Pergamon

Tetrahedron, Vol. 53, No. 32, pp. 11049-11060, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00365-7

Practical Total Synthesis of (+)-Camptothecin: The Full Story

Marco A. Ciufolini*[§1] and Frank Roschangar

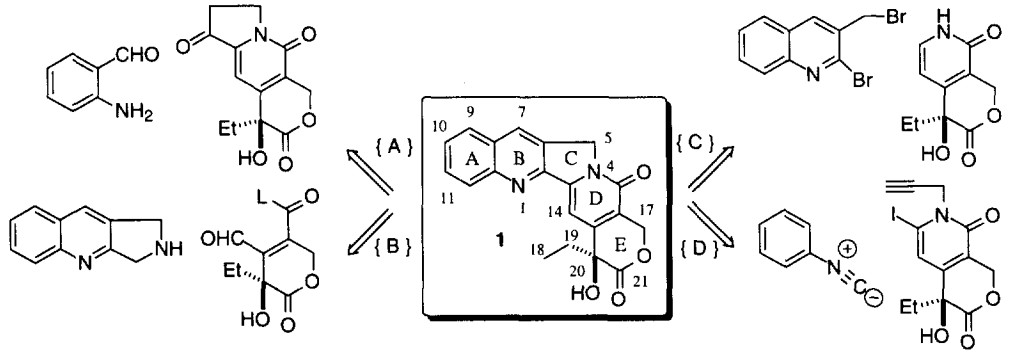
Department of Chemistry, Rice University, P.O. Box 1892, Houston, Texas 77251, U.S.A.

ABSTRACT: The evolution of our strategy for the synthesis of (+)-Camptothecin and related substances is presented in detail. © 1997 Elsevier Science Ltd.

Introduction.. Camptothecin (CPT, **1**)[2] and related compounds[3] have recently returned to the forefront of experimental cancer treatment.[4] Good evidence regarding their biomolecular target and mode of action has been produced.[5] Furthermore, previously unrecognized antiviral properties[6] and modulation of protein synthesis[7] have now been observed for **1** and related natural products. Not surprisingly, renewed biomedical interest, scarcity of the natural product, and difficulties encountered in the preparation of derivatives with a better pharmacological profile directly from **1**, have stimulated a flurry of new synthetic activity in the CPT area.[8]

The numerous syntheses of CPT known to date[8] rest largely[9] on four strategic ideas, depicted in Scheme 1 as retrosynthetic paths A - D. Of these, paths A[10] and B[11] emerged during the "classical" era of CPT chemistry, and the fact that new and ever more efficient developments of these themes continue to appear[12] is a testament to the soundness of the original formulations and the vision of their formulators. Routes C[8c,8d] and D[8f] may be termed "contemporary" and reflect recent advances in synthetic technology.

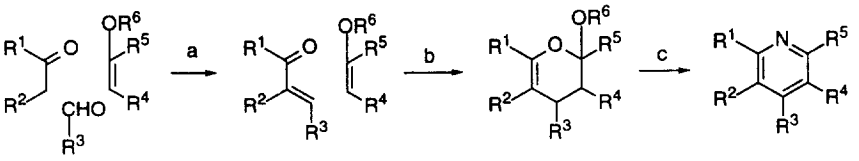
Scheme 1



Our own interest in establishing a practical synthesis of CPT and related substances led us to evaluate the potential of our methodology for the preparation of pyridines (Scheme 2)[13] for the creation of ring D of **1**. The retrosynthetic scenario of Scheme 3 reflects our surmise that the immediate forerunner of CPT should be the *seco* intermediate **2** (L = leaving group), which would have to be amenable to facile formation of the N-4–C-5 bond. The pyridone unit would result upon Polonovski oxidation of pyridine **4**, which in accord with the logic of Scheme 2 would be assembled through merger of quinoline **7**, scalemic aldehyde **8**, and building block **6**. The

[§]It is a pleasure to dedicate this paper to Professor Samuel J. Danishefsky, as an expression of my great admiration for him, and in sincere gratitude for the immense degree of inspiration he provided during our association and ever thereafter.

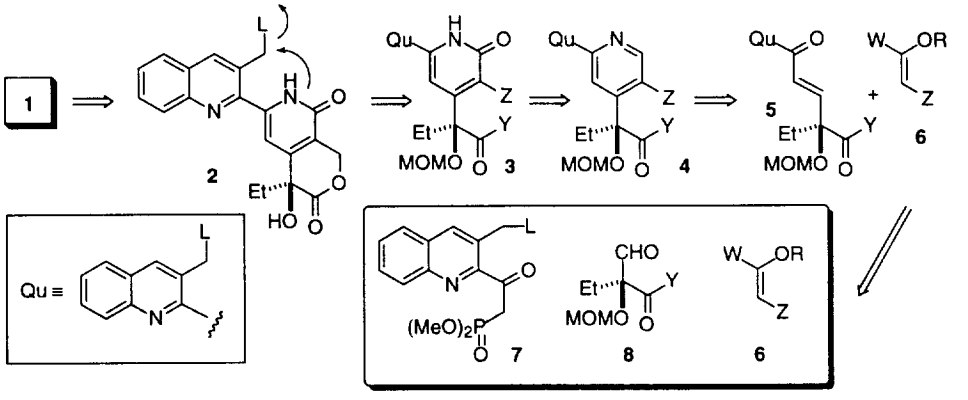
Scheme 2



a. Condense ketone and aldehyde; b. cat. Yb(fod)$_3$, heat; c. HONH$_2$•HCl, heat

precise nature of **6** was to be defined through experiment. It was already apparent that diverse analogues of **1** could be prepared by the same general approach. A communication describing this work has already appeared.[14] Full details of problems and solutions relating to the implementation of this plan are discussed herein.

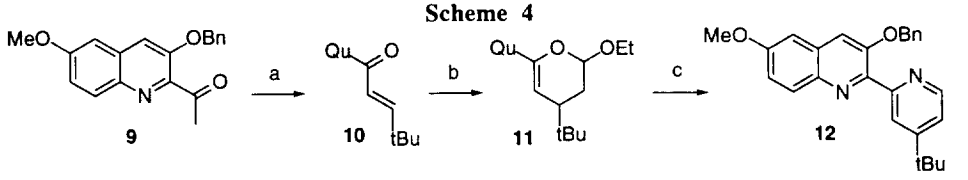
Scheme 3



Initial Investigations . The construction of a competent pyridine forerunner of **1** posed two obvious problems. First, enone **5** required for pyridine formation displays a highly branched C atom (the future C-20 of **1**) immediately adjacent to the π system destined to engage ether **6** in a heterocycloaddition.[15] Steric interactions could well undermine the feasibility of this crucial step. Second, substituent "Z" in **6** must provide the hydroxymethyl segment of the lactone portion of **1**. An expressed CH_2OH is not tolerated during the cycloaddition,[16] while an O-protected variant would render compound **6** unstable. A good synthetic equivalent of a hydroxymethyl group needed to be identified, with the additional proviso that maneuvering and total number of steps be kept to a minimum, in order to create a synthesis competitive with the then-best enantioselective route to CPT.

Steric concerns were soon allayed by the observation that enone **10**[17] reacts well, if slowly, with ethyl vinyl ether (EVE) to give adduct **11**, and thence pyridine **12**, in good overall yield (Scheme 4). The *tert*-butyl group present in **10** seemed a good mimic of the sterically demanding substituent present in the "real" enone **5**.

Scheme 4

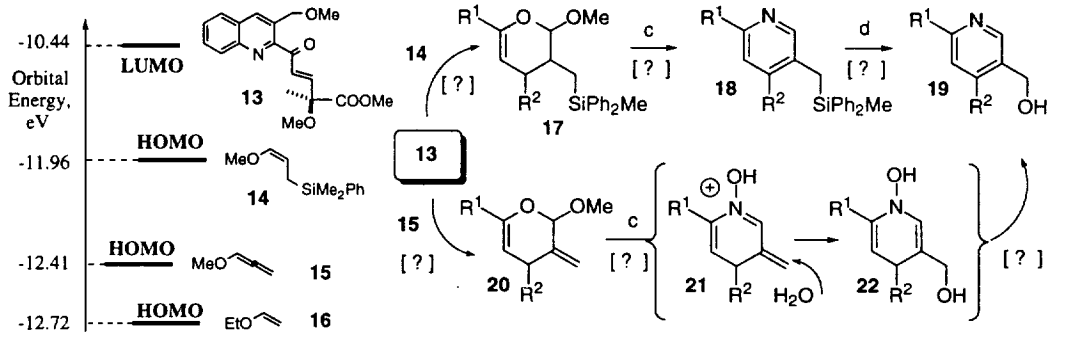


(a) tBu-CHO, aq. EtOH, NaOH, 57 %; (b) CH_2=CHOEt, 2 mol % Yb(fod)$_3$, 1,2-DCE, reflux, 75 %; (c) HO-NH$_2$•HCl, MeCN, reflux, 90 %.

