Supplementary Material Available. A listing of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

References and Notes

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(7) Two other GLC columns successfully used were 1% OV210 on Chromosorb G (6 ft × 2 mm), 100°C, and 2% SP2100 on Chromosorb W (6 ft × 2 mm), 150°C.
(8) We wish to thank Givaudan Corporation for generous gifts of bisabolene and Oil of Myrrh.
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A Short Synthesis of Camptothecin

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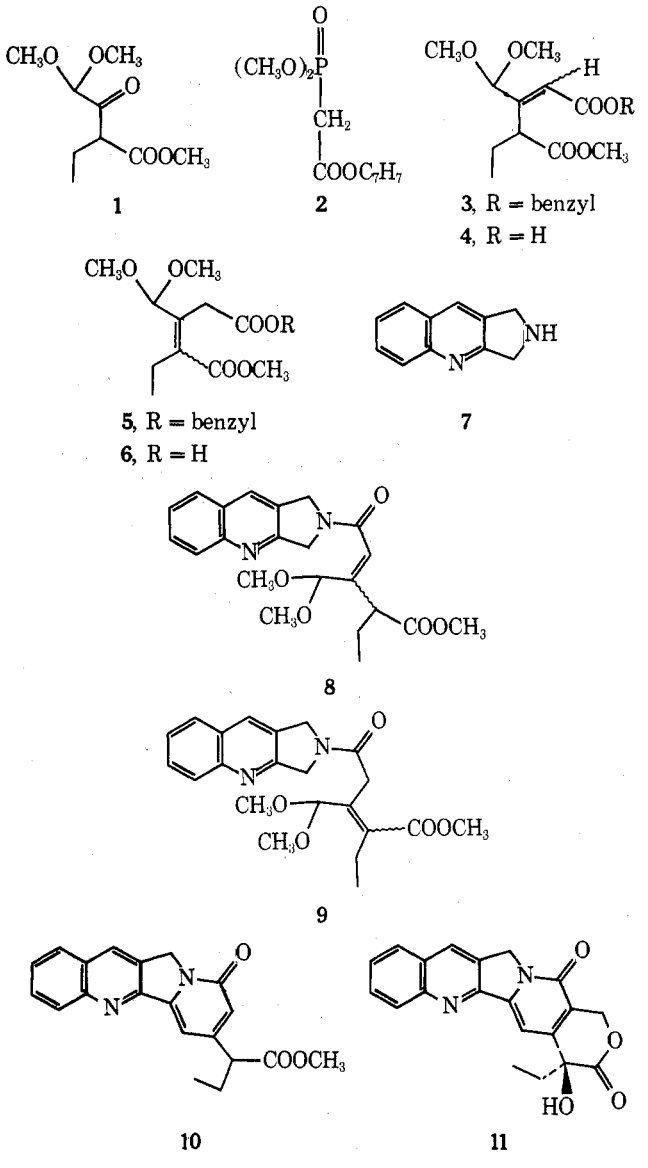
Camptothecin is an alkaloid first isolated from *Camptotheca acuminata*, a tree native to mainland China.[1] Structure **11** was established by x-ray crystallographic analysis of the iodoacetate.[2] Early clinical trials revealed promising antileukemic and antitumor properties causing many laboratories to commence work on total syntheses. Although subsequent testing uncovered the high toxicity of the compound, there is renewed interest in its inhibitory effect on macromolecular synthesis.[3] The first total synthesis of camptothecin (**11**) was completed in 1971[4] and since then a large number of successful approaches have been published.[5] All schemes thus far involve many steps and give low overall yields. In this note we describe another approach, although still not ideal, which does lead to intermediate **10** in five steps with an overall yield of 27%. This tetracyclic pyridone has previously been transformed to camptothecin (**11**) and the synthesis, owing to its convergent design, should be adaptable to the preparation of potentially more useful analogues.

