Synthesis of 18-Noranhydrocamptothecin Analogs Which Retain Topoisomerase I Inhibitory Function

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The total syntheses of compounds **2** and **3** are described. Key departures from previous routes to camptothecin from these laboratories involved (i) early incorporation of C_2 oxygen (see compound **9**) and (ii) recourse to a Heck vinylation for installation of a hydroxymethyl equivalent on the pyridone (see transformation **15** → **16**). The final compounds are of considerable interest in that they are the most drastically modified E ring systems which retain topoisomerase I inhibitory function.

The camptothecin family of cytotoxic drugs has undergone a long, but still inconclusive, evaluation with respect to usefulness in cancer chemotherapy.[1-3] Chemical investigations have been directed to the development of new synthetic routes to the series.[4-7] While several concise syntheses of the natural product have recently emerged,[8-11] it remains to be proven that total synthesis can compete with isolation from *Camptotheca accuminata*[12] as a route to camptothecin itself. However, since the focus has shifted from the natural product to several more clinically manageable analogs[1-3,13-16] (in terms of toxicity and solubility), synthesis may well emerge as the primary source of future generation drugs. Chemical investigations toward that end will undoubtedly continue.

At the biological level, interest in this series has been heightened by the identification of a likely mode of action for these drugs. Thus, the parent camptothecin inhibits the action of topoisomerase I on DNA unwinding.[17,18] Curiously, camptothecin binds neither to the enzyme nor to its DNA target in isolation. Its involvement is directed toward the enzyme–DNA complex.[19-23] Since the effect is reversable (heat, high salt concentrations, and high dilution),[19] it seems that the inhibitory effect is not a consequence of a stable covalent bond to either of the individual macromolecular targets or to the complex.

While some substitutions in the quinoline sector of camptothecin structure have been tolerated with significant maintenance of inhibitory function,[24,25] the requirements in the α-hydroxy δ-lactone sector have been rather strict.[26-29] In the work described herein, we probed the consequences of effecting a significant modification of the E-ring area. The goal was to promote the possibility of covalent bonding between the drug and either element of its two-component target.[30,31] In particular, we identified compounds **2** and **3** as possibilities, hoping that the vinylogous α-methylene-β-dicarbonyl system found in each would serve as a powerful alkylating site. The formation of a stable drug target adduct could provide useful structural leads as to the mode of inhibitory action. At this writing no homogenous *exo*-ethylidene analog (*cf.* **4** or **5**) of the parent camptothecin or its analogs has been reported.[32] We preferred to focus on the *exo*-methylidene targets **2** and **3** as candidates for investigation. The exocyclic methylene group would provide a more electro-

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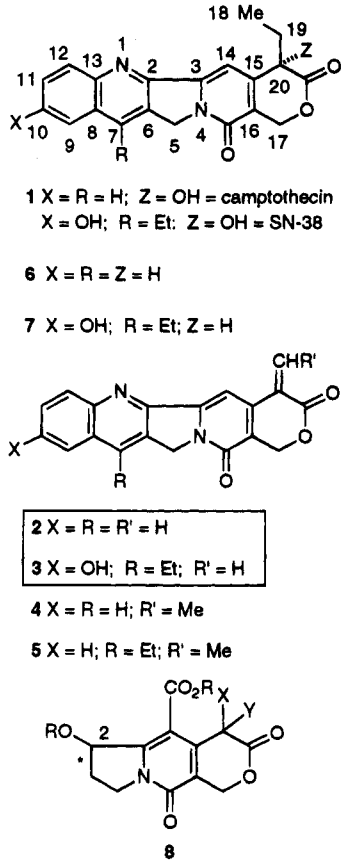


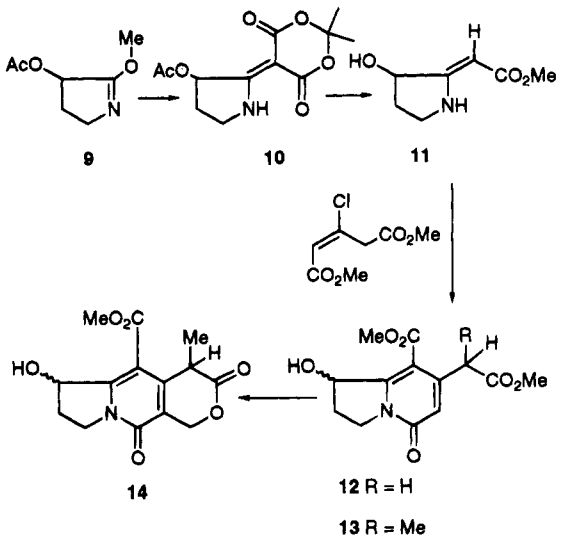
Figure 1.

philic alkylation target. Furthermore, the problem of *E/Z* isomerism is thereby avoided. The possibility of reaching **2** and **3** via degradation of camptothecin seemed to be remote, thus prompting us to undertake a total synthesis.

