77. Ionization Shifts in ^{1}H-NMR Spectra of α,β-Unsaturated Carboxylic Acids

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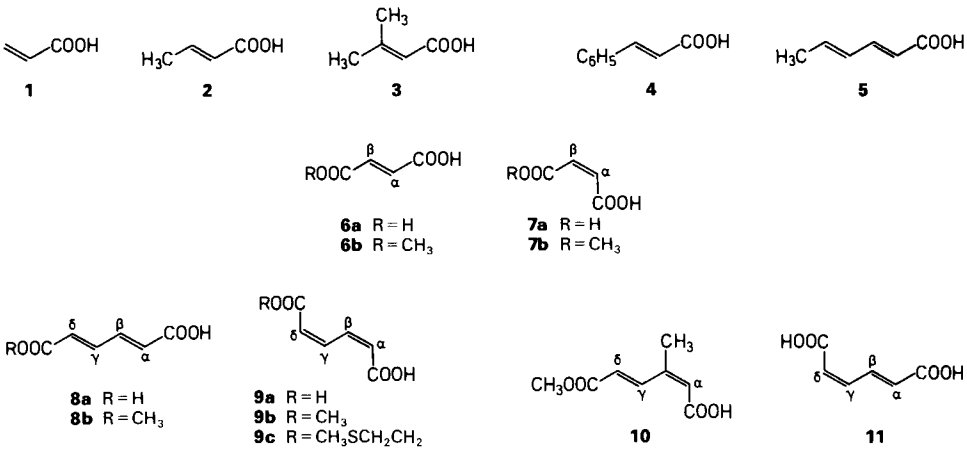
Changes in chemical shifts of olefinic protons in a number of α,β- and $\alpha,\beta,\gamma,\delta$-unsaturated carboxylic acids caused by ionization of the COOH group were investigated. The ionization shifts of α-H-atoms are −0.09 to 0.07 ppm, those of β-H-atoms are 0.32–0.47 ppm. The ionization shifts of δ-H-atoms are substantially larger than those of γ-H-atoms. The ionization shifts can be used for immediate determination of the esterification site in monoesters of (2*E*,4*Z*)-2,4-hexadienedioic (muconic) acid, which are of interest in connection with synthetic studies on verrucarins. Thus, isomerization by heating in aqueous solution of monoesters of (2*Z*,4*Z*)-2,4-hexadienedioic acid yields 1-monoesters rather than 6-monoesters of (2*E*,4*Z*)-2,4-hexadienedioic acid, in accordance with the isomerization mechanism involving anchimeric assistance of the free COOH group. Solutions of the *ABXY* spectra of olefinic protons of monomethyl (2*E*,4*E*)- and (2*Z*,4*Z*)-2,4-hexadienedioate are reported.

It is a well-established fact that conjugation of an olefinic linkage with a COOH group causes characteristic deshielding of the olefinic H-atoms, roughly independent of other substituents [1]. The deshielding of the β-H-atoms is largely due to polarization of the olefinic bond by the C=O group, diminishing the electron density at the β-position [2] [3]; it is, therefore, to be expected that ionization of the COOH group will cause a large upfield shift of the resonances of the H-atoms. Limited information about such ioni-



zation shifts is available [4] [5], in spite of their potential utility as an aid to structure determination by ^{1}H-NMR spectroscopy [6]. Here, we report on the ionization shifts of olefinic H-atoms in a number of α,β- and $\alpha,\beta,\gamma,\delta$-unsaturated carboxylic acids, and demonstrate their practical usefulness in determination of structures of monoesters of (2*E*,4*Z*)-2,4-hexadienedioic acid, which are of interest as building blocks in syntheses of verrucarins [7].

The structures of the model carboxylic acids studied are shown below. The ^{1}H-NMR spectra of monobasic acids in acidic and alkaline solutions, together with derived ionization shifts of olefinic H-atoms [δ(acid)–δ(base)], are reported in *Table 1*. The spectra were recorded in a 1:1 mixture of D_2O and (D_6)DMSO, which could accomodate the whole range of acids and their salts. It is apparent that ionization causes shifts of the α-H-atoms by −0.09 to 0.07 ppm; the shifts are smaller than those observed for α-H-atoms of saturated monocarboxylic acids (0.19–0.25 ppm) [8]. It is characteristic that most of the compounds bearing an ester group at the end of the conjugated acid system exhibit negative (downfield) ionization shifts of H_α. Resonances of the β-H-atoms are, on the other hand, strongly affected, being shifted upfield by 0.32–0.47 ppm. The ionization shift in **7b** is anomalously large, possibly because of steric congestion in the molecule. The shifts of β-H-atoms which are *cis* to the ionized COOH group tend to be less (0.32–0.42 ppm) than those of *trans*-β-H-atoms (0.40–0.47 ppm). The pattern observed for the α- and β-H-atoms is, as expected, followed by the γ- and δ-H-atoms, the ionization shifts of the former (0.03–0.11 ppm) being substantially less than those of the latter (0.17–0.28 ppm). In dibasic acids studied (*Table 2*), where the olefinic protons are affected by two oppositely placed COOH groups, the observed ionization shifts parallel closely those of the monocarboxylic acids, although the shifts are not strictly additive.

