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A Total Synthesis of *dl*-Camptothecin

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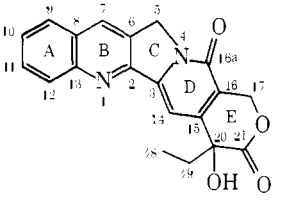
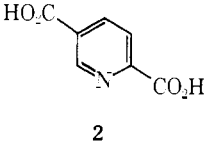
Abstract: *dl*-Camptothecin has been synthesized in 15% overall yield from isocinchomeronic acid. The synthetic design incorporates three rearrangements: rearrangement of a nipecotic acid to an α-methylenelactam, selenium dioxide oxidation of an olefin to an allylic alcohol and acid catalyzed rearrangement of the latter, and Claisen rearrangement involving an allylic alcohol–orthoester system. Thus, isocinchomeronic acid was converted to 1-acetoxy-6-methylene-5-oxooctahydroindolizine *via* 1-oxooctahydroindolizine-6-carboxylic acid in 62% yield. Allylic oxidation–rearrangement led to 1-hydroxy-6-hydroxymethyl-5-oxo-Δ^6-hexahydroindolizine (43%), and the α-butyrate side chain was then introduced by Claisen rearrangement with trimethyl orthobutyrate. The 1-hydroxyl was oxidized to keto and condensed with *N*-(2-aminobenzylidene)-*p*-toluidine to give the tetrahydroindolizino[1,2-*b*]quinoline. Selenium dioxide in acid gave both allylic oxidation–rearrangement and aromatization to the pyridone. Acid catalyzed lactonization and α-hydroxylation (O_2–$CuCl_2$–DMF) of the lactone completed the synthesis.

Camptothecin (**1**) is a novel alkaloid originally isolated from *Camptotheca acuminata* (Nyssaceae)[1] and more recently from *Mappia foetida* Miers (Olacaceae).[2] Its structural elucidation was accomplished in 1968[3] and with the initial report of its potent antileukemic and antitumor activity,[4] many attempts were made to synthesize camptothecin, culminating in a number of successful total syntheses.[5]



1

Our approach to the synthesis of camptothecin, a preliminary account of which has appeared,[1e] was based fundamentally on the bicyclic ketoacid 1-oxooctahydroindolizine-6-carboxylic acid (**3**), which was obtained as the hydrochloride in 85% yield from an inexpensive, commercially available starting diacid, isocinchomeronic acid (**2**). The choice



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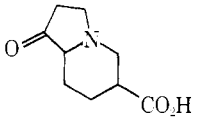
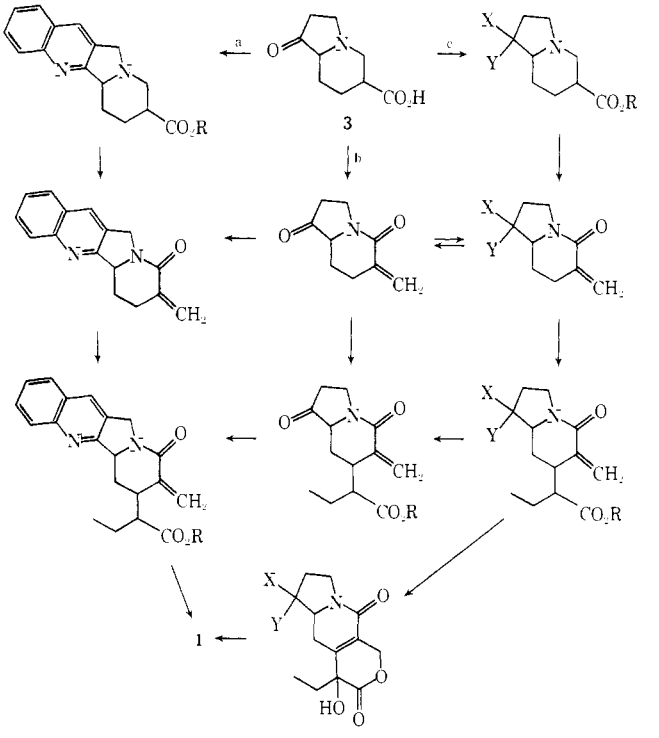


3

of the bicyclic ketoacid was made with the knowledge that the characteristic 2-pyridone D ring of camptothecin (**1**) can be introduced by a simple rearrangement of a nipecotic acid to an α-methylenelactam.[6] The resulting 3-methylene-2-piperidone, after appropriate substitution, can subsequently be oxidized to a pyridone.

From bicyclic ketoacid **3** the overall synthesis consists of three phases: (i) α-methylenelactam rearrangement of a nipecotic acid, (ii) introduction of the quinoline AB rings *via* the Friedländer condensation, and (iii) oxidation of the α-methylenelactam to an allylic alcohol followed by introduction of the butyrate residue at the 4-position of the piperidone D ring, oxidation, and lactonization. As Scheme I shows, the sequence need not be in this order for the synthesis was designed to allow maximum flexibility before converging on camptothecin.

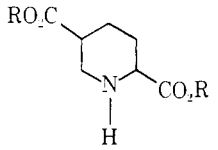
Scheme I. Convergent Routes for Camptothecin Synthesis from **3**



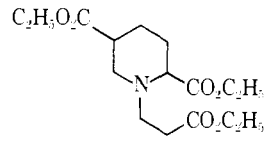
R = H, alkyl
X, Y = H, OH, or OR′

Preparation of bicyclic ketoacid **3** from isochinchomeronic acid (**2**) was begun by hydrogenation of **2** in aqueous ammonia using 5% rhodium on alumina catalyst following a

procedure developed for the hydrogenation of nicotinic acid.[7] The piperidine-2,5-dicarboxylic acid (**4**) formed was converted to the corresponding diethyl ester **5**[8] in 84% over-



4, R = H
5, R = C_2H_5

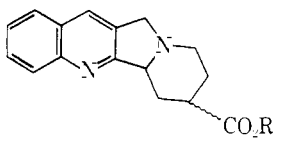


6

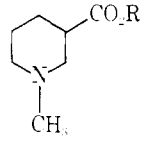
all yield from **2**. Conversion of diethyl piperidine-2,5-dicarboxylate (**5**) to ethyl 3-(2,5-diethoxycarbonylpiperidino)propionate (**6**) was accomplished by treatment with ethyl 3-bromopropionate in the presence of anhydrous sodium acetate. This modification of the reported procedure[9] provided **6** in 80% yield after distillation.

The preparation of bicyclic ketoacid **3** from triester **6** was conducted in toluene with potassium *tert*-butoxide followed by careful hydrolysis and decarboxylation, providing a quantitative yield of **3** (as the hydrochloride). When the four steps, *viz*, hydrogenation, esterification, alkylation, and cyclization, were carried through with purification only of the final product, the overall yield, **2** (→ **4** → **5** → **6**) → **3**, was 85%. Dieckmann cyclization of triester **6** can be envisaged in three modes, that is to form (i) an azabicyclo[2.2.1]heptanone, (ii) azabicyclo[3.3.1]nonanone, and (iii) an oxoindolizine. The latter is the most favorable direction for ring closure, and the product was exclusively the oxoindolizine **3** as established by its properties and subsequent reactions.

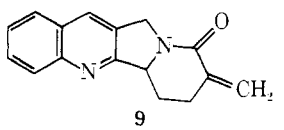
Initially our aim was to incorporate the quinoline AB ring system into the molecule as early as possible before attempting E ring annelation (path a, Scheme I). To examine this approach, bicyclic ketoacid **3** as its sodium salt was dissolved in ethanol–water and condensed with *o*-aminobenzaldehyde in the presence of potassium hydroxide. After esterification, two products were recovered and these were shown to be the two possible diastereomeric esters of structure **7**, designating the lower melting one (121–122°) as **7a**



7, R = C_2H_5
8, R = H



10, R = C_2H_5
12, R = H



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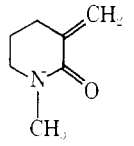


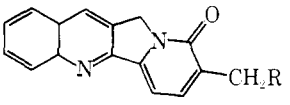
11

and the higher melting one (168–171°) as **7b**. The ratio of **7a** to **7b** was 2:1 after separation and 1:1 at formation by nmr analysis, and the overall yield of **7** (**a** + **b**) reached 52%.

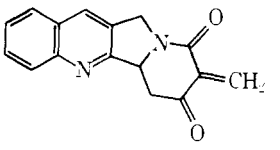
The next step in synthetic path a (Scheme I) required conversion of the tetracyclic carboxylic acid **8** to the α-methylenelactam, **9**. Since the ethyl ester **7** was so readily obtained from the Friedländer quinoline synthesis, the possibility of direct rearrangement of **7** to **9** was examined in a model system. Ethyl *N*-methylnipecotate (**10**)[7] was treated under a wide variety of conditions in an attempt to effect rearrangement to 1-methyl-3-methylene-2-piperidone (**11**), but no rearranged product **11** was detected. Although refluxing the methyl ester analog of **10** has been reported[10] to give **11**, when **10** was refluxed for 10 hr, only traces of **11** could be detected. An analogous attempt to rearrange **7b** to **9** in refluxing toluene gave only partial conversion to the other isomer, **7a**. We also found that, in addition to *N*-methylnipecotic acid (**12**), both the sodium salt and the hydrochloride can be rearranged to **11** in refluxing acetic anhydride. Rearrangement of the sodium salt is reasonably fast, but the reaction is limited by the low solubility of the salt in refluxing acetic anhydride.

