Synthesis of Both Enantiomers of γ-Substituted α,β-Unsaturated γ-Lactones

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Optically active 4-substituted butanolides and but-2-enolides are present in a number of natural products and in particular are found in flavor components and in insect sex pheromones.[1] Furthermore but-2-enolides are useful and versatile chiral templates for the synthesis of biologically interesting compounds.[2] For these reasons several methods of preparation of optically active butenolides have been published either starting from available optically active materials[3] or through asymmetric synthesis of an appropriate precursor such as α-acetylenic alcohols,[4] hydroxy sulfoxides,[5] or epoxides.[6]

We recently reported that addition of organometallic species to the racemic lactol **2** can be highly stereoselective and give either one or the other diastereoisomer **3** or **4** depending on the reaction conditions.[7] We now report an application of this methodology to the synthesis of optically pure γ-substituted-α,β-unsaturated γ-lactones, starting from optically active lactone **1**, easily available via an enzymatic pathway.[8]

The procedure used is outlined in Scheme I.

The lactone **1** (ee ≥ 98%) was reduced with DIBAL in toluene to give the lactol **2** as a mixture of two diastereoisomers in the ratio 88:12. Then, addition of methyl triisopropoxytitanium or of *n*-butyl- and *n*-octylmagnesium bromide in diethyl ether to lactol **2** led respectively to the diastereoisomers **3a–c**, while addition of methyllithium or *n*-octylmagnesium bromide in THF gave the other diastereoisomers **4a,b**. The diastereoisomeric excesses were determined by ^{1}H NMR at 250 MHz: the two singlets due to the bridgehead protons were found at higher field ($\Delta\delta$ = 0.27–0.36) for **3** than for **4**. These diols were oxidized with Jones reagent, and the mixtures obtained were, if necessary, separated at this stage by column chromatography to afford pure lactones **5** or **6**. The endo or exo position of the R group could be easily deduced from ^{1}H NMR spectroscopy considering the different values of the geminal coupling constants $J_{H_AH_B}$ = 3.4 Hz for trans H_A,H_B in **5** and 7.8 Hz for cis H_A,H_B in **6**. Heated at 110 °C in refluxing toluene the tricyclic lactones extruded furan to give the corresponding butenolides (*R*)-**7** or (*S*)-**7** with excellent yields. The optical rotations found for these butenolides were equal or superior to the highest values of optical rotations reported in the literature, indicating a very high degree of optical purity (Table I). We were able to assign an enantiomeric excess ee > 95% to each enantiomer of β-angelica lactones [(*R*)-**7a** and (*S*)-**7a**] by ^{1}H NMR at 250 MHz with the aid of a chiral lanthanide shift reagent [Eu(hfc)$_3$]: for the molar ratio Eu(hfc)$_3$/butenolide = 0.4, the signals due to the methyl group of the racemic compound appeared as two doublets ($\Delta\delta$ = 2.5 Hz), while only one doublet could be observed in the same conditions for each enantiomer. Optically active saturated γ-lactones[11] could be easily obtained from butenolides **7** either by catalytic hydrogenation or by a Michael addition as illustrated by the synthesis of two naturally occuring compounds: γ-dodecanolactone and quercus lactone a.

γ-Dodecanolactone (8) is found in the pyrigidial glands of the rove beetle, and the pyrigidial secretion of this insect is believed to serve as a defensive function. The catalytic