To obtain information about chemical-shift values for **8b**, **9b**, and **9c** in acidic medium, it was necessary to carry out an analysis of the tightly coupled *ABXY* patterns given by these compounds. The observed and calculated *ABXY* spectra of **8b** and **9b** are shown in *Fig. 1* and *Fig. 2*.

The chemical shift differences between H_α and H_δ, and between H_β and H_γ are less than 0.05 ppm. Thus, although specific assignment of the resonances within the pairs is not possible, the effect of this uncertainty on the values of the ionization shifts is quite marginal (*Table 1*). The same is true for **7b**, where the chemical shift difference between olefinic H-atoms in the acidic solution is 0.05, but the ionization shifts of H_α and H_β are readily distinguishable.

The precise values of the ionization shifts may, in general, be solvent-, cation- and temperature-dependent, reflecting changes in H-bonding, ion pairing, and acid dimerization equilibria. Moreover, the shifts may depend on the presence of electronegative substituents attached to the double bond, and are probably very sensitive to changes in conformation of the COOH group upon ionization. Nevertheless, using appropriate model compounds, the ionization shifts can be used for immediate identification of ^{1}H resonances in olefinic acids. For the purpose of the present work, the reference data reported in *Tables 1* and *2* provide sufficient basis to prove unambiguously the structures of monoesters of (2*E*,4*Z*)-2,4-hexadienedioic acid, such as **12** and **13**, of interest in connection with synthetic studies on verrucarins [7].

Verrucarins, an important and still expanding class of macrocyclic toxins produced by various strains of microorganisms [9], contain a (2*E*,4*Z*)-2,4-hexadienedioate frag-

Table 1. *^{1}H-NMR Spectra of Unsaturated Carboxylic Acids and their Salts* (270 MHz)

