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Easy Access to Aroma Active Unsaturated γ-Lactones by Addition of Modified Titanium Homoenolate to Aldehydes

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ABSTRACT: The homo-Reformatsky reaction, in which a metal homoenolate of an ester is added to an aldehyde, was adapted to produce γ-lactones from unsaturated, enolizable aldehydes. By use of titanium homoenolate, 11 different γ-lactones were synthesized in one step with moderate to good yields from readily available aldehydes. In particular, this procedure allowed the rapid preparation of a series of C_{12} unsaturated γ-lactones differing in the position and configuration of the double bond. These reference compounds will be used to identify previously unknown lactones in butter oil. The chromatographic, spectral, and sensory descriptions of the synthesized lactones are provided.

KEYWORDS: homo-Reformatsky reaction, γ-lactone, titanium homoenolate

INTRODUCTION

During research on the identification of aroma active lactones in butter oil, we were faced with many previously unknown, unsaturated γ-dodecalactones that differed in only the double-bond position. Because these isomeric lactones showed similar mass spectra, their firm identification in butter oil required the chemical synthesis of many reference compounds. Saturated γ-lactones are generally synthesized by acid cyclization of 3-alkenoic acids.[1,2] The synthesis of unsaturated γ-lactones requires many steps, as is the case for (*Z*,*Z*)-6,9-dodecadien-4-olide. This product was first discovered by Maurer and Hauser in 1982 as a constituent of tuberose absolute.[3] Its synthesis required five steps from ethyl 4-pentenoate. Similarly, the synthesis of (*Z*)-5-dodecen-4-olide by Dickschat et al. was achieved in six steps starting from 1,4-butanediol.[4]

With the idea of avoiding a multistep synthesis for each of the many lactones hypothesized in butter oil, the direct condensation of a metal homoenolate to an aldehyde seemed very attractive. It would give γ-lactones in one step from aldehydes. We found that titanium homoenolate was the reagent of choice for such a reaction. The one-step synthesis of 11 different unsaturated γ-lactones with moderate to good yields from commercial or easily accessible aldehydes is the subject of this work.

MATERIALS AND METHODS

General. Unless otherwise specified, commercially available reagents and solvents were purchased from Fluka-Sigma-Aldrich, Buchs, Switzerland; Acros Organics, Geel, Belgium; and Carlo-Erba, Val de Reuil, France. Titanium(IV) chloride (1.0 M) in dichloromethane, titanium(IV) *tert*-butoxide, and [(1-ethoxycyclopropyl)oxy]trimethylsilane were obtained from Aldrich. Dess−Martin periodinane was a 15% solution in dichloromethane (Acros).

(*Z*,*Z*)-3,6-Nonadienol was obtained in house by an enzymatic process described previously.[5] Its purity was 80% by gas chromatography−flame ionization detection (GC-FID), and it also contained (*E*,*Z*)-2,6-nonadienol.[5] 8-Nonenal and (*Z*)-6-nonenal are commercial products but were also obtained in house.

Nuclear Magnetic Resonance (NMR) Spectra. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a DPX 400 spectrometer (Bruker, Rheinstetten, Germany) at 25 °C operated at 400 MHz (^{1}H) or 100 MHz (^{13}C), with tetramethylsilane as the internal standard. The ^{13}C signal assignments were obtained from standard gradient-selected correlated spectroscopy, heteronuclear single-quantum coherence, and heteronuclear multiple-bond correlation experiments carried out on a Bruker Avance 500 spectrometer. NMR spectra were processed with Bruker NMR software TopSpin 2.0 (s, singlet; d, doublet; t, triplet; m, multiplet).

GC-FID. The purity of the synthesized compounds was obtained from GC-FID performed on a GC3800 (Varian, Walnut Creek, CA). An SPB-1 column was used (Supelco, Bellefonte, PA; 30 m, 0.25 mm i.d., 0.25 μm film thickness). The oven program was as follows: 70 °C for 0.5 min and then heated to 200 at 10 °C/min under a constant pressure of helium gas at 12 psi. The injector temperature was 250 °C.

GC−Electron Impact−Mass Spectrometry (GC-EI-MS). *Nonpolar Column.* Analyses were carried out by using a 6890/5973 GC-MS (Agilent, Palo Alto, CA) equipped with an HP1 column (Agilent), 60 m, 0.32 mm i.d., 1 μm film thickness: carrier gas, helium, 2.6 mL/min constant flow; oven, 50 °C, 5 min isotherm, then a gradient of 3 °C/min to 120 °C, then a gradient of 5 °C/min to 250 °C, 5 min isotherm, and, finally, a gradient of 15 °C/min to 300 °C followed by a 20 min isotherm. Injection parameters were as follows: standard split/splitless injector at 250 °C; split ratio, 1:5; injection volume, 1.0 μL. Detection parameters were as follows: mass spectra generated at 70 eV; scan mode (*m*/*z* 30−550).

Polar Column. Analyses were performed on an Agilent 6890/5973 equipped with a SupelcoWax 10 column (Supelco), 30 m, 0.25 mm i.d., 0.25 μm film thickness: carrier gas, helium, 0.7 mL/min; oven, 50 °C, 5 min isotherm, then a gradient of 5 °C/min to 240 °C, 15 min isotherm. Injection parameters were as follows: standard split/splitless injector at 250 °C; split ratio, 1:5; injection volume, 1.0 μL. Detection parameters were as follows: mass spectra generated at 70 eV; scan mode (*m*/*z* 30−550).

