tography to afford 434 mg of **5** (81%) as a colorless oil: ^{1}H NMR (60 MHz, CCl_4) δ 1.7 (3 H, s), 3.1 (1 H, br s), 3.75 (2 H, br s), 4.3 (2 H, br s), 6.8–7.3 (10 H, m); IR (neat) 3300 (br), 3050, 3020, 2910, 2850, 1600, 1490, 1450, 1440, 1370, 1240 cm^{-1}.

(2*R*,3*R*)-3,4-Diphenyl-2-methyl-2,3-epoxy-1-butanol (6). To a stirred solution of $Ti(O\text{-}i\text{-}Pr)_4$ (698 mg, 2.45 mmol) in CH_2Cl_2 (20 mL) at −20 °C was added D-(−)-diethyl tartrate (633 mg, 3.07 mmol). The pale yellow solution was stirred at −20 °C for 5 min followed by the addition of allylic alcohol **5** (487 mg, 2.04 mmol) and 6.54 M TBHP (0.63 mL, 4.08 mmol) in CH_2Cl_2. The solution was stirred at −20 °C for 5 h and the reaction was stopped by the addition of saturated Na_2SO_4 (0.5 mL) and Et_2O (1.5 mL). The mixture was warmed to room temperature and stirred for 3 h, filtered through Celite, dried over $MgSO_4$, filtered, and evaporated to give a colorless oil. This residue was dissolved in Et_2O (20 mL) and stirred vigorously with a 10% solution of NaOH in saturated NaCl (10 mL) at room temperature for 30 min. The layers were separated and the organic phase was washed with saturated NaCl (2 × 10 mL), dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography to afford 469 mg of **6** (90%) as a colorless oil: ^{1}H NMR (250 MHz, benzene-d_6) δ 1.00 (3 H, s), 1.67 (1 H, s, D_2O exchange), 3.14 (2 H, AB q), 3.71 (2 H, br s), 6.87–7.15 (10 H, m); IR (neat) 3420 (br), 3080, 3060, 3030, 2960, 2920, 1600, 1580, 1490, 1450, 1445, 1375, 1265 cm^{-1}.

(1*S*,2*R*)-2-Methyl-1-phenyl-1-(phenylmethyl)-1,3-propanediol (7). To a stirred suspension of LAH (120 mg, 3.71 mmol) in Et_2O (10 mL) at room temperature was added epoxy alcohol **6** (315 mg, 1.24 mmol) in Et_2O (5 mL) dropwise. The mixture was stirred at room temperature for 3.5 h and quenched by adding H_2O (125 μL), 20% (w/v) aqueous NaOH (95 μL), and H_2O (450 μL) to give a white granular precipitate. The mixture was filtered, and the filtrate was dried over Na_2SO_4, filtered, and evaporated to give the 1,3-diol **7** (94%) as a colorless oil: ^{1}H NMR (60 MHz, CCl_4) δ 0.75 (3 H, d), 2.0 (1 H, m), 3.1 (2 H, s), 3.0–3.9 (4 H, m), 6.7–7.3 (10 H, m).

(2*S*,3*R*)-1,2-Diphenyl-3-methyl-4-tosyl-2-butanol (8). To a stirred solution of 1,3-diol **7** (300 mg, 1.17 mmol) in pyridine (10 mL) at 0 °C was added tosyl chloride (260 mg, 1.36 mmol) in one portion. Thin layer chromatography (30% EtOAc/Hexane) after 18 h showed about a 1:1 mixture of tosylate and starting 1,3-diol so an additional portion of tosyl chloride (260 mg, 1.36 mmol) was added. The mixture was stirred an additional 4 h, poured onto ice and extracted with Et_2O (50 mL). The Et_2O phase was washed with 1 N HCl (4 × 25 mL) and saturated NaCl (2 × 25 mL), dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography to afford 350 mg of tosylate **8** (73%) as a colorless oil which crystallized on standing: ^{1}H NMR (60 MHz, CCl_4) δ 0.75 (3 H, d), 1.9 (1 H, s, D_2O exchange), 2.0–2.3 (3 H, s and 1 H, m), 3.05 (2 H, s), 3.5–4.1 (2 H, d of AB q), 6.4–7.7 (14 H, m); IR (neat) 3550 (br), 3060, 3020, 2970, 2920, 1600, 1490, 1440, 1350, 1185, 1170 cm^{-1}.

