Allergenic α-Methylene-γ-butyrolactones. Stereospecific Syntheses of (+)- and (−)-γ-Methyl-α-methylene-γ-butyrolactones. A Study of the Specificity of (+) and (−) Enantiomers in Inducing Allergic Contact Dermatitis

Pierre Barbier and Claude Benezra*

Laboratoire de Dermato-Chimie, Associé au CNRS (LA 31), Universite Louis Pasteur de Strasbourg, Clinique Dermatologique, CHU de Strasbourg, 67091 Strasbourg, France. *Received December 30, 1981*

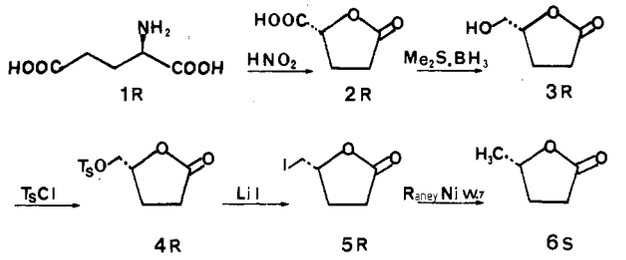
The enantiomers of γ-methyl-α-methylene-γ-butyrolactone have been prepared stereospecifically from (*R*)- and (*S*)-glutamic acid. Three groups of guinea pigs have been sensitized (Feund complete adjuvant technique) to the (+) isomer, the (−) isomer, and the (±) mixture. The animals have been tested with each of the enantiomers and with a mixture of the compounds. Only the (−) enantiomer showed some specificity: guinea pigs sensitized to this enantiomer react weakly to the other compound; in turn, animals sensitized to the (+) enantiomer react similarly to both antipodes. Interestingly, reaction to the (±) mixture in each group of guinea pigs was the *sum* of skin responses to the individual enantiomer. These results should be contrasted with sensitization to (+)- and (−)-frullanolides, sesquiterpene lactones for which strong stereospecificity was observed.

Many contact sensitizers exist in nature in one enantiomeric form only. For instance, Compositae plants contain only one of the two possible enantiomers of sesquiterpene lactones.[1] There are very few examples of different species of plants of the same genus containing both (+)-and (−) enantiomers. These include a liverwort, *Frullania* (Jubulaceae): *F. dilatata L.* contains (+)-frullanolide;[2] *F. tamarisci* contains (−)-frullanolide. Usnic acid occurs in nature in both (+) and (−) forms or as a (±) mixture.[3]

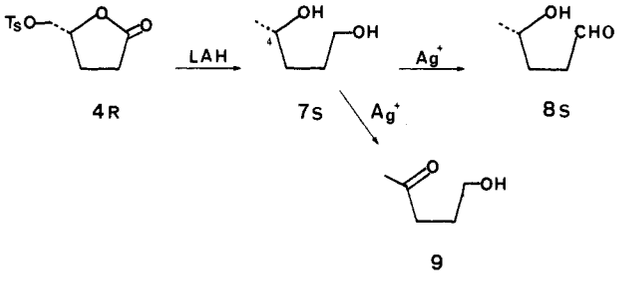
In most cases, therefore, direct comparison of the sensitizing power of (+) and (−) enantiomers is not feasible, simply because they do not coexist naturally. Is there a specificity associated with the (+) or (−) nature of the antipode in allergic contact dermatitis (ACD)? One could expect to observe such a difference, because it is well known that the *d*- and the *l*-enantiomers of biologically active compounds behave very differently in the organism and especially in ligand–receptors interactions (see, for instance, the morphine receptor case[4]). However, in ACD, only an indication of such a specificity has been reported in *clinical cases*: only *d*-usnic acid is reportedly sensitizing[5] (in six patients), while ACD to *Frullania* shows in several cases some stereospecificity (in 51 investigated patients, 21 reacted to *F. dilatata* and not to *F. tamarisci*).[6]

As a part of a continuing study of the mechanism of ACD, and in particular of ACD to α-methylene-γ-butyrolactones,[7] we have undertaken and describe here the preparation of (+)- and (−)-γ-methyl-α-methylene-γ-butyrolactones (or α-methylene-γ-valerolactones), whose racemates are already known but which have never been prepared in pure enantiomeric form, and the experimental sensitization of guinea pigs to each of them, looking for possible cross-reactions to them. We have also sensitized animals to pure (+)- and (−)-frullanolides, and the results show a strong stereospecificity in this case.[8]

