 (27), 81 (29), 68 (100), 55 (16). Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found C, 59.87; H, 5.86.

The mother liquors deposited a trace of a white solid on standing which proved to be identical with the product of the ether extraction noted above. Recrystallization (EtOH) gave the pure dimer of **4**: mp 188–190 °C; IR (Nujol) 1755, 1725, 1690, 1250, 1187, 1068, 1047, 995, 959, 933, 777 $cm^{-1}$; $^1H$ NMR ($Me_2SO/D_2O$) δ 1.42 (m, 2 H), 2.32 (m, 2 H), 2.48 (m, 2 H), 3.05 (m, 2 H) 3.4–4.8 (m, 4 H); mass spectrum, *m/z* (relative intensity) 280 (9), 207 (87), 149 (57), 135 (40), 117 (83), 115 (42), 105 (49), 91 (100), 79 (23), 77 (39).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 60.06; H, 6.03.

The *oxime* of **4**, formed in the usual way from hydroxylamine acetate, crystallized from EtOAc as needles: mp 155–157 °C dec; IR (Nujol) 3150, 1768, 1665 (w), 1240, 1208, 1180, 1157, 1142, 1090, 1052, 1000, 978, 963, 895 $cm^{-1}$; $^1H$ NMR ($Me_2SO$) δ 1.50 (m, 1 H), 1.98 (m, 1 H), 2.45 (m, 2 H), 3.1 (m, 1 H), 3.55 (m, 1 H), 4.00 (q, 1 H, 3-H) 4.36.

Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.14; H, 5.68; N, 8.95.

**6-Chloro-2-hexyn-1-ol (19).** To a Grignard reagent prepared from magnesium (24.3 g) and ethyl bromide (109 g) in tetrahydrofuran (50 mL) was added at 0 °C, over 30 min, a solution of 1-chloro-4-pentyne (102.5 g) in the same solvent (100 mL). The mixture was boiled for 1.5 h and then cooled to 5 °C. Gaseous formaldehyde (from the pyrolysis at 225 °C of 100 g of paraformaldehyde) was then sparged into the solution, which was diluted with additional tetrahydrofuran (200 mL) when half of the formaldehyde had been added. The reaction mixture was stirred for 18 h at 25 °C and then poured into excess 2 N sulfuric acid. Isolation of the product via $Et_2O$ extraction led to a colorless oil which when fractionated through a 15-cm Vigreaux column afforded pure 6-chloro-2-hexyn-1-ol (80.8 g, 61%): bp 83–85 °C (0.4 mmHg) [lit.[6] bp 72–74 °C (0.04 mmHg)]; IR (neat) 3320, 2200 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.0 (m, 2 H), 2.45 (t, 2 H), 3.63 (t, 2 H, $CH_2Cl$), 3.75 (s, 1 H, OH), 4.17 (t, 2 H, $CH_2OH$); mass spectrum, $m/z$ (relative intensity) 134 (0.6), 132 (1.2), 106 (28.5), 104 (100), 83 (20), 79 (20), 73 (23), 70 (74). The dominant loss ($M^+ - 28$) is undoubtedly due to isomerization of the acetylenic alcohol group to the unsaturated aldehyde (via the allenol) followed by decarbonyation.

**6-Cyano-2-hexyn-1-ol.** A mechanically stirred slurry of sodium cyanide (29.4 g) in dimethyl sulfoxide (150 mL) at 80 °C was treated during 15 min with a solution of 6-chloro-2-hexyn-1-ol (26.5 g) in the same solvent (25 mL) under anhydrous conditions. After 1.5 h the solution was cooled and added to brine (500 mL). Isolation of the produce with EtOAc (3 × 200 mL) extraction led to a dark oil which was fractionated through a Vigreaux column to afford 6-cyano-2-hexyn-1-ol as a faintly yellow oil (20.4 g, 85%): bp 110–113 °C (0.06 mmHg); IR 3390, 2243 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.93 (m, 2 H), 2.43 (t, 2 H), 2.55 (t, 2 H, $CH_2CN$), 3.24 (s, 1 H), OH), 4.24 (t, 2 H, $CH_2OH$).

Anal. Calcd for $C_7H_9NO$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.08; H, 7.43; N, 11.09.

**Pent-2-ynyl and 6-Cyanohex-2-ynyl Mesylates.** To methanesulfonyl chloride (20.2 g) in $CH_2Cl_2$ (190 mL) at −5 °C were added, during 45 min with stirring, pent-2-ynol (14 g) and triethylamine (17.8 g) in $CH_2Cl_2$ (50 mL). Stirring at −5 °C was continued for a further 25 min and the precipitate was removed by filtration and washed with cold solvent. The filtrate was washed successively with cold water (100 mL), 5% HCl solution (100 mL), and brine (2 × 50 mL) and then dried ($MgSO_4$). Removal of the solvent at <25 °C under reduced pressure afforded pent-2-ynyl mesylate (28.5 g, 100%) as a mobile faintly yellow oil: IR (neat) 2227, 1350, 1172 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17 (t, 3 H, $CH_3$) 2.30 (q, 2 H, $CH_2$), 3.00 (s, 3 H, $CH_3SO_2$), 4.73 (t, 2 H, $CH_2O$).

