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SYNTHESIS OF (±)-PARASORBIC ACID AND (±)-MASSOILACTONE FROM MELDRUM'S ACID

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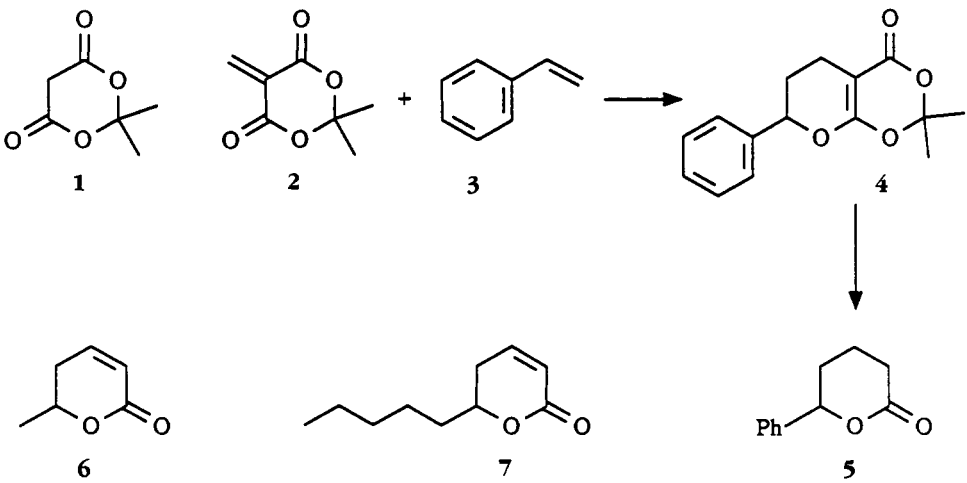
ABSTRACT.—It was found that, under appropriate conditions, aliphatic conjugated unsaturated aldehydes react with Meldrum's acid [**1**] to give δ-alkyl-α,β-unsaturated valerolactones. In this manner, (±)-parasorbic acid [**6**] and (±)-massoilactone [**7**] were synthesized from crotonaldehyde and *trans*-2-octenal, respectively, in a simple one-pot procedure.

Meldrum's acid (2,2-dimethyl-1,3-dioxan-4,6-dione or isopropylidene malonate) [**1**] is a versatile synthetic reagent (1). The 5-methylene derivative **2** ("methylene Meldrum's acid" or isopropylidene methylenemalonate) is a transient species, now readily generated in solution (2) and recognized as a highly reactive dienophile. We have found (3), however, that in reaction with styrene [**3**] it serves instead as a heterodiene, yielding the heterocyclic adduct [**4**]. This 2,4,10-trioxabicyclo-[4.4.0]-dec-1(6)-en-5-one heterocyclic framework is extremely labile (warming in aqueous solutions or attempted recrystallization from common solvents under usual laboratory conditions) and is degraded in excellent yield to the δ-valerolactone **5**. This offers a convenient preparative method for δ-aryl-δ-valerolactones, and we sought to examine the applicability to the synthesis of the δ-alkyl-αβ-unsaturated valerolactones, parasorbic acid [**6**] and massoilactone [**7**], the two earliest isolated examples of this natural product class, of which more than a dozen members are now known.



