Oxazolines. XXI. Kinetic Resolution of *sec*-Alkyl Halides and Simultaneous Asymmetric Synthesis of 3-Alkylalkanoic Acids Using a Chiral Oxazoline. A Method for Determining Absolute Configurations and Maximum Optical Rotations

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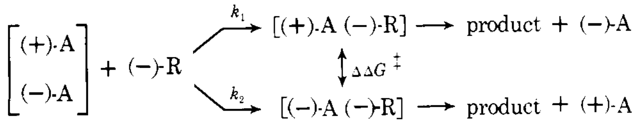
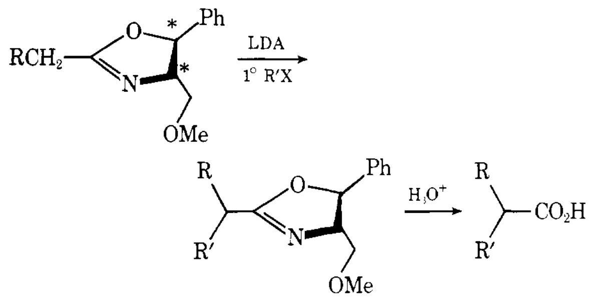
Abstract: Racemic *sec*-alkyl iodides and bromides are kinetically resolved at low temperature (−60 to −70°) with a chiral lithiooxazoline, **5**. The results furnish optically active halides **2** enriched in the *R* enantiomer in the range of 30–49% enantiomeric purity. The concurrently formed alkylated oxazoline **3** after hydrolysis, affords 3-alkylalkanoic acids **4** also enriched in the *R* enantiomer and possessing 30–47% enantiomeric purity. This technique allows the establishment of absolute configurations for *sec*-alkyl halides and 3-substituted carboxylic acids, without the need for any optically active materils other than the chiral oxazoline reagent. In several cases, the method demonstrates the ability to *predict* the maximum rotation of enantiomeric alkyl halides or carboxylic acids provided one of the two are reliably known.

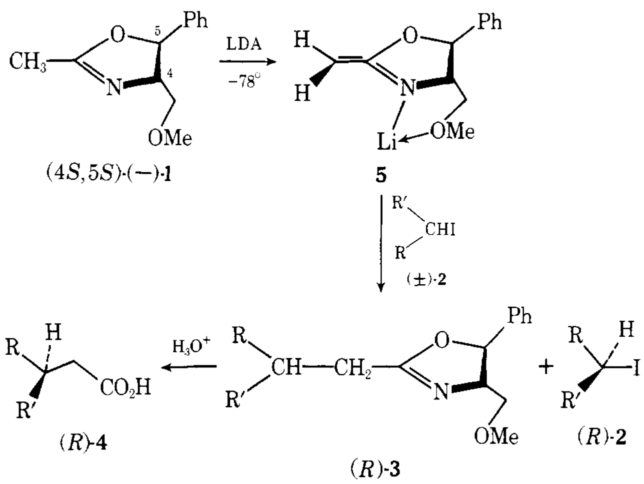
The preferential reaction of a chiral reagent, e.g., (−)-(R), with a racemic substrate (±)-A such that only one of the enantiomers in the racemate is affected is generally termed a kinetic resolution. The process depends upon (−)-R displaying chiral recognition so that it has the ability to distinguish between the enantiomeric forms of a racemic mixture. Kinetically this means that the relative rate constants, k_1 and k_2, are sufficiently different that the diastereomeric transition states are reached at different rates and hence the products from each pathway are formed in unequal amounts. This would also result in one of the enantiomers, A, being recovered in excess at the end of the reaction. The extent of this excess of enantiomeric recovery will depend upon the $\Delta\Delta G^{\ddagger}$ of the competing pathways.[1]





(1)

Scheme I



During our synthetic efforts[2] involving chiral lithio salts of 2-oxazolines and their alkylation to α-alkylalkanoic acids in good enantiomeric purity (eq 1), we elected to ascertain whether the oxazolines **1** would possess chiral recognition with respect to racemic halides (±)-**2**.[3] Thus, **1** was converted to its lithio salt **5** using lithium diisopropylamide in THF at −78° and treated with 2.0 equiv of (±)-2-iodobutane (1 equiv of each enantiomer) at −65° for 14 h (Scheme I). After quenching in water, the excess halide was isolated and found to possess $[\alpha]^{20}\text{D}$ of −10.77° (neat). This corresponded to 34% enantiomeric purity and enriched in the *R* configuration. Isolation of the alkylated oxazoline **3** gave, after hydrolysis (6 N H_2SO_4, reflux, 8 h), 3-methylpentanoic acid (**4**) (R = Me, R′ = Et) whose $[\alpha]^{20}\text{D}$ was −2.79° (neat) and this corresponded to 31% enantiomeric purity, also enriched in the *R* configuration (Table I, entry 1). Inspection of Table I reveals that it is now possible to assign absolute configurations to many alkyl halides and 3-alkylalkanoic acids and their derivatives (alcohols, ketones, hydrocarbons, etc.) by simply employing the commercially available chiral oxazoline **1**. The method does not require any optically active materials other than **1** and the chiral reagents may be recovered and recycled for further use.[4] In all cases, except for halides containing an α-phenyl substituent (entry 12), the *R* configurations of both the carboxylic acid and the halides[5] are obtained. For entry 12, the sequencing priority of the phenyl group over the carboxymethyl results in the *S* configuration. Kinetic resolutions using 3-iodoalkanes were also found to be feasible (entries 9–11). Although the absolute configurations of those halide enantiomers were not known, the levorotatory enantiomers are almost certain to be *R* since the corespondingly resolved dextrorotatory carboxylic acids in entries 9–11 were known to be *R*. The relationship of the recovered *R*-enriched halide **2** and the *R*-enriched carboxylic acids **4** to the chiral oxazoline **1** may be rationalized by considering the following mechanism for the alkylation of the lithiooxazoline **5**. If we assume that the halide approaches the lithiooxazoline **5** from the underside, which is consistent with previously assigned modes of approach for these types of alkyla-

