Synthesis of Some DE and CDE Ring Analogs of Camptothecin

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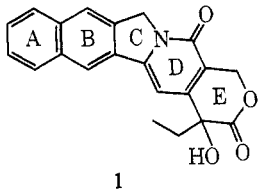
A general method has been devised for synthesizing DE and CDE ring analogs of camptothecin consisting of (a) rearrangement of a properly substituted nipecotic acid to a 3-methylene-2-piperidone, (b) oxidation and rearrangement to the corresponding primary allylic alcohol, (c) introduction of a substituted acetic acid residue at C-4 *via* Claisen rearrangement, and (d) elaboration of lactone ring E by allylic oxidation and rearrangement, dehydrogenation, lactonization, and introduction of the α-hydroxyl group. The syntheses of six analogs are given.

Camptothecin (1) is a novel alkaloid which has been isolated from extracts of the stem wood of *Camptotheca acuminate* (Nyssaceae),[1a] a rare tree indigenous to China, and from *Mappia foetida* Miers (Olacaceae),[1b] a small tree abundant in India. The alkaloid has been shown to possess activity against cancer in animals,[1,2] as well as activity against human intestinal and rectal cancers.[2] Since the structure determination of camptothecin in 1966,[1] several syntheses have been developed.[3] The α-hydroxy lactone functionality present in the E ring appears to be an absolute requirement[4] for antitumor activity; and, as a consequence, synthetic analogs containing this moiety are of potential biological importance. We now present the synthesis of several DE and CDE ring analogs.[5]



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Our synthetic procedure is broadly applicable[6] and consists of essentially three stages. First, a nipecotic acid is subjected to a methylene lactam rearrangement,[7] giving the corresponding 3-methylene-2-piperidone. Second, this methylene lactam is converted to the dihydropyridone–primary allylic alcohol, and the lactone ring carbon atoms are introduced *via* Claisen rearrangement. Third, this 4-substituted 3-methylene-2-piperidone is again converted to a dihydropyridone–primary allylic alcohol, dehydrogenated, lactonized, and oxidized to give the fused pyridone–hydroxy lactone. Examples of this overall process, with variations, are given below.

DE-Ring Analog. Series a. The synthesis of DE ring analog **31a** began with nicotinic acid, which was converted[7] to methylene lactam **12a** (93%) (Chart I) by hydrogenation, N-methylation, and rearrangement. Possible methods for getting to the dihydropyridone–primary allylic alcohol **21a** from **12a** were explored with several reagents known to effect allylic oxidation. Bromination of **12a** with NBS[8] (*N*-bromosuccinimide) in boiling carbon tetrachloride gave a mixture containing equal amounts of starting material and the product of bromine addition across the double bond. A trace of primary allylic bromide was detected in the mixture. Similarly, mixtures were observed with *tert*-butyl hypochlorite and light.[9] Attempted allylic benzoylation of **12a** w th *tert*-butyl perbenzoate[10] gave no oxidation and neither did exposure to singlet oxygen.[11] Selenium dioxide in hot acetic acid did effect an oxidative rearrangement of **12a** into **20a** but in low yield and accompanied by other products.

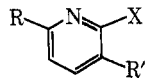
Since none of the foregoing oxidations of methylene lactam **12a** provided a useful route to allylic alcohol **21a**, the corresponding epoxymethylene derivative **14a** was prepared (88%)[7] and its chemistry was studied. Since epoxides can be rearranged to allylic alcohols using strong bases such as potassium *tert*-butoxide[12] or lithium alkylamides,[13] the interaction of epoxide **14a** with several bases was examined. Under a variety of conditions epoxide ring opening resulted with the formation of an amino tertiary alcohol. Lithium perchlorate,[14] on the other hand, was unreactive toward epoxide **14a**.

The rearrangement of **14a** to **21a** under acid catalysis was also examined. Treatment of **14a** with 5 mol % sulfuric acid at room temperature gave no reaction, whereas treatment with 5 mol % *p*-toluenesulfonic acid at 140–150° led to a complex mixture of products including starting material and allylic alcohol **21a**. When epoxide **14a** was heated in a mixture of acetic acid–acetic anhydride at 135–140° for 12 hr, a quantitative yield of glycol diacetate was formed. Pyrolysis of this material at 375–400° afforded the desired dihydropyridone–allylic acetate **20a** but it was contaminated with *ca.* 20% of the isomeric enol acetate.

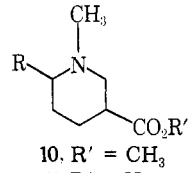
In order to develop a more efficient synthesis of **20a**, epoxide **14a** was first quantitatively converted to glycol **15a**[7] with aqueous perchloric acid, and thence to monoacetate **16a** (95%) by treatment with acetic anhydride–pyridine at room temperature. Conversion of **16a** to its mesylate ester[15] with triethylamine and mesyl chloride, followed by elimination of methanesulfonic acid using various reagents (acetic acid–sodium acetate, tetrabutylammonium acetate, 1,5-diazabicyclo[4.3.0]non-5-ene) gave poor yields of **20a**. Dihydropyridone–allylic acetate **20a** was finally secured in 69% yield by dehydration of glycol monoacetate **16a** with thionyl chloride–pyridine. A by-product of this reaction, which was formed in *ca.* 10% yield and was separable by chromatography on silica gel, was tertiary chloride **17a**. Deacetylation of acetate **20a** to allylic alcohol **21a** was accomplished in quantitative yield with potassium carbonate in aqueous methanol. If the deacetylation of **20a** was performed before its chromatographic purification, the contaminating chloride **17a** was reconverted to epoxide **14a**, which could then be recycled after separation from allylic alcohol **21a**. This was the preferred sequence owing to the relatively easy separation of **14a** and **21a**, and resulted in an overall yield of 67% from methylene lactam **12a** to dihydropyridone–allylic alcohol **21a**.

Introduction of the lactone ring carbon atoms into **21a** at C-4 was accomplished by the recently developed modification of the Claisen rearrangement.[16] Thus, heating a mixture of allylic alcohol **21a**, excess trimethyl orthobutyrate,[17] and a catalytic amount of propionic acid led to the C-4 substituted methylene lactam **23a** (96%) as a mixture of diastereomers. Separation of the isomers could be effected by column chromatography but was not necessary since the isomers converged at a subsequent stage in the synthesis.

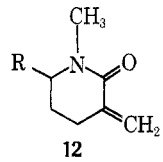
Chart I[a]



2, X = OH; R′ = CN
3, X = Cl; R′ = CN
4, X = H; R′ = CN
5, X = H; R′ = CO_2H
6, X = H; R′ = CO_2CH_3
7, X = H; R′ = $CONH_2$
8, X = H; R′ = COCl
9, X = H; R′ = $CO_2CH_2C_6H_5$



10, R′ = CH_3
11, R′ = H



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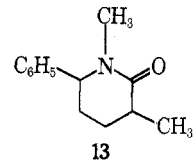

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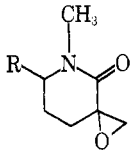

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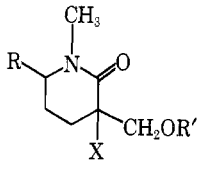
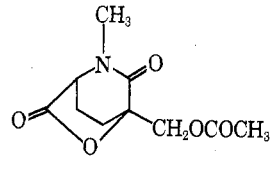


15, X = OH; R′ = H
16, X = OH; R′ = $COCH_3$
17, X = Cl; R′ = $COCH_3$
18, X = OH; R′ = CH_3



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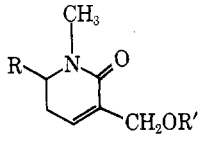
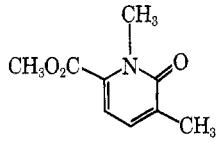


20, R′ = $COCH_3$
21, R′ = H



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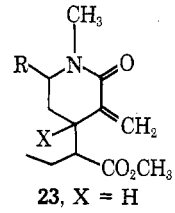
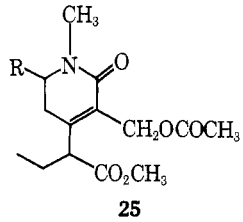


23, X = H
24, X = OH



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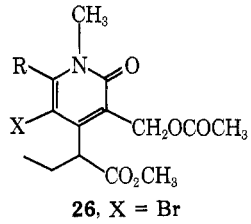
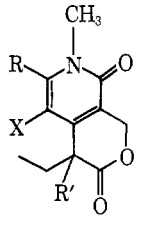


26, X = Br
27, X = H



28, X = Br; R′ = H
29, X = R′ = H
30, X = Br; R′ = OH
31, X = H; R′ = OH

[a] a, R = H; b, R = CO_2CH_3; c, R = C_6H_5.

In order to transform the methylene function in **23a** into a primary allylic alcohol, a two-step process was employed. Allylic oxidation[18] of **23a** with selenium dioxide in refluxing toluene gave a stereoisomeric mixture of tertiary alcohols **24a**, which was rearranged into dihydropyridone-allylic acetate **25a** (69%) by heating in acetic acid–acetic anhydride–sulfuric acid. Attempts to convert dihydropyridone-allylic acetate **25a** directly into the dihydropyridone-lactone (5,6-dihydro **29a**) and thence to **29a** by deacetylation–lactonization were not successful owing to partial exo isomerization of the double bond in the lactone ring.

This problem was overcome by first dehydrogenating dihydropyridone-allylic acetate **25a** and then carrying out the lactonization. The dehydrogenation of **25a** proved to be surprisingly difficult. Both selenium dioxide and mercuric acetate did not react with **25a**. Trityl perchlorate, a strong hydride abstractor,[19] was also employed but gave no useful product. When **25a** was refluxed in *p*-cymene in the presence of 10% Pd/C,[20] a new substance was formed in poor yield and identified as the corresponding 3-methylpyridone. Formation of this product probably occurs by thermal elimination of acetic acid and isomerization of the resulting diene to the pyridone. This process would be expected to be base-catalyzed and some of the 3-methylpyridone was also formed by treatment of **25a** with potassium *tert*-butoxide at room temperature.

Lead tetraacetate and 2,3-dichloro-5,6-dicyanoquinone, both reported to dehydrogenate piperidones,[3a,c,5a] caused a very slow aromatization of **25a** into the desired pyridone. The reaction was too slow, however, to be of preparative use. In an attempt to aromatize **25a** by bromination–dehydrobromination, its reaction with NBS was examined. When the reaction was carried out with 1 molar equiv of NBS in refluxing carbon tetrachloride using AIBN (azoisobutyronitrile) initiation, the main product formed was bromopyridone **26a**. Using 2 molar equiv of NBS, **26a** was isolated in essentially quantitative yield.

