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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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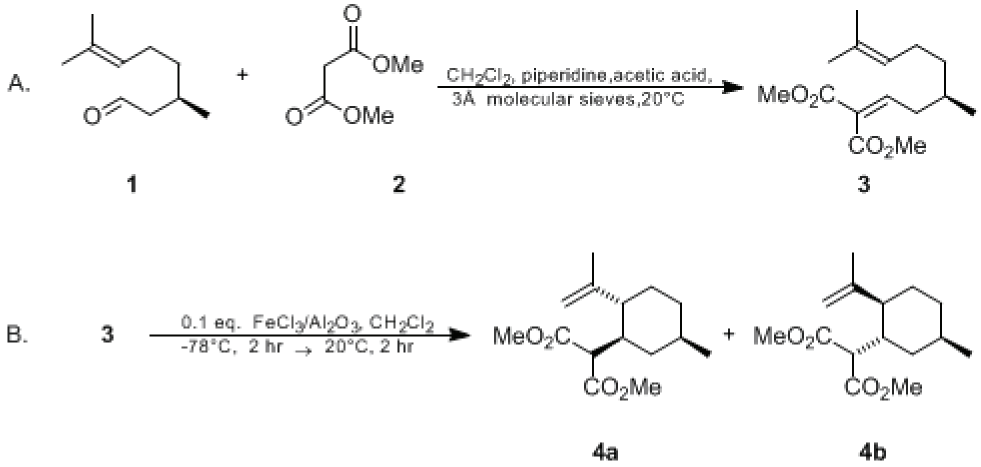
DIASTEREOSELECTIVE FORMATION OF trans-1,2-DISUBSTITUTED CYCLOHEXANES FROM ALKYLIDENEMALONATES BY AN INTRAMOLECULAR ENE REACTION: DIMETHYL (1'R,2'R,5'R)-2-(2'-ISOPROPENYL-5'-METHYLCYCLOHEX-1'-YL)-PROPANE-1,3-DIOATE

[Propanedioic acid, [5-methyl-2-(1-methylethenyl)cyclohexyl]-, dimethyl ester, [1R-(1α,2β,5α)]-]



Submitted by L. F. Tietze and U. Beifuss[1].
Checked by David Rawson and Albert I. Meyers.

1. Procedure

A. *Methyl (5R)-2-(methoxycarbonyl)-5,9-dimethyldeca-2,8-dienoate*, **3**.[2] A dry, 250-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, calcium chloride drying tube, and rubber septum, is charged with 50 mL of dry dichloromethane (Note 1), R-citronellal **1** ((Note 2), 15.4 g, 18.0 mL, 100 mmol), dimethyl malonate, **2** ((Note 3), 14.5 g, 12.5 mL, 110 mmol) and 3 Å molecular sieves ((Note 4), 9.0 g). To the vigorously stirred mixture, piperidine ((Note 5), 0.86 g, 1.00 mL, 10.0 mmol) and acetic acid ((Note 6), 0.63 g, 0.6 mL, 10.0 mmol) are added simultaneously by syringes within a few seconds at room temperature. The reaction mixture is stirred for 30 min, another portion of molecular sieves ((Note 4), 9.0 g) is added, and stirring is continued for another 2 hr (Note 7). After the solvent is removed on a rotary evaporator at 25°C, the resulting slurry is diluted with 30 mL of diethyl ether and the resulting mixture is filtered with suction using a Büchner funnel.

The residue is washed with diethyl ether (4 × 30 mL), and the combined organic layers are washed with water (3 × 30 mL), 1 N hydrochloric acid (3 × 30 mL), saturated sodium bicarbonate solution (3 × 30 mL), water (30 mL), and brine (3 × 30 ml), and finally dried over anhydrous sodium sulfate. Filtration and removal of the solvent on a rotary evaporator at 25°C yields 24.1–25.5 g (90–95%) of the Knoevenagel product as a colorless oil. The crude product is pure enough to be used in the ene reaction. An analytically pure sample of **3** (Note 8) is obtained by column chromatography (SiO_2) (Note 9) with petroleum ether/acetone, 98:2. Compound **3** is acid- and base-sensitive and should be stored under argon in a freezer.

