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Synthesis of Homologues of 4,5-Dihydroxy- and 4-Hydroxy-5-oxohexanoic Acid γ-Lactones

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Several substituted γ-lactones have been found in wines. Synthesis of higher molecular weight homologues of these lactones was necessary for verification of their presence in fermentation systems. The reaction of allylic acetates, $RCHOAcCH{=}CH_2$, with manganic acetate in acetic acid and acetic anhydride to form γ-substituted γ-butyrolactone acetates, where R was methyl, ethyl, isopropyl, isobutyl, or *sec*-butyl, is described. The reaction was not successful with allylic ketones, with allylic alcohols, or when R was benzyl. Basic hydrolysis of the lactone acetates gave hydroxy lactones that were oxidized with Collins reagent to keto lactones. The lactone acetates and hydroxy lactones were separable by GC into diastereomeric pairs. The hydroxy lactones, where R = benzyl, were prepared by cis and trans hydroxylation of 6-phenyl-*trans*-4-hexenoic acid. Tentative assignments of *R* and *S* configurations in the diastereomeric pairs were made by comparison of spectral data and relative GC retention data with previously obtained data for the stereospecifically synthesized hydroxy lactones where R was methyl.

In earlier investigations in our laboratories two optically active diastereomers of 4,5-dihydroxyhexanoic acid γ-lactone (Figure 1: **1a**, 4*R*,5*R* or 4*S*,5*S*; **2a**, 4*R*,5*S* or 4*S*,5*R*) (Muller et al., 1969) and 4-hydroxy-5-oxohexanoic acid γ-lactone (Figure 1: **3a**) (Augustyn et al., 1971) were identified as constituents of various wines. We have proposed (Muller et al., 1973) a biochemical pathway for the formation of these lactones from glutamic acid. This pathway also predicts the likely presence in fermentation systems of the additional lactones **1b–f**, **2b–f**, and **3b–f**, shown in Figure 1, from condensations involving α-keto acids known to be present in such systems. The identification of some of these additional lactones from wines would lend support to the validity of the proposed pathway. So that any of these additional γ-lactones could be detected and identified, the synthesis of the lactones indicated in Figure 1 was necessary. In this paper we report the preparation and characterization of these compounds.

γ-Lactones have been identified as important constituents of the aromas and flavors of many natural substances. γ-Heptalactone, which has a strong coconut-like odor, has been identified in sherry wine (Fagan et al., 1982), peach (Sevenants and Jennings, 1964), passion fruit (Winter and Klöti, 1972), and strawberries (Drawert et al., 1973). γ-Octalactone, which also has a coconut-like odor, has been found in sherry (Fagan et al., 1982), apricots (Tang and Jennings, 1967), peaches (Sevenants and Jennings, 1964), passion fruit (Murray et al., 1972), and grapes (Ramshaw and Hardy, 1969). γ-Nonalactone was identified in sherry (Fagan et al., 1982) and in other wines (Brander et al., 1980; Schreier and Drawert, 1974; Schreier et al., 1976). The synthesis and characterization of the substituted γ-lactones indicated in Figure 1 made possible the identification as sherry constituents of 4-hydroxy-5-oxoheptanoic acid γ-lactone (Figure 1: **3b**) and the tentative identification of an additional 4,5-dihydroxy acid γ-lactone with an MS extremely similar to that of 4,5-dihydroxyheptanoic acid γ-lactone (Figure 1: **1b**) (Fagan et al., 1982).

In 1968, Heiba et al. and Bush and Finkbeiner reported that substituted alkenes reacted with manganic acetate to produce substituted γ-lactones. The reaction conditions utilized by the two groups were very similar. Manganic acetate dihydrate and the alkene were dissolved in acetic acid and refluxed until the dark brown color of the Mn(III) disappeared. Heiba et al. (1968) added potassium acetate to raise the reflux temperature to 135 °C, while Bush and Finkbeiner (1968) reported that the addition of acetic anhydride dramatically shortened reaction times and increased yields. We were successful in preparing most of the γ-lactones indicated in Figure 1 using essentially the conditions of Bush and Finkbeiner.

