COMMUNICATION

Short synthesis of the optically active E-ring portion of (*S*)-camptothecin

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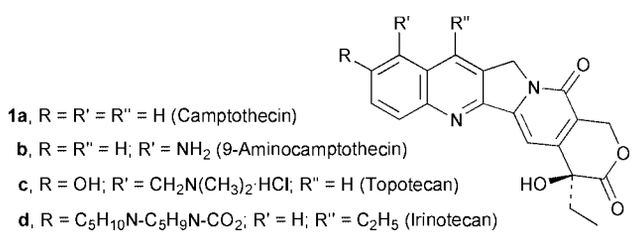
Received (in Cambridge, UK) 5th October 2001, Accepted 11th October 2001
First published as an Advance Article on the web 23rd October 2001

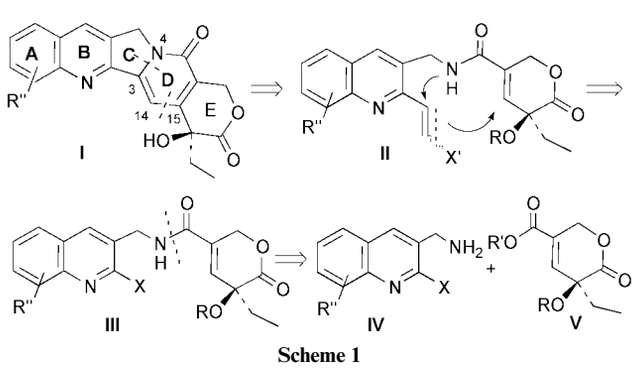
(5*S*)-5-Benzyloxy-5-ethyl-6-oxo-5,6-dihydro-2*H*-pyran-3-carboxylic acid, the protected E-ring moiety of (*S*)-camptothecin, has been rapidly prepared in enantiomerically enriched form (98% ee) through enolate conjugate addition to a β-bromo methacrylate derivative, followed by enzymatic resolution with PLE.

Camptothecin (**1a**) was isolated by Wall *et al.*[1] in 1966 from *Camptotheca acuminata* Decne (Nyssaceae) and immediately generated interest because of significant antitumor activity revealed in murine test systems. At NCI (National Cancer Institute) misleading clinical trials carried out on the more water-soluble seco-acid sodium salt of this alkaloid evidenced severe toxicity, though, and testing was halted. Several subsequently prepared semisynthetic or totally synthetic congeners, such as 9-aminocamptothecin, topotecan, and irinotecan (**1b–d**), however, have demonstrated clinically useful efficacy in the treatment of certain cancers. Camptothecin and, presumably, its analogues act as poisons of topoisomerase I by trapping the cleavable DNA–topoisomerase I complex.[2]



1a, R = R' = R'' = H (Camptothecin)
b, R = R'' = H; R' = NH_2 (9-Aminocamptothecin)
c, R = OH; R' = $CH_2N(CH_3)_2$·HCl; R'' = H (Topotecan)
d, R = $C_5H_{10}N$-C_5H_9N-CO_2; R' = H; R'' = C_2H_5 (Irinotecan)

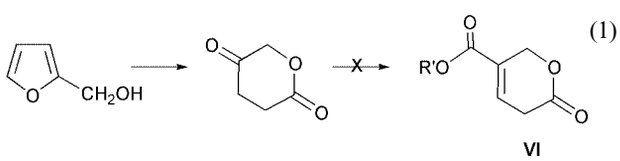
To develop a route to camptothecin and derivatives based on novel bond connections, we have been studying the convergent approach shown retrosynthetically in Scheme 1. N4–C3 C-ring



Scheme 1

closure by amide nitrogen addition to a double or triple bond, followed by photolytic or conjugate-addition driven C14–C15 D-ring formation, oxidation, and removal of the R and/or X′ groups could be expected to allow access to a variety of camptothecinoids from **II**. This intermediate should be accessible by Sonogashira or Stille coupling from halide **III**, which in turn would be available from amine **IV** and the enantiomerically enriched E-ring component lactone acid **V** (R′ = H). The synthesis of this densely functionalized key component is the subject of this paper.

