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Total synthesis of (+)-camptothecin

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Abstract—A total synthesis of (+)-camptothecin is described. The approach is based on a room temperature $LUMO_{diene}$-controlled Diels–Alder cycloaddition of the electron deficient *N*-sulfonyl-1-aza-1,3-butadiene **6** with the electron rich dienophile 1,1,3,3-tetraethoxypropene (**7**) for assembly of a pyridine precursor to the D-ring pyridone. The 20(*S*) tertiary alcohol was installed through a Sharpless asymmetric dihydroxylation reaction on the methyl vinyl ether **12**, using the 3,4,5-trimethoxyphenyl-derived pyrimidine DHQ dimer ligand **16**. In a single reaction vessel, the C and E rings were closed using an acid-catalyzed deprotection of the benzylic ethers to afford the corresponding benzylic bromides (**18**) which underwent intramolecular nucleophilic displacement by the carboxylate and pyridone nitrogen to furnish (+)-camptothecin.

(+)-Camptothecin (CPT, **1**, Fig. 1) is a pentacyclic alkaloid isolated and characterized by Wall and co-workers in 1966 from *Camptotheca acuminata* and shown to exhibit potent cytotoxic activity against a range of tumor cell lines.[1–3] Subsequent to its discovery, CPT was shown to stabilize the cleavable complex of double-stranded DNA and topoisomerase I.[4] Topoisomerase I is responsible for the cleavage of double-stranded DNA to produce a covalently bound 3′-phosphate-enzyme complex[5] and is enlisted to unwind supercoiled DNA ahead of the replication fork.[6] Recent modeling studies of a ternary complex suggest camptothecin intercalates from the minor groove side of DNA forming key hydrogen bond interactions between its lactone and arginine 364 of human topoisomerase I.[7] This prevents religation of double-stranded DNA, provides stabilization of the single strand break, and results in a permanent DNA lesion that leads to cell death.[8–10] Although CPT itself is not used clinically for the treatment of cancer, two closely related analogues Topotecan (**2**) and Irinotecan (**3**) have proven effective in the clinic.[11,12]

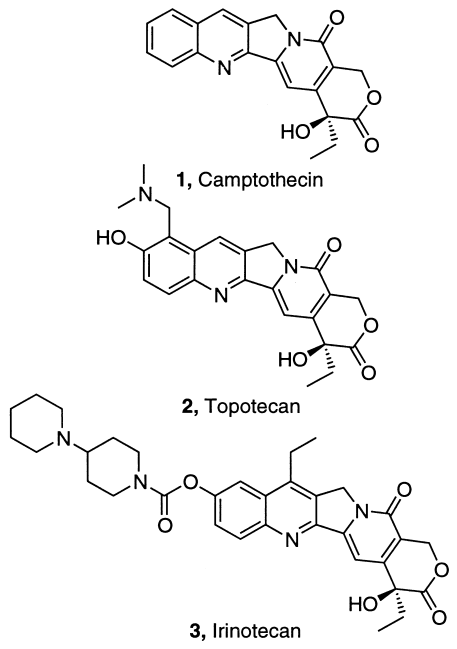

Figure 1.

Since its discovery, camptothecin has been the subject of extensive research especially for the design of water soluble derivatives[11–18] and more recently, stable lactone analogues.[19–23] At physiological pH, the lactone is easily hydrolyzed to the biologically inactive carboxylate, which binds to human serum albumin, lowering the effective concentration of CPT.[24,25] This facile hydrolysis of the lactone represents a challenging problem and its labile nature has been attributed to the α-hydroxy group which is believed to accelerate the hydrolysis through intramolecular hydrogen bonding.[21] Recently, the development of new analogues of CPT which are more stable has been pursued and culminated in the development of homocamptothecin (**4**, Fig. 2).[19,20] Homocamptothecin contains a methylene spacer between the tertiary alcohol and the lactone carbonyl, resulting in prolonged activity in cellular assays.[21]

Although numerous analogues of CPT containing modifications in the lactone ring have been prepared, none have

Keywords: (+)-camptothecin; Diels–Alder cycloaddition; *N*-sulfonyl-1-aza-1,3-butadiene.

