steam for 20 hr. The solvent was evaporated *in vacuo*, the residue was dissolved in 10 ml of water, and the solvent was again evaporated; this process was repeated twice more, and the crystalline residue was twice recrystallized from methanol–acetonitrile to give **11** as the dihydrochloride, $[\alpha]^{25}D$ −7.7 (*c* 1.4, H_2O), −13.4 (*c* 1, 0.2 *M* acetate buffer, pH 5).

α-*N*-Acetyl-2-aminohistamine (10).—A suspension of 5.7 g of **7a** in 200 ml of ethanol was subjected to catalytic hydrogenation, as described above for **4b**. Following removal of the catalyst, the solvent was evaporated *in vacuo* and the residual material was dissolved in 100 ml of water. The solution was extracted with three 100-ml portions of ether and the aqueous layer, containing **10** as its hydrobromide, was applied to a column of Dowex 50W. The column was eluted with dilute ammonium hydroxide, and the effluent was evaporated to dryness. The residual oil was dissolved in ethanol, the solution was decolorized partially with Norit, and the solvent was removed to give 2.3 g of a red-brown, noncrystalline solid. This material could not be crystallized and **10** was characterized as its picrate (Table II).

2-Aminohistamine (12).—A solution of 1.0 g of **10** in 50 ml of 6 *N* hydrochloric acid was heated on steam for 14 hr. The solvent was removed *in vacuo;* to the residual oil was added 50 ml of ethanol and the solvent was evaporated, the process being repeated. The residual oil was dissolved in 100 ml of ethanol, the solution was decolorized with Norit, and the solvent was removed to give 750 mg of a colorless, noncrystalline solid. The amine **12** was characterized as its dipicrate, mp 200–223° dec (95% ethanol).

Registry No.—**1**, 36097-48-0; **3a**, 39037-16-6; **3b**, 39037-17-7; **4a**, 39037-18-8; **4b**, 39004-81-4; **5a**, 39037-19-9; **5b**, 39037-20-2; **6a**, 39050-06-1; **6b**, 39050-07-2; **7a**, 39050-08-3; **7b**, 39050-09-4; **8a**, 39050-10-7; **8b**, 39050-11-8; **9**, 39037-21-3; **10** picrate 39050-12-9; **11**, 39037-22-4; **11** 2HCl, 39037-23-5; **12**, 39050-13-0; **12** dipicrate, 39050-14-1; *N*-acetyl-L-histidine, 2497-02-1; *p*-bromoaniline, 106-40-1; α-*N*-acetylhistamine, 673-49-4.

A Total Synthesis of Camptothecin and Deethyldeoxycamptothecin[1]

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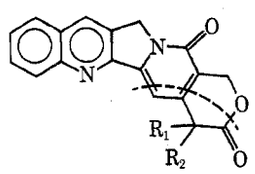
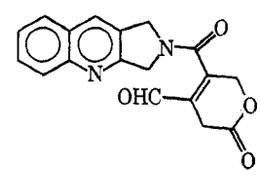
The synthesis of the plant antitumor agent camptothecin, is described. More significantly, the synthesis leads to the pentacyclic lactone **2** in preparative quantities suitable for further study and modification. The scheme involves conversion of the readily available amine **8** to an oxazine amide **7**, which underwent Michael addition with the unsaturated ester **26** leading to the completely functionalized precursor **27**. Borohydride reduction to the tetrahydro-1,3-oxazine **28** followed by cleavage to the aldehyde **29** produced, after borohydride reduction, the hydroxy ester **30**. Acylation of the latter afforded the acetate derivative **41** (R = Me), which was stable to dioxolane cleavage ($BF_3 \cdot Et_2O$) and led to the aldehyde **42** (R = Me). Cyclodehydration of the aldehyde to the pyrrole nucleus gave the dihydropyridone **43** (R = Me), which was aromatized with DDQ to the appropriate pyridone system **45**. Acid hydrolysis then produced the pentacyclic lactone **2** ($R_1 = R_2 = H$), which was converted to racemic camptothecin. A variety of interesting side reactions were encountered during the study, resulting in novel heterocyclic ring systems (*e.g.*, pyrrole oxazines **21**, and *N*-alkyl pyrroles **25**). Certain model experiments having meaningful bearing on the synthesis of camptothecin analogs are also described.

The extensive effort by many groups toward a total synthesis of the plant antitumor agent camptothecin (**1**) has recently culminated in four successful achievements.[3–6] The literature also contains a large number of studies directed toward a total synthesis[7–11] which show varying degrees of promise.

We describe our effort which led to the title compound **1** and is based upon initially obtaining deethyldeoxycamptothecin (**2**) which has already been readily converted to camptothecin by alkylation and hydroxylation of the active methylene group present in the molecule.[6] Construction of **2** was considered most efficient by linking two major units as designated by the dotted line. The precursor **3** was therefore highly desirable, since a cyclodehydration process of the aldehyde to the active methylene group (2 position of quinoline) should produce **2**. Formation of **3** was envisioned as being derived from the open-chain aldehyde **4** and the link-up to form the latter (dotted line) represented the key synthetic transformation in the total synthesis. The formation of **4** required that a Michael addition be performed using the unsaturated ester **5** and the hydroxy amide **6** (or in a masked form, *i.e.*, **7**). Since it is quite unreasonable to expect



1, R_1 = Et; R_2 = OH
2, $R_1 = R_2$ = H



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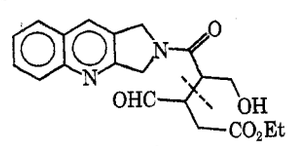

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(1) This study was supported by the National Institutes of Health.

(2) Please direct all communications concerning this paper to Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.

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

(4) R. Volkman, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **93**, 5576 (1971).

(5) M. C. Wani, H. F. Campbell, G. A. Brime, J. A. Kepler, and M. E. Wall, *ibid.*, **94**, 3631 (1972), and earlier studies cited therein.

(6) (a) M. Boch, T. Korth, J. Nelke, D. Pike, H. Radunz, and E. Winterfeldt, *Chem. Ber.*, **105**, 2126 (1972). (b) After this manuscript was submitted, a fifth synthesis was reported: C. Tang and H. Rappoport, *J. Amer. Chem. Soc.*, **94**, 8615 (1972).

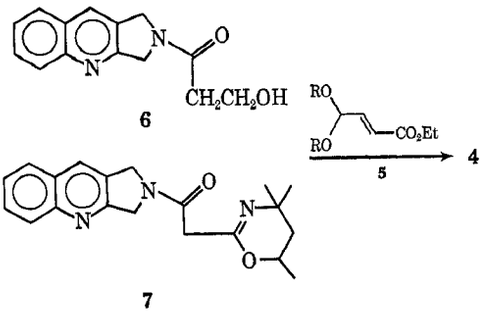
(7) E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *ibid.*, **89**, 6741 (1967).

(8) T. Kametani, H. Nemoto, H. Takeda, and S. Takano, *Tetrahedron*, **26**, 5753 (1970).

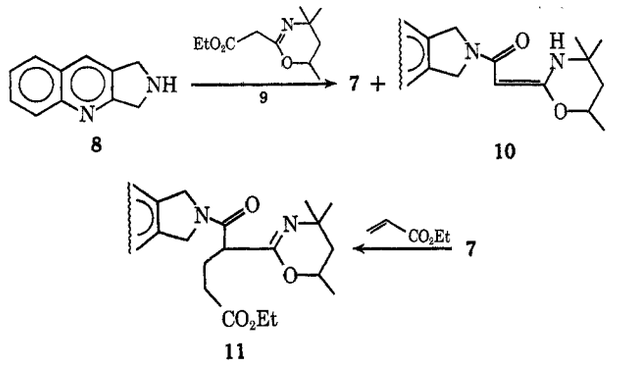
(9) M. Shamma and L. Novak, *ibid.*, **25**, 2275 (1969).

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

(11) R. F. Borch, C. V. Grudzinskas, D. A. Peterson, and L. D. Weher, *J. Org. Chem.*, **37**, 1141 (1972).

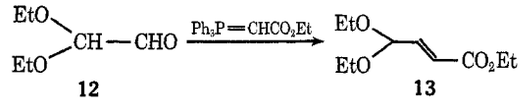


the hydroxy amide **6** to undergo a Michael addition at the α carbon to the amide group, the oxazine amide **7** was viewed as a plausible synthetic equivalent. The conversion of the oxazine ring to an aldehyde function and ultimately to a primary alcohol has already been demonstrated in previous synthetic efforts from this laboratory.[12] The preparation of **7** was accomplished in 85% yield by heating the readily available pyrrolo-[3,4-*b*]quinoline **8**[13] with the ester oxazine **9**[14] in the

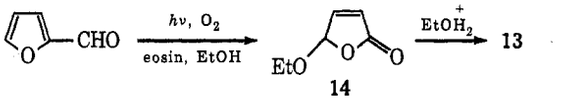


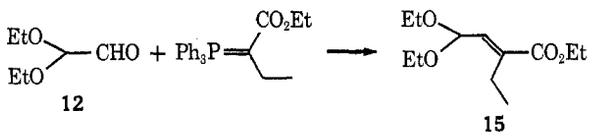
presence of DMF. The oxazine amide was obtained as the nonconjugated tautomer **7**, although exposure to base or heat converted it to an equilibrium mixture containing the exocyclic system **10**. A model experiment to ascertain the ability of **7** to undergo Michael addition with an α,β-unsaturated ester was proven successful when a solution of the oxazine amide and ethyl acrylate gave an 80% yield of the Michael adduct **11** after heating in ethanol overnight.

