Tetrahedron Vol. 49, No 29, pp 6367-6374, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

A Mild Two-Step Hydrolysis of γ,δ-Unsaturated Anilides

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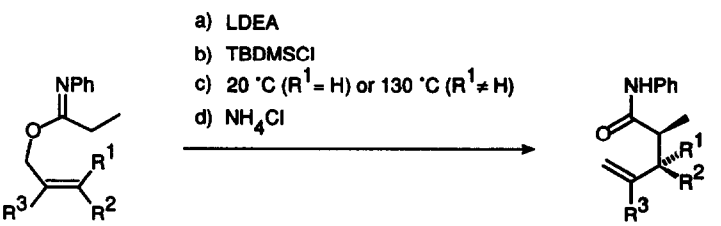
(*Received in Germany* 15 *April* 1993)

Abstract: Iodolactonization of γ,δ-unsaturated anilides **2** in the presence of water and subsequent reduction of the resultant iodolactones **3** using zinc in acetic acid yield the carboxylic acids **4** without significant epimerization α to the carbonyl group. The diastereoselectivity inherent in iodolactonizations of anilides **2** resembles the kinetic stereoselection found for the corresponding transformations of related carboxylic acids.

INTRODUCTION

During studies on rearrangements of allyl imidates,[1-3] the highly diastereoselective conversion of *N*-phenylimidates **1** to amides **2** *via* Claisen rearrangement of *N*-silyl ketene *N,O*-acetals has been achieved (Scheme 1).[2,4] In view of synthetic applications of this procedure, a method was needed which allows for a hydrolysis of anilides **2** to the corresponding carboxylic acids without epimerization α to the carbonyl group. While a saponification of acetoxypivalimide derivatives could be envisioned,[5] this article describes an efficient alternative solution through the use of an iodolactonization/reduction sequence.[6] In addition, the diastereoselectivity of the iodolactonization step is addressed.[7]



1 **2**

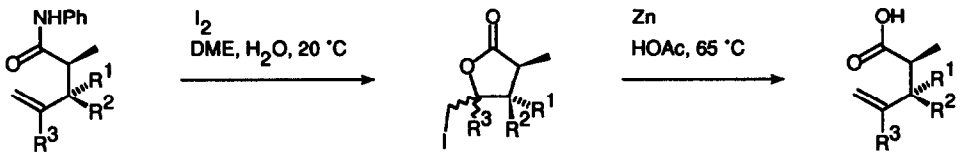
Scheme 1. Claisen rearrangement of allyl *N*-phenylimidates **1** *via* deprotonation/silylation
(LDEA = lithium diethylamide; TBDMSCl = *t*-butyldimethylchlorosilane)

RESULTS AND DISCUSSION

Hydrolysis of Anilides **2**

Reaction of anilides **2** with iodine in 1,2-dimethoxyethane/water[8] led after 3 h at room temperature directly to iodolactones **3**. No lactams[9] were produced and exclusive formation of five-membered rings was observed. Apparently, the intermediate iminolactones are immediately hydrolyzed to **3** under these slightly

acidic conditions. Subsequent reduction of the crude iodolactones **3** with zinc in acetic acid[6] yielded the carboxylic acids **4** (Scheme 2).



2 **3** **4**

Scheme 2. Iodolactonization/reduction sequence
(DME = 1,2-dimethoxyethane)

The presence of water during iodolactonization of **2** is essential. An attempt to effect this transformation under thermodynamic control using iodine in acetonitrile[10,11] resulted in extensive epimerization α to the carbonyl group in *anti*-**2a** and very slow conversion to **3a**. In line with this finding is the reported failure of iodine-induced cyclization of γ,δ-unsaturated secondary amides in tetrahydrofuran.[12]

Three amides of each diastereomeric series were subjected to this two-step hydrolysis (Table 1). As is inferred from the isomeric purities of substrates **2** and products **4**, no significant epimerization took place for any substrate, thus establishing this procedure as a very mild and efficient method for the hydrolysis of γ,δ-unsaturated anilides.

Table 1. Two-Step Hydrolysis of Anilides **2**.

2	*anti* : *syn*[a]	R^1	R^2	R^3	**4**	*anti* : *syn*[b]	Yield **4** [%][c]
anti-**a**	90.5 : 9.5	H	Me	H	*anti*-**a**	90.4 : 9.6	68
anti-**b**	89.8 : 10.2	H	*n*-Pr	H	*anti*-**b**	90.2 : 9.8	68
anti-**c**	98.3 : 1.7	H	Me	Me	*anti*-**c**	97.8 : 2.2	66
syn-**a**	9.0 : 91.0	Me	H	H	*syn*-**a**	9.4 : 90.6	68
syn-**b**	14.1 : 85.9	*n*-Pr	H	H	*syn*-**b**	13.8 : 86.2	68
syn-**c**	5.3 : 94.7	Me	H	Me	*syn*-**c**	5.5 : 94.5	64

