acetate **2**. The sole product was formulated as 3β,9α-dihydroxy-5α-lanost-7-ene (**4a**) on the following basis.

Acetylation with pyridine and acetic anhydride under the usual conditions gave a monoacetyl derivative **4b** which still contained a hydroxyl function. Very brief treatment with a trace of mineral acid converted the alcohol **4b** into dihydroagnosteryl acetate (**3b**). The nmr spectrum of alcohol **4a** showed the presence of a trisubstituted olefin. Further support for the olefin was provided by the mass spectrum, which displayed an *m/e* 426 fragment (M − 18). The foregoing would allow the product to be assigned structure **4a** or **5**, of which **4a** is preferred. In this respect the lithium in ethylamine reduction of epoxide **2** gives the α alcohol.[3] Also, the strong vicinal 14α-methyl-8α-hydroxy steric interaction in **5** is absent in **4**.

When no products involving alkylation of the lanostane skeleton were detected the Grignard study was not pursued further. However, the new syntheses of dihydroagnosterol and alcohol **4** were considered potentially useful in approaches to natural products such as batracheotoxinin A.

Experimental Section[5]

Dihydroagnosteryl Acetate (3b).—To a solution of 3β-acetoxy-8α,9α-oxido-5α-lanostane (0.65 g) in dry ether (25 ml) was added (during 5 min) the Grignard reagent (in ether) derived from magnesium turnings (4.9 g) and methyl iodide (28 g). After 20 hr at 25° dry toluene (75 ml) was added and the ether was removed by distillation. The solution was heated under reflux for 11 days, cooled, and poured over crushed ice. The product was isolated using ether to afford a brown grease which slowly solidified. Adsorption on activated alumina (22 g) from solution in benzene and elution with benzene–chloroform (4:1) gave dihydroagnosterol (**3a**, 0.60 g): mp 150–154°; λ_{max}^{EtOH} 236, 243, and 252 mμ. Acetylation gave dihydroagnosteryl acetate, plates from ethanol: mp 167–169°; λ_{max}^{EtOH} 236, 243, and 252 mμ. Acetate **3b** was identical[5] with an authentic specimen.

Reaction between Allylmagnesium Bromide and Oxide 2.—Allylmagnesium bromide was prepared[6] and stored at 0° in a narrow-necked bottle fitted with a septum cap. The assay[7] was 0.66 *M* and 15 ml of the reagent was added to oxide **2** (0.71 g) in dry ether (20 ml, under an atmosphere of dry nitrogen). The reaction mixture was kept at 22° and monitored by tlc upon removal of 0.5-ml aliquots. After 14 hr the mixture was poured into 5% ammonium sulfate (100 ml) at 5°. Ether (25 ml) was used for isolation. The product (0.69 g) was a clear oil which showed one component on tlc. Crystallization from methanol containing one drop of pyridine gave fine needles (0.30 g), mp 132–133°, of a compound formulated as **4a**: ν_{max}^{KBr} 3500–3200 cm^{-1}; pmr (pyridine) δ 0.8, 0.88, 0.93, 1.03, 1.12 (ring and side-chain methyl groups), 2.06 (s, 3 protons), 3.5 (broad, 1 proton), 4.25 (1 proton), 5.18 and 5.47 ppm (broad, 1 proton); mass spectrum *m/e* 426 (M^+ − 18).

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 80.77; H, 11.64.

The product (0.18 g) in pyridine (1.5 ml)–acetic anhydride (1 ml) was kept at 22° for 19 hr. Ether (30 ml) was added and the solution was washed with 2 *N* sodium bicarbonate until effervescence ceased (5 × 15 ml). Drying and solvent removal furnished a colorless solid (0.18 g), one component on tlc, which crystallized as needles from methanol containing one drop of pyridine. The alcohol weighed 0.13 g: mp 170–175° (raised to 171–175° by further recrystallization from the same solvent system); ν_{max}^{KBr} 3580, 1724, and 1230 cm^{-1}; pmr δ 0.675 (C-13 Me), 0.86 (d, *J* = 6.5 Hz, C-26, 27 methyl groups), 0.90, 0.99, 1.18 (C-4, 10, 14α, and 20 methyl groups), 2.03 (3β-OAc), 4.5 (broad, 3α-H), 5.33 ppm (broad, 7-H).