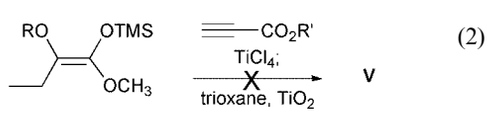
At the outset we believed that the size of this molecule might belie the synthetic challenge that lay ahead, and this indeed turned out to be correct.[3] First efforts were directed toward the preparation of lactone ester **VI**, which, it was hoped, might be transformed into the desired lactone acid **V** [eqn. (1)]. Toward



(1)

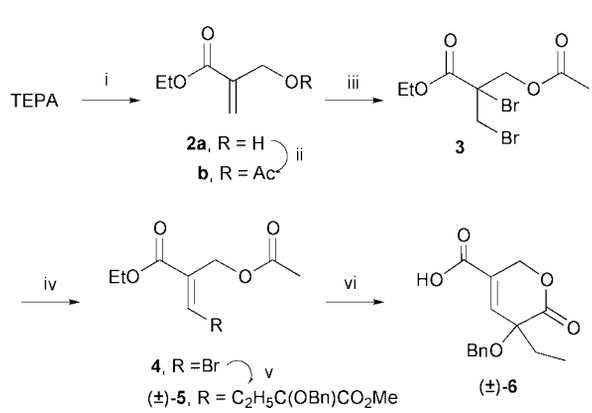
VI

this end, known[4] 4-oxo-δ-valerolactone (ternatolide) was prepared from furfuryl alcohol as previously described[5] for related lactones; however, all attempts to convert this material into the lactone ester **VI** were unsuccessful. Treatment with tris(methylthio)methyllithium yielded the γ-lactone from rapid translactonization of the initial adduct, while attempted palladium-catalyzed carbomethoxylation of the enol triflate† derivative resulted in degradation, most likely through lactone cleavage. In addition, the corresponding cyanohydrin could not be productively advanced. Several alternative approaches to **V**, such as through application of Rousseau and coworkers' three-component coupling[6] [eqn. (2)] or by modification of commercially available methyl coumalate, also proved unfruitful.



(2)

Fortunately, however, a convergent synthesis was eventually developed starting from methacrylate **2a**, easily available by a Baylis–Hillman[7] or Wittig–Horner[8] reaction, and 2-bromobutyric acid (Scheme 2). It was recognized that to reach **V** it was



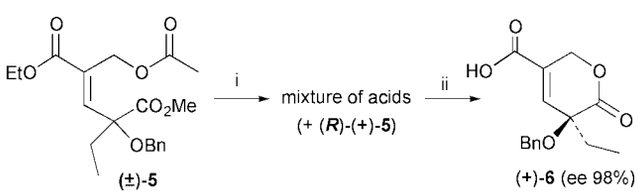
Scheme 2 *Reagents and conditions*: i, CH_2O, K_2CO_3, H_2O, 20 °C, 2 h; ii, Ac_2O, H_2SO_4(cat), Et_2O, 20 °C, 3 h; iii, Br_2, CH_2Cl_2, reflux, 53% from TEPA; iv, TBAF, HMPA, 20 °C, 24 h, 55–68%; v, LDA, $C_2H_5CH(OBn)CO_2Me$ (**7**), THF, −78 °C, 15 min, then **4**, −78 °C, 12 h, 69%; vi, LiOH, THF–H_2O, 20 °C, 12 h, 79%.

DOI: 10.1039/b109071m

only necessary to append, *E*-stereoselectively, a protected 2-hydroxybutyrate to the β-carbon of adduct **2a**. Therefore, methacrylate **2a**, in our hands best secured from triethyl phosphonoacetate (TEPA) and formaldehyde in the presence of potassium carbonate, was converted into its acetate **2b**. Compound **2b** was then treated with bromine in dichloromethane to provide the expected[9] dibromide **3** in 53% overall yield from TEPA. Pure (*E*)-β-bromo acrylate **4** was next secured stereoselectively with tetrabutylammonium fluoride in HMPA[9] in up to 68% yield. Other solvent–base combinations gave inferior yields and generated variable amounts of the corresponding *Z*-isomer in addition to various by-products, which complicated the purification.

