Chiral Synthesis via Organoboranes. 39. A Facile Synthesis of γ-Substituted-γ-butyrolactones in Exceptionally High Enantiomeric Purity

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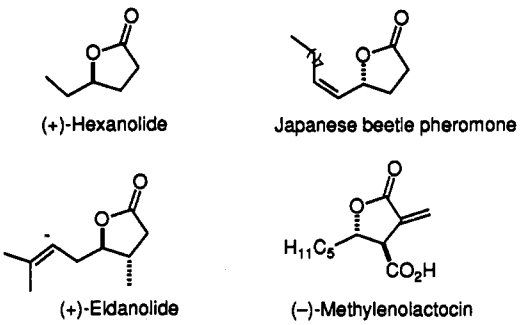
Optically active homoallylic alcohols of exceptionally high enantiomeric purity (98–≥99% ee) readily available via asymmetric allylboration were converted into *p*-nitrobenzoate esters and subjected to hydroboration followed by oxidation with CrO_3 in aqueous acetic acid (10% H_2O) to obtain the corresponding carboxylic acids with the same number of carbon atoms. The protecting ester group was hydrolyzed and the product lactonized *in situ* to the γ-substituted γ-butyrolactones **5** (R = Me, Pr, *i*-Pr, *t*-Bu, Ph, (*E*)-CH=CHCH$_3$) usually without racemization and in good yields. The method is convenient and potentially valuable for the synthesis of highly functionalized γ-butyrolactones in high optical purity.

Introduction

Lactone functionality is present in a large variety of natural products and biologically active compounds. Functionalized chiral γ-lactones have been reported as flavor components,[2] sex attractant pheromones of different insects,[3] and as plant-growth regulators.[4] They are also useful chiral building blocks for the synthesis of natural products such as alkaloids, macrocyclic antibiotics, lignan lactones, pheromones, antileukemics, and flavor components.[5] The physiological activity of these γ-lactones often depends on the optical purity and absolute configuration,[6] especially in the case of insect sex pheromones where the presence of even a small amount of the opposite enantiomer can greatly reduce its biological activity.[7]

Optically active γ-substituted-γ-butyrolactones constitute a very important part of this class of compounds (Chart 1) and there have been an increasing number of reports of their synthesis. They have been prepared using methods such as transformation of chiral natural products,[8] microbial reduction of γ-keto acid,[9] enzymatic resolution,[10] or by chiral induction with chiral chemical reagents.[11] Although these methods are useful for the synthesis of chiral γ-lactones, they suffer from certain drawbacks. Thus while the transformation of chiral natural products into lactones can be cumbersome, enzymatic resolution or microbial reduction is seriously hampered by substrate specificity, and the use of chiral reagents often results in products of low optical purity.

Chart 1



Asymmetric allyl- and crotylboration of aldehydes is now widely regarded as the method of choice for the

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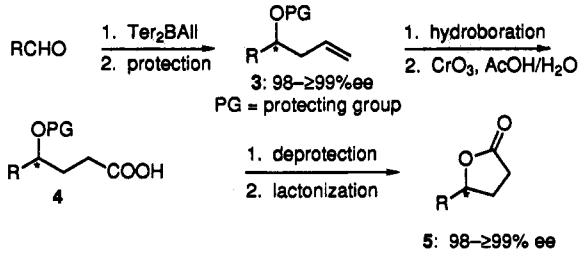
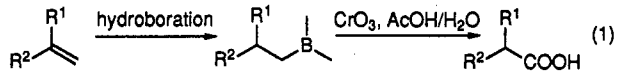
Scheme 1



synthesis of either enantiomer of homoallylic alcohols with excellent relative and absolute stereochemical control.[12] Over the past decade, we have developed terpene based asymmetric allyl/crotylboration reagents, [Ter_2BAll, Ter_2BCrt^Z, and Ter_2BCrt^E; Ter = ^{d}Ipc, ^{l}Ipc, 4-^{d}Icr, 2-^{d}Icr] which can achieve the synthesis of a wide variety of homoallylic alcohols **1** (R^1 = alkyl, aryl; R^2, R^3 = H, alkyl, alkoxy) with enantio- and diastereoselectivities approaching 100%.[13] In this paper, we describe a facile general method for the synthesis of γ-substituted-γ-butyrolactones **2** in exceptionally high enantiomeric purities (98–≥99%) from homoallylic alcohols **1** (R^2, R^3 = H) by applying our recently reported procedure[14] to convert terminal alkenes into carboxylic acids.