Table I. Kinetic Resolution of Racemic Secondary Halides with Lithiooxazoline **5**

						Recovered halide **2**			Acid **4**		
Entry	Molar ratio **2/1**	Halide (±)-**2** R_1	R_2	X	Conditions T, °C (h)	% Excess halide recovered[a]	$[\alpha]^{20\pm3}\text{D}$ (neat)	% optical purity (config.)	% overall yield[b]	$[\alpha]^{24}\text{D}$	% optical purity (config.)
1	2	Me	Et	I	−65 ± 5 (14)	41	−10.77	34[c] (*R*)	86	−2.79 (neat)	34[d] (*R*)
2	6	Me	Et	I	−60 ± 5 (9)	64	−2.87	9 (*R*)	73	−3.29 (neat)	40 (*R*)
3	2	Me	Et	Br	−40 ± 5 (16)	46	−1.82[s]	8 (*R*)	25	−2.17 (*n*-hex)	26 (*R*)
4	2	Me	*n*-Pr	I	−65 ± 5 (13)	60	−14.17	30[e] (*R*)	89	+1.08 (neat)	39[f] (*R*)
5	2	Me	*n*-Bu	I	−65 ± 5 (18)	43	−18.74	49[g] (*R*)	85	+1.98 (neat)	47[h] (*R*)
6	2	Me	*n*-Hex	I	−68 ± 8 (31)	83	−19.97	31[i] (*R*)	81	+2.98 (neat)	39[j] (*R*)
7	10	Me	*n*-Hex	I	−70 ± 5 (22)	90	−2.86	5 (*R*)	85	+3.43 (neat)	45 (*R*)
8	2	Me	*n*-Hex	I	−70 ± 5 (43) 0 − 5 (6)	66	−5.38	8 (*R*)	67	+2.57 (neat)	34 (*R*)
9	2	Et	*n*-Pr	I	−45 ± 5 (5)	50	−4.58	[k] (*R*)	71	+0.57 (neat)	31[l] (*R*)
10	2	Et	*n*-Bu	I	−45 ± 5 (11)	125	−3.76	46[m] (*R*)	48	+0.92 (neat)	20[n] (*R*)
11	2	Et	*n*-Pent	I	−50 ± 5 (8)	120	−3.34	[k] (*R*)	54	+0.97 (neat)	58[o] (*R*)
12	2	Me	Ph	Br	−50 ± 5 (15)	114	+6.31	5[p] (*R*)	50	+7.18 (neat)	13[q] (*S*)[r]

