Novel, Efficient Total Synthesis of Natural 20(*S*)-Camptothecin

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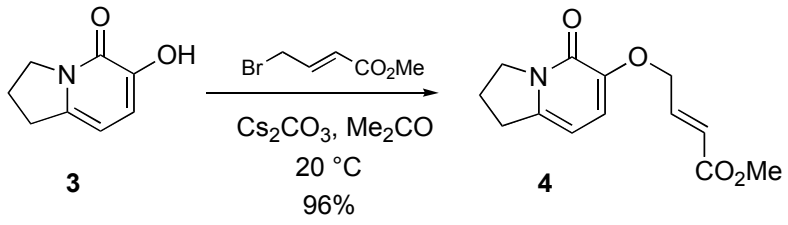
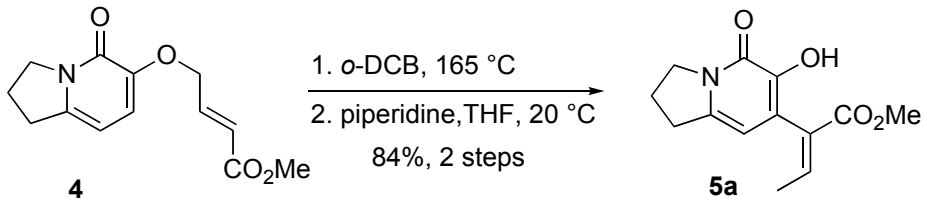
Electronic Supplementary Information

Methyl (2*E*)-4-[(5-Oxo-1,2,3,5-tetrahydroindolizin-6-yl)oxy]but-2-enoate (4)



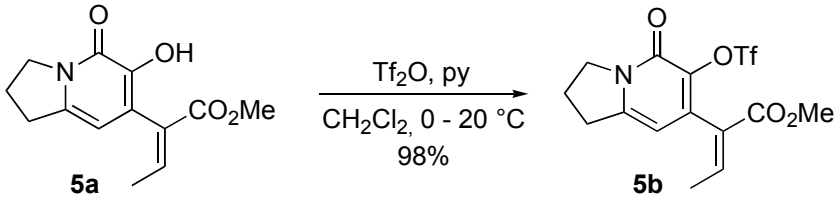
To a well-stirred mixture of 1.13 g (7.48 mmol) of hydroxypyridone **3** and 4.00 g (12.28 mmol) of Cs_2CO_3 in 75 mL of dry acetone (distilled from P_2O_5) under argon at 20 °C was added 2.10 mL (ca. 85%, ca. 15.2 mmol) of methyl 4-bromocrotonate. The resulting mixture was stirred for 2 days and then filtered through Celite with dichloromethane. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on silica gel with AcOEt in CH_2Cl_2 to give 1.78 g (96%) of **4** as a white solid: mp 120.6-121.7 °C (AcOEt); IR (Nujol) 1718, 1652, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15-2.25 (m, 2 H), 3.00 (td, *J* = 7.5, 1.2 Hz, 2 H), 3.74 (s, 3 H), 4.17 (t, *J* = 7.2 Hz, 2 H), 4.78 (dd, *J* = 4.4, 2.1 Hz, 2 H), 5.98 (dt, *J* = 7.5, 1.3 Hz, 1 H), 6.17 (dt, *J* = 15.8, 2.0 Hz, 1 H), 6.70 (d, *J* = 7.4 Hz, 1 H), 7.05 (dt, *J* = 15.8, 4.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 30.9, 48.8, 51.5, 67.8, 99.0, 118.4, 121.8, 142.3, 142.5, 146.0, 157.2, 166.3; MS (DCI, NH_3/isobutane) 250 (MH^+); Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.46; H, 6.14; N, 5.42.