The mesylate (**20**) of 6-cyanohex-2-ynol was obtained (100%) as an oil, using exactly the same procedure as described above: IR (neat) 2250, 1350, 1171 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.97 (m, 2 H), 2.4 (t, 2 H), 2.53 (t, 2 H, $CH_2CN$), 3.12 (s, 3 H, $CH_3SO_2$), 4.87 (t, 2 H, $OCH_2$). It showed a single spot on TLC (PhH/EtOAc, 9:1) and was used without further purification for the alkylation of **3** because it tends to decompose on standing.

***cis*- and *trans*-2-Methyl-2,3-bis(methoxycarbonyl)cyclopentanone (15) and *trans*-2-Methyl-3-carboxycyclopentanone (17).** To a suspension of sodium hydride (1.15 g of 57% NaH dispersion in mineral oil) in dry dimethoxyethane (25 mL) was added during 10 min a solution of **3** (5.0 g) in the same solvent (5 mL). After 15 min at 25 °C hydrogen evolution ceased and methyl iodide (7.1 g) in dimethoxyethane (5 mL) was run in over 5 min. The mixture was heated under reflux for 18 h and then diluted with water (30 mL). Isolation of the produce, via EtOAc extraction, led to a yellow oil which was distilled through a short-path distillation apparatus to give the desired product **15** (4.5 g, 84%) as a colorless oil: bp 121–123 °C (0.27 mmHg); IR (neat) 1750, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.37 (s, 3 H, $CH_3$), 2.50 (m, 5 H), 3.60 (s, 3 H, $\beta$-$CO_2CH_3$), 3.66 (s, 3 H, $\alpha$-$CO_2CH_3$).

The structure of **15** was confirmed as follows. A sample (4.0 g) was heated with 4 N HCl (60 mL) at reflux for 17 h. The solution was taken to dryness under reduced pressure and the residue was dissolved in $CHCl_3$ and dried ($MgSO_4$). Removal of the solvent by evaporation and recrystallization of the residual solid 3 times from ligroin (bp 63–75 °C) containing a trace of $Et_2O$ yielded *trans*-2-methyl-3-carboxycyclopentanone (**17**; 1.9 g, 71%) as lustrous white plates: mp, 91–92.5 °C (lit.[13] mp 94 °C); IR (Nujol) 3365, 2550, 1745, 1705 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.20 (d, 3 H, $CH_3$), 2.37 (m, 5 H), 9.60 (s, 1 H, $CO_2H$), identical in all respects with an authentic sample; mixture mp 91 °C.

***cis*- and *trans*-2-(2-Pentynyl)-2,3-bis(methoxycarbonyl)cyclopentanone (16).** The sodium salt of a sample of **3** (5.0 g) in dimethoxyethane was prepared exactly as described in the preparation of **15**. A solution of 2-pentyn-1-ol mesylate (4.37 g) in dry dimethoxymethane (5 mL) was added over 5 min. The mixture was heated under reflux for 4 h, cooled, and diluted with water (30 mL). Isolation of the product by means of EtOAc extraction led to a yellow oil, which was chromatographed over silica gel (75 g). Elution with $CH_2Cl_2$ afforded the cis and trans isomers of **16** as a colorless slightly viscous oil (5.94 g, 80%): bp 123–124.5 °C (0.03 mmHg) (determined by short-path distillation); IR (neat) 1755, 1735; $^1H$ NMR ($CDCl_3$) $\delta$ 1.12 (t, 3 H, $CH_3$), 2.38 (m, 9 H), 3.69 (3 s, 6 H, $OCH_3$, cis and trans isomers).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.02; H, 6.95.

***cis*- and *trans*-2-(6-Cyanohex-2-ynyl)-2,3-bis(methoxycarbonyl)cyclopentanone (21).** The sodium salt of a sample of **3** (40 g) was prepared as described in the preparation of **15**, using 57% NaH-in-oil dispersion (8.95 g) and dimethoxyethane (200 mL). A solution of the mesylate **20** (40.2 g) in the same solvent 20 mL) was added over 10 min and the stirred mixture was heated at reflux for 5 h. Isolation of the product via dilution with water (150 mL) and EtOAc (5 × 100 mL) extraction led to a crude oil (55.5 g). Purification of this material was accomplished by chromatography over silica gel (600 g). Pure **21** (50.1 g, 82%) was obtained by elution with $CH_2Cl_2$/MeOH (98:2). It is a colorless viscous oil: bp 185–187 °C (0.0 mmHg) (short-path distillation); IR (film) 2245, 1755, 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.88 (m, 2 H), 2.60 (m, 11 H), 3.72 (3 overlapping singlets due to C2–C3 cis–trans isomers, 6 H, $OCH_3$).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.81; H, 6.42; N, 4.34.

***trans*-2-(Pent-2-ynyl)-3-(methoxycarbonyl)cyclopentanone (18).** A solution of **16** (4.0 g) in dry *s*-collidine (5 mL) was added during 10 min to a mechanically stirred boiling solution of $LiI{\cdot}2H_2O$ (7.75 g) in the same solvent (25 mL). Heating under reflux was continued for 10 h during which time a precipitate separated. The mixture was cooled and then added to ice (25 g) and 6 N HCl (40 mL). Extraction with ether (4 × 35 mL) followed by the usual isolation procedure led to a yellow oil (2.3 g), which was subjected to short-path distillation. This afforded pure **18** (1.9 g, 61%) as a faintly yellow oil: bp 103–106 °C (0.1 mmHg); IR (neat) 1745, 1935 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.08 (t, 3 H, $CH_3$) 2.24 (m, 10 H), 3.69 (s, 3 H, $OCH_3$).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.02; H, 7.94.

