as a clear yellow oil (73%). Final characterization was performed on the hydrochloride salt generated by treatment of **4a** with saturated anhydrous hydrochloric acid in diethyl ether. ^{1}H NMR (DMSO-d_6): δ 10.0 (1 H, s), 7.6 (4 H, m), 7.5 (1 H, s), 5.2 (2 H, s), 3.3 (2 H, q, J = 10 Hz), 1.1 (3 H, t, J = 10 Hz), 0.5 (9 H, s). IR (KBr): ν_{max} 2900 (br), 1700, 1200, 850 cm^{-1}. MS (FAB): m/z 303 (M + H$^+$), 257, 245. Anal. Calcd for $C_{16}H_{22}N_2O_2Si$·HCl: C, 54.67; H, 7.00; N, 7.97; Cl, 10.62. Found: C, 54.62; H, 6.84; N, 7.97; Cl, 10.09.[6]

2-[5-(Trimethylsilyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazol-2-yl]benzaldehyde (4b) was prepared according to the procedure for **4a** in 52% yield. ^{1}H NMR (DMSO-d_6): δ 9.9 (1 H, s), 8.1 (1 H, d, J = 10 Hz), 7.7 (3 H, m), 7.3 (1 H, s), 5.2 (2 H, s), 3.2 (2 H, t, J = 9 Hz), 0.7 (2 H, t, J = 9 Hz), 0.4 (9 H, s), −0.1 (9 H, s).[7]

One-Pot Multistep Synthesis of Ortho-Substituted 2-Arylimidazoles: Preparation of 2-(2-Imidazolyl)benzaldehyde (5a) from 1. Under a nitrogen atmosphere, a 1.0-g (6.9-mmol) sample of 2-phenylimidazole (1) was dissolved in 35 mL of anhydrous THF and cooled to −20 °C. This solution was treated with 3.0 mL (7.6 mmol) of 2.5 M n-BuLi in hexanes and stirred for 1 h, after which 1.3 g (1.35 mL, 7.6 mmol) of [2-(trimethylsilyl)ethoxy]methyl chloride was added dropwise. Stirring was continued for 15 min at −20 °C. The reaction mixture was warmed to room temperature and stirred for 3.5 h. The clear yellow solution was cooled to −78 °C, treated with 3.0 mL (7.6 mmol) of 2.5 M n-BuLi in hexanes, and stirred for 1 h, followed by the addition of 0.8 g (0.97 mL, 7.6 mmol) of chlorotrimethylsilane. After 1 h the reaction mixture was warmed to −42 °C, treated with 3.0 mL (7.6 mmol) of 2.5 M n-BuLi in hexanes, and stirred for 2 h. DMF (0.6 mL, 7.6 mmol) was then added, and the reaction mixture was stirred for 1 h in the cold. After warming to room temperature, the reaction mixture was stirred overnight. The reaction mixture was poured into 35 mL of saturated aqueous ammonium chloride, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated to an oil.

Under a nitrogen atmosphere, this oil was treated with 5 equiv of a 1 M solution of tetrabutylammonium fluoride in THF and heated at reflux for 3.5 h. The reaction was then cooled and diluted with pH 7.0 phosphate buffer. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with additional buffer and saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated to an oil. Purified product was obtained by chromatography over silica gel (50% ethyl acetate/hexanes). The product was dissolved in methylene chloride and treated dropwise with saturated anhydrous hydrochloric acid in diethyl ether, resulting in precipitation of the hydrochloride salt. The salt was then collected by filtration in a yield of 41% based on 2-phenylimidazole. ^{1}H NMR (DMSO-d_6): δ 9.89 (s, 1 H), 8.06 (s, 1 H), 7.75 (m, 2 H), 7.53 (m, 2 H), 7.4 (s, 2 H). MS (FAB): m/z 173 (M + H$^+$), 145. Anal. Calcd for $C_{10}H_8N_2O$·HCl·0.25H_2O: C, 56.24; H, 4.51; N, 13.12. Found: C, 56.23; H, 4.91; N, 13.30. TGA (H_2O): Found: 2.7–3.0 wt %.

