Pergamon

Tetrahedron Letters 41 (2000) 859–862

TETRAHEDRON LETTERS

Biogenetically patterned synthesis of camptothecin and 20-deoxycamptothecin

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Received 14 September 1999; accepted 22 November 1999

Abstract

A biogenetically patterned synthetic route to the monoterpenoid quinoline alkaloids 20-deoxycamptothecin and (±)-camptothecin from secologanin and tryptamine via vincoside/strictosidine lactams has now been realized, and hence afforded likely biosynthetic intermediates for testing in vivo.

Keywords: alkaloids; biogenesis; biomimetic; indole; quinoline; terpene.

The alkaloid (+)-camptothecin **1** was isolated in 1966 by Wall and co-workers from *Camptotheca acuminata*, a tree native to China, and shown to possess unique anticancer properties.[1] Hence, over the subsequent three decades its relatively simple structure has been the objective of many total syntheses using a variety of approaches.[1,2] Early biogenetic speculation focused on the similarity of the skeleta of camptothecin and vincoside/strictosidine lactams **6**/**7**, given that conversion of indole to quinoline heterocycles was well known, and this was confirmed by in vivo incorporation of labelled strictosidine lactam **6** into camptothecin.[2] It thus belongs to the monoterpenoid indole alkaloid family, derived from tryptamine **2** and secologanin **3**, but little is known about the details of its biosynthesis beyond what is outlined in Scheme 1. Conversion of **6** to **1** is a net oxidative process requiring: (i) oxidative rearrangement of rings B and C; (ii) reduction of C-17, 18 and 19; (iii) aromatisation of ring D; (iv) hydrolysis of the glucoside; and (v) oxidation of C-21 and C-20. At least seven distinct steps are involved, which could occur in various orders. Through the maze of possible pathways, a biogenetically patterned synthetic route to camptothecin from tryptamine and secologanin has now been found, and likely biosynthetic intermediates produced for eventual testing in vivo.

Condensation of tryptamine and secologanin in pH 4 buffer afforded a ca. 3:2 mixture of the C-3 epimers vincoside **5** and strictosidine **4**, which was converted to a mixture of the corresponding lactams **6**/**7** by heating with aq. Na_2CO_3, or vincoside could be selectively lactamised with Et_3N/MeOH to **7**

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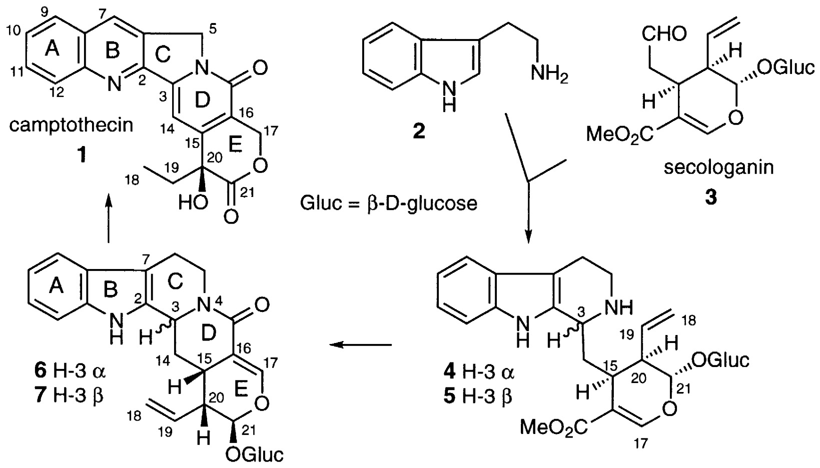
PII: S0040-4039(99)02210-8



Scheme 1.

