TOTAL SYNTHESIS OF dl-CAMPTOTHECIN

by

Joel Chandler Bradley

A.B., Bowdoin College (1970)

Submitted in Partial Fulfillment

of the Requirements for the

Degree of Doctor of Philosophy

at the

Massachusetts Institute of Technology

September, 1975

Signature of Author Signature redacted
Department of Chemistry, September, 1975

Certified by Signature redacted
Thesis Supervisor

Accepted by Signature redacted
Chairman, Departmental Committee on Graduate Students

ARCHIVES
MASS. INST. TECH.
SEP 24 1975
LIBRARIES

This doctoral thesis has been examined by a Committee of the Department of Chemistry as follows:

Professor K. Barry Sharpless — Signature redacted
Chairman

Professor George H. Büchi — Signature redacted
Thesis Supervisor

Professor Glenn A. Berchtold — Signature redacted

Total Synthesis of dl-Camptothecin

by

Joel Chandler Bradley

Submitted to the Department of Chemistry
in August 1975, in partial fulfillment of
the requirements for the degree of
Doctor of Philosophy

Abstract

A synthesis of dl-camptothecin is described *via* preparation of the tetracyclic pyridone ester 20.

Thesis Supervisor: George H. Büchi

Title: Professor of Chemistry

ACKNOWLEDGMENTS

I would like to thank the people in the group, whose broad experience and knowledge have contributed greatly to my professional background. In addition, the friendship and support of many of my coworkers is personally appreciated.

I would like to thank members of the group for helpful discussions in the course of my work. In addition, special thanks go to members of the group who provided me with spectra; Mrs. Ruth Luthi, Dr. John Vederas, Dr. Harold Broughton, and Mr. Kin-Chun Luk. Thanks also go to Dr. Charles Hignite and Dr. Cathy Costello for providing mass spectra and Dr. Robert Engle for providing a sample of starting material. Particular thanks go to Mr. David Williams and Dr. William Moberg for helping proofread this thesis and for their continued friendship. I would also like to thank Mrs. Donna Latz for typing this thesis.

Financial support from the Department of Chemistry (1970-1973) is acknowledged.

Special thanks go to my wife Cindy for her continued help and support in all of my work.

Table of Contents

	Page
Introduction	8
Discussion	19
Experimental	52
Ethyl N-Carbobenzyloxy-N-carboethoxymethyl-β-alaninate (37b)	53
Ethyl N-(2, 2, 2-Trichloroethoxycarbonyl)-N-carboethoxymethyl-β-alaninate (37c)	53
Ethyl N-(o-Nitrophenylsulfenyl)-N-carboethoxymethyl-β-alaninate (37d)	54
Methyl N-(o-Nitrophenylsulfenyl)-N-carboethoxymethyl-β-alaninate (37e)	54
N-Carbobenzyloxy-4-carboethoxy-3-pyrrolidinone (38b)	55
N-(2, 2, 2-Trichloroethoxycarbonyl)-4-carboethoxy-3-pyrrolidinone (38c)	55
N-Benzyl Vinylogous Amide 39a	56
N-Carbobenzyloxy Vinylogous Amide 39b	56
Vinylogous Amide 39c	57
Methyl 2-Carbomethoxy-3-methyl-4-oxohexanoate (43)	57
Ketal Diester 46	58
Bromo Ketal 47	58
2-(1-Bromoethyl)-2-ethyl-1, 3-dioxolane (49)	59
Phosphonium Salt 50	59
Phosphonium Ketal 51	59
2-Ethyl-2-isopropenyl-1, 3-dioxolane (53)	60
2-Acetyl-2-ethyl-1, 3-dioxolane (54)	60
Ylid 55	60
Ethyl 2-Carboethoxy-3-methyl-4-oxo-2-hexenoate (56)	61
Ethyl 3-Bromomethyl-2-carboethoxy-4-oxo-2-hexenoate (41)	61
Bromomethyl Lactone 57	62
(E)-1-Propenyl Trimethylsilyl Ether (60a) and (Z)-1-Propenyl Trimethylsilyl Ether (60b)	62
Ethyl 4, 4-Diethoxytetrolate (64)	63
Ethyl 2-Ethyl-3-(N-pyrrolidyl)-acrylate (65a)	63
Enol Silyl Ether 65b	64
2-Allylbutyric Acid (66)	64
Pyruvic Ester 68	65
Dimethyl Ester 73a	65
Diethyl Ester 73b	66
3-Chloro-3-formylacrylic Acid (75a)	66

Page

Experimental (continued)

tert-Butyl Methyl Ethylmalonate (76) 67
Bromo Diester 77 67
Bromoester 78 68
Lactone Ester 74 68
Vinylogous Urethane 79 69
Di-tert-butyl Tartarate 69
tert-Butyl Glyoxylate (78c) 70
Methyl 4,4-Dimethoxy-2-ethyl-3-oxobutyrate (81) 70
Methyl 3-Acetoxy-4,4-dimethoxy-2-ethylcrotonate (82a) 71
Ester Epoxide 85 71
Methyl 4,4-Dimethoxy-2-ethyl-2-methyl-3-oxobutyrate (86) 72
Methyl 2-Ethyl-3,4,4-trimethoxycrotonate (82b) 72
(Z) and (E) Methyl 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoate (89a and 89b) 73
(E) and (Z) Methyl 4-Carbomethoxy-3-dimethoxymethyl-3-hexenoate (89c and 89d) 74
Methyl 4-Carbomethoxy-3-dimethoxymethyl-2-methyl-3-hexenoate (92) 74
Methylene Diester 93 75
Ethyl Methyl Ester 94 75
Ethyl 4-Carboethoxy-3-dimethoxymethyl-2-hexenoate (95) 76
Methyl 2-Bromo-4-carbomethoxy-3-dimethoxymethyl-3-hexenoate (96) 76
Methyl 4-Carboxy-3-dimethoxymethyl-2-hexenoate (97) 77
Methyl 4-Carbomethoxy-3-methoxymethyl-2-hexenoate (100) 77
Methyl 4-Carbomethoxy-3-dimethoxymethyl-hexanoate (99) 78
Enol Lactone 102 78
tert-Butyl Dimethylphosphonoacetate (105) 79
(Z) and (E) tert-Butyl 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoate (106) 79
tert-Butyl 4-Carbomethoxy-3-dimethoxymethyl hexanoate (107) 80
4-Carbomethoxy-3-dimethoxymethylhexanoic Acid (108) 80
2,2,2-Trichloroethyl 4-Carbomethoxy-3-dimethoxymethylhexanoate (109a) 81
Benzyl 4-Carbomethoxy-3-dimethoxymethyl-hexanoate (109b) 81
Amide Acetal 110 82
Aldehyde 111 83

Page

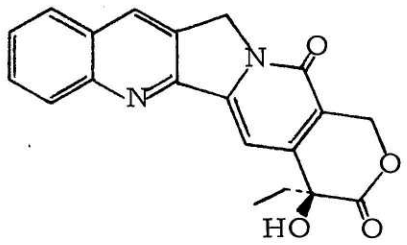
Experimental (continued)

Dihydropyridone 112 83
Benzyl Bromoacetate (116a) 84
Benzyl Dimethylphosphonoacetate (116) 84
(Z) and (E) Benzyl 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoate (117a and 117b) 85
(Z) and (E) Benzyl 4-Carbomethoxy-3-dimethoxymethyl-3-hexenoate (117c and 117d) 85
(Z) and (E) 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoic acid (115) 86
(Z) and (E) 4-Carbomethoxy-3-dimethoxymethyl-3-hexenoic Acid (115a) 86
Amide Acetal 118 87
Amide Acetal 118a 87
Pyridone 20 88

Bibliography 90

Biographical Note 93

INTRODUCTION

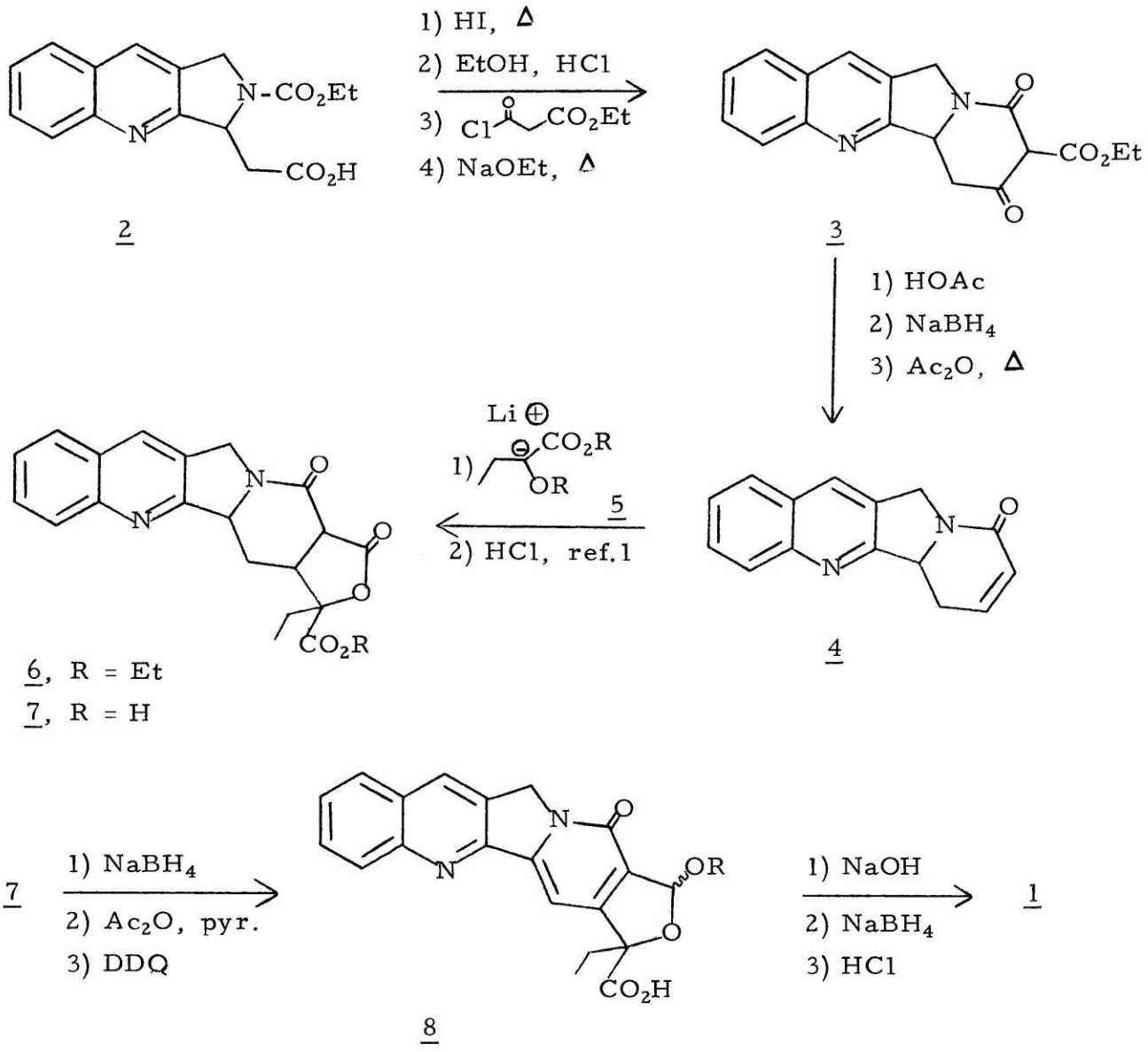


1

Camptothecin is an alkaloid first isolated from the stem wood extracts of Camptotheca acuminata, a tree native to mainland China.[1] An X-ray crystallographic analysis was performed on the iodoacetate derivative, conclusively establishing the structure of camptothecin as 1.[2] Early tests on the pure material showed promising antileukemic and antitumor properties,[1] causing many laboratories to commence work on its total synthesis. Although subsequent clinical testing has shown that camptothecin is not a useful anticancer agent due to its high toxicity, there is renewed interest in its inhibitory effect on macromolecular synthesis.[3] Furthermore, there is still hope of finding clinically useful anticancer agents by preparing structural analogs of camptothecin.

The extensive effort by many groups towards a synthesis of camptothecin resulted in the early publication of three successful approaches.[4,5,6] The first total synthesis of dl-camptothecin (1) was reported by Stork and Schultz in 1971.[4] In this approach, the known[7] tricyclic quinoline acid 2 was converted to the unsaturated lactam 4

via the β-ketoamide 3 in seven steps.



2 3 4

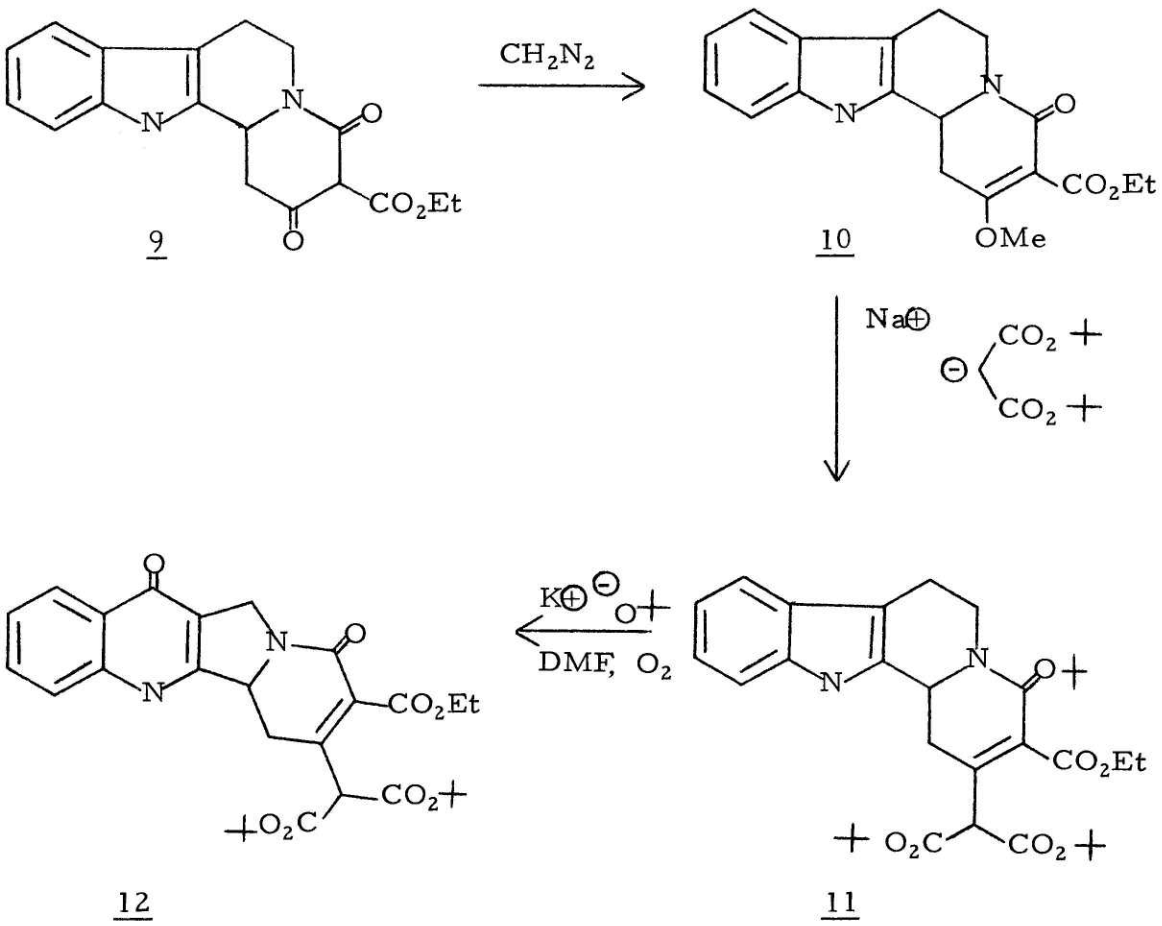
6, R = Et
7, R = H

8

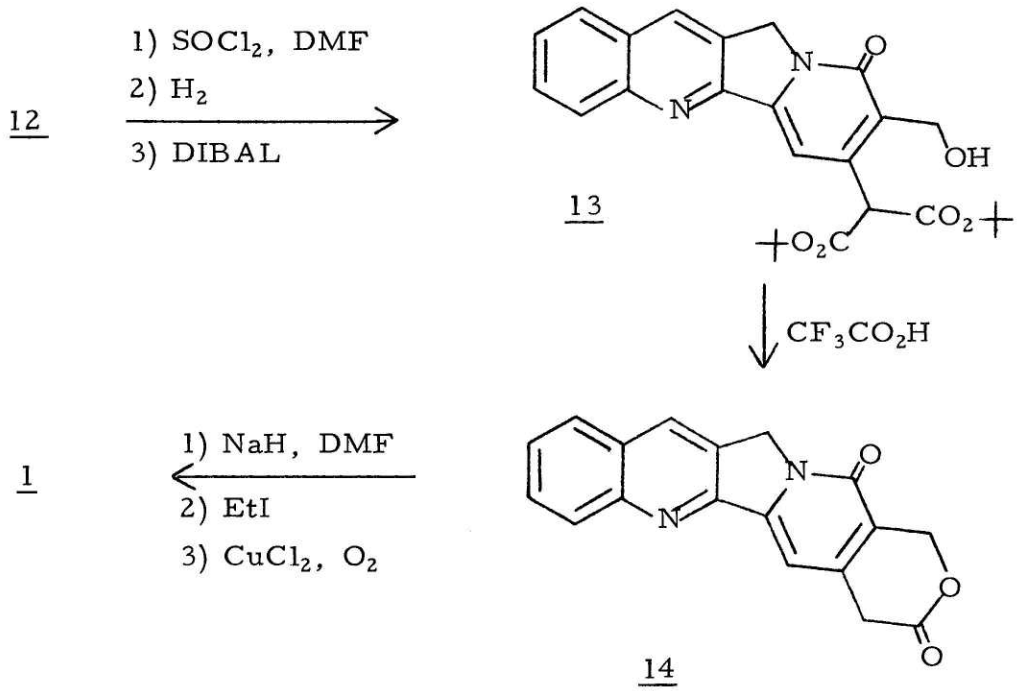
Addition of the lithium anion of butyrate ester 5 followed by hydrolysis gave 7 in low (<20%) yield from 4. Carboxylic acid 7 was converted to pyridone 8 in unreported yield by reduction, acetylation,

and dichlorodicyanoquinone oxidation. The final sequence of reactions used to construct the hydroxylactone ring (also in unreported yield) consisted of base cleavage, reduction, and acid-catalyzed cyclization, completing a synthetic route of some fifteen steps.

In a novel biogenetic-like approach to camptothecin, Winterfeldt made use of an indole-to-quinoline oxidative conversion.[6] Indole 9 (prepared from tryptamine in three steps) was converted to lactam 10 by methylation with diazomethane. Elaboration was continued by conjugate addition of di-tert-butyl malonate anion to give 11, followed by autoxidation to the quinolone 12.



Reduction of 12 was accomplished in two steps by treatment with thionyl chloride in dimethyl formamide, followed by hydrogenolysis of the resulting chloroquinoline. Reduction of the ethyl ester followed by decarboxylation and cyclization of 13 gave lactone 14.

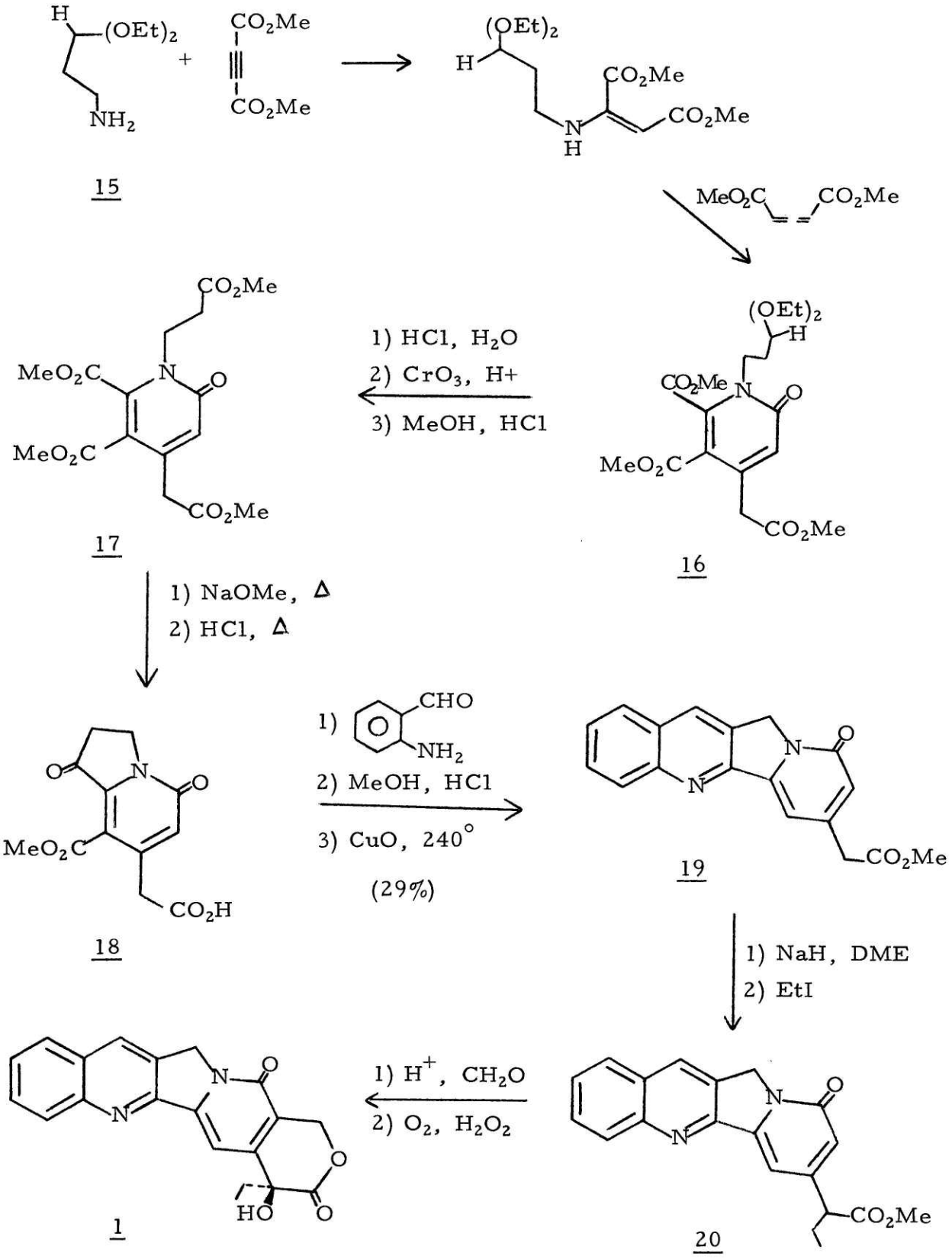


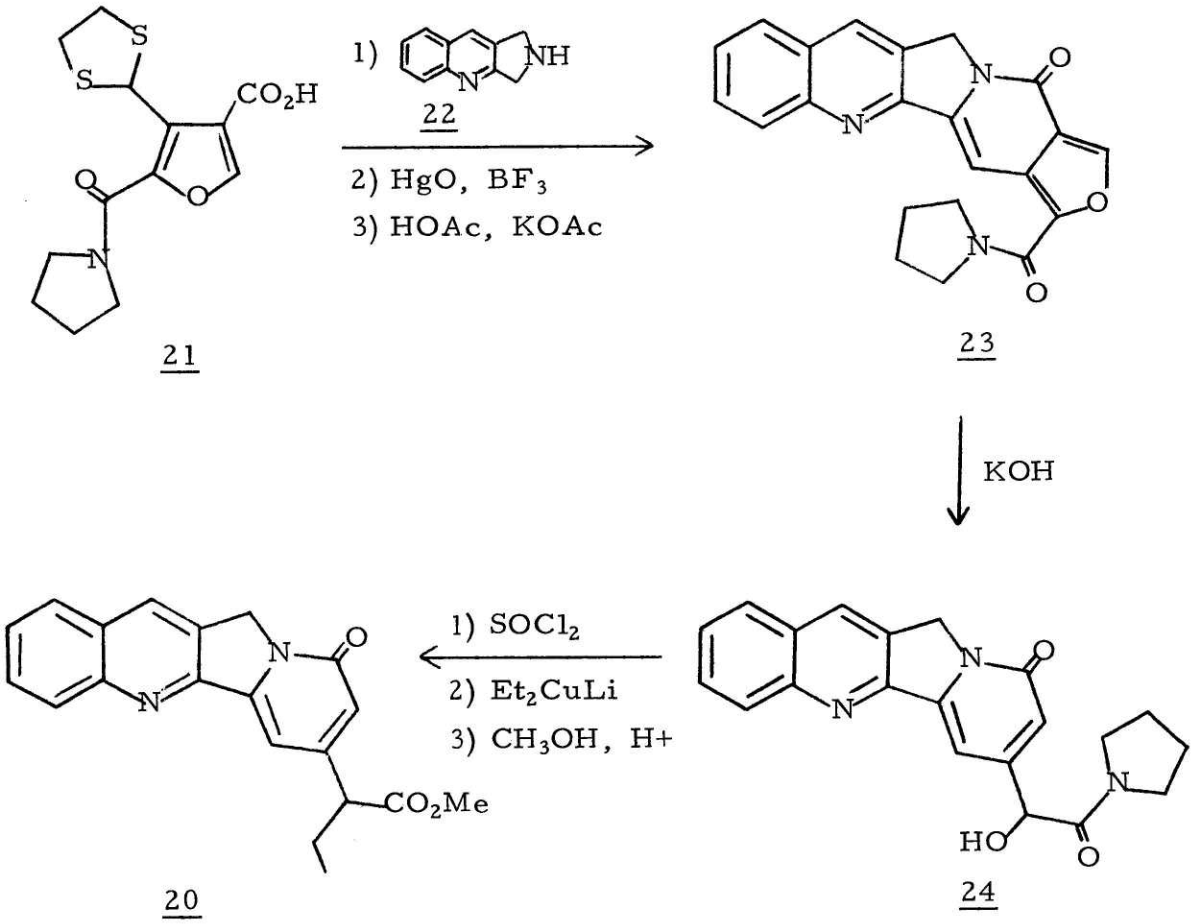
The ethylation of 14 proceeds in low yield (20%) and is one of the serious drawbacks of this and other syntheses which make use of this intermediate[8,9,10] or require a similar alkylation in the late steps.[5,11] The extremely facile oxidation to dl-camptothecin completed this synthesis in twelve steps from tryptamine.