The second key moiety now necessary was the unsaturated ester containing a potential or masked aldehyde function **5**. The simplest system chosen was the diethyl acetal **13**, which was readily prepared by Wittig coupling of the known glyoxal diethyl acetal **12**.[15] Although the seemingly straightforward route gave **13** in pure trans form, the drawback to this method lay in the tedious procedure for obtaining **12** in workable

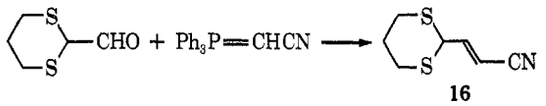


quantities. The best yield of **12** never exceeded 30% after various modifications for cleaving glyceraldehyde ethyl acetal[16] using lead tetraacetate or potassium permanganate (Experimental Section). The most convenient and efficient method for the preparation of **13** was found in the photooxidation[17] of furfural, which produced the lactone **14** in 56% yield. Hydrolysis of



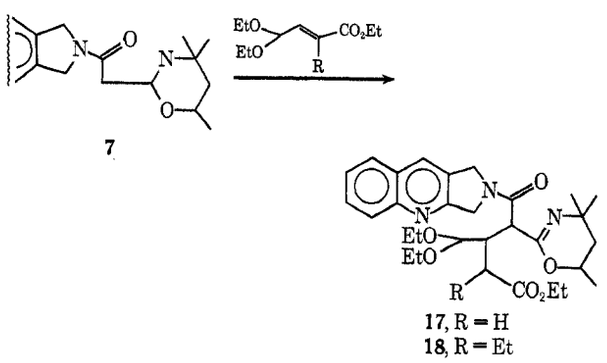


the latter in acidic ethanol led to the desired ester, **13**. In a concomitant effort to arrive at alternate precursors to **1**, the α-ethyl unsaturated ester **15** was also prepared by Wittig coupling to **12**. It was anticipated that the camptothecin precursor, if successfully reached, would then possess the requisite ethyl group, thus eliminating the need for introduction into the target molecule, **2**. An additional route to suitable electrophilic olefins analogous to **13** was devised[18] resulting in the dithiane derivative **16**. This system would also be



expected to serve as a Michael acceptor for **7** and both the nitrile and dithiane functions could be transformed into the needed ester and aldehyde, respectively.

With routes to three potential Michael acceptors in hand (**13**, **15**, and **16**) attention was turned to joining these to **7**, which, if successful, would afford the highly functionalized precursor **4**. After a series of experiments under varying conditions, the desired Michael adduct **17** was formed in 75% yield by heating **7** and **13**



in a sealed tube at 145° for 40 hr. Similar treatment of the ethyl-substituted acrylic ester **15** gave **18** but in only 22% yield. Owing to the poor yield of the latter product, coupled once again with the difficulty already mentioned for obtaining **12**, this approach was abandoned in favor of the readily accessible product **17**.

(12) A. I. Meyers and E. W. Collington, *Tetrahedron*, **27**, 5979 (1971).

(13) M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *Chem. Commun.*, 404 (1970). We wish to thank Dr. Robert Engle, Drug Development Branch, National Cancer Institute, for generous supplies of the hydrobromide salt of **8**.

(14) A. I. Meyers, A. Nabeya, W. A. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).

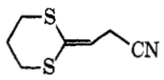
(15) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 514 (1935); L. A. Yanovskaya, R. N. Stepanova, G. A. Kogan, and V. F. Kucherov, *Chem. Abstr.*, **59**, 7368c (1963).

(16) E. J. Witzeman, W. L. Evans, H. Hass, and E. F. Schroeder, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 307.

(17) F. Farina, M. Lora-Tomayo, and M. V. Martin, *Ann. Real. Soc. Espana Fiz. Quim. (Madrid)*, **B60**, 715 (1964); *Chem. Abstr.*, **63**, 4213c (1965). J. J. Degraw, *Tetrahedron*, **28**, 967 (1972), described recent studies leading to the lactone **14**.

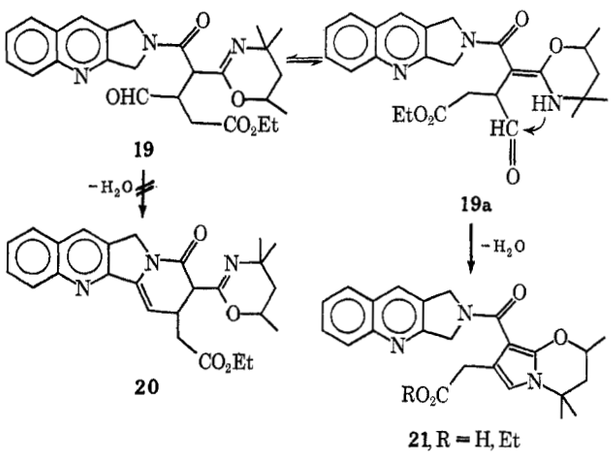
(18) A. I. Meyers and R. C. Strickland, *J. Org. Chem.*, **37**, 2579 (1972).

The Michael addition of **7** with the dithiane system **16** failed to produce any product other than recovered starting materials, which included the isomeric ethylene thioacetal **16a**. The facile isomerization of **16** to **16a** has already been discussed.[18]



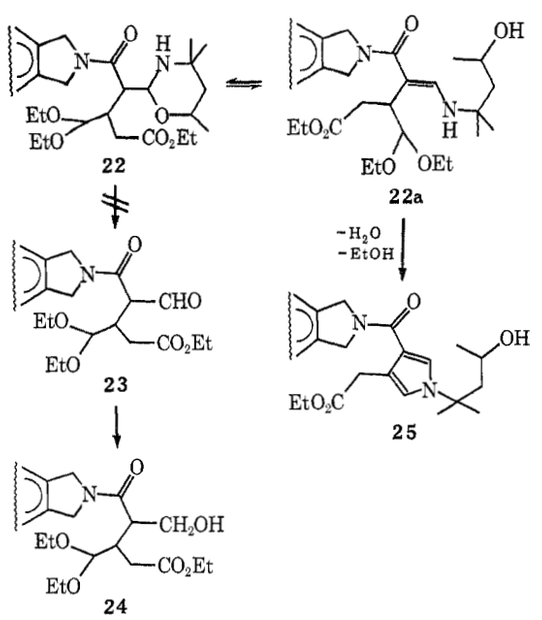
16a

The next step in the synthesis obviously called for the release of the aldehyde from its ketal masking group in **17** followed by condensation of **19** to the



dihydropyridone **20**. When this sequence was attempted under various acidic conditions, only the fused pyrrolooxazine **21** could be isolated. This product arises from the kinetically more favored cyclodehydration of the aldehyde function with tautomer **19a**. This pyrrole cyclization was found to be a general process and was recently demonstrated with a number of other examples.[19]

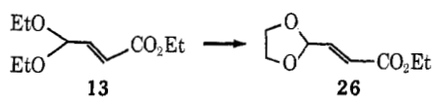
In an effort to circumvent this undesired reaction, the oxazine ring in **17** was reduced according to published procedures[14] to the tetrahydro derivative **22**.



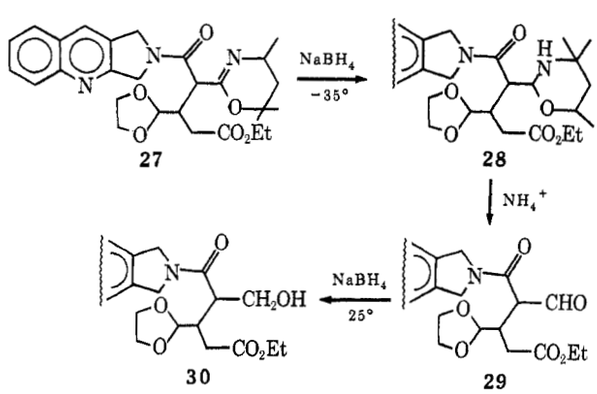
(19) A. I. Meyers, E. W. Collington, and T. A. Narwid, *J. Heterocycl. Chem.*, **8**, 875 (1971).

The goal at this point was to hydrolyze the tetrahydro-1,3-oxazine ring to the aldehyde **23** and *in situ* reduction to the carbinol **24** as performed in the earlier synthetic effort.[12] However, the only product obtained from hydrolytic experiments was the monocyclic pyrrole **25**, presumably derived from the open-chain tautomer **22a**.