Scheme I

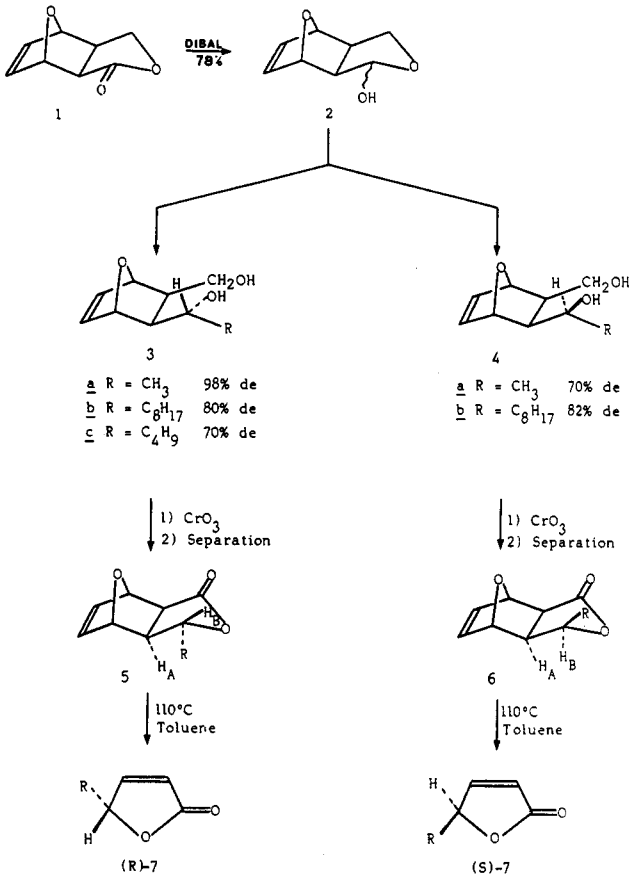

Table I. Optical Rotations of the Butenolides

R	$[\alpha]^{20}_D$ for (*R*)-7, deg		$[\alpha]^{20}_D$ for (*S*)-7, deg	
	measurd[a]	lit. (ref)	measurd	lit. (ref)
CH_3	−100.8	−95.9 (3)	+103.5	+93.8 (9) +101.4 (10)
C_8H_{17}	−66.1	−69.2 (4a)	+66.0	
C_4H_9	−101.0			

[a] In $CHCl_3$, but for R = C_8H_{17} in dioxane.

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(9) Ortuno, R. M.; Alonso, D.; Font, J. *Tetrahedron Lett.* **1986**, *27*, 1079.

(10) Kozikowski, A. P.; Mugrage, B. B.; Li, C. S.; Felder, L. *Tetrahedron Lett.* **1986**, *27*, 4817.

(11) For previous syntheses of optically active γ-lactones, see: Thijs, L.; Waanders, P. P.; Stokkingreef, E. H. M.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 332 and references therein.

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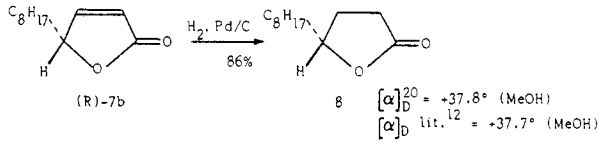
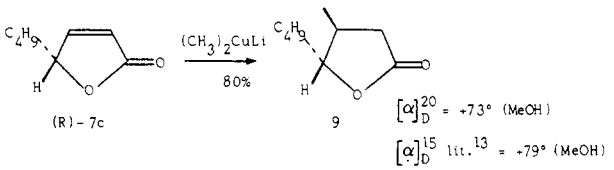
hydrogenation at atmospheric pressure of the butenolide (*R*)-**7b** gave (*R*)-γ-dodecanolactone (**8**) with high yield and an excellent enantiomeric purity attested by the value of its optical rotation.



(3*S*,4*R*)-3-Methyl-4-octanolide (9) or quercus lactone a has been identified in oak wood and aged spirits and wines. The trans configuration of the methyl and the butyl groups has been determined by ^1H NMR spectroscopy and its absolute configuration has been assigned on the basis of an empirical correlation.[13] Quercus lactone a could be easily obtained by a stereospecific 1,4-addition[14] of lithium dimethylcuprate to the butenolide (*R*)-**7c**.



This synthesis constituted the first both diastereo- and enantioselective synthesis of quercus lactone a[15,16] and allowed us to confirm the absolute configuration of this molecule.