The synthesis reported by Danishefsky[5] involved formation of a highly functionalized pyridone as the D-ring precursor. Pyridone triester 16 was prepared in 30% overall yield from acetal 15. After deprotection, oxidation, and esterification, tetraester 17 was cyclized and decarboxylated, giving the bicyclic pyridone 18. Tetracyclic ester 19 was prepared (29% yield) by Friedlander condensation with o-aminobenzaldehyde followed by esterification and decarboxylation. Alkylation of 19 with base and excess ethyl iodide was performed in typically low yield (20%), giving 20 in 1-2% overall yield from 15.

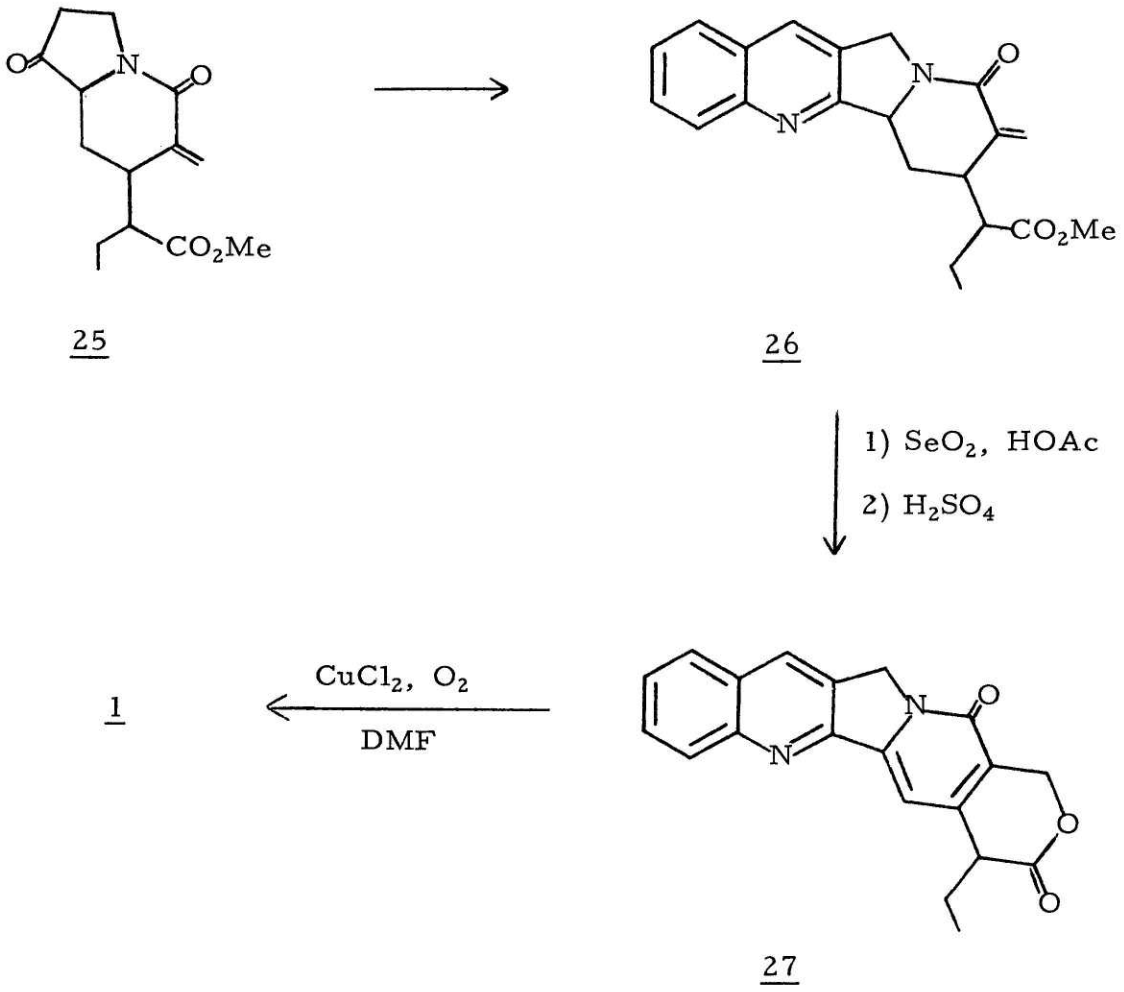
The final step of this synthesis involves a hydroxymethylation-lactonization reaction followed by oxidation to dl-camptothecin. Subsequent studies have reported that this oxidation will proceed spontaneously if deoxycamptothecin is exposed to air, or it can be carried out quantitatively using cuprous chloride, dimethylformamide, and oxygen.[6]

Kende[11] later reported a synthesis in which Danishefsky's precamptothecin pyridone 20 was prepared in fifteen steps. In this scheme, the highly functionalized furan carboxylic acid 21 was synthesized in nine steps from furfural dimethyl acetal (15% overall yield). This E-ring precursor was coupled with the known tricyclic amine 22[12] and cyclized to the pentacyclic furan 23. Basic hydrolysis of 23 to hydroxyamide 24 followed by chlorination, ethylation, and methanolysis gave pyridone ester 20 (9% from 22, 1-2% overall yield).


15
16
17
18
19
20
1
1) HCl, H2O
2) CrO3, H+
3) MeOH, HCl
1) NaOMe, Δ
2) HCl, Δ
1) MeOH, HCl
2) CuO, 240°
(29%)
1) NaH, DME
2) EtI
1) H+, CH2O
2) O2, H2O2

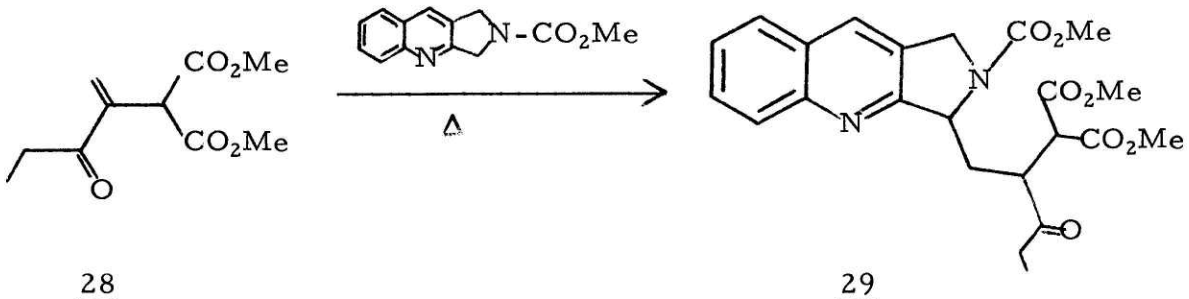


Rapoport[13] published a total synthesis in which α-methylene lactam 25 (prepared in ten steps) was condensed with N-(2-aminobenzylidene)-p-toluidine[14] to give the tetracyclic quinoline 26. After aromatization and oxidation of 26, hydrolysis and lactonization in sulfuric acid gave deoxycamptothecin (27). Oxidation by Winterfeldt's procedure[6] gave dl-camptothecin (1) in fourteen steps with "good" yields claimed for all reactions.



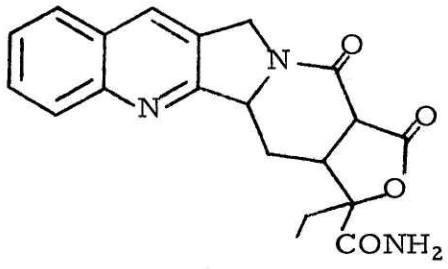
25 26 1 27

Wall and associates[15] reported the first of several syntheses[9,11,16] which make use of the tricyclic amine 22. In this approach, enone 28 was condensed with the carbomethoxy derivative of 22 giving 29. Cyanohydrin formation, followed by two separate hydrolyses, and successive base and acid-catalyzed cyclizations gave lactone 30. The final steps called for D-ring aromatization, followed by selective lactone reduction, amide hydrolysis and lactonization, producing dl-camptothecin in unreported yield in eleven steps.



28 29

1) HCN
2) MeOH, HCl
3) HBr
4) NaOMe
5) pTsa, Δ

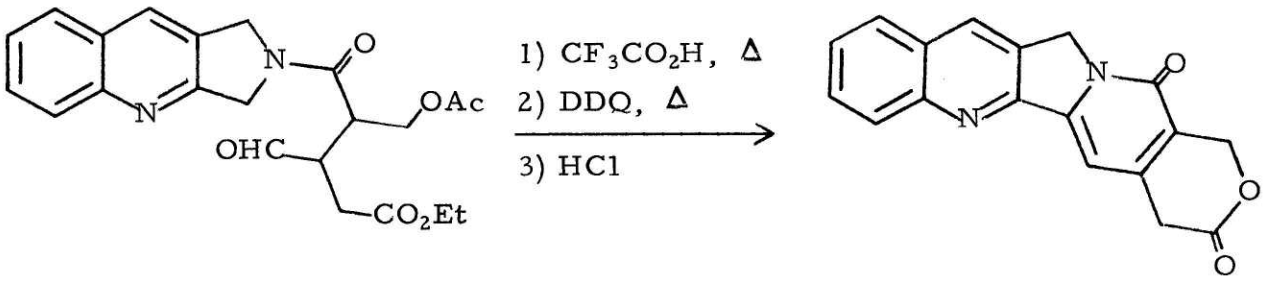


30

1) DDQ
2) $LiBH_4$
3) HCl

1

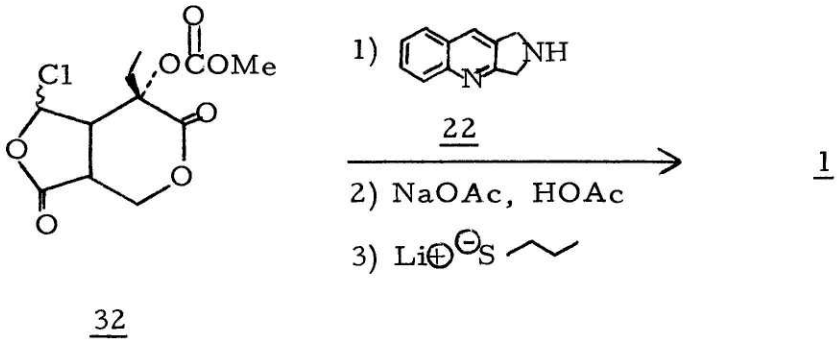
Other syntheses which have appeared[9,10,16] offer little or no improvement in the way of preparatively useful routes. As with the initial publications, later schemes which have been developed require many steps and give low overall yields. Meyers[9] reports the preparation of aldehyde 31 (in eight steps) starting with the tricyclic amine 22 and furfural. This is subsequently converted to 14 in very low yield via cyclization, oxidation, and lactonization.



31 14

This work and the efforts of many other groups which resulted in unsuccessful approaches to camptothecin are included in the comprehensive review article by Schultz.[3]

The most recently published work is a communication by Corey[16] describing the coupling of the resolved intermediate 32 (prepared in fourteen steps) with 22 to ultimately give natural 20(S)-camptothecin in extremely low yield.

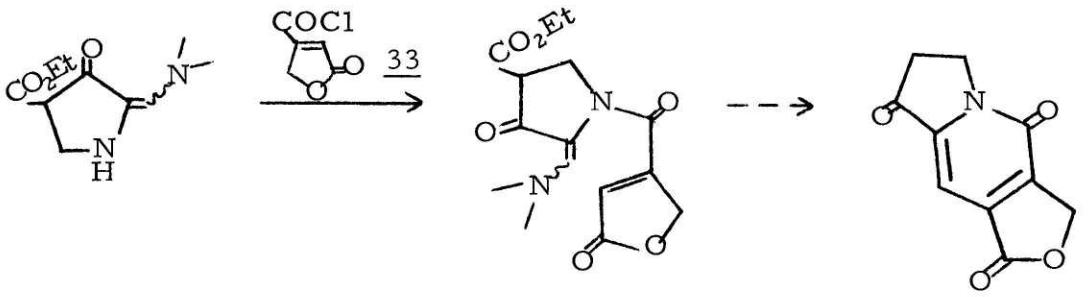


32

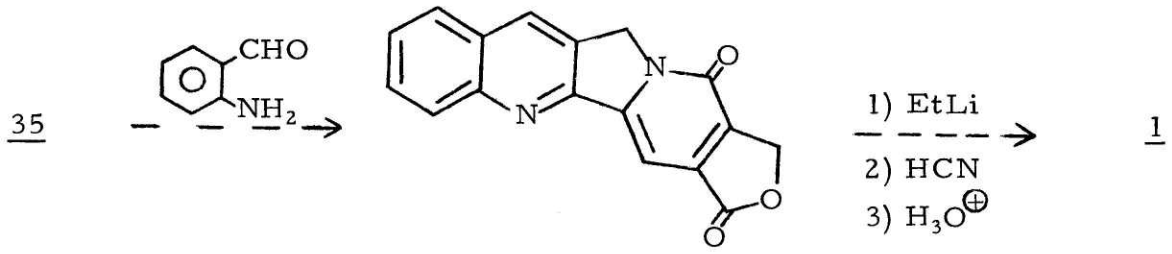
1

DISCUSSION

Initial approaches to camptothecin were directed towards preparation of the functionalized pyrrolidinone 34. It was hoped that this could be coupled with aconyl chloride (33)[17,18] and cyclized to give pyridone 35. This intermediate might then be elaborated further or condensed with o-aminobenzaldehyde to produce the pentacyclic lactone 36. Final elaboration of the E-ring lactone would give camptothecin (1).

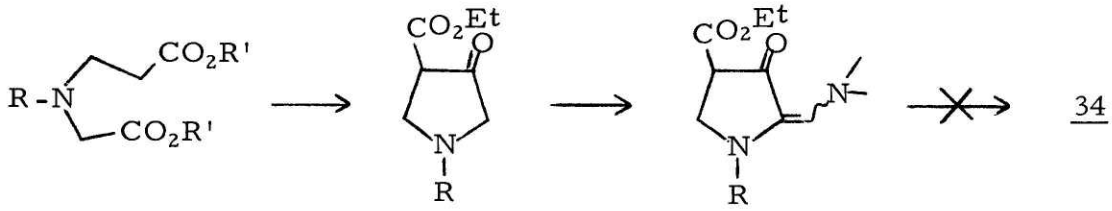


34 34a 35



36

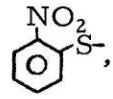
N-Benzyl pyrrolidinone 38a[19] was converted to vinylogous amide 39a by heating with dimethylformamide dimethylacetal in dimethylformamide. When attempts at reductive debenzylation failed to produce any of the free amine 34, several analogs of diester 37a (37b-e) were prepared by altering the N-protecting group on the diester starting material. Dieckmann condensation gave the corresponding pyrrolidinones 38b and 38c in good yield, but neither of the o-nitrophenylsulfenyl diesters 37d and 37e survived the basic conditions required for cyclization. Vinylogous amides 39b and 39c were prepared using dimethylformamide dimethylacetal. Attempted removal of either protecting group under acidic, basic, or neutral conditions led only to decomposition products, however.

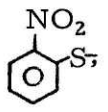


37a, R = Bz, R' = Et

37b, R = BzO, R' = Et

37c, R = Cl_3CCH_2O, R' = Et

37d, R = , R' = Et

37e, R = , R' = Me

38a, R = Bz

38b, R = BzO

38c, R = Cl_3CCH_2O

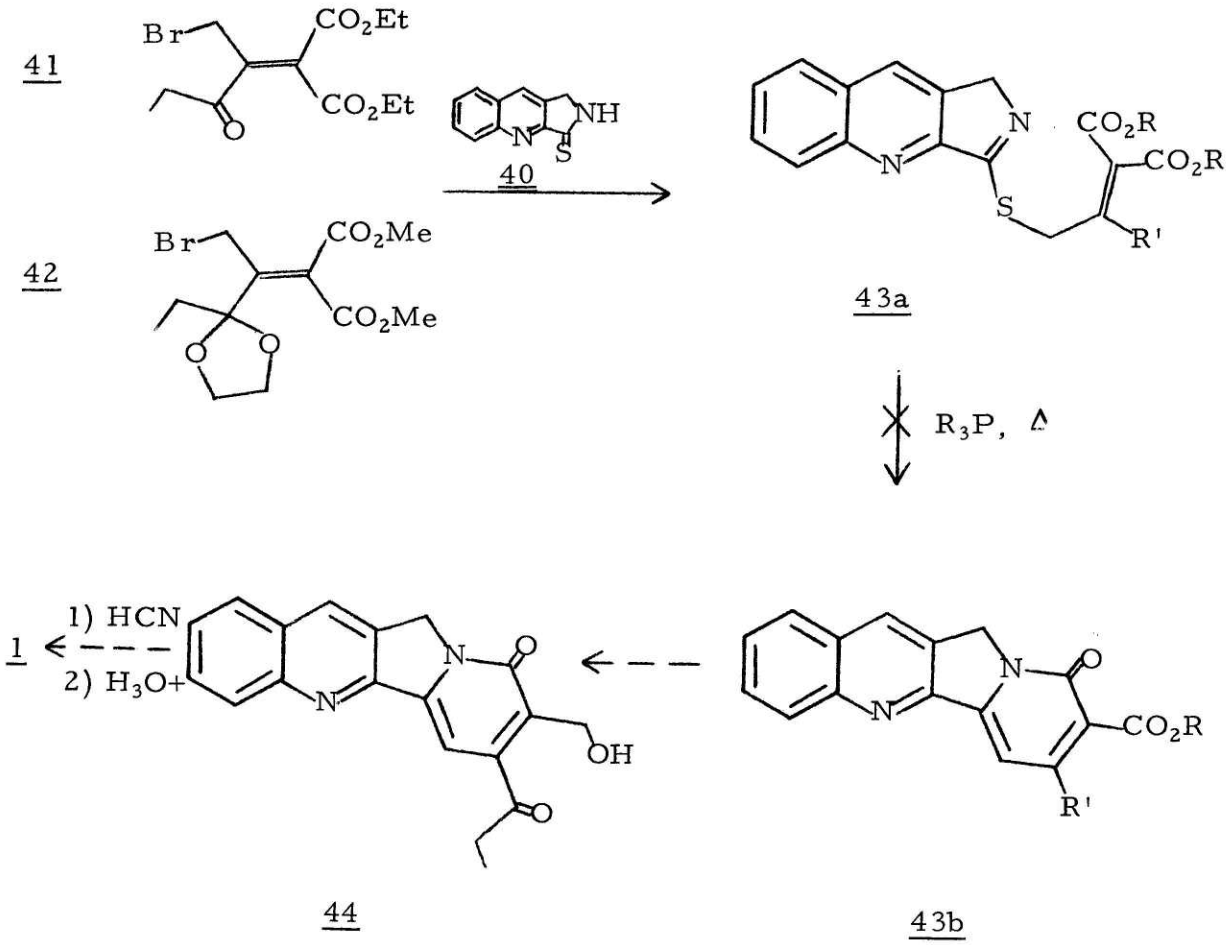
39a, R = Bz

39b, R = BzO

39c, R = Cl_3CCH_2O

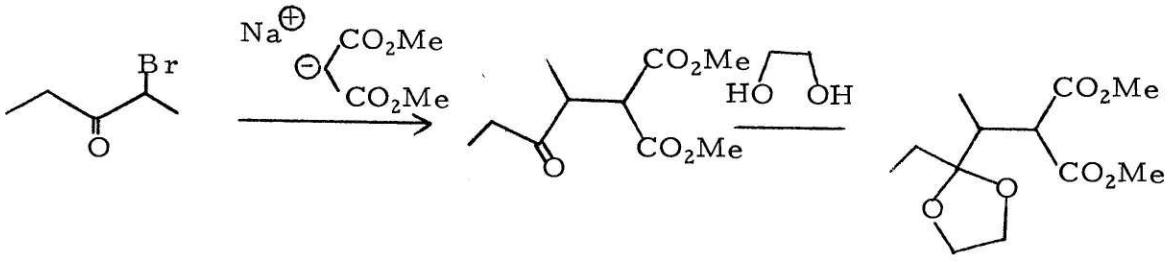
Due to the lack of success in attempts to make 34 and the low yields and difficult purifications involved in obtaining the vinylogous amides 39a-c, this approach was abandoned.

The next approach made use of the known[20] thiopyrrolidone 40 as the precursor to the A, B and C rings in camptothecin (1). The intention was to couple an appropriately functionalized crotonic ester such as 41 or 42 with 40 via S-alkylation followed by sulfide contraction in a sequence analogous to reactions developed by Eschenmoser and coworkers.[21]

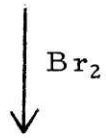


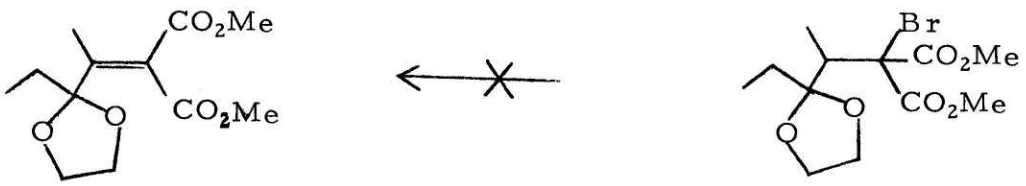
After cyclization to pyridone 43b, deprotection and reduction should give the keto alcohol 44. In planning this route, it was thought that cyanohydrin formation followed by hydrolysis would create the completely elaborated hydroxylactone E-ring, producing camptothecin (1).

The first target was bromoketal 42. By including the ketal in the starting material, a protecting step might be avoided at a later stage in the synthesis. Alkylation of dimethyl malonate with 2-bromo-3-pentanone gave keto diester 45[15a], which was readily ketalized with ethylene glycol to give 46. Although 46 was readily converted to bromide 47, attempts to dehydrobrominate this unactivated system returned the debrominated material 46.



