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Total synthesis of (±)-17-norcamptothecin, a novel E-ring modified camptothecin

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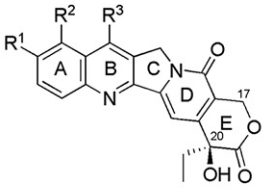
ABSTRACT

The first total synthesis of (±)-17-norcamptothecin, a novel camptothecin analog possessing an α-hydroxy-γ-lactone E-ring, has been accomplished by using a short and flexible route. The stability of this new compound in aqueous medium has been evaluated through fluorescence spectroscopy.

1. Introduction

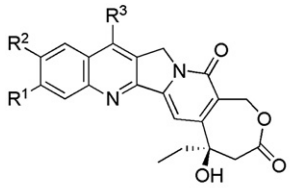
Since the isolation of 20(*S*)-camptothecin (**1**, Fig. 1) from the leaves of the Chinese bush *Camptotheca acuminata* by Wall et al.,[1] a number of analogs of the alkaloid have been prepared and bio-evaluated;[2] the most active of these DNA topoisomerase I inhibitors[3] are generally substituted on the quinoline part of the molecule. Among them, topotecan (**2**, Hycamtin)[4] and irinotecan (**3**, Camptosar)[5] have been approved for clinical use as anticancer drugs by the FDA. In addition, several analogs are in clinical trials and are among the most promising cancer chemotherapeutic agents currently under study.[6]

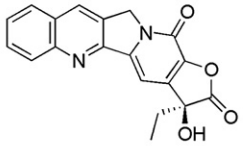


1 $R^1 = R^2 = R^3 = H$ (Camptothecin)
2 $R^1 = OH$, $R^2 = CH_2NMe_2.HCl$, $R^3 = H$ (Topotecan)
3 $R^1 = OCOPipPip$, $R^2 = H$, $R^3 = Et$ (Irinotecan)

Figure 1. Camptothecin and analogs.

A major problem with the C-20 hydroxy δ-lactone derivatives of camptothecin, however, is that they are prone to rapid E-ring-opening in the bloodstream with attendant loss of therapeutic efficacy.[7] Early attempts to modify the E-ring motif produced decreased bioactivity,[8–12] which led to the belief that the C-20 hydroxy δ-lactone motif was essential for biological activity. This dogma, however, was challenged by homocamptothecin (**4**, Fig. 2), a derivative possessing a methylene spacer between C-20 and the carbonyl group.[13] This compound exhibits enhanced stability in solution and potent antitumoral activity and two analogs, **5** and **6**,[14] are currently in clinical trials.[6] The potential of these new anticancer agents has notably revived interest in lactone-modified camptothecins,[15,16] but surprisingly a synthesis of 17-norcamptothecin (**7**), lacking the E-ring methylene group, has yet to be reported. This appeared to be a particularly interesting derivative on the basis of a recent theoretical study reported by Jena and





4 $R^1 = R^2 = R^3 = H$ (Homocamptothecin)
5 $R^1 = F$, $R^2 = F$, $R^3 = H$ (Diflomotecan)
6 $R^1 = Cl$, $R^2 = Me$, $R^3 = CH_2Pip\text{-}4\text{-}Me$ (Elomotecan)

7 17-Norcamptothecin

Figure 2. Structures of homocamptothecins and 17-norcamptothecin.

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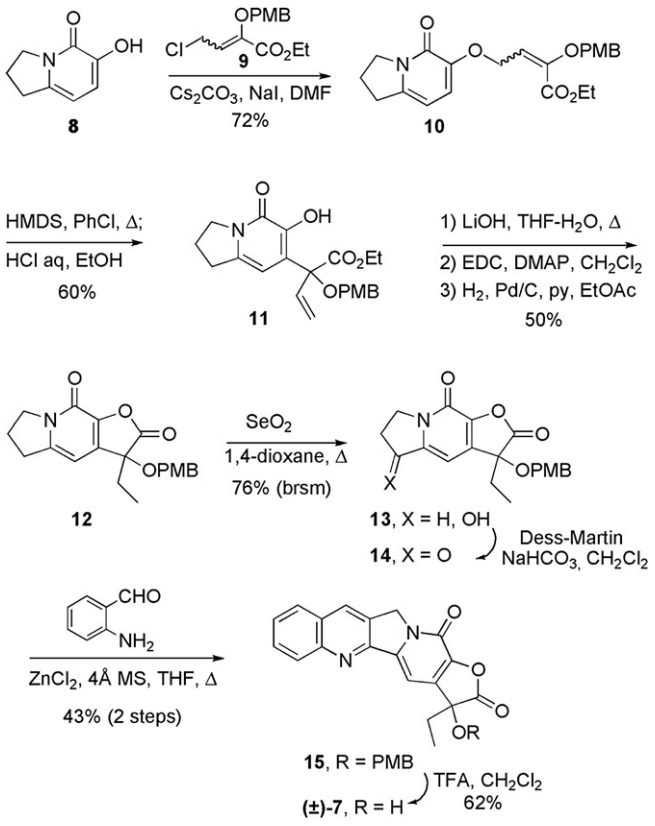
Mishra[17] in which it was found that the γ-lactone of compound **7** is planar, in contrast to the δ-lactone of camptothecin, and consequently hydrogen bonding between the C-20 hydroxyl and the carbonyl group might be largely absent. This, according to the authors, could impart greater chemical stability and enhanced antitumor activity to **7** relative to camptothecin. In this paper, we report an effective, flexible total synthesis of this novel camptothecin analog and a study of its hydrolytic stability.

