mol) of Xb in 35 mL of MeCN was added a slurry of 3.4 g (0.02 mol) of 4-chlorobenzoic acid hydrazide in 35 mL of MeCN. The mixture was stirred for 6.75 h at room temperature and the 4-chlorobenzoic acid hydrazide hydrochloride was removed by filtration. The filtrate was evaporated to dryness in vacuo and the residue was recrystallized from EtOH–$H_2O$ to give 4.2 g (87%) of the product. Anal. ($C_{12}H_6Cl_7N_5O$) C, H, N.

**4-Chlorobenzoic Acid 2-[4-[[3-(Dimethylamino)propyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]hydrazide (XIII).** To a solution of 1.7 g (0.0035 mol) of XII in 20 mL of MeCN was added 0.7 g (0.007 mol) of *N,N*-dimethyl-1,3-propanediamine and the solution was heated under reflux for 1 h. Filtration provided 1.4 g of a solid, which was recrystallized from EtOH to give 1.2 g (75%) of the product, mp 216–217 °C. Anal. ($C_{16}H_{19}Cl_4N_7O$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[4-[[5-(1-pyrrolidinyl)pentyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]guanidine (Compound IVg, Table II).** A mixture of 20.0 g (0.04 mol) of *N*-[4,6-bis(trichloromethyl)-1,3,5-triazin-2-yl]-*N'*-(4-chlorophenyl)guanidine and 12.5 g (0.08 mol) of 1-pyrrolidinepentanamine in 130 mL of $C_6H_6$ was heated under reflux for 30 min. The solution was allowed to cool to room temperature and the solid that formed was collected and recrystallized from EtOH–$H_2O$ to give 8.4 g of the product.

**(3,4-Dichlorophenyl)guanidine.** A mixture of 10.0 g (0.05 mol) of 3,5-dimethylpyrazole-1*H*-carboxamidamide nitrate and 8.1 g (0.05 mol) of 3,4-dichlorobenzenamine was gradually heated to 120 °C and held there for 30 min. The mixture was cooled to room temperature and slurried in petroleum ether. The resulting solid was dissolved in hot MeOH, and the solution was cooled and poured into a large volume of $Et_2O$. Recrystallization of the precipitate from MeCN provided 10.8 g (80%) of the product as the nitrate salt, mp 198–200 °C. Anal. ($C_7H_7Cl_2N_3 \cdot HNO_3$) H, N; C: calcd, 31.48; found, 30.90.

A slurry of 9.5 g (0.035 mol) of the salt in 100 mL of warm $H_2O$ was added to 100 mL of 50% NaOH solution. The warm mixture was stirred for 20 min and the solid was collected, washed with $H_2O$, and recrystallized from $C_6H_6$ to give 5.5 g (77%) of guanidine base.

***N*-[4,6-Bis(trichloromethyl)-1,3,5-triazin-2-yl]-*N'*-(3,4-dichlorophenyl)guanidine.** A solution of 5.5 g (0.027 mol) of (3,4-dichlorophenyl)guanidine and 11.8 g (0.027 mol) of Xa in 100 mL of $C_6H_6$ was heated under reflux for 8 h. The solvent was removed in vacuo and the residue was dried in vacuo at 25 °C for 24 h to provide 13.5 g (96.5%) of the product, mp 191–196 °C, which was used without further purification.

***N*-(4-Chlorophenyl)-*N'*-[4,6-bis(trichloromethyl)-1,3,5-triazin-2-yl]imidodicarbonimidic Diamide (XV).** To a solution of 3.5 g (0.01 mol) of Xb in 30 mL of MeCN was added a solution of 4.6 g (0.02 mol) of *N*-(4-chlorophenyl)imidodicarbonimidic diamide monohydrate in 65 mL of MeCN, and the mixture was stirred at room temperature for 3 h. Filtration removed the *N*-(4-chlorophenyl)imidodicarbonimidic diamide hydrochloride that formed, and the filtrate was concentrated in vacuo to a yellow semisolid. Recrystallization from EtOH–$H_2O$ provided 0.8 g (15%) of the product, mp 217–219 °C. Anal. ($C_{13}H_9Cl_7N_8$) C, H, N.