(2*S*,3*R*)-4-(Dimethylamino)-1,2-diphenyl-3-methyl-2-butanol Hydrochloride (9). To a stirred solution of tosylate **8** (350 mg, 0.853 mmol) in Me_2SO (5 mL) was added dimethylamine (2 mL, 30 mmol). The flask was stoppered and stirred at room temperature for 48 h, diluted with Et_2O (100 mL), and washed with H_2O (3 × 50 mL) and saturated NaCl (2 × 50 mL), dried over $MgSO_4$, filtered, and evaporated to a volume of 15 mL, and anhydrous HCl gas was bubbled through the solution which produced a white precipitate. The mixture was cooled to 0 °C, and the precipitate was filtered from solution and washed with cold Et_2O to afford 216 mg of **9** (79%) as a white solid: mp 242–243 °C (recrystallized from $MeOH/EtOAc/Et_2O$); ^{1}H NMR (250 MHz, D_2O) δ 0.77 (3 H, d), 2.21 (1 H, m), 2.45 (1 H, d of d), 2.57 (6 H, s), 2.85 (1 H, d of d), 3.14 (2 H, AB q), 6.9–7.35 (10 H, m); $[\alpha]^{24}{}_D$ +8.2° (*c* 1.21, EtOH). Authentic Darvon alcohol hydrochloride showed $[\alpha]^{24}{}_D$ +8.7° (*c* 1.20, EtOH) and gave an NMR, melting point (247–248 °C), and mixed melting point (243–244 °C) which proved its identity with our synthetic material. Anal. Calcd for $C_{19}H_{26}NOCl$: C, 71.34; H, 8.19; N, 4.38; Cl, 11.08. Found: C, 71.08; H, 8.14; N, 4.13; Cl, 11.35.

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Registry No. 1, 451-40-1; 2, 3699-66-9; 3, 100191-02-4; 4, 100191-03-5; 5, 100191-04-6; 6, 100191-05-7; 7, 63463-58-1; 8, 70650-46-3; 9, 63526-63-6; dimethylamine, 124-40-3; (−)-diethyl tartrate, 13811-71-7.

New Synthesis of Jasmine Lactone and Related δ-Lactones from 1,2-Cyclohexanedione. Preparation and Dye-Sensitized Photooxygenation of 3-(2-Alkenyl)- and 3-(2-Alkynyl)-1,2-cyclohexanediones

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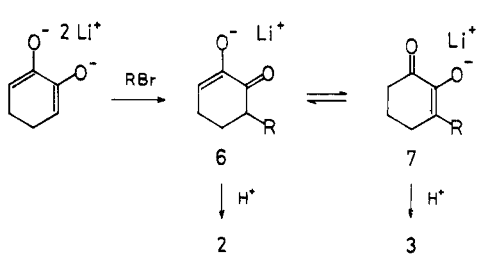
Jasmine lactone (**1c**), a fragrant component of jasmine oil (*Jasminum grandiflorum L.*),[1] was first synthesized in 1962 using cyclopentanone as the starting material.[2] The method has been modified and extended mainly to carry out the oxidative lactonization of the cyclopentanone ring effectively in the presence of a labile unsaturated side chain,[3] although alternative methods using a straight-chain sulfone acetal,[4] glutaraldehyde,[5] or acrolein dimer[5] have also appeared. In this paper, we describe full details of a new synthesis of jasmine lactone and related δ-lactones,[6] which involves monoalkylation of 1,2-cyclohexanedione and dye-sensitized photooxygenation of the resulting 3-substituted 1,2-cyclohexanediones as key steps (Scheme I).

Results and Discussion

α-Monoalkylation of 1,2-Cyclohexanedione. The monoalkylation was carried out via the dianion of 1,2-cyclohexanedione generated by lithium diisopropylamide in THF in a similar manner as reported by Kende and Eilerman in 1973.[7] Although the reaction gave no O-alkylated or polyalkylated products as noted by them, the C-alkylated product was found not to be 3-alkyl-2-hydroxy-2-cyclohexen-1-one (**3**) but to be 6-alkyl-2-hydroxy-2-cyclohexen-1-one (**2**), an enol tautomer of **3**, in spite of the fact that **3** is thermodynamically more stable than **2**. This result indicates that the alkylated lithium enolate anion **6** is hardly in equilibrium with the isomeric anion **7** under the reaction conditions used. Since **2** was



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[2] Demole, E.; Winter, M. *Helv. Chim. Acta* **1962**, *45*, 1256.

