(2) Prepared by treating 10.1 g of glycine ethyl ester hydrochloride in 150 ml of methylene chloride with 1 equiv of benzaldehyde in the presence of 20 ml of triethylamine and 6 g of anhydrous magnesium sulfate at room temperature, filtration, solvent removal (room temperature), water–ether partition washing (brine), drying, and removal of solvent. The substance thus obtained in 95% yield could be kept in the freezer for several months. See also O. Gerngross and A. Olcay, *Ber.*, **96**, 2550 (1963).
(3) For a recent contribution to this field, cf. J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 3267 (1973).
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(5) J. Durand, Nguyèn Trong Anh, and J. Huet, *Tetrahedron Lett.*, 2397 (1974), and references cited therein.
(6) All new compounds gave integrated NMR spectra in complete agreement with their structures which were also confirmed by their further transformations. Kugelrohr distillations are indicated as bp (k).
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(12) On leave from the Université Pierre et Marie Curie, Paris.

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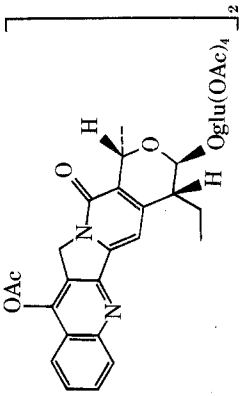
A Biomimetic Synthesis of the Camptothecin Chromophore

Summary: Novel heterocyclic alkaloids (4 and 6), potential synthetic precursors of 20(*S*)-camptothecin (2), are synthesized by 2,3-dichloro-5,6-dicyanobenzoquinone oxidation of tetraacetyl-18,19-dihydrovincoside (18,19-H_2-**1a**) and -isovincoside (18,19-H_2-**1c**) lactams and their corresponding pentaacetyl-18,19-dihydroquinolols (18,19-H_2-**3**).

Sir: We have been studying the chemistry[1] of the penultimate biosynthetic precursor of camptothecin (**2**), isovincoside lactam (**1c**), as a model system for the putative biochemical transformations that occur between **1c** and **2** in vivo.[2] Since D ring oxidation of **1c** to a pyridone may be one requisite of the biosynthetic pathway to **2**, we have examined the oxidation of 18,19-H_2-**1a** and -**1c** using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Alternatively, D ring oxidation of isovincoside quinolol (**3c**) may be a key oxidative step preceding **2** in vivo, since presently we do not know the exact biochemical sequence of events between **1c** and **2**.[3] With both **1** and **3** oxidation with DDQ has been accomplished efficiently, which should enable a convenient synthesis of **2** and novel indole analogues of it, and which may be relevant to in vivo biosynthetic events.[4]

Oxidation of either 18,19-H_2-**1b** or -**1d** $(OAc)_4$ with DDQ (1 equiv or excess) in methanol (reflux, 5 min, N_2) or in a toluene–methanol mixture (25 °C, 5–10 min, N_2) gave a chromatographically resolvable mixture of **4a** {pale yellow solid: mp 145–150 °C dec; 41%; ir ν_{KBr} 3356 (NH), 1761 (OAc), 1667 (pyridone), and 1230 (C–O) cm^{-1}; uv λ_{max}^{MeOH} 386, 367, 296 (sh), 286 (sh), 273, 260, 252, and 213 nm; MS *m/e* 666.2437 ($M^{\cdot+}$ – CH_2O, calcd for $C_{34}H_{38}N_2O_{12}$ 666.2424), 331.1026 [Glu$(OAc)_4^+$, calcd for $C_{14}H_{19}O_9$ 331.1024]; ^1H NMR (90 MHz) δ^{CDCl_3} 0.93 [t, 3 H, J = 7 Hz, C(18)], 1.89 [m, 2 H, C(19)], 2.00–2.07 (4 s, 12 H, 4 OAc), 2.58 [m, 1 H, C(20)], 2.95 [t, 2 H, J = 7 Hz, C(6)], 3.56 (s, 3 H, OCH_3), 4.35 [t, 2 H, J = 7 Hz, C(5)], 5.41 (d, 1 H, J = 3 Hz, C(21)], 5.70 [s, 1 H, C(17)], 6.32 (s, 1 H, C(14)], 7.08–7.54 (4 aromatic H), and 9.51 (br s, NH), glucosyl protons omitted} and **4b** {yellow needles (MeOH); mp 154–156.5°C; 26.5%; ir ν_{KBr} 3333 (NH), 1754 (OAc), 1658 (pyridone), and 1230 (C–O) cm^{-1}; uv λ_{max}^{EtOH} 418, 395 (sh), 324, 277, 257, 248 (sh), and 218 nm; MS *m/e*, 664.1897 ($M^{\cdot+}$ – CH_2O, calcd for $C_{34}H_{36}N_2O_{12}$ 664.2258), 316.1153 [$M^{\cdot+}$ + 1 – CH_3O – (HO-(Glu$(OAc)_4$, calcd for $C_{20}H_{16}N_2O_2$ 316.1027], and 290.1419 (calcd for $C_{19}H_{18}N_2O$); ^1H NMR (90 MHz) δ^{CDCl_3} 1.02 [t, 3 H, J = 7 Hz, C(18)], 1.90 [m, 2 H, C(19)], 1.96–2.07 (4 s, 12 H, 4 OAc), 2.90 [m, 1 H, C(20)],