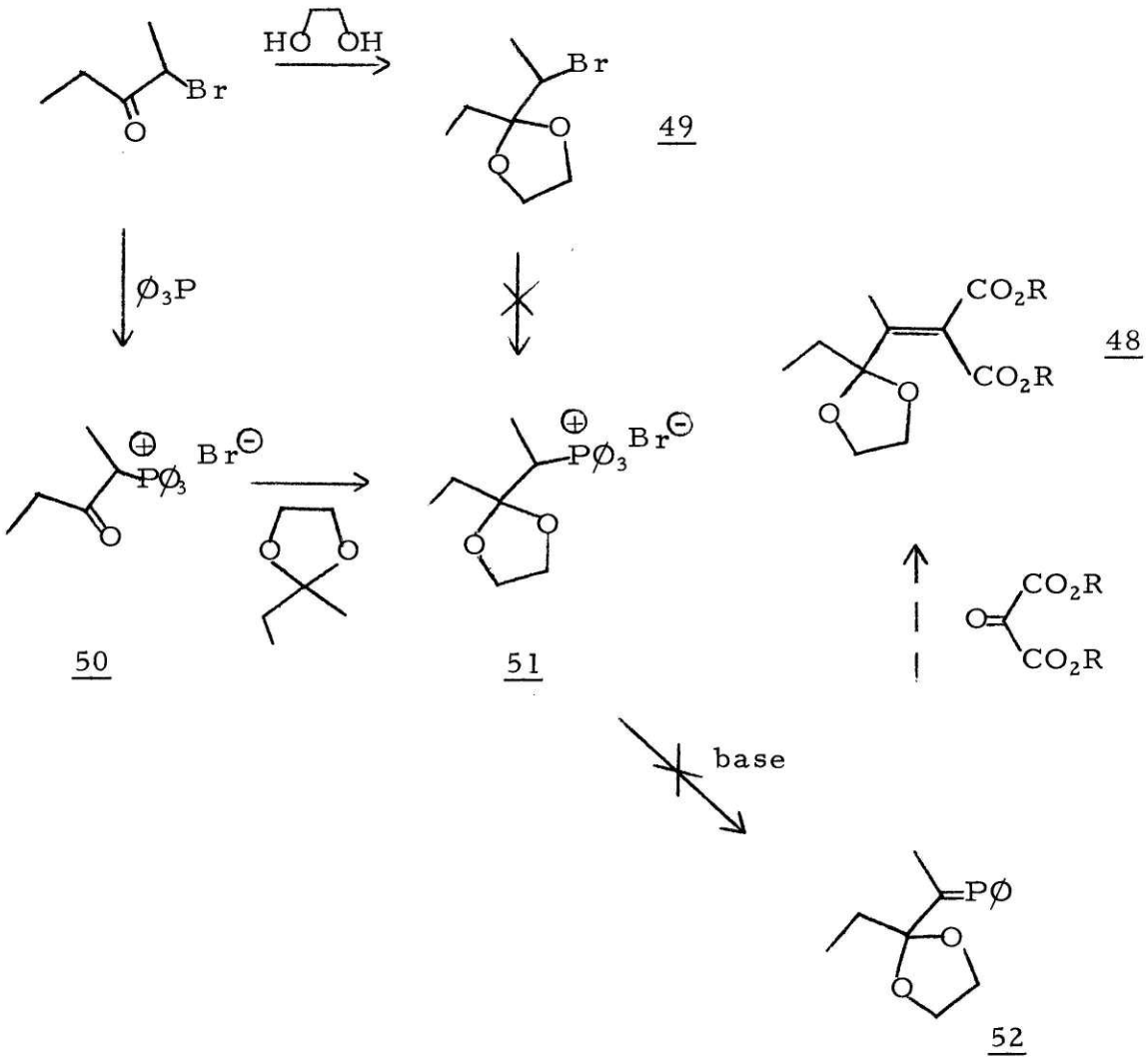
45 46



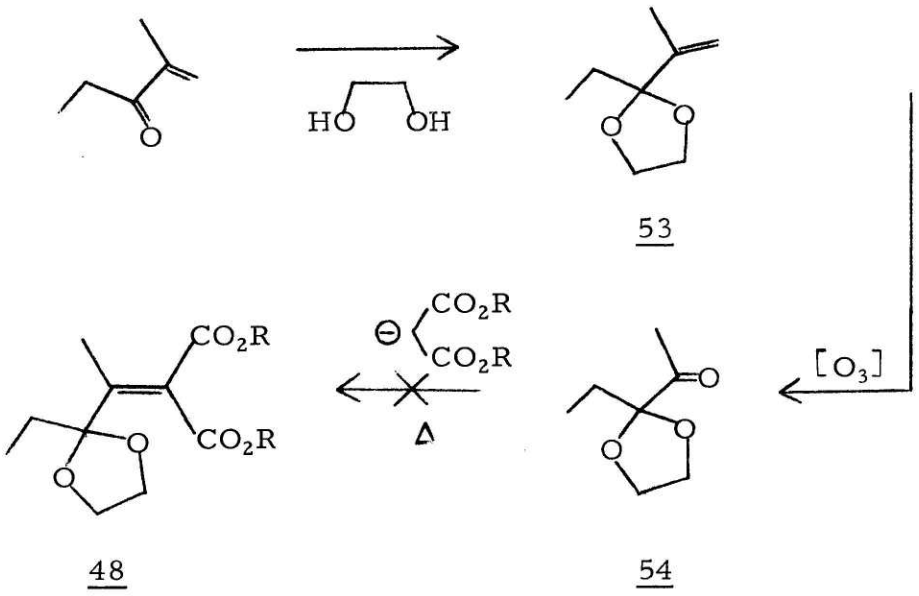


48 47

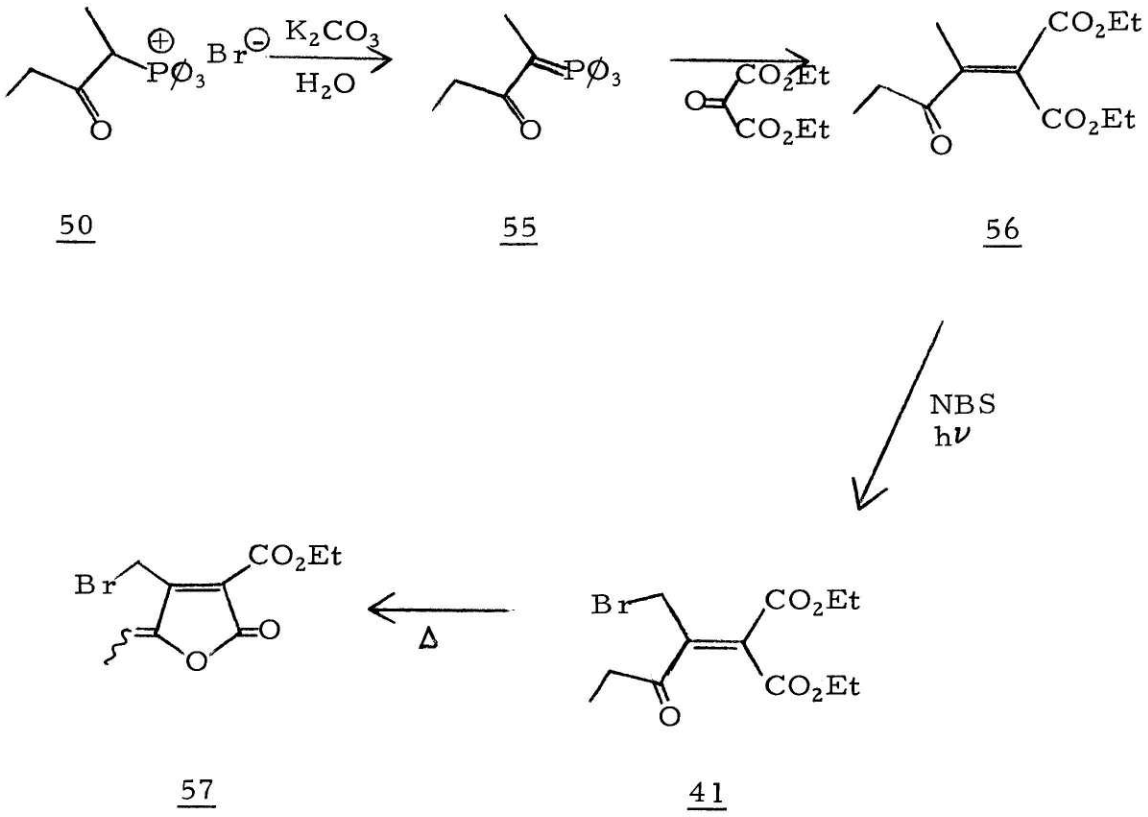
In a second scheme for the preparation of 42, 2-bromo-3-pentanone was ketalized with ethylene glycol giving 49. This bromide was not active enough for conversion to 51, however, so phosphonium salt 50 was prepared from 2-bromo-3-pentanone and triphenylphosphine and ketalized by heating in 2-ethyl-2-methyl-1, 3-dioxolane to give 51. Unfortunately, 51 could not be converted to its ylid 52 for condensation with mesoxalic ester, presumably due to base-induced β-elimination of the ketal alkoxide.



In a third sequence, ethyl isopropenyl ketone[22] was converted to ketal 53, then treated with ozone to give keto ketal 54. It was hoped that malonate would condense with 54 to give 48, but this did not prove to be the case. Treatment of 54 with sodium-, lithium-, or zinc-bromo-malonates at elevated temperatures produced none of the desired product 48.



At the same time, approaches to 41 were more successful. Phosphonium salt 50 was converted to ylid 55, which reacted cleanly with diethyl ketomalonate to give α-β unsaturated diester 56. Although attempts to ketalize 56 did not succeed, allylic bromination with N-bromosuccinimide gave bromo crotonate 41. It is of interest to note in passing that attempted distillation caused 41 to cyclize to the crystalline bromomethyl lactone 57.



50 55 56

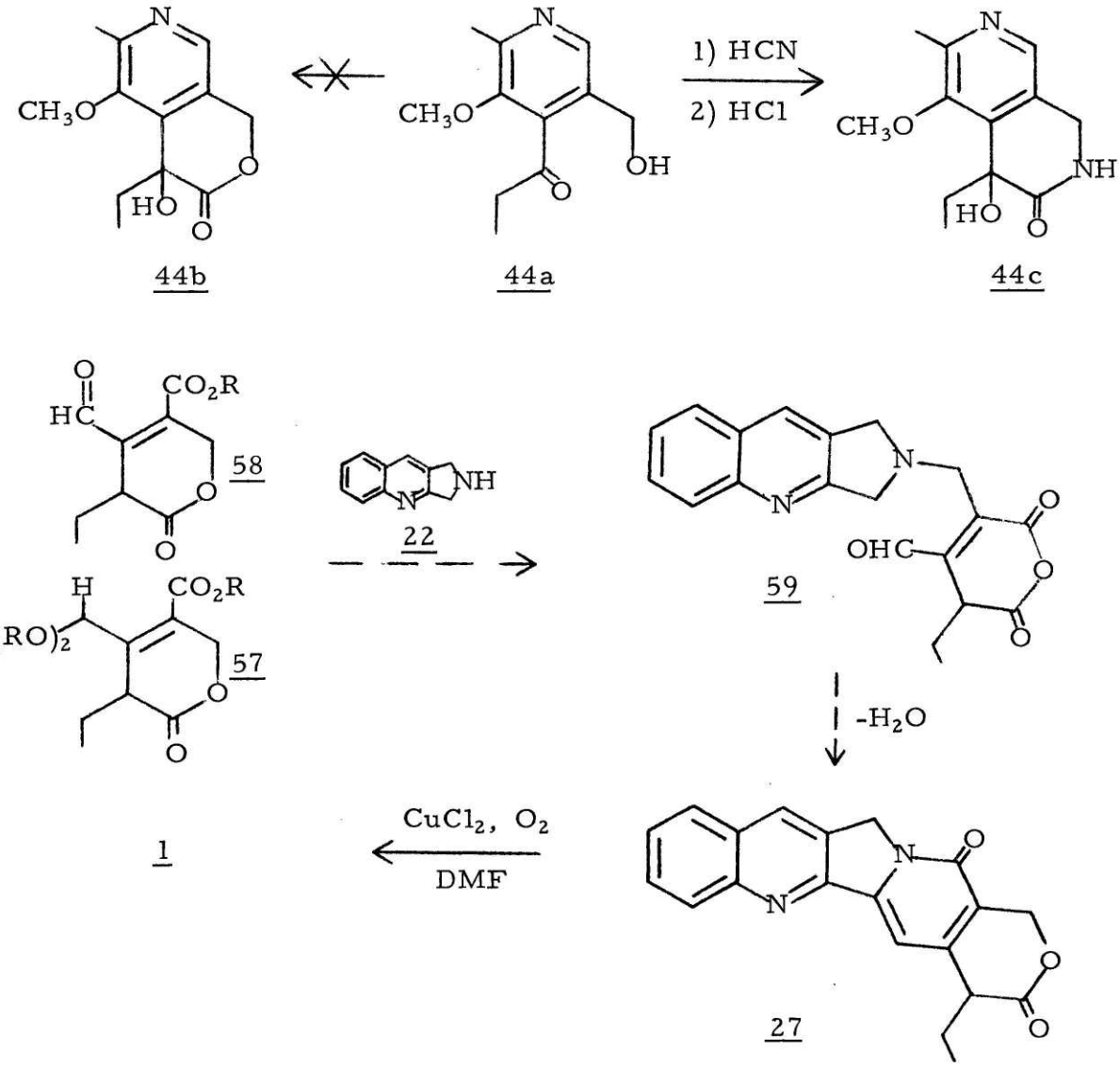
57 41

With 41 available, a series of attempts were made to do alkylative contractions with thioamide 40. Although spectral data obtained from crude intermediates indicated that S-alkylation was occurring, none of a variety of reaction conditions similar to those reported[21] afforded any of the contracted material. As a result of these findings, this approach was terminated.

It is interesting to note at this point that subsequent work published by Kametani[23] in a camptothecin model study indicates that pyridine keto alcohol 44a is transformed into hydroxylactam 44c, not hydroxylactone 44b, after treatment with hydrogen cyanide followed by hydrolysis. These results suggest that intermediates similar to 44

are of limited value in a synthetic plan. Furthermore, Schultz's review[3] credits Wall and coworkers with the preparation of pentacyclic lactone 36, and notes that no further reports have appeared concerning the conversion of 36 into camptothecin.

The next approach called for preparation of an appropriately functionalized lactone E-ring precursor such as 57 or 58, which might be coupled with the known[12] tricyclic amine 22. Cyclization of 59 should then be the only step necessary to give deoxycamptothecin (27).

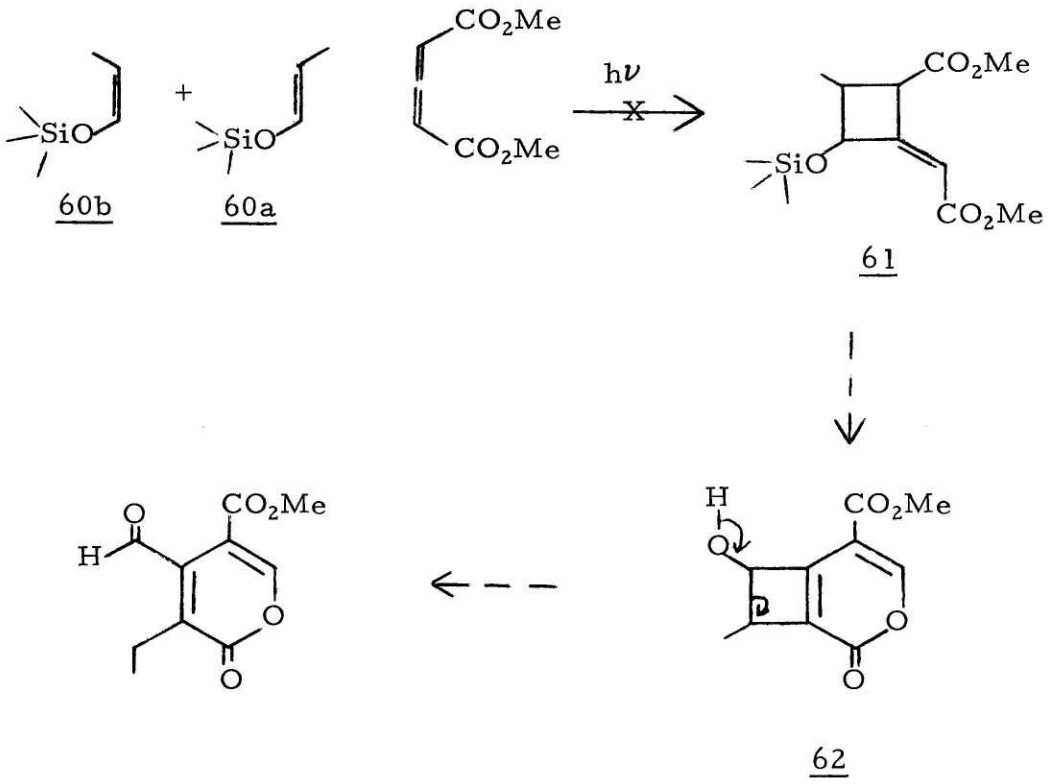


44b 44a 44c

58 22 59

57 1 27

The first attempt at producing an analog of 58 was based on photochemical 2+2 addition of silyl enol ethers 60a and 60b (prepared from propionaldehyde) with 1, 3-dicarbomethoxyallene[24] to give cyclobutane 61. Formylation and lactonization of 61, removal of the silyl ether, and base-induced retro-aldol opening of the cyclobutanol 62 might then give the pyrone 63.



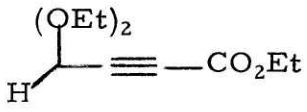
60b 60a 61 62 63

However, attempts at effecting the photochemical addition under a wide variety of conditions failed to give any of the desired product 61.

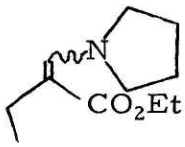
A second approach to 57 attempted to make use of the high degree of functionality and ready availability of acetylenic ester 64.[25] Reports of 2+2 additions of 3-amino acrylic esters or enol ethers with acetylenic

esters[26,27] stimulated the preparation of 65a and 65b. It was hoped that a cycloaddition of 65a or 65b to 64 would lead to a direct precursor of 57. High temperatures and long reaction times produced none of the desired products, perhaps due to the steric bulk of the diethoxymethyl substituents.

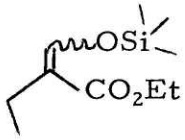
A third approach to 58 began with the coupling of allyl butyric acid (66)[28] with methyl diazopyruvate (67),[29] which was accomplished by heating the acid and the diazopyruvate together at 80° in the presence of copper powder giving 68. The plan then required oxidation of the terminal double bond to give aldehyde 69, which might be cyclized by base-catalyzed attack on the more reactive pyruvate carbonyl to produce 58. However, ozonolysis attempts caused the pyruvate portion of 68 to be cleaved off. Varying the concentrations, amounts of ozone, and solvents had little affect on the outcome. Furthermore, an alternative plan to oxidize the terminal olefin by epoxide formation and cleavage failed due to instability of the pyruvate segment even to mild oxidative conditions.



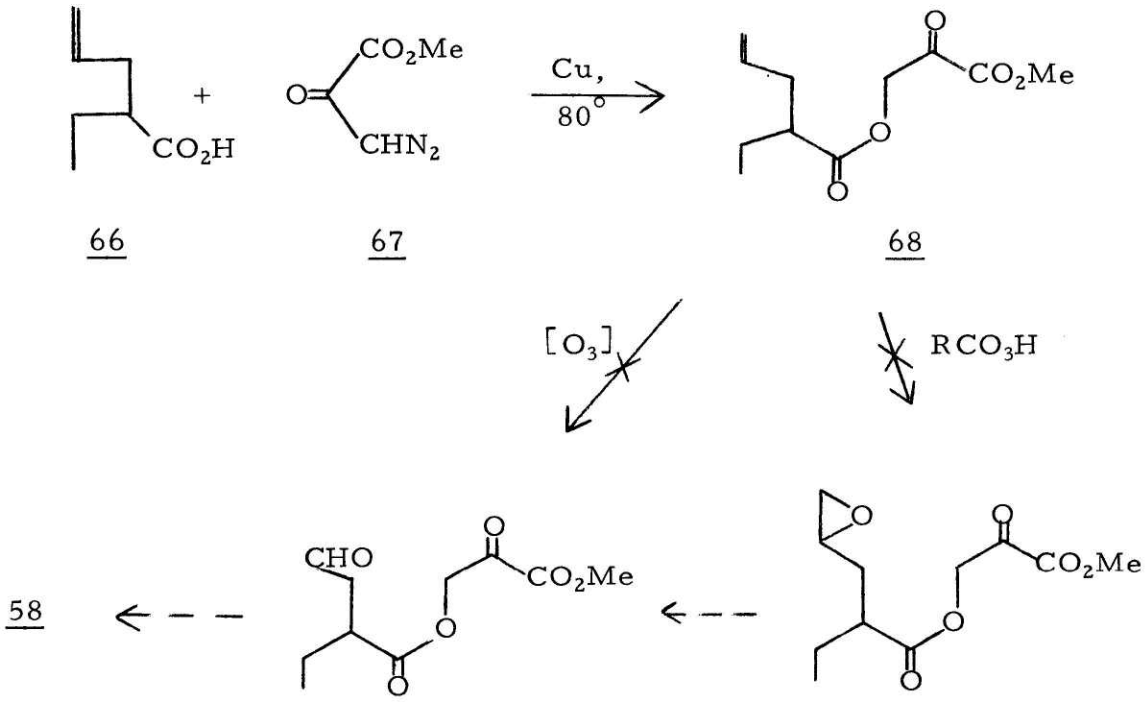
64



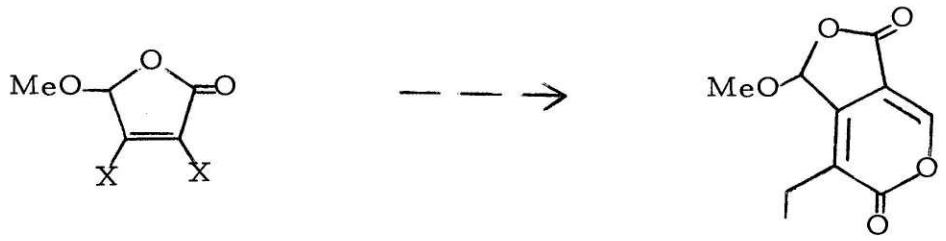
65a



65b



The next approach sought to make 70, a pseudo lactone analog of 58, from the readily available mucochloric or mucobromic acid pseudo esters 71a and 71b.



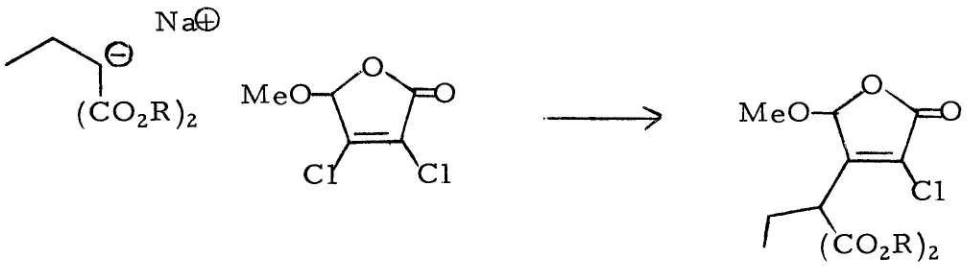
71a, X = Cl

71b, X = Br

70

It was recognized that the mucohalic acids contained the necessary aldehyde and carboxylic acid functionalities, and it seemed likely that conjugate addition by appropriate nucleophiles could be effected.

In practice, it was found that butyrate anions were too strongly basic to react cleanly with 71, but malonic ester anions 72a and 72b formed the desired conjugate addition products 73a and 73b in good yields.

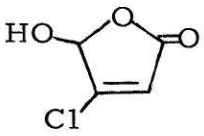


72a, R = Me
72b, R = Et

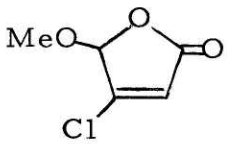
71a

73a, R = Me
73b, R = Et

As the sequence was continued, difficulties arose. Decarboxylation of the malonic esters was prevented by the instability of 73 to strong base. In addition, attempts to remove the vinylic chlorine by catalytic hydrogenolysis gave mixtures of products under all conditions tried. The known[30] 3-chloro-3-formyl acrylic acid 75a was prepared in an effort to avoid incorporation of the undesired α-halide, but all attempts to form the pseudo methyl ester 75b were unsuccessful due to decomposition of starting material.

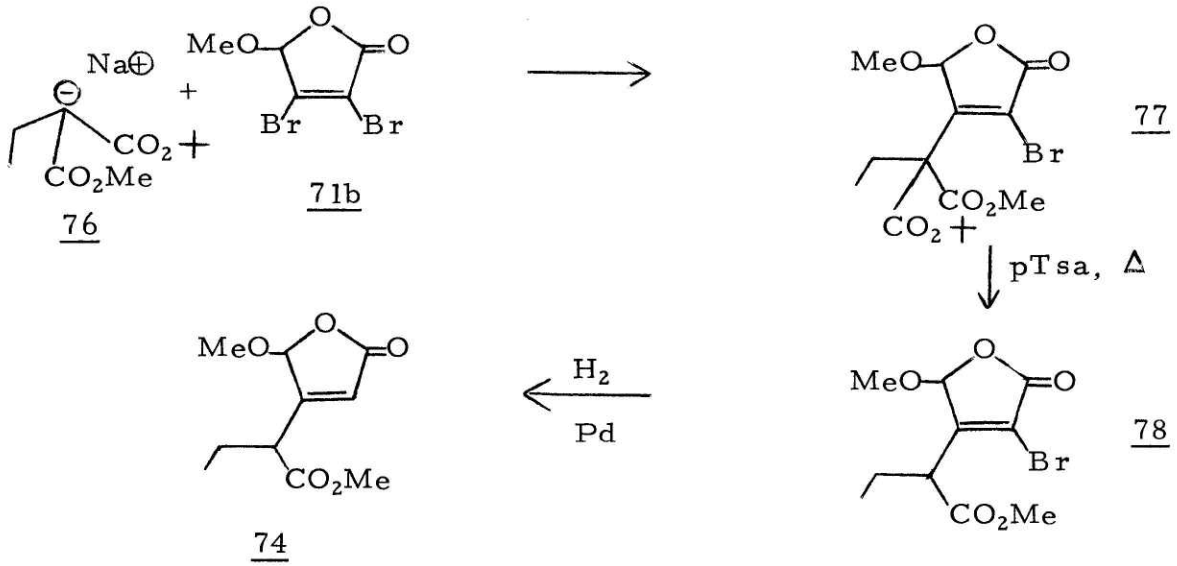


75a



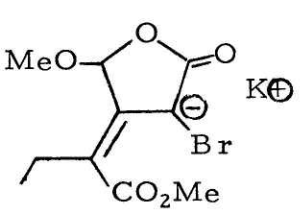
75b

Thus the use of methyl mucobromate (71b) was investigated in hopes that the vinylic bromide might be cleanly hydrogenolyzed. Furthermore, tert-butyl methyl ethylmalonate (76)[31] was prepared in order to facilitate decarboxylation of the adduct 77. Reaction of 71b and 76 provided the tert-butyl methyl ester 77. Monomethyl ester 78 was readily prepared by treating a solution of 77 in refluxing toluene with a trace of p-toluenesulfonic acid. Catalytic reduction of bromide 78 was accomplished with no difficulty by hydrogenation over 5% palladium on carbon in methanol-pyridine giving the desired lactone ester 74 in 90% yield from 77.

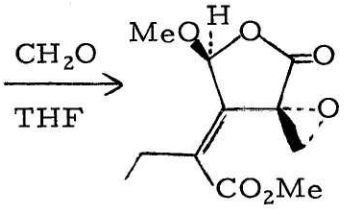


Attempts were then made to formylate 74. Since the pseudo ester lactones had been found to be unstable to some strong bases, 74 was treated with a wide variety of non-nucleophilic bases and formylating reagents in several solvents under a range of reaction conditions. The complete failure of these attempts led to a number of efforts at inducing acid-catalyzed attack of the olefins in 74 and 78 by trimethyl orthoformate or dimethoxymethane. Reactions run under various conditions with several Lewis acid catalysts failed to give any detectable useful product.