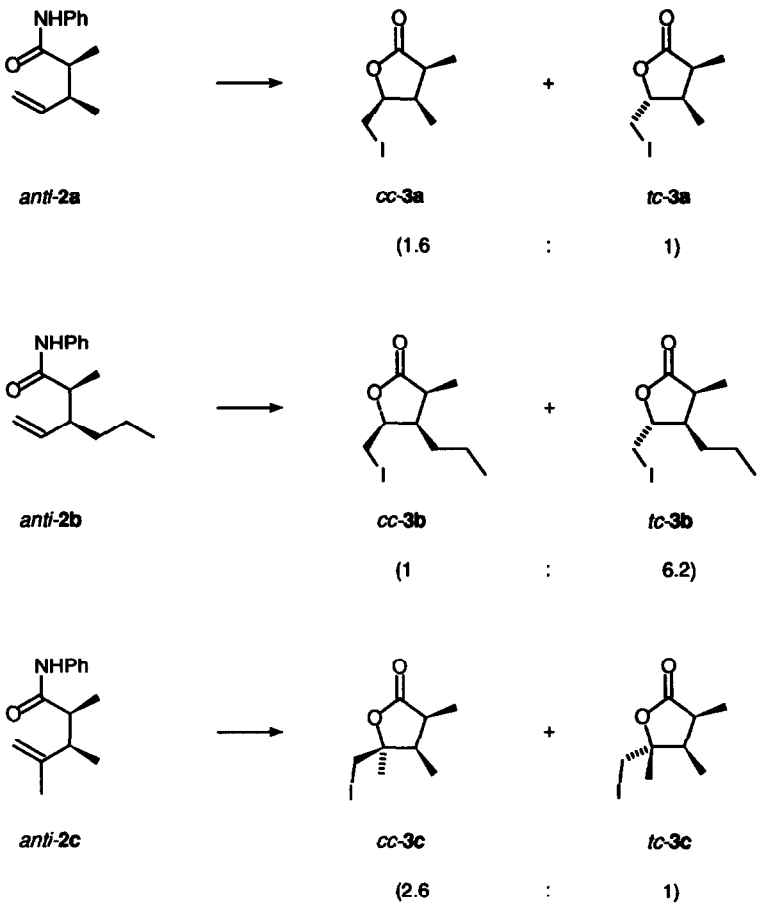
[a] Determined by capillary GC analysis of substrates **2** (**a**: column 1, 190 °C; **b**: column 1, 210 °C; **c**: column 2, 50 °C to 200 °C with 5 °C/min, then 200 °C). [b] Determined by capillary GC analysis of the methyl esters derived from products **4** (**a**, **b**: column 2, 50 °C; **c**: column 1, 50 °C). [c] Total yield of acids **4** from **2** after chromatographic purification.

Diastereoselective Iodolactonization of Anilides **2**

The relative configuration of iodolactones **3** was unambiguously assigned by NOE difference and NOESY spectra[13] of the crude mixtures obtained from amides **2**, and the same samples were used to measure the diastereomeric ratios by ^{1}H NMR integration (Scheme 3, Scheme 4).

Evidently, a delicate balance of nonbonding interactions is responsible for the stereochemical outcome of these iodolactonizations. As is depicted in Scheme 3, the relative configuration of the major product in the *anti* series switches from 2,4-*cis* (*cc*-**3a**) to 2,4-*trans* (*tc*-**3b**) on increasing the size of the substituent R^2 from methyl to *n*-propyl, whereas the additional methyl group at C-4 in *anti*-**2c** does not alter the stereochemical preference for the 2,4-*cis* product (*cc*-**3c**) noted for *anti*-**2a**. On the other hand, exchanging R^1 = Me against R^1 = *n*-Pr in the

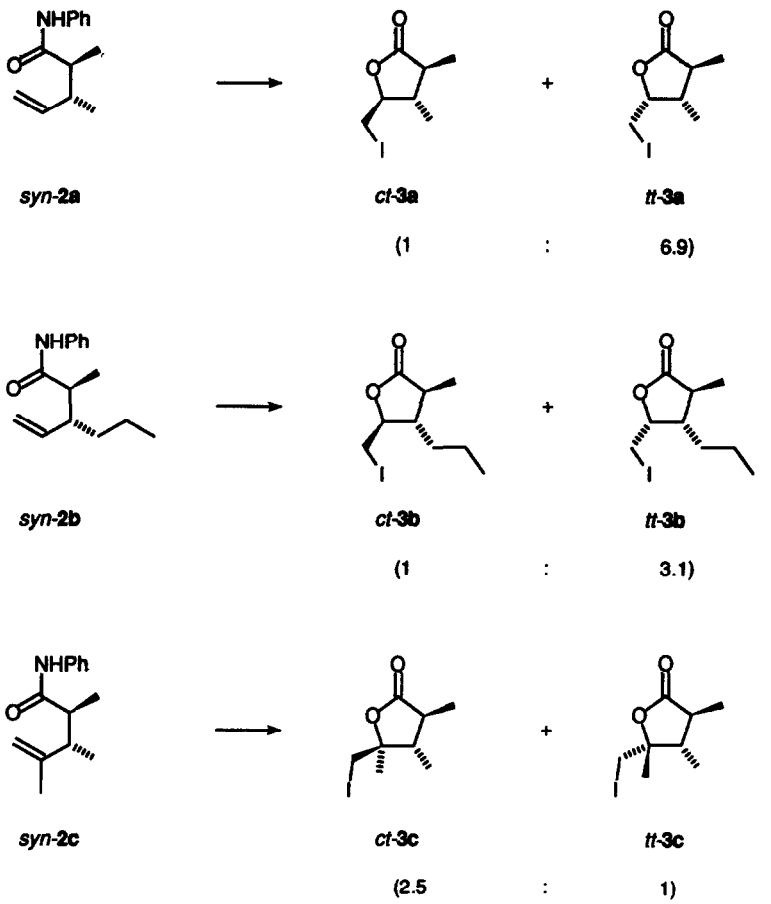
syn-series (Scheme 4) only diminishes the preponderance of the 2,4-trans isomer which is favored for both *syn*-**2a** and *syn*-**2b** (*tt*-**3a** vs. *tt*-**3b**), while the substituent R^3=Me (*syn*-**2c**) again causes a preferential formation of the 2,4-*cis* product (*ct*-**3c**).



