Highly Stereoselective Addition of Organolithium Reagents to Chiral Oxazolines. Asymmetric Synthesis of 3-Substituted Alkanoic Acids and 3-Substituted Lactones

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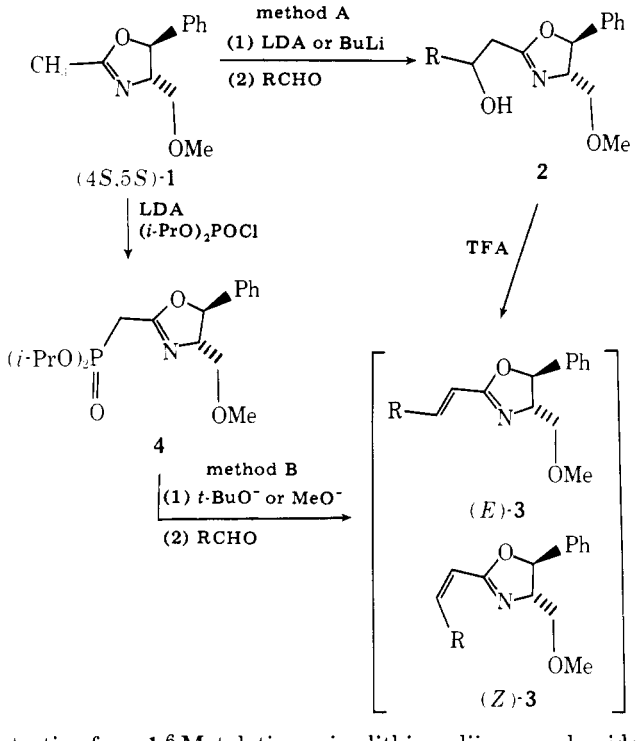
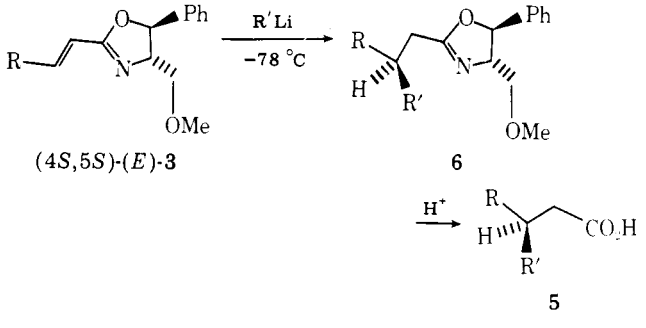
Nucleophilic addition of organolithium reagents to chiral α,β-unsaturated oxazolines **3** furnishes the adducts **6** with a high degree of stereoselectivity. Hydrolysis of these adducts leads to 3-substituted alkanoic acids in >90% enantiomeric excess. A mechanism to account for this highly stereoselective process is advanced consistent with the observed facts. The method allows, by reversing the order of group introduction, a route to either enantiomer in high enantiomeric excess. Use of alkoxy-substituted chiral oxazolines provides a route to 3-substituted valerolactones and benzovalerolactones in >90% ee.

The efforts to successfully provide useful asymmetric syntheses have, in the last five years, shown considerable promise.[1,2] Nucleophilic addition to electrophilic olefins possessing a chiral auxiliary group have been among the most successful in reaching chiral molecules in high enantiomeric excess (ee).[3] Preliminary studies[4] from this laboratory several years ago described the first examples of carbon–carbon bond formation accompanied by high asymmetric induction. This was attributed to the presence of suitable ligands in the chiral electrophilic olefin which imparted a degree of rigidity to the transition state leading to nucleophilic addition. In the past, these reactions proceeded with poor asymmetric induction due to the lack of rigidity and/or the high temperatures required for the addition step.[5] We now report, in detail, the nucleophilic addition to α,β-unsaturated oxazolines **3** using various organolithium reagents. The requisite chiral oxazolines (*E*)-**3** were obtained by two routes (methods A and B)



starting from **1**.[6] Metalation using lithium diisopropylamide (LDA) and addition of the appropriate aldehyde gave the β-hydroxy adduct **2**. Dehydration of the latter under various acid catalyses gave **3** as a mixture of *E–Z* isomers and considerable quantities of polymeric material (Table I). It was also observed that various quantities of isomeric olefinic product had formed in those cases (*R* = *i*-Pr, cyclohexyl) where branching existed at the β carbon. Although the method gave predominantly the *E* isomer, another method of greater efficiency and generality was sought. The use of the Wadsworth–Emmons olefination[7] involving phosphonate-stabilized carbanions is well known to provide a high degree of *E* isomers, and this process was investigated. Application of this technique with the use of the bulky diisopropyl phosphonate **4** as an intermediate gave both high chemical yields of **3** and high *E–Z* ratios (Table I, method B). The intermediate phosphonate, **4**, although formed in situ as an anion, was preferably isolated from the reaction and used in a separate step to produce (*E*)-**3**.[7f] Other methods to reach (*E*)-**3** were also investigated, and in particular the α-trimethylsilyl carbanions of **1**. However, as reported earlier,[8] this method led mainly to **3** with the *Z* isomer predominating. It is *noteworthy that reaction of organolithium reagent with* (*Z*)-**3** *led only to deprotonation of the allylic protons.* Thus, small percentages of (*Z*)-**3** present with the *E* isomer did not interfere with the asymmetric nucleophilic addition, except to lower the yields of product and provide polymeric material. On the other hand, the *E* isomer with allylic protons present [(*E*)-**3**, R = Me, Et] also showed some competitive deprotonation (20–30%) along with nucleophilic addition. This side reaction is reflected in the yields of addition product shown in Table II where R = Me, Et.

With an efficient route to chiral unsaturated oxazolines in hand, the addition of various organolithium reagents to a THF solution of (*E*)-**3** at −78 °C was performed. After quenching, good yields of the adduct **6** were obtained. For most cases, the



crude material was directly hydrolyzed in aqueous sulfuric acid to the chiral 3-substituted alkanoic acid **5** in 38–87% overall yields (from **3**) and in >95% ee (Table II). For those acids **5** (**c, e, g, h. l**) whose maximum rotation was unknown or in doubt, **6** was isolated and the diastereomers were separated using medium-pressure liquid chromatography.[12] Hydolysis of pure **6** gave the acid **5** with the specific rotations listed in Table II. For the chiral methoxy-substituted acids **5** (**k, m, n, q, r, s**), also unknown, the % ee was determined

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Table I. Chiral 2-Alkenyloxazolines 3

RCHO	method A E/Z^a	method A % yield E^b	method B E/Z^a	method B % yield E^b
Me	93:7	44	100:0	80
Et	90:10	37	100:0	89
i-Pr	80:20	43[c]	100:0	93
t-Bu			100:0	89
cyclohexyl	90:10	44		
$MeOCH_2CH_2$	87:13	40	100:0	87
Ph	100:0	65	100:0	82
o-MeOPh	100:0	60		