***trans*-2-(6-Cyanohex-2-ynyl)-3-(methoxycarbonyl)cyclopentanone (22).** A magnetically stirred mixture of **21** (21.5 g), sodium chloride (473 mg), and water (3.06 g) in dimethyl sulfoxide (50 mL) was slowly heated to 155–160 °C under a slow stream of $N_2$ until carbon dioxide evolution (which begins at 135 °C) became very slow (~5 h). The dark mixture was cooled and poured into brine (100 mL) and the resulting solution was extracted with $CH_2Cl_2$ (3 × 80 mL). The combined extracts were washed with 5% aqueous NaOH solution (2 × 60 mL) and brine (3 × 50 mL) and then dried ($MgSO_4$).

Removal of the solvent left a yellow-brown oil, which was chromatographed over silica gel (150 g). Elution with benzene/EtOAc (8:2) afforded pure **22** (9.16 g, 53%) as a slightly yellow, somewhat viscous oil: IR (neat) 2240, 1750, 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.86 (m, 2 H), 2.43 (m, 12 H), 3.75 (s, 3 H, $OCH_3$).

The (2,4-dinitrophenyl)hydrazone obtained as bright-yellow plates ($CH_3OH$) had mp 140.0–140.5 °C.

Anal. Calcd for $C_{20}H_{21}N_5O_6$: C, 56.20; H, 4.95; N, 16.39. Found: C, 56.50; H, 4.95; N, 16.42.

The basic aqueous extract was acidified with 5% HCl solution (120 mL) and extracted with $CH_2Cl_2$ (2 × 50 mL). The latter was dried ($MgSO_4$) and the solvent removed to give a glass, which was dissolved in tetrahydrofuran/$CH_3OH$ (50 mL, 4:1) and treated with a slight excess of $CH_2N_2$. Removal of the solvents afforded a viscous oil (8 g) which showed a single spot on TLC analysis

(benzene/$CH_3OH$, 97:3): IR (film) 2240, 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ $\delta$ 1.92 (m, 4 H), 2.45 (m, 8 H, $CH_2C{\equiv}CCH_2$, $CH_2CN$, $CH_2CO_2CH_3$), 2.87 (m, 2 H, $CHCO_2CH_3$), and a group of singlets at 3.67, 3.69, 3.71, 3.73 (4 s, 9 H) due to the two diastercoisomeric forms of **24**, which in our hands were inseparable chromatographically.

***trans*-2-(Benzyloxycarbonyl)-3-(methoxycarbonyl)cyclopentanone (25).** A mixture of 2,3-bis(methoxycarbonyl)-cyclopentanone (35.0 g) and benzyl alcohol (25.1 g) was heated at 185 °C under a nitrogen stream until MeOH evolution ceased (~1.25 h). The crude product was diluted with EtOH and the resulting solution was added slowly (15 min) with vigorous stirring to a solution of $Cu(OAc)_2{\cdot}H_2O$ (18.0 g) in water 1.1 L). After 4 h the solid copper chelate was removed by filtration and dried. Recrystallization from EtOH afforded the pure copper chelate of **25** (44.8 g, 80%), mp 161–163 °C, as lustrous green plates.

Anal. Calcd for $C_{30}H_{30}CuO_{10}$: C, 58.67; H, 4.92; Cu, 10.34. Found: C, 58.82; H, 5.05; Cu, 10.02.

A solution of the copper chelate (36.0 g) in chloroform (225 mL) was shaken with aqueous 25% sulfuric acid (90 mL) until the organic layer was colorless (4 min). Isolation of the product from this layer in the usual way led to pure **25** as a colorless oil (34 g, 100%); IR (neat) 1755, 1730 $cm^{-1}$; $^1H$ NMR $\delta$ 2.37 (m, 4 H, $CH_2CH_2$), 3.55 (s, 2 H, H at C-2 and C-3), 3.69 (s, 3 H, $OCH_3$), 5.22 (s, 2 H, $CH_2Ph$), 7.36 (s, 5 H, Ph). The (2,4-dinitrophenyl)hydrazone crystallized (MeOH) as shiny felted needles, mp 135–136.5 °C.

Anal. Calcd for $C_{21}H_{20}N_4O_8$: C, 55.26; H, 4.42; N, 12.28. Found: C, 55.31; H, 4.42; N, 12.18.

**2-(6-Cyanohex-2-ynyl)-2-(benzyloxycarbonyl)-3-(methoxycarbonyl)cyclopentanone (26).** A suspension of the sodium salt of **25** (55.2 g) in dimethoxyethane (250 mL) was prepared precisely as described above, for the sodium salt of **3**. A solution of the mesylate **20** (40.2 g) in dry dimethoxyethane (20 mL) was added dropwise over 10 min while the reaction mixture was stirred mechanically and slowly heated to 65 °C. The heat source was removed for 15 min (exotherm) and thereafter the solution was heated at reflux for 5 h and then cooled. Water (150 mL) was added and the product isolated by extraction with EtOAc. This afforded a crude oil (73.9 g), which was dissolved in benzene and purified by chromatography over silica gel (800 g). Benzene/$CH_3OH$ (97:3) eluted pure **26** as a pale-yellow oil (65 g, 85%): IR 2245, 1755, 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.34 (m, 12 H), 3.52 (s, 3 H, $OCH_3$), 3.68 (br s, 1 H, $CH_2CHCO_2$), 5.09 (s, 2 H, $CH_2Ph$), 7.37 (s, 5 H, Ph).

Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.13; H, 6.22; N, 3.71.