Therefore, ester **7** was converted to the potassium salt of **8** using ethanolic potassium hydroxide, and refluxing this salt in acetic anhydride containing 100 mol % of acetic acid provided **9** in 60% yield. Duplication of these results with salts prepared individually from **7a** and **7b** gave identical yields and showed that separation of the two isomers was unnecessary. Also, the potassium salt of **8** could be induced to crystallize directly from an ethanolic solution of the crude product mixture obtained in the Friedländer synthesis, thus precluding the necessity for purification by way of **7**.

The rearrangement reactions always yielded a second product in ~8% yield along with **9**. This product showed strong fluorescence under uv light suggesting that it contained the camptothecin chromophore.[1] Using uv, nmr, and mass spectral data, it was assigned structure **13**. Partial



13, R = H
15, R = OC_2H_5
16, R = CH_3CO_2
17, R = OH



14

conversion of **9** to **13** also could be achieved by refluxing **9** in *p*-cymene in the presence of palladium-on-charcoal catalyst.

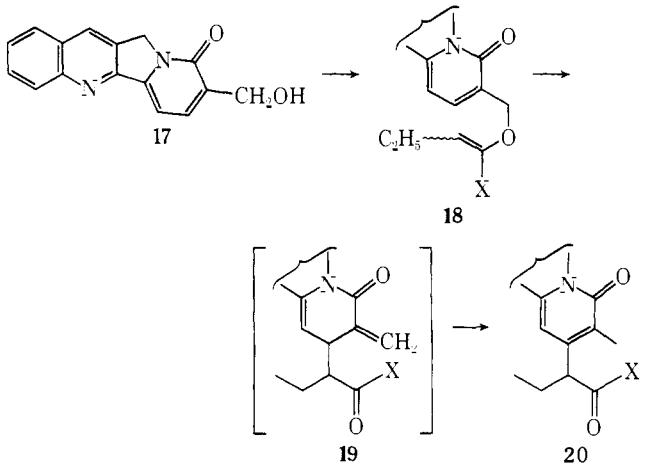
Continuation of the synthetic sequence requires eventual carbon–carbon bond formation at C-15[11] adjacent to the exocyclic methylene. As this position is allylic, selenium dioxide oxidation could lead to a ketone such as **14**. Not surprisingly the alternative fully aromatic systems **15**, **16**, and **17** were formed depending on whether ethanol or acetic acid was used as the solvent. A 60:40 ratio of **16**:**17** formed in quantitative yield when the reaction was performed in glacial acetic acid, and acetate **16** could be hydrolyzed to alcohol **17** or alcohol **17** could be easily acetylated.

Since aromatization to the pyridone (**16**, **17**) had occurred in quantitative yield, rather than oxidation to ketone **14**, we examined the chemistry of **16** and **17** as alternate intermediates upon which ring E might be formed. Two routes were considered: intramolecular Michael addition of a carbanion at C-15 in the acetate **16** and Claisen rearrangement of an enol ether of alcohol **17**.

In an attempt to effect Michael addition of the α-carbanion from the acetate group in **16** at C-15 in the D ring, **16** was treated with lithium diisopropylamide, resulting in an intense blue solution. The color dissipated as the solution warmed to room temperature; upon acidification, the only product recovered was alcohol **17**. Repetition of the reaction and quenching of the blue solution with deuterium methoxide then deuterium oxide gave a yellow solid whose nmr spectrum was identical with that of **17**, except that the absorption assigned to the two protons of the methylene bridge of ring C had vanished. Acetylation gave an acetate with nmr spectrum identical with that of **16**; however, the single absorption assigned to the methylene bridge protons

and the methylene protons of the acetoxymethyl group now showed only two-proton intensity rather than four as in **16** itself. The presence of two deuterium atoms in the product was confirmed by mass spectral analysis. These data establish that the methylene protons in ring C are sufficiently acidic so that their exchange with deuterium can be catalyzed by methoxide ion. Therefore, anionic reactions in the presence of these highly acidic protons did not appear to offer much hope of success, and this approach was abandoned. These observations may in part explain the poor yields others have obtained in numerous attempts[5b,d,f,g] to ethylate deethyldeoxycamptothecin at C-20.

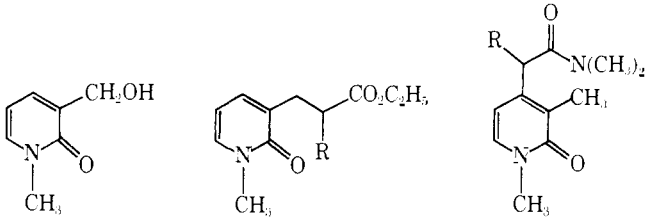
Scheme II



17 **18** **19** **20**

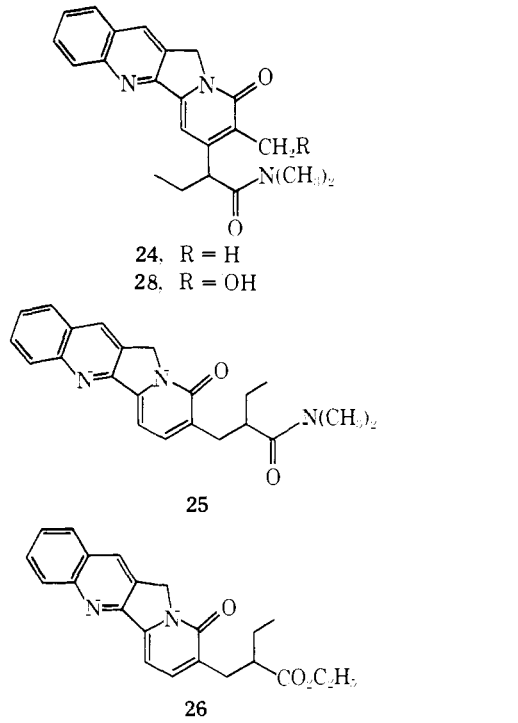
The possibility of forming the final carbon-carbon bond *via* the Claisen rearrangement requires preparation of an enol ether **18** of the hydroxyl group in **17** (Scheme II). Under appropriate conditions, **18** should undergo the Claisen rearrangement to give an exocyclic methylene product such as **19** which then would tautomerize to **20.**

Prior to attempting such a reaction on **17**, it was examined using the model system 3-hydroxymethyl-1-methyl-2-pyridone (**21**).[12] Treatment of **21** with either triethyl orthoacetate or triethyl orthobutyrate resulted in a net 1,3-rearrangement to give esters **22.** With **21** and the diethylacetal of *N,N*-dimethylacetamide[13] or *N,N*-dimethylbutyramide, the desired 3,3-rearrangement occurred to give amides of structure **23.** Along with amide **23b** was also formed the dimethylamide analog of ester **22b.** This product could be minimized by use of an acid catalyst and lower reaction temperatures.[12]



21 **22a**, R = H; **22b**, R = C_2H_5 **23a**, R = H; **23b**, R = C_2H_5

This experience was transferred to tetracyclic alcohol **17.** Treatment with 300 mol % of *N,N*-dimethylbutyramide diethylacetal in *o*-dichlorobenzene with propionic acid catalysis gave 50% yield of the desired amide **24.** Side products formed in the reaction included small amounts of **25** and about 10% of a new type of product from the amide acetal rearrangements, the ester **26**, an analog of **22b** from the monocyclic system. The intermediate ketene acetal (*cf.* **18**, X = OC_2H_5) from which **26** arises must result from elimination of dimethylamine rather than ethanol.

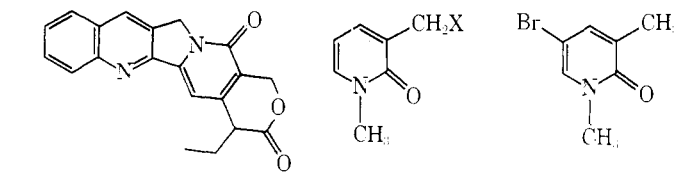


24, R = H
28, R = OH

25

26

Assuming that the entropy effects in forming the six-membered lactone of ring E would facilitate displacement of dimethylamine from the amide, the last major step in the synthesis of deoxycamptothecin **27** (which is readily oxidized to camptothecin) is oxidation of the 14-methyl in **24** to an intermediate such as **28** in which the methyl group is functionalized. There is little precedent for any type of oxidative reaction at the 3-position of 3-methyl-2-pyridones. A single report[14] states that 1,3-dimethyl-2-pyridone (**29**) was converted to 3-bromomethyl-1-methyl-2-pyridone (**30**) upon treatment with *N*-bromosuccinimide (NBS). However, every attempt at duplication of this result in our hands has led to 5-bromo-1,3-dimethyl-2-pyridone (**31**).[15] In



27 **29**, X = H; **30**, X = Br; **32**, X = Cl **31**

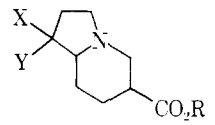
other model studies, functionalizing the 3-methyl group of 1,3-dimethyl-2-pyridone with a variety of oxidizing systems reported[16-19] to oxidize benzylic positions was examined; all failed.

