Antitumour Agents. Part 2.[1] Asymmetric Synthesis of (*S*)-Camptothecin

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The total synthesis of (*S*)-camptothecin by a novel diastereoselective ethylation process is described.

(*S*)-Camptothecin (**1**) is a heterocyclic alkaloid which shows significant antileukemic and antitumour activities in animals, and was originally isolated from *Camptotheca acuminata* (Nyssaceae) by Wall *et al.* in 1966.[2] Since its isolation and the determination of its structure, camptothecin has been, for organic chemists, an attractive target for synthesis because of its unique heterocyclic ring system and pronounced biological activity. Although unfortunately (*S*)-(**1**) had a toxic effect on humans, clinical trials of (*S*)-10-hydroxycamptothecin (**2**)[3] and a derivative of (*S*)-7-ethyl-10-hydroxycamptothecin (**3**)[4] have recently commenced in China and Japan, respectively, and (*S*)-(**1**) remains one of the most potent substances having antitumour activity.

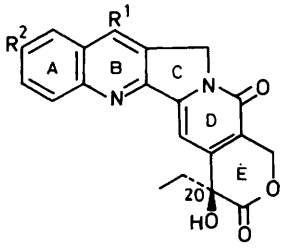
Many attempts have been made to synthesize the alkaloid, culminating in a number of successful total syntheses.[5] Corey *et al.* succeeded in the first total synthesis of optically active (*S*)-(**1**) using an optical resolution process.[6] Recently, Wall *et al.*[7] and our group[8] have independently reported another new route involving the same optical resolution process. However, these methods are not suitable for large-scale preparation because an equal amount of the unnecessary (*R*)-isomer is obtained at the optical resolution stage. As a further extension of this work, we focussed on the development of a more practical route for the synthesis of (*S*)-(**1**), which might be useful for further analogue study. We describe herein the first asymmetric synthesis of (*S*)-(**1**) *via* a novel diastereoselective ethylation.

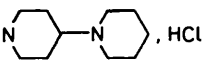
Results and Discussion

Our strategy has two features: a new construction of ring E and a diastereoselective ethylation.

New Construction of Ring E.—The known indolizine (**4**),[9] the CD ring portion of the parent alkaloid, was utilized in the approach to the new construction of ring E. Bromination of (**4**) in the presence of sodium hydride in DME gave the bromide (**5**). When the bromination was performed without anionic conditions, the isolated product was compound (**6**). Treatment of (**5**) with AcONa in a mixture of AcOH and DMF gave the acetate (**7**), which was then ethylated with ethyl iodide to afford the ethyl derivative (**8**). Similarly, the bromide (**10**) was obtained from the known ethyl derivative (**9**).[9] However, treatment of compound (**10**) with AcONa did not yield the acetate (**8**). Furthermore, treatment of (**10**) with $AgNO_3$ or $HgClO_4$ did not give the hydroxy derivative (**11**). These failures may have been due to the poor reactivity of the tertiary bromide because of steric hindrance (Scheme 1).

Reduction of compound (8) in the presence of Raney nickel in a mixture of Ac_2O and AcOH gave the amide (**12**). Treatment of (**12**) with $NaNO_2$ in the same solvent gave the *N*-nitroso derivative, which was then heated in CCl_4 to afford the triester (**13**). This triester was hydrolysed and lactonized to give the tricyclic ketal (**14**). Deketalization of (**14**) with 80% aqueous trifluoroacetic acid gave (**15**). On the other hand, treatment of (**13**) in a solution of DME with 1M H_2SO_4 gave (**15**) directly. Friedländer condensation to construct the pentacyclic ring

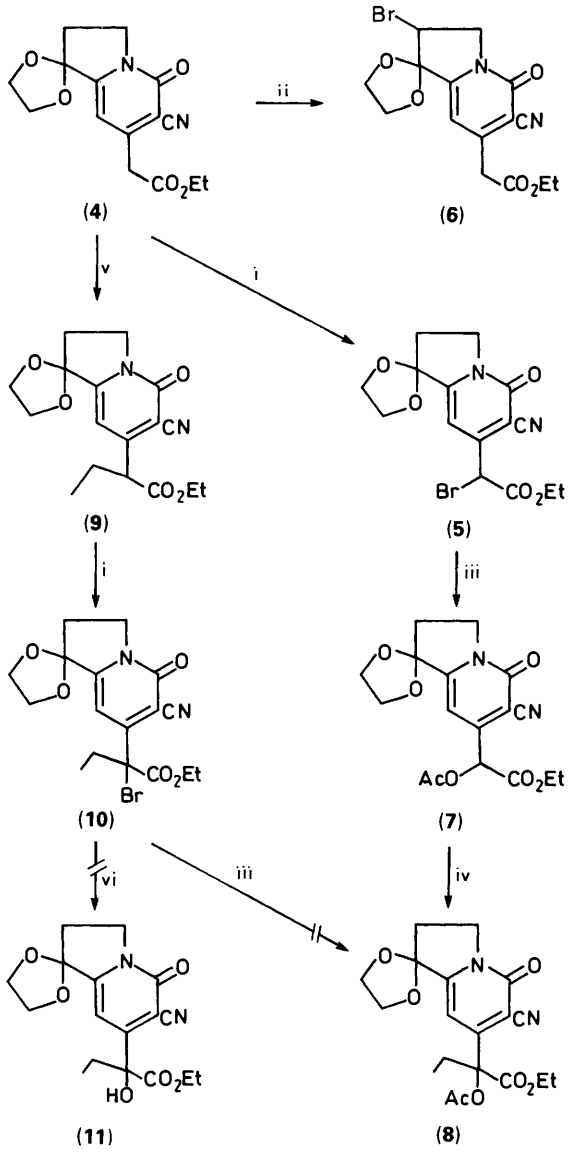


(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = H$, $R^2 = OH$
(**3**) $R^1 = Et$, $R^2 = OCON$  , HCl

system was performed as follows: compound (**15**) and *N*-(2-aminobenzylidene)-*p*-toluidine (**16**)[10] in toluene were heated under reflux in the presence of *p*-TsOH using a Dean–Stark trap to give (*RS*)-(**1**). A new total synthesis of (*RS*)-(**1**) was thus achieved (Scheme 2).