***trans*-2-(6-Cyanohexyl)-3-(methoxycarbonyl)cyclopentanone (29).** A solution of the acetylene **26** (45 g) in EtOH (200 mL) containing pyridine (16.0 g) was shaken at 25 °C with a 5% palladium-on-calcium carbonate catalyst (6.0 g) under hydrogen at 50 psi, using a Parr hydrogenator. After 10.25 h the solution was filtered, and the solvents were removed at reduced pressure. The residual liquid was dissolved in EtOAc (150 mL) and then given both acid (1.5 N HCl) and basic (1.5 N $NaHCO_3$) washes to remove residual pyridine. Reisolation of the product led to an oil (26.9 g), which was dissolved in benzene and chromatographed over silica gel (400 g). Elution with benzene/$CH_3OH$ (98:2) afforded pure **29** (25.5 g, 86%) as a colorless, viscous oil: IR (neat) 2240, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.16 (br m, 18 H), 3.68 (s, 3 H, $OCH_3$).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.79; H, 8.49; N, 5.55.

***trans*-2-(6-Cyanohex-2(*Z*)-enyl)-3-carboxycyclopentanone (30) and Its Methyl Ester (27).** A solution of **26** (11.43 g) in EtOH (125 mL) containing pyridine (4.75 g) was stirred under hydrogen with a 5% palladium-on-barium sulfate catalyst (2.0 g) at 25 °C and normal pressure. After 2 h, slightly more than the required quantity of hydrogen (1.5 L) had been absorbed and the reaction was terminated. The catalyst was removed by filtration, and solvents were removed by distillation ($CO_2$ evolution). The remaining oil was dissolved in EtOAc. This solution was washed successively with 1.5 N HCl (3 × 25 mL), water (50 mL), 1.3 N $NaHCO_3$ (50 mL), and brine (3 × 25 mL) and then dried ($MgSO_4$). Isolation of the product gave **27** as a crude oil (6.78 g, 91.5%): IR (neat) 2240, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.15 (br m, 14 H), 3.68 (s, 0.3 H, $OCH_3$), 3.78 (s, 2.7 H, $OCH_3$), 5.38 (m, 1.8 H, cis CH=CH). The latter spectrum and the mass spectrum (which showed a line at $M^+$ −2) indicated the presence of ~10% of the saturated analogue **29**. Furthr purification was accomplished by hydrolysis to the acid **30** as follows.

The crude ester (15.0 g) was dissolved in a mixture of MeOH (25 mL) and 1 N $Na_2CO_3$ (150 mL) and the resulting solution was heated at 75–80 °C under $N_2$ for 4 h, cooled, and allowed to stand at 25 °C for 18 h. The solution then was washed with EtOAc (3 × 25 mL), cooled to 8 °C, and acidified with 12 N HCl. The yellow oil that separated was isolated via EtOAc (3 × 50 mL) extraction and this afforded crude **30** (12.6 g) as a viscous oil. Purification was accomplished by careful chromatography over silica gel (160 g), using $CHCl_3$ as the eluant. This gave pure **30** (10.6 g, 75%) free of overreduction product, as judged from its spectral properties: IR (neat) 3250, 2600, 2250, 1745, 1712; $^1H$ NMR ($CDCl_3$) $\delta$ 2.13 (br m, 14 H), 5.40 (m, 2 H, cis CH=CH) 9.57 (br s, 1 H, $CO_2H$).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.52; H, 7.08; N, 5.80.

**Reduction of 30 to Mixed Diols 32.** A magnetically stirred solution of the acid **30** (7.0 g) and thionyl chloride (6.85 g) in benzene (175 mL) was heated at reflux for 3 h and then concentrated in vacuo. Fresh benzene (25 mL) was added and the solution again was concentrated then stored at 0.1 mmHg for 2 h. The crude acid chloride **31** [IR (film) 2245, 1792, 1748 $cm^{-1}$] thus obtained (100% yield) was dissolved in dioxane (40 mL) and added dropwise over 30 min to a stirred solution of sodium borohydride (1.4 g) in aqueous dioxane (80 mL; 1:1) at 0–5 °C. An additional quantity of sodium borohydride (0.2 g) was added after 1 h and stirring was continued for a further 45 min. The solution was allowed to warm to 25 °C over 15 min and then was poured into brine (100 mL). Extraction with EtOAc afforded the desired mixture of diols (**32**) as a colorless oil (6.0 g, 96%): IR (film) 3370, 2245, transparent in C=O region; $^1H$ NMR ($CDCl_3$) $\delta$ 1.93 (br m, 15 H), 2.88 (br s, 2 H, OH), 3.60 (m, 2 H, $CH_2O$), 5.53 (m, 2 H, cis CH=CH).

Anal. Calcd for $C_{13}H_{21}O_2N$: C, 69.94; H, 9.42; N, 6.23. Found: C, 70.10; H, 9.35; N, 6.31.

***trans*-2-(6-Carboxyhex-2(*Z*)-enyl)-3-(hydroxymethyl)cyclopentanols (33) and Their Methyl Esters (34).** The mixture of diols **32** (4.0 g) was suspended in a solution of KOH (7.0 g) in aqueous MeOH (55 mL, 10:1) and heated under reflux for 1 h. The clear yellow solution was cooled, washed with $Et_2O$ (3 × 25 mL), and then treated with decolorizing charcoal. After filtration it was acidified with 12 N HCl and extracted with EtOAc (3 × 25 mL). The extract was washed with brine (2 × 25 mL) and dried ($MgSO_4$) and the solvent was removed. This afforded the crude acids **33** (4.0 g, 93%) as a viscous colorless oil: IR (film) 3345, 2650, 1705 transparent in the nitrile region. The TLC (toluene/$CH_3OH$/formic acid, 75:24:1) showed a slightly elongated spot, $R_f$ 0.51.