Lactonization of **26a** to the fused bromopyridone-lactone **28a** was accomplished in quantitative yield by stirring **25a** overnight in 2 *N* sulfuric acid–DME (1,2-dimethoxyethane) at 50°. Hydrogenolysis of **28a** over Pd/C in the presence of triethylamine[21] resulted in smooth debromination and the formation of the fused pyridone-lactone **29a**. Conversion of lactone **29a** into an α-hydroxy lactone as found in camptothecin was readily accomplished by oxidation with oxygen and base.[22] Thus, interaction of **29a** with an oxygenated DMF (dimethylformamide) solution of potassium *tert*-butoxide in the presence of triethyl phosphite at −25° led to α-hydroxy lactone **31a** in 69% yield.

Ester Analog. Series b. The first problem encountered in the syntheses of the ester analog **31b** was obtaining the selectively esterified 6-methoxycarbonylnipecotic acid (**11b**) which is the necessary precursor to the 6-methoxycarbonyl methylene lactam **12b**. The recent high-yield synthesis of 6-methoxycarbonylnicotinic acid (**5b**)[23] allowed a convenient approach to this system.

Although it is known that nicotinic acid may be hydrogenated without decarboxylation in either acidic or alkaline solutions, 6-methoxycarbonylnicotinic acid (**5b**) is insoluble in acidic solutions dilute enough to prevent ester hydrolysis. Although reduction of nicotinic acid has been reported in aqueous ammonia solution over Rh/Al_2O_3,[24] we have found that for the 2,5-pyridine diacids and monoesters extended reaction times are required for complete reduction of the pyridine nucleus, the extended exposure to aqueous alkali causing significant ester hydrolysis. Also, when reduction of the potassium salt of the monoester over PtO_2 in aqueous solution was attempted, some decarboxylation was observed.

These problems prompted using the alternative synthetic pathway of protecting the 5-carboxyl functionality as the benzyl ester. Refluxing 6-carbomethoxynicotinic acid in $SOCl_2$ and treatment of the crude acid chloride **8b** with benzyl alcohol in benzene–pyridine solvent gave in 87% yield the known diester **9b**.[25] This benzyl methyl diester was hydrogenated as the hydrochloride salt,[26] first reducing the pyridine nucleus over PtO_2, then substitut-

ing Pd/C as the catalyst and adding formaldehyde to reductively N-methylate and O-debenzylate in the same step. This sequence allows conversion of the starting pyridine 2,5-diacid to the required selectively esterified nipecotic acid **11b** in 55% overall yield.

Ester acid **11b** as the hydrochloride was converted in 85% yield to methylene lactam **12b** using the same procedure[7] as in the **a** series of compounds, although the acid hydrochloride requires additional solvent and the addition of 0.5 equiv of K_2CO_3 to facilitate reaction.[27] Subsequent treatment of **1b** with MCPA (*m*-chloroperbenzoic acid)–CH_2Cl_2 afforded epoxide **14b** in 98% yield.

Treatment of epoxides with $HClO_4$–MEK (methyl ethyl ketone) has been shown to give glycols in the presence of acid-sensitive esters,[28] but when epoxide **14b** was treated in this manner no reaction occurred in the usual reaction time, and extended reaction time gave only the ketal of the anticipated glycol and MEK. Attempts at epoxide opening using the same procedure used in the **a** series, with a minimum amount of methanol to effect solution, gave ester hydrolysis as well. Increasing the methanol concentration to 95% gave mostly the solvent addition product, methyl ether–tertiary alcohol. Hydroxyacetylation was then effected with acetic acid containing 5% concentrated H_2SO_4 to give the desired hydroxy acetate **16b** as well as acetoxy lactone **19**. An optimized yield of hydroxy acetate was obtained employing refluxing acetic acid alone.

Dehydration of **16b** to give allylic acetate **20b** was effected in 55% yield using essentially the same procedure as for the **a** series. Only extremely small amounts (*ca.* 1%) of tertiary chloride **17b** were formed.

Deacetylation could be accomplished to give **21b** either with 2 *N* H_2SO_4–DME or by transesterification employing K_2CO_3–CH_3OH. Both methods gave comparable yields after chromatographic purification, but the basic method is more convenient even though slightly more care must be taken during chromatography to remove a by-product, methylpyridone **22**. Formation of this product probably occurs in the same manner as the *tert*-butoxide catalyzed elimination–rearrangement of **25**, *i.e.*, base abstraction of an allylic proton, and elimination of acetate to give a diene which subsequently rearranges to the pyridone.

Condensation followed by Claisen rearrangement, selenium dioxide oxidation at the tertiary allylic position, and subsequent allylic rearrangement to give dihydropyridone **25b** proceeded in much the same way as for the **a** series, although in slightly lower yields. Some manipulation of reactant concentration as well as reaction time was necessitated by the increased reactivity of the molecule owing to the presence of the ester functionality.

Dihydropyridone **25b** was aromatized with NBS in the same manner as the **a** series to give directly pyridone **27b** and no bromopyridone **26b**. Examination of the acetoxymethylene region (δ 4.5–5.5) of the nmr of the crude product showed incomplete aromatization, but the disappearance of the ring allylic proton absorption (d, δ 2.75) showed complete allylic bromination at this position. Chromatography of this crude afforded in good yield only pyridone **27b**, the allylic bromide in the crude reaction mixture apparently eliminating hydrogen bromide during chromatography.

Although lactonization and oxidation had been originally envisaged as two separate steps, the enhanced reactivity of the ester pyridone allowed oxidation of the tertiary benzylic position under the mildly alkaline conditions used for lactonization. Thus treatment of **27b** with K_2CO_3–CH_3OH/O_2 gave ester analog **31b** directly. Lactone **28b** may be obtained using K_2CO_3–CH_3OH when oxygen is rigidly excluded from both reaction and isolation, but the total exclusion of oxygen was found to be very difficult and the product was always contaminated with some oxidized material. Uncontaminated lactone **29b** was obtained by mild acidic lactonization in 2 *N* H_2SO_4–DME with rigorous exclusion of oxygen.

Phenyl Analogs. Series c. 3-Cyano-6-phenyl-2-pyridone[29] (**2c**) was prepared by condensation of the sodium salt of benzoylacetaldehyde with cyanoacetamide in the presence of piperidine acetate catalyst, using either the method of Barat[29] or, more conveniently, that of Walford, *et al.*[30] Chlorodehydration of **2c** was effected in excellent yield using phenylphosphonic dichloride,[30,31] and subsequent hydrogenolysis of the 2-chloro substituent gave 6-phenylnicotinonitrile (**4c**) in 80% yield.

Hydrolysis[32] in refluxing aqueous ethanolic sodium hydroxide gave 6-phenylnicotinic acid (**5c**)[33] in almost quantitative yield. Quaternization of **5c** with dimethyl sulfate, methyl *p*-toluenesulfonate, or methyl iodide in refluxing THF (tetrahydrofuran) followed by reduction of the pyridine nucleus gave low yields of the desired methylene lactam precursor **11c**, the sequence failing at the quaternization step. Although the pyridine nucleus of **5c** could be cleanly reduced over Rh/Al_2O_3 in aqueous ammonia,[24] subsequent N-methylation either by reductive means or utilizing refluxing formic acid–formaldehyde also gave low yields of **11c**. Therefore, the methyl ester **6c**,[34] prepared by esterification of **5c** or direct methanolysis of nicotinonitrile **4c**, was quaternized using methyl *p*-toluenesulfonate and subsequently hydrogenated over PtO_2[35] to give ester **10c** in high yield as the desired precursor for methylene lactam rearrangement. An interesting by-product of the reduction of the tosyl salt of **6c** is methyl lactam **13**. Although methyl esters of nipecotic acids may be rearranged,[36] they normally require considerably more vigorous conditions than employed here; thus it is unlikely that methylene lactam **12c** is the precursor of **13**. This by-product **13** accounts for 10–15% of the total crude from the hydrogenation but is easily separated from the desired ester **10c**.

Ester **10c** was then hydrolyzed at room temperature with aqueous methanolic sodium hydroxide. The crude acid **11c** was rearranged to give in 87% yield methylene lactam **12c**, which was converted into dihydropyridone **25c** using the general methods developed in the above-mentioned series. Thus epoxidation with MCPA, hydroxyacetylation with acetic acid, dehydration with $SOCl_2$–pyridine, deacetylation with 2 *N* H_2SO_4, Claisen rearrangement, SeO_2 allylic oxidation, and acid-catalyzed allylic rearrangement gave **25c** in yields comparable with those obtained in the **a** series.

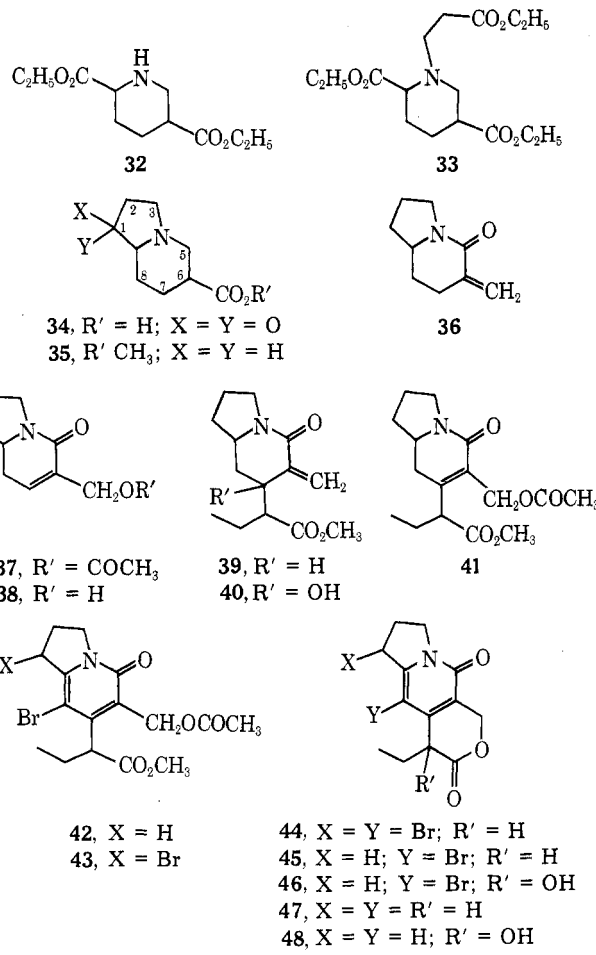
Treatment of dihydropyridone **25c** with NBS–CCl_4 for 8 min in the same manner as for the **b** series gave pyridone **27c** contaminated with trace amounts of bromopyridone **26c**, although occasionally formation of significant amounts of **26c** was observed. Bromopyridone **26c** may be obtained exclusively by utilizing 3 equiv of NBS and somewhat longer reaction times. Both pyridone **27c** and bromopyridone **26c** were lactonized following the procedure of the **a** series of compounds.

