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).

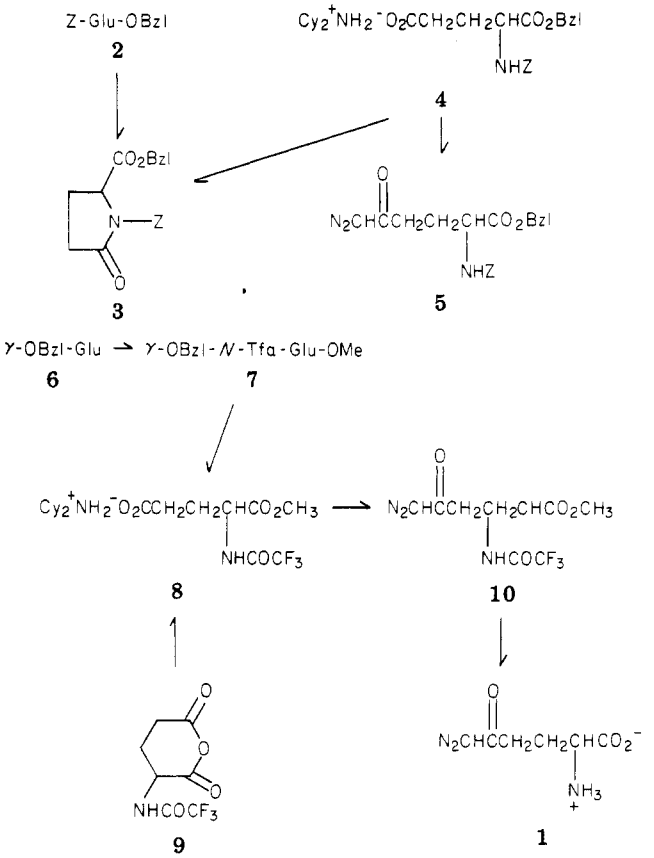
(2) H. W. Dion, S. A. Fusari, Z. L. Jakubowski, J. G. Zora, and Q. R. Bartz, *J. Am. Chem. Soc.*, **68**, 3075 (1956).

(3) K. V. Rao, S. C. Brooks, Jr., M. Kugelman, and A. A. Romano, *Antibiot. Ann.*, 943–949 (1959–1960); see also K. V. Rao, *Antimicrob. Agents Chemother.*, 179–187 (1962).

(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).

0022-3263/83/1948-0741$01.50/0

Scheme I



syntheses of DON were described, albeit in 0.5–1% overall yields.[5]

Because of the relatively poor dosage form (oral),[6] toxicity problems, and introduction of the more effective methotrexate for choriocarcinoma treatment, interest in DON quickly subsided.[4] Fortunately, recent experimental treatment of nude mice bearing human breast (MX-1), colon (CX-2), and lung (LX-1) xenografts with DON has shown this substance to be more effective than current well-known drugs such as adriamycin and methotrexate.[4a] Due to these useful observations, combined with the view that DON enhibits[4a,7] de novo purine biosynthesis by inhibiting transamidations utilizing glutamine,[8] the U.S. National Cancer Institute has renewed clinical trials[4b] of DON. For the purpose of increasing the availability of DON we have devised a new and convenient synthesis.

In one of our initial approaches partially protected L-glutamic acid **2** was treated under a variety of conditions with oxalyl chloride. But instead of the corresponding acid chloride necessary for diazo ketone preparation, only pyroglutamic acid **3** was obtained. However, synthesis of diazo ketone **5** from dicyclohexylamine (Dcha) salt **4** was readily accomplished by uncovering a new and useful method for conversion of amino acids to acid chlorides by reaction (at 0 °C) of a dicyclohexylammonium salt derivative with oxalyl chloride. Unfortunately, a variety of methods such as 5% palladium–carbon catalyzed hydrogenation (in ethanol),[9a] cyclohexene with palladium or 10% palladium–carbon,[9b] and trifluoroacetic acid[9a] for cleavage of the protecting groups resulted in destruction of the diazo ketone. Decomposition was detected by disappearance of the characteristic diazo ketone 2100-cm^{-1} infrared absorption.