Attempts were made to functionalize the 8-methyl group in **24.** Treatment with selenium dioxide in glacial acetic acid gave no reaction at the 8-methyl group, but oxidation did occur elsewhere in the molecule. Reaction of **24** with 200 mol % of NBS in carbon tetrachloride gave a product in which the nmr absorption due to the 8-methyl group was lost, but the absorption assigned to the methylene bridge (C-11) protons also was gone. When the reaction was repeated with a single equivalent of NBS, a different product was formed in which the 8-methyl absorption was gone, but again at least part of the absorption due to the C-11 methylene bridge also was lost.

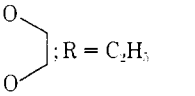
As studies[20] directed to the synthesis of camptothecin analogs indicated the presence of the fully aromatic ABD ring system was the source of the difficulties in this approach to

introduction of ring E by Claisen rearrangement, we modified the design so that aromatization to the pyridone in ring D occurred late in the synthesis. The ease with which the D ring aromatized when attached to the quinoline moiety dictated that A,B ring incorporation also should be postponed to a much later stage. Ideally, the shortest route to the important intermediate keto methylenelactam **42** as originally conceived was to rearrange the ketoacid **3** directly in refluxing acetic anhydride as in path b, Scheme I. Both the ketoacid **3** and its sodium or potassium salt were obtained by addition of 1 equiv and 2 equiv of sodium or potassium hydroxide, respectively, to the hydrochloride of **3**. Each was subjected to the refluxing acetic anhydride conditions, and the course of any rearrangement to the α-methylenelactam was followed by nmr. No vinyl protons typical of α-methylenelactams at δ 5.3 and 6.2 were observed in either case; only resinous material was isolated.

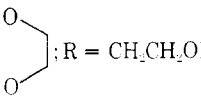
The instability of ketoacid **3** to acetic anhydride rearrangement conditions necessitated a protecting procedure for the ketonic function (path c, Scheme I). Ketals were first considered for this blocking function, and, when ketoacid **3** was dissolved in absolute ethanol, saturated with HCl, and stirred at room temperature, differences in the intensities of the ketonic and ester carbonyl absorptions in the ir showed that an equilibrium mixture (1:4) was always established. Twenty per cent of the mixture had lost the keto absorption and was ketal **34** and/or enol ether **35**, and 80% was ketoester **33**. The same result was obtained starting



3. X,Y = O; R = H
33. X,Y = O; R = C_2H_5
34. X = Y = OC_2H_5; R = C_2H_5



36. X,Y = ; R = C_2H_5

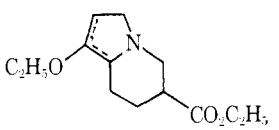


37. X,Y = ; R = CH_2CH_2OH

38. X = Y = SC_2H_5; R = C_2H_5

39. X,Y = ; R = C_2H_5

43. X = H; Y = OH; R = H
44. X = H; Y = OH; R = C_2H_5



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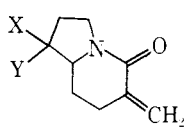
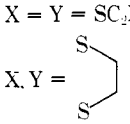


40. X = Y = SC_2H_5



41. X,Y =

42. X,Y = O
45. X = H; Y = $OCOCH_3$
46. X = H; Y = OH

with ketoester **33**; therefore attention was turned to the ethylene ketals. Treatment of a mixture of ketone, boron trifluoride etherate and ethylene glycol at room temperature gave mostly unchanged starting material, while refluxing the mixture of **33** and **34**–**35** with ethylene glycol and *p*-toluenesulfonic acid gave a poor yield of ketal ester **37**. Alkaline hydrolysis of **37** and subjection of the product to acetic anhydride rearrangement conditions gave α-methylenelactam in 20% yield, the major component being polar resinous material.

Thioketals have been used extensively as a protecting group for ketones due to their stability under both alkaline and acidic conditions, but this characteristic also creates difficulties in regenerating the carbonyl function. The added stability seemed essential in the present case, however, so the feasibility of preparing and rearranging the diethyl thioketal **38** and the dithiolane **39** was investigated. Both of these thioketals were formed in 78–80% yield by treating ketoester **33** with excess of the respective thiol in the presence of boron trifluoride etherate.[21]

Diethyl thioketal ester **38** was hydrolyzed with ethanolic potassium hydroxide, and the crude salt of **38** was rearranged in refluxing acetic anhydride. This process gave a 53% yield of α-methylenelactam **40.** Similarly, the dithiolane ester **39** gave a 60% yield of α-methylenelactam **41.** The cause of the low overall yields from ester to rearranged α-methylenelactam appeared to be incomplete ester hydrolysis, and we attempted to improve it by (a) increasing the amount of alkali, (b) increasing the water content of the solvent, and (c) turning to acid-catalyzed hydrolysis. All variations led to decreased yields of α-methylenelactam.

To circumvent this difficulty, we attempted to avoid the esterification step from acid **3** to ester **33** and to ketalize the ketoacid directly. Ketoacid **3** was treated with excess ethanedithiol in acetic acid, required for solubility, and boron trifluoride. After acetic anhydride rearrangement, a 36% yield of α-methylenelactam **41** was obtained. This yield was competitive with the previous method *via* ester hydrolysis, based on their common starting material, the hydrochloride of **3.**

Having obtained the thioketal α-methylenelactams **40** and **41**, the next step was a practical regeneration of the ketone function. The commonly used Hg^{II} salt method[22] failed to give any ketone from thioketal methylenelactam **41.** However, treatment of thioketal **40** with mercuric chloride–cadmium carbonate gave a variable 30–40% yield of ketone **42.** Treatment of thioketal **41** with *N*-chlorosuccinimide (NCS) and silver nitrate[23] gave only 40% of the desired ketone **42.** A series of reactions of varying duration under these conditions showed NCS slowly attacked the double bond of the α-methylenelactam, as was evident from the loss of the characteristic vinyl proton absorptions in the nmr. Chloramine T[22,24] also failed to regenerate the ketone. Dethioketalization *via* alkylation to form a sulfonium salt followed by hydrolysis to regenerate the ketone[25,26] was then applied. Dithioketal **41** was methylated with dimethoxycarbonium tetrafluoroborate[27] in methylene chloride and the sulfonium salt was hydrolyzed with water. This procedure furnished the desired ketone **42** in 80% yield. Despite this improvement in thioketal cleavage, the synthesis of keto methylenelactam **42** from ketoacid **3** was still unsatisfactory in terms of overall yield (30%).

As an alternative, ketoacid **3** was first reduced to the hydroxy acid **43** which after α-methylenelactam rearrangement could be reoxidized to ketone **42.** Reduction of **3** was accomplished with sodium borohydride, and the resulting hydroxy acid **43** was converted to ethyl ester **44** in 80% yield. Hydroxy ester **44** was then hydrolyzed with ethanolic potassium hydroxide and the resulting potassium salt of **43** was rearranged in refluxing acetic anhydride to yield 74% of acetoxy α-methylenelactam **45.** Alternatively, after sodium borohydride reduction of **3**, the crude product was passed through a cation exchange column to give an 87% yield of **43.** Subjecting **43** to the rearrangement conditions gave the acetoxy α-methylenelactam **45** in 84% yield, the overall yield from isocinchomeronic acid **2** being 62%.

At this point the option arose of using the versatile intermediate **45** to converge with path b and subsequently with path a or of carrying it further along path c, as shown in

Scheme I. Following the former route, the acetoxy α-methylenelactam **45** was converted to the hydroxy α-methylenelactam **46** by potassium carbonate in methanol to give a quantitative yield of **46.** It was now essential to oxidize hydroxy methylenelactam **46** to the ketone **42.** Oxidation with Jones' reagent[28] under a variety of conditions gave at best 40% yield of ketone **42.** Attempted oxidation using the chromium trioxide–pyridine complex[29] gave mostly unchanged material (60%) and nonketonic products; lead tetraacetate[30] in pyridine gave no reaction, and the alcohol also proved resistant to ruthenium tetroxide.[31]

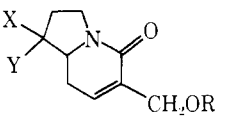
A more selective oxidizing agent, which has been used effectively on hindered secondary alcohols, is the dimethyl sulfoxide (DMSO)–acetic anhydride (Ac_2O) mixture.[32] When **46** was stirred in the mixture of DMSO–Ac_2O at room temperature, the alcohol completely reacted in 6 hr, and ketone **42** was isolated in 57% yield. The remaining 43% was accounted for when 84% of it was recovered as the acetate **45.** This method was potentially a practical one, since acetate **45** could be easily hydrolyzed back to the alcohol **46.** However, using the variation[33] of dicyclohexylcarbodiimide (DCC) in anhydrous DMSO with a catalytic amount of orthophosphoric acid, the ketone α-methylene lactam **42** was obtained directly in 85% yield.