We expected to obtain these "nor" compounds from the phenylseleno derivatives **25** and **27** which might, in turn, be available via the 18-nor-20-desoxy systems **24** and **26** (*vide infra*). Initially, it was thought that the synthesis of these late intermediates would be accomplished by a minor modification of our previously described total synthesis[8] which reached 20-desoxycamptothecin (**6**) or CPT-11 precursor **7**. However, it subsequently transpired that the markedly decreased solubility of the 20-methyl compounds relative to the 20-ethyl systems undermined extension of the original route to the 18-nor series. In particular, it became necessary to incorporate the C-2 benzylic oxygen function well in advance of reaching a tricyclic intermediate (*cf.* **8**). This is in contrast to the later stage introduction practiced in our recently disclosed total synthesis[8]. A major redesign of the camptothecin synthesis, leading to compounds **2** and **3**, is described herein.

The new route starts with the known imino ether **9**[33] which already bears the required oxygen functionality which will eventually become C-2. Compound **9** was condensed with Meldrum's acid under the usual conditions[34] to afford **10** which was converted to **11** upon

Scheme 1



treatment with sodium methoxide. The vinylogous urethane reacted with 1,3-dicarbomethoxyallene (generated *in situ* from dimethyl 3-chloroglutaconate[35]) to afford **12**. Mono C-methylation of the vinylogous malonate moiety afforded **13**. This reaction often proved to be problematic *viz a viz* formation of a dimethylated compound which was difficult to remove from the desired **13**.[36] Although lactomethylation[37,38] of **13** via condensation with formaldehyde did give **14**, the awkwardness associated with the formation of **14** was never overcome. We also wanted the capability to synthesize other goal structures where the formaldehyde lactomethylation reaction fails.[39] An alternative route was developed which solved these problems.

Accordingly, compound **12** was treated with *N*-bromosuccinimide, thereby providing an 88% yield of **15**. The latter underwent vinylation under Heck conditions[40] to afford **16**. With the additional steric hindrance and solubility apparently imposed by the presence of the *o*-vinyl group, clean mono methylation was achieved via reaction of the lithium enolate of **16** with methyl iodide. Ozonolysis of the resultant **17** was followed by reduction with lithium tri-*tert*-butoxyaluminum hydride affording **18** which, after oxidation with the Dess–Martin periodinane,[41–43] provided an 89% yield of **19**.

Friedlander like coupling[44] of **19** with **20** and with **21**[8] afforded **22** and **23**, respectively. The seemingly trivial

(32) The conversion of 20-desoxycamptothecin to an inseparable mixture of *cis* and *trans* 20-ethylidenecamptothecin analogs has been accomplished in these laboratories. This transformation was effected by treatment of 20 - desoxycamptothecin with benzeneselenenyl bromide in pyridine followed by oxidative elimination (80 °C). However, we were unable to separate these compounds.

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(39) Although formation of the camptothecin E ring via lactomethylation with paraformaldehyde in acidic dioxane works quite well when the future 20-position of the seco precursor is monoalkylated, substrates bearing a free methylene group substitution at the 20-position fail to undergo the desired reaction. This is apparently due to attack of the formaldehyde at C-20 which bears vinylogous malonate character.

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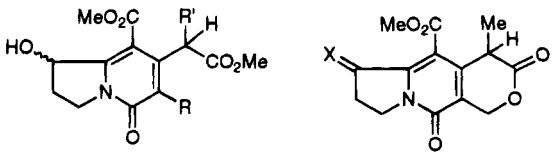


