Asymmetric Synthesis of 2-Substituted Butyrolactones and Valerolactones

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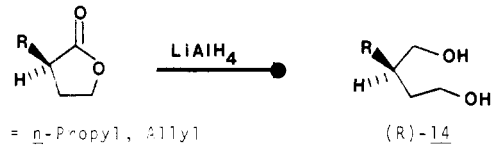
Received February 4, 1980

The use of chiral oxazolines **1**, **2**, **5**, and **8** under asymmetrically induced alkylation conditions gave α-substituted oxazolines **3**, **6**, **9**, and **13** which were hydrolyzed to α-substituted butyro- and valerolactones **4** and **11**. Either enantiomer of the lactones could be prepared in predictable absolute configuration by reversing the order of alkyl group introduction. The lactones were prepared in 60–86% enantiomeric excess which was determined by either chemical correlation or high-pressure liquid chromatography of the diastereomers **10**.

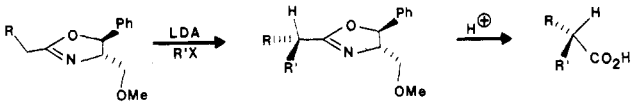
The utility of chiral oxazolines as auxiliary reagents for producing 2-substituted,[1] 3-substituted,[2] and 2-hydroxy[3] carboxylic acids has been recently described. Applying a modified technique for the synthesis of 2-substituted carboxylic acids (Scheme I), we are now able to prepare[4] a series of chiral 2-substituted butyrolactones (Scheme II) and 2-substituted valerolactones (Scheme III). The readily available chiral 2-methyloxazoline **1** is used to prepare either enantiomer of the lactones as shown in the schemes. Metalation of **1** with *n*-butyllithium in dimethoxyethane, followed by addition of ethylene oxide and chlorotrimethylsilane, gave the Me_3Si ether **2** in 80% yield. Use of THF as a solvent gave yields of **2** under 50% along with other unidentified products. Asymmetric alkylation of **2** was accomplished by using lithium diisopropylamide (−78 °C, THF) followed by addition of various alkyl halides at −98 °C. This temperature was found to be optimum for the biased alkylation. The resulting adduct **3** was hydrolyzed in dilute hydrochloric or sulfuric acid to furnish the 2-substituted butyrolactones **4** described in Table I. In addition, the chiral methoxyamino alcohol **7** was recovered and may be used to prepare **1** for further use. Since the maximum rotation and absolute configuration of only the 2-methylbutyrolactone had been reported,[5] it was necessary to determine these properties independently. The CD spectra were taken for all the butyrolactones in Table I, and those which were prepared via **2** showed negative Cotton curves, supporting the similarity of configurations. Furthermore, Pirkle has determined that the 2-ethyl lactone (Table I, footnote *c*) possessed the *R* configuration and was present in 72% ee, using chiral solvents and their ^1H NMR shifts. The 2-propyl- and 2-alkylbutyrolactones were reduced with lithium aluminum hydride to the known 1,4-butanediols **14** previously prepared



4 R = n-Propyl, Allyl (R)-14

by Lwowski and Freudenberg[6] by reduction of the optically active 2-substituted succinic acids. However, no absolute configuration was reported. The percent enantiomeric excess (ee) for the 2-propyl- and 2-allylbutyrolactones was based on the specific rotations given by these authors. The enantiomeric lactones (*S* configuration) given in Table I were prepared in a similar manner by using the 2-alkyl-

Scheme I



Scheme II

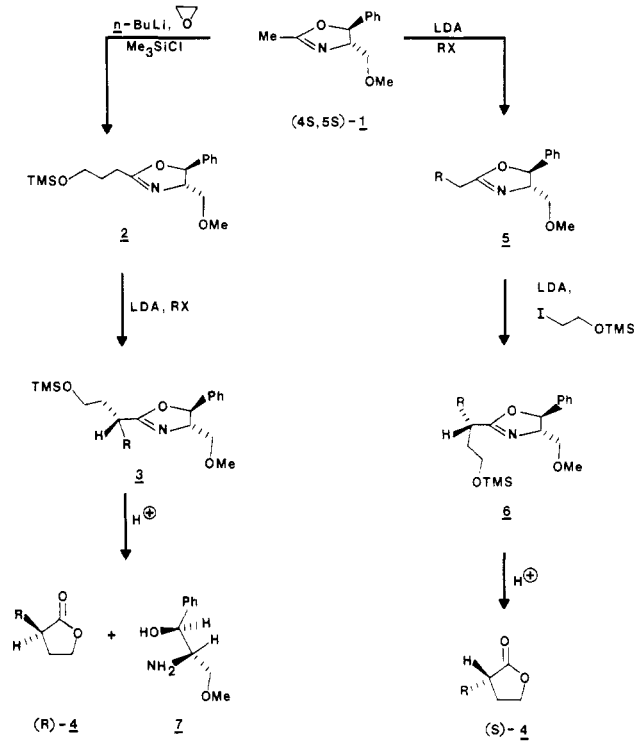


Table I. Chiral 2-Substituted Butyrolactones 4

R	% yield[a]	$[\alpha]_D$ (*c*, EtOH)	% ee	config	$[\theta]_{218}$[b]
Me[e]	58	+14.8 (10.0)	70	*R*	−1430
Et	68	−7.65 (9.8)	72[c]	*R*[c]	−1750
n-Pr	75	−8.05 (5.7)	73	*R*	−1870
allyl	60	−16.05 (4.8)	72	*R*	−1730
n-Bu	71	−7.50 (9.7)	60[d]	*R*	−1600
allyl	54	+20.0 (5.9)	86	*S*	+1790
n-Bu	46	+8.7 (2.5)	70[d]	*S*	+1830

[a] Based on **1**. [b] [θ] in units of (deg cm²)/dmol in acetonitrile. [c] Determined by W. H. Pirkle, D. L. Sikkenga, and M. S. Paulin, *J. Org. Chem.*, 42, 384 (1977). [d] Cf. Helmchen et al., ref 8. [e] Dimethyl sulfate used for alkylation.

