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TOTAL SYNTHESIS OF DL-CAMPTOTHECIN FROM FURFURAL

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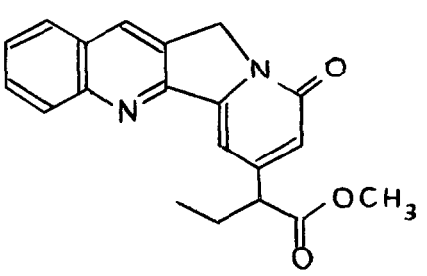
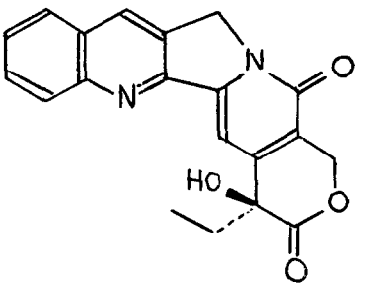
Continuing interest in a practical total synthesis[1] of the rare antineoplastic alkaloid camptothecin (II)[2] prompts us to report a new and regiospecific route to the tetracyclic ester I. Since ester I has been converted to DL-II in two steps,[3] the present work constitutes a formal total synthesis of the racemic alkaloid.

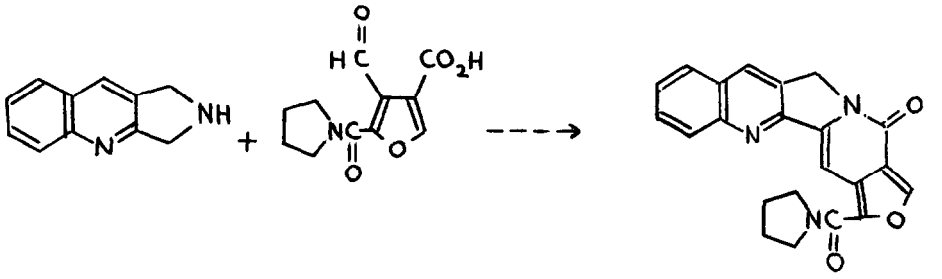


I



II

A key intermediate in our synthesis was the pentacyclic amide III, constructed in two steps by coupling of the readily available synthon A[4], with a blocked derivative of synthon B.