[3] (a) Japanese Patent Sho 45-26096, 1970. (b) Ijima, A.; Mizuno, H.; Takahashi, K. *Chem. Pharm. Bull.* **1972**, *20*, 197. (c) Otsuka, T.; Japanese Patent Sho 54-115320, 1979. (d) Torii, S.; Okumoto, H.; Tanaka, H. *J. Org. Chem.* **1980**, *45*, 1330. (e) Matsubara, S.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983** *56*, 2029.

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[7] Kende, A. S.; Eilerman, R. G. *Tetrahedron Lett.* **1973**, 697. We have found that the dianion reacts with halides better at −50 °C than at −78 °C.

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Scheme I

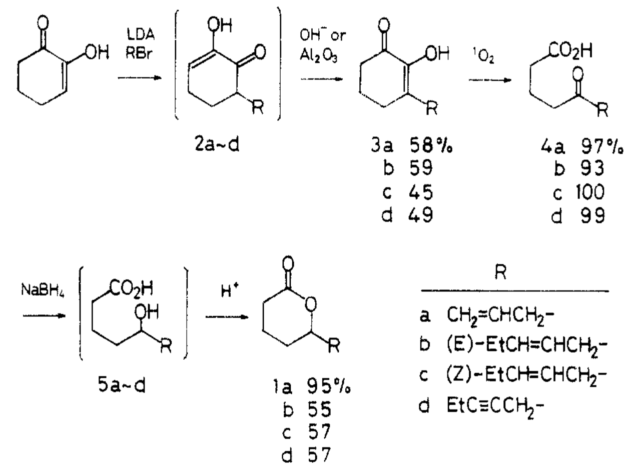


Table I. Isomerization of 6-Alkyl-2-hydroxy-2-cyclohexen-1-one (2) to 3-Alkyl-2-hydroxy-2-cyclohexen-1-one (3)

	conditions				
substrate	catalyst or promoter	solvent	temp, °C	time, h	ratio of components[a]
2a	Na_2CO_3[b]	water	0	0.5	**3a**:**2a** 100:0
2b	Na_2CO_3[b]	THF-water	0	2	**3b**:**2b** 0:100[c]
	NaOH[b]	THF-water	r.t.[h]	2	100:0
2c	NaOH[b]	THF-water	r.t.	2	**3c**:**2c** 100:0
2d	NaOH[b]	THF-water	r.t.	3	*d*
	SiO_2[e] (4)[f]	ether	r.t.	10	**3d**:**2d** 50:50
	Al_2O_3[g] (2.5)[f]	ether	r.t.	14	100:0
	Al_2O_3[g] (7)[f]	ether	r.t.	6	100:0

[a] Estimated from ^1H NMR spectra. [b] One molar equivalent of base was used. [c] The recovery of **2b** was 94%. [d] Unidentified products were obtained. [e] Merck silica gel 60 PF_{254}. [f] (wt of SiO_2 or Al_2O_3)/(wt of **2d**). [g] Merck Al_2O_3 150 PF_{254} type T was effective but HF_{254} Basic type E was harmful to **2d**. [h] r.t. = room temperature.

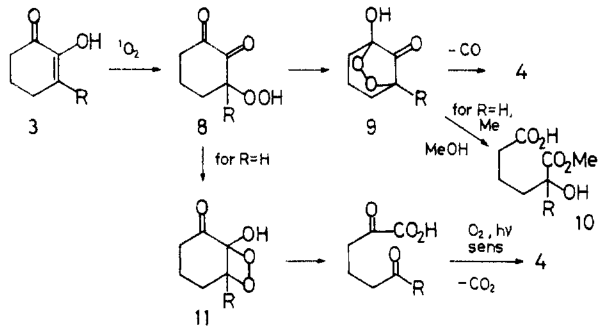
found to be more labile than **3**, it was reasonable to purify the product after the isomerization to **3**. Thus diones **3a–d** were obtained in 45–59% yields after purification by TLC, LC, or vacuum distillation.