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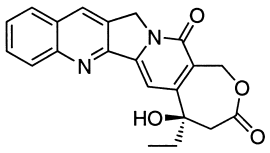
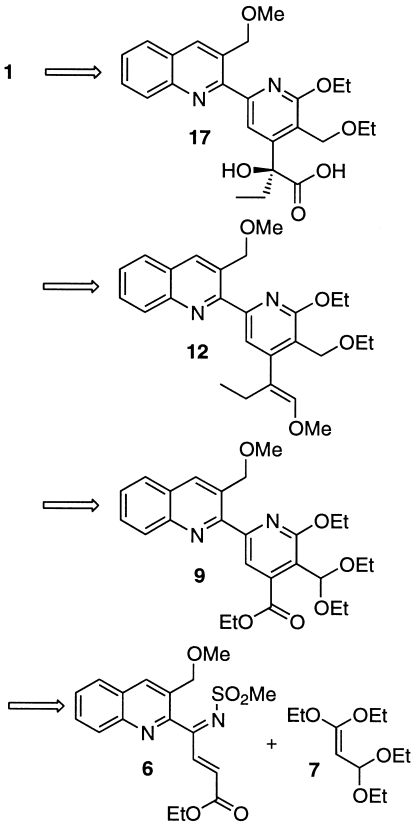


4, Homocamptothecin

Figure 2.

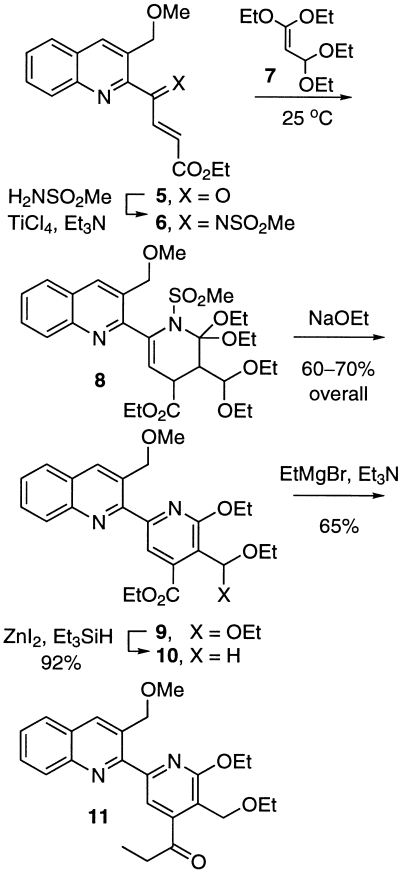
proven to be as active as CPT itself. Herein we detail the development of a versatile route for the asymmetric synthesis of CPT,[26] which allows for modification of the E-ring permitting access to new analogues that may help to define the key interactions between CPT/DNA/topoisomerase I and ultimately aid in the development of second generation CPT derivatives.

The approach is based on the implementation of a room temperature inverse electron demand Diels–Alder reaction of the *N*-sulfonylimine **6**,[27] a *N*-sulfonyl-1-aza-1,3-butadiene,[28–30] with the electron rich dienophile **7** for introduction of the D-ring pyridone. The azadiene **6** incorporates a noncomplementary C4 electron-withdrawing substituent which is known to lower the diene LUMO accelerating its rate of reaction in an inverse electron demand Diels–Alder reaction without altering the inherent regioselectivity of the cycloaddition.[30] Base-catalyzed aromatization of cycloadduct **8** would provide the highly substituted pyridine **9** bearing four of the five pyridone exocyclic substituents, two of which could be further elaborated for introduction of the E-ring. The stereochemistry of the tertiary α-hydroxy group of the E-ring lactone was envisioned to be set by a Sharpless asymmetric dihydroxylation reaction of the corresponding vinyl ether **12**. Finally, the C and E ring closures were expected to come from simultaneous pyridone deprotection and conversion of the benzylic ethers in **17** to the corresponding benzylic bromides, followed by intramolecular displacement upon the addition of base to furnish (+)-camptothecin (Scheme 1).



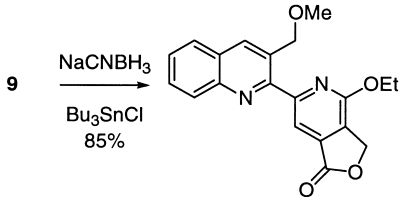
Scheme 1.