2. Results and discussion

The strategy envisioned for the preparation of 17-norcamptothecin was based on our previously developed efficient, modular approach to camptothecinoids, which involves a Claisen rearrangement and a Friedländer condensation as the key steps.[18]

The synthesis commenced with etherification of the readily available hydroxy pyridone **8**[19] with allylic chloride **9** (*E*/*Z* mixture) in the presence of cesium carbonate and sodium iodide in DMF (Scheme 1). The inseparable mixture of allylic ethers **10**, obtained in 72% yield, was then refluxed in chlorobenzene in the presence of HMDS to promote the Claisen rearrangement. After acid treatment of the crude mixture and chromatographic purification, the expected pyridone **11** was isolated in 60% yield. The γ-lactone motif was next elaborated by ester hydrolysis in **11**, followed by cyclization of the resulting seco acid with EDC and DMAP in dichloromethane. In order to prevent hydrogenolysis of *p*-methoxybenzyl (PMB) group, the vinyl-substituted lactone was submitted to hydrogenation over Pd/C in ethyl acetate in the presence of pyridine[20] to afford the tricyclic derivative **12** in 50% overall yield (three steps).



Scheme 1. Synthesis of (±)-17-norcamptothecin.

The transformation of this derivative into ketone **14** was effected by using a standard protocol of hydroxylation with selenium dioxide, followed by Dess–Martin oxidation. This unstable ketone was directly engaged in a Friedländer condensation[21] with *o*-aminobenzaldehyde. While typical conditions (e.g., PTSA in refluxing toluene) produced mostly degradation, fortunately, the use of $ZnCl_2$ in refluxing THF[22] provided the desired pentacyclic compound **14** in 43% non-optimized yield (two steps).[23]

Removal of the PMB protecting group was smoothly and conveniently achieved by treatment of **15** with trifluoroacetic acid in dichloromethane[24] to afford, following a non-aqueous workup and purification, racemic 17-norcamptothecin (**7**) in 62% yield.[25]

The topoisomerase I inhibitory activity of compound **7** was evaluated by using a standard DNA relaxation assay,[26] and surprisingly this new analog was found to be completely inactive. It was postulated that this result could stem from decomposition of **7** under the aqueous conditions of the assay, therefore the stability of this compound in aqueous medium was next investigated. Thus, lactone **7** was treated with PBS buffer solutions of different pH values and the hydrolysis was monitored by fluorescence spectroscopy. Since the differences in the fluorescence spectra of the closed and the opened forms of **7** were particularly pronounced (Fig. 3),[27] this method was well suited for this study.

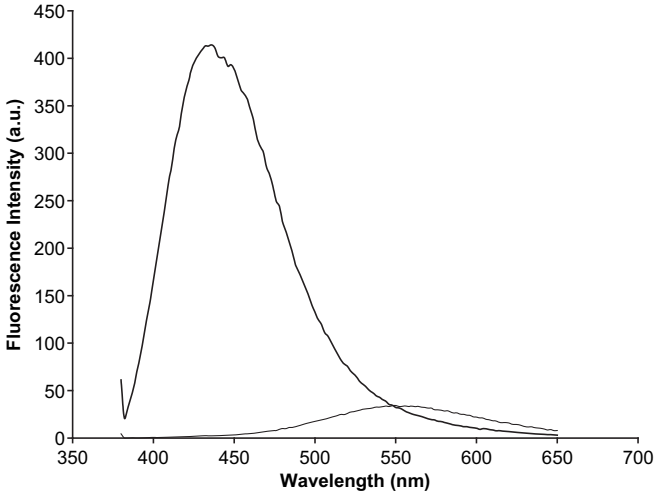


Figure 3. Fluorescence emission spectra of **7**, immediately after treatment with buffer solutions (—) and after complete hydrolysis (−), upon excitation at 375 nm.

The fluorescence parameters were then used to calculate the residual lactone percentage as a function of time by using a previously described methodology.[28] Figure 4 shows the hydrolysis kinetics of **7** at 20 °C at various pH values. At pH=7.4, the starting lactone suffered completely cleavage in less than 5 min ($t_{1/}$

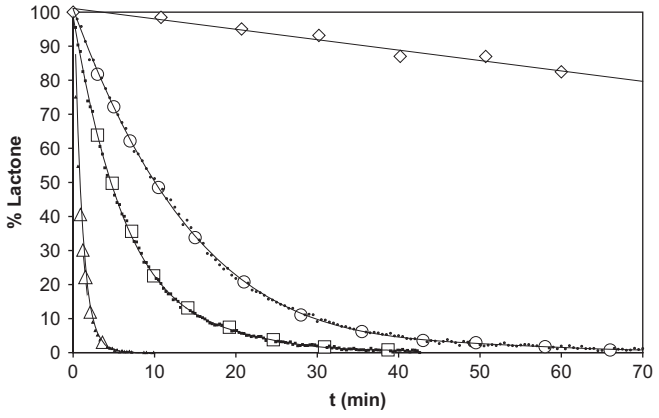


Figure 4. Hydrolysis kinetics of **7** (△: pH=7.4; □: pH=6.4; ○: pH=5.2) and **1** (◇: pH=7.4).

$_2$<1 min), whereas natural camptothecin displayed no significant lactone opening under these conditions.[29] Hydrolysis of lactone **7** also took place in acid medium, albeit less rapidly.