12 R = R' = H

15 R = Br; R' = H

16 R = CH=CH$_2$; R' = H

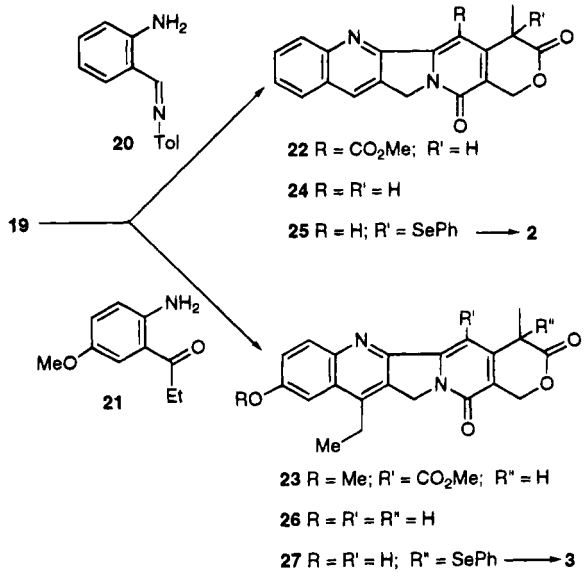
17 R = CH=CH$_2$; R' = Me

18 X = H; OH

19 X = O

Figure 2.

Scheme 2



22 R = CO_2Me; R' = H

24 R = R' = H

25 R = H; R' = SePh → 2

23 R = Me; R' = CO_2Me; R" = H

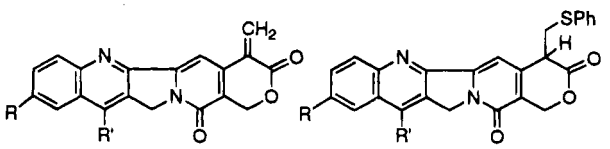
26 R = R' = R" = H

27 R = R' = H; R" = SePh → 3

replacement of the usual 20-ethyl group by a 20-methyl function brought with it a significant aggravation of an already serious solubility problem for the subsequent steps. Thus HBr-induced decarbalkoxylation[45] of **22** produced an incompletely characterized product assigned to be **24**. Treatment of this material with benzeneselenenyl bromide afforded **25**, though in only 36% overall yield from **22**. Finally, oxidative elimination of the phenylseleno group, through the action of hydrogen peroxide, led to the formation of goal system **2** in 53% yield. In a similar way, decarbalkoxylation of **23** with HBr produced **26**, which was isolated in homogenous form (54%). Selenylation as above afforded **27** in 61% yield and subsequent oxidative de-selenylation of **27** gave rise to **3**, albeit in only 40% yield. The rather modest yields encountered in the concluding steps reflect the difficulties associated with processing and purifying highly insoluble materials rather than any clearly definable alternative reaction pathways.

We next attempted to demonstrate that **2** and **3** would indeed function as strong electrophiles. In fact, treatment of each compound with thiophenol in dichloromethane led to consumption of starting material.[46] NMR analysis of the crude reaction mixture indicated formation of the expected adducts **28** and **29**. However, in each case attempted chromatographic purification of these compounds on silica gel and/or aqueous workup

Scheme 3



2 R = R' = H ⇢ 28 R = R' = H

3 R = OH; R' = Et ⇢ 29 R = OH; R' = Et

resulted in decomposition of the apparent adduct with reisolation of small amounts of **2** and **3**.

Of greater interest is the finding that these compounds exhibit potent camptothecin like inhibition of topoisomerase I activity.[47] While cytotoxicity was manifested in compound **3**, the levels are significantly reduced relative to camptothecin, conceivably due to problems in bioavailability. A fuller exposition of the biology of these *exo*-methylidene derivatives will be described shortly. *For the moment it can be said that compound **3** is the most drastically modified E-ring camptothecin analog which still retains enzyme inhibitory function.*

Experimental Section[8]

Acetate 10. To 32.00 g (0.20 mol) of acetate **9** in 125 mL of benzene were added 29.40 g (0.20 mol) of Meldrum's acid and 5.40 mL (0.04 mol) of triethylamine. The resultant solution was heated to reflux under nitrogen for 9 h, cooled to ambient temperature, and triturated with ether, providing 25.80 g of **10** as a brown solid (47%). The mother liquors were concentrated *in vacuo* and subjected to column chromatography (2:1 hexane/ethyl acetate to ethyl acetate), providing a black tar which was triturated with ether to provide an additional 1.80 g of **10** (total yield 50%): ^{1}H NMR ($CDCl_3$) δ 10.20 (br s, 1H), 6.52 (dd, J = 1.4, 6.9 Hz, 1H), 3.90 (m, 1H), 3.82 (m, 1H), 2.53 (m, 1H), 2.17 (m, 1H), 2.07 (s, 3H), 1.71 (s, 3H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.22, 169.33, 166.48, 161.47, 103.35, 81.81, 74.59, 47.10, 28.64, 26.74, 26.20, 20.32; IR (film) 3303, 1737, 1676, 1586 cm^{-1}; HRMS calcd for $C_{12}H_{15}NO_6$ 269.0899, found 269.0894.