B. *Dimethyl (1'R,2'R,5'R)-2-(2'-isopropenyl-5'-methylcyclohex-1'-yl)propane-1,3-dioate*, **4a**.[2] A dry, 500-mL, three-necked, round-bottomed flask, equipped with a circular magnetic stirring bar, two rubber septa, and a three-way stopcock connected to an argon line and a vacuum line, respectively, is charged with ferric chloride on alumina ((Note 10), 9.25 g, 9.50 mmol of ferric chloride). An argon atmosphere is established in the reaction flask by repeated cycles of evacuation and refilling with argon. Through use of a syringe, 210 mL of dry dichloromethane is added to the reaction flask. Under a positive argon stream, one rubber septum is replaced by a thermometer (−110°C to +30°C) and the other rubber septum is replaced by an argon-flushed, pressure-equalizing dropping funnel sealed with a rubber septum and charged with a solution of **3** (25.5 g, 95.0 mmol) in 40 mL of dry dichloromethane (Note 1). The reaction flask is cooled to −78°C and the solution of **3** in dichloromethane is added dropwise over a period of 30–45 min with stirring at this temperature. Stirring is continued for 2 hr at −78°C and the mixture is allowed to warm to room temperature during 2 hr by taking away the dry ice-acetone bath. The solvent is removed on a rotary evaporator and the remaining brown slurry is treated with diethyl ether (50 mL); the resulting suspension is then filtered with suction using a Büchner funnel. The residue is washed with four 50-mL portions of diethyl ether and the combined organic layers are washed with water (50 mL), saturated sodium bicarbonate solution (50 mL), 1 N hydrochloric acid (50 mL), water (50 mL), and brine (50 mL). The ethereal phase is dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to give 24.9 g (98%) of crude **4a**/**4b** as a yellowish oil in a 98.8:1.2 ratio. (The checkers determined the composition of **4a**/**4b** to be 97.4–97.8/2.6–2.2 by GC/MS.) The oil is purified by short path distillation under reduced pressure to yield 17.1–19.7 g 71–77%) of **4a**/**4b** as a clear, colorless, analytically pure liquid (Note 11). Analytically pure samples of **4a**/**4b** can also be obtained by flash column chromatography of the crude material on SiO_2 (Note 12) with diethyl ether/petroleum ether, 1:4) in 87% yield.

2. Notes

1. Dichloromethane is freshly distilled from phosphorus pentoxide or calcium hydride.
2. (R)-Citronellal purchased from Aldrich Chemical Company, Inc., Dragoco, Holzminden, or Takasago, Perfumery Co., Ltd., Tokyo was used as received. (R)-Citronellal can also be synthesized from pulegone with ee >99%.[3] The optical purity of citronellal can be determined by GLC after conversion to the acetal of (−)-(2R,4R)-pentanediol[4] or by HPLC of the amide of citronellic acid and (R)-(+)-1-(1-naphthyl)ethylamine.[4] The chemical purity was checked by TLC. We are grateful to Dr. Brunke, Dragoco, Holzminden, Dr. Kumobayashi, Takasago, Tokyo and Dr. Nürrenbach, BASF, Ludwigshafen for gifts of (+)- and (±)-citronellal.
3. Dimethyl malonate was purified by distillation.
4. Molecular sieves (3 Å) were finely ground and dried under reduced pressure at 100°C for 24 hr prior to use.
5. Piperidine was purified by distillation prior to use.
6. Acetic acid was purified by distillation.
7. The final stirring period can be shortened to 1 hr if an additional 0.6 mL of acetic acid and 1 mL of piperidine are added at this point.
8. The physical properties of **3** are as follows: R_f 0.51 (ether/hexane, 1:1); HPLC 3.4 min (Nucleosil CN-10; ether/hexane, 1:2; flow 1.5 mL/min); IR (film, cm^{-1}: 1730, 1645, 1260, 1225, 1060; UV sh 210 (4.13); ^{1}H NMR (100 MHz, C_6D_6) δ: 0.78 (d, 3 H, J = 6.5, 5-CH_3), 0.94–1.46 (m, 3 H, 5-H, 6-H_2), 1.53 (s br, 3 H, 10-H_3), 1.66 (s br, 3 H, 9-CH_3), 1.91 (q m, 2 H, J = 7, 7-H_2), 2.13 (multiplet centered, 2 H, 4-H_2), 3.39 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 5.10 (tm, 1 H, J = 7, 8-H), 7.06 (t, 1 H, J = 8, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ: 17.66 (C-10), 19.59 (5-CH_3), 25.81 (9-CH_3), 25.81 (C-7), 32.68 (C-5), 36.99 and 37.03 (C-4 and C-6), 51.69 and 51.81 (OCH_3), 124.89 (C-8), 129.80 (C-2), 131.25 (C-9), 148.48 (C-3), 164.20 (2-CO), 165.76 (C-1); MS m/z 268 (1, M^+), 237 (2, M-CH_3O), 136 (47, $C_{10}H_{16}$). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.19; H, 9.03.
9. Compound **3** is isolated in 82% yield by flash chromatography on SiO_2; SiO_2 is Silica Woelm 32–63 active, Fa. Woelm Pharma, Eschwege or Aldrich Grade 951.
10. Iron(III) chloride on alumina is prepared as follows: A two-necked, round-bottomed flask is equipped with a circular magnetic stirring bar, a rubber septum, and an argon inlet adapter. The flask is flushed with argon and an argon atmosphere is maintained during the reaction. By use of a syringe the reaction flask is charged with dry dichloromethane (160 mL, (Note 1)). Iron(III) chloride from Merck AG, Darmstadt or Fluka Chemie AG, Buchs (10.0 g, 61.6 mmol) is added under argon and the suspension is vigorously stirred. Chromatography-grade neutral or basic alumina from Woelm Pharma, Eschwege (50.0 g) is added in small portions under argon. Stirring is continued for 1 hr to achieve homogeneous adsorption and the solvent is then removed on a rotary evaporator under reduced pressure at room temperature. The rotary evaporator is carefully flushed with argon. After drying under reduced