GC-MS peaks were identified and integrated by using HP ChemStation software. Linear retention indices (LRIs) were determined after injection of a series of *n*-alkanes (C_5−C_{28}) eluted with the same oven program.

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GC−High-Resolution Time-of-Flight (HR-ToF) MS. Analyses were performed on a GCT Premier (Waters, Milford, MA) mass spectrometer, a GC Agilent 6890 with an SPB-1 column (Supelco), 30 m, 0.25 mm i.d., 1.0 μm film: oven, 60 °C for 5 min, heated to 250 °C at 5 °C/min; constant He flow, 1.0 mL/min. One microliter of 100 ppm solutions in ethanol was injected: injector, 250 °C; split, 1:50; solvent delay, 3 min. The acquisition time was set to 0.49 s with an interscan delay of 0.01 s over a mass range of 1−800 Da. Spectra were recorded by using an electron energy of 70 eV, emission current of 386 μA, trap current of 200 μA, and source temperature of 200 °C. Calibration was performed by using heptacosa (perfluorotributylamine, mass spectrometry grade, Apollo Scientific Ltd., Bradbury, U.K.). Calibration data were collected for 1 min in centroid mode. A total of 60 spectra were summed to generate a 24-point calibration curve from m/z 69 to 614 Da. The curve was fitted to a second-order polynomial such that the standard deviation of the residuals was 0.001 amu or lower. Heptacosa was continuously introduced into the ion source, and the ion m/z 218.9856 was used as a lock mass. Mass spectra and molecular formula were obtained with MassLynx software (Waters).

Preparation of the Aldehydes as Starting Material. *(E)-3-Nonenal.* TEMPO (2,2,6,6-tetramethylpiperidinyloxy, 1.56 g, 0.010 mol, 0.1 equiv) was introduced in CH_2Cl_2 (70 mL). (*E*)-3-Nonenol[6] (14.2 g, 0.100 mol, 1 equiv) was then added. Iodobenzene diacetate (2.2 g, 0.100 mol, 1 equiv) was added portionwise while the temperature was maintained at 30−35 °C with a water bath. The reaction mixture was then stirred at room temperature for 2.5 h. After 1 h, the color changed from orange to yellow. $NaHSO_3$ (0.1 equiv) was then added to the reaction mixture, followed by ether. The mixture was washed with water (two times), aqueous saturated $NaHCO_3$ (two times), water (two times), and brine (two times), dried over $MgSO_4$, and then concentrated with a rotary evaporator (100 mbar, 45 °C), yielding 31.74 g of crude product. The compound was purified by flash chromatography on silica gel with pentane/ether 98:2, which gave 5.75 g of (*E*)-3-nonenal (purity = 99%, yield = 41%): ^{1}H NMR ($CDCl_3$) δ 9.66 (t, J = 2.1 Hz, 1H), 5.66−5.58 (m, 1H), 5.53−5.45 (m, 1H), 3.13−3.10 (m, 2H), 2.09−2.03 (m, 2H), 1.42−1.34 (m, 2H), 1.33−1.24 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4 (d, C(1)), 137.0 (d, C(4)), 119.0 (d, C(3)), 47.3 (t, C(2)), 32.7 (t, C(5)), 31.4 (t, C(7)), 28.8 (t, C(6)), 22.5 (t, C(8)), 14.0 (q, C(9)); EI-MS, m/z (rel intensity) 140 (0.5), 122 (5), 111 (6), 96 (30), 84 (57), 83 (35), 69 (100), 55 (90), 41 (66); LRI (nonpolar, *polar*) 1075, *1447*.

(E)-4-Nonenal. (*E*)-4-Nonenol (1 g)[6] was diluted in 10 mL of CH_2Cl_2. Dess−Martin periodinane solution (35 g) was added over 2 h. The reaction was stirred for an additional 2 h at room temperature before it was poured onto 50 mL of cold 5% NaOH. The mixture was extracted three times in diethyl ether, which was washed with brine and water, dried over Na_2SO_4, and evaporated. The crude product was submitted to bulb-to-bulb distillation to yield 0.64 g of a pale yellow oil (65% yield, purity = 91% by GC-FID, 99% (*E*), 1% (*Z*)): ^{1}H NMR ($CDCl_3$) δ 9.76 (t, J = 1.8 Hz, 1H), 5.51−5.36 (m, 2H), 2.51−2.47 (m, 2H), 2.36−2.30 (m, 2H), 2.00−1.96 (m, 2H), 1.37−1.25 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 202.4 (d, C(1)), 132.1 (d, C(5)), 127.6 (d, C(4)), 43.6 (t, C(2)), 32.2 (t, C(6)), 31.6 (t, C(7)), 25.2 (t, C(3)), 22.2 (t, C(8)), 13.9 (q, C(9)); EI-MS, m/z (rel intensity) 140 (0.4), 122 (11), 98 (22), 97 (21), 96 (34), 84 (88), 83 (58), 81 (40), 79 (22), 69 (36), 67 (49), 55 (84), 54 (50), 41 (100), 39 (38); LRI (nonpolar, *polar*) 1072, *1429*.

