Synthesis of Substituted 5,6-Dihydro-2*H*-pyran-2-ones. Propiolic Acid Dianion as a Reactive Three-Carbon Nucleophile

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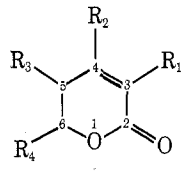
Substituted 5,6-dihydro-2*H*-pyran-2-ones of four basic structural types (I–IV) were synthesized by addition reactions to derivatives of δ-hydroxyacetylenic acids **3**. The acetylenic acids were, in turn, obtained by the reaction of the propiolic acid dianion with epoxides. The addition of methanol, hydrogen, and dialkylcuprates generated three types of dihydropyrones related to biologically active compounds, while the subsequent alkylation or acylation of the vinyl anion derived from dialkylcuprate addition provided a route to the fourth structural type possessing substitution at C-3.

The 5,6-dihydro-α-pyrone ring system represents an intriguing goal for the development of new methods for polyketide synthesis, since there are many compounds of this structural type which show a wide variety of biological responses, including antibacterial and antifungal activity. These biologically active compounds can be classified by their characteristic substitution patterns at C-3 and C-4 as illustrated by the kava lactones,[1] pestalotin,[2a,b] and fungal lactone LL-P880β[3] (type I, **1**, R_1 = H; R_2 = OCH_3); phoma-



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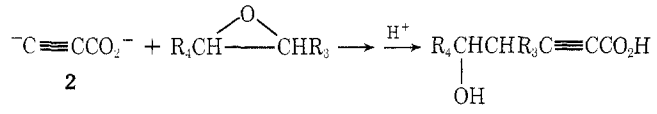
lactone,[4] asperline,[5] boronolide,[6] massiolactone,[7] isoranunculin,[8] parasorbic acid,[9] rubratoxins A and B,[10] goniothalamin,[11] and psilotin[12] (type II, **1**, R_1 = R_2 = H); dioscorine[13] (type III, **1**, R_1 = H; R_2 = CH_3); and the withanolides[14] (type IV, **1**, R_1 = CH_3 or CH_2OH, R_2 = CH_3).

The route to the dihydropyrone system that is presented herein employs the dianion (**2**) of propiolic acid as a stable three-carbon nucleophile[15] that will add in a regiospecific fashion to the less substituted (hindered) end of unsymmetrical epoxides (Table I). Subsequently, the resulting δ-hydroxyacetylenic acid system **3** is subjected to such selective processes as conjugate addition or reduction to generate the various substitution types I–IV (Scheme I).

Table I
Epoxide Addition Reactions

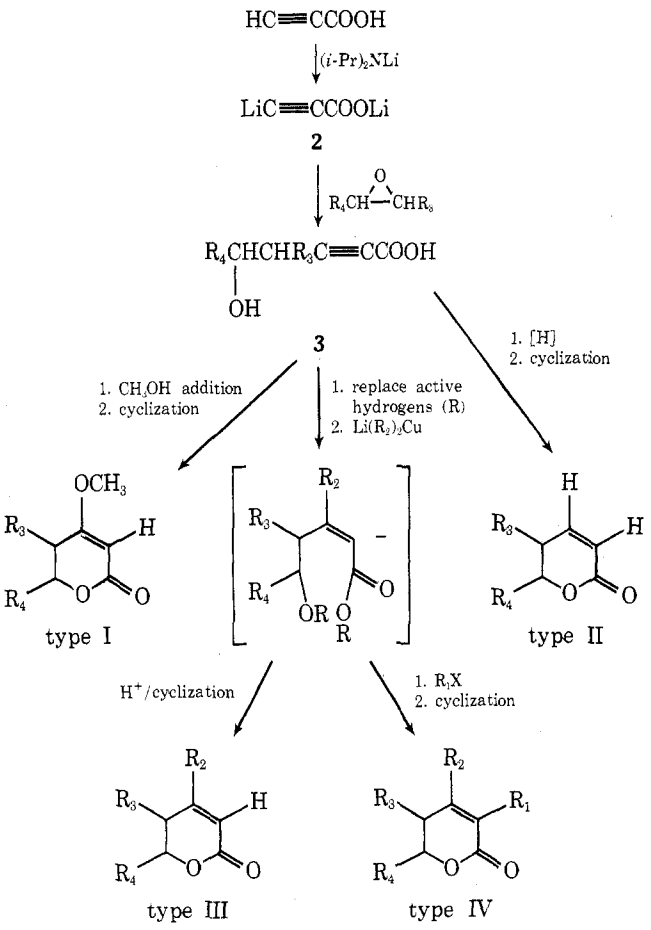


2 **3**

R_4	R_3	Reaction time, days	% yield[a]
C_6H_5[b]	H	2	48
C_2H_5	H	3	46
C_5H_{11}[c]	H	2	40
C_6H_{13}	H	3	40
$C_6H_5CH_2O$ | C_4H_9CH-	H	3	47
$CH_2{=}CHCH_2OCH_2$-	H	5	41
$-CH_2CH_2CH_2CH_2$-		17	30

[a] Determined by NMR of crude product mixture. [b] Previously prepared; see ref 19. [c] V. Lamberti, W. T. Weller, and J. Schagt, *Recl. Trav. Chim. Pays-Bas*, **86**, 504 (1967).