EXPERIMENTAL SECTION

Infrared spectra were measured with a Beckman IR-8 on neat compounds. The ^1H NMR spectra were determined with either a Varian EM-360 or a Varian A-60A spectrometer by using tetramethylsilane as an internal standard. Mass spectra were determined on a Finnigan 3200 quadrupole instrument connected with a Finnigan 6000 data system and accurate masses on a Du Pont 21-492B sector mass spectrometer.

Preparative GLC separations were made on a Loenco Model 70 dual column, dual thermal conductivity chromatograph containing two 3 m × 6.35 mm o.d. stainless steel columns, one packed with 10% FFAP on 80–100-mesh Gas-Chrom Q and the other with 5% SE-30 on 60–80-mesh Gas-Chrom Q. Helium was used as the carrier gas at 75 mL/min on the FFAP column and 55 mL/min on the SE-30 column. The injector temperature was 240 °C and the detector temperature was 250 °C. Samples were trapped from the GLC in 30-cm glass capillary tubes cooled with dry ice. Samples for spectral analyses were purified by one or two passes through the SE-30 column.

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1(a-f): 4R,5R & 4S,5S 3(a-f)

2(a-f): 4R,5S & 4S,5R

Figure 1. Lactones synthesized as possible components of fermentation systems: **a**, R = methyl; **b**, R = ethyl; **c**, R = isopropyl; **d**, R = isobutyl; **e**, R = *sec*-butyl; **f**, R = benzyl.

Table I. Data for Allylic Alcohols 4b-f

compound	bp, °C (torr)	isolated yield, %	IR, cm^{-1} (neat)
4b	110-113 (760)	44	1640, 2890, 2980, 3090, 3350
4c	134-137 (760)	40	1635, 2880, 2970, 3080, 3380
4d	56-57 (11)	49	1640, 2880, 2970, 3090, 3350
4e	57-58 (14)	34	1635, 2890, 2975, 3090, 3380
4f	104-107 (3)	9.5	1635, 2925, 3040, 3390

Table II. Data for Allylic Acetates 8a-f

compound	bp, °C (torr)	isolated yield, %	IR, cm^{-1} (neat)
8a	112-114 (760)	91	1645, 1735, 2940, 2990, 3090
8b		95	1640, 1740, 2890, 2980, 3090
8c		91	
8d	60-62 (12)	90	1640, 1735, 2880, 2970, 3090
8e	35-36 (3)	80	1640, 1740, 2895, 2990, 3100
8f	105-107 (1.5)	70	1640, 1740, 2935, 3040

Final purities of compounds and retention indices (Kovats, 1965) were determined on an F&M 810 gas chromatograph with FID fitted with two 127 m × 0.75 mm i.d. open tubular stainless steel columns, one coated with Carbowax 20M and the other with SF-96(50).

Allylic Alcohols (4b–f) (See Figure 2). Acrolein (0.45 mol), bp 52.5–53.5 °C, was added to the Grignard reagent from the appropriate alkyl bromide (0.6 mol) under the usual Grignard conditions to give the allylic alcohols (**4b–f**). Table I gives the bp, yields, and IR data for allylic alcohols **4b–f**.

Allylic Acetates (8a–f) (See Figure 2). An allylic alcohol (**4b–f**) (0.35 mol) was added to 75 mL of dry pyridine and excess acetic anhydride (0.73 mol). After being stirred at room temperature for 24–48 h, followed by a standard workup, the crude allylic acetate (>95% pure, by GC) was either distilled or used directly for the next step. Table II gives the bp, yield, and IR data for allylic acetates **8a–f**.

Lactones 5a–f and 6a–f (See Figure 2). To a dark reddish brown solution of 14.7 g (55 mmol) of $Mn(OAc)_3 \cdot 2H_2O$ in 300 mL of glacial acetic acid and 100 mL of acetic anhydride at room temperature under a N_2 atmosphere was added 25.0 mmol of allylic acetate (**8a–f**) all at once. The mixture was refluxed for 15 min, by which time the dark brown color was discharged and a precipitate of pinkish white $Mn(OAc)_2 \cdot XH_2O$ had formed. After being cooled to room temperature, the Mn(II) salt was removed by filtration and the solvent distilled out at atmospheric pressure. The lactone mixture (**5** and **6**) was isolated by reduced pressure distillation. Small samples for spectral analyses were purified by column chromatography on Florisil and separated by preparative GC on FFAP at appropriate temperatures. The crude lactone mixtures, **5a–e** and **6a–e**, were used in the next step to obtain **1a–e** and **2a–e**.