Attention was then turned to bromo lactone 78. Its potassium enolate could be formed at -78° in tetrahydrofuran. This species was stable for short periods of time at low temperature. When the enolate of 78 was allowed to react with formaldehyde gas, a mixture of two epimeric epoxides 78a and 78b was produced. However, these could not be rearranged to aldehyde 80 by any of the standard methods.[32,33]

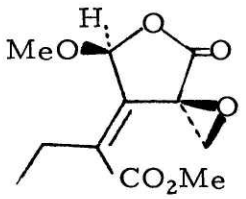


78

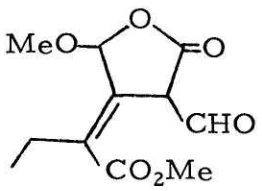


78a

+

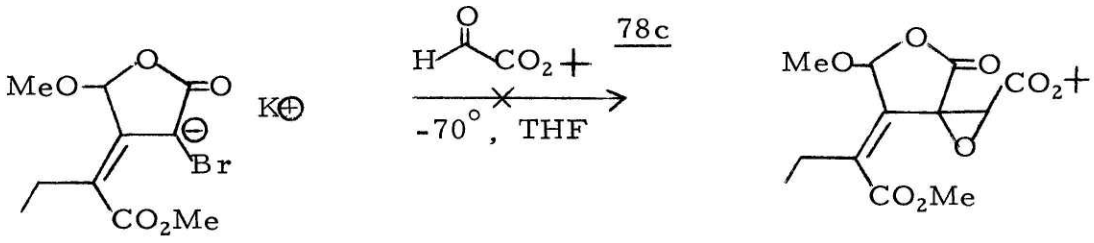


78b



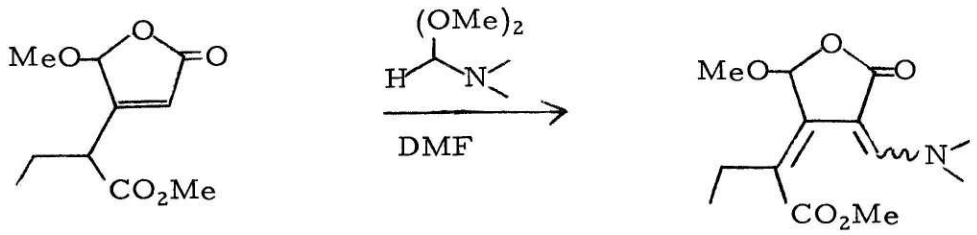
80

In a final effort to form 80 from 78, tert-butyl glyoxylate (78c) (prepared by permanganate cleavage of di-tert-butyl tartrate[34]) was added to a solution of the potassium enolate of 78. In this case, none of the hoped-for glycidic ester 78e was found.



78 78e

Finally, the alternative of condensing 74 with dimethylformamide dimethylacetal in hopes of producing a "masked aldehyde" was tried with positive results; vinylogous urethane 79 being isolated as a yellow crystalline solid. Attempts to hydrolize the dimethylamino methylene functionality using aqueous acid were unsuccessful. It was found upon spectral examination of hydrolysis products that the lactone pseudo ether was being opened selectively while the dimethylamino moiety remained intact. Other attempts at converting 79 to the formyl compound 80 via oxidation, quarternization, or hydrolysis failed, as the severity of conditions required caused decomposition of the lactone ring.

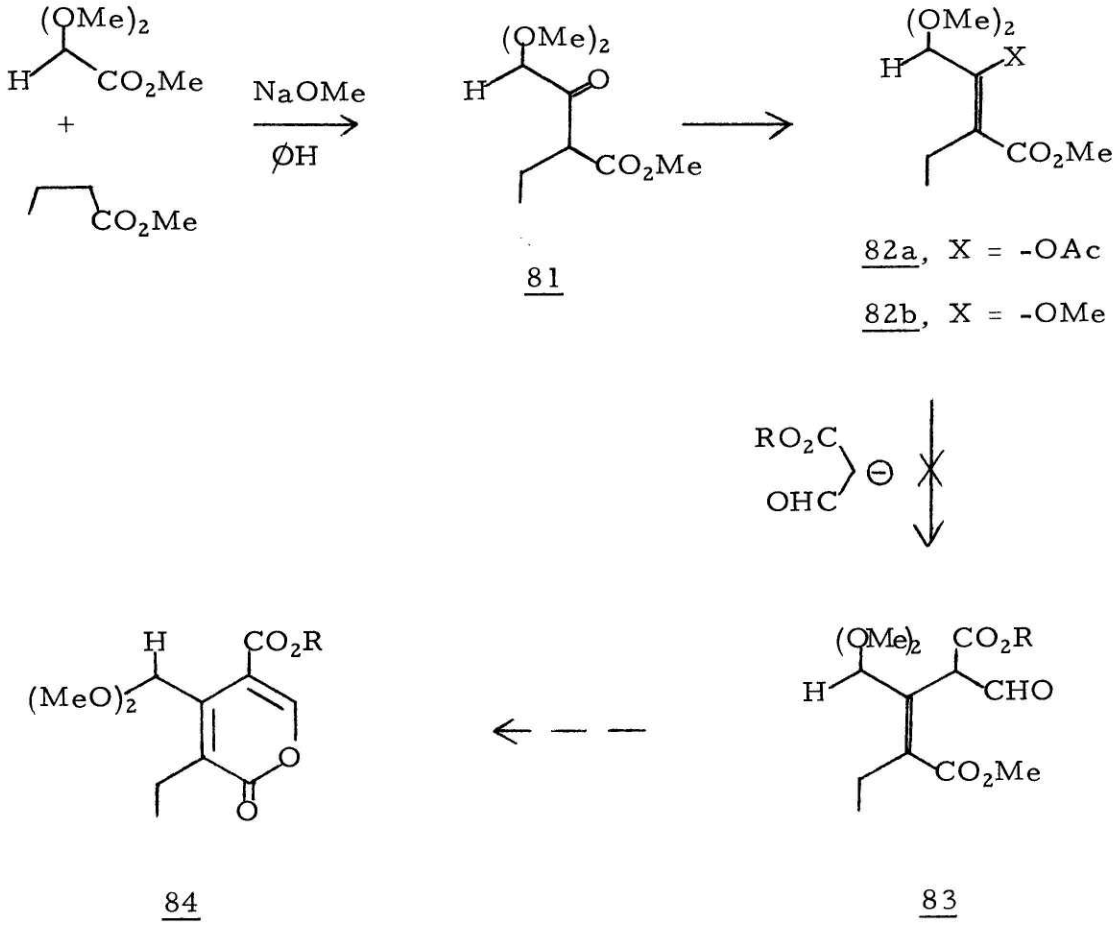


74 79

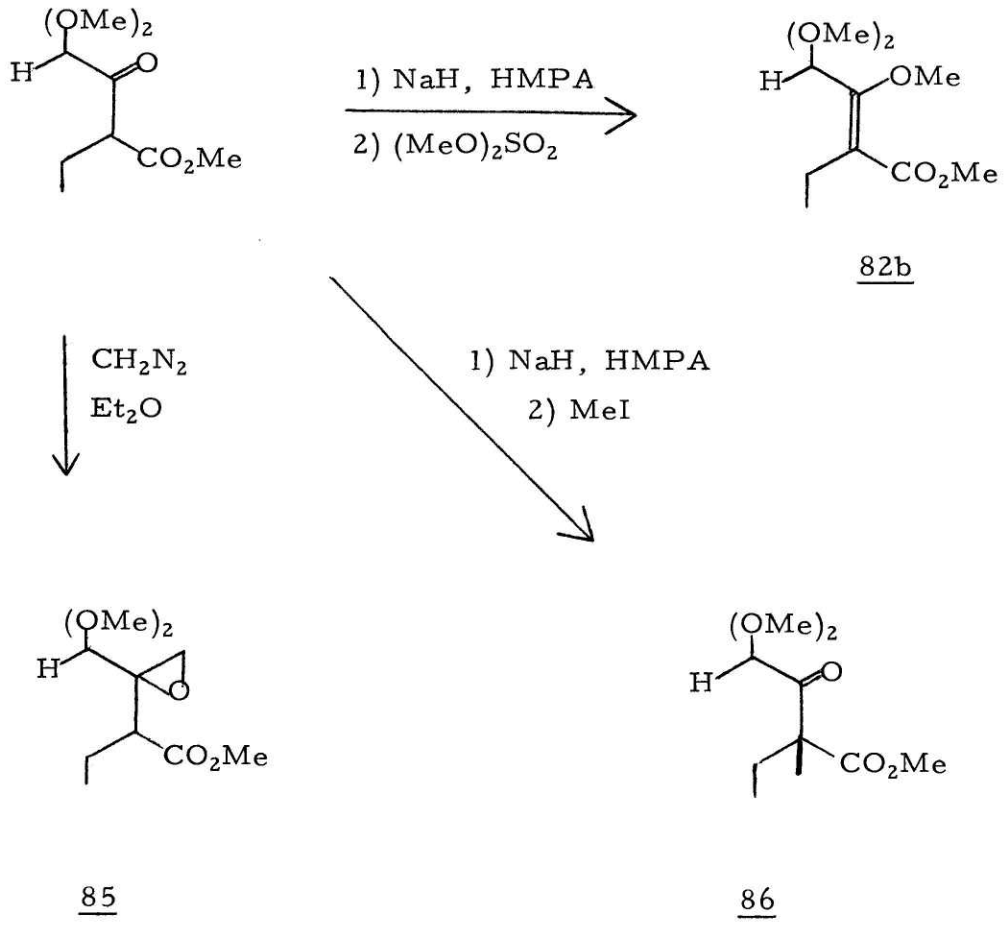
When direct reaction of 79 with tricyclic pyrroloquinoline 22 failed to give any trace of desirable products, this general route was terminated. It is interesting to note that Corey has subsequently reported the coupling of 22 with a pseudo acid chloride lactone in extremely low (6%) yield.[16]

Work on a more successful route began with the β-keto ester 81, which is prepared by condensation of methyl butyrate with methyl dimethoxyacetate.[43] The high degree of appropriately related functionality, combined with its availability, made 81 a potentially valuable starting material.

Originally, it was thought that 81 might be converted into an enol derivative such as 82 where X is an appropriate leaving group. Reaction of 82 with formyl acetic esters followed by lactonization would give the completely functionalized pyrone ester 84. Although efforts to convert 81 into 82, X = Cl, Br, OTs or SR were unsuccessful, enol acetate 82a could be prepared by adding acetyl chloride to the sodium enolate of 81 in dimethoxyethane. In trying to make the enol methyl ether 82b, several reactions were run with rather interesting results. Treatment of 81 with diazomethane in ether gave the epoxide 85 rather



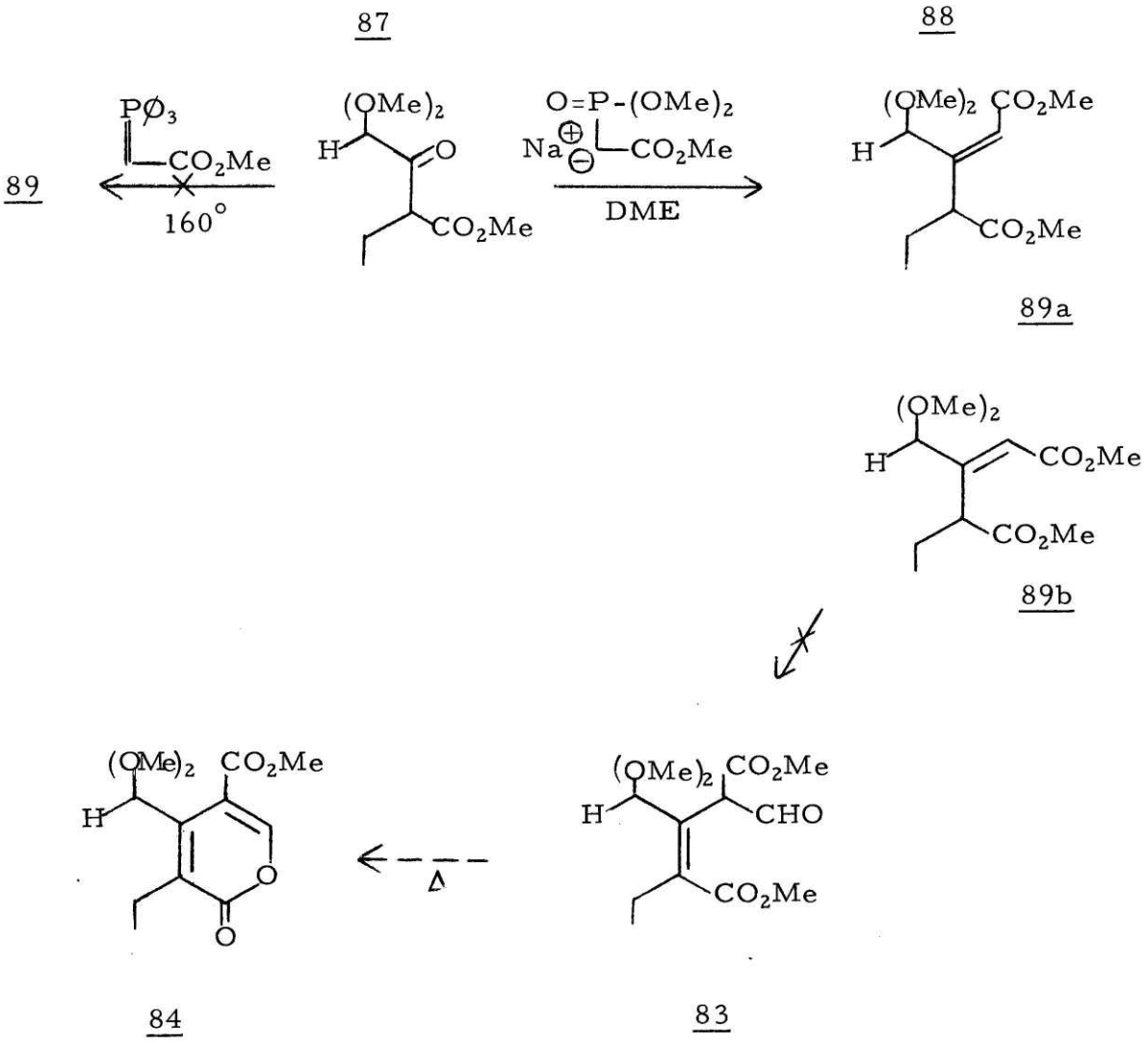
than the expected 82b. When the sodium enolate of 81 in hexamethylphosphoramide was treated with methyl iodide, almost total C-alkylation occurred giving 86 in high yield. However, when an identical enolate solution was treated with dimethyl sulfate, the desired enol methyl ether 82b was formed in 96% yield.



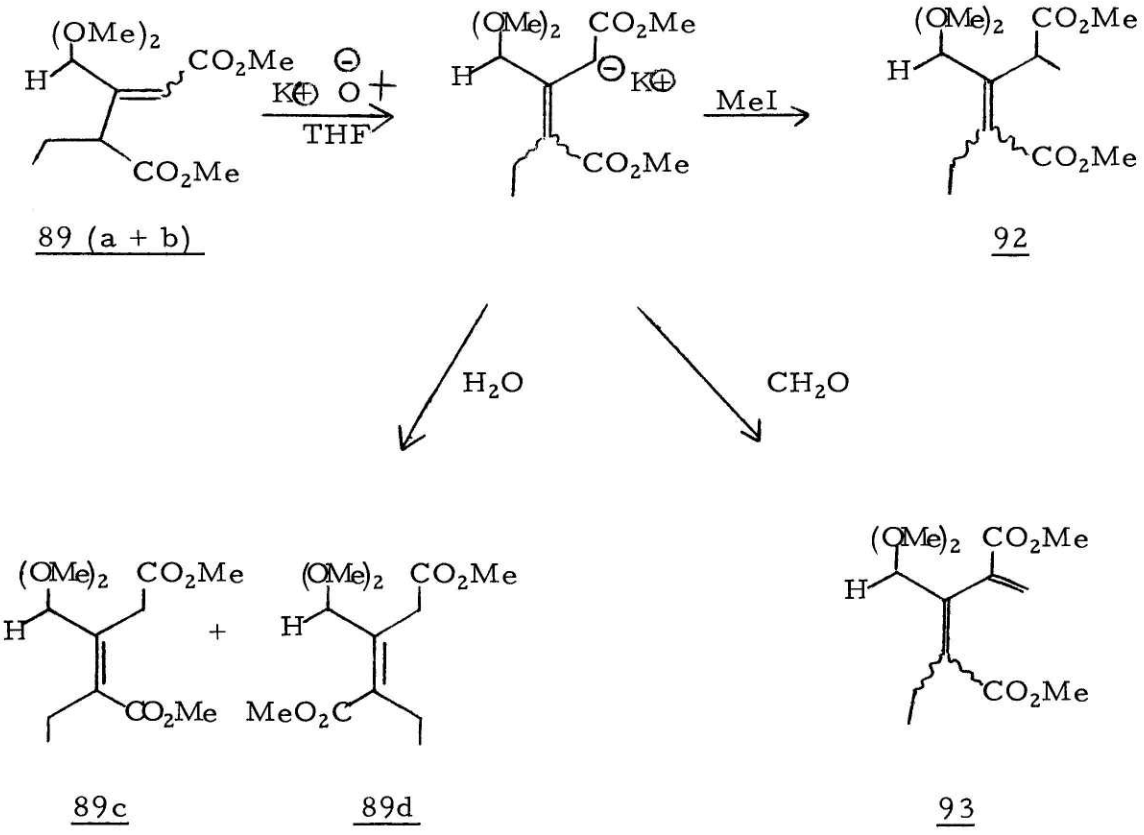
In pursuing this route, formyl acetic esters, malonic esters, and cyanoacetic esters were exposed to 82a and 82b under various basic conditions with the results that no desired addition products were detected. The combination of rather poor leaving groups and weak nucleophiles may be responsible for these results.

Nevertheless, it was believed that 81 should be susceptible to attack by some species which was nucleophilic enough to attack the carbonyl yet not so basic that it would only enolize the β-keto ester. With this concept in mind, attention was turned to the two acetic ester anion

equivalents, triphenyl phosphonium ylid 87[35] and trimethyl phosphonoacetate (88).[36] The less reactive ylid 87 did not attack 81 even when both were combined at elevated temperatures for one to two days. The sodium enolate of the phosphonate, though, reacted cleanly with 81 in refluxing dimethoxyethane giving a mixture of the dimethyl ester isomers 89a and 89b in good yield.

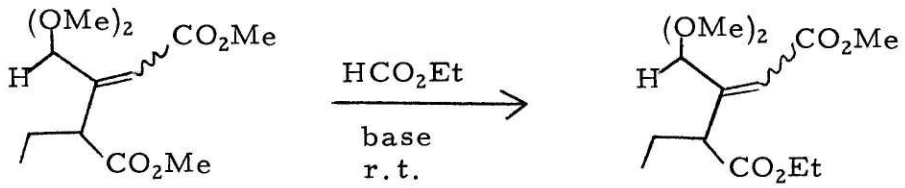


The general plan next called for a formylation followed by cyclization to the pyrone 84. It was clear that enolates of 89 could be formed, for when 89 was treated with potassium tert-butoxide at -60° and then quenched with water, the tetrasubstituted double bond isomers 89c and 89d were formed. The potassium enolate of 89 could also be alkylated with methyl iodide, giving methylated isomers 92. When this enolate was exposed to formaldehyde gas, a reaction occurred, but instead of the desired hydroxymethylated derivative, the exomethylene product 93 was isolated. Varying the reaction and workup conditions did not produce any products other than 93.

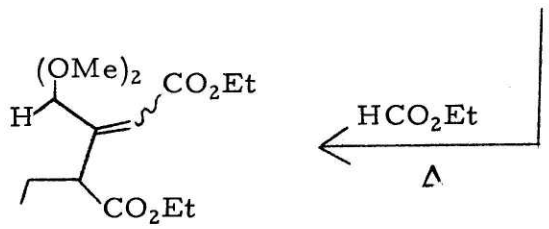


89 (a + b) 92 89c 89d 93

A variety of formylating agents, solvents, bases and reaction conditions gave no trace of formylated product 83, returning instead unreacted starting materials. In formylation attempts with base and methyl formate, all four isomers 89a-d were formed. When ethyl formate was used, only the mono- and diethyl esters 94 and 95 were formed. More reactive agents believed that, just as with the unsaturated lactone ester 74, the highly delocalized anion of 89 is not nucleophilic enough to attack even reactive formates.



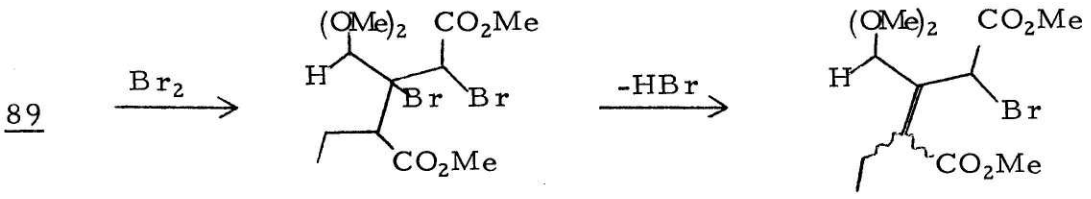
89 94



95

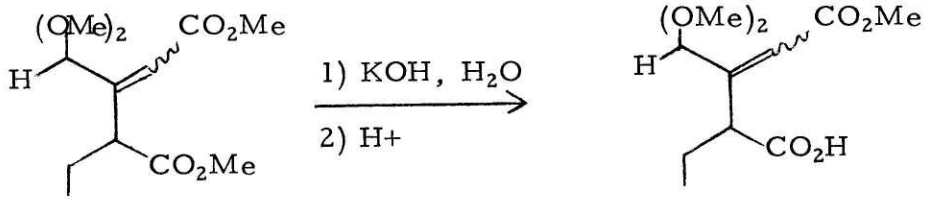
In a slightly modified sequence, diester 89 was brominated and dehydrobromated giving the α-bromoester 96. It was hoped that 96 could be converted via its anion to the formyl intermediate 83. Anions

of 96 proved to be less reactive than the nonbrominated material, though.



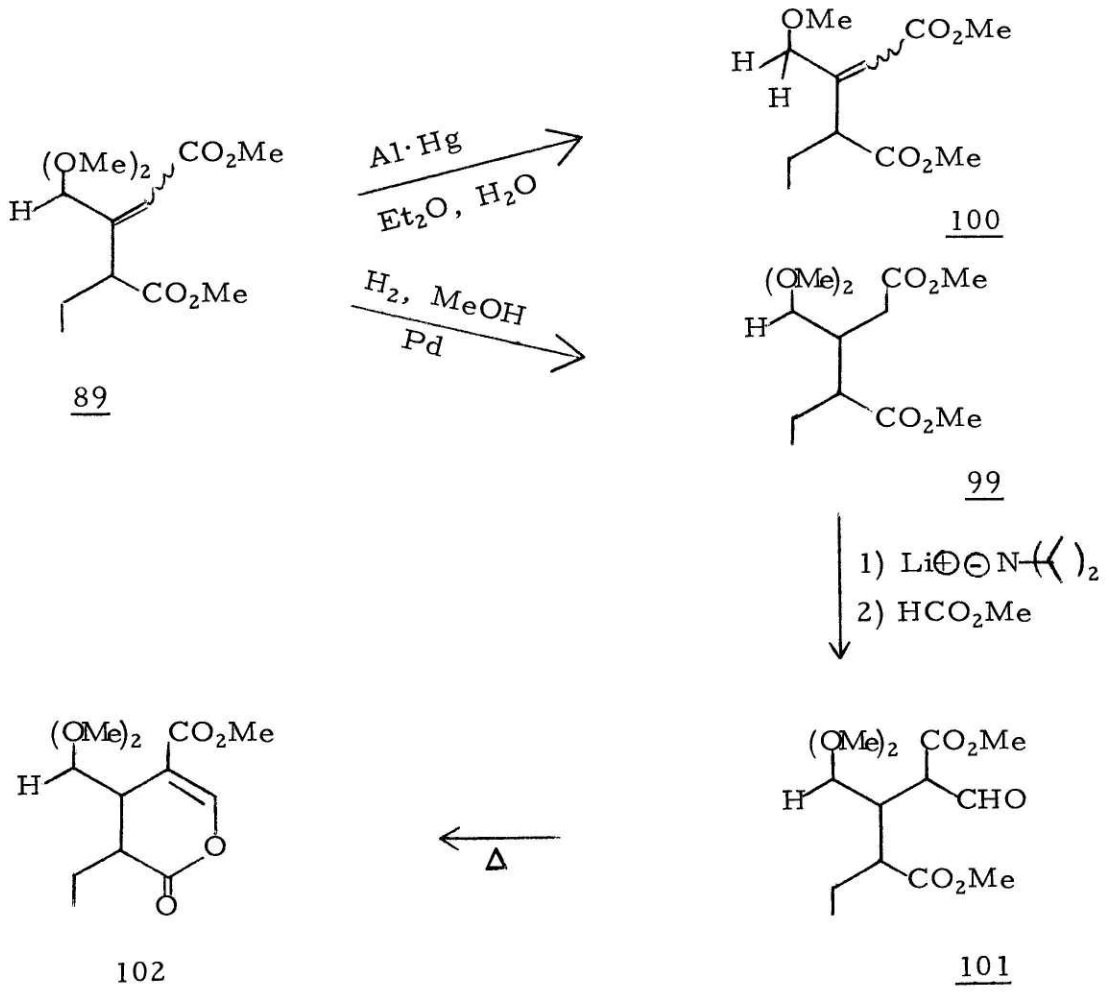
96

In reviewing this series of reactions, it was apparent that the main obstacle to be overcome in the elaboration of 89 or similar esters was the lack of reactivity of the anionic species formed. One attempt to improve matters called for the conversion of diester 89 into a monoester acid via basic hydrolysis. In practice, the acid 97 was formed in good yield by treatment of 89 with one equivalent of potassium hydroxide in water. The structure of this acid was assigned initially by assuming that the unconjugated ester would be attacked preferentially. Later synthetic work resulted in unambiguous preparation of the alternate possibility 115 (see p. 86), confirming the assignment. However, anions of this ester acid proved to be no more reactive than those of the diesters.



89 97

A second modification which aimed at increasing the reactivity of 89 was the reduction of the double bond system. With simple saturated esters, strong base could quantitatively generate a very nucleophilic enolate, which should readily react with formates. In practice, the reduction of 89 to 99 proved to be a problem. Attempts at catalytic hydrogenation gave several products, the main side reaction being hydrogenolysis of the allylic acetal methoxyl groups. Aluminum amalgam reduction of 89 gave a single product, which proved to be unsaturated ester 100 arising from selective removal of one methoxyl group.