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# Stereospecificity in Allergic Contact Dermatitis to Simple Substituted Methylene Lactone Derivatives

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The enantiomers of β,γ-dimethyl- and β-methyl-α-methylene-γ-butyrolactones have been synthesized stereospecifically from glutamic acid and β-hydroxy isobutyric acid, respectively. Guinea pigs have been sensitized (Freund complete adjuvant technique) and tested to them. Both enantiomers of β-methyl lactone as well as (+)-β,γ-dimethyl lactone induced enantiospecific allergic contact dermatitis (ACD); in turn, (−)-β,γ-dimethyl lactone showed no specificity. An interpretation is proposed.

Configuration–activity relationships in bioactive compounds have been demonstrated in pharmacology and enzymology. Specificity exhibited by the reactions involved has been generally related to high specificity in binding to receptors.[1]

Similarly, in allergic contact dermatitis (ACD), it can be imagined that clonal selection leads to a subpopulation of T-lymphocytes specific of a given allergen.[2] One can thus expect at least stereoselectivity in the allergic activity of two enantiomers.

In fact, such enantiospecificity has been described for the first time by Mitchell in 1980 in the case of ACD to usnic acid.[3] Few cases of such enantiospecificity have been reported; they include ACD to frullanolides[4] and Dalber-

† On leave from Kao Corporation.

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0022-2623/87/1830-1948$01.50/0 

**Table I.** Results of Open Epicutaneous Tests

| sensitized[a] with | tested[b] with | skin reactions[c] 2 | 1 | 0.5 | 0 | mean rctn | no. of posit anim |
|---|---|---|---|---|---|---|---|
| (+)-1 | (+)-1 | 0 | 1 | 5 | 2 | 0.4 | 6/8 |
| | (−)-1 | 0 | 3 | 2 | 3 | 0.5 | 5/8 |
| (−)-1 | (+)-1 | 0 | 0 | 0 | 8 | 0 | 0/8 |
| | (−)-1 | 0 | 5 | 3 | 0 | 0.8 | 8/8 |
| (+)-11 | (+)-11 | 0 | 5 | 1 | 0 | 0.9 | 6/6[d] |
| | (−)-11 | 0 | 0 | 0 | 6 | 0 | 0/6[d] |
| (−)-11 | (+)-11 | 0 | 0 | 3 | 4 | 0.2 | 3/7[e] |
| | (−)-11 | 5 | 2 | 0 | 0 | 1.7 | 7/7[e] |

[a] Sensitized by the FCA method, using three injections (every other day) of a FCA/saline (1:1) emulsion of the hapten (2% w/v). [b] Open epicutaneous test using an ethanolic solution of the hapten (1% w/v). [c] The number of animals with 2, 1, 0.5, 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. [d] Two animals died during the experiments. [e] One animal died during the experiments.

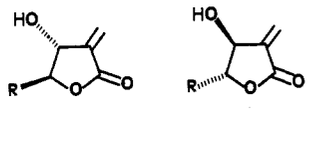



**Figure 1.** Structures of β-hydroxy lactones.

giones.[5] Some limitations appeared when ACD to (+)- and (−)-γ-methyl-α-methylene-γ-butyrolactones was studied: no enantiospecificity was observed.[6] It was proposed that the molecule was too small to show a difference in the large protein environment.

Two questions were in order: (a) how different must the epitopes of hapten–protein complex be to show specificity and (b) is the chiral center too far away from the probable site of protein attack (the methylene group) to make a difference between the resulting diastereomeric hapten–protein conjugates?