Table III gives the bp, yield, and MS data for the lactone esters **5a–f** and **6a–f**: IR (neat) for **5a** 1175, 1240, 1370, 1730, 1775 cm^{-1}; IR (neat) for **5b** 1170, 1235, 1370, 1730, 1770 cm^{-1}; IR (neat) for **5d** 1175, 1235, 1370, 1735, 1775 cm^{-1}; IR (neat) for **5e(A)** 1180, 1235, 1370, 1740, 1780 cm^{-1}; IR (neat)for **5f** and **6f** 700, 730, 1175, 1230, 1370, 1742, 1777 cm^{-1}; IR (neat) for **6a** 1140, 1175, 1240, 1370, 1730, 1770 cm^{-1}; IR (neat) for **6b** 1170, 1230, 1370, 1735, 1778 cm^{-1}; IR (neat) for **6d** 1150, 1175, 1240, 1375, 1740, 1780 cm^{-1}; IR (neat) for **5e(B)** 1180, 1240, 1375, 1740, 1775.

Lactones 1a–e and 2a–e (See Figure 2). Hydrolyses of the lactone acetates (**5b**) were carried out by using a 2-fold excess of sodium methoxide in methanol or sodium hydroxide in aqueous methanol (3:1). The lactone acetate (2–3 mmol) was stirred in the base solution at room temperature for 24–48 h, cooled to 5 °C, acidified to pH 3 with 10% HCl, and stirred for 30 min. The solution was continuously extracted with ether for 3 days, the ether extract dried over Na_2SO_4 and filtered, the solvent removed by distillation at atmospheric pressure, and the acetic acid formed from the hydrolysis removed under reduced pressure. Chromatography of the residue on Florisil and elution with CH_2Cl_2 gave the hydroxy lactones (**1**, **2**) in 70–75% yields. The lactones **1** and **2** were separated and purified by GC for IR and mass spectra while the NMR spectra were determined on 1:1 mixtures of lactones **1** and **2**: NMR ($CDCl_3$) δ for **1a** and **2a** 1.18 (d, 3 H), 2.35 (m, 4 H), 4.0 (m, 2 H), 4.4 (m, 1 H); NMR ($CDCl_3$) δ for **1b** and **2b** 1.00 (t, 3 H), 1.4 (m, 2 H), 2.35 (m, 4 H), 3.75 (m, 2 H), 4.5 (m, 1 H); NMR ($CDCl_3$) δ for **1c** and **2c** 0.97 (d, 6 H), 1.45 (m, 5 H), 3.3 (m, 2 H), 4.55 (m, 1 H); NMR ($CDCl_3$) δ for **1d** and **2d** 0.93 (d, 6 H), 1.4 (m, 8 H), 3.63 (m, 1 H), 4.35 (m, 1 H); NMR ($CDCl_3$) δ for **1e(A,B)** 0.9 (m, 6 H), 1.6 (m, 2 H), 2.45 (m, 6 H), 3.65 (m, 1 H), 4.6 (m, 1 H).

IR (neat) for **1a** 1145, 1190, 1760, 3450 cm^{-1}; IR (neat) for **1b** 1190, 1755, 2985, 3450 cm^{-1}; IR (neat) for **1c** 1190, 1780, 2980, 3500 cm^{-1}; IR (neat) for **1d** 1195, 1740, 2970, 3470 cm^{-1}; IR (neat) for **1e(A)** 1140, 1195, 1780, 2980, 3500 cm^{-1}; IR (neat) for **2a** 1195, 1760, 3440 cm^{-1}; IR (neat) for **2b** 1190, 1750, 2975, 3440 cm^{-1}; IR (neat) for **2c** 1195, 1765, 2980, 3450 cm^{-1}; IR (neat) for **2d** 1190, 1765, 2975, 3440 cm^{-1}; IR (neat) for **2e(B)** 1195, 1760, 2985, 3460 cm^{-1}; MS M_r (% base peak) for **1a** 43 (46), 45 (45), 57 (24), 58 (25), 85 (95), 86 (100), 115 (5); MS M_r (% base peak) for **1b** 41 (25), 43 (18), 58 (50), 59 (70), 85 (100), 86 (99), 102 (7), 115