3. Conclusion

In summary, a short and flexible synthesis of (±)-17-norcamptothecin, a novel E-ring modified camptothecin derivative, has been developed from the easily accessible hydroxy pyridone **8**. The stability of **7** in aqueous medium, predicted through calculations to be greater than that of camptothecin, has been shown by using fluorescence spectroscopy to be, in fact, significantly lower. Efforts to attenuate this phenomenon are planned.

4. Experimental section

4.1. General

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. Pyridine was distilled from CaH_2. Reactions were monitored by TLC using silica gel $60F_{254}$ 0.2 mm-thickness plates with visualization by UV (254 nm) and through staining with a phosphomolybdic acid or $KMnO_4$ solution in EtOH. For preparative scale chromatography, silica gel 60 (0.04–0.063 μm) was used. Melting points were carried out on a Büchi B-545 apparatus. A Fourier transform infrared spectrometer was used to record IR spectra. NMR spectra were recorded at 300 MHz or 400 MHz and referenced to the residual solvent peak. Unless otherwise stated, $CDCl_3$ was used as the solvent. Two and three-bond $^1H-^{13}C$ connectivities were determined by HMBC experiments and one-bond $^1H-^{13}C$ connectivities by HMQC experiments. Mass spectra (MS) were effected using ESI. High resolution mass spectra (HRMS) were recorded at the LCOSB, Université Pierre et Marie Curie, Paris.

*4.1.1. Ethyl 4-chloro-2-(4-methoxybenzyloxy)but-2-enoate (**9**).* A mixture of ethyl 2-diazo-2-diethylphosphonoacetate (2.48 g, 9.93 mmol), 4-methoxybenzyl alcohol (1.65 g, 11.94 mmol), and rhodium (II) acetate (0.044 g, 0.10 mmol) in toluene (8 mL) was heated at 100 °C for 1 h, allowed to cool to 20 °C, and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (Et_2O) to give ethyl 2-(4-methoxybenzyloxy)-2-diethylphosphonoacetate (3.23 g, 90%). IR (neat): ν_{max}=2981, 1745, 1610, 1515, 1250, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.28 (d, $^3J_{H-H}$=8.4 Hz, 2H, $C_{Ar}H$), 6.87 (d, $^3J_{H-H}$=8.4 Hz, 2H, $C_{Ar}H$), 4.74 (d, $^2J_{H-H}$=11.2 Hz, 1H, $C_{Ar}CHHO$), 4.52 (d, $^2J_{H-H}$=11.2 Hz, 1H, $C_{Ar}CHHO$), 4.33 (d, $^2J_{H-P}$=18.8 Hz, 1H, CHP), 4.30–4.15 (m, 6H, $COCH_2$, $POCH_2$), 3.80 (s, 3H, OCH_3), 1.33–1.28 (m, 9H, $P(OCH_2CH_3)_2$, $COCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.2 (CO_2), 159.6 ($C_{Ar}OCH_3$), 130.0 ($C_{Ar}H$), 128.0 ($C_{Ar}CH_2O$), 113.7 ($C_{Ar}H$), 74.5 (d, $^1J_{C-P}$=156.4 Hz, CHPO), 73.6 (d, $^3J_{C-P}$=12.4 Hz, $C_{Ar}CH_2O$), 63.5 (d, $^2J_{C-P}$=5.4 Hz, $POCH_2CH_3$), 63.4 (d, $^2J_{C-P}$=6 Hz, $POCH_2CH_3$), 61.6 ($CO_2CH_2CH_3$), 55.1 (OCH_3), 16.2 ($POCH_2CH_3$), 16.1 ($POCH_2CH_3$), 14.0 ($CO_2CH_2CH_3$). HRMS (ESI): calcd for $C_{16}H_{25}O_7NaP$ 383.1230; found 383.1232.

A solution of ethyl 2-(4-methoxybenzyloxy)-2-diethylphosphonoacetate (3.00 g, 8.33 mmol) in THF (20 mL) was added to a suspension of NaH (60%, 1.00 g, 24.9 mmol) in THF (10 mL) at 0 °C. After the mixtue was stirred at 0 °C for 15 min and at 20 °C for 45 min, a solution of chloroacetaldehyde (obtained from 17 mL of 50% aqueous solution)[30] in THF (2 mL) was added at 0 °C. The reaction mixture was stirred at 20 °C for 1 h, diluted with Et_2O, and poured into water. The organic phase was then washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (EtOAc/pentane, 5/95) gave allylic chloride **9** (1.30 g, 55%) as a 9/10 mixture of diastereoisomers.[31] IR (neat): ν_{max}=2981, 1723, 1640, 1610, 1515, 1246 cm^{-1}. ^1H NMR (400 MHz, acetone d_6): δ=7.36–7.34 (m, 3.80H, $C_{Ar}H$), 6.95–6.92 (m, 3.80H, $C_{Ar}H$), 6.27 (t, $^3J_{H-H}$=8.0 Hz, 1H, $CHCH_2Cl$), 5.54 (t, $^3J_{H-H}$=8.0 Hz, 0.9H, $CHCH_2Cl$), 4.92 (s, 2H, $CHCH_2O$), 4.80 (s, 1.80H, $CHCH_2O$), 4.60 (d, $^3J_{H-H}$=8.0 Hz, 1.80H, $CHCH_2Cl$), 4.30–4.24 (m, 3.80H, CH_2CH_3), 3.79 (s, 5.7H, OCH_3), 1.34–1.28 (m, 5.7H, CH_2CH_3). ^{13}C NMR (100 MHz, acetone d_6): δ=164.3 (CO_2), 164.2 (CO_2), 161.7 ($C_{Ar}OCH_3$), 161.5 ($C_{Ar}OCH_3$), 149.9 (C=CHCH$_2$Cl), 148.5 (C=CHCH$_2$Cl), 132.2 ($C_{Ar}H$), 131.3 ($C_{Ar}H$), 130.5 ($C_{Ar}CH_2O$), 129.9 ($C_{Ar}CH_2O$), 123.5 (C=CHCH$_2$Cl), 115.6 ($C_{Ar}H$), 110.7 (C=CHCH$_2$Cl), 75.4 ($C_{Ar}CH_2O$), 72.0 ($C_{Ar}CH_2O$), 62.9 (CH_2CH_3), 62.8 (CH_2CH_3), 56.5 (OCH_3), 41.8 (CH_2Cl), 38.9 (CH_2Cl), 15.4 (CH_2CH_3), 15.3 (CH_2CH_3). HRMS (ESI): calcd for $C_{16}H_{25}O_7NaP$ 383.1230; found 383.1232.