Although originally it had been thought that the phenyl lactones **28c** and **29c** might exhibit some of the reactivity of deoxycamptothecin itself, when oxidation was attempted with $CuCl_2$–DMF–O_2[3d] both lactone **28c** and bromolactone **29c** were found to be unreactive. Lactonization–oxidation of pyridones **26c** and **27c** in K_2CO_3–CH_3OH–O_2 as used in the **b** series also proved ineffective. Thus oxidation was carried out on both **28c** and **29c** with an oxygenated DMF solution of potassium *tert*-butoxide in a manner analogous to that used for the **a** series analog.

CDE Ring Analogs. Synthesis of CDE ring analogs of

camptothecin began with diethyl piperidine-2,5-dicarboxylate (32)[37] (Chart II) which was alkylated with ethyl 3-bromopropionate to give the triester 33 in 85% yield. Dieckmann cyclization of 33 followed by hydrolysis and decarboxylation led quantitatively to the hydrochloride of 1-oxooctahydroindolizine-6-carboxylic acid (34).[38] Since hydrogenolysis has been reported[39] to occur during the catalytic reduction of several amino ketones, these conditions were applied to keto acid 34. Hydrogenation of 34 with platinum oxide in 6 *N* hydrochloric acid or in acetic acid–H_2O–hydrochloric acid resulted in hydrogenolysis, and subsequently 5-oxo-6-methyleneoctahydroindolizine (36) was isolated by either of the two following procedures. In one case the reduction was followed by ion exchange and rearrangement to give methylene lactam 36 in 57% yield. Somewhat lower yields of 36 were obtained when the reduction of keto acid 34 was followed by esterification to 35, which, after purification, was converted to 36 by hydrolysis and rearrangement.

Chart II



In contrast to monocyclic methylene lactam **12a**, the bicyclic methylene lactam **36** reacted with selenium dioxide in glacial acetic acid to give only one product, the acetoxymethylhexahydroindolizinone **37** in 56% yield. Transformation of **37** into **41** with introduction of the α-butyric ester residue at C-7 followed the same procedure and gave comparable yields as in the **a** series.

For aromatization of 5,6,7-substituted hexahydroindolizine **41**, NBS–CCl_4 was employed as in the **a** series. Reaction of **41** with 2 mol of NBS led to a mixture of products which included, in addition to starting material, a compound containing two bromine atoms. If the reaction was carried out with 3 mol of NBS and allowed to proceed for 10 min, dibromotetrahydroindolizine **43** was formed in good yield. Shortening the reaction time to 5 min but still maintaining 3 mol of NBS resulted in a 20:80 mixture of dibromide **43** and monobromide **42**, respectively. Since debromination conditions had been established for the fused pyridone–lactone system in the case of the **a** series, dibromide **43** or the mixture of **42** and **43** was lactonized with 2 *N* sulfuric acid–DME at 50°. The resulting dibromo lactone **44** and monobromo lactone **45** were then subjected to catalytic debromination as in the **a** series. Lactone **44** rapidly debrominated to a mixture of monobromide **45** (85–90%) and debromo lactone **47** (10–15%), from which pure **45** was obtained by chromatography on silica gel. Reexposure of bromo lactone **45** (or the mixture of **44** and **45**) to catalytic hydrogenation with fresh catalyst gave a good yield of pure **47**.

Oxidation of both bromo lactone **45** and debromo lactone **47** was performed employing the same conditions as in the **a** series to give the camptothecin CDE ring analogs **46** and **48** in 60% yield. As can be seen from the examples presented, this synthetic method appears to be quite general and should serve for the synthesis of numerous camptothecin analogs.

Experimental Section[40]

1-Methyl-3-acetoxymethyl-3-hydroxy-2-piperidone (16a). Glycol **14a**[7] (2.5 g, 15.7 mmol) was dissolved in 50 ml of acetic anhydride containing 1 ml of pyridine. The solution was stirred for 24 hr at room temperature and then evaporated, and the residue was crystallized from hexane–CH_2Cl_2 to give a 95% yield of **16a**: mp 105–106°; ir ($CHCl_3$) 1635, 1735, 3600 cm^{-1}; nmr δ 1.93 (4 H, br s), 2.03 (3 H, s), 2.90 (3 H, s), 3.32 (2 H, m), 4.16 (2 H, s).

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.7; H, 7.5; N, 7.0. Found: C, 53.7; H, 7.4; N, 6.9.

1-Methyl-3-acetoxymethyl-5,6-dihydro-2-pyridone (20a). Hydroxy acetate **16a** (12.8 g, 63.7 mmol) was dissolved in 60 ml of pyridine and treated dropwise with 11.5 g (96.7 mmol) of $SOCl_2$. During the addition, which took 15 min, the reaction mixture was cooled in ice water. After stirring for 5 hr at room temperature, the mixture was poured into ice water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated, and chromatographed on silica gel. Elution with $CHCl_3$ gave 8.1 g (69%) of allylic acetate **20a** and 1.4 g of chloride **17a**: gc on column a[41] at 160°, retention time 8 min; ir 1625, 1665, 1725 cm^{-1}; nmr (CCl_4) δ 1.93 (3 H, s), 2.30 (2 H, m), 2.83 (3 H, s), 3.33 (2 H, t, J = 7 Hz), 4.53 (2 H, s), 6.37 (1 H, t, J = 4 Hz).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.1; N, 7.7. Found: C, 58.8; H, 7.0; N, 7.7.

Chloride 17a was characterized by its nmr spectrum (CCl_4): 2.02 (3 H, s), 2.20 (4, H, m), 2.88 (3 H, s), 3.39 (2 H, m), 4.21 (1 H, d, J = 12 Hz), 4.47 (1 H, d, J = 12 Hz); mass spectrum m/e 219, 220 (M^+).

1-Methyl-3-hydroxymethyl-5,6-dihydro-2-pyridone (21a). A solution of 3.37 g (18.4 mmol) of allylic acetate **20a** in 50 ml of 90% aqueous methanol was treated with 3.8 g (27.6 mmol) of K_2CO_3. The mixture was stirred overnight under N_2, filtered, and evaporated. The residue was diluted with saturated brine and extracted 12 times with CH_2Cl_2, which was dried and evaporated, leaving a 96% yield of allylic alcohol **21a** as an oil: ir 1605, 1665, 3400 cm^{-1}; nmr δ 2.18–2.61 (2 H, m), 2.97 (3 H, s), 3.42 (2 H, t, J = 7 Hz), 4.25 (2 H, br s), 6.50 (1 H, t, J = 4 Hz).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.6; H, 7.9; N, 9.9. Found: C, 59.7; H, 8.0; N, 9.9.

1-Methyl-3-methylene-4-(1-methoxycarbonylpropyl)-2-piperidone (23a). Allylic alcohol **21a** (4.8 g, 34 mmol), 35.5 g (240 mmol) of trimethyl orthobutyrate,[17] and 0.15 ml of propionic acid were heated at 150° under N_2 with distillative removal of methanol. After 3 hr, the mixture was cooled, the excess ortho ester was removed on the rotary evaporator, and the residue was chromatographed on silica gel. Elution with $CHCl_3$ furnished 7.3 g (95%) of Claisen product **23a**. Further chromatography resolved the two diastereomers.

Isomer A was a liquid: gc on column a[41] at 165°, retention time 13 min; nmr (CCl_4) δ 0.85 (3 H, t, J = 7 Hz), 2.92 (3 H, s), 3.65 (3 H, s), 5.18 (1 H, d, J = 3 Hz), 6.10 (1 H, d, J = 3 Hz).

Isomer B had mp 35°; nmr (CCl_4) δ 0.87 (3 H, t, J = 7 Hz), 2.87 (3 H, s), 3.52 (3 H, s), 5.00 (1 H, d, J = 3 Hz), 5.92 (1 H, d, J = 3 Hz).

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 64.0; H, 8.5; N, 6.2. Found: 63.8; H, 8.7; N, 6.2.

1-Methyl-3-methylene-4-hydroxy-4-(1-methoxycarbonylpropyl)-2-piperidone (24a). Claisen product **23a** (2.65 g, 11.8 mmol), 980 mg (8.8 mmol) of SeO_2, and 65 ml of toluene were heated at reflux with vigorous stirring for 3 hr. After the selenium was removed, the solution was evaporated and the residue was chromatographed on silica gel, eluting with $CHCl_3$ to give 980 mg of alcohol isomer A and 800 mg of alcohol isomer B, total yield, 74%. Isomer B was sublimed at 80–83° (15 μ).

Isomer A was an oil: ir 1600, 1655, 1720, and 3400 cm^{-1}; nmr δ 0.94 (3 H, t, J = 7 Hz), 2.97 (3 H, s), 3.75 (3 H, s), 4.00 (1 H, s), 5.80 (1 H, d, J = 2 Hz), 6.33 (1 H, d, J = 2 Hz).

Isomer B had mp 136–137°; nmr δ 0.92 (3 H, t, J = 7 Hz), 2.97 (3 H, s), 3.64 (3 H, s), 4.36 (1 H, s), 5.50 (1 H, s), 6.21 (1 H, s).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.7; H, 7.9; N, 5.8. Found: C, 59.9; H, 7.9; N, 5.8.

1-Methyl-3-acetoxymethyl-4-(1-methoxycarbonylpropyl)-5,6-dihydro-2-pyridone (25a). Tertiary alcohol **24a** (680 mg, 2.82 mmol), 15 ml of acetic acid, 10 ml of acetic anhydride, and 2 drops of concentrated H_2SO_4 were heated at 140° for 3 hr under N_2, cooled, and poured into ice water. Extraction with CH_2Cl_2 followed by drying and solvent removal gave 800 mg of an oil which was chromatographed on silica gel. Elution with $CHCl_3$–benzene (1:3), furnished 764 mg (95%) of pure dihydropyridone **25a**, distilled at (bath) 150° (15 μ): ir 1630, 1650, 1730 cm^{-1}; nmr (CCl_4) δ 0.90 (3 H, t, J = 7 Hz), 1.95 (3 H, s), 2.38 (2 H, t, J = 7 Hz), 2.92 (3 H, s), 3.37 (2 H, t, J = 7 Hz), 3.65 (3 H, s), 4.80 (2 H, s).

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.4; H, 7.5; N, 4.9. Found: C, 59.5; H, 7.3; N, 5.2.