pressure (0.01 atm) for 12 hr, 60 g of alumina-supported iron(III) chloride is obtained that can be stored under argon for several months without substantial loss of catalytic activity.

11. The physical properties of **4a**/**4b** are as follows: R_f 0.56 (diethyl ether/hexane, 1:1); GLC t**(4a)** 16.88 min, t**(4b)** 17.11 min (Chrompack 0.13 µm CpSil 5, 0.32 mm × 25 m; 100°C, 5°C/min), **4a**/**4b** = 98.82: 1.18 ± 0.043, bp 128–129°C/0.5 mbar; $[\alpha]_D^{20}$ −34.6° (CH_3CN, *c* 1,2); IR (film, cm^{-1}) 3065, 1750, 1735, 1645, 1155, 1035, 1020, 895; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.91 (d, 3 H, J = 6.5, 5'-CH_3), 0.95 (dq, 1 H, J = 3.5, 12, 4'-H ax), 1.11 (q, 1 H, J = 11.5, 6'-H ax), 1.24–1.57 (m, 2 H, 3'-H ax, 5'-H ax), 1.65 (multiplet centered, 3 H, 2"-CH_3), 1.57–1.94 (m, 3 H, 3'-H eq, 4'-H eq, 6'-H eq), 2.05 (dt, 1 H, J = 3.0, 11.5, 2'-H), 2.13 (tt, 1 H, J = 3.5, 11.5, 1'-H), 3.56 (d, 1 H, J = 3.5, 2-H), 3.73 (s, 6 H, OCH_3), 4.74 (multiplet centered, 1 H, 1"-H), 4.79 (m, 1 H, 1"-H); double resonance experiment, irradiation at δ 2.13 (1'-H), 3.56 (2-H), 4.79 (1"-H); significant change at δ 3.56 (s, 2-H) and 1.11 (t, 6'-H ax) 2.13 (1'-H), 1.65 (d, 2"-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) of **4a**/**4b**, δ 18.96/19.36 (C-3"), 22.54/17.89 (5'-CH_3), 32.35/26.27 (C-3'), 32.73/27.32 (C-5'), 34.68/31.09 (C-4'), 36.59/33.47 (C-6'), 39.88/34.33 (C-1'), 48.68 (C-2'), 51.80 and 52.22 (OCH_3), 53.22/53.14 (C-2), 112.43/112.22 (C-1"), 147.52 (C-2"), 169.03 and 170.11/169.95 (C-1 and C-3); MS m/z 268 (4, M^+), 136 (100, $C_{10}H_{16}$). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14, H, 9.01. Found: C, 67.22; H, 9.07.