Possible solutions to the second problem were sought in ether **14** and in methoxyallene (**15**) both of which could be predicted to react well with enone **5**, computationally modeled by quinoline **13**. The energy gap between the HOMO of the electron-rich ether and the LUMO of the electron-deficient enone seems to be the most significant qualitative predictor of reaction rates, barring unfavorable sterics.[16] The LUMO of **13** is slightly lower in energy than that of **10** (-10.40 eV),[18] while the steric properties of the two molecules are comparable. Thus,

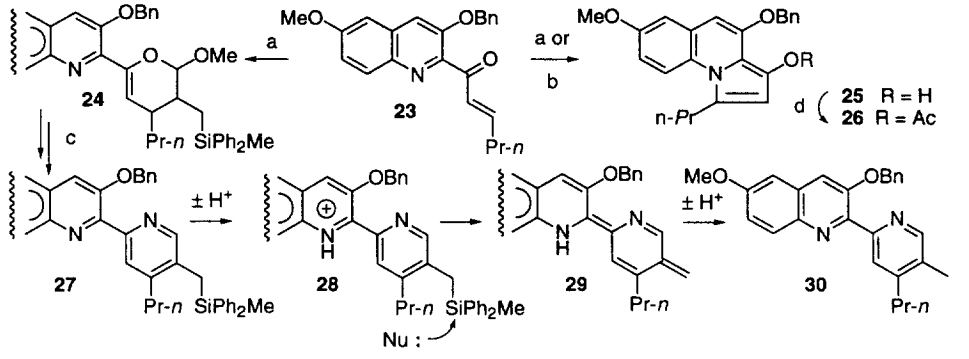
13, and related derivatives (**5**) should react well with EVE, because so does **10**; moreover, reaction with **14** or **15** should be faster yet than with EVE, because the higher-lying HOMO of these ethers diminishes the HOMO-LUMO gap (Scheme 5). Pyridine **18** theoretically available from adduct **17** could then undergo Tamao oxidation[19] to the desired **19**. The logic behind our choice of methoxyallene was more adventurous. It was hoped that adduct **20** would combine with moist HO–NH_2•HCl to form reactive intermediate **21**, which might undergo conjugate addition of H_2O to produce **22**. This molecule resembles a putative reactive intermediate in the Knoevenagel-Stobbe reaction,[20] and therefore it should readily suffer dehydrative aromatization to **19**.

Scheme 5



Despite their appeal, the above hypotheses led only to synthetic dead-ends. Methoxyallene[21] added rapidly to various chalcones, but reaction of the cycloadducts with HO–NH_2•HCl gave complex mixtures containing insignificant amounts of desired hydroxymethyl pyridine. Ether **14**[22] behaved as predicted with ordinary chalcones; however, quinoline-containing enones such as **23** produced the adduct **24** in a meager 29% yield, with the majority of the enone undergoing an unusual aza-Nazarov cyclization to indolizine[23] **25** (Scheme 6), an air-sensitive compound that was best characterized as the acetate **26**. This interesting reaction, which could be induced simply by heating the substrate with 3-5 mol % of $Yb(fod)_3$, has yet to be fully explored, but it already appears to have limited scope. Even more distressingly, exposure of **24** to HO–NH_2•HCl gave only protiodesilylated methylpyridine **30** (79 %) which probably formed as suggested in the mechanism of Scheme 6.

Scheme 6



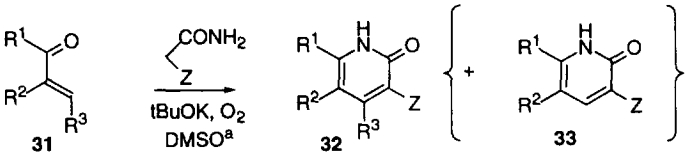
(a) **14**, 3-5 mol % $Yb(fod)_3$, 1,2-DCE, reflux; (b) 3-5 mol % $Yb(fod)_3$, 1,2-DCE, reflux; (c) HO–NH_2•HCl, MeCN, reflux; (d) Ac_2O, pyrid.

Substituent "Z" in **6** clearly could not be a carbonyl or a similar electron-withdrawing group ("EWG") so long as pyridine formation remained the centerpiece of our strategy. Many EWG's would serve well as latent CH_2OH's, but they would also lower the HOMO of the molecule to the point that the crucial cycloaddition would

be seriously compromised. Conversely, pyridine **4** would later be oxidized to a 2-pyridone **3**. Soon, the idea materialized that direct pyridone formation from **5** may actually benefit overall efficiency. In this new light, it was now *desirable* to have Z = EWG, because the pyridone would best be made by oxidative fusion of **5** with an active methylene amide; that is, compound **6** would now have to be malonamic ester or cyanoacetamide.

The merger of active methylene amides with enones constitutes a long-recognized route to 2-pyridones, but as many as three steps may be necessary to complete such an operation.[24] Experiment revealed that a one-step synthesis could be achieved in DMSO solution through *in situ* oxidation (O_2 atmosphere) of Michael adducts of many conjugated carbonyls with the above amides. Details of this chemistry are published elsewhere;[25] therefore, here we shall recount only two weaknesses of the new procedure. Generally, substrates containing base-resistant functionality reacted efficiently; not so those incorporating base-sensitive groups. More significantly, enones **31** wherein group R^3 may depart as a stabilized radical afforded various amounts of abnormal pyridones **33**. Mechanistic implications of this observation have been addressed.[25] The extent of abnormal product formation ranged from none for R^3 = aryl or *n*-alkyl; trace for R^3=cycloalkyl; ca. 5% for R^3=1,1,-diethoxyethyl, to 100% for R^3=3-hydroxy-1-penten-3-yl.[26]

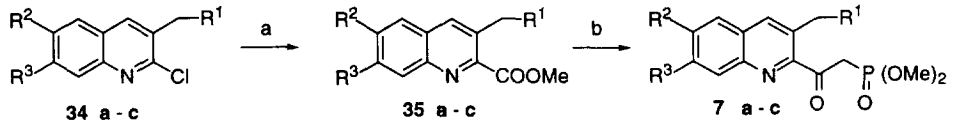
Scheme 7



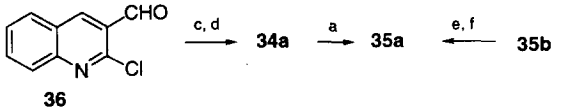
(a) 1.1. eq. NC–CH_2–$CONH_2$ or EtOOC–CH_2–$CONH_2$, 4 eq. of base, no cooling, 60-90% of **38** plus variable amounts of **39** (text).

We were now eager to evaluate the new reaction with several enones of the type **5**, preparation of which required access to phosphonates such as **7** and aldehydes resembling **8**. The quinoline sector of the phosphonates displays a C_1 substituent at position 3, a feature that may be introduced especially readily through the Meth-Cohn quinoline synthesis.[27] This excellent reaction afforded quantities of 2-chloroquinolines, e.g. **34b-c**, which were expected to be amenable to replacement of the halogen atom with an ester unit, thereby opening a Corey-Kwiatkowski[28] avenue to the desired phosphonates. Indeed, many 2-chloroquinolines, unlike most aryl chlorides, were found to undergo Pd-mediated reactions readily and without the need for specialized catalysts.[29] The complex, $[Pd(dppp)_2Cl_2]$ was particularly effective for carbomethoxylation (Scheme 8). In all cases, the esters advanced to the phosphonates in excellent yield. Compound **7a** proved to be especially valuable for the preparation of CPT itself. An early route to this phosphonate commenced with quinoline **35b**,[14] but an even shorter, more efficient synthesis starts with aldehyde **36**, which is now an article of commerce.[30]

Scheme 8



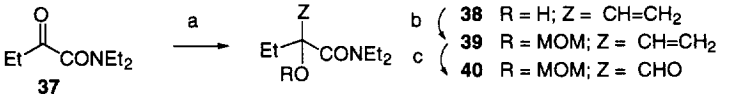
a: R^1 = OMe, R^2 = R^3 = H; **b**: R^1 = R^2 = R^3 = H; **c**: R^1 = H; R^2, R^3 = O-CH_2CH_2-O



(a) 5 mol % $Pd(dppp)_2Cl_2$, NaOAc, MeOH, DMF, 1500 psi CO, 110 °C, 72% for **35a**, 98% for **35b**, 61% for **35c**; (b) 2 eqiv. $(MeO)_2P(O)CH_2Li$, THF, -78°C, 98-100 %; (c) $NaBH_4$, EtOH, 99%; (d) MeI, tBuOK, DMSO, 82%; (e) NBS, CCl_4, Bz_2O_2, hv; (f) MeOH, H_2SO_4, heat, 55 % e-f.