The failure in selectively removing the tetrahydro-1,3-oxazine ring in **22** so that the aldehyde **23** could be prepared suggested that a more stable acetal was required which would remain intact during the conversion **22** → **23**. Since the 1,3-dioxolane masking group is more resistant to hydrolytic cleavage than acetals,[20] this modification was considered. Transacetalization of **13** to its dioxolane **26** was readily ac-



complished by treatment with ethylene glycol catalyzed by boron trifluoride etherate. Michael addition with **7** at 150° or in hot DMF gave the corresponding adduct **27** in good yield as a crystalline product. This is in

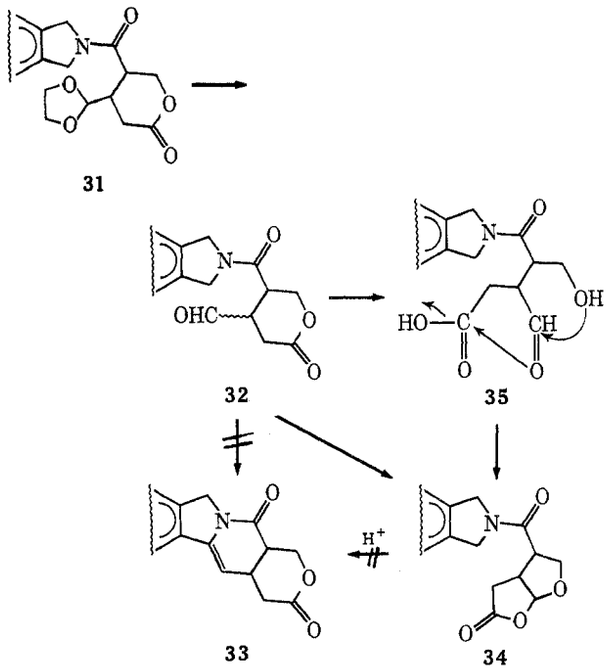


contrast to the adduct **17**, which was obtained as a foam and required purification *via* preparative layer chromatography. Reduction with aqueous sodium borohydride smoothly gave the tetrahydro-1,3-oxazine **28**. Mild hydrolysis using ammonium chloride (ethanol–water) led to the desired aldehyde, **29**, *with the dioxolane moiety remaining intact.* Routine reduction using sodium borohydride in ethanol resulted in the sought-after carbinol **30**, which now represented the synthetic equivalent of **4**.

The lactone **31** was readily prepared by heating the hydroxy ester **30** with sodium hydride in THF. It is of interest to note that alkaline saponification of **30** followed by neutralization did not spontaneously produce the lactone, which for camptothecin is known to form with great facility.[3–6] However, the lactone could be formed by treatment of the hydroxy acid with dicyclohexylcarbodiimide.

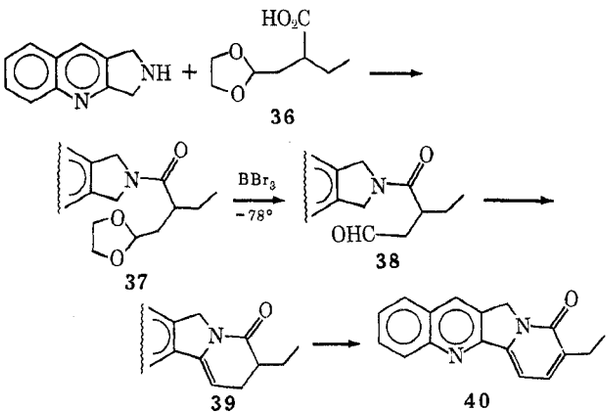
Attempts to release the aldehyde function to **32** followed by cyclodehydration to the pyridone **33** was once again frustrated by a facile rearrangement to the etiolactone **34**. A variety of Lewis acid catalysts were added to the dioxolane and in every case the formyl group preferred reaction with the lactone ring (or the hydroxy acid, **35**) rather than the pyrrolidine ring. The formation of the etiolactone may be considered some-

(20) J. F. W. McOmie, *Advan. Org. Chem.*, **3**, 248 (1963).



what analogous to the pyrrole formation described earlier (**19a** → **21**). Attempts were made to utilize **34** as a precursor to the pyridone **33**, since the former is, in effect, a "protected" aldehyde function which might exist in aqueous medium along with its open-chain equilibrium partner, **35**. Efforts in this direction proved fruitless owing to the stability of **34** under numerous aqueous acidic conditions.

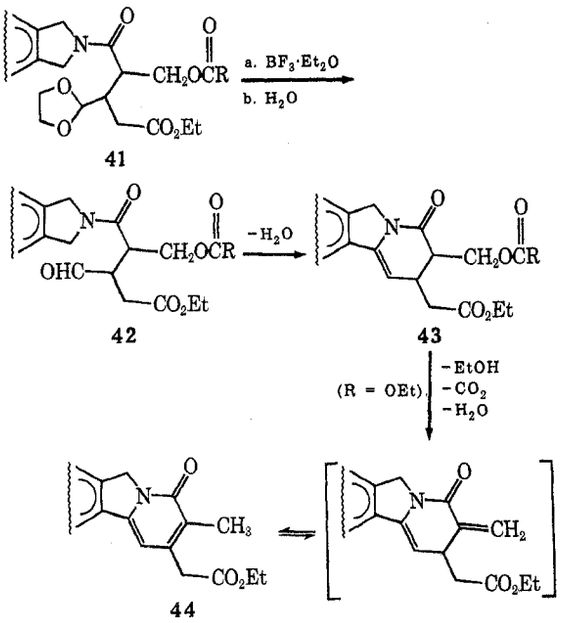
The failure to achieve a cyclodehydration of the aldehydes **32** and **19** (or **17**) to their respective dihydropyridones **33** and **20** prompted a study to ascertain whether this ring closure was indeed a feasible one. In this regard the dioxolane acid **36**[21] was chosen as a



suitable source for a model pyridone synthesis. Condensation with the pyrroloquinoline using dicyclohexylcarbodiimide gave the amide **37**, which surprisingly could not be transformed to the aldehyde **38** under a variety of aqueous acid conditions (1–3 *N* $HClO_4$, HCl, TsOH, TFA in THF, AcOH, EtOH solutions). The recovery of **37** in most cases was unexpected in view of the extensive literature[20] on dioxolane cleavages. The aldehyde was eventually obtained in 94% yield by adding boron tribromide to a dichloromethane solution of **37** at −78° followed by warming to room temperature.[22]

The aldehyde was cleanly cyclized (80%) to the dihydropyridone **39** using a catalytic quantity of trifluoroacetic acid in refluxing toluene. When the cyclization was carried out in benzene at 80°, only trace amounts of the pyridone could be detected using ultraviolet techniques (244 nm). The model study therefore reaffirmed the expectation that a pyridone may be formed efficiently from an aliphatic aldehyde. The addition of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to a benzene solution of **39** resulted in a quantitative conversion to the aromatized pyridone **40**.

Returning now to the hydroxy ester **30**, some modification was necessary to avert the etiolactone formation. The lactone **31** was unsuitable owing to its inability to remain intact during the removal of the dioxolane protecting group. The hydroxy ester was converted into its carbonate ester **41** (R = OEt) in the hope that this



moiety would be stable both to the dioxolane cleavage to **42** and the cyclodehydration to the pyridone **43**. Aqueous acid hydrolysis once again resulted in the etiolactone **34** and similar disappointing results were also obtained for corresponding acetate derivative **41** (R = Me). It was subsequently found that addition of the acetate or the carbonate ester **41** to excess boron trifluoride etherate at −78° followed by quenching this solution in cold water gave approximately 60% cleavage of the dioxolane to the aldehydes **42** (R = OEt and R = Me). The carbonate ester of **42** was treated with trifluoroacetic anhydride in refluxing toluene and the reaction was followed by ultraviolet spectroscopy. A pyridone was indeed formed but uv examination showed it to be aromatized. Further examination confirmed that the product from the cyclization of the carbonate aldehyde **42** was the methyl-substituted pyridone **44**. This material undoubtedly arose from expulsion of carbon dioxide and water from the carbonate, giving the exocyclic methylene tautomer of **44**. The acetate of **42** was next

(21) This was chosen since it was available from another study and possessed the necessary functionality to achieve our purpose.

(22) Although this technique worked exceedingly well in the case cited, an examination into its generality with various other dioxolanes proved disappointing.