Carboxylic acid	Chemical shifts (δ) and coupling constants		Ionization shifts[a]) [ppm]			
	In acid[b])	In base[c])	H_α	H_β	H_γ	H_δ
Propenoic acid (**1**)	6.08 (H_α); 6.30 (H_β(*cis*)); 5.91 (H_β(*trans*)) ($^3J_{cis}$ = 10.5, $^3J_{trans}$ = 17.3, $^2J_{gem}$ = 1.2)	6.04 (H_α); 5.92 (H_β(*cis*)); 5.51 (H_β(*trans*)) ($^3J_{cis}$ = 10.3, $^3J_{trans}$ = 17.4, $^2J_{gem}$ = 2.0)	0.04	*cis:* 0.38, *trans:* 0.40	–	–
(E)-2-Butenoic acid (**2**)	5.79 (H_α); 6.91 (H_β); 1.81 (CH_3) ($^3J_{trans}$ = 15.5, ^3J(Me,H) = 7.0, ^4J(Me,H) = 1.7)	5.73 (H_α); 6.49 (H_β); 1.73 (CH_3) ($^3J_{trans}$ = 15.5, ^3J(Me,H) = 7.0, ^4J(Me,H) = 1.7)	0.06	0.42 (*cis*)	–	–
3-Methyl-2-butenoic acid (**3**)	5.61 (H_α); 1.83, 2.03 (CH_3)	5.55 (H_α); 1.71, 1.91 (CH_3)	0.06	–	–	–
(E)-3-Phenylpropenoic (**4**)	6.45 (H_α); 7.60 (H_β) ($^3J_{trans}$ = 16.2)	6.45 (H_α); 7.28 (H_β) ($^3J_{trans}$ = 16.2)	0.00	0.32 (*cis*)	–	–
(2E,4E)-2,4-Hexadienoic acid (**5**)	5.77 (H_α); 7.21 (H_β); 6.25 ± 0.05 (H_γ, H_δ); 1.80 (CH_3) ($^3J(\alpha,\beta)$ = 14.7)	5.72 (H_α); 6.84 (H_β); 6.15 (H_γ); 5.99 (H_δ); 1.76 (CH_3) ($^3J(\alpha,\beta) = {}^3J(\gamma,\delta)$ = 15.3, $^3J(\beta,\gamma)$ = 10.5, ^3J(Me,δ) = 6.5)	0.05	0.37 (*cis*)	*ca.* 0.10	*ca.* 0.26
(E)-3-Methoxycarbonyl-propenoic acid (**6b**)	6.73 (H_α); 6.73 (H_β); 3.73 (CH_3O)	6.80 (H_α); 6.40 (H_β); 3.71 (CH_3O) ($^3J_{trans}$ = 15.9)	–0.07	0.33 (*cis*)	–	–
(Z)-3-Methoxycarbonyl-propenoic acid (**7b**)	6.34, 6.39[d]) (H_α, H_β); 3.69 (CH_3O) ($^3J_{cis}$ = 11.9)	6.48 (H_α); 5.73 (H_β); 3.64 (CH_3O) ($^3J_{cis}$ = 12.0)	–0.09[d])	0.61[d]) (*trans*)	–	–
(2E,4E)-5-Methoxycarbonyl-2,4-pentadienoic acid (**8b**)	6.31, 6.36 (H_α, H_δ); 7.29, 7.33[e]) (H_β, H_γ); 3.72 (CH_3O)	6.24 (H_α); 6.92 (H_β); 7.30 (H_γ); 6.19[h]) (H_δ); 3.70 (CH_3O) ($^3J_{trans}$ = 15.5, $^3J(\beta,\gamma)$ = 11.3)	0.07	0.37 (*cis*)	0.03	0.17
(2Z,4Z)-5-Methoxycarbonyl-2,4-pentadienoic acid (**9b**)	6.01 (H_α, H_δ); 7.64[f]) (H_β, H_γ); 3.69 (CH_3O)	6.09 (H_α); 7.20 (H_β); 7.56 (H_γ); 5.80[h]) (H_δ); 3.68 (CH_3O) ($^3J_{cis} = {}^3J(\beta,\gamma)^3$ = 11.7)	–0.08	0.44 (*trans*)	0.08	0.21
(2Z,4Z)-5-[2-(Methylthio) ethoxycarbonyl]-2,4-pentadienoic acid (**9c**)	6.03 (H_α, H_δ); 7.65[g]) (H_β, H_γ); 2.76, 4.30 (SCH_2CH_2O); 2.08 (CH_3S)	6.10 (H_α); 7.23 (H_β); 7.54 (H_γ); 5.82[h]) (H_δ); 2.76, 4.28 (SCH_2CH_2O); 2.07 (CH_3S) ($^3J_{cis} = {}^3J(\beta,\gamma)$ = 11.7)	–0.07	0.42 (*trans*)	0.11	0.21
(2Z,4E)-5-Methoxycarbonyl-3-methyl-2,4-pentadienoic acid (**10**)	6.00 (H_α); 8.37 (H_γ); 6.25 (H_δ); 1.99 (CH_3); 3.72 (CH_3O) ($^3J_{trans}$ = 15.9)	6.04 (H_α); 8.32 (H_γ); 5.97 (H_δ); 1.84 (CH_3); 3.70 (CH_3O) ($^3J_{trans}$ = 16.1)	–0.04	–	0.05	0.28
(2Z,4E)-5-Methoxycarbonyl-2,4-pentadienoic acid (**12a**)	6.02 (H_α); 6.81 (H_β); 8.17 (H_γ); 6.24 (H_δ); 3.69 (CH_3O) ($^3J_{cis} = {}^3J(\beta,\gamma)$ = 11.5, $^3J_{trans}$ = 15.6)	6.09 (H_α); 6.34 (H_β); 8.08 (H_γ); 6.01 (H_δ); 3.70 (CH_3O) ($^3J_{cis} = {}^3J(\beta,\gamma)$ = 11.5, $^3J_{trans}$ = 15.6)	–0.07	0.47 (*trans*)	0.09	0.23

(2E,4Z)-5-[2-(Methylthio) ethoxycarbonyl]-2,4-pentadienoic acid (**12b**)	6.01 (H_α); 6.80 (H_β); 8.19 (H_γ); 6.22 (H_δ); 2.74, 4.29 (SCH_2CH_2O); 2.08 (CH_3S) ($^3J_{cis} = {}^3J(\beta,\gamma) = 11.5$, $^3J_{trans} = 15.6$)	6.09 (H_α); 6.35 (H_β); 8.08 (H_γ); 6.03 (H_δ); 2.76, 4.30 (SCH_2CH_2O); 2.09 (CH_3S) ($^3J_{cis} = {}^3J(\beta,\gamma) = 11.5$, $^3J_{trans} = 15.6$)	–0.08	0.45 (*trans*)	0.11	0.19
(2E,4Z)-5-[2-(Methylthio) ethoxycarbonyl]-2,4-pentadienoic acid (**13b**)	6.21 (H_α); 8.19 (H_β); 6.85 (H_γ); 6.06 (H_δ); 2.76, 4.31 (SCH_2CH_2O); 2.08 (CH_3S) ($^3J_{cis} = {}^3J(\beta,\gamma) = 11.5$, $^3J_{trans} = 15.5$)	6.17 (H_α); 7.82 (H_β); 6.80 (H_γ); 5.89 (H_δ); 2.77, 4.30 (SCH_2CH_2O); 2.09 (CH_3S) ($^3J_{cis} = {}^3J(\beta,\gamma) = 11.5$, $^3J_{trans} = 15.5$)	0.04	0.37 (*cis*)	0.05	0.17