12. A mixture of **4a**/**4b** is isolated in 87% yield by flash chromatography on SiO_2; SiO_2 is Silica Woelm 32–63 active, Woelm Pharma, Eschwege or Aldrich Grade 951. Diastereomers **4a** and **4b** can be separated by chromatography, (diethyl ether/petroleum ether, 1:9) which, however, causes loss of material; it is also possible to separate the corresponding diols, that can be obtained by reduction with lithium aluminum hydride ($LiAlH_4$), by crystallization from diethyl ether.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The domino-Knoevenagel-ene reaction is a powerful tool to synthesize five- and six-membered carbocycles.[2,5] The process is exemplified by the diastereoselective synthesis of **4a**. Compound **4a** has been obtained in both enantiomeric forms and as a racemate according to the procedure described here. The sequence includes the Knoevenagel reaction of citronellal, **1**, and dimethyl malonate, **2**, followed by the intramolecular ene cyclization of the chiral 1,7-diene **3** to yield the trans 1,2-disubstituted products **4a** and **4b**. Whereas the thermal cyclization of **3** at 180°C provides **4a** and **4b** in a ratio of only 89.7 : 10.3, the Lewis acid promoted reaction can be performed at a lower temperature and shows a much higher diastereoselectivity.[2] If ferric chloride adsorbed on aluminum oxide is used, the reaction can be carried out at −78°C to give **4a** and **4b** in a ratio of 98:2 in 87% yield.[2] It should be stressed that $FeCl_3/Al_2O_3$ is employed as a catalyst using about 0.1 equiv. In the ene reaction other Lewis acids such as diethylaluminum chloride (Et_2AlCl) and zinc bromide ($ZnBr_2$) may be used; however, they have to be added in at least equimolar amounts.[2] Compound **4a** has been used in the synthesis of terpenoid natural products.[6]

References and Notes

1. Institut für Organische Chemie der Georg-August-Universität, Tammannstrasse 2, D-3400-Göttingen, Germany.
2. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; Tietze, L. F.; Beifuss, U. *Synthesis* **1988**, 359; Tietze, L. F.; Beifuss, U., Ruther, M. *J. Org. Chem.* **1989**, *54*, 3120.
3. Plesek, J. *Collect. Czech. Chem. Commun.* **1957**, *22*, 644.
4. Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004; Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.-i.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596.
5. Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1042; Tietze, L. F.; Beifuss, U.

Tetrahedron Lett. **1986**, *27*, 1767; Tietze, L. F.; Beifuss, U. *Liebigs Ann. Chem.* **1988**, 321; Tietze, L. F.; Beifuss, U.; Ruther, M.; Rühlmann, A.; Antel, J.; Sheldrick, G. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1186.

6. Tietze, L. F.; Beifuss, U.; Antel, J.; Sheldrick G. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 703; Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 3857.

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

alumina

petroleum ether

brine

(+)- and (±)-citronellal

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

acetone (67-64-1)

piperidine (110-89-4)

ferric chloride,
iron(III) chloride (7705-08-0)

dichloromethane (75-09-2)

aluminum oxide (1344-28-1)

lithium aluminum hydride (16853-85-3)

zinc bromide (7699-45-8)

hexane (110-54-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

diethylaluminum chloride

citronellal (106-23-0)

dimethyl malonate (108-59-8)

phosphorus pentoxide (1314-56-3)

pulegone (89-82-7)

(R)-(+)-1-(1-Naphthyl)ethylamine (42882-31-5)

Methyl (5R)-2-(methoxycarbonyl)-5,9-dimethyldeca-2,8-dienoate (106431-76-9)

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

Dimethyl (1'R,2'R,5'R)-2-(2'-isopropenyl-5'-methylcyclohex-1'-yl)propane-1,3-dioate,
DIMETHYL (1'R,2'R,5'R)-2-(2'-ISOPROPENYL-5'-METHYLCYCLOHEX-1'-YL)-PROPANE-1,3-DIOATE

dimethyl malonate, 2

Propanedioic acid, [5-methyl-2-(1-methylethenyl)cyclohexyl]-, dimethyl ester, [1R-(1α,2β,5α)]-
(106431-81-6)