Synthesis of (±)-(*E*,*E*)-2,7-Dimethylocta-2,4-dienedioic Acid

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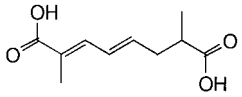
Dedicated to the memory of Professor *George H. Büchi*

(±-(2*E*,4*E*)-2,7-Dimethylocta-2,4-dienedioic acid (**1**) was synthesized efficiently from furan, employing a rhodium-carbenoid-induced furan-ring-unravelling reaction followed by an unusual $NaBH_4/CeCl_3 \cdot 7\,H_2O$ reduction, *Wittig-Horner* olefination, and diester hydrolysis.

Introduction. – The wilty, abscisic acid deficient, mutant tomato variety 'flacca' has been shown to produce a terpenic acid, analyzed to be (±)-(*E*,*E*)-2,7-dimethylocta-2,4-dienedioic acid (**1**) [1][2]. Whereas the compound has been synthesized before [1], it seemed to be suited ideally for construction by the furan-diazo ester decomposition route [3]. Hence, its preparation by this scheme was undertaken.



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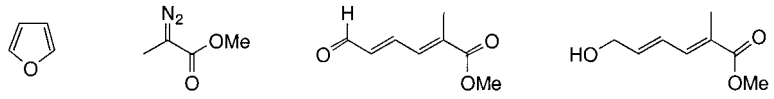
Results and Discussion. – In analogy to an earlier experience with ethyl 2-diazopropanoate [3], an interaction of furan (**2**) and methyl 2-diazopropanoate (**3**) [4] (catalyzed by $[Rh_2(OAc)_4]$), followed by I_2 treatment, furnished aldehydic acid ester **4** in 68% yield[2]). Reduction of freshly purified aldehydic-acid ester **4** by $NaBH_4$ and $CeCl_3 \cdot 7\,H_2O$ in MeOH afforded hydroxy ester **5** [5] (91%).



2 **3** **4** **5**

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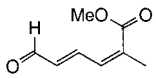
[2]) The compound always was accompanied by its sweet-smelling isomer **i** (*ca.* 1%); pale-yellow liquid: ^{1}H-NMR: 1.46 (br. *s*, Me); 3.65 (*s*, MeO); 6.21 (*dd*, *J* = 8, 15, H–C(5)); 6.64 (*d*, *J* = 12, H–C(3)); 8.11 (*dd*, *J* = 12, 15, H–C(4)); 9.66 (*d*, *J* = 8, H–C(6)). ^{13}C-NMR: 21.1 (Me); 51.8 (MeO); 135.0 (C(5)); 135.6 (C(3)); 136.0 (C(2)); 146.7 (C(4)); 166.6 (C(1)); 193.7 (C(6)).



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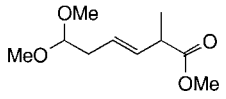
Hydroxy ester **5** had been constructed in the hope of its conversion into an alkylating agent, and subsequent exposure to a propanoate-enolate equivalent would lead to the skeleton of the natural product **1**. However, such a reaction scheme was not consummated as a consequence of the following observation.

Reaction of aldehydic-acid ester **4**, purified two or more weeks prior to use, with the above reduction cocktail yielded none of the hydroxy ester **5**, but, instead, gave acetal **6** (48%), aldehyde **7** (29%), and a mixture (7%) of mono-olefinic alcohols **8**/**9** and their stereoisomers. PCC (pyridinium chlorochromate) oxidation of the alcohol mixture produced aldehyde **7** (78%). Acetal **6** could be converted into aldehyde **7** (81%) with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone = 4,5-dichloro-3,6-dioxocyclohexadiene-1,2-dicarbonitrile) in aq. MeCN [6], making the aldehyde an ideal intermediate en route to the natural product.



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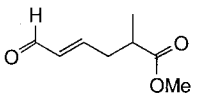

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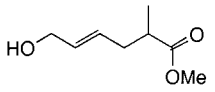

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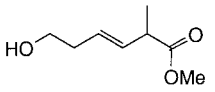

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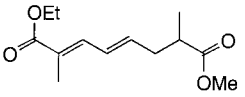
Condensation of aldehydic acid ester **7** with triethyl 2-phosphonopropanoate and NaHMDS (sodium hexamethyldisilazanide) yielded diester **10** (81%), whose hydrolysis (NaOH, H_2O, MeOH) gave the target acid **1** in 88% yield



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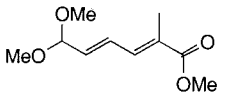