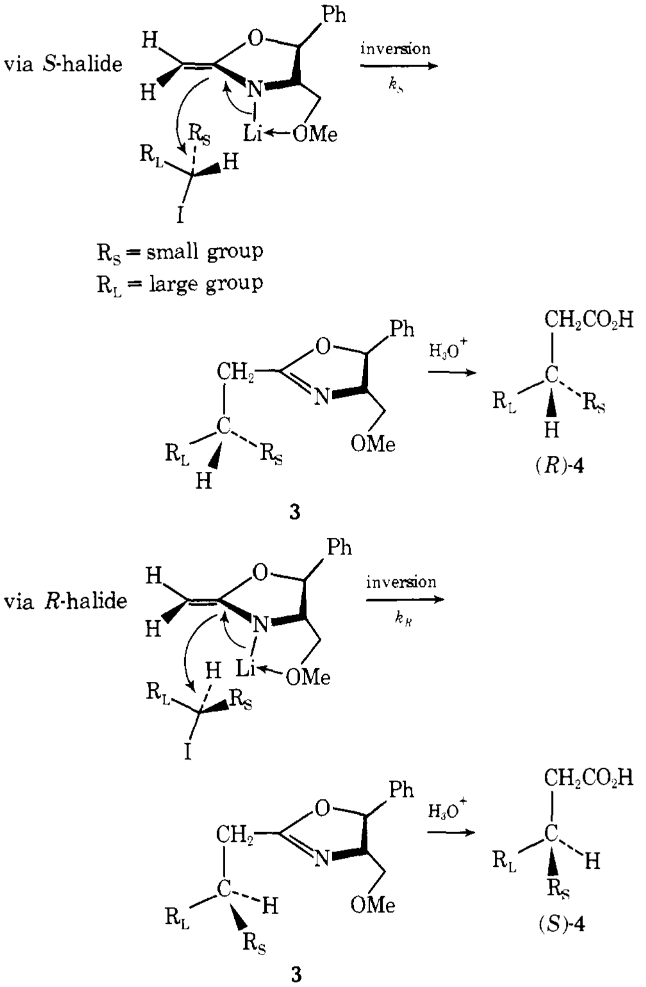
[a] Halides were recovered (wt %) in 92–99% purity by VPC.
[b] Acids were 99.0–99.8% pure by VPC.
[c] Based on $[\alpha]^{7}\text{D}$ −31.98°)neat), R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99,** 45 (1911).
[d] Based on $[\alpha]^{24}\text{D}$ −8.15° (neat), C. G. Overberger and I. Cho, *J. Org. Chem.*, **33,** 3321 (1968).
[e] Based on $[\alpha]^{20}\text{D}$ +46.68° (neat), D. H. Brauns, *Recl. Trav. Chim. Pays-Bas,* **65,** 799 (1946).
[f] Based on $[\alpha]^{25}\text{D}$ +2.77° (neat), P. A. Levene and G. Meyer, *J. Am. Chem. Soc.*, **56,** 245 (1934); B. M. Trost and T. J. Dietsche, *J. Am. Chem. Soc.*, **95,** 8200 (1973).
[g] Based on $[\alpha]^{17}\text{D}$ −38.35° (neat); see ref *c* above.
[h] Based on $[\alpha]^{27}\text{D}$ −4.2° (neat), P. A. Levene and R. E. Marker, *J. Biol. Chem.* **95,** 1 (1932).
[i] Based on $[\alpha]^{20}\text{D}$ −64.2° (neat), H. M. R. Hoffman, *J. Chem. Soc.*, 1249 (1964).
[j] Based on $[\alpha]^{24}\text{D}$ +7.61° (neat), determined in this work.
[k] No literature available.
[l] Based on $[\alpha]^{30}\text{D}$ +1.86° (neat), P. A. Levene et al., *J. Biol. Chem.*, **91,** 687 (1931).
[m] Based on $[\alpha]^{25}\text{D}$ −8.25° (neat), P. A. Levene et al., *J. Biol. Chem.*, **120,** 759 (1937).
[n] Based on $[\alpha]^{20}\text{D}$ +4.6° (neat), P. A. Levene et al., *J. Biol. Chem.*, **115,** 401 (1936).
[o] Based on $[\alpha]^{22}\text{D}$ −1.67° (neat), ref *l* above.
[p] Based on $[\alpha]^{18}\text{D}$ +131.4° (neat), W. Gerrard, *J. Chem. Soc.*, 741 (1946).
[q] Based on $[\alpha]^{25}\text{D}$ −56.5° (neat), D. J. Cram, *J. Am. Chem. Soc.*, **74,** 2137 (1952).
[r] Configuration assignment, G. Tsuchihashi, et al., *Tetrahedron Lett.*, 323 (1973), and references cited therein.
[s] Based on $[\alpha]^{22}\text{D}$ −23.13° (neat), W. J. Gilbert and E. S. Wallis, *J. Org. Chem.*, **5,** 188 (1940).

tions,[6] then it follows that the *N*-lithiomethoxyl chelated moiety generates two cis-fused five-membered rings and creates a rather concave surface through which the halide must enter (Scheme II). By entering the concave area with the two smallest groups (H and R_S), the smallest of these (H) facing the wall of the cavity thus aligning the iodide such that it will be displaced from behind in a classical S_N2 process, it is seen that only the *S* enantiomer fulfills these requirements. After displacement of the iodide from the *S* enantiomer, the oxazoline **3** and ultimately the carboxylic acid are obtained with the *R* enantiomer in excess. Since the reaction between **5** and the *R*-halide is not as sterically favorable, k_R is less than k_S and the halide is indeed recovered enriched in the *R* enantiomer. This technique for assigning absolute configurations to secondary halides should now be useful in relating secondary halides to secondary alcohols and vice versa by also employing the Horeau method which correctly assigned configurations to secondary alcohols.[7] By employing both methods, the danger of misassignment of enantiomers in halide-to-alcohol or alcohol-to-halide transformations may be essentially eliminated.