(E)-6-Nonenal. (*Z*)-6-Nonenal (8 g) and aluminum nitrate (0.25 g) were reacted for 6 h at 130 °C. The mixture was distilled over a Vigreux column (bp 30 °C/0.03 mmHg) to yield 4.73 g (59%) of a mixture of (*E*)- and (*Z*)-6-nonenal in a ratio of 65:35. The mixture was purified over 300 g of silica gel containing 4% of silver nitrate (eluted with 2.5% ethyl acetate in cyclohexane) to give 1.2 g of (*E*)-6-nonenal (purity = 98% by GC-FID, around 1% (*Z*)): ^{1}H NMR ($CDCl_3$) δ 9.76 (t, J = 1.9 Hz, 1H), 5.50−5.33 (m, 2H), 2.42 (dt, J = 7.2, 1.9 Hz, 2H), 2.03−1.96 (m, 4H), 1.68−1.60 (m, 2H), 1.43−1.36 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 202.8 (d, C(1)), 132.6 (d, C(7)), 128.4 (d, C(6)), 43.8 (t, C(2)), 32.2 (t, C(5)), 29.1 (t, C(4)), 25.6 (t, C(8)), 21.6 (t, C(3)), 13.9 (q, C(9)); EI-MS, m/z (rel intensity) 140 (0.2), 122 (20), 107 (7), 93 (25), 83 (23), 81 (48), 79 (22), 67 (51), 55 (69), 54 (46), 41 (100), 39 (35); LRI (nonpolar, *polar*) 1074, *1435*.

(E)-7-Nonenal and (Z)-7-Nonenal. 8-Nonenal (10 g) was reacted at 70 °C for 6 h with 5 mg of rhodium trichloride monohydrate and 100 μL of methanol. The mixture was diluted in 200 mL of diethyl ether and washed with water, dried over Na_2SO_4, and evaporated. The crude product was distilled over a Vigreux column under vacuum (bp 40 °C/0.7 mmHg) to yield 7.2 g (72%) of a mixture of (*Z*)- and (*E*)-7-nonenal in a ratio of about 1:1, together with 8% of the remaining 8-nonenal and some heavier unidentified products. The mixture (4.5 g) was purified over 300 g of silica gel containing 4% of silver nitrate (eluted with 2.5% ethyl acetate in cyclohexane) to yield 2.2 g of (*E*)-7-nonenal (purity = 95% by GC-FID, 98% (*E*), 2% (*Z*)) and 1.7 g of (*Z*)-7-nonenal (purity = 80% by GC-FID, 96% (*Z*), 4% (*E*), containing 17% of the remaining 8-nonenal). 7-Nonenal with unspecified stereochemistry is briefly described in the literature.[7]

Spectral data for (*E*)-7-nonenal: ^{1}H NMR ($CDCl_3$) δ 9.76 (t, J = 1.9 Hz, 1H), 5.42−5.39 (m, 2H), 2.44−2.40 (m, 2H), 2.00−1.95 (m, 2H), 1.66−1.60 (m, 5H), 1.40−1.28 (m, 4H); ^{13}C NMR δ 202.9 (d, C(1)), 131.2 (d, C(7)), 125.0 (d, C(8)), 43.9 (t, C(2)), 32.3 (t, C(6)), 29.3, 28.7 (2t, C(4,5)), 22.0 (t, C(3)), 17.9 (q, C(9)); EI-MS, m/z (rel intensity) 140 (0.4), 122 (17), 107 (10), 98 (23), 93 (23), 83 (22), 81 (35), 79 (27), 67 (37), 55 (100), 41 (57), 39 (31). LRI (nonpolar, *polar*) 1082, *1455*.

Spectral data for (*Z*)-7-nonenal: ^{1}H NMR ($CDCl_3$) δ 9.76 (t, J = 1.9 Hz, 1H), 5.48−5.40 (m, 1H), 5.40−5.33 (m, 1H), 2.44−2.41 (m, 2H), 2.06−2.02 (m, 2H), 1.67−1.61 (m, 2H), 1.61−1.58 (m, 3H), 1.41−1.31 (m, 4H); ^{13}C NMR δ 202.8 (d, C(1)), 130.4 (d, C(7)), 124.0 (d, C(8)), 43.9 (t, C(2)), 29.2, 28.8 (2t, C(4,5)), 26.6 (t, C(6)), 22.0 (t, C(3)), 12.8 (q, C(9)); EI-MS, m/z (rel intensity) 140 (0.4), 122 (20), 107 (12), 98 (24), 93 (29), 83 (25), 81 (41), 79 (32), 67 (44), 55 (100), 41 (71), 39 (37); LRI (nonpolar, *polar*) 1091, *1472*.