Scheme 3. Diastereoselective iodolactonization of anilides **2**; *anti* series
(ratios determined on a sample of the crude products by ^{1}H NMR integration)

As far as comparative data are available, the diastereoselectivity inherent in these iodolactonizations of anilides resembles the kinetic stereoselection found for the corresponding transformations of related carboxylic acids. Thus, *anti*-**2c** and *syn*-**2c** react similarly to 2,3,4-trialkyl substituted carboxylic acids,[14] and also *anti*-**2a**, *syn*-**2a**, as well as *syn*-**2b** display a stereochemical preference that has been observed for comparable 2,3-disubstituted 4-pentenoic acids.[15] However, the iodolactonization of *anti*-**2b** is rather reminiscent of the behavior of *N,N*-dimethyl 2,3-dimethyl-4-pentenamides which, irrespective of their relative configuration, favor the formation of 2,4-*trans* iodolactones.[8]

For some substrates (*anti*-**2b**, *syn*-**2a**), the iodolactonization of anilides **2** reaches quite good levels of diastereoselectivity which might well be exploited synthetically, particularly since the conversion of **2** to **3** is highly efficient.



Scheme 4. Diastereoselective iodolactonization of anilides **2**; *syn* series
(ratios determined on a sample of the crude products by ^{1}H NMR integration)

EXPERIMENTAL

General Remarks

Capillary GC analyses were performed with a Shimadzu GC-14APFsc, a Shimadzu C-R6A integrator, a FFAP CB column, 50 m length, 0.32 mm i. d., 0.25 μm film (column 1), and a SE 54 CB column, 25 m length, 0.25 mm i. d., 0.25 μm film (column 2). ^{1}H NMR spectra (300 MHz, $CDCl_3$), NOE difference spectra (300 MHz, $CDCl_3$) and ^{13}C NMR spectra (75.47 MHz, $CDCl_3$) were obtained on a Bruker WM 300 - m_c = multiplet centered at, br. = broad. ^{13}C multiplicities were determined using INEPT or DEPT pulse sequences. NOESY spectra (360 MHz, $CDCl_3$) were recorded on a Bruker AM 360. IR spectra ($CHCl_3$) were obtained on a Shimadzu IR-408 and a Nicolet 5DXC FT-IR. Mass spectra (GC/MS) were recorded with a Varian MAT CH-7A (70 eV) and a data system Finnigan MAT 200. Methyl esters of carboxylic acids were prepared with excess diazomethane in ether/methanol (9:1) at room temperature. Microanalyses were performed by Mikroanalytisches Laboratorium M. Beller, Göttingen.

Iodolactones **3** - *General Procedure*

Iodine (2.2 mmol) is added to a solution of an amide **2** (1 mmol; for isomeric purities, see Table 1) in 1,2-dimethoxyethane (2.5 ml)/water (2.5 ml) at room temperature and the resultant mixture is stirred at room temperature with exclusion of light for 3 h (complete conversion of **2**). After dilution with ether (50 ml), the mixture is washed successively with 10 % aqueous $Na_2S_2O_3 \cdot 5\ H_2O$ (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude iodolactones **3** as oils (yields >90 %; for diastereomeric ratios, see Scheme 3 and Scheme 4).