We used 4 equiv of bromides to complete the reaction. The excess bromide was recovered unchanged by distillation in the workup. The recovery of 1-bromo-2-pentyne, for example, was more than 90%.

The isomerization of **2** to **3** was achieved under mild conditions as shown in Table I. The allyl-substituted dione **2a** was converted to **3a** by using sodium carbonate as base catalyst, while the pentenyl-substituted diones **2b**,**c** needed sodium hydroxide for the isomerization. The pentynyl-substituted dione **2d**, however, failed to give **3d** with sodium hydroxide. It was effectively isomerized to **3d** by aluminum oxide.[8] The failure is attributable to the lability of **3d** to base, which causes the disappearance of the triple bond.[9]

Dye-Sensitized Photooxygenation. The dye-sensitized photooxygenation was carried out in methanol at 0 °C under an oxygen atmosphere using a 100-W tungsten–halogen lamp without a filter. The absorption of oxygen and the evolution of carbon monoxide were nearly quantitative, and δ-keto acids **4a–d** were obtained in more than 90% yield. The reaction was followed by measuring the oxygen absorbed and carbon monoxide evolved using gas chromatography and manometry.

Scheme II



The active species involved in the present photooxygenation is believed to be singlet oxygen, as evidenced by quenching experiments and solvent deuteration tests,[10] which may attack the unsaturated side chain. Careful search for the byproducts revealed that the attack was negligible, if any. This selectivity constitutes the central importance in the present work and indicates the high reactivity of the enol double bond toward singlet oxygen despite the conjugation of electron-withdrawing carbonyl group. In fact, a competition toward singlet oxygen between 3-methyl-1,2-cyclohexanedione and 2,3-dimethyl-2-butene (TME) has shown that the former is as reactive as the latter.[10] Therefore, the reactivity of the enol double bond toward singlet oxygen is estimated to be 2 orders of magnitude larger than that of the disubstituted olefins in the side chains.

The oxygenation appears to proceed by an ene reaction mechanism to give hydroperoxide **8** that rapidly undergoes cyclization to the unstable endo peroxide **9** (Scheme II) as discussed fully in the previous paper.[10,11] The fact that carbon dioxide has not been detected at all rejects the transient formation of dioxetane **11** in the present reaction. The intermediacy of **9** was proved by trapping to give α-hydroxy ester **10** for the substrate **3** in which R is H or Me. However, the present substrates **3a–d** have afforded no α-hydroxy ester **10**. The absence of **10**, which is favorable for the synthesis, can be explained partly by steric inhibition of nucleophilic attack by methanol due to the bulky unsaturated side chain.

Transformation of δ-Keto Acids 4 to δ-Lactones 1. Reduction of δ-keto acids **4a–d** with sodium borohydride in aqueous $NaHCO_3$ afforded δ-hydroxy acids **5a–d**. The acid **5a** was cyclized to the lactone **1a** in situ, while the lactonization of **5b–d** to **1b–d** was achieved by refluxing in benzene in the presence of *p*-TsOH. The lactone **1d** was hydrogenated to **1c** using Lindlar catalyst in the usual way.[12] The IR and ^1H NMR spectra were completely identical with those reported in the literature.[2,4]

Experimental Section

All boiling and melting points are uncorrected. IR spectra were recorded with a JASCO A-102 spectrometer. ^1H NMR spectra at 60 MHz and ^{13}C NMR spectra at 25 MHz were obtained on JEOL PMX 60 SI and JEOL FX-100 spectrometers, respectively. Me_4Si was used as internal srandard. Bulb-to-bulb distillation was performed by using a Shibata glass tube oven GTO-250. Elemental analyses were performed by Mr. Eiichiro Amano of our laboratory.

Materials. 1,2-Cyclohexanedione was prepared conveniently according to the method reported earlier.[13] 1-Bromo-(*E*)-2-pentene was prepared by bromination of 1-pentene with *N*-

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[8] Merck aluminum oxide 150 PF_{254} type T was effective but Merck aluminum oxide HF_{254} basic type E was harmful.

[9] The loss of triple bond was observed as indicated by IR and NMR spectra althrough the identification of the products was not made.