[a]) δ(acid)–δ(base). *cis* and *trans* designate the position of H_β with respect to the free COOH group.
[b]) In $D_2O/(CD_3)_2SO$ 1:1 (v/v) acidified with 20% DCl in D_2O, with DSS as internal standard.
[c]) In $D_2O/(CD_3)_2SO$ 1:1 (v/v) alkalized with solid K_2CO_3, with DSS as internal standard.
[d]) Reversed assignment of olefinic H-atoms in acid gives an alternative set of ionization shifts of –0.14 and 0.66 for H_α and H_β, respectively.
[e]) See *Fig. 1* for exact parameters. Alternative set of ionization shifts: 0.12 (H_α); 0.41 (H_β); –0.01 (H_γ); 0.12 (H_δ).
[f]) See *Fig. 2* for exact parameters.
[g]) Olefinic proton pattern closely similar to this of **9b**.
[h]) Vicinal pairs of resonances identified by appropriate decoupling experiments.

Table 2. *^{1}H-NMR Spectra of Unsaturated Diacids and their Salts* (270 MHz)

Carboxylic acid	Chemical shifts, δ		Ionization shifts[a]) [ppm]
	In acid[b])	In base[c])	
(E)-Butenedioic acid (**6a**)	6.76 ($H_{\alpha,\alpha'}$)	6.38 ($H_{\alpha,\alpha'}$)	0.38 ($H_{\alpha,\alpha'}$, *cis*)
(Z)-Butenedioic acid (**7a**)	6.35 ($H_{\alpha,\alpha'}$)	5.86 ($H_{\alpha,\alpha'}$)	0.49 ($H_{\alpha,\alpha'}$, *trans*)
(2E,4E)-2,4-Hexadienedioic acid (**8a**)	6.31 ($H_{\alpha,\alpha'}$); 7.33 ($H_{\beta,\beta'}$)	6.06 ($H_{\alpha,\alpha'}$); 6.89 ($H_{\beta,\beta'}$)	0.25 ($H_{\alpha,\alpha'}$); 0.44 ($H_{\beta,\beta'}$, *cis*)
(2Z,4Z)-2,4-Hexadienedioic acid (**9a**)	6.04 ($H_{\alpha,\alpha'}$); 7.66 ($H_{\beta,\beta'}$)	5.80 ($H_{\alpha,\alpha'}$); 7.04 ($H_{\beta,\beta'}$)	0.24 ($H_{\alpha,\alpha'}$); 0.62 ($H_{\beta,\beta'}$, *trans*)
(2E,4Z)-2,4-Hexadienedioic acid (**11**)	6.20 (H_α); 8.20 (H_β); 6.84 (H_γ); 6.03 (H_δ)	5.95 (H_α); 7.67 (H_β); 6.34 (H_γ); 5.90 (H_δ)	0.25 (H_α); 0.53 (H_β, *cis*) 0.50 (H_γ, *trans*); 0.13 (H_δ)

[a]) δ(acid)–δ(base). *cis* and *trans* designate position of the proton with respect to the vicinal COOH group.
[b]) In $D_2O/(CD_3)_2SO$ 1:1 (v/v) acidified with 20% DCl in D_2O, with DSS as internal standard.
[c]) In $D_2O/(CD_3)_2SO$ 1:1 (v/v) alkalized with 20% NaOD in D_2O, with DSS as internal standard.