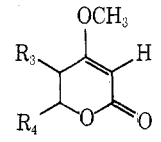
Scheme I

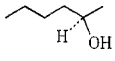
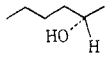


Results and Discussion

A. The Propiolic Acid Dianion. The propiolic acid dianion[15] (**2**) is generated at −45° with lithium diisopropylamide in a 1:1 THF–HMPA solvent system (3 mol of HMPA/mol of propiolic acid), which is necessary to maintain a solution throughout the dianion generation–addition sequence. The dianion **2** is allowed to react with an epoxide at room temperature for ca. 2–3 days to form the hydroxyacetylenic acid **3**. Reactions carried out without HMPA resulted in the formation of little or no addition product **3**. These results parallel the finding[16] that 1–3 mol of HMPA/mol of acid solubilize the dianions of aliphatic acids and accelerate their rate of alkylation in producing α-branched

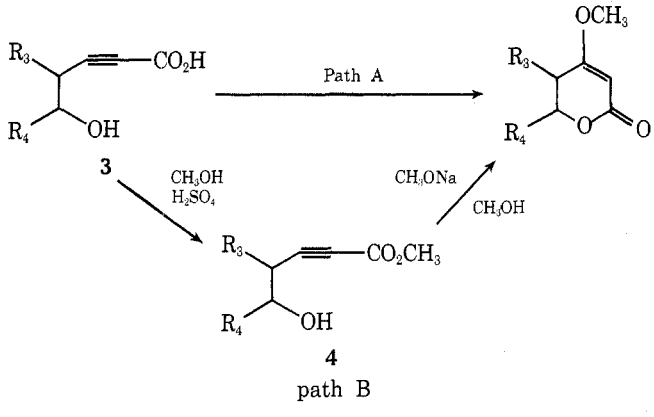
Table II
Type I Pyrones[h]



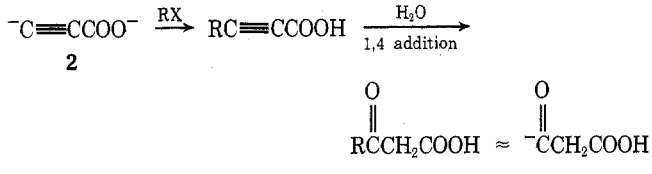
R_4	R_3	Path	% crude yield	Mp, °C	Bp, °C (mmHg)	NMR, δ, ppm ($CDCl_3$)	Registry no.
C_6H_5	H	A	51	144.5–145.5[a]		*b*	54814-58-3
C_2H_5	H	A	65	55.0–55.5		*b*	54814-59-4
C_5H_{11}	H	A	74		105 (0.08)[c]	0.9 (t, 3 H), 1.4 (m, 8 H), 2.4 (m, 2 H), 3.72 (s, 3 H), 5.17 (s, 1 H)	54814-60-7
C_6H_{13}	H	A	79	39.2–40.0		*b*	54814-61-8
$-CH_2CH_2CH_2CH_2-$		A	75	71.0–71.5		*b*	54620-72-3
$CH_2{=}CHCH_2OCH_2-$	H	B	32	49.0–49.7		2.5 (m, 2 H), 3.65 (d, 2 H), 3.72 (s, 3 H), 4.06 (m, 2 H), 4.5 (m, 1 H), 5.25 (m, 2 H), 5.75 (m, 1 H)	54814-62-9
	H	B	82[d]	81–82[e]		*g*	54814-63-0
	H	B	82[d]	71–72[f]		*g*	

[a] Lit.[19] mp 146–147°. [b] See ref 15. [c] Bath temperature. [d] Based on yield of benzyl ether diastereomers prior to cleavage and separation. See ref 15. [e] Lit.[22] mp 82°. [f] Lit.[22] mp 72°. [g] See ref 2. [h] Satisfactory elemental analyses were reported for all new compounds listed in the table.

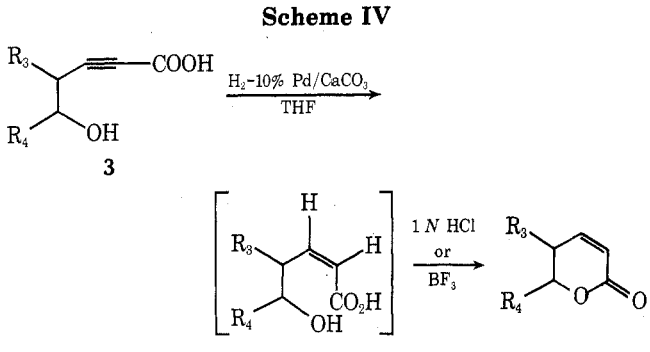
Scheme II



Scheme III



Scheme IV



acids. However, the addition of large quantities of HMPA in a reaction that proceeds for 2–3 days at room temperature raises the possibility of a competing process, whereby the propiolic acid dianion abstracts a proton from HMPA in a fashion analogous to that reported for other alkyllithiums.[17] This competing process may account for the formation of only moderate yields of the desired hydroxyacetylenic acid **3**. The thermal stability of the acetylide **2** should be contrasted with acetylides generated from propiolic acid esters,[18] which decompose at temperatures above −50°. Attempts to add these latter acetylides to epoxides at temperatures below −50° failed.

