#### Table I. <sup>1</sup>H and <sup>14</sup>C NMR Data for Luffolactone in Benzene.d. Solution

		Denzene ut ber	47774
С	<sup>13</sup> C ppm	<sup>1</sup> H ppm	long-range
no.	(mult)	(mult, $J$ in Hz)	<sup>1</sup> H <sup>-13</sup> C correlations
1	39.8 (t)	0.52 (ddd, 15, 12, 4)	
		1.37 (m)	
2	19.0 (t)	1.29 (m)	
		1.29 (m)	
3	41.6 (t)	0.98 (ddd, 13, 13, 4)	
		1.24 (br d, 13)	
4	33.3 (s)		
5	55.2 (d)	0.63 (dd, 12, 2)	
6	19.6 (t)	0.85 (m)	
		1.34 (m)	
7	43.5 (t)	1.71 (ddd, 13, 13, 4)	C8, C23
		1.86 (dt, 13, 3)	
8	86.2 (s)		
9	58.0 (d)	1.16 (m)	C1, C8, C10, C22, C23
10	38.5 (s)		
11	25.6 (t)	1.16 (m)	
		1.52 (m)	
12	34.6 (t)	1.83 (br t, 13)	
		1.97 (ddd, 13, 5, 3)	C9, C11, C13, C14, C24
13	140.0 (s)		
14	131.2 (d)	5.28 (t, 7)	C12, C15, C24
15	33.6 (t)	2.34 (m)	C13, C14, C16, C17
		2.66 (m)	C13, C14, C16, C17
16	69.5 (d)	5.44 (t, 6)	C14, C15, C17, C25, C26
17	166.8 (s)		
18	116.7 (d)	5.64 (br s)	C17, C19, C25
19	172.4 (в)		
20	33.5 (q)	0.75 (s, 3 H)	C3, C4, C5, C21
21	21.8 (q)	0.66 (s, 3 H)	C3, C5, C20
22	15.2 (q)	0.48 (s, 3 H)	C1, C5, C9, C10
23	22.4 (q)	1.11 (s, 3 H)	C7, C8, C9
24	169.3 (s)		
25	70.6 (t)	4.16 (dd, 18, 2)	C17, C18, C19
		4.07 (dd, 18, 2)	C17, C18, C19
26	169.4 (s)		
27	20.3 (q)	1.58 (s, 3 H)	C26

data defined the seven-membered ring and indicated that there was an exocyclic trisubstituted olefin attached at C-13.

The H-14 signal at  $\delta$  5.28 (t, 1 H, J = 7 Hz) was coupled to two methylene proton signals at 2.66 (m, 1 H) and 2.34 (m, 1 H) that were in turn coupled to the H-16 signal at 5.44 (t, 1 H, J = 6 Hz) that was assigned to a CH(OCOR) proton. The corresponding <sup>13</sup>C NMR signal was observed at  $\delta$  69.5 (d, C-16). The remaining <sup>13</sup>C NMR signals at  $\delta$ 172.4 (s), 166.8 (s), 116.7 (d), and 70.6 (t) were assigned to an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone, which is characteristically found, albeit as a  $\gamma$ -hydroxybutenolide, in Luffariella metabolites. Consideration of the structure of neomanoalide (4) led us to examine the possibility of an alternate arrangement of the acetate and lactone ring (i.e. 9), but the long-range carbon-hydrogen correlations clearly showed correlations between H-25 and C-19, between H-16 and C-26, and between H-27 and C-26; these data require a terminal  $\gamma$ -lactone and an acetate group at C-16. An acetate group is found at a similar position in luffolide (10).11 The geometry at C-14 was determined by a NOEDS experiment: irradiation of the H-12 signal at  $\delta$ 1.97 caused a 13.7% enhancement of the H-14 signal at 5.28.