2-(2-Methylphenyl)-1*H*-imidazole hydrochloride (5b) was prepared from 1 using methyl iodide, according to the procedure for **5a** in 56% yield. ^{1}H NMR (DMSO-d_6): δ 7.75 (m, 2 H), 7.50 (m, 2 H), 7.43 (s, 2 H), 2.28 (3 H, s). MS (FAB): m/z 159 (M + H$^+$), 145. Anal. Calcd for $C_{10}H_{10}N_2$·HCl·0.5H_2O: C, 58.97; H, 5.94; N, 13.75. Found: C, 58.67; H, 6.20; N, 13.73. TGA (H_2O): 2.2 wt %.

2-[2-(Methylthio)phenyl]-1*H*-imidazole hydrochloride (5c) was prepared from 1 using dimethyl disulfide, according to the procedure for **5a** in 52% yield. ^{1}H NMR (DMSO-d_6): δ 7.77 (m, 2 H), 7.62 (m, 2 H), 7.42 (s, 2 H), 2.39 (s, 3 H). MS (FAB): m/z 146 (M + H$^+$), 145. Anal. Calcd for $C_{10}H_{10}N_2S$·HCl: C, 52.98; H, 4.45; N, 12.36. Found: C, 52.79; H, 4.82; N, 12.09.

2-(2-Deuteriophenyl)-1*H*-imidazole hydrochloride (5d) was prepared from 1 using deuteriomethanol, according to the procedure for **5a** in 38% yield. ^{1}H NMR (DMSO-d_6): δ 7.73 (m, 2 H), 7.54 (m, 2 H), 7.39 (s, 2 H). MS (FAB): m/z 146 (M + H$^+$), 145. Anal. Calcd for $C_9H_7DN_2$·HCl·0.25H_2O: C, 58.07; H, 4.60; N, 14.90. Found: C, 58.05; H, 5.17; N, 14.53. TGA (H_2O): Found 1.9 wt %.

1-(Ethoxymethyl)-2-(2-formylphenyl)-1*H*-imidazole-5-carboxaldehyde (7). To a solution of 3.0 g of **2a** (15 mmol) in 300 mL of anhydrous THF at −20 °C under nitrogen with stirring was slowly added 24.1 mL of 1.6 M n-BuLi in hexanes (39 mmol), and the resulting dark greenish-brown mixture was stirred for 1 h. Anhydrous DMF (5.0 mL, 4.7 g, 65 mmol) was then added, and the reaction mixture was stirred at −20 °C for 2.5 h. After warming to room temperature, the reaction was poured into 350 mL of saturated aqueous ammonium chloride, the layers were separated, and the aqueous layer was washed twice with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and evaporated to dryness. Chromatography (silica gel, ethyl acetate/hexanes) then yielded 2.0 g of **7** (52%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 9.9 (1 H, s), 9.8 (1 H, s), 8.1 (1 H, m), 7.9 (1 H, s), 7.7 (3 H, m), 5.6 (2 H, s), 3.6 (2 H, q, J = 10 Hz), 1.2 (3 H, t, J = 10 Hz). IR (KBr): ν_{max} 2850 (br), 1720, 1690, 1150 cm^{-1}. MS (CI): m/z 259 (M$^+$), 213. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.99; H, 5.69; N, 10.93.

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Registry No. **1**, 670-96-2; **2a**, 86119-53-1; **2b**, 139975-85-2; **2b**·HCl, 139975-86-3; **3a**, 139975-87-4; **3a**·HCl, 139975-88-5; **3b**, 139975-89-6; **3b**-HCl, 139975-90-9; **4a**, 139975-91-0; **4a**·HCl, 139975-92-1; **4b**, 139975-93-2; **5a**, 139975-94-3; **5a**·HCl, 139975-97-6; **5b**, 61698-31-5; **5c**, 139975-95-4; **5d**, 139975-96-5; **7**, 140110-68-5; $ClCH_2OEt$, 3188-13-4; $ClCH_2O(CH_2)_2SiMe_3$, 76513-69-4.