Methyl (2*E*)-2-(6-Hydroxy-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl)but-2-enoate (5a)



A solution of 1.93 g (7.75 mmol) of crotonate **4** in 30 mL of *o*-dichlorobenzene was stirred at 165 °C for 2 h. After being allowed to cool, the solution was concentrated under reduced pressure to afford a mixture of α,β- and β,γ-unsaturated esters, which was dissolved in 30 mL of THF and treated with 1.10 mL (11.13 mmol) of piperidine. After being stirred at 20 °C for 2 h, the solution was diluted with AcOEt and the organic phase was washed with 1 N HCl and brine. The combined aqueous phases were extracted with CH_2Cl_2 and then the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on silica gel with AcOEt in CH_2Cl_2 afforded 1.63 g (84%, 2 steps) of **5a** as colorless crystals: mp 174.8-175.3 °C (AcOEt); IR (Nujol) 3236 (br), 1710, 1655, 1636, 1586 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76 (d, *J* = 7.2 Hz, 3 H), 2.15-2.29 (m, 2 H), 3.04 (td, *J* = 7.6, 1.2 Hz, 2 H), 3.74 (s, 3 H), 4.18 (t, *J* = 7.2 Hz, 2 H), 5.92 (s, 1 H), 6.77 (br s, 1 H), 7.21 (q, *J* = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 22.2, 30.5, 48.6, 51.8, 103.3, 122.3, 128.6, 137.7, 141.6, 142.1, 157.0, 168.3; MS (DCI, NH_3/isobutane) 250 (MH^+); Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.85; H, 6.04; N, 5.71.

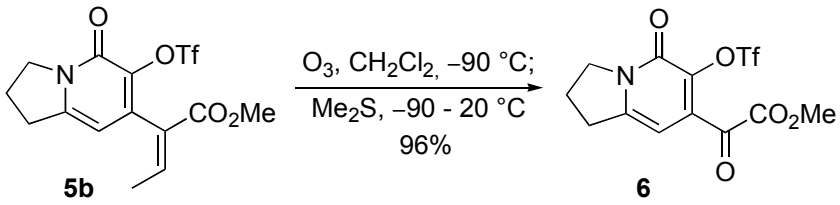
Methyl (2*E*)-2-(5-Oxo-6-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,5-tetrahydro–indolizin-7-yl)-but-2-enoate (5b)



To a well-stirred solution of 0.500 g (2.01 mmol) of alcohol **5a** and 3.0 mL of dry pyridine in 6.0 mL of dry CH_2Cl_2 under argon at 0 °C was added dropwise 0.400 mL (2.38 mmol) of Tf_2O. After being stirred for 1 h, the reaction mixture was allowed to warm to 20 °C and then stirred overnight. The mixture was diluted with EtOAc and the organic phase was washed with 1 N HCl

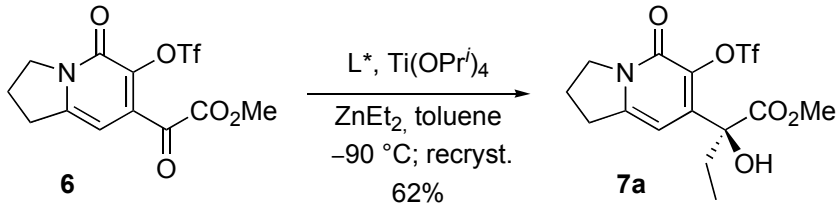
and brine and dried over Na_2SO_4. Removal of the solvents under reduced pressure gave the crude product, which was chromatographed on silica gel with AcOEt-pentane-CH_2Cl_2 (1:1:3) to furnish 0.750 g (98%) of triflate **5b** as an off-white solid: mp 140.7-141.8 °C (AcOEt-pentane); IR (Nujol) 1715, 1669, 1617 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (d, J = 7.1 Hz, 3 H), 2.21-2.35 (m, 2 H), 3.14 (t, J = 7.7 Hz, 2 H), 3.75 (s, 3 H), 4.24 (t, J = 7.3 Hz, 2 H), 5.94 (t, J = 1.1 Hz, 1 H), 7.31 (q, J = 7.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 21.6, 31.6, 49.5, 52.3, 101.5, 118.7 (q, J = 320 Hz), 127.5, 135.4, 139.3, 144.4, 149.2, 155.6, 164.7; MS (DCI, NH_3/isobutane) 382 (MH^+); Anal. Calcd for $C_{14}H_{14}F_3NO_6S$: C, 44.10; H, 3.70; N, 3.67. Found: C, 44.29; H, 3.72; N, 3.67.

