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Chemoenzymatic One-Pot Synthesis of γ-Butyrolactones

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Abstract: The synthesis of enantio- and diastereomerically pure γ-butyrolactones is described using a one-pot, two-enzyme cascade. Ethyl 2-methyl-4-oxopent-2-enoate (**2**) was reduced selectively first in a 1,4-reduction using the old yellow enzyme (OYE1) [EC 1.6.99.1] and consecutively in a 1,2-reduction by an alcohol dehydrogenase [EC 1.1.1.2].

Keywords: alcohol dehydrogenase; asymmetric catalysis; asymmetric synthesis; ene reductase; enzymes; reduction

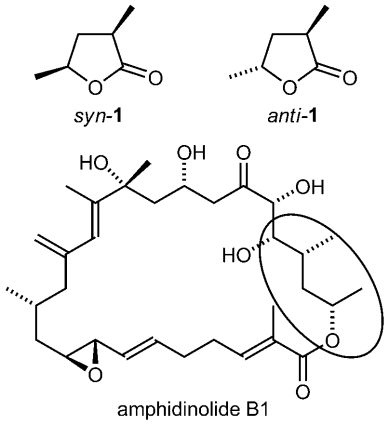


Figure 1. γ-Butyrolactones **1** – key building blocks in natural product syntheses, for example, for amphidinolide B1.

Although enzymes cannot replace every traditional heavy metal catalyst, biocatalysts are recognized as a promising alternative to improve the efficiency and sustainability of reactions.[1] It is not only basic chemicals that are produced by means of biotechnological processes: also key building blocks for natural product synthesis are increasingly synthesized using biocatalytical steps or sequences.[2] Recently, ene reductases have attracted considerable interest due to their ability to reduce C=C-double bonds bearing an electron-withdrawing group in a defined, well understood and stereoselective manner.[3] However, while high conversion and excellent selectivity were regularly observed, compared to alcohol dehydrogenases scalable applications for the synthesis beyond model compounds are scarce.

In this context and in view of our on-going interest in chemoenzymatic approaches towards lactones for natural products,[4] we also intended to approach γ-lactones.[5] Substituted enantiomerically pure γ-lactones are precursors for structural elements of various natural product families as well as pharmacologically active compounds. In particular, the subclass of α,γ-disubstituted γ-butyrolactones **1** has been utilized as key building block in a variety of syntheses, including natural targets such as milbemycin β_3, jasplakinolide, and the amphidinolides (Figure 1).[6] However, the syntheses described for building blocks **1** regularly depend on cost intensive starting materials or require multiple reaction and purification steps. Therefore, elaboration of novel, efficient routes to prepare 2,4-dimethylbutyrolactone (**1**) or its derivatives is highly desirable. Here, we present for the first time the chemoenzymatic synthesis of lactone **1** in a two-step, one-pot reaction from ethyl 2-methyl-4-oxopent-2-enoate (**2**) using an ene reductase (old yellow enzyme, OYE1) and different alcohol dehydrogenases (ADH) (Figure 2).

The first step in our route was the preparation of the substrate for the enzymatic transformations: γ-

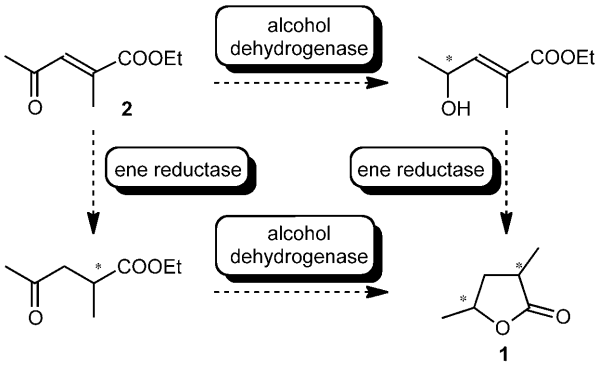
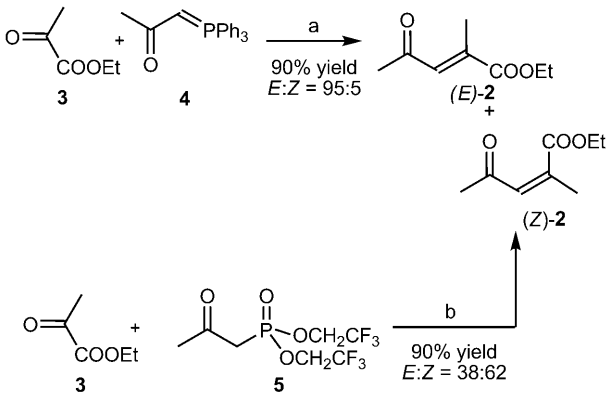


