Concise Total Syntheses of *dl*-Camptothecin and Related Anticancer Drugs

Wang Shen,* Craig A. Coburn,† William G. Bornmann, and Samuel J. Danishefsky

Laboratory for Bioorganic Chemistry, Sloan Kettering Research Institute for Cancer Research, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 106, New York, New York 10021

Received September 14, 1992

The readily available tricyclic ester **10** has been converted to *dl*-camptothecin (**1**) in 39% yield. It was discovered that, with the C_5 carbomethoxy group in place, the C_6 benzylic position of **10** (pyridone numbering) is selectively deprotonated by sodium hexamethyldisilazide. This allows for condensation with benzaldehyde to produce acid **17** which, after ozonolysis and methylation, afforded the tricyclic keto ester **16**. The latter is smoothly converted to camptothecin (**1**), 10-hydroxycamptothecin (**24**), and 7-ethyl-10-hydroxycamptothecin (**31**) via (i) Friedländer condensation with appropriate aminobenzaldehydes, (ii) HBr-induced decarbomethoxylation, and (iii) hydroxylation at C_{20}. In the case of the two analog syntheses, the HBr step also accomplishes concurrent demethylation of the C_{10} methoxyl group.

Introduction

The isolation of camptothecin (**1**) in 1966 by Wall and co-workers,[1] the elucidation of its structure, and above all, the finding of its high anti-tumor activity in various cell line and animal screens triggered a great deal of interest at the chemical level.[2] These efforts were addressed to analog synthesis and to total synthesis. Analog synthesis did achieve significant definition of those areas of the molecule which are central to its tumor shrinking activity.[3] A variety of total syntheses, involving creative adaptations of classical reactions as well as new chemistry inspired by the camptothecin target, were accomplished.[2-5]

Unfortunately, the dramatic early claims of clinical success for camptothecin in human trials were not sustained in subsequent investigations. Between 1973 and 1985 camptothecin commanded only marginal attention at either the biological or clinical levels, although its high activity in various in vitro and animal model screens was always confirmed.[6]

Since then, there has been an enormous resurgence of interest in camptothecin and its congeners. This reemergence has been dictated by two considerations. First was the recognition by Wall and colleagues that the mode of clinical administration of sodium salt **2** in place of camptothecin may have damaged the possibilities for a favorable clinical result.[4c] This protocol had been instituted in light of constraints associated with formulating camptothecin itself as a drug because of its extremely low water solubility. Since compound **2** was per se not active in various in vitro screens, a useful clinical outcome would presumably depend on in vivo lactonization.

Wall's concept brought forth a search for analogs of **1** which would enjoy a superior solubility profile while retaining the antitumor functions of the parent system. Fortunately, promising clinical candidates (cf. topotecan, CPT-11, and 9-aminocamptothecin) have emerged from this line of reasoning and are currently undergoing extensive human subject trials.[7]

A second factor fueling research in the camptothecin area was the discovery of the likely target for its cytotoxic action. Liu and colleagues registered the important finding that camptothecin traps the cleavable complex between topoisomerase I and DNA. In the presence of a protein denaturant, single strand breaks are noted.[8] Camptothecin is thus a member of a growing class of topoisomerase poisons,[9] although its inhibition of action of topoisomerase I is quite unusual. In addition to the intrinsic novelty of the discovery, Liu's work provided the opportunity for screening the likely usefulness of camptothecin congeners.

Given this much more promising situation, in the biological and clinical realms it is not surprising that there is renewed activity in synthetic studies directed toward

† National Science Foundation Postdoctoral Fellow, 1992-1994.

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

(2) Reviews. (a) Cai, J.-C.; Hutchinson, C. R. *Chem. Heterocycl. Compd.* **1983**, *25*, 753. (b) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1097. (c) Cai, J.-C.; Hutchinson, C. R. *The Alkaloids: Chemistry and Pharmacology*; Bross, A., Ed.; Academic Press: New York, 1983; Vol. 21, p 101. (d) Schultz, A. G. *Chem. Rev.* **1973**, 385.

(3) Leading references on the structure-activity relationship: (a) Wani, M. C.; Nicholas, A. W.; Manikumar, G.; Wall, M. E. *J. Med. Chem.* **1987**, *30*, 1774. (b) Nicholas, A. W.; Wani, M. C.; Manikumar, G.; Wall, M. E.; Kohn, K. W.; Pommier, Y. *J. Med. Chem.* **1990**, *33*, 972. (c) Jaxel, C.; Kohn, K. W.; Wani, M. C.; Wall, M. E.; Pommier, Y. *Cancer Res.* **1989**, *49*, 1465. (d) Hertzberg, R. P.; Caranfa, M. J.; Holden, K. G.; Jakas, D. R.; Gallagher, G.; Mattern, M. R.; Mong, S.-M.; Bartus, J. O.; Johnson, R. K.; Kingsbury, W. D. *J. Med. Chem.* **1989**, *32*, 715.

(4) (a) The first total synthesis of (±)-**1** was reported by Stork: Stork, G.; Shultz, A. G. *J. Am. Chem. Soc.* **1974**, *93*, 4074. For other, high yielding syntheses see: (b) Tang, C. S. F.; Morrow, C. J.; Rapoport, H. *J. Am. Chem. Soc.* **1975**, *97*, 159. (c) Wani, M. C.; Ronmann, P. E.; Lindley, J. T.; Wall, M. E. *J. Med. Chem.* **1980**, *23*, 554.

(5) For more recent approaches see: (a). Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863. (b) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *J. Am. Chem. Soc. Perkin Trans. 1* **1990**, 27.

(6) (a) Muggia, F. M.; Creavan, P. J.; Hansen, H. H.; Cohen, M. H.; Selawry, O. S. *Cancer Chemother. Rep. Part 1* **1972**, *56*, 515. (b) Gottlieb, J. A.; Guarurino, A. M.; Call, J. B.; Oliverio, V. T.; Block, J. B. *Cancer Chemother. Rep. Part 1* **1970**, *54*, 461.