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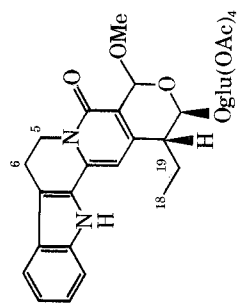
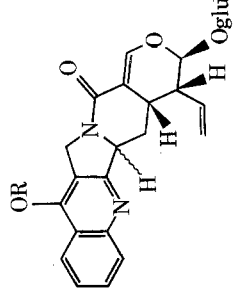
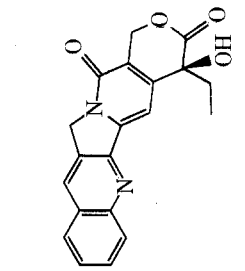


4a

b, $\Delta^{5,6}$



3a, C-3 (*R*), R = H
b, C-3 (*R*), R = Ac
c, C-3 (*S*), R = H
d, C-3 (*S*), R = Ac



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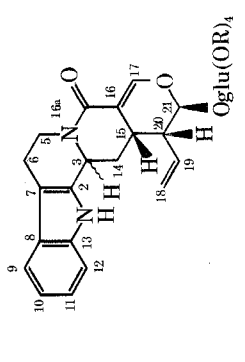


1a, C-3 (*R*), R = H
b, C-3 (*R*), R = Ac
c, C-3 (*S*), R = H
d, C-3 (*S*), R = Ac

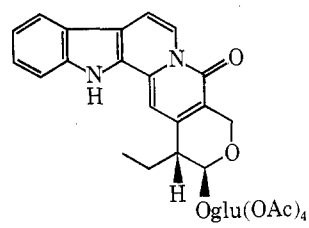
Table I. ^{13}C NMR Assignments[a]

	Carbon resonances at 22.6 MHz[b]																	
Compd	18	19	6	5	20	OMe	21	14	17	12	16	10	9	11	8	13	2	3	15	16a
4a	10.4	19.5	22.7	40.6	42.6	56.2	96.0	96.5	100.1	114.6	119.6	120.2	124.6	125.7	127.2	138.7	138.0	146.7	148.3	160.4
4b	11.1	21.1	111.9	108.8	43.8	56.3	96.1	96.1	98.1	110.6	118.6	120.5[c]	126.7	120.7[c]	129.9	132.9	139.8	144.3	146.5	156.6
6	9.4	20.8	123.9	48.8	42.0		98.5	99.4	89.7	130.8	120.1	122.3	127.9[d]	129.6[d]	121.3	150.8	154.0	145.1	149.4	158.5

[a] Determined in $CDCl_3$ relative to TMS as internal standard by consideration of the ^{13}C NMR assignments of 1b and 1d and 2,[7] SFOR proton decoupling, and low power proton decoupling.[8] [b] Glucosyl tetraacetate resonances omitted. [c] These two assignments may be reversed. [d] These two assignments could be interchanged.

3.66 (s, 3 H, OCH_3), 5.49 [d, 1 H, J = 3 Hz, C(21)], 5.94 [s, 1 H, C(17)], 6.76 (s, 1 H, C(14)], 6.81 [d, 1 H, J = 6 Hz, C(6)], 7.20–7.80 (4 aromatic H), 8.70 [d, 1 H, J = 6 Hz, C(5)], and 9.50 (br s, NH), glucosyl protons omitted}. The EI high resolution MS data for **4a** and **4b** are not so accurate as would be desirable; however, (1) the exact masses for the corresponding ions of 18,19-dehydro-**4a** and -**4b** agreed well with the calculated values,[5] and (2) when the oxidation was done in MeOD, ions at *m/e* 699, 696, and 666 were seen for one isolable product, which must correspond to [16-^{2}H]-15,16-H_2-**4a** (**5**).[6] The structures assigned to **4a** and **4b** were confirmed by ^{13}C NMR analysis (Table I) and **4a** was convertible quantitatively to **4b** by further DDQ oxidation (benzene, 25 °C, 5 min).