(1) A. I. Meyers, *Acc. Chem. Res.*, 11, 375 (1978).
(2) A. I. Meyers, R. K. Smith, and C. E. Whitten, *J. Org. Chem.*, 44, 2250 (1979).
(3) A. I. Meyers and J. Slade, submitted for publication in *J. Org. Chem.*
(4) A preliminary report describing the (*R*)-2-substituted-butyrolactones has appeared: A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, 40, 1187 (1975).
(5) T. Kaneko, K. Wakabayashi, and H. Katsura, *Bull. Chem. Soc. Jpn.*, 35, 1149 (1962).
(6) K. Freudenberg and W. Lowski, *Justus Liebigs Ann. Chem.*, 594, 76 (1955).

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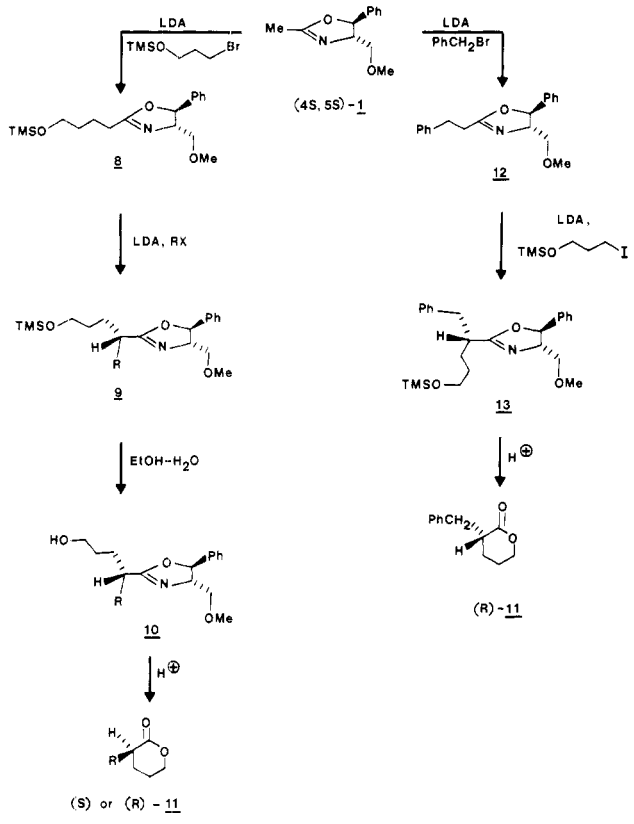
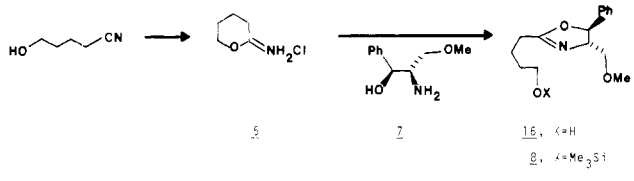
Scheme III



oxazolines **5**. Ethylene oxide could not be introduced after LDA deprotonation due to its poor reactivity at −78 to −98 °C. A synthetic equivalent, 2-(trimethylsilyloxy)ethyl iodide,[7] was employed, and alkylation at −98 °C proceeded smoothly, affording **6**. Acidic hydrolysis produced the *S* lactones **4** in comparable yields and enantiomeric excesses. The proposed absolute configurations for the butyrolactones **4**, in addition to being consistent with the CD spectra and the known 2-methyl lactone, are also in agreement with the mechanistic information previously reported from this laboratory.[8] The validity of this mechanism (vide supra) in assigning absolute configurations is consistent for both the butyro- and the valerolactones described herein.

In a similar fashion, the 2-substituted valerolactones **11** were formed from **1** in the sequence described by Scheme II. Reaction of lithiated **1** with 3-(trimethylsiloxy)propyl bromide gave **8** in 56% yield. The silyl ether was prepared



from 1,3-propanediol by using a routine sequence (Experimental Section). Alternatively, **8** was prepared from 5-hydroxyvaleronitrile, after cyclization to **15** with dry hydrogen chloride and treatment with the amino alcohol **7** which gave the hydroxyoxazoline **16**. Silylation of the latter with chlorotrimethylsilane gave **8** in 73% yield (from **7**). Metalation (LDA) of **8** and introduction of various alkyl halides gave the adduct **9** possessing a new asymmetric center. The efficiency of this biased alkylation was readily determined by first removing the silyl group producing the alcohol **10**. By use of high-pressure liquid chromatography, the ratio of diastereomers was discernible by base-line separations using μ-Porasil columns and elution with 40% THF–hexane. This data and the valerolactones obtained after acidic hydrolysis are given in Table II. As seen from Table II, the valerolactones were generally formed in 60–70% enantiomeric purity. The use of methyl sulfate was once again shown to give higher enantiomeric excesses than methyl iodide as observed in previous alkylations of oxazolines.[1] Since the absolute configuration of the 2-benzyl valerolactones was reported by Helmchen[8] to be *R* for the (+) enantiomer, the (−) enantiomer formed from **8** and benzyl bromide was assigned the *S* configuration. This is consistent with the predicted configuration based on the mechanism (discussed below) for this process. The CD curves for the 2-methyl-, 2-ethyl-, and 2-propylvalerolactones all showed negative Cotton curves and were all assigned the *R* configuration. In order to confirm that the (−)-2-benzyl, (−)-2-allyl, and the remainder of the (−)-lactones all had the same sense of configuration (regardless of priority assignments), we carried out a chemical correlation. Thus, the (−)-2-benzyl lactone **11** was oxidized (ozone, H_2O_2, CH_2N_2) to the (−) ester **17**, whereas the (−)-2-allyl lactone, similarly oxidized, gave the same ester, (−)-**17** (Scheme IV). This confirms that both the benzyl and allyl lactones formed from **8** possessed the same sense of configuration. Furthermore, reduction (H_2/Pd) of the (−)-allyl lactone gave the (−)-2-propyl lactone, also prepared from **8** and this indicates that both the allyl and propyl lactones are configurationally identical. On this basis, coupled with the CD data, the absolute configurations of the (−)-lactones in Table II are assumed to be on firm ground.