(Z,Z)-3,6-Nonadienal. To a solution of 5.85 g of (*Z,Z*)-3,6-nonadienol (41.9 mmol) in 60 mL of dichloromethane was added 207 g of the Dess−Martin periodinane solution (1.76 equiv). The reaction was stirred for 30 min at room temperature before it was poured onto a 5% NaOH solution (500 mL). The mixture was extracted three times in diethyl ether, which was washed with brine and water, dried over Na_2SO_4, and evaporated. The crude product was submitted to bulb-to-bulb distillation to yield 3.7 g of a pale yellow oil (63.5% yield, 79% of (*Z,Z*)-3,6-nonadienal, LRI (nonpolar, *polar*) 1078, *1520*, also containing 11% of (*E,Z*)-2,6-nonadienal, LRI (nonpolar, *polar*) 1130, *1585*). MS and NMR spectra were consistent with those of the literature.[8]

Synthesis of γ-Lactones Using Titanium Homoenolate, Typical Procedure. [(1-Ethoxycyclopropyl)oxy]trimethylsilane (2.2 equiv) was added over 25 min to a solution of titanium tetrachloride (2 equiv). The reaction was slightly exothermic. The mixture became deep red after 5 min of stirring at room temperature. Titanium(IV) *tert*-butoxide (1 equiv) was added, and the reaction was stirred for 1 h. The aldehyde (1 equiv) was then added over 3 h with a syringe pump. Using a slow and steady addition rate is very important. The reaction was stirred for an additional 1 h, poured onto ice and 5% $NaHCO_3$, extracted two times with dichloromethane, dried over Na_2SO_4, and evaporated. Note that the crude product was 4-hydroxyethyl ester, but it was seen as lactone in GC-MS because of its spontaneous cyclization in the GC injector. The crude hydroxy ester was diluted to about 0.1 M in methanol/5% NaOH 1:1, and the reaction was stirred overnight. Methanol was evaporated, and the water phase was washed with ether, acidified to pH 1 with 5% $KHSO_4$, and finally extracted three times with

diethyl ether. After drying over Na_2SO_4 and evaporation of the solvent, the lactones so obtained were purified by distillation under vacuum or by flash chromatography.

All of the following lactones consisted of racemic mixtures.

(E)-5-Dodecen-4-olide, ***1***. From 5.0 g (35.7 mmol) of (*E*)-2-nonenal, purified by distillation over a Vigreux column: bp 65 °C/0.027 mmHg; yield, 37%; 99% by GC-FID, <3% of (*Z*) isomer; ^{1}H NMR ($CDCl_3$) δ 5.85−5.77 (m, 1H−C(6)), 5.52−5.46 (ddt, J = 14.8, 7.1, 1.7 Hz, 1H−C(5)), 4.89 (dd, J = 7.3, 7.1 Hz, 1H−C(4)), 2.56−2.51 (m, 2H), 2.41−2.33 (m, 1H), 2.09−2.03 (m, 2H), 2.02−1.93 (m, 1H), 1.42−1.35 (m, 2H), 1.33−1.25 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (s, C(1)), 135.8 (d, C(6)), 127.4 (d, C(5)), 81.2 (d, C(4)), 32.1 (t, C(7)), 31.6 (t, C(10)), 28.9 (t, C(3)), 28.8 (t, C(2), C(8), C(9)), 22.6 (t, C(11)), 14.1 (q, C(12)); EI-MS, m/z (rel intensity) 196 (1), 153 (6), 136 (10), 125 (14), 111 (100), 98 (19), 85 (19), 81 (24), 67 (19), 55 (28), 41 (28); HR-ToF MS, 196.1466 ($C_{12}H_{20}O_2$, +1.5 ppm).

(E)-6-Dodecen-4-olide, ***2***. From 1.0 g (7.1 mmol) of (*E*)-3-nonenal, purified by bulb-to-bulb distillation: yield, 42%; 94% by GC-FID, <1% of (*Z*) isomer; ^{1}H NMR ($CDCl_3$) δ 5.61−5.53 (m, 1H−C(7)), 5.41−5.33 (m, 1H−C(6)), 4.56−4.49 (m, 1H−C(4)), 2.55−2.51 (m, 2H), 2.48−2.24 (m, 3H), 2.04−1.98 (m, 2H), 1.97−1.87 (m, 1H), 1.39−1.21 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (s, C(1)), 135.5 (d, C(7)), 123.0 (d, C(6)), 80.4 (d, C(4)), 38.3 (t, C(5)), 32.6 (t, C(8)), 31.4 (t, C(10)), 29.0 (t, C(9)), 28.7 (t, C(2)), 26.9 (t, C(3)), 22.5 (t, C(11)), 14.0 (q, C(12)); EI-MS, m/z (rel intensity) 196 (1), 136 (1), 96 (3), 85 (100), 57 (7), 55 (8), 41 (15), 39 (8); HR-ToF MS, 196.1463 ($C_{12}H_{20}O_2$, +0.0 ppm).

(E)-7-Dodecen-4-olide, ***3***. From 0.6 g (4.3 mmol) of (*E*)-4-nonenal, purified by distillation over a Vigreux column: bp 78 °C/0.019 mmHg; yield, 41%; 91% by GC-FID, around 1% (*Z*); ^{1}H NMR ($CDCl_3$) δ 5.50−5.34 (m, 2H), 4.53−4.46 (m, 1H), 2.55−2.51 (m, 2H), 2.36−2.28 (m, 1H), 2.21−2.06 (m, 2H), 2.01−1.96 (m, 2H), 1.91−1.77 (m, 2H), 1.69−1.60 (m, 1H), 1.37−1.25 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (s, C(1)), 132.0 (d, C(8)), 128.2 (d, C(7)), 80.3 (d, C(4)), 35.5 (t, C(5)), 32.2 (t, C(9)), 31.7 (t, C(10)), 28.8 (t, C(2)), 28.3 (t, C(6)), 28.0 (t, C(3)), 22.2 (t, C(11)), 13.9 (q, C(12)); EI-MS, m/z (rel intensity) 196 (2), 136 (5), 121 (4), 111 (9), 96 (100), 85 (43), 81 (61), 67 (40), 55 (37), 54 (48), 41 (31), 39 (13); HR-ToF MS, 196.1467 ($C_{12}H_{20}O_2$, +2.0 ppm).