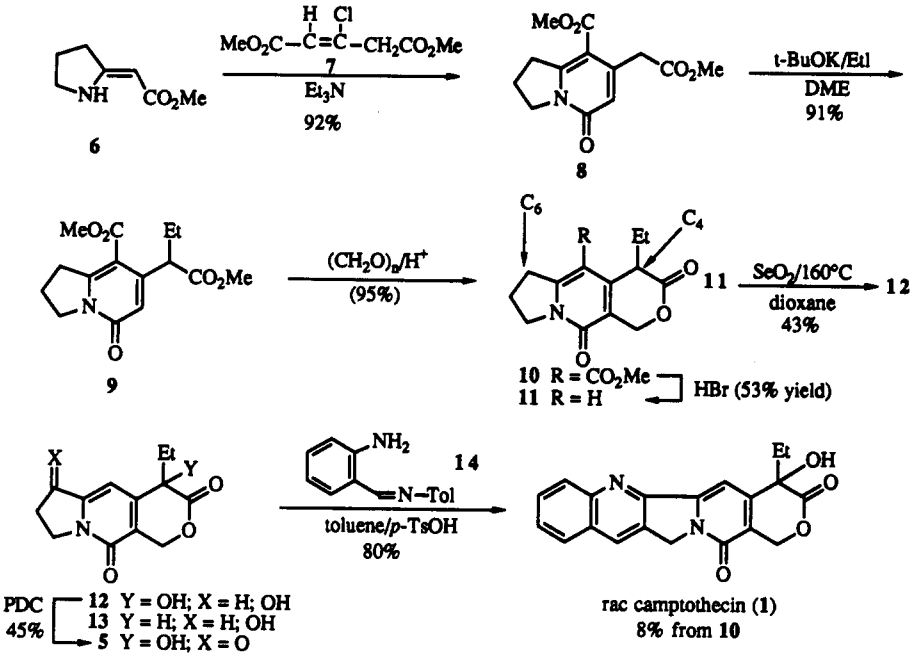
(7) Topotecan: (a) Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R.; Holden, K. G.; Hecht, S. M.; Gallagher, G.; Caranfa, M. J.; McCabe, F. L.; Faucette, L. F.; Johnson, R. K.; Hertzberg, R. P. *J. Med. Chem.* **1991**, *34*, 98. (b) Mattern, M. R.; Hofmann, G. A.; McCabe, F. L.; Johnson, R. K. *Cancer Res.* **1991**, *51*, 5813. CPT-11: (c) Sawada, S.; Okajima, S.; Aiyama, R.; Nokata, K.; Faruka, T.; Yokokura, T.; Sugino, E.; Yamaguchi, K.; Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 1446. 9-Aminocamptothecin: (d) Kharbanda, S.; Rubin, E.; Gungi, H.; Hinz, H.; Giovanella, B.; Pantazis, P.; Kufe, D. *Cancer Res.* **1991**, *51*, 6636.

(8) (a) Hsiang, Y. H.; Hertzberg, R.; Hecht, S.; Liu, L. F. *J. Biol. Chem.* **1985**, *260*, 14873. Hertzberg, R. P.; Caranfa, M. T.; Hecht, S. M. *Biochemistry*, **1989**, *28*, 4629. (b) Liu, L. F. *Annu. Rev. Biochem.* **1989**, *58*, 351. (c) Hsiang, Y. H.; Liu, L. F. *Cancer Res.* **1988**, *48*, 1722. (d) Thomsen, B.; Mollerup, S.; Bonven, B. J.; Frank R.; Blocker, H.; Nielson, O. F.; Westergaard, O. *EMBO J.* **1987**, *6*, 1817.

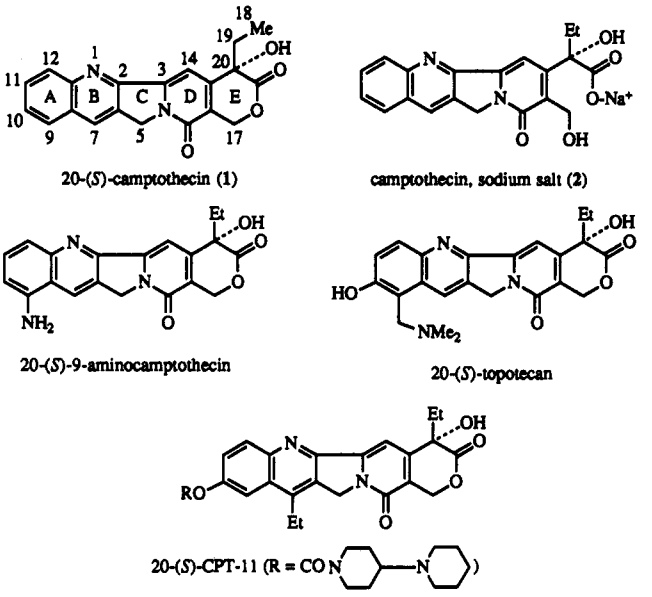
(9) (a) See the following editorial: Chemotherapy: Topoisomers as Targets. *Lancet* **1990**, *335*, 82. (b) Berry, D. E.; Mackenzie, L.; Shultis, E. A.; Chan, J. A.; Hecht, S. M. *J. Org. Chem.* **1992**, *57*, 420.

0022-3263/93/1958-0611$04.00/0

Scheme I



camptothecin and its active analogs. Camptothecin is still a rather difficultly accessible alkaloid.[10] The analogs which are currently of interest are synthesized from the natural product (albeit in good yield).[7,11] Moreover the range of such analogs which would be available in a reasonable way by partial synthesis from camptothecin is necessarily limited. Finally, the sorts of molecular modifications needed to probe in detail the structural basis of the topoisomerase inhibitory properties of the drug are not always available by chemical manipulations of the parent structures. It is with these considerations in mind that we reevaluated the problem of finding a straightforward, decent yielding, and relatively inexpensive route to camptothecin.



Discussion of Results

In this effort we relied on the rather direct route to pyridones which we developed in connection with our original total synthesis (see eq 1).[12] In that work, we used the highly reactive 1,3-dicarbomethoxyallene as our annulating agent. In the interim, a significant simplification was achieved when it was found that the reaction could be conducted equally effectively with the readily available dimethyl 3-chloroglutaconate (7, vide infra) in the presence of triethylamine. Presumably, under these conditions the allene is generated in situ (see Experimental Section for the synthesis of 8).

Another key step in our earlier synthetic study was the construction of the E-ring lactone of the camptothecin type system by the reaction of pyridone-4-acetic acid esters (where C_3 is free) with formaldehyde (see eq 2). Our original total synthesis of camptothecin suffered badly because this hydroxymethylation reaction had been carried out on a substrate where C_5 was also unsubstituted. When so conducted, this reaction produced substantial quantities of the isocamptothecin substitution pattern (vide infra).[12d,e]

During the course of an analog synthesis, Etheredge demonstrated a way in which regioselectivity in the desired precamptothecin sense could be attained.[12c] It was found that the "lactomethylation" reaction could be achieved with a C_5 ester function still in place. Subsequent decarbomethoxylation of this "extraneous" C_5 carbomethoxy group gives rise to the required camptothecin D:E pattern (see Scheme I).

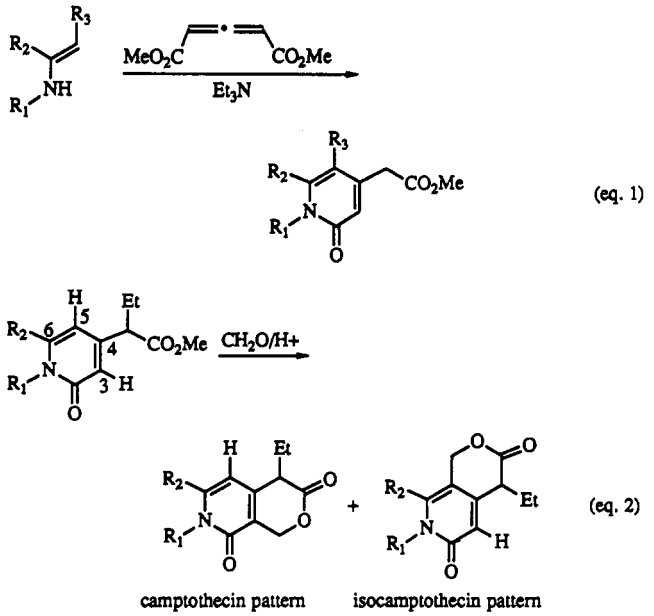
Clearly, a successful Friedländer quinoline synthesis[13] carried out on compound 4 or 5 would give rise to

(10) (a) From *Nothapodytes foetida*: Govindachari, T. R.; Viswanathan, N. *Ind. J. Chem.* **1972**, *10*, 453. (b) From *Camptotheca Acuminata*: Lin, L.-T.; Chao, T.-Y.; Hsu, J.-S. *Hva Hsueh Hsueh Pao*, **1977**, *35*, 227; *Chem. Abstr.* **1978**, *89*, 22078S.