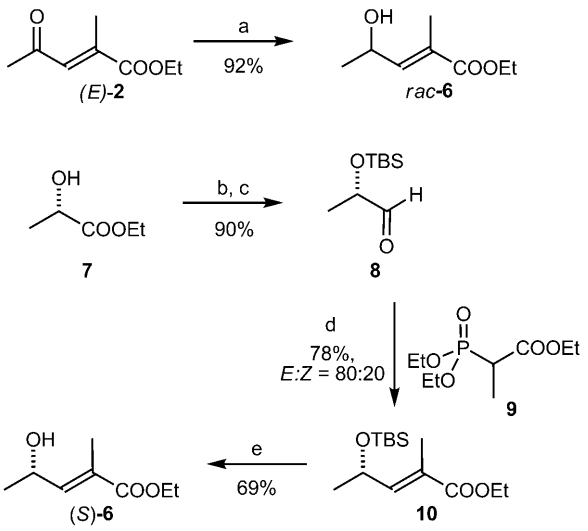
Figure 2. Routes towards lactones **1** from olefin **2**.

oxopentenoate **2** was readily available starting with a Wittig olefination of ethyl pyruvate (**3**) with phosphoranylideneacetone (**4**). The (*E*)-olefin **2** was obtained as the major isomer in the presence of the minor (*Z*)-olefin **2** in good yield (90%, *dr* 95:5).[7] Alternatively, employing the Still–Gennari protocol utilizing phosphonate **5**, the (*Z*)-product **2** was obtained as major component (90%, *dr* 38:62; Scheme 1).



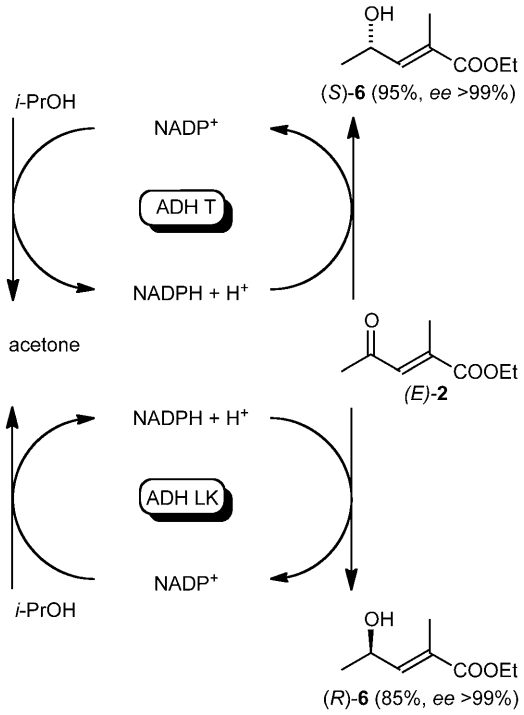
Scheme 1. Synthesis of γ-oxopentenoates **2**. *Reagents and conditions*: a) THF, 3 h, −78 °C to room temperature; b) KHMDS, 18-C-6, THF, 3 h, −78 °C to room temperature.

Next, we wished to investigate the enzymatic reduction. To enable reliable detection and assignment of product **6**, reference compounds were synthesized by conventional methods (Scheme 2). Racemic alcohol **6** was obtained from ketone (*E*)-**2** by $NaBH_4$ reduction (92%), whereas enantiomerically pure product (*S*)-**6** was synthesized from (*S*)-ethyl lactate (**7**). Aldehyde **8** was formed after TBS-protection (TBS: *tert*-butyldimethylsilyl) and selective reduction with DiBAlH (90% yield over two steps).[8] Olefination with phosphonate **9** yielded the silyl ether **10** (78%, *dr* 80:20) that was readily deprotected with TBAF forming the desired reference compound (*S*)-**6** (69%).[9] Gas chromatographic separation of the enantiomers was achieved using Lipodex G as chiral stationary phase (*vide infra*).