The β-keto ester **1**,[6] readily available from methyl dimethoxyacetate and methyl butyrate, served as starting material. Wittig condensation with benzyl dimethylphosphonoacetate (**2**)[7] gave a mixture of *Z* and *E* benzyl esters **3** in 82% yield. Conversion to the carboxylic acids **4** was accomplished quantitatively and without disturbing the carbon–carbon double bond by hydrogenolysis over a 10% palladium on carbon catalyst in methanol. These sensitive acids were coupled without purification with the tricyclic amine **7**[8] by means of dicyclohexylcarbodiimide. The desired amides **8** were obtained in only 56% yield and we next explored the reactivity of the corresponding β,γ-unsaturated acids **6**. These were prepared by catalytic debenzylation of the tetrasubstituted unsaturated esters **5** available



in 96% yield by isomerization of the trisubstituted isomers **3** with potassium *tert*-butoxide in tetrahydrofuran. Dicyclohexylcarbodiimide promoted condensation of the diastereomeric mixture of these acids **6** with the tricyclic diamine **7** afforded the amides **9** (94%). Either isomers **8** or **9** could be converted to pyridone **10**[9] (41% yield) by treatment with boron trifluoride etherate followed by cyclization of the intermediate aldehydes in refluxing toluene containing a trace of trifluoroacetic acid. A sample of **10** recrystallized from ethyl acetate, mp 229–230°,[10] did not depress the melting point of authentic material, mp 228–230°, and infrared as well as ultraviolet spectra were superimposable. Nuclear magnetic resonance and mass spectra revealed a very minor but different impurity in each of the two samples of different derivation but otherwise confirmed identity. Furthermore, the compounds were indistinguishable by chromatographic techniques. Deoxycamptothecin accompanied by minor amounts of an isomer[11] has been prepared earlier in 35% yield by condensing the pyridone **10** with paraformaldehyde. The final conversion of deoxycamptothecin to *dl*-camptothecin (**11**) was accomplished in 55% yield by oxidation with hydrogen peroxide[9] or quantitatively by autoxidation in the presence of copper(II) species.[12]

Experimental Section

Microanalyses were performed by Midwest Microlab, Inc. Dry nitrogen was used in all reactions requiring an inert atmosphere.

Melting points were determined on a Kofler hot-stage microscope and are corrected, as are boiling points. Infrared (ir) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Ultraviolet (uv) spectra were measured on Perkin-Elmer 202 or Cary 14 instruments. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates T-60 instrument, and are given in parts per million (δ) downfield from an internal tetramethylsilane standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra were determined on Hitachi RMU-6D or RMU-6L instruments. The abbreviation M^+ refers to molecular ion. Gas chromatographic (GLC) analyses were done on either F & M 720 or Perkin-Elmer 990 instruments employing 6-ft 15% SE-30 or 3% OV-17 columns. Analytical thin layer chromatography (TLC) was done on Baker-flex silica gel IB-F sheets. Analtech silica gel GF plates (20 × 20 × 2 mm thick) were used for preparative separations. Merck PF_{254} or 0.05–0.2 mm silica gel and Fischer Florisil (100–200 mesh) were used for column chromatography.

Methyl 4,4-Dimethoxy-2-ethyl-3-oxobutyrate (1). This compound was prepared by the method of Royals[6] in 59% yield: bp 112–114° (11 mm); uv max (MeOH) 218 and 272 nm; ir (neat) 1750, 1730 cm^{-1}; NMR (CCl_4) δ 0.96 (t, 3, J = 7 Hz), 1.75 (m, 2), 3.37 (s, 6), 3.6 (m, 1), 3.67 (s, 3), 4.45 (s, 1).

Benzyl Bromoacetate (13). Bromoacetic acid (5.6 g, 0.04 mol) and benzyl alcohol (4.3 g, 0.04 mol) were added to a solution of 50 ml of benzene and 0.5 g of *p*-toluenesulfonic acid in a flask fitted with a Dean-Stark apparatus. The reaction mixture was heated to reflux for 2.5 hr and cooled to room temperature. After adding 100 ml of ether, the solution was extracted with two 25-ml portions of sodium bicarbonate solution, dried (Na_2SO_4), and concentrated, giving 8.1 g (96%) of benzyl bromoacetate (95% pure by GLC): ir (CCl_4) 1745 cm^{-1}; NMR (CCl_4) δ 3.70 (s, 2), 5.08 (s, 2), 7.28 (s, 5).