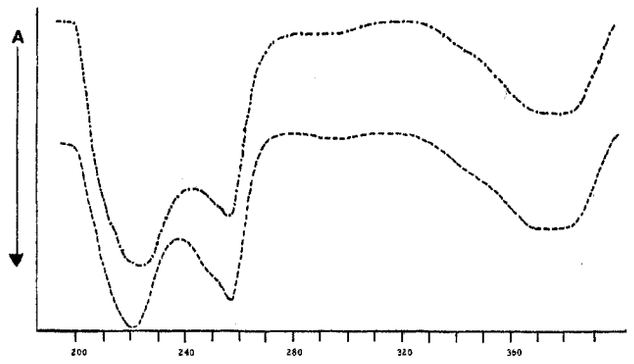
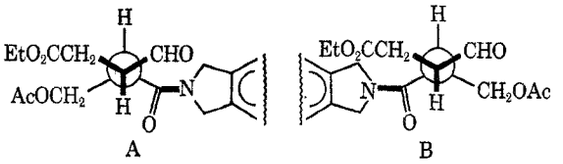


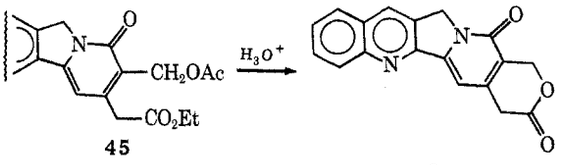
Figure 1.—Ultraviolet spectrum (95% ethanol) of deoxydeethylcamptothecin (-·-·-·) and camptothecin (------).

subjected to cyclization conditions using benzene as the solvent and trifluoroacetic acid or acetic anhydride as the catalyst. In this fashion the dihydropyridone **43** (R = Me) was obtained, which was aromatized to the pyridone **45** in 21% overall yield from the aldehyde **42**. The low yield of cyclization of the aldehyde **42** to the pyridone **43** (R = Me) was due to a mixture of two aldehyde diastereomers in **42**. Thus, when the dioxolane **41** was cleaved with boron trifluoride there were present in the product two aldehyde protons in the ratio 3:1. Owing to the low yield of cyclization, it was felt that one of these diastereomers was incapable of cyclizing because of an unfavorable conformation. Inspection of rotamer structures for **42** reveals that only A is conformationally equipped to cyclize to the



methylene group of the pyrroloquinoline, whereas the other diastereomer has B as its most stable conformer. This hypothesis was confirmed when the mixture of aldehydes **42** was heated in methanol containing silica gel and isomerization occurred to a new ratio (the lesser one originally present in the mixture became the predominant product). When the isomerized material was subjected to acid-catalyzed cyclodehydration in an attempt to prepare the dihydropyridone **43**, only a trace amount was detected; the remainder of the reaction mixture consisted of starting material. Thus, it may be concluded that only the major isomer, formed initially during the boron trifluoride cleavage, may serve as a useful precursor in the synthetic scheme and epimerization of B to A does not take place during the acidic cyclizing conditions.

With the desired dihydropyridone **43** in hand, aromatization to the pyridone **45** was readily achieved



45 2

by DDQ oxidation in benzene. The camptothecin precursor **2** was formed by treatment of the acetate ester with dilute sulfuric acid, causing hydrolysis of both ester functions and spontaneous closure of the lactone ring. Comparison of the ultraviolet spectrum of **2** with that of camptothecin (Figure 1) confirmed the pentacyclic lactone structure. The recent report by Winterfeldt[6] on the total synthesis of camptothecin describes the formation of **2**, although no physical data were given. Since the ethylation and hydroxylation of **2** has already been shown by Winterfeldt to lead to camptothecin, the preparation of this substance formally concluded the total synthesis. Nevertheless, **2** was treated as a suspension in dimethoxyethane (DME) with excess sodium hydride and afforded only moderate yields of the deoxycamptothecin **1** (R_1 = Et; R_2 = H). Also present in the product of this reaction was camptothecin, presumably formed by air oxidation of the anion of **1**. Hydroxylation of the tertiary carbon in **1** (R_1 = Et; R_2 = H) has already been noted by Danishefsky[4] to occur on standing in air. No further effort was expended or is planned in this direction in light of the results by Winterfeldt coupled with the recent clinical data[23] questioning the antitumor activity of camptothecin. It now appears that **2** may be a more valuable system for further study in that it may be alkylated with substituents other than ethyl in an attempt to find enhanced pharmacological activity.

In summary, this approach has been shown to produce the pentacyclic ring system of camptothecin and further effort could conceivably increase the overall efficiency of the synthesis. By far the most serious synthetic difficulty *via* this approach is the alkylation of **2**, which proceeds poorly, and this has been noted by other workers.[4,6,6a] Further studies should be directed toward alkylation of the ester **45**, whose solubility is far greater than that of the lactone **2** and would ultimately provide the α-alkylated lactone upon hydrolysis.

Experimental Section[24]

Pyrrol[3,4-*b*]quinoline (8).—This material was prepared according to the method previously described[13] and also received from the National Cancer Institute as a crude dihydrobromide salt. The unstable free base was liberated as follows. The salt (20 g) was added to 200 ml of dichloromethane in a separatory funnel and treated with 30 ml of 40% sodium hydroxide and 25 ml of water. After shaking for several minutes the salt dissolved and the organic layer separated. The aqueous solution was further extracted with dichloromethane and the combined extracts were dried (K_2CO_3) and concentrated, leaving 9.5 g of tan solid. Purification was achieved by sublimation (90–110°, 0.05 mm), mp 103–104.5°. The material darkens on standing in the atmosphere: ir (KBr) 3200, 1640, 1570 cm^{-1}; nmr ($CDCl_3$) δ 2.4 (NH), 4.4 (br s, 4), 7.3–8.2 (m, 5).

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.59; H, 5.92; N, 16.60.

Oxazine Amide 7.—A mixture consisting of 11.2 g (66 mmol) of **8**, 17.1 g (80 mmol) of ester oxazine **9**,[14] and 3.5 ml of dimethylformamide was placed in a flask equipped with a distillation

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(24) All melting points and boiling points are uncorrected. Microanalyses were performed by Midwest Micro Labs, Indianapolis, Ind. Nmr spectra were taken on a Varian T-60 using tetramethylsilane as an internal standard. Mass spectra were taken on an AEI MS-9 at 70 eV. Ultraviolet and infrared spectra were taken on Perkin-Elmer 202 and 257 instruments, respectively. Preparative layer chromatography was performed using Merck AG, PF_{254} silica gel containing a fluorescent indicator, while column chromatography employed Merck AG, 0.05–0.2 mm silical gel. Thin layer chromatography utilized Eastman chromagram silica gel sheets.

head and lowered into an oil bath preheated to 145–150°. The temperature was raised to 165–170° and maintained for 3.5 hr, upon which the mixture solidified. After cooling, the crude product was recrystallized (ethanol), affording 18.3 g (83%): mp 174–180° (decomposition begins at 168°); ir (Nujol) 1680, 1655 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (s, 6), 1.4 (s, 3), 1.6 (m, 2), 3.4 (s, 2), 4.3 (m, 1), 5.0 (br s, 4), 7.4–8.2 (m, 5); uv (EtOH) 212, 231 nm.

Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 70.94; H, 6.83; N, 12.44.

Michael Addition of 7 with Ethyl Acrylate 11.—A solution of the oxazine amide (189 mg, 0.56 mmol) and ethyl acrylate (52 mg, 0.56 mmol) in 2.5 ml of ethanol was heated to reflux for 20 hr. The solvent was removed and the viscous residue was recrystallized from ethanol to give 101 mg (80%) of **11**: mp 156–157°; ir (Nujol) 1740, 1660, 1630 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.36; H, 7.06; N, 9.71.

Glyoxal Diethyl Acetal 12.—A solution of *dl*-glyceraldehyde diethyl acetal[16] (29.5 g, 0.18 mol) in dry benzene, under nitrogen, was cooled in an ice bath and treated with dry lead tetraacetate (85 g, 0.19 mol) in small portions from Gooch tubing. When the addition was complete, the suspension was stirred at 25° for 1 hr and filtered. The filtrate was treated with 40 g of anhydrous sodium carbonate in small portions while cooling. The suspension was filtered again and the filtrate was concentrated. The residue was taken up in ether, filtered, and evaporated to leave a colorless oil (21.5 g). The ir and nmr spectrum exhibited only a trace amount of carbonyl absorption and aldehyde proton (9.6 ppm), respectively. This product was a dimer or trimer of the desired product **12**. Monomerization was achieved by heating 10-g samples under nitrogen at 270–290° (Wood's metal bath) and collecting the distillate in a Dry Ice–acetone trap. The distillate consisted of a mixture of solid and liquid material, which was separated by filtration, and the solid was washed with ether. The ether washings were combined with the filtrate and the mixture was distilled. The aldehyde boiled at 65° (55 mm), yielding 10.3 g (31%), and could be stored at −20° under nitrogen for 5 days without significant polymerization: ir (film) 1740 cm^{-1}; nmr (CCl_4) δ 1.3 (t, 6), 3.7 (d of q, 4), 4.5 (d, J = 2, 11 Hz, 1), 9.6 (d, J = 2 Hz, 1).

Ethyl 4,4-Diethoxy-2-butenoate (13).—The modified Wittig technique described by Bestmann[25] was employed. A suspension of methyltriphenylphosphonium iodide (6.15 g, 15 mmol) in dry benzene (40 ml) at 0°, under nitrogen, was treated dropwise with *n*-butyllithium (9.51 ml, 15% in hexane). The dark red mixture was stirred for 1 hr at 25° and a solution of ethyl chloroformate (0.82 g, 76 mmol) in 5 ml of benzene was added. After 30 min, a solution of glyoxal diethyl acetal **12** (1.0 g, 7.6 mmol) in 5 ml of benzene was added. The mixture was stirred for 16 hr at 25° and quenched in water. Extraction with ether, drying (K_2CO_3), and concentration produced a residue, which was taken up in pentane and filtered to remove triphenylphosphine oxide. The pentane solution, after concentration, provided an oil which gave upon distillation 0.92 g (60%) of **13**: bp 65° (0.4 mm) [lit.[16] bp 70–73° (0.3 mm)]; ir (film) 1725 cm^{-1}; nmr (CCl_4) δ 1.2 (t, 6), 1.3 (t, 3), 3.6 (d of q, 4), 4.2 (q, 2), 5.0 (d of d, 1), 6.1 (d of m, J = 16 Hz, 1), 6.8 (d of d, J = 4, 16 Hz, 1).