c-4-Iodomethyl-r-2,c-3-dimethyl-γ-butyrolactone (*cc*-**3a**). ^{1}H NMR δ 0.88 (d, 3 H, J = 7.2 Hz, 3-CH_3), 1.19 (d, 3 H, J = 7.3 Hz, 2-CH_3), 2.73 (m_c, 1 H, 3-H), 2.87 (dq, 1 H, J_d = 7.2 Hz, J_q = 7.3 Hz, 2-H), 3.09 (dd, 1 H, J = 10.0, 10.0 Hz, CH_2I), 3.44 (dd, 1 H, J = 5.7, 10.0 Hz, CH_2I), 4.58 (ddd, 1 H, J = 4.6, 5.7, 10.0 Hz, 4-H); selected NOE difference data: irradiation of 3-CH_3 (0.88 ppm) caused enhancement of 5.8 % for one CH_2I proton (3.09 ppm), irradiation of 4-H (4.58 ppm) caused enhancements of 4.5 % for 3-H (2.73 ppm) and 3.6 % for 2-H (2.87 ppm); MS (GC/MS) m/e (relative intensity) 254 (M^+, 23), 169 (3), 141 (CH_2I^+, 3), 127 (M - I, 63), 113 (M - CH_2I, 16), 99 (5), 56 (65), 55 (83), 43 (100), 41 (85).

t-4-Iodomethyl-r-2,c-3-dimethyl-γ-butyrolactone (*tc*-**3a**)[8]. ^{1}H NMR δ 1.08 (d, 3 H, J = 7.1 Hz, 3-CH_3), 1.19 (d, 3 H, J = 7.3 Hz, 2-CH_3), 2.55 (m_c, 1 H, 3-H), 2.83 (dq, 1 H, J_d = 8.5 Hz, J_q = 7.3 Hz, 2-H), 3.34 (m_c, 2 H, CH_2I), 4.13 (ddd, 1 H, J = 4.6, 5.9, 5.9 Hz, 4-H); selected NOE difference data: irradiation of 3-CH_3 (1.08 ppm) caused enhancement of 5.5 % for 4-H (4.13 ppm); MS (GC/MS) m/e (relative intensity) 254 (M^+, 17), 169 (1), 141 (CH_2I^+, 2), 127 (M - I, 45), 113 (M - CH_2I, 33), 99 (8), 56 (27), 55 (42), 43 (100), 41 (51).

c-4-Iodomethyl-r-2-methyl-c-3-propyl-γ-butyrolactone (*cc*-**3b**). ^{1}H NMR δ 1.26 (d, 3 H, J = 7.2 Hz, 2-CH_3), 2.57 - 2.66 (m, 1 H, 3-H), 2.82 (dq, 1 H, J_d = 7.4 Hz, J_q = 7.2 Hz, 2-H), 4.63 (ddd, 1 H, J = 5.5, 7.4, 7.4 Hz, 4-H); selected NOE difference data: irradiation of 4-H (4.63 ppm) caused enhancements of 6.1 % for 3-H (2.57 - 2.66 ppm) and 5.0 % for 2-H (2.82 ppm); MS (GC/MS) m/e (relative intensity) 282 (M^+, 5), 169 (5), 155 (M - I, 30), 141 (CH_2I^+, M - CH_2I, 21), 127 (16), 95 (14), 84 (26), 83 (26), 69 (55), 57 (19), 56 (29), 55 (100), 43 (91), 41 (85).

t-4-Iodomethyl-r-2-methyl-c-3-propyl-γ-butyrolactone (*tc*-**3b**). ^{1}H NMR δ 0.97 (t, 3 H, J = 6.9 Hz, CH_2-CH_3), 1.20 (d, 3 H, J = 7.5 Hz, 2-CH_3), 1.3 - 1.5 (m, 4 H, CH_2-CH_2), 2.39 (m_c, 1 H, 3-H), 2.85 (dq, 1 H, J_d = 8.0 Hz, J_q = 7.5 Hz, 2-H), 3.32 (dd, 1 H, J = 5.1, 10.7 Hz, CH_2I), 3.39 (dd, 1 H, J = 6.2, 10.7 Hz, CH_2I), 4.18 (ddd, 1 H, J = 5.1, 5.6, 6.2 Hz, 4-H); selected NOE difference data: irradiation of 2-CH_3 (1.20 ppm) caused enhancement of 2.5 % for 4-H (4.18 ppm); MS (GC/MS) m/e (relative intensity) 282 (M^+, 6), 169 (3), 155 (M - I, 42), 141 (CH_2I^+, M - CH_2I, 36), 127 (12), 95 (14), 84 (14), 83 (19), 69 (50), 57 (27), 56 (16), 55 (97), 43 (100), 41 (65).

c-4-Iodomethyl-r-2,c-3,4-trimethyl-γ-butyrolactone (*cc*-**3c**). ^{1}H NMR δ 1.02 (d, 3 H, J = 6.7 Hz, 3-CH_3), 1.18 (d, 3 H, J = 7.3 Hz, 2-CH_3), 1.64 (s, 3 H, 4-CH_3), 2.46 (dq, 1 H, J_d = 7.4 Hz, J_q = 6.7 Hz, 3-H), 3.08 (dq, 1 H, J_d = 7.4 Hz, J_q = 7.3 Hz, 2-H), 3.22 (d, 1 H, J = 10.2 Hz, CH_2I), 3.40 (d, 1 H, J = 10.2 Hz, CH_2I); selected NOE difference data: irradiation of 3-CH_3 (1.02 ppm) caused enhancement of 3.4 % for one CH_2I proton (3.22 ppm), irradiation of 4-CH_3 (1.64 ppm) caused enhancements of 4.1 % for 3-H (2.46 ppm) and 5.8 % for 2-H (3.08 ppm); MS (GC/MS) m/e (relative intensity) 268 (M^+, 16), 185 (8), 183 (3), 169 (8), 141 (M - I, CH_2I^+, 13), 127 (M - CH_2I, 89), 113 (7), 97 (23), 69 (21), 57 (14), 56 (50), 55 (100), 43 (67), 41 (48).