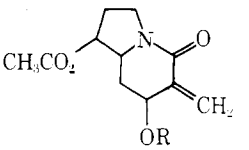
Having obtained ketone **42,** it was now possible to merge with path a, Scheme I, by incorporating the quinoline AB rings. The Friedländer quinoline synthesis is widely used to construct such a system[34] and provided easy access to the indolizino[1,2-*b*]quinoline ring system of the camptothecin skeleton. The condensation to be considered was between ketone **42** and *o*-aminobenzaldehyde (**47**) or its imine with *p*-toluidine, **48.** Two problems are apparent when considering this condensation: one is the ease with which *o*-aminobenzaldehyde self-condenses[35] and the other is the potential self-condensation of ketone **42** in the presence of base.

Initially the condensation was attempted under amine catalysis. In the presence of triethylamine at temperatures up to 120° no reaction occurred; tetramethylguanidine gave mostly polymer and only a small amount of **9.** Alkoxide and hydroxide have been used extensively in the Friedländer condensation with variable results. Investigation of alcoholic potassium hydroxide as the condensing agent under a large variety of conditions gave a maximum yield of 33% of α-methylenelactam **9.**

Turning to the recently reported[36] acid-catalyzed Friedländer condensation using *N*-(*o*-aminobenzylidene)-*p*-toluidine (**48**) and removing the water formed by continuous distillation with toluene, a 76% yield of tetracyclic α-methylenelactam **9** was isolated. A small amount of a highly fluorescent compound with a chromophore at 370 nm was also obtained and was identified as the aromatic side product **13.**

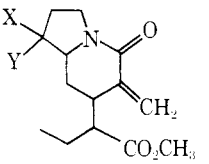
The alternative elaboration of camptothecin from keto methylenelactam **42** *via* path b, Scheme I, or from acetoxy methylenelactam **45** *via* path c is based upon introduction of the butyric acid residue necessary for lactonization using the Claisen rearrangement, prior to quinoline ring formation. To pursue this route required conversion of **45** to the allylic acetate **49** by allylic oxidation-rearrangement, and we sought to accomplish this using the standard selenium dioxide reagent in acetic acid.[20] Repeated efforts under a variety of conditions led to a maximum 58% yield of **49.** Analysis of the course of the reaction established that **45** was oxidatively consumed after 10 min; however, rearrangement was proceeding much more slowly and at this point the product was a mixture of secondary alcohol and acetate, **50** and **51.** In view of this observation, the oxidation was stopped after 10 min and the intermediate, freed of selenium dioxide and selenium, was subjected to rearrangement in acetic anhydride–sulfuric acid to give a 69% yield of **49.** The allylic alcohol **52** was obtained quantitatively from diacetate **49** in anhydrous methanol–potassium carbonate at room temperature, making the overall yield 43% from isocinchomeronic acid (**2**) to diol **52.**

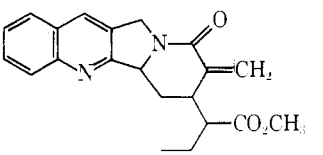




49. X = H; Y = O_2CCH_3; R = $COCH_3$
52. X = R = H; Y = OH

50. R = H
51. R = $COCH_3$





53. X = H; Y = $O_2CC_3H_7$
54. X = H; Y = OH
55. X, Y = O

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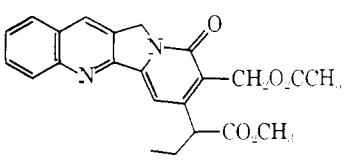
Claisen rearrangement of **52** in excess trimethyl orthobutyrate with a catalytic amount of propionic acid at 145° provided a 75% combined yield of a mixture containing butyrate **53** and alcohol **54.** Incorporation of the butyrate side chain was evident from the appearance of a triplet at δ 0.9 and reappearance of the absorption due to the vinyl protons of the α-methylene moiety at δ 5.3 and 6.2. Hydrolysis of this crude mixture using potassium carbonate in methanol at room temperature removed the esterifying butyrate group and gave a quantitative yield of alcohol **54** as a mixture of stereoisomers. The isomeric mixture was unmistakably present, as its nmr showed singlets at δ 3.4, 3.6, and 3.7, corresponding to the methyl ester, and sets of triplets around δ 0.9, corresponding to the methyl group of the butyrate side chain. Oxidation of alcohol **54** to ketone **55** was accomplished in 76% yield using the DCC–DMSO–H_3PO_4 method previously employed for oxidation of **46** to **42.** This ketone **55** was then incorporated into the quinoline ring in 79% yield through Friedländer condensation with *N*-(2-aminobenzylidene)-*p*-toluidine (**48**) to give the tetrahydroindolizino[1,2-*b*]quinoline **56.**

The remaining tasks were (a) aromatization of ring D, (b) closure of the lactone ring E, and (c) introduction of the α-hydroxy group. Aromatization and formation of the necessary primary alcohol were accomplished in a single step by selenium dioxide oxidation of the α-methylenelactam **56** in glacial acetic acid. Progress of the reaction was followed by disappearance of the characteristic uv absorption of **56,** giving way to absorption of the α-acetoxymethylpyridone **57** at λ_{max} 370, 290, and 253 nm. Also the nmr spectrum of



57

57 showed loss of the α-methylene vinyl protons and concurrent appearance of absorptions due to acetoxymethyl protons and the C-5 protons at δ 5.35 and 5.2, respectively. It is interesting to note that the α-methylenelactam **54** has four asymmetric centers. The presence of many isomers was reflected in its nmr spectrum, which showed overlapping sets of triplets at δ 0.9 integrating for a total of three protons corresponding to the C-18 methyl group, and three distinct singlets at δ 3.4, 3.6 and 3.7, integrating together for

three protons, corresponding to the methyl ester protons of the α-butyrate side chain. The number of asymmetric centers was reduced to three in ketone **55** and tetracyclic α-methylenelactam **56**, and the isomeric mixture of these intermediates finally converged to pyridone **57** which possesses only one asymmetric center at C-20. This was reflected in the collapse of the overlapping triplets and multiple singlets to a single triplet at δ 1.0 and one singlet at δ 3.7. The acetate **57** could be isolated prior to hydrolysis and lactonization to deoxycamptothecin (**27**). However, the one-step hydrolysis–lactonization process could be carried out more efficiently on the crude reaction product **57**, which was treated with 2 *N* sulfuric acid–glyme at 50°, simultaneously effecting lactonization to give deoxycamptothecin (**27**) in 79% yield from α-methylenelactam **56**.

Final oxidation of deoxycamptothecin (**27**) to *dl*-camptothecin (**1**) was accomplished by passing oxygen into a dimethylformamide (DMF) solution of **27** containing a trace of 25% aqueous dimethylamine and cupric chloride.[5d] When freshly prepared anhydrous cupric chloride was used, essentially quantitative oxidation of **27** to **1** was achieved in 5 hr. *dl*-Camptothecin (**1**), having uv, nmr, and high-resolution mass spectrum identical with the natural product,[37] was isolated in an overall yield from isocinchomeronic acid (**2**) of 15%.

Experimental Section[38]

Diethyl Piperidine-2,5-dicarboxylate (5)[7,8] was prepared by hydrogenating 1 mol (167 g) of isocinchomeronic acid, dissolved in 1 l. of water and 200 ml of concentrated ammonium hydroxide, over 40 g of 5% rhodium on alumina at 2 atm of hydrogen. Hydrogen uptake ceased after 24 hr and the crude product was esterified using the ethanol–benzene–H_2SO_4 system and 3A molecular sieves in a Soxhlet cup. Addition of solid $NaHCO_3$, concentration, addition of water, adjustment of the pH to 8.5, extraction with benzene, and distillation of the dried extracts provided the diester **5** in 84% yield as a cis–trans mixture: bp 85–94° (0.3 Torr) (lit.[8] bp 95–98° (0.2 Torr)); gc, 171°; R_T 5.7 and 6.1 min; mass spec *m/e* 230 (M + 1), 229, 184, 156, 110, 82, 56, 55.