*4.1.2. Ethyl 2-(4-Methoxybenzyloxy)-4-(5-oxo-1,2,3,5-tetrahydroindolizin-6-yloxy)but-2-enoate (**10**).* Sodium iodide (50 mg, 0.33 mmol) and a 4/6 mixture of allylic chlorides **9** (141 mg, 0.50 mmol)[31] were added to a suspension of pyridone **8** (50 mg, 0.33 mmol) and cesium carbonate (162 mg, 0.50 mmol) in DMF (0.5 mL). The mixture was stirred at 20 °C for 3 h, whereupon it was filtered through a pad of silica gel. The solids were rinsed with EtOAc and then with EtOAc/EtOH (90/10). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc, then EtOAc/EtOH, 98/2 to 94/6) to give allylic ether **10** (95 mg, 72%). IR (neat): ν_{max}=2955, 1719, 1653, 1597, 1515, 1246, 1220, 1173 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.32–7.27 (m, 5H, $C_{Ar}H$), 6.89–6.87 (m, 5H, $C_{Ar}H$), 6.64 (d, $^3J_{H-H}$=7.5 Hz, 1H, $C_{Py}H$), 6.45 (d, $^3J_{H-H}$=7.8 Hz, 1.5H, $C_{Py}H$), 6.40 (t, $^3J_{H-H}$=6.3 Hz, 1.5H, $CHCH_2O$), 5.96 (d, $^3J_{H-H}$=7.2 Hz, 1H, $C_{Py}H$), 5.91 (d, $^3J_{H-H}$=7.5 Hz, 1.5H, $C_{Py}H$), 5.59 (t, $^3J_{H-H}$=5.4 Hz, 1H, $CHCH_2O$), 5.0 (d, $^3J_{H-H}$=5.4 Hz, 2H, $CHCH_2O$), 4.89 (s, 3H, $C_{Ar}CH_2O$), 4.78 (s, 2H, $C_{Ar}CH_2O$), 4.53 (d, $^3J_{H-H}$=6.0 Hz, 3H, $CHCH_2O$), 4.33–4.22 (m, 5H, CH_2CH_3), 4.15 (m, 5H, NCH_2), 3.80 (s, 7.5H, OCH_3), 3.0 (m, 5H, $C_{Py}CH_2$), 1.33 (m, 5H, $C_{Py}CH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=163.1 (CO_2), 162.8 (CO_2), 159.6 ($C_{Ar}OCH_3$), 159.3 ($C_{Ar}OCH_3$), 157.2 (NCO), 157.0 (NCO), 146.3 (C_{Ar}), 146.1 (C_{Ar}), 145.0 (C_{Ar}), 144.9 (C_{Ar}), 141.1 (C_{Ar}), 141.0 (C_{Ar}), 130.3 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 128.5 ($C_{Ar}CH_2O$), 127.9 ($C_{Ar}CH_2O$), 123.7 (C=CHCH$_2$O), 115.8 ($C_{Py}H$), 115.7 ($C_{Py}H$), 113.8 (C_{Ar}), 113.7 ($C_{Ar}H$), 112.6 (C=CHCH$_2$O), 99.1 ($C_{Py}H$), 99.0 ($C_{Py}H$), 73.6 ($C_{Ar}CH_2O$), 70.2 ($C_{Ar}CH_2O$), 65.6 ($C_{Py}OCH_2$), 63.2 ($C_{Py}OCH_2$), 61.2 (CH_2CH_3), 61.1 (CH_2CH_3), 55.1 (OCH_3), 48.6 (NCH_2), 30.7 ($C_{Py}CH_2$), 22.0 ($C_{Py}CH_2CH_2$), 14.0 (CH_2CH_3). HRMS (ESI): calcd for $C_{22}H_{25}NO_6Na$ 422.1574; found 422.1571.