(11) Sawada, S.; Matsuoka, S.; Nokata, K.; Nagata, H.; Furuta, T.; Yokokura, T.; Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 3183. (b) Sawada, S.; Nokata, K.; Furuta, T.; Yokokura, T.; Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 2574.

(12) Danishefsky, S.; Etheredge, S. J.; Volkmann, R.; Eggler, J.; Quick, J. *J. Am. Chem. Soc.* **1971**, *93*, 5575. (b) Volkmann, R.; Danishefsky, S.; Eggler, J.; Solomon, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 5576. (c) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1974**, *39*, 3430. (d) Danishefsky, S.; Volkmann, R.; Horwitz, S. B. *Tetrahedron Lett.* **1973**, 2521. (e) Quick, J. *Tetrahedron Lett.* **1977**, 327.

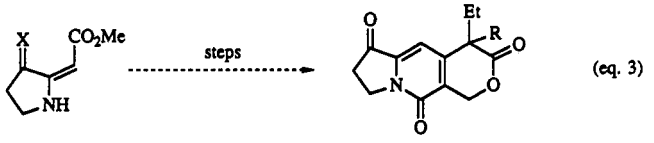
(13) For a review see: Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37.



(eq. 1)

(eq. 2)

desoxycamptothecin (**20**) or camptothecin (**1**), respectively. Our first strategy to reach this series was to try to utilize enamines of the type **3** in the hope that application of our allene annulation reaction to such systems would give rise to such products (eq 3). At this writing, we have not been successful in reducing this approach to practice.



(eq. 3)

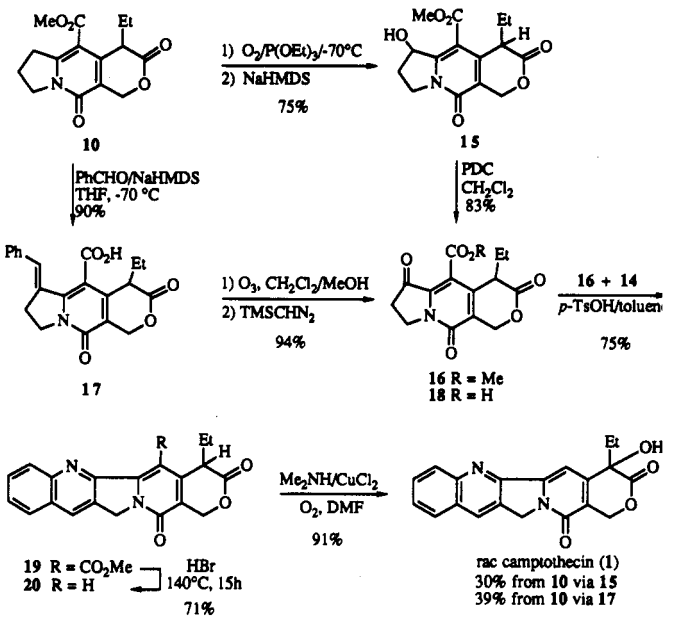
3 X = heterofunctionality

4 R = H → **20**
5 R = OH → **1**

The second phase of our effort involved attempts to convert **11** to the required **4** by oxidation of the C_6 benzylic position. Intermediate **11** is available in three steps from **8** which in turn is obtained from the annulation of vinylogous urethane **6** with **7**. In the intervening years, access to **6** had been much simplified by the work of other laboratories.[14]

It transpired that reaction of selenium dioxide with **11** (dioxane, 160 °C) did indeed afford a 43% yield of the diastereomers **12**. Apparently oxidation reactions of the benzylic position adjacent to C_4 and C_6 (pyridone numbering) are quite competitive, and good yields of **13** were not realized. While it might have been thought that **12** is to be preferred to **13** in that it already contains the future C_{20} hydroxyl, this was not the case in practice. The best yield[15] we achieved for the conversion of **12** to **5** was 45% by PDC oxidation. Unfortunately, the tricyclic α-hydroxy lactone substructure in **12** is rather unstable to oxidation conditions, although no other pure products were isolated. As expected, a Friedländer quinoline synthesis using **5** and **14** occurred smoothly to afford an 80% yield of *dl*-camptothecin (**1**). The overall conversion of **11** to **1** had been accomplished in ca. 15% yield. Unfortunately, removal of the carbomethoxy group of **10** by the action of hot HBr produced product **11** in only 53% yeid. Therefore the yield of camptothecin from **10** by this route is 8%.

Scheme II



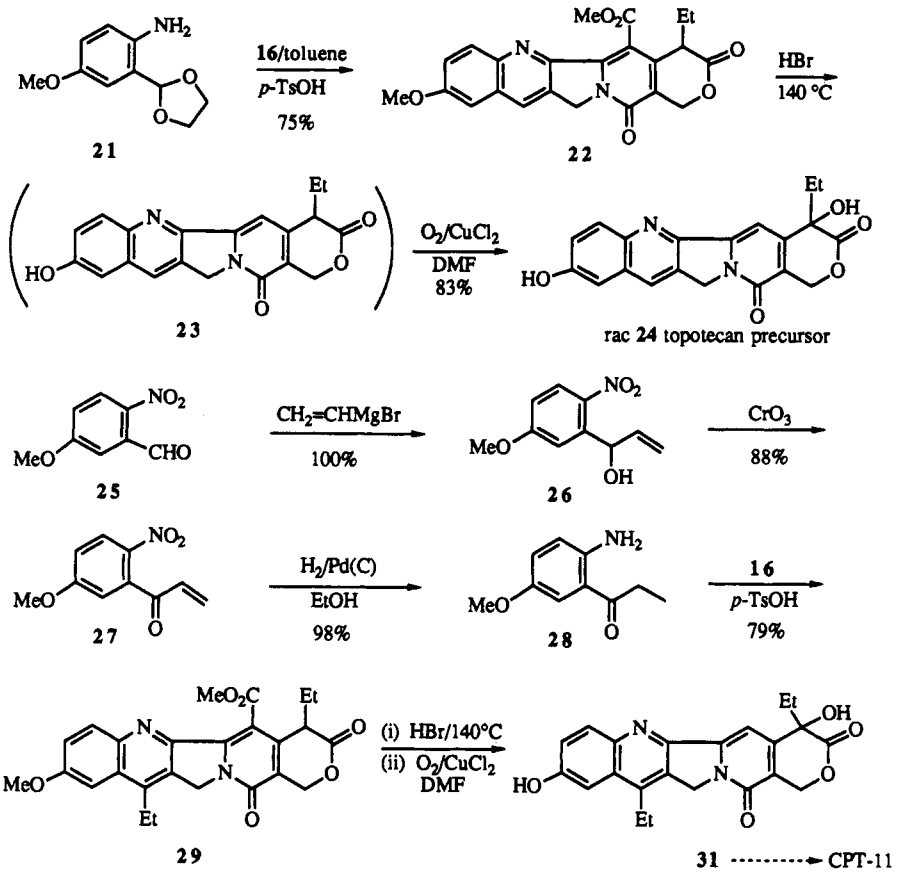
Much greater success was realized through our third approach. This undertaking was based on the hope that inclusion of the C_5 carbomethoxy function (as in compound **10**) might help to render the C_6 benzylic position amenable to selective deprotonation. With the ester in place at C_5 of pyridone **10**, the conjugate base at the C_6 benzylic position is of the vinylogous malonate sort. While this is also the case for deprotonation at the C_4 benzylic center, the C_6 region of the molecule is potentially much less hindered with respect to the action of bases.