(Z)-9-Dodecen-4-olide, ***4***. From 5.6 g (40 mmol) of (*Z*)-6-nonenal, purified by distillation over a Vigreux column: bp 77 °C/0.018 mmHg; yield, 38%; purity, 99% by GC-FID; 94% (*Z*)- and 6% (*E*); ^{1}H NMR ($CDCl_3$) δ 5.41−5.27 (m, 2H), 4.52−4.45 (m, 1H), 2.55−2.51 (m, 2H), 2.36−2.28 (m, 1H), 2.07−1.99 (m, 4H), 1.90−1.80 (m, 1H), 1.78−1.70 (m, 1H), 1.64−1.56 (m, 1H), 1.52−1.45 (m, 1H), 1.44−1.35 (m, 3H), 0.96 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (s, C(1)), 132.1 (d, C(10)), 128.6 (d, C(9)), 81.0 (d, C(4)), 35.5 (t, C(5)), 29.4 (t, C(7)), 28.8 (t, C(2)), 28.0 (t, C(3)), 26.9 (t, C(8)), 24.9 (t, C(6)), 20.5 (t, C(11)), 14.4 (q, C(12)); EI-MS, m/z (rel intensity) 196 (7), 136 (53), 123 (21), 121 (22), 109 (18), 107 (16), 95 (38), 85 (58), 81 (78), 68 (92), 67 (100), 55 (47), 41 (56); HR-ToF MS, 196.1465 ($C_{12}H_{20}O_2$, +1.0 ppm).

(E)-9-Dodecen-4-olide, ***5***. From 1.13 g (7.3 mmol) of (*E*)-6-nonenal, purified by microdistillation (no Vigreux column): bp 72 °C/0.024 mmHg; yield, 26%; 91% by GC-FID; <1% (*Z*); ^{1}H NMR ($CDCl_3$) δ 5.49−5.33 (m, 2H), 4.52−4.45 (m, 1H), 2.55−2.51 (m, 2H), 2.37−2.28 (m, 1H), 2.03−1.96 (m, 4H), 1.90−1.80 (m, 1H), 1.78−1.70 (m, 1H), 1.68−1.55 (m, 1H), 1.50−1.43 (m, 1H), 1.43−1.36 (m, 3H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (s, C(1)), 132.5 (d, C(10)), 128.7 (d, C(9)), 81.0 (d, C(4)), 35.5 (t, C(5)), 32.3 (t, C(8)), 29.3 (t, C(7)), 28.9 (t, C(2)), 28.0 (t, C(3)), 25.6 (t, C(11)), 24.7 (t, C(6)), 14.0 (q, C(12)); EI-MS, m/z (rel intensity) 196 (5), 178 (2), 167 (2), 154 (5), 109 (14), 107 (14), 95 (33), 85 (51), 81 (70), 68 (96), 67 (100), 55 (53), 54 (32), 41 (75), 39 (24); HR-ToF MS, 196.1467 ($C_{12}H_{20}O_2$, +2.0 ppm).

(Z)-10-Dodecen-4-olide, ***6***. From 1.55 g (11 mmol) of (*Z*)-7-nonenal, purified by distillation over a Vigreux column: bp 74 °C/0.014 mmHg; yield, 25%; 91% by GC-FID; <4% (*E*); ^{1}H NMR ($CDCl_3$) δ 5.48−5.33 (m, 2H), 4.52−4.45 (m, 1H), 2.55−2.51 (m, 2H), 2.36−2.28 (m, 1H), 2.07−2.01 (m, 2H), 1.90−1.80 (m, 1H), 1.78−1.70 (m, 1H), 1.65−1.62 (m, 1H), 1.62−1.59 (m, 3H), 1.52−1.42 (m, 1H), 1.41−1.32 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (s, C(1)), 130.5 (d, C(10)), 123.9 (d, C(11)), 81.0 (d, C(4)), 35.6 (t, C(5)), 29.4 (t, C(8)), 28.9 (t, C(2)), 28.9 (t, C(7)), 28.0 (t, C(3)), 26.7 (t, C(9)), 25.2 (t, C(6)), 12.8 (q, C(12)); EI-MS, m/z (rel intensity) 196 (3), 178 (2), 167 (2), 154 (5), 153 (5), 136 (36), 123 (13), 109 (16), 95 (34), 85 (62), 81 (64), 68 (100), 67 (72), 55 (73), 54 (46), 41 (48), 39 (24); HR-ToF MS, 196.1462 ($C_{12}H_{20}O_2$, −0.5 ppm).