Benzyl Dimethylphosphonoacetate (2). Benzyl bromoacetate (35.0 g, 0.15 mol) was stirred in a flask with 30 ml of trimethyl phosphite and heated to 80°. After 48 hr, the contents were distilled giving 34.1 g (91%) of **2**: bp 148–150° (0.1 mm); ir (CCl_4) 1740 cm^{-1}; NMR (CCl_4) δ 2.91 (d, 2, J = 22 Hz), 3.67 (d, 6, J = 11 Hz), 5.09 (s, 2), 7.29 (s, 5).

(*Z*)- and (*E*)-Benzyl 4-Carbomethoxy-3-dimethoxymethyl-2-hexenoate (3). Benzyl dimethylphosphonoacetate (**2**, 16.0 g, 0.06 mol) was added dropwise to a stirred suspension of sodium hydride (1.50 g, 0.062 mol) in 250 ml of dimethoxyethane. The reaction was stirred at 60° for 1 hr to ensure complete enolate formation. Then keto ester **1** (15.7 g, 0.077 mol) was added, and the reaction mixture was heated to reflux. After 24 hr the contents were concentrated to one-half volume, 100 ml of water was added, and the product was extracted with one portion of ether (subsequent extracts showed no desired product by GLC). The ether extract was dried (Na_2SO_4), concentrated, and distilled, giving 16.5 g (82%) of **3** (Z to E ratio 3:1 by GLC): bp 151–159° (0.1 mm); uv max (95% EtOH) 214 nm; ir ($CHCl_3$) 1725, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (t, 3, J = 7 Hz), 1.5–2.0 (m, 2), 3.3 (m, 1), 3.3–3.6 (m, 6), 3.7 (m, 3), 5.12 (s, 2), 5.92 (s, 1), 6.08 (s, 1), 7.33 (s, 5); mass spectrum (70 eV) m/e 336 (M^+).

(*Z*)- and (*E*)-4-Carbomethoxy-3-dimethoxymethyl-2-hexenoic Acid (4). Benzyl ester isomers **3** (3.36 g, 10 mmol) were added to a flask containing 100 ml of methanol and 440 mg of 10% palladium on carbon catalyst. After evacuating and flushing the flask with hydrogen several times, the reaction mixture was stirred under hydrogen at atmospheric pressure and room temperature. When the theoretical uptake (225 ml, 10 mmol) was observed, the reaction flask was removed, 40 ml of methylene chloride was added, and the catalyst was removed by filtration through Celite. The filtrate was concentrated in vacuo at a temperature not above 35°, giving 2.5 g (98%) of acid **4** (a mixture of Z and E isomers): ir (CCl_4) 3530, 1740, 1700, 1650 cm^{-1}; NMR (CCl_4) δ 0.94 (t, 3, J = 7 Hz); 1.67 (q, 2, J = 7 Hz), 3.2 (m, 1), 3.3–3.5 (m, 6), 3.64 (s, 3), 5.86 (s, 1), 5.99 (s, 1), 10.6 (s, 1).

(*Z*)- and (*E*)-Benzyl 4-Carbomethoxy-3-dimethoxymethyl-3-hexenoate (5). A solution of esters **3** (1.68 g, 5 mmol) in 10 ml of tetrahydrofuran was added slowly to a solution of potassium *tert*-butoxide (1.24 g, 11 mmol) in 15 ml of tetrahydrofuran at −65°. The resulting yellow solution was warmed gradually to −30°, water (10 ml) was added, and the solution was extracted with three 50-ml portions of ether. The combined and dried extracts gave 1.61 g (96%) of esters **5** as a mixture of Z and E isomers: uv max (95% EtOH) 214 nm; ir (CCl_4) 1745, 1730 cm^{-1}; NMR (CCl_4) δ 0.9–1.3 (m, 3), 2.2–2.7 (m, 2), 3.2–3.4 (m, 6), 3.4 (m, 2), 3.6–3.8 (m, 3), 4.6 (m, 1), 5.11 (m, 2), 7.24 (br s, 5); mass spectrum (70 eV) m/e 336 (M^+).