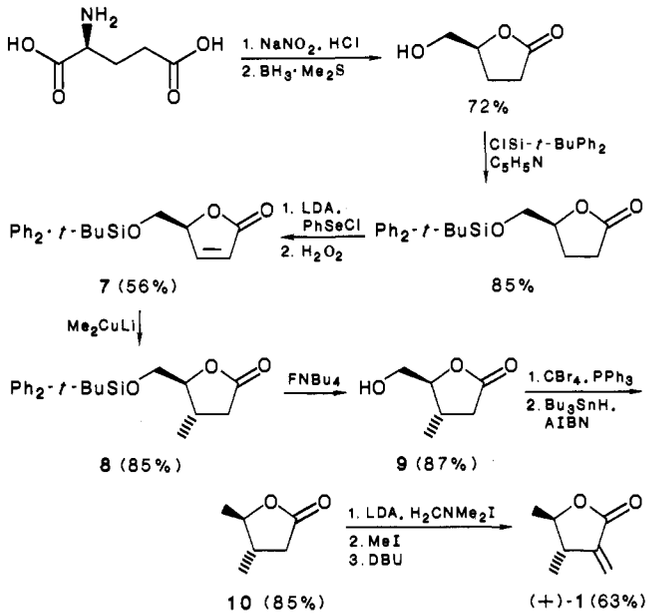
A partial answer to these questions was recently provided in our laboratory[7] where complete enantiospecificity was observed in ACD to (+)- and (−)-tulipalin B X,[8] as well as (+)- and (−)-5-methyltulipalin B Y[9] (Figure 1).

As part of a continuing study of the factors affecting such enantiospecificity, we have undertaken and describe here the preparation of both enantiomers of 4-methyltulipalin A and *trans*-4,5-dimethyltulipalin A, which have never been prepared in optically pure form, and the experimental sensitization of guinea pigs to each of them.

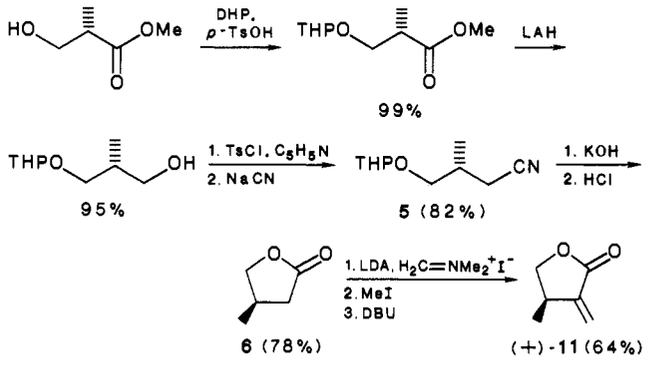
## Chemistry

The strategy for the synthesis of *trans*-β,γ-dimethyl-α-methylene-γ-butyrolactone is based on the well-known high diastereofacial differentiation exhibited by 5-substituted butenolides.[10] Lithium dimethyl cuprate added diastereospecifically to butenolide **7** to yield methyl lactone **8** in 85% yield. The required butenolide **7** is readily available either from L-glutamic acid (Scheme I[11]) or from

**Scheme I.** Synthesis of (+)-*trans*-β,γ-Dimethyl-α-methylene-γ-butyrolactone




**Scheme II.** Synthesis of (+)-β-Methyl-α-methylene-γ-butyrolactone




ribonolactone.[12] The 200-MHz $^1H$ NMR spectrum indicated a coupling constant of 5.6 Hz for $H_4$, $H_5$ corresponding to trans-4,5-substituted lactones.[13] Methyl lactone **8** was then desilylated with TBAF (87% yield). The resulting alcohol **9** was brominated with $CBr_4$ and

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$PPh_3$, and the resulting primary bromide was hydrogenolyzed with $Bu_3SnH$ and catalytic AIBN to give dimethyl lactone **10** in 85% yield. The methylene group was introduced by quenching the lithium enolate of lactone **10** with Eschenmoser's salt and subsequent Hoffmann degradation in 63% overall yield.[14]

The enantiomeric 4(*S*),5(*R*)-dimethyl lactone (−)-**1** was synthesized by identical procedures from D-glutamic acid.

Via Mori's procedure, methyl β-hydroxyisobutyrate was transformed in three steps (Scheme II) into nitrile **5** with an overall 82% yield (for *ent*-**5**, see ref 15). Hydrolysis of this nitrile with KOH, subsequent deprotection of the alcohol, and cyclization with HCl afforded lactone **6** in 78% yield. The methylene group was again introduced with Eschenmoser's salt in 64% yield.

Via the same procedure, 4(*S*)-methyl-α-methylene-γ-lactone (−)-**11** was obtained from commercially available 4(*S*)-methyl lactone *ent*-**6** in an identical yield.