Methyl Oxo(5-oxo-6-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,5-tetrahydroindolizin-7-yl)-acetate (6)



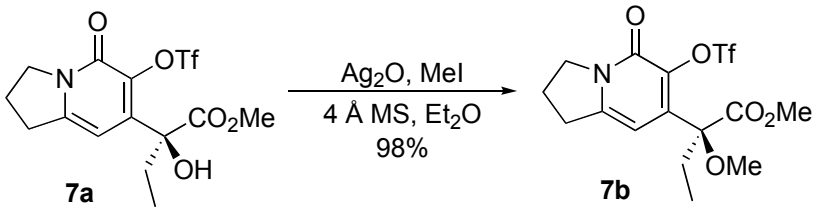
A 518-mg sample (1.36 mmol) of triflate **5b** in 40 mL of CH_2Cl_2 was cooled to –90 °C and a stream of ozone in oxygen was bubbled through for 1 min and then a stream of pure O_2 for 10 minutes. This procedure was repeated 4 times (thus permitting the reaction to be followed by TLC). The reaction mixture was then treated with 2.0 mL of dimethyl sulfide and allowed to warm to 20 °C. After 1 h, the solvents were removed under reduced pressure and the residue was dissolved in AcOEt, which was washed with 1 N HCl. The aqueous phase was extracted with CH_2Cl_2 and then the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was chromatographed on silica gel with AcOEt in CH_2Cl_2 to give 480 mg (96%) of keto ester **6** as a bright yellow, viscous oil: IR (Nujol) 1734, 1670, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27-2.37 (m, 2 H), 3.19 (td, J = 7.9, 1.0 Hz, 2 H), 3.97 (s, 3 H), 4.26 (t, J = 7.3 Hz, 2 H), 6.27 (t, J = 1.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 32.0, 50.2, 53.7, 97.6, 118.7 (q, J = 322 Hz), 135.3, 136.6, 151.7, 155.2, 160.2, 182.7; MS (DCI, NH_3/isobutane) 370 (MH^+); Anal. Calcd for $C_{12}H_{10}F_3NO_7S$: C, 39.03; H, 2.73; N, 3.79. Found: C, 38.59; H, 2.94; N, 3.70.

Methyl (2*S*)-2-Hydroxy-2-(5-oxo-6-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,5-tetra–hydroindolizin-7-yl)butanoate (7a)