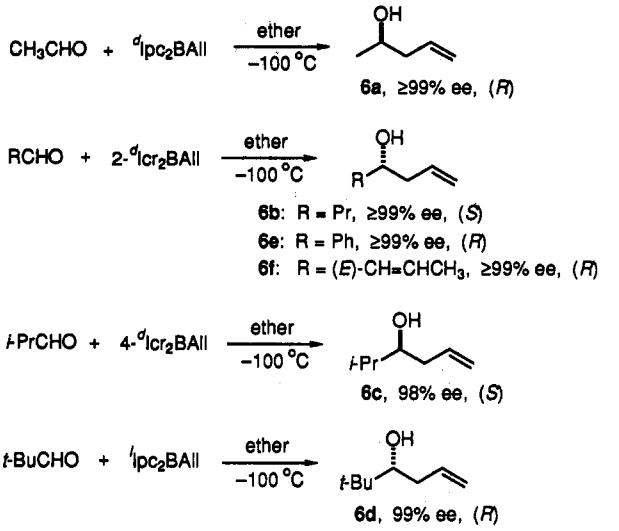
Results and Discussion

Recently we described a simple convenient procedure for the direct synthesis of carboxylic acids from terminal olefins via hydroboration–oxidation (eq 1).[14]



We decided to utilize this procedure for the synthesis of γ-substituted-γ-butyrolactones, by employing as our starting materials essentially enantiomerically pure homoallylic alcohols (98–≥99% ee) available through our asymmetric allylboration method (Scheme 1).

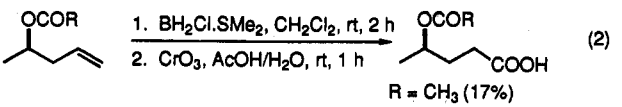
Scheme 2



The optically active homoallylic alcohols **6a–f** were prepared in 98–≥99% ee using ^{d}Ipc_2BAll, ^{l}Ipc_2BAll, 4-^{d}Icr_2BAll, and 2-^{d}Icr_2BAll (Ipc = isopinocampheyl, Icr = isocaranyl) according to our previously reported procedures (Scheme 2).[13c]

The protection of the hydroxyl group in the homoallylic alcohol was based on the following considerations: (1) The protecting group should be stable toward hydroboration, (2) both protection and deprotection should be facile, and (3) it should be able to withstand the oxidation conditions with CrO_3–aqueous acetic acid (10% H_2O). Benzyl or silyl groups did not meet these criteria as the latter are susceptible to hydrolysis under acidic conditions while the former are cleaved during the CrO_3–aqueous acetic acid oxidation.[15] Protection of the alcohol as an ester was therefore our method of choice.

Previously we reported that $BH_2Cl{\cdot}SMe_2$ proved to be the preferred hydroborating agent for the conversion of terminal alkenes into carboxylic acids.[14b] The advantage of using $BH_2Cl{\cdot}SMe_2$ over other hydroborating agents is due to the fact that the organoborane intermediates can be used directly without isolation for the chromic acid oxidation, with the carboxylic acids obtained in excellent yield. Thus (4*R*)-4-penten-2-ol (**6a**) was protected as the acetate and subjected to hydroboration with $BH_2Cl{\cdot}SMe_2$ followed by oxidation with CrO_3 in 90% aqueous acetic acid. Unfortunately, the yield of (4*R*)-4-acetoxypentanoic acid by this method was only 17% (eq 2). The analysis



of the nonacidic products, however, revealed the presence of substantial amounts of unreacted starting material, (4*R*)-4-acetoxy-1-pentene. Thus it appeared that the acetate group was interfering with the hydroboration. As the reason for this behavior was not immediately clear, we examined the reaction of $BH_2Cl{\cdot}SMe_2$ with simple esters such as ethyl acetate, ethyl benzoate, and ethyl *p*-nitrobenzoate at room temperature. We discovered that $BH_2Cl{\cdot}SMe_2$ reduces the acetate at a relatively fast rate, much faster than the rate of reduction of benzoate or

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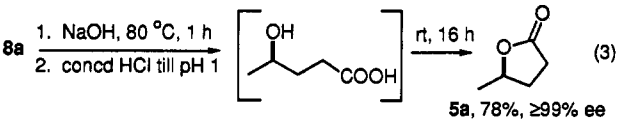
p-nitrobenzoate, probably due to the higher Lewis basicity of the acetate group. Thus the lower yield in the hydroboration of the homoallylic acetate was probably due to the competing reduction of the acetate group. Indeed protection of alcohol **6a** as its *p*-nitrobenzoate ester **7a**, followed by hydroboration–oxidation as before, gave a very good yield (84%) of the carboxylic acid **8a** (eq 2).

