ChemComm

A short synthesis of camptothecin *via* a 2-fluoro-1,4-dihydropyridine

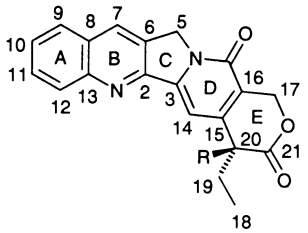
M.-Lluïsa Bennasar,* Cecília Juan and Joan Bosch

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain. E-mail: bennasar@farmacia.far.ub.es

Received (in Liverpool, UK) 19th September 2000, Accepted 1st November 2000
First published as an Advance Article on the web

Addition of the enolate derived from isopropyl α-(methylsulfanyl)butyrate to *N*-(quinolylmethyl)-2-fluoropyridinium triflate 7, followed by oxidation–hydrolysis of the resultant 2-fluoro-1,4-dihydropyridine 8b afforded pyridone 9b, from which 20-deoxycamptothecin (11), a known precursor of camptothecin, was synthesized by a radical cyclization–desulfurization, with subsequent elaboration of the lactone E ring by chemoselective reduction.

Camptothecin and 20-deoxycamptothecin[1] are pentacyclic alkaloids with a pyrrolo[3,4-*b*]quinoline nucleus fused to a 2-pyridone ring. First isolated by Wall *et al.* in 1966 from *Camptotheca acuminata*,[2] camptothecin has recently re-emerged as one of the most promising agents for cancer treatment, topoisomerasa I being identified as the intracellular target for the drug.[3] Due to this interesting cytotoxic activity, camptothecin and its structural derivatives have been the objective of many total syntheses using a variety of approaches.[4,5]



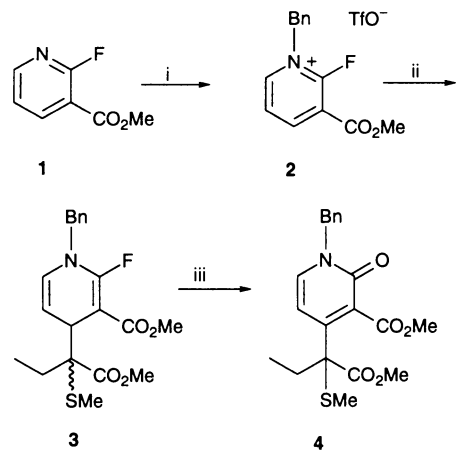
We present here a new, concise synthesis of (±)-20-deoxycamptothecin, a known synthetic precursor of camptothecin. Our approach involves the convergent construction of a suitably substituted and functionalized tetracyclic ABCD derivative **10** and the closure of the lactone E ring at the final synthetic step. For this purpose, we planned to take advantage of the synthetic potential of 1,4-dihydropyridines generated by nucleophilic addition of enolates to *N*-alkyl-3-acylpyridinium salts. In our previous work[6] these dihydropyridines have been further elaborated to complex polycyclic indole alkaloids either after acylation of the unsubstituted enamine moiety or *via* a dihydropyridinium cation generated by protonation or interaction with an electrophile.

For the synthesis of camptothecin we envisaged that, after the regioselective addition of a butyric ester enolate (the C_{18}–C_{21} fragment) to an appropriate *N*-(quinolylmethyl)-2-fluoropyridinium salt, the intermediate 2-fluoro-1,4-dihydropyridine could undergo a different transformation, namely an oxidation with concomitant hydrolysis of the C–F bond, leading to a 4-substituted-2-pyridone. Then, the quinoline and pyridone rings would be connected following the Comins procedure,[5*d–f*] by radical cyclization taking advantage of a bromine atom present at the 2-position of the quinoline nucleus. A methoxycarbonyl substituent at the β-position of the starting pyridinium would not only increase the electrophilicity of the pyridine ring in the nucleophilic attack but would also be subsequently converted to the C-17 oxymethylene group of the alkaloid.