Enamine 11. To a slurry of 27.50 g (0.10 mol) of acetate **10** in 150 mL of methanol was added 30.4 mL (0.13 mol) of sodium methoxide (25 wt % in methanol). The resultant black solution was heated to reflux for 17 h, concentrated *in vacuo*, and acidified to pH 4 via careful addition of 1 M HCl. The aqueous solution was extracted with dichloromethane (5 × 75 mL), dried over Na_2SO_4, and concentrated *in vacuo*, providing 13.0 g (81%) of enamine **11** as a light brown solid:. ^{1}H NMR ($CDCl_3$) δ 7.60 (br s, 1H), 4.72 (s, 1H), 4.67 (m, 1H), 3.65 (s, 3H), 3.61 (m, 1H), 2.77 (d, J = 4.6 Hz, 1H), 2.28 (m, 1H), 1.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 171.29, 166.48, 76.68, 73.77, 50.30, 44.43, 32.01; IR (film) 3370, 3000, 1654, 1627, 1615 cm^{-1}; HRMS calcd for $C_7H_{12}NO_3$ (M + 1) 158.0817, found 158.0821.

Bicyclic Pyridone 12. To 12.9 g (82.2 mmol) of **12** in 100 mL of absolute ethanol under nitrogen were added 17.4 g (90.4 mmol) of dimethyl 3-chloroglutaconate and 13.7 mL (98.6 mmol) of triethylamine. The reaction mixture was stirred at ambient temperature for 72 h and concentrated *in vacuo*. The residue was dissolved in 300 mL of chloroform and washed with 1 M HCl (2 × 100 mL), 100 mL of $NaHCO_{3(sat)}$, and 100 mL of brine, dried over $MgSO_4$, and concentrated *in vacuo* to a black oil. Column chromatography (20 to 30% acetone/chloroform) provided 16.9 g (73%) of **12** as a red viscous oil which solidified to a tan solid on standing: ^{1}H NMR ($CDCl_3$) δ 6.32 (s, 1H), 5.49 (m, 1H), 4.30–4.16 (m, 2H), 4.35 (d, J = 2.3 Hz, 1H), 3.84 (s, 3H), 3.88–3.79 (m, 1H), 3.70 (s, 3H), 3.74–3.65 (m, 1H), 2.46–2.28 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.32, 166.34, 160.26, 157.30, 146.35, 121.38, 106.60, 73.90, 51.97, 51.90, 47.41, 40.74, 28.87; IR (film) 3245, 2959, 1732, 1640,

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1577 cm^{-1}; mp 121–123 °C; HRMS calcd for $C_{13}H_{15}N_1O_6$ 281.0899, found 281.0892.

Monomethylated Pyridone 13. To 204 mg (0.73 mmol) of **12** in 7 mL of THF/7 mL of toluene under nitrogen at −78 °C was added 1.52 mL (1.52 mmol) of LiHMDS (1.0 M/hexane). The solution was immediately warmed to 0 °C for 1.5 h and cooled to −78 °C, and 50 μL (0.80 mmol) of iodomethane (passed through a plug of basic alumina prior to use) was added. The reaction was allowed to warm to ambient temperature over 18 h, quenched with 20 mL of 1 M HCl, and extracted with chloroform (4 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to a red oil which was subjected to column chromatography (25% acetone/chloroform) providing 178 mg (81%) of **13** as an inseparable mixture of diastereomers: ^1H NMR ($CDCl_3$) δ 6.40 (s, 1H), 5.30–5.29 (m, 1H), 4.23–4.11 (m, 3H), 4.01 (br s, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 2.33–2.26 (m, 2H), 1.43 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.20, 167.07, 160.68, 156.89, 152.04, 118.89, 106.83, 74.22, 52.29, 47.65, 43.17, 28.95, 16.65; IR (film) 3308, 2951, 1733, 1717, 1652 cm^{-1}.