1-Methyl-3-acetoxymethyl-4-(1-ethoxycarbonylpropyl)-5-bromo-2-pyridone (26a). Dihydropyridone **25a** (200 mg, 0.7 mmol), 250 mg (1.4 mmol) of NBS, 9 ml of CCl_4, and a trace of AIBN were heated under N_2 to 102°. After heating for 6 min at 100°, the mixture was cooled and poured into a mixture of CH_2Cl_2 and aqueous sodium bisulfite, the organic phase was washed, dried, and evaporated, and the residue of bromopyridone **26a** was chromatographed on silica gel, eluting with $CHCl_3$ to furnish 250 mg (98%) of pure **26a**: nmr δ 0.92 (3 H, t, J = 7 Hz), 2.00 (3 H, s), 3.52 (3 H, s), 3.63 (3 H, s), 5.08 (2 H, s), 7.58 (1 H, s); uv 324 nm; mass spectrum m/e 361 (M^+).

1-Methyl-3-hydroxymethyl-4-(1-carboxypropyl)-5-bromo-2-pyridone Lactone (28a). Bromopyridone **26a** (1.0 g, 2.78 mmol) was dissolved in 25 ml of DME and 25 ml of 2 N H_2SO_4. Stirring at 50° for 20 hr under N_2 was followed by dilution with water and extraction with CH_2Cl_2. The extracts were washed, dried, and concentrated to give a quantitative yield of pure bromo lactone **28a**: bp (bath) 175–180° (0.05 mm); ir 1550, 1605, 1655, 1740 cm^{-1}; uv 318 nm; nmr δ 1.03 (3 H, t, J = 7 Hz), 1.83 (2 H, sextet, J = 7 Hz), 3.50 (1 H, t, J = 7 Hz), 3.52 (3 H, s), 5.14 (2 H, unresolved), 7.71 (1 H, s).

Anal. Calcd for $C_{11}H_{12}NO_3Br$: C, 46.2; H, 4.2; N, 4.9. Found: C, 46.3; H, 4.4; N, 4.7.

1-Methyl-3-hydroxymethyl-4-(1-carboxypropyl)-2-pyridone Lactone (29a). A solution of 685 mg (2.40 mmol) of bromo lactone **28a** in 30 ml of absolute EtOH and 9.5 ml of Et_3N was shaken with hydrogen and 100 mg of 5% Pd/C. The pressure drop ceased after 25 min, at which time the mixture was filtered, and the filtrate was concentrated to 1/6 its original volume and distributed between 1 N H_2SO_4 and CH_2Cl_2. After washing and drying, the organic phase was concentrated to give 490 mg (98%) of lactone **29a**, crystallized from pentane–CH_2Cl_2: mp 91–92°; ir ($CHCl_3$) 1575, 1605, 1660, 1740 cm^{-1}; uv 300 nm (ϵ 6420); nmr δ 1.00 (3 H, t, J = 7 Hz), 1.98 (2 H, sextet, J = 7 Hz), 3.42 (1 H, t, J = 7 Hz), 3.57 (3 H, s), 5.28 (2 H, s), 6.10 (1 H, d, J = 7 Hz), 7.44 (1 H, d, J = 7 Hz).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8. Found: C, 63.7; H, 6.2; N, 6.8.

α-Hydroxy Lactone 31a. Potassium *tert*-butoxide (224 mg, 2 mmol) was dissolved in a mixture of 3 ml of DMF, 0.65 ml of *tert*-butyl alcohol, and 0.17 ml of triethyl phosphite. The mixture was cooled in a Dry Ice–CCl_4 bath and a solution of 290 mg (1.4 mmol) of lactone **28a** in 2.0 ml of THF was added. After dry O_2 was passed through the solution for 2 hr, the mixture was poured into ice-cold 1 N H_2SO_4. Extraction with CH_2Cl_2 followed by chromatography on silica gel, eluting with $CHCl_3$ and then 2.5% CH_3OH in $CHCl_3$, gave 215 mg (69%) of crystalline **31a**: mp 176–177° (lit.[3e] mp 180–181°); ir (KBr) 1555, 1595, 1655, 1710, 3500 cm^{-1}; uv 305 nm (ϵ 5240); nmr δ 0.95 (3 H, t, J = 7 Hz), 1.82 (2 H, q, J = 7 Hz), 3.57 (3 H, s), 2.41 (1 H, broad s), 5.10 (1 H, d, J = 16 Hz), 5.56 (1 H, d, J = 16 Hz), 6.50 (1 H, d, J = 7 Hz), 7.41 (1 H, d, J = 7 Hz).

Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.2; H, 5.7; N, 6.3. Found: C, 59.0; H, 5.8; N, 6.3.

2-Methoxycarbonyl-5-pyridinecarboxylic Acid Chloride (8b). Methyl ester **5b** (12.0 g, 66 mmol) in 100 g of $SOCl_2$ was refluxed for 1.75 hr, when gas evolution had ceased and a clear, homogeneous solution was obtained. The reaction mixture was cooled to room temperature, the excess $SOCl_2$ was evaporated, 75 ml of benzene was added, and the mixture was again evaporated to dryness, giving a solid, mp 98–102°. This material was not purified but carried directly into the next step. A small portion was sublimed at 55° (1 mm) to give material of mp 102–104°, ir ($CHCl_3$) 1755, 1740, 1720 cm^{-1}.

2-Methoxycarbonyl-5-benzyloxycarbonylpyridine (9b). Benzyl alcohol (8.2 g, 76 mmol), 100 ml of benzene, and 12 g (152 mmol) of pyridine were stirred at room temperature under N_2 while 12.6 g (60 mmol) of methyl ester acid chloride **8b** was added over 72 min. After 15 hr, the reaction mixture was filtered, the filtrate was evaporated, and the residue was crystallized from methanol: yield 14.1 g (87%); mp 97–99° (lit.[25] mp 116°); ir (KBr) 1715, 1735 cm^{-1}; nmr δ 4.05 (3 H, s), 5.24 (2 H, s), 7.40 (5 H, s), 8.13 (1 H, d, J = 8 Hz), 8.41 (1 H, d of d, J = 8, 2 Hz), 9.30 (1 H, m); mass spectrum m/e 271 (M^+).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.4; H, 4.8; N, 5.2. Found: C, 66.5; H, 4.7; N, 5.0.

1-Methyl-2-methoxycarbonyl-5-piperidinecarboxylic Acid Hydrochloride (11b). Methyl benzyl diester **9b** (16.5 g, 61 mmol) was dissolved in a minimum amount of chloroform diluted to 500 ml with anhydrous ether, the resulting solution was saturated with dry HCl, and the white precipitate which formed was collected, washed with anhydrous ether, and dried, giving 17.8 g (95%) of the hydrochloride. This material was then dissolved in 200 ml of absolute ethanol, 0.57 g of PtO_2 was added, and the resulting suspension was hydrogenated at 40 psi H_2. After 3 equiv of hydrogen had been absorbed (~4 hr), the hydrogenation was stopped and the catalyst was removed by filtration through super cel. To the resulting solution was added 14.2 g (0.18 mol) of 38% formaldehyde and 2.5 g of 10% Pd/C, and the mixture was hydrogenated at 40 psi H_2 for 16 hr. The catalyst was then removed and the solvent was evaporated. To the oily residue was added 150 ml of H_2O which was then evaporated. This addition and removal was repeated several times, and then the residue was dissolved in 125 ml of ethanol and diluted to 1 l. with anhydrous ether, giving a precipitate which was collected, washed with ether, and dried: yield 9.9 g (69%) after crystallization from ethanol; mp 187–189° dec; nmr (D_2O) δ 1.7–2.6 (m), 2.1–4.5 (m), 3.1 (3 H, s), 3.95 (3 H, s).

Anal. Calcd for $C_9H_{16}NO_4Cl$: C, 45.5; H, 6.8; N, 5.9. Found: C, 45.3; H, 6.9; N, 5.9.

1-Methyl-3-methylene-6-methoxycarbonyl-2-piperidone (12b). A mixture of 9.2 g (39 mmol) of ester acid hydrochloride **11b**, 2.14 g (20.4 mmol) of Na_2CO_3, and 365 ml of acetic anhydride was heated under N_2 at 50° for 4.5 hr. The reaction mixture was then cooled in an ice bath and filtered, and the solvent was removed to give a black residue which was dissolved in 100 ml of $CHCl_3$ and washed with water. The organic extract was dried and evaporated and the residue was chromatographed on silica gel, eluting with 1:1 ether–$CHCl_3$, yield 6.07 g (85%). Pure material also may be obtained by distillation: bp 82–84° (0.02 mm); gc on column b[41] at 170°; ir 1610, 1660, 1740 cm^{-1}; nmr δ 1.8–2.8 (m, 4 H), 3.0 (s, 3 H), 3.8 (s, 3 H), 4.2 (t, 1 H, J = 4 Hz), 5.3 (m, 1 H), 6.3 (m, 1 H); mass spectrum m/e 183 (M^+).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 58.9; H, 7.0; N, 7.7.

1-Methyl-3-epoxymethylene-6-methoxycarbonyl-2-piperidone (14b). Methylene lactam **12b** was epoxidized using the same procedure[7] as for the **a** series. From 3.90 g (21.2 mmol) of methylene lactam **12b** and 7.34 g (42.5 mmol) of MCPA in 50 ml of CH_2Cl_2 at room temperature for 45 hr was obtained 4.24 g (98% yield) of epoxide: oil, gc on column a[41] at 165°; ir 1660, 1740 cm^{-1}; nmr δ 1.1–2.5 (m, 4 H), 2.1 (d, 1 H, J = 6 Hz), 2.95 (s, 3 H), 3.5 (d, 1 H, J = 6 Hz), 3.8 (s, 3 H), 4.2 (t, 1 H, J = 4 Hz); mass spectrum m/e 199 (M^+).

Anal. Calcd for $C_9H_{13}NO_4$: C, 54.3; H, 6.6; N, 7.0. Found: C, 54.1; H, 6.6; N, 6.9.

1-Methyl-3-hydroxy-3-acetoxymethyl-6-methoxycarbonyl-2-piperidone (16b). Epoxide **14b** (4.11 g, 92 mmol) in 100 ml of acetic acid was refluxed for 25 hr, the acetic acid was then evaporated, and the residue was distributed between 100-ml portions of aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was removed,

the aqueous layer was extracted again with $CHCl_3$, the combined organic extracts were dried and concentrated, and the residue was chromatographed on 300 g of silica gel, eluting with $CHCl_3$, to give 914 mg (44%) of acetoxy lactone **19** and 2.813 g (52%) of hydroxy acetate **15b**.

