Tracer Experiment. 2,2,4,4-Tetramethylpentane-3-thione *S*-oxide and 2-propylmagnesium chloride were reacted in ether as described above. The reaction mixture was poured into a saturated deuterium oxide solution of ammonium chloride and the ether layer was worked up as described above. The deuterium content in **4a** was analyzed on a Varian T-60 NMR and Shimadzu LKB-9000S GC–MS spectrometers to be 21 ± 1%.

Reaction of 2,2,4,4-Tetramethylpentane-3-thione with Alkylmagnesium Halide. A Grignard reagent made from methyl iodide or 2-propyl chloride was reacted with the thioketone, **3**, under the same condition as described above. After the usual workup, 2,2,4,4-tetramethylpentane-3-thiol[25] was isolated in 82 or 74% yield, respectively. The Grignard reaction of **3** with allylmagnesium chloride afforded 2,2-dimethyl-3-(1′,1′-dimethylethyl)hex-5-ene-3-thiol in 92% yield as a yellow liquid: NMR ($CDCl_3$, Me_4Si) δ 1.16 (s, 9 H), 1.19 (s, 9 H), 1.34 (s, 1 H), 2.50–2.77 (m, 2 H), 4.84–5.13 (m, 1 H), and 5.92–6.37 (m, 2 H); MS (M^+) *m/e* 200.

Anal. Calcd for $C_{12}H_{24}S$: C, 71.93; H, 12.07. Found: C, 71.94; H, 12.05.

Reaction of 2,2,4,4-Tetramethylpentane-3-thione *S*-Oxide with Alkyllithium. The reactions were carried out similarly to the Grignard reactions described above. The products were identical with those obtained from the reactions of the corresponding Grignard reagents.

Registry No.—**1**, 56956-24-3; **2a**, 69912-55-6; **2b**, 69912-52-3; **2c**, 69912-53-4; **2d**, 69912-54-5; **3**, 54396-69-9; **4a**, 65566-46-3; **4b**, 69543-45-9; 2,2-dimethyl-3-(1′,1′-dimethylethyl)hex-5-en-3-thiol, 65566-36-1; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; allyl chloride, 107-05-1; benzyl chloride, 100-44-7; 2-propyl chloride, 75-29-6; cyclohexyl chloride, 542-18-7; *tert*-butyl chloride, 507-20-0; 2-propanol, 67-63-0; cyclohexanol, 108-93-0; cyclohexene, 110-83-8; *tert*-butanol, 75-65-0; trimethylsulfoxonium iodide, 1774-47-6; phenyldiazomethane, 766-91-6; 2,2,4,4-tetramethylpentane-3-thiol, 57602-97-8.

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Separation of Diastereomers Using a Low Cost Preparative Medium-Pressure Liquid Chromatograph

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A series of diastereomeric oxazolines (**2** and **5**) derived from asymmetric addition of organometallics to the prochiral oxazolines **1** and **4** have been examined on an efficient preparative liquid chromatograph. The pure diastereomers were readily obtained using this component system, and enantiomerically pure acids **3** and **6** were isolated. It is suggested that $[\alpha]_D$ values for pure chiral products be recorded only after this separation scheme is employed. Details for the construction of the liquid chromatograph and its operation are given.

In the course of studying and developing new methodology for asymmetric syntheses, the efficiency of the asymmetric induction is usually evaluated by comparing the specific rotation of the synthetic product with that reported by others, mainly from resolution methods. The tedious procedures associated with repeated crystallization of diastereomeric precursors has, in the main, restricted the scope of asymmetric methodology to those compounds whose specific rotations have been described in the literature, and this has had a regressive effect upon this area of study. Furthermore and probably more significant is the tendency of workers in asymmetric synthesis to rely heavily upon the extent of enantiomeric purity based on optical rotation data. The inherent danger of using *only* optical rotations has already been described by Valentine and Scott,[1] who urged investigators to consider "direct methods to determine the enantiomeric excess of many typical asymmetric synthesis products". The advent of chiral shift reagents and chiral solvents has done much to facilitate enantiomeric determination of chiral products, but this is limited to certain structural features