*4.1.3. (±)-Ethyl 2-(6-hydroxy-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl)-2-(4-methoxybenzyloxy)but-3-enoate (**11**).* A solution of allylic ether **10** (84 mg, 0.21 mmol) in a 1:1 mixture of chlorobenzene and hexamethyldisilazane (1.5 mL) was heated at reflux for 14 h. After removal of the solvents under reduced pressure, the resultant crude trimethylsilyl ether was stirred in a solution of EtOH (1 mL) and 1 N HCl (0.8 mL) at 20 °C for 2 h. The reaction mixture was extracted with CH_2Cl_2 and the organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (EtOAc/CH_2Cl_2, 10/90 to 30/70) gave hydroxy pyridone **11** (50 mg, 60%) as a white solid. Mp 146–148 °C. IR (neat): ν_{max}=3102, 2976, 1740, 1653, 1588, 1510, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.29 (d, $^3J_{H-H}$=8.4 Hz, 2H, $C_{Ar}H$), 7.12 (s, 1H, OH), 6.86 (d, $^3J_{H-H}$=8.4 Hz, 2H, $C_{Ar}H$), 6.40 (dd, $^3J_{H-Hcis}$=10.4 Hz, $^3J_{H-Htrans}$=17.2 Hz, 1H, CH=CH$_2$), 6.36 (s, 1H, $C_{Py}H$), 5.54 (dd, $^2J_{Htrans-Hcis}$=1.6 Hz, $^3J_{Htrans-H}$=7,6 Hz, 1H, CH=CH$_{trans}$H), 5.37 (dd, $^2J_{Hcis-Htrans}$=1.2 Hz, $^3J_{Hcis-H}$=10.8 Hz, 1H, CH=CHH_{cis}), 4.72 (d, $^3J_{H-H}$=0.4 Hz, 1H, $C_{Ar}CHHO$), 4.32–4.21 (m, 3H, CH_2CH_3, $C_{Ar}CHHO$), 4.12 (t, $^3J_{H-H}$=7.2 Hz, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 2.98 (t, $^3J_{H-H}$=7.6 Hz,

2H, $C_{Py}CH_2$), 2.18 (p, J=7.6 Hz, 2H, $C_{Py}CH_2CH_2$), 1.26 (t, $^3J_{H-H}$=7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3 (CO_2), 159.0 (C_{Ar}-OCH_3), 156.8 (NCO), 140.6 ($C_{Py}HC_{Py}C_{Py}OH$), 138.5 ($C_{Py}NCO$), 135.2 (CH=CH_2), 130.3 ($C_{Ar}CH_2$), 129.1 ($C_{Ar}H$), 127.2 ($C_{Py}OH$), 116.7 (CH=CH_2), 113.6 ($C_{Ar}H$), 99.5 ($C_{Py}H$), 81.0 (CCO_2), 66.7 ($C_{Ar}CH_2O$), 61.7 (CH_2CH_3), 55.2 (OCH_3), 48.7 (NCH_2), 30.8 ($C_{Py}CH_2$), 22.3 ($C_{Py}CH_2CH_2$), 14.0 (CH_2CH_3). HRMS (ESI): calcd for $C_{22}H_{25}NO_6Na$ 422.1574; found 422.1572.

*4.1.4. (±)-3-Ethyl-3-(4-methoxybenzyloxy)-6,7-dihydrofuro[2,3-f]indolizine-2,9(3H,5H)-dione (**12**).* A solution of $LiOH\cdot H_2O$ (107 mg, 2.55 mmol) in water (2.5 mL) was added to a solution of above ester (200 mg, 0.50 mmol) in THF (5 mL). The mixture was heated at 80 °C for 3 h, allowed to cool to 20 °C, and diluted with Et_2O (5 mL) and water (5 mL). The organic phase was separated and the aqueous phase was treated with 2:1 AcOH/$CHCl_3$ (7 mL) and then extracted exhaustively with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with Et_2O to provide (±)-2-(6-hydroxy-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl)-2-(4-methoxybenzyloxy)but-3-enoic acid (160 mg, 86%) as a white solid. Mp 136–138 °C. IR (neat): ν_{max}=3263, 2911, 1697, 1532, 1515, 1437, 1237 cm^{-1}. ^{1}H NMR (300 MHz, DMSO d_6): δ=12.80 (br s, 1H, CO_2H), 9.12 (br s, 1H, $C_{Py}OH$), 7.28 (d, $^3J_{H-H}$=7.8 Hz, 2H, $C_{Ar}H$), 6.91 (d, $^3J_{H-H}$=7.8 Hz, 2H, $C_{Ar}H$), 6.34 (dd, $^3J_{H-Hcis}$=10.8 Hz, $^3J_{H-Htrans}$=17.4 Hz, 1H, CH=CH_2), 6,17 (s, 1H, $C_{Py}H$), 5.35 (d, $^3J_{Htrans-H}$=17.4 Hz, 1H, CH=CH_{trans}H), 5.28 (d, $^3J_{Hcis-H}$=10.8 Hz, 1H, CH=CHH_{cis}), 4.56 (d, $^2J_{H-H}$=10.5 Hz, 1H, $C_{Ar}CHHO$), 4.20 (d, $^2J_{H-H}$=10.5 Hz, 1H, $C_{Ar}CHHO$), 3.97 (t, $^3J_{H-H}$=6.6 Hz, 2H, NCH_2), 3.74 (s, 3H, OCH_3), 2.95 (t, $^3J_{H-H}$=6.6 Hz, 2H, $C_{Py}CH_2$), 2.10–2.06 (m, 2H, $C_{Py}CH_2CH_2$). ^{13}C NMR (75 MHz, DMSO d_6): δ=170.8 (CO_2H), 158.5 ($C_{Ar}O$), 156.2 (NCO), 140.8 ($C_{Py}OH$), 138.4 ($C_{Py}NCO$), 136.3 (CH=CH_2), 130.3 ($C_{Ar}CH_2$), 128.8 ($C_{Ar}H$), 127.7 ($C_{Py}HC_{Py}C_{Py}OH$), 115.1 (CH=CH_2), 113.5 ($C_{Ar}H$), 97.7 ($C_{Py}H$), 80.7 (CCO_2H), 65.6 ($C_{Ar}CH_2O$), 55.0 (OCH_3), 48.4 (NCH_2), 30.3 ($C_{Py}CH_2$), 21.7 ($C_{Py}CH_2CH_2$). HRMS (ESI): calcd for $C_{20}H_{21}NO_6Na$ 394.1261; found 394.1265.