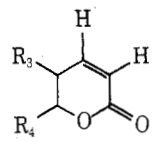
B. Type I Pyrones. Type I pyrones (Table II) were prepared either by the acid-catalyzed addition of methanol to the hydroxyacetylenic acid **3**[15] (path A, Scheme II) or by the base-catalyzed addition of methanol to the hydroxyacetylenic ester **4**[15,20] (path B, Scheme II). The latter two-step pathway was used only for the preparation of acid-sensitive pyrones such as pestalotin.[15,2a] As described previously,[15] this synthesis of type I pyrones represents an example of nucleophilic acyl substitution,[21] i.e., an acyl acetate equivalent (Scheme III).

C. Type II Pyrones. The semihydrogenation with 5% Pd/$BaSO_4$ of hydroxyacteylenic acids **3** obtained by alternate procedures has been reported[19,23] to form, after distillation, type II pyrones. In the present work, the synthetic scheme was modified slightly to use the less active Pd/$CaCO_3$ catalyst[24] and to effect ring closure with 1 *N* HCl or BF_3 (Scheme IV, Table III). Preparation of a type II pyrone **5** containing an exocyclic double bond is possible (Scheme V, Table III), but it is necessary to partially poison the Pd/$CaCO_3$ catalyst with quinoline.[25]

D. Type III Pyrones. The preparation of type III pyrones was carried out as outlined in Scheme VI by conjugate addition of dialkylcopper–lithium reagents[28] to either the hydroxyacetylenic acids[29] **3** or the corresponding bis(trimethylsilyl) derivatives[30,31] **7** (Table IV).

E. Type IV Pyrones. Preparation of tetrasubstituted olefins by conjugate addition of dialkylcopper–lithium reagents to α,β-acetylenic esters and subsequent reaction of the resulting intermediate with iodine[30] or methyl iodide[34]

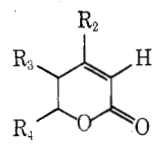
Table III
Type II Pyrones



R_4	R_3	% crude yield	Mp, °C	Bp, °C (mmHg)[b]	NMR, δ, ppm ($CDCl_3$)	Registry no.
C_6H_5	H	75	59–60[a]		2.5 (m, 2 H), 5.3 (t, J = 8 Hz, 1 H), 6.0 (m, J = 10, 1.75 Hz, 1 H), 6.85 (m, 1 H), 7.35 (s, 5 H)	4660-17-7
C_2H_5	H[g]	72		50–55 (0.1)	1.0 (t, 3 H), 1.7 (m, 2 H), 2.35 (m, 2 H), 4.3 (m, 1 H), 6.0 (m, J = 10, 1.5 Hz, 1 H), 6.9 (m, 1 H)	19895-35-3
C_5H_{11}	H	60		70–80 (0.1)[c]	0.9 (t, 3 H), 1.4 (br m, 8 H), 2.4 (m, 2 H), 4.4 (m, 1 H), 6.1 (m, J = 10, 1.5 Hz, 1 H), 7.0 (m, 1 H)	54814-64-1
C_6H_{13}	H[g]	78		80–85 (0.06)[d]	0.9 (t, 3 H), 1.4 (br m, 10 H), 2.35 (m, 2 H), 4.35 (m, 1 H), 6.0 (m, J = 10, 1.5 Hz, 1 H), 6.95 (m, 1 H)	2833-19-4
$-CH_2CH_2CH_2CH_2-$[g]		57	53.0–53.5		1.0–2.5 (br m, 9 H), 3.9 (m, 1 H), 5.85 (dd, J = 10.5, 2.5 Hz, 1 H), 6.65 (m, J = 10 Hz, 1 H)	19895-36-4
$CH_2{=}CHCH_2OCH_2-$	H[g]	*e*		70–85 (0.1)	2.5 (m, 2 H), 3.7 (d, J = 5 Hz, 2 H), 4.1 (d, J = 5 Hz, 2 H), 4.65 (m, 1 H), 5.3 (m, 2 H), 6.0 (m, 2 H), 7.0 (m, 1 H)	54814-65-2
$CH_3CH_2CH_2OCH_2-$	H[f]	*e*			0.8 (t, 3 H), 1.5 (m, 2 H), 2.5 (m, 2 H), 3.4 (d, J = 7.5 Hz, 2 H), 3.7 (d, J = 5 Hz, 2 H), 4.6 (m, 1 H), 6.0 (m, J = 10 Hz, 1 H), 6.9 (m, 1 H)	54814-66-3

[a] Lit.[19] mp 59°. [b] Bath temperature. [c] Lit.[26] bp 85–86° (0.07 mm). [d] Lit.[27] bp 106–109° (0.1 mm Hg). [e] Overall yield 43%, using modified quinoline containing catalyst; NMR of product mixture is consistent with 80:20 mixture of the two lactones **5** and **6** (see text). Lactones were separated by preparative HPLC. [f] Corroborated by mass spectral analysis. [g] A satisfactory elemental analysis was reported for this compound.