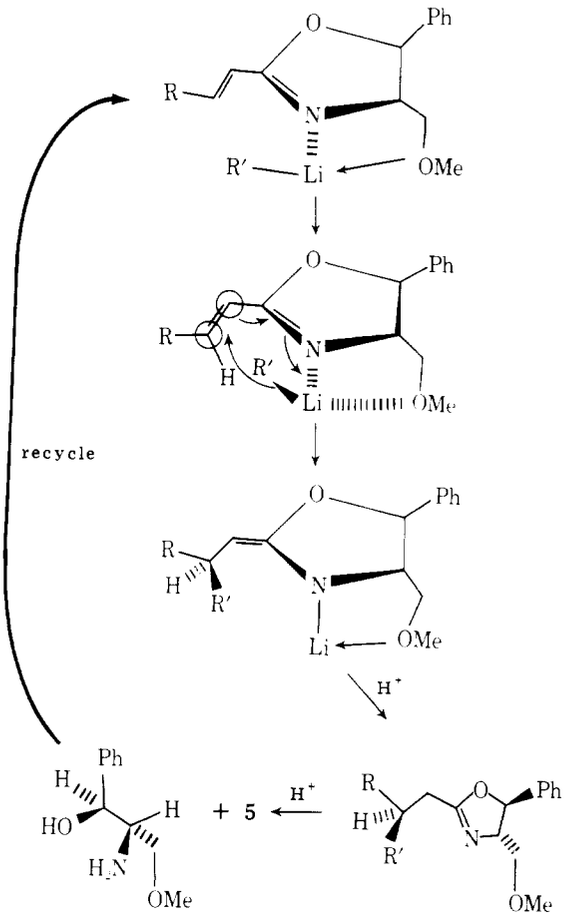
[a] Ratio from NMR determination of crude reaction product. [b] Pure material; isolated by distillation and/or chromatography. Physical data are given in the Experimental Section. Yield is based on 1. [c] Contains 20–30% of isomerized alkene.

using chiral shift reagents on their methyl esters (Table III). In these examples the enantiomeric ratios were found to be 95 ± 2%. Thus, this nucleophilic addition proceeded with a variety of substituents accompanied by remarkably high stereoselectivity. It is also evident from Table II that it is possible to prepare either optical antipode (**5f** and **5o**) by merely reversing the alkyl groups on **3** and the organolithium, respectively. Certain limitations for this process were noted during the course of evaluating its scope. The use of methyllithium failed to add conjugatively to **3**, thus precluding the synthesis of the enantiomers of **5a–d.** A wide variety of conditions and alternative methyl carbanion reagents (MeMgBr, Me_2CuLi, Me_3Al, $LiAlMe_4$, and $LiCH_2SPh$) were examined. Although MeLi could be induced to add to **3**, the conditions (0–25 °C) were such that the product obtained was essentially racemic. A further limitation was noted when stabilized carbanions (ethyl lithioacetate, lithioacetonitrile, *tert*-butyl lithioacetate, lithiodithiane, lithiooxazoline, **1**) were employed. Additions occurred with general success (40–70% yields), but the products were essentially racemic (0–20% ee). Thus, attempts to introduce functionality into **5** are currently limited to methoxy (or related) groups shown in Table II. Further studies in this regard are obviously needed.

The reaction may be envisioned to proceed as shown in Scheme I. The organolithium reagent initially complexes to the nitrogen and the methoxyl ligands and then transfers the carbanion to the ψ face of the olefin (R = alkyl), producing the lithiated adduct. Quenching the reaction followed by acidic hydrolysis furnishes the chiral acid **5** and the methoxyamino alcohol, which may be recycled[6] to prepare (*E*)-**3**. To lend support for this mechanistic proposal, the oxazoline **10** was prepared starting from (*S*)-ethyl serinate hydrochloride and passing through intermediates **7–9.** The enantiomeric purity of **9** was determined using chiral shift reagents (after comparison with racemic **9**) and found to be 80 ± 3%, indicating ~10% racemization during the reduction step (**7** → **8**).[9] Treatment of (4*R*)-**9** with *n*-butyllithium and benzaldehyde gave the unsaturated oxazoline **10** in 51% yield. Since **10** did not possess the 5-phenyl group, it was of interest to see if the conjugate addition of organolithium reagents would proceed with a comparable degree of asymmetric induction to that observed with (*E*)-**3** (R = Ph). Addition of *n*-butyllithium to **10** (−78 °C, THF, 30 min) gave, after hydrolysis, (*S*)-**5p** in 77% ee. Correcting for the 80% enantiomeric purity of **10,** this amounts to ~96% asymmetric synthesis. It is noteworthy that the sense of the asymmetric addition is also identical since (*E*)-**3** has the opposite configuration from **10** at C-4 such that the chiral acid **5** possesses the *R* configuration from the former and the *S* configuration from the latter. From this result, it is safe to assume that the organolithium reagent adds in the manner depicted by Scheme I and that the presence or absence of the C-5 phenyl group is of no consequence to the outcome of this reaction. This should be contrasted to the critical need for the phenyl group in asymmetric electrophilic alkylations of oxazolines.[2]

The chiral methoxy-substituted acids **5k–n** and **5q–s,** whose enantiomeric purity was shown to be ~95%, were subjected to boron tribromide, which transformed them into the lactones **11** and **12,** respectively. These lactones were assumed to possess the same degree of enantiomeric purity and absolute configuration as their precursors **5.** None of the lactones have been reported previously except for **11** (R = Ph), which Jones described as being obtained from enzymatic oxidation.[10] Comparison of both lactones confirmed the high degree of enantiomeric purity for **11** (R = Ph) (Table IV). It was reported earlier[4b] from our laboratory that lactone **11** (R = Ph) possessed an $[\alpha]_{578}$ of −12.6° with the configuration assigned as *S*. However, Jones' report of this (*S*)-lactone possessing a positive rotation ($[\alpha]_D$ 0.78°, 21% ee) caused us to reexamine

Scheme I



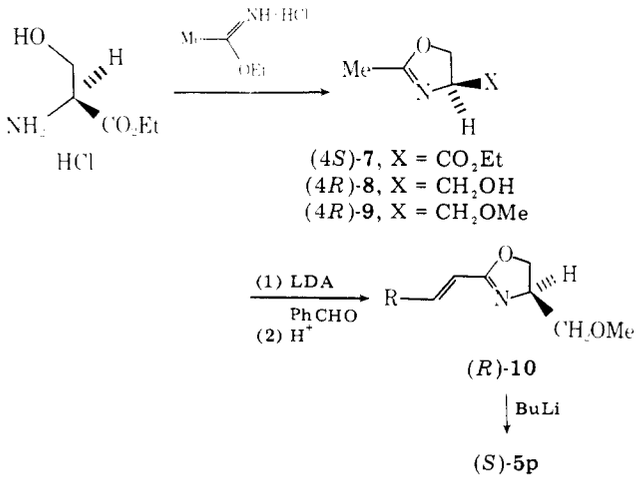
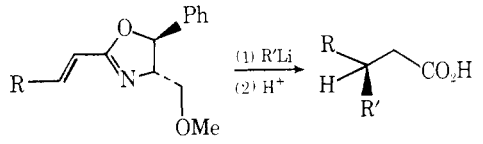


