2,4-Dinitroestrone (1d). To a hot solution of **1a** (0.270 g, 0.001 mol) in acetic acid (10 mL) was added 100% nitric acid (0.135 mL, 0.003 mol). After cooling at room temperature (3 h), the solution was poured into ice and the yellow precipitate filtered off and rinsed with water. Practically pure **1d** was obtained in 90% yields (0.324 g). One crystallization from ethanol afforded an analytically pure sample: mp 175–177 °C; ^{1}H NMR δ 0.95 (s, 3 H, 18-CH_3), 8.30 (s, 1 H, C-1). Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 60.00; H, 5.55 N, 7.77 Found: C, 59.73; H, 5.65; N, 7.68.

Acknowledgment. We thank Prof. A. Fiecchi for many helpful discussions and CNR (Rome) for financial support.

Registry No. **1a**, 53-16-7; **1b**, 5976-73-8; **1d**, 42979-83-9.

Synthesis of (±)-Umbelactone[1]

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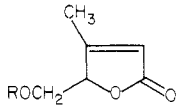
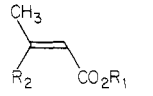
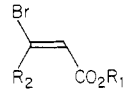
Numerous physiologically active compounds contain an α,β-butenolide system.[2] Umbelactone (**1a**) is an example



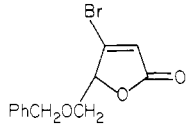
1a, R = H
b, R = CH_2Ph



2a, $R_1 = R_2$ = Li
b, R_1 = H; R_2 = Br



3a, $R_1 = R_2$ = Li
b, $R_1 = R_2$ = H



4

of a naturally occurring γ-(hydroxymethyl)-α,β-butenolide which was isolated recently from *Memycelon Umbelatum* Burm.[3,4] The crude extract of this plant has been shown to exhibit activity against Ranikhe disease virus and also to have spasmolytic and antiamphetamine activity.[5]

We report the first synthesis of (±)-**1a** via preparation of its benzyl derivative **1b** followed by removal of the hydroxyl protecting group by catalytic hydrogenation. Two routes were employed for the synthesis of **1b**. The first and shorter of these involved preparation of lithium (*E*)-3-lithio-2-butenoate (**2a**) by treatment of the corresponding bromo acid **2b** with 2 equiv of *n*-butyllithium in ether at −78 °C[6] and reaction of this organolithium reagent with (benzyloxy)acetaldehyde followed by acidification. The approach allowed the preparation of **1b** in 61% yield and in a single operation but it suffers from the disadvantage that the starting bromo acid **2b** is not readily available. In fact, the best procedure that we have found for the preparation of **2b** allowed its isolation in less than 10% yield. This involved the Favorskii rearrangement of a mixture of tribromobutanones to a mixture of **2b** and the isomeric (*Z*)- and (*E*)-3-bromo-2-methylpropenoic acids and isolation of the desired product by crystallization.[6-8]

Recently, we found that β-bromo-α,β-butenolides may be prepared by reaction of lithium (*E*)-3-bromo-3-lithiopropenoates, e.g., **3a**, with carbonyl compounds in tetrahydrofuran (THF) or diethyl ether at −78 °C followed by acidification.[9] It appeared that if the bromobutenolide **4** could be synthesized by this method that it should be possible to replace the halogen atom by a methyl group by using an appropiate cuprate reagent.[10] This approach to butenolide **1b** was also successful, but we were able to accomplish the last step only in low yield.

