was suggested to contain two rings, another ring must be formed by an ether linkage. The ^1H and ^{13}C chemical shifts of oxymethine groups (C-7, -8, -13, -16, and -17) indicated the absence of the epoxide ring.[9a,b] Since the $\Delta^{9,10}$-double bond was *E*, ether formation from C-7 or C-8 to C-13, C-16, or C-17 is unlikely. The oxygen function at C-17 is a hydroxyl group, because the H-17 signal was coupled with a hydroxyl proton by 4.5 Hz. Thus the ether linkage had to be constructed between C-13 and C-16 by process of elimination to form a tetrahydrofuran ring that is entropically most preferred. Thus the structure of amphidinolide E was concluded to be **1**.[17]

Amphidinolide E (**1**) is a novel antileukemic 19-membered macrolide with an alkyl side chain, and the substitution patterns are different from those of amphidinolides A–D obtained from a different species of the dinoflagellate *Amphidinium* sp.[2,9] Amphidinolide E (**1**) exhibited cytotoxic activity against L1210 (IC_{50} 2.0 μg/mL) and L5178Y (IC_{50} 4.8 μg/mL) murine leukemia cells in vitro.

Experimental Section

General Methods. UV and IR spectra were measured on a Beckmann DU-68 and JASCO IR-810 spectrophotometer, respectively. ^1H and ^{13}C NMR spectra were recorded on a JEOL GSX-270 spectrometer in $CDCl_3$. The 7.26 ppm resonance of residual $CHCl_3$ and 77.0 ppm of $CDCl_3$ were used as internal references, respectively. Mass spectra were obtained on a JEOL HX-100 spectrometer.

Isolation. The procedure for the algal cultivation has been previously described.[9c] The harvested cells (260 g) from 718 L of culture were extracted with methanol/toluene (3:1, 700 mL × 1 and 500 mL × 2). After addition of 1 M NaCl (0.85 L), the mixture was extracted with toluene (500 mL × 3). The toluene-soluble fraction was evaporated under reduced pressure to give a crude residue (13.8 g), which was subjected to silica gel column chromatography (Merck, silica gel 60 (7734); 2.7 × 47 cm) eluted with methanol/chloroform (5:95). The fraction eluting from 320 to 420 mL was further separated by the second silica gel column chromatography (1.6 × 28 cm) eluted with methanol/chloroform (4:96). The fraction eluting from 60 to 160 mL was then purified by HPLC (YMC-Pack AM-323 S-5 120A ODS, Yamamura Chemical, 10 × 250 mm; flow rate, 2.5 mL/min; UV detection at 254 nm; eluant, 88% methanol) to afford amphidinolide E (**1**, 0.9 mg, t_R 12.2 min) together with amphidinolide A (ca. 1 mg, t_R 12.8 min).

Amphidinolide E (1): colorless amorphous solid; UV (MeOH) 230 nm (ε 26 000); IR (film) 3450, 1735, 1460, 1170, and 990 cm^{-1}; ^1H NMR (Table I); ^{13}C NMR ($CDCl_3$) (sp^2 carbons) 174.42 s (C-1), 144.68 s, 144.00 s (C-21 and 25), 135.14 d, 134.93 d, 134.15 d, 133.34 d, 131.40 d, 131.37 d, 129.41 d, 127.93 d (C-3, 4, 5, 6, 9, 10, 22, and 23), 115.70 t, 110.71 t (C-26 and 28); (oxygenated methines) 79.86 d, 78.27 d, 78.04 d, 77.58 d, 76.68 d, 73.20 d (C-7, 8, 13, 16, 17, and 18); (unoxygenated methines) 44.06 d, 32.34 d (C-2 and 19); (aliphatic methylenes) 41.26 t, 36.07 t, 32.60 t, 29.94 t, 28.95 t, 27.14 t (C-11, 12, 14, 15, 20, and 24); (methyls) 22.53 q, 17.52 q, and 15.36 q (C-27, 29, and 30); FABMS (positive ion, glycerol matrix) *m/z* 501 $(M + H)^+$ and 483 $(M - H_2O + H)^+$; FABMS (positive ion, diethanolamine (DEA) matrix) *m/z* 606 $(M + DEA + H)^+$ and 588 $(M + DEA - H_2O + H)^+$.

