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Working with Hazardous Chemicals

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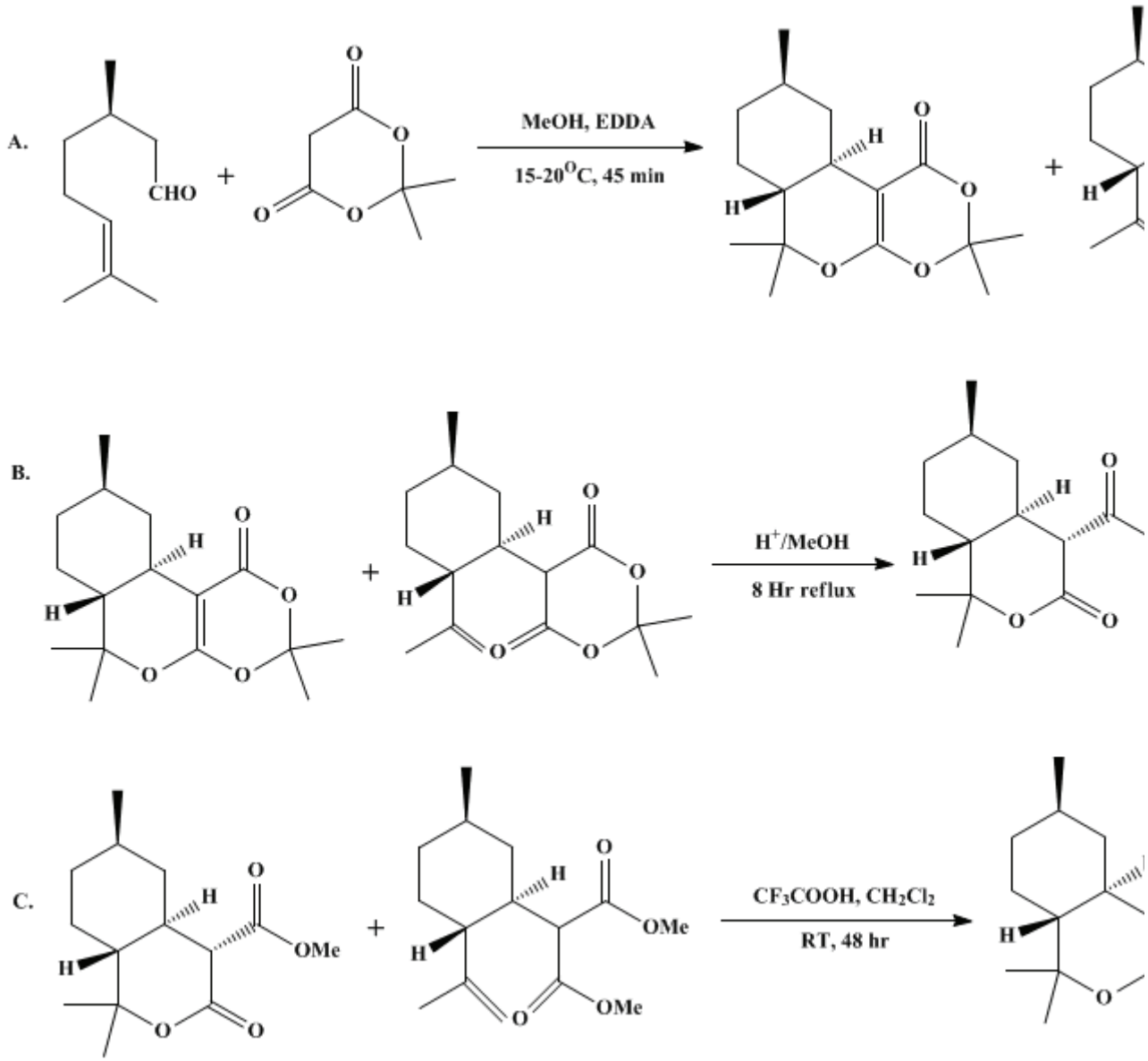
DIASTEROSELECTIVE FORMATION OF α-METHOXYCARBONYL LACTONES THROUGH AN INTRAMOLECULAR DIELS–ALDER REACTION: (4*RS*,4a*RS*,6*RS*,8a*RS*)-, (4*S*,4a*S*,6*S*,8a*S*)- AND (4*R*,4a*R*,6*R*,8a*R*)-4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4A,5,6,7,8,8a-OCTAHYDRO-2,3-BENZOPYRONE [*rac*-5, (+)-5, AND (−)-5]



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Checked by Charles F. Marth and Edwin Vedejs.