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The strange dissimilarity of reduction behavior of aldehydic-acid ester **4** in newly formed state *vs.* aging shape needs explanation. On the assumption that aging permits air oxidation of the aldehyde, the difference in reduction results may be ascribed to the presence of carboxylic acid in the solution of the 'old' aldehyde sample[3]). As test of this concept, freshly purified **4** was exposed to the above reducing medium containing AcOH catalyst. This led to the formation of acetal **11** [7], acetal **6**, and aldehydic acid ester **7** in a 14:4:1 ratio, reminiscent of the results of the reduction of aged **4**. The presence of the acid causes acceleration of the masking of the aldehyde carbonyl group, hence preventing its reduction and liberation of alcohol **5**. The masking may take the form of rapid hemiacetal (or related adducts) formation and even acetal creation (**6**, **11**), although the latter is known also for lanthanide catalysis [8] alone (*i.e.*, $CeCl_3$).

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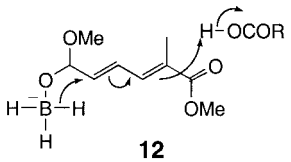
[3]) The aldehyde **4** auto-oxidized slowly at room temperature to its acid, which was evident from the disappearence of the aldehyde peak in the ^{1}H-NMR spectrum of a three-month old (colorless solid) sample.

Once the aldehyde is masked, the dienoate becomes vulnerable to double-bond reduction, a process which may take place intramolecularly (**12** → **13**). The reduced substrate then may serve as precursor for all the observed products.



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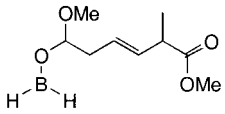

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Conclusion. – A short synthesis of the terpenic diacid of 'flucca' tomatoes was accomplished. The peculiar results of $NaBH_4/CeCl_3 \cdot 7\,H_2O$ reduction of the intermediate aldehydic acid ester **4** were resolved.

Experimental Part

General. TLC: *EM Laboratories* precoated silica gel *60F-25* on 0.2 mm plates. Column chromatography (CC): *EM Laboratories* 60–200 mesh silica gel or *Florisil*; elution with AcOEt/hexane mixtures: MPLC: *Merck Laboratory* (A, B, C) silica gel columns, *Fluid Metering, Inc.* pump. M.p.: *Reichert* micro hot stage; uncorrected. IR Spectra (cm^{-1}): *IBM-9000* spectrophotometer. ^{1}H- and ^{13}C-NMR Spectra ($CDCl_3$): *General Electric-QE-300* spectrometer; δ in ppm, J in Hz. MS: *Hewlett-Packard-5890* GC-MS spectrometers.

*Methyl (*E,E*)-2-Methyl-6-oxohexa-2,4-dienoate* (**4**). A soln. of methyl 2-diazopanoate (0.81 g, 7.1 mmol) in furan (3 ml) was added slowly over 12 h at r.t. to a stirred green suspension of $[Rh_2(OAc)_4]$ (5 mg) in furan (10 ml) under Ar. The resulting soln. was filtered through a short *Florisil* column, to remove the catalyst, and evaporated. The crude mixture was stirred at r.t. overnight with a cat. amount of I_2 in CH_2Cl_2 (20 ml). The mixture was washed with 10% $Na_2S_2O_3$ soln., brine, and dried (Na_2SO_4). CC (silica gel, 5–10% AcOEt/light petroleum ether) afforded **4** (0.81 g, 68%). Yellow oil. ^{1}H-NMR: 2.14 (br. *s*, Me); 3.83 (*s*, MeO); 6.40 (*dd*, J = 8, 15, H–C(5)); 7.31 (br. *d*, J = 12, H–C(3)); 7.45 (*dd*, J = 12, 15, H–C(4)); 9.72 (*d*, J = 8, H–C(6)). ^{13}C-NMR: 13.5 (Me); 52.3 (MeO); 134.3 (C(3)); 136.1 (C(5)); 136.7 (C(2)); 144.8 (C(4)); 167.4 (C(1)); 193.1 (C(6)). MS: 153 ($[M-H]^+$), 125 (100, $[M-29]^+$), 43.