A solution of above carboxylic acid (160 mg, 0.43 mmol), DMAP (74 mg, 0.61 mmol), and EDC (166 mg, 0.87 mmol) in CH_2Cl_2 (3 mL) was stirred at 20 °C for 12 h. The reaction mixture was then diluted with $CHCl_3$ and washed with 1 N HCl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/CH_2Cl_2, 10/90 to 30/70) to afford (±)-3-(4-methoxybenzyloxy)-3-vinyl-6,7-dihydrofuro[2,3-*f*]indolizine-2,9(3*H*,5*H*)-dione (89 mg, 58%) as a white solid. Mp 92–94 °C. IR (neat): ν_{max}=2955, 1810, 1680, 1597, 1510, 1250, 1051 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.16 (d, $^3J_{H-H}$=8.4 Hz, 2H, $C_{Ar}H$), 6.79 (d, $^3J_{H-H}$=8.4 Hz, 2H, $C_{Ar}H$), 6.09 (s, 1H, $C_{Py}H$), 5.98 (dd, $^3J_{H-Hcis}$=10.8 Hz, $^3J_{H-Htrans}$=17.2 Hz, 1H, CH=CH_2), 5.40 (d, $^3J_{Hcis-H}$=10.8 Hz, 1H, CH=CHH_{cis}), 5.36 (d, $^3J_{Htrans-H}$=17.2 Hz, 1H, CH=CH_{trans}H), 4.33 (d, $^2J_{H-H}$=10.0 Hz, 1H, $C_{Ar}CHHO$), 4.27 (d, $^2J_{H-H}$=10.0 Hz, 1H, $C_{Ar}CHHO$), 4.18 (t, $^3J_{H-H}$=7.2 Hz, 2H, NCH_2), 3.74 (s, 3H, OCH_3), 3.10 (t, $^3J_{H-H}$=8.0 Hz, 2H, $C_{Py}CH_2$), 2.23 (p, $^3J_{H-H}$=7.2 Hz, 2H, $C_{Py}CH_2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.2 (CO_2), 159.5 ($C_{Ar}O$), 151.4 (NCO), 148.2 ($C_{Py}NCO$), 140.4 ($C_{Py}O$), 133.5 ($C_{Py}HC_{Py}C_{Py}O$), 132.8 (CH=CH_2), 129.6 ($C_{Ar}H$), 128.4 ($C_{Ar}CH_2$), 120.0 (CH=CH_2), 113.6 ($C_{Ar}H$), 95.3 ($C_{Py}H$), 82.6 (CCO_2), 68.5 ($C_{Ar}CH_2O$), 55.1 (OCH_3), 49.2 (NCH_2), 31.6 ($C_{Py}CH_2$), 21.8 ($C_{Py}CH_2CH_2$). HRMS (ESI): calcd for $C_{20}H_{19}NO_5Na$ 376.1155; found 376.1142.

A mixture of the above lactone (73 mg, 0.21 mmol), 10% Pd/C (12 mg), and pyridine (0.1 mL, 1.2 mmol) in EtOAc (8 mL) was stirred at 20 °C under hydrogen for 1 h. The mixture was then filtered through Celite and the solids were rinsed with $CHCl_3$. Concentration of the filtrate under reduced pressure afforded lactone **12** (74 mg, 100%) as a white solid. Mp 113–115 °C. IR (neat): ν_{max}=2972, 2937, 1810, 1680, 1601, 1515, 1250, 1046 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.14 (d, $^3J_{H-H}$=8.8 Hz, 2H, $C_{Ar}H$), 6.78 (d, $^3J_{H-H}$=8.8 Hz, 2H, $C_{Ar}H$), 6.10 (s, 1H, $C_{Py}H$), 4.23–4.12 (m, 4H, $C_{Ar}CH_2O$, NCH_2), 3.73 (s, 3H, OCH_3), 3.10 (t, $^3J_{H-H}$=7.6 Hz, 2H, $C_{Py}CH_2$), 2.24 (p, $^3J_{H-H}$=7.6 Hz, 2H, $C_{Py}CH_2CH_2$), 2.10–1.92 (m, 2H, CH_2CH_3), 0.82 (t, $^3J_{H-H}$=7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.3 (CO_2), 159.4 ($C_{Ar}O$), 151.4 (NCO), 148.1 ($C_{Py}NCO$), 140.2 ($C_{Py}OH$), 134.0 ($C_{Py}HC_{Py}C_{Py}O$), 129.5 ($C_{Ar}H$), 128.5 ($C_{Ar}CH_2$), 113.6 ($C_{Ar}H$), 94.9 ($C_{Py}H$), 83.6 (CCO_2), 68.8 ($C_{Ar}CH_2O$), 55.1 (OCH_3), 49.1 (NCH_2), 31.6 ($C_{Py}CH_2$), 30.6 (CH_2CH_3), 21.8 ($C_{Py}CH_2CH_2$), 7.0 (CH_2CH_3). HRMS (ESI): calcd for $C_{20}H_{21}NO_5Na$ 378.1312; found 378.1315.