Ethyl β-(2,5-Diethoxycarbonyl-1-piperidino)propionate (6). A mixture of 12.3 g (54 mmol) of diethyl piperidine-2,5-dicarboxylate (**5**), 11.8 g (65 mmol) of ethyl β-bromopropionate, and 8.2 g (100 mmol) of anhydrous sodium acetate was stirred under nitrogen at 70–75° for 7 hr, after which it was cooled and poured into 130 ml of water and 28 g of sodium carbonate. The alkaline solution was extracted with three portions of ether, and the combined extracts were washed with saturated brine, dried, filtered, and concentrated to a residual oil (16.5 g) which was distilled to give 14.2 g (80% yield) of triester **6**: bp 124–126° (0.02 Torr); gc, 180°; R_T 11.3 min; nmr (CCl_4) δ 4.13 (q, *J* = 7 Hz) and 4.06 (2 q, *J* = 7 Hz, 6 H together), 3.45 (t, *J* = 4.5 Hz, 1 H), 1.47–3.27 (m, 11 H), 1.27 (t, *J* = 7 Hz) and 1.23 (2 t, *J* = 7 Hz, 9 H together); mass spec *m/e* 330 (M + 1), 329 (M), 300, 284, 256, 242, 238, 184, 182, 168, 156.

1-Oxooctahydroindolizine-6-carboxylic Acid (3) Hydrochloride. To a solution of 60 ml of dry *tert*-butyl alcohol in 500 ml of dry toluene was added 11.0 g (0.28 mol) of potassium metal and the mixture refluxed under nitrogen until all of the potassium had reacted. The mixture was then cooled to 0°, 60.0 g (0.18 mol) of the triester **6** in 100 ml of dry toluene was added dropwise over 1 hr, the solution was stirred at 0° for 3 hr, 600 ml of 6 *N* HCl was added, and the two-phase mixture was refluxed overnight. The aqueous phase was then removed and concentrated at 40°, leaving a gummy residue which was digested with 500 ml of isopropyl alcohol and filtered to remove the potassium chloride. Isopropyl alcohol was removed <35° to give **3**·HCl as a fluffy glass in quantitative yield.

Ethyl 1-Oxooctahydroindolizine-6-carboxylate (33). A solution of 10.9 g (50 mmol) of ketoacid **3** hydrochloride in 300 ml of absolute ethanol was cooled to 0°, hydrogen chloride gas was bubbled in until saturation, and the acidic solution was allowed to sit at room temperature for 24 hr. After most of the ethanol was evaporated, 100 ml of methylene chloride was added followed by cold saturated sodium carbonate solution to pH 9. The aqueous phase was further extracted with CH_2Cl_2, and the extracts were dried, filtered, and distilled to give 8.5 g (80%) of ketoester **33**: bp 114–116° (0.7 Torr); glc, 170°; R_T 7 min; ir 1725, 1750 cm^{-1}; nmr (CCl_4) δ 1.3 (t, 3 H), 1.8–3.0 (m, 10 H), 3.1–3.7 (m, 2 H), 4.0 (q, 2 H).

8-Ethoxycarbonyl-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline (7). To 4.38 g (20 mmol) of **3** hydrochloride was added 100 ml of 0.2 *N* ethanolic potassium hydroxide. The precipitated potassium chloride was removed, the filtrate was concentrated to 30 ml, and this solution was placed in a dropping funnel attached to a flask containing 2.46 g (20 mmol) of *o*-aminobenzaldehyde[35] in 20 ml of 95% ethanol which was heated to reflux just prior to the addition of 9 ml of 4.5 *N* potassium hydroxide followed by dropwise addition of the solution in the dropping funnel during 0.5 hr at reflux. Reflux was continued for 1.5 hr followed by standing overnight. The ethanol was removed at 50°, 50 ml of water was added, and the alkaline aqueous solution was extracted with ether to give 408 mg (3.4 mmol) of unreacted *o*-aminobenzaldehyde. The aqueous phase was lyophilized and to the gummy residue was added 200 ml of absolute ethanol, 100 ml of benzene, and 5.0 ml of sulfuric acid in 30 ml of absolute ethanol. As distillation of the azeotrope proceeded, the distillate was replaced by solution of 5.0 ml of sulfuric acid in 220 ml of absolute ethanol and 75 ml of benzene. When the reaction solution had been reduced to 350 ml, a Soxhlet extractor containing 3A molecular sieves was attached, and reflux was continued overnight, followed by removal of solvent and addition of 300 ml of saturated sodium bicarbonate solution. The aqueous phase was adjusted to pH 8 and extracted with six 50-ml portions of CH_2Cl_2. The combined extracts were washed with saturated bicarbonate solution, dried, filtered, and evaporated to give 5.2 g of residue, which was dissolved in benzene and applied to a 150-g column of silica gel. Elution with 1:1 hexane–ethyl acetate gave partial separation of the isomeric esters **7a** and **7b** in a total yield of 3.06 g, 52%. Each tetracyclic ester was recrystallized from heptane–benzene solution.

7a: mp 121–122° dec; nmr δ 7.38–8.23 (m, 5 H), 4.16 (q, *J* = 7 Hz) and 4.15 (s, 3 H together), 1.13–3.90 (m) including 1.28 (t, *J* = 7 Hz, 13.5 H together); uv 318 nm (ε 5680), 310 (3810), 304 (4550), 298 (3520), 292 (3620), 274 (3770), 235 (31,700), 232 (34,700), 207 (46,500); mass spec *m/e* 296 (M), 295, 267, 251, 223, 195, 182, 168, 111.5, 111, 110.5, 110, 109.5; high resolution mass spec *m/e* 296.1525 (calcd for $C_{18}H_{20}N_2O_2$, 296.1525).

7b: mp 168–171° dec; nmr δ 7.23–8.12 (m, 5 H), 4.13 (q, *J* = 7 Hz) and 4.06 (s, 3 H together), 1.07–3.82 (m) including 1.23 (t, *J* = 7 Hz, 13 H together); uv 317 nm (ε 5660), 311 (3950), 304 (4440), 298 (3260), 292 (3260), 275 (3260), 234 (23,700), 231 (24,400), 207 (34,800); mass spec *m/e* 296 (M), 295, 267, 251, 223, 195, 182, 168, 111.5, 111, 110.5, 110; high resolution mass spec *m/e* 296.1528 (calcd for $C_{18}H_{20}H_2O_2$, 296.1525).

5b,6,7,8,9,11-Hexahydroindolizino[1,2-*b*]quinoline-8-carboxylic Acid (8), Potassium Salt. A. The tetracyclic ester **7** (1.19 g, 4 mmol) and 20 ml of 0.2 *N* ethanolic potassium hydroxide were heated at reflux for 4.5 hr after which the ethanol was removed to give 1.27 g (quantitative yield) of the potassium salt of **8**: uv 317 nm (ε 7100), 310, 304 (5600), 297 (4200), 291 (4200), 266, 234, 231, 207.

B. Condensation between 32 g (145 mmol) of ketoacid **3** hydrochloride and 18.2 g (150 mmol) of *o*-aminobenzaldehyde was carried out as above through the initial addition at reflux for 1 hr followed by 3 hr of further reflux. The solvent was then removed, and the residue was stirred with ether to remove unreacted *o*-aminobenzaldehyde, then redissolved in ethanol. Evaporative removal of ethanol at 50° was continued until crystals appeared, and this was followed by cooling and filtering. Repetition of this process gave a combined yield of 16.5 g (37%) of crystalline **8** potassium salt, identical with the product prepared by method A.

8-Methylene-9-oxo-5b,6,7,11-tetrahydroindolizino[1,2-*b*]quinoline (9). A. From Tetracyclic Acid 8. Potassium hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (**8**, 1.10 g, 3.6 mmol), 210 mg (3.6 mmol) of acetic acid, and 15 ml of acetic anhydride were heated at reflux for 1.25 hr. The solution was cooled and filtered and the filtrate was concentrated to a residue to which 50 ml of 10% aqueous sodium carbonate was added. Extraction with three portions of CH_2Cl_2, and washing, drying, and evaporating the combined extracts left a residue which was applied to a column of

100 g of silica gel. Elution with 1:1 ether:chloroform gave 540 mg (60% yield) of the tetracyclic methylenelactam **9**: mp 137–139°; tlc on silica gel (3:1 chloroform:acetone) R_F = 0.45 (1:1 ether:chloroform) R_F = 0.26; nmr δ 7.3–8.2 (m, 5 H), 6.36 (finely split s, 1 H), 4.4–5.5 (m) including 5.44 (finely split s, 4 H total), 2.6–3.1 (m, 2 H), 1.1–2.2 (m, 2 H); ir 3030, 1640, 1622, 1604, 1439, 1401, 1310 cm^{-1}; uv 319, 312, 306, 299, 293, 235, 207 nm; mass spec *m/e* 250 (M) 221, 181, 168.

Further elution of the column from the above experiment with 1:19 acetone:chloroform provided 71 mg of 8-methyl-9-oxo-11*H*-indolizino[1,2-*b*]quinoline (**13**): mp 255–260°; nmr δ 7.4–8.4 (m, 7 H), 5.26 (s, 2 H), 2.32 (s, 3 H); uv 365, 291, 253, 247, 217 nm; high resolution mass spec *m/e* 248.0946 (calcd for $C_{16}H_{12}N_2O$, 248.0950).