*Methyl (*E,E*)-6-Hydroxy-2-methylhexa-2,4-dienoate* (**5**). $CeCl_3 \cdot 7\,H_2O$ (0.026 g, 0.55 mmol) was added to a stirred soln. of freshly purified **4** (0.085 g, 0.55 mmol) in MeOH (10 ml) at 0°. After stirring for 5 min, $NaBH_4$ (0.04 g, 1.1 mmol) was added in portions. After 20 min, AcOH was added dropwise up to pH *ca*. 6.0. The mixture was evaporated, the residue taken up in H_2O (5 ml) and extracted with AcOEt (2 × 10 ml), and the soln. washed successively with sat. $NaHCO_3$ soln. and brine, dried (Na_2SO_4) and evaporated: **5** (0.078 g, 91%). ^{1}H-NMR: 1.94 (br. *s*, Me); 3.76 (*s*, MeO); 4.29 (*d*, J = 4, H–C(6)); 4.64 (br. *s*, OH); 6.18 (*td*, J = 4, 15, H–C(5)); 6.58 (*dd*, J = 11, 15, H–C(4)); 7.20 (*d*, J = 11, H–C(3)). ^{13}C-NMR: 12.5 (Me); 51.8 (MeO); 62.6 (C(6)); 125.2 (C(5)); 126.8 (C(2)); 137.6 (C(4)); 139.9 (C(3)); 168.9 (C(1)).

$NaBH_4$ Reduction of Aldehydic-Acid Ester **4**. $CeCl_3 \cdot 7\,H_2O$ (1.16 g, 3.1 mol) was added to a stirred soln. of **4** (0.48 g, 3.1 mmol; purified 2 weeks prior to the reaction) in dry MeOH (10 ml) at 0°. After stirring for 15 min, $NaBH_4$ (0.23 g, 6.1 mmol) was added in portions. After 45 min, the solvent was evaporated, the residue taken up in H_2O (10 ml) and extracted with AcOEt (3 × 10 ml), and the combined extract washed with brine, dried (Na_2SO_4), and evaporated. CC (silica gel, 5–15% AcOEt/light petroleum ether) furnished in order of elution **6**, **7**, and **8/9** (+stereoisomers).

*Methyl (*E*)-6,6-Dimethoxy-2-methylhex-3-enoate* (**6**): Yield 0.30 g (48%). Colorless liquid. ^{1}H-NMR: 1.26 (*d*, J = 7, Me); 2.35 (*t*, J = 6, H–C(5)); 3.14 (*quint.*, J = 7, H–C(2)); 3.33 (*s*, 2 MeO–C(6)); 3.68 (*s*, MeO–C(1)); 4.37 (*t*, J = 6, H–C(6)); 5.51 (*td*, J = 7, 15, H–C(4)); 5.63 (*dd*, J = 7, 15, H–C(3)). ^{13}C-NMR: 17.1 (Me); 35.8 (C(5)); 42.6 (C(2)); 51.6 (MeO); 52.6 (*Me*O–C(6)); 103.8 (C(6)); 126.1 (C(4)); 131.6 (C(3)); 175.0 (C(1)). HR-MS: 202.1173 ($C_{10}H_{18}O_4^+$; calc. 202.1205).

*Methyl (*E*)-2-Methyl-6-oxohex-4-enoate* (**7**): Yield 0.14 g (29%). Light yellow oil. ^{1}H-NMR: 1.24 (*d*, J = 6, Me); 2.49 (*quint.*, J = 6, H–C(2)); 2.69 (*m*, H–C(3)); 3.70 (*s*, MeO); 6.14 (*dd*, J = 8, 15, H–C(5)); 6.81 (*td*, J = 7, 15, H–C(4)); 9.51 (*d*, J = 8, H–C(6)). ^{13}C-NMR: 16.8 (Me); 36.0 (C(3)); 38.2 (C(2)); 51.7 (MeO); 134.3 (C(5)); 154.6 (C(4)); 175.3 (C(1)); 193.5 (C(6)). HR-MS: 156.0752 ($C_8H_{12}O_3^+$; calc. 156.0786).

*Methyl (*E/Z*)-6-Hydroxy-2-methylhex-3- and -4-enoates* (**8**/**9**): Yield 0.034 g (7%), including stereoisomers. Due to the complexity of the ^{1}H-NMR, this fraction was not characterized fully, but was oxidized to **7** (*vide infra*). HR-MS: 158.0938 ($C_8H_{14}O_3^+$; calc. 158.0943).

Oxidation of **8**/**9** *with PCC*. To a stirred mixture of **8**/**9** (0.21 g, 1.33 mmol; including stereoisomers) and *Celite* (0.5 g) in dry CH_2Cl_2 (5 ml), PCC was added at r.t. under Ar. After 12 h, the brown mixture was filtered through a *Celite* pad, washing with Et_2O. Evaporation, followed by CC (silica gel, 10% AcOEt/light petroleum ether) furnished the previously characterized **7** (0.15 g, 78%; *vide supra*).