The mixture of dihydroxy acids (3.10 g) in $Et_2O/CH_3OH$ (25 mL, 4:1) was titrated with a slight excess of $CH_2N_2$ (endpoint; faint yellow color) in $Et_2O$. $Et_2O$ (25 mL) was added and the solution was washed first with 0.8 N $NaHCO_3$ and then brine and dried ($MgSO_4$). Removal of the solvent left the pure diol esters **34**: IR (film) 3355, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.00 (br m, 17 H), 3.59 (m, 2 H, $CH_2O$), 3.66 (s, 3 H, $OCH_3$), 5.48 (m, 2 H, cis CH=CH); mass spectrum disilyl derivative, $M^+$ at 400 is absent, $m/z$ (relative intensity) 327 (1, M − $Me_3Si$), 311 (2 M − $OMe_3Si$), 297 (12, M − $CH_2OMe_3Si$), 256 (12), 220 (13), 147 (71), 155 (71), 119 (100), 103 (84).

**6a-(6-Cyanohex-2-ynyl)hexahydro-1*H*-cyclopenta[*c*]furan-1,6-dione (35).** The keto lactone **4** (20 g) in *t*-BuOH (20 mL) was added in one portion to a solution of potassium metal in the some solvent (350 mL). After 5 min a solution of the mesylate **20** (29 g) in *t*-BuOH (50 mL) was added dropwise over 30 min at room temperature. Two hours after addition was complete the mixture was taken at dryness under reduced pressure at <40 °C. Water (150 mL) and $CH_2Cl_2$ (150 mL) were added and isolation of the material soluble in the organic phase gave **35** as a viscous oil (33 g). This was judged to be pure enough to be used directly in further reactions since its TLC ($CH_2Cl_2$/EtOAc/, 98.2) showed a single spot ($R_f$ 0.6). A small sample (0.31 g) was chromatographed over silica gel (25 g), and $Et_2O/CH_2Cl_2$

(1:9) eluted the pure material (0.3 g) as a colorless oil: IR (neat) 2245 (w), 1777, 1735, 1195, 1158, 1047, 1015 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.85 (m, 2 H, hexynyl 5-$CH_2$), 2.44 (br m, 11 H, CH, $CH_2$), 4.10 (q, 1 H, 3-H), 4.54 (q, 1 H, 3-H).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.29; H, 6.03; N, 5.41.

***trans*-2-(6-Cyanohex-2-ynyl)-3-(hydroxymethyl)cyclopentanone (36).** The lactonic ketonitrile (**35**, 32 g) was mixed with a 20% solution of $Na_2CO_3$ in water (600 mL). The mixture was boiled for 12 h, cooled, and extracted with EtOAc (2 × 70 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residual brown oil (6.0 g) was chromatographed over silica gel (150 g). Elution with $CH_2Cl_2$ gave a small quantity (0.5 g) of $HOCH_2C{\equiv}C(CH_2)_3CN$. Further elution with $CH_2Cl_2/Et_2O$ (85:15, 4 L) led to the desired product **36** (4.2 g, 14.5%), which showed a single spot on TLC ($Et_2O$/EtOAc, 95:5; $R_f$ 0.5). An analytical sample was prepared by thick-layer chromatography: IR (neat) 3435 (s), 2245, 1735, 1158, 1078, 1020 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.86 (m, 2 H, 5-$CH_2$), 2.45 (br m, 12 H, CH, $CH_2$), 3.65 (m, 2 H, $CH_2OH$).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.30. Found: C, 70.76; H, 7.98; N, 6.94.

**2,3-*trans*-2-(6-Cyanohex-2(*Z*)-enyl)-3-(hydroxymethyl)cyclopentanone (38).** A solution of the acetylene (**36**, 2.8 g) in pure pyridine (50 mL) was hydrogenated over a 5% palladium-on-barium sulfate catalyst (0.75 g) until hydrogen absorption (95.5% of theory) virtually had ceased. The catalyst was removed by filtration and the solvent by evaporation under reduced pressure at 100 °C. This led to a colorless liquid (2.8 g) which showed a single spot on TLC analysis ($Et_2O$/EtOAc, 95:5, $R_f$ 0.48). The compound in $CH_2Cl_2$ was percolated through a column of silica gel (100 g) and the first 400 mL of eluate was discarded. Elution with $Et_2O$ (1 L) then afforded the analytically pure ethylenic compound **38** (2.3 g, 82%) as a colorless oil: IR (neat) 3450 (s), 2240, 1735, 1150, 1074, 1035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.64 (m, 2 H, $CH_2OH$), 5.32 (m, 2 H, CH=CH).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.70; H, 8.86; N, 6.70.