(*Z*)- and (*E*)-4-Carbomethoxy-3-dimethoxymethyl-3-hexenoic Acid (6). Benzyl ester isomers **5** (336 mg, 1 mmol) were added to a hydrogenation vessel containing 15 ml of methanol, 25 mg of 10% palladium on carbon catalyst, and 2 drops of triethylamine. After evacuating and flushing the flask with hydrogen several times, the reaction mixture was stirred under hydrogen at atomspheric pressure and room temperature. After 20 min, theoretical uptake (24 ml, 1 mmol) was observed, and the reaction mixture was removed, diluted with 10 ml of methylene chloride, and filtered through Celite. The filtrate was concentrated in vacuo at a temperature not above 35°, giving 248 mg (95%) of acid **6** (a mixture of Z and E isomers which was 95% pure by GLC): ir ($CHCl_3$) 3200, 1720, 1650 cm^{-1}; NMR (CCl_4) δ 1.01 (t, 3, J = 7 Hz), 2.31 (q, 2, J = 7 Hz), 3.1–3.4 (m, 8), 3.6–3.8 (m, 3), 5.0 (m, 1), 9.7 (br s, 1).

Amides 8. Freshly prepared carboxylic acid **4** (0.59 g, 2.4 mmol), dicyclohexylcarbodiimide (453 mg, 2.2 mmol), and tricyclic amine **7** (340 mg, 2 mmol) were combined in 25 ml of methylene chloride. This solution was stirred at room temperature for 12 hr, then filtered, concentrated, dissolved in 6 ml of methylene chloride, filtered again, and concentrated to an oil. The crude product was purified by preparative thin layer chromatography (silica gel GF, 8% methanol in ether) giving 450 mg (56%) of **8** (as a mixture of Z and E isomers). The product was further purified by recrystallization from methylene chloride–ether: mp 190–192°; uv max (95% EtOH) 234 nm (ϵ 40 400), 288 (4100), 294 (4300), 301 (4200), 307 (5600), 314 (4900), 321 (7700); ir ($CHCl_3$) 1730, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (t, 3, J = 7 Hz), 1.5–2.0 (m, 2), 2.2–2.5 (m, 1), 3.3–3.5 (m, 6), 3.6–3.8 (m, 3), 4.4 and 5.7 (2 m, total 1 H), 4.9–5.1 (br s, 4), 6.40 and 6.53 (2 s, total 1 H), 7.5–8.2 (m, 5); mass spectrum (70 eV) m/e 398 (M^+).

Amides 9. Carboxylic acid **6** (50 mg, 0.2 mmol), tricyclic amine **7** (32 mg, 0.2 mmol), and dicyclohexylcarbodiimide (43 mg, 0.21 mmol) were combined in 6 ml of methylene chloride. This solution was stirred at room temperature for 12 hr, then filtered and concentrated to a light solid. The crude product was purified by preparative thin layer chromatography (silica gel GF, 8% methanol in ether), giving 74 mg (93%) of **9** (as a mixture of Z and E isomers). The product was recrystallized from ether, giving colorless needles: mp 135–137°; uv max (95% EtOH) 232 nm (ϵ 48 200), 282 (4000), 288 (4200), 295 (4800), 301 (4900), 308 (6700), 314 (6000), 322 (9100); ir ($CHCl_3$) 1740, 1650, 1425 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, 3, J = 7 Hz), 2.3–2.8 (m, 2), 3.3–3.5 (m, 8), 3.7–3.9 (m, 3), 4.9–5.2 (m, 5), 7.5–8.2 (m, 5); mass spectrum (70 eV) m/e 398 (M^+).