Acetoxy lactone **19** had mp 109–111° from $CHCl_3$–hexane; ir 1690, 1730–1790 cm^{-1}; nmr δ 1.9–2.3 (m), 2.11 (s, 3 H), 3.05 (s, 3 H), 4.05 (m, 1 H), 4.55 (s, 2 H); mass spectrum m/e 227 (M^+), 183 ($M^+ - CO_2$).

Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.9; H, 5.8; N, 6.2. Found: C, 52.8; H, 5.6; N, 6.3.

Hydroxy Acetate 16b had mp 54–56°; ir 1640, 1735 cm^{-1}; nmr δ 1.7–2.5 (m), 2.1 (s), 2.95 (s, 3 H), 3.7 (varies, s, 1 H), 3.78 (s, 3 H), 4.1 (t, 1 H, J = 5 Hz), 4.2 (s, 2 H); mass spectrum m/e 259 (M^+).

Anal. Calcd for $C_{11}H_{17}NO_6$: C, 51.0; H, 6.6; N, 5.4. Found: C, 50.9; H, 6.7; N, 5.2.

1-Methyl-3-acetoxymethyl-6-methoxycarbonyl-5,6-dihydro-2-pyridone (20b). Allylic acetate **20b** was prepared following the same procedure as for the **a** series. From 13.7 g (52.8 mmol) of hydroxy acetate **16b**, 80 ml of pyridine, and 12.4 g (104 mmol) of $SOCl_2$ in 15 ml of pyridine for 5 hr at room temperature was obtained 6.96 g (55% yield) of **20b** as an oil: ir 1625, 1675, 1740 cm^{-1}; nmr δ 2.0–3.15 (m, 2 H), 2.2 (s, 3 H), 3.15 (s, 3 H), 3.75 (s, 3 H), 4.1 (t, 1 H, J = 5 Hz), 4.8 (m, 2 H), 6 42 (m, 1 H); mass spectrum m/e 241 (M^+).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.8; H, 6.3; N, 5.8. Found: C, 54.6; H, 6.2; N, 5.9.

1-Methyl-3-hydroxymethyl-6-methoxycarbonyl-5,6-dihydro-2-pyridone (21b). Acid Hydrolysis. Allylic acetate **20b** (616 mg, 2.54 mmol), 6 ml of DME, and 8 ml of 2 N H_2SO_4 were stirred for 28 hr at room temperature and then extracted into $CHCl_3$. The $CHCl_3$ phase was dried and concentrated, and the residue was chromatographed on silica gel eluting with $CHCl_3$ to give 400 mg (79%) of allylic alcohol **21b** as an oil.

Alkaline Hydrolysis. Allylic acetate **20b** (631 mg, 2.62 mmol), 3 ml of methanol, and 180 mg (1.3 mmol) of K_2CO_3 were stirred at room temperature for 15 min. The reaction mixture was then poured into 5 ml of saturated brine and extracted with $CHCl_3$, and the organic extracts were dried and concentrated. The residue was chromatographed on silica gel, eluting with $CHCl_3$, to give methyl pyridone **22** and 390 mg (75%) of allylic alcohol **21b**.

Allylic alcohol 21b had mp 62–63°; ir ($CHCl_3$) 1625, 1675, 1735 cm^{-1}; nmr (CCl_4) δ 2.8 (m, 2 H), 3.0 (s, 3 H), 3.55 (br s, 1 H), 3.75 (s, 3 H), 4.1 (m, 3 H), 6.4 (m, 1 H); mass spectrum mol wt 199.0842 (calcd for $C_9H_{13}NO_4$, 199.0844).

Methylpyridone 22 was an oil: gc on column a[41] at 180°; ir 1640, 1725 cm^{-1}; nmr (CCl_4) δ 2.08 (d, 3 H, J = 2 Hz), 3.62 (s, 3 H), 3.84 (s, 3 H), 6.60 (d, 1 H, J = 7 Hz), 7.06 (d of d, 1 H, J = 7, 2 Hz).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.7; H, 6.1; N, 7.7. Found: C, 59.5; H, 6.1; N, 7.7.

1-Methyl-3-methylene-4-(1-methoxycarbonylpropyl)-6-methoxycarbonyl-2-piperidone (23b). Claisen product **23b** was prepared following the same procedure as in the **a** series from 1.58 g (7.94 mmol) of allylic alcohol **21b**, 8.19 g (55.4 mmol) of trimethyl orthobutyrate,[17] and 10 μl of propionic acid at 150° for 3 hr: yield 1.83 g (82%); gc on column a[41] at 170°; ir 1615, 1660, 1725, 1745 cm^{-1}; nmr δ 0.9 (m, 3 H), 1.25–3.1 (m), 3.1 (s, 3 H), 3.7 (m, 6 H), 4.2 (m, 1 H), 5.24 (m, 1 H), 6.25 (m, 1 H).

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.3; H, 7.5; N, 4.9. Found: C, 59.2; H, 7.5; N, 4.9.

1-Methyl-3-methylene-4-hydroxy-4-(1-methoxycarbonylpropyl)-6-methoxycarbonyl-2-piperidone (24b). Tertiary alcohol **24b** was prepared following the same procedure as in the **a** series from 1.51 g (5.33 mmol) of Claisen product **23b**, 17 ml of toluene, and 443 mg (4.0 mmol) of SeO_2 for 2 hr at reflux. Chromatography on silica, eluting with $CHCl_3$, gave isomer A followed by more polar isomer B which melted at 126–127° after crystallization from CCl_4–hexane: combined yield 977 mg (61%); ir 1620, 1660, 1730, 1745, 3400 cm^{-1}; nmr (CCl_4), isomer A, δ 0.87 (m, 3 H), 0.75–2.9 (m), 2.87 (s, 3 H), 3.64–4.45 (m), 5.73 (m, 1 H), 6.23 (m, 1 H); isomer B, δ 0.87 (m, 3 H), 1.05–2.93 (m), 2.87 (s, 3 H), 3.66 (s, 3 H), 3.77 (s, 3 H), 4.12 (t, 1 H, J = 7 Hz), 4.33 (s, 1 H), 5.31 (d, 1 H, J = 2 Hz), 6.07 (d, 1 H, J = 2 Hz).

Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.2; H, 7.1; N, 4.7. Found: C, 56.0; H, 6.9; N, 4.7.

1-Methyl-3-acetoxymethyl-4-(1-methoxycarbonylpropyl)-6-methoxycarbonyl-5,6-dihydro-2-pyridone (25b). Dihydropyridone **25b** was prepared following the same procedure as in the **a** series from 470 mg (1.57 mmol) of tertiary alcohol **24b**, 6 ml of acetic acid, 6 ml of acetic anhydride, and 1 drop of concentrated H_2SO_4 at 130° for 3 hr: yield 406 mg (76%); ir 1635, 1665, 1740 cm^{-1}; nmr (CCl_4) δ 0.85 (br t, 3 H, J = 7 Hz), 1.03–2.1 (m), 1.97 (s, 3 H), 2.75 (d, 2 H, J = 4 Hz), 2.98 (s, 3 H), 3.7 (m, 7 H), 4.13 (t, 1 H, J = 4 Hz), 4.82 (s, 2 H).

Anal. Calcd for $C_{16}H_{23}NO_7$: C, 56.3; H, 6.8; N, 4.1. Found: C, 56.0; H, 6.7; N, 4.0.

1-Methyl-3-acetoxymethyl-4-(1-methoxycarbonylpropyl)-6-methoxycarbonyl-2-pyridone (27b). Pyridone **27b** was prepared following the same procedure as in the **a** series from 251 mg (0.74 mmol) of dihydropyridone **25b**, 278 mg (1.56 mmol) of NBS, and 13 ml of CCl_4 at 110° for 12 min: yield 197 mg (79%); gc on column c[41] at 225°; ir 1610, 1655, 1735 cm^{-1}; nmr (CCl_4) δ 0.90 (t, 3 H, J = 7 Hz), 1.05–2.3 (m, 2 H), 1.98 (s, 3 H), 3.68 (m, 7 H), 3.93 (s, 3 H), 5.13 (s, 2 H), 6.75 (s, 1 H).

Anal. Calcd for $C_{16}H_{21}NO_7$: C, 56.6; H, 6.2; N, 4.1. Found: C, 56.8; H, 6.2; N, 4.3.

Ester Lactone 29b. Pyridone **27b** (122 mg, 0.36 mmol), 1.6 ml of deoxygenated DME, and 1.6 ml of deoxygenated 2 N H_2SO_4 were stirred under N_2 at room temperature. After 49 hr the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic extracts were dried and concentrated to give 97 mg of an oil which was chromatographed on silica gel eluting with $CHCl_3$ to give 70 mg (75%) of lactone **29b**, after crystallization from $CHCl_3$–hexane: mp 95–98°; ir 1655, 1735 cm^{-1}; nmr (CCl_4) δ 1.02 (t, 3 H, J = 7 Hz), 1.98 (m, 2 H), 3.35 (t, 1 H, J = 6 Hz), 3.68 (s, 3 H), 3.97 (s, 3 H), 5.26 (s, 2 H), 6.64 (s, 1 H).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.9; H, 5.7; N, 5.3. Found: C, 58.6; H, 5.8; N, 5.3.

Ester α-Hydroxy Lactone 31b. Dry O_2 was bubbled through a stirred solution of 289 mg (0.85 mmol) of pyridone **27b**, 5.7 ml of methanol, and 59 mg (0.428 mmol) of K_2CO_3 at room temperature. After 3.5 hr the reaction mixture was poured into 15 ml of water and acidified with 2 N H_2SO_4. The acidic solution was extracted with $CHCl_3$, which was washed with saturated aqueous NaCl, dried, and concentrated to give 239 mg of an oil which was chromatographed on silica gel, eluting with $CHCl_3$, to give 150 mg (63%) of pure ester α-hydroxy lactone **31b** after crystallization from CCl_4: mp 152–153°; ir (KBr) 1655, 1735, 3540 cm^{-1}; nmr δ 0.97 (t, 3 H, J = 7 Hz), 1.79 (q, 2 H, J = 7 Hz), 3.64 (s, 3 H), 3.94 (s, 3 H), 5.04 (d, 1 H, J = 16 Hz), 5.52 (d, 1 H, J = 16 Hz), 7.0 (s, 1 H); mass spectrum mol wt 281.0901 [calcd for $C_{13}H_{15}NO_4$ (M^+), 281.0899].

Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.5; H, 5.4; N, 5.0. Found: C, 55.5; H, 5.3; N, 5.0.