Indeed, reaction of **10** with sodium hexamethyldisilazide in the presence of oxygen and triethylphosphite[16] afforded a 75% yield of diastereomers **15** which upon PDC oxidation gave an 83% yield of **16**. Friedländer condensation of **16** with Schiff base **14** occurred in 75% yield. The pentacyclic system of **19** proved to be more stable to the action of hot HBr than was the earlier substrate **4**. After being heated with HBr, compound **19** was converted to *dl*-20-desoxycamptothecin **20** in 71% yield. The latter, upon hydroxylation (O_2; Me_2NH; $CuCl_2$),[4b,17] gave a 91% yield of *dl*-camptothecin (**1**). Thus, by this change in the timing of the critical steps, the yield of racemic camptothecin from the readily available **10** was increased to 30%.

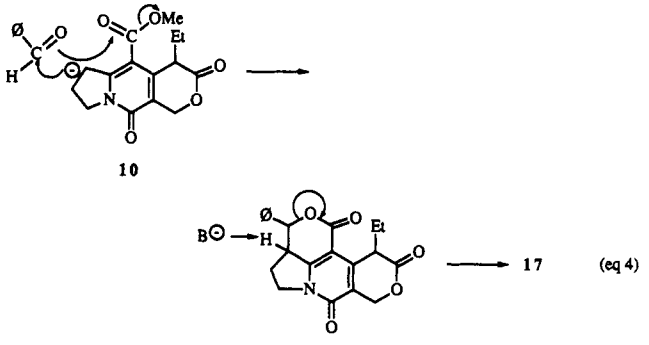
With the welcome finding that the incorporation of the C_4 carbomethoxy function favors deprotonation at the C_6 benzylic position came the prospect of even simpler protocols to reach **16**. In the event, reaction of **10** with sodium hexamethyldisilazide and benzaldehyde afforded a 90% yield of the benzylidene acid **17**. Ozonolysis of this compound afforded a 96% yield of the acid **18** which, upon esterification, provided **16**. Thus, by this three-step protocol, **10** is converted to **16** in 81% yield through the use of simple reagents. (A pathway for the conversion of **10** → **17** which bears some mechanistic similarities to a Stobbe-like condensation[18] is suggested in eq 4). *Through the use of this functionalization method, the yield of*

(14) Celériér, J.-P.; Deloisy, E.; Lhommet, G.; Maitte, P. *J. Org. Chem.* **1979**, *44*, 3089.
(15) Oxidation of **12** with MnO_2, TPAP, DDQ, PCC, and Swern gave lower yields of **5**.
(16) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(17) Boch, M.; Korth, T.; Nelke, J. M.; Pike, D.; Radunz, H.; Winterfeldt, E. *Chem. Ber.* **1972**, *105*, 2126.
(18) Johnson, W. S.; Daub, G. H. *Org. React.* **1951**, *6*, 1.

Scheme III



racemic camptothecin from the abundantly available pyridone 10 via 17 is currently 39%.



With this protocol well in hand for the synthesis of racemic camptothecin, we readily reached the important analogs, i.e., the topotecan precursor 10-hydroxycamptothecin (**24**) and the CPT-11 precursor **31** (Scheme III). Friedländer condensation of **16** with the amino ketal **21**[4c] under acidic conditions afforded **22** (75% yield). Treatment of this compound with HBr at 140 °C resulted in decarbomethoxylation at C_{14} and demethylation at C_{10} to give crude 10-hydroxy-20-desoxycamptothecin (**23**). Hydroxylation (at C_{20}) of this compound under the usual conditions gave an 83% yield (from **22**) of **24**, the phenolic precursor of topotecan.

The synthesis of the CPT-11 precursor **31** started with the quantitative addition of vinylmagnesium bromide to the known **25**.[4c] Oxidation of **26** with CrO_3 gave an 88% yield of **27** which on catalytic reduction (H_2/Pd/(C)/EtOH) gave a 98% yield of **28**. Coupling of this compound with **16** occurred in 79% yield. Concurrent decarbomethoxylation–demethylation of **29** was achieved through the action of hot HBr. Hydroxylation at C_{20} of 7-ethyl-10-hydroxy-20-desoxycamptothecin (**30**) in the usual way smoothly afforded the CPT-11 phenol, **31**.

In summary, incorporation of a seemingly extraneous carbomethoxyl group via the pyridone annulation reaction and its inclusion at C_{14} of the pentacyclic camptothecin skeleton until late in the synthesis has accomplished several strategic goals. The ester stabilizes the enamine (see structure **6**) required for condensation with the allene derived from **7** (see compound **8**). It serves to define the sense of lactomethylation of the pyridone and C_3 (see transformation of **9** → **10**). Moreover, it imparts a high kinetic acidity to the C_6 benzylic position of the resultant pyridone relative to C_4 thereby allowing for ready and selective functionization at this center (see **10** → **15** and **10** → **17**). It further transpired that removal of the carbomethoxy function is more efficiently conducted at a late (pentacyclic) stage.

Further extensions and applications of this straightforward synthesis are well under way. One goal of the program is the achievement of an enantioselective construction at carbon 20 of camptothecin and its analogs. Another is that of providing definitive SAR insights via probe structures not currently available from camptothecin itself. Hopefully this chemistry might lead to even more effective camptothecin analogs.

Experimental Section[19]

4-(Carbomethoxymethyl)-5-carbomethoxy-1,6-cyclopentano-2-pyridone (8). To the solution of enamine **6** (27.6 g, 195 mmol) in absolute ethanol (200 mL) was added dimethyl-3-chloroglutaconate **7**[20] (41.3 g, 215 mmol) and triethylamine (32 mL, 230 mmol). The reaction was stirred at room temperature for 65 h. The reaction mixture was concentrated to near dryness.