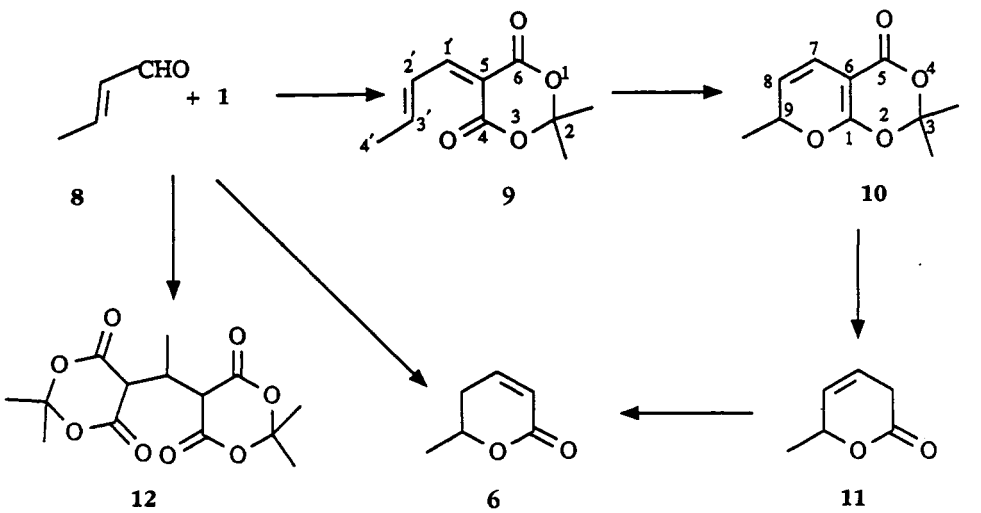
RESULTS AND DISCUSSION

Parasorbic acid is the name given to a product isolated by Hofmann in 1859 from the berries of European mountain ash (*Sorbus aucuparia* L., Rosaceae) (4). Only within the past decade has a second source, the aerial fraction of the American cranberry plant (*Vaccinium macrocarpon*) been reported (5). Following studies by Fittig and Barringer (6) Fittig (7), and Doebner (8), the structure hex-2-en-5-olide [**6**] was convincingly established by Kuhn and Jerchel (9,10) in 1943. The (5*S*) absolute configuration of the natural (+)-enantiomer has been assigned (11–13) and support provided for biosynthesis by an acetate-malonate pathway (14). As would be expected of such a venerable entity that displays fungal growth and seed germination inhibitory action, several syntheses of

(±)-parasorbic acid have been reported (15–24), most of which are multi-step procedures or of modest yield (≤25%). In addition, two syntheses of the natural 5*S*-(+)-isomer have been announced in preliminary form (25,26).

The procedure developed here provides (±)-parasorbic acid in a one-pot reaction without need of chromatography and in 76% yield. In the envisaged scheme, the key required intermediate was the butenylidene derivative **9** of Meldrum's acid, which was expected to undergo intramolecular cyclization thermally to yield 3,3,9-trimethyl-2,4,10-trioxabicyclo[4.4.0]deca-1(6),7-dien-5-one [**10**], hydrolytic degradation of which would give isoparasorbic acid [**11**] known to isomerize readily to **6**.

5-Arylidene and 5-alkylidene derivatives of Meldrum's acid are most commonly prepared by Knoevenagel condensation with both aldehydes and ketones (27). A complication frequently arises, however, with simple unhindered aliphatic aldehydes which yield 2:1 condensation products by further Michael addition of Meldrum's acid to the 5-alkylidene intermediate. Thus, acetaldehyde at room temperature in DMF solution without catalyst gave the 2:1 adduct **12** in quantitative yield (28). In the same paper, it was reported that crotonaldehyde, which we expected to yield **9**, surprisingly gave the same adduct **12** given by acetaldehyde, presumably by occurrence of a reverse aldol reaction. To circumvent this immediate practical difficulty, some initial experiments examining the interaction of **1** and **8** were undertaken.



In the first of these, it was found that heating crotonaldehyde and Meldrum's acid (in 1.4:1 ratio) under reflux in C_6H_6 with pyridine as catalyst for 7 h gave unchanged starting materials (80%) and abysmal yields of the 2:1 adduct **12** (ca. 4%) and the desired butenylidene derivative **9** (<1%). In the second experiment, in which pyridine and HOAc were used with reflux time of 24 h, a 60% yield of the adduct **12** was isolated in addition to a second fraction (14% yield) which was a mixture of the lactones, isoparasorbic acid [**11**] and parasorbic acid [**6**]. This observation carried the significant implication that the condition suitable for formation of **9** was also conveniently appropriate for the two subsequent planned steps (cyclization and degradation). A further improvement in the lactone mixture yield (to 35%) was next effected by conducting the condensation in the presence of molecular sieves. Further yield improvements were then realized by increasing the **8**:**1** ratio to 2.5:1 and increasing the reaction time to 48 h. Under these conditions, distillation of the product mixture from K_2CO_3 (to isomerize **11** to **6**) gave (±)-parasorbic acid in 76% yield.