## Results

The biological activity of compounds (+)-**1**, (−)-**1**, (+)-**11**, and (−)-**11** was determined by experimental skin sensitization of guinea pigs.[18] Results of epicutaneous tests are collected in Table I. Some comments are in order. The first striking result emerging from Table I is the stronger sensitizing activity exhibited by (−)-**11** (average 1.7 reaction) as compared to that of (+)-**11** (average 0.9 reaction). Secondly, guinea pigs sensitized with (−)-**11** reacted with the primary sensitizer with an average 1.7 reaction whereas they gave an average 0.2 reaction to (+)-**11**. On the other hand, animals sensitized with (+)-**11** reacted to (+)-**11** with an average 0.9 reaction and to (−)-**11** with a completely negative reaction. Clearly ACD to these simple, small butyrolactone derivatives seems to be enantiospecific.

Concerning the ACD induced by (+)-**1** and (−)-**1**, the specificity is much less clear. While (−)-**1**-sensitized animals showed complete enantiospecific ACD (0.8 average reaction to the primary sensitizer but 0 average reaction to (+)-**1**), (+)-**1**-induced animals reacted equally well to the (+) or the (−) enantiomer (0.5 average reaction to (−)-**1** and 0.4 average reaction to (+)-**1**). Thus, induced sensitization to the (−) enantiomer seems to be completely enantiospecific while sensitization to the (+) enantiomer seems to be nonspecific.

## Discussion

Recently, similar enantiospecific ACD has been demonstrated in our laboratory concerning skin reactions to hydroxy lactones X,[8] Y,[9] and Z[7] (Figure 1). On the other hand, ACD with α-methylene-γ-methyl-γ-butyrolactones was shown to be nonspecific. Other cases of stereospecific ACD have been described before with larger haptens, i.e., usnic acid,[3] dalbergiones,[5] and frullanolides.[4]

In the generally accepted mechanism of ACD, the hapten penetrates the skin, becomes bound to a protein carrier (which is taken up by the epidermal macrophage, the Langerhans cell[16]), and is presented to T-lymphocytes, triggering a number of reactions that eventually lead to the contact dermatitis observed. Since the protein itself is a pure enantiomer, the conjugates protein–optically pure haptens are diastereomeric and their properties and particularly the recognition by the T-lymphocyte receptors should be different.

The nonspecificity observed in the case of γ-valerolactones (contrasted to the stereospecificity for some larger allergens; cf. above) was tentatively assigned to the small size of the hapten moiety, leading to no discrimination between the two diastereomeric hapten–protein complexes.

The results reported here with (−)- or (+)-**11**, (−)-**1**, and β-hydroxy lactones[7] as well as the studies with the larger haptens cited above indicate that enantiospecific ACD cannot be solely related to the size of the hapten. These results contrast with the nonspecificity of ACD to methylenevalerolactones and seem to relate enantiospecificity to the proximity of the chiral center (or more generally the chiral pattern) with respect to the protein-bonding center (here α-methylene). Indeed, this is the case for all haptens (except (+)-**1**) known to induce enantiospecific ACD. Either a hydroxyl group (able to give H-bonds with protein moieties) or a methyl group (only able to show van der Waals interactions) at the chiral center and close to the attacked methylene group is sufficient to induce enantiospecific ACD. Analogies can be found in asymmetric synthesis. Indeed, the closer the inducing chiral center, the more efficient the asymmetric induction. Recently nucleophilic additions to hydroxy lactones Y[17] (using small cuprates or thiolates as nucleophiles) have been shown to be diastereoselective. By analogy, the protein–hapten complex formed with the *R* or the *S* isomer must therefore be very different.

## Experimental Section

**General Methods.** Proton NMR spectra were recorded either on a Perkin-Elmer 60-MHz spectrometer or where indicated on a Brucker 200-MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with respect to TMS as internal standard. Coupling constants (*J*) are expressed in hertz. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), and m (multiplet). Infrared spectra were obtained on a Beckman Acculab spectrometer using $CHCl_3$ solutions; peaks are reported in reciprocal centimeters. Melting points were determined on a Buchi-Tottoli 510 apparatus and are uncorrected.