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bromosuccinimide.[14] 1-Bromo-(*Z*)-2-pentene was prepared by treatment of (*Z*)-2-penten-1-ol with PBr_3/pyridine.[15] 1-Bromo-2-pentyne was obtained from propargyl alcohol according to a modification of the reported method.[16]

General Procedure for the Alkylation of 1,2-Cyclohexanedione to 6-Alkyl-2-hydroxy-2-cyclohexen-1-ones 2a–d. 6-Allyl-2-hydroxy-2-cyclohexen-1-one (2a). The following procedure illustrates the preparation of **2a–d**. To a solution of diisopropylamine (2.91 g, 28.8 mmol) in dry THF (50 ml) was added a 1.34M solution of *n*-butyllithium in hexane (21.4 mL, 28.7 mmol) with stirring at −10 °C. The mixture was stirred for 15 min and 1,2-cyclohexanedione (1.54 g, 13.7 mmol) in dry THF (7 mL) was added to the solution at −10 °C. Stirring was continued for a further 15 min. Then the solution was cooled to −50 °C and allyl bromide (6.63 g, 54.8 mmol) was added. The reaction mixture was stirred for 6 h and neutralized with dilute hydrochloric acid. The mixture was extracted with ether, and the ethereal solution was dried ($MgSO_4$) and evaporated to afford 2.29 g of crude **2a** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.5–2.8 (m, 7 H), 4.75–5.20 (m, 2 H), 5.35–6.0 (m, 1 H), 5.9 (br s, 1 H), 6.0 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.4 (t), 29.0 (t), 34.3 (t), 46.0 (d), 117.6 (t), 119.1 (d), 136.6 (d), 147.7 (s), 197.9 (s).

6-[(*E*)-2-Pentenyl]-2-hydroxy-2-cyclohexen-1-one (2b): bp 100 °C (2.5 torr); ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H), 1.6–2.8 (m, 9 H), 5.45 (m, 2 H), 6.0 (br s, 1 H), 6.10 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (q) 22.5 (t), 25.6 (t), 28.0 (t), 32.4 (t), 45.5 (t), 117.6 (d), 125.5 (d), 135.0 (d), 146.7 (s), 192.4 (s).

6-(2-Pentynyl)-2-hydroxy-2-cyclohexen-1-one (2d). Alkylation of 1,2-cyclohexanedione (1.12 g, 10.0 mmol) with 1-bromo-2-pentyne (5.88 g, 40 mmol) was accomplished by using the general procedure followed by distillation to afford 4.85 g (bp 20 °C (20 torr)) of the unused bromopentyne and 2.20 g of crude **2d**: bp 100 °C (2 torr); ^1H NMR ($CDCl_3$) δ 1.10 (t, 3 H), 1.7–2.7 (m, 9 H), 5.8 (br s, 1 H), 6.11 (t, J = 5 Hz, 1 H).

Isomerization of 6-Alkyl-2-hydroxy-2-cyclohexen-1-one (2a–d) to 3-Alkyl-2-hydroxy-2-cyclohexen-1-one (3a–d). 3-Allyl-2-hydroxy-2-cyclohexen-1-one (3a). The crude **2a** (2.29 g) was dissolved in a solution of sodium carbonate (1.45 g, 13.7 mmol) in ice water (20 mL) and the resulting solution was stirred for 30 min at 0 °C. The reaction mixture was neutralized and extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to afford 2.29 g of crude **3a** as a yellow oil. Bulb-to-bulb distillation gave 1.70 g of crude **3a**. Purification by preparative TLC (Merck silica gel 60 PF_{254}, acetone–hexane 1:5, R_f 0.44) afforded 1.20 g (58%)[17] of **3a**: bp 60–70 °C (7 torr); IR (neat) 3450, 3150, 1715 (weak), 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–2.2 (m, 2 H), 2.2–2.7 (m, 4 H), 3.08 (m, 2 H), 4.90–5.35 (m, 2 H), 5.50–6.05 (m, 1 H), 6.2 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.5 (t), 28.1 (t), 35.2 (t), 36.0 (t), 116.8 (t), 131.7 (s), 133.7 (d), 143.8 (s), 194.8 (s). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.16; H, 8.00.

