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A FACILE TWO SYNTHON APPROACH TO DEETHYLDEOXYCAMPTOTHECIN.

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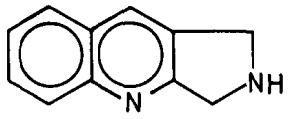
Although camptothecin (8b)[2] has been disqualified as a potential antitumor agent, considerable interest still exists in the development of a facile general synthesis of the alkaloid and its analogs. A new dimension to this interest has been added by the discovery that camptothecin acts as a selective inhibitor of the synthesis of ribosomal and messenger RNA's[3]. The strategy directed towards a general synthesis of camptothecin and its analogs, developed in our laboratory, consisted in the combination of two easily accessible synthons to give an intermediate which would contain the complete atomic architecture of the camptothecin skeleton and incorporate appropriate functionalities that should allow its facile elaboration to the alkaloid. Introduction of suitable modifications (substituents, other heterocyclic systems), especially in one of the synthons, e.g. 1, would provide the corresponding modified camptothecin analogs. A recent report[4] involving a similar approach[4] prompts us to present our own results on the total synthesis of deethyldeoxycamptothecin.

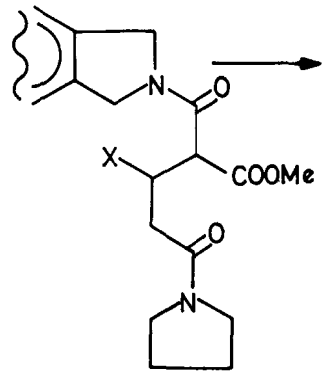
While the tricyclic synthon 1[5] has been described in the literature[6], the second synthon 2d, required for the scheme, was obtained as follows. Ethoxylactone 3, prepared by photooxidation of furfural[7a,b], underwent a smooth Michael addition of diethyl malonate to give trans adduct 4[8,9], (90%). PMR($CDCl_3$), 5,44 (d, $J_{4,5}$=2, C_5-H). Acid hydrolysis of 4 gave the bis-lactone 5[8], (68%) m.p. 140-140°.5) whose cis-stereochemistry was attested by its PMR spectrum. (CF_3COOH), 6.52 (d, $J_{4,5}$=6, C_5-H). Reduction of 5 ($NaBH_4$) under alkaline conditions[10] yielded acid 2a[10a-c] (m.p. 86-88°; 86.5-87°.5[11a], 85-86°[11c], which was converted, via its acid chloride 2b, to to the corresponding pyrrolidinyl amide 2c (m.p. 97-100°) in an overall yield of 59%. The latter was methoxycarbonylated to the required 2d (m.p. 106-108°.5, yield

73%) by treatment with sodiumhydride and dimethyl carbonate[10].

Although the product formed was a single isomer, the stereochemical assignment of the substituents on the lactone ring, in 2d, was complicated by the overlap of the chemical shifts of the C_3-, C_4- and the pyrrolidinyl α-CH_2-protons. δ($CDCl_3$) 3.25-3.55 (m, 6H). From the PMR of the corresponding pyrrolinyl amide it could be seen, that the C_3- and C_4-protons have about the same chemical shifts. δ($CDCl_3$) 3.45 (m, 2H). However, as will be seen in the sequel, a precise knowledge of the stereochemistry of 2d is not critical to the synthetic scheme. Condensation of the two synthons 1 and 2d led to the formation of hydroxyamide 6a in 58% yield; m.p. 175-177°; IR(KBr), 3400, 1730, 1635; PMR($CDCl_3$), 1.9(m, pyrrolidinyl β-CH_2-), 2.5-3.2 (m, C_{15}-H, C_{20}-H_2), 3.45(t, pyrrolidinyl α-CH_2-), 3.3-3.8(C_{14}-H_2), 3.71(s, -CH_3), 4.2-4.7(-OH), 4.3(m, C_{16}-H), 4.92(s, C_5-H_2), 5.2(m, C_3-H_2), 7.3-8.2(m, aromatic protons). It may be noted that 6a represents an intermediate which carries all the atoms of the camptothecin skeleton and is functionally poised for its conversion to deethyldeoxycamptothecin. The hydroxymethylene function of 6a was oxidized; (CrO_3/pyr., CH_2Cl_2) to the corresponding formyl group (6b, 72%, IR(KBr), 1750, 1730, 1660, 1640; PMR($CDCl_3$), 9.90(m, -CHO)) and the resulting aldehyde cyclized by refluxing in acetic acid/potassium acetate to a mixture of 7, yield 25%; m.p. 240-245°; IR(KBr), 1700, 1650, 1630, 1600; PMR($CDCl_3$), 1.95(m, pyrrolidinyl β-CH_2-), 3.51 (m, pyrrolidinyl α-CH_2-), 3.79(s, C_{20}-H_2), 3.94(s, -CH_3), 5.1(s, C_5-H_2), 7.25(m, C_{14}-H), 7.45-8.3(m, aromatic protons); UV(C_2H_5OH), 372(18.300), 289(5270), 256(26700), 215(38600), and the corresponding dihydro product (58%)[12]. Reduction of the ester function in 7 ($LiBH_4$/DME, RT) followed by treatment with conc. HCl yielded crystalline deethyldeoxycamptothecin 8a, (10%, overall[13]) IR(KBr) 1730, 1650, 1590[14a].; PMR(D_6-DMSO), 3.77(s, C_{20}-H_2), 5.15 and 5.21(s, C_5-H_2, C_{17}-H_2), 7.10(s, C_{14}-H), 7.4-8.5(m, aromatic protons); UV(C_2H_5OH), 218, 254, 288, 366 (qualitative); M^+, 304 (100%). Since the conversion of 8a to deoxycamptothecin has been reported by several workers[14a-c] and deoxycamptothecin itself has been successfully transformed to camptothecin[15a,b], the present synthesis of 8a also formally represents a total synthesis of dl-camptothecin.