Dry solvents were freshly distilled before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Toluene was distilled from sodium and degassed. Dichloromethane and acetonitrile were distilled from $P_2O_5$. All air- or moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon.

**5(*S*)-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4(*S*)-methyldihydro-2-furanone (8).** To a solution of lithium dimethyl cuprate prepared from MeLi (8.52 mL, 13.63 mmol; 1.6 M hexane) and CuI (1.30 g, 6.82 mmol) at 0 °C in $Et_2O$ (10 mL) was added at −20 °C a solution of the known butenolide **7** (2.00 g, 5.68 mmol) in $Et_2O$ (5 mL). The mixture was stirred for 40 min, quenched with saturated $NH_4Cl$ (20 mL), and extracted with $Et_2O$ (4 × 20 mL). The crude oil obtained after drying and condensation of the organic layer was flash chromatographed (AcOEt/hexane, 2:8) to afford lactone **8** (1.78 g, 85%): IR 1770 $cm^{-1}$; $^1H$ NMR (200 MHz) δ 7.66–7.36 (10 H, m, Ar *H*), 4.12 (1 H, dt, $J_t$ = 3.5, $J_d$ = 5.6, C*H*O), 3.87 (1 H, A part of a ABX, $H_6$, $J_{66'}$ = 11.5, $J_{65}$ = 3.4), 3.72 (1 H, B part of a ABX, $H_{6'}$, $J_{6'6}$ = 11.5, $J_{6'5}$ = 3.6), 2.84 (1 H, A part of a AB, $H_3$, $J_{33'}$ = 17.1, $J_{34}$ = 8.7), 2.59 (1 H, $H_4$, m), 2.18 (1 H, B part of a AB, $H_{3'}$, $J_{3'3}$ = 17.1, $J_{3'4}$ = 6.8), 1.14 (3 H, d, *J* = 6.8, Me), 1.07 (9 H, s, *t*-Bu); $[\alpha]_D^{20}$ = +31° (c 2.88, $CHCl_3$) (lit.[19] $[\alpha]_D$ = +30.5°).

**5(*S*)-(Hydroxymethyl)-4(*S*)-methyldihydro-2-furanone (9).** A solution of TBAF (6.9 mL, 6.9 mmol; 1 M THF) was added at 0 °C to a solution of lactone **8** (2.62 g, 6.3 mmol) in THF (20

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mL). After 5 min, the temperature was allowed to rise to 25 °C and stirring was continued for 30 min. The mixture was quenched at 0 °C with acetic acid (0.43 mL, 7.55 mmol). The solution was condensed and flash chromatographed (AcOEt/hexane, 9:1) to yield alcohol **9** (0.80 g, yield 87%): IR 3610, 3600–3200, 1780 $cm^{-1}$; $^1H$ NMR ($CHCl_3$ + MeOD, 200 MHz) $\delta$ 4.18–4.11 (1 H, m, C*H*O), 3.91 (1 H, A part of a ABX, $H_6$, $J_{66'}$ = 12.7, $J_{65}$ = 2.1), 3.67 (1 H, B part of a ABX, $H_{6'}$, $J_{6'6}$ = 12.7, $J_{6'5}$ = 4.0), 2.76 (1 H, A part of a AB, $H_3$, $J_{33'}$ = 16.9, $J_{34}$ = 8.4), 2.61–2.45 (1 H, m, C*H*Me), 2.22 (1 H, B part of a AB, $H_{3'}$, $J_{3'3}$ = 16.9, $J_{3'4}$ = 8.6), 1.17 (3 H, d, $J$ = 6.7, Me); $[\alpha]_D^{20}$ = +45° (c 2.04, EtOH).[10]