Table III. Data for Lactone Acetates 5a-f and 6a-f

compound	bp, °C (torr)	yield, %	MS, M_r (% base peak)
5a, 6a	160-170 (3)	40	43 (85), 85 (100), 128 (96)
5b, 6b	124-126 (1.5)	35	43 (82), 85 (100), 128 (78)
5c, 6c	128-137 (1.5)	20	
5d, 6d	164-167 (1.5)	25	41 (35), 43 (74), 85 (100), 86 (39), 111 (40), 128 (100)
5e(A,B,C)	169-171 (1.5)	20	43 (87), 85 (100), 128 (49), 129 (62)
5f, 6f		<5	43 (59), 85 (20), 91 (52), 188 (100)

Table IV. Data for Keto Lactones 3a-e

compound	yield, %	accurate mass, found (calcd)	IR, cm^{-1} (neat)
3a	69	128.0476 (128.0473)	1070, 1145, 1175, 1720, 1775
3b	91	142.0630 (142.0636)	1140, 1160, 1720, 1778
3c	75	156.0816 (156.0786)	1160, 1715, 1775, 2990
3d	88	170.0920 (170.0943)	1040, 1145, 1160, 1720, 1775, 2980
3e	79	170.0958 (170.0943)	1160, 1715, 1780, 2980

(35); MS M_r (% base peak) for **1c** 43 (15), 55 (20), 57 (10), 58 (13), 73 (63), 85 (63), 86 (100), 115 (30); MS M_r (% base peak) for **1d** 43 (25), 58 (18), 69 (45), 85 (47), 86 (100), 87 (27), 115 (8); MS M_r (% base peak) for **1e(A)** 41 (18), 45 (25), 57 (15), 69 (14), 85 (40), 86 (100), 87 (43), 115 (23); MS M_r (% base peak) for **2a** 43 (26), 45 (72), 57 (28), 58 (34), 85 (92), 86 (100), 115 (2); MS M_r (% base peak) for **2b** 41 (16), 44 (17), 57 (27), 59 (46), 85 (82), 86 (100), 115 (5); MS M_r (% base peak) for **2c** 43 (29), 55 (40), 58 (31), 73 (75), 85 (95), 86 (100), 98 (7), 115 (9); MS M_r (% base peak) for **2d** 43 (45), 45 (21), 58 (20), 69 (40), 85 (84), 86 (100), 87 (40), 115 (9); MS M_r (% base peak) for **1e(B)** 45 (33), 57 (16), 58 (10), 69 (11), 85 (69), 86 (100), 87 (47), 98 (8), 115 (5).

Keto Lactones (3a–e) (See Figure 2). To a solution of 690 mg (6.9 mmol) of anhydrous chromium trioxide and 1.09 g (13.8 mmol) of pyridine in 35 mL of CH_2Cl_2 was added 1.15 mmol of one of the diastereomeric mixtures of hydroxy lactones (**1a–e, 2a–e**) in 2 mL of CH_2Cl_2. The solution was stirred at room temperature for 20 min and then decanted from a small amount of tarry precipitate. The reaction flask was rinsed with ether, which was added to the CH_2Cl_2 solution. A precipitate of chromium salts was removed by filtration, 100 mL of ether was added, and the solution was washed with five 20-mL portions of cold 3% HCl, once with water, and twice with 20-mL portions of saturated NaCl, and then dried over Na_2SO_4. The solvent was removed by distillation at atmospheric pressure to give the keto lactones (**3a–e**) in about 95% purity. Final purifications for spectral analyses were by GC. Table IV gives the yield, IR, and accurate mass data for the keto lactones **3a–e**: NMR ($CDCl_3$) δ for **3a** 2.29 (s, 3 H), 2.5 (m, 4 H), 4.82 (m, 1 H); NMR ($CDCl_3$) δ for **3b** 1.12 (t, 3 H), 2.55 (m, 6 H), 4.9 (m, 1 H); NMR ($CDCl_3$) δ for **3c** 1.14 (d, 6 H), 2.60 (m, 4 H), 2.88 (sep, 1 H), 5.1 (m, 1 H); NMR ($CDCl_3$) δ for **3d** 0.94 (d, 6 H), 1.5 (m, 7 H), 4.87 (m, 1 H); NMR ($CDCl_3$) δ for **3e** 1.0 (m, 6 H), 1.5 (q, 2 H), 2.5 (m, 5 H), 4.95 (t, 1 H); MS M_r (% base peak) for **3a** 43 (77), 85 (100), 128 (18); MS M_r (% base peak) for **3b** 39 (12), 57 (63), 85 (100), 86 (11), 142 (15); MS M_r (% base peak) for **3c** 39 (30), 41 (26), 43 (53), 57 (12), 71 (31), 85 (100), 86 (17), 156 (3); MS M_r (% base peak) for **3d** 41 (8), 43 (6), 57 (40), 75 (15), 85 (100), 86 (8), 170 (2); MS M_r (% base peak) for **3e** 39 (8), 41 (21), 57 (84), 58 (9), 85 (100), 86 (40), 170 (3).