Experimental Section

Melting points were determined with a Mettler FP-5 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 682 spectrophotometer. Mass spectra were obtained with a GC/MS R 10-10 spectrometer. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker AM 250 spectrometer with tetramethylsilane as an internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

4,10-Dioxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ol (2). A solution of (+)-(1*S*,2*R*,6*R*,7*R*)-**1** (6 g, 40 mmol) in toluene (400 mL) was cooled to −78 °C under an argon atmosphere. Then a 1 M solution of DIBAL in heptane (60 mL, 60 mmol) was added dropwise over a period of 1 h. The mixture was stirred at −78 °C for 3.5 h, and the excess of DIBAL was destroyed by the addition of a solution of isopropyl alcohol (2 M) in toluene (30 mL, 60 mmol). The solution was then allowed to warm to 0 °C, and water (1 mL), THF (100 mL), and a mixture of silica gel (15 g) and magnesium sulfate (30 g) were added successively. Between each addition the solution was stirred 30 min. After filtration, the solid was washed with THF (2 × 100 mL) and CH_2Cl_2 (100 mL). The filtrate was dried over magnesium sulfate and the solvent evaporated under reduced pressure to give 4.8 g (78% yield) of a mixture of (1*S*,2*R*,3*S*,6*R*,7*R*)- (88%) and (1*S*,2*R*,3*R*,6*R*,7*R*)-**2** (12%) as a white solid sufficiently pure to be used without further purification. IR ($CDCl_3$): 3700 (m); 3610 (m); 3430 (br, m); 3090 (w); 1650 (m); 1100 (s); 1040 (s) cm^{-1}. CIMS (NH_3), *m/e* (relative intensity): 172 (MNH_4^+, 5.7); 155 (MH^+, 6.1); 154 (M^+, 45.2); *137* ($MH^+ - H_2O$, 100). ^1H NMR (δ), major product: 2.40 (1 H, d, *J* = 7.5 Hz); 2.50 (1 H, m); 3.70 (1 H, m); 3.90 (1 H, dd, *J* = 9.2 Hz, *J'* = 2.0 Hz); 4.20 (1 H, dd, *J* = 9.3 Hz, *J'* = 7.3 Hz); 4.80 (1 H, s); 4.95 (1 H, s); 5.40 (1 H, s); 6.40 (2 H, s). Minor product: 2.67 (2 H, m); 3.50–3.60 (1 H, m); 3.70 (1 H, m); 4.02–4.11 (1 H, m); 4.70 (1 H, d); 5.00 (1 H, d); 5.38 (1 H, m); 6.45 (2 H, m).

(−)-(1*R*,2*R*,3*S*,4*S*,8*R*)-2-(Hydroxymethyl)-3-(1-hydroxyethyl)-7-oxabicyclo[2.2.1]hept-5-ene (3a).[17] To a solution of $ClTi(O\text{-}i\text{-}Pr)_3$ (2 mL, 8 mmol) in ether (20 mL) at −40 °C under an argon atmosphere was added dropwise a solution of methyllithium (1.6 M) in ether (5 mL, 8 mmol). The mixture was allowed to reach 0 °C, and a solution of lactol **2** (231 mg, 1.5 mmol) in THF (7 mL) was added dropwise. The mixture was stirred 15 min at 0 °C and 5 h at room temperature. Then it was hydrolyzed with a 10% aqueous HCl solution (20 mL). After separation of the organic layer, the aqueous phase was continuously extracted overnight with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and concentrated to give 374 mg of a white solid, which was purified by flash chromatography (ethyl acetate) to yield 184 mg of pure **3a** (72%). $[\alpha]^{20}_D$ −18.3° ($CHCl_3$, *c* 1); mp 123 °C. IR ($CDCl_3$): 3380 (vs); 3080 (w); 1025 (s); 900 (s) cm^{-1}. CIMS (NH_3), *m/e* (relative intensity): 188 (MNH_4^+, 42.7); *171* (MH^+, 100); 170 (M^+, 2.0). ^1H NMR (δ): 1.38 (3 H, d, *J* = 6.8 Hz); 1.66 (1 H, dd, *J* = 10.5 Hz, *J'* = 7.5 Hz); 1.99 (1 H, m); 3.88 (1 H, d, *J* = 5.5 Hz); 3.90 (1 H, d, *J* = 9.3 Hz); 4.00 (1 H, dq, *J* = 7.5 Hz, *J'* = 6.8 Hz); 4.50 (2 H, m); 4.62 (1 H, s); 4.72 (1 H, s); 6.42 (2 H, s).