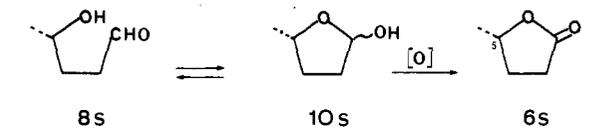
Scheme I



Scheme II



Scheme III



Chemistry. A number of syntheses of (±)-α-methylene-γ-butyrolactones have been described,[9] including the one-step preparation via the Reformatsky reaction of ethyl bromomethacrylate with acetaldehyde.[10]

Pure (+)- and (−)-γ-methyl-γ-butyrolactones have already been prepared from readily available optically pure starting materials (*R*)- and (*S*)-glutamic acids.[11] [Scheme I shows the preparation of (*S*)-γ-methyl-γ-butyrolactone with total retention of configuration]. We have modified

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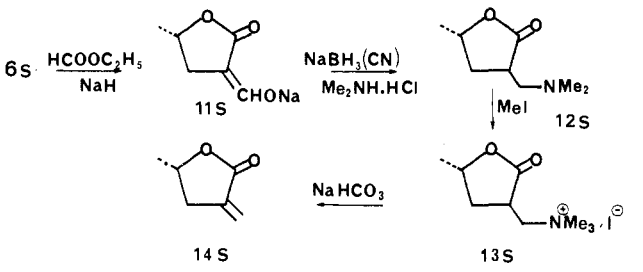
Scheme IV



Scheme I by reducing tosylate 4 with $LiAlH_4$, thus obtaining 1,4-pentanediol 7 (see Scheme II).

The stereospecificity of the scheme chosen was checked by comparing the ORD of (+)- and (−)-1,4-pentanediols that were obtained, respectively, from (−)- and (+)-glutamic acid. These diols were oxidized into γ-methyl-γ-butyrolactone using the silver carbonate on celite oxidation of diols as described for a number of lactones, including racemic γ-methyl-γ-butyrolactone (γ-valerolactone).[12]

This is a key step, since the chiral center 4 in compound 7 is involved. Silver carbonate only oxidizes alcohols into aldehydes or ketones, so that two products can (and do actually) form, the keto alcohol **9** or the aldehyde alcohol 8 (Scheme II).

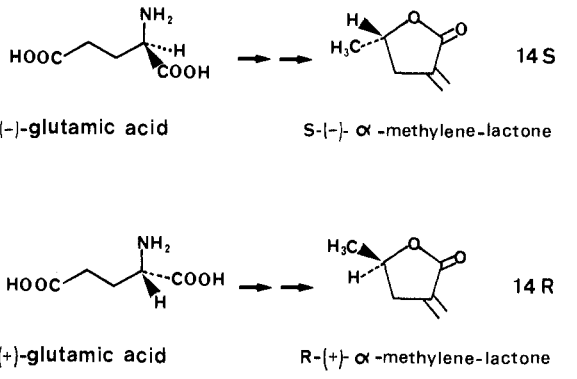
According to the accepted mechanism of γ-lactone formation from diols,[13] a hemiketal **10** (a lactol) is formed from aldehyde 8 and further oxidized by Ag_2CO_3 into lactone **6** (Scheme III). Such a mechanism implies *no change* in the configuration of chiral carbon-5 in compound **6**. In turn, the formation of ketone **9** naturally implies loss of the chiral center.

If the aldehyde–alcohol ⇄ lactol mechanism mentioned above is correct, one should get a γ-methyl-γ-butyrolactone of (*R*)-(−) configuration (when starting from the enantiomeric glutamic acid). This indeed is the case. We obtained (*R*)-(+)-γ-methyl-γ-butyrolactone with a $[\alpha]^{22}_D$ of +30° (*c* 18, $CHCl_3$), compared to a $[\alpha]^{23}_D$ of +30° (*c* = 0.85, CH_2Cl_2) for **6** obtained through the described Scheme I, and (*S*)-(−)-γ-methyl-γ-butyrolactone with a $[\alpha]^{20}_D$ of −30° (*c* 13, $CHCl_3$), compared to the $[\alpha]^{23}_D$ of −29.6 (*c* 1.29, CH_2Cl_2) in the literature. The rest of the synthesis involves the uneventful introduction of an α-methylene group onto a γ-lactone. Among the numerous available methods,[9] we chose the route illustrated in Scheme IV, based on the amino reduction of the sodium salt of hydroxymethylene-γ-lactone 11.[14]

