yields to the **a** series analog. Reaction of **23** with NBS–CCl_4 afforded the dibromide **24** which was lactonized to **25** (mp 175–176°) with aqueous H_2SO_4–monoglyme. Catalytic dehalogenation[10] followed by chromatography gave two fractions; the major product was bromopyridone **26** (mp 169–170°) and the minor product was the debromo analog of **26**. Finally, oxidation of each as described for the **a** series gave the CDE ring analog **27** (mp 195–197°) and debromo-**27** (mp 175–177°).

(24) National Institutes of Health Predoctoral Fellow.

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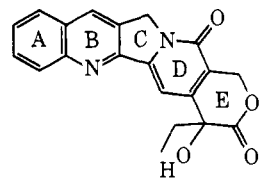
A Total Synthesis of *dl*-Camptothecin

Sir:

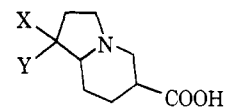
The initial report of potent antileukemic and antitumor activity of the novel alkaloid camptothecin (**1**), whose isolation and structure determination were reported[1] in 1966, has been followed by several total syntheses of this important compound.[2] Recently, there was reported[3] from this laboratory a broadly applicable synthesis of a series of analogs of camptothecin containing the fused pyridone-lactone DE ring system of the parent alkaloid. We now wish to present an extension of this synthetic procedure to the total synthesis of *dl*-camptothecin.

The previously reported syntheses[2] involved formation of the pyridone D ring *via* cyclization followed by elaborations on the pyridone ring, generally effected through Michael-type additions either before or after D ring formation. The route we are presenting has the pyridone D ring intrinsically built into the starting material, pyridine-2,5-dicarboxylic acid. Subsequent methylene lactam rearrangement of a nipecotic acid[4] gives the desired piperidone. The main feature of our synthesis is a facile series of alternate rearrangement–oxidation reactions, proceeding in good yields and culminating in a practical preparation of *dl*-camptothecin.

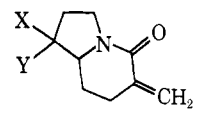
The bicyclic keto acid **2**, obtained[3] in 85% yield from pyridine-2,5-dicarboxylic acid, was reduced by sodium borohydride in methanol–water (0°, 18 hr) to the hydroxy amino acid **3**,[5] obtained in 86% yield after purification by ion exchange. α-Methylene lactam rearrangement[4] in acetic anhydride (145°, 2.5 hr) gave, after chromatography on silica gel, an 84% yield of the piperidone acetate **4** as a mixture of isomers. This mixture was subjected to SeO_2 oxidation in glacial acetic acid (70°, 1 hr), and chromatography gave a 58% yield of the allylic diacetate **6**. Hydrolysis of this diacetate **6** in anhydrous methanol–K_2CO_3 (20°, 30 min) to the diol **7**, *m/e* 183, was achieved quantitatively.



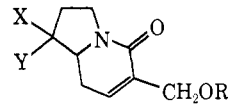
1



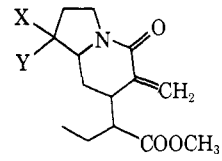
2, X,Y = O
3, X = H; Y = OH

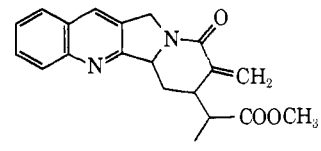


4, X = H; Y = $OCOCH_3$
5, X,Y = O



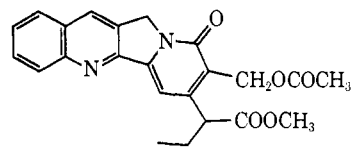
6, X = H; Y = $OCOCH_3$; R = $COCH_3$
7, X = H; Y = OH; R = H



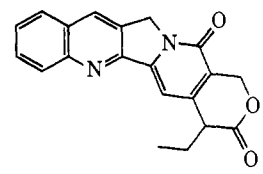


8, X = H; Y = $OCOC_3H_7$
9, X = H; Y = OH
10, X,Y = O

11



12



13

Introduction of the α-butyrate side chain was accomplished by Claisen rearrangement,[6] utilizing diol **7** and excess trimethyl orthobutyrate with a catalytic amount of propionic acid at 145° for 3 hr. The crude reaction mixture was distributed between methylene chloride and dilute aqueous hydrochloric acid and evaporation of the methylene chloride phase gave a 75% yield of material containing the α-butyrate side chain. This material was a mixture of the free alcohol **9** and its butyrate ester **8**. Treatment with anhydrous K_2CO_3 in methanol (20°, 1 hr) and chromatography on silica gel with 5% methanol–chloroform gave the alcohol **9**, obtained as a mixture of isomers in 100% yield.