Pyridone 10. Amide acetal **9** (300 mg, 0.75 mmol) was dissolved in 30 ml of methylene chloride and the resultant solution cooled to −65°. Boron trifluoride etherate (0.5 ml) was added, the cold bath was removed, and the reaction mixture was allowed to warm gradually to room temperature. After 20 min, 10 ml of water was added, and the two-phase system was stirred for 20 min, then brought to pH 5 with sodium bicarbonate solution. The methylene chloride layer was separated, dried (Na_2SO_4), and concentrated, giving 270 mg of crude aldehyde isomers: ir ($CHCl_3$) 1730, 1700, 1650 cm^{-1}. This mixture was dissolved in 20 ml of toluene with 6 μl of trifluoroacetic acid and the solution was heated to reflux. After 14 hr, the reaction mixture was filtered, diluted with 20 ml of methylene chloride, washed with dilute sodium bicarbonate solution, dried (K_2CO_3), and concentrated to an oil. Preparative thin layer chromatography (silica gel GF, 9% methanol in ether) afforded 105 mg (41%) of the pyridone **10**. One recrystallization from ethyl acetate gave plates: mp 229–230° (lit.[10] 228–230°); uv max (95% EtOH) 219 nm (ϵ 42 800), 249 (25 800), 254 (30 600), 287 (6100), 321 (7400), 366 (17 400); ir ($CHCl_3$) 1740, 1670, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (t, 3, J = 7 Hz), 1.8–2.2 (m, 2), 3.48 (t, 1, J = 7 Hz), 3.71 (s, 3), 5.22 (s, 2), 6.64 (m, 1), 7.30 (m, 1), 7.5–8.3 (m, 5); mass spectrum (70 eV) m/e 334 (M^+).

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.86; H, 5.39; N, 8.38. Found: C, 71.90; H, 5.43; N, 8.23.

Acknowledgment. This work was supported by the National Institutes of Health (GM 09868).

Registry No.—**1**, 57443-17-1; **2**, 57443-18-2; (*Z*)-**3**, 57443-19-3; (*E*)-**3**, 57443-20-6; (*Z*)-**4**, 57443-21-7; (*E*)-**4**, 57443-22-8; (*Z*)-**5**, 57443-23-9; (*E*)-**5**, 57443-24-0; (*Z*)-**6**, 57443-25-1; (*E*)-**6**, 57443-26-2; **7**, 34086-64-1; (*Z*)-**8**, 57443-27-3; (*E*)-**8**, 57443-28-4; (*Z*)-**9**, 57443-29-5; (*E*)-**9**, 57443-30-8; **10**, 34141-35-0; *dl*-**11**, 31456-25-4; **13**, 5437-45-6; bromoacetic acid, 79-08-3; benzyl alcohol, 100-51-6; trimethyl phosphite, 121-45-9.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXXIX. Apramycin—an Application of Amine Protonation Parameters[1]

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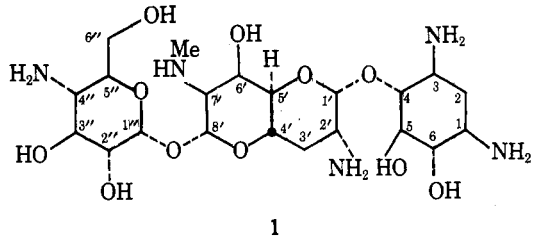
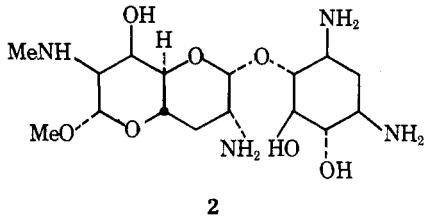
As part of a study of the structures of the nebramycin factors produced by *Streptomyces tenebrarius*[3] the ^{13}C NMR analysis of the kanamycin-like antibiotics has been investigated.[4] Alongside a structure determination of apramycin (**1**), the most complex of the nebramycin factors, by other physical and chemical means[5] the ^{13}C NMR analysis of this antibiotic was undertaken. In this connection recourse was taken to carbon shift perturbations induced by amine protonation, previously found to be an indicator of the substitution pattern in the proximity of the amino carbon.[4]



1

The ^{13}C NMR spectra of the antibiotic and two of its fragments, methyl β-aprosaminide (**2**)[5] and methyl 4-amino-4-deoxy-α-D-glucopyranoside (**3**), were run in aqueous solutions of pH less than 1 and more than 11 and the shift data of trehalose (**4**)[6] and of various compounds from earlier studies were used for the interpretation of the spectra. All chemical shifts are listed in Table I.