t-4-Iodomethyl-r-2,c-3,4-trimethyl-γ-butyrolactone (*tc*-**3c**). ^{1}H NMR δ 1.00 (d, 3 H, J = 6.8 Hz, 3-CH_3), 1.20 (d, 3 H, J = 7.3 Hz, 2-CH_3), 1.53 (s, 3 H, 4-CH_3), 2.74 (dq, 1 H, J_d = 8.7 Hz, J_q = 6.8 Hz, 3-H), 2.94 (dq, 1 H, J_d = 8.7 Hz, J_q = 7.3 Hz, 2-H), 3.38 (m_c, 2 H, CH_2I); selected NOE difference data: irradiation of 4-CH_3 (1.53 ppm) caused no enhancement for 3-H (2.74 ppm) or 2-H (2.94 ppm); MS (GC/MS) m/e (relative

intensity) 268 (M^+, 6), 185 (4), 183 (1), 169 (2), 141 (M - I, CH_2I^+, 3), 127 (M - CH_2I, 100), 113 (4), 97 (4), 69 (10), 57 (8), 56 (30), 55 (46), 43 (97), 41 (32).

c-4-Iodomethyl-r-2,t-3-dimethyl-γ-butyrolactone (*ct*-**3a**). ^1H NMR δ 3.85 (ddd, 1 H, J = 4.2, 5.1, 9.0 Hz, 4-H); MS (GC/MS) m/e (relative intensity) 254 (M^+, 11), 169 (1), 141 (CH_2I^+, 2), 127 (M - I, 38), 113 (M - CH_2I, 15), 99 (5), 56 (24), 55 (33), 43 (100), 41 (46).

t-4-Iodomethyl-r-2,t-3-dimethyl-γ-butyrolactone (*tt*-**3a**)[8]. ^1H NMR δ 1.16 (d, 3 H, J = 7.0 Hz, 3-CH_3), 1.27 (d, 3 H, J = 7.0 Hz, 2-CH_3), 2.36 (m_c, 1 H, 3-H; simplified to dd, J = 6.9, 8.4 Hz on irradiation at 1.16 ppm), 2.45 (m_c, 1 H, 2-H; simplified to d, J = 8.4 Hz on irradiation at 1.27 ppm), 3.28 (m_c, 2 H, CH_2I), 4.70 (ddd, 1 H, J = 6.6, 6.6, 6.9 Hz, 4-H); selected NOE difference data: irradiation of CH_2I (3.28 ppm) caused enhancements of 1.2 % for 3-CH_3 (1.16 ppm) and 1.8 % for 2-H (2.45 ppm), irradiation of 4-H (4.70 ppm) caused enhancement of 6.0 % for 3-H (2.36 ppm); MS (GC/MS) m/e (relative intensity) 254 (M^+, 19), 169 (2), 141 (CH_2I^+, 3), 127 (M - I, 48), 113 (M - CH_2I, 33), 99 (3), 56 (37), 55 (43), 43 (100), 41 (56).

c-4-Iodomethyl-r-2-methyl-t-3-propyl-γ-butyrolactone (*ct*-**3b**). ^1H NMR δ 1.32 (d, 3 H, J = 7.1 Hz, 2-CH_3), 1.93 (m_c, 1 H, 3-H), 2.42 (m_c, 1 H, 2-H; simplified to d, J = 10.3 Hz on irradiation at 1.32 ppm), 3.90 (ddd, 1 H, J = 4.0, 5.2, 8.4 Hz, 4-H); selected NOE difference data: irradiation of 4-H (3.90 ppm) caused enhancement of 2.0 % for 2-H (2.42 ppm); MS (GC/MS) m/e (relative intensity) 282 (M^+, 2), 169 (1), 155 (M - I, 18), 141 (CH_2I^+, M - CH_2I, 12), 127 (5), 95 (7), 84 (10), 83 (14), 69 (26), 57 (18), 56 (12), 55 (69), 43 (100), 41 (53).