*4.1.5. (±)-3-Ethyl-5-hydroxy-3-(4-methoxybenzyloxy)-6,7-dihydrofuro[2,3-f]indolizine-2,9(3H,5H)-dione (**13**).* A mixture of lactone **12** (120 mg, 0.338 mmol) and selenium dioxide (75 mg, 0.68 mmol) in 1,4-dioxane (freshly distilled from sodium) was refluxed for 10 h.[32] After being cooled to 20 °C, the mixture was filtered through Celite and the solids were rinsed successively with CH_2Cl_2 and EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/CH_2Cl_2, 10/90 to 50/50) to provide starting material (57 mg) and an inseparable mixture of diastereomeric alcohols **13** (50 mg, 76% brsm) as an orange solid. Mp 148–160 °C (dec). IR (neat): ν_{max}=3341, 2933, 1810, 1671, 1588, 1246, 1033 cm^{-1}. ^{1}H NMR (400 MHz, CD_2Cl_2): δ=7.12–7.15 (m, 4H, $C_{Ar}H$), 6.77–6.80 (m, 4H, $C_{Ar}H$), 6.40 (s, 2H, $C_{Py}H$), 5.25 (s, 2H, O*H*) 5.22–5.23 (m, 2H, C*H*OH), 4.26–4.32 (m, 2H), 4.13–4.20 (m, 4H), 3.96–4.03 (m, 2H), 3.73–3.74 (m, 6H, OCH_3), 2.49–2.58 (m, 2H), 2.12–2.19 (m, 2H), 2.08–2.10 (m, 4H, CH_2CH_3), 0.83 (t, $^3J_{H-H}$=5.4 Hz, 6H, CH_2CH_3). ^{13}C NMR (75 MHz, CD_2Cl_2): δ=174.6 (CO_2), 174.5 (CO_2), 159.8 ($C_{Ar}O$), 159.7 ($C_{Ar}O$), 151.2 (NCO), 150.0 ($C_{Py}NCO$), 141.5 ($C_{Py}O$), 141.4 ($C_{Py}O$), 134.6 ($C_{Py}HC_{Py}C_{Py}O$), 129.8 ($C_{Ar}H$), 128.9 ($C_{Ar}CH_2$), 128.8 ($C_{Ar}CH_2$), 113.8 ($C_{Ar}H$), 96.1 ($C_{Py}H$), 96.0 ($C_{Py}H$), 83.8 (CCO_2), 83.7 (CCO_2), 73.2 (*C*HOH), 73.1 (*C*HOH), 69.1 ($C_{Ar}CH_2O$), 69.0 ($C_{Ar}CH_2O$), 55.3 (OCH_3), 46.7 (NCH_2), 32.4 ($C_{Py}CH_2$), 32.3($C_{Py}CH_2$), 30.9 (CH_2CH_3), 30.8 (CH_2CH_3), 7.0 (CH_2CH_3). HRMS (ESI): calcd for $C_{20}H_{21}NO_6Na$ 394.1261; found 394.1265.

*4.1.6. (±)-3-Ethyl-3-(4-methoxybenzyloxy)-6,7-dihydrofuro[2,3-f]indolizine-2,5,9(3H)-trione (**14**).* A solution of the Dess–Martin periodinane (15% in CH_2Cl_2, 0.282 mL, 0.134 mmol) was added to a mixture of alcohols **13** (25 mg, 0.07 mmol) and sodium bicarbonate (34 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was diluted with Et_2O and treated with saturated sodium bicarbonate and saturated sodium thiosulfate (1/2, 3 mL). The organic phase was washed with saturated sodium bicarbonate and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide ketone **14** (24 mg, 97%) as a white solid. Mp 142–162 °C (dec). IR (neat): ν_{max}=2933, 1823, 1736, 1680, 1606, 1241, 1189 cm^{-1}. ^{1}H NMR (400 MHz, CD_2Cl_2): δ=7.13 (d, $^3J_{H-H}$=8.8 Hz, 2H, $C_{Ar}H$), 6,85 (s, 1H, $C_{Py}H$), 6,79 (d, $^3J_{H-H}$=8.8 Hz, 2H, $C_{Ar}H$), 4,33 (t, $^3J_{H-H}$=6.4 Hz, 2H, NCH_2), 4,23 (d, $^3J_{H-H}$=10.4 Hz, 1H, $C_{Ar}CHHO$), 4.13 (d, $^3J_{H-H}$=10.4 Hz, 1H, $C_{Ar}CHHO$), 3.74 (s, 3H, OCH_3), 2.93 (t, $^3J_{H-H}$=6.8 Hz, 2H, CH_2CO), 2.01–2.12 (m, 2H, CH_2CH_3), 0.85 (t, $^3J_{H-H}$=7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, CD_2Cl_2): δ=195.5 (CH_2COC_{Py}), 173.7 (CO_2), 159.9 ($C_{Ar}O$), 151.0 (NCO), 147.1 ($C_{Py}NCO$), 137.8 ($C_{Py}O$), 133.4 ($C_{Py}HC_{Py}C_{Py}O$), 129.9 ($C_{Ar}H$), 128.5 ($C_{Ar}CH_2$), 113.8 ($C_{Ar}H$), 98.3 ($C_{Py}H$), 83.4 (CCO_2), 69.4 ($C_{Ar}CH_2O$), 55.3 (OCH_3), 42.7 (NCH_2), 34.0 ($C_{Py}CH_2$), 30.9 (CH_2CH_3), 7.0 (CH_2CH_3). HRMS (ESI): calcd for $C_{20}H_{20}NO_6$ 370.1285; found 370.1273.