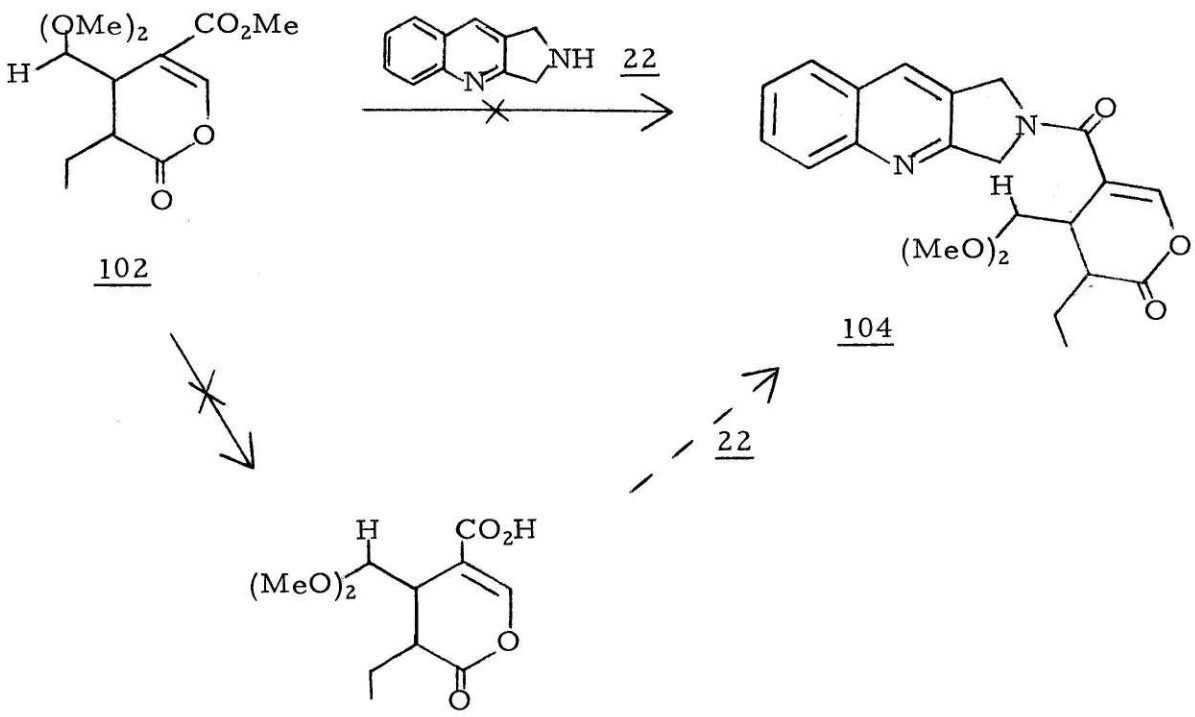


When a report appeared describing the use of borohydride-reduced palladium as a hydrogenation catalyst which suppresses hydrogenolysis of carbon-oxygen bonds[37], the reduction of 89 was again attempted. Careful preparation of the palladium catalyst in methanol followed by hydrogenation of 89 gave the desired diester in high yield (95%).

Formylation of 99 was then readily accomplished using lithium diisopropylamide in tetrahydrofuran at -78°, followed by quenching with methyl formate. The crude formyl ester 101 cyclized upon distillation at 160-180°, giving the long-sought-after lactone 102 in 90% yield. This sequence represented the successful completion of the original plan calling for preparation of a highly functionalized lactone ester such as 102, which could be coupled with amine 22 to give the complete camptothecin ring system.

With both halves of the molecule in hand, the immediate problem became one of acylating pyrroloquinoline 22 with the methyl ester 102. Meyers had reported acylation of amine 22 with esters only under very harsh conditions (170°, several hours).[9] In practice, it was found that heating solutions of 22 and 102 led to rapid decomposition of the lactone at temperatures well below (ca. 100°) those reportedly required.

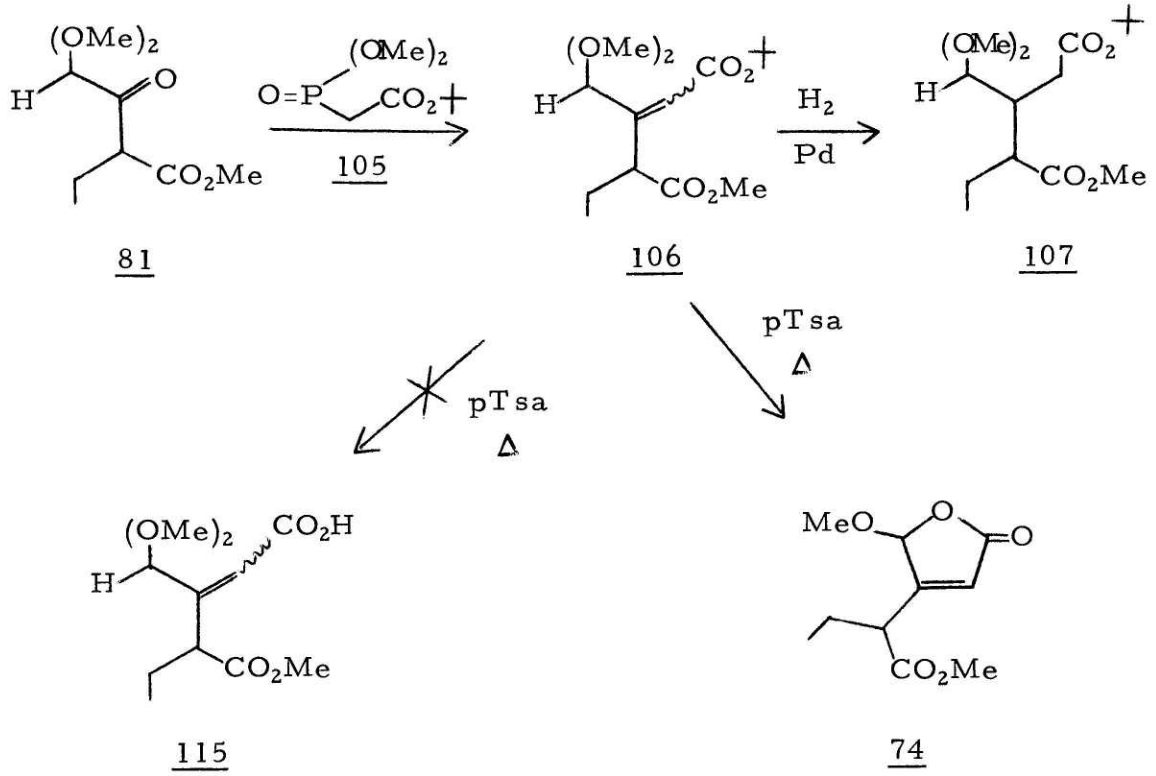
It was soon realized that lactone 102 could be used only if its carboxylic acid derivative 103 were prepared. Unlike esters, carboxylic acids were known to acylate 22 under mild conditions.[11]



102 104 103

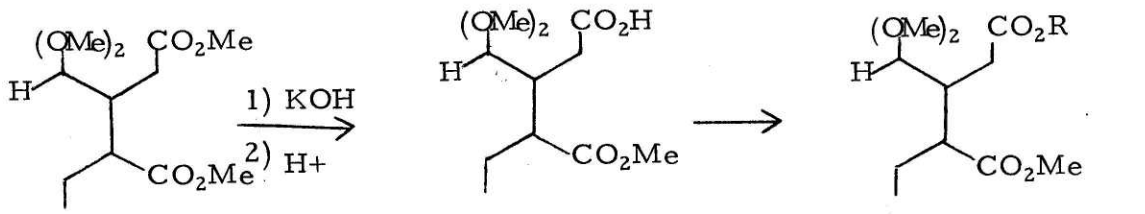
Attempts at selective hydrolysis or demethylation of the ester in 102 via acidic, basic, or other demethylating reagents such as lithium salts and mercaptides caused decomposition of the lactone and gave none of the desired acid 103.

Efforts were thus initiated to prepare an analog of 102 containing an ester which might be selectively removed after lactonization. To this end, tert-butyl dimethylphosphonoacetate (105) (prepared from tert-butyl bromoacetate and trimethyl phosphite) was condensed with 81 to give the unsaturated tert-butyl esters 106.



Reduction of 106, even with borohydride-reduced palladium, was extremely difficult and unpredictable. Hydrogenations of 106 would usually return unreacted starting material or overreacted, complex mixtures, and only occasionally give the desired saturated ester 107. The utility of this scheme was further placed in doubt when it was found that acid-catalyzed removal of the tert-butyl group gave the undesired lactone 74, and none of the free acid 115.

The preparation of other ester analogs of 99 was accomplished by first selectively cleaving the less-hindered ester to give acid 108, then coupling this acid with other alcohols to give new esters 109a and 109b.



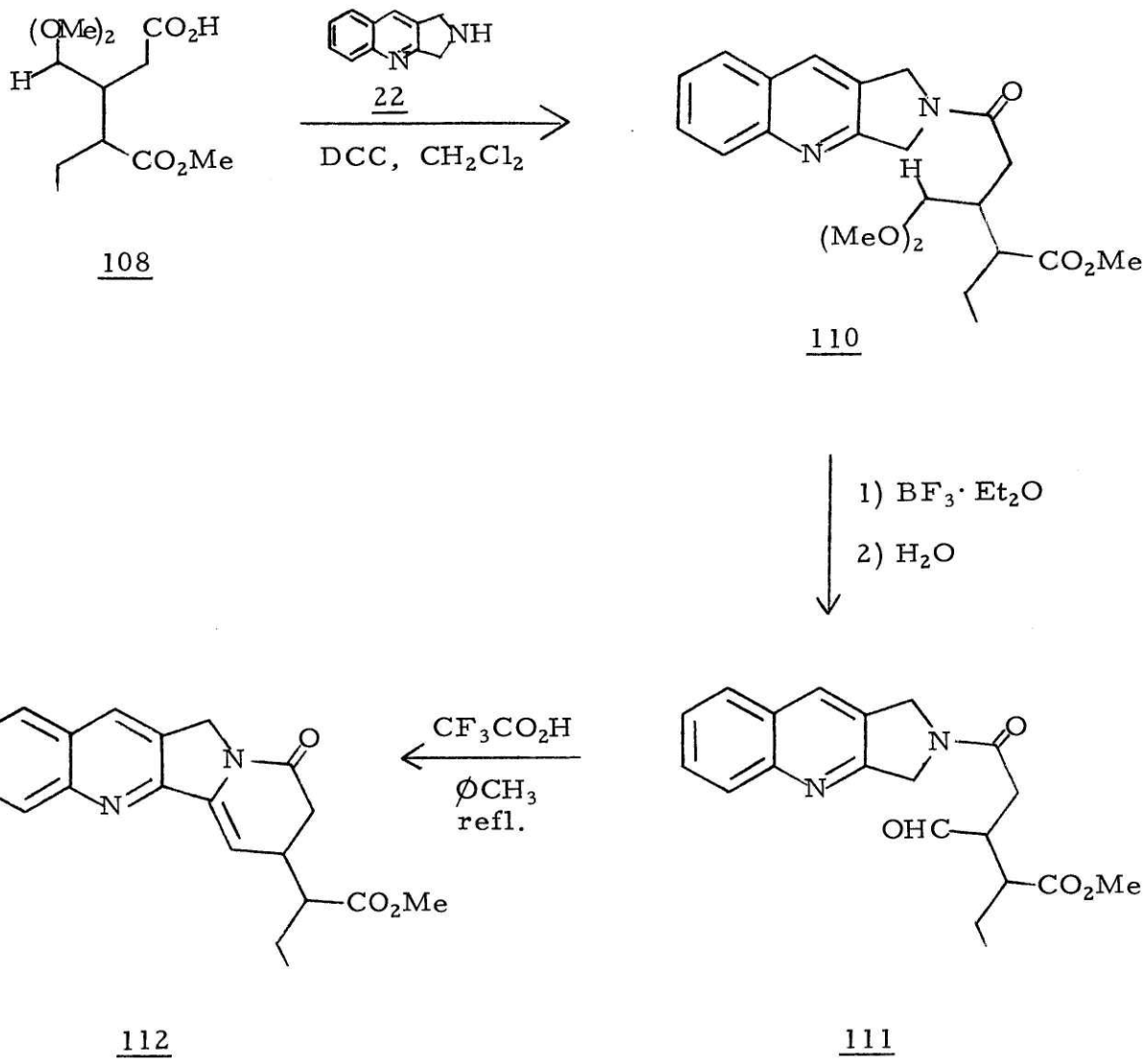
99 108

109a, R = $-CH_2CCl_3$

109b, R = $-CH_2\emptyset$

When previously-used formylation conditions were tried, the result was decomposition of 109a (due to instability to strong base) and recovery of unreacted 109b. This reaction series, however, led to the idea that 108 might be coupled with amine 22 and then elaborated.

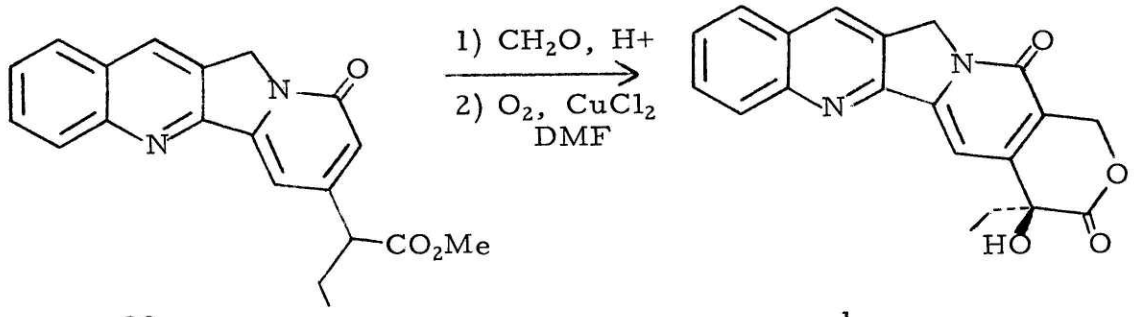
Thus, 108 was coupled with 22 using dicyclohexylcarbodiimide in methylene chloride to give 110 in good yield. The acetal could be removed by treatment of 110 with boron trifluoride etherate followed by aqueous workup, giving aldehyde 111 as a light solid powder in high yield. Cyclization of the aldehyde was best accomplished by refluxing a toluene solution of 111 with a catalytic amount of trifluoroacetic acid.[9] The product, 112, was readily identified by its intense blue fluorescence under longwave ultraviolet light, which is characteristic of these tetracyclic pyridones and dihydropyridones.[10]



108 110 111 112

In the initial synthetic plan, it was hoped that either 110 or 112 might be formylated and cyclized giving deoxycamptothecin (27). When a variety of formylation conditions gave mostly decomposition products and no desired formylated pyridone, attention was turned to the known pyridone 20.[5]

This fully aromatized compound had been prepared previously by Danishefsky[5] and by Kende[11] by lengthy routes in very low yields. Danishefsky reported the conversion of 20 to camptothecin in unspecified yield via hydroxymethylation-lactonization, followed by a low yield (20%) oxidation. However, subsequent work by Winterfeldt[6] which describes a quantitative final oxidation should add significantly to the utility of this process. For these reasons, a short, efficient synthetic route to 20 was highly desirable.

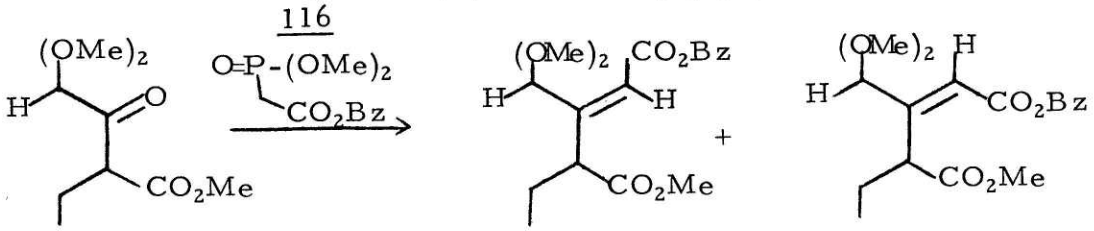


20 1

Dihydropyridone 112 was seen to be one oxidation level below that of 20. Coincidentally, the functionalized carboxylic acid 108 had been prepared via a double bond reduction. If this carbon double bond could be retained in the coupling, a step could be avoided, and a sequence of reactions analogous to those leading to 112 should produce 20 directly.

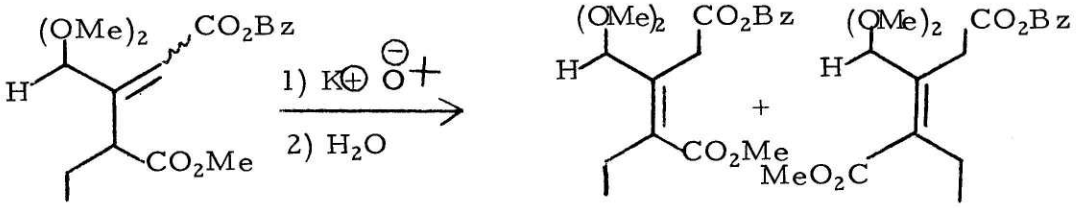
One problem which was anticipated in the preparation of carboxylic acid 115 was the propensity of this material to cyclize, giving the undesired lactone 74. This side reaction was avoided by forming 115 under neutral conditions at room temperature.

Benzyl dimethylphosphonoacetate (116) (prepared from benzyl bromoacetate and trimethyl phosphite)[44] was condensed with 81 in refluxing dimethoxyethane giving (Z) and (E) benzyl esters 117a and 117b in a 3:1 ratio respectively (as shown by glpc).



81 117a 117b

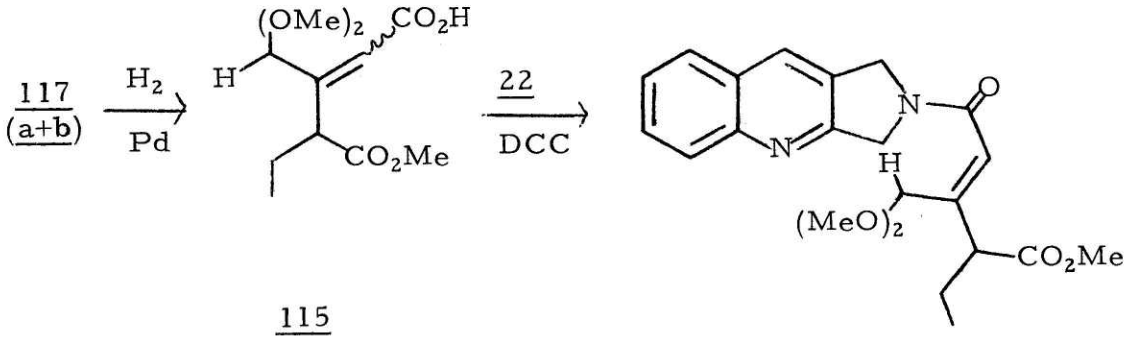
As in the case of the dimethyl esters 89a and 89b, the double bond in 117 could be isomerized into the tetrasubstituted position using potassium tert-butoxide in tetrahydrofuran. The product of this isomerization was again a mixture of two isomers, 117c and 117d.



117 (a + b) 117c 117d

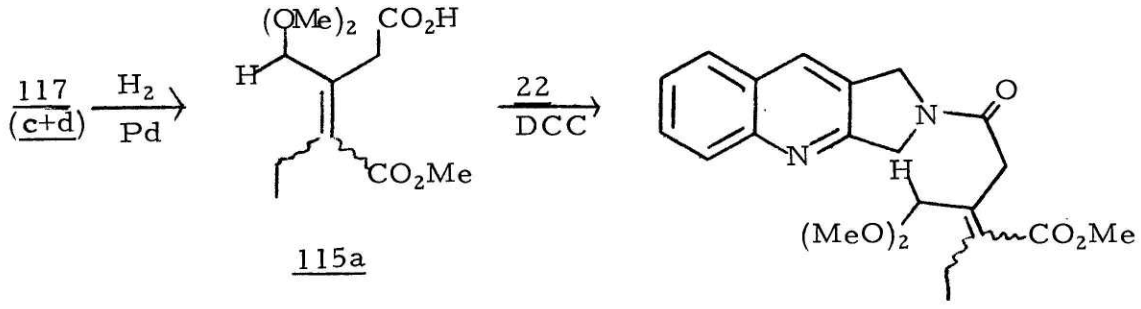
Isomers 117a and 117b were debenzylated by catalytic hydrogenation over 10% palladium on carbon in methanol, giving the desired acid 115. In a similar manner, isomers 117c and 117d were debenzylated to give acid 115a. These somewhat sensitive compounds were used without purification in the next sequence.

Coupling of the two halves was achieved by stirring a methylene chloride solution of 22 and the carboxylic acid in the presence of dicyclohexylcarbodiimide. Although α-β unsaturated acid 115 coupled with 22 to give 118 in only 56% yield, the saturated acid isomer 115a coupled with 22 to give 118a in 94% yield.



115

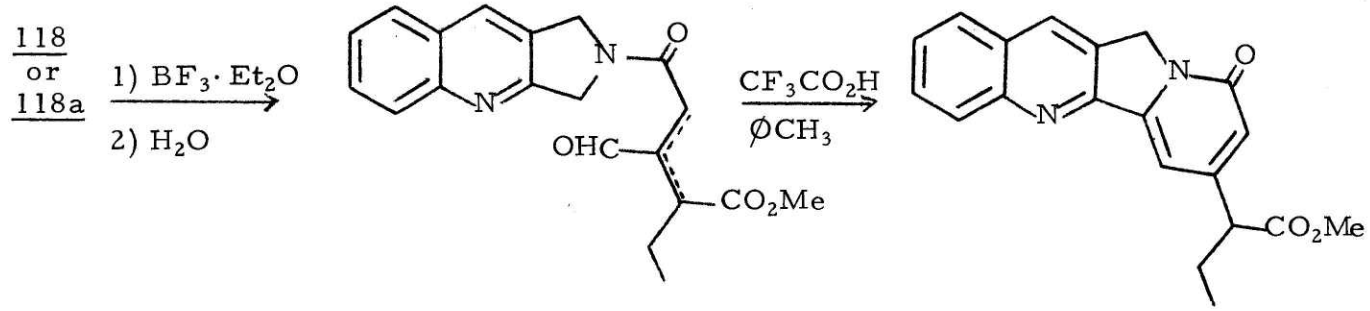
118



115a

118a

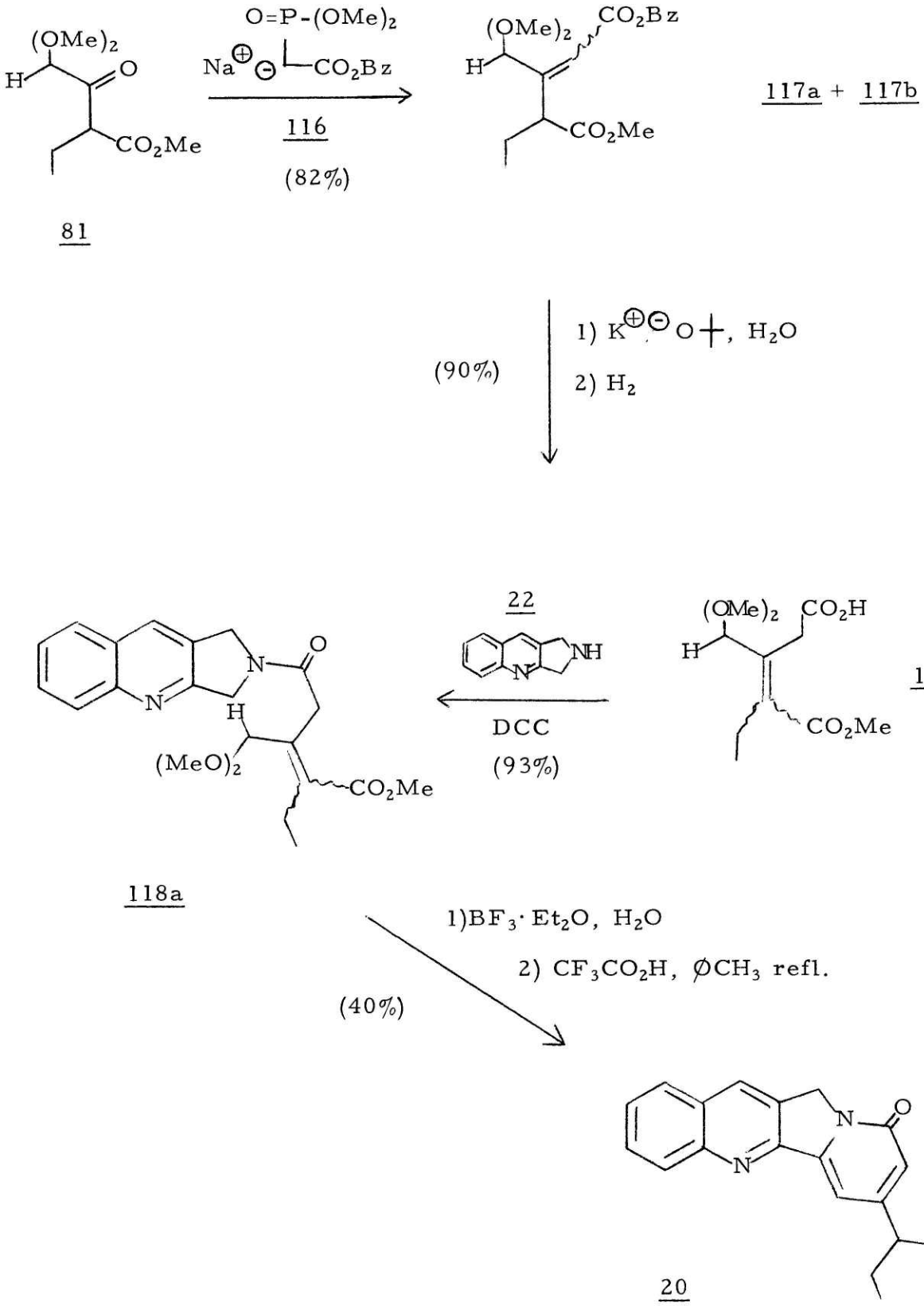
Either isomer 118 or 118a could be converted to pyridone 20 by treatment with boron trifluoride etherate (giving a crude mixture of aldehyde isomers 119) followed immediately by cyclization in refluxing toluene containing a trace of trifluoroacetic acid. Pyridone 20



119 20

exhibited ir, nmr, uv, mass spectra, and elemental analysis consistent with the assigned structure.[47] A sample recrystallized from methanol gave colorless crystals, mp 197-199°, compared to a reported melting point of 198° for the same material prepared by Danishefsky's route.