Hydrolysis of **6**. To a stirred soln. **6** (0.043 g, 0.21 mmol) in MeCN/H_2O 9:1 (1.0 ml) was added DDQ (0.005 g, 0.22 mmol) at r.t. After 6 h, the solvent was evaporated and the crude material chromatographed (silica gel, 10% AcOEt/light petroleum ether): pure **7** (0.027 g, 81%). Light yellow oil. Spectroscopic data: identical to those of the previously obtained material (*vide supra*).

$NaBH_4$ Reduction of **4** *in the Presence of AcOH Catalyst*. To freshly purified **4** (0.21 g, 1.4 mmol) in dry MeOH (10 ml), $CeCl_3 \cdot 7\,H_2O$ (0.051 g, 1.4 mmol) was added at 0°, followed by 2 drops of glacial AcOH. After stirring for 20 min, $NaBH_4$ (0.26 g, 6.8 mmol) was added in portions. After 45 min, the solvent was evaporated, the residue taken up in H_2O (10 ml) and extracted with AcOEt (3 × 10 ml) and the combined extract washed with brine, dried (Na_2SO_4), and evaporated. ^{1}H-NMR of the crude material: **11**/**8**/**4**/**7** 14:4:2:1. These were separated by CC (silica gel, 5–15% AcOEt/light petroleum ether).

*Methyl (*E,E*)-6,6-Dimethoxy-2-methylhexa-2,4-dienoate* (**11**): ^{1}H-NMR: 1.98 (*s*, Me–C(2)); 3.34 (*s*, 2 MeO–C(6)); 3.77 (*s*, MeO); 4.94 (*d*, *J* = 4.5, H–C(6)); 5.96 (*dd*, *J* = 4.5, 15, H–C(5)); 6.69 (*dd*, *J* = 12, 15, H–C(4)); 7.18 (*d*, *J* = 11, H–C(3)).

*(*E,E*)-2,7-Dimethyl-2,4-octadienoic Acid* (**1**). NaHMDS (1M in THF; 1.8 ml, 1.8 mmol) was added to a stirred soln. of triethyl 2-phosphonopropanoate (0.44 g, 1.8 mmol) in dry THF (10 ml) at −78° under Ar. After 0.5 h, a soln. of **7** (0.24 g, 1.5 mmol) in dry THF (3 ml) was added and stirred for 2 h. The mixture then was warmed to r.t., quenched with sat. NH_4Cl soln., and extracted with Et_2O (3 × 10 ml) and the extract washed with brine, dried (Na_2SO_4), and evaporated. CC (silica gel, 5–10% AcOEt/light petroleum ether) furnished *1-ethyl 8-methyl (*E,E*)-2,7-dimethylocta-2,4-dienedioate* (**10**): 0.31 g (84%). Yellow oil. ^{1}H-NMR: 1.09 (*d*, *J* = 6, H–C(8)); 1.22 (*t*, *J* = 7, *Me*CH_2); 1.84 (*s*, Me–C(2)); 2.25 (*quint.*, *J* = 6, H–C(7)); 2.48 (*m*, 2 H–C(6)); 3.59 (*s*, MeO); 4.11 (*q*, *J* = 7, MeCH_2); 5.91 (*td*, *J* = 7, 15, H–C(5)); 6.30 (*t*, *J* = 13, H–C(4)); 7.05 (*d*, *J* = 11, H–C(3)). ^{13}C-NMR: 12.3 (Me); 14.0 (*Me*CH_2); 16.4 (C(8)); 36.8 (C(6)); 39.0 (C(7)); 51.7 (MeO); 60.2 (CH_2O); 125.9 (C(2)); 127.8 (C(4)); 137.6 (C(5)); 138.4 (C(3)); 168.1 (*C*O_2Et)); 175.7 (*C*O_2Me).

A mixture of **10** (0.037 g, 0.15 mmol) and KOH (0.10 g, 1.8 mmol) in MeOH/H_2O 1:1 (5 ml) was stirred at r.t. for 12 h. After evaporation, the residue was taken up in H_2O (3 ml) and extracted with Et_2O (10 ml). The aq. phase was acidified with dil. H_2SO_4 soln. to pH *ca.* 2.0 and extracted with Et_2O (2 × 10 ml). The combined org. extracts were dried and evaporated; **1** (0.027 g, 88%). ^{1}H- and ^{13}C-NMR: identical with those recorded for the natural product [1].

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