Various *racemic* aldehydes of the type **8** were made by straightforward procedures that will not be discussed here, except for the case of (±) **40**. This aldehyde was manufactured from useful, readily available building block **37**[31] as shown in Scheme 9, and it occupies a privileged position in the grand scheme of CPT synthesis, because it furnished enones that could ultimately be advanced to **1** in an especially direct fashion.

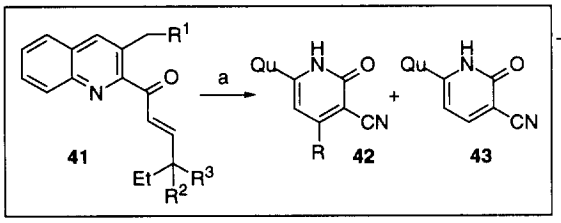
Scheme 9

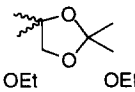


(a) CH_2=CHMgBr, THF, -78°C, 84%; (b) MOMCl, i-Pr_2NEt, r. t., 62%; (c) O_3, CH_2Cl_2-MeOH (4:1), -78°C; then Me_2S, r. t., 70-95%.

An unpleasant turn of events awaited us at this juncture. Whereas Wadsworth-Emmons condensation[32] of pairs of phosphonates **7** and (±)-aldehydes **8** furnished several enones (**41**) in 70-80% yield, most such enones were either poor substrates for pyridone formation or exhibited a strong inclination to fragment as alluded-to earlier. Only three of eleven enones tested *vis-a-vis* cyanoacetamide produced satisfactory results (Scheme 10), but ironically, none of them incorporated functionality conducive to a quick synthetic endgame. A search for ways to circumvent these difficulties was launched immediately. Simultaneously, pyridones **42a-c** were utilized to identify good conditions for conversion of the nitrile to the crucial hydroxymethyl unit.

Scheme 10

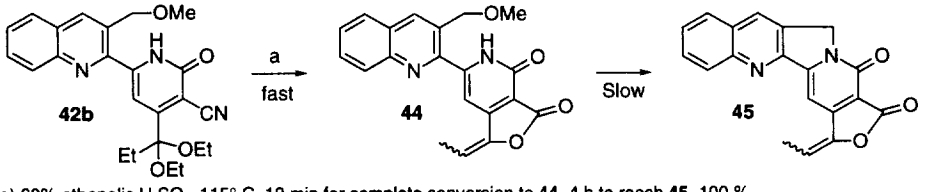


Entry	R^1	R^2	R^3	Yield[b,c]
a	H			76[d]
b	OMe	OEt	OEt	79[d]
c	OMe	H	*n* - Pr	76[e]

(a) 1.1. eq. NC–CH_2–$CONH_2$, DMSO, base, no cooling, precise conditions as per footnotes (d)-(e); (b) unoptimized yields of chromatographed products; (c) in each case, about 5 % of abnormal pyridone was also formed. (d) 5 equiv. t-BuOK, 1 atm O_2; (e) 1 equiv. *t*-BuOK, DMSO, r.t. Ar (completion of Michael step), then 4 equiv. *t*-BuOK.

Chemical or catalytic reduction of the nitrile, or base hydrolysis to an acid as a prelude to further reduction, were problematic. The quinoline seemed to interfere with reductive manipulations, a disturbing observation that foreshadowed the most serious challenge we were yet to encounter in our synthetic venture. Base hydrolysis required vigorous conditions and was inefficient, probably because N-deprotonation of the pyridone strongly diminished the electrophilic reactivity of the nitrile. We thus chose to explore hydrolysis in strongly acidic media. Our experiments soon revealed a key property of those substrates wherein a methoxymethyl substituent is present at position 3 of the quinoline: exposure to strong protonic acid prompted not only nitrile hydrolysis, but also closure of the future ring C of camptothecin. This process appears to be mechanistically related to the Williams oxacycle formation,[33] and it occurred especially efficiently upon heating the starting pyridone in 60% ethanolic

Scheme 11

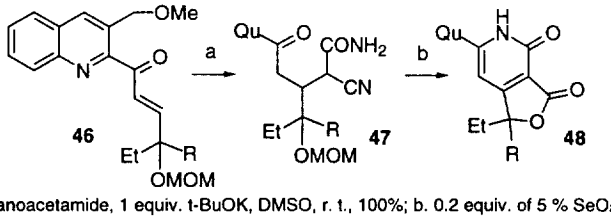


(a) 60% ethanolic H_2SO_4, 115° C, 10 min for complete conversion to **44**, 4 h to reach **45**, 100 %.

H_2SO_4 at 115°C (4 h, essentially 100% yield). Furthermore, *natural camptothecin was perfectly stable under such conditions*. The reaction is exemplified in the conversion of **42b** to **45** (Scheme 11), which also illustrates that the presence of an alcoholic or (latent) enolic OH at the future C-20 of CPT results in rapid lactonization during acid treatment. We therefore assumed that the crucial CH_2OH could be installed by hydride reduction of lactones akin to **45**. These decisive observations became central to the formulation of our ultimate strategy.[34]

Soon, a two-step protocol emerged, that permitted facile pyridone formation from previously recalcitrant substrates. Reaction of enones **46** (Scheme 12) with the anion cyanoacetamide in DMSO delivered Michael adducts **47** in practically quantitative yield. These substances were obtained as a mixture of diastereomers and of ring-chain tautomers; therefore they were not purified beyond a quick filtration through silica gel. We confirmed earlier reports that oxidation of **47** to full-fledged pyridones was most easily accomplished with excess SeO_2 in refluxing acetic acid.[35] A significant advantage of this procedure was that MOM group in **47** was released under the acidic conditions of the reaction, and the resulting alcohol lactonized to **48**. A major disadvantage was that three equivalents of highly toxic SeO_2 were necessary for complete oxidation; furthermore, it was extremely difficult to fully remove reduced forms of selenium from the final pyridone. A significant improvement was realized by the use of *catalytic* (20 mol%) Shirahama SeO_2 on silica gel[36] in conjunction with 70% aq. tert-butyl hydroperoxide (3 equivalents) in AcOH as the solvent. The oxidation thus proceeded faster than with plain SeO_2 (30-60 min. vs. 2-3 hrs), at lower temperature (110°C compared to reflux), and in better yields. To our surprise, no MOM release / lactonization was observed under the new conditions, leading us to speculate that free selenous acid (H_2SeO_3, a strong Brønsted acid) may have been responsible earlier for that desirable event. While subsequent treatment of the pyridones with mineral acid in a separate step did result in lactonization, it was found that addition of 10 vol % of aq. 10% H_2SO_4 to the oxidation reaction *after complete formation of the pyridone had occurred* would again furnish lactones **48** directly from **47** after brief heating, as illustrated in Scheme 12.

Scheme 12



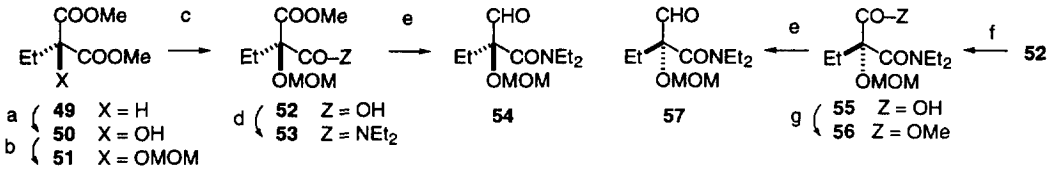
46 47 48

Entry	a	b	c
R^2	COOEt	$CH=CH_2$	$CONEt_2$
Yield %	68	68	70

a. Cyanoacetamide, 1 equiv. t-BuOK, DMSO, r. t., 100%; b. 0.2 equiv. of 5 % SeO_2 on SiO_2, 3 equiv. 70% aq. tBuOOH, AcOH, 110°C, 1h, then add 10 vol % of 10 % aq. H_2SO_4, 110°C, 1 h.