Tricyclic Pyridone 14. To 46 mg (0.16 mmol) of **13** in 3 mL of dioxane in a pressure tube were added 24 mg (0.79 mmol) of paraformaldehyde and 4 pipette drops of H_2SO_4. The reaction vessel was sealed and heated to 110 °C for 24 h, cooled to ambient temperature, and diluted with 1 M HCl. The aqueous mixture was extracted with chloroform (5 × 10 mL), dried over $MgSO_4$, and concentrated *in vacuo* to a rust colored oil. Column chromatography (20% acetone/chloroform) provided 25 mg (54%) of **13** as an amber oil: ^1H NMR ($CDCl_3$) δ 5.55 (d, J = 15.9 Hz, 1H), 5.43–5.38 (m, 1H), 5.12 (d, J = 15.9 Hz, 1H), 4.30–4.11 (m, 3H), 3.93 (s, 3H), 2.42–2.27 (m, 2H), 1.53 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.29, 166.04, 157.50, 157.34, 147.58, 120.21, 104.75, 74.30, 64.39, 52.87, 48.13, 38.69, 28.83, 16.77; IR (film) 3432, 2954, 1738, 1715, 1651 cm^{-1}.

Bromide 15. To 2.00 g (7.12 mmol) of **12** in 50 mL of DMF under nitrogen was added 1.27 g (7.12 mmol) of *N*-bromosuccinimide. The solution was allowed to stir at ambient temperature for 20 h and concentrated *in vacuo*. The residue was dissolved in 75 mL of dichloromethane and washed with 50 mL of water and 50 mL of brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to a red oil which solidified on standing. Column chromatography (50 to 75% ethyl acetate/hexane) provided 2.26 g (88%) of **15** as a pale yellow solid. ^1H NMR ($CDCl_3$) δ 5.35 (d, J = 6.0 Hz, 1H), 4.20 (m, 2H), 4.10 (d, J = 17.1 Hz, 1H), 4.04 (d, J = 17.1 Hz, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 2.38–2.33 (m, 1H), 2.28–2.21 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.20, 165.80, 156.64, 154.72, 144.62, 119.65, 107.43, 73.89, 52.41, 52.05, 48.84, 40.79, 29.03; IR (film) 3380, 2957, 1728, 1624 cm^{-1}; mp 129–131 °C; HRMS calcd for $C_{13}H_{14}BrNO_6$ 359.0005, found 359.0009.

Vinylpyridone 16. To 1.19 g (3.29 mmol) of **15** in 30 mL of acetonitrile in a pressure tube were added 160 mg (0.53 mmol) of tri-*o*-tolylphoshine, 2.5 mL of triethylamine, and 59 mg (0.26 mmol) of palladium(II) acetate. The reaction vessel was sealed, pressurized with 75 psi of ethylene, and heated to 125 °C for 3 h. The black solution was allowed to cool to ambient temperature and concentrated *in vacuo* to a black tar. Radial chromatography (2.5% methanol/dichloromethane; 4 mm silica gel) provided 648 mg (64%) of **15** as a tan solid: ^1H NMR ($CDCl_3$) δ 6.61 (dd, J = 11.7, 17.6 Hz, 1H), 5.85 (d, J = 17.6 Hz, 1H), 5.64 (d, J = 11.6 Hz, 1H), 5.39–5.37 (m, 1H), 4.31–4.18 (m, 2H), 4.02 (d, J = 17.0 Hz, 1H), 3.89 (br s, 1H), 3.85 (d, J = 16.9 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 2.35–2.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.85, 167.13, 159.64, 154.34, 141.08, 129.79, 128.97, 122.69, 107.46, 74.33, 52.30, 52.08, 48.08, 37.38, 28.80; IR (film) 3464, 2951, 1738, 1643 cm^{-1}; mp 125–127 °C; HRMS calcd for $C_{15}H_{17}NO_6$ 307.1056, found 307.1068.

Methylated Pyridone 17. To 1.50 g (4.89 mmol) of **16** in 75 mL of THF under nitrogen at −78 °C was added 10.26 mL (10.26 mmol) of LiHMDS over 10 min. After 1.25 h, 0.33 mL (5.37 mmol) of iodomethane (passed through basic alumina plug prior to use) was added and the reaction mixture was allowed to warm to ambient temperature over 15 h. The reaction was quenched with 25 mL of 1 M HCl and extracted with ethyl acetate (4 × 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to a viscous red liquid. Column chromatography (20% acetone/chloroform) provided 1.40 g (90%) of an inseparable diastereomeric mixture of **17** as an orange foam: ^1H NMR ($CDCl_3$) δ 6.53 (dd, J = 11.7, 17.6 Hz, 1H), 5.92 (dd, J = 1.9, 17.7 Hz, 1H), 5.65 (dd, J = 1.9, 11.7 Hz, 1H), 5.30 (m, 1H), 4.31–4.04 (m, 3H), 3.77 (s, 3H), 3.63 (s, 3H), 2.35–2.28 (m, 3H), 1.52 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.01, 167.55, 159.68, 154.00, 147.55, 129.33, 127.63, 123.06, 106.84, 74.31, 51.91, 51.84, 48.08, 41.92, 28.87, 16.89; IR (film) 3400, 2990, 2951, 1731, 1634 cm^{-1}.