2-Chloro-3-cyano-6-phenylpyridine (3c). Cyanopyridone **2c**[29] (38.1 g, 195 mmol) and 85 g (400 mmol) of $PhPOCl_2$ were heated at 180° under N_2 for 2 hr. The melt was then poured into 700 ml of ice water and stirred for 90 min, concentrated aqueous ammonia was added to pH 10, and the crystalline precipitate was collected: yield 40.8 g (95%) after crystallization from methanol; mp 146–147°; ir 2230 cm^{-1} (nitrile); nmr δ 7.35–8.20 (m).

Anal. Calcd for $C_{12}H_7N_2Cl$: C, 67.2; H, 3.3; N, 13.0. Found: C, 67.2; H, 3.2; N, 13.0.

6-Phenylnicotinonitrile (4c). Chlorocyanopyridine **3c** (10.2 g, 47 mmol) was hydrogenated in 70 ml of DMF containing 4.85 g (48 mmol) of triethylamine, and 1.10 g of 10% Pd/C. The mixture was shaken under 40 psi of H_2 until 1 equiv was absorbed (20 min). The mixture was filtered, the filtrate was diluted to 800 ml with water, and the resulting precipitate was washed with water, dried, and crystallized from ethanol, yield 7.1 g (80%), mp 91–92°. Attempts to reduce larger amounts resulted in a rise in temperature and uncontrolled reduction, leading to lower yields of the desired product.

Anal. Calcd for $C_{12}H_8N_2$: C, 80.0; H, 4.5; N, 15.5. Found: C, 79.9; H, 4.6; N, 15.6.

Methyl 6-Phenylnicotinate (6c). 6-Phenylnicotinonitrile (1.8 g, 10 mmol), 30 ml of methanol, and 30 ml of ether were stirred at 0° while dry HCl was bubbled through the solution for 2 hr. The resulting suspension was stirred at room temperature under N_2 overnight, then 50 ml of ether and 100 ml of ice-cold saturated $NaHCO_3$ were added, and the mixture was stirred as an emulsion at room temperature for 5 hr. The ether phase was separated, the aqueous phase was washed with ether, and the combined ether solutions were dried and evaporated, giving a residue which was eluted from silica gel with $CHCl_3$, yield 1.7 g (80%) of ester **6c**, mp 114–117° (lit.[34] mp 118°). Subsequent washing of the column with 10% acetone–$CHCl_3$ gave the remaining 20% as 6-phenylnicotinamide (**7c**), which may be hydrolyzed in refluxing NaOH–MeOH–water and esterified to the desired ester.

6-Phenylnicotinamide (7c) had mp 221–222° from methanol; ir

(KBr) 1650, 3400 cm^{-1}; nmr (TFA) δ 7.60–8.10 (m, 5 H), 8.42 (d, 1 H, J = 9 Hz), 9.13 (d of d, 1 H, J = 9 Hz, J = 2 Hz), 9.42 (d, 1 H, J = 2 Hz).

Anal. Calcd for $C_{12}H_{10}NO$: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.2; H, 5.0; N, 14.2.

An alternative, more convenient for large-scale preparations, is hydrolysis of the 6-phenylnicotinotrile (**4c**) and subsequent esterification. A solution of 26.8 g (149 mmol) of 6-phenylnicotinonitrile (**4c**), 26 g (650 mmol) of NaOH, and 700 ml of 7:3 ethanol–water was refluxed for 5 hr and cooled to room temperature, and the solvent was evaporated. The residue was dissolved in 800 ml of water, the solution was filtered, and the filtrate was acidified with acetic acid to give 6-phenylnicotinic acid (**5c**), yield 28.7 g (97%), mp 229–232° (lit. mp 229,[42] 232°[33]). The 6-phenylnicotinic acid (**5c**) was esterified by boiling 6.7 g (3.37 mmol) for 23 hr in 100 ml of methanol containing 5.0 g of concentrated H_2SO_4. The reaction mixture was cooled and brought to pH 8 with saturated aqueous $NaHCO_3$ to give 6.0 g (83% yield) of methyl 6-phenylnicotinate (**6c**), mp 114–116° (lit.[34] mp 118°).

1-Methyl-2-phenyl-5-methoxycarbonylpyridinium *p*-Toluenesulfonate. Methyl 6-phenylnicotinate (**6c**), 5.6 g (26.3 mmol), and 5.6 g (31 mmol) of methyl *p*-toluenesulfonate were heated at 115° for 4 hr. The melt was allowed to cool, then dissolved in 20 ml of absolute ethanol and diluted with 200 ml of ethyl acetate, followed by thorough cooling. Concentration of the mother liquor gave a second crop, yield 9.5 g (90%), mp 158–161°.

Anal. Calcd for $C_{21}H_{21}NO_5S$: C, 63.0; H, 5.3. Found: C, 62.9; H, 5.2.

1-Methyl-2-phenyl-5-methoxycarbonylpiperidine (10c). Hydrogenation of 18.5 g (46 mmol) of the methyl *p*-toluenesulfonate of **6c** was carried out in 200 ml of absolute ethanol, with 700 mg of PtO_2 and H_2 at 40 psi until 3 equiv was absorbed and further absorption ceased (45 min). The mixture was filtered and the solvent was evaporated to give an oil which was dissolved in $CHCl_3$. The organic phase was washed with saturated aqueous $NaHCO_3$, dried, and concentrated to give an oil which was separated from methyl lactam **13** by elution from a silica gel column with 1:1 EtOAc–hexane, yield 9.1 g (85%).

Ester 10c: gc on column a[41] at 165°; ir 1735 cm^{-1}; nmr δ 1.0–F.8 (m, 13 H), 1.9 (s), 3.7 (s), 7.2 (s, 5 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.1; H, 8.2; N, 6.1.

Methyl lactam 13: gc on column a[41] at 165°; mp 79–80°; ir 1620 cm^{-1}; nmr δ 1.25 (d, 3 H, J = 7 Hz), 1.1–2.9 (m, 5 H), 2.75 (s, 3 H), 4.4 (t, 1 H, J = 7 Hz), 7.15 (m, 5 H).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.8; H, 8.4; N, 6.9. Found: C, 76.6; H, 8.2; N, 7.0.

1-Methyl-3-methylene-6-phenyl-2-piperidone (12c). A solution of 9.0 g (38 mmol) of ester **10c**, 75 ml of methanol, 75 ml of H_2O, and 3.2 g (80 mmol) of NaOH was stirred overnight at room temperature under N_2. The volume was then reduced to half, 6.0 g (100 mmol) of acetic acid was added, and the solution was evaporated to dryness. The residue was dissolved in 100 ml of acetic anhydride, refluxed for 3 hr, cooled to room temperature, and stirred overnight under N_2, and the methylene lactam was isolated in the same manner as in the **b** series. The crude product was chromatographed on silica gel, eluting with $CHCl_3$, to give 6.9 g (87%) of pure methylene lactam **12c:** sublimed at 60° (50 μ); mp 90–91°; ir (KBr) 1680, 1600 cm^{-1}; nmr δ 1.57–2.63 (m, 4 H), 2.84 (s, 3 H), 4.51 (m, 1 H), 5.13 (br s, 1 H), 6.14 (br s, 1 H), 7.10 (br s, 5 H).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 7.0. Found: C, 77.9; H, 7.8; N, 6.7.

1-Methyl-3-epoxymethylene-6-phenyl-2-piperidone (14c). Epoxide **14c** was prepared[7] from 6.7 g (31 mmol) of methylene lactam **12c**, 10.3 g (60 mmol) of MCPA, and 150 ml of CH_2Cl_2 for 3 days at room temperature: yield 6.9 g (100%) of epoxide which was sublimed at 80° (25 μ); mp 94–95°; nmr ($CDCl_3$) δ 1.47–2.54 (m, 4 H), 2.67 (d, 1 H, J = 6 Hz), 2.82 (s, 3 H), 3.42 (d, 1 H, J = 6 Hz), 4.65 (t, 1 H, J = 5 Hz), 7.27 (br s, 5 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.8; H, 7.0; N, 6.4. Found: C, 71.8; H, 7.0; N, 6.4.

1-Methyl-3-hydroxy-3-acetoxymethyl-6-phenyl-2-piperidone (16c). Hydroxy acetate **16c** was prepared following the procedure of the **b** series from 6.9 g (31 mmol) of epoxide **14c** and 100 ml of acetic acid for 24 hr at reflux: yield 7.4 g (85%) after crystallization from pentane–CH_2Cl_2; mp 172–173°; nmr δ 2.08 (s, 3 H), 2.82 (s, 3 H), 4.26 (s, 2 H), 4.52 (t, 1 H, J = 4 Hz), 7.24 (br s, 5 H).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1. Found: C, 64.9; H, 6.8; N, 5.2.

1-Methyl-3-acetoxymethyl-6-phenyl-5,6-dihydro-2-pyridone (20c). Allylic acetate **20c** was prepared following the procedure of the **a** series from 2.5 g (9 mmol) of hydroxy acetate **15c** in 50 ml of pyridine added dropwise to 5.35 g (45 mmol) of $SOCl_2$ in 50 ml of pyridine for 5.5 hr at room temperature. Chromatography yielded the desired allylic acetate **20:** yield 1.7 g (73%); gc on column c[41] at 178°; nmr (CCl_4) δ 1.90 (s, 3 H), 2.78 (s, 3 H), 4.47 and 4.58 (two d, 1 H, J = 4 Hz), 4.64 (s, 2 H), 6.15 (m, 1 H), 7.09 (br s, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.6; N, 5.4. Found: C, 69.6; H, 6.7; N, 5.1.

1-Methyl-3-hydroxymethyl-6-phenyl-5,6-dihydro-2-pyridone (21c). A solution of 6.9 g (24 mmol) of allylic acetate **20c**, 100 ml of 2 *N* H_2SO_4, and 200 ml of DME was heated for 4 hr at 60° under N_2. The mixture was then cooled to room temperature, aqueous $NaHCO_3$ was added to pH 8, the solution was concentrated to ⅙ volume, and $CHCl_3$ and water were added. The organic phase was separated, dried, and concentrated and the residue was chromatographed on silica gel. Elution with $CHCl_3$ gave 4.2 g (80%) of allylic alcohol **21c:** nmr 1.8–2.6 (m, 2 H), 3.0 (s, 3 H), 4.4 (s, 2 H), 4.8 (t, 1 H, J = 3 Hz), 6.2 (t, 1 H, J = 4 Hz), 7.2 (m, 5 H); mass spectrum mol wt 217.1103 [calcd for $C_{13}H_{15}NO_2$, 217.1102 (M^+)].