***trans*-(6-Carboxyhex-2(*Z*)-enyl)-3-(hydroxymethyl)cyclopentanone (39) and Its Methyl Ester (40).** The nitrile **38** (0.46 g) was dissolved in aqueous EtOH (40 mL, 1:1) containing potassium hydroxide (0.5 g) and the mixture was heated under reflux for 10 h (no further evolution of $NH_3$). The EtOH was removed under reduced pressure and water (20 mL) was added. The solution was washed with $CH_2Cl_2$ to remove neutral material and then acidified with 12 N HCl. Extraction with $CH_2Cl_2$ (2 × 30 mL) led to crude **39** as an orange oil (0.40 g). Ethereal diazomethane was added until effervescence ceased. Removal of the solvent then left a yellow oil, which was applied to a silica gel column (7.0 g). Elution with $Et_2O$/EtOAc (88:12) afforded pure **40** as a colorless oil (0.38 g, 76%): IR (neat) 3450, 1735, 1720, 1628 (w), 1240, 1215, 1160, 1075, 1048, 1020, 860 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.68 (m, 2 H, $CH_2OH$), 5.40 (m, 2 H, CH=CH).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.07; H, 8.77.

***O*-Methyloxime (41) of Lactonic Ketone 4.** Lactonic ketone **4** (2.1 g) was treated with a 2 M solution (15 mL) of methoxyamine acetate in $CH_3OH$. After 2 days at room temperature, the volatiles were removed under reduced pressure at 60 °C, and the product was isolated via the addition of water and $CH_2Cl_2$. The product from the organic phase, a white solid, was recrystallized from $Et_2O$/petroleum ether, affording thick colorless rods of **41** (1.8 g), mp 78–79 °C. A sample recrystallized for analysis had the following: 81–82 °C; IR (Nujol) 1755, 1282, 1248, 1208, 1150, 1087, 1035, 988, 960, 947, 874, 848 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.73 (m, 1 H), 2.14 (m, 1 H), 2.52 (m, 2 H), 3.13 (m, 1 H, 3a-H), 3.55 (d, 1 H, 6a-H), 3.92 (s, 3 H, $OCH_3$), 4.08 (q, 1 H, 3-H), 4.46 (q, 1 H, 3 H). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.62; H, 6.58; N, 8.20.

**C-Methylation of 41 (Preparation of 43).** A solution of potassium (0.105 g) in anhydrous *t*-BuOH (7 mL) was prepared under $N_2$. To this was added, over 3 min at 50 °C with stirring, a solution of the *O*-methyloxime **41** (0.42 g) in the same solvent (4 mL). Ten minutes later methyl iodide (0.418 g) in *t*-BuOH (2 mL) was added dropwise while the temperature in the reaction flask was held at 35 °C. After standing overnight the solvent was removed at 40 °C by evaporation at reduced pressure. To the residue were added water (10 mL) and $CH_2Cl_2$ (20 mL). The organic phase when dried ($MgSO_4$) and evaporated afforded a glass (0.42 g). Crystallization from $Et_2O$/petroleum ether gave the crude product, mp 65–67 °C (0.32 g). Two further crystallizations gave pure **42** (0.26 g): mp 70–76.5 °C; IR (Nujol) 1775, 1220, 1185, 1152, 1092, 1037, 1000, 981, 930, 904, 858, 730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.44 (s, 3 H, $CH_3$), 1.5–3.0 (m, 5 H), 3.89 (s, 3 H, $OCH_3$) 3.90 (q, 1 H, 3-H), 4.41 (q, 1 H, 3-H).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.16; H, 7.16; N, 7.59.

**Attempted Hydrolytic Decarboxylation of 42.** A solution of **42** (99 mg) and potassium carbonate (60 mg) in water (1 mL) and 2-ethoxyethanol (0.5 mL) was heated with a trace of precipitated copper in at sealed tube for 1 h at 160 °C and then at 105 °C for 15 h. The contents of the tube were decanted from tar and diluted with water (20 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 5 mL). This yielded crude **43** as a neutral oil (15 mg): IR (film) 33.80 (s), 1735, 1285, 1155, 1122, 1070, 1042, 1015, 962, 890, 832 $cm^{-1}$; mass spectrum, *m/z* (relative intensity) ($M^+$, 128, 0.8%.

Acidification of the aqueous phase with 1 N HCl followed by extraction with $CH_2Cl_2$ led only to recovered starting material **42** (30 mg). The tarry material from the reaction was not investigated further.

***trans*-2-[6-(Methoxycarbonyl)hex-2(*Z*)-enyl]-3-formylcyclopentanone (5). a. From Diol Ester 34.** A solution of the diol ester **34** (1.328 g) in dry $CH_2Cl_2$ (3 mL) was added with stirring in one portion to a chilled solution of anhydrous chromium trioxide (6.32 g) in the same solvent (150 mL) containing pyridine (9.84 g). The mixture was stirred at 25 °C for 20 min and the dark supernatant liquid was decanted from the tarry residue. The latter was washed with solvent (2 × 100 mL), and the liquid organic phases were combined and washed successively with aqueous 5% solutions of NaOH (3 × 100 mL), HCl (100 mL), $NaHCO_3$ (100 mL), and brine (2 × 100 mL) and then dried ($MgSO_4$). Removal of the solvent then afforded crude aldehyde **5** (1.24 g). This was dissolved in benzene and chromatographed over silica gel (20 g). Elution with benzene/acetone (98:2) then gave the pure aldehyde (1.195 g, 92%) as a colorless mobile oil which showed a single spot on TLC analysis, $R_f$ 0.48 (benzene/acetone, 95:5): IR (neat) 2985, 2935, 2175 (CH of aldehyde) 1738 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.29 (br m, 14 H), 3.64 (s, 3 H, $OCH_3$), 5.41 (m, 2 H, cis CH=CH), 9.70 (d, $J$ = 2.6 Hz, 1 H, CHO); mass spectrum, *m/z* (intensity as percent of base peak) 252 ($M^+$, 0.85) 234 (1.1), 223 (12), 221 (5.5), 203 (7.5), 191 (12), 149 (7), 141 (50), 140 (10), 109 (21), 83 (100), 81 (42); metastable ions (parent ion/fragment ion + neutral species) 217.3 (252/234 + 18), 197.3 (252/223 + 29), 163.5 (252/203 + 49), 199.4 (234/216 + 18), 174.4 (234/202 + 32), 163.6 (223/191 + 32), 89.5 (223/141 + 82), 186.5 (221/203 + 18), 156.7 (191/173 + 18), 84.6 (141/109 + 32). The latter decomposition pattern is in complete agreement with that for structure **5**.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.58; H, 8.16.