Table II. Chiral β-Substituted Alkanoic Acids 5



E-3 5

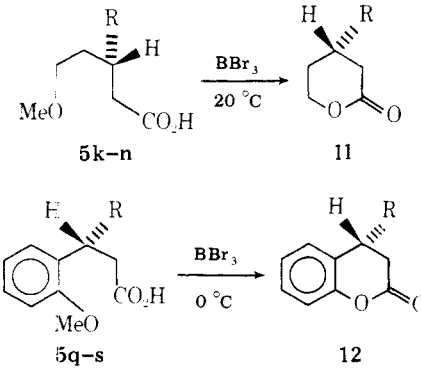
compd	R [in (*E*)-3]	R'Li	% yield	acid 5[a] $[\alpha]^{obsd}_{589}$, deg	$[\alpha]^{lit}_{589}$, deg	% ee	config.
5a	Me	Et	40	−7.44 (neat)	−8.15 (neat)[b]	92	*R*
5b	Me	*n*-Bu	38	+3.84 (neat)	−4.2 (neat)[c]	91	*R*
5c	Me	*n*-hexyl	44	+5.08 (neat)	+5.10 (neat)[d]	99	*R*
5d	Me	Ph	44	+55.80 (*c* 10, PhH)	+57.23 (*c* 9, PhH)[e]	98	*S*
5e	Et	*n*-Bu	55	+2.84 (neat)	+2.94 (neat)[d]	96	*R*[j]
5f	Et	Ph	39	+45.8 (*c* 7, PhH)	−49.66 (*c* 7, PhH)[f]	92	*S*
5g	*i*-Pr	*n*-Bu	53	−0.82 (neat)	−0.82 (neat)[d]	99	*R*[j]
5h	*t*-Bu	*n*-Bu	50	−17.7 (neat)	−18.0 (neat)[d]	98	*R*[j]
5i	cyclohexyl	Et	73	−5.27 (neat)	−5.35 (neat)[g]	99	*R*
5j	cyclohexyl	*n*-Bu	79	−5.90 (neat)	+4.6 (neat)[g]	99	*R*
5k	$MeOCH_2CH_2$	Et	54	+1.46 (neat)	*h*	95	*S*[j]
5l	$MeOCH_2CH_2$	*n*-Pr	50	+1.32 (neat)	+1.32 (neat)[d]	99	*S*[j]
5m	$MeOCH_2CH_2$	*n*-Bu	66	+2.12 (neat)	*h*	95	*S*[j]
5n	$MeOCH_2CH_2$	Ph	60	+9.48 (*c* 10, $CHCl_3$)	*h*	95	*S*[j]
5o	Ph	Et	66	−48.0 (*c* 10, PhH)	−49.66 (*c* 7, PhH)[f]	97	*R*
5p	Ph	*n*-Bu	67	−24.9 (neat)	+23.1 (neat)[i]	99	*R*
5q	*o*-MeOPh	Et	83	−21.3 (*c* 11, PhH)[a]	*h*	95	*R*[j]
5r	*o*-MeOPh	*n*-Bu	75	−21.7 (*c* 10, PhH)[a]	*h*	95	*R*[j]
5s	*o*-MeOPh	Ph	87	−24.8 (*c* 10, PhH)[a]	*h*	95	*S*[j]

[a] All rotations were taken at 24 ± 1° at 589 nm except for **5q–s**, which were recorded at 578 nm. [b] C. G. Overberger and I. Cho, *J. Org. Chem.*, **33**, 3321 (1968). [c] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **95**, 153 (1932). [d] Specific rotation determined in this laboratory[12] using medium-pressure liquid chromatography to separate diastereomeric **6** and hydrolysis to acid. [e] V. Prelog and H. Scherrer, *Helv. Chim. Acta*, **42**, 2227 (1959). [f] L. Lardicci, R. Menicagli, and P. Salvadori, *Gazz. Chim. Ital.*, **98**, 738 (1968). [g] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **97**, 503 (1932). [h] $[\alpha]_D$ not reported; % ee was determined using a chiral shift reagent on the methyl ester and is accurate to ±3% (see Table III). [i] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **97**, 563 (1932). [j] Absolute configurations are predicted from this work only.

Table III. Enantiomeric Excess of Methyl Esters Using Chiral Shift Reagents

methyl ester of	% yield of ester[a]	$[\alpha]^{23}_{578}$, deg	% ee[b]	shift reagent[c] (mg/mg ester)
5k	89	−1.42 (*c* 11, $CHCl_3$)	95 ± 3	$Eu(hfc)_3$ (20/22)
5m	99	+0.33 (*c* 11, $CHCl_3$)	95 ± 3	$Eu(hfc)_3$ (16/18)
5n	99	+1.78 (*c* 10, $CHCl_3$)	95 ± 3	$Eu(hfc)_3$ (18/12)
5q	86	−10.2 (*c* 8, PhH)	95 ± 3	$Eu(tfc)_3$ (12/16)
5r	90	−11.4 (*c*6.5, PhH)	95 ± 3	$Eu(tfc)_3$ (12/15)
5s	68	−32.5 (*c*5, PhH)	95 ± 3	$Eu(tfc)_3$ (25/29)

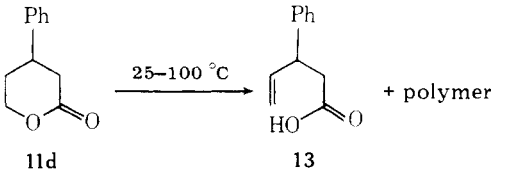
[a] Prepared by use of methanol–H_2SO_4 or diazomethane–ether. [b] Determined by mixing racemic ester and chiral ester (~1:1) and measuring peak ratios in CCl_4 solutions containing indicated amounts of shift reagents. [c] Purchased from Aldrich Chemical Co., Milwaukee, Wis.: $Eu(hfc)_3$ = tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III); $Eu(tfc)_3$ = tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium(III).



5k–n 11

5q–s 12

our earlier work. It was observed that the lactone, purified earlier by chromatography to obtain all of the physical data except $[\alpha]$, was distilled before recording this value. The distilled material (Kugelrohr) gave $[\alpha]_{578}$ −12.6°, which was reported.[4b] It was subsequently found that the lactone decomposed with some elimination on distillation, or after standing at room temperature for 5 days. Refluxing a carbon tetrachloride solution (NMR sample) of **11** (R = Ph) for 30 min also gave considerable change. However, when the phenyl lactone was purified via silica gel (CH_2Cl_2), it exhibited $[\alpha]_D$ +3.63°, which based on Jones' value of 0.78° (21% ee), corresponded to 98% ee. The thermal instability of various valerolactones has been the subject of recent studies;[11] however, for 3-phenyl valerolactones, elimination is apparently unusually facile. Although the unsaturated acid was not isolated,



11d **13**

Table IV. Chiral 3-Substituted Valerolactones 11 and Benzovalerolactones 12

acid	lactone[a]	R	% yield from 5	$[\alpha]^{23}_{589}$, deg	$[\alpha]^{23}_{578}$	(c, solvent), deg	% ee[b]	config.[b]
5k	**11a**	Et	45[d]	−26.0	−27.2	(4.3, $CHCl_3$)	95	*S*
5l	**11b**	*n*-Pr	48[d]	−23.9	−25.0	(8.6, $CHCl_3$)	95	*S*
5m	**11c**	*n*-Bu	45	−22.3	−23.3	(8.9, $CHCl_3$)	95	*S*
5n	**11d**	Ph	60[d]	+3.63	+3.80	(7.2, $CHCl_3$)	98[c]	*S*[c]
5q	**12a**	Et	77		+69.8	(5.9, PhH)	95	*R*
5r	**12b**	*n*-Bu	72		+74.2	(5.0, PhH)	95	*R*
5s	**12c**	Ph	67[e]		+43.7	(5.6, PhH)	95	*S*

[a] Physical data are given in the Experimental Section. [b] Enantiomeric excess and configuration are the same as those of the corresponding acids (Table II) and esters (Table III), except where noted. [c] Based on data reported in ref 10. [d] See ref 10b. [e] Mp 110–112 °C.

the NMR spectrum of the distilled lactone **11** indicated the presence of signals in the vinyl region. The other lactones in Table IV were reexamined in light of this behavior and found to be completely stable to distillation conditions.

In summary, a route to 3-substituted alkanoic acids and their corresponding lactones in high enantiomeric excess has been achieved, and studies extending this methodology to more complex naturally occurring substances are now under way.

Experimental Section[12]

Organolithium Reagents. Commercial phenyllithium (1.86 M in 70:30 benzene–ether), *n*-butyllithium (2.4 M hexane), and ethyllithium (1.24 M in benzene) were employed after titration by either the method of Watson and Eastham[13] or that of Kaufron and Baclawski.[14] It was frequently found that the titer varied from the label concentration by more than 15%, thus suggesting periodic monitoring of this material.