In summary, this route provides a synthesis of 20 in five steps (in which only one distillation and two chromatographic purifications are required) from β-keto ester 81 and 116. Although yields have not been optimized, this pathway gives 20 in 27% overall yield. Since 20 has been converted to (1)[5], this constitutes a formal total synthesis of camptothecin. Furthermore, this synthesis is the only short, efficient route yet developed and, due to its convergent design, should be readily adaptable to the preparation of potentially useful analogs.


(OMe)2
H
O
CO2Me
81
O=P-(OMe)2
Na⊕⊖CO2Bz
116
(82%)
(OMe)2
CO2Bz
H
CO2Me
117a + 117b
(90%)
1) K⊕⊖O+, H2O
2) H2
22
NH
N
DCC
(93%)
(OMe)2
CO2H
H
CO2Me
115a
N
O
N
H
(MeO)2
CO2Me
118a
1)BF3·Et2O, H2O
2) CF3CO2H, ØCH3 refl.
(40%)
N
O
N
CO2Me
20

EXPERIMENTAL

Microanalyses were preformed by Midwest Microlab, Inc. Dry nitrogen was used in all reactions requiring an inert atmosphere. Melting points were determined on a Kofler hot-stage microscope and are uncorrected, as are boiling points. Infrared (ir) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Ultraviolet (uv) spectra were measured on Perkin-Elmer 202 or Cary 14 instruments. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian Associates T-60 instrument, and are given in ppm (δ) downfield from an internal tetramethylsilane standard. The abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. Mass spectra were determined on Hitachi RMU6D or RMU6L instruments. The abbreviation (M^+) refers to molecular ion. Gas chromatographic (glpc) analyses were done on either F and M 720 or Perkin-Elmer 990 instruments employing six foot 15% SE-30 or 3% OV-17 columns. Analytical thin layer chromatography (tlc) was done on Bakerflex silica gel IB-F sheets. Analtech silica gel GF plates (20 x 20 x 2 mm thick) were used for preparative separations. Merck PF_{254} or (0.05-0.2 mm) silica gel and Fischer Florisil (100-200 mesh) were used for column chromatography.

Ethyl N-Carbobenzyloxy-N-carboethoxymethyl-β-alaninate (37b). Ethyl N-carboethoxymethyl-β-alaninate[19] (32.0 g, 0.16 mol) was slurried in a solution of 16 g of sodium carbonate in 200 ml of water and to this was added benzyl chloroformate[39] (27.3 g, 0.16 mol). The reaction was stirred at room temperature for 4 hr and then acidified to pH 2 with hydrochloric acid and extracted with five 100-ml portions of benzene. The combined benzene extracts were dried ($MgSO_4$) and concentrated giving 57.3 g (95%) of the urethane 37b as a light oil (one peak on glpc): ir (neat) 1750, 1730, 1710, 1500 cm^{-1}; nmr (CCl_4) δ 1.0 (m, 6), 2.4 (m, 2), 3.41 (t, 2, J = 6 Hz), 3.9 (m, 6), 5.0 (m, 2), 7.21 (s, 5).

Ethyl N-(2,2,2-Trichloroethoxycarbonyl)-N-carboethoxymethyl-β-alaninate (37c). Ethyl N-carboethoxymethyl-β-alaninate[19] (8.1 g, 0.04 mol) was slurried in a solution of 4.0 g of sodium carbonate in 50 ml of water and to this was added 2,2,2-trichloroethyl chloroformate[39] (8.4 g, 0.04 mol). The reaction was stirred at room temperature for 4 hr, acidified to pH 3 with hydrochloric acid, and extracted with three 50-ml portions of benzene. The benzene extracts were dried (Na_2SO_4) and concentrated giving 13.1 g (87%) of the urethane (37c) as a yellow oil (one spot on tlc): ir (neat) 1745, 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.29 (t, 6, J = 7 Hz), 2.71 (t, 2, J = 6 Hz), 3.67 (t, 2, J = 6 Hz), 4.0-4.3 (m, 6), 4.7 (m, 2).

Ethyl N-(o-Nitrophenylsulfenyl)-N-carboethoxymethyl-β-alaninate (37d). Ethyl N-carboethoxymethyl-β-alaninate[19] (4.06 g, 0.02 mol) was dissolved in a mixture of 10 ml of water and 25 ml of dioxane. o-Nitrophenylsulfenyl chloride[40] (3.79 g, 0.02 mol) was added in 10 equal portions during 0.3 hr as 12 ml of 2N sodium hydroxide was added dropwise to the stirred solution. After 0.5 hr, 200 ml of water was added and the reaction was extracted with two 200-ml portions of ether. The ether extracts were dried (Na_2SO_4) and concentrated giving a yellow crystalline solid. Recrystallization from ether gave 5.8 g (82%) of 37d as yellow crystals: mp 77-78°; ir ($CHCl_3$) 1740, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.1 (m, 6), 2.60 (t, 2, J = 7 Hz), 3.5 (m, 2), 3.9 (m, 2), 4.0-4.5 (m, 4), 7.2-8.3 (m, 4).

Methyl N-(o-Nitrophenylsulfenyl)-N-carbomethoxymethyl-β-alaninate (37e). Methyl N-carbomethoxymethyl-β-alaninate[19] (3.50 g, 0.02 mol) was dissolved in 25 ml of dioxane and to this solution was added o-nitrophenylsulfenyl chloride[40] (3.79 g, 0.02 mol) in 10 equal portions while 12 ml of 2N sodium hydroxide was added dropwise to the stirred solution. After 0.5 hr, 200 ml of water was added, and the reaction was extracted with two 200-ml portions of ether. The ether extracts were dried (Na_2SO_4) and concentrated giving a yellow crystalline solid. Recrystallization from ether gave 5.5 g (84%) of 37e as yellow crystals: mp 87-88°; ir ($CHCl_3$) 1740, 1595, 1570 cm^{-1}; nmr ($CDCl_3$) δ 2.59 (t, 2, J = 7 Hz), 3.4 (m, 2), 3.64 (s, 3), 3.76 (s, 3), 3.9 (m, 2), 7.2-8.4 (m, 4).

N-Carbobenzyloxy-4-carboethoxy-3-pyrrolidinone (38b). Sodium (2.3 g, 0.1 mol) was dissolved in 40 ml of absolute ethanol and to this was added carbobenzyloxy urethane 37b (33.7 g, 0.1 mol). After 0.3 hr, a thick slurry formed in the reaction flask. The light colorless solid was filtered, washed with ethanol, and dissolved in water. The aqueous solution was acidified to pH 2 with hydrochloric acid and extracted with two 100-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4) and concentrated giving 20.4 g (72%) of the pyrrolidinone 38b as a white solid: mp 58-59°; ir (CCl_4) δ 1.20 (t, 3, J = 8 Hz), 3.6-3.9 (m, 3), 4.18 (s, 2), 4.2 (m, 2), 5.06 (s, 2), 7.30 (s, 5).

N-(2,2,2-Trichloroethoxycarbonyl)-4-carboethoxy-3-pyrrolidinone (38c). A solution of urethane 37c (7.56 g, 0.02 mol) in 10 ml of absolute ethanol was added dropwise to a stirred solution of 0.021 mol of freshly prepared sodium ethoxide in 20 ml of ethanol. After 0.5 hr, the precipitated enolate was filtered off, dissolved in 30 ml of 1N hydrochloric acid, and extracted with two 50-ml portions of chloroform. The chloroform extracts were dried (Na_2SO_4) and concentrated giving 4.5 g (69%) of 38c as a clear yellow oil (one spot on tlc): ir (neat) 1770, 1730, 1680, 1640 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (t, 3, J = 7 Hz), 3.6 (m, 1), 4.0-4.35 (m, 4), 4.40 (s, 2), 4.86 (s, 2).

N-Benzyl Vinylogous Amide 39a. N-Benzyl-4-carboethoxy-3-pyrrolidinone[19] (38a) (2.0 g, 8 mmol) was combined with dimethylformamide dimethylacetal (1.6 ml, 12 mmol) in 30 ml of dimethylformamide. The reaction was stirred at 60° for 5 hr and then the solution was reduced to a dark oil by removing the solvents under high vacuum. The crude product was purified by column chromatography on silica gel (0.05-0.2 mm) with 5% methanol in chloroform affording 1.21 g (40%) of vinylogous amide 39a as a viscous oil: (95%EtOH) 325 nm; ir (neat) 1740, 1660, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.21 (t, 3, J = 7 Hz), 2.58 (s, 6), 3.0-3.4 (m, 3), 4.07 (q, 2, J = 7 Hz), 4.24 (s, 2), 7.02 (s, 1), 7.31 (s, 5).

N-Carbobenzyloxy Vinylogous Amide 39b. N-carbobenzyloxy-4-carboethoxy-3-pyrrolidinone (38b) (1.50 g, 5 mmol) was dissolved in 20 ml of dimethoxyethane under nitrogen with dimethylformamide dimethylacetal (0.67 ml, 5 mmol). The reaction was heated to 65° for 5 hr and then evaporated in vacuo to give 1.2 g of crude product. This material was purified by column chromatography on silica gel PF_{254} with 2% methanol in chloroform giving 0.71 g (41%) of the vinylogous amide 39b as an orange oil: uv max (95% EtOH) 350 nm; ir (neat) 1740, 1700, 1610 cm^{-1}; nmr (CCl_4) δ 1.21 (t, 3, J = 7 Hz), 2.86 (s, 6), 3.3 (m, 1), 3.9-4.2 (m, 4), 5.10 (s, 2), 6.95 (s, 1), 7.33 (s, 5).

Vinylogous Amide 39c. Dimethylformamide dimethylacetal (1.0 ml, 8 mmol) was added to 20 ml of dry dimethoxyethane, the resulting solution heated to 60°, and a solution of pyrrolidinone 38c (1.66 g, 5 mmol) in 4 ml of dimethoxyethane was added during 0.5 hr. After 24 hr at 65°, the reaction was concentrated to a dark oil which was purified by column chromatography on silica gel (0.2-0.5 mm) with chloroform giving 0.867 g (44%) of 39c as a yellow oil: uv max (95% EtOH) 235 and 350 nm; ir (neat) 1730, 1680, 1610 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (t, 3, J = 6 Hz), 3.09 (s, 6), 3.2-3.8 (m, 3), 4.1 (m, 2), 4.81 (s, 2), 7.17 (s, 1).

Methyl 2-Carbomethoxy-3-methyl-4-oxohexanoate (43). Dimethyl malonate (13.2 g, 0.1 mol) was added to a stirred suspension of 2.4 g of sodium hydride in 120 ml of dimethoxyethane, the reaction was heated to reflux, and a solution of 2-bromo-3-pentanone[41] (15.0 g, 0.91 mol) in 30 ml of dimethoxyethane was added to the enolate solution. After heating at reflux for 20 hr, the reaction was cooled, filtered, concentrated, and dissolved in 100 ml of ether. The ethereal solution was washed once with 1% hydrochloric acid, then twice with water, dried (Na_2SO_4), concentrated, and distilled giving 16.9 g (86%) of 45: bp 76-77° (0.1 mm); ir (neat) 1740, 1710 cm^{-1}; nmr (CCl_4) δ 1.09 (t, 6, J = 6 Hz), 2.61 (q, 2, J = 6 Hz), 3.0 (m, 1), 3.3 (m, 1), 3.71 (s, 3), 3.78 (s, 3).

Ketal Diester 46. Keto diester 45 (8.64 g, 0.04 mol) was dissolved in a solution of 25 ml of benzene, 3.3 g of ethylene glycol, and 30 mg of p-toluenesulfonic acid. The reaction mixture was heated to reflux under a Dean-Stark apparatus for 36 hr, then washed with water, dried (Na_2SO_4), concentrated, and distilled giving 8.2 g (82%) of the ketal 46: bp 85-88° (0.1 mm); ir ($CHCl_3$) 2860, 1730, 1430 cm^{-1}; nmr (CCl_4) δ 0.8-1.1 (m, 6), 1.56 (q, 2, J = 6 Hz), 2.6 (m, 1), 3.35 (d, 1, J = 8 Hz), 3.69 (s, 6), 3.90 (s, 4).

Bromo Ketal 47. Diester ketal 46 (5.20 g, 0.02 mol) was dissolved in 15 ml of carbon tetrachloride and stirred under a stream of nitrogen. This solution was irradiated with a 100-watt tungsten bulb as 3.40 g of bromine was added dropwise. Hydrobromic acid produced by the reaction was carried off by the nitrogen. Irradiation was continued for 2 hr, at which time the reaction mixture was washed with aqueous sodium bicarbonate solution, dried (Na_2SO_4), and concentrated giving 5.50 g (81%) of crystalline bromide 47: mp 65-67° (recrystallized from ether); ir ($CHCl_3$) 2880, 1730, 1430 cm^{-1}; nmr (CCl_4) δ 1.07 (d, 3, J = 6 Hz), 1.62 (d, 3, J = 7 Hz), 3.2 (m, 3), 3.69 (s, 6), 4.12 (s, 4).

2-(1-Bromoethyl)-2-ethyl-1, 3-dioxolane(49)[45]. A solution of 2-bromo-3-pentanone[41] (1.65 g, 0.01 mol), ethylene glycol (0.9 g), and p-toluenesulfonic acid (20 mg) in 20 ml of benzene was heated to reflux in a flask fitted with a Dean-Stark apparatus. After 10 hr, the reaction was cooled, washed with water, dried (Na_2SO_4), concentrated, and distilled giving 1.60 g (77%) of 49: bp 88-90° (12 mm); ir (neat) 2860, 1450, 1050 cm^{-1}; nmr (CCl_4) δ 0.90 (t, 3, J = 7 Hz), 1.60 (d, 3, J = 7 Hz), 1.8 (m, 2), 4.0-4.2 (m, 5).

Phosphonium Salt 50. A solution of 2-bromo-3-pentanone[41] (4.95 g, 0.03 mol) and triphenyl phosphine (7.9 g, 0.03 mol) in 40 ml of benzene was heated to reflux for 16 hr. The phosphonium salt which precipitated out was filtered off, washed with ether, and dried in a vacuum oven giving 12.1 g (94%) of 50 as white crystals: mp 129-133° ; ir ($CHCl_3$) 1710, 1440 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (t, 3, J = 7 Hz), 2.75 (d of d, 3, J = 18, 7 Hz), 3.1 (m, 3), 7.6-8.3 (m, 15).

Phosphonium Ketal 51. A mixture of phosphonium salt 50 (1.0 g, 2.4 mmol), 20 ml of 2-methyl-2-ethyl-1, 3-dioxolane, and 30 mg of p-toluenesulfonic acid was stirred at 110°. After 48 hr, the solution was cooled and concentrated leaving 0.9 g (85%) of the ketal phosphonium salt 51 as a colorless crystalline solid which had to be kept under nitrogen: mp 100-103°; nmr ($CDCl_3$) δ 0.8-1.2 (m, 3), 1.77 (d of d, 3, J = 18 Hz, 7 Hz), 2.9-3.2 (m, 2), 3.96 (s, 4), 4.2-4.6 (m, 1), 7.5-8.2 (m, 15).

2-Ethyl-2-isopropenyl-1, 3-dioxolane (53). Ethyl isopropenyl ketone[22] (13.7 g, 0.14 mol) was combined with 13.0 g of ethylene glycol, 300 mg of p-toluenesulfonic acid, and 100 ml of benzene, and the resulting solution refluxed under a Dean-Stark apparatus until no more water came off (12 hr). The reaction was cooled, washed with dilute aqueous sodium bicarbonate solution, dried (Na_2SO_4), and concentrated giving 15.4 g (78%) of ketal 53: nmr (CCl_4) δ 0.94 (t, 3, J = 6 Hz), 1.6 (m, 5), 3.86 (s, 4), 4.90 (s, 1), 5.11 (s, 1).

2-Acetyl-2-ethyl-1, 3-dioxolane (54). A solution of ketal 53 (15.4 g, 0.11 mol) in 300 ml of methylene chloride was cooled to -70° and saturated with ozone. This solution was allowed to warm to room temperature, flushed with nitrogen, and mixed with a solution of sodium sulfite (13.9 g, 0.11 mol) in 75 ml of water. After this system had been stirred vigorously for 1 hr, the methylene chloride layer was separated, dried (Na_2SO_4), and concentrated at atmospheric pressure. The resulting oil was distilled giving 11.9 g (83%) of 54: bp 90-95° (12 mm); ir (neat) 1725, 1045 cm^{-1}; nmr (CCl_4) δ 0.89 (t, 3, J = 6 Hz), 1.67 (q, 2, J = 6 Hz), 2.10 (s, 3), 3.97 (s, 4).

Ylid 55. Phosphonium salt 50 (4.27 g, 0.01 mol) was stirred in a solution of 3.3 g of potassium carbonate in 40 ml of water. After 20 hr, the product was filtered off and dried in a vacuum oven giving 3.23 g (93%) of the ylid 55: mp 136-140°; nmr ($CDCl_3$) δ 1.37 (t, 3, J = 7 Hz), 1.90 (d, 3, J = 16 Hz), 2.65 (q, 2, J = 6 Hz), 7.6-8.0 (br s, 15).

Ethyl 2-Carboethoxy-3-methyl-4-oxo-2-hexenoate (56). Ylid 55 (16.0 g, 0.046 mol) was dissolved in 250 ml of tetrahydrofuran and to this solution was added diethyl mesoxalate[39] (8.0 g, 0.046 mol). The reaction was heated to reflux briefly, then allowed to stand at room temperature. After 12 hr, the reaction mixture was concentrated, washed with hexane, and filtered. The hexane filtrate was concentrated and distilled giving 9.55 g (86%) of the keto diester 56: bp 85-89° (0.1 mm); uv max (95% EtOH) 220 and 293 mm; ir (neat) 1780, 1720, 1640 cm^{-1}; nmr ($CDCl_3$) δ 1.0-1.5 (m, 9), 2.05 (s, 3), 2.64 (q, 2, J = 7 Hz), 4.20 (q, 2, J = 7 Hz), 4.3 (q, 2, J = 7 Hz).

Ethyl 3-Bromomethyl-2-carboethoxy-4-oxo-2-hexenoate (41). Diester 56 (2.42 g, 10 mmol) was dissolved in 100 ml of carbon tetrachloride with N-bromosuccinimide (2.30 g) and 11 mg of dibenzoyl peroxide. This suspension was heated at reflux and irradiated with a 100-watt bulb. After 5 hr, the reaction was cooled, filtered, and concentrated giving 2.8 g (87%) of 41 (90% pure by glpc): uv max (95% EtOH) 223 and 315 nm: ir (neat) 1720, 1660 cm^{-1}; nmr ($CDCl_3$) δ 1.0-1.5 (m, 9), 2.8 (m, 2), 4.2-4.6 (m, 6).

Bromomethyl Lactone 57. Bromoester 41 (2.8 g, 8.5 mmol) was distilled (Kugelrohr) at 120-130° (0.1 mm). The distillate crystallized upon standing and was recrystallized from ether giving 1.66 g (74%) of lactone 57: mp 99-100°; ir ($CHCl_3$) 1785, 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.40 (t, 3, J = 7 Hz), 2.09 (d, 3, J = 8 Hz), 4.39 (q, 2, J = 7 Hz), 4.77 (s, 2), 5.98 (q, 1, J = 8 Hz).

(E)-1-Propenyl Trimethylsilyl Ether (60a) and (Z)-1-Propenyl Trimethylsilyl Ether (60b). Propionaldehyde (23.2 g, 0.4 mol) was added to a stirred solution of 75 ml of diglyme, triethylamine (44.5 g, 0.44 mol), and 50 mg of zinc chloride, under an atomosphere of nitrogen. To this was added trimethylsilyl chloride (41.3 g, 0.38 mol) during 0.1 hr. The mixture was stirred and heated at 85°, and after 1 hr, 75 ml of diglyme was added to facilitate stirring of the thick slurry. After 6 hr, the reaction was cooled, filtered, and washed with ether. The filtrate was washed with aqueous sodium bicarbonate, dried (Na_2SO_4), and distilled giving 39.1 g (76%) of the (E) and (Z) silyl ethers 60a and 60b in a ratio of 3:1 (determined by glpc): bp 95-99°. A portion of the isomeric mixture was subjected to preparative glpc (15% SE-30 column): (E) isomer 60a; ir ($CHCl_3$) 1660 cm^{-1}; nmr (CCl_4) δ 0.15 (s, 9), 1.50 (d of d, 3, J = 6 Hz, 2 Hz), 4.44 (d of q, 1, J = 6 Hz, 2 Hz), 6.06 (d, 1, J = 6 Hz, 2 Hz). (Z) isomer 60b; ir ($CHCl_3$) 1670 cm^{-1}.

Ethyl 4,4-Diethoxytetrolate (64).[25] Ethyl propiolate (19.6 g, 0.2 mol), triethyl orthoformate (37.0 g, 0.25 mol), and 1.0 g of zinc iodide were combined in a round-bottom flask fitted with a Vigreux column and condenser. The reaction was heated to 165° on an oil bath, and ethanol was distilled off over a period of 3 hr. Then the mixture was cooled, diluted with 100 ml of petroleum ether, filtered, concentrated, and distilled giving 15.8 g (39%) of 64: bp 129-131° (17 mm); ir (CCl_4) 2240, 1720, 1625 cm^{-1}; nmr (CCl_4) δ 1.0-1.4 (m, 9), 3.63 (q, 4, J = 6 Hz), 4.21 (q, 2, J = 6 Hz), 5.29 (s, 1).

Ethyl 2-Ethyl-3-(N-pyrrolidyl)-acrylate (65a). Ethyl 2-formylbutyrate[38] (1.44 g, 10 mmol) was added to a 50-ml flask containing 25 ml of dry benzene and 2 ml of pyrrolidine. The reaction mixture was then refluxed for 1 hr under a Dean-Stark apparatus, cooled, washed with water, dried (Na_2SO_4), and concentrated giving 1.95 g (98%) of 65a as a clear orange oil (one peak on glpc): uv max (95% EtOH) 295 nm; ir (CCl_4) 1680, 1920, 1600 cm^{-1}; nmr (CCl_4) δ 0.99 (t, 3, J = 7 Hz), 1.2 (t, 3, J = 7 Hz), 1.8-2.1 (m, 4), 2.36 (q, 2, J = 7 Hz), 3.3-3.6 (m, 4), 4.09 (q, 2, J = 7 Hz), 7.30 (s, 1).

Enol Silyl Ether 65b. Ethyl 2-formylbutyrate[38] (0.72 g, 5 mmol) was allowed to react with sodium hydride (120 mg, 5 mmol) in 10 ml of dimethoxyethane. After 1 hr, 0.6 g of trimethylsilyl chloride (which had been treated with 0.2 ml of triethylamine in 1 ml of dimethoxyethane and the precipitated triethylamine hydrochloride centrifuged out) was added to the enolate solution. The reaction was stirred for 1 hr, diluted with 50 ml of ether, filtered, and concentrated giving 1.02 g (96%) of the silyl ether 65b as a clear oil (90% pure by glpc): ir (CCl_4) 1720, 1650 cm^{-1}; nmr (CCl_4) δ 0.19 (s, 9), 1.01 (t, 3, J = 6 Hz), 1.10 (t, 3, J = 7 Hz), 2.11 (q, 2, J = 7 HZ), 6.95 (s, 1).

2-Allylbutyric Acid (66). Diethyl allylethylmalonate[28] (22.8 g, 0.1 mol) was added to a solution of 16 g of sodium hydroxide dissolved in 110 ml of ethanol and 100 ml of water. The resulting solution was then refluxed for 3.5 hr, 100 ml of ethanol was distilled off, and the reaction was cooled to room temperature. After acidifying to pH 2 with hydrochloric acid the product was extracted with two 350-ml portions of ether. The ether extracts were dried (Na_2SO_4), concentrated to an oil, heated at 155° for 1 hr (causing decarboxylation), and then distilled to give 9.0 g (70%) of 66 as a light oil: bp 118-122° (18 mm); ir (neat) 3200, 1750 cm^{-1}; nmr (CCl_4) δ 0.98 (t, 3, J = 6 Hz), 2.0 (q, 2, J = 6 Hz), 2.76 (d, 2, J = 6 Hz), 3.3 (m, 1), 5.0-5.2 (m, 1), 5.3-5.4 (m, 1), 5.4-6.0 (m, 1), 10.3 (s, 1).

Pyruvic Ester 68. Allylbutyric acid (66) (6.0 g) and 0.4 g of copper powder were stirred and heated at 75°, and methyl diazopyruvate (67)[29] (3.2 g, 2.5 mmol) was added in small portions during 0.6 hr. After stirring for 1 hr the reaction was cooled, diluted with 75 ml of ether, washed with six 20-ml portions of sodium bicarbonate solution, dried (Na_2SO_4), and concentrated to give 4.4 g (77%) of pyruvic ester 68 as a light yellow oil (one peak on glpc): ir (CCl_4) 1745, 1710, 1645 cm^{-1}; nmr (CCl_4) δ 0.98 (t, 3, J = 6 Hz), 1.4-2.0 (m, 2), 2.2-2.6 (m, 3), 3.89 (s, 3), 4.95 (br s, 1), 5.11 (s, 2), 5.6-6.0 (m, 1).