*4.1.7. (±)-O-p-Methoxybenzyl-17-norcamptothecin (**15**).* A 0.5 M solution of $ZnCl_2$ in THF (0.325 mL, 0.163 mmol) was added to a mixture of ketone **14** (24 mg, 0.065 mmol), 2-aminobenzaldehyde (28 mg, 0.23 mmol), and 4 Å molecular sieves in dry THF (1 mL). The resultant mixture was heated at reflux for 5 h, allowed to cool

to 20 °C, and diluted with $CHCl_3$. The organic phase was washed with saturated sodium bicarbonate and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide compound **15** (13 mg, 44%) as a yellow solid. Mp 164–167 °C. IR (neat): ν_{max}=2920, 1814, 1979, 1606, 1515, 1254, 1232 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.41 (s, 1H, $C_{Ar}H$), 8.21 (d, $^3J_{H-H}$=8.1 Hz, 1H, $C_{Ar}H$), 7.95 (d, $^3J_{H-H}$=8.1 Hz, 1H, $C_{Ar}H$), 7.84 (t, $^3J_{H-H}$=8.1 Hz, 1H, $C_{Ar}H$), 7.67 (t, $^3J_{H-H}$=8.1 Hz, 1H, $C_{Ar}H$), 7.36 (s, 1H, $C_{py}H$), 7.21 (d, $^3J_{H-H}$=8.7 Hz, 2H, $C_{Ar}H$), 6.81 (d, $^3J_{H-H}$=8.7H, 2H, $C_{Ar}H$), 5.40 (s, 2H, CH_2N), 4.33 (d, $^2J_{H-H}$=10.2 Hz, 1H, $C_{Ar}CHHO$), 4.28 (d, $^2J_{H-H}$=10.2 Hz, 1H, $C_{Ar}CHHO$), 3.71 (s, 3H, OCH_3), 2.27–2.13 (m, 2H, CH_2CH_3), 0.94 (t, $^3J_{H-H}$=7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.9 (CO_2), 159.6 ($C_{Ar}O$), 152.1 (C_{Ar}), 151.1 (CON), 148.9 (C_{Ar}), 143.9 (C_{Ar}), 142.7 (C_{Ar}), 134.9 (C_{Py}), 131.1 ($C_{Ar}H$), 130.7 ($C_{Ar}H$), 129.8 (C_{Ar}), 129.6 ($C_{Ar}H$), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.2 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.8 ($C_{Ar}CH_2$), 113.8 (C_{Ar}), 95.4 ($C_{Py}H$), 83.7 (CCO_2), 69.2 ($C_{Ar}CH_2O$), 55.2 (OCH_3), 50.6 (NCH_2), 31.0 (CH_2CH_3), 7.2 (CH_2CH_3). HRMS (ESI): calcd for $C_{27}H_{23}N_2O_5$ 455.1602; found 455.1603.

*4.1.8. (±)-17-Norcamptothecin (**7**).* Trifluoroacetic acid (1.0 mL, 13.5 mmol) was added to a solution of **15** (24 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) at 0 °C and the reaction mixture was stirred for 1 h at the same temperature. The volatiles were then evaporated under reduced pressure and the residue was triturated with a small amount of CH_2Cl_2 and Et_2O to provide 17-norcamptothecin (11 mg, 62%) as an orange solid. Mp 248–250 °C. ^1H NMR (400 MHz, DMSO d_6): δ=8.72 (s, 1H, $C_{Ar}H$), 8.18 (m, 2H, $C_{Ar}H$), 7.90 (t, $^3J_{H-H}$=7.2 Hz, 1H, $C_{Ar}H$), 7.75 (t, $^3J_{H-H}$=7.2 Hz, 1H, $C_{Ar}H$), 7.33 (s, 1H, $C_{Py}H$), 6.95 (s, 1H, OH), 5.40 (s, 2H, NCH_2), 2.02–2.21 (m, 2H, CH_2CH_3), 0.84 (t, $^3J_{H-H}$=7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, DMSO d_6): δ=176.2 (CO_2), 152.2 (C_{Ar}), 150.2 (CON), 147.8 (C_{Ar}), 143.6 (C_{Ar}), 141.0 (C_{Ar}), 137.3 (C_{Ar}), 131.3 ($C_{Ar}H$), 130.3 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.5 (C_{Ar}), 127.4 ($C_{Ar}H$), 94.3 ($C_{Py}H$), 76.8 (CCO_2), 50.5 (NCH_2), 30.0 (CH_2CH_3), 7.1 (CH_2CH_3). HRMS (ESI): calcd for $C_{19}H_{15}N_2O_4$ 335.1026; found, 335.1019.

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Supplementary data

^1H and ^{13}C NMR spectra of all new compounds and details for the spectrofluorimetric determinations. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.06.003. This data include MOL files and InChIKeys of the most important compounds described in this article.

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