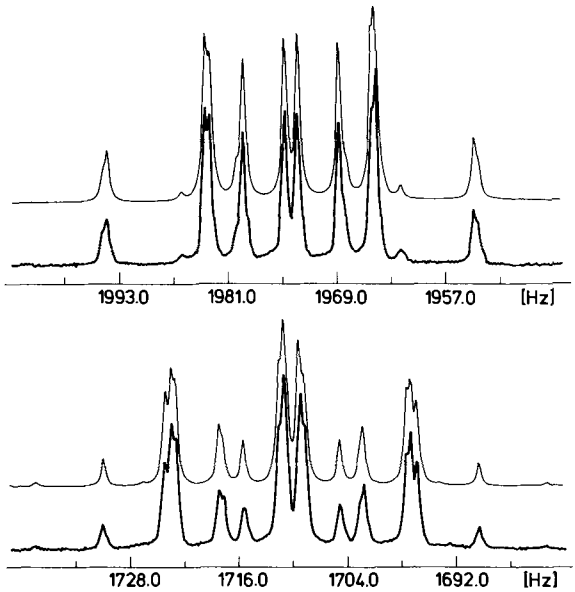


Fig. 1. *Observed* (lower trace) *and simulated* (upper trace) ABXY *spectrum of olefinic protons of* **8b** (in acidic solution) *at 270 MHz*. The simulation parameters are: ν_A 1704.0 Hz, ν_B 1716.5 Hz, ν_X 1968.6 Hz, ν_Y 1979.1 Hz, $^5J_{AB}$ 0.67 Hz, $^3J_{AX}$ 15.42 Hz, $^4J_{AY}$ −0.88 Hz, $^4J_{BX}$ −0.85 Hz, $^3J_{BY}$ 15.45 Hz, $^3J_{YY}$ 11.31 Hz.

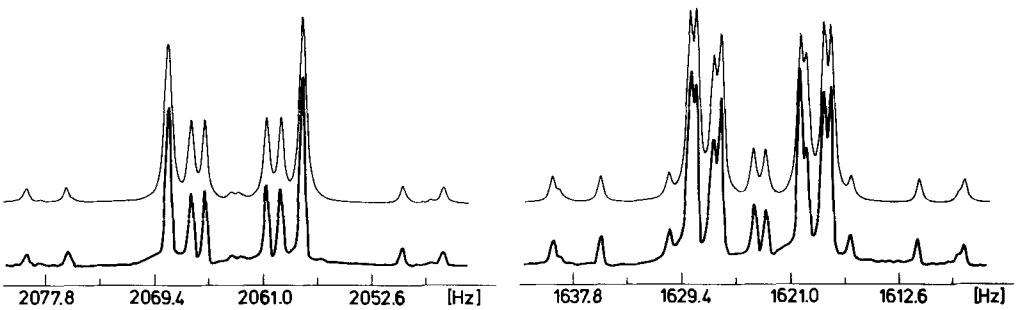
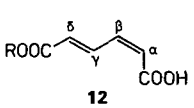


Fig. 2. *Observed* (lower trace) *and simulated* (upper trace) ABXY *spectrum of olefinic protons of* **9b** (in acidic solution) *at 270 MHz*. The simulation parameters are: ν_A 1622.8 Hz, ν_B 1624.1 Hz, ν_X 2062.0 Hz, ν_Y 2064.2 Hz, $^5J_{AB}$ 1.54 Hz, $^3J_{AX}$ 11.62 Hz, $^4J_{AY}$ −1.21 Hz, $^4J_{BX}$ −1.29 Hz, $^3J_{BY}$ 11.70 Hz, $^3J_{XY}$ 11.64 Hz (the two halves of the spectrum were recorded at different amplitudes).

ment, which, in a synthesis, can be introduced as a suitably protected derivative [7]. We found that the required (2*E*,4*Z*)-monoesters **12** can be obtained by isomerization, by heating in H_2O, of the corresponding (2*Z*,4*Z*)-isomers **9b,c** [7], readily available by oxygenation of catechols [10–12]. Interestingly, the isomerization of the monoesters **9b,c** is much slower than the isomerization of the corresponding free diacid **9a** [13] [14]. For



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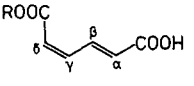
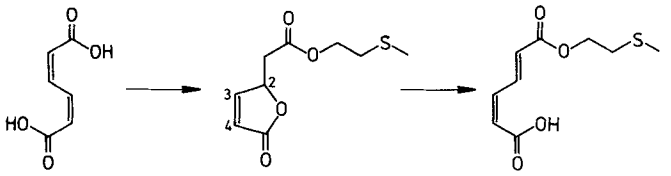