Diastereoselective Ethylation.—Next, we attempted an asymmetric synthesis of optically active (*S*)-(**1**) as a development of the above route. Accordingly, ethylation of compound (**18**), utilizing *N*-tosyl-(*R*)-proline (**17**)[11] as a stereocontrolling unit, produced an 82:18 diastereomeric mixture of compounds (**19**) and (**20**) in quantitative yield. Subsequently, the desired diastereoisomer (**19**) was easily isolated by treatment with propan-2-ol in 56% yield from (**18**) (Scheme 3). The ratio was determined by ^1H n.m.r. spectrometry since the spectra of (**19**) and (**20**) showed distinctly different absorption patterns for the proton of the pyridone moiety. The absolute configuration of compound (**19**) was confirmed by comparing the optical rotation of synthetic camptothecin and that of the natural product. The transition state seems to assume a rigid conformation, since the ratio for the diastereoselective ethylation was unchanged at any of various reaction temperatures between −10 and 60 °C. It was considered that the ethylation to give compound (**19**) as the major stereoisomer takes place from the side opposite to that conveying the tosyl group because of steric hindrance arising from the latter. This diastereoselective ethylation is an instance of 1,4-asymmetric induction; no reports of asymmetric synthesis using optically active *N*-tosylproline have hitherto appeared in the literature.

After reduction of (**19**) and subsequent treatment with $NaNO_2$ by a similar method to that described for (**12**), the optically active triester (**22**) was obtained in 74% yield from (**19**). The triester (**22**) was hydrolysed and lactonized to give the optically active hydroxy lactone (**23**) of (*S*)-configuration in 90% yield; $[\alpha]_D$ +109.7° (*c* 0.76 in $CHCl_3$). *N*-Tosyl-(*R*)-proline (**17**) was recovered in 66% yield without racemization, and could be used again. Hydrolysis of the ketal function in (**23**) gave the optically active key intermediate (**24**) in 79% yield; $[\alpha]_D$ +117.6° (*c* 0.56 in $CHCl_3$). Since (**24**) was easily converted



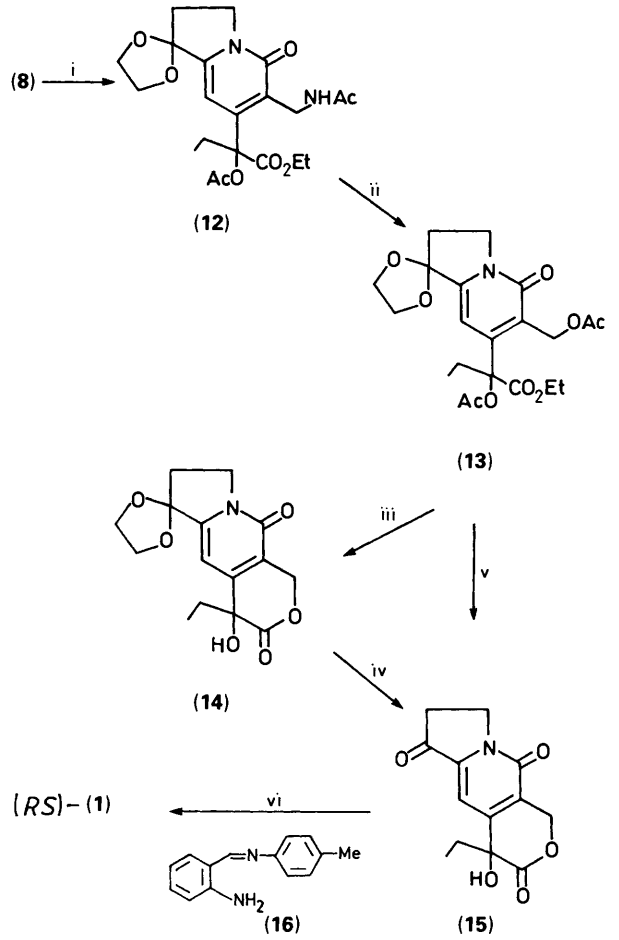
Scheme 1. *Reagents and conditions:* i, NaH, Br_2, DME; ii, Br_2, DME; iii, AcONa, AcOH, DMF; iv, NaH, EtI, DMF; v, KOBu^t, EtI, DME; vi, $AgNO_3$, 50% acetone or $HgClO_4$, HgO, DME

into (*S*)-(**1**) by Friedländer condensation in 84% yield, we thus achieved an efficient total synthesis of (*S*)-(**1**) including an asymmetric ethylation process. The overall yield from (**4**) to (*S*)-(**1**) is approximately 20%. This route enables large-scale preparation of (*S*)-(**1**) and its analogues.

We confirmed that the same procedure using *N*-tosyl-(*S*)-proline instead of *N*-tosyl-(*R*)-proline afforded, as expected, an optically active hydroxy lactone bearing an *R*-configuration as the major diastereoisomer in the same ratio as for the *S*-configuration, and this lactone was converted into unnatural (*R*)-(**1**).