Dimethyl Ester 73a. Dimethyl ethylmalonate (16.0 g, 0.1 mol) was added dropwise to a stirred suspension of sodium hydride (2.4 g, 0.1 mol) in 250 ml of dimethoxyethane. After addition was complete, the reaction mixture was stirred for 0.5 hr, then cooled to -40°, and a solution of methyl mucochlorate[42] (18.5 g, 0.1 mol) in 50 ml of dimethoxyethane was added. The reaction was next stirred at room temperature for 12 hr, diluted with 200 ml of ether, and filtered. The filtrate was concentrated to an oil which was dissolved in 200 ml of ether, washed with 50 ml of water, dried (Na_2SO_4), concentrated, and distilled giving 26.6 g (87%) of 73a: bp 160-164° (0.3 mm); ir (neat) 1790, 1740, 1640 cm^{-1}; nmr (CCl_4) δ 0.99 (t, 3, J = 7 Hz), 2.24 (q, 2, J = 7 Hz), 3.59 (s, 3), 3.80 (s, 6), 6.10 (s, 1).

Diethyl Ester 73b. Using the same procedure as described above for the preparation of dimethyl ester 73a, diethyl ethylmalonate (18.8 g, 0.1 mol) was converted to 25.0 g (75%) of diethyl ester 73b: bp 130-134° (0.1 mm); ir (CCl_4) 1795, 1740, 1635 cm^{-1}; nmr (CCl_4) δ 1.01 (t, 3, J = 7 Hz), 1.30 (t, 6, J = 6 Hz), 2.29 (q, 2, J = 7 Hz), 3.61 (s, 3), 4.30 (q, 4, J = 6 Hz), 6.10 (s, 1).

3-Chloro-3-formylacrylic Acid (75a).[30] One liter of 35% hydrochloric acid was placed in a flask, then cooled to -10° (dry ice-ethanol bath), stirred, and treated with a slurry of 80 g of furfural and 320 g of powdered manganese dioxide (commercial reagent), added in small portions over a period of 3 hr. During the addition the reaction temperature was held below 5°. After addition was complete, the conversion of furfural to product was followed by removing small portions of reaction mixture, working these up, and analysing by glpc (3% OV-17). When the reaction was complete, the contents were rapidly filtered, the solids were washed with 300 ml of water, and the resulting aqueous phase was extracted with three 350-ml portions of ether. The combined ether extracts were washed with 5% aqueous sodium bicarbonate, then dried (Na_2SO_4), and concentrated giving 84.1 g (71%) of 75a as a light yellow oil (95% pure by glpc): ir (CCl_4) 1800, 1760, 1680 cm^{-1}; nmr (CCl_4) δ 6.30 (d, 1, J = 6 Hz), 6.73 (s, 1), 7.60 (d, 1, J = 6 Hz).

tert-Butyl Methyl Ethylmalonate (76). Methyl ethylmalonate[31] (73 g, 0.5 mol) was placed in a 500 ml pressure bottle with freshly condensed liquid isobutylene (85 g, 1.5 mol) and 2.5 ml of concentrated sulfuric acid. This mixture was stirred at room temperature for 20 hr, then the bottle was cooled in a dry ice bath and the pressure fittings removed. The reaction mixture was poured into 100 ml of water containing 10 g of potassium carbonate and the contents stirred and shaken. The resulting two layer system was extracted with three 200-ml portions of ether which were then combined, dried (Na_2SO_4), concentrated, and distilled giving 60.5 g (51%) of 76: bp 95-97° (14 mm); ir (neat) 1755, 1735 cm^{-1}; nmr (CCl_4) δ 0.96 (t, 3, J = 7 Hz), 1.47 (s, 9), 1.8 (m, 2), 3.11 (t, 1, J = 7 Hz), 3.70 (s, 3).

Bromo Diester 77. tert-Butyl methyl ethylmalonate (76) (10.1 g, 0.05 mol) was added dropwise to sodium hydride (1.2 g, 0.05 mol) in 150 ml of dimethoxyethane. After addition was complete, the solution was heated to reflux briefly, then cooled to room temperature. To this was added a solution of methyl mucobromate[30] (12.4 g, 0.046 mol) in 50 ml of dimethoxyethane during 3 hr. After stirring for 1 hr, the reaction was diluted with 100 ml of ether, washed with two 40-ml portions of water, dried (Na_2SO_4), concentrated, and distilled giving 11.4 g (65%) of 77 as a yellow viscous oil: bp 150-154° (0.1 mm); ir (CCl_4) 1790, 1740, 1635 cm^{-1}; nmr (CCl_4) δ 1.00 (t, 3, J = 7 Hz), 1.50 (s, 9), 2.29 (q, 2, J = 7 Hz), 3.58 (s, 3), 3.80 (s, 3), 6.09 (m, 1).

Bromoester 78. Bromodiester 77 (3.93 g, 0.01 mol) was dissolved in 50 ml of dry toluene along with 50 mg of dry p-toluenesulfonic acid, and the solution refluxed for 3 hr. Then the solution was diluted with 40 ml of ether, washed with 15 ml of aqueous potassium carbonate solution, dried (Na_2SO_4), concentrated, and distilled giving 2.90 g (98%) of bromoester 78: bp 125-130° (0.1 mm); uv max (95% EtOH) 239 and 299 nm; ir (CCl_4) 1790, 1740, 1645 cm^{-1}; nmr (CCl_4) δ 0.98 (t, 3, J = 7 Hz), 1.96 (q, 2, J = 7 Hz), 3.3 (m, 1), 3.64 (s, 3), 3.81 (s, 3), 5.98 (s, 1); mass spectrum (70 eV) m/e 279 and 277 (M^+ -15), 263 and 261 (M^+ -31).

Lactone Ester 74. Bromoester 78 (1.46 g, 5 mmol) was placed in a flask with 8 ml of methanol, 175 mg of 10% palladium on charcoal, and 0.5 g of pyridine. This mixture was stirred at room temperature under an atmosphere of hydrogen, and the progress of the reaction followed by glpc. When the reaction was half over, it was necessary to filter the solution and add new catalyst to continue the hydrogenation. When the reaction was complete, the catalyst was removed by filtration, and the filtrate was diluted with 100 ml of ether, washed with 5 ml of 1N hydrochloric acid, dried (K_2CO_3 and Na_2SO_4), concentrated, and distilled (Kugelrohr) giving 1.01 g (94%) of 74: bp 100-105° (0.1 mm); uv max (95% EtOH) 218 nm; (95% EtOH and NaOH) 369 nm (ϵ 9,200); ir ($CHCl_3$) 1800, 1770, 1740, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.01 (t, 3, J = 7 Hz), 1.9 (m, 2), 3.4 (m, 1), 3.61 (s, 3), 3.80 (s, 3), 5.83 (s, 1), 6.14 (s, 1); mass spectrum (70 eV) m/e 183 (M^+ -31), 170 (M^+ -44), 155 (M^+ -59).

Vinylogous Urethane 79. Lactone ester 74 (430 mg, 2 mmol) was dissolved in 4 ml of dimethylformamide under nitrogen and to this was added 2.5 ml of dimethylformamide dimethylacetal. The resulting solution was heated to 65° for 2 hr, then concentrated at high vacuum. The dark residue was taken up in 150 ml of ether, washed with two 20-ml portions of water, dried (Na_2SO_4), and concentrated. The resulting oil was dissolved in 8 ml of carbon tetrachloride and placed in the freezer giving 270 mg (51%) of the crystalline urethane 79: mp 103-105°; uv max (95% EtOH) 230 nm (ϵ 6,800), 292 (10,800), 3.62 (17,800); ir ($CHCl_3$) 1730, 1690, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (t, 3, J = 6 Hz), 2.38 (q, 2, J = 6 Hz), 3.35 (s, 6), 3.56 (s, 3), 3.74 (s, 3), 6.17 (s, 1), 7.19 (s, 1); mass spectrum (70 eV) m/e 269 (M^+).

Di-tert-butyl Tartrate. This compound was prepared by a modification of the procedure of Rapoport.[34] To a solution of di-tert-butyl fumarate (17.1 g, 0.075 mol) in 500 ml of tert-butyl alcohol was added potassium permanganate (8.2 g, 0.052 mol) in 500 ml of water with vigorous stirring. The reaction was followed by glpc. After 3 hr of stirring, another 4.0 g of potassium permanganate in 200 ml of water was added, causing the reaction to go to completion. Then the reaction mixture was extracted with two 1000-ml portions of ether, and the combined extracts were washed with two 500-ml portions of water, dried (Na_2SO_4), and concentrated to a solid residue, which was recrystallized from petroleum ether to give 12.6 g (64%) of di-tert-butyl tartrate: mp 82-84° (lit[34] mp 83-85°, 44% yield).

tert-Butyl Glyoxylate (78c). This compound was prepared by a modification of the procedure of Rapoport.[34] To a cold solution of di-tert-butyl tartrate (5.1 g, 19.5 mmol) in 25 ml of dry benzene was added freshly recrystallized lead tetraacetate (10.1 g, 23 mmol), and the mixture was stirred under nitrogen for 3.4 hr. Then 100 ml of petroleum ether was added and the reaction was stirred for 5 min and decanted. This procedure was repeated, and the combined petroleum ether solutions were concentrated. The residue was taken up in 50 ml of petroleum ether, placed in the freezer overnight, then warmed slightly and filtered. After concentrating this filtrate, the residue was again taken up in 25 ml of petroleum ether, stirred with 1.0 g of phosphorous pentoxide, filtered, concentrated, and distilled (Kugelrohr) giving 3.6 g (72%) (lit[34] 31%) of tert-butyl glyoxylate (78c): bp 59-69° (25 mm); ir ($CHCl_3$) 1745, 1715 cm^{-1}; nmr (CCl_4) δ 1.53 (s, 9), 9.27 (s, 1).

Methyl 4,4-Dimethoxy-2-ethyl-3-oxobutyrate (81). This compound was prepared by the method of Royals[43] in 59% yield: bp 112-114° (11 mm); uv max (MeOH) 218 and 272 nm; ir (neat) 1750, 1730 cm^{-1}; nmr (CCl_4) δ 0.96 (t, 3, J = 7 Hz), 1.75 (d, 2, J = 7 Hz), 3.37 (s, 6), 3.6 (m, 1), 3.67 (s, 3), 4.45 (s, 1).

Methyl 3-Acetoxy-4,4-dimethoxy-2-ethylcrotonate (82a). Keto ester 81 (13.7 g, 0.067 mol) was added dropwise to a stirred suspension of sodium hydride (1.6 g, 0.067 mol) in 100 ml of dimethoxyethane. After 1 hr, a solution of 5.7 g (1.1 equivalents) of acetyl chloride in 20 ml of dimethoxyethane was added rapidly with stirring. The reaction was stirred at room temperature for 0.5 hr and then added to 30 ml of sodium bicarbonate solution, extracted with ether, dried (Na_2SO_4), concentrated, and distilled giving 14.8 g (92%) of the enol acetate 82a: bp 84-88° (0.1 mm); ir (CCl_4) 1760, 1720 cm^{-1}; nmr (CCl_4) δ 1.05 (t, 3, J = 7 Hz), 2.10 (s, 3), 2.44 (q, 2, J = 7 Hz), 3.32 (s, 6), 3.70 (s, 3), 4.98 (s, 1).

Ester Epoxide 85. Keto ester 81 (204 mg, 1 mmol) was dissolved in 1 ml of ether and to this was added 12 mmol of freshly prepared diazomethane in 15 ml of ether. The reaction was allowed to stand at room temperature overnight in the dark, then partially evaporated under a stream of nitrogen. This procedure was repeated twice and then the reaction solution was concentrated giving 209 mg (95%) of 85 as a colorless oil (90% pure by glpc): ir (CCl_4) 1742 cm^{-1}; nmr (CCl_4) δ 0.94 (t, 3, J = 6 Hz), 1.2-1.9 (m, 3), 2.80 (s, 2), 3.33 (s, 3), 3.39 (s, 3), 3.71 (s, 3), 4.10 (s, 1).

Methyl 4,4-Dimethoxy-2-ethyl-2-methyl-3-oxobutyrate (86). Keto ester 81 (204 mg, 1 mmol) was added to sodium hydride (24 mg, 1 mmol) in 2 ml of hexamethylphosphoramide. The reaction was stirred at room temperature for 0.5 hr to ensure complete enolate formation, and a solution of methyl iodide (213 mg, 1.5 mmol) in 1 ml of hexamethylphosphoramide was added. After 10 hr, the reaction was quenched with 10 ml of water and extracted with 20 ml of pentane. The pentane extract was dried (Na_2SO_4) and concentrated to give 200 mg (92%) of 86 as a clear oil (95% pure by glpc): ir (neat) 1760, 1730, 1460 cm^{-1}; nmr ($CDCl_3$) δ 0.91 (t, 3, J = 7 Hz), 1.37 (s, 3), 1.91 (q, 2, J = 7 Hz), 3.39 (s, 6), 3.72 (s, 3), 4.80 (s, 1).

Methyl 2-Ethyl-3,4,4-trimethoxycrotonate (82b). Keto ester 81 (204 mg, 1 mmol) was added to sodium hydride (24 mg, 1 mmol) in 2 ml of hexamethylphosphoramide. The reaction was stirred at room temperature for 0.5 hr to ensure complete enolate formation, and then 1 ml of dimethyl sulfate was added. This solution was stirred for 0.5 hr, added to 15 ml of water, and extracted with 30 ml of pentane. The pentane layer was separated, dried (Na_2SO_4), and concentrated to give 210 mg (96%) of 82b as a clear oil (one peak on glpc): ir (CCl_4) 1730, 1705, 1620 cm^{-1}; nmr (CCl_4) δ 0.99 (t, 3, J = 7 Hz), 2.31 (q, 2, J = 7 Hz), 3.40 (s, 6), 3.68 (s, 3), 3.91 (s, 3), 5.86 (s, 1).

(Z) and (E) Methyl 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoate (89a and 89b). Trimethyl phosphonoacetate (13.7 g, 0.075 mol) was added dropwise to a stirred suspension of sodium hydride (1.8 g, 0.075 ml) in 200 ml of dimethoxyethane. The resulting thick white slurry was stirred vigorously at room temperature for 1 hr, keto ester 81 (9.2 g, 0.045 mol) was added, and the reaction was heated to reflux. After 20 hr, the reaction was cooled to room temperature, concentrated to half volume, added to 100 ml of water, and extracted with three 250-ml portions of ether. The ether extracts were dried (Na_2SO_4), concentrated, and distilled at 0.1 mm giving 2.7 g of 81, and then 7.7 g (66%, 93% based on recovered starting material 81) of a clear oil (bp 78-82°) containing 89a and 89b in a 2:1 ratio. Isomers 89a and 89b could be separated by preparative glpc on a six-foot 15% SE-30 column in an F and M 720 gas chromatograph.

(Z) Ester 89a: uv max (95% EtOH) 216 nm; ir (CCl_4) 1725, 1655 cm^{-1}; nmr (CCl_4) δ 0.91 (t, 3, J = 7 Hz), 1.52 (q, 2, J = 7 Hz), 3.16 (s, 3), 3.51 (s, 3), 3.55 (s, 3), 3.9-4.3 (m, 1), 5.80 (s, 1), 5.87 (s, 1); mass spectrum (70 eV) m/e 260 (M^+).

(E) Ester 89b: uv max (95% EtOH) 219 nm; ir (CCl_4) 1745, 1727, 1655 cm^{-1}; nmr (CCl_4) δ 0.91 (t, 3, J = 7 Hz), 1.3-1.8 (m, 2), 3.17 (s, 3), 3.24 (s, 3), 3.58 (s, 3), 3.65 (s, 3), 4.40 (t, 1, J = 7 Hz), 4.68 (s, 1), 6.01 (s, 1); mass spectrum (70 eV) m/e 260 (M^+).

(E) and (Z) Methyl 4-Carbomethoxy-3-dimethoxymethyl-3-hexenoate (89c and 89d). A solution of isomers 89a and 89b (2.6 g, 10 mmol) in 10 ml of tetrahydrofuran was added slowly to a solution of potassium tert-butoxide (1.24 g, 11 mmol) in 15 ml of tetrahydrofuran at -65°. The resulting clear yellow enolate solution was then warmed gradually to -30°, quenched with 10 ml of water, and extracted with three 50-ml portions of ether. The combined ether extracts were dried (Na_2SO_4) and concentrated giving 2.48 g (95%) of diesters 89c and 89d: uv max (95% EtOH) 218 nm; ir (CCl_4) 1745, 1725, 1655 cm^{-1}; nmr (CCl_4) δ 1.18 (t, 3, J = 7 Hz), 2.40 (q, 2, J = 7 Hz), 3.0-3.4 (m, 8), 3.6-3.8 (m, 6), 5.0 (m, 1); mass spectrum (70 eV) m/e 260 (M^+).

Methyl 4-Carbomethoxy-3-dimethoxymethyl-2-methyl-3-hexenoate (92). To a solution of potassium tert-butoxide (134 mg, 1.2 mmol) in 10 ml of tetrahydrofuran at -65° was added diester isomers 89a and 89b (260 mg, 1 mmol). After stirring the solution for 0.5 hr and warming to -30°, methyl iodide (200 mg, 1.5 mmol) was added and the reaction stirred at room temperature for 10 hr. The resulting solution was added to 5 ml of water and extracted with three 20-ml portions of ether. The ether extracts were dried (Na_2SO_4) and concentrated giving 200 mg (71%) of 92 (a mixture of (Z) and (E) isomers which appeared as one peak on glpc): uv max (95% EtOH) 214 nm; ir (CCl_4) 1745, 1725 cm^{-1}; nmr (CCl_4) δ 0.98 (t, 3, J = 8 Hz), 1.32 (d, 3, J = 7 Hz), 2.1-2.6 (m, 2), 3.2-3.5 (m, 7), 3.6-3.8 (m, 6), 5.0 (m, 1).

Methylene Diester 93. A solution of dimethyl ester isomers 89a and 89b (260 mg, 1 mmol) in 1 ml of tetrahydrofuran was added to potassium tert-butoxide (124 mg, 1.1 mmol) in 5 ml of tetrahydrofuran at -65°, and the resulting solution was stirred and warmed to -30° during 0.5 hr. Then gaseous formaldehyde was passed over the rapidly stirring enolate solution in a stream of nitrogen. The reaction was stirred at room temperature for 1 hr and then worked up by adding water, extracting with ether, drying (Na_2SO_4) the organic phase, and concentrating to give 160 mg (58%) of 93. This product oil was further purified by preparative glpc (six foot 15% SE-30 column) to give pure 93 as a mixture of (Z) and (E) isomers: uv max (MeOH) 234 nm; ir ($CHCl_3$) 1725 cm^{-1}; nmr (CCl_4) δ 0.8-1.2 (m, 3), 2.0-2.6 (m, 2), 3.1-3.3 (m, 6), 3.6-3.8 (m, 6), 4.94 and 5.06 (2S, total 1H), 5.39 and 5.45 (2d, total 1H, J = 2 Hz), 6.06 and 6.29 (2d, total 1H, J = 2 Hz).

Ethyl Methyl Ester 94. A solution of dimethyl esters 89a and 89b (260 mg, 1 mmol) in 3 ml of benzene and 1 ml of ethyl formate was cooled to 0°, and sodium methoxide (60 mg, 1.1 mmol) was added. After stirring for 0.2 hr, the reaction was quenched with 4 ml of water and extracted with 25 ml of ether. The ether extract was dried (Na_2SO_4) and concentrated to an oil, from which the major product (94) was isolated by preparative glpc (15% SE-30 column): uv max (95% EtOH) 216 nm; ir (CCl_4) 1740, 1725 cm^{-1}; nmr (CCl_4) δ 0.93 (t, 3, J = 7 Hz), 1.32 (t, 3, J = 7 Hz), 1.67 (q, 2, J = 7 Hz), 3.2 (m, 1), 3.32 (s, 3), 3.40 (s, 3), 3.67 (s, 3), 4.18 (q, 2, J = 7 Hz), 5.96 (s, 1), 5.98 (s, 1).

Ethyl 4-Carboethoxy-3-dimethoxymethyl-2-hexenoate (95). This compound was prepared by the same method used to make ethyl methyl ester 94, except that the reaction was heated to reflux for 10 hr. The reaction was worked up as before, giving a light oil. The major product was isolated from the residual oil by preparative glpc (15% SE-30 column) giving diethyl ester 95: uv max (95% EtOH) 216 nm; ir (CCl_4) 1745, 1725 cm^{-1}; nmr (CCl_4) δ 0.9-1.5 (m, 9), 2.1-2.6 (m, 2), 3.1-3.4 (m, 7), 4.0-4.4 (m, 4), 4.8-5.1 (m, 1), 5.9-6.1 (m, 1).

Methyl 2-Bromo-4-carbomethoxy-3-dimethoxymethyl-3-hexenoate (96). Dimethyl ester isomers 89a and 89b (2.60 g, 10 mmol) were dissolved in 20 ml of carbon tetrachloride, and to this solution was added 0.6 ml (12 mmol) of bromine. After 12 hr, the reaction was diluted with 50 ml of carbon tetrachloride and washed with aqueous sodium thiosulfate solution. Then the carbon tetrachloride was removed in vacuo and the residual oil dissolved in a solution of 8 ml of dimethoxyethane, 35 ml of water, and 0.8 g of potassium hydroxide pellets. After 0.6 hr the reaction mixture was extracted with 70 ml of carbon tetrachloride and the extracts were dried (Na_2SO_4) and concentrated giving 2.4 g (70%) of 96 as a yellow oil (90% pure by glpc): uv max (MeOH) 247 nm; ir ($CHCl_3$) 1735, 1620 cm^{-1}; nmr ($CDCl_3$) δ 0.8-1.2 (m, 3), 1.60-2.4 (m, 2), 3.2-3.5 (m, 6), 3.6-3.9 (m, 7), 5.06 and 5.15 (2 s, total 1H).

Methyl 4-Carboxy-3-dimethoxymethyl-2-hexenoate (97). Dimethyl ester isomers 89a and 89b (2.6 g, 10 mmol) were added to a stirred solution of 0.8 g of potassium hydroxide pellets in 100 ml of water. After 1 hr the reaction was acidified with dilute hydrochloric acid to pH 6.0 and extracted with 200 ml of methylene chloride. The organic extract was dried (Na_2SO_4) and concentrated giving 2.0 g (81%) of the acid isomers 97 as a clear oil (one peak on glpc): ir ($CHCl_3$) 3400, 1735 cm^{-1}; nmr ($CDCl_3$) δ 0.94 (t, 3, J = 6 Hz), 1.80 (q, 2, J = 6 Hz), 3.2-3.6 (m, 7), 3.6-3.8 (m, 3), 5.8 (m, 1), 6.2 (m, 1), 9.8 (br s, 1).

Methyl 4-Carbomethoxy-3-methoxymethyl-2-hexenoate (100). Diester isomers 89a and 89b (520 mg, 2 mmol) were added to 30 ml of ether containing 0.8 g of aluminum amalgam (prepared by treating aluminum foil with 2% aqueous mercuric chloride solution). During the next 24 hr, 2 ml of water was added in portions, along with an additional 0.3 g of aluminum amalgam. The reaction was filtered, dried (Na_2SO_4), and concentrated giving 0.5 g (90%) of 100 (90% pure by glpc): ir (CCl_4) 1740, 1670 cm^{-1}; nmr (CCl_4) δ 0.83 (t, 3, J = 7 Hz), 1.3-1.7 (m, 2), 2.7-3.0 (m, 2), 3.4-3.7 (m, 10), 5.97 (s, 1).

Methyl 4-Carbomethoxy-3-dimethoxymethylhexanoate (99). A suspension of palladium was prepared by stirring palladium chloride (176 g, 2 mmol) in 10 ml of methanol and adding to this sodium borohydride (80 mg, 2.1 mmol). After stirring for 5 min, unsaturated diesters 89a and 89b (2.6 g, 10 mmol) were added, and the reaction vessel alternately evacuated and flushed with hydrogen. The reaction was stirred under an atmosphere of hydrogen for 2 days, removed, decanted, concentrated, taken up in 40 ml of ether, filtered, reconcentrated, and distilled (Kugelrohr) giving 2.4 g (93%) of the saturated diester 99: bp 100-110° (0.1 mm); ir (CCl_4) 1745, 1460, 1430 cm^{-1}; nmr (CCl_4) δ 0.89 (t, 3, J = 7 Hz), 1.3-1.6 (m, 2), 2.2-2.6 (m, 4), 3.27 and 3.30 (2s, total 6H), 3.62 (s, 6), 4.20 (d, 1, J = 5 Hz); mass spectrum (70 eV) m/e 262 (M^+).

Enol Lactone 102. Diester 99 (2.4 g, 9 mmol) was dissolved in 10 ml of tetrahydrofuran and added dropwise to a solution of 10 mmol of lithium diisopropylamide in 12 ml of tetrahydrofuran at -78° during 0.2 hr. This solution was stirred at -78° for 0.5 hr and then allowed to warm slowly to -70°, at which time 8 ml of methyl formate (freshly distilled from P_2O_5) was added. Stirring was continued for 2 hr as the solution was allowed to warm to room temperature, and then 30 ml of dilute potassium carbonate solution was added. Starting material was extracted from this basic aqueous solution with 30 ml of ether. Formylated product was back extracted from the ether phase with 20 ml of potassium carbonate solution. The ether solution, containing only starting materials (as shown by glpc) was dried (Na_2SO_4) and concentrated giving 0.5 g of 99 (20% recovery).