Tricyclic Pyridone 18. Through a solution of 1.02 g (3.18 mmol) of **17** in 90 mL of dichloromethane at −78 °C was passed a stream of ozone until a blue color persisted. The solution was purged with oxygen followed by nitrogen for 15 min, 2.31 mL (31.8 mmol) of dimethyl sulfide was added, and the reaction mixture was allowed to warm to ambient temperature over 15 h. The yellow solution was concentrated *in vacuo* and the residue dissolved in 70 mL of THF. The yellow solution was cooled to −78 °C and lithium tri-*tert*-butoxyaluminum hydride was added dropwise. After 7 h, 50 mL of 1 M HCl was added, the cooling bath was removed, and the aqueous solution was extracted with dichloromethane (3 × 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to a yellow viscous oil which was subjected to radial chromatography (20 to 25% acetone/chlorofom; 4 mm silical gel), providing 605 mg (65%) of an inseparable diastereomeric mixture of **18** as a white foam. Analytical data are the same as those described above.

Ketone 19. To 1.08 g (3.69 mmol) of **18** in 30 mL of dichloromethane under nitrogen were added 3.12 g (7.37 mmol) of Dess–Martin periodinane. After 1 h the reaction was quenched by the addition of 50 mL of $NaHCO_{3(sat)}$ and 50 mL of 10% $Na_2S_2O_3$. The aqueous mixture was extracted with chloroform (4 × 50 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to a viscous red oil. Column chromatography (20% acetone/chloroform) provided 953 mg (89%) of **19** as a pale yellow foam: ^1H NMR ($CDCl_3$) δ 5.59 (d, J = 17.0 Hz, 1H), 5.24 (d, J = 17.0 Hz, 1H), 4.31 (app t, J = 6.8 Hz, 2H), 3.94 (s, 3H), 3.75 (q, J = 7.5 Hz, 1H), 2.98–2.95 (m, 2H), 1.50 (d, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 194.34, 170.59, 163.91, 157.16, 145.36, 137.73, 125.64, 109.88, 65.14, 53.31, 42.16, 37.15, 33.61, 17.56; IR (film) 2954, 1746, 1659, 1614 cm^{-1}; mp 188–190 °C; HRMS calcd for $C_{14}H_{13}NO_6$ 291.0743, found 291.0750.

14-Carbomethoxy-18-nor-20-desoxycamptothecin (22). To 64.3 mg (0.22 mmol) of **19** in 10 mL of toluene under nitrogen were added 69.6 mg (0.33 mmol) of imine **20** and approximately 2 mg of *p*-toluenesufonic acid. The solution was heated to reflux with azeotropic removal of water for 5 h, cooled to ambient temperature, and concentrated *in vacuo*. Column chromatography (15% acetone/chloroform) provided 57.6 mg (69%) of **22** as a red solid: ^1H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.81–7.77 (m, 1H), 7.66–7.62 (m, 1H), 5.62 (d, J = 16.3 Hz, 1H), 5.28 (d, J = 16.3 Hz, 1H), 5.24 (app s, 2H), 4.11 (s, 3H), 3.85 (q, J = 7.6 Hz, 1H), 1.60 (d, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.36, 165.50, 157.12, 151.19, 148.67, 145.90, 144.27, 130.86, 130.51, 130.19, 128.41, 128.39, 127.93, 127.88, 119.81, 107.98, 65.22, 52.86, 50.08, 37.59, 17.56; IR (film) 3001, 2919, 1731, 1660, 1619 cm^{-1}; mp 277–279 °C; HRMS calcd for $C_{21}H_{16}N_2O_5$ 376.1059, found 376.1071.