3-[(*E*)-2-Pentenyl]-2-hydroxy-2-cyclohexen-1-one (3b). The crude **2b** (416 mg) was dissolved in a solution of sodium hydroxide (92 mg, 2.31 mmol) in THF–water (1:10, 25 mL) at room temperature and the solution was stirred for 2 h. The alkaline solution was neutralized with dilute hydrochloric acid and extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to give 417 mg of crude **3b** as a yellow oil. Purification through a silica gel column (Wako gel C 200, acetone–hexane, 1:20) afforded 350 mg (59%)[17] of **3b**: bp 85 °C (1.5 torr); IR (neat) 3450, 3010, 1710 (weak), 1670, 1650, 965 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H), 1.6–2.7 (m, 8 H), 3.02 (t, J = 5 Hz, 2 H), 5.48 (m, 2 H), 6.1 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (q), 22.5 (t), 25.6 (t), 28.0 (t), 33.9 (t), 35.9 (t), 123.8 (d), 132.8 (s), 134.7 (d), 143.3 (s), 189.4 (s). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H, 8.81.

3-[(*Z*)-2-Pentenyl]-2-hydroxy-2-cyclohexen-1-one (3c). The crude **2c** (425 mg) was isomerized to crude **3c** (373 mg) in a similar way as described for **2b** to **3b**. Preparative TLC of the crude material (Merck silica gel 60 PF_{254}, acetone–hexane, 1:5, R_f 0.4–0.6) gave 163 mg (45%)[17] of **3c** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H), 1.7–2.7 (m, 8 H), 3.08 (d, J = 6 Hz, 2 H), 5.1–5.8 (m, 2 H), 6.1–9.1 (br s).

3-(2-Pentynyl)-2-hydroxy-2-cyclohexen-1-one (3d). The crude **2d** (2.20 g) was mixed with 13 g of aluminum oxide (Merck 150 PF_{254} Type T) in dry ether (130 mL) and the resulting mixture was stirred vigorously under argon at room temperature for 6 h. Aluminum oxide was filtered off and washed 3 times with 30-mL portions of ether. The combined filtrate and washings were evaporated to give 1.85 g of crude **3d**. Purification through a silica gel column (Wako gel C 200, acetone–hexane, 1:20) afforded 868 mg (49%)[17] of **3d** as a pale yellow oil: IR (neat) 3450, 2240 (very weak), 1720 (weak), 1680, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, 3 H), 1.8–2.7 (m, 8 H), 3.24 (m, 2 H), 6.27 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.5 (t), 14.2 (q), 20.2 (t), 22.3 (t), 27.4 (t), 36.0 (t), 74.6 (s), 83.1 (s), 129.3 (s), 143.3 (s), 194.8 (s). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.31; H, 7.74.

General Procedure for the Dye-Sensitized Photooxygenation of 3-Alkyl-2-hydroxy-2-cyclohexen-1-ones 3a–d to δ-Keto Acids 4a–d. 5-Oxo-7-octenoic Acid (4a). The following procedure illustrates the preparation of **4a–d**. A solution of **3a** (289 mg, 1.90 mmol) with methylene blue (3 mg) in methanol (10 mL) was irradiated by a 100-W tungsten–halogen lamp (no filter), under oxygen with stirring at 0 °C. Absorption of oxygen and evolution of carbon monoxide ceased after 3 h, as checked by manometry and GC (molecular sieves, 5 Å, He). After removal of the solvent, the residual oil was dissolved in ether to precipitate the methylene blue used. The ether solution was decanted and evaporated to afford 288 mg (97%) of **4a** as a colorless oil. An analytical sample was obtained by bulb-to-bulb distillation: bp 120 °C (2 torr); IR (neat) 3700–2400, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–2.2 (m, 2 H), 2.2–2.8 (m, 4 H), 3.20 (m, 2 H), 4.95–5.40 (m, 2 H), 5.60–6.35 (m, 1 H), 7.4 (br s); ^{13}C NMR ($CDCl_3$) δ 18.5 (t), 32.9 (t), 40.9 (t), 47.7 (t), 118.9 (t), 130.5 (d), 178.5 (s), 208.3 (s). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.38; H, 7.76.

5-Oxo-(*E*)-7-decenoic Acid (4b): yield 93% (oil); bp 130 °C (1.5 torr); IR (neat) 3600–2400, 1710, 968 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.5–2.7 (m, 10 H), 3.13 (m, 2 H), 5.52 (m, 2 H), 9.6 (br s). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.31; H, 8.79.

5-Oxo-(*Z*)-7-decenoic Acid (4c): yield 100% (oil); ^1H NMR ($CDCl_3$) δ 0.97 (t, 3 H), 1.5–2.7 (m, 10 H), 3.15 (m, 2 H), 5.55 (m, 2 H), 8.7 (br s).