(1*R*,2*R*,3*S*,4*S*,8*S*)-2-(Hydroxymethyl)-3-(1-hydroxyethyl)-7-oxabicyclo[2.2.1]hept-5-ene (4a). To a stirred suspension of lactol **2** (231 mg, 1.5 mmol) in ether (10 mL at −78 °C, under an argon atmosphere was added dropwise a solution of methyllithium (1.6 M) in ether (2.25 mL, 3.6 mmol). The reaction mixture was allowed to reach room temperature and was stirred for 2 h. The solution was decomposed by addition of a saturated ammonium chloride solution (20 mL). After separation of the organic layer, the aqueous phase was continuously extracted overnight with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, concentrated, and the residue purified by flash chromatography (ethyl acetate) to afford 230 mg (90% yield) of a mixture of diastereoisomers **4a** and **3a** in the ratio 83:17. The spectral data for **4a** follow. ^1H NMR (δ): 1.32 (3 H, d, *J* = 6.5 Hz); 1.70 (1 H, dd, *J* = 8.2 Hz, *J'* = 2.5 Hz); 1.85 (1 H, m); 3.83 (1 H, dd, *J* = 11.5 Hz, *J'* = 6.4 Hz); 3.96 (1 H, dd, *J* = 11.5 Hz, *J'* = 4.5 Hz); 4.08 (1 H, qd, *J* = 6.5 Hz, *J'* = 2.5 Hz); 4.30 (2 H, m); 4.93 (1 H, s); 5.08 (1 H, s); 6.42 (2 H, m).

(1*R*,2*R*,3*S*,4*S*,8*R*)-2-(Hydroxymethyl)-3-(1-hydroxy-*n*-nonyl)-7-oxabicyclo[2.2.1]hept-5-ene (3b). To a stirred solution of *n*-octylmagnesium bromide (20 mmol) in ether (30 mL) was added at 0 °C 462 mg (3 mmol) of lactol **2**. The reaction mixture was stirred 6 h at 0 °C and was then allowed to reach room temperature overnight. After addition of a saturated ammonium chloride solution (30 mL) the organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and the residue purified by flash chromatography (ether) to afford 700 mg (87% yield) of a mixture of **3b** (90%) and **4b** (10%). The spectral data for **3b** follow. IR (neat): 3340 (vs); 3080 (w); 1040 (s); 900 (s) cm^{-1}. ^1H NMR (δ): 0.87 (3 H, t); 1.18–1.57 (14 H, m); 1.72 (1 H, dd, *J* = 10.3 Hz, *J'* = 7.8 Hz); 1.97 (1 H, m); 3.50 (2 H, m); 3.76–4.00 (3 H, m); 4.61 (1 H, s); 4.74 (1 H, s); 6.37 (2 H, s).

(1*R*,2*R*,3*S*,4*S*,8*R*)-2-(Hydroxymethyl)-3-(1-hydroxy-*n*-pentyl)-7-oxabicyclo[2.2.1]hept-5-ene (3c). As described above, *n*-butylmagnesium bromide led to a mixture of **3c** (85%) and **4c** (15%): yield of purified product, 446 mg (70%). The spectal data for **3c** follow. IR (neat): 3400 (vs); 3080 (w); 1020 (s); 900 (s) cm^{-1}. CIMS (NH_3), *m/e* (relative intensity): 230 (MNH_4^+, 11.4); *213* (MH^+, 100); 212 (M^+, 1.8). ^1H NMR (δ): 0.92 (3 H, t); 1.27–1.60 (6 H, m); 1.72 (1 H, dd, *J* = 10.3 Hz, *J'* = 7.7 Hz); 1.98 (1 H, m); 3.76–4.00 (3 H, m); 4.30 (2 H, m); 4.63 (1 H, s); 4.75 (1 H, s); 6.38 (2 H, s).