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Supplementary Material Available: COSY, RCT, *J*-resolved 2D NMR, and ^{13}C and DEPT spectra of Amphidinolide E (4 pages). Ordering information is given on any current masthead page.

(17) The stereochemistry of all chiral centers in **1** remains undefined.

Preparation of α-Fluoro Carboxylic Acids and Derivatives

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Incorporation of fluorine in organic molecules leads to changes in chemical and physical properties that yield products which have applications in many fields. Of particular interest is the ability of fluorine to modify the reactivity of biologically active molecules.[1] α-Fluoro carbonyl derivatives[2] are of importance in themselves and can also be used as building blocks to synthesize more complex molecules.[3] α-Fluoro carboxylate esters are often prepared by condensation reactions of the extremely toxic fluoroacetates.[4] They have also been synthesized from bromofluoroacetates.[5] The advantage of the method presented here is that the carbon skeleton is in place prior to introduction of the fluorine atom.

The fluorination of silyl enol ethers in $FCCl_3$ at −78 °C with fluorine diluted in nitrogen in the formation of α-fluoro ketones and α-fluoro aldehydes has previously been reported.[6] In this note, we report that we have been able to extend this methodology to the synthesis of α-fluoro carboxylic acid and derivatives. Esters,[7] malonates,[8] carboxylic acids,[8] dimethyl amides,[9] and a lactone[7] were silylated with chlorotrimethylsilane by standard procedures. The results of the fluorination of these compounds are presented in Table I.

Several observations are worth noting. The difluorocarbonyl compound was the major byproduct formed in the reaction of the ketene silyl acetals. It generally accounted for lower yields of those silyl derivatives with an α-hydrogen: compare entries 1–3 with entry 4 and entry 5 with entries 6 and 7. The overfluorinated impurity could be eliminated during purification by chromatography. Attempts to minimize the formation of difluoro compounds were unsuccessful.

Of all the silyl derivatives investigated, the yields for the free carboxylic acids were the highest. For these compounds no difluorinated product was obtained. Presumably, the fact that F_2 can interact equally with either silyl group on the ketene bis(trimethylsilyl) acetal is the basis of this result. The α-fluoro carboxylic acids could also be easily prepared by hydrolysis and decarboxylation of the corresponding malonates.[10] Thus, α-fluorophenylacetic

(1) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
(2) Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111.
(3) Yamazaki, T.; Yamamoto, T.; Kitazume, T. *J. Org. Chem.* **1989**, *54*, 83.
(4) Welch, J. T.; Plummer, J. S. *Synth. Commun.* **1989**, *19*, 1081.
(5) Thenappen, A.; Burton, D. J. *Tetrahedron Lett.* **1989**, *30*, 3641, 5571, 6113.
(6) (a) Purrington, S. T.; Lazaridis, N. V.; Bumgardner, C. L. *Tetrahedron Lett.* **1986**, *27*, 2715. (b) Purrington, S. T.; Bumgardner, C. L.; Lazaridis, N. V.; Singh, P. *J. Org. Chem.* **1987**, *52*, 4307.
(7) RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083.
(8) Ainsworth, C.; Chen, F.; Kuo, Y. *J. Organomet. Chem.* **1972**, *46*, 59.
(9) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 881.
(10) Reynolds, G. A.; Hauser, C. A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 709.
(11) Rozen, S. *Synthesis*, **1985**, 665.
(12) Hamman, S.; Beguin, C. G. *Tetrahedron Lett.* **1983**, *24*, 57.
(13) Bethell, D.; McDonald, K. *J. Chem. Soc., Perkin Trans. II* **1977**, 671.
(14) Bagnall, R. D.; Coe, P. L.; Tatlow, J. C. *J. Fluorine Chem.* **1973**, *3*, 329.
(15) Purrington, S. T.; Jones, W. A. *J. Org. Chem.* **1983**, *48*, 761.
(16) Middleton, W. J.; Bingham, E. M. *J. Am. Chem. Soc.* **1980**, *102*, 4846.