The principal reason for the selection of *p*-nitrobenzoyl over the benzoyl group as the protecting group was that the formation and alkaline hydrolysis of *p*-nitrobenzoates of secondary alcohols is more facile than the corresponding benzoates, especially when the alcohol is a sterically crowded one, e.g. **6d**. Further, the nitro group does not interfere in the hydroboration step and the protecting group should withstand the oxidation conditions.

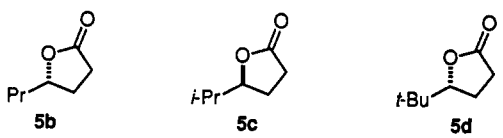
The hydrolysis of (4*R*)-4-[(*p*-nitrobenzoyl)oxy]pentanoic acid (**8a**) was carried out with aqueous 1 N NaOH and the resulting clear solution was then acidified with concd HCl to pH 1. The (4*R*)-4-hydroxypentanoic acid formed *in situ* underwent complete lactonization on stirring for 16 h at room temperature. The isolation of (*R*)-4-methylbutyrolactone (**5a**) was achieved by saturating the aqueous mixture with $NaHCO_3$ (which converted the *p*-nitrobenzoic acid into its soluble sodium salt while the lactone remained unaffected) followed by repeated extraction with a mixture of ether:THF (70:30).[16] The crude lactone **5a**, obtained after drying ($MgSO_4$) and solvent evaporation, was >95% pure by ^1H NMR. Pure **5a** was obtained by distillation under reduced pressure in 78% isolated yield based on the homoallylic *p*-nitrobenzoate **7a**. The optical purity of this γ-lactone **5a** was 99% by comparison of its specific rotation with the literature value,[11n] so that no racemization had taken place in any of the steps during the synthesis.

Thus we had achieved a simple synthesis of (*R*)-4-methylbutyrolactone in exceptional enantiomeric purity from (*R*)-4-penten-2-ol in good yield without any loss of optical purity (eq 3).



(3)

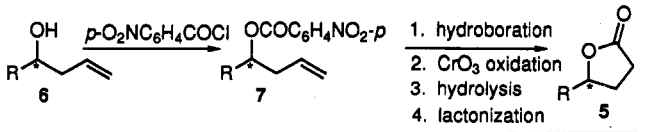
No significant problems were encountered when this method was applied to homoallylic alcohols **6b–d**, providing the corresponding γ-lactones **5b–d** in good yields and high optical purity (Table 1).



In the synthesis of lactones by this method, certain observations deserve a comment: (1) For efficient preparation of *p*-nitrobenzoates from the homoallylic alcohols, a 20% excess of *p*-nitrobenzoyl chloride was always used which led to the formation of *p*-nitrobenzoic anhydride as a byproduct. However the anhydride could be easily separated from the *p*-nitrobenzoates by taking advantage its low solubility in hexane. Thus simply stirring the mixture of the ester and the anhydride, so obtained after the workup, for a few minutes in hexane followed by filtration removed the anhydride impurity. (2) Isolation of the pure carboxylic acids **8b–d** prior to hydrolysis is not necessary. The crude carboxylic acid obtained by workup of the oxidation mixture was directly subjected in every case to alkaline hydrolysis and the resulting solution was washed with a small amount of ether before acidification to completely remove any nonacidic impurities. Clearly, these observations simplify the overall procedure and eliminate the need for any chromatographic separations.

(16) It was found that ether alone was not very effective for the complete extraction of this highly water-soluble lactone **5a** and therefore it was mixed with THF to increase its extractive ability. Increasing the proportion of THF beyond 30% proved to be counterproductive as it precipitated the bicarbonate from the aqueous solution.

