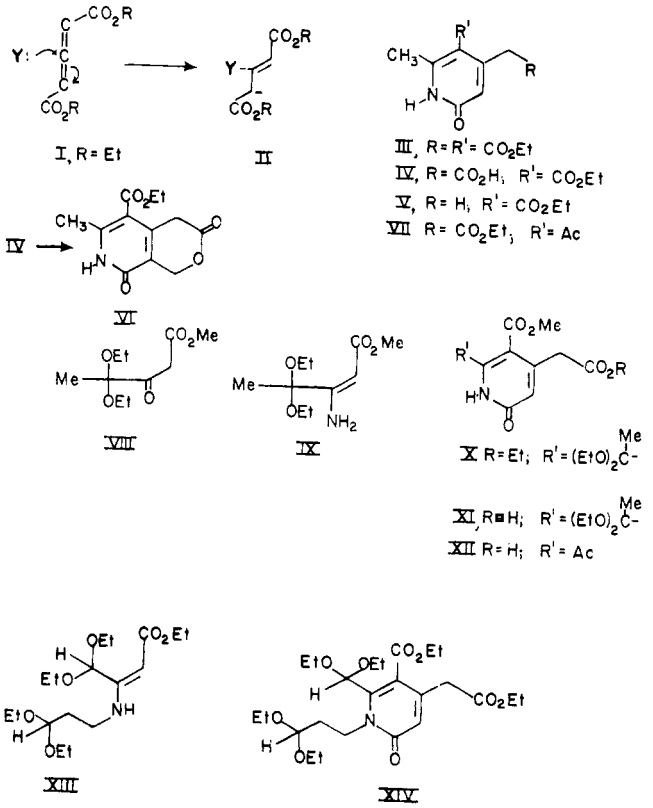

fication affords acid XI,[10,11] mp 195–199° dec, which is smoothly converted (TsOH–acetone–H_2O, room temperature) to 4-carboxy-5-carbomethoxy-6-acetyl-α-pyridone (XII),[10,11] mp 195–199° dec.

The synthesis may be applied to the construction of N-substituted α-pyridones. Treatment of ethyl 3-amino-4,4-diethoxycrotonate[16] (XIII) with allene I in ethanol containing triethylamine gives an adduct which cyclizes through the action of sodium ethoxide to give pyridone XIV[10,11] in 40% yield.

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tion to the pyridone though in some cases subsequent treatment with strong base is necessary. The precise structural factors which favor one-step cyclization (*cf.* enamines VIII and XIII) have not as yet been defined.

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A Total Synthesis of *dl*-Camptothecin

Sir:

Structure XIV was assigned by Wall and coworkers to the alkaloid camptothecin.[1] Early reports ascribing promising antitumor properties to camptothecin[2] coupled with its difficult availability have generated considerable enthusiasm for assembling this compound in the laboratory. This synthetic challenge has been accepted in a variety of laboratories[3a–j] culminating in the first total synthesis of Stork and Schultz.[4] In this paper we report a total synthesis of *dl*-camptothecin using a new pyridone synthesis which we have recently developed.[5]

Enamino diester I[6] (bp 135–138° (0.1 mm)) was produced in 67% yield from the uncatalyzed addition of β-aminopropionaldehyde diethyl acetal to dicarbomethoxyacetylene in ether. Condensation of I with dicarbethoxyallene[5] in methanol containing 1 equiv of triethylamine at room temperature gave the pyridone triester, II,[6,7] mp 50–52°, in 45% yield which, upon deacetalization (HCl–acetone–water), gave quantitatively aldehyde III,[6,7] mp 86–87°. The latter was transformed by oxidation (CrO_3–H_2SO_4–acetone–water) to the acid IV[6] and thence by esterification and transesterification (methanolic HCl, room temperature) to the tetramethyl ester V,[6,7] mp 89–91°, in 86% yield.

The C ring of camptothecin was now established by a Dieckmann closure[8] (3 equiv of sodium methoxide–methanol, reflux 12 hr). These conditions led, reproducibly, in 81% yield to the enolic acid ester VI,[6] 195–197° dec, through some, as yet undefined, hydrolytic pathway. The latter is most readily characterized through its methyl ester VII,[6,7] mp 178–180°. Hydrolysis and selective decarboxylation of VI (4% aqueous HCl, reflux 3 hr) gave in crude form keto acid VIII[6] which was subjected directly to Friedlander condensation (3 equiv of sodium hydroxide, 2 equiv of *o*-aminobenzaldehyde–water, reflux 36 hr). These conditions sufficed to hydrolyze the carbomethoxyl group at the 5 positions of the pyridone ring, and afforded the tetracyclic diacid IX,[6] mp >310°. Without purification this was converted into acid ester X, mp >300° dec, which was decarboxylated by pyrolysis (239–244°, 4 min) over 0.3 equiv of cuprous oxide to give the tetracyclic methyl ester XI,[6,7] mp 209–211°, in 29% yield from VI. Ethylation of XI (1 equiv of sodium hydride dimethoxyethane, excess ethyl iodide (room