Pure (+)- and (−)-γ-methyl-α-methylene-γ-butyrolactones **14R** and **14S** with an $[\alpha]^{20}_D$ of +34° (*c* 8.9, $CHCl_3$) and −33° (*c* 9.5, $CHCl_3$), respectively, were obtained from (*S*)-(+)- and (*R*)-(−)-glutamic acids, respectively (Scheme V). Absolute configurations are deduced from the starting glutamic acid.

Biological Assays. Four groups of six albino female Hartley guinea pigs, each weighing from 250 to 300 g, were sensitized as described by Klečak:[15] on alternate days, the hapten, emulsified in Freund's complete adjuvant (FCA), was injected intradermally (0.1 mL) in the shaved nuchal region of the animal (in all, three injections). The following

Scheme V



sensitizing solutions were used: (−)-α-methylene-γ-methyl-γ-butyrolactone (5%, w/v, in a 1:1 FCA–saline emulsion), (+)-α-methylene-γ-methyl-γ-butyrolactone (5%, w/v, under the same conditions), and the racemate of α-methylene-γ-methyl-γ-butyrolactone (10%, w/v, under the same conditions). After 15 days rest, the elicitation was conducted by an open epicutaneous test: 25 μL of a solution of the lactones in CH_2Cl_2 was deposited on the clipped and shaved flank of the animal (on a 2-cm^2 surface by a standard circular stamp). Tests were read at the 24th, using the following scale: 0 = no reaction; 0.5 = erythema covering part of the test area; 1 = erythema covering the whole test area; 2 = erythema and swelling of the test area; 3 = erythema and swelling going well beyond the test area.

Before any elicitation, irritation thresholds (primary toxicity) were determined on animals injected with 1:1 FCA–saline emulsion (same procedure as for sensitization). Pure isomers were nonirritating at the 2% concentration (same procedure as above for the elicitation).

Results and Discussion

Results are reported in the Table I. Some comments are in order. Concerning the *specificity* of (+)- and (−)-lactone **14S** and **14R**, respectively, in inducing ACD, the (+) enantiomer allows a better "discrimination" than the (−)- enantiomer. While eight of eight guinea pigs induced with the (+) enantiomer were actually sensitive to the (+) enantiomer (1.3 average skin reaction), only five out of these eight reacted to the (−) antipode (with a weaker 0.4 average skin reaction). In turn, all of the (−)-lactone-induced guinea pigs reacted equally well to the (+) or the (−) enantiomer. That this observed phenomenon is a real one is confirmed by the elicitation with a 2% (±) mixture: the average skin reaction is almost the sum of the tests with 1% (+)- and (−)-lactones [first line of Table I: the average skin reaction is 1.8, while the added (+) and (−) reaction is 1.7; second line: the average skin reaction is 1.9 for an expected 0.9 + 0.8 = 1.7 reaction). Since the clinical manifestation of ACD is the result of lymphocyte infiltration, it seems natural that the infiltrations produced by each enantiomer would be additive, provided *no saturation of the cells or of the receptors takes place.*

However, as illustrated by (±)-mixture-sensitized guinea pigs (third entry of Table I), the skin reaction to the (+) and the (−) enantiomer is already an important one (1.7 and 1.4) and there is a 2.0 reaction to the (±) mixture tested at 2.0%. Some saturation of the skin response seems to be taking place (one would have expected a 3.1 = 1.7 + 1.4 reaction). However, when a 1% (±) mixture is used, the observed average skin reaction is 1.5 (half of the 3.1 expected!).