The organolithium reagent **3a**, which was required for the synthesis of **4**, was prepared by treatment of the corresponding (*E*)-bromo acid **3b** with 2 equiv of *n*-butyllithium in THF at −78 °C. ((*E*)-Bromo acid **3b** was easily prepared by heating a neat sample the corresponding *Z* isomer,[11a] which is readily available from Favorskii rearrangement of tribromoacetone,[11b] at 120 °C for 3 h.) Reaction of **3a** with (benzyloxy)acetaldehyde in THF −78 °C followed by acidification gave the β-bromobutenolide **4** in 65% yield. Treatment of this compound with the lithium dimethylcuprate–dimethyl sulfide complex[12] at −78 °C for 4 h followed by warming of the mixture to −30 °C, workup under acidic conditions, and separation of the product from the unreacted β-bromobutenolide by preparative thin-layer chromatography allowed the isolation of the desired β-methylbutenolide **1b** in 28% yield (the yield was 55% based upon unrecovered starting material). Several attempts, using the lithium dimethylcuprate reagent, were made to improve the yield in the conversion of **4** into **1b**. When the reaction was run at −30 °C rather than −78 °C, a significant amount of what appeared to be the β,γ-double bond isomer of **4** was recovered. This suggested that at the higher temperature partial deprotonation of the butenolide by the cuprate reagent had occurred. When a longer reaction time or a larger excess of the cuprate reagent was employed, a smaller quantity of starting material was recovered, but the isolated yield of **1b** was not improved. Lithium methyl(thiophenyl)cuprate has been used successfully for the conversion of cyclic β-halo enones into the corresponding β-methyl enones.[13] However, attempts to use this reagent for the conversion of **4** into **1b** were unsuccessful.

Hydrogenolysis of the benzyl group in **1b** in ethyl alcohol containing 10% palladium–carbon at atmospheric pressure gave crude (±)-umbelactone (**1a**) in ~90% yield. Subjection of the material to preparative TLC gave pure (±)-**1a**, mp 60–62 °C. The synthetic material showed IR

(1) This research was supported by Grant 7810044 from the National Science Foundation, for which we are grateful.

(2) (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (b) Avetisysan, A. A.; Dangyan, M. T. *Russ. Chem. Rev.* **1977**, *46*, 643. (c) Larock, R. C.; Riefling, B.; Fellows, C. A. *J. Org. Chem.* **1978**, *43*, 131.

(3) Agarwal, S. K.; Rastogi, R. P. *Phytochemistry* **1978**, *17*, 1663.

(4) Recently, there has been a considerable amount of interest in the synthesis of optically active γ-(hydroxymethyl)-α,β-butenolides, which are useful starting materials for the synthesis of antileukemic lignan lactones. See: (a) Tomioka, K.; Ishiguro, T.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 652. (b) Tomioka, K.; Ishiguro, T.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2973. (c) Estopa, C.; Font, J.; Moreno-Manas, M.; Sanchez-Ferrando, F.; Valle, S.; Vilamojo, L. *Ibid*, **1981**, *22*, 1467. (d) Camps, D.; Font, J.; Ponsati, O. *Ibid* **1981**, *22*, 1471.

(5) Dhar, M. L; Dhar, M. M.; Dhawan, B. N.; Mehrotra, B. N.; Ray, C. *Indian J. Exp. Biol.* **1968**, *6*, 241.

(6) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 5167.

(7) Rappe, C.; Nilson, T.; Carlson, G.; Andersson, K. *Arkiv. Kemi* **1965**, *24*, 95.

(8) Frobese, A. S. Ph.D. Dissertation, Georgia Institute for Technology, 1979.

(9) Caine, D.; Samuels, W. D. *Tetrahedron Lett.* **1980**, *21*, 4057.

(10) Larock and co-workers[2c] have reported that certain organocuprates react readily with β-chloro-α,β-butenolides to give the corresponding β-alkyl derivatives. However, no specific examples were provided.

(11) (a) It has been shown previously (see: Crout, D. H. G.; Corkill, J. A. *Tetrahedron Lett.* **1977**, 4355) that the (*E*)-bromo acid is thermodynamically favored over the *Z* isomer at higher temperatures. Note that in footnote 6 of this paper the designations of the configurations of the *E* and *Z* acids have been transposed. (b) Rappe, C. *Acta Chem. Scand.* **1965**, *19*, 31.

(12) House, H. O.; Chu, C. Y.; Wilkens, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

(13) Piers, E.; Nagakura, I. *Ibid.* **1975**, *40*, 2694.

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and NMR (^{1}H and ^{13}C) spectral properties identical with an authentic sample of (+)-umbelactone.[14]

The mass spectra of the two samples were also the same within experimental limits on our instruments. However, on electron impact ionization a peak at m/e 129 (M + 1) was the highest mass peak, and on chemical ionization a peak at m/e 257 corresponding to a protonated dimer structuer was observed. Apparently, umbelactone has a very strong tendency to associate in the gas phase.[15] An isomer of **1a** having the methyl group at the α rather than the β position exhibited the same kind of mass spectral behavior as that of **1a**. We are currently investigating the mass spectral properties of other γ-(hydroxymethyl)butenolides.