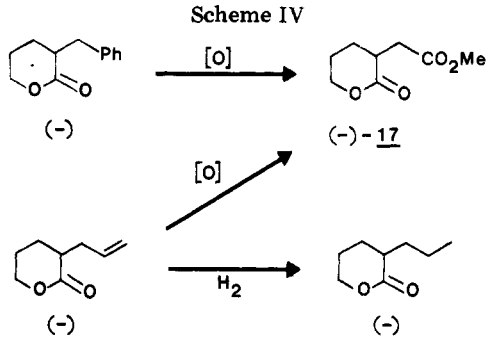
The enantiomeric lactones could also be prepared in this series by reversing the order of alkyl group introduction. Thus, **1** was transformed into the 2-phenethyloxazoline **12** by lithiation and alkylation with benzyl bromide. Treat-

Table II. Chiral 2-Substituted Valerolactones 11

R	% yield[a]	$[\alpha]_D$ (*c*, MeOH)	HPLC ratio[b]	% ee[b]	config	$[\theta]_{225}$[c]
Me[d]	68	−33.5 (4.0)	76:24	52	*R*	
Me[e]	66	−40.7 (3.1)	85:15	70	*R*	−3910
Et	51	−45.3 (2.9)	81:19	61	*R*	−4620
n-Pr	40	−47.0 (3.0)	80:20	60	*R*	−5210
allyl	65	−38.9 (2.9)	86:14	72	*S*	
$PhCH_2$	47	−50.2 (3.4)	82:18	64	*S*	
$PhCH_2$	54	+48.5 (3.7)	19:81	62	*R*	

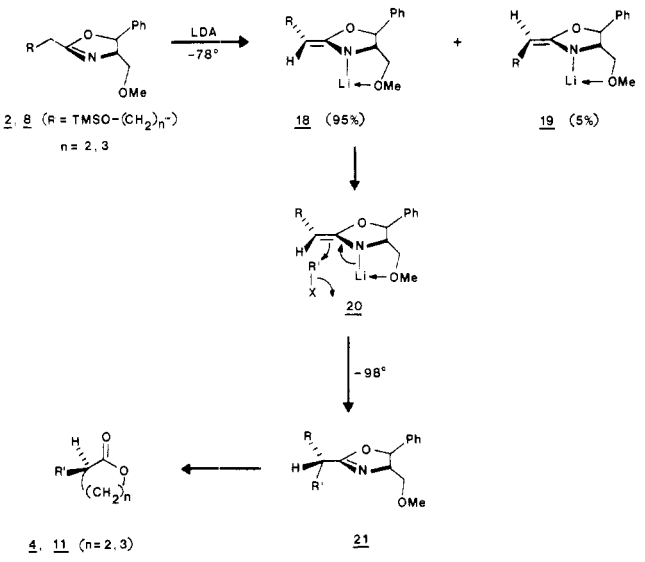
[a] Based on **8** or **12**. [b] Determined by base line separation of **10** (separation factor, α, of 1.3–1.5) with 40% THF-hexane on μ-Porasil and a UV detector at 254 nm. [c] $[\theta]$ in units of (deg cm²)/dmol in hexane. [d] Alkylation was performed by using methyl iodide. [e] Alkylation performed by using dimethyl sulfate.

Scheme IV



(7) E. V. White and J. A. McClosky, *J. Org. Chem.*, **35**, 4241 (1970).
(8) G. Helmchen, G. Nill, D. Flockerzi, and M. S. K. Youssef, *Angew. Chem., Int. Ed. Engl.*, 18, 63 (1979).

Scheme V



ment of the lithio anion of **12** with 3-(trimethylsiloxy)-propyl iodide gave **13** which, after removal of the silyl protecting group, gave epi-**10** (R = $PhCH_2$) with the opposite configuration at the side chain. High-pressure LC analysis showed reversal of the two peaks (**10**, 82:18; epi-**10**, 19:81). Acidic hydrolysis gave (*R*)-(+)-**11** which is the optical antipode of the lactone produced from **8**.