(1*R*,2*R*,3*S*,4*S*,8*S*)-2-(Hydroxymethyl)-3-(1-hydroxy-*n*-nonyl)-7-oxabicyclo[2.2.1]hept-5-ene (4b). To a stirred solution of *n*-octylmagnesium bromide (30 mmol) in THF (30 mL) at 0 °C was added 960 mg (3 mmol) of ZnI_2. After 15 min at 0 °C a solution of lactol **2** (462 mg, 3 mmol) in THF (20 mL) was added dropwise. The solution was stirred 3 h at 0 °C and 2 h at room

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(14) Vigneron, J. P.; Meric, R.; Dhaenens, M. *Tetrahedron Lett.* **1980**, *21*, 2057.
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(16) Optically active quercus lactone has been already prepared either by resolution or by chromatographic separation of diastereoisomers: (a) Günther, C.; Mosandl, A. *Liebigs Ann. Chem.* **1986**, 2112. (b) Marino, J. P.; de la Prandilla, R. F. *Tetrahedron Lett.* **1985**, *26*, 5381.
(17) Diastereoisomeric mixtures of racemic diols **3** + **4** and lactones **5** + **6** have already been prepared without any stereochemical determination: Grandguillot, J. C.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1979**, 325.

temperature. After addition of a saturated ammonium chloride solution (30 mL), the organic layer was separated, the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with a saturated sodium thiosulfate solution (50 mL), dried over magnesium sulfate, and concentrated. The residue was purified by chromatography on silica gel (ether) to give 580 mg (72% yield) of a mixture of diastereoisomers **4b** (91%) and **3b** (9%). The spectral data for **4b** follow. ^{1}H NMR (δ): 0.88 (3 H, t); 1.24–1.65 (14 H, m); 1.72 (1 H, dd, J = 8.4 Hz, J' = 1.5 Hz); 1.82 (1 H, m); 3.68–4.08 (5 H, m); 4.92 (1 H, s); 5.01 (1 H, s); 6.38 (2 H, m).

General Procedure for the Oxidation of Diols 3 and 4. To a stirred solution of the diol (1 mmol) in acetone (10 mL), kept at 0 °C, was added dropwise 1.5 mL of Jones reagent (prepared by dissolution of CrO_3 (2 g, 20 mmol) in water (11.5 mL) and concentrated H_2SO_4 (3.5 mL)). The reaction mixture was allowed to reach room temperature and stirred for 45 min (if necessary, a few drops of Jones reagent were added in order to obtain a persistent orange coloration). The excess of oxidant was then destroyed by addition of isopropyl alcohol. The solution was filtered. The filtrate was concentrated, and the residue was extracted with CH_2Cl_2 (10 mL). The solid was dissolved in water (15 mL), and the aqueous layers were extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate (30 mL) and water (30 mL). The organic layer was dried over magnesium sulfate and concentrated. The crude lactones were purified and separated from the minor diastereoisomer by chromatography on silica gel [R = CH_3, ether; R = C_4H_9, ether–hexane (80–20); R = C_8H_{17}, ether–hexane (60–40)].

(−)-(1*R*,2*S*,5*R*,6*S*,7*S*)-4,10-Dioxa-5-methyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (5a). Yield, 63%; $[\alpha]^{20}_D$ −120° ($CHCl_3$, c 0.5). IR (neat): 3080 (w); 1770 (vs); 1200 (s); 1020 (s) cm^{-1}; CIMS (NH_3), m/e (relative intensity): 184 (MNH_4^+, 5.8); 166 (M^+, 0); *116* (100). ^{1}H NMR (δ): 1.44 (3 H, d, J = 6.5 Hz); 2.31 (1 H, dd, J = 7.8 Hz, J' = 3.4 Hz); 2.88 (1 H, d, J = 7.8 Hz); 4.50 (1 H, qd, J = 6.5 Hz, J' = 3.3 Hz); 5.00 (1 H, s); 5.26 (1 H, s); 6.44 (2 H, m). Anal. Calcd for $C_9H_{10}O_3$: C, 65.06; H, 6.02. Found: C, 65.08; H, 6.32.