Scheme 2. Synthesis of reference compounds. *Reagents and conditions*: a) $NaBH_4$, Et_2O/MeOH, 0 °C, 30 min; b) TBSCl, DMAP, imidazole, CH_2Cl_2, 3 h, 0 °C to room temperature; c) DiBAlH, CH_2Cl_2, 3 h, −78 °C to room temperature; d) KHMDS, 18-C-6, THF, 3 h, −78 °C to room temperature; e) TBAF, THF, 2 h, room temperature.

Initial activity tests for the reduction of ketone (*E*)-**2** with a number of alcohol dehydrogenases indicated that highest conversion was observed using the enzymes ADH-T (from *Thermoanaerobacter* species recombinant in *Escherichia coli*) and ADH-LK (from *Lactobacillus kefir*).[10] The enantioselectivity as determined by GLC was excellent (*ee* > 99%) in both cases providing (*R*)- and (*S*)-alcohols **6**, respectively. The findings could be completely reproduced on a preparative scale now including the recycling of the cofactor with isopropyl alcohol (9 vol%; Scheme 3): reduction with ADH-T led to the (*S*)-enantiomer (*S*)-**6** (in 100 mM KP_i buffer, pH 7: 95%, *ee* > 99%) while ADH-LK provided the (*R*)-enantiomer (*R*)-**6** (in 100 mM KP_i buffer, pH 7: 85%, *ee* > 99%). The absolute configurations were confirmed by comparison of the retention times (see Figure 3) as well as the opti-



Scheme 3. Enzymatic reduction of ketone **2** on a preparative scale. *Reagents and conditions*: substrate **2** (6.4 mmol), KP_i buffer (100 mM, pH 7, 1 mM $MgCl_2$), NADP (0.032 mmol), ADH-solution (~40 U), 9 vol% *i*-PrOH, 30 °C, 24 h.

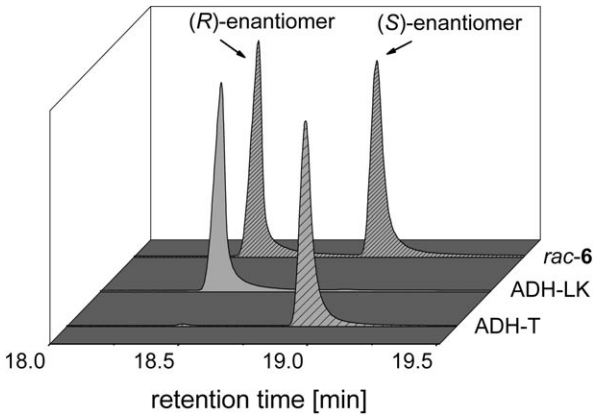
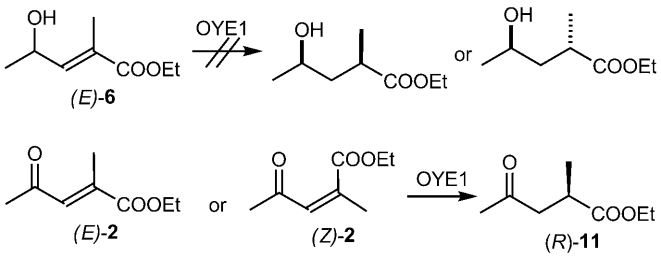


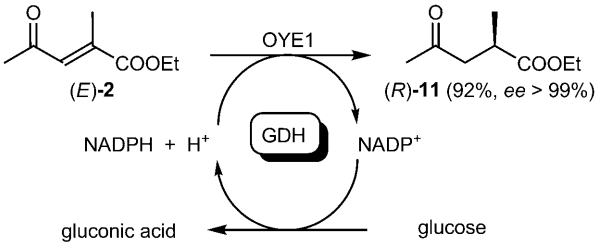
Figure 3. GLC trace for the enzymatic reduction of ketone (*E*)-**2** on a preparative scale. *Reaction conditions:* Lipodex G, H_2 (0.6 bar), 60 °C (5′ iso), 5 °C min^{-1} to 150 °C, (5′ iso) t_R [(*R*)-**6**] = 18.45 min, t_R [(*S*)-**6**] = 18.95 min.