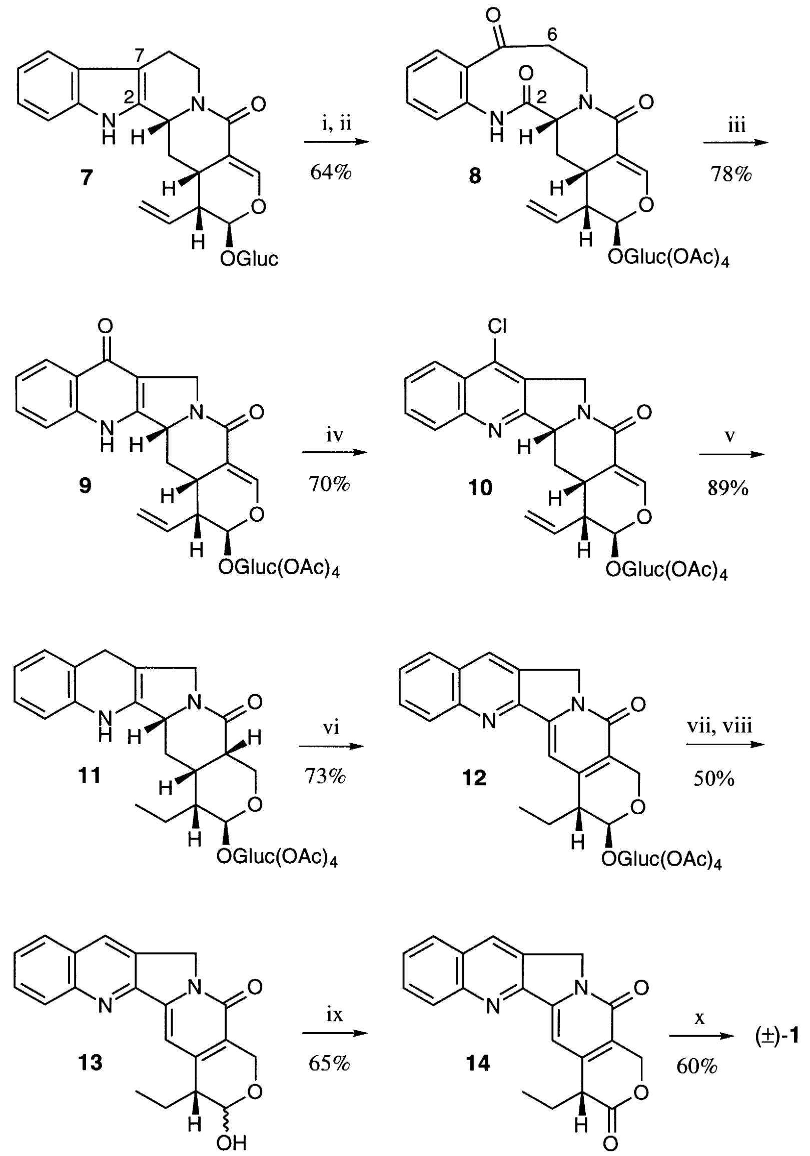
and separated from strictosidine.[3,4] Since H-3 is lost in aromatisation of ring D, we have carried out the complete reaction sequence below on both the lactam mixture and vincoside lactam alone, but for clarity only the latter is described.

In early work it was established that oxidative rearrangement of the tetrahydro-β-carboline system of the lactams **6**/**7** to a pyrroloquinolone could be achieved.[5–7] Also, ring D in 18,19-dihydro-**6**/**7** could be aromatised with DDQ in methanol, if only with incorporation of a methoxy group at C-17, but the product could not be converted further to a quinolone.[5] It was concluded that prior reduction of the 16,17 double bond would facilitate ring D aromatisation. Accordingly, catalytic hydrogenation of vincoside lactam tetra-acetate with Raney Ni afforded an excellent yield of the 16*S*,17,18,19-tetrahydro derivative, mp 279°, but unfortunately conversion to a quinolone and subsequent steps went in unacceptably low yields.[8,9] Eventually the following successful route was devised, as summarised in Scheme 2.

With $NaIO_4$ in refluxing aq. MeOH the indole 2,7-bond in vincoside lactam tetra-acetate was cleaved to a ketolactam **8**, as indicated inter alia by λ_{max}(MeOH) 246 nm; M^+ 698.232 ($C_{34}H_{38}N_2O_{14}$).[7] Heating **8** with Et_3N/MeOH led to aldol condensation between C-2 and C-6 and formation of the pyrroloquinolone **9** [λ_{max} 234, 316, 328 nm; ν_{max}(film) 1750, 1720, 1660, 1570 cm^{-1}; M^+ 680.225 ($C_{34}H_{36}N_2O_{13}$)] with a characteristic ^1H NMR (200 Mhz, $CDCl_3$) signal for the C-5 methylene at δ 5.20. Significantly, the C-3 epimers of **8** and **9**, which we made from strictosidine lactam some time ago,[6,7] have now been isolated as natural products.[10] Treatment of the quinolone with $SOCl_2$ in DMF gave the 7-chloroquinoline **10**, mp 203–205°, identified by a typical quinoline UV spectrum with λ_{max} 218, 240, 372 nm, loss of the NH signal at δ 9.35, ν_{max} 1752, 1663 cm^{-1} and $(M+H)^+$ 699.195 ($C_{34}H_{36}N_2O_{12}{}^{35}Cl$).

In a crucial step, the 7-chloroquinoline in ethanol was treated with hydrogen (50 psi) over freshly prepared Raney Ni catalyst for 24 h. In the event, not only were the 16,17-β-alkoxyacrylamide and 18,19-vinyl groups hydrogenated, and the chlorine hydrogenolysed, but the quinoline was also partially reduced to afford as a single stereoisomer the dihydroquinoline **11**. Its structure was indicated by M^+ 670.276 ($C_{34}H_{42}N_2O_{12}$), ν_{max} 1662 cm^{-1} (δ-lactam), λ_{max} 250 nm (similar to an aniline) and corroborated by the ^1H NMR spectrum[11] with a new NH peak and signals for new CH bonds at C-7, 16, 17, 18 and 19.