Ethyl 2-Ethyl-4,4-diethoxy-2-butenoate (15).—The procedure was the same as described for **13**. From *n*-propyl triphenylphosphonium bromide (2.93 g, 7.6 mmol), *n*-butyllithium (4.76 ml, 15% w/w in hexane), ethyl chloroformate (0.41 g, 3.8 mmol), and glyoxal diethyl acetal (0.5 g, 3.8 mmol), the α-ethyl unsaturated ester **15** was obtained as a colorless oil: bp 77–78° (0.4 mm); 0.67 g (76%); ir (film) 1730 cm^{-1}; nmr (CCl_4) δ 0.8–1.4 (three sets of overlapping triplets, 12), 2.3 (q, 2), 3.5 (d of q, 4), 4.2 (q, 2), 5.2 (d, J = 7 Hz, 1), 6.5 (d, J = 7 Hz, 1).

Preparation of 13 from Photooxidation of Furfural.—Freshly distilled furfural (50 g, 0.52 mol), 29 mg of eosin, and 229 mg of 2,4-di-*tert*-butyl-4-methylphenol dissolved in 430 ml of absolute ethanol were placed in a Pyrex photochemical reaction vessel fitted with an oxygen inlet (fritted disc) and reflux condenser. The entire reaction vessel was then surrounded by aluminum foil and the oxygen was bubbled through the solution at a rapid rate. The light source was turned on (Sylvania FBD 500W, 120 V) and kept cool by a rapid stream of air. Irradiation was carried out for 34 hr, when an additional 25 mg of eosin was introduced and irradiation was continued for 24 hr longer. The progress of the reaction was followed by vpc analysis (UCON-98, 10% on 80–100 Chromosorb W, 6-ft column). When inspection indicated that the reaction was >90% complete, the lamp was turned off and the ethanol was removed *in vacuo*. The residual amber oil was distilled, bp 71–72° (2.8 mm), to give 37 g (56%) of the lactone **14**: ir (film)[17,26] 3100, 1795, 1760 cm^{-1}; nmr ($CDCl_3$) δ 1.4 (t, 3), 3.9 (d of q, 2), 6.0 (d, J = 0.5 Hz, 1), 6.3 (d, J = 6 Hz, 1), 7.4 (d, J = 6 Hz, 1).

Conversion of **14** to the unsaturated ester **13** was achieved by heating to reflux a solution containing 60 g (0.46 mol) of the lactone, 20 ml of boron trifluoride etherate, and 500 ml of absolute ethanol. Removal of samples at 30-min intervals revealed (vpc) that two olefins (cis and trans) were being formed with the cis isomer predominating at the early stages. After 4 hr of reflux, the mixture stabilized to a 4:1 ratio of trans to cis and the heating was terminated. A third, higher boiling component, was also present and was presumed, by cursory nmr examination, to be the Michael addition product of ethanol to the unsaturated ester **13**. The ethanol solution was cautiously treated with anhydrous sodium bicarbonate and the solution was filtered and concentrated. The resulting oil was triturated with ether and filtered to a clear solution. After removal of the ether, distillation was carried out using a 12-in. Vigreux column affording 37 g (40%) of **13** from the fraction boiling at 72–82° (2 mm). The product consisted of a cis–trans mixture (80:20).

Preparation of Dioxolane Unsaturated Ester 26 from 13.—A solution containing 36.3 g (0.18 mol) of **13**, 16.6 g (0.27 mol) of ethylene glycol, and 15 ml of boron trifluoride etherate was stirred at room temperature for 2–4 hr and then treated with 20 ml of water and solid sodium bicarbonate. Upon becoming neutral, the mixture was extracted three times with chloroform, dried (Na_2SO_4), and concentrated. Vpc examination of the residue revealed a small quantity of the diethoxy derivative **13** still present, so the crude product was subjected to 0.3 equiv of ethylene glycol and 5 ml of boron trifluoride etherate. After 2 hr, the reaction was worked up as above and the crude material was totally devoid of **13**. Distillation (bp 83–88°, 2 mm) gave 17.0 g (58%) of the dioxolane derivative as a 10:1 mixture of trans and cis isomers: ir (film) 2990, 2890, 1720, 1660 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (t, 3), 4.0 (s, 4), 4.3 (q, 2), 5.5 (d, 0.85 H, J = 4 Hz), 6.2 (m, 1.15 H, J = 4 Hz), 6.8 (d of d, 0.9 H, J = 4, 16 Hz).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.57; H, 7.12.

Michael Adduct 17.—A mixture consisting of 0.88 g of the diethoxy acetal **13**, 1.1 g of the oxazine amide **7**, 4.5 ml of absolute ethanol, and 5 drops of a sodium ethoxide solution (from 20 mg of sodium and 0.4 ml of ethanol) was heated in a sealed tube at 145–147° for 42 hr. Upon cooling in a Dry Ice–acetone bath, the tube was opened and the solution was concentrated *in vacuo*. The residue was dissolved in ether and, after standing for 1 hr, the precipitate of unreacted oxazine amide **7** was removed (0.09 g) and the filtrate was placed on five 20 × 40 cm plates coated to 1.5 mm with silica gel (Merck PF_{254}). The plates were eluted with acetone–benzene (1:1) and the desired band (R_f 0.76) was recovered with hot methanol. The total yield of **17** was 1.25 g (78%) as a foam: ir (film) 1735, 1675–1650 cm^{-1}; nmr ($CDCl_3$) δ 0.8–1.8 (m, 21), 2.6 (d of d, 2), 3.3 (m, 1), 3.6 (d of q, 4), 4.1 (m, q, 3), 4.6 (d, 1), 5.0 (s, 2), 5.2 (m, 2), 7.4–8.2 (m, 5); *m/e* 539.

Anal. Calcd for $C_{30}H_{41}N_3O_6$: C, 66.77; H, 7.66; N, 7.79. Found: C, 66.41; H, 7.84; N, 7.74.

Michael adduct 18 was prepared in the same manner as the adduct **17** by use of the α-ethyl unsaturated ester **15** and the oxazine amide **7**. The crude product, after being placed on a preparative layer plate (1.5 mm, 20 × 40 cm) and eluted with benzene–acetone (3:2), gave a band (R_f 0.48) which was removed and washed with hot methanol. The residue was a pale yellow glass: ir (film) 1730, 1667, 1655 cm^{-1}; nmr ($CDCl_3$) δ 0.8–2.0 (m, 26), 2.8–3.2 (br m, 1), 3.6 (m, 5), 4.2 (q, m, 3), 4.6 (m, 1), 5.0 (s, 2), 5.3 (br s, 2), 7.4–8.2 (m, 5).

Anal. Calcd for $C_{32}H_{45}N_3O_6$: C, 67.74; H, 7.90; N, 7.14. Found: C, 67.70; H, 7.99; N, 7.40.

Pyrrolooxazine 21 (R = H).—The Michael adduct **17** (302 mg, 0.56 mmol) was added to 3.5 ml of 6% hydrochloric acid and the solution was stirred at room temperature for 21 hr. The precipitate which formed (120 mg) was collected on a filter. The

(25) H. J. Bestmann and H. Schulz, *Angew. Chem.*, **73**, 27 (1961).

(26) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denney, G. O. Schenk, and K. H. Schulte-Elte, *Tetrahedron*, **23**, 2583 (1967).

solid was added to water and the mixture was adjusted to pH 7 with sodium carbonate solution. The solution was extracted with dichloromethane, dried ($MgSO_4$), and concentrated, leaving a colorless, crystalline solid, 86 mg (37%). Recrystallization from ethanol gave pure material: mp 188–189° (carbon dioxide evolution followed by resolidification, mp 238–239°); ir (KBr) 3320, 3025, 2600, 1750, 1575, 1545 cm^{-1}; nmr ($CDCl_3$) δ 1.6 (s, d, 10), 2.0 (t, 2), 3.6 (s, 2), 4.6 (m, 1), 5.2 (br s, 4), 6.4 (s, 1), 7.6–8.3 (m, 5).

Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.45; H, 6.13; N, 10.09.

The product resulting from the decarboxylation of **21** (R = H) and melting at 238–239° was found to be the methyl derivative (RO_2CCH_2 in **21** = CH_3) by heating 50 mg of **21** on a hot stage at ~250°. Recrystallization of the crude material from ethanol, mp 238–239°, showed ir (film) 3020, 1620, 1540 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (s, d, 10), 1.9 (d, 2), 2.1 (s, 3), 4.4 (m, 1), 5.1 (br s, 4), 6.1 (d, J = 2 Hz, 1), 7.5–8.1 (m, 5).

Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.58; H, 6.71; N, 11.19. Found: C, 73.49; H, 6.70; N, 11.20.