Manganic Acetate Dihydrate. A modification of Christensen's (1901) procedure was used to oxidize $Mn(OAc)_2$. A solution of $Mn(OAc)_2 \cdot 4H_2O$ (24.5 g, 100 mmol) in 250 mL of glacial acetic acid was maintained at gentle reflux by the slow addition of 4.0 g (25 mmol) of $KMnO_4$, and reflux was continued for an additional 45 min. Water (85 mL) was added, and the solution was seeded and let stand for 20 h. The precipitate was collected by filtration and washed with cold acetic acid. The reddish brown product (25.5 g, 76%) was used without further purification.

1-Chloro-4-phenyl-*trans*-2-butene (9). Nineteen grams (0.2 mol) of freshly distilled aniline was diazotized and allowed to react with excess butadiene in the presence of 8 g of $CuCl_2$ and 7.5 g of CaO following the procedure of Dombrovskii and Terentyev (1956). After workup the residue was distilled under reduced pressure through a 20-cm Vigreux column to give a fraction of chlorobenzene followed by the collection of 16.4 g (49%) of **9**, bp 70–80 °C at 2 torr.

6-Phenyl-*trans*-4-hexenoic Acid (10). The procedure of Yukhomenko et al. (1963) was used. The 16.4 g (0.1 mol) of **9** was allowed to react with diethyl sodiomalonate to give, after workup, 8.7 g (30% yield) of ethyl 2-carboethoxy-6-phenyl-*trans*-4-hexenoate, bp 135–140 °C at 2 torr. The 8.7 g of diester was hydrolyzed at 80 °C with 40% KOH in absolute ethanol over a 2-h period, evaporated to dryness at 10 °C and 20 torr with a rotoevaporator, and acidified with 6 N HCl, and the crude 2-carboxy-6-phenyl-*trans*-4-hexenoic acid was isolated and then decarboxylated by heating at 150–180 °C until CO_2 evolution ceased. The product was distilled through a 20-cm Vigreux column to give 4.5 g (85% yield based on the diester) of **10**, bp 128–131 °C at 2 torr.

(4*R*,5*S*)- and (4*S*,5*R*)-4,5-Dihydroxy-6-phenylhexanoic Acid γ-Lactone (2f). To a solution of 1.0 g (0.005 mol) of **10** in 5.3 mL of 88% formic acid was added 5.26 mL of 30% H_2O_2 all at once. The temperature rose rapidly but was maintained below 40 °C by cooling. After 30 min an oil bath was used to maintain the temperature at 40 °C for 20 h, and the reaction mixture was then stirred at room temperature for an additional 48 h. Ten milliliters of H_2O was added, the reaction mixture was extracted with six 5-mL portions of ether, the combined ether extracts were washed with saturated NaCl solution, and the ether was removed on a rotoevaporator. The residue was mixed with 80 mL of 0.1 M KOH and stirred at room temperature for 24 h. The mixture was made strongly basic with solid KOH, stirred for 3 h, then made strongly acidic by the dropwise addition of 15% H_2SO_4, and stirred for another hour. The solution was extracted with five 20-mL portions of ether, the combined ether extracts were washed with three 10-mL portions of cold 5% $NaHCO_3$ and once with saturated NaCl, and dried over anhydrous $MgSO_4$. After removal of the drying agent the ether was removed by rotoevaporation to give a pale green oil which, after addition of 4 mL of ether, gave 0.56 g (54% yield) of white crystalline **2f**: mp 71–74 °C; NMR ($CDCl_3$) δ 2.3 (m, 4 H), 2.8 (m, 2 H), 4.1 (m, 1 H), 4.3 (m, 1 H), 7.2 (s, 5 H); IR (melt) 690, 740, 1190, 1775, 2980 cm^{-1}; MS M_r (% base peak) 65 (34), 77 (25), 85 (62), 86 (97), 91 (93), 92 (100), 103 (48), 115 (22), 121 (52), 188 (9), 206 (10).