The carbon skeleton of luffalactone (8) has been reported from Salvia species<sup>12</sup> but has not been encountered previously from a marine source. It may be considered

# **Experimental Section**

Isolation Procedure. Specimens of L. variabilis were collected in Palau using SCUBA. The samples were frozen for short-term storage and subsequently freeze dried. Typically, the freeze-dried sponges were soaked in 10% methanol/dichloromethane (100 g of sponge/L of solvent) for 1-3 days. This process was repeated 3 times. The resulting extract was filtered and chromatographed on LH-20 with 1:1 methanol/dichloromethane. Manoalide-rich fractions were pooled and further purified by reverse-phase HPLC. Fractions enriched in seco-manoalide and dehydromanoalide were stored at -70 °C for several years. (4E,6E)-Dehydromanoalide and luffalactone were obtained from this material as described in the text.

(4E.6E)-Dehydromanoalide (7): pale yellow waxy solid; IR (CHCl<sub>3</sub>) 1745, 1670 cm<sup>-1</sup>; UV (MeOH) 317 (e 34 180), 204 nm (e 23760); UV (MeOH + NaOH) 464 ( $\epsilon$  60080), 290 ( $\epsilon$  3600), 252 (ε 5100), 208 nm (ε 32 900); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.96 (s, 6 H), 1.40 (m, 2 H), 1.55 (s, 3 H), 1.59 (s, 3 H), 1.89 (t, 4 H, J = 6 Hz), 1.98 (m, 4 H), 2.14 (m, 2 H), 2.49 (t, 2 H, J = 7 Hz), 5.11 (t, 1 H, J = 7 Hz), 6.15 (s, 1 H), 6.31 (s, 1 H), 6.81 (d, 1 H, J = 16 Hz), 6.90 (d, 1 H, J = 11 Hz), 7.32 (dd, 1 H, J = 16, 11 Hz), 9.54 (s, 1 H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 194.6 (d, C24), 171.1 (s, C1), 160.1 (s, C3), 146.3 (s, C7), 146.1 (d, C6), 137.8 (s, C11), 136.7 (s, C14), 134.0 (d, C5), 128.3 (d, C4), 126.8 (s, C15), 121.7 (d, C10), 119.4 (d, C2), 97.9 (d, C25), 40.0 (t, C12), 39.6 (t, C18), 34.8 (s, C19), 32.5 (t, C16), 2 × 28.4 (q, C20, C21), 27.6 (t, C13), 27.1 (t, C9), 24.6 (t, C8), 19.6 (q, C22), 19.3 (t, C17), 15.9 (q, C23); HREIMS obsd m/z 398.2429, C<sub>25</sub>H<sub>34</sub>O<sub>4</sub> requires m/z398.2457.

**Luffalactone (8)**: colorless oil;  $[\alpha]_D = +18.8^\circ$  (c 0.48, benzene); IR (CHCl<sub>3</sub>) 1785, 1750, 1695 cm<sup>-1</sup>; UV (MeOH) 212 nm ( $\epsilon$  15600); UV (CH<sub>3</sub>CN) 208 nm (ε 17 260); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 0.74 (s, 6 H), 0.84 (s, 3 H), 1.33 (s, 3 H), 2.07 (s, 3 H), 2.43 (m, 1 H), 2.80 (m, 1 H), 4.74 (d, 1 H, J = 16 Hz), 4.89 (d, 1 H, J =16 Hz), 5.69 (m 2 H), 5.95 (s, 1 H); <sup>1</sup>H NMR (500 MHz, benzene-d<sub>a</sub>) see Table I; <sup>13</sup>C NMR (50 MHz, benzene-d<sub>6</sub>) see Table I; HREIMS obsd m/z 458.2658, C<sub>27</sub>H<sub>38</sub>O<sub>6</sub> requires m/z 458.2668.