To introduce the AB ring system it was now necessary to oxidize the alcohol **9** to ketone **10** in preparation for a Friedlander quinoline synthesis. This was effected by oxidation of the alcohol **9** with dicyclohexylcarbodiimide in DMSO with a catalytic amount of phosphoric acid[7] (20°, 30 hr) giving, after chromatography,

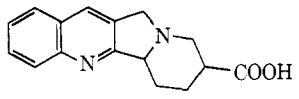
(1) M. E. Wall, M. G. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966).
(2) (a) G. Stork and A. G. Schultz, *ibid.*, **93**, 4074 (1971); (b) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **93**, 5576 (1971); (c) M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, and M. E. Wall, *ibid.*, **94**, 3631 (1972); (d) M. Boch, T. Korth, J. M. Nelke, D. Pike, H. Radunz, and E. Winterfeldt, *Chem. Ber.*, **105**, 2126 (1972).
(3) J. J. Plattner, R. D. Gless, and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 8613 (1972).
(4) M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 3877 (1972).
(5) All new compounds were characterized as to purity by tlc or gc, and their ir and nmr spectra support the assigned structures. Elemental compositions were established by high-resolution mass spectra, combustion analyses, or both. A number of compounds were obtained as isomeric mixtures, but these were not separated since they converged after compound **11**.
(6) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, **92**, 741 (1970).
(7) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **85**, 3027 (1963).

a 76% yield of the ketone **10**. Friedlander condensation between the keto ester–α-methylene lactam **10** and *N*-(2-aminobenzylidene)-*p*-toluidine[8] gave a 75% yield of the tetracyclic α-methylene lactam **11**,[9] containing the indolizino[1,2-*b*]quinoline ring system and having ultraviolet absorption typical for such a substituted quinoline (319, 312, 306, 298, 293, 288, 234 nm).

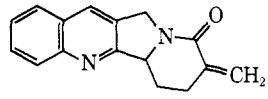
The remaining tasks were aromatization of ring D and formation of the α-hydroxylactone ring E. Both aromatization and formation of the necessary primary allylic alcohol were accomplished in one step by SeO_2 oxidation of α-methylene lactam **11** in glacial acetic acid (80°, 30 min) to the α-acetoxymethylpyridone **12** (uv 370, 290, 253 nm). Hydrolysis–lactonization of **12** in 2 *N* H_2SO_4–glyme at 50° for 5 hr gave a 72% yield of deoxycamptothecin (**13**) from **11**: mp 262–264° dec; uv 370, 290, 253 nm. Oxidation of deoxycamptothecin ($CuCl_2$–DMF–O_2)[2d] is accomplished in quantitative yield to give *dl*-camptothecin (**1**) whose tlc, and uv, nmr, and high-resolution mass spectra are identical with those of the natural product.[10] Although a detailed development of the individual steps has not been made, we have thus obtained *dl*-camptothecin in an overall yield of 11% starting from pyridine-2,5-dicarboxylic acid.

(8) T. K. Liao, W. H. Nyberg, and C. C. Cheng, *J. Heterocycl. Chem.*, **8**, 373 (1971).

(9) The AB rings in camptothecin can be incorporated at earlier stages. Thus, *via* the Friedlander condensation, we have obtained compound i from keto acid **2** and compound ii from the keto-α-methylenepiperidone **5** (prepared by hydrolysis of acetate **4** followed by DCC–DMSO oxidation[7]). These compounds may be further elaborated to camptothecin, and these processes will be reported in detail in the future.



i



ii

(10) Obtained from young (90 day) *C. acuminata* plants by Dr. G. Sheriha. These plants were grown from seeds kindly provided by Mr. R. L. Smith and Dr. R. Perdue of the U. S. Department of Agriculture.

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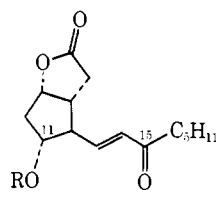
Efficient Generation of the 15*S* Configuration in Prostaglandin Synthesis. Attractive Interactions in Stereochemical Control of Carbonyl Reduction

Sir:

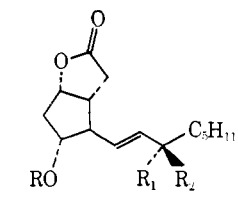
One of the most fascinating problems in the area of prostaglandin synthesis has been the development of synthetic approaches which control stereochemistry, particularly at C-15.[1] We have been interested for some time in devising a method to effect the conversion of I to II (15*S*)[2] with high stereoselectivity. This communication reports a rational attack on this problem.