(−)-(1*R*,2*S*,5*R*,6*S*,7*S*)-4,10-Dioxa-5-*n*-octyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (5b). Yield, 38%; mp 55.5 °C; $[\alpha]^{20}_D$ −56° ($CHCl_3$, c 1). IR ($CDCl_3$): 3070 (w); 1770 (vs); 1190 (s) cm^{-1}. CIMS (NH_3), m/e (relative intensity): 282 (MNH_4^+, 68.3); 265 (MH^+, 0.4); 264 (M^+, 0); *214* (100). ^{1}H NMR (δ): 0.89 (3 H, t); 1.23–1.78 (14 H, m); 2.33 (1 H, dd, J = 7.8 Hz, J' = 3.4 Hz); 2.83 (1 H, d, J = 7.8 Hz); 4.34 (1 H, m); 4.96 (1 H, s); 5.28 (1 H, s); 6.44 (2 H, m). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.73; H, 9.09. Found: C, 72.81; H, 9.30.

(−)-(1*R*,2*S*,5*R*,6*S*,7*S*)-4,10-Dioxa-5-*n*-butyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (5c). Yield, 35%; $[\alpha]^{20}_D$ −69° ($CHCl_3$, c 0.5); IR (neat): 3090 (w); 1760 (vs); 1200 (s); 1020 (s) cm^{-1}. CIMS (NH_3), m/e (relative intensity): *226* (MNH_4^+, 100); 209 (MH^+, 8.5); 208 (M^+, 0.3); *158* (100). ^{1}H NMR (δ): 0.92 (3 H, t); 1.25–1.50 (4 H, m); 1.60–1.77 (2 H, m); 2.32 (1 H, dd, J = 7.8 Hz, J' = 3.4 Hz; 2.83 (1 H, d, J = 7.8 Hz); 4.33 (1 H, m); 4.96 (1 H, s); 5.26 (1 H, s); 6.43 (2 H, m). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.92; H, 8.01.

(−)-(1*R*,2*S*,5*S*,6*S*,7*S*)-4,10-Dioxa-5-methyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (6a). Yield, 31%; mp 124 °C; $[\alpha]^{20}_D$ −132° ($CHCl_3$, c 0.5). ^{1}H NMR (δ): 1.49 (3 H, d, J = 6.5 Hz); 2.60 (1 H, dd, J = J' = 7.8 Hz); 2.91 (1 H, d, J = 7.8 Hz); 4.82 (1 H, dq, J = 7.8 Hz, J' = 6.5 Hz); 5.18 (1 H, s); 5.26 (1 H, s); 6.45 (2 H, m).

(−)-(1*R*,2*S*,5*S*,6*S*,7*S*)-4,10-Dioxa-5-*n*-octyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (6b). Yield, 29%; mp 86.5 °C; $[\alpha]^{20}_D$ −121° ($CHCl_3$, c 0.975). ^{1}H NMR (δ): 0.87 (3 H, t); 1.17–1.75 (14 H, m); 2.58 (1 H, dd, J = J' = 7.8 Hz); 2.90 (1 H, d, J = 7.8 Hz); 4.58 (1 H, m); 5.16 (1 H, s); 5.26 (1 H, s); 6.44 (2 H, m).

General Procedure for the Thermolysis of Lactones 5 and 6. A solution of lactone (1 mmol) in toluene (3 mL) was heated under reflux (bath temperature: 120 °C) for 3 h. The solutions were directly chromatographed on silica gel (20 g) [ether–hexane (60–40)] affording butenolides (−)-(*R*)-**7(a–c)** and (+)-(*S*)-**7(a,b)** with 90–96% yields.