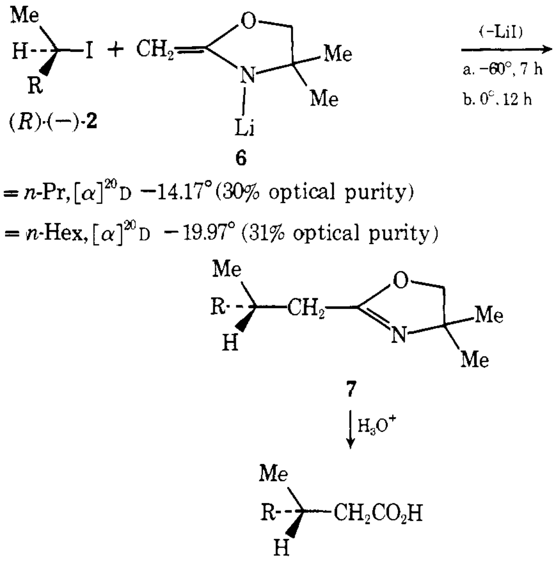
Further examination of Table I reveals that the use of 2.0 equiv of halide to **1** results in the acquisition of the recovered halide and the carboxylic acid in comparable optical purity (entries 1, 4, 5, 6). In other cases where the halide-oxazoline ratio is two, the optical purities of both products were not comparable (entries 3, 8, 10, 12). This is due to two factors: (a) the literature values for optically pure materials are probably incorrect and (b) a certain amount of temperature-dependent halide racemization was taking place during the reaction itself. To show that both of these factors were indeed involved we proceeded to perform the following experiments. When 2.0 equiv of (±)-2-iodooctane was treated with the lithiooxazoline **5** at ∼ −65° and the excess iodide was recovered, it showed $[\alpha]^{24}\text{D}$ −19.97°, corresponding to 31% optical purity. The alkylated oxazoline (**3**) was hydrolyzed to 3-methylnonanoic acid (**4**) (R = Me, R′ = *n*-hexane) and gave $[\alpha]^{20}\text{D}$ of +2.98°. According to the highest rotation in the literature,[8] the pure acid had $[\alpha]^{25}\text{D}$ −4.7° and this would correspond to an optical purity of 63%. The large discrepancy between the optical purites of the recovered 2-iodooctane (31%) and 3-methylnonanoic (63%) acid suggested that the reported value of the latter was too low. The alkylation was repeated with 69% optically pure 2-iodooctane and gave 3-methylnonanoic acid of $[\alpha]^{20}\text{D}$ +5.25°. Since this represented 69% optical purity based upon the starting iodide, the *pure* acid should have $[\alpha]\text{D}$ of 7.6°. Using this value and the $[\alpha]\text{D}$ of +2.98° obtained from the kinetic resolution, the optical purity of the acid is 39% and now more comparable to the 31% optical purity of the recovered iodide.[9] The other discrepancies in optical purities seen in Table I were not checked using this scheme since reliable rotation data for the other halides are not available. It is to be emphasized, however, that failure to obtain comparable optical purities for the halides and the acids using the chiral oxazolines simply indicates the necessity for reliable rotation data for many optically active derivatives.

With regard to racemization of the iodides as a factor in the discrepancies between optical purities of **2** and **4**, Table

Scheme II



Scheme III



2a, R = *n*-Pr, $[\alpha]^{20}D$ −14.17° (30% optical purity)

b, R = *n*-Hex, $[\alpha]^{20}D$ −19.97° (31% optical purity)

4a, R = *n*-Pr, $[\alpha]^{20}D$ −0.75° (27% optical purity)

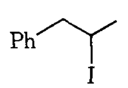
b, R = *n*-Hex, $[\alpha]^{20}D$ −2.24° (29% optical purity)

I, entry 8 reveals a dramatic effect. If, after the alkylation is complete (monitored by VPC), the temperature is allowed to warm to 0–5° and stirred for 6 h prior to work-up, the recovered 2-iodooctane has [α]D −5.38° (8% optical purity), whereas the carboxylic acid has [α]D +2.57° (34% optical purity). This suggests that racemization of the excess iodide took place *after* the alkylation was complete as the solution was allowed to stir at 0–5°. Thus, the discrepancy in optical purity of products in entry 6 (31 vs. 39%) in all likelihood is partially due to 3–5% racemization even at −60°. When α-phenethyl bromide was treated with the lithiooxazoline **5** (entry 12), the reaction probably was accompanied by considerable unimolecular (SN1) displacement giving rise to the carboxylic acid in only 13% optical purity. On the other hand, the recovered phenethyl bromide was only 5% optically pure, further suggesting considerable racemization as the reaction stirred at −50° for 15 h.[10] In an effort to assess the extent of racemization of halides under the conditions of the kinetic resolution, the recovered halides, 2-iodopentane and 2-iodooctane with optical purities designated in Scheme III, were subjected to low temperature alkylation using the lithio salt of an achiral oxazoline **6**.[11] The alkylated products, **7**, were then hydrolyzed in acidic solution to the (*S*)-carboxylic acids **4**. The results given in the scheme clearly indicate that a smooth inversion of (*R*)-(−)-**2** had occurred giving rise to (*S*)-(−)-**4** with optical purities very close to those of the starting halides. Since the reaction of (*R*)-(−)-**2** with **6** is tantamount to generating lithium iodide in situ, it may be said that LiI will not racemize the optically active halides under the conditions employed for the kinetic resolution or for that matter even stirring at 0° for 12 h. Hence, any racemizations observed must have occurred with the chiral oxazoline **3** *after* the alkylation was complete.[12] However, if the entire reaction is performed at −60 to −70° and quenched at this temperature, the extent of halide racemization is minimal (3–5%). It should, therefore, be feasible to predict, within a few percent, the maximum rotation of one of the reaction products (halide or acid) provided that the other is reliably known.

In two instances (entries 2 and 7, Table I), the kinetic resolutions were run under pseudo-first-order conditions using a six- and tenfold excess of the halide. As expected, the optical purity of the carboxylic acids was somewhat higher than those observed when 2.0 equiv of halide were employed. This is simply due to the fact that the concentration of (*S*)-**2** remains essentially constant throughout the course of the reaction when it is present in large excess. The recovered halides in entries 2 and 7 were found to be 9 and 5% optically pure, respectively. However, if one multiplies these values by the equivalents of excess halide present (4 and 8, respectively) the optical purities are 36 and 40%, in good agreement with those found for the corresponding acids. These results indicate that it is not necessary to use the halide and oxazoline in a 2:1 molar ratio to determine absolute configurations and maximum rotations, but any known ratio will accomplish the same task.