5-Oxo-7-decynoic Acid (4d): yield 99% (crystals); mp 50.0–50.5 °C (lit.[3c] mp 50.5 °C) [colorless crystals purified by LC (Wako gel C 200, hexane–acetone–ether, 15:3:2)]; IR (KBr) 3600–2400, 2220, 1715, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, 3 H), 1.6–2.85 (m, 8 H), 3.20 (t, J = 2.5 Hz, 2 H), 8.8 (br s); ^{13}C NMR ($CDCl_3$) δ 12.5 (t), 13.9 (q), 18.5 (t), 32.9 (t), 34.3 (t), 39.8 (t), 71.5 (s), 86.5 (s), 179.1 (s), 205.0 (s). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.71; H, 7.52.

General Procedure for the Conversion of δ-Keto Acids 4a–d to δ-Lactones 1a–d. 5-(2-Propenyl)-5-pentanolide (1a). The following procedure illustrates the preparation of **1a–d**. To a solution of **4a** (174 mg, 1.11 mmol) in 10 mL of water containing sodium hydrogen carbonate (103 mg, 1.23 mmol) was added sodium borohydride (169 mg, 4.46 mmol) at room temperature. The solution was stirred for 2 h and then the pH was adjusted to 2. After being stirred for 1 h, the reaction mixture was extracted with ether. Bulb-to-bulb distillation of the crude product gave 147 mg (95%) of **1a** as a colorless oil: bp 95–100 °C (2 torr); IR (neat) 1735, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–2.2 (m, 4 H), 2.2–2.7 (m, 4 H), 4.40 (m, 1 H), 4.95–5.35 (m, 2 H), 5.56–6.20 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.4 (t), 27.1 (t), 29.4 (t), 40.0 (t), 79.7 (d), 118.4 (t), 132.7 (d), 171.7 (s). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.81; H, 8.53.

5-[(*E*)-2-Pentenyl]-5-pentanolide (1b): yield 55% (purified by distillation); bp 140 °C (2 torr); IR (neat) 3010, 1735, 965 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, 3 H), 1.5–2.7 (m, 10 H), 4.32 (m, 1 H), 5.50 (m, 2 H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.28; H, 9.75. Found: C, 71.39; H, 9.59.

5-[(*Z*)-2-Pentenyl]-5-pentanolide (1c): yield 57% (purified by preparative TLC (Merck silica gel 60 PF_{254}, hexane–ether, 2:1,

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(17) Yield (%) based on 1,2-cyclohexanedione.

R_f 0.33); IR (neat) 3030, 1735, 970, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3 H), 1.3–2.7 (m, 10 H), 4.33 (m, 1 H), 5.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 18.5 (t), 20.7 (t), 27.2 (t), 29.5 (t), 33.3 (t), 80.2 (t), 122.4 (d), 135.1 (d), 171.8 (s).

The ^{13}C NMR spectrum exhibited two minor peaks at 122.8 and 136.3 ppm with the relative intensity of 13/87 to the major peaks (122.4 and 135.1 ppm). The minor peaks are due to the *E* isomer **1b** which arises from 1-bromo-(*E*)-2-pentene present in the used 1-bromo-2-pentene.

3-(2-Pentynyl)-5-pentanolide (1d): yield 57% (purified by preparative TLC); bp 100 °C (2 torr); IR (neat) 2230 (weak), 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3 H), 1.4–2.3 (m, 6 H), 2.3–2.7 (m, 4 H), 4.35 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.4 (t), 14.1 (q), 18.3 (t), 26.0 (t), 29.5 (t), 73.7 (s), 78.7 (d), 84.8 (s), 171.2 (s). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.35; H, 8.25. Found: C, 72.26; H, 8.49

5-[(*Z*)-2-Pentenyl]-5-pentanolide (1c) from 1d. The pentanolide **1d** (107 mg) was hydrogenated using Lindlar catalyst[12] (5% Pd–$BaSO_4$, 25 mg; quinoline, 25 mg) in benzene (3 mL) to afford **1c** in 90% yield as a colorless oil. The ^{1}H NMR spectrum was essentially identical with that for **1c** from **4c**. The ^{13}C NMR spectrum exhibited no peak for *E* isomer. The IR and ^{1}H NMR spectra were identical with those reported.[2,4]