It was deemed necessary to prove that the diastereomeric ratios for **10** were indeed consistent with the percent enantiomeric excess of the lactones **11** in view of any racemiation that may have occurred during the acid hydrolysis. Toward this end, the hydroxyoxazoline **10** (R = $PhCH_2$) was separated by using medium-pressure liquid chromatography.[9] Although the minor component (18%) could not be isolated in sufficient quantity as pure material, the major diastereomer (~80%) was isolated in pure form. Hydrolysis of pure **10** in dilute sulfuric acid gave 2-benzylvalerolactone, $[\alpha]_D$ −77.7° which exceeded the maximum rotation of $[\alpha]_D$ +63.2° reported by Helmchen[8]. Since the ratio by high-pressure LC for diastereomeric **10** was shown to be 18:82, the specific rotation from Table II was given as −50.2°, and the enantiomerically pure benzyl lactone was given as $[\alpha]_D$ −77.7°, both the high-pressure LC ratios and the quotient for $[\alpha]_D$ came out the same, 64 ± 1% ee. Thus, the previously reported maximum rotation of 63.2° for the benzyl lactone is undoubtedly low. These data, therefore, support the fact that little or no racemization of the alkylated oxazolines **10** and **13** has occurred during hydrolysis, and the high-pressure LC data are indeed an accurate assessment of the enantiomeric purity of the valerolactones **11**.

In order to rationalize the absolute configuration and the relatively high enantiomeric purity of lactones **4** and **11**, it is necessary to recall the previous study[10] from this laboratory where it was shown that metalation of the side chain in chiral oxazolines (e.g., **2** and **8**) proceeds with a degree of selectivity, generating two kinetic aza enolates, **18** and **19** in approximately a 95:5 ratio (Scheme V). This mixture was shown not to equilibrate under these conditions and was subjected to bottom-side alkylation (**20**) leading to **21** as the major product. Hydrolysis provides the lactones **4** and **11** with the configurations observed in this study. Bottom-side alkylation of **19** and some (~10%) top-side alkylation of **18** provide 15–20% of the opposite enantiomer formed with the products. Further studies to reach other chiral functionalized molecules with several asymmetric carbons are in progress and will be reported in due course.

Experimental Section

General Methods. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. Circular dichroism spectra were taken on a Cary-Varian 61 instrument using spectrograde acetonitrile or hexane in a cell of 1-cm path length. High-pressure liquid chromatography was carried out on a Waters Associates 440 instrument which included a 30 cm × 3.9 mm column packed with μ-Porasil (10 μm), and elutions of **10** and **13** were carried out by using 40% THF–hexane and monitoring the reaction by UV absorption at 254 nm.

(4*S*,5*S*)-2-[3-[(Trimethylsilyl)oxy]propyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline (2). To 2.05 g (10.0 mmol) of **1**[11] in 35 mL of DME (N_2, −78 °C) was added dropwise 4.55 mL (10.5 mmol) of *n*-butyllithium (2.3 M in hexane) to produce a light yellow solution that was stirred an additional 30 min. Then 2.5 g (57 mmol) of ethylene oxide was added neat, in a stream, via a cannula from the septum-topped reagent bottle. The clear solution was slowly warmed from −78 to 0 °C over a 6-h period. After the mixture was cooled back down to −78 °C, chlorotrimethylsilane (1.4 mL, 11 mmol) was added neat and the solution allowed to warm to ambient temperature. Most of the solvent was then removed on a rotary evaporator, the residue taken up in hexane, and the insoluble matter filtered off. Concentration and distillation gave 2.5 g (80%) of **2** as a clear oil: bp 150 °C (0.015 mm); $[\alpha]^{24}_{589}$ −41.6° (*c* 9.85, $CHCl_3$); IR (film) 1670 cm^{-1}; ^1H NMR (CCl_4) δ 7.27 (s, 5), 5.2 (d, 1), 4.0 (m ,1), 3.8–3.2 (m, 4), 3.38 (s, 3), 2.4 (br t, 2), 1.85 (m, 2), 0.09 (s, 9).

Anal. Calcd for $C_{17}H_{27}NO_3Si$: C, 63.51; H, 8.47. Found: C, 63.61; H, 8.61.

(*R*)-(+)-2-Methyl-γ-butyrolactone (4, R = Me). General Procedure. To 10.5 mmol of lithium diisopropylamide (formed as previously described) in 23 mL of THF at −78 °C under nitrogen was added 3.21 g (10 mmol) of **2** in 10 mL of THF. After the mixture was stirred for 0.5 h, the yellow solution was cooled to −98 °C, and 1.0 mL (10.5 mmol) of dimethyl sulfate was added neat, dropwise. Stirring was continued for 2 h at −98 °C, and then the solution was slowly warmed to room temperature. The mixture was poured into saturated ammonium chloride solution and extracted with ether which was dried ($MgSO_4$) and concentrated. The crude alkylated product **3** was hydrolyzed immediately in 20 mL of refluxing 4.5 N HCl for 15 min to avoid possible racemization. The solution was cooled to 5 °C and extracted (4 × 20 mL) with ether. The aqueous solution was retained to recover the amino alcohol **7** (see below). The combined ether extracts were washed once with saturated sodium bicarbonate solution (to remove acidic impurities), dried ($MgSO_4$), concentrated, and distilled to give 0.58 g (58%) of **4** (R = Me) (95% purity by VPC): bp 85 °C (11 mm); rotation and circular dichroism data are given in Table I.

(1*S*,2*S*)-2-Amino-3-methoxy-1-phenyl-1-propanol (7). The aqueous acid solution from above was neutralized with sufficient KOH (ice bath) to achieve a solution of pH 10–12. The mixture was extracted (5 × 50 mL) with ether and the ethereal extracts were dried (K_2CO_3) and concentrated. The resulting solid was recrystallized from ether, giving **7**: mp 48–49 °C; $[\alpha]^{25}_D$ +26.2° (*c* 11.0, $CHCl_3$).[11]

(*R*)-(−)-2-Ethyl-γ-butyrolactone (4, R = Et). In the same way, **2** (9.4 mmol) and ethyl iodide (11 mmol) gave 3.5 g of crude alkylated product which on hydrolysis in 40 mL of 4.5 N HCl afforded 0.7 g (68%) of **4** (R = Et): 95% VPC purity; bp 90 °C (10 mm); rotation and circular dichroism data are given in Table I.