Anal. Calcd for $C_{32}H_{54}O_3$: C, 78.63; H, 11.55. Found: C, 78.98; H, 11.64.

Conversion of Alcohol 4a to Dihydroagnosterol (3a).—Concentrated hydrochloric acid (1 drop) was added to alcohol **4a** (30 mg) in ethanol (5 ml). The ethanol was removed *in vacuo* and the residue was partitioned between ether (15 ml) and water (15 ml). The ether phase was washed with 2 *N* sodium bicarbonate, dried, and evaporated to a white solid (28 mg) which crystallized from ethanol as needles of dihydroagnosterol (**3a**), mp and mp with an authentic sample 150–154°, λ_{max}^{EtOH} 236, 243, and 252 mμ.

Registry No.—**3a**, 2644-75-9; **3b**, 5600-01-1; **4a**, 34910-26-4; **4b**, 34910-27-5.

(5) The introduction to the Experimental Section of an earlier contribution provides a summary of general methods and reagents employed here; see J. C. Knight, G. R. Pettit, and P. Brown, *J. Org. Chem.*, **35**, 1415 (1970).

(6) O. Grummitt, E. P. Budewitz, and C. C. Chudd, *Org. Syn.*, **36**, 61 (1956).

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The Camptothecin δ-Lactone[1a]

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As part of an approach to total synthesis of the antineoplastic agent[2a–c] camptothecin (**1**),[2d,e] it became necessary to investigate synthesis of the terpenoid unit,[3] or an appropriate subunit, of the alkaloid. Synthesis of camptothecin by combination of appropriate fragment molecules, involving formation of the pyridone amide bond and condensation with the pyrroloidinoquinoline entity, would require an eight-carbon unit. A δ-lactone precursor of the type depicted by

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(2) (a) J. M. Venditti and B. J. Abbott, *Lloydia*, **30**, 332 (1967). (b) W. D. DeWys, S. R. Humphreys, and A. Goldin, *Cancer Chemother. Rep.*, **52**, 229 (1968). (c) J. A. Gottlieb, A. M. Guarino, J. B. Call, V. T. Oliverio, and J. B. Block, *ibid.*, **54**, 1461 (1970). (d) 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). (e) A. T. McPhail and G. A. Sim, *J. Chem. Soc. B*, 923 (1968). Three total synthesis of camptothecin have recently been reported: G. Stork and A. G. Schultz, *J. Amer. Chem. Soc.*, **93**, 4074 (1971); R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **93**, 5576 (1971); M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall, and S. G. Levine, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 12–17, 1971. Recent structure/activity investigations have been summarized by J. A. Beisler, *J. Med. Chem.*, **14**, 1116 (1971); T. K. Liao, W. H. Nyberg, and C. C. Cheng, *J. Heterocycl. Chem.*, **8**, 373 (1971); J. A. Kepler, M. C. Wani, J. N. McNaull, M. E. Wall, and S. G. Levine, *J. Org. Chem.*, **34**, 3853 (1969); M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *Chem. Commun.*, 404 (1970).

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structure **2** seemed attractive and was investigated as follows.