Eventually, application of the base-sensitive trifluoroacetyl N-protecting group and the new acid chloride procedure just noted led to a very convenient synthesis (**6** → **1**) of DON. Commercially available γ-OBzl-Glu was treated with methyl trifluoroacetate–tetramethylguanidine[10] followed by diazomethane to afford (91%) *N*-Tfa-protected glutamic acid **7**. Palladium (5%) catalyzed hydrogenolysis of the benzyl ester and conversion to the dicyclohexylammonium salt **8** proceeded in 95% yield. Alternatively but less effectively (22% recovery), methanolysis of *N*-Tfa-Glu anhydride (**9**) followed by addition of dicyclohexylamine was found to provide Dcha salt **8**. Slow addition of a methylene chloride solution of oxalyl cloride to Dcha salt **8** (in the same solvent at 0 °C) and addition of the resulting acid chloride to an ethereal solution of diazomethane gave (16% following chromatographic purification) diazo ketone **10** as a yellow oil. Rapid (30 min) ambient-temperature saponification followed by Sephadex LH-20 chromatography yielded (88%) DON (**1**) in 12% overall conversion from γ-OBzl-Glu.

The preceding approach to amino acid diazo ketones should simplify the synthesis of such substances[11] and we are presently using these methods for total synthesis of azotomycin.[12]

Experimental Section

Z-L-Glu and γ-OBzl-L-Glu were obtained from Vega Biochemicals and Sigma Chemical Co., respectively. All solvents were redistilled, and solvent extracts were dried over sodium sulfate. Tetrahydrofuran was distilled from lithium aluminum hydride. Silica gel F-254 (0.25 mm, E. Merck, Darmstadt) plates were used for thin-layer chromatography, and the plates were viewed with UV light or developed with a 1% ninhydrin spray. Column chromatography employed silica gel (70–230 mesh) and neutral alumina supplied by E. Merck (Darmstadt) or Sephadex LH-20 manufactured by Pharmacia Fine Chemicals, AB, Uppsala, Sweden.

Melting points were observed with a Kofler melting point apparatus. Optical rotation and infrared measurements were recorded with a Perkin-Elmer 241 polarimeter and a 299 infrared spectrophotometer, respectively. For nuclear magnetic resonance measurements (by Dr. J. Witschel, Varian XL-100, Varian T-60A, and Bruker WH-90 instruments) deuteriochloroform was used as solvent and tetramethysilane as an internal standard. The mass spectra (70 eV and FAB) were recorded by Mr. D. Adams employing a Mat 312 instrument. Elemental analyses were determined by the Spang Microanalytical Laboratory, Eagle Harbor, MI.

Z-L-pGlu-OBzl (3). Procedure A. Oxalyl chloride (0.80 mL, 9.0 mM) was added (dropwise) to a solution of *N*-Z-L-Glu-OBzl (**2**, 2.0 g, 3.6 mM)[13] in dry methylene chloride (35 mL, room temperature). After stirring for 1 h at room temperature, the solution was filtered and solvent evaporated at 25 °C. Solidification was induced by addition of carbon tetrachloride and *n*-hexane. Recrystallization from acetone–*n*-hexane gave 1.05 g

(5) Cf. H. A. DeWald and A. M. Moore, *J. Am. Chem. Soc.*, **80**, 3941 (1958); F. Weygand, H. Bestmand, and E. Klieger, *Chem. Ber.*, **91**, 1037 (1958). The latter report is closely related to our study and was located (during a search of diazo ketone rearrangement reactions) when the present contribution was in press. Apparently the Weygand synthesis was missed in prior summaries of DON syntheses and abstracts.

(6) DON is most stable at pH 4.5–6.5[2] and is probably rapidly destroyed in gastric solutions.

(7) J. Roberts, F. A. Schmid, and H. J. Rosenfeld, *Cancer Treat. Rp.*, **63**, 1045 (1979).