An attempt was made to kinetically resolve 2-bromobutane (entry 3, Table I) by this method. Although the results gave both the recovered halide and carboxylic acid enriched in the *R*-enantiomer, the respective optical purities were at considerable variance. It is, therefore, possible to determine the absolute configurations of alkyl bromides, but not the maximum rotations due to poor alkylation yields and considerable halide racemization. The latter occurs mainly because the alkylation would not proceed below −45° and required 16 h at this temperature.

Additional racemic halides which were examined in order to effect a kinetic resolution are shown below. Under all conditions examined **8–11** gave mainly elimination products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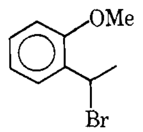
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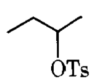
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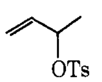
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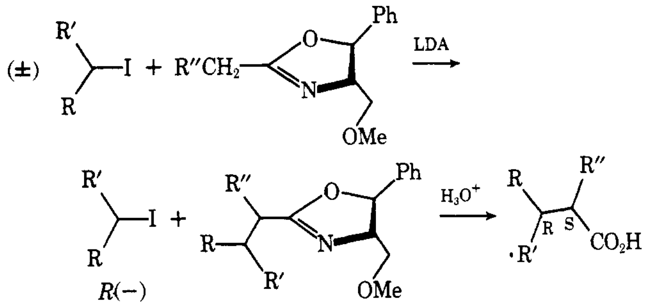
Scheme IV



and very little desired material could be isolated. It appears as though alcohols, via their tosylates, cannot be kinetically resolved and the Horeau method[7] still remains the method of choice for establishing their absolute configurations.

Studies are continuing which involve the kinetic resolution of alkyl halides and the simultaneous formation of α,β-dialkyl carboxylic acids (Scheme IV). Although some preliminary results are in hand which indicate that the *S*-halide is again favored for alkylation, furnishing the (2*S*,3*R*)-carboxylic acid and the *R*-halide, these findings must await further data.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 267 grating instrument. NMR spectra were obtained with a Varian T-60 instrument. Optical rotations were taken on a JASCO DIP-180 automatic polarimeter and ar expressed as specific rotations with concentrations and solvents specified. Melting points were taken on a Buchi apparatus and boiling points are uncorrected. Tetrahydrofuran was distilled from sodium metal-benzophenone ketyl immediately before use. Butyllithium was obtained as hexane solution from Ventron, Beverly, Mass. L-(+)-*threo*-1-Phenyl-2-amino-1,3-propanediol was purchased from Parke-Davis, Industrial Products Division, Detroit, Mich. in 5-kg lots. Purification for use in these studies has been described;[6] $[\alpha]^{25}\mathrm{D}$ +27.8° (*c* 11, MeOH), mp 112-113°. The absolute configuration is (1*S*,2*S*).[6]

(4*S*,5*S*)-2-Methyl-4-methoxymethyl-5-phenyl-2-oxazoline (1). Preparation using ethyl iminoacetate hydrochloride and (1*S*,2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol followed by sodium hydride and methyl iodide has been described:[6] $[\alpha]\mathrm{D}$ −115.9° (*c* 11, $CHCl_3$), bp 77-80° (0.06 Torr); NMR ($CDCl_3$) δ 7.37 (s, 5), 5.38 (d, 1), 4.22 (m, 1), 3.57 (m, 5), 2.20 (s, 3); ir (neat) 1670, 1130 cm^{-1}.

A more recent procedure which may be more convenient follows. A mixture of 27.7 g (165 mmol) of (1*S*,2*S*)(+)-1-phenyl-2-amino-1,3-propanediol, 32.2 g (198 mmol) of triethylorthoacetate, and 100 ml of dry dimethylformamide (dried by distillation from calcium hydride) was heated to 95° for 12 h. The solvent was removed under vacuum, and the residue was treated with 20 ml of anhydrous ether and cooled in a dry ice-acetone bath. The crystalline hydroxymethyloxazoline was collected by suction filtration and washed with 5 ml of cold ether. There was obtained 20.7 g, mp 62-64°. A second crop (1.1 g) was recovered from the chilled filtrate. The combined material was recrystallized from 120-130 ml of anhydrous ether by cooling the clear solution to −78°. Yield 18.8 g (59.5%), mp 64-65°, $[\alpha]^{24}\mathrm{D}$ −173.2° (*c* 10.4, $CHCl_3$); ir (Nujol) 3100-3500 cm^{-1} (OH), 1670 cm^{-1} (C=N); NMR ($CDCl_3$) δ 2.15 (s, 3), 3.4-4.7 (br m, 4), 5.45 (d, 1), 7.4 (s, 5), 5.17 (br s, 1, exchangeable with D_2O); *m/e* 191 (M^+).

Conversion to **1** was accomplished using NaH (118 mmol), the hydroxyoxazoline (49 mmol), and methyl iodide (69 mmol) in 80 ml of THF.