Experimental

M.p.s were determined on a Yanagimoto apparatus and are uncorrected. I.r. spectra were recorded on a Hitachi 260-30 or a 270-30 spectrometer. ^{1}H N.m.r. data were recorded on a Hitachi R-40 (40 MHz) or a JEOL JNM-FX90Q (90 MHz) instrument using $SiMe_4$ as an internal standard. Mass spectra were recorded on a JEOL JMS-01SG-2, JMS-D300, or JMS-HX110 mass spectrometer. Optical rotations were measured with a



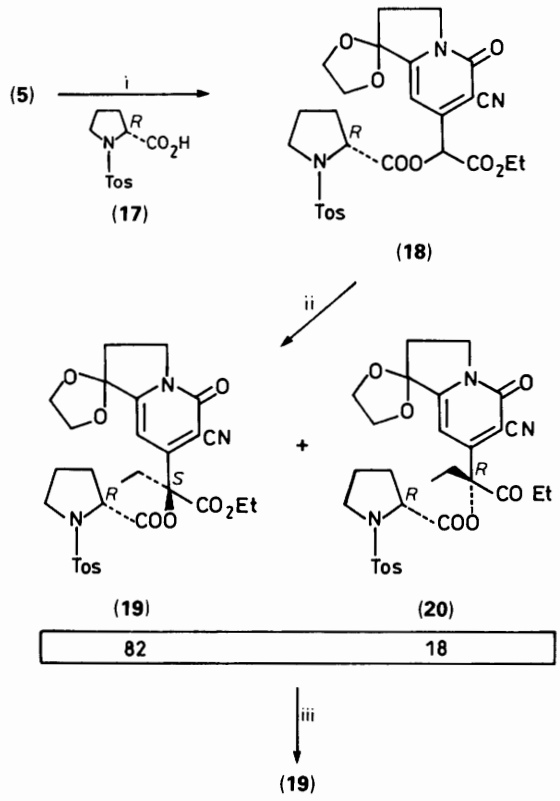
Scheme 2. *Reagents and conditions:* i, Raney Ni, Ac_2O, AcOH; ii, $NaNO_2$, Ac_2O, AcOH; then CCl_4, reflux; iii, LiOH, MeOH, H_2O; then AcOH, CH_2Cl_2; iv, 80% TFA; v, 1M H_2SO_4, DME; vi, *p*-TsOH, toluene, reflux

SEPA-200 polarimeter (Horiba) at 23 °C. Sodium sulphate was employed as a drying agent.

Thin-layer chromatography was performed on silica gel precoated plates 60 F_{254} (Merck). The solvent systems (by volume) were: A, benzene–EtOAc (2:1); B, benzene–EtOAc (1:1); C, $CHCl_3$–MeOH (20:1). Detection was carried out by u.v. illumination and by exposure to iodine vapour.

Ethyl Bromo-[6-cyano-1,1-(ethylenedioxy)-5-oxo-1,2,3,5-tetrahydroindolizin-7-yl] actetate (**5**).—To a solution of (**4**)[9] (15.2 g, 50 mmol) in DME (300 ml) was added 60% sodium hydride (2.1 g, 52.5 mmol) and the resulting mixture was stirred at room temperature for 0.5 h. Bromine (8.8 g, 55 mmol) was added, and the solution was stirred for a further 1 h at room temperature. The solvent was then evaporated and the residue was dissolved in $CHCl_3$ (500 ml). This solution was then washed with 10% aqueous $Na_2S_2O_3$, dried, and concentrated to give a white solid, which was chromatographed on silica gel (benzene–EtOAc, 3:7) to afford the title compound (**5**) (16.3 g, 85.1%) as a colourless powder, m.p. 161—163 °C (Found: C, 47.0; H, 3.9; N, 7.3. $C_{15}H_{15}BrN_2O_5$ requires C, 47.0; H, 3.95; N, 7.3%); R_F (A) 0.17; $\nu_{max.}$(KBr) 2 230, 1 745, and 1 650 cm^{-1}; δ($CDCl_3$) 1.32 (3 H, 5, *J* 7 Hz, CH_2CH_3), 2.42 (2 H, 5, *J* 7 Hz, 2-H_2), 4.16 (4 H, s, OCH_2CH_2O), 4.0—4.5 (4 H, m, 3-H_2 and CH_2CH_3), 5.55 (1 H, s, CHBr), and 6.60 (1 H, s, 8-H); *m/z* 382 (M^+) and 384 ($M^+ + 2$).

Ethyl 2-[2-*Bromo*-6-*cyano*-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-