(8) Such glutamine antagonists may prove useful in the treatment of colon cancer; cf. P. V. Woolley, III, R. Coit, and M. Magno, *Cancer Treat. Rep.*, **63**, 1039 (1979).

(9) (a) G. R. Pettit, "Synthetic Peptides", Vol. 4, Elsevier, Amsterdam, The Netherlands, 1976; (b) A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, **43**, 4194 (1978).

(10) W. Steglich and S. Hinze, *Synthesis*, 399 (1976).

(11) Z. Sajadi, M. Kashani, L. J. Loeffler, and I. H. Hall, *J. Med. Chem.*, **23**, 275 (1980).

(12) G. R. Pettit and G. C. Cragg, "Biosynthetic Products for Cancer Chemotherapy", Vol. 2, Plenum, New York, 1978, p 98.

(13) J. S. Morley, *J. Chem. Soc.*, 2410 (1967).

(82%) of colorless crystals: mp 111–112 °C (lit.[14] mp 106–107, 110 °C); $[\alpha]^{25}_D$ −41.3° (c, 1.375, EtOH, lit.[14] $[\alpha]^{25}_D$ −41.2°).

Procedure B. A solution of Z-L-Glu-OBzl-γ-Dcha salt (4, 3.4 g, 6 mM)[13] in ethyl acetate (20 mL) was stirred while 3.5 N HCl in ethyl acetate (3.5 mL, 12 mM, 2 equiv) was added dropwise. The mixture was agitated for 1.5 h, the solution was filtered, and the solid was washed with ice-cold ethyl acetate. The combined filtrate was washed (4 × 10 mL) with water and evaporated (in vacuo) to a colorless oil. A stirred solution of the oil in dry toluene (40 mL) was treated (dropwise) with oxalyl chloride (1.05 mL, 12 mM) in dry toluene (10 mL) at room temperature. The solution was heated at 50 °C for 2 h, the solvent was evaporated (in vacuo) and dry toluene (30 mL) was twice added and reevaporated to assure removal of excess oxalyl chloride. The residue was dissolved in carbon tetrachloride (25 mL) and cooled (ice bath) to give 1.5 g (60%) of pyroglutamic acid derivative 3 as a colorless solid melting at 116–118 °C.

***N*-Z-6-diazo-5-oxo-L-norleucine Benzyl Ester (5).** To a cold (ice-bath) solution of Z-L-Glu-α-OBzl-γ-Dcha salt (4, 1.5 g, 2.3 mM)[13] in dry methylene chloride (40 mL) was added (dropwise over 10 min) oxalyl chloride (3 mL, 35 mM) in dry methylene chloride (9 mL) with constant stirring. After 15 min, the ice bath was removed, and the mixture was stirred for an additional 5 min. The solvent was evaporated below 10 °C, and cold (and dry) chloroform (10 mL) was twice added and reevaporated. Cold (and dry) tetrahydrofuran (15 mL) was added, the solution was filtered, and the solid was washed with 5 mL of cold tetrahydrofuran. The combined filtrate was added (dropwise over 10 min) to a diazomethane solution (prepared from 5 g of *N*-nitrosomethylurea, 15 mL of 40% aqueous potassium hydroxide, and 50 mL of ethyl ether) and stirred for 0.5 h at ice-bath temperature and 0.5 h at room temperature. Upon removal (in vacuo) of solvent, 1.15 g of the crude diazoketone 5 was obtained as a brown oil and chromatographed on a column of silica gel (40 g) with 5:1 *n*-hexane–acetone as eluent. The fractions exhibiting TLC R_f 0.78 (acetone) were combined, and the solvent was evaporated to yield 0.45 g (42%) of pure diazo ketone 5 as light yellow crystals: mp 84.5–86 °C; $[\alpha]^{30}_D$ +6.76° ($CHCl_3$); EI mass spectrum, *m/e* 367 (loss of N_2, no observable molecular ion); IR (KBr) 3338, 2110, 1735, 1692, 1630, 1390, 1323, 1280, 747, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80–2.60 (m, 4 H)8 4.27–4.57 (m, 1 H, asymmetric α-H), 5.16 (d, 3 H, CH_2Ph overlapping CHN_2), 5.21 (s, 2 H, CH_2Ph), 5.72 (d, *J* = 7 Hz, 1 H, NH), 7.41 (s, 10 H, Ar).