Luffalactone and (4*E*,6*E*)-Dehydromanoalide from the Sponge *Luffariella variabilis*

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The Western Pacific sponge *Luffariella variabilis* is the source of manoalide (**1**), which is a potent antiinflammatory agent and irreversible inhibitor of phospholipase A_2.[2] The isolation and structural elucidation of manoalide (**1**) was reported in 1980 by de Silva and Scheuer,[3] who, in 1981, described *seco*-manoalide (**2**) and (*E*)- and (*Z*)-neomanoalide (**3**, **4**).[4] In order to provide large quantities of manoalide for clinical evaluation,[5] we collected over 400 specimens of *L. variabilis* from three locations in Palau and were surprised to find considerable variation in their secondary metabolite content.[6] We have earlier reported

(1) Current address: Department of Chemistry, University of Melbourne, Parkville, Victoria 3052, Australia.

(2) Jacobs, R. S.; Culver, P.; Langdon, R.; O'Brien, T.; White, S. *Tetrahedron* **1985**, *41*, 981. deFreitas, J. C.; Blankemeier, L. A.; Jacobs, R. S. *Experientia* **1984**, *40*, 864. Lombardo, D.; Dennis, E. A. *J. Biol. Chem.* **1985**, *260*, 7234. Glaser, K. B.; Jacobs, R. S. *Biochem. Pharmacol.* **1986**, *35*, 449. Bennett, C. F.; Mong, S.; Clarke, M. A.; Kruse, L. I.; Crooke, S. T. *Biochem. Pharmacol.* **1987**, *36*, 733. Jacobson, P. B.; Marshall, L. A.; Sung, A.; Jacobs, R. S. *Biochem. Pharmacol.* **1990**, *39*, 1557.

(3) de Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1611.

(4) de Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1981**, *22*, 3147.

(5) The clinical evaluation of manoalide for the treatment of psorriasis produced no evidence of efficacy (Garst, M. E., personal communication).

(6) Since we were involved in a large-scale collection of a previously identified sponge, the specimens were identified in the field by color and form. A random selection of the sponge specimens were extracted on site and the presence of "manoalide" was confirmed by TLC. *Luffariella variabilis* can be distinguished from closely related sponges by the orange skeletal fibers. The orange color may arise by the reaction of manoalide with lysine residues in the proteins that constitute the fibers. The sponges were not examined individually by a taxonomist. Voucher specimens from many collections of *L. variabilis* are available on request.

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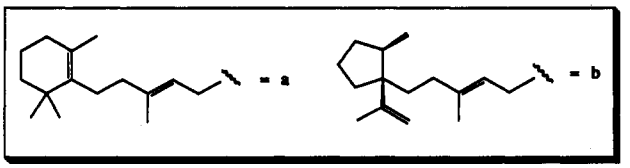
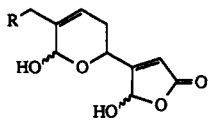
the structural elucidations of luffariellins A (5) and B (6) that replaced manoalide (1) and *seco*-manoalide (2), respectively, in less than 5% of the specimens examined and co-occurred in other specimens.[7] The presence of manoalides or luffariellins in a crude extract could only be determined by ^{1}H NMR analysis because the chromatographic traces and biological activities were identical for both series. In most of the ^{1}H NMR spectra we could observe small and variable quantities of a dehydro derivative of manoalide, which has been incorrectly represented in the past.[8] In this paper, we present the structural elucidations of (4*E*,6*E*)-dehydromanoalide (7) and luffalactone (8), a tetracyclic sesterterpene acetate that eluted with dehydromanoalide during column chromatography.