***n*-Propyllithium.** Lithium wire (4.00 g, 0.577 g-atom, 0.02% Na, Alfa-Ventron) was cut into 60 mL of pentane (olefin-free), the mixture was then heated to reflux, and 22.0 mL of *n*-propyl chloride (Aldrich, twice distilled, bp 43 °C (640 mm), n^{23}_D 1.3885) in 30 mL of pentane was added slowly over 3 h. After being stirred for 2 h at reflux, the mixture was cooled and the suspension was allowed to settle (an additional 25 mL of pentane may be added to facilitate precipitation). The supernatant was removed by cannula to give 117 mL of a yellow solution. Titration[14] gave 0.53 M *n*-propyllithium. The sludge which remains is *pyrophoric*, and caution should be exercised in its disposal.

***n*-Hexyllithium.** A lithium dispersion (oil removed with hexane–ether, 1:1) was covered with 15 mL of ether under an argon atmosphere and cooled with an acetone–dry ice bath to −15 to −10 °C. *n*-Hexyl chloride (3.62 g, 30.0 mmol) in 10 mL of ether was added via a constant rate addition funnel over 2.5 h. The suspension was allowed to settle, and the colorless supernatant was titrated[14] to give 1.25 M (theory, 1.20 M) *n*-hexyllithium. THF (30 mL) was added, and the supernatant was transferred via syringe for use in subsequent reactions. Previous preparations of *n*-hexyllithium[15] gave poor results in this study.

Diisopropyl Phosphonochloridate. Triisopropyl phosphite (20.0 g, 96 mmol, Aldrich) and 150 mL of ether were cooled to −78 °C under nitrogen. Chlorine was added dropwise to the solution (over a −78 °C condenser) until the forming white slurry had retained a green tint. The cold bath was removed, the reaction vessel was attached to a Buchi rotovap, and the solvent, excess chlorine, and isopropyl chloride were removed at subambient temperatures *in a hood*. The residue, which had turned colorless during the evaporation, weighed 19.4 g (~100%). The product may be distilled (bp 50–54 °C (0.10 torr), 16.1 g, 84%); however, excellent results were repeatedly obtained using the crude product immediately after concentration. The phosphonochloridate discolors within 3–4 days at room temperature, but it may be stored as a solid in a freezer (−30 °C) in two nested glass bottles with Teflon liners. The phosphonochloridate is volatile with a flowery odor and fumes in contact with moist air. *The hazards associated with this and related derivatives have been described*[16] *and should be consulted prior to use. If any spills occur, dilute sodium hydroxide solution is suitable for decomposition and/or disposal. It is advisable to have on hand atropine injectors in the event of inhalation.* The NMR spectrum (CCl_4) showed a multiplet at δ 4.75 (1 H) and a doublet (6 Hz) at δ 1.39 (6 H); d^{23} = 1.091 g/cm³.

(4*S*,5*S*)-(−)-2-(Diisopropylphosphonomethyl)-4-methoxy-5-phenyl-2-oxazoline (4). To a solution of 0.37 mol of lithium diisopropylamide (from equimolar amounts of *n*-butyllithium and diisopropyl amine, 0 °C, THF) in 500 mL of anhydrous THF, cooled to −78 °C, was added dropwise over 15 min 36.7 g (0.18 mol) of (−)-1[6] [$[\alpha]_D$ − 116.7° (*c* 8.96, $CHCl_3$)] as a solution in 200 mL of THF. After the mixture was stirred for 2 h, 36.1 mL (0.18 mol) of diisopropyl phosphonochloridate was injected into the solution and stirring was continued for an additional hour. The gold-colored solution was warmed to −50 °C, stirred for 20 min, and poured into 600 mL of water. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over molecular sieves (4Å), and concentrated to give 67.2 g (~100%) of a pale yellow oil. This product can be used without further rectification; however, a sample was distilled (bulb-to-bulb): bp 60 °C (0.01 torr); IR (film) 1668, 1390, 1260, 1130, 1000, 700 cm⁻¹; NMR (CCl_4) δ 7.30 (m, 5), 5.28 (d, *J* = 6 Hz, 1), 4.70 (hept of d, *J* = 6 and 1 Hz, 2), 4.0 (m, 1), 3.7–3.2 (m, 2), 3.3 (s, 3), 2.87 (d, *J* = 21 Hz, 2), 1.30 (d, *J* = 6 Hz, 12); mass spectrum, m/e 369 (M^+), 73 (100); $[\alpha]_D$ −13.2° (neat); d^{23} = 1.092 g/cm³; n^{23}_D 1.4900).

Anal. Calcd for $C_{18}H_{28}NO_5P$: C, 58.52; H, 7.64. Found: C, 57.94; H, 7.53.

Several attempts at satisfactory analysis gave results which were slightly low on carbon. The product decomposes slowly (~1 week) at room temperature and at 70 °C rather rapidly.

α,β-Unsaturated Oxazolines 3. Method B. The following is a typical procedure.

3 (R = *t*-Bu). (Diisopropylphosphonomethyl)oxazoline **4** (prepared above and used in its "crude" state) (20.0 g, 51 mmol) and 8.9 g (102 mmol) of pivaldehyde were cooled to −78 °C in 30 mL of THF with 2 drops of water. Potassium *tert*-butoxide (6.34 g, 56 mmol) in 25 mL of THF was added over 30 min, and the reaction was stirred for 15 h, while slowly warmed to ambient, and then poured into 100 mL of water. The organic products were extracted with petroleum ether, washed with brine, and dried over K_2CO_3. The crude product was filtered through 100 g of silica gel with 20% acetone–hexane and concentrated in vacuo to give 13.6 g (97%) of (*E*)-**3** (R = *t*-Bu) as a thin oil; 1.47 g was distilled [130–140 °C (0.06 torr)] to give 1.36 g colorless oil: 89% overall yield from (−)-**1**; $[\alpha]^{19}_D$ +79.9° (*d* 1.005); mass spectrum, *m/e* 273 (M^+); n^{19}_D 1.5196; IR (film) 1650, 1595 cm; NMR (CCl_4) δ 7.21 (s, 5), 6.60 (d, *J* = 16 Hz, 1), 5.82 (d, *J* = 16 Hz), 5.20 (d, *J* = 6 Hz, 1), 4.02 (m, 1), 3.33 (s, 3), 3.8–3.3 (m, 2), 1.11 (s, 9); d^{19} = 1.0050 g/cm³.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.41; H, 8.32.

3 (R = Ph). Using 27 mmol of crude (phosphonomethyl)oxazoline **4**, 30 mmol of benzaldehyde, 2 drops of water, 29 mmol of potassium *tert*-butoxide, and 125 mL of THF at −78 °C in the manner described above followed by Kugelrohr distillation [150 °C (0.02 torr)] gave 6.5 g (82%) of pure (*E*)-**3** (R = Ph) as a thick oil: IR (film) 6145,1600 cm⁻¹; NMR (CCl_4) δ 7.37 (d, *J* = 16 Hz, 1), 7.22 (s, 10), 6.53 (d, *J* = 16 Hz, 1), 5.30 (d, *J* = 6 Hz, 1), 4.10 (m, 1), 3.29 (s, 3), 3.8–3.2 (m, 2); mass spectrum, *m/e* 293 (M^+); $[\alpha]^{23}_D$ +122° (*c* 10, $CHCl_3$).

3 (R = Me). Employing 15 mmol of the (diisopropylphosphonomethyl)oxazoline **4**, 20 mmol of potassium *tert*-butoxide, 3 drops of water, and 46 mmol of freshly distilled acetaldehyde in the manner described above gave 2.8 g (81%) of **3** as pure *E* isomer: bp 120–125 °C (0.01 torr); $[\alpha]^{25}_D$ +38.0° (*c* 7, $CHCl_3$); IR (film) 3035, 1675, 1642, 1612 cm⁻¹; NMR (CCl_4) δ 7.18 (s, 5), 6.58 (d of t, *J* = 16 and 6 Hz, 1), 5.93 (d, *J* = 16 Hz, 1), 5.22 (d, *J* = 6 Hz, 1), 4.03 (m, 1), 3.8–3.2 (m, 2), 3.29 (s, 3), 1.83 (d, *J* = 6 Hz, 3).