Methane sulfonamide was condensed with *trans*-ketone **5**[27] under dehydrating conditions utilizing $TiCl_4$ and Et_3N to furnish the *N*-sulfonyl-1-aza-1,3-butadiene **6** as previously detailed, Scheme 2.[27,31] The inverse electron demand Diels–Alder cycloaddition between the electron rich 1,1,3,3-tetraethoxypropene (**7**)[32] and the electron deficient *N*-sulfonyl-1-aza-1,3-butadiene **6** proceeded at room temperature and ambient pressure within 4 h to give the desired [4+2] cycloadduct **8**. Addition of sodium ethoxide to the sensitive Diels–Alder cycloadduct resulted in the sequential elimination of methanesulfinic acid and ethanol to provide the highly substituted 2-ethoxypyridine **9** under mild conditions (0°C, 1–1.5 h). Because of the hydrolysis sensitive nature of both the azadiene **6** and the cycloadduct **8**, the three steps enlisted for the conversion of **6** to pyridine **9** were carried out in higher conversions (60–70% overall) without purification of the intermediates. Due to the labile nature of the diethyl acetal **9**, it was converted to the corresponding ethyl ether using ZnI_2 and Et_3SiH which cleanly gave **10** without any competing lactonization products resulting from capture



Scheme 2.

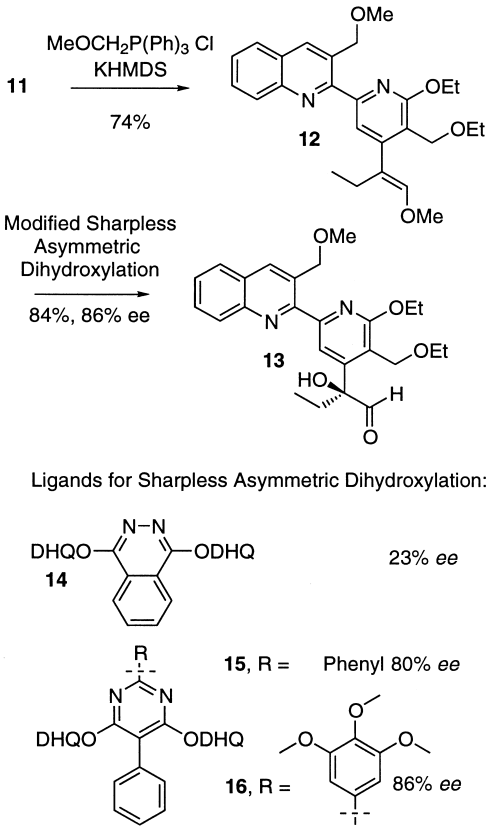
of the oxonium intermediate by the adjacent ester. In contrast, treatment of **9** with $NaCNBH_3$ and Bu_3SnCl[33] provided such a lactone[34] in 85% yield (*t*-BuOH, 80°C, Eq. (1)). Although not extensively investigated, the use of ZnI_2/Et_3SiH was more effective than either $ZnI_2/NaCNBH_3$[35] (20–65%) or TMSOTf/Et_3SiH[36] for conversion of **9** to **10**. In addition, the diethyl acetal of **9** was easily deprotected to provide the corresponding aldehyde[37] (TFA, CH_2Cl_2–H_2O, 0°C, 5–10 min or TsOH, acetone–H_2O, 11 h, quantitative), but alternative routes proceeding through this intermediate have not yet proven competitive.



(1)

