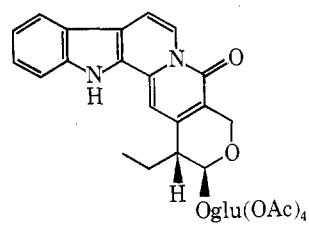
3.66 (s, 3 H, OCH_3), 5.49 [d, 1 H, J = 3 Hz, C(21)], 5.94 [s, 1 H, C(17)], 6.76 (s, 1 H, C(14)], 6.81 [d, 1 H, J = 6 Hz, C(6)], 7.20–7.80 (4 aromatic H), 8.70 [d, 1 H, J = 6 Hz, C(5)], and 9.50 (br s, NH), glucosyl protons omitted}. The EI high resolution MS data for **4a** and **4b** are not so accurate 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



7

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.
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(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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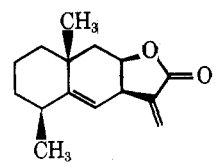
An Annelation Approach to the Eudesmane and Certain Elemane Sesquiterpenes

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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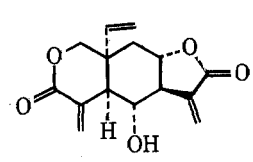
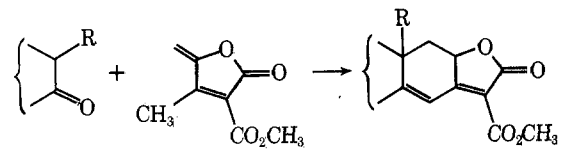


2

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]



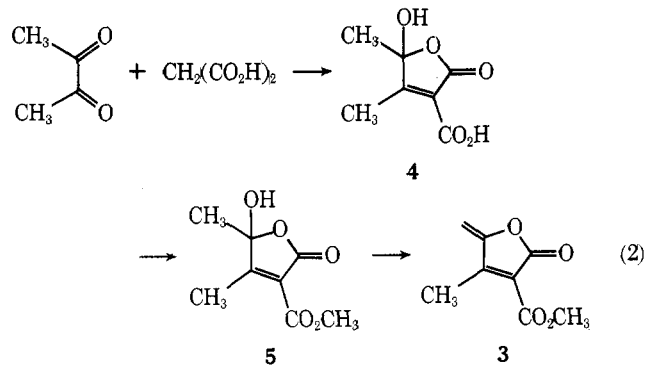
(1)

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-

action between biacetyl and malonic acid derivatives has been reported; not unexpectedly, our initial attempts with standard Knoevenagel methodology were unsuccessful.

However, the desired condensation of biacetyl with malonic acid occurs with titanium tetrachloride[6] in pyridine–tetrahydrofuran (THF) solution to give the pseudo acid **4** in 89% isolated yield. Titration of **4** with diazomethane in ether gives the methyl ester pseudo acid **5** (mp 56 °C). Dehydration of **5**



4 **5** **3** (2)

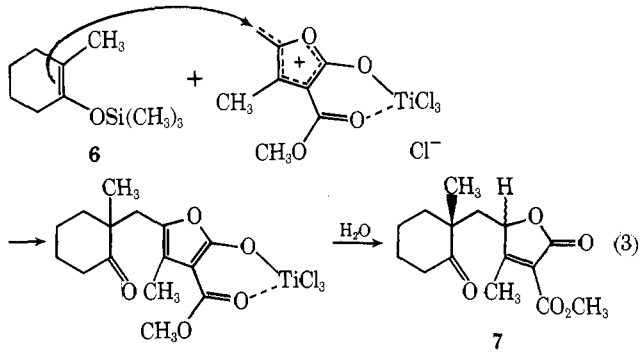
in a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid[4,7] at 25 °C for 1.5 h gives butenolide **3** in 95% isolated yield.

Butenolide **3** may be isolated as an extremely unstable crystalline material (*m/e* 168.0426; calcd 168.0422), which does not exhibit a sharp melting point. The NMR spectrum of **3** in $CDCl_3$ displays singlets at δ 2.50 (3 protons) and 3.93 (3 protons) as well as doublets centered at 5.30 (1 proton, J = 4 Hz) and 5.43 ppm (1 proton, J = 4 Hz), and the ir spectrum is characterized by absorption at 5.58, 5.80, 6.08, and 6.17 μ ($CHCl_3$ solution).