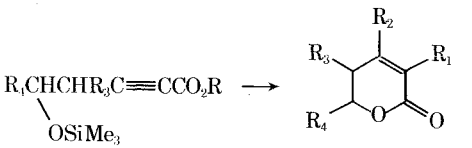
Table IV
Type III Pyrones



R_4	R_3	R_2	Path	% crude yield	Mp, °C	Bp, °C (mmHg)	NMR, δ, ppm ($CDCl_3$)	Registry no.
C_6H_5	H	CH_3	C	70	60.0–61.0[a]		2.02 (s, 3 H), 2.55 (m, 2 H), 5.4 (m, 1 H), 5.95 (m, 1 H), 7.4 (s, 5 H)	29643-79-6
C_2H_5	H	CH_3	C	70		60[b] (0.2)	0.9 (t, 3 H), 1.7 (m, 2 H), 1.9 (m, 3 H), 2.2 (m, 2 H), 4.25 (m, 1 H), 5.7 (m, 1 H)	54814-67-4
C_2H_5	H	CH_3[g]	D	63[c]		60[b] (0.2)	Same as above	
C_6H_{13}	H	CH_3[g]	C	65		100–120[b] (0.18)	0.9 (t, 3 H), 1.2 (m, 10 H), 1.9 (s, 3 H), 2.18 (m, 2 H), 4.3 (m, 1 H), 5.7 (m, 1 H)	54814-68-5
C_6H_{13}	H	CH_3	D	71[c]			Same as above	
CH_2CH_2-[d] / CH_2CH_2-		CH_3[g]	C	88	65.8–66.2		0.9–2.4 (brm), 1.95 (m), 4.0 (m, 1 H), 5.9 (m, 1 H)	29681-61-6
C_6H_5[f]	H	C_4H_9	C	63		150 (0.17)[e]	0.9 (m, 3 H), 1.4 (brm, 4 H), 2.2 (m, 2 H), 2.55 (m, 2 H), 5.4 (m, 1 H), 5.9 (m, 1 H), 7.45 (s, 5 H)	54814-69-6

[a] Lit.[32] mp 61–62°. [b] Bath temperature. [c] Based on starting ester. [d] Previously reported (ref 33). [e] Decomposed. [f] Corroborated by mass spectral analysis. [g] A satisfactory elemental analysis was reported for this compound.

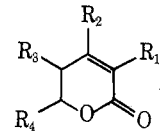
Table V
Preparation of Type IV Pyrones[a]



R_4	R_3	R	R_2	R_1	X	% yield	Mp, °C	Bp, °C (mmHg)	NMR, δ, ppm ($CDCl_3$)	Registry no.
C_6H_5	H	$SiMe_3$	CH_3	CH_3	I	58	97.0–97.5		1.95 (s, 6 H), 2.5 (m, 2 H), 5.3 (m, 1 H), 7.4 (s, 5 H)	54814-70-9
C_6H_5	H	$SiMe_3$	CH_3	I	I	51	85.5–86.0		2.22 (s, 3 H), 2.7 (m, 2 H), 5.4 (m, 1 H), 7.4 (s, 5 H)	54832-64-3
C_6H_5	H	CH_3	CH_3	Ac	Cl	72	95.0–95.4		2.1 (s, 3 H), 2.49 (s, 3 H), 2.6 (m, 2 H), 5.4 (m, 1 H), 7.45 (s, 5 H)	54814-71-0
C_6H_5	H	CH_3	CH_3	$EtOCH_2$–	Cl	62[b]			1.15 (t, 3 H), 2.1 (s, 3 H), 2.5 (m, 2 H), 3.5 (q, 2 H), 4.25 (s, 2 H), 5.3 (m, 1 H), 7.4 (s, 5 H)	54814-72-1
C_6H_5	H	CH_3	CH_3	CH_3S	SCH_3	62	97.5–98		2.21 (s, 3 H), 2.31 (s, 3 H), 2.65 (m, 2 H), 5.35 (m, 1 H), 7.4 (s, 5 H)	54814-73-2
C_6H_5	H	$SiMe_3$	CH_3	$SiMe_3$	See text	See text	76.5–77		0.3 (s, 9 H), 2.1 (s, 3 H), 2.45 (m, 2 H), 5.2 (m, 1 H), 7.35 (s, 5 H)	54814-74-3
C_6H_{13}	H	$SiMe_3$	CH_3	I	I	72	41.5–42.5		0.9 (t, 3 H), 1.3 (br, 10 H), 2.2 (s, 3 H), 2.5 (m, 2 H), 4.4 (m, 1 H)	54814-75-4
OCH_2– $CH_2CH{=}CH_2$	H	CH_3	CH_3	$CH_2{=}CHCH_2$–	Br	85		120–130 (0.05)	1.95 (s, 3 H), 2.4 (m, 2 H), 3.1 (d, 2 H), 3.6 (d, 2 H), 4.0 (d, 2 H), 4.5 (m, 1 H), 5.1 (m, 4 H), 5.75 (m, 2 H)	54814-76-5

[a] Satisfactory elemental analyses were reported for all compounds listed in the table, unless otherwise noted. [b] Mass spectral analysis only.