The results (additivity of the skin response) leave no doubt concerning the reality of the observed phenomenon: induced sensitization to the (+) enantiomer seems to be

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Table I. Results of Open Epicutaneous Test on Sensitized Guinea Pigs

sensitization induced with[a]	(+)-lactone 14R					(−)-lactone 14S					(±) mixture: 14R + 14S (2%)					(±) mixture: 14R + 14S (1%)				
	skin tests intensity				no. of sensitive animals	skin tests intensity				no. of sensitive animals	skin tests intensity				no. of sensitive animals	skin tests intensity				no. of sensitive animals
	2[c]	1	0.5	0	av	2	1	0.5	0	av	2	1	0.5	0	av	2	1	0.5	0	av
(+)-lactone 14R	3	4	1	0	1.3	8/8	0	2	3	3	0.4	5/8	6	2	0	0	1.8	8/8	0	5	1	2	0.7	6/8
(−)-lactone 14S	0	5	3	0	0.8	8/8	0	7	1	0	0.9	8/8	7	1	0	0	1.9	8/8	0	7	1	0	0.9	8/8
(±) mixture	6	1	1	0	1.7	8/8	6	2	0	0	1.8	8/8	6	2	0	0	1.8	8/8	4	4	0	0	1.5	8/8
controls	0	0	0	4	0	0/4	0	0	0	4	0	0/4	0	0	0	4	0	0/4	0	0	0	4	0	0/4

[a] Each animal received three 0.1-mL injections (on each alternate days) of an emulsion made from a 1:1 mixture of Freund complete adjuvant (FCA) and saline and either 5% of the (−) enantiomer, 5% of the (+) enantiomer, or 10% of the racemate (5% of each antipode). [b] The animals were elicited after 2 weeks rest following the last injection: 0.25 mL of 1% [pure (+) or (−) enantiomer and (±) racemic mixture] or 2% [(±) racemic mixture] methylene chloride solution was deposited on a 2-cm² circular area, and tests were read every 24 h. [c] The number of animals with 2, 1, 0.5, and 0 reactions is shown. 0 = no reaction; 0.5 = erythema covering part of the test area; 1 = erythema covering the whole test area; 2 = erythema and swelling of the test area; 3 = erythema and swelling going well beyond the test area. [d] Calculated by adding the test intensities and dividing by the number of animals. [e] Controls received three 0.1-mL injections of a 1:1 FCA–saline emulsion on days 0, 2, and 4.

more *specific* than that to the (−) enantiomer. Also, although one cannot speak truly about real differences in sensitizing power of both enantiomers, the detailed results shown in Table I seem to show that the (+)-enantiomer-induced sensitization is apparently stronger. Since eight out of eight animals were sensitized in both (+) and (−) groups, the difference is only quantitative, and our conclusions will therefore be cautious.

Only a few clinical examples of complete stereospecificity to contact sensitizers have been described. These include *d*- and *l*-usnic acids. According to Mitchell,[5] only *d*-(+)-usnic acid is sensitizing. However, both (+)- and (−)-frullanolides **15** and **16**, sensitizing sesquiterpene lac-

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tones present in *Frullania dilatata* and *F. tamarisci*,[2] respectively, produce allergic contact dermatitis (ACD) in sensitive patients. Since these two species very often coexist in vicinal environments, the possibility of cosensitization ("multiple specific sensitization"[16]) cannot be excluded. Ducombs in Bordeaux[6] has, however, observed cases of patients allergic to *only one* (*F. dilatata*) of the two species. Nevertheless, the majority of the patients *react to both*.

The results mentioned above show some specificity of the (+)-α-methylene-γ-methyl-γ-butyrolactone **14R**. We have found high stereospecificity in the experimental induction of ACD in guinea pigs sensitized to each pure (+)- or (−)-frullanolide.[8] In the generally accepted mechanism of allergic contact dermatitis,[17] the hapten penetrates the skin, becomes bound to a protein carrier (which is taken up by the epidermal macrophage, the Langerhans cell), and is presented to the T-lymphocytes, triggering a number of further reactions that lead eventually to the contact dermatits observed.

The moderate specificity observed in the case of the small haptens (+)- and (−)-γ-methyl-α-methylene-γ-butyrolactones is to be contrasted to the high stereospecificity of the sesquiterpene frullanolides. It seems reasonable that in order to discriminate between the two diastereomeric hapten–protein (the carrier) complexes, the hapten moeity should be large enough.