1. Procedure

A. *Diels–Alder-adduct rac-**3***.[2] A 250-mL, round-bottomed flask equipped with a pressure-equalizing addition funnel with a calcium-sulfate-filled drying tube, a nitrogen inlet, and a magnetic stirring bar is charged with 2,2-diamethyl-1,3-dioxane-4,6-dione **2** (Meldrum's acid) ((Note 1), 10.0 g,

69.4 mmol), a catalytic amount of ethylenediammonium diacetate (EDDA) ((Note 2), 500 mg, 2.77 mmol) and dry methanol (150 mL). (*R,S*)-Citronellal (*rac*-**1**, Sigma; dried over $MgSO_4$ and distilled) ((Note 3), 9.74 g = 11.4 mL, 63.1 mmol) is added under nitrogen (Note 4) over 15 min through the dropping funnel to the well-stirred mixture while the temperature is kept at 15–20°C by cooling the flask with a water bath. The solution is stirred for an additional 45 min at room temperature, the solvent is removed on a rotary evaporator (25°C), and the remaining yellow oil is dissolved in diethyl ether (300 mL). The organic layer is washed with water (50 mL), saturated sodium bicarbonate (2 × 50 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. Filtration and removal of the solvent gives an 8 : 1 mixture (16.5 g) of the Diels–Alder adduct *rac*-**3** and the ene-product *rac*-**4** as a yellow oil (Note 5).

B. *Lactone* ***5***. The crude mixture of *rac*-**3** and *rac*-**4** is dissolved in 300 mL of dry methanol (distilled from sodium) containing 10 drops of concentrated hydrochloric acid and heated under reflux for about 8 hr until the reactants can no longer be detected by thin-layer chromatography (Note 6). The solvent is removed on a rotary evaporator at 25°C and the remaining residue, which consists of an 8 : 1 mixture of lactone *rac*-**5** and dimethyl ester *rac*-**6**, is dissolved in dry dichloromethane (50 mL). The solution is acidified with trifluoroacetic acid (10 mL) and stirred at room temperature for about 48 hr, until the thin-layer chromatogram does not show any dimethyl ester *rac*-**6** (Note 6). The organic layer is washed with water (50 mL), saturated sodium bicarbonate solution (2 × 50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. Distillation of the remaining thick, yellow oil under reduced pressure in a short-path distillation apparatus with an air-cooled condenser gives 12.6 g (79%) of *rac*-**5**, bp 133–135°C at 0.001 mm. The colorless oil is dissolved in *tert*-butyl methyl ether (10 mL) and hexane (80 mL) and the solvent is allowed to evaporate over 2 days to about 15% of the original volume. Lactone *rac*-**5** (8.11 g, 53%) slowly crystallizes (mp 69–71°C) (Note 7) and (Note 8). If the above procedure is repeated with the mother liquor, a variable additional amount of *rac*-**5** (Note 8) is obtained.

With (*S*)-citronellal the (4*S*,4a*S*,6*S*,8a*S*)-lactone (+)-**5** is obtained; with (*R*)-citronellal the (4*R*,4a*R*,6*R*,8a*R*)-lactone (−)-**5** is obtained (Note 3) and (Note 7).