The combined basic extracts were carefully acidified to pH 4.0 with hydrochloric acid and extracted with three 40-ml portions of ether. Combined ether extracts were dried (Na_2SO_4) and concentrated giving 1.95 g of crude formylated material. This crude oil was cyclized by distillation on a Kugelrohr giving 1.65 g (72%, 90% based on recovered starting material) of the enol lactone 102: bp 160-180° (23 mm); uv max (95% EtOH) 243 nm (ε 12,000) and 284 (900); ir (CCl_4) 1745, 1720, 1630 cm^{-1}; nmr (CCl_4) δ 0.96 (t, 3, J = 6 Hz), 1.3-1.8 (m, 2), 2.7-3.2 (m, 2), 3.48 (s, 3), 3.72 (s, 6), 5.6 (m, 1), 7.2 (m, 1); mass spectrum (70 eV) m/e 258 (M^+).

tert-Butyl Dimethylphosphonoacetate (105). tert-Butyl bromoacetate[39] (19.5 g, 0.1 mol) was combined with trimethyl phosphite (13.7 g, 0.11 mol) and heated at 80-90° for 36 hr. The contents were distilled giving 16.0 g (85%) of 105: bp 72-75° (0.2 mm); ir (neat) 1745 cm^{-1}; nmr (CCl_4) δ 1.45 (s, 9), 2.75 (d, 2, J = 22 Hz), 3.73 (d, 6, J = 11 Hz).

(Z) and (E) tert-Butyl 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoate (106). tert-Butyl dimethylphosphonoacetate (105) (4.9 g, 22 mmol) was added dropwise to a stirred suspension of 22 mmol of sodium hydride in 20 ml of dimethoxyethane and the resulting solution was stirred for 1.5 hr. Then keto ester 81 (4.5 g, 22 mmol) was added, and the reaction was heated to reflux for 2 days. After concentrating the reaction mixture to half volume, 20 ml of water was added and the aqueous phase extracted

with two 30-ml portions of ether. The combined ether extracts were dried (Na_2SO_4), concentrated, and distilled giving 5.6 g (85%) of the (Z) and (E) ester isomers 106: bp 100-110° (0.2 mm); uv max (95% EtOH) 218 nm; ir (CCl_4) 1740, 1720, 1650 cm^{-1}; nmr (CCl_4) δ 0.89 (t, 3, J = 7 Hz), 1.50 (s, 9), 1.55-1.80 (m, 2), 3.1 (m, 1), 3.2-3.4 (m, 6), 3.6 (m, 3), 4.3-4.7 (m, 1), 5.9 (m, 1).

tert-Butyl 4-Carbomethoxy-3-dimethoxymethyl hexanoate (107). tert-Butyl methyl ester 106 (mixture of (Z) and (E) isomers) (40 mg, 0.13 mmol) was added to a flask containing 5 ml of methanol and borohydride reduced palladium[37] (25 mg, 0.25 mmol). The reaction mixture was stirred under an atomosphere of hydrogen for 60 hr, filtered, and concentrated. The filtrate was taken up in 15 ml of ether, filtered, and concentrated giving 40 mg (99%) of the saturated diester 107 as a clear oil (one peak on glpc): ir ($CHCl_3$) 1730 cm^{-1}; nmr ($CDCl_3$) δ 0.7-1.0 (m, 3), 1.1-1.3 (m, 2), 1.45 (s, 9), 2.2-2.6 (m, 3), 3.34 (s, 6), 3.5 (m, 1), 3.66 (s, 3), 4.24 (d, 1, J = 6 Hz).

4-Carbomethoxy-3-dimethoxymethylhexanoic Acid (108). Dimethyl ester 99 (5.2 g, 20 mmol) was added to a solution of 80 ml of water, 14 ml of methanol, and 1.45 g of potassium hydroxide pellets. This solution was stirred for 1 hr, then washed with ether, acidified to pH 4.0, and extracted with two 100-ml portions of ether. The ether extracts of the acidified solution were combined, dried (Na_2SO_4), and concentrated,

giving 4.2 g (84%) of acid 108 as clear oil (one peak on glpc): ir (CCl_4) 1740, 1720 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (t, 3, J = 7 Hz), 1.4-1.7 (m, 2), 2.4-2.6 (m, 4), 3.42 (s, 6), 3.70 (s, 3), 4.30 (d, 1, J = 5 Hz), 8.79 (br s, 1).

2,2,2-Trichloroethyl 4-Carbomethoxy-3-dimethoxymethylhexanoate (109a). Carboxylic acid 108 (124 mg, 0.5 mmol) was added to a solution of 2,2,2-trichloroethanol (150 mg, 1 mmol), pyridine (0.2 g), and dicyclohexylcarbodiimide (206 mg, 1 mmol) in 5 ml of methylene chloride. After stirring at room temperature for 12 hr, the reaction was filtered, and the filtrate was washed with 1N hydrochloric acid, sodium bicarbonate solution, dried (Na_2SO_4), and concentrated. Preparative thin layer chromatography (silica gel GF) using chloroform as solvent afforded 200 mg (54%) of 109a as a yellow oil: ir (CCl_4) 1760, 1740 cm^{-1}; nmr (CCl_4) δ 0.92 (t, 3, J = 7 Hz), 1.3-1.8 (m, 3), 2.4-2.6 (m, 3), 3.30 (s, 6), 3.65 (s, 3), 4.25 (m, 1), 4.65 (s, 2).

Benzyl 4-Carbomethoxy-3-dimethoxymethylhexanoate (109b). Carboxylic acid 108 (1.0 g, 4 mmol) was added to 30 ml of 0.15N aqueous potassium hydroxide, and the solution was concentrated in vacuo. Residual water was removed by azeotropic distillation with benzene. The resulting acid salt (1.2 g) was combined with benzyl bromide (0.6 ml, 5 mmol) in 28 ml of dimethoxyethane and 2 ml of dimethylformamide. The resulting slurry was refluxed for 16 hr, cooled, concentrated, and partitioned between

11 ml of 0.1N hydrochloric acid and 50 ml of ether. The ether extract was washed with 10 ml of sodium bicarbonate solution, dried (Na_2SO_4), concentrated, and distilled (Kugelrohr) giving 1.1 g (82%) of benzyl ester 109b: bp 150-160° (0.1 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 0.7-1.0 (m, 3), 1.3-1.7 (m, 2), 2.3-2.6 (m, 4), 3.2 (m, 6), 3.55 (s, 3), 4.10 (d, 1, J = 6 Hz), 5.00 (s, 2), 7.23 (s, 5).

Amide Acetal 110. Tricyclic amine 22[12] (240 mg, 2 mmol) was added to a solution of carboxylic acid 108 (524 mg, 2 mmol) in 18 ml of methylene chloride. Then dicyclohexylcarbodiimide (433 mg, 2.1 mmol) was added, and the reaction was stirred at room temperature for 14 hr, filtered, and concentrated. The residual solid was purified by column chromatography on 12 g of Florisil. Elution with 6% methanol in ether provided 0.61 g (74%) of 110 as a light yellow solid. An analytical sample was recrystallized from methylene chloride-ether giving white crystals: mp 99-100°; uv max (95% EtOH) 231 nm (ϵ 45,3000), 282 (4,1000), 288 (4,300), 294 (4,800), 301 (5,000), 307 (6,900), 314 (6,100), 321 (9,700); ir (CCl_4) 2950, 1740, 1655 cm^{-1}; nmr (CCl_4) δ 0.98 (t, 3, J = 7 Hz), 1.3-1.8 (m, 2), 2.3-2.7 (m, 4), 3.31 (s, 6), 3.65 (s, 3), 4.30 (d, 1, J = 6 Hz), 4.80 (s, 2), 4.96 (s, 2), 7.4-8.0 (m, 5); mass spectrum (70 eV) m/e 400 (M^+).

Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 66.00; H, 7.00; N, 7.00.

Found: C, 66.23; H, 7.23; N, 6.98.

Aldehyde 111. Amide acetal 110 (240 mg, 0.6 mmol) was dissolved in 14 ml of methylene chloride and cooled to -65°. To this was added 0.25 ml of boron trifluoride etherate, then the cold bath was removed and the reaction was stirred and allowed to warm slowly. After 0.3 hr, 5 ml of water was added, and the mixture was stirred for an additional 0.3 hr. The aqueous layer was brought to pH 4.5 and by addition of sodium bicarbonate solution, the methylene chloride layer was separated, dried (Na_2SO_4), and concentrated giving 199 mg (94%) of the aldehyde 111 as a light tan solid. An analytical sample was recrystallized from methylene chloride-ether: mp 140-141°; uv max (95% EtOH) 231 nm (ϵ 45,9000), 282 (4,3000), 288 (4,500), 294 (5,000), 301 (5,200), 307 (7,100), 314 (6,200), 321 (9,800); ir ($CHCl_3$) 1730, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.0 (t, 3, J = 6 Hz), 1.4-2.0 (m, 2), 2.2-3.3 (m, 4), 3.72 (s, 3), 4.91 (s, 2), 4.97 (s, 2), 7.4-8.2 (m, 5), 9.9 (s, 1); mass spectrum (70 eV) m/e 354 (M^+).

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 67.80; H, 6.22; N, 7.92.

Found: C, 67.80; H, 6.38; N, 7.83.

Dihydropyridone 112. Aldehyde 111 (88 mg, 0.25 mmol) was added to 4 ml of toluene containing trifluoroacetic acid (4 μl). This solution was heated to reflux for 12 hr, then cooled and diluted with 4 ml of methylene chloride, washed with sodium bicarbonate solution, dried (Na_2SO_4), and concentrated to an oil. Preparative thin layer chromatography of the residual oil (silica gel GF, 8% methanol in ether) afforded 38 mg (46%) of the product 112 as a tan solid. The product was further purified by

recrystallization from methylene chloride-ether giving a light yellow solid: mp 130-133°; uv max (95% EtOH) 242, 290, 320 and 360 nm; ir (CCl_4) 1740, 1685 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (t, 3, $\underline{J}$ = 7 Hz), 1.4-2.0 (m, 2), 2.2-2.8 (m, 4), 3.72 (s, 3), 4.98 (s, 2), 6.15 (t, 1, $\underline{J}$ = 5 Hz), 7.5-8.2 (m, 5).

Benzyl Bromoacetate (116a).[46] Bromoacetic acid (5.6 g, 0.04 mol) and benzyl alcohol (4.3 g, 0.04 mol) were added to a solution of 50 ml of benzene and 0.5 g of p-toluenesulfonic acid in a flask fitted with a Dean-Stark apparatus. The reaction was heated to reflux for 2.5 hr and cooled to room temperature. After adding 100 ml of ether, the solution was extracted with two 25-ml portions of sodium bicarbonate solution, dried (Na_2SO_4), and concentrated giving 8.1 g (96%) of benzyl bromoacetate (116a) (95% pure by glpc): ir (CCl_4) 1745 cm^{-1}; nmr (CCl_4) δ 3.70 (s, 2), 5.08 (s, 2), 7.28 (s, 5).

Benzyl Dimethylphosphonoacetate (116).[44] Benzyl bromoacetate (116a) (35.0 g, 0.15 mol) was stirred in a flask with 30 ml of trimethyl phosphite and heated to 80°. After 48 hr, the contents were distilled giving 34.1 g (91%) of 116: bp 148-150° (0.1 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 2.91 (d, 2, $\underline{J}$ = 22 Hz), 3.67 (d, 6, $\underline{J}$ = 11 Hz), 5.09 (s, 2), 7.29 (s, 5).

(Z) and (E) Benzyl 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoate (117a and 117b). Benzyl dimethylphosphonoacetate (116) (16.0 g, 0.06 mol) was added dropwise to a stirred suspension of sodium hydride (1.50 g, 0.062 mol) in 250 ml of dimethoxyethane. The reaction was stirred at 60° for 1 hr to ensure complete enolate formation. Then keto ester 81 (15.7 g, 0.077 mol) was added, and the reaction was heated to reflux. After 24 hr the contents were concentrated to one half volume, 100 ml of water was added, and the product was extracted with one 250-ml portion of ether (subsequent extracts showed no desired product by glpc). The ether extract was dried (Na_2SO_4), concentrated, and distilled giving 16.5 g (82%) of 117a-b ((Z) to (E) ratio 3:1 by glpc): bp 151-159° (0.1 mm); uv max (95% EtOH) 214 nm; ir ($CHCl_3$) 1725, 1650 cm^{-1}; nmr ($CDCl_3$) δ 0.91 (t, 3, J = 7 Hz), 1.5-2.0 (m, 2), 3.3 (m, 1), 3.3-3.6 (m, 6), 3.7 (m, 3), 5.12 (s, 2), 5.92 (s, 1), 6.08 (s, 1), 7.33 (s, 5); mass spectrum (70 eV) m/e 336 (M^+)

(Z) and (E) Benzyl 4-Carbomethoxy-3-dimethoxymethyl-3-hexenoate (117c and 117d). This compound was prepared by the same procedure used to isomerize 89a-b to 89c-d. In this manner, diesters 117a and 117b (1.68 g, 5 mmol) were converted to 1.61 g (96%) of diester 117c and 117d (as a mixture of (Z) and (E) isomers): uv max (95% EtOH) 214 nm; ir (CCl_4) 1745, 1730 cm^{-1}; nmr (CCl_4) δ 0.9-1.3 (m, 3), 2.2-2.7 (m, 2), 3.2-3.4 (m, 6), 3.4 (m, 2), 3.6-3.8 (m, 3), 4.6 (m, 1), 5.11 (m, 2), 7.24 (br s, 5); mass spectrum (70 eV) m/e 336 (M^+).

(Z) and (E) 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoic Acid (115). Benzyl ester isomers 117a and 117b (3.36 g, 10 mmol) were added to a flask containing 100 ml of methanol and 440 mg of 10% palladium on carbon catalyst. After evacuating and flushing the flask with hydrogen several times, the reaction was stirred under hydrogen at atmospheric pressure and room temperature. When the theoretical uptake (225 ml, 10 mmol) was observed, the reaction flask was removed, 40 ml of methylene chloride was added, and the catalyst removed by filtration through Celite. The filtrate was concentrated in vacuo at a temperature not above 35° giving 2.5 g (98%) of acid 115 (a mixture of (Z) and (E) isomers): ir (CCl_4) 3530, 1740, 1700, 1650 cm^{-1}; nmr (CCl_4) δ 0.94 (t, 3, J = 7 Hz); 1.67 (q, 2, J = 7 Hz), 3.2 (m, 1), 3.3-3.5 (m, 6), 3.64 (s, 3), 5.86 (s, 1), 5.99 (s, 1), 10.6 (s, 1).

(Z) and (E) 4-Carbomethoxy-3-dimethoxymethyl-3-hexenoic Acid (115a). Benzyl ester isomers 117c and 117d (336 mg, 1 mmol) were added to a flask containing 15 ml of methanol, 25 mg of 10% palladium on carbon catalyst, and 2 drops of triethylamine. After evacuating and flushing the flask with hydrogen several times, the reaction was stirred under hydrogen at atmospheric pressure and room temperature. After 20 min, theoretical uptake (24 ml, 1 mmol) was observed, and the reaction was removed, diluted with 10 ml of methylene chloride, and filtered through Celite. The filtrate was concentrated in vacuo at a temperature not above 35° giving 248 mg (95%) of acid 115a (a mixture of (Z) and (E) isomers which was 95% pure by glpc): ir ($CHCl_3$) 3200, 1720, 1650 cm^{-1};

nmr (CCl_4) δ 1.01 (t, 3, $\underline{J}$ = 7 Hz), 2.31 (q, 2, $\underline{J}$ = 7 Hz), 3.1-3.4 (m, 8), 3.6-3.8 (m, 3), 5.0 (m, 1), 9.7 (br s, 1).

Amide Acetal 118. Freshly prepared carboxylic acid 115 (0.59 g, 2.4 mmol), dicyclohexylcarbodiimide (453 mg, 2.2 mmol), and tricyclic amine 22 (340 mg, 2 mmol), were combined in 25 ml of methylene chloride. This solution was stirred at room temperature for 12 hr, then filtered, concentrated, dissolved in 6 ml of methylene chloride, filtered again, and concentrated to an oil. The crude product was purified by preparative thin layer chromatography (silica gel GF, 8% methanol in ether) giving 450 mg (56%) of 118 (as a mixture of (Z) and (E) isomers). The product was further purified by recrystallization from methylene chloride-ether giving a light solid: mp 190-192°; uv max (95% EtOH) 234 nm (ϵ 40,4000), 288 (4100), 294 (4300), 301 (4200), 307 (5600), 314 (4900), 321 (7700): ir ($CHCl_3$) 1730, 1630 cm^{-1}; nmr ($CDCl_3$) δ 0.99 (t, 3, $\underline{J}$ = 7 Hz), 1.5-2.0 (m, 2), 2.2-2.5 (m, 1), 3.3-3.5 (m, 6), 3.6-3.8 (m, 3), 4.4 and 5.7 (2m, total 1H), 4.9-5.1 (br s, 4), 6.40 and 6.53 (2s, total 1H), 7.5-8.2 (m, 5); mass spectrum (70 eV) $\underline{m/e}$ 398 (M^+).

Amide Acetal 118a. Freshly prepared carboxylic acid 115a (50 mg, 0.2 mmol), tricyclic amine 22 (32 mg, 0.2 mmol), and dicyclohexylcarbodiimide (43 mg, 0.21 mmol), were combined in 6 ml of methylene chloride. This solution was stirred at room temperature for 12 hr, then filtered and concentrated to a light solid. The crude product

was purified by preparative thin layer chromatography (silica gel GF, 8% methanol in ether) giving 74 mg (93%) of 118a (as a mixture of (Z) and (E) isomers). The product was recrystalized from ether giving colorless needles: mp 135-137°; uv max (95% EtOH) 232 nm (ε 48,200), 282 (4000), 288 (4200), 295 (4800), 301 (4900), 308 (6700), 314 (6000), 322 (9100); ir ($CHCl_3$) 1740, 1650, 1425 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (t, 3, J = 7 Hz), 2.3-2.8 (m, 2), 3.3-3.5 (m, 8), 3.7-3.9 (m, 3), 4.9-5.2 (m, 5), 7.5-8.2 (m, 5); mass spectrum (70 eV) m/e 398 (M^+).

Pyridone 20. Amide acetal 118 or 118a (300 mg, 0.75 mmol) was dissolved in 30 ml of methylene chloride and the resultant solution cooled to -65°. Boron trifluoride etherate (0.5 ml) was added, the cold bath was removed, and the reaction was allowed to gradually warm to room temperature. After 20 min, 10 ml of water was added, and the two-phase system was stirred for 20 min, then brought to pH 5 with sodium bicarbonate solution. The methylene chloride layer was separated, dried (Na_2SO_4), and concentrated giving 270 mg of crude aldehyde isomers 119: ir ($CHCl_3$) 1730, 1700, 1650 cm^{-1}. The crude aldehyde was dissolved in 20 ml of toluene with 6 μl of trifluoroacetic acid and the whole solution was heated to reflux. After 14 hr, the reaction mixture was filtered, diluted with 20 ml of methylene chloride, washed with dilute sodium bicarbonate solution, dried (K_2CO_3), and concentrated to an oil. Preparative thin layer chromatography (silica gel GF, 9% methanol in ether) afforded 105 mg (41%) of the pyridone 20. Three recrystallizations from methanol provided an analytical sample as light crystals: mp 197-

199° (lit[5] 198°); uv max (95% EtOH) 219 nm (ε 42,800), 249 (25,800), 254 (30, 600), 287 (6,100), 321 (7,400), 366 (17,400); ir ($CHCl_3$) 1740, 1670, 1600 cm^{-1}; nm ($CDCl_3$) δ 0.99 (t, 3, J = 7 Hz), 1.8-2.2 (m, 2), 3.48 (t, 1, J = 7 Hz), 3.71 (s, 3), 5.22 (s, 2), 6.64 (m, 1), 7.30 (m, 1), 7.5-8.3 (m, 5); mass spectrum (70 eV) m/e 334 (M^+).

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.86; H, 5.39; N, 8.38.

Found: C, 71.90; H, 5.43; N, 8.23.

BIBLIOGRAPHY

1. M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail and G. A. Sim, J. Amer. Chem. Soc. 88, 3888 (1966).

2. A. T. McPhail and G. A. Sim, J. Chem. Soc. B, 923 (1968).

3. A. G. Schultz, Chem. Rev. 73, 386 (1973).

4. G. Stork and A. G. Schultz, J. Amer. Chem. Soc. 93, 4074 (1971).

5. R. Volkman, S. Danishefsky, J. Egger and D. M. Solomon, J. Amer. Chem. Soc. 94, 3631 (1972).

6. M. Boch, T. Korth, J. Nelke, D. Pike, H. Radunz and E. Winterfeldt, Chem. Ber. 105, 2126 (1972).

7. J. A. Kepler, M. C. Wani, J. M. McNaull, M. E. Wall and S. G. Levine, J. Org. Chem. 34, 3853 (1969).

8. T. Sugasawa, T. Toyota and K. Sasakura, Tetrahedron Lett, 5109 (1972).

9. A. I. Meyers, R. L. Nolen, E. W. Collington, T. A. Warwick and R. C. Strickland, J. Org. Chem. 38, 1974 (1973).

10. M. Shamma, D. A. Smithers and V. St. Geogiev, Tetrahedron 29, 1949 (1973).

11. A. S. Kende, T. J. Bentley, R. W. Draper, J. K. Jenkins, M. Joyeux and I. Kubo, Tetrahedron Lett., 1307 (1973).

12. L. H. Zalkow, J. B. Nabors, K. French and S. C. Bisarya, J. Chem. Soc. C., 3551 (1971).

13. C. Tang and H. Rapoport, J. Amer. Chem. Soc. 94, 8615 (1972).

14. T. K. Liao, W. H. Nyberg and C. C. Cheng, J. Heterocycl. Chem. 8, 373 (1971).

15. M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall and S. G. Levine, J. Amer. Chem. Soc. 94, 3631 (1972).

15a. After this work was completed, the preparation of this compound was reported by a similar method; M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall and S. G. Levine, J. Amer. Chem. Soc. 94, 3631 (1972).

16. E. J. Corey, D. N. Crouse, J. E. Anderson, J. Org. Chem. 40, 2140 (1975).

17. A. Funke and H. Dubendorfer, Bull. Soc. Chim. Fr., 346 (1950).

18. T. E. Jackson, Ph.D. Thesis, M.I.T., 1971.

19. I. E. Jaeger and J. H. Biel, J. Org. Chem. 30, 740 (1965).

20. T. Sugasawa, T. Toyota K. Sasakura and T. Hidaka, Chem. Pharm. Bull. 19, (9) 1971 (1971).

21. M. Roth, P. Dubs, E. Gotschi and A. Eschenmoser, Helvetica Chimica Acta 54, 2, 710 (1971).

22. J. Cologne and L. Curnet, Bull. Soc. Chim. Fr., 838 (1947).

23. T. Kametani, S. Takano, H. Nemoto and H. Takeda, Yakugaku Zasshi 91, 966 (1971).

24. G. Büchi and J. A. Carlson, J. Amer. Chem. Soc. 91, 6470 (1969).

25. R. Epsztein and I. Marszak, Bull. Soc. Chim. Fr., 313,(1) (1968).

26. K. C. Brannock, R. D. Burpitt, V. W. Goodlett and J. G. Thweatt, J. Org. Chem. 28, 3134 (1963).

27. C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson and P. Strachan, J. Org. Chem. 28, 1697 (1963).

28. M. Moura Campos and L. Amaral, Arch. Pharm., 298 (2), 92 (1965).

29. I. Ernest, Chem. Listy. 48, 847 (1954).

30. Y. Hachihama, T. Shono and S. Ikeda, J. Org. Chem. 29, 1371 (1964).

31. H. Becker, Chem. Techn. 9, 477 (1957).

32. B. Rickborn and R. M. Gerkin, J. Amer. Chem. Soc. 93, 1694 (1971).

33. E. J. Gasson, A. R. Graham, A. F. Millidge, I. K. M. Robson, W. Webster, A. M. Wild and D. P. Young, J. Chem. Soc., 2170 (1954).

34. J. Blake, J. R. Tretter, G. J. Juhasz, W. Bonthrone and H. Rapoport, J. Amer. Chem. Soc. 88, 4061 (1966).

35. H. J. Bestmann and H. Schulz, Ber. 95, 2921 (1962).

36. W. S. Wadsworth and W. D. Emmons, J. Amer. Chem. Soc. 83, 1733 (1961).

37. T. W. Russell and D. M. Duncan, J. Org. Chem. 39, 3050 (1974).

38. L. Legrand and N. Lozardi, Bull. Soc. Chim. Fr., 79 (1955).

39. Aldrich Organic Chemical.

40. M. H. Hubacher, Org. Syn. Coll. Vol. 2, 445 (1943).

41. R. Belcher, W. Hoyle and T. S. West, J. Chem. Soc., 2743 (1958).

42. D. T. Moury, J. Amer. Chem. Soc. 72, 2535 (1950).

43. E. E. Royals and A. G. Robinson, J. Amer. Chem. Soc. 78, 4161 (1956).

44. This compound was prepared in the same general manner described for the alkylation of alkyl phosphites with bromoacetic esters; K. Kim, J. Markstein and K. Erickson, J. Org. Chem. 36, 1024 (1971).

45. This compound has also been prepared by a different method; Hoffmann-LaRoche Co., Chem. Abs. 70, 77323k (1969).

46. L. A. Shchukina and A. L. Zhuze, Chem. Abs. 68, 30016f (1968).

47. This material was found to be identical to the pyridone previously prepared by Danishefsky and subsequently converted into dl-camptothecin.

BIOGRAPHICAL NOTE

The author was born to Anne Claverie Bradley and John Colton Bradley on September 5, 1947 in Boston, Massachusetts. After graduation from Thayer Acadamy in 1966, he attended Bowdoin College and received an A.B. degree with high honors in chemistry in June of 1970. In September of 1970 graduate study in organic chemistry was begun at M.I.T. On October 2, 1971 the author married Cynthia Gail Grover in Brownsville, Vermont.