**4(*S*),5(*R*)-Dimethyldihydro-2-furanone (10).** To a mixture of alcohol **9** (0.70 g, 5.38 mmol) and $CBr_4$ (2.50 g, 7.53 mmol) in $CH_3CN$ (10 mL) was added, portionswise at 0 °C, $PPh_3$ (1.98 g, 7.53 mmol). The mixture was stirred overnight at 25 °C, condensed, and taken up in $Et_2O$ (20 mL). The suspension was filtered and the filtrate evaporated. The crude oil was dissolved in degassed toluene (10 mL), and $Bu_3SnH$ (1.43 mL, 5.38 mmol) and a crystal of AIBN were added. The solution is refluxed for 3 h, cooled, and cautiously evaporated. The crude liquid was flash chromatographed (hexane and then AcOEt/hexane, 2:8) to give lactone **10** (0.52 g; yield 85%): IR 1770 $cm^{-1}$; $^1H$ NMR $\delta$ 4.10 (1 H, dq, $J_q$ = 6, $J_d$ = 8, C*H*O), 3-2 (3 H, m, C*H*Me, $CH_2$COO), 1.35 (3 H, d, $J$ = 6, Me), 1.11 (3 H, d, $J$ = 6, Me); $[\alpha]_D^{20}$ = +56.9° (c 1.8, $CHCl_3$) (lit.[20] $[\alpha]_D$ = +56.8° (c 1.6, $CHCl_3$)).

**3-Methylene-4(*S*),5(*R*)-dimethyldihydro-2-furanone ((+)-1).** To a solution of LDA prepared as usual from diisopropylamine (0.25 mL, 1.8 mmol) and BuLi (1.09 mL, 1.6 M hexane) in THF (2 mL) was added at −78 °C a solution of lactone **10** (0.18 g, 1.6 mmol) in THF (2 mL). After 1 h of stirring, Eschenmoser's salt (0.45 g, 2.4 mmol) was added in one portion. The mixture was stirred 1 h at −78 °C and overnight at room temperature and evaporated. The residue was taken up in MeOH (15 mL), and MeI (2 mL) was added. The solution was stirred for 20 h at room temperature and evaporated. The remaining crystals were washed with ether and suspended in a mixture of aqueous 10% $NaHCO_3$ (4 mL) and $CH_2Cl_2$ (5 mL) until they dissolved. The solution was extracted with ether (5 × 20 mL) and the organic layer dried and cautiously condensed. The residue was flash chromatographed (AcOEt/hexane, 2:8) to yield methylene lactone (+)-1 (0.13 g, 63% yield): IR 1755 $cm^{-1}$; $^1H$ NMR $\delta$ 6.16 (1 H, d, $J$ = 3.5, C=C*H*), 5.50 (1 H, d, $J$ = 3.5, C=C*H*), 4.04 (1 H, dq, $J_d$ = 6, $J_q$ = 6, OCMe*H*), 2.8–2.3 (1 H, m, C*H*Me), 1.42 (3 H, d, $J$ = 6, Me), 1.21 (3 H, d, $J$ = 6, Me); $[\alpha]_D^{20}$ = +16.4° (c 1.10, $CHCl_3$). Anal. ($C_7H_{10}O_2$) C, H.

The 4*R*,5*S* enantiomer was synthesized by the same procedures, starting from D-glutamic acid. The spectral data of all intermediates were identical with those reported above. The optical rotations were as follows.

**5(*R*)-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4(*R*)-methyldihydro-2-furanone (*ent*-8):** $[\alpha]_D^{20}$ = −32.0° (c 2.96, $CHCl_3$).

**5(*R*)-(Hydroxymethyl)-4(*R*)-methyldihydro-2-furanone (*ent*-9):** $[\alpha]_D^{20}$ = −45.9° (c 1.35, EtOH).

**4(*R*),5(*S*)-Dimethyldihydro-2-furanone (*ent*-10):** $[\alpha]_D^{20}$ = 59.7° (c 2.06, $CHCl_3$).

**4(*R*),5(*S*)-Dimethyldihydro-2-furanone (*ent*-1):** $[\alpha]_D^{20}$ = −16.0° (c 1.00, $CHCl_3$).

(20) Najera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289–300.

**4(*R*)-Methyldihydro-2-furanone (6).** A solution of nitrile **5** (1.50 g, 8.2 mmol) in ethylene glycol (2 mL) was added to a solution of KOH (0.90 g) in water (1 mL). The mixture was refluxed for 6 h, cooled, acidified with concentrated HCl (1.5 mL), and heated at 100 °C for 15 min. After cooling, the mixture was diluted with AcOEt (60 mL), dried, and filtered over silica gel (10 g). The filtrates were condensed, and the residue was flash chromatographed (AcOEt/hexane, 3:7) to afford lactone **6** (0.64 g, 78%): IR 1775 $cm^{-1}$; $^1H$ NMR $\delta$ 4.6–3.6 (2 H, m, $CH_2O$), 2.9–1.9 (3 H, m, C*H*Me + $CH_2$COO), 1.14 (3 H, d, $J$ = 6, Me); $[\alpha]_D^{20}$ = +24.0° (c 3.32, $Et_2O$) (lit.[15] $[\alpha]_D$ = +22.97° (c 0.37, MeOH)).