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Table I. Preparative Separations of Diastereomers 2 and 5

compd	R	R′	grams of mixture on MPLC	grams recovered pure[a]	carboxylic acids[b] no.	$[\alpha]_D$, deg	$[\alpha]_{lit}$, deg
2	*n*-hexyl	Me	4.1	1.3	3	5.10 (neat)	*c*
2	*n*-Bu	Et	4.4	2.4	3	2.95 (neat)	4.69[d]
2	*n*-Bu	*t*-Bu	4.0	2.7	3	−18.00 (neat)	*c*
2	*n*-Bu	*i*-Pr	4.1	2.8	3	−0.82 (neat)	*c*
2	*n*-Pr	$MeOCH_2CH_2$	4.3	1.5	3	1.32 (neat)	*c*
5	Me		3.85	1.96	6	36.3 (EtOH)	35.3[e]
5	Et		0.90	0.26	6	33.3 (EtOH)	33.7[f]

[a] Purity was ascertained by analytical high-pressure liquid chromatography (Waters 244 HPLC instrument). Both **2A** and **2B** (or **5A** and **5B**) were discernible on the HPLC instrument prior to preparative MPLC separation, and each pure diastereomer showed only a single peak after separation. [b] Obtained by hydrolysis of pure **2** or **5**, using a Perkin-Elmer 241 automatic polarimeter to determine $[\alpha]_D$. [c] Not previously reported. [d] Marker, R. E.; Levene, P. A. *J. Biol. Chem.* **1936**, *115*, 401. [e] Barnes, R. A.; Juliano, B. R. *J. Am. Chem. Soc.* **1959**, *81*, 6462. [f] Mitsui, S. *Chem. Ind. (London)* **1964**, 233.

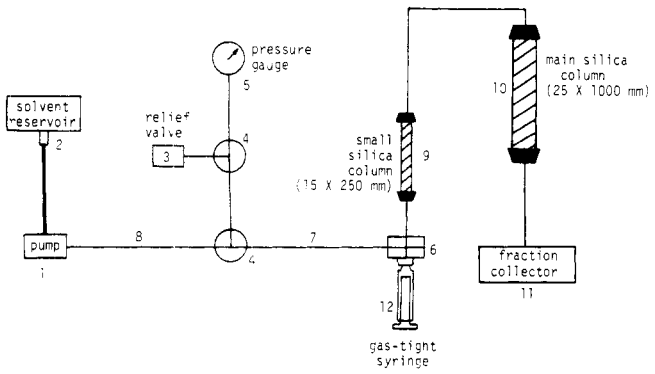
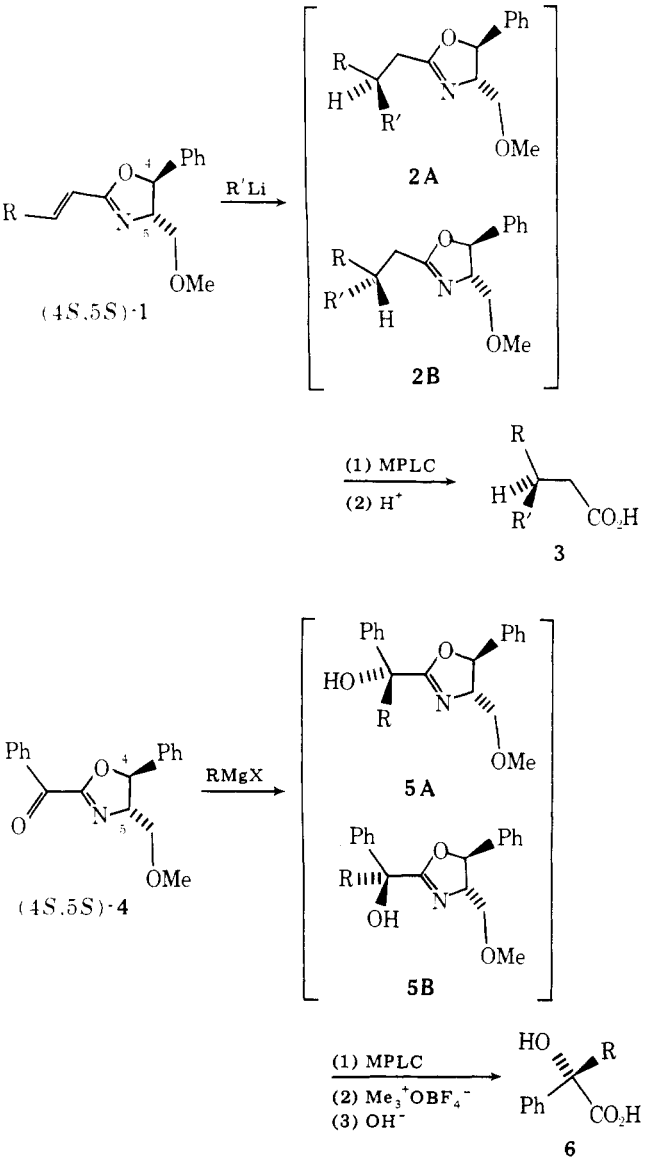