Methyl 2-benzyloxybutyrate (**7**) could be readily prepared from 2-bromobutyric acid through reaction with benzyl alcohol in the presence of sodium hydride, followed by Fischer esterification (77% yield). After some experimentation, it was found that the conjugate addition–elimination reaction was best performed by using equimolar amounts of **4** and **7** and LDA as the base in THF at −78 °C. Under these conditions the desired adduct (±)-**5** to the exclusion of the allylic bromide was formed; this was fully expected on the basis of the substantially greater nucleofugal character of the bromide in comparison with the acetoxy group (69% yield). Again, only the *E*-derivative was produced. The desired lactone acid **6**, in racemic form, was next obtained in good yield from the triester through treatment with lithium hydroxide in aqueous THF.[10]

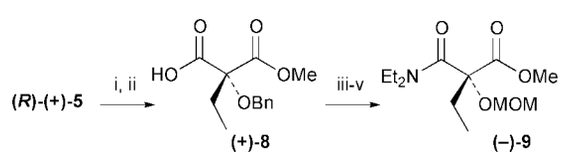
Triester (±)-**5** also proved a suitable precursor for the required (*S*)-lactone acid (Scheme 3). From (±)-**5**, with pig liver



Scheme 3 *Reagents and conditions*: i, PLE, pH 7 phosphate buffer, MeCN, 25 °C, 48 h, separation; ii, mixture of acids, LiOH, THF–H_2O, 20 °C, 12 h, recrystallisation, 98% ee, 34% of theory.

esterase (PLE)[11] in pH 7.0 phosphate buffer and acetonitrile at 25 °C for 48 h (55% conversion), a mixture of partially hydrolyzed products together with recovered (*R*)-(+)-triester was produced. The latter was converted into the (*R*)-(−)-lactone acid (75% ee‡). The former on saponification and recrystallization gave the required (*S*)-(+)-lactone acid (98% ee, ‡ 34% of theory, overall).

The assignment of configuration in the lactone acids was made by conversion of the recovered (*R*)-(+)-triester to the amide ester (−)-**9** of known[12] absolute stereochemistry (Scheme 4).



Scheme 4 *Reagents and conditions*: i, O_3, CH_2Cl_2, −78 °C, then Me_2S, −78 °C ⟶ 20 °C, 12 h, 55%; ii, $NaClO_2$, $Me_2C{=}CHMe$, NaH_2PO_4, *t*-BuOH–H_2O, 20 °C, 12 h, 86%; iii, 2-chloro-1-methylpyridinium iodide, Et_3N, Et_2NH, CH_2Cl_2, 20 °C, 24 h, 73%; iv, H_2, 10% Pd/C, EtOH, 20 °C, 6 h, 84%; v, $MeOCH_2Br$, *i*-Pr_2EtN, CH_2Cl_2, 20 °C, 48 h, 92%.

In summary, an effective synthesis of lactone acid (+)-**6** in highly enantio-enriched form has been realized as part of a novel approach to the camptothecinoids. Amides of the general structure **II**, readily prepared from this key compound, are at present being subjected to N4–C3, C14–C15 bicyclization tactics, the results of which will be disclosed at a later date.

Experimental

(±)-(*E*)-2-Acetoxymethyl-4-benzyloxy-4-ethylpent-2-ene-1,5-dioic acid 1-ethyl 5-methyl diester (±)-5

A solution of diisopropylamine (0.720 cm^3, 520 mg, 5.14 mmol) in THF (10 cm^3) at −30 °C under argon was treated with *n*-BuLi in hexanes (2.3 M, 2.16 cm^3, 5.0 mmol) and then stirred at 0 °C for 15 min, whereupon it was cooled to −78 °C, and ester **7** (936 mg, 4.49 mmol) dissolved in THF (4 cm^3) was added. The resulting solution was stirred for 15 min and then treated with a solution of bromide **4** (1.13 g, 4.50 mmol) in THF (6 cm^3). After being stirred at −78 °C for 12 h, the reaction mixture was processed in the usual manner and the crude product was purified by SiO_2 column chromatography with 30% Et_2O in pentane to provide (±)-**5** (1.17 g, 69%) as an oil. ν_{max}/cm^{-1} 1744, 1719, 1651, 1234; δ_H (300 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.5), 1.33 (3H, t, *J* 7.2), 1.90 (3H, s), 2.13 (2H, m), 3.82 (3H, s), 4.28 (2H, q, *J* 7.2), 4.48 (2H, ABq, J_{AB} 11.0, $\delta_A - \delta_B = 0.05$), 5.11 (2H, s), 7.36 (6H, m); δ_C (75.5 MHz, $CDCl_3$) 8.3, 14.5, 20.8, 32.4, 52.9, 58.4, 61.6, 67.6, 84.0, 127.5, 127.9, 128.6, 131.6, 138.1, 143.7, 166.2, 170.4, 172.1 [Found: $(M + H)^+$, 379.1783. $C_{20}H_{26}O_7$ + H requires *M*, 379.1757].