Trituration of the residue with dry ether (50 mL) afforded **8** as a white solid (47.8 g, 92%): ^{1}H NMR ($CDCl_3$) δ 6.21 (s, 1 H), 4.11 (t, J = 7.4 Hz, 2 H), 3.74 (s, 3 H), 3.73 (s, 2 H), 3.66 (s, 3 H), 3.44 (t, J = 7.9 Hz, 2 H), 2.16 (quintet, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.9, 165.8, 161.0, 157.4, 147.1, 120.1, 106.5, 52.1, 51.6, 49.1, 41.1, 34.7, 20.6; IR (neat) 2953, 1734, 1716, 1656, 1652, 1520, 1436, 1294, 1203 cm^{-1}.

4-(1-Carbomethoxypropyl)-5-carbomethoxy-1,6-cyclopentano-2-pyridone (9). To a solution of pyridone **8** (47.0 g, 177 mmol) in DME (700 mL) at −70 °C was added potassium *tert*-butoxide (20.8 g, 186 mmol). After 20 min, EtI (50.3 g, 354 mmol) was added, and the solution was allowed to warm to room temperature and stirred for 30 h. The reaction mixture was then poured into brine (300 mL) and the aqueous layer extracted with CH_2Cl_2 (4 × 200 mL). The combined organic phase and the extracts were dried ($MgSO_4$), filtered, and concentrated. The semisolid residue was then recrystallized (EtOAc) to give **9** as pale yellow-green solid (36.54 g, two crops). The mother liquor was subjected to flash chromatography with ethyl acetate to afford an additional 11.2 g (total yield of 91%), mp 92.5–94.0 °C: ^{1}H NMR ($CDCl_3$) δ 6.35 (s, 1 H), 4.13 (dt, J = 1.2, 7.5 Hz, 2 H), 3.99 (t, J = 7.2 Hz, 1 H), 3.80 (s, 3 H), 3.64 (s, 3 H), 3.39 (dt, J = 2.6, 8.0 Hz, 2 H), 2.17 (quintet, J = 7.6 Hz, 2 H), 2.05 (m, 1 H), 1.73 (m, 1 H), 0.91 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.0, 166.1, 161.1, 156.3, 151.6, 117.2, 107.0, 53.1, 51.7, 49.8, 49.2, 34.5, 25.4, 20.7, 12.4; IR (neat) 1741, 1710, 1668 cm^{-1}.

4-Carbomethoxy-de-*AB*-deoxycamptothecin (10). A mixture of ester **9** (5.01 g, 17.1 mmol), paraformaldehyde (3.08 g), concentrated H_2SO_4 (1 mL), and water (1 mL) in dioxane (25 mL) in a sealed thick wall tube was heated at 107 °C for 24 h. The resulting solution was then poured into brine (60 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to a pale yellow oil which eventually solidified upon standing: ^{1}H NMR ($CDCl_3$) δ 5.48 (d, J = 5.8 Hz, 1 H), 5.13 (d, J = 5.8 Hz, 1 H), 4.34 (dd, J = 5.1, 9.1 Hz, 1 H), 4.19 (dt, J = 2.9, 7.6 Hz, 2 H), 3.85 (s, 3 H), 3.48 (dt, J = 3.6, 7.9 Hz, 2 H), 2.22 (quintet, J = 7.6 Hz, 2 H), 1.65–2.01 (m, 2 H), 1.08 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.3, 165.2, 157.9, 157.0, 147.3, 118.5, 104.9, 65.0, 52.0, 49.5, 44.3, 34.8, 25.3, 20.7, 11.9; IR (neat) 1734, 1713, 1650 cm^{-1}.

De-*AB*-deoxycamptothecin (11). A mixture of tricycle **10** in aqueous HBr (48%, 50 mL) was heated in a sealed tube at 105 °C for 18 h. The resulting solution was then poured into brine (60 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was then subjected to flash chromatography (50/50/1 $CHCl_3$/EtOAc/MeOH) to afford **11** as an off-white solid (2.11 g, 53%): mp 146.0–147.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.98 (s, 1 H), 5.38 (d, J = 5.7 Hz, 1 H), 5.20 (d, J = 5.7 Hz, 1 H), 4.12 (t, J = 7.3 Hz, 2 H), 3.35 (t, J = 6.6 Hz, 1 H), 3.08 (t, J = 7.7 Hz, 2 H), 2.21 (quintent, J = 7.4 Hz, 2 H), 1.80–1.98 (m, 2 H), 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.4, 158.5, 150.5, 146.6, 117.2, 100.2, 66.1, 48.6, 45.8, 31.8, 25.1, 21.5, 11.3; IR (neat) 1739, 1651, 1574 cm^{-1}.

7-Hydroxy-de-*AB*-camptothecin (12). A mixture of **11** (778 mg, 3.33 mmol) and SeO_2 (1.85 g, 16.7 mmol) in 20 mL of 95% dioxane was heated together in a sealed tube at 160 °C for 4 h. The solution was then poured into water and extracted with CH_2Cl_2 (4 × 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The dark solid residue was then chromatographed (3:1 $CHCl_3$/acetone, 300 mL, and then 30:20:1 $CHCl_3$/acetone/MeOH, 500 mL) to afford **12** as a yellow solid (377.4 mg, 43%). The diastereomeric ratio is about 1/1: ^{1}H NMR (DMSO-d_6 with 1 small drop of D_2O) δ 6.51 (s, 1 H), 5.25 (dd, J = 15.4, 19.0 Hz, 2 H), 5.13 (t, J = 7.0 Hz, 1 H), 4.08 (m, 1 H), 3.83 (m, 1 H), 2.42 (m, 1 H), 1.93 (m, 1 H), 1.76 (m, 2 H), 0.82 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 172.59, 172.54, 156.87, 152.94, 152.90, 149.83, 149.78, 116.33, 97.37, 72.71, 72.09, 72.04, 71.94, 65.16, 59.68, 45.62, 31.25, 31.19, 30.30, 30.26, 7.66 ppm (21 peaks observed); IR (KBr) 3392, 1741, 1652, 1570 cm^{-1}; HRMS calcd for $C_{13}H_{15}NO_5$ (M^+) 265.0950, found 265.0952.

7-Oxo-de-*AB*-camptothecin (5). To the suspension of **12** (356.1 mg, 1.34 mmol) and 4-Å molecular sieves (activated powder, 1.50 g) in CH_2Cl_2 (15 mL) at 0 °C was added pyridinium dichromate (1.01 g, 2.68 mmol). After 3.5 h, 30 mL of EtOAc was added to the mixture, and the slurry was filtered through a plug of silica gel and Celite. Evaporation of the filtrate and chromatography (1:1 $CHCl_3$/EtOAc) gave **5** (159.6 mg, 45%). ^{1}H NMR ($CDCl_3$) δ 7.23 (s, 1 H), 5.68 (d, J = 7.1 Hz, 1 H), 5.25 (d, J = 7.1 Hz, 1 H), 4.35 (t, J = 6.8 Hz, 2 H), 3.65 (s, 1 H), 2.97 (t, J = 6.8 Hz, 2 H), 1.82 (m, 2 H), 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.0, 173.3, 157.7, 149.3, 139.9, 124.5, 100.8, 72.3, 66.3, 42.2, 33.7, 31.8, 7.7; IR (neat) 3404, 1736, 1656, 1598 cm^{-1}; HRMS calcd for $C_{13}H_{13}NO_5$ (M^+) 263.0794, found 263.0809.