Figure 1. Schematic diagram for medium-pressure liquid chromatograph. Details and specifications for each component are given in the Experimental Section.



readily discernible in the ^1H or ^{13}C NMR spectra.[2] In recent years, separation technology has been greatly improved by use of pressurized liquid chromatography[3] and gas chromatography[4] applied to separation of diastereomers.

In this report, we describe separation techniques associated with two asymmetric syntheses which pass through diastereomeric intermediates **2** and **5** and ultimately furnish the chiral products **3** and **6**. Although the details of the asymmetric synthesis leading to **3** have been described[5] and those leading to the α-hydroxy acids **6** will be reported in due course, the present paper will demonstrate the feasibility of obtaining, by preparative medium-pressure liquid chromatography (MPLC), pure diastereomers of **2** and **5**. Hydrolysis of the latter produces the enantiomerically pure acids **3** and **6** as standards for assessing the extent of the asymmetric addition to **1** and **4**. Specific rotation data for a number of chiral acids **3** have not been reported previously, and in some cases the $[\alpha]_D$ values which were known created doubt with regard to their measure of enantiomeric purity. For this reason, we undertook a routine scheme to separate the diastereomers **2** and **5** on a preparative scale and, after confirming their homogeneity using analytical HPLC, transformed each pure diastereomer into the acids whose specific rotation was determined. Only then did we have unquestionable faith in the $[\alpha]_D$ values which were employed to assess enantiomeric purities.[5] In the absence of this sequence, specific rotation data can give highly erroneous results.[6]

The data presented in Table I indicate the multigram scale of separations employed. Although separations have been performed on larger amounts (up to 12 g), the scale given in the table suffices for determining pure diastereomers and pure chiral acids. For **2** (R = *n*-Bu, R′ = Et), it was found that the corresponding acid **3** had an $[\alpha]_D$ of +2.95° as opposed to the literature value of 4.69°. This is an example of the wide discrepancy frequently observed when relying solely on optical rotation data. The other pure chiral products in Table I have not been previously reported, except in the cases of the α-hydroxy acids **6** (R = Me, Et) where reasonably close agreement was found with the literature.

Separations of the diastereomeric mixture of **2** and **5** were performed on a unit constructed from various commerical components (Figure 1) whose total cost was under $1700. The

unit has the capability of efficiently separating 0.5–15.0 g of material using, in this instance, a hexane–acetone solvent pair. Preliminary TLC examination allows the appropriate solvent choice by reaching an R_f value of ~0.25–0.4. Although no spot separation is apparent in many cases from TLC examination, the unit may be expected to provide useful and preparative separations. The eluted material was monitored only with thin-layer chromatography examining each tube for its contents. Thus, no expensive detection device is required, but one may be incorporated in accordance with individual needs. After the products are collected, the remaining material on the column is removed by backflushing with a polar solvent (e.g., ethyl acetate) and the system is now ready for further use (see Supplementary Material Available).

The liquid chromatograph unit described herein for the separation of diastereomers **2** and **5** has also been used for a variety of other separations (cis,trans olefins, aromatic isomers, other diastereomeric mixtures, etc.).

Experimental Section

Diastereomeric oxazolines 2 were prepared by addition of organolithium reagents to the vinyloxazoline **1** as previously described.[5] Separations were performed on ~4.0 g of a mixture (**2A, 2B**) by injecting a solution [4g/10 mL of acetone–hexane (1:1)] into the four-way valve (Figure 1, no. 6). The sample was eluted using 17% acetone–hexane to provide pure material as given in Table I. The remainder of the material collected in the tubes contained overlapping products and the other pure diastereomer. For the purposes of this study, the overlapping fractions were not recycled to obtain complete separation, but this is indeed possible. The homogeneity of the pure diastereomers of **2** was confirmed by high-pressure liquid chromatography using a Waters Associates instrument equipped with a 12-in. μ-Porosil column (10% acetone–hexane). In each instance only a single peak was observed, noting the absence of the other diastereomer originally observed when the mixture was examined.