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Benzylic Hydrogen Atom Abstraction Utilizing Diethyl Bromomalonate as a Radical Source<sup>1</sup>

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The addition of  $\alpha$ -bromo esters to alkenes was shown to be a free-radical process by Kharasch in the 1940s.<sup>4</sup> A

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<sup>(1)</sup> Initial presentation of certain results at the 45th Northwest-10th Rocky Mountain Regional Meeting of the American Chemical Society, Salt Lake City, UT, June 14, 1990. (2) Oregon State University.

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Scheme I. A Mechanism for Photolytic Benzylic Bromination by Diethyl Bromomalonate with the Malonyl Type Radical as the Hydrogen Atom Abstracting Agent



wide range of such esters have been studied under conditions involving either photolytic or thermal initiation. The earlier literature has been reviewed with particular attention usually directed toward regiochemical considerations.<sup>5</sup>

We have recently undertaken studies in which several simple  $\alpha$ -bromo esters, derivatives of 2-bromomalonic acid, including diesters, an ester nitrile, and the dinitrile, and diethyl esters of 2-alkyl-2-bromomalonic acids, were reacted with pairs of alkenes.<sup>6,7</sup> The relative reactivities of the alkenes were influenced by both electronic and steric factors. The latter became especially critical as the size of the attacking radical increased. This is also the probable cause of observed changes in reaction pathway. For example, 2,3-dimethyl-2-butene (tetramethylethylene, TME) behaved in a normal manner with diethyl bromomalonate to form 1:1 adducts. The related compound, 3,4-diethyl-3-hexene (tetraethylethylene, TEE), however, reacted with the diethyl malonyl radical chiefly via hydrogen atom abstraction (eq 1). Thus 85% of the diethyl bromo-

$$\begin{array}{c} CO_2 Et \\ CH_3 CH_2, C=C, CH_2 CH_3 \\ CH_3 CH_2 \\ CH_3 CH_2 \\ CH_3 CH_2 \\ CH_3 CH_2 \\ CH_2 CH_3 \\ CH_2 CH_3 \\ CH_2 CH_3 \\ CH_2 CH_3 \\ CH_2 CH_2 \\ CH_2 CH_2$$

malonate which reacted in this system led directly to formation of the debrominated diester. The difference in behavior between these two alkenes may be readily rationalized. The double bond in TME is more accessible than that in TEE while the reactive allylic hydrogen atoms in TEE are secondary and hence more labile than the primary allylic hydrogen atoms found in TME.

Because the electronic and steric demands of radicals generated from such  $\alpha$ -bromo esters and related compounds can vary tremendously, said systems may be used to assess the characteristics of the hydrogen atom abstraction process. Rather than investigate the reaction occurring at some allylic position, wherein a competing addition reaction is always possible, benzylic hydrogen atom abstraction (eq 2) has been initially chosen for study.

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A generalized mechanism is given in Scheme I. The results are discussed below.

Table I. Relative Rates for the Photoinitiated Reaction between Diethyl Bromomalonate and Substituted Toluenes at 70 °C

substituent	$\Sigma \sigma^+$	$k_{ m rel}$	no. of runs
p-methoxy	-0.78	4.12 • 0.39	4
<i>p</i> -methyl	-0.31	$2.14 \pm 0.09^{a}$	4
toluene	0.00	1.00	
p-chloro	0.11	$1.20 \pm 0.10$	6
<i>m</i> -chloro	0.40	$0.48 \pm 0.07$	6
3,5-dibromo	0.81	$0.19 \pm 0.03$	6

<sup>a</sup>Statistically corrected.

Table II. Representative  $\rho$  Values for Hydrogen Atom Abstractions from Substituted Toluenes by Electrophilic Radicals at 70 °C

radical source	ρ <sup>a</sup>	correlation coefficient
DEBM $(h\nu)$	0.87	0.98
NBS $(h_{\nu})^{b}$	-1.19	0.97
$BrCCl_3 (hv)^b$	-0.69	0.95
BrCCl <sub>3</sub> (AlBN) <sup>b</sup>	-0.38	0.98

<sup>a</sup> Using  $\sigma^+$  constants. <sup>b</sup>Reference 9.