3 (R = Et). Using 15 mmol of the (phosphonomethyl)oxazoline **4**, 20 mmol of potassium *tert*-butoxide, 3 drops of water, and 40 mmol of propionaldehyde in the manner described above gave 89% of the

pure (*E*)-butenyloxazoline **3** (R = Et) as an oil: bp 125 °C (0.01 torr); $[\alpha]^{23}_D$ +31.1° (*c* 9.7, $CHCl_3$); IR (film) 3065, 3035, 1671, 1632, 1611 cm^{-1}; NMR (CCl_4) δ 7.26 (s, 5), 6.74 (d of q, J = 16 and 6 Hz, 1), 5.94 (d of d, J = 16 and 2 Hz, 1), 5.28 (d, J = 6 Hz, 1), 3.8–4.3 (m, 1), 3.2–3.9 (m, 2), 3.37 (s, 3), 2.25 (m, 2), 1.10 (t, 3); mass spectrum, *m/e* 245 (M^+).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.19; H, 7.66.

3 (R = $MeOCH_2CH_2$). (Diisopropylphosphonomethyl)oxazoline **4** (13.6 g, 37 mmol) and 4.84 g (55 mmol) of 3-methoxypropionaldehyde[17] in 100 mL of THF were cooled to −78 °C, and a slurry of 4.93 g (44 mmol) of potassium *tert*-butoxide, 3–4 drops of water, and 90 mL of THF was added over 30 min. The solution was stirred for 4 h and the cold bath removed. After 2 h, the orange mixture was poured into 200 mL of 10% sodium acetate. The organic products were extracted with petroleum ether, washed with brine, dried over molecular sieves (4Å), and filtered through Florisil with ether. Concentration left 8.8 g (87%) of **3** (R = $MeOCH_2CH_2$) as a pale yellow oil; homogeneous by TLC (silica, 50% $CHCl_3$–ethyl acetate), R_f = 0.17. An analytical sample was prepared by bulb-to-bulb (Kugelrohr) distillation, 150 °C (0.05 torr): $[\alpha]^{23}_D$ +34.1° (*c* 5.8, $CHCl_3$); IR (film) 3055, 3030, 1670, 1642, 1610 cm^{-1}; NMR (CCl_4) δ 7.28 (s, 5), 6.67 (d of t, J = 16 and 6 Hz, 1), 6.00 (d, J = 16 Hz, 1) 5.27 (d, J = 6 Hz, 1), 3.8–4.3 (m, 1), 3.2–3.8 (m, 10, singlet at 3.40 and 3.28 for the two MeO groups), 2.47 (q, J = 6 Hz, 2). Elemental analysis was not performed since lactones derived from this compound were known.

3 (R = i-Pr). Using 54 mmol of crude **4**, 139 mmol of isobutyraldehyde, 60 mmol of potassium *tert*-butoxide, 3 drops of water, and 250 mL of THF at −78 °C in the manner described above gave 93% of **3** as the pure *E* isomer. Attempted distillation resulted in isomerization to the nonconjugated isomer. The crude compound was used in reactions with alkyllithiums with no difficulty: IR (film) 1650, 1595 cm^{-1}; NMR (CCl_4) δ 7.20 (s, 5), 6.60 (d of d, J = 16 and 7 Hz, 1), 5.83 (d, J = 16 Hz, 1), 4.00 (m, 1), 3.33 (s, 3), 2.38 (m, 1), 3.7–3.2 (m, 2), 1.03 (d, J = 7 Hz, 6).

α,β-Unsaturated Oxazolines 3. Method A. The following procedure is typical for **3** prepared by this method.

3 (R = Cyclohexyl). A solution of 16.4 g (80 mmol) of **1** in 160 mL of THF was cooled to −78 °C under nitrogen and treated rapidly dropwise with 36.7 mL (88.0 mmol) of 2.4 M *n*-butyllithium in hexane. After 1 h at −78 °C, the reaction mixture had turned to a pasty mass, a solution of 9.86 g (88.0 mmol) of cyclohexanecarboxaldehyde in 44 mL of THF was added dropwise over 30 min, and stirring was continued for 1 h (−78 °C) after the addition was complete. The reaction was quenched in 6 mL of absolute methanol. The mixture was allowed to warm to ambient and was poured into 100 mL of saturated aqueous ammonium chloride. The organic phases were separated, the aqueous layer was extracted with ether, and the combined organic layers were washed with 10% sodium bisulfite solution and saturated brine and dried (Na_2SO_4). Concentration gave 22.9 g (90%) of crude **2**. Dehydration to **3** was performed by dissolving **2** in 125 mL of benzene (or toluene), adding 550 mg of trifluoroacetic acid, and heating the solution (Dean-Stark trap) until no more water separated (~6 h). The cooled solution was washed with 5% sodium bicarbonate, dried (Na_2SO_4), and concentrated to give 21.0 g (88% based on **1**) of the (cyclohexylvinyl)oxazoline, which was purified by medium-pressure liquid chromatography[12] in 7–8-g batches [$[\alpha]^{25}_{578}$ +39.4° (*c* 12.4, $CHCl_3$)] in 44% overall yield from **1**: IR (film) 3080, 3045, 1680, 1655, 1620 cm^{-1}; NMR (CCl_4) δ 7.25 (s, 5), 6.58 (d of d, J = 16 and 6 Hz, 1), 5.92 (d, J = 16 Hz, 1), 5.25 (d, J = 6 Hz, 1), 4.0–4.2 (m, 1), 3.8–3.2 (m, 3), 3.38 (s, 3), 2.4–0.9 (br m, 10).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 76.07; H, 8.50.

3 (R = *o*-MeOPh). A solution of 10.25 g (50 mmol) of **1** in 100 mL of THF at −78 °C (N_2) was treated rapidly dropwise with 22.5 mL (55 mmol) of 2.4 M *n*-butyllithium in hexane. After 1 h, a solution of 7.48 g (55 mmol) of *o*-anisaldehyde in 50 mL of THF was added dropwise over 30 min and stirring was continued for 1 h. After being quenched with 3 mL of absolute methanol at −78 °C, the reaction mixture was worked up as described for **3** (R = cyclohexyl). The crude hydroxyoxazoline **2** (R = *o*-MeOPh) was dehydrated (benzene or toluene, TFA, heat) to yield 15.9 g (104%) of a yellow oil, purified on medium-pressure liquid chromatography.[12] An analytical sample was prepared by bulb-to-bulb distillation, 210 °C (0.02 torr). The yield was 3.3 g (60%) based on **1**: $[\alpha]^{25}_{578}$ +141° (*c* 5.5, $CHCl_3$); IR (film) 3060, 3020, 1648, 1595 cm^{-1}; NMR ($CDCl_3$) δ 7.86 (d, J = 17 Hz, 1), 6.8–7.7 (m, 4), 7.41 (s, 5), 6.82 (d, J = 17 Hz, 1), 3.26 (d, J = 6 Hz, 1), 4.28–4.30 (m, 1), 3.56 (s, 3), 3.6–3.9 (m, 2), 3.45 (s, 3).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55. Found: C, 74.00; H, 6.33.