Anal. Calcd for $C_{21}H_{21}N_5O_3$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.86; H, 5.34; N, 10.55.

γ-OBzl-*N*-Tfa-L-Glu-OMe (7). A suspension of γ-OBzl-L-Glu (2.0 g, 8.4 mM) in methyl trifluoroacetate (10 mL) was cooled (ice bath) and stirred while tetramethylguanidine (1.5 g, 13 mM) was added dropwise. The ice bath was removed, and stirring was continued for 16.5 h at room temperature. Water (30 mL) was added, and the mixture was acidified with concentrated hydrochloric acid and extracted (2 × 100 mL) with ethyl acetate. The organic layer was washed (3 × 50 mL) with water, dried, and concentrated to yield 2.8 g of colorless oil. The oil was dissolved in dry ether (30 mL) and cooled (ice bath) and an ethereal solution of diazomethane (prepared from 5 g of *N*-nitrosomethylurea) was added (dropwise) until a slight yellow color persisted. After 15 min at room temperature, the solvent was evaporated by using a stream of nitrogen (hood) to afford 3.0 g of crude diester 7. The product was purified by chromatography on silica gel (45 g), and the fractions (TLC R_f 0.75 with 1:2 ethyl acetate–methylene chloride) eluted by 1:19 ethyl acetate–methylene chloride gave 2.63 g (90%) of diester 7 as a colorless oil that solidified on standing (all attempts at crystallization failed): mp 44–45 °C; $[\alpha]^{34}_D$ +17.7° ($CHCl_3$); EI mass spectrum, *m/e* 347 (M^+), 240, 213, 212, 185, 180, 153, 152; IR (neat) 3325, 1722 br, 1550, 1453, 1439, 1210, 1168, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00–2.63 (m, 4 H), 3.78 (s, 3 H, OMe), 4.48–4.82 (m, 1 H), 5.17 (s, 2 H), 7.42 (s, 5 H, Ar), 7.56–7.66 (m, 1 H, NH).

Anal. Calcd for $C_{15}H_{16}F_3NO_5$: C, 51.88; H, 4.64; N, 4.03. Found: C, 51.92; H, 4.59; N, 4.03.

***N*-Tfa-L-Glu-OMe-γ-Dcha Salt (8). Procedure A.** A mixture of γ-OBzl-*N*-Tfa-L-Glu-OMe (7, 2.8 g, 8 mM) in 95% ethanol (350 mL) and 5% palladium–carbon (2 g) was stirred at room temperature while a current of hydrogen was passed through the reaction flask (equipped with a mercury bubbler) for 1 h. After filtering (Celite) the solvent was evaporated under reduced pressure to yield a pink oil. To a solution of the oil in diethyl ether (100 mL) was added (dropwise) dicyclohexylamine (2.35 mL, 11.8 mM) with stirring. After cooling overnight, filtration, and recrystallization of the ammonium salt from chloroform–ethyl acetate, 3.35 g (95%) of small colorless crystals were obtained: mp 165–167 °C; $[\alpha]^{34}_D$ +35.1° ($CHCl_3$); FAB mass spectrum, *m/e* 439 (MH^+) 280, 258; IR (KBr) 3410 br, 2948, 2860, 1752, 1722, 1640, 1545, 1409, 1187, 1152 cm^{-1}; ^{1}H NMR (CDCl) δ 0.90–2.54 (m, 24 H), 2.68–3.22 (m, 2 H), 3.79 (s, 3 H, OMe), 4.14–4.57 (m, 1 H), 7.20–8.18 (br m, 3 H, NH and NH_2^+).

Anal. Calcd for $C_{20}H_{33}F_3NO_{20}$: C, 54.8; H, 7.59; N 6.39. Found: C, 54.70; H, 7.58; N, 6.36.