(4*R*,5*R*)- and (4*S*,5*S*)-4,5-Dihydroxy-6-phenylhexanoic Acid γ-Lactone (1f). To a solution of 1.0 g (0.005 mol) of **10** and 0.44 g KOH in 20 mL of H_2O was added 7 mL of a solution containing 0.0035 mol of $KMnO_4$ dropwise over 5 min. The solution was stirred an additional 10 min at room temperature, the solid MnO_2 was separated by centrifugation, and the separated supernatant was acidified to pH 2 with 15% H_2SO_4. The acidified solution was stirred at room temperature for 1.5 h and then extracted with four 10-mL portions of ether. The combined ether extracts were washed with three 10-mL portions of cold 5% Na_2CO_3 solution and once with 10 mL saturated NaCl and dried over $MgSO_4$. After removal of the drying agent the ether was removed by rotoevaporation to leave 0.55 g of pleasant-smelling oil that was shown by

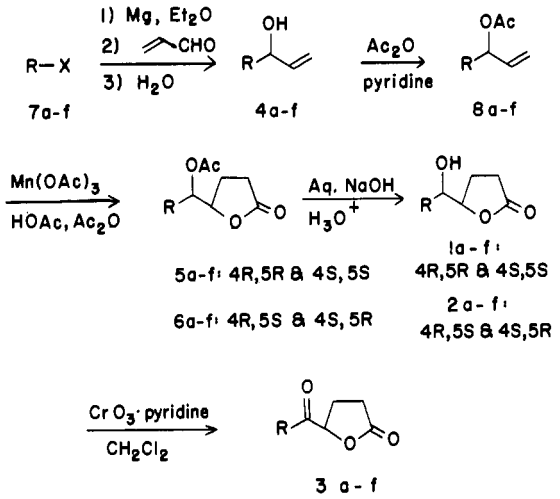


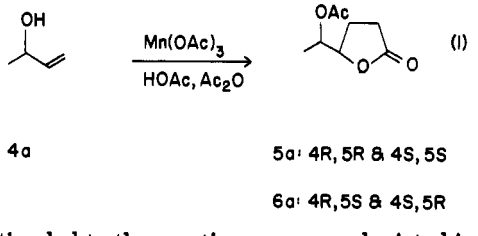
Figure 2. Synthesis of hydroxy and keto lactones: **a**, R = methyl; **b**, R = ethyl; **c**, R = isopropyl; **d**, R = isobutyl; **e**, R = *sec*-butyl; **f**, R = benzyl.

IR to contain 20% of **1f**. Pure **1f** was obtained by preparative GC on SE-30 at 230 °C for spectral analyses: NMR ($CDCl_3$) δ 2.35 (m, 4 H), 2.9 (m, 2 H), 3.8 (m, 1 H), 4.45 (m, 1 H), 7.25 (s, 5 H); IR (neat) 695, 745, 1185, 1765, 2980 cm^{-1}; MS M_r (% base peak) 65 (25), 77 (18), 85 (34), 86 (50), 91 (100), 92 (93), 103 (29), 115 (28), 121 (31), 188 (6), 206 (7).

4-Hydroxy-5-oxo-6-phenylhexanoic Acid γ-Lactone (3f). A 0.55-g (0.003-mol) sample of **2f** was oxidized with Collins reagent as previously described to give a mixture of unreacted **2f** and the keto lactone **3f**. The keto lactone was purified by preparative GC on SE-30 at 230 °C for spectral analysis: NMR ($CDCl_3$) δ 2.35 (m, 4 H), 3.95 (s, 2 H), 4.85 (m, 1 H), 7.35 (s, 5 H); IR (neat) 690, 730, 1020, 1180, 1715, 1760 cm^{-1}; MS M_r (% base peak) 51 (21), 57 (30), 65 (61), 77 (25), 85 (90), 86 (68), 91 (100), 92 (88), 103 (31), 115 (18), 119 (19), 121 (31), 204 (4). Accurate mass: Found, 204.0777; calculated, 204.0786.