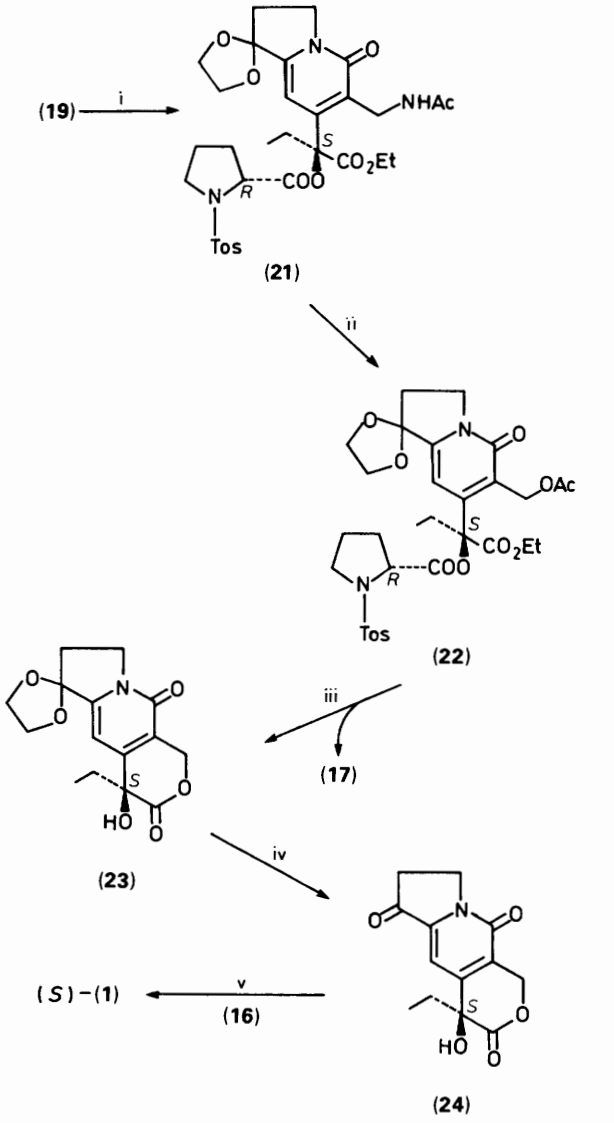


Scheme 3. *Reagents and conditions:* i, Na_2CO_3, DMF; ii, NaH, EtI, DMF; iii, recrystallization from propan-2-ol

tetrahydroindolizin-7-yl]acetate (**6**).—To a solution of (**4**) (0.61 g, 2 mmol) in DME (12 ml) was added bromine (0.35 g, 2.2 mmol) and the resulting mixture was stirred for 6 h at room temperature. After a similar work-up procedure to that used for the preparation of (**5**) above, compound (**6**) (0.18 g, 23.5%) was obtained as a white solid, m.p. 147—151 °C (Found: C, 47.35; H, 3.9; N, 7.35. $C_{15}H_{15}BrN_2O_5$ requires C, 47.0; H, 3.95; N, 7.3%); R_F (A) 0.29; $\nu_{max.}$(KBr) 2 210, 1 725, and 1 650 cm^{-1}; $\delta(CDCl_3)$ 1.26 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.76 (2 H, s, 7-CH_2), 4.23 (4 H, s, OCH_2CH_2O), 4.0—4.7 (5 H, m, CH_2CH_3, 2-H, and 3-H_2), and 6.37 (1 H, s, 8-H); *m/z* 382 (M^+) and 384 ($M^+ + 2$).

Ethyl Acetoxy-[6-*cyano*-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-*tetrahydroindolizin*-7-*yl*]*acetate* (**7**).—To a solution of AcOH (80 ml), DMF (80 ml), and AcONa (1.81 g, 22 mmol) was added (**5**) (7.66 g, 20 mmol) and the resulting mixture was stirred for 2 h at 80 °C. It was then diluted with $CHCl_3$ (300 ml), washed, dried, and concentrated to give a crude solid, which was chromatographed on silica gel ($CHCl_3$–MeOH,98:2) to give the acetate (**7**) (5.5 g, 76.0%) as a white solid, m.p. 150—154 °C (Found: C, 55.0; H, 4.95; N, 7.7. $C_{17}H_{18}N_2O_7 \cdot \frac{1}{2}H_2O$ requires C, 55.0; H, 5.15; N, 7.55%); R_F (B) 0.35; $\nu_{max.}$(KBr) 2 225, 1 750, and 1 650 cm^{-1}; $\delta(CDCl_3)$ 1.26 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.21 (3 H, s, Ac), 2.3—2.5 (2 H, m, 2-H_2), 4.14 (4 H, s, OCH_2CH_2O), 4.0—4.5 (4 H, m, CH_2CH_3 and 3-H_2), 6.13 (1 H, s, 7-CH), and 6.36 (1 H, s, 8-H); *m/z* 362 (M^+).

Ethyl 2-*Acetoxy*-2-[6-*cyano*-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3-5-*tetrahydroindolizin*-7-*yl*]*butanoate* (**8**).—To a solution of (**7**) (3.62 g, 10 mmol) in DMF (60 ml) was added 60% sodium hydride (0.48 g, 12 mmol) and the resulting mixture was stirred for 0.5 h at 0 °C. Ethyl iodide (1 ml, 12 mmol) was then added, and the mixture was allowed to warm to room temperature when it was stirred for 3 h. After this the solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (300 ml). The organic layer was then washed, dried, and concentrated to give a crude solid, which was chromatographed on silica gel (benzene–EtOAc,7:3) to afford the title compound (**8**) (3.35 g, 85.9%) as a white solid, m.p. 176–183 °C (Found: C, 58.15; H, 5.65; N, 7.25. $C_{19}H_{22}N_2O_7$ requires C, 58.45; H, 5.7; N, 7.2%); R_F (B) 0.36; $\nu_{max.}$(KBr) 2 225, 1 750, and 1 640 cm^{-1}; $\delta(CDCl_3)$ 0.85 (3 H, t, *J* 7 Hz, CCH_2CH_3), 1.23 (3 H, t, *J* 7 Hz, OCH_2CH_3), 2.27 (3 H, s, Ac), 2.2—2.7 (4 H, m, 2-H_2 and CCH_2CH_3), 4.12 (4 H, s, OCH_2CH_2O), 4.0—4.5 (4 H, m, OCH_2CH_3 and 3-H_2), and 6.42 (1 H, s, 8-H); *m/z* 390 (M^+).