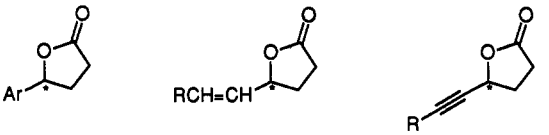
Table 1. Synthesis of γ-Substituted-γ-butyrolactones from Homoallylic Alcohols



R	7 (% yield)	5 (% yield,[a] % ee, configuration)
Me	**7a** (90)	**5a** (78, ≥99,[b] *R*)
n-Pr	**7b** (92)	**5b** (80, ≥99,[b] *S*)
i-Pr	**7c** (92)	**5c** (82, 98,[c] *S*)
t-Bu	**7d** (85)	**5d** (75, >98,[c] *R*)
Ph	**7e** (93)	**5e** (68, >98,[c] *R*)
(*E*)-CH=CHCH$_3$	**7f** (89)	**5f** (54, >98,[c] *R*)

[a] Based on *p*-nitrobenzoate **7**. [b] By comparison of the optical rotation with the published value. [c] By ^1H NMR chemical shift analysis in the presence of the chiral shift reagent Eu(tfc)$_3$ as in ref 17.

Chart 2



However, problems were encountered in attempting the synthesis of the phenyl-substituted lactone **5e** by this procedure. The lactone was obtained in only 30% yield, and ^1H NMR analysis in presence of chiral shift reagent[17] showed it to be of only 80% ee. Evidently racemization had taken place since the starting alcohol was of ≥99% ee. Experiments revealed that the low yield of the lactone was due to the much lower solubilities of the intermediates of the hydrolysis and lactonization steps in the aqueous medium. In order to circumvent this problem the hydrolysis of the carboxylic acid **8e** by NaOH was carried out in methanol rather than in water. Under these conditions hydrolysis of the *p*-nitrobenzoate group was rapid and complete in only a few minutes at 25 °C. Next we tackled the lactonization step. The lactonization was carried out by addition of dry benzene and refluxing for 3 h with azeotropic removal of water (Dean–Stark apparatus).[11s] Use of this modified procedure increased the yield of lactone **5e** to 73%; unfortunately, the optical purity of the lactone still remained low (82%).

It is well known that optically active aryl-, alkenyl-, or alkynyl-substituted hydroxy acids and lactones (Chart 2) are prone to racemization in the presence of strong mineral acids such as HCl.[11s] Therefore acidification of the hydrolysis reaction mixture was carried out only until pH 4 (monitored by pH meter) using 1 N HCl instead of concd HCl. However this did not solve the racemization problem.

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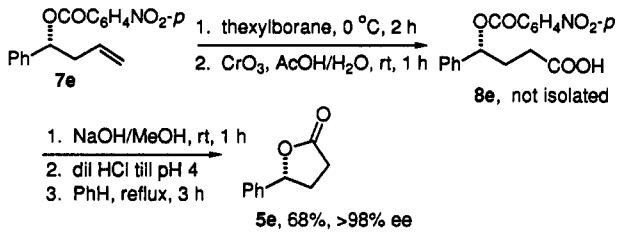
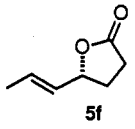
Scheme 3



Further, oxidation with PDC in DMF[14b] or $Na_2Cr_2O_7$[14b] also did not improve the results.

Surprisingly, the use of thexylborane instead of $BH_2Cl{\cdot}SMe_2$ for hydroboration gave lactone **5e** in 68% yield without racemization (Scheme 3). Presumably the absence of HCl in the oxidation mixture may be vital for avoiding racemization.

For the synthesis of the alkenyl-substituted lactone **5f**, a hydroborating agent capable of selective hydroboration of the terminal double bond was necessary. We chose disiamylborane because the byproduct isopropyl methyl ketone formed during the CrO_3 oxidation could be easily removed under vacuum prior to the hydrolysis step. The workup of the oxidation reaction mixture was carried out according to the procedure described above for **5e**. The lactone **5f** was obtained in somewhat low yield (54%) probably due to the competing allylic oxidation. However the optical purity of the lactone was found to be >98%, confirming that the modified workup described above for **5e** works even for **5f**.



5f

Conclusion

A practical method has been developed for the synthesis of optically active γ-substituted-γ-butyrolactones from optically active homoallylic alcohols without any racemization.[18] The generality of this method can be seen from the efficient synthesis of γ-lactones of any configuration having a wide range of γ-substituents such as simple alkyl, branched alkyl, aryl, and alkenyl groups. Further, this method could be easily extended to the synthesis of a wide range of highly functionalized lactones **2** from the corresponding homoallylic alcohols **1** which are readily available in exceptionally high enantio- and diastereomeric purities via asymmetric allyl- and crotylboration.