Spectal data of each butenolide are in good agreement with those given in the literature.[5b,16]

(+)-(*R*)-γ-Dodecanolactone (8). To a stirred suspension of 10 mg of 10% palladium on coal in ethanol (3 mL) under an hydrogen atmosphere was added 98 mg (0.5 mmol) of butenolide (−)-(*R*)-**7b** in ethanol (2 mL). When the required amount of hydrogen had been taken up (11.2 mL), the catalyst was removed by filtration. The filtrate was then concentrated, and the residue was purified by chromatography on silica gel [ether–hexane (50–50)] to yield 85 mg (86%) of lactone 8. $[\alpha]^{20}_D$ +37.8° (MeOH, c 1). IR (neat): 1780 (vs); 1180 (s); 1130 (m); 1020 (m) cm^{-1}. MS, m/e (relative intensity): 198 (M^+, 0); 180 ($M^+ - H_2O$, 0.8); *85* (100); 84 (24.6); 56 (10.2); 55 (14.0); 41 (11.8). ^{1}H NMR (δ): 0.90 (3 H, t); 1.20–1.95 (15 H, m); 2.24–2.42 (1 H, m); 2.55 (2 H, dd, J = 9.7 Hz, J' = 6.7 Hz); 4.51 (1 H, m).

(+)-(3*S*,4*R*)-3-Methyl-4-octanolide (9). To a stirred solution of lithium dimethylcuprate (2.5 mmol; prepared from addition of a solution of methyllithium (1.5 M) in ether (3.3 mL, 5 mmol) to CuI (525 mg, 2.5 mmol) at −20 °C) in ether (10 mL) was added dropwise a solution of (−)-(*R*)-**7c** (70 mg, 0.5 mmol) in ether (5 mL) at −60 °C. The reaction mixture was allowed to reach room temperature over a period of 2 h. Then the solution was hydrolyzed by addition of a 10% aqueous HCl solution (5 mL). The resulting mixture was filtered on Celite, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified by chromatography on silica gel [ether–hexane (50–50)] to yield 62 mg (80%) of **9**. $[\alpha]^{20}_D$ +72.8° (MeOH, c 1). Spectral data are in good agreement with those given by Günther.[15a]

Registry No. (+)-**1**, 104485-85-0; (3*S*)-**2**, 110013-05-3; (3*R*)-**2**, 110013-06-4; **3a**, 110013-07-5; **3b**, 110013-09-7; **3c**, 110013-11-1; **4a**, 110013-08-6; **4b**, 110013-10-0; **4c**, 110013-12-2; **5a**, 110043-13-5; **5b**, 110013-13-3; **5c**, 110013-14-4; **6a**, 110013-15-5; **6b**, 110013-16-6; (−)-**7a**, 62322-48-9; (+)-**7a**, 92694-51-4; (−)-**7b**, 74841-72-8; (+)-**7b**, 93528-05-3; **7c**, 110013-17-7; **8**, 69830-91-7; **9**, 80041-01-6; *n*-octylmagnesium bromide, 17049-49-9; *n*-butylmagnesium bromide, 693-03-8.

Preparation and Reactions of Trianions from the Dimethylphenols

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Many aromatics containing primary alkyl groups are best prepared by two-step one-pot sequences consisting of (1) dimetalating readily available aromatics such as the xylenes[1] and the cresols[2] in the benzylic positions to give delocalized dianions such as **1** and **2** (Chart I) and (2) adding electrophiles or oxidizing agents; such aromatics cannot be readily prepared by Friedel–Crafts reactions due to carbonium ion rearrangements and orientation limitations. All three isomeric *tri*anions **3** have also been prepared[3–5] (the 1,3,5-isomer, with the largest resonance stabilization,[5] in 86% yield), and we now wish to report efforts to prepare the corresponding trianions containing one and two oxygens, i.e., trianions **4** from the dimethylphenols and trianions **5** from the dihydroxytoluenes. While only the

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