(*R*)-(−)-2-*n*-Propyl-γ-butyrolactone (4, R = *n*-Pr). Utilization of **2** (9.4 mmol) and *n*-propyl iodide (10.3 mmol, 1.1 equiv)

(9) A. I. Meyers, J. Slade, R. K. Smith, E. D. Mihelich, F. M. Hershenson, and C. D. Liang, *J. Org. Chem.*, **44**, 2247 (1979).

(10) A. I. Meyers, E. S. Snyder, and J. J. Ackerman, *J. Am. Chem. Soc.*, **100**, 8186 (1978). For another study on this subject see M. A. Hoobler, D. E. Bergbreiter, and M. Newcomb, *ibid.*, **100**, 8182 (1978).

(11) A. I. Meyers, G. Knaus, K. Kamata, and M. Ford, *J. Am. Chem. Soc.*, **98**, 567 (1976).

gave 0.9 g (75%) of 4 (R = *n*-Pr): 94% VPC purity; bp 90 °C (8 mm); rotation and circular dichroism data are given in Table I.

(*R*)-(−)-2-Allyl-γ-butyrolactone (4, R = Allyl). As usual, 2 (15.4 mmol) and allyl chloride (16.9 mmol) afforded 1.15 g (60%) of 4 (R = allyl): 96% VPC purity; bp 90 °C (7 mm); rotation and circular dichroism data are given in Table I.

(*R*)-(−)-2-*n*-Butyl-γ-butyrolactone (4, R = *n*-Bu). In the same way a reaction on 13.3-mmol scale with *n*-butyl iodide gave 1.37 g (75%) of pure (<99% VPC) 4 (R = *n*-Bu): bp 110 °C (8 mm); rotation and circular dichroism data are given in Table I.

(4*S*,5*S*)-2-*n*-Pentyl-4-(methoxymethyl)-5-phenyl-2-oxazoline (5, R = *n*-Bu). To a solution of lithium diisopropylamide in THF [prepared from 7.84 g (77.5 mmol) of diisopropylamine and 33.7 mL (77.5 mmol) of *n*-butyllithium (2.3 M in hexane) in 200 mL of THF] was added dropwise (under N_2) a solution of 15.9 g (77.5 mmol) of 1 in 70 mL of THF at −78 °C over 30 min. The mixture was stirred for 45 min at −78 °C, and a solution of 1-iodobutane (17.1 g, 93 mmol) in 40 mL of THF was added slowly (2–3 h). After complete addition, the mixture was stirred an additional 4 h, allowed to slowly warm to −50 °C (to avoid polyalkylation), and quenched by pouring it into ice–water. The aqueous mixture was extracted (3 × 150 mL) with ether, and the combined ether extracts were then washed with saturated brine, dried ($MgSO_4$), and concentrated. Distillation afforded 15 g (74%) of 5 (R = Bu): bp 115–116 (0.01 mm); $[\alpha]^{24}_{589}$ −75.5° (*c* 11.3, $CHCl_3$); IR (film) 1670 cm^{-1}; ^1H NMR (CCl_4) δ 7.3 (s, 5), 5.25 (d, 1), 4.2–3.2 (m, 3), 3.42 (s, 3), 2.35 (br t, 2), 2.0–1.1 (m, 6), 0.97 (br t, 3).

Oxazoline 5 (R = Allyl). In the manner described above, with the same stoichiometry, 1 was treated with allyl chloride to give 5 (R = allyl): 70%; bp 97–98 °C (0.03 mm), $[\alpha]^{24}_D$ −80.8° (*c* 5.78, $CHCl_3$); IR (film) 1665, 1642, cm^{-1}; ^1H NMR (CCl_4) δ 7.25 (s, 5), 6.3–5.6 (m, 1), 5.3–4.7 (m, 3), 4.2–3.2 (m, 3), 3.40 (s, 3), 2.44 (m, 4).

(*S*)-(+)-2-*n*-Butyl-γ-butyrolactone (4, R = *n*-Bu). The anion of 5 (R = *n*-Bu; 0.653 g, 2.5 mmol) in 35 mL of THF was formed as described in the General Procedure for the (*R*)-(−)-lactones by using LDA (1.1 equiv). Alkylation as before (−98 °C) utilizing the trimethylsilyl ether of 2-iodoethanol[7] (0.67 g, 2.75 mmol) afforded 0.91 g of crude product which was hydrolyzed in 20 mL of 4.5 N HCl to yield 0.160 g (46%) of pure (96% by VPC) lactone after bulb-to-bulb distillation (pot temperature 115 °C, 11 mm). The spectral properties (IR, NMR) were identical with (*R*)-(−)-4. Rotation and CD data are given in Table I.

(*S*)-(+)-2-Allyl-γ-butyrolactone (4, R = Allyl). In the manner described above the anion of 5 (R = allyl; 0.858 g, 3.5 mmol) was formed in 35 mL of THF with LDA (3.86 mmol, 1.1 equiv). To the yellow solution at −98 °C was added iodoethyl trimethylsilyl ether (0.94 g, 1.1 equiv), and the mixture was stirred at −98 °C for 2 h and then at −78 °C for 5 h. After being warmed slowly to 0 °C, the solution was quenched with ammonium chloride solution, and standard isolation gave 1.22 g of crude product. Hydrolysis as usual (20 mL of 4.5 N HCl) gave 0.240 g (54%) of (*S*)-(+)-4: 92% VPC purity after distillation (bulb-to-bulb, pot temperature 114 °C, 11 mm); spectrally identical with to (*R*)-(−)-4; rotation and circular dichroism data are given in Table I.