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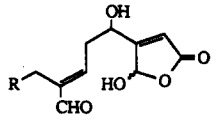

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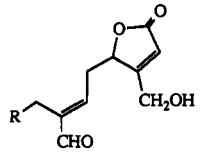

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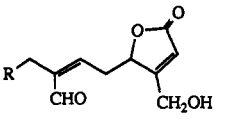
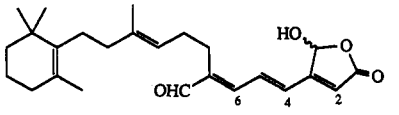


4 R = a



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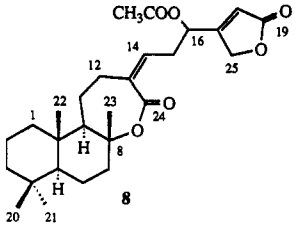

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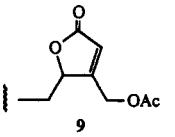

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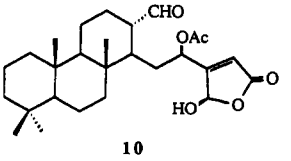

10

During the large-scale isolation of manoalide, chromatographic fractions enriched in *seco*-manoalide (2) and dehydromanoalide were pooled and stored at −70 °C for several years. A portion of this material was chromatographed on silica gel to obtain a fraction that was further purified by LC on Partisil using 1:1 or 3:2 hexane–ethyl acetate as eluant to obtain luffalactone (8; 35 mg, 2 × 10^{-4}% dry weight), which eluted just after (4*E*,6*E*)-dehydromanoalide (7; 575 mg, 3.2 × 10^{-3}% dry weight).

(4*E*,6*E*)-Dehydromanoalide (7) was obtained as a pale yellow waxy solid that darkens on standing. The molecular formula, $C_{25}H_{34}O_4$, which was determined by high-resolution mass measurement (*m*/*z* 398.2429), indicated that 7 was a dehydration product of manoalide (1) or *seco*-manoalide (2). The UV absorption at 317 nm (ε 34 180) showed a strong bathochromic shift to 464 nm (ε 60 080) on treatment with base, indicating the presence of an extended chromophore.[9] The ^{1}H NMR spectrum contained signals at δ 9.54 (s, 1 H), 7.32 (dd, 1 H, *J* = 16, 11 Hz), 6.90 (d, 1 H, *J* = 11 Hz), and 6.81 (d, 1 H, *J* = 16 Hz) that were assigned to an α,β,γ,δ-unsaturated aldehyde. All other prominant signals in the ^{1}H NMR spectrum could be assigned by analogy to manoalide (1), and all signals in the ^{13}C NMR were assigned by interpretation of the XHCORR and COLOC data. The (4*E*,6*E*)-stereochemistry was determined from $J_{4,5}$ = 16 Hz and a 6% nuclear Overhauser enhancement of the H-6 signal at δ 6.90 on irradiation of the aldehyde proton signal.

Luffalactone (8), $[\alpha]_D$ = +18.8° (*c* 0.48, benzene), was isolated as a colorless oil. The molecular formula, $C_{27}H_{38}O_6$, was determined from high-resolution EIMS data (*m*/*z* 458.2658). The IR spectrum contained bands at 1785, 1750, and 1695 cm^{-1} that indicated the presence of three carbonyl groups. The UV absorption in methanol at 212 nm (ε 15 600) is appropriate for one or more unsaturated ester or lactone groups. The ^{13}C NMR spectrum contained three carbonyl signals and four olefinic signals, which requires that 8 must contain four rings. Since the ^{1}H NMR spectrum ($CDCl_3$) contained an acetate methyl signal at δ 2.07 (s, 3 H), we concluded that 8 was a tetracyclic sesterterpene acetate.