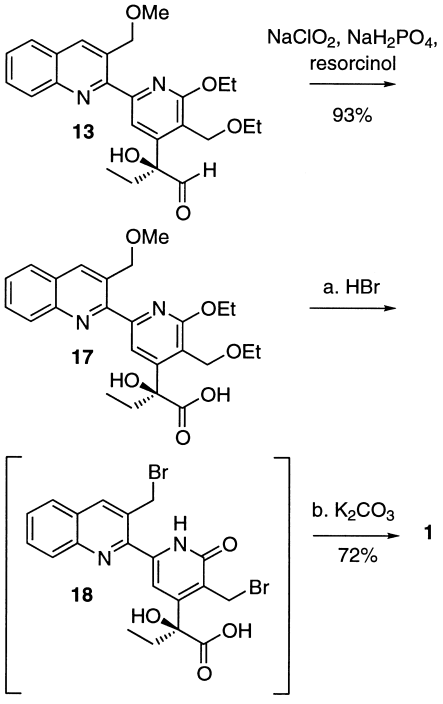
The ethyl ester **10** was directly converted to ethyl ketone **11** by addition of EtMgBr in the presence of excess Et_3N.[38] The vinyl ethers **12** were formed through a Wittig reaction of ethyl ketone **11** and methoxymethenetriphenylphosphorane to furnish a 3:1 mixture of *trans*/*cis* isomers (98%), which could be easily separated providing *E*-**12** (74%), Scheme 3. Analogous to the two additional total syntheses of CPT[26s,v,y] that utilized a Sharpless asymmetric dihydroxylation,[39] the AD reaction of *trans* vinyl ether **12** proved to be difficult initially. Using the commercially available β-AD mix containing ligand **14**, the desired α-hydroxy aldehyde **13** was obtained in low yields and poor enantiomeric excess. Instead of **13** as the major product, ketone **11** was predominately formed resulting from the subsequent oxidative cleavage of the corresponding C–C bond. Reducing the amount of $K_3Fe(CN)_6$ to 1.3 equiv. and supplementing the reaction with an additional equivalent at a later time while increasing the amount of ligand **14** and OsO_4 led to an improved yield of the desired product. However, the enantiomeric excess remained low (23% ee).[40] The enantiomeric excess of the reaction was increased remarkably by utilization of the $(DHQ)_2$-pyrimidine ligand **15** resulting in 80% ee. The enantioselectivity was further increased to 86% with the 4,6-$(DHQ)_2$-5-phenyl-1,3-pyrimidine-2-(3,4,5-trimethoxyphenyl) ligand **16** providing material suitable for incorporation into the total synthesis of **1**. When the *cis* vinyl ether was used with the $(DHQD)_2$ version of **16**, **13** was obtained in lower ee's (60–70% ee). Interestingly, when the $(DHQD)_2$ variant of this ligand was used with the *trans* isomer, greater than 99% ee of the corresponding unnatural 20(*R*) enantiomer was obtained.

Once formed, α-hydroxy aldehyde **13** was immediately oxidized to the corresponding carboxylic acid **17** with sodium chlorite[41] in a buffered solution containing resorcinol, Scheme 4. The aryl ethyl ether and the two benzylic ethers were cleaved upon exposure to a saturated solution of HBr(g) in a 2,2,2-trifluoroethanol at 80°C[27,29a] to give the corresponding pyridone **18** containing two benzyl bromides. Addition of potassium carbonate to the reaction mixture catalyzed the intramolecular nucleophilic ring closures to give **1**, without detection of competing elimination products.

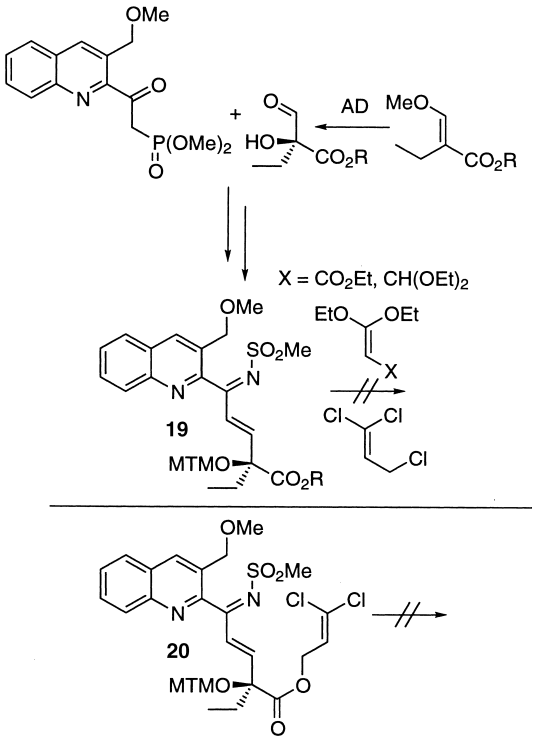


Scheme 3.

Although unanticipated, alternative approaches to camptothecin employing the readily available and more advanced, but more sterically hindered and less electron deficient, *N*-sulfonyl-1-azadiene **19** employing a full range of electron



Scheme 4.



Scheme 5.

rich dienophiles have not proven successful, Scheme 5. Similarly surprising, the intramolecular cycloaddition of the *N*-sulfonyl-1-azadiene **20** was also not successful.