To test the viability of our proposal for the construction of the pyridone moiety we first applied the nucleophilic addition–oxidation sequence to the model *N*-benzyl-2-fluoropyridinium salt **2** (Scheme 1). Knowing the reluctance of 2-halopyridines to undergo alkylation with alkyl halides and tosylates,[7] 2-fluoropyridinium salt **2** was prepared by alkylation of the corresponding 2-fluoropyridine **1**[8] with benzyl triflate. Without isolation, pyridinium triflate **2** was allowed to react with the enolate derived from methyl α-(methylsulfanyl)butyrate, which in related additions had exhibited better C-4 regioselectivity than the corresponding unsubstituted butyrate enolate.[9] Following our synthetic plan, the resulting 1,4-dihydropyridine adduct **3** was converted into the desired pyridone **4**[10] by oxidation with DDQ with hydrolysis of the C–F bond. The overall yield of the three-step sequence from 2-fluoropyridine **1** was 65%.

The application of the above strategy to the synthesis of camptothecin required starting from the pyridinium salt **7**, which incorporates the 2-bromoquinolyl-3-methyl fragment needed for the closure of the five-membered C ring. This salt was obtained by alkylation of 2-fluoropyridine **1** with triflate **6**, prepared from 2-bromo-3-(iodomethyl)quinoline (**5**).[11] Pyridinium triflate **7** was allowed to react as in the above *N*-benzyl series with the enolate derived from methyl α-(methylsulfanyl)butyrate and then with DDQ to provide pyridone **9a** in 50% overall yield from 2-fluoropyridine **1**. This pyridone already incorporates all the carbon atoms of the natural product. As expected, treatment of **9a** with tris(trimethylsilyl)silane–AIBN brought about both a radical arylation[12] and desulfurization to give the key tetracycle **10a** in 65% yield (Scheme 2).

The construction of the lactone E ring of camptothecin required the chemoselective reduction of the conjugate ester rather than the aliphatic one of **10a**. This transformation had already been reported from the diethyl ester analog **10c** by treatment with DIBAL (no details given).[5*k*] However, in our hands, the sequential treatment of **10a** with DIBAL–CH_2Cl_2 at −70 °C or DIBAL–THF at −40 °C and $NaBH_4$ gave the diol **12** as the only isolable product in 80% yield. Neither were we able to induce this transformation from diethyl ester **10c**, prepared in



Scheme 1 Model studies. *Reagents and conditions*: i, BnOTf, Et_2O, rt, 10 min; ii, methyl α-(methylsufanyl)butyrate, LDA, THF, −70 °C, then −40 to −10 °C, 1.5 h; iii, DDQ, 3:1 THF–MeOH, rt, 12 h.

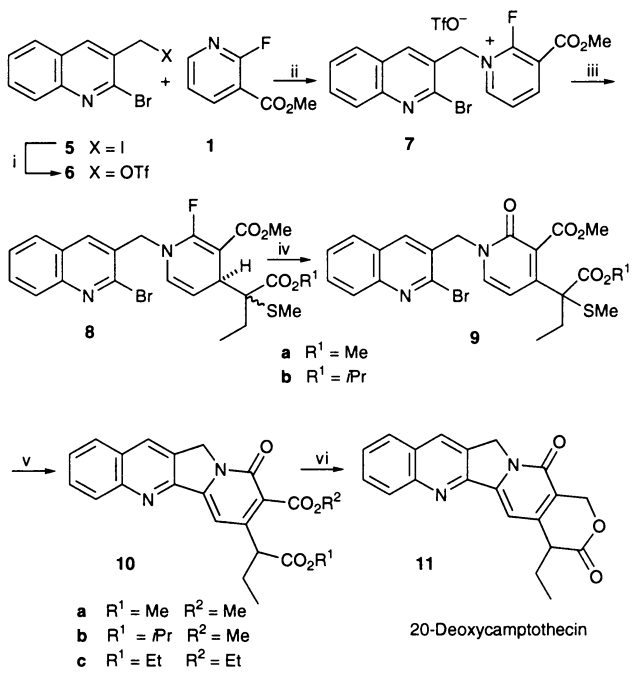
DOI: 10.1039/b007814j

90% yield by transesterification of **10a** (EtOH, KF, reflux, 3 days). Diol **12** was also formed as the major product in 75% yield.