Procedure B. A solution of *N*-Tfa-L-Glu anhydride (5.6 g, 25 mM)[14] in absolute methanol (120 mL) was stirred at room temperature for 48 h. After removal of solvent the thick oily residue was chromatographed on a column of silica gel (550 g) with 90:10:1 chloroform–methanol–water as eluent. After passage of 3 L the solvent system ratio was changed to 70:30:2. Fractions containing the component with TLC F_f 0.33 (80:20:2 chloroform–methanol–water) were collected and concentrated to yield 1.5 g of a colorless oil. To a solution of the oil in tetrahydrofuran (50 mL) was added dicyclohexylamine (1.16 mL). The mixture was stirred for 2 h and allowed to stand overnight in a refrigerator. The solid was collected and washed with tetrahydrofuran to provide 2.4 g (22%) of Dcha salt 8.

6-Diazo-5-oxo-*N*-Tfa-L-norleucine-OMe (10). Oxalyl chloride (0.42 mL, 4.7 mM) in dry methylene chloride was added dropwise to a stirred solution of *N*-Tfa-L-Glu-OMe-γ-Dcha salt (8, 2.0 g, 4.6 mM) in dry methylene chloride (45 mL) at 0 °C, and the solution was filtered (cooling) through a fine sintered glass filter into an addition funnel and added dropwise at 0 °C to an ethereal solution of diazomethane (from 5 g of *N*-nitrosomethylurea). The resultant solution was stirred at 0 °C for 0.5 h, and the solvent was removed from the cold solution by using a stream of nitrogen (hood). A solution of the residue in a minimum amount of methylene chloride was chromatographed on a column of deactivated alumina (7.9% water, 105 g, EM neutral act. I) with the same solvent. Fractions containing the product with TLC R_f 0.14 (2:1 *n*-hexane–ethyl acetate) afforded 0.20 g (16%) of diazo ketone 10 as a yellow oil: $[\alpha]^{25}_D$ +25° (c, 1.42, $CHCl_3$); FAB mass spectrum, *m/e* 282 (MH^+); IR 3300 br, 2108, 1727 br, 1634, 1555, 1442, 1210, 1170 d cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.85–2.78 (m, 4 H), 3.80 (s, 3 H, OMe), 4.35–4.82 (m, 1 H), 5.35 (s, 1 H, CHN_2), 7.82–8.28 (m, 1 H, NH).[15]

6-Diazo-5-oxo-L-norleucine (1, DON). To a cold (ice bath) solution of 6-diazo-5-oxo-*N*-Tfa-L-norleucine-OMe (0.38 g, 1.35 mM) in methanol (0.5 mL) was added sodium hydroxide (1.0 N, 4.0 mL, 4.05 mM) dropwise with stirring. Upon stirring for 30 min at ambient temperature the mixture was acidified with cooling (ice bath) to pH 6.9 with 0.5 N hydrochloric acid. The aqueous solution was extracted with chloroform (2 × 10 mL) and diethyl ether (1 × 10 mL). Following lyophilization the light brown solid residue was dissolved in 1:1 water–methanol (2 mL) and chromatographed on a column (2.5 × 150 cm) of Sephadex LH-20 (250 g, 1-L bed volume) with methanol. Fractions containing the component with TLC R_f 0.14 (2:3 chloroform–methanol, tailing, UV visible) were combined, and the solvent was evaporated to yield a light yellow solid. Recrystallization was accomplished by dissolving the solid in 6 drops of water followed by enough dry methanol to sufficiently reduce the solubility of DON. The solid was collected and washed with a few drops of dry methanol and a few drops of diethyl ether to give 0.204 g (88%) of 6-diazo-5-oxo-L-norleucine (1) as a yellow-green solid decomposing at 146 °C (lit.[2] mp 144–155 °C dec); $[\alpha]^{34}_D$ +19.5° (c, 2.05 in water; lit.[2] $[\alpha]^{26}_D$ +21° in water); UV λ_{max} (H_2O) 274 nm (ε 10889); FAB mass spectrum, *m/e* 194 (M + Na), 172 (M + H); IR (KBr)[16] 3430, 2109, 1633, 1590, 1505, 1390 cm^{-1}; ^{1}H NMR (D_2O)[16] δ 2.13 (m, 2 H), 2.59

(14) (a) F. Waygand and E. Leising, *Chem. Ber.*, **87**, 248 (1954); (b) E. Klieger and H. Gibian, *Liebigs Ann. Chem.*, **655**, 195 (1962).