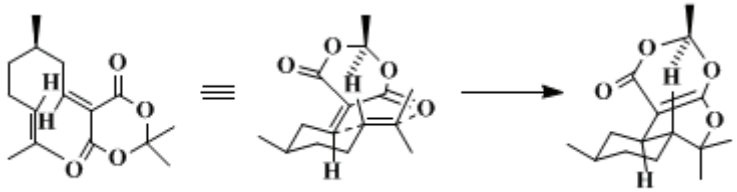
2. Notes

1. Meldrum's acid is commercially available from Merck-Schuchardt, Fluka, or Aldrich Chemical Company, Inc., or it can be prepared by the reaction of malonic acid with acetone.[3]
2. Ethylenediammonium diacetate (EDDA) is prepared as follows.[4] A 250-mL, round-bottomed flask with a stirring bar and a pressure-equalizing addition funnel with a calcium-sulfate-filled drying tube is charged with dry ethylenediamine (12.0 g. 0.20 mol) and dry ether (100 mL). Acetic acid (24.0 g, 0.40 mol) in dry ether (20 mL) is added through the dropping funnel to the stirred solution. The reaction mixture is left at 4°C for 14 hr and the crystals are collected by filtration and washed with ether. Recrystallization from methanol provides 19.8 g (83%) of pure EDDA, mp 114°C, as white needles; IR (KBr) cm^{-1}: 3500–2000 (NH), 2180 (MH_3^+), 1650 (C=O), 1600–1400 (CO_2^-); ^1H NMR ($CDCl_3$) δ: 1.90 (s, 6 H, CH_3), 3.20 (s, 4 H, CH_2), 5.75 (s, 6 H, NH_3^+).
EDDA is the best catalyst for the condensation. Piperidine acetate gives side products.
3. (*R,S*)-Citronellal can be purchased from BASF; and (*R*)-citronellal, from Dragoco, Fluka, or Takasgo Perfumery Co., Ltd., Japan. (*R*)-Citronellal can also be synthesized from pulegone with ee >99%.[5] (*S*)-Citronellal may be obtained by oxidation of (*S*)-citronellol,[6] which is accessible by different routes with ee 95%.[7] The optical purity of citronellal can be determined by GLC after conversion to the acetal of (−)-(2*R*,4*R*)-pentanediol.[8] For the reactions described, (*R,S*)-citronellal from BASF, (*R*)-citronellal from Dragoco, and (*S*)-citronellol from Fluka were used. (*R,S*)-Citronellal and (*S*)-citronellal were distilled under nitrogen before use (bp 83–85°C/11 mm), (*S*)-citronellal: $[\alpha]_D^{20}$ −11.5° (chloroform, *c* 0.1); (*R*)-citronellal ($[\alpha]_D^{20}$ + 13 ± 1°) and (*S*)-citronellal ($[\alpha]_D^{20}$ −4.9 ± 0.2°) were used as purchased.
4. The reaction can also be performed without using inert gas, but the yields may be lower.
5. The pure Diels–Alder adduct **3** can be obtained by crystallization of the crude reaction product from ether/hexane: white needles, mp 104–106°C; IR (KBr) cm^{-1}; 2950, 2930, 2860 (C-H), 1715 (C=O), 1615 (C=C), 1400, 1265; ^1H NMR ($CDCl_3$) δ: 0.40 (m, 1 H, 4 β-H), 0.7–2.5 (m, 7 H, CH + CH_2), 0.90 (d, 3 H, J = 7, CH_3), 1.23, 1.43, 1.70, 1.73 (s, 3 H, CH_3), 2.75 (dt, 1 H, J_1 = 12, J_2 = 2, 4-H). When the pure Diels–Alder adduct **3** is heated in dry methanol under reflux for 3 hr, **5** (mp 68–70°C) is obtained