Synthesis of (+)-Camptothecin. The value of compound **46c** as a forerunner of **1** is now apparent. The carbon atoms that will eventually translate into ring E of camptothecin are in the correct oxidation state, removing the need for later redox operations. In particular, the future CPT lactone carbonyl is present as a robust diethylamide, minimizing the likelihood of interference during reductive manipulation of intermediate **48c** to a diol. In turn, the diol was expected to cyclize readily to **1** under the acidic conditions of Scheme 11. We embarked toward the climax of our endeavor by charting an efficient enantioselective synthesis of the crucial fragment **40**. Issues of practicality and cost-effectiveness immediately ruled out the use of resolution methods or chiral auxiliaries. The hidden symmetry present in **40** suggested an enzymatic desymmetrization of a malonate[37] as a viable alternative. Accordingly, compound **51** was prepared from commercial dimethyl 2-ethylmalonate (**49**, Fluka, Scheme 13) by hydroxylation and MOM protection. Hydroxylation was best effected by solid-state reaction with ozone,[38] and while excellent results were also obtained in the reaction of the enolate of **49** with the Davis oxaziridine,[39] the convenience of the highly effective ozone protocol was *sans pareil*. Enantioselective hydrolysis of **51** with pig liver esterase[40,41] provided what later proved to be the *R* enantiomer of carboxylic acid **52**, $[\alpha]_D^{25} = +10.0°$ ($CHCl_3$, c = 6.15), of at least 98 % ee, as determined by scrutiny of ^1H NMR spectra of crude amides obtained by condensation of scalemic and racemic **52** with enantiopure (*S*)-α-methylbenzylamine. Initially, the configuration of this acid was not secure, nor could we easily conduct a correlation with simple materials of known absolute stereochemistry. While the Jones model for PLE selectivity[42] would predict the *S* configuration for **52** (the opposite of that shown in Scheme 13), we were aware that the Jones rule is not infallible.[43] It was fortunate

Scheme 13



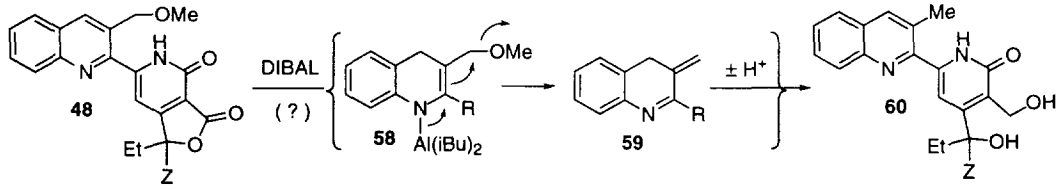
(a) O3, SiO2, 25°C, 71 %; (b) MOMCl, iPr2NEt, CH2Cl2, 25°C, 100 %; (c) PLE, 25 % aq. DMSO, pH 6.8-7.4, 35°C, 90 %; (d) N-methyl-2-chloropyridinium iodide, Et2NH, Et3N, CH2Cl2, 25 °C, 90 %; (e) DIBAL, THF, –78 °C, 100 %; (f) Et2NLi, THF, –78° to 0°C; (g) CH2N2, 62 % f-g.

indeed that the *R* acid was in fact obtained from this reaction, because this antipode of **52** may be more expeditiously incorporated into CPT. However, we felt that the stereochemical ambiguity could be safely resolved only by manufacturing both enantiomers of aldehyde **40** from **52**, and by advancing each individual antipode of the aldehyde to the corresponding enantiomer of **1**: stereocorrelation would be made with the natural product.

Acid **52** was best converted to the diethylamide under Mukaiyama conditions.[44] Chemoselective DIBAL reduction of the emerging **53**, $[\alpha]_D^{25}$ = –43.3° ($CHCl_3$, c = 5.25), proceeded quantitatively to afford aldehyde (*S*)-(–)-**40**, shown in Scheme 13 as compound **54**, $[\alpha]_D^{25}$ = –40.8° ($CHCl_3$, c = 10.25), which in "crude" form was already spectroscopically and microanalytically pure. Preparation of (*R*)-(+)-**40**, indicated above as **57**, was achieved by exposure of **52** to excess Et_2NLi, followed by diazomethane esterification and DIBAL reduction.

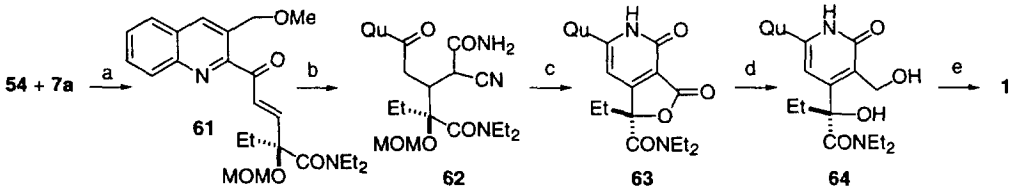
Condensation of **54** with phosphonate **7a** (Scheme 15) produced enone **61**, $[\alpha]_D^{25}$ = –56.1° (c 4.720), 80% yield, which was advanced in 68% yield to lactone **63**, $[\alpha]_D^{25}$ = –38.8° (c 1.025), as discussed above. We were ready to execute the reduction of **63** to the diol, a step that we naively regarded as nothing more than a footnote to the camptothecin story. We were dismayed to find that this seemingly trivial operation was extremely problematic. Veiled warnings exist in the literature concerning the perils associated with reduction of lactones similar to **63**,[45] but the extent of such difficulties does not seem to have ever been explicitly addressed. It was astonishing to observe pure **63** and related lactones of the type **48** rapidly degrade to complex mixtures of overreduced products, among which only small and variable amounts of the desired diol were evident, upon exposure to one boron– or aluminum hydride reagent after another. This complication loomed large, and for a time it cast a dark shadow on our overall synthetic design. Powerful hydride agents (LAH, RedAl) caused overreduction of the quinoline unit, decarbonylative loss of the amide group, and generally formation of complex mixtures. Similar difficulties were encountered with $LiBH_4$, reportedly the reagent of choice for the reduction of related lactones lacking the quinoline portion.[46] Reaction of lactones of the type **48** with DIBAL in CH_2Cl_2 (–78° to 0°C) resulted not only in formation of the diol, but also in clean demethoxylation to **60**, probably through the mechanism delineated in Scheme 14. This disastrous side reaction seemed to occur at a rate comparable to that of lactone reduction and could not be suppressed. Its perniciousness derived from our inability to reactivate the quinoline methyl group as required for ring C formation, e.g., through radical bromination (mixtures of products). Even more serious problems were encountered upon attempted reduction of intermediates with a complete ring C. It is noteworthy that in a landmark 1977 *Science* paper, H. W. Moore hypothesized that CPT may require bioreductive activation to an intermediate related to **58** in order to express cytotoxicity.[47] That provocative surmise now appears to be untenable, but one cannot help to wonder whether the ease of quinoline reduction in many CPT precursors / analogues, especially those with ring C in place, may be at the roots of some of the other physiological effects of **1**.

Scheme 14



Overreduction could be controlled, but not repressed, by the use of $NaBH_4$ in refluxing ethanol. Diol **64** was thus isolated from the reaction mixture in disappointing yield; moreover, a large excess of $NaBH_4$ (>20 equivalents, added in portions over 24 h) was necessary to complete the reaction. Reduction with a *suspension* of $NaBH_4$ in refluxing THF fared better and gave the diol in about 40-45 % yield.[48] Innumerable experiments finally brought to light an outstanding solution in the form of a modified Luche reduction.[49] Ethanolic $NaBH_4/CeCl_3 \cdot 7H_2O$ at 0°C induced fast (20 min), clean conversion of **63** to a mixture of diastereomeric lactols, which rapidly converged to diol **64** upon warming to 45°C. No demethoxylation or quinoline reduction was apparent. The diol is a polar substance that was best advanced to the next step without purification. Fully synthetic, pure 20-(*S*)-(+) camptothecin, **1**, identical in all respects, including rotation, $[\alpha]_D^{25}$ = +34.8° (8:2 $CHCl_3$ - MeOH, c = 0.565; lit.:[2] +35°) to authentic samples from two different sources,[50] emerged in 94 % yield after flash chromatography, upon treatment of **64** with hot ethanolic H_2SO_4. In an identical manner and yields, biologically inactive *ent*–**1** was prepared from **57**, thus completing the stereochemical correlation of all our intermediates. The soundness of our plan had been fully vindicated.

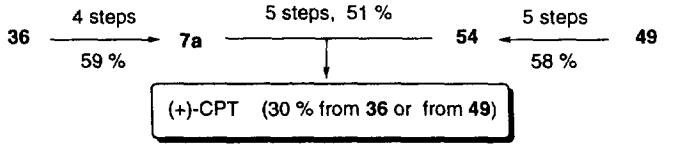
Scheme 15



(a) tBuOK, DME, reflux, 80 %; (b) **6**, tBuOK, DMSO, 100 %; (c) 5 % SeO_2 on silica gel, tBuOOH, AcOH, 110° C, then add 10 % aq. H_2SO_4, 70 %; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, 0–45°C; (e) 60 % H_2SO_4 in EtOH, 115° C, 94 % chrom. d-e.

In summary, CPT was obtained in 30 % overall yield through a sequence requiring a maximum of ten linear steps from **49** (Scheme 16). This compares favorably with the best enantioselective alternatives currently available (8 steps longest sequence & 15 % overall yield for the Comins-Glaxo synthesis; 10 steps longest sequence & 3 % overall yield for the Curran synthesis). We are hopeful that the synthesis detailed above will facilitate the creation of novel CPT analogues for bioassay and for the eventual development of better anticancer resources based on this interesting natural product.