The crystalline butenolide rapidly decomposes at room temperature to uncharacterized polymeric material; similar decomposition occurs in solution on treatment with aqueous sodium bicarbonate or amines. However, methylene chloride solutions of **3** may be refrigerated (−15 °C) for several hours with little decomposition. The extreme instability to a variety of bases suggests that **3** will not be useful in situations requiring classical Michael reaction conditions. In fact, even attempted addition of benzenethiol catalyzed by a trace of triethylamine resulted in instantaneous polymerization.[8]

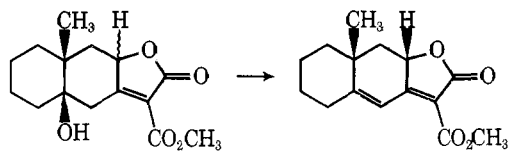
Recently Mukaiyama and coworkers have shown that silyl enol ethers react with α,β-unsaturated ketones in the presence of titanium tetrachloride to give 1,5-diketones.[9] We have found that butenolide **3** and silyl enol ethers undergo a remarkably rapid reaction with titanium tetrachloride to give 1,7-dicarbonyl compounds. The following procedure for the preparation of **7** is representative. To a solution of $TiCl_4$ (8.92 mmol, 0.98 ml) in dry CH_2Cl_2 (50 ml) at −78 °C is rapidly added a solution of **3** (8.92 mmol, 1.50 g) in CH_2Cl_2 (8 ml). After 2 min, a solution of silyl enol ether **6**[10] (8.92 mmol, 1.64 g) in CH_2Cl_2 (5 ml) is rapidly added. After the mixture is stirred for 4 min at −78 °C, aqueous K_2CO_3 (1.12 g in 50 ml of H_2O) is added to the deep blue solution to give **7**, isolated as a crystalline mixture of diastereomers in 50% yield (electron impact mass spectrum *m/e* 280). A possible mechanism for this transformation is presented in eq 3; a more definitive statement must await further study.

Completion of the desired annelation is accomplished by treatment of **7** with potassium carbonate in aqueous methanol to give a diastereomeric mixture of alcohols **8** in nearly quantitative yield.[11] Dehydration of **8** in a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid at room temperature gives a mixture of diastereomeric dienes, which when treated with a trace of potassium carbonate in anhydrous methanol gives mainly one diastereomer **9** (95:5),



6 **7** (3)

which may be obtained in pure form by crystallization from ether (mp 143–144 °C; *m/e* 262.1203; calcd 262. 1205; 60% yield from **7**).[12,13,14]



8 **9**

Thus, we have demonstrated that butenolide **3** should be a useful annelating reagent in the construction of linear tricyclic γ-lactones. Application of the methodology discussed here with respect to sesquiterpene total synthesis is currently being explored.

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References and Notes

(1) For approaches to the eudesmane class of sesquiterpenes, see R. B. Miller and R. D. Nash, *J. Org. Chem.*, **38**, 4424 (1973), and references cited therein.
(2) Vernomenin and the related tumor inhibitor vernolepin have been the object of extensive synthetic effort. Recently, two total syntheses of these sesquiterpenes have been reported; see P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976); S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *ibid.*, **98**, 3028 (1976), and references cited therein, for related synthetic activity.
(3) For other 1,6-additions see S. Danishefsky, W. E. Hatch, M. Sax, E. Abola, and J. Pletcher, *J. Am. Chem. Soc.*, **95**, 2410 (1973), and references cited therein. Annelation of 1,3-dicarbonyl compounds with β-vinylbutenolide also has been reported; see F. Kido, T. Fujishita, K. Tsutsumi, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 337 (1975).
(4) For an alternative approach to the synthesis of α-carboalkoxy-γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides, see A. G. Schultz and Y. K. Yee, *J. Org. Chem.*, **41**, 561 (1976).
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(7) P. E. Eaton, G. R. Carlson, and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973).
(8) In contrast, treatment of the somewhat more stable α-carboethoxy-β-methyl-γ-ethylidene-$\Delta^{\alpha,\beta}$-butenolide with benzenethiol and a trace of triethylamine has been reported to result in nearly instantaneous 1,6-addition; see ref 4.
(9) K. Narasaka, K. Soai, and T. Mukaiyama, *Chem. Lett.*, 1223 (1974).
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(11) Suggested stereochemistry in **8** is proposed in accord with the base-catalyzed annelation of α-methylcyclohexanone with methyl vinyl ketone, which has been reported to give *cis*-10-methyl-2-decalon-9-ol; see H. B. Henbest and J. McEntee, *J. Chem. Soc.*, 4478 (1961), and J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).
(12) Stereochemical assignment in **9** is based on a ^1H NMR double resonance experiment. Irradiation of the angular methyl resonance in the spectrum of **9** resulted in a 25% enhancement of the intensity of the resonance due to the methine hydrogen, indicating a cis relationship between these two substituents. We thank Iwao Miura of Columbia University for performing this valuable NOE experiment.
(13) Compounds **7**, **8**, and **9** give correct elemental analyses.
(14) **Note Added in Proof:** Diene **9** may be isolated in 80% overall yield from **7** more directly by treatment of **8** with acetic anhydride–sodium acetate at 105 °C for 6 h.

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