B. From Ketomethylenelactam 42. A solution of 187 mg (1.5 mmol) of *o*-aminobenzaldehyde (**47**) in 5 ml of absolute ethanol was heated to reflux and 0.3 ml of 4 *N* KOH in absolute ethanol was then added, followed by the dropwise addition, over 1 hr, of 100 mg (0.6 mmol) of ketomethylenelactam **42** in 40 ml of absolute ethanol. After 24 hr of reflux, the absorbance at 319 nm ceased to increase, the ethanol was evaporated, and the residue was chromatographed to give 50 mg of the tetracyclic α-methylenelactam **9** (33% yield), mp 137–139°.

Alternatively, 129 mg (0.6 mmol) of *N*-(2-aminobenzylidene)-*p*-toluidine,[36] 100 mg (0.6 mmol) of ketomethylenelactam **42** and 5 mg of *p*-toluenesulfonic acid in 15 ml of toluene were heated under reflux with azeotropic removal of water. After 3 hr, the solution was cooled, the toluene was evaporated, and the residue was dissolved in chloroform. Addition of ethyl ether precipitated 8 mg of a solid, which was removed, and the filtrate was evaporated. Chromatography of the residue on silica gel with 10% chloroform–ether gave 115 mg (76%) of the tetracyclic α-methylenelactam **9** and less than 5 mg of **13.**

8-Ethoxymethyl-9-oxo-11*H*-indolizino[1,2-*b*]quinoline (15). 8-Methylene-9-oxotetrahydroindolizino[1,2-*b*]quinoline (**9**, 100 mg, 0.4 mmol), 4 ml of 95% ethanol, and 67 mg (0.6 mmol) of selenium dioxide were heated at reflux for 4.5 hr. After filtration, the solvent was evaporated to give 85 mg of a solid residue which was partitioned between CH_2Cl_2 and saturated sodium bicarbonate solution, the aqueous phase being extracted with three additional portions of CH_2Cl_2. The combined organic phase was washed, dried, and evaporated leaving 34 mg (29% yield) of the ethoxy derivative **15**: mp 210–215°; nmr δ 7.0–8.4 (m, 7 H), 5.17 (s, 2 H), 4.59 (s, 2 H), 3.68 (q, J = 7 Hz, 2 H), 1.31 (t, J = 7 Hz 3 H); ir 3065, 1665, 1600, 1200 cm^{-1}; uv 365, 291, 253, 247, 217 nm; mass spec *m/e* 293 (M + 1), 264, 263, 248, 219, 205, 131.5.

8-Acetoxymethyl-9-oxo-11*H*-indolizino[1,2-*b*]quinoline (16). 8-Methylene-9-oxotetrahydroindolizino[1,2-*b*]quinoline (**9**, 500 mg, 2 mmol), 24 ml of glacial acetic acid, and 333 mg (3 mmol) of selenium dioxide were heated at 75° for 2 hr. The acetic acid was removed at 50° (1 Torr), and the residue was applied to a 30-g column of silica gel. Elution with 5% acetone–chloroform gave 358 mg in fractions 6–12, which was recrystallized from benzene–hexane, 59% yield: mp 214–215° dec; nmr δ 7.1–8.4 (m, 7 H), 5.20 (broadened s, 4 H), 2.15 (s, 3 H); ir (KBr) 2980, 1722, 1650, 1613, 1597, 1494, 1321, 1247, 1020 cm^{-1}; uv 362, 288, 254, 248, 217 nm; mass spec *m/e* 306 (M), 263, 248.

8-Hydroxymethyl-9-oxo-11*H*-indolizino[1,2-*b*]quinoline (17). Further elution of the column from which **16** was obtained, using 5% methanol–chloroform provided an additional 210 mg of solid which was recrystallized from hexane–benzene, 40% yield: mp 223–224° dec; the combined yield of **16** and **17** is 99%. **17**: nmr ($CDCl_3$–CD_3OD) δ 7.2–8.6 (m, 7 H), 5.27 (s, 2 H), 4.72 (s, 2 H); ir (KBr) 3410, 2941, 1656, 1606, 1591, 1578, 1410, 1205, 1067; uv 364, 290, 253, 248, 217 nm; mass spec *m/e* 264 (M), 248, 235.

The initial reaction product mixture of **16** and **17**, resulting from the reaction of **9** with CH_3CO_2H–SeO_2, could be converted quantitatively to acetoxy derivative **16** by treatment with acetic anhydride–pyridine on the steam bath for 10 min. Alternatively, the mixture or acetoxy compound **16** were converted quantitatively to alcohol **17** by standing overnight in concentrated hydrochloric acid.

8-Hydroxymethyl-9-oxo-11*H*-indolizino[1,2-*b*]quinoline-*11-d*$_2$ and Its Acetate. To 0.45 ml (0.32 mmol) of diisopropylamine in 5 ml of tetrahydrofuran (THF), cooled to −75°, was added 0.20 ml of 1.6 *N* *n*-butyllithium in hexane. An immediate blue color appeared in the reaction mixture upon dropwise addition of acetate **16** (65 mg, 0.2 mmol in 5 ml of THF). Stirring at −75° for 0.5 hr was followed by addition of 18 mg (0.5 mmol) of methanol-d_4 in 1 ml of THF, and after warming to −40° an additional 0.1 ml of methanol-d_4 was added followed by 0.2 ml of deuterium oxide to give a green solution. Decolorization was completed by addition of 3.5 ml of 0.1 *N* hydrochloric acid. All the liquid was evaporated and the residue examined by nmr. The spectrum was identical with that of **17** except that the absorption at 5.27 ppm for the methylene protons at C-11 was lacking. The residue was treated with 0.5 ml of dry pyridine and 0.5 ml of acetic anhydride and heated on the steam bath for 5 min. Excess reagents were removed and the residue was chromatographed as above to give 8 mg of **16-*11-d*$_2$**: nmr δ 7.2–8.5 (m, 7 H), 5.25 (s, 2 H), 2.17 (s, 3 H); mass spec *m/e* 308 (M), 307 (40% of 308), 265, 250, 175, 149.

***N,N*-Dimethyl-2-[8-methyl-9-oxo-7(11*H*)-indolizino-[1,2-*b*]quinolyl]butyramide (24).** To 8-hydroxymethyl-9-oxo-11*H*-indolizino[1,2-*b*]quinoline (**17**, 264 mg, 1 mmol), 4 ml of *o*-dichlorobenzene, and 6 μl (8 mol %) of propionic acid was added a solution of 1.33 g of a mixture of dimethylbutyramide diethyl acetal[13] and its ethanol elimination product. The mixture was stirred at room temperature for 45 min, heated at 150° for 23 hr, and applied to a column of 25 g of silica gel. Elution with hexane removed the *o*-dichlorobenzene, chloroform removed the excess butyramide acetal and ester **26** which is characterized below, and 400 ml of 95:5:1 chloroform:acetone:95% ethanol followed by 400 ml of 90:10:2 chloroform:acetone:95% ethanol gave 270 mg of the butyramide **24**, 75% yield, mp 208–210° after recrystallization from hexane–benzene: nmr δ 7.27–8.44 (m, 5 H), 5.25 (s, 2 H), 3.92 (t, J = 7 Hz, 1 H), 3.00 (s) and 2.94 (s, 6 H together), 2.38 (s, 3 H), 1.4–2.3 (m, 2 H), 0.98 (t, J = 7 Hz, 3 H); mass spec *m/e* 362, 361 (M), 316, 288, 259, 247, 219, 218, 205, 169, 149.

Ethyl 3-[9-Oxo-8(11*H*)-indolizino[1,2-*b*]quinolyl]-2-ethylpropanoate (26). Treatment with hexane of the residues from chloroform elution of the column described in the previous experiment provided a 10% yield of a product which was recrystallized from hexane–benzene: mp 183–184°; nmr δ 7.05–8.33 (m, 7 H), 5.16 (s, 2 H), 4.04 (q, J = 7 Hz, 2 H), 2.90 (finely split s, 2 H+), 1.40–2.40 (m) including 1.62 (finely split q, J = 7 Hz, 2 H+ total), 1.17 (t, J = 7 Hz) and 0.97 (t, J = 7 Hz, 6 H together); mass spec *m/e* 362 (M) 347, 333, 317, 300, 289, 288, 287, 273, 259, 248, 247.

Ethyl 1,1-(1,3-Dithiolane)octahydroindolizine-6-carboxylate (39) and Ethyl 1,1-Bis(ethylthio)octahydroindolizine-6-carboxylate (38). To a solution of 7.8 g (37 mmol) of ketoester **33** in 32 ml of ethanedithiol cooled in an ice bath, was added over a period of 15 min, 32 ml of distilled boron trifluoride etherate. The ice bath was then removed, the mixture was allowed to stand at room temperature for 24 hr, saturated sodium carbonate solution was added, and the alkaline aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed, dried, filtered, and evaporated, finally at 90° for 15 hr. Chromatography of the residue on silica gel gave 8.3 g (78% yield) of ethylenedithioketal ester **39** as an oil: ir 1725 cm^{-1}; nmr δ 1.25 (2 sets of t, 3 H), 1.6–3.7 (m, with two singlets at 3.19, 3.2, 16 H), 3.98, 4.0 (2 sets q, 2 H).