#### **Results and Discussion**

Unlike the preceding radical addition processes, it was observed that reaction between toluene and diethyl bromomalonate (DEBM) could not be thermally initiated at 70 °C with either AIBN or benzoyl peroxide. Photoinitiation with a GE 275-W sunlamp, however, led to disappearance of both starting materials. Reaction times were significantly longer than those encountered in bromination with N-bromosuccinimide (NBS) or bromotrichloromethane. Thus, after 48 h only 10% of the toluene had undergone reaction. After 96 h this had increased to 25%. A relatively short chain length must be involved. Also, the possibility exists that hydrogen atom abstraction by bromine atom formed in the photoinitiation may complicate the overall situation. This last concern will be discussed below.

Once effected, reasonably good material balances were found in the above reaction. In five replicate runs the amount of diethyl malonate formed to DEBM consumed was 1:1 within experimental error. The average consumption of toluene was 70% of either of the above. The benzyl bromide formed was slightly less than the toluene utilized. All the above are consistent with subsequent reaction of the initially formed benzyl bromide with additional brominating agent. No bibenzyl was found among the reaction products.

The relative rates of hydrogen atom abstraction from a series of substituted toluenes are given in Table I. All data were determined by direct competition between a pair of substrates for the diethyl malonyl radical. All reactions were run in replicate at 70 °C under a low-pressure nitrogen atmosphere. Benzene was employed as a solvent. Reaction times varied from 15 to 141 h corresponding to 4-75% reaction of the toluene substrates.

A Hammett  $\rho$  value of -0.87 was obtained. This optimum correlation (coefficient of 0.98) was found when  $\sigma^+$ constants were utilized. This is not an uncommon situation for hydrogen atom abstraction reactions by electrophilic radicals.<sup>8</sup> Table II lists examples of some  $\rho$  values recently obtained under similar conditions for purposes of comparison.<sup>9</sup>

The present value is indicative of a reaction whose sensitivity to substituent group variations is less than that

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A. Goldfinger Analog



B. Tanner Analog



of bromine atom as generated from NBS. It is not possible, however, to state that this value represents hydrogen atom abstraction only by the diethyl malonyl radical. Indeed, it is possible by analogy with either the Goldfinger mechanism for NBS bromination<sup>10</sup> or that for bromination by bromotrichloromethane under photolytic conditions developed by Tanner and co-workers<sup>11</sup> to propose mechanisms in which DEBM is no more than a reservoir for chain carrying bromine atoms. These are shown in Scheme II. The first of these reactions should be of particular concern since the reaction of hydrogen bromide with the bromo ester can proceed as shown.<sup>12</sup>

While it seems unlikely, based on  $\rho$  values, that bromine atom is the sole chain-carrying species, it may be partially responsible for the above reactivity trend. In order to assess the degree of bromine atom participation, it was decided to investigate benzylic hydrogen atom abstraction from certain related systems.

It is expected that hydrogen atom abstraction from a tertiary benzylic position should be more facile than similar abstractions from secondary positions which in turn are more reactive than their primary counterparts. Russell and DeBoer have found, for example, that the relative reactivities (statistically corrected and obtained at 40 °C) of toluene:ethylbenzene:cumene toward bromine atom are 1:17:37.<sup>13</sup> Since bromine atom is relatively modest in its steric demands, these results are quite in keeping with the general expectation presented above. Larger hydrogen atom abstracting agents, however, might find it more difficult to attack a tertiary position. Thus, while cumene is still more reactive than ethylbenzene toward trichloromethyl radical generated thermally from bromotrichloro-

Table III. Relative Rates for Photoinitiated Reaction between Diethyl Bromomalonate and Unsubstituted Alkylbenzenes at 70 °C

system	H atom type	k <sub>rel</sub> <sup>a</sup>	no. of runs
cumene	3°	$11.50 \pm 0.42$	4
sec-butylbenzene	3°	$3.24 \pm 0.14$	4
ethylbenzene	2°	1.00	
3-phenylpentane	3°	$0.60 \pm 0.06$	4
n-propylbenzene	2°	$0.58 \pm 0.02$	4
isobutylbenzene	2°	$0.25 \pm 0.04$	4
toluene	1°	$0.02 \pm 0.01$	5

<sup>a</sup> Statistically corrected for number of benzylic hydrogens.