Scheme 16



Acknowledgment. We gratefully thank the National Institutes of Health (CA-55268), the National Science Foundation (CHE 95-26183), the Robert A. Welch Foundation (C-1007), and the Alfred P. Sloan Foundation, for support of our research, and Dr. Monroe E. Wall, Research Triangle Institute, NC, for a gift of natural **1**.

Experimental Section[51]

Methyl Ether 34a. A solution of 2-chloroquinoline-3-carbaldehyde **36** (7.7 g, 40.1 mmol) in EtOH (80 mL) was treated with $NaBH_4$ (1.9 g, 48.2 mmol) at 0°C. The mixture was allowed to warm to room temperature. Upon completion of the reduction (TLC) the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ether. The extracts were washed (sat. aq. NaCl), dried (Na_2SO_4) and evaporated to yield the intermediate alcohol (7.7 g, 99%), white crystals, m.p. 149°C, which was methylated without further purification. Thus, MeI (508 µL, 8.1 mmol) was added at room temp. to a solution of this alcohol (520 mg, 2.7 mmol) in DMSO (27 mL) containing suspended finely ground KOH (301 mg, 5.4 mmol). The reaction completed instantaneously. The mixture was poured into sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed (H_2O, then sat. aq. NaCl), dried (Na_2SO_4) and concentrated. Chromatography (10% EtOAc / hexanes) afforded 463 mg (82%) of desired **34a** as a yellow oil. ^1H: 8.18

(s, 1H), 7.99-7.96 (d, 1H, J=8.2 Hz), 7.79-7.76 (d, 1H, J=8.1 Hz), 7.70-7.63 (dt, 1H, J_1=7.0 Hz, J_2=1.5 Hz), 7.54-7.47 (dt, 1H, J_1=7.0 Hz, J_2=1.2 Hz), 4.61 (d, 2H, J=1.0 Hz), 3.53 (s, 3H). ^{13}C: 148.9, 146.7, 136.2, 130.1, 130.0, 128.0, 127.4, 127.1, 126.9, 70.8, 58.9. IR: 1619, 1597, 1568, 1330, 1116. MS: 207 (M^+), 176, 140 (100%). HRMS Calc. for $C_{11}H_{10}NO^{35}Cl$: 207.0451 (M^+), Found: 207.0450.

Quinoline Ester 35a. An open vial containing a stirring bar, 2-chloroquinoline **34a** (137 mg, 0.7 mmol), $Pd(OAc)_2$ (3 mg, 0.01 mmol), 1,3-bis-(diphenylphospino)propane (11 mg, 0.02 mmol), NaOAc (54 mg, 0.7 mmol), MeOH (0.2 mL) and 1-methyl-2-pyrrolidinone (0.6 mL), was placed inside a Parr bomb, which was sealed and pressurized to 105 atm of CO. The mixture was stirred for 2 days at 100°C, then cooled, diluted with ether, filtered through celite, washed (H_2O, then sat. aq. NaCl), dried (Na_2SO_4) and concentrated. Chromatography of the residue with 20% EtOAc / hexanes gave 110 mg (72%) of pure **35a** as a pale yellow oil that solidified upon standing, m.p. 63-64°C. ^{1}H: 8.43 (d, 1H, J=0.7 Hz), 8.25-8.22 (d, 1H, J=8.4 Hz), 7.89-7.86 (dd, 1H, J_1=8.1 Hz, J_2=0.9 Hz), 7.79-7.72 (dt, 1H, J_1=6.9 Hz, J_2=1.4 Hz), 7.67-7.60 (dt, 3H, J_1=7.0 Hz, J_2=1.2 Hz), 4.95 (d, 2H, J=1.0 Hz), 4.05 (s, 3H), 3.54 (s, 3H). ^{13}C: 166.0, 146.4, 145.7, 135.0, 131.5, 129.5, 128.3, 128.0, 127.1, 70.6, 58.4, 52.5. IR: 1723. MS: 231 (M^+), 216, 184 (100%). HRMS Calc. for $C_{13}H_{13}NO_3$: 231.0895 (M^+), Found: 201.0895.

Phosphonate 7a. A 2.5 M solution of n-BuLi in hexanes was added dropwise to a cold (–78°C) solution of 2-3 crystals of 1,10-phenanthroline in THF (4.5 mL) in a flame-dried flask. When the indicator changed color (2-3 drops), 5 mL of BuLi solution was added (12.5 mmol), followed by slow addition of neat dimethyl methylphosphonate (1.4 mL, 12.9 mmol). The mixture was stirred -78°C for 30 minutes, then quinoline ester **35a** (1.4 g, 5.9 mmol) in THF (4 mL) was added. Stirring at -78°C was continued for 2.5 hours, then the reaction was carefully quenched with 3.15 mL of 4 N HCl and warmed to room temperature. Extraction with EtOAc and concentration left a residue that was Kugelrohr-purified at 55°C. The thick yellow oil left in the distillation flask was microanalytically pure **7a** (1.9 g, 100%), which slowly solidified upon standing, m.p. 51°C. ^{1}H: 8.52 (d, 1H, J=0.8 Hz), 8.18-8.14 (dd, 1H, J_1= 8.5 Hz, J_2=0.5 Hz), 7.91-7.88 (dd, 1H, J_1=8.0 Hz, J_2=1.0 Hz), 7.80-7.73 (dt, 1H, J_1=8.5 Hz, J_2=1.5 Hz), 7.69-7.63 (dt, 1H, J_1=8.1 Hz, J_2=0.5 Hz), 4.99 (d, 2H, J=1.2 Hz), 4.28-4.19 (d, 2H, J=22.3 Hz), 3.79-3.74 (d, 6H, J=11.2 Hz), 3.58 (s, 3H). ^{13}C: 195.6, 195.5, 149.3, 145.6, 134.8, 132.7, 130.0, 129.9, 129.4, 129.1, 127.6, 71.2, 58.9, 53.0, 52.9, 46.3, 37.7, 35.6. IR: 1797. MS: 323 (M+), 308, 291, 182 (100%). HRMS Calc. for $C_{15}H_{18}NO_5P$: 323.0923 (M^+) Found: 323.0919. EA: (Calc.): C: 55.43 (55.73); H: 5.91 (5.61); N: 4.11 (4.33); P 9.86 (9.58).

Hydroxymalonate 50. Ozonized oxygen was passed through ethyl dimethylmalonate, **49** (5.5 g, 20.5 mmol) adsorbed onto silica gel (66 g) at room temperature for 2 h. The mixture was transferred to a chromatographic column. Elution with 10% EtOAc/hexanes gave 1.1 g (20%) 54 and 4.3 g (71%) of hydroxymalonate **50** as a colorless oil. ^{1}H: 3.81 (s, 6H), 3.73 (s, 1H), 2.12-2.03 (q, 2H, J=7.4 Hz), 0.94-0.88 (t, 3H, J=7.4 Hz). ^{13}C: 171.0, 79.4, 53.3, 28.1, 7.4. IR: 1691.

MOM Ether 51. Chloromethyl methyl ether (11.9 mL, 157 mmol; **CAUTION**: carcinogenic) was added at room temp. to a solution of alcohol **50** (9.1 g, 52.0 mmol) and iPr_2NEt (46 ml, 265 mmol) in CH_2Cl_2 (36 mL), and the mixture was then stirred at room temp. for 3 days. The reaction mixture was added to sat. aq. $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed (H_2O, then sat. aq. NaCl), dried (Na_2SO_4) and concentrated. The residue was chromatographed (10% ethyl acetate / hexanes) to furnish 11.4 g (100%) of **51** as a pale yellow oil. ^{1}H: 4.86 (s, 2H), 3.77 (s, 6H), 3.36 (s, 3H), 2.17-2.08 (q, 2H, J=7.5 Hz), 0.91-0.85 (t, 3H, J= 7.4 Hz). ^{13}C: 169.5, 93.2, 56.2, 52.7, 27.0, 7.4. IR: 1696. MS (CI+): 221 (MH^+), 189 (100%). HRMS (CI): Calc. for $C_9H_{17}O_6$: 221.1025 (MH^+) Found: 221.1025.

Carboxylic Acid 52. Malonate **51** (1.4 g, 6.3 mmol) was suspended in 42 mL of 25% aq. DMSO maintained at 35°C, and the pH was adjusted to 7.0 with 1 N NaOH. Pig Liver Esterase (Sigma, 1568 units) was added and the pH was maintained between 6.9 and 7.4 by addition of 1 N NaOH. When one equivalent of base had been added (3.5 hours), the reaction came to a halt (no further pH drop) and the system had become homogeneous. The mixture was basified to pH 8 and washed with ether, then acidified to pH 2, saturated with solid NaCl, and extracted with EtOAc. The extracts were dried (Na_2SO_4), and concentrated. Kugelrohr removal of DMSO at 45°C provided 1.2 g (90%) of pure **52** as a colorless oil, $[\alpha]_D^{25}$ = +10.0° (c 6.15, $CHCl_3$). ^{1}H: 8.81 (br, 1H), 4.84 (s, 2H), 3.75 (s, 3H), 3.36 (s, 3H), 2.17-2.07 (dq, 2H, J_1=7.4 Hz, J_2=2.9 Hz), 0.91-0.85 (t, 3H, J=7.5 Hz). ^{13}C: 172.3, 169.3, 93.1, 82.9, 56.3, 52.8, 26.6, 7.2: IR: 1691. MS (CI): 207 (MH^+), 175 (100%). HRMS (CI) Calc. for $C_8H_{15}O_6$: 207.0869 (MH^+) Found: 207.0870.