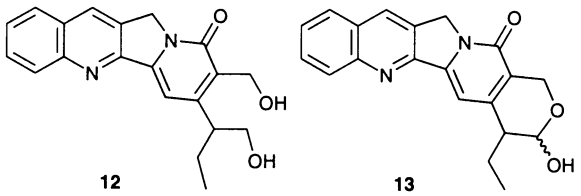
The above results prompted us to differentiate the two ester groups as in the pioneering Winterfeldt synthesis of camptothecin from a closely related tetracyclic substrate.[13] Thus, we focused our attention on tetracycle **10b**, which was prepared by reaction of pyridinium triflate **7** with the enolate derived from isopropyl α-(methylsulfanyl)butyrate, followed by DDQ oxidation (50% overall yield from **1**) and subsequent radical cyclization (65% yield). Gratifyingly, treatment of **10b** with DIBAL–hexanes in DME at −70 °C and then with $NaBH_4$ in isopropanol afforded a 1:1 mixture of the target lactone **11** (20-deoxycamptothecin)[5a] and lactol **13** (65% yield), which were easily separated by column chromatography. The conversion of lactol **13** into **11** (65% yield) has recently been reported.[5n] Taking into account that 20-deoxycamptothecin (**11**) has previously been converted by hydroxylation at C-20 either to racemic (Me_2NH, $CuCl_2$, O_2, DMF)[5a] or natural [(+)-(20*S*)]-camptothecin [LHDMS, THF, (+)-(2*R*,8a*S*)-(camphorylsulfonyl)oxaziridine],[5m] the above synthesis constitutes a formal total synthesis of this natural product.

The above results significantly expand the methodology for the synthesis of nitrogen compounds based on the addition of carbon nucleophiles to *N*-alkyl-3-acylpyridinium salts as they open new synthetic possibilities for the subsequent elaboration of the initially formed 1,4-dihydropyridine adducts.

Financial support from the DGICYT, Spain (project PB94-0214) is gratefully acknowledged. Thanks are also due to the



Scheme 2 Synthesis of (±)-20-deoxycamptothecin. *Reagents and conditions*: i, AgOTf, CH_2Cl_2, rt, 45 min; ii, CH_2Cl_2, rt, 1 h; iii, methyl or isopropyl α-(methylsufanyl)butyrate, LDA, THF, −70 °C, then −40 to −10 °C, 1.5 h; iv, DDQ, 3:1 THF–MeOH, rt, 12 h; v, TTMSS (2 equiv.), AIBN, C_6H_6, reflux, 4 h; vi, DIBAL–hexane (3 equiv.), DME, −70 °C, 30 min, then $NaBH_4$, iPrOH, rt, 1 h.



'Comissionat per a Universitats i Recerca' (Generalitat de Catalunya) for Grant 1999SGR00079 and for a fellowship to C. J.

Notes and references

1 C. R. Hutchinson, *Tetrahedron*, 1981, **37**, 1047.

2 M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail and G. A. Sim, *J. Am. Chem. Soc.*, 1966, **88**, 3888.

3 Y. Fan, J. N. Weinstein, K. W. Kohn, L. M. Shi and Y. Pommier, *J. Med. Chem.*, 1998, **41**, 2216, and references cited therein.

4 For synthetic references up to 1992, see: J. C. Cai and C. R. Hutchinson, in *Indoles, The Monoterpenoid Indole Alkaloids*, ed. J. E. Saxton, in *The Chemistry of Heterocyclic Compounds*, ed. A. Weissberger and E. C. Taylor, Wiley, New York, 1983, vol. 25, part 4, p. 753; M. E. Wall and M. C. Wani, in *Monoterpenoid Indole Alkaloids*, ed. J. E. Saxton, in *The Chemistry of Heterocyclic Compounds*, ed. E. C. Taylor, Wiley, Chichester, 1994, vol. 25, suppl. to part 4, p. 689.