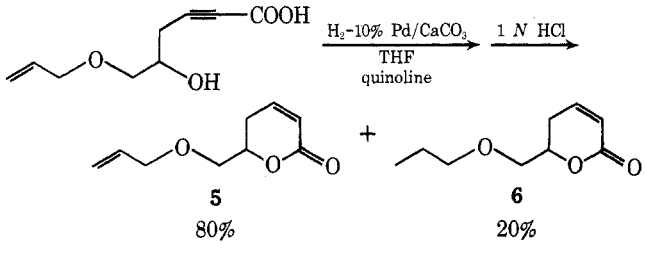
Table VI
Kirby-Bauer[36] Test Results[a]



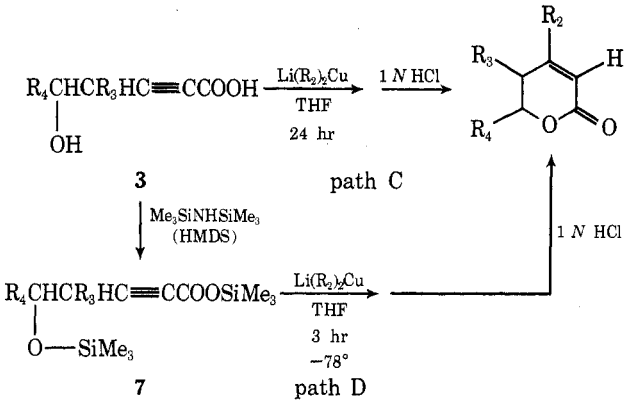
Type	R_4	R_3	R_2	R_1	Inhibition zone, mm					
					S. aureus			*E. coli*		
					100 μg	200 μg	300 μg	100 μg	200 μg	300 μg
I	C_5H_{11}	H	OCH_3	H		7	8–9			
I	$-CH_2CH_2CH_2CH_2-$		OCH_3	H			15			23
II	C_6H_5	H	H	H	8		10		6	9
II	C_5H_{11}	H	H	H			16		8	10
II	$-CH_2CH_2CH_2CH_2-$		H	H			16		9	18
II	C_6H_{13}	H	H	H			12			

[a] Sample of (−)-pestalotin was graciously provided by Lederle Laboratories.[2] This sample, as well as the synthetic *dl* material, gave a negative response by the Kirby-Bauer test above.

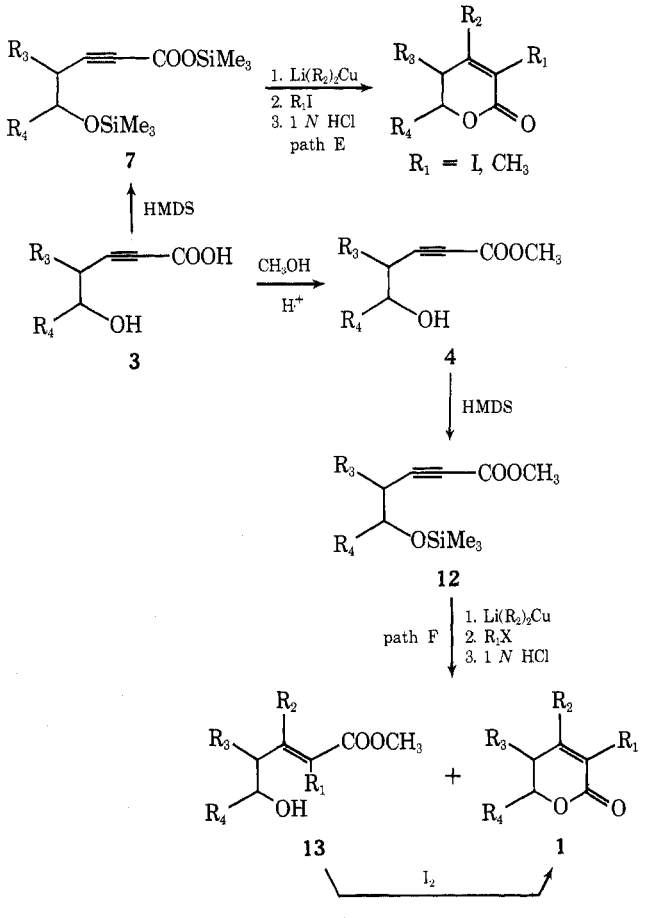
Scheme V



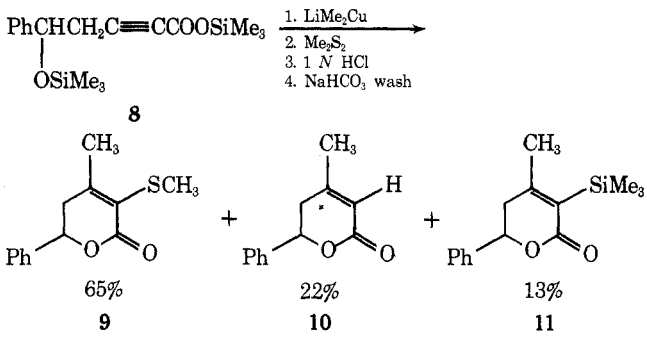
Scheme VI



Scheme VII



Scheme VIII



has been reported. However, attempts to react this intermediate with other electrophiles such as trimethylchlorosilane, acetic anhydride, or hexadeuterioacetone failed.[34] In contrast to these latter findings, we have found that this synthetic scheme can be extended to include a wide variety of electrophilic reagents as exemplified by the synthesis of the type IV pyrones described below.