**3-Methylene-4(*R*)-methyldihydro-2-furanone ((+)-11).** An identical procedure as for the synthesis of the dimethyl lactone was used with diisopropylamine (1.0 mL, 7.0 mmol) and BuLi (4.4 mL, 1.6 M in hexane) in THF (6 mL), lactone (0.64 g, 6.4 mmol) in THF (3 mL), Eschenmoser's salt (1.80 g, 9.6 mmol), MeOH (50 mL), MeI (5 mL), aqueous 10% $NaHCO_3$ (12 mL), and $CH_2Cl_2$ (15 mL). Flash chromatography (AcOEt/hexane, 25:75) yielded methylene lactone (+)-11 (0.46 g, 64% yield): IR 1760 $cm^{-1}$; $^1H$ NMR $\delta$ 6.20 (1 H, t, $J$ = 3.5, C=C*H*), 5.58 (1 H, $J$ = 3.5, C=C*H*), 4.7–3.6 (2 H, m, $CH_2O$), 3.5–2.9 (1 H, m, C*H*Me), 1.25 (3 H, d, $J$ = 7, Me); $[\alpha]_D^{20}$ = +73.3° (c 6.17, $CHCl_3$). Anal. ($C_6H_8O_2$) C, H.

Via exactly the same procedure, the *S* enantiomeric methylene lactone (−)-11 was obtained from commercially available (*S*)-β-methylbutyrolactone *ent*-6: $[\alpha]_D^{20}$ = −73.9° (c 6.20, $CHCl_3$).

**Biological Assays.** Albino Himalayan spotted Fullingsdorf (from Hoffman La Roche, Basel) female guinea pigs weighing from 300 to 500 g were sensitized as described by Klecak.[18] 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). After 15 days of rest the animals were boosted with one injection of the hapten in FCA. After 15 days more of rest, the elicitation was conducted by an open epicutaneous test (OET): 25 μL of an ethanolic solution of hapten was deposited on the shaved flank of the animal (on a 2-$cm^2$ surface with a standard circular stamp). Tests were read at 24 h with the following scale: 0 = no reaction, 0.5 = slight erythema not covering the whole test area, 1 = erythema covering all the test area, 2 = erythema plus swelling of the test area. Before any sensitization, irritation thresholds (primary toxicity) were determined on FCA-injected controls (same procedure as above for elicitation). Concentrations up to 1% (1) and 1% (11) in ethanol were nontoxic. Control groups of eight animals (FCA treated) were used in each experiment.

The Student's *t* test was used to assess the significance of the average skin reaction intensities, comparing each time two groups of animals: (a) sensitized vs. nonsensitized (control) guinea pigs, (b) in (+)-enantiomer-sensitized animals, comparison between tests with (+) and (−) enantiomers, and (c) in (−)-enantiomer-sensitized animals, comparison between tests with (+) and (−) enantiomers. The Student's *t* test was at the 0.05 level of significance for the results of all couples. The only exception was the result for (+)-1-sensitized animals, comparing tests with (+)- and (−)-1; the results in these groups showed no statistically significant difference.

**Registry No.** (+)-1, 110171-20-5; (−)-1, 110171-21-6; **5**, 110171-23-8; (+)-**6**, 65284-00-6; (−)-**6**, 64190-48-3; (*S*)-**7**, 99315-76-1; (*R*)-**7**, 110171-24-9; (+)-**8**, 103233-14-3; (−)-**8**, 110098-09-4; (+)-**9**, 81474-44-4; (−)-**9**, 85428-29-1; (+)-**10**, 90026-46-3; (−)-**10**, 110171-22-7; (+)-11, 62322-50-3; (−)-11, 110098-10-7.