1-Methyl-3-methylene-4-(1-methoxycarbonylpropyl)-6-phenyl-2-piperidone (23c). Claisen product **23c** was prepared following the same procedure as in the **a** series using 480 mg (2.2 mmol) of allylic alcohol **21c**, 2.2 g (15 mmol) of trimethyl orthobutyrate,[17] and 8 μl of propionic acid at 150° for 3.5 hr: yield 580 mg (90%); gc on column a[41] at 170°; ir 1610, 1660, 1735 cm^{-1}; nmr δ 0.9 (m, 3 H), 1.2–3.05 (m), 3.55–3.85 (m, 3 H), 4.6 (m, 3 H), 5.35 (m, 1 H), 6.35 (m, 1 H), 7.32 (m, 5 H).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7; N, 4.7. Found: C, 71.9; H, 7.6; N, 4.7.

1-Methyl-3-methylene-4-(1-methoxycarbonylpropyl)-4-hydroxy-6-phenyl-2-piperidone (24c). Tertiary alcohol **24c** was prepared following the same procedure as in the **a** series using 5.4 g (18 mmol) of Claisen product **23c**, 1.43 g (13.5 mmol) of SeO_2, and 90 ml of toluene for 5 hr, at reflux: yield 5.2 g (92%); nmr δ 1.0 (t, 3 H, J = 6 Hz), 1.6–3.4 (m), 2.9 (m, 3 H), 3.6–4.0 (m, 3 H), 5.6–6.0 (m, 1 H), 6.5 (m, 1 H), 7.4 (m, 5 H); mass spectrum mol wt 317.1622 [calcd for $C_{18}H_{23}NO_4$, 317.1626 (M^+)].

1-Methyl-3-acetoxymethyl-4-(1-methoxycarbonylpropyl)-6-phenyl-5,6-dihydro-2-pyridone (25c). Dihydropyridone **25c** was prepared following the same procedure as in the **a** series from 5.2 g (16.5 mmol) of tertiary alcohol **24c**, 60 ml of acetic acid, 40 ml of acetic anhydride, and 1 drop of concentrated H_2SO_4, at 130° for 3.5 hr: yield 4.4 g (74%); nmr (CCl_4) δ 0.4 (t, J = 6 Hz), 0.85 (t, J = 6 Hz), 1.92 (s, 3 H), 2.89 (s, 3 H), 3.57 (s, 3 H), 4.55 (m, 1 H), 4.86 (s, 2 H), 7.14 (br s, 5 H).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.8; H, 7.0; N, 3.9. Found: C, 66.8; H, 6.8; N, 3.8.

1-Methyl-3-acetoxymethyl-4-(1-methoxycarbonylpropyl)-6-phenyl-2-pyridone (27c). Pyridone **27c** was prepared following the same procedure as in the **b** series from 325 mg (0.91 mmol) of dihydropyridone **25c**, 320 mg (1.78 mmol) of NBS, and 14 ml of CCl_4 for 8 min at 100°, yield 186 mg (57%). Normally only traces of bromo pyridone **26c** were formed, although occassionally formation of larger quantities of this difficult to separate by-product was observed: nmr (CCl_4) δ 1.0 (t, 3 H, J = 6 Hz), 2.02 (s, 3 H), 3.34 (s, 3 H), 3.69 (s, 3 H), 3.82 (t, 1 H, J = 6 Hz), 5.17 (s, 2 H), 6.00 (s, 1 H), 7.37 (br s, 5 H); mass spectrum mol wt 357.1570 [calcd for $C_{20}H_{23}NO_5$, 357.1576 (M^+)].

1-Methyl-3-acetoxymethyl-4-(1-methoxycarbonylpropyl)-5-bromo-6-phenyl-2-pyridone (26c). Dihydropyridone **25c** (1.0 g, 2.8 mmol) was dissolved in 50 ml of CCl_4, and 1.5 g (8.4 mmol) of NBS and 5 mg of AIBN were added. The mixture was refluxed for 15 min and cooled to room temperature, and the product was isolated in the same manner as the **a** series bromopyridone. Chromatographic purification gave 580 mg (48%) of bromopyridone **26c** as a viscous oil: nmr δ 1.2 (t, 3 H, J = 8 Hz), 2.2 (s, 3 H), 3.7 (s, 3 H), 4.0 (s, 3 H), 4.2 (t, 1 H, J = 8 Hz), 5.35 (s, 2 H), 7.2 (m, 5 H).

Anal. Calcd for $C_{20}H_{22}NO_5Br$: C, 55.1; H, 5.1; N, 3.2. Found: C, 54.8; H, 4.9; N, 3.3.

Phenyl lactone 29c was prepared following the procedure used in the **a** series from 270 mg (0.76 mmol) of pyridone **27c**, 25 ml of 2 *N* H_2SO_4, and 45 ml of DME at 50° for 20 hr: yield 210 mg (96%) after crystallization from hexane–EtOH; mp 151–153°; nmr δ 1.00 (t, 3 H, J = 6 Hz), 1.92 (m, 2 H), 3.38 (s, 3 H), 5.33 (s, 2 H), 6.03 (s, 1 H), 7.48 (m, 5 H).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.1; N, 4.9. Found: C, 71.9; H, 6.0; N, 4.9.

Phenyl bromo lactone 28c was lactonized using the procedure described above in 95% yield: nmr δ 1.2 (t, 3 H, J = 7 Hz), 1.92 (q, 2 H, J = 7 Hz), 3.34 (s, 3 H), 3.9 (t, 1 H, J = 7 Hz), 5.25 (d, 1 H, J = 15 Hz), 5.68 (d, 1 H, J = 15 Hz), 7.4 (m, 5 H).

Anal. Calcd for $C_{17}H_{16}NO_3Br$: C, 56.4; H, 4.5; N, 3.8. Found: C, 56.5; H, 4.5; N, 3.7.

Phenyl α-Hydroxy Lactone 31c. Lactone **29c** (100 mg, 0.35 mmol) was oxidized with O_2 in the presence of 59 mg (0.53 mmol) of potassium *tert*-butoxide as in the **a** series. Chromatography on silica gel, eluting with $CHCl_3$, gave 60 mg (57%) of phenyl analog **31c**, after crystallization from benzene–hexane: mp 170–171°; nmr δ 1.00 (t, 3 H, J = 6 Hz), 1.82 (q, 2 H, J = 6 Hz), 3.37 (s, 3 H), 5.13 (d, 1 H, J = 16 Hz), 5.62 (d, 1 H, J = 16 Hz), 6.43 (s, 1 H), 7.34 (m, 5 H).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.4; H, 5.7; N, 4.7.

Phenyl α-hydroxy bromo lactone 30c was prepared as in the **a** series using 200 mg (0.55 mmol) of lactone **28c** in 5 ml of THF, 112 mg (1 mmol) of potassium *tert*-butoxide in 4 ml of DMF, and O_2, −30° during addition and then −10° for 3 hr: yield 170 mg (83%) after crystallization from CCl_4; mp 175–176°; nmr δ 1.02 (t, 3 H, J = 7 Hz), 2.17 (q, 2 H, J = 7 Hz), 3.26 (s, 3 H), 3.98 (s, 1 H), 5.17 (d, 1 H, J = 17 Hz), 5.70 (d, 1 H, J = 17 Hz), 7.08–7.70 (m, 5 H); mass spectrum mol wt 377.0263 [calcd for $C_{17}H_{16}NO_4Br$, 377.0263 (M^+)].

Anal. Calcd for $C_{17}H_{16}NO_4Br$: C, 54.0; H, 4.3; N, 3.7. Found: C, 53.7; H, 4.3; N, 3.7.

5-Oxo-6-methyleneoctahydroindolizine (36) and Methyl Octahydroindolizine-6-carboxylate (35). A solution of 10 g (45.6 mmol) of the HCl salt of 1-oxooctahydroindolizine-6-carboxylic acid (**34**),[38b] prepared by Dieckmann cyclization[38a] of triester **33**, in 125 ml of 4:1 acetic acid–water in which 8 g of HCl gas had been dissolved, was hydrogenated over 875 mg of PtO_2 at 50 psi. After H_2 absorption ceased, the mixture was filtered, the filtrate was evaporated, and the residue was dissolved in water and passed through ion exchange resin (AG-50W X8, H^+) to give the free amino acid. This was rearranged in 65 ml of acetic anhydride.[7] Chromatography on silica gel, eluting with $CHCl_3$, afforded 3.85 g (56%) of methylene lactam **36**, distilled at 80° (0.15 mm): ir ($CHCl_3$) 1600, 1650 cm^{-1}; nmr δ 1.05–2.75 (m, 8 H), 3.34–3.87 (m, 3 H), 5.23 (m, 1 H), 6.13 (m, 1 H).

Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.7; N, 9.3. Found: C, 71.6; H, 8.6; N, 9.0.

Alternatively, the residue from the hydrogenation of 8.6 g (39.3 mmol) of the HCl salt of **34** was esterified in 250 ml of absolute methanol saturated with HCl. After 24 hr, the mixture was concentrated, and the residue was distributed between aqueous $NaHCO_3$ and CH_2Cl_2. Evaporation of the dried CH_2Cl_2 phase and distillation of the residue gave 4.85 g (67.5% from **34**) of ester **35**: bp 80–84° (1 mm); gc on column a[41] at 123°, retention time 4.5 min; ir 1730 cm^{-1}; nmr (CCl_4) δ 3.59 and 3.63 (3 H, 2 S, CO_2CH_3).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.5; H, 9.4; N, 7.6. Found: C, 65.7; H, 9.1; N, 7.6.

This ester was then hydrolyzed and rearranged to give methylene lactam **36** by stirring overnight at room temperature a solution of 6.21 g (33.9 mmol) of ester **35** dissolved in 35 ml of 60% aqueous methanol containing 2.09 g (52.3 mmol) of NaOH. The solvent was evaporated and to the residue was added 50 ml of acetic anhydride and 2 ml of acetic acid. Rearrangement was effected as described to give 3.5 g (68%) of methylene lactam **36**.

5-Oxo-6-acetoxymethyl-Δ^6-hexahydroindolizine (37). A mixture of 836 mg (5.5 mmol) of methylene lactam **36**, 610 mg (5.5 mmol) of SeO_2, and 30 ml of acetic acid was heated at 85° for 2.5 hr. Cooling was followed by concentration, and the residue was chromatographed on silica gel. Elution with 1% methanol in $CHCl_3$ furnished 640 mg (55%) of allylic acetate **37**: gc on column c[41] at 160°, retention time 13 min; ir 1740, 1665, 1615 cm^{-1}; nmr δ 2.05 (3 H, s), 3.44–4.06 (3 H, m), 4.82 (2 H, s), 6.53 (1 H, m).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.0; H, 7.2; N, 6.7.