The bis(trimethylsilyl) compound **7** provided a suitable starting point for the preparation of 3-methyl- and 3-iodopyrones (Scheme VII). However, when less reactive electrophiles were used, significant amounts of 3-unsubstituted and 3-trimethylsilylpyrones[35] were isolated in addition to the desired 3-substituted pyrones. For example, a reaction starting with the ester **8** and using dimethyl disulfide as the electrophile produced a 45% yield of a mixture of three pyrones, **9**, **10**, and **11**, in a ratio of 65:22:13 (Scheme VIII). This ratio was determined by comparison of the NMR spectrum and analytical liquid chromatograph of the mix-

ture with those of the pure compounds, whose isolation is described elsewhere in this work.

These difficulties encountered with less reactive electrophiles were alleviated by using the trimethylsilyl methyl ester **12**. Thus, addition of dimethylcopper–lithium to **12** ($R_4 = C_6H_5$; $R_3 = H$) and treatment of the resulting intermediate with acetyl chloride gave a 1:1 mixture of the desired lactone **1** ($R_4 = C_6H_5$; $R_3 = H$; $R_2 = CH_3$; $R_1 = CH_3C{=}O$) and the uncyclized ester **13** ($R_4 = C_6H_5$; $R_3 = H$; $R_2 = CH_3$; $R_1 = CH_3C{=}O$), plus some minor unidentified compounds. Treatment of the mixture with a catalytic amount of iodine led to isomerization and ring closure of the ester to the desired pyrone **1** in an overall yield of 72% (Scheme VII). Similarly, for all the other electrophiles except I_2 or MeI listed in Table V, mixtures of lactones and uncyclized esters were obtained and treated with iodine to produce good yields of types IV pyrones.

F. Biological Testing. All pyrones prepared in this work were tested for antibacterial activity against. *E. coli* and *S. aureus* using the Kirby–Bauer method[36] (Table VI).

Experimental Section

General. Melting points (uncorrected) were obtained on a Thomas-Hoover capillary apparatus. Infrared spectra were taken on a Beckman IR-33. NMR spectra were obtained with a Varian A-60D instrument using Me_4Si as internal standard. Analytical liquid chromatographs were obtained on Waters Associates equipment, including refractive index and ultraviolet detectors, and two 28-mm Micro Porasil columns. The flow rate was 3 ml/min and 1:1 ether–hexane was used in most cases. For preparative work three 56-mm Porasil A columns were sometimes substituted and a flow rate of 9.9 ml/min was used. The propiolic acid was used as received from Farchan and Aldrich Chemical Co. The alkyllithiums were obtained from Alfa Products. The THF (Baker Analyzed, <0.003% H_2O) was maintained under nitrogen in a septum-capped bottle from which the solvent was removed by syringe. The HMPA (Aldrich) was stored in a septum-capped bottle under nitrogen over 4-Å sieves for several weeks before use. The cuprous iodide was Fisher Certified. The acetyl chloride (Baker Analyzed) was distilled from pyridine to remove traces of HCl. All reactions involving organometallic reactants were carried out under nitrogen in septum-capped flasks with introduction of reagents via syringe. Elemental analyses were performed by Robertson Laboratories, Florham Park, N.J. Mass spectra were run on a Varian CH5 by Mr. Douglas Kuehl, National Water Quality Laboratory, Duluth, Minn.

Preparation of Hydroxyacetylenic Acid 3. The procedure previously reported was employed.[15] In nearly all cases the crude product mixture (mostly hydroxyacetylenic acid **3** and ether) was used directly in subsequent reactions.

Preparation of Hydroxyacetylenic Methyl Ester 4. The δ-hydroxyacetylenic acid **3** (0.01 mol) was treated with 20 ml of a 1% sulfuric acid solution in methanol for 1–2 days. The reaction was saturated with solid sodium bicarbonate, filtered, and concentrated. The residue was diluted with ether and the organic layer was washed with saturated sodium bicarbonate solution and brine. After drying over magnesium sulfate, the ether was evaporated to yield the ester **4**, which was used without further purification. Yield data are presented in Table VII.

Preparation of Type I Pyrones. The previously described procedures[15] were used. The crude products were purified when necessary by preparative liquid chromatography before recrystallization or distillation (Table II).