Pyrrolooxazine 21 (R = Et).—Heating a solution of **17** (220 mg, 0.41 mmol) in 5 ml of xylene containing 7 mg of *p*-toluenesulfonic acid and 2 ml of water for 18 hr gave, after evaporation of the solvent, a gummy solid. The latter was chromatographed on a preparative layer plate (1.5 mm) using benzene–acetone (2:1) as the eluent. The band with R_f 0.4 was cut from the plate and washed with hot methanol. After concentration, there was obtained 141 mg (78%) of the pyrrolooxazine: mp 88–89°; ir (film) 3010, 1735, 1620 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (t, 3), 1.5 (m, 9), 2.0 (d, 2), 3.7 (s, 4), 4.1 (q, 2), 4.4 (m, 1), 5.2 (s, 4), 6.3 (s, 1), 7.4–8.2 (m, 5); *m/e* 447.

Anal. Calcd for $C_{26}H_{29}N_3O_4$: C, 69.78; H, 6.53; N, 9.39. Found: C, 68.85; H, 6.41; N, 8.82.

Reduction of Michael Adduct 17 to the Tetrahydro-1,3-oxazine 22.—A solution of the Michael adduct **17** (200 mg, 0.37 mmol) in 10 ml of tetrahydrofuran–ethanol (1:1) was cooled to −40° in a Dry Ice–acetone bath. A solution of sodium borohydride (4 mg, 0.37 mmol in 0.75 ml of water containing a drop of 20% sodium hydroxide) was added dropwise simultaneously with 10% hydrochloric acid solution such that the pH of the reaction remained at 5 and the temperature at −35 to −45°. After the addition was complete, the temperature was kept at −40° for 1 hr and the mixture was poured into 10 ml of water. The solution was rendered alkaline by the addition of 20% sodium hydroxide and then extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated, leaving 185 mg of crude **22**. Purification on preparative layer chromatography using acetone–benzene (1:1) as the eluent provided 120 mg (60%) of pure **22**: mp 37–40°; ir (film) 3220, 1740, 1660 cm^{-1}; *m/e* 541.

Anal. Calcd for $C_{30}H_{43}N_3O_6$: C, 66.52; H, 8.00. Found: C, 66.30; H, 7.76.

Pyrrote 25.—A solution of the tetrahydro-1,3-oxazine **22** (70 mg) in 20 ml of wet benzene containing 10 mg of *p*-toluenesulfonic acid was heated to reflux with a Dean–Stark trap for 18 hr. After cooling, the solution was evaporated and the residue was placed on a preparative layer plate. Elution with acetone–benzene (1:1) provided a band (R_f 0.28) which was cut from the plate and removed with methanol, giving 19 mg (32%) of a foam: ir (film) 3300, 1740, 1620 cm^{-1}; nmr ($CDCl_3$) δ 1.1 (d, 3), 1.2 (t, 3), 1.2 (br, OH), 1.6 (s, 3), 1.7 (s, 3), 1.9 (m, 2), 3.8 (m, 1), 3.7 (s, 2), 4.2 (q, 2), 5.2 (br s, 4), 6.9 (d, 1), 7.3 (d, 1), 7.5–8.1 (m, 5); *m/e* 449.

Michael Adduct 27. A. Sealed-Tube Reaction.—A mixture of 3.8 g (11.3 mmol) of the oxazine amide **7**, 2.9 g (17 mmol) of the dioxolane ester **26**, 17 ml of absolute ethanol, and 5–6 drops of sodium ethoxide solution was heated to 145–150° in a Pyrex tube which had been sealed under vacuum. Heating was continued for 8–10 hr and the solution was cooled, leaving a colorless precipitate under the amber-colored solution. Removal of the solid by filtration afforded 4.31 g (75%) of the Michael adduct: mp 202–203°; R_f 0.74 (acetone–benzene, 1:1) on Eastman chromagram silica gel; ir (KBr) 3050, 1737, 1660, 1645 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (s, 6), 1.3 (d, t, 6), 1.6 (d of t, 2), 2.6 (m, 3), 3.3 (m, 1), 3.9 (m, 4), 4.2 (m, 3), 5.0–5.2 (s, m, 5), 7.5–8.2 (m, 5); *m/e* 509.

Anal. Calcd for $C_{28}H_{35}N_3O_6$: C, 65.99; H, 6.92; N, 8.51. Found: C, 65.72; H, 6.74; N, 8.46.

B. Heating in Dimethylformamide.—A solution containing 559 mg of **7** and 425 mg of **26** in 3 ml of dry DMF was heated to reflux for 30 hr. The reddish-brown solution was cooled, treated with 4 ml of ether, and stored at −20° overnight. The precipitate which formed was removed by filtration, 468 mg (51%), mp 201–202°. The spectral characteristics were identical with those of the product formed in the sealed-tube experiment.

Tetrahydro-1,3-oxazine 28.—The Michael adduct **27** (4.00 g, 7.9 mmol) was dissolved in 150 ml of hot ethanol and to this was added 150 ml of tetrahydrofuran. The solution was cooled, with magnetic stirring, to −45° by a Dry Ice–acetone bath. The pH was adjusted to 5 with 3 *N* hydrochloric acid and a solution of sodium borohydride (0.29 g in 0.5 ml of water containing a drop of 20% sodium hydroxide) was added dropwise. The pH was maintained at 5–6 by the simultaneous addition of 3 *N* HCl (monitored by pH paper). Stirring was continued after the hydride addition was complete at −40° and the solution was poured into 300 ml of cold water saturated with brine. The aqueous mixture was extracted with several portions of dichloromethane, and the extracts were dried ($MgSO_4$) and concentrated, leaving a foamy residue. The crude product was chromatographed on silica gel (0.05–0.2 mm, Merck AG-Darmstadt) through a 5 × 0.75 in. column using acetone–benzene (1:1) as the eluent. The desired product came off first and 3.5 g (87%) was obtained as a colorless foam: ir (film) 3450 (broad), 3330, 1730, 1640 cm^{-1}; nmr ($CDCl_3$) δ 0.9–1.6 (m, 14), 2.6 (m, 4), 3.4 (m, 1), 3.9 (m, 5), 4.2 (q, 2), 4.8 (d, 1), 5.0 (s, 2), 5.2 (m, 3), 7.5–8.2 (m, 5); *m/e* 511.

Anal. Calcd for $C_{28}H_{37}N_3O_6$: C, 65.81; H, 7.11; N, 8.23. Found: C, 65.71; H, 7.39; N, 7.99.

Ester Aldehyde 29.—To 35 ml of a gently refluxing ammonium chloride solution (25%) was added, dropwise, 1.38 g (2.7 mmol) of the tetrahydro-1,3-oxazine **28** dissolved in 9 ml of ethanol. The solution was heated for an additional 45 min and then cooled and treated with 50 ml of saturated brine solution. The contents were then extracted with chloroform (3 × 15 ml) and the extracts were dried ($MgSO_4$) and concentrated. The residue, a tan-colored foam, was chromatographed on silica gel eluting with acetone–benzene (1:1). Thin layer examination indicated that the aldehyde (R_f 0.63 on Eastman chromagram sheets) was free of impurities. The product, a colorless foam, weighed 800 mg (72%): ir (film) 3420 (broad), 3060, 2760, 1735, 1725, 1640 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (two overlapping triplets, 3), 2.6 (t, 2), 3.4 (m, 2), 3.9 (m, 4), 4.1 (q, 2), 4.9 (s, 2), 5.2 (m, 3), 7.5–8.1 (m, 5), 9.6 (d, 0.5 H), 9.7 (d of d, 0.5 H) (the spectral data are consistent with some enolic character for the aldehyde); *m/e* 412.

Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.79; H, 6.02; N, 6.78.

Hydroxy Ester 30.—To 3.56 g (8.1 mmol) of the above aldehyde **29** in 30 ml of ethanol previously cooled to 0° was added 0.31 g of sodium borohydride. The cold solution was stirred for 10 min, made acidic (pH ~4) with 3 *N* hydrochloric acid, and then saturated with sodium chloride. Extraction with chloroform (3 × 50 ml) followed and the extracts were dried (Na_2SO_4) and concentrated to provide an orange foam, 3.33 g. The product was purified by elution with acetone–benzene (1:1) through a 12 × 1 in. column packed with silica gel (Merck AG, 0.05–0.2 mm). Thin layer examination revealed that the hydroxy ester (R_f 0.53, Eastman chromagram) was pure and was obtained as a solid: mp 134–136°; 1.7 g (52%); ir (KBr) 3400 (br), 1730, 1625, 1580 cm^{-1}; nmr ($CDCl_3$) δ 1.4 (t, 3), 2.8 (s, m, 3), 3.5 (m, 1), 3.8–4.5 (m, q, 9), 5.0 (s, 2), 5.1–5.4 (m, 3), 7.5–8.2 (m, 5); *m/e* 414.

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.54; H, 6.59; N, 6.71.