(1) See, for example: (a) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 1491 (1971); (b) C. J. Sih, R. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *ibid.*, **94**, 3643 (1972); (c) E. J. Corey and T. Ravindranathan, *ibid.*, **94**, 4013 (1972); (d) E. J. Corey and P. L. Fuchs, *ibid.*, **94**, 4014 (1972); (e) J. Fried, J. C. Sih, C. H. Lin, and P. Dalven, *ibid.*, **94**, 4343 (1972); (f) R. Pappo and P. W. Collins, *Tetrahedron Lett.*, 2627 (1972).

(2) Prostanoic acid numbering.

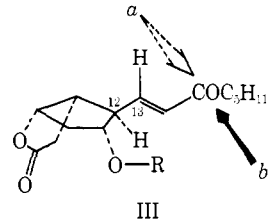


I

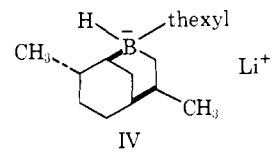


II(15*S*), R_1 = OH; R_2 = H
II(15*R*), R_1 = H; R_2 = OH

The reduction of I with R = CH_3CO, $CH_3(CH_2)_7CO$, or *i*-$Pr(CH_3)_2Si$ using borohydride type reagents, *e.g.*, $NaBH_4$–C_2H_5OH at −30° or $Zn(BH_4)_2$–dimethoxyethane at 0° or various lithium trialkylborohydrides ($R_1R_2R_3BH^-Li^+$) at <−90°, affords II with a ratio 15*S*/15*R* of between 50/50 and 60/40. Similarly the 11-deoxy derivatives of I or $\Delta^{10(11)}$-dehydro-11-deoxy-I are reduced by these hydrides to equal mixtures of 15*S* and 15*R* alcohols. One reason for the difficulty in achieving selective reduction of I is the occurrence of both s-cis and s-trans conformations of the enone unit in I as can be seen from the infrared spectra of esters of structure I with varying R which manifest enone carbonyl absorption (in $CHCl_3$ at 25°) as a doublet of comparably intense bands at 5.90 (s-cis) and 5.97 μ (s-trans).[3] Even assuming that the ketone I adopts a trans coplanar arrangement of hydrogen at C-12 and C-13 as shown in III, stereospecificity of carbonyl reduction would demand not only a preferred direction of hydride attack (axis *a* or *b*) but also a single enone conformation. Therefore, it is not sufficient merely to choose a group R of sufficient steric bulk to block approach along axis *b*, but it is also necessary to control the enone conformation as s-cis in order to direct the formation of 15*S* alcohol.



III



IV

In an earlier phase of this work[1a] the derivatives I and II were prepared in which R = *p*-phenylbenzoyl, and it was found that this protecting group was advantageous since (1) the intermediates in the synthesis were nicely crystalline, (2) the 15*S* and 15*R* forms of II were readily separable by chromatography, and (3) the ultraviolet chromophore simplified analytical and chromatographic work. It was subsequently discovered[1a] that the reduction of I, *p*-phenylbenzoyl, favored formation of 15*S* alcohol to a larger degree than was observed with screening groups at C-11, *e.g.*, R = $CH_3(CH_2)_7CO$. Using the reagent IV[1a] in tetrahydrofuran–ether–pentane at −120 to −130°, it was possible to convert I, R = *p*-$C_6H_5C_6H_4CO$, to a mixture of 15*S* and 15*R* alcohols in a ratio of 82:18.[1a,4,5]

(3) See K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

(4) The reagent IV is superior to all other trialkylborohydrides which have been tested so far for the selective formation of (15*S*)-II. The following reagents of the type $R_1R_2R_3BH^-Li^+$ have been found to give the 15*S*/15*R* ratios indicated: dicyclohexyl-*tert*-butyl (59/41); dicyclohexyltrityl (64/36); diisopinocamphenenylmethyl (68/32); triphenyl (67/33); tri-*exo*-2-norbornyl (59/41); diisobutyl-*tert*-butyl (74/26); di-*sec*-butylthexyl (80/20); tri-*sec*-butyl (78/22). In addition, IV yielded considerably higher ratios of 15*S*/15*R* II than did various cyclic boro-