General Procedure for Preparation of Type II Pyrones. The hydroxyactylenic acid **3** (0.007 mol) with ca. 0.1 g of 10% Pd/$CaCO_3$ in 15 ml of THF was allowed to take up ca. 85% of the theoretical amount of hydrogen. The reaction mixture was then poured into 1 *N* HCl[37] and stirred for 1–2 hr. The mixture was extracted with ether and the combined ether extracts were washed with saturated sodium bicarbonate solution and brine. After drying over magnesium sulfate, the ether was evaporated to give crude lactone, which was purified, if necessary, by preparative liquid chromatography before recrystallization or distillation (Table III). For the preparation of pyrone **5**, with an exocyclic double bond, the amount of catalyst was decreased to 0.02 g and 50% by weight of quinoline was added (see text).

Table VII
δ-Hydroxyacetylenic Esters 4

$$\underset{\textbf{3}}{R_4\underset{|\atop OH}{C}HCR_3HC{\equiv}CCOOH} \xrightarrow[H_2SO_4]{CH_3OH} \underset{\textbf{4}}{R_4\underset{|\atop OH}{C}HCHR_3C{\equiv}CCOOCH_3}$$

R_4	R_3	% yield
C_6H_5[a]	H	90
C_2H_5	H	70
C_5H_{11}	H	62
C_6H_{13}	H	80
$C_4H_9CHOCH_2C_6H_5$	H	90
$CH_2{=}CHCH_2OCH_2{-}$	H	79
$-CH_2CH_2CH_2CH_2-$		85

[a] See ref 19.

Table VIII
Preparation of Bis(trimethylsilyl) Compounds 7

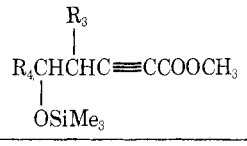
$$\underset{\textbf{3}}{R_4\underset{|\atop OH}{C}HCH_2C{\equiv}CCOOH} \xrightarrow[THF]{HMDS} \underset{\textbf{7}}{R_4\underset{|\atop OSiMe_3}{C}HCH_2C{\equiv}CCOOSiMe_3}$$

R_4	% yield after distillation	Bp, °C (mmHg)	NMR, δ, ppm ($CDCl_3$)
C_6H_5	67	95–125 (0.30)	0.10 (s, 9 H), 0.31 (s, 9 H), 2.65 (d, *J* = 6 Hz, 2 H), 4.90 (t, *J* = 6 Hz, 1 H), 7.35 (s, 5 H)
C_2H_5	81	81–89 (0.25)	0.11 (s, 9 H), 0.29 (s, 9 H), 0.90 (t, 3 H), 2.55 (m, 2 H), 2.45 (d, 2 H), 3.80 (m, 1 H)
C_6H_{13}	60	111–119 (0.25)	0.12 (s, 9 H), 0.30 (s, 9 H), 0.89 (t, 3 H), 1.3 (m, 10 H), 2.42 (d, 2 H), 3.8 (m, 1 H)
$CH_2{=}CHCH_2OCH_2{-}$	67	80–110 (0.14)	0.13 (s, 9 H), 0.30 (s, 9 H), 2.5 (m, 2 H), 3.45 (d, 2 H), 4.0 (m, 3 H), 5.25 (m, 2 H), 5.8 (m, 1 H)

General Procedure for the Preparation of Bis(trimethylsilyl) Compounds 7. The hydroxyacetylenic acid **3** (1 equiv), hexamethyldisilazane (HMDS, ca. 4 equiv), and enough THF to effect solution were refluxed for 24–48 hr. The THF and excess HMDS were removed in vacuo and the product was distilled (Table VIII).

General Procedure for Preparation of Type III Pyrones. From Hydroxyacetylenic Acids 3. The cuprous iodide (0.014 mol, 3.05 equiv) was slurried in 40 ml of THF under N_2 at 0°. Dropwise addition of 0.028 mol (6.10 equiv) of methyllithium (1.65 *M* in ether) formed a clear, colorless solution which was stirred for 5 min at 0° [38] and then cooled to −78°. The hydroxyacetylenic acid **3** (0.0046 mol, 1.0 equiv) dissolved in 5 ml of THF was then added. The Dry Ice–acetone bath was packed with Dry Ice and allowed to slowly come to room temperature overnight. The reaction mixture was poured into 250 ml of vigorously stirred 1 *N* HCl, and after stirring for 1 hr the mixture was extracted with ether. The combined ether extracts were washed with a saturated solution of sodium bicarbonate and brine. After drying over magnesium sulfate the ether was evaporated to give crude lactone, which was purified, if necessary, by preparative liquid chromatography before recrystallization or distillation (Table IV). For bis(trimethylsilyl)

Table IX
Trimethylsilyl Methyl Esters 12



R_4	R_3	% yield after distillation	Bp, °C (mmHg)[a]	NMR, δ, ppm ($CDCl_3$)
C_6H_5	H	74	110–120 (0.35)	0.07 (s, 9 H), 2.66 (d, J = 6 Hz, 2 H), 3.71 (s, 3 H), 4.9 (t, J = 6 Hz, 1 H), 7.33 (s, 5 H)
C_6H_{13}	H	68	92–100 (0.20)	0.16 (s, 9 H), 0.91 (t, 3 H), 1.30 (m, 10 H), 2.50 (d, 2 H), 3.80 (s, 3 H), 3.88 (m, 1 H)
CH_2=$CHCH_2OCH_2$–	H	83	95 (0.25)	0.17 (s, 9 H), 2.55 (m, 2 H), 3.40 (d, 2 H), 3.72 (s, 3 H), 4.0 (m, 3 H), 5.25 (m, 2 H), 5.75 (m, 1 H)

[a] Bath temperature.

compounds **7**, the above procedure was modified to use only 1.1 equiv of cuprous iodide and 2.2 equiv of methyllithium and a reaction time of only 3 hr at −78° before work-up.