1. Experimental

1.1. General

1.1.1. 3-Diethoxymethyl-2-ethoxy-6-(3-methoxymethylquinolin-2-yl)isonicotinic acid ethyl ester (9). $TiCl_4$ (1.0 M in CH_2Cl_2, 4.2 mL) and Et_3N (1.4 mL) was added to a solution of ketone **5**[27] (630 mg, 2.1 mmol) and methane sulfonamide (400 mg, 4.2 mmol) in CH_2Cl_2 (63 mL) at −42°C. The brown solution was stirred at −42°C for 40 min, warmed to 25°C, and stirred for an additional 60 min. The crude mixture was poured over a plug of Celite (2.5×7.5 cm) and eluted with a 50% EtOAc–hexane (250 mL). The eluent was concentrated and poured over a plug of silica gel (2.5×7.5 cm) and eluted with 50% EtOAc–hexane (250 mL). The eluent was concentrated and redissolved in benzene (10.5 mL). 1,1,3,3-Tetraethoxypropene (**7**,[32] 1.82 g, 8.4 mmol) was added and the solution was stirred for 4 h. The reaction mixture was concentrated in vacuo and the residue was redissolved in THF (21 mL). NaOEt (3.0 M in EtOH, 5.6 mL, 16.8 mmol) was added to the solution at 0°C. The mixture was stirred at 0°C for 75 min and then diluted with EtOAc (50 mL) and H_2O (30 mL). The organic layer was removed and the aqueous layer was washed with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 2.5×20 cm, 5–10% EtOAc–hexane gradient elution) afforded **9** (664 mg, 68%) as a colorless solid: mp 109–113°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.43 (s, 1H), 8.11 (d, J=8.3 Hz, 1H), 7.84 (d, J=8.3 Hz, 1H), 7.82 (s, 1H), 7.68 (apparent t, J=7.5 Hz, 1H), 7.53 (apparent t, J=7.5 Hz, 1H), 5.75 (s, 1H), 5.02 (s, 2H), 4.49 (q, J=7.0 Hz, 2H), 4.37 (q, J=7.0 Hz, 2H), 3.70 (dq, J=8.8, 7.0 Hz, 2H), 3.60 (dq, J=7.6, 8.7 Hz, 2H), 3.47 (s, 3H), 1.42 (t, J=7.0 Hz, 3H), 1.38 (t, J=7.0 Hz, 3H), 1.23 (t, J=7.0, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.4, 160.1, 155.8, 153.7, 146.5, 143.2, 134.2, 131.1, 129.4, 129.2, 127.8, 127.3, 127.0, 117.6, 115.8, 97.9, 72.1, 63.1 (2C), 62.4, 61.5, 58.6, 15.0 (2C), 14.7, 14.0; IR (KBr) ν_{max} 2978, 2919, 1731, 1560 cm^{-1}; MALDI-HRMS (dihydroxybenzyl alcohol, DHB) m/z 469.2353 (M+H$^+$, $C_{26}H_{32}N_2O_6$ requires m/z 469.2333).

1.1.2. 2-Ethoxy-3-ethoxymethyl-6-(3-methoxymethylquinolin-2-yl)isonicotinic acid ethyl ester (10). A slurry of ZnI_2 (136 mg, 0.42 mmol), **9** (100 mg, 0.21 mmol), and Et_3SiH (409 μL, 2.56 mmol) in CH_2Cl_2 (750 μL) was stirred for 5 days at 25°C. The slurry was filtered through a plug of silica gel (1×5 cm) and eluted with 30% EtOAc–hexane. Chromatography (SiO_2, 2.5×10 cm, 20% EtOAc–hexane) afforded **10** (83 mg, 92%) as a colorless solid: mp 75–77°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43 (s, 1H), 8.13 (d, J=8.5 Hz, 1H), 8.03 (s, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.69 (apparent t, J=7.9 Hz, 1H), 7.54 (apparent t, J=7.6 Hz, 1H), 5.02 (s, 2H), 4.81 (s, 2H), 4.46 (q, J=7.0 Hz, 2H), 4.40 (q, J=7.0 Hz, 2H), 3.56 (t, J=7.0 Hz, 2H), 3.47 (s, 3H), 1.43 (t, J=7.0 Hz, 3H), 1.40 (t, J=7.0 Hz, 3H), 1.20 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 160.8, 155.4, 154.0, 146.5, 142.7, 134.4, 131.1, 129.3, 129.3, 127.8, 127.4, 127.0, 119.2, 116.7, 72.2, 66.2, 63.0, 62.5, 61.5, 58.6, 15.1, 14.7, 14.1; IR (film) ν_{max} 2976, 2868, 1723, 1596, 1562, 1440 cm^{-1}; MALDI-HRMS (DHB) m/z 425.2071 (M+H$^+$, $C_{24}H_{28}N_2O_5$ requires m/z 425.2071).