5-Oxo-6-hydroxymethyl-Δ^6-hexahydroindolizine (38) was prepared following the procedure of the **a** series from 3.5 g (16.7 mmol) of allylic acetate **37** and 2.75 g (19.9 mmol) of K_2CO_3 in 50 ml of 4:1 methanol–water at room temperature overnight. Allylic alcohol **38** was obtained in 95% yield after chromatography on silica gel: bp (bath) 135–140° (0.1 mm); ir 1600, 1650, 3400 cm^{-1}; nmr δ 1.03–2.77 (6 H, m), 3.23–3.87 (3 H, m), 4.13 (2 H, br s), 6.35 (1 H, unresolved pair of d); mass spectrum mol wt 167.0954 [calcd for $C_9H_{13}NO_2$, 167.0946 (M^+)].

5-Oxo-6-methylene-7-(1-methoxycarbonylpropyl)octahydroindolizine (39) was prepared following the procedure used in the **a** series. From 1.3 g (7.8 mmol) of allylic alcohol **38**, 8.2 g (55 mmol) of trimethyl orthobutyrate,[17] and 34 μl of propionic acid at 150° for 3 hr was obtained 1.9 g (97% yield) of **39**: gc on column a[41] at 175°, retention time 16 min; ir 1600, 1660, 1730 cm^{-1}; nmr (CCl_4) δ 1.00 (3 H, t), 1.27–3.00 (1 H, d, J = 2 Hz).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 66.8; H, 8.2; N, 5.7.

5-Oxo-6-acetoxymethyl-7-(1-methoxycarbonylpropyl)-Δ^6-hexahydroindolizine (41). Claisen product **39** (1.85 g, 7.8 mmol) was oxidized as in the **a** series using 695 mg (6.27 mmol) of SeO_2 in 38 ml of toluene for 3 hr at reflux. Tertiary alcohol **40** (1.4 g) was obtained as a mixture of diastereomers and was immediately rearranged using the procedure of the **a** series (3:2 acetic acid–acetic anhydride, 2 drops of concentrated H_2SO_4, 140°, 3.5 hr) to give 1.45 g (63% from **39**) of hexahydroindolizinone **41**: ir 1630, 1655, and 1735 cm^{-1}; nmr (CCl_4) δ 0.90 (3 H, t, J = 7 Hz), 1.93 (3 H, s), 3.57 (3 H, s), 4.87 (2 H, br s); mass spectrum mol wt 309.1571 [calcd for $C_{16}H_{23}NO_5$, 309.1576 (M^+)].

Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.1; H, 7.5; N, 4.5. Found: C, 61.8; H, 7.4; N, 4.6.

1,8-Dibromo-5-oxo-6-acetoxymethyl-7-(1-methoxycarbonylpropyl)-$\Delta^{6,8}$-tetrahydroindolizine (43) was prepared following the procedure for phenylbromopyridone **26c** using 325 mg (1.05 mmol) of hexahydroindolizinone **41**, 561 mg (3.15 mmol) of NBS, 14 ml of CCl_4, and a trace of AIBN at reflux for 10 min, yield 485 mg (99%). If the reaction was stopped after 5 min the major product obtained was monobromide **42** contaminated with *ca.* 20% of dibromide **43**. Since both products appeared to decompose on standing, dibromide **43** was used immediately in the next step: nmr (CCl_4) δ 0.94 (3 H, t, J = 7 Hz), 1.95 (3 H, s), 3.60 (3 H, s), 3.87 (1 H, t, J = 7 Hz), 4.27 (2 H, m), 4.96 (2 H, s), 5.17 (1 H, d, J = 5 Hz); uv 334 nm.

Dibromotetrahydroindolizinone lactone 44. Dibromide **43** (465 mg, 0.99 mmol) was lactonized using the procedure of the **a** series (25 ml of 1:1 DME–2 N H_2SO_4, 50°, 20 hr) to give 310 mg (79%) of dibromo lactone **44** after chromatographic purification: mp 175–176° dec; nmr δ 1.03 (3 H, t, J = 7 Hz), 1.90 (2 H, m), 2.68 (2 H, m), 3.73 (1 H, t), 4.36 (2 H, m), 5.30 (3 H, m); ir ($CHCl_3$) 1600, 1655, 1740 cm^{-1}; uv 326 nm (ϵ 7070).

Bromotetrahydroindolizine Lactone 45. A solution of 330 mg (0.84 mmol) of dibromide **44** in 5.5 ml of absolute ethanol, 6 ml of ethyl acetate, and 4.25 ml of triethylamine was shaken with 50 mg of 5% Pd/C and hydrogen at 20 psi. After 15 min, the catalyst was removed by filtration and the filtrate was concentrated to ⅕ its original volume. Distribution of the residue between CH_2Cl_2 and 2 N sulfuric acid was followed by washing and drying of the organic layer. Evaporation of the solvent and chromatography on silica gel gave 218 mg (83%) of monobromide **45** and 27 mg (12%) of debromo lactone **47**. The monobromide may be crystallized from carbon tetrachloride: mp 169–170°; ir ($CHCl_3$) 1580, 1645, 1735 cm^{-1}; uv 315 nm (ϵ 4180); nmr δ 1.00 (3 H, t, J = 7 Hz), 1.93 (4 H, m), 3.10 (2 H, t, J = 7 Hz), 3.67 (1 H, t, J = 7 Hz), 4.17 (2 H, t, J = 7 Hz), 5.01 (1 H, d, J = 16 Hz), 5.40 (1 H, d, J = 16 Hz); mass spectrum mol wt 311.0155 [calcd for $C_{13}H_{14}NO_3Br$, 311.0157 (M^+)].

5-Oxo-6-hydroxymethyl-7-(1-carboxypropyl)-$\Delta^{6,8}$-tetrahydroindolizine Lactone (47). Dibromide **44** (330 mg, 0.84 mmol) was hydrogenated and the product was isolated as above to give crude monobromide **45**. This crude was immediately resubmitted to hydrogenation using fresh catalyst and the crude product was chromatographed on silica gel eluting with $CHCl_3$, yielding 185 mg (94%) of lactone **47** after crystallization from CH_2Cl_2–pentane: mp 149–150°; ir ($CHCl_3$) 1585, 1655, 1740 cm^{-1}; uv 303 mm (ϵ 7570); nmr δ 1.00 (3 H, t, J = 7 Hz), 2.10 (4 H, m), 3.14 (2 H, t, J = 7 Hz), 3.55 (1 H, t, J = 7 Hz), 4.11 (2 H, t, J = 7 Hz), 5.23 (2 H, s), 6.05 (1 H, s).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 66.7; H, 6.3; N, 6.0.

CDE analog 48 was prepared following the procedure used for the **a** series from 110 mg (0.47 mmol) of lactone **47** in 2.5 ml of DMF, 57 mg (0.51 mmol) of potassium *tert*-butoxide in 2 ml of DMF, 0.15 ml of *t*-BuOH, 0.15 ml of triethyl phosphite, and O_2 at −25° for 2 hr. The crude product was crystallized from ether–$CHCl_3$ to give 70 mg (60%) of the desired analog **48**: mp 175–177°; ir ($CHCl_3$) 1585, 1655, 1740, 3550 cm^{-1}; uv 302 nm (ϵ 8640); nmr δ 0.95 (3 H, t, J = 7 Hz), 1.78 (2 H, q, J = 7 Hz), 2.20 (2 H, m), 3.10 (2 H, t, J = 7 Hz), 4.10 (2 H, t, J = 7 Hz), 5.03 (1 H, d, J = 16 Hz), 5.50 (1 H, d, J = 16 Hz), 6.40 (1 H, s).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.6; H, 6.1; N, 5.6. Found: C, 62.5; H, 6.0; N, 5.6.

Bromo CDE Analog 46. Bromo lactone **45** (55 mg, 0.26 mmol) was oxidized using the same procedure as for the above CDE ring analog: yield 36 mg (61%); mp 196–197°; ir ($CHCl_3$) 1505, 1650, 1740 cm^{-1}; uv 318 nm (ϵ 6625); nmr δ 0.98 (3, H, t, J = 7 Hz), 2.10 (4 H, m), 3.25 (2 H, t, J = 8 Hz), 4.28 (2 H, t, J = 8 Hz), 5.02 (d, 1 H, J = 17 Hz), 5.57 (d, 1 H, J = 17 Hz).

Anal. Calcd for $C_{18}H_{14}NO_4Br$: C, 47.6; H, 4.3; N, 4.3. Found: C, 47.7; H, 4.2; N, 4.3.

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Registry No. 2c, 43083-13-2; **3c,** 43083-14-3; **4c,** 39065-54-8; **5b,** 17874-76-9; **6c,** 4634-13-3; **6c** methyl *p*-toluenesulfonate, 43083-18-7; **7c,** 43083-19-8; **8b,** 43083-20-1; **9b,** 24202-72-0; **10c,** 43083-22-3; **11b,** 43083-23-4; **12b,** 40163-13-1; **12c,** 40163-17-5; **13,** 43083-26-7; **14a,** 30932-83-3; **14b,** 40318-22-7; **14c,** 43083-29-0; **15c,** 43083-30-3; **16a,** 40163-04-0; **16b,** 40163-14-2; **16c,** 43083-33-6; **17a,** 43083-34-7; **19,** 43083-35-8; **20a,** 43083-36-9; **20b,** 43083-37-0; **20c,** 43083-38-1; **21a,** 40163-05-1; **21b,** 43083-40-5; **21c,** 43083-41-6; **22,** 43083-42-7; **23a** isomer A, 43083-43-8; **23a** isomer B, 43083-74-5; **23b,** 43083-75-6; **23c,** 43083-76-7; **24a** isomer A, 43083-77-8; **24a** isomer B, 43083-78-9; **24b,** 43083-79-0; **24c,** 43083-80-3; **25a,** 40163-07-3; **25b,** 43083-82-5; **25c,** 43083-83-6; **26a,** 40163-08-4; **26c,** 43083-85-8; **27b,** 40163-15-3; **27c,** 43083-87-0; **28a,** 40163-09-5; **28c,** 43083-89-2; **29a,** 40163-10-8; **29b,** 43083-91-6; **29c,** 43083-92-7; **30c,** 43083-93-8; **31a,** 40163-11-9; **31b,** 40163-16-4; **31c,** 40163-18-6; **33,** 40163-19-7; **34** HCl, 43083-00-7; **35,** 40163-20-0; **36,** 40163-21-1; **37,** 43083-03-0; **38,** 40163-22-2; **39,** 43083-05-2; **41,** 40163-23-3; **43,** 43083-06-3; **44,** 40163-24-4; **45,** 40163-25-5; **46,** 40163-26-6; **47,** 43083-10-9; **48,** 40163-27-7; trimethyl orthobutyrate, 43083-12-1.

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