13

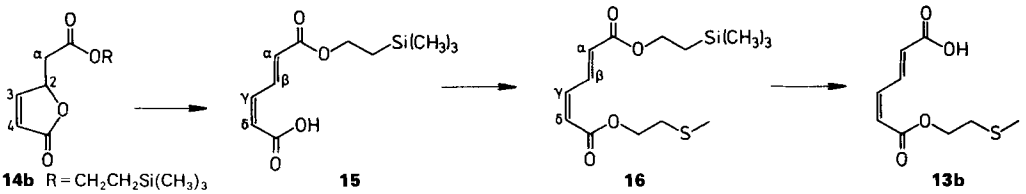
a R = CH_3
b R = $CH_3SCH_2CH_2$

the isomerization products of **9b,c**, the alternative structures, *i.e.* **12** and **13**, must be considered. Measurements of the ionization shifts immediately identifies the isomerization products as **12**, *cf. Table 1*, in accord with the isomerization mechanism involving anchimeric assistance of the free COOH group [15]. An alternative route to the isomers **12** consists of ring opening of 2,5-dihydro-5-oxo-2-furanacetates [7] [13], as shown in *Scheme 1*. The isomeric monoester **13b** was eventually obtained, as depicted in *Scheme 1*, from **14b** *via* **15** and **16**.

Scheme 1



Scheme 2



Originally, the monoester obtained by isomerization of **9c** was erroneously assigned structure **13b**, because the sample showed a ^{13}C-NMR spectrum significantly different from the spectrum of a specimen obtained as shown in *Scheme 1* [7]. The ^{13}C-NMR spectra of 2,4-hexadienedioic acids and their monoesters are expected to be strongly pH-dependent, being apparently also moisture- and concentration-dependent in aprotic solvents, for the reasons similar to those discussed here in connection with the ^{1}H-NMR data. The NMR spectra of such compounds [16] cannot thus be compared unless when recorded under carefully standardized conditions, preferably in buffered solutions. Use of monoesters of (2*E*,4*Z*)-2,4-hexadienedioic acid in synthesis of verrucarins will be the subject of a separate paper [17].

The *Bruker HX-270* spectrometer used in this work was purchased by the *Danish Natural Science Research Council*. Support from the *Swiss National Science Foundation* to the Basel group is gratefully acknowledged.

Experimental Part

General. IR and UV spectra were recorded on a *Perkin Elmer 781* and a *Beckman 25* spectrophotometer, respectively. The ^{1}H-NMR spectra reported in *Table 1* were recorded at 33° on a *Bruker HX-270* spectrometer, with a digital resolution of *ca.* 0.1 Hz per data point. Solutions of the acids (0.2–0.5M except of the solutions of **8a** and **8b**, which were saturated) in $D_2O/(CD_3)_2SO$ 1:1 were made acidic or alkaline by adding 20% DCl in D_2O, or solid K_2CO_3, or 20% NaOD in D_2O, and filtered. Other NMR spectra were obtained with a *Bruker WH-90* instrument. Simulation and iterative refinement of ^{1}H-NMR patterns were performed using the MIMER program [18]. Mass spectra were obtained on a *VG 70-250* spectrometer.

Model carboxylic acids **1**–**5**, **6a**, **7a**, and **8a** were commercial samples. (*Z*)-3-Methoxycarbonylpropenoic acid (**7b**) was obtained by methanolysis of maleic anhydride [19] [20], and the liquid used without purification. The

(*E*)-isomer **6b** was obtained from **7b** (1 g) by refluxing in toluene (150 ml) containing 200 mg of I_2 during 10 h and recrystallization from Et_2O/petroleum ether, m.p. 146–146.5° ([20]: 143°). The monoester **9b** was obtained by oxygenation of catechol in the presence of Cu_2Cl_2, pyridine, and methanol [10–12] and was recrystallized from hexane, m.p. 79–80° ([14]: 80°). The (2*E*,4*E*)-isomer **8b** was obtained in practically quant. yield by refluxing **9b** (300 mg) in toluene (50 ml) containing I_2 (20 mg) during 3 h, evaporation, and crystallization of the residue from acetone, m.p. 162–163° ([14]: 163°). The (2*E*,4*Z*)-isomer **12a** was obtained from **9b** (200 mg) by refluxing 2 h in H_2O (30 ml), evaporation, and crystallization of the residue from Et_2O/petroleum ether; yield 130 mg (65%), m.p. 99–100° ([14]: 101°). The diacids **9a** (m.p. 180–185°; [13]: 179–183°) and **11** (m.p. 190–193°; [13]: 190–191°) were obtained by hydrolysis of **9b** and **12a**, respectively, with 2M NaOH during 2 h at r.t., acidification, and extraction with Et_2O. Larger quantities of **9a** were obtained by oxidation [21] of phenol (24.9 g) with freshly prepared, 13.3% peracetic acid (480 g) during two weeks at r.t. in the dark; the yield of precipitated product was 12.5 g (33%). The monoester **10** was obtained by oxygenation of 4-methylcatechol [10–12] and fractional crystallization of the reaction mixture [15] from Et_2O/petroleum ether (m.p. 128–130°; [22]: 132–134°).