Experimental Section

All reaction flasks and equipment were dried at 150 °C for several hours prior to use and assembled hot under a stream of nitrogen. Special techniques for handling air-sensitive materials are described elsewhere.[19] Melting and boiling points reported are uncorrected. All ^1H NMR spectra were recorded at 300 MHz while all ^{13}C NMR spectra were recorded at 50.1 MHz in $CDCl_3$ with TMS as an internal standard. Chemical shifts in the ^1H and ^{13}C NMR spectra are reported as parts per million (ppm) downfield from TMS. Flash column chromatography was performed on silica gel (230–400 mesh, Merck). Preparative gas chromatography was performed on a 6 ft × 0.25 in. column packed with 10% SE-30 on chromosorb W (100–120 mesh, AW DMCS). Elemental analyses were performed by the Purdue University microanalytical laboratory. Specific rotations [α] were determined at the sodium D line at 25 °C. IR spectra were recorded with neat samples.

$BH_2Cl{\cdot}SMe_2$, $BH_3{\cdot}SMe_2$, 2,3-dimethyl-2-butene, and 2-methyl-2-butene were purchased from Aldrich and were used directly. Dichloromethane (spectral grade, Baker analyzed) was stored over 4-Å molecular sieves and used directly in all experiments. CrO_3 (AR grade) was purchased from Mallinkrodt and used directly. The optically active homoallylic alcohols **6a–e** were prepared as shown in Scheme 2 according to published procedures.[13c] Alcohol **6f** was also prepared using the similar procedure in ≥99% ee: $[\alpha]^{25}_D = +18.75°$ ($c = 1.90$, $CHCl_3$) (lit.[20] $[\alpha]^{25}_D = -8.9°$ ($c = 9.4$, CH_2Cl_2)) for the (*S*) enantiomer of 72% ee. The enantiomeric purity of alcohols **6a–f** was determined by capillary gas chromatographic analysis of its Mosher ester or menthyl carbonate derivatives. Thexylborane and disiamylborane were prepared according to published procedure.[21]

General Procedure for the Preparation of *p*-Nitrobenzoates 7a–f. The procedure described for the preparation of (4*R*)-4-[(*p*-nitrobenzoyl)oxy]-1-pentene (**7a**) is representative.

To a stirred solution of *p*-nitrobenzoyl chloride (4.45 g, 24.0 mmol) and DMAP (0.244 g, 2.0 mmol) in CH_2Cl_2 at 0 °C was added Et_3N (3.04 g, 30.0 mmol) followed by alcohol **6a** (1.72 g, 20.0 mmol) dropwise over a period of 5 min. After the addition was complete, the ice bath was removed and the reaction mixture was allowed to stir for 2 h. The precipitate of $Et_3N{\cdot}HCl$ was filtered off under suction and the filtrate was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) followed by 1 N HCl (25 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue containing **7a** contaminated by small amount of *p*-nitrobenzoic anhydride was stirred in hexane (40 mL) for a few minutes and filtered under suction. Concentration of the filtrate in vacuo gave crude **7a** (4.21 g, 90%) as a slightly yellowish oil. ^1H NMR analysis showed it to be >95% pure and was therefore used without purification for the next step. For spectroscopic analysis, an analytical sample of **7a** was obtained by flash column chromatography on silica gel (98:2 hexane/ethyl acetate): bp 116–20 °C (0.25 mmHg); ^1H NMR δ 8.29 (d, $J = 9.0$ Hz, 2 H), 8.20 (d, $J = 9.0$ Hz, 2 H), 5.75–5.90 (m, 1 H), 5.20–5.32 (m, 1 H), 5.08–5.19 (m, 2 H), 2.39–2.57 (m, 2 H), 1.40 (d, $J = 6.3$ Hz, 3 H); ^{13}C NMR δ 164.14, 150.46, 136.13, 133.21, 130.63, 123.48, 118.26, 72.01, 40.27, 19.52.