***dl*-Camptothecin (1).** A suspension of **5** (185.2 mg, 0.704 mmol) and amino toluidine 14[21] (178 mg, 0.844 mmol) in toluene (20 mL) was refluxed for 0.5 h. Then, *p*-TsOH (10 mg) was added, and the reaction was refluxed with a Dean-Stark trap for 3.5 h. The solution was cooled to room temperature, and the solvent was removed. Column chromatography (100:10:1 $CHCl_3$/MeCN/MeOH) gave 196.5 mg (80%) of **1** as a tan solid. Recrystallization (10% MeOH/$CHCl_3$) gave 173.1 mg of **1** as an off-white solid: mp 264–265 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.70 (s, 1 H), 8.16 (m, 2 H), 7.88 (t, J = 7.5 Hz, 1 H), 7.72 (t, J = 7.3 Hz, 1 H), 7.36 (s, 1 H), 6.54 (s, 1 H), 5.43 (s, 2 H), 5.30 (s, 1 H), 1.87 (m, 2 H), 0.88 (t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.4, 156.8, 149.9, 147.9, 145.4, 131.6, 130.3, 129.8, 129.0, 128.4, 127.9, 127.6, 119.0, 96.6, 72.3, 65.2, 50.2, 30.2, 7.7 ppm (19 peaks observed); IR (KBr) 3271, 1755, 1651, 1583 cm^{-1}; HRMS calcd for $C_{20}H_{16}N_2O_4$ (M + 1$^+$) 349.1188, found 349.1184.

4-Carbomethoxy-7-hydroxy-de-*AB*-deoxycamptothecin (15). To an oxygenated solution of **10** (291 mg, 1.00 mmol) and 0.38 mL (2.20 mmol) of $P(OEt)_3$ in 20 mL of THF at −70 °C was added NaHMDS (1.1 mL, 1.1 mmol) over 2 min. The solution was warmed to room temperature over 7 h and was quenched with saturated NH_4Cl (10 mL). The reaction mixture was extracted with $CHCl_3$ (30 mL × 3), and the extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was then loaded to a flash column and eluted with 9:1 $CHCl_3$/MeOH to give alcohol **15** (230 mg, 75%) as a mixture of diastereomers (1.3:1 ratio from integration of ^{1}H NMR): ^{1}H NMR ($CDCl_3$) δ 5.40–5.52 (m, 3 H), 5.10 (m, 2 H), 4.42 and 4.05 (1 H), 4.24 (m, 2 H), 3.90 (s, 3 H), 2.31 (m, 2 H), 1.70–1.91 (m, 2 H), 1.09 and 0.98 (2 t's, J = 7.3 Hz, 3 H); IR (neat) 3390, 2958, 1732, 1651 cm^{-1}; HRMS calcd for $C_{15}H_{17}NO_6$ (M^+) 307.1056, found 307.1062.

4-Carbomethoxy-7-oxo-de-*AB*-deoxycamptothecin (16). A mixture of alcohol **15** (595 mg, 1.94 mmol), PDC (2.18 g, 5.80 mmol), and activated 4-Å molecule sieve powder (2.20 g) in CH_2Cl_2 (20 mL) was stirred at 0–5 °C for 4 h. It was then diluted with EtOAc (30 mL) and filtered through Celite. The flask and the residue were rinsed and washed with 1:1 EtOAc/$CHCl_3$ (20 mL × 5), and the filtrate was concentrated to give pure **16** (490.2 mg, 83%): ^{1}H NMR ($CDCl_3$) δ 5.55 (d, J = 17.2 Hz, 1 H), 5.24 (d, J = 17.2 Hz, 1 H), 4.32 (t, J = 6.8 Hz, 2 H), 3.93 (s, 3 H), 3.68 (dd, J = 5.2, 8.6 Hz, 1 H), 2.97 (t, J = 6.8 Hz, 2 H), 2.01 (m, 1 H), 1.80 (m, 1 H), 1.04 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 194.3, 169.5, 164.0, 157.2, 144.6, 137.7, 126.4, 110.2, 65.7, 53.4, 43.6, 42.2, 33.7, 26.1, 11.5; IR (neat) 1742, 1658 cm^{-1}; HRMS calcd for $C_{15}H_{15}NO_6$ (M^+) 305.0899, found 305.0911.

Benzylidene (17). To a solution of 587 mg (2.0 mmol) of ester **10** and 0.19 mL (1.9 mmol) of benzaldehyde in 15 mL of THF at −70 °C was added 2.2 mL (2.2 mmol) of NaHMDS (1 M in THF). The orange solution was allowed to warm to room temperature over 16 h before it was quenched with 15 mL of 5% HCl. After an additional 2 h, the mixture was extracted with 4:1 $CHCl_3$/MeOH (5 × 20 mL), dried ($MgSO_4$), and concentrated. The resulting yellow solid was triturated with THF to afford 624 mg (90%) of **17** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 6 H), 5.32 (d, J = 16.1 Hz, 1 H), 5.01 (d, J = 16.1 Hz, 1 H), 3.98 (t, J = 7.4 Hz, 2 H), 3.63 (m, 1 H), 3.04 (dt, J = 2.3, 6.2 Hz, 2 H), 1.88 (m, 1 H), 1.68 (m, 1 H), 0.89 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 171.4, 167.1, 157.6, 146.9, 145.4, 135.4, 132.5,

(19) Melting points are uncorrected and were measured using a digital melting point Electrothermal IA 9100 apparatus. Infrared spectra (IR) were obtained with a Perkin-Elmer 1600 Series Fourier-Transform (FT). NMR spectra were recorded using Bruker AMX-400 spectrometer instrument. High-resolution mass spectra (HRMS) were recorded at the Department of Chemistry of Columbia University. Flash chromatography was performed using EM Science silica gel 60 230–400 mesh. Reactions were conducted under a nitrogen atmosphere unless otherwise described.

(20) Bryson, T. A.; Dolak, T. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 505.

128.8, 117.9, 107.9, 65.4, 46.6, 44.3, 27.7, 25.4, 11.4; IR ($CHCl_3$) 3500–2400, 1739, 1717, 1622, 1574, 1531, 1214 cm^{-1}; HRMS calcd for $C_{21}H_{19}NO_5$ (M^+) 365.1302, found 365.1311.