Ethyl α-carbethoxy-γ-ethylglutaconate (**3a**) was known[4] and appeared a suitable first stage for the proposed synthesis. Accordingly, base condensation of diethyl malonate with chloroform and concomitant elimination of hydrogen chloride yielded the sodium salt of tetraethyl 1-propene-1,1,3,3-tetracarboxylate (ethyl α,γ-dicarbethoxy-α-glutaconate),[5] which was ethylated directly to give ethyl α,γ-dicarbethoxy-α-ethylglutaconate.[4] Treatment of the latter compound with 1 molar equiv of sodium ethoxide was reported to yield triester **3a** in 95% yield.[4] However, the decarbethoxylation reaction was accompanied, under a variety of reaction conditions, by the formation of diethyl ethylmalonate. In our hands, this competing mode of reaction could only be suppressed to about 25% of the reaction product. The desired triester **3a** was apparently formed by ethoxide attack at either of the C-3 carbethoxy groups, followed by elimination of ethyl carbonate to yield the resonance-stabilized anion **3b**, while attack at the C-1 carbethoxy group leads to the formation of diethyl ethylmalonate. Attack at the C-1 carbethoxy groups was confirmed by the isolation of the other product, ethyl propiolate, as its trimer triethyl 1,3,5-benzenetricarboxylate.[6] The triester product **3a** was separable, by gas–liquid chromatography, into a major component and two minor components, presumably corresponding to the cis and trans 2 olefins and the 1 olefin. The triester mixture was used as such for the next step, as this involved a base condensation with resultant formation of the resonance-stabilized anion **3b**. The anion structure would be expected, of course, to be independent of the actual olefin isomer or isomer mixture used for its genesis.

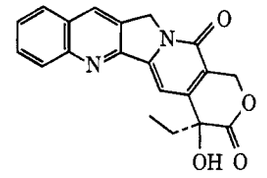
Base condensation of the triester mixture **3a** with formaldehyde gave the desired lactone, diethyl 3-ethyl-5,6-dihydro-2*H*-pyran-2-one-5,5-dicarboxylate (**2**). Formation of neutral lactone **2** would be expected to regenerate base as ethoxide ions, and should, therefore, proceed in the presence of a catalytic amount of base. Indeed, this mechanistic consideration proved to be critical, as the use of 1 molar equiv of sodium ethoxide gave a complex reaction mixture containing virtually no lactone. Increasing the proportion of solvent, ethanol, also gave poorer yields. The reaction was best accomplished in the absence of solvent and with catalytic amounts of sodium ethoxide.

The mass spectrum of lactone **2** showed a weak molecular ion at *m/e* 270 in accord with observed weak or zero molecular ions for substituted diethyl malonates.[7] The spectrum showed similarities to those reported for substituted diethyl malonates in which there was no possibility of a McLafferty rearrangement of the alkyl substituents.[7] The base peak at *m/e* 198 could be obtained by hydrogen rearrangement to give a M − $COOC_2H_4$ ion as well as by initial expulsion of CO_2 from the lactone[8] followed by loss of C_2H_4 (226 → 198). The *m/e* 198 peak showed metastable ion peaks for loss of H_2O (M − 90) followed by loss of 28 (C_2H_4) leading to *m/e* 152, the second most abundant peak, and for loss of 28 (C_2H_4) (M − 100), as expected for ethyl esters. There was a metastable peak for the conversion *m/e* 198 → 125 corresponding to loss of $COOC_2H_5$.

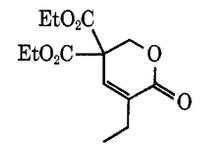
The isomeric lactone, diethyl 5-ethyl-5,6-dihydro-2*H*-pyran-2-one-3,5-dicarboxylate (**4**), was obtained as a minor product from the lactonization reaction *via* attack at C-3 of the triester anion **3b** by formaldehyde. The structure was confirmed by analysis of the nuclear magnetic resonance spectra of the two lactones (**2** and **4**). The vinylic proton of lactone **4** underwent a downfield shift of 62.4 Hz relative to that of lactone **2** due to the electron-withdrawing carbethoxy group at C-5, while the methylene protons of the ethyl group showed a corresponding upfield shift of 31.2 Hz corresponding to the change in environment from allylic to saturated.

Direct hydroxylation of lactone **2** with, *e.g.*, monopersuccinic acid in water, as well as other methods, such as osmium tetroxide or ruthenium tetroxide, were unsuccessful. Generally, lactone **2** was isolated in good recovery. Interestingly, application of the persuccinic acid reaction[9] to isomeric lactone **4** gave only epoxide **5**.