Experimental Section[16]

Reaction of Lithium (*E*)-3-Lithio-2-butenoate (2a) with (Benzyloxy)acetaldehyde. To a solution of 1.65 g (10 mmol) of (*Z*)-3-bromo-2-butenoic acid in 100 mL of anhydrous ether at −78 °C was added dropwise with stirring under nitrogen 18.00 mL (20 mmol) of 1.08 M *n*-butyllithium. The reaction mixture was stirred for 4 h at −78 °C, and a solution of 1.50 g (10.00 mmol) of (benzyloxy)acetaldehyde in 10 mL of anhydrous ether was added dropwise with stirring. The mixture was stirred for 3 h at −78 °C and allowed to warm to room temperature. Water (50 mL) was added, and after the layers were separated, the aqueous layer was acidified with 3 N HCl and extracted with three 30-mL portions of ether. The combined ethereal extracts were washed with a saturated solution of $NaHCO_3$ and with a saturated brine solution and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo the crude sample was subjected to preparative TLC on silica gel plates with 1:1 ethyl acetate–hexane as the eluting solvent to yield 1.33 g (61%) of the butenolide **1b** as a colorless oil: IR (CCl_4) 3060, 3020, 2900, 2855, 1785, 1645, 1480, 1450, 1435, 1380, 1360, 1282, 1165, 1145, 1115, 1069, 937, 858, 845, 690 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.18 (d, J = 1 Hz, 3 H), 3.75 (d, J = 4 Hz, 2 H), 4.60 (m, 2 H), 4.82 (m, 1 H), 5.78 (m, 1 H), 7.24 (m, 5 H); mass spectrum, m/e (70 eV) M$^+$ 218.0980 (calcd 218.0943).

Reaction of Lithium (*E*)-3-Bromo-3-lithiopropenoate (3a) with (Benzyloxy)acetaldehyde. To solution of 2.0 g (13.3 mmol) of (*E*)-3-bromopropenoic acid (**3b**) in 150 mL of anhydrous THF was added dropwise with stirring at −78 °C under nitrogen 18.0 mL (22.5 mmol) of 1.25 M *n*-butyllithium. The mixture was stirred for 4 h at −78 °C, and a solution of 1.0 g (6.67 mmol) of (benzyloxy)acetaldehyde in 10 mL of dry THF was added dropwise via a syringe. The mixture was stirred for 3 h at −78 °C and then allowed to warm to room temperature. Water (50 mL) was added, and the aqueous layer was separated, acidified with cold 3 N HCl and extracted with three 20-mL portions of ether. The combined ethereal extracts were washed with two 20-mL portions of a saturated solution of $NaHCO_3$ and two 20-mL portions of saturated brine and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo recrystallization of the residue from low-boiling petroleum ether gave 1.23 g (65%) of butenolide **4** as off-white crystals: mp 57.0–58.0 °C; IR (CCl_4) 3020, 2920, 2850, 1785 (br), 1605, 1540, 1450, 1360, 1320, 1240, 1140, 1051, 1000, 920, 850 cm^{-1}; ^{1}H NMR (CCl_4) δ 3.80 (d, J = 2 Hz, 1 H), 3.85 (d, J = 2 Hz, 1 H), 4.52 (s, 2 H), 4.94 (m, 1 H), 6.02 (d, 2 Hz, 1 H), 7.22 (m, 5 H). Anal. Calcd for $C_{12}H_{11}BrO_3$: C, 50.90; H, 3.92. Found: C, 50.93; H, 3.93.