Lactone 31.—A mixture of 601 mg of the hydroxy ester **30** in 14 ml of 1 *N* sodium hydroxide was heated to reflux for 75 min. After cooling, the solution was acidified to pH 4 with dilute hydrochloric acid and extracted with dichloromethane (8 × 20 ml). The extracts were dried ($MgSO_4$) and concentrated, affording the hydroxy acid as a colorless foam (429 mg, 82%): ir (KBr) 3200–3500, 1710, 1625 cm^{-1}; *m/e* 368 (386 − 18). Without further purification the hydroxy acid (636 mg) was treated with 340 mg of dicyclohexylcarbodiimide in 25 ml of tetrahydrofuran and stirred at room temperature for 18 hr. The solid which appeared was triturated with a small quantity of chloroform to separate the lactone from the insoluble dicyclohexylurea. After several repetitive chloroform treatments, the chloroform was concentrated to give 353 mg (58%) of **31**: mp 185–190°; *m/e* 368; ir (KBr) 1730, 1635 cm^{-1}. The lactone was insufficiently soluble in chloroform to obtain a clean nmr spectrum; however, a spectrum in trideuterioacetonitrile was taken, δ 2.8

(m, 3), 3.4 (m, 1), 3.8 (br s, 4), 4.6 (t, 2), 4.6–5.0 (m, 5), 7.5–8.2 (m, 5).

The lactone was also prepared by treating the hydroxy ester **30** in dimethylformamide with 1.0 equiv of sodium hydride and stirring at 25° for 4 hr. Quenching in water, followed by extraction with dichloromethane, gave the lactone after evaporation of the solvent.

Etiolactone 34 from Lactone 31.—A solution of **31** (300 mg) in wet toluene containing 0.2 equiv of *p*-toluenesulfonic acid (or trifluoroacetic acid) was heated to reflux in the presence of a Dean–Stark trap for 3 hr. Neutralization with solid sodium bicarbonate followed by *in vacuo* removal of the solvent left 157 mg of a colorless solid: mp 215–222° dec; *m/e* 324; ir (KBr) 1775, 1640 cm^{-1}; nmr ($CDCl_3$) δ 2.8 (d of d, 2), 3.2 (m, 1), 3.6 (d of d, 1), 4.4 (t of d, 2), 5.0 (br s, 4), 6.2 (d, J = 6 Hz, 1), 7.5–8.1 (m, 5); R_f 0.61 (benzene–acetone, 1:1, Eastman chromagram sheets). The etiolactone **34** was also formed when the hydroxy ester **30** was treated with 5% perchloric acid in tetrahydrofuran (1:1) and stirred for 16 hr at room temperature.

Dioxolane Amide 37.—The pyrroloquinoline **8** (2.23 g, 13.1 mmol) and the dioxolane carboxylic acid **36** (2.26 g, 13.1 mmol) were dissolved in 40 ml of dichloromethane and treated with 2.9 g (14 mmol) of dicyclohexylcarbodiimide in dichloromethane in a dropwise fashion. The reaction was mildly exothermic. The mixture was stirred at room temperature for 24 hr, after which the dicyclohexylurea was removed by filtration. The filtrate was concentrated and the mixture of oil and solid residue was triturated with ether. The solid was collected on a filter, 2.2 g (50%), and recrystallized from ethanol–ether: mp 137–138.5°; ir (KBr) 1635 cm^{-1}; nmr ($CDCl_3$) δ 1.0 (t, 3), 1.8 (m, 2), 2.3 (d of t, 1), 2.8 (m, 2), 3.9 (q, 4), 5.0 (m, 5), 7.5–8.2 (m, 5).

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.17; H, 6.58; N, 8.72.

Aldehyde Amide 38.—A solution of the dioxolane amide **37** (835 mg, 2.56 mmol) in 40 ml of dichloromethane was cooled to −78° (Dry Ice–2-propanol) and treated with 1.8 ml of boron tribromide at a rapid rate of addition. A precipitate formed immediately and agitation was continued for 2 hr at −78°. The cold bath was removed and the solution was allowed to reach room temperature, wherein the precipitate had mostly dissolved. Saturated sodium bicarbonate (25 ml) was added until the pH reached 7–7.5. The organic layer was removed and the aqueous layer was extracted with dichloromethane. The extracts were combined, dried (Na_2SO_4), and passed through Norit to remove the deep amber coloration. Evaporation of the solvent left a gummy material, 675 mg (93%). Purification was achieved by elution through neutral alumina with dichloromethane: ir (film) 2700, 1730, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.0 (t, 3), 1.6 (m, 2), 2.4–3.4 (m, 3), 5.0 (br s, 2), 5.2 (q, 2), 7.5–8.2 (m, 5), 10.0 (s, 1). The aldehyde was used without further purification for the next step.

Dihydropyridone 39.—To the aldehyde **38** (612 mg, 2.17 mmol) in 25 ml of freshly distilled toluene was added 10–15 mg of trifluoroacetic acid and the solution was heated, under nitrogen, to reflux in the presence of a Dean–Stark trap for 4 hr. The cooled reaction mixture was diluted with 25 ml of ether and the solution was washed with 10 ml of saturated sodium bicarbonate solution. The organic layer was dried (K_2CO_3) and concentrated, leaving 558 mg of a crude solid. The entire product was chromatographed on silica gel (0.05–0.2 mm, Merck AG) using ethanol–dichloromethane (1:50) as the eluent. There was obtained 456 mg (80%) of a light green, crystalline solid, mp 150–154°. The analytical sample was crystallized from ethanol: mp 152–156°; ir (KBr) 1660 cm^{-1}; uv (EtOH) 360, 295, 244 nm;[27] nmr ($CDCl_3$) δ 1.1 (t, 3), 1.8 (m, 2), 2.6 (m, 3), 5.0 (s, 2), 6.2 (d, t, 1), 7.5–8.2 (m, 5).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.29; H, 6.40; N, 10.58.

Pyridone 40.—A solution of the dihydropyridone **39** (100 mg) in benzene (3 ml) was treated with 1.1 equiv (90 mg) of 2,3-dichloro-5,6-dicyanoquinone. A precipitate formed almost immediately and the mixture was stirred at room temperature for 2.5 hr. After removal of the solid material, which was washed with ether, the combined filtrates were concentrated to a small volume and added to a silica gel column. Elution with ethanol–chloroform (1:3) gave 97 mg (96%) of a crystalline product. Recrystallization from ethanol gave 70 mg of pyridone: mp 261–262° dec; ir (KBr) 1670, 1650, 1600 cm^{-1}; uv (EtOH) 365, 286, 253, 246, 218 nm; nmr ($CDCl_3$) δ 1.3 (t, 3), 2.8 (q, 2), 5.2 (s, 2), 7.3–8.4 (m, 7, the AB pattern of the pyridone protons is mixed with the multiplet of aromatic protons and is, therefore, not readily sorted out); *m/e* 262.

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 78.06; H, 5.21; N, 10.86.

Carbonate Dioxolane 41 (R = OEt).—Ethyl chloroformate (20 mg) was added dropwise to a previously cooled (0°) solution of the hydroxy ester **30** (80 mg, 0.2 mmol) in 4 ml of pyridine. The resulting solution, after stirring for 16 hr at room temperature, was poured into cold 0.5 *N* hydrochloric acid and extracted with dichloromethane (3 × 10 ml). After the extract was washed with dilute sodium bicarbonate solution, it was dried ($MgSO_4$) and concentrated, leaving a tan-colored foam, 82 mg (87%). The carbonate was purified by preparative layer chromatography (R_f 0.71) using acetone–benzene (1:1): ir (film) 1755–1740 (br), 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (t, 6), 2.7 (m, s, 3), 3.4 (m, 1), 3.9 (br s, 4), 4.2 (q, 4), 4.5 (t, 2), 5.0 (s, m, 5), 7.5–8.2 (m, 5); *m/e* 486.

Acetate Dioxolane 41 (R = CH_3).—A solution of the hydroxy ester **30** (130 mg, 0.31 mmol) in 2 ml of pyridine previously cooled to 0° was treated with 30 mg of acetyl chloride. The solution was stirred at 0° for 1 hr and then 2 hr at room temperature. The resulting mixture was poured into cold dilute 1 *N* hydrochloric acid and the aqueous solution was extracted with dichloromethane. The combined extracts were washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated to give a tan oil (128 mg, 90%), R_f 0.70 (acetone–benzene, 1:1). The product could be, if desired, eluted through a silica gel column. However, this was found to be unnecessary, as the material was of sufficient purity to proceed further: ir (film) 1730–1740, 1670, 1645 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (t, 3), 2.0 (s, 3), 2.7 (m, s, 3), 3.5 (m, 1), 4.0 (br s, 4), 4.2 (q, 2), 4.5 (d, 2), 5.0 (s, 2), 5.2 (m, 3), 7.5–8.3 (m, 5).