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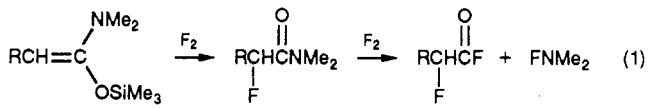
Table I

product	yield (%) (purified)	^{19}F NMR	$^2J_{HF}$	$^3J_{HF}$	lit. ref
1. $CH_3(CH_2)_5CHFCO_2Et$	69	-194.0 (m)	48.0	24.0	11
2. $CH_3CH_2CHFCO_2Et$	57	-194.4 (m)	49.1	24.4	12
3. $C_6H_5CHFCO_2CH_3$	53	-174.4 (d)	48.0		13
4. $(CH_3)_2iCFCO_2CH_3$	76	-146.5 (m)		21.1	14
5. $CHF(CO_2Et)_2$	59	-196.3 (d)	48.0		15
6. $CH_3CF(CO_2Et)_2$	68	-158.0 (q)		24.4	15
7. $C_6H_5CF(CO_2Et)_2$	73	-162.4 (s)			15
8. $CH_3CH_2CHFCON(CH_3)_2$	44[a]	-187.3 (m)	48.8	24.4	*b*
9. $C_6H_5CHFCON(CH_3)_2$	53[c]	-174.6 (d)	49.5		16
10. $CH_3CH_2CHFCO_2H$	83	-194.4 (m)	48.5	24.4	16
11. $C_6H_5CHFCO_2H$	82	-180.5 (d)	48.0		16
12. $O{=}\overline{COCH_2CH_2}CHF$	31	-162.7 (m)			17

[a] $CH_3CH_2CHFCO_2H$ (35%) also obtained. [b] Anal. Calcd for $C_6H_{12}FNO$: C, 52.53; H, 8.83; N, 10.21. Found: C, 52.27; H, 9.19; N, 9.96. [c] $C_6H_5CHFCO_2H$ (31%) also obtained.

acid was prepared in 86% yield from the diethyl phenylfluoromalonate (entry 7).

Fluorination of the ketene silyl amides (entries 8 and 9) led to rather unusual results. The product consisted of a mixture of fluorinated amide and carboxylic acid. Direct fluorination of amides is known to lead to cleavage of the C-N bond.[18] We propose that after formation of the α-fluoro amide, fluorine-promoted cleavage of the dimethylamino group results in *N*-fluorodimethylamine and the acid fluoride (eq 1). A ^{19}F NMR spectrum of the crude reaction mixture showed a multiplet at +24.5; the signal of $FNMe_2$ is reported to be at +24.5.[19] The signal for acyl fluorides is also in this range. On aqueous workup, the acid fluoride hydrolyzes to the observed α-fluoro carboxylic acid.



(1)

The low yield obtained from the lactone (entry 12) is attributed to difficulty in purifying the fluoro derivative. In conclusion, direct fluorination of silyl derivatives of carboxylic acids, other than amides, provides a convenient route to their α-fluoro counterparts.

Experimental Section

The ^1H NMR (90 MHz) and ^{19}F NMR (90 MHz) spectra were obtained on a Varian EM-390 NMR spectrometer. Chemical shifts are reported in ppm downfield relative to external Me_4Si for ^1H NMR and internal $CFCl_3$ for ^{19}F NMR, with $CDCl_3$ as the solvent in both cases. The microanalysis was performed by Atlantic Microlab, Inc., Norcross, GA. The 5% F_2 in N_2 was supplied by Air Products. Solvents used (DMF and THF) were distilled from sodium benzophenone ketyl prior to use. Chlorotrimethylsilane, diisopropylamine, and hexamethyldisilazane were distilled from CaH_2 under N_2 prior to use. The esters, malonates, amides, carboxylic acids, and lactone were distilled under pressure prior to use. Their ketene silyl acetals were prepared by standard procedures.[7-9] All glassware was oven dried and flame dried.

Fluorinations. Fluorinations were done following standard procedure reported earlier.[6] All fluorinations in $FCCl_3$ were done at -78 °C. The fluorine was passed through a NaF trap to remove HF. The reaction vessel was purged with nitrogen for 10 min prior to addition of 5% fluorine in nitrogen and after addition was completed. Potassium iodide traps (0.5 g/200 mL) were used to destroy any unreacted fluorine eluting from the reaction vessel and to determine when the reaction was completed.