Amide 53. 2-Chloro-N-methylpyridinium iodide (6.3 g, 23.9 mmol) was carefully added to a cold (0°C) solution of acid **52** (3.1 g, 14.9 mmol), Et_2NH (3.1 mL, 29.9 mmol) and Et_3N (7.3 mL, 52.4 mmol) in CH_2Cl_2 (150 mL). The mixture was allowed to warm to room temp. over 20 min. Upon completion of the reaction (NMR), the mixture was added to sat. aq. $NaHCO_3$ and extracted with EtOAc. The extracts were washed (H_2O, then sat. aq. NaCl), dried (Na_2SO_4) and concentrated. Chromatography (10% EtOAc / hexanes) gave 3.5 g (90%) of desired **53** as a pale yellow oil, $[\alpha]_D^{25}$ = – 67.4° (c 6.85, $CHCl_3$). ^{1}H: 4.69 (s, 3H), 3.76 (s, 3H), 3.72-3.10 (m, 4H), 3.41 (s, 3H), 2.36-2.06 (m, 2H), 1.12-1.06 (t, 3H, J=7.1 Hz), 1.07-1.02 (t, 3H, J=7.1 Hz), 0.87-0.81 (t, 3H, J=7.5 Hz). ^{13}C: 170.5, 166.4, 92.7, 84.9, 56.8, 52.3, 40.6, 40.4, 27.1, 13.1, 11.9, 7.4. IR: 1711, 1650. MS (CI+): 262 (MH^+), 230 (100%). HRMS (CI) Calc. for $C_{12}H_{24}NO_5$: 262.1654 (MH^+), Found: 262.1654. EA (Calc.): C: 55.48 (55.17); H: 8.88 (8.81); N: 5.29 (5.36).

Aldehyde 54. Diisobutylaluminum hydride (1.5 M in toluene, 13.9 mL, 20.9 mmol) was added at a slow dropwise rate into a cold (-78°C) solution of ester **53** (2.0 g, 7.7 mmol) in toluene (19 ml). The mixture was stirred at -78°C for 2 hours after completion of addition, then treated with cold MeOH (-78°C, 3.5 ml) and poured into cold sat. aq. $NaHCO_3$ (0°C), with vigorous swirling, over 15 minutes. The resulting slurry was extracted with EtOAc and the extracts were washed (sat. aq. NaCl), dried (Na_2SO_4) and concentrated to give 1.8 g of microanalytically pure **54** (100%), pale yellow oil, $[\alpha]_D^{25}$ = – 49.5° (c 6.60, $CHCl_3$). ^{1}H: 9.58 (s, 1H), 4.68-4.61 (AB, 2H, J=6.9 Hz), 3.56-3.04 (m, 4H), 3.30 (s, 3H), 2.21-2.09 (m, 1H), 1.91-1.79 (m, 1H), 1.09-1.01 (dt, 6H, J=6.9 Hz), 0.82-0.76

(t, 3H, J=7.6 Hz). ^{13}C: 196.1, 167.2, 92.7, 86.7, 56.1, 40.5, 40.1, 24.6, 13.5, 12.1, 7.6. IR: 1785, 1646-1619 (br). MS (CI): 232 (MH^+), 200 (100%). HRMS (CI) Calc. for $C_{11}H_{22}NO_4$: 232.1549 (MH^+), Found: 232.1539. EA (Calc.): C: 57.50 (57.14); H: 9.25 (9.09); N: 5.88 (6.06).

Enone 61. Phosphonate **7a** (1.5 g, 4.6 mmol) in 1,2-dimethoxyethane (DME, 3.0 mL) was transferred into a cold (0°C) solution of tBuOK (603 mg, 5.1 mmol) in DME (3.3 ml) in a flame-dried flask, and the resulting mixture was stirred at 0°C for 30 min. The ice bath was removed and aldehyde **54** (1.3 g, 5.6 mmol) in DME (3.0 mL) was added. The mixture was heated to 50°C for 12 hours, then cooled, poured into sat. aq. $NaHCO_3$ and extracted with ether. The extracts were washed (sat. aq. $NaHCO_3$, then H_2O, then sat. aq. NaCl), dried (Na_2SO_4) and concentrated. The residue was chromatographed with 10% EtOAc / hexanes to provide 1.588 g (80%) of enone **61** as a yellow oil, $[\alpha]_D^{25} = -56.1°$ (c 4.72, $CHCl_3$). ^{1}H: 8.45 (d, 1H, J=0.7 Hz), 8.16-8.13 (d, 1H, J=8.0 Hz), 7.89-7.86 (dd, 1H, J_1=8.1 Hz, J_2=1.1 Hz), 7.78-7.72 (dt, 1H, J_1=6.8 Hz, J_2=1.5 Hz), 7.78-7.71 (d, 1H, J=16.1 Hz), 7.67-7.60 (dt, 1H, J_1=6.9 Hz, J_2=1.2 Hz), 7.12-7.06 (d, 1H, J=16.1 Hz), 4.98 (br. s, 2H,), 4.77-4.69 (AB, 2H, J=6.4 Hz), 3.88-3.22 (m, 4H), 3.55 (s, 3H), 3.49 (s,3H), 2.36-2.24 (m, 1H), 2.08-1.93 (m, 1H), 1.19-1.13 (t, 3H, J=7.0 Hz), 1.11-1.06 (t, 3H, J=7.0 Hz), 0.94-0.88 (t, 3H, J=7.4 Hz). ^{13}C: 191.6, 169.0, 148.0, 145.9, 134.8, 132.4, 130.0, 129.6, 128.9, 128.6, 127.5, 126.0, 92.8, 84.4, 77.2, 71.4, 58.9, 56.8, 41.5, 40.8, 28.6, 13.6, 12.3, 7.4. IR: 1677, 1641, 1619. MS: 428 (M+), 383, 328, 100 (100%). HRMS Calc. for $C_{24}H_{32}N_2O_5$: 428.2311 (M^+), Found: 428.2310. EA (Calc.): C: 67.20 (67.27); H: 7.69 (7.53); N: 6.40 (6.54).

Lactone 63. A mixture of tBuOK (523 mg, 4.4 mmol), 2-cyanoacetamide (345 mg, 4.1 mmol), and DMSO (27 mL) in a flame-dried flask was stirred at room temp for 15 min prior to addition of a solution of enone **61** (1.6 g, 3.7 mmol) in DMSO (10 mL). The mixture was stirred at room temp. for 30 min, then it was poured into sat. aq. $NaHCO_3$-NaCl solution and extracted with 2:8 EtOH/$CHCl_3$. The extracts were washed (H_2O, then sat. aq. NaCl), dried (Na_2SO_4) and concentrated. Flash chromatography (0.5% MeOH / $CHCl_3$) provided Michael adduct **62** (mixture of isomers, 1.9 g, 3.7 mmol, 100 %). This material was dissolved in AcOH (38 mL) containing 5 % SeO_2 on silica gel (2.1 g, 0.9 mmol) and 70% aq. tBuOOH (1.5 mL) and heated to 110°C for one hour (complete oxidation to a pyridone, TLC), then 10% aq. H_2SO_4 was added (4 ml) and stirring at 110°C was continued for one additional hour. The solution was cooled to room temp., neutralized with sat. aq. $NaHCO_3$-NaCl (**CAUTION**: vigorous foaming), and extracted with 2:8 EtOH / $CHCl_3$. The extracts were washed (H_2O, then sat. aq. NaCl), dried (Na_2SO_4) and concentrated to afford 1.1 g (68% from enone **61**) of **63** as a yellow foam, $[\alpha]_D^{25} = -38.8°$ (c 1.02, $CHCl_3$). ^{1}H: 8.38 (s, 1H), 8.18-8.14 (dd, 1H, J_1= 8.7 Hz, J_2=0.7 Hz), 7.93-7.89 (dd, 1H, J_1=8.6 Hz, J_2=0.9 Hz), 7.87-7.81 (dt, 1H, J_1=6.9 Hz, J_2=1.4 Hz), 7.71-7.65 (dt, 1H, J_1=7.0 Hz, J_2=1.2 Hz), 7.63 (s, 1H), 4.84-4.67 (AB, 2H, J=11.2 Hz), 4.00-3.91 (m, 1H), 3.64 (s, 3H), 3.61-3.45 (m, 1H), 3.38-3.17 (m, 2H), 2.51-2.39 (m, 1H), 2.23-2.08 (m, 1H), 1.30-1.25 (t, 3H, J=7.0 Hz), 1.19-1.13 (t, 3H, J=7.0 Hz), 1.00-0.94 (t, 3H, J=7.4 Hz). ^{13}C: 169.3, 166.4, 166.2, 157.4, 148.3, 148.2, 146.8, 140.4, 131.3, 129.5, 128.9, 128.7, 128.0, 127.5, 113.7, 104.7, 88.9, 72.3, 58.6, 42.7, 31.9, 14.8, 14.1, 7.7. IR: 1780, 1677, 1635. MS: 449 (M+), 349, 317, 100 (100%). HRMS Calc. for $C_{25}H_{27}N_3O_5$: 449.1951 (M^+), Found: 449.1951. EA (Calc.): C: 66.99 (66.80); H: 6.52 (6.05); N: 8.95 (9.35).