Experimental Section

Infrared (IR) spectra were determined on a Beckmann Acculab spectrophotometer using $CHCl_3$ solutions; wavenumbers (reciprocal centimeters) are given. Proton nuclear magnetic resonance (NMR) spectra were recorded on Perkin-Elmer R24B (60 MHz) or R32 (90 MHz) spectrometer. Chemical shifts are reported as δ values in part per millions (ppm) relative to tetramethylsilane (δ 0.0) as an internal standard: coupling constants (J) are expressed in hertz. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter, using a 10-cm long quartz cell of 1-mL volume. Silica gel columns for chromatography utilized Merck

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silica gel 60, 70–230 mesh, AST11. The abbreviations used are as follows: H, hexane; EE, ethyl ether; EtOH, ethanol; THF, tetrahydrofuran; LAH, lithium aluminum hydride; br, broad; s, singlet; m, multiplet; d, doublet; t, triplet. By "usual workup" we mean extraction with a solvent (CH_2Cl_2 or EE) washing with water, 5% aqueous $NaHCO_3$ or HCl and water, drying over Na_2SO_4 (or $MgSO_4$), and removal of solvent.

(*S*)-(+)- and (*R*)-(−)-γ-[(Tosyloxy)methyl]-γ-butyrolactone (4S and 4R). Product **4S** was synthesized from (*S*)-(+)-glutamic acid (**1S**) as described[18] via the crystalline lactonic acid **2S**, which was reduced to (*S*)-(+)-γ-(hydroxymethyl)-γ-butyrolactone (**3S**) by borane–methyl sulfide complex. Tosylation of **3S** yielded the crystalline tosylate **4S**. The overall yield from **1S** was 36%. The same sequence of reactions starting from (*R*)-(−)-glutamic acid afforded (*R*)-(−)-γ-[(tosyloxy)methyl]-γ-butyrolactone (**4S**) with an overall yield from **1R** of 30%.

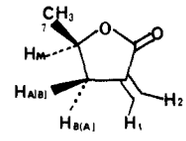
(*R*)-(−)- and (*S*)-(+)-1,4-Pentanediol (7R and 7S). The tosylate **4S** (35 g, 0.13 mol) dissolved in 150 mL of dry THF was added dropwise to a stirred ice-cooled suspension of LAH (14.75 g, 0.387 mol) in dry THF (500 mL, freshly distilled from LAH) under nitrogen. The mixture was heated under reflux for 3 h and then cooled with an ice bath, and the reaction was quenched by the careful addition of 15 mL of H_2O, 15 mL of 15% NaOH, and 45 mL of H_2O.[19] The ice bath was removed, and the mixture was stirred for 30 min. The white granular suspension was filtered, and the solid phase was washed with dry THF. The filtrate was dried ($MgSO_4$), evaporated to dryness, and purified by column chromatography (silica column, 350 g, elution with an 85:15 mixture of $CHCl_3$–EtOH) to give 10 g of **7R** (74% yield): $[\alpha]^{22}_D$ −11° (*c* 38, EtOH). The product was identical in all respects (IR and NMR) with an authentic sample of commercial racemic 1,4-pentanediol (Aldrich Chemical Co.). The enantiomer **7S** was prepared in the same way, with an overall yield of 70%: $[\alpha]^{22}_D$ +11° (*c* 44, EtOH) [lit[20] $[\alpha]^{16}_D$ for **7R**, −10.1° (EtOH); lit.[21] $[\alpha]^{22}_D$ for **7S** +6.1° (EtOH)].

(*R*)-(−)- and (*S*)-(+)-γ-Methyl-γ-butyrolactone (6R and 6S). The diol **7R** (3.8 g, 37 mmol) dissolved in 50 mL of $CHCl_3$ was added to a stirred suspension of Ag_2CO_3 on Celite (220 g, 0.8 mol, freshly prepared and dried for 5 h at 60 °C under 10^{-3} torr) in 1.5 L of $CHCl_3$. The mixture was refluxed for 12 h and then filtered by suction. The Celite cake was washed thoroughly with CH_2Cl_2. The filtrate was evaporated to dryness, and the residue was purified by column chromatography (100 g, elution EE–H, 1:1) to give lactone **6R** (1.46 g, 40% yield): $[\alpha]^{20}_D$ +30° (*c* 18, $CHCl_3$); IR 1765 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (d, 3 H, CH_3, J = 6.2 Hz), 2.0–2.6 (m, 4 H, CH_2CH_2), 4.65 [q, J = 2 Hz, 1 H, $CH_3CH(CH_2)_2COO$]. The enantiomer **6S** was prepared as described above from **7S** with an overall yield of 40%: $[\alpha]^{20}_D$ −30° (*c* 13, $CHCl_3$). Both enantiomers were obtained in a pure state (as shown by TLC and by NMR spectroscopy). They were identical (IR and NMR) with a (±) mixture, which was commercially available (Aldrich Chemical Co.).