t-4-Iodomethyl-r-2-methyl-t-3-propyl-γ-butyrolactone (*tt*-**3b**). ^1H NMR δ 0.98 (t, 3 H, J = 7.0 Hz, CH_2-CH_3), 1.28 (d, 3 H, J = 7.3 Hz, 2-CH_3), 1.35 - 1.6 (m, 4 H, CH_2-CH_2), 2.24 (m_c, 1 H, 3-H), 2.52 (m_c, 1 H, 2-H; simplified to d, J = 9.2 Hz on irradiation at 1.28 ppm), 3.22 (dd, 1 H, J = 7.8, 10.9 Hz, CH_2I), 3.35 (dd, 1 H, J = 5.0, 10.9 Hz, CH_2I), 4.71 (ddd, 1 H, J = 5.0, 7.4, 7.8 Hz, 4-H); selected NOE difference data: irradiation of 4-H (4.71 ppm) caused enhancement of 6.3 % for 3-H (2.24 ppm); ^{13}C NMR δ 1.76 (t), 14.08 (q), 14.81 (q), 20.79 (t), 29.75 (t), 39.41 (d), 45.96 (d), 79.62 (d), 178.40 (s); MS (GC/MS) m/e (relative intensity) 282 (M^+, 2), 169 (1), 155 (M - I, 18), 141 (CH_2I^+, M - CH_2I, 18), 127 (4), 95 (8), 84 (14), 83 (10), 69 (34), 57 (17), 56 (17), 55 (78), 43 (100), 41 (57).

c-4-Iodomethyl-r-2,t-3,4-trimethyl-γ-butyrolactone (*ct*-**3c**). ^1H NMR δ 1.13 (d, 3 H, J = 6.7 Hz, 3-CH_3), 1.26 (d, 3 H, J = 6.9 Hz, 2-CH_3), 1.42 (s, 3 H, 4-CH_3), 2.17 (dq, 1 H, J_d = 12.1 Hz, J_q = 6.7 Hz, 3-H), 2.36 (dq, 1 H, J_d = 12.1 Hz, J_q = 6.9 Hz, 2-H), 3.37 (d, 1 H, J = 11.0 Hz, CH_2I), 3.48 (d, 1 H, J = 11.0 Hz, CH_2I); selected NOESY data: strong cross-peak connecting 4-CH_3 (1.42 ppm) and 3-CH_3 (1.13 ppm); selected NOE difference data: irradiation of 4-CH_3 (1.42 ppm) caused enhancement of 3.3 % for 2-H (2.36 ppm); ^{13}C NMR δ 13.29 (q), 13.48 (q), 13.92 (t), 20.31 (q), 42.00 (d), 45.83 (d), 83.15 (s), 176.76 (s); MS (GC/MS) m/e (relative intensity) 268 (M^+, 8), 185 (7), 183 (4), 169 (9), 141 (M - I, CH_2I^+, 31), 127 (M - CH_2I, 90), 113 (18), 97 (8), 69 (14), 57 (22), 56 (45), 55 (67), 43 (100), 41 (39).

t-4-Iodomethyl-r-2,t-3,4-trimethyl-γ-butyrolactone (*tt*-**3c**). ^1H NMR δ 1.18 (d, 3 H, J = 7.0 Hz, 3-CH_3), 1.24 (d, 3 H, J = 7.0 Hz, 2-CH_3), 1.57 (s, 3 H, 4-CH_3), 2.15 (m_c, 1 H, 3-H), 2.53 (dq, 1 H, J_d = 12.2 Hz, J_q = 7.0 Hz, 2-H), 3.30 (s, 2 H, CH_2I); selected NOESY data: no cross-peak connecting 4-CH_3 (1.57 ppm) and either 3-CH_3 (1.18 ppm) or 2-CH_3 (1.24 ppm); selected NOE difference data: irradiation of 4-CH_3 (1.57 ppm) caused enhancement of 5.5 % for 3-H (2.15 ppm), irradiation of 2-H (2.53 ppm) caused enhancement of 1.5 % for the two CH_2I protons (3.30 ppm); ^{13}C NMR δ 9.45 (t), 12.56 (q), 13.69 (q), 27.02 (q), 41.42 (d), 47.35 (d), 83.00 (s), 177.30 (s); MS (GC/MS) m/e (relative intensity) 268 (M^+, 5), 185 (5), 183 (1), 169 (4), 141 (M - I, CH_2I^+, 9), 127 (M - CH_2I, 100), 113 (2), 97 (8), 69 (8), 57 (11), 56 (28), 55 (38), 43 (77), 41 (25).

Acids **4** *- General Procedure*

The crude iodolactones **3** (from 1 mmol **2**) are dissolved in glacial acetic acid (2 ml) and treated with zinc dust (10 mmol). The mixture is heated to 65 °C for 1 - 2 h (complete conversion of **3**), cooled to room temperature, and 1 N HCl (20 ml) is added. After extraction with ether (7 x 20 ml) and drying over $MgSO_4$, the solvent is removed *in vacuo* (rotary evaporator, 5 min at 40 °C bath temperature). Filtration of the crude product through a short column filled with silica gel (2 cm length, 2 cm i. d.) using ether (20 ml) as eluent and subsequent evaporation of the solvent *in vacuo* (rotary evaporator, 10 min at 35 °C bath temperature) give the pure acids **4** as colorless liquids (for yields and diastereomeric ratios, see Table 1).