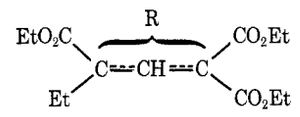
An extensive effort was devoted to developing a means for partial decarboxylation of malonate **2** to provide ethyl ester **6**. However, application of various



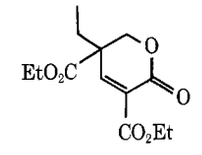
1



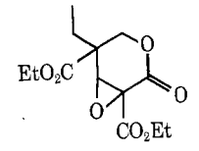
2



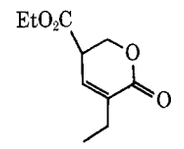
3a, R = H
b, R = –



4



5



6

acidic and basic reaction conditions led to a variety of different products arising from a facile retroaldol degradation of lactone **2**. Several neutral methods (*e.g.*, dimethyl sulfoxide–sodium cyanide and lithium iodide) offered no regress and other approaches to camptothecin were eventually considered more promising. Nevertheless, the convenient synthesis developed for lactone **2** should prove valuable in evaluating camptothecin E-ring structure/activity relationships.

Experimental Section

Melting points are uncorrected and were recorded on a Kofler melting point apparatus. All organic solvent extracts were

(4) F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, 2187 (1911).

(5) (a) M. Conrad and M. Guthzert, *Ber.*, **15**, 2841 (1882); (b) C. K. Ingold and E. A. Perren, *J. Chem. Soc.*, 1582 (1921).

(6) The trimerization of ethyl propiolate to aromatic compounds has been described by L. S. Meriwether, E. C. Colthup, G. W. Kennerly, and R. N. Reusch, *J. Org. Chem.*, **26**, 5155 (1961).

(7) J. H. Bowie, D. H. Williams, S. O. Lawesson, and G. Schroll, *ibid.*, **31**, 1792 (1966).

(8) L. Friedmann and F. A. Long, *J. Amer. Chem. Soc.*, **75**, 2832 (1953).

(9) R. Lombard and G. Schroeder, *Bull. Soc. Chim. Fr.*, 2800 (1963).

dried over either anhydrous magnesium sulfate or anhydrous sodium sulfate. The nuclear magnetic resonance (nmr) spectra ($CDCl_3$, TMS internal standard) were recorded by Miss K. Reimer using a Varian A-60 spectrometer. Gas–liquid chromatography was performed with a Varian 1200 instrument (flame ionization detector) using nitrogen as carrier gas. Elemental microanalytical data was provided by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach uber Engelskirchen, West Germany. Mass spectral data was obtained by Mr. R. Scott, employing an Atlas CH-4B mass spectrometer equipped with a molecular beam inlet system.

Tetraethyl 1-Pentene-1,1,3,3-tetracarboxylate (Ethyl α,γ-Dicarbethoxy-α-ethylglutaconate).—The following method is a modification of those reported by Ingold and Perren,[6b] for the preparation of the sodium salt of tetraethyl 1-propene-1,1,3,3-tetracarboxylate, and Thole and Thorpe,[4] for the ethylation reaction.

Sodium (46 g, 2 mol) was dissolved in ethanol (absolute, 750 ml). Diethyl malonate (160.2 g, 1 mol) was added over 30 min with heating and stirring and the mixture was heated at reflux for a further 15 min. Heating was stopped and, as soon as reflux had subsided, chloroform (60.5 g, 0.51 mol) was added at a rate sufficient to maintain vigorous reflux (over 15 min). Heating was resumed and the mixture was heated at reflux for 3 hr. The apparatus was arranged for distillation and 110 ml of the solvent was distilled from the reaction vessel.[10] The apparatus was returned to the reflux position, ethyl iodide (85.8 g, 0.55 mol) was added over 10 min, and the mixture was refluxed for a further 36 hr. After cooling the reaction mixture was poured into water (750 ml) and extracted with chloroform (10 × 200 ml). The chloroform layer was washed with potassium hydroxide solution (10%, 5 × 200 ml) and water (5 × 200 ml) and dried, and the solvent was removed under reduced pressure to give an orange oil (203.2 g). Fractionation (Vigreux column) gave tetraethyl 1-pentene-1,1,3,3-tetracarboxylate (46–63%), bp 153–157° (1.5 mm) [reported[4] bp 213° (20 mm)]. The nmr spectrum showed δ 0.88 (3 H, triplet, J = 7.6 Hz, protons on C-5 coupled to C-4 methylene protons), 1.28 and 1.325 (12 H, two triplets, J = 7.1 Hz, methyl protons), 2.22 (2 H, quartet, J = 7.6 Hz, protons on C-4 coupled to C-5 methyl protons), 4.0–4.5 (8 H, complex methylene multiplet), 7.61 ppm (1 H, singlet, vinylic proton on C_2).