(*R*)-(+)- and (*S*)-(−)-γ-Methyl-α-methylene-γ-butyrolactone (14R and 14S). A 55% NaH dispersion in mineral oil (0.736 g, 17 mmol) was washed three times with dry hexane and suspended in ethyl ether (20 mL, freshly distilled from LAH) under nitrogen. A mixture of **6R** (1.628 g, 16.3 mmol) and ethyl formate (1.206 g, 16.3 mmol, dried over K_2CO_3 and distilled from P_2O_5) was slowly added to the stirred suspension, immediately following the addition of absolute ethanol (0.1 mL); after stirring overnight at room temperature, the reaction mixture was rapidly filtered, and the resulting solid material was thoroughly washed with dry ethyl ether and evaporated to dryness to give the sodium salt **11R** as a light powder (2.04 g, 84% yield), which was used for the next step without further purification.

The sodium salt **11R** (2.04 g, 13.6 mmol) and dimethylamine hydrochloride (2.21 g, 27.2 mmol) were suspended in dry dimethoxyethane (130 mL, distilled from LAH) containing Linde 3Å molecular sieves (ca. 1.7 g); $NaCNBH_3$ (0.884 g, 13.6 mmol) was added, and the reaction mixture was stirred at room temperature under nitrogen for 24 h. The resulting brown slurry was filtered through a Celite pad, the filtrate was acidified to pH 2 with concentrated HCl, and the solvent was evaporated to dryness. Usual workup of the residue gave **12R** as a faintly yellow liquid (1.448 g, 68%), showing one spot on TLC. This crude was directly used for the next step.

Compound **12R** without any further purification was allowed to react with excess methyl iodide in methanol at room temperature for 24 h. The resulting colorless crystals (2.6 g, 9.2 mmol, 94% yield), obtained by filtration, were dried under vacuum and then added to a separatory funnel containing a mixture of 5% aqueous $NaHCO_3$ (17 mL, 10.1 mmol) and CH_2Cl_2 (30 mL) and shaken until all the solide phase had dissolved; the usual workup afforded a yellowish liquid. Percolation of this crude product through a short silica gel column (20 g, elution EE–H, 1:1) gave **14R** as a liquid (0.633 g, 5.65 mmol, 65% yield): $[\alpha]^{20}_D$ +34° (*c* 89, $CHCl_3$); IR 1765 (C=O), 1665 (CH_2=C) cm^{-1}, ^1H NMR ($CDCl_3$), $ABMX_3$, δ 1.42 (d, 3 H, CH_3CH_M, J = 6.0 Hz), 2.56 [ddt,



1 H, $H_{A(B)}$, J_{AB} = 16.80 Hz, $J_{AM(BM)}$ = 5.85 Hz, $J_{AH_1(BH_1)} = J_{AH_2(BH_2)}$ = 2.90 Hz], 3.13 [ddt, 1 H, HB(A), J_{BA} = 16.80 Hz, $J_{BM(AM)}$ = 7.35 Hz, $J_{BH_1(AH_1)} = J_{BH_2(AH_2)}$ = 2.62 Hz], 3.70 (ddq, 1 H, J = 2.67 Hz), 6.22 (large t, 1 H, J = 3.0 Hz).

(*S*)-(−)-α-Methylene-γ-butyrolactone (14S) was prepared in the same way as the (*R*)-(+) enantiomer in a 64% overall yield from lactone **6S**: $[\alpha]^{20}_D$ −33° (*c* 9.5, $CHCl_3$). (*R*)-α-Methylene-γ-valerolactone and (*S*)-α-methylene-γ-valerolactone were identical in all respects with (±)-γ-methyl-α-methylene-γ-valerolactone prepared from acetaldehyde and ethyl bromomethylmethacrylate in the presence of zinc.[7]

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