Diol 64. $NaBH_4$ (366 mg, 9.4 mmol) was added in two portions to a cold (0°C) solution of lactone **63** (424 mg, 0.9 mmol) and cerium(III) chloride (624 mg, 2.4 mmol) in EtOH (47 mL). The mixture was allowed to warm to room temp., whereupon reduction of the lactone to the corresponding lactol occurred (20 minutes). The mixture was then heated to 45°C for 30 minutes to effect reduction to the diol, cooled, poured into sat. aq. $NaHCO_3$-NaCl, and extracted with 2:8 EtOH / $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated to afford extremely polar diol **64** (428 mg, 100%, yellow foam), $[\alpha]_D^{25} = +72.1°$ (c 1.20, $CHCl_3$), which was used without further purification. ^{1}H: 8.31 (s, 1H), 8.14-8.11 (d, 1H, J=8.4 Hz), 7.90-7.86 (dd, 1H, J_1=8.2 Hz, J_2=1.0 Hz), 7.83-7.77 (dt, 1H, J_1=7.0 Hz, J_2=1.3 Hz), 7.66-7.60 (t, 1H, J=7.2 Hz), 7.51 (s, 1H), 5.44 (s, 1H), 4.78-4.60 (AB, 2H, J=11.4 Hz), 4.71 (s, 2H), 4.31 (s, 1H, br), 3.63-3.04 (m, 4H), 3.55 (s, 3H), 2.28-2.08 (m, 2H), 1.20-1.15 (t, 3H, J=7.0 Hz), 1.00-0.94 (t, 3H, J=7.3 Hz), 0.94-0.88 (t, 3H, J=7.2 Hz). ^{13}C: 171.8, 164.1, 151.4, 149.1, 146.8, 140.3, 140.0, 132.2, 130.9, 129.3, 128.2, 127.7, 127.5, 106.9, 77.2, 76.7, 72.6, 58.4, 42.1, 41.6, 31.3, 12.7, 12.4, 7.7. IR: 3330 (br), 1623. MS (CI): 454 (MH^+).

(20S)-(+)-Camptothecin 1. A solution of crude diol **64** (428 mg, 0.9 mmol) in 60% ethanolic H_2SO_4 (19 mL) was heated to 115°C for 5 hours. The cooled reaction mixture was added to sat. aq. $NaHCO_3$-NaCl (**CAUTION**: vigorous foaming) and extracted with 2:8 EtOH / $CHCl_3$. The extracts were dried (Na_2SO_4), and concentrated and the residue was chromatographed (1% MeOH / $CHCl_3$) to yield 309 mg (94% from lactone **63**) of pure **1**, m.p. 273-274°C (dec., lit. m.p. 276, dec.), identical in all respects, including rotation, $[\alpha]_D^{25} = +34.8°$ (c 0.40, 8:2 $CHCl_3$ / MeOH; lit. + 35°) to two authentic samples of natural **1**. ^{1}H: 8.40 (s, 1H), 8.26-8.23 (d, 1H, J=8.4 Hz), 7.96-7.93 (d, 1H, J=8.3 Hz), 7.87-7.81 (t, 1H, J=7.0 Hz), 7.71-7.64 (t, J=8.0 Hz), 7.69 (s, 1H), 5.80-5.28 (AB, 2H, J=16.4 Hz), 5.31 (s, 2H), 3.74 (s, 1H), 1.99-1.82 (m, 2H), 1.08-1.02 (t, 3H, J=7.4 Hz). MS: 348 (M^+, 100%), 304, 275, 248, 219. HRMS Calc. for $C_{20}H_{16}N_2O_4$: 348.1110 (M^+), Found: 348.1112.

References and Footnotes

1. Fellow of the Alfred P. Sloan Foundation, 1994-1996.
2. Leading references and Reviews: (a) Wall, M. E.; Wani, M. C., in: *The Chemistry of Heterocyclic Compounds: Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; John Wiley & Sons: Chichester, UK, 1994; vol. 25 (4), pp. 689-713; (b) Wall, M. E.; Wani, M. C. Nicholas, A. W.; Manikuma, G.; Tele, C.;Moore, L.; Truesdale, A.; Leitner, P.; Besterman, J. M. *J. Med. Chem.* **1993**, *36*, 2689; (c) Suffness, M.; Cordell, G. A. in: *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1985, vol 25, ch. 1. See esp. p. 75 ff.
3. Cf. ref. 2 as well as: (a) Luzzio, M. J.; Besterman, J. M.; Emerson, D. L.; Evans, M. G.; Lackey, K.; Leitner, P. L.; McIntyre, G.; Morton B.; Myers, P. L.; Peel, M.; Sisco, J. M.; Sternbach, D. D.; Tong, W. Q.; Truesdale, A.; Uehling, D.

E.; Vuong, A.; Yates, J. *J. Med. Chem.* **1995**, *38*, 395; (b) Uehling, D. E.; Nanthakumar, S. S.; Croom, D.; Emerson, D. L.; Leitner, P. L.; Luzzio, M. J.; McIntyre, G.; Morton B.; Profeta, S.; Sisco, J. M.; Sternbach, D. D.; Tong, W. Q.; Vuong, A.; Yates, J.; Besterman, J. M. *J. Med. Chem.* **1995**, *38*, 1106.