(−)-Massoilactone [**7**] was first isolated (29,30) from the bark oil of *Cryptocarya massoia* (Lauraceae), which has folk medicine attributes. Other sources include formicine ants (*Camponotus*) (31), cane molasses (32), leaves of *Polianthes tuberosa* L. (Amaryllidaceae) (33), and "sweet grass, holy grass" (*Hierochloe odorata*) which is used as a vodka flavorant (34). Following early synthesis of (±)-**7** (35,36), realization of specific odor impression of several natural δ-valerolactones has stimulated work on practical syntheses of this class of compounds. Additional syntheses of (±)-massoilactone have resulted (37–43), and both (+)- and (−)-enantiomers of **7** have been synthesized (24). Using the conditions developed here for the synthesis of (±)-parasorbic acid, Meldrum's acid was treated with *trans*-2-octenal and gave (±)-massoilactone [**7**] in a one-pot reaction in 60% yield and without necessity of recourse to chromatographic purification.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-nmr spectra were determined in $CDCl_3$ solution with TMS as internal standard, using a Varian EM390 instrument. Si gel used for chromatography was Kieselgel 40 (70–230 mesh). Petroleum ether (bp 20–40°) was from J.T. Baker, and C_6H_6 was distilled from a solution containing the blue ketyl formed by reaction of sodium metal with a small quantity of benzophenone. Molecular sieves (4Å, 4–8 mesh, Aldrich) were flame-dried (5 h) and stored in oven (195°) prior to use.

REACTIONS OF CROTONALDEHYDE WITH MELDRUM'S ACID.—*Experiment A.*—Pyridine (3 ml) was added to a stirred solution of crotonaldehyde (0.9 ml, 10.5 mmol) and Meldrum's acid (1 g, 7 mmol) in C_6H_6 (20 ml). After 2 h at room temperature with stirring, the reaction mixture [revealed by tlc examination with $CHCl_3$-petroleum ether (1:1) to contain products and starting materials] was heated under reflux with a Dean-Stark trap for a further 7 h, then evaporated under reduced pressure. The residual yellow oil was dissolved in $CHCl_3$-petroleum ether (1:1) and chromatographed on Si gel; 25-ml aliquots were collected. Fractions 1–5 gave no residue, followed by fractions 6–9 which yielded isopropylidene 5-(but-2′-enylidene) malonate [**9**] as an oil (9 mg): ^{1}H nmr δ 1.74 (s, 2 × C-2 Me), 2.10 (d, J = 7 Hz, 4′-Me), 6.5–7.0 (m, H-3′), 7.4–7.8 (m, H-2′), 8.00 (d, J = 11 Hz, H-1′); ir ν max ($CHCl_3$) 1720 (C=O), 1617 (C=C) cm^{-1}. After fractions 10–12 gave no residue, fractions 13–18 gave diisopropylidene ethylidenedimalonate [**12**] as a solid (92 mg), mp 152–154° after crystallization from aqueous Me_2CO [lit. (28) mp 153°]; ^{1}H nmr δ 1.13–1.21 (m, ethylidene CH), 1.12 (d, J = 8 Hz, ethylidene Me), 1.71 (s, 2 × Me), 1.73 (s, 2 × Me), 3.72 (d, J = 7 Hz, 2 × -COCHCO-); ir ν max 1776 and 1745 (C=O) cm^{-1}. Unchanged Meldrum's acid (800 mg) was recovered from the column by elution with CH_2Cl_2-MeOH (95:5), and the original C_6H_6 solvent distillate contained unchanged crotonaldehyde.

Experiment B.—Pyridine (0.3 ml) and HOAc (0.9 ml) were added to a solution of crotonaldehyde (0.9 ml, 10.5 mmol) and Meldrum's acid (1 g, 7 mmol) and the mixture heated under reflux for 24 h. H_2O was added to the cooled mixture which was then extracted with Et_2O.