Triethyl 3-Ethyl-1(2)-pentene-1,1,3-tricarboxylate (Ethyl α-Carbethoxy-γ-ethylglutaconate) (3a).—Sodium (5.36 g, 0.233 mol) was dissolved in ethanol (absolute, 670 ml) and the solution was cooled to 10°. Tetraethyl 1-pentene-1,1,3,3-tetracarboxylate (83.4 g, 0.233 mol) in ethanol (absolute, 670 ml) was added over 30 min with the temperature maintained between 6 and 10° (immersion in an ice bath), and a deep yellow color appeared. The reaction mixture was stirred for 20 hr at 10° and then poured into chloroform (500 ml) and shaken well with hydrochloric acid (0.6 N, 375 ml). The aqueous layer was extracted with chloroform (3 × 200 ml) and the combined chloroform layer was washed with saturated salt solution (3 × 250 ml), dried, and evaporated under reduced pressure to give a yellow oil (57.5 g). Glc [column, 3% QF_1 on Chromosorb W (60–80 mesh), 5 ft × 0.125 in., Pyrex; flow rate, 12 ml/min; temperature, initial 80°, final 215°, at an average of 3.75° per minute] showed diethyl ethylmalonate (appearance temperature 117–120°) and three peaks with an appearance temperature around 170° in the ratio of 28:26:64. Diethyl ethylmalonate was removed by fractional vacuum distillation and the mixture of isomers of triethyl 3-ethyl-1(2)-pentene-1,1,3-tricarboxylate (**3a**) was used as such for the next step.

Diethyl 3-Ethyl-5,6-dihydro-2*H*-pyran-2-one-5,5-dicarboxylate (2).—Sodium ethoxide (60 mg), triethyl 3-ethyl-1(2)-pentene-1,1,3-tricarboxylate (7.68 g), and paraformaldehyde (0.801 g) were heated to 97° over 60 min (the reaction mixture becoming clear at about 80°) and then maintained at 97° for 3.25 hr. The mixture was cooled and dissolved in ether (50 ml), and the ethereal solution was washed with dilute hydrochloric acid (1 N, 3 × 10 ml) and water (2 × 10 ml), dried, and evaporated under reduced pressure to give an oil (5.96 g). Chromatography on 24 g of silica gel (Merck 0.05–0.2 mm) gave diethyl 3-ethyl-5,6-dihydro-2*H*-pyran-2-one-5,5-dicarboxylate (**2**) (2.15 g) as a colorless oil, eluted with ligroin–benzene (4:1). The nmr spectrum showed δ 1.11 (3 H, triplet, J = 7.4 Hz), 1.28 (6 H, triplet, J = 7.0 Hz), 2.40 (2 H, doublet of quartets, J = 7.4, 7.4, 7.4, 1.4 Hz), 4.26 (4 H, quartet, J = 7.0 Hz), 4.69 [2 H, narrow signal showing small (0.8 Hz) splitting], 6.71 ppm (1 H, narrow signal, $W_{1/2}$ = 3.6 Hz).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.98; H, 6.88.