RESULTS AND DISCUSSION

In an attempt to prepare lactones **3a** and **3b** (Figure 1) in a one-step synthesis, 1-buten-3-one and 1-penten-3-one were used as the alkenes under the conditions of Bush and Finkbeiner (1968). No γ-lactones could be detected in the reaction products obtained from either alkene. A similar reaction of 1-buten-3-ol (**4a**) with manganic acetate did not give the lactones **1a** and **2a** but did give the acetate esters (**5a** and **6a**) of **1a** and **2a** as the major constituents of a complex mixture of products (eq 1). This experimental



observation led to the reaction sequence depicted in Figure 2 that was successfully used to prepare the desired lactones **1a–e**, **2a–e**, and **3a–e**.

1-Buten-3-ol (**4a**) was obtained commercially, while Grignard reactions were used to obtain compounds **4b–e** in excellent yields without concomitant allylic rearrangements. Compound **4f** was obtained in less than 10% yield due to the abnormal addition products of benzyl magnesium chloride (Karasch and Reinmuth, 1954). The allylic acetates **8a–f** were allowed to react with, typically, a 2:1 mole ratio of manganic acetate dihydrate to alkene in glacial acetic acid containing 25% acetic anhydride. No potassium acetate was added to raise the reflux temperature, and yet the dark brown Mn(III) color was always discharged after 15 min of reflux. It was found that varying the acetic acid:acetic anhydride ratio from 10:1 to 1:1 had no noticeable effect on reaction time or yield. The formation of the γ-lactones under these reaction conditions undoubtedly occurs by the free radical mechanism proposed by Heiba et al. (1974).

Table V. GC Retention Indices (Kovats) for the Substituted γ-Lactones

lactone acetates (5, 6)	SF96(50), 175 °C	CB20M, 190 °C
5a	1323	2288
6a	1332	2325
5b	1400	2342
6b	1409	2381
5d	1522	2417
6d	1532	2454
5e(A)	1535	2418
5e(B)	1549	2441
5e(C)		2471
hydroxy lactones (1, 2)	**SF96(50), 188 °C**	**CB20M, 190 °C**
1a	1224	2355
2a	1230	2402
1b	1323	
2b	1329	
1c	1360	2427
2c	1380	2501
1d	1457	
2d	1463	
1e(A)	1468	2510
1e(B)	1468	2522
1e(C)	1484	2607
keto lactones (3)	**SF96(50), 150 °C**	**CB20M, 190 °C**
3a	1111	2123
3b	1204	2167
3c	1246	2188
3d	1327	2253
3e	1328	2241

When the allylic acetate (**8e**, R = *sec*-butyl) reacts with manganic acetate the lactone formed contains three chiral centers and should consist of four pairs of enantiomers theoretically separable by gas chromatography. In fact only three discrete peaks [**5e(A,B,C)**] corresponding to enantiomeric pairs could be detected by gas chromatography. The third peak to elute was much larger than the first two peaks and could well be a mixture of two pairs of enantiomers that could not be separated under the conditions used. The infrared spectra of the three fractions show only subtle differences in the fingerprint region, consistent with the diastereomeric nature of the compounds.

The preparation of the lactones **5f** and **6f** by reaction of the allylic acetate **8f** with manganic acetate was not successful even though the brown color of the Mn(III) was again discharged after 15 min of heating. Only trace amounts of **5f** and **6f** were obtained while most of the starting alkene **8f** was recovered. The $\cdot CH_2COOH$ radicals generated by thermolysis of the manganic acetate undoubtedly reacted with the aromatic ring or the benzylic hydrogens of the allylic acetate (**8f**) via several possible pathways (van der Ploeg et al., 1968) faster than it added to the alkene.