(4*S*)-4-[(*p*-Nitrobenzoyl)oxy]-1-heptene (7b): bp 134–5 °C (0.25 mmHg); ^1H NMR δ 8.29 (d, $J = 8.7$ Hz, 2 H), 8.20 (d, $J = 8.7$ Hz, 2 H), 5.74–5.90 (m, 1 H), 5.19–5.28 (m, 1 H), 5.05–5.15 (m, 2 H), 2.47 (apparent t, $J = 7.2$ Hz, 2 H), 1.60–1.82 (m, 2 H), 1.32–1.52 (m, 2 H), 0.95 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR δ 164.32, 150.46, 136.08, 133.31, 130.64, 123.50, 118.13, 75.10, 38.65, 35.76, 18.63, 13.92.

(4*S*)-4-[(*p*-Nitrobenzoyl)oxy]-5-methyl-1-hexene (7c): bp 130–1 °C (0.25 mmHg); ^1H NMR δ 8.30 (d, $J = 9.0$ Hz, 2 H), 8.22 (d, $J = 9.0$ Hz, 2 H), 5.60–5.83 (m, 1 H), 5.00–5.38 (m, 3 H), 2.44 (t, $J = 6.8$ Hz, 2 H), 1.20 (m, 1 H), 0.98 (d, $J = 6.8$ Hz, 3 H), 0.97 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR δ 164.34, 150.47, 136.08, 133.71, 130.66, 123.55, 117.90, 79.41, 36.03, 31.21, 18.72, 17.65.

(4*R*)-4-[(*p*-Nitrobenzoyl)oxy]-5,5-dimethyl-1-hexene (7d). In this case the acylation reaction mixture was stirred at 40 °C for 24 h prior to workup: mp 64–5 °C (off-white needles from hexane); ^1H NMR δ 8.30 (d, $J = 9.0$ Hz, 2 H), 8.20 (d, $J = 9.0$ Hz, 2 H), 5.65–5.88 (m, 1 H), 4.90–5.13 (m, 3 H), 2.25–2.60 (m, 2 H), 1.02 (s, 9 H); ^{13}C NMR δ 164.38, 150.46, 136.02, 134.70, 130.63, 123.56, 117.60, 81.65, 34.87, 34.71, 26.05.

(4*R*)-4-[(*p*-Nitrobenzoyl)oxy]-4-phenyl-1-butene (7e): high boiling liquid; ^1H NMR δ 8.29 (d, $J = 9.0$ Hz, 2 H), 8.23 (d, $J = 9.0$ Hz, 2 H), 7.30–7.45 (m, 5 H), 6.07 (dd, $J = 7.8$ and 5.7 Hz,

(18) Racemic γ-disubstituted-γ-butyrolactones have previously been prepared from tertiary homoallylic alcohols in a one-pot reaction via hydroboration with $BH_3{\cdot}SMe_2$ followed by oxidation with $Na_2Cr_2O_7/H_2SO_4/H_2O$. However, chiral secondary homoallylic alcohols give very low yields of the corresponding lactones probably due to the regioselectivity problems in hydroboration, harsh oxidation conditions, and losses due to oxidation of the secondary alcohol group; see: Mandal, A. K.; Mahajan, S. W. *Synthesis* **1991**, 311.

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1 H), 5.69–5.84 (m, 1 H), 5.05–5.19 (m, 2 H), 2.66–2.90 (m, 2 H); ^{13}C NMR δ 163.86, 150.55, 139.41, 135.77, 132.89, 130.74, 128.64, 128.37, 126.53, 123.56, 118.59, 76.90, 40.78.

(*E*)-(4*R*)-4-[(*p*-Nitrobenzoyl)oxy]-1,5-heptadiene (7f): bp 140 °C (0.1 mmHg); ^{1}H NMR δ 8.29 (d, J = 9.0 Hz, 2 H), 8.20 (d, J = 9.0 Hz, 2 H), 5.73–5.94 (m, 2 H), 5.49–5.62 (m, 2 H), 5.07–5.19 (m, 2 H), 2.46–2.62 (m, 2 H), 1.74 (d, J = 6.0 Hz, 3 H); ^{13}C NMR δ 163.91, 150.47, 136.13, 133.06, 130.68, 130.52, 128.42, 123.50, 118.23, 75.78, 39.12, 17.79.

General Procedure for the Synthesis of γ-Substituted-γ-butyrolactones 5a–d. The procedure described for the synthesis of (*R*)-γ-methyl-γ-butyrolactone (**5a**) is representative.