The mass spectrum showed m/e (rel intensity at 70 and 12 eV, respectively) 271 (M + 1, 13, 2), 270 (M, 1.5, 4), 226 (10, 27), 198 (100, 100), 180 (27, 26), 170 (25, 7), 169 (19, 3), 152 (94, 25), 151 (38, 0), 125 (83, 6), 124 (30, 2); M^+ at 173.3 (calcd for 226 → 198, 173.5), 163.5 (198 → 180, 163.6), 146.0 (198 → 170, 145.9), 143.5 (226 → 180, 143.4), 128.3 (180 → 152, 128.3), 106.8 (270 → 170, 107.0), 101.5 (152 → 124, 101.2).

Further elution of the column gave **diethyl 5-ethyl-5,6-dihydro-2H-pyran-2-one-3,5-dicarboxylate (4, 0.42 g)** as a colorless oil. The nmr spectrum showed δ 0.98 (3 H, triplet, J = 7.2 Hz), 1.23 (3 H, triplet, J = 7.0 Hz), 1.35 (3 H, triplet, J = 7.0 Hz), 1.88 (2 H, quartet, J = 7.2 Hz), 4.0–4.5 (6 H, complex multiplet), 7.75 ppm (1 H, singlet).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.65; H, 6.78.

Diethyl 5-Ethyl-3,4-epoxytetrahydro-2*H*-pyran-2-one-3,5-dicarboxylate (5).—A suspension of peroxydisuccinic acid[9] (135 mg) in water (1 ml) was heated and stirred at 50° for 1 hr. The resulting aqueous solution was cooled to 42° and diethyl 5-ethyl-5,6-dihydro-2*H*-pyran-2-one-3,5-dicarboxylate (**4**) (135 mg) was added. The reaction mixture was stirred at 42° for 8 hr, cooled to about 10°, neutralized with sodium bicarbonate, and extracted with ether. The ethereal solution was washed with water (2 × 10 ml), dried, and evaporated under reduced pressure to give a quantitative yield of diester **5**. Recrystallization from ligroin gave colorless crystals: yield 43 mg; mp 50–51°; glc [column, 5% SE-30 on Chromosorb W (60–80 mesh), 5 ft × 0.125 in., stainless steel; temperature, −178°; flow rate, 10 ml/min] retention time 10.5 min relative to starting material 9.5 min. The glc of the mother liquors showed only the one peak corresponding to the isolated solid. The mass spectrum showed a peak at m/e 286 (calcd for $C_{13}H_{18}O_7$, M^+ 286). The nmr spectrum showed δ 1.02 (3 H, triplet, J = 7 Hz), 1.32 (3 H, triplet J = 7 Hz), 1.33 (3 H, triplet, J = 7 Hz), 1.8 (2 H, quartet, J = 7 Hz, exhibiting further splitting), 4.0–4.6 ppm (7 H, complex multiplet).

Anal. Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.40; H, 6.27.

Registry No.—**2**, 34993-71-0; **4**, 34993-72-1; **5**, 34993-73-2; tetraethyl 1-pentene-1,1,3,3-tetracarboxylate, 34993-74-3.

(10) This removal of a quantity of the solvent was necessary to ensure optimization of the ethylation reaction; otherwise, unethylated material was obtained, as the pyrone, ethyl 6-ethoxy-2*H*-pyran-2-one-3,5-dicarboxylated, *via* elimination of ethanol from tetraethyl 1-propene-1,1,3,3-tetracarboxylate. See M. Guthzeit and O. Dressel, *Ber.*, **22**, 1413 (1889).

Catalytic Deoxygenation of Organic Compounds by Carbon Monoxide. II.[1] Direct Synthesis of Schiff Bases from Aromatic Nitro Derivatives, Aldehydes, and Carbon Monoxide

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The subject of the present communication is a novel synthesis of Schiff bases by intercepting *in situ* deoxygenated nitro derivatives by aldehydes. Thus, in the presence of a group VIII metal catalyst (*e.g.*, rhodium carbonyl), the interaction of benzaldehyde and aromatic nitro compounds under a pressure of

(1) For part I, see A. F. M. Iqbal, *Tetrahedron Lett.*, 3385 (1971).