(2Z,4Z)-5-[2-(Methylthio)ethoxycarbonyl]-2,4-pentadienoic Acid (**9c**). Through a mixture of 5.93 g of Cu_2Cl_2, 60 ml of pyridine, and 6.9 g of 2-(methylthio)ethanol, O_2 was bubbled with vigorous stirring during about 30 min. During 4 h, a soln. of 1.1 g of catechol in 20 ml of pyridine containing 0.5 ml of 2-(methylthio)ethanol was added dropwise under O_2. The mixture was evaporated *in vacuo* and hydrolyzed by adding 250 ml of 2M HCl and 200 ml of CH_2Cl_2. After filtration, the org. layer was dried and evaporated, and the residue purified by recrystallization from hexane: 1.5 g (69%) of **9c**. UV (EtOH): λ_{max} 262. IR (KBr): 1720, 1680, 1585, 1245, 1165. ^{13}C-NMR ($CDCl_3$): 15.8; 32.7; 63.3; 123.6; 124.6; 137.9; 139.8; 165.3; 170.6.

(2E,4Z)-5-[2-(Methylthio)ethoxycarbonyl]-2,4-pentadienoic Acid (**12b**). A soln. of 900 mg of **9c** in 200 ml of H_2O was kept at 80° for 2 h, cooled, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated, and the residue crystallized from hexane/CH_2Cl_2: 730 mg (81%) of **12b**, m.p. 84–85°. UV (EtOH): λ_{max} 264. IR (KBr): 1730, 1690, 1600, 1315, 1230. ^{13}C-NMR ($CDCl_3$): 15.9; 32.6; 63.8; 124.0; 129.4; 138.7; 142.4; 165.8; 170.2. Anal. calc. for $C_9H_{12}O_4S$: C 50.00, H 5.60, S 14.81; found: C 49.74, H 5.76, S 14.99.

2-(Trimethylsilyl)ethyl [2,5-Dihydro-5-oxo-2-furan]acetate (**14b**). To a soln. of 395 mg of **9a** in 4 ml of DMF/CH_2Cl_2 3:1 were added 20 mg of 4-(dimethylamino)pyridine, 650 mg of 2-(trimethylsilyl)ethanol and, after cooling to 0°, 620 mg of dicyclohexylcarbodiimide. The mixture was stirred for 5 min at 0° and then for 3 h at r.t. The soln. was filtered, diluted with Et_2O, washed with 2M HCl, sat. aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. Column chromatography of the residue (silica gel, CH_2Cl_2/CH_3OH 97:3) followed by distillation (2 Torr, oven temp. 230°) afforded 1.9 mmol of **14b** as a colorless oil. IR (film): 2960, 2905, 1790, 1765, 1735, 1255. ^{1}H-NMR ($CDCl_3$): 7.60 (*dd*, $^3J(2,3) \approx 2$, $^3J(3,4) = 6$, H–C(3)); 6.20 (*dd*, $^3J(2,4) = 2$, $^3J(3,4) = 6$, H–C(4)); 5.40 (br. *m*, H–C(2)); 4.20 (*m*, CH_2O); 3.3–3.2 (*m*, CH_2); 0.9 (*m*, CH_2Si); 0.1 ($(CH_3)_3Si$); (*cf.* data of the parent acid reported in [23]). ^{13}C-NMR ($CDCl_3$) –1.5; 17.4; 38.0; 63.3; 79.1; 121.8; 155.8; 168.9; 172.1. Anal. calc. for $C_{11}H_{18}O_4Si$: C 54.52, H 7.48; found: C 54.48, H 7.68.

(2E,4Z)-5-[2-(Trimethylsilyl)ethoxycarbonyl]-2,4-pentadienoic Acid (**15**). The lactone **14b** (1.5 g) was dissolved in 4 ml of anh. CH_2Cl_2, cooled to 0°, and 1.42 g of 3,3,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene (*Eschenmoser*'s base) added under N_2. After 3 h at 0°, the mixture was diluted with CH_2Cl_2, washed with 2M HCl and then with brine, dried ($MgSO_4$), and evaporated. Column chromatography (silica gel, Et_2O) and recrystallization (Et_2O/hexane) yielded 1.1 g (73%) of **15** as colorless plates, m.p. 69–71°. UV (EtOH): λ_{max} 262. IR (KBr): 2965, 1715, 1705, 1680, 1595, 1240. ^{1}H-NMR ($CDCl_3$): 11.32 (COOH); 8.26 (H–C(4)); 6.67 (H–C(3)); 6.02 (H–C(5)); 5.87 (H–C(2)); 4.2 (*t*, $^3J = 8$, CH_2O); 0.96 (*t*, $^3J = 8$; CH_2Si); 0.06 ($(CH_3)_3Si$) ($^3J_{trans} \approx 16$, $^3J_{cis} = {}^3J$(H–C(4), H–C(3)). ^{13}C-NMR ($CDCl_3$): –1.4; 17.5; 63.2; 123.8; 130.2; 138.1; 142.6; 166.2; 170.2. MS: 242 (M^+).