in 92% yield from **3**.
6. Macherey-Nagel Polygram SIL G/UV_{254}-plates were used with 2 : 5 v/v ether/hexane as eluant. The Diels–Alder product **3** (R_f = 0.29), is visible under short-wavelength ultraviolet light, whereas the detection of **4** (R_f = 0.33), *rac*-**5** (R_f = 0.22) and **6** (R_f = 0.47) is effected by development in an iodine chamber.
7. The physical properties of *rac*-**5**, (+)-**5**, and (−)-**5** are as follows: (+)-**5**, $[\alpha]_D^{20}$ +44.1° (chloroform, *c* 1.004); (−)-**5**, $[\alpha]_D^{20}$ −44.0°, (chloroform, *c* 0.995); IR (KBr) cm^{-1}: 2980, 2950, 2930, 2870, (CH), 1745, 1725 (C=O), 1450, 1320; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.74 (ddd, 1 H, *J* = 12, 12, 12, 5β-H), 0.86–1.7 (m, 5 H, 6, 7β, 8a, 8α, 8β-H), 0.95 (d, 3 H, *J* = 6.5, 6-CH_3), 1.36 (s, 3 H, 1α-CH_3), 1.7–1.9 (m, 2 H, 5α, 7α-H), 1.42 (s, 3 H, 1β-CH_3), 2.16 (dddd, 1 H, *J* = 3.5, 12, 12, 12, 4a-H), 3.09 (d, 1 H, *J* = 12, 4-H), 3.81 (s, 3 H, OCH_3); >^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 22.0 (1α-CH_3), 23.3 (6-CH_3), 27.2 (C-7), 28.2 (1β-CH_3), 31.6, (C-6), 34.2 (C-8), 36.0 (C-8a), 40.5 (C-5), 45.9 (C-4a), 52.6 (OCH_3), 55.1 (C-4), 86.6 (C-1), 167.1 (C=O), 169.6 (C-3); MS (70 eV): *m/e* = 254 (1%, M^+), 239 (6%, M–CH_3), 223 (2%, M–OCH_3), 196 (50%, M–C_3H_6O), 168 (15%, 196-CO), 109 (22%, 168-CO_2CH_3), 101 (100%), 59 (55%, CO_2CH_3).
8. Crystallization of the crude material without distillation from *tert*-butyl methyl ether/hexane affords 56% of *rac*-**5**, mp 68–70°C, as pale-yellow crystals. The submitters obtained a second crop of 1.5 g from crystallization of distilled material; mp 68–78°C, starting from citronellal purchased from BASF. The checkers found that citronellal from Sigma required distillation and gave an impure second crop of **5** only with difficulty.

3. Discussion

Lactone **5** can be obtained in both enantiomeric forms or as racemate according to the described procedure. The reaction sequence includes the in situ formation of an alkylidene-1,3-dicarbonyl system **7**, which can act as a heterodiene in an intramolecular hetero-Diels–Alder addition. A small amount of the ene product **4** with diastereomeric excess (de) > 98% is formed at room temperature as well. The remarkable selectivity in formation of diastereomer **3** is explained by an energetically more favorable *exo* transition state **8** with a pseudochair arrangement having the methyl group quasiequatorial. Polycyclic *cis*-fused compounds can also be synthesized by the procedure above,[9] and a related sequence to the cannabinoid skeleton has been described using appropriate 1,3-dicarbonyl reactants.[10]



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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

brine

(4RS,4aRS,6RS,8aRS)-, (4S,4aS,6S,8aS)- AND (4R,4aR,6R,8aR)-4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4A,5,6,7,8,8a-OCTAHYDRO-2,3-BENZOPYRONE [rac-5, (+)-5, AND (−)-5]

2,2-diamethyl-1,3-dioxane-4,6-dione

(−)-(2R,4R)-pentanediol

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium (13966-32-0)

dichloromethane (75-09-2)

Malonic acid (141-82-2)

$MgSO_4$ (7487-88-9)

ethylenediamine (107-15-3)

hexane (110-54-3)

piperidine acetate

trifluoroacetic acid (76-05-1)

citronellal (106-23-0)

MELDRUM'S ACID (2033-24-1)

pulegone (89-82-7)

ethylenediammonium diacetate

(S)-Citronellol (7540-51-4)

(R)-Citronellal,
(R,S)-citronellal (2385-77-5)

tert-butyl methyl ether (1634-04-4)

(S)-citronellal