(±)-5-Benzyloxy-5-ethyl-6-oxo-5,6-dihydro-2*H*-pyran-3-carboxylic acid (±)-6

A solution of triester (±)-**5** (252 mg, 0.67 mmol) and LiOH·H_2O (185 mg, 4.41 mmol) in 20% aqueous THF–H_2O (20 cm^3) was stirred at 20 °C for 12 h. Usual treatment of the reaction mixture provided (±)-**6** (145 mg, 79%), mp 134 °C. ν_{max}/cm^{-1} 3483, 1751, 1713, 1668; δ_H (200 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.5), 1.96 (2H, m), 4.45 (2H, ABq, J_{AB} 10.6, $\delta_A - \delta_B = 0.12$), 5.10 (2H, AB of ABX, J_{AB} 17.5, J_{AX} 1.0, J_{BX} 2.1, $\delta_A - \delta_B$ = 0.16), 7.11 (1H, X of ABX), 7.31 (5H, m), 10.91 (1H, s); δ_C (50.3 MHz, $CDCl_3$) 7.6, 31.8, 67.1, 68.7, 76.6, 127.8, 127.9, 128.3, 128.7, 137.1, 141.6, 167.1, 169.1; *m*/*z* (CI) 294 (100) $(M + NH_4)^+$, 277 $(M + H)^+$ [Found: C, 65.3; H, 5.75. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%].

(*S*)-(+)-5-Benzyloxy-5-ethyl-6-oxo-5,6-dihydro-2*H*-pyran-3-carboxylic acid (+)-6

To a solution of triester (±)-**5** (943 mg, 2.49 mmol) in MeCN (7.0 cm^3) was added pH 7.0 phosphate buffer solution (35 cm^3) and pig liver esterase (1.35 cm^3, suspension in 3.2 M $(NH_4)_2SO_4$ solution, *ca.* 1800 units, Fluka). The reaction mixture was stirred vigorously at 25 °C for 48 h, whereupon volatiles were removed under vacuum and 10% NaOH was added. Et_2O extraction provided, following filtration of the crude material over SiO_2 with CH_2Cl_2, (*R*)-(+)-**5** (420 mg) $[\alpha]_D^{25}$ +9.0 (*c* 1.15, $CHCl_3$). The aqueous phase was then acidified with 5% HCl and extracted with Et_2O to give a mixture of acids (350 mg). A 348 mg sample of this mixture was treated with LiOH as described above to afford the lactone acid as a solid. The mother liquor from recrystallization (CH_2Cl_2–C_6H_{12}) of this material yielded (+)-**6** (118 mg, 34% of theory): mp 81–83 °C; $[\alpha]_D^{25}$ +79 (*c* 2.26, $CHCl_3$).

Acknowledgements

We thank Professor Y. Vallée, Dr P. Léon, and Dr B. Hartmann for their interest in our work, Professor K. J. Hale for some unpublished information, and Dr A. Tatibouët for some preliminary experiments. Financial support from the CNRS (UMR 5616) and Aventis Pharma and a fellowship award (to S. G.) from Aventis CropScience are gratefully acknowledged.

Notes and references

† The IUPAC name for triflate is trifluoromethanesulfonate.

‡ The enantiomeric excess was determined by HPLC of the corresponding ethyl ester: Chiralcel OD-H column, 5 mm, propan-2-ol–hexane = 10 : 90, 0.5 mL min^{-1}, T_r (*R*) 16.51 min, T_r (*S*) 18.09 min.

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