generated by solvolysis give stereochemical results which differ from those we have found.[2] Although trans additions to acetylenes have frequently been explained by ion-pair mechanisms,[13] trans addition is not the inevitable pathway, as illustrated by the CF_3SO_3D addition to 1-hexyne, described above. Peterson and Duddey[14] have shown that trifluoroacetic acid adds to 3-hexyne at 60° to give nearly equal amounts of (*E*)- and (*Z*)-hex-3-en-3-yl trifluoroacetates. We have studied the addition of trifluoroacetic acid to 2-butyne and to 1,2-butadiene at 75°. In both cases (*E*)-II-$OOCCF_3$ predominated over (*Z*)-II-$OOCCF_3$ by a ratio of 3.3. An even more striking stereochemical preference for the attack of the but-2-en-2-yl cation cis to the β-methyl group has been observed with carbon monoxide in superacid.[15]

The buffered acetolyses of alkyl-substituted vinyl triflates tend to proceed with predominate, but not exclusive, inversion in the substitution products. We conclude that ion-pair SN1 mechanisms with the leaving group blocking the front side probably best account for these results.

Acknowledgments. This work was supported by grants from the National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, and Hoffmann-La Roche, Nutley, N. J. The program of research in vinyl triflates at Princeton has benefited from collaborative effects with Professor P. J. Stang, Utah, and Professor M. Hanack, Saarbrücken. We thank Dr. R. L. Hansen of the 3M Company for samples of trifluoromethanesulfonic acid, and Professor R. G. Bergman for his comments.

(13) R. C. Fahey, *Top. Stereochem.*, **3**, 237 (1968).
(14) (a) P. E. Peterson and J. E. Duddey, *J. Amer. Chem. Soc.*, **85**, 2865 (1963); (b) P. E. Peterson and J. E. Duddey, *ibid.*, **88**, 4990 (1966).
(15) H. Hogeveen and C. F. Roobeck, *Tetrahedron Lett.*, 3343 (1971).
(16) National Science Foundation Predoctoral Fellow, 1969–1972.

R. H. Summerville,[16] P. v. R. Schleyer*
Department of Chemistry, Princeton University
Princeton, New Jersey 08540
Received January 22, 1972

Plant Antitumor Agents. IX. The Total Synthesis of *dl*-Camptothecin[1]

Sir:

In 1966 a communication from this laboratory described the isolation and structure of a novel alkaloid camptothecin (**1**).[2] Initial promising reports of excellent antitumor activity[2,3] and encouraging clinical data[4,5] have stimulated wide interest in the synthesis of comptothecin and analogous compounds.[6] These efforts have culminated in two recent reports of the total synthesis of camptothecin.[7,8] We wish to report at this time an independent synthesis based on rather different principles. Some features of this synthetic procedure are also adaptable to the preparation of camptothecin analogs.[9]

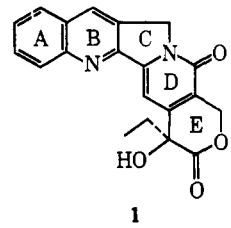
The key step in our approach involves the Michael condensation of 1,3-dihydro-2-methoxycarbonyl-2*H*-pyrrolo[3,4-*b*]quinoline (**2**) with methyl 3-methylene-2-methoxycarbonyl-4-oxohexanoate (**3**).[9] The compound **2**[10] (mp 185–186°) was prepared in quantitative yield by the reaction of the corresponding amine[11] with methyl chloroformate in dilute sodium carbonate solution.

The Michael condensation[12] of **2** and **3** at 110° without added catalyst gave **4** as a viscous oil (81%) after chromatography on silica gel. Introduction of the additional carbon atom needed for the elaboration of ring E of camptothecin and protection[13] of the ketone function were achieved in one step by the reaction of **4** with liquid hydrogen cyanide in the presence of a catalytic amount of potassium cyanide. The intermediate cyanohydrin spontaneously lactonized to give a mixture[14] of isomeric cyano lactones **5** in 82% yield. Treatment of **5** with methanolic hydrogen chloride (25°, 2 days) gave the amide **6** as a mixture of diastereomers[13,14] in 76% yield.