(2E,4Z)-5-[2-(Methylthio)ethoxycarbonyl]-2,4-pentadienoic Acid (**13b**). The monoester **15** (700 mg) was esterified with 320 mg of 2-(methylthio)ethanol, 40 mg of 4-(dimethylamino)pyridine, and 655 mg of dicyclohexylcarbodiimide in 3 ml of CH_2Cl_2 as described above for **14b**, yielding, after column chromatography (silica gel, CH_2Cl_2), 740 mg of the oily diester **16**. ^{1}H-NMR ($CDCl_3$): 8.23 (H–C(3)); 6.57 (H–C(4)); 5.97 (H–C(2)); 5.82 (H–C(5)) ($^3J_{trans} = 15$, $^3J_{cis} = {}^3J$(H–C(3), H–C(4)) ≈ 11); 4.24 (*t*, $^3J = 7$, OCH_2CH_2S); 4.18 (*t*, $^3J = 8$, OCH_2CH_2Si); 2.68 (*t*, $^3J = 7$, CH_2S); 2.11 (CH_3S); 0.98 (*t*, $^3J = 8$, CH_2Si), 0.06 ($(CH_3)_3Si$).

The diester **16** (540 mg) was dissolved in 2 ml of THF and cooled in an ice bath. Under N_2, 3.5 ml of 1M Bu_4NF was added, the bath was removed after 15 min, and the mixture stirred for additional 2 h. The soln. was diluted with Et_2O, washed with 2M HCl and with brine, dried ($MgSO_4$), and evaporated to give, after recrystallization from CH_2Cl_2/petroleum ether, 330 mg (89%) of **13b** as colorless plates, m.p. 77–78°. UV (EtOH): λ_{max} 262. IR (KBr): 1710, 1680, 1595, 1235, 1195. ^{13}C-NMR ($CDCl_3$): 15.7; 32.6; 63.4; 125.2; 128.1; 140.4; 140.7; 164.9; 171.2. Anal. calc. for $C_9H_{12}O_4S$: C 50.00, H 5.60; found: C 49.93, H 5.77.

(2E,4Z)-5-[2-(Methylthio)ethoxycarbonyl][2-^{2}H]-2,4-pentadienoic Acid ([2-^{2}H]-**12b**). The deuterated lactone **14a** was obtained from deuterated **9a** (prepared by recrystallization from EtOD) and (D)-2-(methylthio)ethanol similarly as described for **14b**; yield 67%. IR (film): 2920, 1755, 1735. ^{1}H-NMR ($CDCl_3$): 7.63 (*dd*, $^3J(2,3) = 2$, $^3J(3,4) = 4.5$, H–C(3)); 6.19 (*dd*, $^3J(3,4) = 4.5$, $^3J(2,4) = 2$, H–C(4)); 5.40 (br. *m*, H–C(2)); 4.34 (*t*, $^3J = 6$, CH_2O); *ca.* 2.9 (br. *m*, 1 H, CHD); 2.70 (*t*, $^3J = 6$, CH_2S); 2.20 (CH_3S). ^{13}C-NMR ($CDCl_3$): 15.7; 32.6; 37.6 (*t*); 37.9; 63.6; 78.9; 122.2; 155.4; 168.6; 172.0. MS: 217 (M^+).

The lactone (400 mg) was dissolved in 5 ml of acetone and cooled in an ice bath, 0.3 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene added, and the mixture kept at 0° for 3 h. After dilution with Et_2O, the crude product was washed with 2M HCl and brine, dried ($MgSO_4$), and evaporated. Purification by column chromatography (silica gel, AcOEt) yielded 350 mg (87%) of pure [2-^{2}H]-**12b**. UV (EtOH): λ_{max} 264. IR (KBr): 1725, 1600, 1245, 1165. ^{1}H-NMR ($CDCl_3$): 8.35; 6.73; 6.17 (½ H); 5.98 *(cf. Table 1)*; 4.38 (CH_2O, $^3J = 7$), 2.80 (CH_2S, $^3J = 7$); 2.20 (CH_3S). ^{13}C-NMR ($CDCl_3$): 15.8; 32.6; 63.8; 124.1; 129.4 (*t*); 138.6; 142.4; 165.8; 170.2. MS: 217 (M^+).

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