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Efficient Preparation of Polyfunctional α-Diketones from Carboxylic Acids

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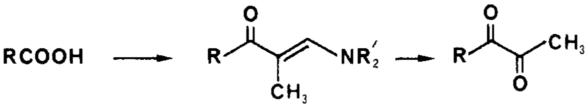
Many enzymes contain an essential arginyl residue at the active site. Butanedione and other simple α-diketones characteristically inactivate these enzymes by bonding covalently to arginine.[1] In an effort to confer specificity to this interaction, we have sought methods for incorporating an α-diketone moiety into polyfunctional inhibitors of such enzymes.[2] The ideal synthetic method for our purpose would involve the conversion of an existing carboxylic acid function into an α-diketone under mild conditions. Here we report on studies directed to developing such a route.

Results and Discussion

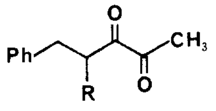
Since substrates, inhibitors, or cofactors that contain carboxylate or phosphate groups are usually involved in ion-pair formation with the guanidinium moiety of an arginyl residue at an enzyme active site, our intent was to develop a synthetic route that would transform a carboxyl group in an inhibitor molecule into an α-diketone without disturbing the integrity of other functionality. The target compounds **1** and **2** are derivatives of carboxylic acids with known inhibitory activity toward carboxypeptidase,[3,4] and **3** is an analogue of proline, an amino acid which is a component of a number of peptidase inhibitors.[5]

The synthetic approach that ultimately afforded the best results involved the conversion of a carboxylic acid to an α-enamino ketone which was photooxygenated[6] to yield the desired α-diketone (Scheme I). The route to the α-enamino ketone depended on whether or not the carboxylic acid is branched at the α′-position.

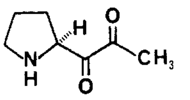
Scheme I



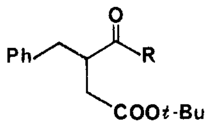
Diketone **1** was synthesized from carboxylic acid **5** which was obtained by treatment of the lithium enolate of ethyl 3-phenylpropanoate with *tert*-butyl iodoacetate followed by saponification of the resultant diester **4**. The acid **5** was converted to the 2-pyridyl thio ester[7] **6** which reacted cleanly with ethylmagnesium bromide to afford ethyl ketone **7**. Conversion of **7** to enamino ketone **8** was effected with 2.5 equiv of Bredereck's reagent,[8] $(Me_2N)_2CHO$-*t*-Bu. The crude product was photooxygenated at once to produce the diketo ester **9**, which, upon formolysis, afforded the diketo acid **1**. This compound displays broadened ^{1}H NMR resonances (particularly CH_3, δ 2.2) and a displaced carboxylic absorption (1800 cm^{-1}) in the IR spectrum, suggesting the predominance of cyclic hemiacylal tautomers.

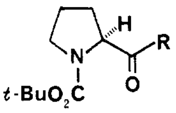


1 R=CH_2COOH
2 R=H

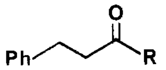


3

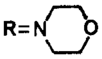


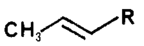


	R	
4	OEt	
5	OH	**10**
6	S-Pyr	**11**
7	CH_2CH_3	**12**
8	$C(CH_3)=CHNMe_2$	**13**
9	$COCH_3$	**14**

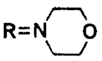


15 R=Cl
16 R=$C(CH_3)=CHN(i\text{-Bu})_2$
17 R=





18 R=$N(i\text{-Bu})_2$
19 R=



Prolylmethyl diketone **3** was prepared by a similar sequence starting with Boc-proline **10**. This involved the intermediacy of the corresponding thio ester **11**, ethyl ketone **12**, enamino ketone **13**, and BOC-diketone **14**. Intermediate **14** was cleaved with periodate to give Boc-proline **10** with an optical purity of 82%. The unprotected diketone **3** was isolated as the hydrochloride salt. This compound appeared to be stable at 0 °C but decomposed upon attempted crystallization from chloroform.

Since one of the α-positions in the ethyl ketones **7** and **12** is branched, condensation with Bredereck's reagent afforded a single enamino ketone (**8** and **13**, respectively). However, if an identical route were employed for synthesis

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