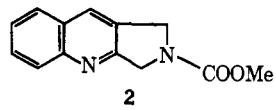
The next crucial step involved the selective removal of the *N*-carbomethoxy function in the presence of the sensitive amide and ester functions in **6** in order to construct the D ring of camptothecin. Hydrogen bromide in glacial acetic acid has been used for the selective removal of an *N*-carbobenzyloxy group without affecting an amide or ester function in peptides.[15] It was felt that the *N*-carbomethoxy group could also be removed under these conditions without affecting the ester and amide functions in **6**. Selective removal of the *N*-carbomethoxy group could indeed be accomplished by the treatment (25°, 18 hr) of **6** with glacial acetic acid saturated with hydrogen bromide. Basification (pH 8) of the dihydrobromide of **7** with sodium methoxide in methanol at 0° followed by refluxing (4 hr) in benzene yielded a mixture of lactams **8** (17%, mp 289–290°) and **9** (32%, mp 220–223°) separable by preparative tlc. The latter could be lactonized in nearly quantitative yield by refluxing (6 hr) in benzene in the presence of half its weight of *p*-toluenesulfonic acid.

(1) Previous paper in this series: M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, and A. T. McPhail, *J. Amer. Chem. Soc.*, **93**, 2325 (1971).
(2) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *ibid.*, **88**, 3888 (1966).
(3) For a review article describing the antitumor and antileukemic activity of camptothecin and a number of its derivatives *cf.* M. E. Wall, Abstracts, 4th International Symposium on the Biochemistry and Physiology of Alkaloids, Halle, DDR, Academic Press, Berlin, 1969, p 77.
(4) J. A. Gottlieb, A. M. Quarino, J. B. Call, V. T. Oliverio, and J. B. Block, *Cancer Chemother. Rep.*, **54**, 461 (1970).
(5) Subsequent clinical studies carried out under the sponsorship of Drug Research and Development, National Cancer Institute, National Institutes of Health, have proved considerably less encouraging but full studies of this compound have been hampered because of the limited availability of camptothecin from natural sources.
(6) For a complete listing of all the publications in this field see ref 7.
(7) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Amer. Chem. Soc.*, **93**, 5576 (1971).
(8) G. Stork and A. Schultz, *ibid.*, **93**, 4074 (1971).
(9) M. E. Wall, H. F. Campbell, M. C. Wani, and S. G. Levine, *ibid.*, **94**, 3632 (1972).
(10) The ir, nmr, and high-resolution mass spectra of all new compounds are consistent with assigned structures.
(11) M. C. Wani, J. A. Kepler, S. G. Levine, and M. E. Wall, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., 1968, No. MEDI 16. It is a pleasure to thank Dr. R. E. Engle of Drug Research and Development, National Cancer Institute, National Institutes of Health, for supplying us with a large sample of the dihydrobromide of **8**.
(12) M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *J. Chem. Soc. D*, 404 (1970).
(13) Generation of the free amine in the presence of the keto group of **4** or the cyano group of **5** led to undesired side reactions.
(14) A preparative tlc of this mixture yielded two products. The high-resolution mass spectra, combustion analyses, ir, and uv spectra of both these products were consistent with their formulation. However, these products still appear to be mixtures of diastereomers on the basis of their complex nmr spectra and melting point behavior.
(15) R. A. Boissonnas, *Advan. Org. Chem.*, **3**, 159 (1963).

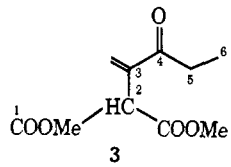
Dehydrogenation of **8** with dichlorodicyanoquinone in refluxing *p*-dioxane (4 hr) proceeded in high yield to give the pyridone **10**[16] (mp >310°). Reduction of **10**



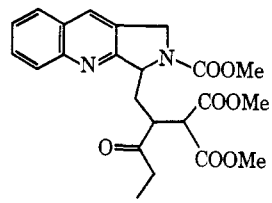
1



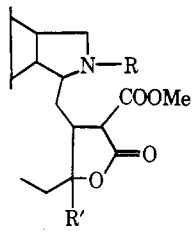
2



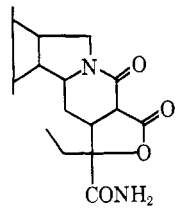
3



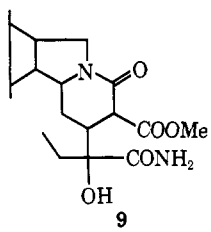
4



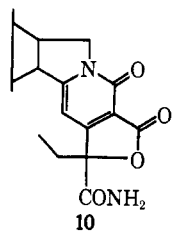
5, R = COOMe; R′ = CN
6, R = COOMe; R′ = $CONH_2$
7, R = H; R′ = $CONH_2$



8



9



10

with lithium borohydride in refluxing (6 hr) tetrahydrofuran, followed by acidification with dilute hydrochloric acid and heating (0.5 hr) on a steam bath, gave *dl*-camptothecin whose tlc properties and low-resolution mass spectrum were identical with those of the natural material.