Keto Acid 18. A −70 °C solution of 7.0 mg (0.020 mmol) of 17 in 10 mL of MeOH and 10 mL of CH_2Cl_2 was subjected to O_3 for 10 min before the addition of Me_2S. The mixture was allowed to warm to room temperature over 12 h then evaporated to leave 5.6 mg (96%) of ketone 18 which was used without further purification: ^1H NMR (DMSO-d_6/$CDCl_3$) δ 5.58 (d, J = 17.2 Hz, 1 H), 5.21 (d, J = 17.2 Hz, 1 H), 4.29 (t, J = 7.2 Hz, 2 H), 3.80 (m, 1 H), 2.97 (t, J = 7.2 Hz, 2 H), 2.11 (m, 1 H), 1.84 (m, 1 H), 0.91 (t, J = 7.2 Hz, 3 H); IR (neat) 3426, 1738, 1712, 1659 cm^{-1}.

4-Carbomethoxy-7-oxo-de-*AB*-deoxycamptothecin (16). A solution of 291 mg (1.0 mmol) of keto acid 17 in 3 mL of benzene and 1 mL of MeOH was treated with 0.65 mL of $TMSCHN_2$ (2 M in hexane). After the solution was stirred for 3 h the solvents were evaporated and the residue was chromatographed (95:5 $CHCl_3$/MeOH) to afford 287 mg (94%) of ester 16.

14-Carbomethoxy-20-deoxycamptothecin (19). A solution of keto ester 16 (601 mg, 1.97 mmol) and amine 14[21] (497 mg, 2.36 mmol) in toluene (20 mL) was refluxed for 40 min. TsOH (20 mg) was added, the reaction flask was equipped with a Dean-Stark trap, and the whole was refluxed for 4 h before the reaction was cooled to room temperature. The mixture was concentrated (10 mL), and the resulting solid was filtered and recrystallized ($CHCl_3$) to give 19 (578 mg, 75%): mp 300–302 °C dec; ^1H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 8.11 (d, J = 8.4 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 7.81 (dt, J = 1.2, 7.7 Hz, 1 H), 7.66 (t, J = 7.5 Hz, 1 H), 5.62 (d, J = 16.2 Hz, 1 H), 5.30 (d, J = 16.2 Hz, 1 H), 5.28 (s, 2 H), 4.12 (s, 3 H), 3.78 (dd, J = 5.2, 8.7 Hz, 1 H), 2.12 (m, 1 H), 1.93 (m, 1 H), 1.11 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.2 165.6, 157.2, 151.4, 148.8, 145.1, 144.4, 130.9, 130.6, 130.3, 128.53, 128.48, 128.04, 127.99, 120.5, 108.3, 65.7, 52.9, 50.2, 44.1, 26.0, 11.6; IR (KBr) 2930, 1732, 1652, 1616, 1452 cm^{-1}; HRMS calcd for $C_{22}H_{18}N_2O_5$ (M^+) 390.1216, found 390.1231.

20-Desoxycampothecin (20). A solution of ester 19 (207.5 mg, 0.531 mmol) in 48% aqueous HBr (8 mL) in a sealed tube was heated for 15 h at 140 °C. After it was cooled, the reaction mixture was concentrated to near dryness via vacuum. The mixture was then carefully neutralized with 2 N NaOH and saturated $NaHCO_3$ to pH 7.5. The aqueous mixture was extracted with $CHCl_3$ (15 mL × 10), and the combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed (49:1 $CHCl_3$/MeOH) to give 20 (124.3 mg, 71%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 8.21 (d, J = 8.4 Hz, 1 H), 7.93 (d, J = 7.0 Hz, 1 H), 7.83 (dt, J = 1.4, 6.9 Hz, 1 H), 7.66 (dt, J = 1.0, 7.5 Hz, 1 H), 7.19 (s, 1 H), 5.57 (d, J = 16.3 Hz, 1 H), 5.39 (d, J = 16.3 Hz, 1 H), 5.29 (s, 2 H), 3.62 (t, J = 6.6 Hz, 1 H), 2.09 (m, 2 H), 1.09 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 157.9, 152.4, 148.9, 147.2, 146.0, 131.2, 130.7, 129.7, 1289.6, 128.2, 128.1, 120.7, 99.8, 66.1, 50.0, 45.9, 25.4, 11.4; HRMS calcd for $C_{20}H_{16}N_2O_3$ (M^+) 332.1161, found 332.1151.

***dl*-Camptothecin (1).** To a solution of 20 (47.8 mg, 0.144 mmol), $CuCl_2$ (80 mg) and dimethylamine (100 μl) in DMF (16 mL) was bubbled in oxygen for 7 h. The reaction mixture was concentrated in vacuo to about 5 mL and was then diluted with water. A solution of saturated NH_4Cl was used to adjusted the pH to 6, and the resulting mixture was extracted with chloroform (10 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed (98:2 $CHCl_3$/MeOH) to give 1 (45.5 mg, 91%).

14-Carbomethoxy-10-methoxy-20-deoxycamptothecin (22). A solution of amino acetal 21[4b] (329 mg, 1.69 mmol) and ketone 16 (429 mg, 1.41 mmol) in 15 mL of toluene was heated for 30 min before the addition of 10 mg of *p*-TsOH. The resulting red solution was heated at reflux with removal of water for 3.5 h. The solvent was removed, and the residue was chromatographed (99:1 $CHCl_3$/MeOH) and then triturated with a 2:1 ether/THF solution to afford 444 mg (75%) of ester 22 as an off-white solid: ^1H NMR ($CDCl_3$) δ 8.24 (s, 1 H), 7.99 (d, J = 9.3 Hz, 1 H), 7.44 (dd, J = 2.8, 9.3 Hz, 1 H), 7.13 (d, J = 2.7 Hz, 1 H), 5.61 (d, J = 16.3 Hz, 1 H), 5.29 (d, J = 16.2 Hz, 1 H), 5.24 (s, 2 H), 4.15 (s, 3 H), 3.97 (s, 3 H), 3.85 (m, 1 H), 2.13 (m, 1 H), 1.88 (m, 1 H), 1.10 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.3, 165.7, 159.3, 157.1, 145.0, 144.9, 131.6, 129.4, 129.1, 123.7, 119.6, 105.0, 65.6, 55.7, 52.8, 50.1, 43.9, 25.9, 11.5; IR (KBr) 1731, 1651 cm^{-1}; HRMS calcd for $C_{23}H_{21}N_2O_6$ (M + H) 421.1477, found 421.1421.

10-Hydroxycamptothecin (24). A solution containing 24.1 mg (0.057 mmol) of ester 22 in 2 mL of 48% HBr was heated at 140 °C in a sealed tube for 15 h. The solvent was evaporated, and the residue was made neutral by the addition of saturated $NaHCO_3$ solution. The aqueous solution was extracted with 4:1 $CHCl_3$/MeOH (5 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave crude 10-hydroxy-20-deoxycamptothecin (23) which was immediately dissolved in 2 mL of DMF. After the addition of $CuCl_2$ (40 mg) and Me_2NH (50 μL), O_2 was passed through the solution for 8 h. The mixture was then diluted with water (3 mL), and saturated NH_4Cl was added to adjust the pH to 6. Extraction with $CHCl_3$ (5 × 10 mL), drying ($MgSO_4$), chromatography (9:1 $CHCl_3$/MeOH), and recrystallization (13% MeOH/$CHCl_3$ and EtOAc) afforded 17.3 mg (83%) of 24, mp 266–268 °C (lit.[4b] mp 265–268 °C).