anti-2,3-Dimethyl-4-pentenoic acid (*anti*-**4a**)[16]. 1.5 h 65 °C; ^{1}H NMR δ 1.08 (d, 3 H, *J* = 6.6 Hz, CH-C*H*$_3$), 1.13 (d, 3 H, *J* = 6.9 Hz, CH-C*H*$_3$), 2.36 (m$_c$, 1 H, C*H*-CH$_3$), 2.46 (m$_c$, 1 H, C*H*-CH$_3$), 5.04 (br. d, 1 H, *J* = 10.2 Hz, CH=CH-*H*), 5.06 (br. d, 1 H, *J* = 17.1 Hz, CH=CH-*H*), 5.66 (ddd, 1 H, *J* = 8.2, 10.2 Hz, 17.1 Hz, CH$_2$=C*H*-CH); ^{13}C NMR δ 14.29 (q), 18.32 (q), 40.75 (d), 44.89 (d), 115.32 (t), 140.45 (d), 182.62 (s); IR 3600 - 2400 (O-H), 1700 (C=O) cm^{-1}; MS (GC/MS; methyl ester) m/e (relative intensity) 142 (M$^+$, 1), 127 (M - CH$_3$, 29), 111 (M - CH$_3$O, 12), 110 (M - CH$_3$OH, 7), 88 (CH$_3$O-CO-C$_2$H$_5^+$, 45), 83 (M - CH$_3$O-CO, 50), 82 (M - CH$_3$OH - CO, 15), 55 (CH$_2$=CH-CH-CH$_3^+$, 100).

anti-2-Methyl-3-propyl-4-pentenoic acid (*anti*-**4b**). 1 h 65 °C; ^{1}H NMR δ 0.88 (t, 3 H, *J* = 6.8 Hz, CH$_2$-C*H*$_3$), 1.1 - 1.5 (m, 7 H, including d with *J* = 6.7 Hz at 1.11 ppm, CO-CH-C*H*$_3$, C*H*$_2$-C*H*$_2$-CH$_3$), 2.27 - 2.46 (m, 2 H, CO-C*H*-CH$_3$, CH-C*H*-CH$_2$), 5.05 (dd, 1 H, *J* = 1.9, 16.9 Hz, CH=CH-*H*), 5.09 (dd, 1 H, *J* = 1.9, 10.1 Hz, CH=CH-*H*), 5.49 (ddd, 1 H, *J* = 9.2, 10.1 Hz, 16.9 Hz, CH$_2$=C*H*-CH); ^{13}C NMR δ 13.85 (q), 13.91 (q), 20.29 (t), 34.68 (t), 43.82 (d), 46.51 (d), 117.00 (t), 138.81 (d), 182.86 (s); IR 3600 - 2400 (O-H), 1700 (C=O) cm^{-1}; MS (GC/MS; methyl ester) m/e (relative intensity) 155 (M - CH$_3$, 6), 141 (M - C$_2$H$_5$, 2), 139 (M - CH$_3$O, 4), 138 (M - CH$_3$OH, 5), 128 (M - C$_3$H$_6$, 3), 127 (M - C$_3$H$_7$, 4), 111 (M - CH$_3$O-CO, 5), 110 (M - CH$_3$OH - CO, 8), 88 (CH$_3$O-CO-C$_2$H$_5^+$, 100), 83 (CH$_2$=CH-CH-C$_3$H$_7^+$, 30), 69 (51), 55 (96), 41 (84). Anal. Calcd for C$_9$H$_{16}$O$_2$: C, 69.21; H, 10.33. Found: C, 69.18; H, 10.28.

anti-2,3,4-Trimethyl-4-pentenoic acid (*anti*-**4c**). 1.5 h 65 °C; ^{1}H NMR δ 1.08 (d, 3 H, *J* = 6.6 Hz, CH-C*H*$_3$), 1.11 (d, 3 H, *J* = 6.5 Hz, CH-C*H*$_3$), 1.64 (br. s, 3 H, CH$_2$=C-C*H*$_3$), 2.3 - 2.5 (m, 2 H, CH-C*H*-CH$_3$, CO-C*H*-CH$_3$), 4.79 (br. s, 2 H, C*H*$_2$=C); ^{13}C NMR δ 16.09 (q), 18.14 (q, very intense: presumably 2 x CH$_3$), 43.53 (d), 44.62 (d), 112.44 (t), 146.45 (s), 183.17 (s); IR 3500 - 2400 (O-H), 1690 (C=O) cm^{-1}; MS (GC/MS; methyl ester) m/e (relative intensity) 156 (M$^+$, 5), 141 (M - CH$_3$, 20), 125 (M - CH$_3$O, 4), 124 (M - CH$_3$OH, 7), 97 (M - CH$_3$O-CO, 49), 96 (M - CH$_3$OH - CO, 14), 88 (CH$_3$O-CO-C$_2$H$_5^+$, 32), 83 (27), 69 (CH$_2$=C(CH$_3$)-CH-CH$_3^+$, 74), 55 (49), 41 (C$_3$H$_5^+$, 100). HRMS (GC/MS; methyl esters of *anti*-**4c** and *syn*-**4c**) Calcd for C$_9$H$_{16}$O$_2$ (M$^+$): 156.1150. Found: 156.1172.