(*R*)-(+)-2-*n*-Propyl-1,4-butanediol (14, R = *n*-Pr). A solution of 1.12 g (8.7 mmol) of (*R*)-(−)-4 (R = *n*-Pr) in 50 mL of dry ether was added dropwise to a 0 °C slurry of 0.33 g (8.7 mmol) of lithium aluminum hydride in 100 mL of ether and stirred for 1 h at 0 °C follwed by 2 h at room temperature. The mixture was quenched with just enough water to turn the color from gray to white while being vigorously stirred. The particulate solid was filtered and extracted with the ethereal solution by using a Soxhlet apparatus (12 h). The clear solution was then dried (Na_2SO_4), concentrated, and distilled (bulb-to-bulb; pot temperature 140 °C, 7 mm) to yield 1.03 g (90%) of the clear, viscous oil (*R*)-14: $[\alpha]^{23}_{589}$ +3.47° (neat) [lit.[6] $[\alpha]^{23}_{589}$ +4.73° (neat)]; IR (film) 3340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.5 (s, 2), 3.6 (m, 4), 2.0–0.8 (m, 10).

(*R*)-(+)-2-Allyl-1,4-butanediol (14, R = Allyl). By use of the procedure from above, 1.05 g (8.35 mmol) of (*R*)-(−)-4 (R = allyl) afforded 1.00 g (92%) of viscous (*R*)-(+)-14 (R = allyl) after bulb-to-bulb distillation (pot temperature 140 °C, 7 mm): $[\alpha]^{23}_{589}$ +3.60 (neat) [lit.[6] $[\alpha]^{23}_{589}$ +5.0° (neat)]; IR (film) 3340, 3085, 1645, 1050, 1000, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.8 (m, 1), 5.1 (m, 2), 4.0–3.4 (m, 4), 3.5 (s, 2), 2.3–1.4 (m, 5).

3-[(Trimethylsilyl)oxy]-1-bromopropane. To 3-bromopropanol (Aldrich; 24.6 g, 177 mmol) and 2,6-lutidine (20.8 g, 194 mmol) in carbon tetrachloride (177 mL) was added trimethylchlorosilane (21.1 g, 195 mmol) dropwise at 0 °C. The mixture was stirred at room temperature for 3.3 h. After filtration, carbon tetrachloride was distilled off at ordinary pressure. Distillation gave an oil: 34.2 g (92%); mp 57 °C (10 mm); ^1H NMR (CCl_4) δ 0.10 (s, 9), 1.77–2.20 (m, 2), 3.42 (t, 2), 3.66 (t, 2).

5-Hydroxyvaleronitrile. In a manner similar to that above, 4-chloro-1-butanol was transformed into its trimethylsilyl ether (82%, bp 58–59 °C, 12 mm), and then 29.5 g (0.16 mol) of this was added to 21 g (0.32 mol) of potassium cyanide and 5.3 g (0.032 mol) of potassium bromide in 200 mL of 2-butanone. The solution was heated to reflux for 7 days, the solids were removed by filtration and the solution was concentrated. The residue was heated in 200 mL of ethanol containing 1 mL of 4.5 N HCl for 1 h, the solution was evaporated, and the residue was taken up in ether and the mixture dried ($MgSO_4$) and concentrated. Distillation of the ethereal residue gave 9.4 g (58%) of an oil [bp 77–80 °C (1 mm)] whose IR and ^1H NMR spectra were consistent with the structure.

2-Iminotetrahydropyran 15. Hydrogen chloride was introduced to 5-hydroxyvaleronitrile (14.6 g, 0.147 mol) at 0 °C until 5.4 g (0.148 mol) of hydrogen chloride was absorbed. The mixture was allowed to stand at 0 °C for 3 h, and it solidified. The solid was collected and washed with ether (yield 12 g, 60%). The material contained a small quantity of ammonium chloride but was used for the preparation of oxazoline 8 without further purification: mp 123–125 °C; IR (KBr) 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.55–2.01 (m, 4), 2.71–3.18 (m, 2), 4.50–4.77 (m, 2).

(4*S*,5*S*)-2-[4-[(Trimethylsilyl)oxy]butyl]-4-methoxy-5-phenyl-2-oxazoline (8). Method A. To diisopropylamine (11.4 g, 0.11 mol) in THF (90 mL) was added *n*-butyllithium (44.9 mL of a 2.45 M solution, 0.11 mol) with ice cooling. The resultant LDA was added to 1 (20.5 g, 0.10 mol) in THF (200 mL) dropwise at −78 °C, and the mixture was stirred an additional hour. A THF solution (50 mL) of 3-[(trimethylsilyl)oxy]-1-bromopropane (23.0 g, 0.11 mol) was added over 2 h, the mixture was stirred at −78 °C for 10 h and at room temperature for 5 h, and the reaction was quenched with water. The aqueous layer was extracted with ether, and the organic layer was washed with saturated brine, dried ($MgSO_4$), and concentrated. Distillation gave an oil which was purified by silica gel column chromatography (15% acetone–hexane). Bulb-to-bulb distillation gave 8: 18.8 g (56%); bp 130 °C (0.05 mm); $[\alpha]^{23}_D$ −48.1° (*c* 10.4 $CHCl_3$); IR (film) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 9), 1.40–2.02 (m, 4), 2.20–2.66 (m, 2), 3.43 (s, 3), 3.43–3.83 (m, 4), 3.98–4.33 (m, 1), 5.33 (d, 1), 7.40 (s, 5).