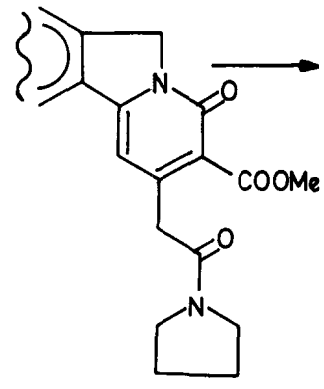
1



6

a X= CH_2OH

b X= CHO



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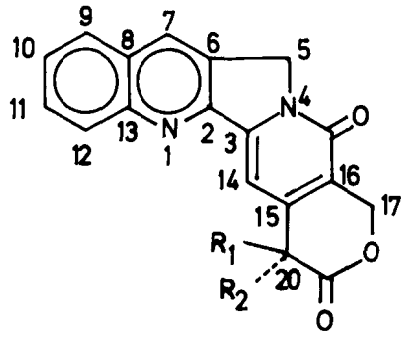
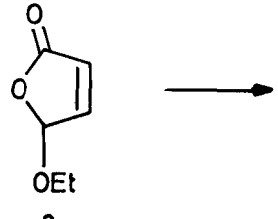


8

a· $R_1 = R_2 = H$

b· R_1 =OH, R_2 = Et



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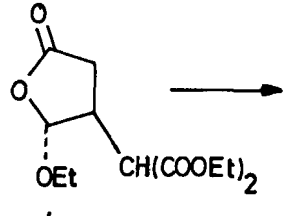

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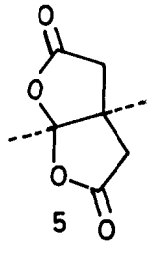

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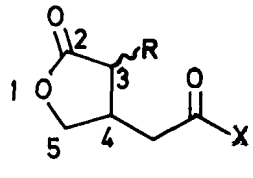

2

	R	X
a	H	OH
b	H	Cl
c	H	N $(CH_2)_4$
d	COOMe	N $(CH_2)_4$

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1. Taken in part from the forthcoming doctorate thesis of H.G.M. Walraven, University of Amsterdam.

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12. The dihydro compound is the primary product of the reaction. It is, however, oxidized during the workup to 7. This transformation was established independently. IR(KBr), 1725, 1670, 1630; PMR($CDCl_3$), 5.04(s, C_5-H_2), 6.33(d, $J_{14,15}$= 4.5, C_{14}-H).

13. No attempts have been undertaken to optimalize these steps.

14a. IR spectrum of 8a was identical to that of the sample of deethyldeoxycamptothecin synthesized by Meyers et.al. J. Org. Chem., 38, 1974 (1973). We wish to thank Dr. A.I. Meyers for providing us the tracings of the IR and NMR spectra.
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