Conversion of β-Bromobutenolide 4 into the β-Methylbutenolide 1b by Reaction with $(CH_3)_2CuLi\cdot(CH_3)_2S$. A solution of methyllithium (3.20 mL of 1.7 M CH_3Li in ether) was added dropwise with stirring under nitrogen to a solution of 0.8 g (4 mmol) of $CuBr\cdot S(CH_3)_2$ in 5 mL each of $(CH_3)_2S$ and anhydrous ether at −20 °C until the initially formed yellow precipitate of CH_3Cu just dissolved. The resulting colorless solution was cooled to −78 °C, and a solution 0.56 g (2.00 mmol) of butenolide **4** in 10 mL of dry THF was added dropwise with stirring. The mixture was stirred at −78 °C for 4 h and allowed to warm to −30 °C, and 1 mL of 2 N HCl was added. Then, 250 mL of a saturated solution of NH_4Cl was added, and the mixture was stirred vigorously for 15 min while being allowed to warm to room temperature. The mixture was filtered, and the layers were separated. The organic layer was washed with a saturated brine solution and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo the residue was subjected to preparative TLC on silica gel plates using 1:1 ethyl acetate–hexane as the developing solvent. This led to the recovery 0.28 g of the starting butenolide **4** and 0.12 g (55% based upon unrecovered starting material) of the β-methylbutenolide **1b**. The product showed spectral properties identical with those reported above.

Preparation of (±)-Umbelactone (1a). A stirred mixture of 100 mg of 5% palladium–carbon in 20 mL of absolute ethyl alcohol was presaturated with hydrogen. Then, 0.42 g of the butenolide **1b** in 10 mL of absolute ethyl alcohol was added via a syringe. Hydrogenolysis of the mixture was carried out at 25 °C and 1 atm until the theoretical amount of hydrogen (~40.00 mL) was absorbed. The catalyst was removed by filtration, and the ethyl alcohol was removed in vacuo. The residue oil was dissolved in 50 mL of ether, and the solution was dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo the residue was subjected to preparative TLC on silica gel plate using a 4:1 hexane–ethyl alcohol mixture to give 0.19 g (76%) of (±)-umbelactone **1a**, mp 60–62 °C.

Registry No. (±)-**1a**, 84412-93-1; (±)-**1b**, 84304-02-9; **2b**, 591-02-6; **3b**, 69169-56-8; (±)-**4**, 84304-03-0; (benzyloxy)acetaldehyde, 60656-87-3.

(14) We are grateful to Dr. R. P. Rastogi for providing us with an authentic sample of (+)-umbelactone.

(15) In order to confirm that umbelactone exists as a monomer in the solid state, an X-ray diffraction analysis was performed on a single crystal of (±)-umbelactone. We are grateful to Dr. Dan VanDever and Mr. Everett Crews for carrying out this analysis for us.

(16) Melting points were determined with a Fisher-Johns hotstage and are uncorrected. The IR spectra were determined with a Perkin-Elmer 457 infrared spectrophotometer. The ^{1}H NMR spectra were determined at 60 MHz with a Varian Model T-60 spectrometer or at 300 MHz with a Bruker Model WM-300 NMR spectrometer. The ^{13}C spectra were determined at 75 MHz with a Bruker Model WM-300 NMR spectrometer. The chemical shifts are expressed in δ values relative to Me_4Si as the internal standard. The mass spectra were obtained with either a Hitachi Perkin-Elmer Model RMU-7 or a Varian Mat Model 1125 mass spectrometer. Microanalyses were performed by Atlantic Microlabs, Inc., Atlanta, GA.

Synthesis of the *Streptomyces ambofaciens* Antineoplastic Constituent 6-Diazo-5-oxo-L-norleucine[1]

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The antineoplastic antibiotic 6-diazo-5-oxo-L-norleucine (**1**, Scheme I), commonly known as DON, was first isolated by Dion and colleagues[2] from a Peruvian soil *Streptomyces* and by Rao and co-workers[3] from *Streptomyces ambofaciens*. About 20 years ago DON was given a few brief human trials and found e.g., to cure two of four patients with choriocarcinoma and one of four with testicular cancer. DON also proved effective in correcting hypercalcemia and hypercalciuria arising from bone metastases typical of breast cancer.[4] In the same period several total

(1) The 84th part of the series Antineoplastic Agents: for contribution 85 refer to G. R. Pettit, G. M. Cragg, D. L. Herald, J. M. Schmidt, and P. Lohavanijaya, *Can. J. Chem.* **60**, 1374 (1982).

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(4) For leading references consult (a) R. Catane, D. D. von Hoff, D. L. Glaubiger, and F. M. Muggia, *Cancer Treat. Rep.*, **63**, 1033 (1979) and (b) R. H. Earhart, J. M. Koeller, and H. L. Davis, *ibid.* **66**, 1215 (1982).

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