To a solution of **7a** (2.35 g, 10.0 mmol) in CH_2Cl_2 (10.0 mL) was added $BH_2Cl{\cdot}SMe_2$ (0.61 g, 5.5 mmol, 0.57 mL) dropwise with stirring at 25 °C. After stirring for 2 h, the reaction mixture was cooled to 0 °C and added with stirring to a solution of CrO_3 (5.99 g, 60.0 mmol) in acetic acid (36.0 mL) and water (4.0 mL) keeping the temperature of the reaction mixture below 5 °C during the addition. After the addition was complete, the reaction mixture was stirred at 25 °C for 2 h and quenched by addition of water (100 mL) and CH_2Cl_2 (30 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The crude carboxylic acid **8a** obtained after washing the combined organic extracts with water (2 × 50 mL) and solvent evaporation was hydrolyzed without isolation[22] by heating the residue in aqueous 1 N NaOH (40.0 mL, 40.0 mmol) at 80 °C for 1 h. The resulting aqueous solution was washed with ether (10 mL), acidified by dropwise addition of concd HCl until the pH was about 1, and stirred at 25 °C for 16 h. It was then treated with solid $NaHCO_3$ until saturation and extracted with 70:30 ether:THF (6 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo, and the crude product was purified by bulb-to-bulb distillation to give **5a** (0.78 g, 78%, >95% pure by ^{1}H NMR). An analytical sample of **5a** was obtained by preparative gas chromatography: bp 88–93 °C (20 mmHg) [lit.[11n] bp 90–100 °C (25 mmHg)]; $[\alpha]^{25}_D$ +36.7° (c = 1.48, CH_2Cl_2) [lit.[11n] of (*S*) enantiomer $[\alpha]^{25}_D$ −36.8° (c = 1.44, CH_2Cl_2)]. Other spectral data compared favorably with that reported in the literature.[23]

(*S*)-γ-Propyl-γ-butyrolactone (5b):[9b] bp 145–50 °C (20 mmHg); $[\alpha]^{25}_D$ −55.9° (c = 1.54, THF) [lit.[9d] of (*R*) enantiomer $[\alpha]_D$ +56.2° (c = 1.56, THF)]; ^{1}H NMR δ 4.46–4.56 (m, 1 H), 2.48–2.58 (m, 2 H), 2.33 (sextet, J = 6.3 Hz, 1 H), 1.34–1.93 (m, 5 H), 0.96 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 177.35, 80.85, 37.66, 28.87, 28.03, 18.58, 13.83; IR 1771 cm^{-1}.

(*S*)-γ-(*i*-Propyl)-γ-butyrolactone (5c): bp 124–6 °C (52 mmHg); $[\alpha]^{25}_D$ +43.5° (c = 1.92, $CHCl_3$); ^{1}H NMR δ 4.20 (apparent q, J = 7.2 Hz, 1 H), 2.49–2.58 (m, 2 H), 2.19–2.32 (m, 1 H), 1.79–1.98 (m, 2 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 177.38, 85.87, 33.03, 29.17, 25.61, 18.42, 17.33; IR 1771 cm^{-1}. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.66; H, 9.62.

(*R*)-γ-(*t*-Butyl)-γ-butyrolactone (5d): bp 122–4 °C (30 mmHg); $[\alpha]^{25}_D$ −44.6° (c = 2.00, THF); ^{1}H NMR δ 4.21 (dd, J = 10.8 and 6.8 Hz, 1 H), 2.48–2.61 (m, 2 H), 1.87–2.23 (m, 2 H), 0.96 (s, 9 H); ^{13}C NMR δ 177.51, 88.25, 33.81, 29.35, 24.90, 22.93; IR 1771 cm^{-1}. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.25; H, 10.22.

(22) In one case the carboxylic acid was isolated for characterization using standard acid–base workup.[14b] (*4R*)-4-[(*p*-Nitrobenzoyl)oxy]-pentanoic acid (**8a**): mp 92–3 °C (CH_2Cl_2–hexane); $[\alpha]^{25}_D$ −45.7° (c = 4.27, $CHCl_3$); ^{1}H NMR δ 11.4 (bs, 1 H), 8.28 (d, J = 9.0 Hz, 2 H), 8.19 (d, J = 9.0 Hz, 2 H), 5.26 (m, 1 H), 2.48 (t, J = 7.2 Hz, 2 H), 2.07 (q, J = 7.2 Hz, 2 H), 1.42 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 179.02, 164.15, 150.51, 135.75, 130.69, 123.51, 71.93, 30.59, 30.12, 19.89. Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 54.08; H, 4.61; N, 5.13.