From an initial inspection of the NMR spectra, it was obvious that the carbon skeleton of luffalactone was not similar to that of manoalide. The four ^{1}H NMR signals at δ ($CDCl_3$) 0.73 (s, 3 H), 0.74 (s, 3 H), 0.84 (s, 3 H), and 1.33 (s, 3 H, Me-23) could be assigned to the methyl groups on a labdane-type bicyclic skeleton with oxygen substitution at C-8.[8] The 500-MHz ^{1}H NMR spectrum in benzene-d_6 showed much better signal separation than the $CDCl_3$ spectrum and was completely assigned as shown in Table I. The ^{13}C NMR data for C-1–C-10 and C-20–C-23 agreed well with the predicted values obtained from model compounds,[10] particularly after correcting for the presence of an ester at C-8, and clearly indicated that the methyl group at C-8 is in the axial orientation. The geometry about the ring junctions was confirmed by NOEDS experiments; irradiation of the H-5 signal at δ 0.63 caused enhancement of the H-9 signal at 1.16, and irradiation of the Me-23 signal at 1.11 resulted in enhancement of the Me-22 signal. The methyl proton signals showed long-range ^{1}H–^{13}C correlations to the expected carbon signals (see Table I). The COSY spectrum suggested that there might be two methylene groups attached at C-9, but overlap of the H-9 signal with one of the two H-11 signals made this a risky assignment. However, in the HMBC experiment there were long-range ^{1}H–^{13}C correlations between the H-12 signal at δ 1.97 (ddd, 1 H, *J* = 13, 5, 3 Hz) and C-9, C-11, the C-24 carbonyl signal at δ 169.3, and two olefinic carbon signals at 140.0 (s, C-13) and 131.2 (d, C-14), and between H-14 and C-12, C-15, and C-24. These

(7) Kernan, M. R.; Faulkner, D. J.; Jacobs, R. S. *J. Org. Chem.* **1987**, *52*, 3081.

(8) Glaser, K. B.; de Carvalho, M. S.; Jacobs, R. S.; Kernan, M. R.; Faulkner, D. J. *Mol. Pharmacol.* **1989**, *36*, 782.

(9) The bathochromic shift takes place over several minutes. The base-catalyzed reaction and its reversal using acid were monitored by ^{1}H NMR spectroscopy to ensure that no rearrangement had occurred.

(10) Djura, P.; Stierle, D. B.; Sullivan, B.; Faulkner, D. J.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1435.

Table I. ^1H and ^{13}C NMR Data for Luffolactone in Benzene-d_6 Solution

C no.	^{13}C ppm (mult)	^1H ppm (mult, J in Hz)	long-range ^1H–^{13}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 (s)		
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 δ 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 C*H*(OCOR) proton. The corresponding ^{13}C NMR signal was observed at δ 69.5 (d, C-16). The remaining ^{13}C NMR signals at δ 172.4 (s), 166.8 (s), 116.7 (d), and 70.6 (t) were assigned to an α,β-unsaturated γ-lactone, which is characteristically found, albeit as a γ-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 γ-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 δ 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[12] but has not been encountered previously from a marine source. It may be considered related to other metabolites from *L. variabilis* due to the similar oxidation patterns. Luffalactone showed 52% inhibition of edema in the mouse ear assay at 50 μg/ear (n = 5). The biological activity of (4*E*,6*E*)-dehydromanoalide has been described elsewhere.[8]

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. (4*E*,6*E*)-Dehydromanoalide and luffalactone were obtained from this material as described in the text.

(4*E*,6*E*)-Dehydromanoalide (7): pale yellow waxy solid; IR ($CHCl_3$) 1745, 1670 cm^{-1}; UV (MeOH) 317 (ϵ 34 180), 204 nm (ϵ 23 760); UV (MeOH + NaOH) 464 (ϵ 60 080), 290 (ϵ 3600), 252 (ϵ 5100), 208 nm (ϵ 32 900); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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, $C_{25}H_{34}O_4$ requires m/z 398.2457.

Luffalactone (8): colorless oil; $[\alpha]_D$ = +18.8° (c 0.48, benzene); IR ($CHCl_3$) 1785, 1750, 1695 cm^{-1}; UV (MeOH) 212 nm (ϵ 15 600); UV (CH_3CN) 208 nm (ϵ 17 260); ^1H NMR (200 MHz, $CDCl_3$) 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); ^1H NMR (500 MHz, benzene-d_6) see Table I; ^{13}C NMR (50 MHz, benzene-d_6) see Table I; HREIMS obsd m/z 458.2658, $C_{27}H_{38}O_6$ requires m/z 458.2668.

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Benzylic Hydrogen Atom Abstraction Utilizing Diethyl Bromomalonate as a Radical Source[1]

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The addition of α-bromo esters to alkenes was shown to be a free-radical process by Kharasch in the 1940s.[4] A

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