cal rotations with literature data.[9a,11] It should be noted that these products have been regularly used in the synthesis of biologically active compounds see, e.g., refs.[9,11,12]

After the promising results obtained for the alcohol dehydrogenase catalyzed transformation, we focussed on the subsequent reduction of the C=C bond utilizing the flavoenzyme oxidoreductase from *Saccharomyces carlsbergensis* (OYE1 – old yellow enzyme 1; EC 1.6.99.1),[13] a known ene reductase.[2a–e] However, no conditions were found to reduce alcohol **6**, while the double-activated α,β-unsaturated alkenes **2** readily reacted (Scheme 4). We were surprised to find that independent of the olefin configuration the reduction led to the exclusive formation of the (*R*)-enantiomer (*ee* > 99%) of compound **11**. When performing the reaction on a preparative scale, obviously a cofactor regeneration system was required. The use of an ADH was ruled out, since the formation of alcohol **6** would be an expected side-product. Instead we utilized a glucose dehydrogenase (GDH; EC 1.1.1.47)[14] oxidizing glucose. After some optimization (amount of cofactor NADP/temperature), we could reduce the olefin **2** on a gram-scale at 30 °C with high conversion



Scheme 4. Enzymatic reduction of olefins **2** and **6** on an analytical scale. *Reagents and conditions*: KP_i buffer (50 mM, pH 7), 20 μL NADPH (50 mM), 100 μL glucose (500 mM), 2 μL GDH, 1 U OYE1, 30 °C, 600 rpm, 24 h.



Scheme 5. Enzymatic reduction of olefin **2** on a preparative scale. *Reagents and conditions*: Substrate **2** (6.4 mmol), KP_i buffer (100 mM, pH 7), NADP (0.064 mmol), glucose (250 mM), GDH (~10 U), OYE1 (~15 U), 30 °C, 250 rpm, 8 h.

(Scheme 5). The product **11** was isolated in good yield (92%) and excellent enantiomeric excess (*ee* > 99%; Figure 4).

Finally, the γ-butyrolactone **1** was obtained by subsequent enzymatic reduction of ketone **11** with an alcohol dehydrogenase. The bioreduction was performed using both ADH-LK and ADH-T, yielding the corresponding alcohols followed by spontaneous lactonization to the substituted γ-butyrolactones **1**. Based on the reported data, the assignment of configuration for the lactones (and hence also for the starting ketone **11**) was possible, proving that the ADH-LK gave the *anti*-product *anti*-**1** (60%, *ee* > 99%), whereas the *syn*-configurated lactone *syn*-**1** (80%, *ee* > 99%) was formed when using ADH-T (Scheme 6). In order to achieve the ultimate goal, a one-pot procedure was attempted with both biocatalytic steps – utilizing first the ene reductase followed by the alcohol dehydrogenase – being integrated in one sequence. $NADP^+$/GDH was used as the cofactor recycling system of choice for both enzymatic steps. As expected, the γ-butyrolactones *syn*-**1** and *anti*-**1**

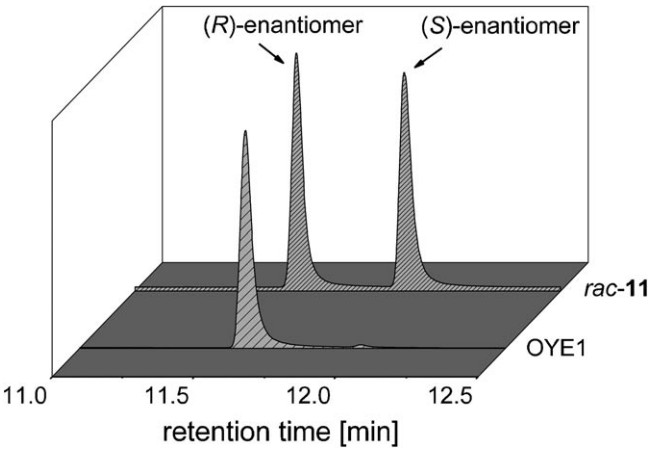
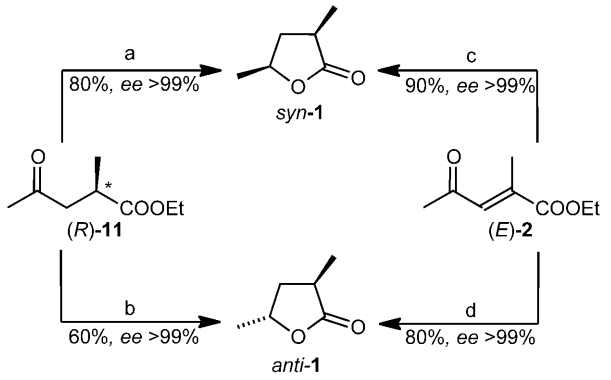