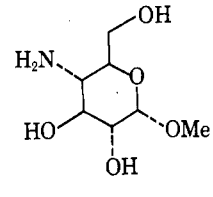


2

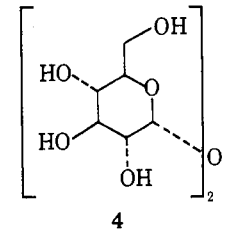
Table I
Carbon Chemical Shifts[a]

	1		2		3		
	>pH 11	<pH 1	>pH 11	<pH 1	>pH 11	<pH 1	4
C(1)	50.2	49.8	50.2	49.8			
C(2)	35.5	28.2	35.5	28.2			
C(3)	49.3	48.6	49.3	48.6			
C(4)	86.7	77.7	86.9	78.0			
C(5)	75.7	74.8	75.7	74.8			
C(6)	77.3	72.3	77.2	72.4			
C(1′)	100.4	94.9	100.5	95.1			
C(2′)	48.7	48.0	48.8	48.0			
C(3′)	32.0	26.8	32.1	26.9			
C(4′)	66.7[b]	65.7	66.3[c]	65.3			
C(5′)	69.8[b]	69.2	70.0[c]	69.4			
C(6′)	65.2	62.5	64.8	62.6			
C(7′)	61.2	59.3	61.8	60.2			
C(8′)	95.2	92.4	101.8	98.3			
C(1″)	94.1	94.1			99.1	98.9	92.9
C(2″)	70.7	70.2			72.0	71.2	71.9
C(3″)	73.0	68.9			72.9	68.9	72.5
C(4″)	52.3	52.4			52.4	52.8	69.6
C(5″)	72.4	68.4			71.4	67.4	70.9
C(6″)	60.7	60.3			60.8	60.4	60.4
NMe	32.0	30.4	32.1	30.5			
OMe			56.9	57.4	54.7	55.2	

[a] In parts per million downfield of Me_4Si; 1:1 D_2O–H_2O solutions with dioxane as internal reference. [b,c] The signals may be reversed. If so, they must be reversed at both pH values.



3



4

The δ values of all carbons of the monoglycoside model **3**, except the anomeric carbon shift, are nearly identical with five of the carbons of the monosaccharide unit of the antibiotic, reflecting an α-anomeric attachment of the remainder of the skeleton to this moiety. Two of the three anomeric carbon signals move upfield on lowering of the pH. Since this behavior reflects the vicinality of amino groups to two anomeric carbon sites,[4] the anomeric carbon shift impervious to pH change must be that of the monoglycosyl fragment. The ca. 6 ppm shielding of the latter's anomeric carbon in the face of the normally invariant ca. 100 ppm α-glucopyranosyl anomeric carbon shift[4] implies the presence of a 1-*tert*-alkoxy substituent, e.g., as the fructosyl moiety in sucrose, or of a 1,1 linkage between the glucopyranosyl unit and another glycosyl function, as in trehalose (**4**). The latter molecular array in apramycin followed from further analysis (vide infra).

A comparison of the spectra of apramycin (**1**), methyl β-aprosaminide (**2**),[5] and neamine (**5**) reveals their common 2-deoxystreptamine unit. The identity of the six resonances of this ring in the three substances at high and low pH shows the attachment of the inosamine unit to be the same in all cases and hence to involve a C(4) ether linkage. The alternate C(6) oxygen attachment is precluded, since it introduces a different spatial environment around the amino groups of the deoxystreptamine moiety and its