Scheme 4. *Reagents and conditions:* i, Raney Ni, Ac_2O, AcOH; ii, $NaNO_2$, Ac_2O, AcOH; then CCl_4, reflux; iii, LiOH, MeOH, H_2O; then AcOH, CH_2Cl_2; iv, 80% TFA; v, *p*-TsOH, toluene, reflux

Ethyl 2-*Bromo*-2-[6-*cyano*-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-*tetrahydroindolizin*-7-*yl*]*butanoate* (**10**).—In the same manner as for the preparation of (**5**) from (**4**), compound (**9**)[9] (1.33 g, 4 mmol) was brominated to give the title compound (**10**) (1.42 g, 86.4%) as a white solid, m.p. 125—131 °C (Found: C, 49.7; H, 4.65; N, 6.9. $C_{17}H_{19}BrN_2O_5$ requires C, 49.65; H, 4.65; N, 6.8%); R_F (A) 0.26; $\nu_{max.}$(KBr) 2 225, 1 735, and 1 650 cm^{-1}; $\delta(CDCl_3)$ 0.93 (3 H, t, *J* 7 Hz, CCH_2CH_3), 1.31 (3 H, t, *J* 7 Hz, OCH_2CH_3), 2.3—2.6 (2 H, m, 2-H_2), 2.56 (2 H, q, *J* 7 Hz, CCH_2CH_3), 4.16

(4 H, s, OCH_2CH_2O), 4.32 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.0—4.4 (2 H, m, 3-H_2), and 6.74 (1 H, s, 8-H); *m/z* 410 (M^+) and 412 ($M^+ + 2$).

Ethyl 2-*Acetoxy*-2-[6-(*acetylaminomethyl*)-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-*tetrahydroindolizin*-7-*yl*]*butanoate* (**12**).—A solution of (**8**) (2.72 g, 6.97 mmol) in a mixture of AcOH (25 ml) and Ac_2O (90 ml) was hydrogenated in the presence of Raney Ni (6 ml; prewashed with AcOH) over 3 h. The catalyst was filtered off, and the filtrate was concentrated to give a crude oil, which was chromatographed on silica gel ($CHCl_3$–MeOH,98:2) to afford the title compound (**12**) (3.04 g, ~100%) as an oil (Found: M^+, 436.1831. $C_{21}H_{28}N_2O_8$ requires *M*, 436.1846); R_F (C) 0.43; $\nu_{max.}$ (neat, film) 1 740 and 1 629 cm^{-1}; δ($CDCl_3$) 0.84 (3 H, t, *J* 7 Hz, CCH_2CH_3), 1.17 (3 H, s, *J* 7 Hz, OCH_2CH_3), 1.94 (3 H, s, Ac), 2.21 (3 H, s, Ac), 2.1—2.7 (4 H, m, CCH_2CH_3 and 2-H_2), 4.13 (4 H, s, OCH_2CH_2O), 3.8—4.4 (4 H, m, OCH_2CH_3 and 3-H_2), 4.3—4.9 (2 H, m, 6-CH_2), 6.44 (1 H, s, 8-H), and 6.7—7.2 (1 H, br, NH).

Ethyl 2-*Acetoxy*-2-[6-(*acetoxymethyl*)-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-*tetrahydroindolizin*-7-*yl*]*butanoate* (**13**).—To a solution of (**12**) (1.12 g, 2.56 mmol) in a mixture of Ac_2O (15 ml) and AcOH (5 ml) at 0 °C was added $NaNO_2$ (0.76 g, 11 mmol) and the reaction mixture was stirred for 4 h. The inorganic salt was removed by filtration and the solvent was evaporated at room temperature to afford the *N*-nitroso intermediate as an oil. To this oil, CCl_4 (50 ml) was added and the solution was heated under reflex for 5 h. The organic layer was washed, dried, and evaporated to give an oil, which was chromatographed on silica gel (benzene–EtOAc, 3:1) to afford the title compound (**13**) (0.95 g, 84.9%) as an oil (Found: C, 55.2; H, 6.2; N, 3.25. $C_{21}H_{27}NO_9 \cdot H_2O$ requires C, 55.4; H, 6.4; N, 3.1%); R_F (C) 0.71; $\nu_{max.}$ (film) 1 743, and 1 665 cm^{-1}; δ($CDCl_3$) 0.82 (3 H, t, *J* 7 Hz, CCH_2CH_3), 1.22 (3 H, t, *J* 7 Hz, OCH_2CH_3), 2.04 (3 H, s, Ac), 2.12 (3 H, s, Ac), 2.2—2.7 (4 H, m, CCH_2CH_3 and 2-H_2), 4.12 (4 H, s, OCH_2CH_2O), 3.9–4.4 (4 H, m, OCH_2CH_3 and 3-H_2), 5.28 (2 H, s, 6-CH_2), and 6.33 (1 H, s, 8-H); *m/z* 437 (M^+).