When the oxidation of 18,19-H_2-**1d** was done in benzene (reflux, N_2, 30 min), several blue fluorescent products were produced (TLC); the principal one (~25% yield) appeared to be **7** [uv (MeOH) identical with that of **4b**; ^{1}H NMR resonances characteristic for hydrogens at C(5), C(6), and C(18)–C(21); MS *m/e* 664 (M^+)]. Interestingly, when **7** was obtained (in low yield) from oxidation of 18,19-H_2-**1d** with DDQ



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in MeOD, it did not contain ^{2}H suggesting that an intramolecular hydrogen migration had occurred to generate the C(17) methylene.[6]

The analogous oxidation of **3b** or **3d** (benzene, reflux, 20 h) gave the interesting dimer, **6** {pale yellow needles from $CHCl_3$–CH_2Cl_2–MeOH, mp 160 °C dec; 73%; ir ν_{KBr} 1761 (acetate), 1667 (pyridone), and 1230 (C–O) cm^{-1}; uv λ_{max}^{THF} 385, 367, 335 (sh), 290, 253, and 245 nm; MS *m/e* 678 (½ dimer – CH_3CO), and 330.0986 [½ dimer – CH_3CO – (HO)glu(OAC)$_4$; calcd for $C_{20}H_{14}N_2O_3$ 330.1001]; ^{1}H NMR (270 MHz) δ^{CDCl_3} 0.95 [t, J = 7 Hz, 3 H, C(18)], 1.90 [m, 2 H, C(19)], 2.03–2.09 (8 s, 24 H, 8 OAc), 2.51 [s, 3 H, C(7) OAc], 2.91 [m, 1 H, C(20)], 5.18 [s, 2 H, C(5)], 5.89 [d, 1 H, C(21)], 6.45 [d, 1 H, C(17)], 7.24 [s, 1 H, C(14)], 7.60–8.15 (4 aromatic H), glucosyl protons omitted}. Anal. Calcd for $C_{72}H_{74}N_4O_{28}$·$CHCl_3$: C, 56.11; H, 4.84; N, 3.59. Found: C, 56.34; H, 4.80; N, 3.52. Although the foregoing data, except for the observation of eight distinct acetate methyl resonances, could be interpreted as evidence for a monomeric structure, the dimeric nature of **6** was confirmed by the following data. (1) A molecular weight analysis (vapor pressure osmometry) gave 1390 as the true molecular weight (calcd 1443). (2) The ^{13}C NMR signal of C(17) at δ 89.7 (Table I) appeared primarily as a doublet on SFOR proton decoupling with $^2J_{CH}$ fine structure indicative of an ABX spin system, which is evidence for the subunit, –CO(H)–(H)OC–.[9] No ^{13}C NMR signal corresponding to a C(17) methylene was present, and the ^{13}C NMR assignments of the aromatic carbons of **6** were nearly identical with those of **2**.[2] (3) The CD spectrum (*c* 0.056 mg/ml, dioxane) of **6** { $[\theta]_{450}$ 0, $[\theta]_{376}$ – 2.39 × 10^5, $[\theta]_{358}$ – 1.24 × 10^5, $[\theta]_{351}$ 0, $[\theta]_{345}$ + 5.60 × 10^4, $[\theta]_{331}$ + 7.14 × 10^5, and — $[\theta]_{255}$ 0}, when compared with that of the 21(*R*) 21-OMe acetal of **2**[10] which has only a very weak (–) cotton effect between 450 and 350 nm, is good evidence for the presence of a substituent at C(17) giving an *S* absolute stereochemistry.[11]

The relative ease and efficiency of the oxidation of **1** and **3**, which also occurs on standing in the air, may be significant in the biosynthesis of **2**. Nevertheless, the preparation of **6** from tryptamine and secologanin in 36% overall yield should enable a high-yielding synthesis of **2** as well as novel heterocyclic analogs of it.[12]