**b. From Keto Alcohol 40.** Alcohol **40** (97 mg) was dissolved in $CH_2Cl_2$ (7 mL) and added in one portion to a solution of chromium trioxide (170 mg) in a mixture of $CH_2Cl_2$ (7 mL) and pyridine (0.5 mL). After the mixture was stirred for 1 h at 24 °C, the organic solvent was decanted from the tarry residue. The latter was washed with $Et_2O$ (25 mL) and then discarded. The combined organic extracts were washed consecutively with 2% KOH solution (2 × 25 mL), water (2 × 25 mL), 1 N HCl solution (3 × 25 mL), and 5% $NaHCO_3$ solution (2 × 25 mL) and then dried ($MgSO_4$). Removal of the solvent led to a colorless oil (77 mg). The material was further purified by percolation $CH_2Cl_2$/EtOAc, 19:1), through a short column of silica gel (3 g). Evaporation of the eluate afforded the pure aldehyde **5** (70 mg, 71%), identical in all respects with the sample prepared from the diol ester **34**, as described above.

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**Registry No.** (±)-**3**, 81159-11-7; (±)-**3** hydrazone, 81159-12-8; (±)-**3** Na, 81159-13-9; (±-**4**, 72525-94-1; (±)-**4** dimer, 81159-47-9; (±)-**4** oxime, 81159-14-0; (±)-**5**, 81203-30-7; (±)-**6**, 81159-15-1; (±)-**7**,

81159-16-2; (±)-10, 72581-32-9; (±)-11, 81203-31-8; (±)-12, 72581-33-0; 13, 81159-17-3; (±)-cis-15, 33783-53-8; (±)-trans-15, 81159-18-4; (±)-cis-16, 81159-19-5; (±)-trans-16, 81159-20-8; (±)-17, 81159-21-9; (±)-18, 81159-22-0; 19, 1002-37-5; 20, 77493-17-5; (±)-cis-21, 81159-23-1; (±)-trans-21, 81159-24-2; (±)-trans-22, 81159-25-3; (±)-trans-22 hydrazone, 81159-26-4; (±)-23 (isomer I), 81159-27-5; (±)-24 (isomer I), 81159-28-6; (±)-25, 81159-29-7; (±)-25 hydrazone, 81159-30-0; (±)-25 Na, 81159-31-1; 25 copper chelate, 81177-95-9; 26, 69285-46-7; (±)-27, 81203-32-9; (±)-cis-28, 81159-32-2; (±)-trans-29, 81159-33-3; (±)-30, 81203-33-0; (±)-31, 81203-34-1; (±)-32 (isomer I), 81203-35-2; (±)-32 (isomer II), 81203-36-3; (±)-33 (isomer I), 81203-37-4; (±)-33 (isomer II), 81203-38-5; (±)-34 (isomer I), 81203-39-6; (±)-34 (isomer II), 81203-40-9; (±)-35, 81159-34-4; (±)-36, 81159-35-5; (±)-37 (isomer I), 81159-36-6; (±)-38, 81159-37-7; (±)-39, 81159-38-8; (±)-40, 81159-39-9; (±)-41, 81159-40-2; (±)-42, 81159-41-3; 43, 81159-42-4; methyl cyclohex-3-enecarboxylate, 49543-03-5; ethyl bromide, 74-96-4; 1-chloro-4-pentyne, 14267-92-6; 6-cyano-2-hexyn-1-ol, 69285-47-8; pent-2-ynol, 6261-22-9; pent-2-ynyl mesylate, 81159-43-5; benzyl alcohol, 100-51-6; (±)-23 (isomer II), 81159-44-6; (±)-24 (isomer II), 81159-45-7; (±)-37 (isomer II), 81159-46-8.

# Synthesis of the *E* and *Z* Isomers of the Antiestrogen Tamoxifen and Its Metabolite, Hydroxytamoxifen, in Tritium-Labeled Form

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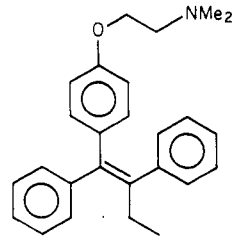
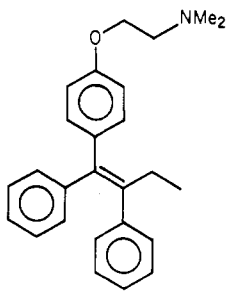
Both isomers of the potent antiestrogen tamoxifen (1,2-diphenyl-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-butene: *E* isomer = ICI-47699; *Z* isomer = ICI-46474, Nolvadex) and its metabolite, hydroxytamoxifen (1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-(4-hydroxyphenyl)-2-phenyl-1-butene), have been synthesized in a high specific activity, tritium-labeled form by catalytic tritium–halogen exchange performed on brominated precursors. The synthesis of another precursor to labeled tamoxifen which would enable the incorporation of three tritium atoms into the molecule by tritium–halogen exchange is reported.