(15) Because of the instability of this compound at room temperature, elemental analyses were not obtained.

(16) An authentic sample (Sigma Chemical Co.) was identical with the synthetic specimen.

(t, J = 7 Hz, 2 H), 3.77 (t, J = 4 Hz, 1 H), 5.95 (s, 1 H, CHN_2); ^{13}C NMR (1:1 D_2O–D_3COD, 0 °C) δ 27.0, 36.5, 55.0, 58.1, 174.4, 198.4.

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Registry No. 1, 157-03-9; 2, 3705-42-8; 3, 71389-33-8; 4·DCHA, 53363-74-9; 5, 84332-53-6; 6, 1676-73-9; 7, 84369-01-7; 8·DCHA, 84344-29-6; 9, 1535-57-5; 10, 7589-24-4.

Oxidation of Acylphosphoranes with Sodium Hypochlorite. Substituted Carboxylic Acids through Charge-Directed Conjugate Addition Reactions

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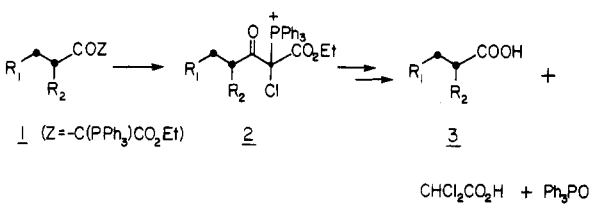
We have previously described a useful new approach to conjugate addition–alkylation reactions involving the charge-directed conjugate additions of a variety of nucleophiles to unsaturated acylcarbalkoxytriphenylphosphoranes with subsequent capture of intermediate ylide anions by electrophiles.[1] The resulting substituted ylides **1** may then be transformed into esters by acid catalyzed alcoholysis,[1a] into methyl ketones through decarbalkoxylation of *tert*-butyl ylide esters,[1c] and into highly substituted ketones by reduction of the ylide moiety and subsequent transformations of derived β-keto esters.[1d]

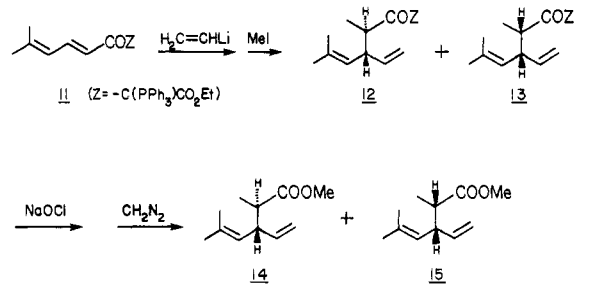
In the course of applying this new methodology to several natural product syntheses, we have found that the transformation to simple esters through the acid-catalyzed alcoholysis of the acyl ylide function is unsatisfactorily slow in cases where both C_α and C_β are highly substituted and that trisubstituted olefins undergo alcohol addition under the acidic reaction conditions.[2] We therefore required a mild method for the conversion of the ylide moiety to the carboxyl group and were led to investigate haloform-type oxidative cleavages,[3] in that, unlike acylphosphoranes,[1e] acylcarbalkoxyphosphoranes are not cleaved in neutral or alkaline media.[1f] We now report that phosphoranes such as **1** are readily cleaved by slightly more than 2 equiv of alkaline NaOCl (Scheme I) giving good yields of carboxylic acids.[3] Typical examples are shown in Table I. The reaction presumably occurs through chlorinated phosphonium intermediate **2**, which then undergoes either direct cleavage by hydroxide ion attack at the C-3 carbonyl group or through hydroxide ion displacement at phosphorous to give triphenylphosphine oxide and the chlorinated β-keto ester anion, which can then undergo a classical haloform reaction.[3]