Formation of 1 Using Recovered (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol from Hydrolysis of 3. The methoxyoxazoline **1** has been prepared by treating the methoxyamino alcohol, $[\alpha]^{23}\mathrm{D}$ +24.4° (*c* 10.6, $CHCl_3$), mp 48.5-50.0°,[6,15] with ethyl iminoacetate as previously described.[6]

A recent procedure involves treating the methoxyamino alcohol (26.5 g) with 28.4 g of ethyl orthoacetate in 125 ml of 1,2-dichloroethane and heating to reflux for 1.5 h. After cooling and removal of the solvent by rotary evaporation, the residue was distilled, bp 70-71° (0.03 Torr), to give 28.3 g (944%) of **1** as a colorless oil, $[\alpha]^{24}\mathrm{D}$ −117.4° (*c* 10.2, $CHCl_3$).

Kinetic Resolutions Using (−)-1 and Racemic Alkyl Iodides. Typical Procedure. All of the kinetic resolutions involving 2.0 equiv of racemic halide and 1.0 equiv of (−)-**1** (5.13 g, 25 mmol) were carried out using the following procedure for (±)-2-iodooctane. The temperatures of the individual reactions were, however, varied and these are given in Table I. All reactions were performed under anhydrous conditions and in a nitrogen atmosphere. Physical data for all products are given in Table II.

A solution of lithium diisopropylamide (prepared from 2.53 g (25 mmol) of freshly distilled diisopropylamine and 10.9 ml of *n*-butyllithium (2.3 M in hexane in 15 ml of THF at 0°)) was added dropwise to a stirred solution of 5.13 g (25 mmol) of (−)-**1** in 70 ml of THF at −78° over 15 min.

After stirring the reaction for 30 min, a solution of 12.0 g (50 mmol) of (±)-2-iodooctane in 20 ml of THF was added over 10 min and the mixture stirred between −60 and −76° for 31 h.[13] The contents of the reaction vessel were poured into 100 ml of ice water and extracted with ether (150 ml, followed by 2 × 50 ml). The ethereal extracts were washed with saturated brine solution and dried over $MgSO_4$. The ether was removed by rotary evaporation[14] or distillation through a short Vigreux column. The residue was then distilled under vacuum (Table II) and the excess 2-iodooctane was collected in a flask immersed in a Dewar cooled to −78°.

After dissolving the distillate in 45 ml of ether, the solution was washed successively with 1 N H_2SO_4 and saturated brine, and dried over $MgSO_4$. Distillation, after removal of the solvent, gave 4.98 g (83% recovery) of 2-iodooctane, 96.1% purity (VPC using a 6 ft UCW-98 (10%) column at 200°; $[\alpha]^{20}\mathrm{D}$ −19.97° (neat, 10-cm cell)). The residue from the first distillation was taken up in ether

Table II. Physical Data for Halides, Oxazolines, and Acids. Oxazoline Hydrolysis Conditions

Entry from Table I	Halides (**2**)			Oxazolines (**3**)		Hydrolysis[d] conditions (95°) **3** to **4**	Acids (**4**)		
	Bp, °C (Torr)	Purity[a,e]	d_4^{24} [b]	% yield[c]	% purity[a]		Bp, °C (Torr)	% purity[a]	d_4^{24} [b]
1	103-104	94.1	1.522	>99.0	98.6	6 N H_2SO_4, 8 h	94-95 (11)	>99.0	0.917
4	41 (15)	90.2	1.475	98.8	98.3	6 N H_2SO_4, 8 h	107-108 (10)	>99.8	0.909
5	82-84 (51)	97.0	1.388	>99.0	75.6	6 N H_2SO_4, 6.5 h	110-111 (6)	>99.5	0.901
6	78 (5)	96.1	1.302	>99.4	96.0	6 N H_2SO_4, 8 h	77-78 (0.08)	>99.5	0.889
9	42-43 (7)	96.5	1.429	>99.5	92.0	6 N H_2SO_4, 3 h	108-109 (7)	>99.5	0.917
10	65-67 (8)	94.4	1.366	85.1	93.0	6 N H_2SO_4, 3.3 h	124-125 (7)	>99.0	0.907
11	20-23 (0.05)	95.0	1.322	84.1	95.0	6 N H_2SO_4, 4 h	128-129 (7)	98.9	0.899
12	23 (0.05)	96.0	1.329	78.0	69.0	6 N H_2SO_4, 3.5 h	116 (1.2)	99.0	1.065

[a] Purity determined using a Hewlett-Packard 5750 gas chromatograph equipped with an electronic integrator and a 6-ft UCW-98 (10%) column heated accordingly between 105 and 230°. [b] Densities were determined in a 1-cm^3 pycnometer at 24° and these values were then used to determine $[\alpha]^{24}\mathrm{D}$ (neat). [c] These are crude yields determined after the alkyl halides were pumped off. [d] Hydrolyses were carrried out using 6-8 g of **3** in 100 ml of 6 N H_2SO_4. [e] All of the halides contained, in addition to traces (1-4%) of solvent (Et_2O or THF), 5-8% of the corresponding alkenes, which were collected from the VPC instrument and confirmed by NMR.

and then concentrated to give 8.30 g of **3** (R = Me, R′ = *n*-Hex) (96% purity, VPC using a 6 ft UCW-98 (10%) column at 230°). See Table II for physical data. This material was hydrolyzed without further purification. A mixture of 8.30 g of **3** above in 100 ml of 6 N H_2SO_4 was heated under reflux for 8 h and then allowed to cool. After extraction of the acidic solution[15] with ether (3 × 50 ml), the extracts were shaken with 5% K_2CO_3 solution (2 × 40 ml) and the aqueous layer was acidified (3 N HCl) and extracted with ether. The combined ethereal extracts were washed with 5% sodium bisulfite ($NaHSO_3$) and then with saturated brine, dried ($MgSO_4$), and concentrated. The oily residue (3.51 g) was distilled to give 3.30 g of **4** (R = Me, R′ = *n*-Hex) $[\alpha]^{24}_{\mathrm{D}}$ +2.98° (neat, 10-cm cell).