Table IV. Relative Rates for Photoinitiated Reaction between Diethyl Bromomalonate and Substituted Cumenes at 70 °C

substituent	$\sigma^+$	$k_{\rm rel}{}^a$	no. of runs
<i>p</i> -methoxy	-0.78	$16.7 \pm 1.4$	6
p-isopropyl	-0.28	8.87 单 0.47 <sup>b</sup>	6
<i>m</i> -isopropyl	-0.06	$6.09 \pm 0.81^{b}$	6
hydrogen	0.00	$5.75 \pm 0.21$	4
p-chloro	0.11	$4.18 \pm 0.11$	4
p-nitro	0.79	$1.27 \pm 0.03$	6

<sup>a</sup>Ethylbenzene used as reference compound. <sup>b</sup>Statistically corrected.

methane, sec-butylbenzene and 3-phenylpentane exhibit a decrease in reactivity.<sup>10</sup> Indeed, the last of these tertiary benzylic systems is significantly less reactive than ethylbenzene. Table III contains a listing of relative reactivities of several alkylbenzenes toward DEBM. The low lability of the single benzylic hydrogen atom in 3-phenylpentane prominently stands out. The relative reactivity of 3phenylpentane and ethylbenzene has also been evaluated for reaction with di-tert-butyl bromomalonate<sup>14</sup> under identical conditions. The malonyl type radical generated from this substrate should be similar to that obtained from DEBM in its electronic nature. Its steric demands, however, must be far greater. With regard to this particular pair of hydrocarbon substrates, a relative reactivity of 0.16  $\pm 0.02$  was obtained. This increase in selectivity, in comparison to that obtained with DEBM  $(0.60 \pm 0.06)$ , strongly suggests that an appreciable amount of the chain-propagating reaction involves hydrogen atom abstraction by malonyl type radicals rather than bromine atom.

A related study on benzylic hydrogen atom abstraction from substituted cumenes has also been carried out. The  $\rho$  value for this series of compounds with bromine atoms is -0.29 when correlated with  $\sigma^+$  constants.<sup>15</sup> In photolytic reaction with bromotrichloromethane, a corresponding value of -0.67 was obtained under the same conditions.<sup>15</sup> Both these  $\rho$  values are less in absolute magnitude than those observed for hydrogen atom abstraction from substituted toluenes. The latter example, however, suggests that the electronic factors associated with stabilization of a tertiary radical and decreased substituent dependence may undergo partial compensation by steric factors due to the involvement of a larger radical. Table IV contains the relative rates of a series of substituted cumenes toward DEBM. A  $\rho$  value of -0.73 (determined with  $\sigma^+$  constants, correlation coefficient of 0.99) was obtained. This value is far closer to that for the toluenes (-0.87) than is observed for bromine atom or the probable mixture of bromine atom and trichloromethyl radical discussed above. This is explicable in terms of the steric demands of the abstracting

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radical and again suggests that hydrogen abstraction by bromine atom is not the major chain-propagating step.