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(*R*)-γ-Phenyl-γ-butyrolactone (5e):[10d] A solution of **7e** (2.97 g, 10.0 mmol) in CH_2Cl_2 (10.0 mL) cooled to 0 °C, was added to neat thexylborane (0.54 g, 5.5 mmol) at 0 °C and the reaction mixture was stirred for 2 h. This mixture was then added to a solution of CrO_3 (8.0 g, 80.0 mmol) in acetic acid (48.0 mL) and water (5.3 mL) maintained at about 5 °C during the addition. After stirring for 1 h at 25 °C, the reaction was quenched by addition of water (125 mL) and CH_2Cl_2 (40 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated to obtain crude **8e**. This was hydrolyzed by treatment with 1 N NaOH/MeOH (40.0 mL, 40.0 mmol) for 1 h at 25 °C. After removal of methanol under reduced pressure and addition of water (40 mL), the aqueous solution was washed with ether (10 mL) and acidified by dropwise addition of 1 N HCl to pH 4. Extraction with 70:30 ether:THF (5 × 20 mL) followed by drying ($MgSO_4$) and concentration gave a crude mixture of hydroxy acid **5e** and *p*-nitrobenzoic acid. Dry benzene (30 mL) was added to this mixture and refluxed for 3 h with azeotropic removal of water using the Dean–Stark trap. The residue obtained by the evaporation of benzene was stirred with saturated aqueous $NaHCO_3$ solution (25 mL) for 10 min and extracted with 70:30 ether:THF (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvents were evaporated to give the crude product. It was purified by bulb-to-bulb distillation under reduced pressure to give **5e** (1.10 g, 68%). An analytical sample was obtained by flash column chromatography on silica gel (hexane/ethyl acetate 9:1): bp 99–105 °C (0.1 mmHg); $[\alpha]^{25}_D$ +35.5° (c = 2.52, $CHCl_3$) [lit.[9f] of (*S*) enantiomer $[\alpha]^{25}_D$ −32.5° (c = 4.3, $CHCl_3$)]; ^{1}H NMR δ 7.26–7.47 (m, 5 H), 5.51 (dd, J = 8.0 and 6.2 Hz, 1 H), 2.57–2.75 (m, 3 H), 2.06–2.32 (m, 1 H); ^{13}C NMR δ 176.89, 139.36, 128.75, 128.43, 125.27, 81.21, 30.97, 28.95; IR 1778 cm^{-1}.

(*R*)-γ-[(*E*)-Propenyl]-γ-butyrolactone (5f). To a solution of disiamylborane (11.0 mL, 1.0 M, 11.0 mmol) in CH_2Cl_2 at 0 °C was added **7f** dropwise while the mixture was stirred. After the addition was complete, the reaction mixture was stirred at 0 °C for 1 h and added to a solution of CrO_3 (9.99 g, 100.0 mmol) in acetic acid (60 mL) and water (6.7 mL) maintained at about 5 °C during the addition. It was stirred at 25 °C for 1 h and quenched by addition of water (150 mL) and CH_2Cl_2 (50 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with water (2 × 50 mL), dried ($MgSO_4$), and subjected to reduced pressure to remove the solvent and the byproduct methyl isopropyl ketone formed during oxidation. The crude carboxylic acid **8f** was hydrolyzed and worked up as described in the case of **5e** to obtain **5f** (0.68 g, 54%). An analytical sample was obtained by preparative gas chromatography: bp 142–5 °C (18 mmHg); $[\alpha]^{25}_D$ −49.2° (c = 2.63, $CHCl_3$); ^{1}H NMR δ 5.83 (qd, J =15.3 and 6.6 Hz, 1 H), 5.52 (qdd, J = 15.3, 7.2, and 1.6 Hz, 1 H), 4.89 (q, J = 7.2 Hz, 1 H), 2.50–2.58 (m, 2 H), 2.31–2.43 (m, 1 H), 1.91–2.05 (m, 1 H), 1.74 (dd, J = 7.2, and 1.6 Hz, 3 H); ^{13}C NMR δ 177.21, 130.63, 128.86, 81.24, 28.88, 17.79 (one carbon less due to fortuitous overlap of two resonances); IR 1771 cm^{-1}. Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.49; H, 8.18.

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Supplementary Material Available: ^{1}H and ^{13}NMR spectra for all new compounds described in the Experimental Section (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.