Addition of 3 to Organolithium Reagents and Hydrolysis to 3-Substituted Alkanoic Acids 5. General Procedures. (*R*)-(+)-3-Methylnonanoic Acid (5c). *n*-Hexyllithium (30 mmol) was diluted with 170 mL of THF (0.18 M), and the solution was cooled to −78 °C. A solution of 4.0 g (13.6 mmol) of **3** (R = Me) in 40 mL of THF was added dropwise over 3 h, and the mixture was stirred (−78 °C) for an additional 5 min. The reaction was quenched with 2.3 mL (40 mmol) of glacial acetic acid in 10 mL of THF and the cold bath was removed. After 20 min, the reaction was poured into 150 mL of 5% $NaHCO_3$ and the organic products were removed by ether extraction. The etheral solution was washed with brine and water and dried (4Å molecular sieves). Filtration through Florisil, followed by ethyl acetate to remove all organic material, gave a combined ether–ethyl acetate solution which was concentrated to give 4.15 g (~95%) of crude **6** (R = Me, R′ = *n*-hexyl) as an organe oil. TLC (silica gel, 2% ethanol in ethyl acetate) showed one major spot and two minor lower R_f impurities. The crude material was directly hydrolyzed in 80 mL of 1.5 M sulfuric acid heated at reflux under an oil trap for 24–36 h. The crude 3-methylnonanoic acid was extracted with methylene chloride and then concentrated. The residue was dissolved in ether and extracted with 1 M KOH. The aqueous layer was neutralized with 2 M HCl, and the organic acid was extracted with methylene chloride, washed with brine, dried (molecular sieves), and concentrated to leave an oil which was distilled (bulb-to-bulb), 90 °C (0.20 torr), to give 1.03 g [44% overall from **3** (R = Me)]: $[\alpha]^{23}_D$ +5.08° (neat); d^{23} = 0.889 g/cm^3; NMR (CCl_4) δ 12.13 (s, 1), 2.4–0.7 (m, 16), 0.95 (d, J = 7 Hz, 3); IR (film) 3500–2500, 1710 cm^{-1}; n^{23}_D 1.4352.

Previously Unreported Acids. (*R*)-(−)-3-Isopropylheptanoic Acid (5g): n^{23}_D 1.4384; $[\alpha]^{23}_{589}$ −0.82°, $[\alpha]^{23}_{578}$ −0.89° (neat); d^{23} = 0.9732 g/cm^3; oil distilled bulb-to-bulb, 100 °C (0.02 torr).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.79, H, 11.90.

(*R*)-(−)-3-*tert*-Butylheptanoic Acid (5h): n^{23}_D 1.4444; $[\alpha]^{23}_{589}$ −17.7°, $[\alpha]^{23}_{578}$ −18.5° (neat); d^{23} = 0.9192 g/cm^3; oil distilled bulb-to-bulb, 110 °C (0.07 torr).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.17; H, 11.84.

(*S*)-(+)-3-(2-Methoxyethyl)hexanoic Acid (5l): n^{23}_D 1.4430; d^{23} = 0.976 g/cm^3; $[\alpha]^{23}_{589}$ +1.32°, $[\alpha]^{23}_{578}$ +1.38° (neat); oil distilled bulb-to-bulb, 93 °C (0.03 torr).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.24; H, 10.40.

(*S*)-(+)-3-(2-Methoxyethyl)pentanoic Acid (5k): n^{23}_D 1.4402; d^{23} = 1.000 g/cm^3; $[\alpha]^{23}_{589}$ +1.46°, $[\alpha]^{23}_{578}$ +1.52° (neat) [in solution $[\alpha]^{23}_{578}$ was *negative*, −1.30° (*c* 14.5, benzene)]; oil distilled bulb-to-bulb, 100 °C (0.05 torr).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 60.04; H, 9.75.

(*S*)-(+)-3-(2-Methoxyethyl)heptanoic Acid (5m): n^{23}_D 1.4437; d^{22} = 0.9628 g/cm^3; $[\alpha]^{23}_{589}$ +2.12°, $[\alpha]^{23}_{578}$ +2.21° (neat); oil distilled bulb-to-bulb, 130 °C (0.04 torr).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.69; H, 10.51.

(*S*)-(+)-5-Methoxy-3-phenylpentanoic Acid (5n): viscous oil distilled bulb-to-bulb, 160 °C (0.05 torr); $[\alpha]^{23}_{589}$ +9.48°, $[\alpha]^{23}_{578}$ 10.97° (*c* 10, $CHCl_3$).

Anal. Calcd for $C_{12}H_{16}O$: C, 69.21; H, 7.75. Found: C, 69.13; H, 7.81.

(*R*)-(−)-3-(*o*-Methoxyphenyl)pentanoic Acid (5q): viscous oil distilled bulb-to-bulb, 150 °C (0.02 torr); $[\alpha]^{23}_{578}$ −21.3° (*c* 11.2, benzene).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.42; H, 7.55.

(*R*)-(−)-3-(*o*-Methoxyphenyl)heptanoic Acid (5r): viscous oil distilled bulb-to-bulb, 155 °C (0.05 torr); $[\alpha]^{24}_{578}$ −24.8° (*c* 10.3, benzene).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Erratic analyses were observed ranging from 71 to 77% C due to ready decarboxylation during combustion.

(*S*)-(−)-3-(*o*-Methoxyphenyl)-3-phenylpropionic Acid (5s): mp 102–115 °C (as an enantiomeric mixture estimated by shift reagent to be 95 ± 3% pure); $[\alpha]^{24}_{578}$ −24.8° (*c* 10, benzene).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.96; H, 6.29. Found: C, 74.72; H, 6.31.

Methyl Esters of Methoxy Acids (5k–n, 5q–s) Prepared for % ee Determinations (Table III). Method A. Diazomethane. A solution of 1–5 mmol of methoxy acid was dissolved in 10 mL of ether, and diazomethane was added until the yellow color persisted. Excess diazomethane was destroyed by addition of acetic acid in ether. The reaction mixture was washed with 50 mL of $NaHCO_3$, and then the

ethereal solution was dried and concentrated to give crude ester. Distillation (bulb-to-bulb) gave pure esters. This method was used to prepare methyl esters of **5k** and **5n.**

Method B. MeOH–Sulfuric Acid. A solution of 1–5 mmol of methoxy acid was dissolved in 50 mL of absolute methanol, and 2 drops of concentrated H_2SO_4 were added. The mixture was heated to reflux with a Dean-Stark trap attached. The collection arm was filled to within 2–3 cm of the overflow level with solid potassium carbonate. Heating was performed for 12 h, and then most of the methanol was distilled off. The residue was taken up in a two-phase ether–$NaHCO_3$ solution, the layers were separated, and the ether layer was dried ($MgSO_4$) and concentrated. Purification was accomplished by bulb-to-bulb distillation. This method was used to prepare methyl esters of **5l, 5m,** and **5q–s.** Physical properties and GLC and TLC analyses indicated that all esters were of >98% purity.

% Enantiomeric Excess of Methoxy Acids 5k–m and 5q–s as Determined through Their Methyl Esters. The chiral methyl esters exhibited only a single methoxy singlet for the MeO ether and the MeO ester upon addition of various amounts of Eu shift reagents. However, *racemic acids,* prepared using the alkenyl derivatives of 4,4-dimethyl-2-oxazolines, showed, after transformation to their methyl esters, two cleanly resolved MeO peaks (δ 3.2) of equal intensity. Thus, mixtures of esters of **5** and racemic esters were carefully prepared by weighing in known amounts and subjecting them to the Eu shift reagent in Table III. The relative areas of the enantiomer–racemate mixture were assessed by "cut-and-weigh" procedures. In this fashion, the % ee was determined to be 95 ± 3%.