(+)-2-Iodooctane. A solution of phosphorus triiodide in carbon disulfide (prepared by the addition of 2.4 g of white phosphorus to a mixture of 29.3 g iodine in 160 ml CS_2) was added dropwise (1.2 h) to a stirred solution of 9.8 g (75.4 mmol) of (−)-2-octanol, $[\alpha]_{\mathrm{D}}$ −8.97° (neat), in 50 ml of CS_2 at −10 to −13° under nitrogen. The resulting mixture was allowed to warm to room temperature and stirred for 23 h, after which it was poured over crushed ice. The CS_2 layer was separated and washed successively with 10% sodium carbonate, 10% sodium thiosulfate, and water, then dried (Na_2SO_4) and concentrated. Distillation of the residue gave 8.62 g (47.6%), bp 77-77.5° (6 Torr), d_4^{24} 1.3214, 97% purity by VPC (UCW-98 (10%), 6 ft, 200°); $[\alpha]^{24}_{\mathrm{D}}$ 44.07° (neat). A second fraction, bp 75-77° (6 Torr) gave 2.07 g (96% purity, VPC); $[\alpha]^{24}_{\mathrm{D}}$ +43.77° (neat). The literature value[16] for (+)-2-iodooctane is +62.6° (neat), and for (−)-2-iodooctane is −64.2° (neat).[17] Thus, the optical purity of (+)-2-iodooctane obtained is 68.6-70.4% based on the values reported.

(+)-3-Methylnonanoic Acid (4) (R = Me, R′ = Hex). A mixture of the lithiooxazoline **5** prepared from 4.11 g (20 mmol) of (−)-**1** in 60 ml of tetrahydrofuran, prepared as described above, was treated with 8.37 g (35 mmol) of (+)-2-iodooctane ($[\alpha]^{24}_{\mathrm{D}}$ +44.07°) at −50° for 6 h. The resulting mixture was worked up as described in the Typical Procedure and gave 6.26 g (98%) of oxazoline **3** (93% purity, VPC) and 2.61 g (73.1% recovery) of colorless (+)-2-iodooctane, bp 25° (0.15 Torr), 95% purity, 3.7% octene (VPC), $[\alpha]^{24}_{\mathrm{D}}$ +40.54° (neat). Crude **3** (6.16 g, 19.4 mmol) was heated to reflux in 70 ml of 3 N HCl for 2.5 h, cooled, and worked up as described earlier, to give 1.84 g of a light yellow oil. Distillation, bp 131-132° (6 Torr) gave 1.25 g (>98% purity) of colorless acid, $[\alpha]^{24}_{\mathrm{D}}$ +5.25° (neat).

Based on the optical purity of the (+)-2-iodooctane (+44.07°) and the optical purity of the recovered iodooctane (+40.54°), the (+)-3-methylnonanoic acid is judged to be 71 ± 2% optically pure. Thus, the rotation[18] for optically pure (+)-3-methylnonanoic acid is 7.4 ± 0.2°.

Reaction of Recovered (−)-2-Iodooctane with the Achiral Lithiooxazoline (6). A solution of lithium diisopropylamide (21.5 mmol), prepared as described in the Typical Procedure, was added dropwise (15 min) to a solution of 2.44 g (21.5 mmol) of 2,4,4-trimethyl-2-oxazoline in 45 ml of THF at −78°. After 30 min, the lithiooxazoline **6** was treated dropwise with 4.70 g (19.6 mmol) of (−)-2-iodooctane ($[\alpha]^{24}_{\mathrm{D}}$ −19.97° (neat)) in 5 ml of THF and the resulting solution stirred at −70 ± 8° for 7 h and at 0° for 12 h. Work-up was performed in the manner used for the chiral oxazoline alkylations and gave 4.16 g of crude **7** (R = Hex): ir (film) 1663 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.5 Hz, 3), 1.30 (s, 6), 2.0-2.4 (m, 2, 3.90 (s, 2). The crude oxazoline (4.10 g) was heated to reflux in 60 ml of 6 N H_2SO_4 for 1.25 h and worked up following previous hydrolysis procedures to give 2.62 g (77.5%) of (*S*)-(−)-**4b** as a colorless oil: bp 75-77° (0.05 Torr), 99.9% purity (VPC UCW-98 (10%), 6 ft column heated to 200°), d_4^{24} 0.8910; $[\alpha]^{24}_{\mathrm{D}}$ −2.24° (neat, *l* = 10 cm); ir (film) 1708 cm^{-1}; NMR (CCl_4) δ 0.90 (t, *J* = 6 Hz, 3), 0.98 (d, *J* = 6.5 Hz, 3), 2.1-2.5 (m, 2), 11.98 (br s, 1, exchangeable with D_2O).