Similarly, bisethylthioketal ester **38** was obtained as an oil from thioethanol in 80% yield: ir 1725 cm^{-1}; nmr (CCl_4) δ 1.25 (2 sets of t, 9 H), 1.6–3.4 (m, 16 H), 4.0 (q, 2 H).

1,1-(1,3-Dithiolane)-6-methylene-5-oxooctahydroindolizine (41) and 1,1-Bis(ethylthio)-6-methylene-5-oxooctahydroindolizine (40). To a solution of 6.0 g (20.9 mmol) of ethylenedithioketal ester **39** in 150 ml of ethanol was added 2.34 g (41.8 mmol) of potassium hydroxide. The solution was heated at reflux for 5 hr, the ethanol was evaporated, finally at 80° for 6 hr, and the residue was boiled with 150 ml of acetic anhydride for 2.5 hr. Evaporation of the acetic anhydride, digestion of the residue with chloroform and filtration, and evaporation of the chloroform left a residue which was chromatographed on silica gel, eluting with chloroform, to give 3 g (60% yield) of α-methylenelactam ethylenedithioketal **41**: mp 126–128°; ir 1601, 1650 cm^{-1}; nmr δ 1.9–2.8 (m, 6 H), 3.3 (s, 4 H), 3.4–3.9 (m, 3 H), 5.3 (split s, 1 H), 6.25 (split s, 1 H).

Similarly, α-methylenelactam bisethylthioketal **40** was obtained from its ester **38** in 53% yield as an oil: ir 1601, 1650 cm^{-1}; nmr (CCl_4) δ 1.25 (t, 6 H), 1.8–2.9 (m, 10 H), 3.4–3.9 (m, 3 H), 5.2 (split s, 1 H), 6.05 (split s, 1 H).

6-Methylene-1,5-dioxooctahydroindolizine 42. 1. Mercuric Chloride–Cadmium Carbonate Cleavage[22] of Bisethylthioketal 40.

To a solution of 11.25 g (41.5 mmol) of bisethylthioketal **40** in 400 ml of acetone, 200 ml of benzene, and 20 ml of water was added 14.3 g (83 mmol) of $CdCO_3$ and 225 g (83 mmol) of $HgCl_2$. The mixture was stirred vigorously at room temperature overnight then was filtered, and the filtrate was evaporated to dryness. Chromatography of the residue on silica gel with 20% chloroform–benzene gave a 40% yield of ketone **42**, which was recrystallized from chloroform–hexane: mp 68–72°; ir 1601, 1650, 1750 cm^{-1}; nmr (CCl_4) δ 1.1–2.9 (m, 6 H), 3.15–3.9 (m, 2 H), 4.2–4.6 (m, 1 H), 5.3 (split s, 1 H), 6.1 (split s, 1 H).

2. *N*-Chlorosuccinimide–Silver Nitrate Cleavage[23] of Ethylenedithioketal 41. A solution of 0.14 g (0.58 mmol) of ethylenedithioketal lactam **41** in 2 ml of acetonitrile was added to a well-stirred solution of 0.31 g (2.3 mmol) of NCS and 0.44 g (2.6 mmol) of $AgNO_3$ in 25 ml of 80% aqueous acetonitrile at room temperature.

The mixture was stirred for 15 min, saturated sodium sulfite was added followed by saturated Na_2CO_3 and NaCl solutions, the mixture was filtered through celite, and the celite was washed thoroughly with CH_2Cl_2. The aqueous phase of the filtrate was extracted exhaustively with CH_2Cl_2, the combined CH_2Cl_2 layers were dried, filtered, and evaporated, and the residue was chromatographed on silica gel to give a 40% yield of the ketone **42.**

3. Dimethoxycarbonium Tetrafluoroborate Cleavage[25,26] of Ethylenedithioketal 41. A solution of 650 mg (2.7 mmol) of thioketal **41** in 15 ml of CH_2Cl_2 was added to 972 mg (6.0 mmol) of dimethoxycarbonium tetrafluoroborate[27] in 3 ml of CH_2Cl_2 at room temperature with stirring. After 1 hr the CH_2Cl_2 was decanted from an oil which formed, the oil was digested with CH_2Cl_2, which was also decanted, and water was added to dissolve the oil. Continuous extraction of the aqueous solution with CH_2Cl_2 for 24 hr and evaporation of the CH_2Cl_2 gave 356 mg (80% yield) of ketone **42.**

1-Acetoxy-6-methylene-5-oxooctahydroindolizine (45). 1. From Ethyl 1-Hydroxyoctahydroindolizine-6-carboxylate (44). A solution of 2.19 g (10 mmol) of ketoacid **3** hydrochloride in 50 ml of water was titrated with 20% sodium hydroxide solution to pH 9. The solution was diluted with 60 ml of methanol and cooled in an ice bath, a solution of 1.5 g (40 mmol) of sodium borohydride in 10 ml of water was added dropwise over a 5 min period, and stirring was continued at 0° for 15 hr. Concentrated hydrochloric acid then was added to pH 2 and, after 0.5 hr, the solvent was evaporated, the residue was dissolved in 50 ml of absolute ethanol, and the resulting solution was cooled and saturated with HCl gas. After isolation similar to that described for ketoester **33** and chromatography on silica gel, 1.7 g (80% yield) of the hydroxy ester **44** was obtained as an oil: ir 1720, 3450 cm^{-1}; nmr δ 1.2 (t, 3 H), 1.5–3.3 (m, 12 H), 4.1 (q over m, 3 H).

To a solution of 1.66 g (7.8 mmol) of hydroxy ester **44** in 50 ml of ethanol was added 1.03 g (15.6 mmol) of potassium hydroxide followed by water until the suspension cleared, the solution was heated to reflux for 3 hr, and the ethanol then was evaporated. Acetic anhydride was added to the residue and the mixture was heated at reflux for 1.5 hr. Isolation was carried out as described for the α-methylenelactam thioketals **40** and **41.** Chromatography on silica gel with chloroform gave 1.2 g (74% yield) of the α-methylenelactam acetate **45** as an oily mixture of isomers: ir 1601, 1650, 1730 cm^{-1}; nmr (CCl_4) δ 1.3–2.7 (m with s at 2.03, 9 H), 3.3–3.9 (m, 3 H), 4.7 (q, 0.5 H, one isomer), 5.2 (m, 1.5 H, the other isomer), 6.1 (split s, 1 H). Three crystallizations from methylene chloride–hexane gave a single diastereomer, mp 85–86°.

2. From 1-Hydroxyoctahydroindolizine-6-carboxylic Acid (43). A solution of 12 g (55 mmol) of ketoacid **3** hydrochloride in 27 ml of water and 330 ml of methanol was adjusted to pH 8.5 with 10% aqueous sodium hydroxide, and to the solution at 0° was added 1.55 g of sodium borohydride in 55 ml of water dropwise over 0.5 hr. The solution was stirred at 0° for 20 hr, concentrated HCl was added until pH 2, the solution was concentrated to one-fourth volume, and it was applied to a cation exchange column (AG-50W-X8, hydrogen form), eluting with 1 *N* ammonium hydroxide until a negative ninhydrin test was obtained. Evaporation of the aqueous ammonium hydroxide gave 8.86 g (87% yield) of the hydroxyamino acid **43** which was very hygroscopic.

A solution of 7.98 g (43.2 mmol) of the hydroxy acid **43** in 200 ml of acetic anhydride was heated at reflux for 2.5 hr. The solution was evaporated to dryness and the residue chromatographed on silica gel, eluting with chloroform to give 7.6 g (84% yield) of α-methylenelactam acetate **45**, identical with that described above.

1-Hydroxy-6-methylene-5-oxooctahydroindolizine (46). To a solution of 1.2 g of α-methylenelactam acetate **45** in 25 ml of 95% ethanol was added 200 mol % of potassium hydroxide and the solution was stirred at room temperature overnight. The ethanol was evaporated, chloroform was added, and the mixture was stirred for 0.5 hr after which it was filtered and the precipitate washed with chloroform. The filtrate and washings were evaporated, and the residue was recrystallized from chloroform–hexane to give a 95% yield of hydroxymethylenelactam **46:** mp 106–112°; ir 1601, 1650, 3350 cm^{-1}; nmr δ 1.7–2.15 (m, 4 H), 2.4–2.7 (m, 2 H), 3.3–4.3 (m, 5 H), 5.2 (split s, 1 H), 6.1 (split s, 1 H).

6-Methylene-1,5-dioxooctahydroindolizine (42). By Oxidation of Alcohol 46 Using Dicyclohexylcarbodiimide (DCC)–Dimethyl Sulfoxide (DMSO)–Phosphoric Acid.[33] To a solution of 2.4 g (14.3 mmol) of alcohol **46** and 8.9 g (43.2 mmol) of freshly sublimed DCC in 120 ml of DMSO was added 480 mg of orthophosphoric acid. The mixture was stirred for 7 hr and filtered, and the precipitate was washed with carbon tetrachloride. Evaporation of the solvent left a residue which was chromatographed on silica gel, eluting with chloroform, to give 2 g (85% yield) of the keto α-methylenelactam **42**, identical with that prepared earlier by thioketal cleavage.