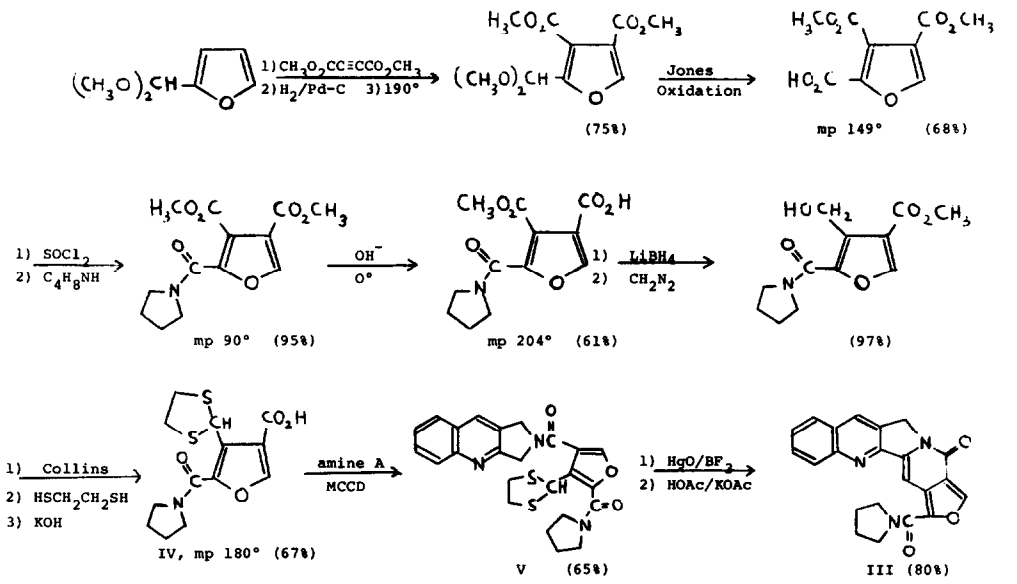


A B III

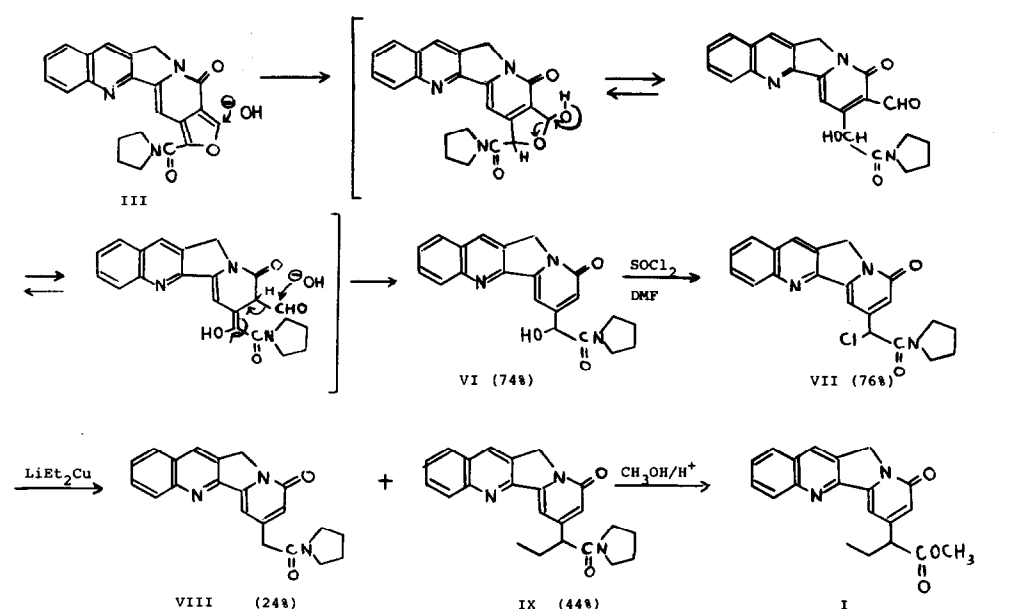
The appropriate form of synthon B, the acid IV, was prepared in six synthetic operations from furfuraldehyde dimethylacetal as shown in Scheme I.[5] Coupling of IV with amine A using the water-soluble reagent β-morpholinoethyl cyclohexylcarbodiimide metho-p-tosylate (MCCD) produced 65% of the amide V which was deblocked and cyclized to give 80% of the yellow crystalline pentacyclic amide III having $\lambda_{max}^{CH_3OH}$ 397, 378, 289 and 252 nm (ε_{max} 21,800, 22,100, 24,100, 37,400)[6].

Since the pentacyclic furopyridone III contains the full carbon skeleton of desethylcamptothecin extensive efforts were made to achieve mild cleavage of the furan ring by oxidation or acid hydrolysis. None of these experiments produced intermediates appropriate for direct elaboration of the E-ring. However, we found that III undergoes remarkably facile alkaline hydrolysis with loss of one carbon atom to yield 74% of the crystalline hydroxyamide VI (nmr: δ1.7-2.1, 4H, m; 3.2-3.7, 4H, m; 5.07, 1H, s; 5.15, 2H,s; 6.60, 1H,s; 7.2-8.3, 6H,m). This unusual ring opening and deformylation, perhaps by the mechanism shown, paved the way for completion of our synthesis as outlined in scheme II. Thus hydroxyamide VI was smoothly transformed into the chloroamide VII which at 0° was converted by $LiEt_2Cu$ in tetrahydrofuran to the ethyl derivative IX (nmr: δ0.96, 3H,t; 1.6-2.2, 6H,m; 3.3-3.8, 5H, m; 5.25, 2H,s; 6.65, 1H,s; 7.2-8.4, 6H,m) accompanied by the reduction product VIII (nmr: δ1.83-2.03, 4H,m; 3.4-3.83, 4H,m;

SCHEME I. SYNTHESIS OF PENTACYCLIC FUROPYRIDONE III



SCHEME II. SYNTHESIS OF TETRACYCLIC ESTER I



3.5, 2H,s; 5.23, 2H,s; 6.63, 1H,s; 7.25-8.4, 6H,m). Amide IX, isolated by preparative tlc, underwent clean methanolysis (CH_3OH-H_2SO_4, 5 days reflux) to yield the target methyl ester I, identical in all respects with a sample kindly provided by Professor S. Danishefsky.

The above sequence permits conversion of one mole of furfural into ca 9 grams of tetracyclic ester I in thirteen synthetic operations involving highly crystalline intermediates. Details of these and related studies as well as an alternative route to camptothecin from furopyridone III will be reported in our full paper.

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References

1. Total syntheses of DL-camptothecin include a) G. Stork and A. G. Schultz, J. Amer. Chem. Soc., 93, 4074 (1971); b) R. Volkmann, S. Danishefsky, J. Eggler and D. M. Solomon, J. Amer. Chem. Soc. 93, 5576 (1971); c) E. Winterfeldt, T. Korth, D. Pike and M. Boch, Angew. Chem. Intern. Ed. Engl., 11, 289 (1972); d) M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall and S. G. Levine, J. Amer. Chem. Soc., 94, 3631 (1972); e) C. Tang and H. Rapoport, J. Amer. Chem. Soc., 94, 8615 (1972); f) A. I. Meyers, R. L. Nolen, E. W. Collington, R. Strickland and T. A. Narwid, private communication. The vigorous research activity in this field has been thoroughly reviewed by A. G. Schultz, Chem. Revs. in press.

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

3. Reaction of I with paraformaldehyde in sulfuric acid effects lactomethylation; oxidation of the resulting lactone gives DL-camptothecin.[2b] Yields in this two step sequence are presently ca 24% overall. (S. Danishefsky, private communication.)

4. L. Zalkow, J. B. Nabors, K. French and S. C. Bisarya, J. Chem. Soc., (C). 3551 (1971).

5. All new substances gave satisfactory uv, ir, nmr and mass spectroscopic data; in addition, good combustion analyses were obtained on all compounds through V in the synthetic sequence.

6. Cf. the benzenoid counterpart, described by M. Shamma and L. Novak in Tetrahedron 25, 2275 (1969), which had λ_{max} 376, 363, 283 nm (log ε 4.52, 4.49, 4.34).