Reaction of Recovered (−)-2-Iodopentane with the Achiral Lithiooxazoline 6. In a similar fashion used for **4b**, 2.70 g (24 mmol) of 2,4,4-trimethyl-2-oxazoline was converted to its lithio salt using 24 mmol of LDA in 45 ml of THF. Treatment with 4.50 g (22.7 mmol) of (−)-2-iodopentane ($[\alpha]^{24}_{\mathrm{D}}$ −14.17° (neat)) at −70 ± 8° for 7 h and 0° for 12 h gave, after work-up, 4.02 g of crude **7** (R = *n*-Pr): ir (film) 1665 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (d, *J* = 6 Hz, 3), 1.27 (s, 6), 2.04-2.44 (m, 2), 3.90 (s, 2). The crude material (4.00 g) was heated under reflux in 60 ml of 6 N H_2SO_4 for 1.25 h and after work-up gave 2.39 g (80.7%) of **4a**. Distillation gave 1.89 g: bp 109-110° (12 Torr), 99.5% purity (VPC as above); d_4^{24} 0.9096, $[\alpha]^{24}_{\mathrm{D}}$ −0.75° (neat, *l* = 10 cm); ir (film) 1710 cm^{-1}; NMR (CCl_4) δ 0.99 (d.*J* = 6.5 Hz, 3),2.1-2.5 (m, 2), 11.83 (s, 1, exchangeable with D_2O).

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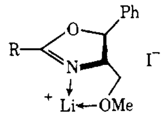
References and Notes

(1) For a discussion on kinetic resolutions and examples reported in the literature see the excellent monograph by J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, pp 30–35.
(2) A. I. Meyers and G. Knaus, *J. Am. Chem. Soc.*, **96**, 6508 (1974).
(3) A preliminary report has appeared, A. I. Meyers and K. Kamata, *J. Org. Chem.*, **39**, 1603 (1974).
(4) Upon hydrolysis of **3**, the chiral methoxyamino alcohol may be reconverted to the starting oxazoline **1** (see Experimental Section).
(5) W. Klyne, *Prog. Stereochem.*, **1**, 197 (1954), and appropriate references in Table I.
(6) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.*, **97**, 6266, (1975). (−)-**1** is commercially available from Aldrich or ELARS Bioresearch, Ft. Collins, Colo. 80522.
(7) A. H. Horeau, *Tetrahedron Lett.*, 506 (1962); A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964); A. Horeau and A. Nouaille, *Tetrahedron Lett.*, 3953 (1966); A. Horeau, A. Nouaille, and K. Mislow, *J. Am. Chem. Soc.*, **87**, 4957 (1965); R. Wiedman and A. Horeau, *Bull. Soc. Chim. Fr.*, 117 (1967), A. Horeau, *Ibid.*, 2673 (1964).
(8) A. othen and P. A. Levene, *J. Chem. Phys.*, **7**, 975 (1939). Other $[\alpha]_{\mathrm{D}}$ values reported are: (a) −4.51° and +4.44° (neat), F. S. Prout, D. E. Dickson, and R. J. Klimkowski, *J. Org. Chem.*, **24**, 826 (1959); (b) −4.20° (neat), E. LeGoff, S. E. Ulrich, and D. B. Denny, *J. Am. Chem. Soc.*, **80**, 622 (1958).
(9) All of the recovered secondary halides contained 5–7% olefins due to some elimination. In Table I the purity of the recovered halides was 92–99% (by VPC) and this results in a slight lowering of the $[\alpha]_{\mathrm{D}}$ values observed.
(10) Lithium bromide is known to rapidly racemize α-phenethyl bromide; E. D. Hughes, F. Juliusburger, A. D. Scott, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1173 (1936).
(11) A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2778 (1974).
(12) Since the chiral oxazolines **1** and **3** have the adjacent methoxy methyl group (absent in **6**) the possibility of a highly ionic lithium iodide A being present which is capable of *nucleophilic displacement at low temperatures* must be considered. Unpublished work in our laboratory indicates that lithium salts (LiCl, LiI) have enhanced solubility in organic solvents in the presence of **1**.



A

(13) A well-packed cooling bath of dry ice and acetone in an insulated vessel (e.g., Dewar flask) will keep the temperature of the reaction mixture in the desired range for 12–15 h. A low temperature refrigeration unit (Kelvinator, −70°) serves as an excellent cooling container for these reactions.
(14) Low boiling halides (2-iodobutane, 2-iodopentane, etc.) were removed mainly with the solvent and this condensate was totally trapped in a flask immersed in a Dewar flask containing dry-ice–acetone. The solution was washed successively with ice-cold 1 N H_2SO_4, saturated brine, and cold water, then dried over $MgSO_4$. The volatile halides were then recovered by distillation through a 12 in. Vigreux under appropriate vacuum (see Table II).
(15) This solution, upon rendering it alkaline (pH 10 with KOH) and extraction with ether, gives the methoxyamino alcohol which may be used to make (−)-**1**.
(16) M. C. Berlak and W. Gerrard, *J. Chem. Soc.*, 2309 (1949); W. Gerrard and H. P. Hudson, *ibid.*, 2310 (1964).
(17) See footnote *i* in Table I.
(18) See footnote *j* in Table I.