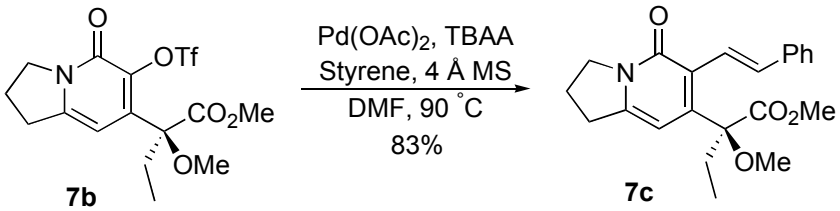
A 335-mg sample (0.53 mmol) of the piperidine (*S*,*S*) salen ligand[15a] in a Schlenk flask was dried under high vacuum for 1 h and then placed under argon and dissolved in 3 mL of dry toluene. Freshly distilled $Ti(OPr^i)_4$ (0.147 mL, 0.50 mmol) was added and the resulting solution was stirred at 20 °C for 1 h, whereupon the toluene and *i*-PrOH were removed under high vacuum to leave the Ti-salen catalyst as a bright yellow oil. To this catalyst in 10 mL of dry toluene under argon at –40 °C was added 4.1 mL (1.1 M in toluene, 4.5 mmol) of Et_2Zn over 1 h with a syringe pump. Following the addition, the catalyst solution was cooled to –105 °C and a pre-chilled (–90 °C) solution of 1.31 g (3.55 mmol) of α-ketoester **6** in 8 mL of toluene was introduced through a cannula. The reaction mixture was stirred at –90 °C overnight and then treated with saturated NH_4Cl and allowed to warm to 20 °C. The mixture was filtered through Celite with CH_2Cl_2 and the filtrate concentrated. The dark yellow residue was now filtered through a short plug of silica gel with 1:1 AcOEt-CH_2Cl_2 and the filtrate was concentrated. The pale yellow residue (1.24 g), containing the desired product (ee 90% by HPLC) and a trace of starting material, was recrystallized from 16 mL of 1:1 AcOEt-pentane (reflux to –5 °C) to give 0.885 g (62%) of pure (ee >99%) **7a** as colorless needles: mp 140.7-141.8 °C (AcOEt-pentane); $[\alpha]_D^{26}$ +80.6° (*c* 1.0 in $CHCl_3$); IR (Nujol) 3244 (br), 1732, 1655, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.0 Hz, 3 H), 2.07-2.31 (m, 4 H), 3.13 (td, *J* = 8.3, 1.1 Hz, 2 H), 3.80 (s, 3 H), 3.89 (br s, 1 H), 4.20 (td, *J* = 7.0, 1.9 Hz, 2 H), 6.36 (t, *J* = 1.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 21.8, 30.5, 32.0, 49.7, 53.7, 60.5, 98.3, 118.9 (q, *J* = 320 Hz), 135.7, 145.2, 149.2, 155.6, 173.0; MS (DCI, NH_3/isobutane) 400 (MH^+); Anal. Calcd for $C_{14}H_{16}F_3NO_7S$: C, 42.11; H, 4.04; N, 3.51. Found: C, 42.38; H, 4.13; N, 3.51.

Methyl (2*S*)-2-Methoxy-2-(5-oxo-6-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,5-tetrahydro-indolizin-7-yl)butanoate (7b)



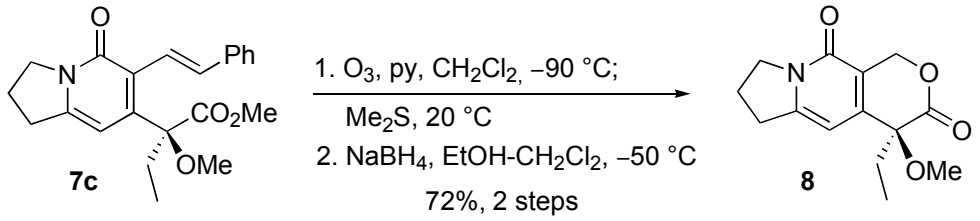
A mixture of 743 mg (1.86 mmol) of alcohol **7a**, 1.79 g of powdered 4 Å molecular sieves, and 2.30 g (9.93 mmol) of Ag_2O in 30 mL of dry Et_2O was treated with 11.0 mL (177 mmol) of MeI and stirred, protected from light, at 20 °C for 3 days. The mixture was then filtered through Celite with CH_2Cl_2 and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by chromatography on silica gel with AcOEt in CH_2Cl_2 to afford 756 mg (98%) of ether **7b**: mp 83-85°C (AcOEt/pentane); $[\alpha]_D^{20}$ –6.7° (*c* 0.8 in $CHCl_3$). The spectra of **7b** were identical with those of the racemic material.[12b]

Methyl (2*S*)-2-Methoxy-2-{6-[(*E*)-2-(phenyl)vinyl]-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl}-butanoate (7c)