Figure 4. GLC trace for the enzymatic reduction of olefin (*E*)-**2** on a preparative scale. *Reaction conditions:* Lipodex G, H_2 (0.6 bar), 60 °C (5′ iso), 5 °C min^{-1} to 150 °C, t_R [(*R*)-**11**] = 11.60 min, t_R [(*S*)-**11**] = 11.95 min.



Scheme 6. Enzymatic reductions. *Reagents and conditions*: substrate **2** or **11** (6.4 mmol), a) KP_i buffer (100 mM, pH 7, 1 mM $MgCl_2$), NADP (0.064 mmol), 9 vol% *i*-PrOH, ADH-T solution (~70 U), 30 °C, 250 rpm; b) KP_i buffer (100 mM, pH 7, 1 mM $MgCl_2$), NADP (0.064 mmol), glucose (250 mM), GDH (~10 U), ADH-LK solution (~160 U), 30 °C, 250 rpm; c) KP_i buffer, NADP, glucose, OYE1 (~15 U), GDH (~10 U), 30 °C, 250 rpm, 12 h, then *i*-PrOH, ADH-T solution (~70 U), 24 h; d) KP_i buffer, NADP, glucose, OYE1 (~15 U), GDH (~10 U), 30 °C, 250 rpm, 12 h then ADH-LK solution (~160 U), GDH (~10 U), 24 h. For details of the one-pot procedures see Experimental Section.

were again synthesized in high enantiopurity (*ee* > 99%), but gratifyingly also in excellent yields (90% and 80%, respectively).

In conclusion, we have described a convenient chemoenzymatic method for the preparation of the two diastereoisomeric lactones **1** from enone **2** in good yields and enantiopurity in a one-pot set-up. The ene reductase catalyzed steps were shown to be scalable providing enantiomerically pure products in high yield. It should be noted that also the simple alcohol **6** is a highly desirable building block that was conveniently obtained by a direct enzymatic reduction.

Experimental Section

Representative Procedures for the One-Pot Reduction:

Synthesis of (2R,4S)-2,4-dimethylbutyrolactone (syn-1): Enone **2** (1 g, 6.4 mmol) was placed in 250-mL flask and 50 mL KP_i buffer (pH 7), NADP (50 mg, 0.064 mmol), 2.25 g glucose (250 mM), 10 μL GDH solution (~10 U in KP_i buffer, pH 7), 10 mg OYE (lyophilized powder, ~15 U) were added. The reaction was run for 12 h at 30 °C. Reaction pH was controlled through the automated addition of 1 M NaOH. After full conversion was detected (as determined by GLC), 200 μL ADH-T solution (~50% in glycerol, as supplied by Julich Chiral Solutions, 70 U) and 5 mL *i*-PrOH (9 vol%) were added. The reactions mixture was stirred at 30 °C and 250 rpm (quant. conversion as judged by GLC). After 48 h the products were extracted with Et_2O, the organic layer dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*n*-pentane:Et_2O, 80:20) to afford product *syn*-**1** as a colourless oil; yield: 670 mg (5.8 mmol, 90%); $[\alpha]_D^{20}$: −4.6 (*c* 1.1 in $CHCl_3$),[6c] 99% *ee* as determined by GLC [Lipodex G, H_2 (0.6 bar), 60 °C (5' iso), 5 °C min^{-1} to 150 °C (iso)]: (2*R*,4*S*)-**1**: t_R = 10.2 min; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (d, 3H, $^3J_{Me,2}$ = 7.1 Hz, Me), 1.42 (d, $^3J_{Me,4}$ = 6.2 Hz, 3H, Me), 1.49 (ddd, $^2J_{3a,3b}$ = 12.4 Hz, $^3J_{3a,2}$ = 12.1 Hz, $^3J_{3a,4}$ = 10.3 Hz,1H, 3-H_a), 2.50 (ddd, $^2J_{3b,3a}$ = 12.4 Hz, $^3J_{3b,2}$ = 8.3 Hz, $^3J_{3b,4}$ = 5.3 Hz,1H, 3-H_b), 2.68 (ddq, $^2J_{2,3a}$ = 12.1 Hz, $^3J_{2,3b}$ = 8.3 Hz, $^3J_{2,Me}$ = 7.1 Hz, 1H, 2-H), 4.48 (dqd, $^3J_{4,3a}$ = 10.3 Hz, $^3J_{4,Me}$ = 6.2 Hz, $^3J_{4,3b}$ = 5.3 Hz, 1H, 4-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 15.1 (Me at C-2), 20.9 (Me at C-4), 36.4 (C-2), 39.1 (C-3), 74.9 (C-4), 179 (C-1); IR (film): $\tilde{\nu}$ = 2977, 2935, 1767, 1455, 1388, 1350, 1180, 1122, 1043, 951, 872, 703 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 114 (3) [M^+], 99 (21) [$M-CH_3^+$], 70 (72) [$M-CO_2^+$], 55 (100) [$C_4H_7^+$].[6d]