14-Carbomethoxy-7-Ethyl-10-methoxy-18-nor-20-desoxy-camptothecin (23). To 950 mg (3.26 mmol) of **19** in 75 mL of toluene under nitrogen were added 876 mg (4.89 mmol) of amino ketone **21** and approximately 10 mg of *p*-toluenesulfonic acid. The solution was heated to reflux with azeotropic removal of water for 15 h, cooled to ambient temperature, and concentrated *in vacuo*. Column chromatography (10 to 15% acetone/chloroform) provided 992 mg (70%) of **23** as a red solid: ^1H NMR ($CDCl_3$) δ 7.99 (d, J = 9.2 Hz, 1H), 7.42 (dd, J = 2.6, 9.2 Hz, 1H), 7.26 (d, J = 2.6 Hz, 1H), 5.64 (d, J = 16.2 Hz, 1H), 5.28 (d, J = 16.1 Hz, 1H), 5.19 (app s, 2H), 4.09 (s, 3H), 3.98 (s, 3H), 3.85 (q, J = 7.5 Hz, 1H), 3.11 (q, J = 7.7 Hz, 2H), 1.60 (d, J = 7.6 Hz, 3H), 1.36 (t, J = 7.6 Hz, 3);

^{13}C NMR ($CDCl_3$) δ 171.52, 165.67, 159.18, 157.28, 148.34, 146.07, 145.43, 145.37, 143.33, 132.59, 128.06, 127.22, 122.57, 118.89, 107.28, 101.27, 65.24, 55.62, 52.75, 49.49, 37.67, 23.04, 17.54, 13.48; IR (film) 2928, 1726, 1660, 1620, 1226 cm^{-1}; mp 284–285 °C; HRMS calcd for $C_{24}H_{22}N_2O_6$ 434.1478, found 434.1465.

18-Nor-20-desoxycamptothecin (24). A solution of 57 mg (0.15 mmol) of **22** in 3 mL of 48% hydrobromic acid was heated in a sealed tube to 130 °C for 24 h, cooled to ambient temperature, and concentrated *in vacuo*. The crude product was used directly in the next step without any further purification. An analytical sample was prepared via column chromatography (25% acetone/chloroform): ^1H NMR ($CDCl_3$) δ 8.34 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.72–7.68 (m, 1H), 7.56–7.52 (m, 1H), 7.28 (s, 1H), 5.42 (d, J = 15.5 Hz, 1H), 5.21 (dd, J = 1.7, 15.4 Hz, 1H), 5.16 (app s, 2H), 3.60 (q, J = 7.1 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.42, 157.88, 151.96, 149.02, 148.52, 146.29, 131.65, 130.84, 129.04, 128.61, 128.21, 128.12, 120.63, 99.06, 64.83, 50.09, 38.91, 14.03; IR (film) 2919, 1724, 1652, 1599; mp 269–271 °C; HRMS calcd for $C_{19}H_{14}N_2O_3$ 318.1004, found 318.1004.

7-Ethyl-10-hydroxy-18-nor-20-desoxycamptothecin (26). A solution of 243 mg (0.56 mmol) of **23** in 18 mL of 48% hydrobromic acid was heated in a sealed tube to 130 °C for 14 h, cooled to ambient temperature, and concentrated *in vacuo*. The residue was dissolved in 4:1 chloroform/methanol and washed with $NaHCO_{3(sat)}$. The aqueous solution was extracted with three additional portions of 4:1 chloroform/methanol, dried over $MgSO_4$, and concentrated *in vacuo* to 109 mg (54%) of **26** which was used without any further purification: ^1H NMR ($CDCl_3$) δ 7.90 (d, J = 9.0 Hz, 1H), 7.29 (dd, J = 1.8, 9.2 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.19 (s, 1H), 5.43 (d, J = 15.4 Hz, 1H), 5.20 (d, J = 15.4 Hz, 1H), 5.08 (app s, 2H), 3.58 (q, J = 6.8 Hz, 1H), 2.98 (q, J = 7.7 Hz, 2H), 1.56 (d, J = 7.2 Hz, 3H), 1.24 (t, J = 7.7 Hz, 3H); IR (film) 3213, 2919, 1733, 1652 cm^{-1}.

18-Nor-20-phenylselenylcamptothecin (25). To crude **24** (prepared above) in 5 mL of degassed pyridine under nitrogen was added 72 mg (0.31 mmol) of benzeneselenenyl bromide. After 24 h the reaction mixture was concentrated *in vacuo* and the residue was subjected to column chromatography (5% acetone/chloroform), providing 26 mg (36% over two steps) of **25** as a pale yellow solid: ^1H NMR ($CDCl_3$) δ 8.39 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.83 (dt, J = 1.3, 8.4 Hz, 1H), 7.67 (app t, J = 7.1 Hz, 1H), 7.58–7.56 (m, 2H), 7.44–7.41 (m, 2H), 7.31 (app t, J = 7.6 Hz, 2H), 5.48, d, J = 16.5 Hz, 1H), 5.32 (d, J = 19.0 Hz, 1H), 5.25 (d, J = 19.1 Hz, 1H), 5.00 (d, J = 16.5 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.23, 157.44, 152.45, 148.94, 147.22, 146.01, 137.98, 131.16, 130.70, 130.55, 129.68, 129.27, 128.52, 128.19, 128.04, 126.40, 121.88, 97.66, 65.59, 49.93, 44.09, 22.42; IR (film) 2918, 1728, 1656, 1603, 1232; mp 271–273 °C.