5 For recent syntheses of camptothecin, see: (*a*) W. Shen, G. A. Coburn, W. G. Bornmann and S. J. Danishefsky, *J. Org. Chem.*, 1993, **58**, 611; (*b*) A. V. Rama Rao, J. S. Yadav and M. Valluri, *Tetrahedron Lett.*, 1994, **35**, 3613; (*c*) F. G. Fang, S. Xie and M. W. Lowery, *J. Org. Chem.*, 1994, **59**, 6142; (*d*) D. L. Comins, H. Hong, J. K. Saha and G. Jianhua, *J. Org. Chem.*, 1994, **59**, 5120; (*e*) D. L. Comins, H. Hoang and G. Jianhua, *Tetrahedron Lett.*, 1994, **35**, 5331; (*f*) D. L. Comins and J. K. Saha, *Tetrahedron Lett.*, 1995, **36**, 7995; (*g*) S. Jew, K. Ok, H. Kim, M. G. Kim, J. M. Kim, J. M. Hah and Y. Cho, *Tetrahedron: Asymmetry*, 1995, **6**, 1245; (*h*) J. M. D. Fortunak, J. Kitteringham, A. R. Mastrocola, M. Mellinger, N. J. Sisti, J. L. Wood and Z.-P. Zhuang, *Tetrahedron Lett.*, 1996, **37**, 5683; (*i*) N. Murata, T. Sugihara, Y. Kondo and T. Sakamoto, *Synlett*, 1997, 298; (*j*) M. A. Ciufolini and F. Roschangar, *Tetrahedron*, 1997, **53**, 11049; (*k*) S. P. Chavan and M. S. Venkatraman, *Tetrahedron Lett.*, 1998, **39**, 6745; (*l*) H. Josien, S.-B. Ko, D. Bom and D. P. Curran, *Chem. Eur. J.*, 1998, **4**, 67; (*m*) K. Tagami, N. Nakazawa, S. Sano and Y. Nagao, *Heterocycles*, 2000, **53**, 771; (*n*) R. T. Brown, L. Jianli and C. A. M. Santos, *Tetrahedron Lett.*, 2000, **41**, 859.

6 For a review, see J. Bosch and M.-L. Bennasar, *Synlett*, 1995, 587. For more recent work, see: M.-L.Bennasar, B. Vidal and J. Bosch, *J. Org. Chem.*, 1997, **62**, 3597; M.-L. Bennasar, J.-M. Jiménez, B. Vidal, B. A. Sufi and J. Bosch, *J. Org. Chem.*, 1999, **64**, 9605.

7 Y. Ban, R. Sakaguchi and M. Nagai, *Chem. Pharm. Bull.*, 1965, **18**, 931; A. P. Dobbs, K. Jones and K. T. Veal, *Tetrahedron Lett.*, 1997, **38**, 5833. See also J. A. Vega, J. J. Vaquero, J. Alvarez-Builla, J. Exquerra and C. Hamdouchi, *Tetrahedron*, 1999, **55**, 2317.

8 Prepared from 2-fluoropyridine and $ClCO_2Me$ according to the procedure reported by T. Güngör, F. Marsais and G. Queguiner, *J. Organomet. Chem.*, 1981, **215**, 139.

9 M.-L. Bennasar, E. Zulaica, C. Juan, L. Llauger and J. Bosch, *Tetrahedron Lett.*, 1999, **40**, 3961.

10 All new compounds were fully characterized by spectroscopic analysis (NMR) and gave satisfactory HRMS and/or combustion data.

11 Prepared by iodine–bromine exchange of 2-bromo-3-(bromomethyl)-quinoline D. L. Comins, M. F. Baevsky and H. Hong, *J. Am. Chem. Soc.*, 1992, **114**, 10971.

12 For the radical arylation of 2-pyridones, see R. Nadin and T. Harrison, *Tetrahedron Lett.*, 1999, **40**, 4073. See also reference 5*e*.

13 E. Winterfeldt, T. Korth, D. Pike and M. Boch, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 289; K. Krohn and E. Winterfeldt, *Chem. Ber.*, 1975, **108**, 3030.