#### Conclusion

Photolytic bromination at benzylic positions by diethyl bromomalonate is a slow process probably indicative of short radical chain length. Despite this, it appears that the major chain-propagating species is the diethyl malonyl radical. This species shows sensitivity toward electronic changes which are typical of electrophilic radicals. Its size, however, causes it to be very selective with regard to reaction at hindered benzylic sites. Unfortunately, the present data does not allow a more detailed analysis of the differences between the two radicals to be made. The relative positions of the benzylic hydrogen atom abstraction by bromine atom and diethyl malonyl radical can vary on the reaction coordinate. An additional complication is due to the known reversibility of the former process.<sup>11</sup>

### **Experimental Section**

**Compounds.** The majority of compounds used in this study were commercially available. The preparation of specific substituted toluenes,<sup>10</sup> substituted cumenes,<sup>15</sup> and bromo esters<sup>7</sup> have been discussed in earlier papers from this laboratory. All compounds were purified by standard procedures before use.<sup>16</sup>

Kinetics. All kinetic studies were run on pairs of compounds. The reactions were run in a thermostated oil bath. The reaction times were varied to ensure from 4% to 75% reaction for each substrate. The reaction mixtures were divided among several ampoules which were then sealed under a reduced pressure of nitrogen after three freeze-thaw cycles. In each case, one of the sealed ampoules was reserved for analysis of starting material. Reaction mixtures contained a pair of compounds, an internal standard (either 1,2-dichlorobenzene or chlorobenzene), DEBM, and benzene in an approximate molar ratio of 1:1:1:1:5. The ampoules were placed in the bath, just below the surface of the oil, and irradiated with a GE 275-W sun lamp. Reaction times varied from 15 to 141 h.

Analysis. All analyses were carried out using one of the following gas chromatographs: a HP 5730A equipped with a flame ionization detector and a 10-ft  $\times$  1/4-in. 12% Carbowax 20M column, a HP 5710A equipped with a thermal conductivity detector and a 6-ft  $\times^{1}/_{8}$ -in. 10% SP2100 column, or a Varian 3400 equipped with a flame ionization detector, autosampler, and a DB-17 capillary column.

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## A Regioselective Decarbonylation

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Carboxylic acid dianion oxidative coupling provides convenient synthetic methodology for the construction of certain natural products.<sup>1</sup> In a mechanistic study on oxidative coupling of systems related to phenylacetic acid dianion, Fox reported<sup>2</sup> isolation of an unusual reaction product 1 from oxidative coupling of the hindered diphenylacetic acid dianion. Formation of diacid 1 is reminiscent of the major product 2 produced<sup>3</sup> during attempted preparation<sup>4</sup> of hexaphenylethane.

Compound 1 serves as an easily accessible substrate with which to compare the chemical reactivity of two carboxylic acid groups that are located within the same molecule but which have obviously different steric and electronic environments. To probe this issue, we sought to ascertain whether or not the two carboxylic acid groups in 1 would exhibit distinguishable behavior in the presence of concentrated sulfuric acid. Solvation and protonation effects of sulfuric acid as a reaction medium have been the subject of a monograph.5

Crude samples of 1 containing siginificant amounts (5-10%) of both polymer and diacid 4 result from treatment of diphenylacetic acid dianion with molecular iodine.<sup>2</sup> Similar solubility and polarity properties of 1 and 4 as well as the presence of polymeric byproducts necessitated a simple, if tedious, purification protocol. Trituration of crude 1 with a mixture of ether and ligroin followed by addition of excess diazomethane to the residue<sup>2</sup> provided a reaction mixture that is predominantly diester 5. Further purification of 5 by chromatography, saponification under forcing conditions, and a final recrystallization then affords analytically pure diacid 1. Since diacid 4 should readily undergo loss of water,<sup>6</sup> consistent obtention of 3 as a newly formed nonpolar dehydration product (chromatographed yield 8%) upon admixture of crude 1 and warm concentrated  $H_2SO_4$  confirms the presence of 4 in crude 1.







Using carefully purified 1, optimal conditions for the

COOCH<sub>3</sub>

COOCH3 COOEt

COOEt

coci

7 ОН

10

11

CI OCH<sub>3</sub>

OEt

OH

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