Diastereomeric oxazolines 5 were prepared by addition of ethyl- or methylmagnesium bromide to the benzoyloxazoline **4**, and on workup the crude diastereomeric mixture[7] was injected into the liquid chromatographic unit as described above. Separations were monitored on HPLC to assess purity. Results are given in Table I.

Chiral carboxylic acids 3 were obtained by acid hydrolysis (1.5 M H_2SO_4) and distillation, affording the analytically pure material[5] whose specific rotations are recorded in Table I.

Chiral α-alkyl-α-(hydroxyphenyl)acetic acids 6 were prepared by treating pure **5A** with 1.0 equiv of triethyloxonium fluoroborate in methylene chloride to form the *N*-ethyl quaternary salt, which was then treated with 2 N KOH in Me_2SO to generate the free carboxylate of **6**. Acidification gave the acid **6**, which was freed of solvent (Me_2SO) by filtering through silica gel [**6** (R = Me), mp 114–116 °C; **6** (R = Et), mp 125–126 °C]; cf. footnotes *e* and *f* of Table I.

Components of the Liquid Chromatograph (Figure 1): (1) pump, 1/4 in. piston, flow rate 0–19 mL/min at 100 psi; (2) glass fritted filter for removing suspended material; (3) pressure relief valve, rated at 50–150 psi, to protect glass columns from pressures exceeding 100 psi; (4) T-connector for 0.8-mm tubing; (5) pressure gauge, 0–200 psi; (6) four-way valve with Luer fitting for gas-tight syringe (sample injected through this component); (7) plastic tubing (Teflon), 0.8 mm i.d.; 1.5 mm o.d. for all connections to the *right* side of T-connector (4); (8) plastic tubing (Teflon), 1.5 mm i.d.; 3.0 mm o.d. for all connections to the *left and above* the T-connector (4); (9) small scrubber column, 15 × 100, for preliminary removal of tarry or highly polar materials; this column may also be used to separate 50–200 mg of material; this column is packed with silica gel 60 (E. Merck), 40–60 μm; (10) main separation column, 25 × 1000 cm for 2–15-g separations or 15 × 1000 cm for 0.5–3.0 g; these columns are also packed with silica gel 60, 40–60 μm; (11) fraction collector with siphon to deliver 5-mL portions of eluents and containing at least 90 test tubes; (12) syringe plunger to fit on 10- or 20-mL standard syringes. Additional details concerning components, their availability, and suggested operational techniques are available as supplementary material.

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Registry No.—**2A** (R = *n*-hexyl, R′ = Me), 69765-92-0; **2A** (R = *n*-Bu, R = Et), 69831-02-3; **2A** (R = *n*-Bu, R′ = *t*-Bu), 69765-93-1; **2A** (R = *n*-Bu, R′ = *i*-Pr), 69765-94-2; **2A** (R = *n*-Pr, R′ = $MeOCH_2CH_2$), 69765-95-3; **2B** (R = *n*-hexyl, R′ = Me), 52230-95-2; **2B** (R = *n*-Bu, R′ = Et), 69853-51-6; **2B** (R = 2-Bu, R′ = *t*-Bu), 69765-96-4; **2B** (R = *n*-Bu, R′ = *i*-Pr), 69765-97-5; **2B** (R = *n*-Pr, R′ = $MeOCH_2CH_2$), 69765-98-6; **3** (R = *n*-hexyl, R′ = Me), 59614-86-7; **3** (R = 2-Bu, R = Et), 42330-40-5; **3** (R = *n*-Bu, R′ = *t*-Bu), 69765-99-7; **3** (R = *n*-Bu, R′ = *i*-Pr), 69766-00-3; **3** (R = *n*-Pr, R′ = $MeOCH_2CH_2$), 69766-01-4; **5A** (R = Me), 63007-16-9; **5A** (R = Et), 69766-02-5; **5B** (R = Me), 63007-17-0; **5B** (R = Et), 69766-03-6; **6** (R = Me), 13113-71-8; **6** (R = Et), 24256-91-5.

Supplementary Material Available: Setup for LC using medium pressure, four-way slider valve configurations, setups for normal and backflushing operations, specifications for each component, purchasing information for a single complete unit, and general comments on use of the LC unit (6 pages). Ordering information is given in any current masthead page.

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