7-Ethyl-10-hydroxy-18-nor-20-(phenylselenyl)camptothecin (27). To 107 mg (0.30 mmol) of crude **26** (prepared above) in 10 mL of degassed pyridine under nitrogen was added 140 mg (0.59 mmol) of benzeneselenenyl bromide. After 24 h the reaction mixture was concentrated *in vacuo* and subjected to column chromatography (20% acetone/chloroform), providing 93 mg (61%) of **27** as a yellow solid: ^1H NMR ($CDCl_3$) δ 7.91 (d, J = 9.1 Hz, 1H), 7.43–7.41 (m, 2H), 7.35 (s, 1H), 7.32–7.26 (m, 3H), 7.20–7.16 (m, 2H), 5.31 (d, J = 16.2 Hz, 1H), 5.11 (d, J = 18.8 Hz, 1H), 5.05 (d, J = 18.7 Hz, 1H), 4.85 (d, J = 16.3 Hz, 1H), 2.98 (q, J = 7.6 Hz, 2H), 1.93 (s, 3H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.56, 157.26, 156.62, 148.77, 147.54, 146.94, 144.46, 143.72, 137.96, 131.56, 131.49, 130.53, 129.25, 129.14, 128.69, 126.89, 126.33, 122.63, 120.66, 105.17, 97.26, 65.51, 44.12, 23.07, 22.22, 13.50; IR (film) 3167, 2972, 1731, 1650, 1590, 1235 cm^{-1}; mp 176–179 °C; HRMS calcd for $C_{27}H_{23}N_2O_4Se$ (M + 1) 519.0823, found 519.0815.

7-Ethyl-10-hydroxy-18-noranhydrocamptothecin (3). To 94 mg (0.18 mmol) of **27** in 19 mL of dichloromethane at 0 °C was added 0.54 mL (0.54 mmol) of hydrogen peroxide (1.0 M in methanol). After 3 h the cooling bath was removed, and the reaction mixture was allowed to warm to ambient temperture over 30 min and concentrated *in vacuo*. The residue was dissolved in 150 mL of 4:1 chloroform/methanol, and 500 mg of silica gel was added. The mixture was concentrated *in vacuo* and applied to a silica gel column as a slurry in chloroform. Elution with 2 to 6% methanol/chloroform provided 26 mg (40%) of **3** as a yellow solid: ^1H NMR ($CDCl_3$) δ 7.90 (d, J = 9.0 Hz, 1H), 7.42 (s, 1H), 7.29 (dd, J = 2.6, 9.0 Hz, 1H), 7.26 (d, J = 2.5 Hz, 1H), 6.73 (s, 1H), 6.45 (s, 1H), 5.36 (s, 2H), 5.09 (s, 2H), 2.98 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H); IR (film) 3583, 2924, 1731, 1716, 1654, 1583 cm^{-1}; mp 176 °C dec.

18-Noranhydrocamptothecin (2). To 33 mg (0.08 mmol) **of 25** in 2 mL of dichloromethane at 0 °C was added 0.10 mL (0.10 mmol) of hydrogen peroxide (1.0 M in methanol). After 4 h at 0 °C, the reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (2% methanol/chloroform), providing 15 mg (57%) **of 2** as a pale yellow solid: ^1H NMR ($CDCl_3$) δ 8.39 (s, 1H), 8.16 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.82–7.78 (m, 1H), 7.65–7.63 (m, 1H), 7.57 (s, 1H), 6.84 (s, 1H), 6.54 (s, 1H), 5.46 (s, 2H), 5.26 (s, 2H); IR (film) 2924, 1732, 1698; mp 261–263 °C; HRMS calcd for $C_{19}H_{12}N_2O_3$ 316.0848, found 316.0845.

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Supplementary Material Available: Copies of ^1H and/or ^{13}C NMR spectra of **10–17**, **19**, **22–27** (31 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.