Method B. A mixture of (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-(methoxymethyl)-1-propanol (7; 890 mg, 4.9 mmol) and 15 (1.3 g, 9.6 mmol) in dichloromethane (20 mL) was stirred at room temperature for 3 h. The mixture was washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue 16 (1.3 g) and 2,6-lutidine (0.58 g, 5.4 mmol) were dissolved in carbon tetrachloride (26 mL), and trimethylchlorosilane (0.58 g) was added dropwise at 0 °C. The mixture was stirred at room temperature for 1.5 h, and 2 drops of methanol were added. After filtration and concentration, the residue was distilled to give 8 (73%, 1.2 g) identical with that formed in method A.

(*R*)-(−)-2-Methylvalerolactone (11, R = Methyl). General Procedure. To diisopropylamine (0.64 g, 6.3 mmol) in THF (8.8 mL) was added *n*-butyllithium (2.56 mL, of a 2.45 M solution, 6.3 mmol) at 0 °C. The resultant LDA was added to 8 (2.0 g, 6.0 mmol) in THF (40 mL) at −78 °C over 30 min and the mixture stirred an additional 1 h. Dimethyl sulfate (0.78 g, 6.2 mmol) in THF (10 mL) was added over 1 h, and the mixture was stirred at −78 °C for 6 h. The reaction was quenched by the addition of water, and the aqueous layer was extracted with ether, the extracts being washed with saturated brine, dried ($MgSO_4$), and concentrated to leave an oil (2.0 g) which was used in the next step without further purification. The dialkylated oxazoline 9 was heated in a mixture of ethanol (20 mL) and water (10 mL) under reflux for 2.5 h. Evaporation gave an oil, and water was distilled off completely by forming the azeotrope with ethanol. The resultant 10 (1.7 g) was analyzed by high-pressure LC without

any purification to give the diastereomeric ratios presented in Table II. The oxazoline **10** (1.6 g) was heated in 4.5 N sulfuric acid (16 mL) under reflux for 15 min. After cooling with ice–water, the mixture was extracted with ether, and the extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue (650 mg) was heated with *p*-toluenesulfonic acid monohydrate (6.5 mg) in benzene (13 mL) with a Dean–Stark apparatus for 15 min. The mixture was washed with 10% K_2CO_3 and then with saturated brine and dried over magnesium sulfate. Distillation (bulb-to-bulb) gave **11** (R = Me): 450 mg (66% from **8**); bp 100–105 °C (12 mm) [lit.[12] 104–108 °C (13–14 mm) for racemate]; $[\alpha]^{23}_D$ −40.7° (*c* 3.08, MeOH); IR (film) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3), 1.38–2.80 (m, 5), 4.20–4.51 (m, 2).

(*R*)-(−)-2-Methylvalerolactone (11, R = Me) was prepared from **8** and methyl iodide: yield 68%; $[\alpha]^{23}_D$ −33.5° (*c* 4.0, MeOH).

(*R*)-(−)-2-Ethylvalerolactone (11, R = Et) was prepared from **8** and ethyl iodide: yield 51%; bp 108–112 °C (12 mm); $[\alpha]^{23}_D$ −45.3° (*c* 2.97, MeOH); IR (film) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, 3), 1.20–2.70 (m, 7), 4.20–4.50 (m, 2).

(*R*)-(−)-2-Propylvalerolactone (11, R = *n*-Pr) was prepared from **8** and propyl iodide: yield 40%; bp 115–120 °C (12 mm) [lit.[13] bp 118–120 °C (10 mm) for the racemate]; $[\alpha]^{23}_D$ −47.0° (*c* 2.98, MeOH); IR (film) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68–1.06 (m, 3), 1.06–2.71 (m, 9), 4.20–4.47 (m, 2).

(*S*)-(−)-2-Allylvalerolactone (11, R = allyl) was prepared from **8** and allyl bromide: yield 65%; bp 123–127 °C (12 mm); $[\alpha]^{23}_D$ −38.1° (*c*, 2.97, MeOH); IR (film) 3075, 1733, 995, 912 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–2.88 (m, 7), 4.20–4.48 (m, 2), 4.90–5.32 (m, 4), 5.50–6.23 (m, 1).

(*S*)-(−)-2-Benzylvalerolactone (11, R = $PhCH_2$) was prepared from **8** and benzyl bromide: yield 47%; bp 110–120 °C (0.05 mm); $[\alpha]^{23}_D$ −50.2° (*c* 3.43, MeOH); IR (film) 1733, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55–2.15 (m, 4), 2.52–2.93 (m, 2), 3.13–3.54 (m, 1), 4.20–4.48 (m, 2), 7.28 (br s, 5).

(*R*)-(+)-2-Benzylvalerolactone (11, R = $PhCH_2$). By use of the 2-phenethyloxazoline **12**[11] and 3-[(trimethylsilyl)oxy]-1-bromopropane (or the iodide) according to the General Procedure for **4** gave the 2-benzyl lactone (54%, from **5**) after hydrolysis; $[\alpha]_D^{23}$ +48.5° (*c* 3.68, MeOH).