syn-2,3-Dimethyl-4-pentenoic acid (*syn*-**4a**)[16]. 1.5 h 65 °C; ^{1}H NMR δ 1.04 (d, 3 H, *J* = 6.7 Hz, CH-C*H*$_3$), 1.13 (d, 3 H, *J* = 6.9 Hz, CH-C*H*$_3$), 2.47 (m$_c$, 1 H, C*H*-CH$_3$), 2.54 (m$_c$, 1 H, C*H*-CH$_3$), 5.02 (br. d, 1 H, *J* = 10.3 Hz, CH=CH-*H*), 5.06 (br. d, 1 H, *J* = 17.3 Hz, CH=CH-*H*), 5.78 (ddd, 1 H, *J* = 7.3, 10.3, 17.3 Hz, CH$_2$=C*H*-CH); ^{13}C NMR δ 13.09 (q), 15.96 (q), 40.04 (d), 44.49 (d), 114.61 (t), 141.17 (d), 182.07 (s); IR 3600 - 2400 (O-H), 1709 (C=O) cm^{-1}; MS (GC/MS; methyl ester) m/e (relative intensity) 127 (M - CH$_3$, 24), 111 (M - CH$_3$O, 9), 110 (M - CH$_3$OH, 5), 88 (CH$_3$O-CO-C$_2$H$_5^+$, 39), 83 (M - CH$_3$O-CO, 45), 82 (M - CH$_3$OH - CO, 13), 55 (CH$_2$=CH-CH-CH$_3^+$, 100).

syn-2-Methyl-3-propyl-4-pentenoic acid (*syn*-**4b**). 1 h 65 °C; ^{1}H NMR δ 0.89 (t, 3 H, *J* = 7.0 Hz, CH$_2$-C*H*$_3$), 1.1 - 1.5 (m, 7 H, including d with *J* = 7.0 Hz at 1.15 ppm, CO-CH-C*H*$_3$, C*H*$_2$-C*H*$_2$-CH$_3$), 2.26 (m$_c$, 1 H, CH-C*H*-CH$_2$), 2.49 (m$_c$, 1 H, CO-C*H*-CH$_3$), 5.03 (br. dd, 1 H, *J* = 1.8, 16.7 Hz, CH=CH-*H*), 5.06 (dd, 1 H, *J* = 1.8, 10.3 Hz, CH=CH-*H*), 5.64 (ddd, 1 H, *J* = 9.2, 10.3 Hz, 16.7 Hz, CH$_2$=C*H*-CH); ^{13}C NMR δ 13.95 (q), 14.05 (q), 20.29 (t), 33.28 (t), 43.89 (d), 46.70 (d), 116.40 (t), 139.40 (d), 182.14 (s); IR 3600 - 2300 (O-H),

1690 (C=O) cm^{-1}; MS (GC/MS; methyl ester) m/e (relative intensity) 155 (M - CH_3, 6), 141 (M - C_2H_5, 2), 139 (M - CH_3O, 4), 138 (M - CH_3OH, 2), 128 (M - C_3H_6, 4), 127 (M - C_3H_7, 30), 111 (M - CH_3O-CO, 4), 110 (M - CH_3OH - CO, 7), 88 (CH_3O-CO-$C_2H_5^+$, 64), 83 (CH_2=CH-CH-$C_3H_7^+$, 27), 69 (47), 55 (100), 41 (76). Anal. Calcd for $C_9H_{16}O_2$: C, 69.21; H, 10.33. Found: C, 69.05; H, 10.39.

syn-2,3,4-Trimethyl-4-pentenoic acid (*syn*-**4c**). 2 h 65 °C; ^1H NMR δ 1.03 (d, 3 H, J = 6.8 Hz, CH-CH_3), 1.11 (d, 3 H, J = 6.7 Hz, CH-CH_3), 1.73 (br. s, 3 H, CH_2=C-CH_3), 2.49 (m_c, 1 H, CH-CH_3), 2.59 (m_c, 1 H, CH-CH_3), 4.74 (br. s, 1 H, CH=CH-H), 4.78 (br. s, 1 H, C=CH-H); ^{13}C NMR δ 12.96 (q), 15.23 (q), 20.31 (q), 42.92 (d), 43.02 (d), 111.04 (t), 147.68 (s), 182.55 (s); IR 3600 - 2400 (O-H), 1700 (C=O) cm^{-1}; MS (GC/MS; methyl ester) m/e (relative intensity) 156 (M^+, 9), 141 (M - CH_3, 29), 125 (M - CH_3O, 6), 124 (M - CH_3OH, 11), 97 (M - CH_3O-CO, 85), 96 (M - CH_3OH - CO, 21), 88 (CH_3O-CO-$C_2H_5^+$, 31), 83 (39), 69 (CH_2=C(CH_3)-CH-CH_3^+, 79), 55 (65), 41 ($C_3H_5^+$, 100). For HRMS data, see *anti*-**4c**.

Acknowledgement

Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

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