1-Acetoxy-6-acetoxymethyl-5-oxo-Δ^6-hexahydroindolizine (49). α-Methylenelactam (**45**) (400 mg, 1.9 mmol) in 8 ml of acetic acid and 213 mg of selenium dioxide were heated at 100° for 15 min, the mixture was cooled to 50° and filtered through filter aid, and the acetic acid was evaporated at <50°. The residue was dissolved in CH_2Cl_2 and filtered again, and the filtrate was evaporated to give 560 mg of residue, which was dissolved in 12 ml of acetic acid and 8 ml of acetic anhydride. To this was added 2 drops of concentrated sulfuric acid, the solution was heated at 140° for 30 min and then concentrated, and the residue was chromatographed on silica gel, eluting with 1% methanol–chloroform to give 348 mg (69% yield) of allylic acetate **49** as an oil: nmr δ 2.05 (s, 6 H), 1.9–2.65 (m, 4 H), 3.6 (m, 3 H), 4.75 (broad s, 2 H), 4.9 (q, 0.5 H) and 5.4 (q, 0.5 H), 6.5 (broad t, 1 H).

1-Hydroxy-6-hydroxymethyl-5-oxo-Δ^6-hexahydroindolizine (52). To a solution of 3.11 g (11.6 mmol) of diacetate **49** in 60 ml of absolute methanol was added 805 mg of anhydrous potassium carbonate. The mixture was stirred at room temperature for 0.5 hr and filtered, and the filtrate was evaporated to give a quantitative yield of the isomer mixture of diol **52:** high resolution mass spec *m/e* 183.0898 (calcd for $C_9H_{13}NO_3$, 183.0895). Repeated crystallization from methylene chloride gave one pure isomer, mp 168–169°.

Methyl 2-(1-Hydroxy-6-methylene-5-oxo-7-octahydroindolizinyl)butyrate (54). Diol **52** (1.51 g, 8.25 mmol), 6.95 g (57.7 mmol) of trimethyl orthobutyrate, and 27 μl of propionic acid were heated at 145° for 3 hr, removing methanol by distillation during the period. Excess trimethyl orthobutyrate was then evaporated, and to the cooled residue was added CH_2Cl_2 and 50 ml of 1 *N* HCl. The CH_2Cl_2 phase was washed with water, dried, filtered, and evaporated to give 1.99 g of diester **53** and alcohol **54** as a mixture of isomers (75% yield). The mixture of **53** and **54**, dissolved in 15 ml of absolute methanol to which 840 mg of anhydrous K_2CO_3 was added, was stirred at room temperature for 1 hr and filtered. Evaporation of the filtrate gave a quantitative yield of hydroxy ester **54** as a mixture of isomers: mp 93–103°; nmr δ 0.9 (overlapping sets of t, 3 H), singlets at 3.4, 3.6, 3.7 (isomers, $COOCH_3$), 4.2 (broad s, 1 H), split singlets at 5.2, 5.45, 6.1, 6.3 (isomers corresponding to $C{=}CH_2$).

Methyl 2-(6-Methylene-1,5-dioxo-7-octahydroindolizinyl)butyrate (55). Hydroxy α-methylenelactam (**54**) (554 mg, 2.1 mmol), 1.35 g (6.56 mmol) of DCC in 18.3 ml of DMSO, and 73 mg of orthophosphoric acid were stirred at room temperature for 30 hr, then the resulting precipitate was removed and washed with CH_2Cl_2. The combined filtrate and washings were evaporated, the residue was digested with CCl_4 and filtered, and the filtrate was evaporated. Chromatography of the residue gave 415 mg (76% yield) of ketoester **55** as an oily mixture of isomers: ir (CCl_4) 1601, 1650, 1725, 1750 cm^{-1}; nmr δ 0.9 (overlapping sets of t, 3 H), singlets at 3.6 and 3.7 and multiplets at 3.5–4.8 (total 6 H), split singlets at 5.1, 5.2, 6.0, 6.2 ($C{=}CH_2$), isomers.

Methyl 2-[8-Methylene-9-oxo-7(11*H*)-indolizino[1,2-*b*]quinolinyl]butyrate (56). A solution of 255 mg (0.96 mmol) of ketoester **55**, 261 mg (1.24 mmol) of *N*-(*o*-aminobenzylidene)-*p*-toluidine

(**48**), and 8.3 mg of *p*-toluenesulfonic acid in 25 ml of toluene was heated at reflux for 3 hr with azeotropic distillation of water. The toluene was removed under vacuum and the residue was chromatographed to give 266 mg (79% yield) of the tetracyclic α-methylenelactam **56** as a mixture of isomers: mp 132–138° dec; uv 319, 312, 306, 298, 288, 234 nm; nmr δ 0.9 (overlapping sets of t, 3 H), 1.5–2.4 (m, 3 H), 2.55–3.4 (m, 3 H), 3.55, 3.6, 3.75, 3.85 (all s, 3 H, isomers), 4.4–5.5 (m, 4 H), 6.3, 6.45 (2 split s, 1 H, isomers), 7.4–8.1 (m, 5 H).

Methyl 2-[8-Acetoxymethyl-9-oxo-7(11*H*)-indolizino[1,2-*b*]quinolinyl]butyrate (57). α-Methylenelactam **56** (388 mg, 1.11 mmol) and 122 mg of selenium dioxide in 15 ml of acetic acid were heated at 80° for 2.5 hr followed by filtration and evaporation of the filtrate. A 10% aliquot was purified by chromatography (SiO_2), eluting with chloroform to give the pyridone acetate **57** while the remaining crude was carried on to deoxycamptothecin. For **57** from chloroform–hexane: mp 171–178° dec; uv 370, 290, 253 nm; nmr δ 1.0 (t, 3 H), 2.05, 2.1 (s and m, respectively, 5 H), 3.7 (s, 3 H), 3.9 (t, 1 H), 5.2 (s, 2 H), 5.35 (s, 2 H), 7.35 (s, 1 H), 7.5–8.3 (m, 5 H).

Deoxycamptothecin (27). The crude oxidation product above, dissolved in 14 ml of dimethoxyethane (DME) and 27 ml of 2 *N* sulfuric acid, was heated at 50° for 7 hr. The DME was evaporated, and the residual aqueous layer was cooled to 0°, adjusted to pH 7.1 with saturated sodium bicarbonate solution, and extracted with chloroform. Evaporation of the dried chloroform gave crude deoxycamptothecin (**27**) which was chromatographed on silica gel, eluting with chloroform to give 262 mg (79% yield) of deoxycamptothecin (**27**): mp 262–264° dec (lit.[5b,f] mp 258–264°); uv 370, 290, 253 nm; nmr δ 1.05 (t, 3 H), 2.1 (m, 2 H), 3.6 (t, 1 H), 5.25 (broad s, 2 H), 5.45 (broad s, 2 H), 7.1 (s, 1 H), 7.6–8.35 (m, 5 H); high resolution mass spec *m/e* 332.1161 (calcd for $C_{20}H_{16}N_2O_3$, 332.1161).

***dl*-Camptothecin (1).** Following the suggested procedure,[5d] oxygen was bubbled (*via* a dispersion tube) through a solution of 300 mg of deoxycamptothecin (**27**) in 100 ml of dry DMF containing 500 mg of freshly prepared anhydrous $CuCl_2$ and 1 ml of 25% aqueous dimethylamine at room temperature. Monitoring by tlc (4% methanol in chloroform) indicated the disappearance of starting material after 5 hr, after which water was added, the pH was adjusted to 6.5 with dilute hydrochloric acid, and the mixture was extracted with methylene chloride. Evaporation of the dried methylene chloride left 310 mg (99% yield) of crystalline *dl*-camptothecin (**1**), mp 276–278° (lit. mp 275–277°,[5b] 276–278°[5f]), identical with natural material[37] in its uv, nmr, and high resolution mass spectrum.

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(37) Obtained from young (90 day) *C. acuminata* plants by Dr. G. Sherlha. These plants were grown from seeds kindly provided by Mr. R. L. Smith and Dr. R. Perdue of the U.S. Department of Agriculture.
(38) Solvent evaporations were carried out *in vacuo* using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared spectra were measured in $CHCl_3$, ultraviolet spectra were measured in 95% ethanol, and nuclear magnetic resonance spectra were taken in $CDCl_3$ (with internal TMS) unless otherwise noted. Gas chromatography was performed on a 0.25 in. × 10 ft column packed with 5% SE30 on Chromosorb W, AW-DMCS, and an He flow rate of 100 ml/min, and mass spectra were obtained on CED 103 and 110B instruments. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley; acceptable values for C, H and N were obtained for all new compounds.