(E)-10-Dodecen-4-olide, ***7***. From 1.55 g (11 mmol) of (*E*)-7-nonenal, purified by distillation over a Vigreux column: bp 78 °C/0.019 mmHg; yield, 41%; 91% by GC-FID; <2% (*Z*); ^{1}H NMR ($CDCl_3$) δ 5.45−5.38 (m, 2H), 4.52−4.45 (m, 1H), 2.56−2.51 (m, 2H), 2.36−2.28 (m, 1H), 2.00−1.94 (m, 2H), 1.90−1.80 (m, 1H), 1.77−1.68 (m, 1H), 1.65−1.63 (m, 3H), 1.62−1.55 (m, 1H), 1.51−1.41 (m, 1H), 1.38−1.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (s, C(1)), 131.3 (d, C(10)), 124.9 (d, C(11)), 81.0 (d, C(4)), 35.6 (t, C(5)), 32.4 (t, C(9)), 29.4 (t, C(7)), 28.9 (t, C(2)), 28.8 (t, C(8)), 28.0 (t, C(3)), 25.1 (t, C(6)), 17.9 (q, C(12)); EI-MS, m/z (rel intensity) 196 (5), 178 (2), 167 (2), 154 (6), 136 (42), 123 (15), 109 (17), 95 (37), 85 (66), 81 (67), 68 (100), 67 (72), 55 (79), 54 (44), 41 (44), 39 (23); HR-ToF MS, 196.1464 ($C_{12}H_{20}O_2$, +0.5 ppm).

11-Dodecen-4-olide, ***8***. From 5.6 g of 8-nonenal (40 mmol), purified by distillation over a Vigreux column: bp 93 °C/0.026 mmHg; yield, 77%; 95% by GC-FID; ^{1}H NMR ($CDCl_3$) δ 5.85−5.75 (m, 1H−C(11)), 4.99 (dd, J = 17.1, 1.7 Hz, 1H−C(12)), 4.93 (dd, J = 10.2, 1.3 Hz, 1H−C(12)), 4.52−4.45 (m, 1H−C(4)), 2.55−2.51 (m, 2H), 2.36−2.28 (m, 1H), 2.07−2.01 (m, 2H−C(9)), 1.90−1.80 (m, 1H), 1.77−1.69 (m, 1H), 1.65−1.55 (m, 1H), 1.50−1.43 (m, 1H), 1.41−1.30 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (s, C(1)), 139.0 (d, C(11)), 114.3 (t, C(12)), 81.0 (d, C(4)), 35.6 (t, C(5)), 33.7 (t, C(10)), 29.2 (t, C(7)), 28.9 (t, C(8)), 28.9 (t, C(2)), 28.8 (t, C(9)), 28.0 (t, C(3)), 25.2 (t, C(6)); EI-MS, m/z (rel intensity) 196 (0.1), 136 (22), 95 (28), 85 (100), 81 (40), 68 (52), 67 (51), 55 (72), 54 (61), 41 (88), 39 (47); HR-ToF MS, 196.1467 ($C_{12}H_{20}O_2$, +2.0 ppm).

(Z)-11-Tetradecen-4-olide, ***9***. From 6.05 g (36 mmol) of (*Z*)-8-undecenal, purified by distillation over a Vigreux column: bp 95 °C/0.019 mmHg; yield, 52%; 99% by GC-FID; 94% (*Z*)- and 6% (*E*); ^{1}H NMR ($CDCl_3$) δ 5.40−5.28 (m, 2H), 4.52−4.45 (m, 1H), 2.55−2.50 (m, 2H), 2.36−2.28 (m, 1H), 2.07−1.99/m, 4H), 1.90−1.80 (m, 1H), 1.77−1.69 (m, 1H), 1.64−1.55 (m, 1H), 1.50−1.32 (br m, 8H), 0.95 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (s, C(1)), 131.7 (d, C(12)), 129.1 (d, C(11)), 81.0 (d, C(4)), 35.6 (t, C(5)), 29.6 (t, C(9)), 29.2 (t, C(7)), 29.1 (t, C(8)), 28.9 (t, C(2)), 28.0 (t, C(3)), 27.0 (t, C(10)), 25.2 (t, C(6)), 20.5 (t, C(13)), 14.4 (q, C14)); EI-MS, m/z (rel intensity) 224 (5), 164 (9), 150 (8), 136 (13), 122 (11), 109 (22), 95 (53), 85 (63), 82 (68), 81 (77), 68 (100), 67 (94), 55 (74), 41 (84); HR-ToF MS, 224.1779 ($C_{14}H_{24}O_2$, +1.3 ppm).

(Z,Z)-6,9-Dodecadien-4-olide, ***10***. From 2.7 g (20 mmol) of (*Z,Z*)-3,6-nonadienal, purified by distillation over a Vigreux column, bp 87 °C/0.017 mmHg, and then by flash chromatography (cyclohexane/THF 86:14): yield, 8%; purity, 60% by GC-FID and NMR. It contained 20% of (*E,Z*)-5,9-dodecadien-4-olide and impurities from the solvent. Spectral data were consistent with those described by Maurer and Hauser.[3] HR-ToF MS: 194.1305 ($C_{12}H_{18}O_2$, −1.0 ppm).