Silyl compound (1-2 g) was diluted in approximately 25 mL of $FCCl_3$. The dilute fluorine was bubbled through the reaction vessel at a rate of 2 bubbles per second for 1.5-3.0 h. The addition of fluorine was stopped when the second potassium iodide trap began to change color. After fluorination, the solvent was removed by rotary evaporation, leaving the crude α-fluoro products. After obtaining a crude NMR spectrum, the sample was washed with water dried over $MgSO_4$ and chromatographed. The pure mono-α-fluoro carbonyl products were obtained by eluting the concentrated reaction mixtures over silica gel using various organic solvents. The α-fluoro carboxylic acids could be purified by acid-base extraction.

Synthesis of α-Fluorobenzeneacetic Acid. This compound was prepared by minor modification of standard procedures reported earlier.[10] Diethyl fluorophenylmalonate (0.50 g, 1.97 mmol) was added to a 50-mL round-bottom flask equipped with a cold water condenser and magnetic stirrer. A solution of glacial acetic acid (5 mL), concentrated sulfuric acid (0.63 mL), and water (3.3 mL) was added and the mixture was refluxed for 18 h. The cooled solution was made basic with 20% NaOH. The aqueous layer was made acidic with 10% sulfuric acid and extracted with ether. The combined ether extracts were dried with $MgSO_4$. The ether was removed by rotary evaporation, leaving the product (0.26 g) 86% yield. ^{19}F NMR -181.0 (d) (lit.[16] -181.4 (d)).

(17) Shian-Jan, S.; Partridge, J. J.; Uskokovic, M. R. *J. Org. Chem.* **1988**, *53*, 1040.
(18) Grakauskas, V.; Baum, K. *J. Org. Chem.* **1970**, *35*, 1545.
(19) Williamson, S. M.; Gupta, O. D.; Shreeve, J. M. *Inorg. Synth.* **1986**, *24*, 64.

Synthesis and Properties of Aryl-1,3-dioxo Carboxylic Acids

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Aryl 1,3-diketones have been used extensively as intermediates in organic synthesis. A number of methods for the preparation of aryl 1,3-dione alkanoic acids and their equivalents have been reported. The most common method employs the Knoevenagel condensation[1] of a benzoate and a substituted malonate. Following the condensation, an additional decarboxylation step is necessary. Another well-investigated method involves benzoylation of acetoacetate dianions;[2-5] however, this method limits the side-chain length of the resultant dione acid to a single methylene unit. A more versatile approach involves the reaction of mono acid chloride esters with the enolates of aryl ketones which allows for more variations in the dione side chain.[6] A related synthesis prepares 6-hydroxyl-1,3-hexanediones by sodium hydride catalyzed condensation of methyl ketones with lactones.[7]

In our synthetic efforts toward a number of heterocyclic systems we required a more versatile method for the synthesis of a wide variety of aryl 1,3-dione alkanoic and benzoic acids. Dibasic anhydrides, i.e. succinic, maleic, glutaric, etc. serve as a good pool for the keto acid portion of the molecule. Aryl methyl ketones serve as a source for the remainder of the molecule.

We found that by forming the anion of an arylmethyl ketone with LDA at -78 °C in THF, and quenching it with

(1) Jones, G. *Organic Reactions*; John Wiley & Sons, Inc.: New York, 1969; Vol. 15, Chapter 2.
(2) Wolfe, J. F.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3249.
(3) Hucklin, S. N.; Weiler, L. *Tetrahedron Lett.* **1972**, *23*, 2405.
(4) Hucklin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343.
(5) Narasimhan, N. S.; Ammanamanchi, R. *J. Org. Chem.* **1983**, *48*, 3945.
(6) Hauser, C. R.; Linn, O. *J. Am. Chem. Soc.* **1957**, *79*, 731.
(7) Detty, M. R. *J. Org. Chem.* **1979**, *44*, 2073.

0022-3263/90/1955-3424$02.50/0