Tetrahydrofuran (THF) and acetonitrile (AN) were found to be the best solvents for this reaction with somewhat faster rates being observed in acetonitrile. Lower yields were generally observed when MeOH was employed (see entry 5). The higher pH (≥10) required for the aqueous phase was difficult to maintain with EtOAc as the solvent though the previously reported acceleration in the rate of hypohalite reactions in this solvent was observed.[4] Triphenylphosphine oxide resulting from the reaction is readily removed by extraction prior to acidification of the aqueous phase, and extraction of the acidified mixture with pentane allows efficient separation of the desired carboxylic acid from an equal amount of water-soluble dichloroacetic acid, which is also formed.[5] In general, oxidations proceeded readily at 25 °C except in the case of entry **3**, which required somewhat more vigorous conditions owing to the presence of a less reactive carbonyl group. The more highly substituted ylides **8–10**, which undergo the acid-catalyzed alcoholysis process only very slowly, were also readily converted to the corresponding carboxylic acids. Equally noteworthy is the conversion shown in entry **4**, which demonstrates the compatability of the trisubstituted olefin moiety in **7** with these reaction conditions.

Scheme I



Scheme II



The utility of this conversion is demonstrated in a synthesis[6] of racemic methyl *epi*-santolinate[7] shown in Scheme II. In accordance with our previous finding that diene acyl ylides undergo 1,4-additions[1a] rather than the 1,6-additions common with Gilman reagents,[8] treatment of **11** with vinyllithium gave an intermediate ylide anion that upon alkylation with methyl iodide provided diastereomeric alkylated ylides **12** and **13** in 73% yield. The mixture was composed predominately of the 2R*,3R* isomer **12** (**12**:**13** = 9:1) as expected on the basis of steric considerations. Treatment of the mixture with NaOCl in acetonitrile gave the intermediate carboxylic acids (77%), which were esterified with CH_2N_2 giving esters **14** and **15** in 92% yield. The major component, **14** was identical with

(1) (a) Cooke, M. P., Jr.; Goswami, R. *J. Am. Chem. Soc.* **1977**, *99*, 642. (b) Cooke, M. P., Jr. *Tetrahedron Lett.* **1979**, *20*, 2199. (c) Cooke, M. P., Jr.; Burman, D. L. *J. Org. Chem.* **1982**, *47*, 4955. (d) Cooke, M. P., Jr. *Ibid.* **1982**, *47*, 4963. (e) Cooke, M. P., Jr. *Ibid.* **1973**, *38*, 4082. (f) Chopard, P. A.; Searle, R. J. G.; Devitt, F. H. *Ibid.* **1965**, *30*, 1015.

(2) Acidic methanolysis of **7** (1.7 equiv of HCl, 20 h at reflux) gives predominately methyl 5-methoxy-5-methoxy-5-methylhexanoate.

(3) Fuson, R. C.; Bull, B. A. *Chem. Rev.* **1934**, *15*, 275.

(4) Lee, G. A.; Freedman, H. H. *Tetrahedron Lett.* **1976**, 1641.

(5) Attempts to avoid the generation of dichloroacetic acid through the use of the corresponding *tert*-butyl ester ylide (**5**, Z = C(PPh$_3$)COO-*t*-Bu) were not successful. Hydrocinnamic acid was obtained in 87% yield after 8 h at 25 °C, however.

(6) A synthesis giving predominately methyl santolinate (**13**) has been reported: Boyd, J.; Epstein, W. *J. Chem. Soc., Chem. Commun.*, **1976**, 380.

(7) Noble, T. A.; Epstein, W. W. *Tetrahedron Lett.* **1977**, 3931.

(8) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Corey, E. J.; Chen, R. H. K. *Tetrahedron Lett.* **1973**, 1611. (c) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240.

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