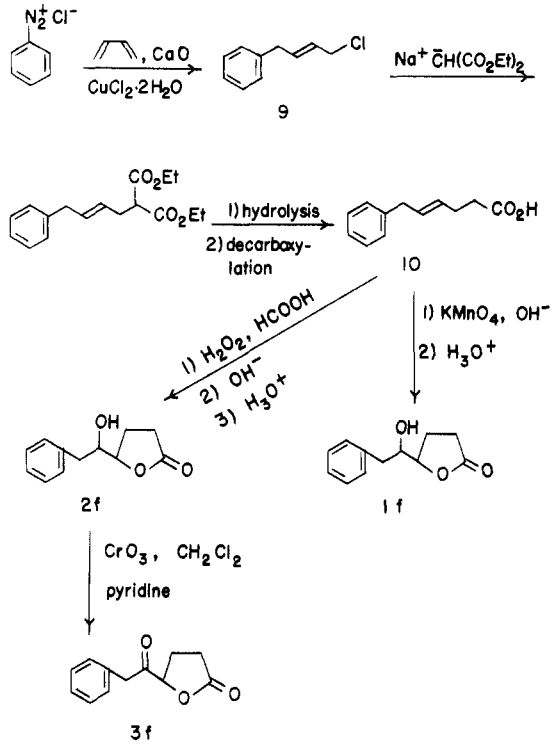


Figure 3. Synthesis of 4,5-dihydroxy-6-phenylhexanoic acid γ-lactones and 4-hydroxy-5-oxo-6-phenylhexanoic acid γ-lactone.

The hydrolyses of lactones **5a–e** and **6a–e** were carried out on the mixtures of enantiomeric pairs (**5** and **6**) by using either sodium methoxide in methanol or sodium hydroxide in aqueous methanol. The product mixtures, lactones **1** and **2**, were isolated by continuous ether extraction and then separated by column chromatography on Florisil followed by final purification by preparative gas chromatography. Lactones **1a** and **2a**, each pairs of enantiomers, were identified by comparison of their spectra with published spectra (Muller et al., 1969) of the stereospecifically synthesized lactones. The homologues of **1a** and **2a** were assigned 4*R*,5*R* and 4*S*,5*S* or 4*R*,5*S* and 4*S*,5*R* configurations by comparison of their experimental data to the published data on **1a** and **2a**. Comparison of the infrared spectra shows that **1a** differs from **2a** much the same as **1b** differs from **2b**, **1c** from **2c**, and **1d** from **2d**, noting especially the regions 1000–1150 and 1200–1300 cm^{-1}. Lactones **1** always eluted ahead of lactones **2** on an FFAP gas chromatographic column, as reported previously for **1a** and **2a**. In addition, lactones **2** always eluted from Florisil ahead of lactones **1**. These experimental results permitted the assignment of lactones **1a–d** the 4*R*,5*R* and 4*S*,5*S* and lactones **2a–d** the 4*R*,5*S* and 4*S*,5*R* configurations. No similar assignments of configurations could be made for the lactones where *R* was *sec*-butyl (lactone **e**) because of the additional chiral center in the molecules.

The keto lactones (**3a–e**) were prepared by a Collins et al. (1968) oxidation of the corresponding hydroxyl lactones in 69–91% yields. Final purification of the keto lactones for spectral analyses and determination of accurate masses was by preparative gas chromatography. Since lactone **3e** has two chiral centers it should exist as two pairs of optically inactive diastereomers. These could not be separated by gas chromatography, and the analytical data presented is for the mixture. The GC retention indices for lactones **5a–e**, **6a–e**, **1a–e**, **2a–e**, and **3a–e** are listed in Table V.

Due to the unsuccessful reaction between the allylic acetate (**8f**) and manganic acetate, another route was employed to obtain lactones **1f**, **2f**, and **3f**. The keto lactone **3f** was prepared by the Collins et al. (1968) oxidation of the hydroxy lactone **2f**. Lactones **1f** and **2f** were prepared by the cis and trans hydroxylation, respectively, and subsequent lactonization of 6-phenyl-*trans*-4-hexenoic acid (**10**). This latter compound was prepared by the reaction of 1-chloro-4-phenyl-*trans*-2-butene (**9**) with the sodium salt of diethyl malonate followed by ester hydrolysis and decarboxylation using the method of Yukhomenko et al. (1963). The 1-chloro-4-phenyl-*trans*-2-butene was obtained by the reaction of butadiene with phenyldiazonium chloride using the procedure of Drombrovskii and Terentyev (1956). This reaction sequence is depicted in Figure 3.

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