4-*Ethyl*-6,6-(*ethylenedioxy*)-1,4,7,8-*tetrahydro*-4-*hydroxypyrano*[3,4-f]*indolizine*-3,10(6H)-*dione* (**14**).—To a solution of (**13**) (150 mg, 0.34 mmol) in a mixture of MeOH (3 ml) and H_2O (1 ml) was added $LiOH \cdot H_2O$ (71 mg, 1.7 mmol). The resulting mixture was stirred for 2 h at room temperature, then evaporated to *ca.* one-quarter of the volume to remove most of the MeOH. Water (3 ml), CH_2Cl_2 (20 ml), and AcOH (1 ml) were added, and the mixture was stirred for 24 h at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 ml × 2). The combined organic extracts were washed, dried, and concentrated. The residue was then chromatographed on silica gel ($CHCl_3$–MeOH,99:1) and crystallized from EtOAc–hexane to afford the dione (**14**) (91 mg, 87.5%) as colourless crystals, m.p. 180 °C (Found: C, 58.55; H, 5.55; N, 4.55. $C_{15}H_{17}NO_6$ requires C, 58.65; H, 5.6; N, 4.55%); R_F (C) 0.52; $\nu_{max.}$(KBr) 3 250, 1 745, and 1 650 cm^{-1}; δ($CDCl_3$) 0.96 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.77 (2 H, q, *J* 7 Hz, CH_2CH_3) 2.38 (2 H, t, *J* 7 Hz, 7-H_2), 4.12 (6 H, m, OCH_2CH_2O and 8-H_2), 5.12, 5.47 (2 H, ABq, *J* 16 Hz, 1-H_2), and 6.53 (1 H, s, 5-H); *m/z* 307 (M^+).

4-*Ethyl*-1,4,7,8-*tetrahydro*-4-*hydroxypyrano*[3,4-f]*indolizine*-3,6,10-*trione* (**15**) *from Compound* (**14**) *or* (**13**).—A solution of (**14**) (1.0 g, 3.25 mmol) in 80% aqueous trifluoroacetic acid (10 ml) was stirred for 3 h at room temperature under nitrogen. The solvent was evaporated and the residue was diluted with CH_2Cl_2. The organic layer was then washed, dried, and evaporated and the residue was crystallized from EtOAc–ether to afford the trione (**15**) (0.70 g, 81.9%) as colourless crystals, m.p. 193—195 °C (decomp.) (Found: C, 59.2; H, 5.15; N, 5.2. $C_{13}H_{13}NO_5$ requires C, 59.3; H, 5.0; N, 5.3%); R_F (C) 0.42; $\nu_{max.}$(KBr) 3 450, 3 300, 1 740, and 1 660 cm^{-1}; δ($CDCl_3$) 0.96 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.80 (2 H, q, *J* 7 Hz, CH_2CH_3), 2.93 (2 H, t, *J* 7 Hz, 7-H_2), 4.30 (2 H, t, *J* 7 Hz, 8-H_2), 5.21, 5.62 (2 H, ABq, *J* 17 Hz, 1-H_2), and 7.16 (1 H, s, 5-H); *m/z* 263 (M^+).

The triester (**13**) (150 mg, 0.34 mmol) was dissolved in DME (1 ml) and 1M H_2SO_4 (1 ml) and the mixture stirred at 55 °C for 24 h. It was then diluted with water (3 ml) and extracted with CH_2Cl_2 (20 ml). The organic layer was washed, dried, filtered, and concentrated to give an oil, which was chromatographed on silica gel ($CHCl_3$–MeOH,99:1) to afford the trione (**15**) (30 mg, 33.5%), spectroscopically identical with the material produced previously.

(RS)-*Camptothecin* (**1**).—A solution of the tricyclic ketone (**15**) (250 mg, 0.95 mmol) and (**16**)[10] (240 mg, 1.14 mmol) in toluene (20 ml) was heated to reflux under nitrogen. After 30 min, *p*-TsOH (3 mg) was added and the reaction mixture was heated under reflux for a further 3 h using a Dean–Stark trap. The precipitate obtained on cooling was filtered off and recrystallized from CH_3CN–MeOH to afford the title compound (**1**) (230 mg, 69.5%) as a microcrystalline solid, m.p. 265—272 °C (decomp.) (Found: C, 68.8; H, 4.6; N, 8.0. $C_{20}H_{16}N_2O_4$ requires C, 68.95; H, 4.8; N, 8.1%); R_F (C) 0.55; $\nu_{max.}$(KBr) 1 740, 1 650, and 1 590 cm^{-1}; δ([$^2H_6$]-DMSO) 0.9 (3 H, t, *J* 7.5 Hz, CCH_2CH_3), 1.89 (2 H, q, *J* 7.5 Hz, CCH_2CH_3). 5.32 (2 H, s, CH_2), 5.45 (2 H, s, CH_2), 6.54 (1 H, s, OH), 7.40 (1 H, s, ArH), 7.6—8.3 (4 H, m, ArH), and 8.74 (1 H, s, ArH); *m/z* 348 (M^+).

Ethyl 2-[N-*Tosyl*-(R)-*prolyloxy*]-2-[6-*cyano*-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-*tetrahydroindolizin*-7-*yl*]*acetate* (**18**).— To a solution of *N*-tosyl-(*R*)-proline (**17**)[11] (14.4 g, 50 mmol) and Na_2CO_3 (1.91 g, 18 mmol) in DMF (50 ml) was added compound (**5**) (9.35 g, 24.4 mmol) and the mixture was stirred for 1 h at 70 °C under nitrogen. After evaporation of the solvent, the residue was diluted with $CHCl_3$ (300 ml). The organic layer was then washed with 5% aqueous $NaHCO_3$ (200 ml) and water (100 ml), dried and concentrated. The residue was chromatographed on silica gel (toluene–EtOAc,7:3) to afford the diastereoisomeric mixture (**18**) (13.0 g, 93.2%) as a white solid (Found: C, 55.45; H, 5.0; N, 7.3. $C_{27}H_{29}N_3O_9S \cdot \frac{3}{4}H_2O$ requires C, 55.4; H, 5.25; N, 7.2%); R_F (C) 0.73; $\nu_{max.}$(KBr) 2 224, 1 764, and 1 664 cm^{-1}; δ($CDCl_3$) 1.28, 1.30 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.5—2.6 (6 H, m, 2-H_2 and $CH_2CH_2CH_2CH$), 2.43 (3 H, s, Ar*Me*), 3.0—3.8 (2 H, m, $CH_2CH_2CH_2CH$), 3.8—4.6 (9 H, m, 3-H_2, OCH_2CH_2O, CH_2CH_3, and CH_2CHCO), 6.18, 6.29 (1 H, s, 7-CH), 6.61, 6.64 (1 H, s, 8-H), 7.31 (2 H, d, *J* 9 Hz, *m*-ArH), and 7.72 (2 H, d, *J* 9 Hz, *o*-ArH).