Acknowledgments. We wish to thank Dr. David Rosenthal and Mr. Fred Williams of the Research Triangle Center for Mass Spectrometry for mass spectral data. Their work was supported by the Biotechnology Resources Branch, Division of Research Resources, National Institutes of Health, under Grant No. PR-330. We wish also to thank Mr. J. B. Thompson for expert technical assistance. Dr. Campbell was supported by NIH Grant No. CA 08673-05.

(16) For preparative purposes the sequence of reactions leading to the synthesis of **10** from **4** could be accomplished without chromatography.

M. C. Wani,* H. F. Campbell, G. A. Brine
J. A. Kepler, Monroe E. Wall
Chemistry and Life Sciences Division, Research Triangle Institute
Research Triangle Park, North Carolina 27709

S. G. Levine
Department of Chemistry, North Carolina State University
Raleigh, North Carolina 27607
Received February 18, 1972

Plant Antitumor Agents. X. The Total Synthesis of a Ring DE Analog of Camptothecin[1]

Sir:

Since the initial communication from this laboratory on the isolation, structure, and antitumor activity of the novel alkaloid, camptothecin[2] (**1**), there has been much interest in the chemistry and synthesis of this interesting compound culminating in three recent total syntheses.[1,3,4] Several years ago Wall[5] reviewed the structure–function activity in the camptothecin series and showed that the α-hydroxy lactone moiety in camptothecin was an absolute requirement for antitumor activity. In an attempt to delineate the parameters of the molecule required for activity we have instituted a systematic approach to the synthesis of camptothecin analogs which will incorporate the requisite α-hydroxy lactone moiety. This report presents the first total synthesis of a ring DE analog **13** which has also potentialities for further elaboration to **1** and also describes the preparation of intermediates useful for a variety of syntheses in the camptothecin series.

3-Pentanone was brominated in aqueous bromine in the presence of potassium chlorate[6] to yield the known 2-bromo-3-pentanone,[7] which on treatment with potassium dimethyl malonate in dimethylformamide yielded methyl 2-carbomethoxy-3-methyl-4-oxohexanoate[8] (**2**), bp 69–70° (0.005 mm), in 85% yield. Bromination of **2** as the sodium salt under special anionic conditions[9] in the presence of sodium hydride in dimethoxyethane smoothly yielded the 2-bromo ketone[10] **3**, which without purification[11] was immediately dehydrobrominated in refluxing pyridine, giving a mixture of the exo olefin **4** and the endo olefin **5**, ratio 65/35[12] (bp 79–82° (0.02 mm)) in 50% yield from **2**. The olefinic mixture was suitable for the next step which involved a Michael condensation of nitromethane with the olefin mixture in the presence of Triton B in re-

(1) Previous paper in this series: 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).

(2) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *ibid.*, **88**, 3888 (1966).

(3) G. Stork and A. Schultz, *ibid.*, **93**, 4074 (1971).

(4) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **93**, 5576 (1971).

(5) M. E. Wall, Abstracts, 4th International Symposium on the Biochemistry and Physiology of Alkaloids, Halle, DDR, Academic Press, Berlin, 1969, p 77.

(6) J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(7) H. Pauly, *Chem. Ber.* **34**, 1771 (1901).

(8) The ir, nmr, and high-resolution mass spectra of all new compounds are consistent with assigned structures.

(9) Specific reaction conditions: a solution of **3** in dry dimethoxyethane (DME) is added to a 15–20% excess of sodium hydride in DME chilled in an ice bath. After hydrogen evolution ceases, an equivalent quantity of bromine in DME is added dropwise. As soon as bromine color persists, the addition of bromine is stopped, salts are filtered, and solvent is evaporated *in vacuo* at room temperature.

(10) For our purposes either the 2-bromo or 3-bromo derivative of **2** was suitable for conversion to the requisite olefin **4** or **5**. Under standard acidic bromination conditions only the undesired 5-bromo derivative was obtained contrary to the general expectation that substitution of bromine adjacent to a ketone takes place on the most substituted carbon atom (*cf.* H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 146–147). In this case steric hindrance at position 3 may rationalize the observed findings.

(11) The bromo ketone **3** was unstable and could not be distilled without extensive decomposition.

(12) The olefinic mixture could not be separated by fractional distillation; the ratio of the isomers was readily determined by pmr spectroscopy.