(E,Z)-5,9-Dodecadien-4-olide, ***11***. From 4.98 g (36 mmol) of (*E,Z*)-2,6-nonadienal, purified by distillation over a Vigreux column: bp 94 °C/0.027 mmHg; yield, 36%; 98% by GC-FID; ^{1}H NMR ($CDCl_3$) δ

5.85−5.78 (m, 1H−C(6)), 5.52 (dd, J = 15.3, 7.1 Hz, 1H−C(5)), 5.43−5.37 (m, 1H−C(10)), 5.33−5.27 (m, 1H−C(9)), 4.90 (dd, J = 7.3, 7.1 Hz, 1H−C(4)), 2.56−2.51 (m, 2H), 2.43−2.33 (m, 1H), 2.16−2.09 (m, 4H), 2.06−1.99 (m, 2H), 1.98−1.93 (m, 1H), 0.96 (t, J = 7.6 Hz, 3H−C(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (s, C(1)), 134.8 (d, C(6)), 132.5 (d, C(10)), 127.8 (d, C(5)), 127.7 (d, C(9)), 81.0 (d, C(4)), 32.2 (t, C(7)), 28.8 (t, (C(3)), 28.7 (t, C(2)), 26.4 (t, C(8)), 20.6 (t, C(11)), 14.3 (q, C(12)); EI-MS, m/z (rel intensity) 194 (0.1), 126 (30), 84 (17), 81 (36), 79 (19), 69 (37), 68 (31), 67 (27), 55 (21), 53 (16), 41 (100), 39 (32); HR-ToF MS, 194.1302 ($C_{12}H_{18}O_2$, −2.6 ppm).

Sensory Descriptions. The lactones have been evaluated by a panel of four in-house expert flavorists who tasted these compounds at 20 ppm in water. The descriptor *fruity* is typically used for decan-4-olide, *peach* for undecan-4-olide, *creamy* for tetradecan-5-olide or dodecan-4-olide, *buttery* for diacetyl, *fatty* for (*E*,*E*)-2,4-decadienal, *oily* for oleic acid, *waxy* for stearic acid, *cardboard* for (*E*)-2-nonenal, and *green* for (*Z*)-3-hexenol.

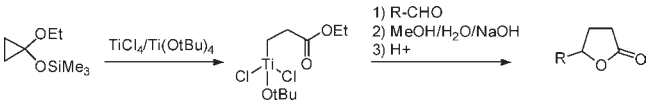
RESULTS AND DISCUSSION

The homoaldol reaction has been reviewed by Hoppe[9] with emphasis on regio- and stereoselectivity in the synthesis of polysubstituted hydroxy esters or lactones using prepared reagents such as metalated allyl carbamates or phosphonates. Nakamura et al. described the general utility of zinc homoenolates of esters.[10] They prepared zinc ethyl homoenolate from the commercially available [(1-ethoxycyclopropyl)oxy]trimethylsilane, the so-called cyclopropane route. The catalytic version of this cyclopropane route proposed by Ochino et al.,[11] in which a catalytic amount of zinc iodide is used, seemed particularly attractive for the quick synthesis of many different lactones, as the reaction conditions are simple (room temperature, dichloromethane as the solvent). However, Ochino et al. described higher yields with benzaldehyde (89%) than with an enolizable aldehyde such as heptanal (44−51%).[11]

Ochiai et al. described the use of chlorotitanium(IV) transmetalation reagents such as $(OiPr)_3TiCl$ to increase the reactivity of zinc homoenolate toward carbonyl electrophiles.[12] Again, excellent yields were obtained with nonenolizable aldehydes such as benzaldehyde but also with butanal (>95%). Nakamura et al. described the direct formation and reaction of titanium(IV) homoenolate without the transmetalation step.[13] There was evidence that the reaction of silyloxycyclopropane derivatives with $TiCl_4$ gave the expected titanium(IV) homoenolate.[14] The scope of this reaction was studied in detail;[13] titanium homoenolates could react with less electrophilic carbonyls such as ketones if they were modified with titanium alkoxides. Despite the foreseen synthetic interest of this reaction, we could not find any reference to its use in the preparation of naturally occurring lactones.

When we used zinc homoenolate, we obtained poor results either in the catalytic[11] or in the stoichiometric conditions.[10] When we reacted octanal with zinc homoenolate under various conditions, we did not observe significant amounts of the expected silylated hydroxy ester. The two diastereoisomeric silylated aldols resulting from the self-condensation of octanal, as well as octanal silyl enol ether, were obtained instead. This confirmed the lack of nucleophilicity of zinc homoenolate.[10] Titanium homoenolate formed by reaction of titanium tetrachloride with [(1-ethoxycyclopropyl)oxy]trimethylsilane[13] gave a much cleaner and faster reaction with octanal. Unfortunately,