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References and Notes

(1) For the preceding paper, see C. R. Hutchinson, G. J. O'Loughlin, R. T. Brown, and S. B. Fraser, *J. Chem. Soc., Chem. Commun.*, 928 (1975).
(2) C. R. Hutchinson, A. H. Heckendorf, P. E. Daddona, E. W. Hagaman, and E. Wenkert, *J. Am. Chem. Soc.*, **96**, 5609 (1974).
(3) Dr. A. H. Heckendorf (unpublished results) has demonstrated that neither **3a** or **3c** are incorporated into **2** at a time (parallel feeding experiments) when **1c** is incorporated. The validity of such negative results must be held questionable, until confirmed by appropriate positive incorporations.
(4) C. R. Hutchinson and A. H. Heckendorf, *J. Am. Chem. Soc.*, submitted for publication.
(5) 18,19-dehydro-**4a**: *m/e* 314.105 [$M^+ - H_2$ – (HO)glu(OAC)$_4$, calcd for $C_{20}H_{14}N_2O_2$ 314.108]. 18,19-dehydro-**4b**: *m/e* 312.089 [$M^{+\cdot} - H_2$ – (HO)glu(OAC)$_4$; calcd for $C_{20}H_{12}N_2O_2$ 312.092].
(6) R. T. Brown, University of Manchester, England, personal communication, 1974.
(7) A. H. Heckendorf, K. C. Mattes, C. R. Hutchinson, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, **41**, 2045 (1976).
(8) I. H. Sadler, *J. Chem. Soc., Chem. Commun.*, 809 (1973).
(9) K. D. Barrow, R. B. Jones, P. W. Pemberton, and L. Phillips, *J. Chem. Soc., Perkin Trans. 1*, 1406–1407 (1975).
(10) Prepared from **2** by (i) reduction with $NaBH_4$ in $CHCl_3$–MeOH then (ii) acetalization with $(MeO)_3CH$, H^+ in refluxing MeOH {mp 288–90 °C; CD (*c* 0.025 mg/ml, dioxane) $[\theta]_{450}$ 0, $[\theta]_{369}$ –1.09 × 10^4, $[\theta]_{331}$ – 2.9 × 10^3, $[\theta]_{323}$ 0, $[\theta]_{302}$ + 1.05 × 10^4, and $[\theta]_{265}$ 0}.
(11) (a) G. G. DeAngelis and W. C. Wildman, *Tetrahedron*, **25**, 5099 (1969); (b) G. Snatzke and P. C. Ho, *ibid.*, **27**, 3645 (1971).
(12) In view of the continued, successful use of **2** in cancer chemotherapy by the mainland Chinese (P. Potier, personal communication, 1976), additional studies of this drug need to be done.
(13) Career Development Awardee of the National Cancer Institute (CA 00253), 1976–1980.

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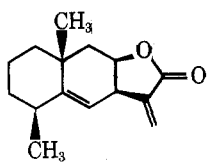
An Annelation Approach to the Eudesmane and Certain Elemane Sesquiterpenes

Summary. A potentially general route to eudesmane and certain elemane sesquiterpenes is demonstrated by synthesis of diene–lactone **9**.

Sir: We wish to describe what we consider to be a potentially general route to the eudesmane[1] and certain elemane sesquiterpenes, here illustrated by alanolactone (**1**) and ver-



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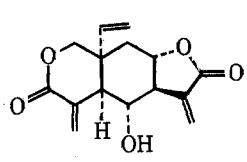

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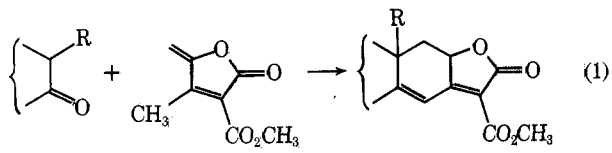
nomenin (**2**),[2] respectively. Our approach (eq 1), features the 1,6-annelation reagent α-carbomethoxy-β-methyl-γ-methylidene-$\Delta^{\alpha,\beta}$-butenolide (**3**), which incorporates the structural components of the γ-lactone (and furan) rings characteristic of these sesquiterpenes.[3]



(1)

3

An exceedingly simple and high yield preparation of the required butenolide from equivalent amounts of biacetyl and malonic acid has been developed (80% overall yield, eq 2).[4] Although biacetyl has been reported to undergo multiple condensation with aldehydes in low to negligible yields using Knoevenagel conditions,[5] to our knowledge no successful re-