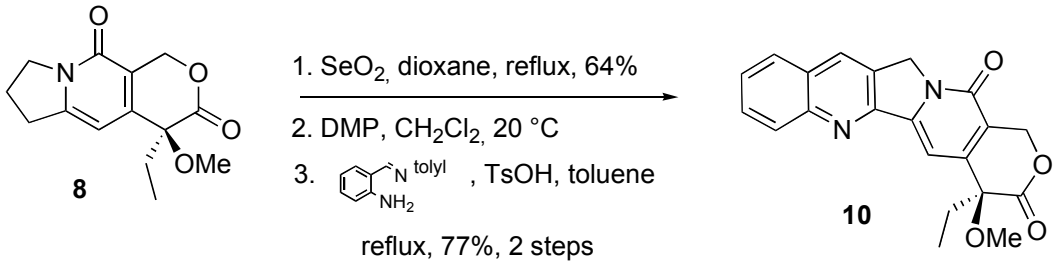
The styryl derivative **7c** was prepared from **7b** as described for the racemic material,[12b] except DMF was used and the reaction required only 1.5 h. Styryl derivative **7c**: mp 177-178 °C (AcOEt); $[\alpha]_D^{20}$ –45.3° (*c* 0.3 in $CHCl_3$). The spectra of **7c** were identical with those of the racemic material.

(4*S*)-4-Ethyl-4-methoxy-7,8-dihydro-1*H*-pyrano[3,4-*f*]indolizine-3,10(4*H*,6*H*)-dione (8)



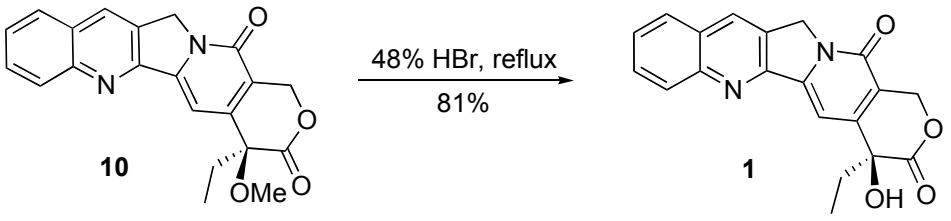
Lactone **8** was prepared from **7c** as described for the racemic material.[12b] Lactone **8**: mp 123-124 °C (AcOEt/pentane); $[\alpha]_D^{20}$ +78.9° (*c* 0.9 in $CHCl_3$). The spectra of **8** were identical with those of the racemic material.

(*S*)-*O*-Methylcamptothecin (10)



The methyl ether of camptothecin (**10**) was prepared from **8** as described for the racemic material.[12b] The spectra of **9**, **10,** and the intermediate ketone were identical with those of the racemic compounds. Ether **10**: mp 267-270 °C (dec, AcOEt); $[\alpha]_D^{20}$ +7.6° (*c* 0.6 in $CHCl_3$).

20(*S*)-Camptothecin (1)



Ether **10** (18 mg, 0.05 mmol) was stirred in 5 mL of refluxing aqueous HBr (48%) under argon for 25 min. The reaction mixture was then allowed to cool and was concentrated under

reduced pressure. The resulting residue was filtered over silica gel with 10% MeOH in $CHCl_3$ to give a light brown solid (17 mg), which was recrystallized from 4:1 MeCN-MeOH at –30 °C to afford 14 mg (81%) of 20(*S*)-camptothecin (**1**) as a pale yellow powder: mp 260-264 °C (dec, MeCN-MeOH); $[\alpha]_D^{20}$ +40.0° (*c* 0.2, 1:4 MeOH-$CHCl_3$); HRMS (FT, ESI^+) Calcd for $C_{20}H_{16}N_2O_4$ + H^+: 349.1188. Found: 349.1180. Synthetic **1** was spectroscopically (^1H NMR, ^{13}C NMR) and chromatographically (chiral HPLC) identical with a sample of natural **1** obtained from Sigma-Aldrich.