1.1.3. 1-[2-Ethoxy-3-ethoxymethyl-6-(3-methoxymethylquinolin-2-yl)pyridin-4-yl]propan-1-one (11). EtMgBr (380 μL, 3.0 M in Et_2O) was added to a solution of ester **10** (220 mg, 0.52 mmol) and Et_3N (2.89 mL, 20.8 mmol) in toluene (10.4 mL) at −5°C and the solution was stirred at −5°C for 5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The organic layer was removed and the aqueous layer washed with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. PTLC (SiO_2, 20% EtOAc–hexane) afforded **11** (141 mg, 66%) as a colorless solid: mp 102–105°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.44 (s, 1H), 8.12 (d, J=8.5 Hz, 1H), 7.85 (d, J=8.1 Hz, 1H), 7.74 (s, 1H), 7.69 (dt, J=8.1, 8.4 Hz, 1H), 7.54 (dt, J=8.1, 8.1 Hz, 1H), 5.04 (s, 2H), 4.65 (s, 2H), 4.45 (q, J=7.4 Hz, 2H), 3.52 (q, J=7.0 Hz, 2H), 3.48 (s, 3H), 2.92 (q, J=7.3 Hz, 2H), 1.42 (t, J=7.4 Hz, 3H), 1.22 (t, J=7.4 Hz, 3H), 1.19 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.0, 160.1, 155.2, 154.0, 151.5, 146.5, 134.4, 131.2, 129.3 (2C), 127.8, 127.4, 127.0, 117.0, 114.3, 72.3, 66.6, 63.7, 62.4, 58.6, 36.1, 15.0, 14.7, 7.6; IR (film) 2970, 2860, 1701, 1596, 1555, 1437, 1378, 1331 cm^{-1}; MALDI-HRMS (DHB) m/z 409.2134 (M+H$^+$, $C_{24}H_{28}N_2O_4$ requires m/z 409.2122).

1.1.4. 2-[6-Ethoxy-5-ethoxymethyl-4-(1-methoxymethylenepropyl)pyridin-2-yl]-3-methoxymethylquinoline (12). KHMDS (0.5 M in toluene, 6.61 mL) was added to a

slurry of methoxymethyltriphenylphosphonium chloride (1.18 g, 3.31 mmol) in THF (10 mL) at 0°C. The red solution was stirred at 0°C for 30 min before ketone **11** (270 mg, 0.66 mmol) was added in THF (1 mL). The solution was warmed to 25°C and stirred for 10 h. Saturated aqueous NH_4Cl (5 mL) was added and the organic layer removed. The aqueous layer was washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 2.5×10 cm, 5–10% EtOAc–hexane gradient elution) afforded a high R_f oil (213 mg, 74%) and a lower R_f oil (76 mg, 26%).

High R_f product (*trans*-**12**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (s, 1H), 8.12 (d, J=8.5 Hz, 1H), 7.84 (d, J=8.2 Hz, 1H), 7.68 (apparent t, J=7.6 Hz, 1H), 7.63 (s, 1H), 7.52 (apparent t, J=7.6 Hz, 1H), 6.35 (s, 1H), 5.03 (s, 2H), 4.48 (s, 2H), 4.44 (q, J=7.3 Hz, 2H), 3.70 (s, 3H), 3.65 (q, J=6.8 Hz, 2H), 3.48 (s, 3H), 2.55 (q, J=7.6 Hz, 2H), 1.43 (t, J=6.8 Hz, 3H), 1.28 (t, J=7.0 Hz, 3H), 0.96 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.1, 155.1, 154.4, 152.8, 147.5, 146.5, 134.0, 131.4, 129.3, 129.0, 127.7, 127.4, 126.7, 118.2, 117.8, 117.7, 72.3, 65.8, 64.8, 62.0, 59.9, 58.6, 21.8, 15.4, 14.8, 12.9; IR (film) 2968, 2926, 2864, 1651, 1594, 1547, 1444, 1372, 1330 cm^{-1}; MALDI-HRMS (DHB) m/z 437.2435 (M+H$^+$, $C_{26}H_{32}N_2O_4$ requires m/z 437.2435).