3-Substituted Valerolactones 11a–d (Table IV). General Procedure. To a solution of 4.0 mmol of the methoxy acids **5l–m** in 25 mL of methylene chloride at 0 °C (nitrogen) was added a precooled (0 °C) solution of 12 mmol of freshly distilled boron tribromide in 10 mL of methylene chloride. After addition was complete, the cooling bath was removed and the mixture was stirred for 45 min at ambient. The excess BBr_3 was destroyed by careful dropwise addition of 60 mmol of sodium bicarbonate in 30 mL of water. The contents of the reaction vessel were transferred with ether to a separatory funnel, and 50 mL of ether was added. The organic layer separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined ethereal solutions were dried ($MgSO_4$) and concentrated (0–5 °C) in vacuo. The residue was initially distilled under vacuum, but considerable decomposition occurred. Therefore, the pure lactones were obtained by chromatography (2% acetone–$CHCl_3$) on silica using either preparative plates or a gravity column. All of these lactones exhibited strong absorption at 1735–1745 cm^{-1} (film).

3-Substituted Benzovalerolactones 12a–c (Table III). General Procedure. A solution of **5q–s** (2.0 mmol) in 20 mL of methylene chloride was cooled to −78 °C (nitrogen) and treated with 6–7 mmol of freshly distilled boron tribromide in 10 mL of methylene chloride. After addition was complete (5–7 min), the cooling bath was replaced by an ice–water bath and the reaction mixture was stirred for 1 h at 0 °C. Excess BBr_3 was destroyed by addition of 4.0 g of sodium carbonate in 20 mL of water. The reaction mixture was transferred to a separatory funnel, extracted, dried, and concentrated in vacuo to give a residue which was distilled (bulb-to-bulb) at ~120 °C (0.05 torr). In the case of **12c,** the residue, after solvent evaporation, solidified and the melting point of the highly enriched enantiomeric mixture was 110–112 °C. All of these lactones exhibited a strong absorption at 1760–1770 cm^{-1} (film).

All IR, NMR, and TLC data were totally consistent; however, elemental analyses of lactones **11** and **12** were not determined due to a general deterioration after several weeks. These products should be utilized as soon as possible for further work.

(4*S*)-4-(Carbethoxy)-2-methyl-2-oxazoline (7). To a suspension of 12.4 g (100 mmol) of ethyl acetimidate hydrochloride and 16.9 g (100 mmol) of L-serine ethyl ester hydrochloride in 200 mL of methylene chloride at 25 °C was added, dropwise, 20.2 g (200 mmol) of triethylamine in 50 mL of methylene chloride over 20 min. The reaction mixture was stirred overnight, and the solvents were removed under vacuum. The residue was washed (3 × 50 mL) with ether, and the ethereal solution was dried ($MgSO_4$) and concentrated to afford crude **7** as a yellow oil. Distillation via a 7-cm Vigreux column at 98.5–100 °C (11 torr) gave 11.8 g (75%) of pure **7**: IR (film) 1735, 1665 cm^{-1}; NMR (CCl_4) δ 4.8–4.2 (m, 3), 4.21 (q, 2), 2.0 (s, 3), 1.35 (t, 3); $[\alpha]^{25}_{589}$ +182.3° (*c* 10.0, $CHCl_3$); VPC purity 99%.

(4*R*)-4-(Hydroxymethyl)-2-methyl-2-oxazoline (8). A solution of 15.7 g (100 mmol) of **7** in 100 mL of ether was added over 20 min to a solution of 110 mmol (31.4 mL of 3.5 M in benzene) of bis(2-methoxyethoxy)aluminum hydride ("Red-Al", Aldrich) in 220 mL of ether. The reaction mixture was stirred for 15 min at 0 °C and then quenched by the injection of 4.2 mL of water, 4.2 mL of 15% (w/w) aqueous sodium hydroxide, and finally 12.6 mL of water. A white precipitate of aluminum salts formed initially, but disappeared into the lower aqueous layer after 2 h of stirring. The ether layer was decanted, and the aqueous layer was extracted (50 mL) with ether. The combined ether solution was dried ($MgSO_4$) and concentrated. Distillation through a 7-cm Vigreux column gave initially 2-methoxyethanol (bath 60–90 °C, 15 torr), and the column was removed for a short-path apparatus to afford at 56–59 °C (0.03 torr) 8.42 g (73%) of **8**: IR (film) 3600–2400, 1668 cm^{-1}; NMR (CCl_4) δ 5.07 (s, 1), 4.13 (m, 3), 3.53 (m, 2), 1.95 (s, 3); $[\alpha]^{25}_{589}$ +157° (*c* 10.4, $CHCl_3$); VPC purity 99%.

A sample of the above material dissolved in ether gave, after several days in the refrigerator, a crystalline material, mp 52–54 °C, $[\alpha]_{589}$ +181.0° (*c* 9.9, $CHCl_3$), which when transformed into the methyl ether **9** showed 97 ± 3% ee by chiral shift reagent (see below).

(4*R*)-4-(Methoxymethyl)-2-methyl-2-oxazoline (9). A solution of 6.94 g of **8** ($[\alpha]_{589}$ 157°) in 50 mL of THF was added dropwise to a washed suspension of 1.60 g of sodium hydride (from 3.17 g of a 50% mineral oil dispersion) in 15 mL of THF. The reaction was stirred for 18 h at 25 °C, and 9.37 g of methyl iodide in 20 mL of THF was added to the slurry at 0 °C. Stirring was continued for 20 h, and then the reaction mixture was quenched into 25 mL of 20% NH_4Cl solution. The organic layer was diluted with 100 mL of ether and separated while the aqueous layer was extracted with ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), concentrated, and distilled (short-path) at 56–59 °C (8 torr) to give 3.98 g (53%) of **9**: IR (film) 1670 cm^{-1}; NMR (CCl_4) δ 4.13 (m, 3), 3.0–3.7 (m, 2), 3.35 (s, 3), 1.92 (s, 3); $[\alpha]_{589}$ +108° (*c* 10.7, $CHCl_3$).

When **8** ($[\alpha]_D$ +181.0°) was treated with methyl iodide–sodium hydride, the methoxyoxazoline **9** obtained had $[\alpha]_{589}$ +120.8° (*c* 10.7, $CHCl_3$). Enantiomeric purity as determined by Eu–Optishift I was 95 ± 3% (vide infra).

Enantiomeric Purity of (4*R*)-4-(Methoxymethyl)-2-methyl-2-oxazoline (9). A solution of 30 mg of racemic **9** (prepared via **7** and **8** using (±)-serine ethyl ester hydrochloride) in 0.5 mL of CCl_4 was treated with 3–5-mg portions of Eu–Optishift I [tris[[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium(III)] until separation of the C-2 methyl signal at δ 1.9 corresponding to the two enantiomers was observed. The ratio of the signal intensities was found to be 49.6:50.4, insuring the general accuracy of the method. Next, a solution of 22.1 mg of racemic **9** and 27.4 mg of "nonracemic" **9** (from L-serine) in 1.0 mL of CCl_4 was examined in the presence of Eu–Optishift I. In this case, using the ratios of racemic to nonracemic oxazoline, the enantiomeric purity was found to be 80 ± 3%. Finally, a solution of nonracemic **9** in 0.5 mL of CCl_4 was treated with Eu–Optishift I, and integration of the two C-2 methyl signals further confirmed the % ee as 82 ± 3%.

Using this method, the chiral oxazoline which had crystallized (mp 52–54 °C) and transformed into its methyl ether gave a % ee of 95 ± 3%, although this was not used in the subsequent reactions.