Synthesis of (2R,4R)-2,4-dimethylbutyrolactone (anti-1): Enone **2** (1 g, 6.4 mmol) was placed in 250-mL flask and 100 mL KP_i buffer (pH 7), NADP (50 mg, 0.064 mmol), 4.50 g Glucose (250 mM), 10 μL GDH-solutions (~10 U in KP_i buffer, pH 7), 10 mg OYE (lyophilized powder, ~15 U). The reaction was run for 12 h at 30 °C. Reaction pH was controlled through the automated addition of 1 M NaOH. After full conversion was detected (as determined by GLC), 200 μL ADH-LK solution (~50% in glycerol, 160 U) and 10 μL GDH were added. The reaction mixture was stirred at 30 °C and 250 rpm (quant. conversion as judged by GLC) and worked up as described above; yield: 670 mg (5.8 mmol, 90%); $[\alpha]_D^{20}$: +36.5 (*c* 1.1 in $CHCl_3$),[6g] 99% *ee* as determined by GLC [Lipodex G, H_2 (0.6 bar), 60 °C (5' iso), 5 °C min^{-1} to 150 °C (iso)]: (2*R*,4*R*)-**1**: t_R = 10.1 min; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (d, 3H, $^3J_{Me,2}$ = 7.4 Hz, Me), 1.38 (d, 3H, $^3J_{Me,4}$ = 6.4 Hz, Me), 2.04 (ddd, $^2J_{3a,3b}$ = 12.8 Hz, $^3J_{3a,2}$ = 7.4 Hz, $^3J_{3a,4}$ = 7.4 Hz, 1H, 3-H_a), 2.08 (ddd, $^2J_{3b,3a}$ = 12.8 Hz, $^3J_{3b,2}$ = 8.8 Hz, $^3J_{3b,4}$ = 4.9 Hz, 1H, 3-H_b), 2.73 (dqd, $^3J_{2,3b}$ = 8.8 Hz, $^3J_{2,3a}$ = 7.8 Hz, $^3J_{2,Me}$ = 7.4 Hz, 1H, 2-H), 4.68 (dqd, $^3J_{4,3a}$ = 7.4 Hz, $^3J_{4,Me}$ = 6.4 Hz, $^3J_{4,3a}$ = 4.9 Hz, 1H, 4-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 15.7 (Me at C-2), 21.1 (Me at C-4), 34.0 (C-2), 37.1 (C-3), 74.6 (C-4), 179.9 (C-1); IR (film): $\tilde{\nu}$ = 2977, 2935, 1767, 1455, 1388, 1350, 1180, 1122, 1043, 951, 872, 703 cm^{-1}; MS (EI, 70 eV): *m/z* = 114 (3) [M^+], 99 (36) [$M-CH_3^+$], 70 (75) [$M-CO_2^+$], 55 (100) [$C_4H_7^+$].[15]

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