In addition, aqueous extracts were combined, adjusted to pH 2 with 6M HCl and extracted with $CHCl_3$ (300 ml). The organic layer was washed, dried, and concentrated to give an oil, which was then crystallized from benzene to afford *N*-tosyl-(*R*)-proline (**17**) (7.52 g) as colourless crystals, spectroscopically identical with the authentic sample; $[\alpha]_D$ +92.3° (*c* 1.0 in $CHCl_3$).

Ethyl (S)-2-[N-*Tosyl*-(R)-*prolyloxy*]-2-[6-*cyano*-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-*tetrahydroindolizin*-7-*yl*]*butanoate* (**19**).—To a solution of (**18**) (3.5 g, 6.12 mmol) in DMF (28 ml) was added 60% sodium hydride (0.248 g, 6.2 mmol) and the resulting mixture was stirred for 1 h at room temperature. Ethyl iodide (5 ml, 62.2 mmol) was then added and the mixture stirred for a further 3 h. After this the solvent was evaporated and the residue was diluted with $CHCl_3$ (500 ml) and the solution washed, dried, and evaporated to give an oil. This was chromatographed on silica gel (benzene–EtOAc,7:3) to afford 3.67 g (~100%) of (**19**) and (**20**) as a diastereoisomeric mixture. To this mixture was added propan-2-ol (300 ml) and the mixture was refluxed for 1 h, cooled to room temperature, and

allowed to stand for 24 h. The precipitate was filtered off and the filtrate was concentrated to give the optically active compound (**19**) (2.07 g, 56.4%) as a white solid, m.p. 75—80 °C (Found: C, 58.0; H, 5.65; N, 7.0. $C_{29}H_{33}N_3O_9S$ requires C, 58.1; H, 5.55; N, 7.0%); R_F (C) 0.73; $\nu_{max.}$(KBr) 2 224, 1 764, and 1 662 cm^{-1}; δ($CDCl_3$) 0.90 (3 H, t, *J* 7 Hz, CCH_2CH_3), 1.31 (3 H, t, *J* 7 Hz, OCH_2CH_3), 1.5—2.5 (4 H, m, 2-H_2 and CCH_2CH_3), 2.43 (3 H, s, Ar*Me*), 2.1—2.8 (4 H, m, $CH_2CH_2CH_2CH$), 3.0—3.8 (2 H, m, $CH_2CH_2CH_2CH$), 3.8—4.6 (9 H, m, 3-H_2, OCH_2CH_2O, OCH_2CH_3, and CH_2CHCO), 7.32 (2 H, d, *J* 8 Hz, *m*-ArH), and 7.78 (2 H, d, *J* 8 Hz, *o*-ArH); *m/z* 599 (M^+).

Ethyl (S)-2-[N-*Tosyl*-(R)-*prolyloxy*]-2-[6-(*acetylaminomethyl*)-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-*tetrahydroindolizin*-7-*yl*]*butanoate* (**21**).—Compound (**19**) (2.0 g, 3.34 mmol) was subjected to reductive acetylation in the same manner as described for the preparation of (**12**) to give the acetylamino compound (**21**) (2.15 g, 99.8%) as a white solid (Found: C, 55.6; H, 5.75; N, 6.4. $C_{31}H_{39}N_3O_{10}S\cdot\frac{5}{4}H_2O$ requires C, 55.7; H, 6.25; N, 6.3%); R_F (C) 0.35; $\nu_{max.}$(KBr) 1 745, 1 645, and 1 590 cm^{-1}; δ($CDCl_3$) 0.89 (3 H, t, *J* 7 Hz, CCH_2CH_3), 1.29 (3 H, t, *J* 7 Hz, OCH_2CH_3), 1.95 (3 H, s, Ac), 2.24 (3 H, s, Ar*Me*), 1.5—2.8 (8 H, m, 2-H_2, $CH_2CH_2CH_2CH$, and CCH_2CH_3), 3.0—3.8 (2 H, m, $CH_2CH_2CH_2CH$), 3.8—5.0 (11 H, m, 3-H_2, OCH_2CH_2O, $CH_2CH_2CH_2CH$, OCH_2CH_3, and 6-CH_2), 6.78 (1 H, s, 8-H), 7.0—7.5 (1 H, br, NH), 7.39 (2 H, d, *J* 7 Hz, *m*-ArH), and 7.84 (2 H, d, *J* 7 Hz, *o*-ArH); *m/z* 645 (M^+).