(4*R*)-4-(Methoxymethyl)-2-(β-styryl)-2-oxazoline (10). A solution of 3.23 g (25 mmol) of (4*R*)-4-(methoxymethyl)-2-methyl-2-oxazoline (**9**) in 100 mL of THF at −78 °C (N_2) was treated dropwise with 10.4 mL of a 2.5 M solution of *n*-butyllithium (26 mmol). After 1 h at −78 °C, 2.8 g (26 mmol) of benzaldehyde in 20 mL of THF was added over 15 min. The reaction mixture was stirred at −78 °C for 1 h and then quenched by injection of 2 mL of absolute methanol. Workup as in **3** (R = cyclohexyl) gave 5.72 g (97%) of the crude β-hydroxy adduct. The NMR spectrum of the latter indicated that the diastereomeric ratio was 65:33. Dehydration to **10** was performed by heating to reflux in 50 mL of benzene containing 143 mg of trifluoroacetic acid for 3 h. Workup as in **3** (R = cyclohexyl) followed by distillation gave 2.78 g (51%) of **10:** bp 121–124 °C (0.03 torr); IR (film) 3045, 3018, 1650, 1630 cm^{-1}; NMR ($CDCl_3$) δ 7.48 (d, 1), 7.3–7.6 (m, 5), 6.68 (d, 1), 4.2–4.7 (m, 3), 3.4–3.8 (m, 2), 3.42 (s, 3); $[\alpha]^{25}_{589}$ +100.5° (*c* 7.97, $CHCl_3$). This material was 81 ± 3% ee based upon the **9** used ($[\alpha]_{589}$ 108°).

(*S*)-(+)-Phenylheptaoic Acid from (4*R*)-10. Following the general procedure for **5c,** 40 mmol (1.6 mL of 2.5 M) of *n*-butyllithium in 20 mL of THF was added to 434 mg (2.0 mmol) of **10** at −78 °C. Workup and purification gave 274 mg (65%) of (*S*)-(+)-3-phenylheptanoic acid, $[\alpha]_{589}$ 19.1° (*c* 8, C_6H_6), which corresponded to 77% ee based on pure material having $[\alpha]_{589}$ 24.9°. If **10** was only 81% enantiomerically pure, then the product represents a 96% asymmetric synthesis.

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Registry No.—(−)-**1**, 52075-14-6; **2** (R = cyclohexyl), 53480-81-2; **2** (R = *o*-MeOPh), 69795-83-1; (*E*)-**3** (R = Me), 57403-82-4; (*Z*)-**3** (R = Me), 69853-65-2; (*E*)-**3** (R = ·Et), 57403-83-5; (*Z*)-**3** (R = Et), 69853-66-3; (*E*)-**3** (R = *i*-Pr), 69795-84-2; (*Z*)-**3** (R = *i*-Pr), 69795-85-3; (*E*)-**3** (R = *t*-Bu), 69795-86-4; (*E*)-**3** (R = cyclohexyl), 69814-85-3; (*Z*)-**3** (R = cyclohexyl), 69795-87-5; (*E*)-**3** (R = $MeOCH_2CH_2$), 61198-39-8; (*Z*)-**3** (R = $MeOCH_2CH_2$), 69880-56-4; (*E*)-**3** (R = Ph), 57403-84-6; (*E*)-**3** (R = *o*-MeOPh), 61198-40-1; **4**, 69795-88-6; **5a**, 16958-25-1; **5b**, 57403-74-4; **5c**, 52075-16-8; **5d**, 772-15-6; **5e**, 57403-75-5; **5f**, 16460-78-9; **5g**, 69795-89-7; **5h**, 69795-90-0; **5i**, 16497-93-1; **5j**, 69795-91-1; **5k**, 61198-41-2; **5l**, 69795-92-2; **5m**, 61198-42-3; **5n**, 61198-43-4; **5o**, 2845-27-4; **5p**, 57403-76-6; **5q**, 61198-44-5; **5r**, 61198-45-6; **5s**, 61198-46-7; **5k** methyl ester, 61198-55-8; **5l** methyl ester, 69795-93-3; **5m** methyl ester, 61198-56-9; **5n** methyl ester, 61198-57-0; **5q** methyl ester, 61198-58-1; **5r** methyl ester, 61198-59-2; **5s** methyl ester, 61198-60-5; **6** (R = Me, R′ = *n*-hexyl), 69795-94-4; (4*S*)-**7**, 61999-29-9; (±)-**7**, 69853-67-4; (4*R*)-**8**, 61999-31-3; (±)-**8**, 69853-68-5; (4*R*)-**9**, 61999-33-5; (±)-**9**, 69853-69-6; (*R*)-**10**, 62174-10-1; **11a**, 61198-47-8; **11b**, 69853-70-9; **11c**, 61198-48-9; **11d**, 61198-49-0; **12a**, 61198-50-3; **12b**, 61198-51-4; **12c**, 61198-52-5; MeCHO, 75-07-0; EtCHO, 123-38-6; *i*-PrCHO, 78-84-2; *t*-BuCHO, 630-19-3; $C_6H_{11}CHO$, 2043-61-0; $MeOCH_2CH_2CHO$, 2806-84-0; PhCHO, 100-52-7; *o*-MeOPhCHO, 135-02-4; EtLi, 811-49-4; *n*-BuLi, 109-72-8; *n*-HexLi, 21369-64-2; PhLi, 591-51-5; *n*-PrLi, 2417-93-8; *n*-propyl chloride, 540-54-5; *n*-hexyl chloride, 544-10-5; diisopropyl phosphonochloridate, 2574-25-6; triisopropyl phosphite, 116-17-6; ethylacetimidate hydrochloride, 2208-07-3; L-serine ethyl ester hydrochloride, 26348-61-8; (*S*)-(+)-3-phenylheptanoic acid, 61999-35-7.

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Physicochemical Properties of Schiff Bases. 4. Tautomeric Equilibrium and Kinetics of Hydrolysis of *N*-Benzylideneaniline Derivatives

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The kinetics of hydrolysis of *N*-(X-benzylidene)aniline, with X = OH or OCH_3 in the ortho, meta, or para position, have been investigated in the pH range from −1 to 14 at 30 °C by means of ultraviolet spectrophotometry. The mechanism of hydrolysis of these Schiff bases was found to be critically dependent on the presence of the ketoamine tautomer in some of these compounds, as was the case for the Schiff bases derived from isopropylamine.[1] The tautomeric constants have been estimated by various methods and consistent results have been obtained when comparison was possible.

In previous studies of *N*-benzylidene-2-aminopropane derivatives,[1] it has been shown that the presence of an hydroxy substituent in ortho or para positions in the benzaldehyde ring produces a tautomeric equilibrium between the phenolimine and the ketoamine form of the Schiff bases and that this equilibrium has an important effect on the hydrolysis of these Schiff bases at various pHs. The tautomeric equilibrium of Schiff bases has been studied by various workers,[2] while others[3] have denied its existence.

In the case of Schiff bases derived from aromatic amines, other mechanisms have been proposed[4,5] for the hydrolysis reaction. In order to see if special mechanisms are required in the latter case, we have investigated the reaction of hydrolysis of *N*-(X-benzylidene)aniline with X = OH or OCH_3 in ortho, meta, and para positions in the whole pH range from −1 to 14. We have also tried to estimate the amount of the ketoamine tautomer present in the various compounds in order to see if this amount is relevant in the interpretation of the observed variation of k_{obsd} with pH.

Experimental Section

The Schiff bases were prepared by condensation of commercially available aniline carefully distilled, with the appropriate aldehyde, following known procedures.[6]

Acetate, phosphate, borate, and carbonate buffers were used in their appropriate range.[7] Buffer concentrations were typically 0.05 M in acetate, dihydrophosphate, and hydrophosphate and 0.025 M in borax and bicarbonate. Buffer catalysis was never important except for the *o*-hydroxy compound as mentioned below. Extrapolated values of k_{obsd} at zero buffer concentration were at least 90% of the values corresponding to maximum buffer concentration. For the *o*-hydroxy

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