Benzylic Alcohol 26. To a −70 °C solution of 860 mg (4.75 mmol) of 5-methoxy-2-nitrobenzaldehyde (25) in 20 mL of THF was added 6.65 mL (6.65 mmol) of vinylmagnesium bromide. After being stirred for 3.5 h, the mixture was quenched with 20 mL of 0.010 N HCl and diluted with 100 mL of ether (3 × 25 mL). The yellow extracts were dried ($MgSO_4$) and concentrated to afford 993 mg (100%) of alcohol 26: ^1H NMR (CDCl3) δ 7.95 (d, J = 9.1 Hz, 1 H), 7.19 (d, J = 2.8 Hz, 1 H), 6.79 (dd, J = 2.8, 9.1 Hz, 1 H), 5.96 (m, 1 H), 5.84 (d, J = 5.2 Hz, 1 H), 5.30 (dt, J = 1.3, 17.5 Hz, 1 H), 5.13 (dt, J = 1.3, 17.5 Hz, 1 H), 3.84 (s, 3 H), 3.40 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 163.8, 141.4, 140.6, 138.0, 127.5, 115.8, 113.1 (2 lines), 69.7, 55.8; IR (neat) 3437, 1613 cm^{-1}; HRMS calcd for $C_{10}H_{11}NO_4$ (M^+) 209.0727, found 209.0699.

Enone 27. Freshly prepared Jones reagent (1.1 mL, 2.67 M) was added dropwise to 418 mg (2.0 mmol) of alcohol 26 in 4 mL of acetone at room temperature. After 10 min, ice–water (5 mL) was added followed by 1 mL of saturated $NaHSO_3$. The resulting mixture was extracted with ether (4 × 10 mL) and then filtered through Florisil. Evaporation of the solvent left 363 mg (88%) of ketone 27 as an off-colored oil: ^1H NMR ($CDCl_3$) δ 8.08 (d, J = 9.1 Hz, 1 H), 6.99 (dd, J = 2.8, 9.0 Hz, 1 H), 6.75 (d, J = 2.8 Hz, 1 H), 6.59 (m, 1 H), 5.97 (d, J = 10.6 Hz, 1 H), 5.78 (d, J = 17.6 Hz, 1 H), 3.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 193.3, 164.1, 139.2, 138.1, 136.5, 130.9, 126.9, 115.3, 113.4, 56.2; IR (neat) 1681 cm^{-1}; HRMS calcd for $C_{10}H_9NO_4$ (M^+) 207.0571, found 207.0535.

5-Methoxy-2-aminopropiophenone (28). A solution of 207 mg (1.0 mmol) of nitro enone 27 in 3 mL of absolute EtOH containing 10 mg of 10% Pd(C) was stirred under an atmosphere of H_2 for 4 h. After this time, the mixture was filtered through Celite and the solvent was evaporated to afford pure amino ketone 28 as a white solid: mp 57–58 °C (lit.[22] mp 58 °C); ^1H NMR ($CDCl_3$) δ 7.25 (d, J = 1.2 Hz, 1 H), 6.96 (dd, J = 1.2, 8.9 Hz, 1 H), 6.63 (d, J = 9.6 Hz, 1 H), 3.77 (s, 3 H), 2.96 (q, J = 7.2 Hz, 2 H), 1.60 (bs, 2 H), 1.22 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.5, 150.2, 144.7, 122.7, 118.7, 117.9, 113.9, 56.0, 32.4, 8.6; IR (neat) 3469, 3352, 1659 cm^{-1}.

14-Carbomethoxy-7-ethyl-10-methoxy-20-deoxycamptothecin (29). A solution of amino ketone 28 (179 mg, 1.00 mmol) and tricyclic ketone 16 (244 mg, 0.800 mmol) in 10 mL of toluene were heated together for 30 min before the addition of 10 mg of *p*-TsOH. The resulting red solution was heated at reflux with removal of water for 7.25 h. The solvent was removed, and the residue was chromatographed (9:1 $CHCl_3$/MeOH) and then triturated with a 2:1 ether/THF solution to afford 283 mg (79%) of ester 29 as an off-white solid: ^1H NMR ($CDCl_3$) δ 8.02 (d, J = 9.2 Hz, 1 H), 7.45 (dd, J = 2.7, 9.2 Hz, 1 H), 7.29 (d, J = 2.7 Hz, 1 H), 5.64 (d, J = 16.3 Hz, 1 H), 5.31 (d, J = 16.3 Hz, 1 H), 5.22 (s, 2 H), 4.11 (s, 3 H), 4.02 (s, 3 H), 3.79 (m, 1 H), 3.15 (q, J = 7.7 Hz, 2 H), 2.10 (m, 1 H), 1.94 (m, 1 H), 1.38 (t, J = 7.7 Hz, 3 H), 1.11 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.3, 165.7, 159.2, 157.3, 148.4, 145.8, 145.4, 145.1, 143.4, 132.6, 128.1, 127.2, 122.6, 119.4, 101.2, 65.6, 55.7, 52.8, 49.5, 44.0, 25.9, 23.1, 13.5, 11.6; HRMS calcd for $C_{25}H_{25}N_2O_6$ (M + H) 448.9835, found 448.9818.

(21) Borsche, W.; Doeller, W.; Wagner-Roemmich, M. *Chem. Ber.* **1943**, *76*, 1099.

(22) Goutarel, R.; Janot, M. M.; Corrodi, H.; Prelog, V. *Helv. Chim. Acta* **1954**, *37*, 1805.

7-Ethyl-10-hydroxycamptothecin (31). A solution containing 44.8 mg (0.10 mmol) of ester **29** in 5 mL of 48% HBr was heated at 140 °C in a sealed tube for 15 h. The solvent was evaporated, and the residue was made neutral by the addition of saturated $NaHCO_3$ solution. The aqueous solution was extracted with 4:1 $CHCl_3$/MeOH (5 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave crude 7-ethyl-10-hydroxy-20-deoxycamptothecin (**30**) which was immediately dissolved in 4 mL of DMF. After the addition of $CuCl_2$ (80 mg) and Me_2NH (100 uL), O_2 was passed through the solution for 8 h. The mixture was then diluted with water (10 mL), and saturated NH_4Cl was added to adjust the pH to 6. Extraction with $CHCl_3$ (5 × 15 mL), drying ($MgSO_4$), and chromatography (9:1 $CHCl_3$/MeOH) afforded 32.5 mg (83%) of **31**. This material had spectroscopic properties (^1H NMR and IR) identical to the previously reported (+)-isomer, mp 214–217 °C (lit.[7c] mp 214 °C).

Acknowledgment. We thank V. Parmakovich and B. Sporer from the Department of Chemistry at Columbia University for mass spectral analyses. C.A.C. is grateful to the National Science Foundation for a Postdoctoral Fellowship award.

Supplementary Material Available: Spectroscopic data (^1H NMR, ^{13}C NMR, and IR) for compounds **1**, **5**, **8–12**, **16**, **17**, **19**, **20**, **22**, and **26–29** (49 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.