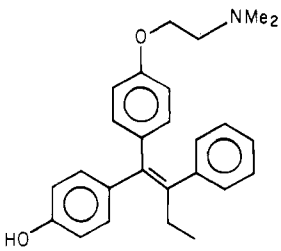
Antiestrogens are a group of compounds which block, at least in part, the action of estrogens on estrogen target tissues. Although originally prepared as potential human antifertility agents,[1] an application for which they have not proven useful, antiestrogens are used clinically for controlling mammary and endometrial carcinomas and managing a number of endocrine disorders.[2] They have also been useful as tools for probing the action of estrogens on a molecular level.[3] Recently, much interst has been focused on tamoxifen[4] (1, ICI-46,474, Nolvadex), an antiestrogen first described by Harper and Walpole.[5] Tamoxifen inhibits the development and growth of mammary tumors in rats[6] and is effective in treating estrogen-dependent, metastatic breast cancer in humans.[7] In vivo, tamoxifen is transformed to hydroxytamoxifen (3), which has a much higher binding affinity for the estrogen receptor and appears to be the compound responsible, in part, for the biological actions of tamoxifen.[8] Enigmatically, the *E* isomer of tamoxifen, usually referred to as *cis*-tamoxifen (2, ICI-47,699), has no clinical uses and is not antiestrogenic; in fact, in the rat it is a full estrogen agonist.[9]




tamoxifen
(1, *Z* isomer, ICI-46,474)




*cis*-tamoxifen
(2, *E* isomer, ICI-47,699)




hydroxytamoxifen (3)

To continue our studies on the mechanism of action, metabolism, and pharmacokinetics of antiestrogens,[10] we needed tamoxifen and hydroxytamoxifen in a high specific activity, tritium-labeled form.[11] We also desired to have

(1) Lerner, L. J.; Holthaus, J. F.; Thompson, C. R. *Endocrinology (Baltimore)* **1958**, *63*, 295–318.

(2) For reviews of the pharmacological uses of antiestrogens, see: Henningsen, B.; Linder, F.; Steichele, C., Eds. "Recent Results in Cancer Research"; Springer-Verlag: West Berlin, 1980; Vol 71. Lunan, C. B.; Klopper, A. *Clin. Endocrinol. (Oxford)* **1975**, *4*, 551–572. Tagnon, H. J. *Cancer* **1977**, *39*, 2959–2964.

(3) Katzenellenbogen, B. S. *Annu. Rev. Physiol.* **1980**, *42*, 17–35 and references cited therein.

(4) Produced by ICI, Ltd., under the trade name Nolvadex. For reviews of the pharmacology see: Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. *Drugs* **1978**, *16*, 1–24. Furr, B. J.; Patterson, J. S.; Richardson, D. N.; Slater, S. R.; Wakeling, A. E. In "Pharmacological and Biochemical Properties of Drug Substances"; Goldberg, M. E., Ed.; American Pharmaceutical Association: Washington, DC, 1979; Vol. 2, pp 335–399.

(5) Harper, M. J. K.; Walpole, A. L. *Nature (London)* **1966**, *212*, 87.

(6) Jordan, V. C. *J. Steroid Biochem.* **1974**, *5*, 354. Jordan, V. C. *Eur. J. Cancer* **1976**, *12*, 419–424. Jordan, V. C., Allen, K. E. *Ibid.* **1980**, *16*, 239–251.

(7) Wasterberg, H. *Cancer Treat. Rep.* **1980**, *64*, 117–121. Lerner, H. J.; Band, P. R.; Israel, L.; Leung, B. S. *Ibid.* **1976**, *60*, 1431–1435 and subsequent papers in this issue. Kiang, D. T.; Frenning, D. H.; Vosika, G. J.; Kennedy, B. J. *Cancer* **1980**, *45*, 1322–1325.

(8) Borgna, J.-L.; Rochefort, H. *C. R. Hebd. Seances Acad. Sci.* **1979**, *289*, 1141–1144; *J. Biol. Chem.* **1981**, *256*, 859–868. Fromson, J. M.; Pearson, S.; Bramah, S. *Xenobiotica* **1973**, *3*, 693–709, 711–714. Jordan, V. C.; Collins, M. M.; Rowsby, L.; Prestwich, C. *J. Endocrinol.* **1977**, *75*, 305–316.

(9) Jordan, V. C.; Haldeman, B.; Allen, K. E. *Endocrinology (Baltimore)* **1981**, *108*, 1353–1361 and references cited therein.

(10) Katzenellenbogen, B. S.; Pavlik, E. J.; Robertson, D. W.; Katzenellenbogen, J. A. *J. Biol. Chem.* **1981**, *256*, 2098–2915. Tatee, T.; Carlson, K. E.; Katzenellenbogen, J. A.; Robertson, D. W.; Katzenellenbogen, B. S. *J. Med. Chem.* **1979**, *22*, 1509–1517. Katzenellenbogen, B. S.; Katzenellenbogen, J. A.; Eckert. R. L.; Hayes, J. R.; Robertson, D. W.; Tatee, T.; Tsai, T. L. *Prog. Cancer Res. Ther.* **1980**, *14*, 309–320. Hayes, J. R.; Rorke, E. A.; Robertson, D. W.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Endocrinology (Baltimore)* **1981**, *107*, 164–172.

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