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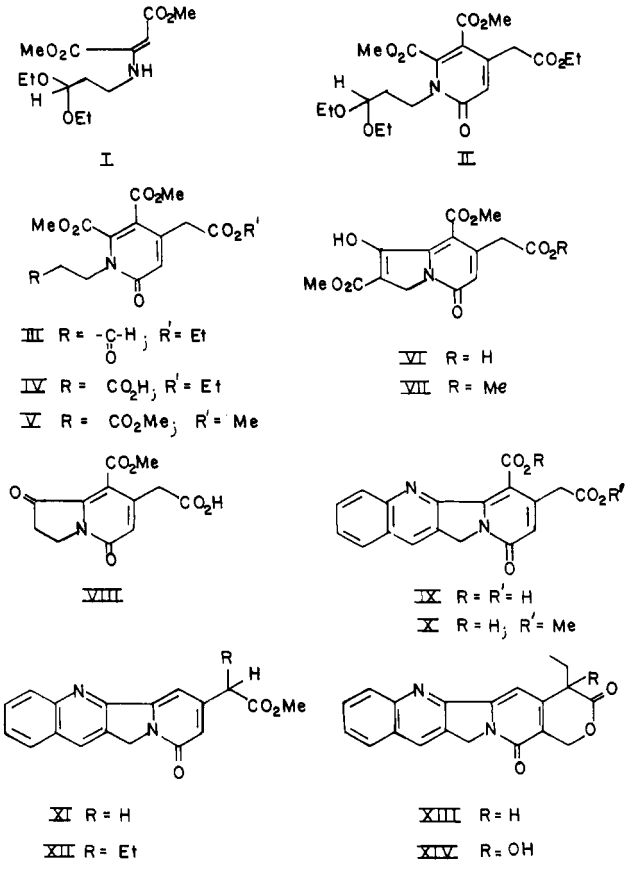
(6) The nmr and mass spectra of this compound are consistent with the assigned structure.

(7) Carbon, hydrogen, and nitrogen combustion analyses within 0.3% of theory were obtained for this compound.

(8) Clearly some subtle and, as yet undefined, factors are involved in the success of this reaction relative to β elimination of the pyridone group [*cf.* ref 3a and 3i]. We encountered the β elimination problem in the reaction of pyrrolidine on aldehyde III. This gave, cleanly, 4-carbethoxymethyl-5,6-dicarbomethoxy-α-pyridone,[6,7] mp 105–106°.



temperature)) gave a 20% yield of ethylated monoester XII,[6] mp 198–200°.[9]

Treatment of XII with paraformaldehyde (in dioxane containing a trace of concentrated H_2SO_4, 100°, 16 hr) gave *dl*-desoxycamptothecin (XIII), mp 258–264° dec, identical with an authentic sample[10] in its chromatographic properties, and nmr, ultraviolet, and mass spectra.[11] With desoxycamptothecin in hand, it soon became clear that this substance undergoes oxidation to camptothecin (XIV) with remarkable facility. For instance, a solution of XIII dissolved in methylene chloride exposed to air soon begins to exhibit, on thin-layer chromatographic analysis, a spot corresponding in its R_f value and mass spectrum to camptothecin. There remained only the translation of this analytical observation to the preparative scale. Our first attempts at this involved passing oxygen through a solution of the anion of XIII (*via* potassium *tert*-butoxide in DMSO–DMF containing 1 equiv of triethyl phosphite). While the formation of camptothecin could be detected, the rate was quite slow and other, as yet unidentified, products were generated.

(9) The difficulty associated with the ethylation of compound XI led us to rework the synthesis. Treatment of compound II under the same conditions as XI smoothly gave the required ethylated product which was converted to XII using the same series of reactions which converted II into XI.

(10) (a) We thank Dr. Monroe E. Wall of the Research Triangle, Durham, N.C., for furnishing us with a procedure for preparing desoxycamptothecin from the natural product. (b) We thank Dr. Harry B. Wood of the Cancer Chemotherapeutic National Service Center, Bethesda, Md., for furnishing us with a sample of camptothecin.

(11) A minor product of this reaction, mp 258–260°, was also obtained. Its mass spectrum is essentially identical with that of XIII, but it is clearly differentiated from desoxycamptothecin chromatographically. It is tentatively assigned as isodesoxycamptothecin arising from hydroxymethylation at the 5 position of the pyridone followed by lactonization.

We then found that treatment of the anion of XIII (*via* potassium *tert*-butoxide in DMSO–BuOH) with 1 equiv of aqueous hydrogen peroxide[12] afforded *dl*-camptothecin, mp 275–277° dec, in 20% yield. The *dl*-camptothecin so produced was identical with the natural product in its mass spectrum and R_f value in a variety of solvents. Its infrared spectrum (Nujol) was superimposable with that of the previously prepared *dl* compound.[4,13]

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(13) We thank Dr. A. Schultz, Columbia University, for comparing our sample with his.

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Studies of the Aromatic Chirality Method. The Optical Rotatory Powers of Di- and Tribenzoate Systems

Sir:

The aromatic chirality method,[1] an extension of the benzoate sector rule,[2] has proven to be a convenient method for determining absolute configurations or conformations. It has successfully been applied to a variety of complex natural products including terpenoids,[3,4] antibiotics,[5,6] sugars,[7] and alkaloids.[1]

According to the molecular exciton theory[8–14] related to the optical rotation properties, the rotational strength R_{ao} of two interacting chromophores (i and j) which exhibit strong $\pi^* \rightarrow \pi$ transitions can be ap-

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