Acetate Aldehyde 42 (R = CH_3).—To a solution of 1.18 g (2.58 mmol) of the acetate dioxolane **41** (R = CH_3) obtained above, in 80 ml of dichloromethane cooled to −78° under argon, was added 6.5 ml (20 equiv) of boron trifluoride etherate. The cold bath was removed and the reaction mixture was allowed to warm to ambient temperature, at which time 20 ml of water was introduced and the mixture was stirred for 30 min. Partial neutralization to pH ~4 with 10% sodium hydroxide followed and the organic phase was separated, dried (Na_2SO_4), and concentrated. The residue (992 mg) was again dissolved in dichloromethane and treated with 2.7 ml (10 equiv) of boron trifluoride under the conditions described previously. Isolation, exactly in the same manner as above, was accomplished, producing 950 mg (94% based upon total yield of aldehyde) of a foam, R_f 0.87 (acetone–benzene, 1:1). The product, however, was a mixture containing ~30% of unidentifiable material and 70% of two diastereomeric aldehydes (**42**, R = CH_3). Owing to the similarity in tlc behavior, this mixture could not be separated and was used as such in the subsequent step: ir (film) 2720, 1745–1725 (br), 1645 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (two triplets in the ratio of 7:3, 3), 2.0 (s, 3), 2.6–4.6 (m, 10, these signals contained two additional protons which are attributed to the impurity mentioned above), 5.0 (s, 2), 5.2 (m, 2), 7.5–8.3 (m, 5). Since the last two signals integrated perfectly with those at 2.0 and 1.3 ppm, the impurity does not appear to contain the pyrroloquinoline moiety nor the ethoxy or acetate groupings. Thus, it may be concluded that some rupture of the amide bond occurred during the dioxolane cleavage with boron trifluoride. Also present in the nmr spectrum of **42** are two aldehyde signals at δ 9.7 and 10.0 in the ratio 1:3, respectively.

Carbonate Aldehyde 42 (R = OEt).—The carbonate **41** (R = OEt) (300 mg, 0.7 mmol) was treated under the same conditions as the acetate **41** (R = CH_3) with boron trifluoride etherate, initially with 20 equiv and finally with 10 equiv, giving 237 mg of the crude corresponding aldehyde **42**. The product (81%) was also a mixture of two diastereomeric aldehydes and a substance derived from loss of the pyrroloquinoline moiety: ir (film) 2720, 1755–1730, 1648 cm^{-1}; nmr ($CDCl_3$) δ 1.2–1.4 (overlapping triplets, 6), 2.8–4.6 (m, 10), 5.0 (s, 2), 5.2 (m, 2), 7.5–8.3 (m, 5), 9.65 and 9.97 (total integration, 0.84 H) in the ratio of 1:3, respectively. The aldehyde mixture could not be separated from the impurity (~20%) and was used as such for the next step.

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Methylpyridone 44.—Trifluoroacetic anhydride (14 mg), toluene (4 ml), and the above carbonate aldehyde (**42**, R = OEt, 30 mg) were heated to reflux for 18 hr. The solution took on an immediate red color and, after the heating period, became very dark. The solution was diluted with 20 ml of chloroform and then washed with saturated sodium bicarbonate solution. Drying (Na_2SO_4) and concentration left a dark semisolid, 10 mg of which was subjected to preparative layer chromatography (silica gel, benzene–acetone, 1:1). A pure product, 2 mg, was cut from the plate: mp 258–261° dec; *m/e* 334; ir (film) 1730, 1650, 1600 cm^{-1}; uv (EtOH) 220, 253, 365 nm; nmr ($CDCl_3$) δ 1.3 (t, 3), 2.4 (s, 3), 3.7 (s, 2), 4.3 (q, 2), 5.2 (s, 2), 7.3 (s, 1), 7.6–8.5 (m, 5).

Dihydropyridone 43 (R = CH_3).—The acetate aldehyde (**42**, R = CH_3), as already described, was used as the diastereomeric mixture. A solution containing 500 mg (only 45% of which contained the usable precursor) of aldehyde mixture, 0.14 ml of acetic anhydride, and 50 ml of anhydrous benzene was heated to reflux for 24 hr. The cooled solution was treated with 10 ml of water and stirred at room temperature for 1 hr followed by neutralization with sodium bicarbonate. The benzene layer was separated, dried (Na_2SO_4), and concentrated, leaving a brown oily residue (375 mg). Although the product could not be purified (column or preparative layer chromatography), the ultraviolet spectrum indicated the presence of a dihydropyridone group (244, 295, and 360 nm), which compared favorably with the spectrum of **39**. The infrared and nmr spectrum indicated, among other products, the uncyclized aldehyde (δ 9.65). The crude dihydropyridone was then subjected without further rectification to the aromatization step which follows.

Pyridone 45.—The crude mixture from above (375 mg) was dissolved in anhydrous benzene (20 ml) and treated dropwise with 227 mg of 2,3-dichloro-5,6-dicyanoquinone (DDQ) as a solution in benzene. There was an immediate formation of a precipitate and the reaction was stirred at room temperature for 18 hr. The amber-colored solution was removed by filtration and the solid was washed with 15 ml of benzene. The combined filtrates were concentrated to a dark brown oil which was chromatographed on a silica gel column using ethanol–chloroform (3:1) as the eluent. The pyridone rapidly passed down the column and was followed by tlc, which showed an intense blue fluorescence upon exposure to an ultraviolet lamp. Evaporation of the solvents followed by addition of cold ethanol to the residue produced 48 mg (22% based upon the aldehyde **42**) of a solid. Recrystallization from hot ethanol gave 38 mg of pure pyridone: mp 242–244° dec; R_f 0.87 (acetone–benzene); *m/e* 392; ir (KBr) 1740, 1650, 1600 cm^{-1}; uv (EtOH) 220, 254, 361, 383 nm; nmr ($CDCl_3$) δ 1.3 (t, 3), 2.1 (s, 2), 4.8 (s, 2), 4.2 (q, 4), 5.3 (s, 2), 5.4 (s, 2), 7.3 (s, 1), 7.7–8.5 (m, 5).

Pentacyclic Lactone 2 (R_1, R_2 = H).—A mixture containing 24 mg of the pyridone ester **45**, 4 ml of ethanol, and 3 ml of 10% sulfuric acid was heated to reflux on a steam bath for 30 hr. Upon cooling the ethanolic solution, yellow crystals appeared: 17 mg (94%); mp 256–259° dec; *m/e* 304; ir (KBr) 1745, 1660, 1605 cm^{-1}; nmr (trifluoroacetic acid) δ 4.2 (s, 2), 5.8 (s, 2), 5.9 (s, 2), 8.0–9.5 (m, 6); for uv (EtOH) see Figure 1.

(±)-Deoxycamptothecin 1 (R_2 = H) and Camptothecin 1.—A suspension of 7 mg of **2** in 3 ml of 1,2-dimethoxyethane or dimethylformamide was treated with 1.0 mg of sodium hydride and the mixture was heated for 1.5 hr at 60°. Upon cooling to 0°, 1.5 mg of ethyl iodide was added and the mixture was slowly allowed to warm to ambient temperature and then stirred overnight. After quenching in water, the solid was collected and dried *in vacuo*. The infrared spectrum (KBr) exhibited bands at 1743, 1660, and 1600 cm^{-1}, identical with those of an authentic sample[28] of deoxycamptothecin **1** (R_2 = H). The mass spectrum exhibited a parent ion at *m/e* 332. An aged sample of the latter (2–4 days) in dichloromethane was examined by mass spectroscopy and found to give a molecular ion at *m/e* 348 as noted by Danishefsky.[4] In view of the reports by Winterfeldt[6] and Danishefsky[4] of the successful conversion of deoxycamptothecin to camptothecin coupled with the limited quantities on hand, no further effect was expended to prepare large quantities of **1**.

Registry No.—**1**, 7689-03-4; **2**, 38390-42-0; **7**, 39013-35-9; **8**, 34086-64-1; **8** (2HBr), 34086-65-2; **9**, 36867-19-3; **11**, 39013-39-3; **12**, 5344-23-0; **13**, 2960-65-8; **14**, 2833-30-9; **15**, 39010-34-9; **17**, 39013-42-8; **18**, 39013-43-9; **21** (R = H), 39013-44-0; **21** (RO_2CCH_2 = Me), 39013-45-1; **21** (R = Et), 39013-46-2; **22**, 39013-47-3; **25**, 39013-48-4; *cis*-**26**, 39013-49-5; *trans*-**26**, 39013-50-8; **27**, 39013-51-9; **28**, 39013-52-0; **29**, 39013-53-1; **30**, 39013-54-2; **31**, 39013-55-3; **34**, 39007-99-3; **36**, 39008-00-9; **37**, 39008-01-10; **38**, 39008-02-1; **39**, 39008-03-2; **40**, 39008-04-3; **41** (R = OEt), 39008-05-4; **41** (R = CH_3), 39062-22-1; *R**,*S**-**42** (R = CH_3), 39010-34-9; *R**,*R**-**42** (R = CH_3), 39010-35-0; *R**,*S**-**42** (R = OEt), 39010-36-1; *R**,*R**-**42** (R = OEt), 39010-37-2; **43**, 39062-20-9; **44**, 39008-06-5; **45**, 39008-07-6; ethyl acrylate, 140-88-5; *dl*-glyceraldehyde diethyl acetal, 10487-05-5; furfural, 98-01-1; hydroxy acid of **30**, 39008-08-7.

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