Low R_f product (*cis*-**12**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43 (s, 1H), 8.11 (d, J=8.5 Hz, 1H), 7.84 (d, J=8.2 Hz, 1H), 7.61 (apparent t, J=8.2 Hz, 1H), 7.61 (s, 1H), 7.51 (apparent t, J=8.2 Hz, 1H), 6.01 (s, 1H), 5.08 (s, 2H), 4.51 (s, 2H), 4.45 (q, J=7.0 Hz, 2H), 3.57 (q, J=7.0 Hz, 2H), 3.54 (s, 3H), 3.50 (s, 3H), 2.33 (q, J=7.3 Hz, 2H), 1.43 (t, J=7.0 Hz, 3H), 1.22 (t, J=7.0 Hz, 3H), 1.03 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.6, 154.9, 154.5, 151.0, 146.5, 142.3, 133.8, 131.4, 129.3, 129.0, 127.7, 127.4, 126.6, 118.5, 118.3, 117.5, 72.4, 65.9, 64.4, 61.9, 59.6, 58.6, 26.8, 15.3, 14.8, 13.3; IR (film) 2968, 2919, 2860, 1661, 1590, 1548, 1437, 1378, 1331 cm^{-1}; MALDI-HRMS (DHB) m/z 437.2423 (M+H$^+$, $C_{26}H_{32}N_2O_4$ requires m/z 437.2435).

1.1.5. 2-[2-Ethoxy-3-ethoxymethyl-6-(3-methoxymethyl-quinolin-2-yl)pyridin-4-yl]-2-hydroxybutyraldehyde (13). A slurry of $(DHQ)_2$-Pyr$(OMe)_3$ (**16**, 4.1 mg, 0.0047 mmol), K_2CO_3 (12.3 mg, 0.09 mmol), $K_3Fe(CN)_6$, and OsO_4 (23 μL of 4% wt in H_2O, 0.0035 mmol) in H_2O (300 μL) was stirred at 0°C for 5 min before *trans*-**12** (13 mg, 0.030 mmol) in *t*-BuOH (300 μL) was added. After 4 h at 0°C, additional $K_3Fe(CN)_6$ (10 mg, 0.03 mmol) was added and the solution was stirred at 0°C for 4 h. Solid sodium sulfite (40 mg, 0.3 mmol) was added and the solution stirred for 30 min at 0°C. CH_2Cl_2 (600 μL) was added and the organic layer was removed. The aqueous layer was extracted (3×600 μL) with CH_2Cl_2 and the combined organic layers were passed through a small plug of silica gel (1×4 cm) and eluted with 50% EtOAc–hexane. The eluent was concentrated by a steady stream of N_2. Chromatography (SiO_2, 20% EtOAc–hexane) afforded **13** (11 mg, 84%) as a colorless oil: $[\alpha]_D^{25}$=+20 (*c* 0.011, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.74 (s, 1H), 8.44 (s, 1H), 8.13 (d, J=8.3 Hz, 1H), 7.90 (s, 1H), 7.86 (d, J=7.9 Hz, 1H), 7.70 (apparent t, J=7.0 Hz, 1H), 7.55 (apparent t, J=7.0 Hz, 1H), 5.49 (br s, 1H), 5.02 (s, 2H), 4.89 (d, J=11.4 Hz, 1H), 4.65 (d, J=11.4 Hz, 1H), 4.44 (q, J=7.0 Hz, 2H), 3.60 (q, J=7.0 Hz, 2H), 3.48 (s, 3H), 2.27 (m, 2H), 1.42 (t, J=7.0 Hz, 3H), 1.27 (t, J=7.0 Hz, 3H), 1.01 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 200.6, 161.6, 155.3, 154.3, 150.7, 146.6, 134.4, 131.2, 129.5, 129.3, 127.8, 127.4, 127.0, 117.9, 116.4, 82.7, 72.3, 66.2, 63.5, 62.6, 58.7, 29.6, 14.9, 14.7, 7.4; IR (film) 3389, 2919, 2848, 1731, 1549, 1378, 1331 cm^{-1}; MALDI-HRMS (DHB) m/z 439.2219 (M+H$^+$, $C_{25}H_{30}N_2O_5$ requires m/z 439.2227).