General Procedure for the Preparation of Trimethylsilyl Methyl Esters 12. The hydroxyacetylenic ester **4** (1 equiv), HMDS (ca. 4 equiv), and enough THF to effect solution were refluxed for 24–48 hr. The THF and excess HMDS were removed in vacuo and the product **12** was distilled (Table IX).

General Procedure for the Preparation of Type IV Pyrones. The bis(trimethylsilyl) compound **7** or the trimethylsilyl methyl ester **12** was treated with 1.1 equiv of dialkylcopper–lithium reagent in THF as described above for type III pyrones. After stirring for 3 hr at −78°, 2.2 equiv of HMPA was added to the nonhomogeneous reaction mixture to form a solution, followed by the electrophile (2.2 equiv). The Dry Ice–acetone bath was packed with Dry Ice and allowed to gradually warm to room temperature. After stirring for 24 hr after the electrophile addition, the reaction mixture was poured into 1 *N* HCl and stirred for 1 hr. The aqueous mixture was extracted with ether and the combined ether extracts were dried over magnesium sulfate and evaporated. The mixture obtained (see text) was refluxed with 0.1 equiv of iodine in THF for 0.5 hr.[39] The mixture was diluted with ether, washed with a 10% sodium sulfite solution, and dried over magnesium sulfate. Evaporation of the ether gave crude lactone, which was purified, if necessary, by preparative liquid chromatography prior to recrystallization or distillation (Table V).

Biological Testing. The technique used for determining the susceptibility of *Escherichia coli*[40] and *Staphylococcus aureus* was described by Difco.[41] The disks containing the agent were prepared by the application of the test compound via syringe onto 6-mm paper disks[42] and allowing approximately 15 min for the solvent to air dry. The Petri dishes[43] could easily accommodate four disks in an outer ring, three containing the agent at a concentration of 100–200–300 μg per disk. The fourth disk was a prepared standard[44] and the final disk was a blank. All zones were read to the nearest millimeter following 16–24 hr of incubation (Table VI).

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Registry No.—**2**, 54620-69-8; **3** (R^3 = H; R^4 = CH_2=$CHCH_2OCH_2$), 54814-77-6; **3** (R^3 = C_6H_5; R^4 = H), 54814-78-7; **3** (R^3 = C_2H_5; R^4 = H), 54814-79-8; **3** (R^3 = C_5H_{11}; R^4 = H), 27003-14-1; **3** (R^3 = C_6H_{13}; R^4 = H), 54814-80-1; **3** (R^3 = R^4 = $CH_2CH_2CH_2CH_2$), 54814-81-2; **3** (R^3 = H; R^4 = C_6H_5), 54814-82-3; **3** (R^3 = H; R^4 = C_2H_5), 54814-83-4; **3** (R^3 = H, R^4 = C_5H_{11}), 16400-66-1; **3** (R^3 = H; R^4 = C_6H_{13}), 54814-84-5; **3** (R^3 = H; R^4 = $CH_3CH_2CH_2OCH_2$), 54814-85-6; **4** (R^3 = CH_2=$CHCH_2OCH_2$; R^4 = H), 54814-86-7; **4** (R^3 = $CH(OH)CH_2CH_2CH_2CH_3$; R^4 = H), 54814-87-8; **7** (R^4 = C_6H_5), 54814-88-9; **7** (R^4 = C_2H_5), 54814-89-0; **7** (R^4 = C_6H_{13}), 54814-90-3; **7** (R^4 = CH_2=$CHCH_2OCH_2$), 54814-91-4; **12** (R^3 = H; R^4 = C_6H_5), 54814-92-5; **12** (R^3 = H; R^4 = C_6H_{13}), 54814-93-6; **12** (R^3 = H; R^4 = CH_2=$CHCH_2OCH_2$), 54814-94-7; $Li(CH_3)_2Cu$, 15681-48-8; $Li(Bu)_2Cu$, 24406-16-4; I_2, 7553-56-2; MeI, 74-88-4.

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(39) For type IV pyrone **1** (R_4 = C_6H_5; R_3 = H; R_2 = CH_3; R_1 = SCH_3), 1.3 equiv of iodine and a reflux time of 1.5 hr was required.
(40) Difco Bactrol Disks, *Staphylococcus aureus and Escherichia coli.*
(41) "Quality Control in Bacteriology with Bactrol Disks", Difco Technical Information, Feb 1973.
(42) Eaton-Dikeman No. 301–85.
(43) Fisher 100 × 15 mm sterilized, disposable plastic Petri dishes.
(44) Erythromycin, Difco Dispens-O-Disc (15 μg).