Ethyl (S)-2-[N-*Tosyl*-(R)-*prolyloxyl*]-2-[6-(*acetoxymethyl*)-1,1-(*ethylenedioxy*)-5-*oxo*-1,2,3,5-*tetrahydroindolizin*-7-*yl*]-*butanoate* (**22**).—Compound (**21**) (1.98 g, 3.07 mmol) was treated in the same manner as described for the preparation of (**13**) to give the acetoxy compound (**22**) (1.46 g, 73.6%) as a white solid (Found: C, 56.6; H, 5.8; N, 4.2. $C_{31}H_{38}N_2O_{11}S\cdot\frac{1}{2}H_2O$ requires C, 56.8; H, 6.0; N, 4.25%); R_F (C) 0.59; $\nu_{max.}$(KBr) 1 746, 1 659, and 1 614 cm^{-1}; δ($CDCl_3$) 0.89 (3 H, t, *J* 7 Hz, CCH_2CH_3), 1.23 (3 H, t, *J* 7 Hz, OCH_2CH_3), 2.04 (3 H, s, Ac), 1.5—2.8 (8 H, m, CCH_2CH_3, 2-H_2, and $CH_2CH_2CH_2CH$), 2.43 (3 H, s, Ar*Me*), 3.0—4.0 (2 H, m, $CH_2CH_2CH_2CH$), 3.9—4.6 (9 H, m, 3-H_2, OCH_2CH_2O, $CH_2CH_2CH_2CH$, and OCH_2CH_3, 5.24 (2 H, s, 6-CH_2), 6.76 (1 H, s, 8-H), 7.29 (2 H, d, *J* 8 Hz, *m*-ArH), and 7.75 (2 H, d, *J* 8 Hz, *o*-ArH); *m/z* 646 (M^+).

(S)-4-*Ethyl*-6,6-(*ethylenedioxy*)-1,4,7,8-*tetrahydro*-4-*hydroxypyrano*[3,4-f]*indolizine*-3,10(6H)-*dione* (**23**).—To a solution of (**22**) (324 mg, 0.50 mmol) in a mixture of EtOH (6 ml) and water (3 ml) was added $LiOH\cdot H_2O$ (72 mg, 1.7 mmol) and the resulting mixture was stirred for 1 h at room temperature. The solvent was evaporated, water (3 ml), CH_2Cl_2 (10 ml), and AcOH (2 ml) were added, and the mixture was stirred for 24 h at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (40 ml). The combined organic extracts were washed with 5% aqueous $NaHCO_3$ and water, dried, and evaporated under reduced pressure. The residue was then chromatographed on silica gel ($CHCl_3$–MeOH,98:2) and crystallized from CH_2Cl_2–hexane to afford the optically active dione (**23**) (138 mg, 89.8%) as colourless needles, m.p. 170–171 °C (Found: 56.8; H, 5.55; N, 4.55. $C_{15}H_{17}NO_6\cdot\frac{1}{2}H_2O$ requires C, 56.95; H, 5.75; N, 4.45%); $[\alpha]_D$ +109.7° (*c* 0.76 in $CHCl_3$); *m/z* 307 (M^+). The t.l.c., i.r., and n.m.r. data of (**23**) were identical with those of the racemic compound (**14**).

* *N*-Tosyl-(S)-proline·$\frac{1}{2}C_6H_6$ is reported in reference 11. *N*-Tosyl-(*R*)-proline was obtained in the same manner and 0.25 mole of C_6H_6 was present in compound (**17**): $[\alpha]_D$ +92.8° (*c* 1.0, $CHCl_3$).

The alkaline aqueous extracts were also combined, adjusted to pH 2 with 6M HCl, and extracted with benzene (50 ml). The extract was washed, dried, and evaporated to give a colourless oil, which was then crystallized from benzene to afford *N*-tosyl-(*R*)-proline·$\frac{1}{2}C_6H_6$ (**17**) (102 mg, 66.2%); $[\alpha]_D$ +88.6° (*c* 1.0 in $CHCl_3$).* The t.l.c. data and the n.m.r. spectrum of this compound were identical with those of the authentic sample.

(S)-4-*Ethyl*-1,4,7,8-*tetrahydro*-4-*hydroxypyrano*[3,4-f]*indolizine*-3,6,10-*trione* (**24**).—Compound (**23**) (120 mg, 0.39 mmol) was treated in the same manner as described for the preparation of racemic (**15**) from (**14**) to give the optically active trione (**24**) (81 mg, 79.0%) as colourless crystals, m.p. 176—177 °C (decomp.) (Found: C, 58.15; H, 4.9; N, 5.25. $C_{13}H_{13}NO_5\cdot\frac{1}{4}H_2O$ requires C, 58.3; H, 5.1; N, 5.25%); $[\alpha]_D$ +117.6° (*c* 0.56 in $CHCl_3$){lit., $[\alpha]_D$ +120.6° ($CHCl_3$),[8] +96° ($CHCl_3$–MeOH, 4:1)[7]}; *m/z* 263 (M^+). The t.l.c., i.r., and the n.m.r. data of (**24**) were identical with those of the racemic compound (**15**).

(S)-*Camptothecin* (**1**).—The tricyclic ketone (**24**) (45 mg, 0.2 mmol) and (**16**) (43 mg, 0.2 mmol) were treated in the same manner as described for the preparation of (*RS*)-camptothecin to give optically active (*S*)-camptochecin (**1**) (50 mg, 84.4%) as a microcrystalline solid, m.p. 265—266 °C (decomp.) (Found: C, 68.8; H, 4.85; N, 7.95. $C_{20}H_{16}N_2O_4$ requires C, 68.95; H, 4.65; N, 8.05%); $[\alpha]_D$ +42.0° (*c* 0.51 in $CHCl_3$–MeOH, 4:1) {lit., $[\alpha]_D$ +40.7°,[12] +42.8°[13] ($CHCl_3$–MeOH, 4:1)}; *m/z* 348 (M^+). The t.l.c., i.r., and n.m.r. data of this compound were identical with those of racemic (**1**).

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