Subsequent aromatisation of both rings B and D in **11** was achieved with DDQ in dioxane to give the conjugated quinolinopyridone **12**, possessing the same UV chromophore as camptothecin, as indicated by a similar spectrum with λ_{max} 252, 288, 360 nm. In the NMR spectrum there were new aromatic proton singlets at δ 7.15 and 8.34 for H-14 and H-7, respectively, and the molecular ion at *m/z* 664.229 analysed for the required $C_{34}H_{36}N_2O_{12}$.



Scheme 2. Reagents and conditions: (i) Ac_2O/py 12 h; (ii) $NaIO_4$/aq. MeOH/Δ 30 min; (iii) Et_3N/MeOH/Δ 30 min; (iv) $SOCl_2$/DMF/0°C 10 min; (v) Raney Ni/H_2/EtOH 24 h; (vi) DDQ/dioxane/Δ 10 min; (vii) NaOMe/MeOH 2 h; (viii) β-glucosidase/pH 5 buffer 3 days; (ix) PCC/DCM 30 min; (x) O_2/$CuCl_2$/DMF 10 h

After Zemplen deacetylation, the glucose was removed with β-glucosidase in pH 5.0 buffer to yield the lactol **13**, characterised by a hydroxyl peak at 3385 cm^{-1} in the IR spectrum and a doublet at δ 4.81 assigned to H-21, together with loss of all sugar protons in the NMR spectrum. No molecular ion could be detected in its MS but a peak at *m/z* 317.127 corresponded to ready loss of OH ($C_{20}H_{17}N_2O_2$). Oxidation of the lactol with PCC/CH_2Cl_2 gave a lactone, as indicated by loss of the IR peak at 3385 cm^{-1} and the NMR signal for H-21, together with a new carbonyl band at 1738 cm^{-1}. Corroboration that the product corresponded to the known alkaloid 20-deoxycamptothecin[12] **14**, was obtained from M^+ 332.118 ($C_{20}H_{16}N_2O_3$), and comparison of UV and ^1H NMR spectra.[13]

Finally, H-20 was oxidised to a hydroxyl group by $O_2/CuCl_2$[14] but with consequent loss of chirality so that the product was racemic camptothecin, identical with an authentic sample of (+)-**1** by TLC, MS, IR, UV and ^{1}H NMR spectra.[15] However, routes to the (+)-isomer using enzymatic oxidation of **14** or the intrinsic chirality of **11** are in progress. We have thus achieved the target of a biomimetic synthesis of camptothecin, and also prepared the likely biosynthetic intermediates **12**, **13** and **14**. These and others, such as the C-3 epimers of **8** and **9** from strictosidine lactam **4**, can now be prepared with labels for in vivo experiments.

Acknowledgements

We thank Drs. L. Akhter, D. Curless, S. B. Fraser, A. G. Lashford, and P. Richards for their pioneering work in this area, and the British Council, the CVCP and the Chemistry Department, Manchester University for financial support (JL).

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11. Compound **11**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (bs, NH), 7.00–6.45 (m, 4 Ar-H), 5.37 (bs, H_2-5), 5.20 (t, J=9 Hz, H-3′), 5.08 (dd, J=9, 8 Hz, H-4′), 5.05–4.88 (m, H-2′, H-3, H-1′), 4.42 (d, J=9 Hz, H-21), 4.30 (m, J=6 Hz, H_2-6′), 4.12 (dd, J=12, 5.5 Hz, H-17β), 3.90 (dd, J=12, 9 Hz, H-17α), 3.75 (m, J=8, 6 Hz, H-5′), 3.40 (d, J=13 Hz, H-7b), 3.28 (d, J=13 Hz, H-7a), 2.78 (m, J=9, 5.5, 5 Hz, H-16β), 2.57 (m, J=5, 6, 6, 12 Hz, H-15), 2.34 (m, J=13, 6, 2.5 Hz, H14β), 2.10–1.95 (4 s, 4 OAc), 2.00–1.80 (m, H-14α, H-19b), 1.65–1.38 (m, H-20β, H-19a), 0.98 (t, J=8 Hz, H_3-18).
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13. Compound **14**: λ_{max} 254, 288, 360 nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, H-7), 8.20 (d, J=8 Hz, H-12), 7.93 (d, J=8 Hz, H-9), 7.82 (t, J=8 Hz, H-10/11), 7.66 (t, J=8 Hz, H-11/10), 7.44 (s, H-14), 5.56 (d, J=17 Hz, H-17b), 5.38 (d, J=17 Hz, H-17a), 5.29 (s, H_2-5), 3.62 (t, J=6 Hz, H-20), 2.08 (m, H_2-19), 1.07 (t, J=8 Hz, H_3-18).
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15. Compound **1**: λ_{max} 252, 288, 367 nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, H-7), 8.22 (d, J=8 Hz, H-12), 7.92 (d, J=8 Hz, H-9), 7.82 (t, J=8 Hz, H-10/11), 7.70 (s, H-14), 7.65 (t, J=8 Hz, H-11/10), 5.75 (d, J=17 Hz, H-17b), 5.33 (s, H_2-5), 5.31 (d, J=17 Hz, H-17a), 1.87 (m, H_2-19), 1.07 (t, J=8 Hz, H_3-18).