4. (a) Curran, D. P. "The Camptothecins - A Reborn Family of Antitumor Agents." *J. Chin. Chem. Soc.* **1993**, *40*, 1; (b) Potmesil, M. *Cancer Res.* **1994**, *54*, 1431.
5. The activity of **1** is believed to result from inhibition of topoisomerase I: (a) Kingsbury, W. D.; Boehm, J. C.; Jackas, 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) Kjeldsen, E.; Svejstrup, J. Q.; Gromova, I. I.; Alsner, J. Westergaard, O. *J. Mol. Biol.* **1992**, *228*, 1025; (c) Jakob F.; Seufert, J.; Sarrazin, C.; Schneider, D.; Kohrlz, J.; Tony, H. P. *Bioch. Biophys. Res. Commun.* **1994**, *199*, 531; (d) Husain, I; Mohler, J. L.; Seigler, H. F.; Besterman, J. M. *Cancer Res.* **1994**, *54*, 539, and references cited therein.
6. (a) Priel, E.; Showalter, S. D.; Blair, D. G. *AIDS Res. Hum. Retroviruses* **1991**, *7*, 65; (b) Pendrak, I.; Whittrock, R.; Kingsbury, W. D. *J. Org. Chem.* **1995**, *60*, 2912.
7. Janavs, J. L.; Florez, J. C.; Pierce, M. E.; Takahashi, J. S. *J. Neurosci.* **1995**, *15 (1)* , 298.
8. Thorough reviews of earlier synthetic activity are available in refs. 2. Some recent syntheses of (±)-**1**: (a) Wang, S, Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611; (b) Rama Rao, A. V.; Yadav, J. S.; Valluri, M. *Tetrahedron Lett.* **1994**, *35*, 3613. Recent syntheses or formal syntheses of (+)-**1**: (c) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971; (d) Fang, F. G.; Xie, S. P.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142; (e) Jew, S. S.; Oh, K. D.; Kim, H. J.; Kim, J. M.; Hah, J. M.; Cho, Y. S. *Tetrahedron Asymm.* **1995**, *6*, 1245; (f) Curran, D. P.; Ko, S.-B.; Joisien, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2683.
9. For a synthesis that departs from the patterns of Scheme 1 see: Krohn, K., Winterfeld, E. *Chem. Ber.* **1975**, *108*, 2126.
10. Path A: (a) Stork, G.; Schultz, A. G. *J. Am. Chem. Soc.* **1971**, *93*, 4074; (b) Volkmann, R.; Danishefky, S.; Eggler, J.; Solomon, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 5576.
11. Path B: Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140.
12. E.g.: (a) Wall, M. E.; Wani, M. C.; Nichloas, A. W.; Manikumar, G.; Tele, C.; Moore, L.; Truesdale, A.; Leitner, P; Besterman, J. M. *J. Med. Chem.* **1993**, *36*, 2689; (b) Shen, W.; Coburn, C. A.; Bornmann, W. G., Danishefsky, S. *J. Org. Chem.* **1993**, *58*, 611; (c) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 27.
13. Cf. Ciufolini, M. A.; Shen, Y. C.; Bishop, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 12460, and references cited therein.
14. (a) Ciufolini, M. A.; Roschangar, F. *Angew. Chem.* **1996**, *107*, 1789; (b) Ciufolini, M. A.; Roschangar, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *24*, 1692.
15. The term "cycloaddition" is used throughout this paper to indicate the gross outcome of particular reactions. No mechanistic inferences should be drawn from this usage, particularly with respect to issues of concertedness.
16. The pyridine-forming reaction has been reviewed in detail: Ciufolini, M. A., in *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, ch. 1.
17. The starting methyl ketone **9** was prepared by benzylation of the corresponding phenolic quinoline, made according to Tennant, G. *J. Chem. Soc., Chem. Commun.* **1975**, 782.
18. These values were obtained by extended Hückel molecular orbital calculations performed on MM+ geometries. All calculations were carried out with the Hyperchem® package, version 4, available from Hypercube, Inc., Ontario, Canada, and running on a pentium / 100 PC system.
19. Tamao, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 861.
20. Cf. Ciufolini, M. A.; Byrne, N. E. *J. Chem. Soc., Chem. Commun.* **1988**, 1230, and refs. cited therein.
21. Prepared according to Hoff, S.; Brandsma, L.; Arens, J. F. *Rec. Trav. Chim. Pays-Bas* **1968**, *87*, 916.
22. Prepared as described by: Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.* **1978**, *43*, 2551.
23. Review of these unusual heterocycles: Flitsch, W. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. P.; Rees, C. W., Eds.; Pergamon Press, Elsmfeld, NY, **1984**, Vol. 3, pp. 443 (esp. pp.476).
24. Cf. McKillop, A.; Boulton, A. J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. P.; Rees, C. W., Eds.; Pergamon Press, Elsmfeld, NY, **1984**, Vol. 2, pp. 67 and pp. 395.
25. Jain, R.; Roschangar, F.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 3307.
26. It should be mentioned that while 3-carbethoxy pyridones (cf. **32**, Z=COOEt) might have permitted more facile introduction of a 3-CH_2OH unit than their cyano analogues, the tedious preparation of the malonamic ester (Snyder, H. R.; Elston, C. T. *J. Am. Chem. Soc.* **1954**, *76*, 3039) required for their synthesis overshadowed their projected usefulness.
27. Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1537.
28. Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.
29. Carbonylation of chloroarenes requires special catalysts: Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742.
30. This aldehyde is available from the Aldrich Chemical Co. or it may be easily made as detailed in ref. 27.
31. Cuvigny, T., Larcheveque, M., Normani, H. *Synthesis* **1978**, 857.
32. Wadsworth, W. S., Jr.; Emmons, W. D. *J. Org. Chem.* **1964**, *29*, 2816.
33. Williams, D. R.; Phillips,J. G.; Barner, B. A. *J. Am. Chem. Soc.* **1981**, *103*, 7398.

34. An especially direct route to **1** could be visualized from **44** or **45** through the Alper carbonylation, which may be carried out in an enantioselective fashion (Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803). Unfortunately, neither **44/45** nor simpler related lactones (Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171) were substrates for this useful reaction. The lactones also resisted acid catalyzed carbonylation or hydrocyanation.
35. Cf. (a) Otto, H. H.; Rinus, O. *Arch. Pharm.* **1979**, *312*, 548; (b) Wojcik, M. *Dissertation*; Harvard University, 1970.
36. Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1981**, 1703.
37. (a)Schneider, M.; Engel, M; Boensmann, H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 66; (b) Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron* **1985**, *41*, 1347; (c) Ahmar, M.; Bloch, R.; Bortolussi, M. *Synth. Commun.* **1991**, *21*, 1071.
38. This procedure was patterned after: Cohen, Z.; Varkony, H.; Keinan, E.; Mazur, Y. *Org. Synth., Coll. Vol. VI*, **1988**, 43. Apparently, no examples of hydroxylation of malonates with ozone have ever been described in the literature.
39. Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774.
40. Reviews: Cf. (a) Azerad, R. *Bull. Soc. Chim. Fr.* **1995**, *132*, 17; (b) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071; (c) Ohno, M.; Otsuka, M. *Org. React.* **1989**, *37*, 1.
41. Maximum enantioselectivity is obtained with PLE in 25 % aq. DMSO: Andrade, M. A. C.; Andrade, F. A. C.; Phillips, R. S. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 373. The MOM group promotes high enantioselectivity and fast rate of hydrolysis: Luyten, M.; Müller, S.; Herzog, B.; Keese, R. *Helv. Chim. Acta* **1987**, *70*, 1250.
42. (a) Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946; (b) Toone, E. J.; Jones, J. B. *Tetrahedron Asymmetry* **1991**, *2*, 1041; (c) Provencher, L.; Jones, J. B. *J. Org. Chem.* **1994**, *59*, 2729.
43. (a) Moorlay, H.; Kellog, R. M. *Tetrahedron Asymmetry* **1991**, *2*, 705; (b) Tamm, C. *Indian J. Chem.* **1993**, *32B*, 190.
44. Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045. Mixed anhydrides or the DCC method gave unsatisfactory results.
45. Cf. Schultz, A. G. *Chem. Rev.* **1973**, *73*, 385.
46. Cf. Wall, M. E.; Campbell, H. F.; Wani, M. C. *J. Am. Chem. Soc.* **1972**, *94*, 3632.
47. Moore, H. W. *Science* **1977**, *197*, 527.
48. Other reagents/conditions: DIBAL in tol or THF at various temps. with or without tBuOK (overreduction, demethoxylation); $NaBH_4$ at room temp. in EtOH or in THF, KBH_4 with or without 18-cr-6, Bu_4NBH_4, $NaBH(OAc)_3$, all with or without 1-3 eq. of EtOH added (no reaction); $Zn(BH_4)_2$ in refl. THF (complex mixtures); K- or L-Selectride, $LiBEt_3H$ (severe overreduction).
49. Luche, J. M., L. Rodriguez-Hahn, P. Crabbé, *J. Chem. Soc., Chem. Commun.* **1978**, 601.
50. Natural CPT was purchased from Aldrich and obtained as a gift from Dr. Monroe E. Wall, Research Triangle Institute, NC.
51. Melting points (uncorr.) were measured on a Fischer-Johns hot stage apparatus. Unless otherwise indicated: (a) NMR spectra (ppm, δ) were recorded at 25°C on a Bruker AC 250 spectrometer (^1H=250 Mhz; ^{13}C=62.5) from CDCl3 solns. Splitting is described as "s" (singlet), "d", "dd", etc. (doublet, doublet of doublets, etc.), "t" (triplet), "q" (quartet), "m" (multiplet), and further characterized as "app"(apparent), "br" (broad), or "c" (complex). (b) IR spectra (cm^{-1}) were obtained with a Perkin Elmer 1600 FTIR spectrophotometer from films deposited on NaCl plates. (c) Low- and high res. mass spectra (m/e) were obtained on a Finnigan-MAT 4000 instrument in the EI (70 eV) mode. (d) Optical rotations were measured at 25°C on a JASCO polarimeter in $CHCl_3$ solns. Analytical and preparative TLC was carried out with Merck silica gel 60 plates with fluorescent indicator. Spots were visualized with UV light or stained with iodine, molybdic acid (solution of 24 g $(NH_4)_6Mo_7O_{24}$ and 0.5 g $Ce(SO_4)_2$ in 500 mL of 10 % aq. H_2SO_4) anisaldehyde, or Dragendorff reagents (Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; John Wiley & Sons: New York, NY, 1972; pp. 378 - 379). Chromatographic silica gel was purchased from Spectrum. All reactions involving air-/moisture-sensitive reagents were carried out under argon atmosphere. MeOH was dried over 4 Å molecular sieves; EtOAc and ethyl vinyl ether was distilled at atm. press.; DME, Et_3N, Et_2NH, iPr_2NEt and PhMe were dist. from CaH_2 at atm. press.; DMF, DMSO and NMP were vacuum-dist. from CaH_2; THF was dist. from Na/Ph_2CO; CH_2Cl_2 was first passed through alumina, then dist. from CaH_2. All other reagents and solvents were used as received. Microanalyses were performed at Galbraith Laboratories, Knoxville, TN.

(*Received* 16 *August* 1996; *accepted* 8 *October* 1996)