1.1.6. 2-[2-Ethoxy-3-ethoxymethyl-6-(3-methoxymethyl-quinolin-2-yl)pyridin-4-yl]-2-hydroxybutyric acid (17). Aldehyde **13** (10 mg, 0.023 mmol) and resorcinol (25 mg, 0.23 mmol) were dissolved in DMSO (600 μL). NaH_2PO_4 (18 mg, 0.115 mmol) in H_2O (200 μL) was added and the mixture cooled to 0°C before $NaClO_2$ (10.3 mg, 0.115 mmol) was added. The purple mixture was stirred for 1 h at 0°C before saturated aqueous NH_4Cl (1 mL) was added. The solution was extracted with EtOAc (4×500 μL) and the combined organic layers were dried ($NaSO_4$), filtered, and concentrated. Chromatography (SiO_2, 50–100% EtOAc–hexane, followed by 15% MeOH–CH_2Cl_2) afforded **27** (9.6 mg, 93%) as an amorphous solid: $[\alpha]_D^{25}$=+29 (*c* 0.010, MeOH); ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.49 (s, 1H), 8.12 (s, 1H), 8.08 (d, J=8.2 Hz, 1H), 8.05 (d, J=7.6 Hz, 1H), 7.75 (apparent t, J=7.0 Hz, 1H), 7.62 (t, J=7.0 Hz, 1H), 4.99 (m, 3H), 4.69 (d, J=10.0 Hz, 1H), 4.38 (q, J=7.0 Hz, 2H), 3.53 (q, J=7.0 Hz, 2H), 3.41 (s, 3H), 3.25–3.40 (br s, 1H), 2.04 (m, 2H), 1.37 (t, J=7.0 Hz, 3H), 1.14 (t, J=6.8 Hz, 3H), 0.82 (t, J=7.0 Hz, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 174.5, 161.9, 154.9, 152.8, 145.9, 134.1, 131.1, 129.5, 128.7, 127.7, 127.1, 126.9 (2C), 118.8, 116.2, 79.1, 71.6, 65.3, 63.3, 61.5, 58.1, 32.2, 15.3, 14.8, 8.8; IR (film) 3334, 2974, 2922, 1644, 1691, 1510, 1592, 1548, 1372, 1333 cm^{-1}; MALDI-HRMS (DHB) m/z 455.2172 (M+H$^+$, $C_{25}H_{30}N_2O_6$ requires m/z 455.2177).

1.1.7. (+)-Camptothecin (1). A sample of **17** (9.4 mg, 0.021 mmol) was added to a freshly prepared solution of concentrated HBr(g) in 2,2,2-trifluoroethanol (1.88 mL). The mixture was warmed at reflux for 24 h in a sealed vial, cooled to 25°C, and stirred for an additional 14 h. K_2CO_3 (14 mg, 0.1 mmol) was added to the solution and the mixture was stirred for 1 h. The mixture was filtered through a plug of silica gel (1×5 cm) and eluted with 10% MeOH–CH_2Cl_2. The eluent was concentrated and purified by chromatography (SiO_2, 0–10% MeOH–CH_2Cl_2) to afford **1** (5.2 mg, 72%) as an off-white solid identical in all respects with authentic material: $[\alpha]_D^{25}$= +30 (*c* 0.001, MeOH–CH_2Cl_2, 1:4), lit $[\alpha]_D^{25}$=+32 (*c* 0.4, MeOH–CH_2Cl_2, 1:4);[1] ^{1}H NMR (CD_2Cl_2/CD_3OD, 600 MHz) δ 8.48 (s, 1H), 8.18 (d, J=8.3 Hz, 1H), 7.98 (d, J=7.9 Hz, 1H), 7.82 (apparent t, J=7.0 Hz, 1H), 7.67 (t, J=7.0 Hz, 1H), 7.67 (s, 1H), 5.63 (d, J=16.2 Hz, 1H), 5.30 (d, J=16.2 Hz, 1H), 5.28 (s, 2H), 1.90 (m, 2H), 0.99 (t, J=7.4 Hz, 3H); ^{13}C NMR (CD_2Cl_2/CD_3OD, 150 MHz) δ 174.1, 158.4, 152.8, 151.5, 149.0, 146.5, 132.2, 131.2, 129.5, 129.4, 128.8, 128.8, 1128.5, 119.6, 99.0, 73.3, 66.4, 50.7, 31.7, 7.8; MALDI-HRMS (DHB) m/z 349.1185 (M+H$^+$, $C_{20}H_{16}N_2O_4$ requires m/z 349.1183).

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