(−)-2-[(Carbomethoxy)methyl]valerolactone (17). (a) From (*S*)-(−)-2-Benzyl Lactone 11. The 2-benzyl lactone (200 mg, 1.05 mmol) of somewhat lower optical purity [$[\alpha]^{23}_D$ −21.0° (*c* 4.5 MeOH)] in 20 mL of acetic acid was treated with ozone at room temperature for 5 h. The reaction was monitored by TLC (silica gel, 15% acetone–hexane). When the starting benzyl lactone was gone, hydrogen peroxide (30%, 1.2 g) was added and the mixture stirred at ambient temperature overnight. The solvents were distilled away, and the residue was again treated with acetic acid (20 mL) and hydrogen peroxide (30%, 1.2%). After the solvents were distilled off, the residue was taken up in ether and an ethereal diazomethane solution was added until the yellow color persisted. Evaporation gave **17** (80 mg, 44%). The analytical sample was obtained by preparative GLC: $[\alpha]^{23}_D$ −12°, $[\alpha]^{23}_{365}$ −47° (*c* 0.28, $CHCl_3$); IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.34 (m, 4), 2.43–3.18 (m, 3), 3.72 (s, 3), 4.30–4.52 (m, 2).

(b) From (*S*)-(−)-2-Allyl Lactone 11. The allyl lactone [200 mg, 1.43 mmol, $[\alpha]^{23}_D$ −38.6° (*c*, 2.81, MeOH)] in methanol (20 mL) was treated with ozone at −78 °C for 5 min. After the methanol was distilled off, the residue was treated with formic acid (3 mL) and hydrogen peroxide (30%, 1.7 g, 14.7 mmol), and the solvents were distilled off at ordinary pressure. This treatment was repeated twice. The residue was dissolved with ether, and ethereal diazomethane was added until the yellow color persisted. Evaporation gave **17** (100 mg, 41%). The analytical sample was obtained by preparative GLC: $[\alpha]^{23}_D$ −40°, $[\alpha]^{23}_{365}$ −146° (*c* 0.20, $CHCl_3$).

Hydrogenation of (*S*)-(−)-2-Allyl Lactone 11. The allyl lactone [200 mg, 1.4 mmol, $[\alpha]^{23}_D$ −38.6° (*c* 2.81, MeOH)] was hydrogenated over palladium/carbon (5%, 20 mg) in ethanol at ordinary pressure. After evaporation, distillation gave (*R*)-(−)-**11** (R = *n*-propyl) [180 mg (89%); $[\alpha]^{23}_D$ −39.4° (*c* 3.15, MeOH)] identical with that prepared from **8** and propyl bromide.

Separation of 10 into Pure Diastereomers. Maximum Rotation of (*S*)-(−)-11 (R = $PhCH_2$). The separation on a preparative liquid chromatograph[9] was performed on 5.6 g of a mixture of isomers of **10** which was eluted by using 40% THF–hexane to provide pure material: 1.0 g; $[\alpha]^{23}_D$ +11.8° (*c* 2.29, $CHCl_3$). The remainder of the material collected contained overlapping products. The homogeneity of the pure diastereomer was confirmed by high-pressure LC (Table I). Successive hydrolysis and cyclization under the same conditions as those used for the mixture gave **11**: yield 41%; $[\alpha]^{23}_D$ −77.7° (*c* 4.05, MeOH). The literature $[\alpha]^{23}_D$ value for (*S*)-(−)-**11** (R = $PhCH_2$) was reported[8] to be 63.2°.

Acknowledgment. The authors are grateful to the National Institutes of Health in the early phases of this work and to the National Science Foundation in the latter phases for financial support.

Registry No. **1**, 52075-14-6; **2**, 55232-20-7; **3** (R = Me), 73746-59-5; **3** (R = Et), 73746-60-8; **3** (R = Pr), 73746-61-9; **3** (R = allyl), 73746-62-0; **3** (R = Bu), 73746-63-1; (*R*)-**4** (R = Me), 55254-35-8; (*R*)-**4** (R = Et), 55232-21-8; (*R*)-**4** (R = Pr), 55232-22-9; (*R*)-**4** (R = allyl), 55232-23-0; (*R*)-**4** (R = Bu), 55232-24-1; (*S*)-**4** (R = allyl), 73746-64-2; (*S*)-**4** (R = Bu), 73746-65-3; **5** (R = Bu), 73713-17-4; **5** (R = allyl), 73746-66-4; **6** (R = Bu), 73746-67-5; **6** (R = allyl), 73746-68-6; **7**, 51594-34-4; **8**, 73746-69-7; **9** (R = Me), 73758-09-5; **9** (R = Et), 73746-70-0; **9** (R = Pr), 73746-71-1; **9** (R = allyl), 73746-72-2; **9** (R = $PhCH_2$), 73746-73-3; **10** (R = Me), 73746-74-4; **10** (R = Et), 73758-10-8; **10** (R = Pr), 73746-75-5; **10** (R = allyl), 73746-76-6; **10** (R = $PhCH_2$), 73746-77-7; epi-**10** (R = $PhCH_2$), 73746-78-8; (*R*)-**11** (R = Me), 73746-79-9; (*R*)-**11** (R = Et), 73788-99-5; (*R*)-**11** (R = Pr), 73746-80-2; (*S*)-**11** (R = allyl), 73746-81-3; (*S*)-**11** (R = $PhCH_2$), 68975-03-1; (*R*)-**11** (R = $PhCH_2$), 68975-22-4; **12**, 51594-38-8; **13**, 73758-11-9; (*R*)-**14** (R = Pr), 55232-18-3; (*R*)-**14** (R = allyl), 55232-19-4; **15**, 2455-02-9; **16**, 73746-82-4; **17**, 73746-83-5; iodoethyl trimethylsilyl ether, 26305-99-7; 3-[(trimethylsilyl)oxy]-1-bromopropane, 34714-04-0; 3-bromopropanol, 627-18-9; trimethylchlorosilane, 75-77-4; 5-hydroxyvaleronitrile, 2427-16-9; 4-chloro-1-butanol, 928-51-8; 4-chloro-1-butanol trimethylsilyl ether, 13617-19-1; 2-butanone, 78-93-3.

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