The organic extracts were washed successively with 10% HCl, 5% NaOH solution, and H_2O, then dried and evaporated. The residual product was chromatographed as in experiment A (see above). Fractions 5–7 gave the lactone mixture (compounds **6** and **11**) as an oil (110 mg): ^{1}H nmr δ (attributable to parasorbic acid [**6**]) 1.40 (d, J = 7 Hz, 5-Me), 2.26–2.34 (m, H-4), 4.50–4.55 (m, H-5), 5.90–6.10 (m, H-2), and 6.88–6.93 (m, H-3); ^{1}H nmr (attributable to isoparasorbic acid [**11**]) 1.41 (d, J = 7 Hz, 5-Me), 3.00–3.10 (m, H-2), 4.50–4.55 (m, H-5), 5.01–5.09 (m, H-3,4); ir ν max ($CHCl_3$) 1748 (C=O) and 1738 (conjugated C=O) cm^{-1}. After fractions 8–11 gave no residue, fractions 12–21 gave the 2:1 adduct **12** (1.3 g).

Experiment C.—Experiment B was repeated with addition of molecular sieves (1 g). Under these conditions there was obtained the lactone mixture (compounds **6** and **11**) (270 mg, 35% yield) and 2:1 adduct **12** (1.25 g, 57% yield.)

Experiment D.—Experiment C was repeated except that ratio of crotonaldehyde to Meldrum's acid was increased from 1.4:1 to 2.5:1. This yielded the lactone mixture (compounds **6** and **11**) in 51% yield and 2:1 adduct **12** in 39% yield.

Experiment E.—Repetition of experiment D with increased (48 h) time of reflux gave the mixture of compounds **6** and **11** in 73% yield and **12** in 20% yield. When reflux time was increased to 72 h, the yield of lactone mixture **6** and **11** was diminished, and sorbic acid (hexa-2,4-dienoic acid) could be isolated from the base extract.

(±)-PARASORBIC ACID (HEX-2-EN-5-OLIDE) [**6**].—Pyridine (0.3 ml) and HOAc (0.9 ml) were added to a stirred solution of crotonaldehyde (0.75 ml, 8.75 mmol) and Meldrum's acid (0.5 g, 3.5 mmol) in dry C_6H_6 (20 ml), and the mixture was heated under reflux over molecular sieves (1 g) for 48 h. H_2O (20 ml) and Et_2O were added to the cooled solution, and the organic layer extract was washed with 10% HCl (3 × 10 ml), 5% NaOH solution (3 × 10 ml), and H_2O, then dried ($MgSO_4$) and evaporated under reduced pressure. K_2CO_3 (14 mg) was added to the residue (326 mg) which was heated to 118°. Following an exothermic reaction (temperature rise to 130°), the mixture was maintained at 115° for 15 min and distilled under reduced pressure to give parasorbic acid [**6**] as a colorless oil (298 mg, 76% yield), bp 104–106°/14 mm Hg [lit. (19) bp 110°/15 mm]; ^{1}H nmr δ 1.41 (d, J = 7 Hz, Me), 2.30–2.34 (m, H-4), 4.50–4.54 (m, H-5), 5.96–6.09 (m, H-2), 6.86–6.98 (m, H-3); ir ν max (CCl_4) 1740 (C=O) cm^{-1}.

(±)-MASSOILACTONE (DEC-2-EN-5-OLIDE) [**7**].—*trans*-Oct-2-enal (1.3 ml, 8.75 mmol) was reacted with Meldrum's acid with quantities and conditions exactly as for (±)-parasorbic acid above. Product distillation gave massoilactone [**7**] as a colorless oil (343 mg, 59% yield), bp 103–104/0.5 mm Hg [lit. (36) bp 85–86°/0.07 mm Hg], ^{1}H nmr δ 0.88–0.93 (m, 10-Me), 1.28–1.41 (m, H-6,-7,-8,-9), 4.39–4.46 (m, H-5), 6.0 (dt, J = 9,2 Hz, H-2), and 6.90 (dt, J = 9,3 Hz, H-3); ir ν max ($CHCl_3$) 1732 (C=O) cm^{-1}.

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