Scheme 1. Synthesis of γ-Lactones by the Cyclopropane Route



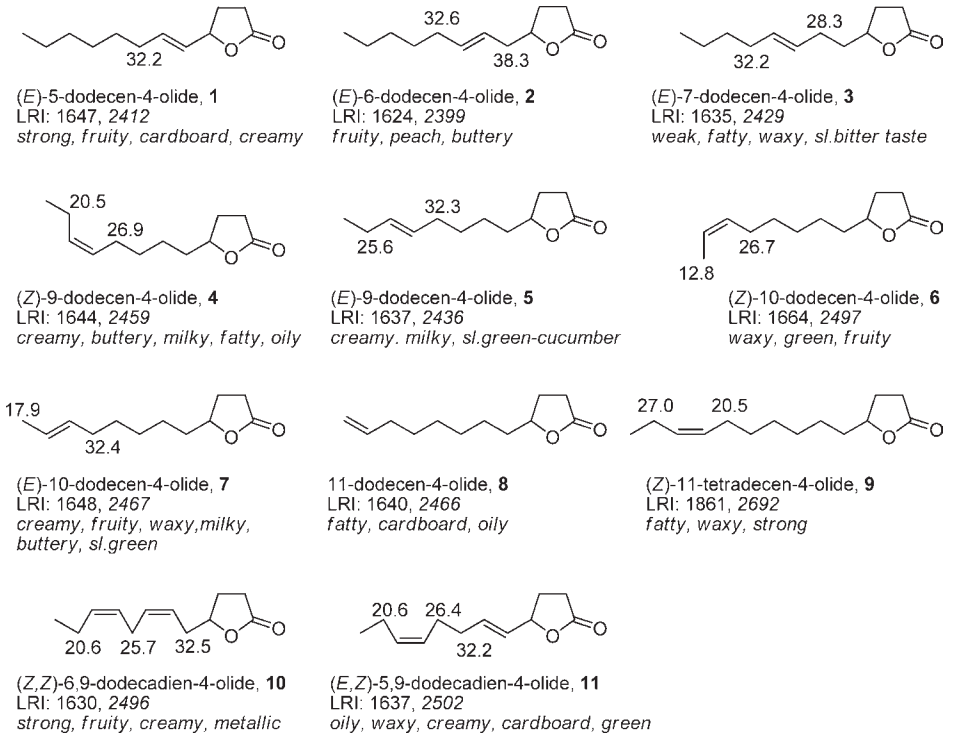


Figure 1. Structures of the γ-lactones synthesized, ^{13}C NMR shifts justifying double-bond configurations, LRIs (nonpolar, *polar*), and sensory evaluations.

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under the same reaction conditions, more reactive aldehydes such as (*Z*,*Z*)-3,6-nonadienal were rapidly degraded by the Lewis acid $TiCl_4$ and thus did not give the expected unsaturated lactones. Whether the aldehyde was added before (as in ref 13) or after the homoenolate had been formed did not change the outcome of the reaction. Nakamura et al.[13] describe the enhancement of the nucleophilicity of titanium homoenolate when it was modified with titanium alkoxides. In particular, $Ti(OtBu)_4$ should allow the homoenolate to react on ketones.[13] Thus, we formed the titanium homoenolate modified by $Ti(OtBu)_4$ in the absence of the aldehyde. Then the subsequent very slow addition of the aldehyde to this modified homoenolate gave satisfying results. It should be noted that this reaction does not directly give the lactone, but the hydroxy ester.[13] A saponification step on the crude product followed by an acid−base extraction was necessary to obtain the desired lactone. The whole process (Scheme 1) was used to prepare many lactones (Figure 1) from different aldehydes with moderate-to-good yields.

The reaction has not been fully optimized, and the moderate yields might be explained by the small scale and the purification step. The same yields were obtained from monounsaturated aldehydes or diunsaturated aldehydes (Figure 1, lactones **1**−**7**, **9**, **11**: yields 29−52%). 8-Nonenal (Figure 1, lactone **8**) gave a higher yield. The presence of one conjugated double bond in the aldehyde was tolerated (Figure 1, lactones **1** and **11**), but 2,4-nonadienal did not react. The case of (*Z*,*Z*)-3,6-nonadienal was special. Even if the aldehyde was added very slowly to the homoenolate solution, it was still significantly degraded. The reaction ran better on the impurities present in the starting material (6-nonenal, nonanal) than on the diunsaturated aldehyde, and thus the desired (*Z*,*Z*)-6,9-dodecadien-4-olide **10** was more difficult to purify from the complex reaction mixture.

As expected, the reaction did not modify the stereochemistry of the double bond(s) of the starting material. This was established from the downfield chemical shift observed in ^{13}C NMR for the carbon atoms next to the double bonds of (*Z*) configuration as compared to those of (*E*) configuration (Figure 1 and Materials and Methods). This shielding effect, sometimes called the *gamma gauche* effect,[15] suffers very few exceptions[16] and has been used to confirm the structure of dienic aldehyde pheromones.[17]

Thus, the titanium homoenolate route offers an easy access to unsaturated lactones with various double-bond positions and configurations. Considering that alternative synthesis of these lactones would have required many steps, the titanium homoenolate route with its moderate yields could be considered as rather efficient.

The sensory descriptors of the lactones given in Figure 1 were obtained from the evaluation by in-house flavorists who tasted the compounds at 20 ppm in water. The lactones synthesized in this work were used as reference material to confirm their possible natural occurrence in butter oil. This analytical work will be the subject of another publication.

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ABBREVIATIONS USED

GC-EI-MS, gas chromatography−electron impact−mass spectrometry; GC-FID, gas chromatography−flame ionization detection; NMR, nuclear magnetic resonance.; HR-ToF MS, high resolution time-of-flight mass spectrometry.

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